# The CLL hunters: finally, BTK got arrested

Loic Ysebaert

Service d'Hématologie, IUCT-Oncopole, Toulouse, France

E-mail: Ysebaert.Loic@iuct-oncopole.fr

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| **TITLE** | Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. |
| **AUTHORS** | Byrd JC, Furman RR, Coutre SE, et al. |
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The *Mindhunters* Netflix series shows how two FBI agents study and interview imprisoned serial killers, to better understand them, and hunt down one of the most dreadful American psychopaths of the seventies, called BTK (a name he gave himself, referring to his *modus operandi* "Bind-Torture-Kill"). Back to 1952, in the *Pediatrics* journal, Dr O. Bruton reported his cases of agammaglobulinemia in several children (later described as Bruton's syndrome). The gene defect, mapped to the Xq21.3 locus, would be published in 1993 in the *Science* journal and code-named: BTK (Bruton-Tyrosine-Kinase, this time).

The hunt for BTK inhibitors started in the mind of a chemist at Celera Genomics, which developed (but did not patent) the first covalent inhibitor ("not ideal for a drug", according to the chemist's assumptions) as a "tool compound" (for rheumatoid arthritis). The drug was soon acquired by Pharmacyclics, a small company co-founded by a chemist (who experienced chemotherapy himself as a lymphoma survivor) and his oncologist, but they rapidly needed bigger investors in order to enter the clinical evaluation phase. When a successful businessman took the position of Chief Executive Office, and saved the company from bankruptcy, he also allowed and funded with his own money the first human trial of PCI-32765. Because access to cancer cells was important to monitor drug covalent binding, and despite it being unusual to include them in a lymphoma development plan, some patients with chronic lymphocytic leukemia (CLL) were allowed among the different lymphoma patients…It rapidly turned out that they were the ones who benefited most from the therapy.[1]

CLL lacks a single genetic target (like *BCR-ABL* in chronic myeloid leukemia), but "Chronic activation of BCR" is what actually best defines the pathophysiology behind the "deviancy of B cells" (together with "improved resistance to apoptosis": but that is a different story).

Promising preliminary results prompted the initiation of a phase Ib/II trial.[2] Eight US centers and 85 patients participated in the study (around Dr J. Byrd and Dr S. O'Brien as principal investigators) to assess the safety, efficacy, pharmacokinetics and pharmacodynamics of ibrutinib: 51 patients received 420 mg and 34 received 840 mg. The overall response rate was 71% in both dose groups, and an additional 20% and 15% of patients in the respective groups had a partial response with lymphocytosis (a brand new response criterion had to be created). Of note, the overall response rate was consistent across groups with different clinical and genomic risk factors, including disease-refractoriness to chemotherapy and the 17p deletion. At 26 months, the estimated progression-free survival and overall survival rates were 75% and 83%, respectively. To put this result in the context of relapsed/refractory CLL back in 2012, registered monoclonal antibodies yielded a median progression-free survival of 11 months and a median overall survival of 16 months. These ground-breaking results led to the first accelerated approval by the Food and Drug Administration of a BTK inhibitor for this indication. The drug was also registered for other B-cell lymphomas, alone or in combination. Since the introduction of antiCD20 monoclonal antibodies 15 years previously, no single agent had improved overall and progression-free survival as ibrutinib did.

After up to 8 years of follow-up of the PCYC-1102 study (including high-risk patients treated with frontline ibrutinib in the extension study), sustained responses were still reported, confirming that the chemists at Celera had done a really nice job 20 years earlier. The overall response rate was 89% with complete response rates of 10% (in the relapsed/refractory setting) to 35% (as first-line treatment), the 7-year progression-free survival rates were 34% (in the relapsed/refractory setting) to 83% (as first-line treatment),

