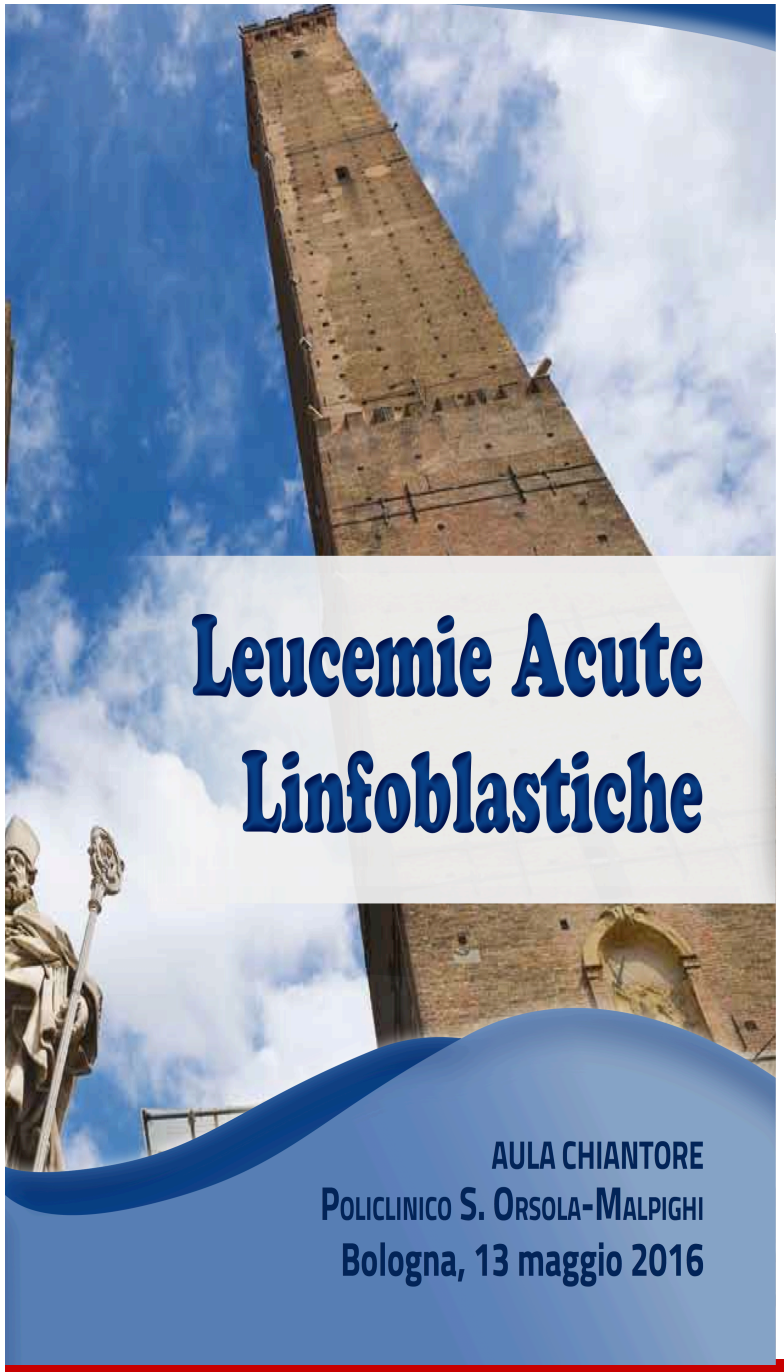


Therapy of Ph+ ALL elderly patients

Cristina Papayannidis, MD, PhD

DIMES

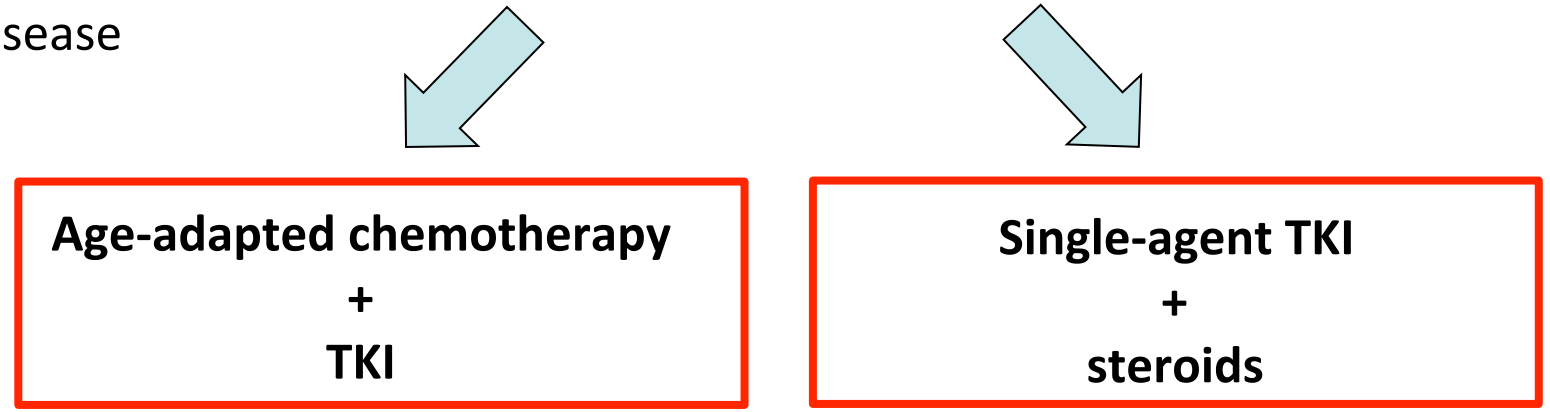
University of Bologna

Ph+ ALL in the elderly: background

- Philadelphia chromosome is the most frequent recurrent cytogenetic abnormality in elderly ALL patients, involving approximately 50% of ALL patients aged 60 years and over

- Until the recent era of TKIs, most studies devoted to elderly population with ALL made no distinction between Ph+ and Ph- cases, due to equally poor long term survival (below 10%)

- Two different approaches were developed for the management of this disease



blood
2010 116: 3409-3417
Prepublished online July 23, 2010;
doi:10.1182/blood-2010-01-242750

