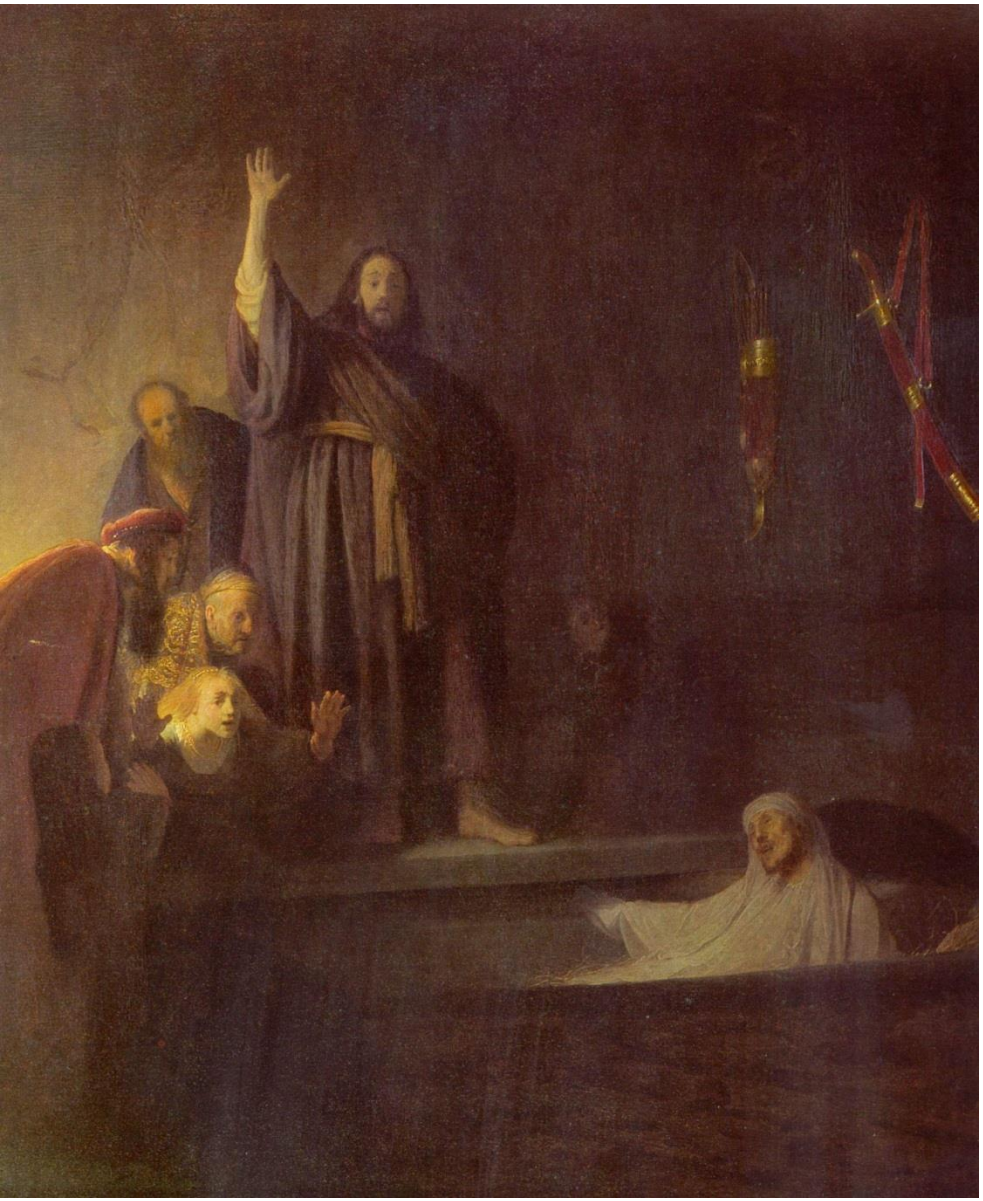
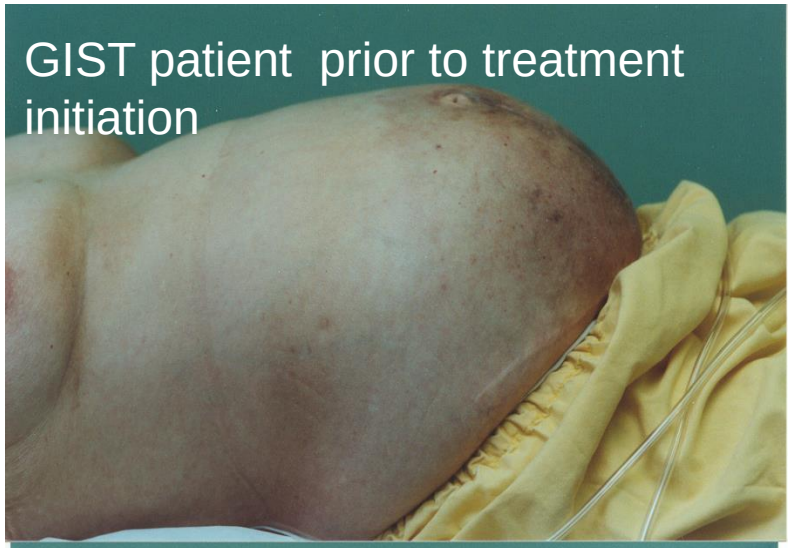


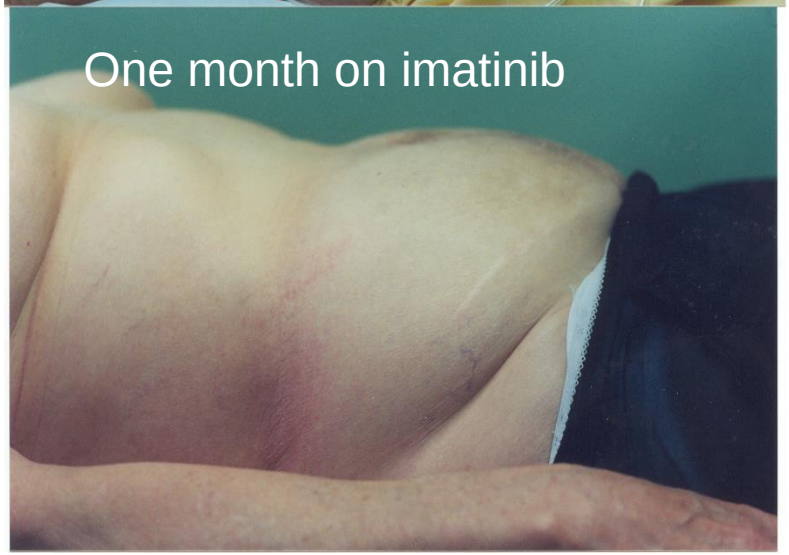
Rembrant, approximately in 1630

From molecular biology to Lazarus responses

Heikki Joensuu
University of Helsinki &
Helsinki University Central Hospital

”Lazarus response”





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JOURNAL OF CLINICAL ONCOLOGY

E D I T O R I A L

The “Lazarus Response” in Treatment-Naïve, Poor Performance Status Patients With Non–Small-Cell Lung Cancer and Epidermal Growth Factor Receptor Mutation

Corey J. Langer, *Thoracic Oncology, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA*

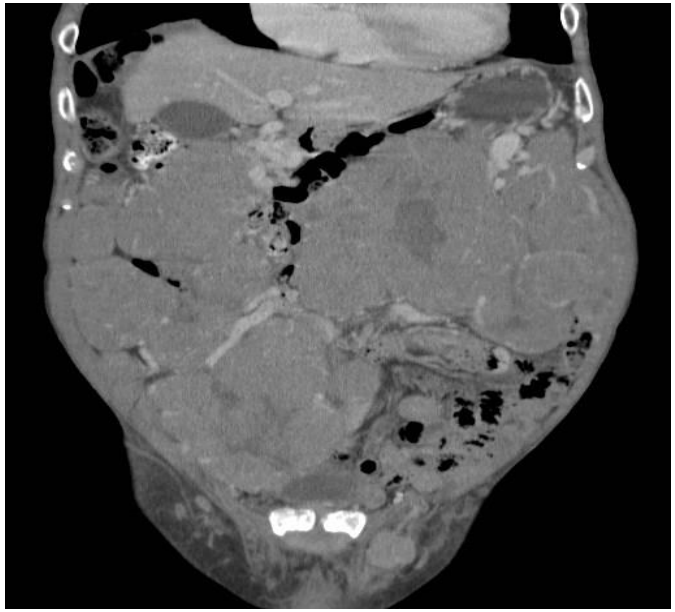
BACKGROUND: PERFORMANCE STATUS 2 PATIENTS WITH NON–SMALL-CELL LUNG CANCER

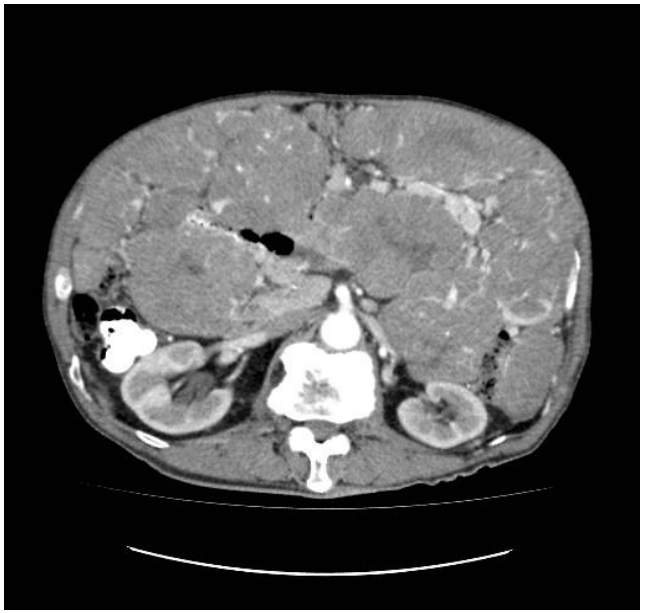
In a series of more than 500 non–small-cell lung cancer (NSCLC)

Baseline comorbidities and anticipated toxicities are a major impediment to more aggressive therapy in poor PS patients with NSCLC. For example, work by LeChevalier et al comparing vinorelbine, either alone or in combination with cisplatin, to vindesine and

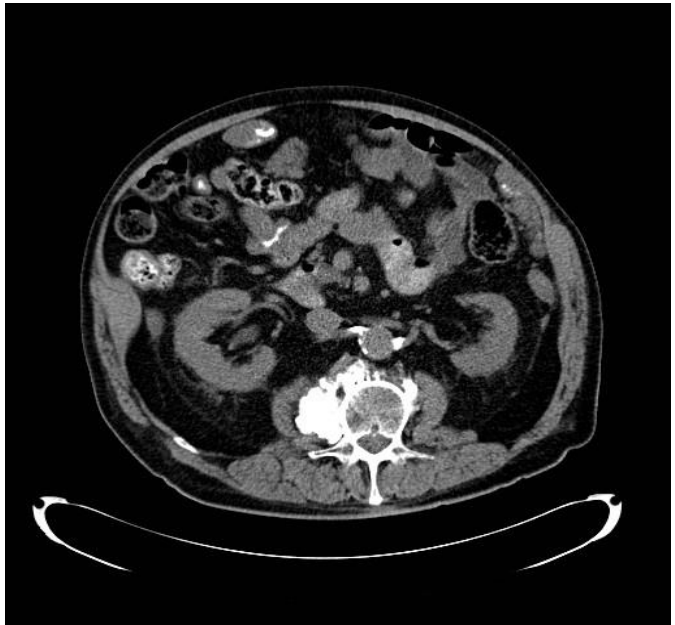
Lazarus responses may be durable

A patient with many bulky GIST metastases at presentation





The same patient with ongoing response; 4 years on imatinib



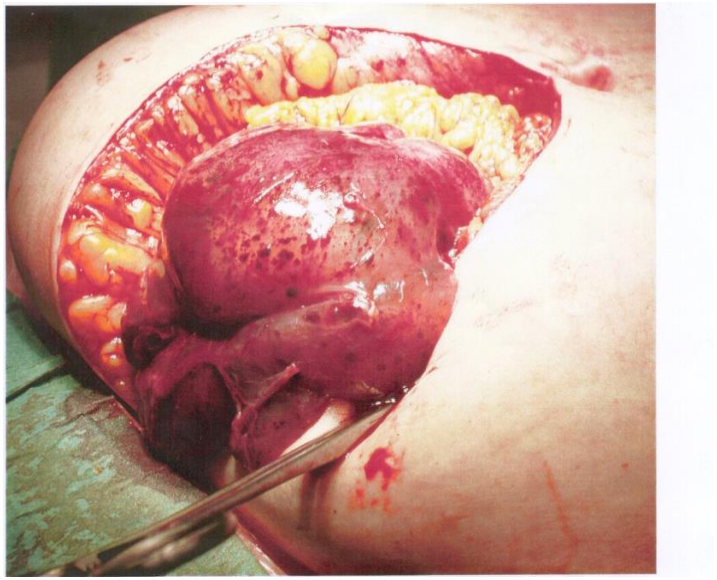
Survival prior to the era of targeted therapies

- Patients with metastatic disease had median survival of only 10 to 20 months in the 1990's
- Conventional chemotherapy had little efficacy[1]

[1]Plaat BE et al. J Clin Oncol 2000; 18:3211-20.

Gastrointestinal stromal tumour (GIST)

•The first solid tumour where a tyrosine kinase inhibitor proved highly effective (imatinib)



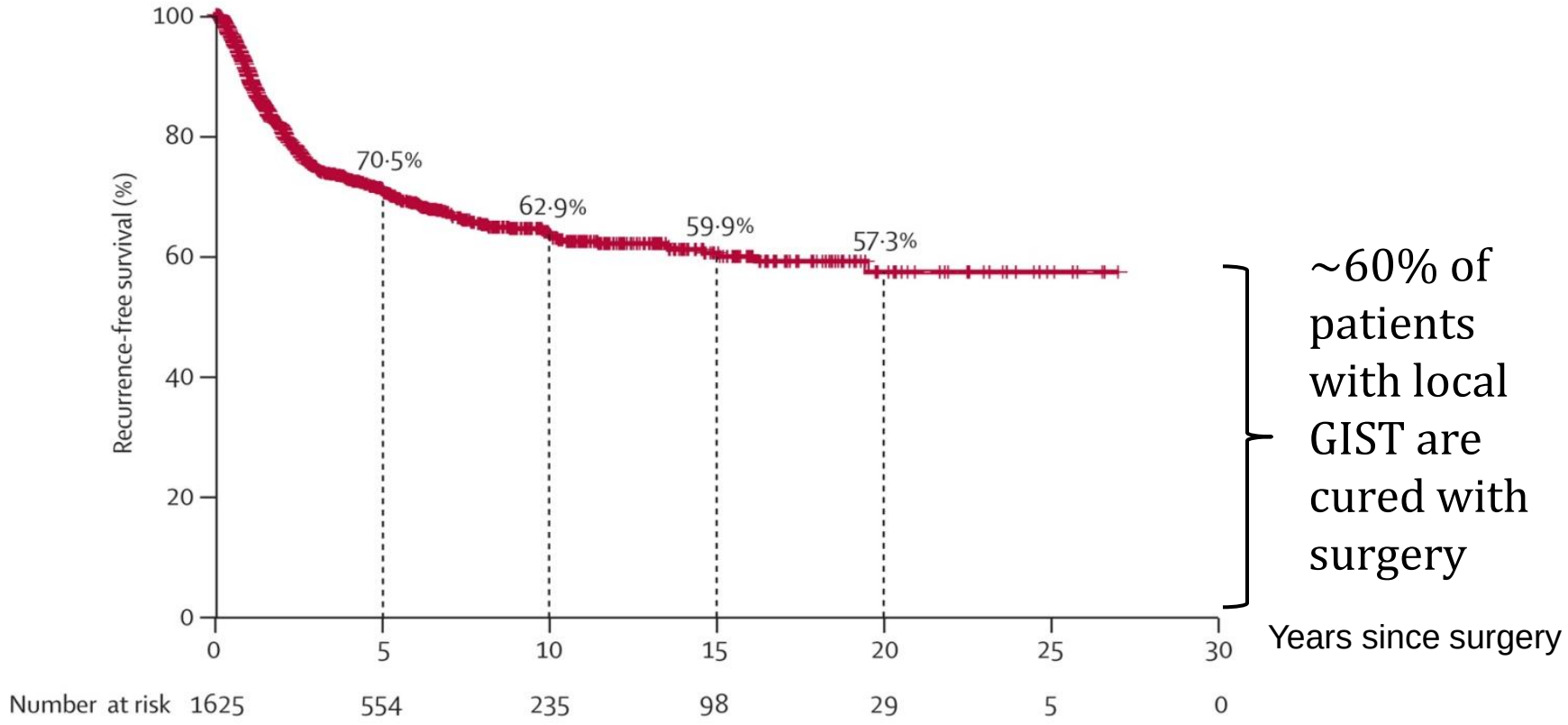
The most common type of soft tissue sarcoma[1]

Annual incidence 10 cases per million[2]

[1]Ducimetière F et al. PLoS One 2011; 6:e20294; [2]Nilsson et al. Cancer 2005; 103:821-9.

GISTs frequently give rise to metastases

- 10-20% of patients present with distant metastases
- 40% of local GISTs give rise to metastases during follow-up

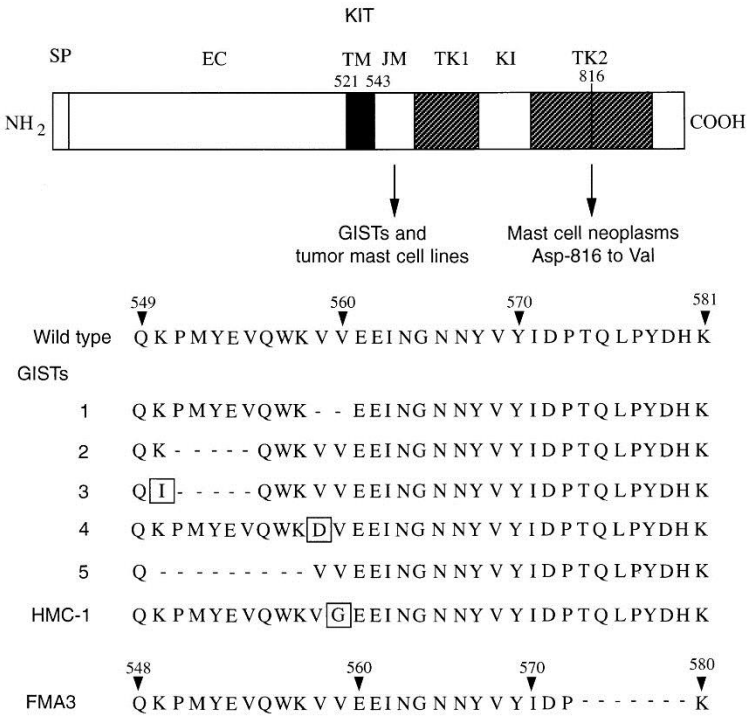


Pooled data from 10 population-based series. Joensuu et al. Lancet Oncol 2012; 13:265-74.

Mutations in *KIT* oncogene discovered

- Hirota et al. found activating *KIT* mutations in GIST at Osaka University in 1998[1]
- *KIT* encodes KIT receptor tyrosine kinase (ligand, stem cell factor)

Prof. Seiichi Hirota



[1]Hirota S et al. Science1998; 279:577-80.

STI-571 (inhibitor of BCR-ABL and KIT) found highly effective for chronic myeloid leukemia

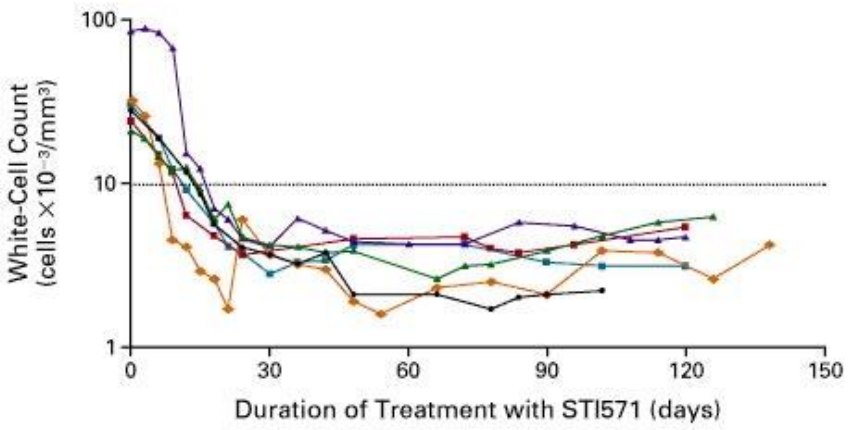
The New England
Journal of Medicine

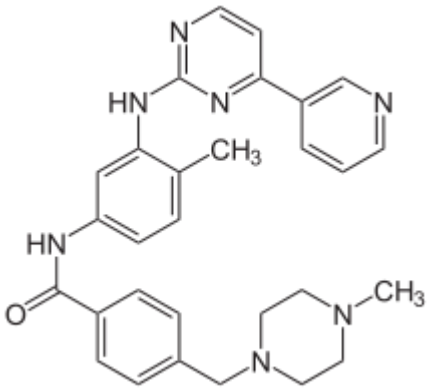
VOLUME 344 APRIL 5, 2001 NUMBER 14

EFFICACY AND SAFETY OF A SPECIFIC INHIBITOR OF THE BCR-ABL TYROSINE KINASE IN CHRONIC MYELOID LEUKEMIA

BRIAN J. DRUKER, M.D., MOSHE TALPAZ, M.D., DEBRA J. RESTA, R.N., BIN PENG, PH.D., ELISABETH BUCHDUNGER, PH.D., JOHN M. FORD, M.D., NICHOLAS B. LYDON, PH.D., HAGOP KANTARJIAN, M.D., RENAUD CAPDEVILLE, M.D., SAYURI OHNO-JONES, B.S., AND CHARLES L. SAWYERS, M.D.


Brian Druker





STI-571
(imatinib)

Brief Report

Effect of the Tyrosine Kinase Inhibitor STI571 in a Patient with a Metastatic Gastrointestinal Stromal Tumor

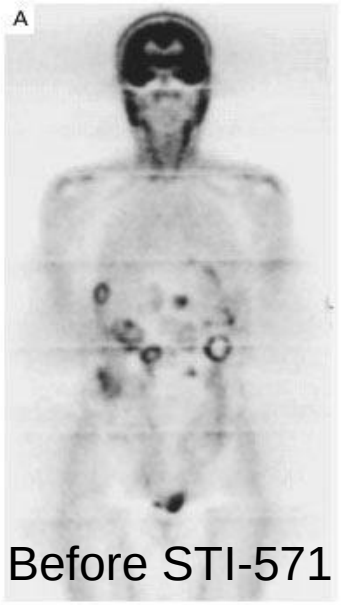
Heikki Joensuu, M.D., Peter J. Roberts, M.D., Maarit Sarlomo-Rikala, M.D., Leif C. Andersson, M.D., Pekka Tervahartiala, M.D., David Tuveson, M.D., Ph.D., Sandra L. Silberman, M.D., Ph.D., Renaud Capdeville, M.D., Sasa Dimitrijevic, Ph.D., Brian Druker, M.D., and George D. Demetri, M.D.

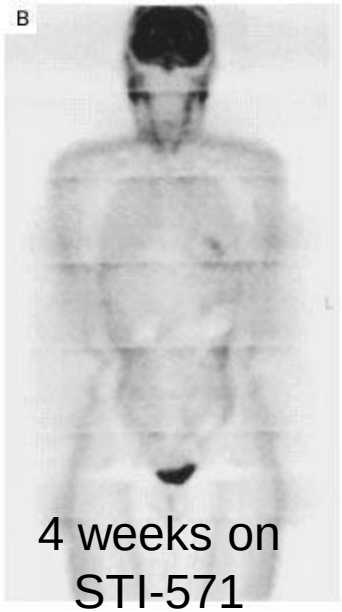
phosphatidylinositol 3-kinase and mitogen-activated protein kinases. Gastrointestinal stromal tumors are notoriously unresponsive to cancer chemotherapy, and there is no effective therapy for advanced, metastatic disease.[6]

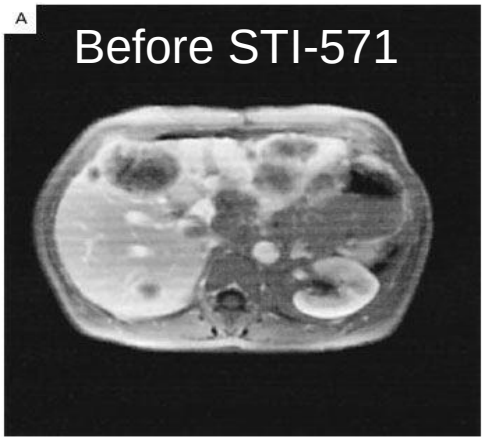
We used STI571 (Glivec, Novartis, Basel, Switzerland),[7] an inhibitor of the tyrosine kinase activity of c-kit, in a patient with a gastrointestinal stromal tumor.

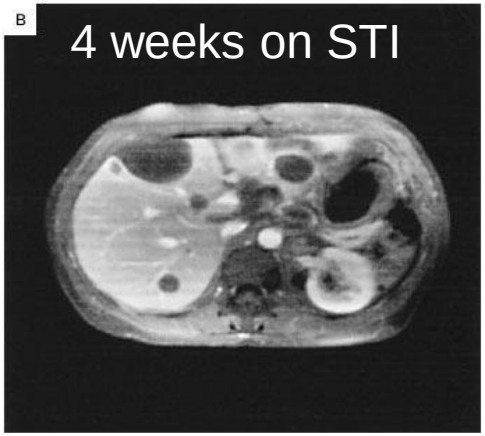
CASE REPORT

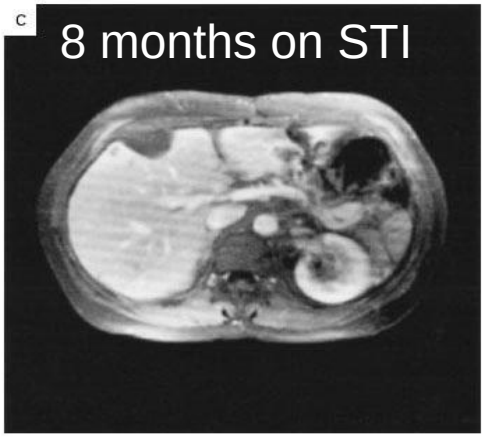
In October 1996, a 50-year-old, previously healthy woman presented with mild abdominal discomfort and a large mass in the upper abdomen. Two tumors, 6.5 and 10 cm in diameter, were removed from the stomach by proximal gastric resection, and the greater omentum and mesocolic peritoneum were removed because of the presence of multiple metastatic nodules 1 to 2 mm in diameter. Histologic examination of the specimens revealed more than 20 cells undergoing mitosis per 10 high-power fields and identified the masses as a gastrointestinal stromal tumor. The diagnosis was confirmed by immunostaining for CD117, and a c-*kit* mutation consisting of a deletion of 15 bp from exon 11 was de-









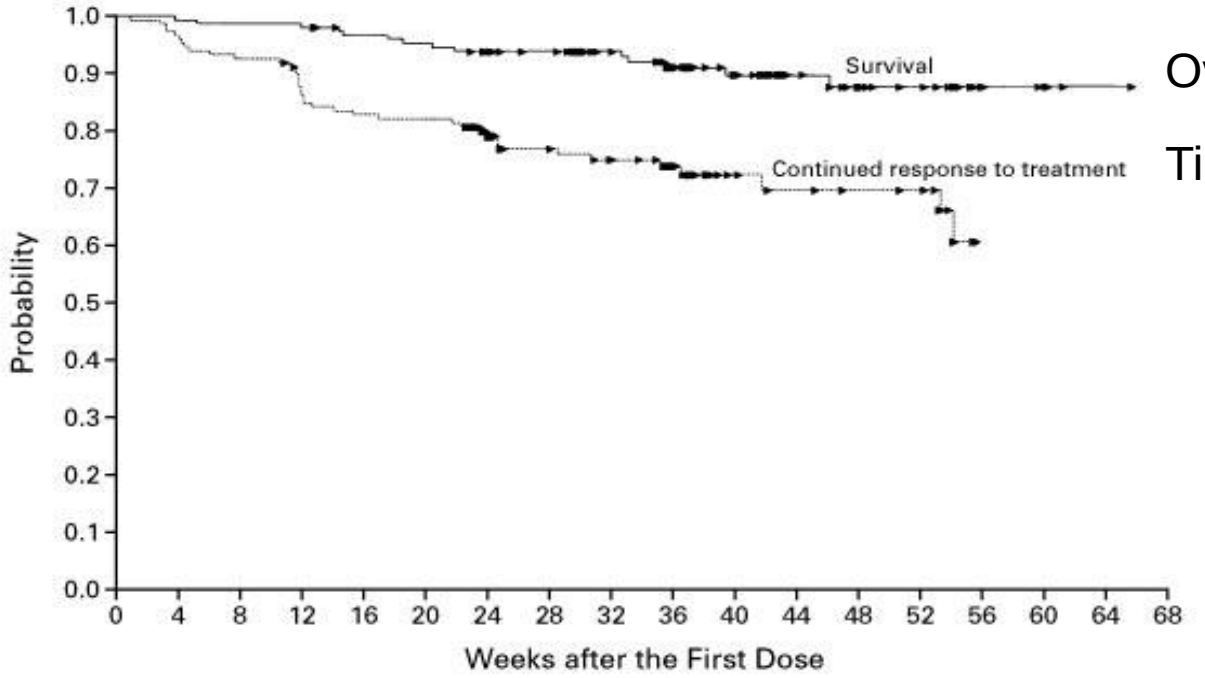


N Engl J Med 2001;344:1052-6.

Imatinib (STI-571) proved to be the first highly effective agent for advanced GIST

The B2222 (the U.S. – Finland trial)

- •120 (85.7%) out of the 140 evaluable patients responded or had stable disease
- • Most responses were durable
- • Therapy was generally well tolerated



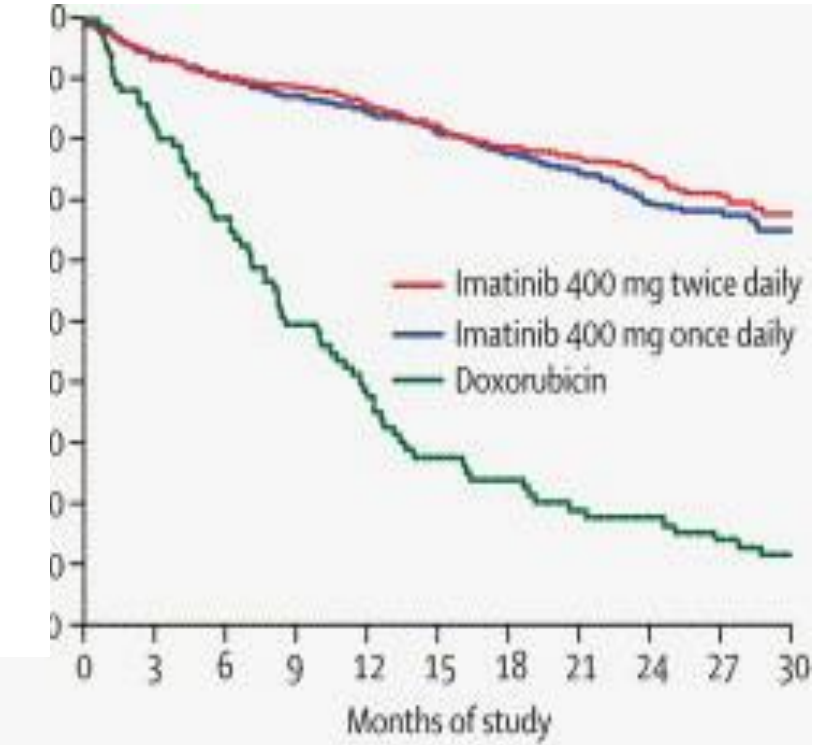
Overall survival

Time to treatment failure

Demetri GD et al.
N Engl J Med
2002; 347:472-80.

A randomised trial comparing imatinib to chemotherapy was never conducted

• Comparisons with historical data suggested substantially improved outcome in advanced GIST



Comparison of 2 imatinib groups with historical GIST controls treated with doxorubicin-based chemotherapy (from the EORTC database)

Verweij et al. Lancet 2004; 364:1127-34.

Up to 30% of patients with advanced GIST survive for ≥10 years in the era of targeted therapy

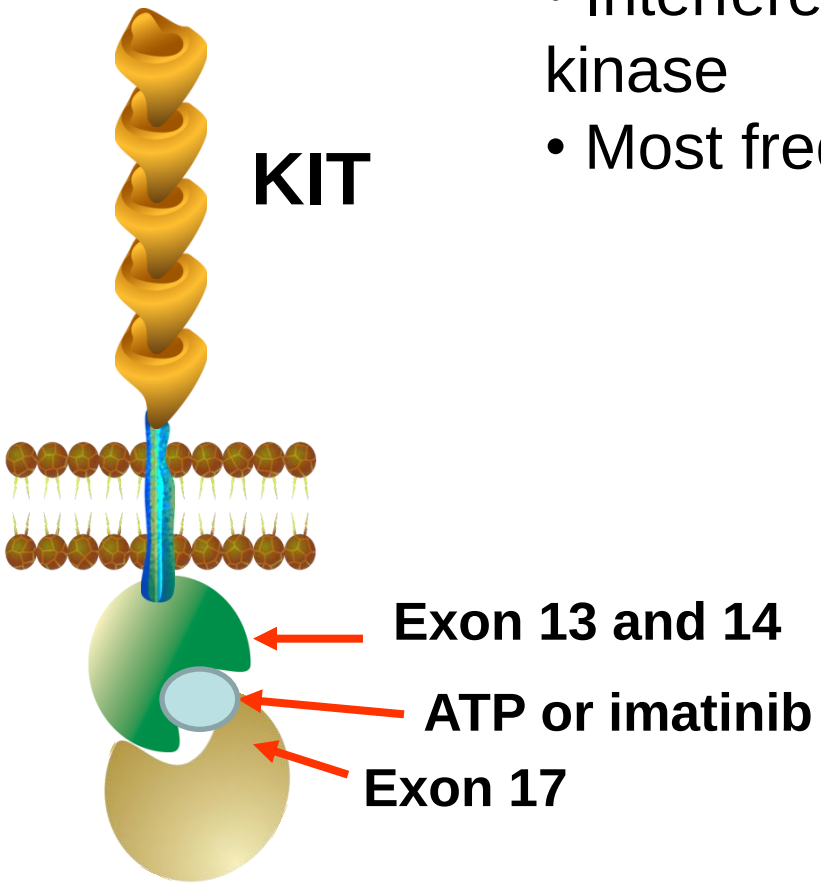
Series	Overall survival (OS) estimate
B2222 trial[1]	9-year OS 35%*
S0033 trial[2]	10-year OS 22%
Helsinki series	10-year OS 29%

*58% of patients with the tumour bulk within the lowest quartile survived for 9 years

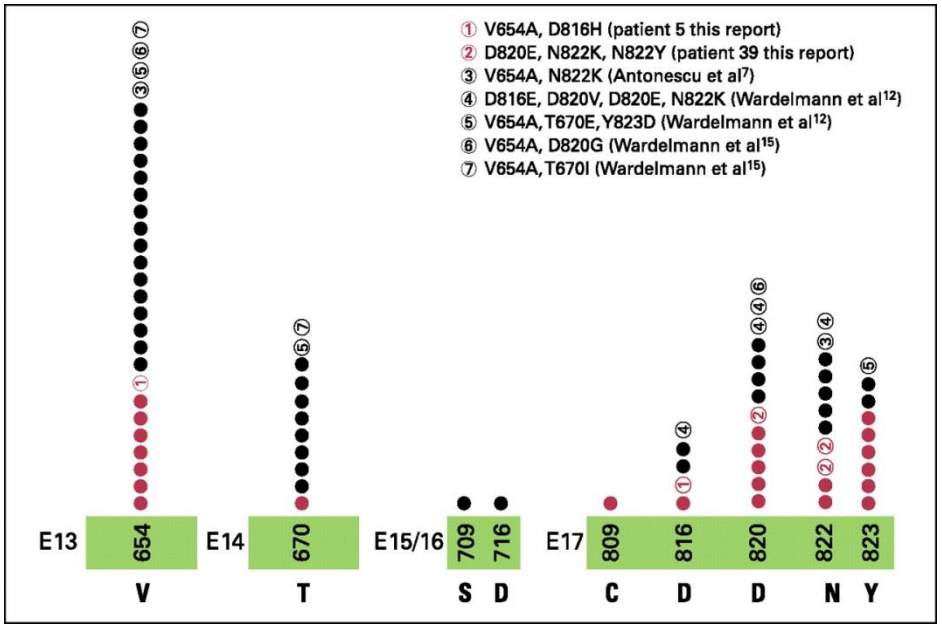
- A small tumour bulk identified as a favourable prognostic factor for long-term survival

[1]von Mehren et al. JCO 2011; 29:609s; [2]Demetri et al. JCO 2014; 32:670s

Secondary *KIT* mutations are the most important cause for treatment failure



- Interfere with imatinib binding to the kinase
- Most frequent in *KIT* exons 13, 14 and 17



Heinrich MC et al. JCO 2006;24:4764-74

Secondary mutations leading to drug resistance

- May occur by chance
- The time to drug resistance likely the shorter the greater the number of tumour cells
  - Early and long enough TKI treatment leads to survival benefits?

Adjuvant imatinib in GIST: Randomised trials

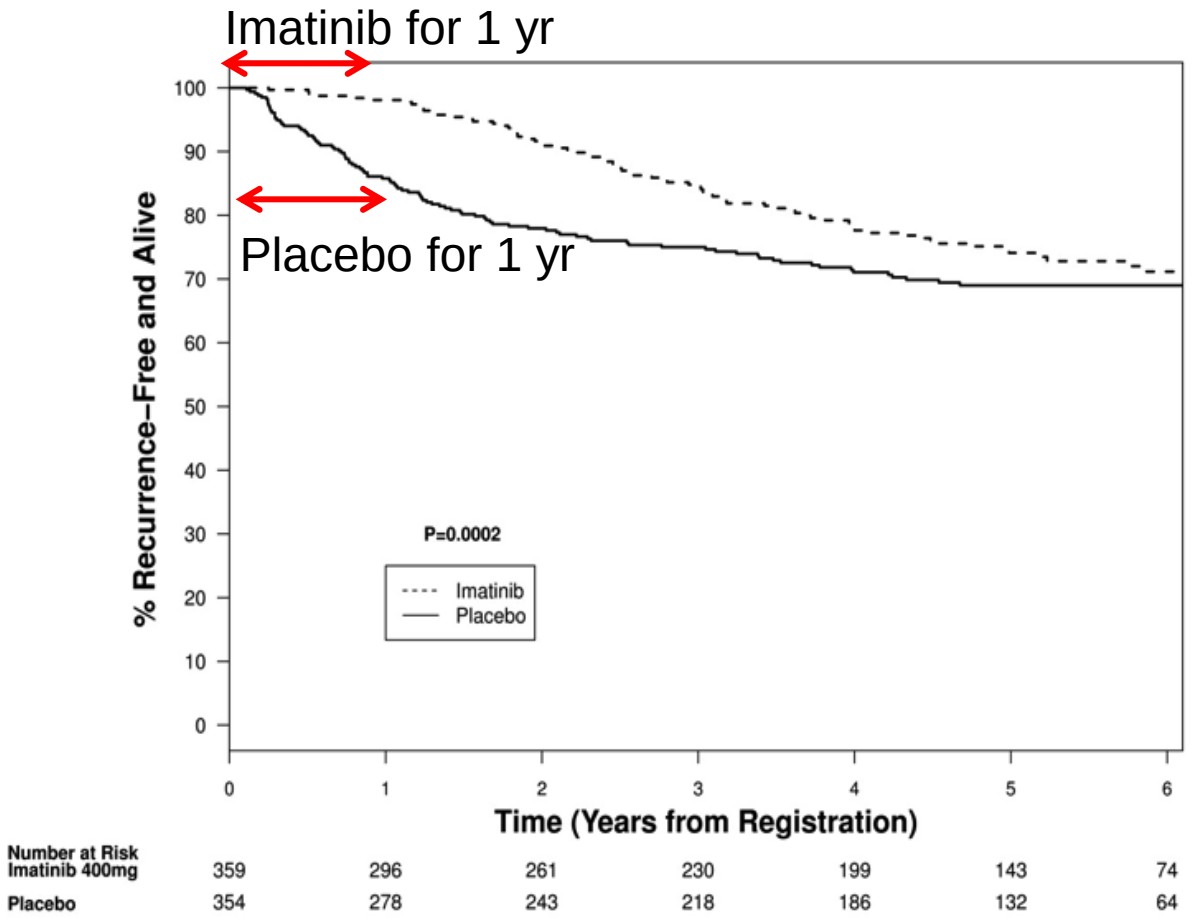
- ACOSOG Z9001[1,2]
  - 1 year of imatinib vs. placebo
- EORTC 62024[3]
  - 2 years of imatinib vs. observation
- SSG/AIO XVIII[4]
  - 1 vs. 3 years of imatinib

ACOSOG, American College of Surgeons Oncology Group
EORTC, European Organisation for Research and Treatment of Cancer
SSG, Scandinavian Sarcoma Group
AIO, Arbeitsgemeinschaft Internistische Onkologie

[1]DeMatteo et al. Lancet 2009; 373:1097-1104; [2]Corless et al. JCO 2014; 32:1563-70; [3]Casali et al. JCO 2013; 31:632s; [4]Joensuu et al. JAMA 2012; 307:1265-72.

ACOSOG Z9001 trial

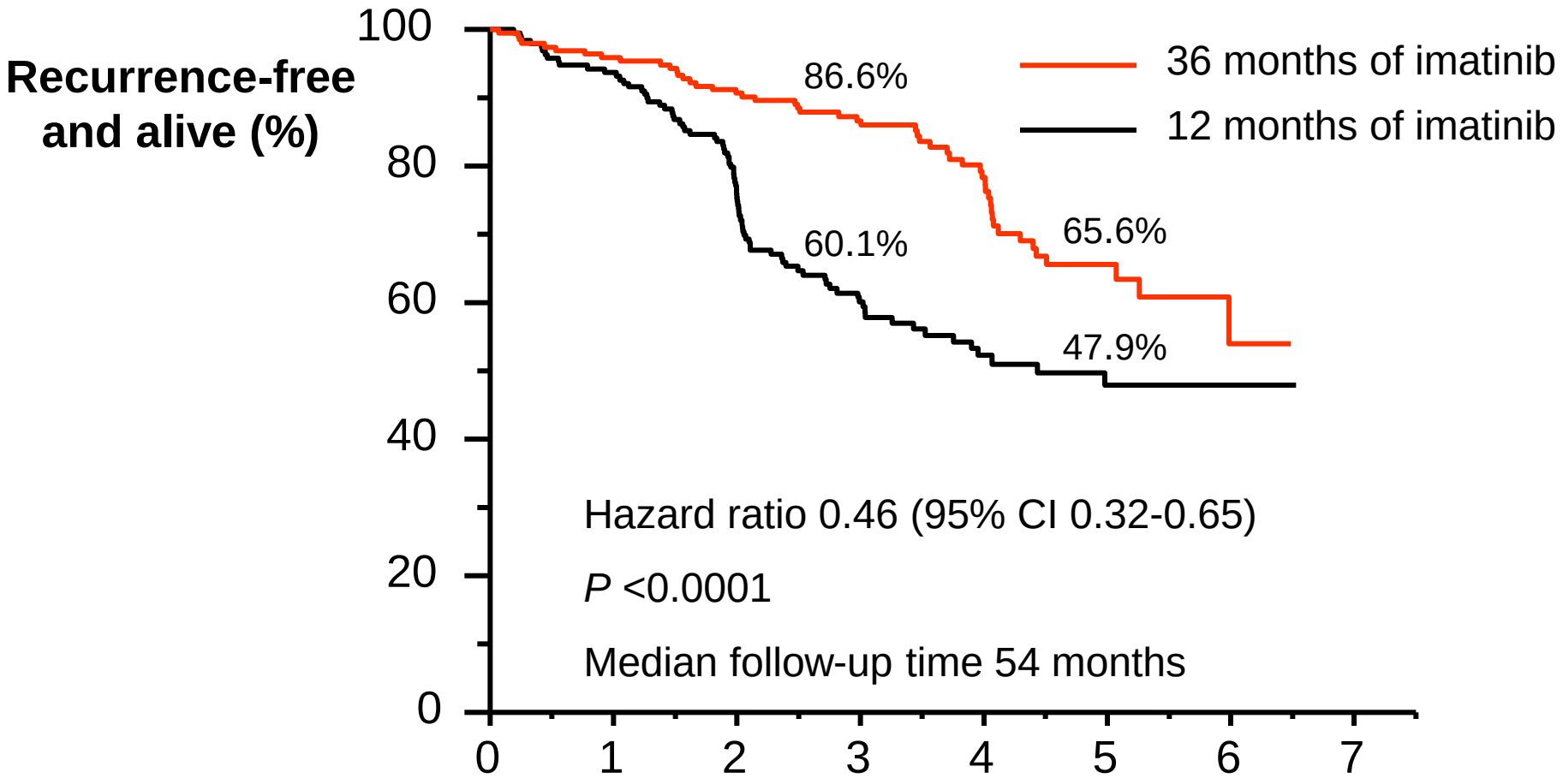
- Patients had GIST ≥3 cm in size (low or high risk tumour)
- RFS favoured imatinib, but no overall survival benefit



Median follow-up time
74 months

Corless CL et al. J Clin Oncol 2014, 32:1563-70.

SSGXVIII/AIO trial in high-risk GIST

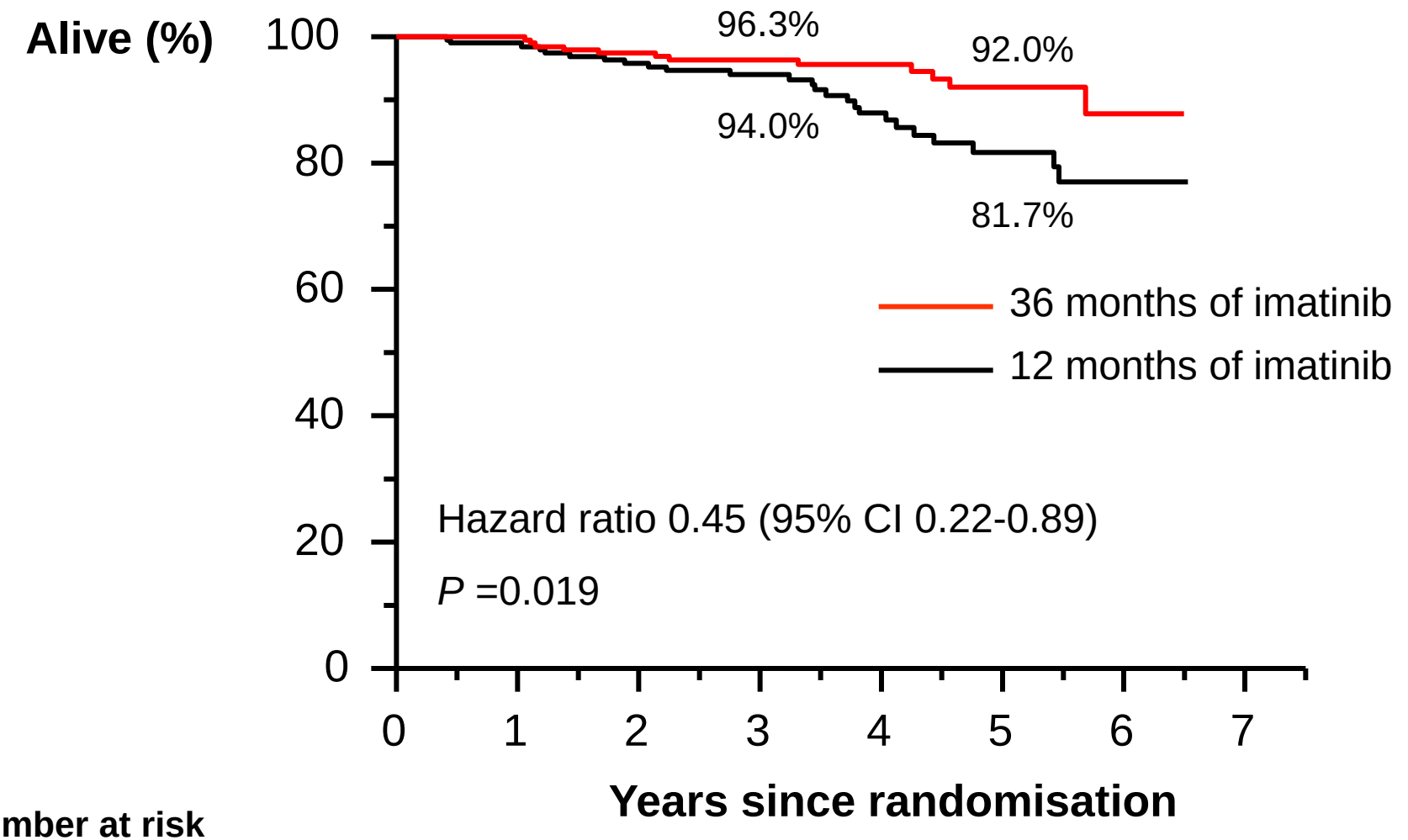


Number at risk

36 months of imatinib	198	184	173	133	82	39	8	0
12 months of imatinib	199	177	137	88	49	27	10	0

Joensuu et al. JAMA 2012;307:1265-72.

SSGXVIII/AIO trial: Overall survival



Number at risk

36 Months of imatinib	198	192	184	152	100	56	13	0
12 Months of imatinib	199	188	176	140	87	46	20	0

Next steps

- Advanced setting
  - Novel agents with improved inhibition of KIT and PDGFRA kinases
  - Combinations of targeted agents
  - Rotation of targeted agents
- Adjuvant setting
  - Longer (> 3 years) adjuvant treatments will be tested

Cancer research can produce magnificent results

- Even patients with bulky GIST metastases may now survive for many years
- GIST recurrence can be postponed/prevented in the adjuvant setting

Scandinavian
Sarcoma Group

Finnish Breast
Cancer Group

Thank you!

AIO

Arbeitsgemeinschaft
Internistische Onkologie

Patients