Neoplasias Mieloproliferativas Crónicas

Eduardo Olavarria

Complejo Hospitalario de Navarra, Pamplona

New insights give new therapy possibilities

JAK2V617F
TET2
MPL
ASXL1
LNK
EZH2
IDH1/2

These mutations and other findings

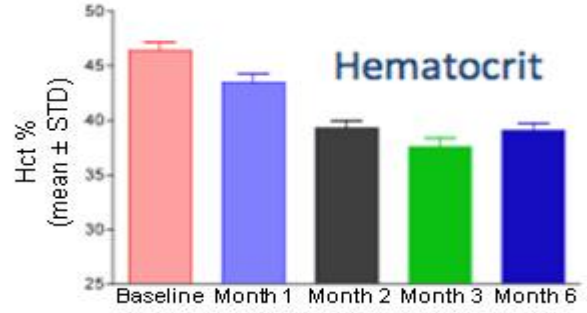
- explain the pathogenesis of MPNs
- give basis for targeted therapies
  - ✓JAK2 inhibitors
  - ✓Epigenetic drugs
  - ✓mTOR inhibitors
  - ✓ Immunomodulators
  - ✓ HDAC inhibitors etc

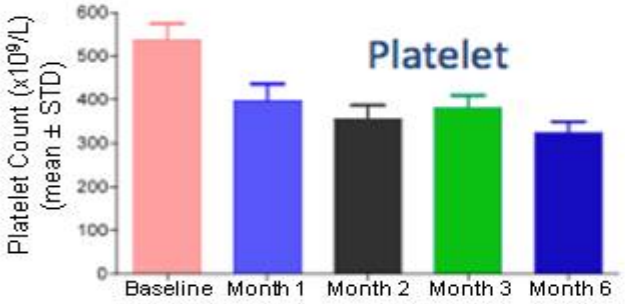
Ongoing and future clinical trials in PV

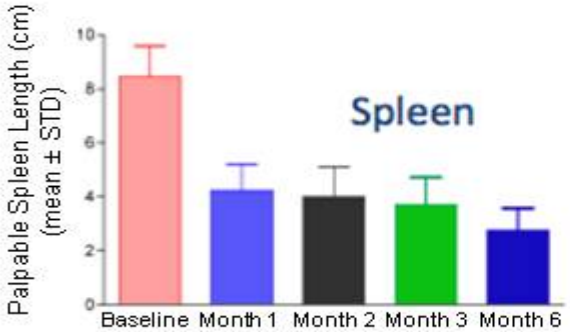
Agent(s)	MOA	Phase	Status
Ruxolitinib (INCB018424)	JAK inhibition	2 3	Ongoing Ongoing
Lestaurtinib (CEP-701)	JAK inhibition	2	Completed
SAR302503	JAK inhibition	2	Ongoing
PEG Interferon α	Multiple MOAs	3 3	Ongoing Ongoing
GIVINOSTAT (ITF2357) in combination with HU	HDAC inhibition	3	Completed
MK-0683	HDAC inhibition	2	Ongoing
Erlotinib	TKI	2	Ongoing
Imatinib	TKI	2	Completed

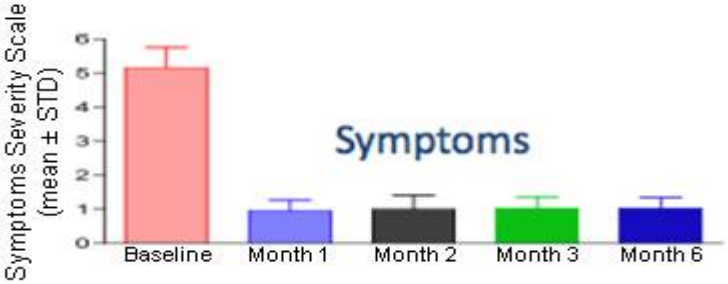
RUXOLITINIB IN POLYCYTEMIA VERA

Trend of Improvement of Outcomes





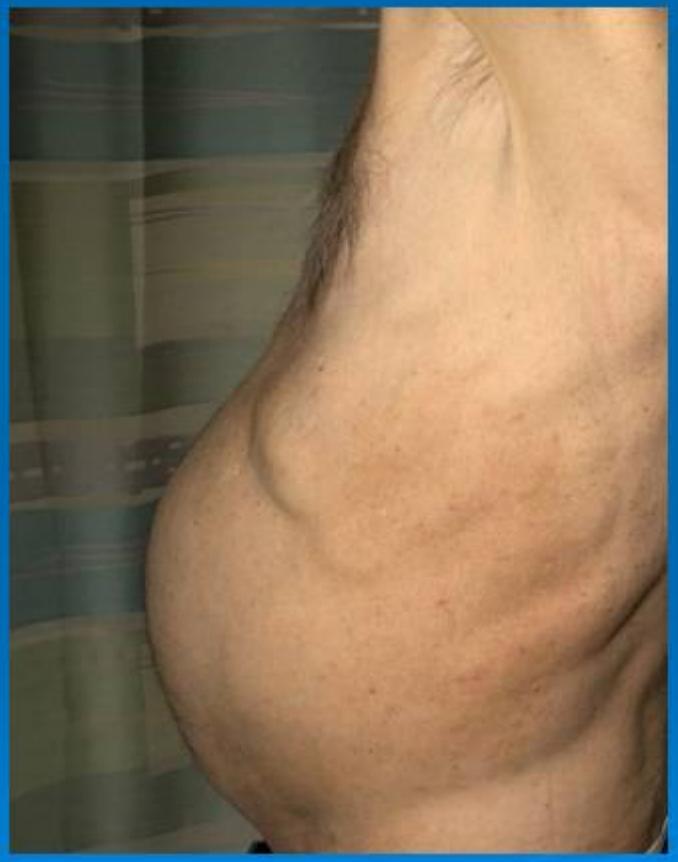




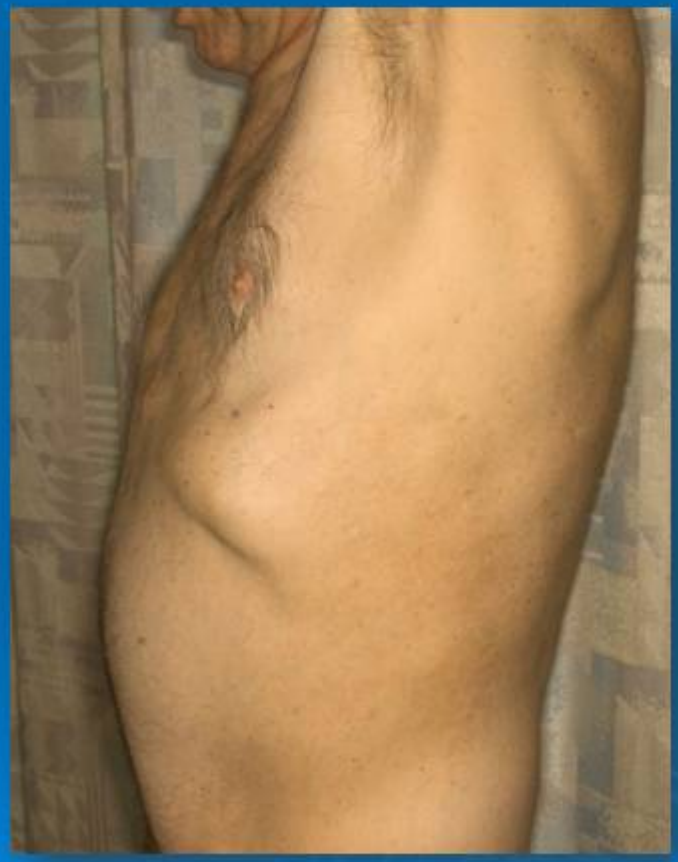
Verstovsek et al. Abstract 313, ASH 2010.

RUXOLITINIB IN IDIOPATHIC MYELOFIBROSIS

Spleen Size Reduction in Patient Treated With INC424



MF Patient Pre-Therapy



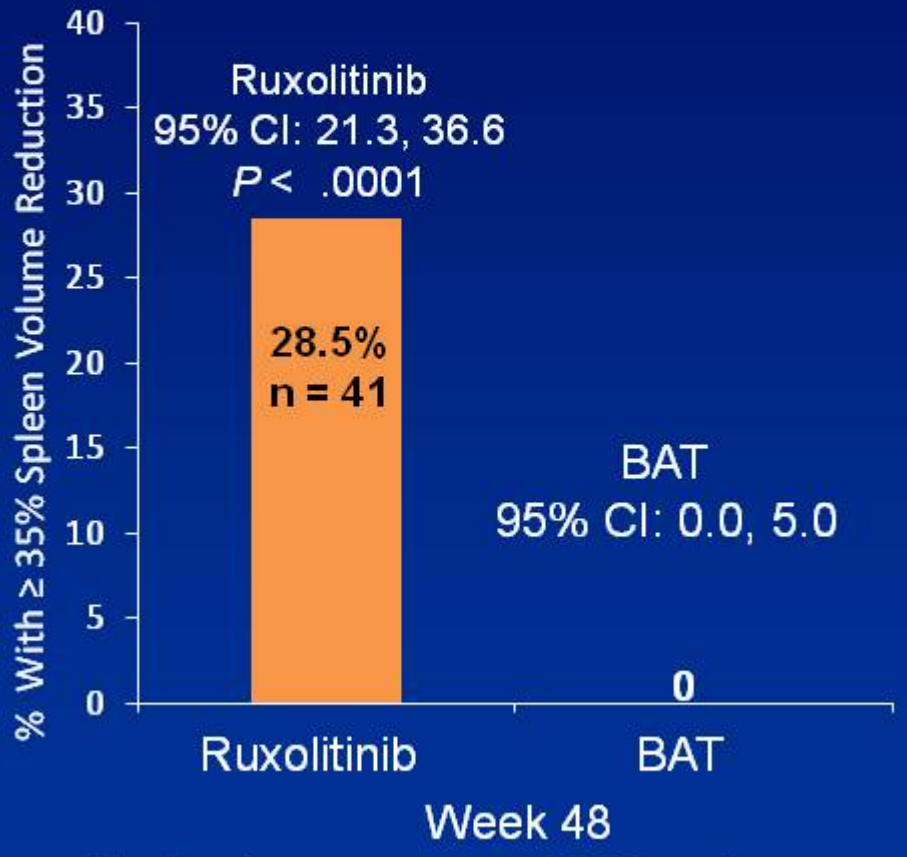
Patient After 2 Months of Therapy

Photos used with permission from MD Anderson Cancer Center.

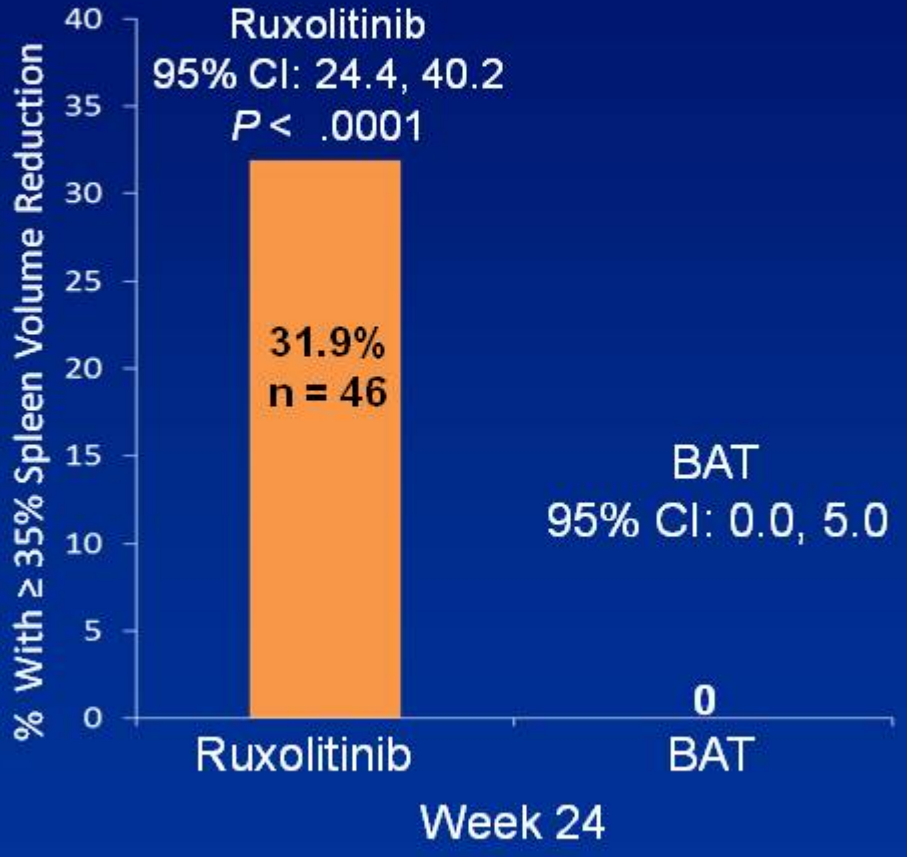
COMFORT-II

Efficacy Results (ITT)

