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Novità dal Meeting della Società Americana di Ematologia

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Leucemia mieloide cronica

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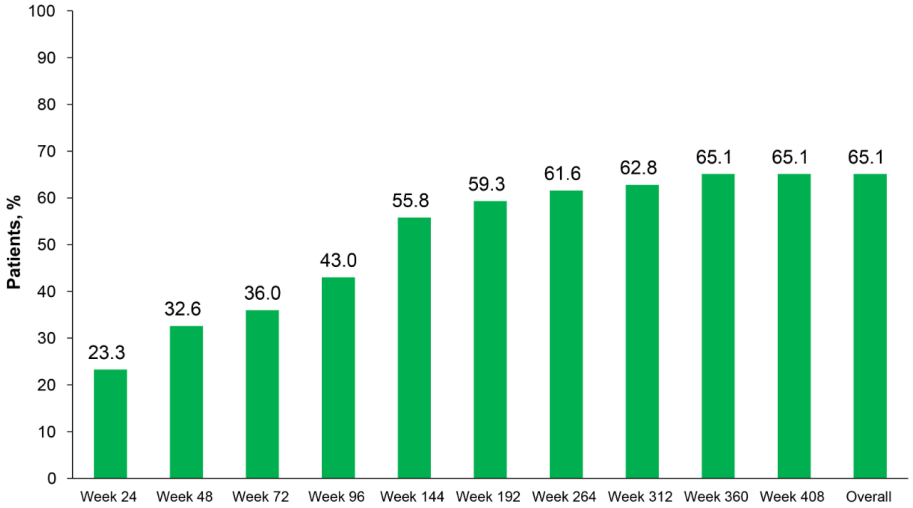
New TKIs

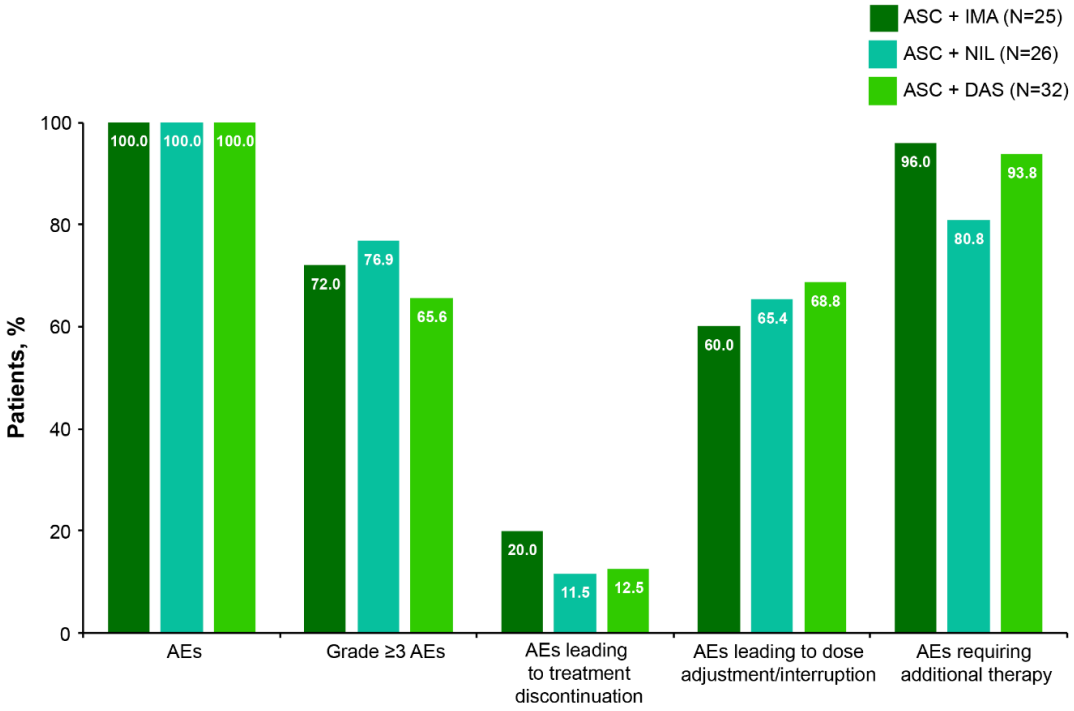
Asciminib phase 1 study: up to 8-year FU



- 115 pts without T315I. he median exposure duration was 5.9 y, with a maximum exposure of 8.4 y; 112 pts (97.4%) had received ≥2 prior TKIs and 82 (71.3%) had received ≥3 prior TKIs.
- While most responses were observed by wk 48, cumulative MMR rates continued to increase up to wk 144
- Among the 56 pts who achieved MMR, 50 maintained or improved the response up to data cutoff. At wks 24, 48, and 96, respectively, 18.9%, 17.9%, and **23.6% of pts achieved MR[4]** and 13.2%, 15.1%, **and 18.9% achieved MR[4.5]**.
- The most frequent all-grade AEs included arthralgia (40.9%), increased lipase (39.1%), fatigue (38.3%), and headache (38.3%), and only 13.0% of pts experienced AEs leading to Tx discontinuation.

