ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

POLICLINICO DI
SANT'ORSOLA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna

# Ponatinib

Fausto Castagnetti
University of Bologna

New Drugs in Hematology

President: Pier Luigi Zinzani
Co-President: Michele Cavo

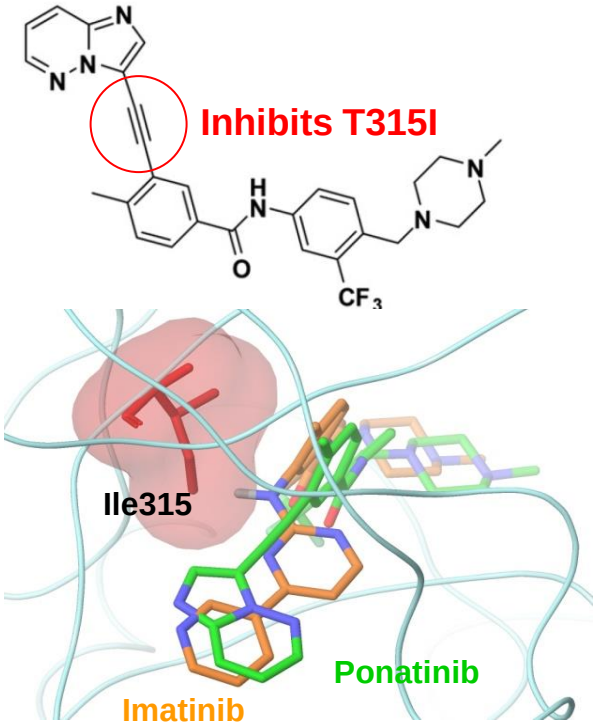
Bologna,
Royal Hotel Carlton
January 15-17, 2024

# Disclosures of FAUSTO CASTAGNETTI

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| Novartis | X | | X | | X | X | |
| Incyte | | | X | | X | X | |
| Pfizer | X | | X | | X | | |
| BMS | X | | X | | X | | |

# PONATINIB
# A PAN-BCR-ABL INHIBITOR

- ATP competitive inhibitor of BCR-ABL
- Rationally designed to accommodating gatekeeper residue and active against T315I mutant
- Potent activity against an array of BCR-ABL variants
- Also targets other therapeutically relevant kinases (FLT3, FGFR, VEGFR and PDGFR, and c-KIT)
- Once-daily oral activity
- Approved by FDA and EMA: 1) in CML patients who cannot tolerate or do not respond to DAS or NIL and for whom other TKIs are not appropriate, 2) in T315I+ patients




O'Hare T, et al. Cancer Cell 2009;16:401-412
Reference Number: EMA/199822/2013

# ASH Meeting 2012 - PACE Study Response in CP-CML

| Response Rate, n (%) | N=267 |
|---|---|
| Any Cytogenetic Response | 180 (67) |
| MCyR | 149 (56) |
| CCyR | 124 (46) |
| MMR | 91 (34) |
| $MR^{4.5}$ | 39 (15) |
| BCR-ABL ≤10% at 3 months, n/N(%) | 142/240 (59) |
| 1 prior approved TKI | 14/16 (88) |
| **Median Time to Response, months [range]** | |
| MCyR | 2.8 [1.6 – 11.3] |
| MMR | 5.5 [1.8 – 19.2] |

