

Qué biomarcadores son realmente necesarios en carcinoma urotelial avanzado ?

Yves Allory

Disclosures

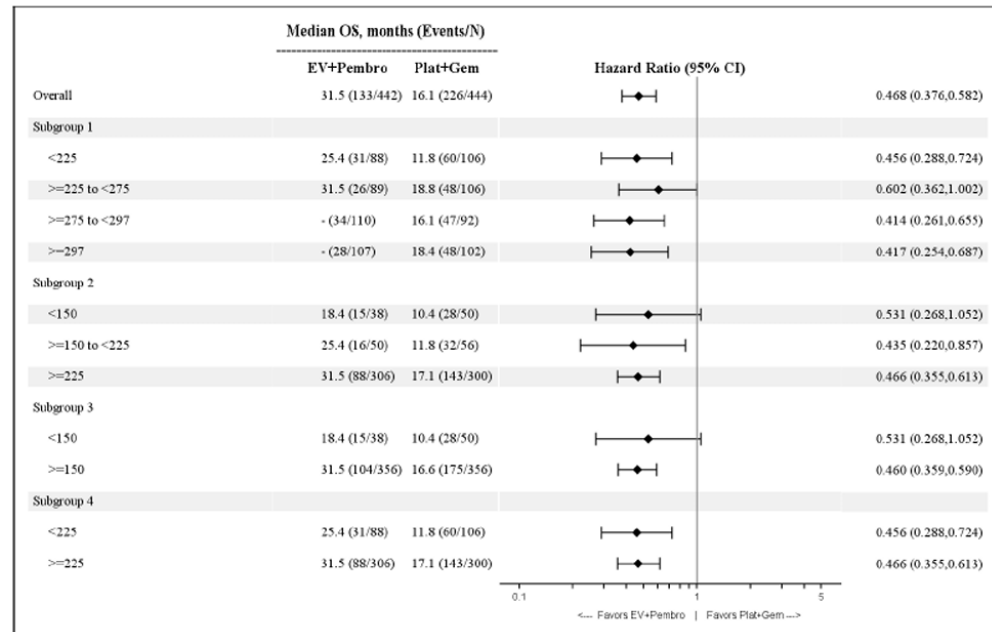
- Consultant : AstraZeneca, Janssen, MSD, VitaDx
- Invited speaker: Astellas, AstraZeneca, Bristol-Myers Squibb, Janssen, MSD, Sanofi
- COBLAnCE cohort support : Bristol-Myers Squibb, MSD
- Public and charity fundings : INCa, ANR, Ligue Contre le Cancer, Fondation ARC

Required biomarkers for advanced urothelial carcinoma ?

- E.M.A. approvals
- Real life for oncologists : helping choice !
 - Antibody Drug Conjugates : is immunohistochemistry necessary ...or helpful?
 - Immunological Check-points Inhibitors : is PD-L1 status necessary?
 - FGFR inhibitors (Erdafitinib) : which *FGFR3* testing ?
- Diagnostic needs for pathologists...

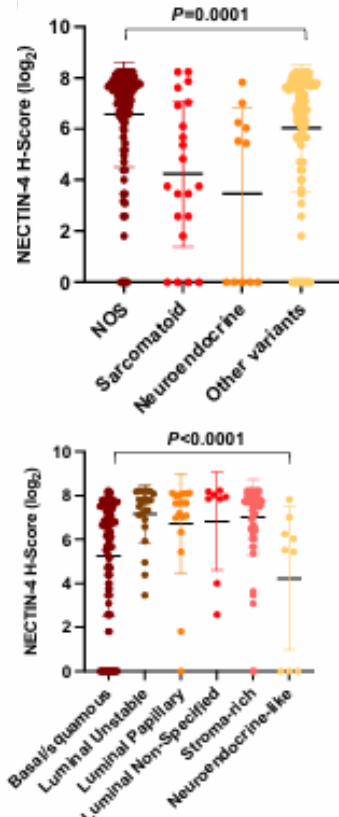
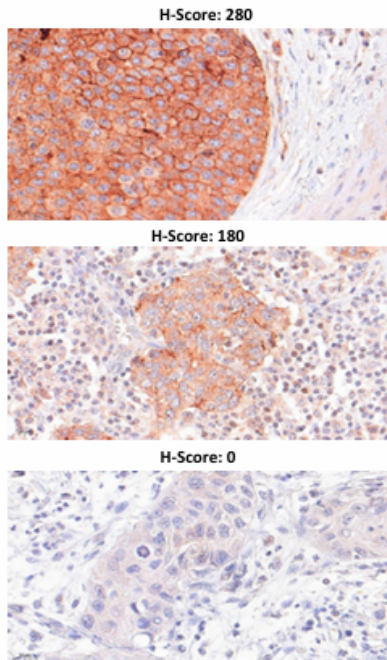
Enfortumab Vedotin + Pembolizumab : Nectin-4 target

Figure 43: Subgroup Analysis of Overall Survival for H-Score of Nectin-4 Expression (EV-302 ITT Analysis Set)



