Advances in Therapy

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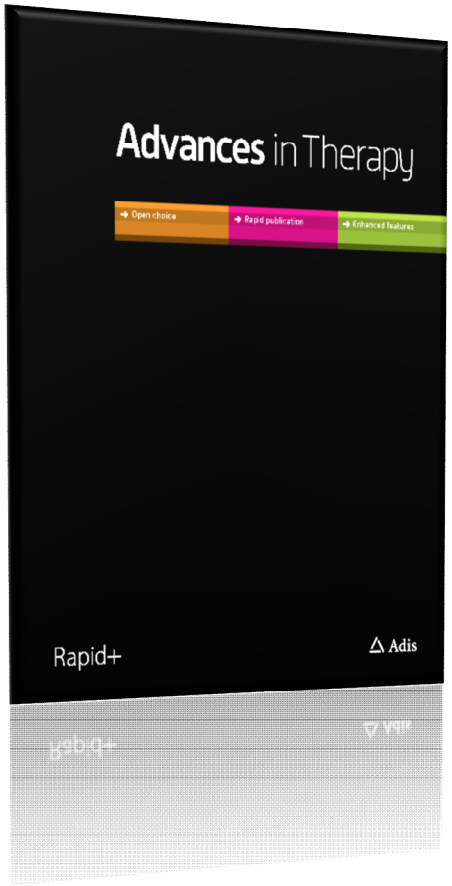


Breccia, M. Chronic Myeloid Leukemia Data at ASH 2021: A Podcast on Patient Unmet Needs and Later Line Treatment Developments. Adv Ther. 2022.

Podcast Title: CML: ASH 2021 podcast

This podcast represents the opinions of the authors. For a full list of declarations, including funding and author disclosure statements, please see the full text online.

Unmet Needs

- Sequential use of TKIs is associated with a decreased probability of response and worse overall survival.
- A second line of treatment with a second generation TKI rescued about 45-50% of patients.
- Available TKIs have off-target effects that can lead to long-term safety issues and about 20% of patients discontinued their treatment due to adverse events.

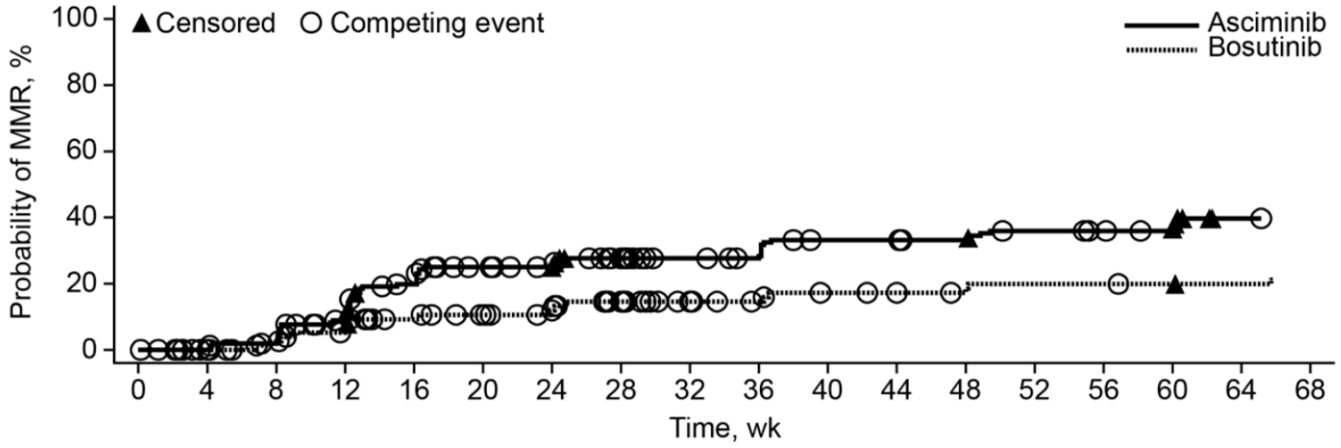
Clinical Resistance to Tyrosine Kinase Inhibitors

- Sequential treatment induces new mutations (T315I or compound mutations).
- T315I mutation frequency was reported ranging between 3 and 15%.
- Current option is ponatinib and allogeneic stem cell transplants.
- Allogeneic stem cell transplants have been suggested by international guidelines [1] in:
  1. Patients with poor response to a frontline second generation TKI followed by ponatinib
  2. Patients with the emergence of mutant clones poorly responsive to available TKIs
  3. Patients are intolerant to multiple TKIs or with inadequate recovery of normal hematopoiesis

