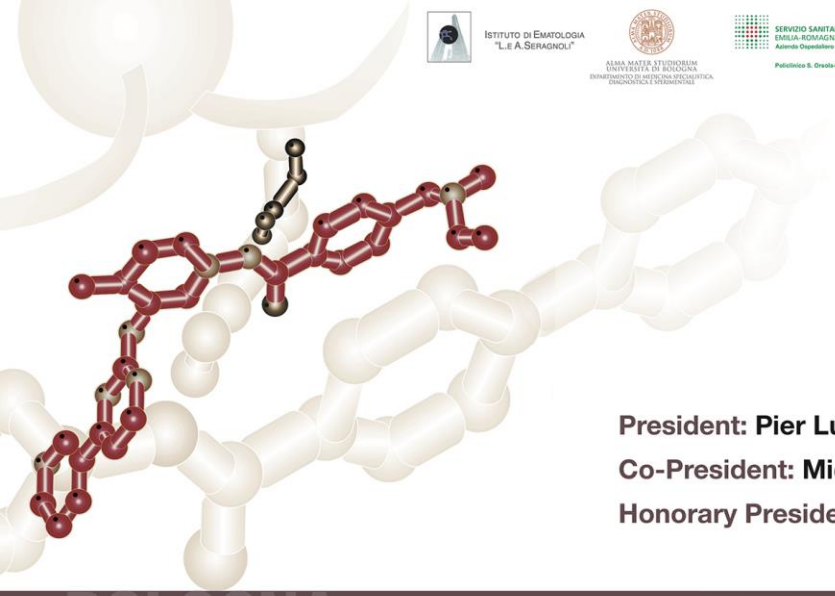
ISTITUTO DI EMATOLOGIA "L. e A. SERAGNOLI"
ALMA MATER STUDIORUM UNIVERSITÀ DI BOLOGNA
SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna
Policlinico S. Orsola-Malpighi



New Drugs in Hematology

President: Pier Luigi Zinzani
Co-President: Michele Cavo
Honorary President: Sante Tura

Bologna,
Royal Hotel Carlton
October 1-3, 2018

BOLOGNA, ROYAL HOTEL CARLTON

# ABL001 and combination

Massimo Breccia
Az. Policlinico Umberto I
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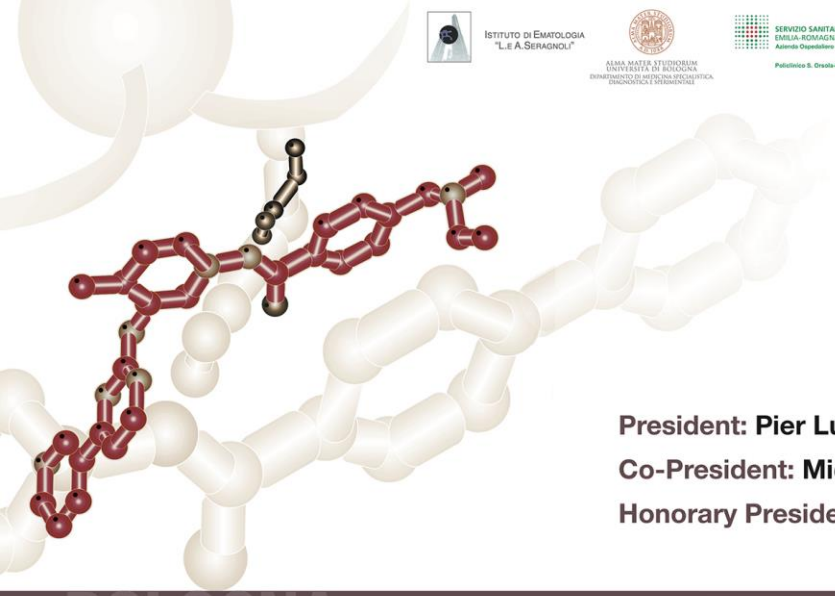

ISTITUTO DI EMATOLOGIA "L. E A. SERAGNOLI"

ALMA MATER STUDIORUM UNIVERSITÀ DI BOLOGNA DIPARTIMENTO DI MEDICINA SPECIALISTICA, DIAGNOSTICA E SPERIMENTALE

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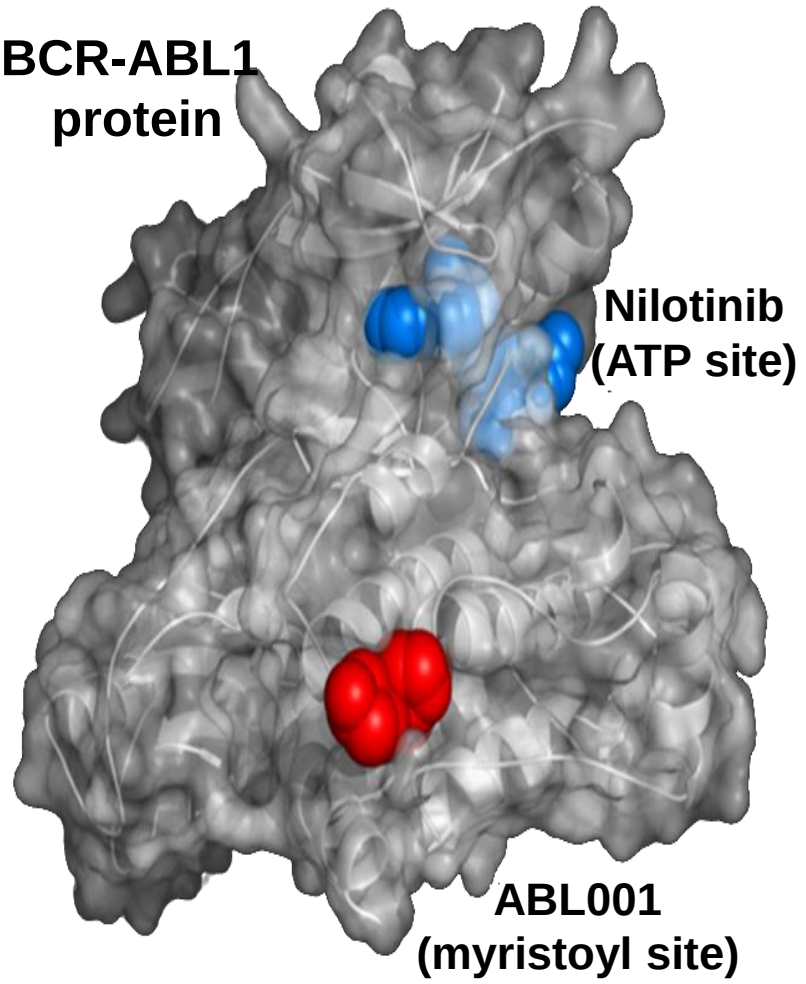
## Disclosures of NAME SURNAME

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| Novartis | | | x | | x | x | |
| BMS | | | x | | | | |
| Incyte | | | x | | | x | |
| Pfizer | | | x | | | | |
| Celgene | | | x | | | | |

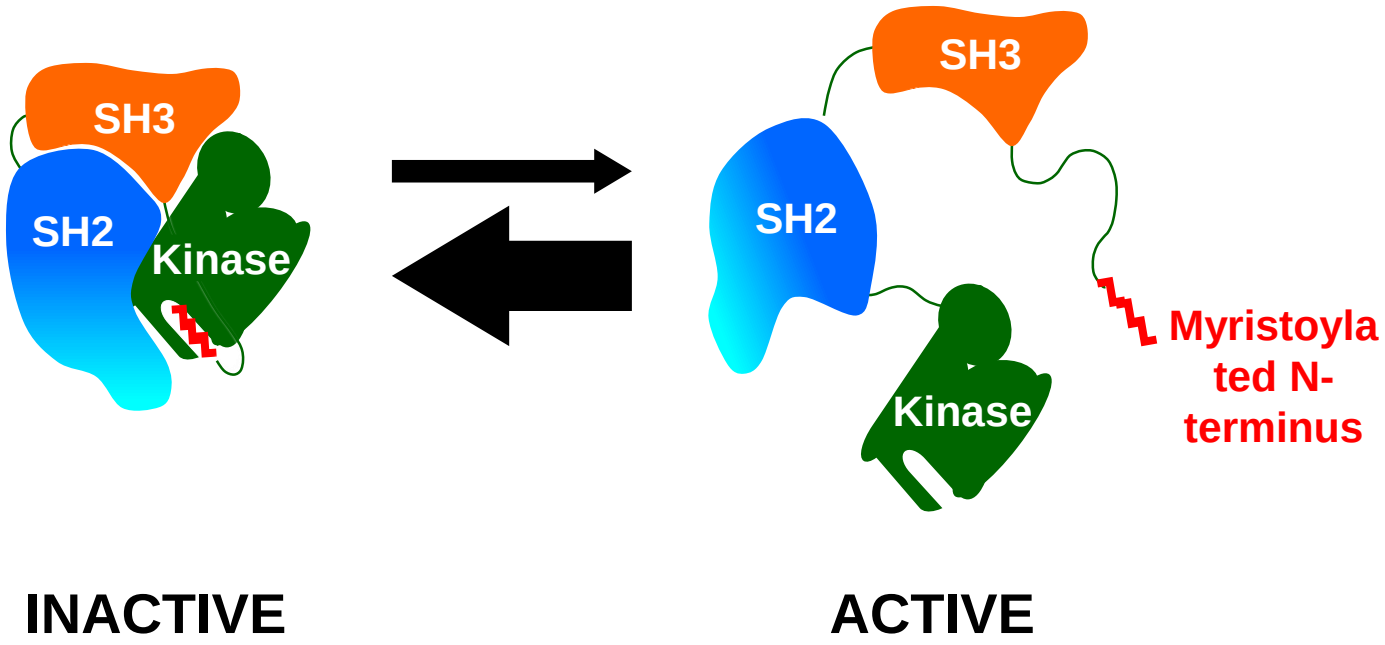
# ABL001 is a potent, specific inhibitor of BCR-ABL1 with a distinct allosteric mechanism of action

- Developed to gain greater BCR-ABL1 inhibition, with activity against BCR-ABL1 mutations conferring resistance to TKIs
- Potential to combine with TKIs for greater pharmacologic control of BCR-ABL1




Ottmann OG, *et al. Blood* 2015:126 [abstract 138].

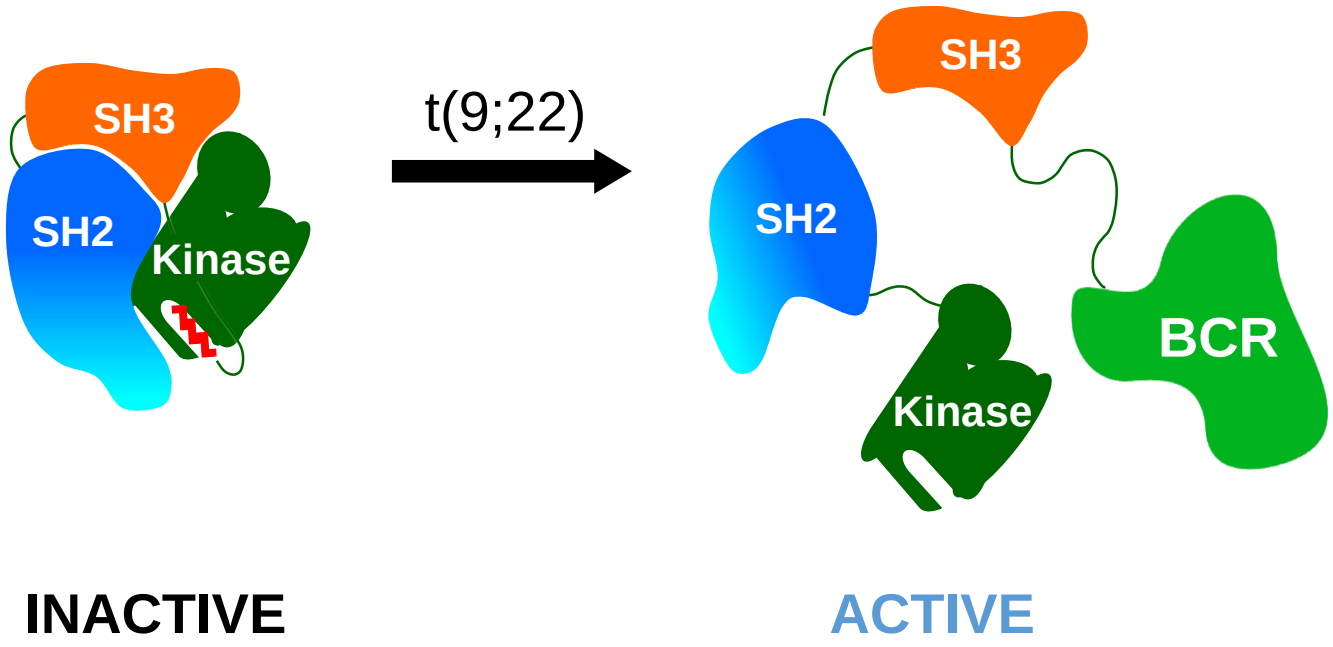
# Autoinhibition of ABL1 by engagement of myristoyl binding site




- The kinase domain is normally occupied by the myristoylated N-terminus of ABL1, which serves as a key negative regulator of ABL kinase activity

SH2, Src homology 2; SH3, Src homology 3. Nagar B, *et al*. *Cell* 2003;112:859–871.

