

# GIST Survival Strategies

## Optimizing Gleevec Therapy



**LIFEFEST 2008**  
**JERRY CALL**  
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## Disclaimer



- This presentation was prepared by Jerry Call, LRG Science Coordinator
- It is based upon practical experiences and observations relating to hundreds of GIST patients and their medical histories and an extensive review of the medical literature
- Of course, none of this information is intended to be a substitute for discussing GIST management and treatment with your physician

# Survival Strategies Overview



- **Encompasses many topics**
  - Adjuvant Gleevec
  - Finding the right doctors
  - Being proactive
  - Monitoring treatment
  - Optimizing Gleevec therapy
  - Optimizing Sutent therapy
  - Managing progression

# Optimizing Gleevec Therapy



- This presentation focuses on one Survival Strategy-  
Optimizing Gleevec Therapy
  - Other topics to be covered in the Personal Survival Plan session
- Keys to optimizing Gleevec therapy
  - Getting to the right dose
    - ✦ Understanding plasma testing
  - Understanding the Gleevec sensitive window
  - Managing side effects
  - Importance of taking medication

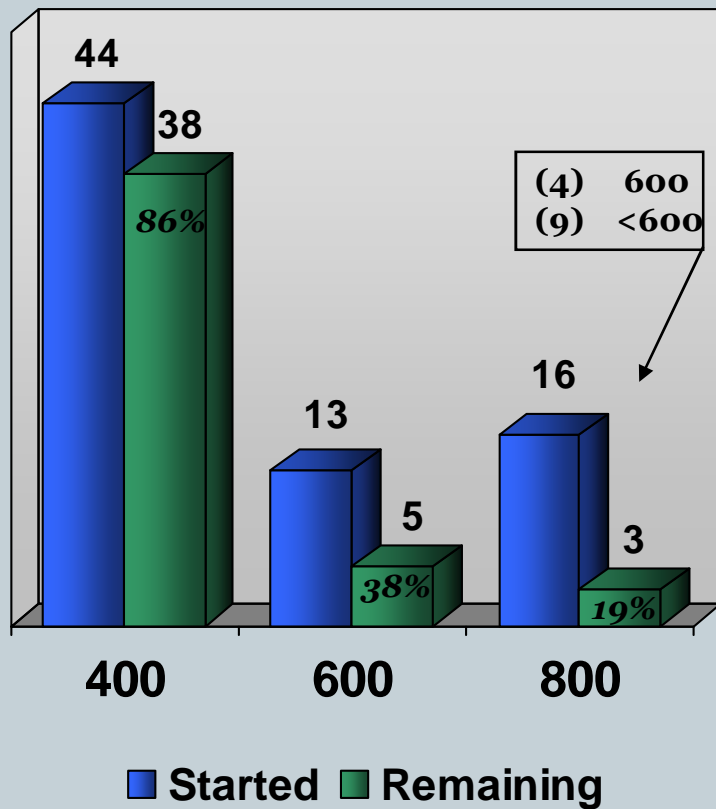
# Key to Optimizing Gleevec



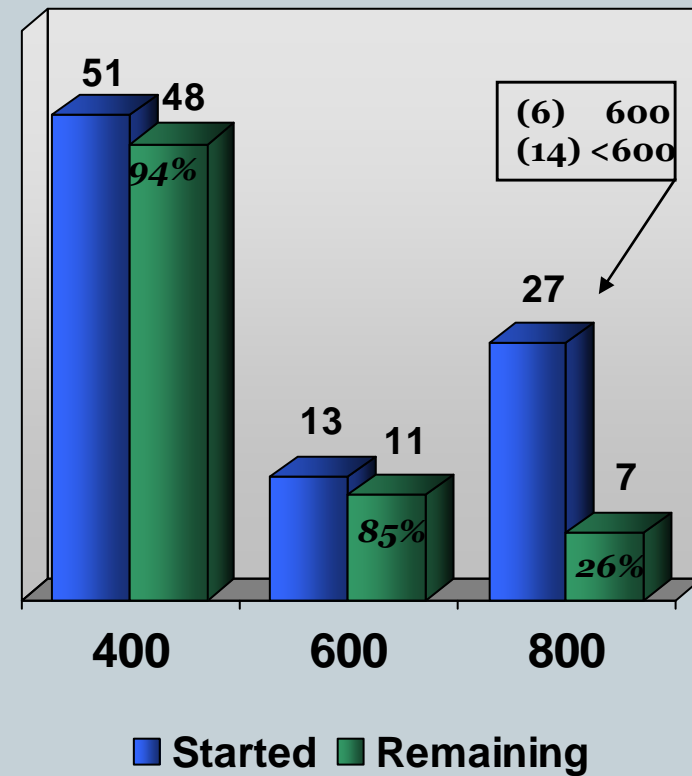
- Gleevec does product side effects
  - Worse at higher doses
- Gleevec side effects get better over time . . .
- Often . . . much better!
- Gleevec levels fall over time
  - May require dose escalation to maintain adequate Gleevec levels
- Understanding plasma testing

# LRG Data: Dose Reductions are Common at Higher Doses

## Females



## Males



## Side Effects Get Better Over Time



- Analysis of toxic effects over time showed that they were mostly recorded during the first 8 weeks of treatment\*

\*Progression-free survival in GIST tumours with high-dose imatinib: randomized trial  
