LEUKEMIA2022

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AIL President: P. Toro
Coordinators: A.M. Carella, S. Amadori

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ASSOCIAZIONE ITALIANA CONTRO LEUCEMIE LINFOMI E MIELOMA

UNDER THE AUSPICES OF:

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

GITMO

SIES Società Italiana Emergenza Sportiva

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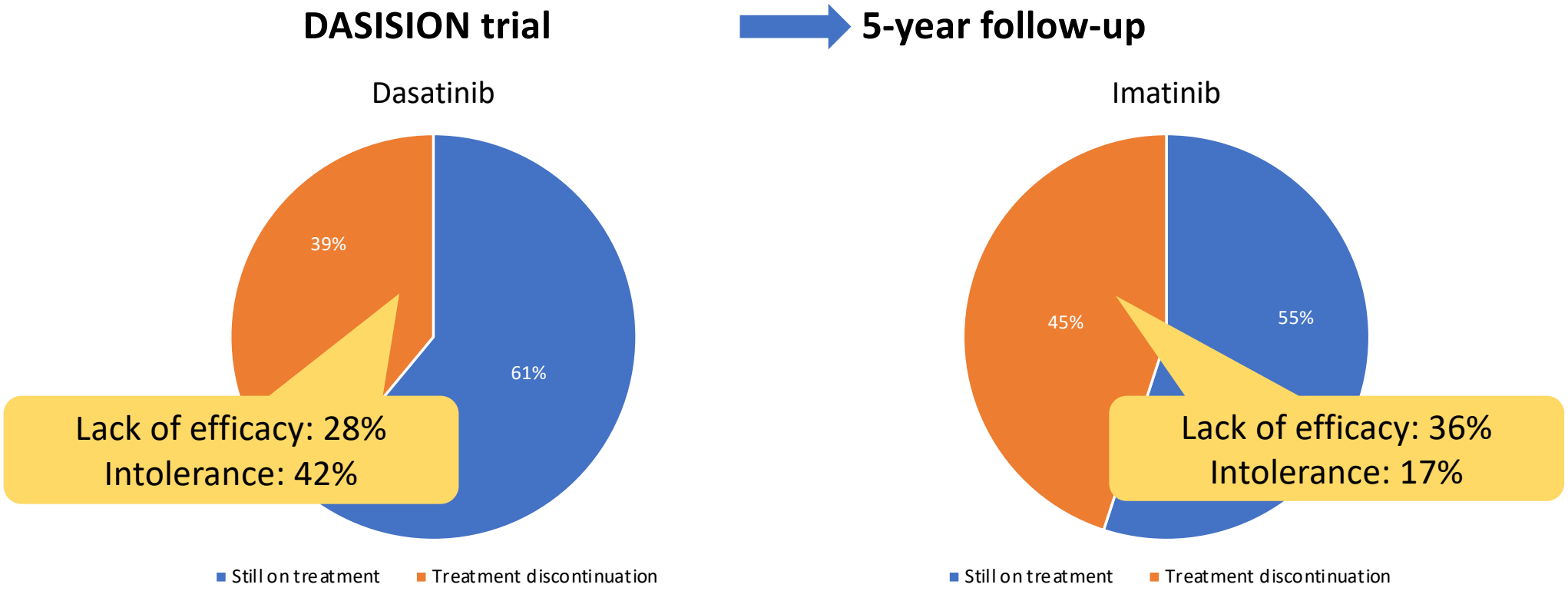
Future perspectives of novel therapies

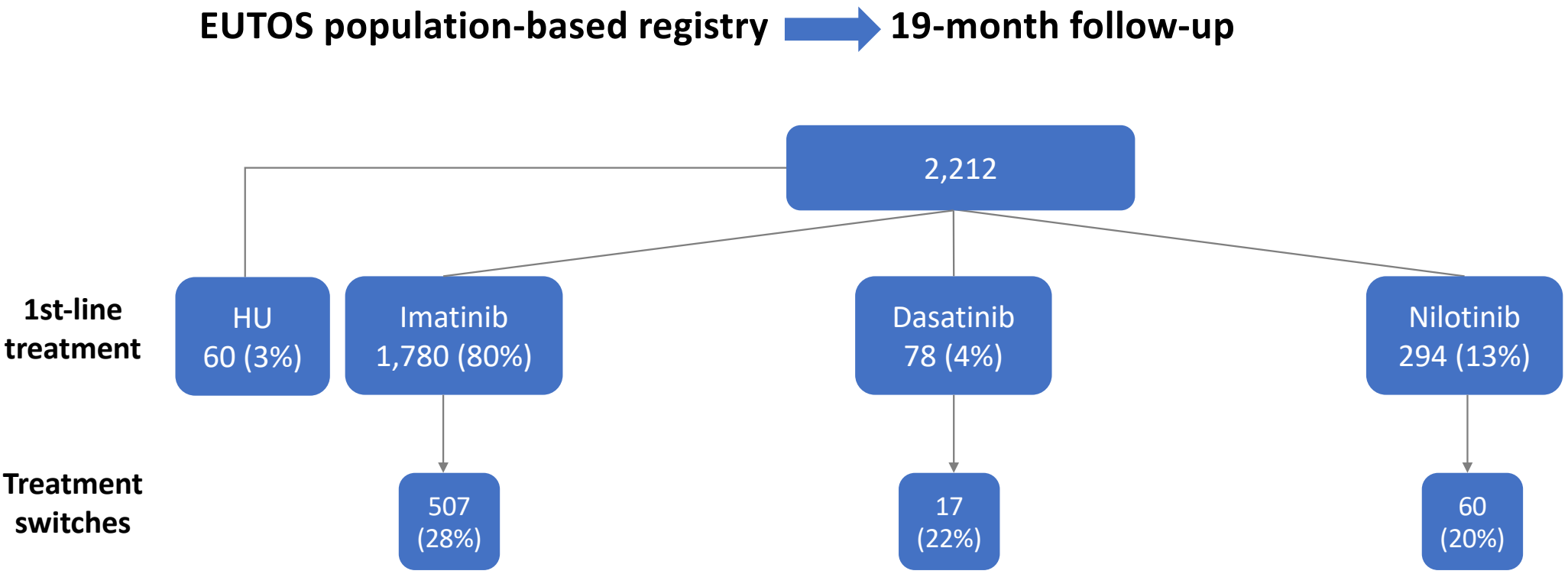
Massimo Breccia
AZ. Policlinico Umberto I
Sapienza University
Roma

What are the reasons for treatment failure in 1st-line CML patients?



Cortes JE, et al. J Clin Oncol. 2016;34:2333-40.

