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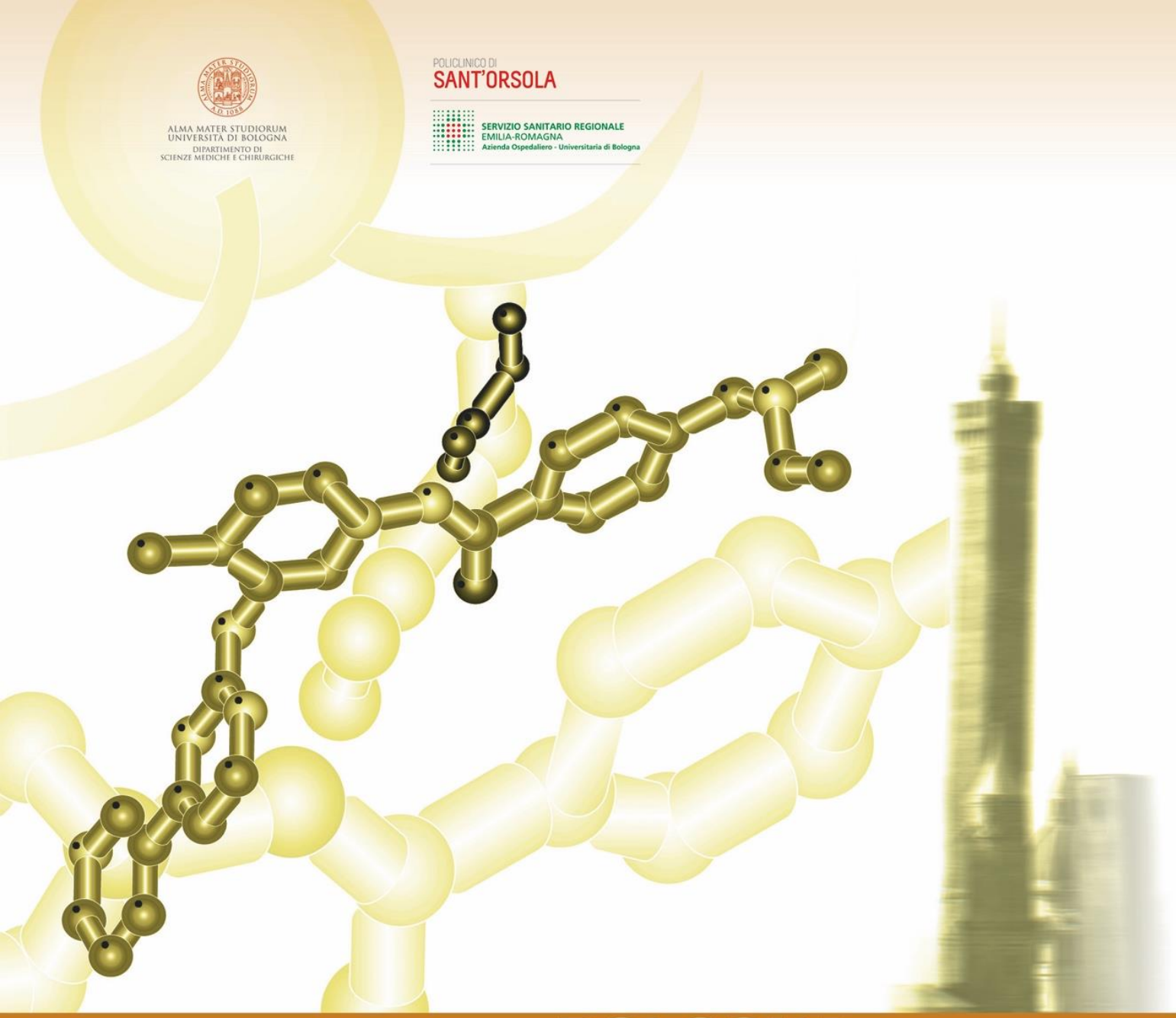

# New Drugs in Hematology

**President:** Pier Luigi Zinzani

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**Bologna,**
**Royal Hotel Carlton**
**January 15-17, 2024**

BOLOGNA BOLOGNA, ROYAL HOTEL CARLTON

**New Drugs in Hematology**
**Session VIII CML**
**January 15-17, 2024, Bologna, Italy**

# Chronic myeloid leukemia: asciminib

Dr Delphine Rea, MD, PhD

Département Médico-Universitaire d'Hématologie et Immunologie

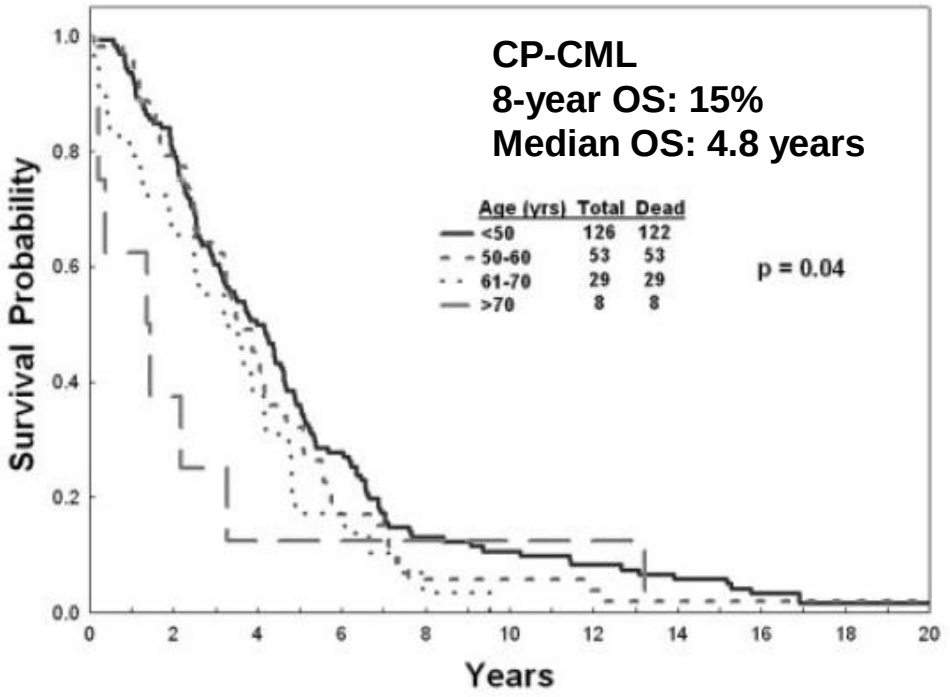
Hôpital Saint-Louis, Paris, France

# Disclosures of Dr Delphine REA

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| Novartis | | | X | | | X | X |
| Incyte | | | | | | | X |
| Pfizer | | | | | | | X |
| Terns | | | X | | | X | |