Verweij et al, Lancet 2004; 364:1127-134

## Gleevec Levels Drop Over Time - 2



- Gleevec levels may drop 30% to 42% within one year
- At least 3 different explanations
  - Increased drug clearance
  - Decreased drug transport across the intestinal barrier
  - Decreased patient adherence
    - Side effects management
    - Dose escalation strategies

# Implications of Falling Drug Levels



- Patients on lower doses may be more at risk for progression
- Starting at a lower dose and increasing the dose over time may restore drug levels
- If we had routine drug-level testing dosage could be adjusted (**whatever the cause**)
  - Data on plasma levels is preliminary
  - Better at following a patient over time
  - Moves the question of falling drug levels from theoretical to practical

# North American Intergroup Phase III Study of Imatinib in Advanced GIST

Dose Reduction	400 mg (376 pts)	800 mg (370 pts)	800 mg X-Over
1	10%	*44%	16%
2	7%	26%	5%
3	2%	11%	0%
4	1%	4%	0%

- Patients crossing over to 800 mg after being on 400 mg required far fewer dose reductions than those starting at 800 mg
- \* Interim data – this number eventually reached 60%

## Dose Escalation



- Side effects drop over time
- Gleevec blood levels may drop over time
- Higher dose Gleevec given as initial therapy is not well tolerated, especially by women
  - 60% of patients will require a dose reduction if they start at 800 mg

### However

- Dose escalation AFTER side effects decline should allow more patients to reach drug level goals

## Current Consensus – Gleevec Dose



- Starting dose of 400 mg
- Increase to 800 mg for progression
- Exon 9 patients may benefit from 800 mg dose as initial treatment (quick dose escalation?)
  
- Small increased benefit in PFS for 800 mg
- No increased benefit in OS for 800 mg
- 60% dose reductions in the phase III trials (800 mg)
  - How does this affect the results?

