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Pharmacodynamic Analysis of Target Receptor Tyrosine Kinase Activity and Apoptosis in GIST Responding to Therapy with SU11248

D Davis, D McConkey, J Heymach, J Desai, S George, J Jackson, C Bello, C Baum, D Shalinsky, G Demetri

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Disclosure

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Introduction

- Most gastrointestinal stromal tumors (GIST) contain activating mutations in the *c-kit* gene
  - KIT is a key receptor tyrosine kinase (RTK) in GIST progression
- Imatinib mesylate, a potent inhibitor of KIT RTK activity, is currently first-line treatment for unresectable or metastatic GIST
- However, treatment effectiveness is hampered by imatinib resistance, with early resistance being noted in approximately 14% of GIST patients[1]

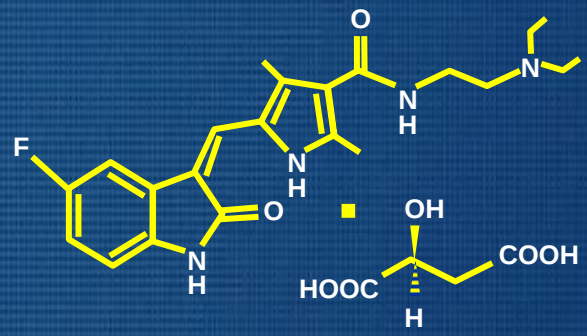
[1]Demetri GD, et al. *N Engl J Med* 2002;347:472

SU11248: Multitargeted Receptor Tyrosine Kinase Inhibitor

Split Kinase Domain RTKs

VEGFR-1
VEGFR-2
VEGFR-3
Fms

PDGFRα
PDGFRβ
CSF1R
KIT
FLT3



Enzymatic K_i (μM)

