Future research: Asciminib, and other future drugs

Using new drugs in CML

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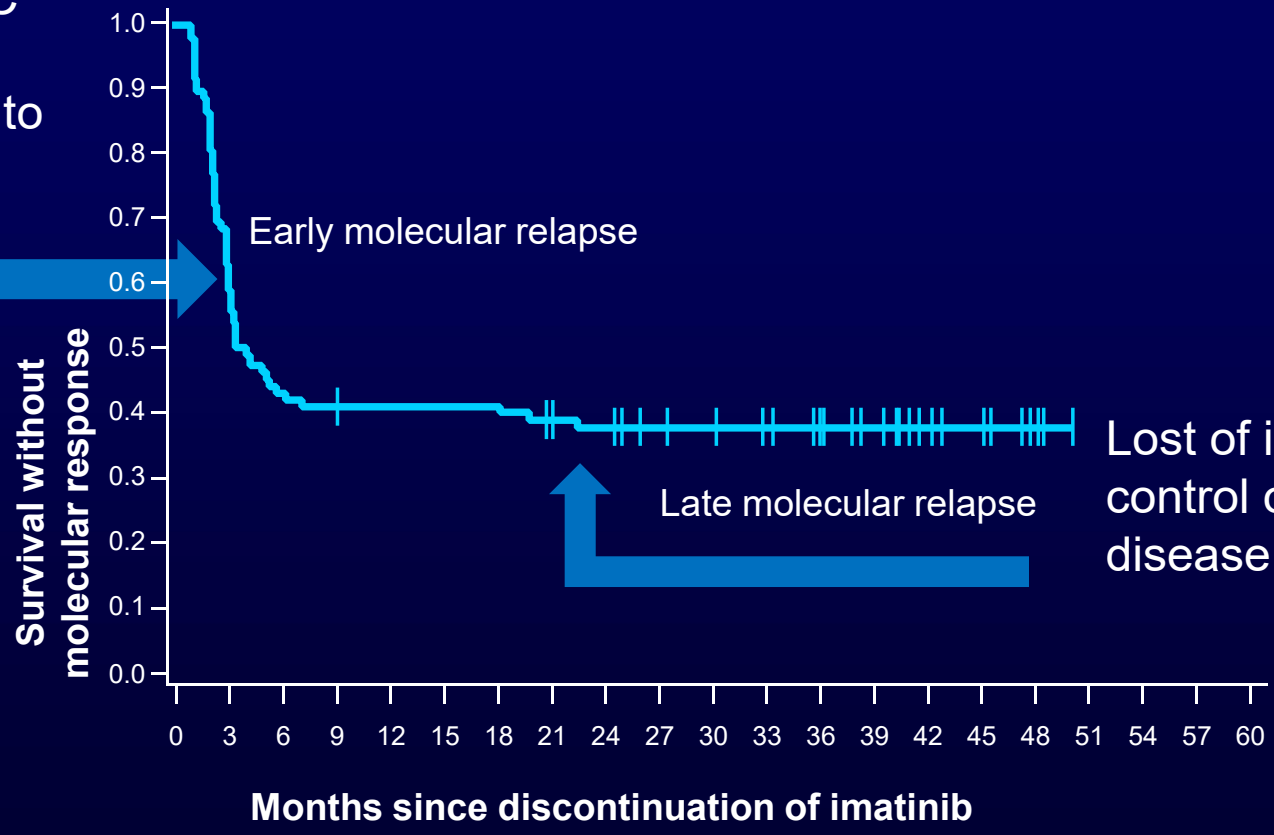
Université Bordeaux, France

Hypothesis for recurence or relapse after stopping TKI

Persistence of LSC cells with LIC properties resistant to TKI



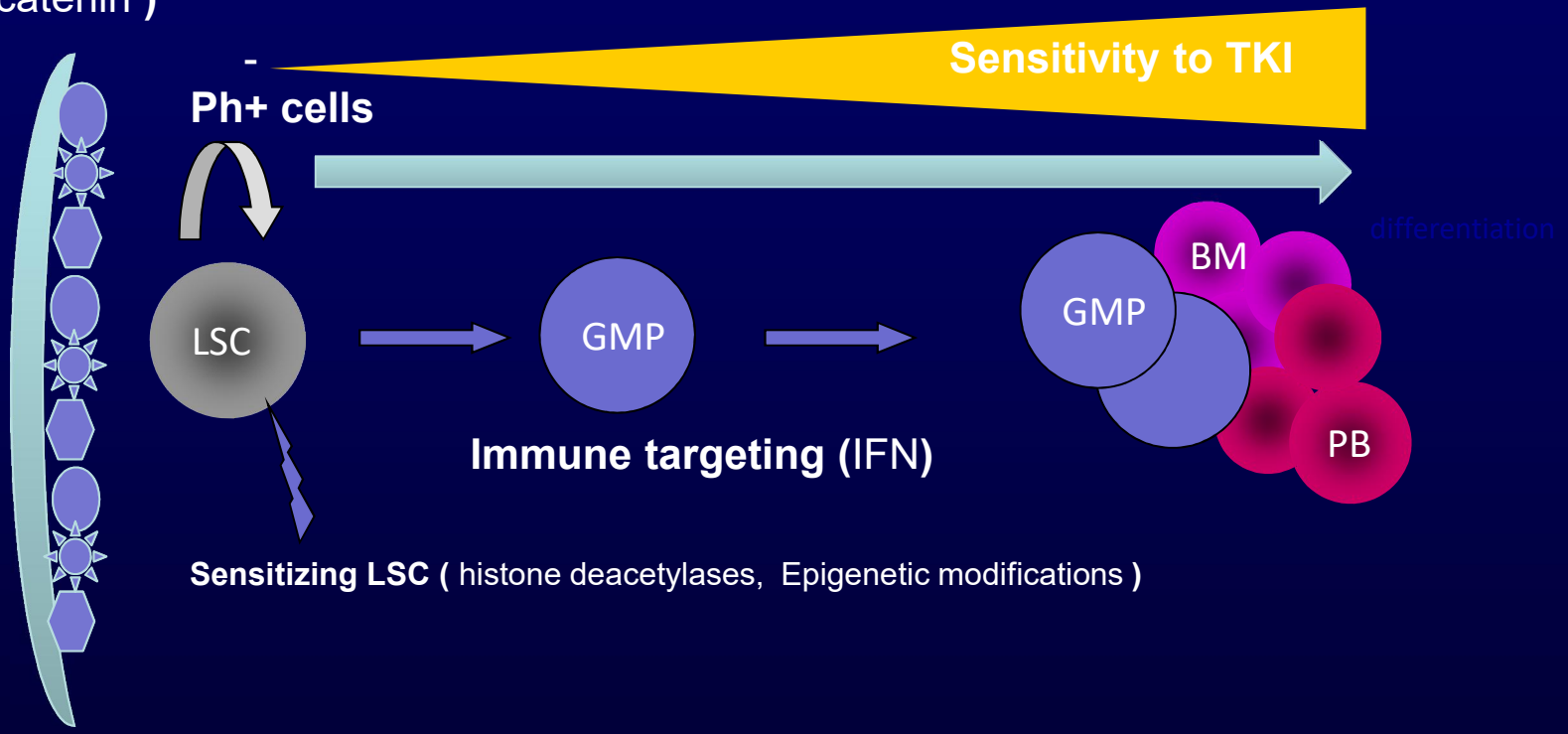
Lost of immune control of the disease

LIC, leukemia-initiating cell; LSC, leukemic stem cell.

Strategies of CML stem cell Targeting : few examples

Inhibiting survival/renewal pathways (Hedgehog or Wntβ catenin **)**

Ph+ Proliferating and differentiated cells

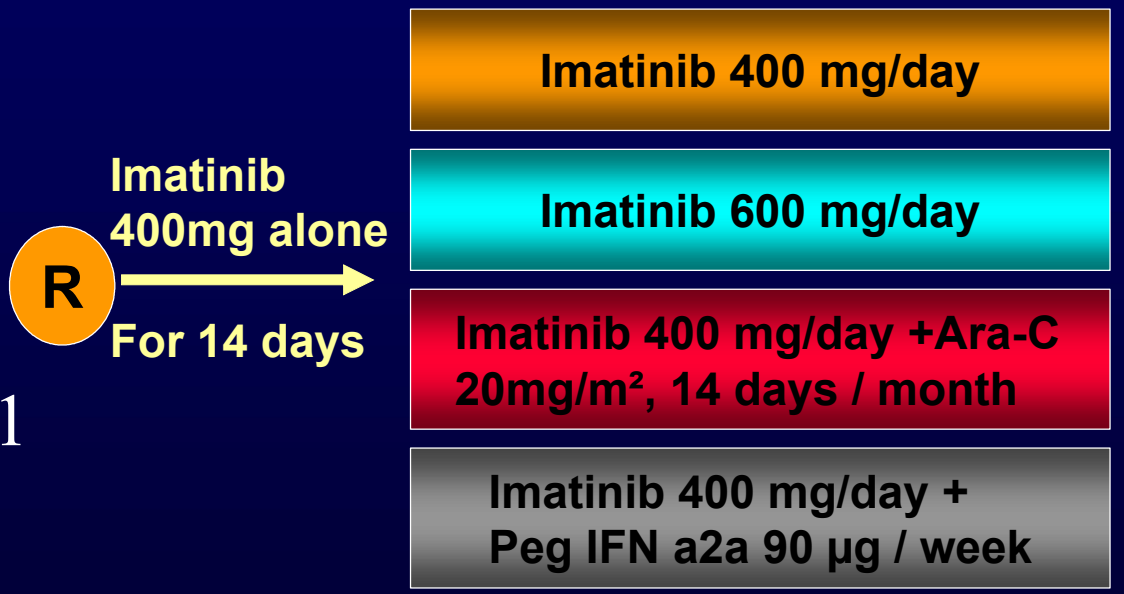


Modifying the bone marrow niche (Jak/STAT inhibitor, PP2A phosphatase activator**)**

