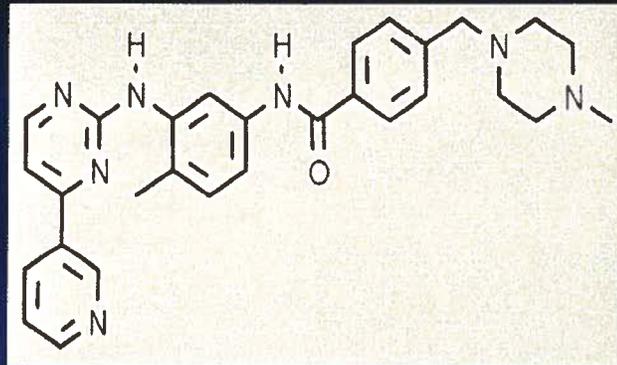


# STI 571

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OHSU



The New England Journal of Medicine – April 5, 2001 – Vol. 344, No. 14

ORIGINAL ARTICLE

## Efficacy and Safety of a Specific Inhibitor of the BCR-ABL Tyrosine Kinase in Chronic Myeloid Leukemia

Brian J. Druker, Moshe Talpaz, Debra J. Resta, Bin Peng, Elisabeth Buchdunger, John M. Ford, Nicholas B. Lydon, Hagop Kantarjian, Renaud Capdeville, Sayuri Ohno-Jones, Charles L. Sawyers

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### Abstract

**Background.** BCR-ABL is a constitutively activated tyrosine kinase that causes chronic myeloid leukemia (CML). Since tyrosine kinase activity is essential to the transforming function of BCR-ABL, an inhibitor of the kinase could be an effective treatment for CML.

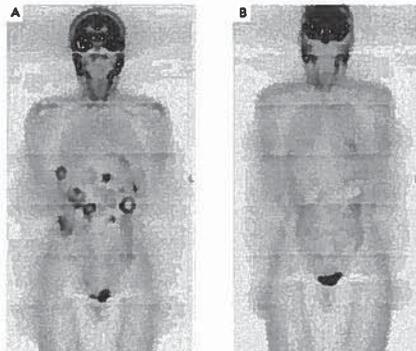
**Methods.** We conducted a phase 1, dose-escalating trial of STI571 (formerly known as CGP 57148B), a specific inhibitor of the BCR-ABL tyrosine kinase. STI571 was administered orally to 83 patients with CML in the chronic phase in whom treatment with interferon alfa had failed. Patients were successively assigned to 1 of 14 doses ranging from 25 to 1000 mg per day.

**Results.** Adverse effects of STI571 were minimal; the most common were nausea, myalgias, edema, and diarrhea. A maximal tolerated dose was not identified. Complete hematologic responses were observed in 53 of 54 patients treated with daily doses of 300 mg or more and typically occurred in the first four weeks of therapy. Of the 54 patients treated with doses of 300 mg or more, cytogenetic responses occurred in 29, including 17 (31 percent of the 54 patients who received this dose) with major responses (0 to 35 percent of cells in metaphase positive for the Philadelphia chromosome); 7 of these patients had complete cytogenetic remissions.

**Conclusions.** STI571 is well tolerated and has significant antileukemic activity in patients with CML in whom treatment with interferon alfa had failed. Our results provide evidence of the essential role of BCR-ABL tyrosine kinase activity in CML and demonstrate the potential for the development of anticancer drugs based on the specific molecular abnormality present in a human cancer. (N Engl J Med 2001;344:1031-7.)

**Brief Report: Effect of the Tyrosine Kinase Inhibitor STI571 in a Patient with a Metastatic Gastrointestinal Stromal Tumor**

Heikki Joensuu, Peter J. Roberts, Maarit Sariomo-Rikala, Leif C. Andersson, Pekka Tervahartiala, David Tuveson, Sandra L. Silberman, Renaud Capdeville, Sasa Dimic-Jovic, Brian Druker, George D. Demetri



PET Studies with [<sup>18</sup>F]Fluorodeoxyglucose as the Tracer.  
Before STI571 therapy (Panel A), there were multiple metastases in the liver and upper abdomen. There was also marked retention of [<sup>18</sup>F]fluorodeoxyglucose in the right renal pelvis and ureter, a finding indicative of hydronephrosis. After four weeks of treatment (Panel B), there was no abnormal uptake of tracer in the liver or right kidney.

## Gastrointestinal Stromal Tumors

- **Although this is a rare disease affecting approximately 1000 patients in the U.S./year, this is a major advance for the following reasons:**
  - **No other therapeutic options exist for these patients**
    - **an extremely active agent is now available in the context of a clinical trial**
  - **This is one of the first examples of a specific molecularly-targeted agent with significant activity in a solid tumor**
  - **This will lead the way for clinical investigations of agents targeted to specific genes or cellular pathways in other solid tumors**

## STI571 Potential Tumor Targets

### c-kit

- GIST#
- Small cell lung cancer ##
- Melanoma ##
- Non-Small cell lung ##
- Seminoma#
- Neuroblastoma ##
- AML
- Breast ##
- (Mastocytosis) #S

### PDGFr

- Glioma ##
- Sarcoma ##
- Gastric ##
- Chronic myelomonocytic leukemia ##
- Non-small cell lung ##
- Ovary ##
- Breast
- Desmoplastic small round cell ##

# = activating mutations

#\$ = activating mutation, but that involving codon 816 is resistant to STI571

## = autocrine regulation

### = constitutively active fusion protein

## STI571 CTEP-Development Plan

### Combinations with other active agents in CML & Ph+ ALL

- Phase 1/2 of STI571 plus Interferon in Patients with CML in Chronic Phase - in review
- Phase 1/2 Trial of STI571 plus High-dose Cytarabine in Myeloid Blast Crisis of CML - in review
- A Phase 1/2 Trial of STI571 plus daunorubicin, vincristine, and decadron in Lymphoid Blast Crisis CML and Ph+ ALL - in review
- Phase 2 Study of STI571 plus low-dose Cytarabine in Patients with chronic phase CML - in review
- Phase 2 Study of Sequential Chemotherapy, STI571 and Transplantation for Adults with Newly Diagnosed Ph-positive Acute Lymphoblastic Leukemia - in development
- Phase 1 Trial of STI571 with Related or Unrelated Donor T-lymphocyte Depleted (Allogeneic) Hematopoietic Stem Cell Transplantation Therapy for CML - in development

