# New bullets in the fight against cancer

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| **TITLE** | Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. |
| **AUTHORS** | O'Brien SG, Guilhot F, Larson RA, et al; IRIS Investigators. |
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"There is new ammunition in the war against cancer. These are the bullets". This dramatic headline was devoted to STI571, later known as imatinib, on the cover of *Time* magazine in May 2001.[1]

The 'bench to bedside' journey of tyrosine kinase inhibitors (TKI) for chronic myeloid leukemia (CML) started in 1960 with the initial report, by Nowell and Hungerford, of a 'minute chromosome abnormality' unique to chronic granulocytic leukemia. This was followed by the characterization of the 'Philadelphia-chromosome' by Janet Rowley and the *BCR-ABL* fusion gene by others as the pivotal genetic event causing CML, and culminated with the development of STI571, the first targeted therapy for this disease.

CML, once incurable without allogeneic transplantation and a potentially fatal myeloid neoplasm, has become a disease that entails a near-normal lifespan for patients with an oral, and possibly time-limited therapy.

It took almost two decades of efforts pioneered by Dr. Lydon and Dr. Matter in collaboration with Dr. Druker and many others until the first clinically effective and tolerable BCR-ABL inhibitor was developed. In the early phase trials, STI571 was administered to patients with advanced CML with excellent results in those with chronic-phase disease in whom interferon-$\alpha$ had failed. These results led to the first, accelerated approval by the Food and Drug Administration of a TKI for this indication.[2]

In the International Randomized Study of Interferon *versus* STI571 (IRIS), 1,106 patients with newly diagnosed CML were randomized to receive STI571 or low-dose cytarabine in combination with interferon, which was the standard of care at that time. Imatinib outperformed the control treatment arm in all outcome measures assessed: complete hematologic response (95.3% *vs*. 55.5%, respectively), rates of major cytogenetic response (87.1% *vs*. 34.7%), rates of complete cytogenetic response (76.2% *vs*. 14.5%), progression-free survival (92.1% *vs*. 73.5%) and freedom from progression to accelerated-phase or blast-crisis CML (96.7% *vs*. 91.5%) with excellent tolerability (Figure 1). The crossover design of this study enabled patients in the low-dose cytarabine plus interferon arm to receive effective salvage with STI571 at failure or intolerance, and blunted the overall survival effect between the study groups (Figure 1).[3] Subsequent analyses of the IRIS trial informed the molecular roadmap for response assessment in CML and paved the way for the principles of modern management of this disease.

The development of imatinib marked the dawn of targeted therapies in hematology. It was among the first TKI developed for hematologic malignancies and was to be followed by many others over the years.

Newer generations of TKI are now available for patients with CML and Philadelphia-positive acute lymphoblastic leukemia. Inhibitors against other targets such as JAK2 inhibitors for the treatment of myeloproliferative neoplasms, FLT3 inhibitors for acute myeloid leukemia and inhibitors of Bruton tyrosine kinase for lymphoma and chronic lymphocytic leukemia have transformed the therapeutic landscape of hematologic malignancies.

In parallel to the astonishing progress and promise entailed in these targeted therapies, time and experience also taught us the limitations and challenges of utilizing TKI on a large scale in hematology. Over the years we learned that monotherapy with a TKI may not suffice for the treatment of aggressive clonally complex disorders. The financial burden of these drugs is a great challenge and limits access in environments with poor resources.

The journey of TKI and targeted therapies is ongoing and I eagerly look forward to new magic bullets in the fight against cancer.