LSC: Leukemic stem cell
GMP granulocyte macrophage progenitor, BM Bone marrow differentiated cells
PB peripheral blood cells

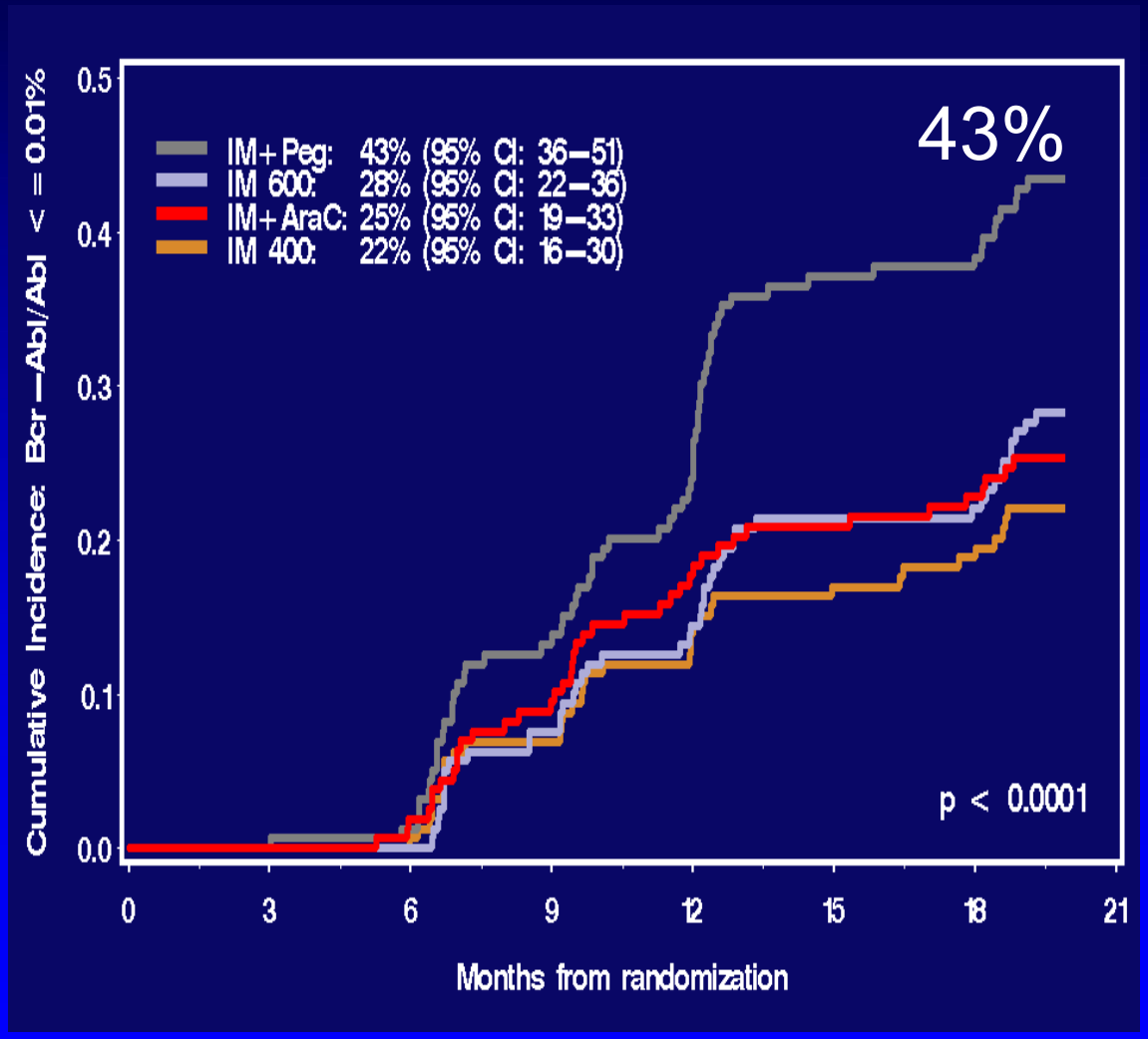
IFN + TKI
SPIRIT trial: Study design

- Eligibility criteria
  - CP CML
  - ≤ 3 months from diagnosis
  - Front-line treatment
- Randomization 1:1:1:1
- Study initiation:
  - Sept 2003

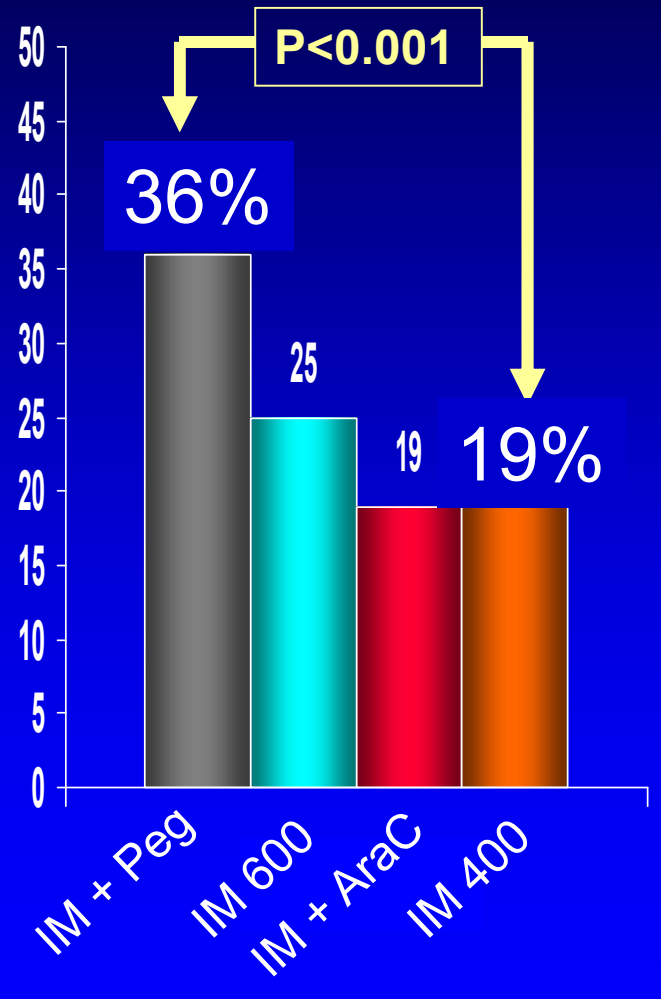


Optimal Molecular Response (Bcr-Abl/Abl ≤ 0.01%)

636 Patients with 18 months follow-up *(ITT)*



Cumulative incidence by 18 Months



OMR at 18 months

Phase II study: Nilopeg trial

Nilotinib and peginterferon alfa-2a for newly diagnosed chronic-phase chronic myeloid leukaemia (NiloPeg): a multicentre, non-randomised, open-label phase 2 study

Franck E Nicolini, Gabriel Etienne, Viviane Dubruille, Lydia Roy, Françoise Huguet, Laurence Legros, Stéphane Giraudier, Valérie Coiteux, Agnès Guerci-Bresler, Pascal Lenain, Pascale Cony-Makhoul, Martine Gardembas, Eric Hermet, Philippe Rousselot, Shanti Amé, Marie-Claude Gagnieu, Christine Pivot, Sandrine Hayette, Veronique Maguer-Satta, Madeleine Etienne, Stéphanie Dulucq, Delphine Rea, François-Xavier Mahon

Lancet Haematol 2015; 2: e37–46

CP CML ≤ 3 *Months*

Priming
PEG-Interferon -α2a
90 µg/wk

Nilotinib
300 mgx2/d
+
PEG-Interferon -α2a
45 µg/wk

Follow-up
24 months

Screening Inclusion

Month 1 — Month 24

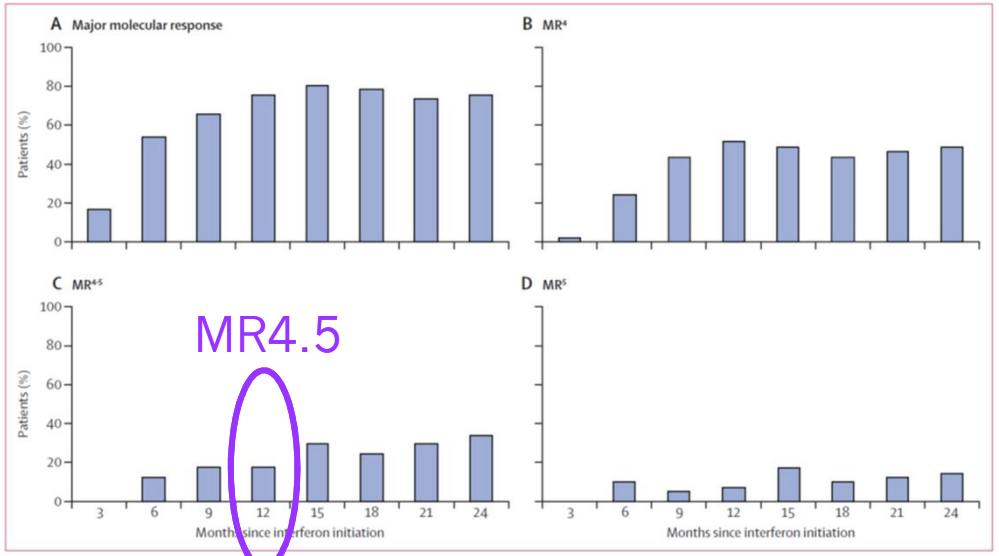


Figure 1: Percentage of patients in molecular response at different timepoints.
(A) Major molecular response. (B) MR⁴. (C) MR⁴·⁵. (D) MR⁵. MR=molecular response. MR⁴=MR 4 log. MR⁴·⁵=MR 4·5 log. MR⁵=MR 5 log.

