Abstract No. 715

Receptor Tyrosine Kinase Activity and Apoptosis in Gastrointestinal Stromal Tumors: a Pharmacodynamic Analysis of Response to Sunitinib Malate (SU11248) Therapy

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Disclosure

- This work was supported by:

  Pfizer Global Research and Development

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

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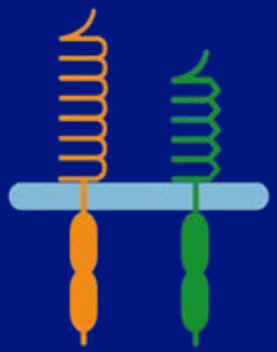
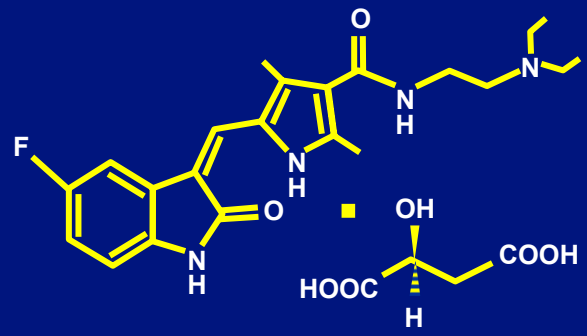
SU11248: Multitargeted Receptor Tyrosine Kinase Inhibitor

Split Kinase Domain RTKs



VEGFR-1
VEGFR-2
VEGFR-3
Fms

PDGFR-α
PDGFR-β
CSF1R
KIT
FLT-3



Enzymatic K_i (μM)

PDGFR-β	VEGFR-2	VEGFR-3	FGFR-1	EGFR
0.008	0.009	0.017	0.83	>10

***Cellular IC_{50} (μM)**

PDGFR-β	VEGFR-2	KIT	FLT-3 (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

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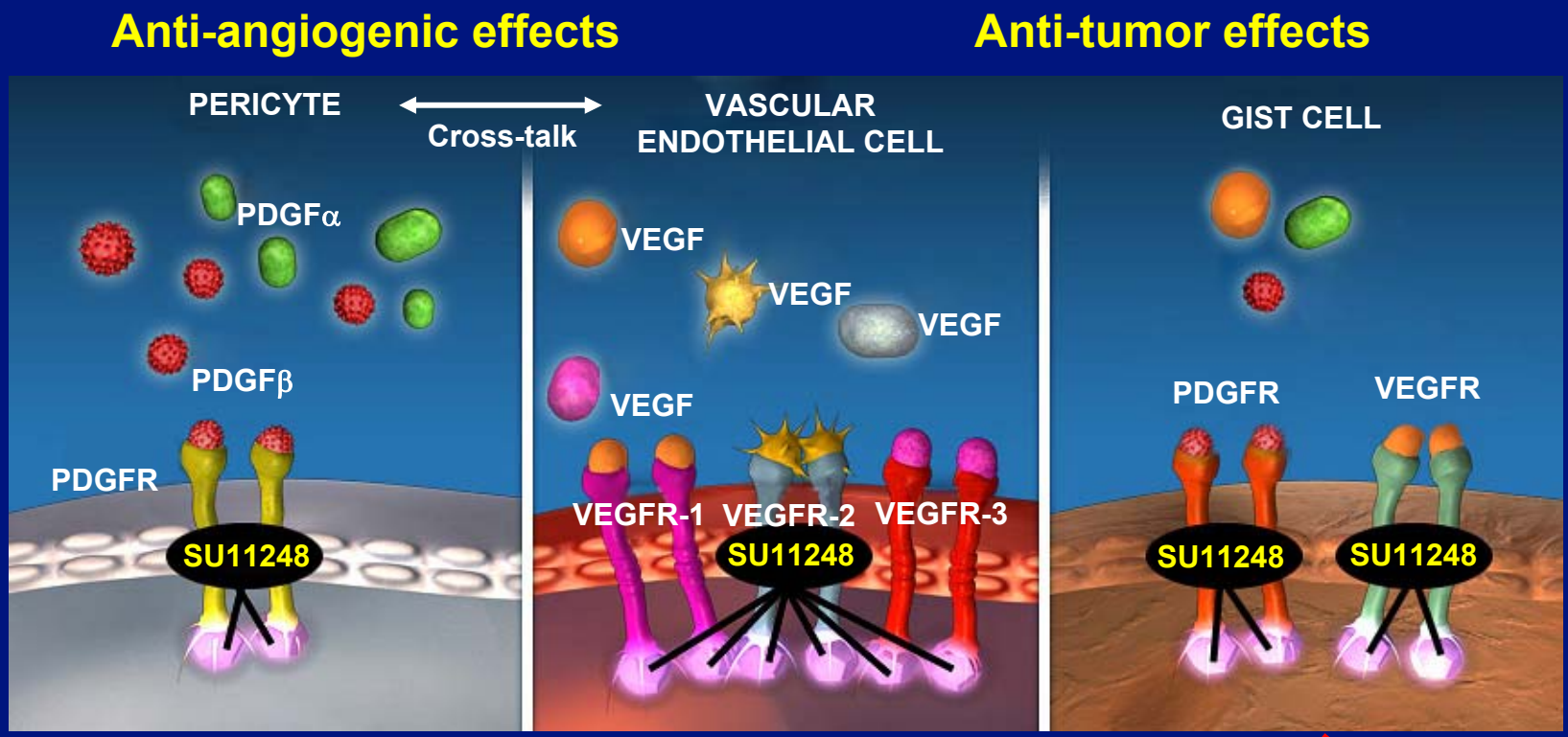
Hypothesis: SU11248 Inhibits RTKs on Tumor Cells, Pericytes and Endothelial Cells to Produce its Anti-cancer Efficacy