PDGFRβ	VEGFR-2	VEGFR-3	FGFR1	EGFR
0.008	0.009	0.017	0.83	>10

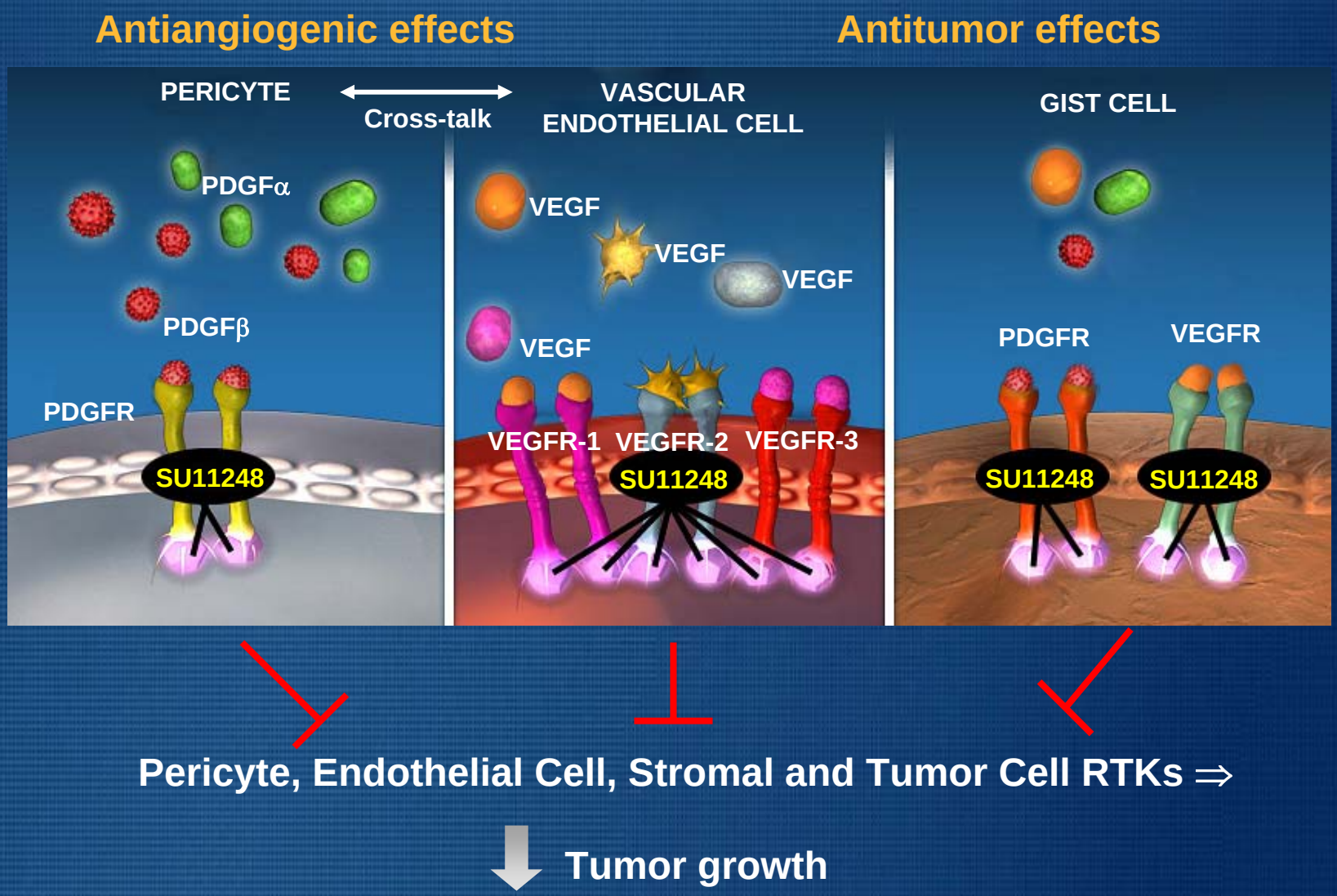
***Cellular IC_{50} (μM)**

PDGFRβ	VEGFR-2	KIT	FLT3 (WT)	EGFR	MET
0.008	0.009	0.01	0.25	8.9	12.0

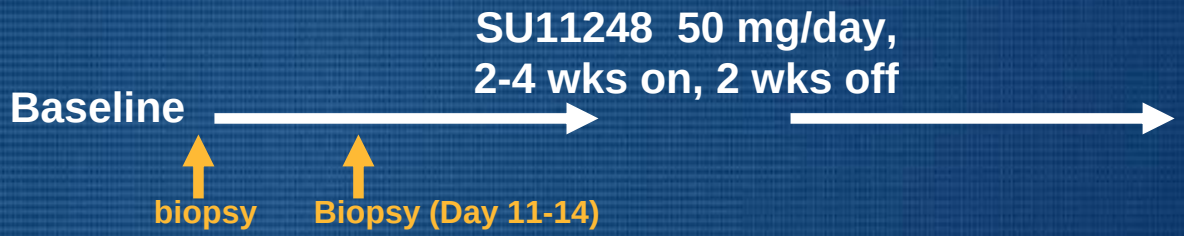
***Receptor phosphorylation**

Mendel DB, et al. *Clin Cancer Res* 2003;9:327–37

Hypothesis: SU11248 inhibits RTKs on tumor cells, pericytes and endothelial cells to produce its anticancer efficacy



Phase I/II trial of SU11248 in imatinib-resistant GIST



Baseline (97 Total) & Post-treatment Biopsies (20 patients)

PET scan

Pharmacodynamic Biomarker Analysis Plan[1,2]

Tumor analysis

pPDGFRs/PDGFRs
pKIT/KIT
pVEGFRs/VEGFRs

Tumor Effects
Endothelial Cell Death
Microvessel Density

Blood-based markers

VEGF
sVEGFR-2
sKIT

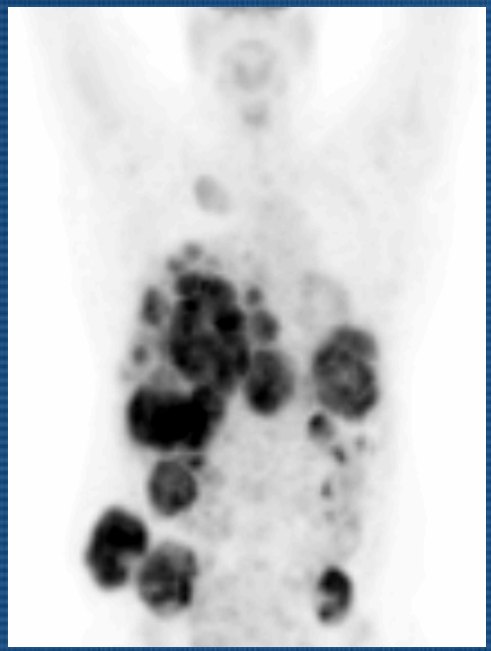
Circulating ECs
monocytes

(May 15, 2005, 1:00-5:00 pm Sarcoma)

