Biomarker Updates

Thomas Powles

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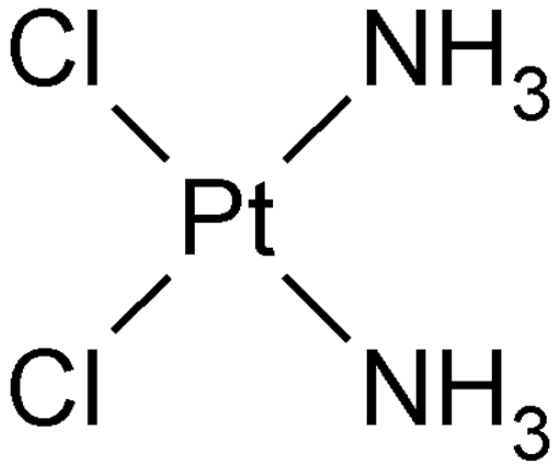
DISCLOSURES

- **Consulting Fees: AstraZeneca, BMS, Exelixis, Incyte, Ipsen, Merck, MSD, Novartis, Pfizer, Seattle Genetics, Merck Serono, Astellas, Johnson & Johnson, Eisai, Roche**
- **Contracted Research: AstraZeneca, BMS, Exelixis, Ipsen, Merck, MSD, Novartis, Pfizer, Seattle Genetics, Merck Serono, Astellas, Johnson & Johnson, Eisai, Roche**
- **Other (Travel/Accommodation/Expenses): Roche, Pfizer, MSD, AstraZeneca, Ipsen**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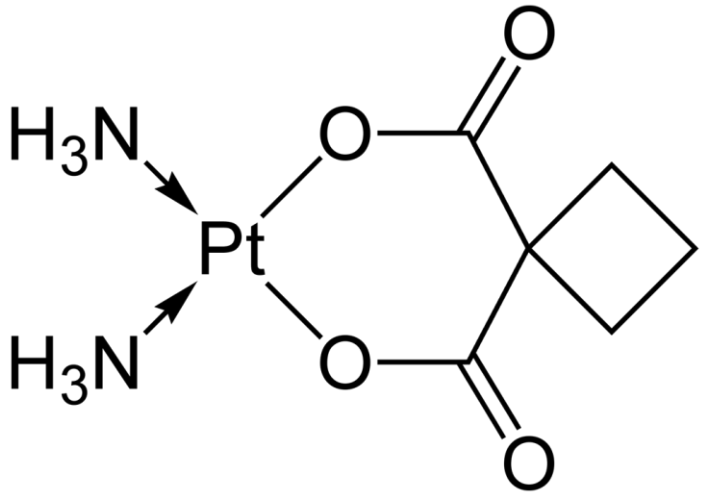
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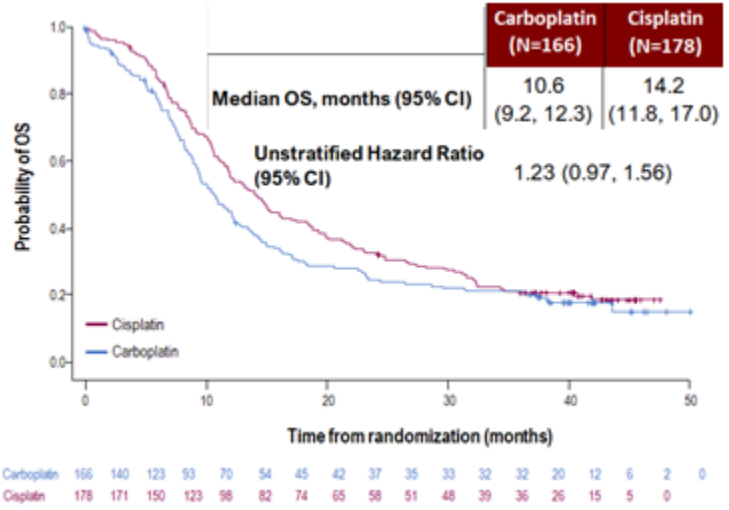
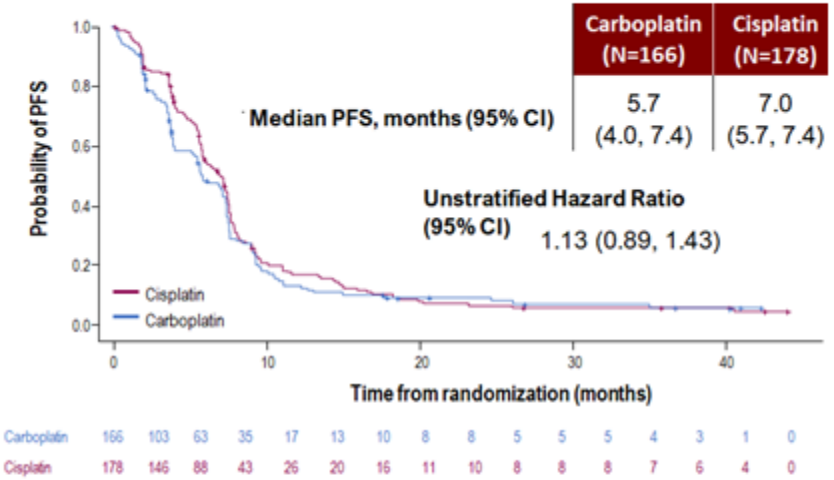
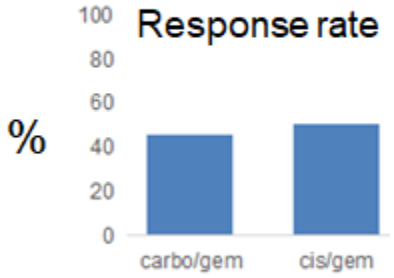
Indirect comparison of cisplatin and carboplatin in bladder cancer

	Carboplatin (N = 166)	Cisplatin (N = 178)
Liver metastasis at baseline		
Yes	53 (31.9)	40 (22.5)
No	113 (68.1)	138 (77.5)
Number of Bellmunt risk factors		
0	53 (31.9)	77 (43.3)
1	74 (44.6)	74 (41.6)
2	33 (19.9)	21 (11.8)





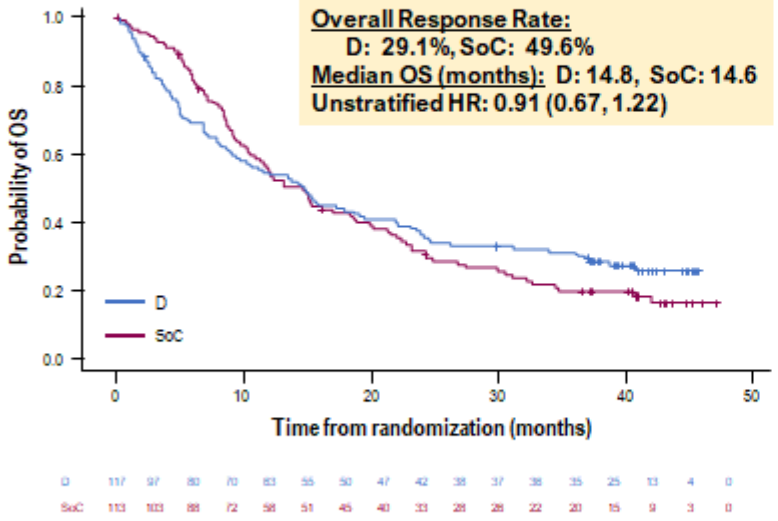


Method:
Adhoc analysis of the control arm from DANUBE
RIII study 1st line UC trial.

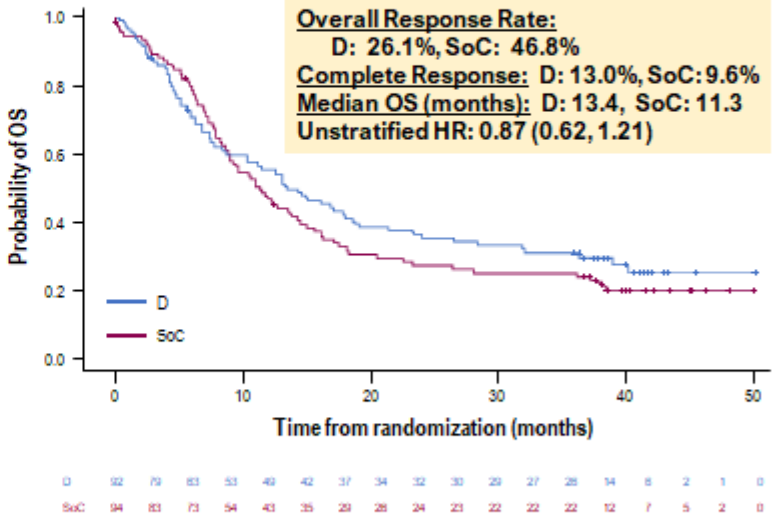
Powles et al EAU 2021

Overall Survival by Cisplatin-Eligibility, PD-L1 High
Durvalumab vs. SoC

Cisplatin-eligible population



Cisplatin-ineligible population



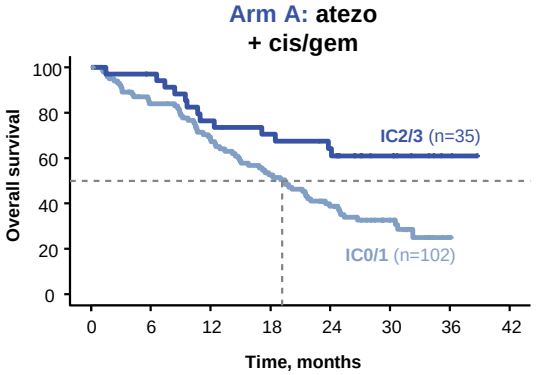
2021 ESMO congress

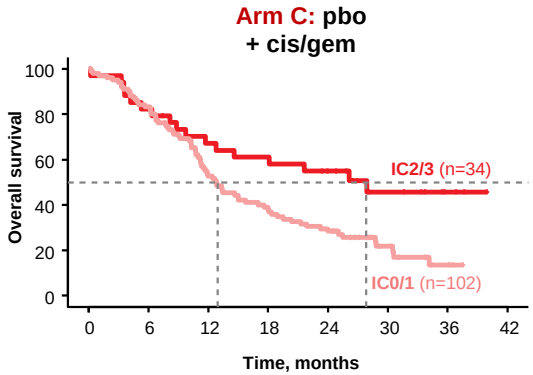
Cisplatin-related immunomodulation and efficacy with atezolizumab + cisplatin- vs carboplatin-based chemotherapy in metastatic urothelial cancer

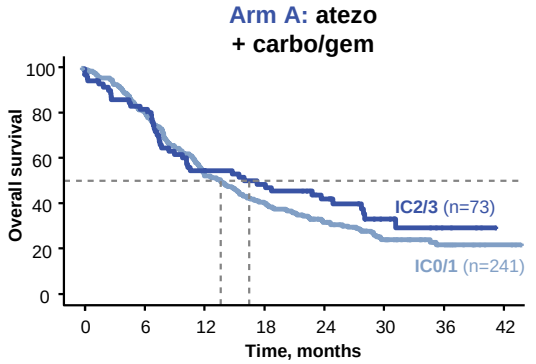
Matthew D. Galsky,[1] Xiangnan Guan,[2] Romain Banchereau,[2] Li Wang,[3,4] Jun Zhu,[3,4] Haocheng Yu,[4] Deepali Rishipathak,[2] Emma Hajaj,[5] Rebecca H. Herbst,[5] Ian D. Davis,[6] Enrique Grande,[7] Aristotelis Bamias,[8] Maria De Santis,[9] José Ángel Arranz,[10] Eiji Kikuchi,[11] Jingbin Zhang,[12] Chooi Lee,[13] Xiaodong Shen,[2] Peter C. Black,[14] Sanjeev Mariathasan[2]

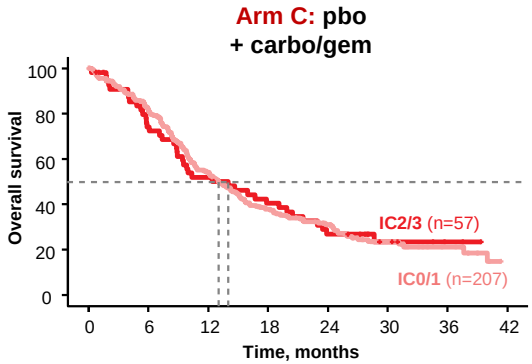
[1]Icahn School of Medicine at Mount Sinai/Tisch Cancer Institute, New York, NY, USA; [2]Genentech Inc, South San Francisco, CA, USA; [3]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [4]Sema4, a Mount Sinai Venture, Stamford, CT, USA; [5]Immunai, New York, NY, USA; [6]Eastern Health Clinical School, Monash University and Eastern Health, Melbourne, Australia; [7]MD Anderson Cancer Center Madrid, Madrid, Spain; [8]National & Kapodistrian University of Athens, Athens, Greece; [9]Charité Universitätsmedizin, Department of Urology, Berlin, Germany, and Medical University of Vienna, Department of Urology, Vienna, Austria; [10]Gregorio Maranon Hospital, Madrid, Spain; [11]St. Marianna University School of Medicine, Kawasaki, Japan; [12]Hoffmann-La Roche Limited, Mississauga, ON, Canada; [13]Roche Products Limited, Welwyn Garden City, UK; [14]Vancouver Prostate Centre, University of British Columbia, Vancouver, BC, Canada

