GONORTE
Grupo Oncológico

REUNIÓN POST CONGRESO DE LA SOCIEDAD EUROPEA DE ONCOLOGÍA MÉDICA 2021

Lunes, 27 de septiembre de 2021

Presentaciones más destacadas en cáncer urotelial

Enrique Grande

MD Anderson Cancer Center
Madrid • España

Disclosures

Honoraria for speaker engagements, advisory roles or funding of continuous medical education:

Advanced Accelerator Applications, AMGEN, Angelini, Astellas, Astra Zeneca, Bayer, Blueprint, Bristol Myers Squibb, Caris Life Sciences, Celgene, Clovis-Oncology, Dr. Reddy's, Eisai, Esteve, Eusa Pharma, Genetracer, GSK, Guardant Health, HRA-Pharma, IPSEN, ITM-Radiopharma, Janssen, Lexicon, Lilly, Merck KGaA, MSD, Nanostring Technologies, Natera, Novartis, ONCODNA (Biosequence), Palex, Pharmamar, Pierre Fabre, Pfizer, Roche, Sanofi-Genzyme, Servier, Taiho, Thermo Fisher Scientific

Research Grants:

Astellas, Astra Zeneca, IPSEN, Lexicon, Merck KGaA, MTEM/Threshold/Tersera, Nanostring Technologies, Pfizer, Roche

Leadership roles in medical societies:

ENETS, GETHI, GETNE, Grupo Centro de Tumores Genitourinarios

Private Healthcare provider:

MD Anderson Cancer Center Madrid (workplace)

Commercial Medical Education provider:

Universidad Europea de Madrid (UEM), Universidad CEU Cardenal Herrera, Universidad Rey Juan Carlos, Oncinfo

Stocks or ownership interest:

None

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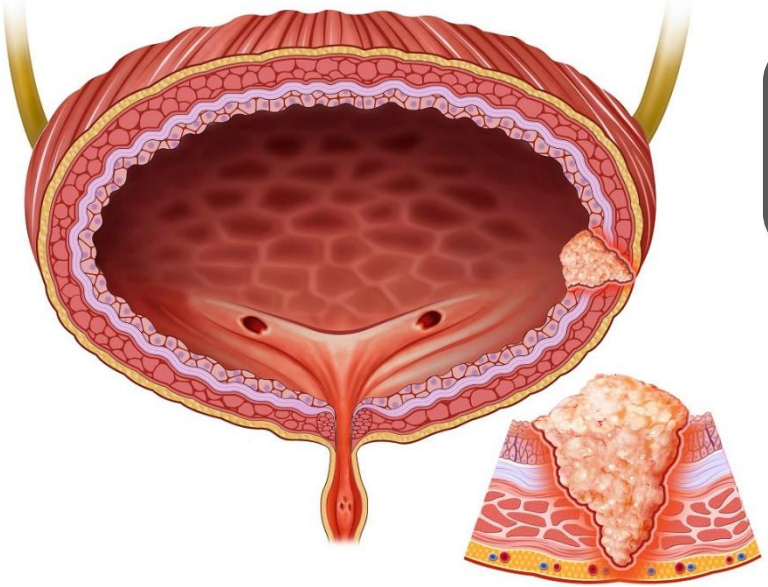
Clinical scenarios in Urothelial tumors



Perioperative	Upfront metastatic	Savage metastatic
Neoadjuvant chemotherapy	**Chemotherapy followed by maintenance avelumab**	**IO** (if not given before) or **ADCs** or **FGFR-inhibitor**
Adjuvant chemotherapy	IO single agent	Chemotherapy

IO: Immunoncology agent
ADC: Antibody drug-conjugate
FGFR: Fibroblast growth factor receptor

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Modified from https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. NCCN Guidelines in Bladder Cancer version 4.2021

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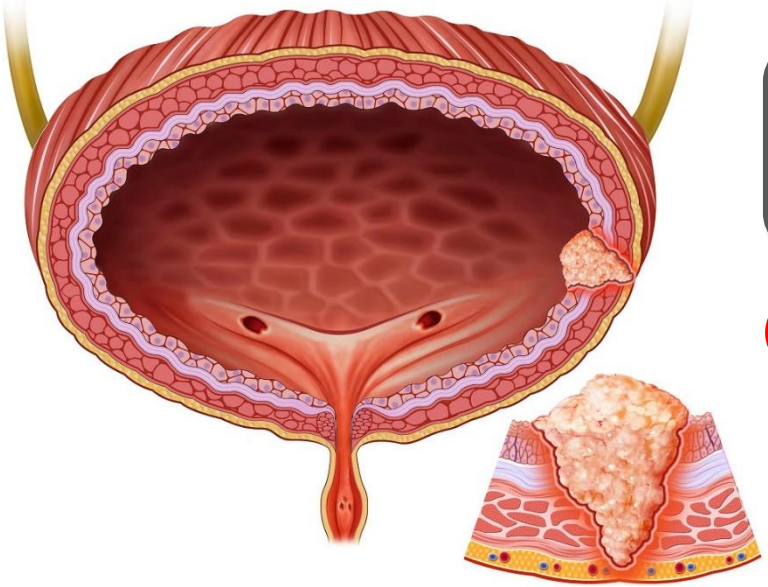

