Neoadjuvant systemic therapy for MIBC

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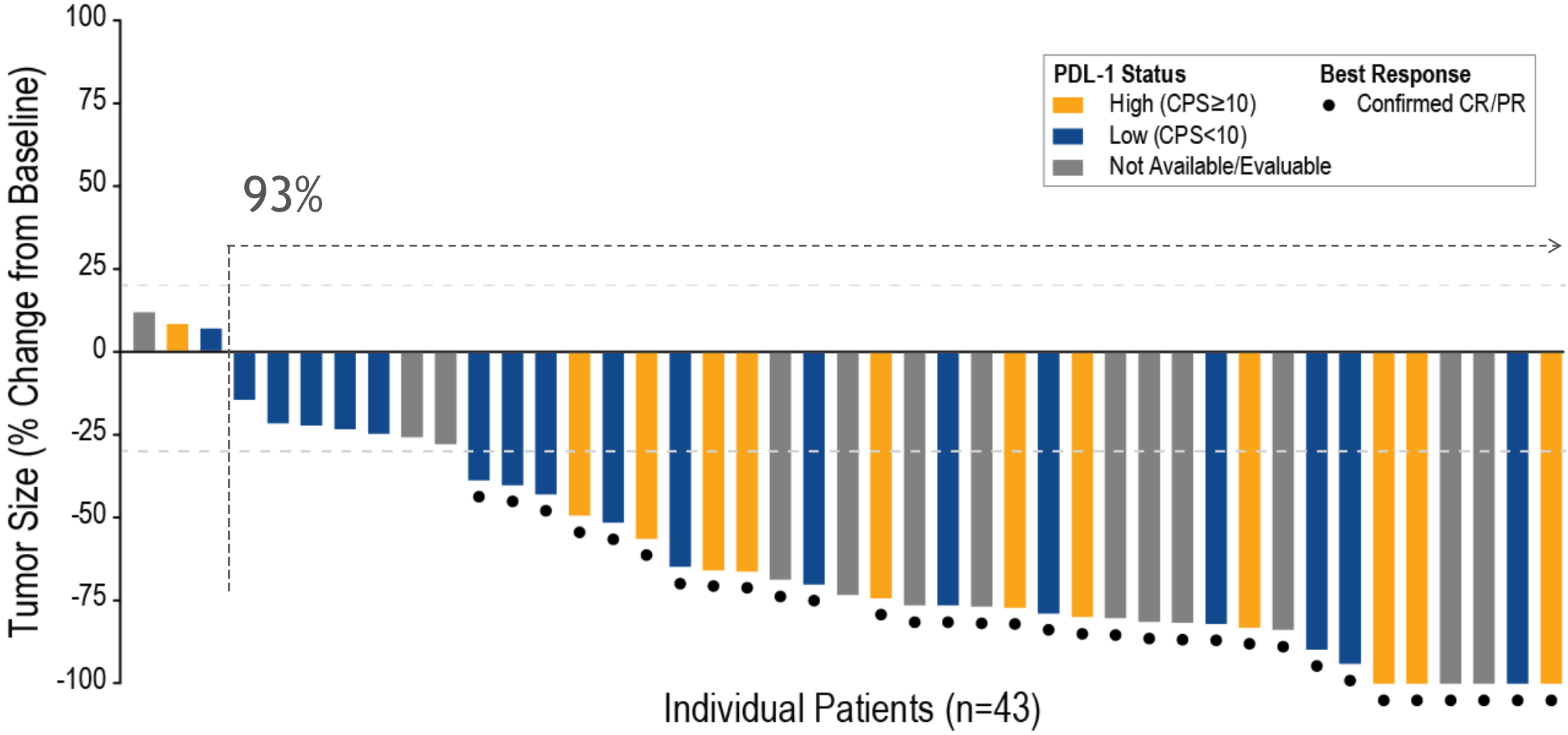
DISCLOSURES

Reaserch funding/honoraria/travel costs:

MSD, Merck, Pfizer, GSK, Novartis, Roche, AZ, BMS, Exelexis, Ipsen, Seattle Genetics, Esai, Genentech.

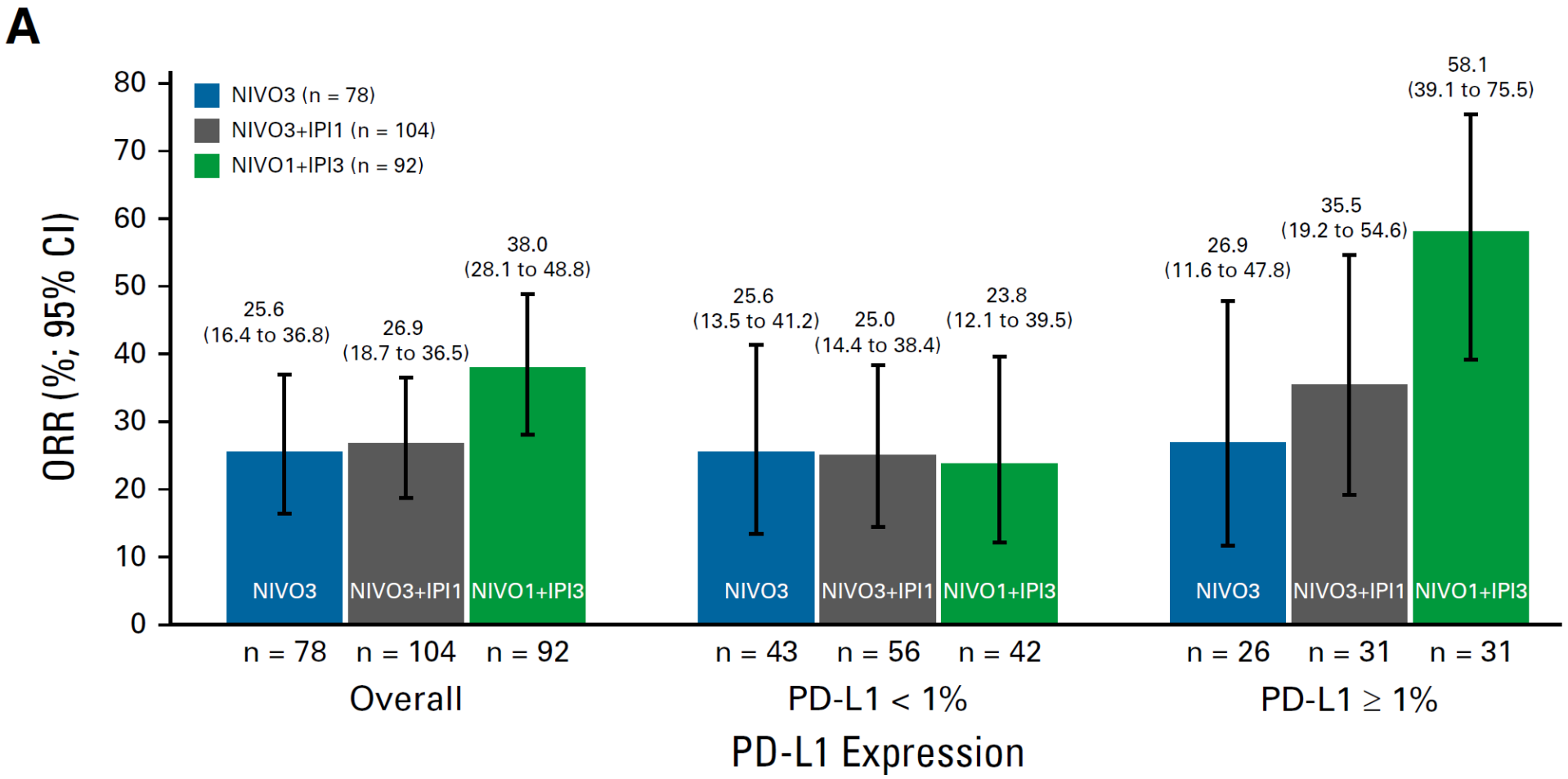
	Study arm	endpoint	OS HR	OS outcome
DANUBE	Durvalumab	PD-L1+ve	0.89	-ve
	Durvalumab/tremilimumab	ITT	0.85	-ve
IMVIGOR 130	atezolizumab	PD-L1+ve	0.68	Awaited
	Atezolizumab/chemotherapy	ITT	0.83	Awaited
KEYNOTE 361	pembrolizumab	PD-L1+ve	1.01	-ve
	Pembrolizumab/chemotherapy	ITT	0.86	-ve
JAVELIN100	Avelumab maintenance	ITT	0.69	+ve
CHECKMATE 901	Ipilimumab/nivolumab	PD-L1+ve	NA	-ve
	Chemotherapy/nivolumab	ITT		Awaited
NILE	Chemotherapy/durva/tremi			Awaited
	Chemotherapy/durvalumab			Awaited

PEMBROLIZUMAB + ENFORTUMAB VEDOTIN IN FIRST LINE PLATINUM INELIGIBLE DISEASE



PD-L1 tested using the 22C3 PharmDx assay from Agilent/Dako

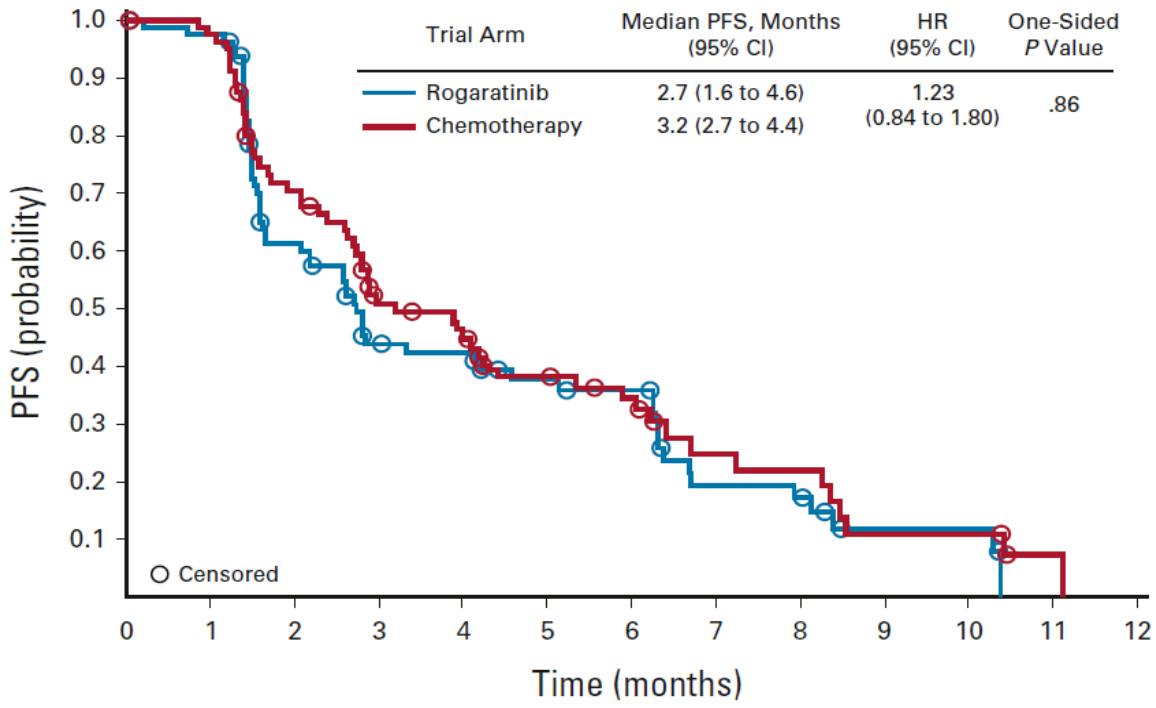
Non randomised study for nivolumab and ipilimumab combinations in platinum refractory UC showing good outcome for the PD-L1+ve with Ipi3 nivo1

