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Novità dal Meeting della Società Americana di Ematologia

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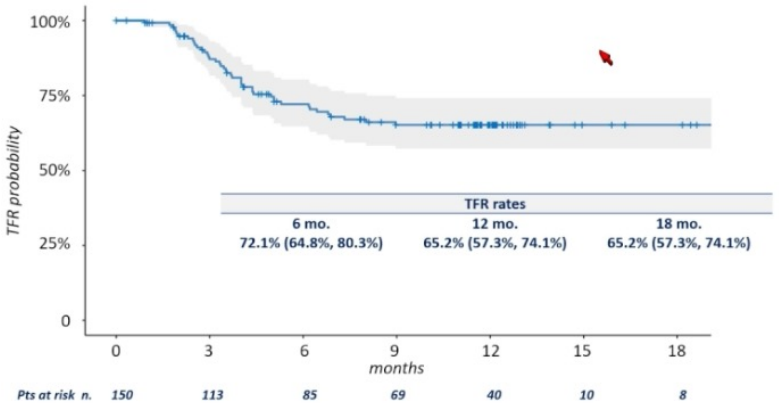
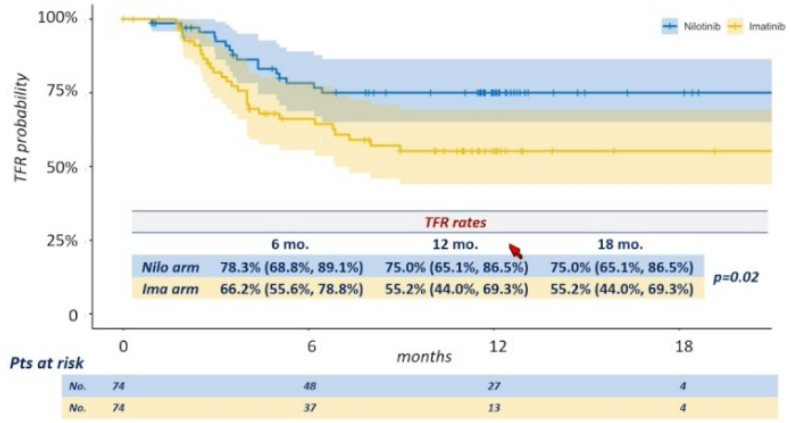
AOP					x	x	
Abbvie					x	x	
GSK					x	x	
Servier					x	x	
Otsuka					x		

1L Treatment

SUSTRENIM trial: updated results

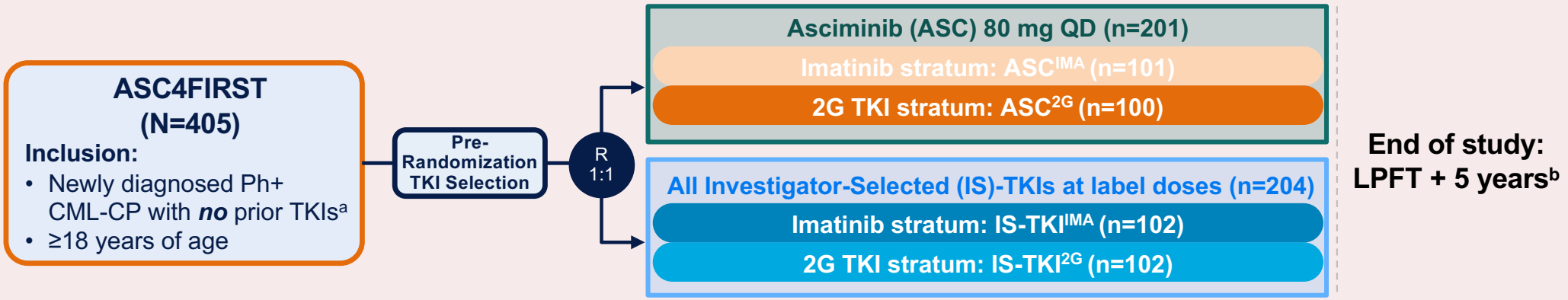
- Of the **448** randomized patients, **151 were eligible for TFR entry after the first 48 mo**. of observation (median 58 mo.) at the time of the present analysis and were evenly distributed between the two arms of the trial (77 in the IM and 74 in the NIL arm, respectively).
- **After 6 and 12 mo. of follow-up, 72.1% (95% CI: 64.8-80.3) and 65.2% (95% CI: 57.3-74.1) of these patients were still in TFR.** Interestingly, multivariate analysis showed that only two independent factors predict successful TFR: treatment arms (IM vs NIL) and ELTS score (Low vs Int/High) but not the Sokal risk nor age or others.
- **75.0% (95% CI: 65.1-86.5) of patients randomized in the NIL arm were in TFR at 12 mo. vs 55.2% (95% CI: 44.0-69.3) of those in the IMA arm (p<0.02).**
- **67.5% of ELTS low patients of the IMA arm vs 86.1% of the NIL arm remained in TFR at 6 months and 58.6% vs 84.0% at 12 months of follow-up** (p=0.0041).





Breccia et al ASH 2025; abst 905

ASC4FIRST: Phase 3 – Study Schema



From Hochhaus A, et al. *N Engl J Med*. 2024;391(10):885-898. Copyright © 2024 Massachusetts Medical Society. Adapted with permission from Massachusetts Medical Society.

Pre-randomization TKI Selection

- The TKI a patient will take if randomized to IS-TKI arm is selected by physician in consultation with patient

Stratification by:

- Pre-randomization TKI selection (IMA or 2G TKI)
- ELTS risk category (low/intermediate/high)

Primary endpoint*:

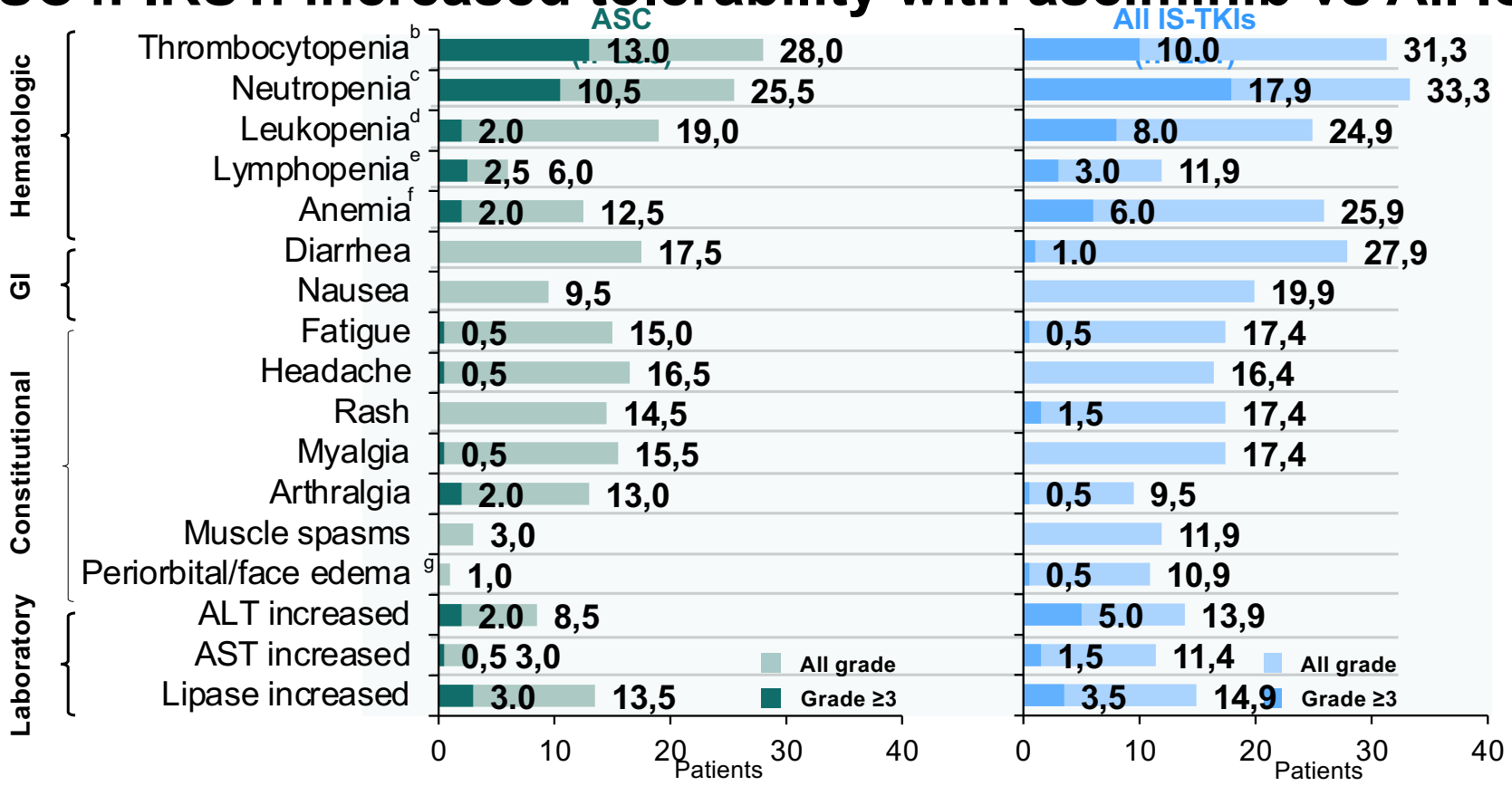
- MMR at week 48 with ASC vs all IS-TKIs
- MMR at week 48 with ASC^{IMA} vs IS-TKI^{IMA} (imatinib stratum)

Secondary endpoints†:

- MMR at week 96 with ASC vs all IS-TKIs
- MMR at week 96 with ASC^{IMA} vs IS-TKI^{IMA} (imatinib stratum)

Hochhaus A, et al. N Engl J Med. 2024;391(10):885-898.

ASC4FIRST: increased tolerability with asciminib vs All IS-TKIs



Most relevant AEs were lower with ASC than all IS-TKIs by the week 96 cutoff

Hughes et al ASH 2025; abst 5549

Low rates of dose reduction, interruptions and discontinuation with asciminib vs ima and 2gen TKIs

ASC4FIRST: Week 96 PROs in ND CP-CML

Methods

- ≥1 PRO assessment: ASC (n=194), IS-TKIs (n=195)
- Completion rates in pts (with PRO assessments at baseline and ≥1 post baseline) receiving ASC vs IS-TKI were balanced for QLQ-C30 and QLQ-CML24

EORTC QLQ-C30*

- **More patients receiving ASC** vs IS-TKIs had improvements in:
  - **Fatigue, pain, dyspnea, appetite loss, and physical, role, cognitive and social functioning**
- **Fewer patients receiving ASC** vs IS-TKIs had improvements in:
  - **Diarrhea and constipation**
  - **Overall, 37.5% vs 17.7% of pts receiving ASCIMA vs IS-TKIIMA and 58.9% vs 28.6% receiving ASC2G vs IS-TKI2G, respectively, had improvements in global health status/QOL**

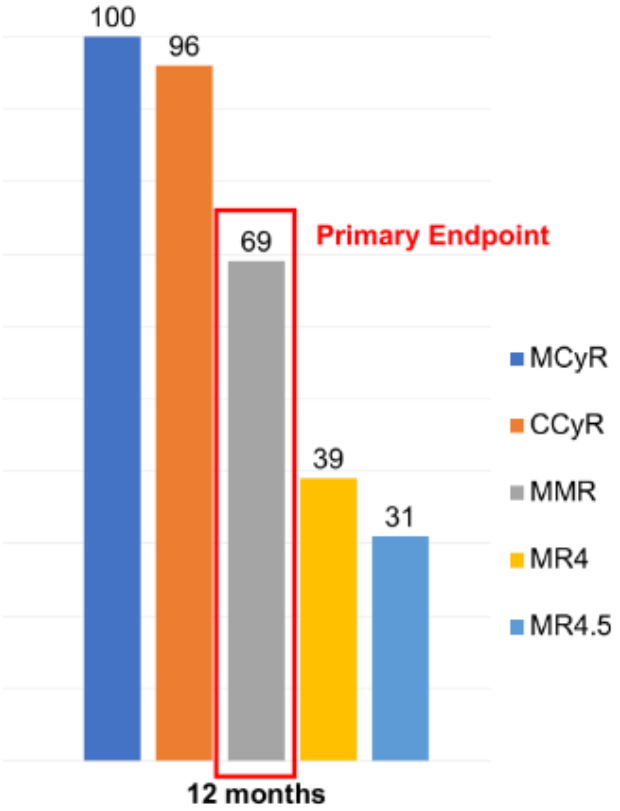
EORTC QLQ-CML24*

- **More patients receiving ASC** vs IS-TKIs had improvements in:
  - **Symptom burden, impact on daily life, worry/mood, body image, and satisfaction with care and information. Satisfaction in social life in pts treated with asciminib vs 2gen TKIs**

