Targeting *FGFR* as a biomarker in urothelial carcinoma

Janssen Precision Medicine

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Testing for molecular alterations that drive tumor growth in UC, even if not currently actionable, could help to identify future biomarkers[1–3]

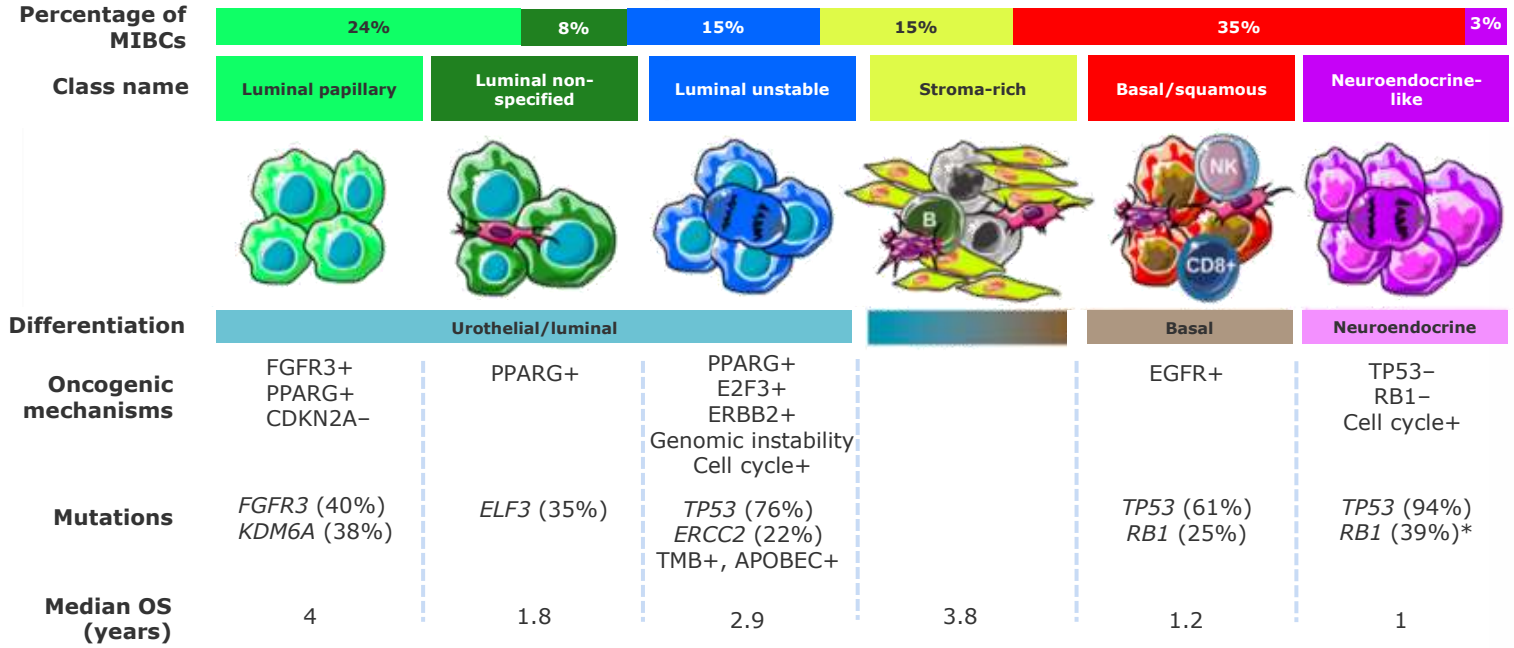
ESMO and NCCN guidelines recommend early molecular/genomic testing, ideally at initial diagnosis of advanced bladder cancer, in order to facilitate treatment decision-making and prevent delays in administering later lines of therapy[4–6]

ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; UC, urothelial carcinoma.

1. Helsten T, et al. *Clin Cancer Res.* 2016;22:259–267; 2. Presta M, et al. *Pharmacol Ther.* 2017;179:171–187; 3. Bellmunt J, et al. *Ann Oncol.* 2014;25(Suppl 3):iii40–iii48; 4. Flaig TW, et al. *J Natl Compr Canc Netw.* 2020;18:329–354; 5. NCCN Clinical Practice Guidelines in Oncology. Bladder Cancer Version 3. 2023. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1417. Accessed January 2024; 6. Powles T, et al. *Ann Oncol.* 2022;33:244–258.

