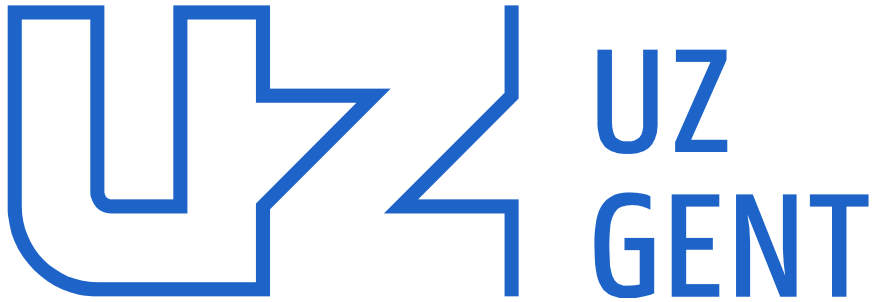

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Department of Medical Oncology UZGent

CPIs in bladder cancer: neo-adjuvant, adjuvant and maintenance

Daan De Maeseneer
Sylvie Rottey

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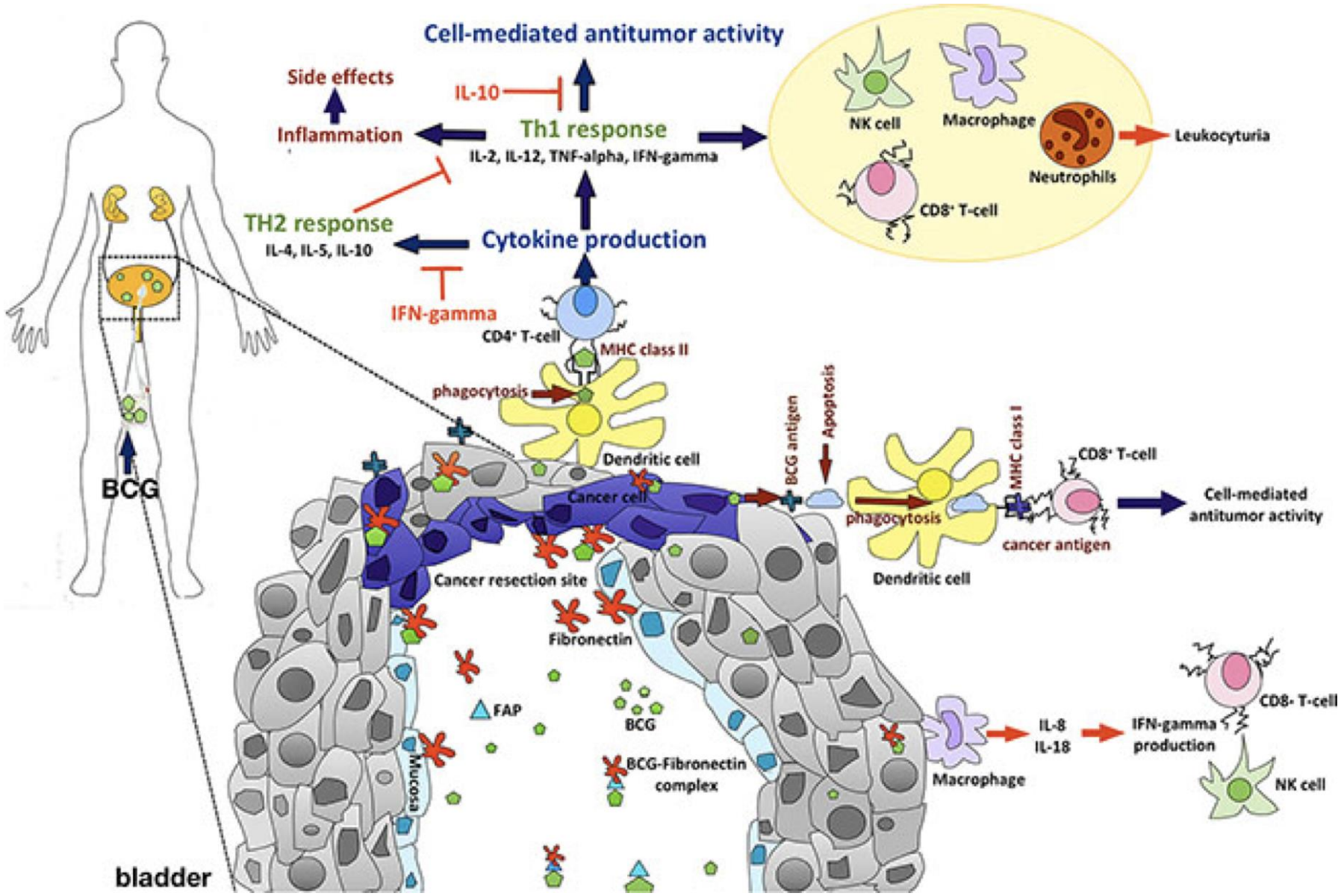
Bladder cancer is an immune responsive disease



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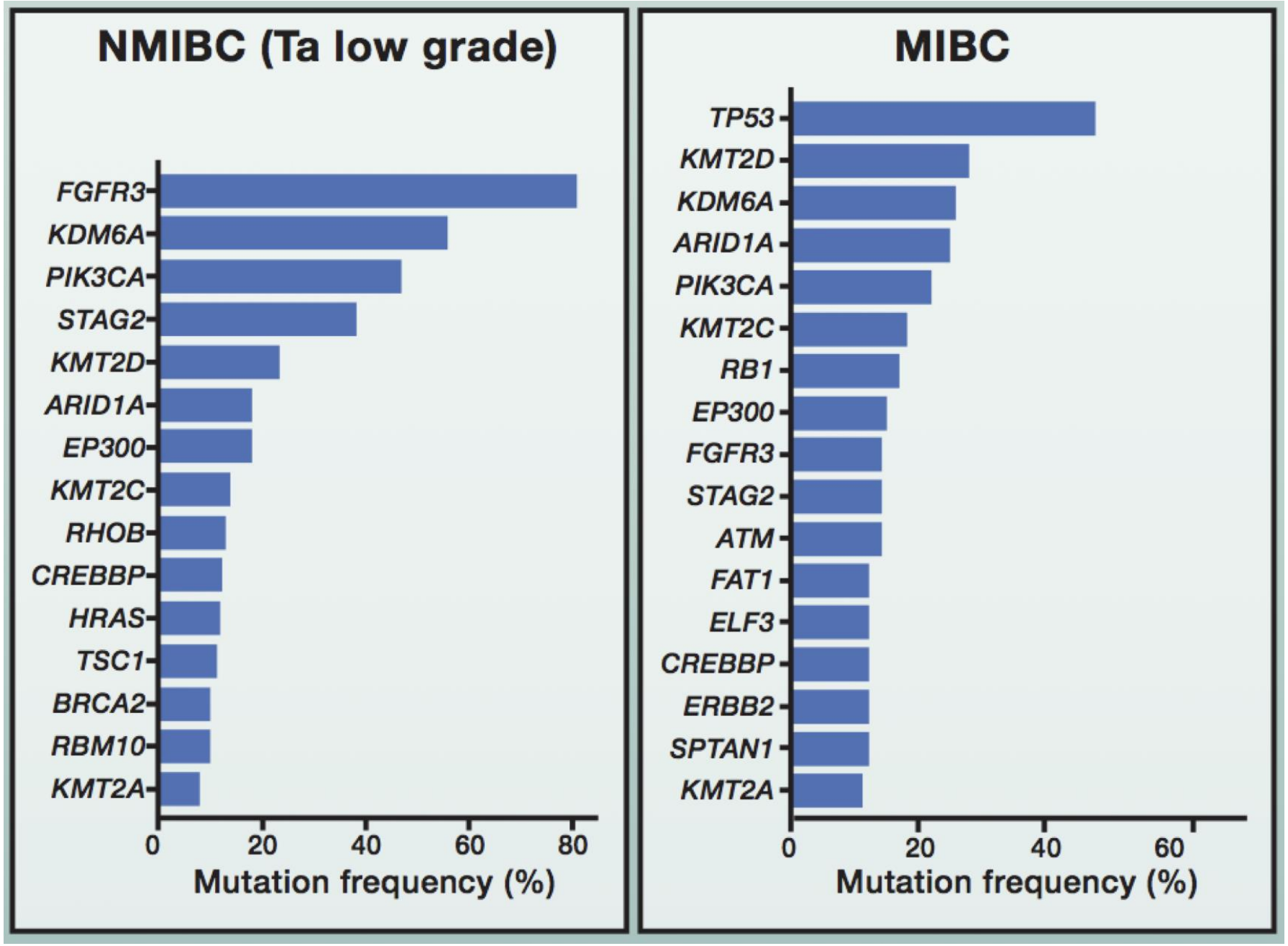
Bladder cancer is an immune responsive disease