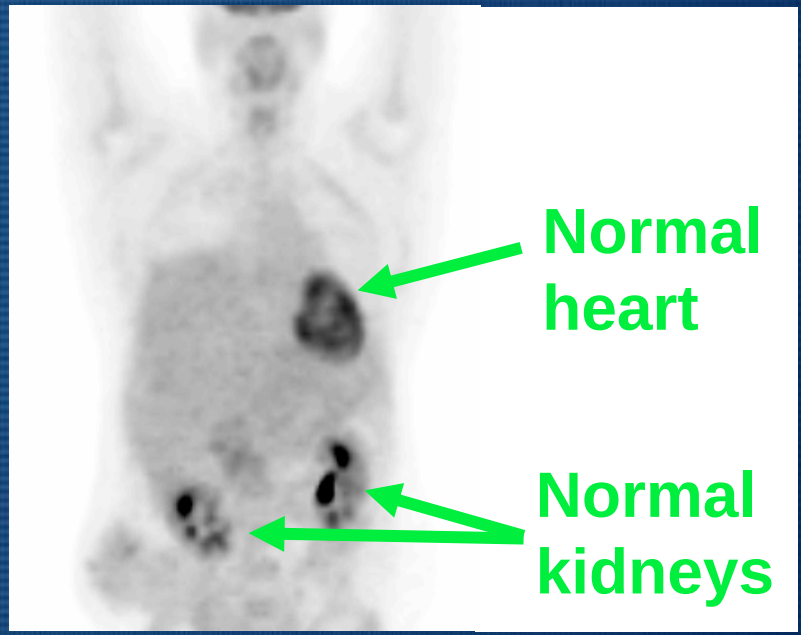
[1]Norden-Zfoni A, et al. *Proc Am Soc Clin Oncol* 2005;Abstract 9036;
[2]Manning W, et al. *Proc Am Soc Clin Oncol* 2003;22:Abstract 768

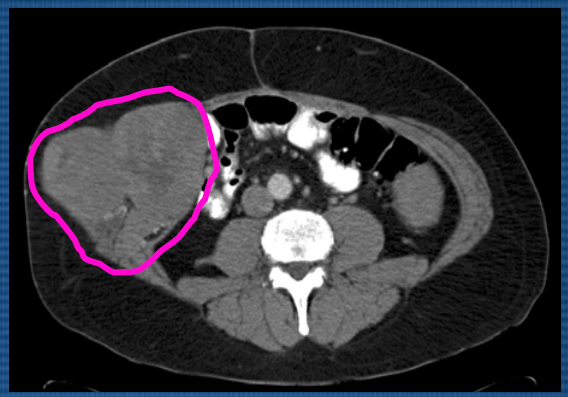
SU11248 control of imatinib-resistant GIST in a patient with primary resistance to imatinib