A wide range of genomic alterations exist in UC, each conferring different survival outcomes[1]

MIBC subclasses, oncogenic mechanisms and alterations, and associated OS rates[1]



Gene fusions are increasingly recognised as distinctive tumor markers and possible targets for personalised therapy[2]

~2–3% of all UC/BC cases harbour an *FGFR–TACC3* fusion partner[2,3]

5′ gene	3′ gene	tumor type
FGFR1	*NTM*	UC
FGFR3	*TNIP2*	UC
FGFR3	***TACC3***	**BC**
FGFR3	*BAIAP2L1*	BC

Almost a third of patients with high-risk† NMIBC or MIBC were shown to express PD-L1 (using IHC staining methods). PD-L1 expression was associated with high-grade tumors (OR: 2.4 [95% CI: 1.20–4.72]; p=0.009)‡,[4]

MIBC molecular subtypes

*94% of these tumors present either *RB1* mutations or deletions. †Defined as high risk because of the presence of CIS (n=14), pathologic grade 3/3 (n=22), tumor size ≥3 cm (n=15), multiple (≥3) tumors (n=13) and/or microscopic invasion of the lamina propria (n=20). ‡Analysis consisted of two patient groups; 1) 44 patients with high-risk NMIBC UCs prospectively identified from 1997–2000 who were treated with intravesicle BCG after initial transurethral resection of their bladder tumors and then followed for recurrences, and 2) 236 radical cystectomy cases, treated from 1983–2002, for MIBC UC.

BC, bladder cancer; BCG, Bacillus Calmette-Guérin; CI, confidence interval; FGFR, fibroblast growth factor receptor; IHC, immunohistochemistry; MIBC, muscle-invasive bladder cancer; NK, natural killer; NMIBC, non–muscle-invasive bladder cancer; OR, odds ratio; OS, overall survival; PD-L1, programmed death ligand-1; UC, urothelial carcinoma.

1. Kamoun A, et al. *Eur Urol.* 2020;77:420–433; 2. Pederzoli F, et al. *Nat Rev Urol.* 2020;17:613–625; 3. Chen L, et al. J Exp Clin Cancer Res. 2021;40:345; 4. Inman BA, et al. *Cancer.* 2007;109:1499–1505.

FGFR alterations are prevalent in various cancers and represent important biomarkers to target[1]

FGFR alterations are **prevalent potential disease drivers in oncology**, with continuous activation of the FGFR pathway driving multiple oncogenic processes across tumor types[1,2]

The type of *FGFR* alteration most commonly found can differ in different cancer types:[1,3]

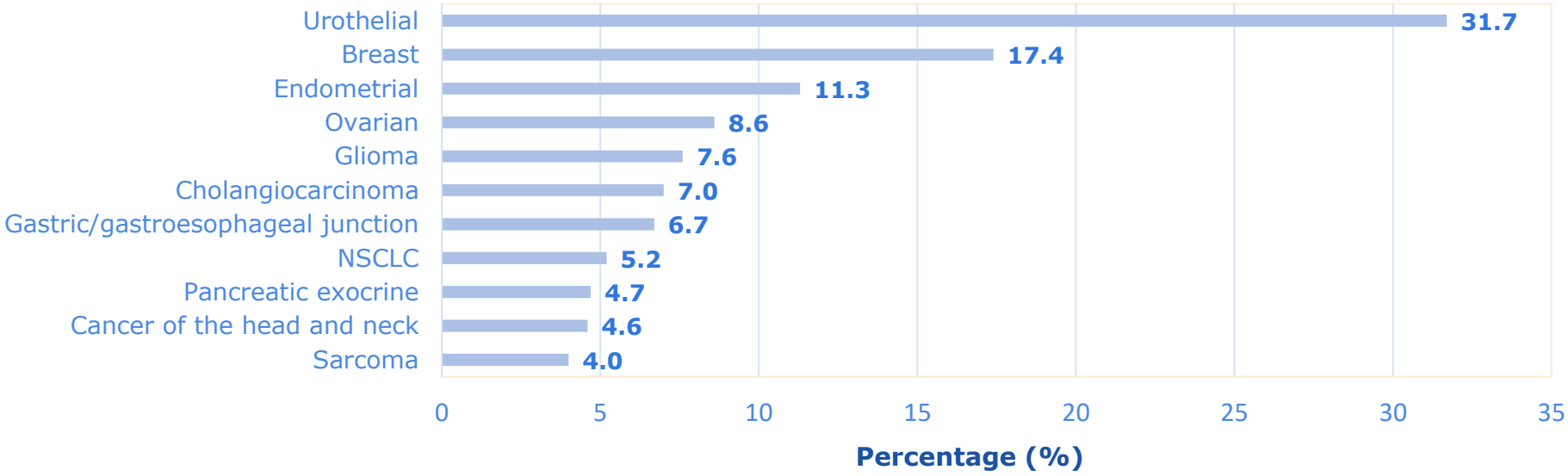
- *FGFR1* amplifications predominate in squamous cell lung, breast and ovarian cancers[1]
- *FGFR3* mutations are prevalent in bladder and other urothelial tumors[3]

FGFR, fibroblast growth factor receptor; UC, urothelial carcinoma.

1. Helsten T, et al. *Clin Cancer Res.* 2016;22:259–267; 2. Presta M, et al. *Pharmacol Ther.* 2017;179:171–187;
3. Helsten T, et al. *Clin Cancer Res.* 2016;22:259–267 (supplementary material).