How I treat Philadelphia chromosome–positive acute lymphoblastic leukemia

Adele K. Fielding

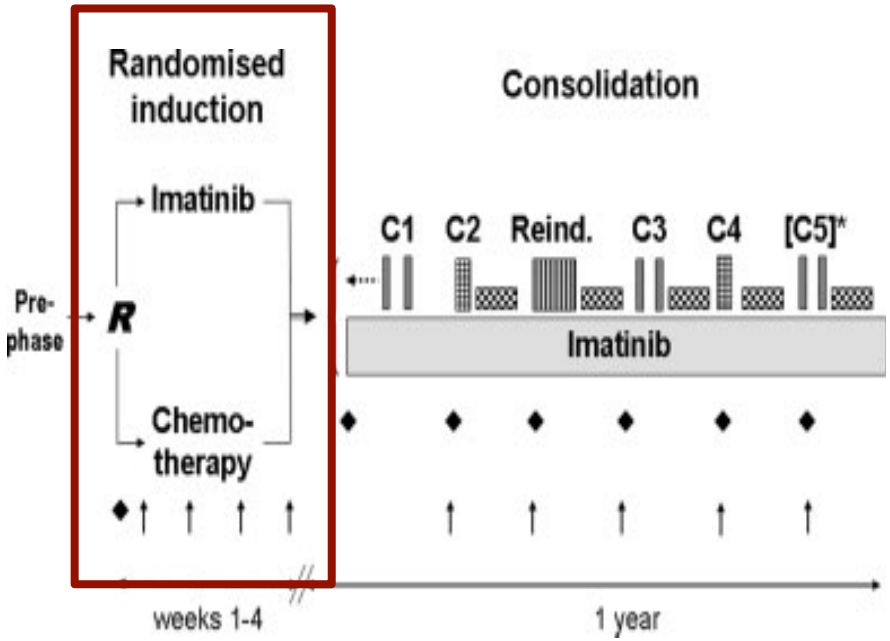
Table 2. Studies of imatinib in newly diagnosed Ph+ ALL

Author, year	Study group	Study name	N	Dose	CR (%)	BMT rate (%)	Overall survival
Adults							
Thomas et al, 2004[22]	MD Anderson	N/A	20	400 mg (600 mg in maintenance)	93	50	75% at 20 mo
Yanada et al, 2006[26]	JALSG	ALL202Ph+	80	600 mg	96	61	75% at 1 y
Wassmann et al, 2006[20]	GMALL	N/A	92	400-600 mg	95	77	36% (alternating schedule), 43% (concurrent schedule) at 2 y
de Labarthe et al, 2007[23]	GRAALL	GRAAPH-2003	45	600 mg	96	48	65% at 18 mo
Ribera et al, 2010[25]	PETHEMA	CSTIBES02	30	400 mg	90	70	30% at 4 y
Bassan et al, 2010[27]	NILG	09/00	59	600 mg	92	63	38% at 5 y
Older adults							
Vignetti et al, 2007[24]	GIMEMA	LAL0201-B	30	800 mg	100	N/A	74% at 12 mo
Ottmann et al, 2007[32]	GMALL	N/A	55	600 mg	96 (imatinib), 50 (chemo)	N/A	42% at 24 mo
Children							
Schultz et al, 2009[36]	COG	AALL0031	92	340 mg/m^2	Not stated	N/A*	80% (EFS) at 3 y
Ongoing studies							
N/A	UK NCRI, ECOG	UKALLXII/ECOG2993	175	600 mg	95	Awaited	Awaited
N/A	GRAALL	GRAAPH-2COG05	188	800 mg	100 (imatinib DIV), 96 (imatinib hyperCVAD)	62	62% at 2 y

Imatinib vs Chemotherapy

Imatinib Compared With Chemotherapy as Front-Line Treatment of Elderly Patients With Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ALL)

Oliver G. Ottmann, MD[1]
Barbara Wassmann, MD[1]
Heike Pfeifer, MD[1]
Aristoteles Giagounidis, MD[2]
Matthias Stelljes, MD[3]
Ulrich Dührsen, MD[4]
Marc Schmalzing, MD[5]
Lydia Wunderle, MD[1]
Anja Binckebanck[1]
Dieter Hoelzer, MD[1]
for the GMALL Study Group



n=55, median age 68 years

CR: IMA 96.3%
Chemo 50%

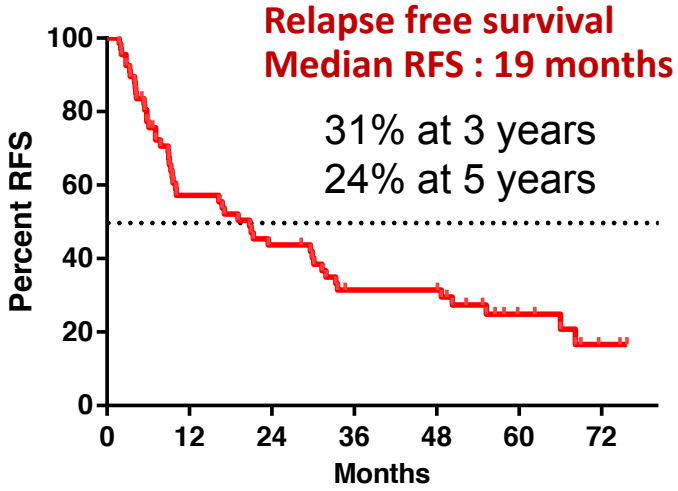
2 pts DDI Chemo

Toxicity: SAEs 39% vs 90%

Estimated OS: 42% at 24 months
(no difference between the 2 cohorts)

Dasatinib plus Chemotherapy

- First-line dasatinib + CTx
  - N=71 patients (median age, 69y)