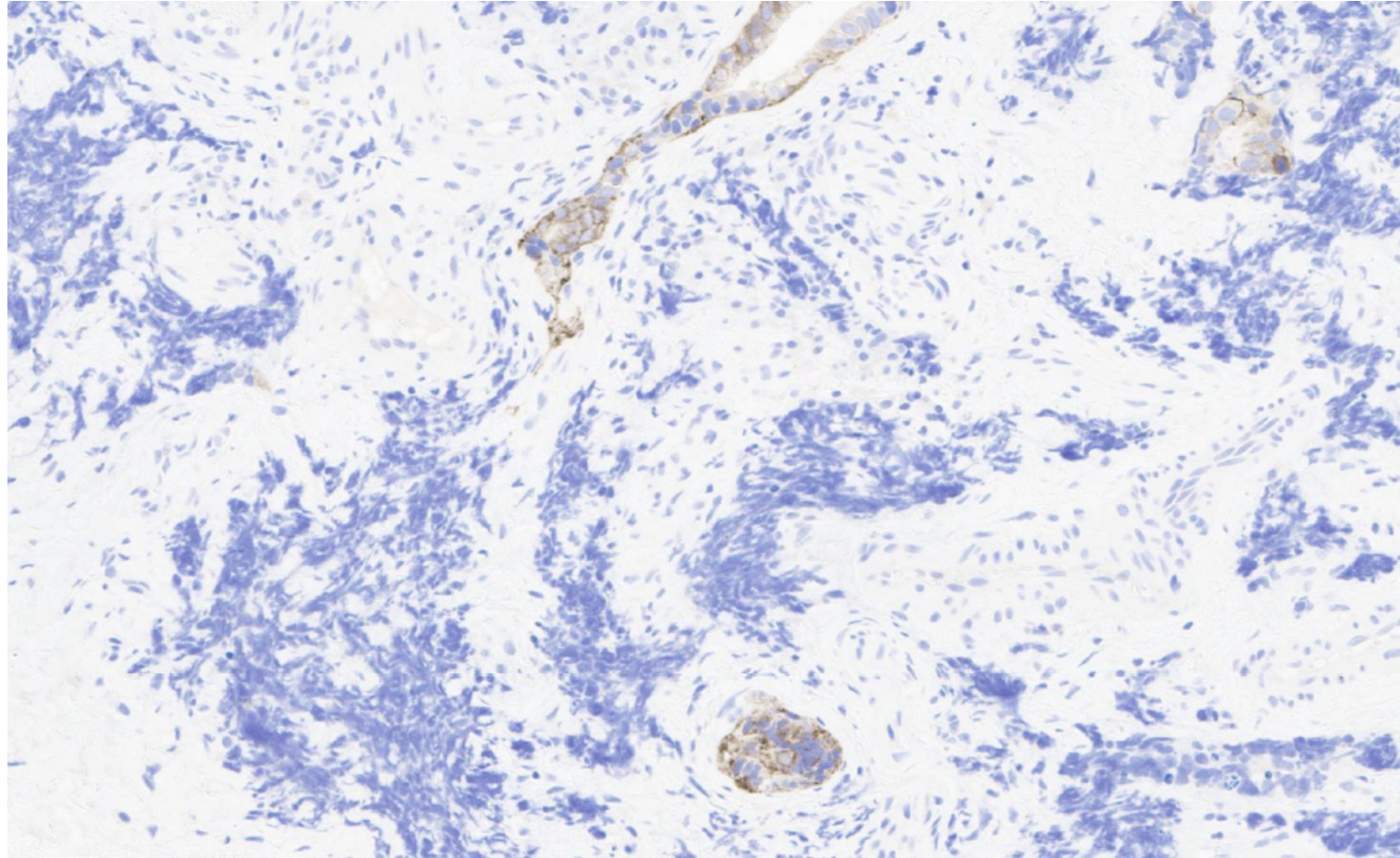
No indication for Nectin-4 immunostaining
prior to treatment decision

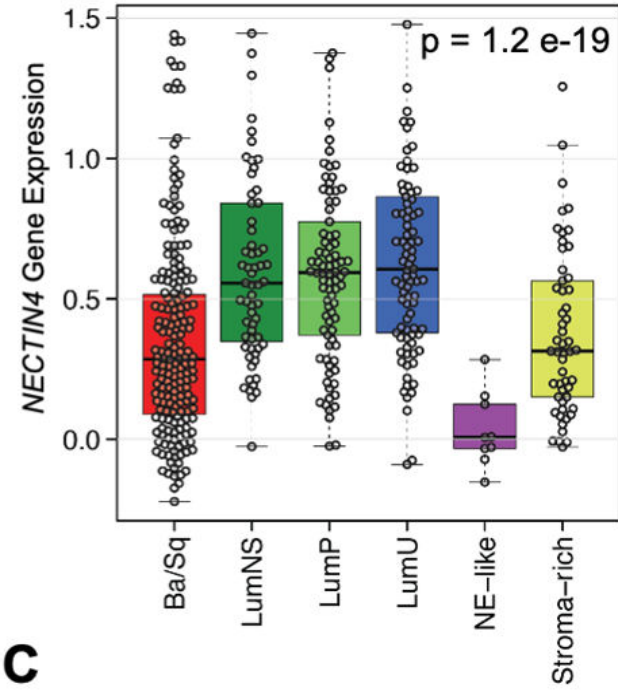
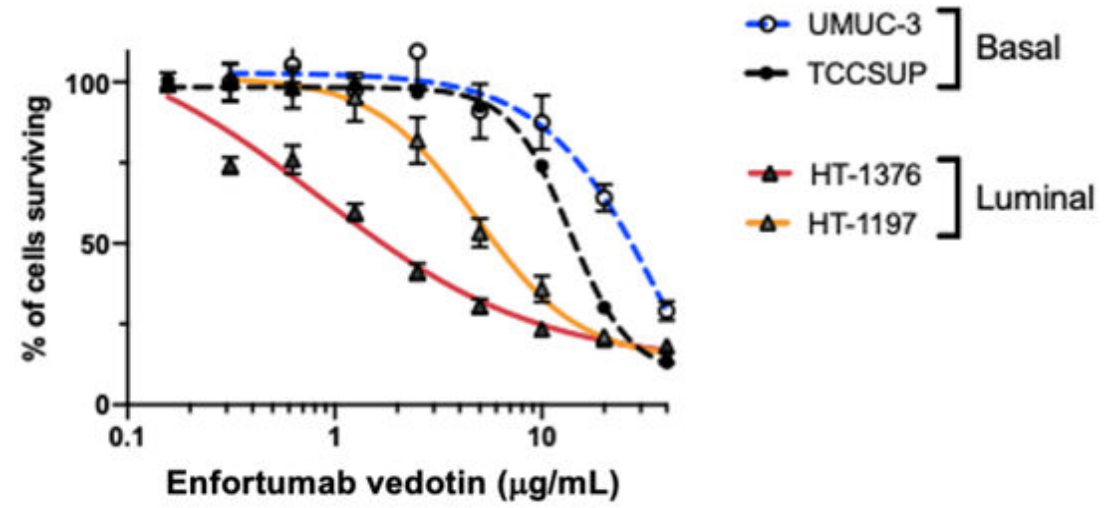
Nectin-4 is not expressed in all urothelium carcinoma but it is still unknown whether it impacts response to EV+Pembro...



