Manuscript: *FGFR2*-fusions define a clinically actionable molecular subset of pancreas cancer

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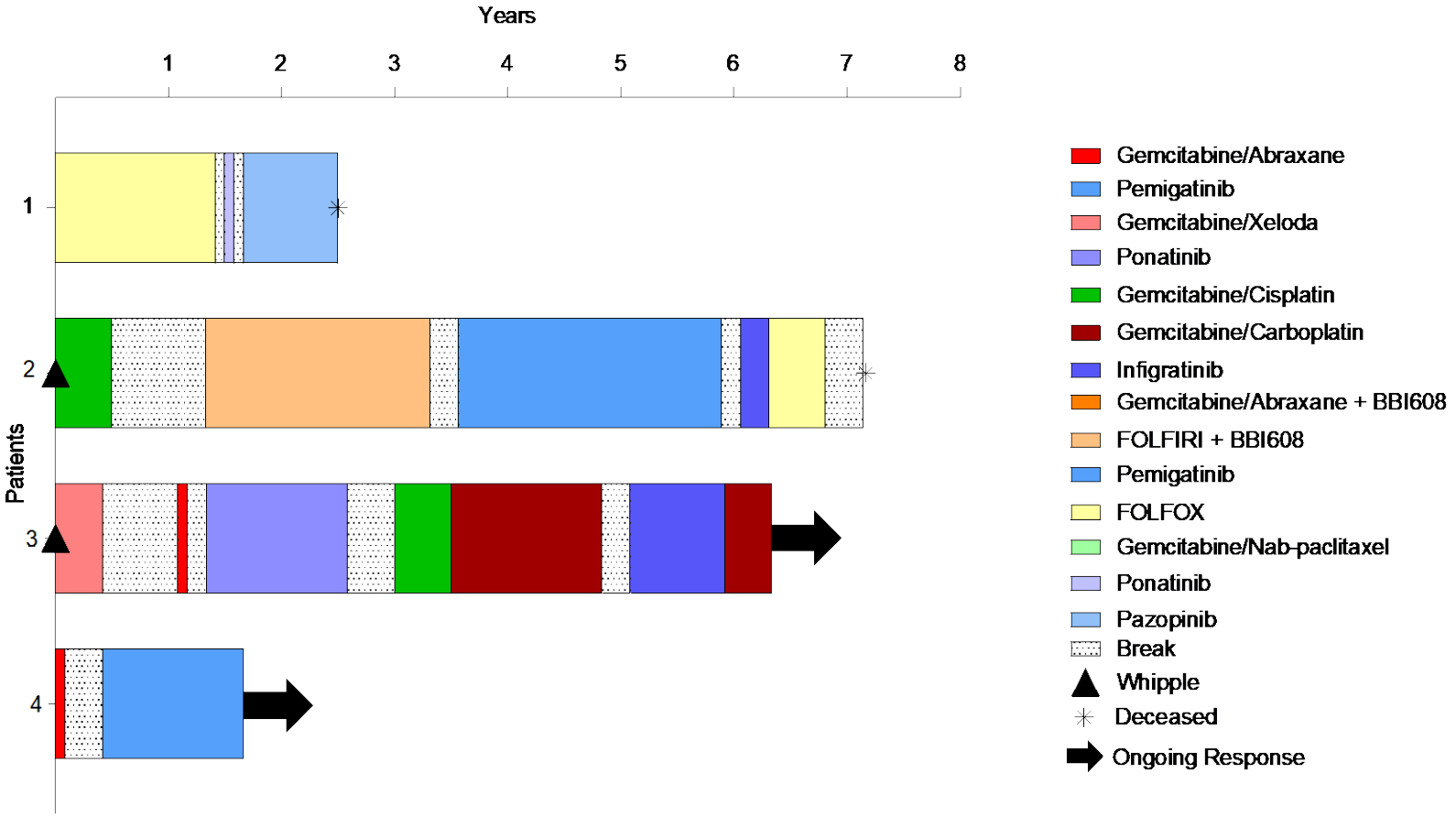
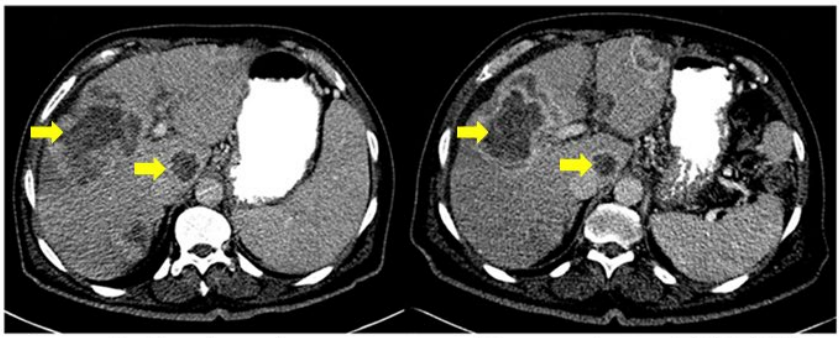
Supplementary Data



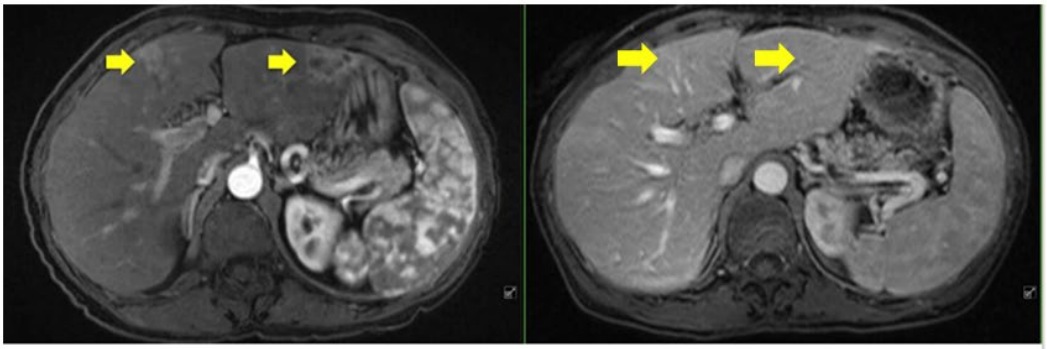
Supplementary Figure 1. Treatment durability and response to chemotherapy and FGFR kinase inhibitors in patients with metastatic PDAC and *FGFR2*-fusions. Patient 1 exhibited a best response of stable disease while on pazopanib for 10 months while patient 2 exhibited a partial response on pemigatinib for 28 months, patient 3 exhibited partial response to infigratinib for 10 months, and patient 4 exhibited an ongoing, partial response on off-label pemigatinib. Abbreviations: FOLFOX, folinic acid, fluorouracil, and oxaliplatin; BBI608, STAT3 inhibitor (Napabucasin); FOLFIRI, folinic acid, fluorouracil, irinotecan.

