LEUKEMIA2020-2021

ASSOCIAZIONE ITALIANA
CONTRO LE LEUCEMIE-LINFOMI E MIELOMA
ONLUS

April 26-27, 2021

Coordinator: A.M. Carella
AIL President: S. Amadori

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

GITMO
GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

SIE - Società Italiana di Ematologia

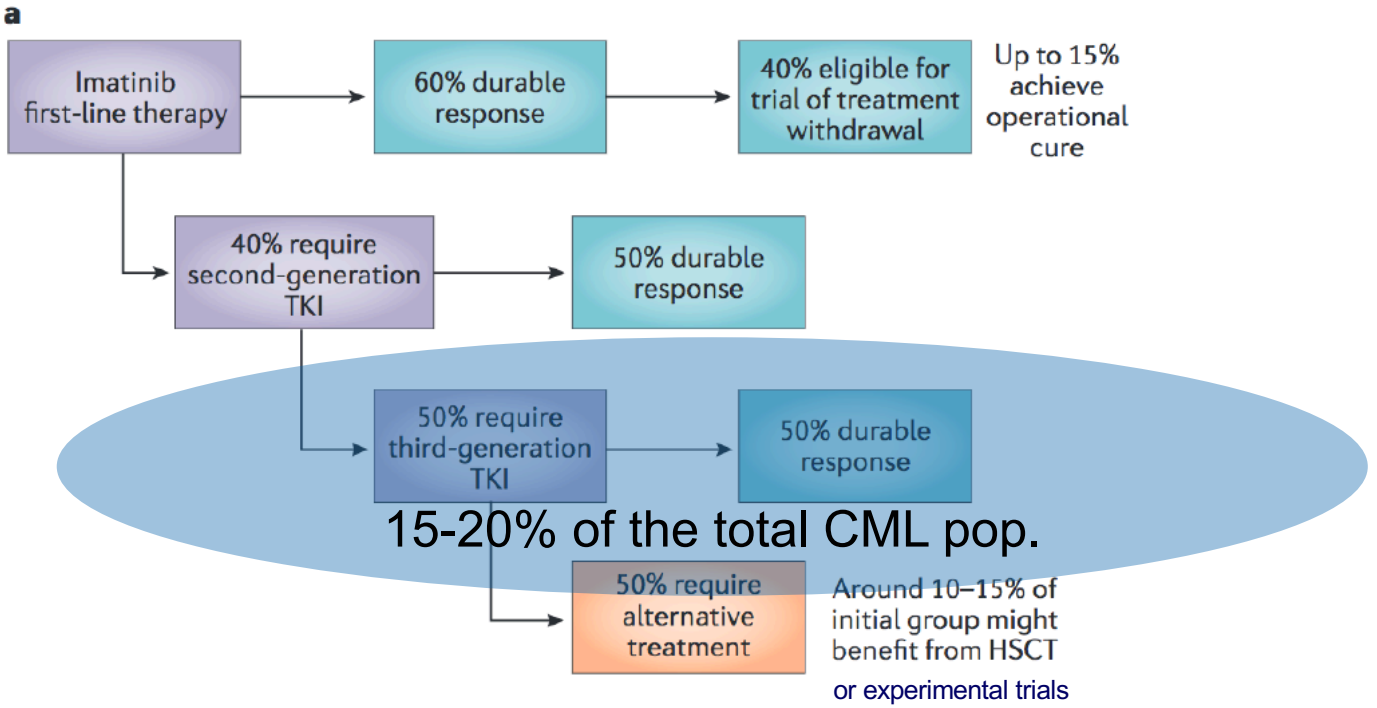
Future perspectives of novel therapies

Giuseppe Saglio
University of Turin

Main clinical needs present in CML therapy

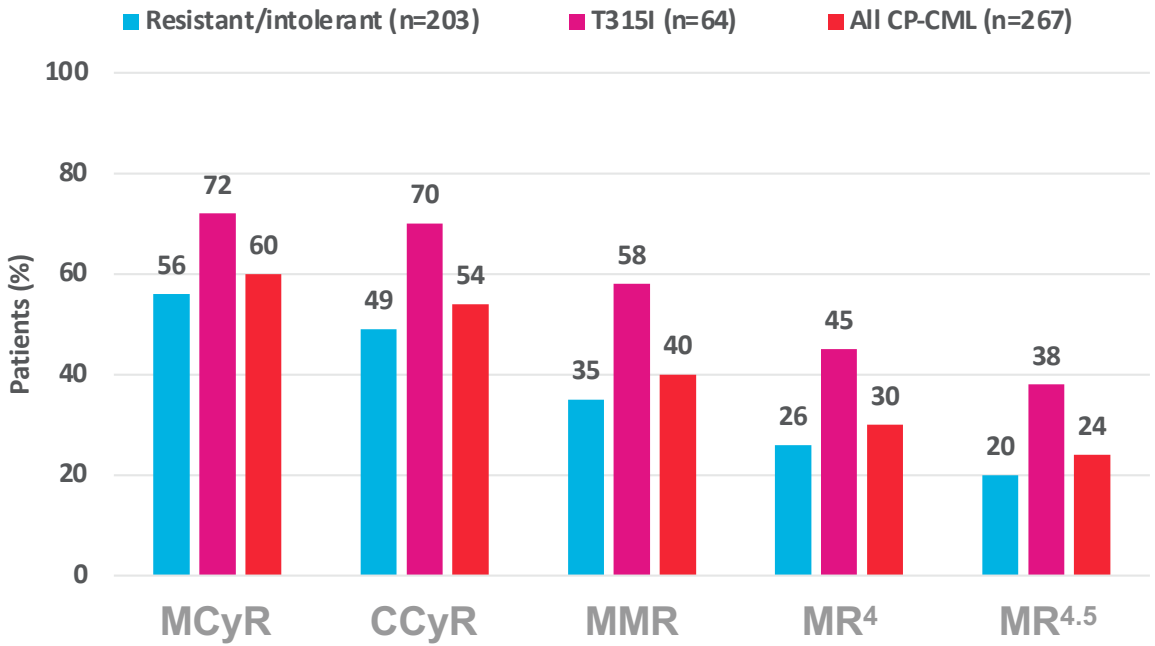
- Treatment discontinuation (to achieve definitive cure)
- Treatment of TKI resistant patients (who remain at risk of progression)