Effects of cisplatin ± atezo on OS are most prominent in patients with PD-L1 IC–high tumours







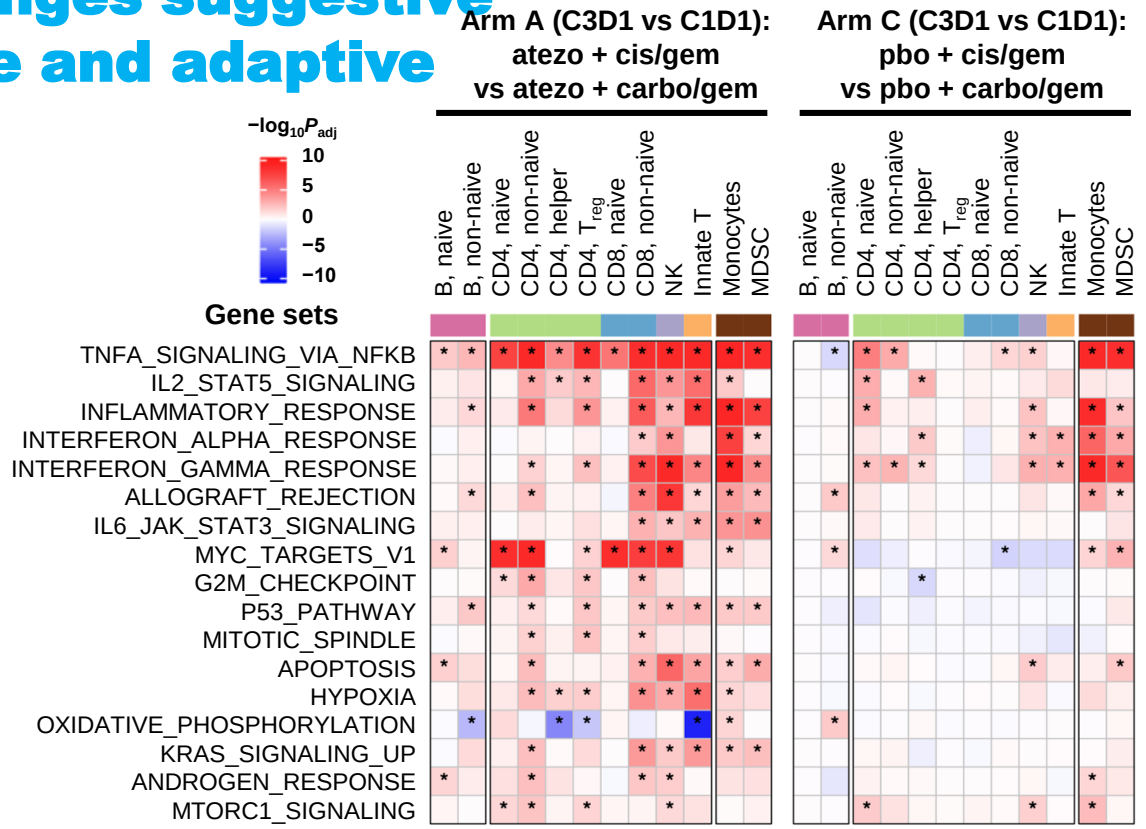


IMvigor130: OS by PD-L1 status and chemo

		mOS, mo		OS HR (95% CI)
		IC0/1	IC2/3	
Arm A	Atezo + cis/gem	19.5	NR	0.46 (0.25, 0.83)
	carbo/gem	13.9	16.6	0.85 (0.61, 1.17)
Arm C	Pbo + cis/gem	12.8	27.9	0.51 (0.30, 0.86)
	carbo/gem	13.0	14.0	1.00 (0.71, 1.42)

Cisplatin vs carboplatin leads to gene expression changes suggestive of induction of innate and adaptive immunity

- **IMvigor130:** Cis- vs carbo-treated patients showed on-treatment enrichment of TNF-α signalling via NFκB, inflammatory response gene sets and interferon response gene sets across immune cell clusters
- **Neoadjuvant cohort:** TNFα signaling via NFκB was also enriched in paired tumour samples (post- vs pre-cis/gem)

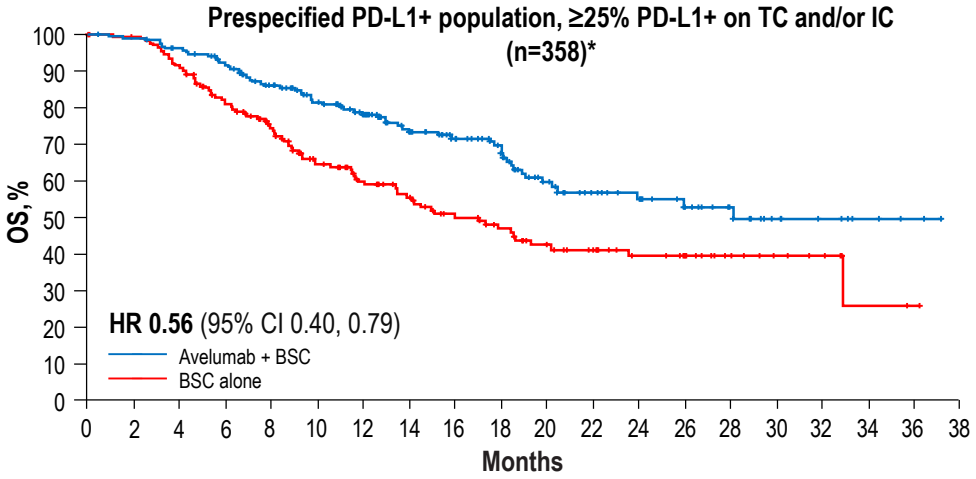


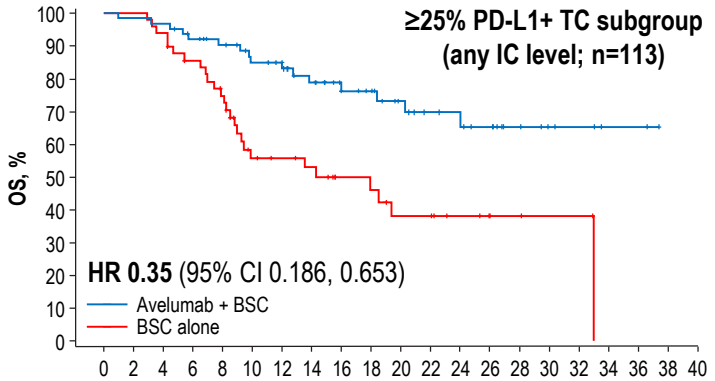
The PD-L1 biomarker consists of many different biomarker and should be considered as such.

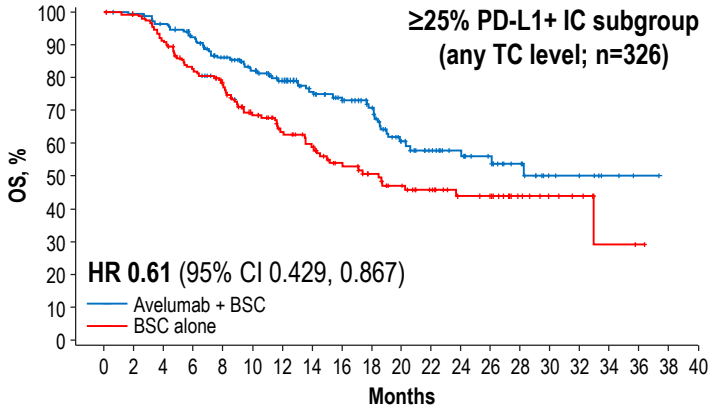
Randomized trials testing PD-L1 in UC

Drug	setting	Result
atezolizumab	Platinum refractory	-ve
atezolizumab	Adjuvant	-ve
Durvalumab	1st line	-ve
Pembrolizumab	1st line	-ve
nivolumab	adjuvant	+ve for ITT and PD-L1+ve
Avelumab	1st line maintenance	+ve for ITT and PD-L1+ve

PD-L1 biomarker: TC vs IC component



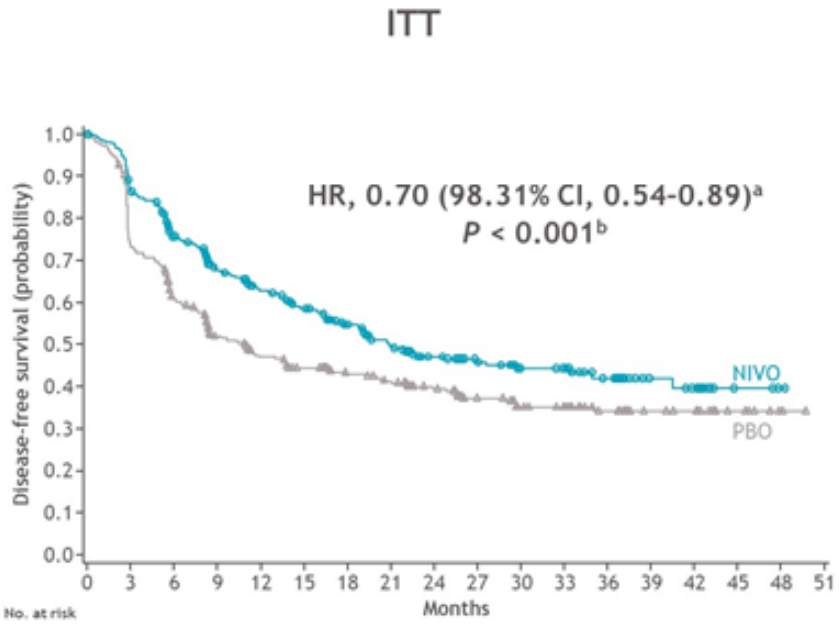


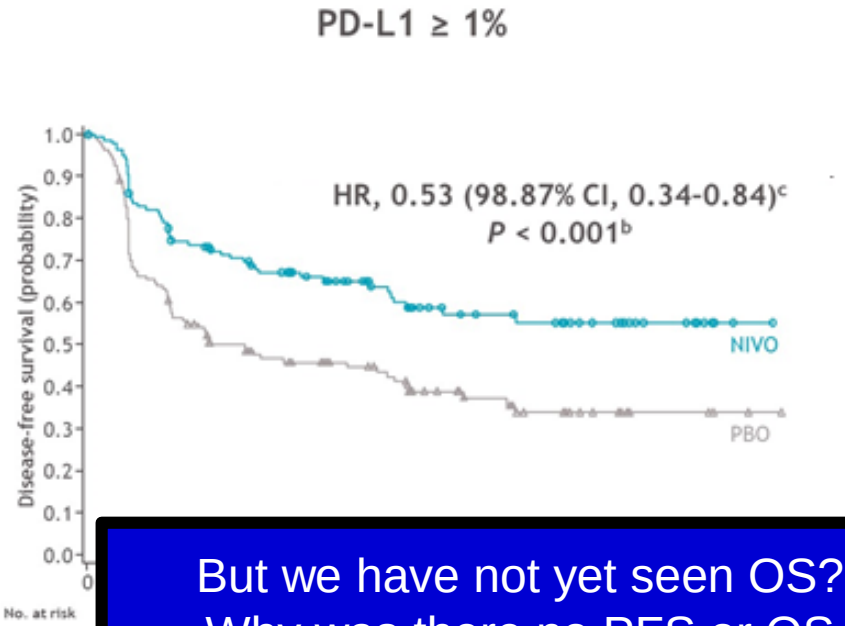


Neither PD-L1+ TC nor IC alone fully predicts OS benefit

- **TC,** tumor cell**; IC**, immune cell; **NE,** not evaluable.
- *PD-L1 expression in ≥25% of TC or in ≥25% or 100% of IC if the percentage of IC was >1% or ≤1%, respectively, using the Ventana SP263 assay.

Adjuvant nivolumab in high-risk urothelial cancer.