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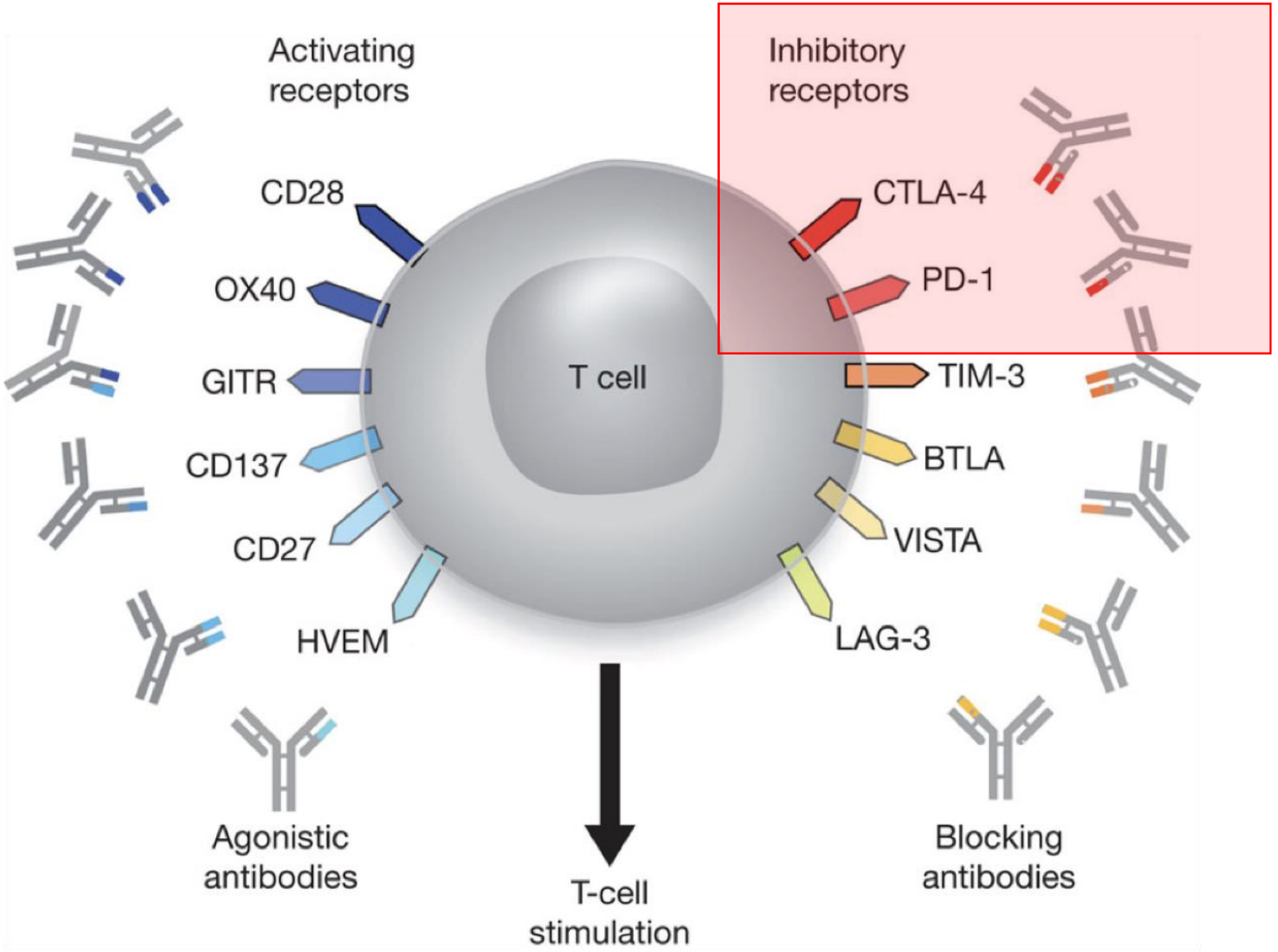
High mutational load from early stage. Hurst et al. Cancer Cell *34*, August 13, 2018

Checkpoint inhibition is effective in bladder cancer

T cell targets for immunoregulatory antibody therapy.



I Mellman *et al. Nature* **480**, 480-489 (2011) doi:10.1038/nature10673

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nature

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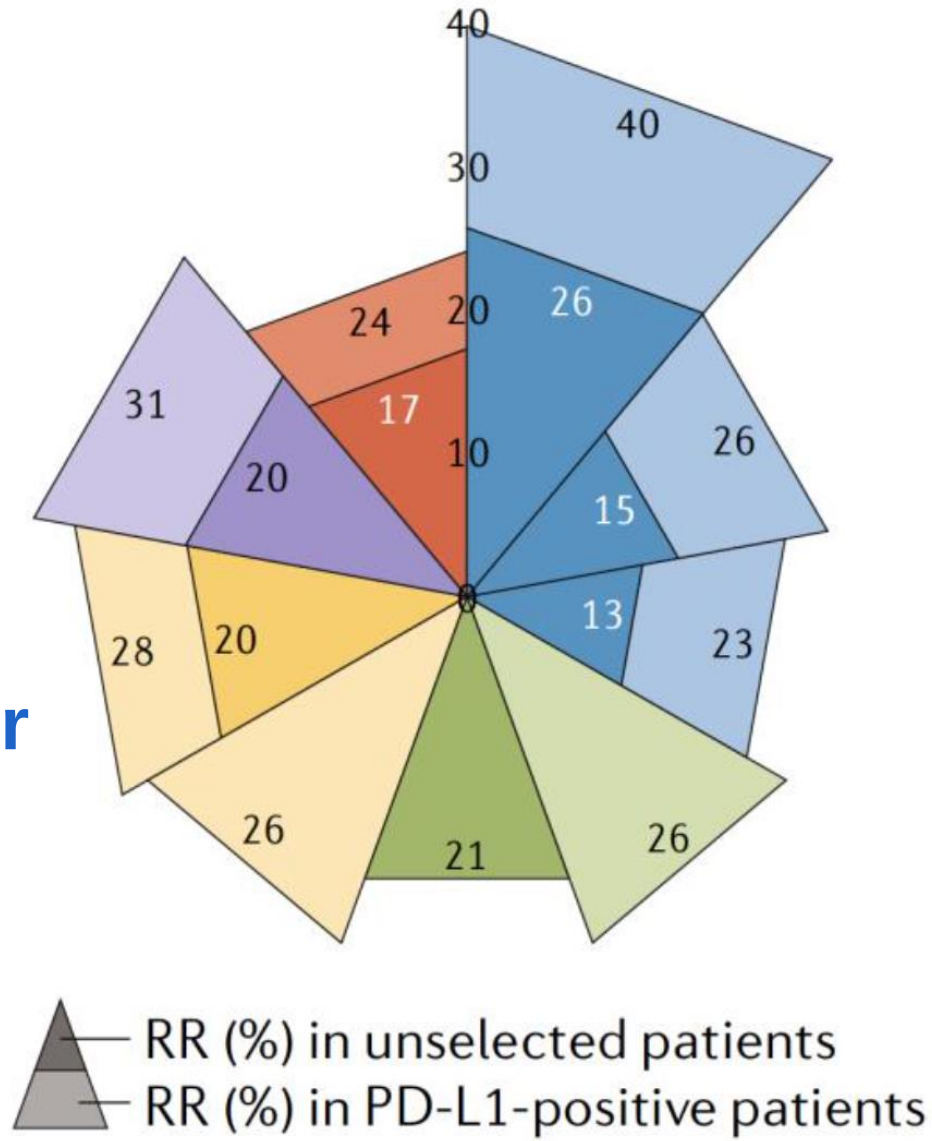
Checkpoint inhibition is effective in bladder cancer



	RR
unselected	13-26%
PD-L1+	23-40%

Powles et al. Nat Rev Urol (2018)

Immunotherapy (IO)	Atezolizumab	Nivolumab	Pembrolizumab	Durvalumab	Avelumab

What is the best sequence in mUCC?