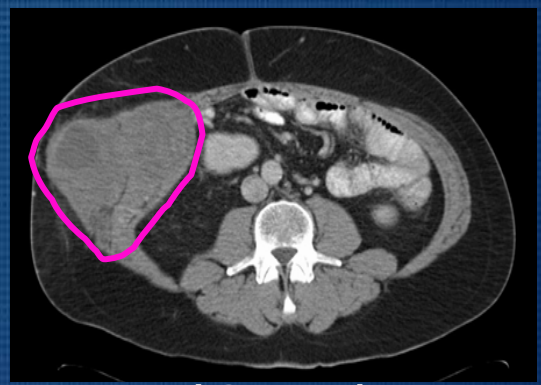
Baseline



Day 7 PET



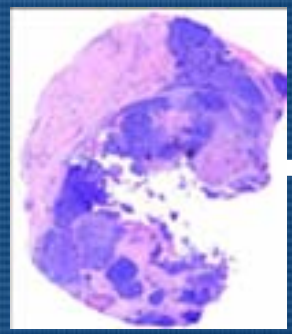




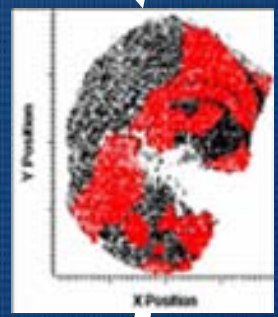
CT after 2 months of SU11248

Demetri GD, et al. *Proc Am Soc Clin Oncol 2005*

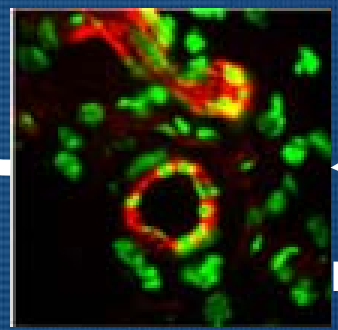
Quantitative analysis of RTK activity and apoptosis in tumors[1]



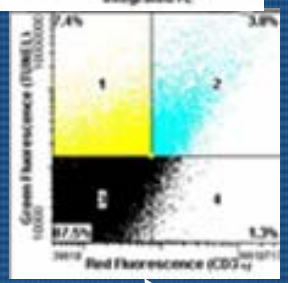
Pathological verification of tumor



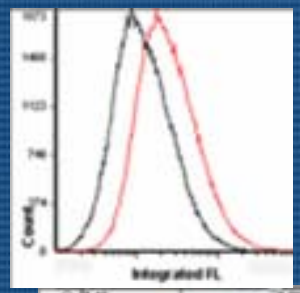
LSC-mediated tumor tissue mapping



Laser-mediated scan of immunofluourescent biomarkers



LSC-generated scattergram displays cell populations



LSC-generated histogram

LSC = laser scanning cytometry

[1]Davis DW et. al. *Br J Cancer* 2003

LSC-mediated analysis of biomarkers in clinical studies of RTK inhibitors

Agent	Diagnosis	Key biomarkers	Reference
SU5416	**Sarcoma**	**Apoptosis < 5%, 20% p-KDR Inhibition in 1 case**	Davis DW *Clin Cancer Res* 2004
SU6668	**Colon/ Liver Met.**	**Apoptosis < 5%, 50% p-KDR and p-PDGFR Inhibition in 2 cases**	Davis DW *Clin Cancer Res* 2005
Imatinib	**Melanoma**	**Apoptosis in responder > 10%**	in press
Imatinib	**GIST**	**Apoptosis 10%, 50% p-KIT Inhibition**	Work in progress
SU11248	**GIST**	**Apoptosis, p-PDGFR, p-KDR**	Work in progress

LSC = laser scanning cytometry

Does SU11248 target only KIT or multiple RTKs in GIST?