Cortes et al, Poster 1997 ASH 2025

Asciminib 1st line: MDACC experience

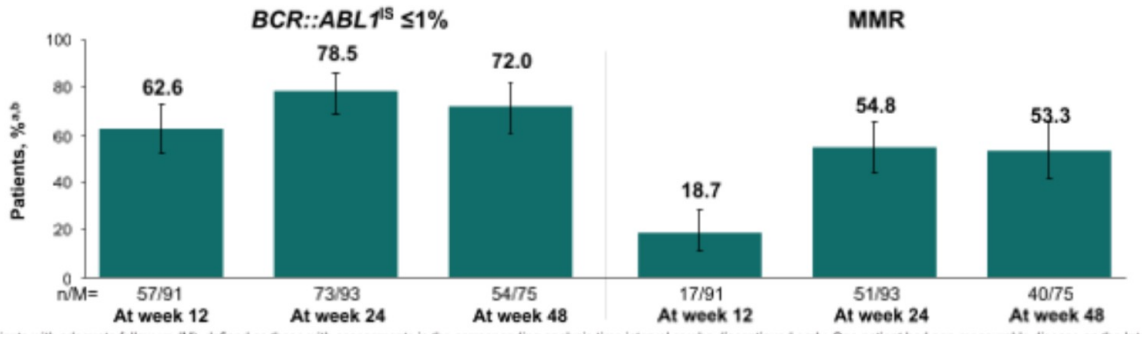
- **50 pts**, median age 49 years
- High Sokal 18%
- With a median follow-up of 7.7 months (95% CI, 5.5-9.9), the cumulative best overall response was MCyR in 40 patients (80%), CCyR in 36 (72%), MMR in 24 (48%), MR4 in 15 (30%), and MR4.5 in 11 (22%);
- **The MMR rate by 12 months was 69%. MR4 39%, MR4.5 31%**
- **EMR 95%**
- The most frequent adverse events that were possibly related to asciminib included elevated lipase (Grade[G]2, n=8), myalgia (G1, n=6; G2, n=1), and abdominal pain (G1, n=3; G2, n=3). Two patients developed pancreatitis (G2, n=1; G3, n=1) and one patient developed G2 pericardial effusion and later a G3 brain stroke leading to asciminib discontinuation.
- **The 6-month rates of FFS, EFS, and OS were 85%, 97%, and 97%, respectively.**

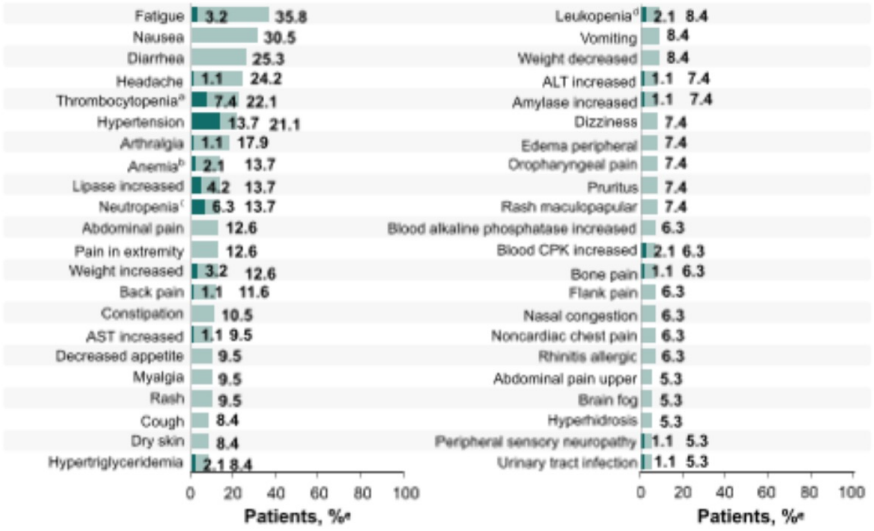


Haddad et al ASH 2025; abst 5565

ASC2ESCALATE: newly diagnosed pts

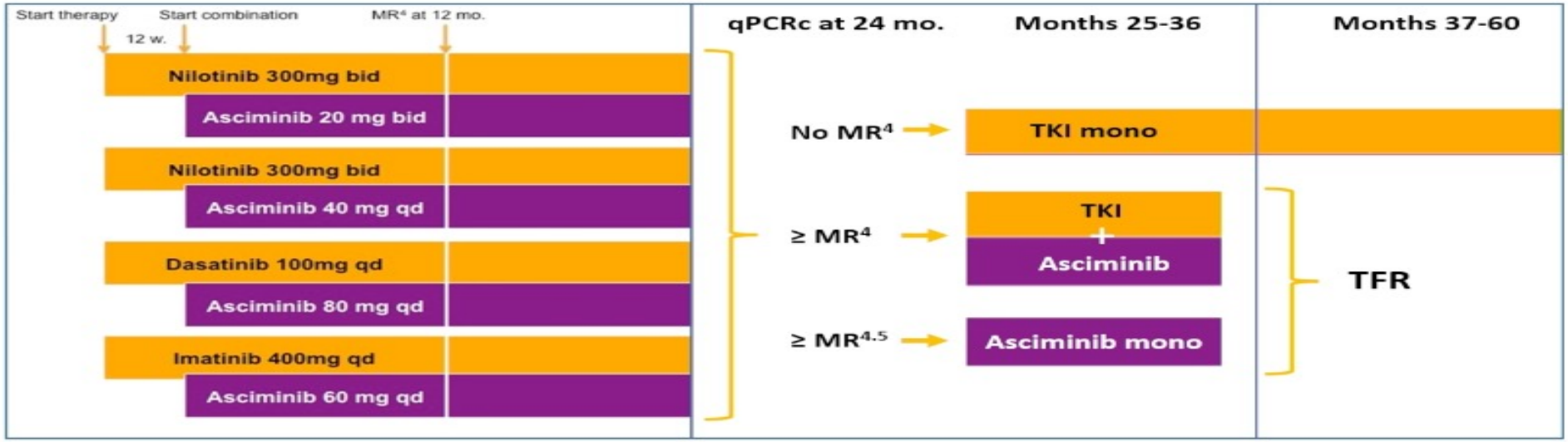
- **All pts started treatment (Tx) with ASC 80 mg once daily (QD). Pts with BCR::ABL1IS >1% at wk 24 had their dose increased to 200 mg QD. Pts with BCR::ABL1IS >0.1% at wk 48 had their dose increased from 80 to 200 mg QD or from 200 mg QD to 200 mg BID or could be taken off study.**
- **95 pts**, median FU 11 mos, 76.8% < 65 years, male prevalence
- 73.7% pts remained on treatment
- **Dose escalation from 80 to 200 mg QD occurred in a total of 16/95 pts** (16.8%) due to suboptimal response at wk 24 (n=8) or 48 (n=8); 3 of 8 pts with dose escalation from 80 to 200 mg QD at wk 24 escalated to 200 mg BID at wk 48.
- **EMR 91.2%, MMR at week 24 and 48 was 54.8% and 53.3%**
- **MR4 and MR4.5 at week 48 were 24% and 12%**
- Grade ≥3 AEs (≥5%) were hypertension (13.7%), thrombocytopenia (7.4%), and neutropenia (6.3%).
- AEs led to discontinuation in 11 pts (11.6. **Arterial-occlusive events (AOEs) occurred in 4 pts (4.2%).**





Levy et al ASH 2025; abst 3775

FASCINATION trial (asciminib in combination): updated results



	MMR (%)	MR⁴ (%)	MR⁴·⁵ (%)	MR⁵ (%)	MR⁵·⁵ (%)	N (total)
At month 12	77 (68)	**43 (38%)**	25 (22)	9 (8)	3 (3)	114
At month 24	95 (86)	54 (49)	37 (34)	26 (24)	19 (17)	110
At month 36	92 (91)	66 (65)	45 (45)	27 (27)	20 (20)	101

