Title

Recall of ibrutinib and issues with therapeutic approval

Journal

BMJ Oncology, 3(1)

ISSN

2752-7948

Authors

Lipfert, Colton
Kim, Myung Sun
Haslam, Alyson
et al.

Publication Date

2024-08-01

DOI

10.1136/bmjonc-2024-000418

BMJ Oncology

Recall of ibrutinib and issues with therapeutic approval

Colton Lipfert,[1] Myung Sun Kim ,[2] Alyson Haslam ,[3] Vinay K Prasad[3]

To cite: Lipfert C, Kim MS, Haslam A, *et al*. Recall of ibrutinib and issues with therapeutic approval. *BMJ Oncology* 2024;**3**:e000418. doi:10.1136/bmjonc-2024-000418

[1]Columbia University, Manhattan, New York, USA
[2]Compass Oncology, Portland, Oregon, USA
[3]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California, USA

Correspondence to
Vinay K Prasad;
vinayak.prasad@ucsf.edu

In April 2023, AbbVie voluntarily recalled ibrutinib (Imbruvica) for the treatment of mantle cell lymphoma (MCL) and marginal zone lymphoma (MZL) in the USA.[1] This withdrawal marks the end of, for now, 10 years of the product's marketing and sales for this indication. Here, we describe the approval history and regulatory implications of ibrutinib's withdrawal from the US market.

Ibrutinib, a first-in-class inhibitor of Bruton's tyrosine kinase (BTK), showed encouraging results for MCL at the American Society of Hematology's annual conference in 2012. Wang *et al* reported that 68% of patients with MCL (75/111) who received ibrutinib had an objective response, with few serious adverse events.[2] These results were encouraging enough for the Food and Drug Administration (FDA) to grant ibrutinib accelerated approval on 13 November 2013 on the condition that AbbVie conduct a 'randomised, double-blind, placebo-controlled phase III clinical trial (PCI-32765MCL3002) of ibrutinib in combination with bendamustine and rituximab in patients with newly diagnosed MCL'.[3]

The trial—later called SHINE—set progression-free survival (PFS) as the primary endpoint and overall survival (OS) as the secondary endpoint. 261 patients with MCL were randomised to receive ibrutinib and 262 to receive placebo.[4] The results were published 9 years later in the *New England Journal of Medicine* in June 2022.

After the FDA's approval, latter-line ibrutinib became the standard of care in the USA for MCL. This treatment course, while sensible, had no formal clinical data to support its efficacy over alternatives. SHINE, however, would assess ibrutinib in the front-line setting, not the salvage setting.[4] Ibrutinib has yet to be assessed in the salvage setting.

SHINE's treatment group experienced an improvement in median PFS relative to the control group (80.6 vs 52.9 months; HR: 0.75; 95% CI, 0.59 to 0.96).[4] However, there was no difference in OS: 104 patients (39.8%) in the treatment arm died during treatment versus 107 patients (40.8%) in the control arm (HR: 1.07; 95% CI, 0.81 to 1.40).[4] The ibrutinib group also experienced worse safety issues.[4] Finally, only 38.7% of eligible patients on the control arm (41/106) received second-line treatment with a BTK inhibitor.[4] The investigators claim that this was comparable for the time, but it was still substandard care in the USA, where AbbVie was seeking approval.

In a press release, AbbVie announced that ibrutinib had failed to extend either PFS or OS for patients with MZL (SELENE has yet to be published).[1] After these two negative trials, AbbVie withdrew ibrutinib for MCL and MZL indications in the USA in April 2023.

The regulatory history of ibrutinib raises four points.

First, OS, not PFS, would be the more informative primary endpoint. OS has intrinsic relevance to patients and has comparable speed to surrogate endpoints. On average, OS trials are just 12% slower than PFS trials, with an average time difference of only 11 months.[5]

Second, SHINE failed to answer a clinically relevant question. By November 2013, most oncologists considered the treatment used in SHINE's control arm—bendamustine and rituximab without latter-line ibrutinib or any BTK inhibitor—substandard care. It is unclear how SHINE's results could have informed clinical practice when it tested an uncommon treatment (front-line ibrutinib) against a substandard therapy (treatment without a BTK inhibitor on progression). Control arm patients should be crossed-over to BTK inhibitor therapy on progression, when it is an approved standard of care for that locality.