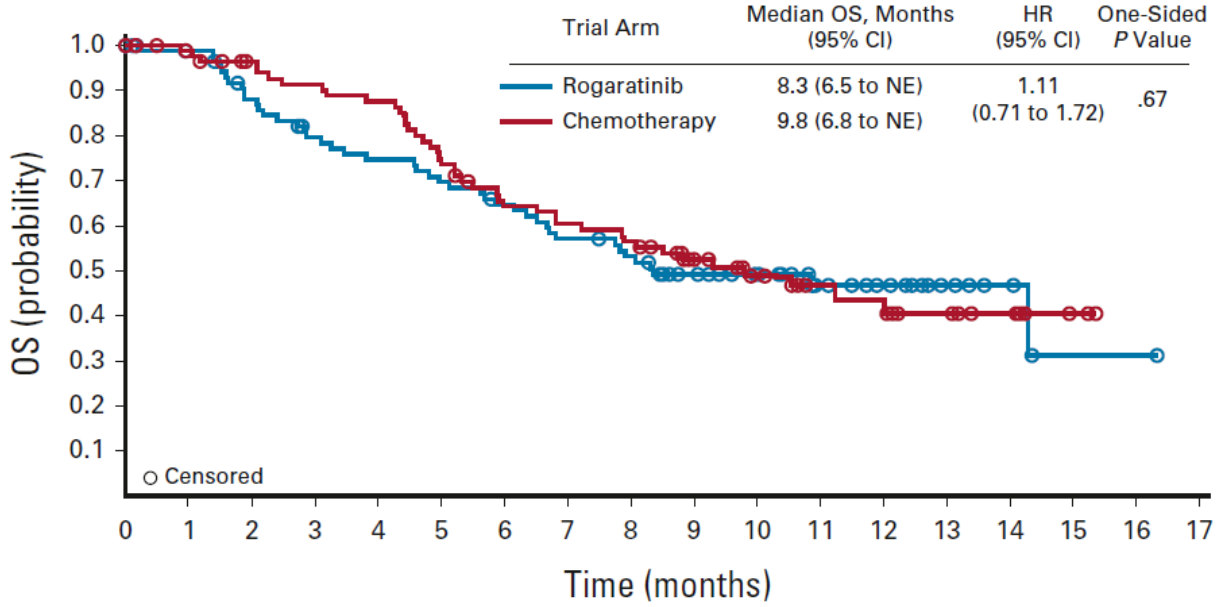


FGFR inhibition (rogaratinib) vs chemotherapy in FGFR+ve platinum refractory UC

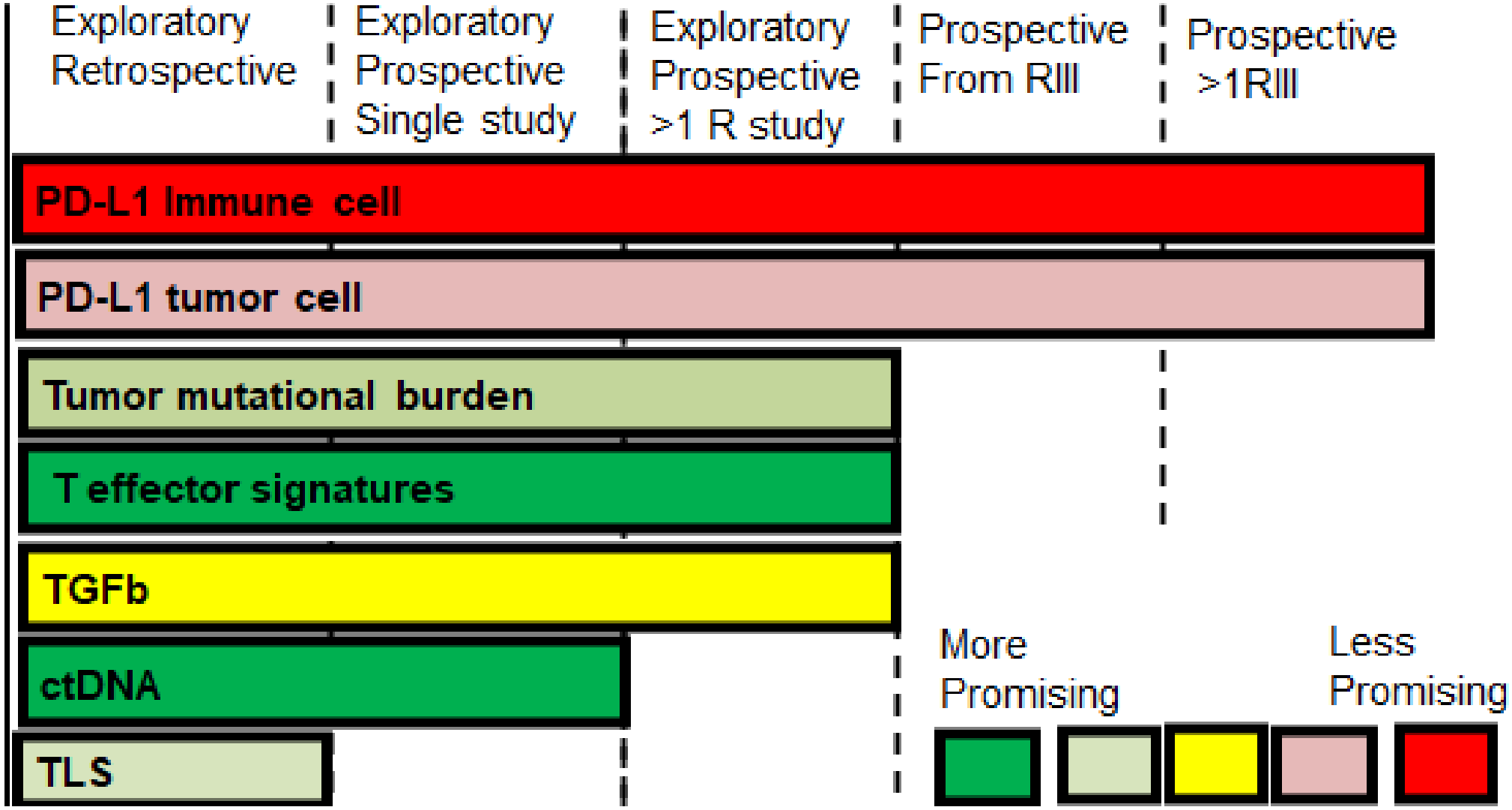
Response rate	25%
Biomarker method	RNA FGFR 1+3
% biomarker positive	68% +ve
Toxicity	43% grade 3/4 toxicity
Toxicity type	Hyperphosphatemia

Other FGFR inhibitors (single arm trials)		
Drug	Biomarker	RR + PFS
Erdafitinib (n=99)	FGFR3 PCR	40% + 5.5 mnths
AZD4547 (n=16)	FGFR2/3 DNA	31% +4.5 months
BGJ398 (n=67)	FGFR3	25%
INDB05842 (n=100)	FGFR3 DNA	25%





A brief overview for biomarkers for PD (L)1 therapy in UC



Learning points from advanced disease to consider in perioperative setting

The chemotherapy combinations with immune therapy appears antagonistic.

The biomarkers are a mess

EV appears to combine will with immune therapy

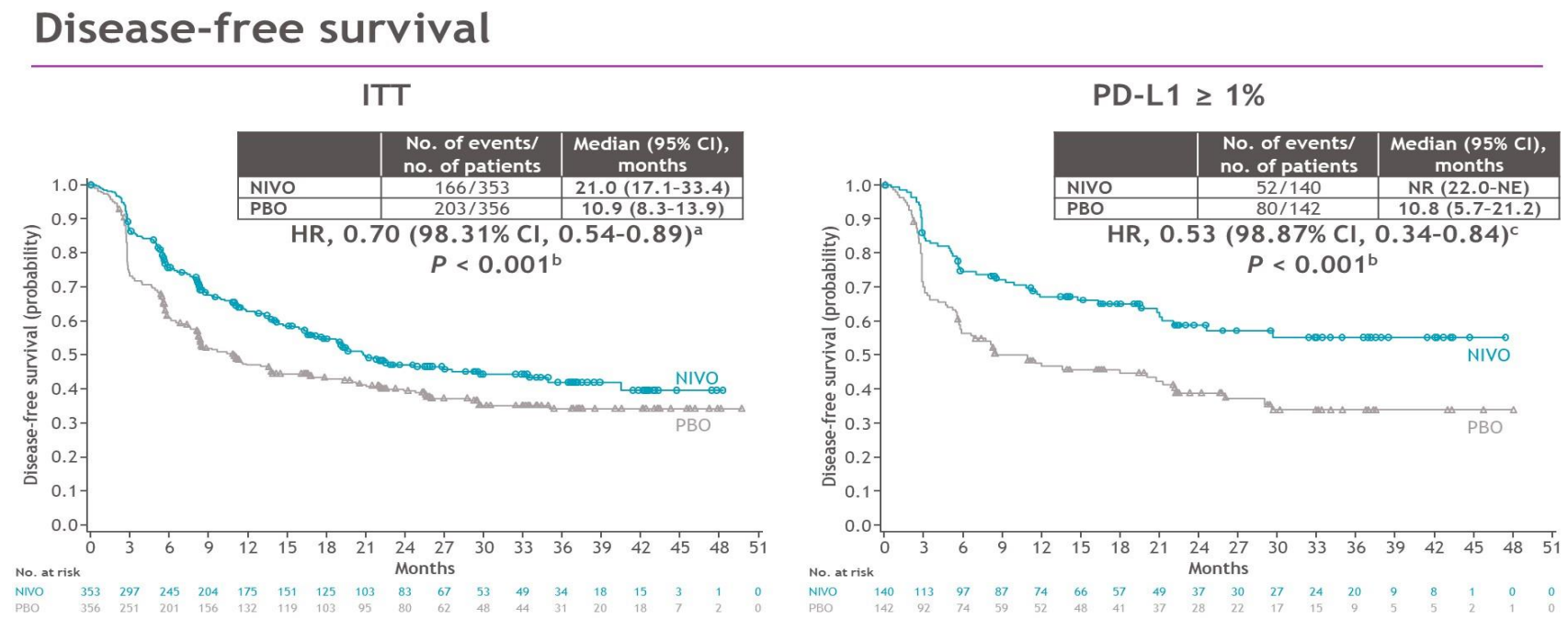
CTLA-4 and FGFR have activity in UC, but we don’t know how much

Duration of immune therapy and ADCs are unclear.

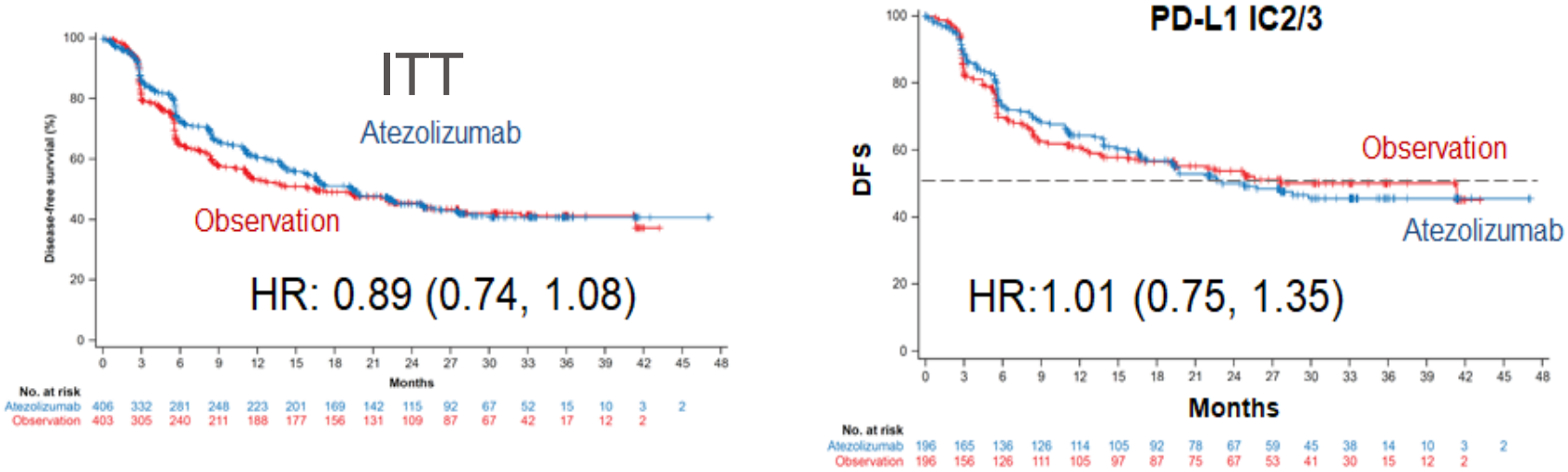
Adjuvant atezolizumab and nivolumab in UC