4-6 lines
Platinum

CPI

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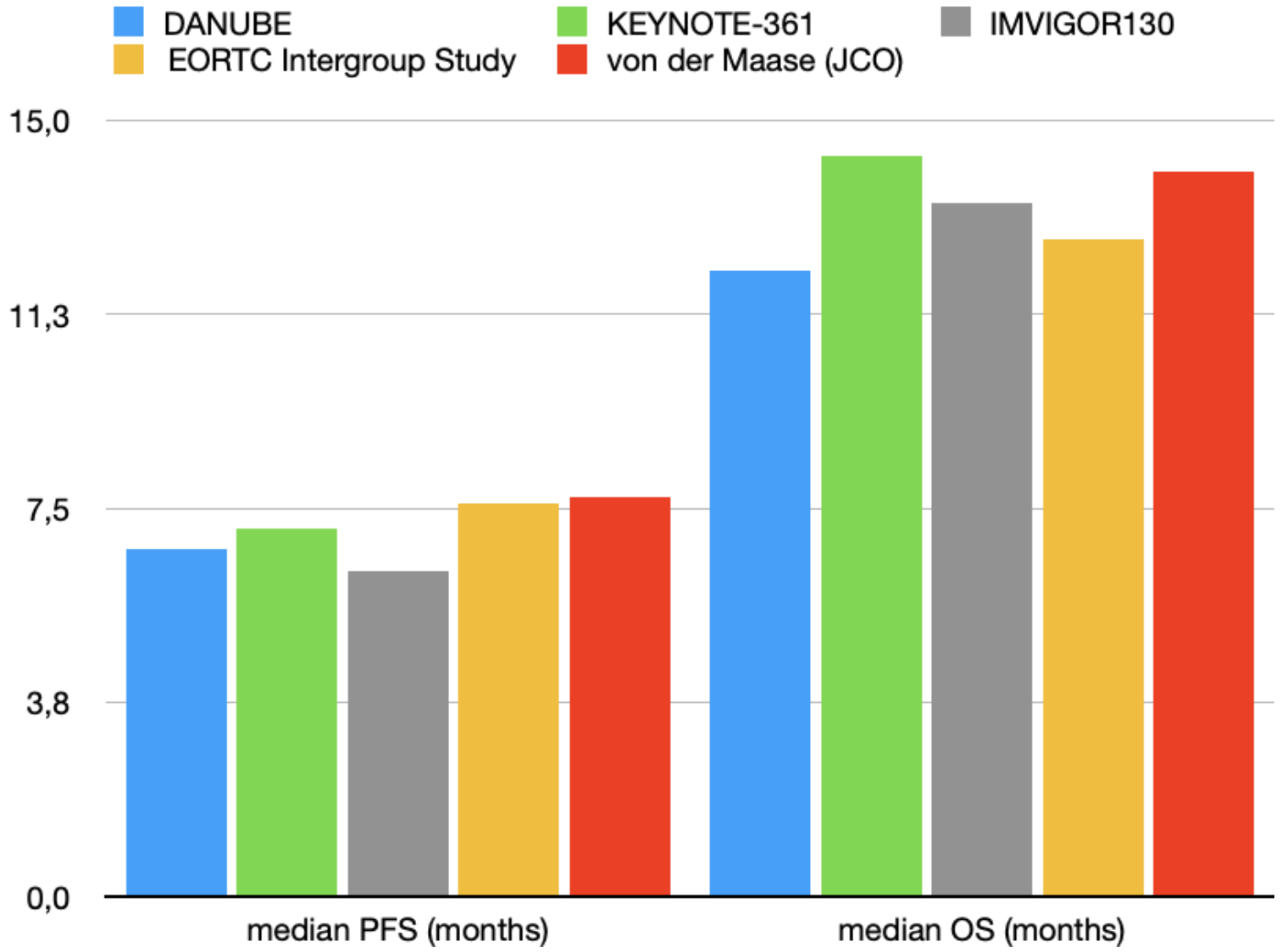
What is the best sequence in mUCC?

4-6 lines
Platinum



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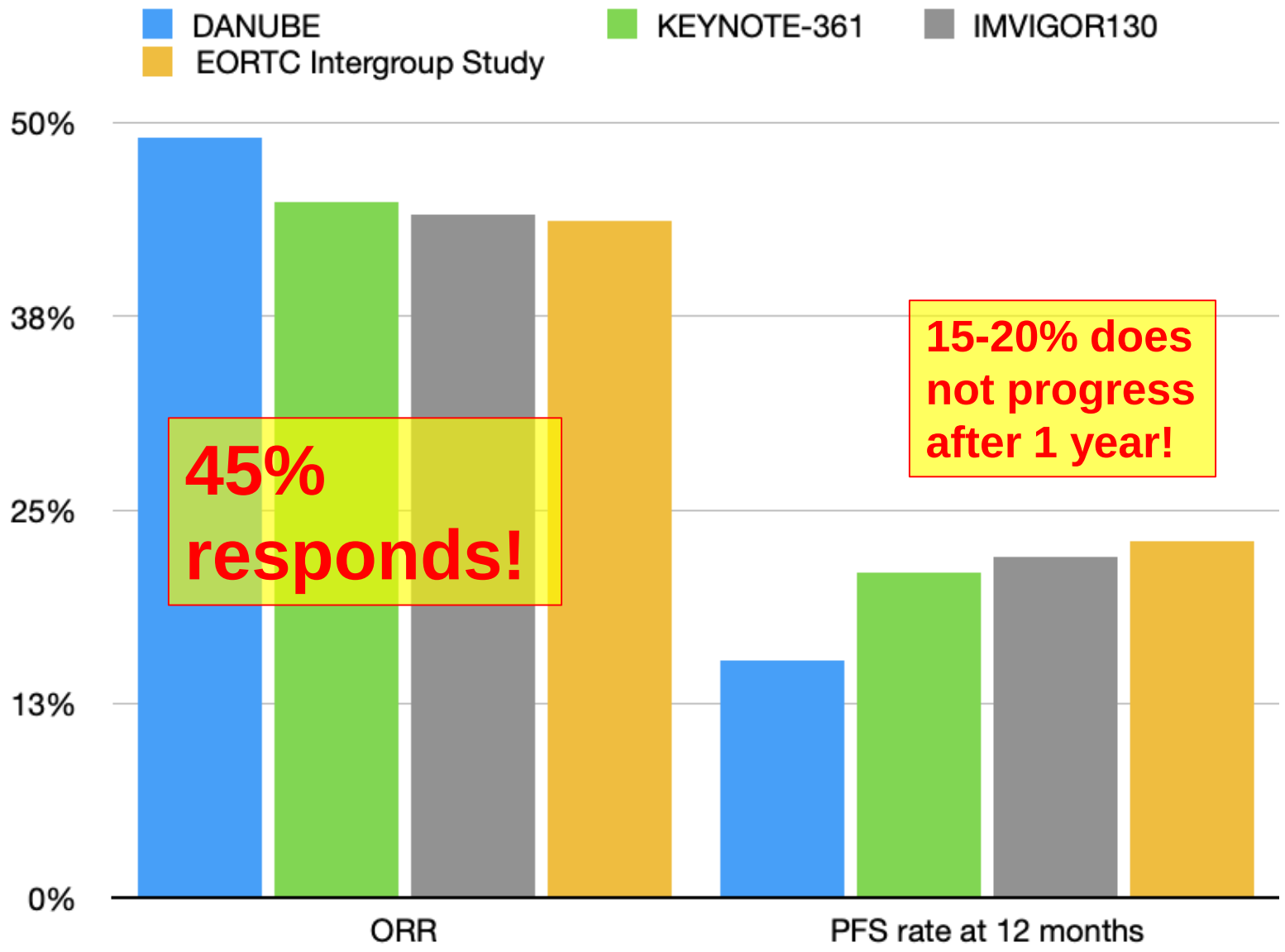
What is the best sequence in mUCC?

4-6 lines
Platinum



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What is the best sequence in mUCC?

