

What could be the near future in non metastatic bladder cancer ?

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Disclosures (Past three years)

- Clinical investigator of trials sponsored by : Amgen, Astellas, Astra Zeneca, Boehringer, Bayer, Bicycle Therapeutics, BMS, Dayichii Sanchio, Exelixis, Gilead, Incyte, Janssen, Lilly, Merck KGaA, MSD, Orion, Pfizer, Roche, Seagen, Tahio, TYRA
- Research grants: Amgen, Astellas, Celsius, MSD, One biosciences, Roche, Veracyte
- Lectures: Astellas, Astra Zeneca, BMS, Janssen, Merck KGaA, MSD, Pfizer, Roche

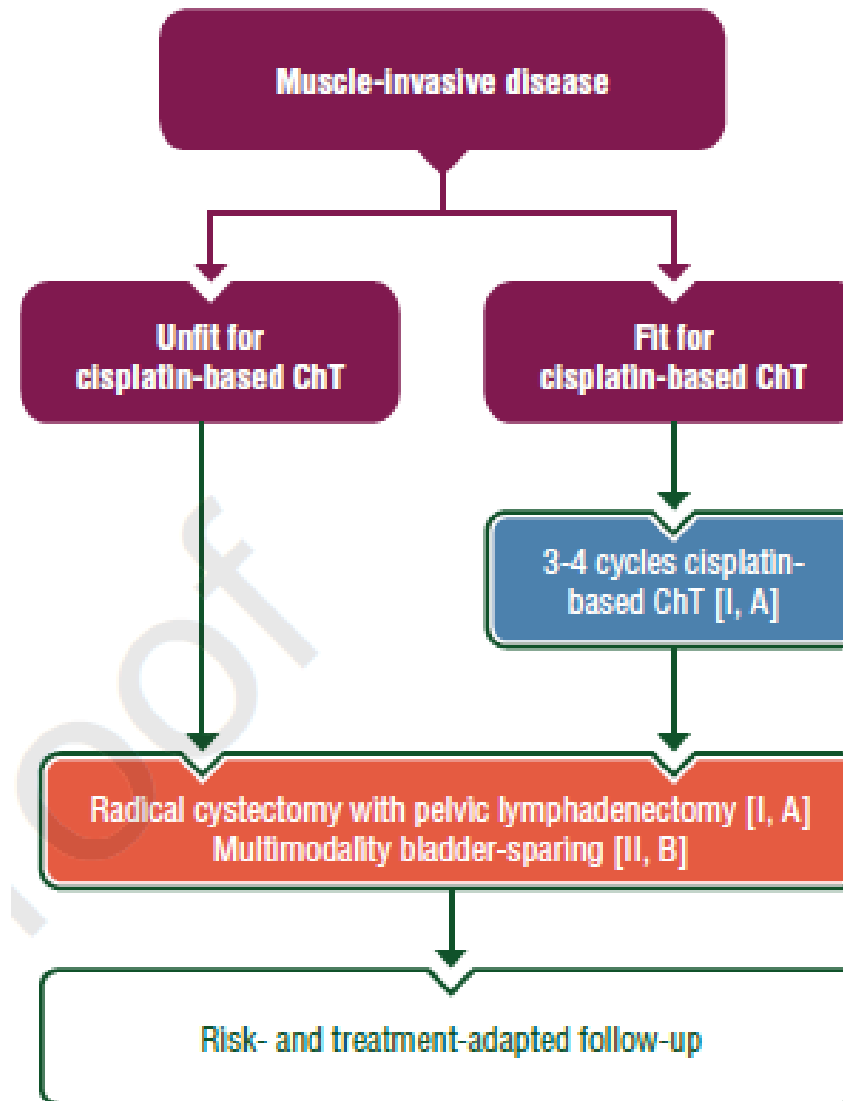
Outline

- 1- we will have access to immunotherapy in peri-operative setting and other very effective drugs
- 2- we will offer more bladder preservation thanks to highly effective systemic drugs
- 3- Decision-making will be based on MRD

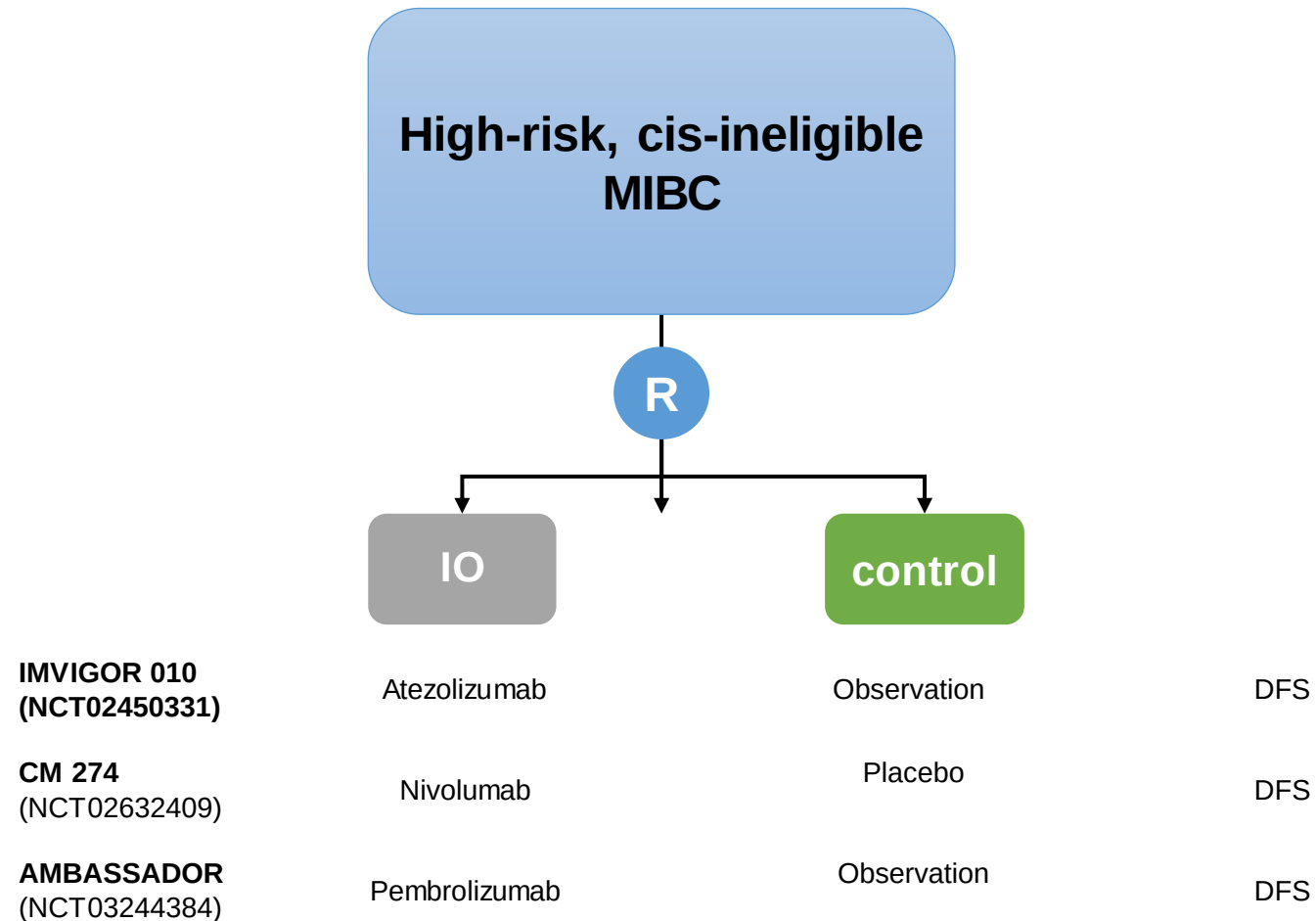
Outline

- 1- we will have access to immunotherapy in peri-operative setting and other very effective drugs
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ESMO guidelines (to be revisited) (T2–T4a, N0, M0)



Immunotherapy now is approved in adjuvant setting



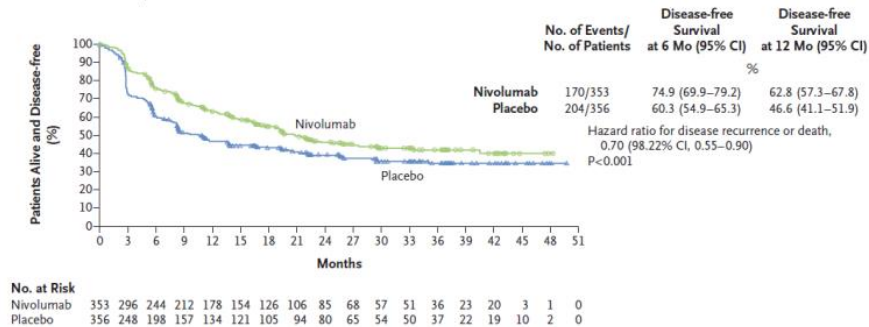
Adjuvant immunotherapy

ORIGINAL ARTICLE

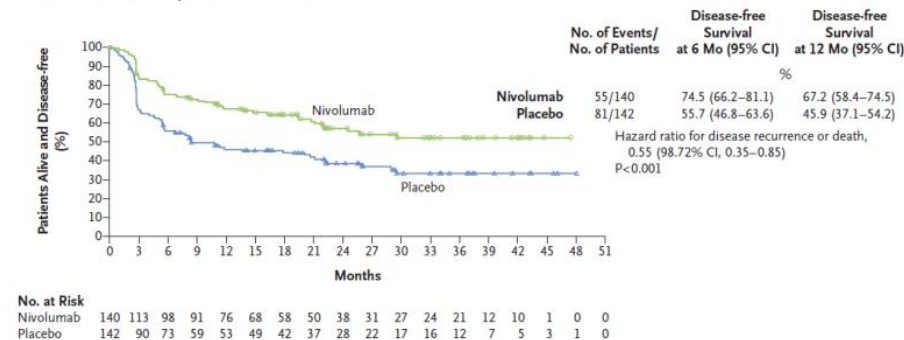
Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma

D.F. Bajorin, J.A. Witjes, J.E. Gschwend, M. Schenker, B.P. Valderrama, Y. Tomita, A. Bamias, T. Lebre, S.F. Shariat, S.H. Park, D. Ye, M. Agerbaek, D. Enting, R. McDermott, P. Gajate, A. Peer, M.I. Milowsky, A. Nosov, J. Neif Antonio, Jr., K. Tupikowski, L. Toms, B.S. Fischer, A. Qureshi, S. Collette, K. Unsal-Kacmaz, E. Broughton, D. Zardavas, H.B. Koon, and M.D. Galsky

A Intention-to-Treat Population

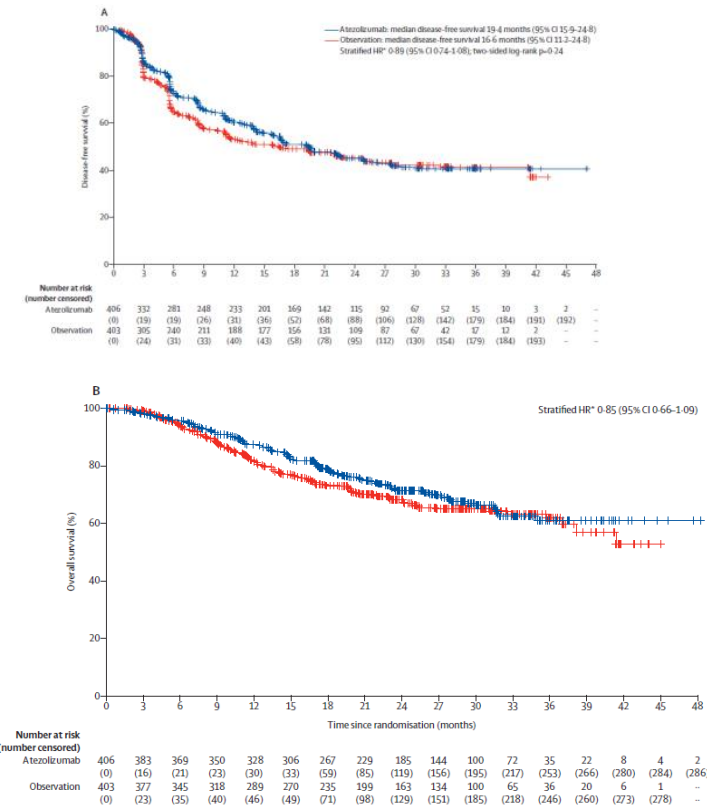


B Patients with a PD-L1 Expression Level of $\geq 1\%$

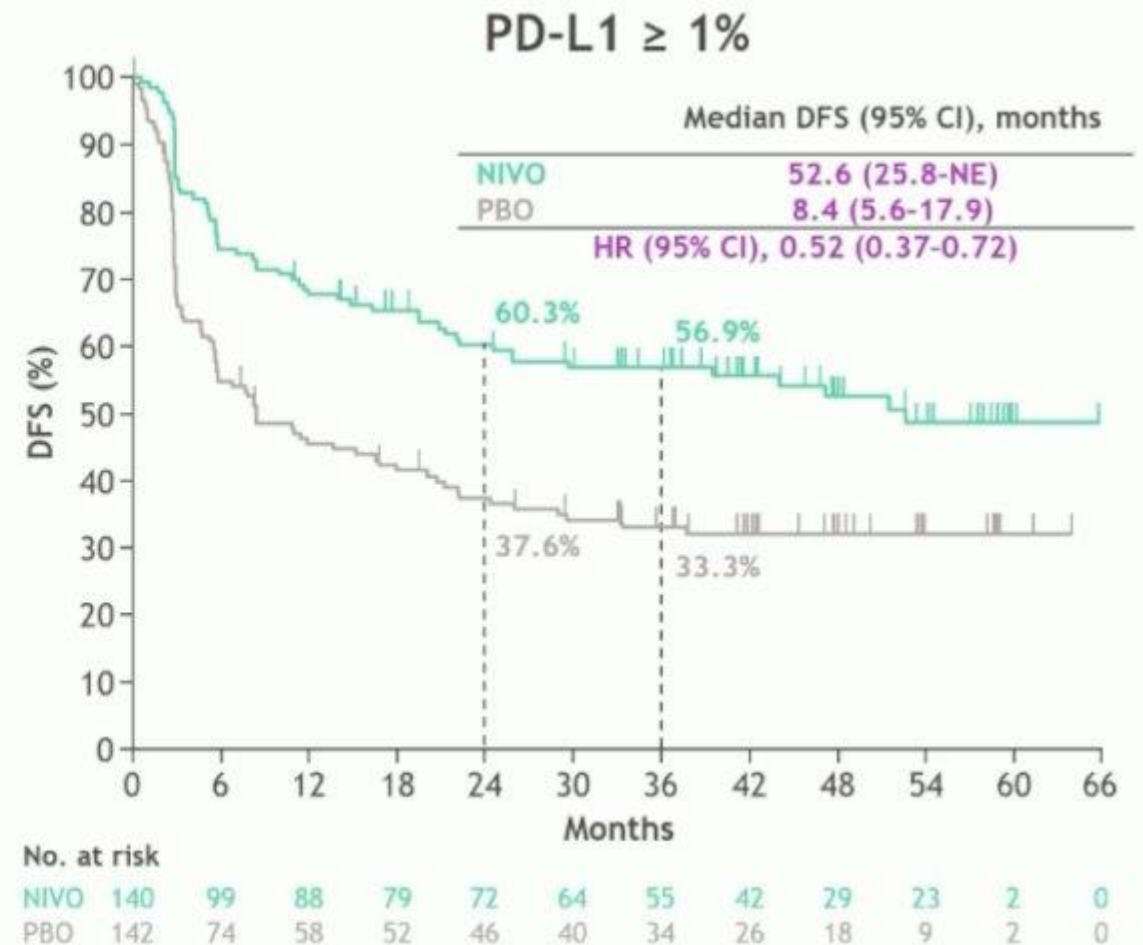
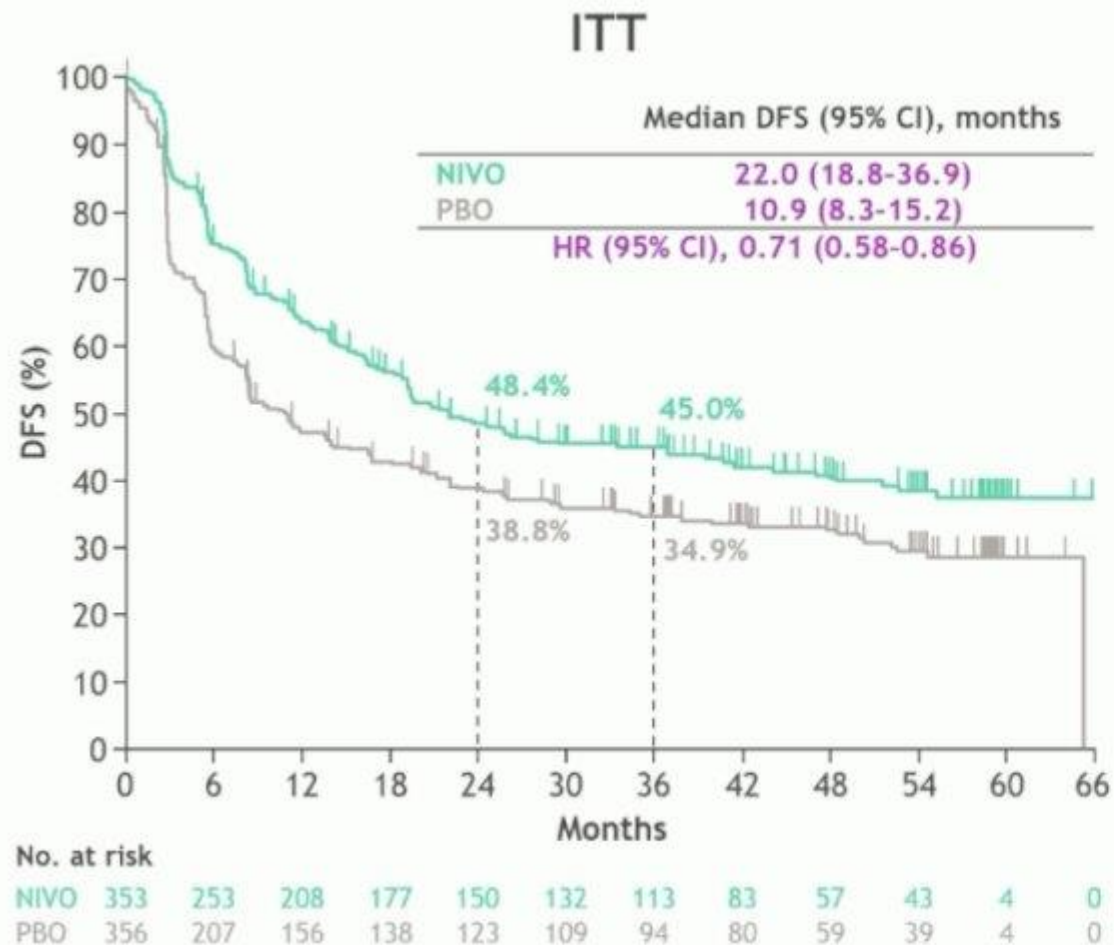


Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvig010): a multicentre, open-label, randomised, phase 3 trial

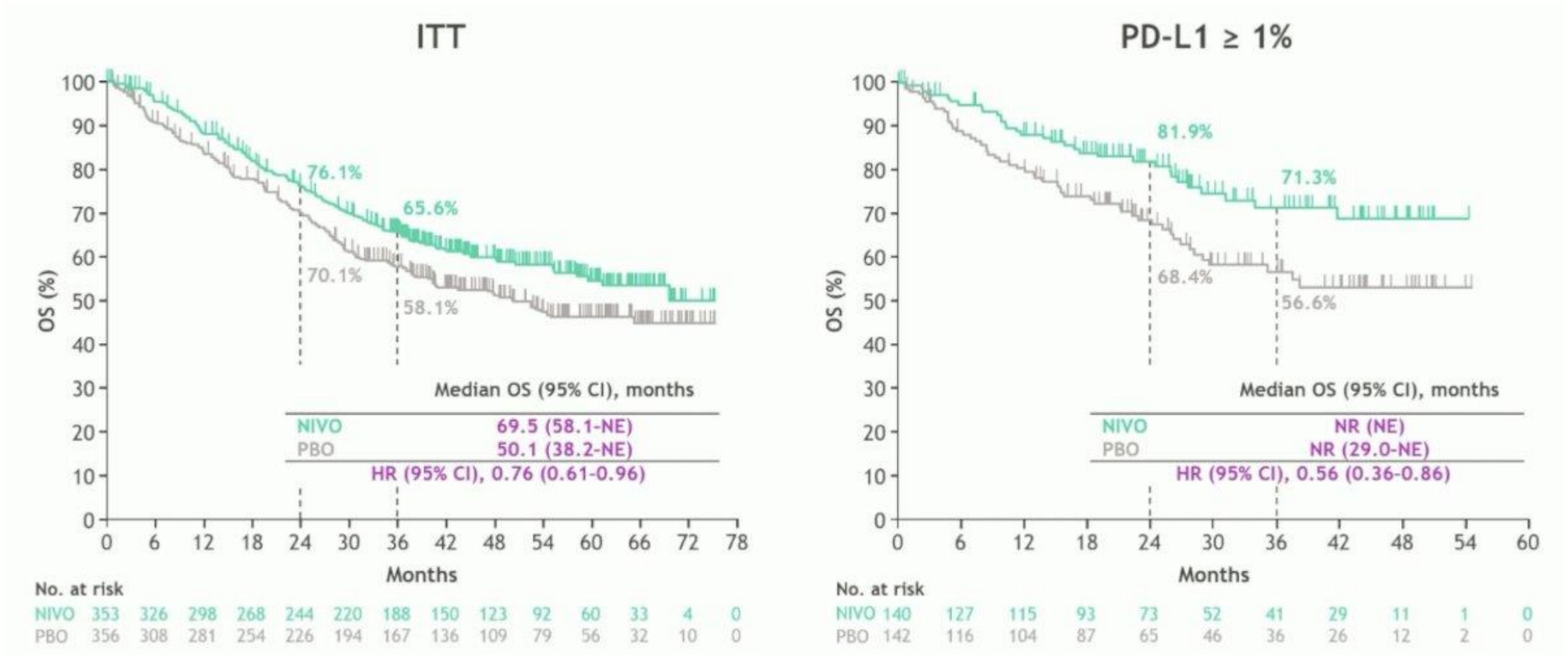
Joaquim Bellmunt, Maha Hussain, Jürgen E Gschwend, Peter Albers, Stephane Oudard, Daniel Castellano, Siamak Daneshmand, Hiroyuki Nishiyama, Martin Majchrowicz, Viraj Degaonkar, Yi Shi, Sanjeev Mariathasan, Petros Grivas, Alexandra Drakaki, Peter H O'Donnell, Jonathan E Rosenberg, Daniel M Geynisman, Daniel P Petrylak, Jean Hoffman-Censits, Jens Bedke, Arash Rezazadeh Kalebasty, Yousef Zakharia, Michiel S van der Heijden, Cora N Sternberg, Nicole N Davarpanah, Thomas Powles, for the IMvig010 Study Group*



Nivolumab should be the SOC in adjuvant disease



Nivolumab might improve OS in adjuvant disease



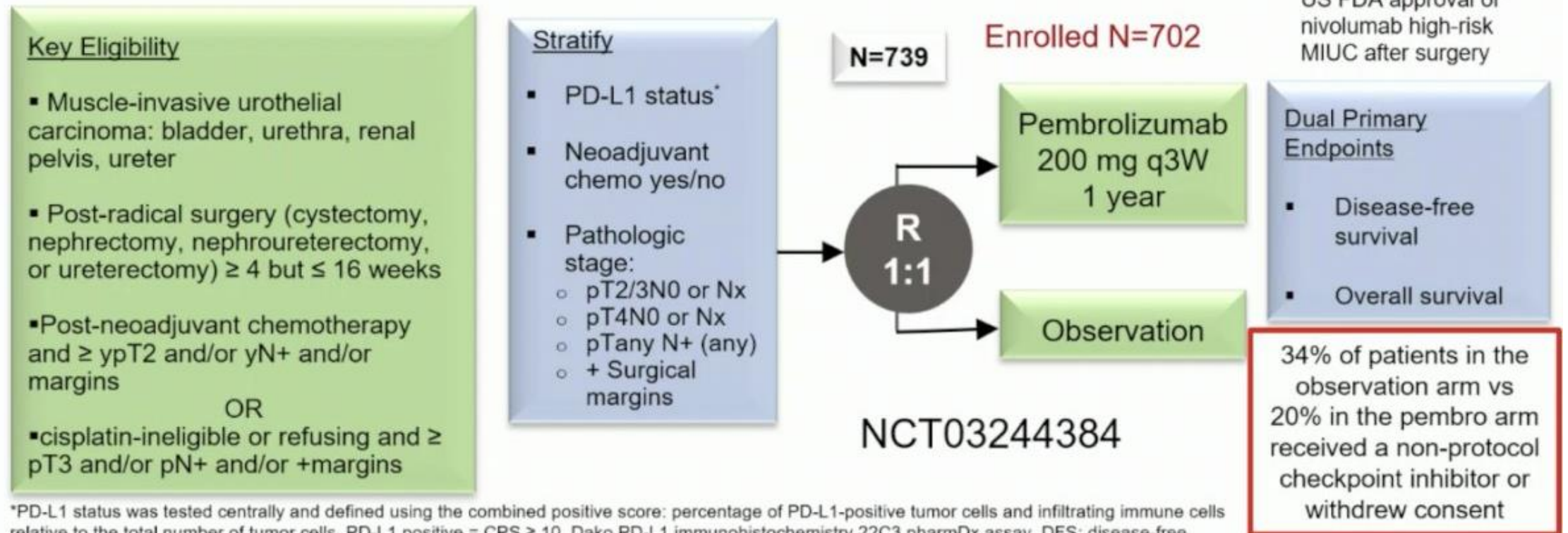
AMBASSADOR study

A031501 AMBASSADOR: Study Design

Phase 3 randomized, open label, multicenter study of adjuvant pembrolizumab vs observation in patients with high-risk muscle-invasive urothelial carcinoma

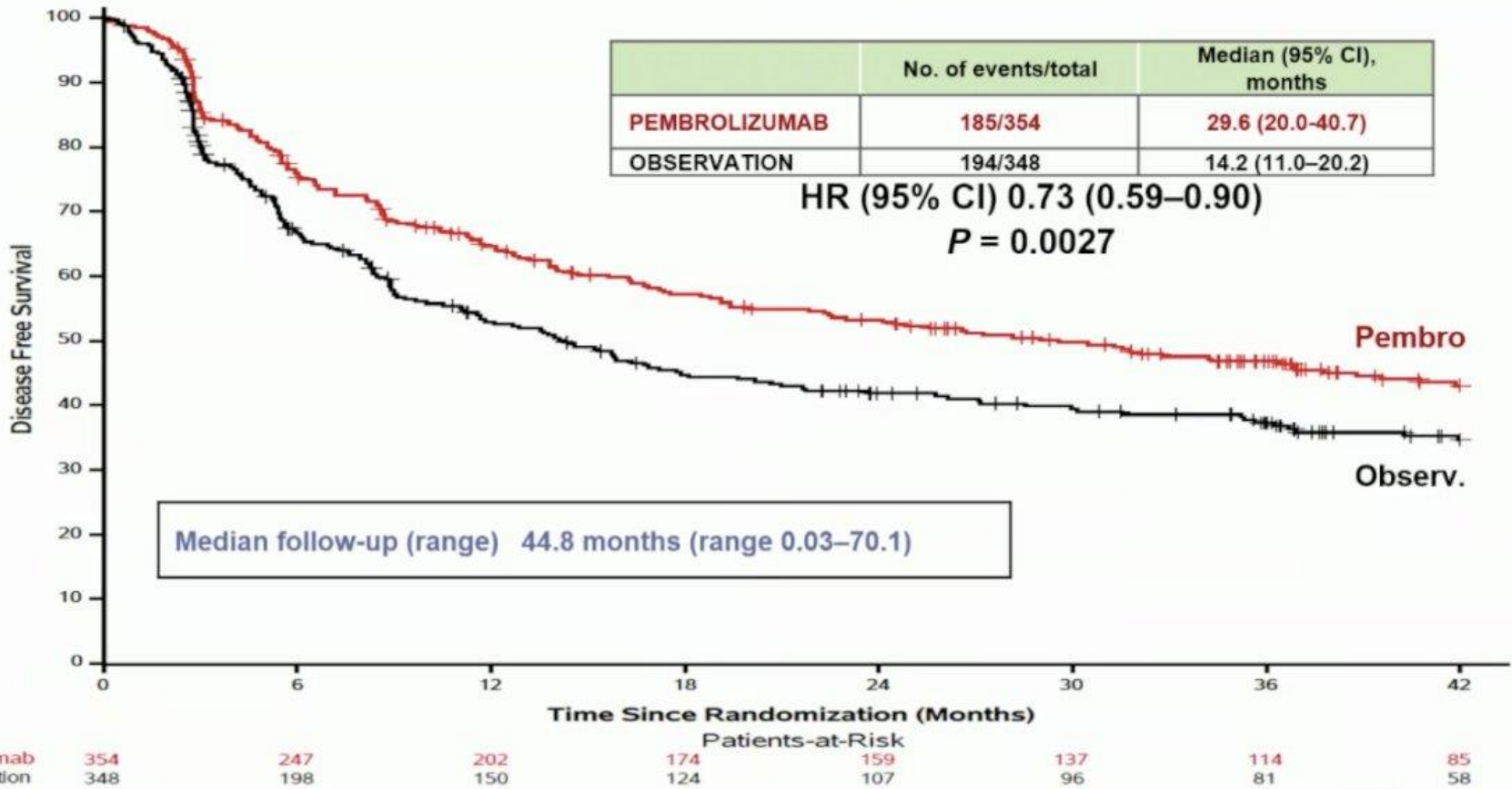


Early closure due to US FDA approval of nivolumab high-risk MIUC after surgery



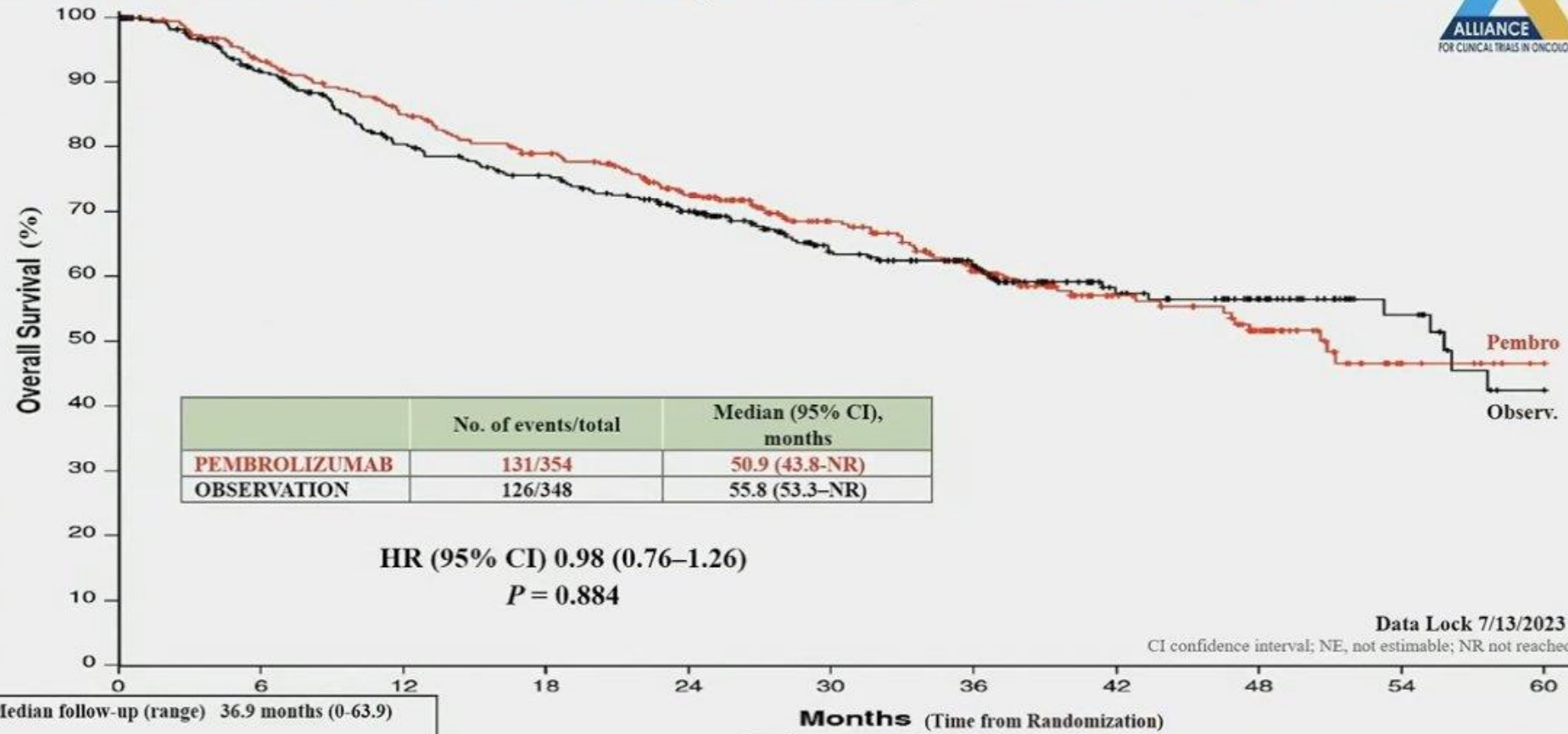
*PD-L1 status was tested centrally and defined using the combined positive score: percentage of PD-L1-positive tumor cells and infiltrating immune cells relative to the total number of tumor cells. PD-L1 positive = CPS ≥ 10, Dako PD-L1 immunohistochemistry 22C3 pharmDx assay. DFS: disease-free survival (defined as new MIUC, metastatic disease, or death without recurrence); OS: overall survival

AMBASSADOR study



AMBASSADOR study

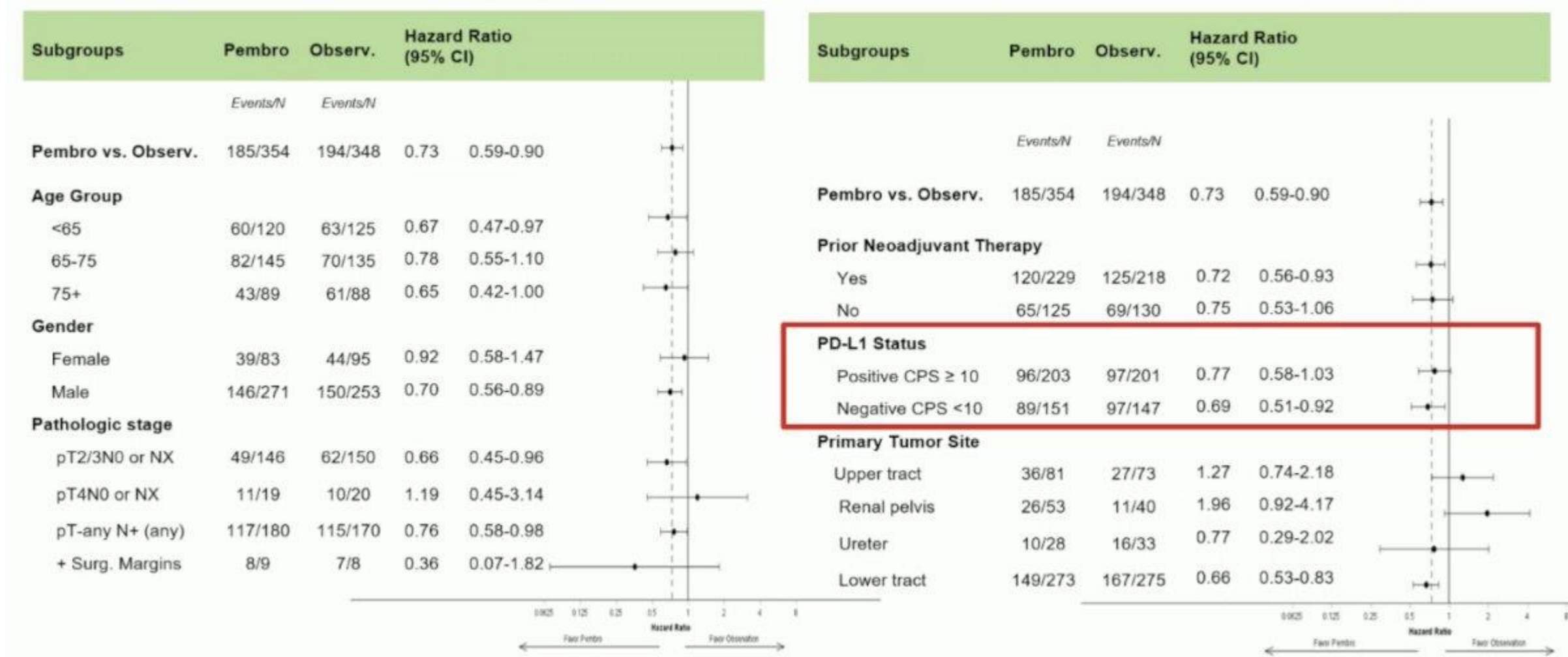
A031501 AMBASSADOR: (interim) Overall Survival