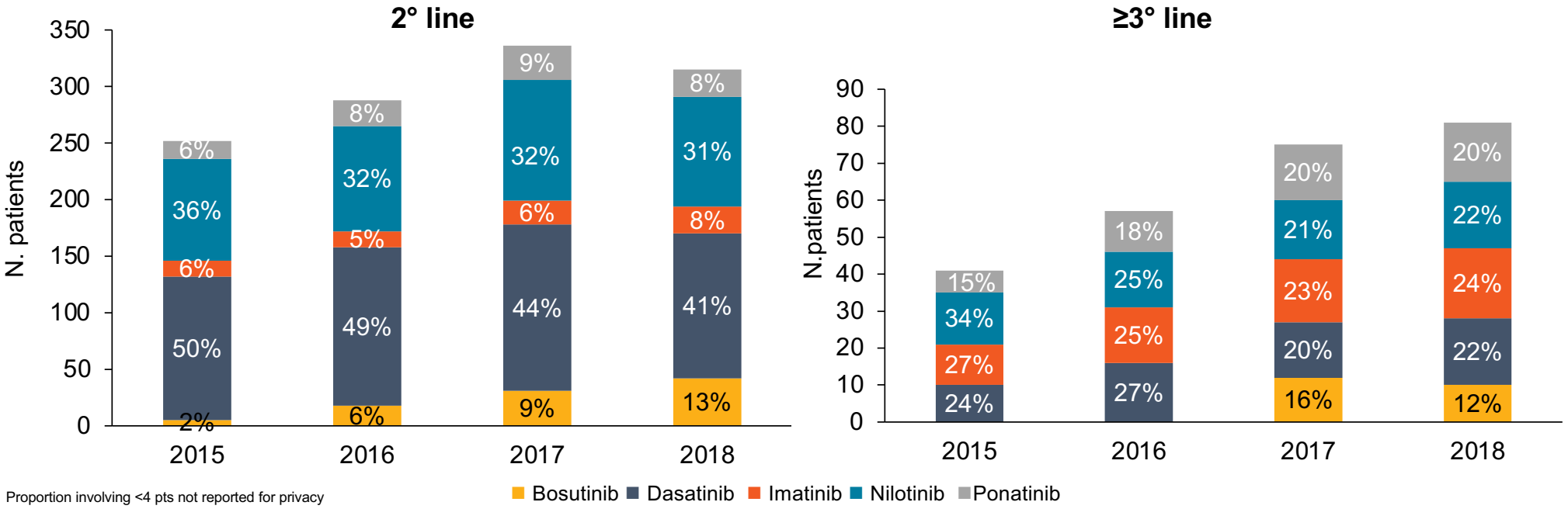
Population based registry: rate of discontinuation



HU, hydroxyurea.

Hoffman VS, et al. Leukemia. 2017;31:593-601.

RWE: increasing trend of 3L in Italy



Proportion involving <4 pts not reported for privacy

- In each calendar year from 2015 to 2018, the incidence of patients who entered a 2nd line was around 22-28%.
- Higher values were reported for incidence of patients starting a third or subsequent line of treatment (37-47% within each year).
- An increasing trend in the number of patients treated in ≥3rd line of treatment was observed, with a **97.6% increment**.

Breccia et al, ASH 2021

Unmet needs in 3L setting

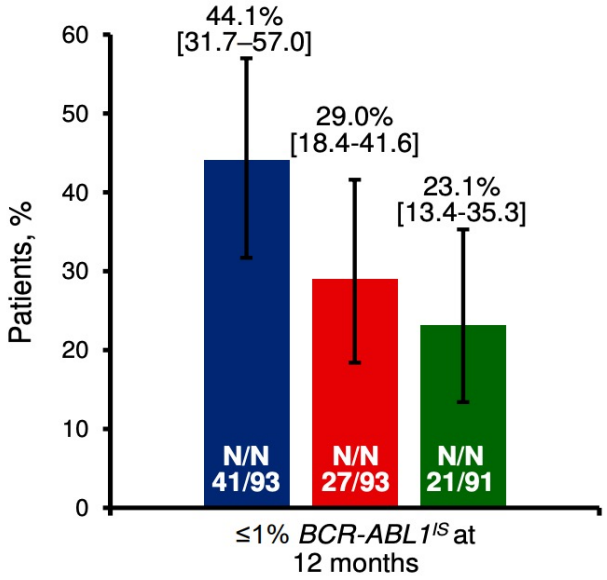
- Sequential TKI use is associated with a decreased probability of response and worse OS
- By 5 years, 30–50% of patients discontinue imatinib and resistance rates are even higher during 2L treatment (about 50% of patients failing to achieve a CCyR)
- Available TKIs have off-target effects that can lead to long-term safety issues; about 20% of patients discontinue the treatment due to AEs
- Sequential treatment induces the emergence of new mutations. The frequency of T315I mutation was reported to be 3–15%. Currently, the unique available option is ponatinib and allogeneic SCT

AE, adverse event; CCyR, complete cytogenetic response; OS, overall survival; SCT, stem cell transplant; TKI, tyrosine kinase inhibitor.

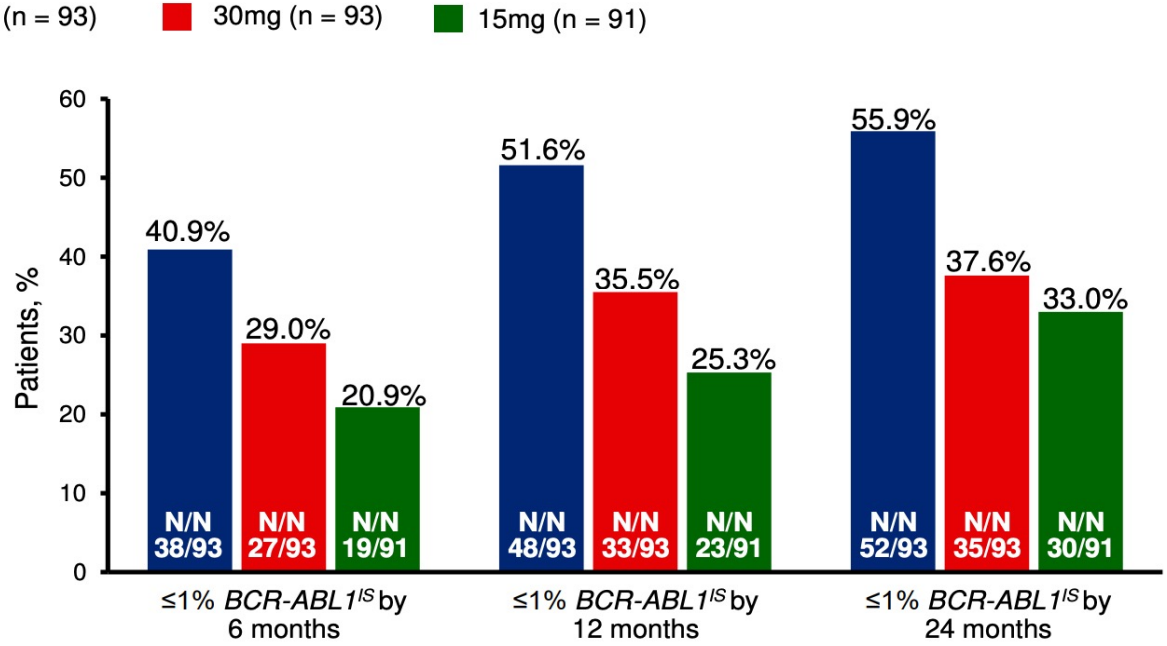
Cortes JE, et al. J Clin Oncol. 2016;34:2333-40.
Hochhaus A, et al. Leukemia. 2016;30:1044-54.
Kantarjian HM, et al. Blood. 2011;117:1141-5.
Shah NP, et al. Haematologica. 2010;95:232-40.
Soverini S, et al. Blood. 2009;114:2168-71.
Steegmann JL, et al. Leukemia. 2016;30:1648-71.

