100P

Co-mutational landscape of key fibroblast growth factor receptor (*FGFR*) alterations in intra-hepatic cholangiocarcinoma (iCCA), bladder cancer (BC) and glioma

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Summary

Our hypothesis-generating findings may help to stratify patients with cancer in clinical trials and guide optimal targeted therapy in those with *FGFR* alterations.

Introduction

- Selective tyrosine kinase inhibitors targeting *FGFR1–4* GAs are in development or have been granted FDA-accelerated approval for *FGFR*-altered cancers (e.g. advanced iCCA and BC).[1–6]
- Understanding FGFR inhibitor-resistance mechanisms is increasingly relevant; the genomic co-mutational landscape influencing inhibitor response requires comprehensive analysis.

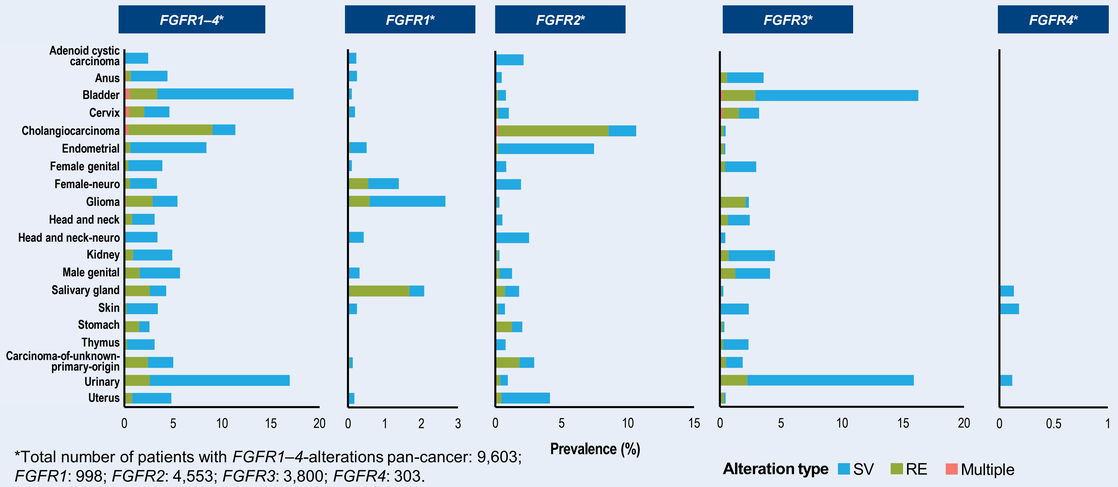
Methods

- iCCA, BC and glioma solid tissue samples underwent hybrid capture-based CGP (Foundation Medicine, Inc., Cambridge, MA, USA) to assess all classes of GAs. CGP is a next-generation-sequencing-based method that detects novel and known variants of the four main classes of GAs (insertions and deletions, REs, CNAs, substitutions), and genomic signatures (e.g. TMB and MSI).
- TMB (non-driver somatic mutations per megabase) was determined on up to 1.1 megabases of sequenced DNA and MSI on up to 114 loci.
- Samples were classified as TMB-high if they had ≥ 10 mutations/megabase, and TMB-low if they had < 10 mutations/megabase.
- *P* values of categorical variables were estimated by the Fisher's exact test.

Results

- The landscape of *FGFR1–4* GAs in the 20 tumour types with the greatest prevalence is shown in the Figure (all tumour types shown in the supplementary figure). The most common *FGFR* GAs for iCCA, BC and glioma were *FGFR2* REs (n = 618/6,641 [9.3%]), *FGFR3* SVs (1,051/7,739 [13.6%]) and *FGFR1* SVs (239/11,550 [2.1%]), respectively.
- *FGFR2* RE-altered iCCAs were significantly less likely to be TMB-high and MSI-high vs. their unaltered counterparts (TMB-high: n = 3/618 [0.5%] vs. 243/6,023 [4.0%], $P = 1.34 \times 10^{-7}$; MSI-high: 2/618 [0.3%] vs. 81/6,023 [1.3%], $P = 0.03$). *FGFR3* SV-altered BCs were significantly less likely to be TMB-high and more likely to be MSI-high vs. unaltered tumours (TMB-high: 260/1,051 [24.7%] vs. 2,336/6,688 [34.9%], $P = 3.49 \times 10^{-11}$; MSI-high: 17/1,051 [1.6%] vs. 45/6,688 [0.7%], $P = 0.004$).
- Select significantly co-occurring GAs in iCCA, BC and glioma are shown in the Table:
  - Across the cohort, *TP53* and *EGFR* GAs were significantly depleted in *FGFR*-altered vs. *FGFR*-unaltered tumours.
  - In iCCA and BC, *ERBB2* and *KRAS* GAs were depleted, while *BAP1* was enriched.
  - For iCCA and glioma, *IDH1* and *TERT* GAs were depleted; in glioma, *ATRX* and *H3-3A* were both enriched. *CDKN2A/B*, *TERT* and *STAG2* GAs had contrasting trends between BC and glioma.