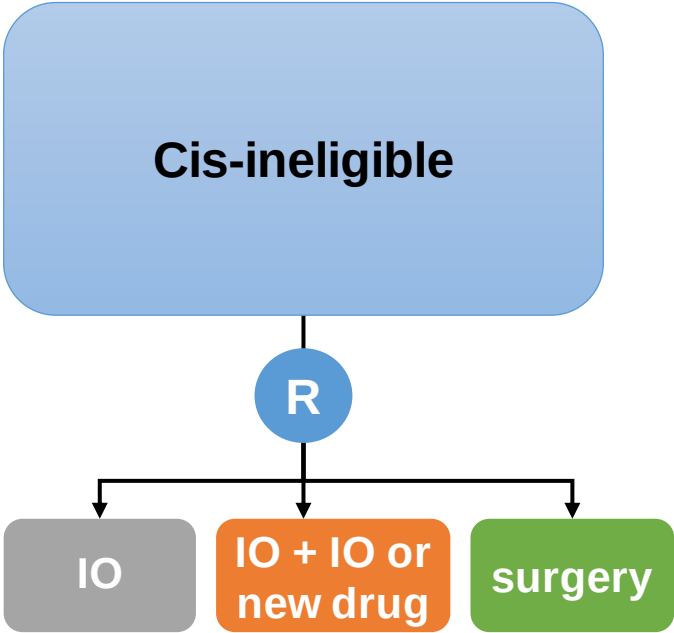
Median follow-up (range) 36.9 months (0–63.9)

Pembro	354	313	280	253	218	152	115	69	50	17	10
Observ.	348	296	249	227	195	139	117	65	45	23	12

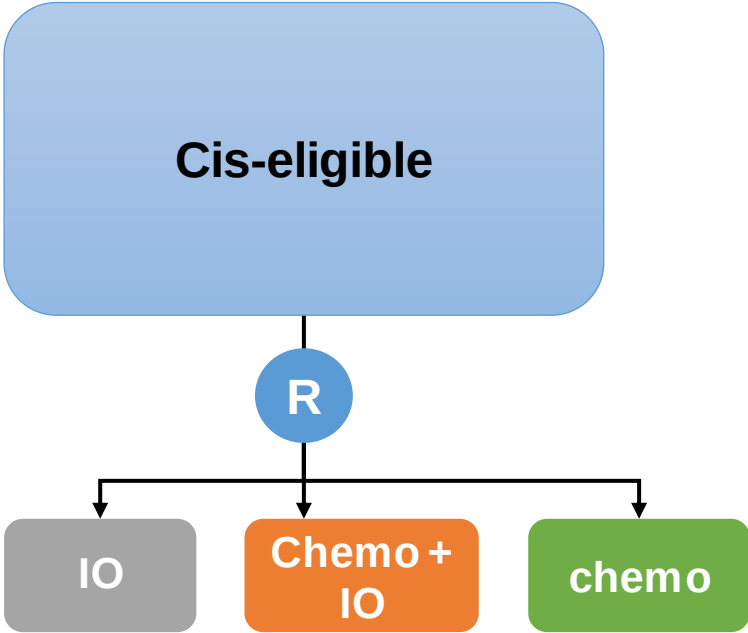
AMBASSADOR study



New drugs (IO and ADC) may refine also the neoadjuvant setting

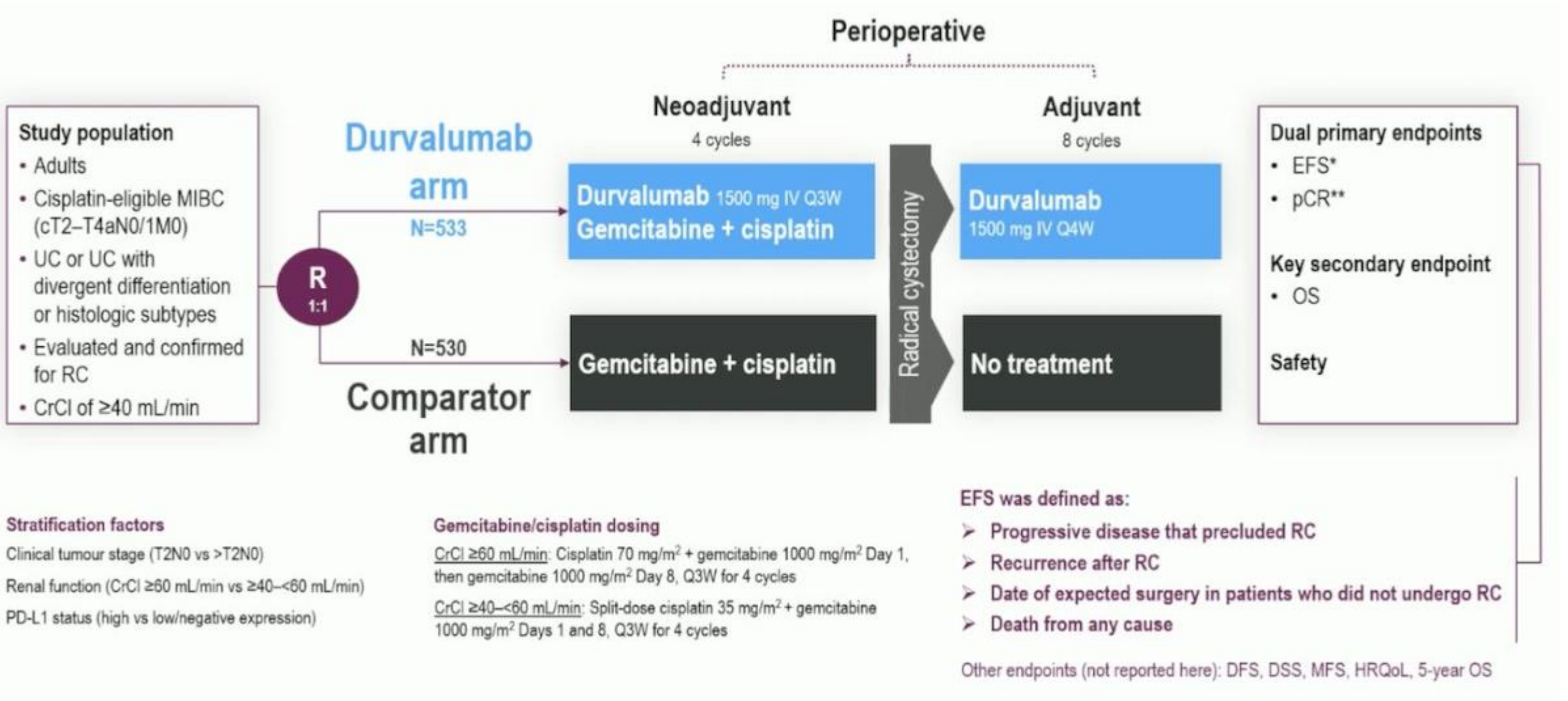


MK-905 (NCT03924895)	Pembro	Pembro + EV	—	pCR, EFS
PIVOT-IO-09 (NCT04209114)	Nivo	Nivo + NKTR-214	—	pCR, EFS
VOLGA (NCT04960709)	Durva + EV	Durva + Treme + EV	—	Safety, EFS, OS



MK-866 (NCT03924856)	—	CDDP-GEM + pembro	Chemo	pCR, EFS
NIAGARA (NCT03732677)	—	CDDP-GEM + durva	Chemo	pCR, EFS
MK-B15 (NCT04700124)	—	EV + pembro	Chemo	pCR, EFS
ENERGYZE (NCT04700124)	Chemo + nivo + linrodostat	Chemo + nivo	Chemo	pCR, EFS

NIAGARA Study



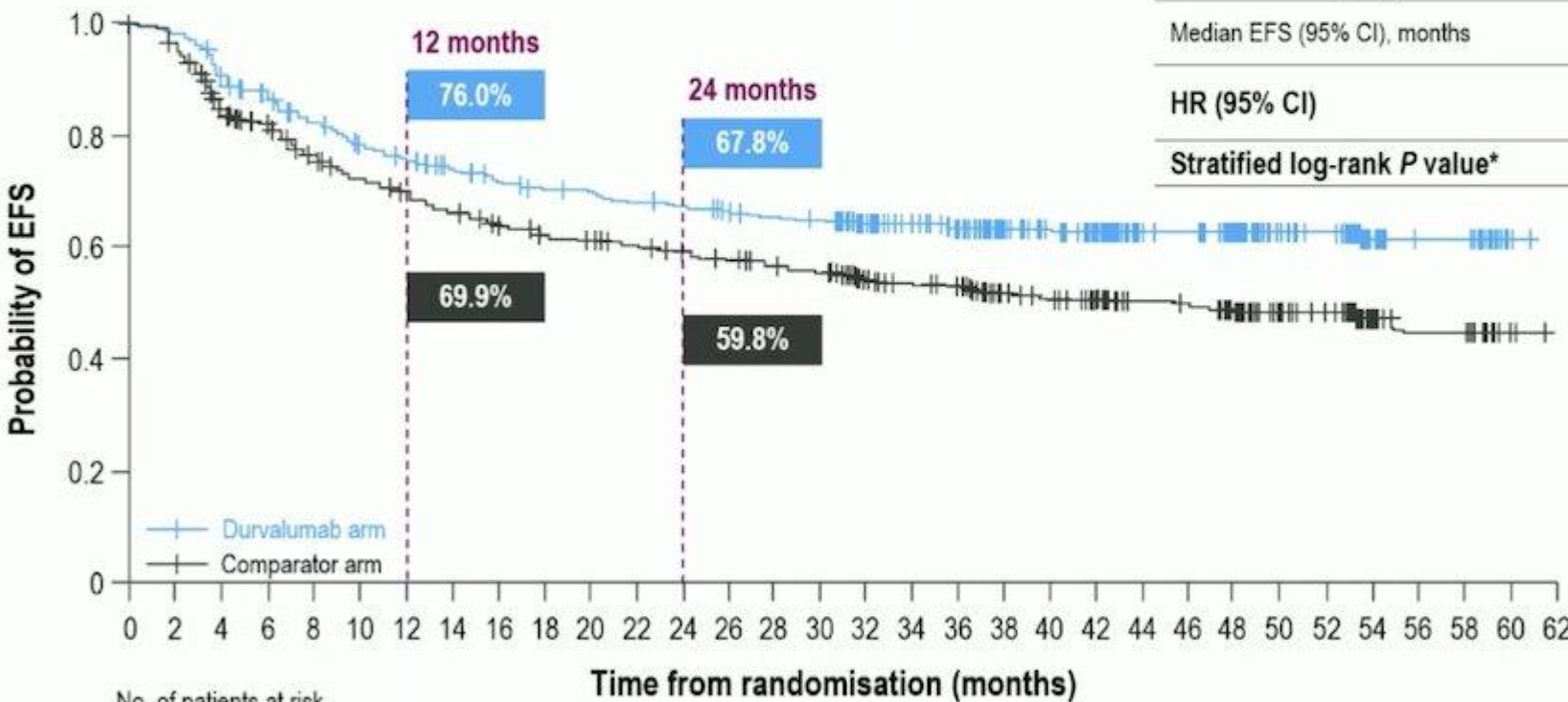
NIAGARA Study

Characteristics		Durvalumab arm N=533	Comparator arm N=530
Age	Median, years (range)	65 (34–84)	66 (32–83)
Sex, %	Male	82	82
Race, %	White	66	68
	Asian	29	27
	Black/Other	2	1
	Not reported	3	4
ECOG PS, %	0	78	78
	1	22	22
Smoker, %	Yes (current or former)	71	75
Renal function*, %	CrCl ≥60 mL/min	81	81
	CrCl ≥40–<60 mL/min	19	19
Tumour stage*, %	T2N0	40	40
	>T2N0	60	60
PD-L1 expression†, %	High	73	73
	Low/negative	27	27
Histology, %	UC	86	83
	UC with divergent differentiation or histologic subtypes	14	17
Regional lymph nodes, %	N0	95	94
	N1	5	6

NIAGARA Study

NIAGARA: Event-free Survival by Blinded Independent Central Review (ITT)

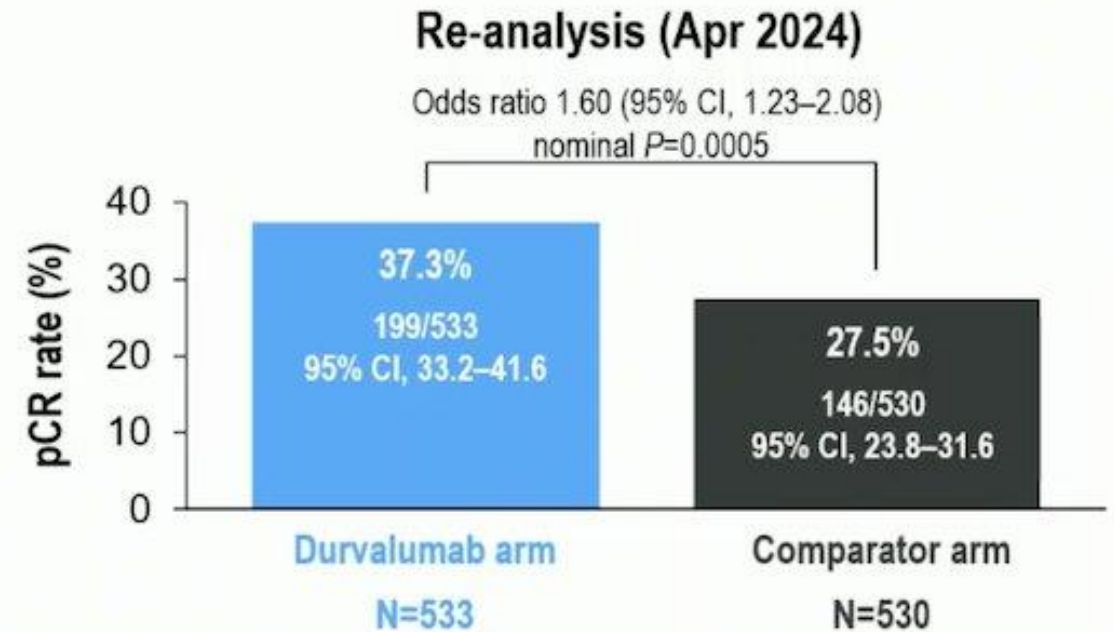
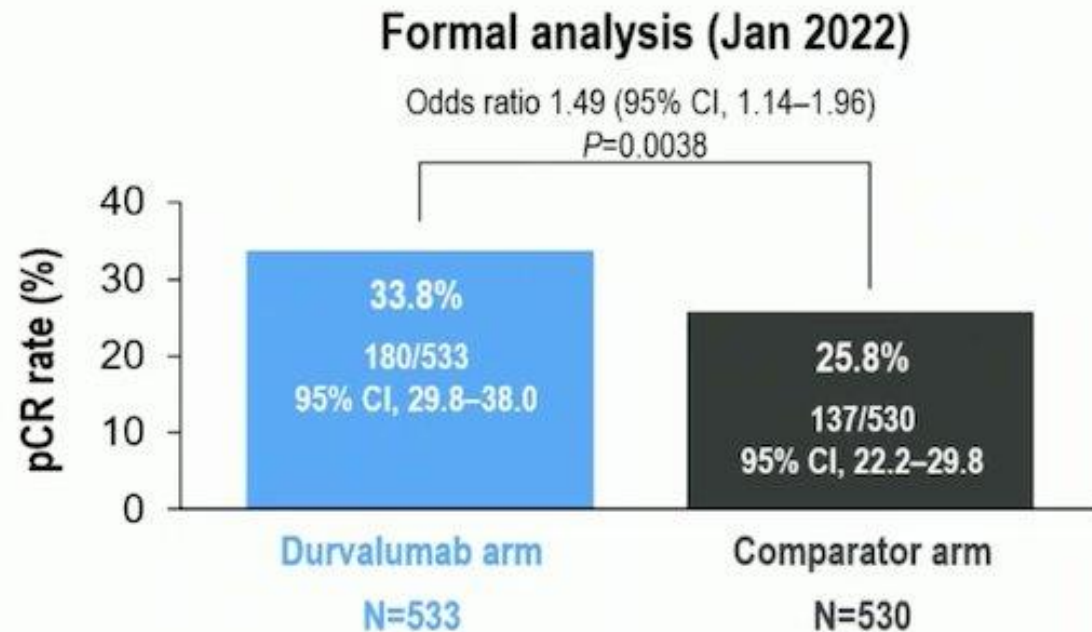
	Durvalumab arm N=533	Comparator arm N=530
Number of events, n (%)	187 (35.1)	246 (46.4)
Median EFS (95% CI), months	NR (NR–NR)	46.1 (32.2–NR)
HR (95% CI)	0.68 (0.56–0.82)	
Stratified log-rank <i>P</i> value*	<0.0001	



Durvalumab arm	533	519	475	454	424	401	386	370	356	348	344	335	330	321	315	312	282	269	255	214	202	180	141	140	115	86	81	32	20	20	1	0
Comparator arm	530	498	437	416	381	358	343	328	313	300	296	288	281	273	264	259	228	219	214	177	172	159	132	129	94	69	62	24	18	16	2	0

