The ROYAL MARSDEN NHS Foundation Trust

ICR The Institute of Cancer Research

Abstract 1096: Phase II study of AZD4547 in *FGFR* amplified tumours: gastroesophageal cancer (GC) cohort clinical and translational results

Elizabeth Smyth[1], Nicholas Turner[1,2], Clare Peckitt[1], Gina Brown[1], Sue Chua[1], Alex Pearson[2], Anne Thomas[3], Ros Cutts[2], Angela Gillbanks[1], Elaine Kilgour[4], Neil R. Smith[4], Clare Rooney[4], David Watkins[1], Ian Chau[1], Sanjay Popat[1], and David Cunningham[1]

[1]Royal Marsden, London & Surrey, United Kingdom, [2]Institute of Cancer Research, London, United Kingdom
[3]Leicester Royal Infirmary, Leicester, United Kingdom, [4]Astra Zeneca, Alderley Park, United Kingdom

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NHS National Institute for Health Research

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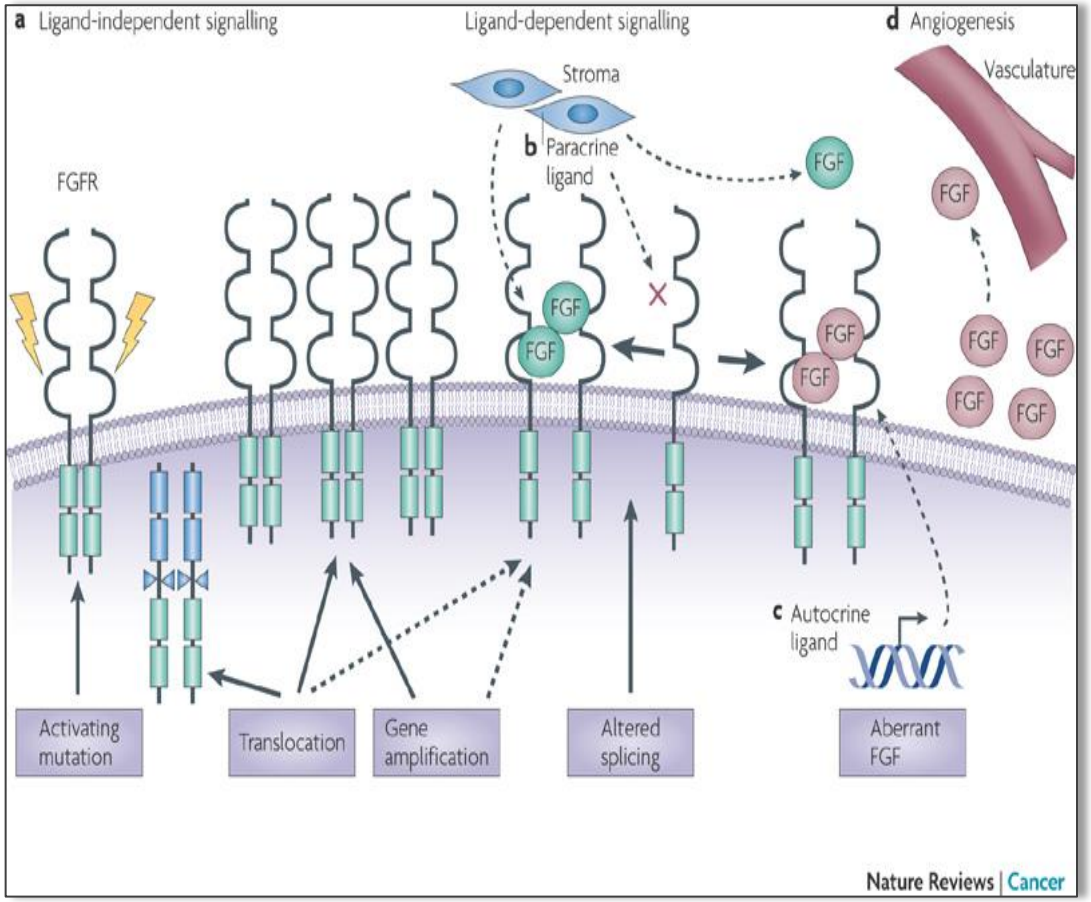
Disclosure slide

- Elizabeth Smyth: No disclosures

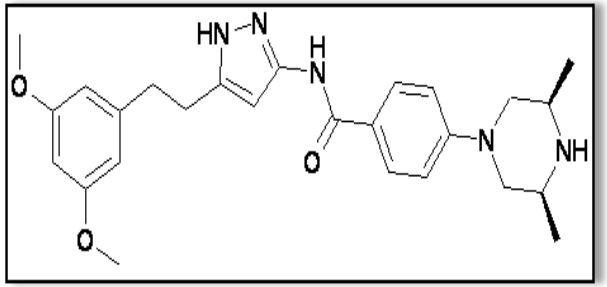
FGFR signalling dysregulation is an oncogenic driver in many cancers

Amplification	
FGFR1	ER+ breast cancer (9-23%) SqNSCLC (10-20%)
FGFR2	Gastroesophageal (9%)
Fusion	
FGFR2	Cholangiocarcinoma (15%)
FGFR3	Bladder (6%) Glioblastoma (3-7%)
Mutation	
FGFR1	Endometrial (12%)
FGFR3	Bladder (10%-60%)



