Clinical Trials

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SARC Sarcoma Alliance for Research through Collaboration

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

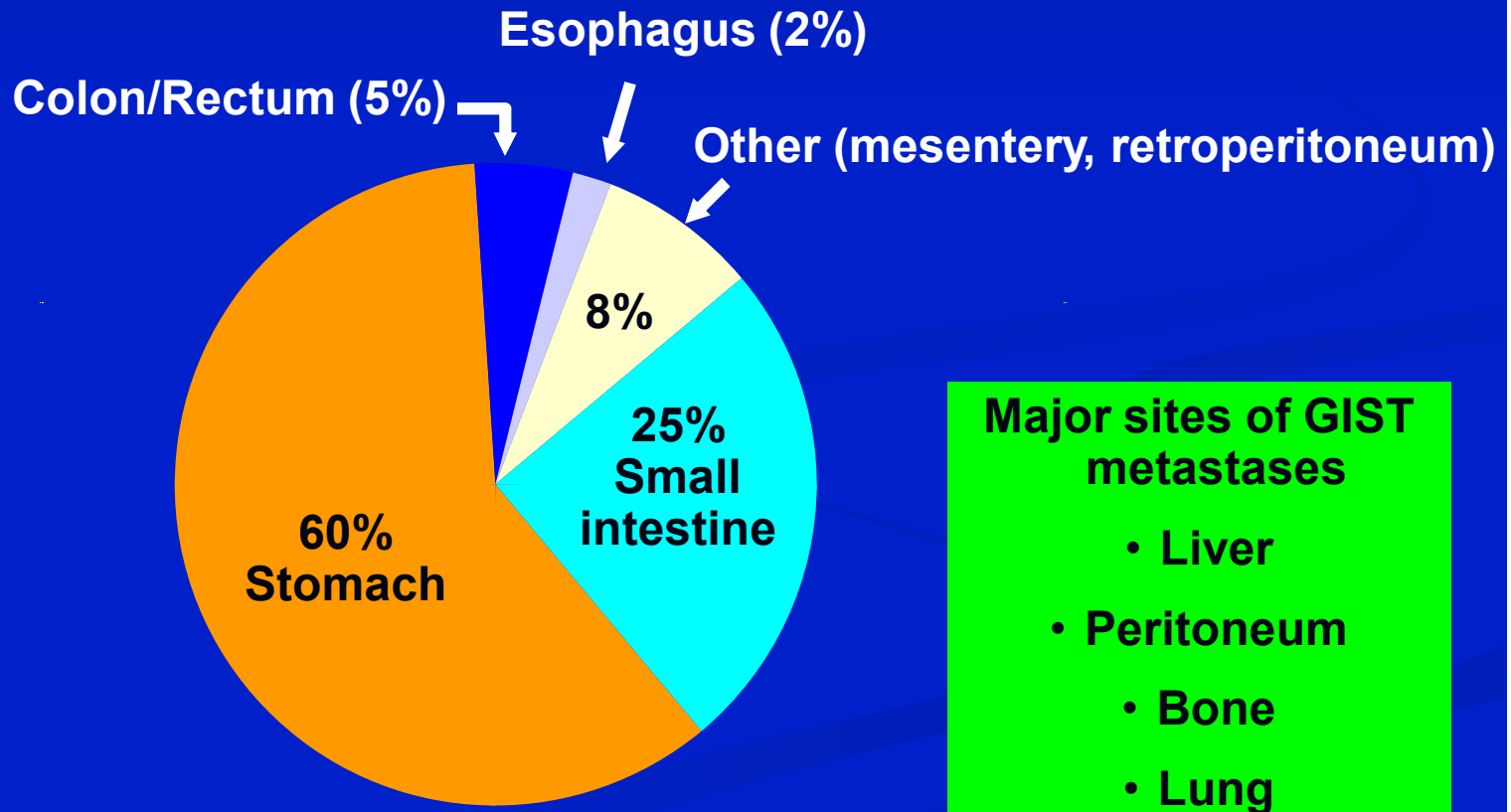
GIST Overview

- 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

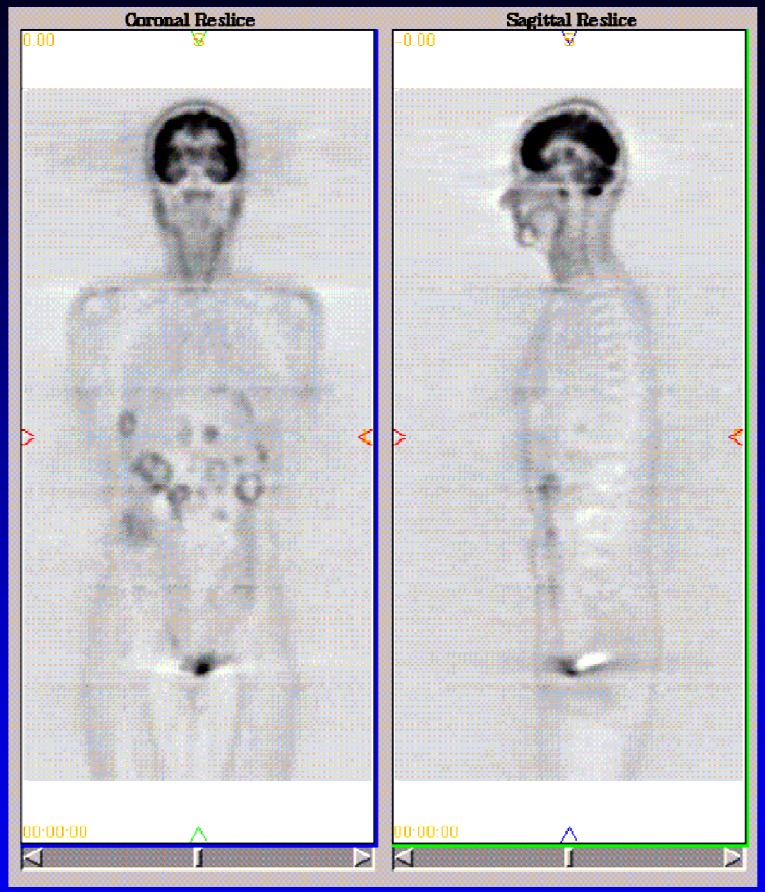
Regimen	Number of Patients	Partial Response n (%)
DOX + DTIC	43	3 (7%)
DOX + DTIC +/– IF	60	10 (15%)
IF + VP-16	10	0 (0%)
Paclitaxel	15	1 (7%)
Gemcitabine	17	0 (0%)
Liposomal DOX	15	0 (0%)
DOX	12	0 (0%)
DOX or docetaxel	9	0 (0%)
High-dose IF	26	0 (0%)
EPI + IF	13	0 (0%)
Various	40	4 (10%)
DTIC/MMC/DOX/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