Primary Endpoint



Key Secondary Endpoint

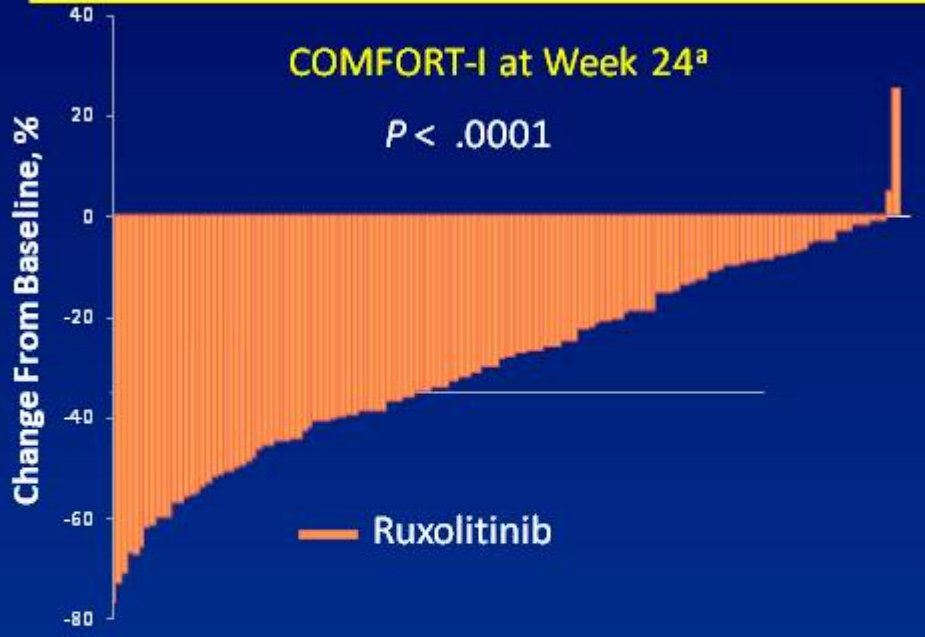


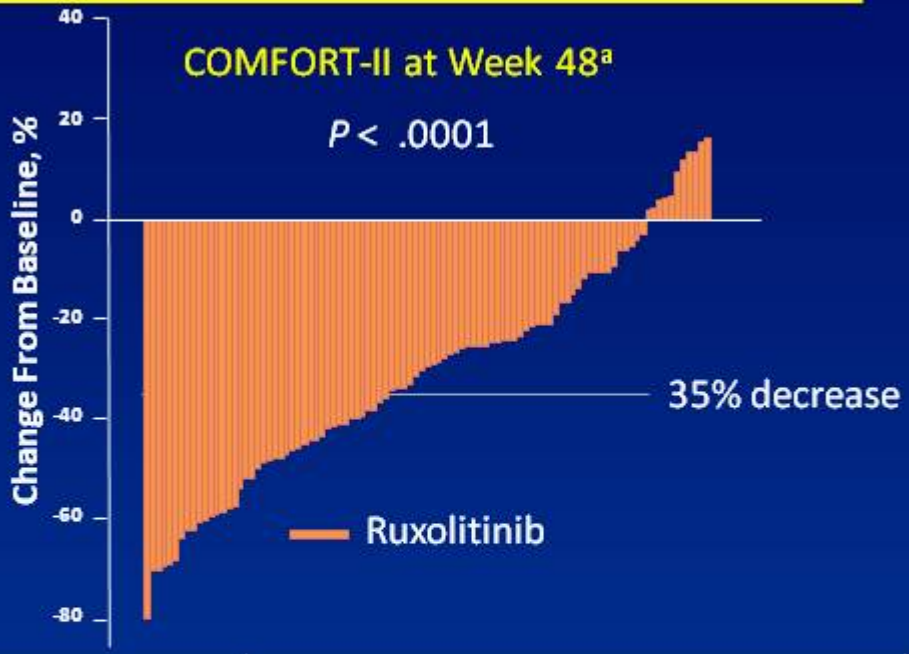
- Median time to response, 12.29 weeks
- Median duration has not been reached

Harrison C. et al. N Engl J Med. 2012 Mar 1;366(9):787-98.

COMFORT-I and COMFORT-II

Comparison of Spleen Volume Reductions

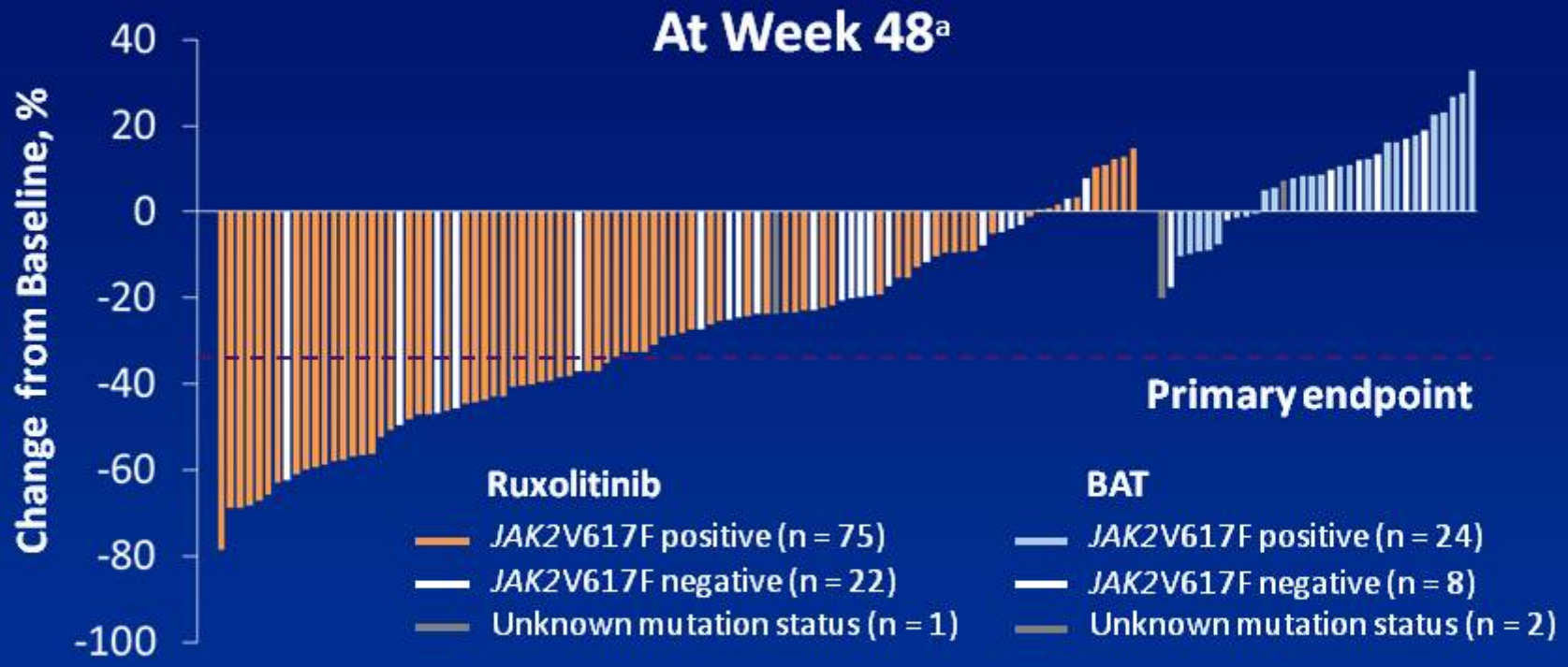




Ruxolitinib Arm	COMFORT-I	COMFORT-II	
	Week 24	Week 24	Week 48
≥ 35% spleen vol. ↓, n (%) 95% CI P value	65 (41.9)[a] (34.1, 50.1) < 0.0001	46 (31.9)[b] (24.4, 40.2) < 0.0001	41 (28.5)[a] (21.3, 36.6) < .0001
Percentage spleen vol. ↓, mean (SD) Median	–31.6 (18.9) –33.0	–29.2 (19.5) –27.5	–30.1 (22.1) –28.3

[a]Primary endpoint; [b]Key secondary endpoint.

Percent Change from Baseline in Spleen Volume by *JAK2*V617F Mutation Status



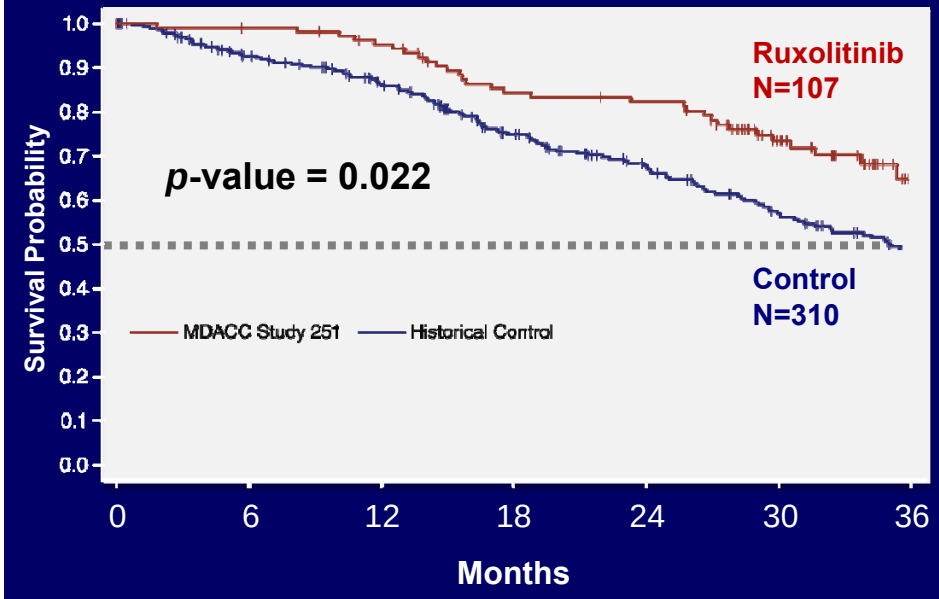
- At week 48, the vast majority of patients receiving ruxolitinib experienced spleen volume reductions, including *JAK2*V617F-positive (88% [66/75]) and *JAK2*V617F-negative (91% [20/22]) patients

[a] For patients with spleen volume assessments by MRI/CT at both baseline and week 48.

Harrison C, et al. Oral presentation at ASH Annual Meeting; Dec 10-13, 2011. Abstract 279.