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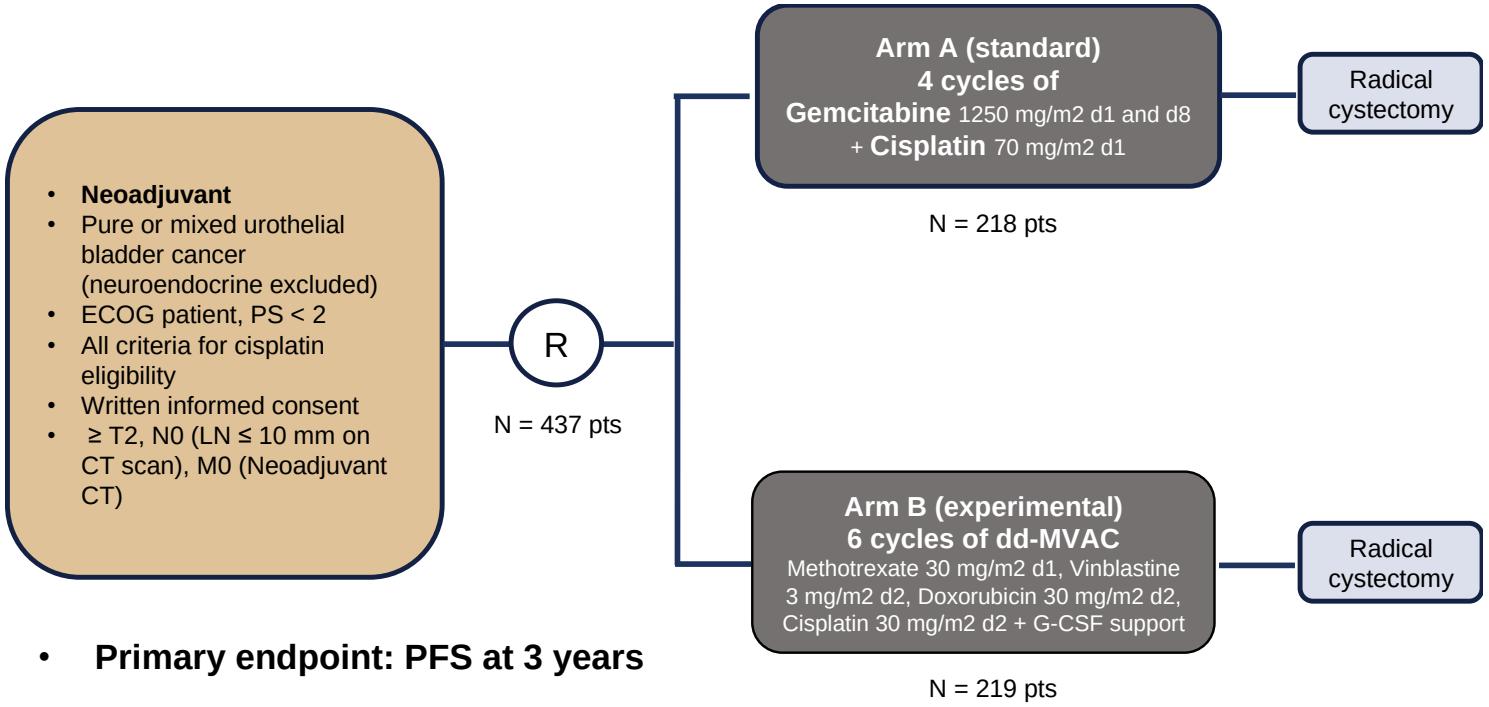
GETUG/AFU V05 VESPER Phase III Trial (Neoadjuvant)



- **Primary endpoint: PFS at 3 years**

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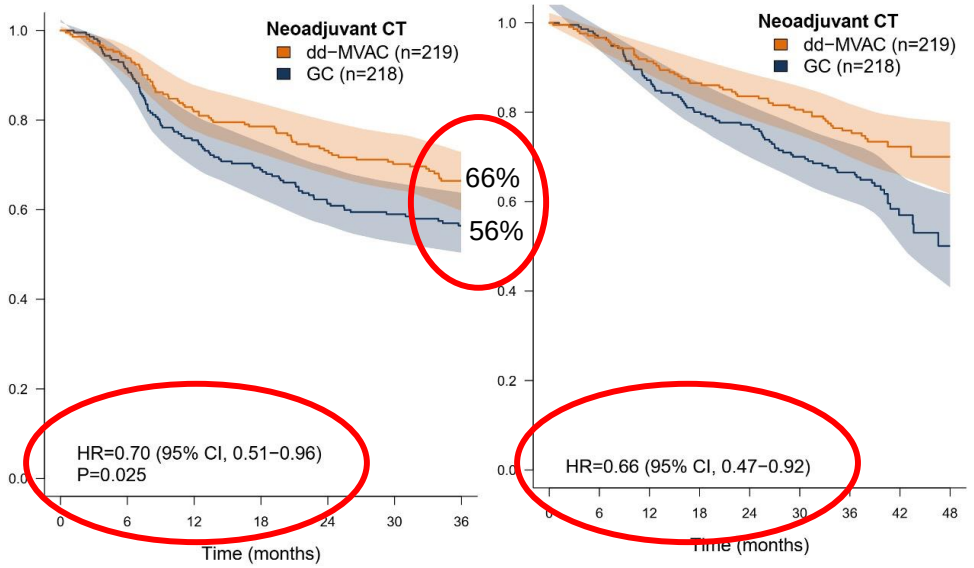
Pfister C, et al. Contemp Clin Trials Commun. 2020
Pfister C, et al. Eur Urol 2021
Pfister C, et al. ESMO 2021 #Abstract 6520

GETUG/AFU V05 VESPER Phase III Trial (Neoadjuvant)

Pathological response (neoadjuvant CT +cystectomy performed only)		
	GC	dd-MVAC
ypT0 N0	71 (36%)	84 (42%)
ypTis,Ta or T1 and ypN0	27 (14%)	42 (21%)
ypT2 N0	26 (13%)	28 (14%)
≥ ypT3 or ypN+	73 (37%)	43 (22%)



PFS **Overall Survival**

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Pfister C, et al. ESMO 2021 #Abstract 6520

GETUG/AFU V05 VESPER Phase III Trial (Neoadjuvant)

ACTIVITY in perspective

Consistent data in the control arm

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

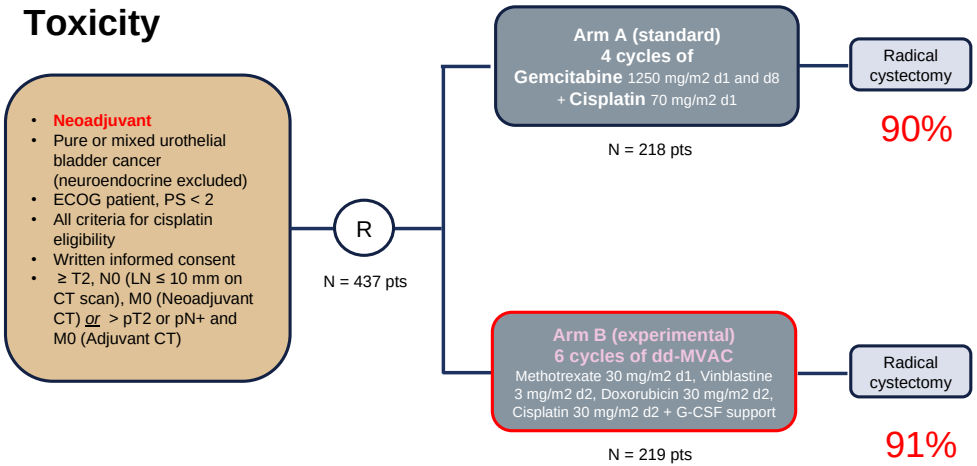
Outcome correlated with dose intensity?

