

# LEUKEMIA

## ANCO's ASH Highlights

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02/10/2009

### TOPICS

- CML
  - Abstract 181 and 182
  - Abstract 186 and 335
- CLL
  - Abstract 325 and 45
- APL
  - Abstract 138
- ALL
  - Abstract 427 and 428

## CML

- Rosti et al. High and Early Rates of Cytogenetic and Molecular Response with Nilotinib 800 Mg Daily as First Line Treatment of Ph-Positive Chronic Myeloid Leukemia in Chronic Phase: Results of a Phase 2 Trial of the GIMEMA CML Working Party. Abstract 181
- Cortes J et al. Efficacy of dasatinib in patients (pts) with previously untreated chronic myelogenous leukemia (CML) in early chronic phase (CML-CP). Abstract 182.
- O'Brien S et al. The IRIS Study in Early Chronic Phase CML: 7 year Follow-up. Abstract 186.
- Cortes J et al. A Phase III, Randomized, Open-Label Study of 400 Mg Versus 800 Mg of Imatinib Mesylate (IM) in Patients (pts) with Newly Diagnosed, Previously Untreated Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Using Molecular Endpoints: 1-Year Results of TOPS (Tyrosine Kinase Inhibitor Optimization and Selectivity) Study. Abstract 335.

High and Early Rates of Cytogenetic and  
Molecular Response with Nilotinib 800 Mg  
Daily as First Line Treatment of Ph-Positive  
Chronic Myeloid Leukemia in Chronic Phase:  
Results of a Phase 2 Trial of the GIMEMA  
CML Working Party

## Abstract 181

- Imatinib 400 mg daily is the standard treatment for CML in chronic phase:
  - IRIS trial (72 months)
    - OS- 95%
    - EFS and PFS were 83% and 93%
    - Cumulative rate of CCgR @ 60 months was 87%
- Nilotinib, a second generation TKI, has a higher binding affinity and selectivity for Abl
  - 20 to 50 times more active than imatinib
- Investigate the therapeutic efficacy and the safety of nilotinib 400 mg BID in untreated, ECP, CML patients, the italian GIMEMA CML Working Party
  - Open-label, single stage, multicentric, phase II study trial
  - The median age was 51 years (range 18–83),
  - Median follow-up is currently 210 days (range 68–362).

## Abstract 181

- 73 enrolled (at 3 and 6 months):
  - CHR rate was 100% and 98%
  - the CCgR rate 78% and 96%
  - A MMR (BCR-ABL:ABL ratio < 0.1%) was 59% and 74%.
- Median daily average dose was 789 mg (range 261 – 800).
- Grade 3/4 hematologic toxicity - 5%
- Frequent biochemical laboratory abnormalities (grade III) were total bilirubin increase (15%), AST/ALT increase (11%) and lipase increase (4%).
- ECG monitoring: 22% transient and not clinically relevant ECG abnormalities have been recorded
  - 3% revealed a transient and uneventful QTc prolongation (>450 but <499 msec).
- Nilotinib is highly effective and safe in chronic phase CML

Efficacy of dasatinib in patients (pts) with previously untreated chronic myelogenous leukemia (CML) in early chronic phase (CML-CP)

## Abstract 182

- Imatinib induces CCyR in 82% of patients with early chronic phase CML
- Molecular complete remissions infrequent with standard dose imatinib
- Dasatinib induced CCyR in:
  - 45% with imatinib resistance
  - 78% with imatinib intolerance

## Study Design

- Patients randomized to daily vs. twice daily schedule

Dose level	Dose in mg/dose	
	Daily	Twice daily
+1	140 mg	70 mg
<b>Starting dose</b>	<b>100 mg</b>	<b>50 mg</b>
-1	80 mg	40 mg
-2	40 mg	20 mg

- Maximum 50 patients per arm
- Two endpoints: MMR and toxicity by 12 months

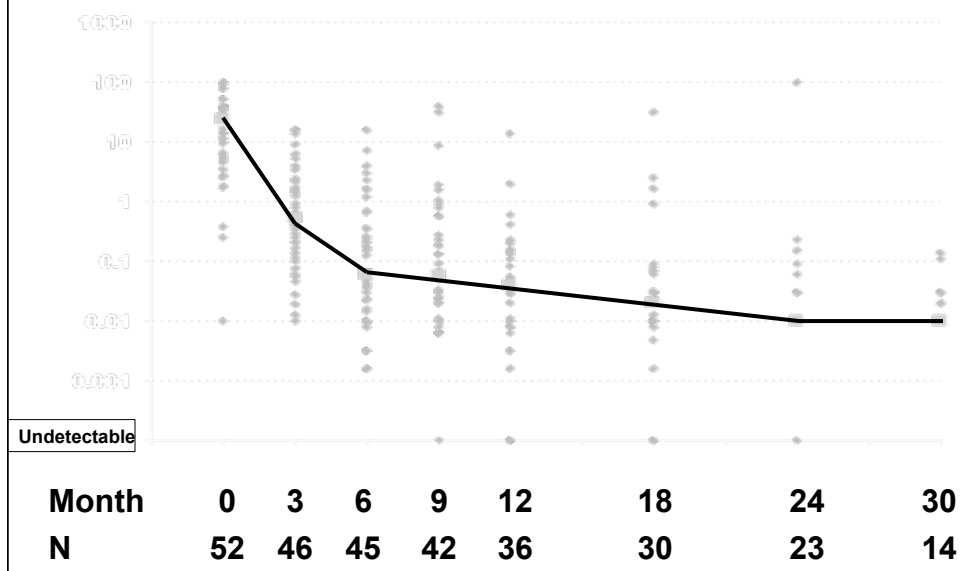
## Patient Characteristics (N=52)

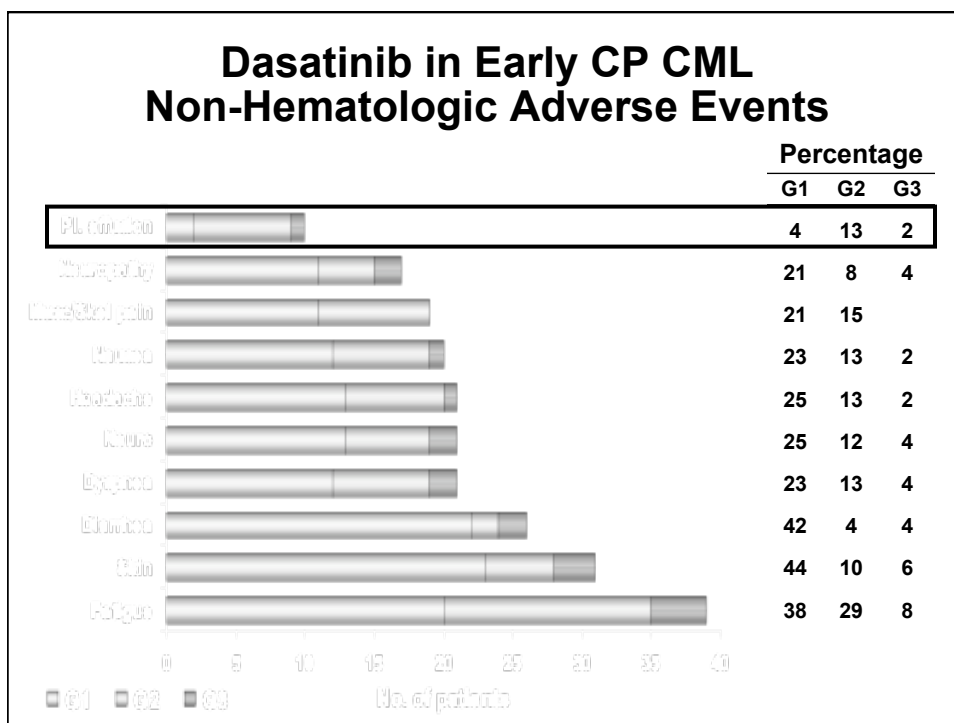
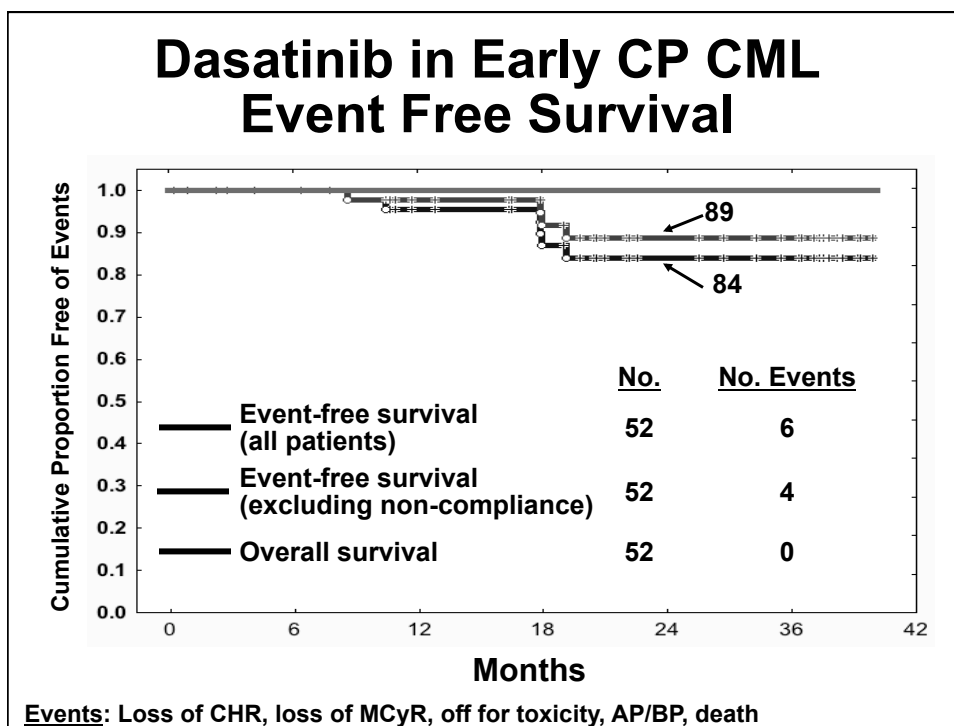
Characteristics	No.(%) or Median (range)
<b>Age, yr</b>	<b>46 (19-77)</b>
<b>Schedule</b>	
<b>QD</b>	<b>26 (50)</b>
<b>BID</b>	<b>26 (50)</b>
<b>Follow-up, mo</b>	<b>23 (1-34)</b>