Hughes et al ASH 2023, 450

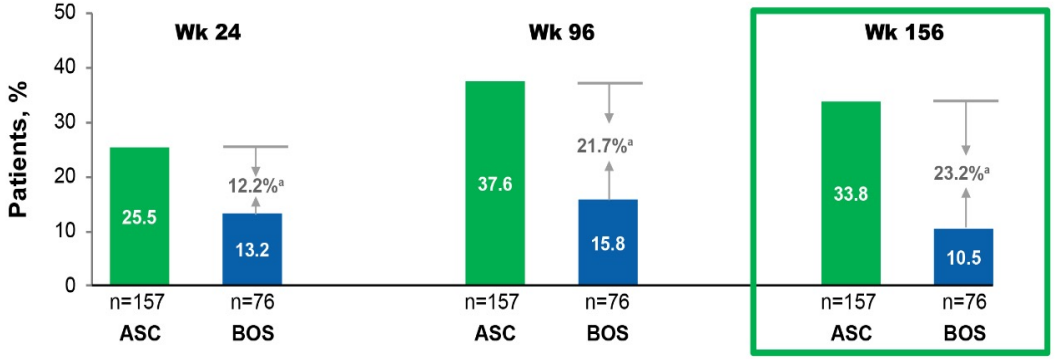
Asciminib in combination: phase 1 study



- Of 25, 26, and 32 pts in the ASC + IMA, ASC + NIL, and ASC +DAS arms, 25, 25, and 31, respectively, had CML-CP and 0, 1, and 1, respectively, had CML-AP. Only 2 pts in the ASC + DAS arm had the T315I mutation at screening.
- All grade arterial occlusive events (AOEs) were experienced by 3 (12.0%), 2 (7.7%), and 3 (9.4%) pts in the ASC + IMA, ASC + NIL, and ASC + DAS arms, respectively.
- **By wk 96**, major molecular response (MMR) was achieved by **45.0%, 31.8%, and 46.2% of MMR**-evaluable pts (excluding pts with atypical transcripts and those in MMR at baseline) in the ASC + IMA, ASC + NIL, and ASC + DAS arms, respectively.

Cortes et al ASH 2023, 868

ASCEMBL study: 156 weeks FU

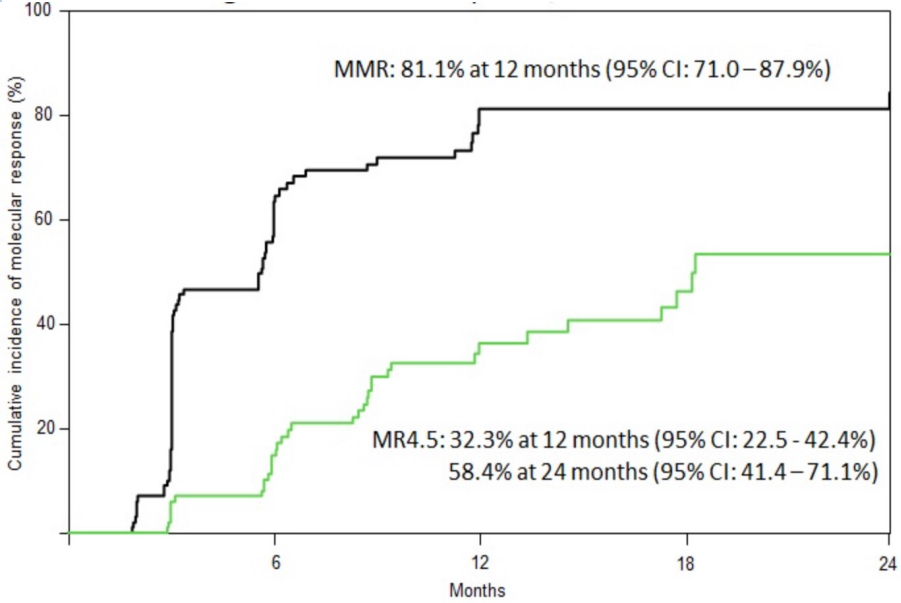


- 233 pts without T315I
- MMR rate at wk 156 continued to be higher with ASC (33.8%) than with BOS (10.5%)
- Safety/tolerability of ASC continued to be better compared with BOS and were consistent with previous analyses (8.3% vs 27.6%).
- Exposure-adjusted incidence rates of arterial occlusive events (AOEs) with ASC decreased since the wk 96 cutoff, from 3.0 to 2.2 per 100 pt-y, and no new AOEs occurred with ASC, indicating that the risk of AOEs did not increase over time.
- 28 pts switched from bosu to asc but none achieved MMR at week 48 (8% achieved <1%).