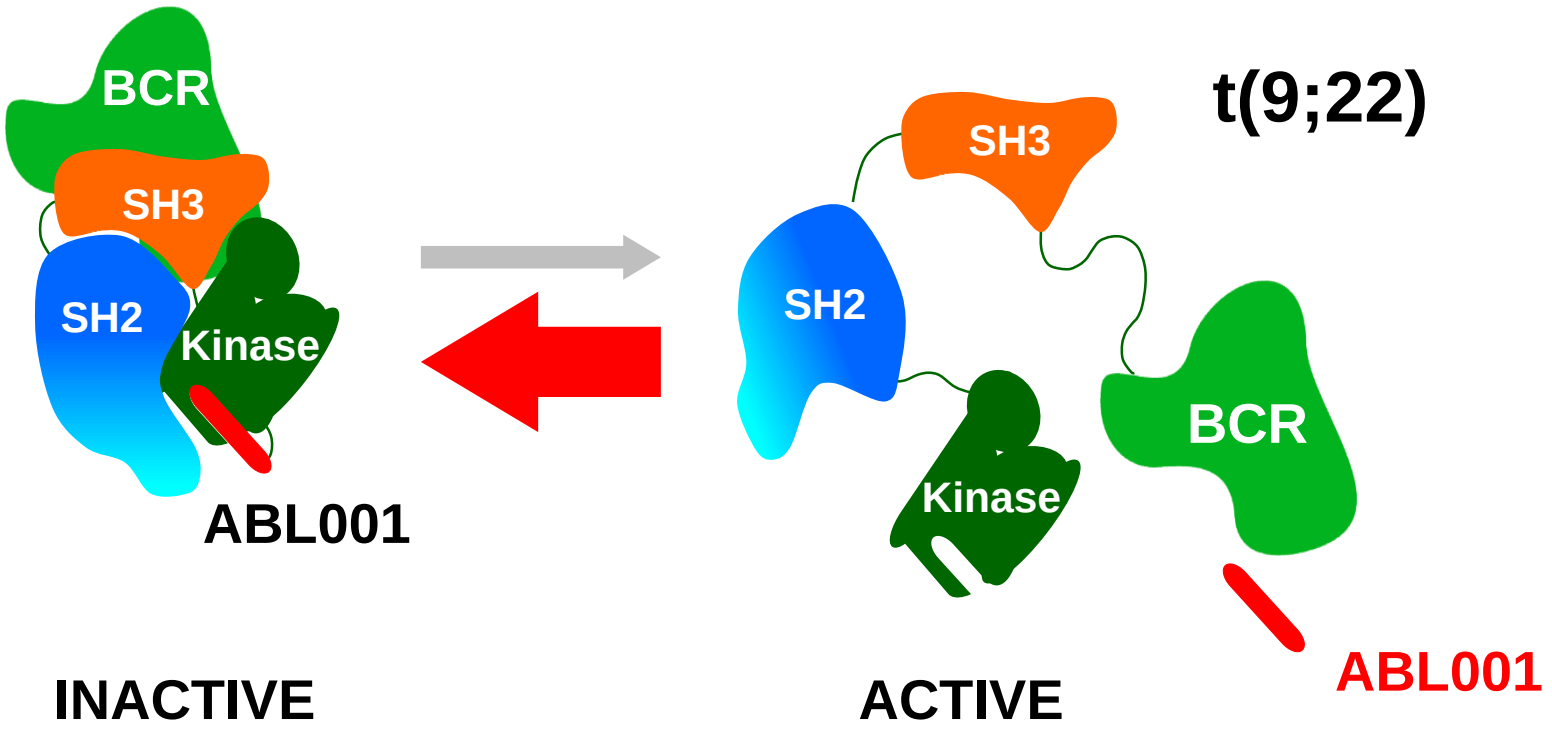
# Loss of ABL1 autoinhibition due to BCR-ABL1 translocation




- The fusion between BCR and ABL1 results in the loss of this regulatory element, which contributes to the constitutive activation of the kinase activity

Hantschel O & Superti-Furga G. *Nat Rev Mol Cell Biol* 2004;5:33–44.

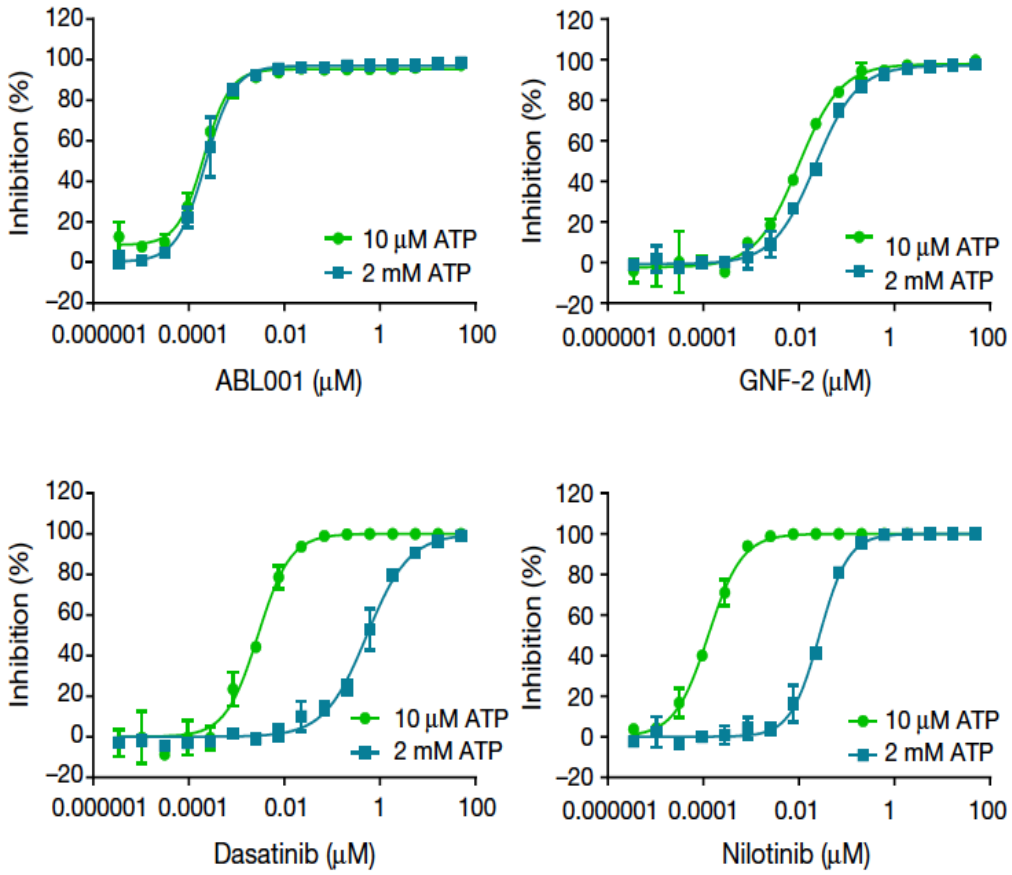
# ABL001 allosterically inhibits BCR-ABL1 kinase activity




- ABL001 functionally mimics the role of the myristoylated peptide by occupying its vacant binding site and restoring the negative regulation of the kinase activity

Hantschel O & Superti-Furga G. *Nat Rev Mol Cell Biol* 2004;5:33–44; Adrian FJ, *et al*. *Nat Chem Biol* 2006;2:95–102.

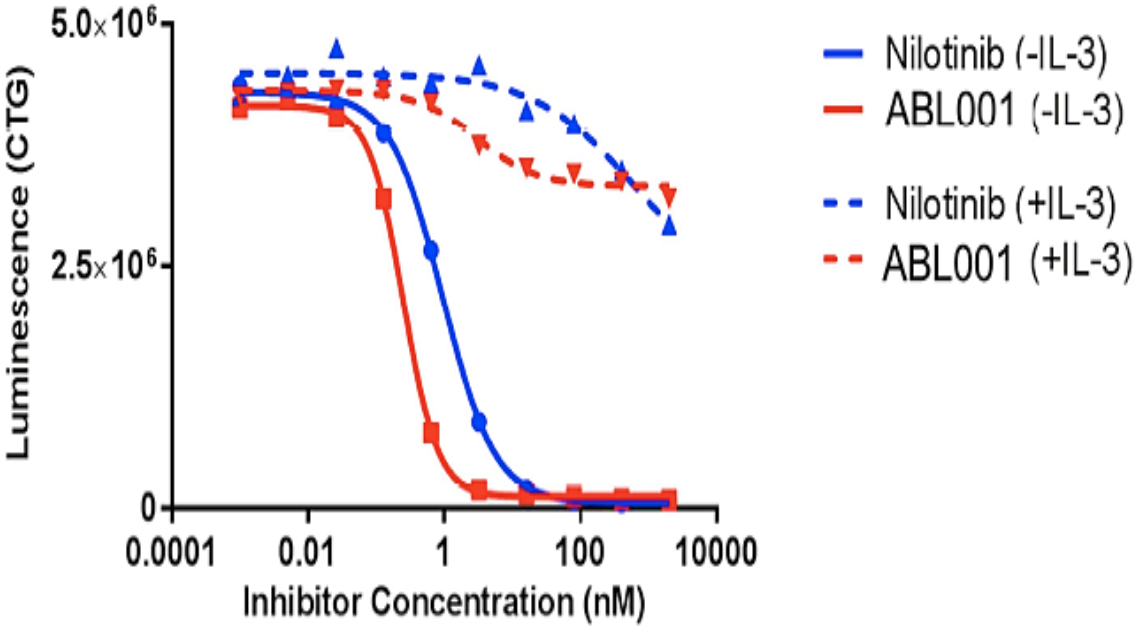
# ABL001: biochemical assay at high and low ATP concentration




- ABL001 is able to inhibits ABL1 kinase regardless of high or low ATP concentration as compared to second generation TKIs

Wylie et al, Nature 2017

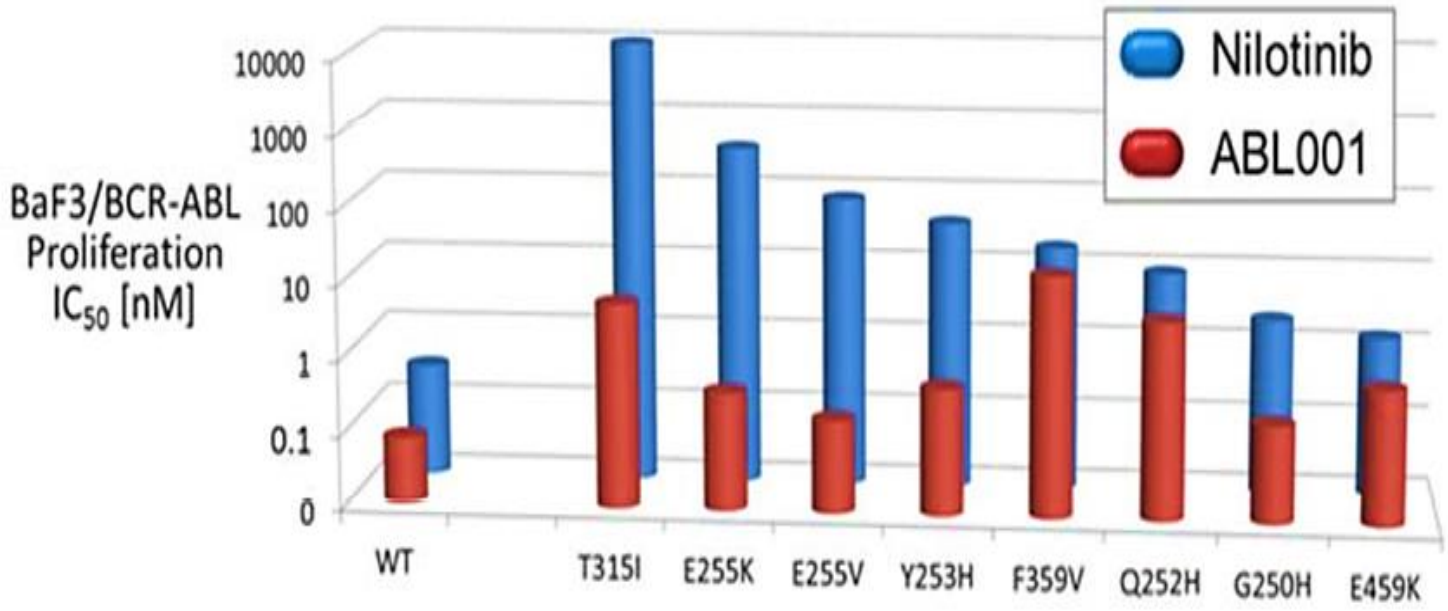
# ABL001: *In vitro* cellular activity




- Using the BaF3/BCR-ABL system that does not require IL3 to grow and is dependent on BCR-ABL for proliferation (nilotinib used as positive control):
  - ABL001 inhibited BaF3 with an $IC_{50}$ of 0.25 µM
  - If IL3 was added, the $IC_{50}$ was 2 µM (the highest dose tested)

Hantschel O & Superti-Furga G. *Nat Rev Mol Cell Biol* 2004;5:33–44; Adrian FJ, *et al*. *Nat Chem Biol* 2006;2:95–102.