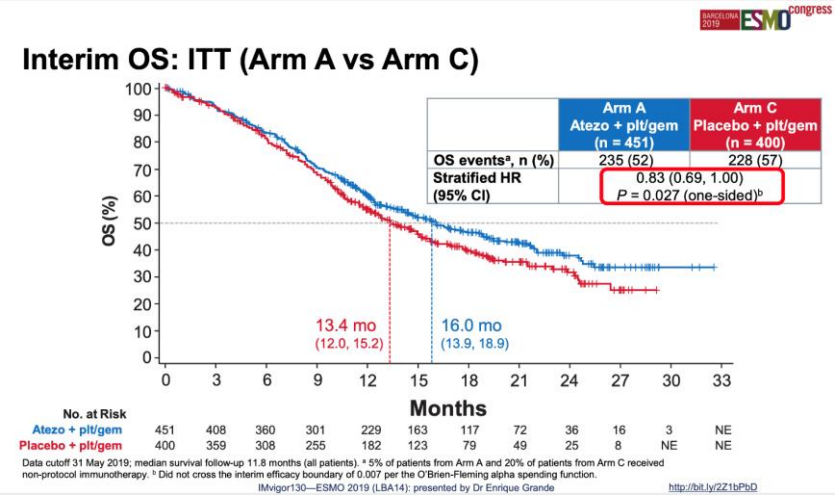
Combination

4-6 lines Platinum

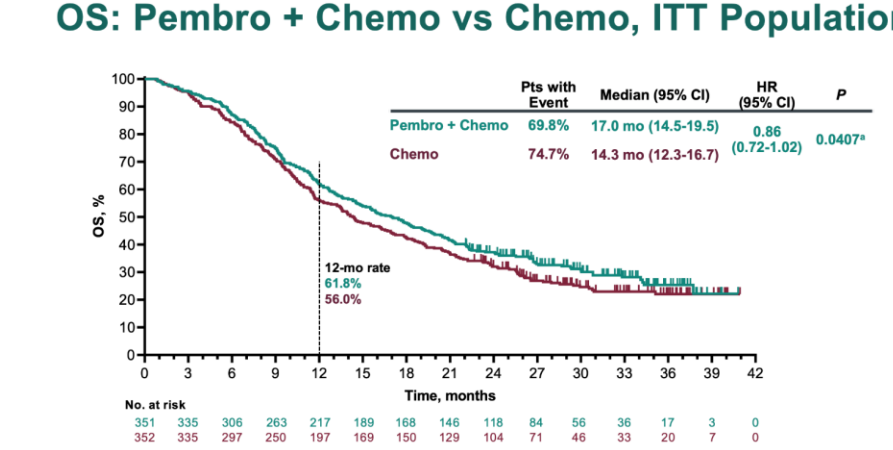
\+

CPI

IMVIGOR130



Keynote361



No survival benefit!

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What is the best sequence in mUCC?

Combination

4-6 lines Platinum

+

CPI

LAST CHANCE !

- CHECKMATE 901: Nivo+Ipi vs Nivo+Pt/Gem vs Pt/Gem
- NILE: Durva+ Pt/Gem vs Durva+Treme+Pt/Gem vs Pt/Gem
- IMVigor 130 : mature data @ ESMO 2021

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What is the best sequence in mUCC?

Sequential

4-6 lines Platinum

PD →

CPI

Pembrolizumab,
Nivolumab,
Atezolizumab,
Durvalumab,
Avelumab

6-7 months PFS

+

10-12 months OS

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10 months Keynote 45 (pembrolizumab)
11.1 months Imvigor211 (atezolizumab)

What is the best sequence in mUCC?

Maintenance

4-6 lines Platinum → CPI

SD or PR/CR

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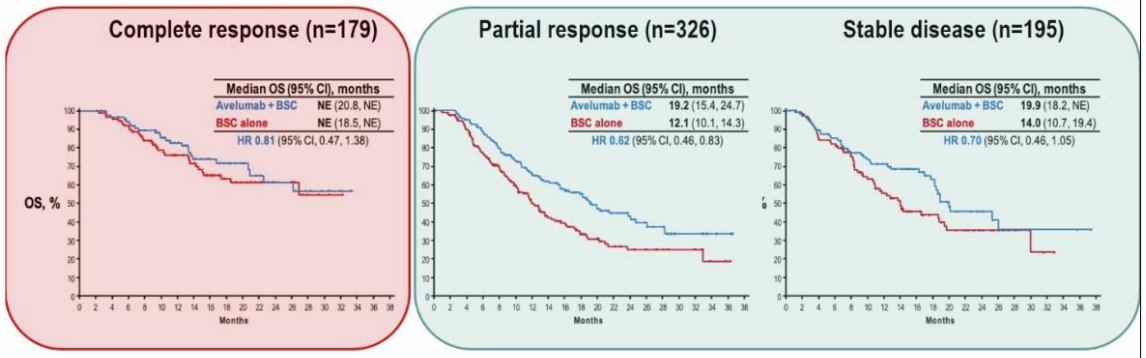
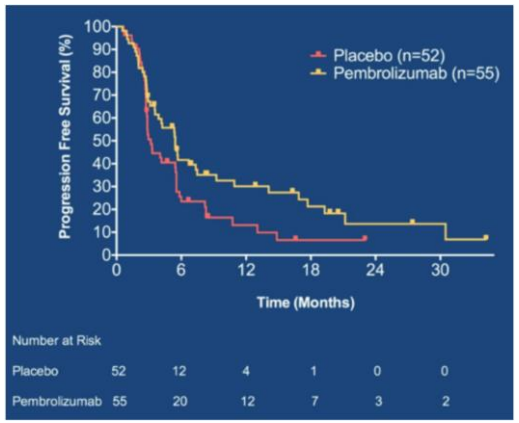
OS by best response to chemotherapy





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21.4 months **Javelin 100** (avelumab)

22 months HCRN GU14 – 182 (pembrolizumab)

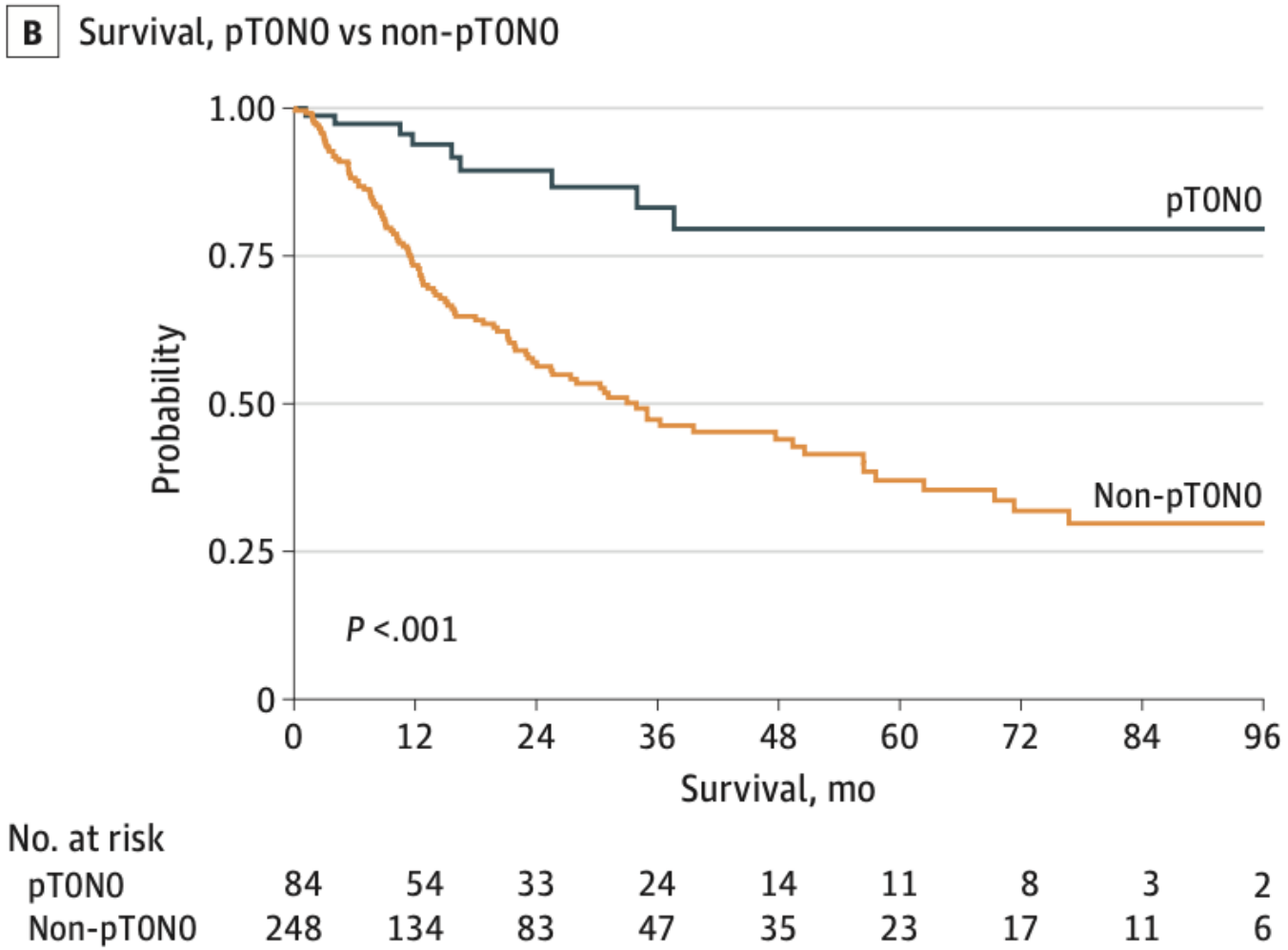
What is the best strategy in first line treatment of mUCC?