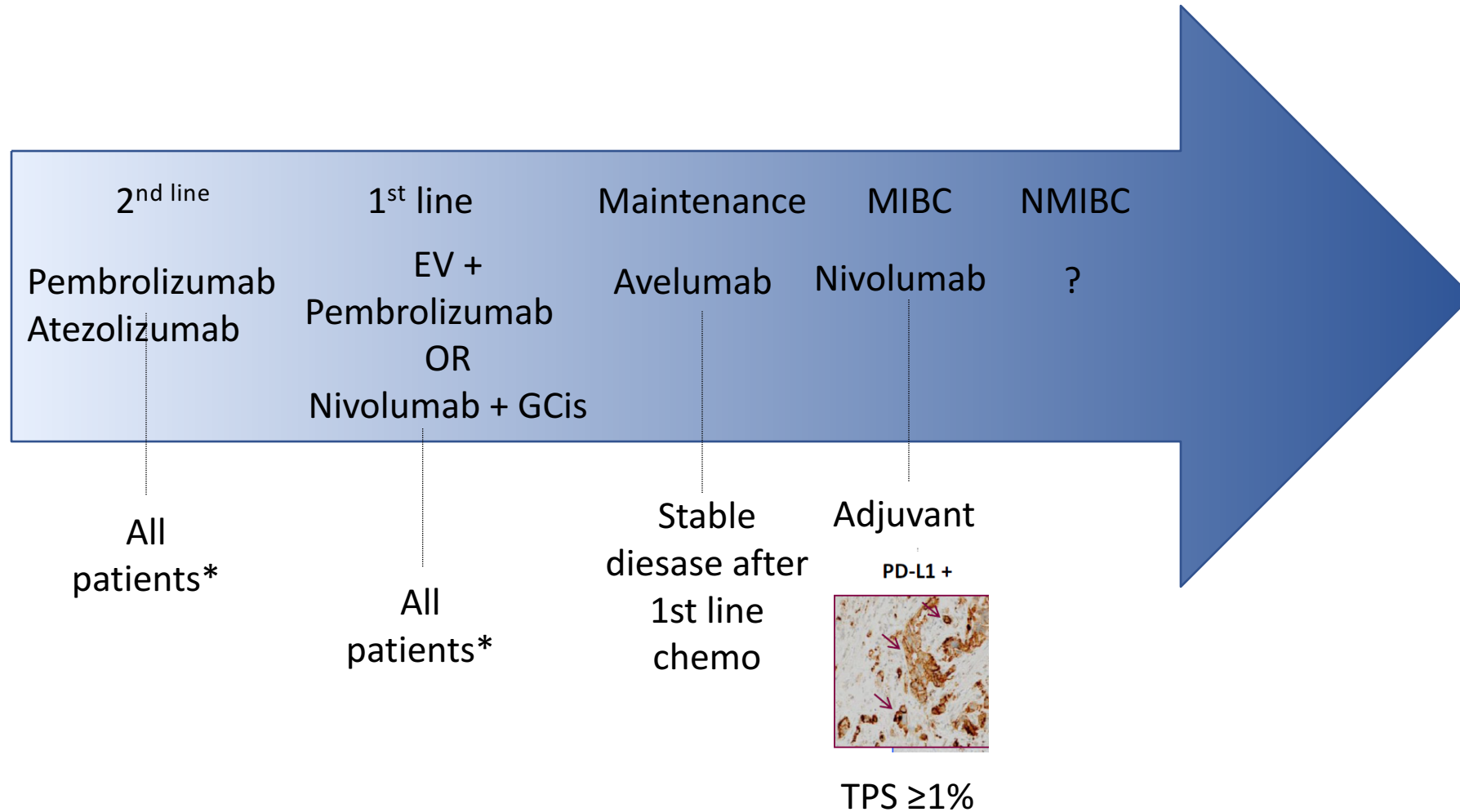
	Both markers expressed	No marker expression	Only TROP2 not expressed	Only Nectin 4 not expressed	Not available	
Total number	177	5	8	15	42	
Histology						
Neuroendocrine	2 (1.1)	4 (80.0)	4 (50.0)	0		
Sarcomatoid	11 (6.2)	1 (20.0)	2 (25.0)	3 (20.0)		
Large nested	6 (3.4)	0	0	1 (6.7)		
Squamous	46 (25.8)	0	0	7 (46.7)		
Other variants		0	0	0		
Not other specified	81 (45.5)	0	2 (25.0)	4 (26.7)		<i>P=0.0006</i>
Molecular subtypes						
Consensus subtypes						
Basal/squamous	80 (46.2)	2 (40.0)	3 (37.5)	13 (92.9)		
Luminal nonspecified	7 (4.0)	0	0	0		
Luminal Papillary	15 (8.7)	0	0	0		
Luminal Unstable	18 (10.4)	0	0	0		
Neuroendocrine-like	2 (1.2)	2 (40.0)	4 (50.0)	0		
Stroma-rich	51 (29.5)	1 (20.0)	1 (12.5)	1 (7.1)		<i>P<0.0001</i>
Protein-based subtypes						
Luminal	118 (66.7)	1 (20.0)	5 (62.5)	6 (40.0)		
Basal	59 (33.3)	3 (60.0)	1 (12.5)	9 (60.0)		<i>P<0.0001</i>
Double negative	0	1 (20.0)	2 (25.0)	0		
FGFR3 alteration status						
Altered	19 (10.7)	0	0	3 (20.0)		
Wild type	159 (89.3)	5 (100.0)	8 (100.0)	12 (80.0)		<i>P=0.26</i>
PD-L1 assessment						
Immune cell score (IC)						
IC < 5%	118 (66.3)	4 (80.0)	6 (75.0)	9 (60.0)		
IC ≥ 5%	60 (33.7)	2 (20.0)	2 (25.0)	6 (40.0)		<i>P=0.80</i>
Combined Positive Score (CPS)						
CPS < 10	99 (55.6)	3 (60.0)	6 (75.0)	9 (60.0)		
CPS ≥ 10	79 (44.4)	2 (40.0)	2 (25.0)	6 (40.0)		<i>P=0.72</i>