### **STI571 CTEP-Development Plan**

#### **Studies in Gastrointestinal Stromal Tumors (GIST)**

- **Phase III Randomized, Intergroup, Trial of two dose levels of STI571 in Patients with Unresectable or Metastatic GIST) - Active**
  - Time from concept to protocol activation was 4 weeks
- **Neoadjuvant/Adjuvant Trial of STI571 in Patients with Potentially Curable High-Risk GIST - in development**

#### **FUTURE TRIALS**

- **Phase II Adjuvant Trial of STI571 in Patients with High-Risk GIST**
- **Phase III Adjuvant Trial of STI571 versus observation in Patients with Potentially Curable Low-Risk GIST**

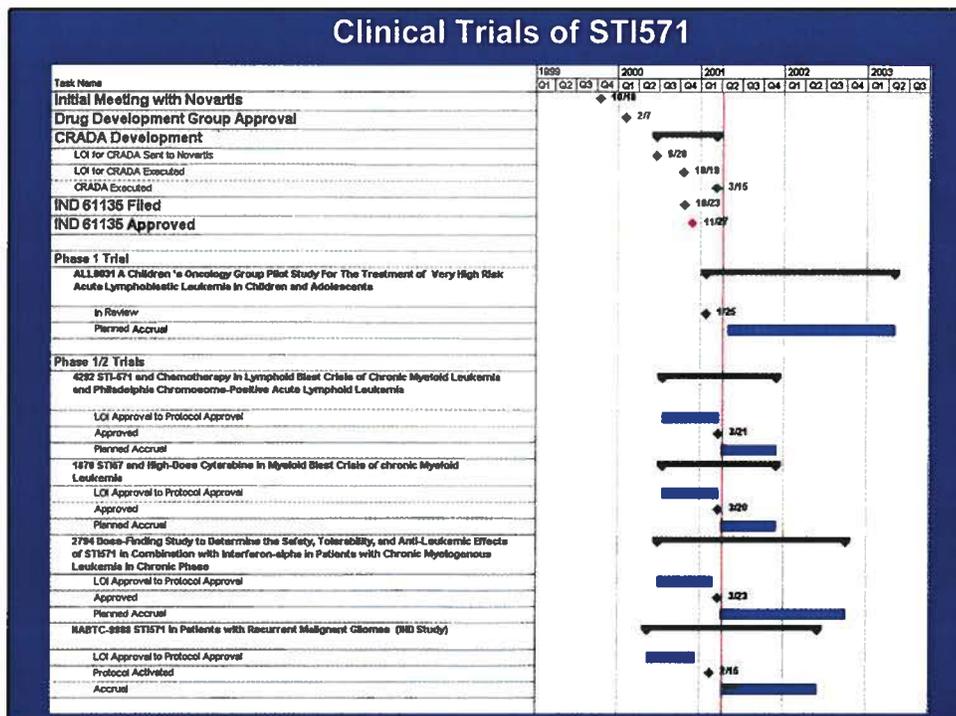
### **STI571 CTEP-Development Plan**

- **Phase 1/2 Trial in Recurrent Malignant Gliomas - approved**
- **Primary endpoints:**
  - **Safety and Pharmacokinetics - Phase 1**
  - **Progression free survival - Phase 2**
    - Given cytostatic activity observed in preclinical glioma model
- **Laboratory correlative studies:**
  - **Immunoassay for bFGF/VEGF in serum**
    - may be modulated by inhibition of PDGFr
  - **Glioma tissue analysis post-treatment for STI571 levels, activated PDGFr, MAP kinase activation, AKT and CREB**