- Concomittant therapy is not superior to monotherapy

- **First line cisplatin/carboplatin + gemcitabine has a high response rate (45%), good responders (15-20%) have a long response (>1 year)**

- IO
  - Sequential therapy at progression (2nd line) : good results with long treatment free period for a subset of patients (maybe CR ?)
  - **Maintenance therapy in Pt-responding patients has good results**, but not an option for non-responders and **overtreatment** of a subset of patients is unavoidable
  - A subset of PD-L1 high expressing patients, benefit from IO in first line.

Why adjuvant and neo-adjuvant therapy in MIBC?



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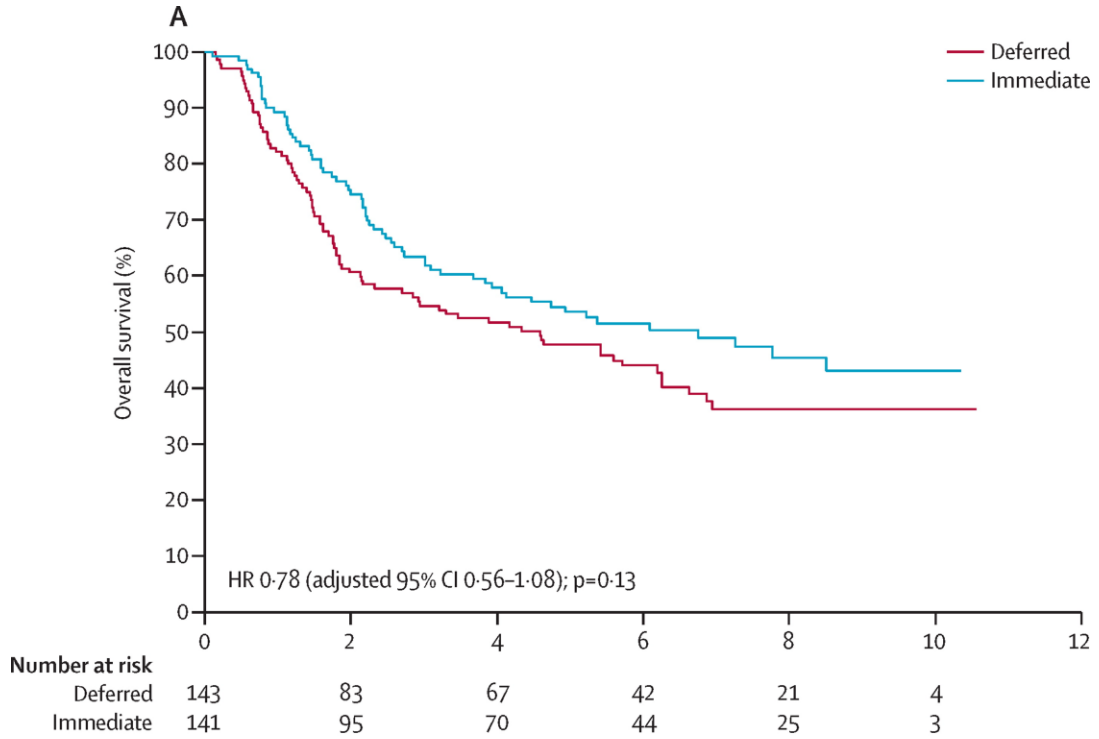
Peyton et al. JAMA Oncol. 2018;4(11):1535-1542

Why adjuvant and neo-adjuvant therapy in MIBC?

EORTC 30994: immediate versus deferred chemotherapy after radical cystectomy in patients with pT3–pT4 or N+ M0 urothelial carcinoma of the bladder: an intergroup, open-label, randomised phase 3 trial



Sternberg et al. Volume 16, Issue 1, January 2015, Pages 76-86

What is the best neo-adjuvant option in MIBC?

4-6 lines
Platinum

VS

CPI

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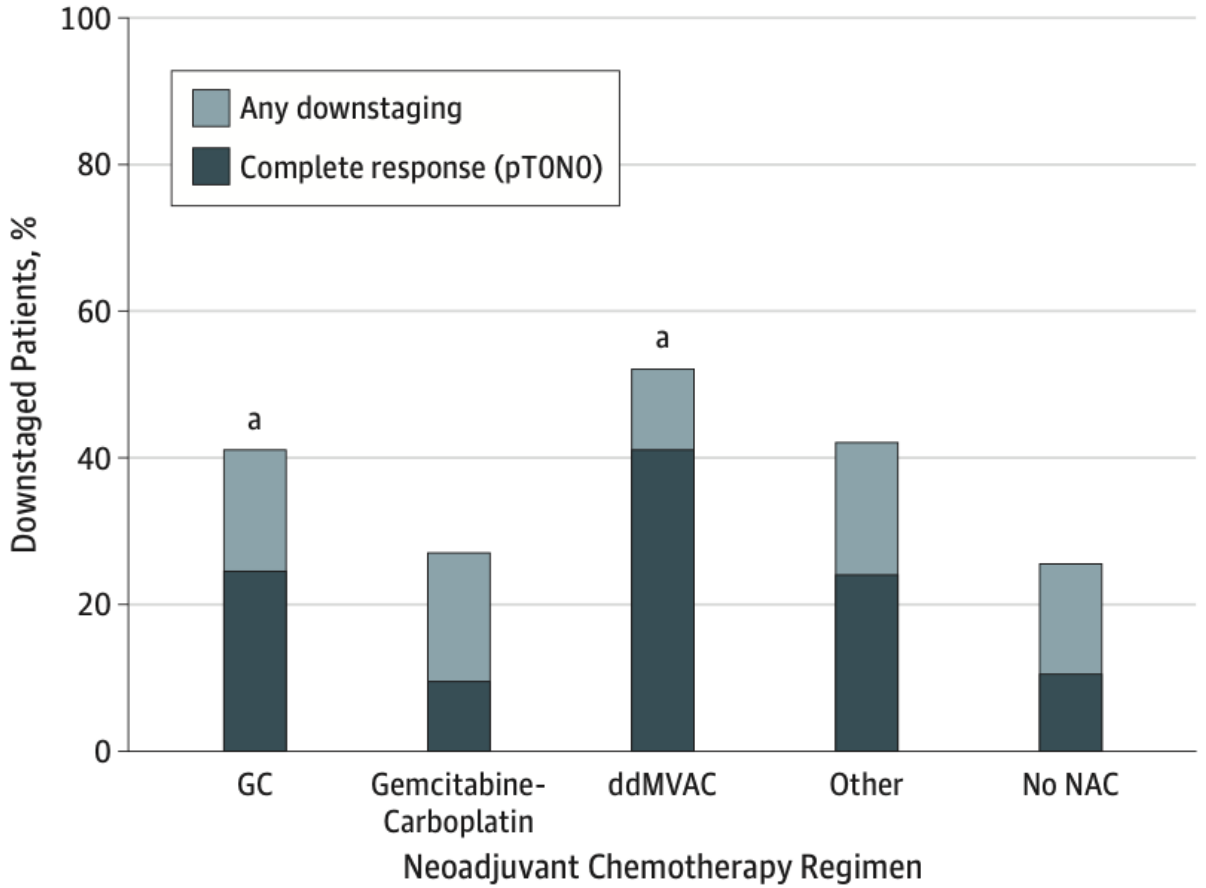
NAC

4-6 lines
Platinum

ddMVAC > Cis/Gem

Figure 2. Downstaging and Complete Pathologic Response (pT0N0) Rates by Neoadjuvant Chemotherapy Group



ddMVAC indicates dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; GC, gemcitabine-cisplatin; and NAC, neoadjuvant chemotherapy.