Pericyte, Endothelial Cell, Stromal and Tumor Cell RTKs ⇒

Tumor growth

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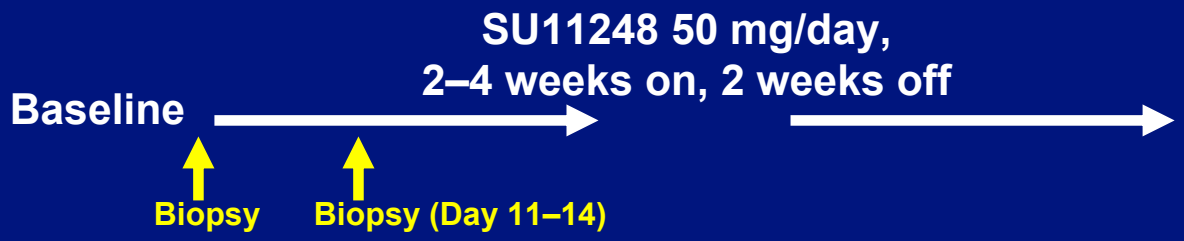
Phase I/II Trial of SU11248 in Imatinib-resistant GIST



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

[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

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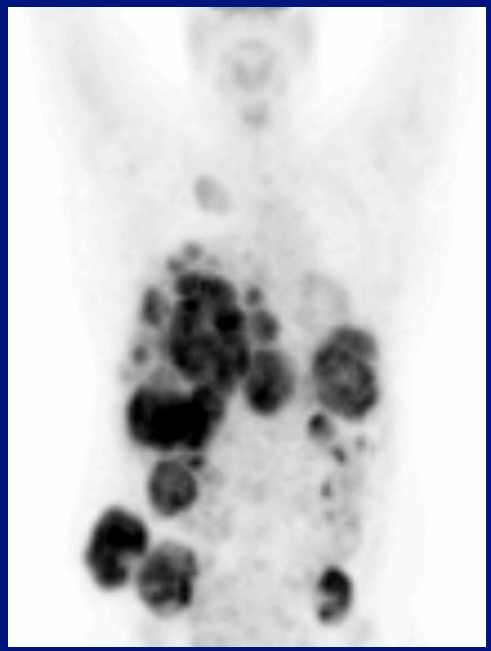
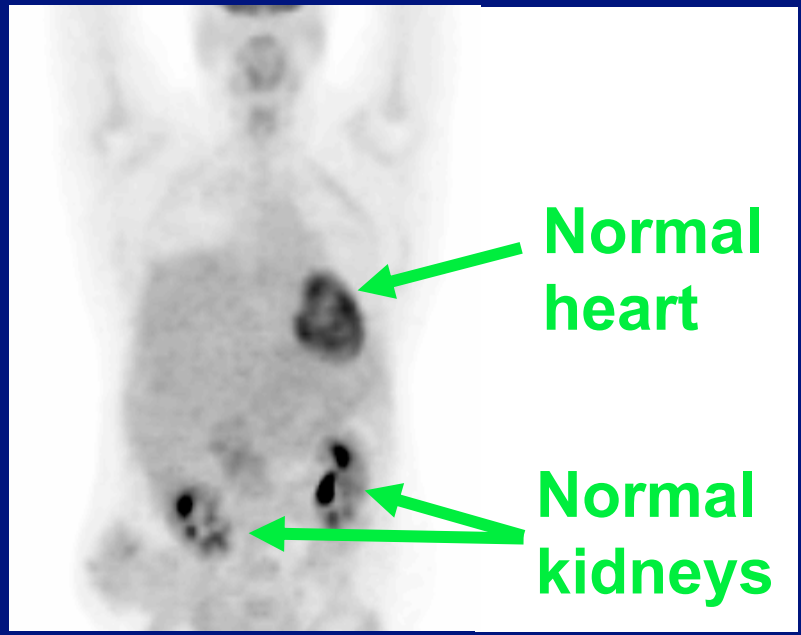
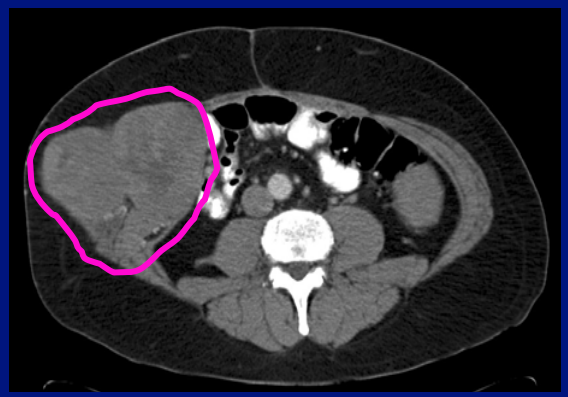