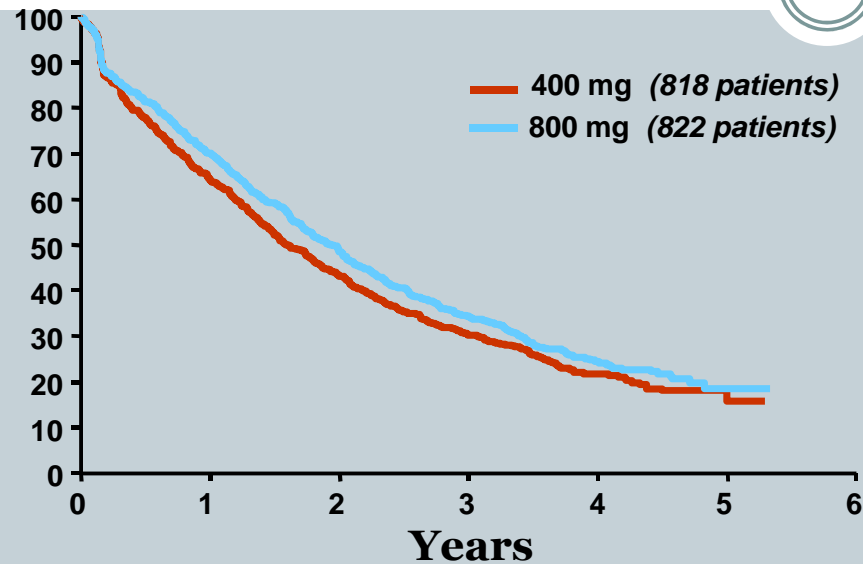
# Methods for Evaluating Dose



- **Starting Dose (Intent-to-treat; Intended dose)**
  - Traditional method
  - Used in phase II and phase III clinical trials
- **Actual Dose (Delivered Dose)**
  - Prescribed by physician
  - Actually taken by patient
    - ✦ Known by physician
    - ✦ Not known by physician

# PFS Data Using Starting Dose

## Comparison: MetaGIST Project vs. LRG

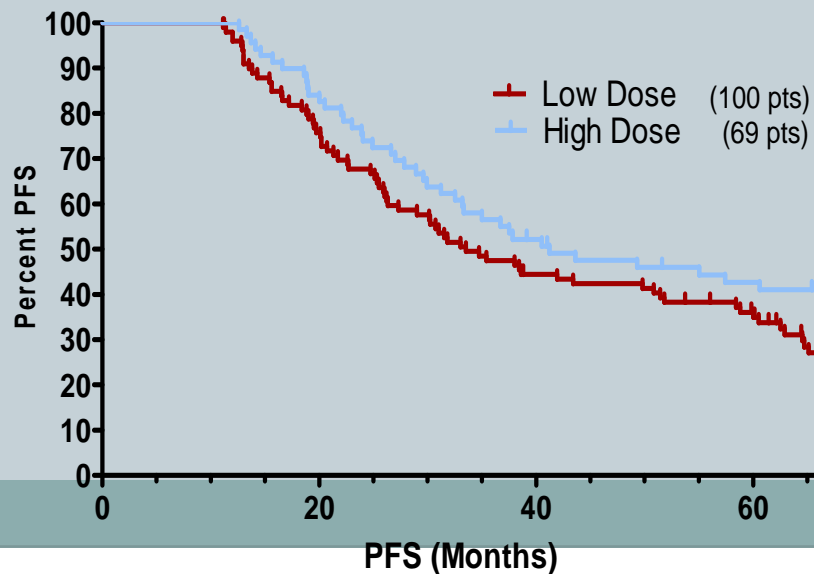


### MetaGIST Project\*

<b>Median PFS (months)</b>	<b>19 / 23</b>
<b>3-year estimate (%)</b>	<b>30 / 34</b>
<b>Hazard ratio</b>	<b>1.12**</b>
<b>P value (logrank test)</b>	<b>0.04</b>
<b>Median PFS benefit</b>	<b>4 months</b>