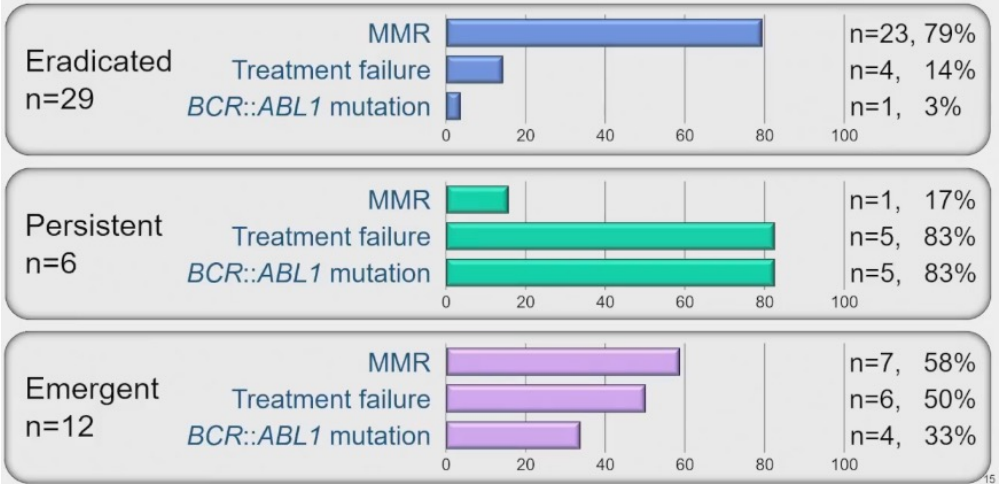
Ernst et al ASH 2025; abst 903

ASXL1 patterns over time in ASC4FIRST study

- The allelic burden of ASXL1+ clones at BL was incidentally higher in pts receiving ASC **(24% variant allele frequency [VAF]) vs IS-TKI (10% VAF).**
- **341 pts analyzed. AGA in 21% of them 11% ASXL1**. On-treatment emergence of at least one new ASXL1+ clone was observed in 12 pts (6 ASC vs 6 IS-TKI).
- **Eradication of BL ASXL1+ was observed in 74% (29/39) of pts irrespective of initial clonal burden** (VAF: 1.2%–44%). ASXL1+ clones detectable at BL were persistent at the last evaluation in 6 pts (4 ASC vs 2 ISTKI). **Pts with ≥1 persistent ASXL1+ clone had a higher probability of TF as compared to pts who had on treatment eradication of BL ASXL1+ clones in either treatment arm.**
- The overall TF rate was comparable between treatment arms (8/24 on ASC vs 9/26 on IS-TKI) among patients with detectable ASXL1+ at any time.

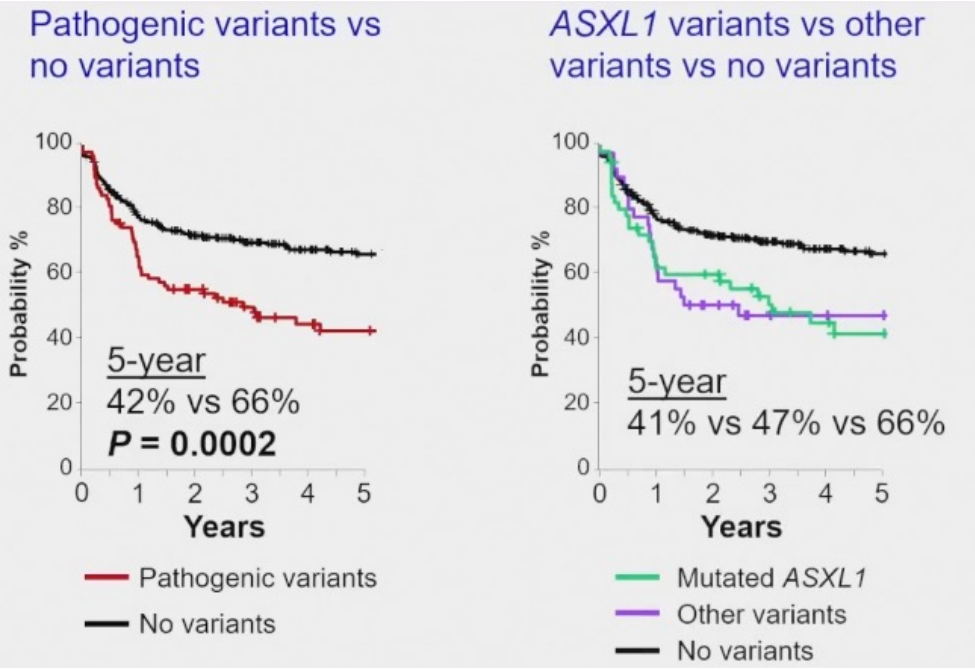
Branford et al ASH 2025; abst 73

Molecular response rates by week 96, n (%)	Asciminib n=169		IS-TKIs n=172	
	ASXL1- n=151	*ASXL1+* n=18	*ASXL1-* n=152	*ASXL1+* n=20
MMR	120 (79)	9 (50)	76 (50)	10 (50)
MR^4	86 (57)	6 (33)	46 (30)	8 (40)
$MR^{4.5}$	61 (40)	3 (17)	26 (17)	7 (35)



Somatic mutations in imatinib-treated pts: iCMLf analysis

- **468 pts in CP treated with imatinib** at diagnosis or selected based on treatment failure
- **96/468 pts were mutated: ASXL1 (11.3%)** was the most frequently mutated gene: 53/468 patients, 11.3%.
- **No difference in overall survival** whereas whereas PFS was 76.3% vs 83.1% (overall PFS comparison P=0.041). **Five-year failure-free survival** (FFS) for patients with pathogenic variants compared to patients with no pathogenic variants was **43.8% vs 65.2%** (overall comparison P <0.0001).
- The 5-year probability of acquiring BCR::ABL1 mutations for patients with pathogenic variants at diagnosis compared to patients with no pathogenic variants was 20.0% vs 11.4% (overall comparison P=0.067, Gray test).
- For ASXL1: no difference in overall survival or PFS. **Patients with mutated ASXL1 had the lowest 5-year FFS compared to patients with other pathogenic variants and those with no variants: 41.0% vs 49.3% vs 65.2%** (overall comparison P value=0.0005). T



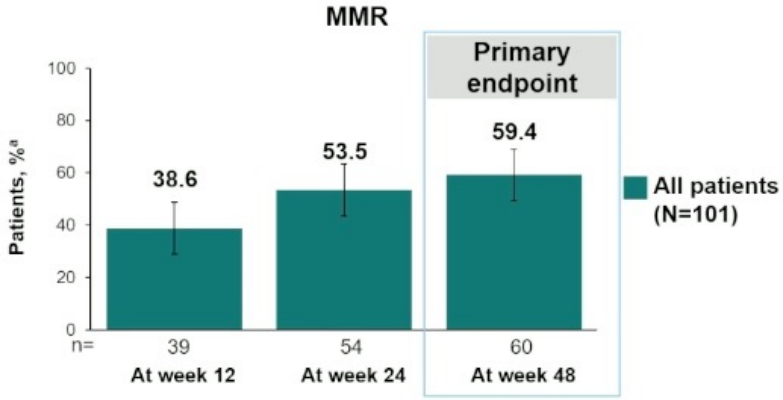
Branford et al ASH 2025; abst 75

2L Treatment

ASC2ESCALATE: Asciminib dose escalation in 2L

- Phase II trial.
- Single arm with dose escalation in ND or in 2L
- In 2L, pts were enrolled after warning (31.7%), resistance (24.8%) or intolerance (43.6%)
- Starting dose 80 mg QD; at 24 week possible increased to 200 mg QD if BCR::ABL1 > 1%; at 48 week if >0.1%
- **101 pts included** (16 pts escalated to 200 mg)
- 16 pts discontinued asciminib (most for AE)
- **MMR at 48 was 59%, MR4 25%, MR4.5 11.1%**
- Pts with previous intolerance achieved higher responses

- The most common (>15%) all-grade AEs were headache and nausea. Grade 3 were hypertension, thrombocytopenia and neutropenia. AOE occurred in 2 pts.



