Clinical and Translational Findings of Pemigatinib in Previously Treated Solid Tumors With Activating *FGFR1–3* Alterations in the FIGHT-207 Study

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Disclosure Information

Jordi Rodón

I have the following relevant financial relationships to disclose:

- Consultant for: AADi, Avoro Capital Advisors, Boxer Capital, Chinese University of Hong Kong, Clarion Healthcare, Columbus Venture Partners, Cullgen, Debiopharm Group, Ellipses Pharma, Envision Pharma Group, Incyte, iOnctura, Macrogenics, Merus, Monte Rosa Therapeutics, Oncology One, Pfizer, Sardona Therapeutics, Vall d'Hebron Institute of Oncology/Ministerio de Empleo y Seguridad Social, and Tang Advisors
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- and -

My additional financial relationship disclosures are

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Background

- Oncogenic *FGFR* alterations have been detected in many malignancies[1]
- Pemigatinib, a selective, potent, oral FGFR1–3 inhibitor, demonstrated antitumor activity in multiple pretreated solid tumors with *FGF/FGFR* alterations[2]
- FIGHT-207 was an open-label, single-arm phase 2 basket study evaluating pemigatinib in previously treated advanced/metastatic or unresectable solid tumors with confirmed activating *FGFR* mutations or fusions/rearrangements

Objective: To report the efficacy and safety of pemigatinib and a detailed analysis of *FGFR* alterations and co-altered genes in FIGHT-207

1. Murugesan K, et al. *ESMO Open.* 2022;7(6):100641. **2.** Subbiah V, et al. *Ann Oncol.* 2022;33 (5):522–533.
FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor.

FIGHT-207 Study Design and Patient Disposition (NCT03822117; EudraCT, 2018-004768-69)

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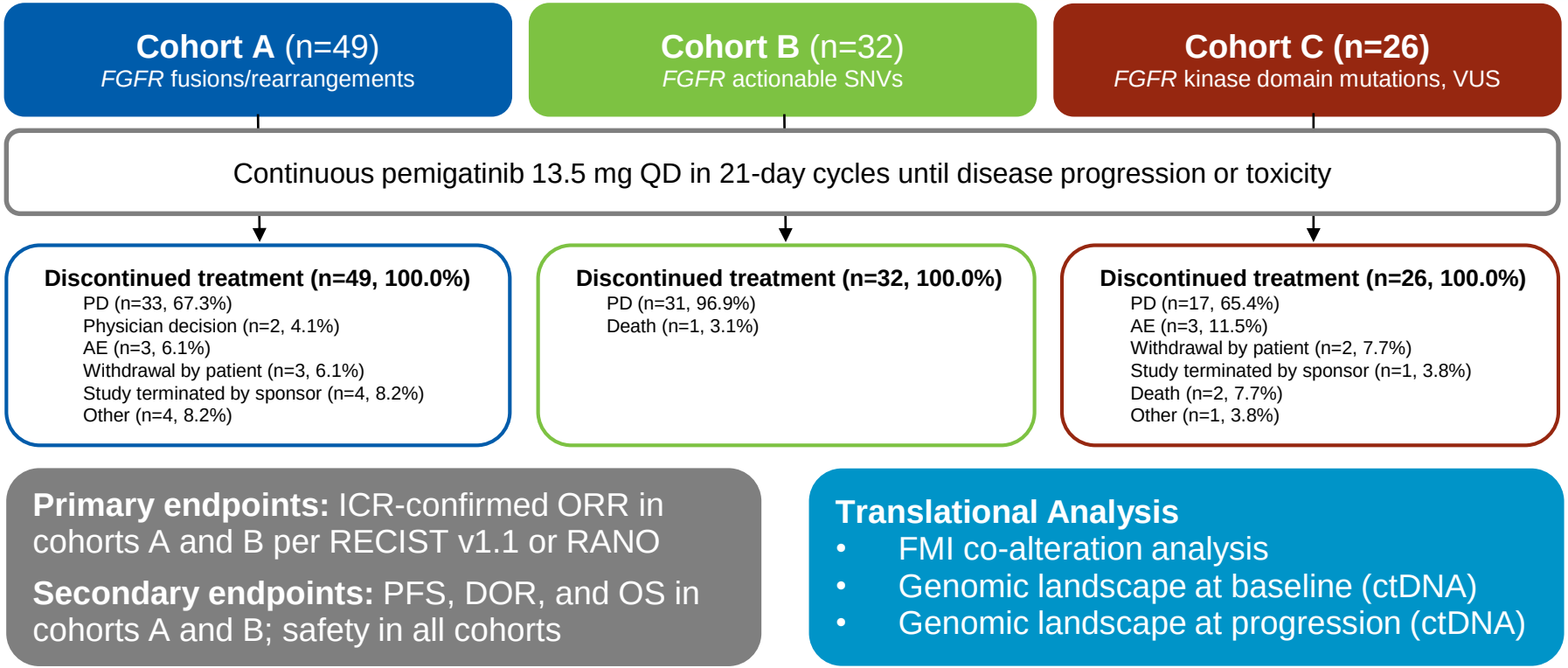