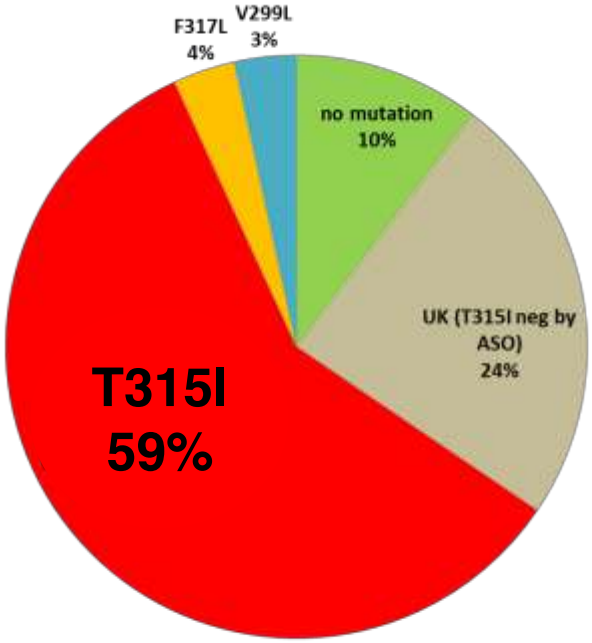


  - Patients were censored at HSCT

CR 96%
DDI: 3 pts
TRM: 6 pts

36 pts relapsed

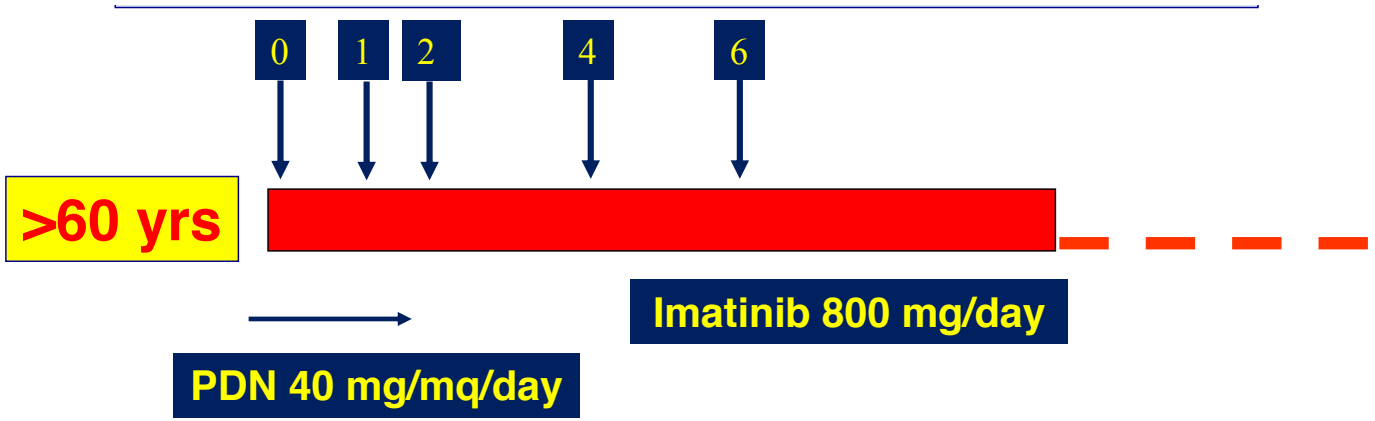
Dasa discontinuation:
AEs 14 pts
AlloBMT 7 pts



Mutation at relapse

Rousselot P. et al, Blood 2016

Gimema LAL0201B



Enrolled: 45 patients

Median age 68; range 61–89

Evaluable: 37 patients

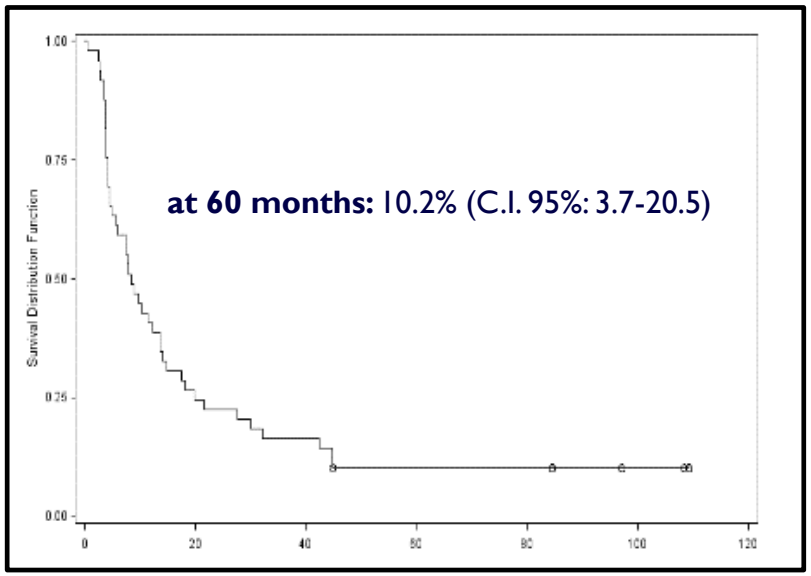
Hematologic CR 100%

Median OS: 24 months

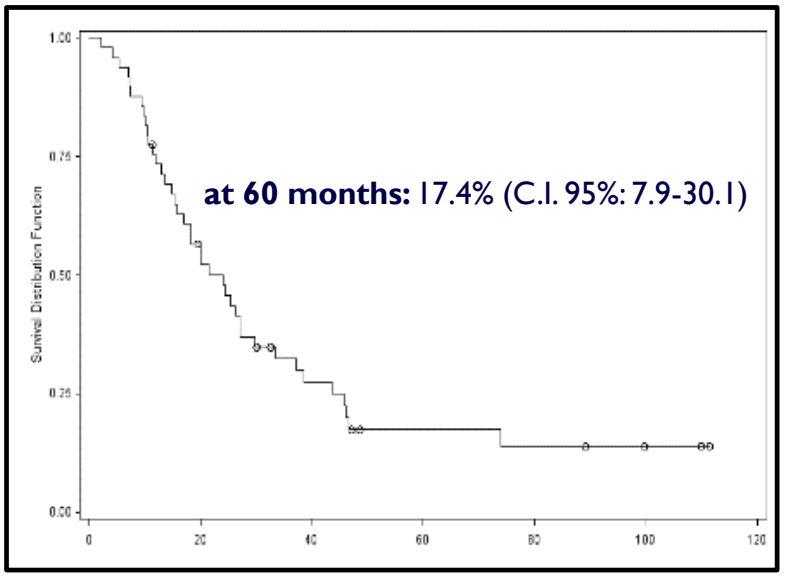
Vignetti M et al, Blood 2007;109:3676–3678

Gimema LAL0201B: updated 2013

DFS



OS



Median follow-up: 89 months

Some patients (n = 5) are, also considering age, long survivors

GIMEMA LAL1408

Front-line treatment of Ph positive (Ph+)/Bcr-Abl positive Acute Lymphoblastic Leukemia (ALL) with two tyrosine kinase inhibitors (TKI)

(Imatinib and Nilotinib).

