Chronic myeloid leukaemia (CML) is caused by BCR-ABL1, a constitutively active fusion tyrosine kinase that is generated from the Philadelphia chromosome (Ph), the result of the translocation t(9;22)(q34;q11). CML begins with a chronic phase (CML-CP) that is characterized by the expansion of functionally normal myeloid lineage cells. Without effective therapy, there is progression to blastic phase (CML-BP) as CML progenitors lose terminal differentiation capacity (BOX 1). BCR-ABL1 is the central therapeutic target in CML and the prognostically poor Ph+ acute lymphoblastic leukaemia (Ph+ ALL) (BOX 2). Small-molecule tyrosine kinase inhibitors (TKIs) of BCR-ABL1 have fundamentally improved CML prognosis, turning a fatal disease into a paradigm for molecularly targeted therapy. A wealth of clinical and molecular data has emerged, accompanied by a refined understanding of disease biology. This Review aims to provide a framework for interpreting the successes and limitations of targeted therapy for CML from a biological perspective.

The most therapeutically advanced facet of CML treatment is TKI-based therapy. Current efforts focus on optimizing TKI design and dosing to seal off BCR-ABL1 mutational escape routes. Third-generation TKIs that are capable of targeting BCR-ABL1 \( ^{31} \) bring this objective within closer reach, though BCR-ABL1 compound mutations (two or more mutations in the same BCR-ABL1 molecule) also warrant consideration. The two extremes of the CML response are the persistence of minimal residual disease (MRD) despite continued TKI therapy, and the presence of active disease despite BCR-ABL1 inhibition; in both cases we are confronted with BCR-ABL1 independence. MRD is thought to reside in leukaemia stem cells (LSCs) that are not fully addicted to BCR-ABL1, whereas advanced CML can exhibit a substantial degree of BCR-ABL1 independence, thus defining a limit for any BCR-ABL1-targeted biochemical therapy. Progress in delineating the nuanced relationships between BCR-ABL1, signals from the bone marrow microenvironment, and survival and self-renewal of CML LSCs has paved the way for innovative, targeted therapeutic approaches. At the centre of these strategies is pharmacological silencing of BCR-ABL1 combined with simultaneous inhibition of other crucial targets. Ideally, these combinations may lead to the elimination of CML LSCs at all stages of disease, ranging from MRD to advanced CML. Here, we highlight progress towards optimizing BCR-ABL1 TKIs to achieve maximum disease control, we explore whether TKIs can achieve cure and we discuss strategies to target CML LSCs.

**TKI-based CML therapy**

BCR-ABL1 is causal to CML pathogenesis, exhibiting constitutive kinase activity that drives the survival and proliferation of CML cells. Advances in analysing this intricate pathway continue to uncover new layers of regulation and signalling connectivity. The unique presence of BCR-ABL1 in all CML cells and its absence from normal cells opened a therapeutic opportunity that became a reality with the discovery of imatinib, a small-molecule BCR-ABL1 TKI. The 5-year follow-up of newly diagnosed patients with CML-CP treated on the International randomized study of interferon and STI571 (IRIS) trial reported a cumulative complete cytogenetic response (CCyR) (BOX 3) rate of 87% and projected overall and progression-free survival rates of 89% and 93%, respectively. This was a ‘quantum leap’ compared with interferon-α (IFNα)-based regimens, the prior standard therapy. Further updates have continued...
At a glance