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

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

GETUG/AFU V05 VESPER Phase III Trial (Neoadjuvant)

Toxicity



	GC (N=245)	dd-MVAC (N=248)	P value
Nausea/vomiting	7 (2.9%)	24 (9.7%)	0.003
Diarrhea	2 (0.81%)	3 (1.2%)	-
Asthenia	10 (4.1%)	35 (14%)	<0.001
Cardiovascular	17 (6.9%)	16 (6.5%)	>0.9
Kidney	13 (5.3%)	15 (6.0%)	0.9
Liver	13 (5.3%)	7 (2.8%)	0.2
Neuropathy	0	2 (0.81%)	-
Anemia	19 (7.8%)	54 (22%)	<0.0001
Neutropenia	113 (46%)	97 (39%)	0.14
Febrile neutropenia	6 (2.4%)	16 (6.5%)	0.053
Thrombopenia	41 (17%)	49 (20%)	0.5
Chemotherapy-related deaths	1	3	-

Treatment delivery:

- 60% of patients received the planned 6 cycles of dd-MVAC
- 84% received the 4 cycles of GC

Delay of surgery:

- 48 days for GC and 51 days for ddMVAC

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Pfister C, et al. ESMO 2021 #Abstract 6520

GETUG/AFU V05 VESPER Phase III Trial (Neoadjuvant)

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
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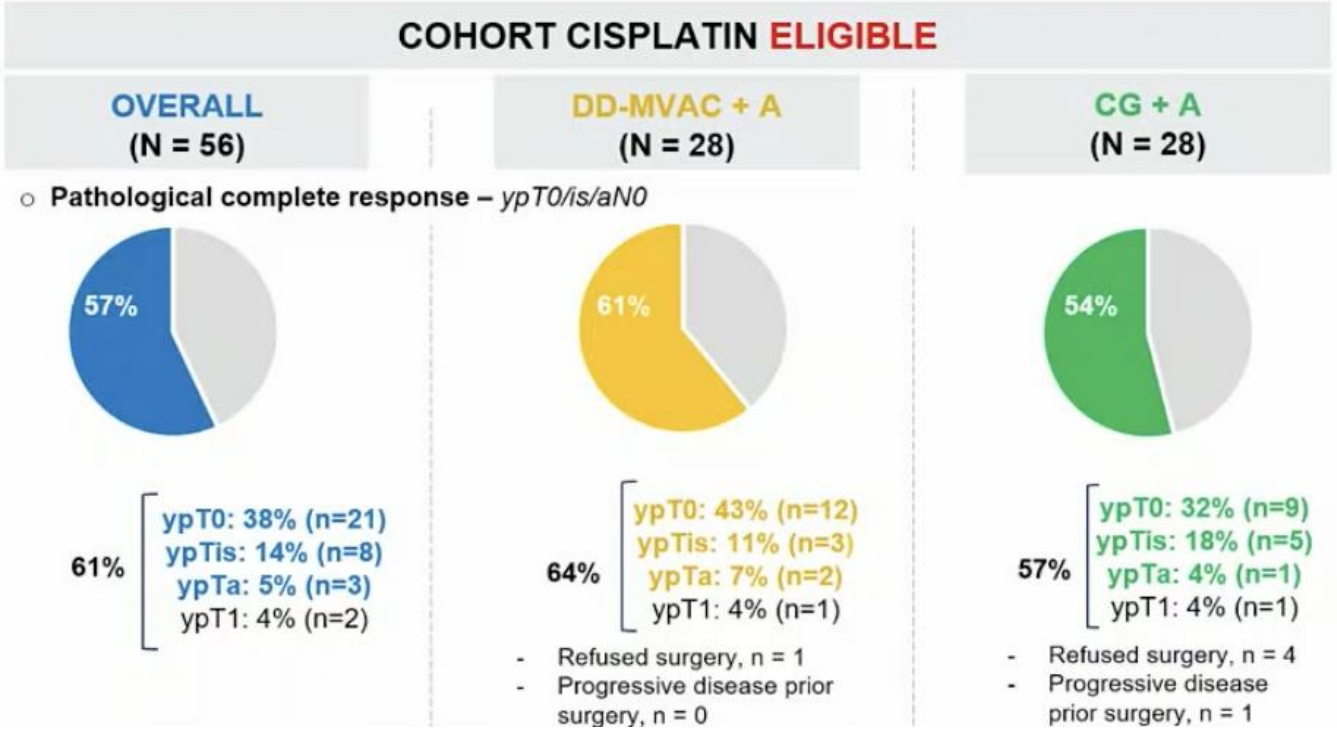
Rose TL, et al. J Clin Oncol 2021
Funt SA, et al. ASCO 2021

AURA: Avelumab as a neoadjuvant treatment in MIBC



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Martínez-Chanza N, et al. ESMO 2021

✓ VESPER trial supports dd-MVAC as the most active regimen in the Neoadjuvant approach to MIBC with an acceptable cost in toxicity

- Is it better a Neoadjuvant or the Adjuvant approach?
- ddMVAC vs Cisplatin + Gemcitabine?
- What's the optimal duration/intense of treatment?

VESPER

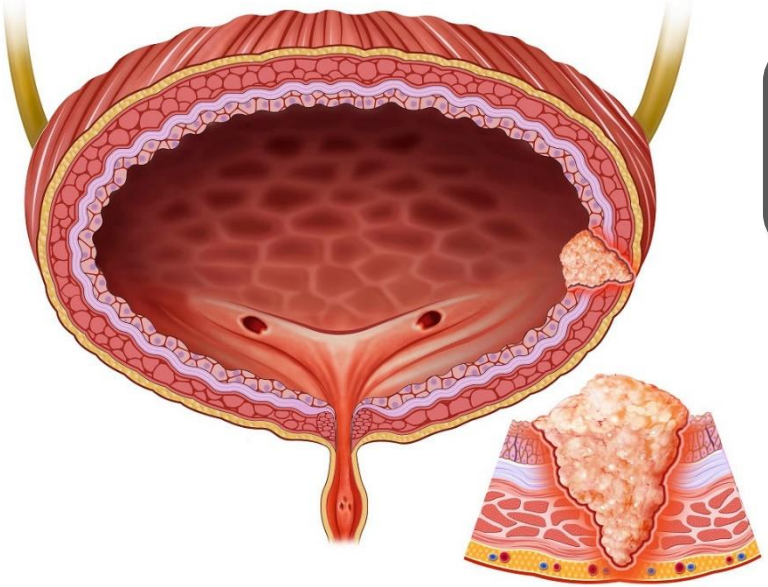
- Does radiation play a role?
- Lack of reliable biomarkers
- Any option for cisplatin-ineligible patients?

Still unanswered

- Role of immunotherapy and targeted agents → Should ongoing phase 3 studies rethink their control arms?

Enrique Grande, MD, PhD @drenriquegrande

Clinical scenarios in Urothelial tumors



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?