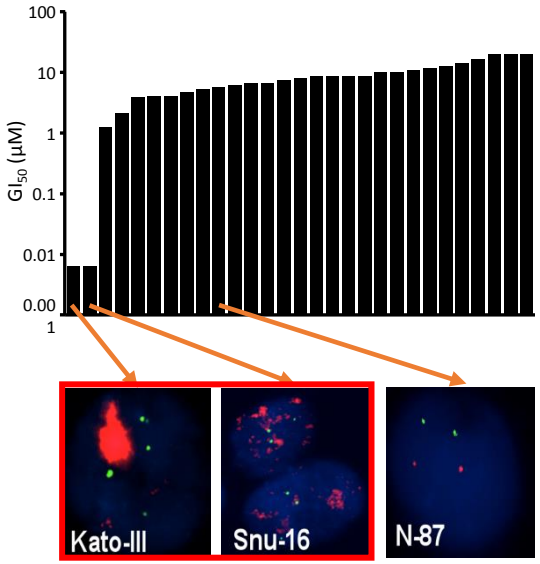
Turner N, Grose, R. Nature Reviews Cancer 10, 116-129

AZD4547 is a potent, selective inhibitor of *FGFR* 1, 2 and 3 receptor tyrosine kinases

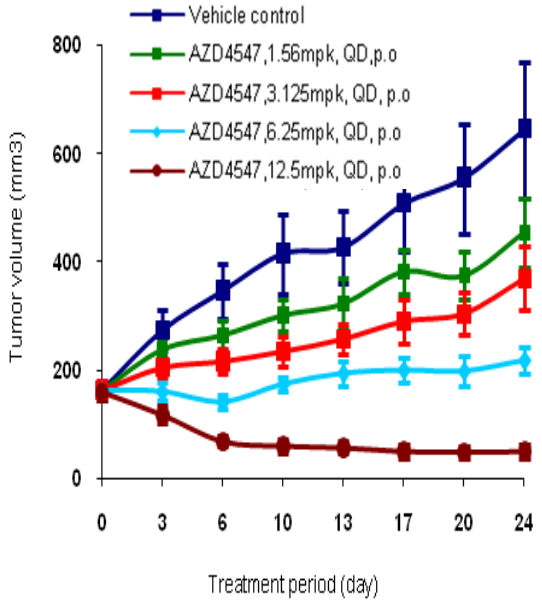


Kinase	Enzyme IC_{50}, nmol/L	Cellular IC_{50}, nmol/L
FGFR1	0.2 ± 0.06	12 ± 3
FGFR3	1.8 ± 0.33	40 ± 1
FGFR2	2.5 ± 0.23	2 ± 0.2
KDR	24 ± 0.001	258 ± 17
FGFR4	165 ± 30.3	142 ± 29

Correlation between *FGFR2* gene amplification and sensitivity to AZD4547 in cell lines[1]



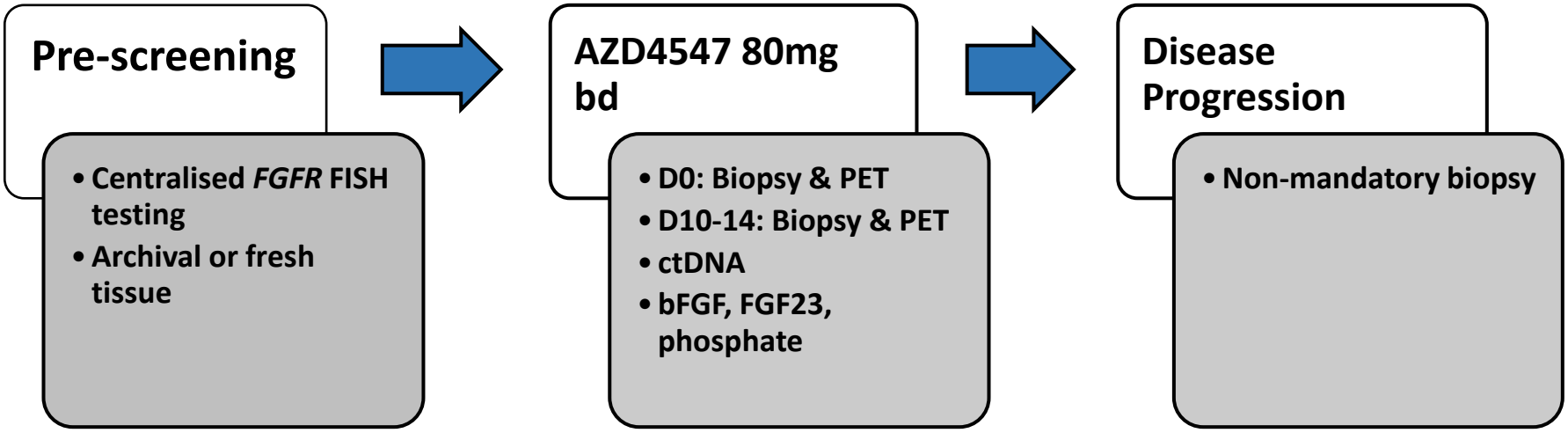
Effect of AZD4547 treatment on tumour growth in the SNU-16 xenograft model[2]



[1]Paul R. Gavine et al. Cancer Res 2012;72:2045-2056
[2]Liang Xie et al. Clin Cancer Res 2013;19:2572-2583