- Small-molecule BCR-ABL1 tyrosine kinase inhibitors (TKIs) have fundamentally improved the treatment of chronic myeloid leukaemia (CML) and have become a paradigm for molecularly targeted therapy, but they fail to kill leukaemic stem cells (LSCs).
- BCR-ABL1-dependent resistance to currently approved TKIs typically involves single point mutations within the BCR-ABL1 tyrosine kinase domain that interfere with drug binding.
- Third-generation TKIs that comprehensively cover single BCR-ABL1 mutants, including the T315I mutant (BCR-ABL1^T315I^), are in development. With respect to resistance, these TKIs are vulnerable to certain compound mutations (two or more mutations in the same BCR-ABL1 molecule) in vitro model systems. The extent to which BCR-ABL1 compound mutation-based resistance tempers the effectiveness of third-generation TKIs in the clinical setting remains to be established.
- BCR-ABL1-independent TKI resistance occurs despite effective inhibition of BCR-ABL1 kinase activity.
- Other crucial targets in addition to BCR-ABL1 will probably need to be inhibited in both cases. Candidate pathways include Hedgehog, WNT-β-catenin, PP2A and transforming growth factor-β (TGFβ)-Forkhead box protein O3 (FOXO3A)-BCL-6.

BCR-ABL1-dependent resistance

Targeting BCR-ABL1-dependent resistance with TKIs. BCR-ABL1 activation requires dimerization through the amino-terminal coiled-coil domain of BCR followed by successive transphosphorylation and autophosphorylation on regulatory tyrosines. Crystallographical analysis has revealed exclusive binding of imatinib to a catalytically inactive, type II conformation of ABL1 kinase. Studies of patients with imatinib resistance demonstrated that reactivation of BCR-ABL1 signalling often correlates with mutations in the kinase domain. These mutations occur at residues that make direct contact with imatinib or that are crucial for BCR-ABL1 to adopt the inactive conformation required for drug binding. Kinase domain mutations at more than 55 residues conferring varying levels of imatinib resistance have been identified (reviewed in REFS 22,23) (FIG. 2a).

These findings guided the design of the second-generation inhibitors nilotinib, an imatinib derivative with ~30-fold higher potency24, and dasatinib, a SRC and ABL1 inhibitor that is ~300-fold more potent than imatinib25,26. Nilotinib, like imatinib, binds to the inactive type II conformation of ABL1 (REF 24), but dasatinib more readily occupies the active type I conformation of ABL1 (REFS 26,27). Each of these second-generation TKIs controls the majority of BCR-ABL1 mutations that confer resistance to imatinib, with partially complementary exceptions (FIG. 2b,c). Another BCR-ABL1 TKI, bosutinib28–30, is being evaluated in the setting of BCR-ABL1 TKI resistance31,32 and as a first-line therapy (ClinicalTrials.gov identifier: NCT00574873). Bosutinib is a dual SRC and ABL1 inhibitor with a unique binding mode32 (FIG. 2d) that accommodates several BCR-ABL1 mutations30,31 that confer resistance to nilotinib and dasatinib. Currently, the most problematic point mutation is the BCR-ABL1^T315I^ ‘gatekeeper’ mutation, which sterically interferes with inhibitor binding by eliminating the opportunity for a hydrogen bond between inhibitor and enzyme and by biasing the kinase domain towards an active type I conformation31. BCR-ABL1^T315I^ is insensitive to all three approved therapies and to bosutinib, exposing a glaring gap in coverage34. The much anticipated arrival of third-generation BCR-ABL1 TKIs with activity against BCR-ABL1^T315I^ may provide the first targeted therapeutic option for relapsed patients harbouring this mutation. Two such inhibitors, ponatinib and DCC-2036, are currently in clinical evaluation.