Phase III randomized trial, comparing MR4.5 rates at 12 months in *de novo* Philadelphia positive CP CML, treated with nilotinib 600 mg daily *versus* nilotinib 600 mg daily plus Pegylated Interferon-alpha 2a

PEgylated interferon-α2a and TAsigna® for first Line therapy of chronic phase CML patientS

Franck E. Nicolini, Gabriel Etienne, Françoise Huguet, Agnès Guerci-Bresler, Aude Charbonnier, Martine Escoffre-Barbe, Viviane Dubruille, Hyacinthe Johnston-Ansah, Laurence Legros, Valérie Coiteux, Pascale Cony-Makhoul, Pascal Lenain, Lydia Roy, Philippe Rousselot, Denis Guyotat, Jean-Christophe Ianotto, Martine Gardembas, Fabrice Larosa, Denis Caillot, Pascal Turlure, Stéphane Courby, Philippe Quittet, Eric Hermet, Shanti Amé, Simona Lapusan, Vérane Schwiertz, Stéphane Morisset, Madeleine Etienne, Delphine Rea, Stéphanie Dulucq, François-Xavier Mahon

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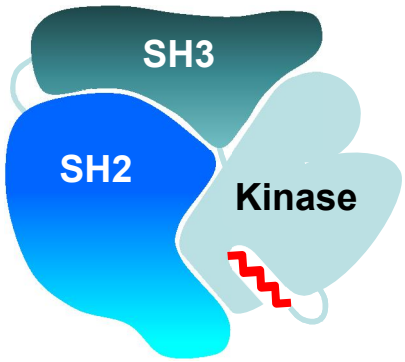
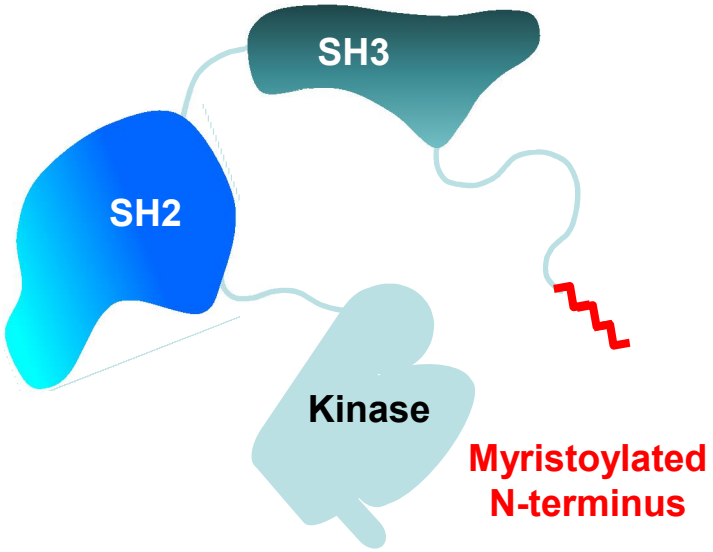
Allosteric inhibitors : a new class of drugs

Update on Asciminib Clinical Development

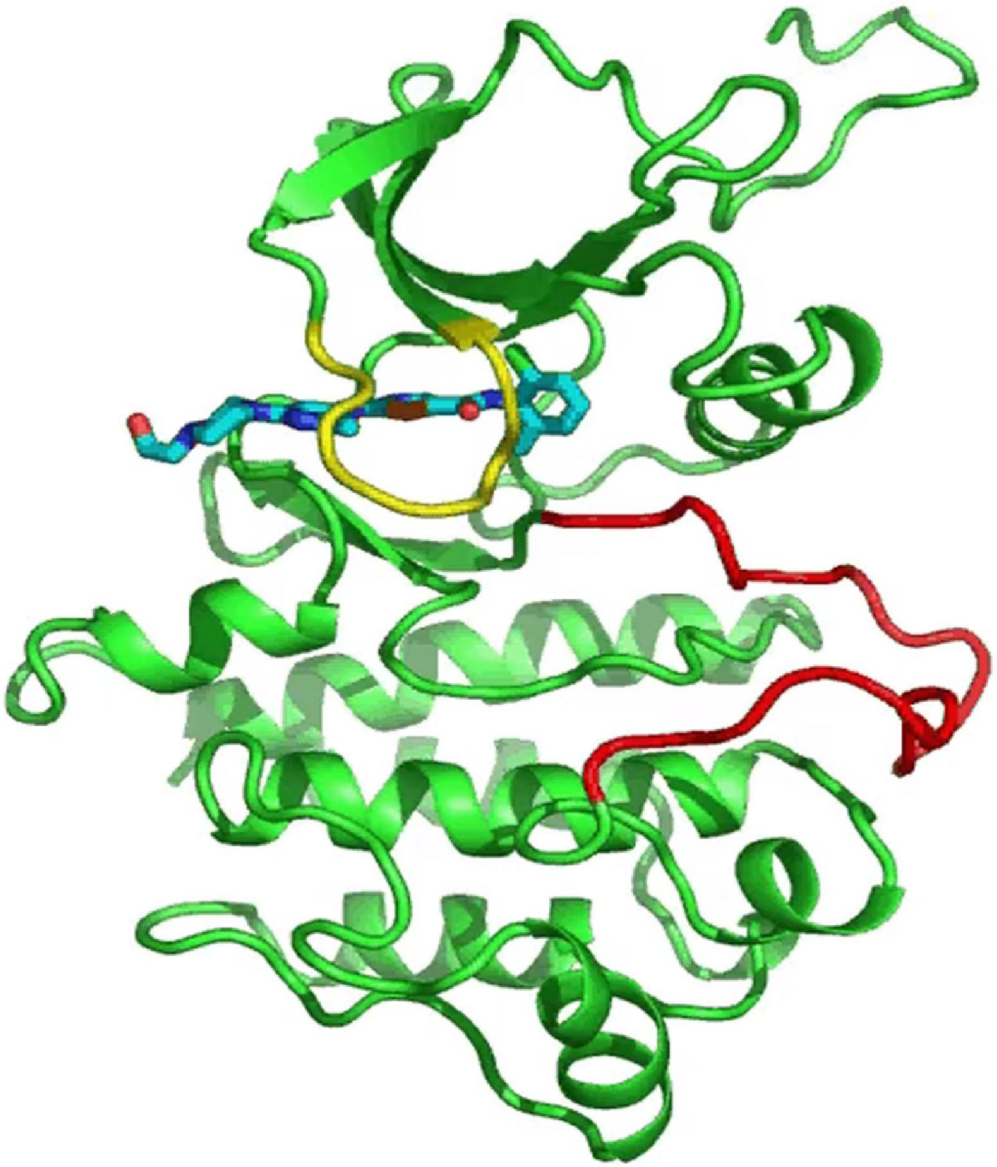




Autoinhibition of ABL1 by engagement of the myristoyl binding site

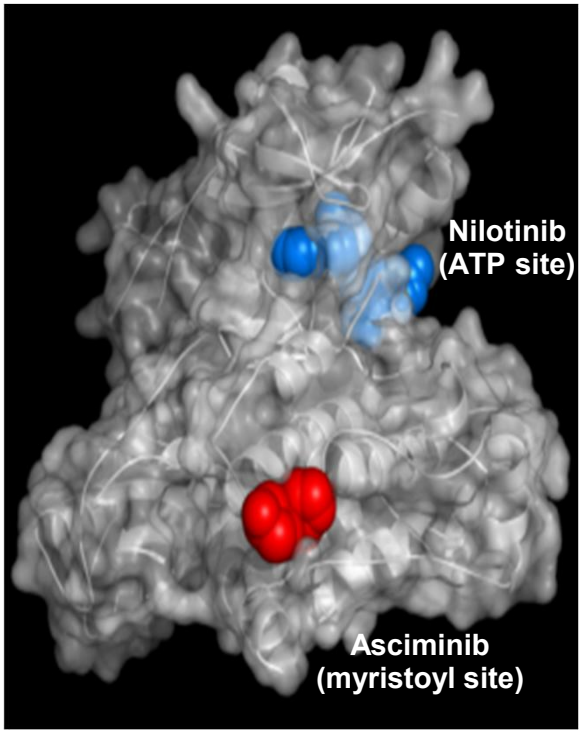
ABL1
INACTIVE CONFORMATION

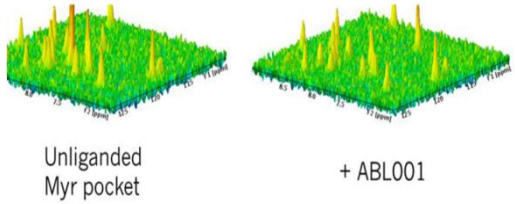
A model of targeted therapy



asciminib is a potent and specific BCR-ABL inhibitor

- Biochemistry
  - Caliper ABL1 assay IC_{50} – 0.4 nM
- Biophysics
  - ITC ABL1 assay IC_{50} – 0.7 nM
- Selectivity
  - Kinase selectivity restricted to ABL1 and ABL2
- Cardio-safety profile
  - hERG assay > 30 µM
  - No evidence of QT prolongation in dog jacketed telemetry up to 600 mg/kg