Nectin-4 in a mixed carcinoma associating urothelial carcinoma with glandular divergence and neuroendocrine small cell carcinoma



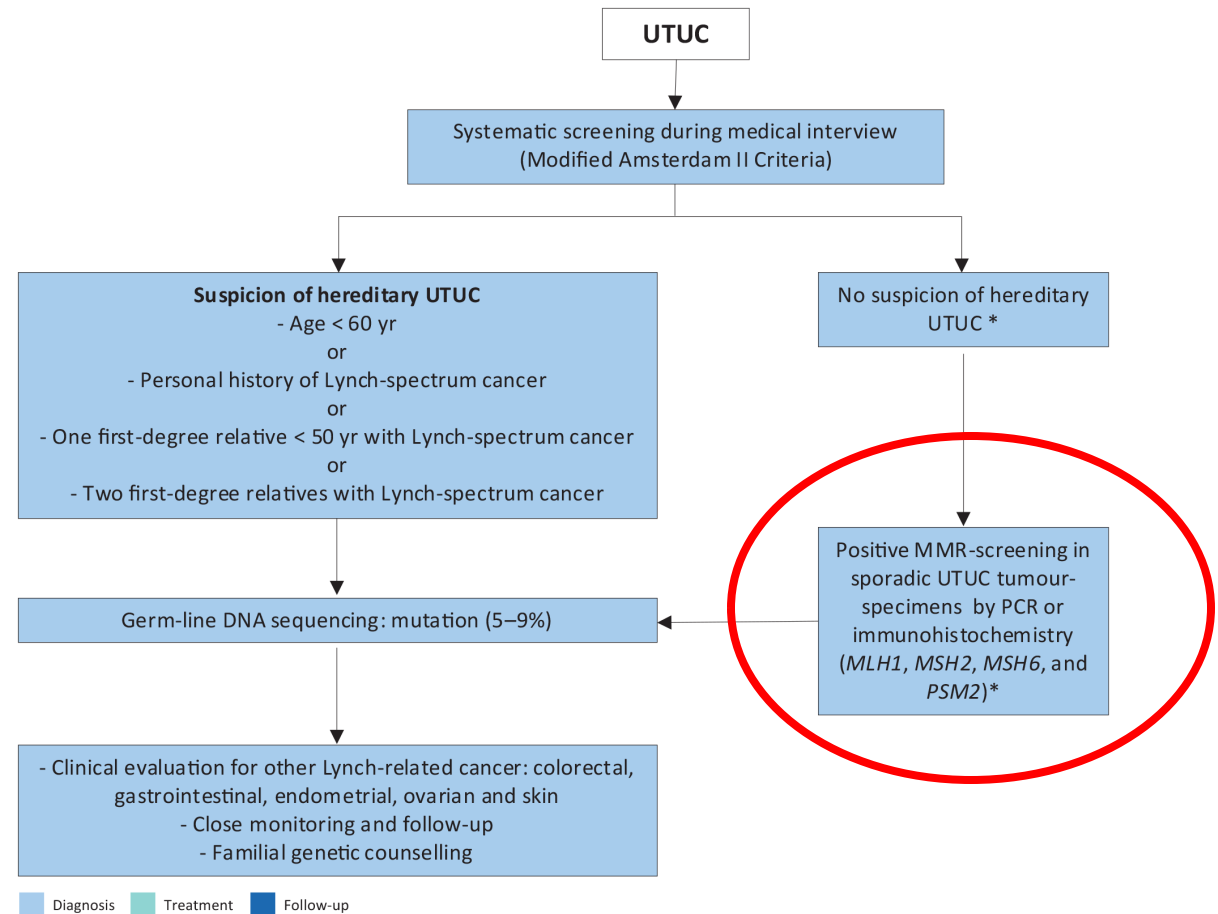
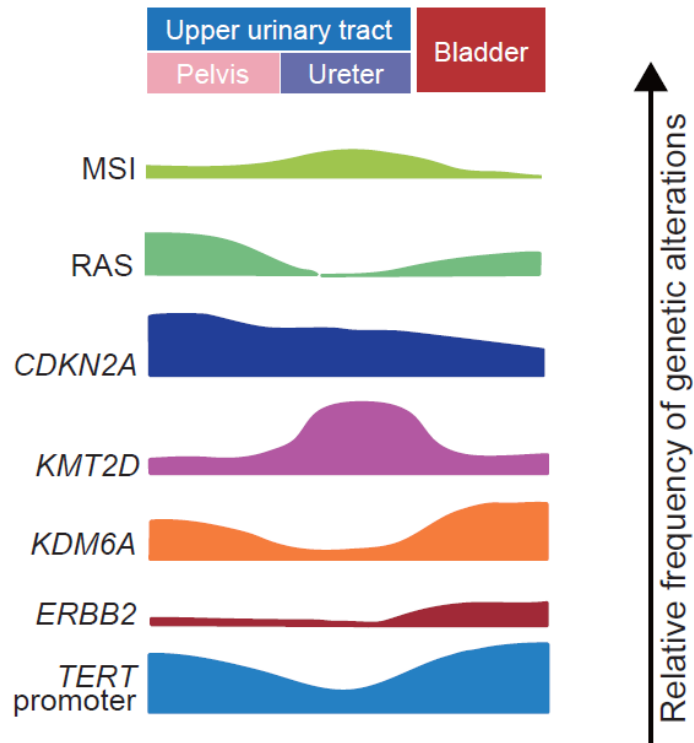
B**C****F**