Results of the current TKI sequential therapy



Innes AC. Et al., Nature Reviews in Clin Onc., 2015

PACE trial
Response at Any Time in CP-CML



- **Median time to MCyR (range) for all CP-CML patients: 2.8 months (1.6 – 58.0)**
- **Response at any time in CP-CML patients with resistance to prior dasatinib or nilotinib (n=215):**
  - **MCyR: 54%; CCyR: 46%**

Kantarijan H et al , ASCO 2017

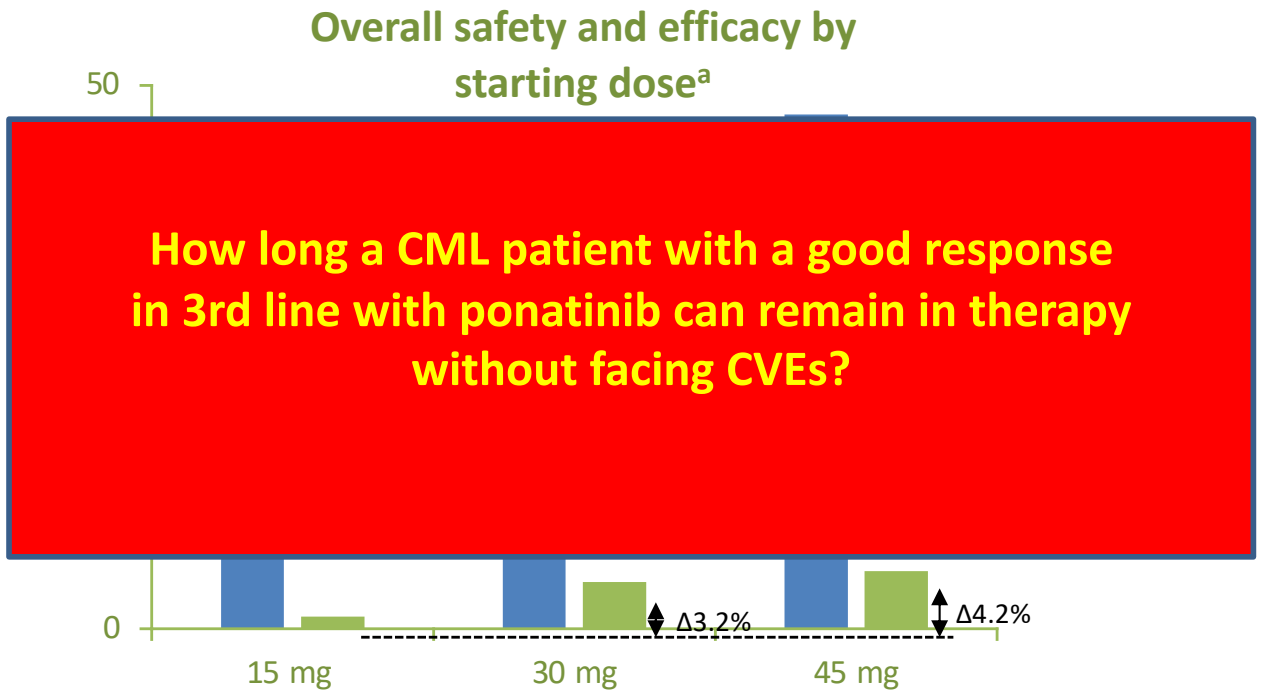
Ponatinib- PACE trial
Cumulative and Exposure-Adjusted Incidences of AOEs and VTEs[a]

	5-Year Update				4-Year Update	
	CP-CML (n=270)		All (N=449)		All (N=449)	
	AE	Serious AE	AE	Serious AE	AE	Serious AE
AOEs, n (%):	84 (31)[b]	69 (26)[c]	111 (25)[d]	90 (20)[e]	104 (23)	83 (19)
Cardiovascular	42 (16)	33 (12)	59 (13)	44 (10)	56 (13)	41 (9)
Cerebrovascular	35 (13)	28 (10)	41 (9)	33 (7)	39 (9)	31 (7)
Peripheral vascular	38 (14)	31 (11)	48 (11)	38 (8)	40 (9)	31 (7)
Exposure-adjusted AOEs[f]	14.1	10.9	13.8	10.6	14.1	10.7
VTEs, n (%)	15 (6)	13 (5)	27 (6)	23 (5)	25 (6)	22 (5)
Exposure-adjusted VTEs[f]	2.1	1.8	2.8	2.4	2.9	2.5

[a] Categorization of AOEs and VTEs is based on a broad collection of >400 MedDRA preferred terms related to vascular ischemia or thrombosis; no individual term occurred in >10% of patients; [b] 46 patients had >1 AOE; [c] 31 patients had >1 serious AOE; [d] 57 patients had >1 AOE; [e] 38 patients had >1 serious AOE;

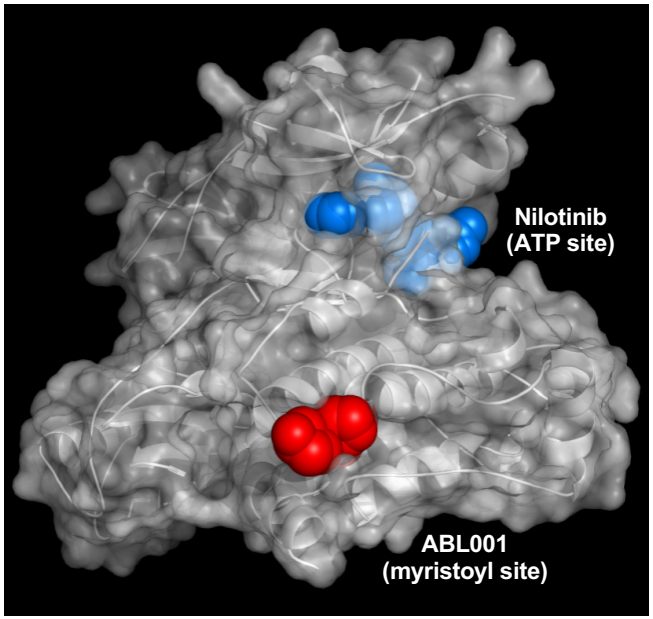
Cortes JE, et al. Blood. 2018;132:393-404.

