POST-SAN DIEGO 2024
Novità dal Meeting della Società Americana di Ematologia

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Bologna
Palazzo Re Enzo
13-15 Febbraio 2025

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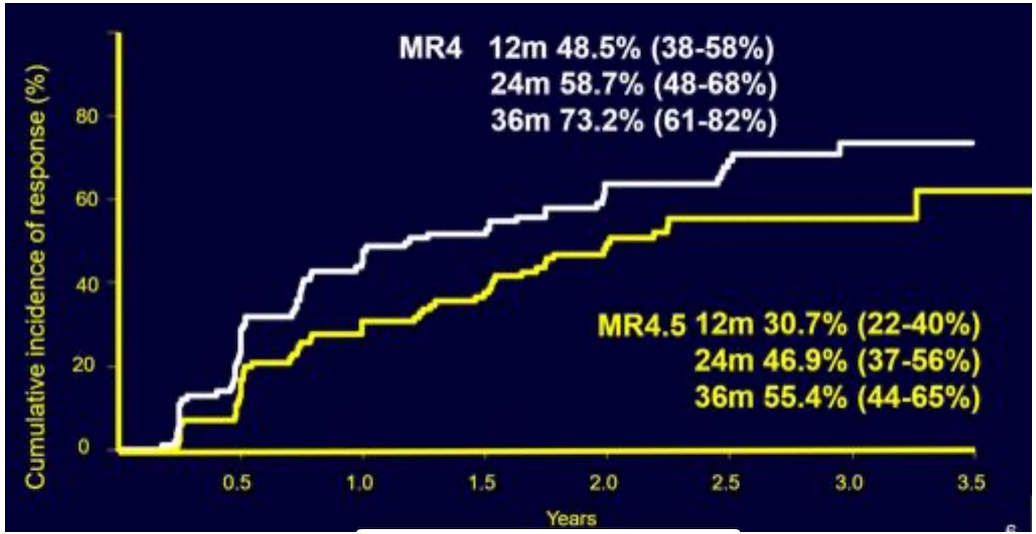
Novartis					x	x	
Incyte					x		
BMS					x	x	
AOP					x		
GSK					x	x	
Pfizer					x		

ASCEND: 28 months follow-up



- Phase II trial. **101 pts** in CP-CML
- Patients with treatment failure (*BCR::ABL1* >10% at 3 or 6 months; *BCR::ABL1* >1% at 12 or 18 months) continue asciminib and add either imatinib, dasatinib or nilotinib, according to physician preference.
- Patients who have not failed, but have not achieved optimal response at 6, 12, or 18 months, have their asciminib dose doubled to 80mg BID
- Co-primary end points are achievement of early molecular response (EMR, *BCR::ABL1* ≤10% at 3 months) and major molecular response (*BCR::ABL1* ≤0.1%) by 12 months
- **EMR at 3 months 93%; MMR at 12 months 79%**
- Most common AEs reported were hypertension (22%), increased amylase/lipase (21%)
- 20 pts discontinued: 5 loss of response; 1 sudden BC with myristoilic site mutations

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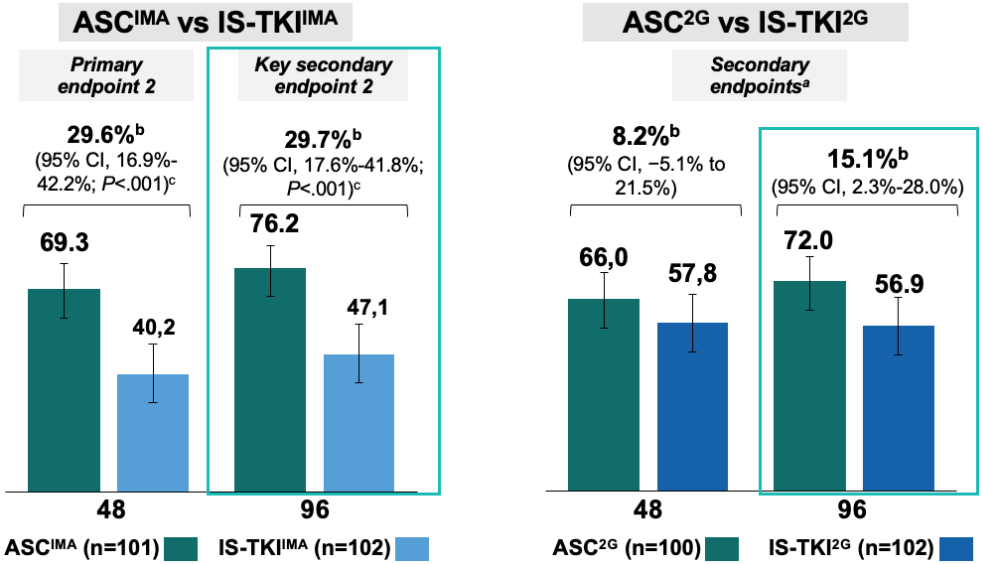
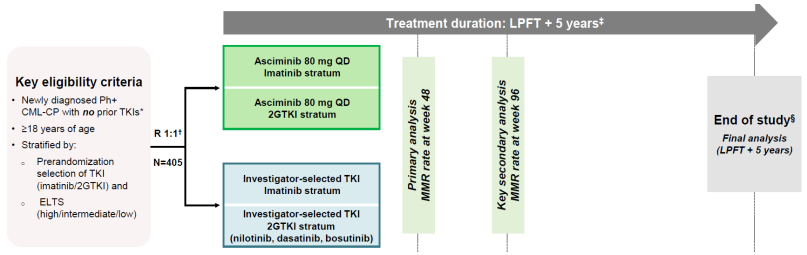
ASC4FIRST: 96 week follow-up

