Clinical Trials

Phase II Studies

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SARC Sarcoma Alliance for Research through Collaboration

THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER
Making Cancer History™

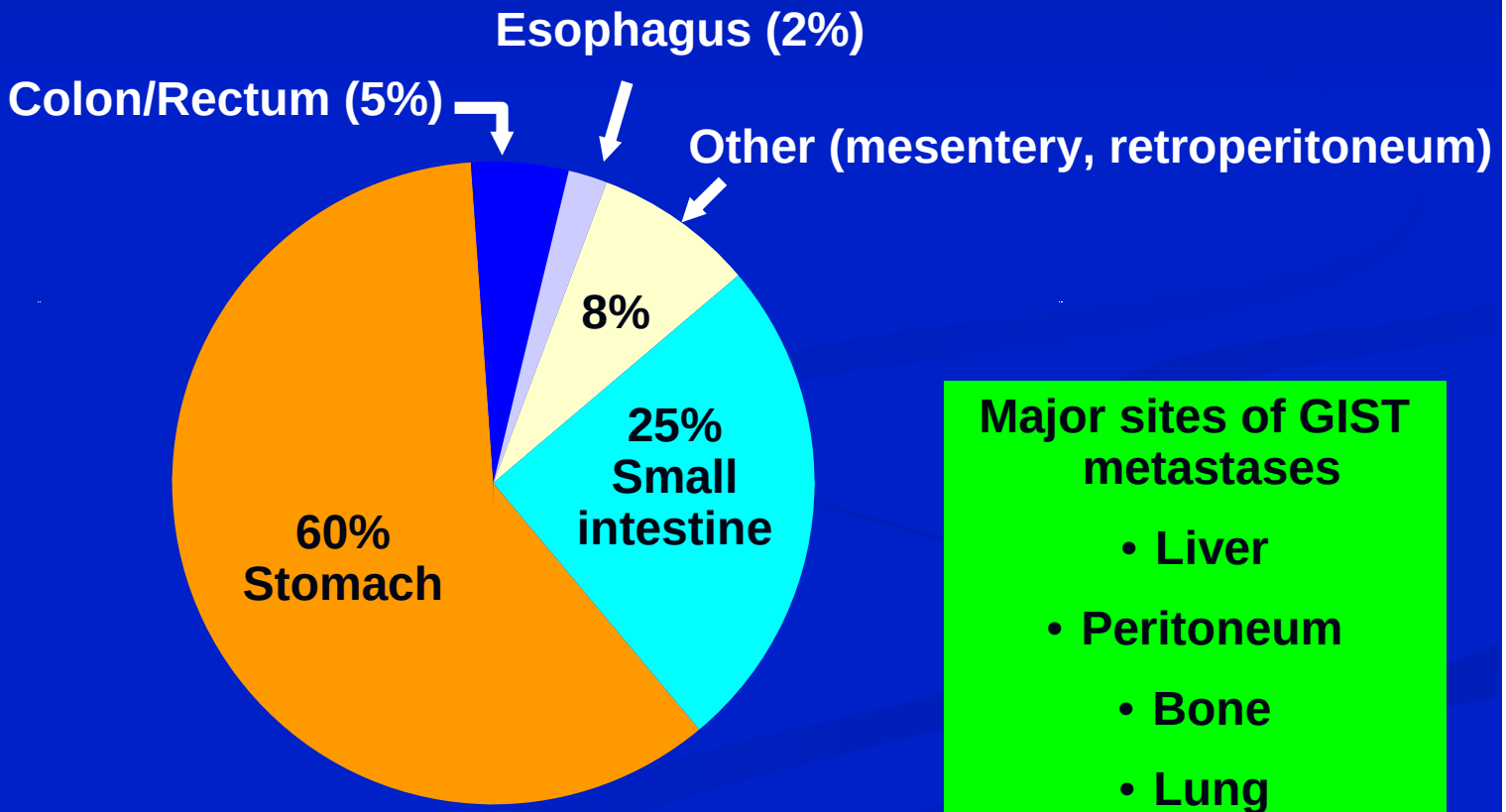
GIST Overview

- GIST have an incidence of 3-6,000 annually and a prevalence of ~40,000 individuals
- 0.2% of all GI tumors, but 80% of GI sarcomas
- Highest incidence in the 40-60 year age group
- Similar male/female incidence
- Clinical presentation is variable
  - Pain, hemorrhage, anemia, anorexia, nausea, perforation
  - May be asymptomatic

Miettinen M et al. *Virchows Arch.* 2001;438:1-12.
Fletcher CDM et al. *Hum Pathol.* 2002;33:459-465.
Nilsson B et al. *Cancer.* 2005;103:821-829

GIST Overview

GIST may occur anywhere along the GI tract or elsewhere in the abdomen or retroperitoneum



Major sites of GIST metastases

- Liver
- Peritoneum
- Bone
- Lung

Corless et al. *J Clin Oncol*. 2004;22:3813.

GIST

Chemotherapy Trials

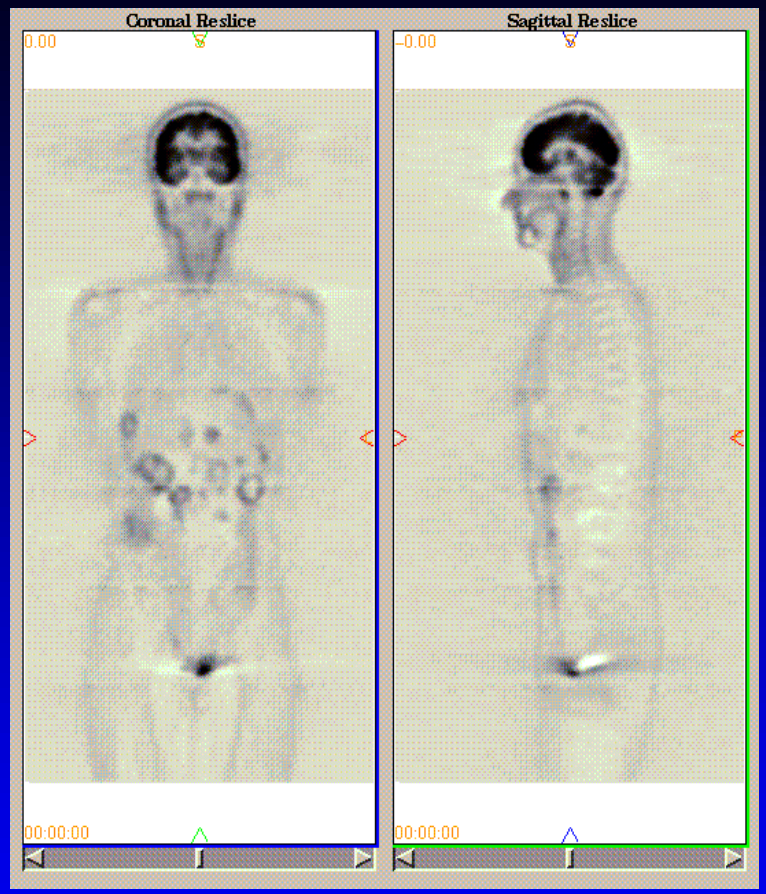
Regimen	Number of Patients	Partial Response n (%)
DOX + DTIC	43	3 (7%)
DOX + DTIC +/– IF	60	10 (15%)
IF + VP-16	10	0 (0%)
Paclitaxel	15	1 (7%)
Gemcitabine	17	0 (0%)
Liposomal DOX	15	0 (0%)
DOX	12	0 (0%)
DOX or docetaxel	9	0 (0%)
High-dose IF	26	0 (0%)
EPI + IF	13	0 (0%)
Various	40	4 (10%)
DTIC/MMC/DOX/ CDDP/GM–CSF	21	1 (5%)
Temozolamide	19	0 (0%)
TOTAL	280	19 (6.8%)

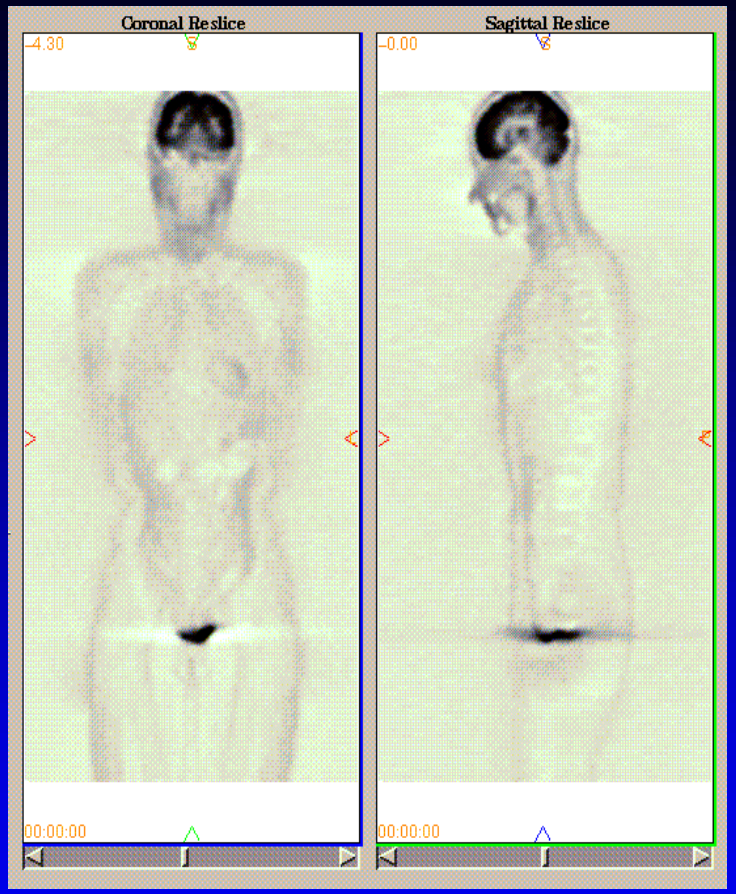
GIST: Therapy

- KIT is expressed on GIST cells
- Gene mutation in most cases
  - *KIT*: 80%-85%
  - *PDGFRA:* 5%-7%
  - *Wild Type*: 12%
- Gene mutation results in constitutively activated receptor tyrosine kinase activity
- Imatinib is effective in CML

Trent JC et al. *Curr Opin Oncol.* 2006;18:386-395.

Marked Biologic Response Revealed by PET Scan



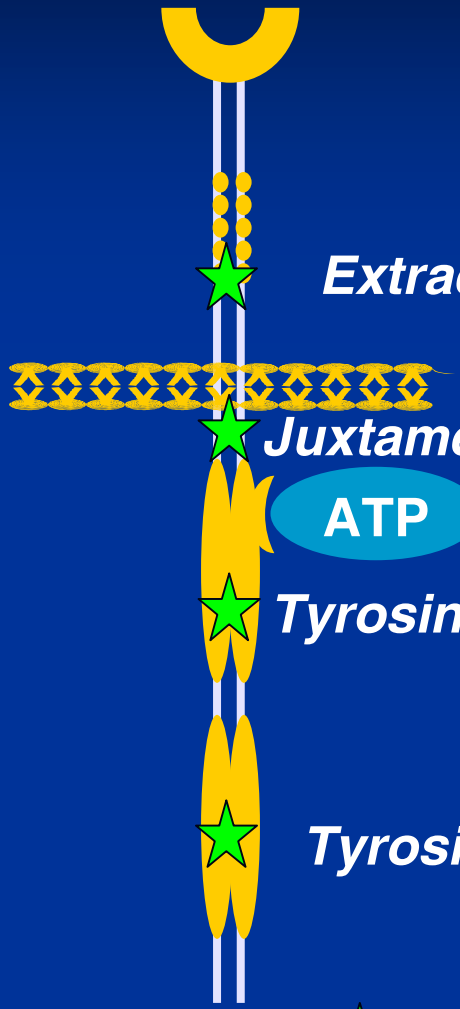


Multiple liver and upper abdominal ^{18}FDG-accumulating metastases

A marked decrease in ^{18}FDG uptake 4 weeks after starting imatinib mesylate

Joensuu H et al. *N Engl J Med* 2001;344:1052-1056.