Immunotherapies in Europe in 2025



* Without physical conditions forbidding use

Screening of patients with Upper Urinary Tract Urothelial Carcinoma for MSI or Lynch syndrome might also argue for ICI use



Fujii, Cancer Cell 2021

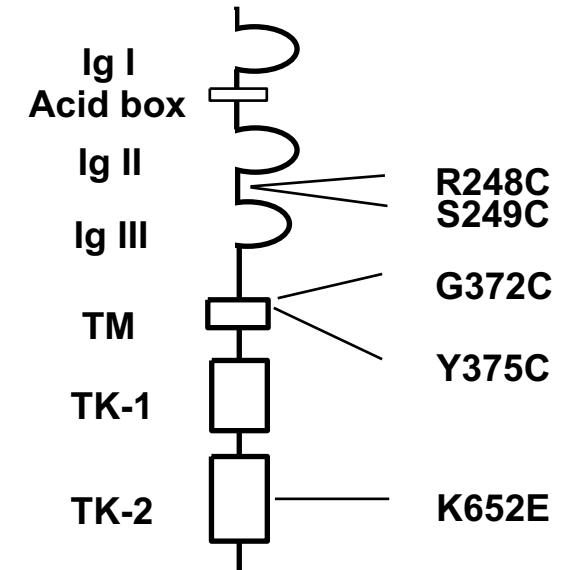
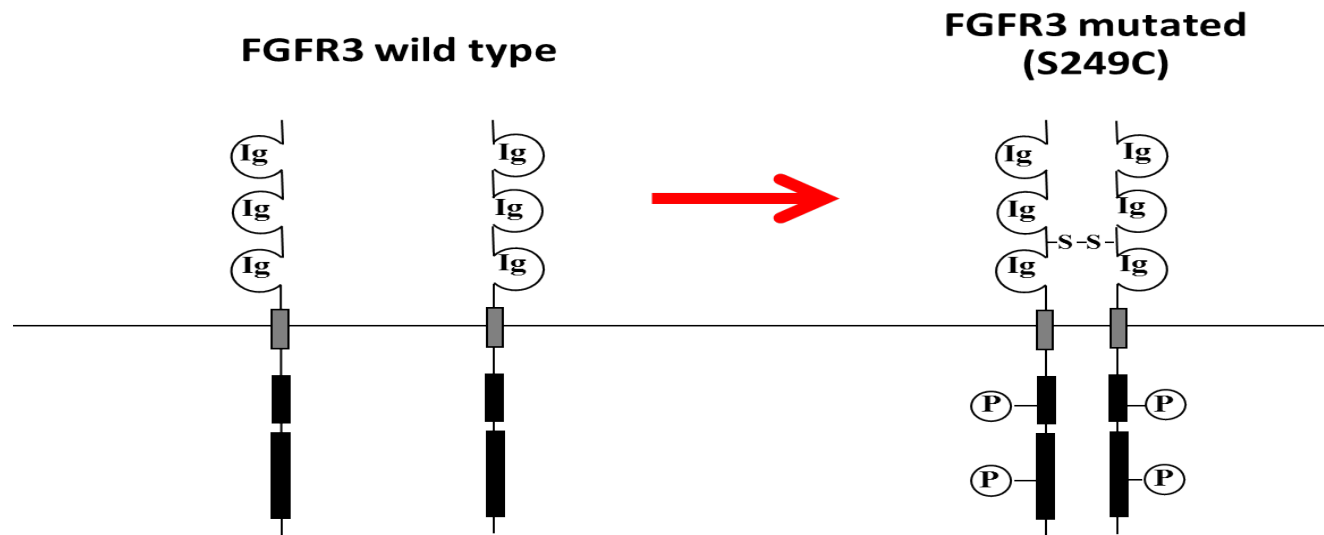
FGFR3 testing for advanced urothelial carcinoma

“Balversa as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic urothelial carcinoma (UC), harbouring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor in the unresectable or metastatic treatment setting”