# Improved survival in CML with ATP-competitive TKIs

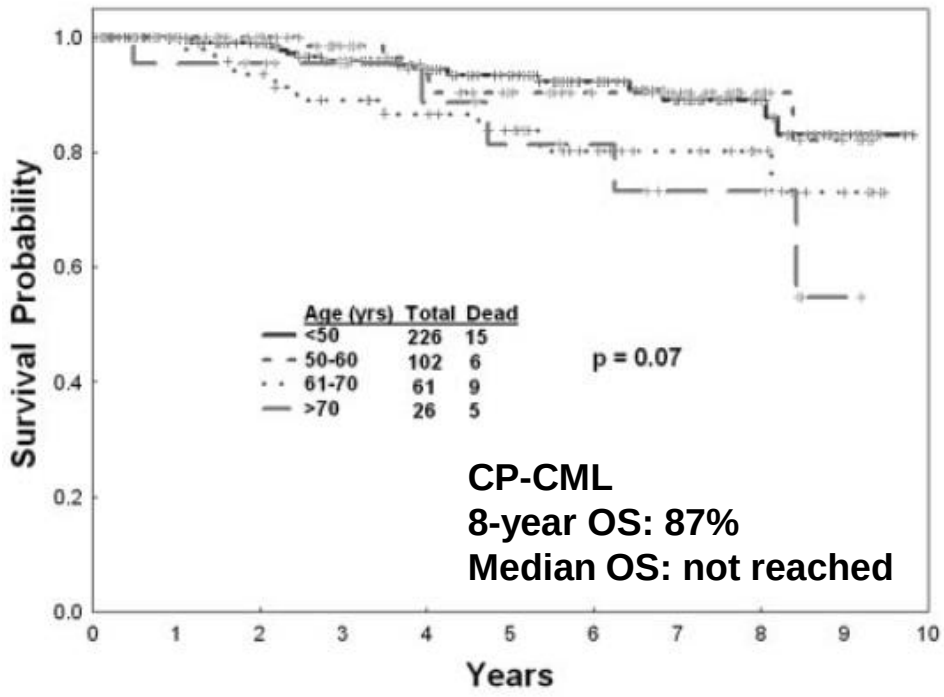
**Before 1983**





**Imatinib**
**Bosutinib**
**Dasatinib**
**Nilotinib**
**ponatinib**

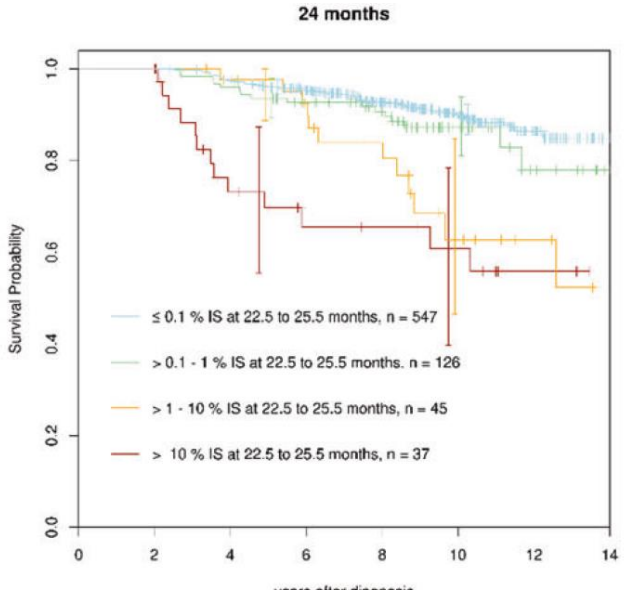
**Since 2001**




Kantarjian H, et al. Blood 2012; 119(9): 1981-1987.

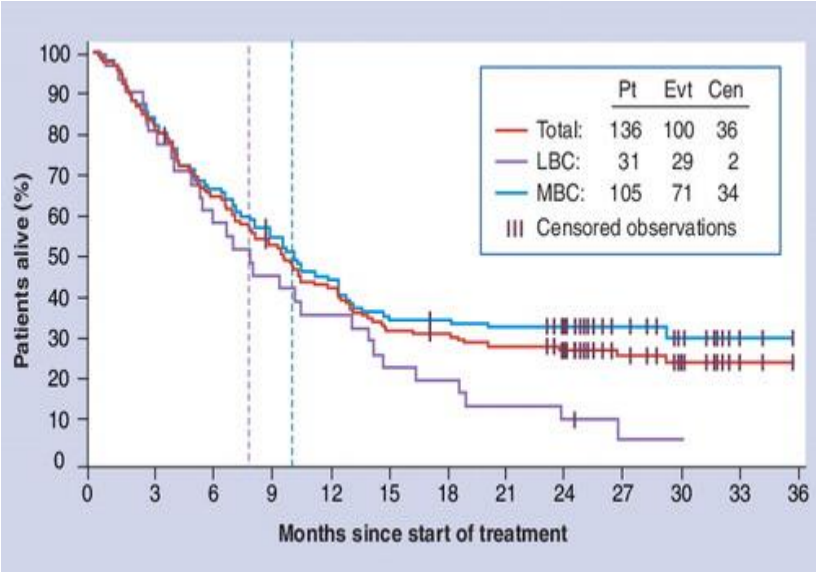
# Problems with ATP-competitive TKIs

## 1. Survival inferiority if resistance



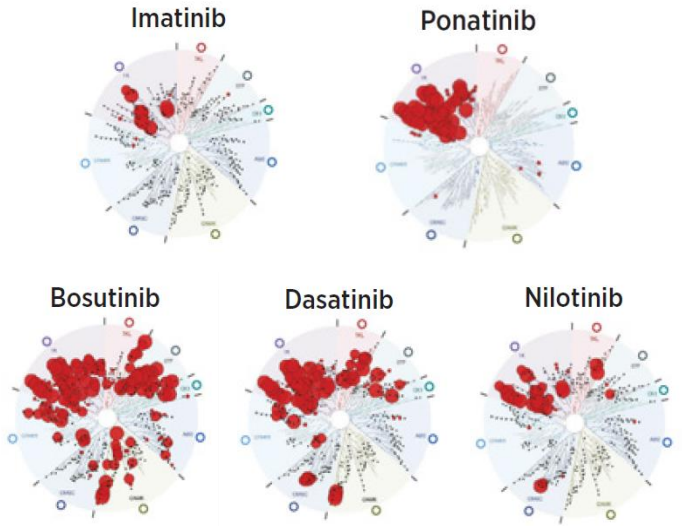

**OS in patients failing optimal/warning milestones**
**at 24 months: 55% at 10 years**

## 2. Survival inferiority if progression




**Median survival: 10.5 months**

## 3. Drug-related adverse: morbidity and reduced QoL




**Highly conserved structures of ATP sites: poor selectivity**

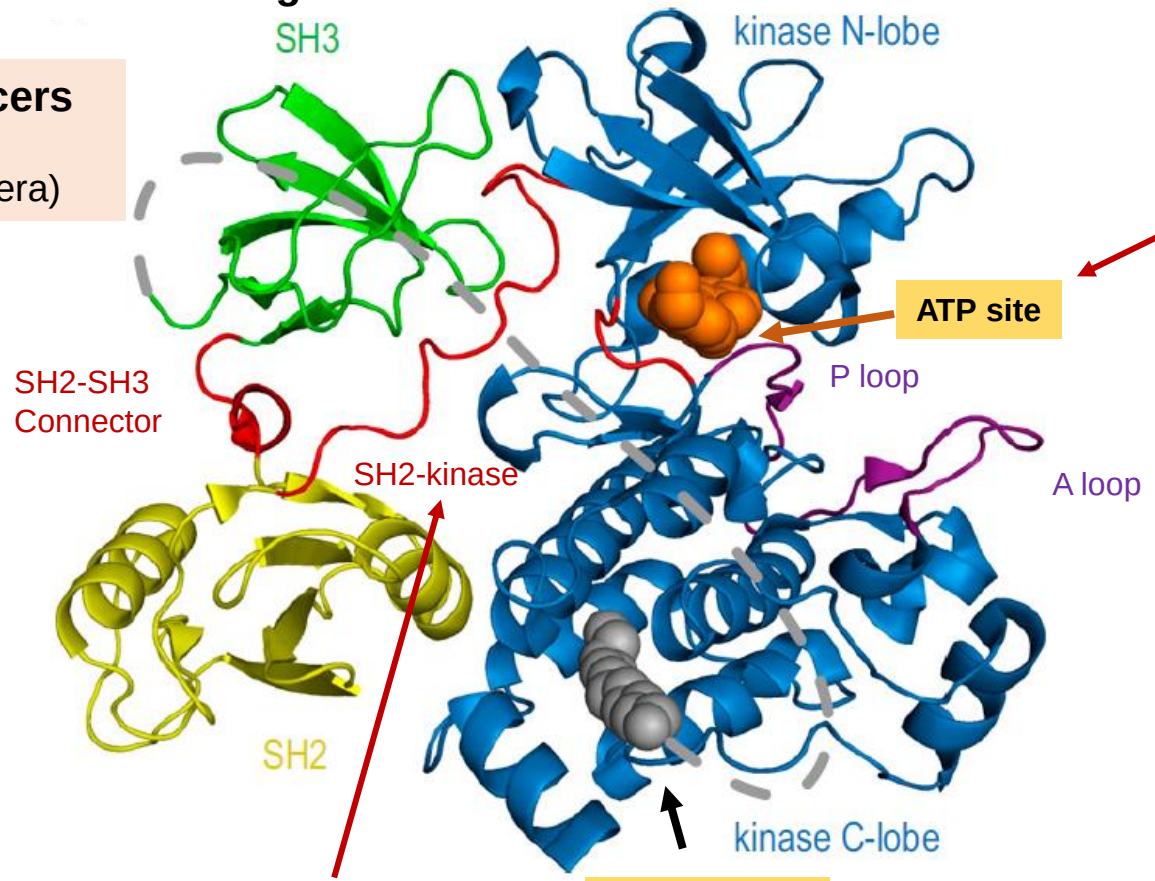
## 4. Functional cure only for a minority