Molecular response at week 48, n (%)[a]	Baseline *BCR::ABL1*[IS] level >0.1% to ≤1% (n=40)[b]	>1% to ≤10% (n=31)[b]	>10% (n=30)[b]	All patients (N=101)[b]
≤0.1%	25 (62.5)	22 (71.0)	13 (43.3)	60 (59.4)
>0.1% to ≤1%	13 (32.5)	4 (12.9)	5 (16.7)	22 (21.8)
>1% to ≤10%	0	0	2 (6.7)	2 (2.0)
>10%	0	0	0	0
Missing assessment	2 (5.0)	5 (16.1)	10 (33.3)	17 (16.8)[c]

Compared with baseline, *BCR::ABL1*[IS] level category at week 48: Improved | Did not change | Worsened

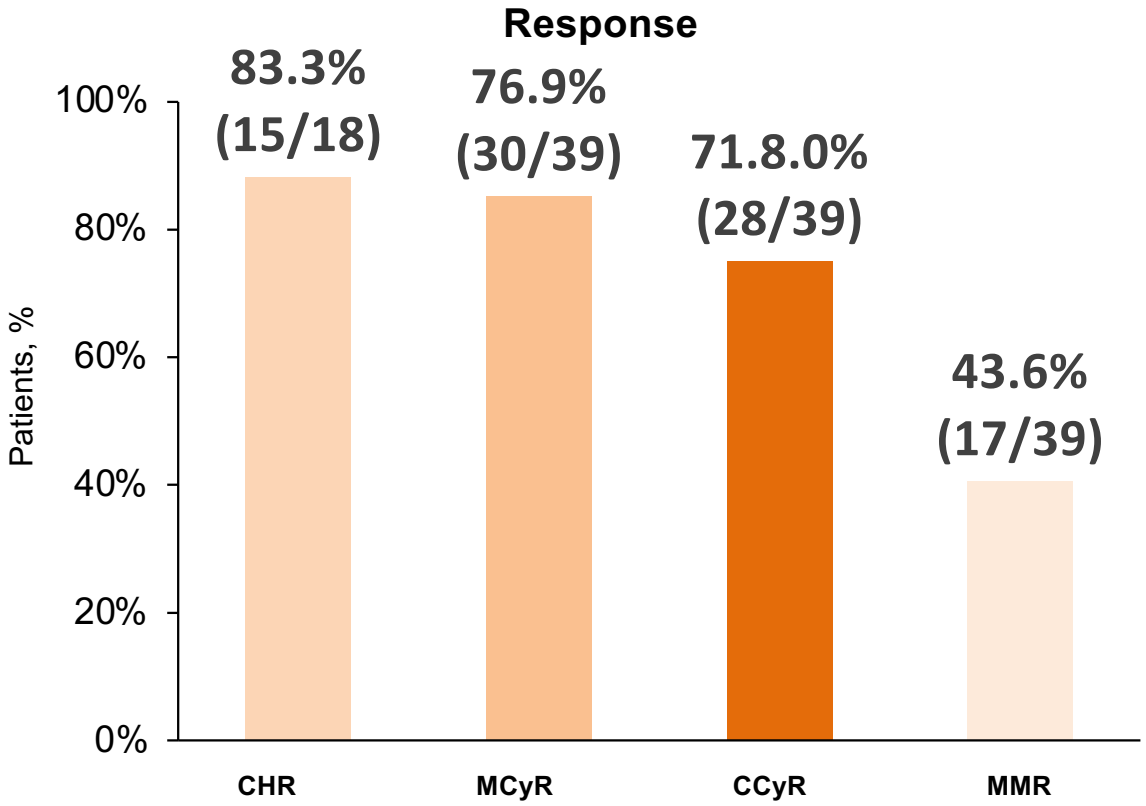
Cortes et al ASH 2025

Olverembatinib 2L in CP-CML Resistant/Intolerant to Prior 1L TKIs without T315I

Patient Characteristics

- Patients resistant/intolerant after 1 TKI without T315I
- **N=47** (91.5% resistant to 1L, 74.5% after 2nd gen TKI)
- Median age: 42 years
- Male: 66%
- Mutations: 11 patients

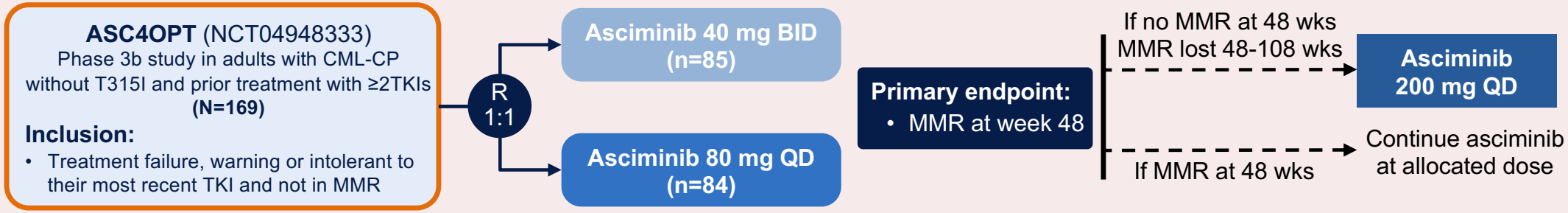
Efficacy Evaluable, n (%)	N=39
CCyR	28 (71.8)
MMR	17 (43.6)
Pretreated with 2nd Gen TKI as 1L Treatment, n (%)	**n=30**
CCyR	23 (76.7)
MMR	13 (43.3)
Patients Treated with Imatinib, n (%)	**n=9**
CCyR	5 (55.6)
MMR	4 (44.4)



Weiming L, et al. ASH 2025 3782

3L+ Treatment

ASC4OPT: Phase 3b – Asciminib 40 mg BID vs 80 mg QD in ≥ 3L CP-CML



MMR, n (%)	Asciminib 40 mg BID (n=83)	Asciminib 80 mg QD (n=82)	All patients (N=165)
At Week 48	36 (43.4)	29 (35.4)	65 (39.4)
At Week 96	38 (45.8)	34 (41.5)	**72 (43.6)**

- 40 pts escalated to 200 mg QD. 17.5% at week 96 obtained MMR. The most common AESI was GI toxicity (7 patients, 17.5%) with no Grade ≥3 events.
- In the exploratory cohort, 86.7% of pts maintained MMR regarding the dosing schedule