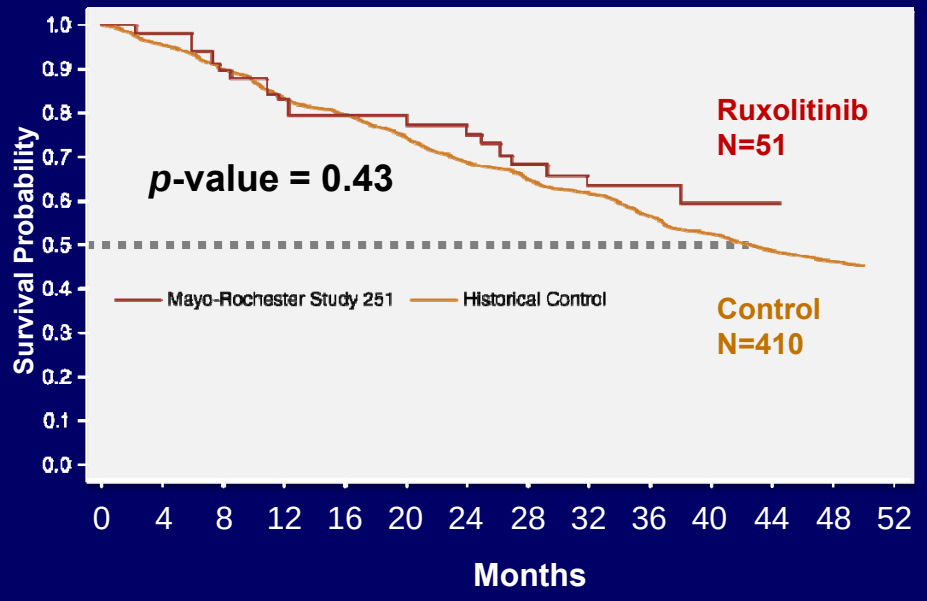
Overall Survival: Phase 1-2 Study Cohorts vs. Historical Controls

MDACC



Estimated survival (%)	Ruxolitinib	Historical Control
12 months	95	86
24 months	82	67
36 months	65	49

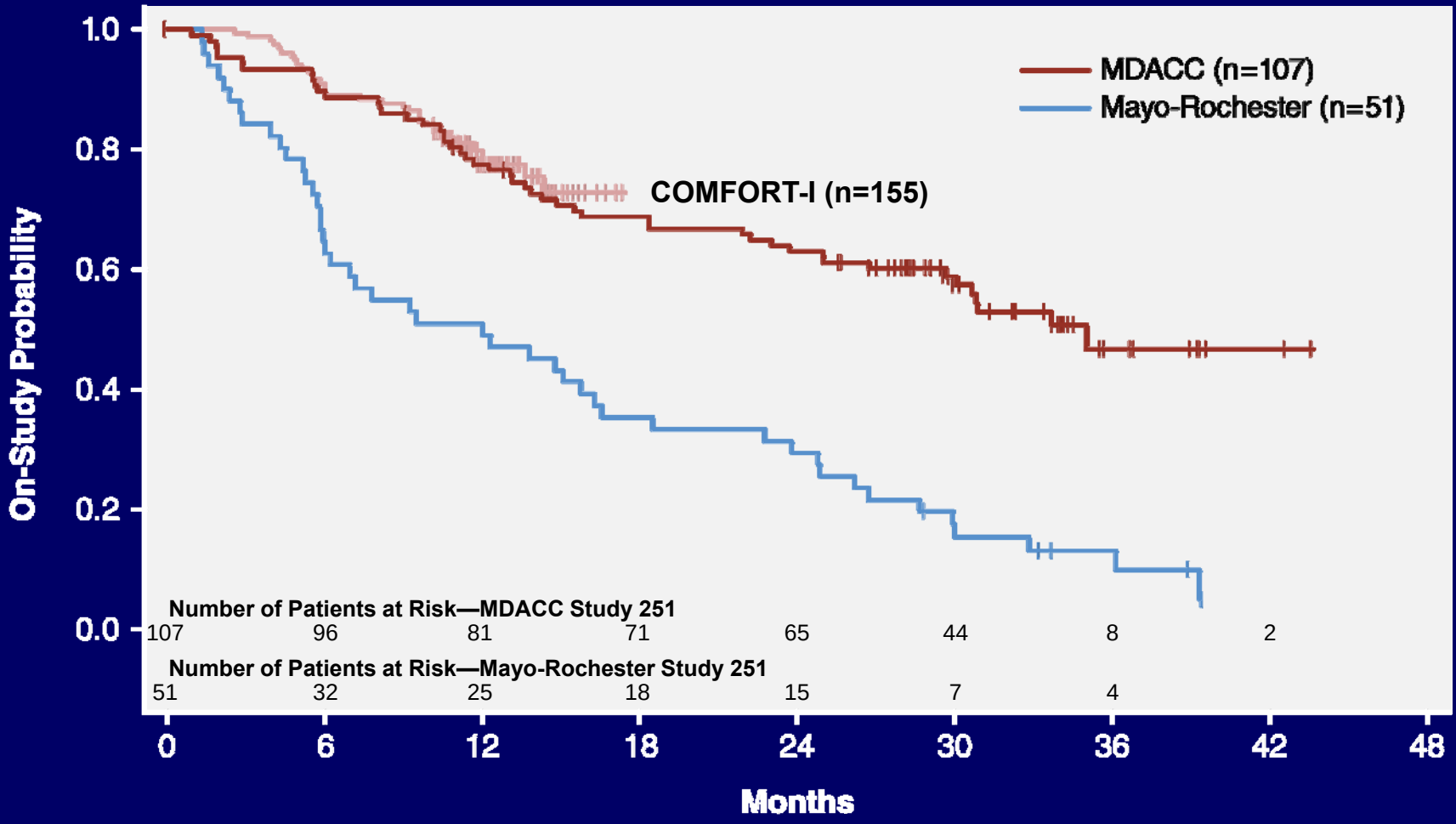
Mayo-Rochester*



Estimated survival (%)*	Ruxolitinib	Historical Control
12 months	83	83
24 months	75	69
36 months	62	57

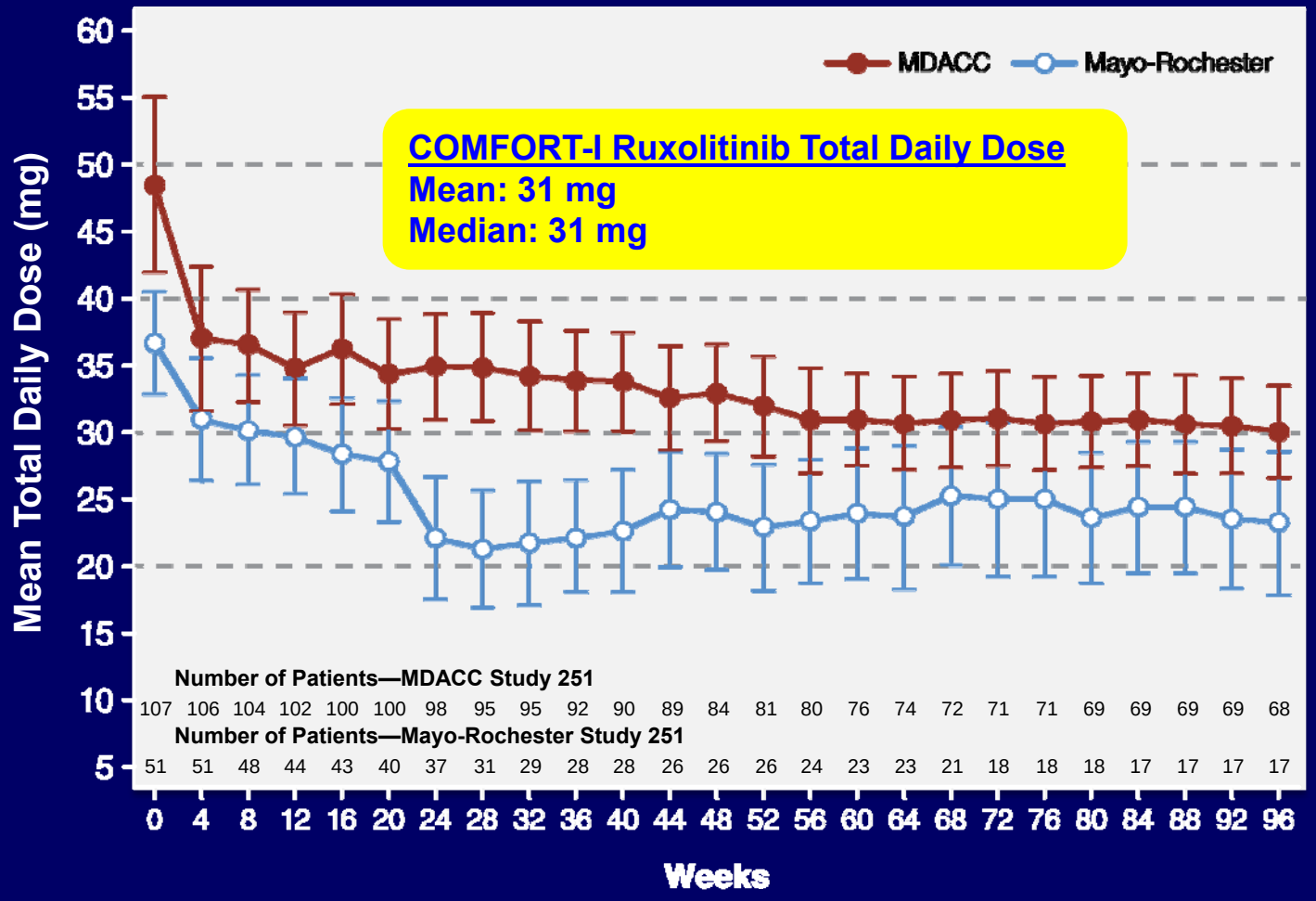
*Estimated from Tefferi A, et al (Correspondence). *N Engl J Med*. 2011;365(15):1455-7.

Discontinuation Rates: Phase 1-2 Study MDACC and Mayo-Rochester Cohorts



Data provided by Incyte Corporation upon MDACC request.

Mean Ruxolitinib Dosing Over Time in Phase 1-2 Study: MDACC and Mayo-Rochester Cohorts



Data provided by Incyte Corporation upon MDACC request.

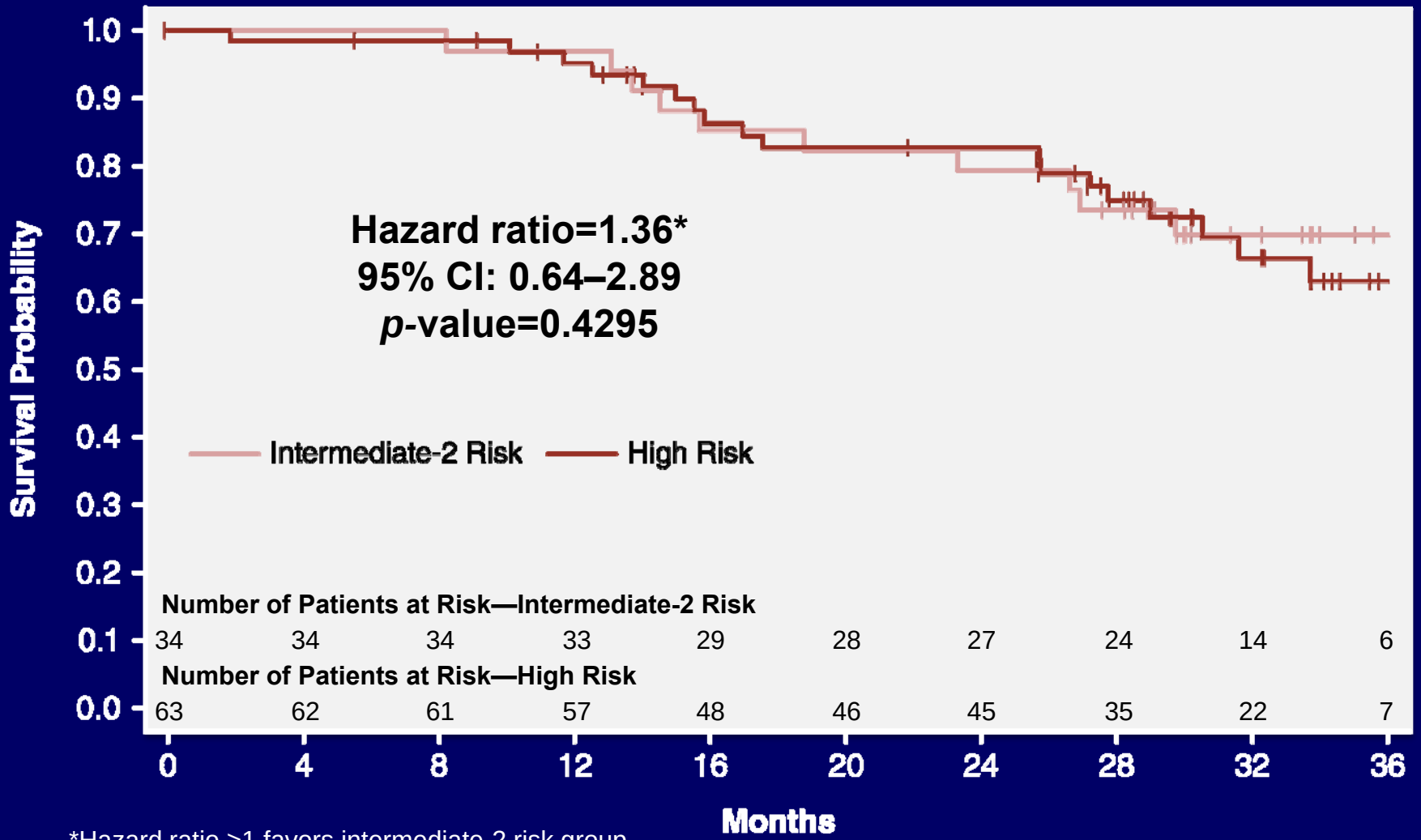
Rates and Reasons for Discontinuation in Phase 1-2 Study: MDACC and Mayo-Rochester Cohorts

Variable	MDACC (N = 107)	Mayo-Rochester (N=51)
Number (%) remaining on study	58 (54%)	5 (10%)
Number (%) patients discontinued	49 (46%)	46 (90%)
Primary reason for discontinuation*, n (%)		
Death	**13 (12.1%)**	**4 (7.8%)**
Progressive disease	**12 (11.2%)**	**10 (19.6%)**
Patient withdrawal of consent	**7 (6.5%)**	**15 (29.4%)**
Physician decision to discontinue	**5 (4.7%)**	**12 (23.5%)**
Intercurrent illness	**3 (2.8%)**	**0**
Unacceptable toxicity	**3 (2.8%)**	**1 (2.0)**
Other	**6 (5.6%)**	**3 (5.9)**

*As categorized by defined headings on study case report forms.