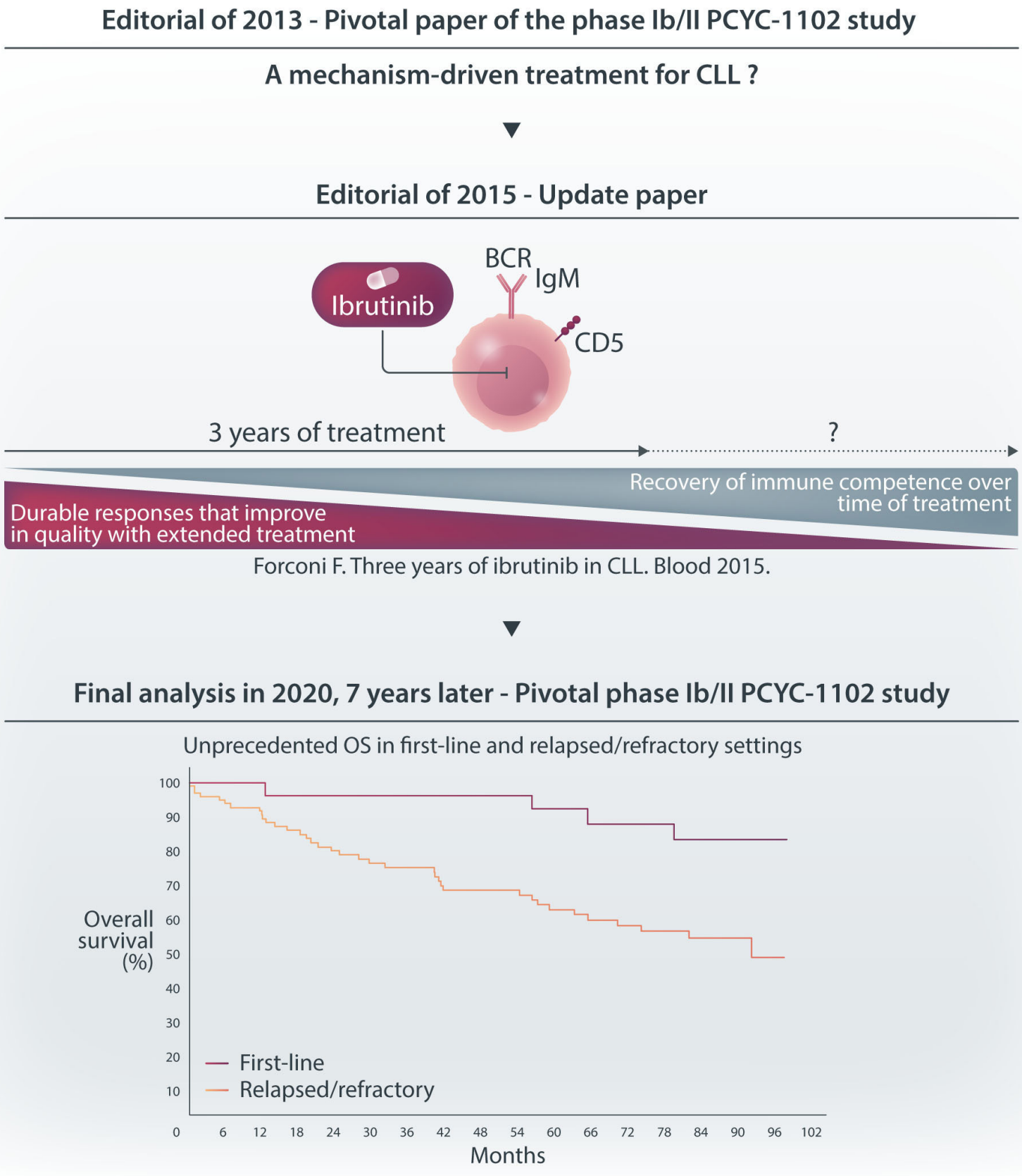


**Figure 1. Timelines of pioneer publications regarding ibrutinib in the treatment of chronic lymphocytic leukemia: a new hope.** BCR: B-cell receptor; CLL: chronic lymphocytic leukemia; OS: overall survival.

and the corresponding 7-year overall survival rates were 55% and 84%.[3]

CLL, still incurable, has nevertheless become a disease that is compatible with a near-normal lifespan for patients receiving an oral, well-tolerated, albeit expensive, therapy. New-generation covalent BTK inhibitors are now registered: these have similar efficacy (or maybe superior in specific subsets of patients), but improved tolerance, meaning we have not ended our journey among the BTK inhibitors (non-covalent kinase inhibitors, and even BTK degraders, can help to manage patients in whom first-generation BTK inhibitors have failed). When B cells become “insane”, we can kick them out from their tissue niches, anergize or kill them, and keep them quiet for more than a decade in half of patients, without chemotherapy or allogeneic stem cell transplantation and their fearsome side effects, fulfilling the dreams of the former developers of PCI-32765.

## Disclosures

*No conflicts of interest to disclose.*

## References

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