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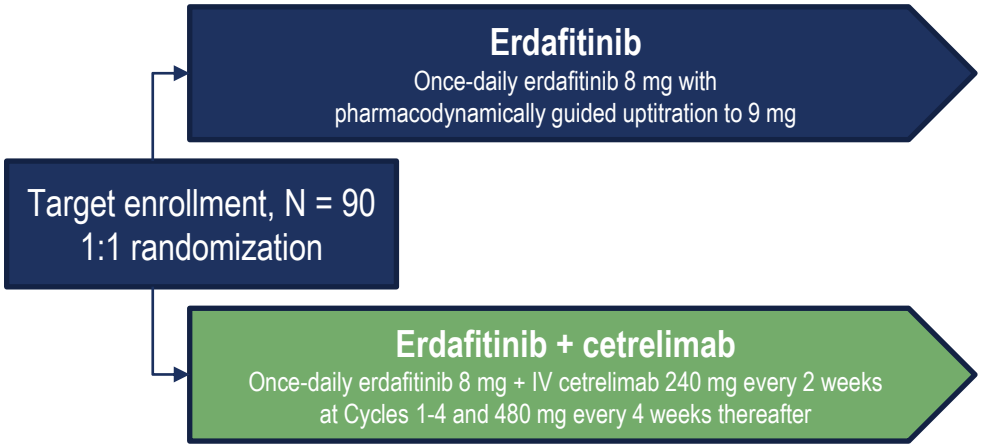
Modified from https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. NCCN Guidelines in Bladder Cancer version 4.2021

NORSE: Erdafitinib or Erdafitinib + Cetrelimab upfront metastatic Urothelial Carcinoma and FGFR+ Alterations

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

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Powles T, et al. ESMO 2021

NORSE: Erdafitinib or Erdafitinib + Cetrelimab upfront metastatic Urothelial Carcinoma and FGFR+ Alterations

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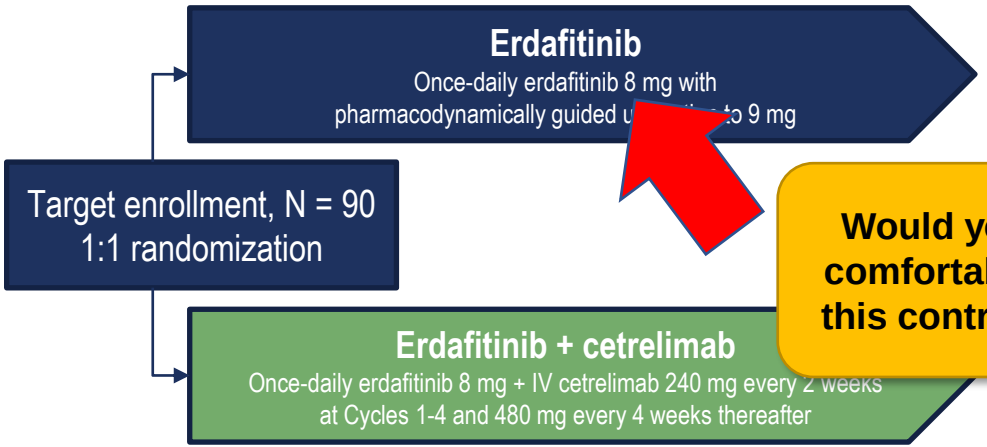

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NORSE: Baseline Demographics

Characteristic	Erdafitinib (n = 26)	Erdafitinib + Cetrelimab (n = 27)
Age, median (range), years	75 (45-92)	69 (56-91)
Men, n (%)	19 (73%)	20 (74%)
Presence of visceral metastases[a], n (%)	14 (54%)	14 (52%)
ECOG PS, n (%)[b]		
0-1	20 (77%)	17 (63%)
2	6 (23%)	9 (33%)
Primary tumor location, n (%)		
Lower tract	19 (76%)	22 (85%)
Upper tract	6 (24%)	4 (15%)
PD-L1 positive status[c], n (%)		
Yes	2 (8%)	2 (7%)
No	10 (39%)	7 (26%)
Unknown[d]	14 (54%)	18 (67%)
*FGFR*a[e], n (%)		
Mutations	23 (88%)	18 (67%)
Fusions	3 (12%)	7 (26%)
Mutations and fusions	0	1 (4%)

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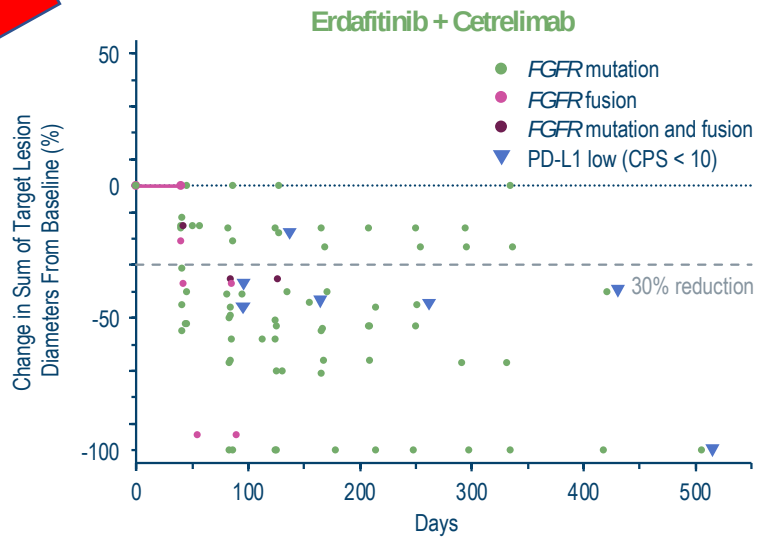
NORSE: Activity

	Erdafitinib (n = 18)	Erdafitinib + Cetr (n = 19)
ORR[a], n (%) [95% CI]	6 (33%) [13%-59%]	13 (68%) [43%-87%]
Complete response, n (%)	1 (6%)	4 (21%)
Partial response, n (%)	5 (28%)	9 (47%)
DOR, median, months [95% CI]	NE [4.4-NE]	6.9 [1.6-NE]
Responses ongoing, n (%)	5 (28%)	10 (53%)
Time to response, median (range), months	2.3 (1-6)	1.8 (1-4)
DCR, n (%) [95% CI]	18 (100%) [82%-100%]	17 (90%) [67%-99%]



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NORSE: Toxicity

Patients with TEAE, n (%)	Erdafitinib (n = 24)	Erdafitinib + Cetrelimab (n = 24)
TEAE of any grade	23 (96%)	23 (96%)
Most frequent (≥ 25% of patients)		
Hyperphosphatemia	14 (58%)	14 (58%)
Stomatitis	15 (63%)	13 (54%)
Diarrhea	12 (50%)	10 (42%)
Dry mouth	5 (21%)	14 (58%)
Dry skin	5 (21%)	9 (38%)
Anemia	6 (25%)	6 (25%)
Drug-related TEAEs leading to treatment discontinuation[a]	2 (8%)	Erdafitinib and/or cetrelimab: 7 (29%)[b] Both erdafitinib and cetrelimab: 2 (8%)