\*Includes pts w/primary resistance

\*\* Adjusted to match LRG analysis method



### LRG Project\*\*\*

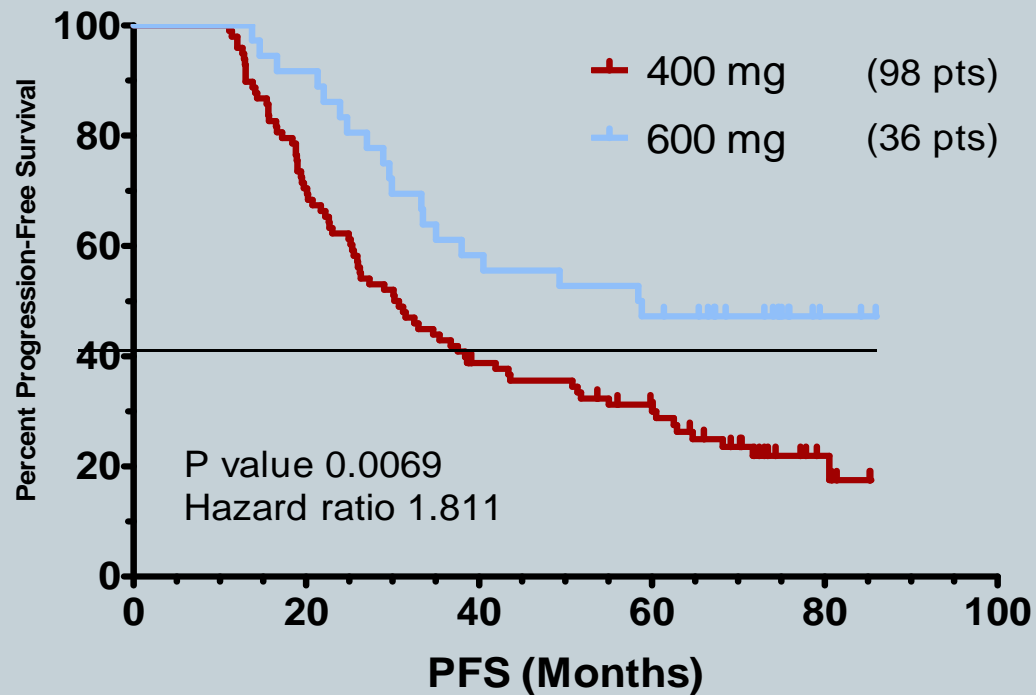
<b>Median PFS (months)</b>	<b>33.5 / 41.2</b>
<b>3-year estimate (%)</b>	<b>47.5 / 56.5</b>
<b>Hazard ratio</b>	<b>1.36</b>
<b>P value (logrank test)</b>	<b>0.10</b>
<b>Median PFS benefit</b>	<b>7.7 months</b>