Cortes J et al. ASH 2012 Abstract 163

# Early Ponatinib Timeline

- December 2012: FDA approval
- July 2013: EMA approval
- **October 2013:**

  **1) EPIC study termination (First-line Ponatinib in CML)**

  **2) dose reduction to 30 or 15 mg in the PACE study,**

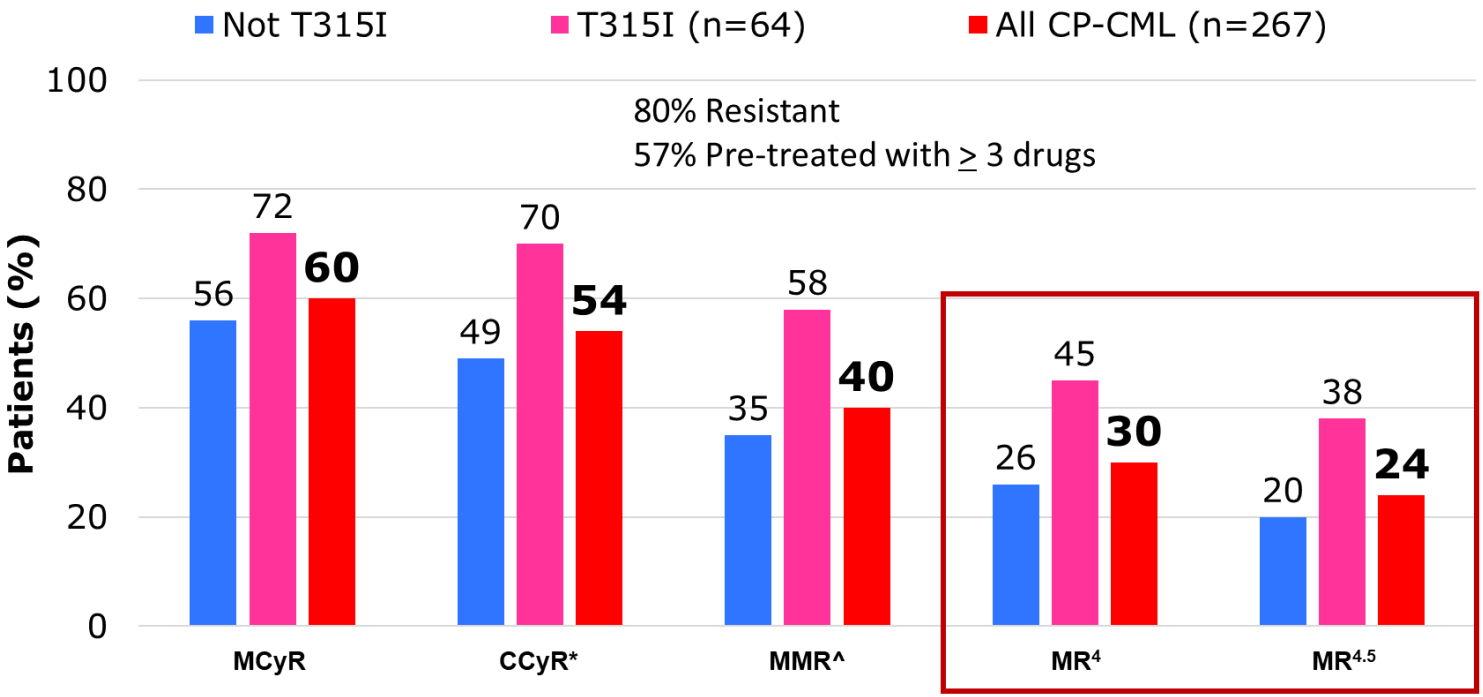
  **3) suspended sales due to serious safety concerns**
- December 2013: Return to the market (patients with T315I mutation or for whom no other TKI therapy was indicated)
- In the PACE study, 5-year cumulative incidence of AOEs 31%, VTEs 6%