FGFR Trial: Study Design

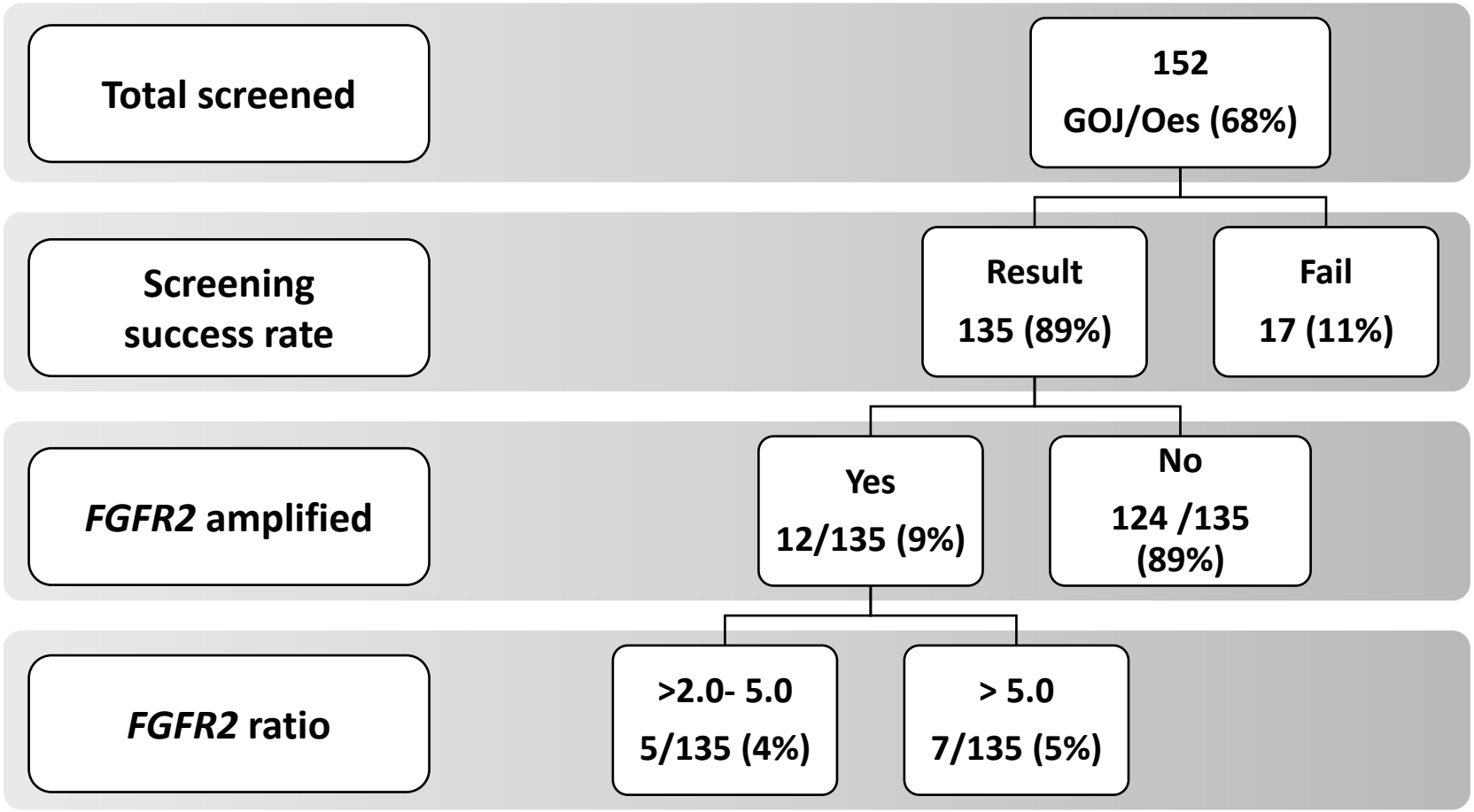
- Phase II, non-randomised study
- 3 independent previously treated advanced disease tumour types
  - oesophagogastric (*FGFR2*), HER-2 negative breast and squamous NSCLC (*FGFR1*)



Primary endpoint: objective confirmed response rate in each tumour group

Simon 2 stage design: If ≥ 1 response in initial 9 patients per group, then proceed to 17 patients. If ≥ 3/17 demonstrate response then further research is indicated

FGFR Study Screening Results: OG cohort



FGFR study: OG cohort patient characteristics

Baseline characteristics (n=9)	
Male:Female	8:1
Median age (years) Range	64 35-77
ECOG PS 0-1/2	 8/1
Number prior lines therapy 1/2/>2	 5/3/1
Sites of metastases 1/2/>2	 2/5/2
Site of primary tumour GEJ/Gastric	 9/0

AEs are consistent with known AZD4547 toxicities

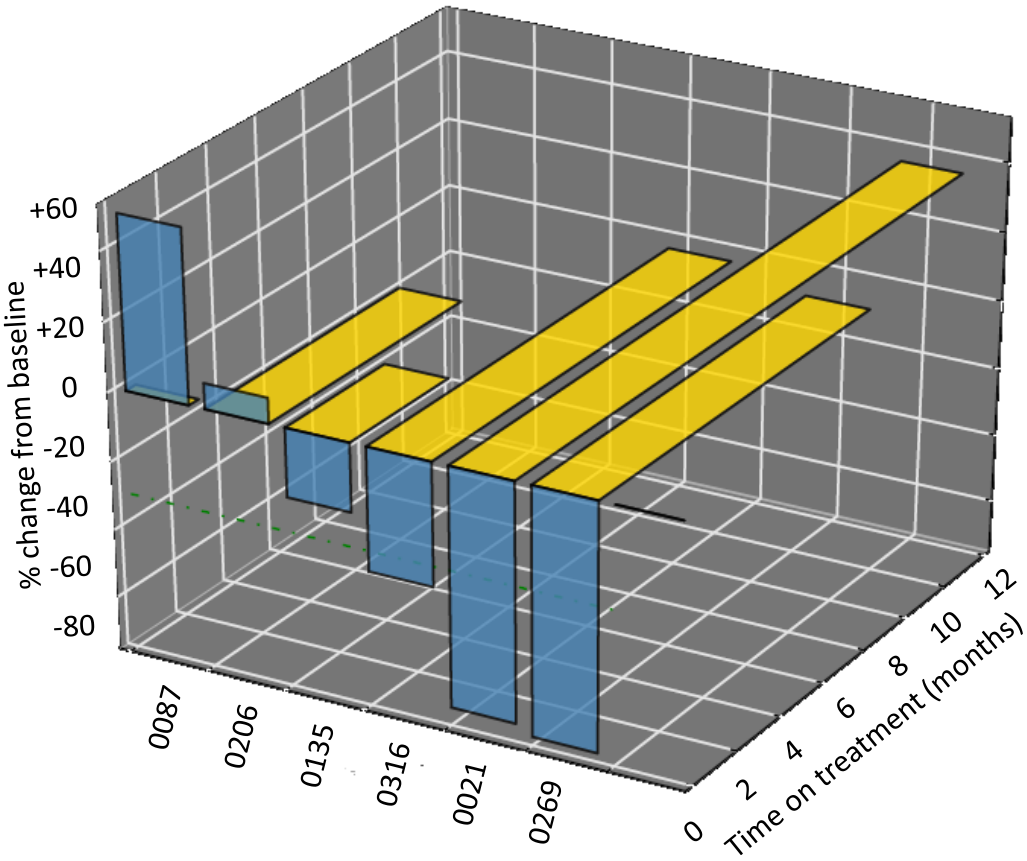
Adverse events occurring in >10% of patients				
Toxicity	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**All grades n (%)**
Fatigue	3 (33%)	2 (22%)	2 (22%)	7 (77%)
Constipation	3 (33%)	3 (33%)	-	6 (66%)
Skin changes	-	2(22%)	1 (11%)	**3 (33%)**
Mucositis	1 (11%)	1(11%)	1(11%)	**3 (33%)**
Eye changes	3 (33%)	-	-	**3(33%)**
PPE	1(11%)	2 (22%)	-	3(33%)
Nail changes	2 (22%)	-	-	2(22%)
Hyperphosphataemia	2 (22%)	-	-	**2(22%)**
Hypertension	1(11%)	1(11%)	-	2 (22%)
Diarrhoea	1(11%)	-	-	1(11%)

