# Notes on the Preclinical Development of Imbruvica (Ibrutinib)

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Arianna Schouten

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## Introduction and findings

The preclinical research that led to the development and FDA approval of Imbruvica/Ibrutinib benefited from studies and research by companies now owned by the drug sponsors (AbbVie and Johnson&Johnson), as well as independent research funded by the US National Institutes of Health (NIH), the German government, the European Union, the Cancer Prevention and Research Institute of Texas, the CLL Global Research Foundation, the Leukemia & Lymphoma Society, the Howard Hughes Medical Institute, and the D Warren Brown Foundation.

## Background

Standard therapy for patients with chronic lymphocytic leukemia (CLL) has included chemotherapy and, more recently, chemoimmunotherapy regimens. Despite this, none of the chemoimmunotherapy regimens are curative and carry many toxicities, which provides a strong motivation for developing effective and better tolerable agents.[1]

Imbruvica is an oral inhibitor of Bruton's tyrosine kinase (BTK). BTK is a key protein of the B-cell receptor pathway and BTK plays an important role in the functioning of certain immune cells (such as B lymphocytes). Imbruvica inhibits the B-cell receptor pathway, leading to several effects on malignant B lymphocytes, such as:

- Directly causing some of the malignant B lymphocytes to self-destruct (apoptosis);
- Stopping B lymphocytes from growing and dividing (proliferation); and
- Changing how lymphocytes move around in the body. When the lymphocytes leave their 'protective environment' they become more vulnerable and can lead to more cell death (egress lymphocytes).

## 1991: The founding of Pharmacyclics

Ronald Levy co-founded IDEC with his Stanford colleague Richard Miller. IDEC delivered rituximab, the first monoclonal antibody approved by the FDA for cancer. Miller then left IDEC and co-founded Pharmacyclics in 1991. Initially, Pharmacyclics focused on a class of molecules called texaphryins, but after unsuccessful clinical trials, they needed to think of another avenue of focus.

## 1998 - 2001: Celera Genomics

Celera Genomics emerged in 1998 and began working towards the same goal as the Human Genome Project: to generate the first sequence of the human genome. Celera was headed by geneticist and businessman Craig Venter, a former NIH scientist, initially to compete with the publicly funded Human Genome Project, in part with the prospect of gaining control over potential patents.[2] Celera's stock later plummeted in reaction to President Bill Clinton and Prime Minister Tony Blair stating that genetic information should be made public.[3]

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[1] Davids MS, Brown JR. Ibrutinib: a first in class covalent inhibitor of Bruton's tyrosine kinase. Future Oncol. 2014 May;10(6):957-67. doi: 10.2217/fon.14.51. PMID: 24941982; PMCID: PMC4632638. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632638/

[2] See: Georgina Ferry and John Sulston, *The Common Thread: A Story of Science, Politics, Ethics and the Human Genome*, Joseph Henry Press, 2002.

[3] Kristen Philpkoski, Investors Sue Celera: A class action lawsuit was filed against Celera for making misleading statements in SEC documents, *Wired*, May 18, 2000. https://www.wired.com/2000/05/investors-sue-celera/.

As the business model of selling access to sequence data was not successful, Celera changed gears, and in 2001 acquired Axys Pharmaceuticals for $174 million.[4] With this purchase, Celera intended to tie together its database and begin the development of small molecule compounds, and in 2002, Venter left Celera, "a casualty of the company's bid to transform itself from a force in genetic decoding to a discoverer and producer of new medicines," according to the Wall Street Journal.[5]

## 2006: Initial preclinical work and the sale of some Celera assets to Pharmacyclics

In a study published in 2006, researchers from Celera reported the discovery of selective irreversible inhibitors for BTK. They had conducted a number of experiments and screenings to identify compounds that could selectively and irreversibly inhibit BTK activity. Their study resulted in the discovery of potential inhibitors that could serve as the basis for further drug development.[6]

**Table 1: Pan et al. Celera funded**

| | |
|---|---|
| Study | Pan Z, Scheerens H, Li SJ, et al. Discovery of selective irreversible inhibitors for Bruton's tyrosine kinase. *ChemMedChem.* 2007;2(1):58-61 |
| Summary | Pivotal study where researchers identified a set of compounds that effectively inhibit BTK activity. |
| Funding | Celera |

The same year, Celera announced the sale of their therapeutic programs to Pharmacyclics. Under the terms of the agreement, Pharmacyclics acquired Celera technology and intellectual