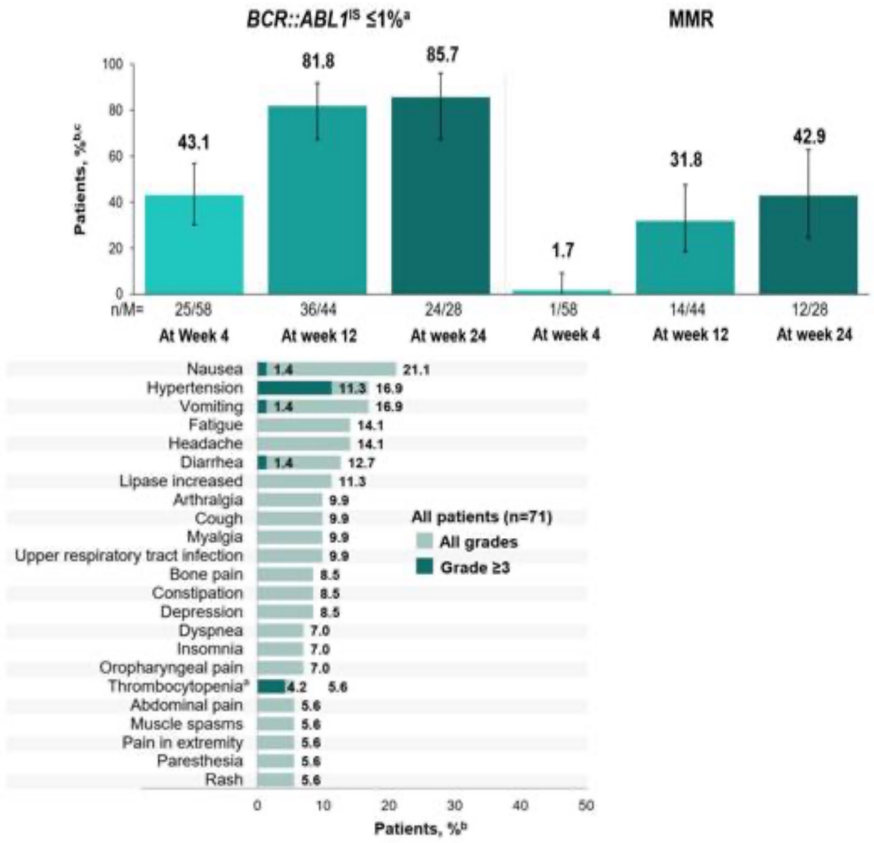




- Safety/tolerability of ASC was more favorable vs IMA and individual 2G TKIs. Any-grade AEs leading to Tx **discontinuation** were lower with ASC (4.5%) vs IMA (11.1%), NIL (8.2%), DAS (11.9%), and BOS (9.1%).
- Any-grade AEs leading to **dose adjustment and/or interruption** were lower with ASC (30.0%) vs IMA (39.4%), NIL (49.0%), DAS (54.8%), and BOS (63.6%).
- **Arterial occlusive events** occurred in 2 (1.0%) pts with ASC (arteriosclerosis coronary artery, n=1; cerebrovascular accident, n=1), 1 (1.0%) with NIL (vertebral artery arteriosclerosis), and 1 (1.0%) with DAS (myocardial infarction and ischemia). Two pts had cardiac failure with DAS.

ASC2ESCALATE: 2L interim analysis

- Phase II trial.
- Single arm with dose escalation in ND or in 2L
- In 2L, pts were enrolled after warning, resistance or intolerance
- Starting dose 80 mg QD; at 24 week possible increased to 200 mg QD if BCR::ABL1 > 1%; at 48 week if >0.1%
- **43 pts included** (prior resistance in 62.8%)
- 2 pts discontinued asciminib
- Deeper responses were achieved at wk 12 (MMR, 6 [27.3%]; MR^4, 2 [9.1%]; $MR^{4.5}$, 1 [4.5%]) and wk 24 (MMR, 8 [57.1%]; MR^4, 4 [28.6%]; $MR^{4.5}$, 1 [7.1%]). **Two pts had dose escalation** from 80 to 200 mg QD per protocol (1 at wk 24 and 1 at wk 48).
- The most common (>15%) all-grade AEs were fatigue and hypertension (16.3% each).



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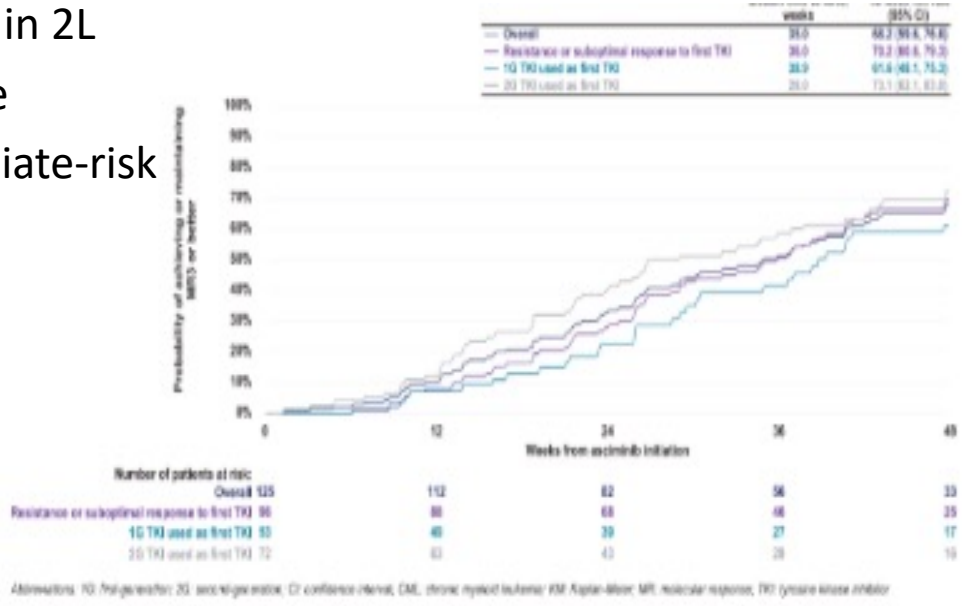
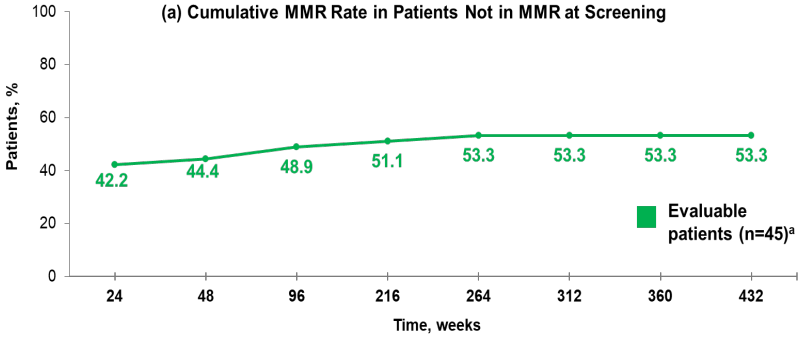
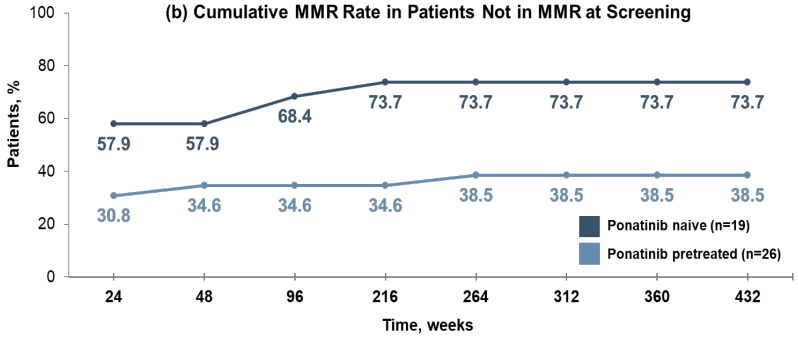
Asciminib 2L: chart review in US

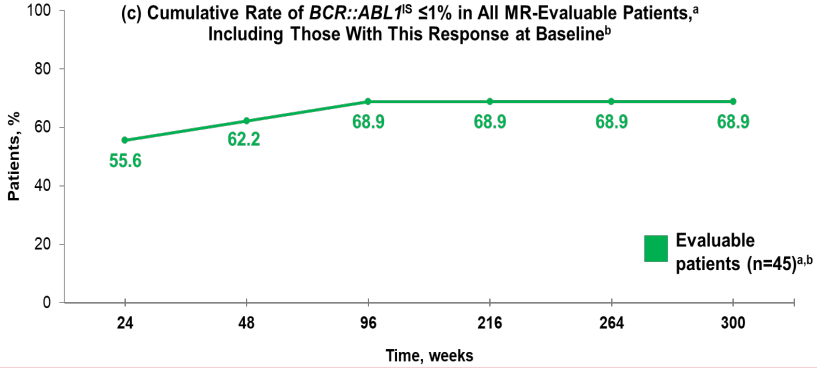
- 149 pts with T315I who started asciminib in 2L
- Median age 63 years, male predominance
- At CML diagnosis, 65.8% had an intermediate-risk and 12.8% a high-risk Sokal score.
- **Previous resistance in 44% of cases**
- 93% remained in asciminib by 48 weeks
- **68% achieved or maintained MMR**
- **MR4 or better in 45%**
- **No progression**
- **AE: fatigue, headache, rash, abdominal pain**