Lauseker M, et al. Leukemia 2023; 37: 2231-2236.
Wilson LJ, et al. Cancer Res 2017; 78(1): 15-29.
Larson RA, et al. Leukemia 2012; 26: 2197-2203.

# Approaches to inhibiting BCR::ABL1

## *An expanding treatment landscape*

**C-ABL1 fragment 83-534**




**BCR::ABL1 degradation inducers**
Omacetaxine
PROTAC (proteolysis targeting chimera)

**Active site targeting**

**Orthosteric inhibition: ATP-competitive TKI**
Imatinib
Bosutinib
Dasatinib
Nilotinib
ponatinib

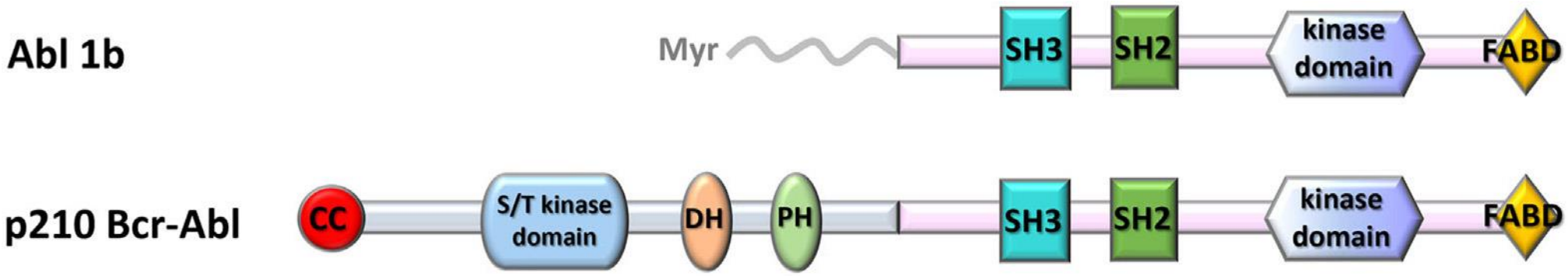
**Regulatory site targeting**

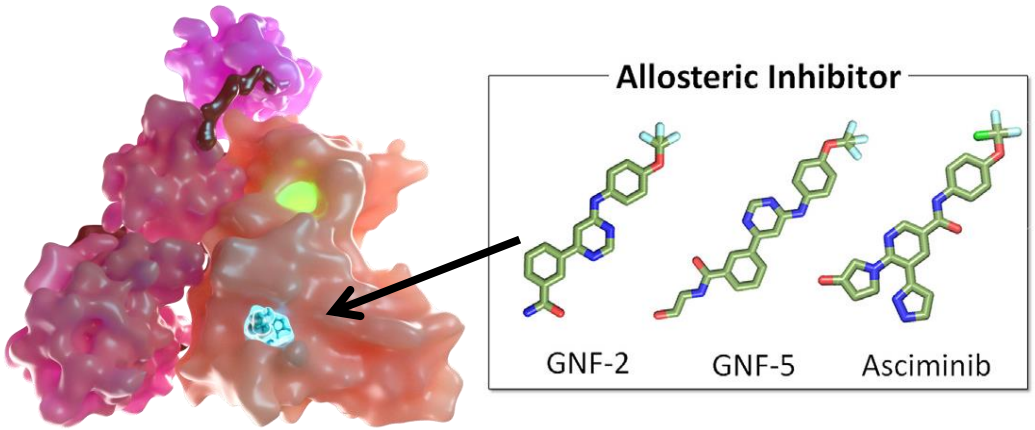
**Allosteric inhibition**
Asciminib
TERNS 701
TGRX 678

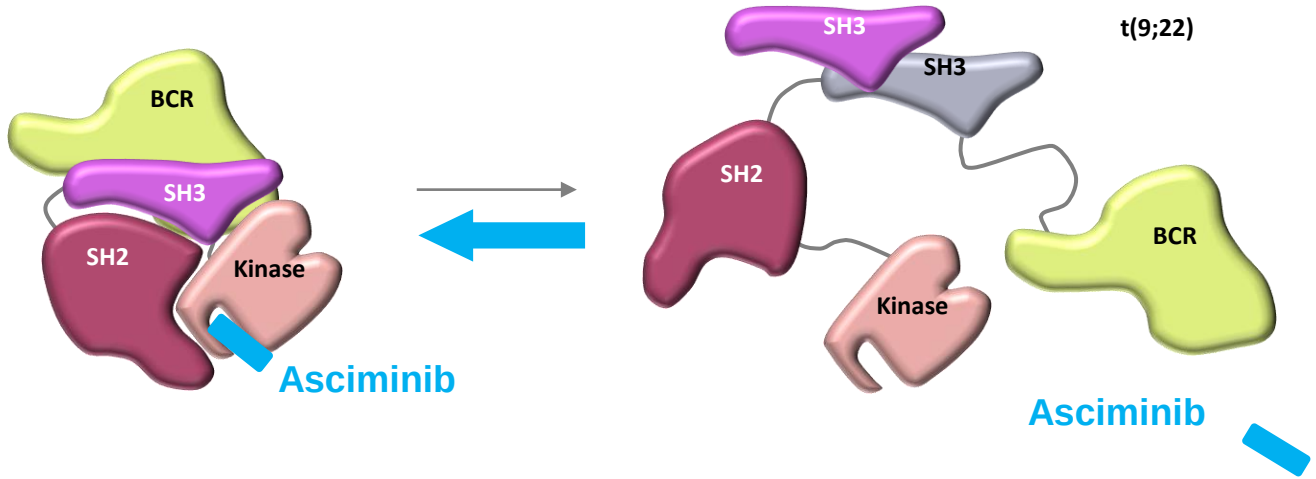
**Disruption of the SH2 kinase interface**

Grebien F, et al.Cell 2011; 147: 306-319.