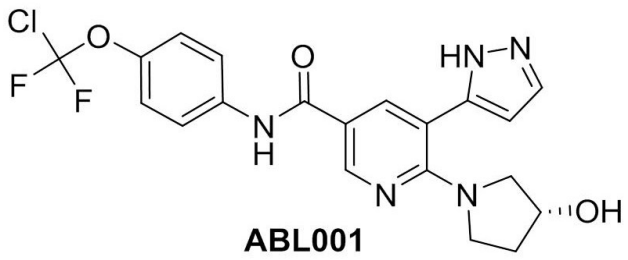
Overall safety and efficacy data in OPTIC



Asciminib is a potent specific BCR-ABL inhibitor

- Biochemistry
  - Caliper ABL1 assay IC_{50} – 0.4nM
- Biophysics
  - ITC ABL1 assay IC_{50} – 0.7nM
- Selectivity
  - Kinase selectivity restricted to ABL1 and ABL2
- Cardio-safety profile
  - hERG assay >30uM
  - No evidence of QT prolongation in dog jacketed telemetry up to 600mg/kg



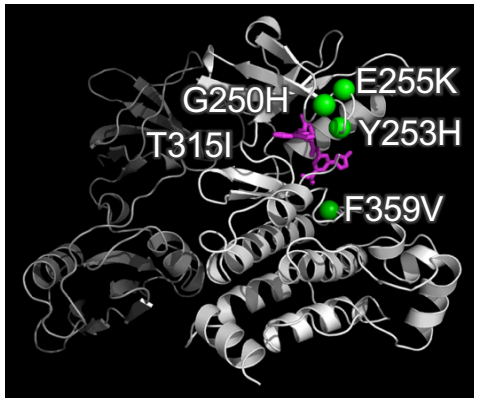


ABL001

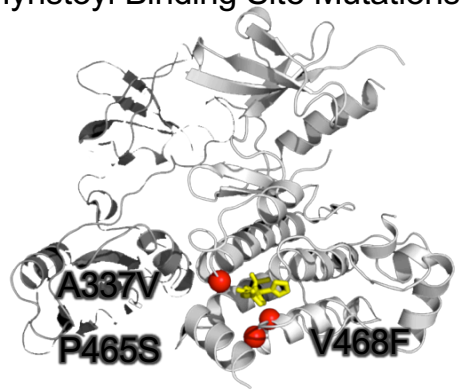
A A Wylie *et al. Nature* 1–5 (2017) doi:10.1038/nature21702