OPTIC: primary endpoint

A. ≤1% *BCR-ABL1*^{IS} ***at*** 12 Months (98.3% CI)



B. Median dose intensity and ≤1% *BCR-ABL1*^{IS} ***by*** 6, 12, and 24 Months



	Median dose intensity, mg/d		
Cohort	6 months	12 months	24 months
45mg	35.2	15.0	15.0
30mg	30.0	28.0	15.0
15mg	15.0	15.0	15.0

Cortes et al Blood 2021

Final analysis of BYOND study

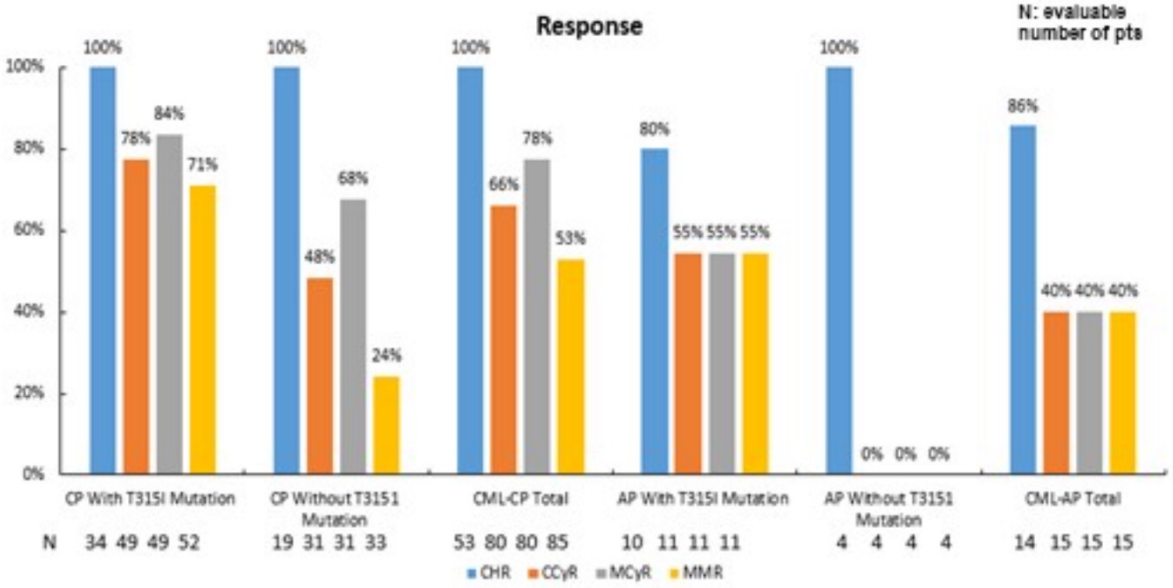
- Of 163 pts, 48% still receive treatment after a median follow-up of 47.8 months
- Most common reason for discontinuation was adverse events (26.9%)
- Median dose intensity 300 mg/day with dose reduction in 79.5% of patients
- CCyR (achieved and/or maintained) 81%
- MMR 71.8%
- MR4.5 48.3% (probability to maintain at 36 months 80%)
- OS 88%
- Only 2 death CML-related

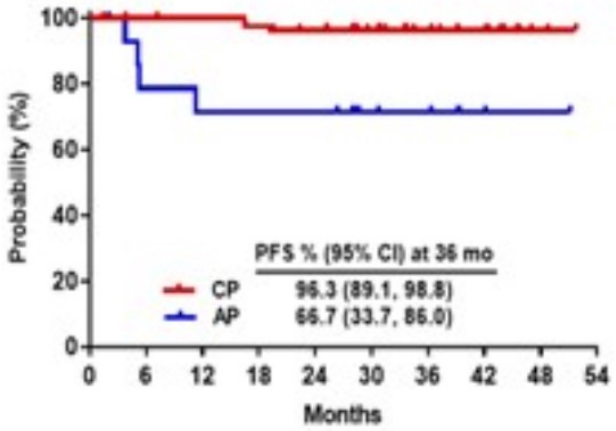
	Best response on treatment, *BCR-ABL1* IS, n (%)						
	Baseline Total (N)	**>10%**	**>1 to 10%**	**>0.1 to 1%**	**>0.01 to 0.1%**	**≤0.01%**	**Not Evaluable**
Baseline *BCR-ABL1* IS							
>10%	27	14 (51.9)	1 (3.7)	0	3 (11.1)	5 (18.5)	4 (14.8)
>1 to 10%	24	2 (8.3)	2 (8.3)	2 (8.3)	4 (16.7)	13 (54.2)	1 (4.2)
>0.1 to 1%	28	0	1 (3.6)	5 (17.9)	7 (25.0)	15 (53.6)	0
>0.01 to 0.1%	33	0	1 (3.0)	1 (3.0)	4 (12.1)	26 (78.8)	1 (3.0)
≤ 0.01%	37	0	0	1 (2.7)	2 (5.4)	32 (86.5)	2 (5.4)

Gambacorti-Passerini et al ASH 2021 abst 1475

OLVEREMBATINIB: update of phase 1 study

- 101 pts (86 in CP and 15 in AP)
- 83% treated with 2 prior lines of TKI; 62% harbored the T315I mutation
- Treatment responses were durable and unaffected by baseline mutational status
- AEs: 86% skin hyperpigmentation; 11% hypertriglyceridemia, 5% proteinuria
- 77% thrombocytopenia