# Asciminib: mechanism of action




Inactive

Active

**Asciminib allosterically inhibits BCR::ABL1 kinase activity**

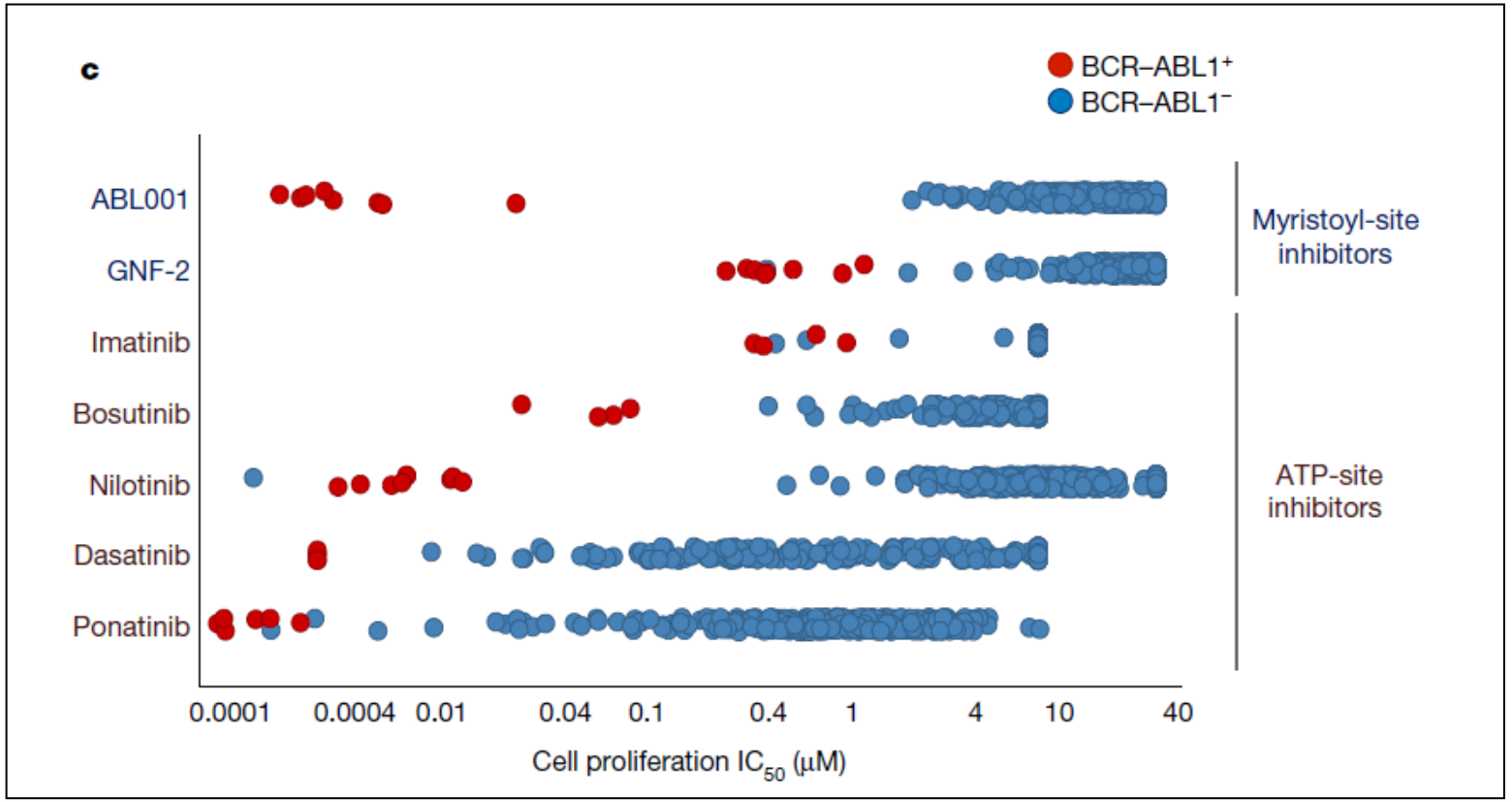

Skora et al. PNAS 2013; 110: E4437-E4445.
Wylie et al. Nature 2017; 543: 733-737.
Zhang et al. Nature 2010; 463: 501-506.
Liu Y, et al. Computational and Structural Biotechnology Journal 20 (2022) 4257–4270
Nussinov R, et al. Journal of Molecular Biology 2022; 434(17):167569.

# Potency and selectivity of asciminib in vitro

**Activity of ABL001 in biochemical assays**

| Kinase assay | IC50 (mM) |
|---|---|
| ABL1 | 0.00045 |
| ALK | >10 |
| BTK | >10 |
| FGFR1-R4 | >10 |
| FLT3 | >10 |
| JAK1-2 | >10 |
| KIT | >10 |
| LCK | >10 |
| LYN | >10 |
| PDGFRA | >10 |
| SRC | >10 |
| ZAP70 | >10 |

**Anti-proliferative activity *in vitro***




Adapted from: Wylie et al. Nature 2017; 543: 733-737.

# Development of single agent asciminib in humans

## Achieved

Phase 1 FIH trial
2014-2022
X2101

→

Phase 3 trial in CP-CML 3rd line setting or beyond
A2301 (ASCEMBL)

→

Approval
in CP-CML 3rd line setting or beyond
2022 (EU)

## Ongoing

Optimization trial in the 3rd line setting or beyond
A2302

Phase 3 registration trial(s) in 1st line
J2301
J2302

Pediatric setting

## Lacking

High dose T315I (EU)
2nd line setting

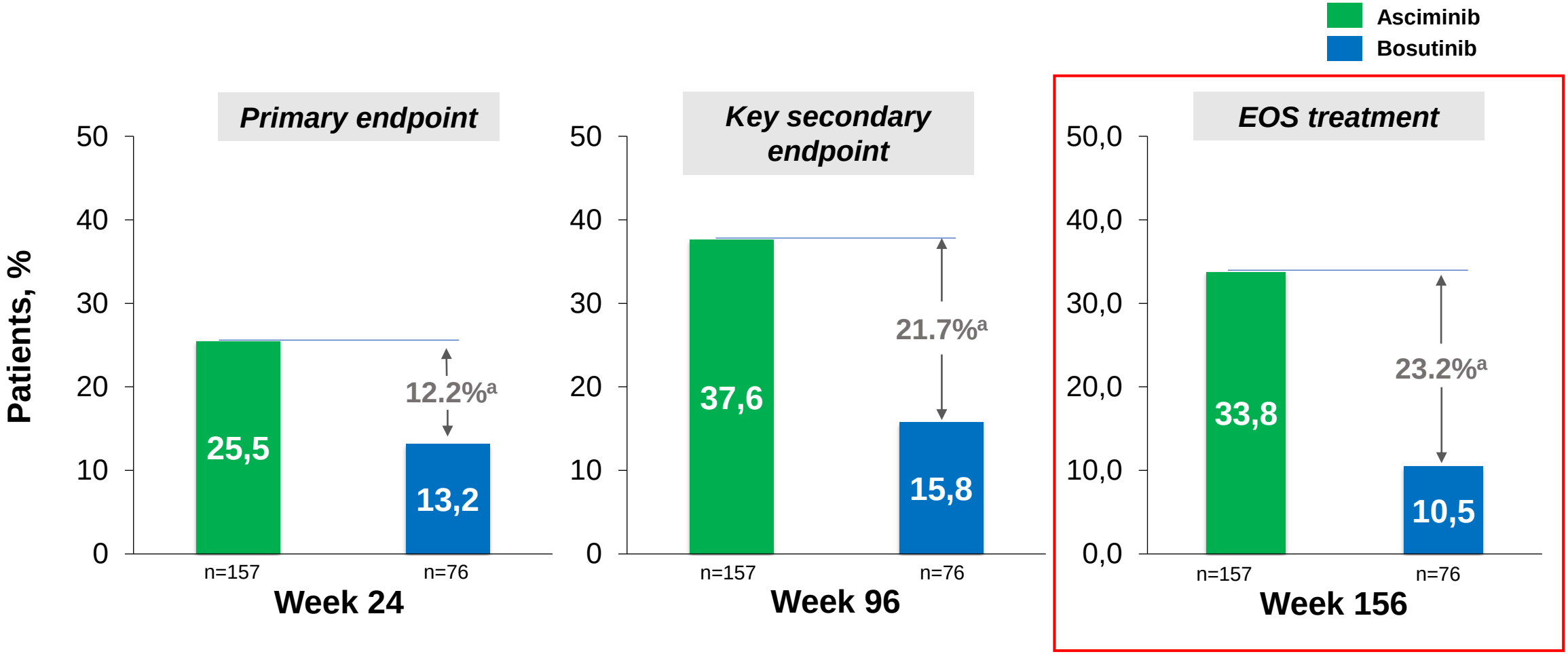
# Asciminib: recommended doses and pharmacology

| | Asciminib |
|---|---|
| Dose range during FIH study | 10mg QD to 200mg BID |
| DLT, MTD | None |
| Year of 1st approval | 2021 USA, 2022 Europe |
| Approved dose 3rd line non-T315I | 40mg BID (80mg QD under evaluation) |
| Approved dose T315I (USA only) | 200mg BID |
| Absorption | Max within 2h post dose, 33% to 57% |
| ↑by fatty food (800-1000kcal, 50% lipids taken within 30 min) | Yes |
| ↓ by ↑ gastric pH | No |
| Half life | 11.7 h |
| Main metabolizing enzyme | UGT 2B7, CYP3A4 |
| Elimination | Biliary fecal route |
| Hepatic or renal impairment | No effect |

Hughes T, et al. NEJM 2019; 381: 2315-2326.
Hoch M, et al. J Clin Pharma 2021; 6(11): 1454-1465.
Hoch M, et al. Clin Pharmacol Drug Dev 2021; 11(2): 207-219.
Tran P, et al. Xenobiotica 2019; 50:2: 160-179.