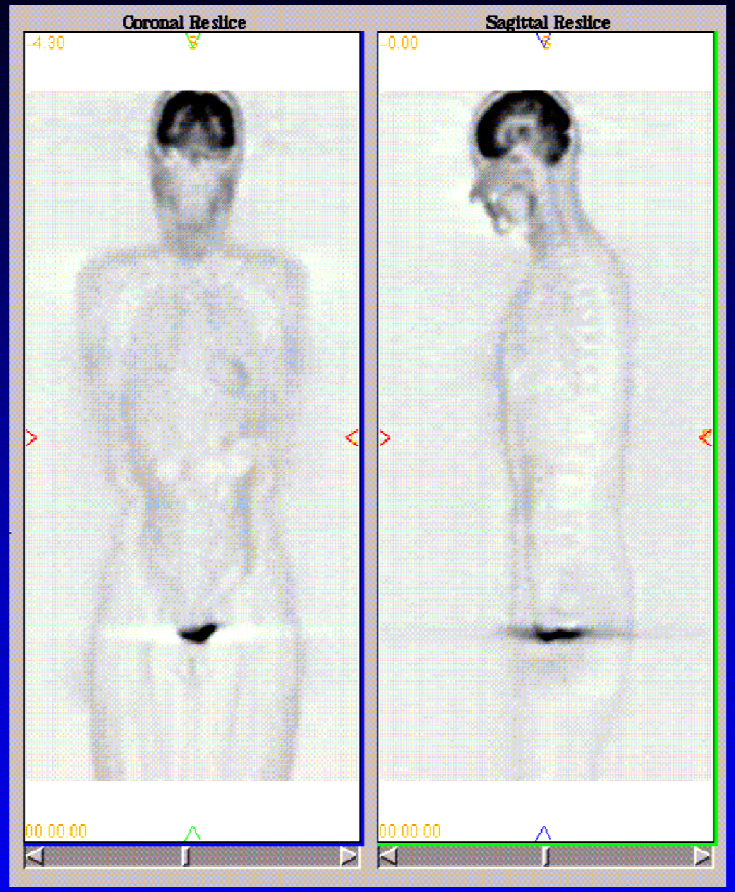
GIST: Therapy

- 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



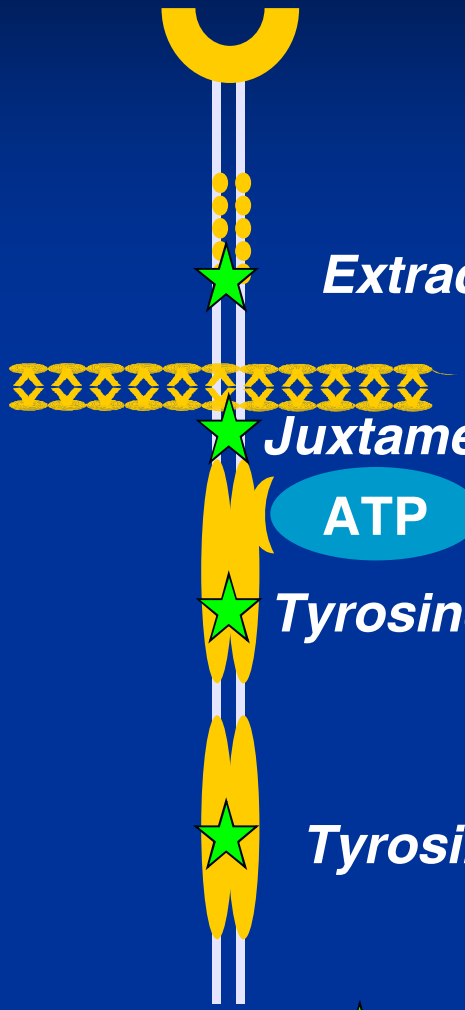


Multiple liver and upper abdominal ^{18}FDG-accumulating metastases

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%)

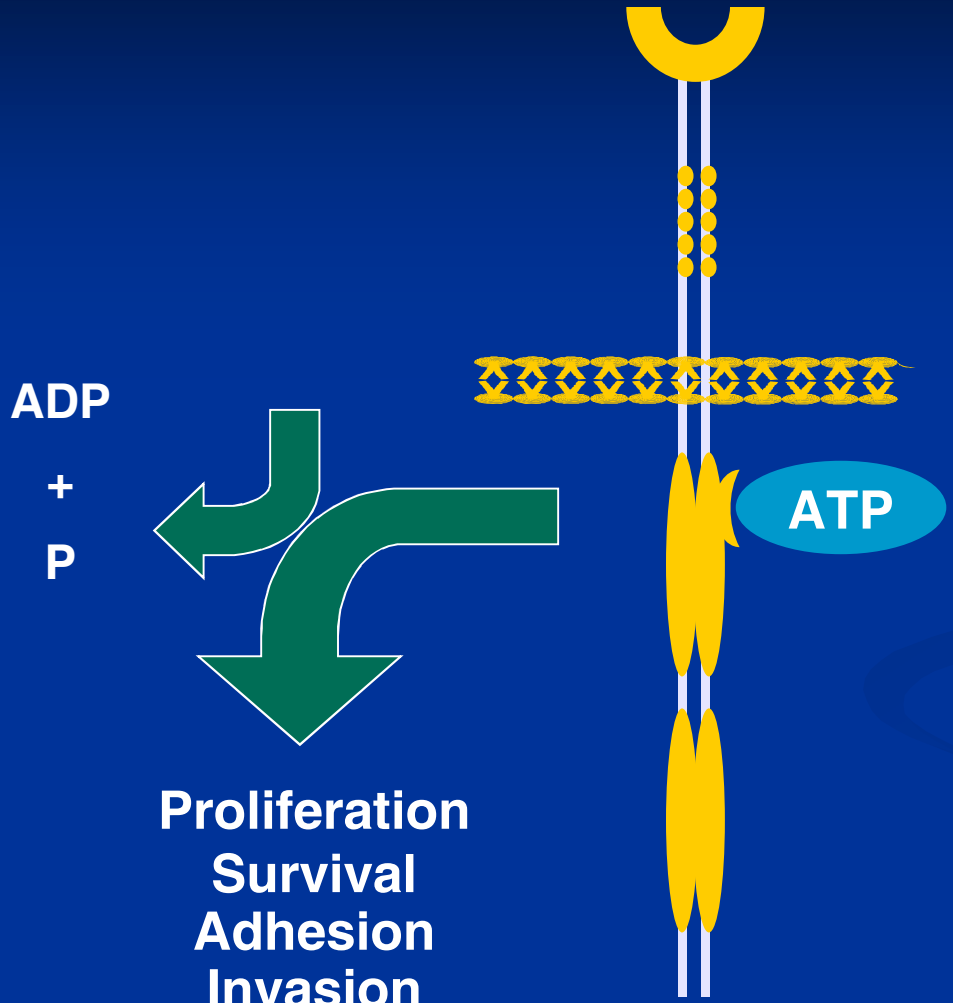
ATP

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

Tyrosine Kinase Domain II (exon 17, 0.6%)