A



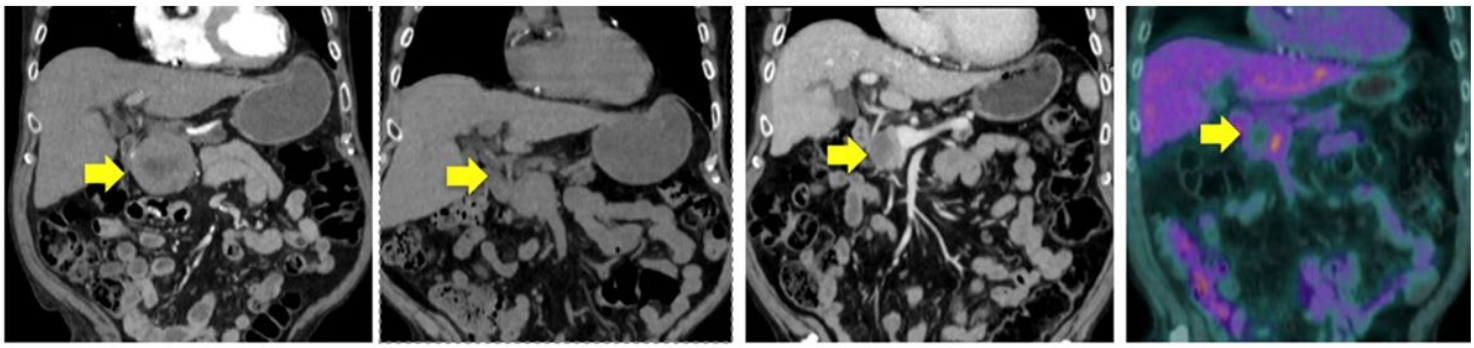
Pretreatment Six months on FOLFOX

B



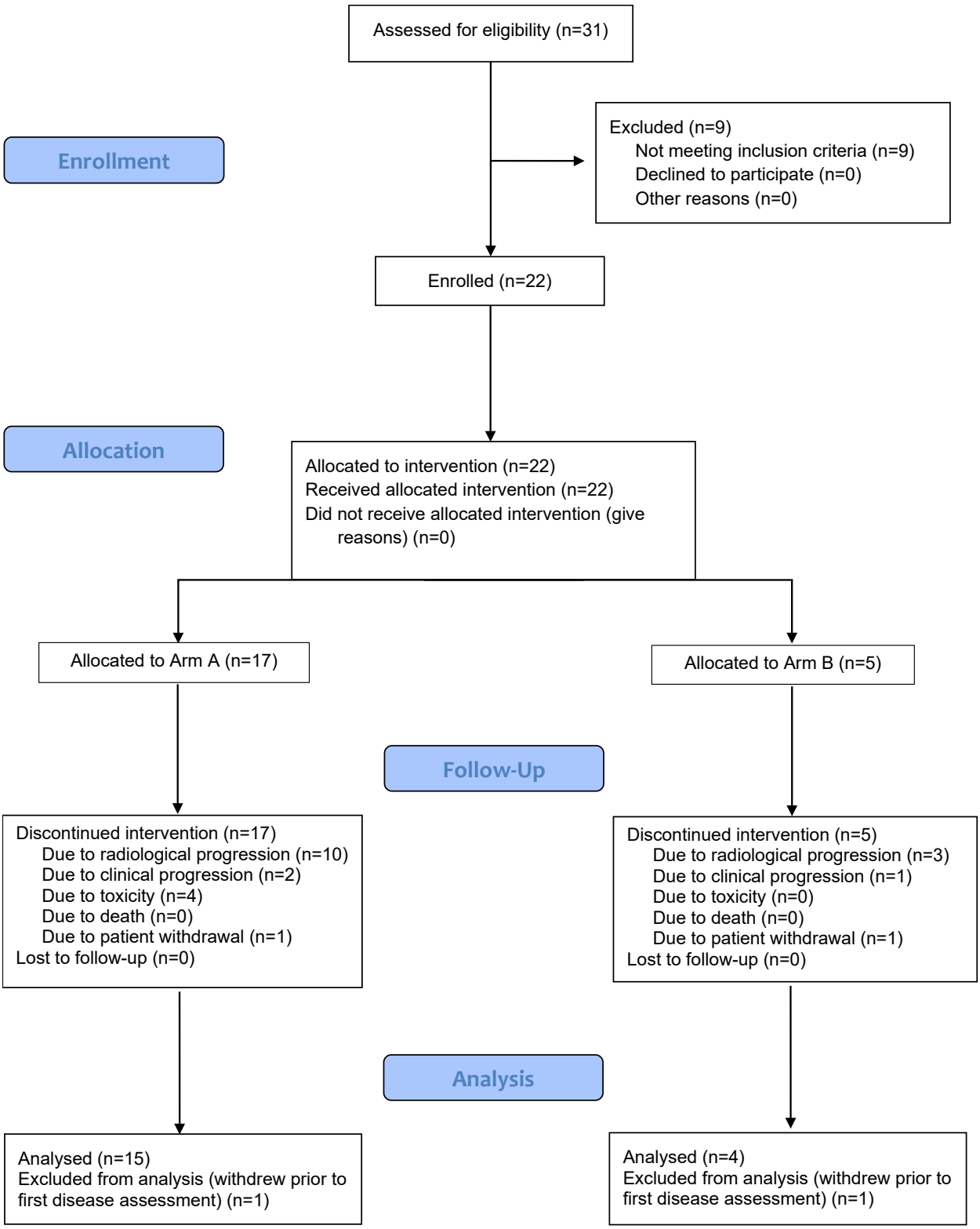
Pretreatment Three months on pemigatinib