Kit Receptor Structure



Extracellular Domain (exon 9, 10.2%)

Juxtamembrane Domain (exon 11, 66.1%)

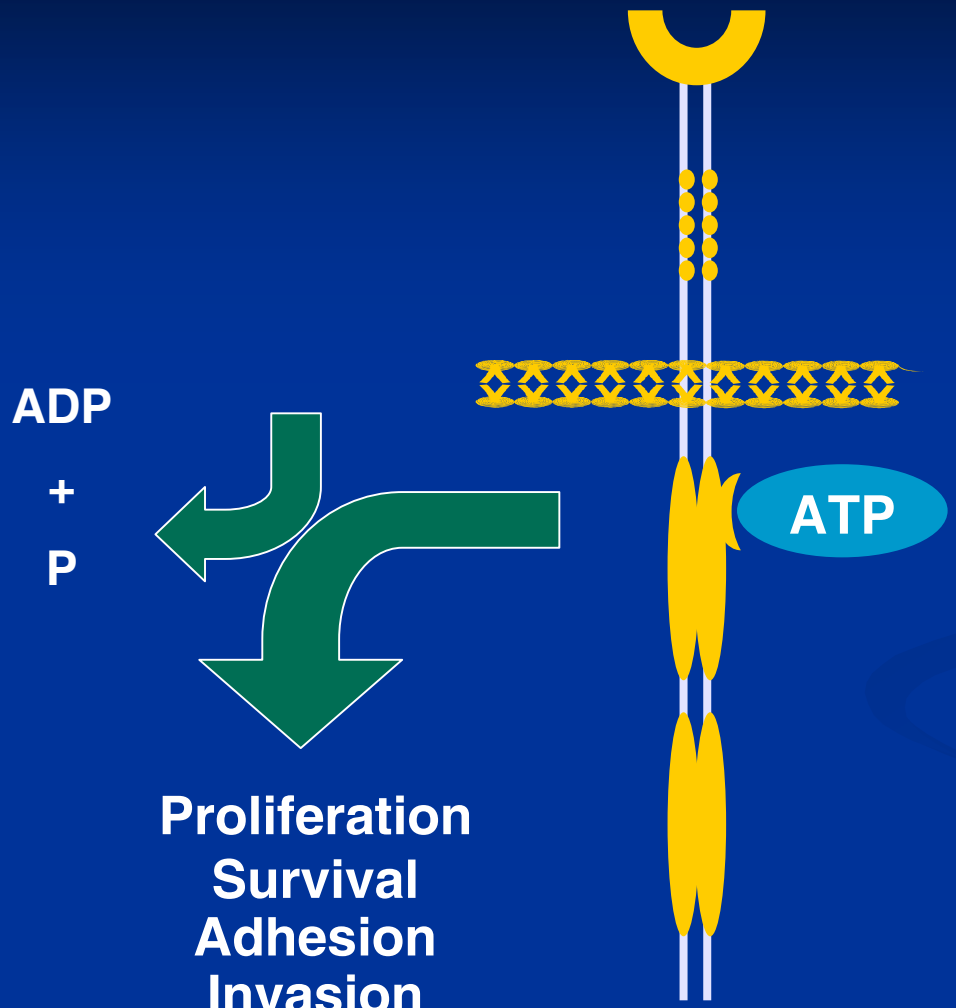
ATP

Tyrosine Kinase Domain I (exon 13/14, 1.2%)

Tyrosine Kinase Domain II (exon 17, 0.6%)

★ = common mutation site

Kit Receptor Phenotype



Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

Imatinib Mesylate

Formula: $C_{30}H_{35}N_7SO_4$

MW: 589.7

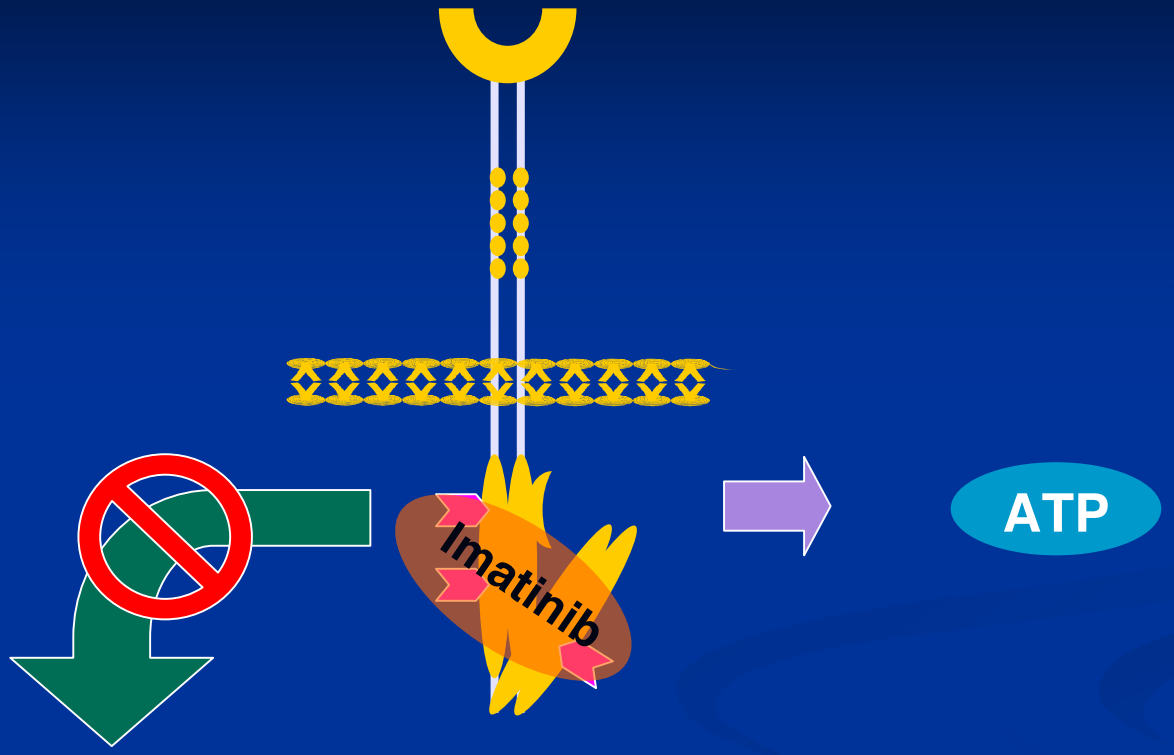
- Rational drug design
  - 2-phenylamino pyrimidine
  - Based on structure of ATP binding site
  - Highly water soluble
  - Oral bioavailability

Inhibitor of selective tyrosine kinases

bcr-abl
PDGF-R
c-kit

Potent ($IC_{50} \approx 0.1\mu M$)