# Ponatinib in CML today

#10YearsChallenge

PACE 5-year update

# Response at Any Time: CP-CML

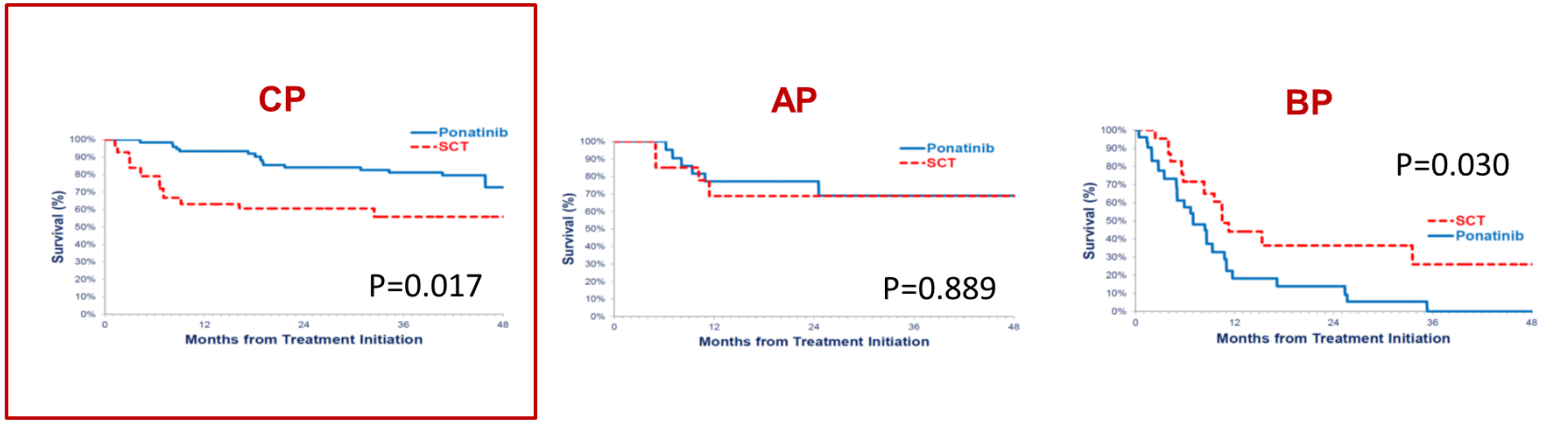



**Datacut:** February 6, 2017

Cortes et al. Blood 2018; DOI 10.1182/blood-2016-09-739086

# Ponatinib or SCT for T315I CML

- Pts ≥18 yrs with CML *T315I* in any stage enrolled in PACE (n=449) or EBMT (n=222)
- Median age (yr): CP 53 vs 48; AP 55 vs 46; BP 47 vs 44; Ph+ ALL 55 vs 36




Nicolini FE, et al. Cancer 2017 ;123(15):2875-2880

# Second-line treatment in CP-CML after 2GTKIs

## ELN 2020

**In patients with resistance to a 2GTKI ponatinib is preferred rather than an alternative 2GTKI unless cardiovascular risk factors preclude its use.**

If indicated, the criteria for the choice of the second-line 2GTKI are almost entirely patient related (age, comorbidities, toxicity).

## NCCN 2023

Subsequent therapy with an alternate 2G TKI may be considered in patients with identifiable BCR::ABL1 mutations that confer resistance to first-line TKI therapy.

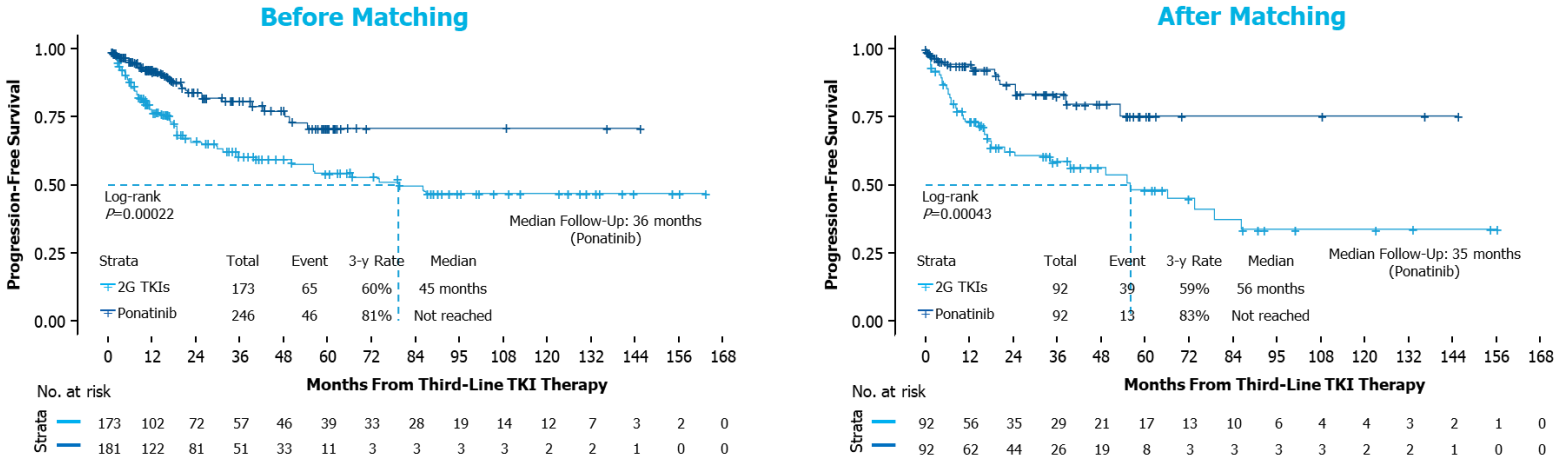
**Ponatinib is preferred for patients with no identifiable BCR::ABL1 mutations and for patients with a T315I mutation in any phase.**

Asciminib is a treatment option for CP-CML patients with the T315I mutation.

