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ABL001 (asciminib) trials

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Conflict of interest disclosure

- Speaker during scientific events: BMS, Incyte, Novartis and Pfizer
- Membership on scientific advisory boards: BMS, Novartis
- Clinical trial steering committee member: Novartis

The ABL tyrosine kinase

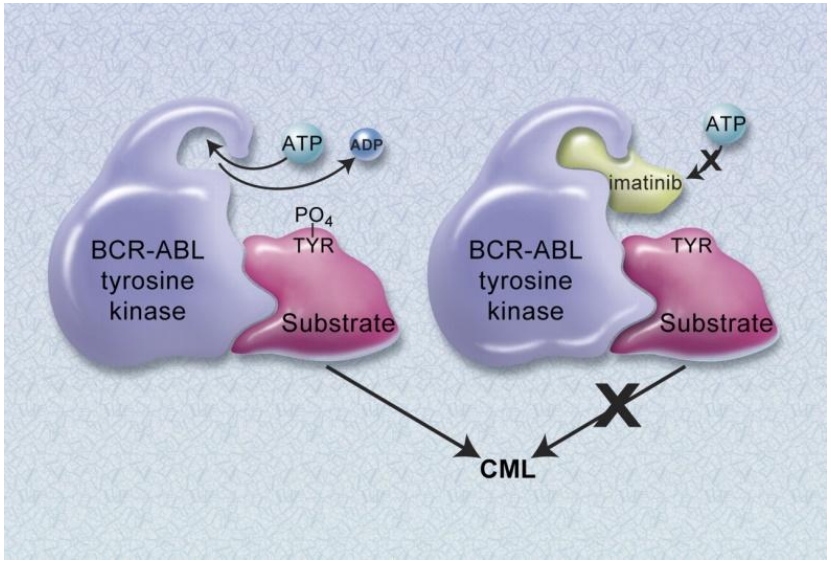
- Non-receptor tyrosine kinase.
- Interacts with a variety of intracellular proteins.
- Involved in the regulation of a range of cellular processes:
  - Proliferation, survival, response to oxidative stress and DNA damage, adhesion, migration.
- Activity tightly regulated: auto-inhibition.
- Aberrant (consitutionnally high levels) activity associated with the BCR-ABL onco-protein leads to leukemia.

Hantschel O, Superti-Furga G. Nature Review Mol Cell Biol 2004; 5: 33-44.

Inhibition of BCR-ABL activity: *ATP-competitive inhibitors*

- Bind to the ATP-binding pocket of ABL and BCR-ABL and force the kinase to adopt an inactive (dephosphorylated) conformation: substrate binding and catalysis are no longer possible.
- Type 1 (bind to the active form of BCR-ABL): dasatinib and bosutinib.
- Type 2 (bind to the inactive form of BCR-ABL): imatinib, nilotinib and ponatinib.

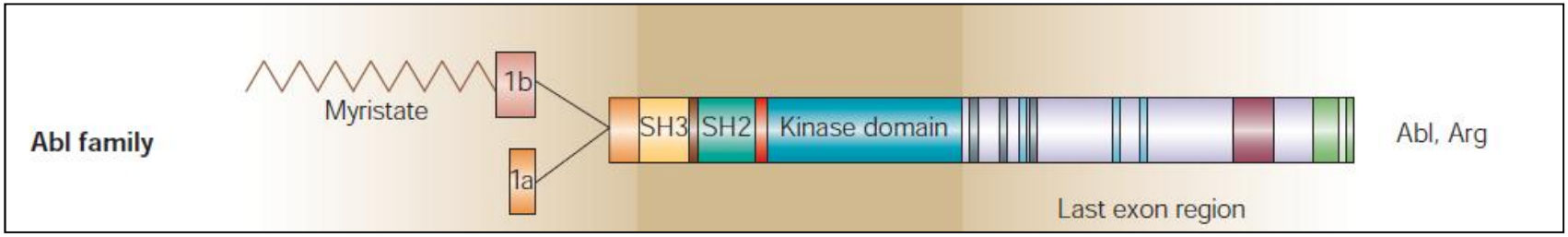
BCR-ABL ABL in complex with imatinib (STI571)



Hantschel O, Superti-Furga G. Nature Review Mol Cell Biol 2004; 5: 33-44.

