

Strategies for the next chapter in CML



New areas for research in the treatment of
chronic myeloid leukemia (CML)

CHALLENGES



The TKI revolution

Our understanding of CML was transformed by the discovery that Bcr-Abl, the protein synthesized by the *Bcr-Abl* fusion gene on the Philadelphia chromosome, defines the disease.¹ This oncoprotein is a constitutively active tyrosine kinase that promotes the proliferative and antiapoptotic signals leading to the pathogenesis of CML.^{2,3}

Tyrosine kinase inhibitors (TKIs) were designed to target and block the ATP binding site of the Bcr-Abl tyrosine kinase domain.^{1,2} TKIs revolutionized the treatment of CML by providing hematologic and cytogenetic responses in the vast majority of patients.^{1,2,4}

REMAINING CHALLENGES

Despite the outstanding results seen with TKIs, several challenges remain:

- Approximately 40% of patients receiving imatinib did not retain a major cytogenetic response over the first 5 years of treatment.^{5*}
 - Of imatinib-resistant patients who switched to dasatinib, 55% experienced a major cytogenetic response at 2-year follow-up.⁶
- Some patients treated with imatinib develop resistance, which can manifest as disease relapse or progression.⁷
- Because TKIs do not eradicate CML, most patients must take them for the rest of their lives to control their disease.^{8,9}

*Although the IRIS trial demonstrated imatinib efficacy, the analysis was not performed on an intent-to-treat basis. Therefore, long-term outcomes may have been overestimated.⁵

RESISTANCE

Facing today's challenges

TKI RESISTANCE

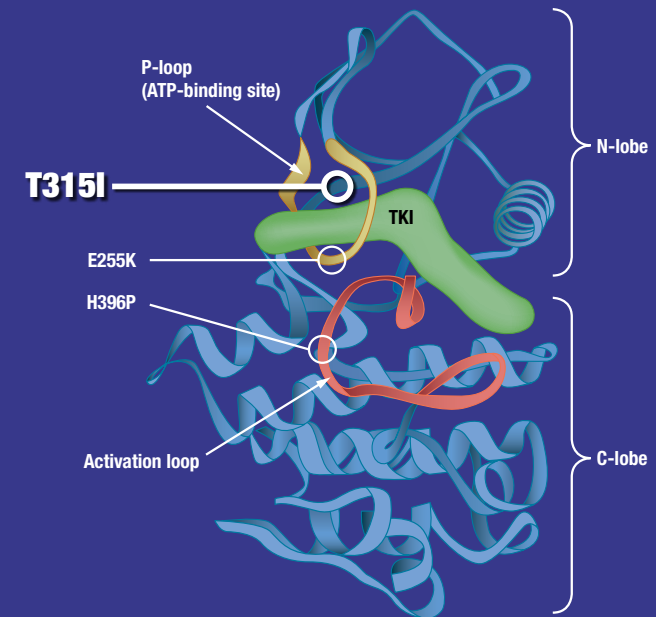
Acquired TKI resistance is the loss of complete hematologic response and major cytogenetic response while on TKI therapy.¹⁰

- Approximately 50% to 80% of imatinib resistance is caused by a Bcr-Abl kinase domain mutation that impairs drug binding.¹⁰⁻¹³
- One of these mutations, the T315I mutation, prevents TKI binding and results in a total lack of clinical response.¹⁴⁻¹⁷

LIMITED TREATMENT OPTIONS

Acquired TKI resistance is commonly managed by switching the patient to a second-generation TKI. However, CML patients with the T315I mutation are insensitive to all TKIs, including second-generation TKIs.¹⁵⁻¹⁷

For appropriate patients, allogeneic hematopoietic stem cell transplantation (HSCT) is a treatment option. However, the morbidity and mortality associated with HSCT limits its use in older patients.¹⁸



Patients with the T315I mutation are insensitive to all TKIs.