Asciminib and Classical TKIs Exhibit Complementary Mutation Profiles

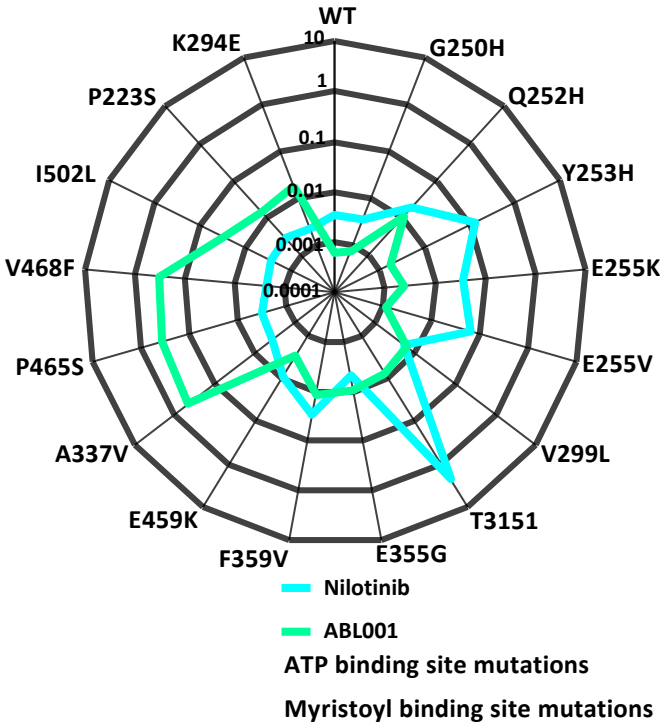
ATP Binding Site



Myristoyl Binding Site Mutations



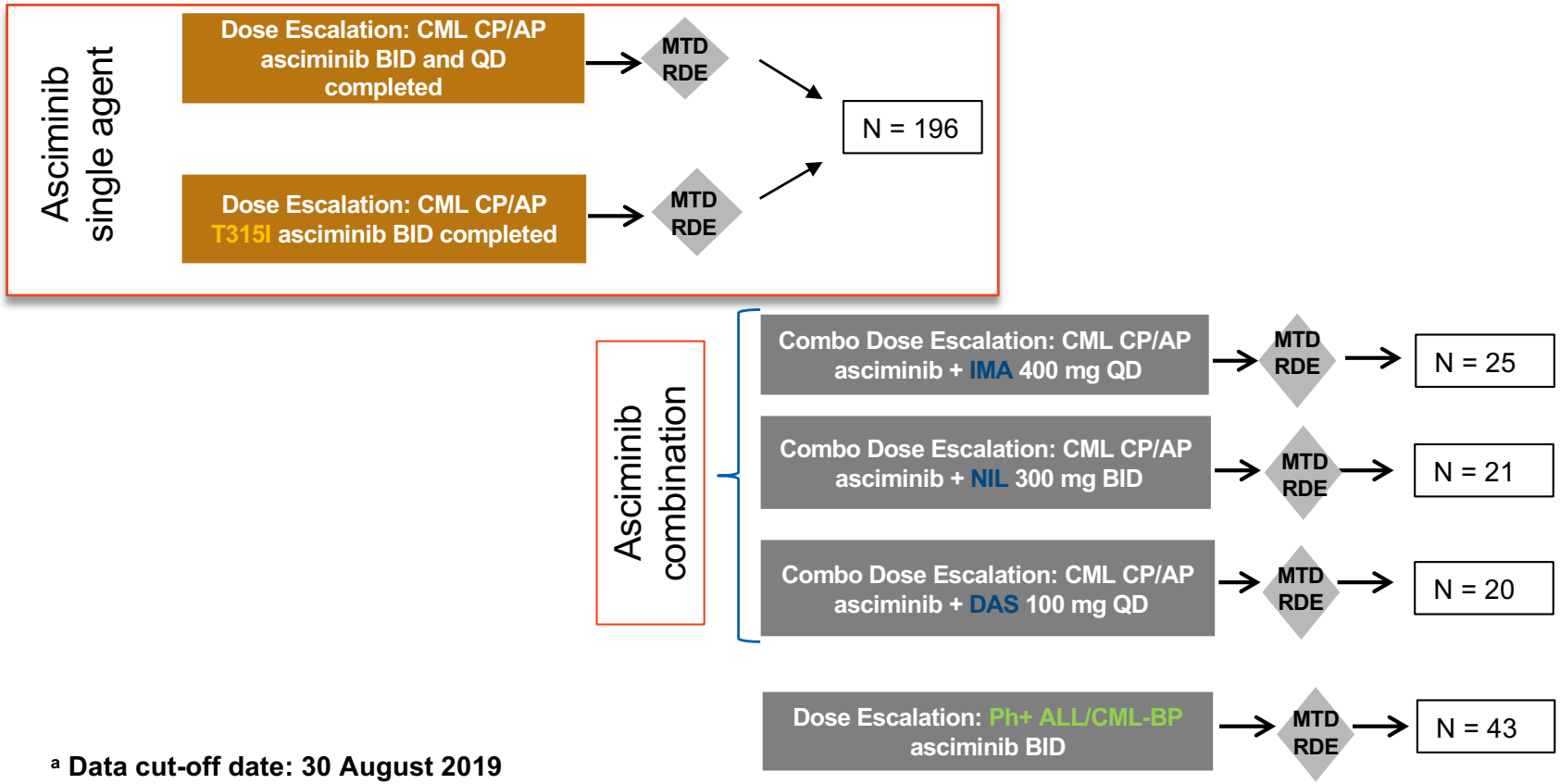
Proliferation IC_{50} Profiles in Ba/F3 *BCR-ABL1*–Mutant Lines



Wylie A, et al. *Blood*. 2014; 124 (21): [abstract 398].
Ottmann O, et al. *Blood*. 2015; 126(23): [abstract 138].

First-in-human Phase 1 Study Design[a]

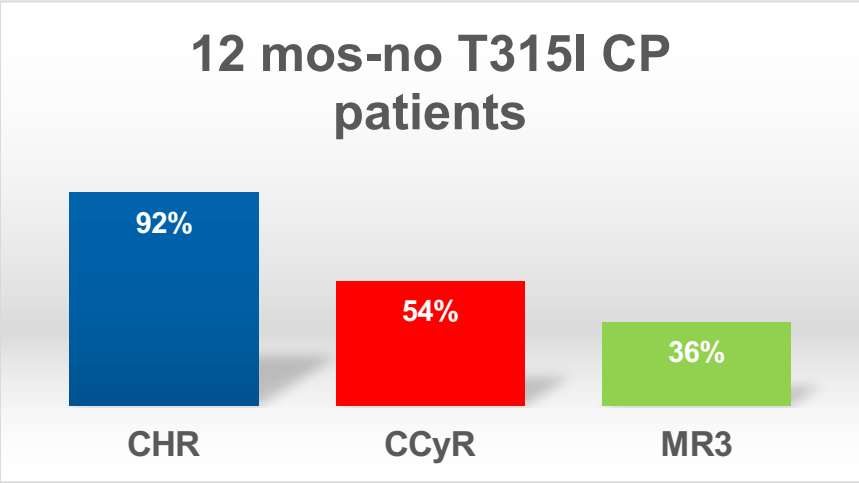
CABL001X2101 study



[a] **Data cut-off date: 30 August 2019**

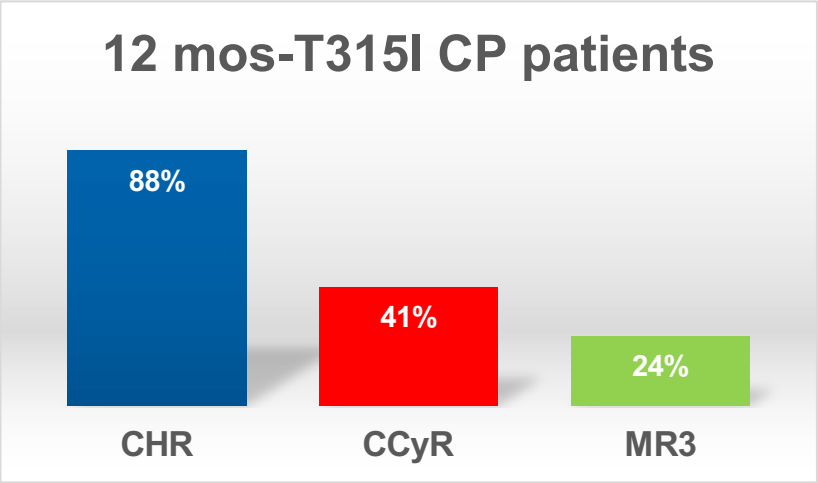
Hughes T et al. NEJM 2019

Asciminib: efficacy



- 87% of patients maintained CCyR by 12 months
- 95% of patients maintained MR3 by 12 months

- MR3 in pts with <2 previous TKIs: 47%
- MR3 in pts with >2 previous TKIs: 34%
- MR3 in pts pretreated with ponatinib: 40%



