

An educational day for European fellows,
on behalf of EUTOS for CML

CEINGE - Naples, 18-19 May, 2009

Failure of treatment in a young high Sokal risk patient

Gianantonio Rosti

Institute "Seràgnoli", Bologna

GIMEMA CML WP

CASE PRESENTATION

- 27 yrs old, male, CML/HR (4/2005) (NO HLA-ID SIBLINGS)
- Enrolled in a phase 3 trial of the GIMEMA CML WP comparing imatinib 400 mg vs 800 mg in HR/CML
- Random: arm SD (400 mg daily)
- Adherence to the treatment is good
- CHR at 3 months, CCyR at 6, confirmed at 12, 18 and 24 months (with MMR)
- June 2007, loss of MMR (ratio 1.1%IS) and (July 2007), confirmed loss of MMR and loss of CCyR (40% Ph+)
- BLT: not available yet

IRIS TRIAL at 6 yrs Sokal Risk and Outcome

SOKAL RISK	OS	EFS	PFS
	%	%	%
LOW	94	91	97
INTERMEDIATE	87	81	92
HIGH	76	67	82

All P values < 0.001

Hochhaus et al, Leukemia 2009

CASE PRESENTATION

- **MUTATIONAL STATUS: WILD TYPE**
- **A 10/10 MUD available (female, 32 yrs old)**

CASE PRESENTATION

- 1. DOSE ESCALATION TO 800 mg**
- 2. NILOTINIB**
- 3. DASATINIB**
- 4. NILOTINIB OR DASATINIB**
- 5. ALLOGENEIC SCT STRAIGHTFORWARD**

CASE PRESENTATION

1. DOSE ESCALATION TO 800 mg

Response to dose escalation :

Clinical milestones achieved by 12 months after dose escalations as per ELN recommendation (N=48)

Reason for dose escalation according to ELN criteria	N	Clinical response by 12 months after dose escalation	Number clinically responding by 12 months after dose escalation	Best cytogenetic response and time to that response
3 months: failure or suboptimal response (no HR or <CHR)	7	CHR	6	2 of these 6 patients achieved CCyR at 8 and 33 months
6 months: failure (no CHR, no CyR)	1	CHR or MCyR	0	-
12 months: suboptimal response (no CCyR)	4	CCyR	0	1 of these 4 patients achieved MCyR at 12.5 months 2 achieved CCyR at 14 and 15.5 months
12 months: failure (no MCyR)	11	MCyR	5	These 5 responses occurred between 2.5 and 11 months 1 additional patient achieved MCyR at 21 months and 1 patient achieved CCyR at 24 months
18 months: failure (no CCyR)	10	CCyR	2	The 2 responses occurred at 3 and 9 months 1 additional patient achieved CCyR at 29 months
Failure at any time, confirmed loss of CHR or loss associated with progression to AP/BC, or loss of CCyR	15	CHR	0	The 7 cytogenetic responses occurred between 2 and 10 months 2 additional patients achieved a CCyR at 15 and 21 months
		MCyR	3	
		CCyR	4	
Total	48	-	20 (42%)	-

CASE PRESENTATION

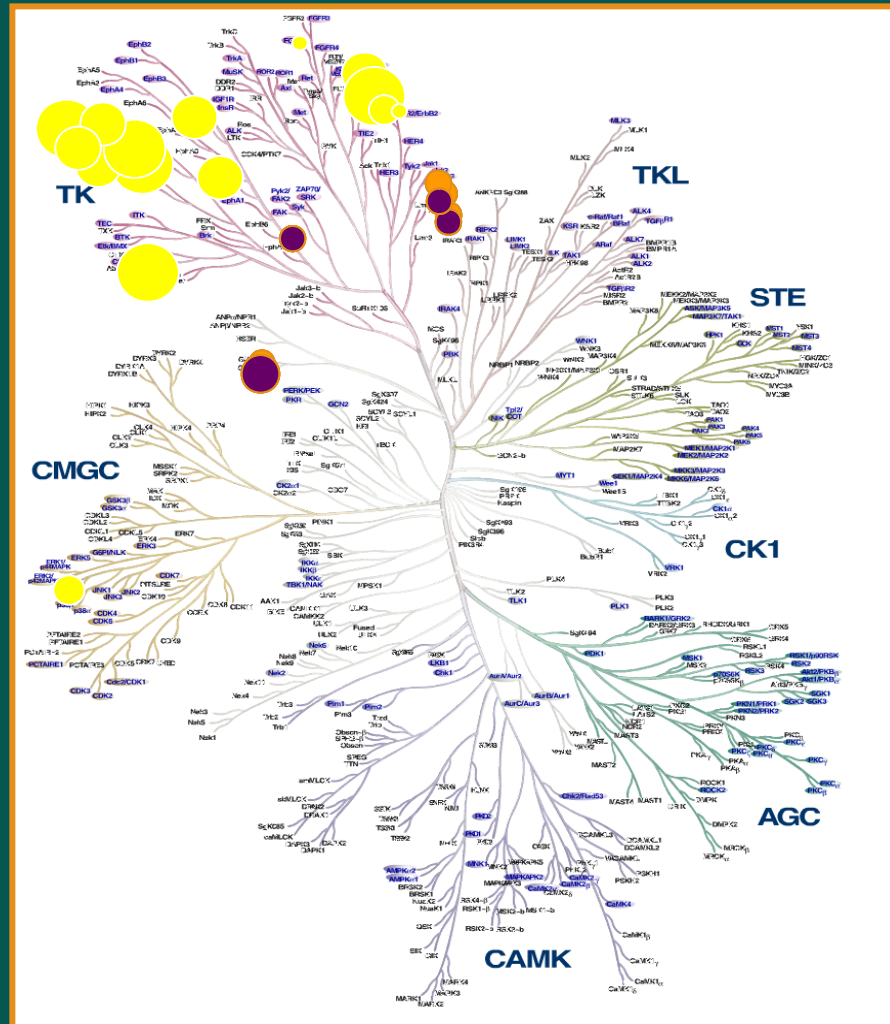
- **NILOTINIB**
- **DASATINIB**
- **NILOTINIB OR DASATINIB**

Kinase selectivity profiles of Imatinib, Nilotinib, and Dasatinib





Imatinib
4 targets

Nilotinib
4 targets

Dasatinib
15 (49) targets



IC_{50}

-  $< 10 \text{ nM}$
-  $10-50 \text{ nM}$
-  $50-250 \text{ nM}$
-  $250-1000 \text{ nM}$

1. ALLOGENEIC SCT STRAIGHTFORWARD

ICSG on CML

RISK FACTORS	transplant related mortality		
		RISK SCORE	TRM
DONOR, UNRELATED	1		
STAGE, ACCELERATED	1	0-1	23%
STAGE BLASTIC	2	2	31%
AGE 20-40	1	3	46%
AGE>40	2	4	51%
FEMALE DONOR/MALE REC.	1		
TIME TO BMT>1 YEAR	1	5-6	72%

GRATWOHL et al, LANCET, 352, 1087, 1998

Istituto "Seràgnoli" - Bologna

CASE PRESENTATION

1. ALLOGENEIC SCT AFTER 2° GEN TKI FAILURE