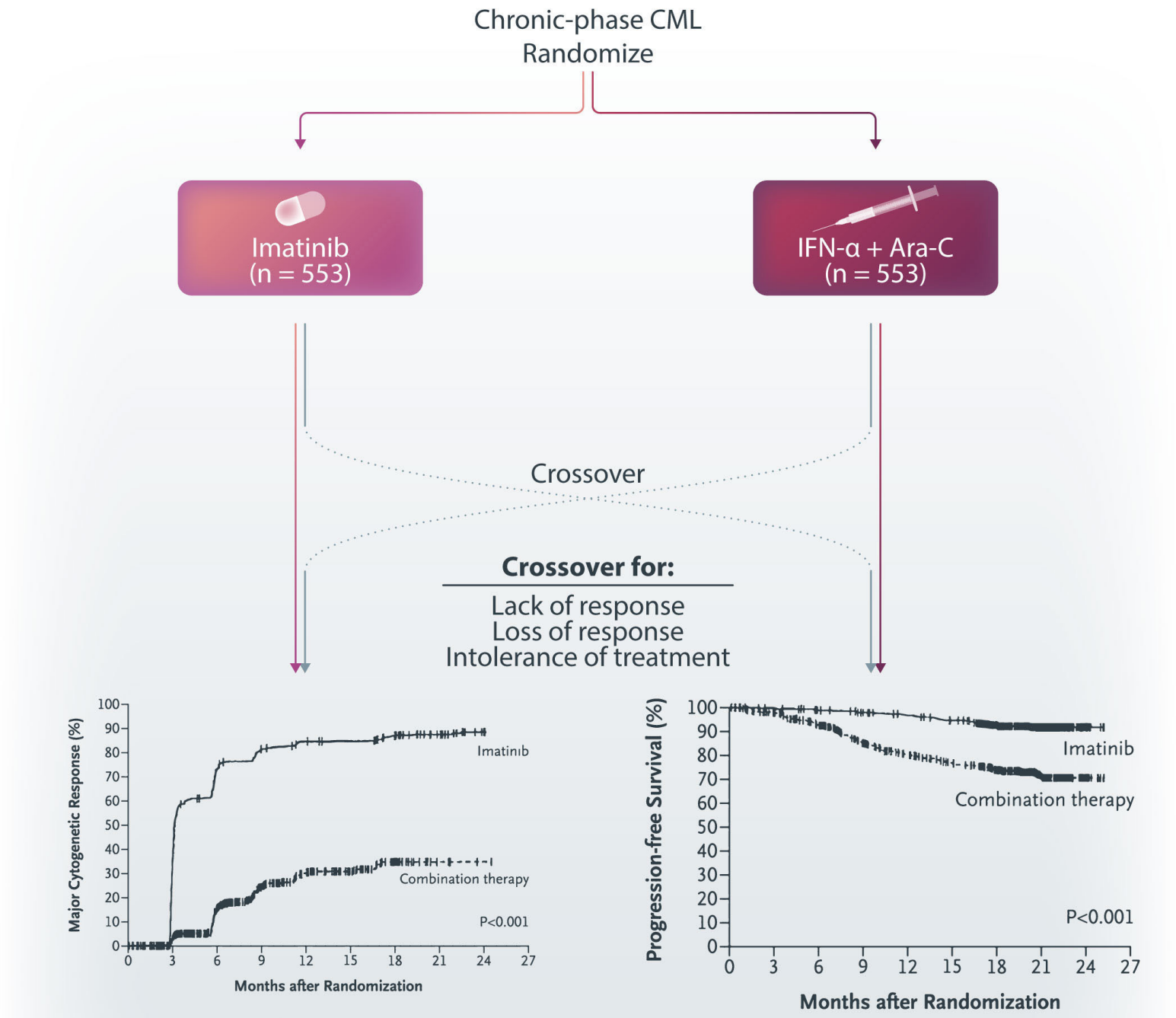


**Figure 1. Study design and selected results of the international trial of imatinib treatment for chronic myeloid leukemia.** CML: chronic myeloid leukemia;IFN: interferon; Ara-C: cytarabine; combination therapy: cytarabine plus inteferon-α. *Figure adapted with permission from Figures 1 and 2 of the paper by O'Brien et al.*[3]

**Disclosures**

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