C

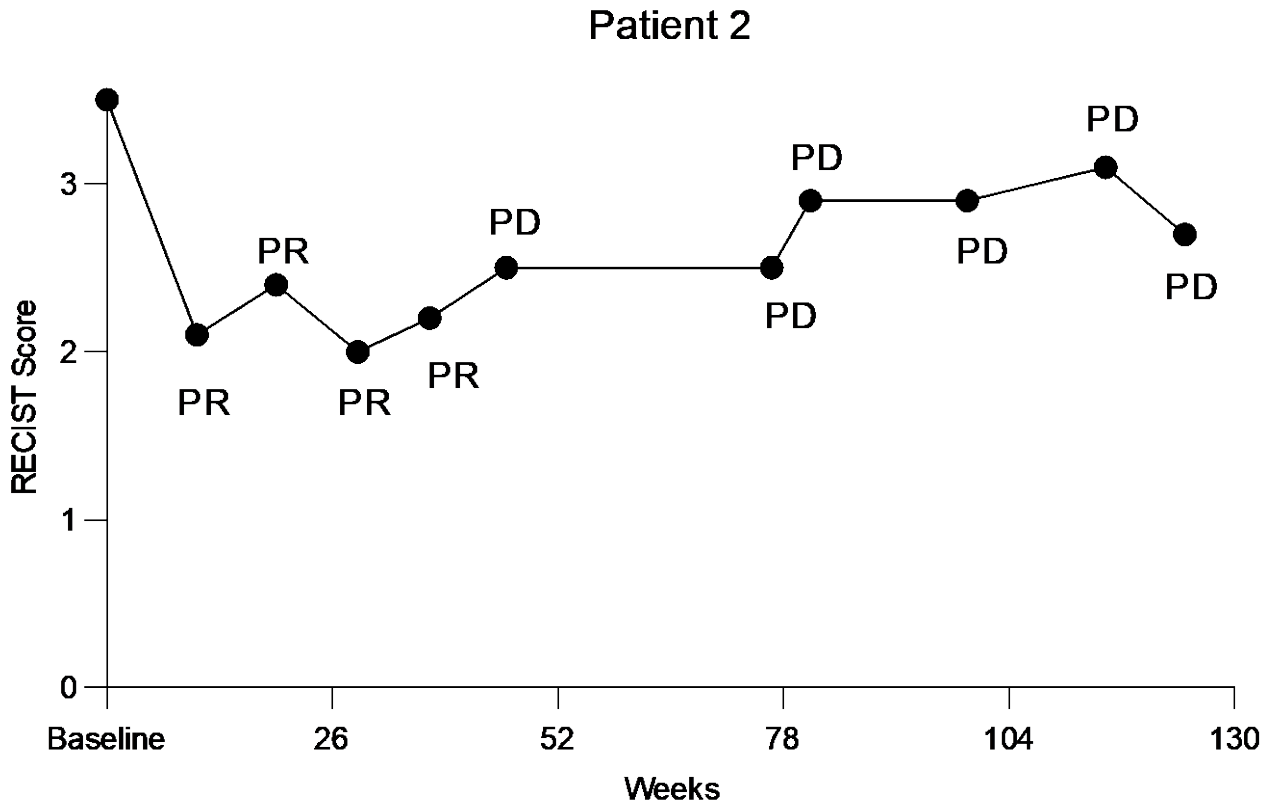


Pretreatment | Three months on pemigatinib | Five months on pemigatinib | Eight months on pemigatinib

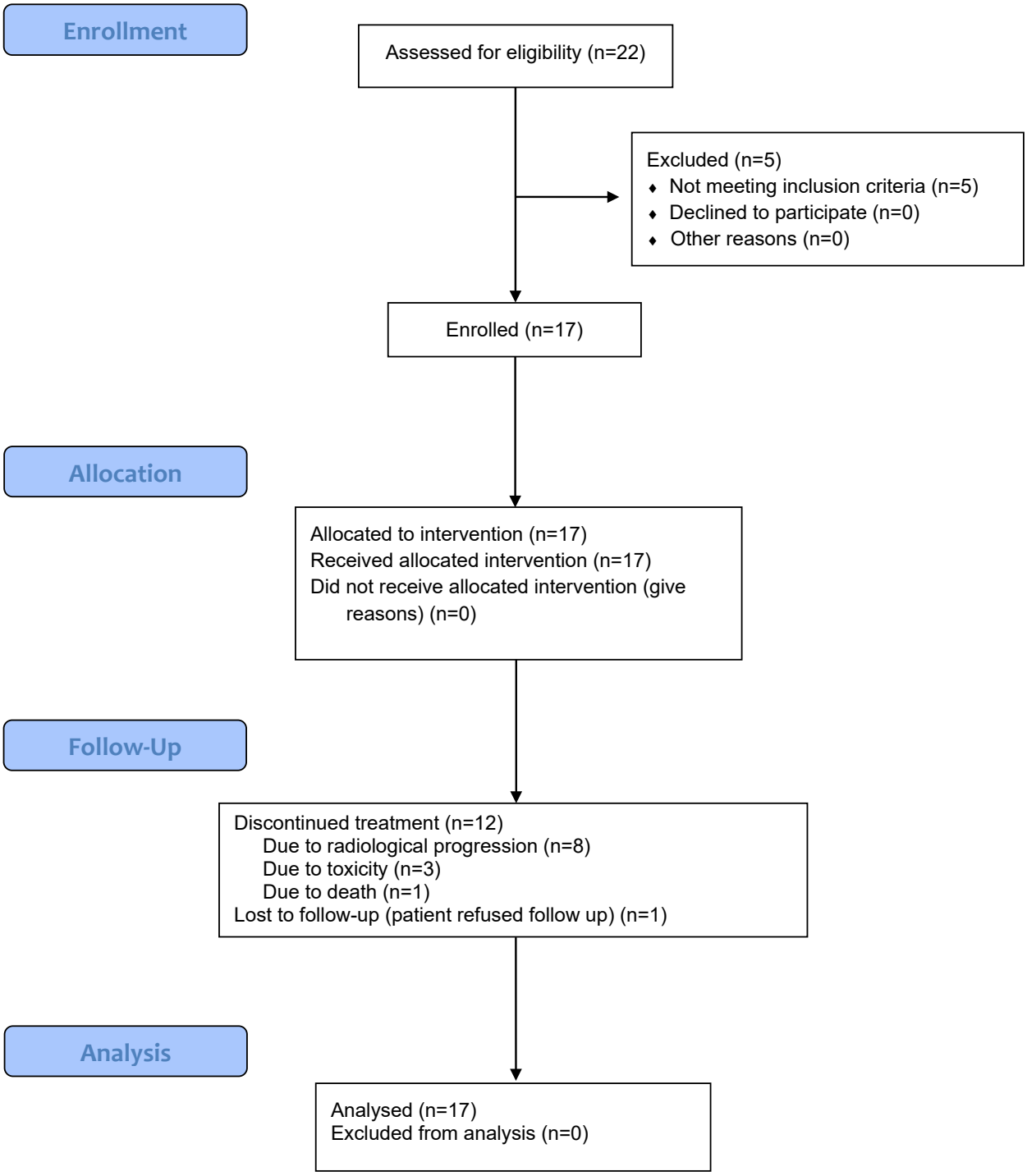
Supplementary Figure 2. Radiologic scans of patient 1, 2, and 4's best response. A, CT scans of patient 1's best response of stable disease while on FOLFOX. **B,** MRI of patient 2's best response of partial response while on pemigatinib basket trial (NCT02393248). **C,** Pretreatment, three months, and five months on pemigatinib CT scans of patient 4's partial response to off label pemigatinib. The last scan is a PET scan due to the patient's chronic kidney disease.