Ponatinib. Ponatinib was designed and has shown promise as a true pan-BCR-ABL1 inhibitor with activity against all clinically important BCR-ABL1 kinase domain mutants. The binding modes of ponatinib and imatinib are similar except that the carbon–carbon triple bond of ponatinib enforces compatibility with the T315I residue. Preclinical evaluation of ponatinib demonstrated potent inhibition of BCR-ABL1^T315I^ and other resistant mutants34–36. However, BCR-ABL1^E255V^ was the least sensitive mutant (FIG. 2e), and certain T315I-inclusive BCR-ABL1 compound mutations conferred high-level resistance. The Ponatinib Ph+ ALL and CML evaluation (PACE) trial (NCT01207440) is
Phase II trial for evaluating the safety and efficacy of ponatinib in patients with treatment-refractory CML or Ph+ ALL. Patients with resistance or intolerance to dasatinib or nilotinib or to a confirmed BCR-ABL1T315I mutation were eligible. Among patients in the resistance or intolerance cohort, 62% did not harbour any detectable BCR-ABL1 baseline mutation, suggesting a degree of BCR-ABL1 independence. As reported at the 2011 American Society of Hematology annual meeting, 392 patients were evaluable for primary end points with a median follow-up of 5.6 months. For patients in CML-CP, the overall rates of major cytogenetic response (MCyR) and CCyR were 47% and 39%, respectively, including 65% MCyR and 58% CCyR for patients with the T315I mutation. Overall rates of major haematological response were 67% for advanced phase CML (CML-AP; 46% for T315I patients) and 37% for CML-BP or Ph+ ALL (37% for T315I patients). Longer follow-up will allow the assessment of the durability of responses and will provide insights into mechanisms and frequency of treatment failure. It will be important to verify the extent to which T315I-inclusive compound mutations (for example, BCR-ABL1E255V/T315I) temper the effectiveness of ponatinib. Also, it remains possible that point mutations that confer resistance to ponatinib but not to nilotinib or dasatinib will emerge in patients with CML, although no such mutations were identified in preclinical screens. If proved to be safe and effective, ponatinib may join or replace dasatinib and nilotinib as salvage therapy and could represent a potentially unique candidate in the first-line setting.

**DCC-2036.** DCC-2036 is a switch control inhibitor that engages key residues that are involved in BCR-ABL1 kinase conformational regulation, most notably E282 and R386, and that induces a type II, catalytically inactive state. The inhibitor also extends into the hinge region of the ATP-binding pocket to complete its high-affinity interaction. The distinctive binding mode of DCC-2036 may insulate this TKI from pre-existing resistance mutations such as BCR-ABL1T315I. Indeed, in vitro and in vivo preclinical assays have shown DCC-2036 to be effective against BCR-ABL1 mutants, including BCR-ABL1T315I.

In an in vitro screen for point mutations that confer resistance to DCC-2036, E282 and R386 were not implicated, possibly because changes at these residues are incompatible with kinase function. The key sites of vulnerability were select phosphate binding loop mutations (G250E, Q252H, Y253H and E255K/V) that engage key residues that are involved in BCR-ABL1 kinase conformational regulation, most notably E255K/V. DCC-2036 is in Phase I clinical evaluation for treatment-refractory CML and Ph+ ALL (NCT00827138). As DCC-2036 and ponatinib
Box 2 Targeted therapy in Ph⁺ acute lymphoblastic leukaemia

Although chronic myeloid leukaemia (CML) and Philadelphia chromosome (Ph⁺) acute lymphoblastic leukaemia (ALL) are both BCR-ABL1-driven diseases, Ph⁺ ALL typically follows a more aggressive disease course than chronic phase CML (CML-CP). One question is whether the cellular context in which BCR-ABL1 arises, or other factors, explain the divergent disease properties. A number of additional genetic alterations are thought to cooperate with BCR-ABL1 in Ph⁺ ALL leukaemogenesis, including deletion of IKZF1 (also known as IKAROS), PAIX, EBF1 or CDKN2A and CDKN2B. Tyrosine kinase inhibitors (TKIs) are a therapeutic component in Ph⁺ ALL care, most often in combination with chemotherapy. Similar to blast phase CML (CML-BP)135, patients with Ph⁺ ALL experience transient responses due to BCR-ABL1 mutation-mediated resistance or less well-understood mechanisms of disease progression. Unlike CML, leukaemic stem cells (LSCs) and progenitor cells, which are thought to undergo sequential clonal evolution17,147, a recent study demonstrates a pattern of branching at the level of Ph⁺ ALL leukaemia-initiating cells (LICs)135, a complex hierarchy that may have consequences on perturbation with TKI therapy. Another important discovery is that, on challenge with BCR-ABL1 TKIs, the BCL-6 transcriptional response network triggers counterbalancing signals that have a major role in limiting TKI effectiveness against Ph⁺ ALL. The recognition that this compensatory response is directly primed by BCR-ABL1 inhibition opens an opportunity to combine TKI-based therapy with targeting of the BCL-6 transcriptional network28,132,149,151,154. A peptidomimetic called retro-inverso BCL-6 peptide inhibitor (RI-BPI) injected intraperitoneally into mice with Ph⁺ ALL markedly enhanced the effectiveness of TKIs, which was comparable to genetic knockout of Bcl6. In addition, new evidence suggests that BMI1, a Polycomb group protein known to be upregulated in advanced disease, can induce conversion of lymphoid CML progenitors into Ph⁺ ALL LICs135. The role of BMI1 in the transition to CML-BP and Ph⁺ ALL is not fully understood. Effective therapy for Ph⁺ ALL will require the elimination of LICs, and the studies discussed here, as well as other studies, reveal important new information in this pursuit.