- The safety profile of erdafitinib + cetrelimab was generally similar to that of erdafitinib alone
- Grade 3-4 TEAEs occurred in 9 patients (38%) in the erdafitinib arm and 12 patients (50%) in the erdafitinib + cetrelimab arm; most frequent were:
  - Erdafitinib arm: anemia (n = 3 patients [12.5%]) and general physical health deterioration (n = 3 [12.5%])
  - Erdafitinib + cetrelimab arm: stomatitis (n = 3 [12.5%]), lipase increased (n = 3 [12.5%]), and fatigue (n = 2 [8.3%])
- 1 death in the erdafitinib + cetrelimab arm was determined to be related to cetrelimab (respiratory failure)

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NORSE trails in perspective: the challenging treatment of heterogeneous Cisplatin-ineligible 1st line setting

	Erdafitinib (n=18)	Erdafitinib + Cetrelimab (n=19)	Rogaratinib + Atezolizumab (n=25)	Enfortumab Vedotin (EV) + Pembrolizumab (n=45)	Gemcitabine + Carboplatin (n=119)	Pembrolizumab (n=370)
ORR, n (%)	6 (33%)	13 (68%)	11 (44%)	33 (73%)	49 (41%)	106 (29%)
Complete Response, n (%)	1 (6%)	4 (21%)	4 (16%)	7 (16%)	4(3.4%)	33 (9%)
Partial Response, n (%)	5 (28%)	9 (47%)	7 (28%)	26 (58%)	45 (38%)	73 (20%)
Median duration of response (mos)	NE	6.9 mo	-	25.6 mo	-	30.1 mo
Responses ongoing n (%)	5 (28%)	10 (53%)	-	12 (36%)	-	32 (9%)
Time to response, median (range), mos	2.3 (1-6)	1.8 (1-4)	-	2 (1.4-4.2)	-	2.1 (1.3-9)
DCR, n (%)	18 (100%)	17 (90%)	17 (68%)	93%	74%	173 (47%)

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Sridhar S, et al. ESMO 2021

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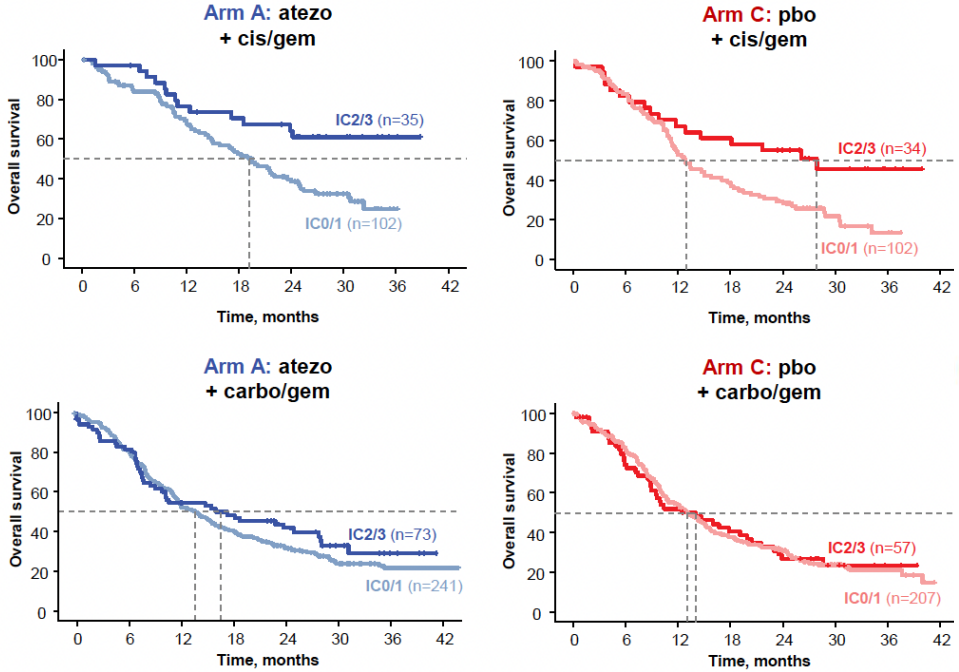
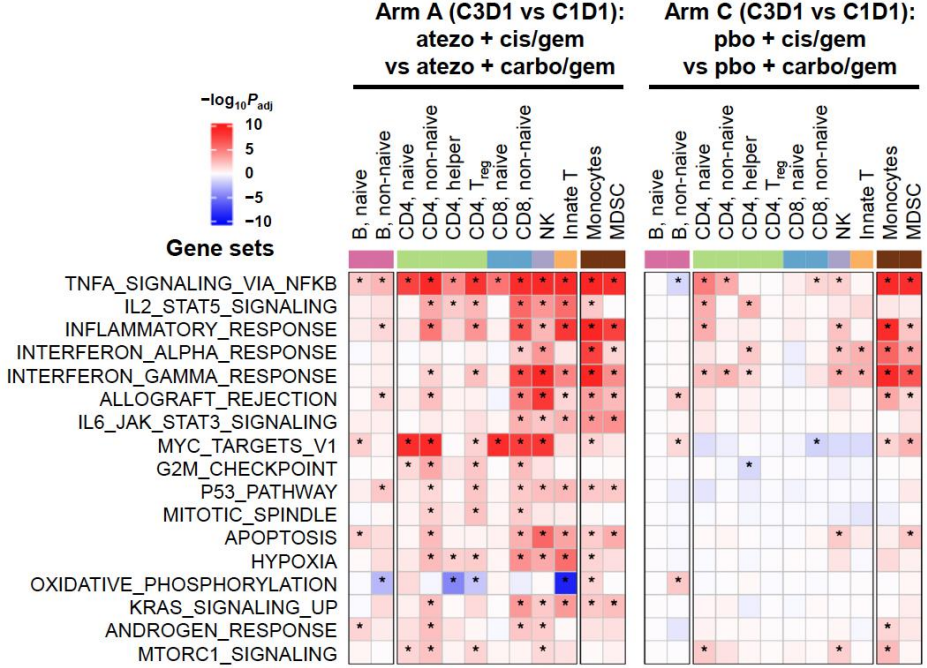
IMVIGOR 130: Cisplatin-related immunomodulation with atezolizumab + CIS or CARBO-based chemo in mUC