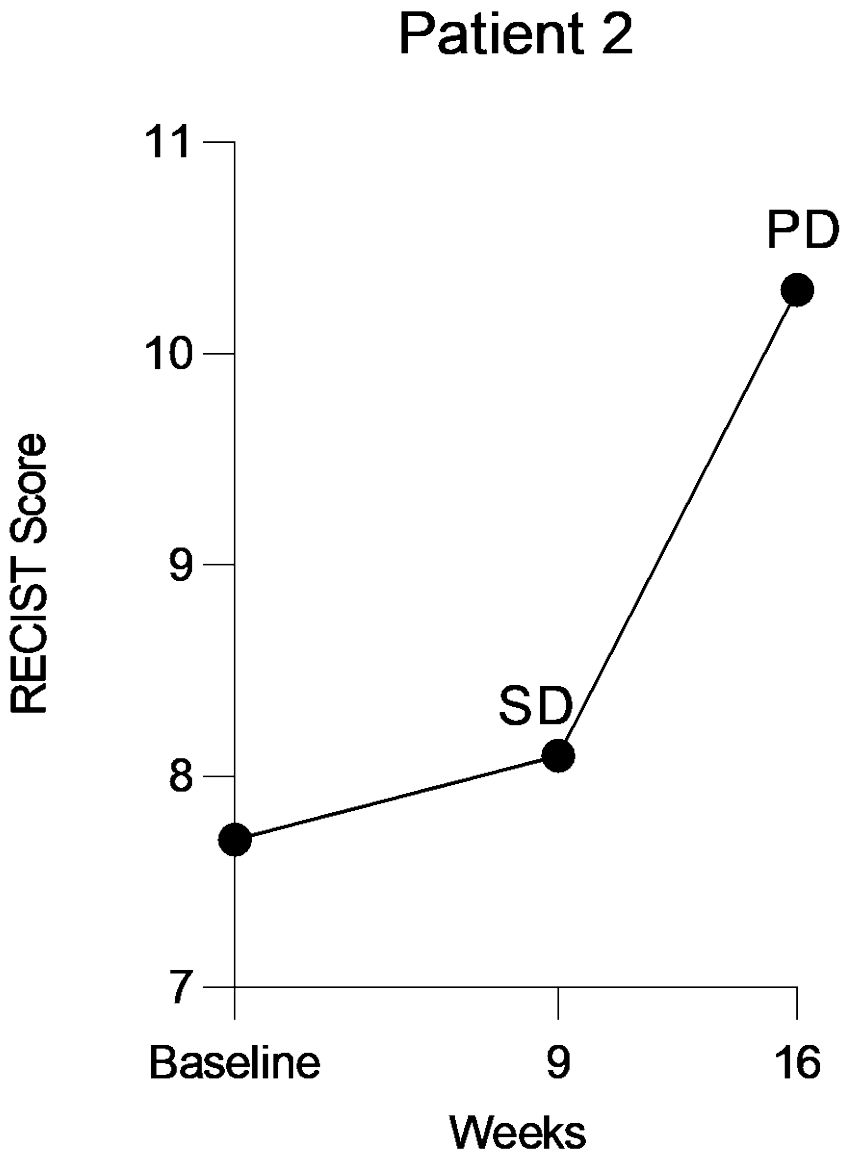
Supplementary Figure 3. CONSORT flow diagram for clinical trial OSU-14078 (NCT02272998) for ponatinib.



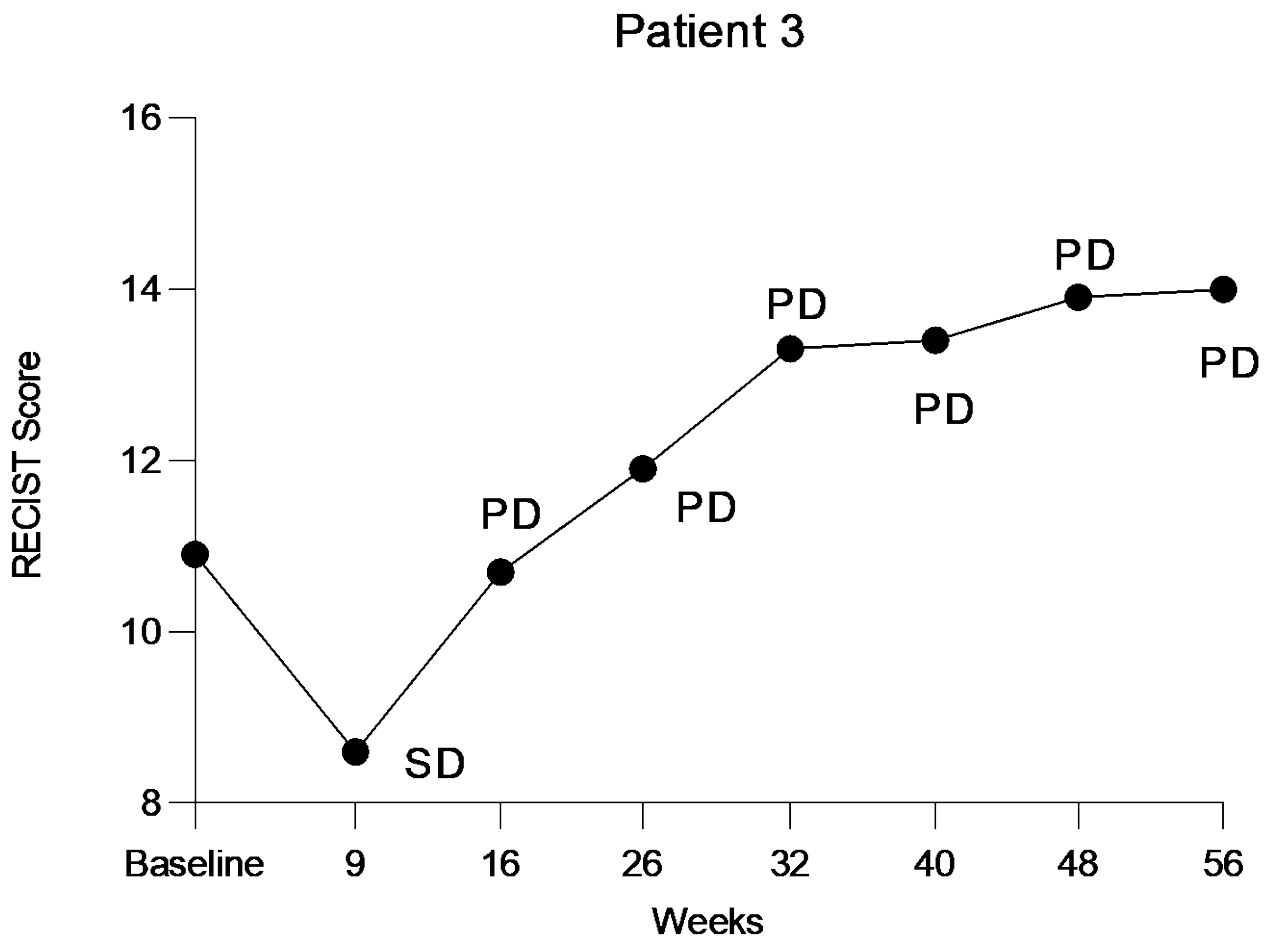
Supplementary Figure 4. Patient 2's RECIST scores on pemigatinib. Patient 2's response to pemigatinib according to RECIST scores starting with baseline scans at week 0 of infigratinib treatment. Even after disease progressed, Patient 2 still underwent treatment per Principal Investigator's request, since she was still clinically benefitting from being on therapy with no other disease evident. Abbreviations: PR, partial response; PD, progressive disease.