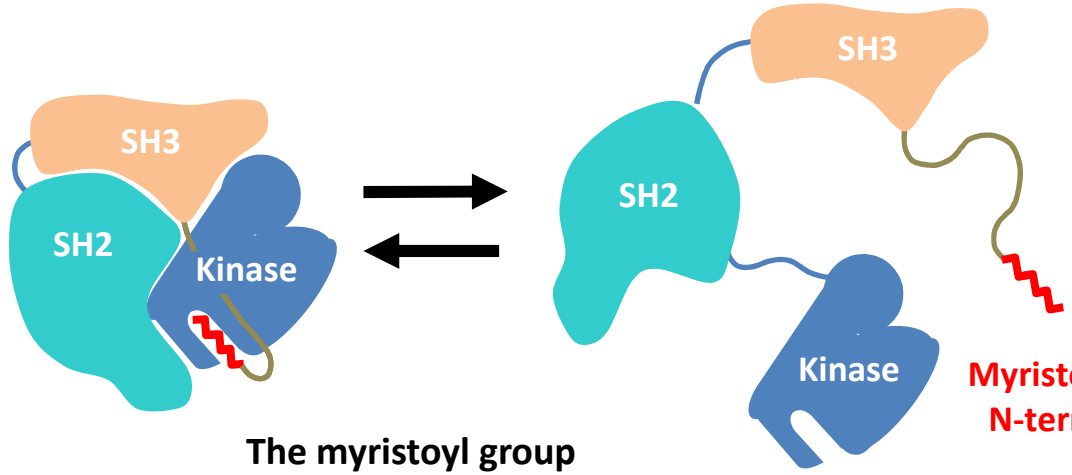
Auto-inhibition of ABL: myristoylation

NH2 **COOH**



ABL isoform Ib
Inactive conformation

ABL isoform Ib
Active conformation



ABL is auto-inhibited, thus inactive.

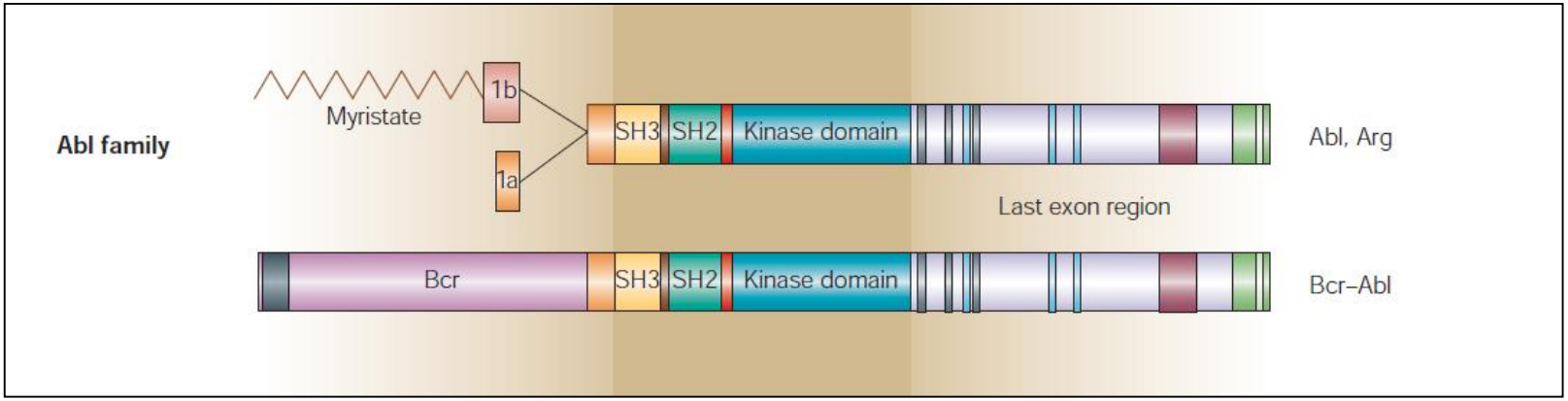
The isoform Ib of ABL can be myristoylated.