CheckMate 274

Nivolumab

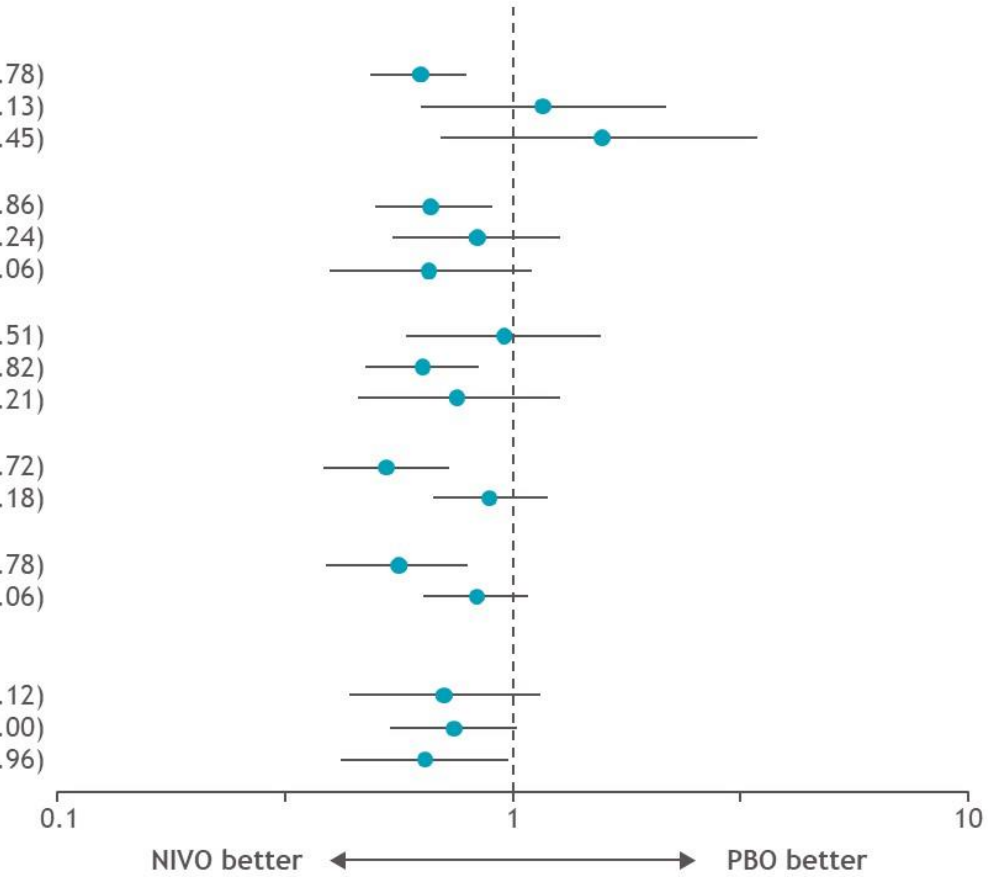


Atezolizumab



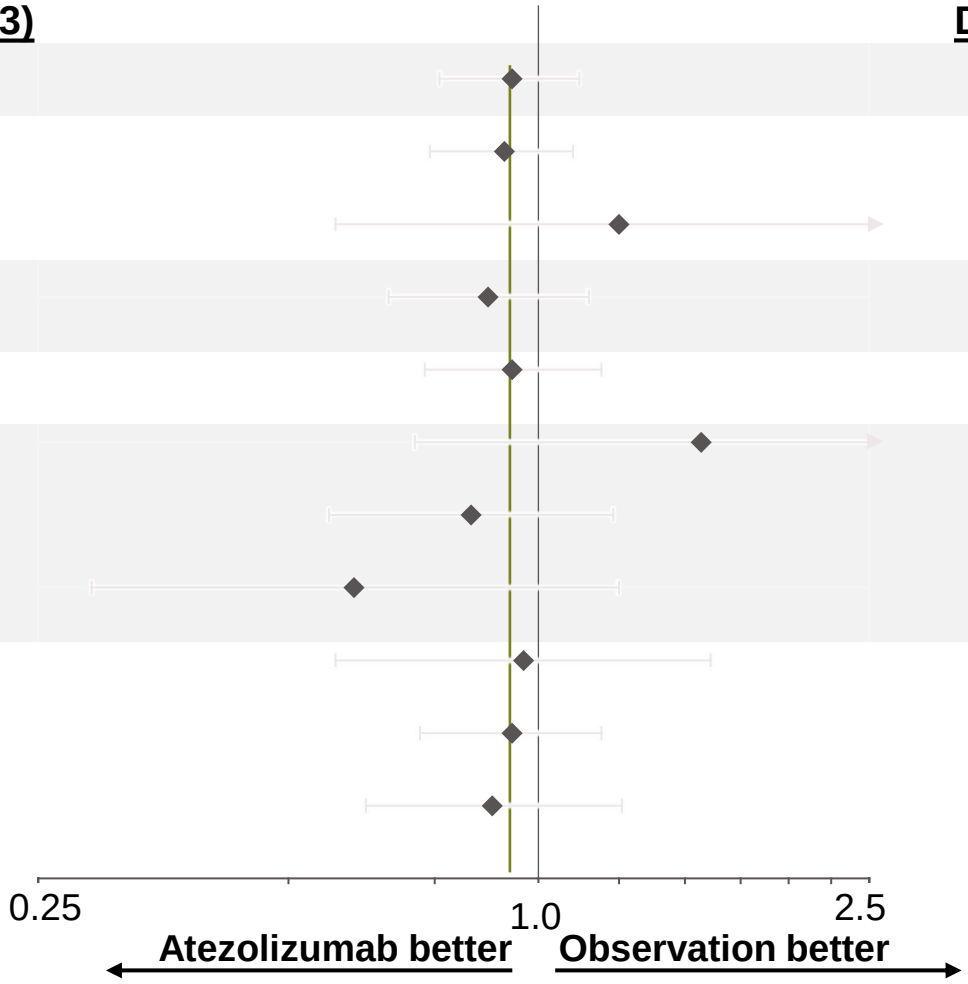
Disease-free survival in select subgroups: ITT patients

Subgroup	Nivolumab	Placebo	HR (95% CI)
	no. of events/ no. of patients		
Initial tumor origin			
Urinary bladder	126/279	165/281	0.62 (0.49-0.78)
Renal pelvis	23/44	25/52	1.16 (0.63-2.13)
Ureter	17/30	13/23	1.55 (0.70-3.45)
Pathologic lymph node status			
N+	95/167	115/168	0.65 (0.49-0.86)
N0/x with < 10 nodes removed	44/94	50/99	0.82 (0.54-1.24)
N0 with ≥ 10 nodes removed	27/91	37/88	0.64 (0.39-1.06)
Pathologic status			
pT0-2	36/80	40/86	0.93 (0.58-1.51)
pT3	94/206	119/204	0.62 (0.47-0.82)
pT4a	34/57	40/62	0.74 (0.45-1.21)
Prior neoadjuvant cisplatin			
Yes	69/153	99/155	0.53 (0.39-0.72)
No	97/200	104/201	0.89 (0.67-1.18)
Baseline PD-L1 expression			
≥ 1%	52/139	78/141	0.55 (0.39-0.78)
< 1%	113/210	120/209	0.82 (0.63-1.06)
Time from IUC surgery to randomization, days			
> 30-60	43/79	39/70	0.70 (0.43-1.12)
> 60-90	76/165	93/177	0.73 (0.53-1.00)
> 90-120	45/103	62/95	0.64 (0.42-0.96)



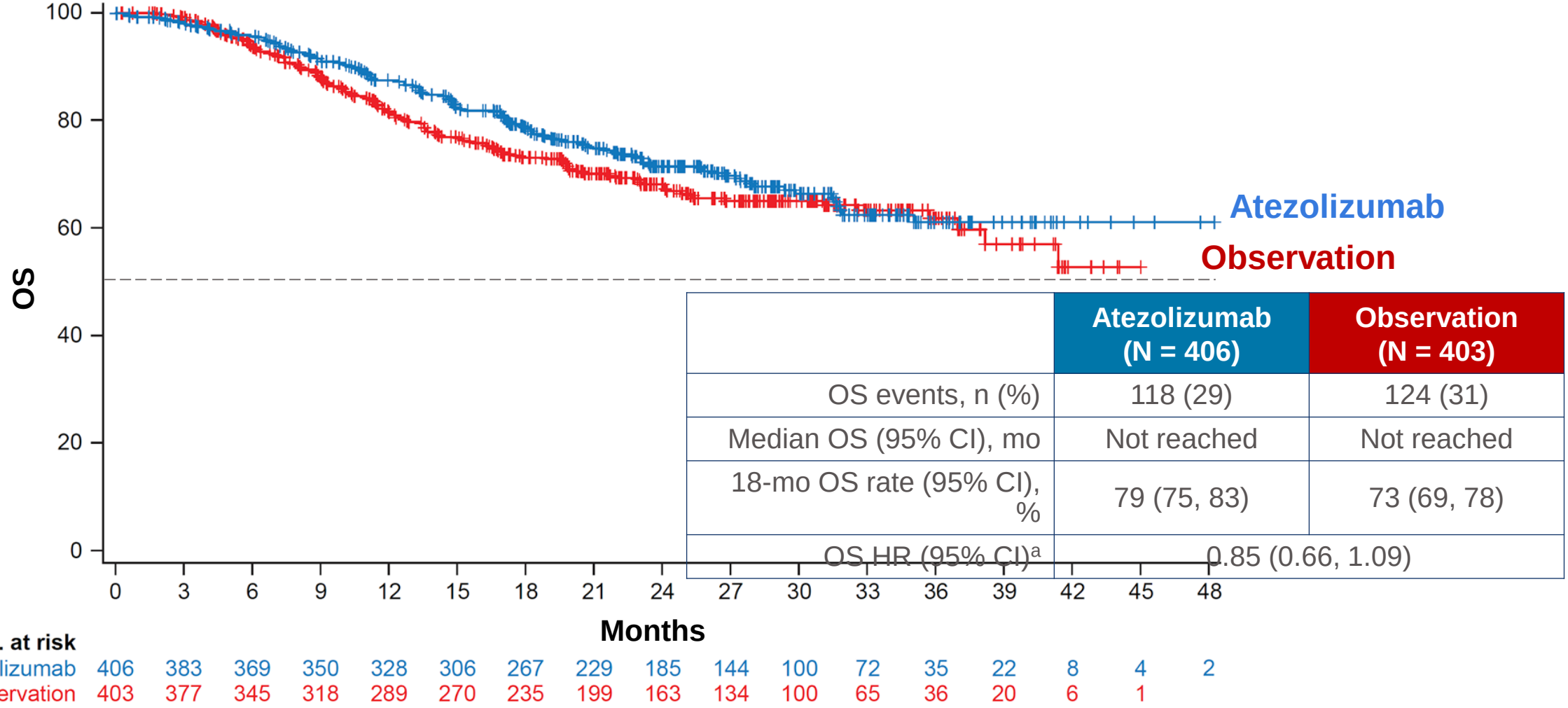
DFS by Clinical Subgroup

Population (n)	Median DFS, mo: Atezolizumab (N = 406)	Median DFS, mo: Observation (N = 403)	DFS HR (95% CI)[c]
All patients (809)	19.4	16.6	0.93 (0.76, 1.12)
Bladder (755)	19.6	15.8	0.91 (0.74, 1.10)
Upper tract (ureter, renal pelvis) (54)	14.2	28.1	1.25 (0.57, 2.74)
Prior neoadjuvant chemotherapy (385)[a]	19.8	16.5	0.87 (0.66, 1.15)
Positive pathologic node status (420)[a]	13.9	8.9	0.93 (0.73, 1.19)
pT2N0 (73)[b]	NE	NE	1.57 (0.71, 3.46)
pT3N0 (243)[b]	NE	24.9	0.83 (0.56, 1.23)
pT4N0 (65)[b]	NE	14.2	0.60 (0.29, 1.25)
Asia (125)	23.1	24.8	0.96 (0.57, 1.61)
Europe (437)	19.1	12.3	0.93 (0.72, 1.19)
North America (241)	19.8	16.5	0.88 (0.62, 1.26)



Australian subgroups not shown (n = 6).
NE, not evaluable. [a] Per IxRS. [b] Per eCRF. [c] Unstratified analyses.

The only OS data for immune therapy in adjuvant bladder cancer



	Atezolizumab (N = 406)	Observation (N = 403)
OS events, n (%)	118 (29)	124 (31)
Median OS (95% CI), mo	Not reached	Not reached
18-mo OS rate (95% CI), %	79 (75, 83)	73 (69, 78)
OS HR (95% CI)[a]	0.85 (0.66, 1.09)	

Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. Most common subsequent non-protocol therapies included immunotherapy (9% in atezolizumab arm vs 21% in observation arm), chemotherapy (27% vs 25%) and targeted therapy (5% vs 2%). [a] OS results are shown for descriptive purposes only. HR stratified by tumor stage, nodal status and PD-L1 status.

Hussain M. IMvigor010 primary analysis [abs 5000].

https://bit.ly/2SKSAD3

Why have the agencies gone in different direction

uncertainty

noun

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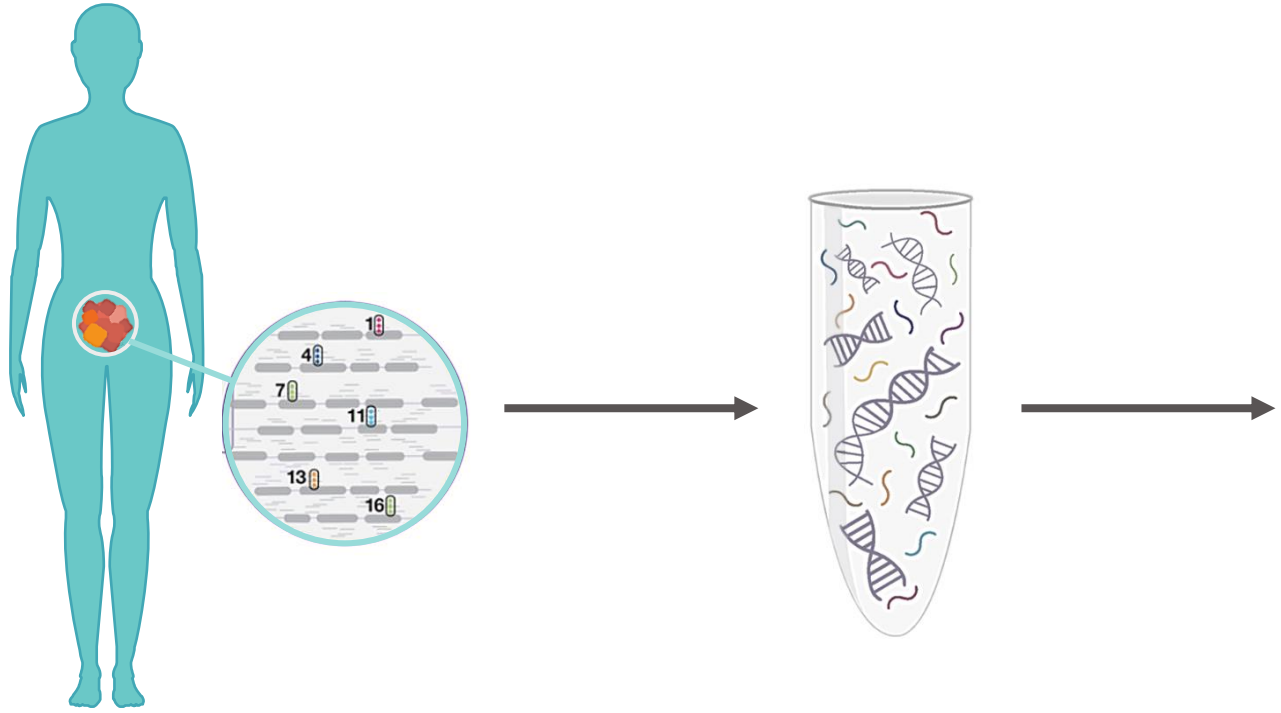
un·cer·tain·ty | \ ˌən-ˈsər-tᵊn-tē \