- One patient developed grade 5 febrile neutropenia as a result of marrow failure
- One patient developed grade 4 increased LFTS secondary to biliary obstruction
- One patient developed asymptomatic retinal pigmented epithelial detachment

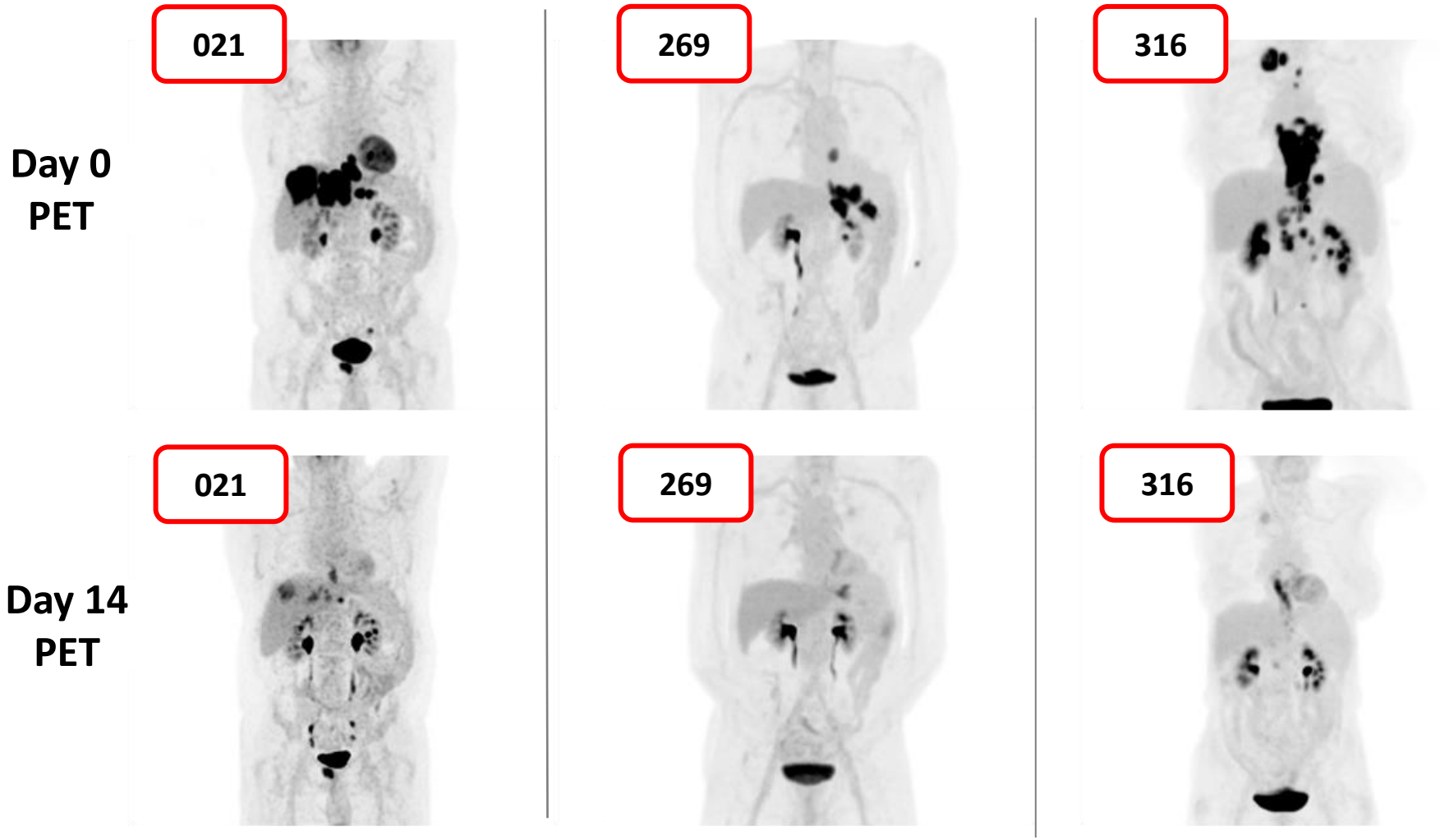
Durable responses demonstrated in OG cohort