Breccia et al ASH 2025; abst

TGRX-678 -1001: Updated Results of Phase 1 Study

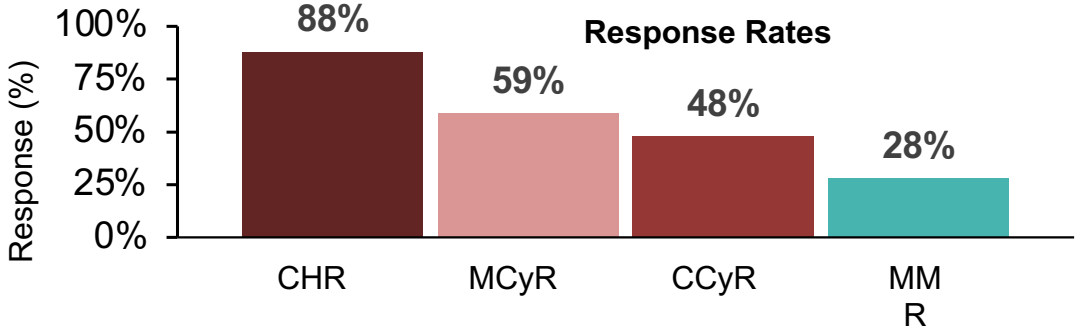
Background/Patient Characteristics

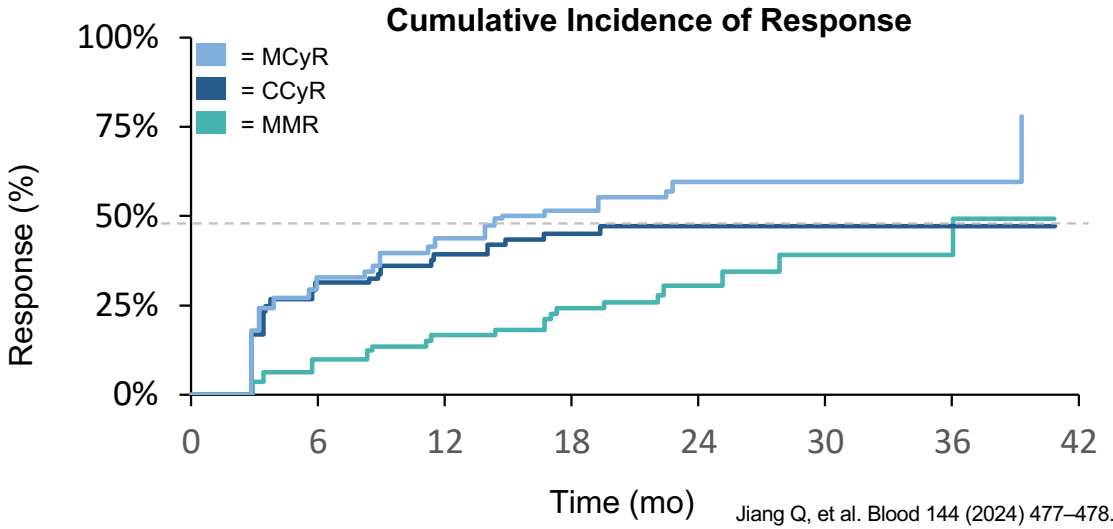
- TGRX-678 acts on myristoyl pocket (STAMP), wildtype and common mutations including T315I
- **158 pts treated** (108 CP-CML, 50 AP-CML) with QD and BID escalating doses
- Median treatment duration = 13 months
- Received >2 TKIs = 66%
- T315I = 23%
- BCR::ABL1 >10% = 84%

CML-CP, %	N=108
CCyR	40
MMR	**26**
Patients with T315I (n=25)	
CCyR	69
MMR	50
CCyR in patients previously treated with ponatinib and asciminib	17

AEs Grade ≥3 occurring in more than 5%	N=158
Hypertriglyceridemia	54
Thrombocytopenia	46
Neutropenia	44
Hypercholesterolemia	30
Hyperglycemia	29
Anemia	27

Most TRAEs were grades 1-2

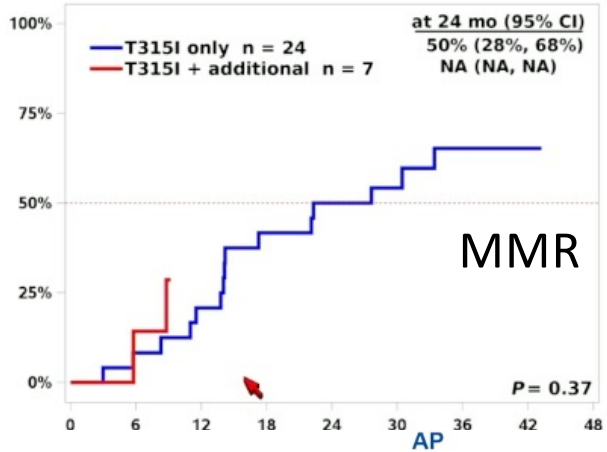


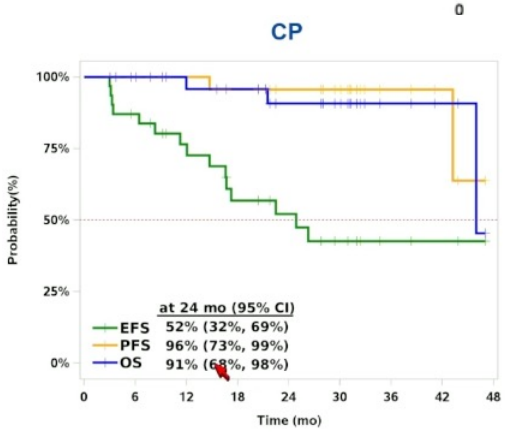


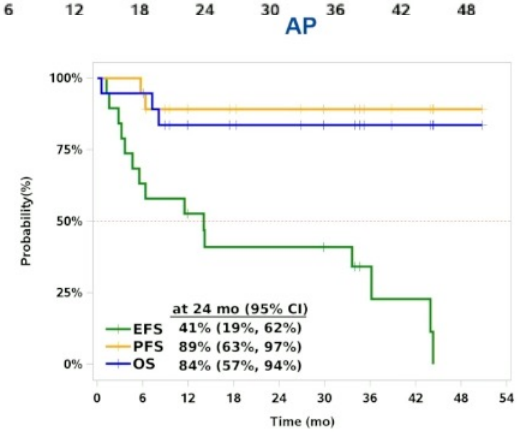
Jiang Q, et al. Blood 144 (2024) 477–478.