Figure. Prevalence of *FGFR1–4* GAs by tumour type



*Total number of patients with *FGFR1–4*-alterations pan-cancer: 9,603; *FGFR1*: 998; *FGFR2*: 4,553; *FGFR3*: 3,800; *FGFR4*: 303.

Table. Select significantly co-occurring GAs in iCCA, BC and glioma

Gene	iCCA (n = 6,641): *FGFR2* RE			BC (n = 7,739): *FGFR3* SV			Glioma (n = 11,550): *FGFR1* SV		
	Altered	Unaltered	*P* value	Altered	Unaltered	*P* value	Altered	Unaltered	*P* value
ATRX	0.5	0.6	1	1	1	1	25.1	15.3	9.1×10^{-5}
BAP1	31.1	11.9	2.7×10^{-32}	4.2	2.1	0.0002	0	0.2	1
CDKN2A/B	29.8	30.8	0.6	63.8	32.7	9.0×10^{-81}	20.1	45.9	1.6×10^{-16}
EGFR	0.8	2.3	0.01	0.8	4.8	2.3×10^{-12}	1.7	28.5	1.7×10^{-28}
ERBB2	0	5.6	3.7×10^{-15}	6.8	17.5	1.1×10^{-21}	0.4	0.2	0.38
H3-3A	0	0.1	1	0.4	0.3	0.56	26.8	3.1	6.4×10^{-39}
IDH1	1.1	15.8	1.4×10^{-33}	0.1	0.3	0.51	4.2	21.4	1.2×10^{-13}
KRAS	1.3	22	1.2×10^{-50}	1.4	6.8	6.2×10^{-15}	2.9	2.1	0.36
NF1	0.6	2.9	0.0002	2.1	3	0.11	26.8	15.3	7.6×10^{-6}
STAG2	0.3	0.3	1	20.7	5.8	5.5×10^{-49}	0.4	2.6	0.035
TERT	2.3	6.6	2.7×10^{-6}	81.6	70.3	5.2×10^{-15}	12.1	58.6	1.3×10^{-49}
TP53	10.8	35.8	3.2×10^{-42}	29.5	66.6	3.9×10^{-114}	13	39.6	3.3×10^{-19}

Conclusions

- Appropriate combination therapy may differ between *FGFR*-altered tumours.
- CGP can inform molecular-based patient stratification for future clinical trials, next-generation FGFR inhibitor development and combination therapy for *FGFR*-altered tumours.

Abbreviations

BC, bladder cancer; CGP, comprehensive genomic profiling; CNA, copy number alteration; FDA, US Food and Drug Administration; FGFR, fibroblast growth factor receptor; GA, genomic alteration; iCCA, intra-hepatic cholangiocarcinoma; MSI, microsatellite instability; RE, gene rearrangement; SV, short variant; TMB, tumour mutational burden.

References

1. Janssen Products LP. BALVERSA® (erdafitinib) PI; 2. QED Therapeutics Inc. TRUSELTIQ® (infigratinib) PI; 3. Incyte Corporation. PEMAZYRE® (pemigatinib) PI; 4. Goyal L, *et al. J Clin Oncol* 2020; 38:Abstract 108; 5. Taiho Oncology, Inc. FDA BTD for futibatinib. 2021. Available at: https://www.taihooncology.com/us/news/2021-04-01_toi_tpc_futibatinib_btd/. Accessed July 2022; 6. Goyal L, *et al. Mol Cancer Ther* 2021; 20:Abstract P02.

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Conflicts of interest

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