\*\*\*Excludes pts w/primary resistance

# LRG Data: PFS by Actual Dose



## PFS - Actual Dose 400 mg vs 600 mg



P value 0.0069  
Hazard ratio 1.811

### PFS (Months)

Median PFS

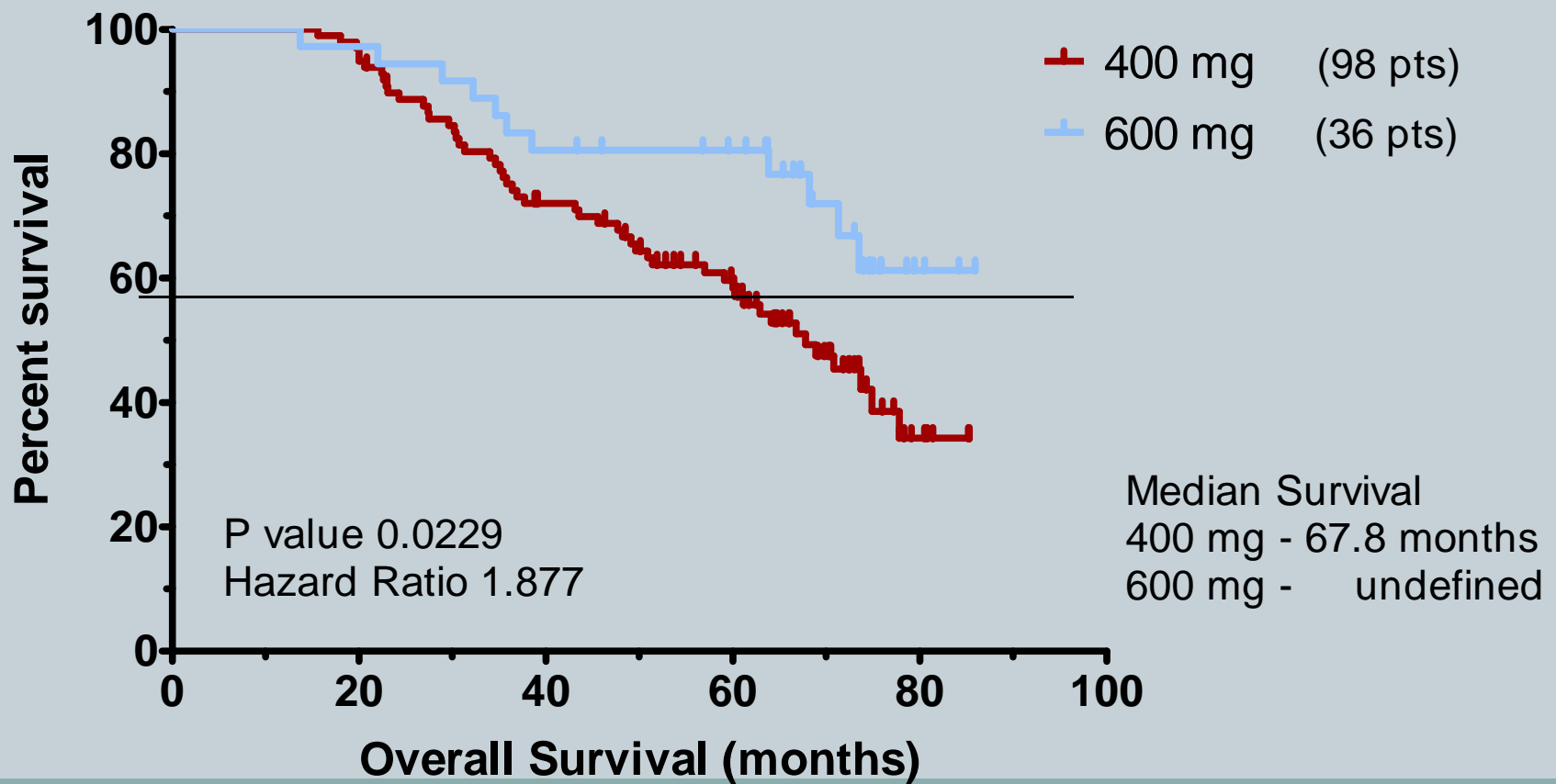
Low dose - 30.2 months

High dose - 58.6 months

Difference = 28.4 months

# LRG Data: OS by Actual Dose

## Overall Survival - Actual dose 400 mg vs 600 mg



## Plasma Levels May Affect Response



- 2008 GI ASCO – Preliminary new info on Gleevec Plasma levels

“... we may have been under-dosing some people.\*”

	Objective response	Median time to progression	Objective response exon 11 patients
Quartile 1 <1,110 ng/ml	44%	11.3 months	55.6%
Quartile 2+3 >1,110 ng/ml- <2,040 ng/ml	67%	30.6 months	94.1%
Quartile 4	74%	33.1 months	92.3%

\*Dr. George Demetri – Dana Farber Cancer Institute

## 2008 GI ASCO



- B2222 phase II GIST study – started in 2000
  - FDA registration trial
  - About 20% of patients still on drug
- PK samples on day 1 and day 29
- New plasma data based on day 29 plasma levels
  - How does plasma levels falling over time affect this?
  - How do dose reductions after 29 days affect this; especially those in the 600 mg arm?
    - ✦ Dose reductions were not reported for this trial