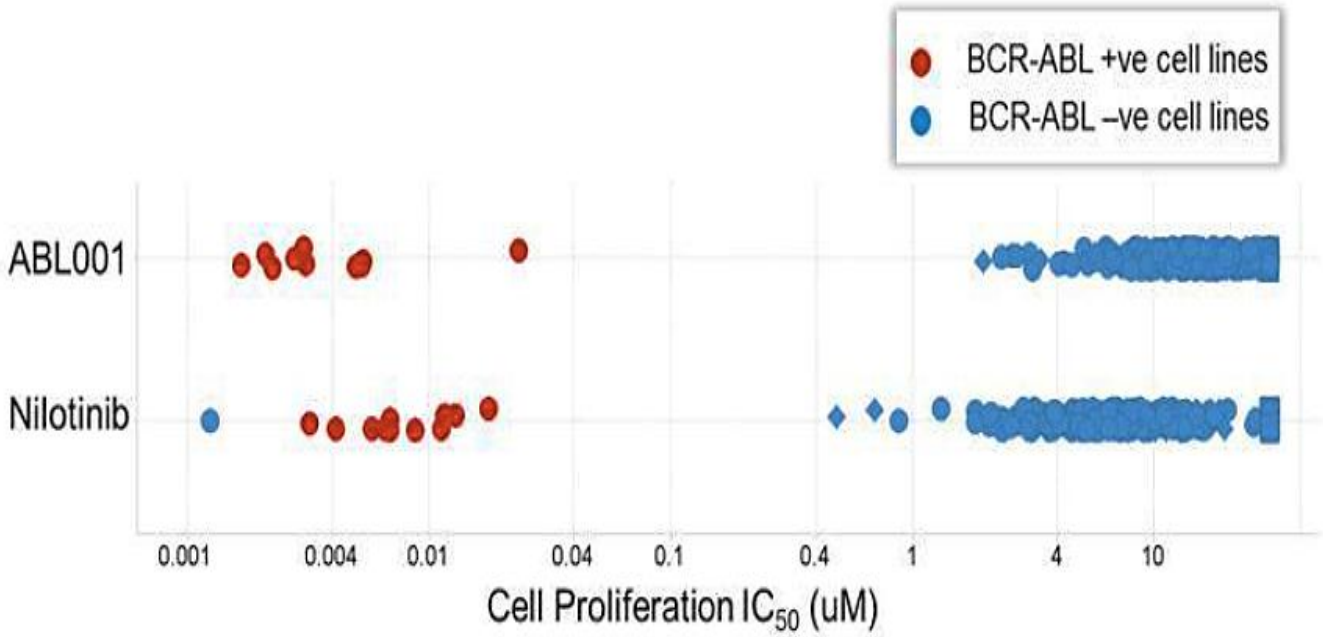
# Effect of ABL001 on BaF3-containing mutations




- Using the BaF3/BCR-ABL system containing point mutations, ABL001 maintained activity against all mutations, at concentrations below 50 nM
- ABL001 inhibits cells with T315I, whereas nilotinib is inactive at concentrations up to 10 µM

Adrian FJ, *et al*. *Nat Chem Biol* 2006;2:95–102.

# Effect of ABL001 on proliferation of cancer cell lines

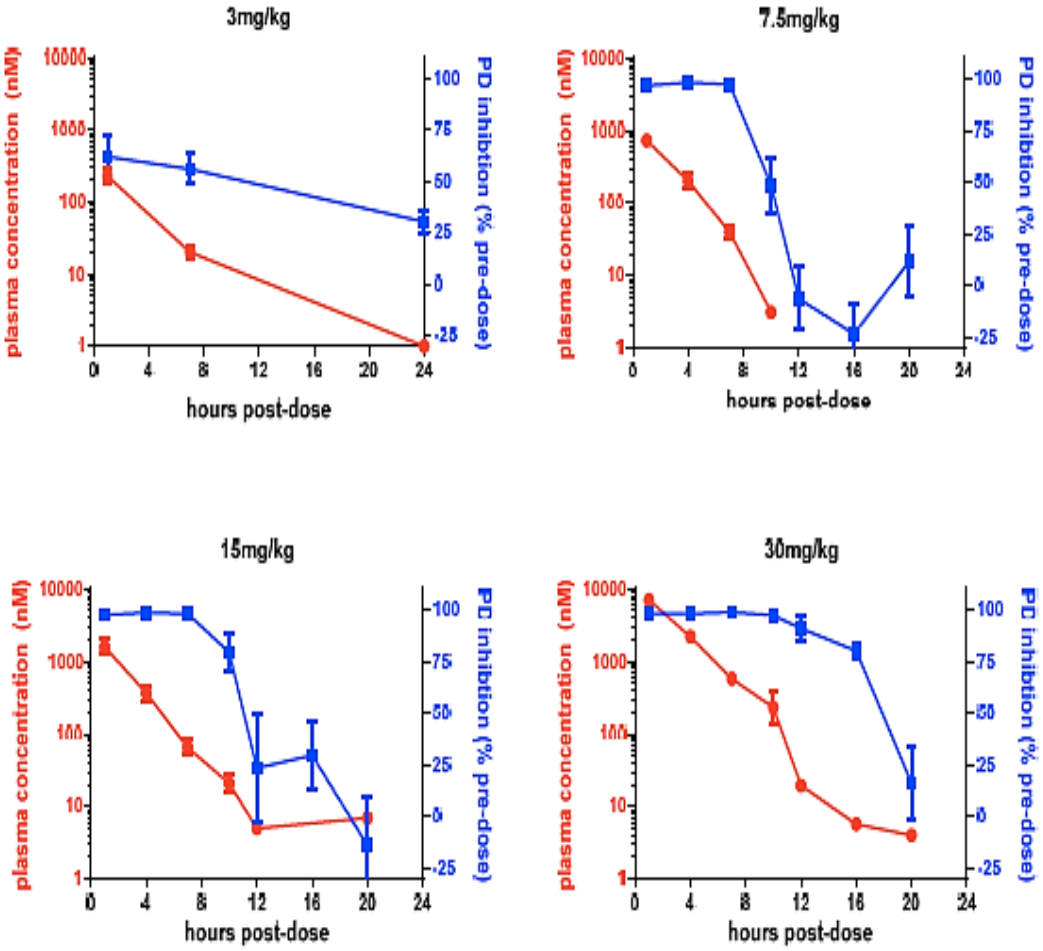



- ABL001 was tested in 500+ cell line panels and selectively inhibits only BCR-ABL1-positive cells with $IC_{50}$ ranging from 1–12 nM
- Cell lines that did not express BCR-ABL1 remained unaffected until the concentrations reached 2–30 µM

Adrian FJ, *et al*. *Nat Chem Biol* 2006;2:95–102; Wylie A, *et al. Blood* 2014:124 [abstract 398].

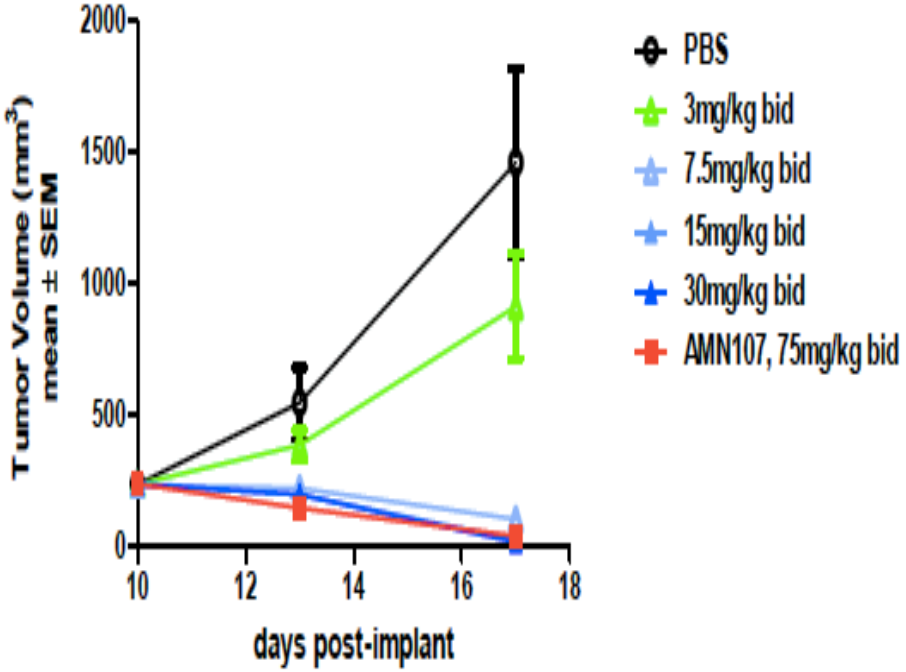
# Administration of ABL001 in a KCL-22 xenograft model

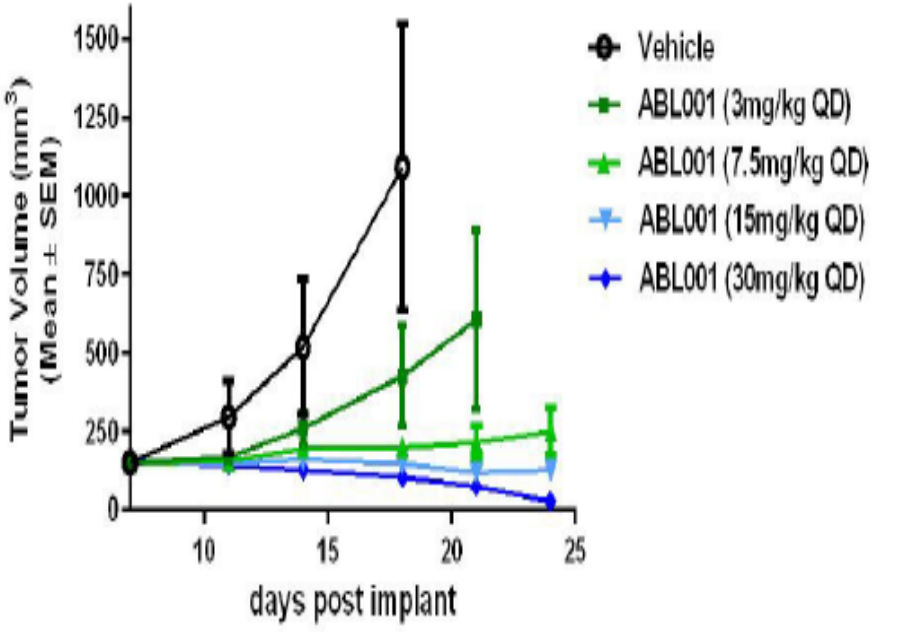
- KCL-22 (BC cell line) was selected to test the PK/PD relationship for ABL001
- A single oral dose of ABL001 at 3.0, 7.5, 15.0, and 30.0 mg/kg resulted in maximal pSTAT5 inhibition of 62%, 98%, 99%, and 99%, respectively
- At the 30 mg/kg dose level, >80% pSTAT5 inhibition was maintained for 16 hours post dose