Data provided by Incyte Corporation upon MDACC request.

Overall Survival in MDACC Phase 1-2 Study Cohort: Intermediate-2 vs. High Risk



*Hazard ratio >1 favors intermediate-2 risk group.

Ba/F3 model: Effects of Ruxolitinib and Panobinostat Treatment on Bioluminescence Imaging on Day 11

- Enhanced efficacy was observed with a combination of RUX and PAN
- There was no major change in tolerability, as assessed by body weight, between panobinostat alone or in combination with ruxolitinib

* $P < 0.05$ vs. vehicle control; † $P < 0.05$ vs. ruxolitinib; ‡ $P < 0.05$ vs .panobinostat at same dose

Baffert F, et al. Oral presentation at ASH Annual Meeting; Dec 10-13, 2011. Abstract 798.

Combination of Panobinostat and Ruxolitinib in MF: Phase I

Countries:

France, Germany, Italy, UK, Ireland

FPFV: November 9th, 2011

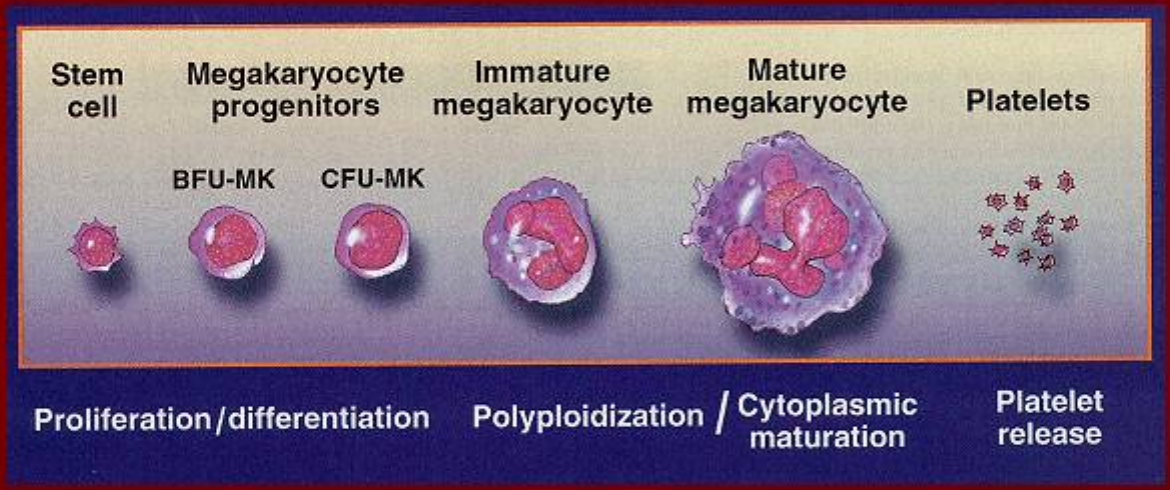
Update at EHA

MTD = maximum tolerated dose; RPID = recommended phase II dose; FPFV = first patient first visit

A new therapeutic strategy, a new class of drugs:

Rho kinase inhibitor dimethylfasudil (diMF)

Background: nuclear ploidy in MK necessary for normal differentiation. Reduced ploidy induces hyperproliferation.



New principle: diMF increases nuclear ploidy, inhibits growth of clonal MKs

Qiang *Jeremy Wen*, Ross Levine, ASH 2011, Abstr. 64

A new therapeutic strategy, a new class of drugs:

Rho kinase inhibitor dimethylfasudil (diMF)

Mouse results:

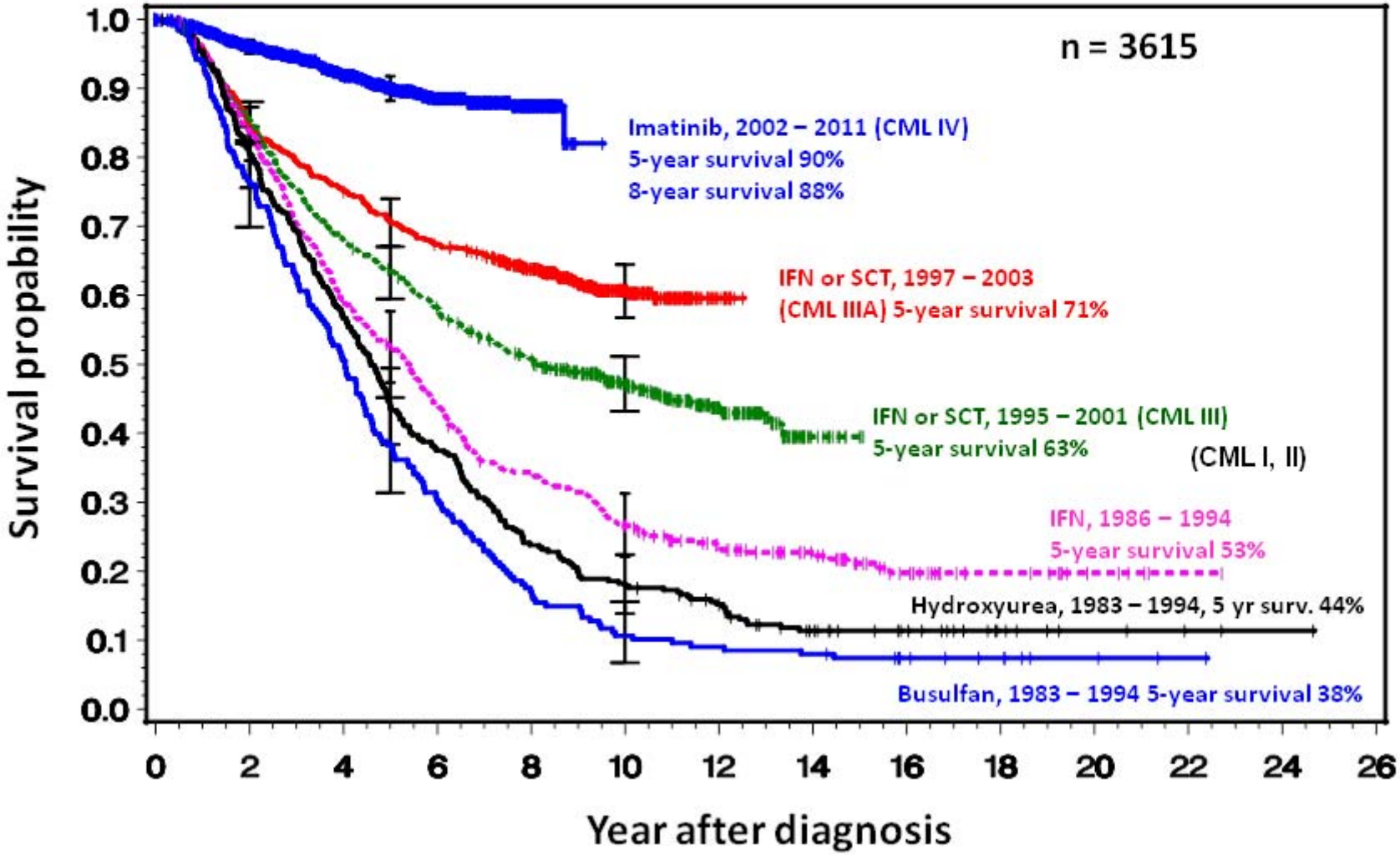
- significant *decrease of fibrosis* in the bone marrow of mouse PMF

- significant reduction in the platelet count

Synergism with JAK2 inhibitors

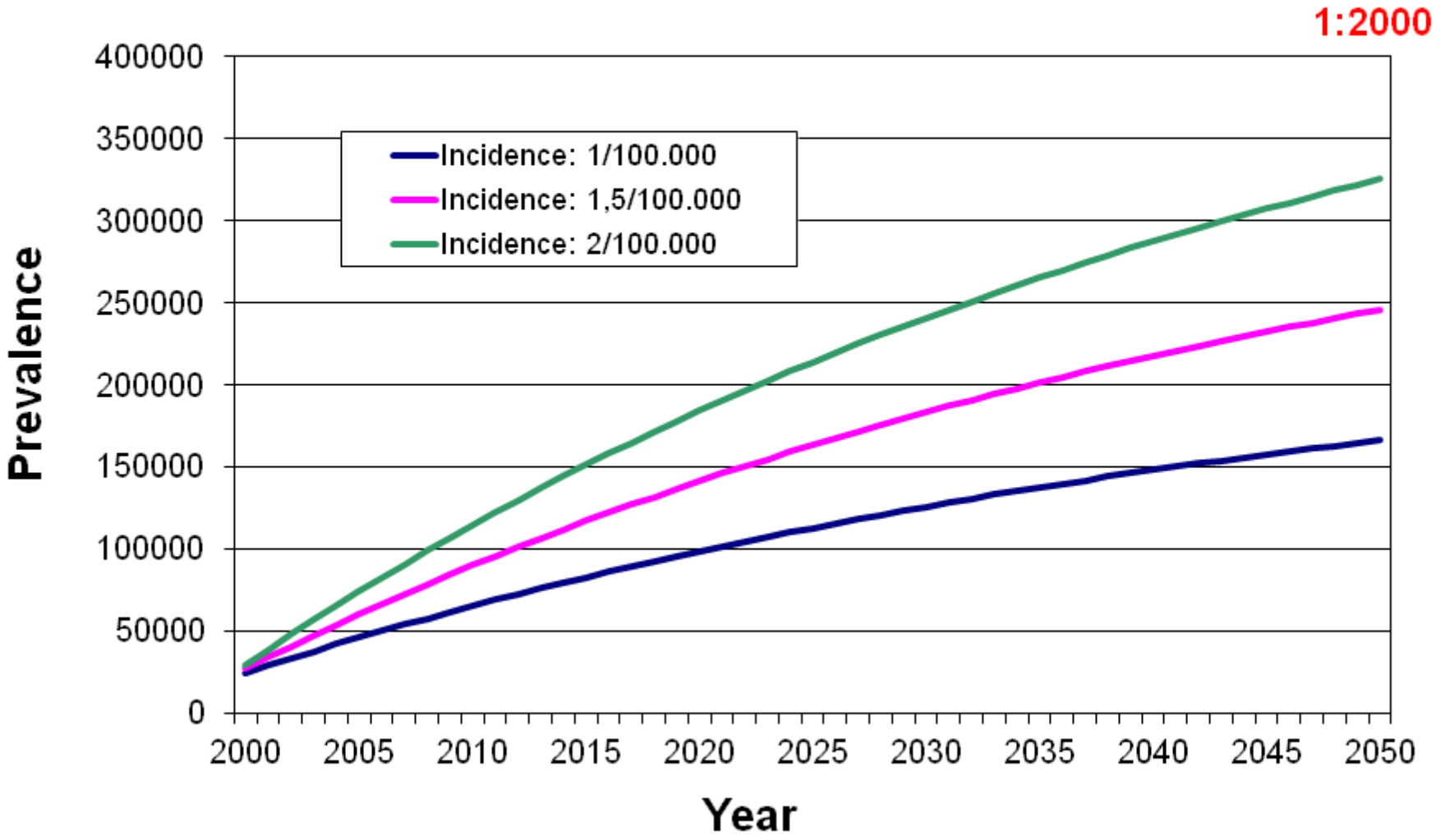
Qiang *Jeremy Wen,* Ross Levine, ASH 2011, Abstr. 64