Hochhaus et al. Leukemia 2020
NCCN CML Guidelines Version 1.2024

# Third-line Ponatinib vs 2nd Gen TKIs

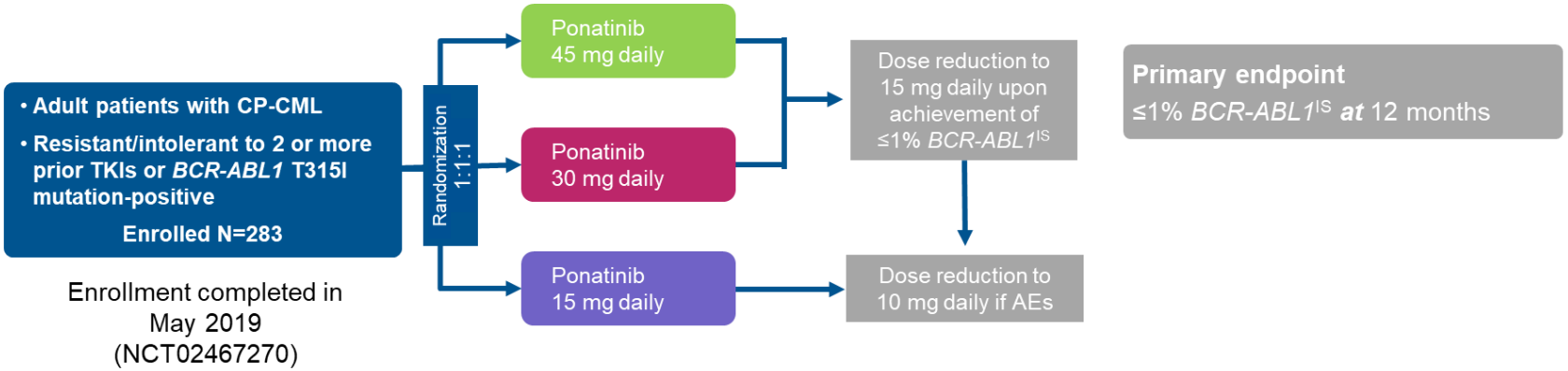
## A Propensity Score Analysis, Progression-free survival




The 3-year PFS rate was 59% versus 83% ($P<0.001$) after propensity matching in patients treated with 2G TKIs and ponatinib, respectively