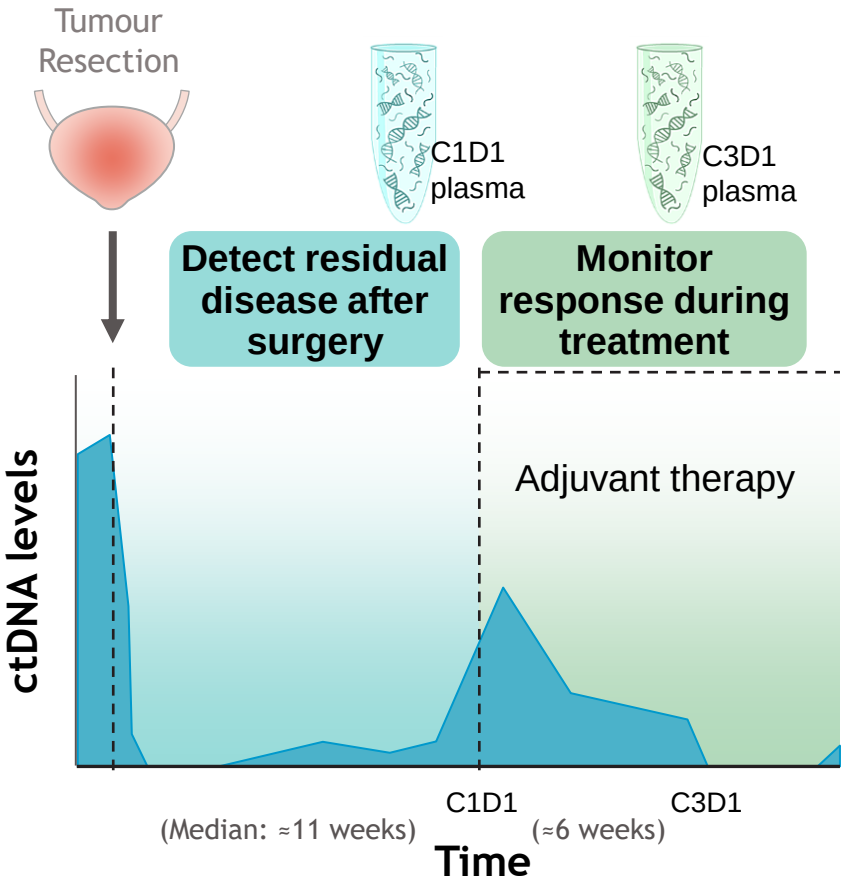
Definition of *uncertainty*

1: the quality or state of being uncertain : DOUBT

2: something that is uncertain

Evaluation of ctDNA





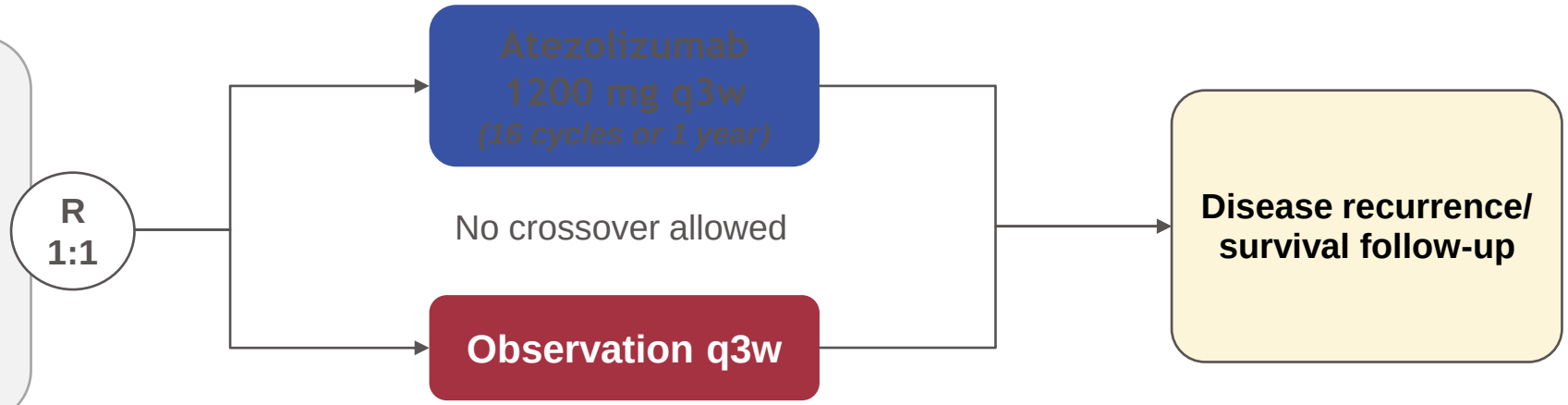
1. Tumour tissue and germline material were sequenced (whole exome sequencing)
2. Up to 16 mutations for personalised mPCR ctDNA assay were identified for each patient
3. Plasma samples were sequenced to ≈100,000×
4. If ≥2 mutations were detected, sample was defined as ctDNA(+)
5. MRD sample timepoint before adjuvant treatment (C1D1) was collected
6. On-treatment sample (C3D1; week 6) was also collected

Powles et al. IMvigor010 ctDNA
https://bit.ly/2IxYllE

Phase 3 IMvigor010 adjuvant study in MIUC

Key eligibility

- High-risk MIUC (bladder or upper tract)
- Radical surgery with lymph node dissection within ≤14 weeks
- Tissue sample for PD-L1 testing



Endpoints

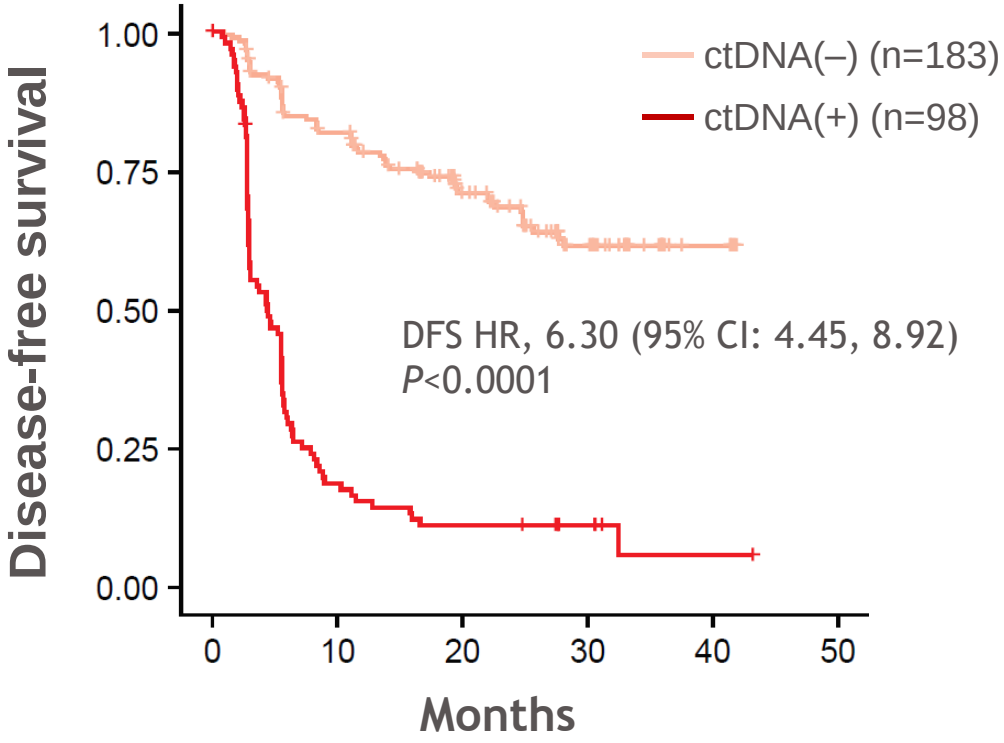
- Primary: DFS (ITT population)
- Key secondary: OS (ITT population)
- Other: Safety
- **Exploratory: predictive, prognostic and pharmacodynamic biomarkers in tumour tissue and blood and their association with disease recurrence**

- IMvigor010 did not meet its primary endpoint (DFS in the ITT population)[1]
  - A pre-planned interim OS analysis was performed but could not be formally tested
  - OS follow-up is immature and ongoing in the ITT population
- The PD-L1 and TMB biomarkers did not identify patients benefitting from atezolizumab vs observation in the ITT population
- A pre-specified ctDNA biomarker analysis was performed

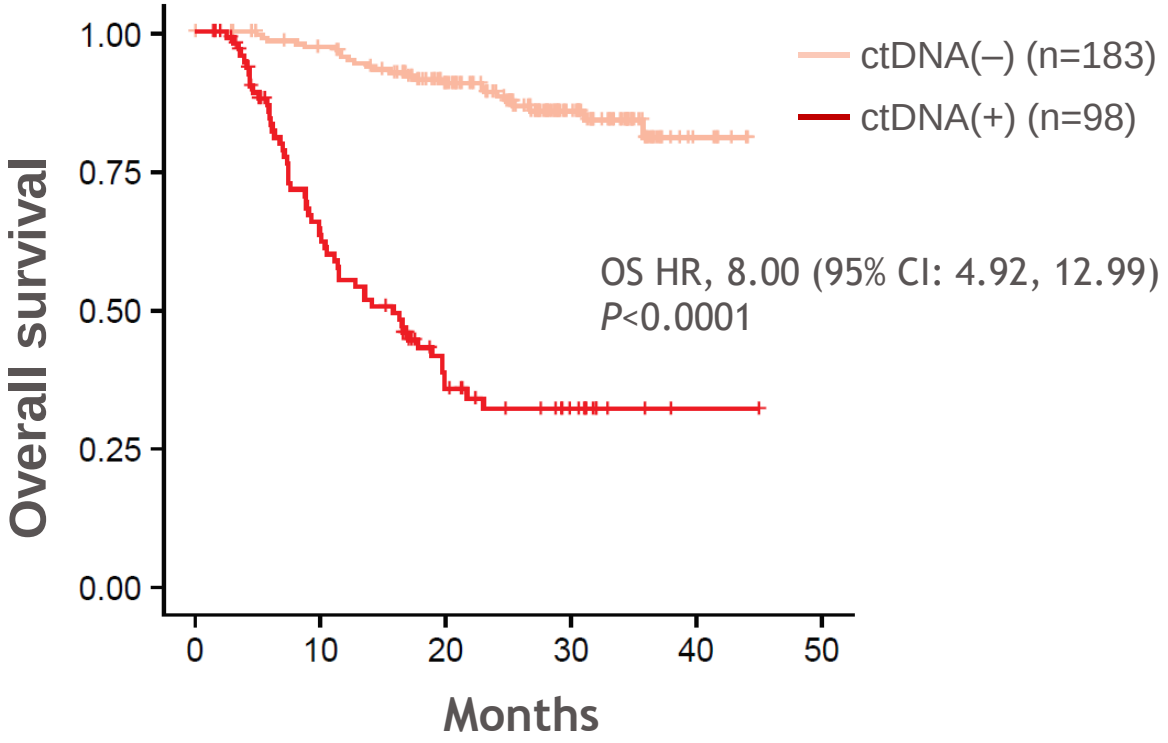
Powles et al. IMvigor010 ctDNA
https://bit.ly/2IxYllE