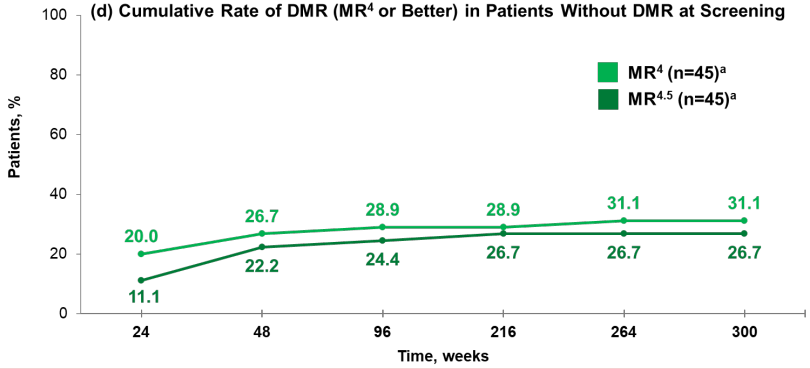


Asciminib in T315I: cumulative rate of MMR, BCR::ABL1^{IS} ≤0.1% and DMR

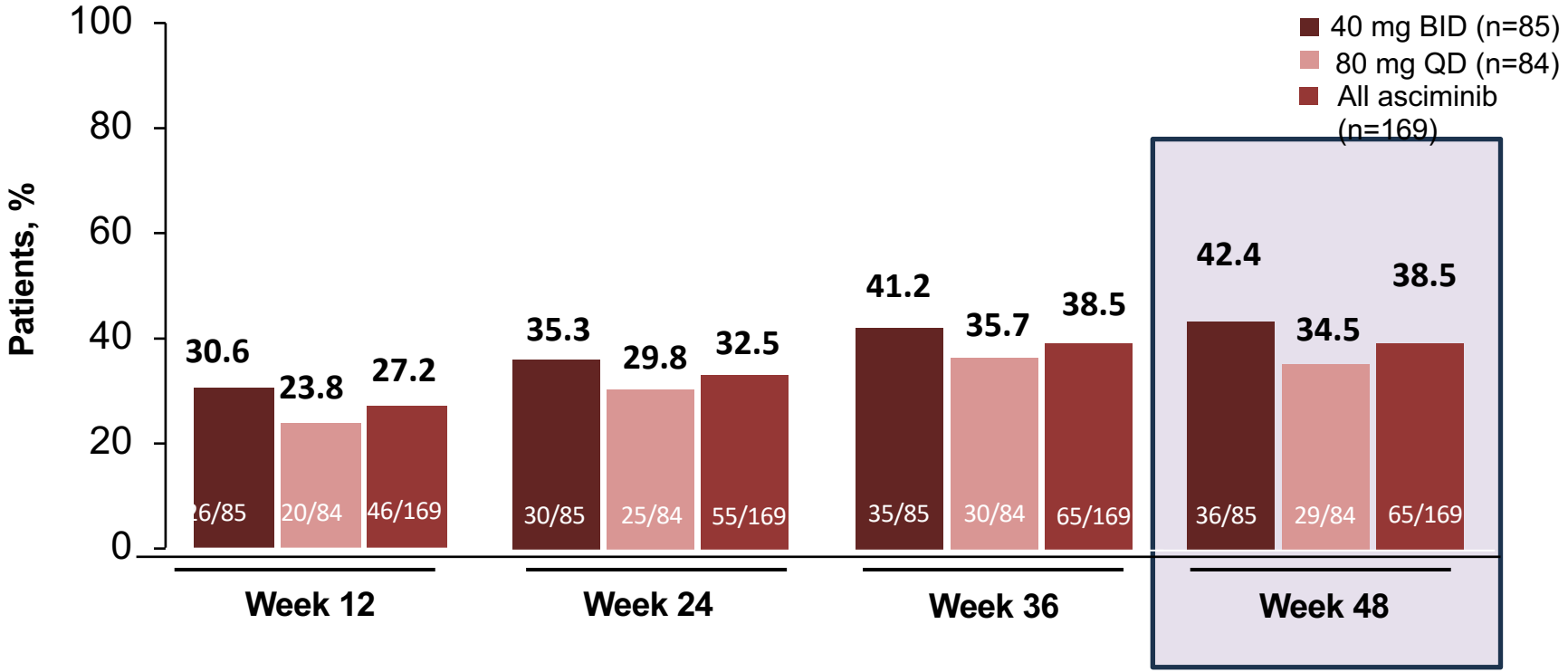






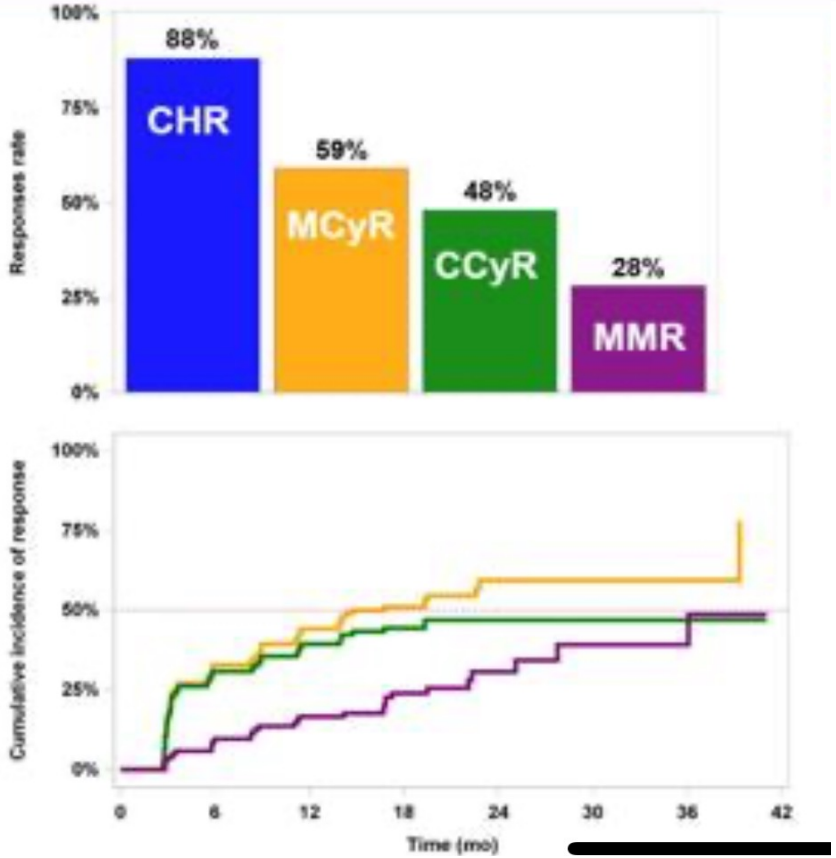


ASC4OPT: 40 mg BID vs 80 mg QD

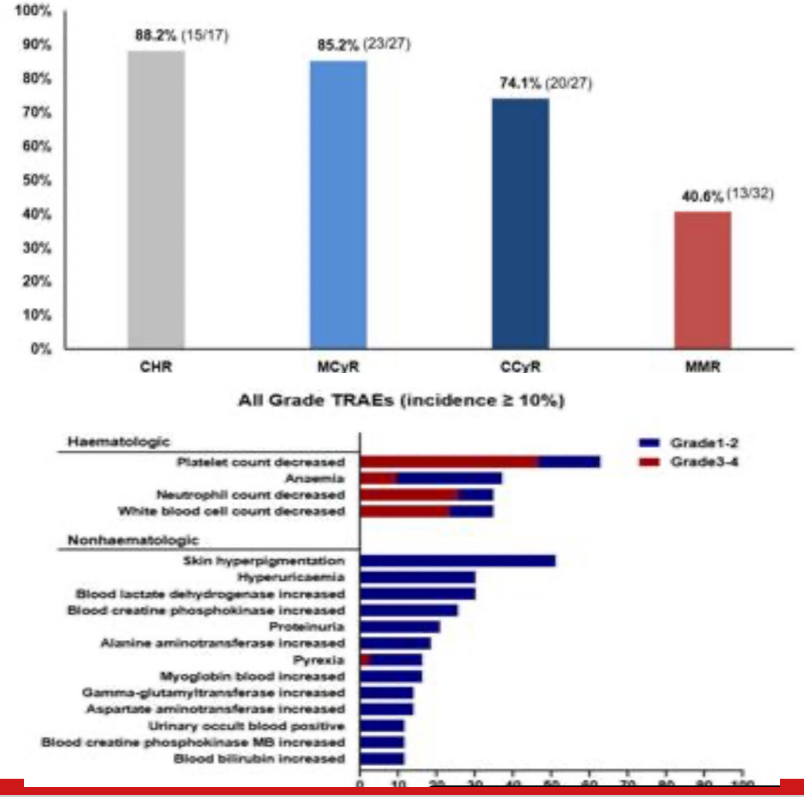


TGRX-678: a novel allosteric TKI

- It acts on myristoyl pocket (STAMP), WT and common mutations including T315I
- **158 pts treated** (108 CP, 50 AP) with QD and BID escalating doses
- Median treatment duration 13 months
- In CP, 66% received > 2 TKIs, **23% with T315I**
- 84% in CP had BCR::ABL1 > 10%
- **In CP pts, 40% of CCyR and 26% MMR**
- **In pts with T315I, 69% in CCyR and 50% in MMR**
- In pts previously treated with pona and asciminib 17% reached a CCyR
- Most treatment-related adverse events (TRAEs) were grade 1-2. AEs ≥ grade 3 that happened more than 5% were thrombocytopenia (46%), neutropenia (44%), anemia (27%) and hypertriglyceridemia (54%), hyperglycemia (29%), hypercholesterolemia (30%).



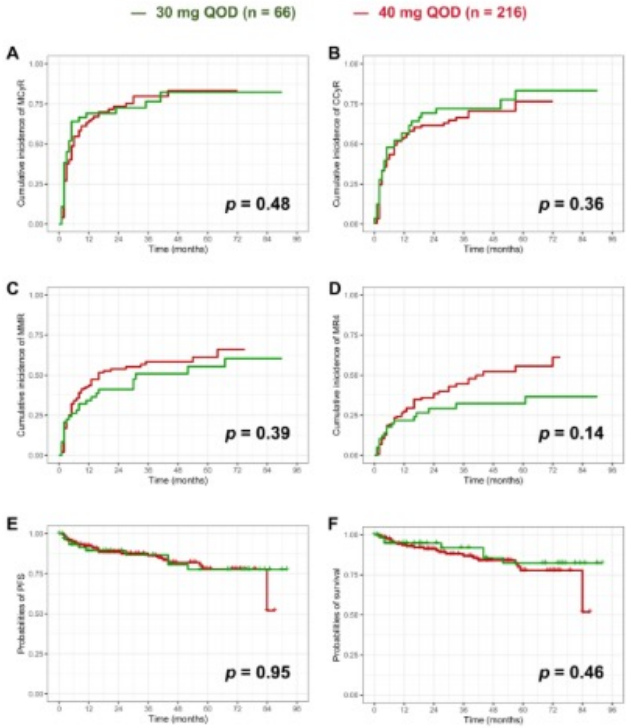
Olverembatinib 2L in CP patients res/intoler to a previous 1L



- Pts res/intoler after 1 TKI without T315I
- **42 pts**
- 92.9% resistant to 1L (71% after 2gen TKI)
- 11 pts with mutations
- Median age 45 years, 69% male
- **75% achieved CCyR**
- **40.6% MMR**