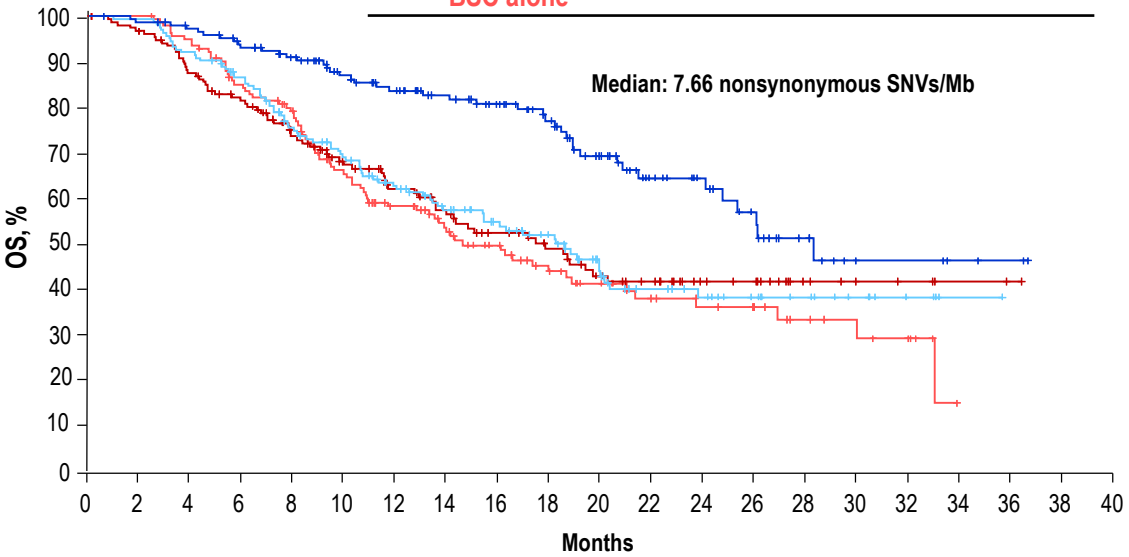




But we have not yet seen OS?
Why was there no PFS or OS advantage for atezolizumab?
Why didn't the biomarker work with atezo?

•OS benefit in subgroups defined by Tumor Mutation Burden (TMB) and PD-L1 status

Arm	TMB	HR (95% CI)
Avelumab + BSC / BSC alone	>Median	**0.48** (0.332, 0.707)
Avelumab + BSC / BSC alone	≤Median	**0.88** (0.643, 1.197)



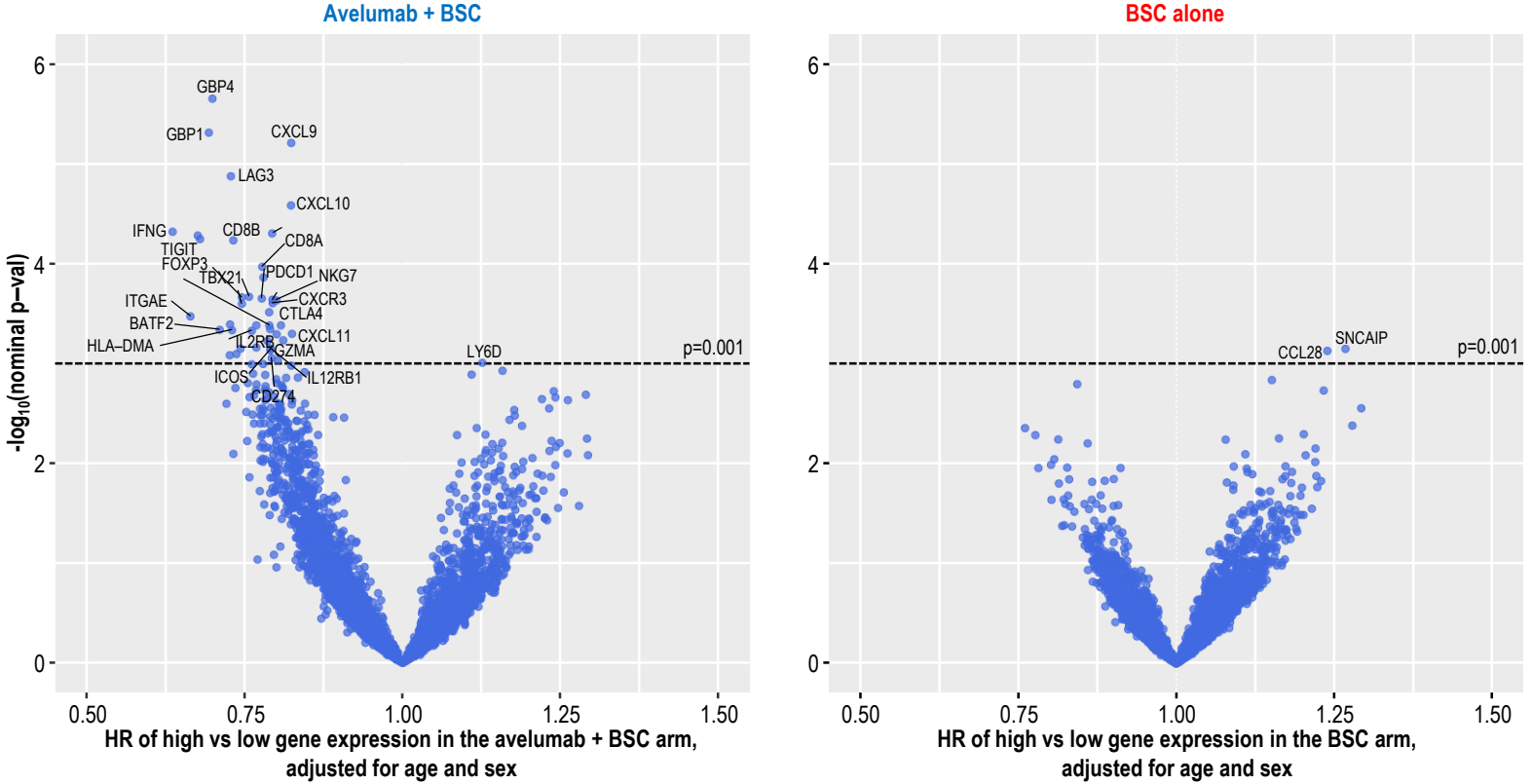
Subgroup	HR (95% CI) Avelumab + BSC vs BSC alone
PD-L1+	0.56 (0.400, 0.790)
PD-L1−	0.85 (0.616, 1.181)
TMB-high	0.46 (0.321, 0.673)
TMB-low	0.93 (0.665, 1.289)
TMB-high, PDL1+ (n=190)	0.49 (0.291, 0.812)
TMB-high PDL1− (n=105)	0.42 (0.247, 0.732)
TMB-low PDL1+ (n=148)	0.62 (0.389, 0.995)
TMB-low, PDL1− (n=140)	1.40 (0.871, 2.252)

Neither TMB nor PD-L1 status alone fully predict OS benefit

EAU2021

•Tumor gene expression data can identify genes that may be associated with OS benefit from avelumab

Immune-related genes are associated with OS benefit from avelumab



•Genes of interest with p < 0.001 are labeled

•Relationship between immune cell gene expression signatures and OS with avelumab

Multiple immune cell signatures may predict OS benefit with avelumab

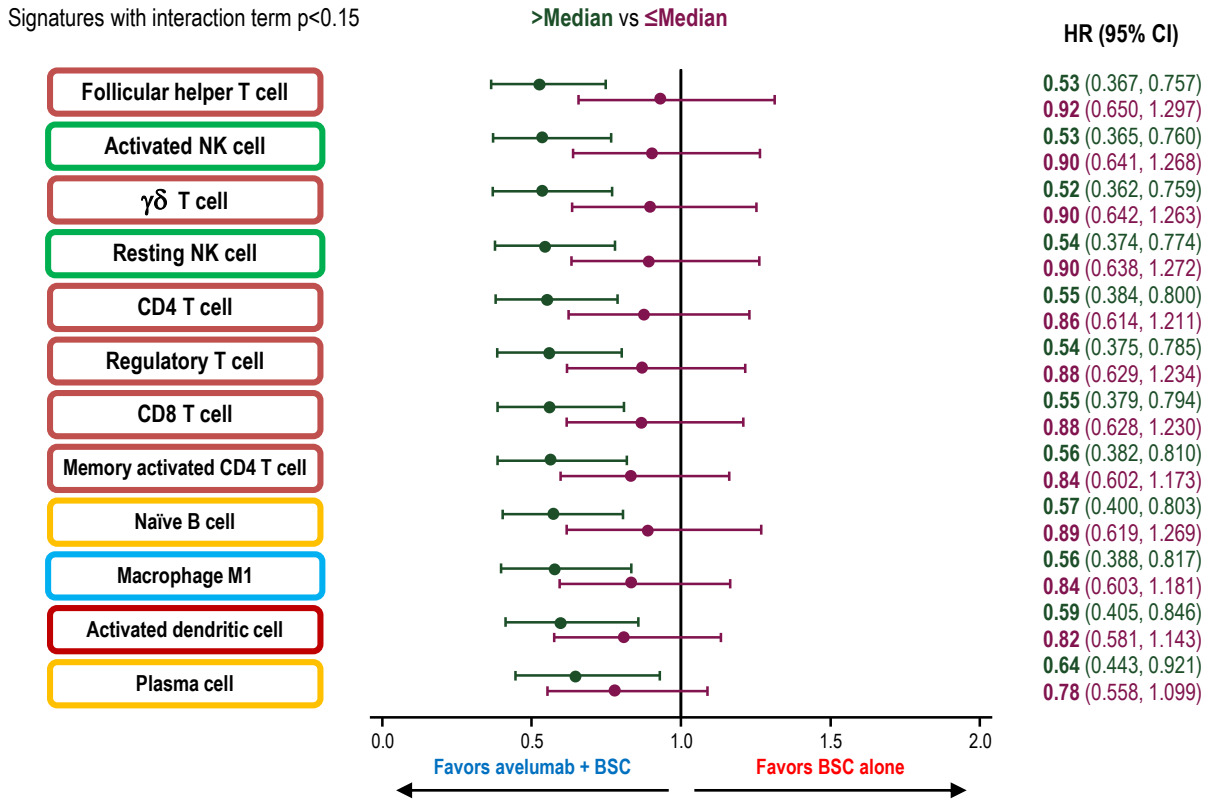
T cell

NK cell

Macrophage

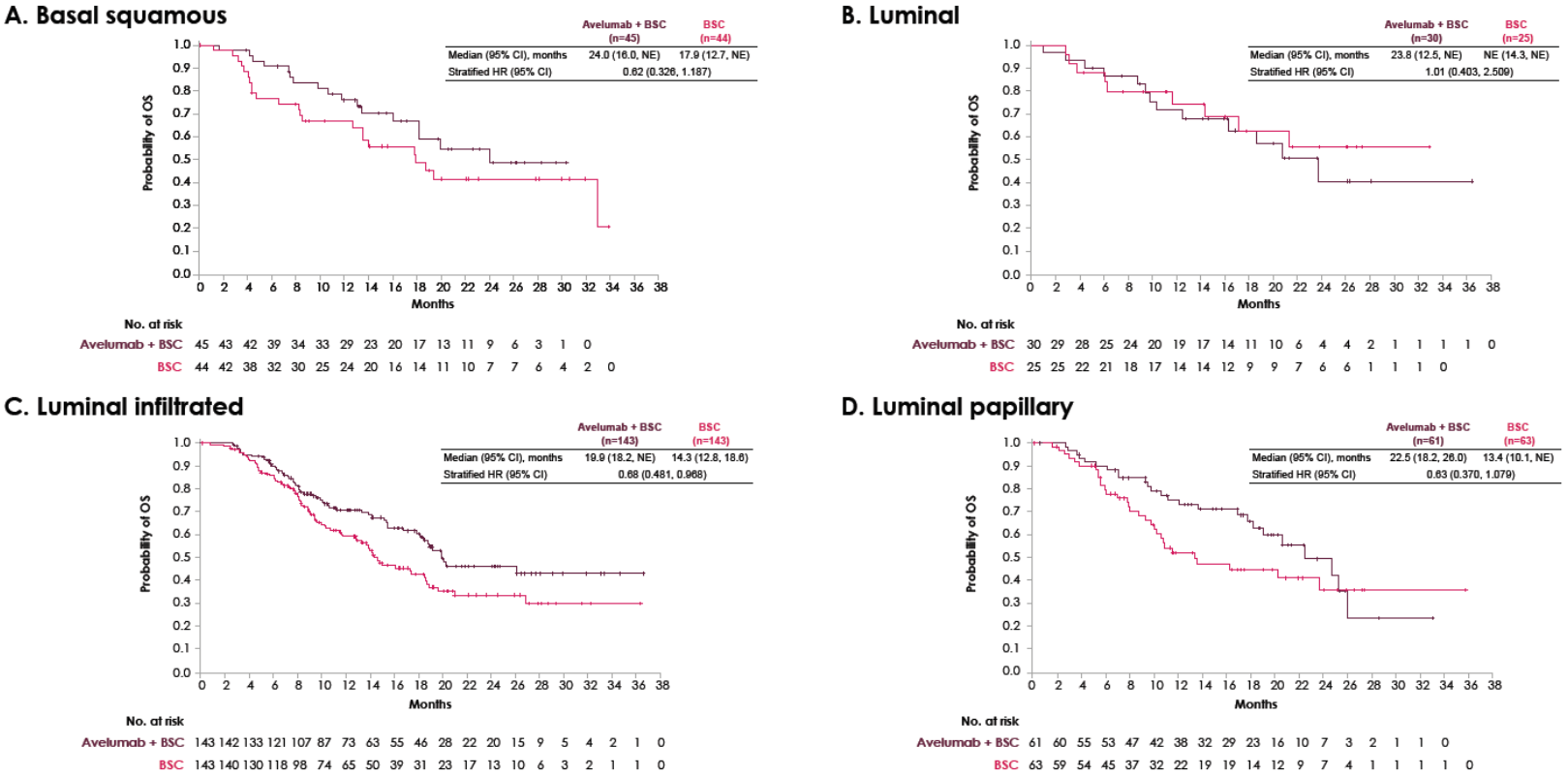
Dendritic cell

B cell



Gene signatures are from the Leukocyte gene signature matrix (LM22), Newman et al (2015) Nature Methods, https://doi.org/10.1038/nmeth.3337