Mauro et al ASH 2023, 4536

ASCEND trial: median FU of 20 months

- Phase II trial
- Patients with treatment failure (*BCR::ABL1* >10% at 3 or 6 months; *BCR::ABL1* >1% at 12 or 18 months) continue asciminib and add other TKIs, according to physician preference; pts in suboptimal, 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
- **101 pts enrolled with a median FU of 20 months**
- Most common AEs reported were neutropenia (6%), thrombocytopenia (5%), increased amylase/lipase (8%)
- 15 pts discontinued: 2 case of resistance (1 sudden lymphoid BC with myristoilic site mutations)
- **EMR 93% MMR 48%**
- 6 pts escalated the dose



Yeung et al ASH 2023; 865

Olverembatinib: phase 2, randomized trial

- 76 pts
- Randomized 3:3:2 to olverembatinib 30, 40, 50 QD
- 51% received 4 or 5 previous TKIs
- 53% received ponatinib and 28% asciminib before
- 32% T315I mutated
- More common AES were: thrombocytopenia (17%); neutropenia (13.8%); elevated blood creatine phosphokinase (13.8%); leukopenia (7.7%); and anemia and elevated lipase (4.6% each).
- In CP (50 pts evaluable): CCyR 57%, MMR 43%

- The drug was effective in T315I mutated (MMR 44%) or WT, regardless the previous treatment with ponatinib or asciminib

- Good responses also in AP/BP/Ph+ ALL

CML-CP	Total	*T315I* mutation		Ponatinib pretreated		Asciminib pretreated	
		Positive	Negative	Resistant	Intolerant	Resistant	Intolerant
Efficacy population	50	16	34	16	6	8	2
Cytogenetic response							
No. of evaluable subjects-n	44	15	29	15	4	7	0
CCyR, n (%)	25 (56.8)	9 (60.0)	16 (55.2)	8 (53.3)	3 (75.0)	3 (42.9)	0
Molecular response							
No. of evaluable subjects-n	49	16	33	16	6	8	2
MMR, n (%)	21 (42.9)	7 (43.8)	14 (42.4)	6 (37.5)	1 (16.7)	3 (37.5)	0
Advanced Ph⁺ leukemia	Total	Positive	Negative	Resistant	Intolerant	Resistant	Intolerant
Efficacy population	13	5	8	9	2	6	0
Cytogenetic response							
No. of evaluable subjects-n	11	5	6	7	2	5	-
MCyR, n (%)	4 (36.4)	1 (20.0)	3 (50.0)	3 (42.9)	0	1 (20.0)	-
CCyR, n (%)	3 (27.3)	1 (20.0)	2 (33.3)	2 (28.6)	0	0	-
Molecular response							
No. of evaluable subjects-n	13	5	8	9	2	6	-
MMR, n (%)	3 (23.1)	1 (20.0)	2 (25.0)	2 (22.2)	0	0	-

Jabbour et al ASH 2023; 1798

Olverembatinib vs BAT: registrational phase 2 study in later lines

Table 1. Patient Characteristics and Response N = 144

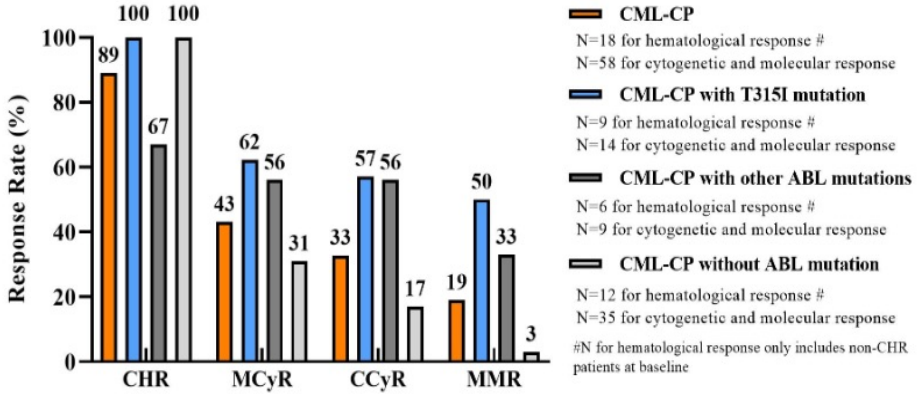
	Olverembatinib group (n = 96)	BAT group (n = 48)
Demographic and clinical characteristics of the patients at baseline in the ITT population		
Media age (range), yr	48.5 (18-77)	49.0 (24-75)
Sex, n (%)		
Male	70 (72.9)	30 (62.5)
Female	26 (27.1)	18 (37.5)
ECOG PS, n (%)		
0	56 (58.3)	25 (52.1)
1	39 (40.6)	22 (45.8)
2	1 (1.0)	0
Median time from diagnosis to randomization (range), yr	6.12 (0.3-19.2)	6.54 (0.6-17.5)
Treatment status of patients		
Median duration of treatment (range), mo	21.40 (0.6-40.9)	2.99 (0.2-40.4)
Discontinued treatment	56 (58.3)	41 (85.4)
Response rates, n (%)		
Hematologic response		
Evaluable patients	60	23
CHR	51 (85.0)	8 (34.8)
Cytogenetic response		
Evaluable patients	88	37
MCyR	42 (47.7)	11 (29.7)
CCyR	32 (36.4)	6 (16.2)
Molecular response		
Evaluable patients	88	37
MMR	24 (27.3)	3 (8.1)
[illegible]	[illegible]	[illegible]
$MR^{4.5}$	19 (21.6)	1 (2.7)
CMR	18 (20.5)	1 (2.7)