ctDNA(+) patients have poor prognosis

Observation arm



Observation arm

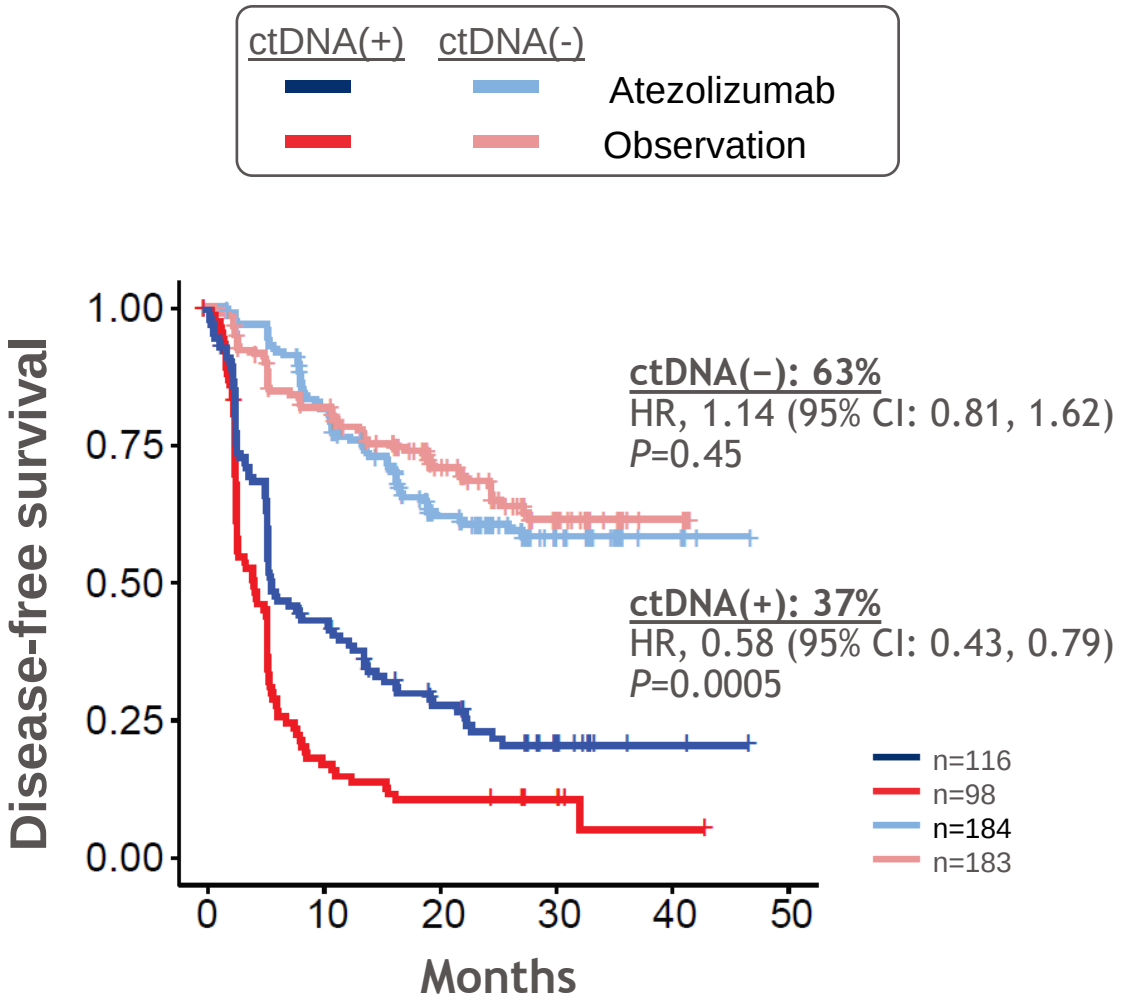


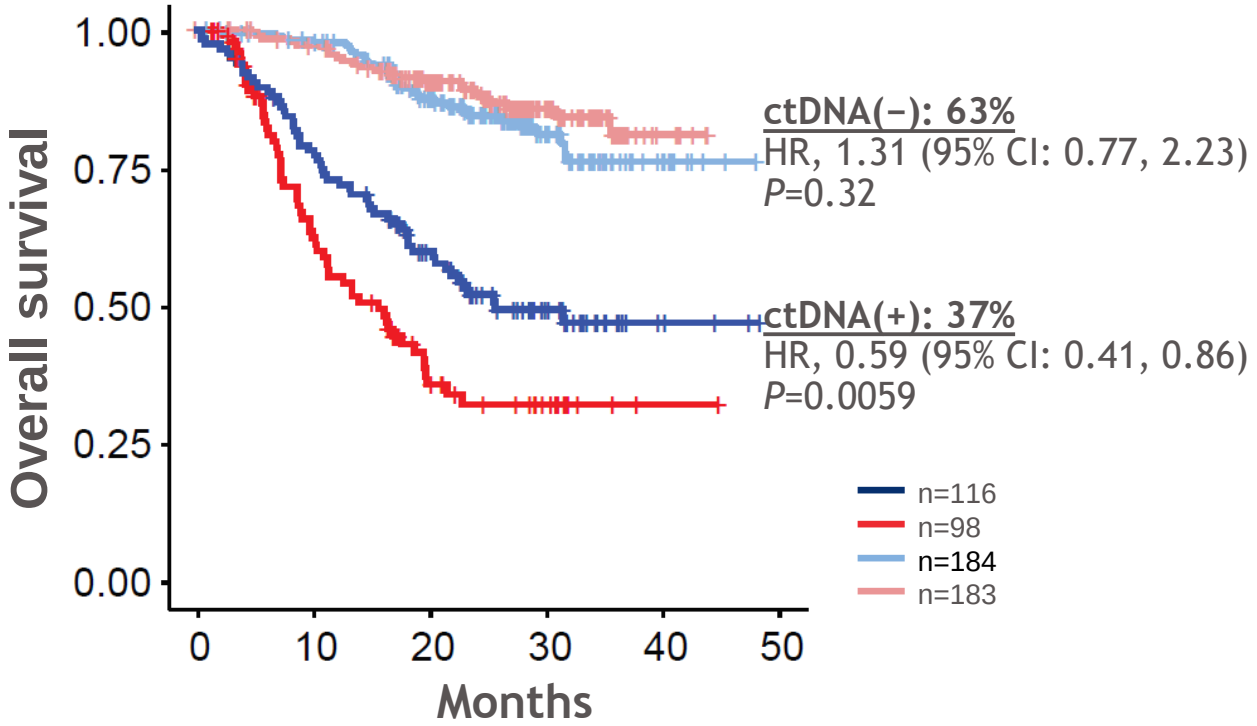
- IMvigor010 confirmed the prognostic value of ctDNA status

Powles et al. IMvigor010 ctDNA
https://bit.ly/2IxYllE

ctDNA(+) patients in the BEP had improved DFS and OS with atezolizumab vs observation

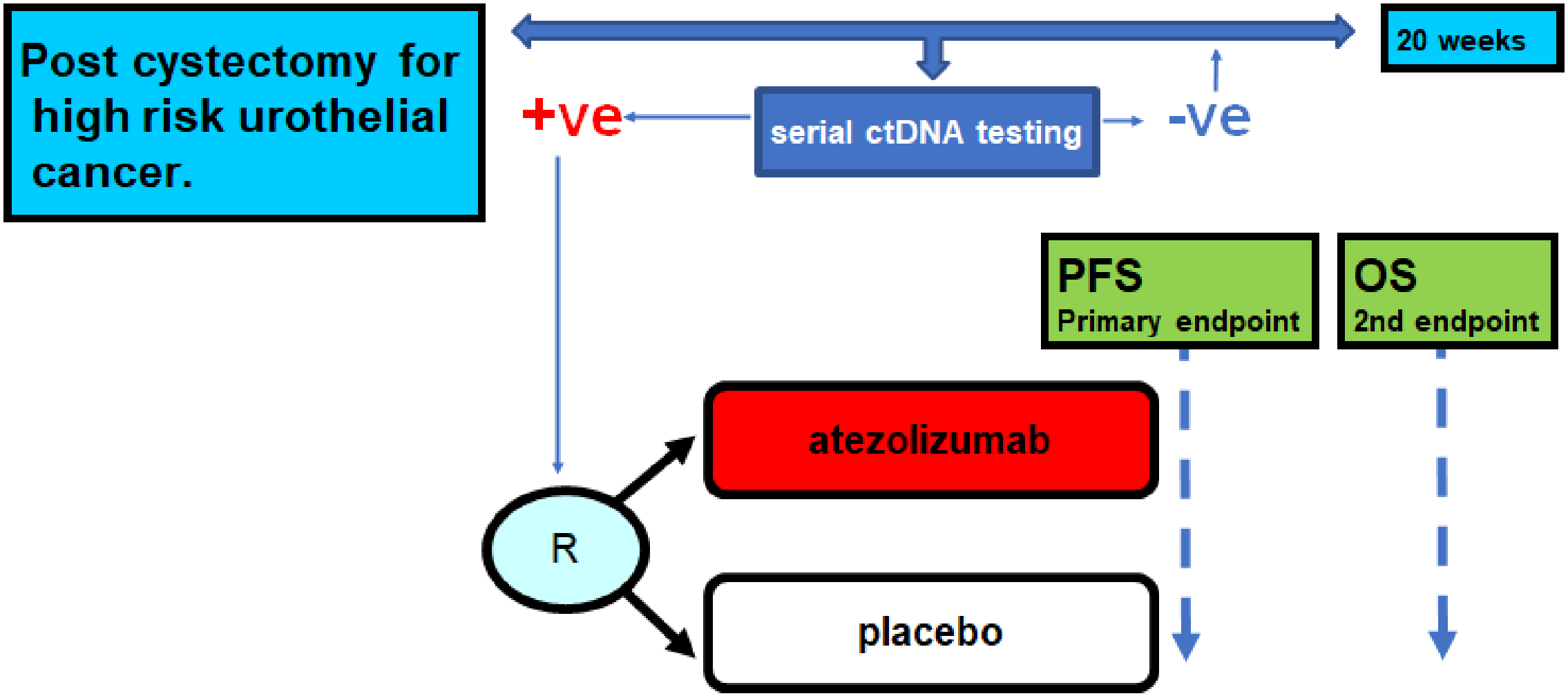
	ctDNA(+) patients	
	Atezolizumab	Observation
Median DFS (95% CI), mo	5.9 (5.6, 11.2)	4.4 (2.9, 5.6)
Median OS (95% CI), mo	25.8 (20.5, NR)	15.8 (10.5, 19.7)



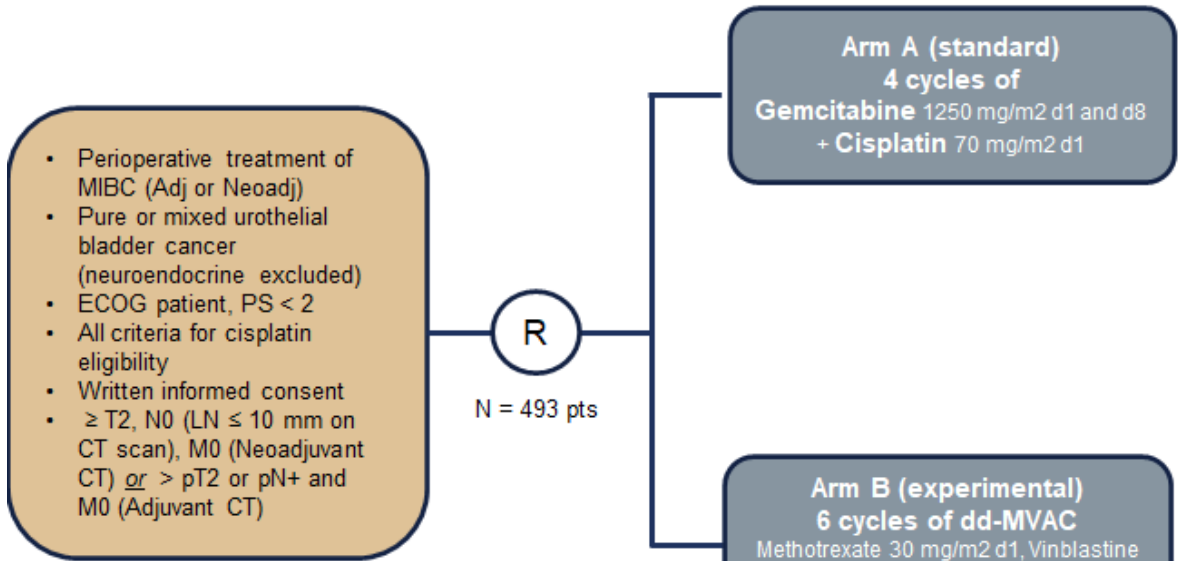


Powles et al. IMvigor010 ctDNA
https://bit.ly/2IxYllE

Adjuvant Atezolizumab vs Placebo in High-Risk Muscle-Invasive Bladder Cancer Who Are ctDNA Positive Following Cystectomy (IMvigor011)



A phase III trial of dd-MVAC or Gemcitabine and Cisplatin as perioperative treatment in muscle-invasive bladder cancer (MIBC). Christian Pfister



- **Primary endpoint: PFS at 3 years**
- **median follow-up 40 months**

Pathological response (neoadjuvant CT +cystectomy performed only)		
	GC	dd-MVAC
ypT0 N0	71 (36%)	84 (42%)

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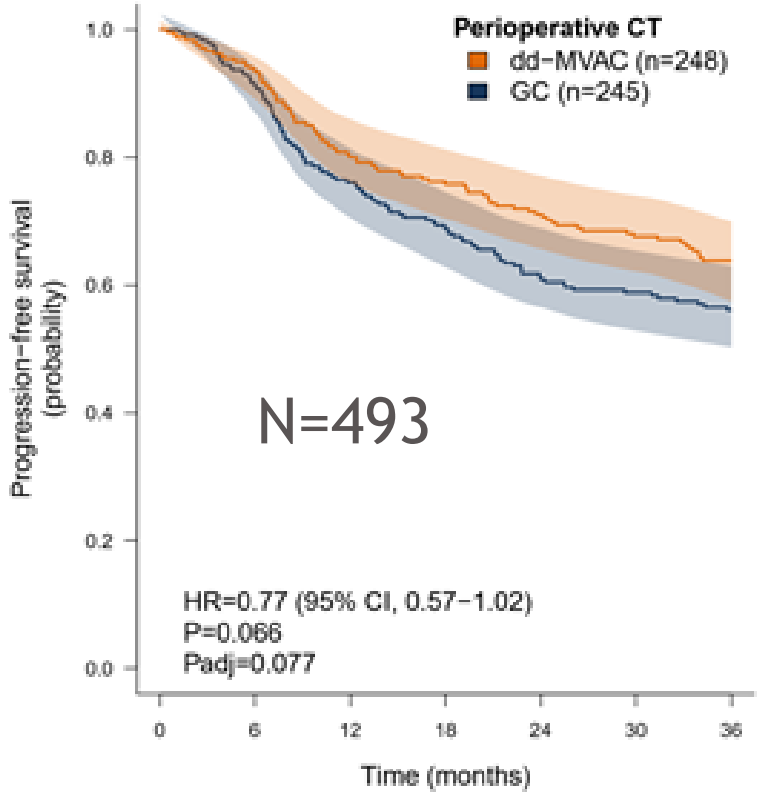