Unliganded
Myr pocket

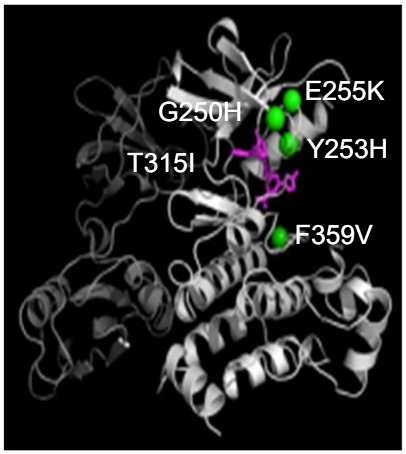
+ Asciminib

ABL, Abelson; ABL1, Abelson murine leukaemia viral oncogene homologue 1; ATP, adenosine triphosphate; BCR-ABL, breakpoint cluster region-ABL; hERG, human ether-a-go-go-related gene; IC_{50}, half-maximal inhibitory concentration; ITC, isothermal titration calorimetry; Myr, myristoyl; QT, Q wave, T wave interval.

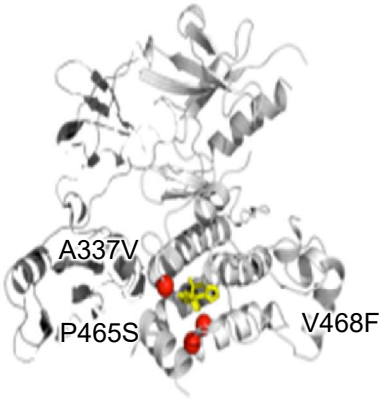
Wylie AA, et al. Nature. 2017;543:733-7.

Asciminib and classic TKIs exhibit complementary mutation profiles

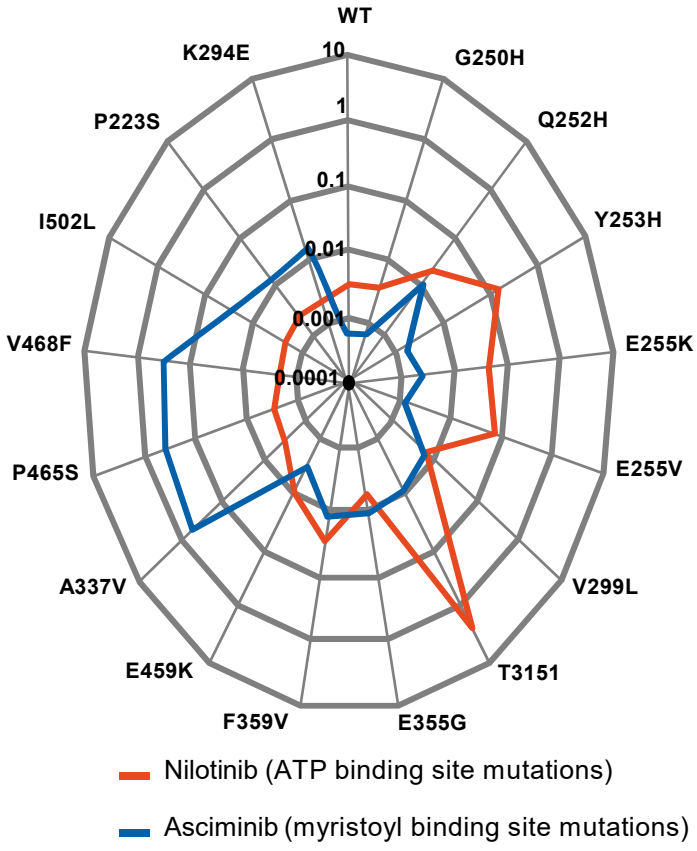
ATP binding site mutations



Myristoyl binding site mutations



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



TKI, tyrosine kinase inhibitor; WT, wild type.

Ottmann O, et al. Blood. 2015;126:abstract 138.
Wylie A, et al. Blood. 2014;124:abstract 398.

asciminib is very well tolerated

Dose-limiting toxicities

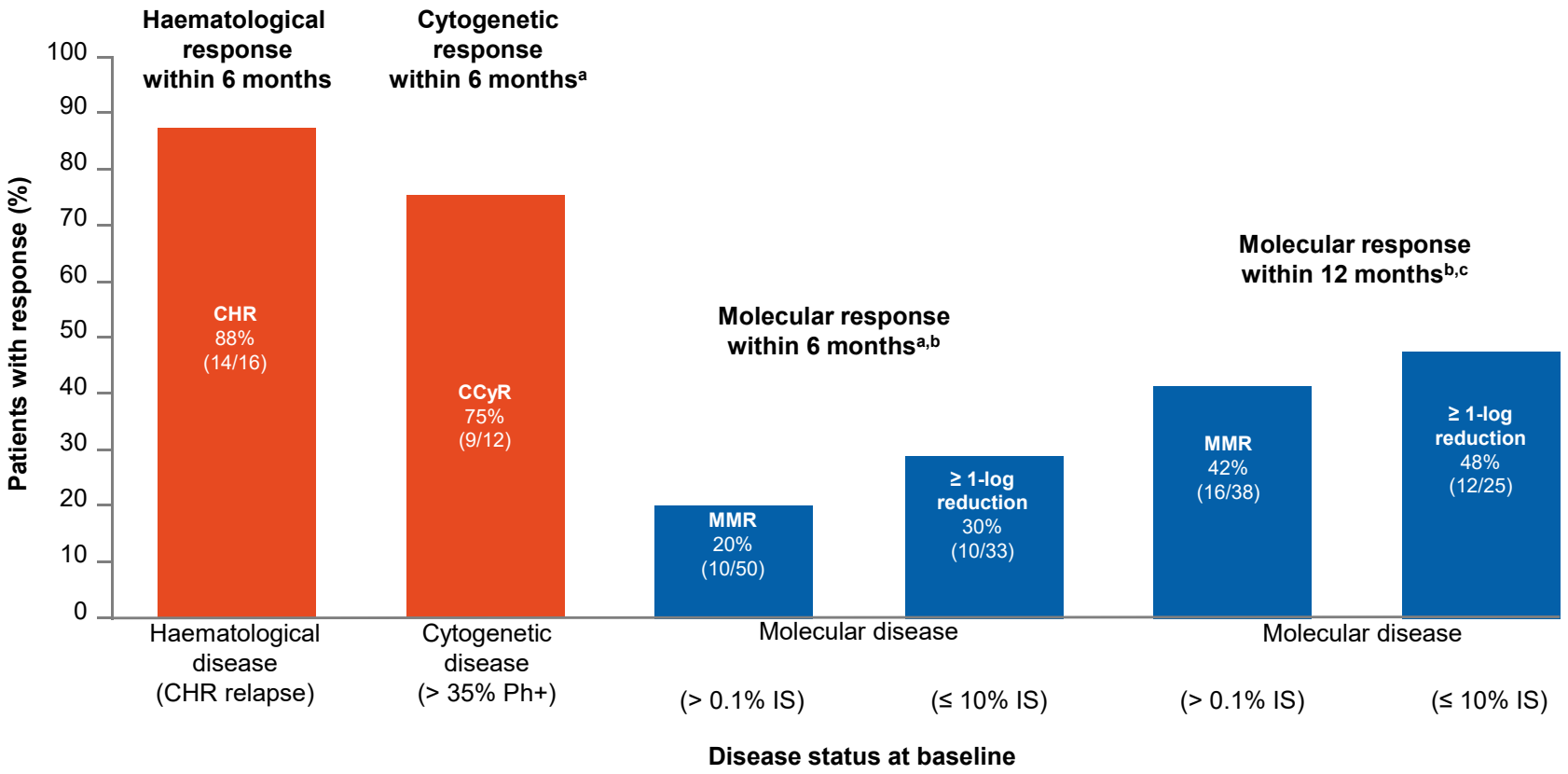
- 92 patients evaluable for dose escalation
- There were 6 dose-limiting toxicities
  - Grade 3 lipase increase (n = 3; 40 mg b.i.d., 200 mg OD, asciminib 40 mg b.i.d. + dasatinib 100 mg OD)
  - Grade 2 myalgia/arthralgia (80 mg b.i.d.)
  - Grade 3 acute coronary event (150 mg b.i.d.)
  - Grade 3 bronchospasm (200 mg b.i.d.)
- 1 death due to multi-organ failure not related to study drug (80 mg b.i.d.)
- **MTD not declared; 40 mg b.i.d. declared as recommended dose for single-agent b.i.d. schedule in CML-CP**
  - Based on combined analyses of safety, preliminary efficacy, and results of a population-based PK-response model

CML, chronic myeloid leukemia; CP, chronic phase; MTD, maximum tolerated dose; OD, once daily; PK, pharmacokinetic.