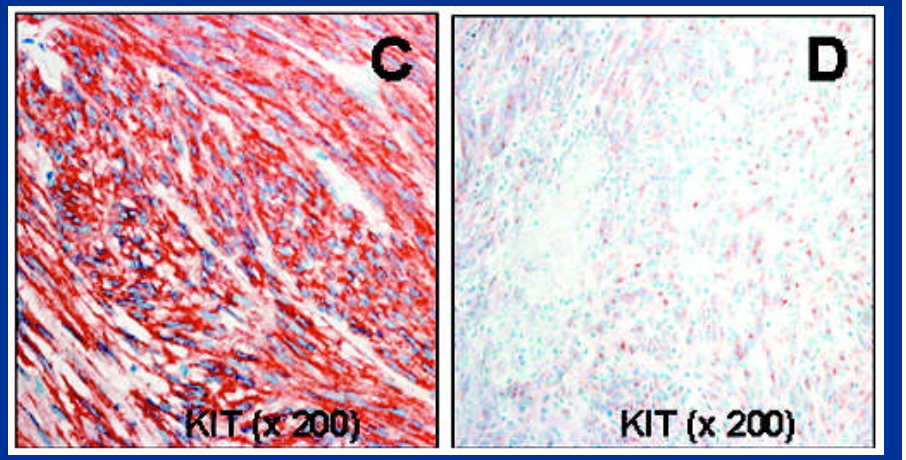
Kit Receptor Phenotype

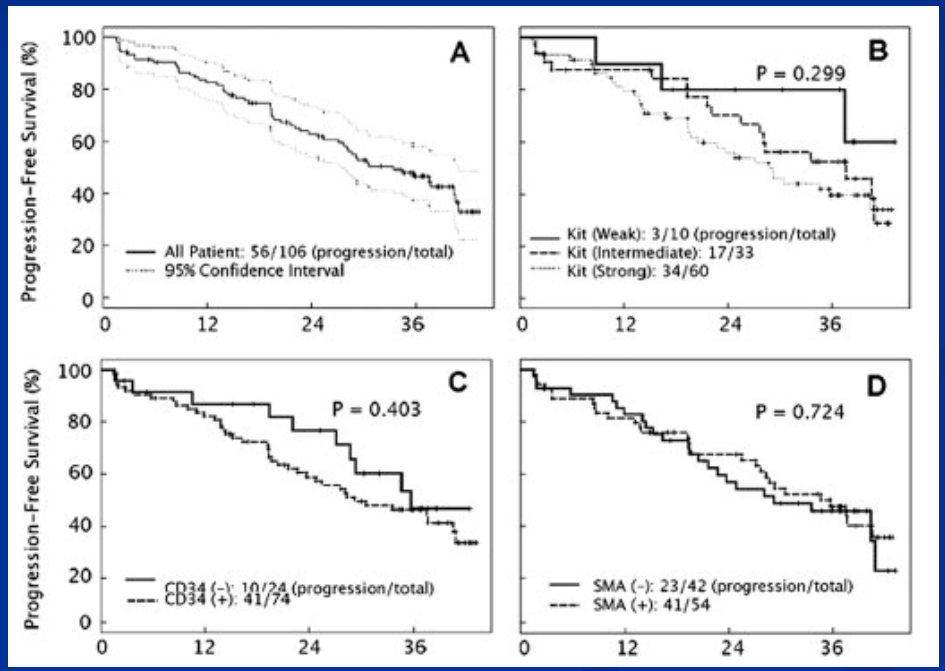


Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

= imanitib contact point

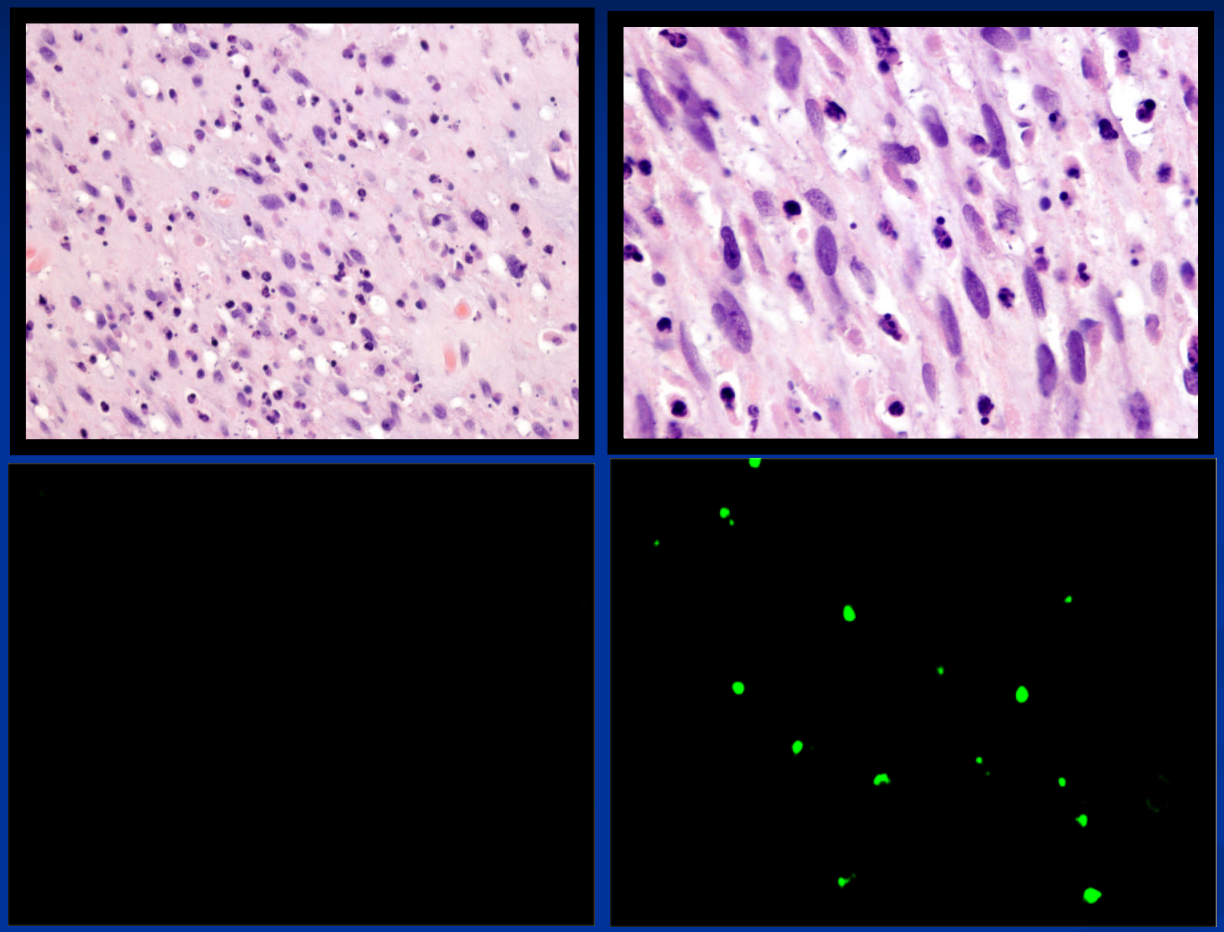
Low KIT Expression Correlates With Benefit From Imatinib





Chirieac, Trent. Cancer 2006

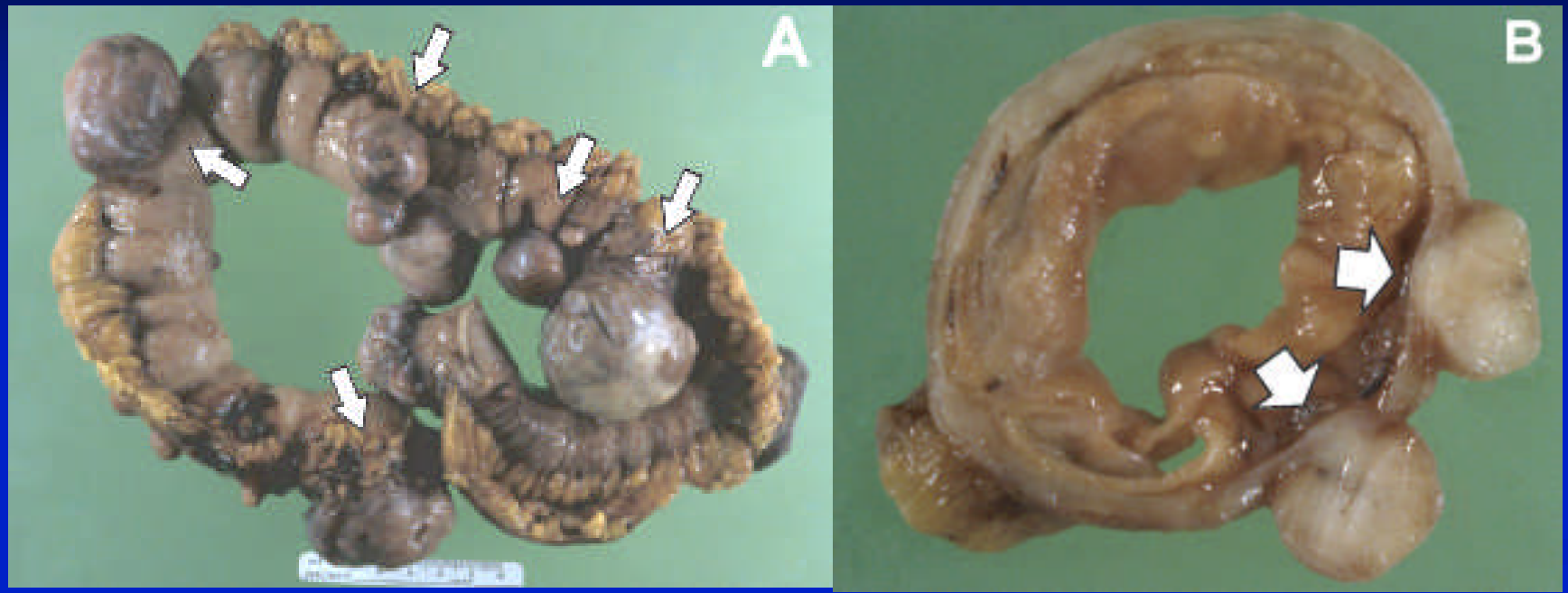
Apoptosis After Imatinib (5 DAYS)

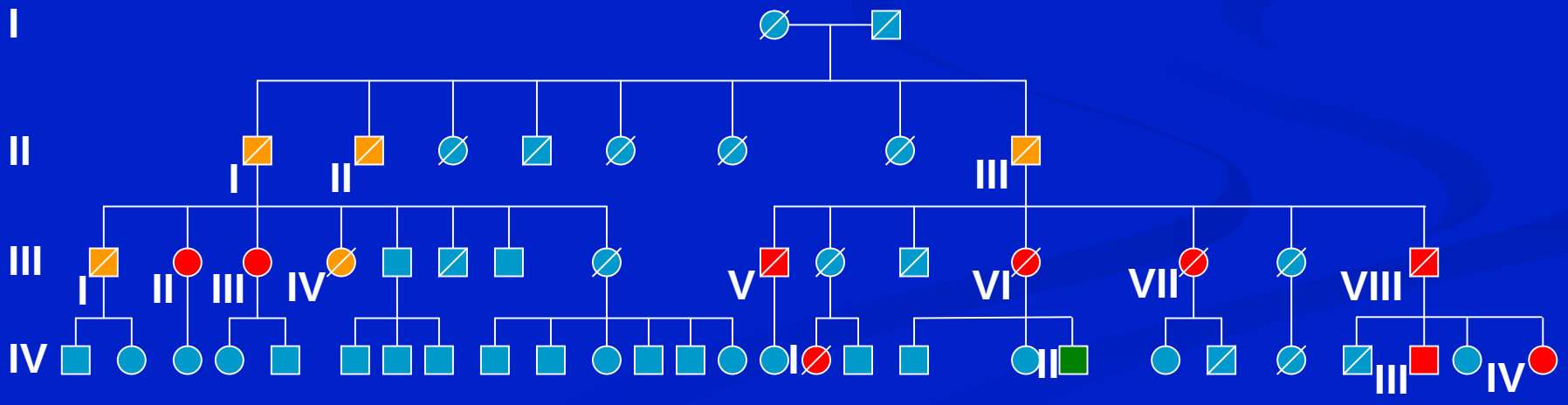


Baseline

5 days
post-imatinib

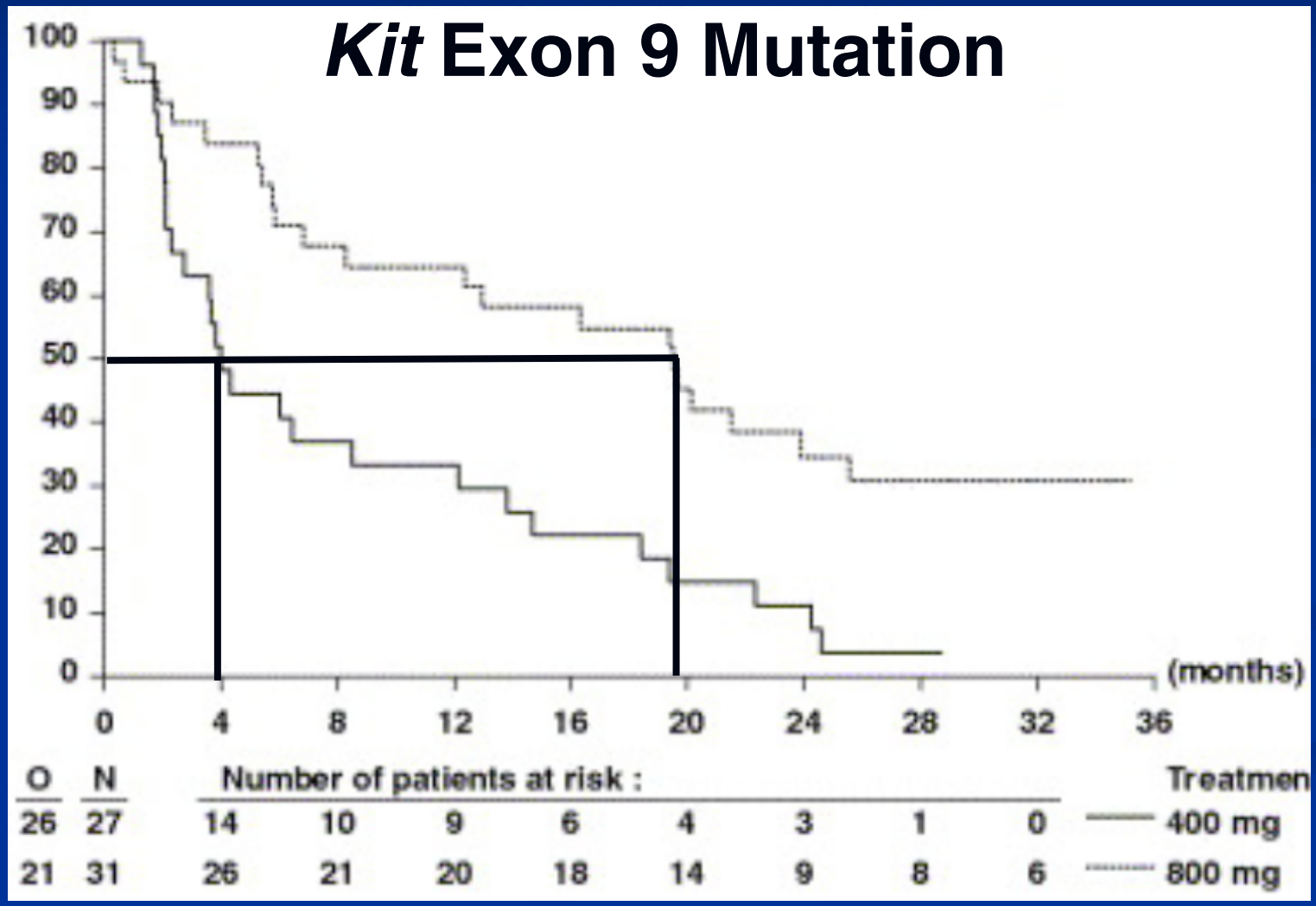
Familial GIST





Kleinbaum et al, ASCO 2006

Progression-free Survival By Imatinib Dose



Debiec-Rhycter et al, 200

A Clinical Trial is a Scientific Study in Humans

A Clinical Trial Must Be Ethically and Scientifically Sound

A Clinical Trial Should Be Ethically and Scientifically Sound , While Providing a Therapeutic Option For Patients

Clinical Trial Elements

- Objectives
- Background
- Patient Eligibility
- Pretreatment Evaluation
- Treatment Plan
- Evaluation During and after Treatment
- Criteria for Response
- Criteria for Removal from Study
- Laboratory Correlates
- Statistical Considerations
- Informed Consent

What Are The Objectives of The Clinical Trial?