A phase II exploratory multicentric study in elderly patients and in patients unfit for program of intensive therapy and allogeneic stem cell transplantation

Primary objective of the trial is to evaluate the Disease-Free Survival (DFS) at 24 weeks (after 4 courses of treatment)

Secondary objectives:

Complete Hematological Response (CHR) rate at 6, 12 and 24 weeks

Complete Cytogenetic Response (CCgR) rate at 6, 12 and 24 weeks and duration of CCgR

Complete molecular response rate (CMR) at 12 and 24 weeks and duration of CMolR

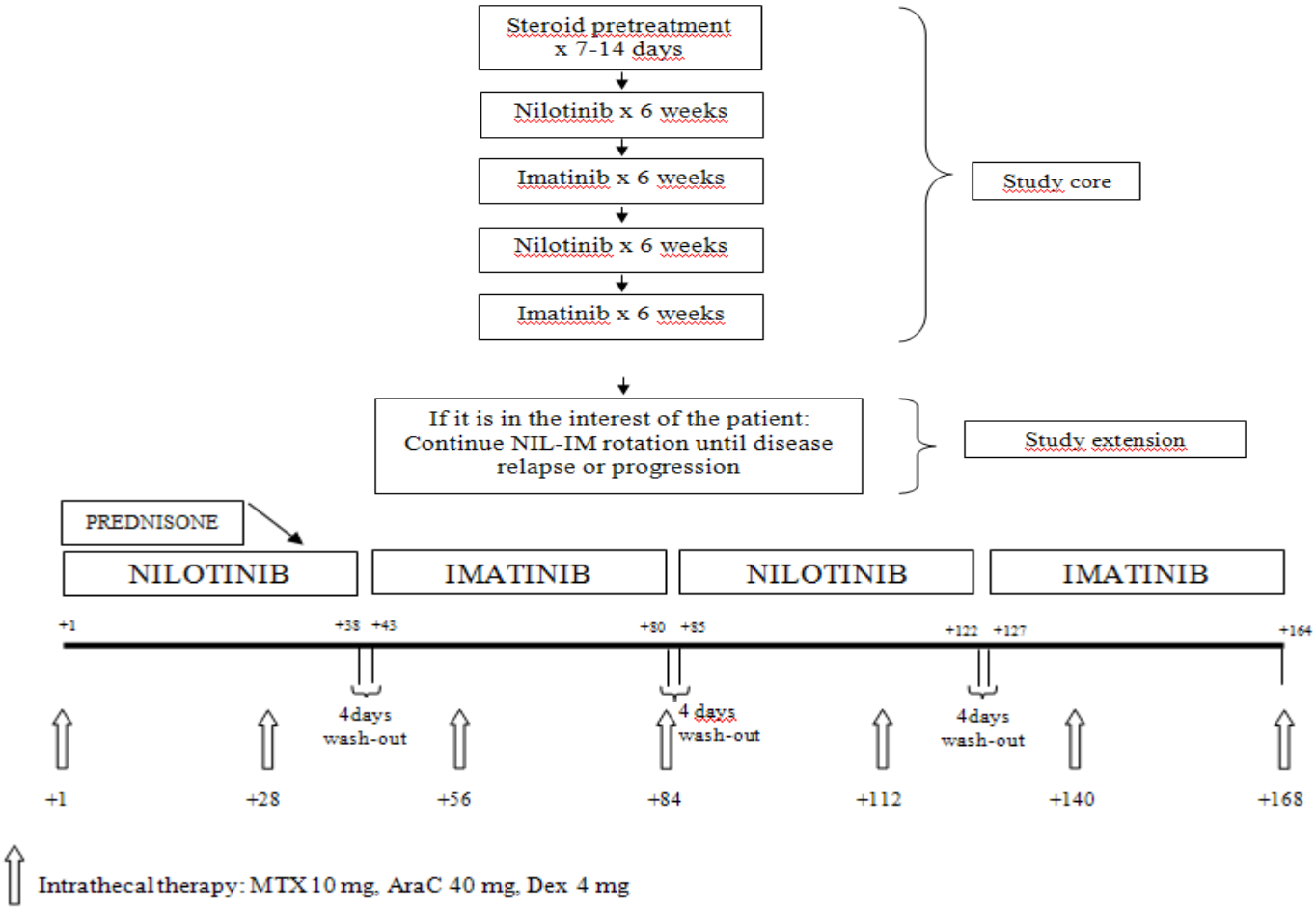
Type and number of BCR-ABL kinase domain mutations developing during and after the study

Relationship between the response, biomarkers and gene expression profile (GEP)

Event-Free Survival (EFS) and Overall Survival (OS)

Side effects, adverse events (AE) and serious AE (SAE)

GIMEMA LAL1408



GIMEMA LAL1408

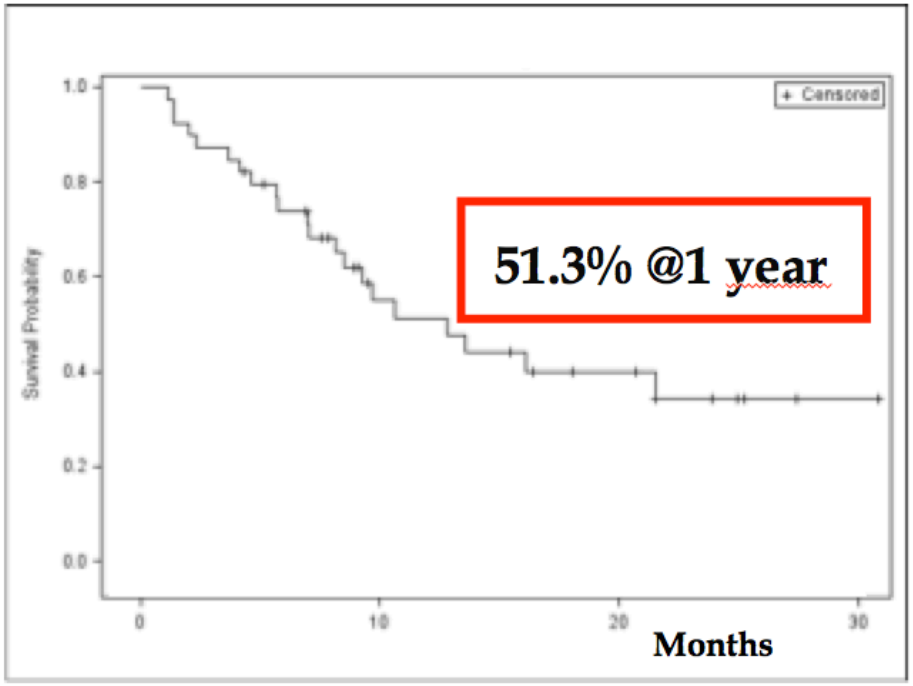
	n=39
Median Age (range)	66 yrs (28-84)
Unfit (<60 yrs)	8
M/F	19/20
p190/p210	27/5
p190+p210	7
T/B phenotype biphenotypic	1/37 1
WBC median (range)	6.9 x 10^3/mmc (0.8-226.3 x 10^3/mmc)
Hb median (range)	9.5 g/dL (8.6-15.8 g/dL)