[a] *P* = .02 for pT0N0 downstaging and *P* = .10 for any downstaging.

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Peyton et al. JAMA Oncol. 2018;4(11):1535-1542

NAC - Limitations

40–67%

of patients with pT3–T4a or lymph node-positive disease relapse after RC alone, with a poor 5-year OS (25–30%)[1,2]

12–13%

of MIBC patients undergoing radical cystectomy receive neoadjuvant chemotherapy, despite current guidelines[3,4]

50%

of patients who receive neoadjuvant chemotherapy have residual high-risk disease (≥pT2) with an associated median survival of 3.4 years[5]

50%

of patients are ineligible for cisplatin-based adjuvant chemotherapy, and there is no standard of care for these patients[5–7]

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1. Gschwend et al. Eur Urol 2002; 2. Shariat et al. J Urol 2006; 3. Burger et al. Eur Urol 2012; 4. Huo et al. Eur Urol Oncol 2019; 5. Dash et al. Cancer 2006; 6. Sonpavde et al. J Urol 2011; 7. Galsky et al. J Clin Oncol 2011

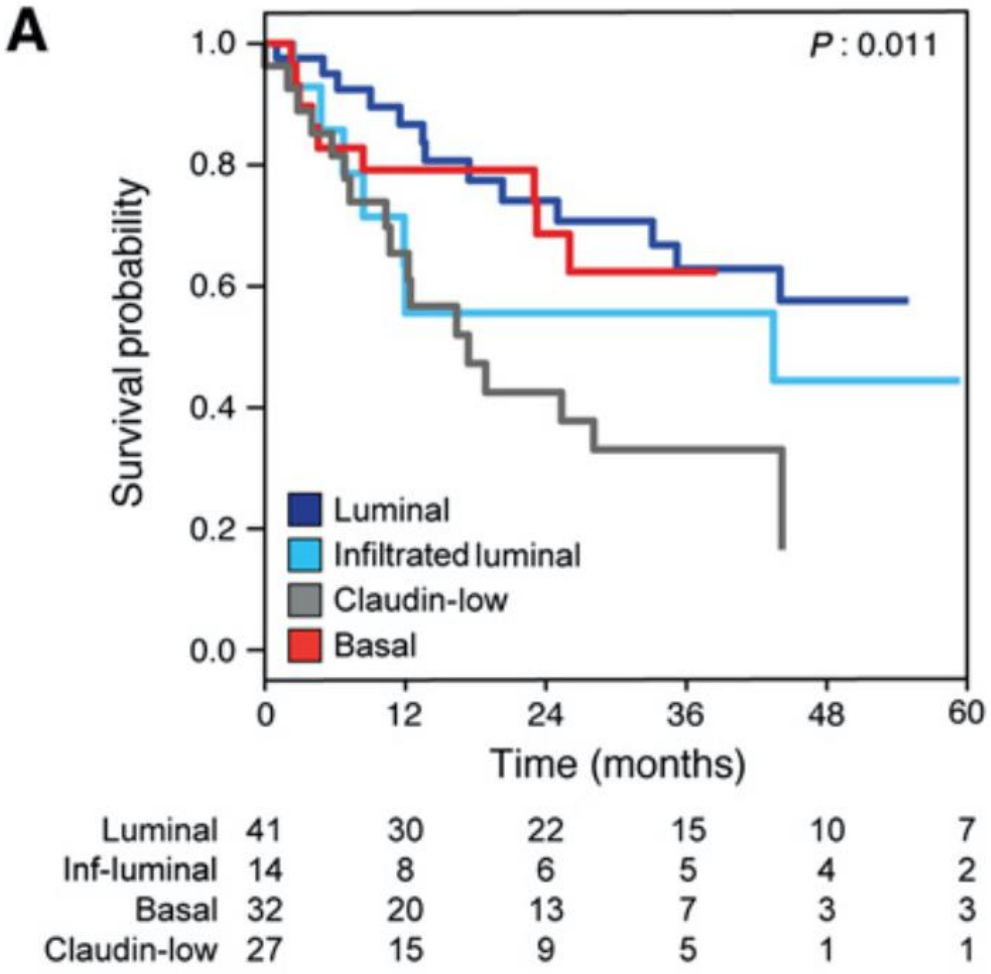
Neoadjuvant checkpoint inhibition in patients with MIBC
- **September 2020 update**

	PURE-01	ABACUS	NABUCCO	HOG GU14-188		BLASST	DUTRENEO
Treatment	**Pembrolizumab**	**Atezolizumab**	**Ipilimumab > Ipi/Nivolumab > Nivo**	**Pembrolizumab-GEM/CIS**	**Pembrolizumab-GEM**	**Nivolumab-GC**	**Durva/Treme**
Reference	[1]	[2]	[3]	[4]	[5]	[6]	[7]
Sample size	114	88	24	43	37	41	23
cT2-stage	54% (CT+mpMRI)	73%	0	47%	43.2	90%	78.2%
cN+ stage	0 (but 6% PET+)	0	42%	0	0	3%	8.7%
pT0N0 rate	**37%**	**31%**	**46%**	**44.4%**	**45.2%**	**34%**	**34.8%**
pT≤1N0 rate	55%		58%	61.1%	51.6%	66%	56.5%
1-y RFS	91% (85-98) [EFS: 87%] [8]	79% (95%CI: 67-87)	92%	2-y: 66%	67%	n.a.	n.a.
Biomarkers	PD-L1+ (TMB) Immune-gene signatures	Pre-existing T-cell activation+ (CD8/GZMB, tGE8-high)	PD-L1+	none	none	Immune-gene signatures	Pre-selected with 18-gene IFN-γ signature

References:

1. Necchi A, et al. *Eur Urol*. 2020;77:439-446; 2. Powles, T, et al. *Nat Med*. 2019;25:1706-1714; 3. van Dijk N, et al. ASCO 2020; 4. Holmes CJ, et al. ASCO 2020; 5. Kaimakliotis HZ, et al. ASCO 2020; 6. Gupta S, et al. GU-ASCO 2020; 7. Grande E, et al. ASCO 2020; 8. Bandini M, et al. *Ann Oncol*. 2020 (Epub ahead of print)

Good biomarkers?



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Seiler et al. Clin Cancer Res; 25(16) August 15, 2019

Good biomarkers?