Data cutoff date: April 30, 2023

- 144 pts [96, olverembatinib; 48, BAT (TKIs, IFN, HU)] were enrolled (90% received >3 TKIs)
- 66 (45.8%) pts had >1 *BCR::ABL1* mutation and 39 (27.1%) *BCR::ABL1*^{T315I}
- Any-grade AEs (> 20% incidence) included thrombocytopenia; leukopenia; anemia; neutropenia; elevated CPK, ALT, and AST; and hypertriglyceridemia. Serious AEs (SAEs) (>5%) included thrombocytopenia. 7 SAEs related to olverembatinib were cardiac events.
- **Estimated EFS at 6, 12, and 24 months was 73%, 58.7%, and 46.9%, respectively. In the BAT group, it was 32.6%, 26.1%, and 16.9%, respectively.** Median OS was NR in either group.

Jiang et al ASH 2023; 869

TGRX-678: a novel allosteric TKI

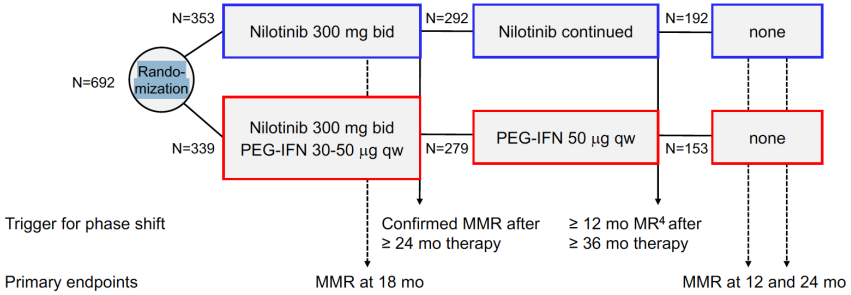


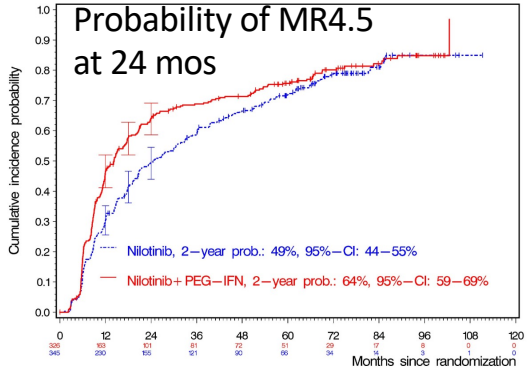
- It acts on myristoyl pocket (STAMP), WT and common mutations including T315I
- 95 pts treated (58 CP, 37 AP) with QD and BID escalating doses
- Median treatment duration 8 months
- 98% received > 2 TKIs, 30% with T315I
- In CP pts, 33% of CCyR and 19% MMR
- In pts with T315I, 57% in CCyR and 50% in MMR
- In pts previously treated with pona and asciminib, 22 pts (14%) reached a CCyR
- Most treatment-related adverse events (TRAEs) were grade 1-2. AEs ≥ grade 3 that happened more than 5% were thrombocytopenia (50%), neutropenia (42%), anemia (24%) and hypertriglyceridemia (9%).

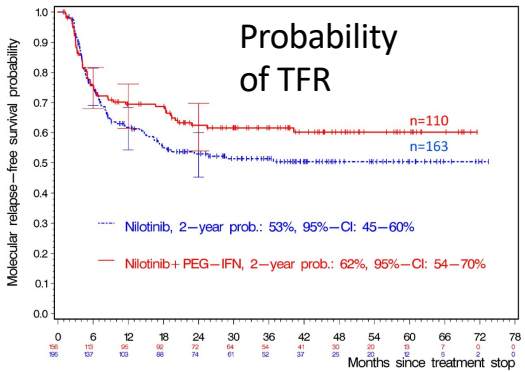
Jiang et al ASH 2023; 867

Ongoing trials

TIGER trial: nilo vs nilo+peg-IFN







- The combination is associated with a higher rate of DMR but also impaired tolerability.
- Grades 3-5 were arterio-vascular disorders in 9 vs 8%, fatigue in 2 vs 4%, thrombocytopenia in 8 vs 8%, and alanine aminotransferase elevation in 4 vs 9% of pts in the NIL vs NIL/IFN arms, respectively.
- QoL analyses revealed the perception of a decreased cognitive function and higher rates of fatigue in pts in the NIL/IFN arm, particularly in pts older than 40 years.