# ASCEMBL TRIAL

## MMR Rates at Weeks 24, 96, and 156

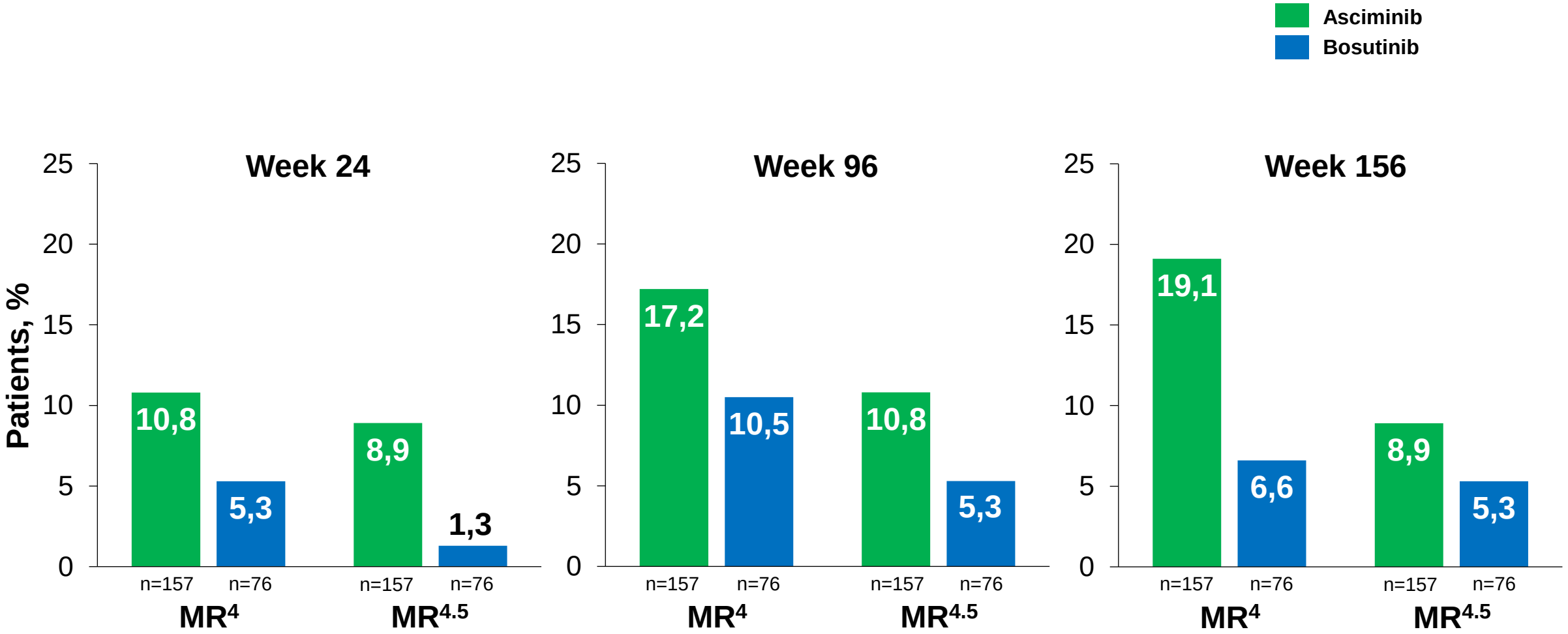



[a] The treatment difference after adjusting for the baseline MCyR status, was 12.2% (95% CI, 2.19%-22.3%; 2-sided *P*=0.029) at Week 24**,** 21.74% (95% CI, 10.53%-32.95%; two-sided *P*=0.001) at Week 96**,** and 23.16% (95% CI: 13.14, 33.18; 2-sided *P*<0.001) at Week 156.

Mauro MJ, et al. ASH 2023. Poster 4536.

# ASCEMBL TRIAL

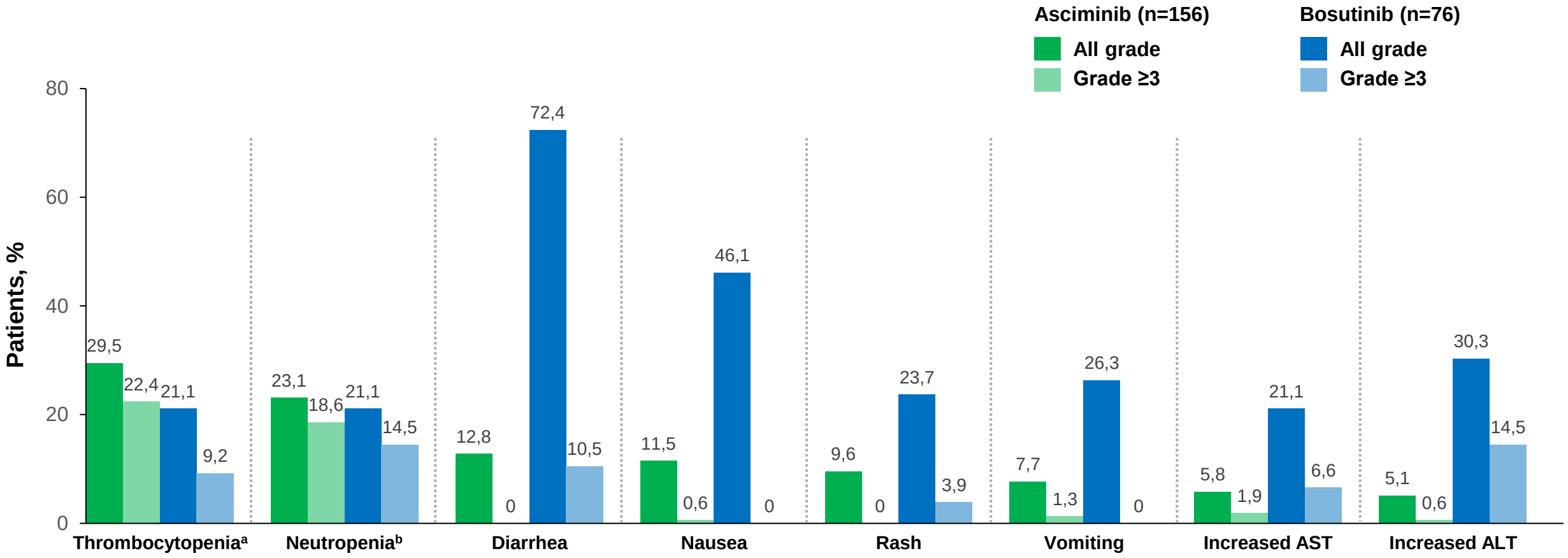
## $MR^4$ and $MR^{4.5}$ Rates at Weeks 24, 96, and 156




Mauro MJ, et al. ASH 2023. Poster 4536.

# ASCEMBL TRIAL

## Most Frequent AEs By the End of Study Treatment Cutoff (in ≥20% of Patients in Any Treatment Arm)




[a] Includes thrombocytopenia and platelet count decreased.
[b] Includes neutropenia and neutrophil count decreased.

Mauro MJ, et al. ASH 2023. Poster 4536.

# ASCEMBL TRIAL

## Mutations at Baseline and Best Response by End Of Study (W156 )

| Mutation at baseline[a] | Asciminib 40 mg twice daily | | | |
|---|---|---|---|---|
| | All patients, n | Best response[e] | Discontinued treatment | Mutations at end of study treatment |
| **Patients with any mutation** | **17** | | **17** | **9** |
| **G250E[b]** | 1 | MMR or better | Yes | None detected |
| | 1 | MMR or better | Yes | None detected |
| Y253H[b] | 1 | *BCR::ABL1*$^{IS}$ >10% | Yes | Y253H |
| | 1 | MMR or better | Yes | None detected |
| **E255K[b]** | 1 | MMR or better | Yes | None detected |
| | 1 | MMR or better | Yes | None detected |
| **E255V[b]** | 1 | MMR or better | Yes | None detected |
| F317L[b] | 1 | *BCR::ABL1*$^{IS}$ >1% to ≤10% | Yes | E355G[f] |
| | 1 | *BCR::ABL1*$^{IS}$ >10% | Yes | F317L |
| **F359C[b]** | 1 | *BCR::ABL1*$^{IS}$ >10% | Yes | F359C |
| **F359V[b]** | 1 | *BCR::ABL1*$^{IS}$ >1% to ≤10% | Yes | F359V |
| | 2 | *BCR::ABL1*$^{IS}$ >10% | Yes | F359V |
| E459K[c] | 1 | *BCR::ABL1*$^{IS}$ >10% | Yes | None detected |
| W478R[d] | 1 | MMR or better | Yes | None detected |
| L248V/F317L[b] | 1 | *BCR::ABL1*$^{IS}$ >0·1% to ≤1% | Yes | F317L |
| Y253H[b]/F486S[d] | 1 | *BCR::ABL1*$^{IS}$ >10% | Yes | M244V[g] |
| M244V[b] | – | – | – | – |
| Q252H[b] | – | – | – | – |
| F359I[b] | – | – | – | – |
| R473Q[d] | – | – | – | – |

Mauro MJ, et al. ASH 2023. Poster 4536.

# ASCEMBL: *BCR::ABL1* mutations[a] at study discontinuation

**Patients discontinuing asciminib due to lack of efficacy or disease progression**

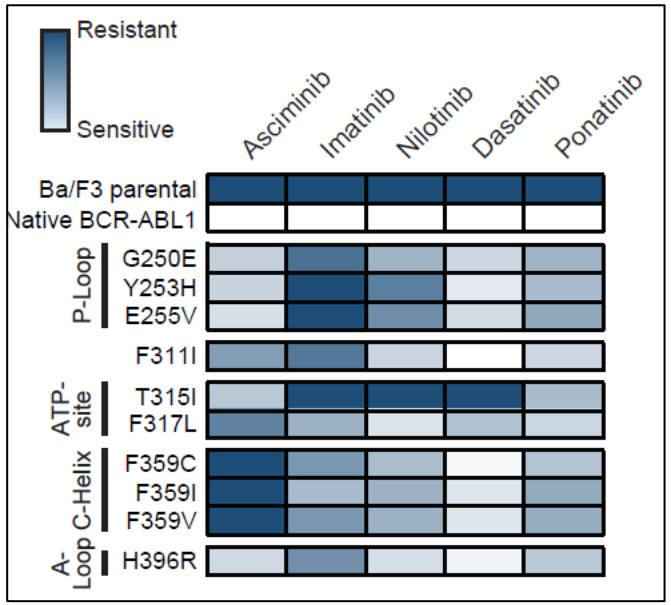
| n (%) | Asciminib 40 mg twice daily (n=39) |
|---|---|
| No mutations detected at end of treatment | 22 (56.4) |
| Missing assessments at end of treatment | 1 (2.6) |
| Mutations detected at end of treatment | 16 (41.0) |
| **Newly emerging mutations at end of treatment** | **10 (25.6)** |
| ATP-binding site | • **M244V (n=3)[b]**<br>• **E355G (n=1)[c]**<br>• **F359V (n=1)**<br>• **T315I (n=1)** |
| Myristoyl pocket | • **A337T (n=3)**<br>• **P465S (n=1)** |
| **Mutations at baseline and end of treatment** | **6 (15.4)** |
| ATP-binding site | • **F317L (n=2)**<br>• **F359C/V (n=3)**<br>• **Y253H (n=1)** |

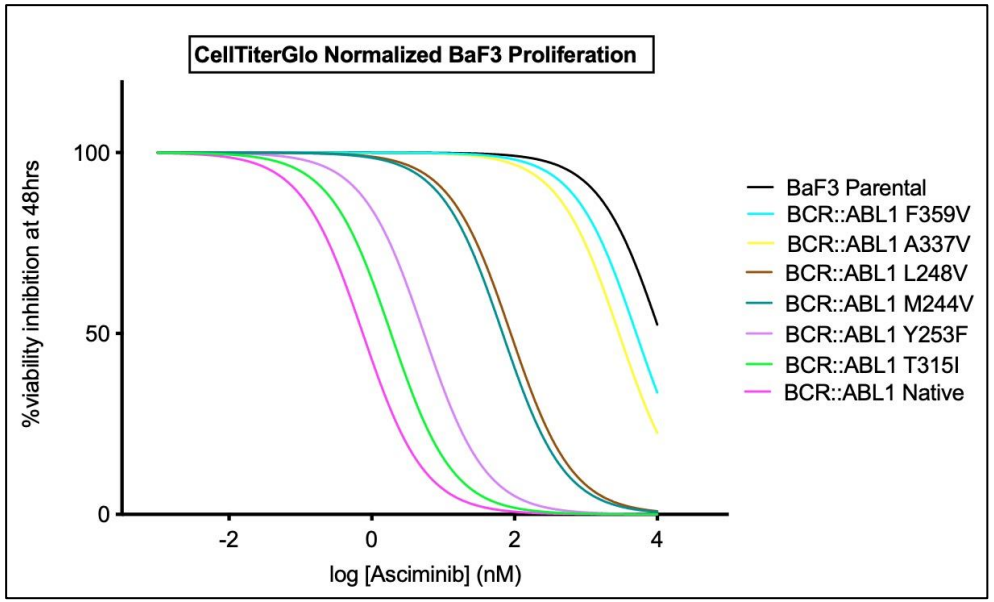
[a] Determined by Sanger sequencing, mutation analysis was performed on week 1 day 1 and at the end of treatment. In case mutations were detected on week 1 day 1, additional assessments were performed every 12 weeks during the study.
[b] 1 patient had Y253H and F486S mutations at baseline that were not detected at the time of discontinuation.
[c] Patient had the F317L mutation at baseline, which was not detected at the time of discontinuation.