Outcome of avelumab in TCGA subtypes.



nature medicine

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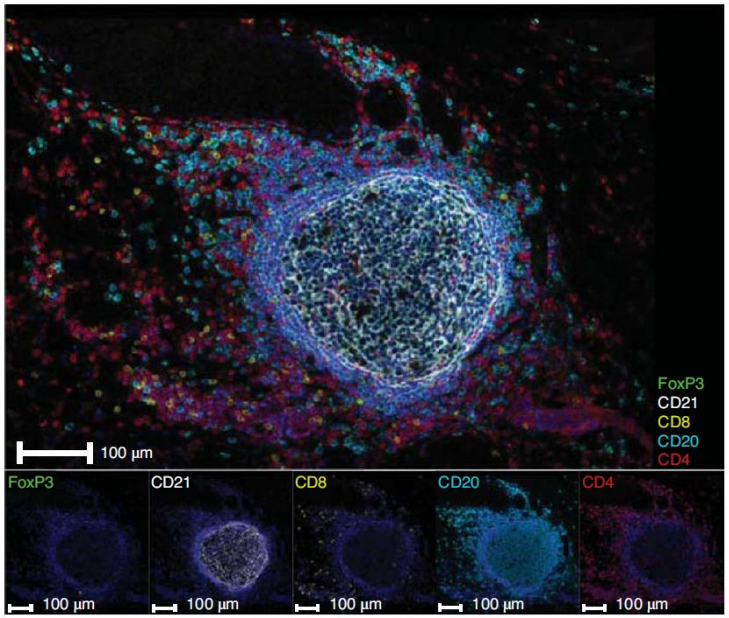
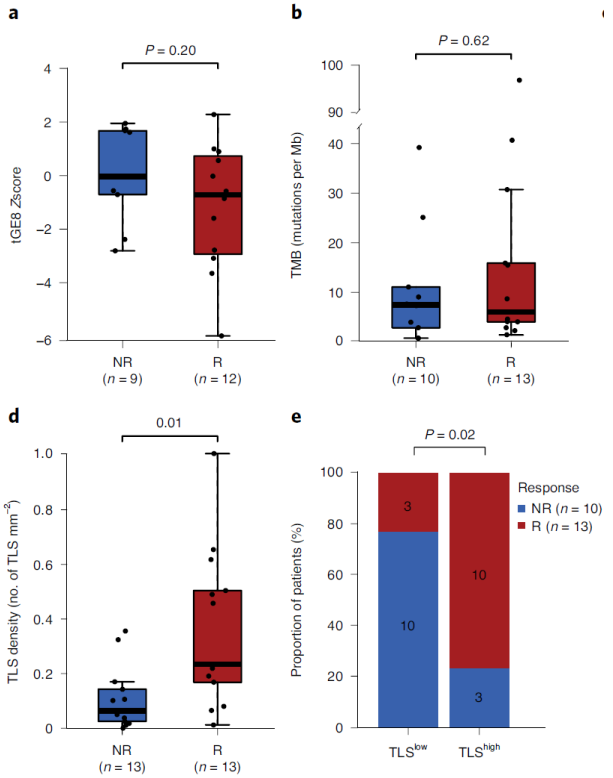
https://doi.org/10.1038/s41591-020-1086-y

Check for updates

Neoadjuvant PD-L1 plus CTLA-4 blockade in patients with cisplatin-ineligible operable high-risk urothelial carcinoma

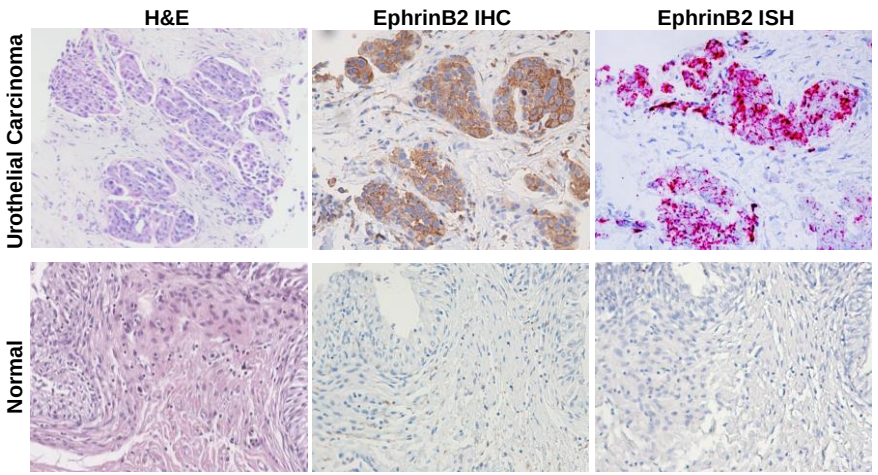




GAO et al 2020

Phase II trial of pembrolizumab (P) in combination with sEphB4-HSA (B4) in previously treated metastatic urothelial carcinoma (mUC)

- EphrinB2 is a transmembrane protein expressed in developing arterial capillary endothelium; it is minimally expressed in adults but re-expressed in tumors and tumor blood vessels
- EphB4, the high affinity cognate receptor, is also expressed in developing venous endothelium and is re-induced in tumors and tumor vessels
- EphrinB2-EphB4 interaction activates bidirectional signaling to promote development and tumor progression by direct effects on tumor cell viability, tumor angiogenesis and immune cell response
- EphrinB2 and EphB4 are highly expressed in urothelial tumors and are negative prognostic markers[1]

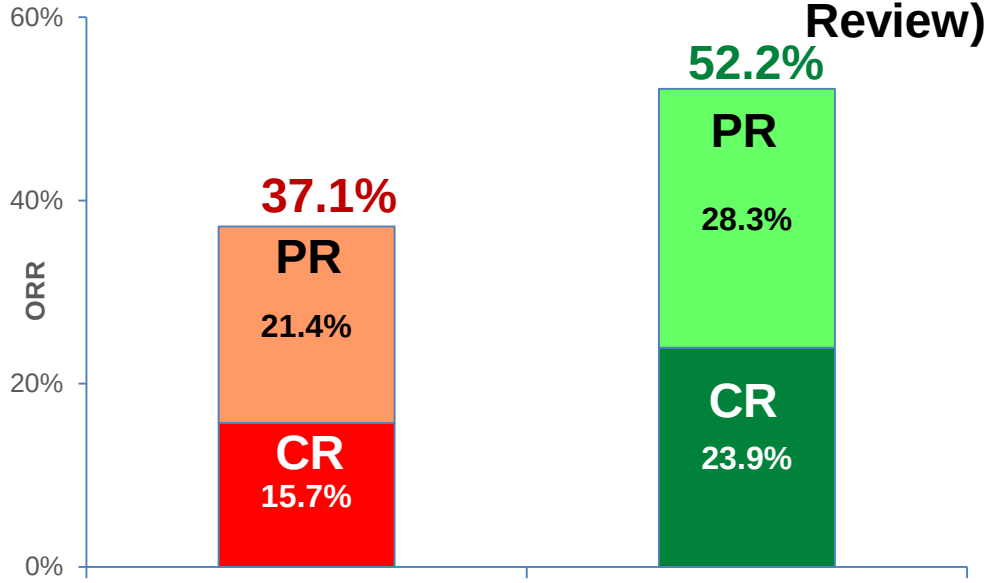


EphrinB2 membrane staining ≥ 1% is considered positive

1. Chandrashekar et al, Neoplasia 2017, PMID 28732212

Intent to Treat Confirmed ORR and DOR (Independent Review)

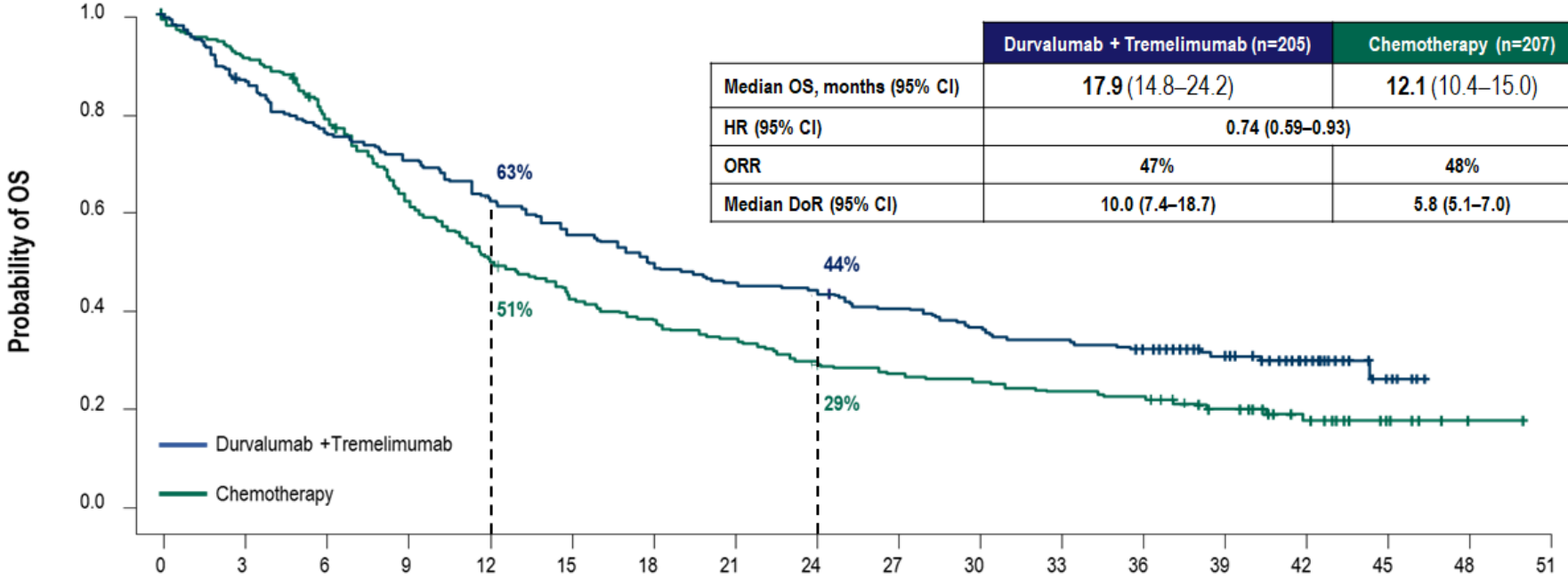
Median follow up
23.0 months
95% CI (18.1, 36.3)



Median DOR (95% CI), months	**Not Reached (13.3, NE)**	**Not Reached (11.9, NE)**

OS With Durvalumab + Tremelimumab vs Chemotherapy in the PD-L1 High Population (Secondary Endpoint)

	Durvalumab + Tremelimumab (n=205)	Chemotherapy (n=207)
Median OS, months (95% CI)	**17.9** (14.8–24.2)	**12.1** (10.4–15.0)
HR (95% CI)	0.74 (0.59–0.93)	
ORR	47%	48%
Median DoR (95% CI)	10.0 (7.4–18.7)	5.8 (5.1–7.0)



Number at risk

Durvalumab+Tremelimumab	205	177	156	144	129	114	101	92	89	81	73	68	63	41	21	6	0	0
Chemotherapy	207	186	161	126	101	86	74	66	57	51	48	44	42	27	16	8	2	0

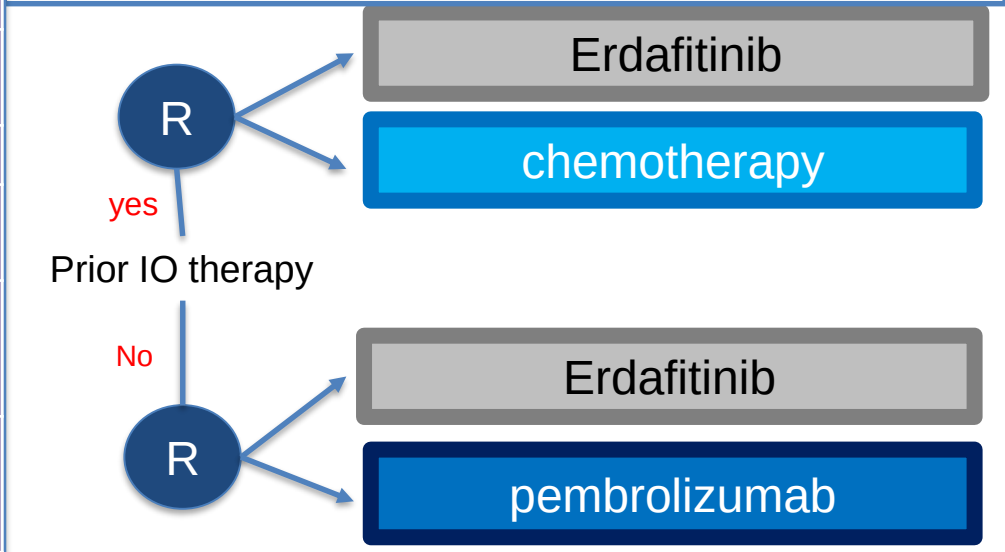
FGF-3 inhibitor in selected patients with urothelial cancer.