SU11248 Control of Imatinib-resistant GIST in a Patient with Primary Resistance to Imatinib

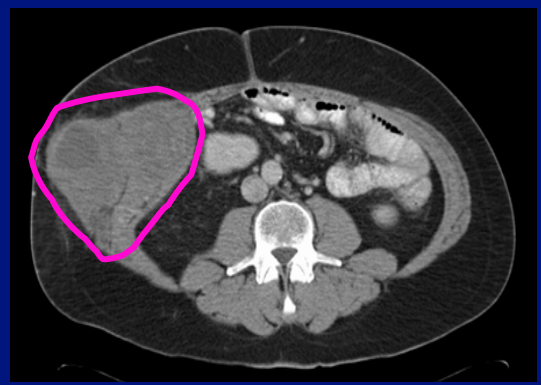
Baseline



Day 7 PET







CT after 2 months of SU11248

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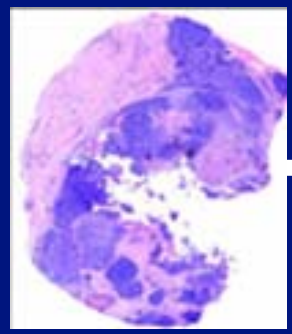
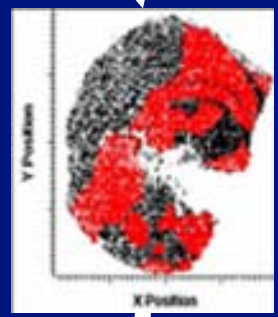
Demetri GD, et al. *Proc Am Soc Clin Oncol 2005*

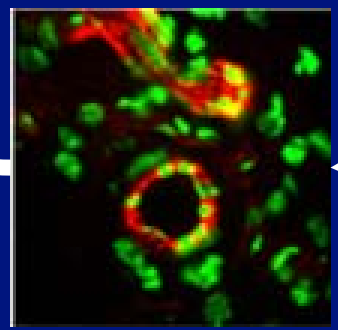
Quantitative Analysis of RTK Activity and Apoptosis in Tumors[1]