# B2222 IM Trough Distribution



## Imatinib Cmin (Trough) Distribution – Day 29

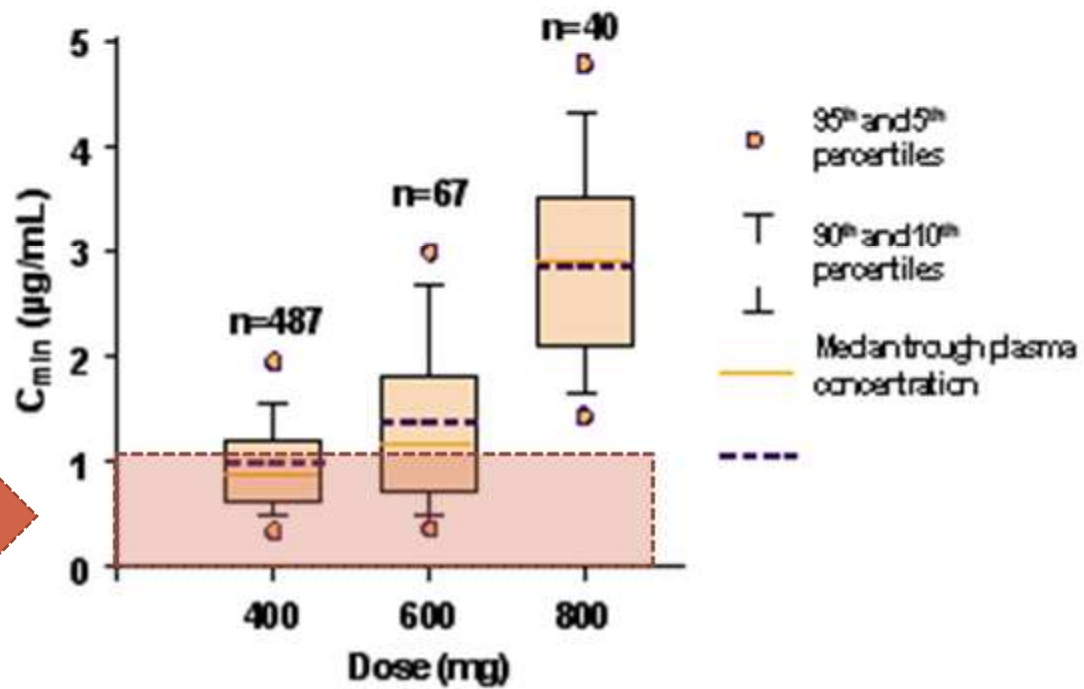
Overall mean, 1570 ± 722 ng/mL

Range 410 to 4180 ng/ml

Number of patients = 73

		Q1	Q2-3	Q4
	400 mg (n=34)	11 (32%)	16 (47%)	7 (21%)
	600 mg (n=39)	7 (18%)	20 (51%)	12 (31%)

# Imatinib Plasma Levels



This box indicates patients below 1100 ng/mL (Quartile 1 patients)

This chart is a compilation from several sources including Merrill Egorin, MD and Novartis

# Median Plasma Levels at Different Time Points



Study/Series	Timepoint	400 mg	600 mg	800 mg
B2222 Phase II	Day 29	1476 ng/mL	1659 ng/mL	N/A
Egorin/Novartis	Mixed	900 ng/mL	1200 ng/mL	2900 ng/mL
French CML	Mixed	825 ng/mL		

phase II day 29 levels  
39% to 46% lower

day 29 levels  
28% lower

## Estimated Benefit using Different Methods



Method	PFS and (Benefit)	% Benefit Increase
Dose -Intent-to-treat 400 mg vs 800 mg	19/23 (4 months)	21%
Dose-Actual Dose* 400 mg vs 600 mg	30.2/58.6 (28 months)	94%
Plasma Levels-(day 29)** Q1 vs Q2-3	11.3/30.6 (19 months)	171%
Plasma Levels-Actual	?	?

\*Select group- on Gleevec at least 12 months-eliminates those w/primary resistance

\*\* Are day 29 levels closer to intent-to-treat than actual?