Qian et al ASH 2021 abst 311

Olverembatinib (HQP1351): update of phase 2 studies

- **CC201 study (CP with T315I, 40 mg QD)**

41 pts, 32 completed 12 cycles

78% pretreated with > 2 TKIs

100% CHR, 75.6% MCyR, 56% MMR

12-months PFS 89.3%

AEs: thrombocytopenia 70.7%, skin pigmentation 56.1%

- **CC202 study (AP pts with T315I)**

23 pts, 14 completed 12 cycles

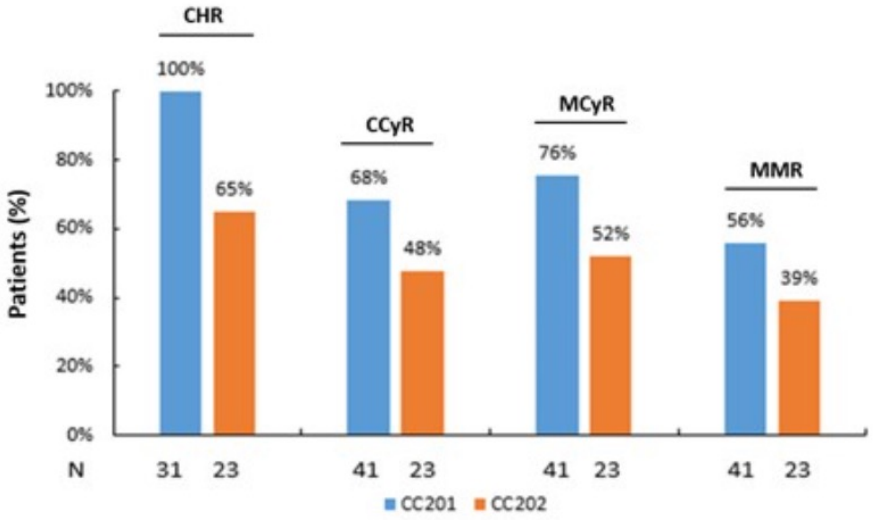
73.9% MaHR (65.2% CHR), 52% MCyR, 39% MMR

12-months PFS 74%

AEs: thrombocytopenia 73%, skin pigmentation 69.6%

48% proteinuria and hypocalcemia

56.5% hyperthrygliceridemia

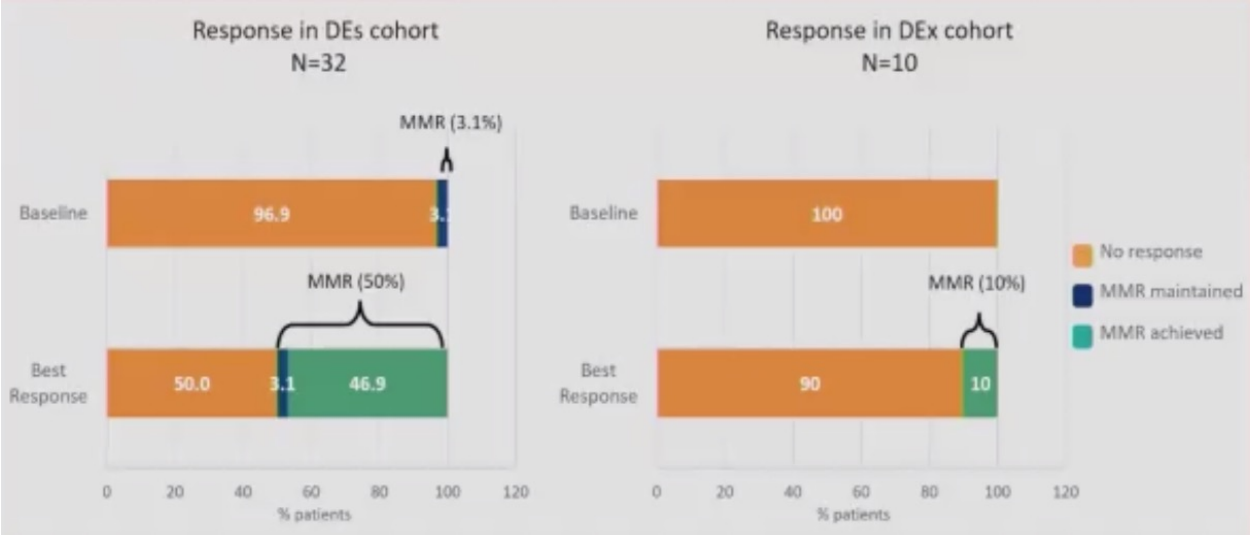


Qian et al ASH 2020 abstract 3598

Vodobatinib: update of phase 1 study

52 pts enrolled

Parameter	Dose Escalation N (%)	Dose Expansion N (%)
Number of patients	41	11
Median age in years (range)	61 (23 – 85)	47 (35 – 60)
Response to prior therapy		
Refractory to prior TKI	24 (58%)	7 (64%)
Intolerant to prior TKI	17 (42%)	4 (36%)
Previous TKI therapy		
Median number of TKIs received (range)	3 (1- 6)	2 (1 – 3)
Pts receiving ≥ 4 TKIs	19 (46%)	-
Pts receiving prior ponatinib therapy	22 (54%)	-
Other previous therapies		
Omacetaxine	5 (12%)	NA
Chemotherapy (excluding hydroxyurea)	9 (22%)	NA
Baseline mutation		
Pts with single mutation	13 (32%)	4 (36%)
Pts with double mutation	2 (5%)	1 (9%)
Pts with cardiovascular co-morbidities	25 (61%)	3 (27%)



- Seventeen CP-CML pts had prior ponatinib treatment, of which 11 (65%) had MCyR (4 achieved CCyR, 4 maintained CCyR, 3 achieved PCyR); while 8 (47%) achieved MMR. In the remaining 15 pts ponatinib naïve CP-CML: 10 (66%) had CCyR (7 achieved CCyR, 3 maintained CCyR); with 7 (47%) with MMR (6 achieved, 1 maintained).
- Most common any grade TEAEs included thrombocytopenia (33%), cough (19%), anaemia & diarrhoea (17% each). Ten (19%) pts reported cardiovascular TEAEs

