Future research: Asciminib, and other future drugs

Using new drugs in CML

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Hypothesis for recurrence or relapse after stopping TKI

Persistence of LSC cells with LIC properties resistant to TKI

Survival without molecular response

Early molecular relapse

Late molecular relapse

Lost of immune control of the disease

Months since discontinuation of imatinib

LIC, leukemia-initiating cell; LSC, leukemic stem cell.
Strategies of CML stem cell Targeting: few examples

Inhibiting survival/renewal pathways (Hedgehog or Wnt/β catenin)

Ph+ Proliferating and differentiated cells

Sensitivity to TKI

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

Sensitizing LSC (histone deacetylases, Epigenetic modifications)

Ph+ cells

Immune targeting (IFN)

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

IM + Peg: 43% (95% CI: 36–51)
IM 600: 28% (95% CI: 22–36)
IM + AraC: 25% (95% CI: 19–33)
IM 400: 22% (95% CI: 16–30)

P<0.001

IM + Peg: 43%
IM 600: 36%
IM + AraC: 19%
IM 400: 19%

Cumulative Incidence: Bcr-Abl/Abl ≤ 0.01%
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-Makhou, Martine Gardembas, Eric Hermet, Philippe Rousselot, Shanti Armé, Marie-Claude Gagnieu, Christine Pivot, Sandrine Hayette, Veronique Maguer-Satta, Madeleine Etienne, Stéphanie Dulucq, Delphine Rea, François-Xavier Mahon


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

Figure 1: Percentage of patients in molecular response at different timepoints. (A) Major molecular response. (B) MR². (C) MR³. (D) MR⁴. MR=x=molecular response. MR¹=MR 4 log. MR²=MR 4.5 log. MR³=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

**PEglylated interferon-α2a and TAsigna®** for first Line therapy of chronic phase CML patients

Allosteric inhibitors: a new class of drugs

Update on Asciminib Clinical Development

Autoinhibition of ABL1 by engagement of the myristoyl binding site
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

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.

Asciminib and classic TKIs exhibit complementary mutation profiles

ATP binding site mutations

Myristoyl binding site mutations

Proliferation IC\textsubscript{50} profiles in Ba/F3 BCR-ABL\textsubscript{1} mutant lines

TKI, tyrosine kinase inhibitor; WT, wild type.

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.
asciminib is highly effective alone

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

<table>
<thead>
<tr>
<th>Disease status at baseline</th>
<th>Haematological disease (CHR relapse)</th>
<th>Cytogenetic disease (&gt; 35% Ph+)</th>
<th>Molecular disease (&gt; 0.1% IS)</th>
<th>Molecular disease (≤ 10% IS)</th>
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<tbody>
<tr>
<td>Patients with response (%)</td>
<td>CHR 88% (14/16)</td>
<td>CCyR 75% (9/12)</td>
<td>MMR 20% (10/50)</td>
<td>MMR 42% (16/38)</td>
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<td>≥ 1-log reduction 30% (10/33)</td>
<td>≥ 1-log reduction 48% (12/25)</td>
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<tr>
<th>CHR, complete haematological response; CCyR, complete cytogenetic response; IS, International Scale; MMR, major molecular response; Ph+, Philadelphia chromosome-positive</th>
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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.
First-in-human phase 1 study design (Bordeaux, Paris)

Dose Escalation: CML
asciminib BID completed
10 – 200 mg BID

Dose Escalation: CML T315I
asciminib BID and QD completed
Asciminib QD
80 – 200 mg

MTD RDE

Dose Expansion: CML (20 mg and 40 mg BID) completed

Dose Escalation: T315I mutation (200 mg BID) ongoing

Dose Expansion: CML

Dose Expansion: Ph+ ALL/CML-BP
asciminib BID
40 – 280 mg

MTD RDE

Dose Expansion: Ph+ ALL/CML-BP

Combo Dose Escalation: CML
asciminib + NIL 300 mg BID
20 and 40 mg BID

MTD RDE

Dose Expansion: CML

Combo Dose Escalation: CML
asciminib + IMA 400 mg QD
40, 60, and 80 mg QD; 40 mg BID

MTD RDE

Dose Expansion: CML

Combo Dose Escalation: CML
asciminib + DAS 100 mg QD
80 mg QD; 40 mg BID

MTD RDE

Dose Expansion: CML

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)

- CML-CP with ≥ 2 prior ATP binding-site TKIs
- Failure of or intolerance to the last previous TKI
- \( BCR-ABL1^{IS} \geq 1\% \) at screening
- No T315I or V299L mutations

**2:1 randomization** (stratified by MCyR vs no MCyR)
\( N = 222 \)

**Primary endpoint**
MMR at 24 weeks

**Key secondary endpoint**
MMR at 96 weeks

**Treatment duration:** 96 weeks

**Asciminib 40 mg BID**
\( n = 148 \)

**Bosutinib 500 mg QD**
\( n = 74 \)

**Survival follow-up**

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*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.

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

**Screen**
- CML-CP
- ≥ 2 years of frontline imatinib
- BCR-ABL1 IS > 0.01% to ≤ 1.0%

**Randomize**
1:1:1:1
N = 120

**Treatment duration: 96 wk**
- First 48 wk
  - Asciminib 40 mg QD + imatinib 400 mg QD
  - Asciminib 60 mg QD + imatinib 400 mg QD

- Second 48 wk
  - Asciminib 60 mg QD + imatinib 400 mg QD (Crossover allowed for patients who have not achieved MR\(^{4.5}\))

- Continue imatinib 400 mg QD
- Switch to nilotinib 300 mg BID

**Primary endpoint analysis**

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;
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 4\textsuperscript{th} Generation Inhibitor of Bcr-Abl

- PF-114: 4\textsuperscript{th} 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 profile of kinase inhibition confirms the concept of improved selectivity

Residual kinase activity at 100 nM of PF-114

\begin{align*}
\text{PF-114} & \quad \text{Residual kinase activity at 100 nM of PF-114}
\end{align*}

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\text{PF-114} & \quad \text{Residual kinase activity at 100 nM of PF-114}
\end{align*}
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.


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

Walid Warda¹,², Fabrice Larosa³, Mathieu Neto Da Rocha¹, Rim Trad¹, Eric Deconinck¹,³, Ziad Fajloun², Cyril Faure⁴, Denis Caillot⁵, Marius Moldovan⁶, Severine Valmary-Degano⁷, Sabeha Biichle¹, Etienne Daguingau¹,³, Francine Garnache-Ottou¹, Sebastien Tabruyn⁸, Olivier Adotevi¹, Marina Deschamps¹, and Christophe Ferrand¹

Warda et al. Cancer Res. 2019
CURING CML is like to land on the Moon
21ST ANNUAL JOHN GOLDMAN CONFERENCE ON CHRONIC MYELOID LEUKEMIA:
BIOLOGY AND THERAPY

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