TGRX-678: results of phase 1 trial in T315I mutated

- **53 T315I-mutated CML pts (32 CP and 21 AP)** were enrolled. 11 (21%) pts had additional ABL1 mutations. Doses ranged between 40 mg and 240 mg/d
- **23 pts discontinued**, mostly due to physician's decision
- **81% CP pts and 80% AP achieved complete hematological response (CHR)** and major hematological response (MaHR), respectively.
- **Efficacy outcomes were comparable across T315I mutation status (single vs. compound mutations) and TGRX-678 dose levels**
- **Among patients with prior exposure to ponatinib, olverembatinib, asciminib, or HS-10382, the cumulative incidences of CCyR and MMR were significantly lower**







CARDINAL trial: TERN-701 in CP CML

Part 1 Dose Escalation

- Received ≥2 TKIs OR had treatment failure/suboptimal response to frontline 2G TKI
- Prior asciminib/ponatinib failure/intolerance allowed; myristate pocket resistance mutations excluded
- T315I and non-T315I mutations allowed

Part 2 Dose Expansion

- Treatment failure OR suboptimal response to ≥1 prior TKI
- Prior asciminib/ponatinib treatment failure/intolerance allowed; myristate pocket resistance mutations excluded
- Only non-T315I mutations allowed

Data cutoff:
September 13, 2025

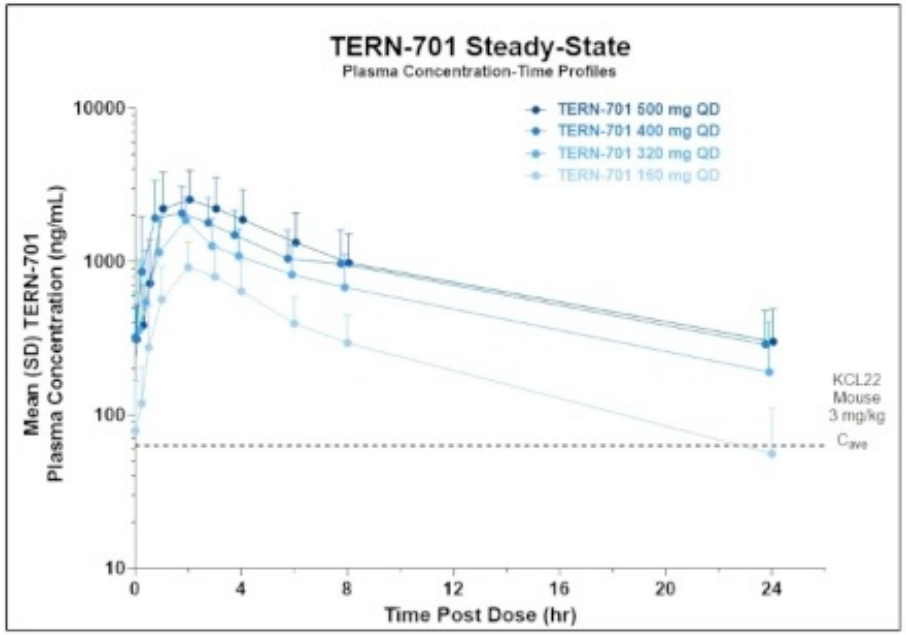
Primary Endpoints: Safety and tolerability (including dose-limiting toxicities)

Secondary Endpoints: Efficacy (molecular responses) and pharmacokinetics

Jabbour et al ASH 2025; abst 901

CARDINAL trial: characteristics and PK

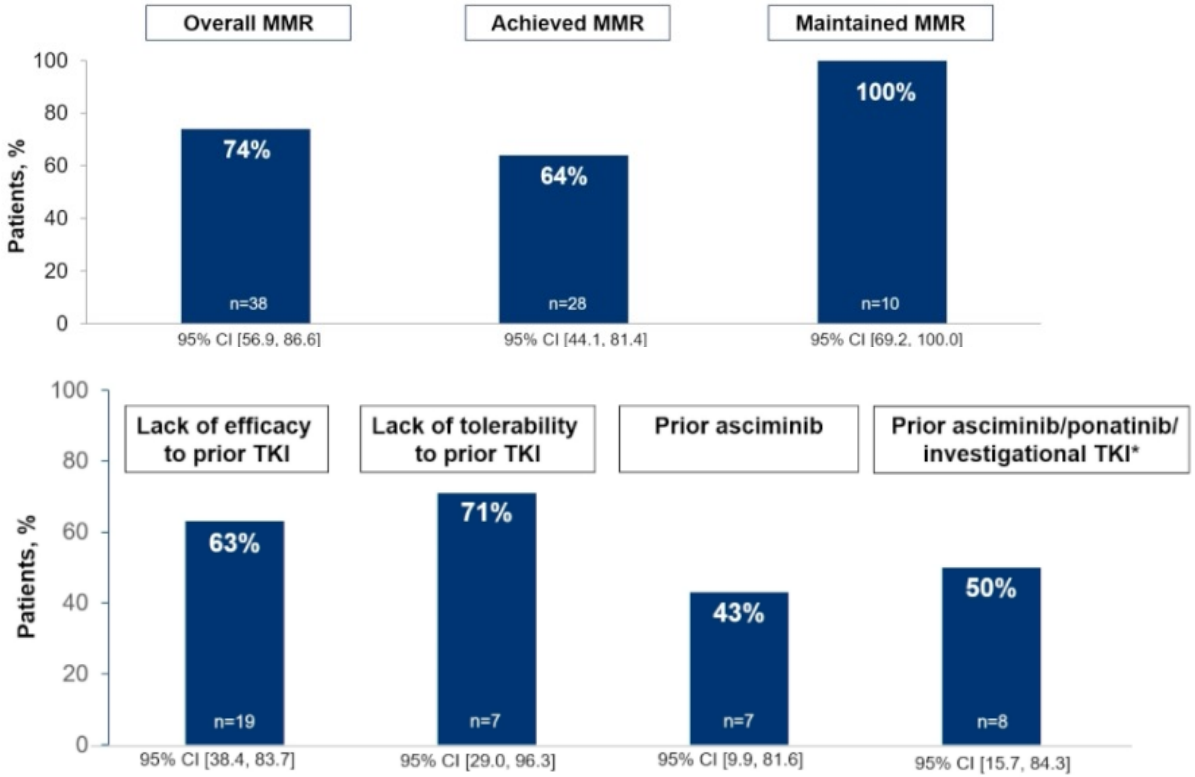
- **63 pts were enrolled**, (56% male; median age 58 years [29–86]). Forty-eight pts remained on treatment
- **Median 3 prior TKIs** 60% (38% had prior asciminib; 22% had prior ponatinib). 44% had baseline BCR::ABL1>10%. **15% with BCR::ABL1 mutations** (10% T315I). 64% and 29% had lack of efficacy (per ELN 2020 criteria) and intolerance to last TKI, respectively.
- **No dose-limiting toxicities (DLTs) were observed in dose escalation**, and a maximal tolerated dose (MTD) was not reached. The majority (74%) of treatment-emergent adverse events (TEAEs) were low grade with no apparent dose relationship. **The most common TEAEs were diarrhea (21%), headache (19%), and nausea (19%), all Grade 1 or 2.**
- Of 32 efficacy-evaluable pts, **75% (24/32) were in > MMR by 24 wks**, of whom 64% (14/22) achieved and 100% (10/10) maintained that response.