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

# Efficacy of ABL001 in a KCL-22 xenograft model (tumor volume)

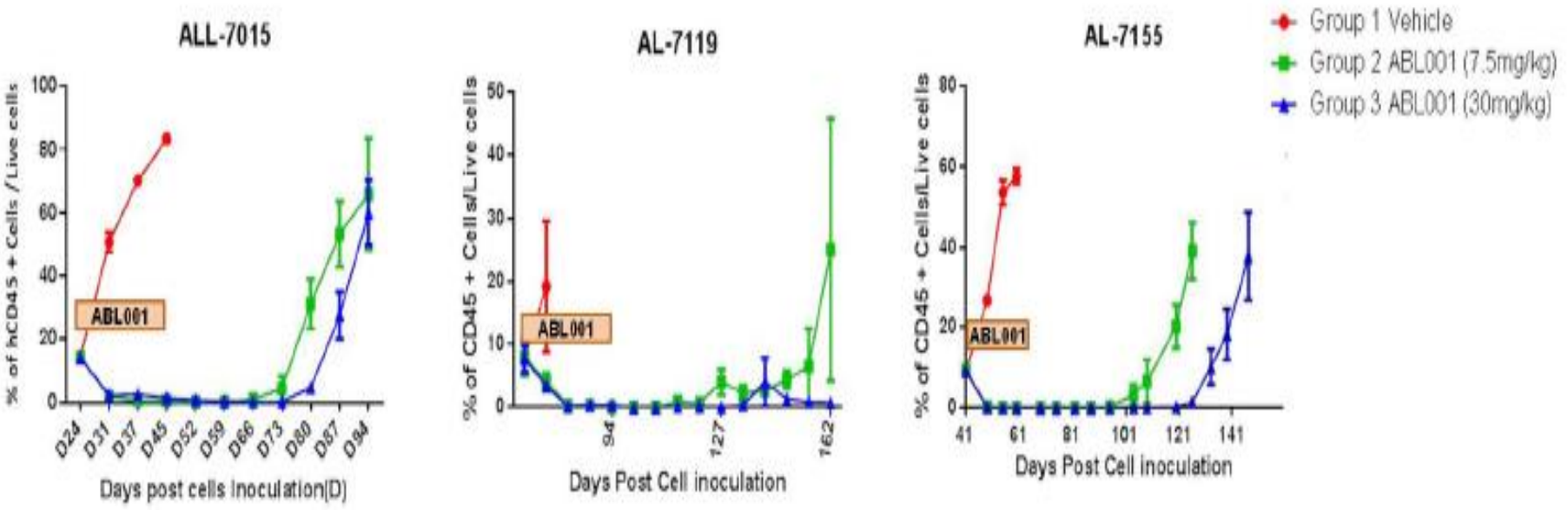



- Tumor growth inhibition:
  - 3 mg/kg corresponds to tumor growth inhibition of 55%
  - 30 mg/kg corresponds to tumor growth inhibition of 92%

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

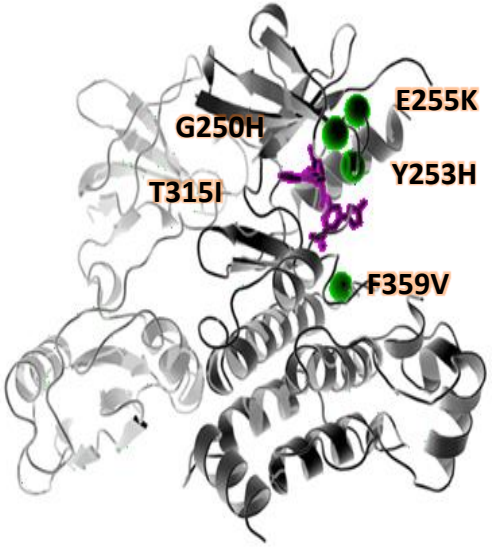
# Efficacy of ABL001 in a 3 patients-derived ALL systemic xenograft models



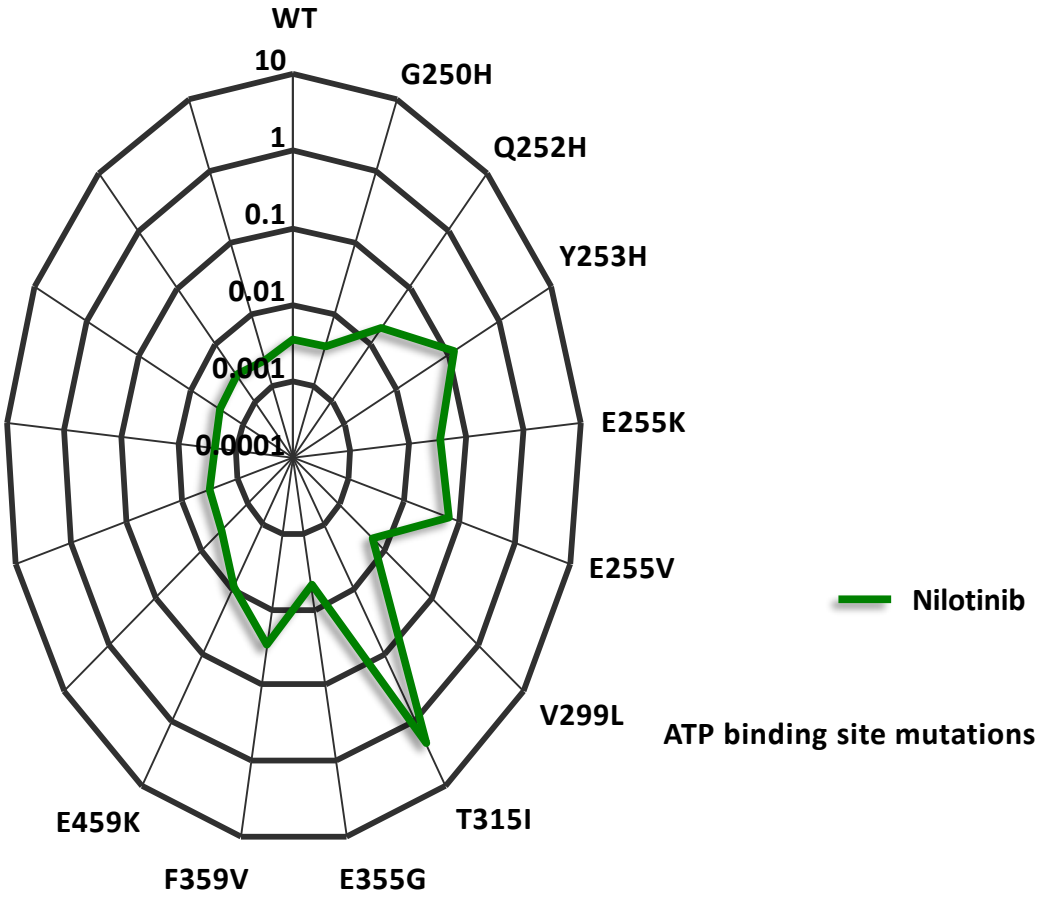

- FACS monitoring of the percentage of CD45+ cells per live cell in blood samples:
  - A control group was treated with PBS vehicle
  - 30 mg/kg corresponds to long-lasting inhibition

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

# ABL001 and classical TKIs exhibit complementary mutation profiles

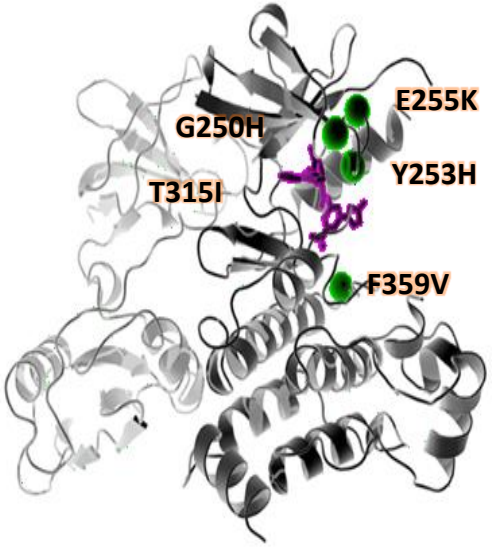



**Proliferation $IC_{50}$ profiles in Ba/F3 *BCR-ABL1*-mutant lines**

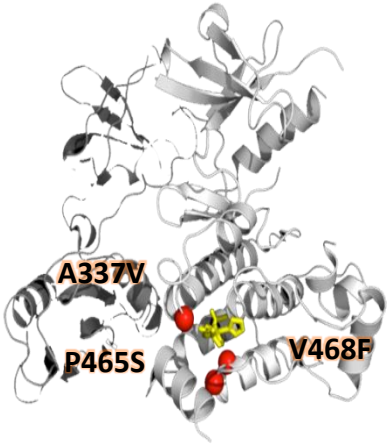



Wylie A, *et al. Nature 2017; 543: 733-737*

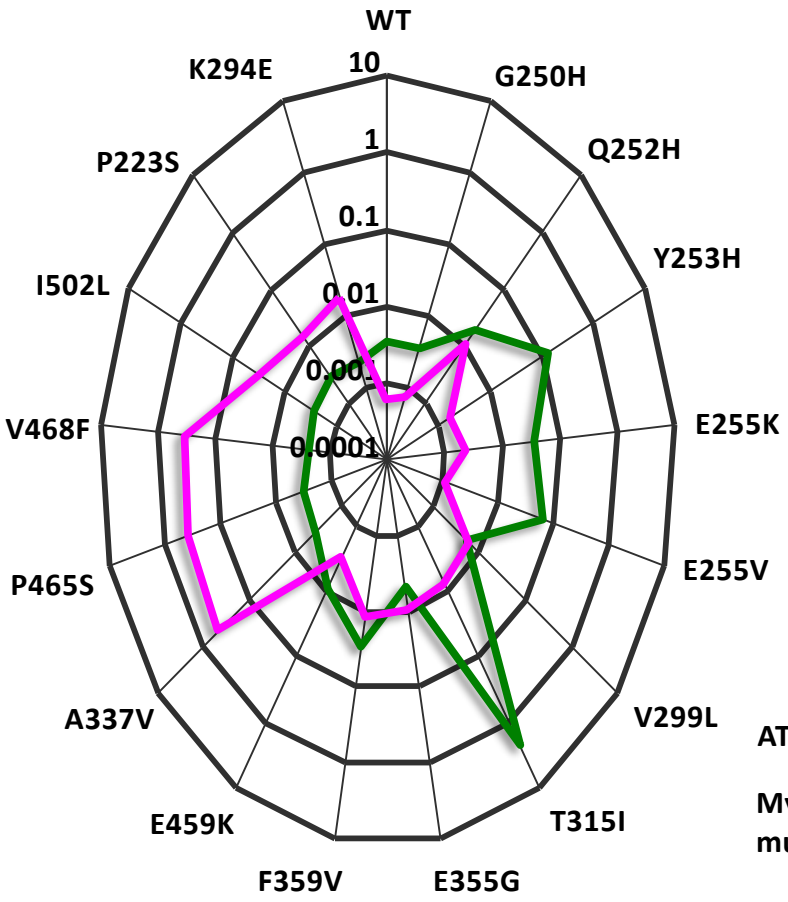
# ABL001 and classical TKIs exhibit complementary mutation profiles