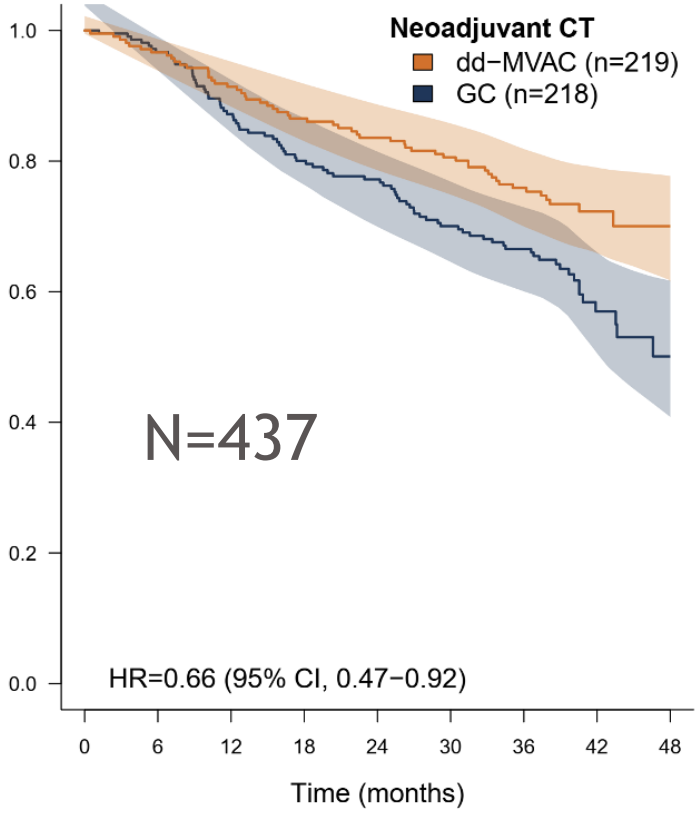

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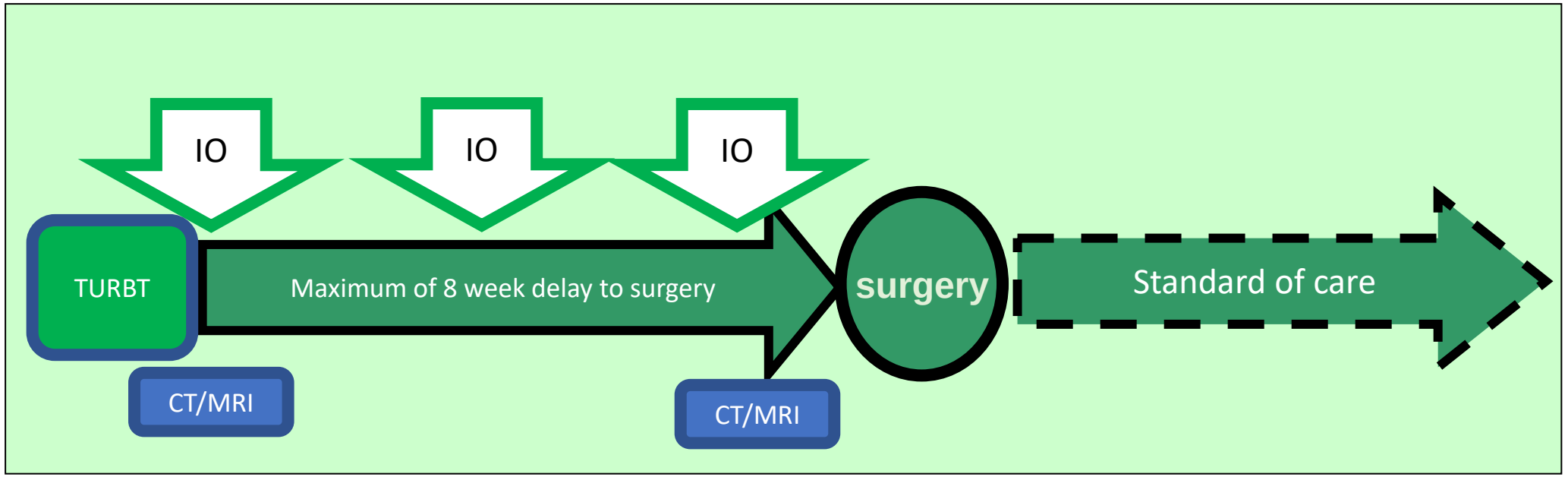
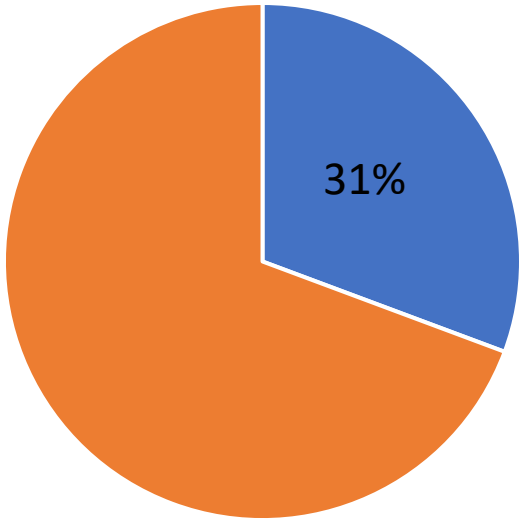
PURE1 and ABACUS : Trial Design

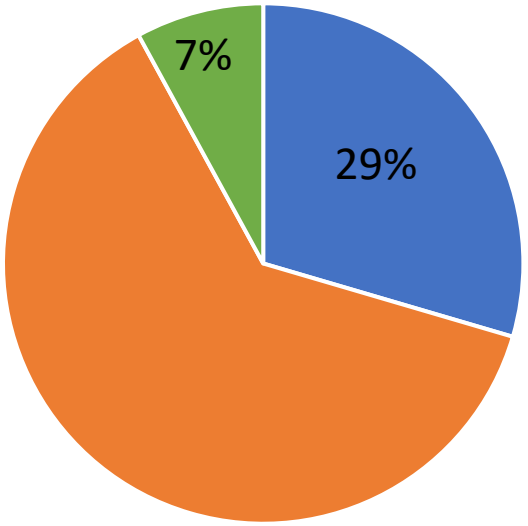


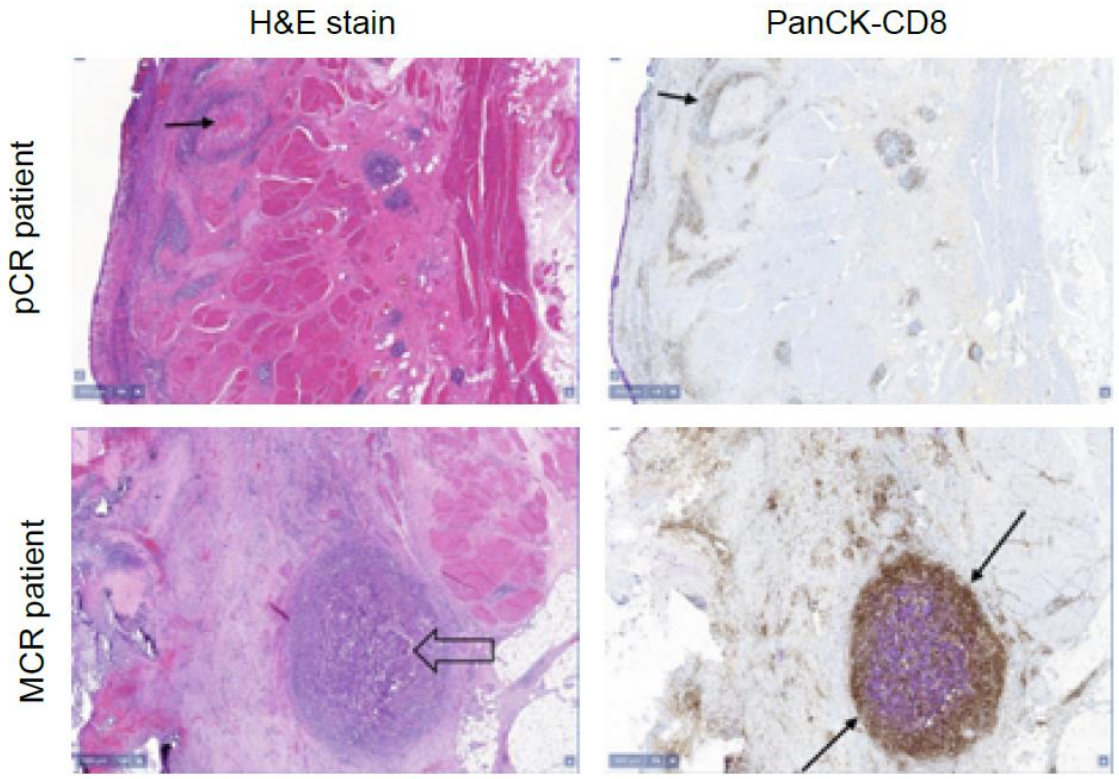
Pathological response rate in Abacus

Investigator assessed response



Central review



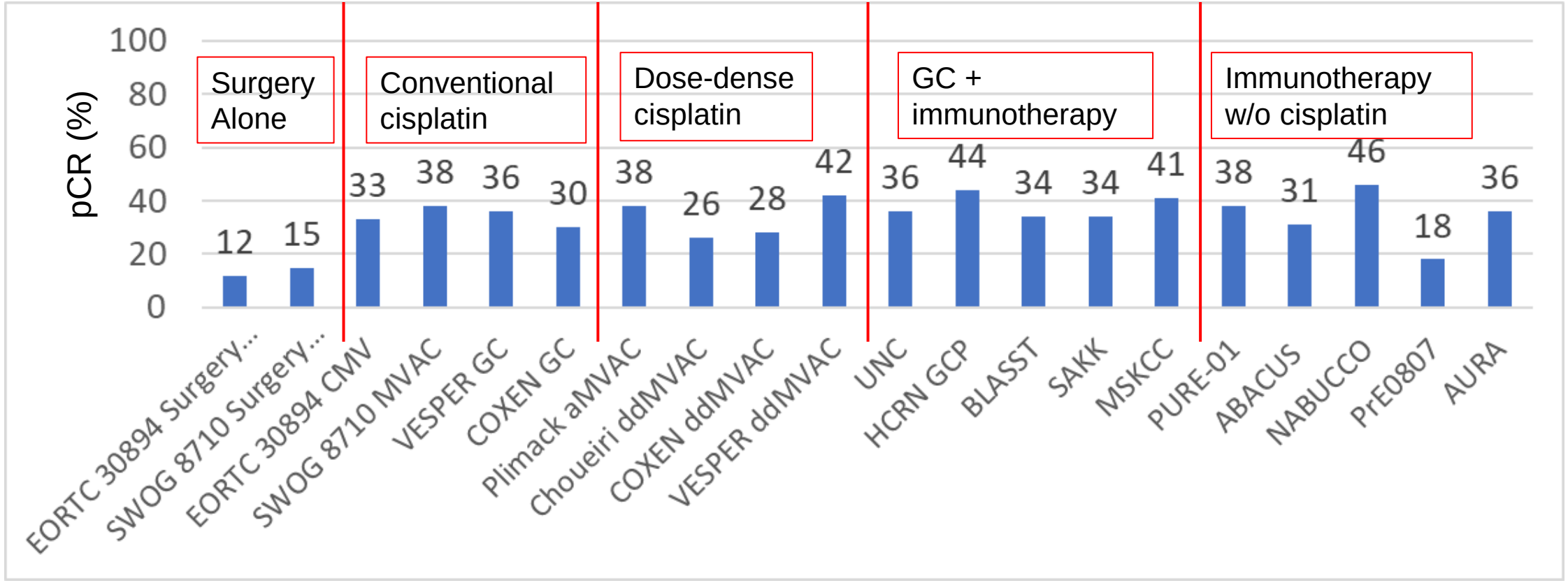


Pathological complete response

Major pathological response (90% necrosis + CD8 infiltration)

Remainder

Immune therapy neoadjuvant trials.



Grossman et al. NEJM 2003
Flaig et al, CCR 2021
Gupta et al, JCO 38,6_supp (Feb 2020).
Necchi et al, JCO 2018
Grivas et al, ASCO Annual Mtg 2021; abstr 4518

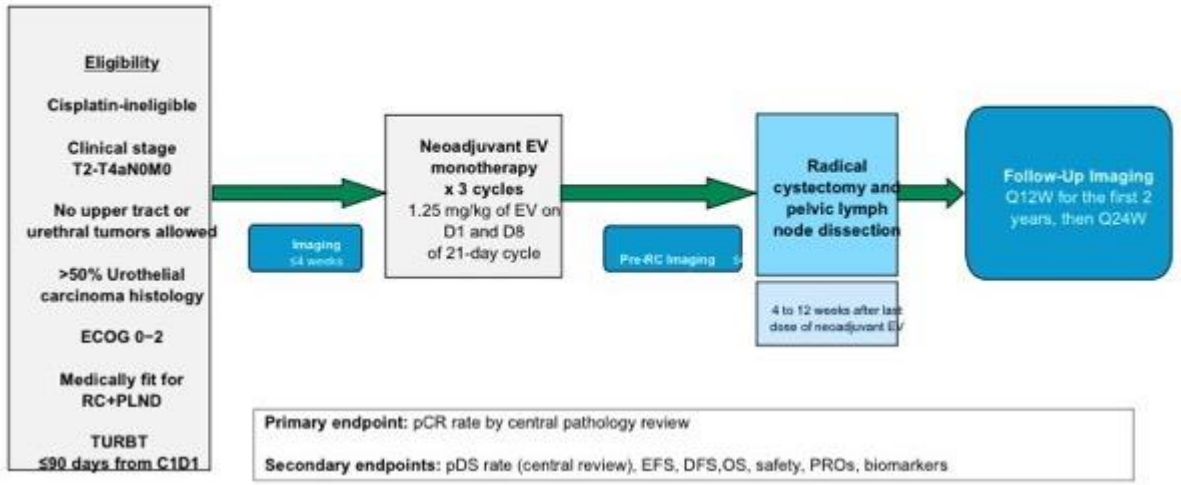
EORTC 30894, JCO 2011
Rose et al, GU ASCO 2021, abstr 396.
Cathomas et al, GU ASCO 2021, abstr 430.
Powles et al, Nat Med 2019
Kaimakliotis et al, ASCO Annual

Pfister et al, Euro Urol 2021
Hoimes et al, ESMO 2018, abstr 5681.
Funt et al, ASCO Annual Meeting, abstr 4517.
Van Dijk et al, ASCO Annual Mtg 2020;abstr 5020

What about DFS and OS endpoint.