Patients' characteristics at diagnosis

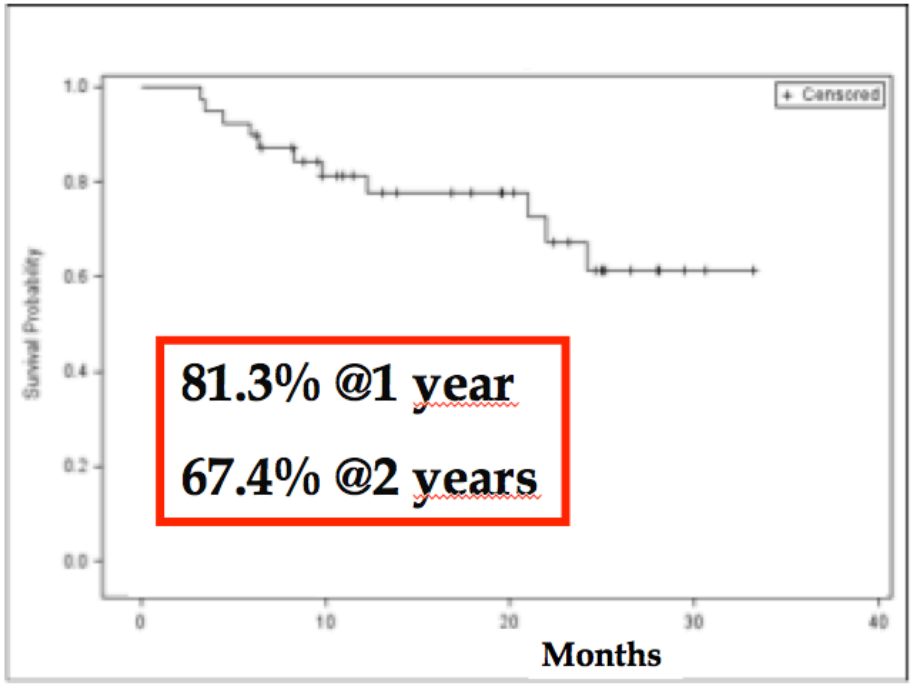
Papayannidis et al. ASCO 2013

GIMEMA LAL1408

DFS



OS



Disease Free Survival and Overall Survival

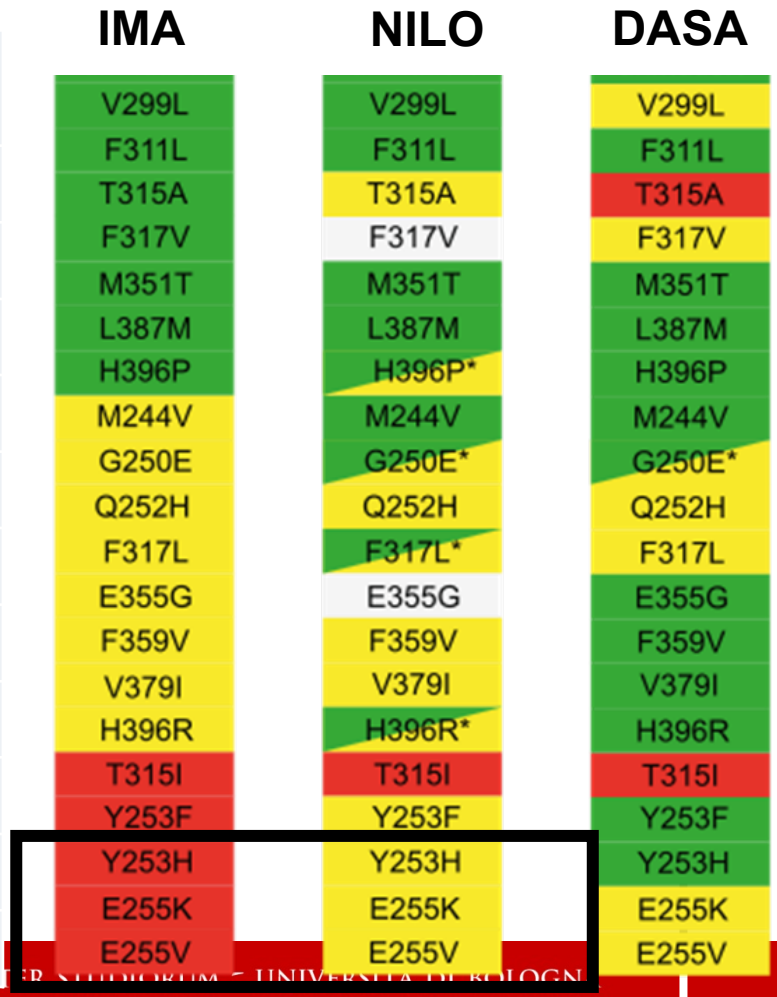
Papayannidis et al. ASCO 2013

GIMEMA LAL1408

- ✓ One patient was primary resistant
- ✓ 13 patients have relapsed

Median TTR: 7.6 months

Pts	Mutation	Time to relapse (months)
006001	Y253H, E255V	5.5
006012	T315I, Y253H	20.1
006018	E255K, T315I	3
006020	Y253H	8.8
006026	E255K	7.3
008007	T315I	2.5
008015	Y253H	14.5
012035	WT	3.8
042004	WT	10.1
043009	Y253H	17.4
043030	T315I	7.3



Take home messages (I)

- The sequence of two TKIs, even does not prevent peculiar mutations and relapse, is associated with extremely high rate of complete hematological responses, reduced hospidalization, reduced infection, and low/absent hematological toxicity.