Analysis of ctDNA conducted with Predicine using the PredicineCare assay. ctDNA, circulating tumor DNA; DOR, duration of response; FGFR, fibroblast growth factor receptor; FMI, Foundation Medicine Inc; ICR, independent central review; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; QD, once daily; RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria in Solid Tumors; SNV, single nucleotide variant; VUS, variant of unknown significance.

Baseline Demographics and Disease Characteristics

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Parameter	Cohort A (n=49) *FGFR* fusions/rearrangements	Cohort B (n=32) *FGFR* actionable SNVs	Cohort C (n=26) *FGFR* kinase domain mutations, VUS	Total* (N=111)
Age, median (range), y	61.0 (25–82)	67.5 (45–82)	62.0 (29–84)	62.0 (25–84)
Women, %	57.1	59.4	53.8	55.9
ECOG PS ≤1, n (%)	98.0	96.9	88.5	95.5
Prior systemic therapies, %				
0 or 1	55.1	34.4	34.6	44.1
≥2	44.9	65.6	65.4	55.9
Most common tumor types, %				
Breast	0	3.1	19.2	5.4
Cholangiocarcinoma	18.4	15.6	11.5	16.2
Central nervous system	20.4	0	11.5	11.7
Gynecologic	8.2	18.8	11.5	12.6
Non-small cell lung cancer	12.2	3.1	0	6.3
Pancreatic	16.3	0	0	7.2
Urothelial tract/bladder	2.0	34.4	0	10.8

* Includes 4 patients with *FGFR* alterations unconfirmed by the central laboratory.
ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; SNV, single nucleotide variant; VUS, variant of unknown significance.

Efficacy and Safety

Parameter	Cohort A (n=49) *FGFR* fusions/rearrangements	Cohort B (n=32) *FGFR* actionable SNVs	Cohort C (n=26) *FGFR* kinase domain mutations, VUS
ORR, % (95% CI)	26.5 (15.0, 41.1)	9.4 (2.0, 25.0)	3.8 (0.1, 19.6)
DCR, % (95% CI)	65.3 (50.4, 78.3)	56.3 (37.7, 73.6)	34.6 (17.2, 55.7)
DOR, median (95% CI), mo	7.8 (4.2, NE)	6.9 (4.0, NE)	–
PFS, median (95% CI), mo	4.5 (3.6, 6.3)	3.7 (2.1, 4.5)	2.0 (1.8, 3.7)
OS, median (95% CI), mo	17.5 (7.8, NE)	11.4 (6.6, NE)	11.0 (3.9, NE)

- Safety was generally consistent with previous findings[1,2]
- Hyperphosphatemia was the most common TEAE (83.8%; grade ≥3, 0.9%), followed by stomatitis (53.2%; grade ≥3, 9.0%), alopecia (40.5%; grade ≥3, 0.9%), diarrhea (38.7%; grade ≥3, 0.9%), and constipation (33.3%; grade ≥3, 0.9%)

1. Abou-Alfa GK, et al. *Lancet Oncol.* 2020;21(5):671–684. **2.** Subbiah V, et al. *Ann Oncol.* 2022;33 (5):522–533. ORR was based on ICR-confirmed tumor responses. DCR, disease control rate; DOR, duration of response; FGFR, fibroblast growth factor receptor; ICR, independent central review; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SNV, single nucleotide variant; TEAE, treatment-emergent adverse event; VUS, variant of unknown significance.