[4] https://money.cnn.com/2001/06/13/deals/celera/index.htm; Andrew Pollack, Technology; Genome Research Pioneer to Buy Drug Maker, *The New York Times*, June 14, 2001. https://www.nytimes.com/2001/06/14/business/technology-genome-research-pioneer-to-buy-drug-maker.html

[5] Scott Hensley, Craig Venter Leaves Celera as Firm Seeks New Direction. *Wall Street Journal*, January 23, 2002. https://www.wsj.com/articles/SB1011714052194210440

[6] Pan, Z., Scheerens, H., Li, S.J., Schultz, B.E., Sprengeler, P.A., Burrill, L.C., Mendonca, R.V., Sweeney, M.D., Scott, K.C., Grothaus, P.G. and Jeffery, D.A., 2007. Discovery of selective irreversible inhibitors for Bruton's tyrosine kinase. ChemMedChem: Chemistry Enabling Drug Discovery, 2(1), pp.58-61.

property relating to drugs that target histone deacetylase (HDAC) enzymes, selective HDAC enzymes, angiogenesis molecules and B-cell tyrosine kinases.[7]

The deal was focused on Celera's Phase 1 HDAC assets, however, the co-founder of Pharmacyclics noted that he was keen for the BTK inhibitor program to be included in the acquisition as well. This was an easy task since the perceived value of the BTK program was close to zero.[8]

The transaction included an upfront cash payment of $2 million and an equity payment of between five hundred thousand and one million shares of Pharmacyclics common stock. If the programs met certain milestone events and resulted in drugs that became approved and commercialized, they would generate potential future milestone payments to Celera of up to $144 million. In addition, Celera would be entitled to royalty payments in the mid-to high single digits based on annual sales of any drugs commercialized from the three programs.[9]

## 2007: Publicly-funded study shows positive conclusions

During this time, the results of a significant preclinical study came to positive conclusions about the role of B-cell receptors (BCR) for B-cell development (see Table 1). This study had promising implications for the understanding of B-cell development and immune responses. By modulating BCR signaling, the immune system can regulate the activation and survival of B-cells.

### Table 2: The Waisman et al. Celera study

| | |
|---|---|
| Study | Waisman, A., Kraus, M., Seagal, J., Ghosh, S., Melamed, D., Song, J., Sasaki, Y., Classen, S., Lutz, C., Brombacher, F. and Nitschke, L., 2007. IgG1 B cell receptor signaling is inhibited by CD22 and promotes the development of B cells whose survival is less dependent on Igα/β. The Journal of experimental medicine, 204(4), pp.747-758. |

[7] Celera Genomics Announces Sale Of Therapeutic Programs To Pharmacyclics, Press Release. April 10, 2006.
https://www.sec.gov/Archives/edgar/data/949699/000094969906000018/exh99-1.pdf
[8] David Shaywitz, The Wild Story Behind A Promising Experimental Cancer. *Forbes*, April 5, 2013.
Drughttps://www.forbes.com/sites/davidshaywitz/2013/04/05/the-wild-story-behind-a-promising-experimental-cancer-drug/?sh=4695d6db5857
[9] Celera Genomics Announces Sale Of Therapeutic Programs To Pharmacyclics, Press Release. April 10, 2006.
https://www.sec.gov/Archives/edgar/data/949699/000094969906000018/exh99-1.pdf

| | |
|---|---|
| Summary | Examined the signaling pathways and factors that influence the survival of B-cells. Study concluded that the CD22 protein has an inhibitory effect of the specific B-cell receptors (so the protein can put brakes on certain signals within B-cells). While not explicit at the time, the findings have implications on therapies targeting B-cells. |
| Funding | This work was supported by the FP6 Marie Curie Research Training Network (grant MRTN-CT-2004-005632 to A. Waisman), the Deutsche Forschungsgemeinschaft (grant SFB 243 to K. Rajewsly, grant SFB 490 to A. Waisman, and grant SFB 466 to L. Nitschke), and the National Institutes of Health (grant 1 R37 AI054636-01). |

### 2008: Leadership change at Pharmacyclics

In 2008, Miller (the co-founder of Pharmacyclics) was forced out of Pharmacyclics by Robert Duggan, who is a member of and one of biggest donors to the Church of Scientology. Miller had played a pivotal role in the company's early stages. Duggan had invested in Pharmacyclics when its shares were worth 1-3$ per share. He acted as CEO and Chairman of Pharmacyclics from 2008 until 2015.

