Bladder cancer :

Preservation strategies

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Disclosures

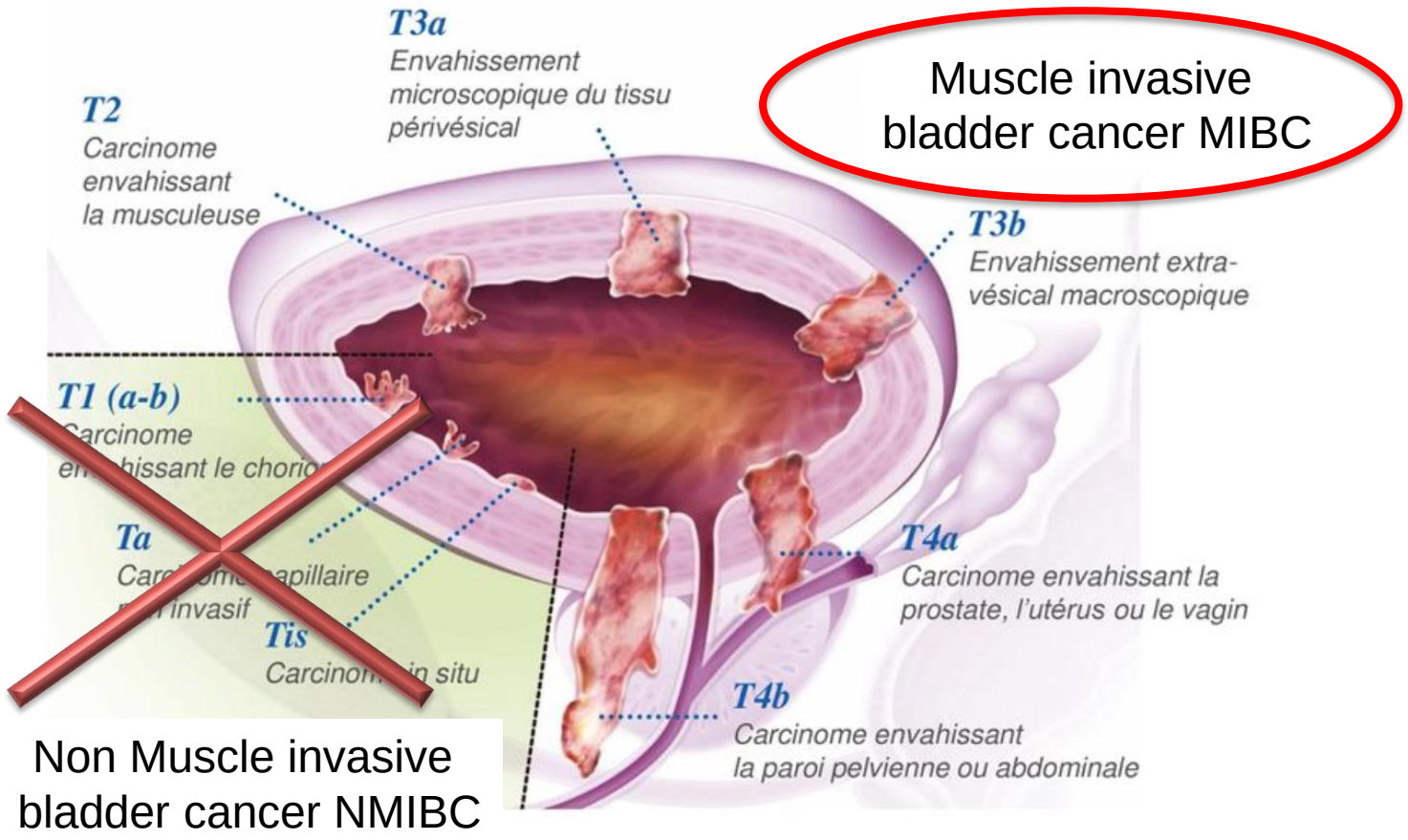
- **Advisory board, Consulting**
  - Pfizer, MSD, BMS, Ipsen, Merck,
  - Roche, Sanofi, Janssen Cilag, Novartis, Esai

- **Honoraria**
  - Astellas, Astra Zeneca

Outline

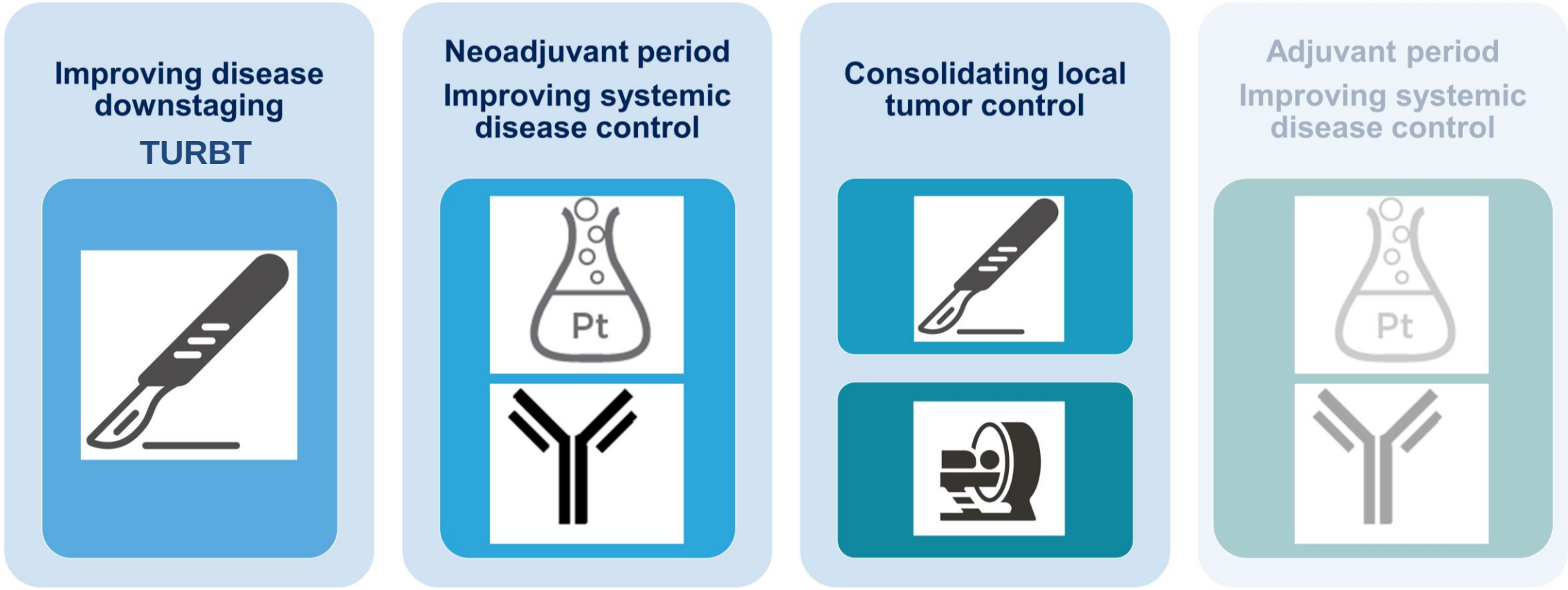
- *Introduction*
  - *Current recommandations*
- *Bladder preservation approach*
  - *Strategies - Trimodality*
  - *Who is the best candidate*
- *Future - Next steps*
  - *How to go forward ?*

Muscle invasive bladder cancer



1. INCa CCAFU. Recommandations en cancérologie urologique 2013.

Current management of localized MIBC



What can we expect from neoadjuvant CT for local control?