## Overall Response (N=49)

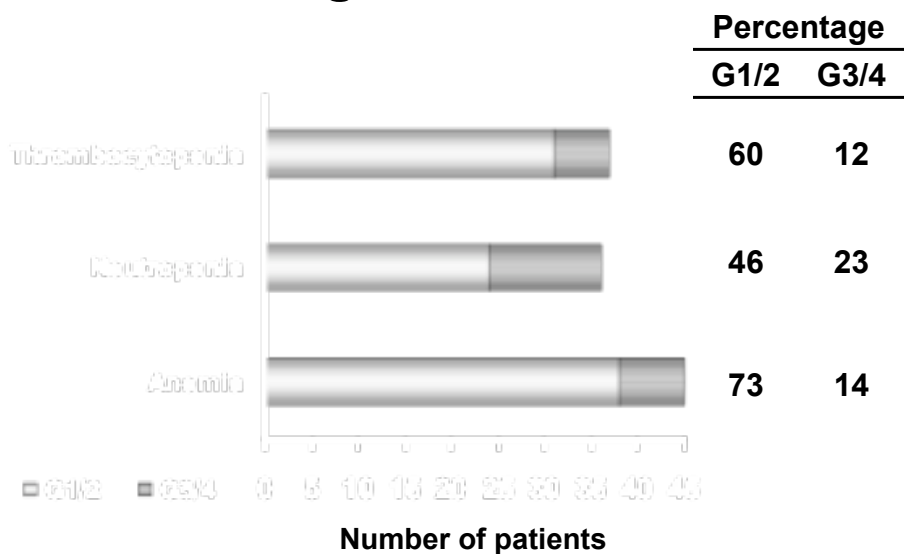
Response	No. (%)
<b>CHR</b>	<b>49/49 (100)</b>
<b>Cytogenetic Response*</b>	
<b>CCyR</b>	<b>47/48 (98)</b>
<b>Molecular Response</b>	
<b>MMR</b>	<b>24/48 (50)</b>
<b>CMR</b>	<b>3/48 (6)</b>

## Molecular Responses





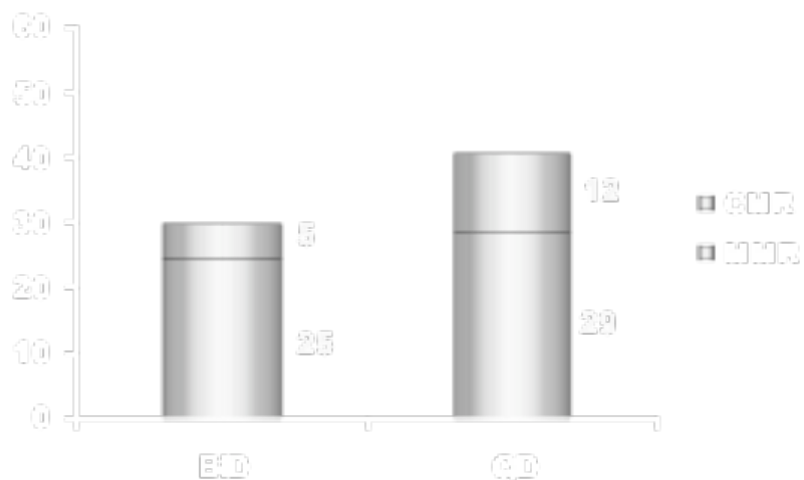
## Dasatinib in Early CP CML Hematologic Adverse Events



## Dose Intensity

- Pts with Rx interruptions 28 (54%)
- Median days Rx interrupted (range) 10 (1-149)
- Median daily dose (range) 100 (20-100)
- Dose reduction by schedule BID 12/26, QD 8/26

### Dasatinib in Early CP CML Molecular Response at 12 Months by Dose Schedule (N=36)



### CCR in Early CP CML

Parameter	Percent CCyR		
	IM 400 N=50	IM 800 N=205	Dasatinib* N=52
3 mo	37	62	79
6 mo	54	82	93
12 mo	65	86	95
18 mo	68	90	88

\* Evaluable: 48 at 3 mo, 43 at 6 mo, 37 at 12 mo, 32 at 18 mo.

## MMR in Early CP CML

Parameter	Percent MMR		
	IM 400 N=50	IM 800 N=205	Dasatinib* N=40
6 mo	0	34	20
12 mo	24	47	35
18 mo	42	52	48

\* Evaluable: 45 at 6 mo, 36 at 12 mo, 30 at 18 mo

## Conclusions

- **Dasatinib induced rapid complete cytogenetic responses in most patients**
- **Most patients able to receive target dose**
- **Cytogenetic responses faster than with standard dose imatinib**
- **Molecular responses comparable with high-dose imatinib at 18 months**

## **The IRIS Study in Early Chronic Phase CML: 7 year Follow-up**

O'Brien S et al. *Blood* 2008;112(11): Abstract 186 (oral)

### **IRIS 7 Year Update: Main Points**

- What happened to all the patients?
  - Discontinuation
  - Survival
- Late progression events
- PCR data
- Adverse Events
- Conclusions

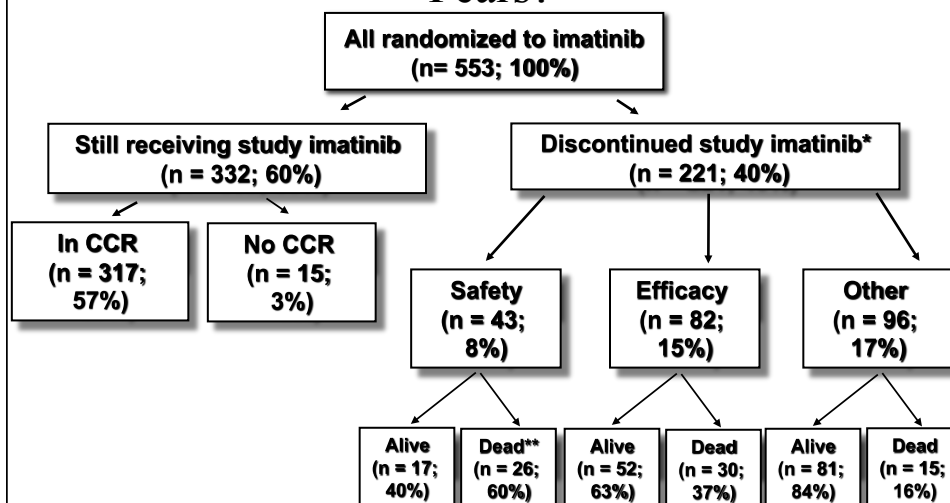
O'Brien S et al. *Blood* 2008;112(11): Abstract 186 (oral)

## IRIS 7 Year Update

- This report is the 7 year update of IRIS
  - 1106 patients originally, 553 per arm
  - 554 of 1106 (50%) patients remained on study
    - 545 of these 554 (98.4%) patients were on imatinib
      - 332 on first-line (60% of patients randomized to first-line imatinib, 400 mg daily)
      - 213 patients crossed over from IFN/Ara-C (39% of patients randomized to IFN/Ara-C)
    - 9 patients (1.6%) remained on IFN/Ara-C

O'Brien S et al. *Blood* 2008;112(11): Abstract 186 (Oral).