## 2008 - 2010: Preclinical studies supporting PCI-32765

Pharmacyclics was eager to explore the potential of BTK inhibitors with B-cell cancers. They contributed to the following preclinical studies, which had early promising results (see Table 3). In addition to the industry funded preclinical work, at the same time, there was research published in *Nature* which showed that PCI-32765 showed the promotion of some of the malignant B lymphocytes to self-destruct (see Table 4).Together, these preclinical studies provided critical support for the development of PCI-32764 as a therapeutic agent for the treatment of CLL and other diseases. These studies set the stage for the subsequent phases of development and clinical trials.

### Table 3: Honigberg et al. Pharmacyclics study

| | |
|---|---|
| Study | Honigberg, L.A., Smith, A.M., Sirisawad, M., Verner, E., Loury, D., Chang, B., Li, S., Pan, Z., Thamm, D.H., Miller, R.A. and Buggy, J.J., 2010. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. Proceedings of the National Academy of Sciences, 107(29), pp.13075-13080. |

| | |
|---|---|
| Summary | Studied the ability of PCI-32765 to inhibit the activation of B-cells. The study found that it blocked the activation of B-cells, indicating that it would be a promising drug candidate. |
| Funding | Industry |

**Table 4: Davis et al. publicly-funded study**

| | |
|---|---|
| Study | Davis, R., Ngo, V., Lenz, G. et al. Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. Nature 463, 88–92 (2010). |
| Summary | BTK was identified as an essential kinase for survival in a subset of diffuse large cell lymphomas driven by activated BCR where an irreversible BTK inhibitor (PCI-32765) showed the promotion of apoptosis. |
| Funding disclosure | This research was supported by the Intramural Research Program of the National Institutes of Health, the National Cancer Institute, the Center for Cancer Research, the National Institute of Allergy and Infectious Disease, and the National Human Genome Research Institute. P.B.R. was a Howard Hughes Medical Institute-National Institutes of Health Research Scholar. |

## 2011: Co-development agreement with Janssen

Beginning in 2010, Phase I and Phase II trials were launched involving PCI-32765, the drug later named Ibrutinib. Johnson and Johnson, through its Janssen subsidiary, entered into an agreement with Pharmacyclics to co-develop the drug, using the brand name Imbruvica. Janssen paid Pharmacyclics $150 million upfront and up to $825 in milestone payments. The companies entered into a worldwide 50/50 profit-loss agreement, sharing development and commercialization activities,[10] with each company leading the development of specific indications with a cost share of 40/60 (Pharmacyclics/Janssen).

[10] Janssen Biotech, Inc. Announces Collaborative Development And Worldwide License Agreement For Investigational Anti-Cancer Drug, PCI-32765, Press Release. December 8, 2011. https://www.jnj.com/media-center/press-releases/janssen-biotech-inc-announces-collaborative-development-and-worldwide-license-agreement-for-investigational-anti-cancer-drug-pci-32765

## 2011 - 2012: Further studies

The following three studies, published before the first FDA approval, provided further support for the use of Ibrutinib in the treatment of chronic lymphocytic leukemia (CLL) and received various funding sources.

### Table 5: de Rooij et al. Pharmacyclics funded

| | |
|---|---|
| Study | de Rooij, M. F., Kuil, A., Geest, C. R., Eldering, E., Chang, B. Y., Buggy, J. J., ... & Spaargaren, M. (2012). The clinically active BTK inhibitor PCI-32765 targets B-cell receptor–and chemokine-controlled adhesion and migration in chronic lymphocytic leukemia. Blood, The Journal of the American Society of Hematology, 119(11), 2590-2594. |
| Summary | In this study, the authors evaluated PCI-32765 and found that it effectively targeted and inhibited BTK, which was significant because it disrupted the signaling pathways that promote the growth and survival of CLL cells. |
| Funding disclosure | Pharmacyclics |

### Table 6: Herman et al. charitable and publicly funded study

| | |
|---|---|
| Study | Herman, S. E., Gordon, A. L., Hertlein, E., Ramanunni, A., Zhang, X., Jaglowski, S., ... & Byrd, J. C. (2011). Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by PCI-32765. Blood, The Journal of the American Society of Hematology, 117(23), 6287-6296 |
| Summary | In this study, the authors evaluated PCI-32765 and found that it effectively targeted and inhibited BTK, which was significant because it disrupted the signaling pathways that promote the growth and survival of CLL cells. |
| Funding disclosure | This work was supported by the Leukemia & Lymphoma Society, the NIH (P50-CA140158, PO1-CA95426, PO1 CA81534, 1K12 CA133250), and The D. Warren Brown Foundation. A.J.J. is a Paul Calabresi Scholar. |