Hughes TP, et al. Blood. 2016;128:abstract 625.

asciminib is highly effective alone

CABL001X2101: responses in CML with asciminib b.i.d.



[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.
CHR, complete haematological response; CCyR, complete cytogenetic response;
IS, International Scale; MMR, major molecular response; Ph+, Philadelphia chromosome-positive

Hughes TP, et al. Blood. 2016;128:abstract 625.

Clinical development of asciminib

Phase 1 first-in-human study (NCT02081378)[1]

- Patients with Ph+ leukemias
- Failure of ≥ 2 ATP binding-site TKIs
- Multiple asciminib doses/regimens

Randomized phase 3 study (NCT03106779)[2]

- Patients with CML-CP and failure of ≥ 2 ATP binding-site TKIs

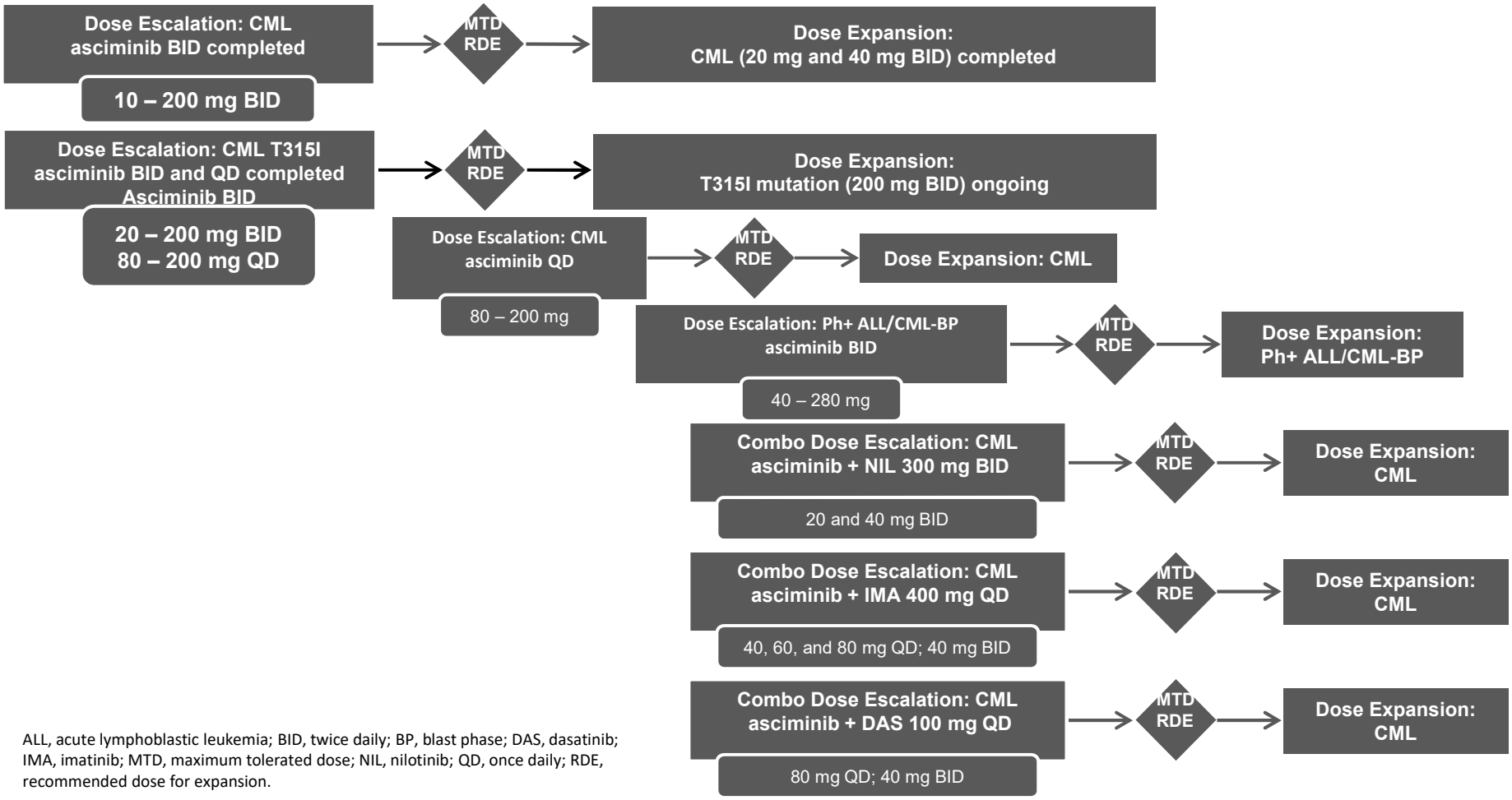
Randomized phase 2 study (NCT03578367)[3]

- Patients with CML-CP and no DMR after ≥ 2 y of 1L imatinib

1L, frontline; CP, chronic phase; DMR, deep molecular response; Ph+, Philadelphia chromosome–positive.

1. Hughes TP, et al. *Blood*. 2016;128: abstract 625. 2. Mauro MJ, et al. *J Clin Oncol*. 2018;36: abstract TPS7081. 3. Saglio G, et al. Presented at the 20th Annual John Goldman Conference on Chronic Myeloid Leukemia: Biology and Therapy; September 13-16, 2018; Miami, Florida.

First-in-human phase 1 study design (Bordeaux, Paris)

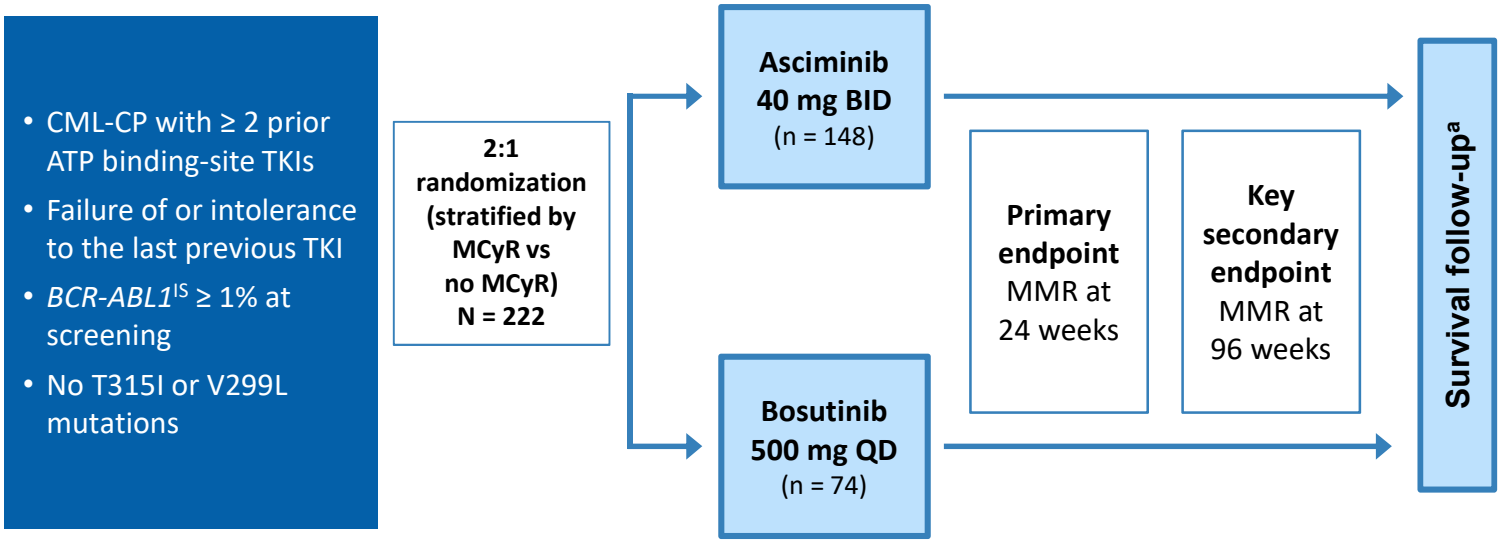


ALL, acute lymphoblastic leukemia; BID, twice daily; BP, blast phase; DAS, dasatinib; IMA, imatinib; MTD, maximum tolerated dose; NIL, nilotinib; QD, once daily; RDE, recommended dose for expansion.

Asciminib monotherapy in 3L+ phase 3 study design (CABL001A2301)

(Bordeaux, Paris, Lyon, Marseille, Nancy, Lille)

ASCEMBL



Treatment duration: 96 weeks[b]

[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.
Mauro MJ, et al. *J Clin Oncol.* 2018;36 [abstract TPS7081].