Efficacy in OG cohort (n=9)	
Complete response	0
Objective Response (CR + PR)	3 (33.3%)
Stable disease	2 (22.2%)
Disease control rate (CR + PR + SD)	55.5%
Mean duration of response (months)	5.7 (SD 2.4)
3 patients were inevaluable • 1 toxicity (recurrent grade 3 rash) • 1 withdrew consent • 1 clinical progressive disease	

RECIST response vs. time on treatment

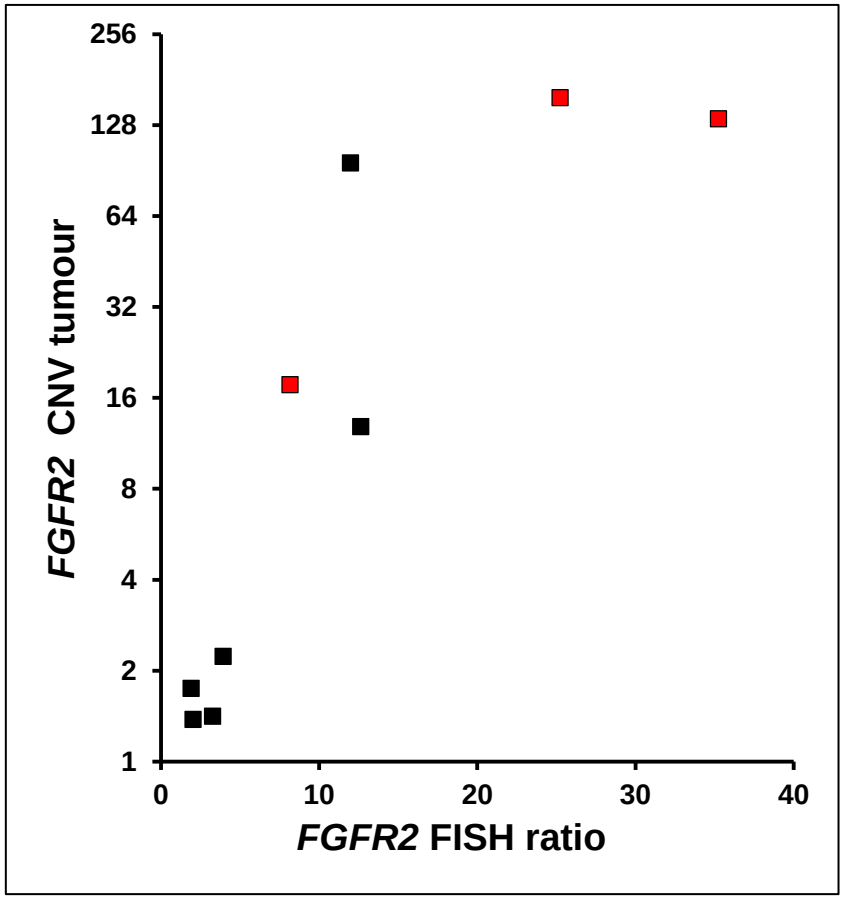


D14 PET identifies rapid responses in OG patients

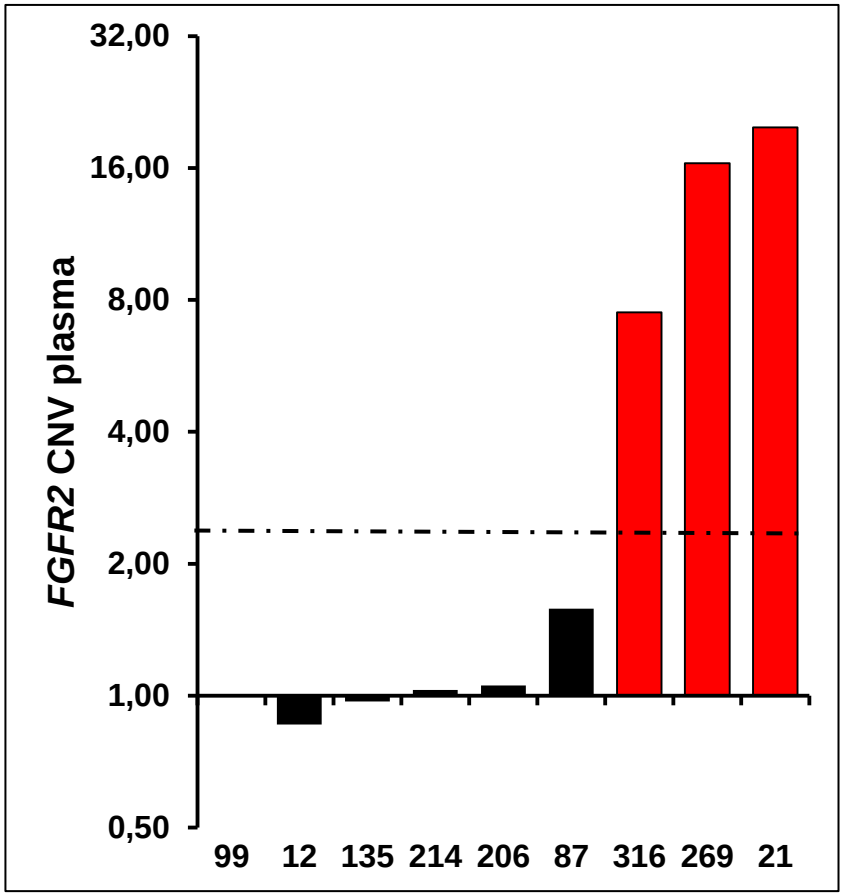


FGFR2 CNV in plasma predicts response to AZD4547

FGFR2 FISH ratio vs CNV (oesophagogastric)