Jabbour E, et al. Am J Hematol. 2023;98(4):658-665

# OPTIC (Optimizing Ponatinib Treatment In CP-CML)
# Multicenter, Randomized Phase 2 Trial



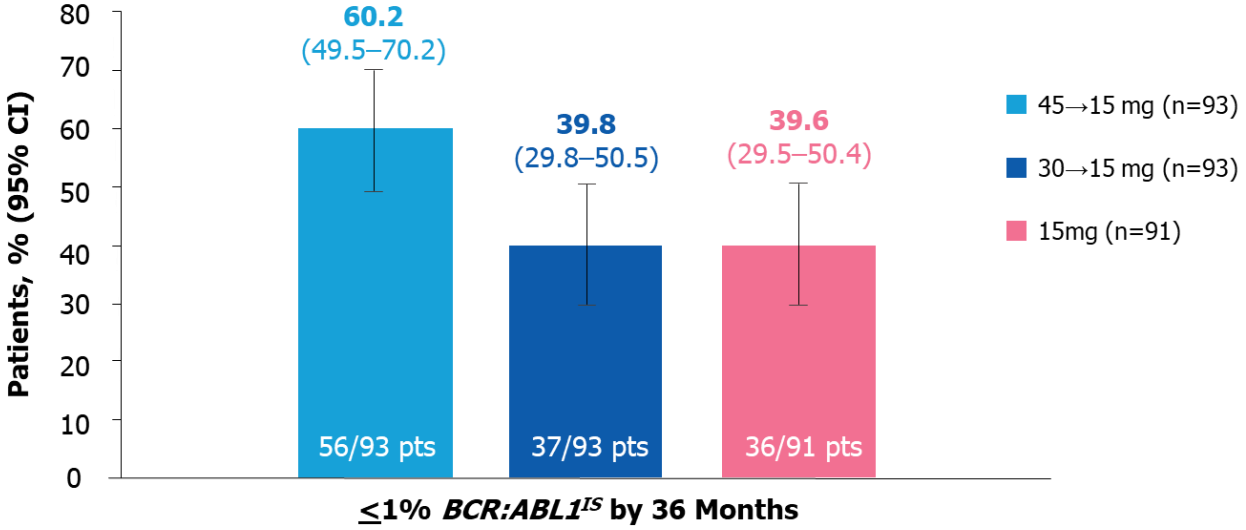

Enrollment completed in May 2019 (NCT02467270)

- Median (range) duration of follow-up: 54 months (1–80)

Dose reductions due to AEs were permitted
Escalation to the starting dose allowed for patients who lost their response following dose reduction
No dose escalation allowed beyond starting dose

Cortes et al. Blood 2021;138(21):2042-2050
Cortes J, et al. Oral presentation at: ASH 2022; New Orleans, LA, USA [Abstract #620].

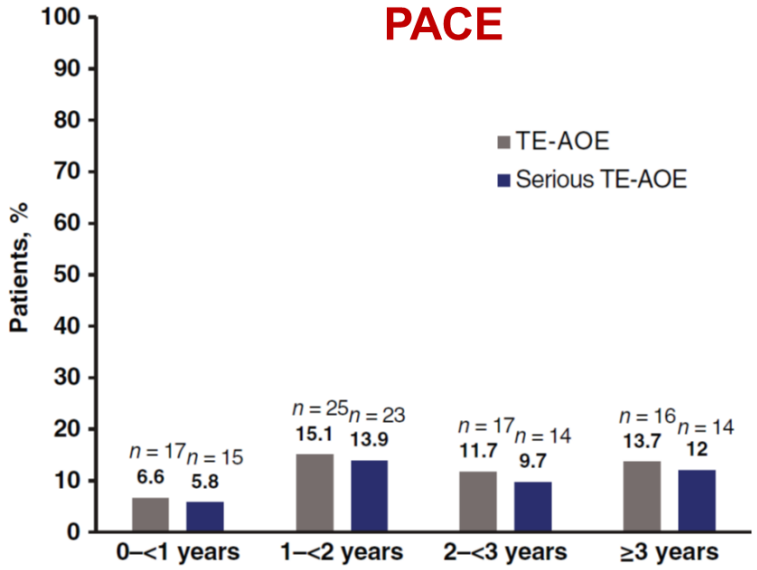
# OPTIC Study: BCR::ABL1IS ≤1% by 36 Months (95% CI)



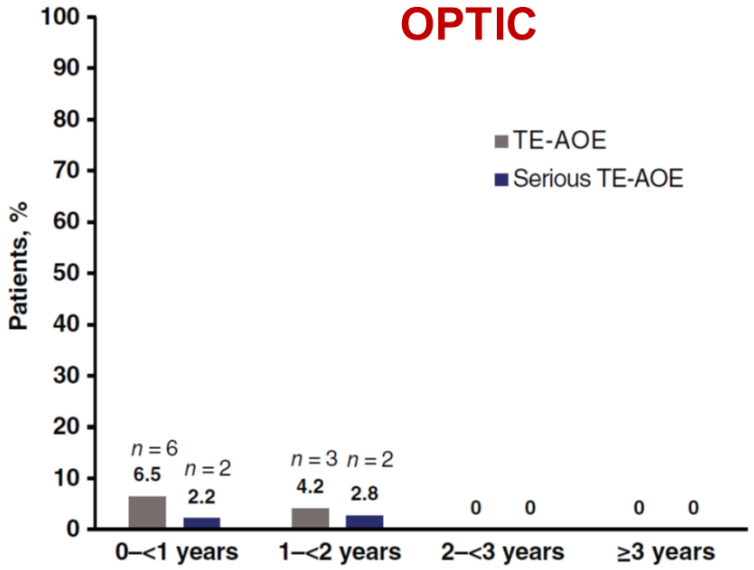

Ongoing patients 53%, 43% and 46% per arm, respectively.
Median duration of response was not reached in any treatment arm.