	Erdafitinib	INCB054828
Population	Platinum refractory	Platinum refractory
Number	99	100
Phase	II	II
biomarker	Mutations and fusions	Mixed (2 cohorts)
RR	40%	25%
PFS months	5.5 months (4.2-6)	na
Toxicity (grade 3)	Stomatitis Nail tox. Hypophosphatemia	Alopecia Fatigue Hypophoshatemia.
Median OS	9 .5 months (8-19)	NA

Siefker-Radtke et al ASCO 2018

Powles T ESMO 2018 (Review)

THOR: Randomised phase III erdafitinib vs chemotherapy or pembrolizumab in biomarker +ve UC

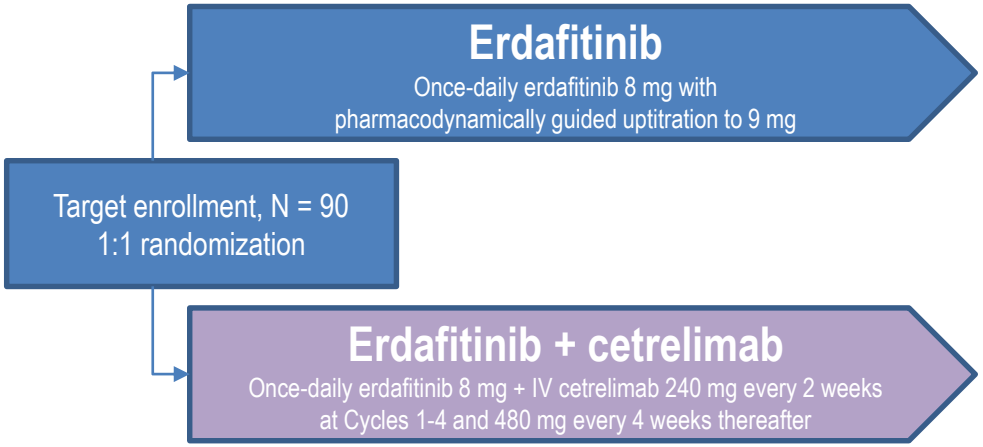


NORSE Phase 2 Study Design[a]

Key eligibility criteria

- Age ≥ 18 years
- mUC diagnosis
- Ineligible for cisplatin
- Select *FGFRa* (mutation/fusion)
- Measurable disease
- No prior systemic therapy for mUC

Patients with any PD-L1 status could be enrolled



Primary end points

- ORR
- Safety

Key secondary end points

- DCR
- DOR
- Time to response

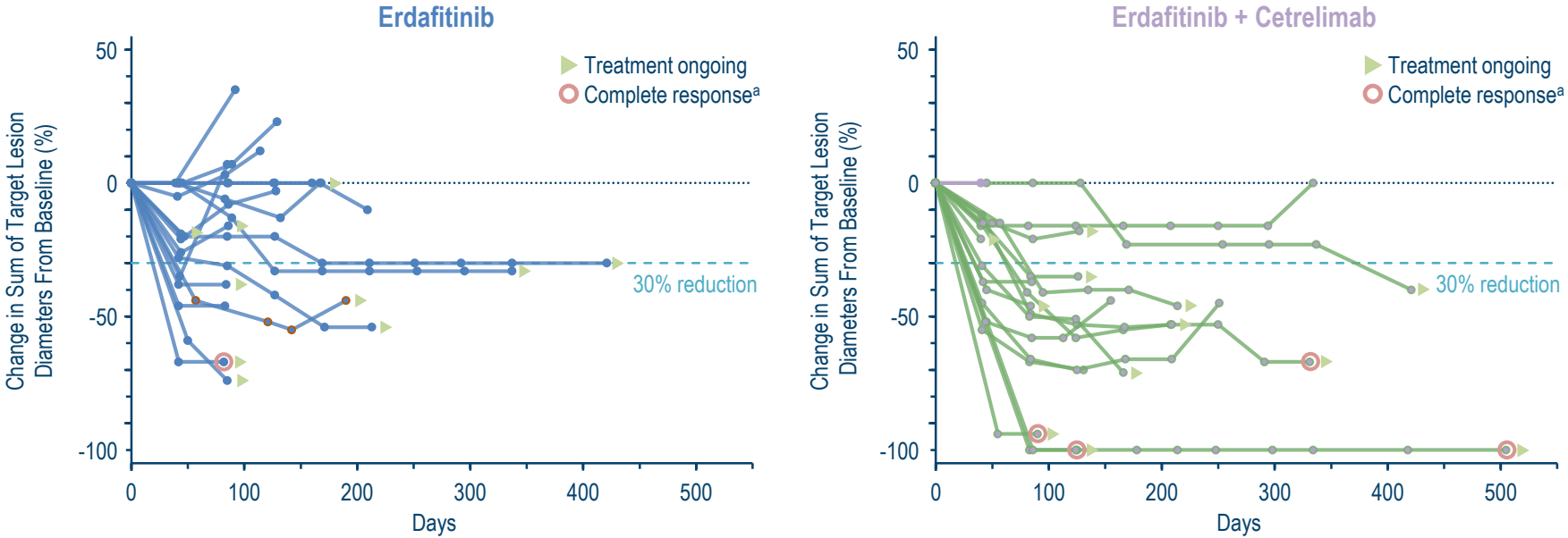
No formal statistical comparisons between arms are prespecified

Point estimates along with 95% CI will be presented for each arm.

- *Sample size determination:* Assuming a true ORR of 45% in the erdafitinib arm and 55% in the erdafitinib + cetrelimab arm, n ≈ 45 patients in each arm would result in an estimated ORR that is above a 95% CI lower bound of 30% and 40%, respectively
- A review of safety and efficacy data was planned per the data review committee charter when ~40 patients were response-evaluable

DCR, disease control rate; DOR, duration of response; IV, intravenous; ORR, overall response rate.
[a]Enrollment began in April 2018. The data cut-off for this analysis was July 19, 2021.

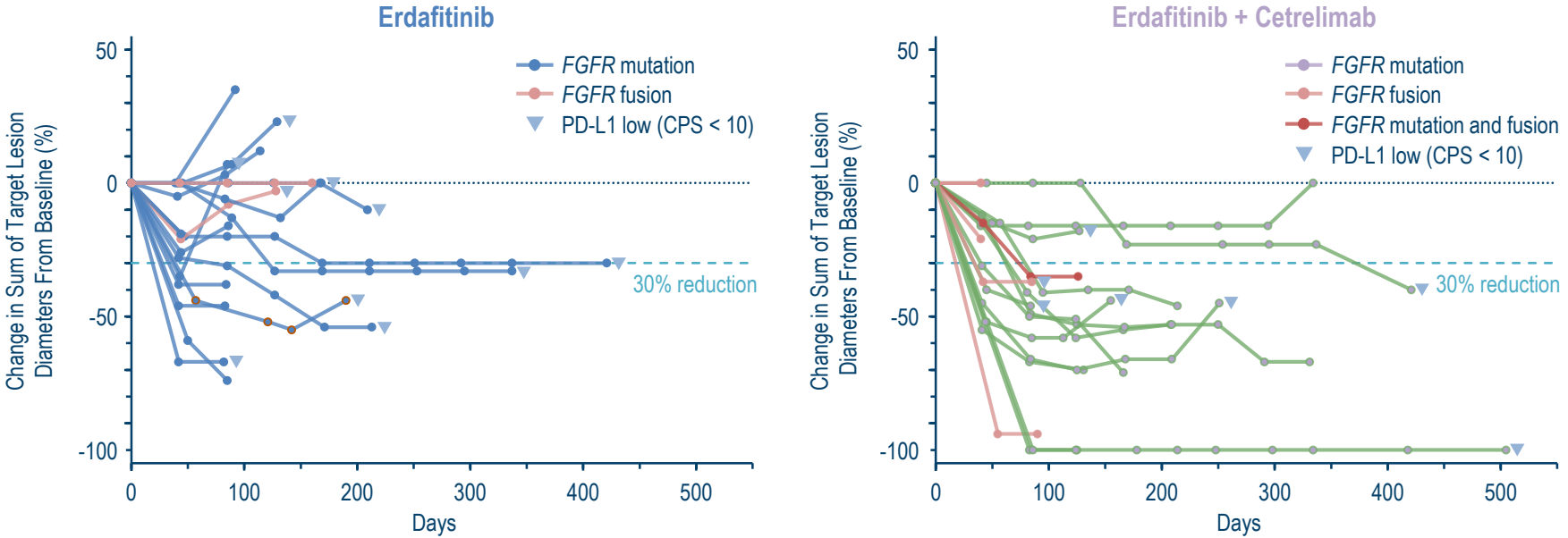
NORSE: Antitumor Activity Over Time



- Patients in both treatment arms had a durable reduction in the sum of target lesion diameters over time
- Median of the maximum reduction in the sum of target lesion diameters was 28% in the erdafitinib arm and 51% in the erdafitinib + cetrelimab arm

[a]Complete responses include patients who had sum of target lesions > 0 mm; in patients with lymph node target lesions, a diameter < 10 mm is required for complete response per RECIST 1.1.

NORSE: Antitumor Activity Over Time, by *FGFRa* type and PD-L1 status



- Responses were observed in patients with both *FGFR* mutations and fusions
- In patients with PD-L1 low status, responses were observed in 50% in the erdafitinib arm (5 of 10) and in 71% patients in the erdafitinib + cetrelimab arm (5 of 7); few patients with PD-L1 positive status had available data at the time of this analysis

nature medicine

LETTERS

https://doi.org/10.1038/s41591-021-01317-6

An adaptive, biomarker-directed platform study of durvalumab in combination with targeted therapies in advanced urothelial cancer