FGFR2 plasma CNV (oesophagogastric)



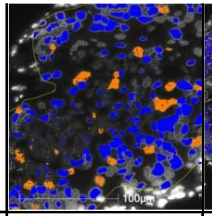
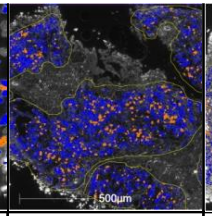
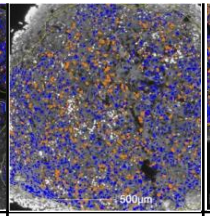
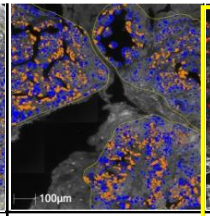
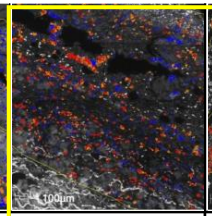
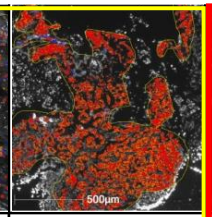
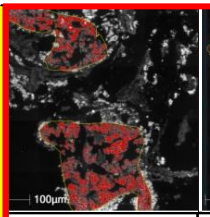
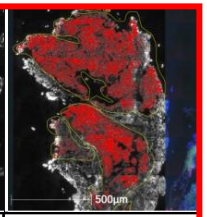
*99 = no sample

= response

High level homogenous *FGFR2* amplification is required for response to AZD4547

Sections were digitally scanned using the x40 objective of a MIRAX Panoramic 250 Flash II (3D Histech)

Tumor was marked and z-stack levels examined for evidence of heterogeneity.

								
% amplified	**14.1**	**27**	**28**	**37**	**44**	**94**	**99**	**99**
FISH ratio (MIRAX)	**1.1**	**1.4**	**1.6**	**1.9**	**10**	**43**	**30**	**34**
FISH ratio (manual)	**1.9**	**2.0**	**3.3**	**3.9**	**12.6**	**12.0**	**25.2**	**35.3**

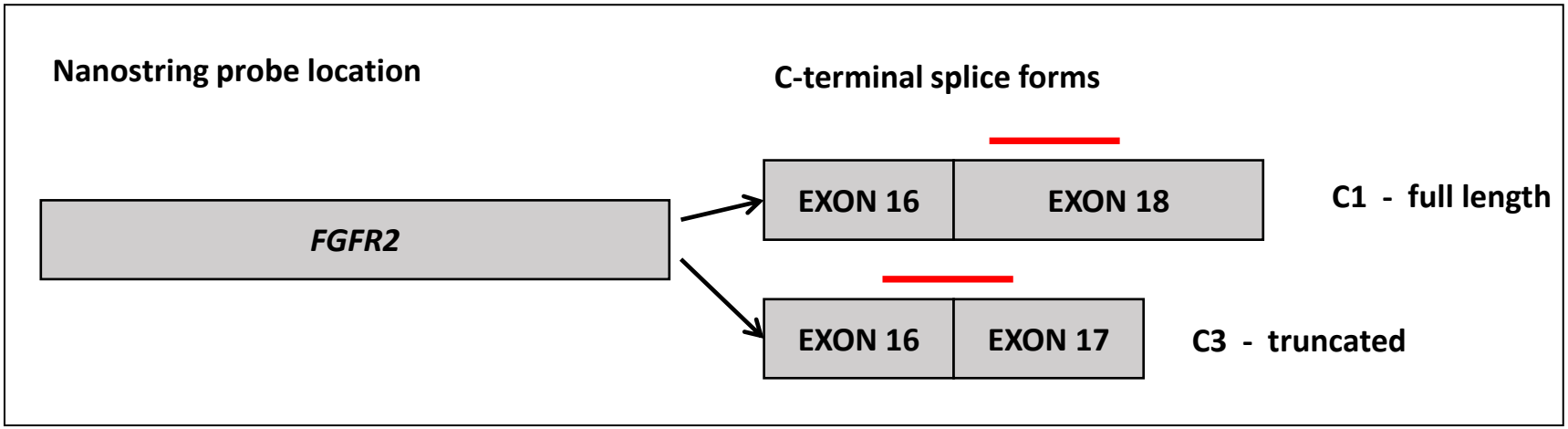
Unamplified tumour cell Amplified tumour cell