Cortes J, et al. Oral presentation at: ASH 2022; New Orleans, LA, USA [Abstract #620].

# Exposure-Adjusted AOEs in PACE and OPTIC (45 mg ARM)




Median dose: 30 mg at 12-24 mos, 15 mg at 36 mos




Median dose: 15 mg at 12-24-36 mos

Jabbour et al. ASH 2021. Abstract 2550
Kantarjian et al. Am J Hematol. 2022 Nov;97(11):1419-1426.

# Impact of prior exposure to nilotinib on AOEs

## Mayo Clinic experience with ponatinib in CP-CML

| Side effects | All patients N = 55 | Age <60 N = 43 | Age ≥60 N = 12 | p value | Patients with ≤2 prior TKIs N = 20 | Patents with 3/4 prior TKIs N = 35 | p value | Patients with prior Nilotinib N = 35 | Patients without prior Nilotinib N = 20 | p value |
|---|---|---|---|---|---|---|---|---|---|---|
| Arterial vascular events, *n* (%) | 4 (7%) | 1 (2%) | 3 (25%) | **0.01** | 1 (5%) | 3 (8%) | 0.6 | 4 (11%) | 0 (0%) | **0.05** |
| Arterial thrombosis | 1 (1.8%) | 0 (0%) | 1 (8%) | 0.07 | 0 (0%) | 1 (2%) | 0.33 | 1 (3%) | 0 (0%) | 0.33 |
| Angina | 1 (1.8%) | 0 (0%) | 1 (8%) | 0.07 | 0 (0%) | 1 (2%) | 0.33 | 1 (3%) | 0 (0%) | 0.33 |
| Acute coronary artery | 1 (1.8%) | 0 (0%) | 1 (8%) | 0.07 | 0 (0%) | 1 (2%) | 0.33 | 1 (3%) | 0 (0%) | 0.33 |
| Carotid artery stenosis/stroke | 1 (1.8%) | 1 (2%) | 0 (0%) | 0.48 | 1 (5%) | 0 (0%) | 0.15 | 1 (3%) | 0 (0%) | 0.33 |

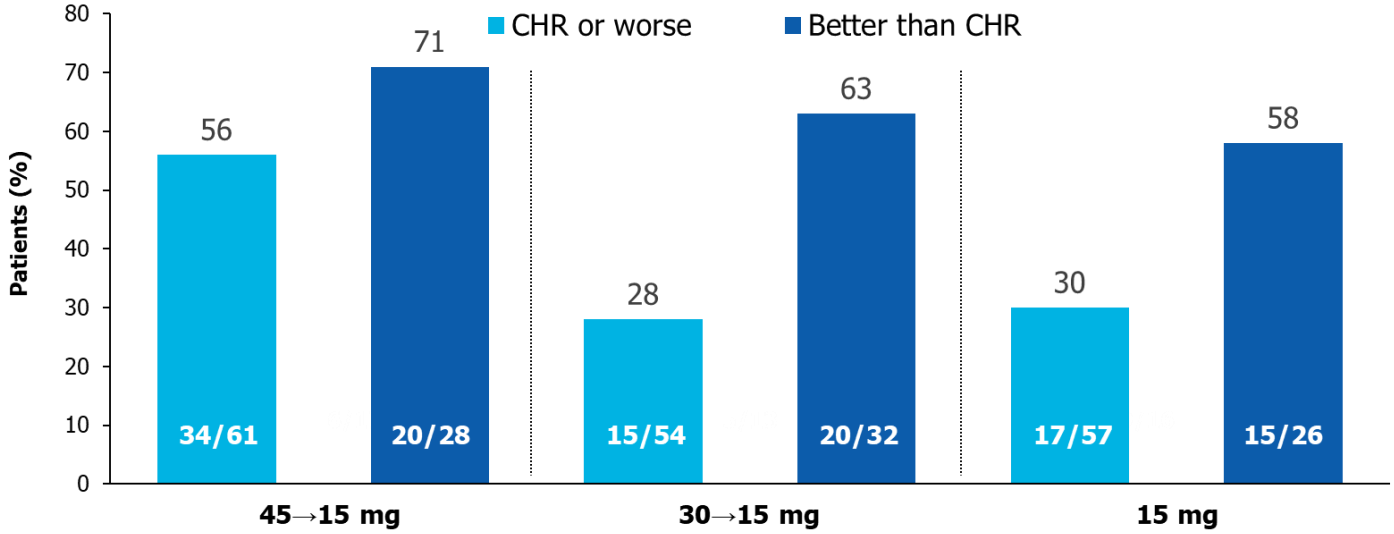
4 out of 55 patients (7.3%) had Arterial Occlusive Events (AOEs), median follow-up: 42 months