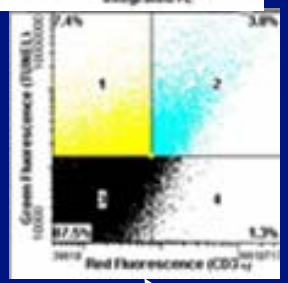
Pathological verification of tumor



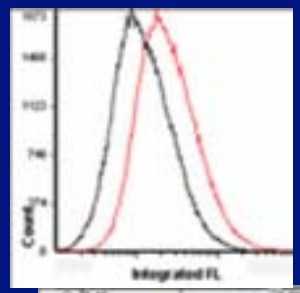
LSC-mediated tumor tissue mapping



Laser-mediated scan of immunofluourescent biomarkers



LSC-generated scattergram displays cell populations



LSC-generated histogram

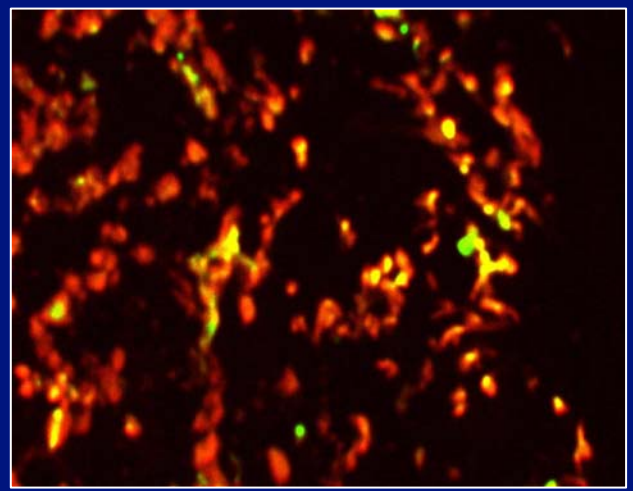
LSC = laser scanning cytometry

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

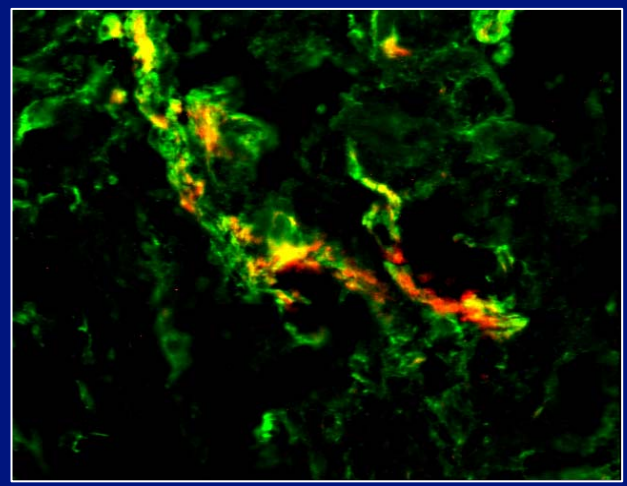
LSC-mediated Analysis of Biomarkers in Clinical Studies of RTK Inhibitors

Agent	Diagnosis	Key biomarkers	Reference
SU5416	Sarcoma	Apoptosis <5%, 20% p-KDR inhibition in 1 case	Heymach JV *Clin Cancer Res. 2004 Sep*
SU6668	Colon/ Liver Met.	Apoptosis <5%, 50% p-KDR and p-PDGFR inhibition in 2 cases	Davis DW *Clin Cancer Res. 2005 Jan*

VEGFR-2 Phosphorylation



PDGFR Phosphorylation



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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