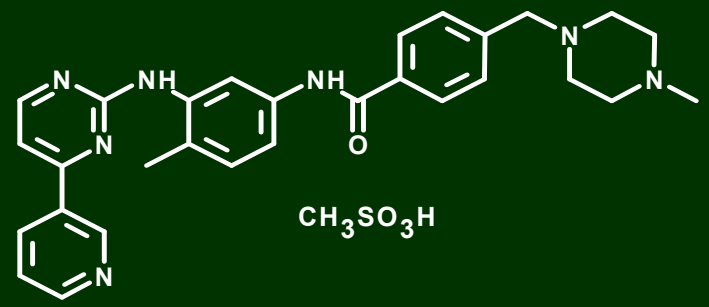
★ = common mutation site

Kit Receptor Phenotype



Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

Imatinib Mesylate



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

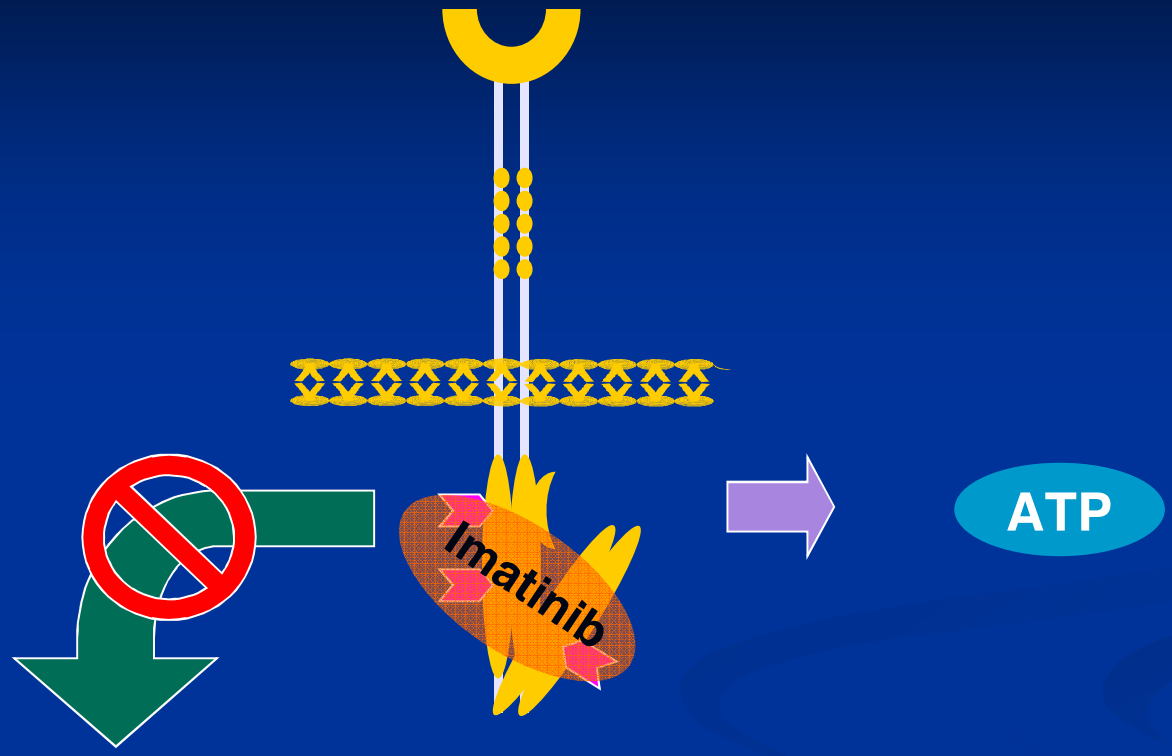
MW: 589.7

- 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} ≈ 0.1μM)