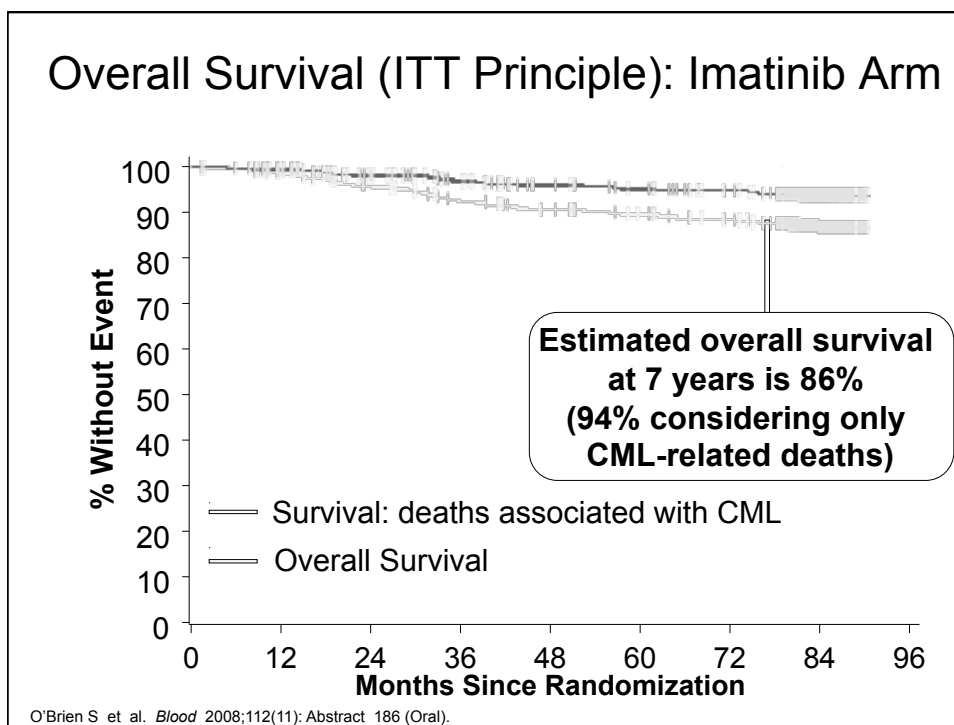
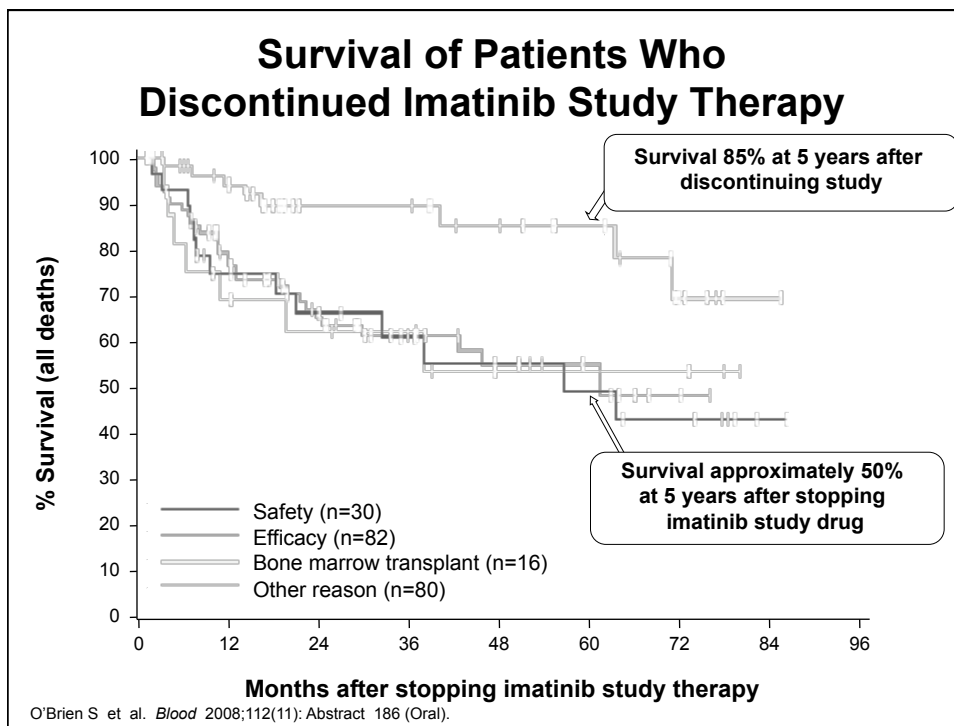
## What Happened To The Patients After 7 Years?



\*\*Including primary discontinuation reason 'Death' (n=13)

\*Patients may have continued imatinib off study.

O'Brien S et al. *Blood* 2008;112(11): Abstract 186 (Oral).



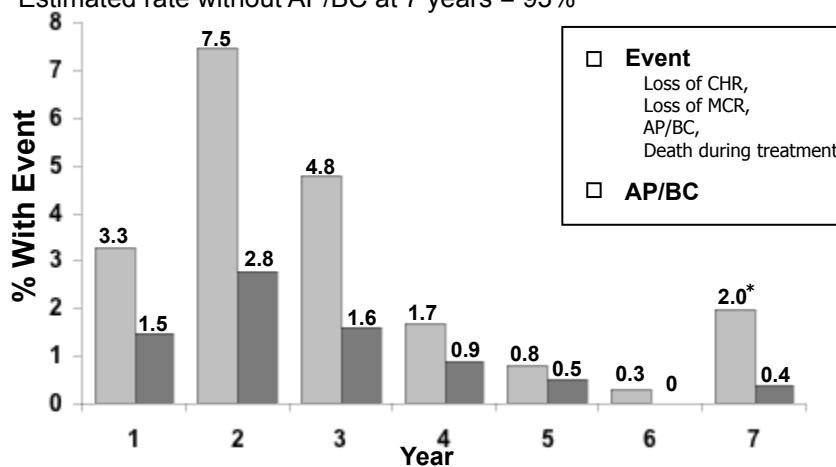
## IRIS 7 Year Update: Main Points

- What happened to all the patients?
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O'Brien S et al. *Blood* 2008;112(11): Abstract 186 (Oral).

## Annual Event Rates: Imatinib Arm

- EFS at 7 years = 81%
- Estimated rate without AP/BC at 7 years = 93%



\*Total events (n=5) including loss of MCR (n=3) and deaths (n=2, one of which was coded as progression to AP/BC in a patient in CMR 6 months prior to death).

O'Brien S et al. *Blood* 2008;112(11): Abstract 186 (Oral).