Hochhaus A, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia

ASCEMBL: Update at 48 Weeks

- The cumulative incidence of major molecular response was **33.2% with asciminib and 18.6% with bosutinib.**
- The cumulative incidence of *BCR-ABL1*^{IS} ≤1% by week 48 in patients without this level of response at baseline was 50.8% with asciminib and 33.7% with bosutinib.
- **MR^4 and MR$^{4.5}$ rates were 14.0% and 9.6% with asciminib and 6.6% and 2.6% with bosutinib**, respectively.
- 91.0% of pts on asciminib and 97.4% of pts on BOS reported ≥1 all-grade AEs.
- The most common AEs leading to treatment discontinuation included thrombocytopenia (3.2%) and neutropenia (2.6%) in the asciminib arm and increased alanine aminotransferase (5.3%) and neutropenia (3.9%) in the bosutinib arm.



Mauro et al ASH 2021 abst 310

ASCIMINIB MAP in Russian Federation

- **39 pts** who received asciminib for at least 3 months (results presented on 32).
- 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.**

Table 1 Univariate analyses of factors for the 6 month MMR rate on asciminib therapy in highly pretreated CML patients (n=29)

Patients with no MMR at baseline		Number of pts (n=29)	CI MMR At 6 month (%)	p
Initial dose of asciminib, mg	80	20	25%	0,69
	400	9	22%	
History of the advanced phase of CML	CP	22	18%	0,13
	AP/BC	7(6/1)	43%	
History of BCR-ABL mutations	Wild type	12	17%	0,14
	Other than T315I	9	44%	
	T315I	8	13%	
Best molecular response any time before asciminib, BCR-ABL% IS	<1%	13	54%	0,0008
	1-10%	9	0%	
	> 10%	7	0%	
Molecular response at baseline	0,1-10%	9	44%	0,035
	> 10%	20	15%	
Nunber of TKIs before asciminib	2-4	20	30%	0,20
	≥5	9	11%	
Time on previous TKIs, years	≤ 8	14	21%	0,74
	> 8	15	27%	

Table 2 Adverse events in 32 CML patients on asciminib treatment

Adverse events	All grades, n (%)	Grade 1-2, n (%)	Grade 3-4, n(%)
Thrombocytopenia	5 (15)	1 (3)	4 (12,5)
Neutropenia	2 (6)		2 (6)
Pleural effusion	1 (3)	1 (3)	
Symptomatic epilepsy	1 (3)		1 (3)
Tremor	1 (3)	1 (3)	
Diarrhea	1 (3)	1 (3)	
↑ triglycerides	1 (3)	1 (3)	
↑ AST, ALT	2 (6)	2 (6)	
Total	14 (44)	7 (22)	7 (22)

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.

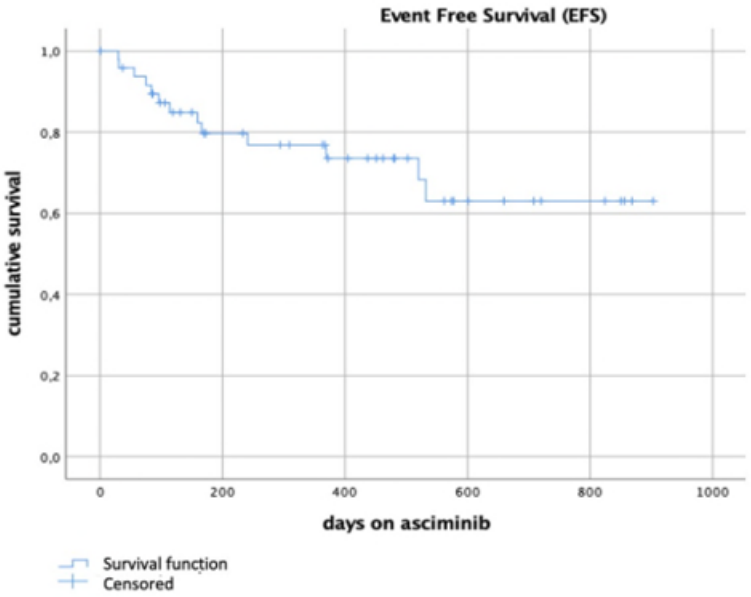


Tabla 2. Response to asciminib to last follow-up		Resistant (17)	Intolerant (30)	Total (47)
All patients	CHR[a], n(%)	14/17 (83,35)	30/30 (100)	44/47 (93,62)
	CCyR[a], n(%)	3/17 (17,65)	17/30 (56,66)	21/47 (44,68)
	MMR[a], n(%)	2/17 (11,77)	8/30 (26,67)	10/47 (21,28)
	MR4[a], n(%)	0/17	0/30	0/47
Patients 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