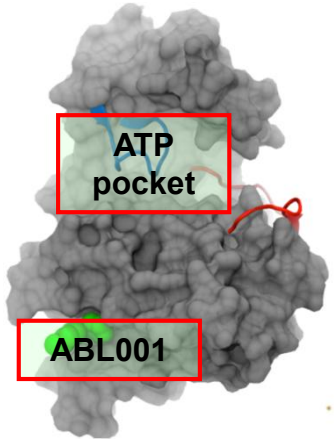
The myristoyl group binds to a hydrophobic pocket in the C lobe of the kinase.

Fedorov O et al, Nat Chem Biol 2010; 6: 166-169.
Hantschel O, Superti-Furga G. Nature Review Mol Cell Biol 2004; 5: 33-44.

Inhibition of BCR-ABL activity:
Allosteric inhibitors

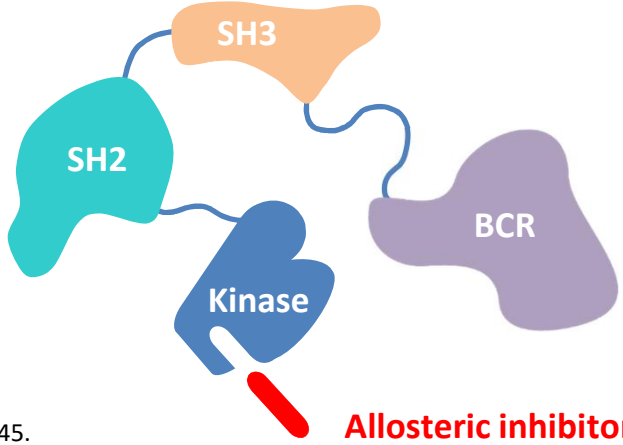
NH2 COOH





BCR-ABL1 kinase domain

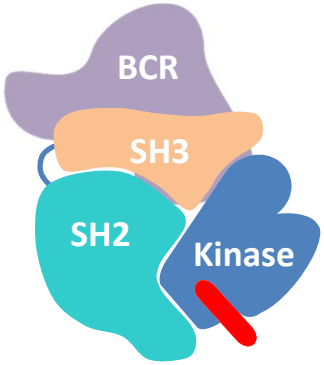
BCR-ABL
Active conformation



Allosteric inhibitor

GNF-2
GNF-5
ABL001

BCR-ABL
Inactive conformation

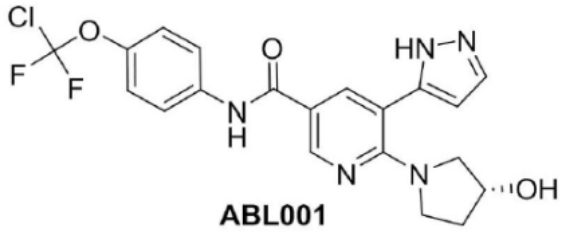


Allosteric inhibitor

Skora et al. PNAS 2013; 110: E4437-E4445.
Wylie et al. Nature 2017; 543: 733-737.
Zhang et al. Nature 2010; 463: 501-506.

ABL001 (asciminib)

- Potent and selective allosteric inhibitor of BCR-ABL.
- Active against cell lines with ATP binding site BCR-ABL mutants.
- Combination of ABL001 and nilotinib prevents the mergence of resistant tumors in murine models