Hochhaus et al ASH 2023; 446

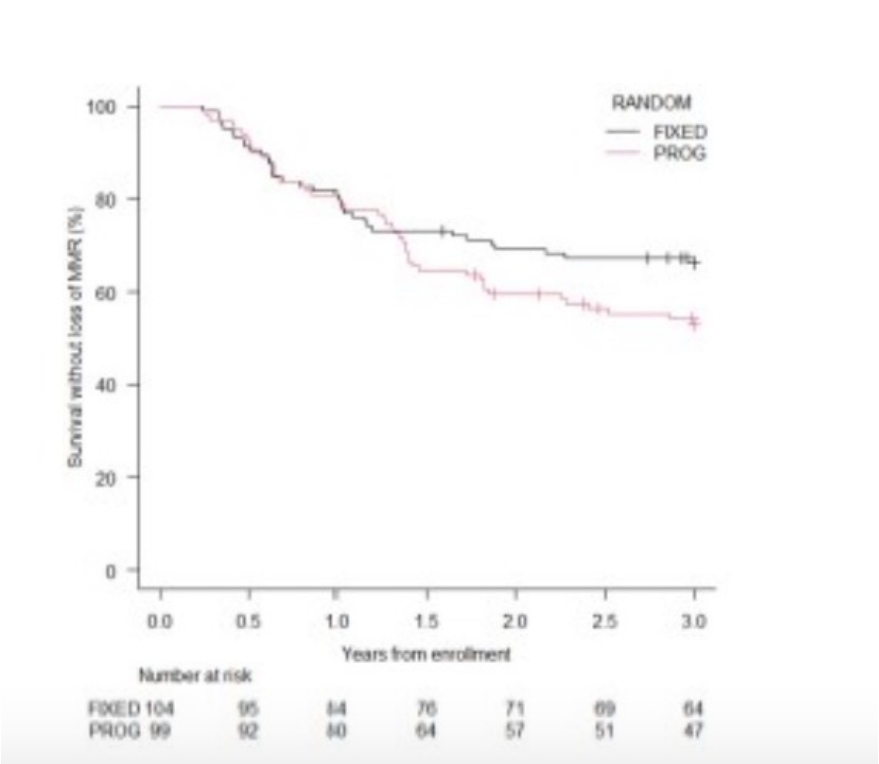
Dasa + venetoclax: phase 2 study in ND CP-CML

Responses	Dasatinib-single agent N=85	Dasatinib + Venetoclax N=65	*P*
Cumulative 12-month MMR, %	78	79	0.68
Cumulative 24-month CCyR, %	94	97	0.68
Cumulative 24-month MMR, %	88	93	0.76
Cumulative 24-month MR4, %	70	64	0.93
Cumulative 24-month MR4.5, %	63	53	0.62
Cumulative 24-month CMR, %	46	49	0.60
Survival			
2-year failure-free survival, %	92	96	0.13

- 65 pts enrolled
- 57% female, 5% high Sokal risk
- By 12 months of the combination, 85% of the pts had achieved MMR or deeper response. The median time to MMR, MR4, and MR4.5 were 6.2 months, 13 months, and 23.9 months from the time of TKI start, respectively.
- 2 pts discontinued therapy due to adverse events (GI intolerance, and pleural effusion)
- With a median follow-up of 2 years, the cumulative resposne of dasatinib + venetoclax is similar to that of dasatinib single-agent without adding significant toxicities.
- Further follow-up is needed for the evaluation of TFR.