Vodobatinib: Update of Phase 1 Study

- 52 pts enrolled.
- 41 in a dose escalation and 11 in the dose expansion part.
- Thirty-one patients were resistant and 46% received more than 4 TKIs.
- 42 patients were evaluable for response and 24 patients achieved and/ or maintained a complete cytogenetic response, while 15 patients achieved an MMR.
- Most common any grade TEAEs included thrombocytopenia (33%), cough (19%), anaemia & diarrhoea (17% each). Ten (19%) pts reported cardiovascular TEAEs (only 1 related to the drug).

Table 2: Overall Efficacy Outcomes: Cytogenetic Response

Efficacy	Ponatinib treated (PT) N = 16	Ponatinib naïve (PN) N = 15
Cytogenetic Response		
Achieved CCyR	4** (25%)	7* (47%)
Maintained* CCyR	4 (25%)	3 (20%)
Achieved PCyR	3 (19%)	0 (0%)
Stable disease **	3 (19%)	1 (7%)
Progressive disease	2 (12%)	4 (26%)

*Where CCyR = Complete Cytogenetic Response, PCyR = Partial Cytogenetic Response; MCyR = Major Cytogenetic Response (PCyR + CCyR); * pts with intolerance,** Stable disease: Pt with less than MCyR maintaining hematological response; **2 pts were refractory and 2 were intolerant with loss of response; *5 pts were refractory and 2 were intolerant with loss of response;*

Table 3: Overall Efficacy Outcomes: Molecular Response

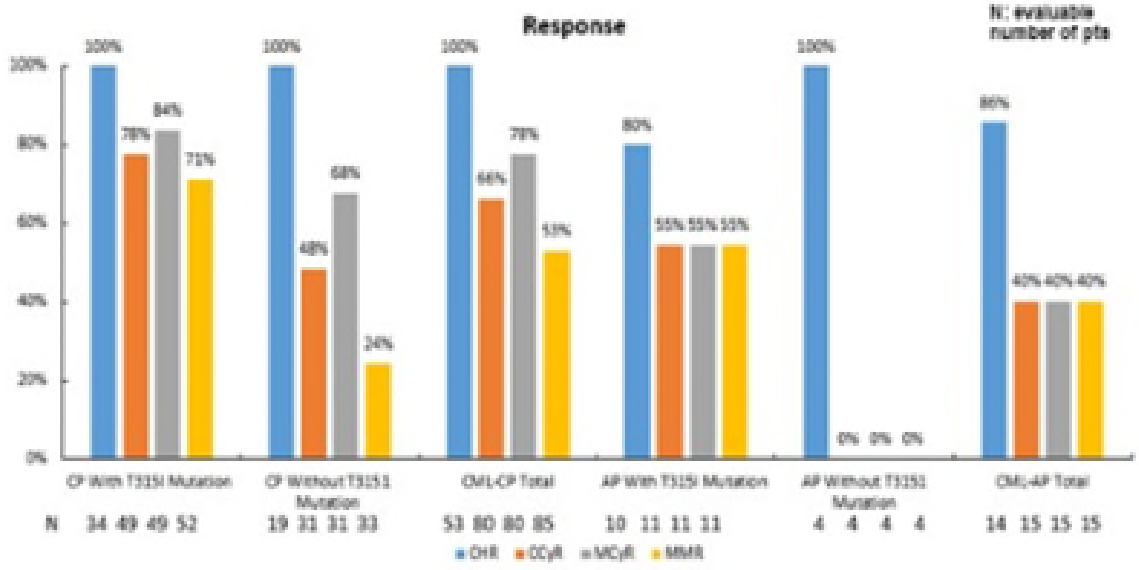
Efficacy	Ponatinib treated (PT) N = 16	Ponatinib naïve (PN) N = 15
Molecular Response		
Achieved DMR	2 (12%)	1 (7%)
Achieved MMR	3 (19%)	4 (26%)
Maintained* DMR	0 (0%)	1 (7%)