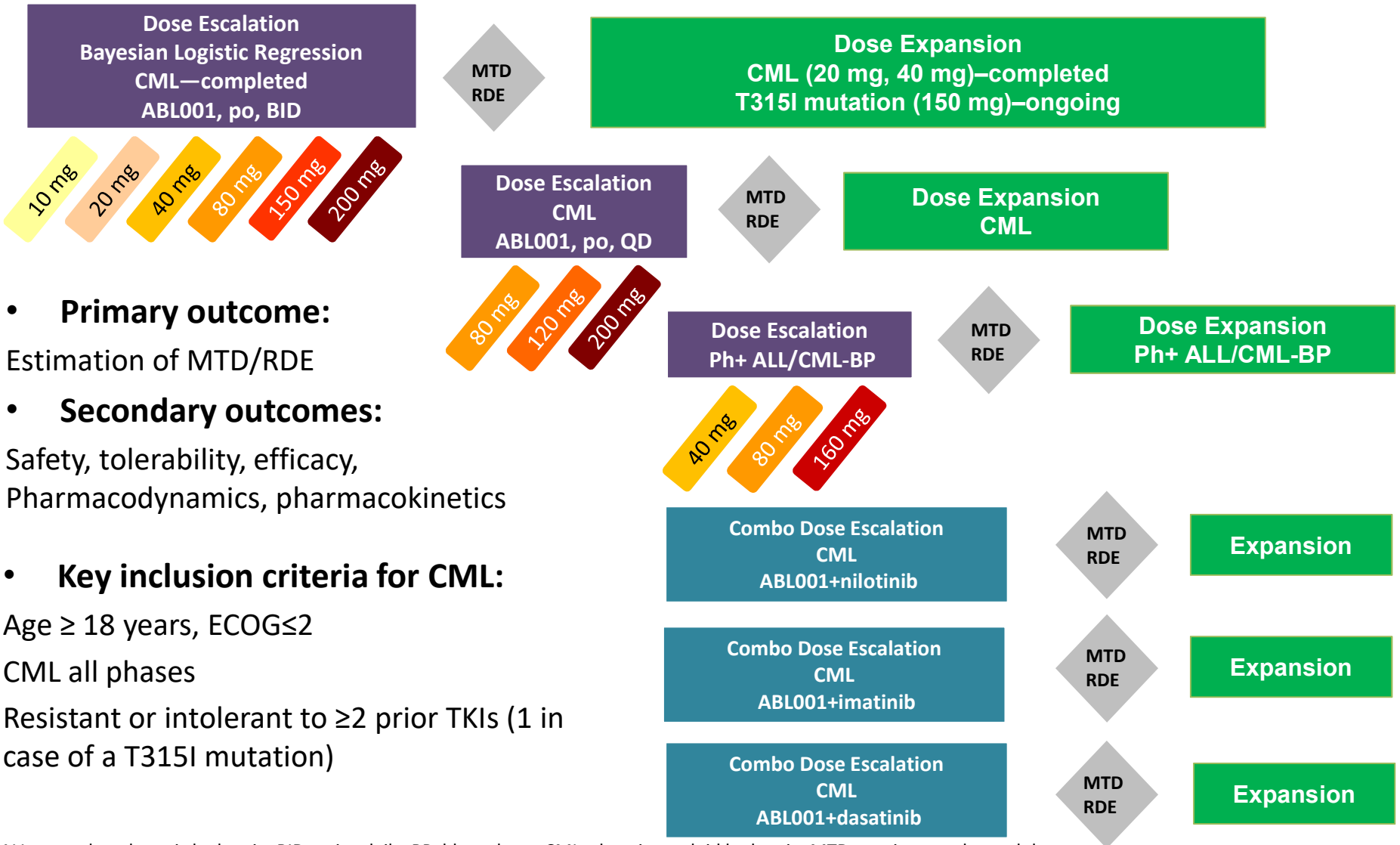
ABL001

Fold reduction in cell potency (Ba/F3) due to presence of BCR-ABL mutations

	Nilotinib	ABL001	
WT	1	1	Myristoyl -site
A337V	2	10640	
P465S	1	13620	
V468F	1	10053	
WT	1	1	ATP-site
T315I	>30000	55	
E255K	1267	4	
E255V	268	2	
Y253H	132	5	
F359V	64	167	
Q252H	30	44	
G250H	7	2	
E459K	4	7	

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

ABL001X2101: phase 1 first-in-human study



- **Primary outcome:**

Estimation of MTD/RDE

- **Secondary outcomes:**

Safety, tolerability, efficacy, Pharmacodynamics, pharmacokinetics

- **Key inclusion criteria for CML:**

Age ≥ 18 years, ECOG≤2

CML all phases

Resistant or intolerant to ≥2 prior TKIs (1 in case of a T315I mutation)

ALL, acute lymphocytic leukemia; BID, twice daily; BP, blast phase; CML, chronic myeloid leukemia; MTD, maximum tolerated dose; Ph+, Philadelphia chromosome–positive; po, peroral; QD, once daily; RDE, recommended dose for expansion.