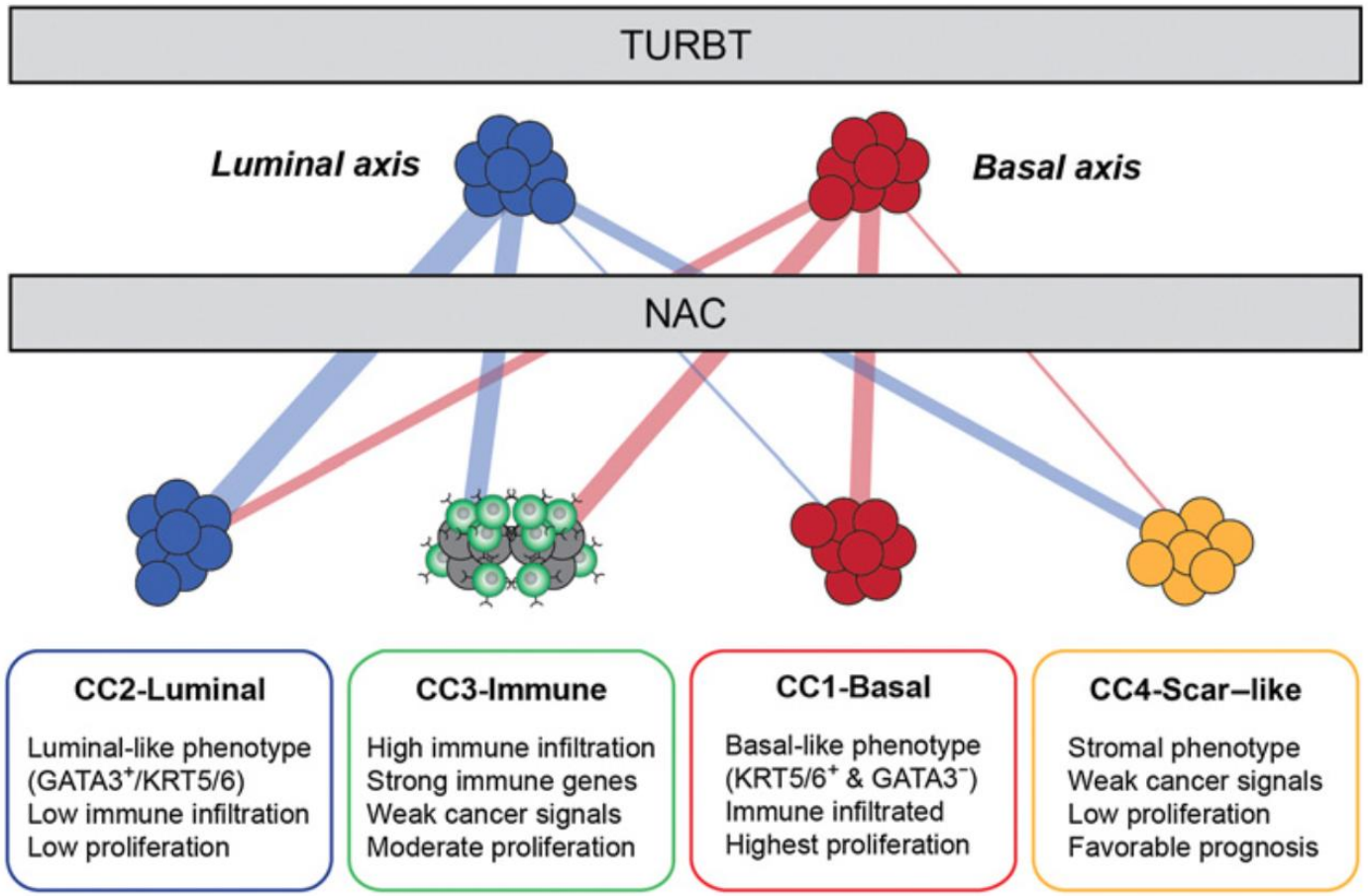

Figure 6.
Scheme indicating the classes identified after NAC and their phenotype and biological characteristics.

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Seiler et al. Clin Cancer Res; 25(16) August 15, 2019

Neo-adjuvant trials

CPI

Cis-ineligible : poor outcome patients !

Low response rates in CPI monotherapy compared to chemo

Combination therapy (but results in mUCC are poor) ?

Adjuvant studies CPI = answer?

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Overview of Neoadjuvant Immunotherapy Phase III Trials in MIBC

Single-Agent Therapy	Country	Eligibility	Cisplatin Eligibility	Trial Identifier	Status
• Pembrolizumab > RC vs Pembro + Enfortumab vedotin > RC vs RC alone (KEYNOTE-905/EV-303)	Multicenter international	T2-4aN0M0	No	NCT03924895	Recruiting
• Nivolumab > RC vs RC alone	Multicenter international	T2-4aN0M0	No	NCT04209114	Not yet recruiting
Immune Combination Therapy					
• Nivolumab + NKTR-214 > RC vs RC alone	Multicenter international	T2-4aN0M0	No	NCT04209114	Not yet recruiting
Chemoimmunotherapy Combinations					
• Gem/Cis + pembrolizumab vs Gem/Cis (KEYNOTE-866)	Multicenter international	T2-4aN0M0	Yes	NCT03924856	Recruiting
• Gem/Cis + durvalumab vs Gem/Cis (NIAGARA)	Multicenter international	T2-4aN0M0	Yes	NCT03732677	Recruiting
• Gem/Cis + nivolumab ± BMS-986205 vs Gem/Cis (ENERGIZE)	Multicenter international	T2-4aN0M0	Yes	NCT03661320	Recruiting

Adjuvant trials
Possible benefits

CPI

Better selection of patients possible (residual disease?)

More time for biomarker assessment

Adjuvant studies = answer?

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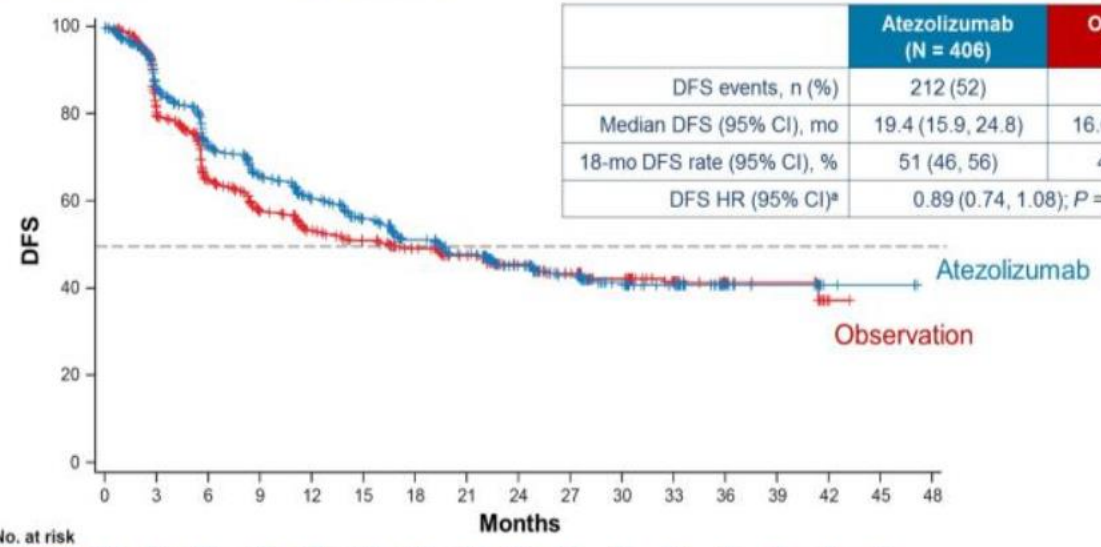
IMvigor-010: adjuvant atezolizumab did not prolong survival in MIBC

DFS in ITT Population



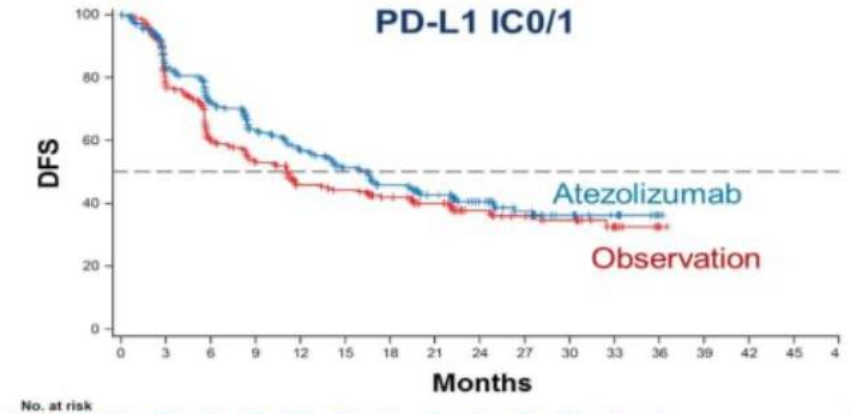
	Atezolizumab (N = 406)	Observation (N = 403)
DFS events, n (%)	212 (52)	208 (52)
Median DFS (95% CI), mo	19.4 (15.9, 24.8)	16.6 (11.2, 24.8)
18-mo DFS rate (95% CI), %	51 (46, 56)	49 (44, 54)
DFS HR (95% CI)[a]	0.89 (0.74, 1.08); $P = 0.2446$[b]	

No. at risk																
Atezolizumab	406	332	281	248	223	201	169	142	115	92	67	52	15	10	3	2
Observation	403	305	240	211	188	177	156	131	109	87	67	42	17	12	2	

Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. [a] Stratified by post-resection tumor stage, nodal status and PD-L1 status. [b] 2-sided.