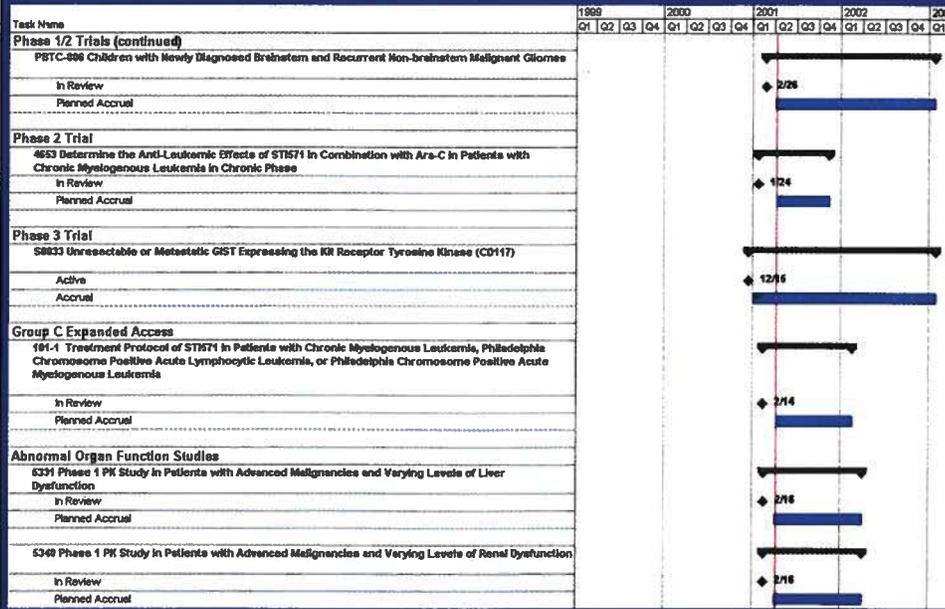
## STI571 CTEP-Development Plan

### Future single agent studies (Phase 2)

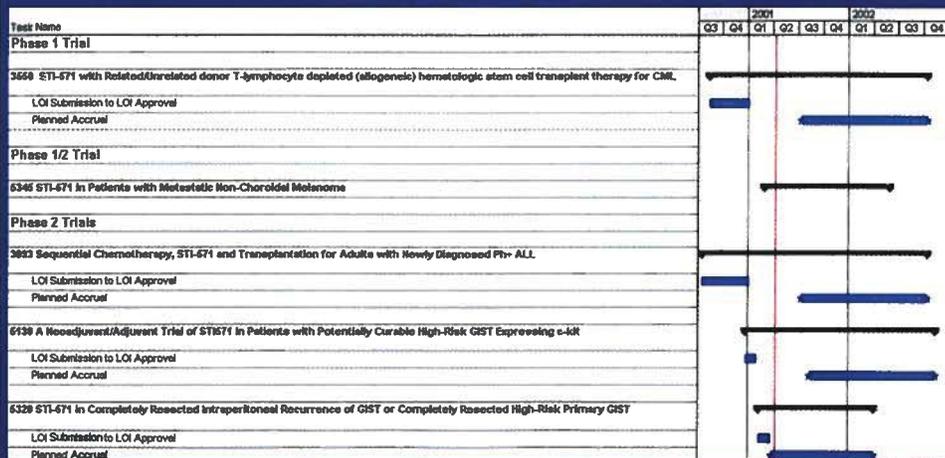
- Small cell lung cancer (c-kit)
  - Extensive disease post chemotherapy
  - Limited disease post chemo/RT
- Germ cell (seminoma) (c-kit)
- Melanoma (c-kit)
- Non-small cell lung (c-kit; PDGF)
- Gastric carcinoma (PDGF)
- Breast (c-kit; PDGF)
- Ovary (PDGFr)
- CMML, PDGFr+ Myeloproliferative Disorders
- AML (c-kit)
- Soft tissue sarcoma (PDGFr)
- Pediatric solid tumors (desmoplastic small cell tumor; neuroblastoma, sarcoma)

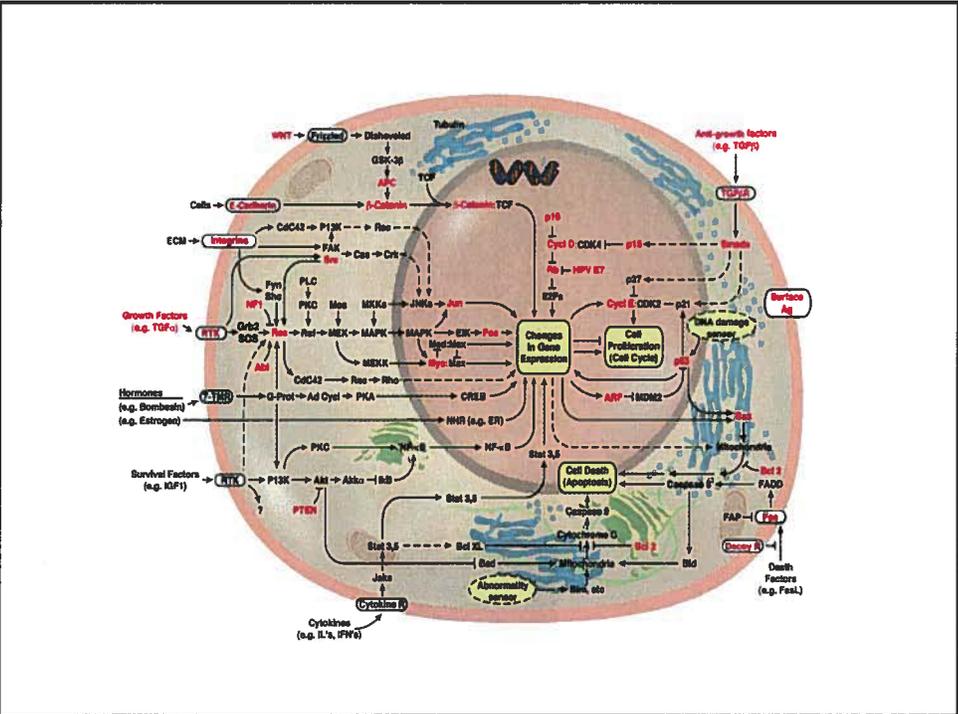
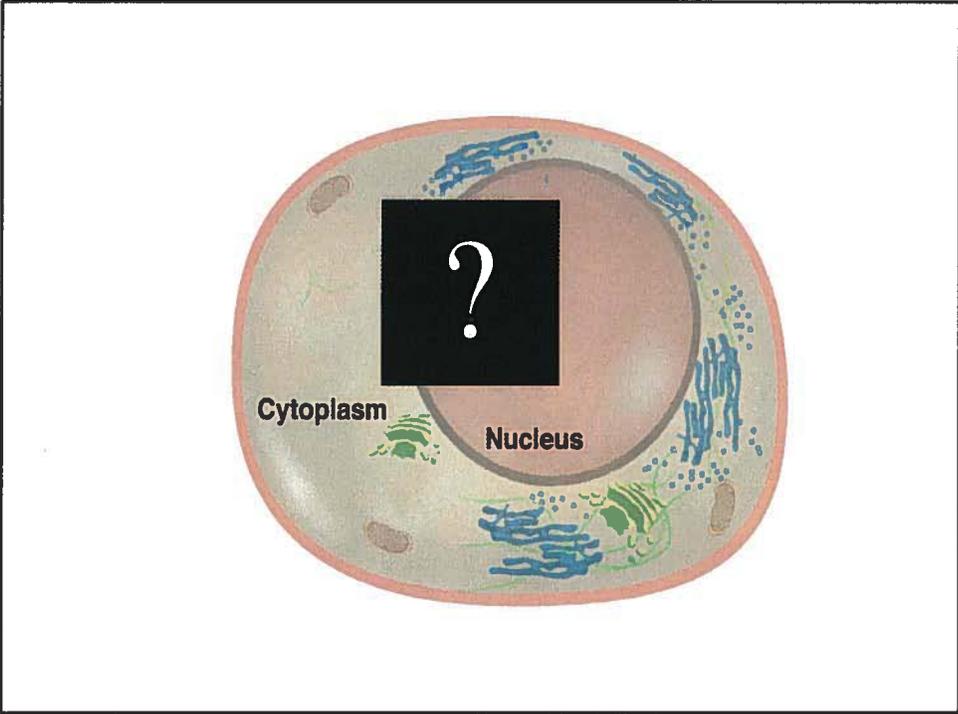