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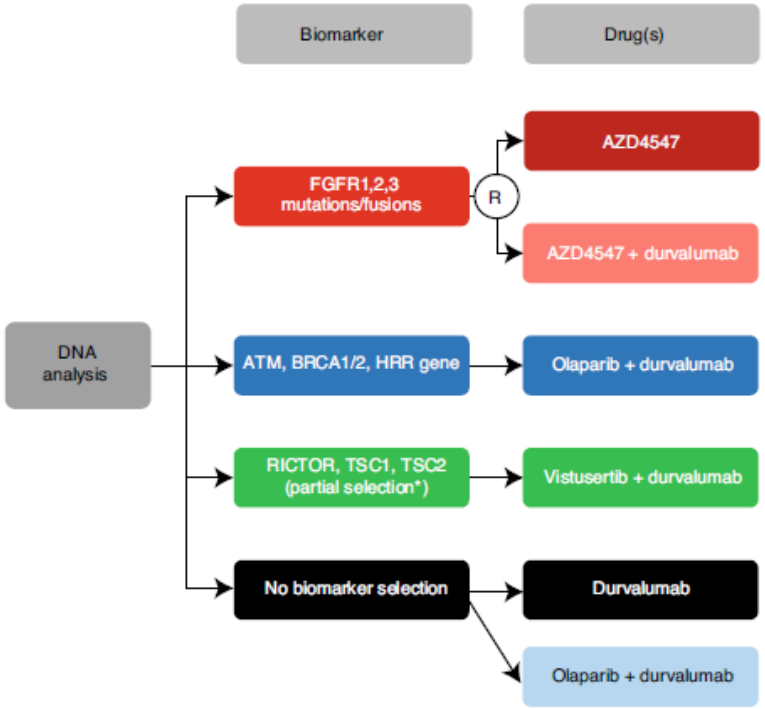
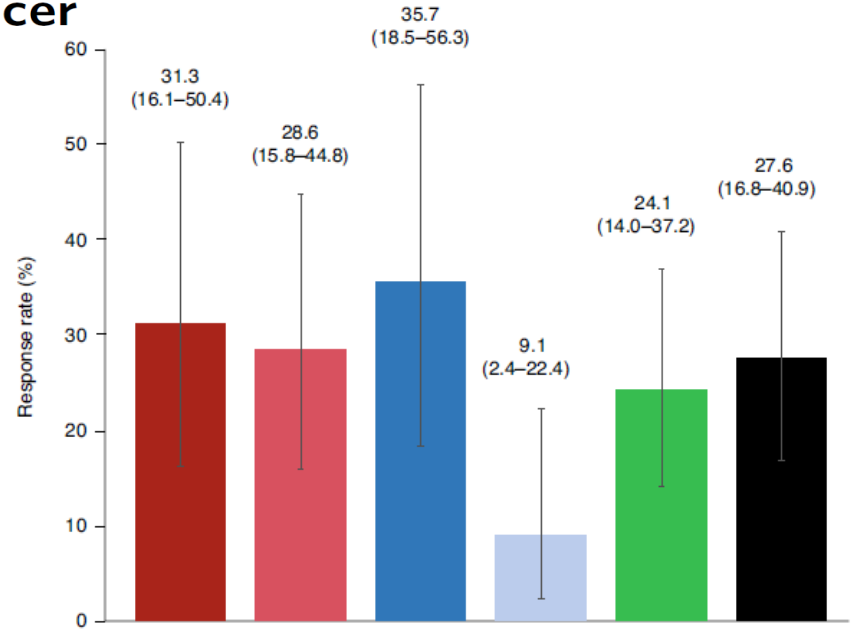




	AZD4547	AZD4547 + durvalumab	Olaparib + durvalumab selected	Olaparib + durvalumab unselected	Vistusertib + durvalumab	Durvalumab
Number of patients	16	21	14	22	29	29

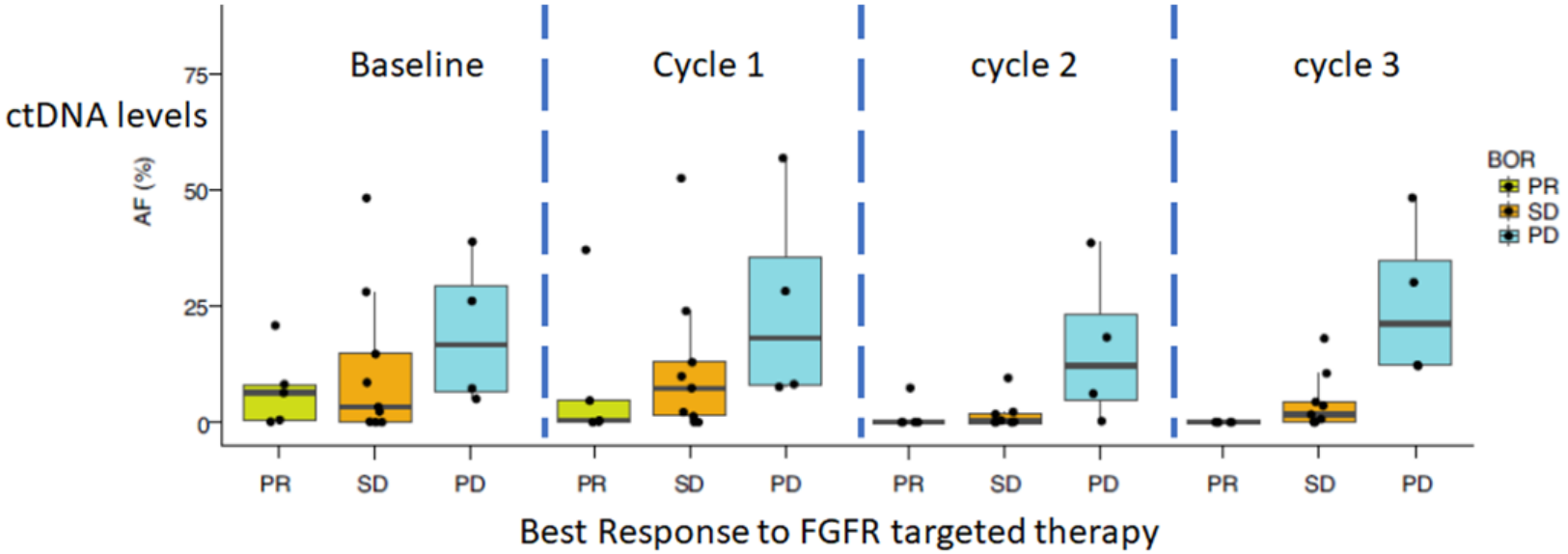
Powles et al 2021

FGFR DNA alterations from tissue at ctDNA strongly correlate

nature medicine
LETTERS
https://doi.org/10.1038/s41591-021-01317-6

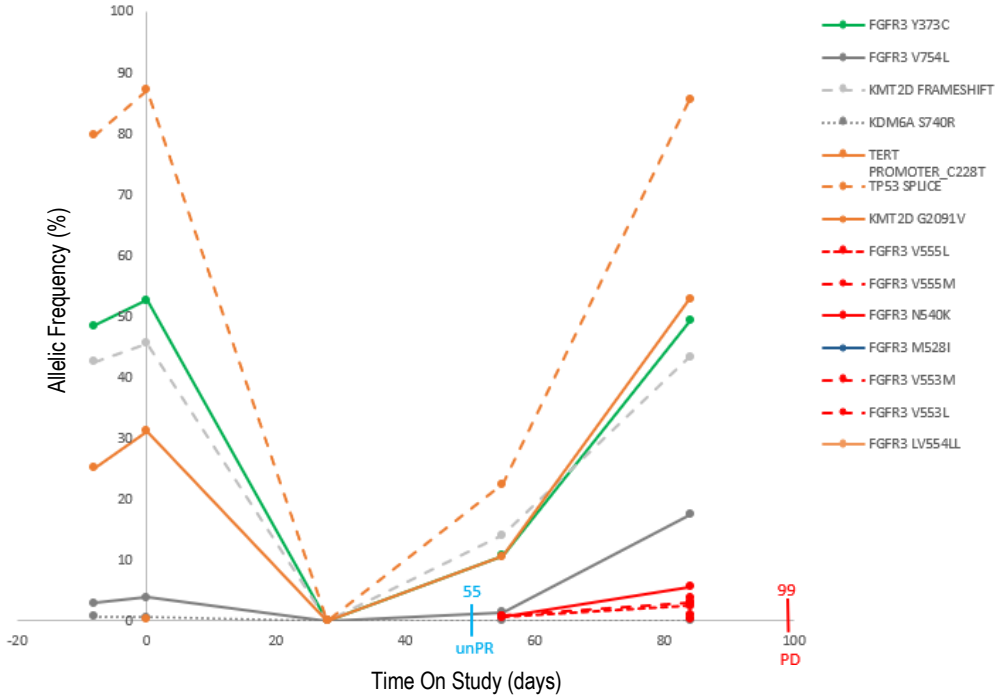
An adaptive, biomarker-directed platform study of durvalumab in combination with targeted therapies in advanced urothelial cancer

Response to FGFR targeted therapy correlating with changes to tracked FGFR mutations



Powles et al 2021

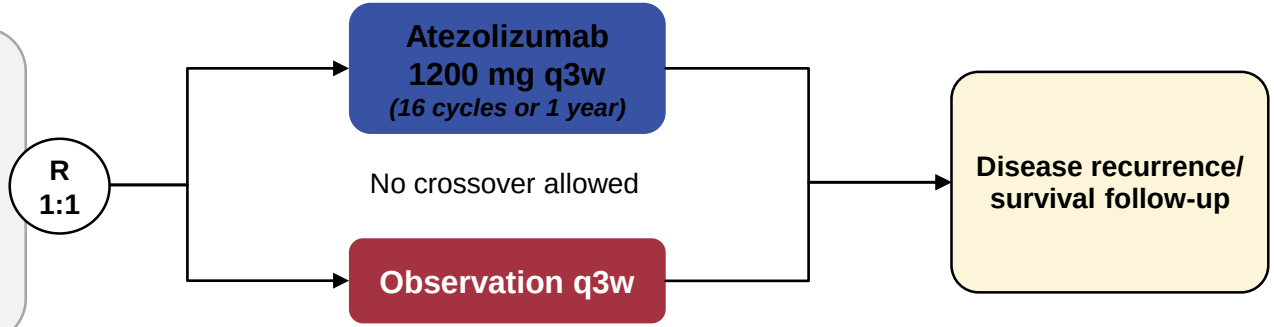
Presence of new FGFR3 clones at progression on FGFR using personalised ctDNA analysis.



Patient BISCAY76

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

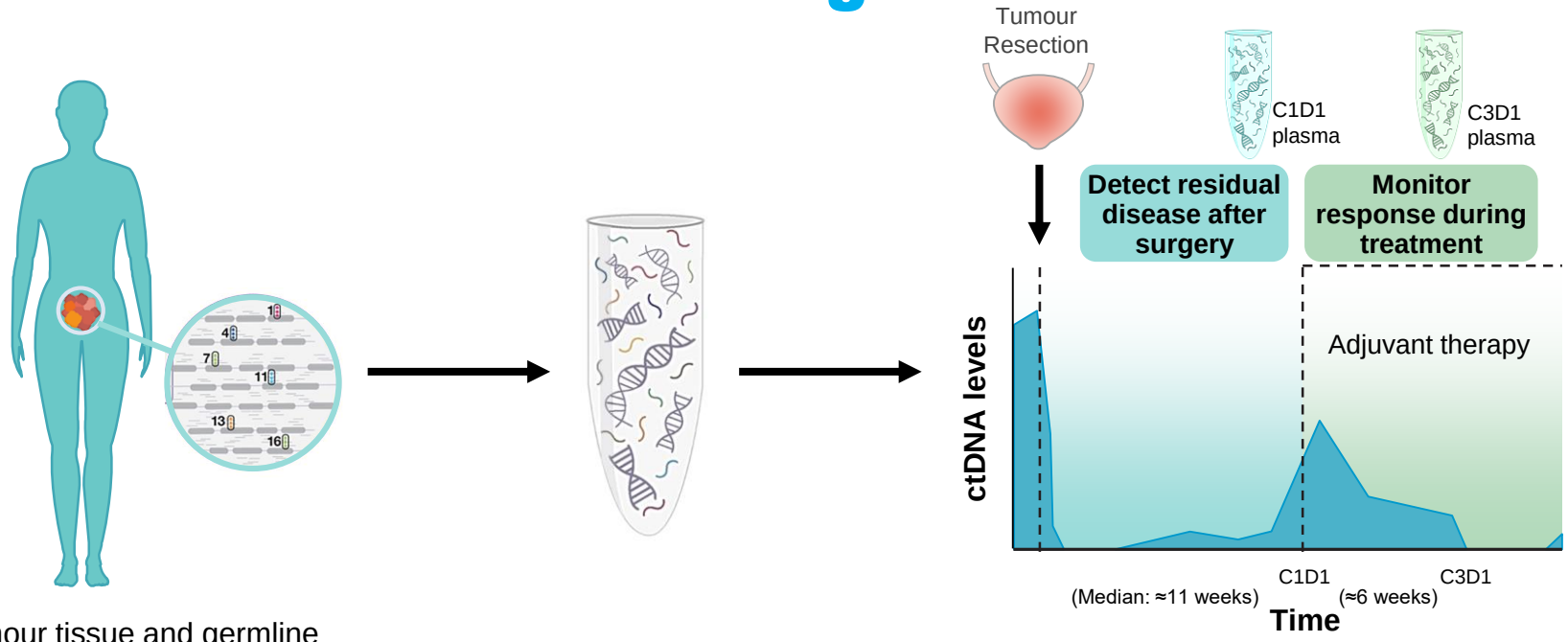


Endpoints
- Primary: DFS (ITT population)
- Key secondary: OS (ITT population)
- Other: Safety
- **Exploratory: predictive, prognostic and pharmacodynamic biomarkers in tumour tissue and blood and their association with disease recurrence**

- 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/2IxYIlE

Evaluation of ctDNA in IMvigor010



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

C, cycle; D, day;