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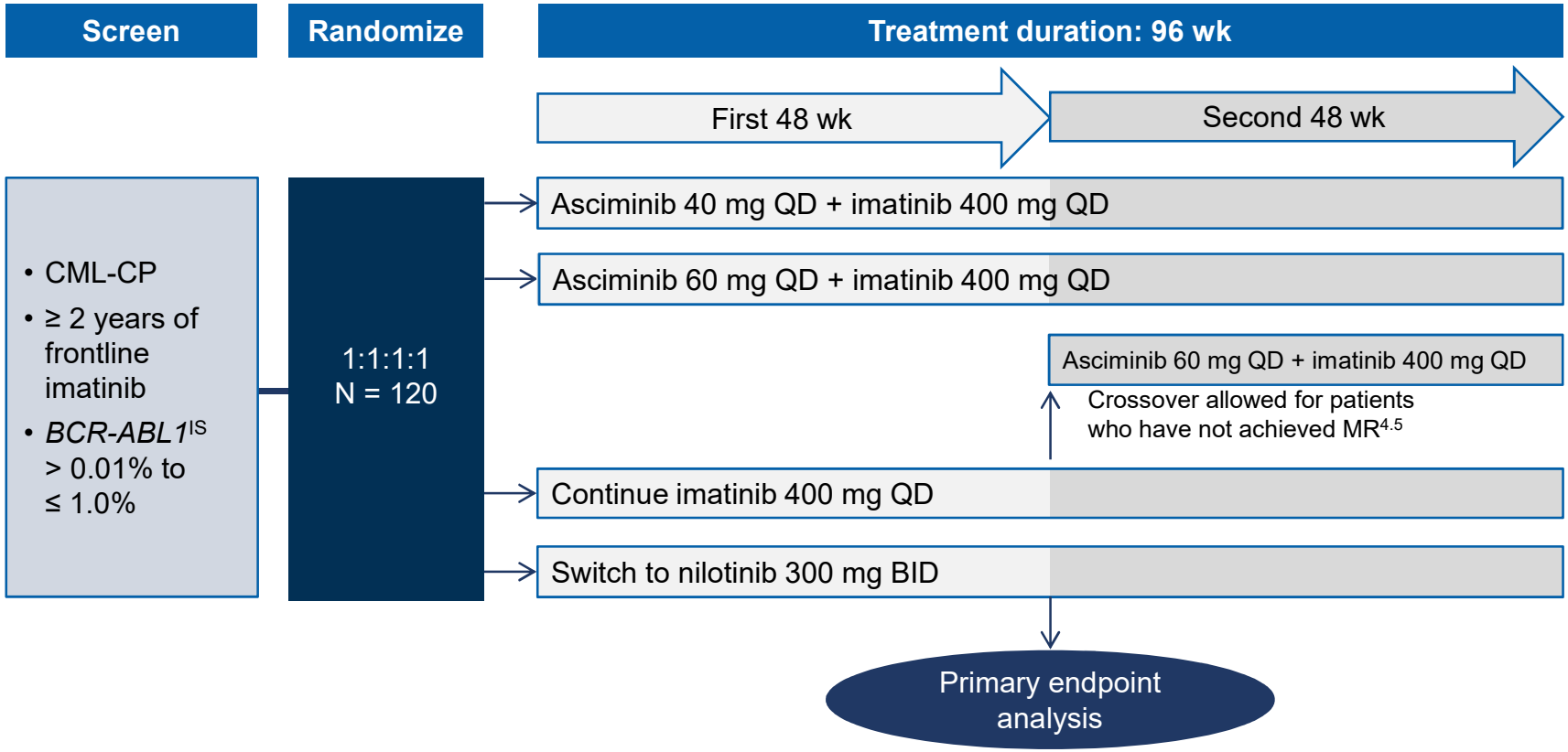
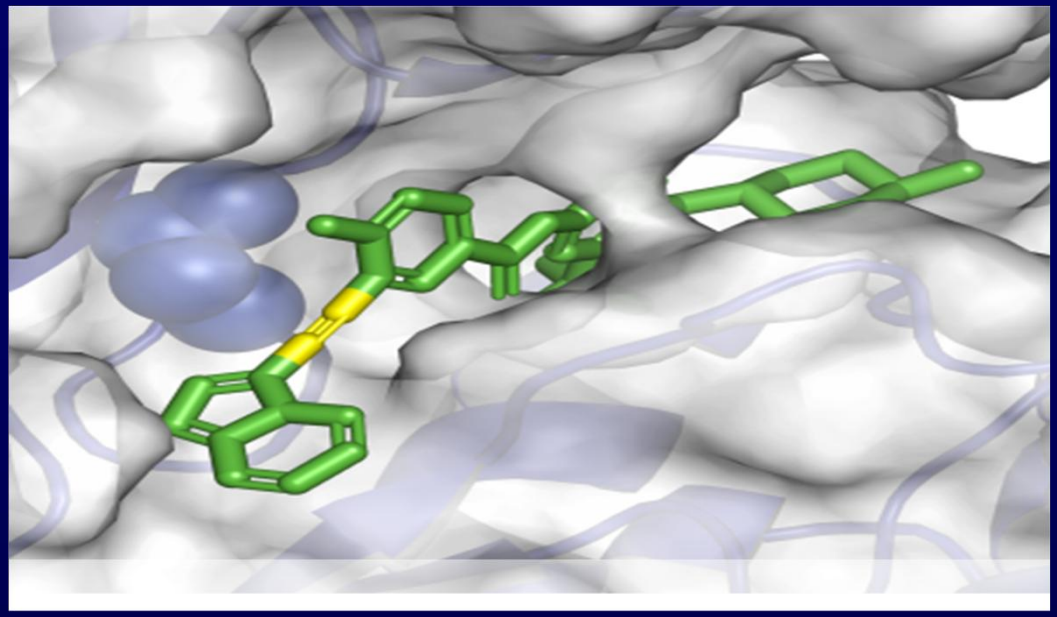
Asciminib add-on to 1L imatinib for DMR phase 2 study design (CABL001E2201) (Bordeaux)



Saglio G, et al. Presented as a poster at the European School of Haematology 20th Annual John Goldman Conference on Chronic Myeloid Leukemia: Biology and Therapy; 13-16 September 2018; Miami, Florida.

For external presentation in response to an unsolicited medical request—not for distribution.

Ponatinib like drugs



PF-114 Mesylate, a Novel Third Generation ATP-Competitive BCR-ABL Tyrosine Kinase Inhibitor: First Safety and Efficacy Data from a Phase I Study in Patients with CML with Failure of Prior TKI Therapy.
Turkina et al. Blood 2017 130:895;

Safety and Efficacy of HQP1351, a 3rd Generation Oral BCR-ABL Inhibitor in Patients with Tyrosine Kinase Inhibitor—Resistant Chronic Myelogenous Leukemia: Preliminary Results of Phase I Study
Qian Jiang et al , Blood 2018 132:791;

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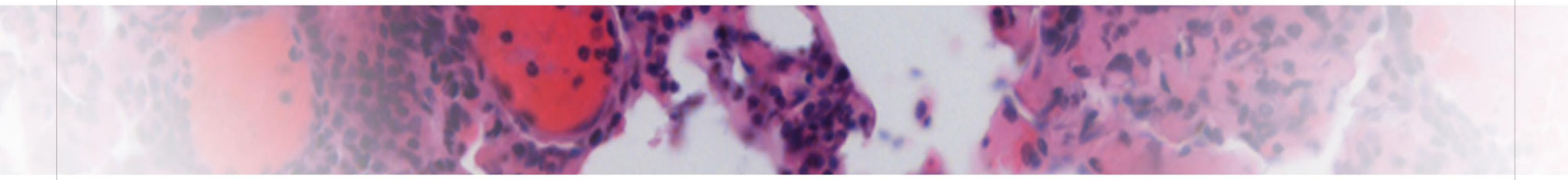


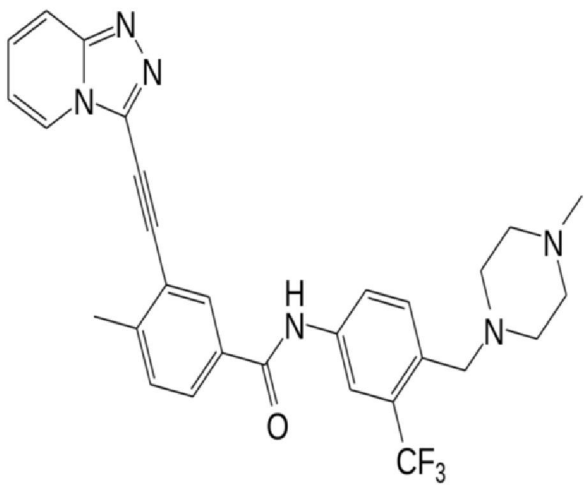
Phase-1 Study of PF-114 Mesylate in CML Failing Prior Tyrosine Kinase-Inhibitor Therapy