Improvement of survival of CML by therapy 1983 – 2011



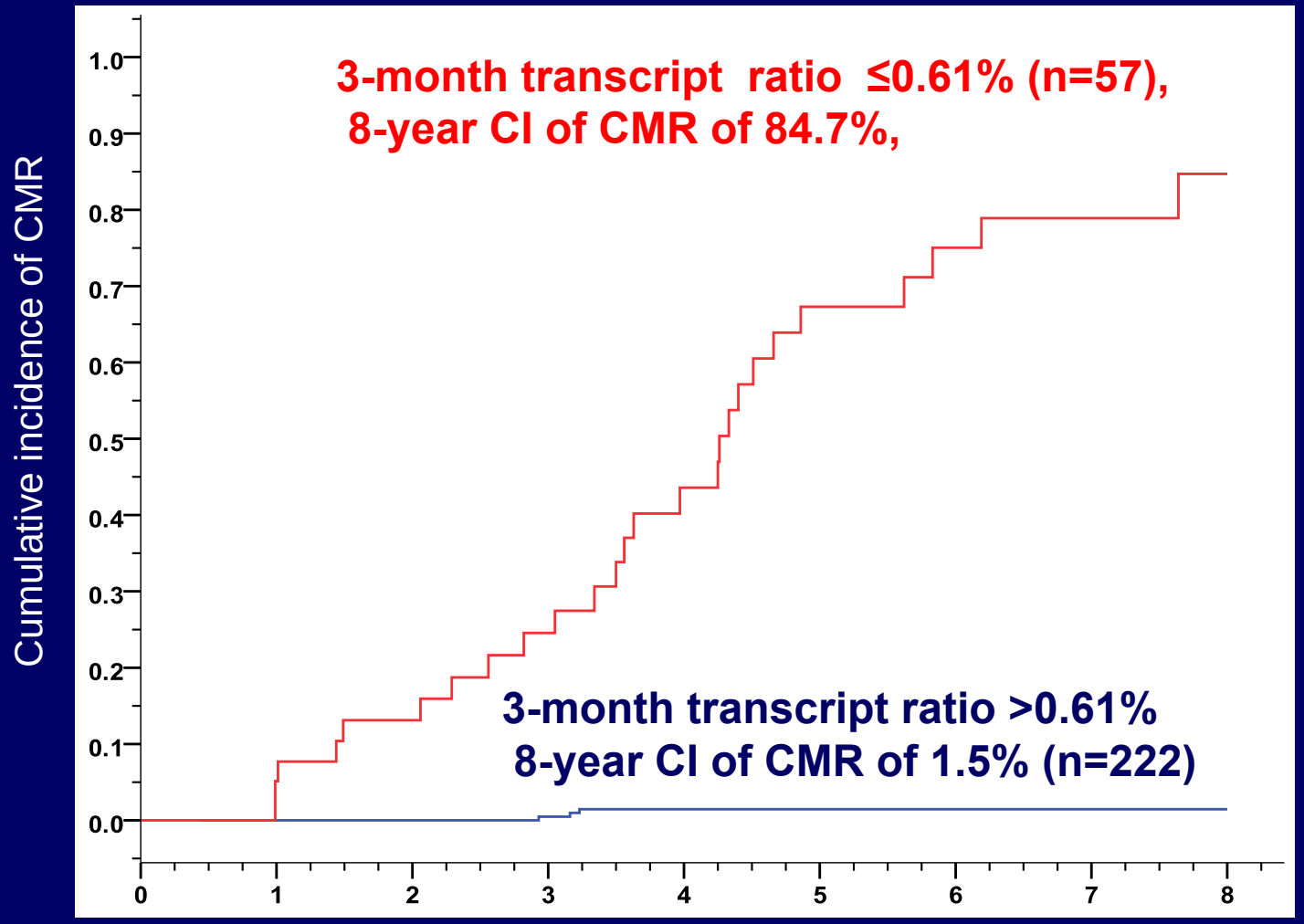
German CML Study Group

Estimated Prevalence of CML in Europe until 2050



Assumptions: Population 500 million, mortality 2% per year, incidence constant.
Courtesy to Hasford and Pfirrmann.

8-year cumulative incidence of CMR on imatinib therapy according to the BCR-ABL transcript level at 3 months: Cut-off below 0.61%



Marin et al, JCO 2012. 30; 232-238

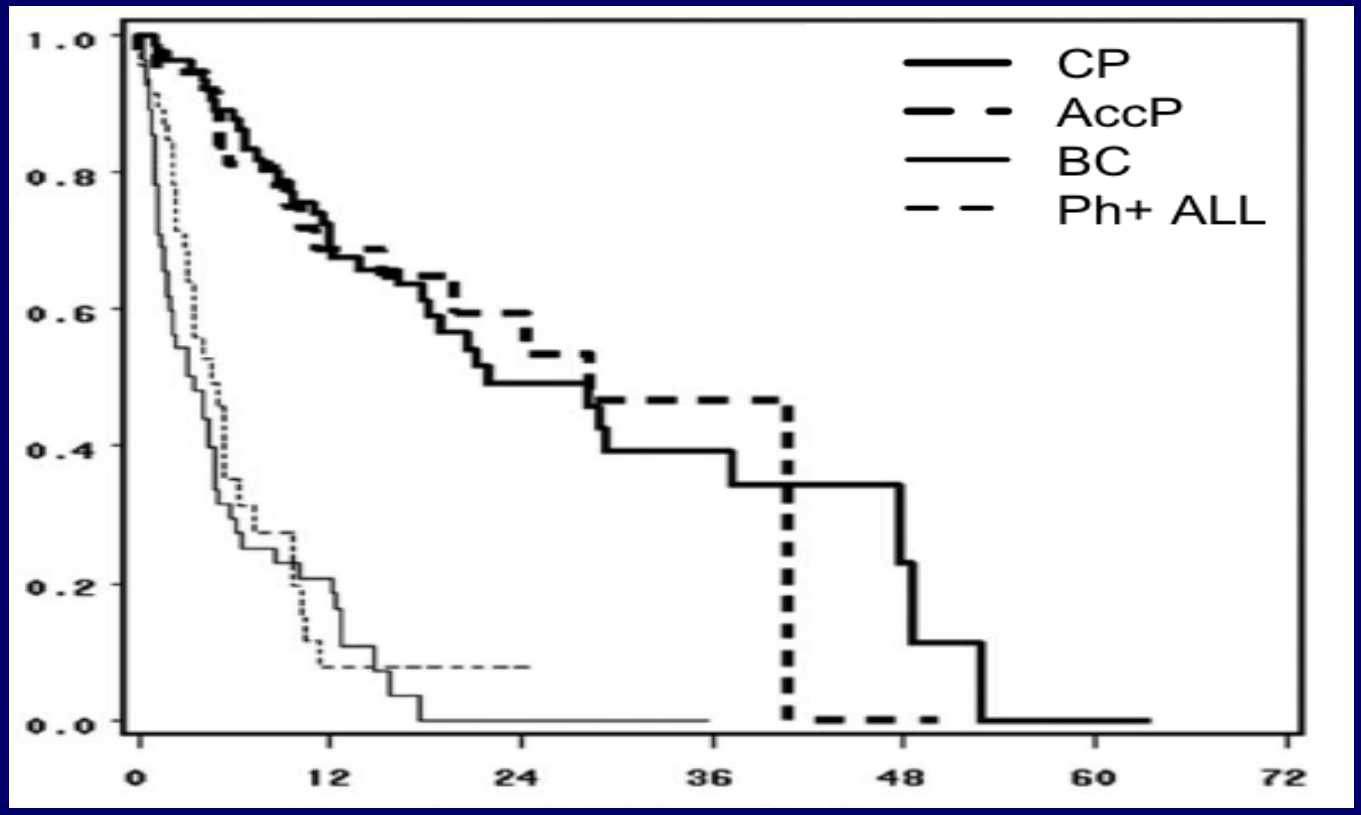
CML Patient outcomes on Imatinib

According with the transcript level measured at 3 months

Outcome	cut-off (%)	Number of patients at risk	Eight years probability of the outcome	P value
OS	**≤9.84** **>9.84**	211 68	**93.3** **56.9**	p<0.0001
PFS	**≤9.54** **>9.54**	208 71	**92.8** **57.0**	p<0.0001
EFS	**≤9.84** **>9.84**	211 66	**65.1** **6.9**	p <0.0001
CCyR	**≤8.58** **>8.58**	169 79	**99.4** **21.7**	p<0.0001
MMR	**≤2.81** **>2.81**	141 137	**82.5** **21.1**	p<0.0001
CMR	**≤0.61** **>0.61**	57 222	**84.7** **1.5**	p<0.0001

Marin et al, JCO 2012. 30; 232-238

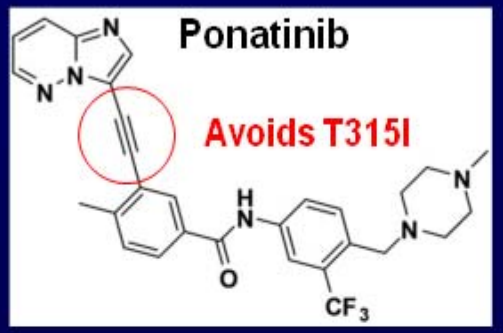
Overall Survival after failing BCR-ABL inhibitor therapy due to T315I mutation

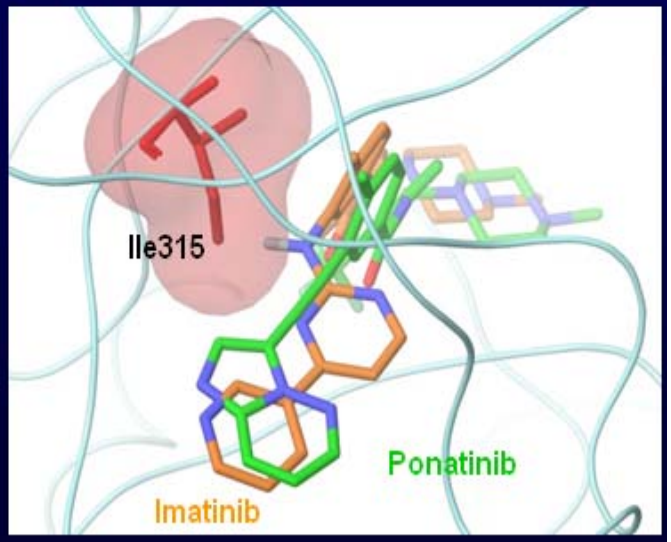


Nicolini F, et al. Blood 2011.

Ponatinib
A Pan-BCR-ABL Inhibitor

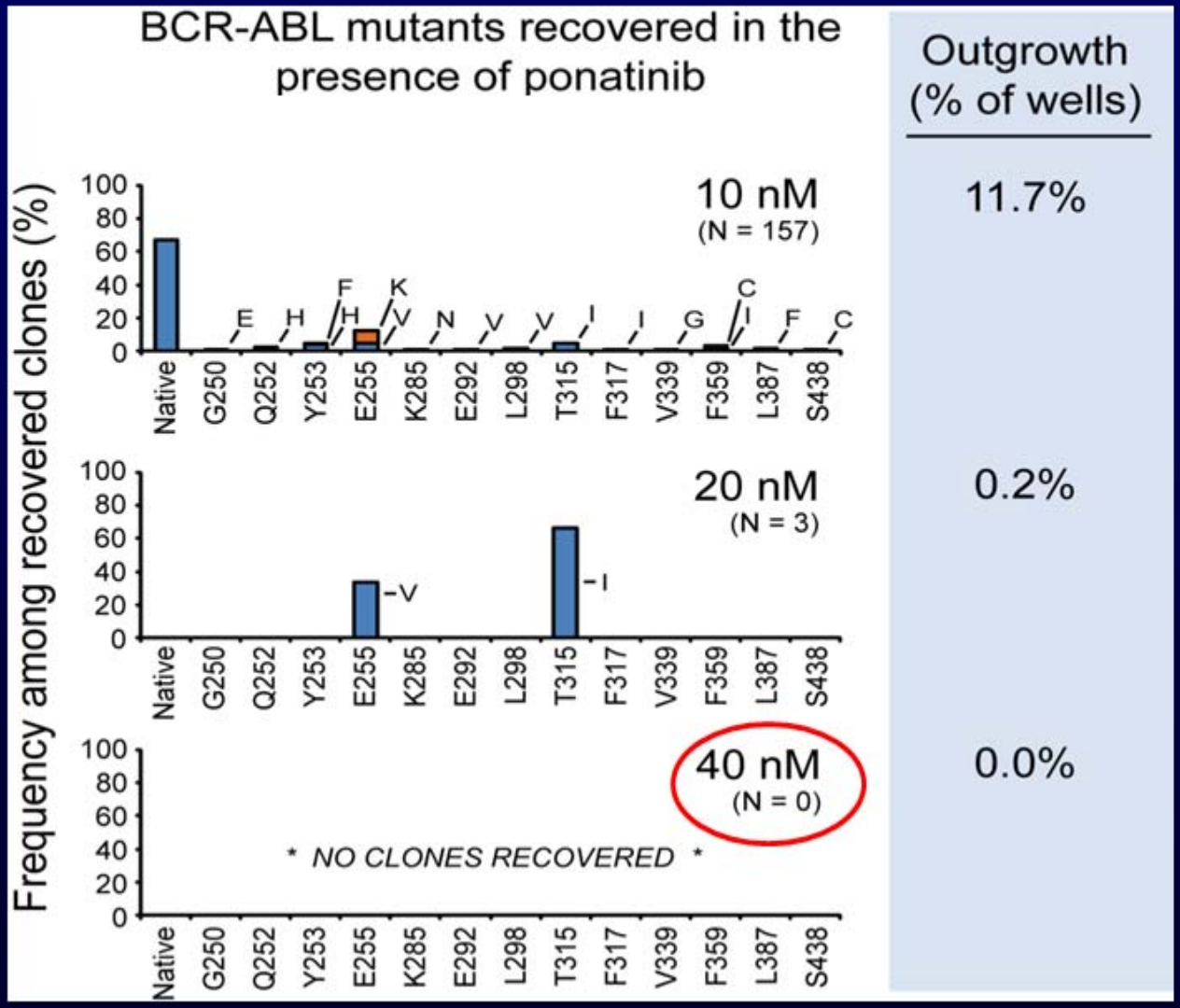
- Rationally designed inhibitor of BCR-ABL
- Active against T315I mutant
  - Unique approach to accommodating gatekeeper residue
- Potent activity against an array of BCR-ABL variants
- Also targets other therapeutically relevant kinases:
  - Inhibits FLT3, FGFR, VEGFR and PDGFR, and c-KIT
- Once-daily oral activity in murine models