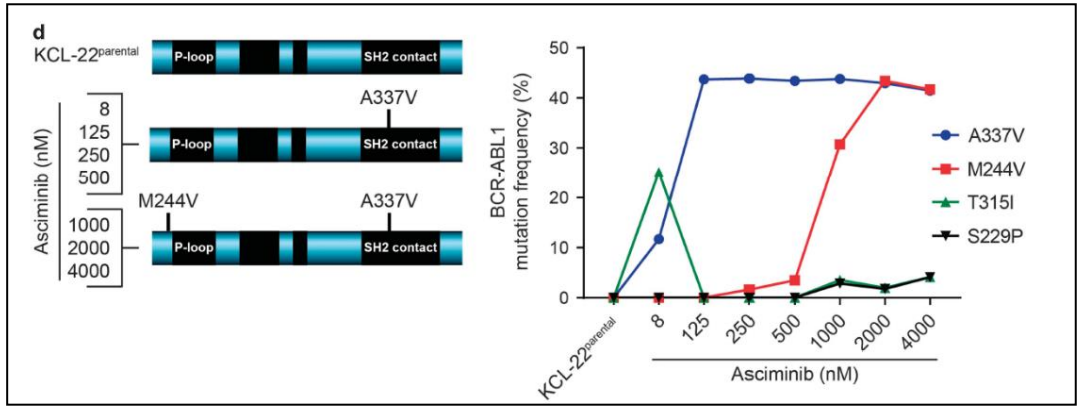
Rea D, et al. EHA 2022. Oral presentation: (EHA) 4005

# Asciminib in case of ABL1 point mutations

| BCR::ABL1 | Asciminib<br>Growth inhibition of BCR-ABL1 transfected Luc-Ba/F3 cells (mean $IC_{50}$ value nM ± SD) |
|---|---|
| wild-type | 0.61 ± 0.21 |
| G250H | 0.74 ± 0.27 |
| E255V | 1.17 ± 0.54 |
| Y253H | 1.71 ± 0.75 |
| E255K | 2.35 ± 0.71 |
| E459K | 3.01 ± 1.37 |
| V299L | **6.12 ± 4.21** |
| T315I | **7.64 ± 3.22** |
| E355G | **9.33 ± 2.14** |
| Q252H | **10.9 ± 3.53** |
| F359V | **11.5 ± 4.87** |
| P223S | 15.0 ± 5.74 |
| K294E | 18.2 ± 9.80 |
| I502L | 30.2 ± 10.3 |
| V468F | 322 ± 83 |
| P465S | 369 ± 119 |
| A337V | 453 ± 70 |



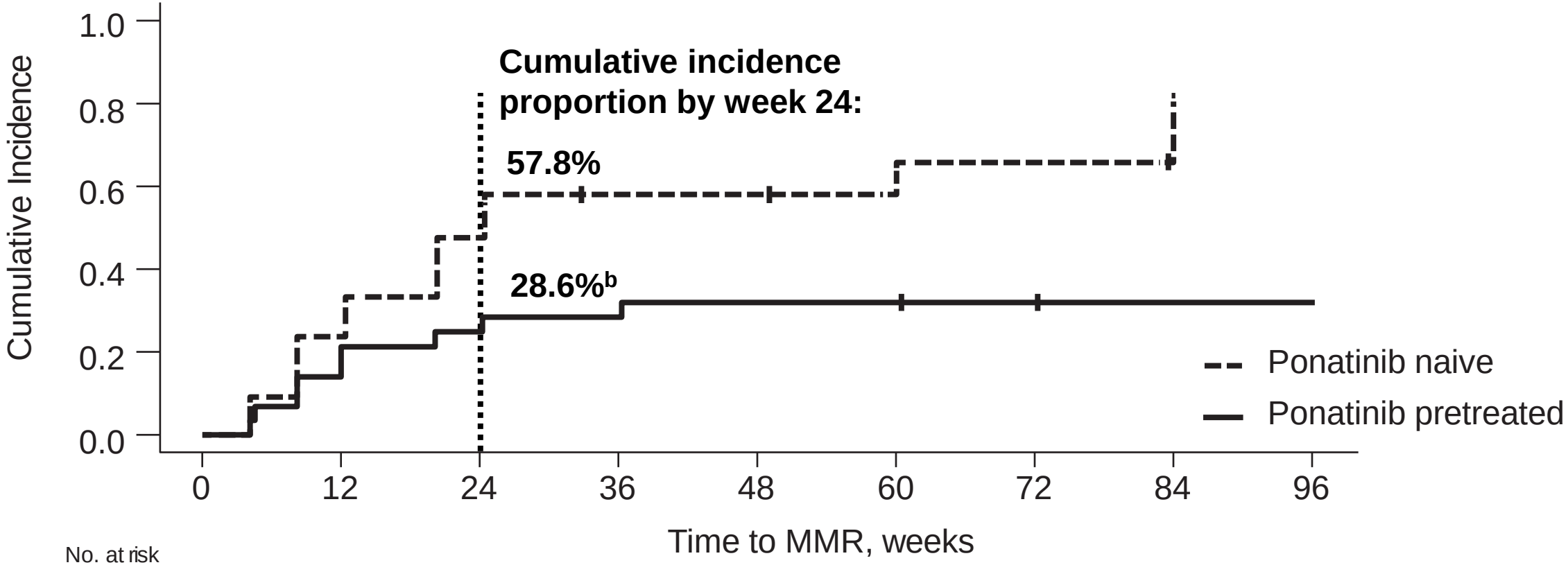





Wylie AA, et al. Nature 2017; 543: 733-737
Eide AE, et al. Cancer Cell 2019;36: 431-443.
Schoepfer J, et al. J Med Chem 2018; 61: 8120-8135.
Manley PR et al. Leuk Res 2020; 98: 106458
Qiang W, et al. Leukemia 2017; 31: 233-2852
Leyte-Vidal A et Shah N. et al. ASH 2022. Poster 4323

# Asciminib at 200mg BID in T315I (CABL001X2101): MMR in Ponatinib-Naive and Ponatinib-Pretreated Patients[a]



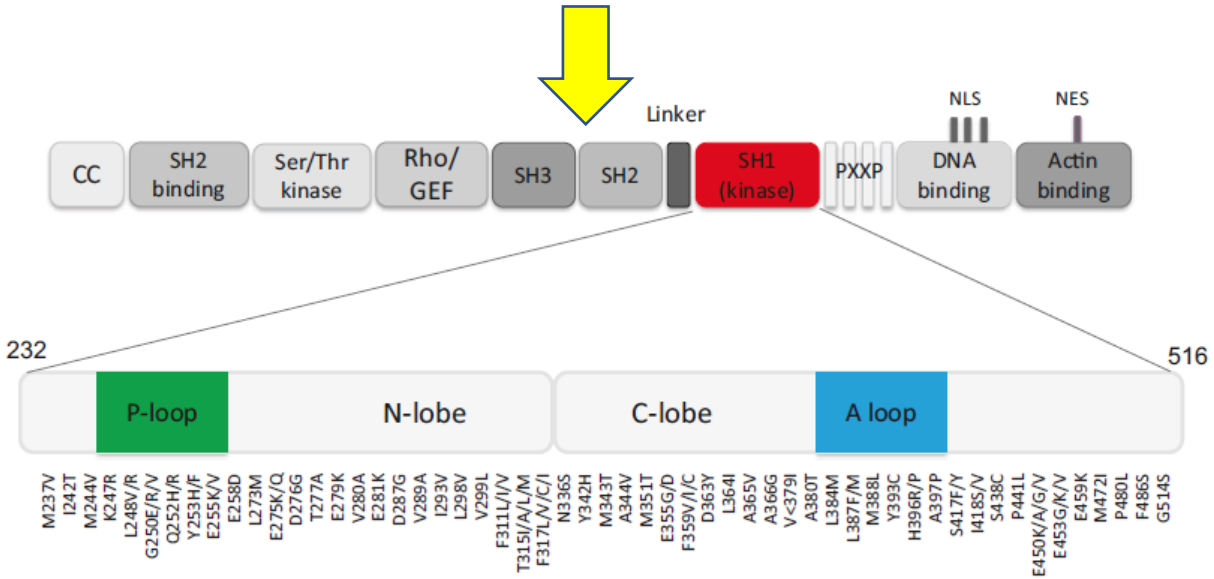

| No. at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Ponatinib naive | 21 | 15 | 9 | 5 | 5 | 3 | 2 | 1 | 0 |
| Ponatinib pretreated | 28 | 23 | 16 | 12 | 9 | 8 | 6 | 5 | 5 |