NCT02885766

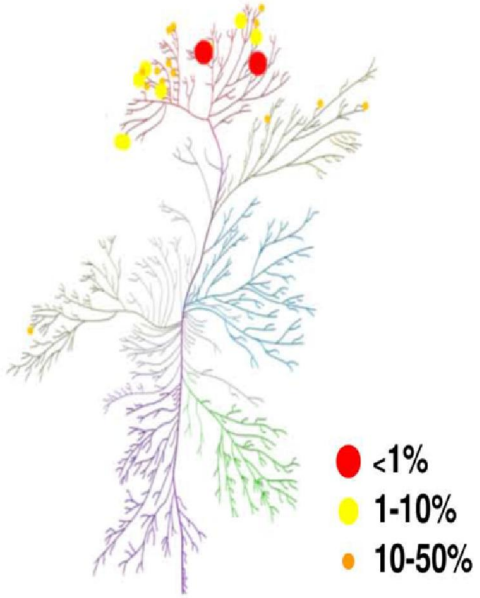
60th ASH Annual Meeting
December 1-4, 2017
San Diego, CA

PF-114 – Novel 4th Generation Inhibitor of Bcr-Abl

- PF-114: 4th generation Abl inhibitor, close structural analog of ponatinib
- PF-114 rationally designed to avoid inhibition of numerous off-target kinases and potentially avoid life-threatening side effects



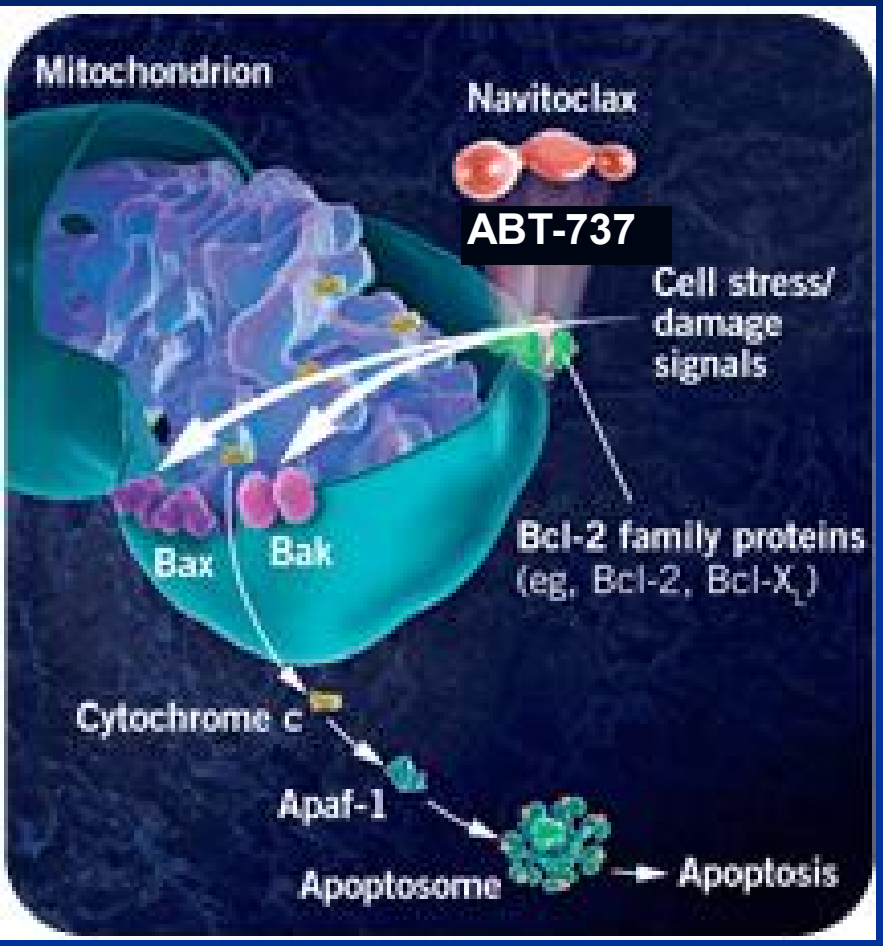
PF-114

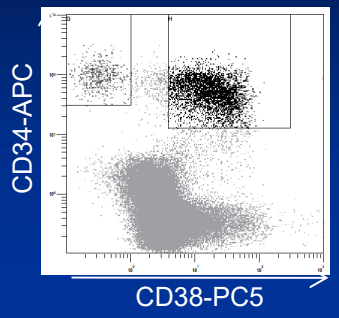


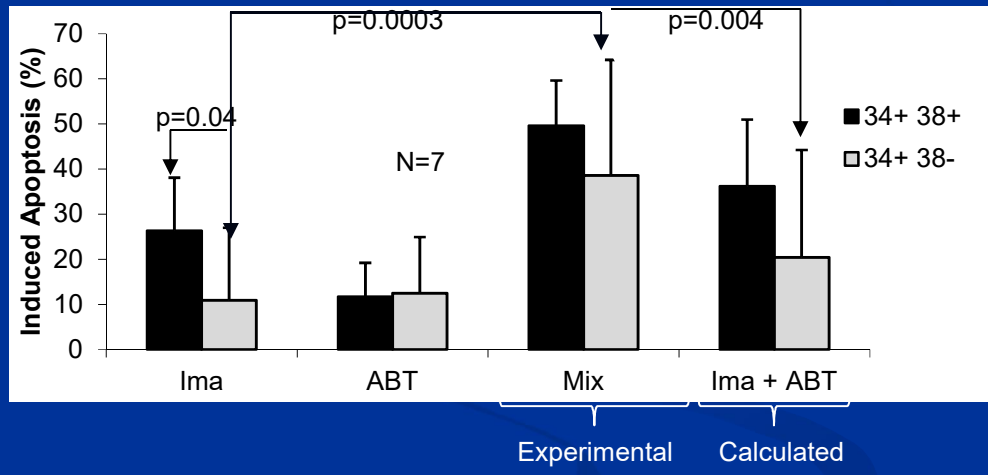
Residual kinase activity at 100 nM of PF-114

PF-114 profile of kinase inhibition confirms the concept of improved selectivity

ABT-737 cooperates in synergism with tyrosine kinase inhibitor to induce apoptosis in CML





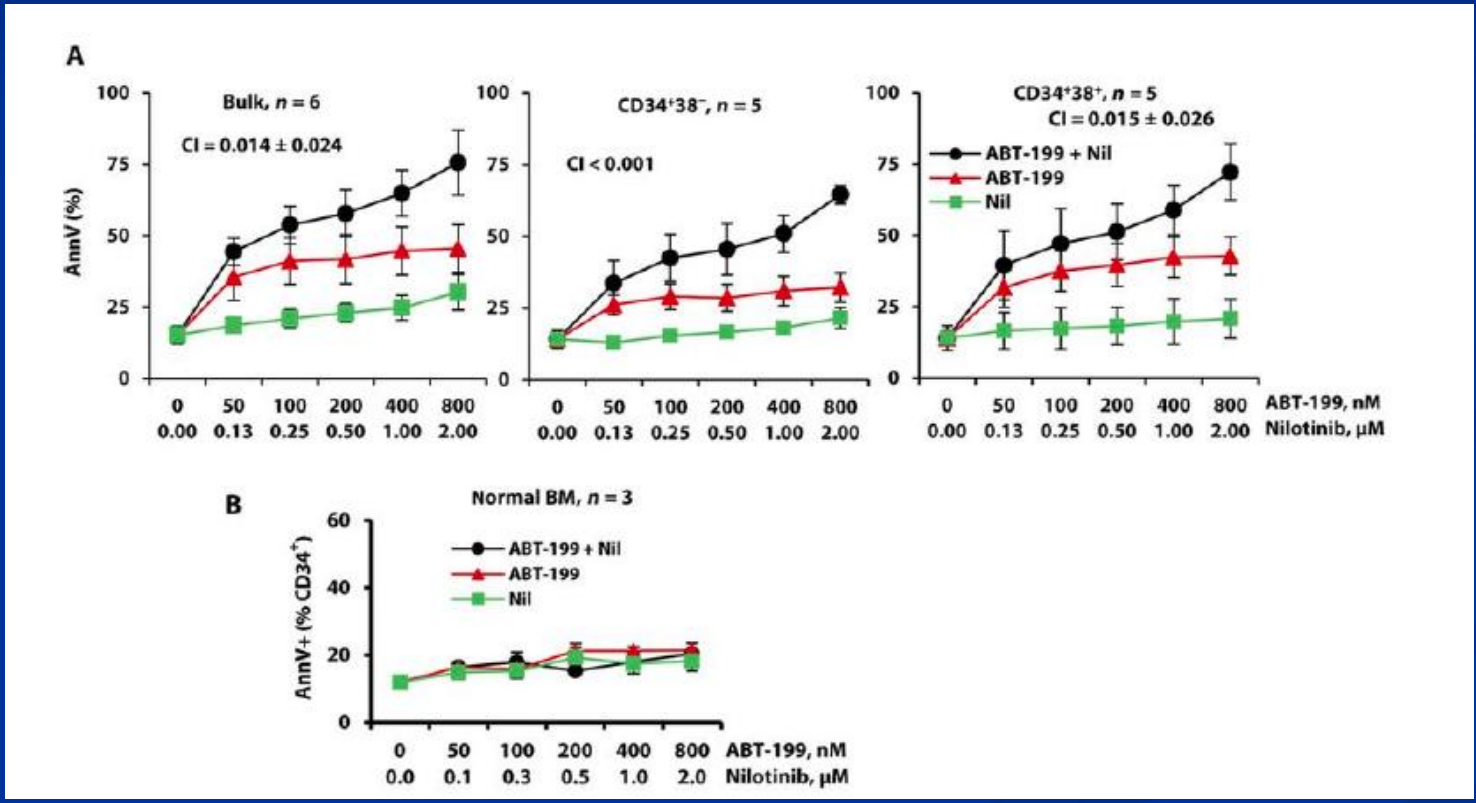


ABT-737 increases tyrosine kinase inhibitor-induced apoptosis in chronic myeloid leukemia cells through XIAP downregulation and sensitizes CD34(+) CD38(-) population to imatinib.