## Clinical Trials of STI571

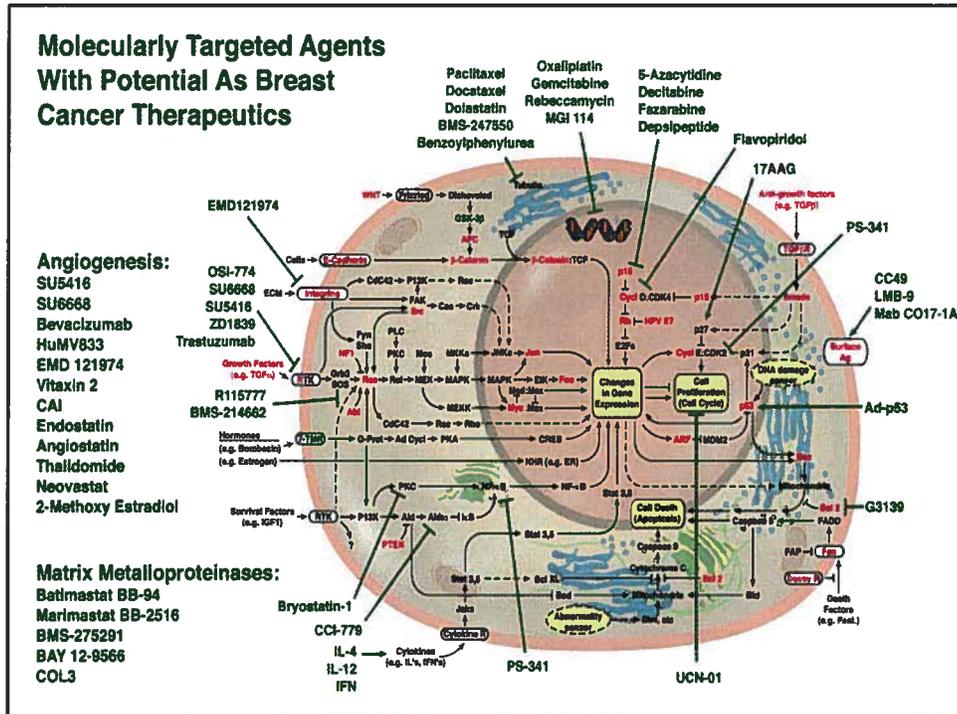


## Letters of Intent for STI571

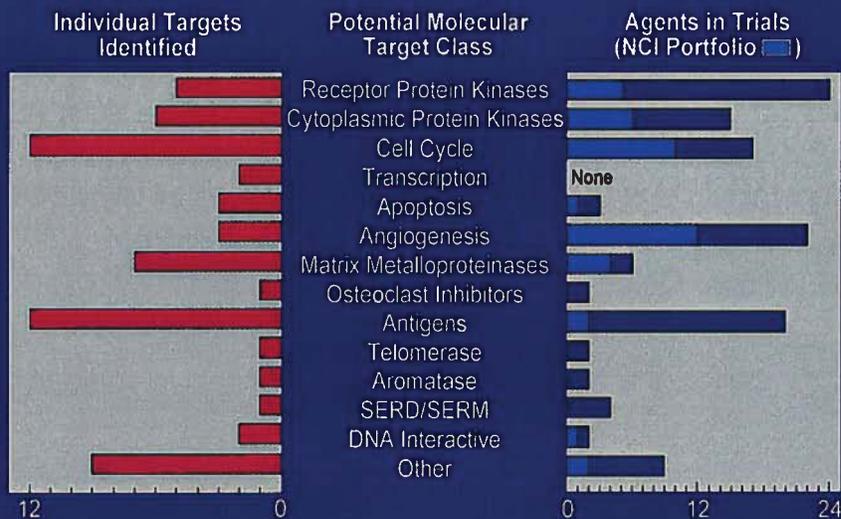


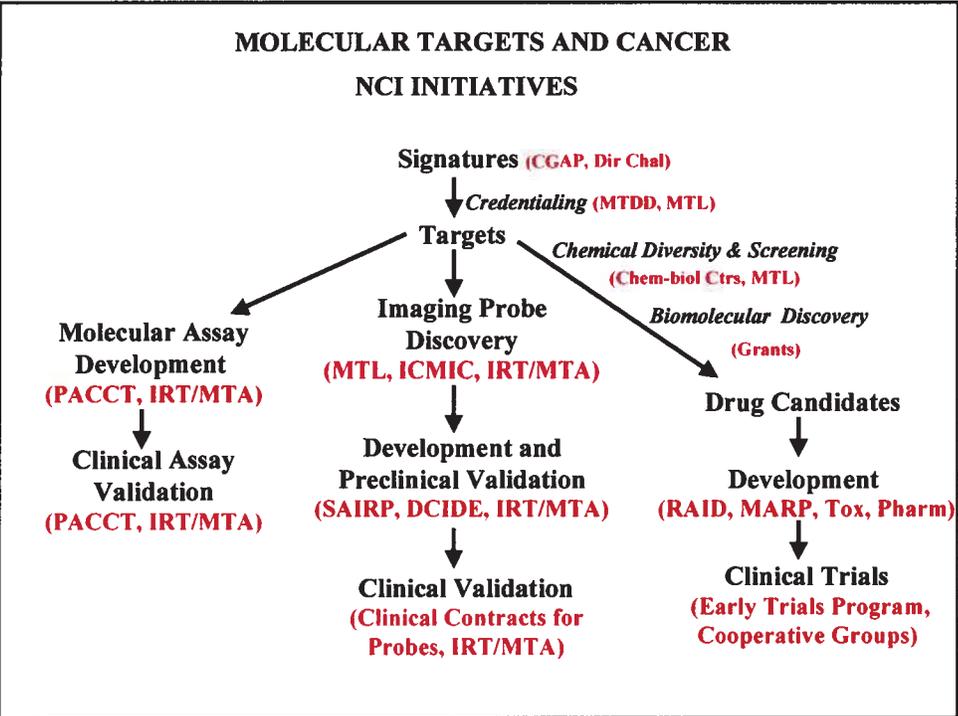
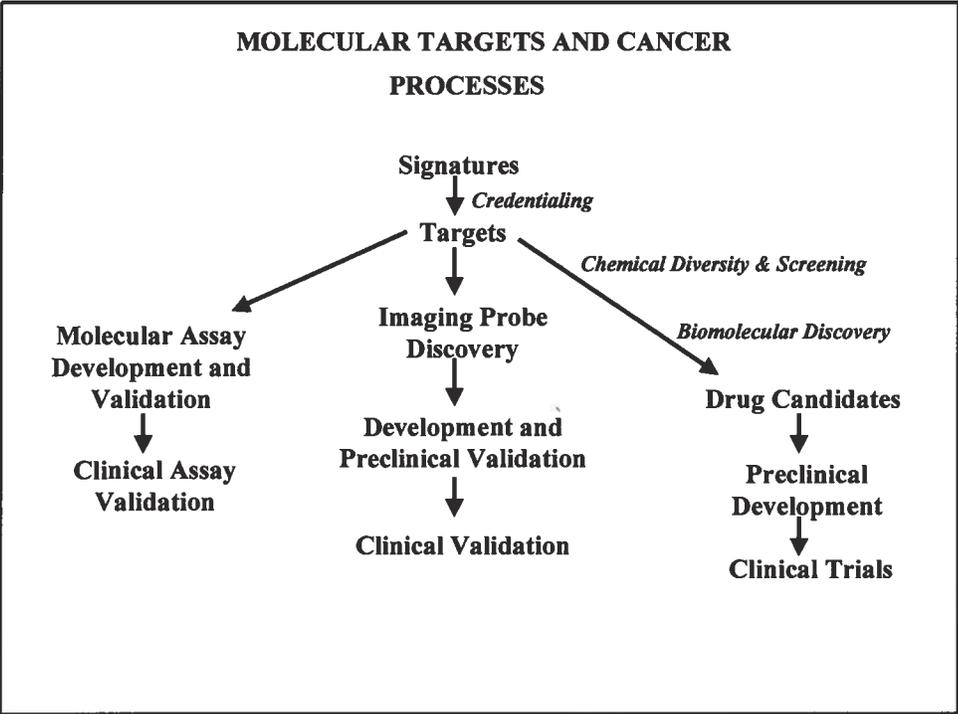


## Molecularly Targeted Agents With Potential As Breast Cancer Therapeutics



## Breast Cancer Molecular Target Class





# **The Cancer Molecular Analysis Project**

## **CMAP**

### **Cancer Genome Anatomy Project**

- Facilitate the interface of genomics and cancer research through the establishment of platform information and technology infrastructures
- Make all project resources accessible through public databases and resource centers



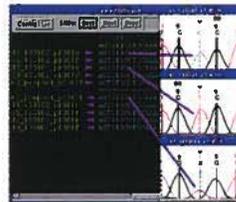
### Tumor Gene Index

A	B	C	D	E	Gene Index	Gene Description
13q1	17p11	17q31	17q32	17q33	BRCA1	Human breast cancer 1 (BRCA1)
17q31	17q32	17q33	17q34	17q35	BRCA2	Human breast cancer 2 (BRCA2)
17q31	17q32	17q33	17q34	17q35	TP53	TP53 tumor suppressor gene (TP53)

### Cancer Chromosome Aberration Project



### Genetic Annotation Initiative



## New CGAP Web Site (<http://cgap.nci.nih.gov>)

**CGAP How To**

The NCI's Cancer Genome Anatomy Project is creating a comprehensive molecular characterization of normal, precancerous, and malignant cells.

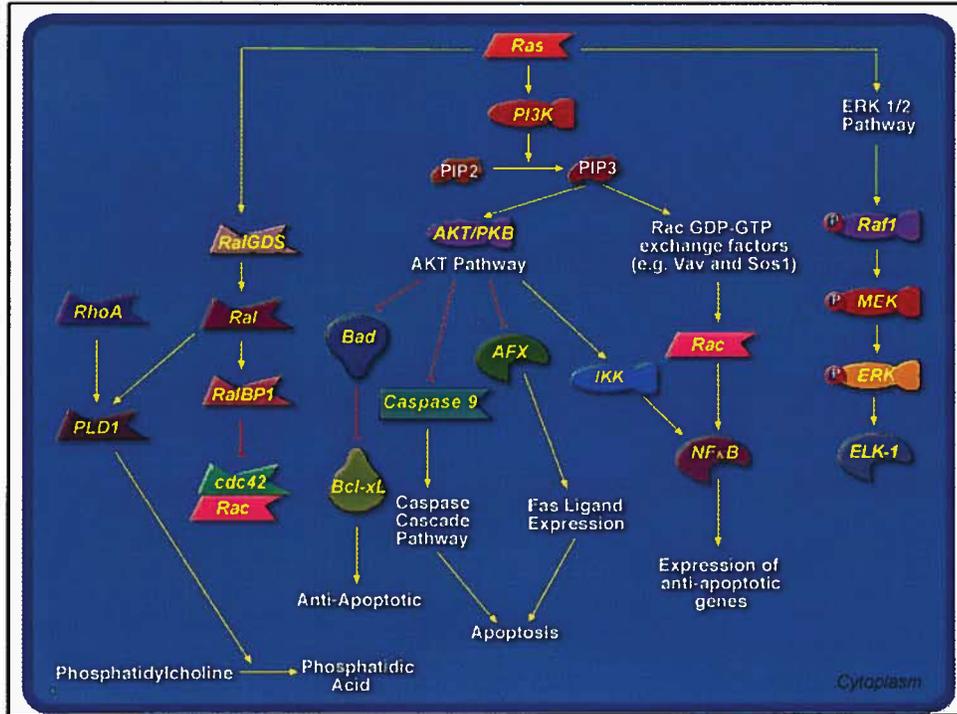
This site is intended to provide cancer researchers access to the information generated by this project. This site contains:

- Genomic data for humans and mouse, including transcript sequences, gene expression patterns, SNPs, clone resources, and cytogenetic information
- Information on methods followed and reagents used in deriving the genomic data and how to obtain them
- Informatics tools to query and analyze the data

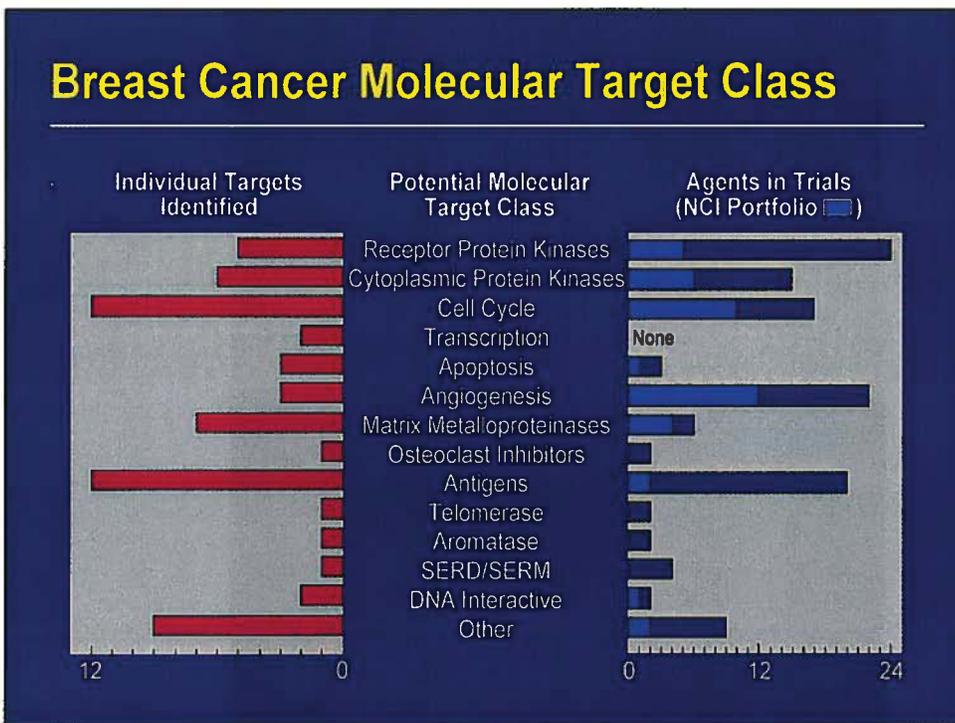
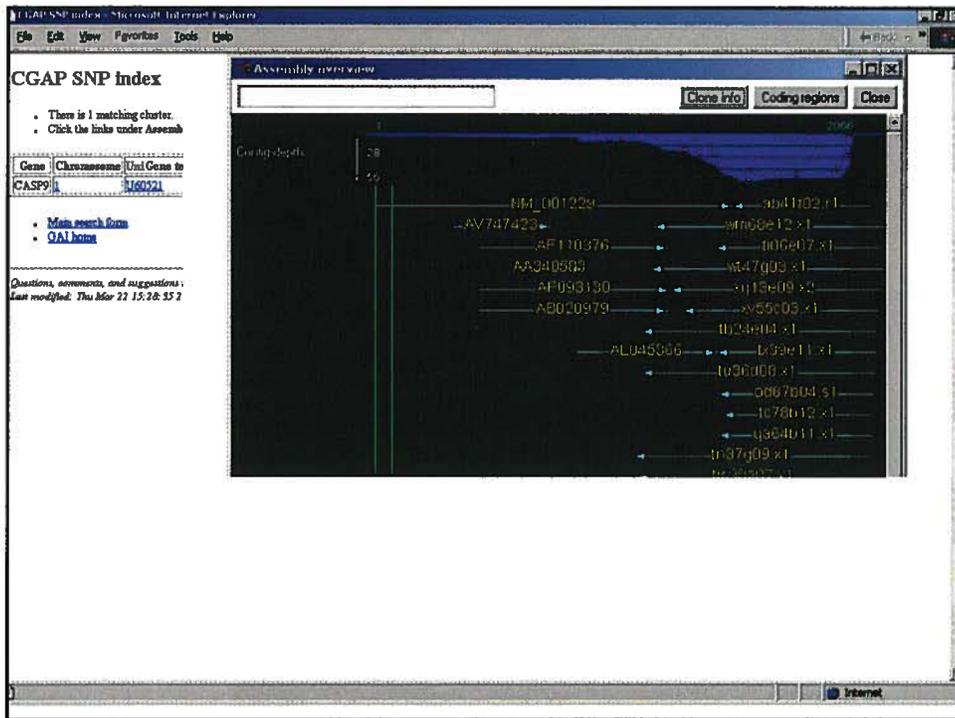
One can access the information resource from multiple, interrelated perspectives:

- Genes**: Detailed information on specific genes and collections of genes
- Chromosomes**: Gene mapping and chromosome aberration information
- Pathways**: Network diagrams of biochemical pathways will be available
- Tissues**: Information on CGAP (and other) cDNA libraries and on gene expression by tissue
- Methods**: Concepts and experimental protocols
- Reagents**: Collections of CGAP-generated laboratory resources
- Tools**: Analytic and data mining tools developed for the project
- CGAP Catalog**: Comprehensive index to all information and resources available at this site





Tissue	ESI Data			SAGE Data		
	Normal	Cancer	Other	Normal	Cancer	Other
adipose	+	+	+	+	+	+
adrenal cortex	+	+	+	+	+	+
adrenal medulla	+	+	+	+	+	+
b-cell	+	+	+	+	+	+
bone	+	+	+	+	+	+
bone marrow	+	+	+	+	+	+
brain	+	+	+	+	+	+
cerebellum	+	+	+	+	+	+
cerebrum	+	+	+	+	+	+
cervix	+	+	+	+	+	+
colon	+	+	+	+	+	+
ear	+	+	+	+	+	+
endocrine	+	+	+	+	+	+
esophagus	+	+	+	+	+	+
eye	+	+	+	+	+	+
gastrointestinal tract	+	+	+	+	+	+
genitourinary	+	+	+	+	+	+
germ cell	+	+	+	+	+	+
head and neck	+	+	+	+	+	+
heart	+	+	+	+	+	+
kidney	+	+	+	+	+	+
liver	+	+	+	+	+	+
lung	+	+	+	+	+	+
lymph node	+	+	+	+	+	+
mammary gland	+	+	+	+	+	+



**The National Cancer Institute's Comprehensive Site  
for Clinical Trials Information Online  
<http://cancertrials.ncl.nih.gov>**



A service of the National Cancer Institute

[Information about  
cancer research studies](#)

[search  
contact us](#)

● **Understanding Trials**

What are clinical trials?  
Deciding whether to participate.

● **Types of Cancer**

Information about specific cancers.

● **Finding Trials**

Locate an ongoing trial.

● **News and Features**

[Prostate Patients May Benefit from Bone-Targeted Drug](#)

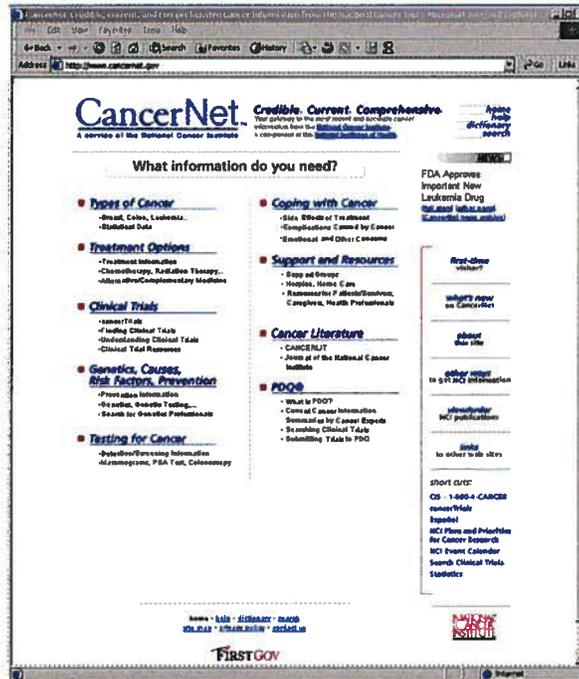
[Cancer Advocates in Research: The Movement Evolves  
More...](#)

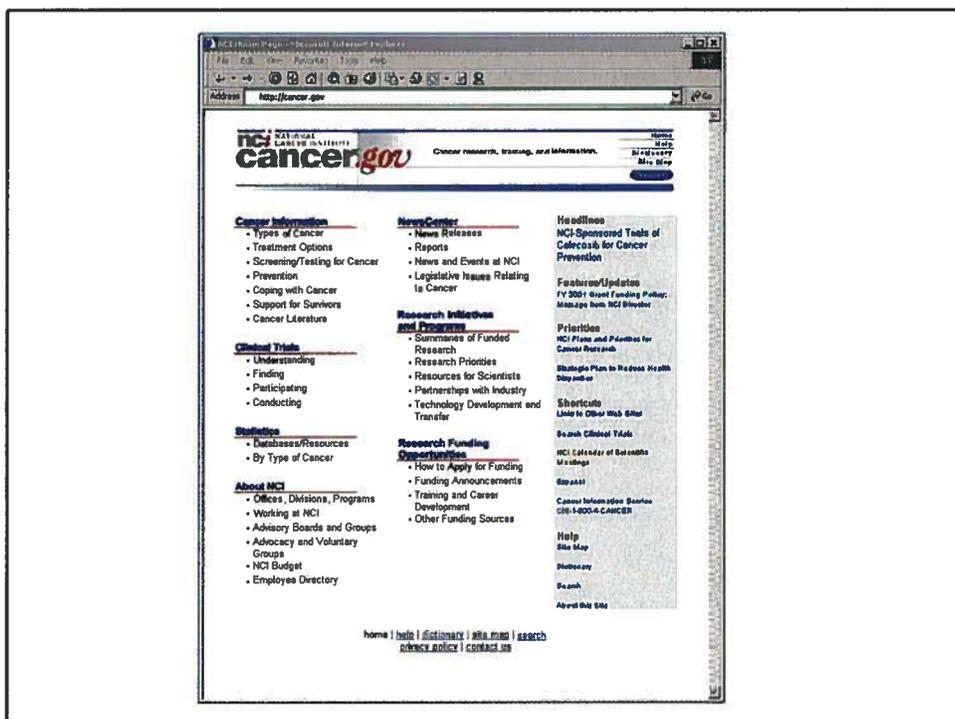
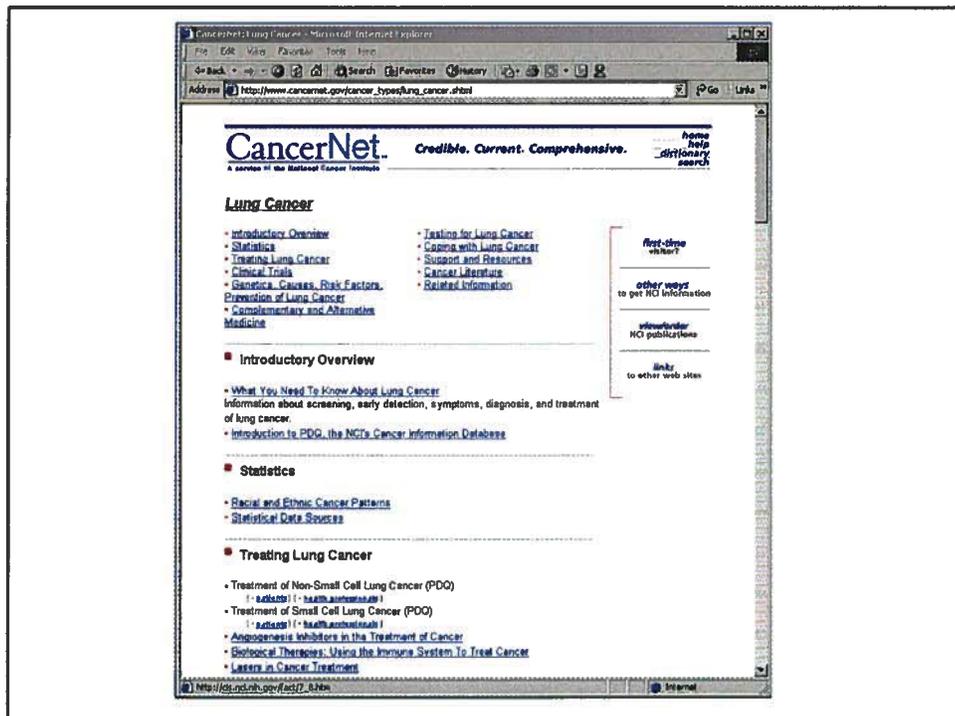
● **Resources for Researchers**