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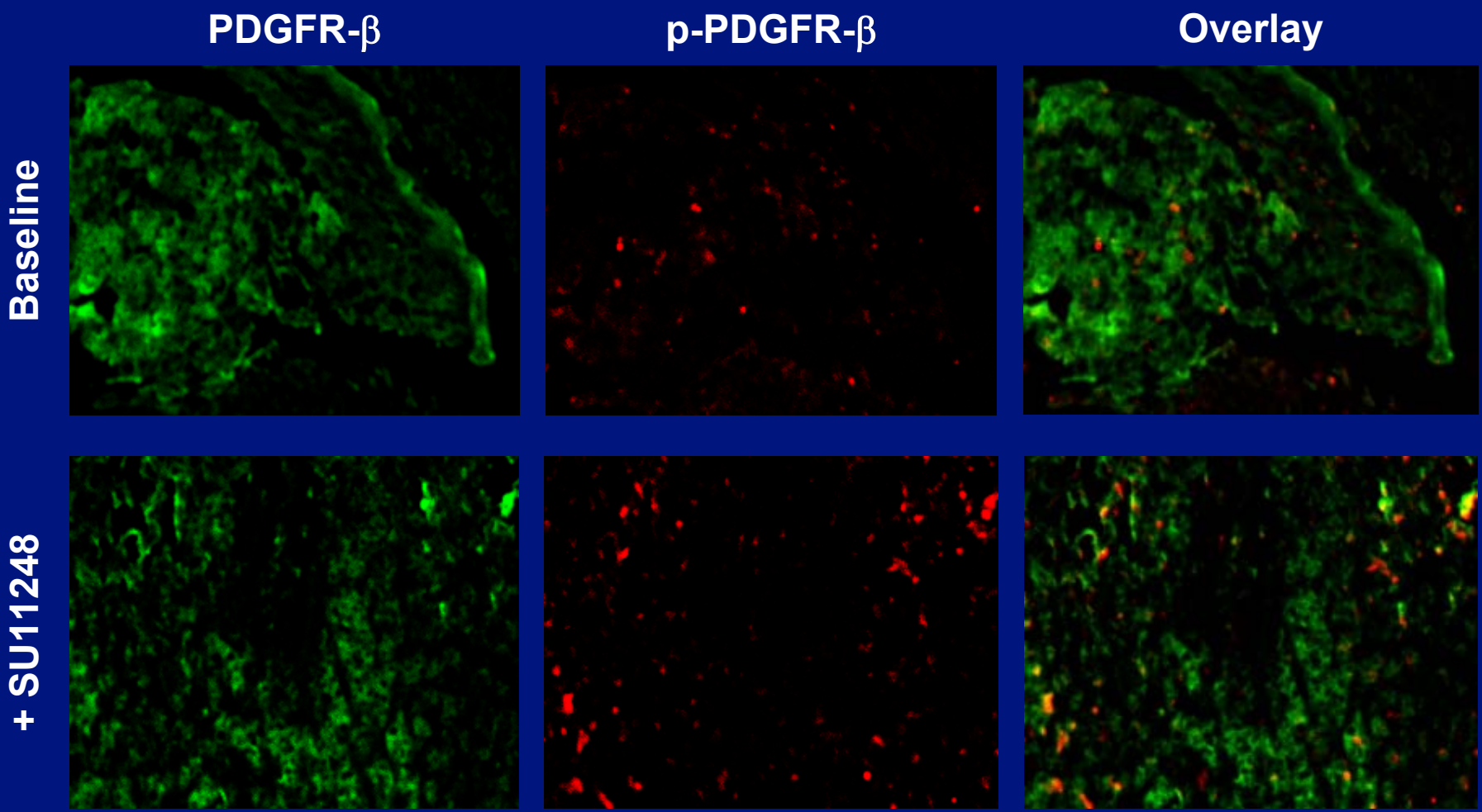
Phosphorylated-PDGFR-β Levels Increased in Patients Progressing on SU11248[1]