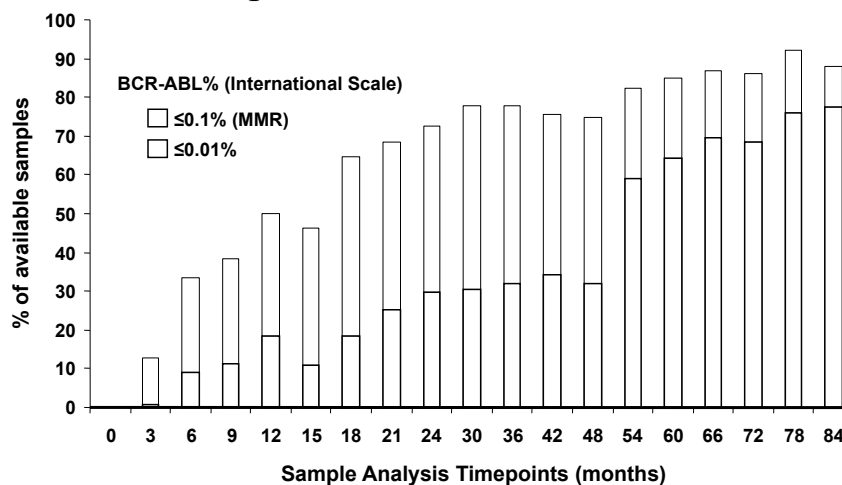
## IRIS 7 Year Update: Main Points

- What happened to all the patients?
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  - Survival
- Late progression events
- PCR data
- Adverse Events
- Conclusions

O'Brien S et al. *Blood* 2008;112(11): Abstract 186 (Oral).

## Molecular Response Rates

- Major molecular response (MMR) and the depth of molecular response increase over time



O'Brien S et al. *Blood* 2008;112(11): Abstract 186 (Oral).

## IRIS 7 Year Update: Main Points

- What happened to all the patients?
  - Discontinuation
  - Survival
- Late progression events
- Durability of complete cytogenetic response (CCR)
  - Is CCR a 'safe haven'?
- PCR data
- Adverse Events
- Conclusions

O'Brien S et al. *Blood* 2008;112(11): Abstract 186 (Oral).

## Most Frequently Reported AEs

<b>Most Common AE (by 5 Years)</b>	<b>All Grade AEs Patients, %</b>	<b>Grade 3/4 AE's Patients %</b>
Superficial Edema	60	2
Nausea	50	1
Muscle cramps	49	2
Musculoskeletal pain	47	5
Diarrhea	45	3
Rash/skin problems	40	3
Fatigue	39	2
Headache	37	<1
Abdominal pain	37	4
Joint pain	31	3

- Grade 3/4 adverse events decreased in incidence after years 1-2

## IRIS SAEs in Years 6 and 7

- No unique, previously unreported AEs attributed to imatinib observed over the past 24 months
- In years 6 and 7, 13 SAEs with suspected relationship to imatinib were reported:
  - Congestive Heart Failure (n=3): all of the patients had pre-existing cardiac disease prior to study entry
  - Second malignancy (n=3)\*
  - Myositis (n=1); elevated CK (n=1); multiple sclerosis (n=1)
  - Pancreatitis (n=1); vomiting (n=1)
  - Renal failure (n=1), Dermatitis (n=1)

O'Brien S et al. *Blood* 2008;112(11): Abstract 186 (Oral).

## Conclusions

- Overall Survival 86%
- Event Free Survival 81%; 7% progressed to AP/BC on imatinib
- 40% patients discontinued *study* imatinib
- CCR achieved by 456 of 553 (82%) of patients
  - 17% of those achieving CCR subsequently lost CCR
  - 3% of those achieving CCR progressed to AP/BC
  - Of 456 patients who achieved CCR, 10 (2%) died from CML
  - Time taken to achieve CCR did not correlate with rates of progression to AP/BC
- MMR rates and the depth of molecular responses in patients increase over time

O'Brien S et al. *Blood* 2008;112(11): Abstract 186 (Oral).

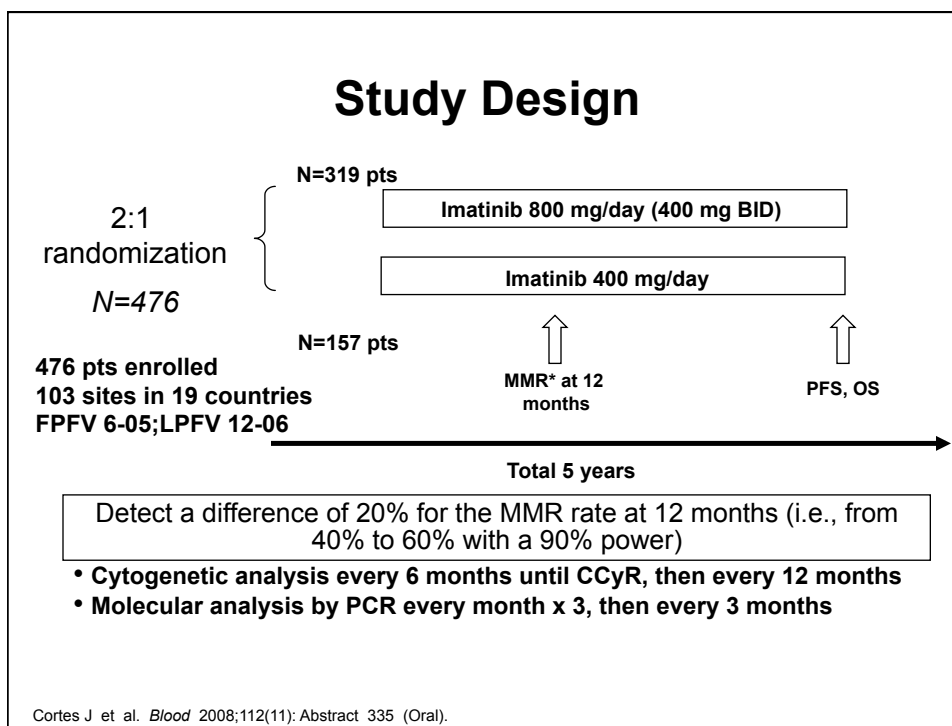
**A Phase III, Randomized, Open-Label Study  
of 400 Mg Versus 800 Mg of Imatinib  
Mesylate (IM) in Patients (pts) with Newly  
Diagnosed, Previously Untreated Chronic  
Myeloid Leukemia in Chronic Phase (CML-  
CP) Using Molecular Endpoints: 1-Year  
Results of TOPS (Tyrosine Kinase Inhibitor  
Optimization  
and Selectivity) Study**

Cortes J et al. *Blood* 2008;112(11): Abstract 335 (Oral).

**Background**

- **Frontline imatinib therapy induces high rates of durable cytogenetic and molecular response**
- **Most patients may remain with residual disease**
- **Early responses may minimize risk of progression**
- **Dose escalation may improve outcome of patients after failure to 400 mg**

Cortes J et al. *Blood* 2008;112(11): Abstract 335 (Oral).

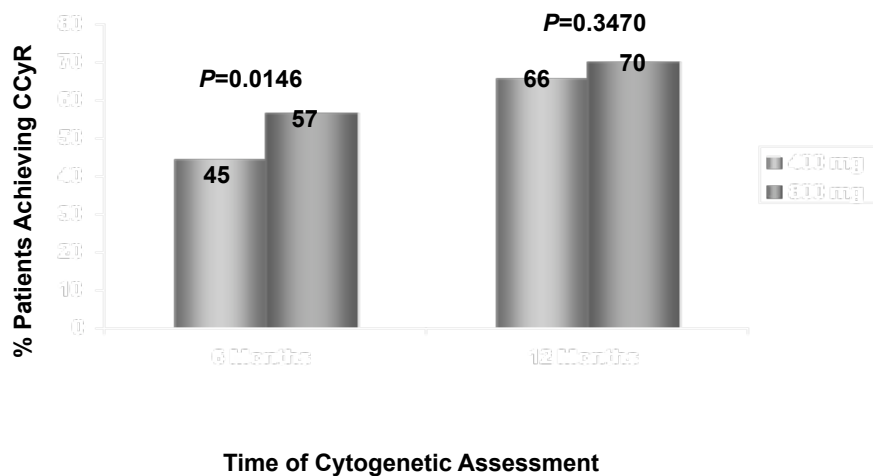


## Patient Disposition at 12 Months (ITT)

Disposition	No. (%)	
	400 mg N=157	800 mg N=319
Still on treatment	145 (92.4)	288 (90.3)
Discontinued treatment	12 (7.6)	31 (9.7)
Adverse events	2 (1.3)	18 (5.6)
Abnormal laboratory values	1 (0.6)	1 (0.3)
Unsatisfactory therapeutic effect	6 (3.8)	6 (1.9)
Protocol violation	2 (1.3)	1 (0.3)