O'Hare T, et al. Cancer Cell. 2009;16:401-412

Ponatinib
Suppression of Mutant Outgrowth



- Cells exposed to increasing ponatinib concentrations
- BCR-ABL resistance mutations completely suppressed at 40 nM
- 40 nM target trough plasma ponatinib concentration
- 40 nM attained at doses ≥30 mg

Cortes J, et al. Blood (ASH Annual Meeting Abstracts) 2010; 116: Abstract 210

PACE: Response of CP-CML Cohorts

Response	N (%)		
	Overall	R/I Cohort	T315I Cohort
CHR	193/271 (92)	193/207 (93)	55/64 (86)
MCyR*	116/248 (47)	79/191 (41)	37/57 (65)
CCyR	96/248 (39)	63/191 (33)	33/57 (58)
MMR	51/265 (19)	31/205 (15)	20/60 (33)

*MCyR is primary endpoint

Data as of 02 Dec 2011

Cortes et al, Blood (ASH Annual Meeting Abstracts) 2011 118: Abstract 109

How May Leukemic Stem Cells be Targeted?

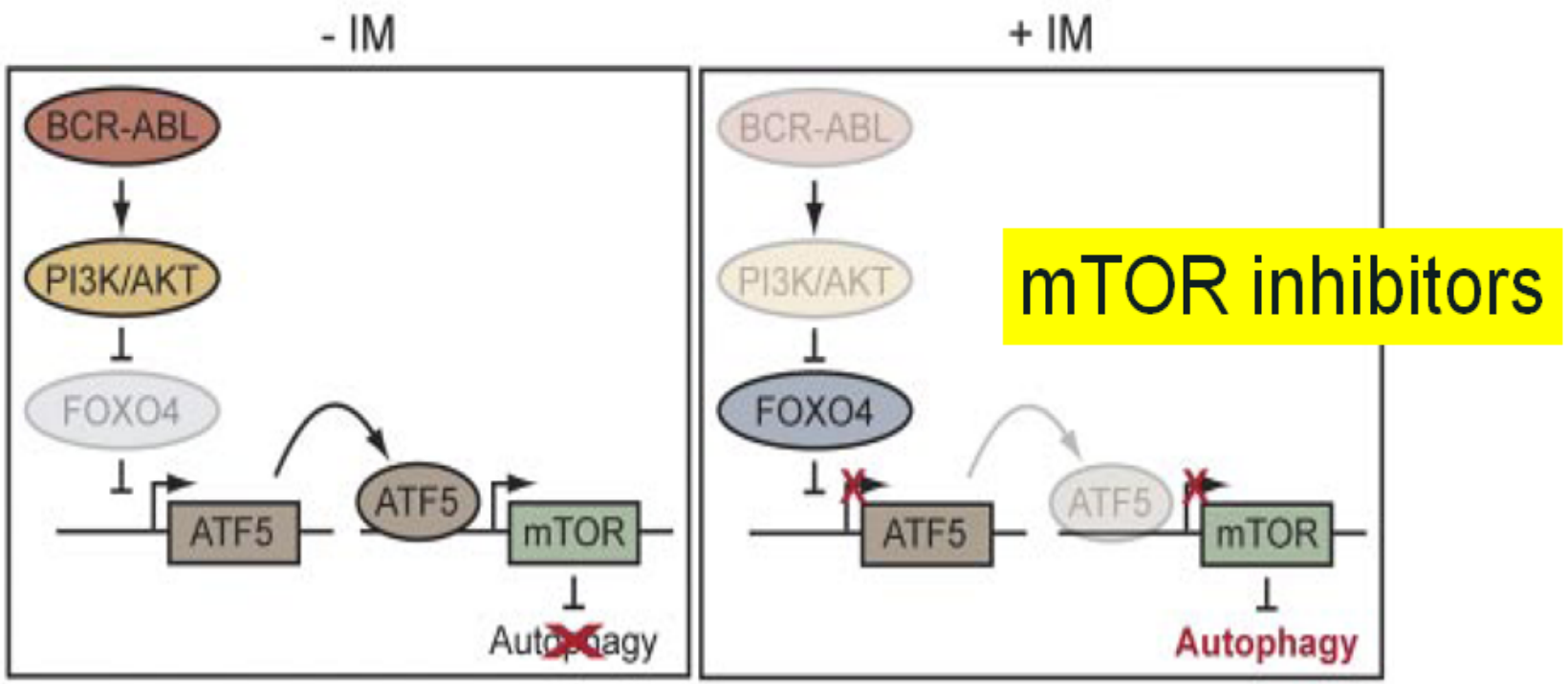
- Targeting critical pathways
  - Hedgehog (LDE225)[1]
  - Janus kinase (JAK2)[2]
- Disrupting interaction of leukemic stem cells with the bone marrow stroma
  - $CXCR^4$ antagonists
  - Granulocyte colony-stimulating factor
- Using immunologic approaches
  - Interferon-α[3]
  - Vaccines
- Using other agents
  - Autophagy inhibitors
  - Histone deacetylase inhibitors[4]
  - Heat shock protein inhibitors[5]
- Using a combination of novel agents with nilotinib?

1. Medina V, et al. *Clin Transpl Oncol*. 2009;11(4):199-207.
2. Kuroda J, Taniwaki M. *Curr Cancer Ther Rev*. 2009;5:303-309.
3. Essers MA, et al. *Nature*. 2009;458(7240):904-908.
4. Isaacs JS, et al. *Cancer Cell*. 2003 Mar;3(3):213-217.
5. Botrugno O, et al. *Cancer Lett*. 2009;208:134-144.

BCR-ABL suppresses autophagy through ATF5-mediated regulation of *mTOR* transcription

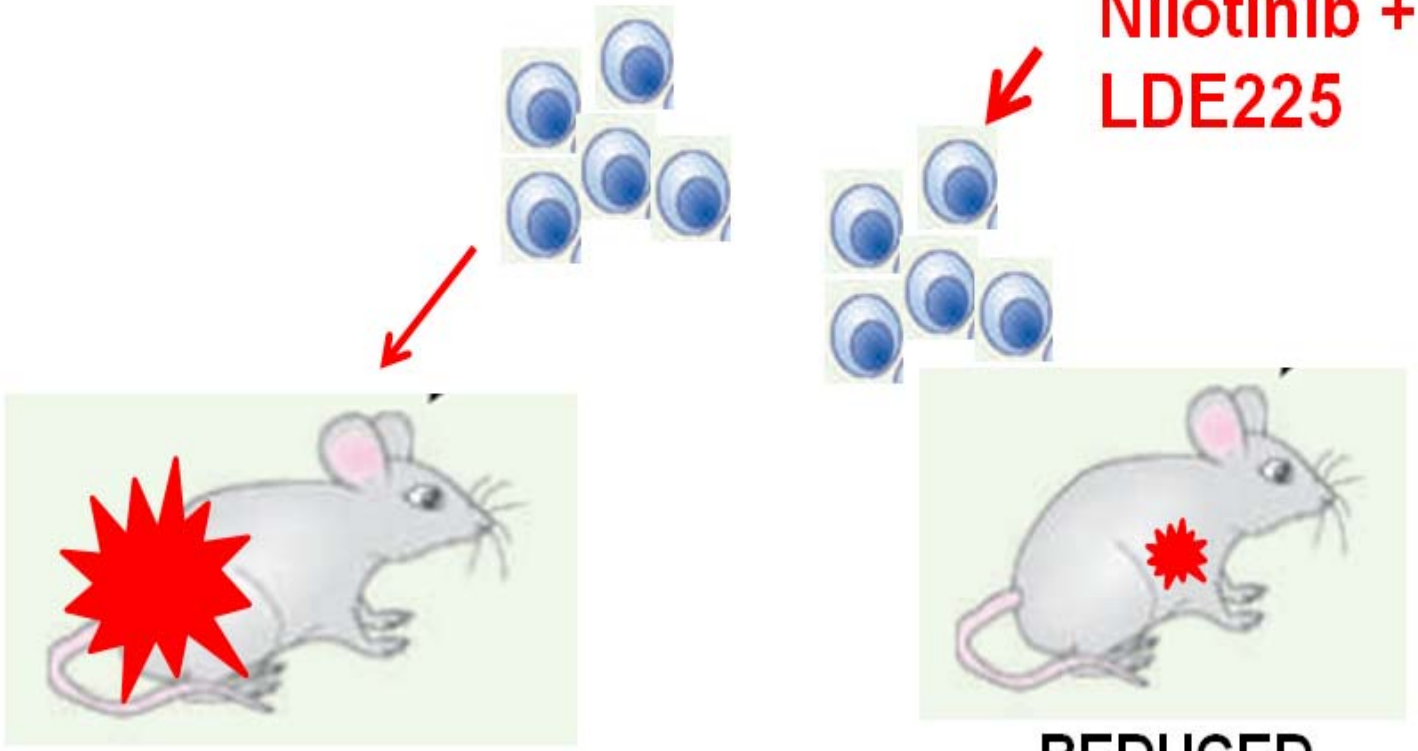
Zhi Sheng,[1] Leyuan Ma,[1] Jiaoyuan E. Sun,[1] Lihua J. Zhu,[2] and Michael R. Green[1]

[1]Howard Hughes Medical Institute, Programs in Gene Function and Expression and Molecular Medicine, University of Massachusetts Medical School, Worcester, MA; and [2]Programs in Gene Function and Expression and Molecular Medicine, University of Massachusetts Medical School, Worcester, MA



Sheng Z et al. Blood. 2011;118(10):2840-8. Epub 2011 Jun 29

Inhibition of Chronic Myeloid Leukemia Stem Cells by the Combination of the Hedgehog Pathway Inhibitor LDE225 with Nilotinib