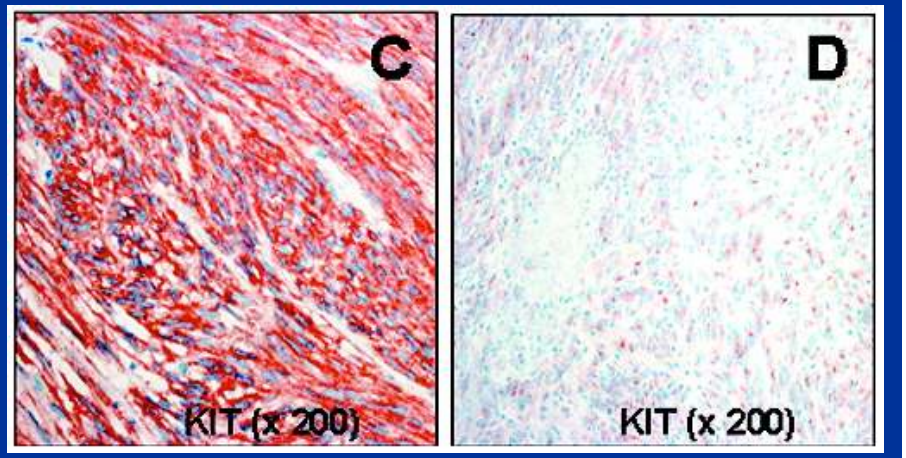
Kit Receptor Phenotype

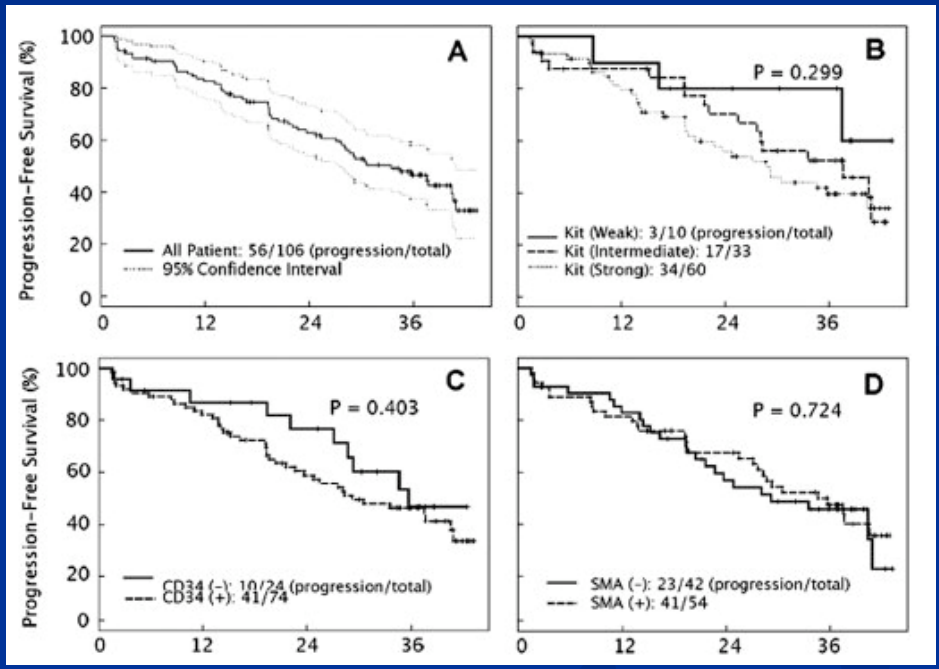


Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

= imanitib contact point

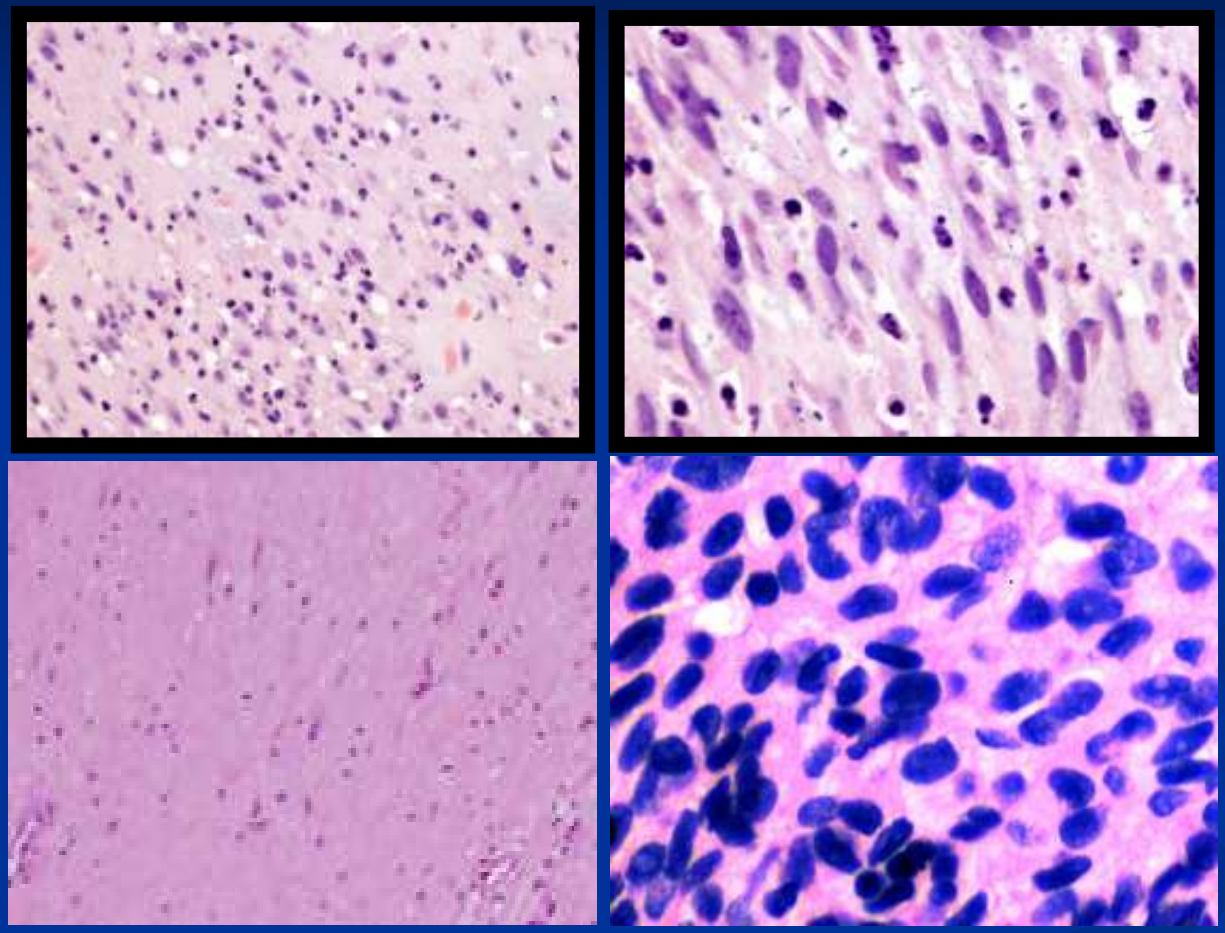
Low KIT Expression Correlates With Benefit From Imatinib





Chirieac, Trent. Cancer 2006

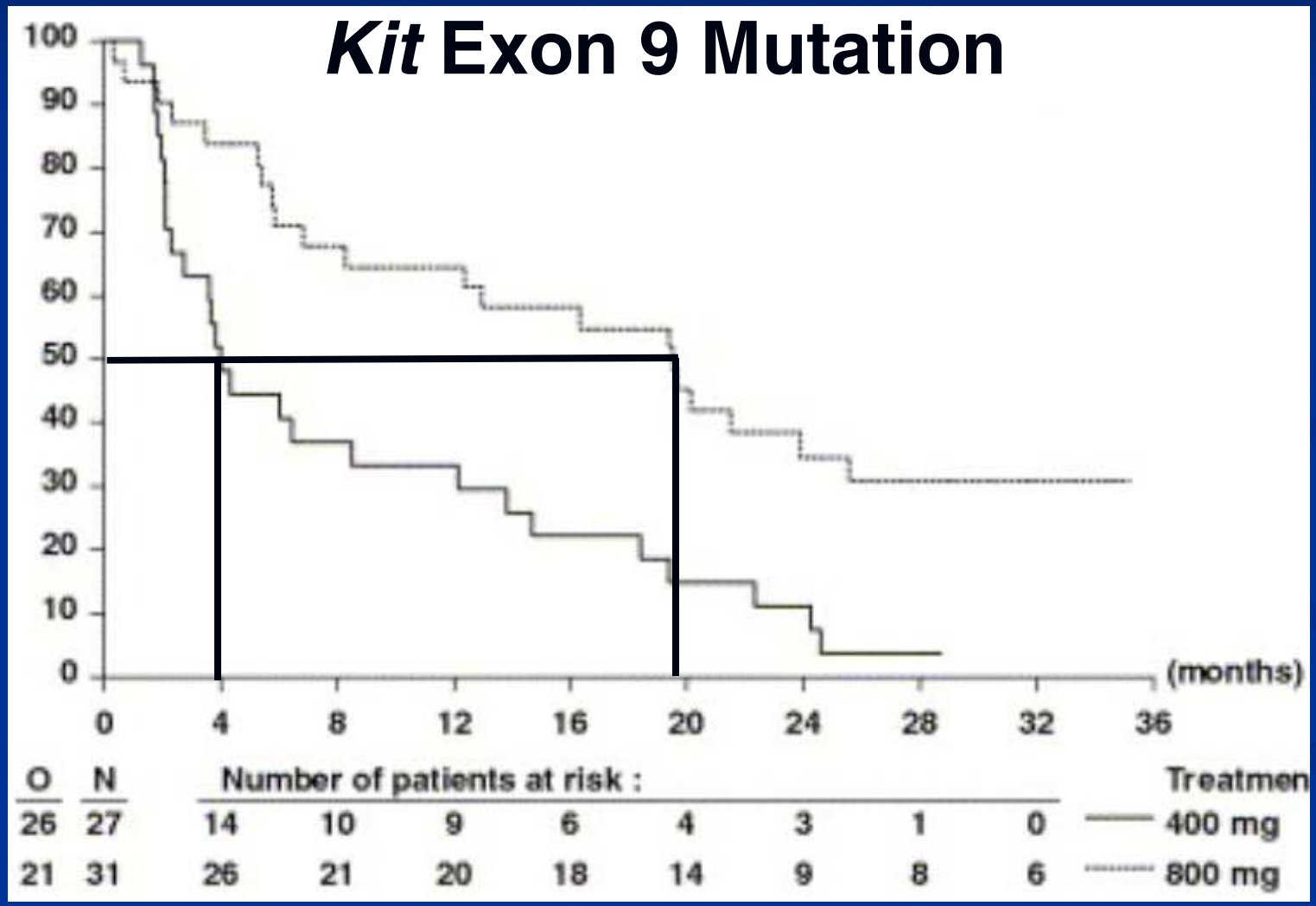
Apoptosis After Imatinib (5 DAYS)