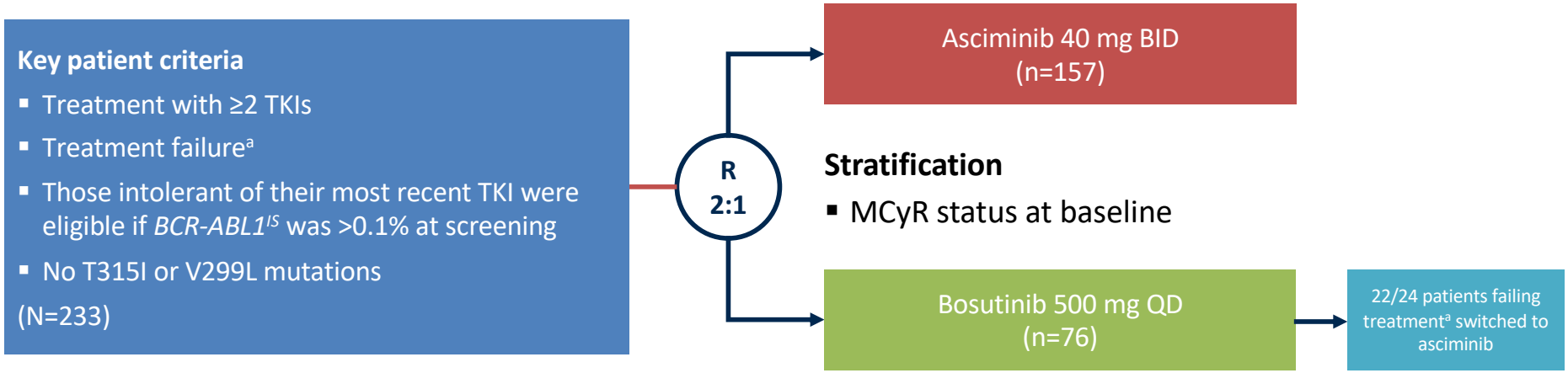
- 67% of patients maintained CCyR by 12 months
- 1/18 patient maintained MR3 by 12 months

- MR3 in pts with <2 previous TKIs: 38%
- MR3 in pts with >2 previous TKIs: 11%
- MR3 in pts pretreated with ponatinib: 17%

Hughes et al. New Engl J Med 2019

ASCEMBL study design

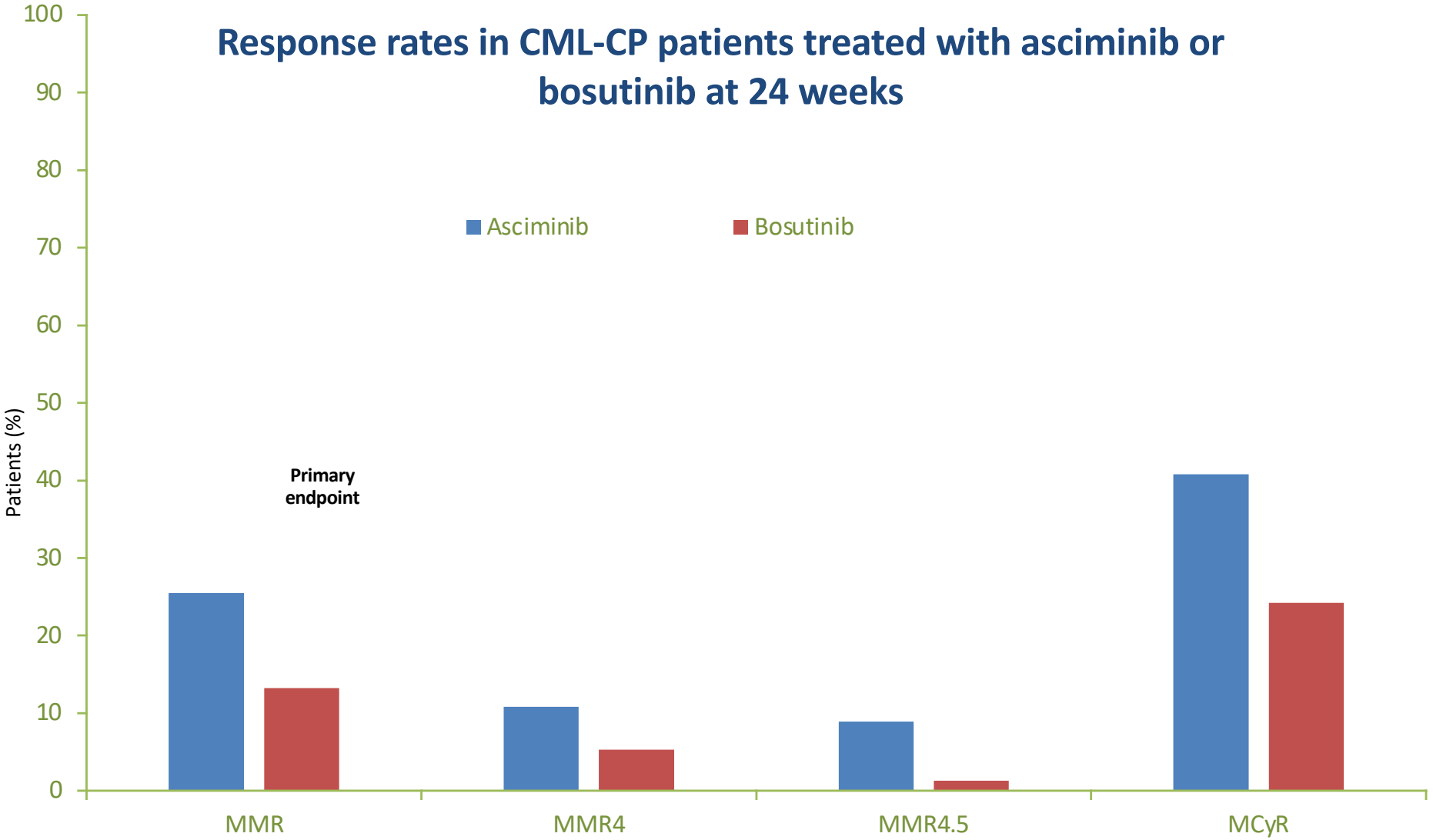
- Study objective
  - To demonstrate superior efficacy for asciminib versus bosutinib in adults with CML-CP previously treated with ≥2 TKIs



- Primary endpoint: MMR at 24 weeks
- Median follow-up: 14.9 months (study cut-off, May 25, 2020)