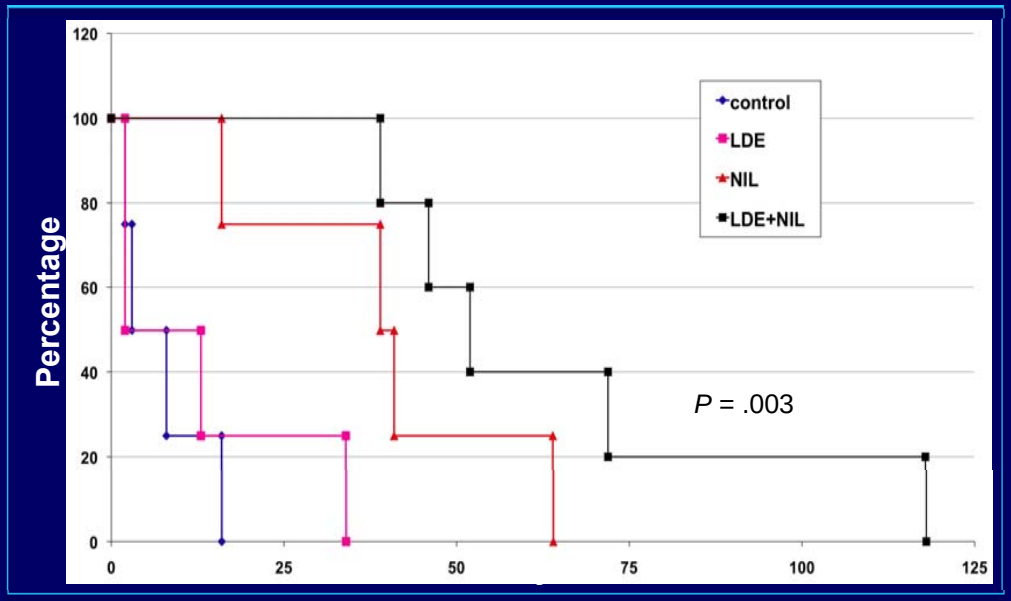


Zhang et al. Blood (ASH annual meeting) 2010; 116: abstract 514

Combination of Nilotinib and LDE225 in CML

Pre-Clinical Rationale

- LDE225 is an inhibitor of the hedgehog signaling pathway, which may be important for survival of leukemic stem cells
- Mice treated with LDE225 + nilotinib demonstrated enhanced survival following discontinuation of treatment



Day 0 = On completion of 3 weeks treatment

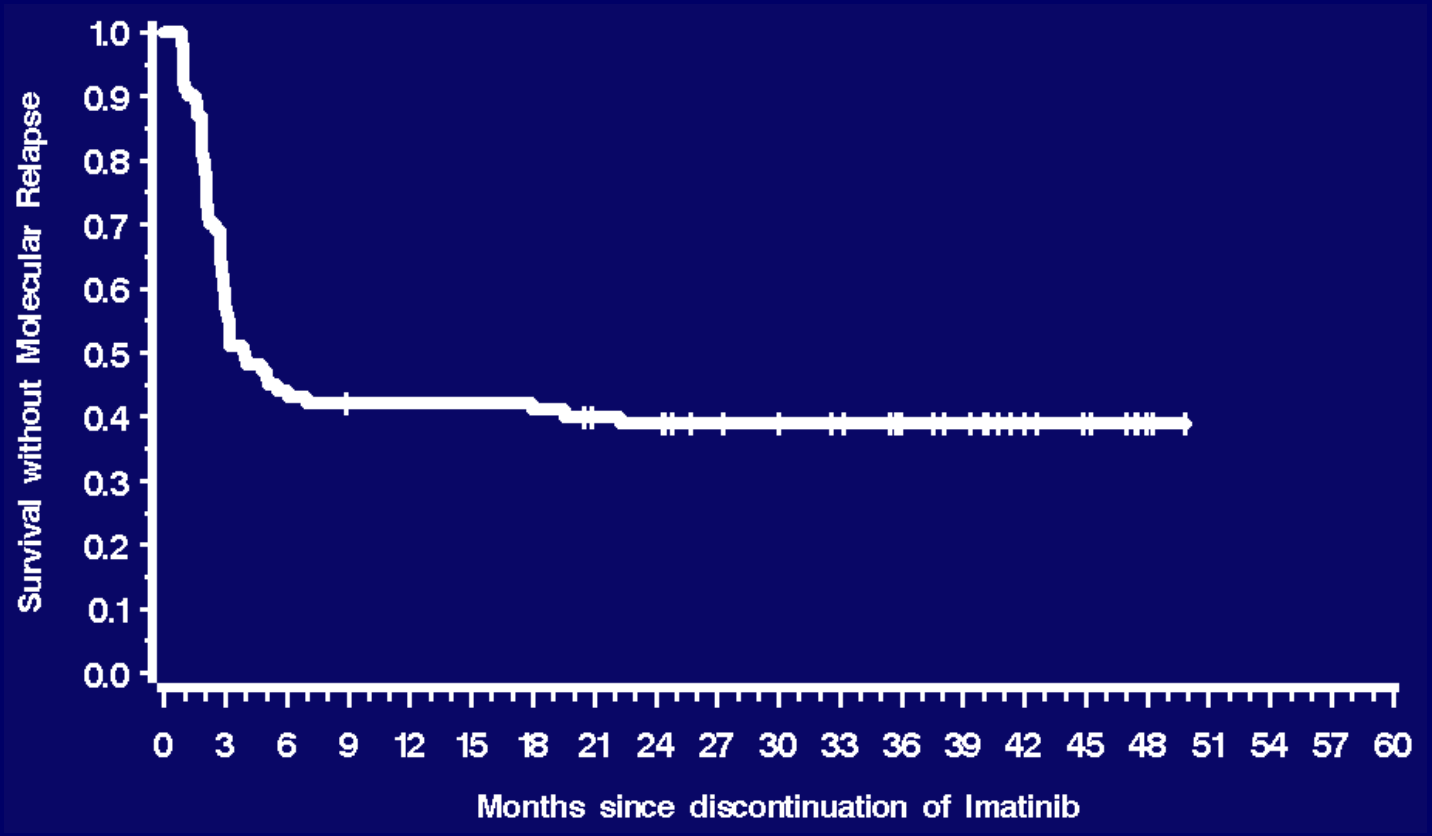
Clinical Study Plan

- Phase I/II study in 2nd/3rd line CML patients beginning in 2011
- Plans for subsequent dose expansion phase
- Data expected 2013-14
- Exploratory biomarkers for activity against leukemic stem cells

Zhang B, et al. *Blood*. 2010;116(21):227 [abstract 514].

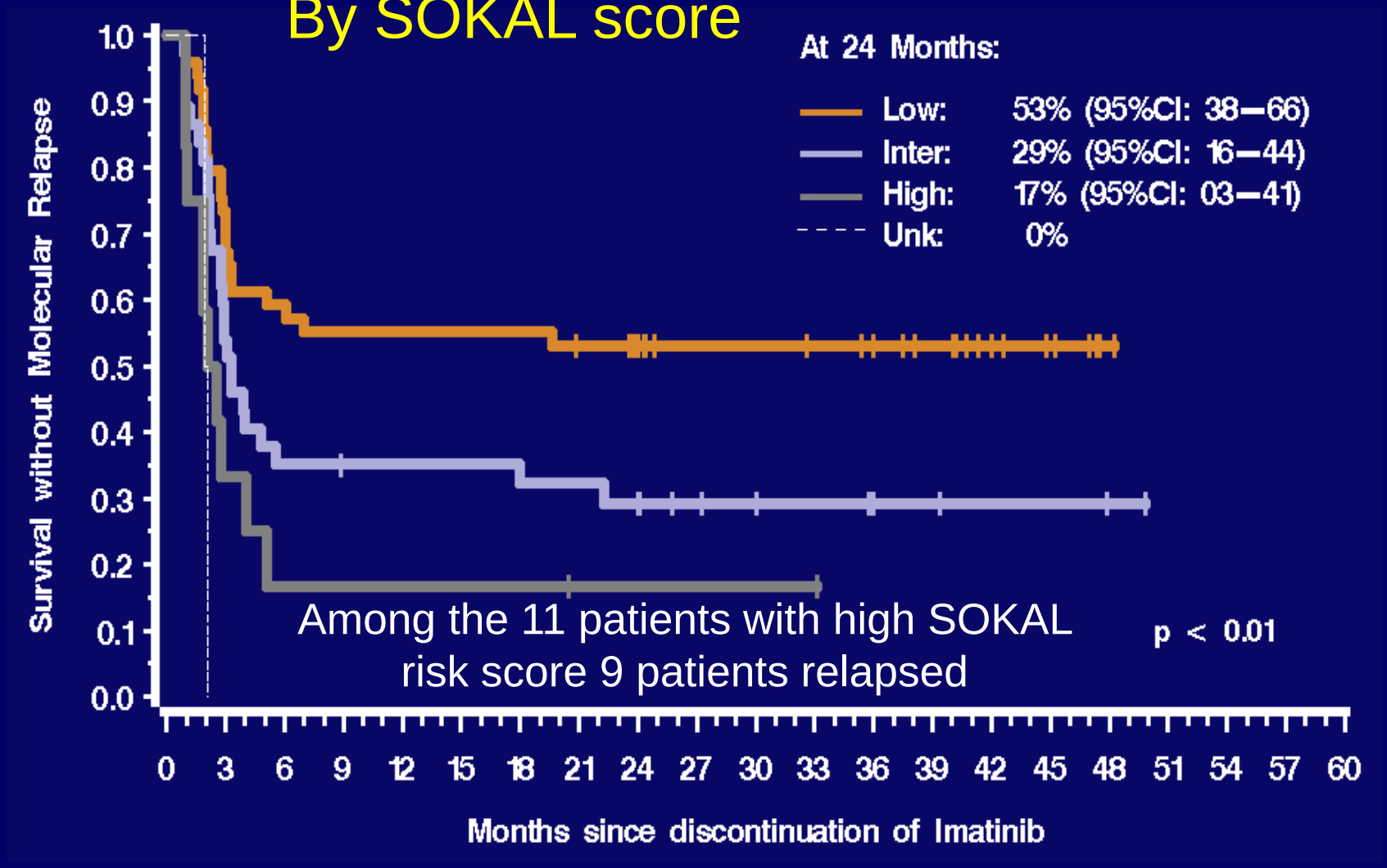
Kaplan-Meier estimates of CMR after discontinuation of imatinib

The overall probability of maintenance of CMR at 24 and 36 months was 39% (95% CI 29-48).

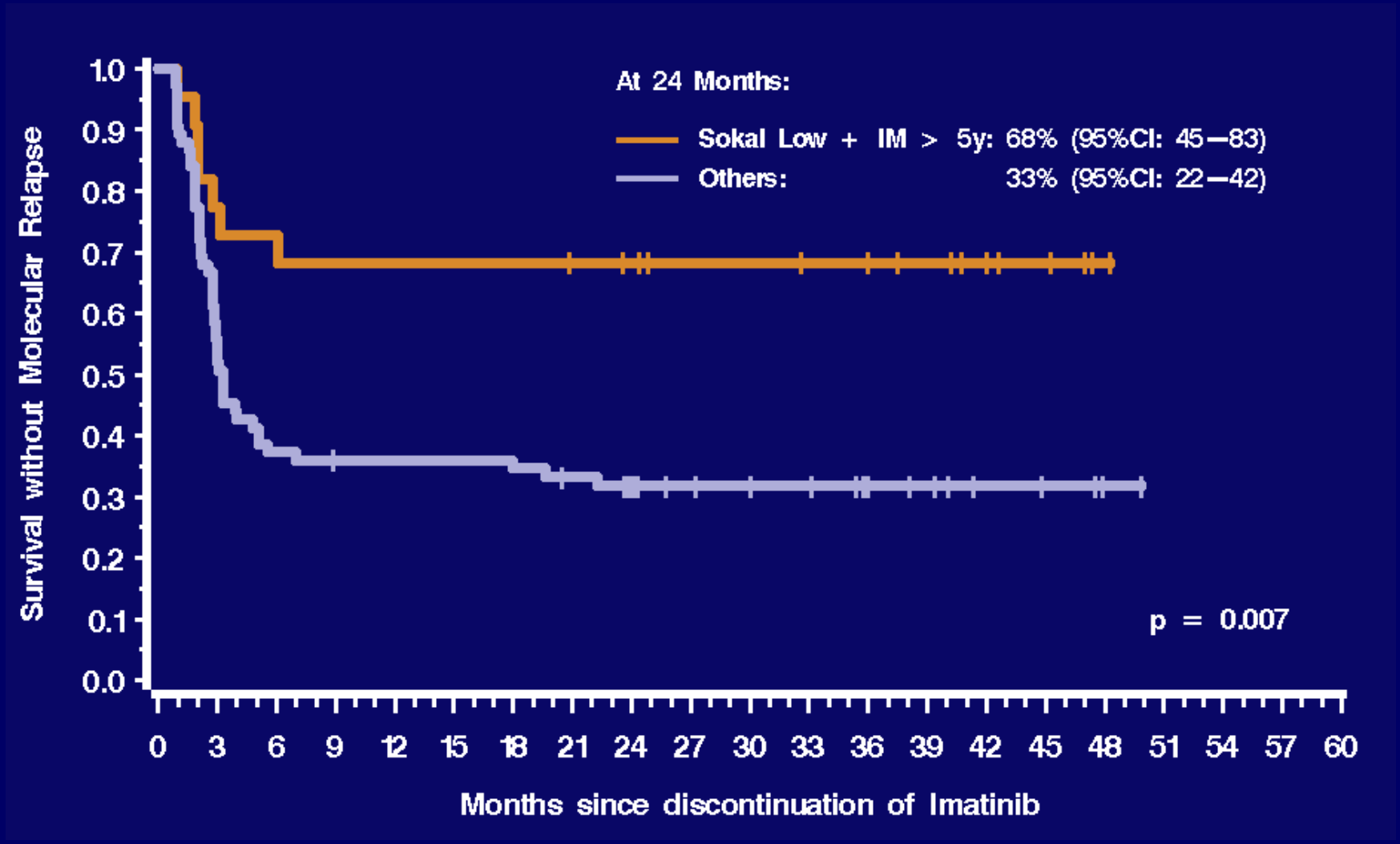


Molecular relapse occurred in 61 pts with 58 relapses occurring during the first 7 months 3 late relapses at month 19, 20 and 22, respectively