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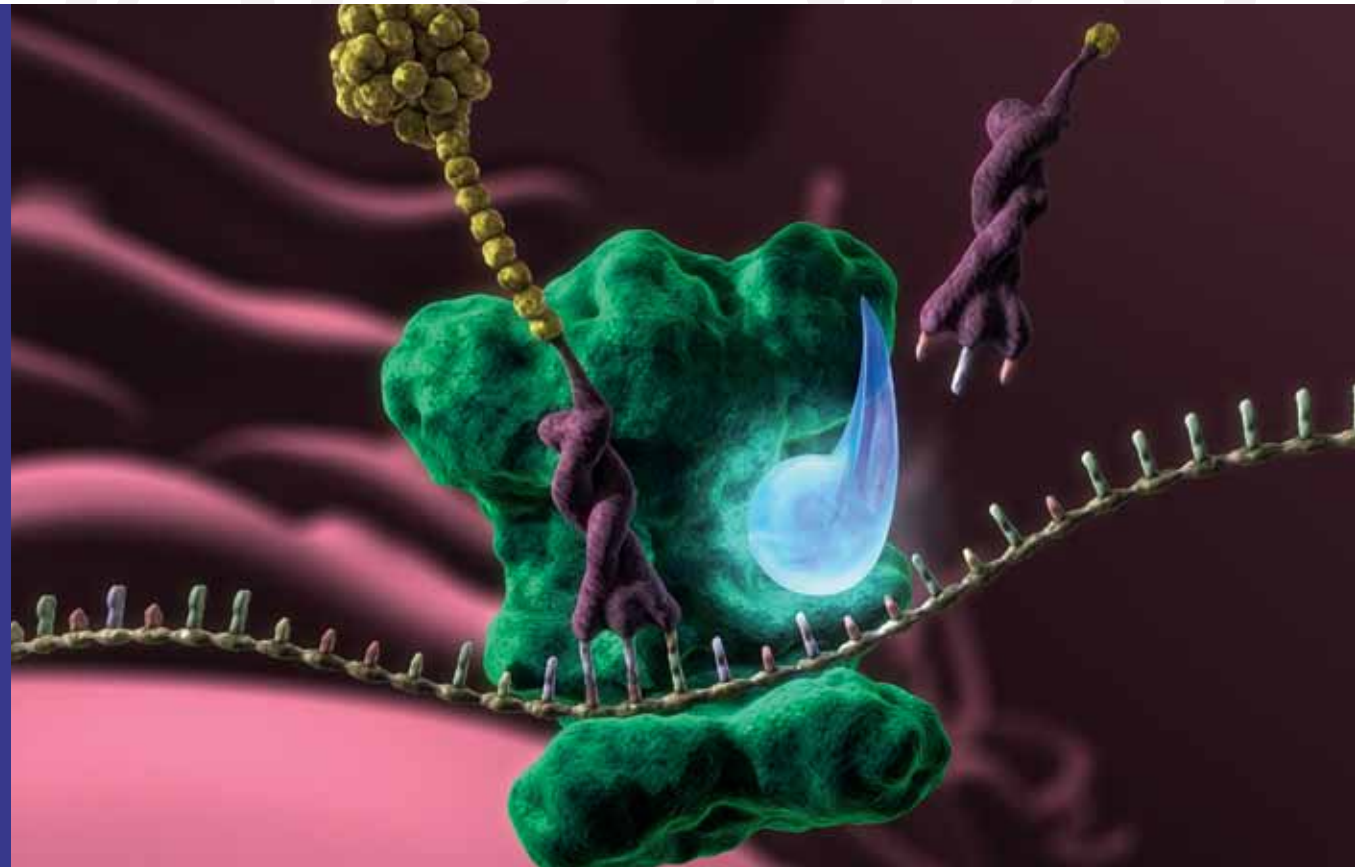
WHAT'S NEXT

Omacetaxine at work

Omacetaxine may offer a unique approach to overcoming some of the unmet needs in the treatment of CML.

Omacetaxine has a mechanism unique from that of TKIs and independent of Bcr-Abl tyrosine kinase activity. Omacetaxine binds to the ribosomal A-site cleft.²⁰ This inhibits protein translation, thereby reducing the levels of key short-lived oncoproteins important in pathogenesis, such as²¹:

- Mcl-1, which inhibits apoptosis
- Cyclin D1, which promotes proliferation
- c-Myc, which inhibits differentiation



Omacetaxine binds to the ribosomal A-cleft, preventing the translation and elongation of short-lived oncoproteins.

Investigating a unique approach in CML

Omacetaxine is an investigational agent currently being studied in patients with CML who have the T315I mutation (study CML-202) and also in a broader population of patients with CML who are resistant to multiple TKIs (study CML-203). Omacetaxine has not been approved for use in patients with CML.

For more information, visit www.ChemGenex.com.

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