- AOEs was more frequent in patients exposed to nilotinib (11% vs 0; age-adjusted p = 0.04)
- AOEs also correlated with age ≥60 years (p = 0.01)
- By contrast, neither the ponatinib dose range nor the number of prior TKIs AOE

Abdelmagid et al. Blood Cancer Journal (2023) 13:122 ;

# OPTIC Study - 36 months update

## BCR::ABL1IS ≤1% Rate by Best Response to Last Prior TKI

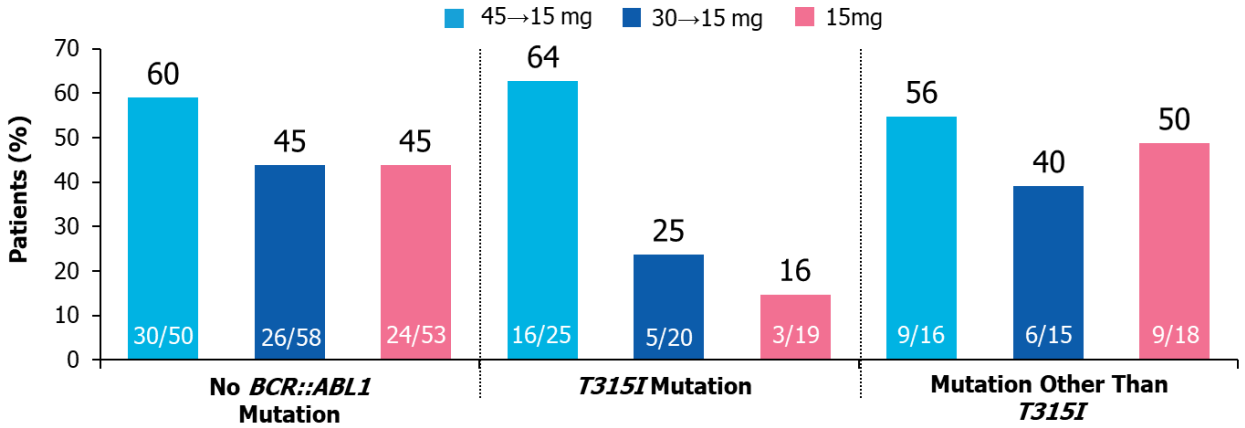



Among patients who achieved CHR or worse to last prior therapy, *BCR::ABL1*$^{IS}$ ≤1% rates were highest in the 45→15 mg cohort.

Cortes J, et al. Oral presentation at: ASH 2022; New Orleans, LA, USA [Abstract #620].

# OPTIC Study - 36 months update

## *BCR::ABL1*$^{IS}$ ≤1% Rate by Mutation Status at Baseline




Regardless of the presence of the *BCR::ABL1* mutation, response rates in the 45→15 mg cohort were comparable

Cortes J, et al. Oral presentation at: ASH 2022; New Orleans, LA, USA [Abstract #620].

Registries of the Italian Medicines Agency (AIFA)