*No sample available for one responder

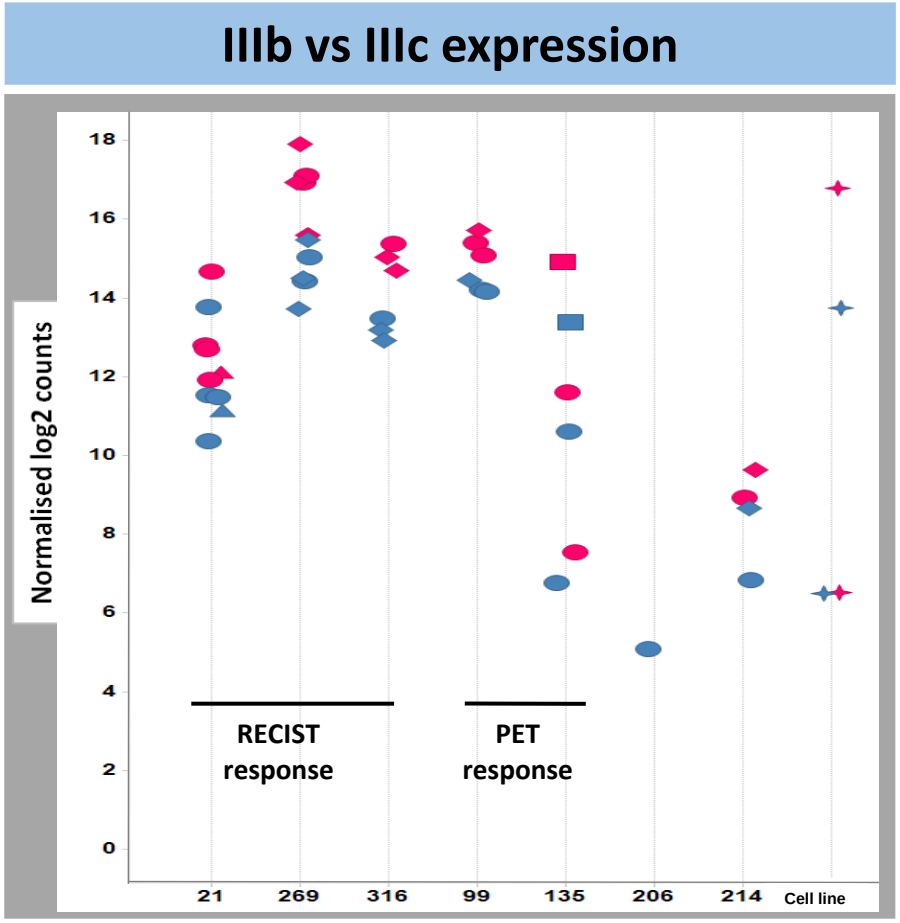
Correlation between screening FISH and MIRAX ratio is high (r =0.9963).

FGFR2 Nanostring analysis

- *FGFR2* IIIb and IIIC isoforms demonstrate differential expression in epithelial and mesenchymal tissues and have distinct ligand specificities
- *FGFR* C3 truncated variant is associated with decreased receptor internalisation leading to constitutive receptor activation
- *FGFR2* IIIb and IIIc isoforms and both full length and truncated (C3) *FGFR2* expression were examined using Nanostring panel



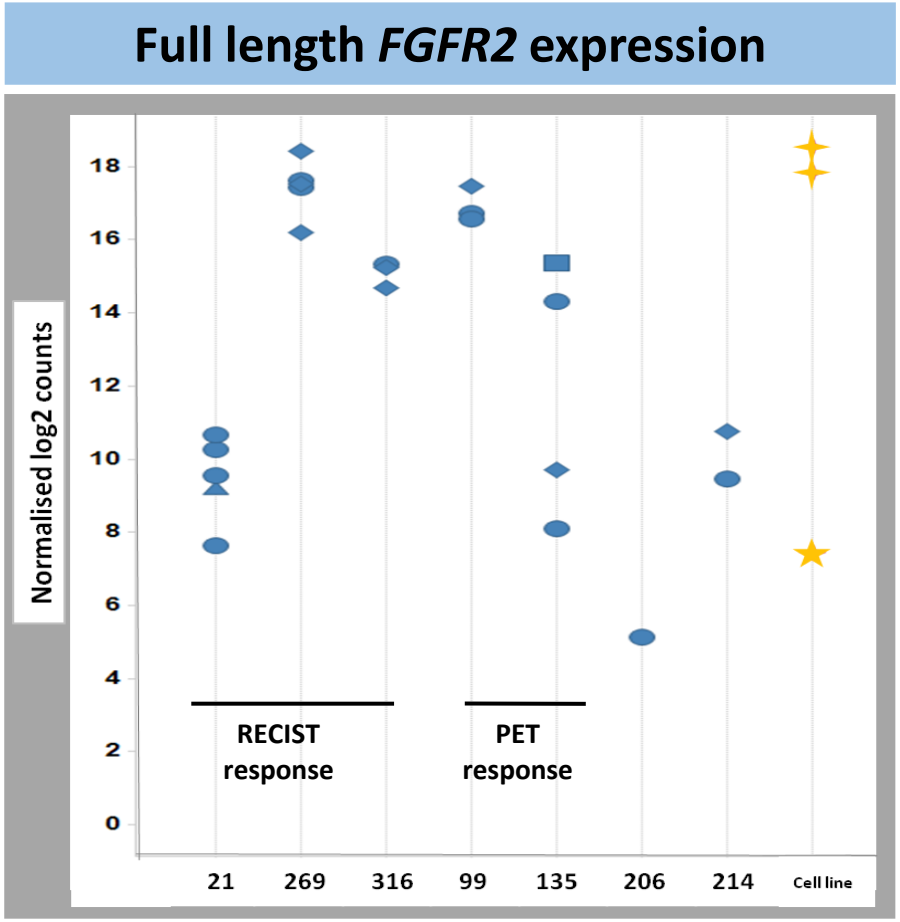
FGFR2 IIIb vs IIIc isoform expression



- Majority of tumour samples express both *FGFR2* IIIb and *FGFR2* IIIc isoforms
- Non-amplified cell line expresses both FGFR2IIIb and FGFRIIIc isoforms at low levels
- Amplified cell lines demonstrate high expression of both *FGFR2* IIIb and *FGFR2* IIIc isoforms
- All biopsies from primary gastroesophageal tumour

FGFR2 IIIb
FGFR2 IIIc
Amplified line
Non-amplified line
Archive
Day 0
Day 14
Progressive disease