- In 32 efficacy-evaluable pts, 23 pts were pretreated with 2G TKIs as 1L treatment, of whom 19 (82.68%) achieved CCyR and 10 (43.5%) achieved MMR.
- In 9 pts pretreated with imatinib, 5 pts achieved CCyR (55.6%) and 3 MMR (33.3%).
- Nonhematologic TRAEs included skin hyperpigmentation (38.1%), hyperuricemia (23.8%), and creatine phosphokinase increased (21.4%).
- Thrombocytopenia 38%
- 4.8% hypertension

Weiming et al ASH 2024; 480

Olverembatinib 30 vs 40 QOD in R/I pts: propensity score



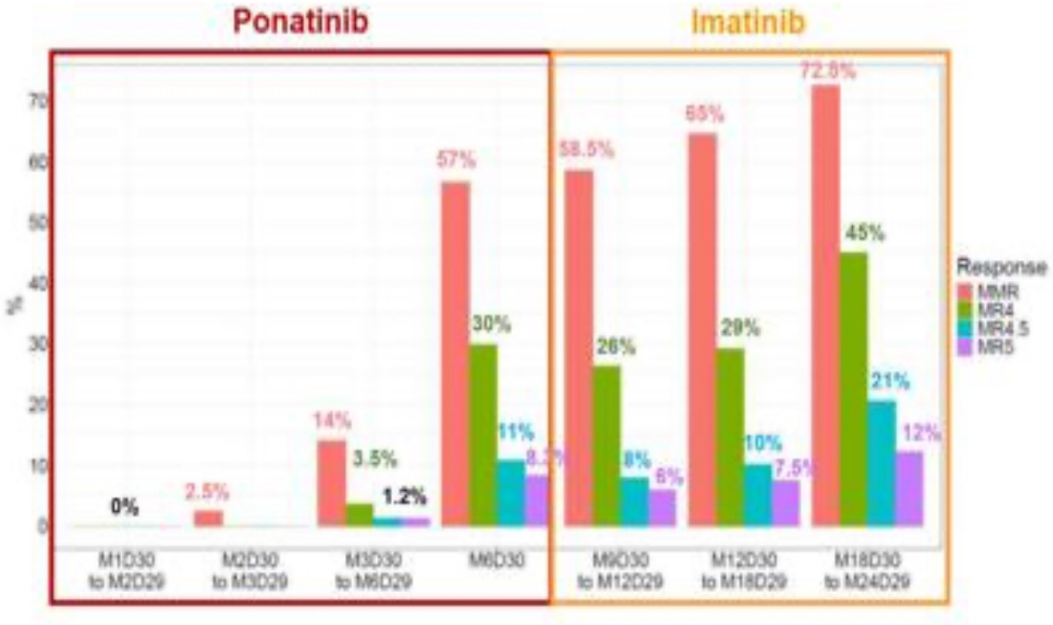
- **282 pts** (66 with 30 mg and 216 with 40 mg)
- Median age at the start of olverembatinib therapy was 39 years (IQR, 25-46 years). 130 (46%) received ≥ 3 prior TKIs.
- **161 (57%) patients harbored the single *T315I* mutation**
- There were **no significant differences** in the 4-year cumulative incidences of MCyR (p = 0.43), CCyR (p = 0.46), MMR (p = 0.45) and MR^4 (p = 0.17), as well as PFS (p = 0.99) and survival (p = 0.56) between the 2 dose cohorts.
- **Similar rates of suspension or reduction of the dose for toxicity**
- The proportion of patients still receiving the original dose at the last follow-up was significantly higher in the 30 mg cohort compared to the 40 mg cohort (67% *versus* 46%, p = 0.003)
- **Permanent discontinued treatment due to TRAEs in the 30 mg cohort was significantly lower than that in the 40 mg cohort** (18% *versus* 39%, p = 0.002).