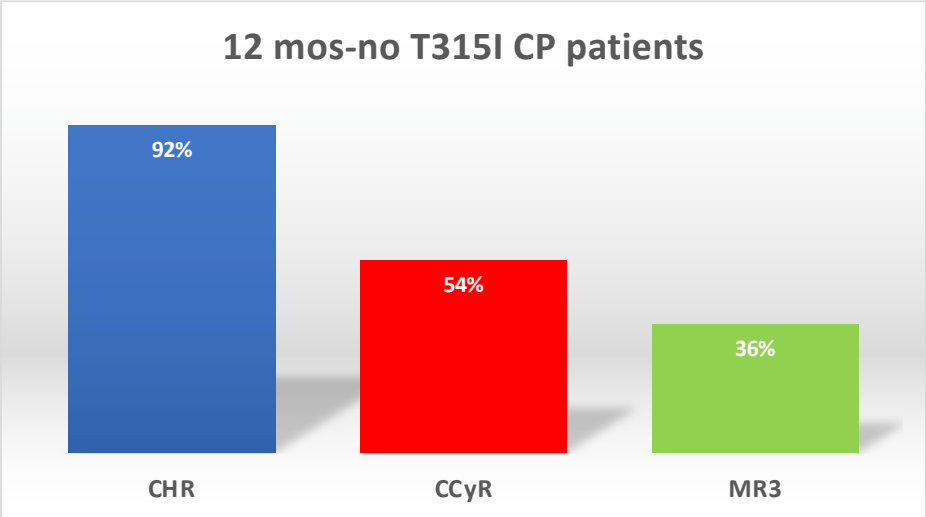
Cortes et al ASH 2021 abst 309

PF-114 in CML pts after failure (including T315I)

- Final results of phase 1 study with PF-114 drug, a 4th generation TKI
- 3+3 dose-escalation study to determine maximum tolerated dose (MTD) and dose-limiting toxicity (DLT). Secondary objectives included safety and efficacy based on haematological, cytogenetic and molecular response criteria
- 51 subjects (5 with accelerated phase CML, 46 – with chronic CML)
- 16 subjects had T315I mutation.
- 25 subjects received ≥ 3 prior TKIs.
- CHR 47%, MCyR 34%, CCyR 22%, MMR 15.6%
- The MTD was 600 mg with the grade-3 psoriasis-like skin AE as the DLT. There were no vascular occlusive events or deviations of ankle-brachial index.

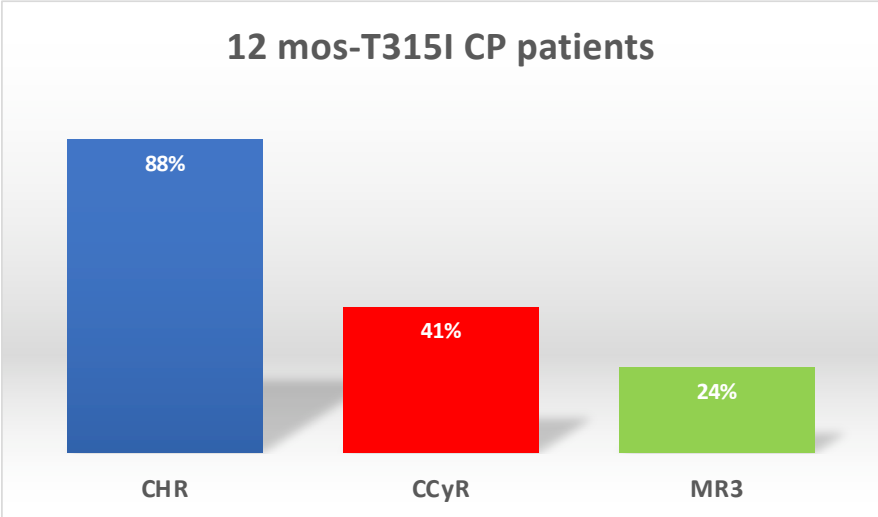
Turkina et al ASH 2021 abst 1482

Asciminib: efficacy in phase 1 study



- 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%

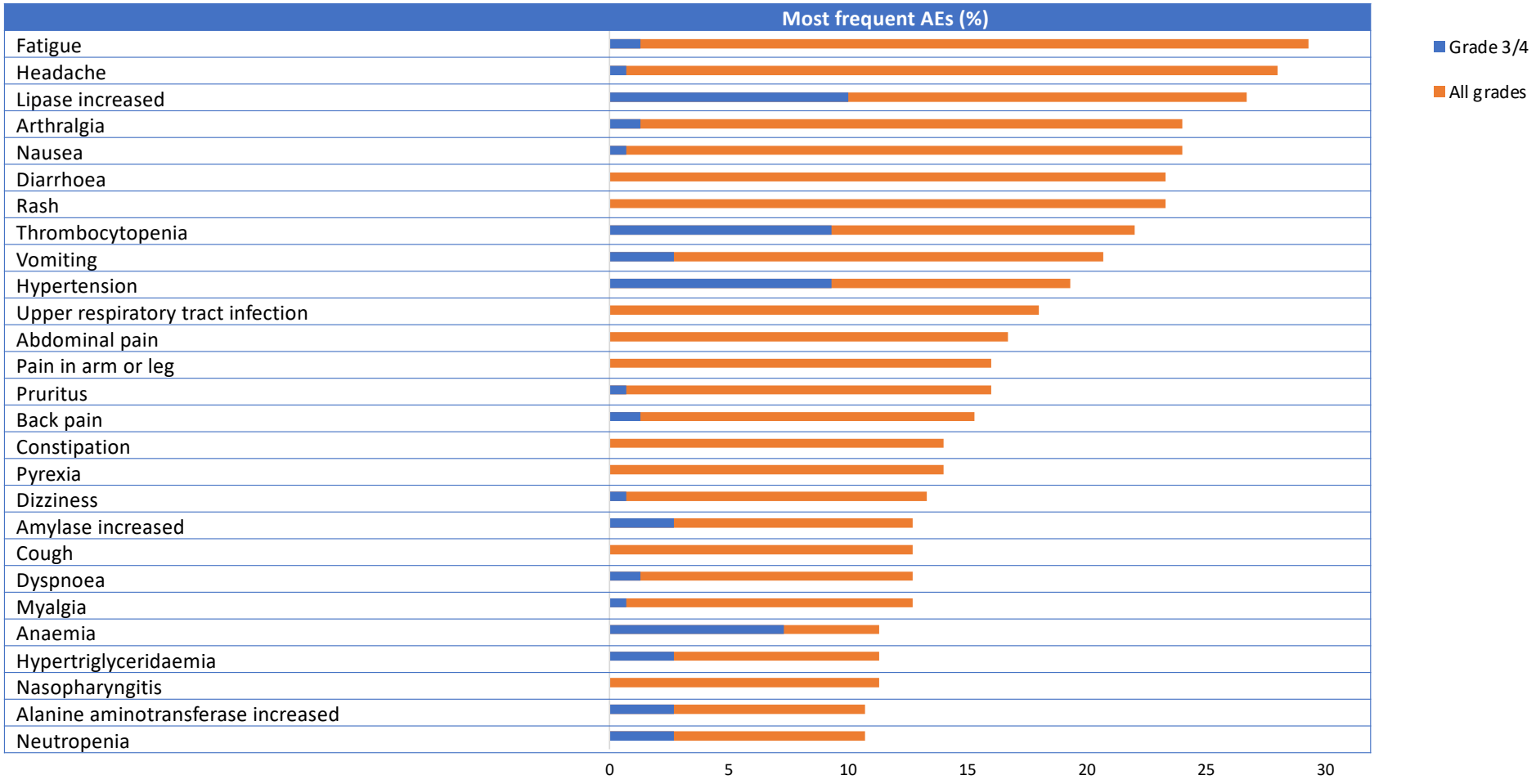


- 67% of patients maintained CCyR by 12 months
- 1/18 patient maintained MR3 by 12 months