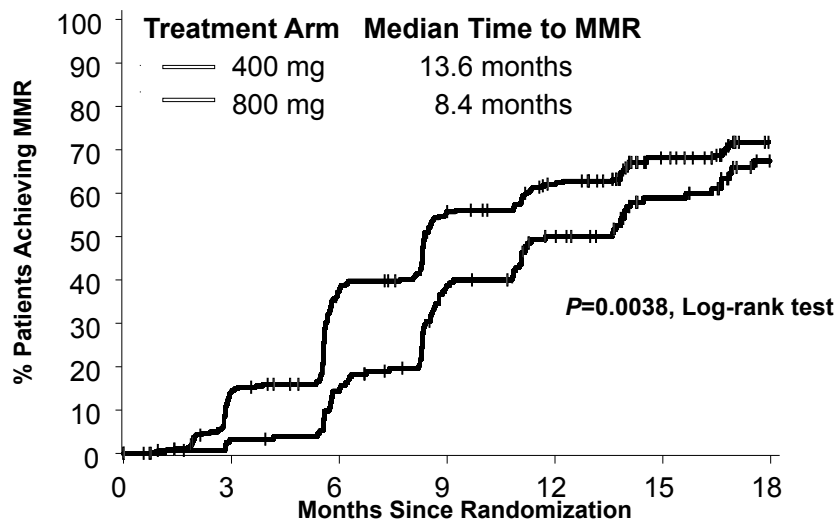
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## Complete Cytogenetic Response Rates



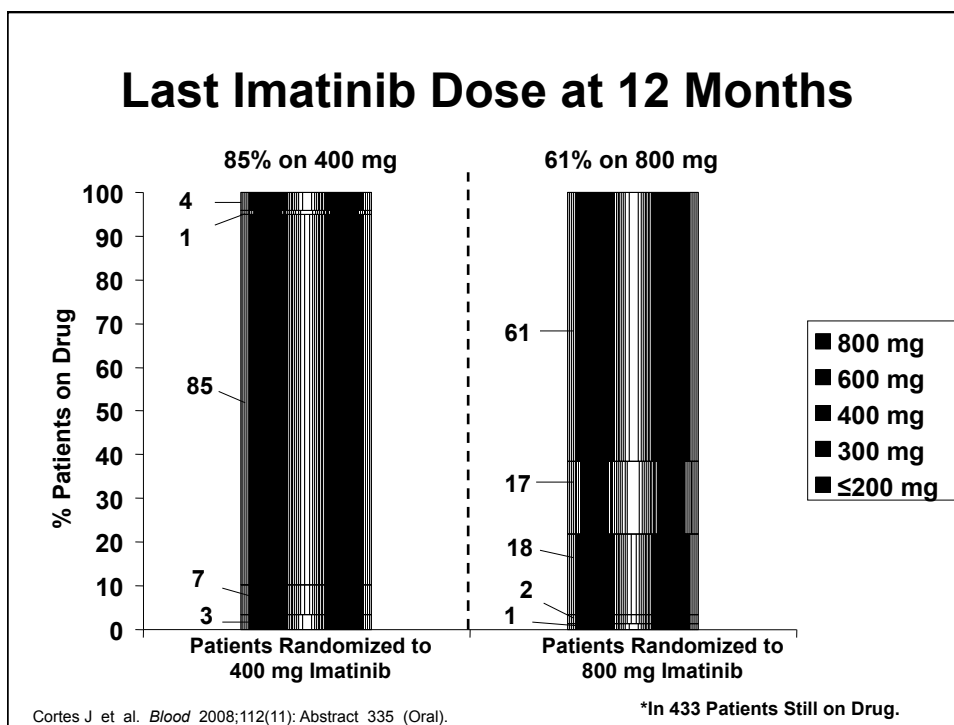
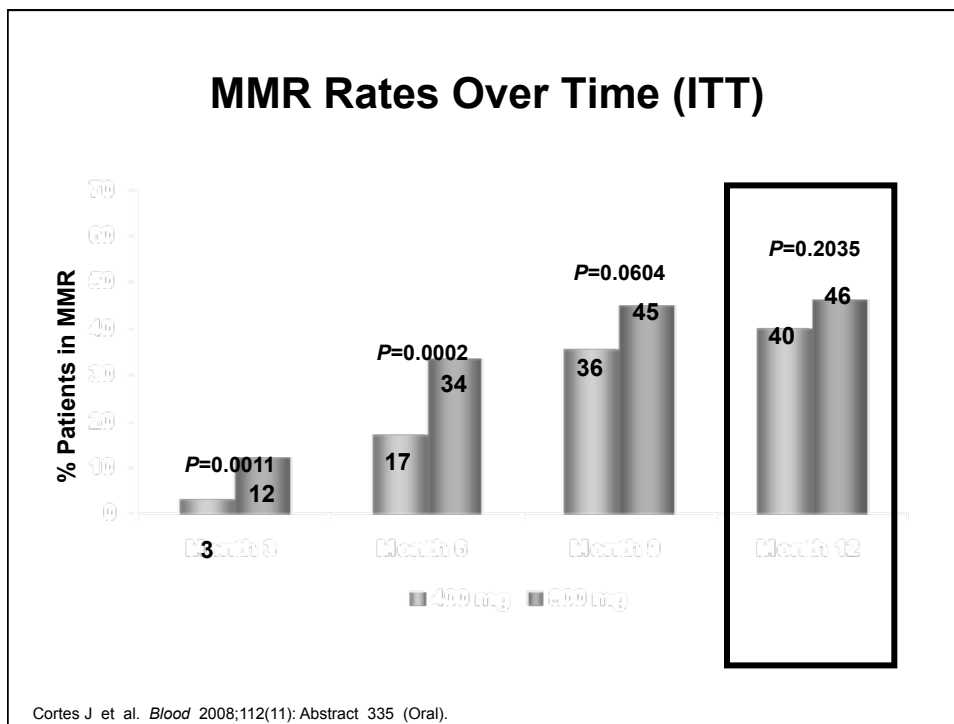
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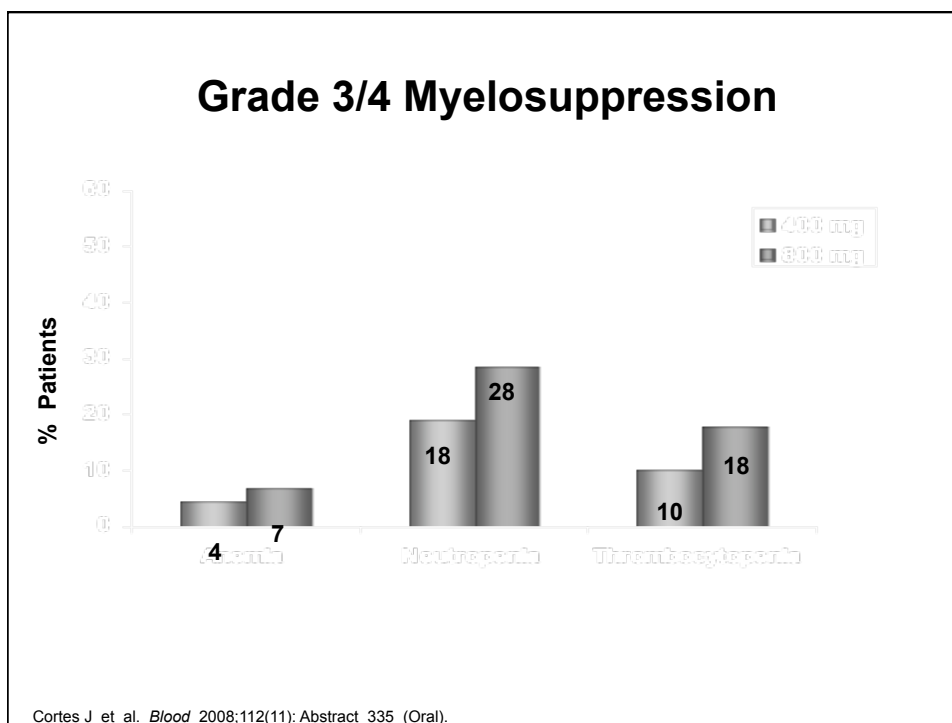
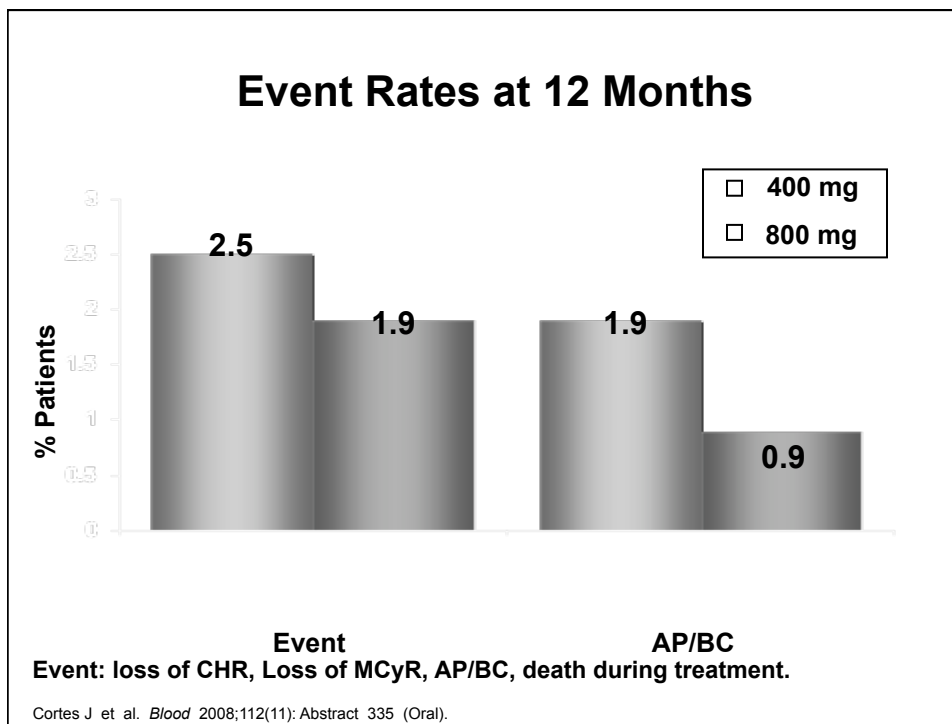
## Time to First MMR\* by Treatment Arm