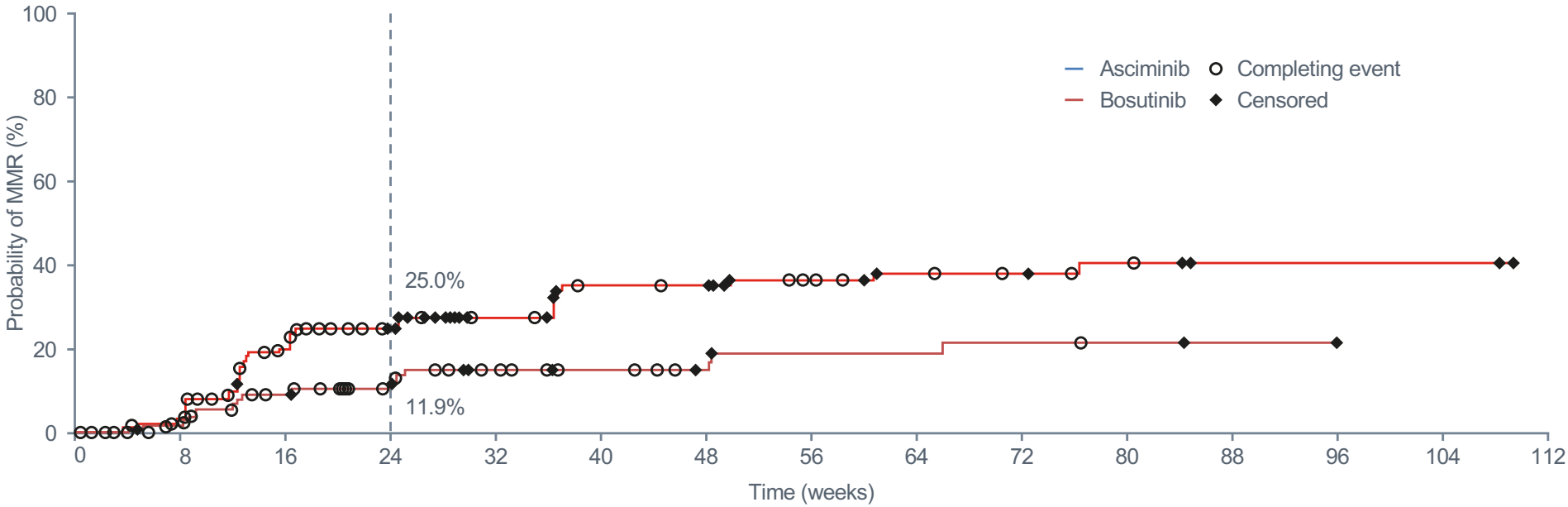
Hochhaus A et al., ASH 2020

ASCEMBL efficacy data



Hochhaus A et al., ASH 2020

ASCEMBL
Cumulative incidence of MMR



Median time to MMR: 12.7 weeks for asciminib and 14.3 weeks for bosutinib

CI, confidence interval; CML-CP, chronic phase chronic myeloid leukemia; MCyR, major cytogenetic response (Ph+ metaphases ≤35%); MMR, major molecular response; OR, odds ratio

Hochhaus A et al., ASH 2020

ASCEMBL- Patient Disposition

Patients, n (%)	Asciminib 40 mg Twice Daily (n=157)	Bosutinib 500 mg Once Daily (n=76)	All Patients (N=233)
Treated*	156 (99.4)	76 (100.0)	232 (99.6)
Treatment ongoing†	97 (61.8)	23 (30.3)	120 (51.5)
Discontinued from treatment	59 (37.6)	53 (69.7)	112 (48.1)
< Week 24	26 (16.6)	25 (32.9)	51 (21.9)
≥ Week 24 and < Week 48	22 (14.0)	27 (35.5)	49 (21.0)
≥ Week 48 and < Week 96	11 (7.0)	1 (1.3)	12 (5.2)
Reason for discontinuation			
Lack of efficacy	33 (21.0)	24 (31.6)	57 (24.5)
Adverse event	8 (5.1)	16 (21.1)	24 (10.3)
Physician decision	10 (6.4)	6 (7.9)	16 (6.9)
Patient decision	4 (2.5)	3 (3.9)	7 (3.0)
Death	1 (0.6)	0	1 (0.4)
Lost to follow-up	1 (0.6)	1 (1.3)	2 (0.9)
Progressive disease	1 (0.6)	3 (3.9)	4 (1.7)
Protocol deviation	1 (0.6)	0	1 (0.4)
Switched to receive asciminib‡	NA	22 (28.9)	NA

Hochhaus A et al., ASH 2020

ASCEMBL safety data

Safety profile of asciminib in ASCEMBL

Category, %	Asciminib (n=156)		Bosutinib (n=76)	
	All grades	Grade ≥3	All grades	Grade ≥3
All AEs	89.7	50.6	96.1	60.5
Treatment-related AEs	63.5	29.5	88.2	50.0
Treatment-related fatal AEs	0.0	0.0	1.3	1.3
Treatment-related AEs causing discontinuation	4.5	3.8	18.4	13.2
AEs causing dose interruption/adjustment	37.8	34.0	60.5	48.7
AEs requiring additional therapy	66.0	28.2	88.2	40.8

Hochhaus A et al., ASH 2020

Arterial Occlusive Events

Arterial-Occlusive Event, n (%)	Asciminib 40 mg Twice Daily (n = 156)	Bosutinib 500 mg Once Daily (n = 76)
Patients with arterial-occlusive events	5 (3.2)	1 (1.3)
Myocardial ischemia	2 (1.3)*†	0
Coronary artery disease	1 (0.6)	0
Ischemic stroke	1 (0.6)*	0
Mesenteric artery embolism/thrombosis	1 (0.6)*†	0
Acute coronary syndrome	0	1 (1.3)

- Arterial-occlusive events on asciminib
  - Myocardial ischemia (n = 2) and coronary artery disease (n = 1) based on ECG performed as per protocol after dosing and coronary arteriography performed due to medical history, respectively, and without clinical manifestations
  - Prior TKIs: 5/5 patients received imatinib and nilotinib; *3/5 received dasatinib; †2/5 received ponatinib (mesenteric artery embolism/thrombosis occurred after 7 days on ponatinib and 15 days since asciminib discontinuation)
- Arterial-occlusive events on bosutinib

Hochhaus A et al., ASH 2020

Asciminib in CML with T315I
Phase I design

- Analysis objective
  - To assess the efficacy of asciminib in heavily pretreated CML patients with T315I mutations

Key patient criteria

- Adults with CML-CP/AP
- Treatment with ≥2 TKIs, or ≥1 TKI if T315I mutations were present and no other effective treatment was available
- Patients with uncontrolled cardiovascular conditions were excluded

