Correlation of PET/CT and CT RECIST Response in GIST Patients with PDGFRA D842V Gene Mutations Treated with Crenolanib

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BACKGROUND

- GISTs express KIT, a tyrosine kinase growth factor receptor; 85% of GISTs contain mutations in the *KIT* gene. ~1/3 of the remaining 15% contain mutations in PDGFRA exon 12 or 18.
- Only a portion of the constitutively active PDGFRA mutations are inhibited by imatinib. The missense D842V mutation (60% of PDGFRA mutations) confers primary resistance to imatinib, sunitinib and nilotinib.
- Crenolanib (CP-868,596), a highly potent and selective, orally bioavailable PDGFR TKI, has pre-clinical data suggesting activity against PDGFRA D842V mutant cell lines.
- Prior studies have established comparable sensitivity and positive predictive value in staging recurrent/metastatic GIST (in patients without PDGFRA mutations) with FDG-PET and standard CT.

METHODS

- Patients with advanced GIST with PDGFRA D842 related mutations and deletions, including D842V, with residual measurable disease were eligible for enrollment at 1 of 2 study sites (Fox Chase Cancer Center, Philadelphia, PA; or Oregon Health & Science University Knight Cancer Institute, Portland, OR).
- Restaging CT was conducted every 2 cycles during the first 6 months, then every 3 cycles thereafter. When feasible, FDG-PET images were done at baseline and following cycle 1 of therapy to determine metabolic response. Patients with a baseline PET/CT and a follow-up PET/CT after 1 cycle of crenolanib were included in this analysis.
- One nuclear medicine specialist interpreted the scans and provided SUV estimates for index lesions at baseline and after 1 cycle and assessed metabolic response using EORTC PET criteria. RECIST measurements (version 1.1) were provided by the local interpreting radiologist.
- An exploratory objective of this trial was to determine the metabolic response following one cycle of therapy as a predictor of response by RECIST.

RESULTS: PATIENTS CHARACTERISTICS

Table 1: Patient Characteristics

Patient Study ID	Age (years)	Sex	Primary Race	ECOG PS	# prior systemic therapies	Prior Exposure to TKIs?	If yes, list TKI(s):	Best Response PET/CT	Best Response CT RECIST
FCCC-001	75	F	White	0	3	Yes	Imatinib, dasatinib, sunitinib	PR	SD
FCCC-002	68	F	Black	0	2	Yes	Imatinib, sutent	PD	PD
FCCC-004	67	F	White	1	0	No		SD	SD
FCCC-005	46	M	White	0	2	Yes	Imatinib, dasatinib	SD	PD
FCCC-007	73	M	White	1	1	Yes	Imatinib	SD	PD
OHSU-001	62	M	White	0	1	Yes	Dasatinib	PD	SD
OHSU-002	74	F	White	0	1	Yes	Imatinib	PD	SD
OHSU-003	58	M	White	1	4	Yes	Nilotinib, imatinib, sunitinib, sorafenib	PD	PD
OHSU-004	63	F	White	0	0	No		SD	PR
OHSU-005	64	F	White	0	1	Yes	Imatinib	PR	PD
OHSU-006	60	M	White	0	5	Yes	Nilotinib, imatinib, sunitinib, sorafenib, regorafenib	SD	SD
OHSU-007	51	M	White	0	2	Yes	Imatinib, sunitinib	SD	SD
	Mean Age 63	50% F	92% White	75% PS 0	Mean 1.83	10/12 (83%)	9/12 (75%) prior imatinib	SD = stable disease	

RESULTS: RADIOGRAPHIC RESPONSE

- All 12 patients had the D842V mutation in PDGRFA
- Mean SUV_{max} was 8.6. Excluding subject FCCC-002 (SUV_{max} 39.7), mean SUV_{max} was 4.6. Prior reports have published mean SUV_{max} ranging from 4.83 to 10.6
- There were no complete responses
- Partial response: 2 (17%) by PET, 1 (8%) by CT (no concordance)
- Stable disease: 6 (50%) by PET, 6 (50%) by CT (3 concordant)
- Progressive disease: 4 (33%) by PET, 5 (42%) by CT (2 concordant)
- 8/12 (67%) patients demonstrated metabolic tumor control (SD or PR). Only 5 of the 8 (63%) demonstrated RECIST SD or PR.
- The concordance between RECIST and metabolic response overall was low, 5/12 (42%)

RESULTS: RADIOGRAPHIC RESPONSE

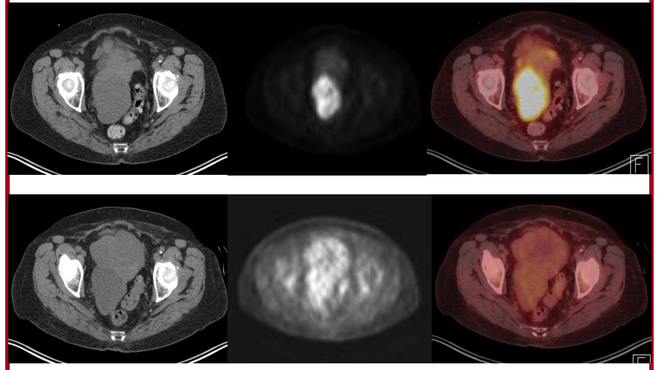
Table 2: Radiographic Response

# of patients	PET Metabolic Response	CT RECIST
3	SD	SD
2	PD	PD
2*	PD	SD
2*	SD	PD
1*	PR	SD
1*	PR	PD
1*	SD	PR

* Indicates non-concordance

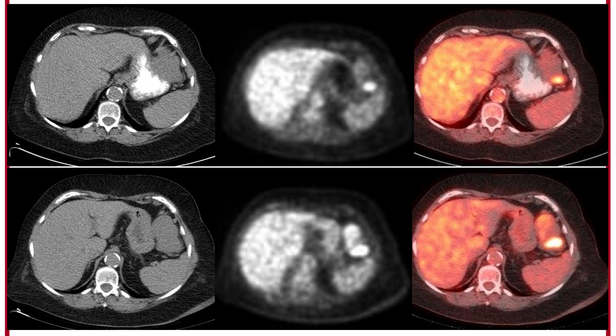
CT: Stable Disease, PET/CT: Partial Response

FCCC-001



CT: Stable Disease, PET: Progressive Disease

OSHU-002



CONCLUSIONS

- In this study, patients with PDGFRA D842V mutations had lower than expected SUV activity on PET
- In contrast to prior studies in patients without known PDGFRA mutations, metabolic response did not predict response by RECIST. In only 5 of 12 cases (42%) did PET response predict RECIST response.
- These results suggest that PET/CT may not be an optimal method for predicting, evaluating and following response for GIST patients with PDGFRA D842V mutations.
- Further study of this select patient population may determine the role of FDG-PET in staging and predicting response to therapy

References

Hirota S, et al. Science 1998;279:577-80
Gayed I, et al. J Nucl Med 2004;45:17-21
Wong CS, et al. Eur J Radiol 2012;81:2122-6
Young H, et al. Eur J Cancer 1999;35:1773-82
Prior JO, et al. J Clin Onc 2009;27:439-445