- Some of the mutations that occurred at the time of relapse were sensitive to other TKIs (Y253H→Dasatinib; T315I→Ponatinib)

- Rates of relapse and progression in elderly patients are at least not different from the rates observed with other TKIs alone (e.g.Vignetti et al., Blood 2007)

- Safety profile of rotational use of TKIs is not different from the safety profile with single TKI inhibitor.

Gimema Clinical Trial LAL1811

Front-line treatment of newly diagnosed Philadelphia positive **(Ph+)/BCR- ABL positive Acute Lymphoblastic Leukemia (ALL)** with AP24534 (Ponatinib), a new potent tyrosine kinase inhibitor (TKI).

A phase II exploratory **multicentric study** in patients **more than 60 years** old **or unfit** for a program of intensive chemotherapy and stem cell transplantation

ClinicalTrial number CT01641107

GIMEMA
Gruppo Italiano Malattie EMatologiche dell'Adulto

Study Rationale

- ✓ The emergence of Imatinib-resistant BCR-ABL clones is a major issue in Ph positive ALL patients
- ✓ After a very good initial response to one TKI, many patients relapse within one year, and a BCR-ABL kinase domain point mutation usually occurs *(Vignetti M. et al, Blood 2007; Foà R. et al, Blood 2011)*
- ✓ These patients can be rescued by another TKI, but the second remission is usually shorter than the previous one
- ✓ Could Ponatinib, be able, as first line therapy, to improve the outcome of these patients?

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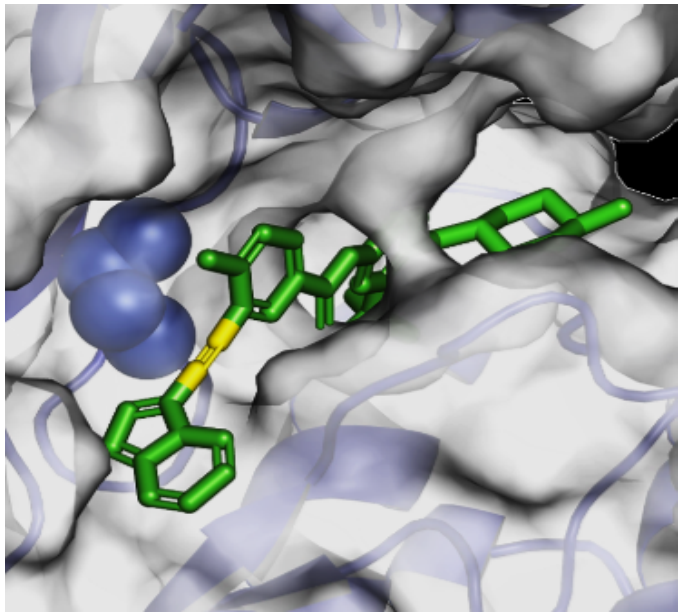
Ponatinib

- ✓ Rationally designed inhibitor of all the most clinically relevant BCR-ABL variants
- ✓ Active against T315I mutant
- ✓ Also targets other therapeutically relevant kinases (FLT3, FGFR, VEGFR, PDGFR, c-KIT)
- ✓ Phase II Trial, in relapsed/refractory Ph+ALL:
  41% MaHR
  38% CCyR



O'Hare T, et al. Cancer Cell. 2009;16:401-412
Cortes J. et al., NEJM 2013; 369(19):1790

Inclusion Criteria

- ✓ Patients must have >20% blasts in bone marrow at the time of diagnosis and no prior history of CML
- ✓ Age ≥ 60 years old or age ≥ 18 years old, but unfit for program of intensive therapy and allogeneic SCT
- ✓ Adequate **hepatic function**
- ✓ Adequate **pancreatic function** as defined by the following criterion:
  - serum lipase and amylase ≤1.5 × ULN
- ✓ Signed written informed consent according to ICH/EU/GCP and national local laws.

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Exclusion Criteria

- ✓ Active HBV or HCV hepatitis
- ✓ History of acute pancreatitis within 1 year of study or history of chronic pancreatitis
- ✓ History of alcohol abuse
- ✓ Ongoing or active infections
- ✓ Uncontrolled hypertriglyceridemia (triglycerides >450 mg/dL).
- ✓ **Clinically significant, uncontrolled or active cardiovascular disease**, specifically including, myocardial infarction, stroke, or revascularization, unstable angina or transient ischemic attack **within 6 months prior to enrollment,** congestive heart failure within 6 months prior to enrollment, or left ventricular ejection, history of clinically significant atrial arrhythmia or **venous thromboembolism** including deep venous thrombosis or pulmonary embolism

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Primary Objectives

✓**To evaluate the therapeutic effects of Ponatinib** in patients with Ph+ ALL who are 60 or more than 60 years old, or are unfit for chemotherapy and stem cell transplantation

✓Since in these patients, the rate of CHR with other TKIs is already closed to 100% *(Vignetti et al., Blood 2007; Foà et al., Blood 2011)*, but the relapse rate at 1 year is 50% or more, the purpose of this study is **to induce better and longer remissions**

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Secondary Objectives

To evaluate:

- ✓ The **Complete Hematological Response (CHR)** and the **Complete Cytogenetic Response (CCgR)** at 6, 12, 24, 36 and 48 weeks, and the duration of CCgR
- ✓ The **Complete Molecular Response (CMolR)** and Major Molecular Response (MMR) at 12, 24, 36 and 48 weeks, and the duration of CMolR.
- ✓ Type and number of **BCR-ABL kinase domain mutations** developing during and after the study
- ✓ Event Free Survival **(EFS)**
- ✓ Overall Survival **(OS)**
- ✓ Failure Free Survival (FFS)
- ✓ The **treatment toxicity**