ACTIVITY in perspective

Consistent data in the control arm

Outcome correlated with dose intensity?

Study	VESPER	SWOG-1314
	GC (x4)	GC (x4)
N	218	82
ypT0 N0	36	35
ypTis,Ta or T1 and ypN0	14	15
≥ ypT2 or ypN+	50	50

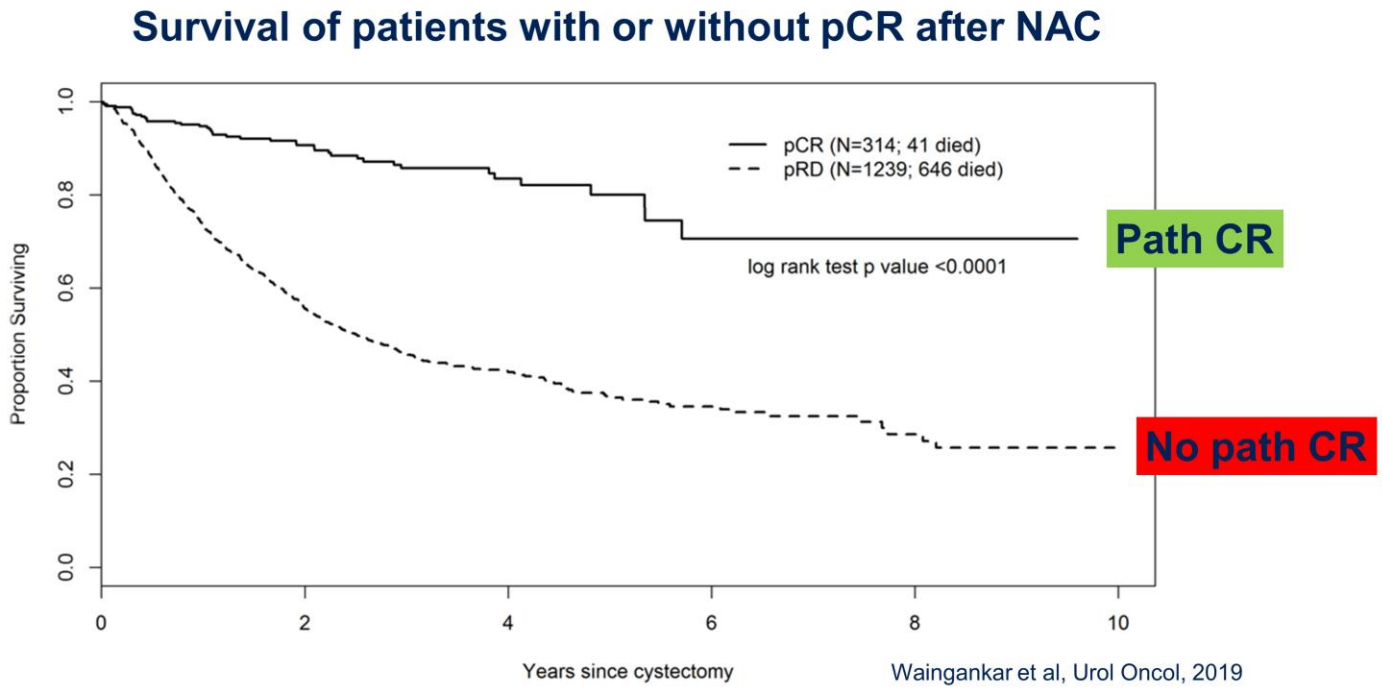
Study	VESPER	SWOG-1314	SWOG-8710	Plimack	Choueiri	Anari
	dd-MVAC (x6)	ddMVAC (x4)	dd-MVAC (x9)	AMVAC (x3)	dd-MVAC (x4)	dd-MVAC (x3)
N	219	85	153	44	39	31
ypT0 N0	42	32	38	38	26	32
ypTis,Ta or T1 and ypN0	21	24	44	16	49	13
≥ ypT2 or ypN+	36	44	56	48	51	NR

How does VESPER data compare with novel chemo + IO combos?

Study	VESPER	BLASST-1	LCCC1520	Funt
	dd-MVAC (x6)	CG + Nivo (4)	CG + Pembro (4)	CG + Atezo (4)
N	219	41	39	39
ypT0 N0	42	49	36	44
ypTis,Ta or T1 and ypN0	21	51	21	25
≥ ypT2 or ypN+	36	0	41	28