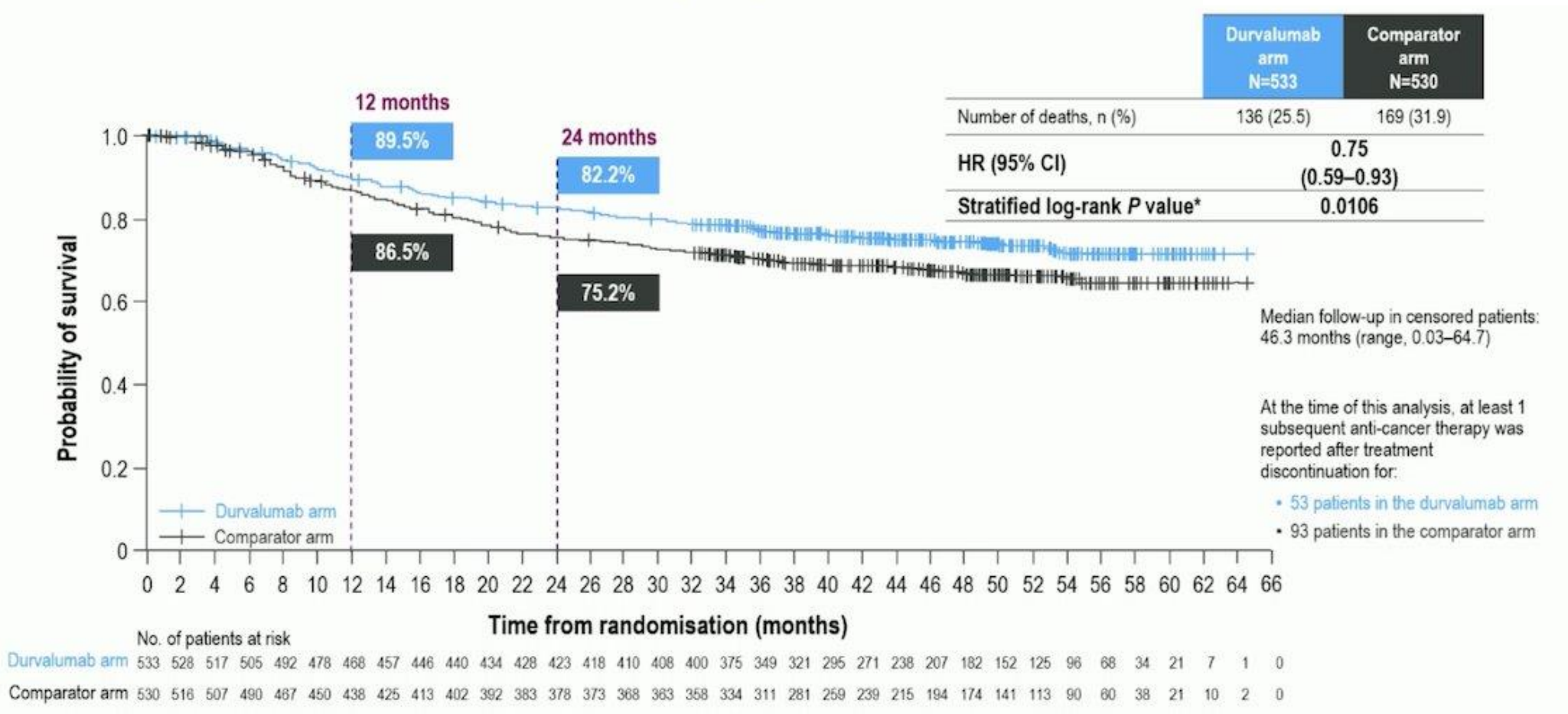
NIAGARA Study

NIAGARA: Pathologic Complete Response (ITT)



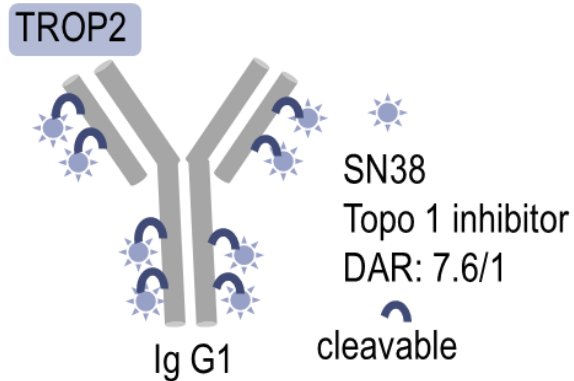
NIAGARA Study

NIAGARA: Overall Survival (ITT)



ADC in urothelial cancer

Sacituzumab govitecan

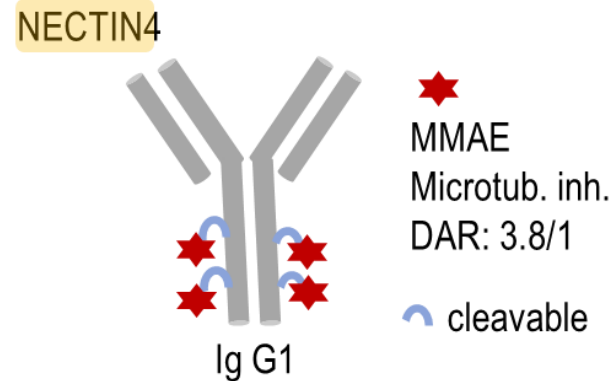


Indication (accelerated app)
Post chemo, PD(L)1 (FDA)

Main toxicities

- diarrhea
- alopecia
- Fatigue
- cytopenia

Enfortumab vedotin

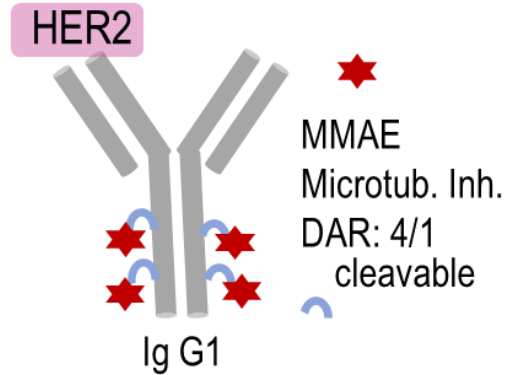


Indication
Post chemo, post PD(L)1
1L cis-ineligible (FDA)

Main toxicities

- Alopecia - neuropathy
- Skin toxicities- hyperglycemia

Disitamab vedotin

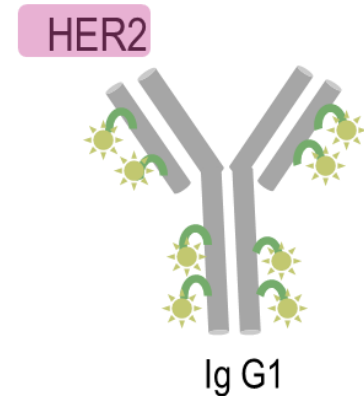


Indication
Clinical investigation

Main toxicities

- alopecia
- neuropathy
- fatigue

Trastuzumab deruxtecan



Indication
TBD

Main toxicities

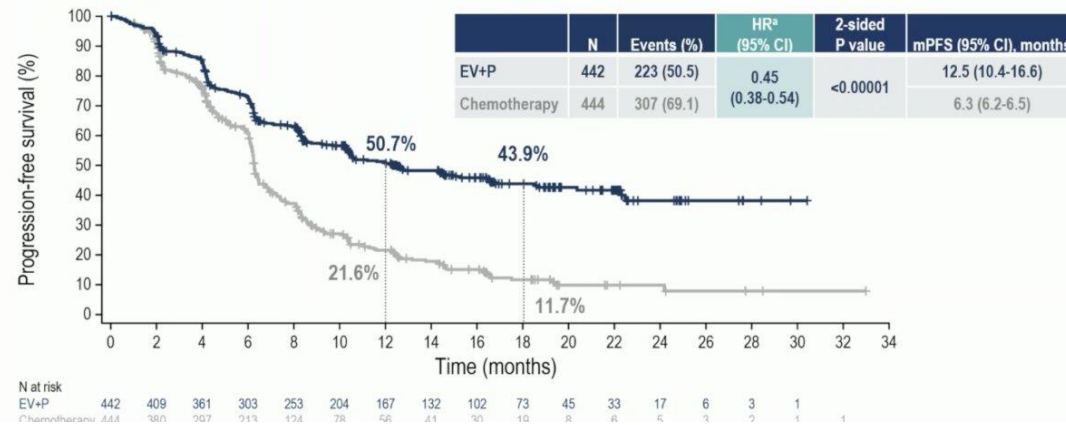
- nausea
- diarrhea
- Anemia
- ILD

We can expect even more from EV + pembrolizumab

In metastatic setting

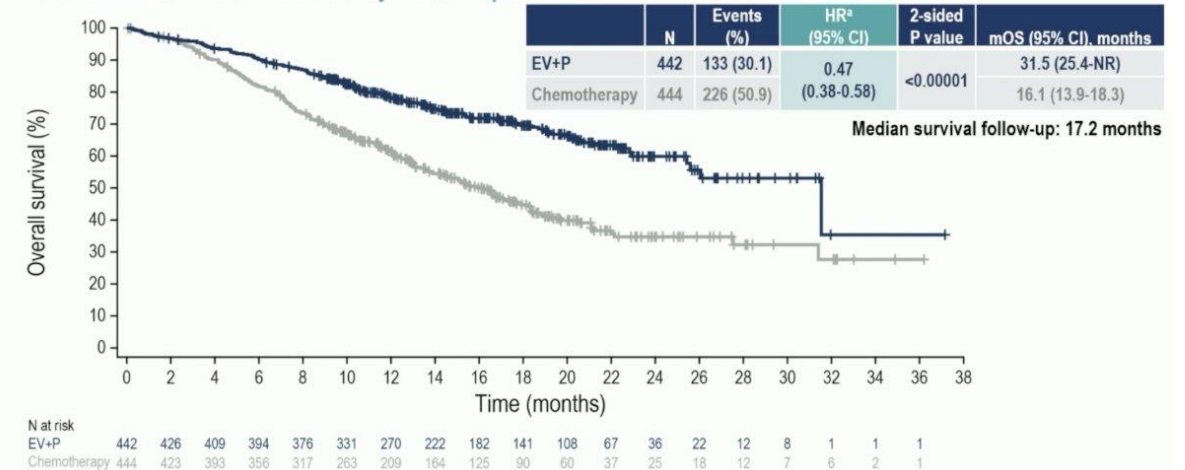
Progression-Free Survival per BICR

Risk of progression or death was reduced by 55% in patients who received EV+P



Overall Survival

Risk of death was reduced by 53% in patients who received EV+P



In peri-operative setting ?

Phase II RC48-C017 trial: DV + PD1 inhibitor (Toripalimab)

Key Eligible Criteria:

- Histologically confirmed urothelial carcinoma;
- MIBC at stage of cT2-T4a, N0-1, and M0;
- Eligible for radical cystectomy (RC) + pelvic lymph node dissection (PLND);
- HER2 expression: IHC 1+, 2+, or 3+.



	Patients Received RC N=33
Pathological response	
pCR (ypT0N0), n (%)	21 (63.6)
95% CI	45.1-79.6
Pathological response (≤ypT1N0M0), n (%)	25 (75.8)
95% CI	57.7-88.9
Pathological staging, n (%)	
ypT0N0	21 (63.6)
ypT≤1N0	4 (12.1)
ypTisNx*	1 (3.0)
ypT2N0	4 (12.1)
ypT3N0	3 (9.1)
ypT4 or ypTanyN+	0

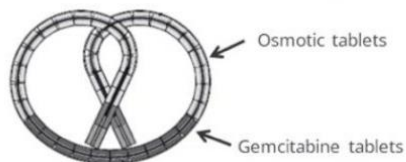
Pathological tumor response was assessed by the local pathologists based on the postoperative pathology.
*Pelvic lymph-node dissection was not performed.



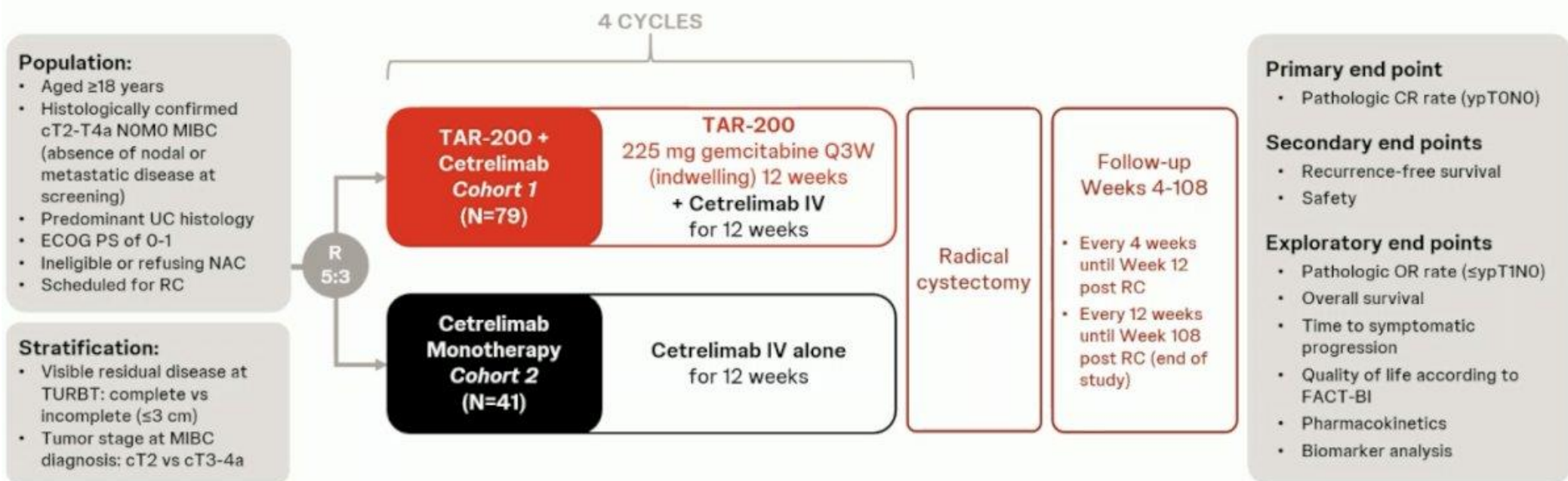
- Cross comparison with other trial challenging
- Inconsistent definition of pCR

Other promising drug include new intravesical devices

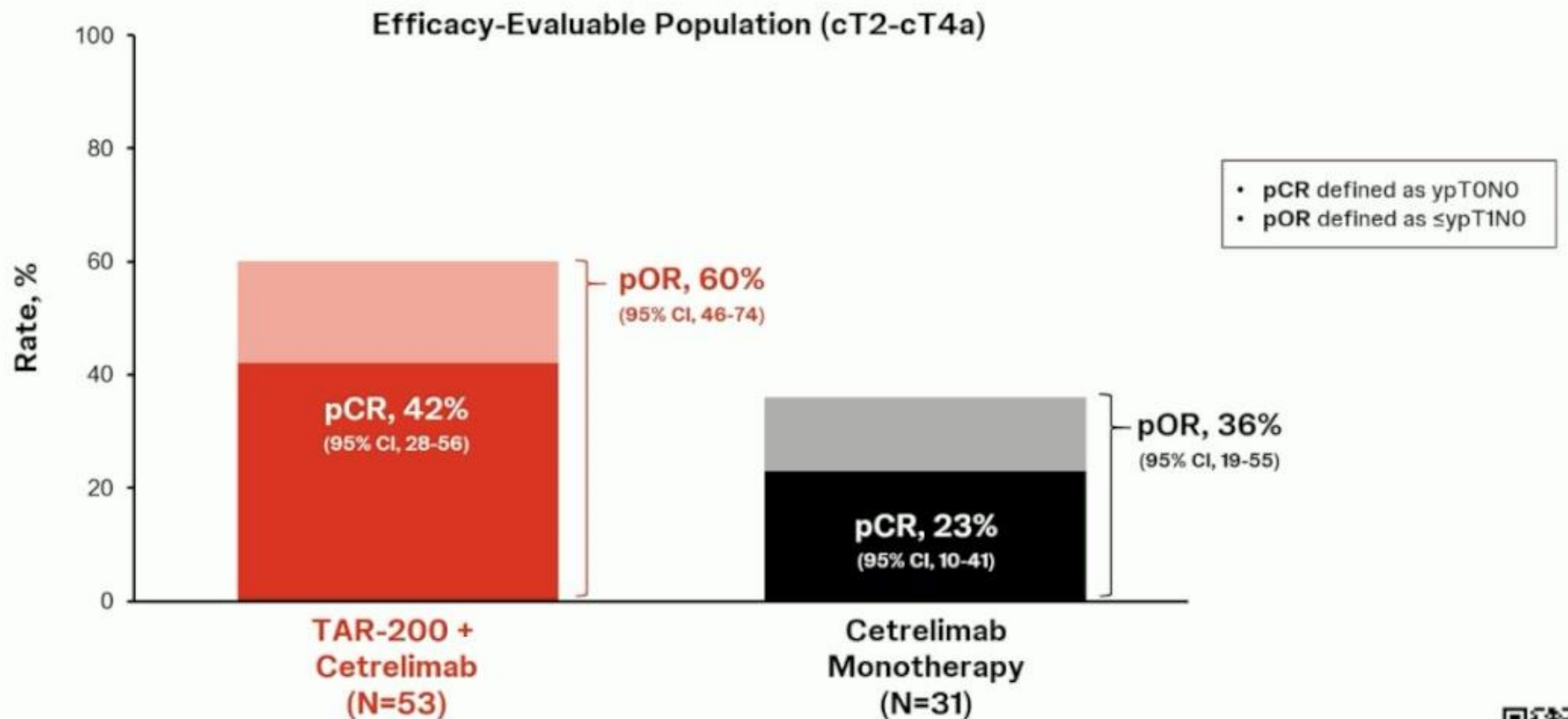
TAR-200 Two Minitablet Design



SunRISe-4: Phase 2b Study of Neoadjuvant TAR-200 + Cetrelimab in Patients With MIBC (cT2-T4a N0M0)