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

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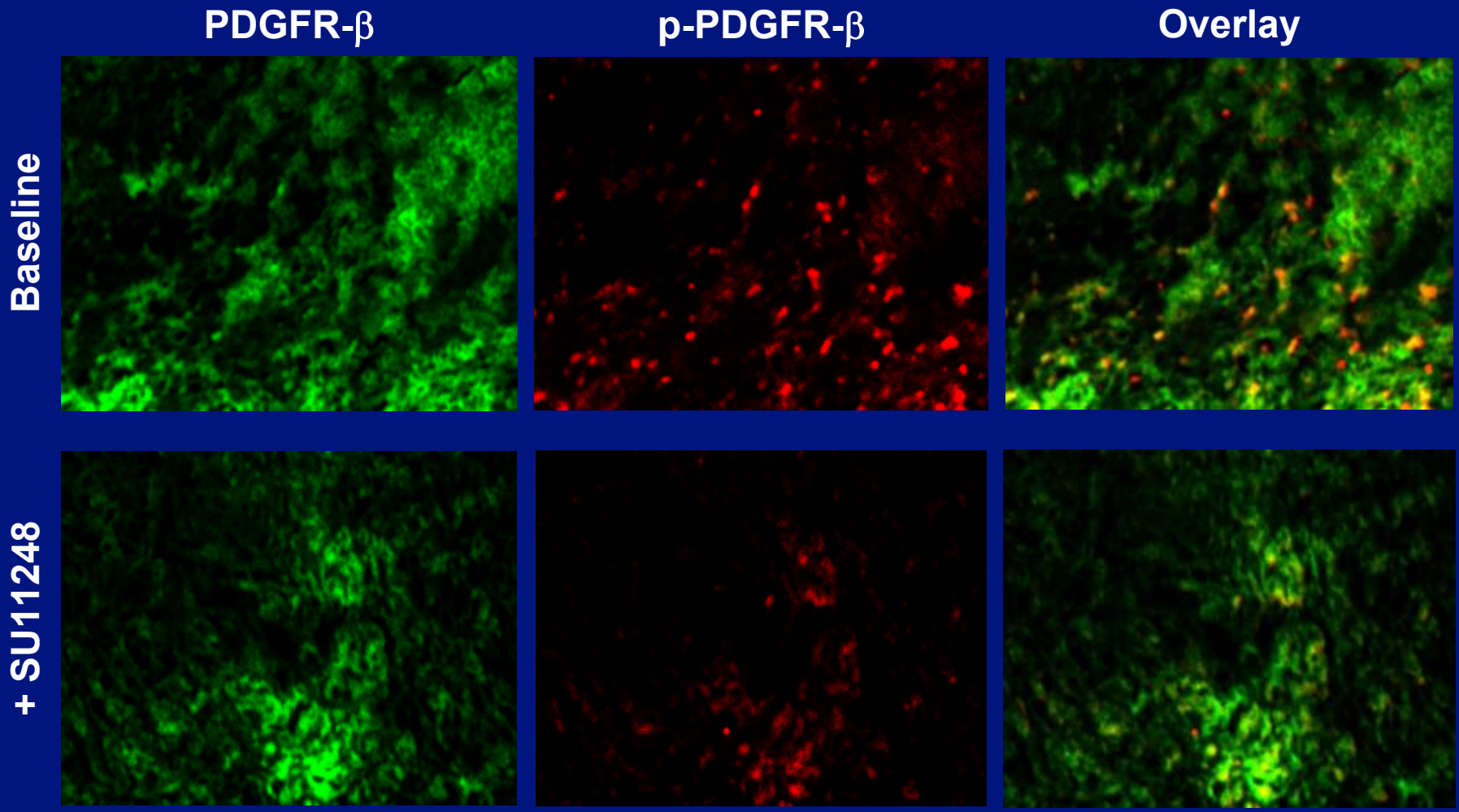
Phosphorylated PDGFR-β Decreased in Responding Patients[1]