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

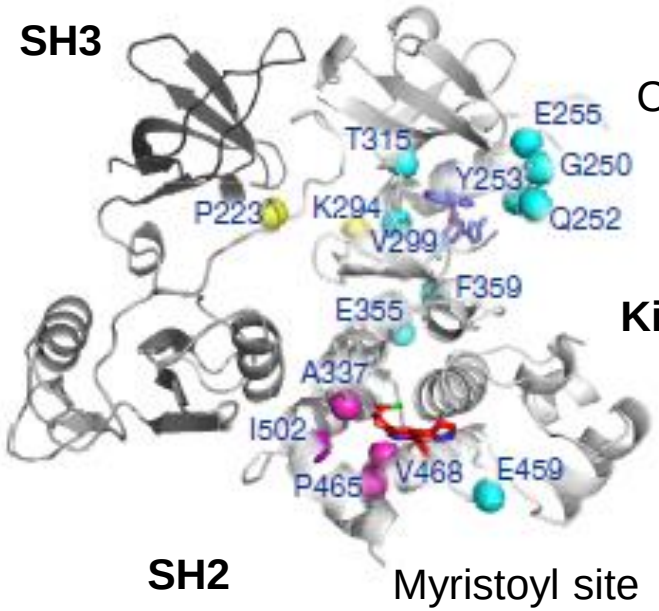
Cortes JE, et al. Blood (ASH) 2020: abstract 650

# New ELN laboratory recommendations

## ABL1 *Mutation testing*




**Location of point mutations on ABL1**




| | |
|---|---|
| **Mutations conferring resistance to asciminib**[b] | G109D, Y115N, M244V, V289I, A337V/T, E355G, F359V, E462K, G463D/S, P465S, V468F, S501R, I502L |

1. Targeted NGS recommended in case of failure or warning or relapse
2. Sanger acceptable
3. dPCR not recommended unless ruling out specific mutations of interest before very rapid TKI switch
4. **Some asciminib-resistant mutations are located outside the TKD (e.g. P223S, G109D, Y115N)**

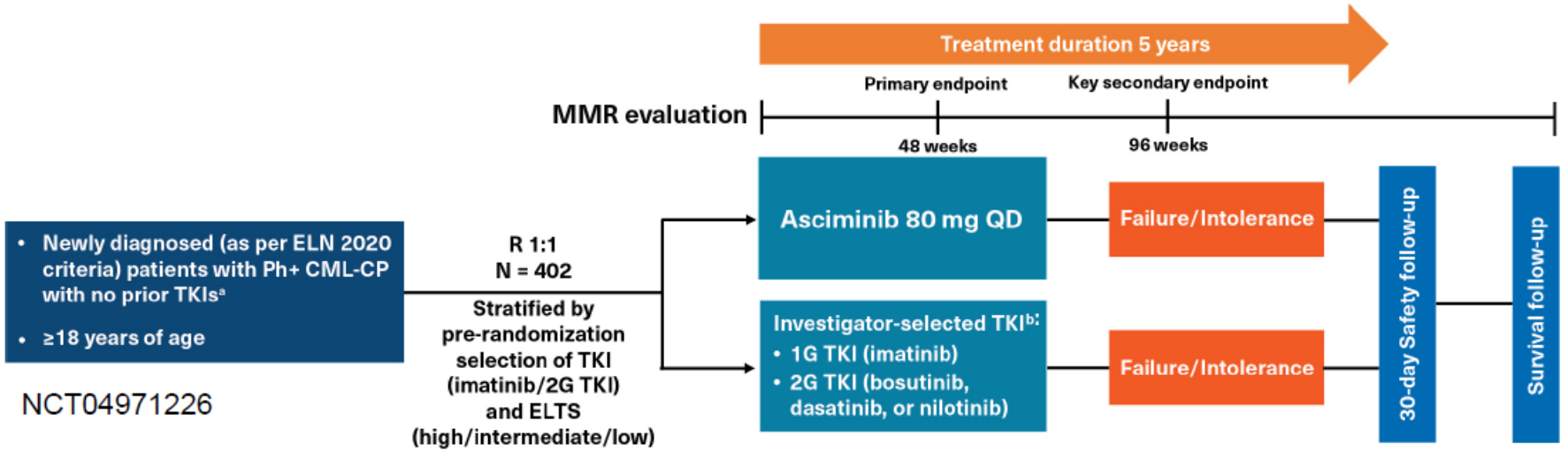
Cross NCP, et al. Leukemia 2023; 37: 2150-2167.

# TKI approval in CML in 2024

| Line | ATP-competitive | | | | | Allosteric |
|---|---|---|---|---|---|---|
| | 1st generation | 2nd generation | | | 3rd generation | |
| | Imatinib | Bosutinib | Dasatinib | Nilotinib | Ponatinib | Asciminib |
| 1st line | X | X | X | X | | Trials in progress |
| 2nd line | | X | X | X | X | |
| 3rd line and beyond | | X | X | X | X | X |

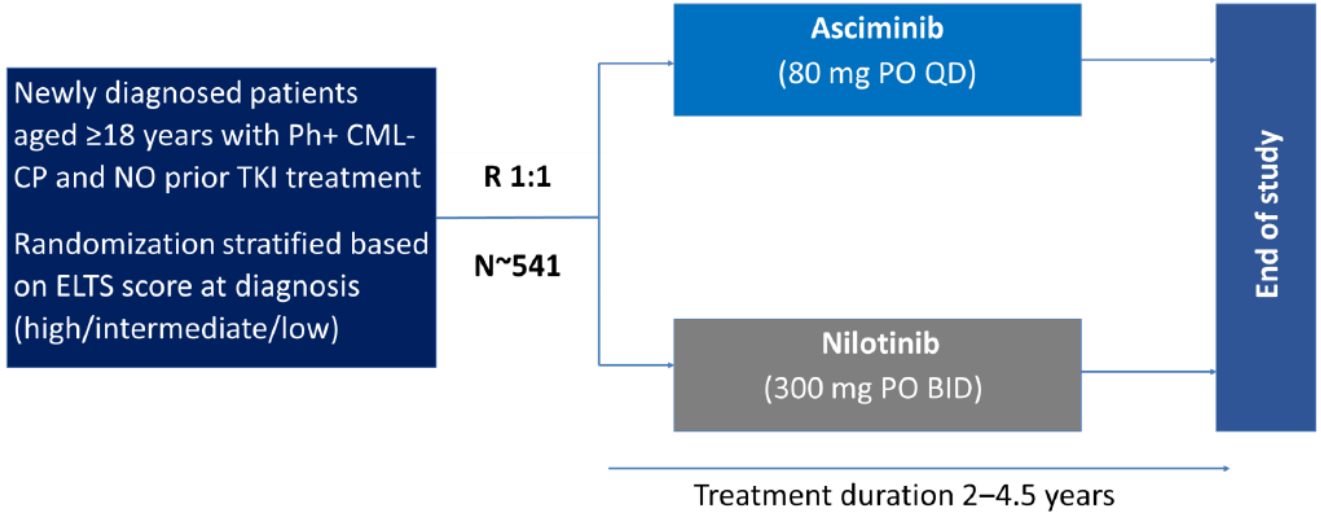
Hochhaus A, et al. Leukemia 2020; 34: 966-984.
NCCN Guidelines. Chronic Myeloid Leukemia. V1.2023.

# Asciminib 1st line in CP-CML ASC4FIRST and ASC4START




**ASC4FIRST**

**ASC4START**



# Take home messages

- Asciminib is the first allosteric BCR::ABL1 inhibitor approved for use to fight CML
- Its efficacy and tolerance profile in the ≥3$^{rd}$ line salvage context is highly favorable despite few weaknesses against some ABL1 KD point mutation that may be overcome in part by high dose asciminib like T315I
- Unlike 2$^{nd}$ or 3$^{rd}$ generation ATP-competitive TKIs, older age or comorbid conditions may not limit asciminib use
- Asciminib may replace ATP-competitive TKIs upfront in case a better clinical benefit emerges in 1$^{st}$ line studies