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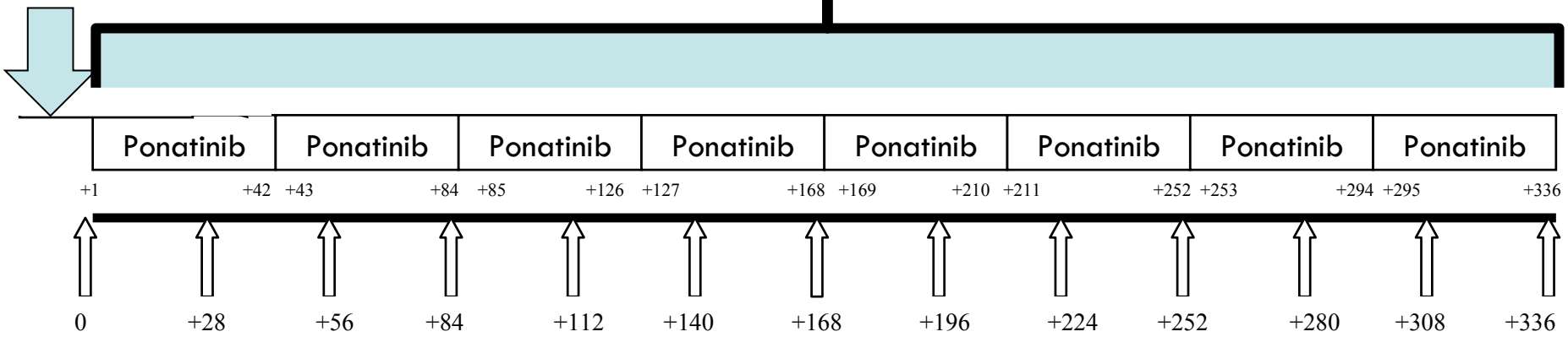
Treatment Schedule

Steroid pre-treatment x 7-14 days
(and for 28 days
during Ponatinib administration)

Ponatinib 45 mg/daily x 6 weeks (1 course) x 8 courses



= Intrathecal therapy: MTX 10 mg, AraC 40 mg, Dex 4 mg

Extension Phase:
Ponatinib until disease relapse

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Sample Size

- ✓ Coordinating Center: Bologna University
- ✓ Number of **participating Centers**: **36**
- ✓ Number of patients to be enrolled: **44**
- ✓ Study duration (enrollment + therapy duration + follow-up): approximately **5 years**
- ✓ Start enrollment: **December 2014**

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Enrollment update

Enrolled patients	N 28 (+1 pt in screening)
Median age (range)	67 (42-74)
WBC/mmc median (range)	4830 (182-186900)
Hb g/dl median (range)	8.7 (7.1-10.1)
PLTs/mmc median (range)	38000(8000-125000)
CHR@6 weeks	24/24 (4 not already evaluated)
Hematological Relapse	1 (no treatment adherence @ day +250)
Out of the study	2 in CR of which: - 1 pt→ HSCT - 1 pt for investigator choice (fusion transcript reached 0.12x10000ABL)

Main monitoring

- MRD status is assessed every 6 weeks
- AEs and SAEs collected for the entire duration of the study
- Physical examination/vital signs, Performance status (WHO), Blood counts and differential, symptoms and side effects collected weekly or monthly (according to the schedule timetable)
- Coagulative parameters and Thromboembolism risk assessed before each course

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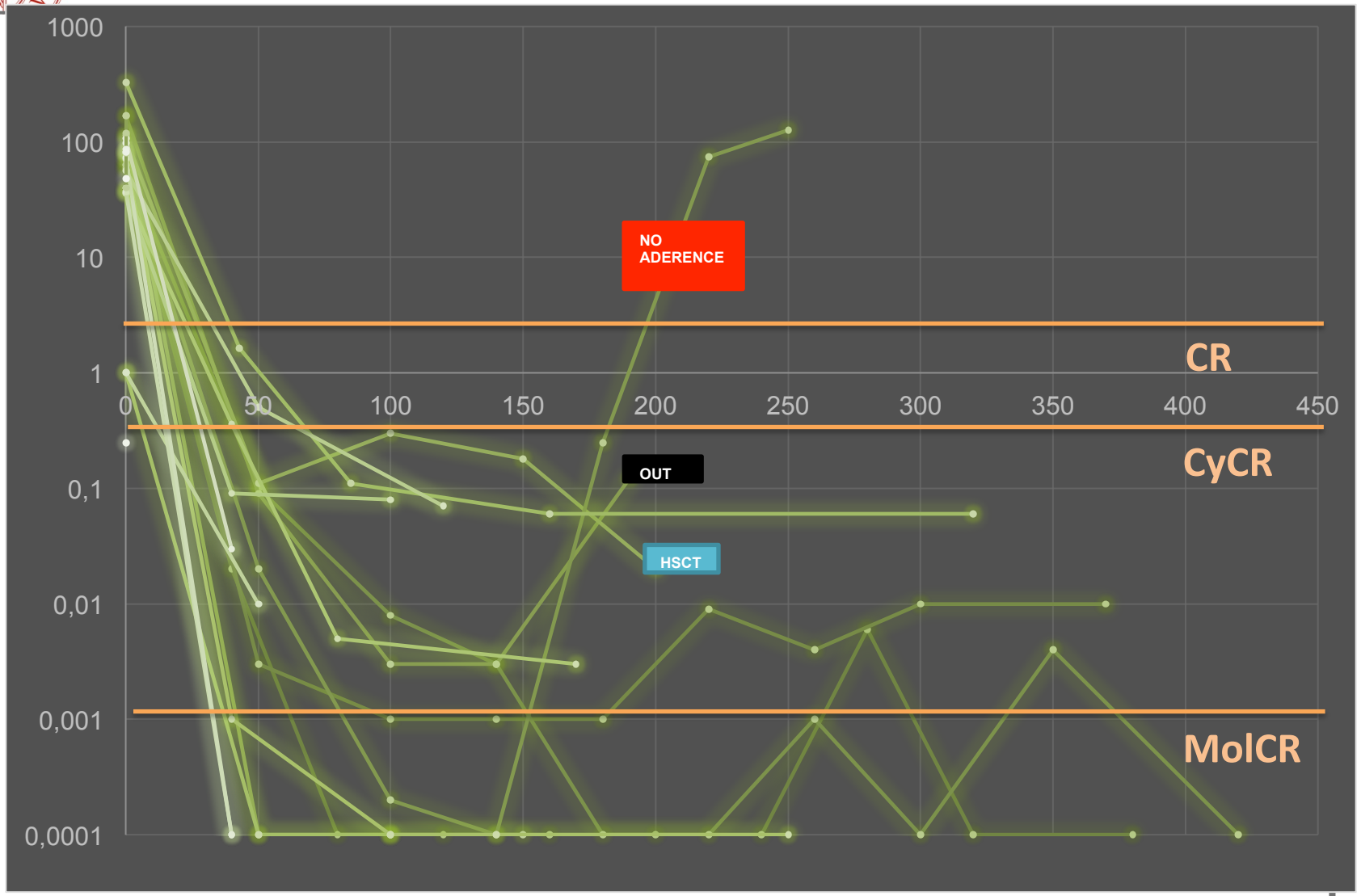
Efficacy