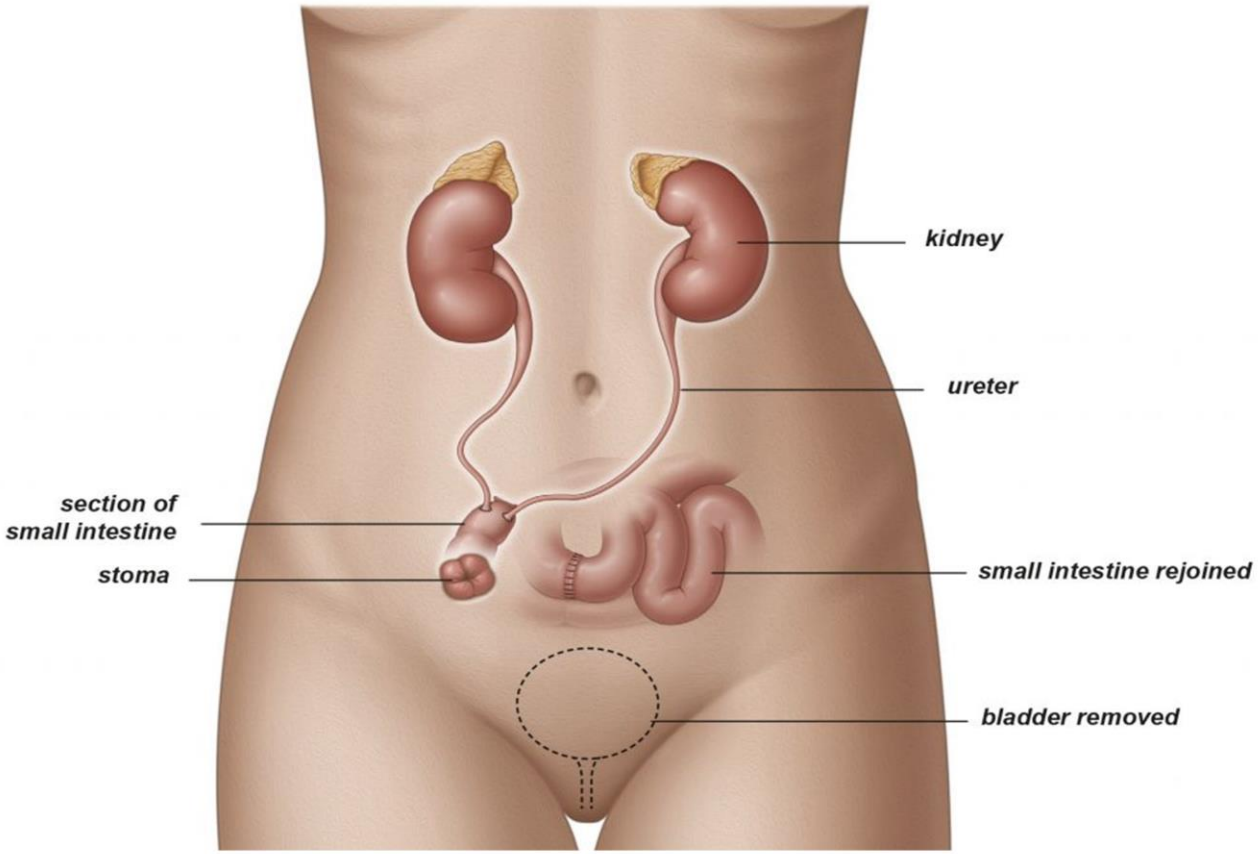
Pfister C, et al. ESMO 2021 #Abstract 6520
Flaig TW, et al. Clin Cancer Res 2021
Grossman HB, et al. N Engl J Med 2003
Plimack ER, et al. J Clin Oncol 2014
Choueiri, TK, et al. J Clin Oncol 2014
Anari F, et al. Eur Urol Oncol 2018
Gupta S, et al. ASCO GU 2020
Rose TL, et al. J Clin Oncol 2021
Funt SA, et al. ASCO 2021

pCR : a surrogate endpoint – associated with outcome



A pathological CR is achieved in ~30-40% of patients with cisplatin-based NAC for MIBC and is associated with favorable outcomes

Unfortunately pathological staging is only determined after the bladder has already been removed…



RADICAL CYSTECTOMY

Gold standard treatment for MIBC

EAU Guidelines on
Muscle-invasive and Metastatic Bladder Cancer

Summary of evidence	LE
For MIBC, offer radical cystectomy (RC) the curative treatment of choice.	3

Recommendations	Strength rating
Offer RC in T2-T4a, N0M0, and high-risk non-muscle-invasive BC.	Strong

We possibly overtreat +/- 30-40% of patients after NAC !

What about bladder preservation strategies?

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Hautmann et al, Eur Urol 2012

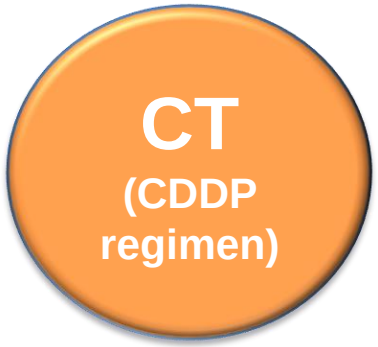
"The best bladder you will ever have is the one you are born with"

(even if it has had an aggressive TURBT and some radiation)

Anthony Zietman

Bladder preservation strategies

One patient out of two is not suitable for surgery



N=133

30% NMIBC 30% MIBC

RC > > EBRT

40 % pCR ; 5y OS = 49 %

Trimodality approach

Recommendation		Strength rating
Do not offer transurethral resection of bladder tumour alone as a curative treatment option as most patients will not benefit.		
cancer.		
cancer.		Strong