Baseline

5 days
post-imatinib

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 two therapies (drug, dose, formulation, BSC)

Maximum Tolerated Dose

- Highest dosage of a drug, drug combination or other treatment modality that patients can safely tolerate. Usually determined by Phase I Trial.
- The dosage level below the level of DLT is then defined as the **maximum tolerated dose** (MTD).
- MTD: Appearance of side effects during treatment that are severe enough to prevent further increase in dosage or strength of treatment agent, or to prevent continuation of treatment at any dosage level.

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

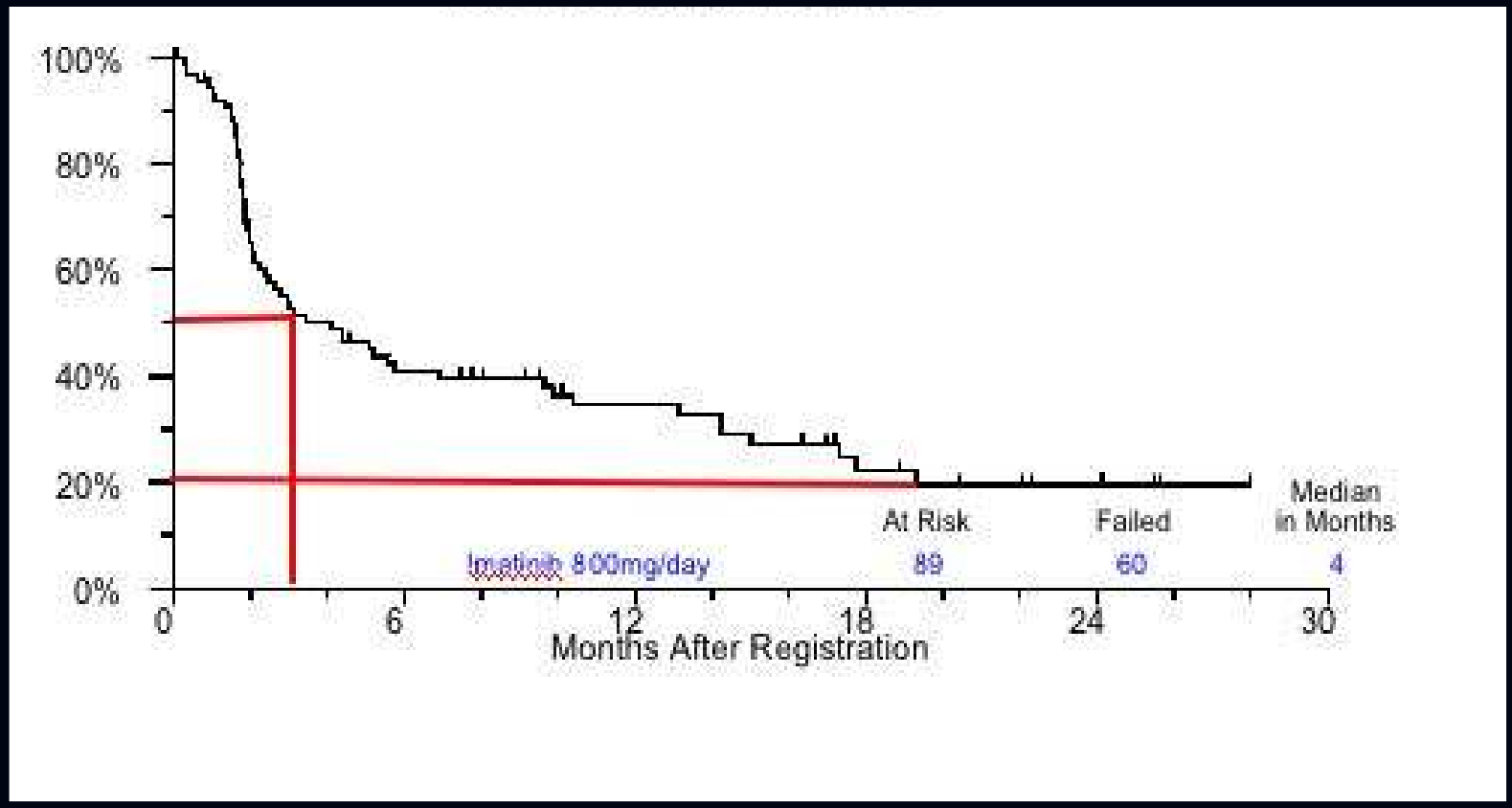
Selection of Patients

- 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**
  - **Nilotinib (Tasigna)**: Kit and Abl inhibitor
  - HSP90 inhibitor vs. Placebo (randomized)

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

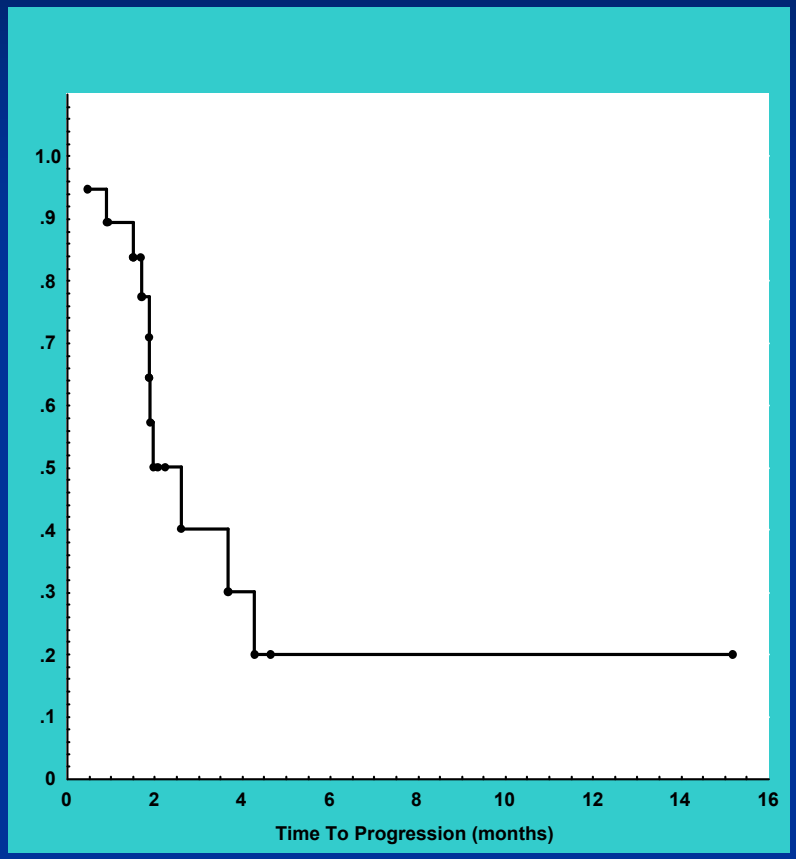
Phase II Study Design

- Endpoints
  - Response rate
  - Time to progression
  - Progression Free Survival (PFS)
  - Overall Survival (OS)
  - Improved Quality of Life