	2y PFS/EFS	2y OS
VESPER		
dd-MVAC	~ 77%	~ 88%
GC	~ 62%	~ 79%
SAKK		
GC-D	76%	87%
ABACUS	68%	77%
PURE1	73%	91%

ASCO-GU22 Update: New players



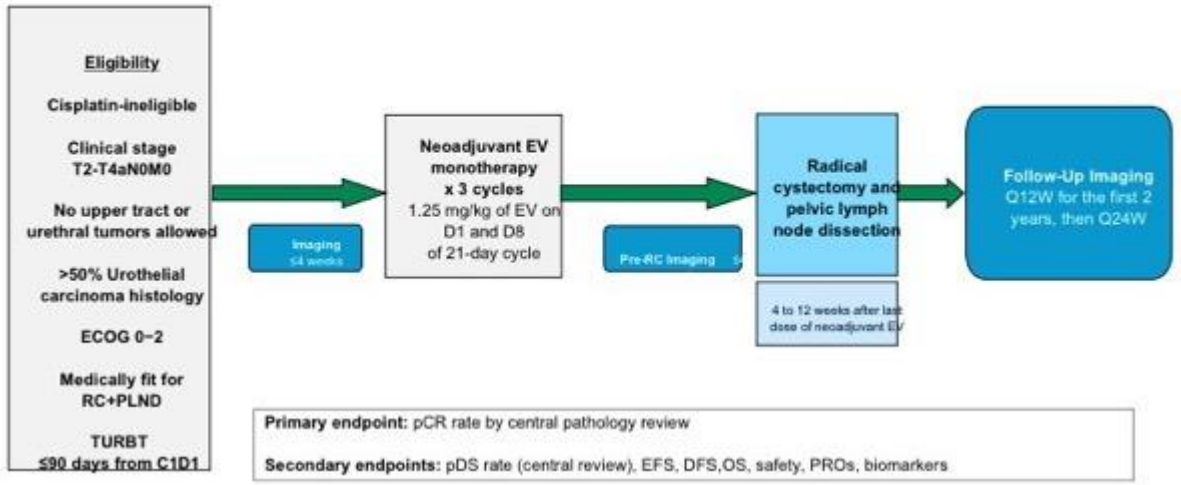
	Cohort H (N=22)
Male sex, n (%)	20 (90.9)
Median age (range), years	74.5 (56–81)
White race, n (%)	22 (100)
Current or former smoker, n (%)	21 (95.5)
Median enrollment time from diagnosis (range), months	1.6 (1–3)
ECOG performance status	
0	13 (59.1)
1	8 (36.4)
2	1 (4.5)
Current stage, n (%)	
cT2N0	15 (68.2)
cT3N0	6 (27.3)
cT4aN0	1 (4.5)
Histology type, n (%)	
Transitional cell carcinoma (TCC) only	15 (68.2)
TCC with squamous differentiation	3 (13.6)

#GU22TCC

Pathological Response	Central Pathology Results (N=22) n (%) [95% Confidence Interval]
Pathological Complete Response Rate (defined as absence of any viable tumor tissue: ypT0 and N0)	**8 (36.4%)** [17.2–59.3]
Pathological Downstaging Rate (defined as presence of ypT0, ypTis, ypTa, ypT1, and N0)	**11 (50.0%)** [28.2–71.8]

Petrylak DP, et al. *J Clin Oncol*. 40, 2022 (suppl 6; abstr 435)

ASCO-GU22 Update: New players



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Enfortumab vedotin
Pembrolizumab

T2-4a MIBC
Cisplatin ineligible
Cispaltin refusing

Petrylak DP, et al. *J Clin Oncol.* 40, 2022 (suppl 6; abstr 435)

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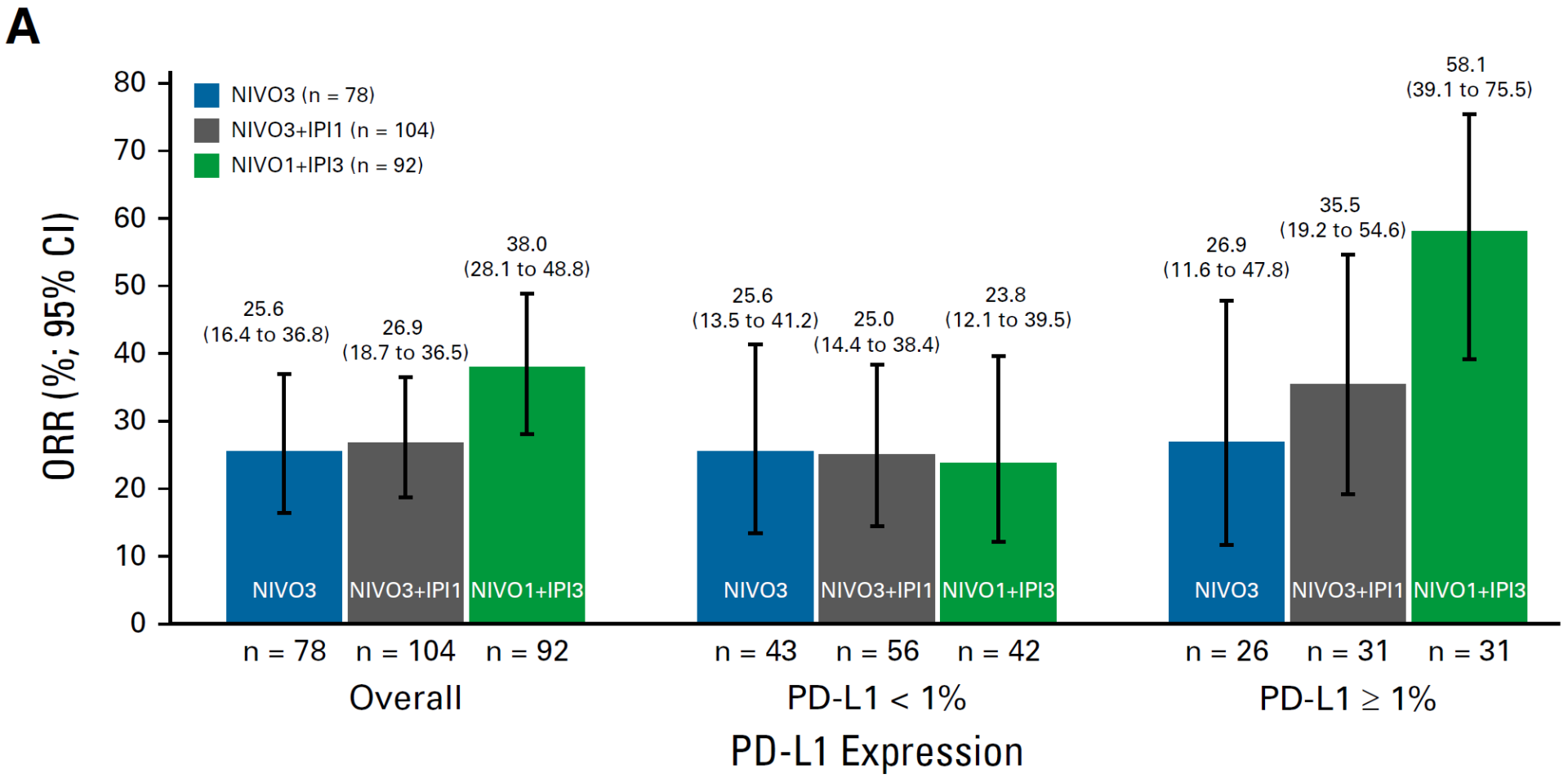
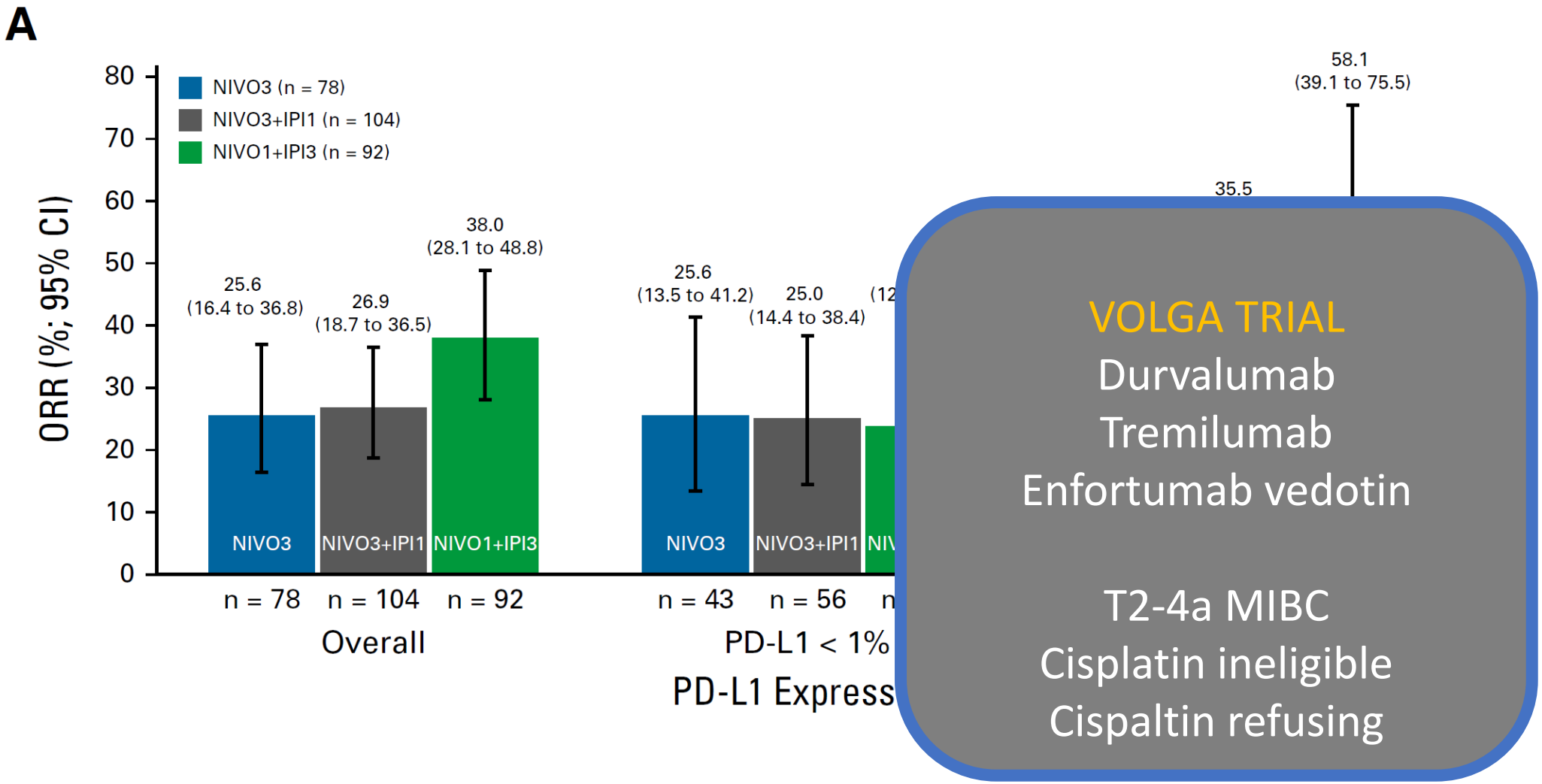


Non randomised study for nivolumab and ipilimumab combinations in platinum refractory UC showing good outcome for the PD-L1+ve with Ipi3 nivo1



VOLGA TRIAL

Durvalumab

Tremilumab

Enfortumab vedotin

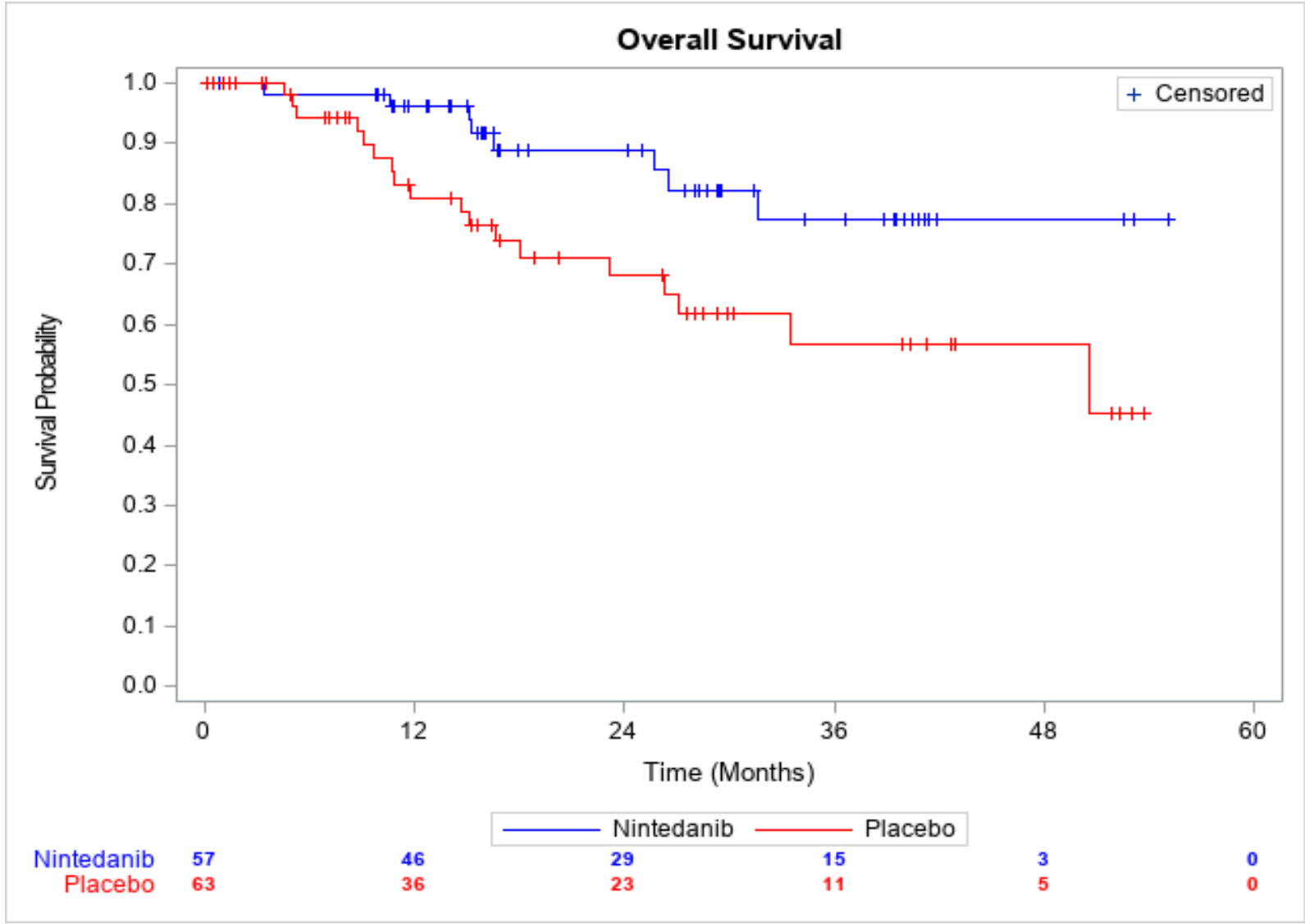
T2-4a MIBC

Cisplatin ineligible

Cispaltin refusing

Randomised phase II of Nintedanib +/- Gemcitabine/Cisplatin in muscle invasive bladder cancer

- 24 month OS
  - Placebo: 69%
  - Nintedanib: 89%
- Hazard Ratio:
- **0.38 (0.16, 0.87); P=0.018**



Prof. Syed A Hussain Lancet Oncol 22

Perioperative trials fall in 4 broad groups.

