Few new treatments in oncology and haematology have had the success that imatinib has had for chronic myeloid leukaemia (CML). This drug represents one of the best cases in the history of medicine for the development of an innovative treatment, proving that the treatment and prognosis of a fatal neoplastic disease can be drastically modified by human intervention. Additionally, imatinib constitutes the first example of a drug that was rationally developed to block a known oncogene and which, as monotherapy, has substantially changed the biology and clinical course of a human cancer.

The 1996 paper by Druker and colleagues represents a fundamental milestone in the development of this targeted treatment and marks the beginning of what is now known as the “imatinib era”. Three main findings from this study were: imatinib (then known as CGP57148B) was a fairly specific kinase inhibitor; inhibition of the kinase activity of BCR-ABL was able to selectively block the proliferation of BCR-ABL-transformed cells in vitro and in vivo; and imatinib was preferentially active in leukaemic cells versus normal colony-forming-unit granulocyte macrophages and burst-forming unit-erythroblasts.

This important contribution to the development of imatinib as a targeted treatment did not develop in a vacuum, because the possibility of targeting BCR-ABL kinase activity had already been proposed in 1993 by Anafi and colleagues. However, despite the fact that these researchers had the right idea, they were using the wrong molecules. They used compounds, known as tyrphostins, which competed for the substrate site of the enzyme, instead of competitors of the ATP site, such as imatinib, which binds to ABL in a pocket close to the ATP site.

Key findings from the 1996 paper by Druker and colleagues:
- Imatinib is a fairly specific ABL inhibitor
- Inhibition of BCR-ABL kinase activity is able to selectively block the proliferation of BCR-ABL-transformed cells in vitro and in vivo
- Imatinib is more active on leukaemic cells compared with normal colony-forming-unit granulocyte macrophages and burst-forming unit-erythroblasts

Over the following years, tyrphostins were shown to be much less valuable than ATP competitors for the development of clinically active inhibitors. In fact, the two tyrphostins used by Anafi and colleagues had low inhibition of BCR-ABL autophosphorylation and no convincing selectivity. Additionally, Anafi and colleagues believed that the main mechanism of action of BCR-ABL inhibition involved the induction of differentiation in leukaemic cells, and they fell short of advocating an in-vivo use for their compound, restricting its possible use as an ex-vivo purging instrument.

However, the paper by Druker and colleagues also left some important aspects of the treatment undefined. Their in-vivo data did not show complete tumour regression and cure. Moreover, no direct data was provided indicating that apoptosis was induced by imatinib, and left the issue of apoptosis versus induction of differentiation as the main cellular effect of BCR-ABL-inhibition unresolved. Chronic-phase CML has no major differentiation block and the self elimination of leukaemic cells is, in fact, essential in understanding how bone marrow that is more than 95% Philadelphia (Ph) positive can become more than 95% Ph-negative after 3 months (or an even shorter duration) of treatment.

Although, Druker and colleagues failed to identify all the relevant features of this new drug, they laid the foundations for further work over the following 2 years, which clarified outstanding issues and delineated the overall profile of imatinib. These achievements led to the use of imatinib in clinical trials, and its subsequent success as a targeted treatment. Too many other cancers await a similar breakthrough.

Conflicts of interest
The author was involved in the development of imatinib.

References
4 Deininger MWN, Goldman JM, Lydon N, Melo JV. The tyrosine kinase inhibitor CGP57148B selectively inhibits the growth of BCR-ABL positive cells. Blood 1997; 90: 3691–98.