Haddad et al ASH 2023; 870

3-years of OPTKIMA trial

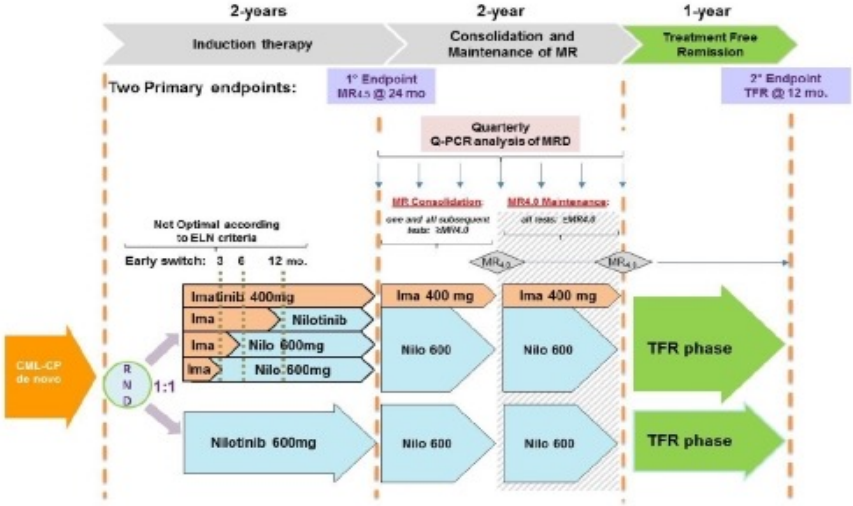


- Elderly patients in sustained (≥ 2 years) confirmed MMR or deep molecular response (MR4.0 or deeper) were randomly assigned to receive a FIXED intermittent schedule (1 month on/1 month off) vs a PROGRESSIVE intermittent schedule (1 month on/1 month off for the 1st year, 1 month on/2 months off for the 2nd year, 1 month on/3 months off for the 3rd year).
- 203 patients are evaluable after randomization (104 FIXED vs 99 PROGRESSIVE).
- At 3rd year (end of study protocol), by ITT, 28/104 (27%) and 45/99 (45%) patients discontinued OPTkIMA because of MR3.0 loss in the FIXED vs PROGRESSIVE arm (p=0.005).
- Clinicians' choice was to maintain the ongoing intermittent schedule in 46% vs 28% of the cases (p=0.01), discontinue TKI with the goal of TFR in 36% vs 58% (p=0.03), and resume the TKI continuously in 18% vs 14% of the patients (p=0.59).

Malagola et al ASH 2023, 3165

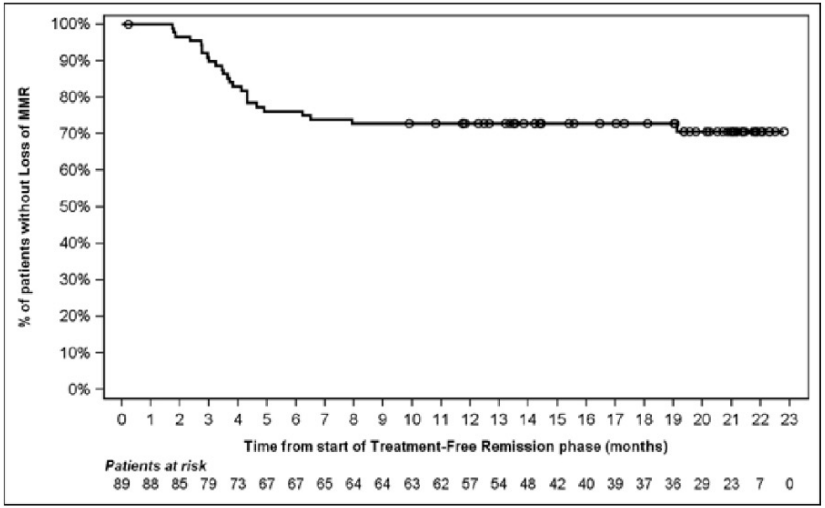
SUSTRENIM trial: eligibility to treatment discontinuation

- **289 pts had at least 48-month observation at the time of the present analysis and were evaluated for TFR eligibility**.
- **93 patients (32%) showed a sustained MR4 in the 4th year and were deemed eligible for treatment discontinuation, 45 in the IM arm (32%) and 48 in the NIL arm (32%). Of the remaining 196 patients, 59 did not have the criteria to discontinue treatment and 137 previously went off study.**
- Sustained MR4 achievement was significantly associated with low ELTS (81.7% vs 47.2% p<0.0001) and Sokal scores (50.5% vs 34.2%, p=0.008). There is a weak correlation to the age, being those eligible younger (median 52.5 vs 55 years, p=0.037).
- Within the IM arm, patients who switched to NIL were 60/141 (43%), 44 within the first 12 months and 16 after the first year; those patients had a lower probability of starting the TFR phase compared to patients continuing IM (22% vs 40%, p=0.025).