Objectives

- **Phase I**
  - To determine maximum tolerated dose
  - To assess safety
  - To assess efficacy
- **Phase II**
  - To assess efficacy
  - To assess safety
  - Laboratory Correlates
- **Phase III**
  - To assess small differences in efficacy between to therapies (drug, dose, formulation, BSC)

Background

- Provide an overview of the disease and the drug.
- Why are the objectives important?
- How will this improve patient care?
- What are the risks and benefits to the patients?

Phase II Study Design

- Patient population
- Selection of agent(s)
- Dose
- Definition of endpoints
- Statistical design

Eligibility Criteria

Selection of Patients

- Patient population
  - Type of cancer
  - Prior therapy
  - Stage of disease
  - Presence of drug target

Eligibility Criteria

Selection of Patients

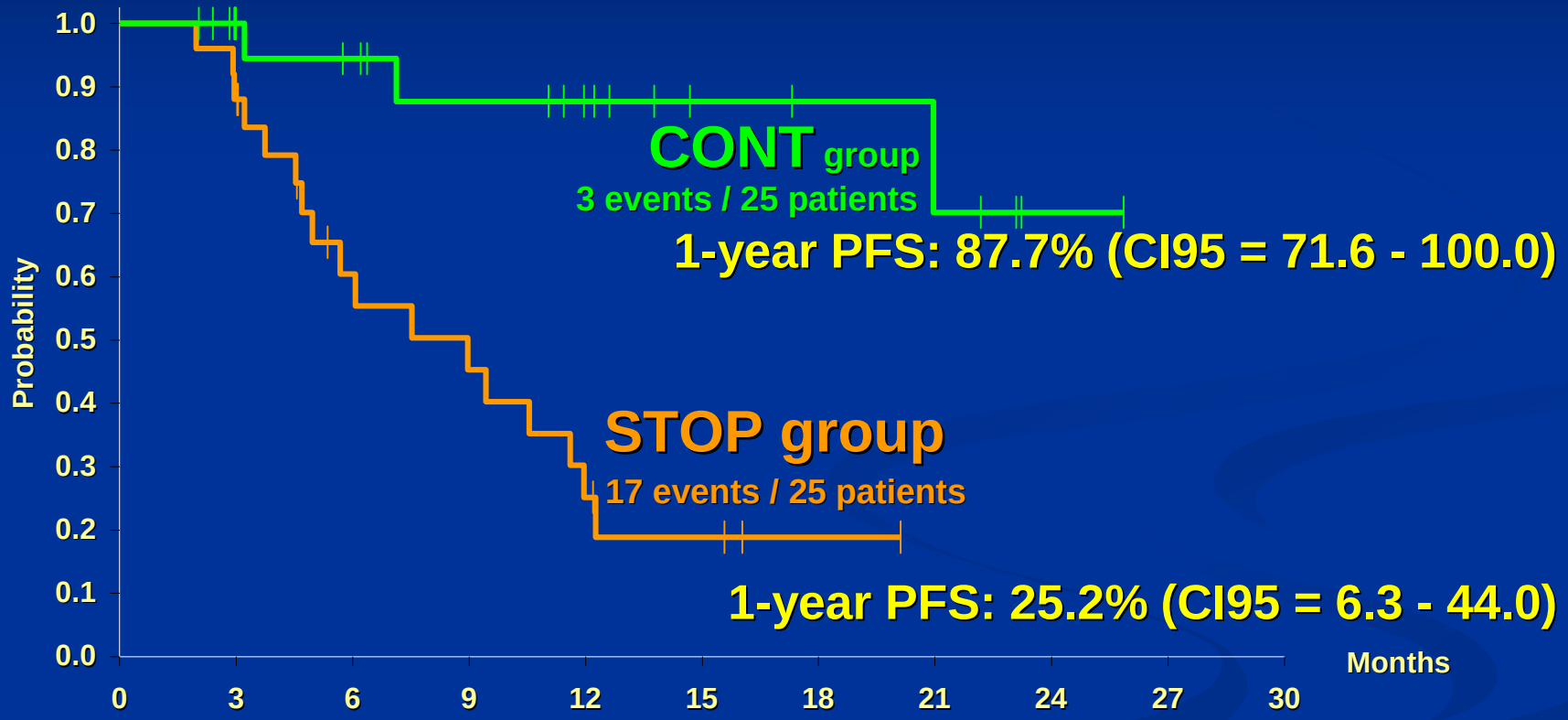
- Select patients who have progressing disease
- Should not be overly strict on exclusion criteria
  - Prior therapy
  - Prior cancer history

Selection of Study Drug

- **Phase II studies in advanced GIST**
  - **Perifosine** (AKT/MapK/p21 inhibitor)+**Imatinib**
  - **Tasigna**: Kit and Abl inhibitor
  - HSP90 inhibitor vs. Placebo (randomized)

BFR14 3-yr randomization

Progression Free Survival



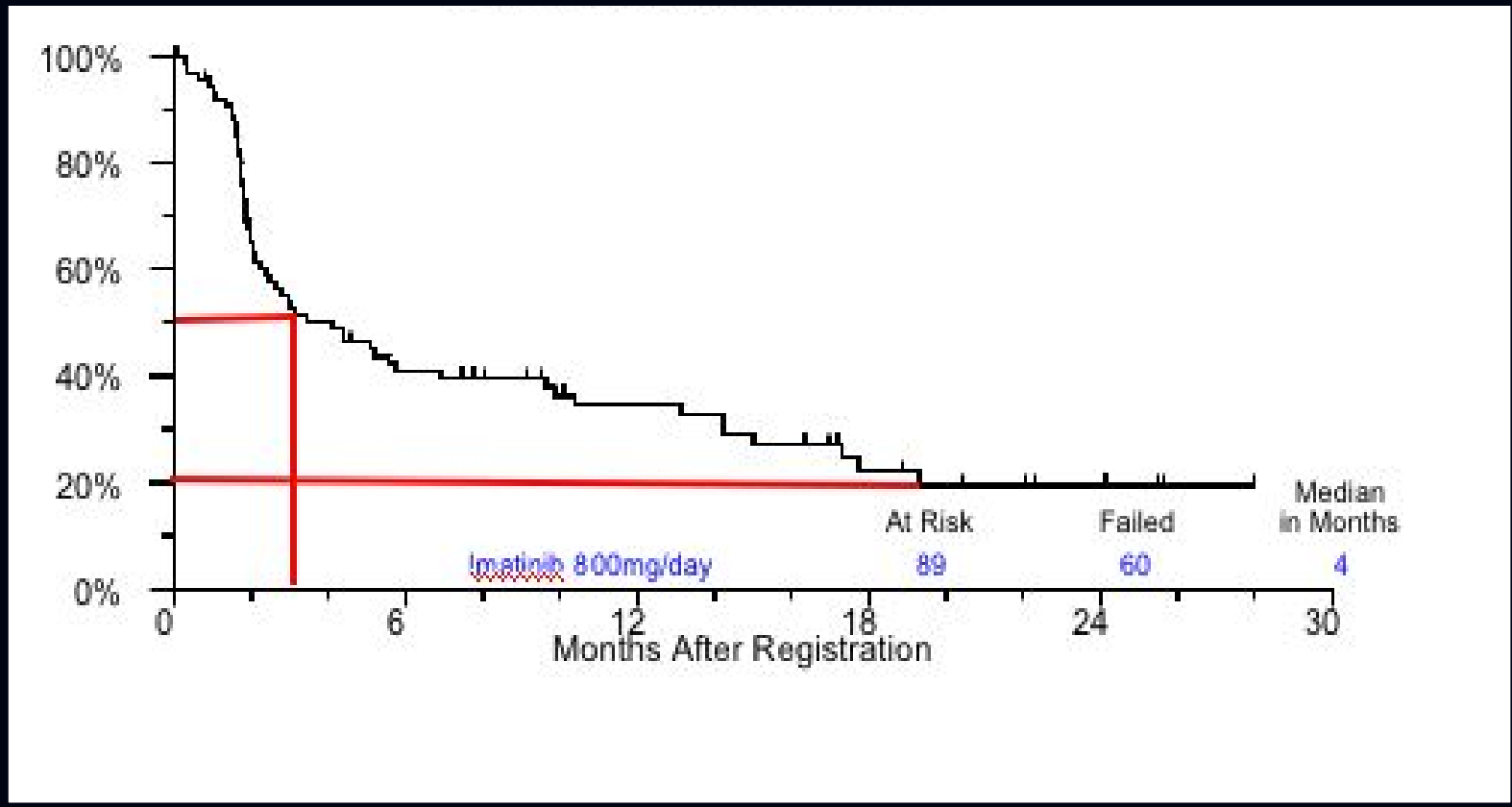
Rate of PD in STOP group

at 6 months: 40%
at 9 months: 55%
at 1 year: 75%

Median f.u.: 11 m
(IC95: 4.8 – 13.8)

Log-rank test : p <.0001

Imatinib 400mg vs 800mg
Time to Progression on Crossover



Clinical Trial Evaluations

Measuring Efficacy

- Pre-treatment
  - Baseline measurement
- During Treatment
  - Response assesment (same method as baseline)
  - Survival
- Post-treatment
  - “on study” until event