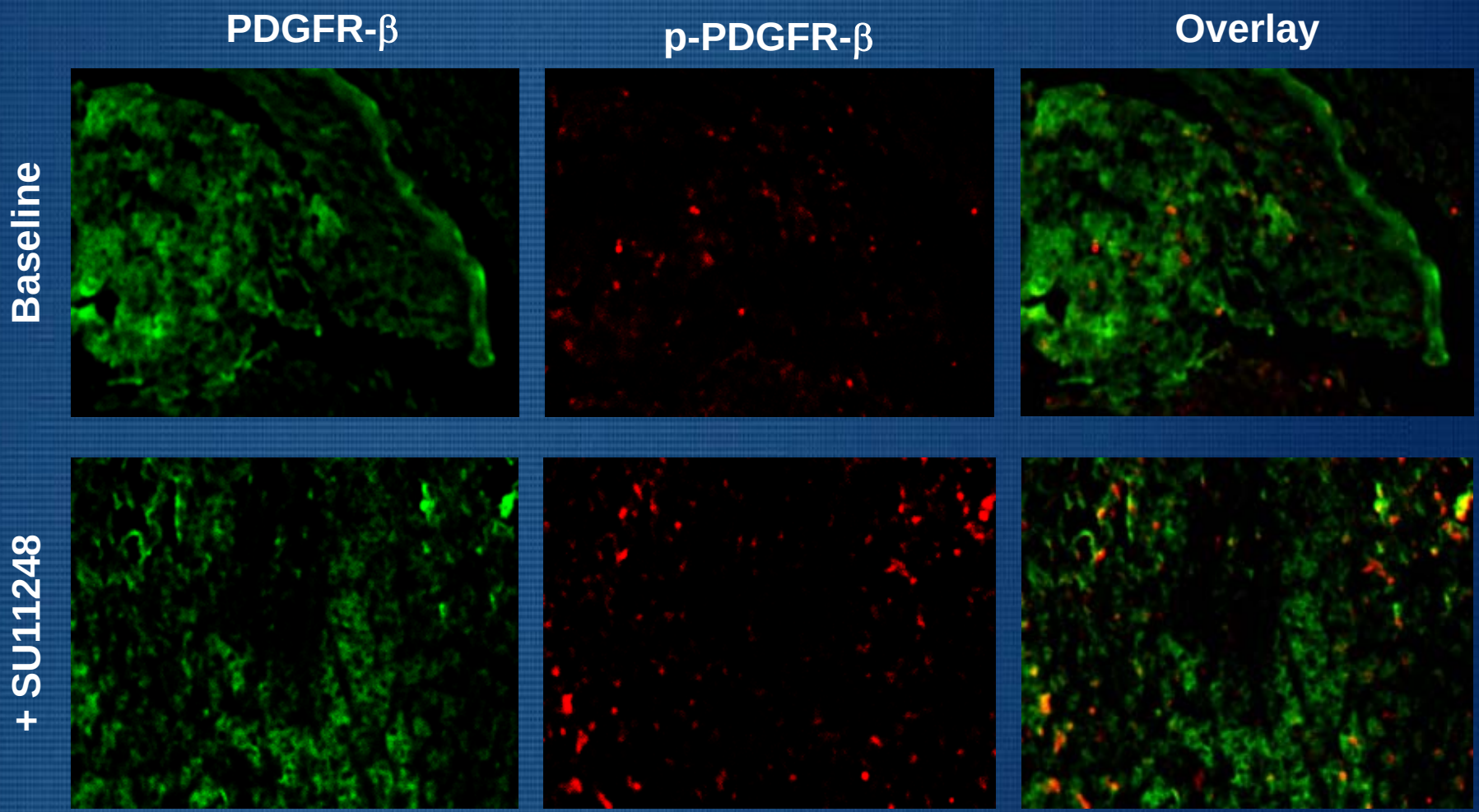
- To answer, assess effects of SU11248 on the activity of:

PDGFR-β

VEGFR-2

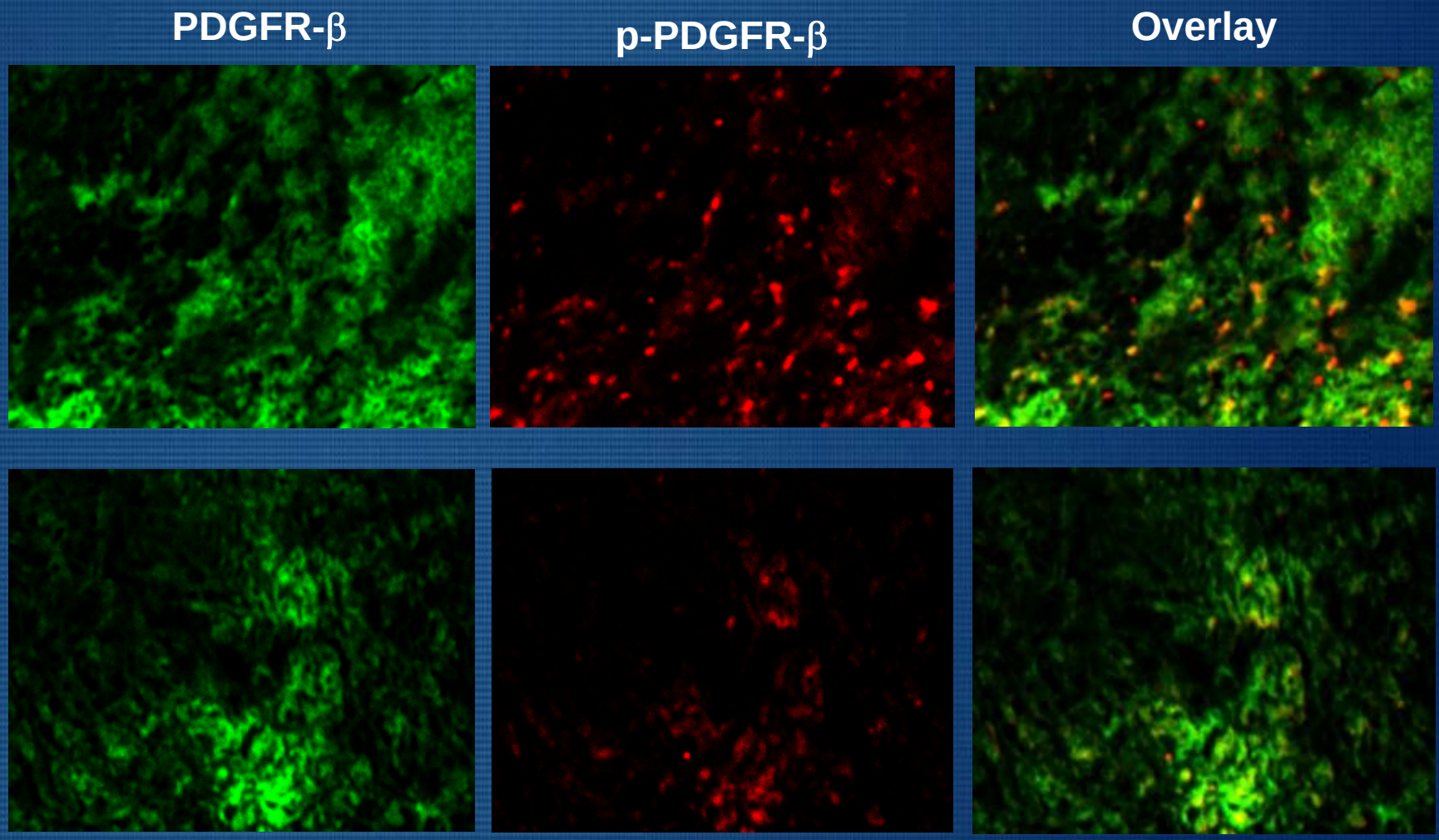
KIT

Phosphorylated-PDGFR-β levels increased in patients progressing on SU11248[1]