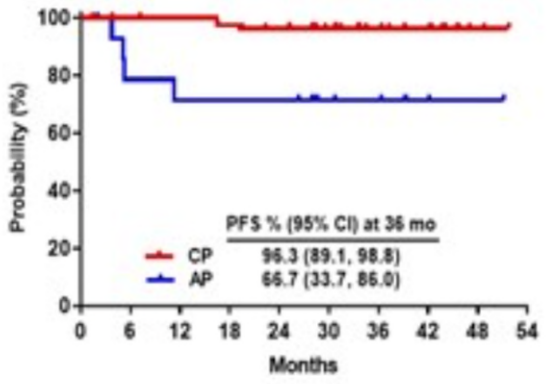
*DMR = Deep Molecular Response (<0.01 % IS BCR-ABL); MMR = Major Molecular Response (<0.1 % IS BCR-ABL); * pts with intolerance*

Cortes et al ASH 2021 abst 309

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.

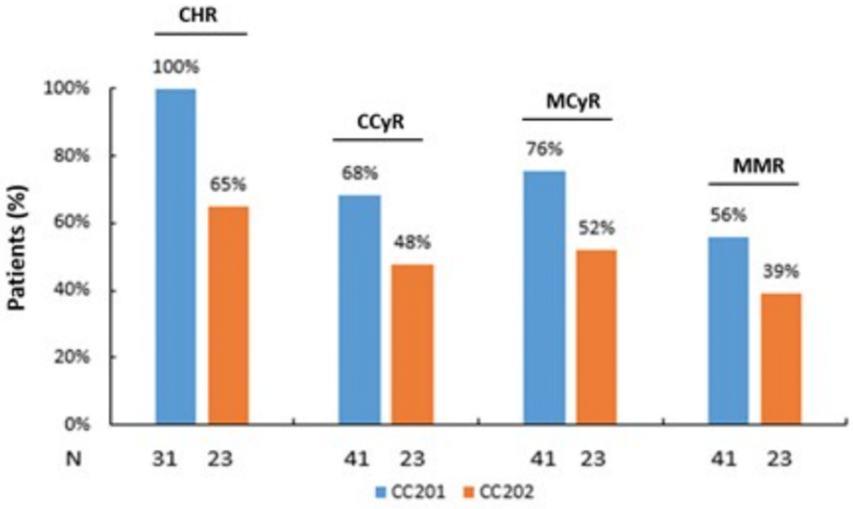




Qian et al ASH 2021 abst 311

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

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 and dose-limiting toxicity. 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 maximum tolerated dose was 600 mg with the grade-3 psoriasis-like skin AE as the dose-limiting toxicity. There were no vascular occlusive events or deviations of ankle-brachial index.

Turkina et al ASH 2021 abst 1482

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.

Table 1. Shift from Baseline by *BCR-ABL1* Transcript Levels in Patients with CP CML*

	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)

*Includes patients with a valid baseline assessment.

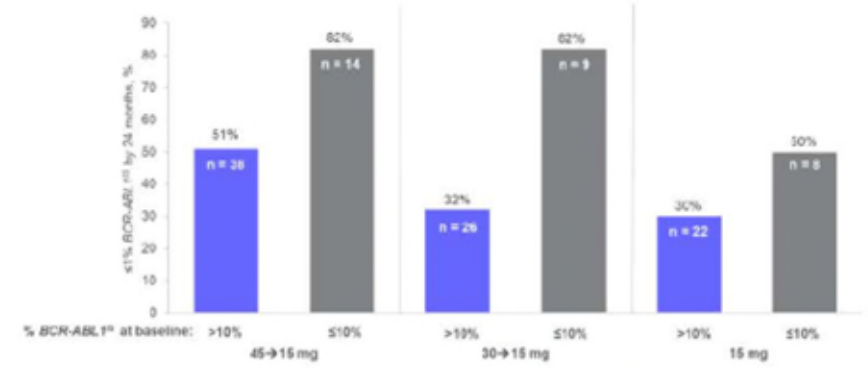
IS=international scale.

Gambacorti-Passerini et al ASH 2021 abst 1475

OPTIC: Responses According to baseline BCR/ABL1 Level and Mutation Status

- At baseline, 84.1% of pts had a high (>10% *BCR-ABL1* ^{IS}) disease burden; 23.8% had T315I mutation, 17.0% had a mutation other than T315I, and 57.8% had no mutation.
- Pts with T315I mutations had the highest ≤1% *BCR-ABL1*^{IS} response rates (60%) by 3 years with the 45 mg → 15 mg dose compared with the other cohorts.
- 97 pts without T315I mutations (ie, no mutation or with mutations other than T315I) achieved ≤1% *BCR-ABL1*^{IS}.
- Across all 3 cohorts, 79% of pts who achieved ≤1% *BCR-ABL1*^{IS} maintained this response during the study.
- Of those who lost response, 11 had T315I, 10/11 dose re-escalated; of those who re-escalated, 6/10 regained ≤1% *BCR-ABL1*^{IS} after dose re-escalation.