Phase II Study Design

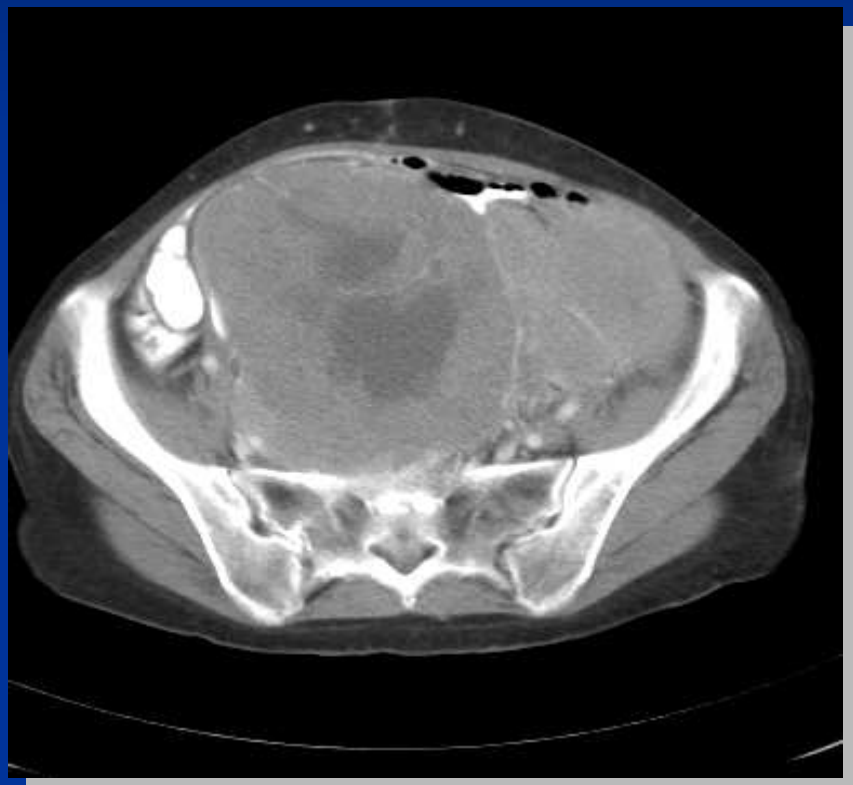
- Endpoints
  - Response rate
  - Time to progression
  - Progression Free Survival
  - Overall Survival
  - Improved Quality of Life

Phase II Study Design

- Definition of response
  - Clinical
  - Radiographic
  - Histological
  - Molecular
  - Improved Quality of Life

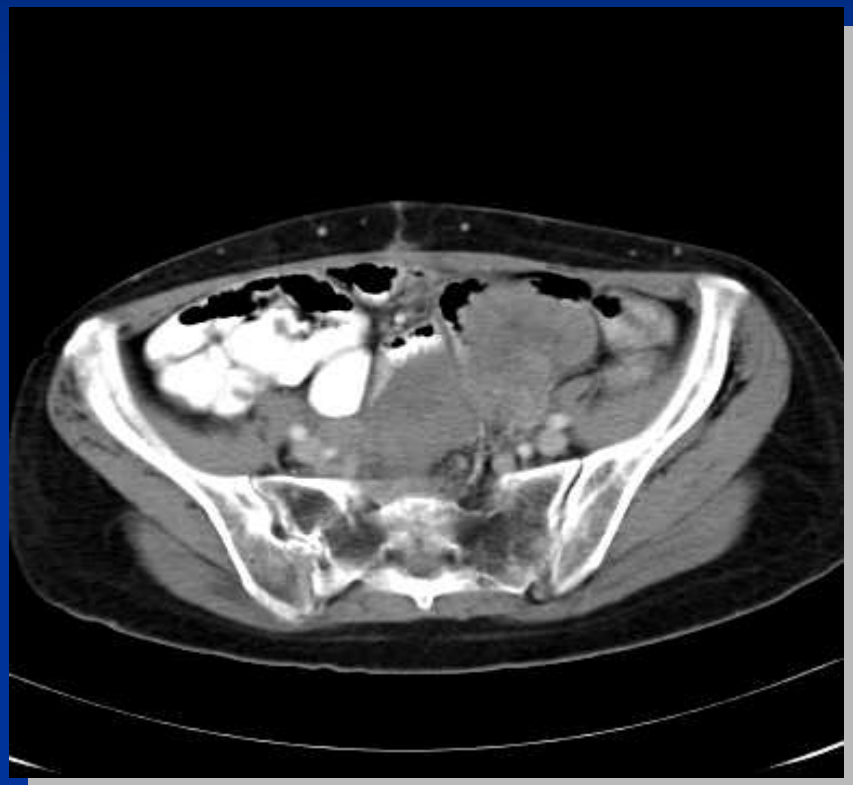
CT Scan Results

Jun 27, 2000



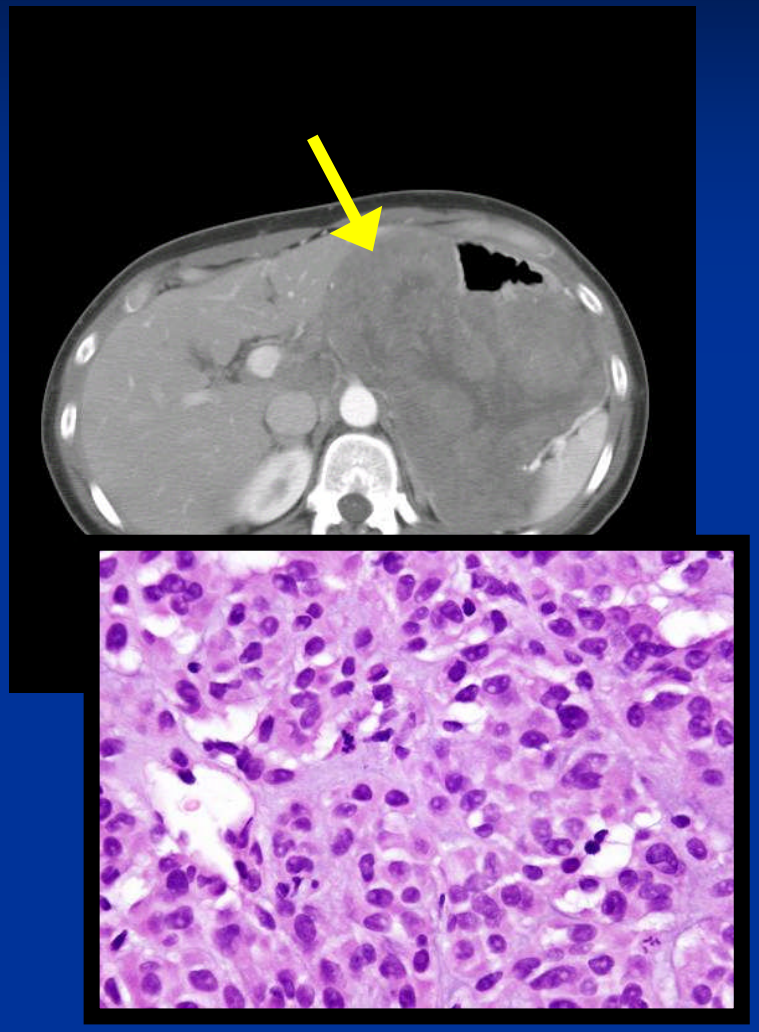
Before Imatinib

Oct 4, 2000

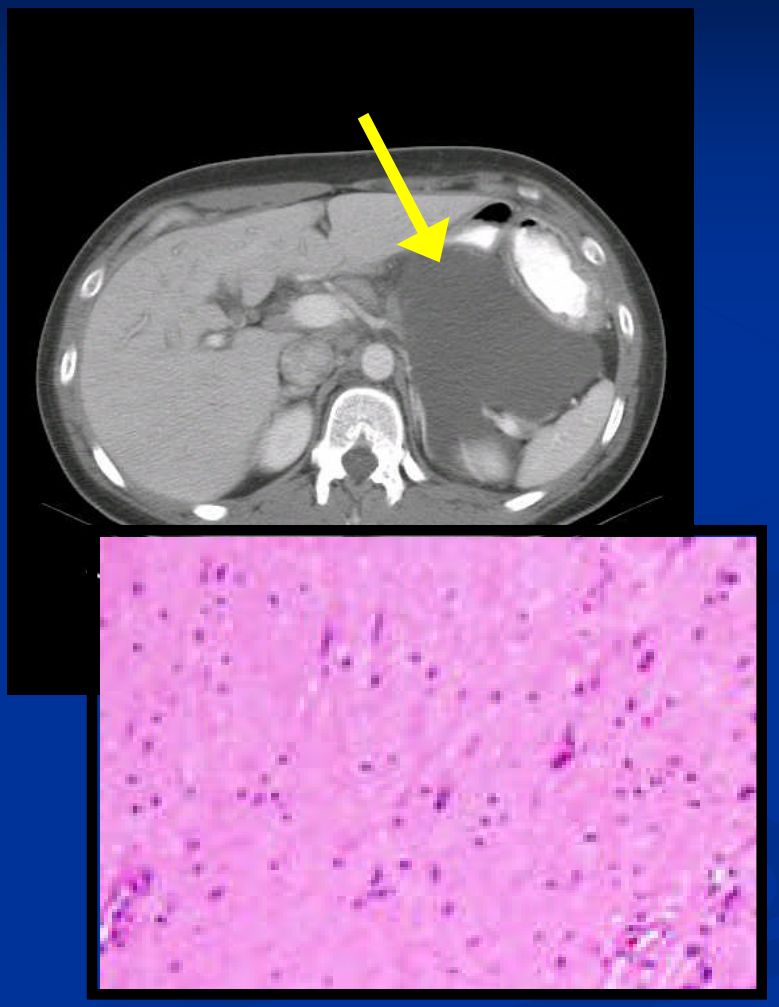


After Imatinib

Response

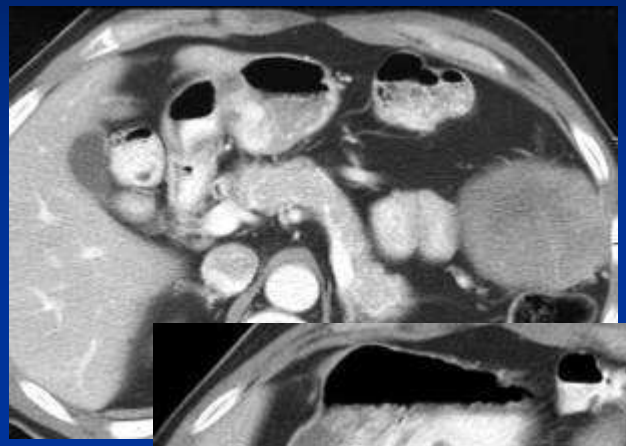


Pre-Imatinib



Post-Imatinib (8 weeks therapy)

Effects of Imatinib on GIST: CT and PET findings



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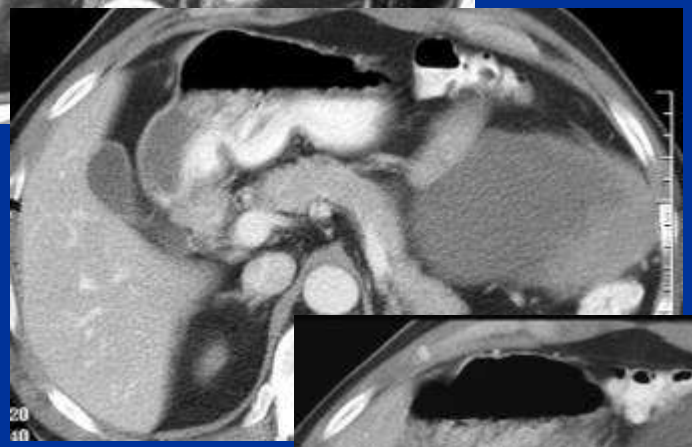