have different mechanisms of action, it will be interesting to see whether patients failing one of these therapies can be salvaged with the other.

HG-7-85-01. Additional BCR-ABL1315–active TKIs are in preclinical development49. HG-7-85-01 arose from an effort to design ATP-competitive inhibitors with tailored activity against BCR-ABL1315 and other clinically important gatekeeper mutants such as KIT870I in gastrointestinal stromal tumours (reviewed in REF 41) and platelet-derived growth factor-receptor-α (PDGFRα)587,42 in hypereosinophilic syndrome, while retaining a restricted kinase selectivity profile. HG-7-85-01 is an excellent BCR-ABL1315 inhibitor, but is less effective in vitro against certain BCR-ABL1 mutants (for example, BCR-ABL1F317L) unless combined with nilotinib51.

Allosteric inhibitors. New ways to selectively target BCR-ABL1 aside from directly interfering with kinase activity are being explored. For example, regulatory control mechanisms governing ABL1 kinase activity include an interaction between a myristoyl-modified glycine residue near the N terminus and its cognate myristate-binding pocket in the kinase domain42,43. The ABL1 N-terminal region is absent from the BCR-ABL1 fusion protein, presumably leaving the vestigial myristate-binding pocket unoccupied. GNF2 and its increased-potency analogue, GNF5, bind in the myristate-binding pocket with surprising consequences. As a single agent, GNF2 is a selective non-ATP competitive inhibitor of BCR-ABL1 activity54 with potency comparable to that of imatinib. Although neither GNF2 nor GNF5 effectively inhibits BCR-ABL1T315I, high concentrations of both GNF5 with nilotinib55 and GNF5 with HG-7-85-01 (REF 46) do block its kinase activity. The discovery that an allosteric inhibitor such as GNF5 can relay conformational changes to the catalytic site and remotely influence TKI potency has triggered mechanistic studies54,7,4.

Three recent examples reveal additional strategies for inhibiting BCR-ABL1 outside of its kinase domain. First, working from knowledge that the kinase activation state of ABL1 is influenced by conformational changes in the neighbouring SH2 domain, the importance of this mechanism to constitutively activated BCR-ABL1 was examined. The findings open the possibility that the SH2-kinase domain interface could serve as a therapeutic target46. Secondly, the N-terminal coiled-coil dimerization domain in the BCR component of the fusion kinase is crucial for BCR-ABL1 autophosphorylation, and it has been explored as a target in the past. Recent efforts have yielded peptides that are capable of interacting with this domain on BCR-ABL1 while exhibiting low self-dimerization tendencies57. In both cases, limitations with respect to intracellular delivery of therapeutics will have to be addressed46,47. A third new alternative strategy is to selectively sequester BCR-ABL1 in aggresomes using ubiquitin cycle inhibitors58. These approaches should not be affected by BCR-ABL1 mutation status and may lead to therapeutic options for TKI-resistant patients with CML.
Patients with mutation-based imatinib resistance are prone to fail subsequent therapies with additional mutations, and the presence of low-level, subclinical mutations may predict which patients are most predisposed to this route of failure. By contrast, patients that exhibit resistance to imatinib without a detectable BCR-ABL1 mRNA in two consecutive samples with a 4.5-log detection limit are resistant to imatinib. This definition may become inadequate once sensitivity increases beyond the 4.5-log level. It may be best to indicate test sensitivity and avoid the term CMR. Classifications of failure and suboptimal response for newly diagnosed patients in early chronic phase CML treated with 400 mg imatinib daily were recommended by European LeukemiaNet and adopted by National Comprehensive Cancer Network (NCCN) and National Comprehensive Cancer Network (EUSA). Classifications will need to be adjusted for new tyrosine kinase inhibitors, including dasatinib and nilotinib. Response milestones for advanced phase CML are not standardized.