Responses to Pemigatinib Occurred Across Tumor Types

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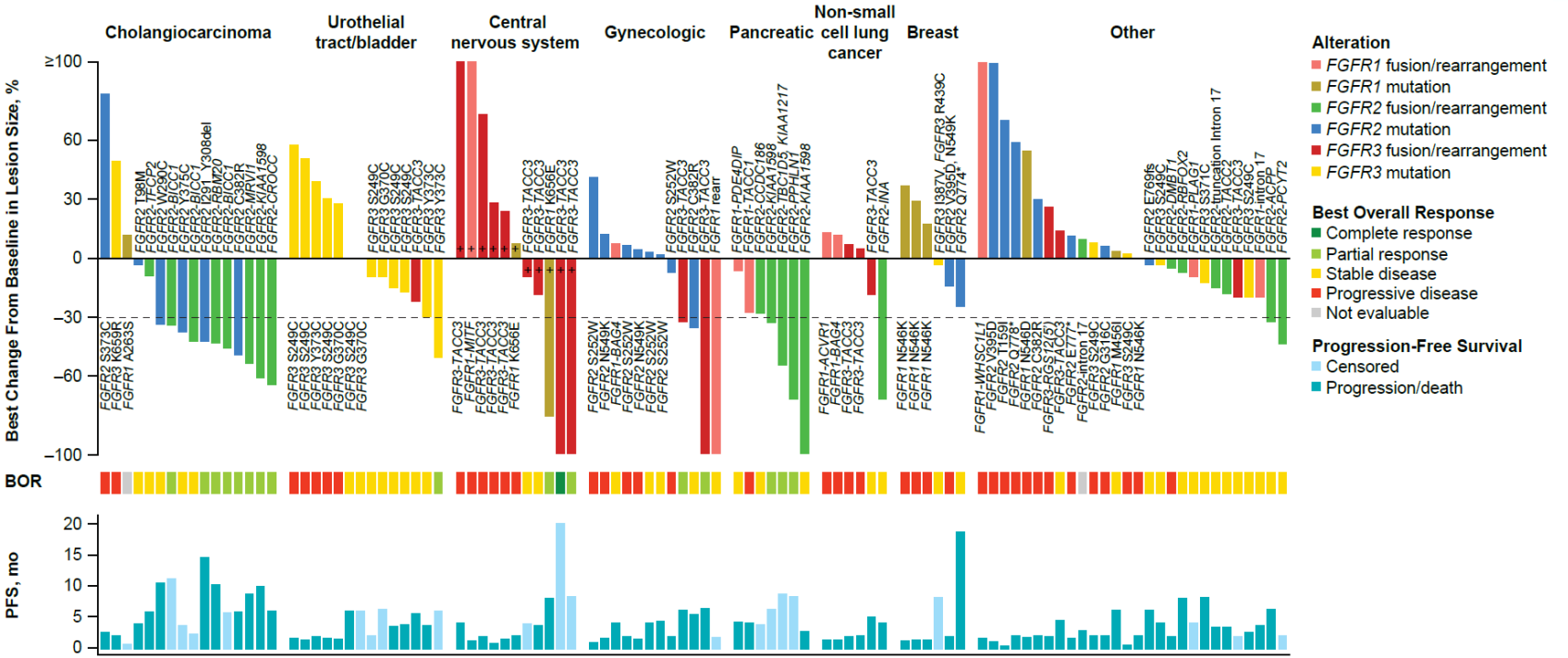

- Most responses were observed in cholangiocarcinoma, central nervous system, gynecologic, and pancreatic tumors with actionable *FGFR* alterations

Response was assessed by ICR per RECIST or RANO (denoted by '+'). Dashed line indicates criterion for partial response. BOR, best overall response; FGFR, fibroblast growth factor receptor; PFS, progression-free survival; RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria in Solid Tumors.