\*MMR = BCR-ABL/control gene  $\leq$ 0.1% utilizing the International Scale (IS)

Cortes J et al. *Blood* 2008;112(11): Abstract 335 (Oral).





## Grade 3/4 Adverse Events

Non-laboratory Toxicity (if >1.5% in either group)	% NCI-CTC Grade 3/4 AEs	
	400 mg N=157	800 mg N=316
Rash	2.5	5.7
Diarrhea	1.3	4.1
Myalgia	0.6	3.5
Superficial edema	0	3.2
Arthralgia	1.9	2.5
Dyspnea	0	2.5
Fatigue	2.5	2.2
Anorexia	0.6	2.2
Pain in extremity	0.6	2.2
Headache	0	2.2
Weight increase	2.5	1.9
Nausea	0	1.9
Vomiting	1.3	1.6

Cortes J et al. *Blood* 2008;112(11): Abstract 335 (Oral).

## Conclusions

- **Confirmed efficacy and safety of imatinib in CML-CP**
- **Faster molecular responses with HD-IM**
- **Trend for lower rate of events and progression**
- **Both doses safe and generally well tolerated**
- **HD-IM dose intensity maintained in majority of patients**
  - **MMR rate increased with increasing dose intensity**

Cortes J et al. *Blood* 2008;112(11): Abstract 335 (Oral).

## CLL

- Hallek et al. Immunochemotherapy with Fludarabine (F), Cyclophosphamide (C), and Rituximab (R) (FCR) Versus Fludarabine and Cyclophosphamide (FC) Improves Response Rates and Progression-Free Survival (PFS) of Previously Untreated Patients (pts) with Advanced Chronic Lymphocytic Leukemia (CLL). Abstract 325
- Ferrajoli et al. Lenalidomide as Initial Treatment of Elderly Patients with Chronic Lymphocytic Leukemia. Abstract 45.

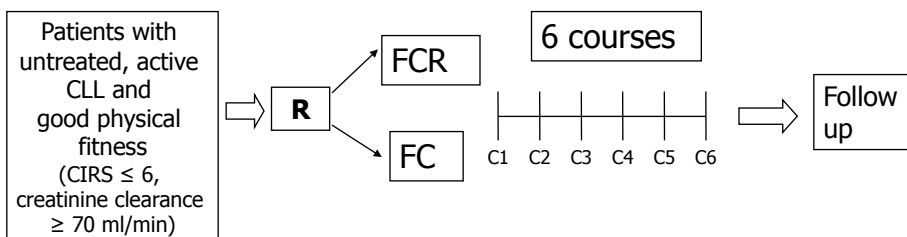
Chemoimmunotherapy with Fludarabine (F), Cyclophosphamide (C), and Rituximab (R) (FCR) versus Fludarabine and Cyclophosphamide (FC) improves response rates and progression-free survival (PFS) in previously untreated patients (pts) with advanced chronic lymphocytic leukemia (CLL)

Hallek M\*, Fingerle-Rowson G, Fink A-M, Busch R, Mayer J, Hensel M, Hopfinger G, Hess G, von Grünhagen U, Bergmann M, Catalano J, Zinzani PL, Caligaris Cappio F, Seymour J, Berrebi A, Jäger U, Cazin B, Trnny M, Westermann A, Wendtner C-M, Eichhorst BF, Staib P, Boettcher S, Ritgen M, Stilgenbauer S, Mendila M, Kneba M, Döhner H, Fischer K on behalf of an international group of investigators and of the German CLL Study Group (GCLLSG).

\*University of Cologne, Germany



## CLL8 Study Design



Primary endpoint  
-Progression-free survival (PFS)

Secondary endpoints  
- Overall survival  
- Rates of molecular, complete and partial remission  
- Rates of treatment-related adverse effects

## CLL8 Study Medication

**FC**

Fludarabine

25 mg/m<sup>2</sup>, i.v., d 1-3

Cyclophosphamide

250 mg/m<sup>2</sup>, i.v., d 1-3

**FCR**

FC +

Rituximab

Cycle 1: 375 mg/m<sup>2</sup>, d 0

Cycles 2-6: 500 mg/m<sup>2</sup>, d 1

**Recommendations for concomitant treatment with rituximab:**

Antihistaminic (e.g. 2 mg clemastine i.v.) +  
paracetamol 1000 mg orally  
30 min prior to 1st administration of rituximab.

For patients with lymphocytosis > 25 x 10<sup>9</sup>/L (at risk of infusion-related reaction or tumor lysis syndrome)  
a) appropriate hydration and allopurinol (300 mg po once daily) 12 to 24 hours prior to initiating treatment and thereafter until the risk of the IRR/TLS is ruled out.  
b) prednisone/prednisolone (100 mg i.v.) may be used 30 min prior to start of rituximab infusion.

No antiinfective prophylaxis,  
growth factor support according to ASCO guidelines.

### Patients: ITT population (n=817) of the CLL8 protocol

	FC (n = 409)	FCR (n = 408)
Female	105 (26%)	105 (26%)
Male	304 (74%)	303 (74%)
Median age	61 (range 36-81)	61 (range 30-80)
Binet A	22 (5.4%)	18 (4.4%)
Binet B	259 (63.6%)	263 (64.6%)
Binet C	126 (31%)	126 (31%)
B symptoms*	197 (48%)	167 (41%)
Median cumulative illness rating scale (CIRS)	1 (range 0-8)	1 (range 0-7)
Trisomy 12	14.4%	9.6%
Del(13q)	59.9%	53.7%
Del(11q23)	22.5%	26.7%
Del(17p13)	9.5%	7.0%

\*P&lt;0,05

### All adverse events of CTC grade 3 and 4

	FC	FCR	p
Total number of patients with $\geq 1$ grade 3/4 event	248 (62.6%)	309 (77.5%)	< 0.0001
Hematological toxicity	39.4%	55.7 %	< 0.0001
Neutropenia	21.0%	33.7%	< 0.0001
Leukocytopenia	12.1%	24.0%	< 0.0001
Thrombocytopenia	10.9%	7.4%	0.09
Anemia	6.8%	5.4%	0.42
Infection	14.9%	18.8%	0.14
Tumor lysis syndrome	0.5%	0.2%	0.55
Cytokine release syndrome	0.0%	0.25	0.32