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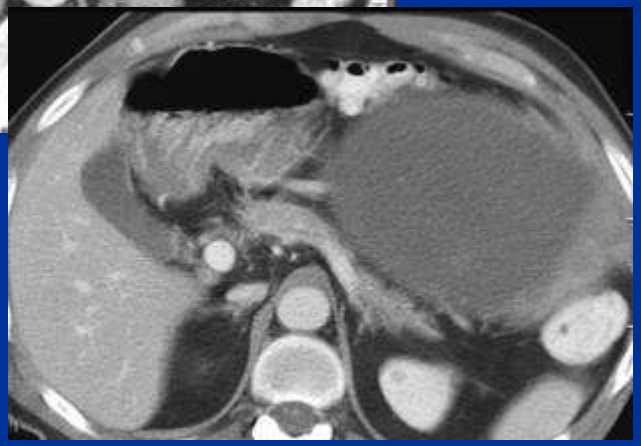
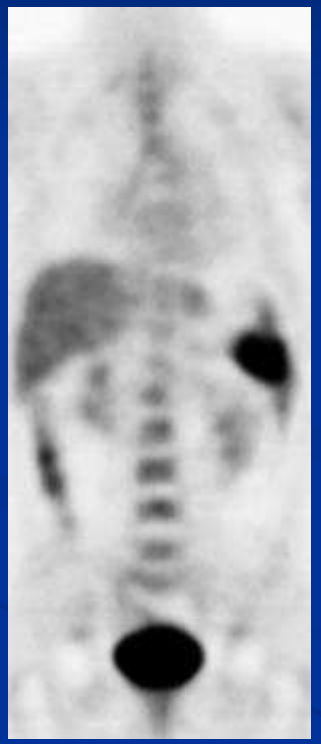


10/8

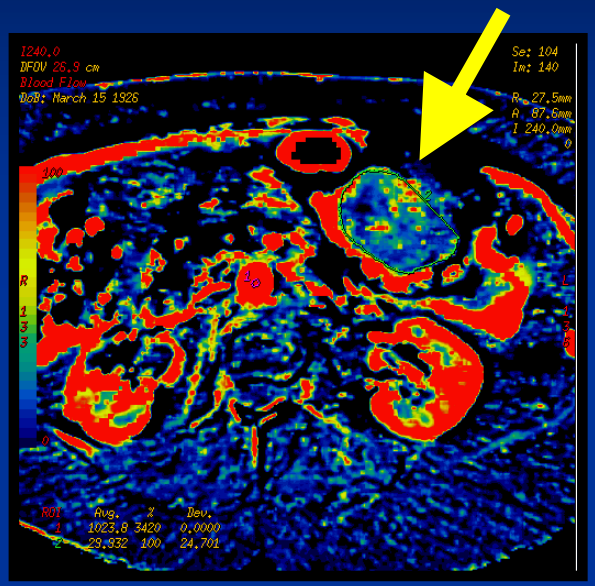


1/26

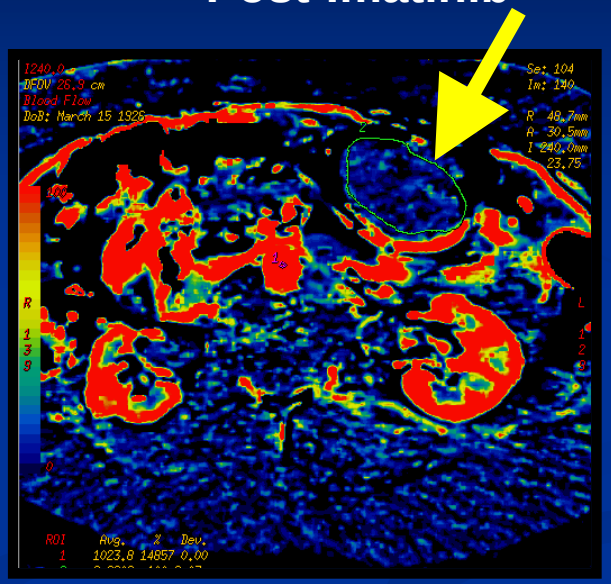
10/9

Effect of Imatinib on Vascularity

Pre-Imatinib



Post-Imatinib



Perfusion Parameter	Pre-Imatinib	Post-Imatinib	*P* Value
BF (mL/100g/min)	36.84	24.55	0.017
BV (mL)	3.90	2.84	0.005
MTT (s)	9.47	9.96	0.26

Statistical Considerations

Study Design

Statistical Considerations

- Number of patients
- Rate of accrual
- Power
- Significance
- What can you demonstrate?

Statistical Considerations

- Allow quantitation of objectives
- Require "clinical considerations"
- When done properly ensure a safe, ethical, and successful study

Phase II Study Design

- Statistical design
  - 1-stage design
  - 2-stage designs
  - Newer Bayesian approaches

Clinical Trials

- Clinically Sound: Ensure the Best Patient Care
- Scientifically rigorous
- Ethical
- Offer a therapy to patients that have no other treatment options
- Learn about the disease and the therapy so that the next Clinical Trial is better.

Why Participate In A Trial?

- No other therapeutic options are available.
- Therapy or testing are free.
- To allow researchers to understand GIST and help future patients.
- Freireich's Law #6: A good clinical trial offers the best patient care

Clinical Trials

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- *What is a clinical trial, and when should a patient consider entering a trial?
- *What are the various phases of trials and their goals?
- *Who sponsors a trial and how does this affect goals? (Government, pharma, intergroup trials, etc)
- *What are the various surrogate endpoints in clinical trials, and what does each imply for a patient (time to progression, overall survival, time to treatment change, time to secondary resistance, etc?)
- *What makes a trial "scientific/unbiased" and how does this differ from voluntary internet polls about pt results?
- *How does a patient find a trial? Who pays for trial participation?
- *What are some key areas of investigational drugs for GIST pts and why are these important? (HSP90i, HDACi, PI3Ki, other KIT inhibitors, non-ATP competitive KIT inhibitors, antibodies, etc)

Eligibility Criteria

Selection of Patients

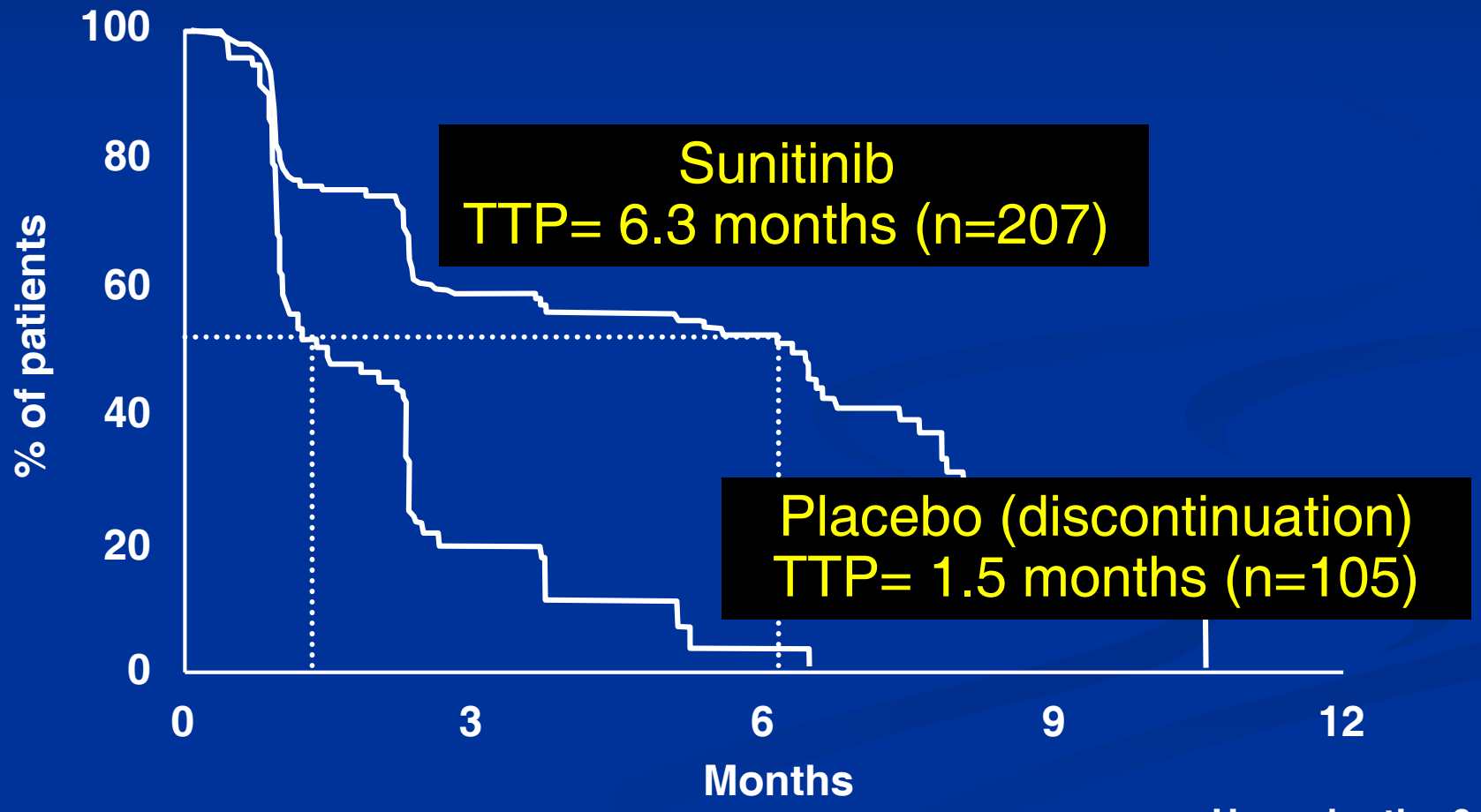
- Imatinib in Sarcomas
  - Response Rate: 10%
- Imatinib in Kit + GIST
  - Response Rate: 85%

Eligibility Criteria

Selection of Patients

- Select Patients whose tumor expresses the target
- Don't Select Patients whose tumor expresses the target