# Optimizing Dose



- Toxicity
  - Excessive toxicity trumps other considerations
- Mutations
  - Data for high dose for exon 9 patients is compelling
- Plasma Levels
  - Intriguing preliminary data
  - Consider testing for
    - ✦ Minimum trough levels *in the absence of excess toxicity*
    - ✦ Falling drug levels
    - ✦ In cases of excess toxicity-are high Gleevec levels the cause?
    - ✦ Compliance
- Dose

## The Gleevec-sensitive Window



- Median duration of response - 2 years
  - 50% of patients will become Gleevec-resistant by 2 years of treatment
- High-level clinical evidence on plasma levels may not be available for many years
- Your personal situation
  - Can you wait 5 or more years for conclusive evidence?
  - Making a decision based on current evidence

## LRG: First Dose Study Revisited



### **November 2004: CTOS Presentation**

Of 169 Metastatic GIST Patients

91 Patients had not relapsed

78 Patients had relapsed

# LRG: First Dosage Study Revisited



## December 2007

Of the 91 patients who had not relapsed  
as of October 2004:

11% died

Of the 78 patients who had relapsed  
as of October 2004:

81% died

- Suggesting a strong relationship between avoiding relapse and survival.
  - In 2008, patients have more options than in 2004
- Can relapse be prevented with optimized doses?

# Managing Side Effects



- Despite publicity to the contrary, Gleevec can have significant side effects
- But side effects do tend to get better over time
  - Could be related to the theory of Gleevec drug levels falling over time (levels can decline over 40% within 12 months)

## Managing Side Effects - 2



- Being able to manage Gleevec side effects is a key step that allows patients to take their Gleevec as prescribed
- Start slowly and if higher doses are needed (exon 9) or desired, escalate the dose slowly (exon 9 patients may need faster dose escalation)

# Patient/Doctor Communications



- It is important for patients to report side effects and discuss their management with their doctor
- The material presented here is for information purposes only

# Compliance to Gleevec



- “Drugs don’t work in people that don’t take them\*”
- Only about half of people with chronic health conditions continue to take medication as directed

## Benchmark compliance rates:

• Disease	• Rates of noncompliance
○ Epilepsy	○ 30% to 50%
○ Arthritis	○ 50% to 71%
○ Hypertension	○ 40% (average)
○ Diabetes	○ 40% to 50%
○ Oral contraceptives	○ 8%
○ HRT	○ 57%
○ Asthma	○ 20%
○ CML/GIST	○ 25%

# Gleevec Compliance



- **Study of 878 Gleevec patients (CML, GIST, others)<sup>1</sup>**
  - 30% interrupted treatment for at least 30 consecutive days in the first year
  - Women were twice as likely to discontinue as men
  - Overall compliance was 75%
- **Study of 267 CML patients<sup>2</sup>**
  - Median Medication Possession Ratio(MPR) (total days supply/365) was 77.7%
  - Compliance (MPR) went down with
    - ✦ More concomitant medications
    - ✦ More complex cancer
    - ✦ Higher starting dose
    - ✦ Women were twice as likely to have a treatment interruption