- No significant differences in exposure when dosed fasted or with high-fat meal

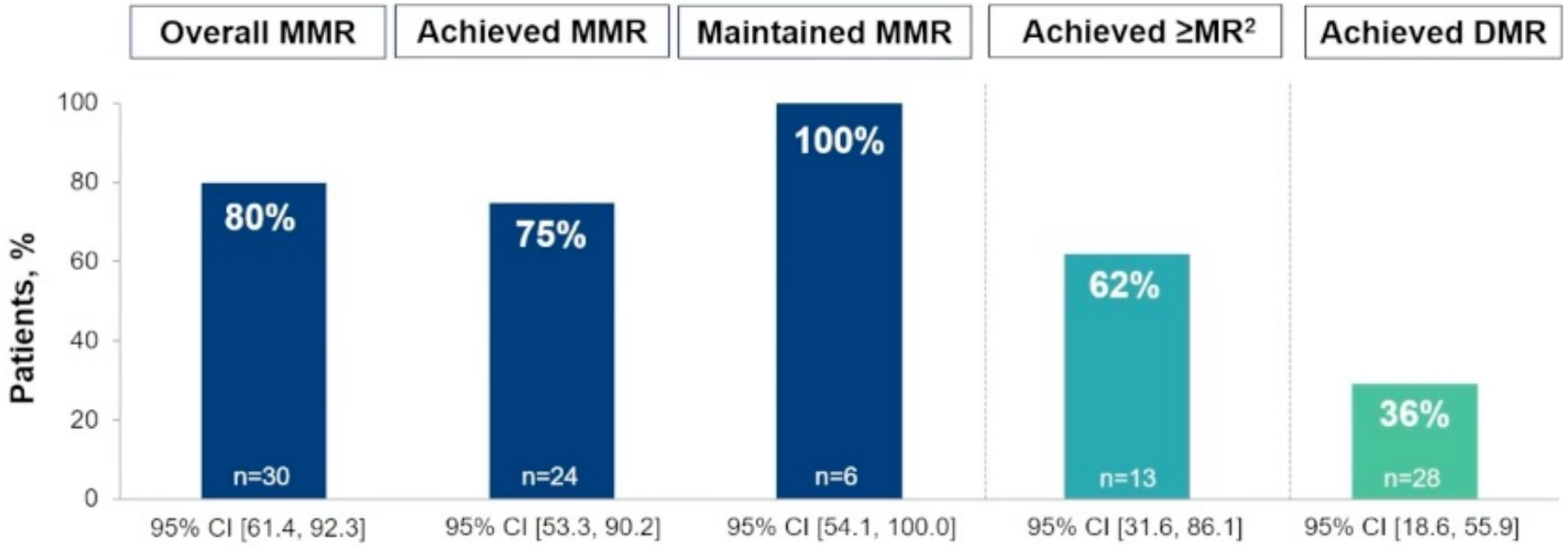
Jabbour et al ASH 2025; abst 901

CARDINAL trial: molecular responses



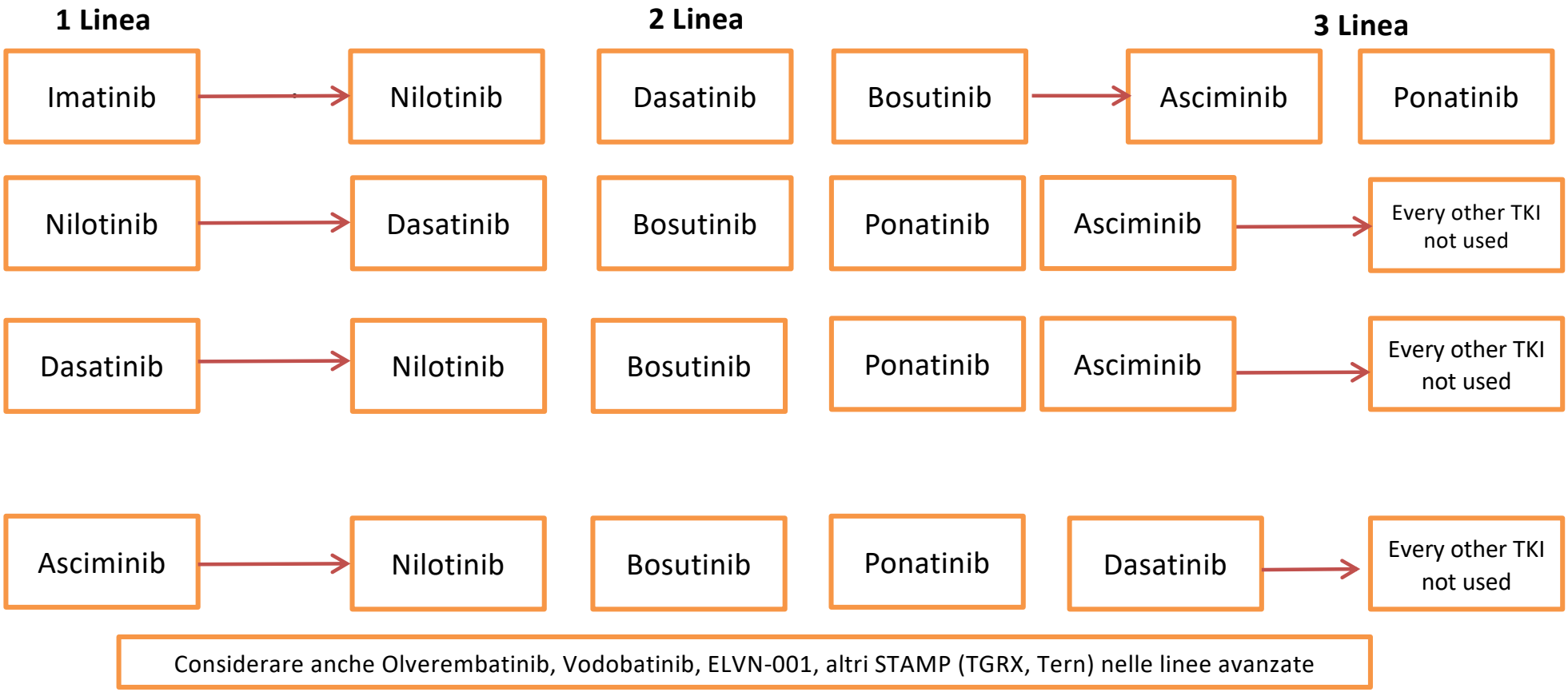
Jabbour et al ASH 2025; abst 901

CARDINAL trial: molecular responses in pts treated with > 320 mg QD



Jabbour et al ASH 2025; abst 901

Possible future algorithm (?)



Considerare anche Olverembatinib, Vodobatinib, ELVN-001, altri STAMP (TGRX, Tern) nelle linee avanzate

Conclusions

- **The SUSTRENIM study** confirm nilotinib in low risk patient as optimal for TFR
- **Asciminib**, the first example of allosteric inhibition, has been **approved by FDA and EMA as frontline treatment** and NCCN guidelines were updated introducing the drug as preferred for newly diagnosed patients
- **Unmet needs remain in later lines CML**: new drugs are on the horizon, while asciminib and ponatinib are currently the best choice
- **TERN-701 and TGRX-678** are new STAMPi still ongoing