Other promising drugs include new intravesical devices



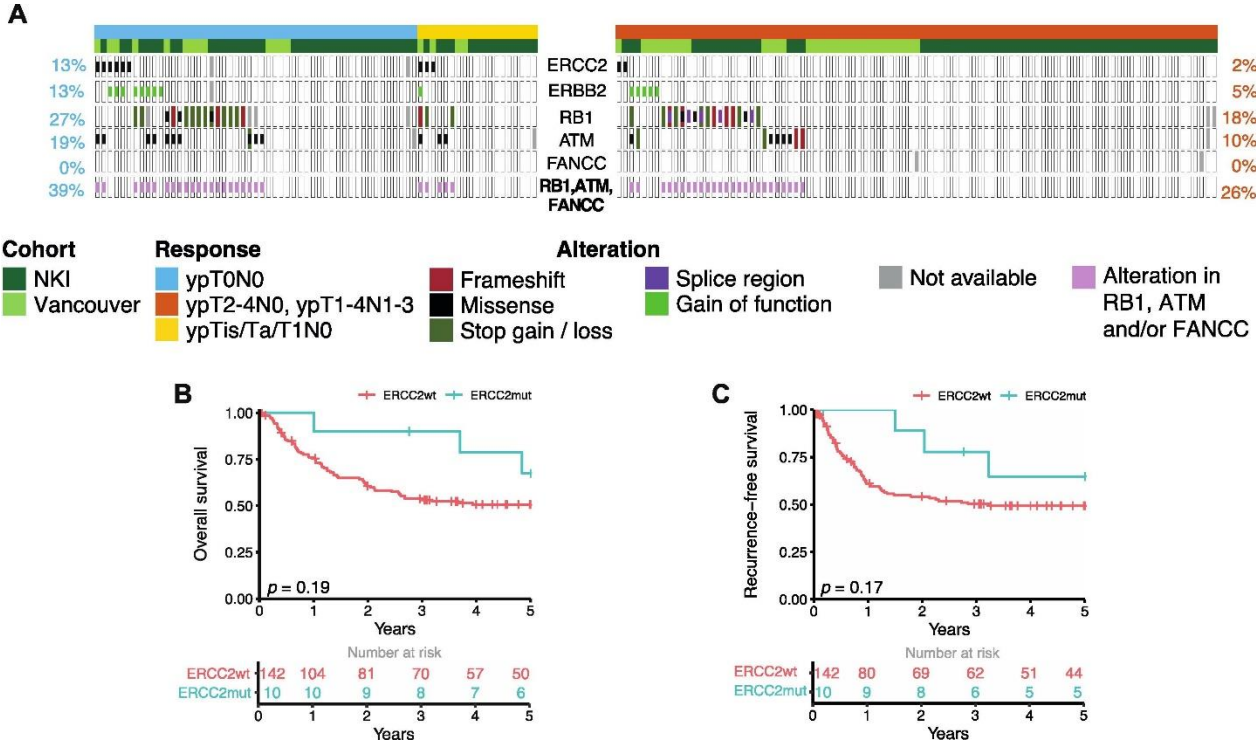
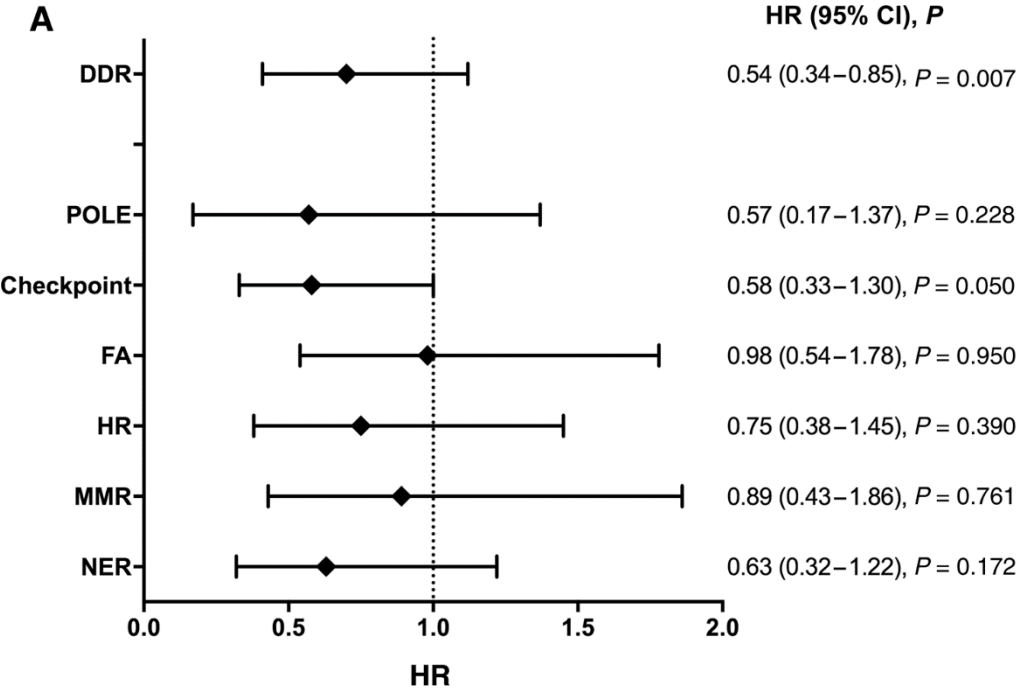
Outline

- 1- we will have access to immunotherapy in peri-operative setting and other very effective drugs
- 2- we will offer more bladder preservation thanks to highly these effective systemic drugs
- 3- Decision-making will be based on MRD
- 4- We will cure more patients with NMIBC

Challenge : Biomarkers and clinical complete response

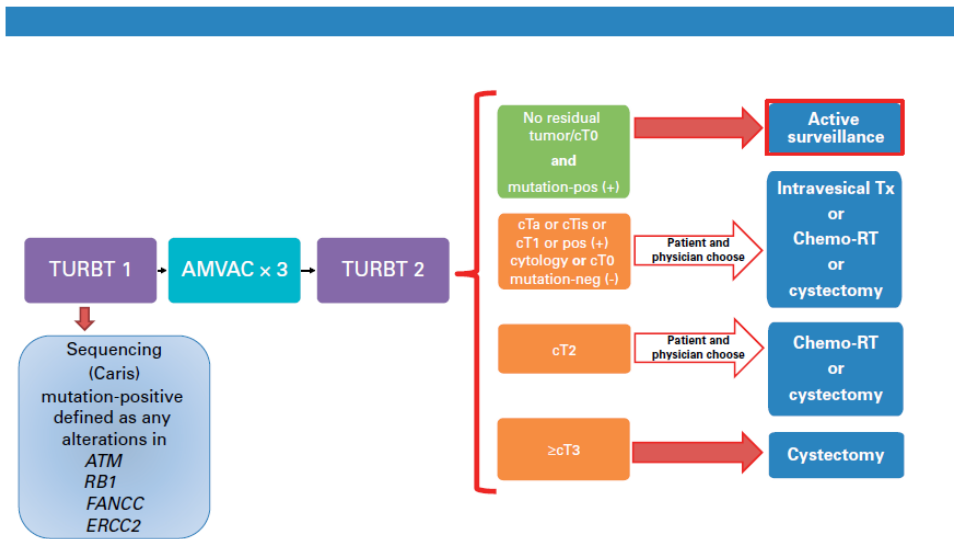
- The definition of a complete clinical response to identify those who can safely avoid radical cystectomy remains unstandardized.
- Various trials, such as Alliance (incorporating DDR gene alterations, imaging, and TURBT), HCRN GU 16-257 (using cytology, imaging, and TURBT), and RETAIN (focusing on gene alterations, imaging, and TURBT), have attempted to define response criteria.
- Despite these efforts, a significant number of patients on active surveillance after induction chemotherapy have experienced recurrence.

First question : genomic biomarkers and chemotherapy ?



First question : genomic biomarkers and chemotherapy ?

Prospective validation: RETAIN-1 trial



- Primary endpoint: MFS at 2 years ($P \geq 0.64$)
- 2 year MFS for the II patients: 72.9% (lower bound : 62.8%)
- Primary endpoint not met
- 48% of the AS group avoided cystectomy
- No association bewteen mutation and MFS

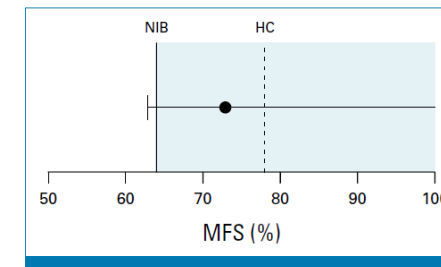
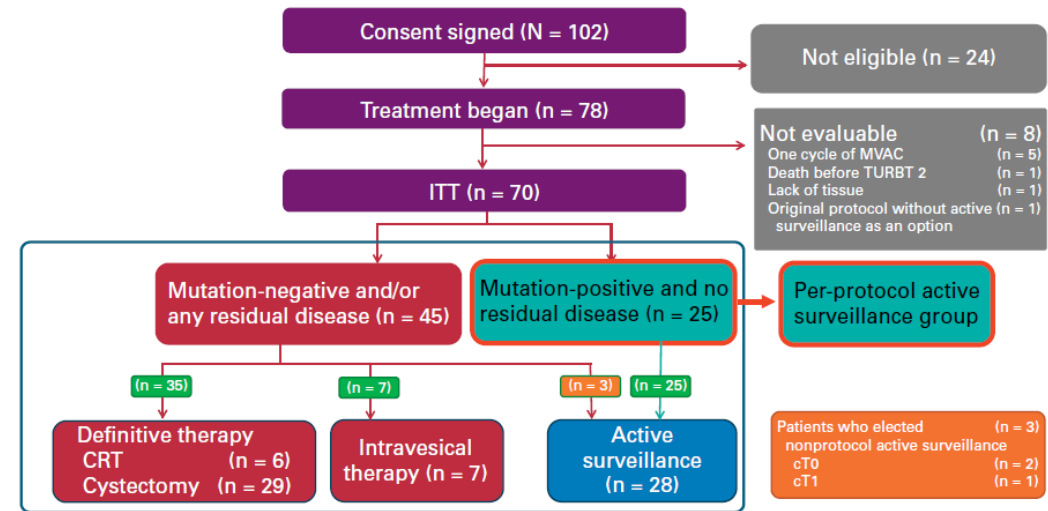
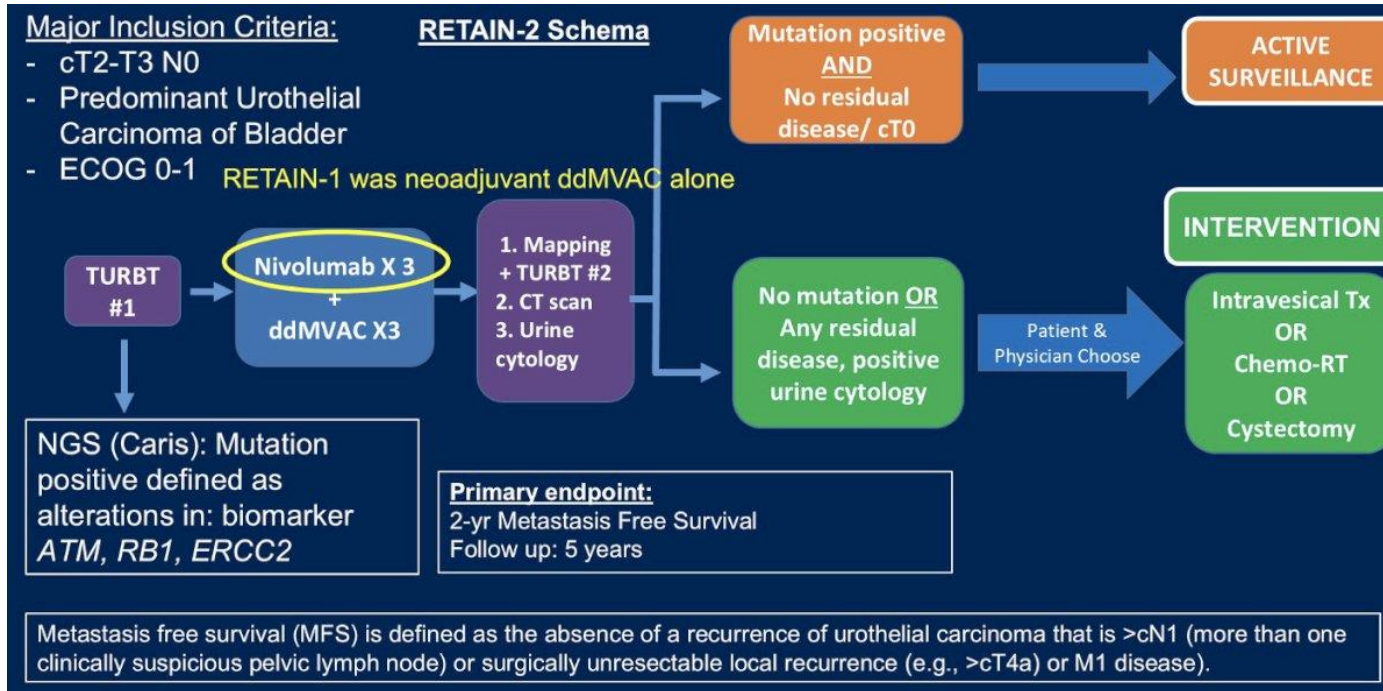


FIG A3. MFS and *ERCC2* status. HC, historic control; MFS, metastasis-free survival; NIB, non inferiority boundary.

Preliminary data from RETAIN-2 study

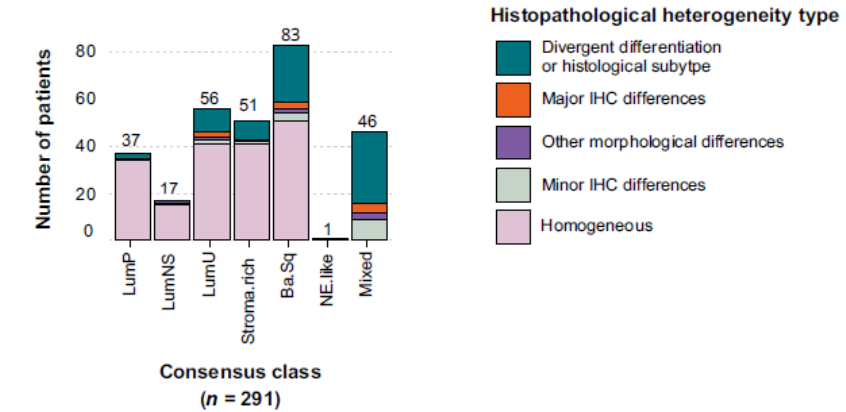
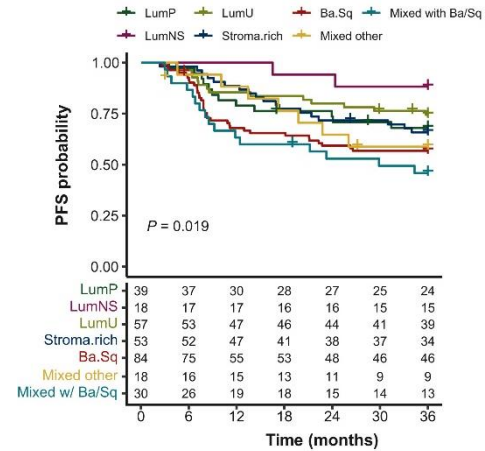
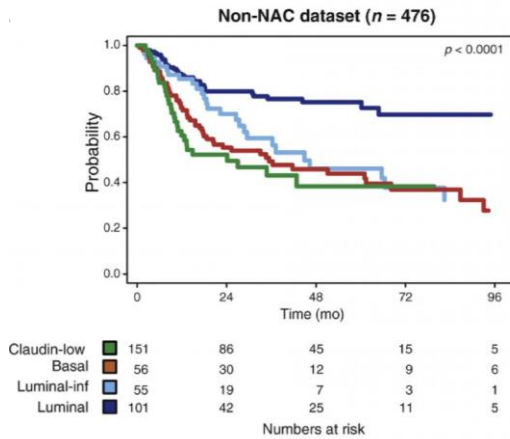


RETAIN-1 vs RETAIN 2

- MFS in active surveillance patients is superior 82% versus 64
- Higher ypT0 rates in cystectomy patients (40% versus 15%)
- Local recurrence rates in AS patients are lower (32% versus 62%)
- The metastasis-free and intact unirradiated bladder proportion is higher (60% versus 48%)

- At the time of interim analysis, chemoimmunotherapy with ddMVAC + nivolumab was associated with a metastases-free survival rate of 84.2% in ITT and 82% in the active surveillance arm
- 60% of active surveillance patients are metastases-free and with an intact un-irradiated bladder
- Suggests an additive benefit of adding nivolumab to ddMVAC

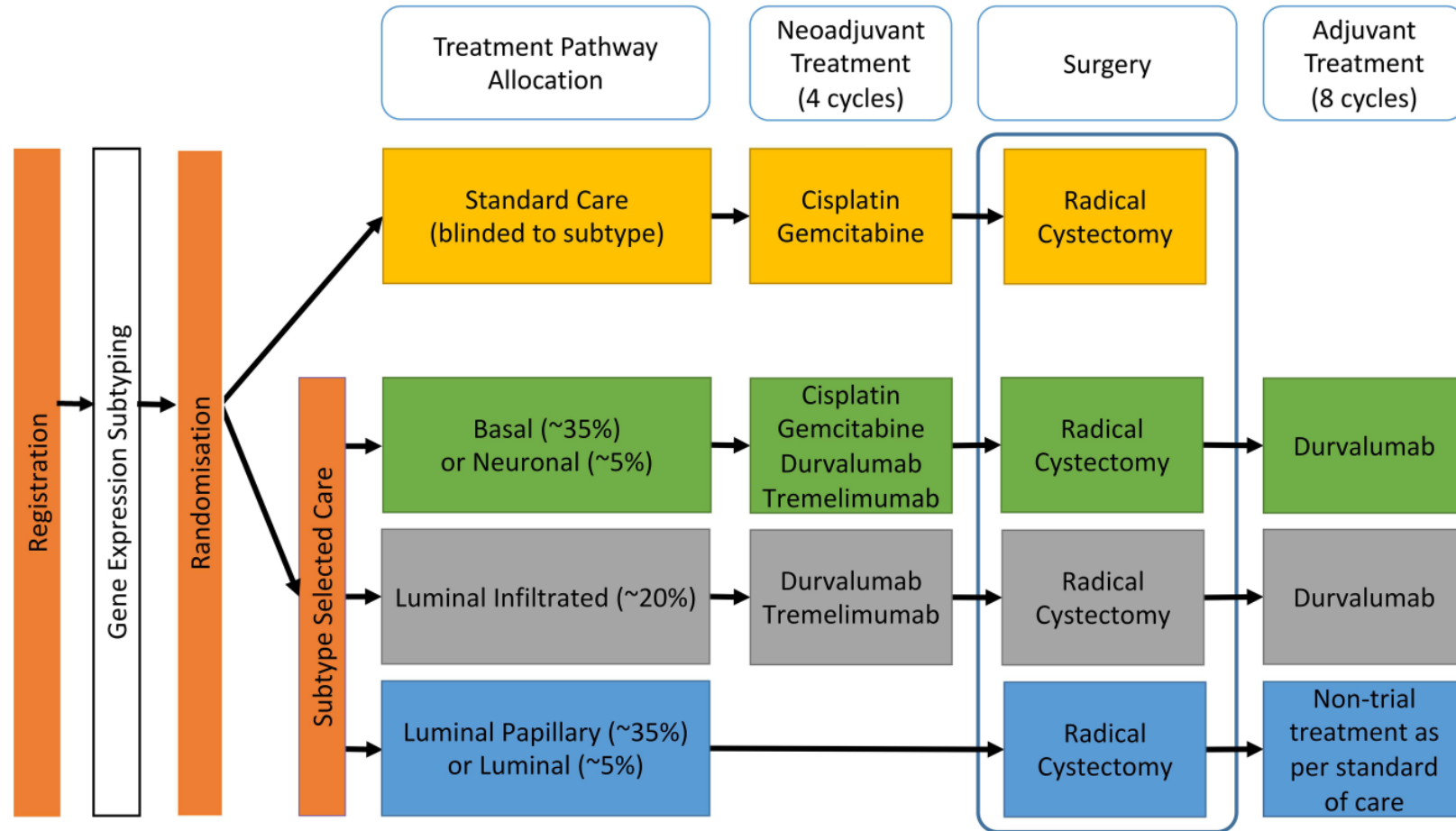
Second question : Molecular subtyping and chemotherapy ?