Responses to Pemigatinib Occurred in All *FGFR* Alteration Categories

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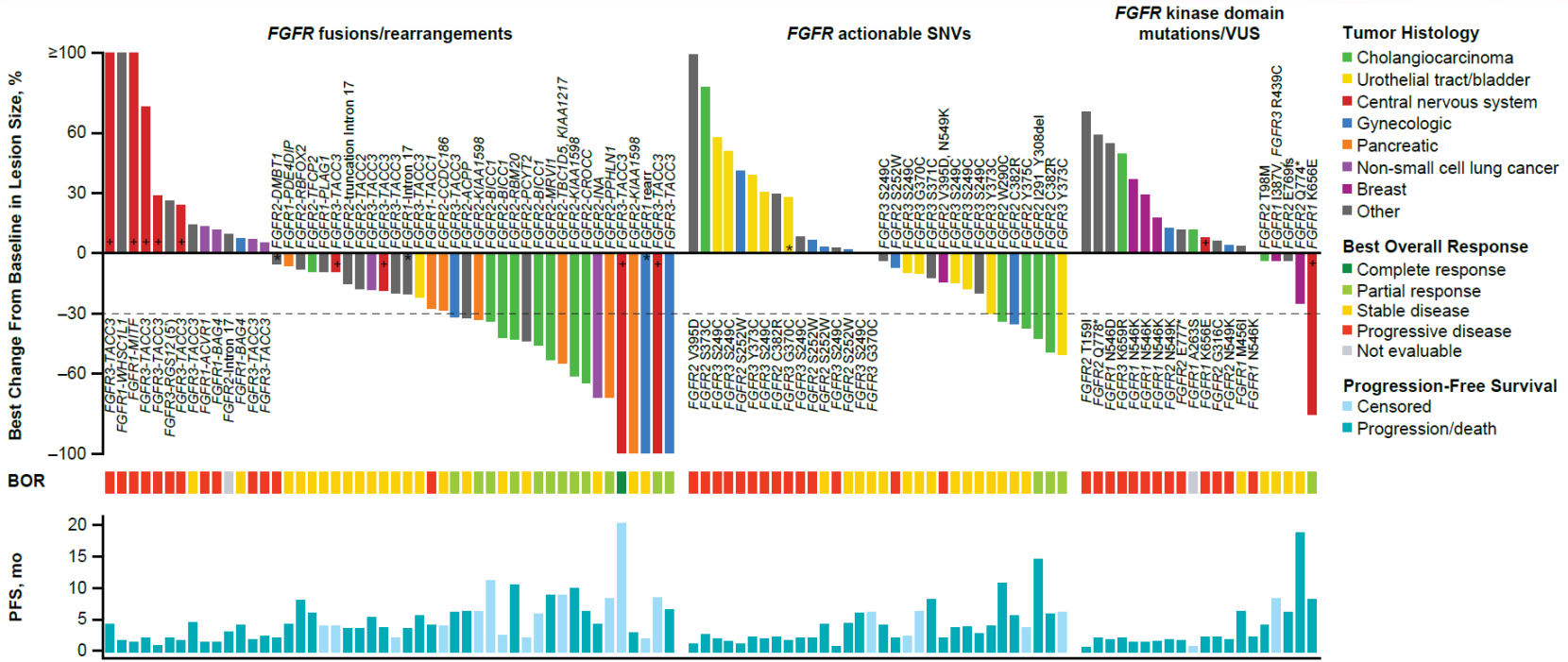

- Responses were observed in all cohorts, including patients with *FGFR* alterations not previously considered actionable and previously uncharacterized *FGFR* alterations

Response was assessed by ICR per RECIST or RANO (denoted by '+'). Dashed line indicates criterion for partial response. * Patients originally assigned to cohort C. BOR, best overall response; FGFR, fibroblast growth factor receptor; PFS, progression-free survival; RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria in Solid Tumors. SNV, single nucleotide variant; VUS, variant of unknown significance.