### Optimal response

CHR and ≤65% Ph+ metaphases at 3 months of imatinib therapy, ≤35% Ph+ metaphases at 6 months, CCyR at 12 months and MMR at 18 months.

### Failure

No CHR at 3 months of imatinib therapy, >95% Ph+ metaphases at 6 months, >35% Ph+ metaphases at 12 months and no MMR at 18 months. Loss of CHR or CCyR, clonal cytogenetic evolution, BCR-ABL1 mutations define failure at any time during treatment.

### Suboptimal response

Not fulfilling criteria for either optimal response or failure. The validity of this category has been questioned.

**Box 3** | Monitoring therapeutic responses in CML

| Complete haematological response (CHR) | Normalization of blood counts and spleen size and disappearance of chronic myeloid leukaemia (CML) symptoms (see the figure). |
| Complete cytogenetic response (CCyR) | Absence of Philadelphia chromosome (Ph) in 20 of 20 bone marrow metaphases by karyotyping. |
| Major cytogenetic response (MCyR) | Presence of Ph in 0–35% of 20 metaphases. |
| Molecular response | Following quantitative real-time PCR (qRT-PCR) analysis, the BCR-ABL1/control gene transcript ratio is determined using the International Scale (IS) standardized baseline. ≥3 log10 reduction in BCR-ABL1 transscripts (≤0.10% IS) is major molecular response (MMR). There is no universal definition of complete molecular response (CMR). Some studies used nested PCR negativity to define CMR, but this is problematic owing to test variability. Another study suggested that CMR be defined as undetectable BCR-ABL1 mRNA in two consecutive samples with a 4.5-log detection limit. This definition may become inadequate once sensitivity increases beyond the 4.5-log level. It may be best to indicate test sensitivity and avoid the term CMR. Classifications of failure and suboptimal response for newly diagnosed patients in early chronic phase CML treated with 400 mg imatinib daily were recommended by European LeukemiaNet and adopted by National Comprehensive Cancer Network (NCCN) and National Comprehensive Cancer Network (EUSA). Classifications will need to be adjusted for new tyrosine kinase inhibitors, including dasatinib and nilotinib. Response milestones for advanced phase CML are not standardized. |

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Not fulfilling criteria for either optimal response or failure. The validity of this category has been questioned.

**Dasatinib, Dasatinib versus imatinib study in treatment naive CML patients; ENESTnd, Evaluating nilotinib efficacy and safety in clinical trials of newly diagnosed Philadelphia-positive CML patients.**
MAPK was seen in some patients who developed TKI resistance without BCR-ABL1 mutations. Few somatic mutations outside of BCR-ABL1 have been identified in TKI-resistant CML cells, and the primary events leading to BCR-ABL1-independent resistance remain poorly understood in every disease phase.

CML stem cells. Patients in whom the CML clone has been therapeutically suppressed to very low levels experience a situation of deep remission called MRD (BOX 4). Prospective studies have started to address whether imatinib can be discontinued in patients with a defined level of MRM or CMR (BOX 3) after anecdotal reports revealed a mixed picture. Currently, the overwhelming majority of patients require continued, lifelong TKI treatment to avoid the risk of re-establishing active CML-CP from MRD on discontinuation of therapy. The fact that fully competent LSCs have survived in the presence of TKIs raises the question of whether these cells are resistant to TKI exposure owing to BCR-ABL1 kinase-dependent or BCR-ABL1 kinase-independent mechanisms.