Olverembatinib overcomes pona and asciminib failure

- **80 pts enrolled in a phase II trial**, 67 in CP
- 14 had received 2 prior lines of TKIs, 21 3 lines and 34 > 4 lines
- 46 were pre-treated with ponatinib and 25 with asciminib
- 19 pts harbored a T315I mutation
- 67 pts experienced treatment-related side effects: the more common were the increased CPK, thrombocytopenia, increased ALT

- CCyR was achieved by 58.3% of pts, and MMR by 45%
- **in ponatinib-pretreated , 53.6% of pts achieved CCyR and 40% achieved MMR**
- **in asciminib-pretreated , 37.5% of pts achieved CCyR and 30% achieved MMR**

TIPI trial: imatinib after ponatinib induction

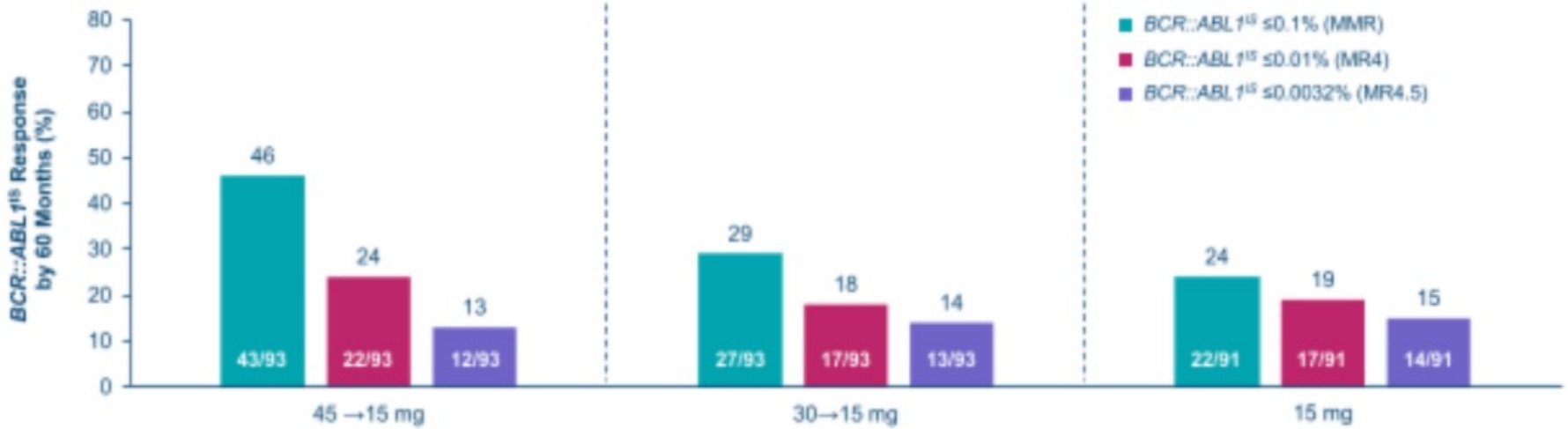


- **169 pts aged < 65 years** (median age 45)
- High ELTS score in 16%
- ESC score < 2% in 93% of pts

- After the first 6 months, only a minority of side effects recorded with imatinib (33%) of them 11 non-hematological. No CV observed.
- EFS 86% at month 18
- **97% in EMR with ponatinib**
- **MMR at M18 68% with imatinib**
- MR4 40%, MR4.5 13% at months 18

- Ponatinib induction followed by imatinib consolidation induces high rates of MMR and DMR at M18, higher than that with TKI2 as front-line therapy as reported in the literature in CP-CML pts.

OPTIC: 5-y of follow-up



- 73 pts remained in treatment. Most common reason occurrence of AE
- By 60 months, 60%, 41%, 40% achieved < 1% with 45, 30, 15 mg
- Higher responses in T315I mutated pts
- Estimated OS were similar across all dosing cohorts
- AOE: 14%, 10%, 5%

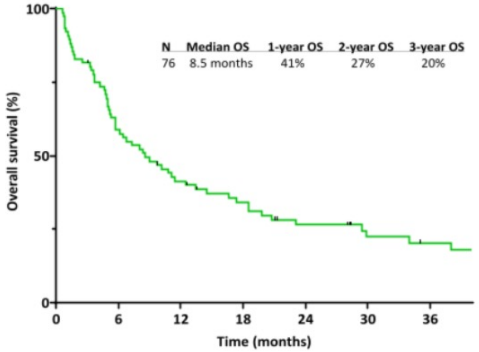
Cortes et al, ASH 2024

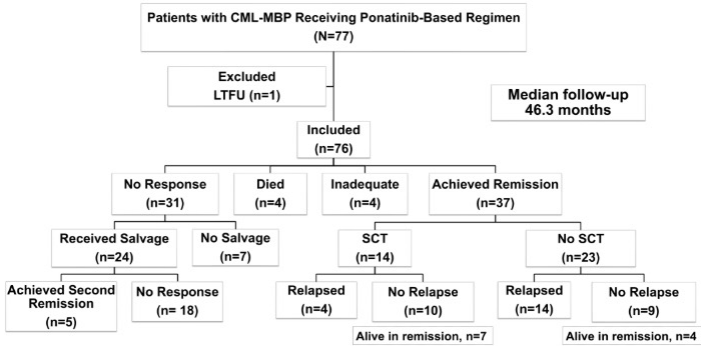
Ponatinib in blast crisis: MDACC experience

- **76 patients** for myeloid BP between 2008 and 2023
- Median age 50 y
- **50 pts as 1L** (4 de novo and 46 transformed form previous early CP)
- **26 as salvage therapy**
- 47% had at least 1 mutation (8 T315I)
- Ponatinib was given with intensive CHT in 28 pts, with IC+venetoclax in 7 pts, with HMA+Ven in 18 pts, with HMA only in 6 pts and as monotherapy in 17 pts

Response Rates by Subgroup

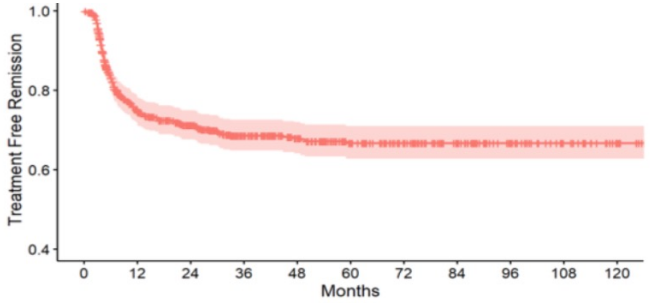
Subgroup	ORR, n (%)	CR/CRi, n (%)
Line of therapy		
Newly diagnosed MBP	30 (60)	25 (50)
Relapsed/refractory MBP	7 (27)	5 (19)
Type of therapy		
IC+ven+ponatinib	2 (29)	2 (29)
IC+ponatinib	15 (54)	13 (46)
HMA+ven+ponatinib	12 (67)	8 (44)
HMA+ponatinib	3 (50)	3 (50)
Ponatinib monotherapy	5 (29)	4 (24)
ABL1 KD mutation		
Present	18 (56)	16 (50)
Absent	15 (42)	11 (31)