**Table 7: Ponader et al. Pharmacyclics and charity funded study**

| | |
|---|---|
| Study | Ponader, S., Chen, S. S., Buggy, J. J., Balakrishnan, K., Gandhi, V., Wierda, W. G., ... & Burger, J. A. (2012). The Bruton tyrosine kinase inhibitor PCI-32765 thwarts chronic lymphocytic leukemia cell survival and tissue homing in vitro and in vivo. *Blood*, The Journal of the American Society of Hematology, 119(5), 1182-1189. |
| Summary | This study aimed to assess the potential of PCI-32765 as a treatment for CLL. The study included in vitro and in vivo experiments and found that the drug inhibited BTL, thus impeding the survival and growth of CLL cells. This was observed in both in vitro and in vivo. The findings of the research suggest that PCI-32765 had the potential to be a valuable therapeutic option of CLL. |
| Funding disclosure | The study was supported by CLL Global Research Foundation grants (W.G.W., V.G., and J.A.B.), by Pharmacyclics Inc, and by a Cancer Prevention and Research Institute of Texas (CPRIT) grant (J.A.B.). |

## Summary Table: Selected published studies essential for Ibrutinib development prior to FDA approval and funders cited in papers

| Year published | Published paper describing study | Funders cited in paper |
|---|---|---|
| 2007 | Pan Z, Scheerens H, Li SJ, et al. Discovery of selective irreversible inhibitors for Bruton's tyrosine kinase. *ChemMedChem.* 2007;2(1):58-61. doi:10.1002/cmdc.200600221 | Celera |
| 2007 | Waisman A, Kraus M, Seagal J, et al. IgG1 B cell receptor signaling is inhibited by CD22 and promotes the development of B cells whose survival is less dependent on Ig alpha/beta. *J Exp Med.* 2007;204(4):747-758. doi:10.1084/jem.20062024 | FP6 Marie Curie Training Network (grant MRTN-CT-2004-005632, the European Commission) |
| | | Deutsche Forschungsgemeinschaft (grant SFB 243, German government funded research foundation) |
| | | Deutsche Forschungsgemeinschaft (grant SFB 466, German government funded research foundation) |
| | | NIH<br>(1 R37 AI054636-01) |
| 2010 | Honigberg LA, Smith AM, Sirisawad M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. *Proc Natl Acad Sci U S A.* 2010;107(29):13075-13080. doi:10.1073/pnas.1004594107 | Pharmacyclics |
| 2010 | Davis, R., Ngo, V., Lenz, G. et al. Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. *Nature* 463, 88–92 (2010). https://doi.org/10.1038/nature08638 | Howard Hughes Medical Institute (Author PBR was a research scholar) |
| | | NIH (NIH0011349228) |
| | | NIH (NIH0011349228) |
| 2011 | de Rooij, M. F., Kuil, A., Geest, C. R., | Pharmacyclics |

| Year published | Published paper describing study | Funders cited in paper |
|---|---|---|
| | Eldering, E., Chang, B. Y., Buggy, J. J., ... & Spaargaren, M. (2012). The clinically active BTK inhibitor PCI-32765 targets B-cell receptor–and chemokine-controlled adhesion and migration in chronic lymphocytic leukemia. Blood, The Journal of the American Society of Hematology, 119(11), 2590-2594. https://doi.org/10.1182/blood-2011-11-390989 | |
| 2011 | Herman SE, Gordon AL, Hertlein E, et al. Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by PCI-32765. *Blood*. 2011;117(23):6287-6296. doi:10.1182/blood-2011-01-328484 | Leukemia & Lymphoma Society |
| | | NIH (P50-CA140158) |
| | | NIH (PO1-CA95426) |
| | | NIH (PO1 CA81534) |
| | | NIH (1K12 CA133250) |
| | | D Warren Brown Foundation |
| 2012 | Sabine Ponader, Shih-Shih Chen, Joseph J. Buggy, Kumudha Balakrishnan, Varsha Gandhi, William G. Wierda, Michael J. Keating, Susan O'Brien, Nicholas Chiorazzi, Jan A. Burger, The Bruton tyrosine kinase inhibitor PCI-32765 thwarts chronic lymphocytic leukemia cell survival and tissue homing in vitro and in vivo. *Blood* (2012) 119 (5): 1182–1189. https://doi.org/10.1182/blood-2011-10-386417 | Pharmacyclics |
| | | Cancer Prevention and Research Institute of Texas (State of Texas) |
| | | CLL Global Research Foundation Grant |