ABL001X2101: key inclusion criteria for CML patients

- Adult patients (aged ≥ 18 years).
- CML in chronic, accelerated, or blast phase.
- Relapsed/refractory to ≥ 2 prior TKIs or intolerant of TKIs.
  - Patients with T315I mutation eligible after 1 prior TKI.
- ECOG performance status 0-2

Hughes TP, et al. Blood. 2016:[abstract 625].

ABL001X2101: Demographics and baseline characteristics

	N = 123
Median age (range), years	55 (23-79)
Male/female, %	61 / 39
ECOG performance status 0/1 or 2, %	72 / 28
Prior lines of therapy, median (range)	3 (1-5)
1 prior TKI, %	5
2 prior TKIs, %	30
≥ 3 prior TKIs, %	65
CML-CP/CML-AP/CML-BP/ALL, %	88 / 4 / 2 / 6
TKD non-mutated/mutant[a]/not evaluable, %	46 / 30[a] / 24

[a] T315I (17), E255K (3), F317L (3), G250E (3), M244V (2), V299L (2) Y253H (2), E279K (1), L248V/G250E/V299L (1), T315I/F359V (1), T315I/M351T (1), T315I/Y253H (1)

Hughes TP, et al. Blood. 2016:[abstract 625].

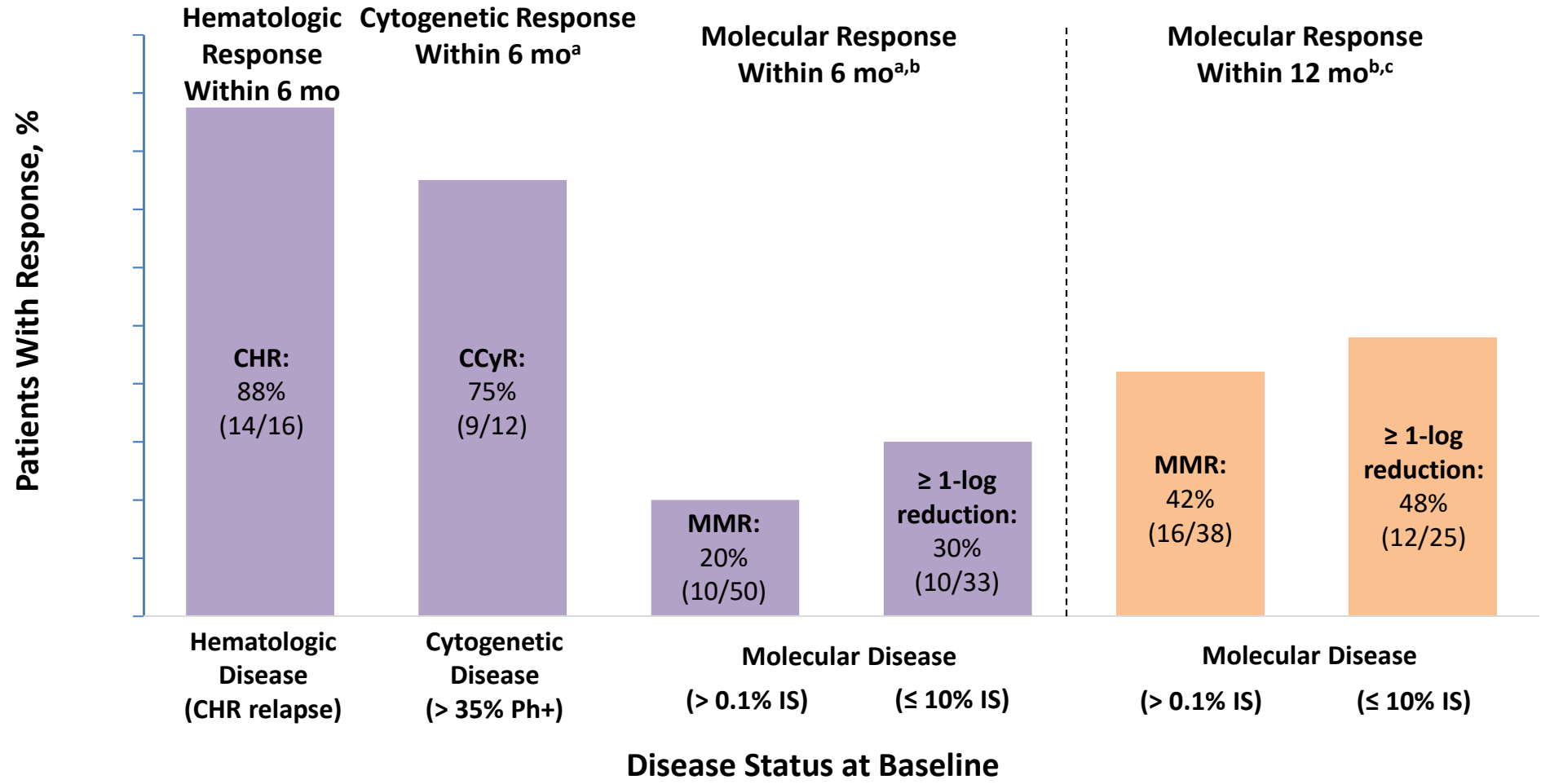
ABL001X2101: patient disposition-single agent ABL001 in CML