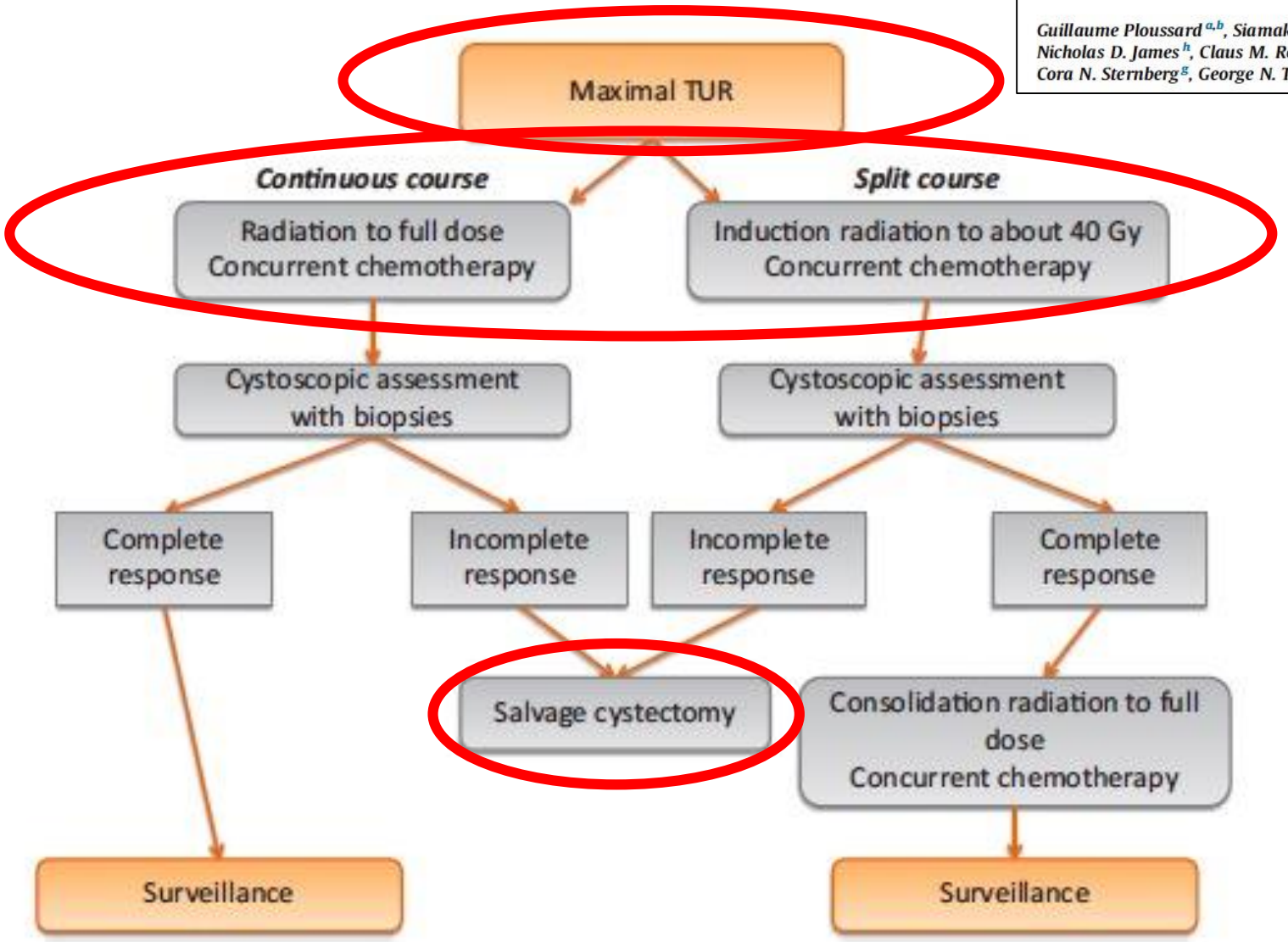
Trimodality approach

European Association of Urology

Collaborative Review – Bladder Cancer

Critical Analysis of Bladder Sparing with Trimodal Therapy in Muscle-invasive Bladder Cancer: A Systematic Review

Guillaume Ploussard[a,b], Siamak Daneshmand[j], Jason A. Efstathiou[c], Harry W. Herr[d], Nicholas D. James[h], Claus M. Rödel[f], Shahrokh F. Shariat[e], William U. Shipley[c], Cora N. Sternberg[g], George N. Thalmann[i], Wassim Kassouf[a,]*



Results : retrospective / prospective trials

Table 1 – Published series of trimodal therapy for bladder preservation: homogeneous treatment regimens

Study	Design and follow-up	Stage	No. of patients	Concomitant chemotherapy	RT	CR rate	Salvage cystectomy rate	CSS	OS
Large sample size (>50 patients) series									
PROSPECTIVE PHASE 3 STUDIES									
James et al., 2012[†] [14]	Continuous Phase 3 (second arm: RT alone) 69.9 mo	T2–T4a N0	182	5-FU, MMC x2 (Neoadjuvant chemotherapy: $n = 57$)	55 Gy or 64 Gy	–	11.4% (at 2 yr)	–	5 yr: 48
Tunio et al., 2012 [20]	Continuous Phase 3 5 yr	T2–T4 N0/Nx	200	Cisplatin weekly	65 Gy ST	93%	–	–	5 yr: 52
Shipley et al., 1998[‡] [58]	Split Phase 3 (second arm: chemotherapy-RT with neoadjuvant chemotherapy) 60.0 mo	T2–T4a N0/Nx	62	Cisplatin x3	64.8 Gy ST	60%	25.8%	–	5 yr: 49
Housset et al., 1993[**] [16]	Split Phase 3 27 mo	T2–T4 N0/N1: $n = 4$	54	Cisplatin + 5-FU x4	44 Gy BID	74%	N/A[**]	3 yr: 62	3 yr: 59
PHASE 2 OR RETROSPECTIVE STUDIES									
Lagrange et al., 2011 [51]	Split Phase 2 8 yr	T2–T4a N0/Nx	51	Cisplatin + 5-FU x3	63 Gy ST	–	33.3%	–	8 yr: 36
Gogna et al., 2006 [56]	Continuous Phase 2 23 mo	T2–T4a N0/Nx <10 cm T1	113	Cisplatin weekly	63–64 Gy ST	70%	15%	5 yr: 50	–
Kragelj et al., 2005 [57]	Continuous Phase 2 10.3 yr	T2–T4a N0/Nx T1	84	Vinblastine weekly	63.8–64 Gy ST	78%	8.3% (***)	9 yr: 51	9 yr: 25
Weiss et al., 2007 [30]	Continuous Retrospective 27 mo	T2–T4a N0/N1: $n = 58$ T1: $n = 54$	112	Cisplatin + 5-FU x2	55.8–59.4 Gy ST	88%	17%	5 yr: 82 (for T2–4: 73)	5 yr: 74 (for T2–4: 63)

Who is the good candidate ?

Patient Selection For Bladder Preservation

Preferred or Ideal	Less than Ideal	Relative Contraindications	Absolute Contraindications
• T2 • No hydronephrosis • No CIS • Visibly complete TURBT • Unifocal tumor • Good bladder function and capacity	• T3a • Incomplete TURBT • Multifocal tumor • Poor bladder function or capacity	• T3b–T4a • Diffuse CIS • Lymph node positive disease	• T4b • Tumor-Related Hydronephrosis • Prior pelvic radiation therapy • Not a candidate for chemotherapy • Prostatic stromal invasion

The one likely to have complete response

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Premo et al, Urol Clin North Am 2015

Who is the good candidate ?

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Trimodality approach is an alternative for selected patients !!

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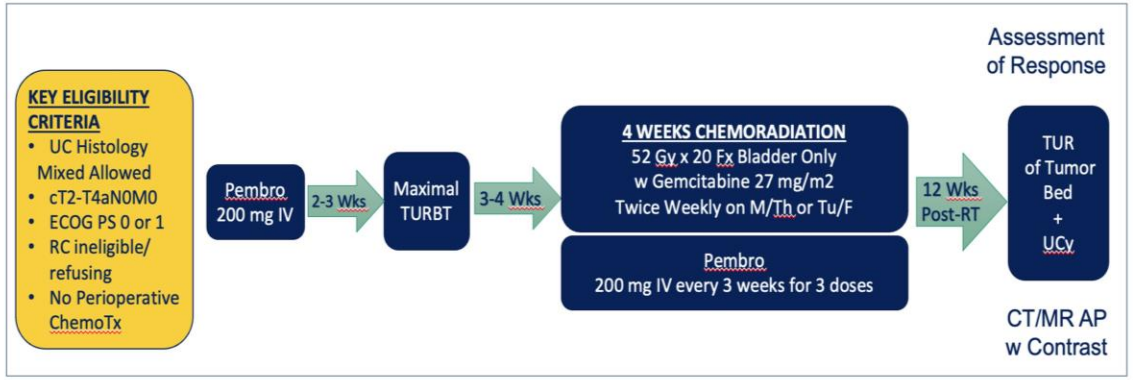
Premo et al, Urol Clin North Am 2015