FGFR3 mutations in urothelial cancer

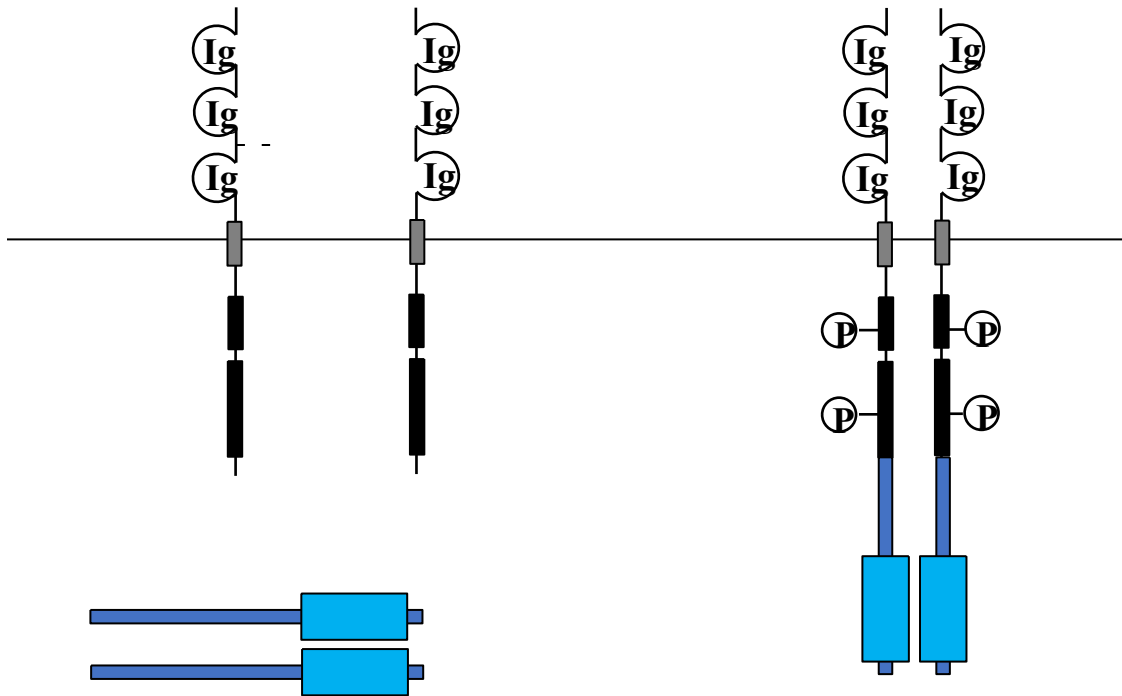


François Radvanyi

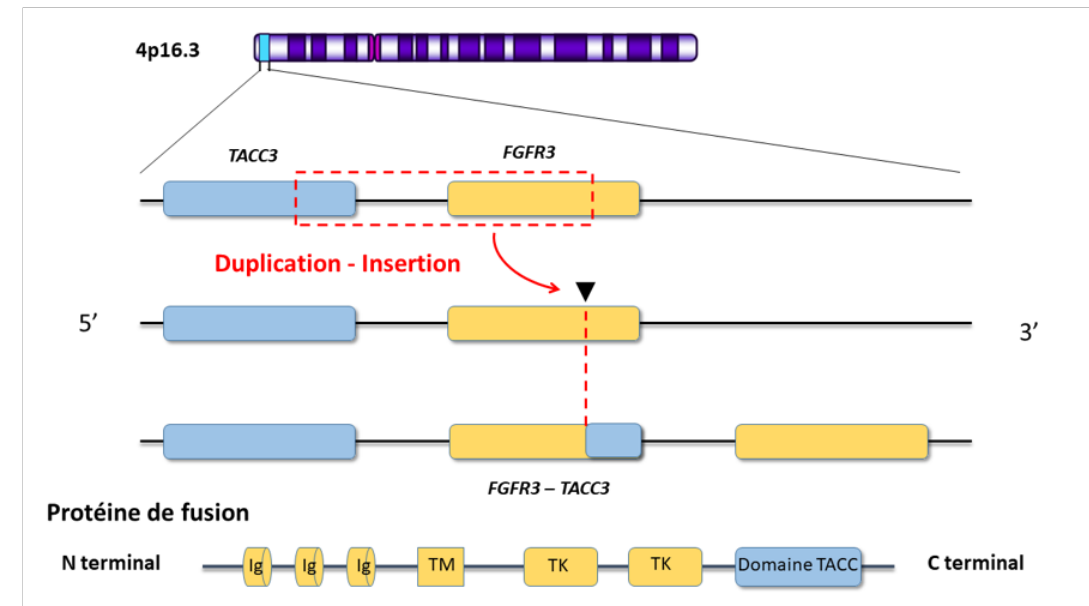


Other mechanism of *FGFR3* activation : gene fusion

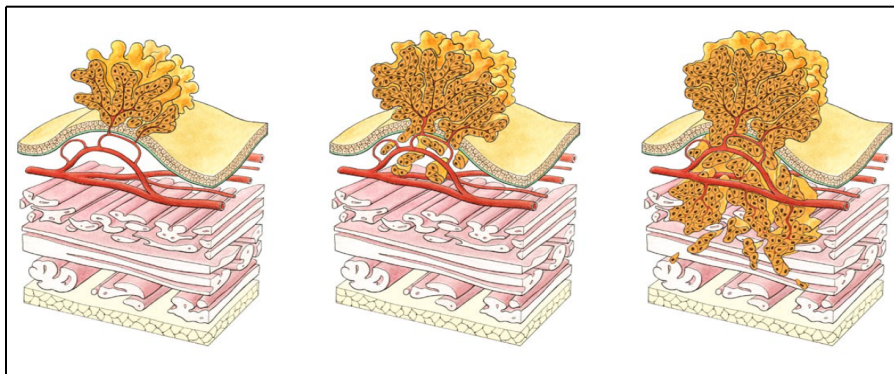
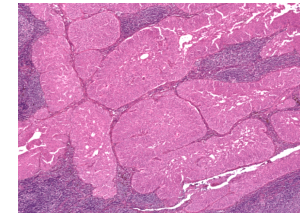
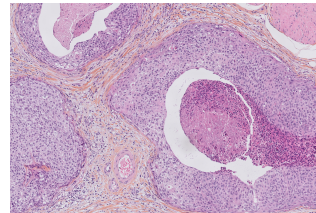
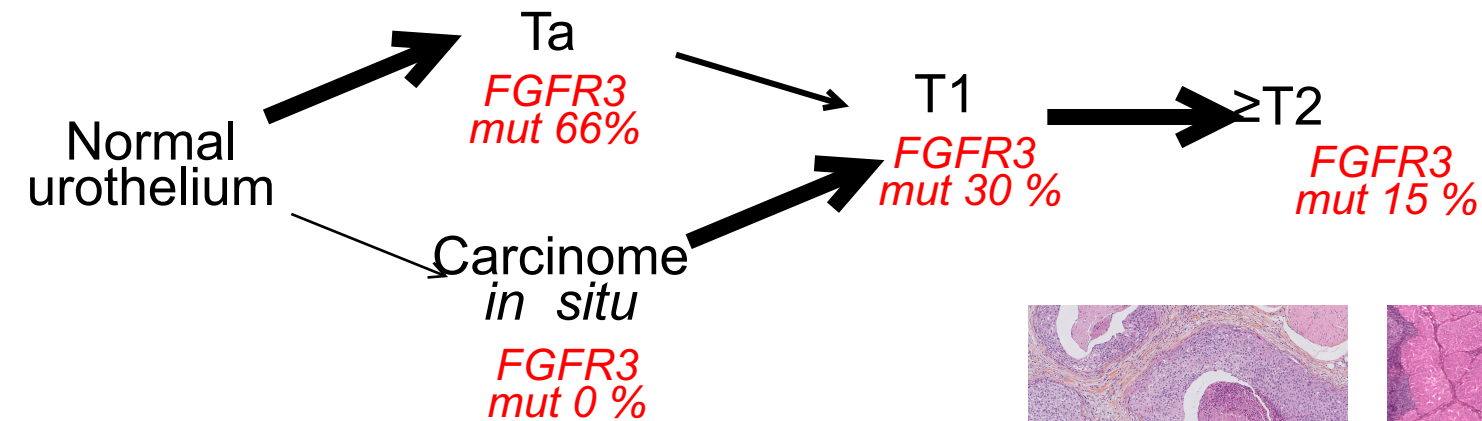
FGFR3 wild type