	ABL BID						ABL QD			Total
mg	10	20	40	80	150	200	80	120	200	
N	1	14	35	12	10	5	6	10	6	99
Median duration of exposure, weeks	49	37.6	29.6	81.0	52.6	69.4	16.8	51.6	53.6	37.6
Ongoing, n (%)	0	14 (100)	30 (86)	9 (75)	7 (70)	3 (60)	6 (100)	10 (100)	5 (83)	84 (85)
Discontinued, n (%)	1 (100)	0	5 (14)	3 (25)	3 (30)	2 (40)	0	0	1 (17)	15 (15)
Reason for discontinuation, n (%)										
Adverse Event	0	0	2 (6)	1 (8)	2 (20)	1 (20)	0	0	0	6 (6)
Disease progression[a]	0	0	2 (6)	0	1 (10)	0	0	0	1 (17)	4 (4)
Patient/guardian decision	1 (100)	0	1 (3)	1 (8)	0	1 (20)	0	0	0	4 (4)
Death	0	0	0	1 (8)	0	0	0	0	0	1 (1)

[a] Only 1 of 8 patients with relapsed or progressive disease had detectable myristoyl binding pocket mutations (V468H, I502L)

Hughes TP, et al. *Blood*. 2016:[abstract 625].

ABL001X2101: Responses in CML - Single-Agent BID ABL001 (≥ 3 months exposure)



CCyR, complete cytogenetic response; CHR, complete hematologic response; IS, International Scale; MMR, major molecular response.

[a] Patients had ≥ 6 months of treatment exposure or achieved response within 6 months.

[b] *BCR-ABL1*^{IS} reduction achieved.

[c] Patients had ≥ 12 months of treatment exposure or achieved response within 12 months.

Hughes TP, et al. Blood. 2016:[abstract 625].

ABL001X2101: Responses in CML patients with the T315I mutation

- 11 of 77 (14%) CML patients treated with BID ABL001 had T315I mutations at baseline; 10 had 3 months' follow-up
  - 4 of 10 patients > 35% Ph+ achieved CCyR by 6 months
  - 6 patients have maintained stable disease without achieving CCyR or MMR
  - No patients have progressed to blast crisis
  - 1 patient has maintained baseline MMR for > 1 year
- Dose escalation for T315I-mutant patients (160mg and 200mg BID) is ongoing to explore whether higher doses can achieve deeper molecular responses