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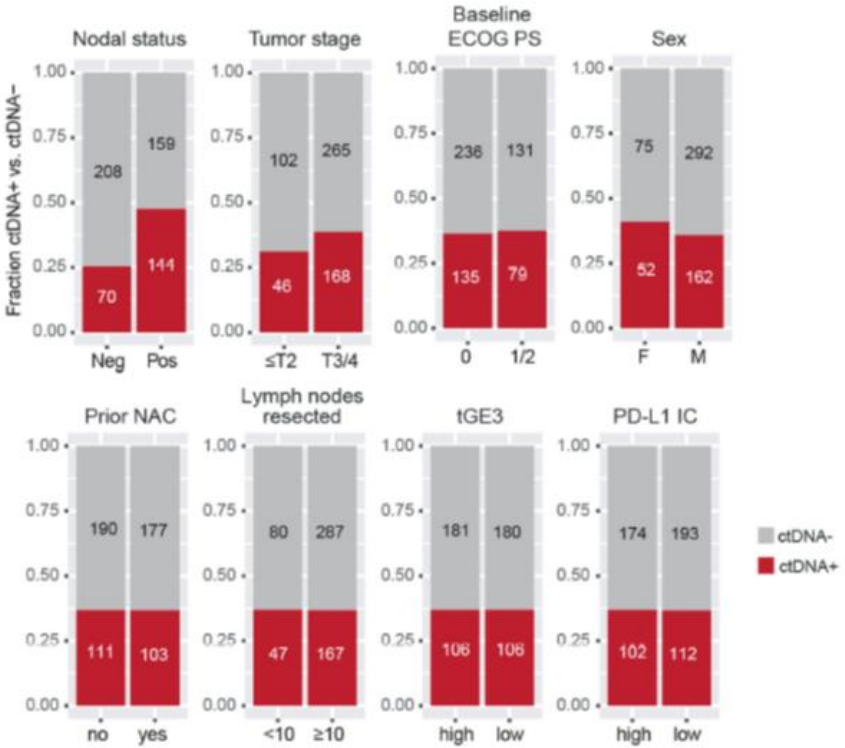
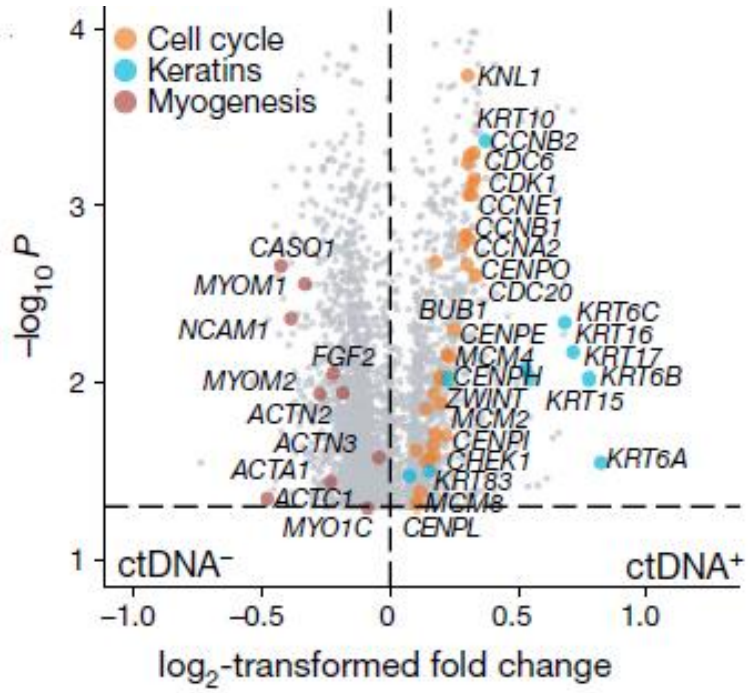
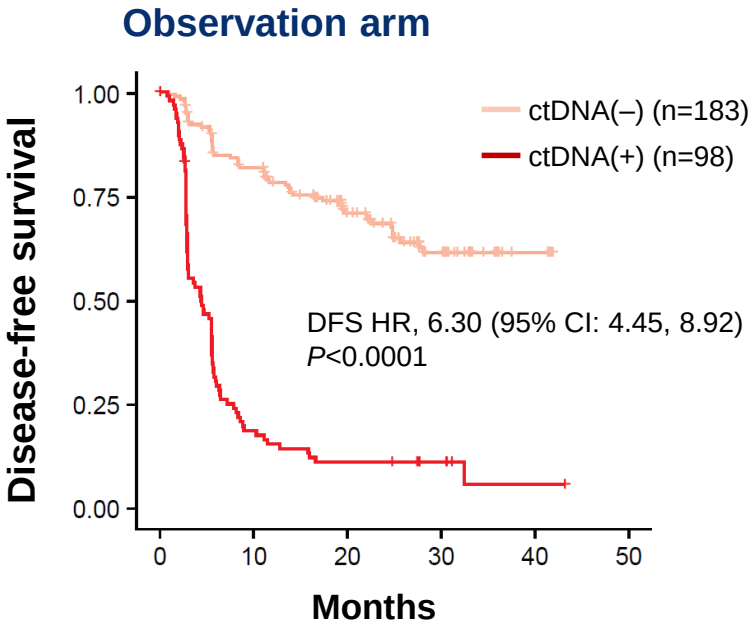
ctDNA is expresses across broad clinical subgroups and have high expression of cell cycle and keratin genes.

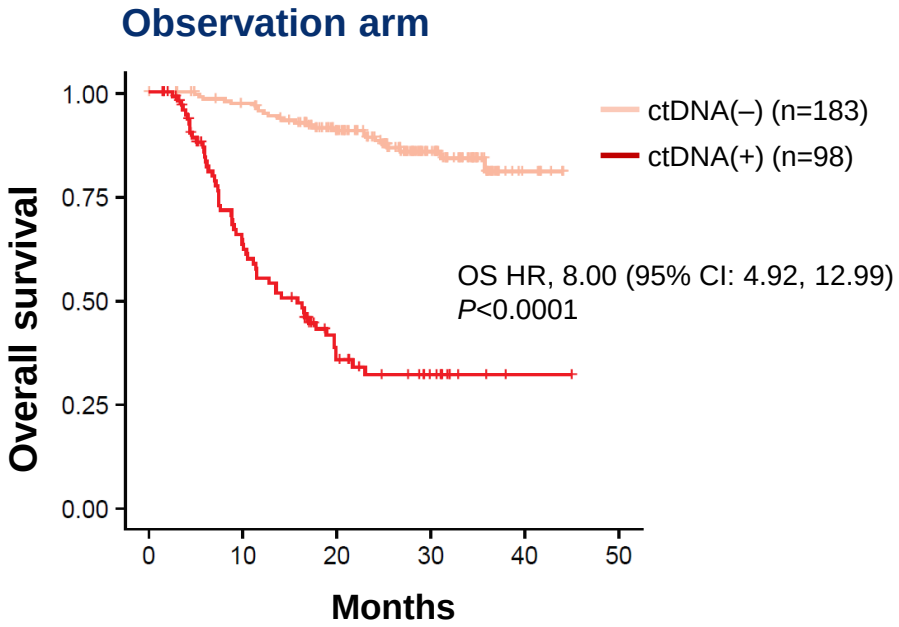




Powles et al Nature 2021

ctDNA(+) patients have poor prognosis





- IMvigor010 confirmed the prognostic value of ctDNA status

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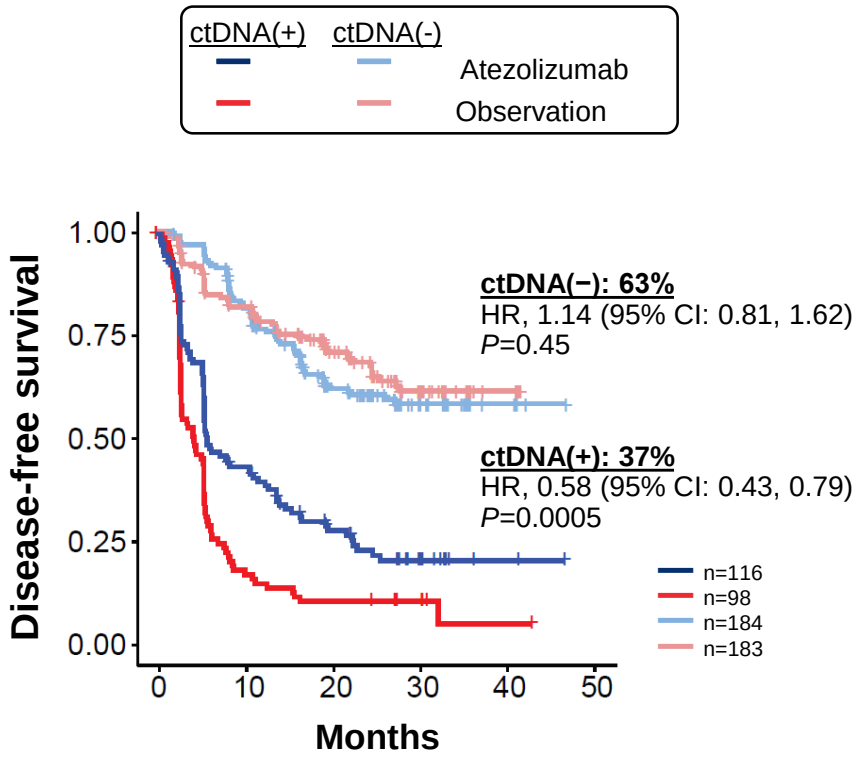
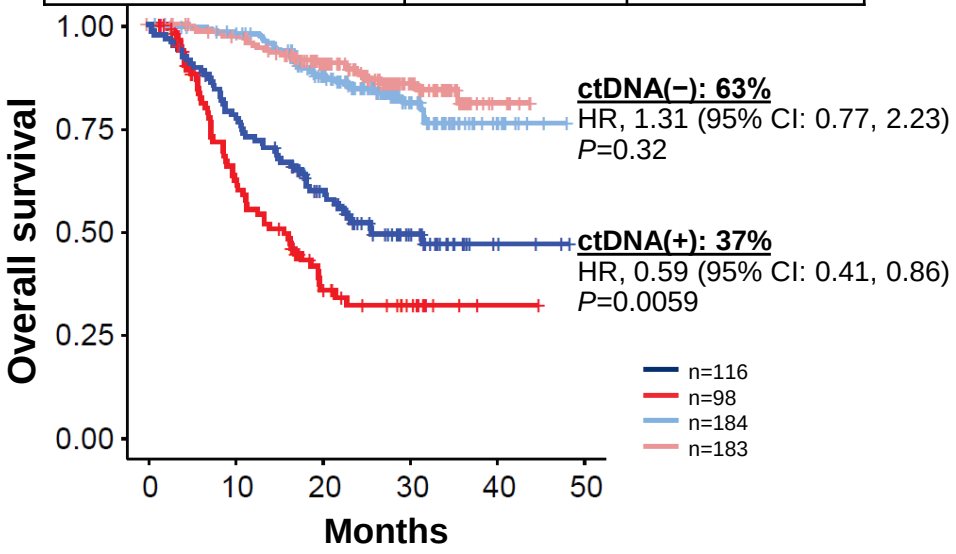
ctDNA(+) patients in the BEP had improved DFS and OS with atezolizumab vs observation

	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)

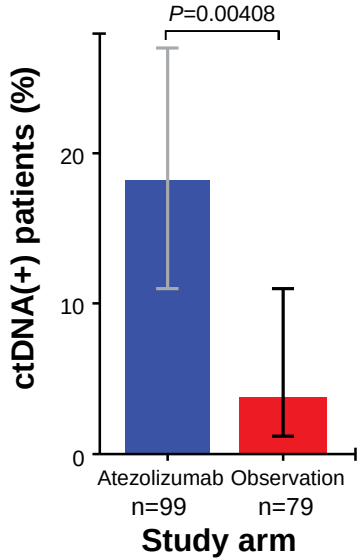




NR, not reached.