Full length *FGFR2* expression

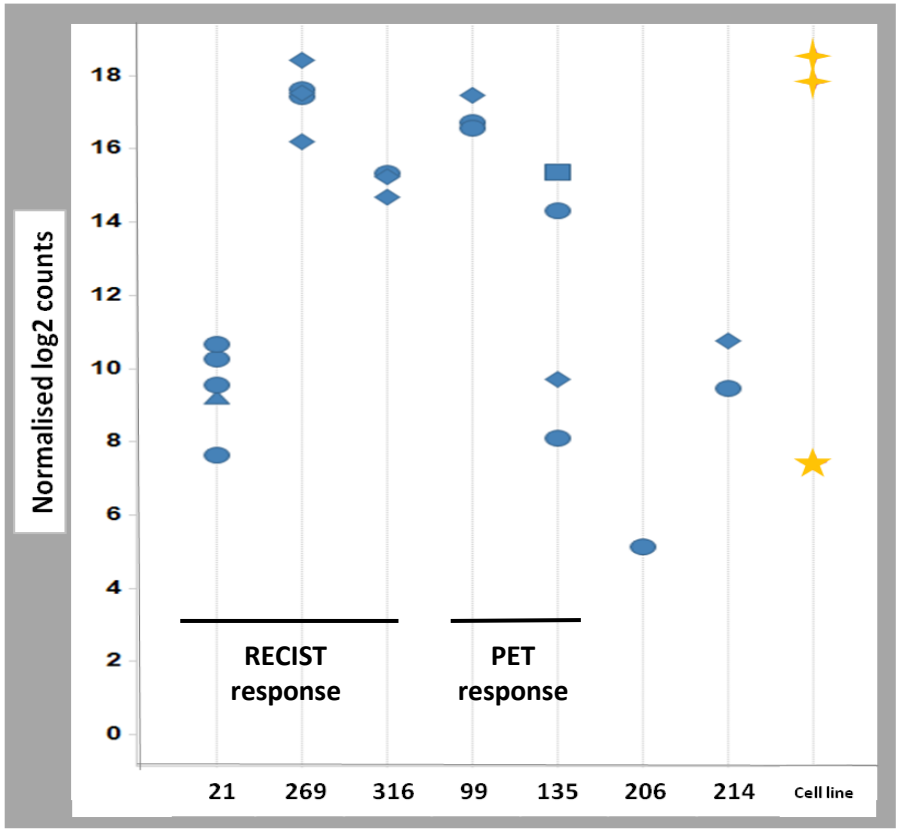


- Full length *FGFR2* was detected in all tumour samples.
- High expression demonstrated in
  - amplified cell-lines
  - patients 269, 316 (responders)
  - patient 99 (PET response)
- Patient 21 (responder) did not have high level full length *FGFR2*
- Variable expression in patient 135 tumour samples (heterogenous tumour)

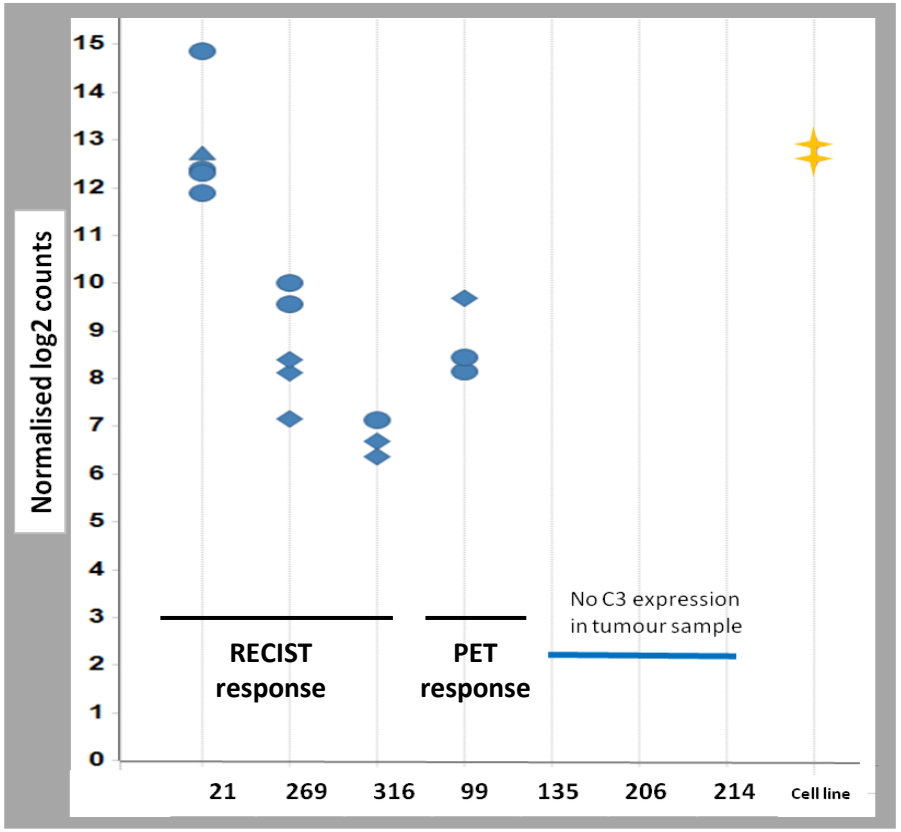
Cell line
Patient
Amplified line
Non-amplified line
Archive
Day 0
Day 14
Progressive disease

Full length vs truncated C3 isoform *FGFR2* expression

Full length *FGFR2* expression



Truncated *FGFR* C3 isoform expression



C3 isoform only present in amplified cell-lines & in patients 21, 269, 316, 99

Cell line
Patient
Amplified line
Non-amplified line
Archive
Day 0
Day 14
Progressive disease

Conclusions

- AZD4547 demonstrated promising activity in *FGFR2* amplified oesophagogastric cancer with significant and durable responses in 33% patients treated on study

- Response was associated with:

  High level homogenous *FGFR2* amplification in tissue

  Presence of *FGFR2* ctDNA in plasma

  Truncated C3 isoform expression on NanoString

- *FGFR2* copy number gain detected in plasma ctDNA using ddPCR is currently being used to select patients for study entry

Acknowledgements

All the patients and their families

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