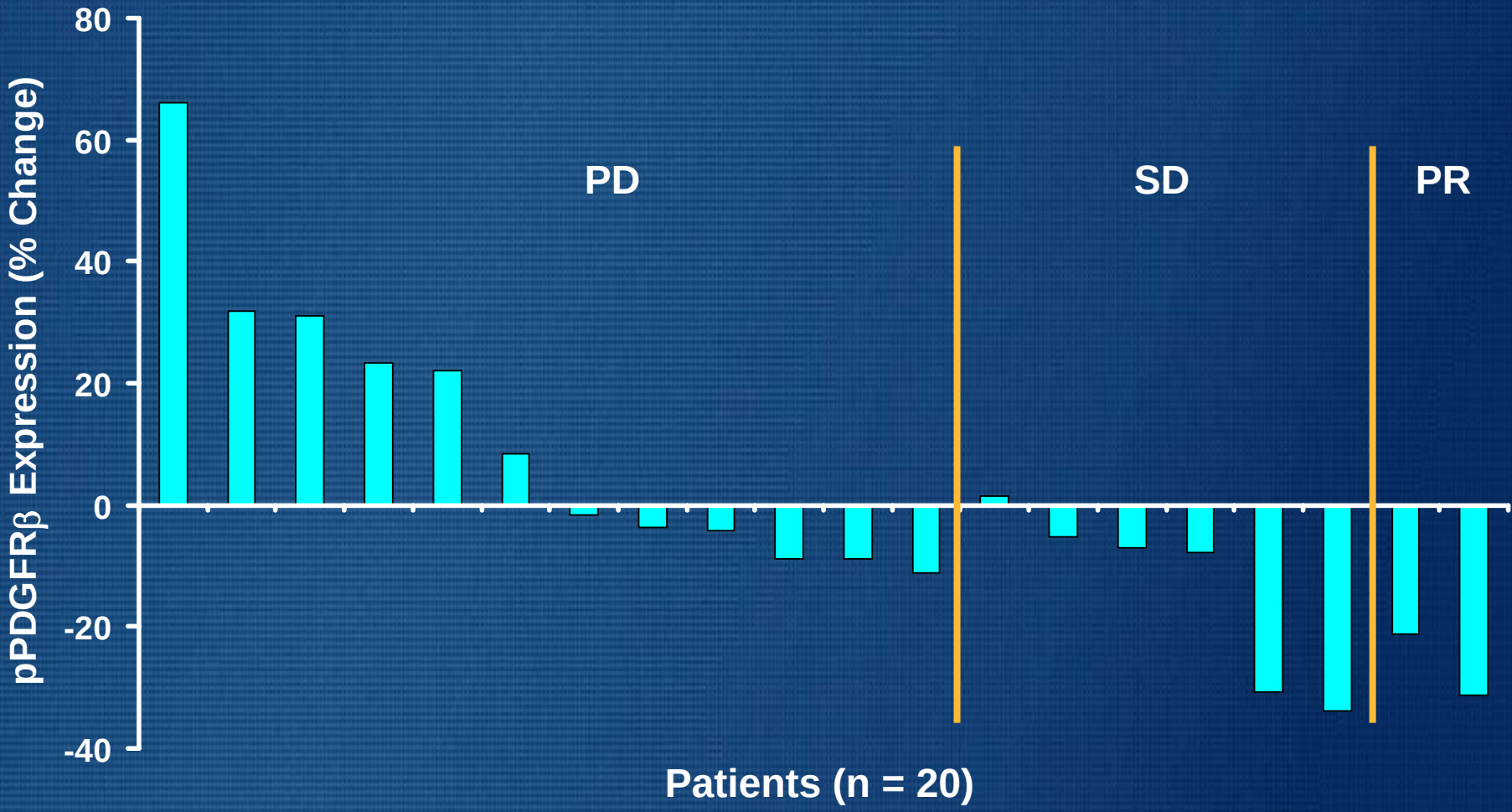
[1]After 11 days of therapy
(Scale x20)

Phosphorylated PDGFR-β decreased by 31% in responding patients[1]



[1]After 11 days of therapy
(Scale x20)

Quantitative analysis of pPDGFR-β Expression (% Change)