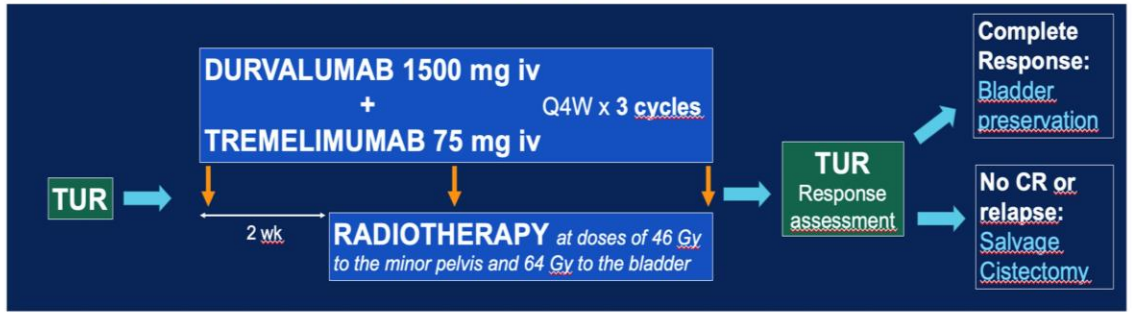
What's new in 2021 : Recent results

Abstracts 4504 & 4505: Combining RT and Immune-checkpoint inhibition

Balar AV, et al, abstract 4504



Garcia del Muro X, et al, abstract 4505



1. Radiosensitizing effect of checkpoint inhibition
   Primary Endpoint: cCR (4505)
2. Systemic tumor control of IO added to a putative abscopal effect of local RT
   Primary Endpoint: BI-DFS (4504)

Dovedi SJ, et al. *Cancer Res*. 2014
Grimaldi AM, et al. *Oncoimmunology*. 2014
Solanki AA, et al. *Eur Urol Oncol*. 2019

ASCO 2021 : Results

	Balar	Garcia del Muro	Benchmark CT/RT study
Treatment (added to TURBT)	CT-IO-RT	IO-IO-RT	CT-RT
Proportion of CR	80%	78%	88%[1]
Treatment eligibility			
Addition of immune-related AEs			
Addition of local RT-related symptoms			

12 months Bladder intact DFS

88%

73%

WE NEED LONGER FOLLOW UP !!

Ongoing trials of concomitant ChemoRT IO

Study	Phase	Experimental compound	Eligibility	Primary endpoint	N
NCT03775265 (SWOG/NRG-1806)[2]	III	Atezo	T2–T4a N0 M0	BI-EFS	475
NCT04241185 (KEYNOTE-992)[3]	III	Pembro	T2–T4 N0 M0	2-year BI-DFS	636
NCT02621151	II	Pembro	T2–T4a N0 M0	2-year BI-DFS	54
NCT03617913	II	Ave	T2–T4a N0 M0	CR	27
NCT03747419	II	Ave	T2–T4a N0 M0	CR	24
NCT0266206 (PCR-MIB)	II	Pembro	T2–T4a N0 M0	Safety	30
NCT03620435	II	Atezo	T2–T4 N0 M0	Safety	25
NCT03844256 (CRMI)	I/II	Nivo; Nivo/Ipi	T2–T4a N0–1 M0	Safety; DFS	50
NCT04216290 (INSPIRE)	II	Durva	Any T N1–2 M0	CR	114
NCT03421652 (NUTRA)	II	Nivo	T2–T4b N0/+ M0	PFS	34
NCT03747419	II	Ave	T2–T4 N0 M0	CR	24
NCT02891161 (DUART)	I/II	Durva	T2–4 N0–2 M0	Safety; PFS/DCR	42
NCT03702179 (IMMUNOPRESERVE)	II	Durva/Treme	T2–T4 N0 M0	CR	32
NCT04073160 (TRIO Bladder)	I	Durva/Treme > DurvaRT	T2–T4 N0-3 M0	Safety	30
NCT03993249	II	Nivo+CRT	T2-4a N0 M0	2y locoregional control	78

1. Basile G, et al. *Urol Oncol*. 2021 Mar 22:S1078-1439(21)00081-8; 2. Singh P, et al. *J Clin Oncol* 38, 2020 (suppl 6; abstr TPS586);
3. Balar AV, et al. *J Clin Oncol* 38: 2020 (suppl; abstr TPS5093)

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NEXT STEP : Can we remove any radical local therapy ?

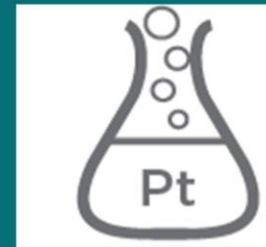
Improving disease downstaging

Neoadjuvant period

Improving systemic disease control

Adjuvant period

Improving systemic disease control



TURBT + chemotherapy is associated with long-term bladder-intact survival in a subset of patients

		Invasive Local Relapse	10-Year Survival	
			Overall	Bladder Intact
	Total N	N (%)	N (%)	N (%)
No cystectomy	28	8 (29%)	21 (75%)	17 (61%)
Partial cystectomy	15	5 (33%)	11 (73%)	8 (53%)
Radical cystectomy	17	0	11 (65%)	0

Herr et al, JCO, 1998

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Abstract #4503: HCRN GU16-257