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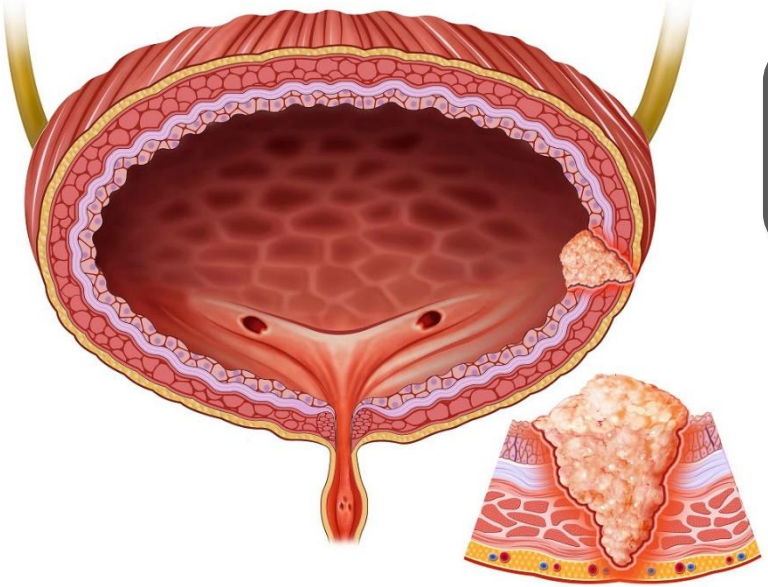
Galsky M, et al. ESMO 2021 Abstract #4107

Clinical scenarios in Urothelial tumors



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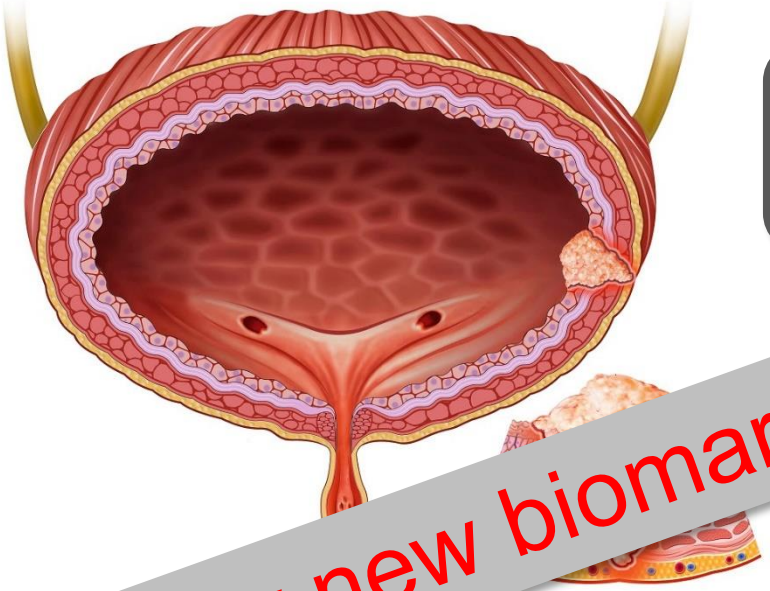

Perioperative	Upfront metas…	…static
Neoad…	…therapy followed by maintenance avelumab	**IO** (if not given before) or **ADCs** or **FGFR-inhibitor**
Adjuvant chemotherapy	IO sin…e agent	Chemot…erapy

Any new biomarkers or targets in mUC?

?

IO: Immun…
ADC: Antibo… …gate
FGFR: Fibrob… …growth factor receptor

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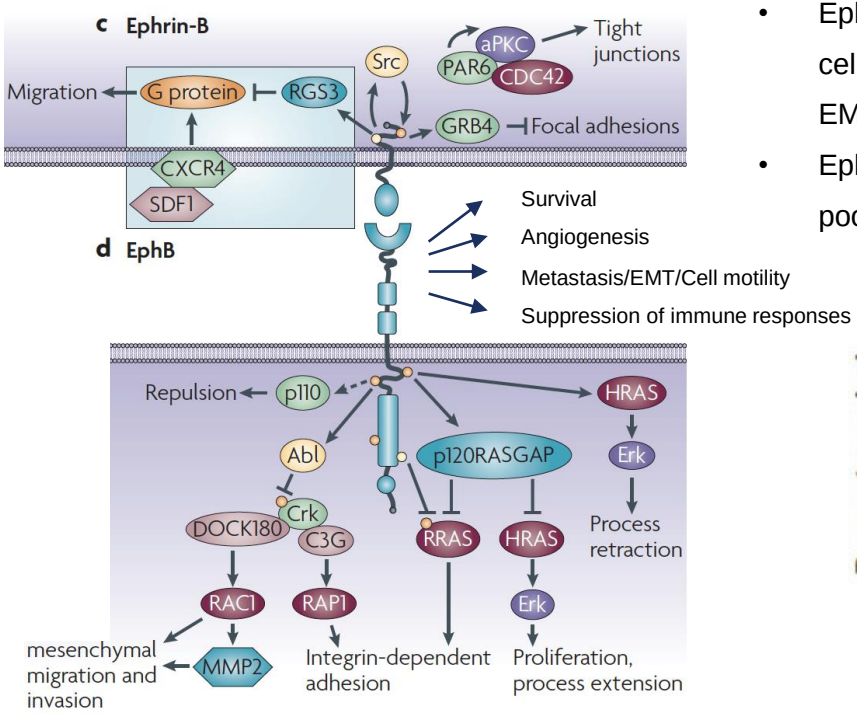
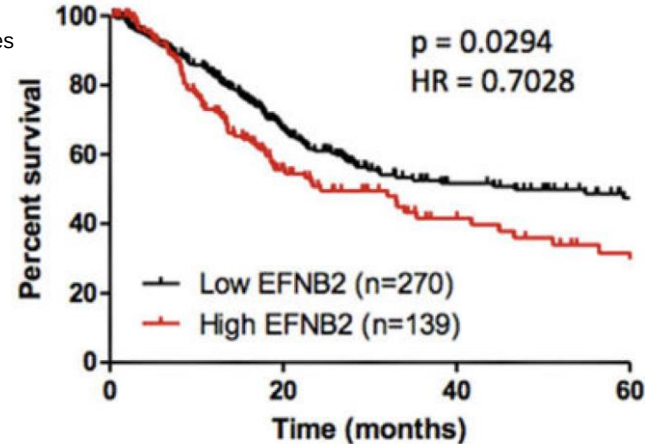
Modified from https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. NCCN Guidelines in Bladder Cancer version 4.2021

Bidirectional signalling of Eph receptors and ephrins in urothelial cancer



- Eph receptor tyrosine kinases and their ephrin ligands are present in cancer cells launching a complex bidirectional signalling involved in angiogenesis, EMT, tumor development and immune-suppression
- EphB2 and B4 are expressed in 34% and 94% of UC and correlate with poor outcome based on TCGA data (mRNA)