Airiau K et al. Exp Hematol. 2012 May;40(5):367-78.

Tse C, et al. ABT-263: a potent and orally bioavailable Bcl-2 family inhibitor. *Cancer Res*. 2008;68:3421-3428.

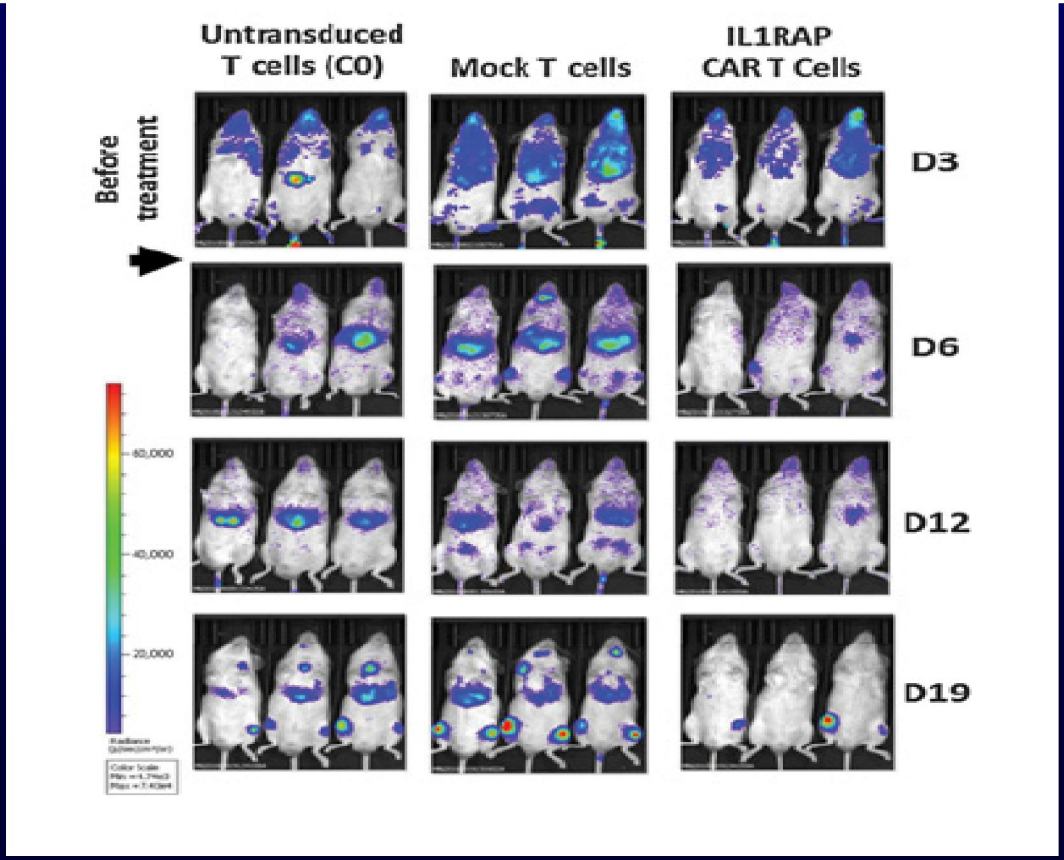
Results suggest that BCL-2 is a key survival factor for CML stem/progenitor cells and that combined inhibition of BCL-2 and BCR-ABL tyrosine kinase has the potential to significantly improve depth of response and cure rates of chronic-phase and BC CML.



Combined targeting of BCL-2 and BCR-ABL tyrosine kinase eradicates chronic myeloid leukemia stem cells
Carter BZ et al. ↲Science Translational Medicine 07 Sep 2016: Vol. 8, Issue 355, pp. 355ra117

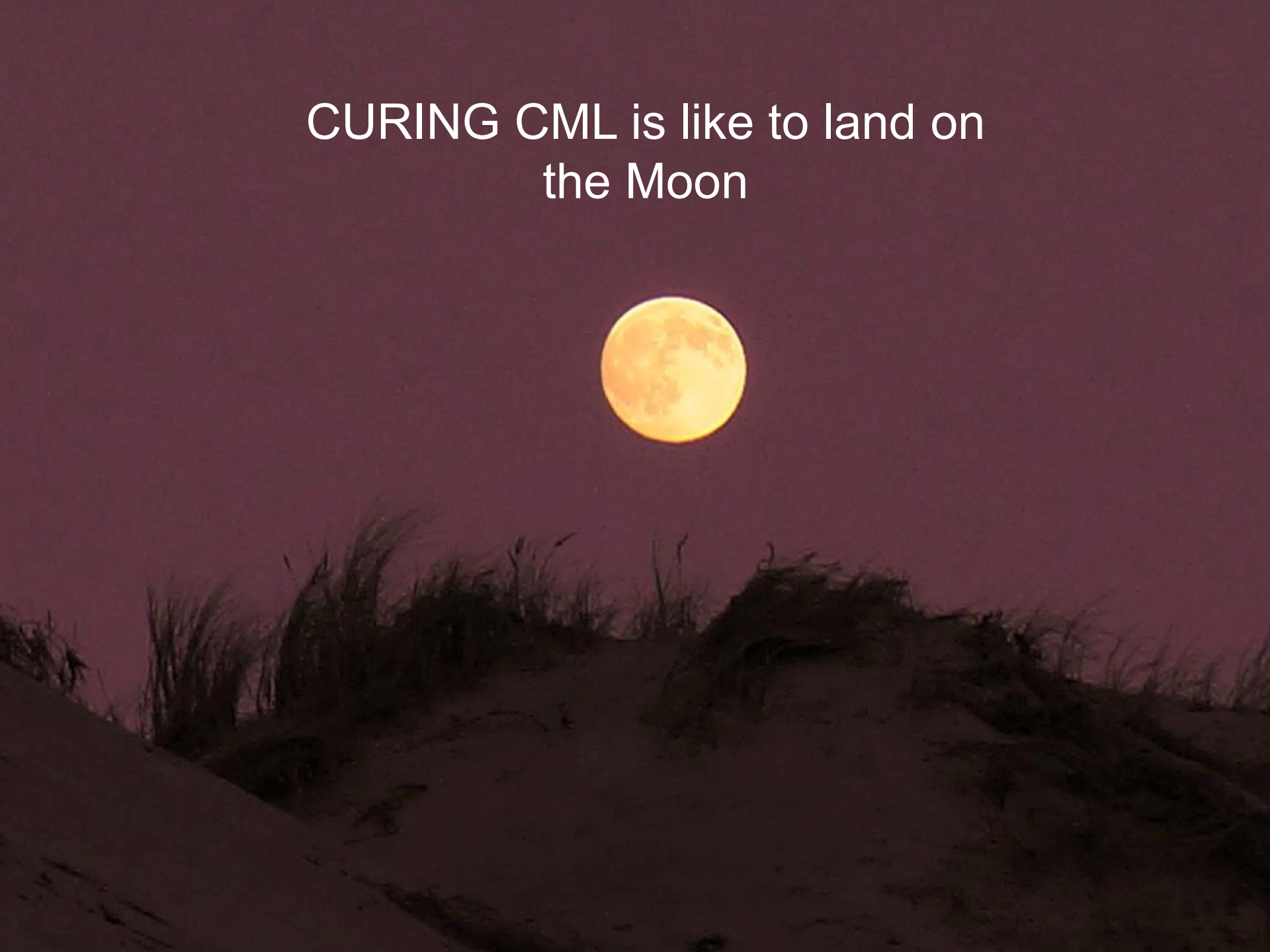
CML Hematopoietic Stem Cells Expressing IL1RAP Can Be Targeted by Chimeric Antigen Receptor–Engineered T Cells

Walid Warda[1,2], Fabrice Larosa[3], Mathieu Neto Da Rocha[1], Rim Trad[1], Eric Deconinck[1,3], Ziad Fajloun[2], Cyril Faure[4], Denis Caillot[5], Marius Moldovan[6], Severine Valmary-Degano[7], Sabeha Biichle[1], Etienne Daguindau[1,3], Francine Garnache-Ottou[1], Sebastien Tabruyn[8], Olivier Adotevi[1], Marina Deschamps[1], and Christophe Ferrand[1]



Warda *et al.* Cancer Res. 2019

CURING CML is like to land on the Moon



21TH ANNUAL JOHN GOLDMAN CONFERENCE ON CHRONIC MYELOID LEUKEMIA: BIOLOGY AND THERAPY

BORDEAUX, FRANCE
SEPTEMBER **12-15**, 2019

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Co-Organizers: **R. Bhatia, M. Copland, M. Deininger, F-X. Mahon, D. Perrotti, J. Radich, D. Réa**

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