44% cT3-4N0M0
Balar et al.: 30%
Garcia el Muro et al.: 12%

76 patients

cT2-4aN0M0

Gemcitabine + Cisplatin + Nivolumab X 4 cycles

64 patients

Clinical Restaging

Cysto + biopsies
Urine cytology
MRI

31 patients

≤Ta LG
Normal imaging
(-) cytology

Clinical CR

30 patients

No cystectomy → Nivo x 4 mos

* Treatment based on p

Adjuvant/maintenance IO treatment

Cystectomy

1 patient

33 patients

No Clinical CR

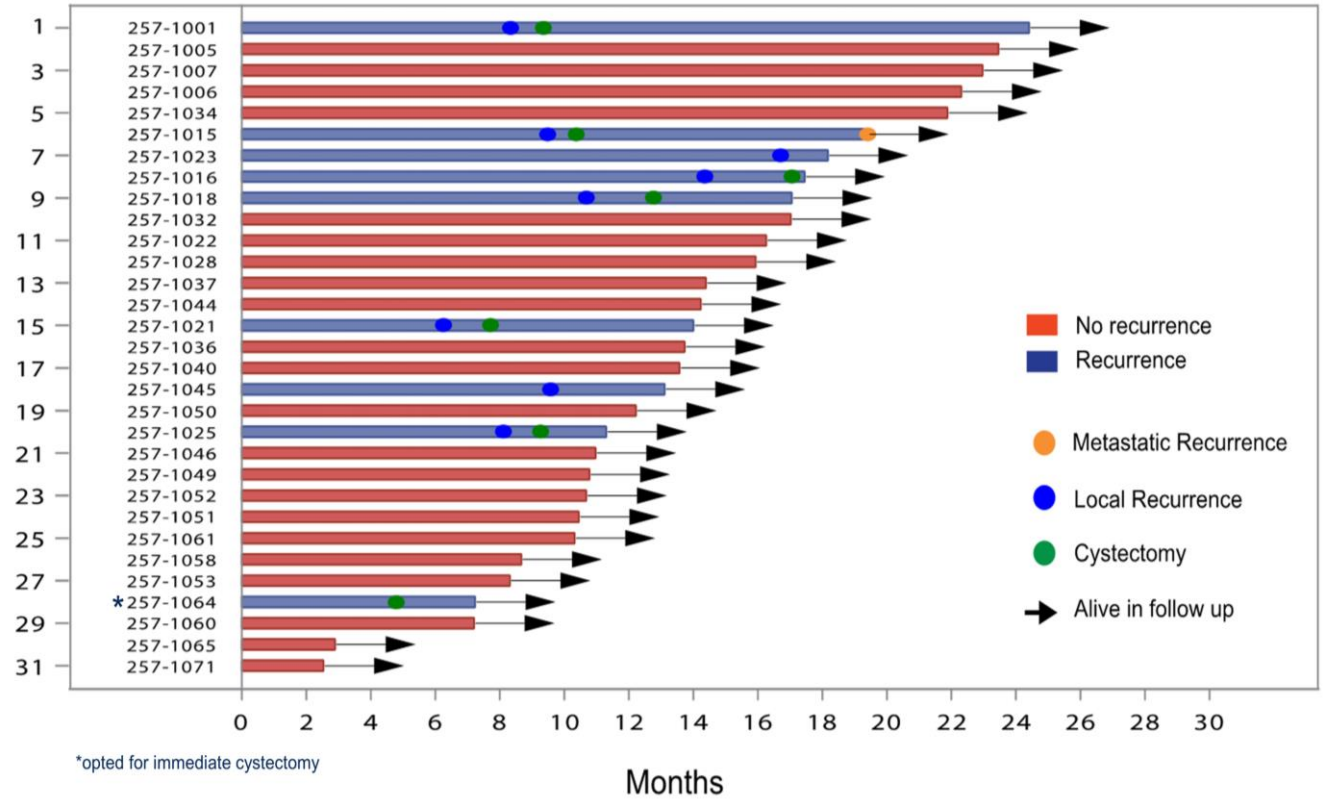
Cystectomy

Patients' adherence to novel therapeutic options alternative to surgery/RT is generally high. Important for the next trials design

Clinical complete response rate = 48% (95% CI 36%, 61%)

Galsky et al, ASCO 2021

Outcomes of patients with clinical CR



8/30 salvage cystectomy:
6 pathological reports available

Pathological stage	N (%)
ypT0N0	1 (17%)
ypTaN0	1 (17%)
ypTisN0	1 (17%)
ypT2N0	2 (32%)
ypT4N1	1 (17%)

How can we move forward ?

Tumor imaging

- mpMRI, Metabolic imaging …

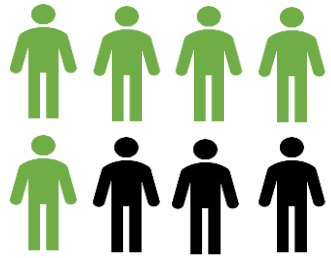
Biomarker

- -omics, microbiota, ctDNA,…

Use of new drugs

- ADC, FGFRi

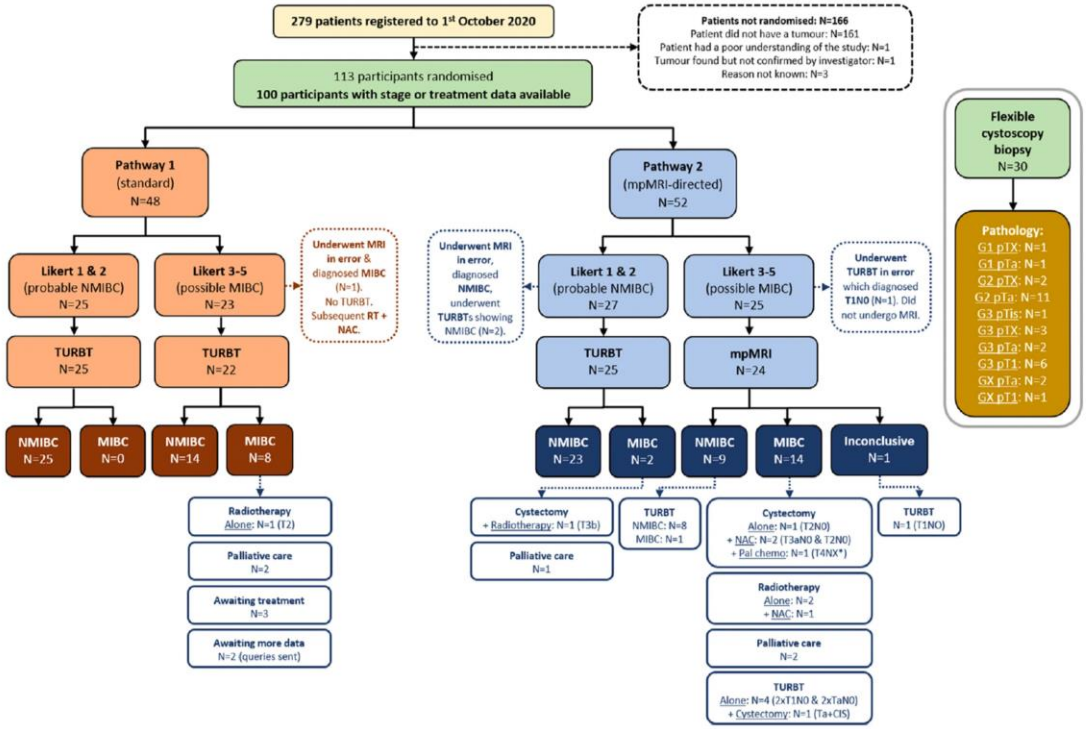
Improve Patient's selection



Improve pCR rate

mpMRI : a “tool” to identify cCR (pCR)

BladderPath trial (N=24 mpMRI)



PURE-01 trial (N=164 mpMRI)

mpMRI as a Noninvasive Assessment of Tumor Response to Neoadjuvant Pembrolizumab in Muscle-invasive Bladder Cancer: Preliminary Findings from the PURE-01 Study

Necchi et al. Eur Urol 2019

Methods

Objective: Evaluate the association between bladder mpMRI after pembro and pT0 rates

82 pts: pre/post pembro mpMRI (n=164 MRIs)

Internal & external assessment

Results

- In 37 pts with radiologic CR
  - Internal: 62% pT0 rate
  - External: 73% pT0 rate
- AUC of radiologic CR for pT0
  - Internal: 0.76 (95%CI 0.68-0.83)
  - External: 0.74 (95%CI 0.66-0.82)
- pT0 rate for mpMRIs suggestive of residual disease:
  - Internal: 4%
  - External: 8%