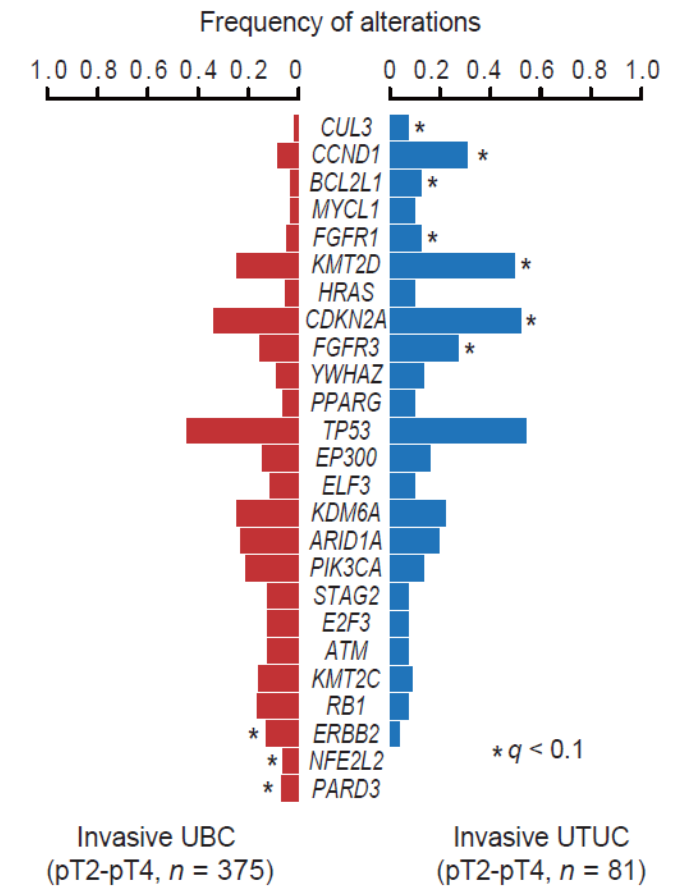
TACC3 wild type



FGFR3 mutations are associated with papillary pathway



FGFR3 mutations more frequently detected in upper urinary tract



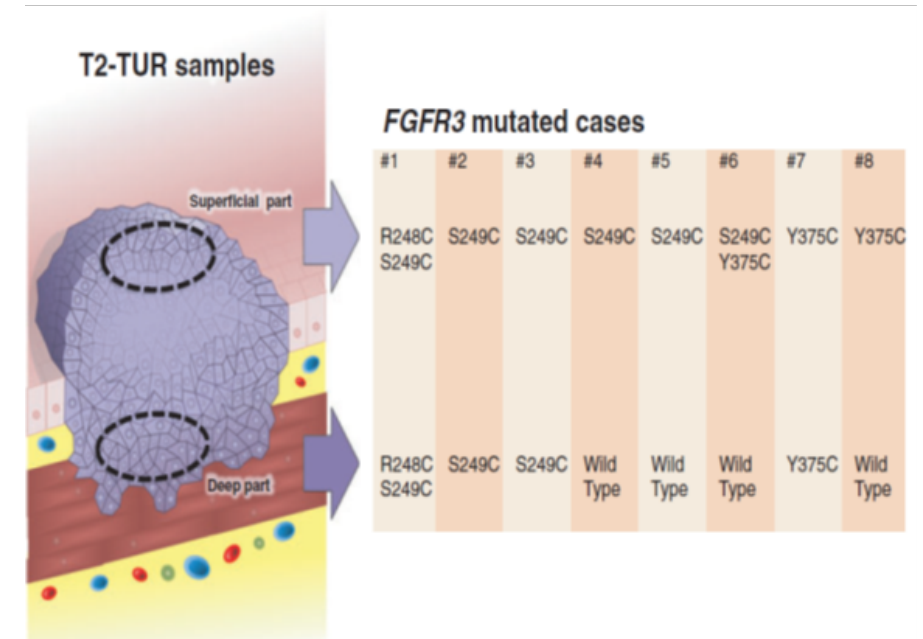
Fujii, Cancer Cell 2021

FGFR3 mutations & fusions screening before Erdafitinib

- **Targeted approach** : Therascreen FGFR RGQ RT-PCR Kit
 - Extraction ARN FFPE
 - mutations exon 7 [p.R248C (c.742C>T), p.S249C (c.746C>G)], exon 10 [p.G370C (c.1108G>T), p.Y373C (c.1118A>G)]
 - fusions (*FGFR3:TACC3v1*, *FGFR3:TACC3v3*, *FGFR3:BAIAP2L1*)
- **NGS approach**
 - Extraction RNA +/-DNA FFPE
 - RNAseq +/-DNAseq
 - Kit Archer FusionPlex