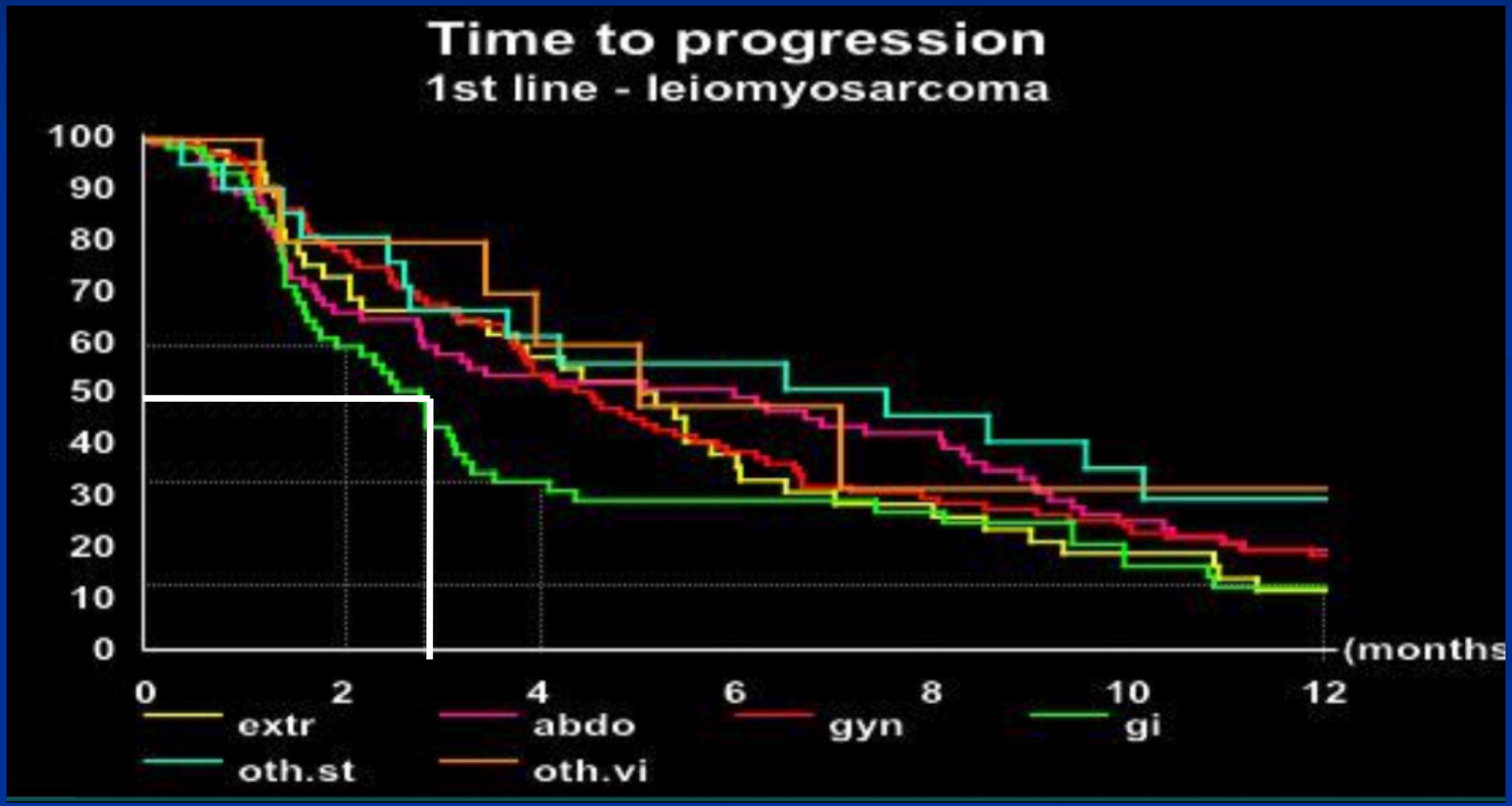
Phase III Trial of Sunitinib
Time to Progression



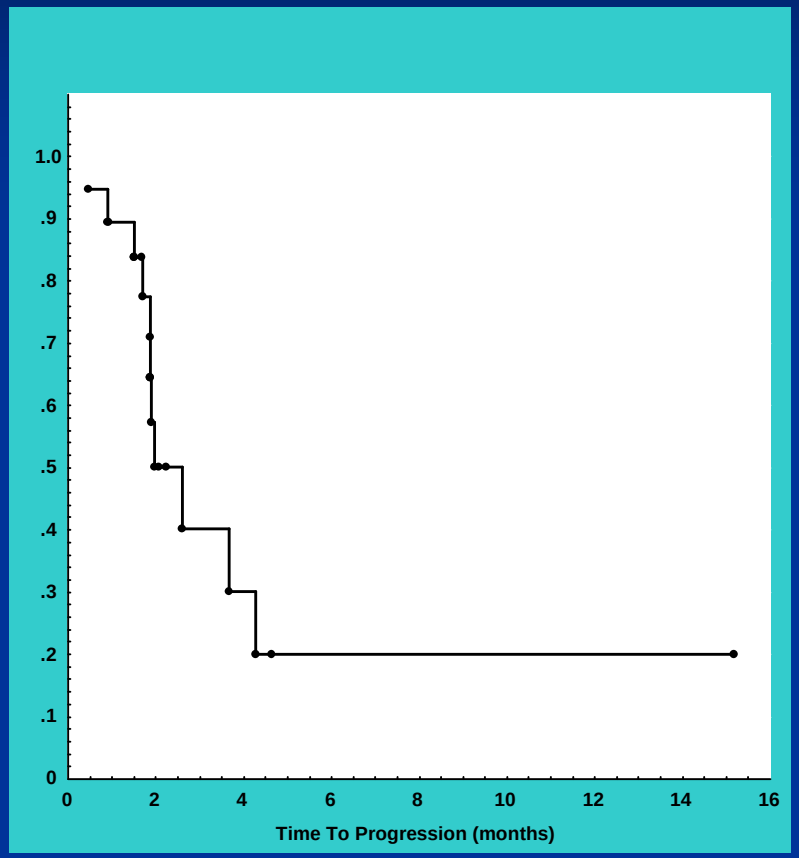
Hazard ratio=0.335
P<0.00001

Demetri et al. *J Clin Oncol.* 2005;23(Suppl 16):308s. Abstract 4000. Updated from oral presentation.

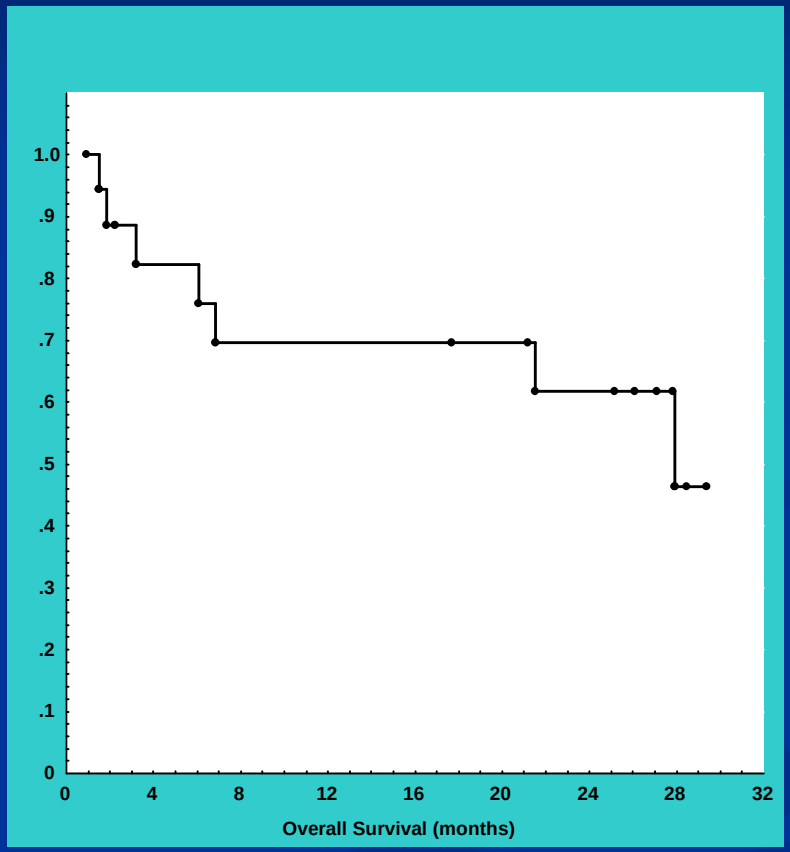
EORTC 1st Line Chemotherapy: Active Single Agents or Combinations



Temozolamide in GIST
Overall Survival



TTP 2 months



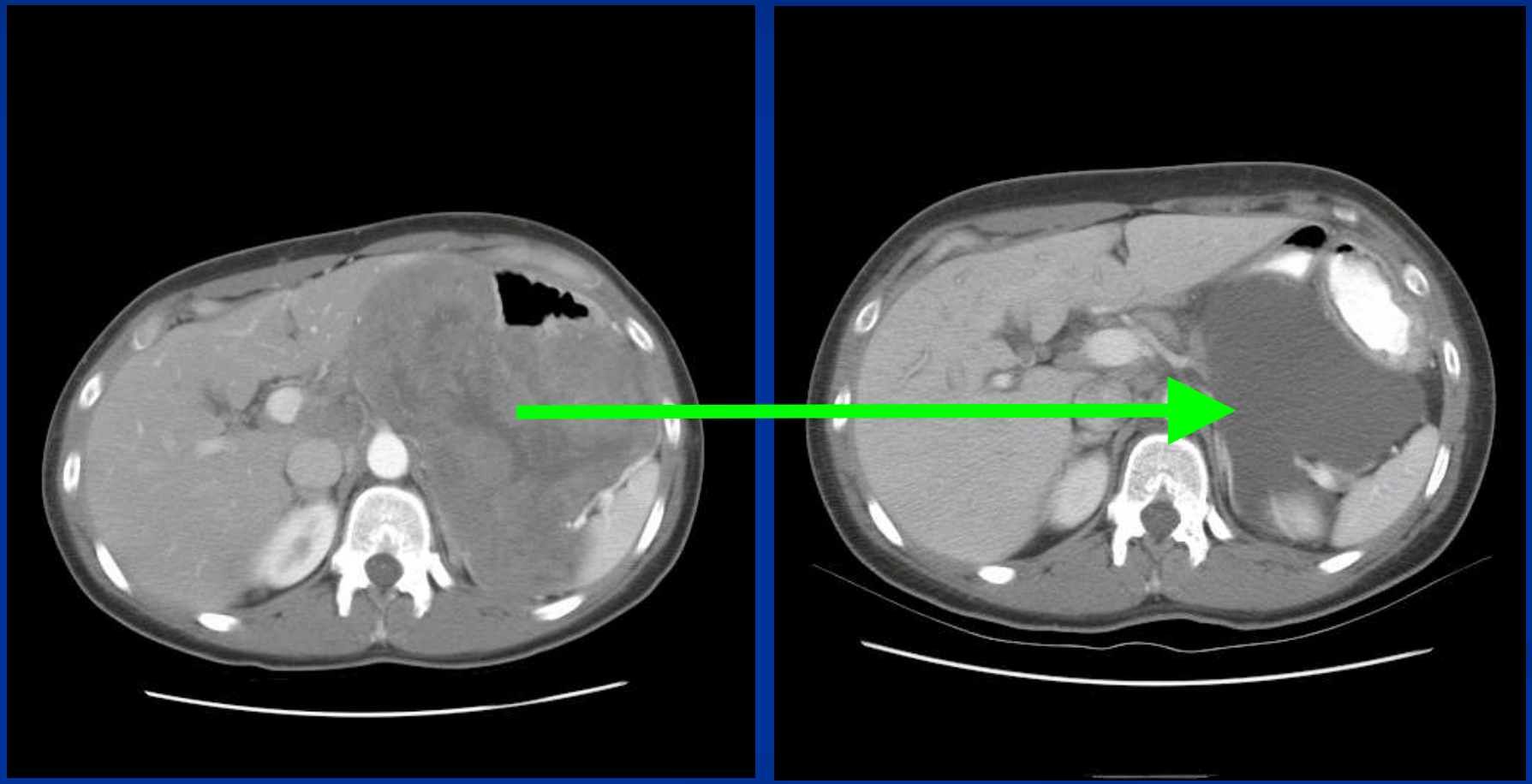
OS (28 months)