Myristoyl binding site mutations

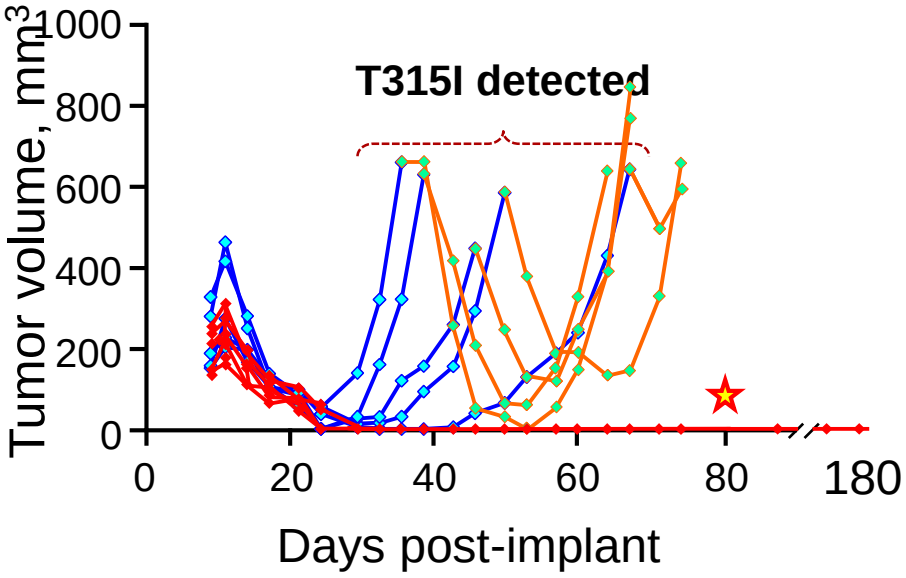


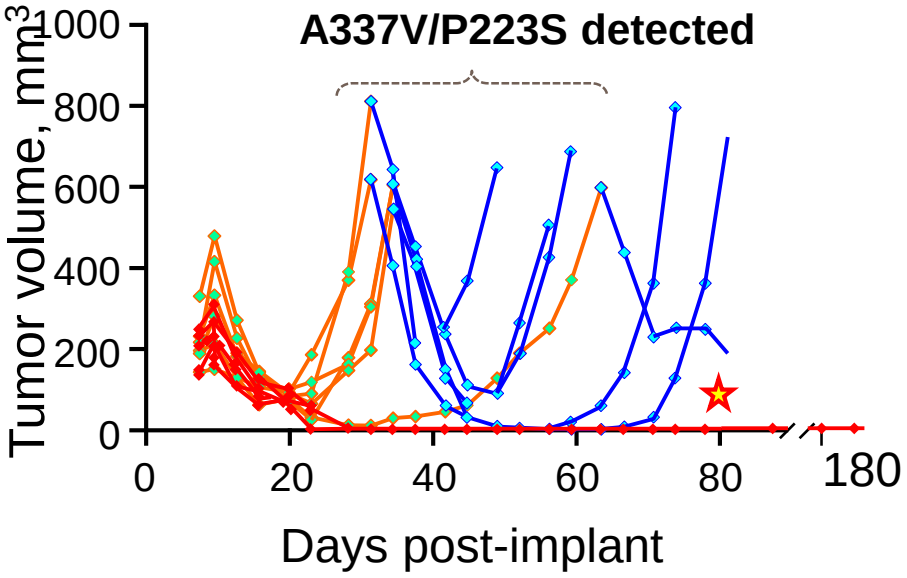

**Proliferation $IC_{50}$ profiles in Ba/F3 *BCR-ABL1*-mutant lines**




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

# Combination of ABL001 and nilotinib prevents the emergence of resistance (KCL-22 CML xenograft)*




**Nilotinib (75 mg/kg) BID**

**ABL001 (30 mg/kg) BID**

**Nilotinib (75 mg/kg) BID + ABL001 (30 mg/kg) BID**

**Dosing stopped on Day 77; all mice remain disease free >176 days**

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

# PK and metabolic profile

- In animal models (rat, dog, monkey), following oral dosing, $T_{max}$ ranged from 0.5–4 h
- Absorption is formulation-dependent
- Low to moderate bioavailability
- Binding of ABL001 to protein is high, and independent of concentration
- ABL001 is extensively distributed to most tissues
- No distribution to CNS and minimal penetration to the reproductive system

- Following administration, ABL001 is the predominant circulating form
- Biliary excretion is the major elimination pathway
- Metabolic profile different for different species (glucuronidation most readily in humans through UGT1A3, UGT1A4, UGT2B7, and UGT2B17)

- ABL001 shows reversible inhibition of CYP3A4/5, CYP2C8, CYP2C9, CYP2B6
- ABL001 is an inhibitor of BCRP, pGp, and a weak inhibitor of OCT1

BCRP, ATP binding cassette protein; CNS, central nervous system; CYP, cytochrome P450; OCT1, organic cation transporter 1; pGp, p-glycoprotein; $T_{max}$, time to maximum concentration; UGT, UDP-glucuronosyltransferase.

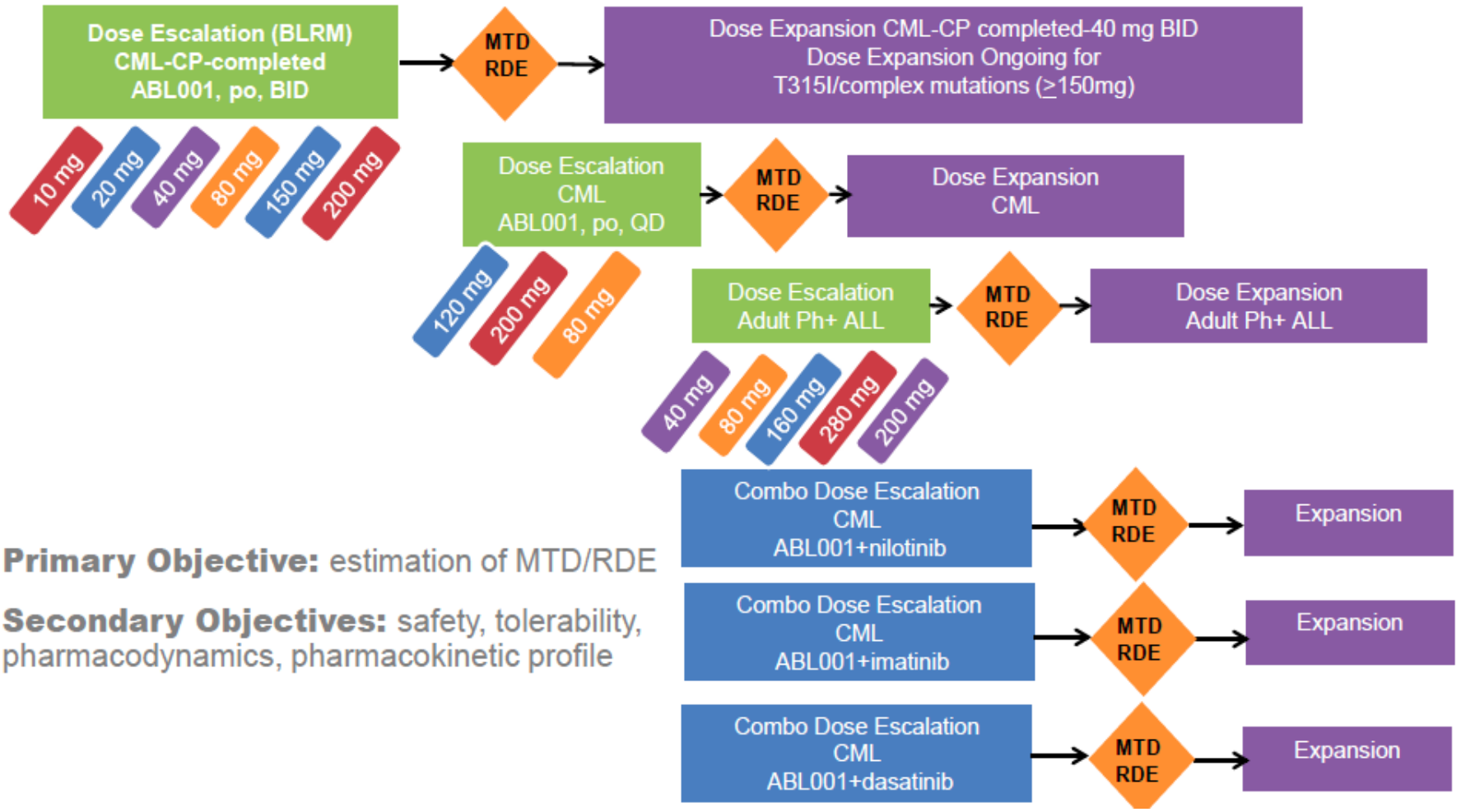

- Wylie A, *et al. Nature 2017; 543: 733-737*

# Bioavailability and food effect for 2 tablet formulations of asciminib in a 2-arm, crossover, randomized, open label study in healthy volunteers

- A single-center, open-label, randomized, crossover, two-arm study in 45 healthy subjects
  - 22 subjects treated with oral formulation (variant AAA)
  - 23 subjects treated with tablet formulation (variant NXA)
- Both arms compared under fasting conditions, or after a low- or high-fat meal
- ABL001 exhibited a negative food effect, and low- and high-fat meals decreased the bioavailability of ABL001 by 30% and 65%, respectively
- ABL001 administered twice-daily was rapidly absorbed with a $T_{max}$ of 2–3 h, independent of dose
- $C_{max}$ and AUC increased in an approximately dose-proportional manner
- Steady state was reached before Day 15 of Cycle 1

Menssen et al, Clin Pharmacol Drug Dev 2018.

# ABL001X2101: Study design
## A multicenter, Phase I, first-in-human study




**Primary Objective:** estimation of MTD/RDE

**Secondary Objectives:** safety, tolerability, pharmacodynamics, pharmacokinetic profile

Hughes TP, *et al. Blood* 2016:625.

# Key inclusion/exclusion criteria

- **Key inclusion criteria**
  - Patients (aged ≥18 years)
  - CML in chronic, accelerated or blastic phases
  - Failed (relapsed/refractory) ≥2 prior TKIs or intolerant of TKIs
    - Patients with T315I mutation eligible after 1 prior TKI
  - ECOG performance status 0–2
- **Key exclusion criteria**
  - Strong inhibitors or inducers of CYP3A4 or CYP3A4 substrates with narrow therapeutic index
  - Laboratory parameters
    - ANC <500/$mm^3$
    - Platelet count <50,000 $mm^3$
    - Bilirubin >1.5 × ULN or >3.0 × ULN in patients with Gilbert's syndrome
    - AST or ALT >3.0 × ULN
    - Creatinine >1.5 × ULN

Hughes TP, *et al. Blood* 2016:625.

# Demographics and baseline characteristics

| | N=123 |
|---|---|
| Median age (range), years | 55 (23–79) |
| Male / female, % | 61/ 39 |
| ECOG PS 0–1 / 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 / -AP, / CML-BP/ALL, % | 88/4/2/6 |
| TKD non-mutated / mutant / not evaluable, % | 46/30/24 |

Hughes TP, *et al. Blood* 2016:625.

# Patient disposition: single agent ABL001 in CML

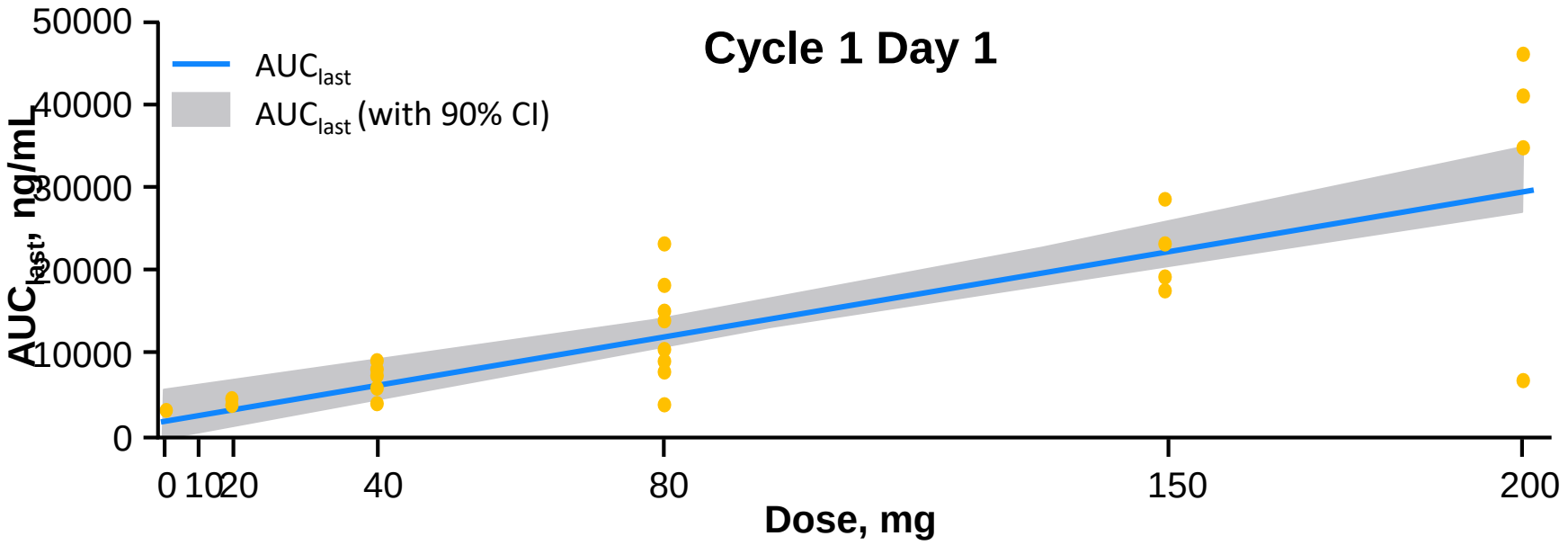
| | Monotherapy BID | | | | | | Monotherapy QD | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| **mg** | **10** | **20** | **40** | **80** | **150** | **200** | **80** | **120** | **200** | |
| **n** | **1** | **14** | **35** | **12** | **10** | **5** | **6** | **10** | **6** | **99** |
| Median duration of exposure, weeks | 49 | 37.6 | 29.6 | 81 | 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 (%) | | | | | | | | | | |
| AE | 0 | 0 | 2 (6) | 1 (18) | 2 (20) | 1 (20) | 0 | 0 | 0 | 6 (6) |
| Pt/guardian decision | 1 (100) | 0 | 1 (3) | 1 (8) | 0 | 1 (20) | 0 | 0 | 0 | 4 (4) |
| Disease progression* | 0 | 0 | 2 (6) | 0 | 1 (10) | 0 | 0 | 0 | 1 (17) | 4 (4) |
| Death | 0 | 0 | 0 | 1 (8) | 0 | 0 | 0 | 0 | 0 | 1 (1) |

*only 1 pt with detectable myristoil binding pocket mutations (V648H, I502L)

Hughes TP, *et al. Blood* 2016:625.