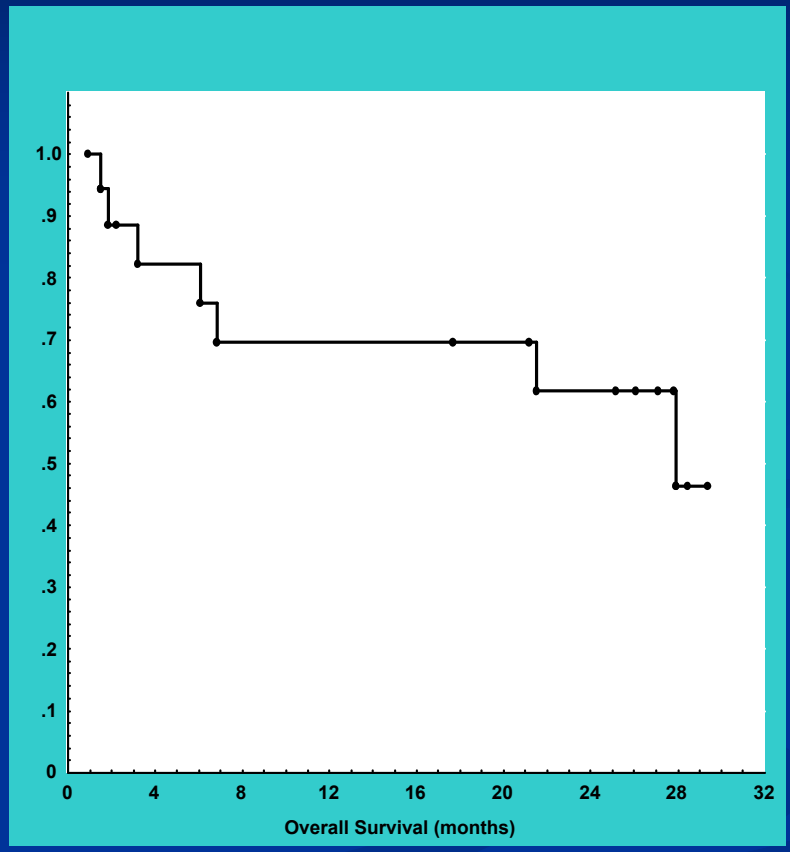
Progression Free Survival (PFS)

- Advantage over OS
  - PFS can reflect tumor growth and be assessed before the determination of a survival benefit
  - PFS is not confounded by subsequent therapy or crossover
  - Smaller sample size and shorter follow-up necessary compared with survival studies
  - Measurement of stable disease included

Temozolamide in GIST
Overall Survival



TTP 2 months



OS (28 months)