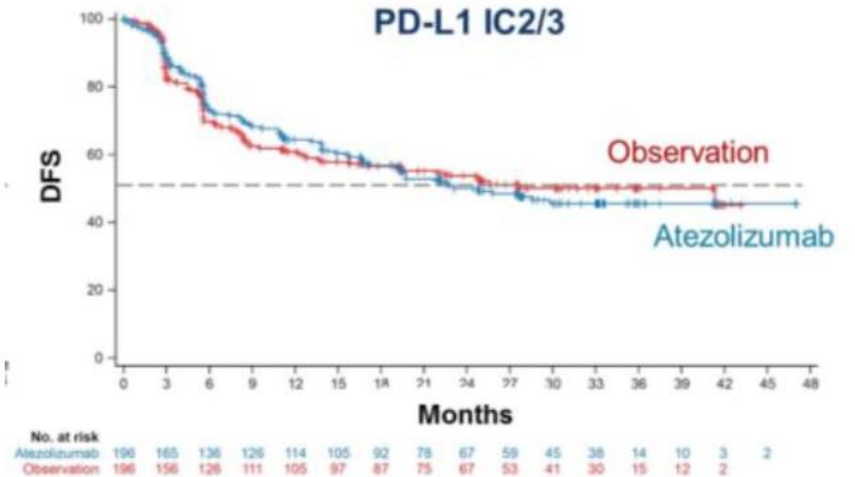
DFS by PD-L1 Status

PD-L1 IC0/1



No. at risk													
Atezolizumab	210	167	145	122	109	96	77	64	48	33	22	14	1
Observation	207	149	114	100	83	80	69	56	42	34	26	12	2

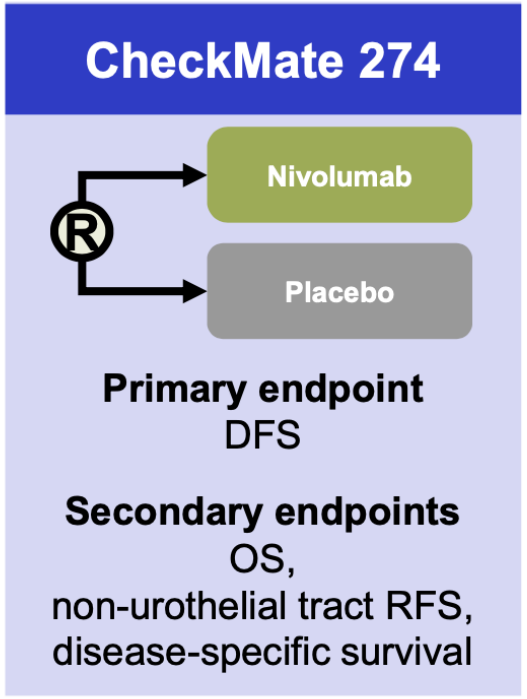
PD-L1 IC2/3



No. at risk																
Atezolizumab	196	165	136	126	114	105	92	78	67	59	45	38	14	10	3	2
Observation	196	156	126	111	105	97	87	75	67	53	41	30	15	12	2	

Hussain M, et al. *Journal of Clinical Oncology* 38, no. 15_suppl (May 20, 2020) 5000-5000

Adjuvant trials - CPI



Opdivo (nivolumab) Significantly Improves Disease Free-Survival vs. Placebo as Adjuvant Therapy for Patients with High-Risk, Muscle-Invasive Urothelial Carcinoma in Phase 3 CheckMate -274 Trial

In an interim analysis, CheckMate-274 met primary endpoints of disease-free survival in both all randomized patients and in patients whose tumor cells express PD-L1 ≥1%

Businesswire.com; September 24, 2020

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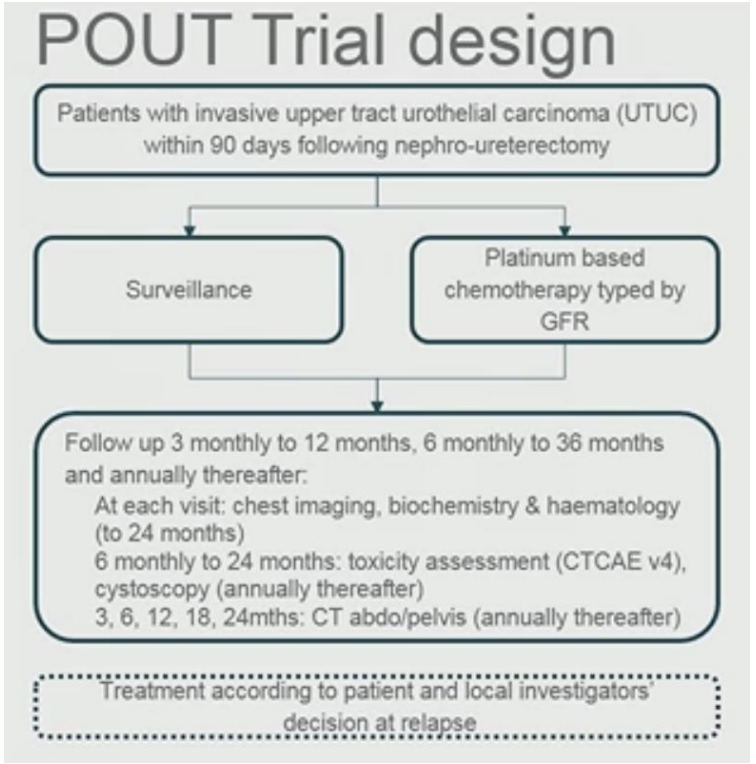
Why adjuvant and neo-adjuvant therapy in MIBC?

(Neo-)adjuvant chemotherapy in UTUC



ASCO GU 2018

Why adjuvant and neo-adjuvant therapy in MIBC?

(Neo-)adjuvant chemotherapy in UTUC

POUT chemotherapy regimen

Four 21 day cycles:

All patients:

Gemcitabine

- 1000mg/m^2 day 1 & 8

With:

If GFR ≥ 50 ml/min:

Cisplatin

- 70mg/m^2 day 1

OR

If GFR 30-49ml/min:

Carboplatin*

- AUC 4.5/AUC 5 day 1

*only permitted for impaired renal function

Supportive care according to local practice

< 90 days post-surgery

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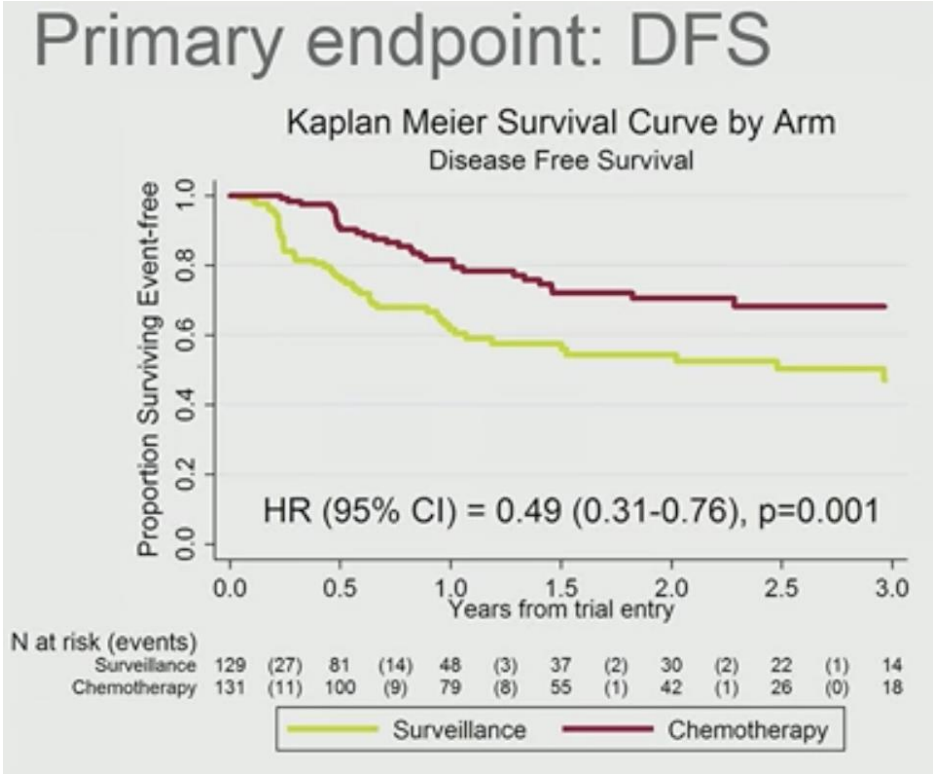
Why adjuvant and neo-adjuvant therapy in MIBC?

(Neo-)adjuvant chemotherapy in UTUC



ASCO GU 2018