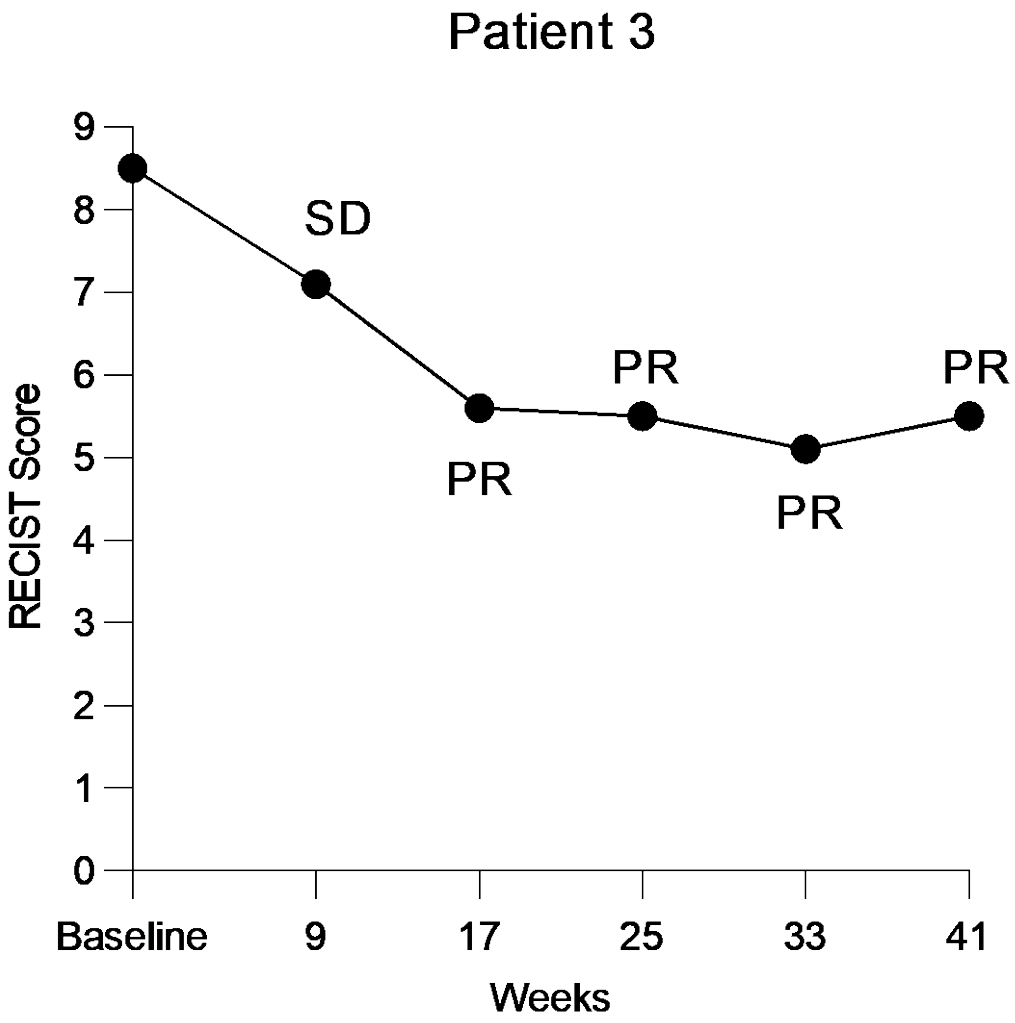
Supplementary Figure 5. CONSORT flow diagram clinical trial OSU-19041 (NCT04233567) for infigratinib.