# ABL001 pharmacokinetic profile exhibits dose proportionality from 10 to 200 mg BID

**Dose proportionality using C1D15 (steady state) $AUC_{last}$ from individual patients: 10 to 200 mg BID**




- Rapid absorption (median $T_{max}$≈2 to 3 h)
- Dose-proportional increase in exposure following single and repeated dosing
- Low (<2-fold) to moderate (≈2-fold) accumulation on repeated dosing
- Short apparent elimination half-life (median≈5 to 6 h)

Hughes TP, *et al. Blood* 2016:625.

# Safety: AE suspected of being related to study drug occurring in ≥5% of patients

| 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) |



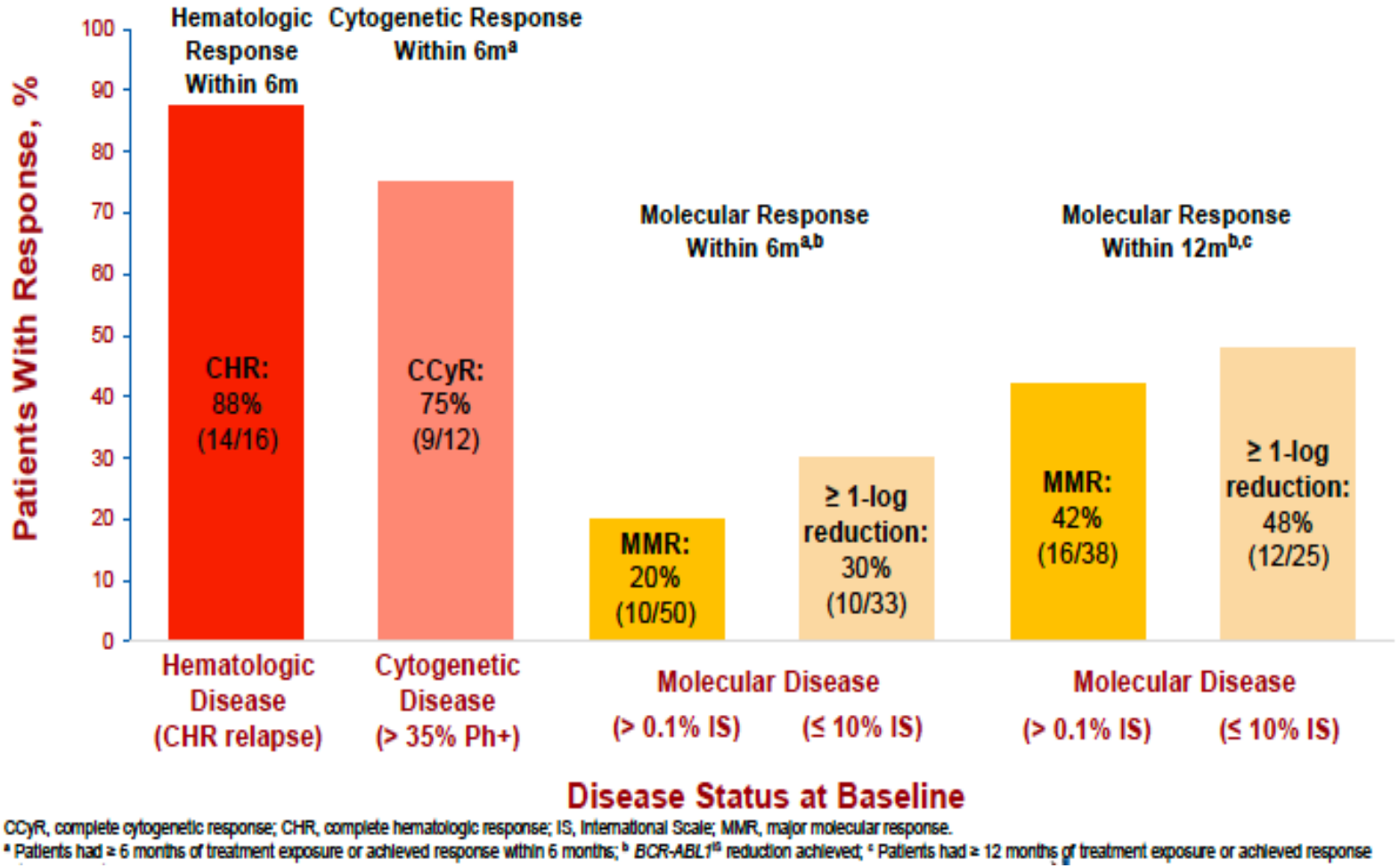
Hughes TP, *et al. Blood* 2016:625.

# Safety: dose-limiting toxicities

- 92 patients evaluable for dose escalation
- There were 6 dose-limiting toxicities:
  - Grade 3 lipase increase (n = 3; 40 mg BID, 200 mg QD, ABL001 40 mg BID + dasatinib 100 mg QD)
  - Grade 2 myalgia/arthralgia (80 mg BID)
  - Grade 3 acute coronary event (150 mg BID)
  - Grade 3 bronchospasm (200 mg BID)
- MTD not declared; 40 mg BID declared as recommended dose for single-agent BID schedule in CML-CP
  - Based on combined analyses of safety, preliminary efficacy, and results of a population-based PK-response model

Hughes TP, *et al. Blood* 2016:625.

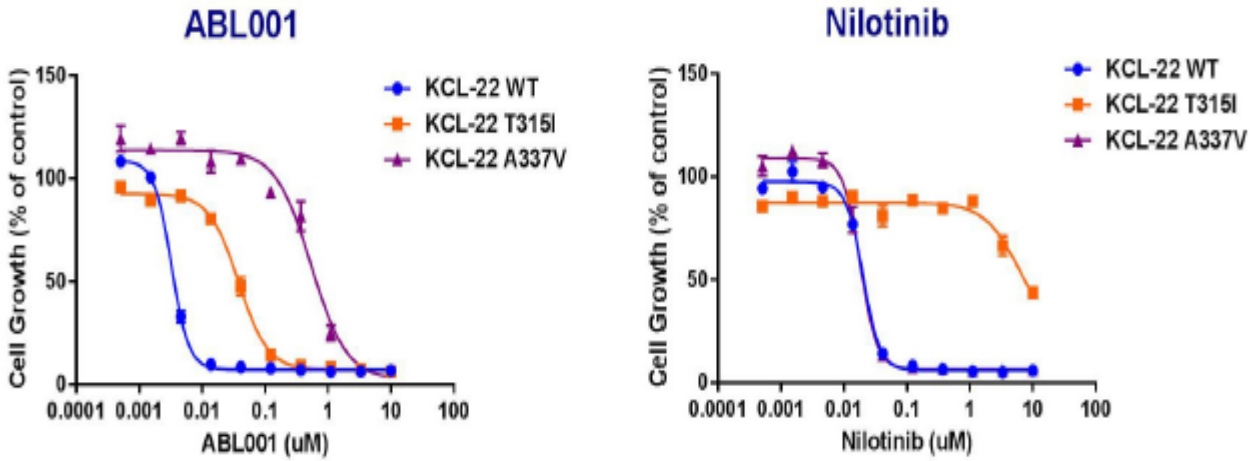
# Responses with single agent asciminib BID ≥ 3 mos exposure on study



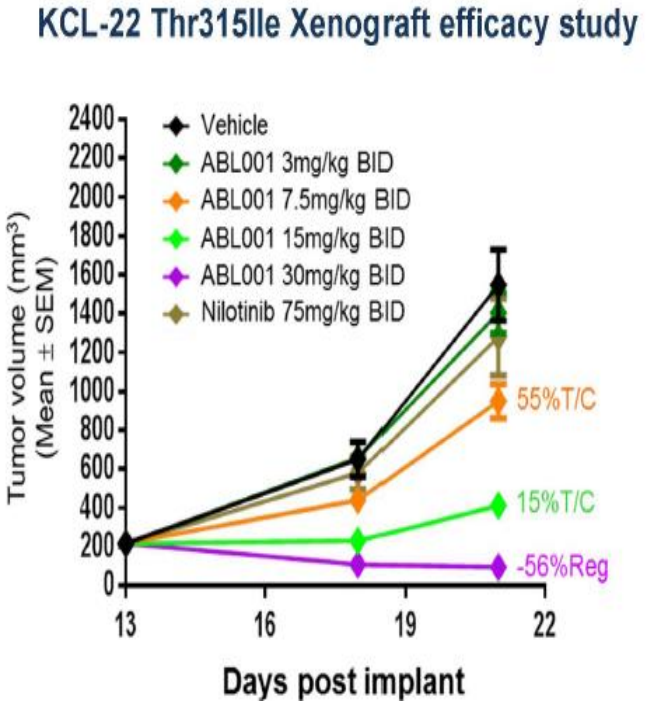

CCyR, complete cytogenetic response; CHR, complete hematologic response; IS, International Scale; MMR, major molecular response.
[a] Patients had ≥ 6 months of treatment exposure or achieved response within 6 months; [b] *BCR-ABL1*[IS] reduction achieved; [c] Patients had ≥ 12 months of treatment exposure or achieved response

Hughes TP, *et al. Blood* 2016:625.

# *In vitro and in vivo* activity against T315I mutation




- Sensitivity of parental KCL-22WT, KCL-22 T315I and KCL-22 A337V to ABL001 and Nilotinib




- KCL-22 T315I were implanted in a xenograft model and ABL001 tested at increased dose

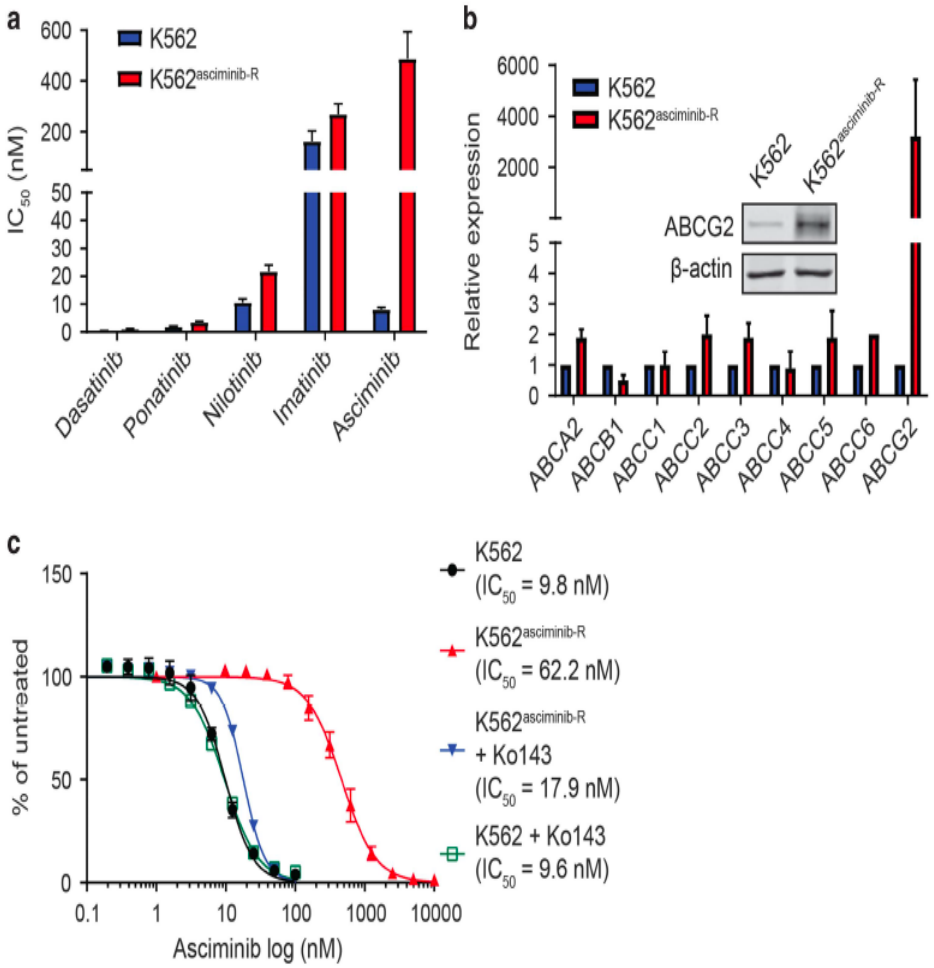
Wylie et al Nature 2017.

# Responses in CML patients with T315I mutation

- 11 of 77 (**14%**) CML patients treated with BID ABL001 had T315I mutations
- ABL001 exhibits a similar duration of exposure in CML patients regardless of T315I mutation status
- Responses in T315I mutant CML patients treated with single agent ABL001 BID for ≥ 3 months
  - **4 of 10 patients in cytogenetic relapse at baseline (> 35% Ph+) achieved CCyR by 6 mo**
  - **6 patients have maintained stable disease without achieving CCyR or MMR**
  - **1 patient has maintained a baseline MMR for > 1 year**
  - **No patients have progressed to blast crisis**

Hughes TP, *et al. Blood* 2016:625.

# Possible mechanisms of resistance to asciminib (I)




- **Upregulation of the ABCG2 efflux pump**

-Generation of 5 asciminib resistant cell lines

-Asciminib level was measured by mass spectrometry

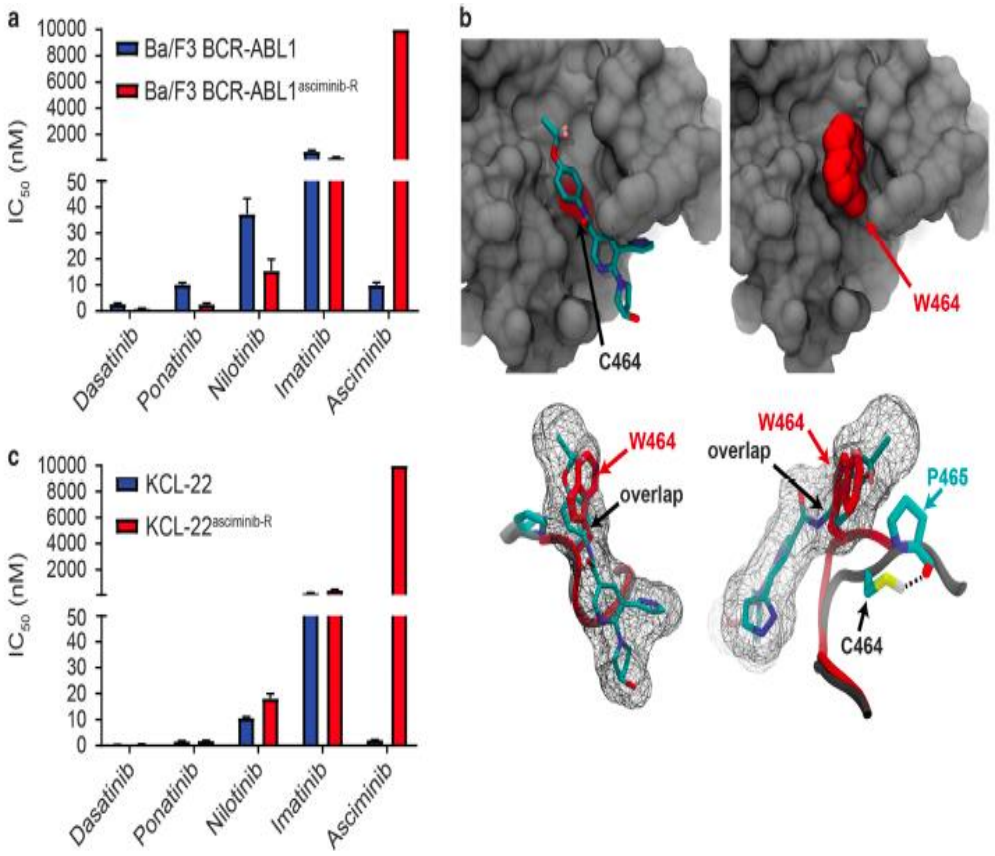
-Asciminib was undetectable in K562 $^{\text{asciminib-R}}$

-ABCG2 inhibitor (Ko143) restored asciminib effectiveness against K562 $^{\text{asciminib-R}}$

-Asciminib resistance can be override by dose escalation of the drug or the association with ABCG2 inhibitor

Qiang *et al. Leukemia 2017; 31: 2844*

# Possible mechanisms of resistance to asciminib (II)




- **Emergence of BCR-ABL1 mutations at the myristoil binging site and at a distant residue**

-C464W as asciminib-resistant mutant: the bulky tryptophan residue prevents access of asciminib to the myristoil-binding pocket

-Other mutations near the myristoil-binding pocket that can confer resistance are:
A337V, P465S, V468F or compound mutation M244V/A337V

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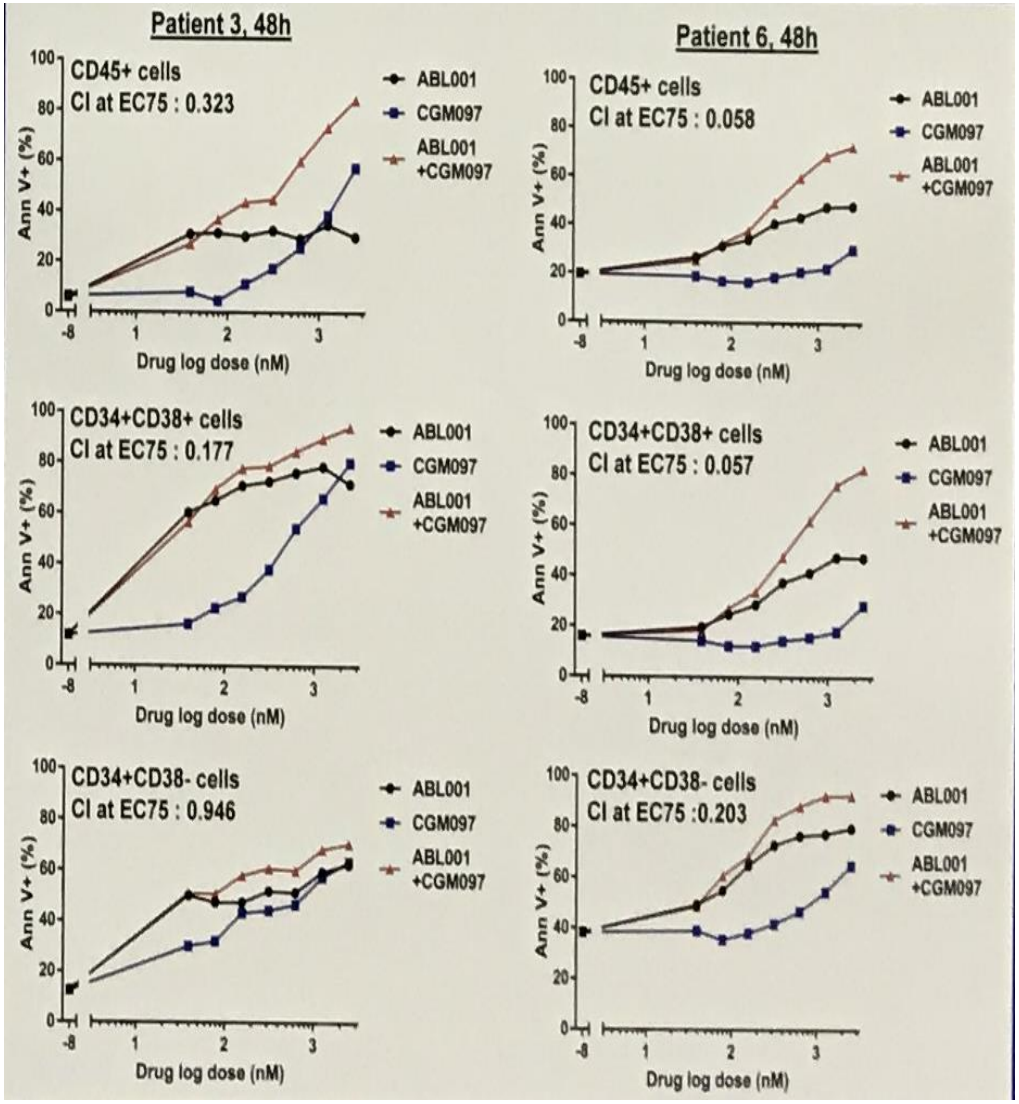
# ABL001 overcomes TKI resistance and enhances MDM2 inhibitor activity in blast crisis

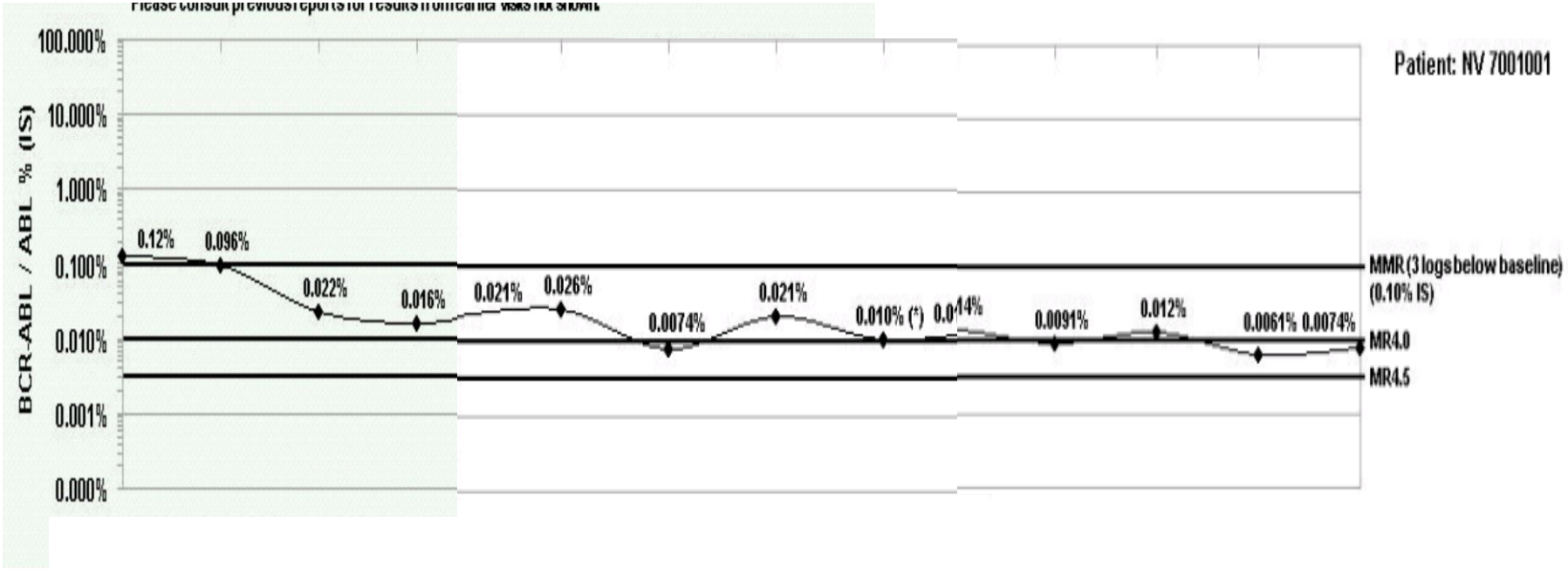



- ABL001 exhibits cytotoxicity in cell from BC patient samples with multiple mutations treated with various TKIs
- Activation of p53 by MDM2 inhibition induces apoptosis and enhances the activity of ABL001 in apoptosis induction in CD45+, CD34+CD38+ or CD34+CD38- cells
- ABL001 overcomes BCR-ABL TKI resistance and enhances MDM2 inhibitor activity in BC-CML

Tao et al, Blood 2017: abs 1586.