Baseline Co-Alterations in Tumor Suppressors Were Associated With Response

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Individual Co-Alterations Analysis (tissue)*

Gene, n (%)	CR+PR (N=15)	SD+PD (N=57)	P†	Q‡
BAP1	7 (46.7)	2 (3.5)	<0.001	0.009
TP53	0	23 (40.4)	0.002	0.043

- Co-alterations in the tumor suppressors *BAP1* and *TP53* were mutually exclusive in baseline archival tumor tissue samples
- *BAP1* was significantly associated with response
- *TP53* co-alterations were generally associated with poor response

Pathway Analysis (tissue, ctDNA)*

Pathway, n (%)	CR+PR (N=16)	SD+PD (N=62)
MAPK§ (*KRAS, NRAS, BRAF, NF1)*	0	9 (14.5)
PI3K§ (*PIK3CA, PTEN, PIK3R1*)	3 (18.8)	32 (51.6)

- Genomic analysis of archival tissue samples and baseline ctDNA found that pathogenic co-alterations in MAPK and PI3K pathway genes were generally associated with lack of objective response to pemigatinib

* Only patients in cohorts A and B with centrally confirmed *FGFR* alterations included. † Calculated with Pearson's chi-squared test; Fisher's exact test. ‡ False discovery rate correction for multiple testing. § The association of co-alterations in genes belonging to the pathway with lack of response to pemigatinib was not statistically significant. Analysis of ctDNA conducted with Predicine using the PredicineCare assay. CR, complete response; ctDNA, circulating tumor DNA; PD, progressive disease; PR, partial response; SD, stable disease.

FGFR Resistance Mutations Were Detected in ctDNA at Baseline and Disease Progression

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Primary

Pt	Tumor	BOR	Mutation
1	GBM	SD	*FGFR1* N546K
2	Breast	PD	*FGFR2* N549K
3	Breast	PD	*FGFR1* N546K
4	Breast	PD	*FGFR1* N546K
5	Breast	PD	*FGFR1* N546K
6	CUP	PD	*FGFR2* N549K
7	SFT	PD	*FGFR1* N546K
8	Endometrial	PD	*FGFR2* N549K