Pasquale EB. Nat Rev Cancer 2010
Oweida A, et al. Mol Carcinog 2017
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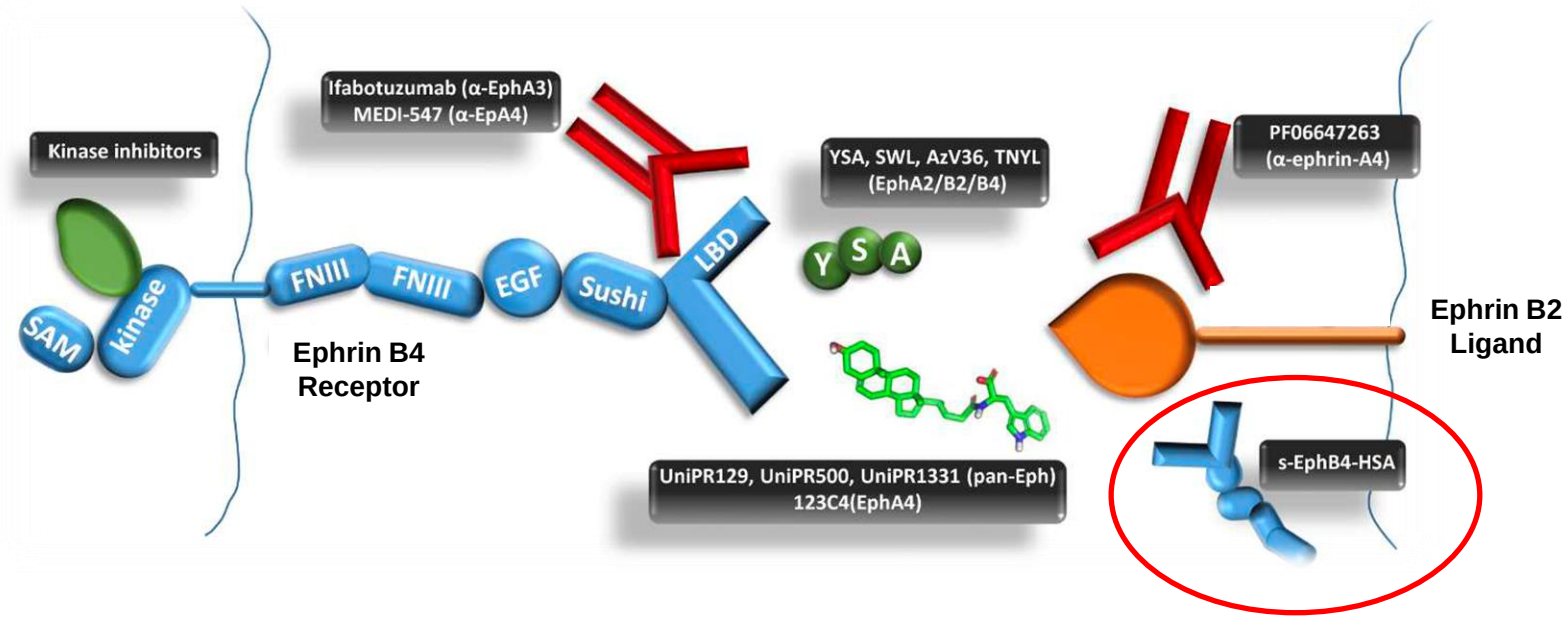
Ieguchi & Maru. Cancer Sci 2019
Li X, et al. PLOS One 2014

sEphB4-HSA: a fusion protein of soluble EphB4 and albumin that binds to EphrinB2



Modified from Lodola A, et al. Eur J Med Chem 2017
https://www.cancer.gov/publications/dictionaries/cancer-drug/def/recombinant-ephb4-hsa-fusion-protein
Shi S, et al. J Pharm Sci 2012
Thomas JS, et al. Journal of Clinical Oncology 36, no. 4_suppl (February 01, 2018) 285-285

Phase II trial of pembrolizumab in combination with sEphB4-HSA in previously treated mUC

- 70 platinum-refractory mUC pts with no prior PD1/PDL1 tx
- Most pts were treated just after platinum (91.4%)
- Well balanced by prognostic Bellmunt's criteria
- 46 (65.7%) pts expressed EphrinB2