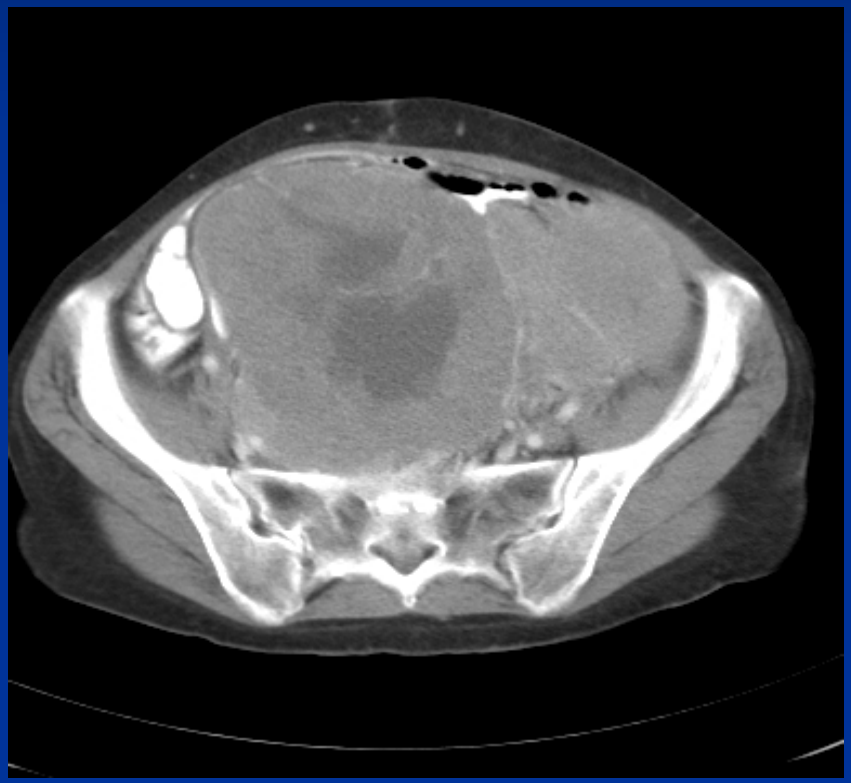
Trent et al, Cancer 2003

Phase II Study Design

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

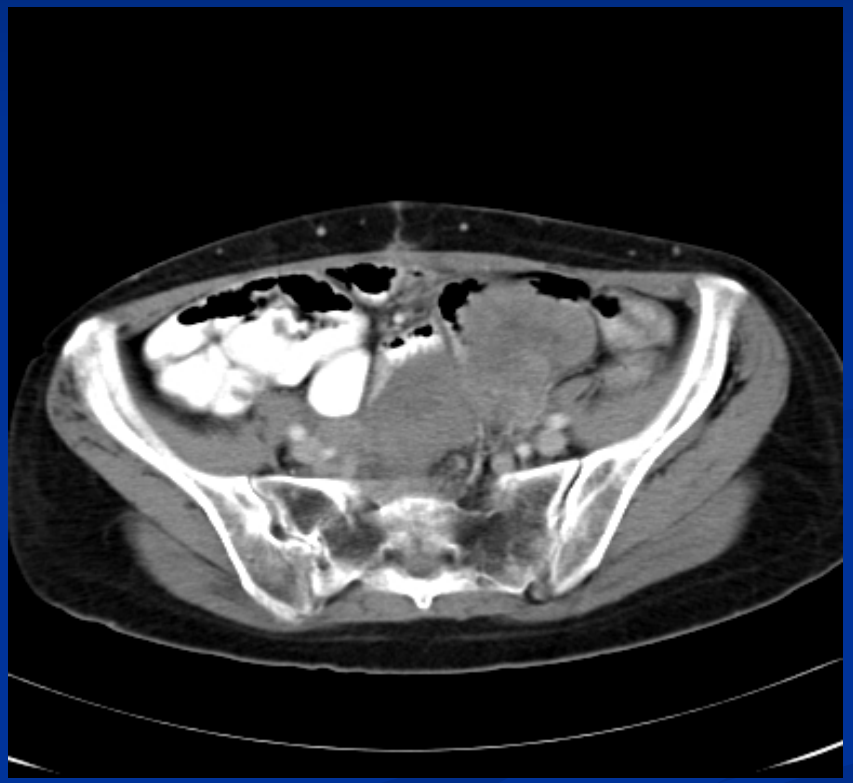
CT Scan Results

Jun 27, 2000



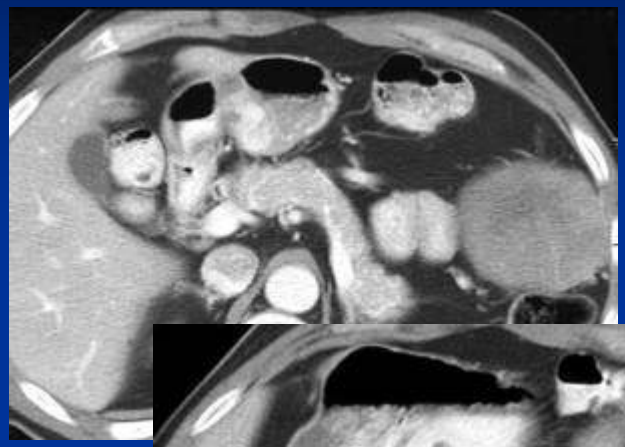
Before Imatinib

Oct 4, 2000



After Imatinib

Effects of Imatinib on GIST: CT and PET findings



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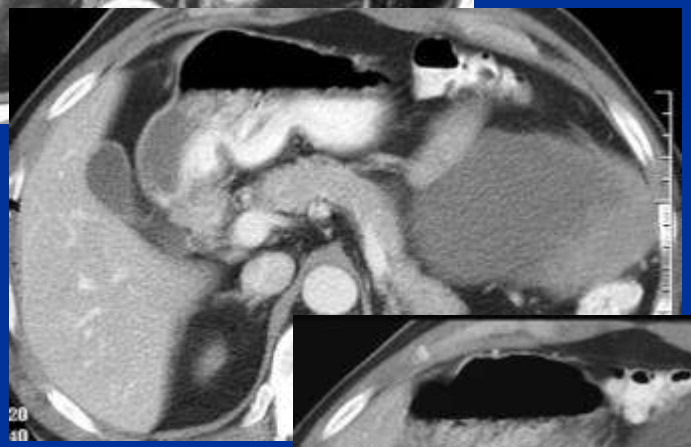

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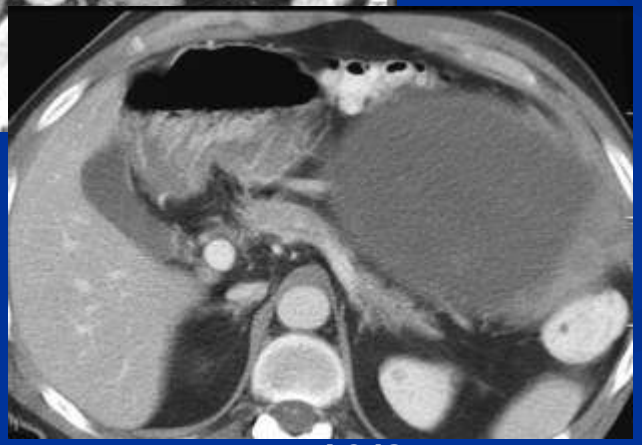
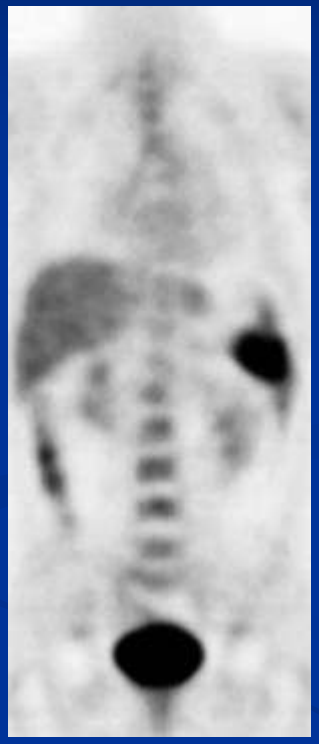