PD = Progressive Disease; SD = Stable Disease; PR = Partial Response

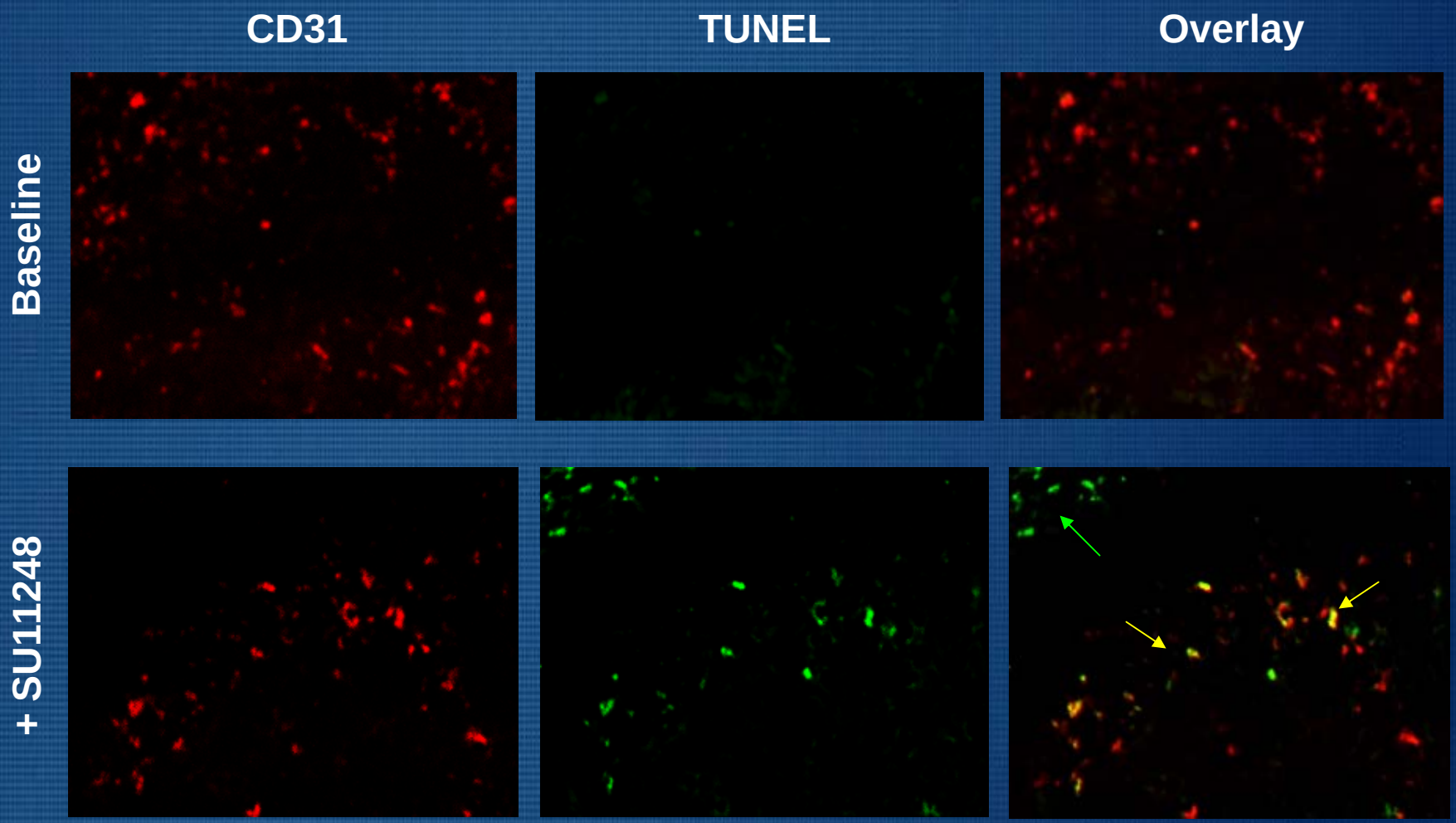
Change in pPDGFR-β activity: Correlation with clinical benefit

Clinical outcome	No. of patients	Δ p-PDGFR activity
Clinical benefit (PR or SD >6 months)	**8**	**18.2% ↓ (p=0.006)**
- PR	2	26.1% ↓ (p=0.001)
- SD	6	13.9% ↓ (p=0.04)
Progressive disease (< 6 months)	**12**	**9.9% ↑ (p=0.06)**

PR = partial response; SD = stable disease

Was inhibition in p-PDGFRb sufficient to induce apoptosis?

SU11248 increased apoptosis in patients with clinical benefit[1]



[1]After 11 days of therapy
(Scale: x20)

Effects of SU11248 on Endothelial and Tumor Cell Apoptosis

Clinical Outcome	EC Apoptosis (Fold Change)[1]	TC Apoptosis (Fold Change)[1]
Clinical Benefit	9.55 (p = 0.017)	5.80 (p = 0.002)
Progressive Disease	1.78 (p = 0.289)	1.15 (p = 0.406)

- Patients with CB displayed significantly higher levels of EC (p = 0.007) and TC (p = 0.006) apoptosis than patients with PD

EC = Endothelial Cell; TC = Tumor Cell

[1] Compared to Baseline

Summary

- PDGFR-β phosphorylation decreased in tumors in patients with CB from SU11248
- EC & TC apoptosis increased during SU11248 treatment to a greater extent in the CB group than the PD group
- Suppression of PDGFR-β activity implicates other key RTKs in addition to KIT as targets for SU11248 in GIST
- We hypothesize that the multi-targeted nature of SU11248 inhibits RTKs on tumor and vascular cells producing anticancer efficacy

CB = Clinical Benefit; PD = Progressive Disease

Acknowledgements

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