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

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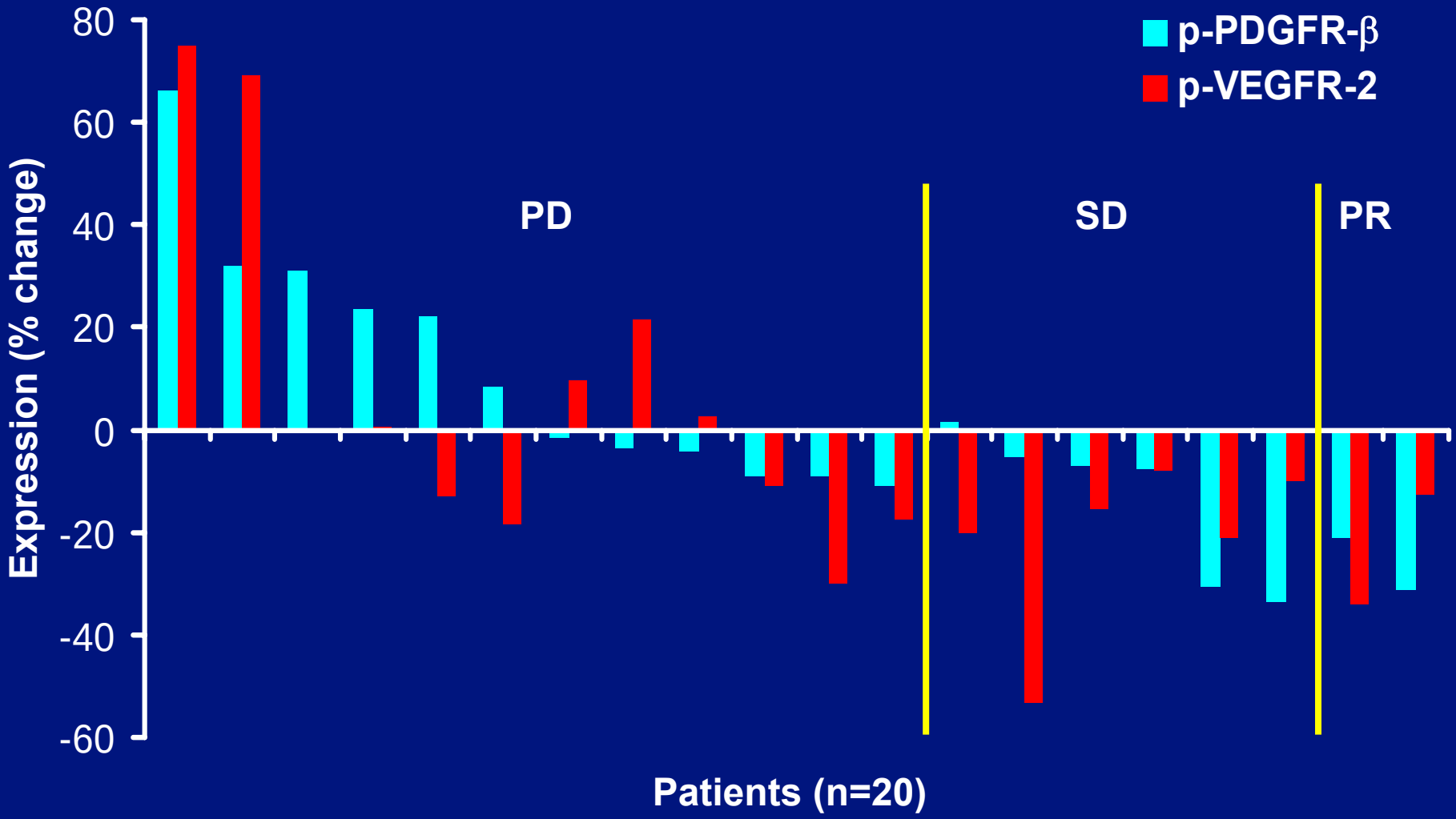
Quantitative Analysis of p-PDGFR-β and p-VEGFR-2 Expression (% Change)



PD = progressive disease; SD = stable disease; PR = partial response

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Change in p-PDGFR-β and p-VEGFR-2 Activity: Correlation with Clinical Benefit

Clinical outcome	Number of patients	Δ p-PDGFR-β activity	Δ p-VEGFR-2 activity
Clinical benefit (PR or SD >6 months)	8	18.2% ↓ p=0.006	26.67% ↓ p=0.02
Progressive disease (<6 months)	12	9.9% ↑ p=0.06	9.62% ↑ p=0.22

PR = partial response; SD = stable disease

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Was Inhibition in p-PDGFR-β and p-VEGFR-2 Sufficient to Induce Apoptosis?