Adjuvant therapy in unselected patients

- Atezolizumab
- Pembrolizumab
- Nivolumab

Adjuvant therapy in selected patients

- ctDNA to select for atezolizumab

Neoadjuvant therapy in cisplatin eligible patients

- Gemcitabline cisplatin + durvalumab
- Gemcitabline cisplatin + Pembrolizumab
- Enfortumab Vediton + pembrolizumab
- Gemcitabine + nivolumab + IDO

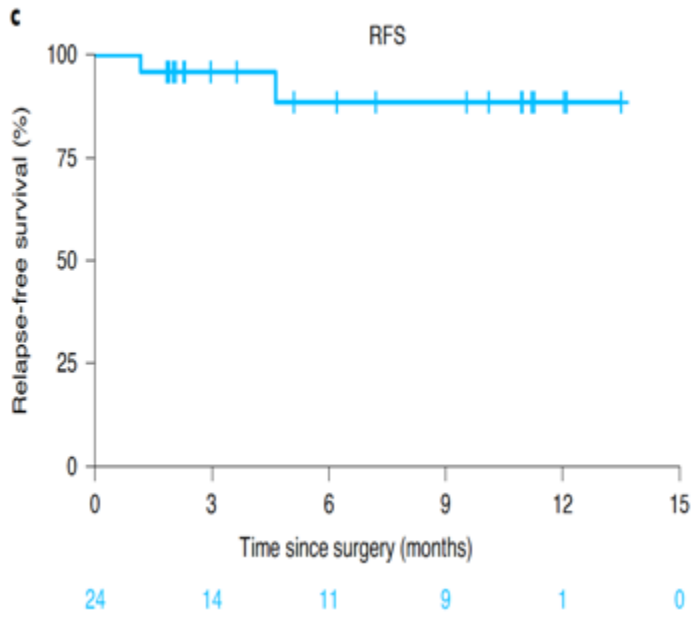
Neoadjuvant therapy in cisplatin ineligible/refusing patients

- Pembrolizumab
- Pembrolizumab + EV
- Durvalumab EV
- Durvalumab tremilimumab EV

Are a few immunotherapy courses able to control the disease?

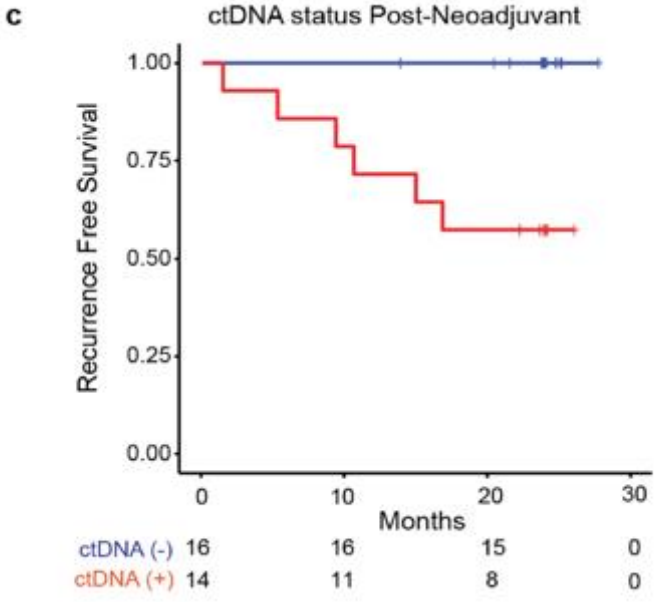
Survival after short-course neoadjuvant IO and radical cystectomy

NABUCCO[1]
Ipilimumab/Nivolumab



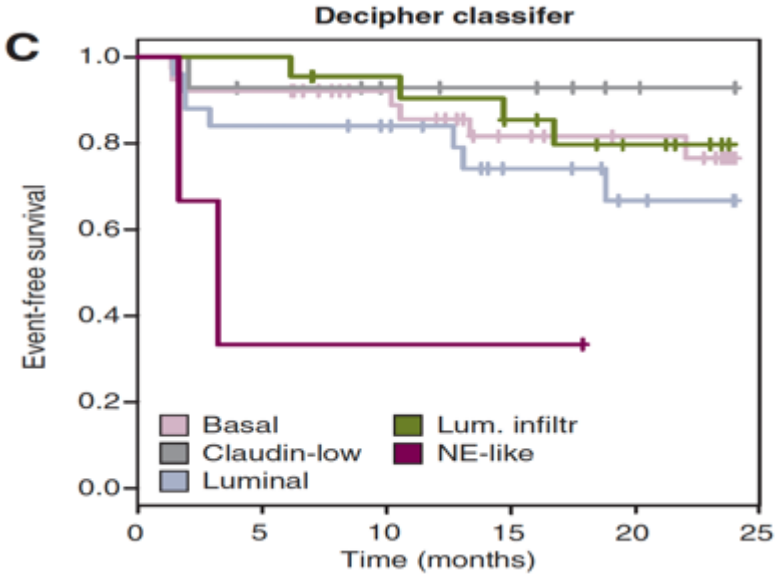
Biomarker-unselected patients!

ABACUS[2]
Atezolizumab



ctDNA(-) patients

PURE-01[3]
Pembrolizumab

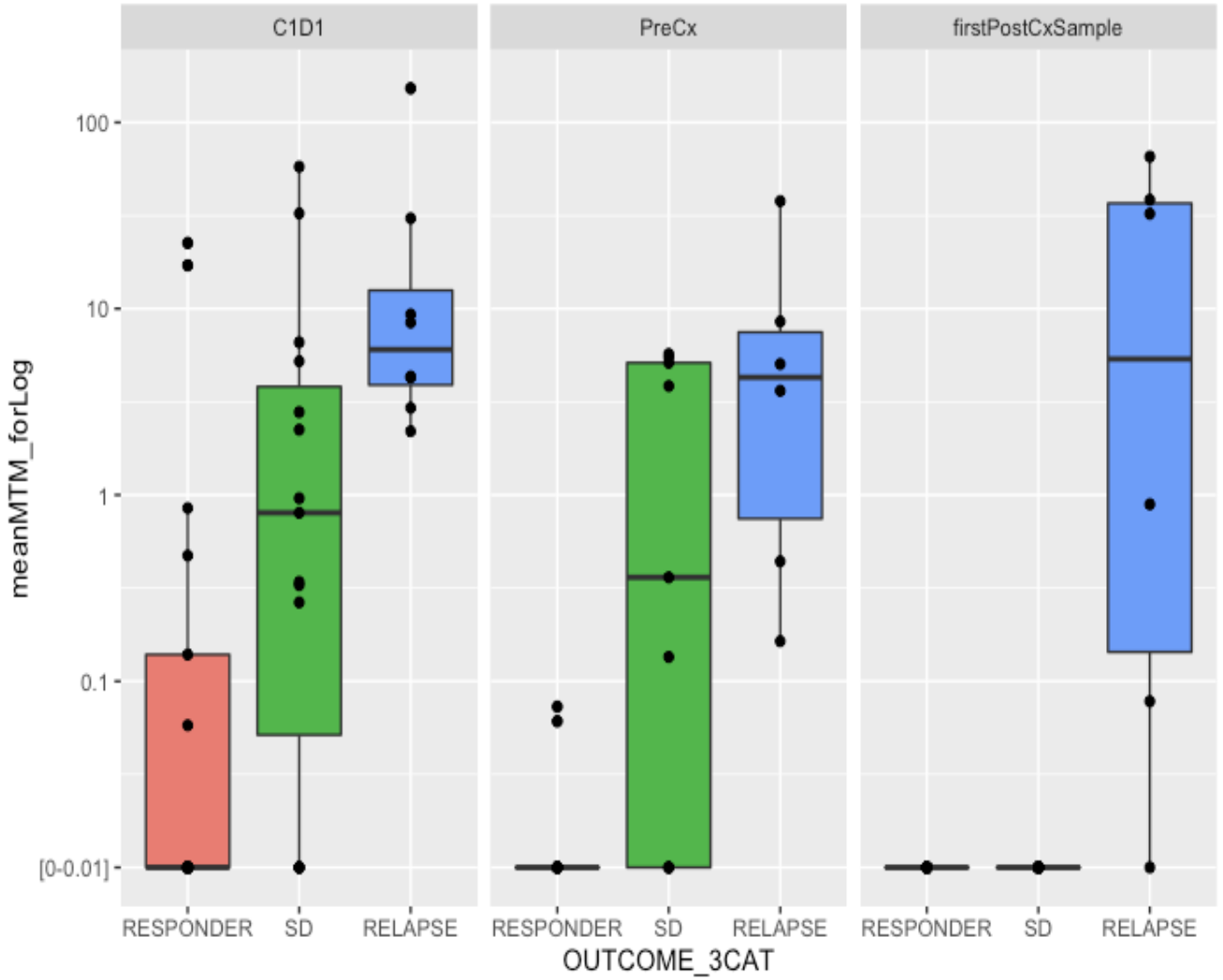


Claudin-Low tumors on TURBT

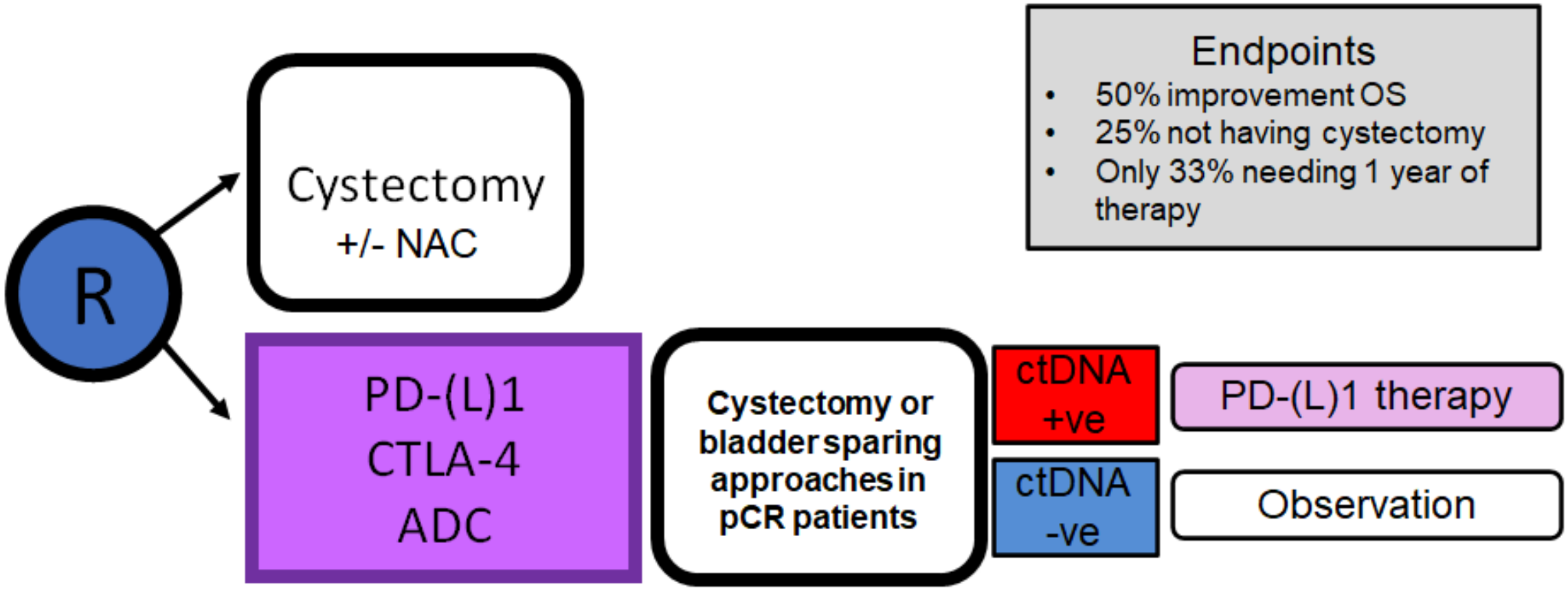
1. Van Dijk N, et al. *Nat Med*. 2020 Oct 12. doi: 10.1038/s41591-020-1085-z. 2. Powles T, et al. *Nature*. 2021 Jun 16. doi: 10.1038/s41586-021-03642-9. Online ahead of print. 3. Bandini M, et al. *Ann Oncol*. 2020 Dec;31(12):1755-1763.

ctDNA and outcome during therapy (MTM mean)

Baseline post atezo post surgery



Neoadjuvant trials for the future: Triplet personalized therapy with surgery sparing approaches. How can we do this?



Conclusions

- Neoadjuvant cisplatin based chemotherapy is associated with a survival benefit
- Neoadjuvant immune checkpoint inhibitors holds much promise
- Tissue based biomarker discovery in this setting has not been consistent.
- Circulating biomarkers will advance the field.
- Adjuvant immune therapy and chemotherapy has become confusing
- There are 7 randomized phase III trials for immune therapy in the neoadjuvant setting asking different questions.