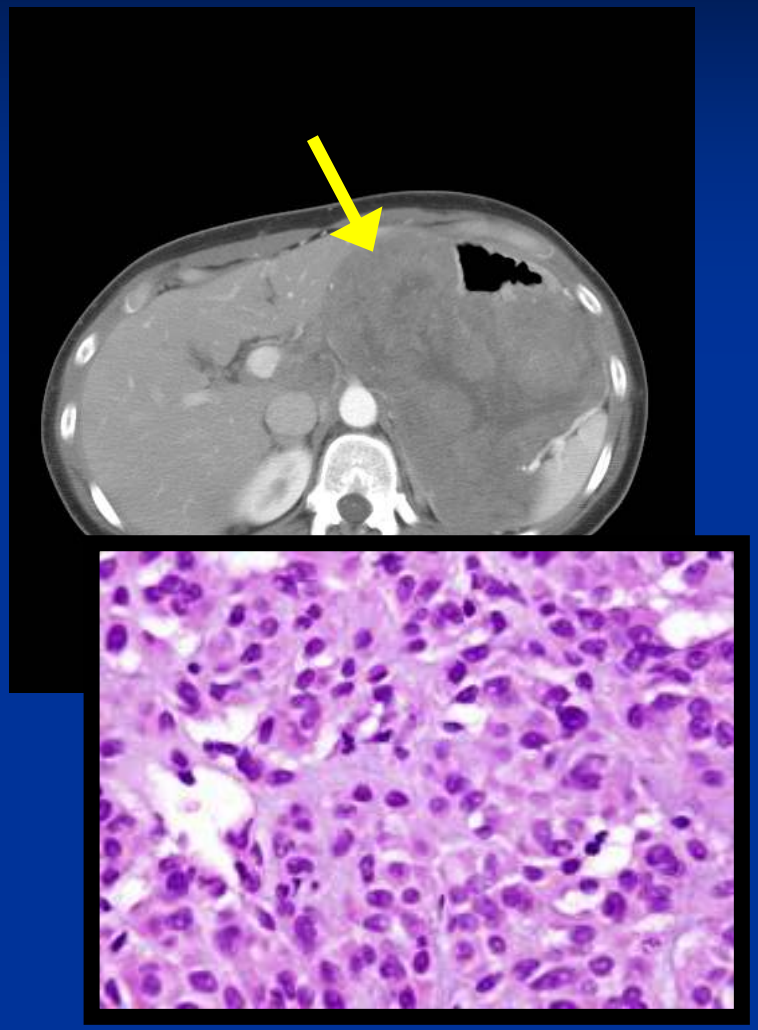
10/8



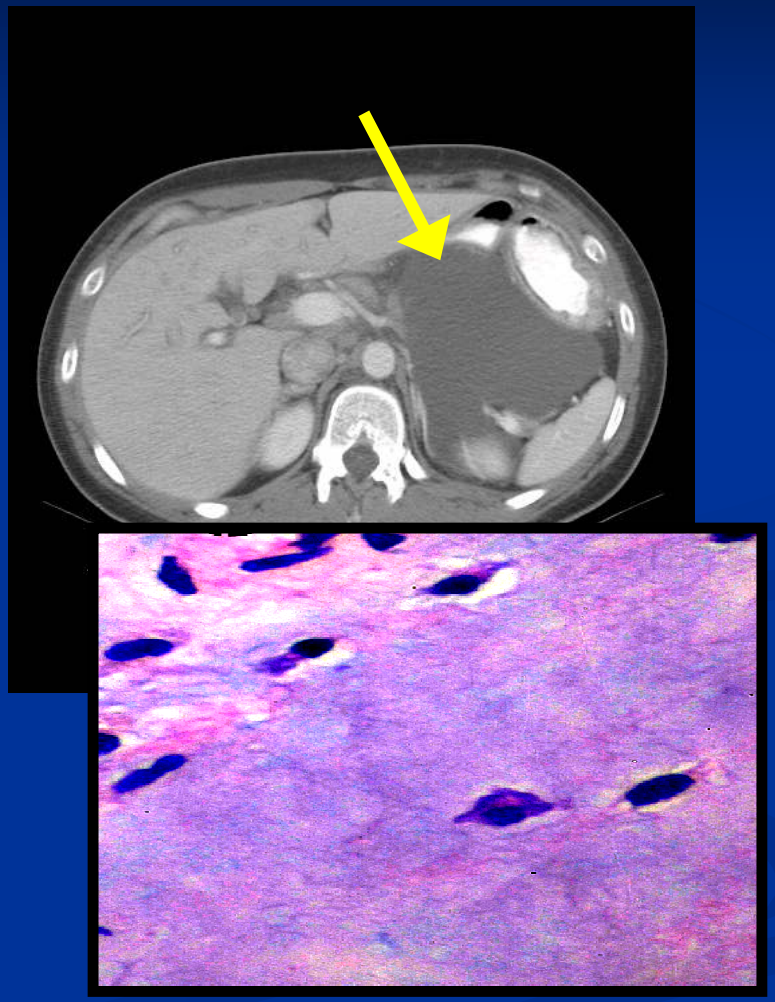
1/26

10/9

Response



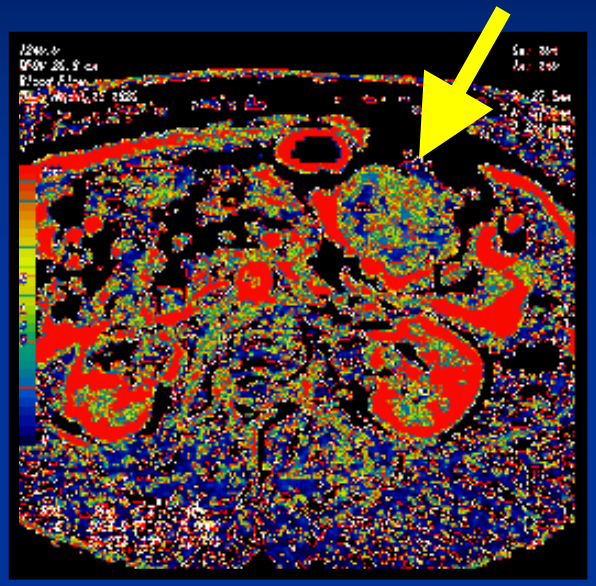
Pre-Imatinib



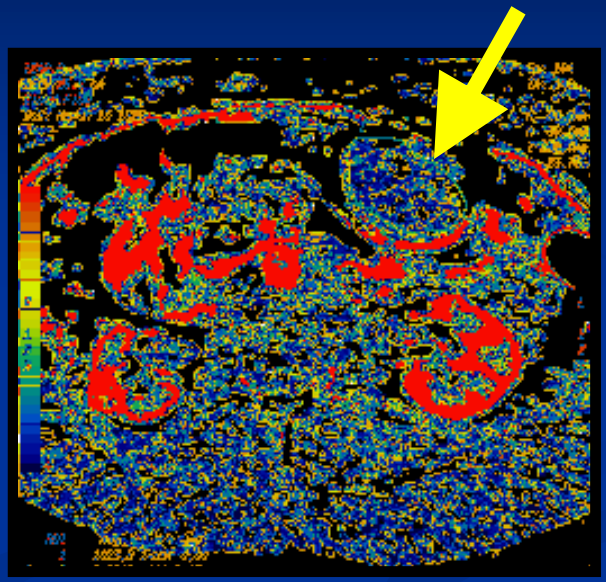
Post-Imatinib (8 weeks therapy)

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

Toxicities

- What are grade 1, 2, 3, and 4 toxicities:
  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
  - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL

Toxicities Continued

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL

Toxicities Continued

- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

Phase III Studies: Control Arm

- Phase III trials are designed to demonstrate the potential advantages of a new therapy over other therapies already on the market
- Why do Phase I and II studies not have a control arm
  - Phase I – Focus is safety of the new drug
  - Phase II – Some do but cost can be an issue

Statistical Considerations

Study Design

Statistical Considerations

- Power: The **power** of a statistical test is the probability that the test will reject the null hypothesis when the null hypothesis is false (i.e. that it will not make a Type II error, or a false negative decision).
- A **type II error**, also known as a **false negative**, occurs when the test fails to reject a false null hypothesis. For example, if a null hypothesis states a patient is healthy, and the patient is in fact sick, but the test fails to reject the hypothesis, falsely suggesting that the patient is healthy.

Statistical Considerations

- Significance: A result is called **statistically significant** if it is unlikely to have occurred by chance.

Statistical Considerations

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

Statistical Considerations

- Confidence Interval: A range around a measurement that conveys how precise the measurement is.
- If independent samples are taken repeatedly from the same population, and a confidence interval calculated for each sample, then a certain percentage (confidence level) of the intervals will include the unknown population parameter. Confidence intervals are usually calculated so that this percentage is 95%, but we can produce 90%, 99%, 99.9% (or whatever) confidence intervals for the unknown parameter.

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

- A Study to Investigate the Safety and Efficacy of AT13387 (HSP inhibitor), Alone or in Combination With Imatinib, in Patients With GIST (phase II)
- Raf inhibitor – Phase II for Raf mutant GIST
- Pazopanib in Imatinib Refractory or Intolerant Gastrointestinal Stromal Tumors (GIST) (Phase II)
- A Study Evaluating STA-9090 in Patients With Metastatic and/or Unresectable Gastrointestinal Stromal Tumor (GIST) (Phase II)

How To Find a Clinical Trial

- Clinicaltrials.gov

Clinical Trials

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SARC Sarcoma Alliance for Research through Collaboration

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