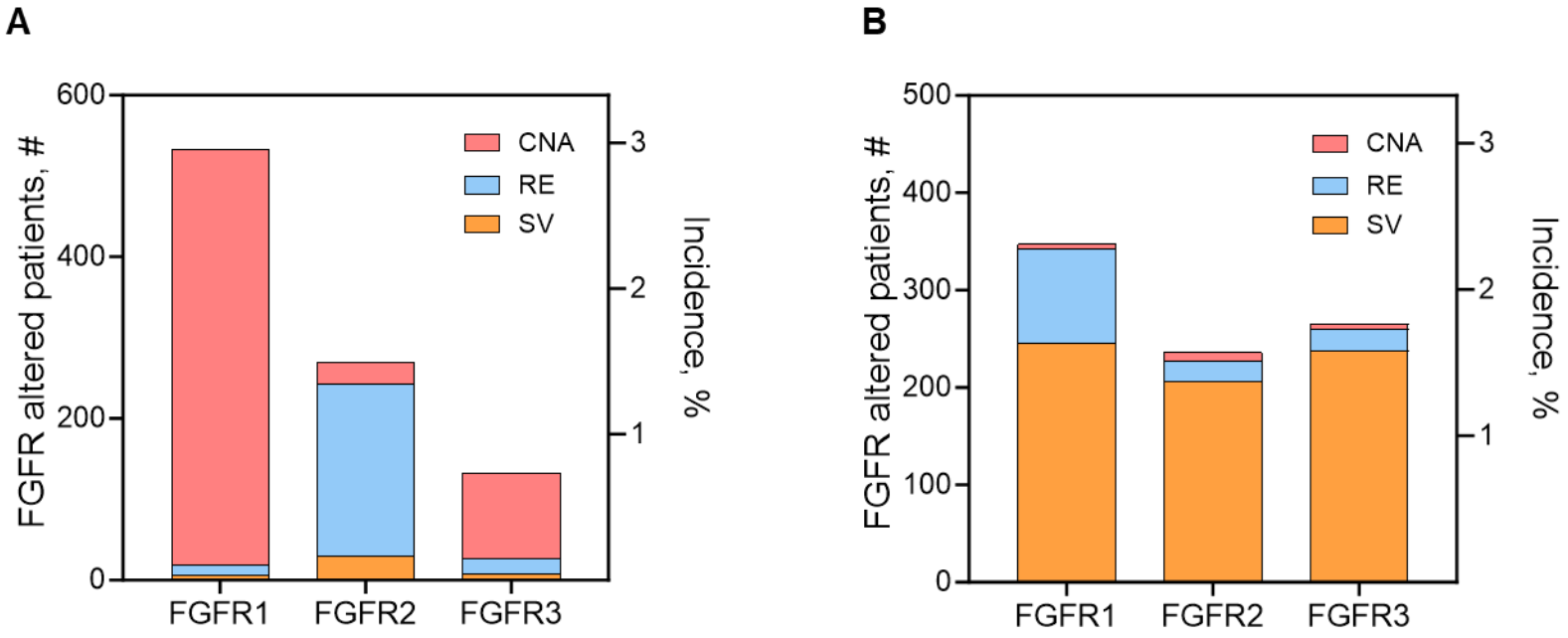
Supplementary Figure 6. Patient 2's RECIST scores on infigratinib. Patient 2's response to infigratinib according to RECIST scores starting with baseline scans at week 0 of infigratinib treatment. Abbreviations: SD, stable disease; PD, progressive disease.



Supplementary Figure 7. Patient 3's RECIST scores on ponatinib. Patient 2's response to ponatinib according to RECIST scores starting with baseline scans at week 0 of ponatinib treatment. Treatment with ponatinib was continued after progressive disease was documented per Principal Investigator's request due to a decrease in CA19-9, clinical benefit, and disease control outside of one of the target lesions. Abbreviations: SD, stable disease; PR, partial response; PD, progressive disease.

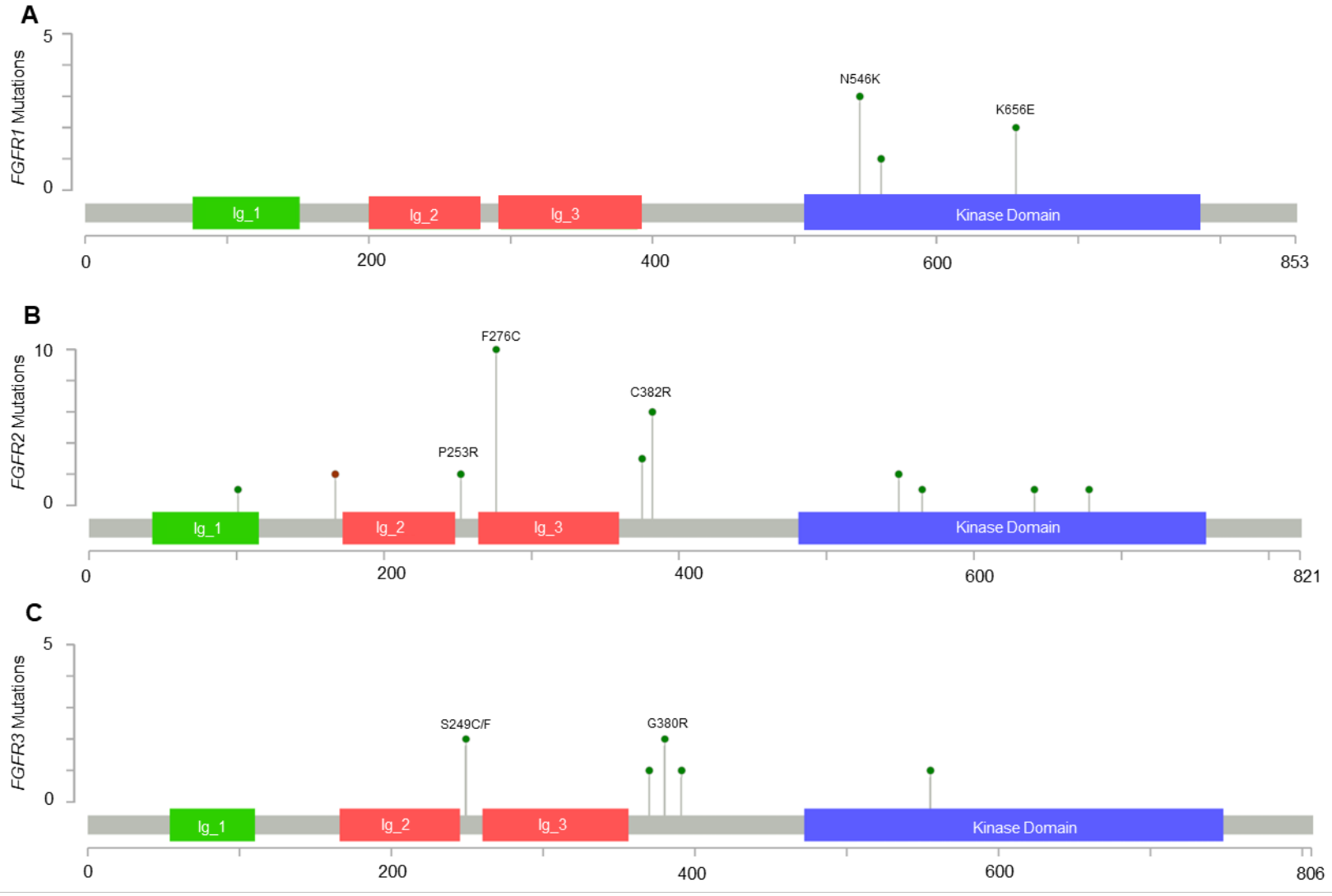


Supplementary Figure 8. Patient 3's RECIST scores on infigratinib. Patient 3's response to infigratinib according to RECIST scores starting with baseline scans at week 0 of infigratinib treatment. Abbreviations: SD, stable disease; PR, partial response; PD, progressive disease.