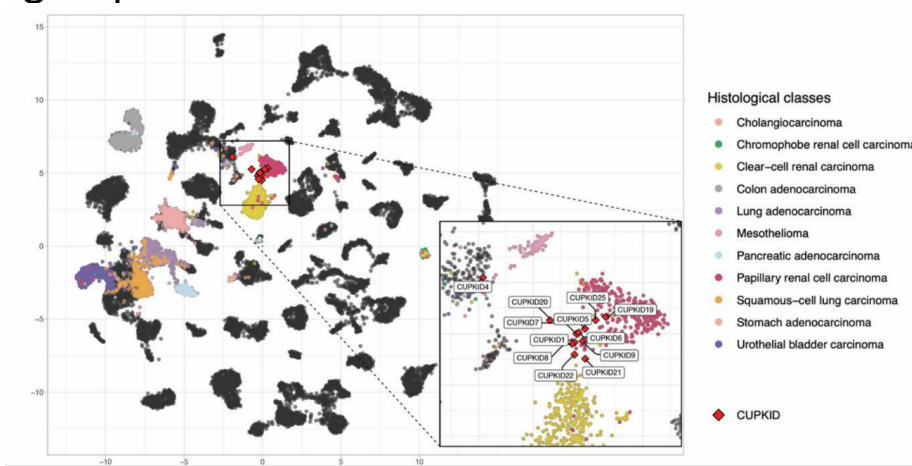
FGFR3 testing recommendations

- *FGFR3* mutations are more frequently associated with large nested or inverted growth pattern but testing must be done for all urothelial carcinoma when erdafitinib option is considered.
- FGFR3 immunohistochemistry is not currently validated as a surrogate marker for genetic alterations.
- FISH is inappropriate to detect *FGFR3* gene alteration in urothelial carcinoma.
- In metastatic setting, molecular tests should be done using metastatic tissue or invasive part of primary tumor.

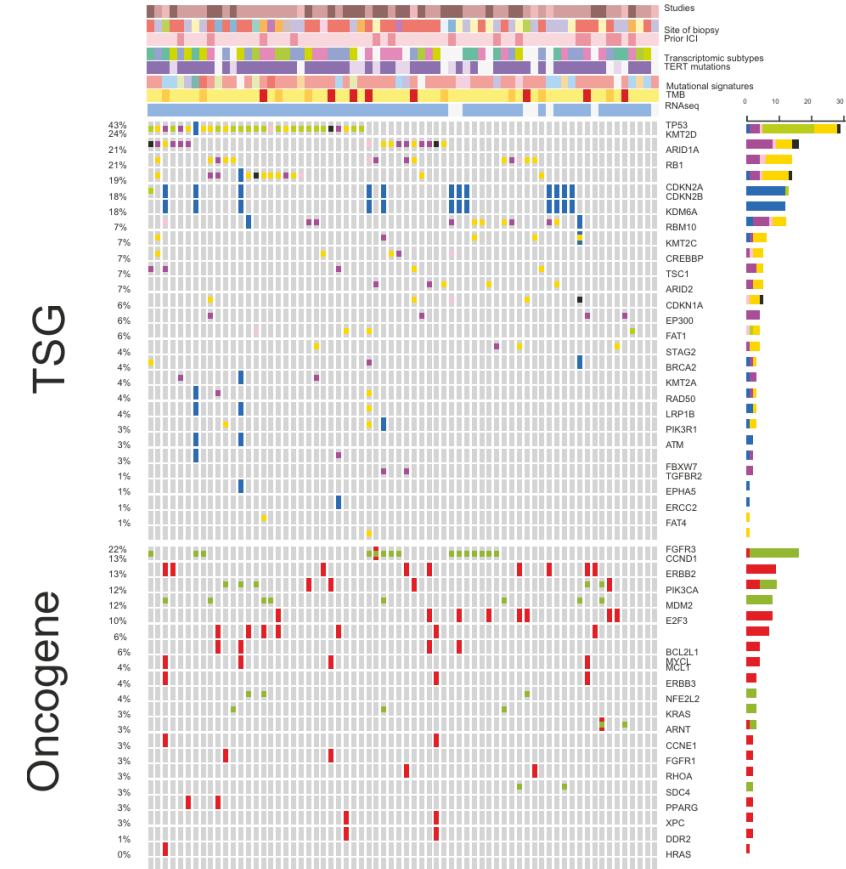


Molecular pathology for poorly differentiated carcinoma or metastatic carcinoma of unknown primary

- Large gene panel NGS can provide a list of mutations suggestive of a primary tumor :
Example : TERT + APOBEC signature for urothelial carcinoma (UC)
- RNASeq profile can be compared to a reference library to identify the nearest group of tumors



Jacquin, NPJ Precis Oncol 2024



WES in metastatic UC

Loriot, Nat Com 2024

Key-points

- Antibody Drug Conjugate : nectin-4 and trop-2 immunohistochemistry are not reglementary necessary but could be of interest for some histological subtypes to help treatment decision ; for HER-2, it is required.
- Immunotherapy : no PD-L1 status is necessary at metastatic stage for urothelial carcinoma to guide treatment ; MSI status is necessary for upper tract urothelial carcinoma.
- FGFR inhibitor : *FGFR3* mutations and fusions must be searched for erdafitinib decision at metastatic stage.
- Urothelial diagnosis matters for poorly differentiated carcinoma in the context of therapeutic opportunities and can be supported by molecular approaches.

¡Gracias!