Third, even though ibrutinib has been pulled from the US market, the second-generation BTK inhibitors with the same mechanism of action, namely zanubrutinib and acalabrutinib, will remain on the market

until the phase III trials result. These trials (which also use PFS as a primary endpoint)[6 7] have not finished recruiting. As such, these medications will remain on the market for many years, despite the first-in-class drug failing to show efficacy.

Fourth, withdrawing ibrutinib from the market means that all US patients with MCL have lost access to it, including patients in the salvage setting who might benefit from its administration. Unfortunately, it is unlikely that AbbVie will investigate ibrutinib's efficacy in other settings. However, given that the drug has other approvals, the National Comprehensive Cancer Network may continue to endorse it for latter-line treatment, as an off-label use.

Ibrutinib's approval exemplifies many of the issues with the current trials and approval landscape: accelerated approval based on uncontrolled findings, inappropriate trial design, unanswered clinically relevant questions, substandard care, and poor use of regulatory authority. 10 years after its approval, ibrutinib's therapeutic role remains unclear. These issues must be addressed by all players in the drug development ecosystem, including sponsors, trialists, and the FDA. A few changes in the assessment of ibrutinib—such as conducting a randomised trial in the salvage setting followed by a front-line trial—would have rendered a firm verdict on this first-in-class medication.

Contributors VKP conceptualised study design. CL gathered and reviewed data. All authors contributed to the analysis of the results and to the writing and critical revision of the manuscript. All authors take full responsibility for the finished work.

Funding This study was supported by the Arnold Ventures (NA).

Competing interests VKP receives research funding from Arnold Ventures through a grant made to UCSF and royalties for books and writing from Johns Hopkins Press, MedPage and the Free Press. He declares consultancy roles with UnitedHealthcare and OptumRX; He hosts the podcasts, Plenary Session, VPZD, Sensible Medicine, writes the newsletters, Sensible Medicine, the Drug Development Letter and VP's Observations and Thoughts and runs the YouTube channel Vinay Prasad MD MPH, which collectively earn revenue on the platforms: Patreon, YouTube and Substack.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

ORCID iDs
Myung Sun Kim http://orcid.org/0000-0002-2042-1262
Alyson Haslam http://orcid.org/0000-0002-7876-3978

REFERENCES

1 Abbvie. Update on IMBRUVICA® (ibrutinib) U.S. Accelerated approvals for mantle cell lymphoma and marginal zone lymphoma indications. Abbvie; 2023. Available: https://news.abbvie.com/news/press-releases/update-on-imbruvica-ibrutinib-us-accelerated-approvals-for-mantle-cell-lymphoma-and-marginal-zone-lymphoma-indications.html
2 Wang ML, Rule S, Martin P, *et al*. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med* 2013;369:507–16.
3 U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Ibrutinib NDA 205552 approval letter, December 23, 1999. Retrieved May 12, 2023. Available: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2013/205552Orig1s000ltr.pdf
4 Wang ML, Jurczak W, Jerkeman M, *et al*. Ibrutinib plus bendamustine and rituximab in untreated mantle-cell lymphoma. *N Engl J Med* 2022;386:2482–94.
5 Chen EY, Joshi SK, Tran A, *et al*. Estimation of study time reduction using surrogate end points rather than overall survival in oncology clinical trials. *JAMA Intern Med* 2019;179:642–7.
6 A study of BR alone versus in combination with acalabrutinib in subjects with previously untreated MCL. Clinicaltrials.gov; 2024. Available: https://clinicaltrials.gov/study/NCT02972840 [Accessed 1 May 2024].
7 Study comparing zanubrutinib + rituximab versus bendamustine + rituximab in participants with untreated mantle cell lymphoma. Clinicaltrials.gov; 2024. Available: https://clinicaltrials.gov/study/NCT04002297 [Accessed 1 May 2024].