UC harbours FGFR alterations more commonly compared with other cancer types

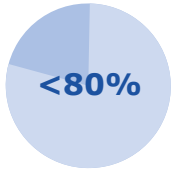
In an analysis of 4,853 cancers, those that commonly harboured *FGFR* alterations included:*,[1,2]



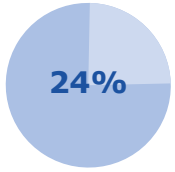
*Samples from 4,853 cancers of various types were analysed for *FGFR* alterations on physician request. UCs included cancers of the renal pelvis (21 cases), ureter (6), bladder (90) and not otherwise specified (9). Gliomas included glioblastoma (84 cases), astrocytoma (21), ependymoma (7), oligodendroglioma (17) and glioma not otherwise specified (15).[1,2]
FGFR, fibroblast growth factor receptor; NSCLC, non-small cell lung cancer; UC, urothelial carcinoma.
1. Helsten T, et al. *Clin Cancer Res.* 2016;22:259–267; 2. Helsten T, et al. *Clin Cancer Res.* 2016;22:259–267 (supplementary material).

FGFR alterations are common in UC, supporting the value of routine *FGFR* testing in clinical settings[1,2]

FGFR alterations are found in all stages and grades of bladder cancer:[3] advanced, muscle invasive[1] and non–muscle invasive[2]



FGFR3 alterations have been found in up to **80% of Ta** non–muscle-invasive papillary bladder cancer tumors[1]



24% of muscle-invasive bladder cancer tumors are luminal papillary, a subtype strongly associated with **high *FGFR3* expression**[4,5]

FGFR mutations are now actionable in advanced/metastatic UC,[6–9] so knowing the *FGFR* status of your patients with UC can help to provide them with an appropriate treatment and optimise outcomes[10,11]

FGFR, fibroblast growth factor receptor; UC, urothelial carcinoma.

1. Knowles MA and Hurst CD. *Nat Rev Cancer.* 2015;15:25–41; 2. Necchi A, et al. *Eur Urol Focus.* 2019;5:689–692; 3. di Martino E, et al. *Future Oncol.* 2016;12:2243–2263; 4. Kamoun A, et al. *Eur Urol.* 2020;77:420–433; 5. Bonaventura P, et al. *Front Immunol.* 2019;10:168; 6. BALVERSA® (erdafitinib) Prescribing Information. 2022. Available at: https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/BALVERSA-pi.pdf. Accessed January 2024; 7. ClinicalTrials.gov. NCT05086666. Available at: https://clinicaltrials.gov/ct2/show/NCT05086666. Accessed January 2024; 8. ClinicalTrials.gov. NCT03773302. Available at: https://clinicaltrials.gov/ct2/show/NCT03773302. Accessed January 2024; 9. ClinicalTrials.gov. NCT05242822. Available at: https://clinicaltrials.gov/ct2/show/NCT05242822. Accessed January 2024; 10. Gopalakrishnan D, et al. *Ther Clin Risk Manag.* 2018;14:1019–1040; 11. Malone ER, et al. *Genome Med.* 2020;12:8.

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

FGFR alterations in UC: key takeaways

Aberrant *FGFR* signalling can drive oncogenesis and is implicated in impacting response to some types of anticancer therapies[1]

FGFR alterations may be present in **as many as one-fifth of advanced UCs**, most commonly *FGFR3* mutations[1–4]

***FGFR* mutations may be actionable in UC**,[5–8] so determining the *FGFR* status of patients can be used to **tailor treatments and optimise treatment outcomes**[9,10]

It is essential to determine tumor molecular subtypes and test for actionable biomarkers, including *FGFR* alterations, to ensure as many patients as possible are treated with optimal therapy where available[2,9,11]

FGFR, fibroblast growth factor receptor; UC, urothelial carcinoma.

1. Presta M, et al. *Pharmacol Ther.* 2017;179:171–187; 2. Helsten T, et al. *Clin Cancer Res.* 2016;22:259–267; 3. di Martino E, et al. *Future Oncol.* 2016;12:2243–2263; 4. Necchi A, et al. *Eur Urol Focus.* 2019;5:689–6925; 5. BALVERSA® (erdafitinib) Prescribing Information. 2022. Available at: https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/BALVERSA-pi.pdf. Accessed January 2024; 6. ClinicalTrials.gov. NCT05086666. Available at: https://clinicaltrials.gov/ct2/show/NCT05086666. Accessed January 2024; 7. ClinicalTrials.gov. NCT03773302. Available at: https://clinicaltrials.gov/ct2/show/NCT03773302. Accessed January 2024; 8. ClinicalTrials.gov. NCT05242822. Available at: https://clinicaltrials.gov/ct2/show/NCT05242822. Accessed January 2024; 9. Gopalakrishnan D, et al. *Ther Clin Risk Manag.* 2018;14:1019–1040; 10. Malone ER, et al. *Genome Med.* 2020;12:8; 11. Mendiratta P and Grivas P. *Ann Transl Med.* 2018;6:250.

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson