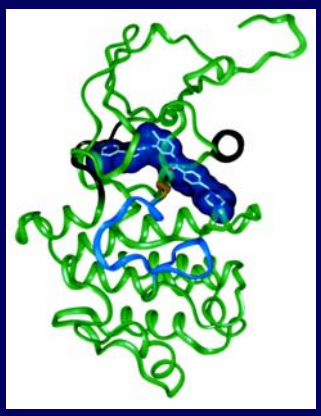
Extending The Imatinib Paradigm



OHSU CANCER INSTITUTE

Brian J. Druker, MD

Where Has Imatinib Worked?

- **Tumors in which ABL, KIT, or PDGFR have a critical role in the growth and survival of the cancer**

Where Has Imatinib Worked?

- **Tumors in which ABL, KIT, or PDGFR have a critical role in the growth and survival of the cancer**
  - **CML (ABL)**
  - **GIST (KIT)**
  - **HES (PDFGR)**

Where Hasn't Imatinib Worked?

- Brain tumors
- Breast cancer
- Prostate cancer
- Melanoma
- Numerous others

Where Hasn't Imatinib Worked?

- Brain tumors
- Breast cancer
- Prostate cancer
- Melanoma
- Numerous others
  - None of these tumors are critically dependent on a target of imatinib

What Lessons Can Be Learned From the Clinical Trials of Imatinib?

Target Expression Versus Response

Expression Versus Response

	Target Frequency	Target Response Rate	Observed Response Rate
100 patients	100%		
100 patients	50%		
100 patients	25%		
100 patients	10%		

Expression Versus Response

	Target Frequency	Target Response Rate	Observed Response Rate
100 patients	100%	60%	
100 patients	50%	60%	
100 patients	25%	60%	
100 patients	10%	60%	

Expression Versus Response

	Target Frequency	Target Response Rate	Observed Response Rate
100 patients	100%	60%	60%
100 patients	50%	60%	30%
100 patients	25%	60%	15%
100 patients	10%	60%	6%

Imatinib Responses in Advanced Malignancies

Disease	Target Expression	Partial Response Rate
CML blast crisis	Bcr-Abl + 100%	50-60%
GIST	KIT + > 90%	50-60%

Expression of a molecular target correlates with response to an agent directed against that target

Is Expression Sufficient to Predict Response?

Activation Versus Response

	Target Expression	Target Activation	Target Response Rate	Observed Response Rate
100 pts	100%			
100 pts	100%			
100 pts	100%			
100 pts	100%			

Activation Versus Response

	Target Expression	Target Activation	Target Response Rate	Observed Response Rate
100 pts	100%		80%	
100 pts	100%		80%	
100 pts	100%		80%	
100 pts	100%		80%	

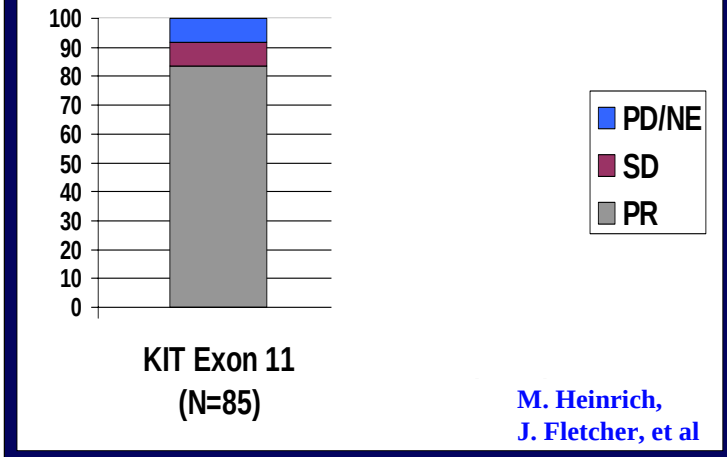
Activation Versus Response

	Target Expression	Target Activation	Target Response Rate	Observed Response Rate
100 pts	100%	90%	80%	
100 pts	100%	50%	80%	
100 pts	100%	25%	80%	
100 pts	100%	10%	80%	

Activation Versus Response

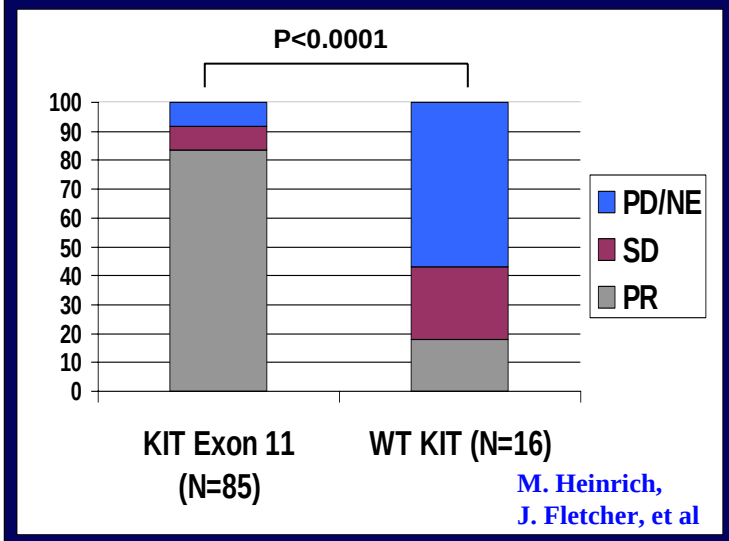
	Target Expression	Target Activation	Target Response Rate	Observed Response Rate
100 pts	100%	90%	80%	72%
100 pts	100%	50%	80%	40%
100 pts	100%	25%	80%	20%
100 pts	100%	10%	80%	8%

Response to Imatinib in GIST Patients



M. Heinrich,
J. Fletcher, et al

Response to Imatinib in GIST Patients



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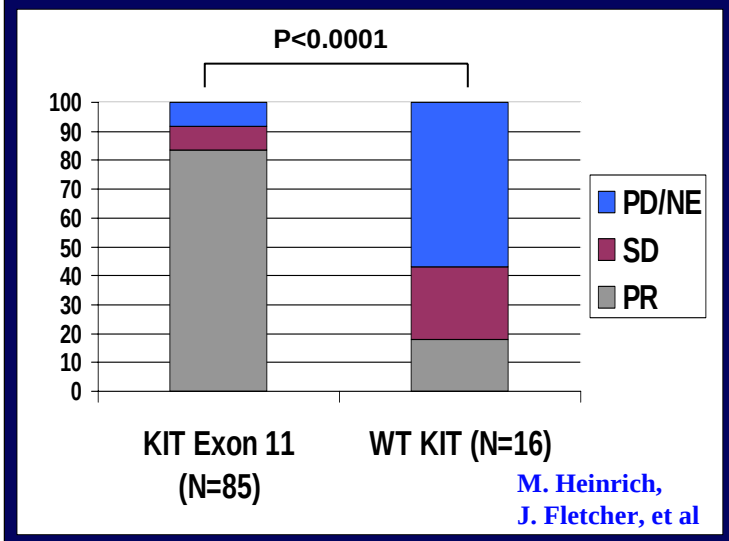
Expression of a molecular target does not guarantee a response to an agent that modulates the target

Response to Imatinib in GIST Patients



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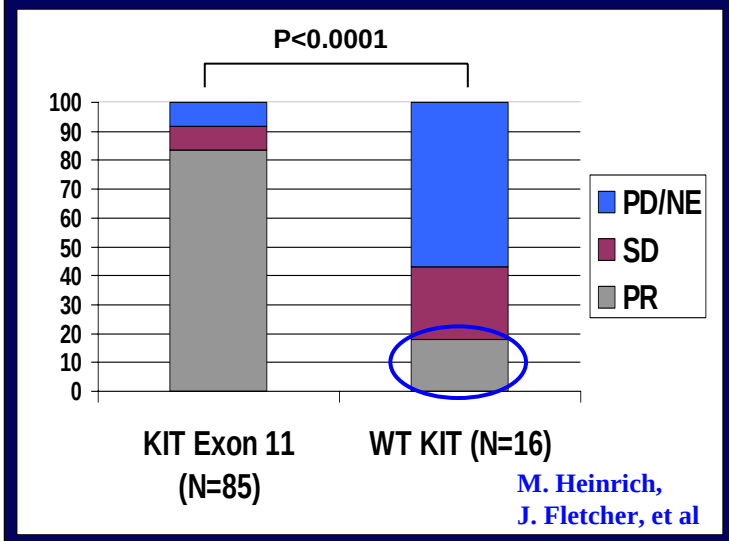

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PDGFR Activating Mutations in GIST

- 6/16 (37.5%) wild-type KIT patients had PDGFRA activating mutations in two different exons

M. Heinrich et al, Science 299:708-9, 2003

PDGFR Activating Mutations in GIST

- 6/16 (37.5%) wild-type KIT patients had PDGFRA activating mutations in two different exons
- One set of mutations was imatinib sensitive
  - 2/3 patients had PRs

M. Heinrich et al, Science 299:708-9, 2003

Gefitinib and Erlotinib

- **Inhibit EGF receptor kinase**
  - **EGFR broadly expressed in cancer**

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- **Inhibit EGF receptor kinase**
  - **EGFR broadly expressed in cancer**
- **10-20% response rate in advanced non-small lung cancer**
  - **No correlation with EGFR expression**
  - **Female, non-smokers, bronchoavelolar histology**

Gefitinib and Erlotinib

- **Responding patients have EGFR mutations**

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  - **More sensitive to inhibitors than wild-type receptor**

Gefitinib and Erlotinib

- Responding patients have EGFR mutations
  - More sensitive to inhibitors than wild-type receptor
- Careful study of subsets of patients may reveal important insights

What If The Response to a Molecularly Targeted Agent Is Low?

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What If The Response to a Molecularly Targeted Agent Is Low?

- Is the target expressed?
- Is the target modulated by the agent?
- Is the target critical to the growth or survival of the tumor?
- Is there a subset of patients who respond well?

Lessons Learned From Clinical Trials With Imatinib

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IT'S THE TARGET!

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Good Target + Good Drug

Lessons Learned From Clinical Trials With Imatinib

IT'S THE TARGET!

Good Target + Good Drug

=

Good Results

What Makes BCR-ABL Such an Ideal Target?

- Causative molecular abnormality of CML
- Sole oncogenic event early in the disease

What Makes BCR-ABL Such an Ideal Target?

- **Ease of selection of patients for clinical studies based on the presence of the target**
  - **Ph chromosome – BCR-ABL**

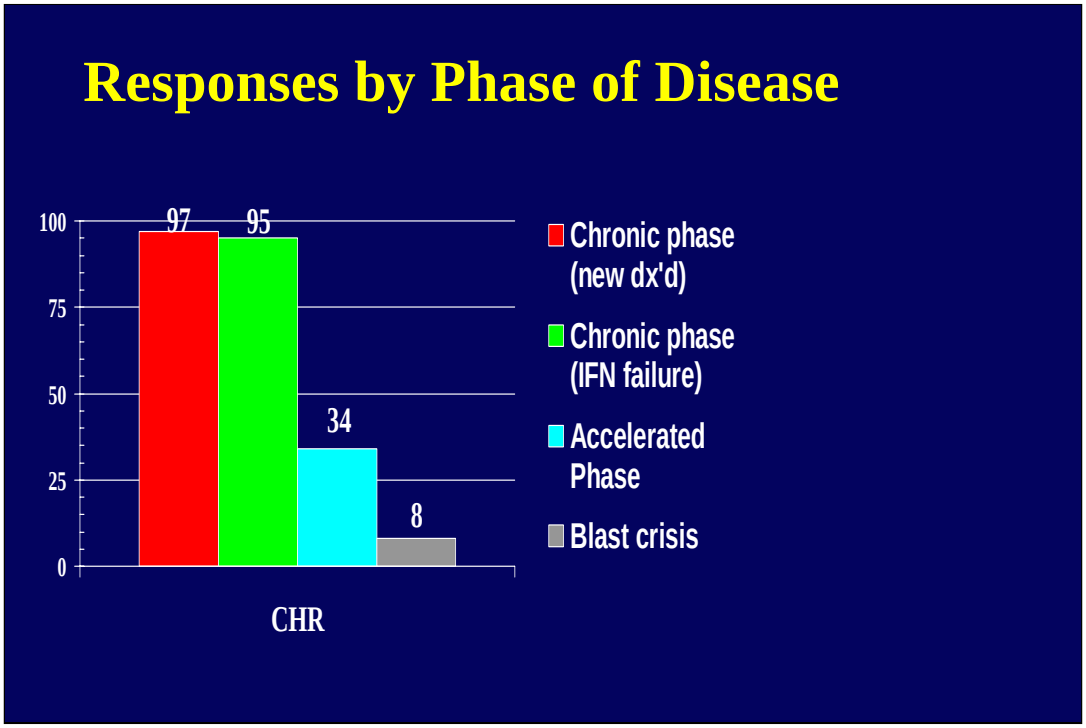
Why is KIT an Ideal Target in GIST?

- KIT mutations are seen in early, incidental tumors
- KIT mutations are acquired before cytogenetic abnormalities
- Familial syndromes of GIST have germline KIT mutations

Lessons Learned From Clinical Trials With Imatinib

Old News

Treatment earlier in the course of a disease yields better responses


Responses by Phase of Disease
100
75
50
25
0
97
95
34
8
CHR
Chronic phase (new dx'd)
Chronic phase (IFN failure)
Accelerated Phase
Blast crisis

Translating the Success of Imatinib to Other Malignancies

- Identify the appropriate therapeutic targets
  - Early molecular pathogenetic events

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Translating the Success of Imatinib to Other Malignancies

- Identify the appropriate therapeutic targets
  - Early molecular pathogenetic events
- Treat early in the course of the disease
  - Develop reliable techniques for early detection
- Match the right patient with the right drug

The 21st Century

- **Identification of the molecular pathogenetic events in all cancers**

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- **Development of improved diagnostic/imaging techniques**
- **Improved methods of drug discovery**
- **Understanding of an individual's cancer risk based on genetic analyses**

The 20th Century

Leading causes of mortality

1900

1) **Pneumonia**
2) **Tuberculosis**
3) **Enteritis**
4) **Heart Disease**
5) **Stroke**
6) **Liver Disease**

The 20th Century

Leading causes of mortality

	1900	2000
1)	Pneumonia	Heart Disease
2)	Tuberculosis	Cancer
3)	Enteritis	Stroke
4)	Heart Disease	COPD
5)	Stroke	Accidents
6)	Liver Disease	Pneumonia

Factors Leading to Eradication and Treatability of Infections

- **Improved sanitation and refrigeration**
- **Antibiotics**
- **Vaccination**

Factors Leading to Eradication and Treatability of Infections

- Improved sanitation and refrigeration — Prevention
- Antibiotics
- Vaccination

Factors Leading to Eradication and Treatability of Infections

- Improved sanitation and refrigeration — Prevention
- Antibiotics — Specific treatments
- Vaccination

Factors Leading to Eradication and Treatability of Infections

- Improved sanitation and refrigeration — **Prevention**
- Antibiotics — **Specific treatments**
- Vaccination — **Immune modulation**

The 21st Century

Broad-based approach to cancer

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- **Specific therapies directed at critical targets**

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Broad-based approach to cancer

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Acknowledgements

OHSU CANCER INSTITUTE

Novartis

International Imatinib Study Group

Funding agencies