### Infectious adverse events, grade 3 and 4

	FC	FCR	p
Infections, total	14.9%	18.8%	0.14
Infections, if specified	9.3%	13.6%	0.06
Bacterial	1.3%	2.2%	0.30
Viral	4.0%	4.2%	0.90
Fungal	0.3%	0.7%	0.33
Parasitic	0.0%	0.2%	0.32

Differences not statistically significant

Treatment related mortality: 2.0% in the FCR and 1.5% in the FC arm

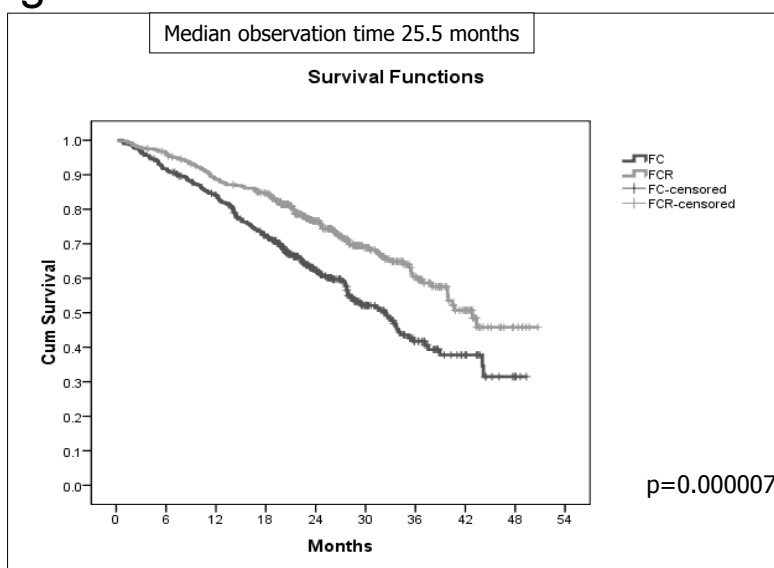
### Side effects: the effect of age

	FC			FCR		
	< 70 yrs n = 359	≥ 70 yrs n = 37	p	< 70 yrs n = 361	≥ 70 yrs n = 43	p
Total AEs gr 3/4	61.0%	78.4%	0.04	75.6%	83.7%	0.24
Anemia	6.7%	8.1%	0.74	5.5%	4.7%	0.81
AIHA	1.1%	0.0%	0.52	0.6%	2.3%	0.20
Leukocytopenia	12.0%	13.5%	0.79	24.9%	16.3%	0.21
Neutropenia	19.5%	35.1%	0.03	32.4%	44.2%	0.12
Thrombopenia	11.4%	5.4%	0.26	7.8%	4.7%	0.46
Infections, unspecified	9.5%	8.1%	0.79	13.0%	18.6%	0.31
Infections, bacterial	0.7%	5.4%	0.02	1.9%	4.7%	0.26

## Response to treatment

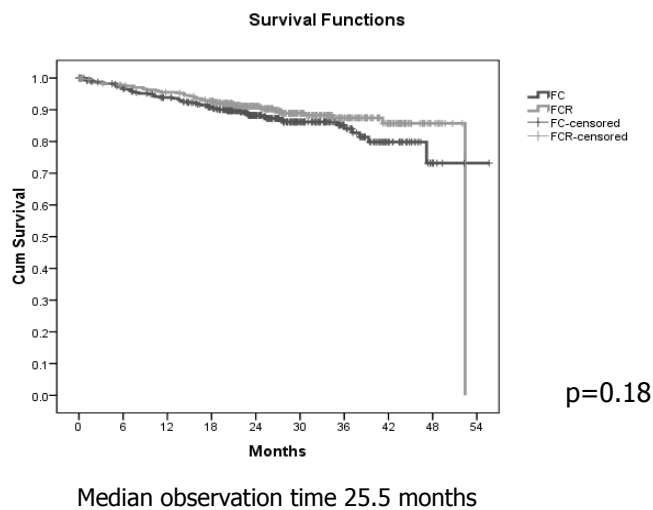
	FC	FCR	p
CR	22.9%	44.5%	<0.01
CR <sub>u</sub>	5.1%	3.3%	0.22
CR <sub>i</sub>	1.9%	2.6%	0.52
nPR	4.9%	2.8%	0.15
PR	50.4%	39.6%	<0.01
SD	6.7%	3.9%	0.08
PD	8.1%	3.3%	<0.01

## Progression free survival: FCR versus FC

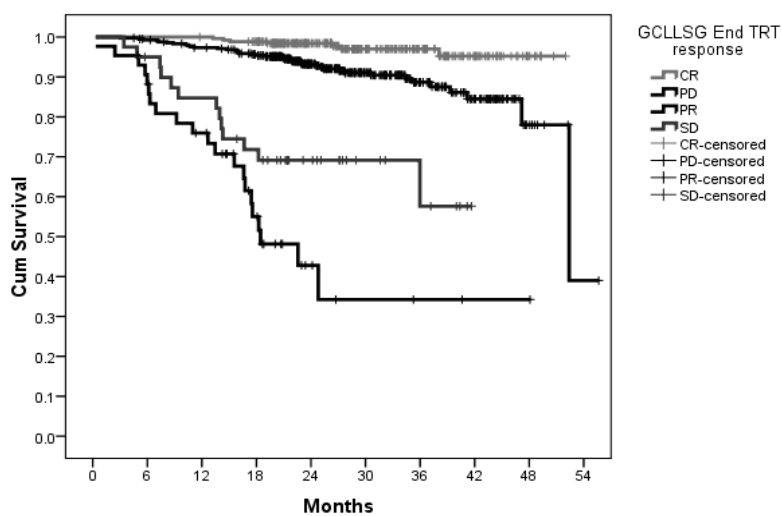


Median PFS: 32.3 months for FC vs 42.8 months for FCR

# Overall survival



# Overall survival and type of response



## Conclusion: FCR first-line treatment in CLL

- FCR is superior to FC with regard to:
  - Response rates (CR, OR).
  - Progression-free survival.
- FCR treatment is safe:
  - FCR causes more neutropenias
  - FCR does not cause more infections or other severe side.
  - FCR is well tolerated in physically fit patients > 65 or 70 years.
- FCR is the new standard treatment for physically fit CLL patients

Data on prognostic factors and minimal residual disease assessment will be presented by Stephan Stilgenbauer (ASH # 781) and Sebastian Böttcher (ASH # 326).

## **Lenalidomide as Initial Treatment of Elderly Patients with Chronic Lymphocytic Leukemia**

## **Background**

- **Elderly patients with CLL  
median age at diagnosis 72 yrs  
underrepresented in clinical trials**
- **Lenalidomide is active in relapsed  
CLL**

## **Study Design**

- **Phase II, 60 patients**
- **Untreated and symptomatic**
- **Age  $\geq$  65 yrs**
- **Creatinine  $<$ 2 mg/dL, bilirubin  $<$ 2 mg/dL**
- **Zubrod/WHO performance status 0-2**

## Doses and Schedule

### Lenalidomide

- 5 mg orally daily x 2 cycles (56 days)
- ↑ by 5 mg/cycle (28 days) → max 25 mg daily
- Treatment continued until progression

Allopurinol 300 mg d 1 -14

No antibiotic or anti-viral prophylaxis required

No DVT prophylaxis required

## Patient Characteristics (N=45)

Characteristic	Value
Median age (range), yrs	71 (66-85)
Rai stage III/IV, N (%)	18 (40)
11q-, N (%)	9 (20)
17p-, N (%)	5 (11)
Median $\beta$ 2M (range), mg/dL	4.4 (2.0-10.2)
Unmutated $V_H$ , N (%)	27/40* (65)
ZAP-70+, N(%)	29/43** (67)

## Responses

Time on therapy Evaluable	Cycle 3 45	Cycle 9 33
Nod. Partial Response, N (%)	1 (2)	2 (6)
Partial Response, N (%)	19 (42)	15 (45)
Overall Response, N (%)	20 (44)	17(52)
Stable disease**, N (%)	21 (47)	5 (15)
Discontinuation, N (%)	3 (7)	7 (21)
Progression, N (%)	1 (2)	4 (12)

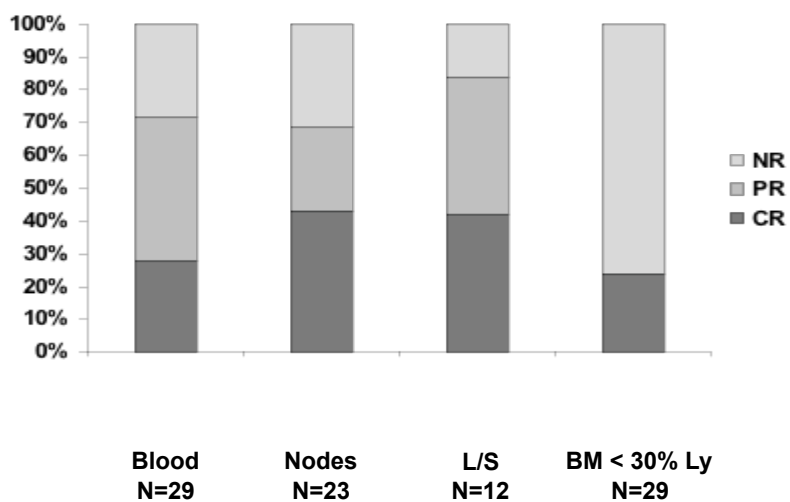
\*1996 NCI-WG guidelines ; \*\*Continue lenalidomide treatment.