Figure 1. Response by baseline disease burden (% BCR-ABL^{IS} >10% or ≤10%)



	45 mg → 15 mg		30 mg → 15 mg		15 mg	
	No T315I mut	T315I	No T315I mut	T315I	No T315I mut	T315I
≤1% *BCR-ABL1*^{IS} by 3 years, n/N (%)	36 (54.5%)	15 (60.0%)	30 (41.1%)	5 (25.0%)	31 (43.7%)	2 (10.5%)
PFS at 3 years, %	71	75	75	49	74	61
OS at 3 years, %	90	86	93	79	94	85

Deininger et al ASH 2021 abst 307

OPTIC vs PACE: Dose Modification Dynamics

- 364 pts received 45 mg.
- Efficacy outcomes were generally comparable or better in OPTIC when compared with PACE, including ≤1% *BCR-ABL1*^{IS} response by 24 months (PACE, 52%; OPTIC, 56%), 2-year PFS (68%; 80%), and 2-year OS (86%; 91%).
- Median time to ≤1% *BCR-ABL1*^{IS} response, 5.6 months (PACE) and 6 months (OPTIC).
- Median relative dose intensity was 27 mg/d in PACE and 15 mg/d in OPTIC, and dose reduction occurred more rapidly compared with PACE median. Dose reductions due to AEs occurred in 82% of patients in PACE and 46% in OPTIC.
- A 60% reduction in relative risk for AOEs in OPTIC vs PACE was observed.

Figure. Median dose intensity over time

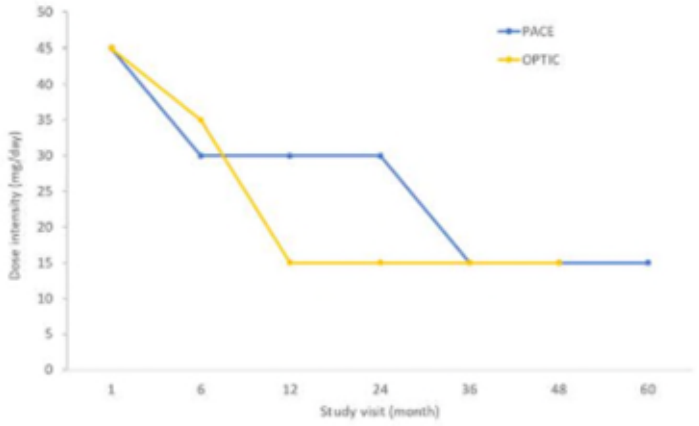


Table 2. Safety Summary

Safety Parameter	PACE CP-CML (N=270)	OPTIC 45 mg → 15 mg (N=94)
Any TEAE, n (%)*	270 (100)	94 (100)
Grade 3/4, n (%)	221 (82)	64 (68)
Exposure-adjusted AOEs (per 100 patient-years)		
0–1 y	15.8	7.6
1–2 y	15.1	5.9

*Data from analysis at 2 years.
AOE, arterial occlusive event; CP-CML, chronic-phase chronic myeloid leukemia; TEAE, treatment-emergent adverse event.

Jabbour et al ASH 2021 abst 2550

Impact on Patient Outcomes

- Considering the subset of patients resistant or intolerant to several treatments, the results of these new agents seem promising.
- Too early to define an algorithm of treatment, even according to the type of resistance and type of mutations.
- Most of the drugs are very selective and the toxicity seems to be limited to few events with a reduced rate of grade 3/4.
- And until now off-target effects were not reported.

Abbreviations

- AEs = adverse events
- AOEs = arterial occlusive events
- AP = accelerated phase
- BP = blast phase
- CCyR = Complete Cytogenetic Response
- CHR: complete hematologic response
- CML = Chronic Myeloid Leukemia
- CP = chronic phase
- MaHR: major hematologic response
- MCyR = Major Cytogenetic Response
- MMR = Major Molecular Response
- MR = molecular response
- OS = Overall Survival
- PCyR = Partial Cytogenetic Response
- PFS: progression-free survival
- Pts = Patients
- TEAE = Treatment emergent adverse events
- TKIs = Tyrosine Kinase Inhibitors

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