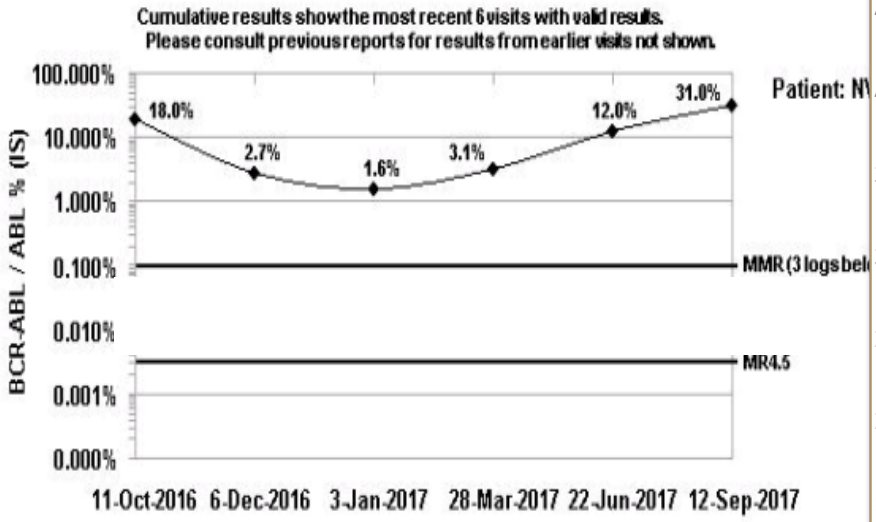
# Clinical case (1): our first and long-term treatment pts

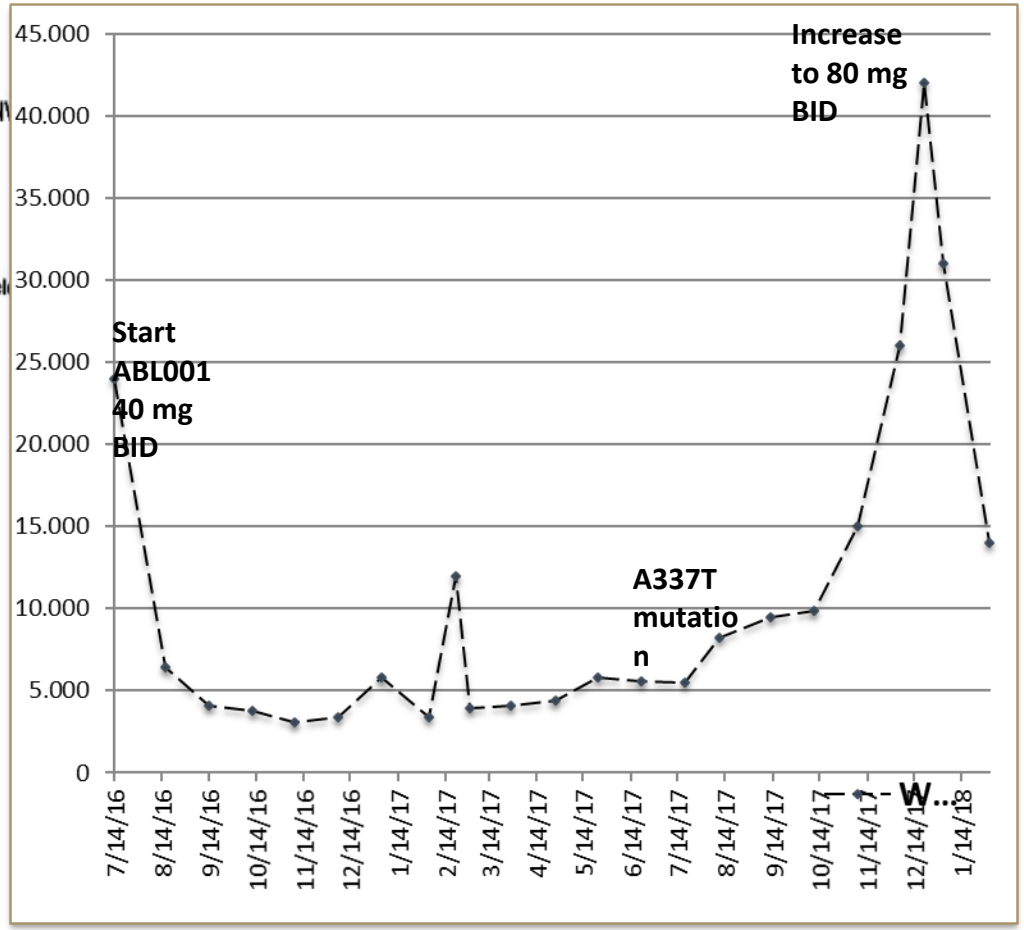
- Previously resistant to imatinib, nilotinib and dasatinib. Also intolerant to dasatinib 100 mg, with several episodes of hematologic toxicity (Grade 3 thrombocytopenia)



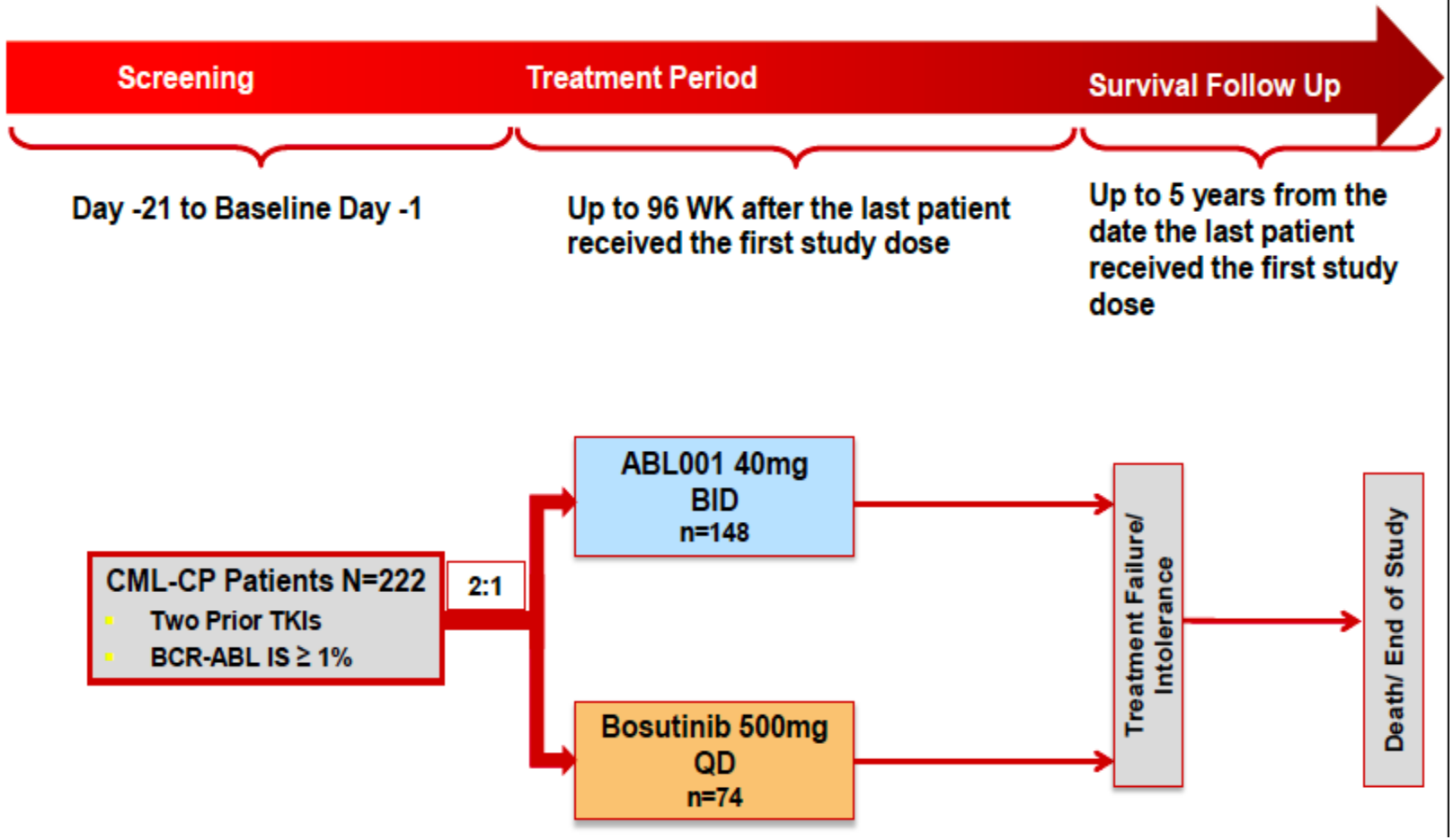
# Clinical case (2): a patient who developed resistance to ABL001 but was rescued with dose escalation

- Previously resistant to imatinib (ACA/OCA) and dasatinib (F317V, also intolerant to dasatinib with neutropenia, mouth ulcers). Previous thrombotic events.



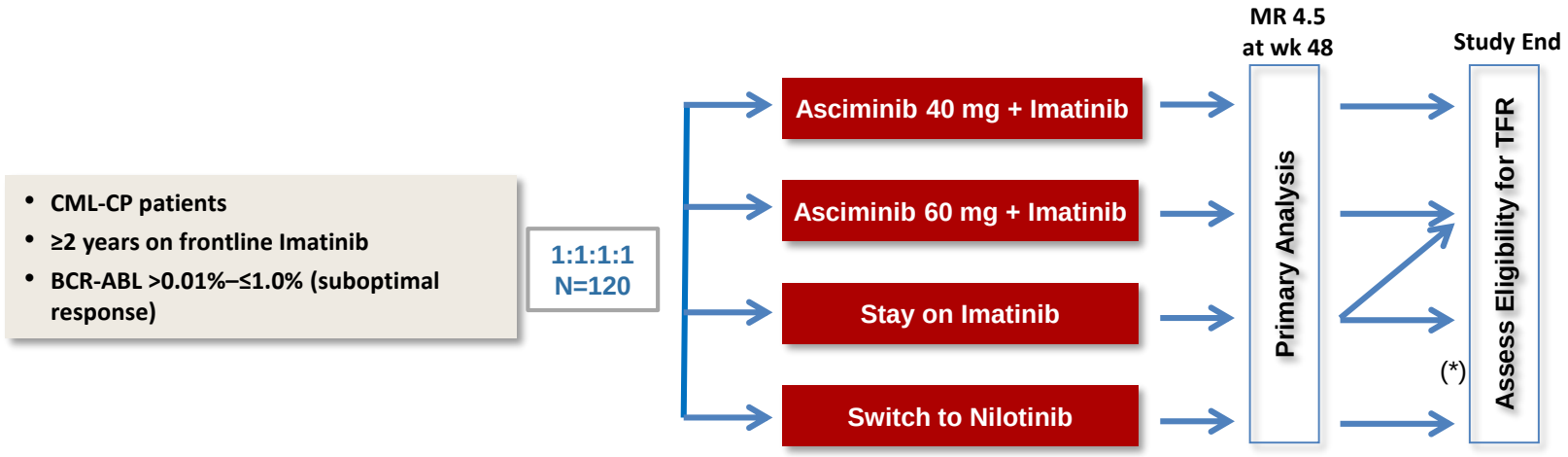
# ABL001 vs bosutinib in CML pts prevously treated with 2 or more TKIs




- **Primary endpoint: to compare the rate of MR3 at 24 weeks**

# Phase II Study Design –Asciminib add on to 1L Imatinib (CABL001E2201)

## 4 Arm Study Design Allows Evaluation of 2 dose levels against 2 controls




* Patients on imatinib continuation without MR4.5 after 48 weeks of treatment will be offered to crossover to combination treatment

| | |
|---|---|
| **Primary Objective** | • Compare MR4.5 rate at 48 weeks with asciminib (40 or 60 mg) + imatinib vs continued imatinib |
| **Secondary Objective** | • Estimate difference in MR4.5 rate at 48 weeks between asciminb (40 or 60 mg)+imatinib and switch to Nilotinib<br>• Assess additional efficacy parameters with asciminib (40 or 60 mg) vs continued imatinibor switch to nilotinib<br>• Safety and tolerability profile of Asciminib + Imatinib vs continued Imatinib or switch to Nilotinib<br>• Assess PK profile of Asciminib (40 or 60 mg) +Imatinib |
| **Exoloratory Objective** | • Patient –reported outcomes<br>• Biomarkers |

# Conclusions

- ABL001 was generally well tolerated in heavily-treated CML patients resistant to or intolerant of prior TKIs
- Preliminary pharmacokinetic exposures appear linear in the dose range tested
- Evidence of single-agent efficacy at 40 mg BID
  - Clinical activity across several TKI-resistant mutations (e.g, V299L, F317L, Y253H)
  - Myristoyl binding pocket mutations (V468H, I502L, A337V, C464W) may lead to clinical resistance
- Allosteric inhibition of BCR-ABL1 is a promising therapeutic approach in patients with CML