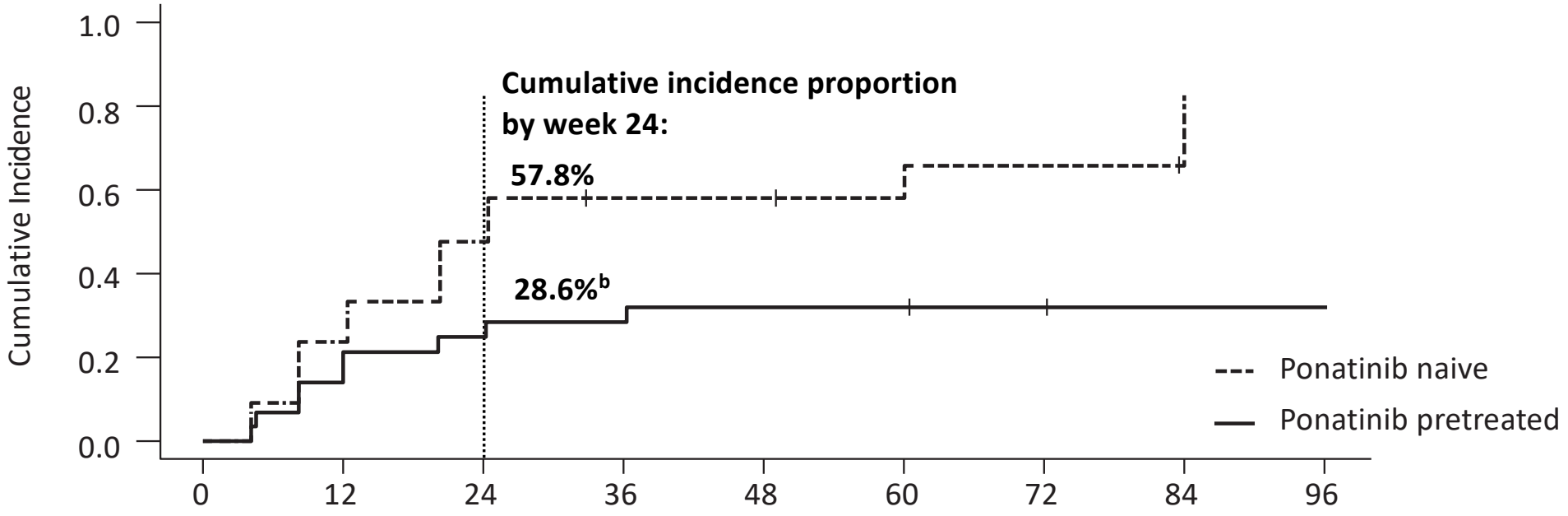
- MR3 in pts with <2 previous TKIs: 38%
- MR3 in pts with >2 previous TKIs: 11%
- MR3 in pts pretreated with ponatinib: 17%

Hughes et al. NEnglJMed 2019

Asciminib: most frequent adverse events



MMR in Ponatinib-Naive and Ponatinib-Pretreated Patients: 200 mg BID

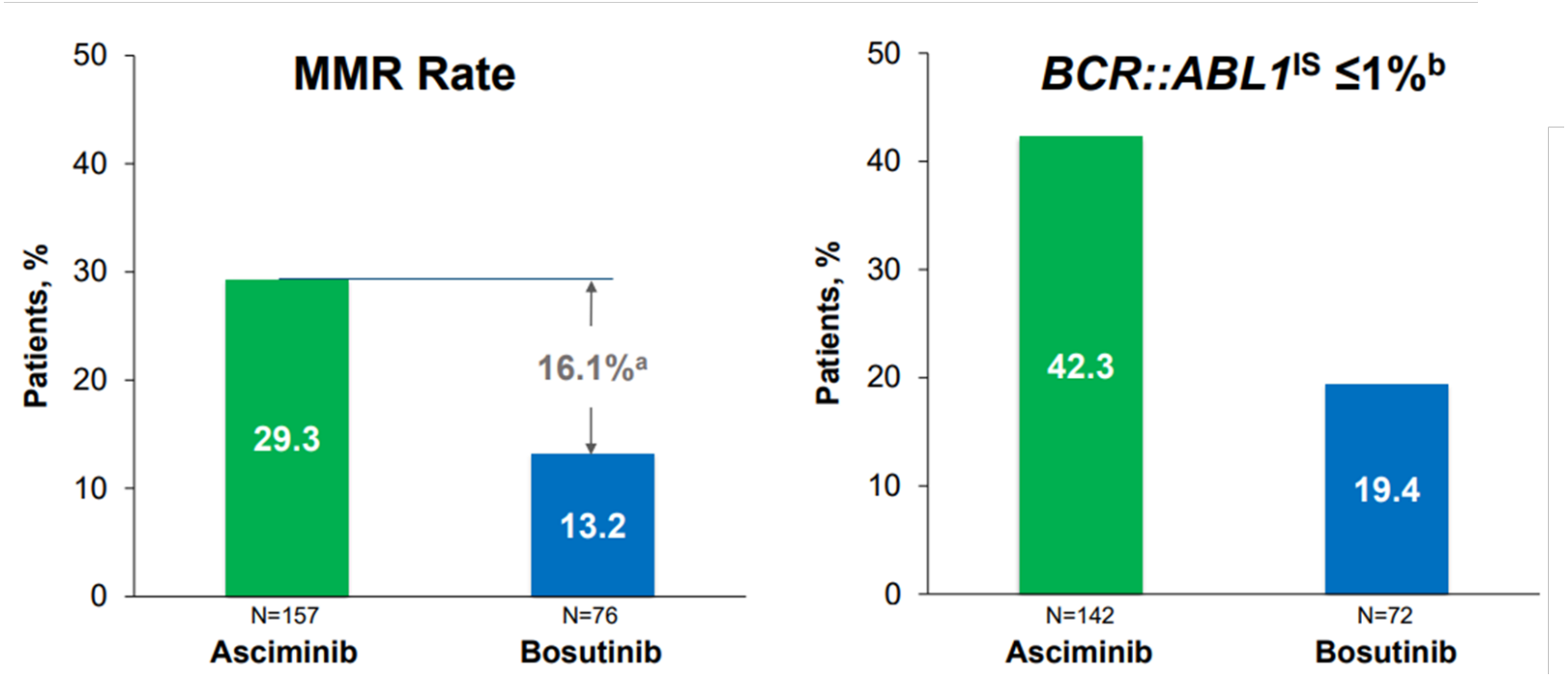


No. at risk									
Ponatinib naive	21	15	9	5	5	3	2	1	0
Ponatinib pretreated	28	23	16	12	9	8	6	5	5