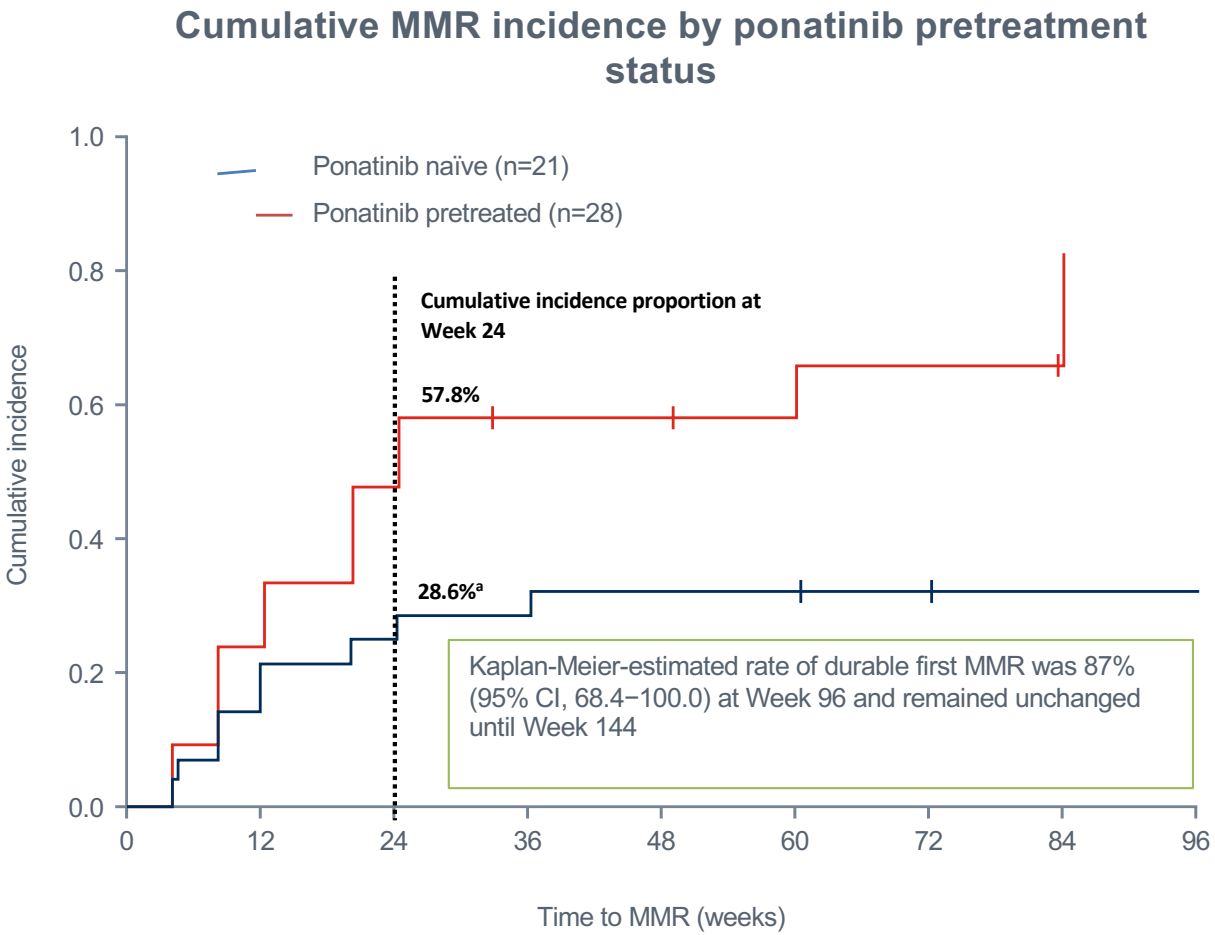
→ Asciminib 200 mg BID (dose-expansion cohort) (n=52) → Cut-off April 2, 2020

- 94% had T315I mutation only
- 83% had received ≥2 TKIs
- 60% were pretreated with ponatinib
- Ponatinib-pretreated vs –naïve patients:
  - Median years from diagnosis: 5.2 vs 1.8
  - ≥2 prior TKIs: 100% vs 57%

1. Hughes TP *et al. N Engl J Med*. 2019;381:2315–26.
CI, confidence interval; CML-CP/AP, chronic or accelerated phase chronic myeloid leukemia; TKI, tyrosine kinase inhibitor