- The luminal molecular subtype appears to have less aggressive clinical presentation (in many cases), reflected by good outcomes.
- Luminal tumors are more likely to be organ-confined (pT1-2N0) at surgery.
- Basal tumors might have greater benefit from neoadjuvant chemotherapy.
- The issue: intratumor heterogeneity and reproducibility of such biomarker,

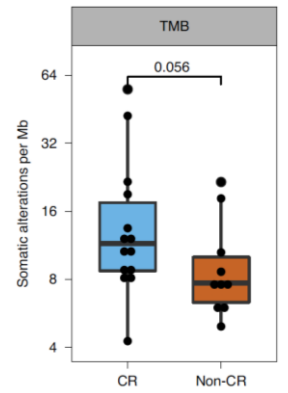
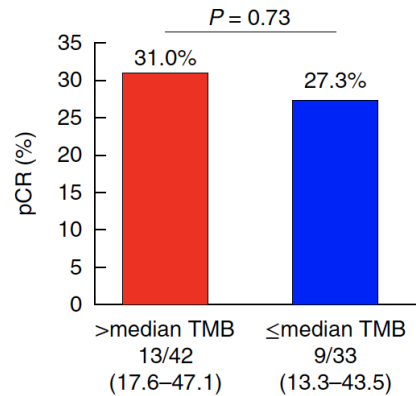
Will gene expression subtype guided neoadjuvant chemotherapy and/or immunotherapy ?

Gusto trial

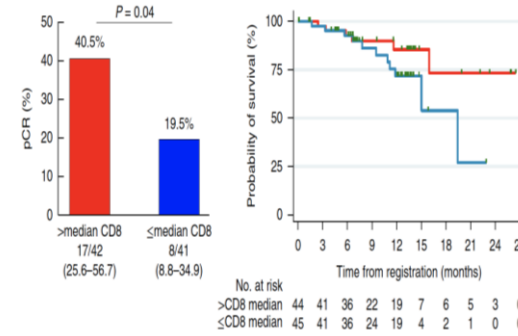
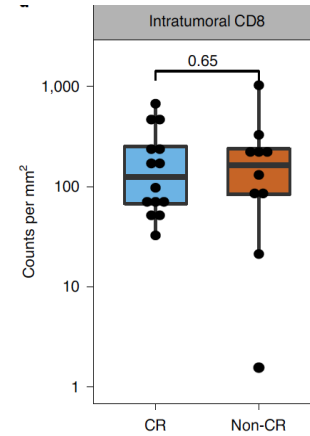


Third question : Immune biomarkers and and IO

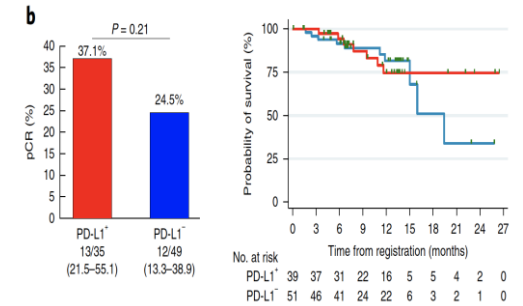
Role of TMB: unclear



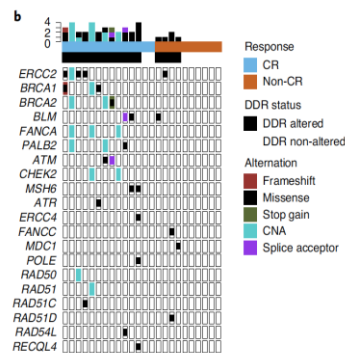
Role of pre-existing T cell immunity is unclear



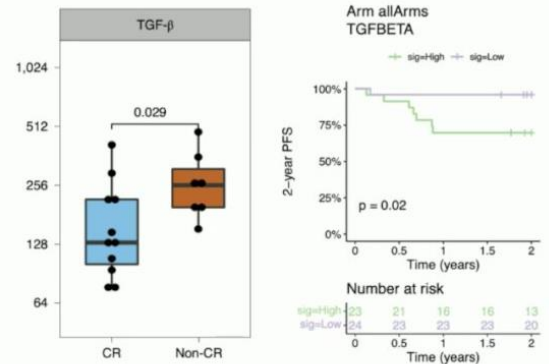
Role of PDL1 is unclear



Role of DDR: unclear

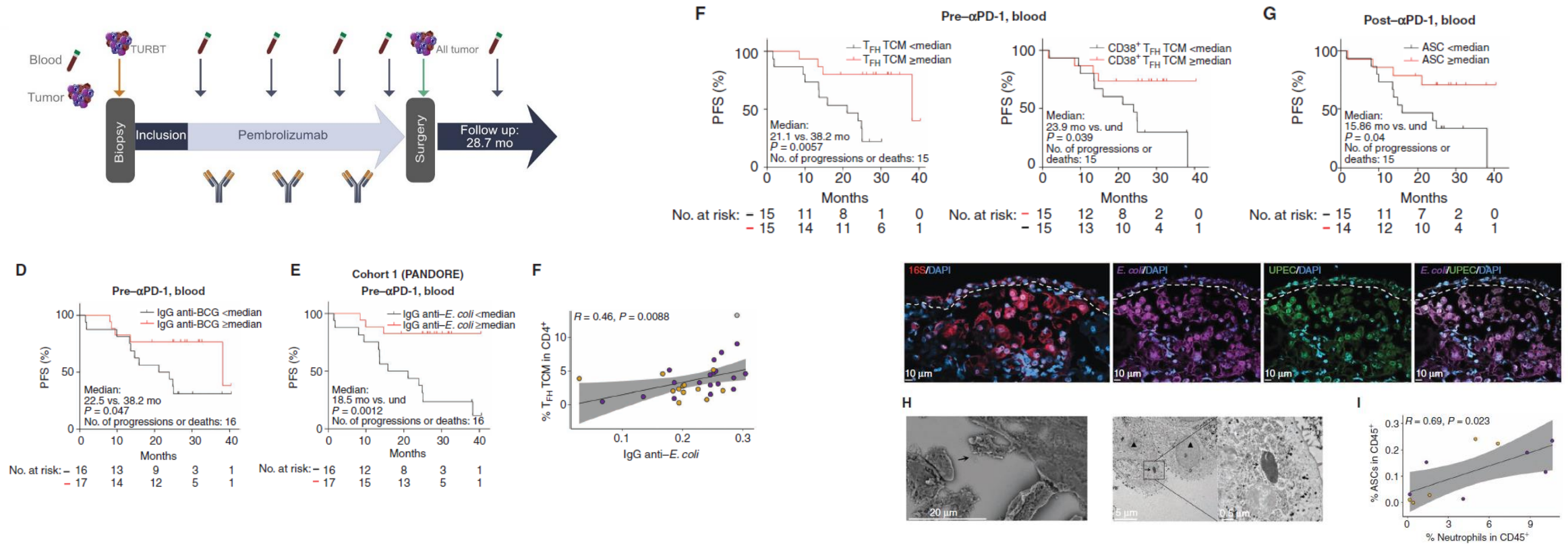


TGF-B predicts resistance



- Pre-existing immunity may predict the outcome of monotherapy immune checkpoint blockade.
- However, this is less obvious for combination IO.
- Moreover, cellular distances may better predict response

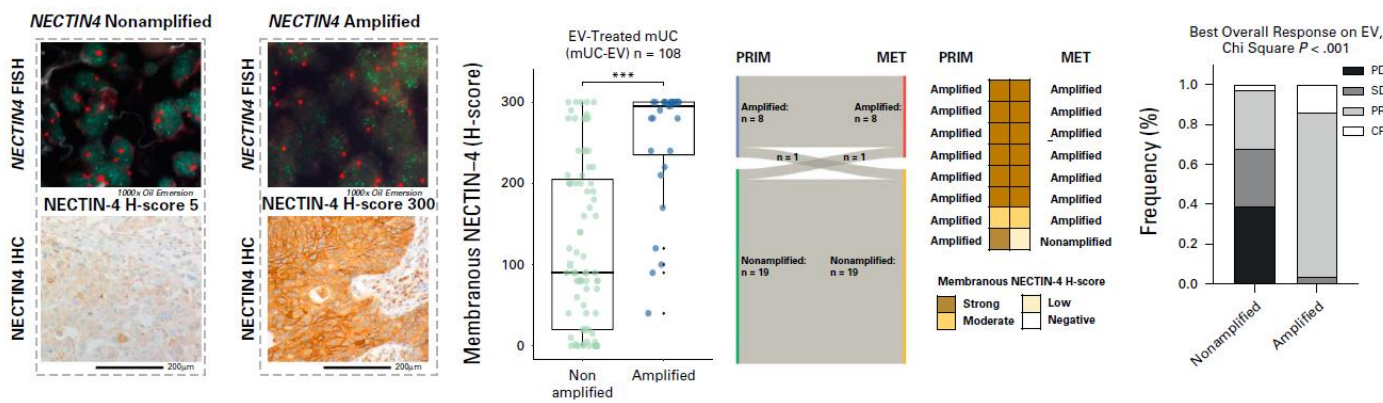
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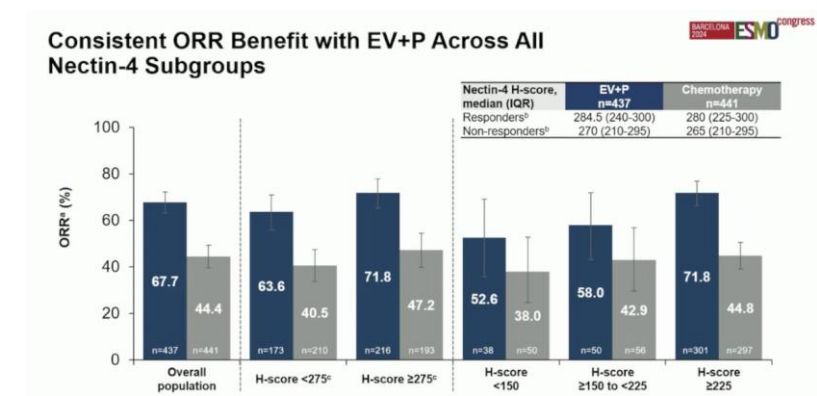
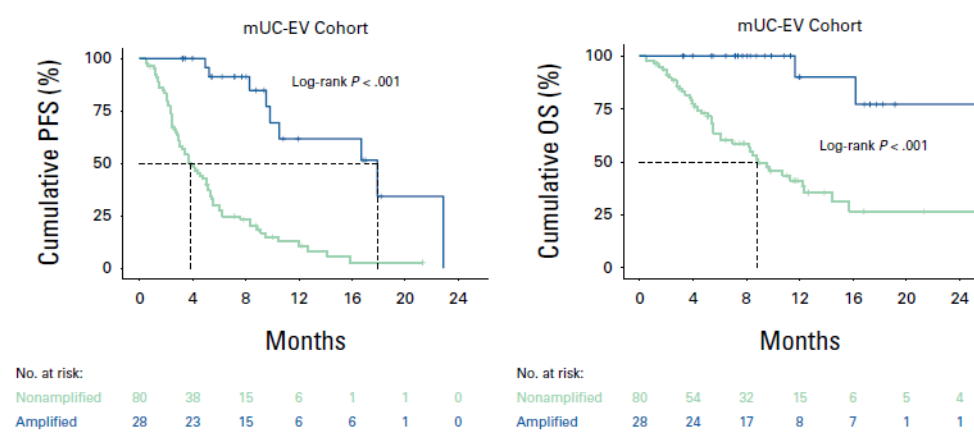
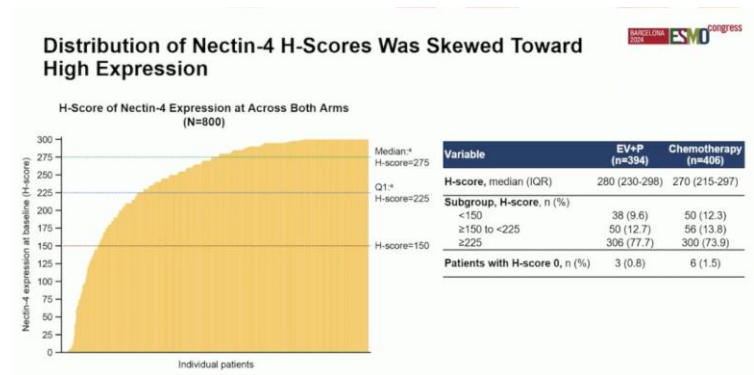
- Follicular helper CD4⁺ T cells and IgG against urothelium-invasive *Escherichia coli* were found to direct clinical response such as progression-free survival after pembrolizumab treatment.
- CXCL13 produced by tumor-localized blood central memory T_{FH} cells was found in the plasma of patients who responded

Fourth question : biomarkers and EV+pembro (if MK-B15 and MK-905 are positive) ?

NECTIN-4 amplification ?

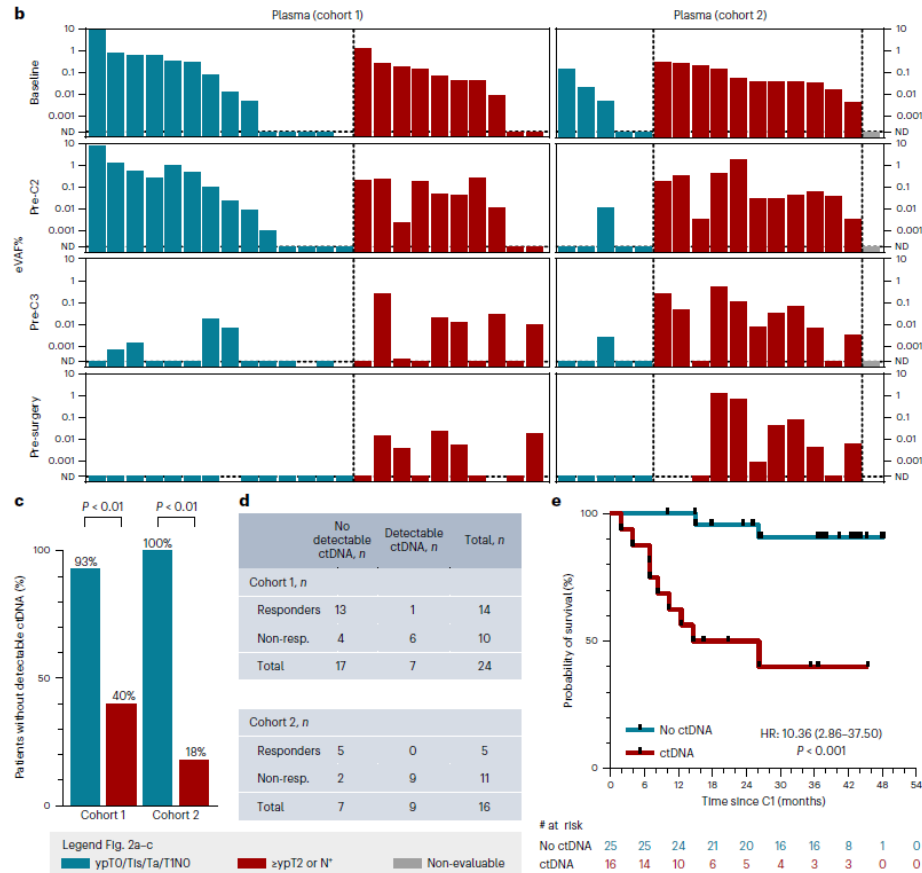


NECTIN-4 and PDL1 expression ?

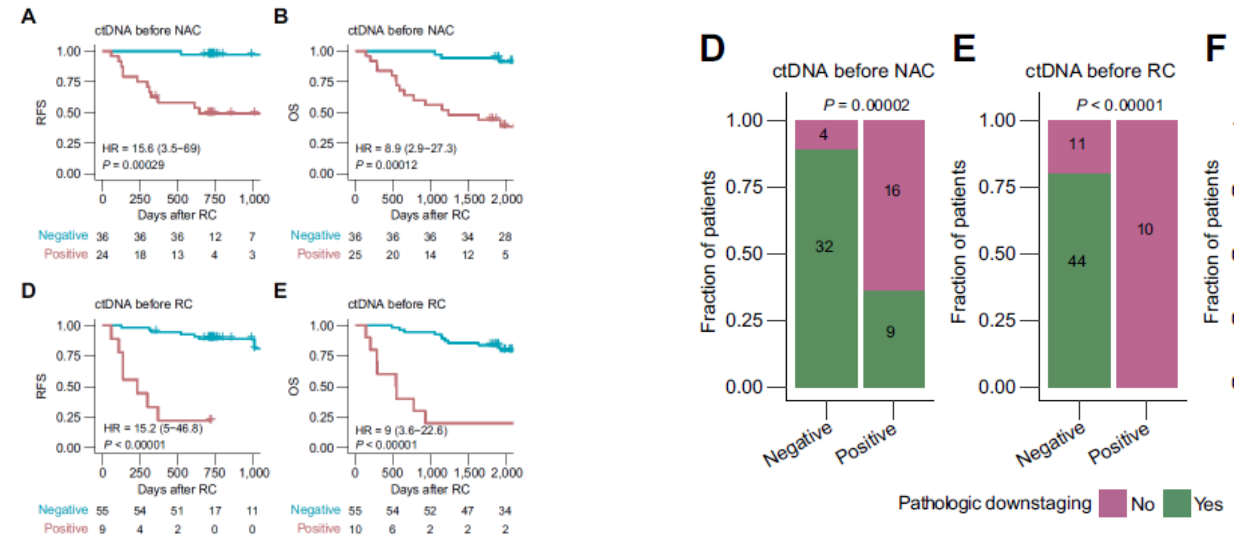


Fifth question: Can we predict response to therapy with ctDNA ?