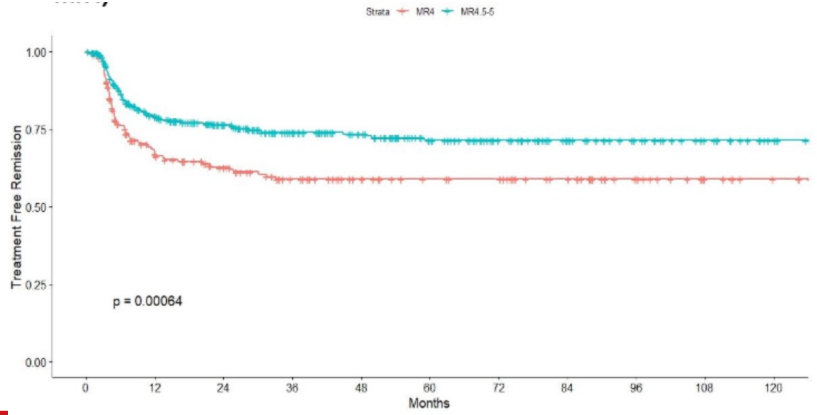
TFR in Italy: 657 patients

	Imatinib (N=378)	2nd or 3rd gen TKI (N=279)	Overall (N=657)
Age at diagnosis			
Mean (SD)	48.7 (14.5)	50.0 (15.1)	49.2 (14.8)
Age at STOP			
Mean (SD)	59.1 (14.5)	57.7 (15.0)	58.5 (14.7)
Sex			
Male	217 (56.1%)	143 (50.0%)	360 (53.5%)
Female	170 (43.9%)	143 (50.0%)	313 (46.5%)
Sokal Score			
Low	204 (58.3%)	120 (46.2%)	324 (53.1%)
Intermediate	113 (32.3%)	91 (35.0%)	204 (33.4%)
High	33 (9.4%)	49 (18.8%)	82 (13.4%)
ELTS			
Low	127 (77.0%)	87 (69.6%)	214 (73.8%)
Intermediate	33 (20.0%)	27 (21.6%)	60 (20.7%)
High	5 (3.0%)	11 (8.8%)	16 (5.5%)
Type of transcript			
b2a2	87 (25.8%)	73 (29.9%)	160 (27.5%)
b3a2	244 (72.4%)	165 (67.6%)	409 (70.4%)
e1a2	0 (0%)	1 (0.4%)	1 (0.2%)
Rare	6 (1.8%)	5 (2.0%)	11 (1.9%)



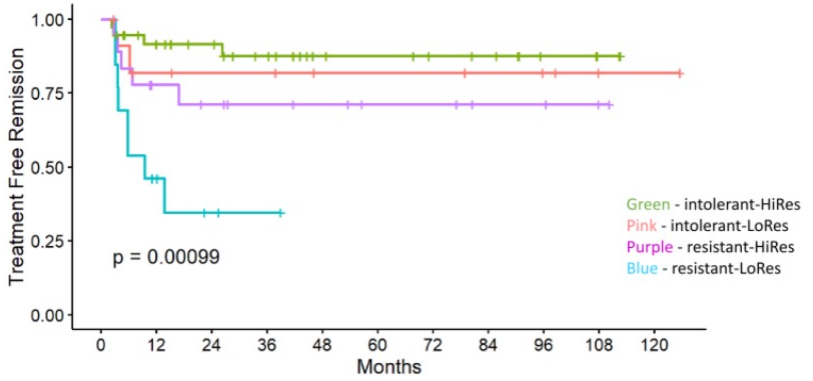
MULTIVARIATE ANALYSIS FOR RISK FACTORS

BAYESIAN MODEL AVERAGING	PI	HR	Post Prob
Last TKI (2 nd or 3 rd gen vs 1 st gen)	89,6	0,51	0,99
Duration of DMR (1% risk reduction for any additional month)	84,3	0,99	0,99
Level of molecular response at STOP (MR4.5 vs MR4; MR5 vs MR4) → FIGURE 2	32,9	0,51	0,99
Duration of the TKIs therapy before STOP (1% risk reduction for any additional month)	35,7	0,99	0,97



TFR in second or later lines

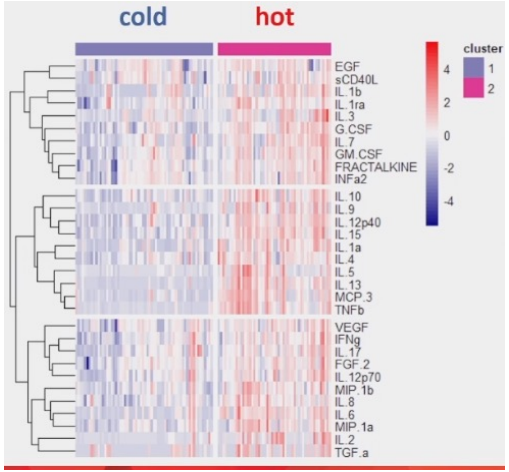
		Resistant (n=33)	Intolerant (n=53)	p
Age at discontinuation		51 [42 – 63]	50 [41 – 64]	0.442
Sex	M	19 (57.6%)	29 (54.7%)	0.827
Sokal Risk	Low	11 (36.7%)	20 (43.5%)	**0.021**
	Int	7 (23.3%)	20 (43.5%)	
	High	12 (40.0%)	6 (13.0%)	
1st TKI	1st gen	31 (94%)	41 (77.3%)	0.292
	2nd gen	2 (6%)	11 (20.8%)	
	3rd gen	0 (0%)	1 (1.9%)	
Last TKI	1st gen	1 (3%)	7 (13.2%)	0.292
	2nd gen	31 (94%)	43 (81.1%)	
	3rd gen	1 (3%)	3 (5.7%)	
Line of treatment at discontinuation	2nd	31 (93.9%)	43 (81.1%)	**0.030**
	3rd	1 (3.0%)	10 (18.9%)	
	4th	1 (3.0%)	0 (0%)	
Best response to 1stTKI	CCyR	18 (56.3%)	37 (75.5%)	**0.004**
	<CCyR	14 (43.8%)	12 (24.5%)	
Duration of treatment with any TKI		111 [81.0 - 151]	102 [74.0 - 128]	0.144
Duration of treatment with last TKI		74.0 [57.0 - 92.3]	50.0 [31.0 - 76.5]	**0.002**
Molecular response at 3 mos of last TKI	Less than MMR	9 (34.6%)	3 (8.8%)	**0.002**
	MMR	12 (46.2%)	7 (20.6%)	
	MR4	3 (11.5%)	16 (47.1%)	
	MR4.5	1 (3.8%)	5 (14.7%)	
	MR5	1 (3.8%)	3 (8.8%)	
Duration of DMR		52.0 [42.5 - 89.0]	51.5 [31.0 - 79.3]	0.565



	PI	HR	Post Prob
Duration of treatment before last TKI	73,8	0,95	0,89
Resistant	85,0	9,32	0,98
Best response to previous TKI: high responders	28,1	0,37	0,85
Response at 3 mos: MMR or DMR	42,2	0,24	0,91
Duration of last TKI	82,9	0,93	0,94
DMR duration from 1st treatment start	97	0,97	0,99