# CML management with ponatinib in a real-life setting

| Characteristics | Chronic phase 515 (77.32%) | Accelerated phase | Blast phase | Overall 666 (100%) |
|---|---|---|---|---|
| Age | | | | |
| Median age (iqr) | 57.99 (44.79–67.79) | 58.95 (47.02–70.48) | 61.39 (49.07–70.04) | **58.70 (44.96–68.57)** |
| Diagnosis | | | | |
| Time since diagnosis years | 2.65 (1.36–6.82) | 1.93 (0.67–5.91) | 1.17 (0.46–2.65) | **2.35 (1.10–6.24)** |
| Therapeutic lines | | | | |
| 2 | 190 (36.89%) | 19 (38.00%) | 50 (49.50%) | **259 (38.89%)** |
| 3 | 209 (40.58%) | 15 (30.00%) | 36 (35.64%) | **260 (39.04%)** |
| **4+** | **116 (22.52%)** | **16 (32.00%)** | **15 (14.85%)** | **147 (22.07%)** |
| Previous TKI | | | | |
| Previous imatinib | 296 (57.48%) | 25 (50.00%) | 44 (43.56%) | **365 (54.80%)** |
| Previous 2nd gen. TKI | 499 (96.89%) | 44 (88.00%) | 85 (84.16%) | **628 (94.29%)** |
| BCR-ABL (%) | | | | |
| Lower or equal than 0.1 | 61 (11.84%) | 1 (2.00%) | 6 (5.94%) | **68 (10.21%)** |
| 0.1–1 | 125 (24.27%) | 8 (16.00%) | 7 (6.93%) | **140 (21.02%)** |
| 1–10 | 143 (27.77%) | 11 (22.00%) | 13 (12.87%) | **167 (25.08%)** |
| Greater than 10 | 186 (36.12%) | 30 (60.00%) | 75 (74.26%) | **291 (43.69%)** |

Breccia et al. Br J Haematol. 2022;198(6):965-973.

# Treatment-Free Remission after Ponatinib Cessation in CP CML
# The Ponastop Observational Study

- 15 CP-CML patients analyzed, median age 43 (24-79) years
- 3 patients were *ABL1*$^{T315I}$ mutated
- Previous treatment: 1 patient had 4 previous lines of TKI prior to ponatinib, 4 patients 3 prior lines, 5 patients 2 prior lines, 4 patients 1 prior line and 1 patient was in ponatinib first-line (EPIC trial)
- **10 patients were resistant to prior TKI before ponatinib, 3 were intolerant, 1 intolerant and resistant and 1 was in first-line**
- **13 arterial events occurred, all prior to ponatinib cessation**
- **The median survival without MMR loss after ponatinib cessation was 69%**



Nicolini et al. Poster presentation ASH 2023 Abs n. 1799

# Imatinib after Ponatinib Induction in First-line CP-CML
# The French TIPI study

- Phase II trial enrolling newly diagnosed adult CP-CML pts ≤65 years without underlying cardio-vascular disease
- Patients were treated with **ponatinib 30 mg QD for 6-months**, followed by imatinib 400 mg QD until TFR criteria achievement (MR4.5 ≥2 years)
- The primary endpoint is the achievement of TFR criteria at M36 (not presented).
- 169 patients, median age 48 (18-65) years; ELTS low 40%, int 44%, high 16%
- **6 (4.5%) Grade 3-5 cardiac events (1 fatal cardiac arrest)** and 17 (12.5%) vascular events (15 newly hypertensive pts, 1 pulmonary embolism, 1 carotid stenosis)
- **The median halving time was 13.5 days; 30% patients were in DMR at M6**



Nicolini et al. Oral presentation ASH 2023 Abs n. 445

# Efficacy of Consolidation with Ponatinib 15mg on TFR
# Results of the Ponazero Trial

- Multicenter open-label, single-arm, phase II, prospective clinical trial
- Patients CP-CML with discontinuation criteria according to ELN recommendations, with ≥ 4 years of imatinib therapy and MR4 ≥ 12 months
- 2 phases: **ponatinib 15 mg consolidation (48 weeks)**, and TFR phase (48 weeks)
- 23 patients, median age 52 years
- Median time on prior imatinib was 10 years, median time on MR4 was 3.6 years
- **3/22 (13.6%) had AEs leading to treatment discontinuation**: thrombophlebitis, erectile dysfunction, and intermittent claudication.
- **14/19 (74%) of the patients who entered the TFR phase are still in MMR**



Perez-Lamas et al. Poster presentation ASH 2023 Abs n. 1795

# Conclusions and perspectives

- The physician's perception of ponatinib changed over time;
- Ponatinib is a well established second-line treatment option, not only in case of resistance to 2GTKIs or in case of T315I mutation;
- Dose optimization (45 → 15 mg) is the most effective strategy to minimize the potential ponatinib CV toxicity; patient selection, CV risk assessment and concomitant medications may are mandatory;
- The clinical significance of high rates of deep molecular response induced by ponatinib are under evaluation → any role in the achievement of TFR?

# Thank you for attention!

fausto.castagnetti@unibo.it