Conclusions

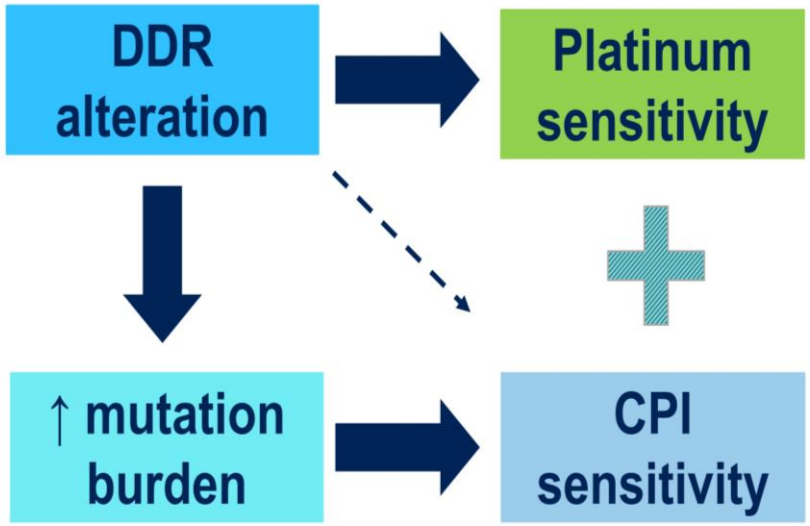
In post-pembrolizumab MIBC, mpMRI assessment of *radiological CR predicts pT0* (AUC 0.74-0.76)

Pending validation, this tool may be used for bladder-sparing IO therapies

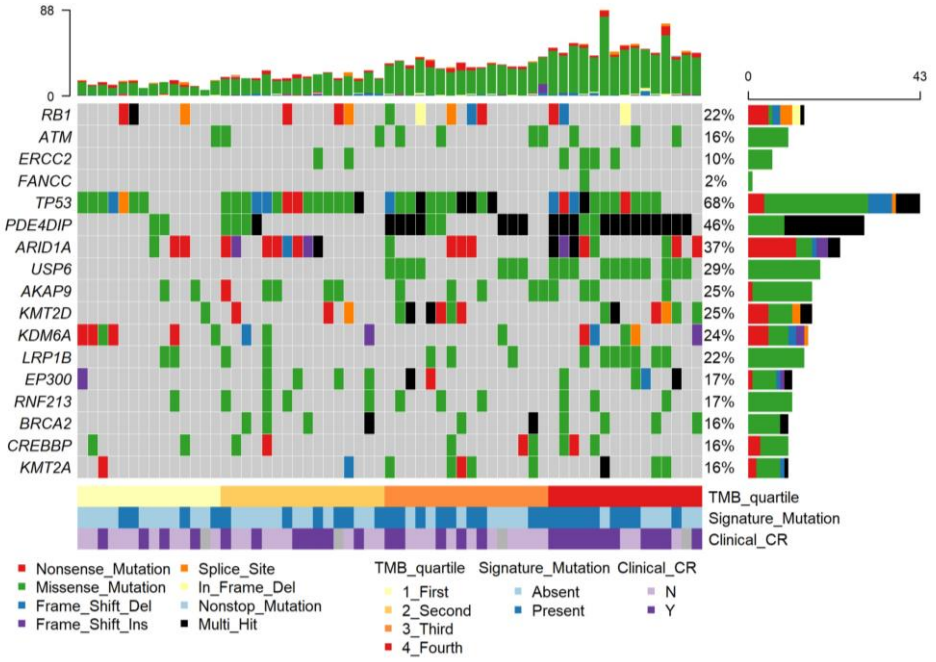
Necchi A, et al. *Eur Urol*. 2020;77:636-643; Bryan RT, et al. *Eur Urol*. 2021 Feb 27;S0302-2838(21)00141-X (ePub ahead of print)

Biomarkers

DDR alterations, TMB, molecular subtypes …



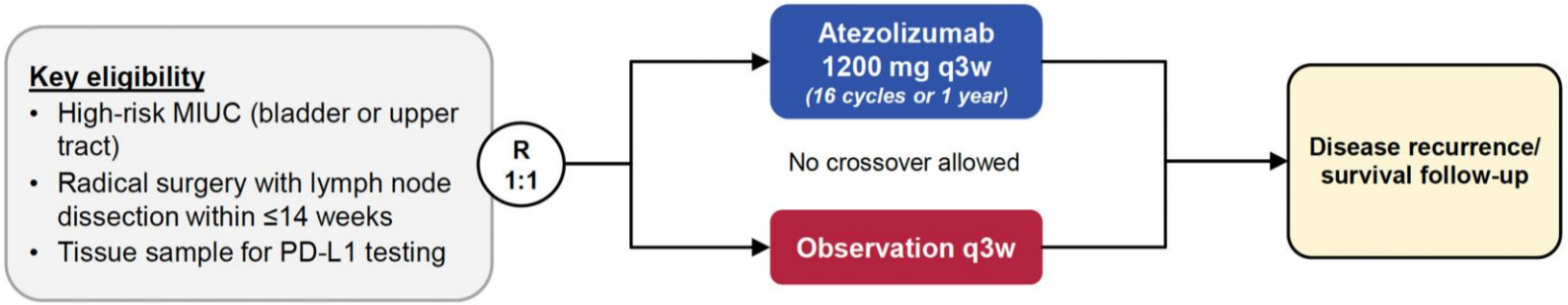
Galsky, Eur Urol, 2018, Plimack et al, Eur Urol, 2017, Van Allen et al, Cancer Discovery, 2015, Teo et al, JCO, 2018