* Patients evaluated for at least 50 days

Safety: SAEs

System Organ Class	Preferred term	Severity	Outcome	Relationship
Pregnancy, puerperium and periantal condition	Pregnancy	Mild	Recovered	Unrelated
Infections **(Paziente non arruolabile)**	Pneumonia	Fatal	Fatal	Unrelated
Infections **(Paziente non arruolabile)**	Pneumonia	Fatal	Fatal	Unrelated
General disorders	Pyrexia	Severe	Unchanged	Unrelated

Fatal SAEs verified in patients that didn't meet exclusion criteria

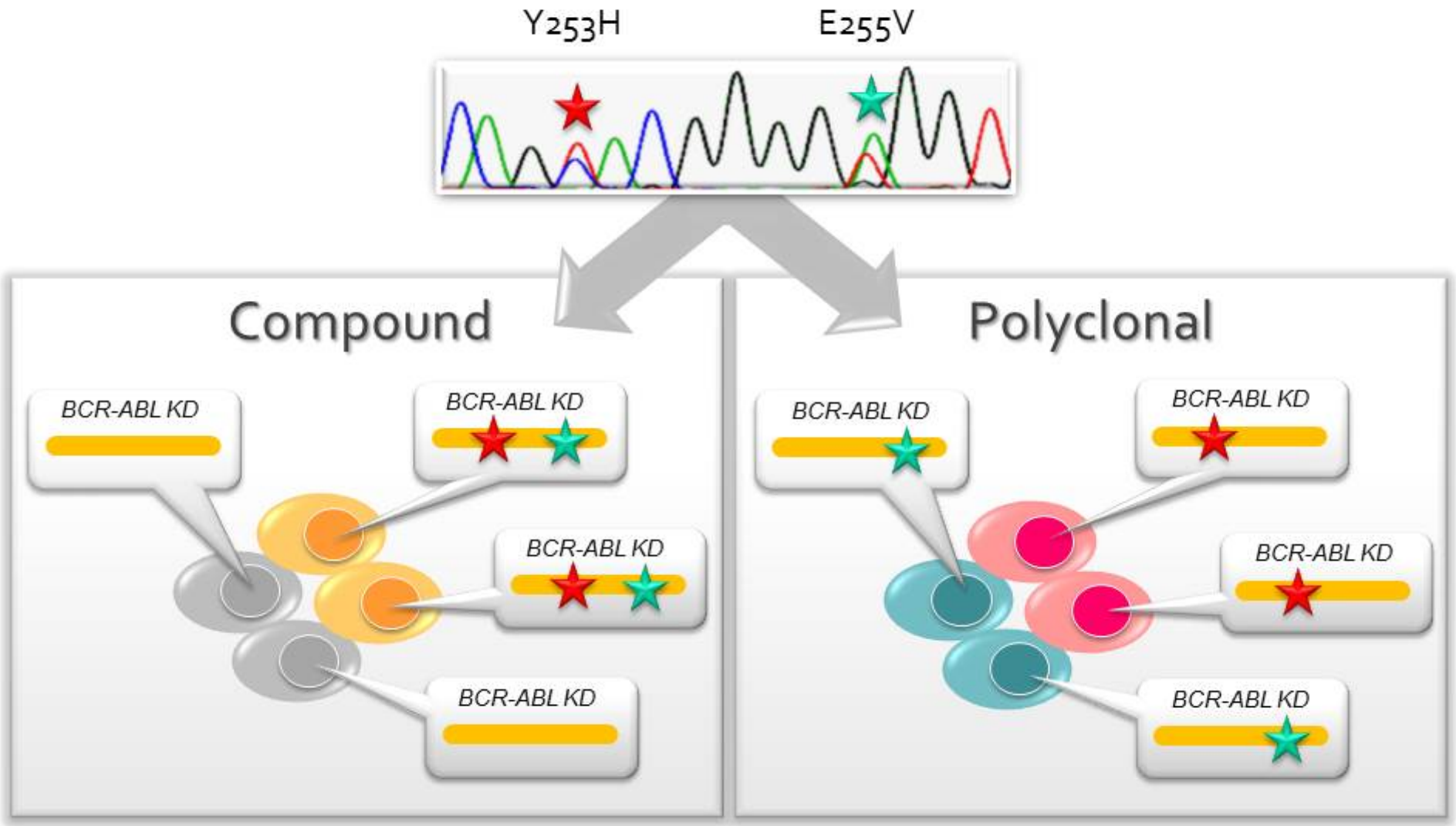
Safety: AEs

- First 8 weeks of treatment
  - Rash grade 1-2
  - Nausea grade 1
- Week 8-52
  - Neutropenia gr1
- After 1 year of treatment
  - A patient reported new onset *claudication* (leg)

Take home messages (II)

- Ponatinib, at the standard dosage, is showing a good safety profile. No cardiovascular toxicity has been reported so far
- All the patients reached a CHR, confirming the efficacy and feasibility of a chemo-free approach, at least in elderly population
- A quick reduction of BCR-ABL fusion transcript was observed in all the enrolled patients
- No severe infections occurred
- Data from NGS approach will try to elucidate the mechanisms of resistance to the drug

Compound mutations are critical in Ph+ ALL



Conclusions

- TKIs have improved outcome of Ph+ elderly ALL patients
- Virtually, all patients may achieve a CHR with a TKI plus steroids as first line therapy approach
- No deaths during induction occurred in GIMEMA chemo-free clinical trials
- Ponatinib is showing a tremendous efficacy in this setting

Open questions

- Ponatinib (and TKIs)…at which dosage, and how long?
- Which mechanisms of resistance?
- How to combine TKIs with MRD-oriented therapy (e.g. Blinatumomab?)

Acknowledgments

GRUPPO DI RICERCA
CURA DELLE LEUCEMIE
E MIELODISPLASIE

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ELN European LeukemiaNet

AACR American Association for Cancer Research

cost EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY

AIRC Associazione Italiana per la Ricerca sul Cancro
Con la ricerca, contro il cancro.

FONDAZIONE DEL MONTE 1473

SEVENTH FRAMEWORK PROGRAMME

NEXT GENERATION SEQUENCING for Targeted Personalized Therapy of Leukemia

AIL Bologna

AIRC

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