Like their normal counterparts, CML LSCs are lineage-restricted by BCR-ABL1 kinase activity in primitive lineage CML-CP cells at diagnosis. CML progenitor cells or LSCs could conceivably survive in vivo TKI exposure owing to high levels of BCR-ABL1 (maintaining some kinase-active protein in the presence of TKIs) or low levels of BCR-ABL1 (identifying themselves as less BCR-ABL1 dependent). Several groups showed that BCR-ABL1 expression is higher in primitive lineage CML-CP cells than in lineage CD34^-CD38^- progenitor cells, suggesting that primitive cells may be more resistant to TKIs. Conversely, BCR-ABL1 mRNA expression in myeloid colonies cultured from patients with TKI-induced MMR was found to be lower than in colonies cultured from untreated patients, which is consistent with the in vitro selection of progenitors that are less reliant on BCR-ABL1, in contrast to in vivo selection that favours progenitors with high BCR-ABL1 expression. Analogous results were seen in normal human CD34^- cells that were infected with BCR-ABL1 retrovirus.

Patients with MMR or CMR following imatinib treatment harbour 0.09% to 1.61% BCR-ABL1^+ cells in the CD34^-CD38^ fraction, identified as LSCs by multilineage engraftment in immunodeficient mice. This is consistent with the low proportion of BCR-ABL1^+ cells in the CD34^-CD38^ population detected by fluorescence in situ hybridization. Much higher rates of BCR-ABL1^+ colony-forming or long-term culture-initiating cells (LTC-ICs; a population enriched for haematopoietic stem cells (HSCs)), were reported in another study of patients with undetectable residual leukaemia who maintained responses for several years after discontinuation of IFNα. Despite these partially conflicting results, there is a consensus that TKIs inhibit BCR-ABL1 kinase activity in primitive lineage CD34^-CD38^- cells. However, in contrast to progenitor cells, these cells undergo little apoptosis following TKI exposure, and clonogenic cells can survive in the absence of cytokines. Thus, the crucial target cells are not (or not completely) addicted to BCR-ABL1.

On closer view, this fits well with some fundamentals of CML biology. The presence of BCR-ABL1 in all haematopoietic lineages indicates that the initial Ph translocation occurs in a pluripotent HSC. Consistent with this, a murine CML model demonstrated that...
**Long-term culture-initiating cells**

An in vitro assay in which mononuclear cells or immuno-phenotypically selected haematopoietic cells (for example, CD34+ cells) are cultured on bone marrow stromal cells as feeders for up to 6 weeks, sometimes longer. After a defined interval of culture, the haematopoietic cells are harvested and assayed for clonogenic potential (colony growth) in semisolid medium.

**P-loop**

A conserved loop present in the ABL1 and BCR-ABL1 kinase domains that forms the roof of the active site and coordinates the γ-phosphate group of ATP.

**Activation loop**

A flexible loop that extends into the active kinase domain and functions as a binding platform for the peptide substrate to be phosphorylated.

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**Figure 2 | A partially overlapping network of BCR-ABL1 kinase domain mutations confer resistance to certain TKIs.** The crystal structure of the ABL1 kinase domain in complex with the indicated tyrosine kinase inhibitor (TKI; indicated in green) is shown. The P-loop is shown in yellow and the activation loop in green. Mutations at the highlighted residues confer resistance to the indicated TKI in vitro, with orange (moderate) and red (high) spheres indicating the level of resistance. a | For imatinib[22,24], orange indicates a half-maximal inhibitory concentration (IC50) ≤ 3,000 nM and red indicates an IC50 ≥ 3,000 nM. b | For nilotinib[24,25], orange indicates an IC50 ≤ 500 nM and red indicates an IC50 ≥ 500 nM. c | For dasatinib[25,27], orange indicates an IC50 ≤ 60 nM and red indicates an IC50 ≥ 60 nM. d | For bosutinib[24,29], orange indicates an IC50 ≤ 500 nM and red indicates an IC50 ≥ 500 nM. e | For ponatinib[34], orange indicates an IC50 < 40 nM and red an IC50 ≥ 40 nM. f | For DCC-2036 (REFS 37,38), orange indicates an IC50 < 200 nM and red indicates an IC50 ≥ 200 nM. Each TKI is susceptible to a different, partially overlapping set of resistance mutations. Compared with imatinib, the newer inhibitors have less vulnerability to kinase domain mutations and, in total, provide a potential option for every known BCR-ABL1 point mutation. For a comprehensive compilation of resistance mutations see REF 22,29,52. Compound mutations such as BCR-ABL1T315I/V299L confer high-level resistance to all of these TKIs. For resistance profiles of TKIs with respect to BCR-ABL1 compound mutations see REF 34,38,57.