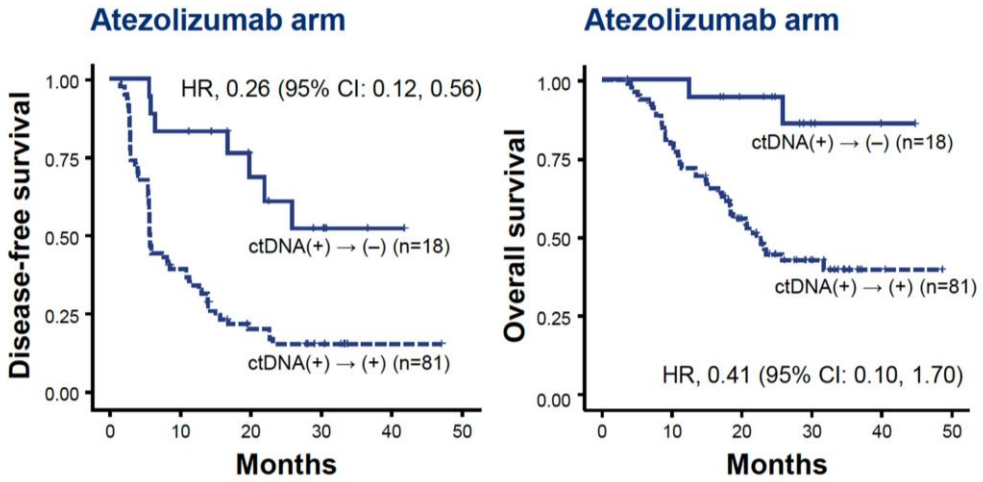


TMB > 10mut/Mb (p=0.02)
and **mERCC2** (p=0.02)
associated with cCR or pCR

Galsky ASCO 2021

Improving biomarker use by looking outside of the tumor



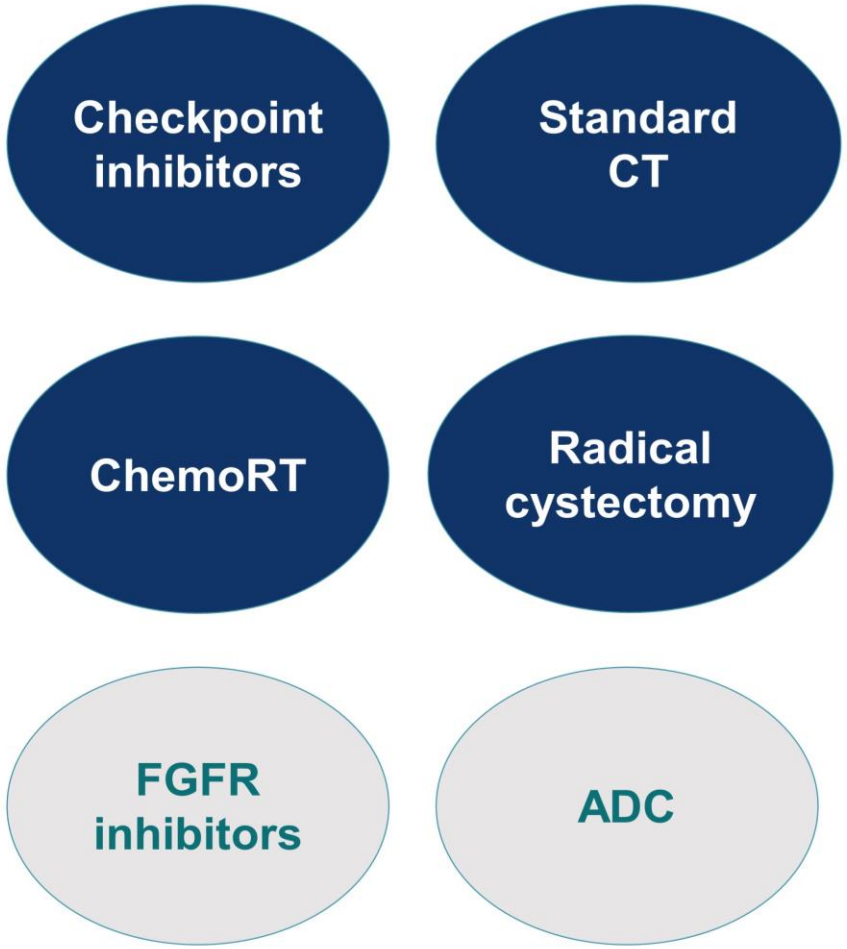


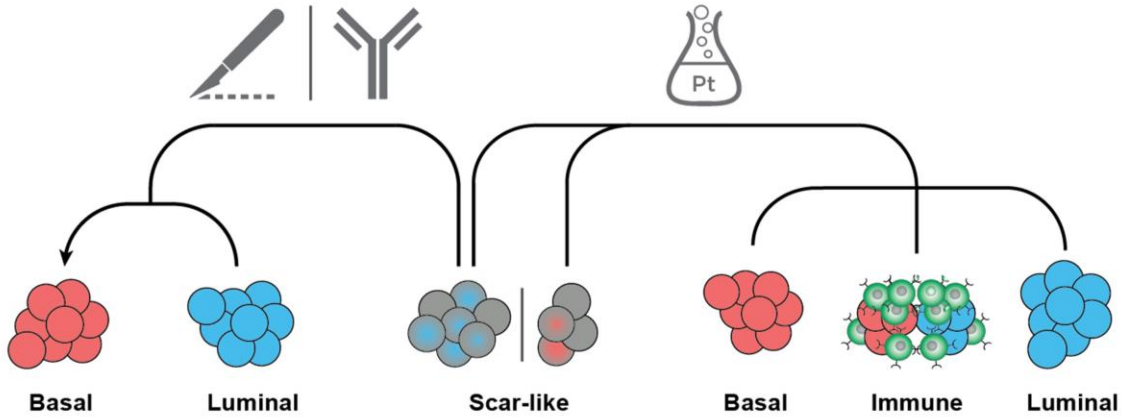
- ctDNA clearance was associated with improved DFS and OS outcomes in the atezolizumab arm

- 'Minimal residual disease' in MIBC
- Best candidate biomarker for next-generation studies of peri-operative therapy

Powles T, et al. *Ann Oncol*. 2020;31 (suppl_7):S1417-S1424.

Incorporating new “players” in our strategies





Basal

Basal-like phenotype
(KRT5/6+ & GATA3-)
Immune infiltrated
Highest proliferation

Expressed targets:
PD-L1
PD-1
CTLA4

Luminal

Luminal-like phenotype
(GATA3+ / KRT5/6)
Low immune infiltration
High NECTIN4, TROP2

Expressed targets:
NECTIN4
TROP2
[FGFR3]

Scar-like

Stromal phenotype
(MYH11+ / KRT5/6-)
Improved prognosis
High angiogenesis

Expressed targets:
VEGFR

Immune

High immune activity
(CD8+, CD274+)
Weak cancer signals
Moderate proliferation

Expressed targets:
PD-L1
PD1
CTLA4

Necchi A, et al. *Eur Urol*. 2021 Mar 27:S0302-2838(21)00212-8

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Take home message :

- **Bladder preservation : option for a selected population**
  - *T2, no hydronephrosis, no CIS, unifocal,*
- **Next steps:**
  - *Improve pCR rate : ADC, IO agents, FGFRi, …*
  - *Improve pts selection:*
    - *Definition of « clinical complete response » : mpMRI, …*
    - *Biomarker : TMB, DDR, ctDNA, molecular subgroups, microbiota …*
- **Overcome**
  - *Reluctance of urologists*

Thanks for your attention

Urology
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Véronique Lindner

Radiology
Catherine Roy
Melanie Mollion

Radiotherapy
Ines Menoux
Gianni Pietta

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