Inflammatory citokines associated with TFR

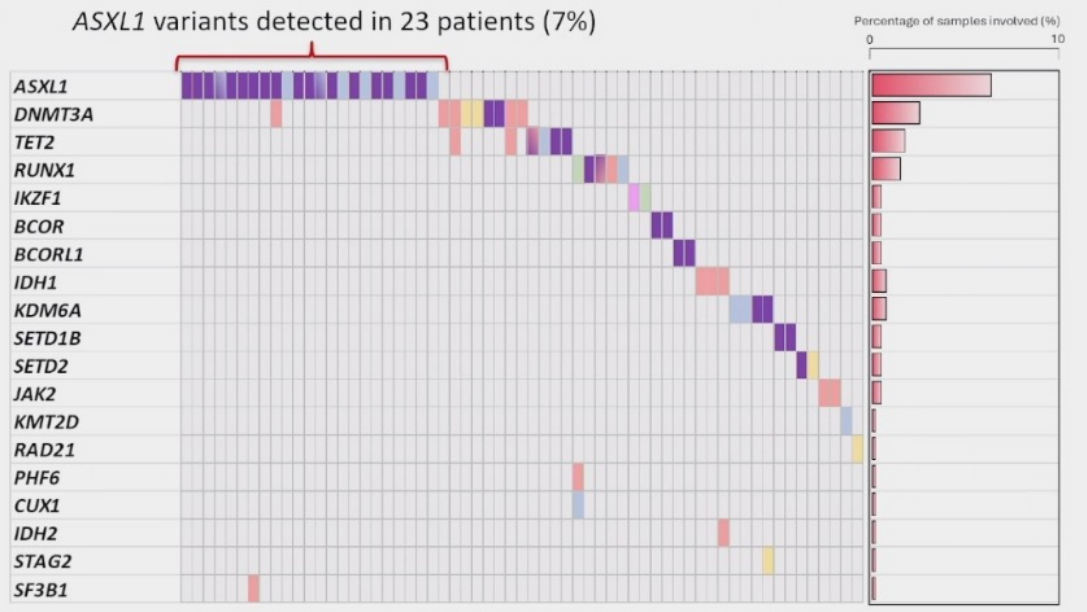
- 113 patients
- The levels of **38 cytokines**, chemokines and growth factors were measured in plasma samples
- Median follow-up after TKI cessation was 24.2 months
- The probability of sustained MMR after TKI cessation at 36 mths was 47.6% .
- **6 cytokines (IL-15, TNFb, IL-13, IL-6, IL-1a and G-CSF) as the most discriminating to define hot and cold clusters.**
- Two distinct clusters in the AU samples were identified. **Cluster 1 (COLD**, n=62) had lower global 38-cytokines expression compared to **cluster 2 (HOT**, n=51, median 84 vs 104 pg/mL, p<0.001).
- **At 12 mths, the hot cluster pts had a higher probability of sustained MMR (73%) compared to the cold cluster (39%, p<0.001).** This difference was more pronounced at 36 mths (73% vs 18%).



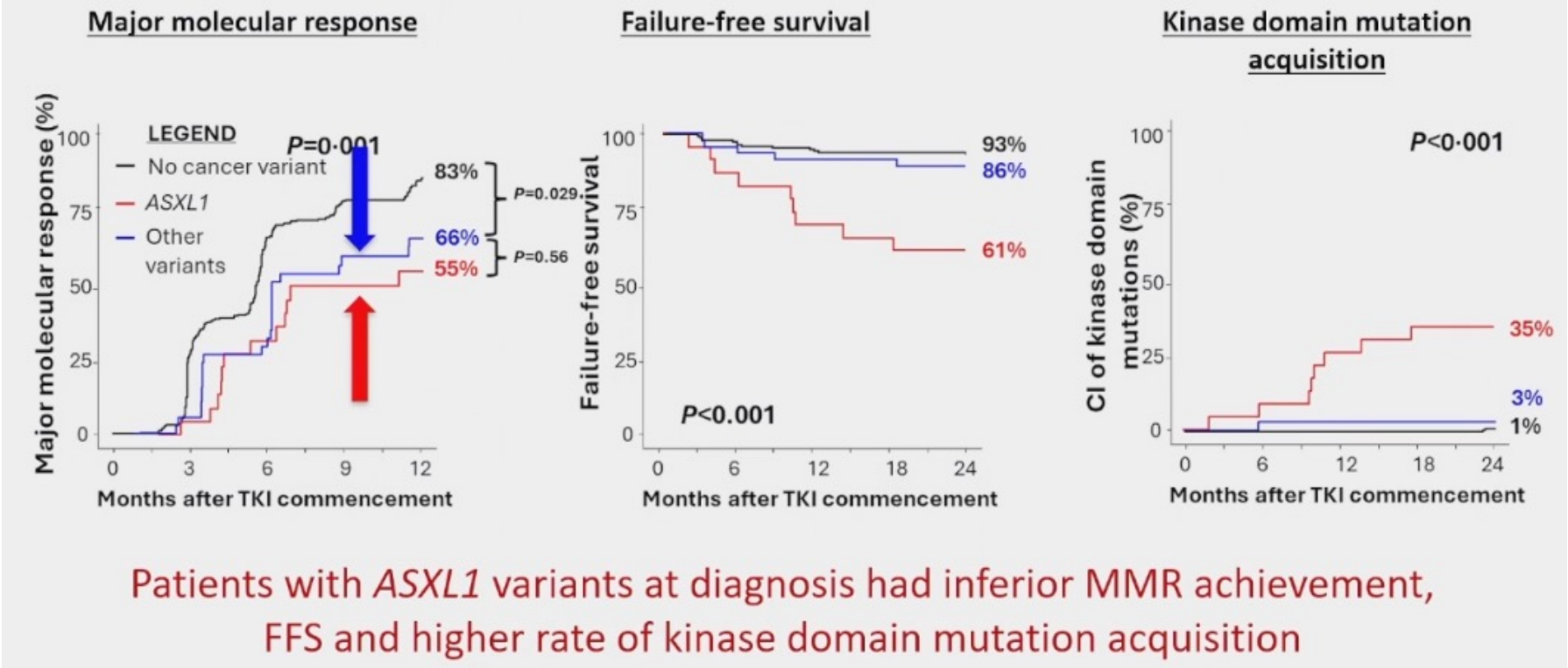
Ross et al ASH 993

Cancer gene variants after frontline Tx with 2gen TKIs (+asciminib)

- 315 patients
- Cancer gene variants (CGVs 18%) and Ph-associated rearrangements (Ph-ass 18%). *ASXL1* variants were most frequently detected: 41/515 pts (8%).