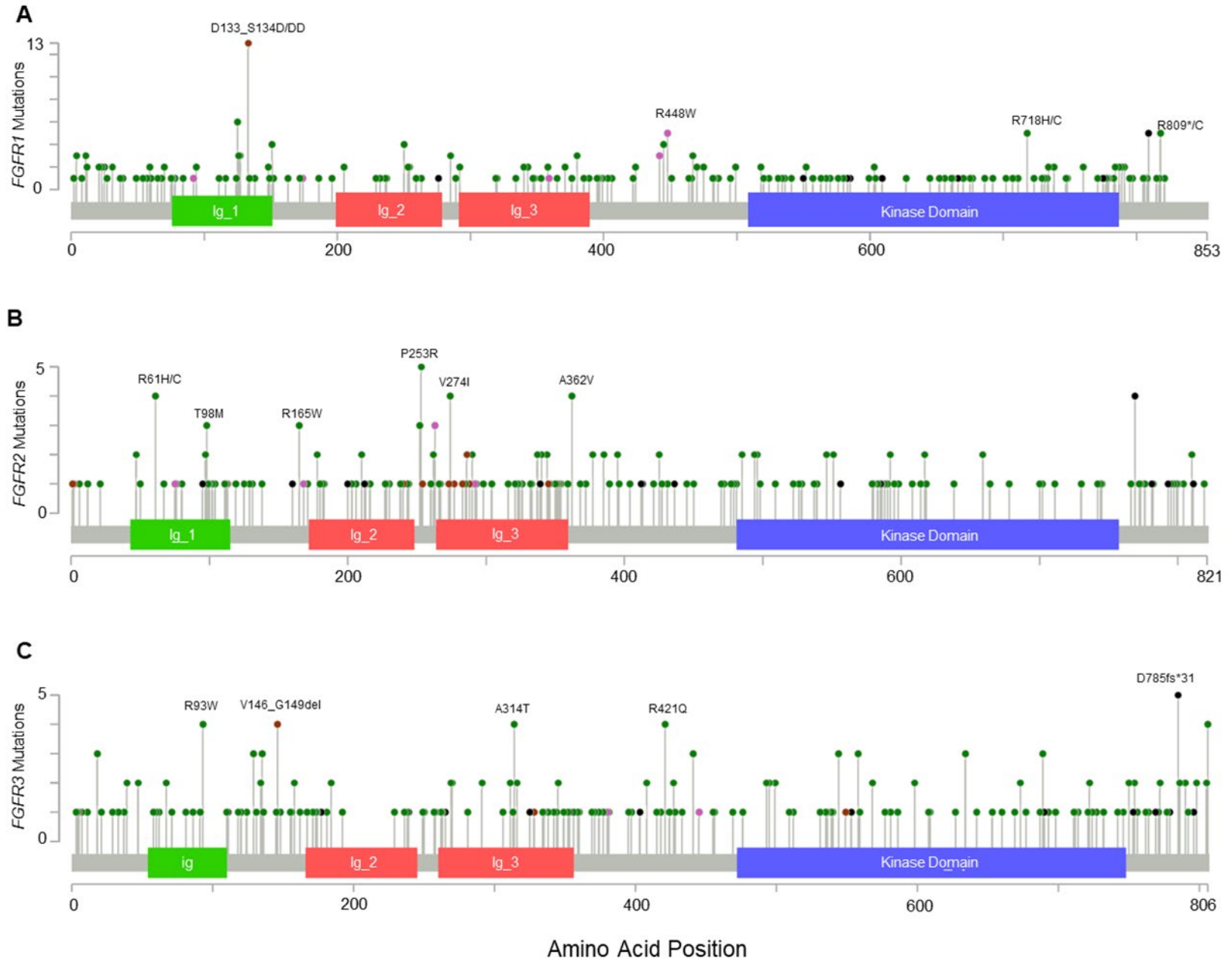


Supplementary Figure 9. Prevalence of *FGFR1-3* CNAs, SVs, and REs in pancreatic adenocarcinoma. A, *FGFR1-3* known pathogenic *FGFR1-3* alterations in pancreatic adenocarcinoma. CNAs were most observed in *FGFR1* while REs are most observed in *FGFR2*. There are very little REs and SVs with known function in *FGFR4*. **B,** *FGFR1-3* likely pathogenic and variants of unknown significance in pancreatic adenocarcinoma. REs of unknown function are most observed in *FGFR1* while SVs of unknown function occur similarly across *FGFR1-3*. This highlights the ongoing need to characterize these alterations that still have unknown function.