Investigator resources, including  
continuing education.

Most Requested Pages:

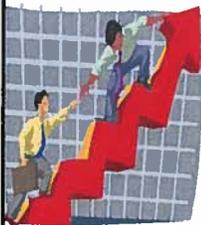
● **Beyond cancerTrials**



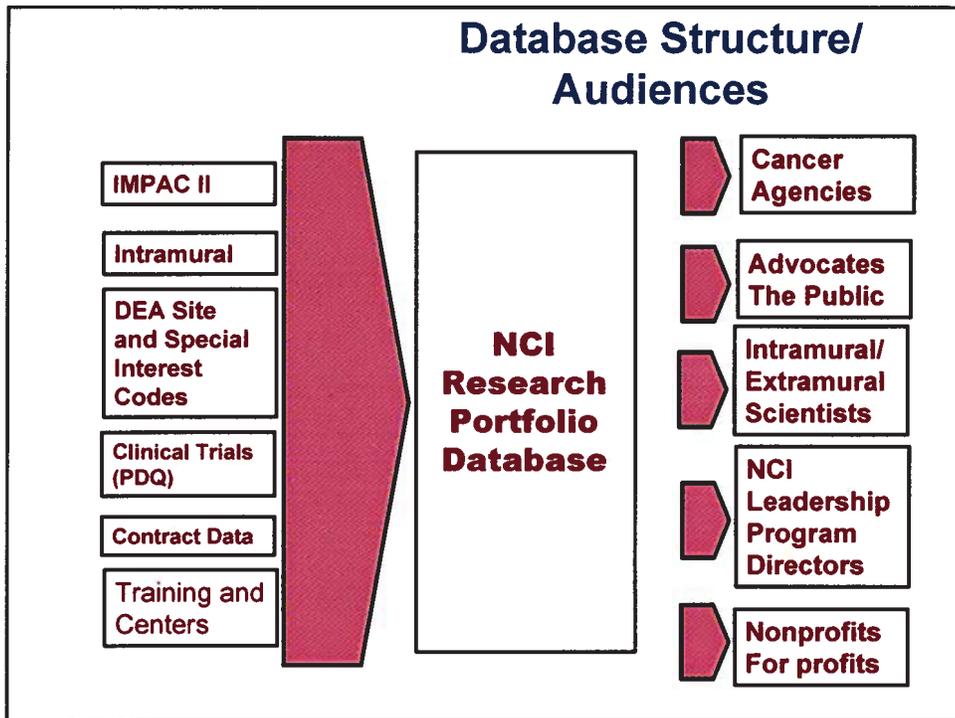


## Cancer Information Service

## Significant Happenings



- **READY TO LAUNCH**
  - All extramural and intramural projects in **ONE** database
  - Coded to Site and CSO
  - Web accessible
  - Includes ER dollars and percent relevance for internal use
  - Training coded to CSO
  - Usability tested



## What Can We Do With This Tool? PRG Portfolio Analyses

- **Search and retrieve research projects by:**
  - Cancer type
  - Scientific category
  - Research mechanism
  - Institution
  - State
  - Year Funded
- **Full Text Search**

**NCI Extramural Brain Tumor Research Portfolio**  
Percent of Projects by Scientific Area  
FY 2000

Scientific Area	Percentage
Treatment	64%
Biology	17%
Early Detection, Diagnosis, Prognosis	11%
Etiology	8%
Prevention	7%
Control, Survivorship, Outcomes Research	2%
Scientific Model Systems	1%

<http://researchportfolio.cancer.gov/>

## Common Scientific Outline Partners

- National Cancer Institute
- Congressionally Directed Medical Research Program (DOD)
- American Cancer Society
- California Breast Cancer Research Program
- Cap CURE
- California Cancer Research Program
- Cancer Research Campaign of the UK
- Medical Research Council of the UK
- Oncology Nursing Society
- Susan G. Komen Breast Cancer Foundation

## CSO Partner Activities

- Significant milestones
  - Data sharing agreement among the CSO Partner organizations
  - Accepted CSO as standard coding tool
  - Changes to CSO frozen until Jan. 2001
  - First round of coding to CSO categories
  - Snapshot of CSO Partner portfolio by CSO category
  - Next steps--code projects to cancer sites