Pane et al ASH 2023, 3169

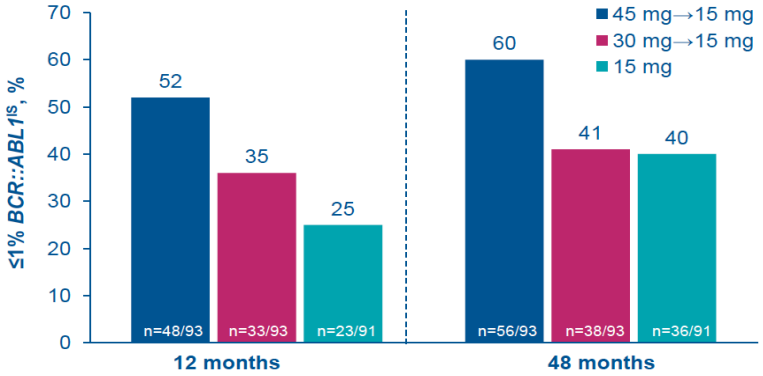
DANTE trial: 96-weeks of follow-up

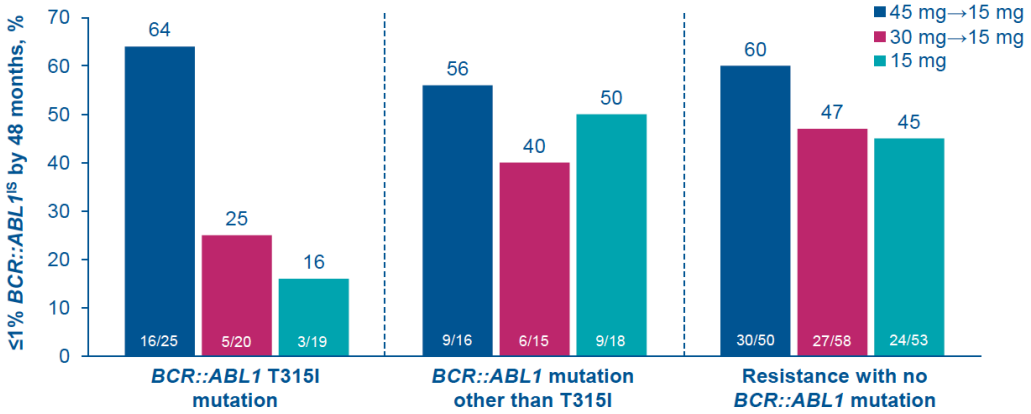


- Frontline NIL de-escalation in terms of full treatment-free remission (FTFR) (primary endpoint) and TFR rate (secondary endpoint) 96 weeks after the start of consolidation in CML-CP Italian patients.
- 98/107 (92%) completed the consolidation phase, while 9 pts discontinued permanently
- 89/107 (83%) with sustained DMR entered in the TFR phase, while 9 pts maintained MMR but not sustained DMR (7 entered in NIL half dose follow-up period and were in FTFR at 96 weeks, while 2 discontinued the study before week 96).
- At 1 year cut-off data, **71/107 pts (66.4%) were in FTFR**
- 64/89 pts **(72%) who entered in the TFR phase remained in MMR or better** after a median duration of 20.4 months (interquartile range [IQR] 1.9-32.4), meeting the main secondary endpoint of the study.

Iurlo et al ASH 2023; 4534

OPTIC trial at 48 months of FU





Characteristic	45 mg→15 mg (n=94)	30 mg→15 mg (n=94)	15 mg (n=94)
TE-AOEs, n (%)			
Any TE-AOE	11 (12)	8 (9)	4 (4)
Grade 3–4 TE-AOEs	6 (6)	7 (7)	4 (4)
Grade 5 TE-AOEs	0	0	0
Dose modifications for TE-AOEs, n (%)			
Discontinuation	5 (5)	4 (4)	1 (1)
Reduction	0	2 (2)	0
Interruption	3 (3)	5 (5)	2 (2)
Exposure-adjusted AOEs, patients with events/100 person-years (95% CI)	3.87 (1.45–6.30)	3.66 (1.11–6.20)	1.73 (0.02–3.44)

Cortes et al ASH 2023; 3164

Biological data

CHIP detected at the time of stop predicts TFR

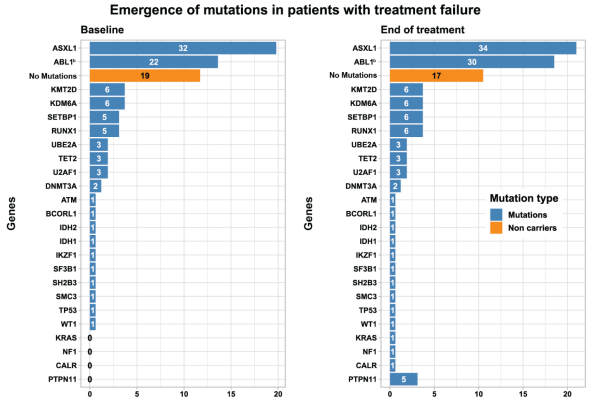
	n	β-coefficient	HR	95% CI	*P*	Concordance index
TFR 12 months						
CHIP^{TOC} vs No CHIP^{TOC}	150	1.31	3.70	1.55-8.88	**.003**	0.693
BCR::*ABL1* halving time, fast vs slow*	133	1.02	2.79	1.57-4.95	**.0005**	
BCR::*ABL1* transcript, e14a2 (+e13a2) vs e13a2	146	0.56	1.76	1.01-3.04	**.045**	
TFR 84 months						
CHIP^{TOC} vs No CHIP^{TOC}	150	0.67	1.95	1.01-3.78	**.047**	0.676
BCR::*ABL1* halving time, fast vs slow*	133	0.84	2.31	1.37-3.92	**.002**	
BCR::*ABL1* transcript, e14a2 (+e13a2) vs e13a2	146	0.55	1.74	1.04-2.90	**.036**	