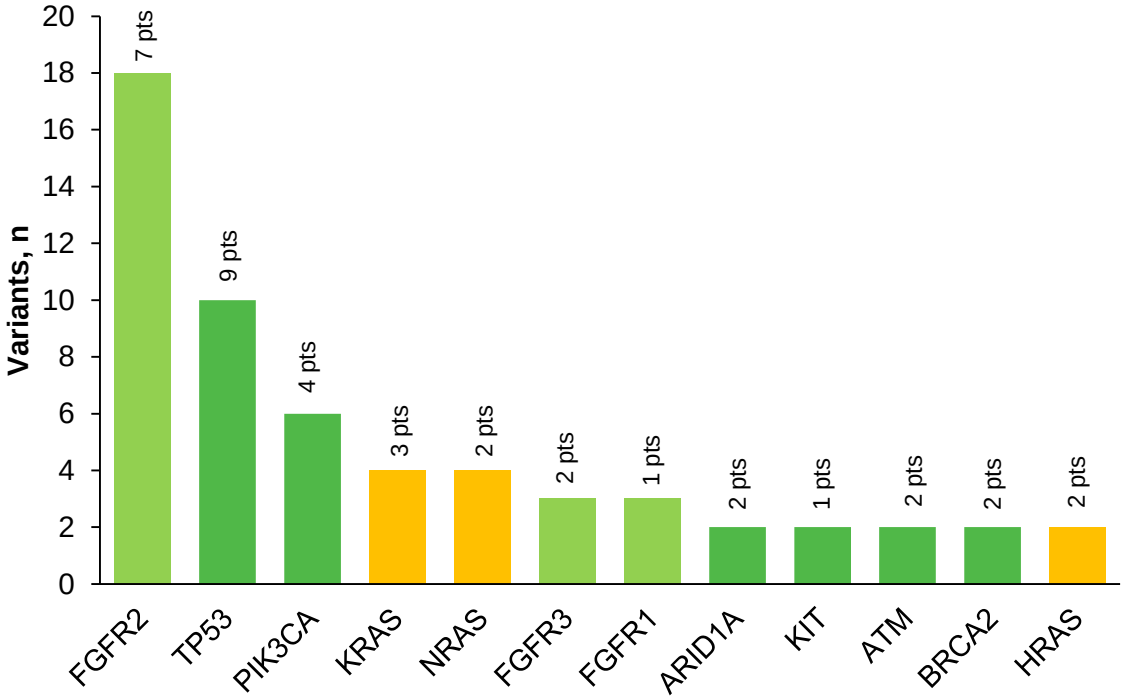
Acquired

Pt	Tumor	BOR	Enrolled Alteration	Mutation
1	CCA	PR	*FGFR2-CROCC*	*FGFR2* N549K/H, V564I/L/F
2	CCA	PR	*FGFR2-BICC*	*FGFR2* N549K, K569M
3	CCA	PR	*FGFR2-KIAA1598*	*FGFR2* V564L
4	Gastric	SD	*FGFR2-TACC2*	*FGFR2* N549K, V564I/L
5	Gastric	Not eval.	*FGFR2* rearrangement	*FGFR2* V564F
6	Pancreatic	SD	*FGFR1-PDE4DIP*	*FGFR1* N544K, V559L/M
7	NSCLC	SD	*FGFR3-TACC3*	*FGFR3* V555L/M
8	CUP	PD	*FGFR1* L567P, *FGFR2* C382R	*FGFR2* N549L, E565A

- *FGFR* baseline mutations in “molecular brake” residues were generally associated with PD
- *FGFR* gatekeeper residue and molecular brake mutations were detected at progression

BOR, best overall response; CCA, cholangiocarcinoma; ctDNA, circulating tumor DNA; CUP, cancer of unknown primary origin; FGFR, fibroblast growth factor receptor; GBM, glioblastoma; not eval., not evaluable; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; pt, patient; SD, stable disease; SFT, solitary fibrous tumor.

Genes with Most Frequent Emergent Pathogenic Variants at Progression by ctDNA



ctDNA, circulating tumor DNA; pts, patients.