Kaplan-Meier estimates of CMR after discontinuation of imatinib in 100 patients with CML according to factor

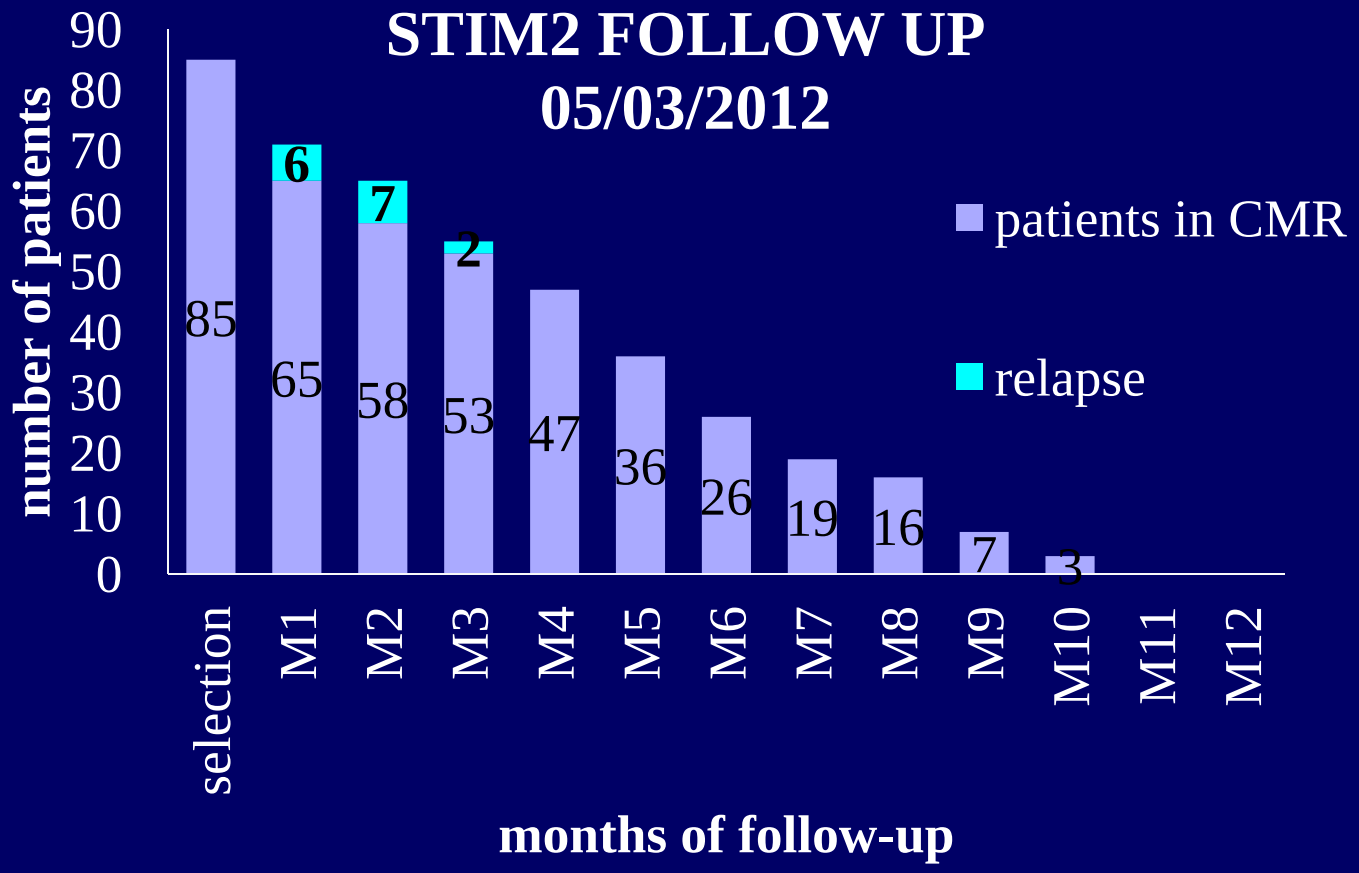


Kaplan-Meier estimates of CMR after discontinuation of imatinib in 100 pts according to combined factors



STIM 2 study

- Start in June 2011
- Median duration of CMR before stopping : 41 months (25-99)
- 15 pts confirmed molecular recurrence*
- 30 pts unconfirmed molecular recurrence

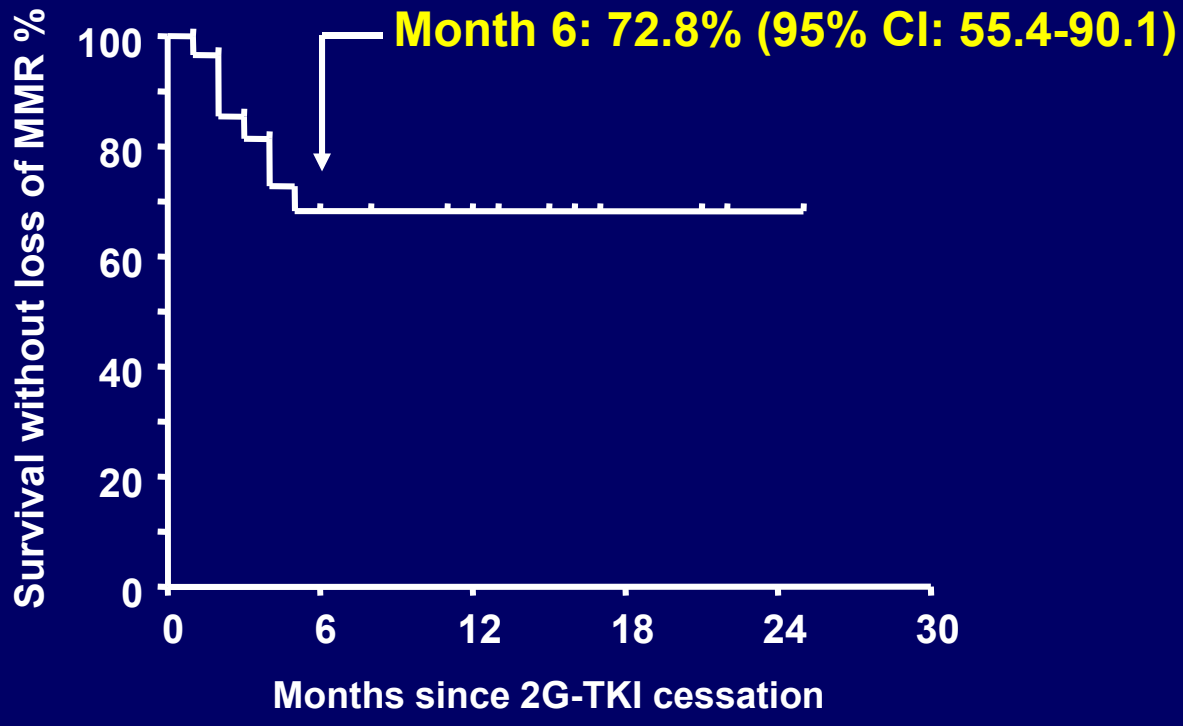


*Molecular recurrence was defined as positivity of *BCR–ABL* transcript in quantitative RT-PCR confirmed by *a* second analysis point, indicating the increase of one log in relation to the first analysis point at two successive assessments or loss of MMR at one point.

2G-TKI stopping study
Stable MMR by 6 months

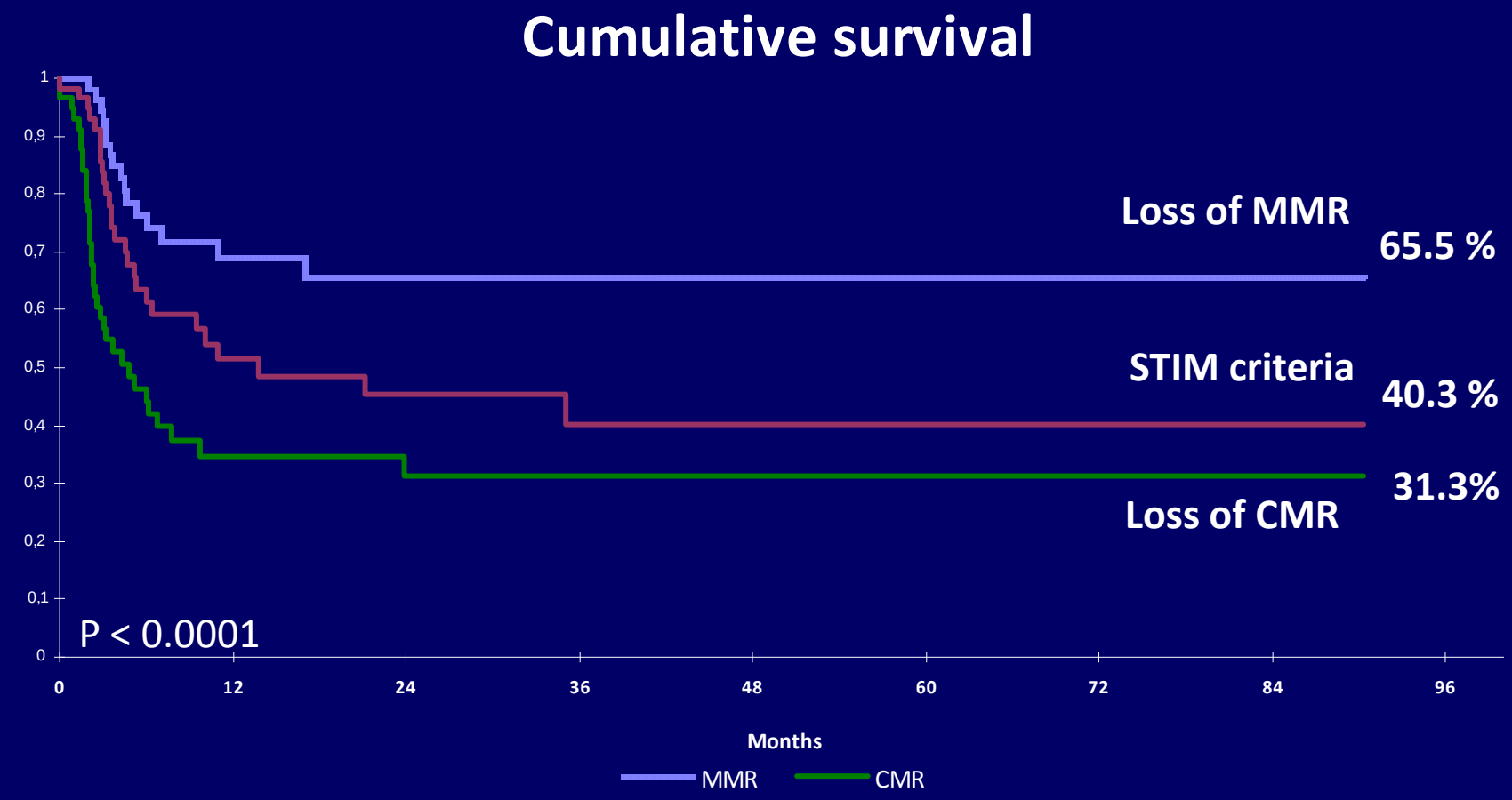
- **Following 2G-TKI cessation, 8 pts lost MMR after a median time off-therapy of 2 months (2-5)**

Kaplan-Meier estimate of stable MMR after 2G-TKI cessation



Rea et al. Blood. 2011;118(21) [abstract 604].

Impact of the use of loss of MMR as a relapse criteria



Muchas Gracias…