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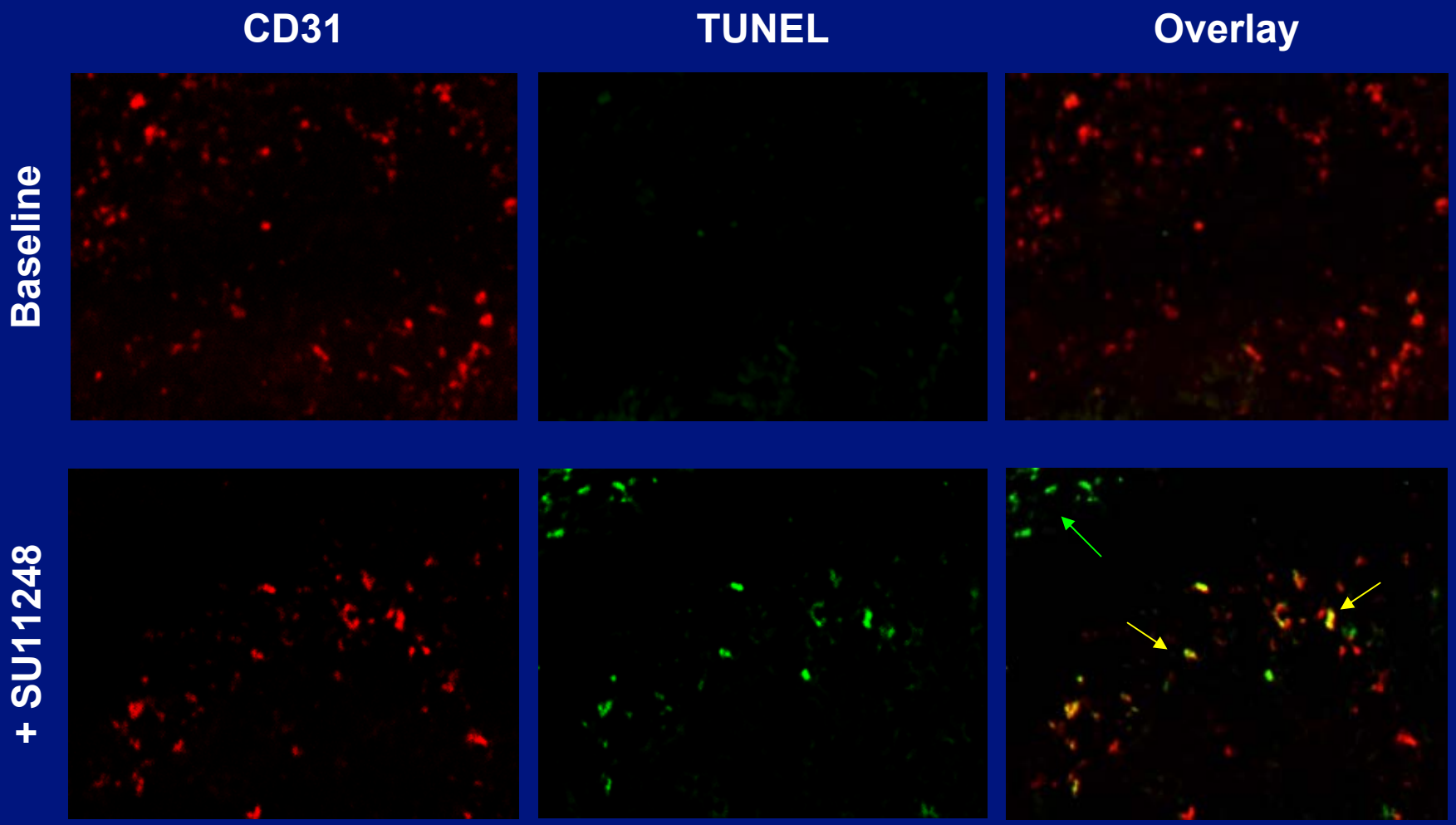
SU11248 Increased Apoptosis in Patients with Clinical Benefit[1]



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

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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

[1]Compared to baseline
EC = endothelial cell; TC = tumor cell

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Summary

- PDGFR-β and p-VEGFR-2 phosphorylation decreased in tumors in patients with CB from SU11248
- EC and TC apoptosis increased during SU11248 treatment to a greater extent in the CB group than the PD group
- Suppression of PDGFR-β and VEGFR-2 activity implicates 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

Acknowledgments

Dana Farber Cancer Institute
George Demetri
Suzanne George
Jesse Jackson
Jayesh Desai

MD Anderson Cancer Center
David J McConkey
John Heymach

Pfizer, La Jolla
Ann-Marie Martino
Samuel DePrimo
David Shalinsky
Charles Baum

SUGEN Inc
Bill Manning
Julie Cherrington

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