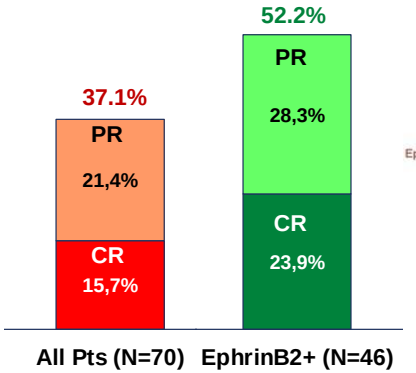
sEphB4-HSA

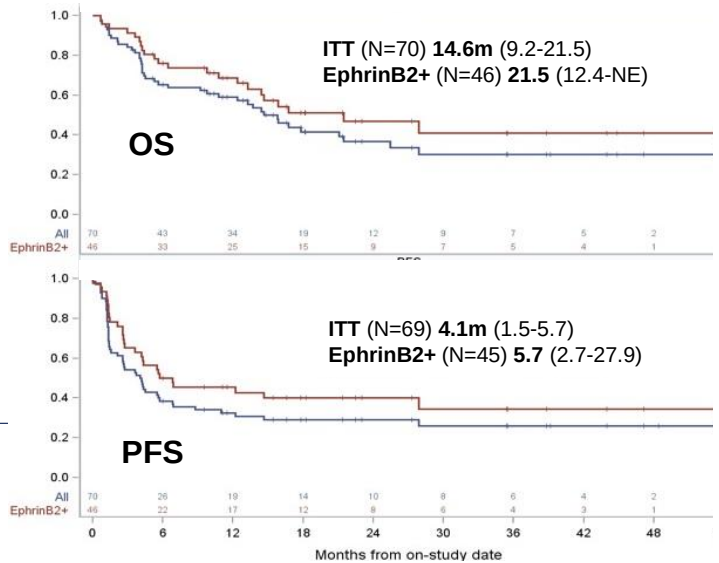
10 mg/Kg IV q1W

+

Pembrolizumab

200mg IV q3W

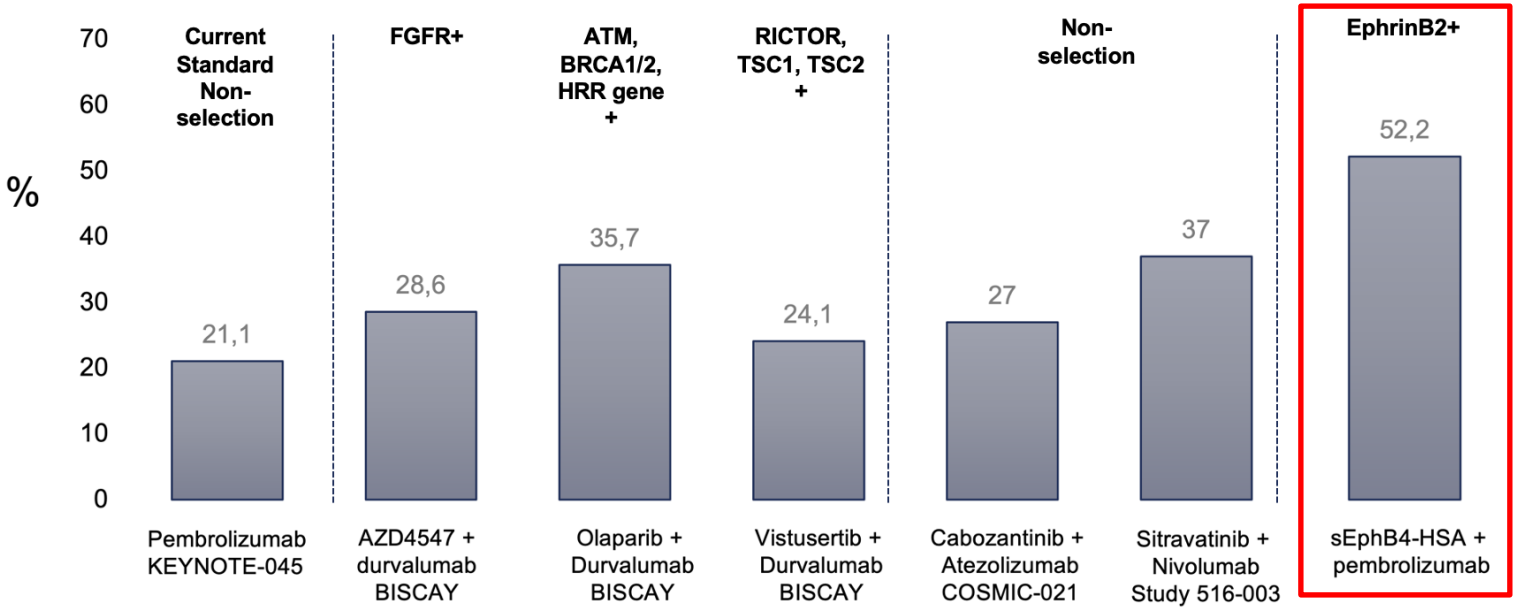




Sadeghi S, et al. ESMO 2021 #Abstract 6510

Can we consider the expression of EphrinB2 a good biomarker in mUC?

ORR with IO + targeted agents or TKI + IO combo in platinum-refractory mUC molecularly-enriched population



Bellmunt J, et al. N Engl J Med 2017
Powles T, el al. Nat Med 2021
Pal S, et al. ASCO 2020 virtual poster presentation
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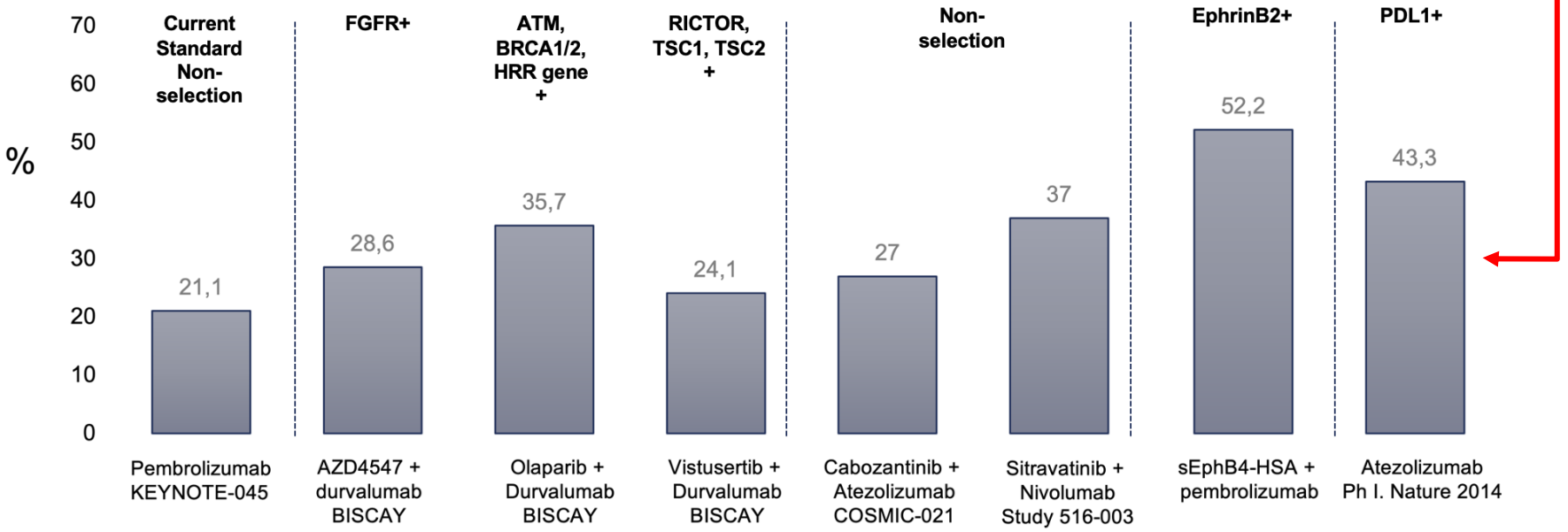
Careful when overinterpreting small and non-randomized trials



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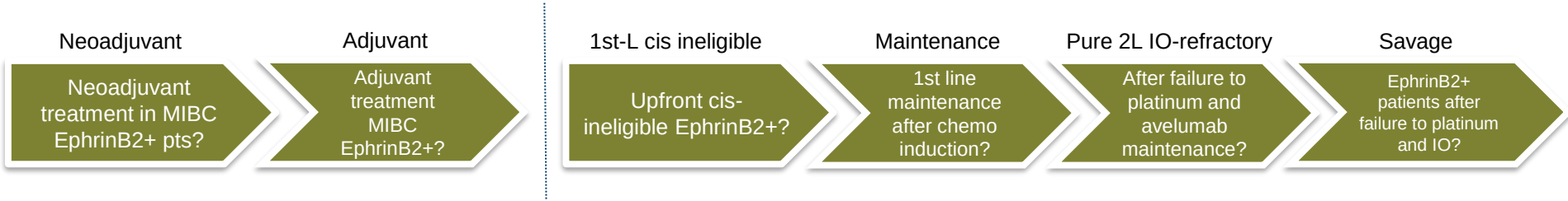
Did we find the Holy Grail for urothelial tumors? Maybe, why not? But there are many questions still pending

- Does EphrinB2 membrane IHC staining really correlate with poor prognosis?
- Does the activity of sEphB4-HSA correlate with levels of EphrinB2 expression?
- Any insights of the activity of chemo or novel ADCs in EphrinB2+ patients?
- Is there a correlation between EphrinB2 and PDL1 expression?
- Next steps for the combo sEphB4-HSA + pembrolizumab?



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Grupo Oncológico

REUNIÓN POST CONGRESO DE LA SOCIEDAD EUROPEA DE ONCOLOGÍA MÉDICA 2021

Lunes, 27 de septiembre de 2021