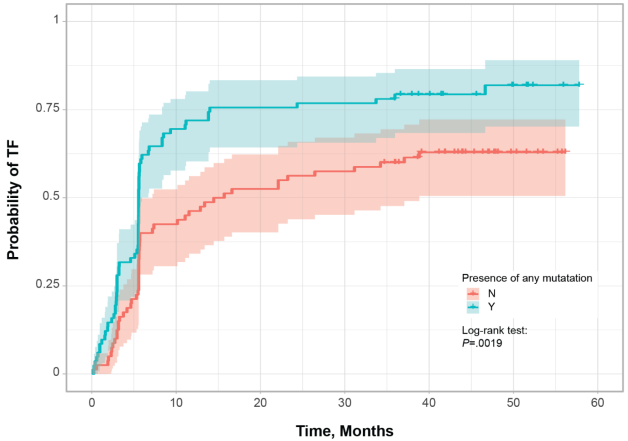
- 150 pts who attempt TFR
- CHIP at the time of cessation, termed CHIP^{TOC}, was defined as 1) **≥1 CHIP mutant with VAF ≥2.0%** (n=30 patients) or 2) **a novel criterion for patients with multiple CHIP mutants where the combined VAF was ≥2.0%** (n=7). Overall, 25/37 patients (68%) with CHIP^{TOC} had multiple mutations, range 2-7.
- CHIP^{TOC} was detected in 37/150 patients (25%).
- More frequently in elderly.
- Twelve genes were mutated and the most frequent were *TET2*, *DNMT3A*, *ASXL1* and *PPM1D*.

- **CHIP^{TOC} was associated with TFR**. At 84 months, 62.9% of patients with CHIP^{TOC} maintained TFR versus 49.6% of patients without CHIP^{TOC}, P=.014. The rate of late relapse, defined as loss of MMR >12 months after cessation, was higher in patients with CHIP^{TOC}.
- The independent predictors of TFR at 84 months were the presence of CHIP^{TOC} at TKI stop, a more rapid initial *BCR*::*ABL1* decline and the e14a2 (plus e14a2/e13a2) *BCR*::*ABL1* transcript type.

Branford et al ASH 2023; 447

ASCEMBL study: mutational analysis



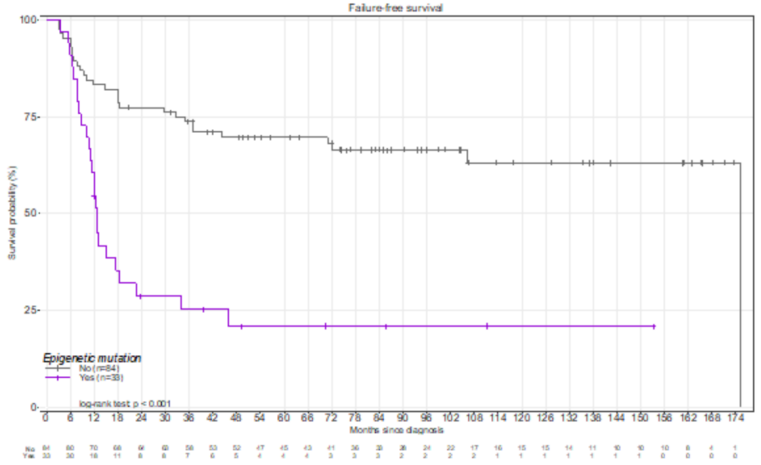


- Of 162 pts (ASC, n=110; BOS, n=52) with available sequencing data at BL, 102 had >1 mutation: 69 (63%) on ASC and 33 (63%) on BOS.
- Overall, 159 mutations were detected in 23 genes at BL, ranging from 0 to 5 per pt. The median variant allele frequency (VAF) was 19.6% (range, 0.9%-58%).
- *ASXL1* (in 31% of pts) and *ABL1* kinase domain (in 17% of pts) mutations were the most frequently detected.
- The presence of any mutation at BL was significantly prognostic of TF in the total cohort of 162 pts . In an unadjusted analysis, the presence of an *ASXL1* mutation with VAF >5% at BL was a prognostic factor of TF. In 73 pts with TF, most BL mutations were also detected at EOT (110/116 mutations in 48/54 carriers)

Branford et al ASH 2023; 449

Residiag study: mutation of epigenetic regulators at diagnosis

- 60 pts responders to TKIs sequenced using asymmetric capture sequencing (aCAP-Seq)
- CML patients who experienced treatment failure (ELN 2020) were sequentially analyzed at diagnosis and at failure (n=53), at diagnosis only (n=1), and at failure only (n=3). **At diagnosis, the number of mutations was higher (p<0.001) in the failure group (0.9±0.1) as compared with responders (0.18± 0.05).**
- ***ASXL1*, *DNMT3A*, and *TET2* were more frequently mutated at diagnosis in the failure group** (38.6%, p<0.001; 10.5%, p=0.01, and 4.3%, p=0.025 respectively) as compared with responders (6.7%, 0% and 0% respectively) and the presence of a mutation in one of these genes was highly associated with a reduced failure-free survival (p<0.001).
- **At first failure, 69% of patients had additional mutations in *ASXL1* (39%), *ABL1-TK* (38%), *DNMT3A* (18%), or *TET2* (15%),** while other genes were rarely (<5%) mutated. *ASXL1* mutations found at diagnosis were still detectable in 18/22 patients at failure and VAF suggested that double mutant *BCR::ABL1*/*ASXL1* clones were driving TKI failure with or without BCR::*ABL1* tyrosine kinase domain mutation (TKD).



Guerineau et al ASH 2023; 4540