[a] Discontinuations and deaths treated as competing risks. [b] Includes 5 patients who showed signs of resistance to ponatinib prior to study entry.

Cortes et al ASH 2020 abstract 650

ASCEMBL trial: response Rate (48W)

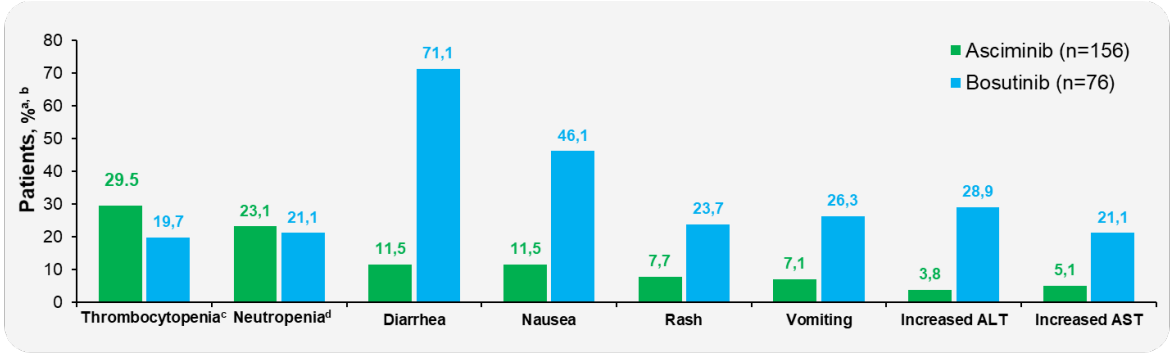


Response rates continued to be higher with asciminib than bosutinib with longer follow-up

ASCEMBL: safety

Category, n (%)[a]	Asciminib 40 mg BID (n=156)		Bosutinib 500 mg QD (n=76)	
	All grades	Grade ≥3	All grades	Grade ≥3
AEs	142 (91.0)	85 (54.5)	74 (97.4)	51 (67.1)
Fatal AEs	2 (1.3)	2 (1.3)	1 (1.3)	1 (1.3)
AEs leading to discontinuation	11 (7.1)	10 (6.4)	19 (25.0)	14 (18.4)

AE, adverse event; BID, twice daily; CML-CP, chronic myeloid leukemia in chronic phase; QD, once daily; TKI, tyrosine kinase inhibitor.
[a] A patient with multiple severity grades for an AE is only counted once under the maximum grade.

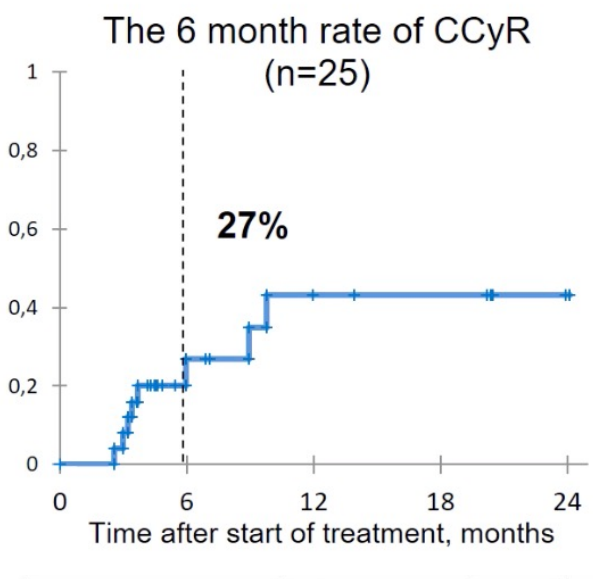


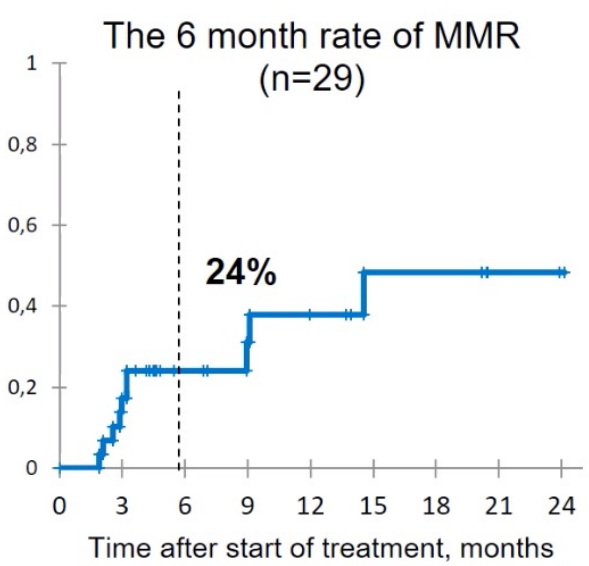
By week 48, the safety and tolerability profile of asciminib remained consistent with that at the time of primary analysis

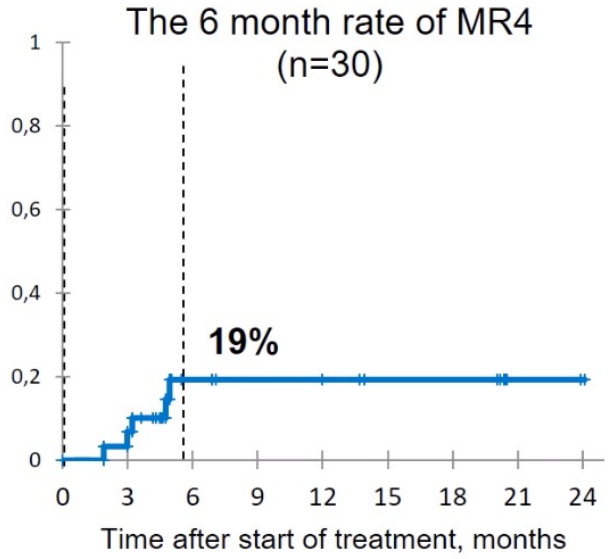
Exposure-adjusted AOE rate (per 100 patient-years) in the current analysis (3.4) was comparable to that in the primary analysis (3.3)