Landscape of Co-Alterations and Pathways Associated With Response

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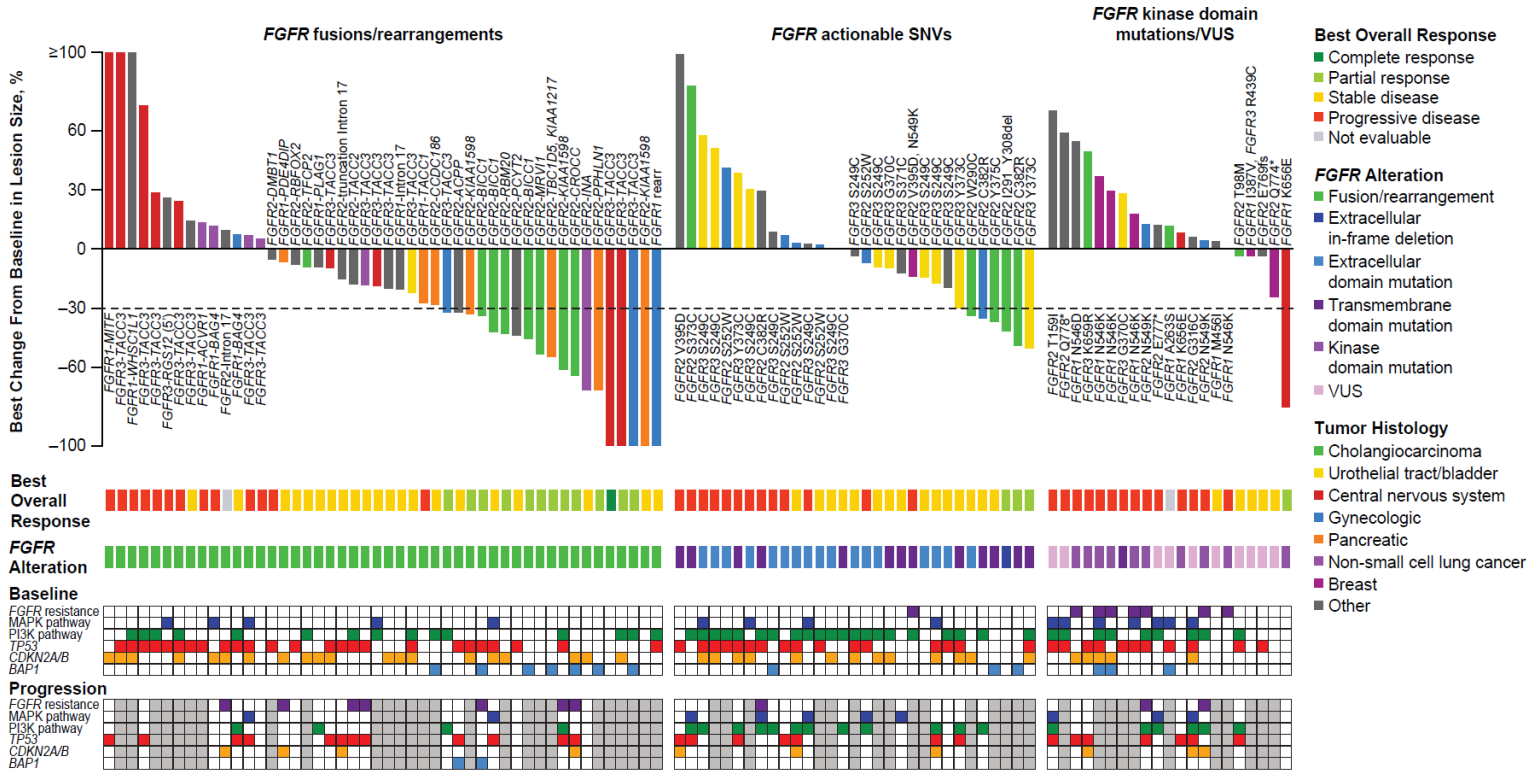

36 and 21 patients with *FGFR* fusions/rearrangements had ctDNA samples at baseline and progression, respectively. 25 and 16 patients with *FGFR* actionable SNVs had ctDNA samples at baseline and progression, respectively. 18 and 10 patients with *FGFR* kinase domain mutations or VUS had ctDNA samples at baseline and progression, respectively. ctDNA, circulating tumor DNA; FGFR, fibroblast growth factor receptor; SNV, single nucleotide variant; VUS, variant of unknown significance.

Conclusions

- Pemigatinib showed clinical activity in cholangiocarcinoma, central nervous system and gynecologic tumors, and pancreatic cancer
- Responses to pemigatinib were detected in patients with *FGFR* rearrangements and *FGFR* SNVs, including gene alterations not previously known to be actionable
- *BAP1* co-alterations were significantly associated with response to pemigatinib
- Pathogenic co-alterations in *TP53* were generally associated with poor response
- Safety of pemigatinib 13.5 mg continuous dosing was consistent with prior reports
- The study design of FIGHT-207 allowed the identification of new areas for therapeutic intervention with FGFR inhibitors

FGFR, fibroblast growth factor receptor; SNV, single nucleotide variant.

Ongoing Pemigatinib Clinical Studies

FIGHT-302 (clinicaltrials.gov: NCT03656536)

Phase 3, randomized study in adults with previously untreated cholangiocarcinoma and documented *FGFR2* rearrangements

FIGHT-209 (clinicaltrials.gov: NCT05267106)

Phase 2, single arm study in adults with previously treated recurrent glioblastoma or other adult-type diffuse glioma or circumscribed astrocytic tumors and *FGFR1–3* alterations

FGFR, fibroblast growth factor receptor

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