Cortes J et al., ASH 2020

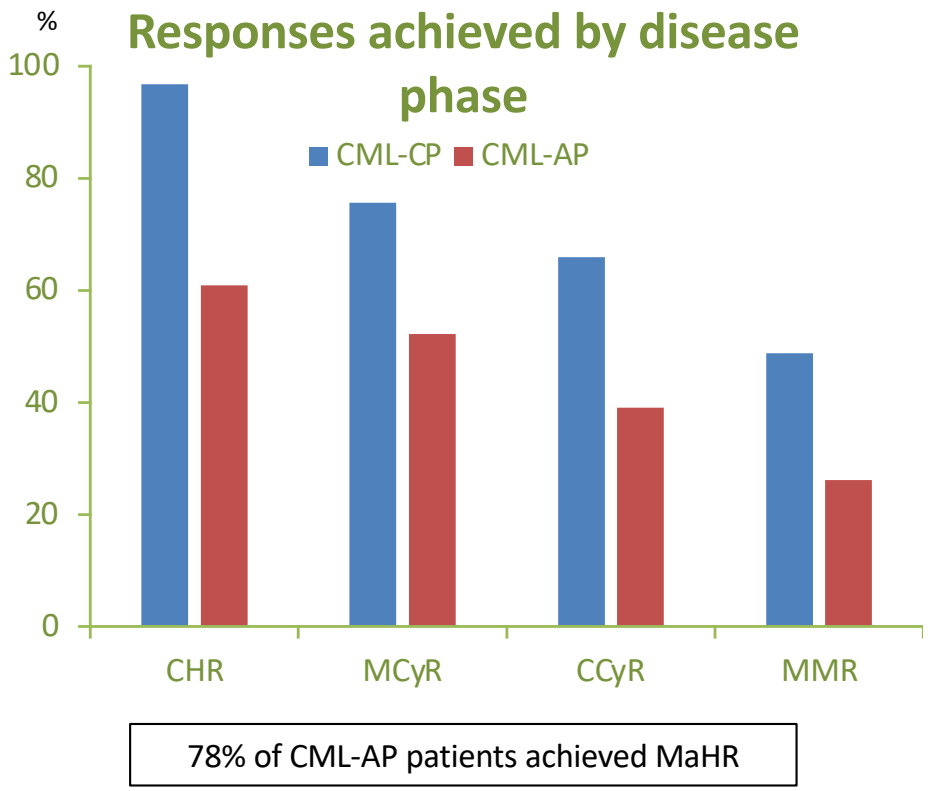
Phase I efficacy data



Cortes J et al., ASH 2020

Olverembatinib phase II studies

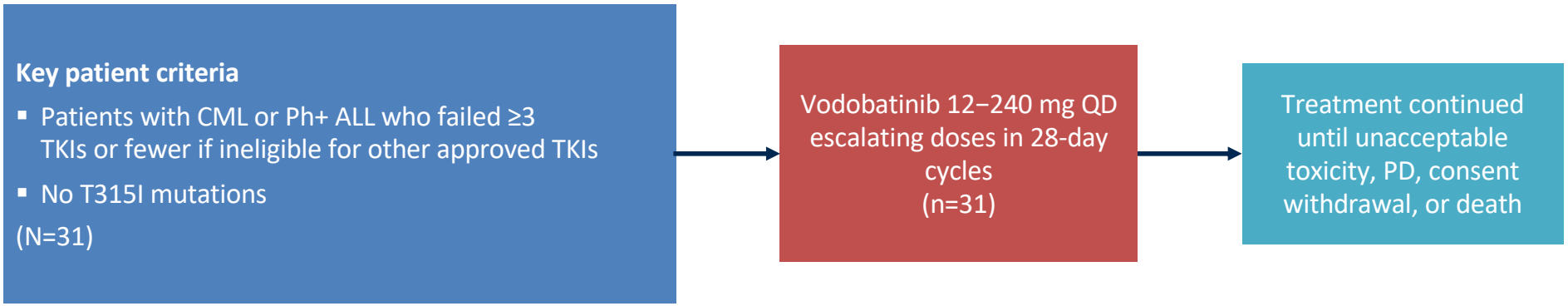
- Adult patients with CML and T315I mutations were given olverembatinib 40 mg QOD for 28 days/cycle over 24 months in two single-arm, multicenter, open-label phase II studies:
  - CP (primary endpoint: MCyR, n=41)
  - AP (primary endpoint: MaHR, n=26)
- ≥94% of CHRs and MCyRs were sustained up to three months in both studies
- Common hematological TEAEs (grade 3−4)
  - CML-CP: thrombocytopenia (48.8%), anemia (24.4%), leukopenia (12.2%), and neutropenia (19.5%)
  - CML-AP: thrombocytopenia (52.2%), anemia (39.1%), leukopenia (30.4%), and neutropenia (21.7%)
- Grade 1−2 skin pigmentation: ~70−80% across studies



Qian Jiang et al. ASH 2020

Vodobatinib phase I study design

- Study objective
  - To determine the MTD or recommended phase II dose

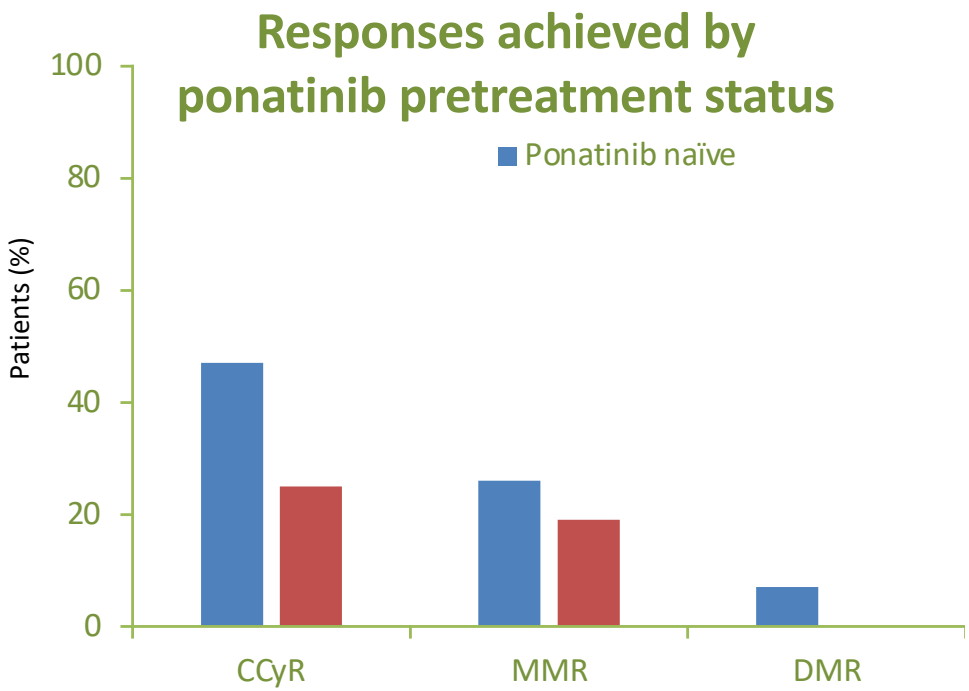


- Primary endpoint: determination of the MTD or recommended phase II dose
- The present analysis focused on the actions of vodobatinib in CML patients
- This analysis also explored treatment efficacy by ponatinib pretreatment status

Cortes J et al., ASH 2020

Vodobatinib phase I efficacy data

- Median duration of treatment was 17.3 (range, 0.6−36) and 14.8 (range, 0.5−42) months in ponatinib-treated (n=16) and -naive (n=15) patients, respectively
- MCyR was observed in 68% of CML-CP patients
- Stable disease was achieved in 19% of ponatinib-treated patients and 7% of ponatinib-naïve patients
- PD was observed in 13% of ponatinib-treated patients, all with double mutations, and in 26% of ponatinib-naïve patients, with T315I, Y253H, F317L or E255V baseline mutations



Cortes J et al., ASH 2020

Grazie

Thank you