BCR-ABL1 fails to confer self-renewal capacity to committed progenitor cells, suggesting that CML originates from a cell with intrinsic self-renewal capacity[35]. The situation changes at the time of transformation to CML-BP, when granulocyte–macrophage progenitor cells acquire self-renewal capacity, presumably owing to the activation of β-catenin[36]. At diagnosis, most LTC-ICs are frequently Ph1−, in contrast to the mostly Ph1+ myeloid progenitor cell population. Thus, the initial proliferative thrust targets the progenitor cell compartment almost exclusively; the expansion of this compartment leads to clinical disease, and the hierarchy of myeloid differentiation remains mostly intact[37].

These biological fundamentals of CML are reflected in clinical responses to TKIs. First, inhibition of BCR-ABL1 is predicted to roll back the progenitor cell expansion, clinically evident by the rapid haematological and profound cytogenetic responses to TKIs. Second, given the limited effects of BCR-ABL1 on CML LSCs, it is not surprising that they are generally insensitive to
Box 4 | TKIs and curing CML: minimal residual disease

The Stop imatinib (STIM) trial studied 100 patients who discontinued imatinib after maintaining complete molecular response (CMR) for at least 2 years. In a recent update at the 2011 American Society of Hematology annual meeting it was reported that, with 30 months median follow-up, 61 patients experienced molecular recurrence (detectable BCR-ABL1 transcripts in two consecutive tests), and 56 were sensitive to tyrosine kinase inhibitor (TKI) re-challenge. All but three recurrences happened within 7 months, suggesting two biologically distinct patient populations: early recurrence versus no recurrence. This study raises the question of whether imatinib cures some cases of chronic myeloid leukaemia (CML) and how one should define cure in the context of TKI therapy. A clean definition would equate cure with the elimination of all CML cells. However, as test sensitivity is ultimately limited and some responses are maintained despite intermittent detection of residual leukaemia, this definition is impractical. A more reasonable approach may be to define cure as a risk of clinical CML equal to that of the general population. Late relapses after allogeneic stem cell transplant underscore the need for caution and long-term follow-up. A shorter duration of imatinib treatment and high Sokal risk score at diagnosis were predictive of recurrence in the STIM trial. The first observation suggests that optimizing TKI therapy may reduce recurrence risk. The higher rates of CMR with dasatinib or nilotinib in first-line therapy indicate that more patients will be eligible for a trial of discontinuation. An analogous study has begun to address the feasibility of discontinuing nilotinib or dasatinib. Preliminary results show that four of 16 patients experienced recurrence within 4 months, while 12 maintained response with a median follow-up of 13 months. Thus far, no predictive factors have been identified.

Allogeneic stem cell transplant

The transfer of genetically similar but not identical cells from the bone marrow, peripheral blood or cord blood from one individual to another.

Sokal risk score

A prognostic score determined at diagnosis of chronic myeloid leukaemia to classify the patient as either low risk, intermediate risk or high risk. This is the most widely used scoring system, developed in 1984, when busulphan was the standard treatment. The score is based on spleen size, age, blast count and platelet count at diagnosis.

Synthetic lethality

In genetics, an interaction between two non-lethal mutations that, in combination, confer lethality. In chemical genetics, this term can refer to interaction between a drug and a mutation that confers greater drug sensitivity than with the wild type.