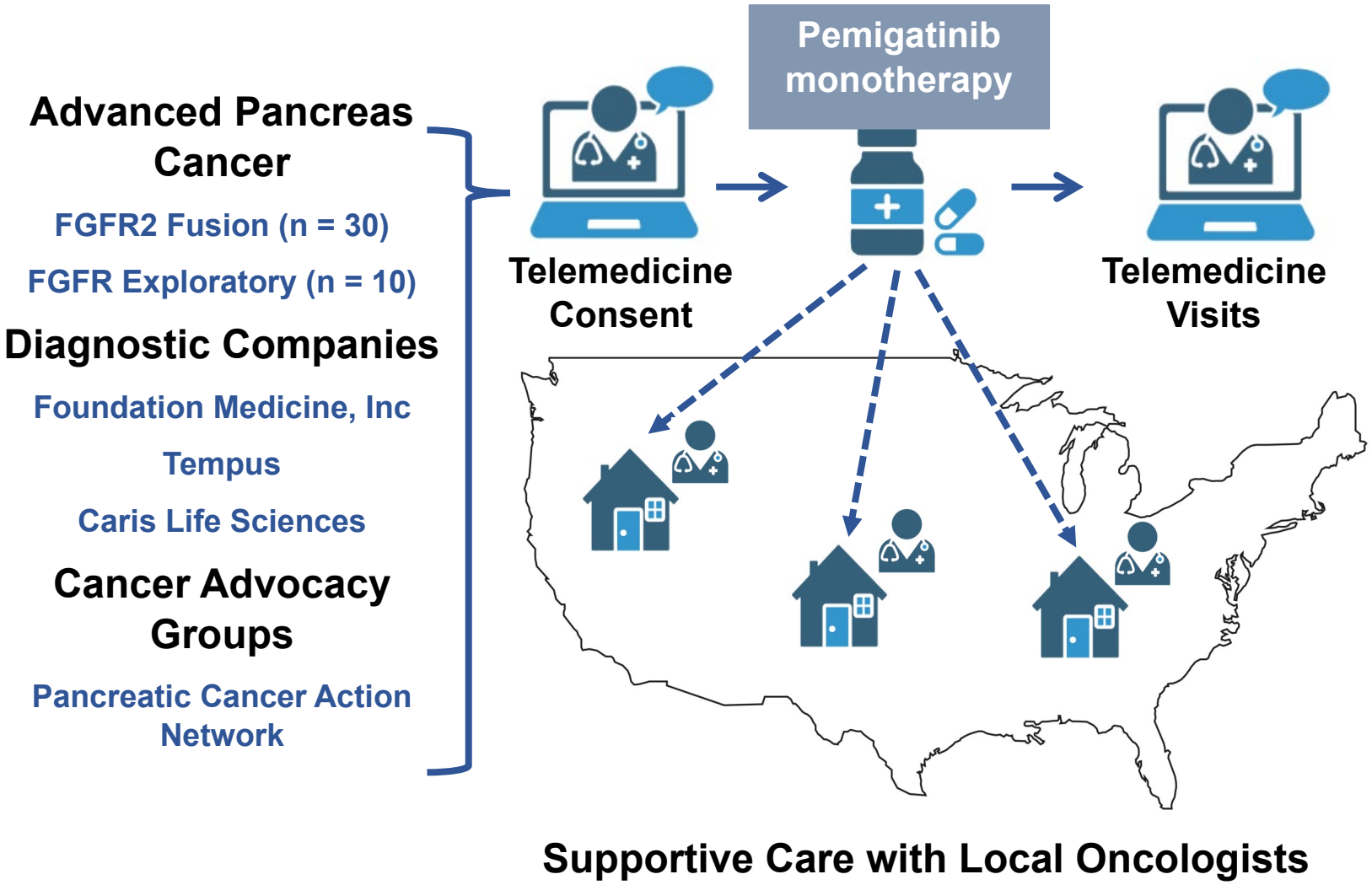
Supplementary Figure 10



Extended Figure 10. Known gain-of-function *FGFR1-3* SVs in pancreatic adenocarcinoma. Lollipop depiction of the most common known SVs (N=18) **A,** *FGFR1* (3), **B,** *FGFR2* (10), and **C,** *FGFR3* (5) missense (green dots) alterations and in-frame indels (brown dots) observed in *FGFR*-altered pancreatic cancer. Each alteration is represented by protein domain location and frequency (height). Figure was generated using cBioPortal MutationMapper[1,2].



Supplementary Figure 11. *FGFR1-3* short variants of unknown significance (VUS) and likely pathogenic short variants in pancreatic adenocarcinoma. Lollipop depiction of unknown function SVs (N=563) **A,** *FGFR1* (188), **B**, *FGFR2* (183), and **C,** *FGFR3* (192) missense (green dots) alterations, truncating alterations including nonsense, nonstop, frameshift indels, and splice sites (black dots), and in-frame indels (brown dots), and all other alterations (pink dots) observed in *FGFR*-altered pancreatic cancer. Some of the likely pathogenic *FGFR* SVs include *FGFR1 S125L, FGFR1 R445W, FGFR1 G818R, FGFR2 P253R, FGFR2 Y769*, FGFR2 M537I, FGFR2 372C,* and *FGFR3 R621H.* These SVs labeled as likely pathogenic are rare *FGFR* mutations that warrant further investigation. Each alteration is represented by protein domain location and frequency (height). Figure was generated using cBioPortal MutationMapper[1,2].



Supplementary Figure 12. Scheme of a Phase II, telemedicine trial with pemigatinib in unresectable or metastatic pancreatic cancer with *FGFR* genomic alterations.

Supplementary Table 1

Variable	Patient 1	Patient 2	Patient 3	Patient 4
Age (at diagnosis)	61	44	71	79
Gender	Male	Female	Male	Male
Race	African American	White	White	White
Cancer Histology	Poorly differentiated carcinoma	Moderately differentiated adenocarcinoma	Adenocarcinoma	Adenocarcinoma
# of systemic therapies	4	7	6	2
Systemic therapies	Gemcitabine/nab-paclitaxel; FOLFOX; Ponatinib; Pazopanib	Gemcitabine/Cisplatin; Gemcitabine/nab-paclitaxel/BB1608; FOLFIRI/BB1608; Pemigatinib; Infigratinib; FOLFIRINOX	Gemcitabine/Capecitabine; Gemcitabine/nab-paclitaxel; Ponatinib; Gemcitabine/Cisplatin; Gemcitabine/Carboplatin; Infigratinib	Gemcitabine/nab-paclitaxel; Pemigatinib
Genomic alteration	FGFR2-INA; FGFR2 amplification	FGFR2-USP33	FGFR2-CEP55	FGFR2-INA; FGFR2 amplification
Smoking status (pack years)	21	0	0	15

Supplementary Table 2

Supplementary Table 1. Comparison of Patient 1-4 demographics.

		***FGFR1-4 RE* mt (N=245)**	***FGFR1-4 RE* wt (N=**29984)
Gender: Males (n, %)[1]		116 (47.3)	15995 (53.3)
Median age (IQR; years)[2]		61 [52-69]	66 [59-73]
Age ≥ 18 years (n, %)		244 (99.6)	29943 (99.9)
Genomic ancestry (n, %)[3]	AFR	27 (11.0)	2831 (9.4)
	AMR	15 (6.1)	1444 (4.8)
	EAS	11 (4.5)	1024 (3.4)
	EUR	184 (75.1)	23526 (78.5)
	SAS	2 (0.8)	229 (0.8)
Metastatic (n, %)[4]		204 (78.4)	14849 (49.1)

Supplementary Table 2. Comparison of demographics characteristics between the *FGFR1-4* rearranged and *FGFR1-4* rearrangement wildtype cohort of patients. Gender variable had a missingness rate of 0.03% (n=10). Age variable had a missingness rate of 0.08% (n=25) in the dataset. Median age comparison was significant by Wilcoxon rank sum test, P=2.3e-10. Genomic ancestry variable had a missingness rate of 3.1% (n=936). Metastatic variable had a missingness rate of 8.1% (n=2457) in the dataset. Abbreviations: AFR, Africa; AMR, Americas; EAS, East-Asia; EUR, Europe; SAS, South-Asia

References

1. Cerami, E.*, et al.* The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov* **2**, 401-404 (2012).
2. Gao, J.*, et al.* Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. *Sci Signal* **6**, pl1 (2013).