Nabucco trial (Ipi + Nivo) using multiplex PCR-based NGS

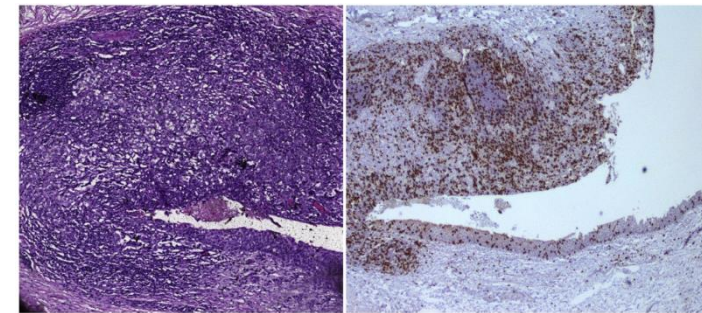
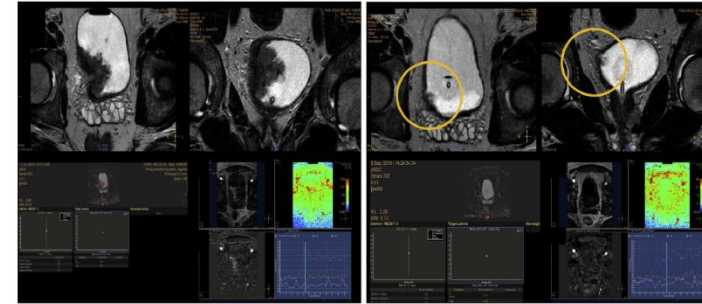
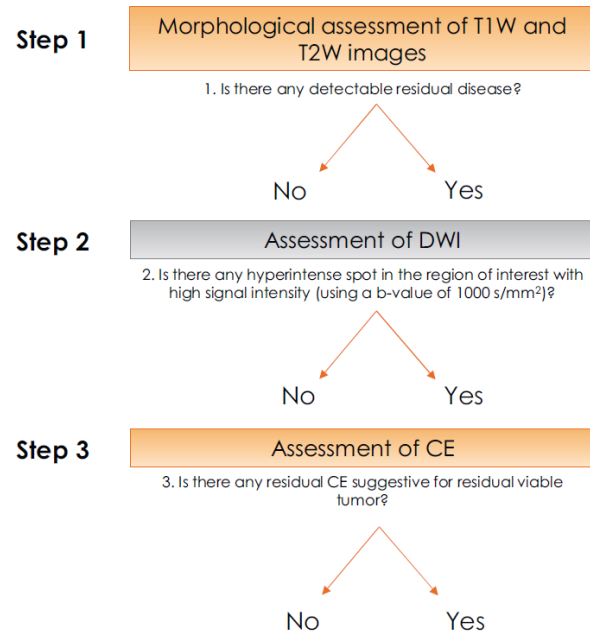


Arrhus cohort: personalized ctDNA assays using multiplex PCR-based NGS



ctDNA detection before cystectomy is associated with response and PFS

Does imaging help ?

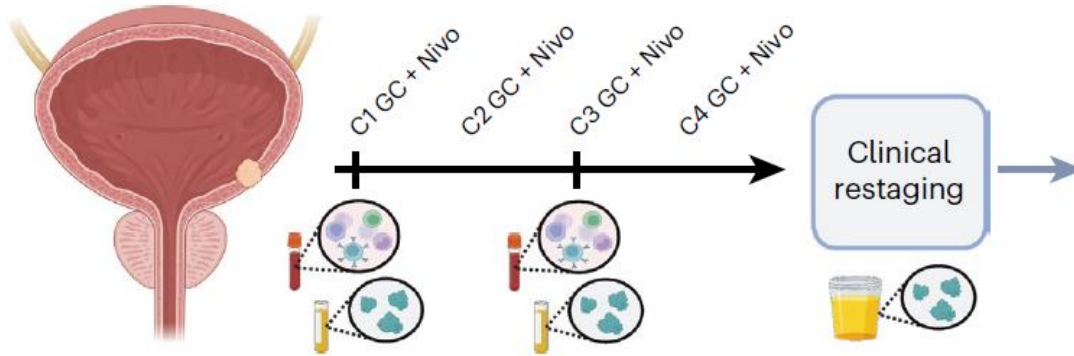


yes

BUT

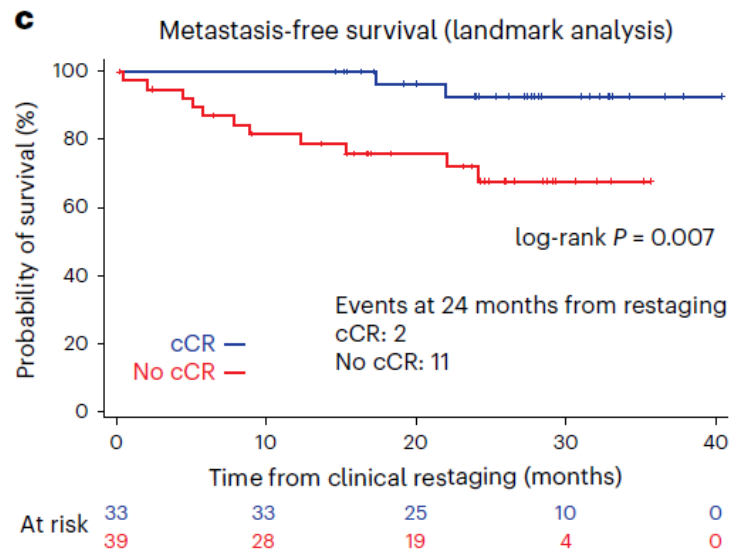
- Agreement between the internal and external assessments is modest (K values: 0.05- 0.76)
- Similar results for chemotherapy
- Consensus needed
- AI may help

Do we need to combine multiple assays ?



cCR definition:

- 1) no evidence of malignancy on biopsy except Ta
- 2) No malignant cells on urine cytology
- 3) No evidence of relapse on cross-sectional imaging (MRI)



Primary objectives

- Positive predictive value of cCR for 2-year MFS and $<pT1N0$
- cCR rate

PPV of cCR (for MFS) was 0.97
cCR rate : 43%

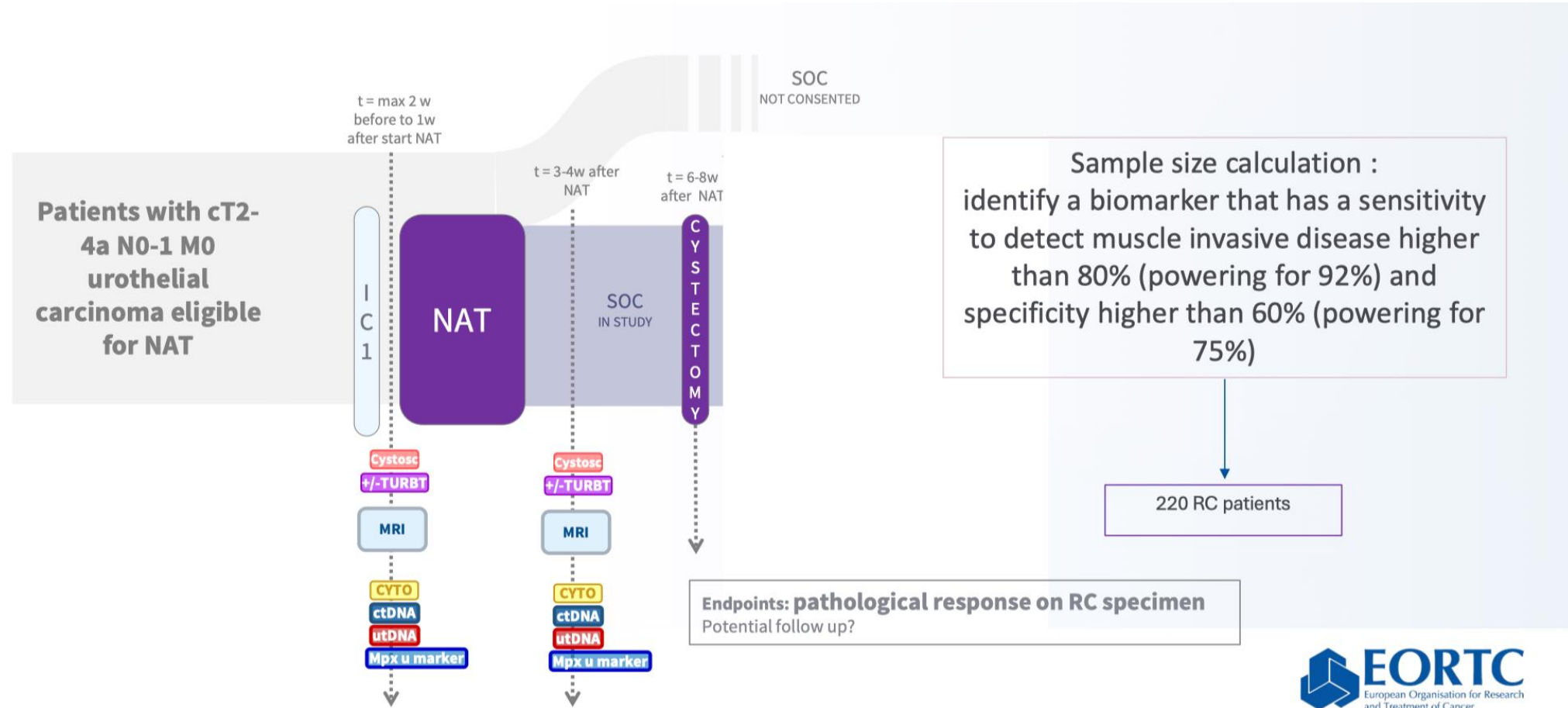
	Composite outcome measure*	
	Yes	No
cCR	31	1
No cCR	4	33

Sensitivity: 0.89 (95% CI: 0.78, 0.99)
Specificity: 0.97 (95% CI: 0.91, 1)
Positive predictive value: 0.97 (95% CI: 0.91, 1)
Negative predictive value: 0.89 (95% CI: 0.79, 0.99)

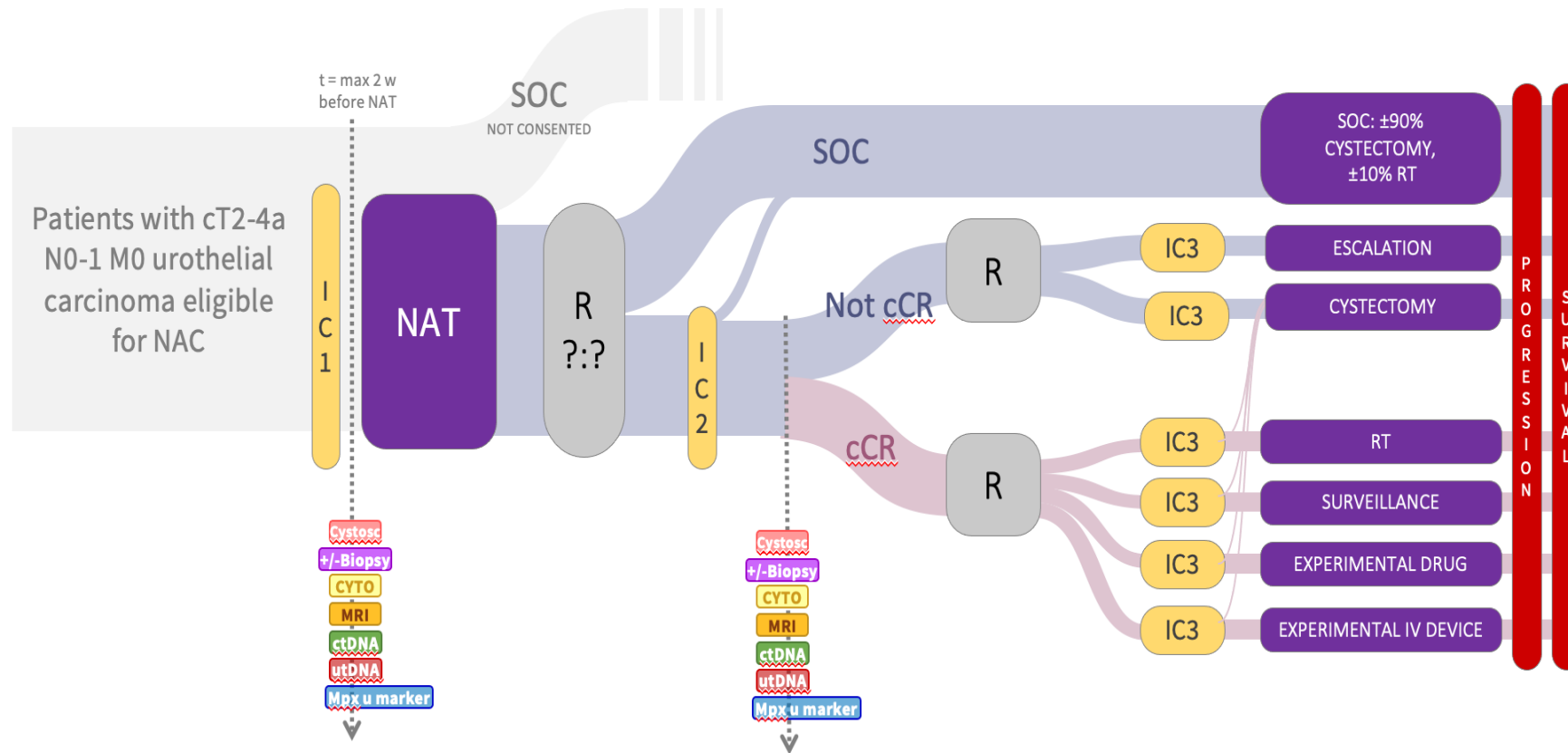
Performance of cCR for 2 year BI survival of $<ypT1$

Measure	Performance metric
cCR	
Sensitivity	0.85 (95% CI: 0.72, 1.00)
Specificity	0.79 (95% CI: 0.66, 0.91)
Positive predictive value	0.72 (95% CI: 0.56, 0.87)
Negative predictive value	0.89 (95% CI: 0.79, 0.99)

The need of prospective validation: STARBUST-1 trial

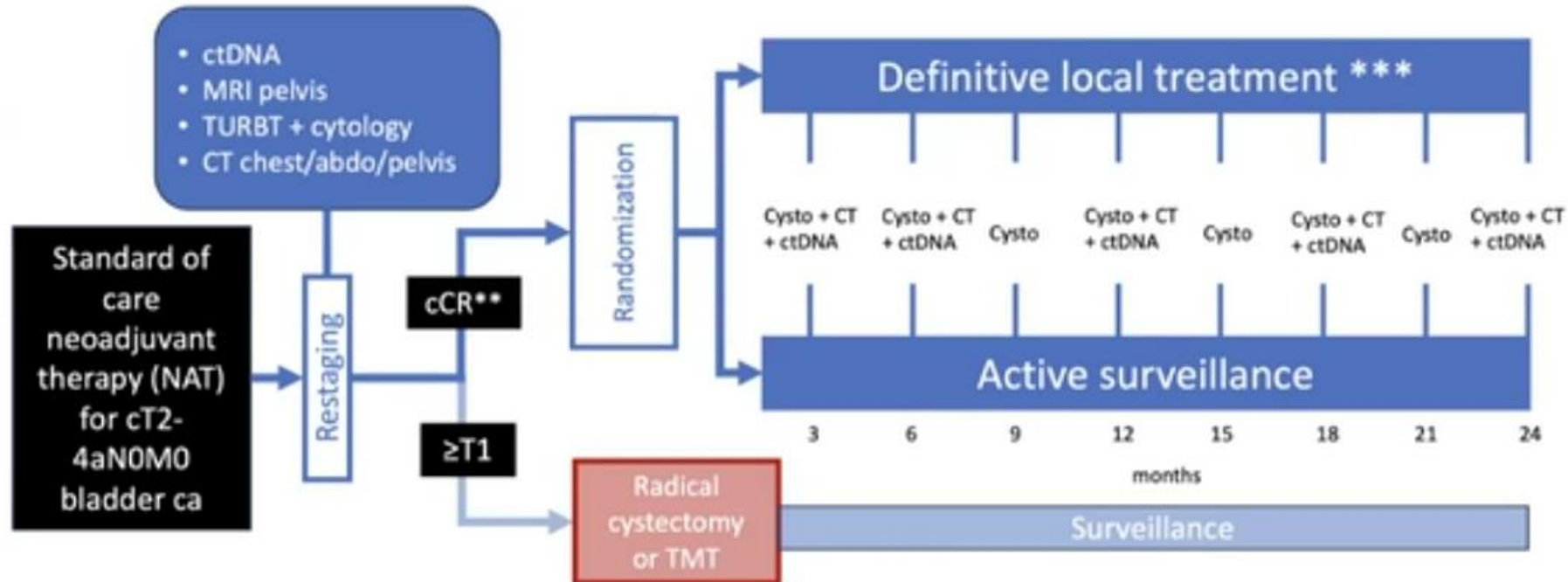


The need of prospective validation: STARBUST-2 trial



The need of prospective validation: NEO-BLAST trial

NEO-BLAST: Neoadjuvant Therapy for Bladder Cancer Followed by Active Surveillance vs Treatment NCT06537154



**Definition of cCR:

- Negative MRI (VI-RADS 0-1-2)
- Negative repeat TURBT (< cT1, no extensive CIS)
- Negative ctDNA
- No mets (negative conventional CT/MRI or PET-CT)