Trent et al, Cancer 2003

Biological Endpoints

Phase II trial to understand the biology of response to therapy

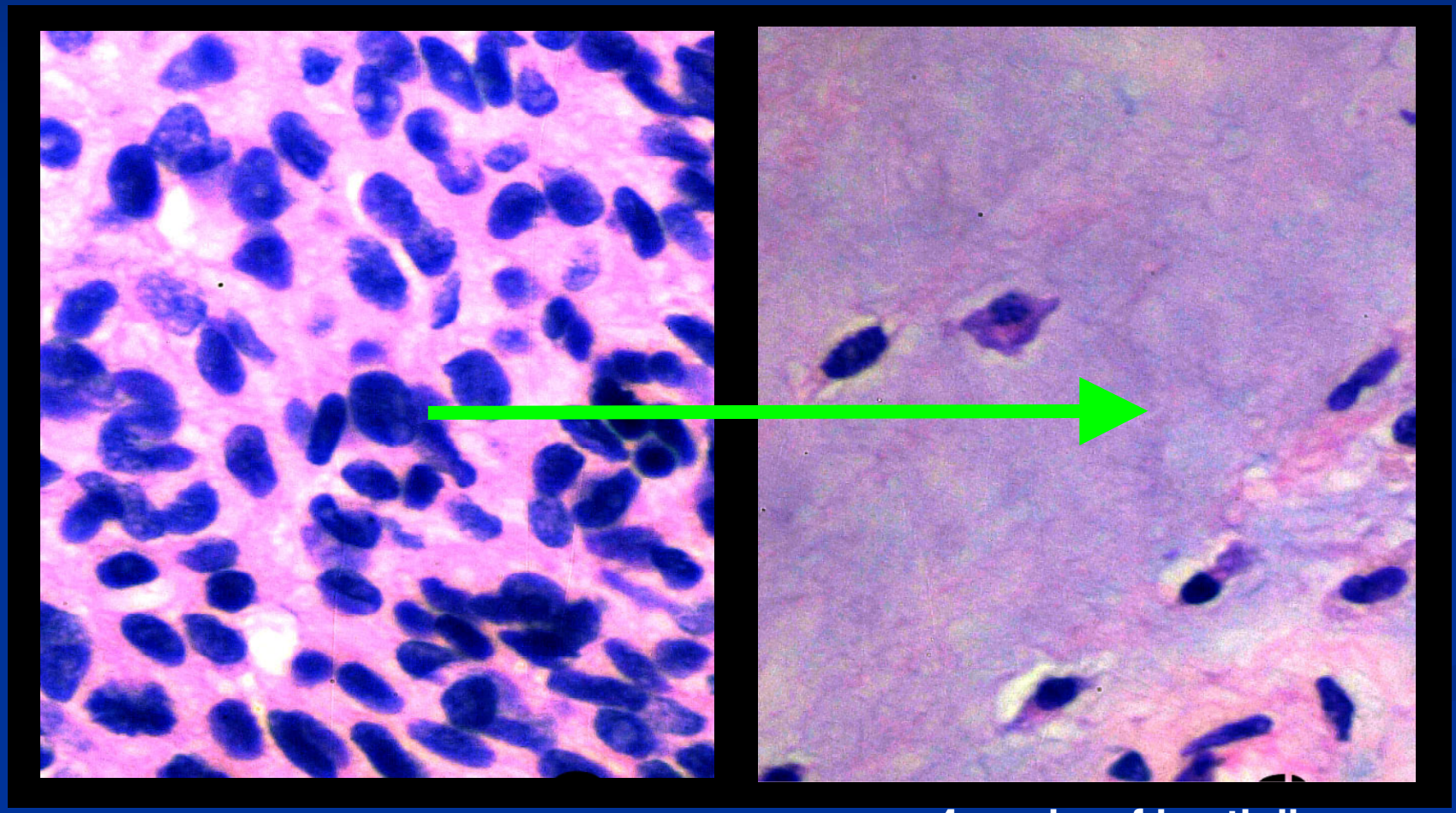
Mechanisms of Activity of Imatinib in GIST



Baseline

8 weeks of imatinib

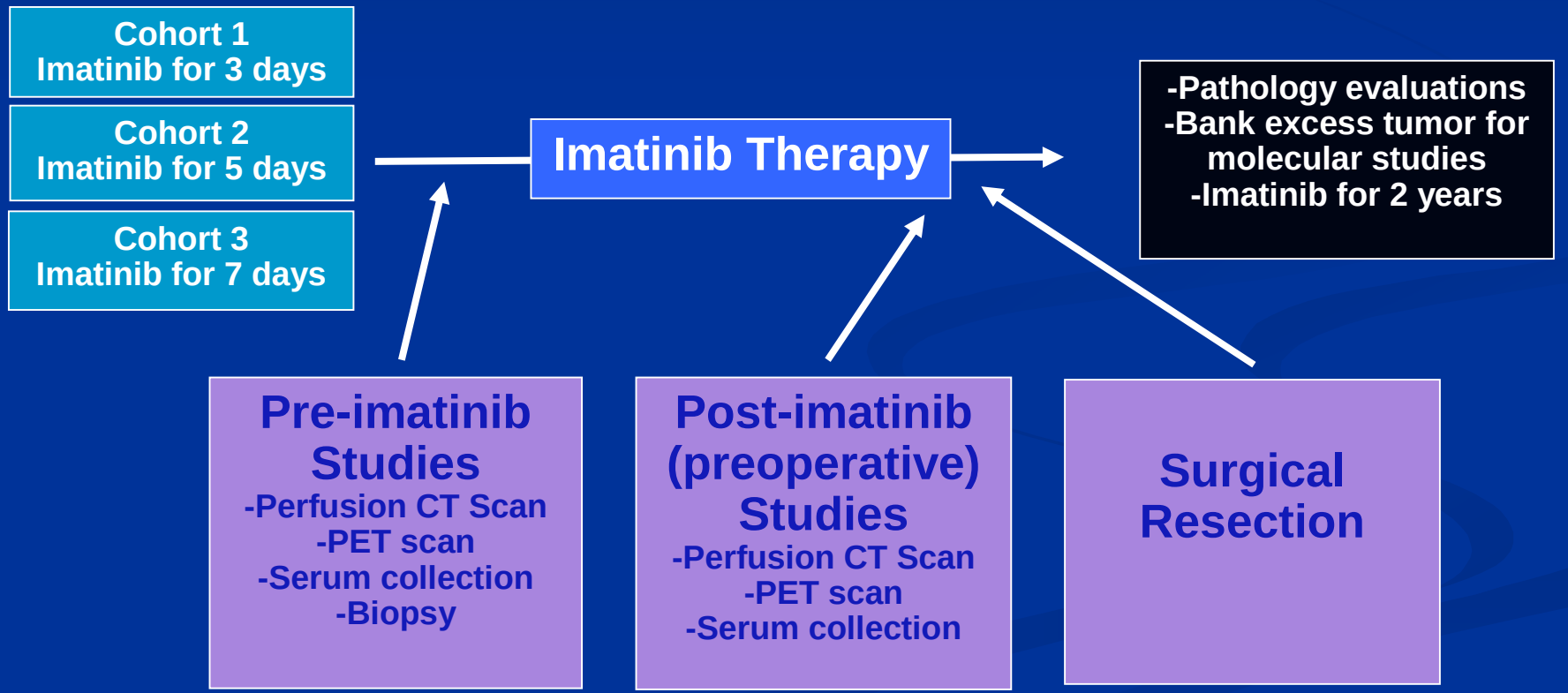
Mechanisms of Activity of Imatinib in GIST

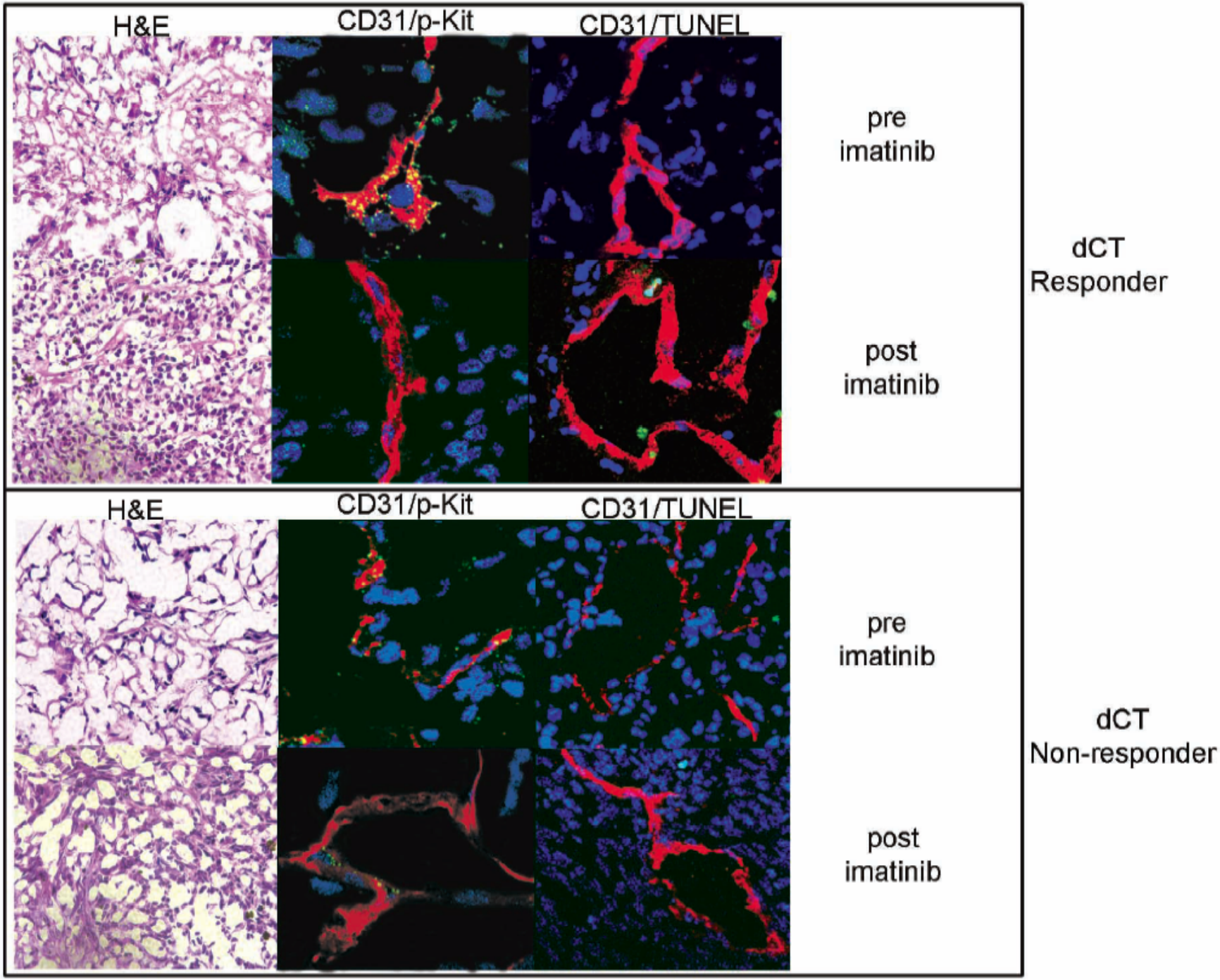


Baseline

4 weeks of imatinib

Mechanisms of Activity of Imatinib in GIST




H&E
CD31/p-Kit
CD31/TUNEL
pre imatinib
post imatinib
dCT Responder
H&E
CD31/p-Kit
CD31/TUNEL
pre imatinib
post imatinib
dCT Non-responder

Early Mechanisms of Activity of Imatinib in GIST

- Apoptosis pathway interrogation
- Anti-Vascular pathway interrogation
- Genomic pathway analysis (Gene Ontology)
- Proteomic analysis of tissue protein changes (RPPA)
- microRNA modulation of genomic changes
- Methylation changes after imatinib therapy