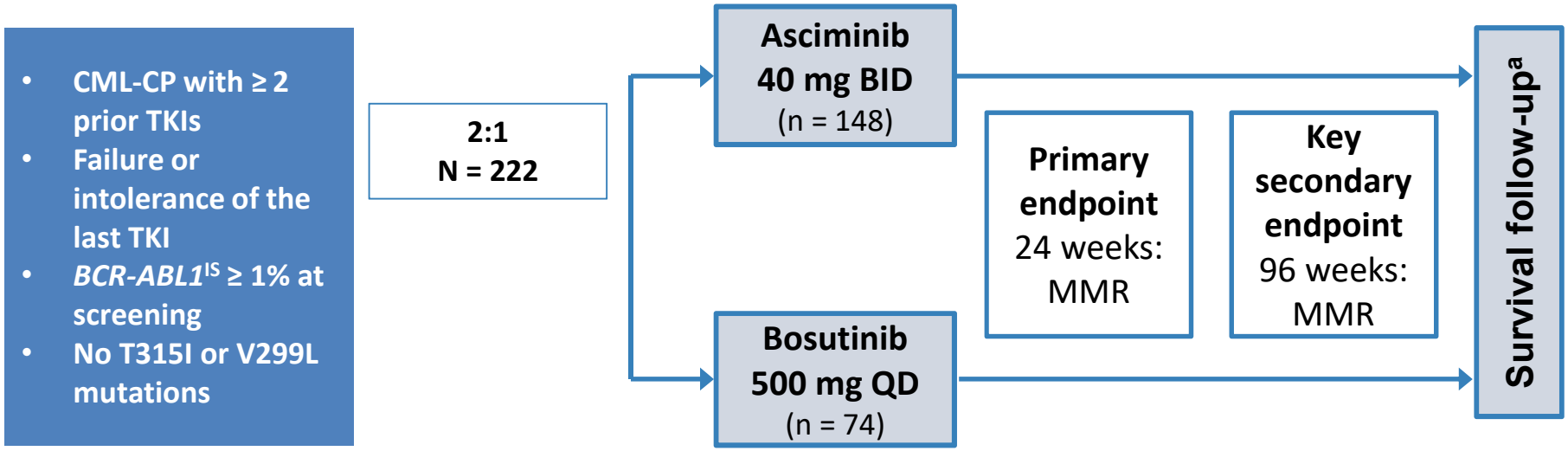
Hughes TP, et al. Blood. 2016:[abstract 625].

ABL001X2101: AEs Suspected of Being Related to Study Drug Occurring in ≥ 5% of Patients (n = 123)

Adverse Event	All Grades, n (%)	Grade 3/4, n (%)
Lipase increase	26 (21)	12 (10)
Rash	19 (15)	0
Thrombocytopenia	16 (13)	7 (6)
Fatigue	15 (12)	1 (1)
Nausea	14 (11)	0
Arthralgia	13 (11)	0
Amylase increased	12 (10)	1 (1)
Headache	12 (10)	0
Pruritus	11 (9)	1 (1)
Anemia	9 (7)	5 (4)
Diarrhea	9 (7)	0
Myalgia	9 (7)	1 (1)
Vomiting	9 (7)	0
Hypophosphatemia	7 (6)	1 (1)
Neutropenia	7 (6)	5 (4)

Hughes TP, et al. *Blood*. 2016:[abstract 625].

CABL001A2301: Asciminib Phase 3 Study Design



Treatment duration: 96 weeks[b]

Anticipated timeline:

- **FPFV: Oct 2017**
- **LPLV: 2019**
- **Submission: 2020**
- **Approval: 2021**

[a] Patients who discontinue study treatment at any time will continue to be followed up for survival and progression to AP/BC for up to 5 years after the last patient's first dose.
[b] Patients will continue to receive study treatment for up to 96 weeks after the last patient's first dose.

Conclusions and perspectives

- ABL001 (asciminib) is the first allosteric inhibitor of BCR-ABL to be tested in humans.
- Highly specific: few off-target effects expected.
- Potential targeting of mutants including T315I at specific doses.
- Combination with ATP-competitive TKI is possible.
- Updated results of the phase 1 study pending.
- Drug development is ongoing.