Exploratory: Negative utDNA

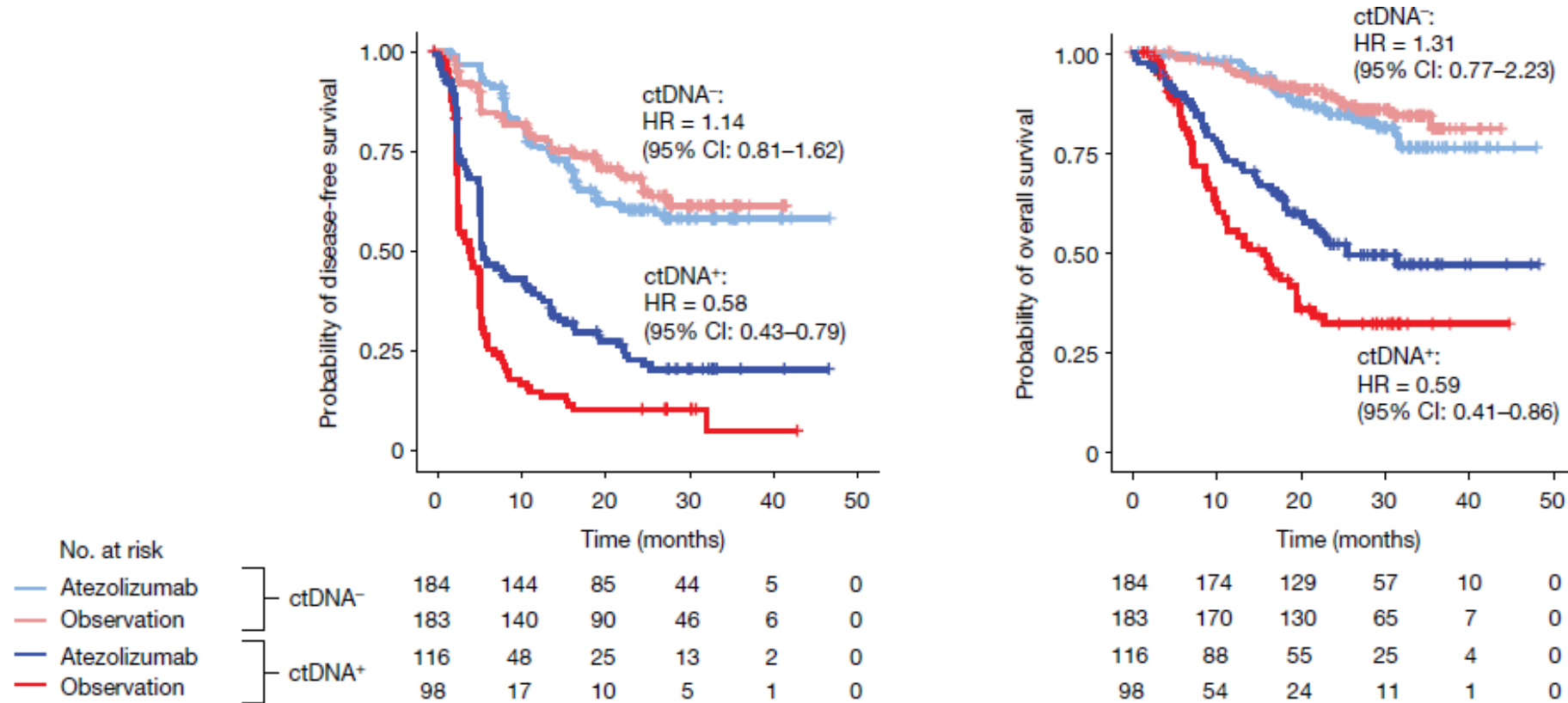
*NAT = any SOC regimen approved at time of enrolment (Cisplatin, EV, IO, etc.)

*** Patient/investigator's choice; Radical cystectomy or TMT

Outline

- 1- we will have access to immunotherapy in peri-operative setting and other very effective drugs
- 2- we will offer more bladder preservation thanks to highly effective systemic drugs
- 3- Decision-making will be based on MRD

Molecular residual disease

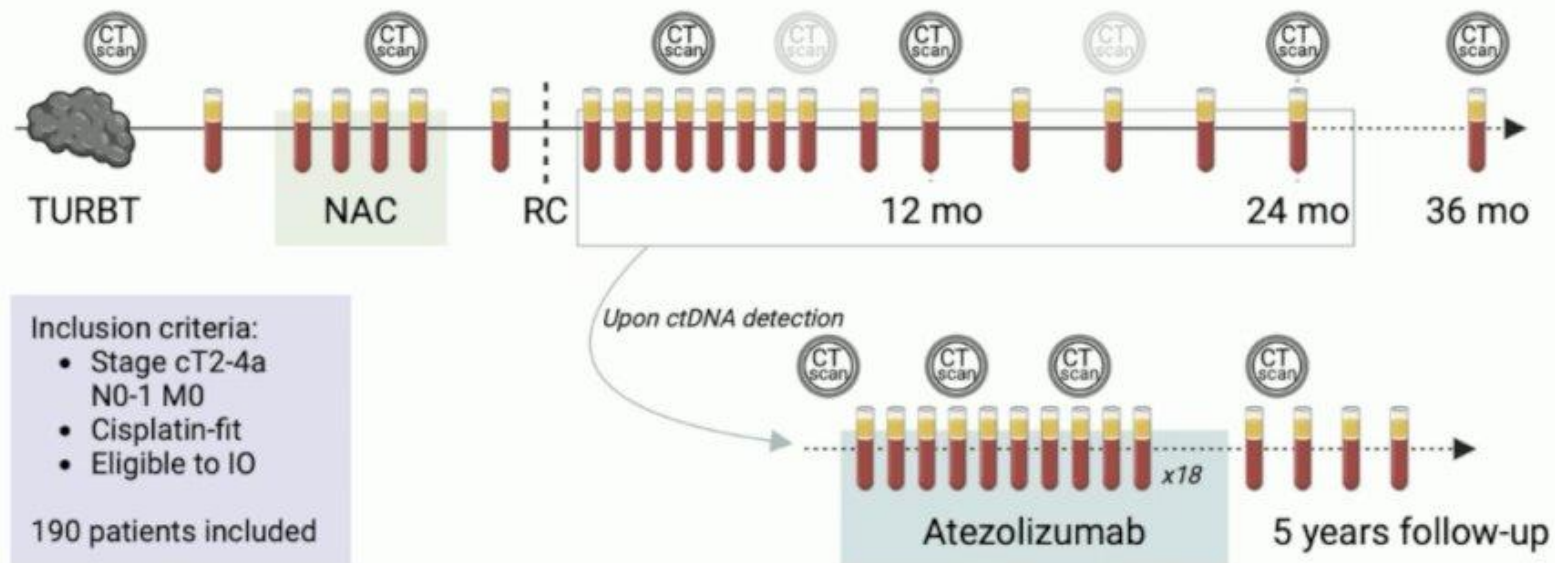


- Prognostic value of detectable ctDNA after cyctectomy
- predictive value of detectable ctDNA after cyctectomy

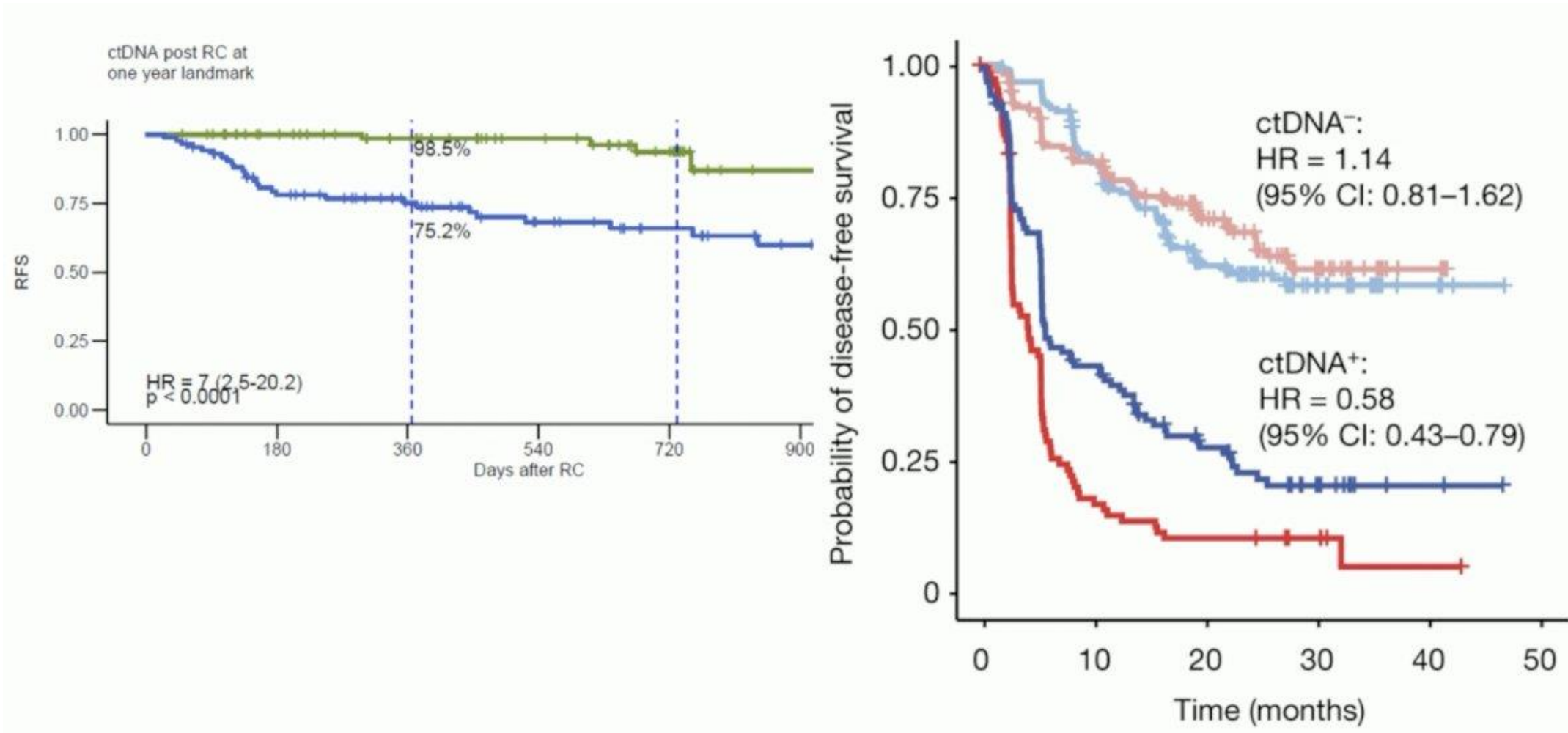
ctDNA impact management decisions

TOMBOLA

A national, non-randomized, ctDNA based intervention study



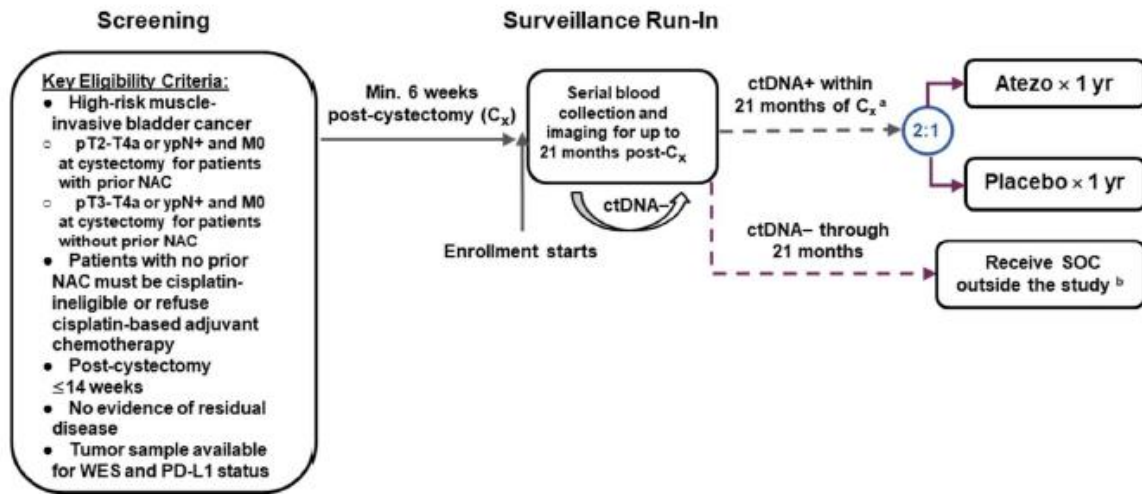
ctDNA impact management decisions but does it change the outcome ?



Of the ctDNA⁻ patients, only 2 (3%) developed metastases (different from the IMvigor011 trial that demonstrated a 10% metastatic rate in ctDNA⁻ patients)

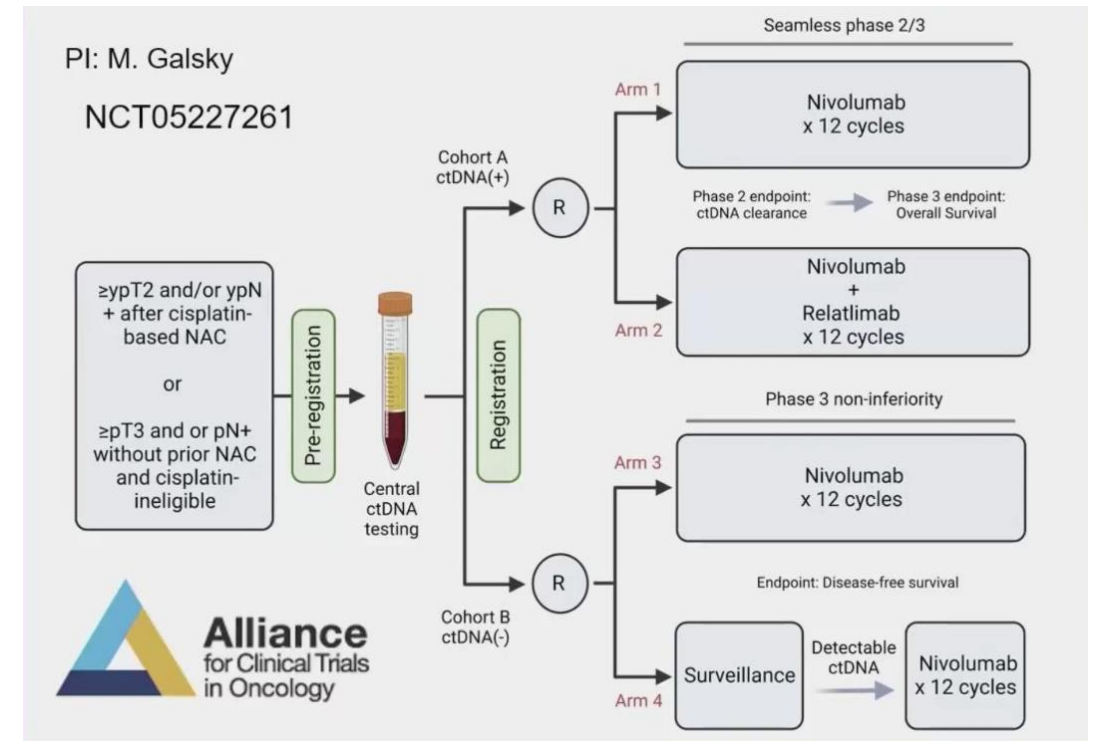
Biomarker-driven trials are ongoing

IMVIGOR 011 study (ctDNA + tumors)



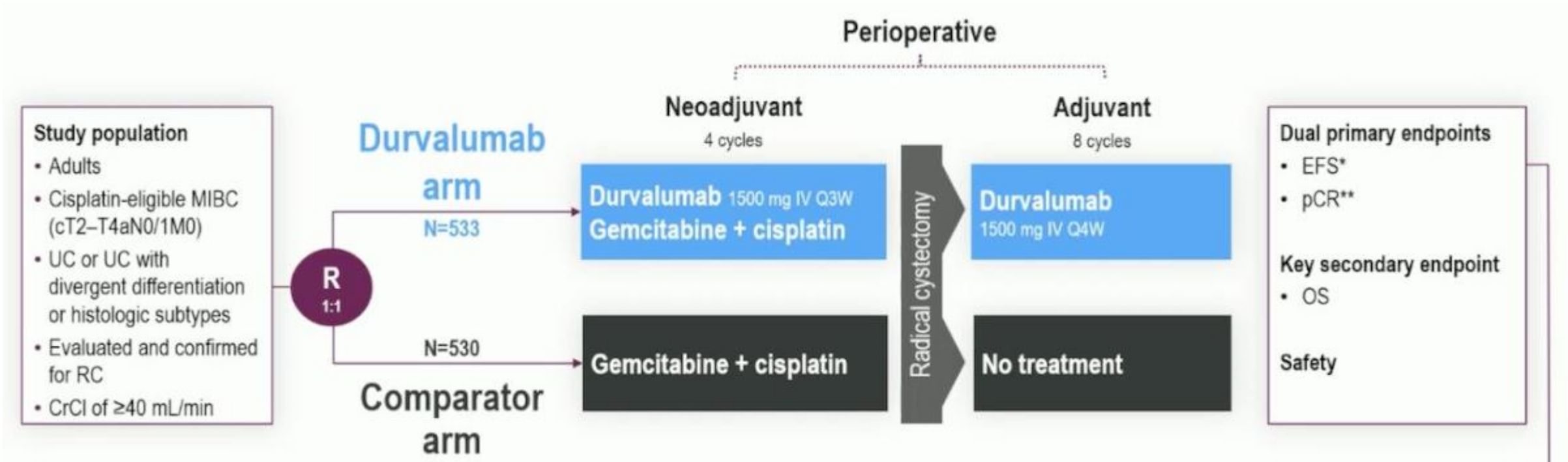
NCT04660344

MODERN Study



NCT05227261

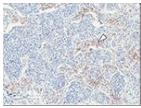
NIAGARA Study



- What is the contribution of neoadjuvant phase vs adjuvant phase ?
- Does ctDNA help ?

Biomarkers in perioperative setting

PDL1 expression



Predicts relapse



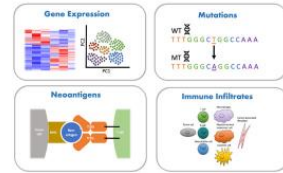
Predicts response to NAC



Predicts response to IO



Other immune biomarkers



Predicts relapse



Predicts response to NAC



Predicts response to IO



MRD



Predicts relapse



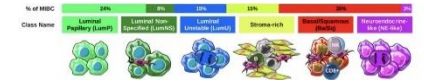
Predicts response to NAC

?

Predicts response to IO



Molecular subtyping



Predicts relapse



Predicts response to NAC



Predicts response to IO



Conclusion

- 1- we will have access to immunotherapy in peri-operative setting and other very effective drugs
- 2- we will offer more bladder preservation thanks to highly effective systemic drugs
- 3- Decision-making will be based on MRD

Thank you