1. Compliance and persistency with imatinib, Feng et al. 2006

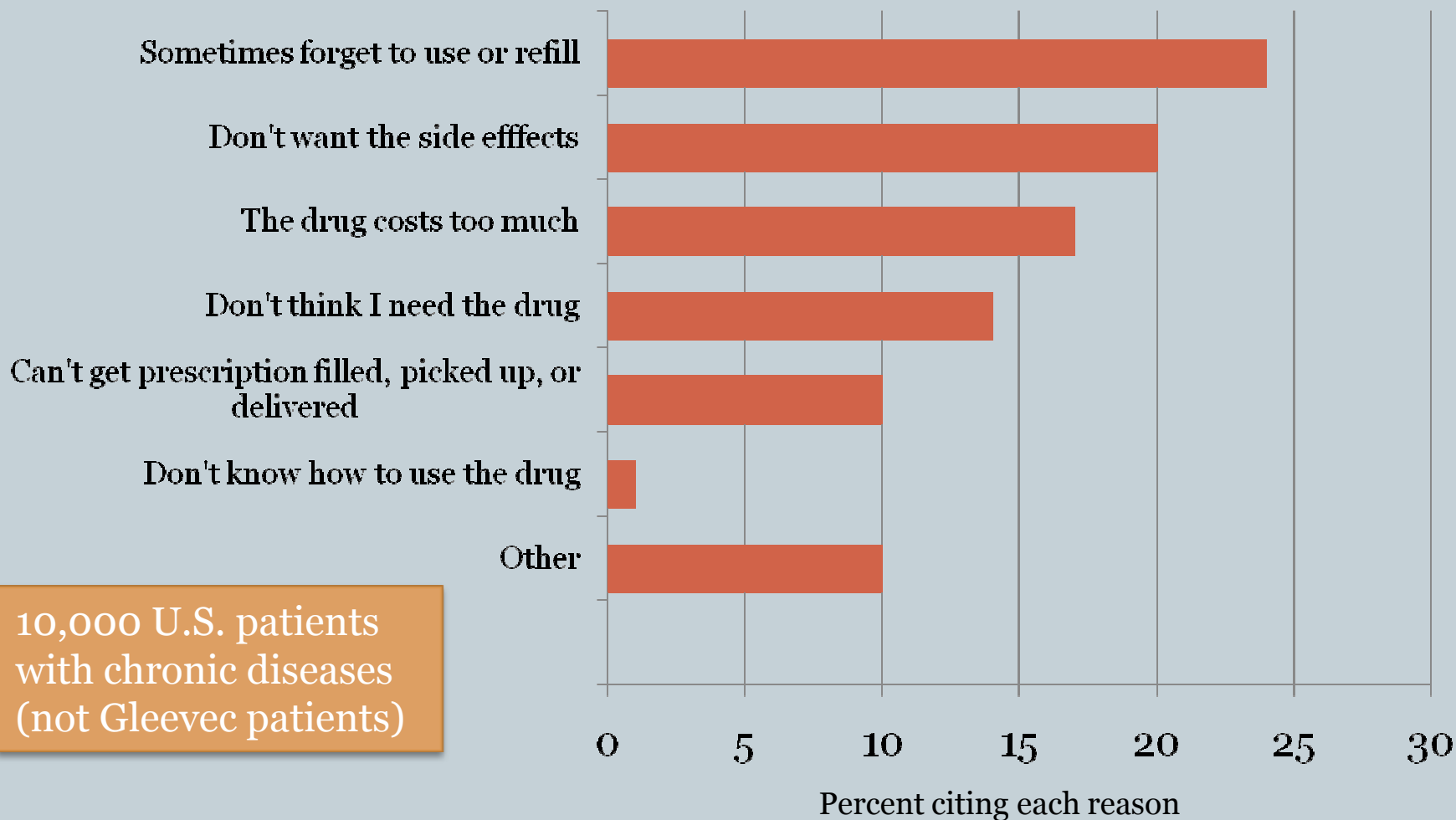
2. Treatment interruptions and non-adherence with imatinib. . . Darkow, et al.

## Who is least likely to comply?



- Women (2 to 1 for Gleevec)
- Patients that are **MOST INVOLVED** in their own care are the least compliant!

# Why don't patients comply



10,000 U.S. patients  
with chronic diseases  
(not Gleevec patients)

SOURCES: BCG analysis; *Harris Interactive 10,000 Patients Survey, 2002.*

## Summary



- Side effects get better over time
  - Use this to your advantage
- Drug levels fall over time
  - Caution – Danger ahead?
- Gleevec sensitive window
  - Can we reliably reverse resistance?
- Gleevec plasma testing
  - Can you afford to wait for definitive data?