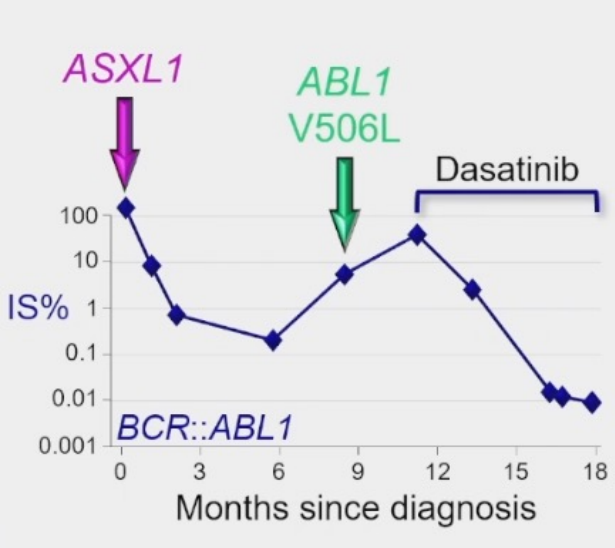


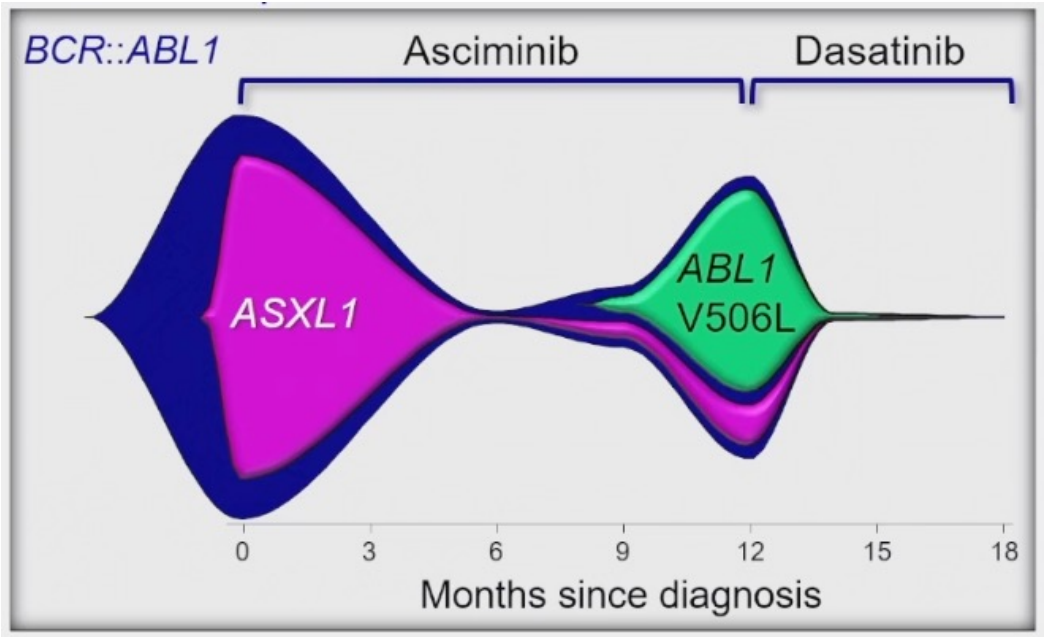
Cancer gene variants after frontline Tx with 2gen TKIs (+asciminib) (II)



Patients with *ASXL1* variants at diagnosis had inferior MMR achievement, FFS and higher rate of kinase domain mutation acquisition

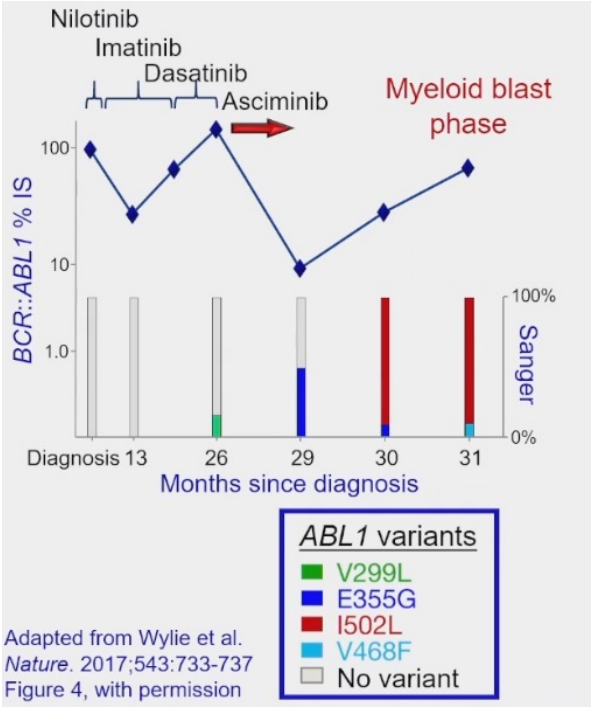
Longitudinal tracking of CGV: need for combination Tx

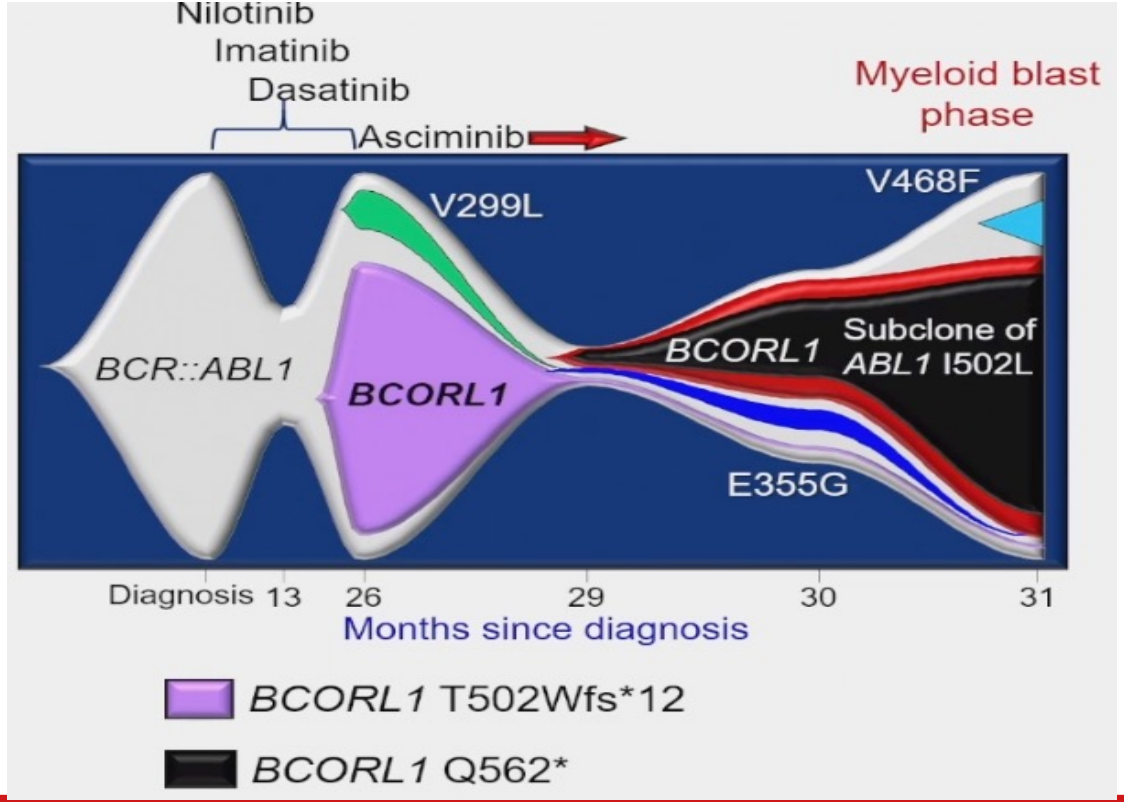




- The large mutated BCR::ABL1 ASXL1 clone at diagnosis was initially sensitive to asciminib
- The acquired ABL1 variant was a separate clone and the driver of resistance
- All clones were sensitive to dasatinib

Longitudinal tracking of CGV: need for combination Tx (II)





Conclusions

- Asciminib, first example of allosteric TKI, is a manageable and effective option in third and in first line. Few data still in 2L.
- Other selective TKIs have been developed based on the structure of 2 or 3 gen TKIs (olverembatinib, TGRX-678, etc)
- Most of these drugs are also effective in T315I mutated patients.
- Even the new allosteric TKIs seems not active on specific somatic mutations (ASXL1). Somatic mutations at diagnosis can drive different therapeutic strategies and can help to design possible therapeutic algorithms.