## Responses over Time

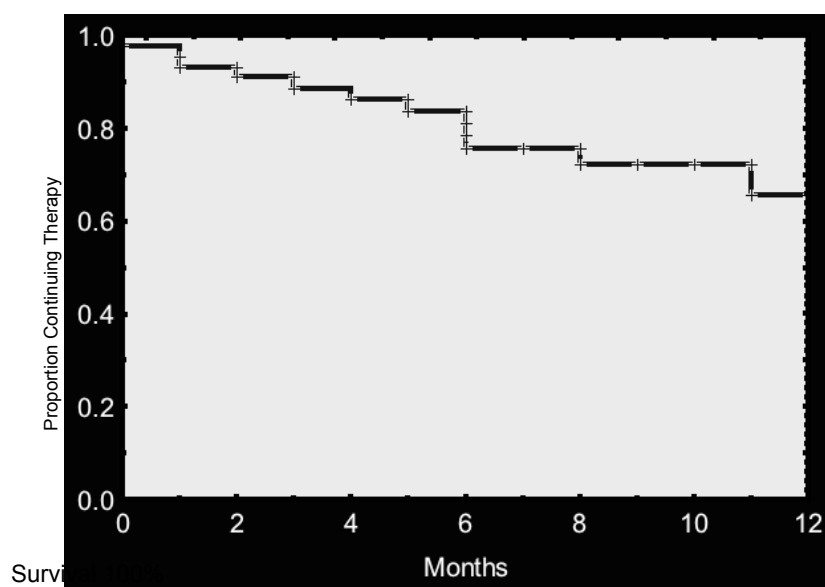
Cycle 3		Cycle 9			
		NPR	PR	SD	PD/Tox
11 PR	⇒	2	8		1
17 SD	⇒	-	7	5	5

Median lenalidomide at cycle 9 → 5 mg/day

### Response by Disease Sites after 9 Cycles



### Time to Treatment Failure



## Toxicities (N=45 )

Grade $\geq$ 3 Adverse Event	N. (%)
• Hematological	
Neutropenia	12 (27)
Thrombopenia	4 (9)
• Non-hematological	
FUO	3 (7)
Pneumonia	1 (2)
Syncope	1 (2)
Tumor flare	
Grade 3	1 (2)
Grade 1-2	20 (44)
Fatigue	
Grade 1-2	21 (47)

No tumor lysis observed

## Conclusions

- Lenalidomide well tolerated in elderly pts with CLL
- Myelosuppression is common
- No deaths or increased rate of infections
- After 9 cycles: OR 52%; SD 15%
- Response rate improves with continued treatment
- Median Time to Treatment Failure not been reached

## APL

- Sanz M et al. **Risk-Adapted Treatment of Acute Promyelocytic Leukemia: Results of the PETHEMA LPA2005 Trial Using All-*Trans* Retinoic Acid and Anthracycline with Cytarabine for High-Risk Patients.** Abstract 138

## Abstract 138

- PETHEMA and French-Belgian-Swiss groups suggested a role for cytarabine in high-risk APL patients.
- Thus, a new risk-adapted PETHEMA trial (LPA 2005) was designed and initiated in July 2005.

## Abstract 138

- AIDA regimen (ATRA 45 mg/m<sup>2</sup>/d ATRA until CR and idarubicin 12 mg/m<sup>2</sup>/d on days 2, 4, 6 and 8) was given as induction therapy.
- Patients in CR received 3 monthly courses of risk-adapted consolidation therapy as follows:
  - i."low-risk" patients received ATRA (45 mg/m<sup>2</sup>/d x 15) simultaneously with idarubicin 5 mg/m<sup>2</sup>/d x 4 (#1), mitoxantrone 10 mg/m<sup>2</sup>/d x 3 (#2), and idarubicin 12 mg/m<sup>2</sup>/d x 1 (#3);
  - ii."intermediaterisk" patients received ATRA (45 mg/m<sup>2</sup>/d x 15) in combination with reinforced chemotherapy (idarubicin 7 mg/m<sup>2</sup>/d in the course #1 and 2 days in #3).
  - iii."high-risk" patients < 60 years received ATRA (45 mg/m<sup>2</sup>/d x 15) and idarubicin in courses #1 and #3 at the same dose than for low-risk patients but with the addition of cytarabine (1000 mg/m<sup>2</sup>/d x 4 in #1 and 150 mg/m<sup>2</sup>/8 h days 1 - 4 in #3) and mitoxantrone in course #2 (5 days).
- Maintenance therapy consisted of 50 mg/m<sup>2</sup>/d mercaptopurine orally, 15 mg/m<sup>2</sup>/week methotrexate intramuscularly, and 25 mg/m<sup>2</sup>/d ATRA for 15 days every three months during 2 years.

## Abstract 138

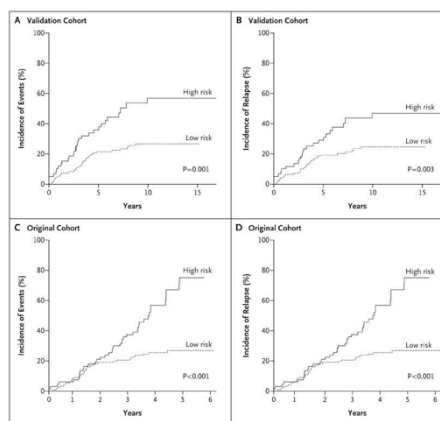
- 319 patients enrolled in the LPA 2005 trial between July 2005 - July 2008.
- CR was achieved in 268 patients (92%).
  - No resistant cases were observed.
- Toxicity was manageable during consolidation and there were 2 deaths in CR during consolidation.
  - Median follow-up was 21 months (range, 2–38).
  - Six patients presented hematological relapse and 3 molecular relapse.
- Overall, the 2-year cumulative incidence of relapse (CIR), disease-free survival, and overall survival were 5%, 94%, and 92%, respectively.
- The 2-year CIR:
  - low-risk – 0%
  - intermediate-risk – 6%
  - high-risk patients – 8%
    - A comparison of these results with those obtained with the LPA99 trial show a statistically significant lower CIR in high-risk patients (p=0.047).
- Significant improvement of the outcome observed in high-risk patients

## ALL

- Mullighan et al. Deletion of IKZF1 (Ikaros) Predicts Poor Outcome and Impaired Maturation in B-Progenitor Acute Lymphoblastic Leukemia. Abstract 427.
- IacoBucci et al. Identification and Molecular Characterization of Two Recurrent Genomic Deletions (Type A and Type B) on 7p12 in *IKZF1* Gene in a Large Cohort of *BCR-ABL1*-Positive Acute Lymphoblastic Leukemia (ALL): on Behalf of the GIMEMA ALL Working Party. Abstract 428.

## Ikaros in ALL

- Deletion on 7p12 of *IKZF1*, (encodes **Ikaros**) identified in 61% adult Ph-positive ALL



- IacoBucci I et al. Abstract 428

**Ikaros deletions found in 28% of non-Ph-positive, high-risk pediatric ALL**

Mullighan C et al. N Engl J Med 2009;10.1056/NEJMoa0808253

# Questions