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

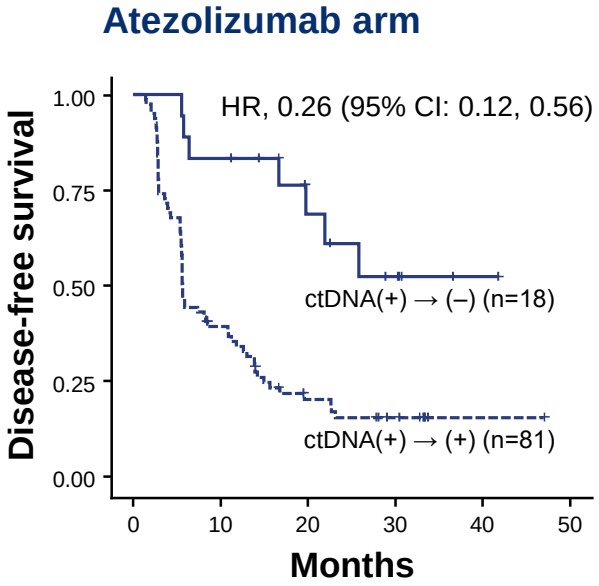
ctDNA clearance was associated with improved outcomes in the atezolizumab arm

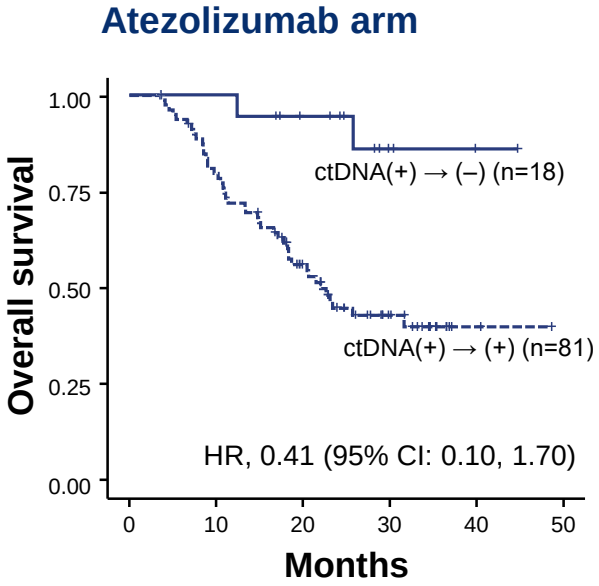


ctDNA(+) → (–)	18 (18.8%)	3 (3.8%)
ctDNA(+) → (+)	81 (81.82%)	76 (96.2%)

- ctDNA clearance occurs at a higher rate in the atezolizumab vs observation arm (C1 → C3)

Assessed using

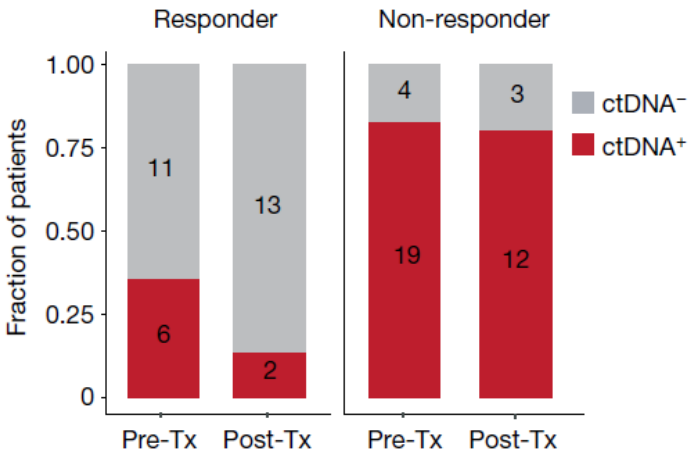


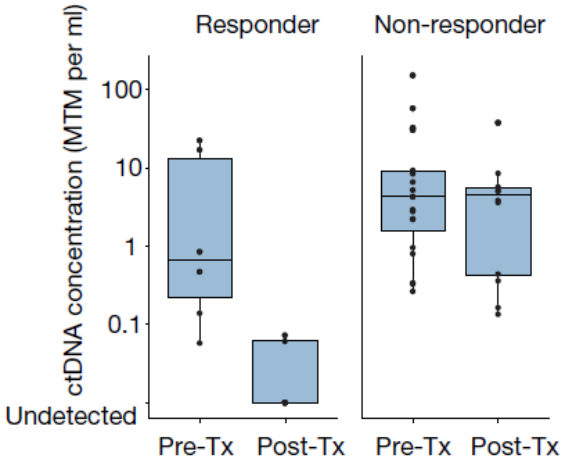


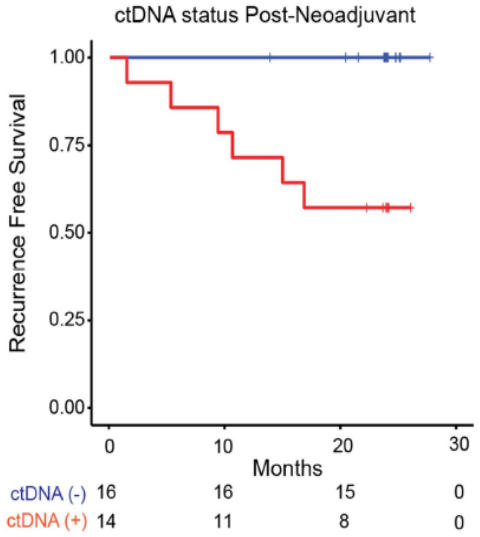
- ctDNA clearance was associated with improved DFS and OS outcomes in the atezolizumab arm

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

ctDNA levels also fall with neoadjuvant atezolizumab in MIBC.

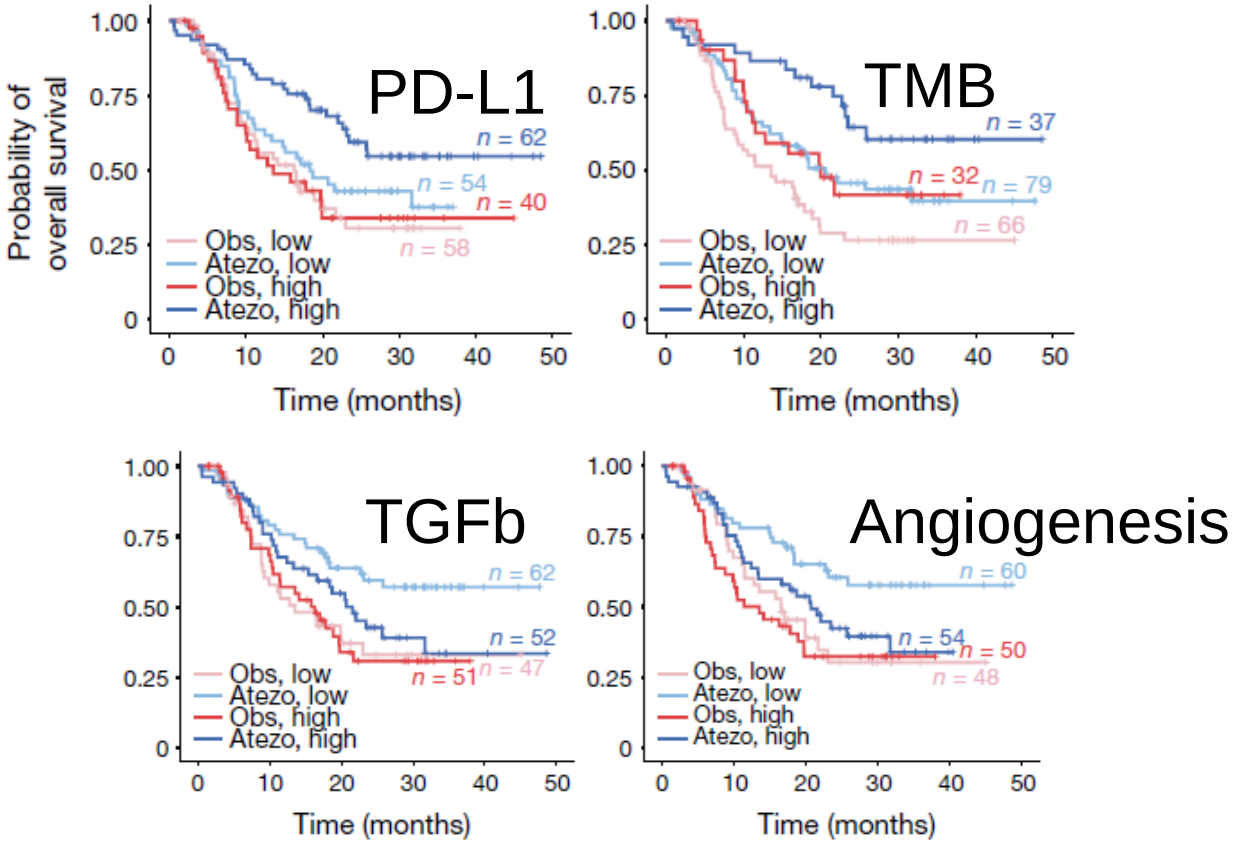






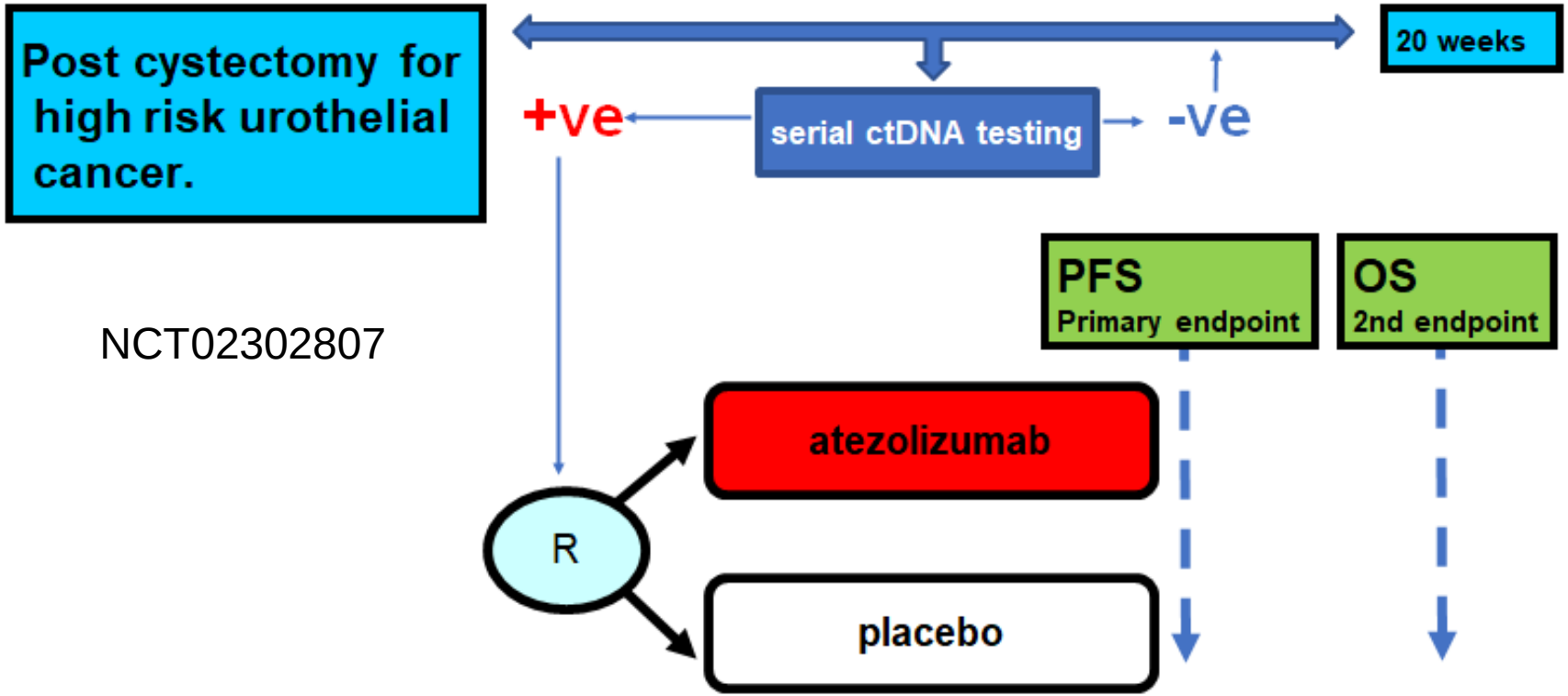
Powles et al Nature 2021

Outcome in ctDNA+ve patients is related to tissue based immune biomarkers



Powles et al Nature 2021

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



NCT02302807

RC48-ADC in Advanced HER2+ Urothelial Cancer

- In an open-label, multicenter, single-arm, non-randomized phase II study 43 eligibility patients
- HER2-positive (IHC 2+ or 3+)
- 51% *confirmed objective response rate* (cORR) per independent central review.
- The most commonly observed treatment-related adverse events included hypoesthesia (numbness), alopecia and hemotoxicity.
- The presented results are expected to support a global late stage clinical trial, including

Summary

- The first generation of biomarkers for single agent ICIs (PD-L1 and TMB) have not changes therapy in metastatic disease. They may have a role in combination with other biomarkers or therapies.
- T effector gene RNA signatures continue show a strong relationship with response but have not (and may not) be utilized.
- There is a rapid move towards circulating biomarkers with much promise.
- Novel combinations are developing new biomarkers. It would be good to not make the same mistakes.
- Tissue based and circulating biomarkers in combination may be transformative.