ASCIMINIB MAP in Russian Federation

- **32 pts** available who received asciminib for at least 3 months
- Median age 54 years; 23 in CP, 7 in AP and 2 in BP
- 59% mutated and 31% T315I
- 66% received > 4 TKIs and 44% were previously treated with ponatinib
- 4 pts discontinued due to lack of efficacy
- **32% of pts achieved CCyR, 34% MMR, 17% MR4**





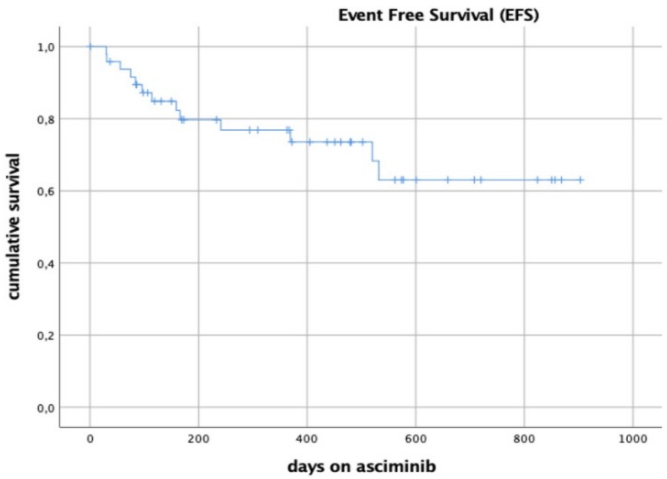


Turkina et al ASH 2021 abst 1483

ASCIMINIB MAP in Spain

- **49 pts** available who received asciminib for a median time of 11.69 months
- Median age 64 years; 48 in CP, 1 in AP
- 30.6% mutated and 20% T315I
- 92% received > 3 TKIs and 36% were previously treated with ponatinib
- 36 pts continued the drug
- Probabilities to obtain CCyR and MMR in resistant and intolerant patients were 29% (4/14) vs 55% (6/11) and 27% (4/15) vs 52% (11/21), respectively.
- In pts previously treated with ponatinib: probabilities of reaching or maintaining previous response were 53% (9/17) and 35% (6/17) for CCyR and MMR respectively, and 30% (3/10), 23% (3/13) displayed improvement of response.
- Fatigue (16,2%), joint pain (13,5%) and nausea (8,1%) the most frequent AEs

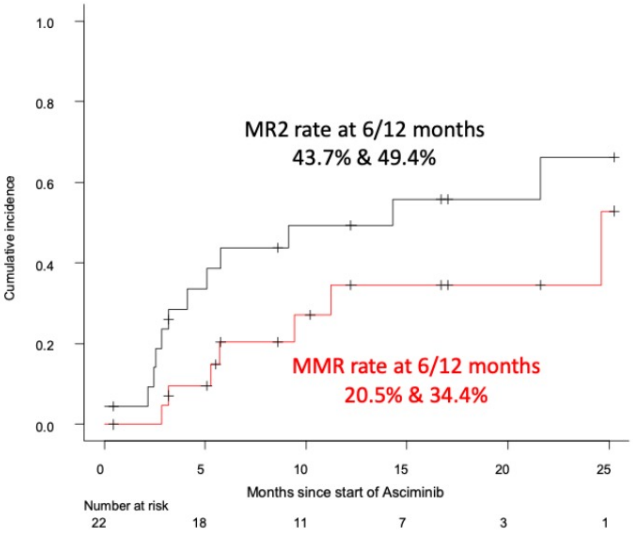
Tabla 2. Response to asciminib to last follow-up		Resistant (17)	Intolerant (30)	Total (47)
All patients	CHR[a], n(%)	14/17 (83,35)	30/30 (100)	44/47 (93,62)
	CCyR[a], n(%)	3/17 (17,65)	17/30 (56,66)	21/47 (44,68)
	MMR[a], n(%)	2/17 (11,77)	8/30 (26,67)	10/47 (21,28)
	MR4[a], n(%)	0/17	0/30	0/47
Patients without response at baseline	CCyR[b], n(%)	4/14 (28,57)	6/11 (54,55)	10/25 (40,0)
	MMR[b], n(%)	4/15 (26,67)	11/21 (52,38)	15/36 (41,67)
	MR4[b], n(%)	2/17 (11,77)	13/28 (46,43)	15/45 (33,33)



Perez-Lamas et al ASH 2021 abst 2563

ASCIMINIB MAP in Canada

- 22 patients (19 in 1° CP, 77% treated with 3 lines of TKIs) with 16 months of follow-up
- 77% with a previous history of CV event
- 4 pts with T315I mutation
- 68% resistant to previous treatment
- The CI of MMR at 12 months was 38%
- Side effects included myalgias (n=4), elevated lipase (n=2) and pleural/pericardial effusions (n=2). No CV events were noted in 22 pts.



	MR2 6 months	MR2 12 months	MMR 6 months	MMR 12 months
Overall population (n=22)	7/17 (41%)	4/8 (50%)	3/17 (18%)	3/8 (38%)
Ponatinib naïve (n=12)	5/9 (56%)	1/3 (33%)	2/9 (22%)	2/3 (67%)
Ponatinib pre-treated (n=10)	1/8 (13%	1/5 (20%)	1/8 (13%)	1/5 (20%)
Without T315 mutation (n=18)	5/14 (36%)	2/6 (33%)	2/14 (14%)	2/6 (33%)
With T315I mutation (n=4)	2/3 (67%)	1/2 (50%	1/3 (33%)	1/2 (50%)
Resistant/suboptimal	4/12 (33%)	2/6 (33%)	2/12 (17%)	2/6 (33%)
Intolerant	2/5 (40%)	1/2 (50%)	1/5 (20%)	1/2 (50%)
Pts having past history of cardiovascular event (n=17)	4/13 (31%)	3/6 (50%)	2/13 (15%)	3/6 (50%)

Khadadah et al ASH 2021 abst 3610

Conclusions

- New drugs have been developed to counteract resistance/intolerance
- Among these, Asciminib is a promising therapeutic approach (even in combination)
- Asciminib, at increased dose of 200 mg BID seems to be a treatment option in T315I positive patients
- Several trials with other new TKIs are still ongoing