Autophagy

A cellular response in which the cell metabolizes its own contents and organelles to maintain energy production. Although such a process can eventually result in cell death, it can also be used to maintain cell survival under conditions of limiting nutrients.

BCR-ABL1 inhibition, as evidenced by disease persistence. Nonetheless, responses are often durable as few residual LSCs equate with little opportunity for additional mutations and the presence of TKIs may mitigate genetic instability caused by BCR-ABL1 kinase activity. Third, once the hierarchical structure of CML haematopoesis is destroyed by the acquisition of self-renewal capacity at the level of progenitor cells, the pool of fully leukaemogenic cells at risk of resistance mutations expands, which is consistent with the poor response of CML-BP to TKI therapy. If CML LSCs are not addicted to BCR-ABL1 kinase activity, the prediction is that BCR-ABL1 TKIs will be unable to eliminate this crucial cell population. Emerging data from the DASISION and ENESTnd studies may support this view. Compared with imatinib, both dasatinib and nilotinib induce MMR much faster; despite this, the rates of CMR, although superior to imatinib, may be lower than expected in view of the enhanced potency of these agents.

Targeting CML stem cells. The reason for the fundamental difference between TKI effects on progenitor cells versus LSCs is unknown. One attractive explanation is that all three approved BCR-ABL1 TKIs also inhibit KIT, the receptor for stem cell factor (SCF; also known as KIT ligand), directly and/or through inhibition of SRC family kinases downstream of the receptor. Effective elimination of BCR-ABL1-expressing murine myeloid progenitor cells requires the inhibition of both KIT and BCR-ABL1 (REF 95), and preliminary data suggest that imatinib effects on human CML progenitor cells may be mimicked by combining a KIT-blocking antibody and a BCR-ABL1-specific TKI. Fortuitous BCR-ABL1–KIT dual inhibitory activity in the same TKI may generate synthetic lethality in progenitor cells and could underlie the profound haematological and cytogenetic responses. Given that CML LSCs are not eliminated under these conditions, suppression of BCR-ABL1 and a second pathway other than KIT may be necessary to eliminate these cells.

A CML stem cell with suppressed BCR-ABL1 kinase activity could represent a loss-of-function, gain-of-function or neutral variant compared with an LSC with full BCR-ABL1 activity. A loss-of-function variant would result if pharmacologically silenced BCR-ABL1 operated in a dominant-negative manner. This could explain why expression of BCR-ABL1 renders Mo7e cells, a cytokine-dependent human myeloid cell line, growth factor-independent, but cytokines fail to rescue these cells following TKI inhibition of BCR-ABL1 (REF 88). The same explanation might apply to the observation of lower BCR-ABL1 expression in colonies cultured from patients with MMR. A gain-of-function variant could be based on functions of BCR-ABL1 that persist despite effective suppression of kinase activity. Indeed, it has been shown that a kinase-inactive BCR-ABL1 mutant enhances migration and reduces adhesion, and activation of SRC family kinases can persist in the presence of TKIs. Some transcriptional targets of BCR-ABL1, such as arachidonate 5-lipoxygenase (ALOX5; also known as 5-LO), do not require kinase activity. Another mechanism to consider is epigenetic changes imparted by active BCR-ABL1 that persist despite effective inhibition of kinase activity. For example, BMS-214662, a compound originally developed as a farnesyl transferase inhibitor (FTI), selectively induces apoptosis in CML stem and progenitor cells in a protein kinase Cβ (PKCβ)-dependent manner, with or without concomitant inhibition of BCR-ABL1, and it has been suggested that this might be due to an epigenetic imprint as a result of prior exposure to BCR-ABL1 activity. Inhibition of kinase-independent BCR-ABL1 functions or epigenetically activated pathways may be required to kill CML LSCs. Finally, inactive BCR-ABL1 could be neutral, producing an LSC that is biologically indistinguishable from a normal HSC. In this case, selective elimination of residual leukaemia through biochemical means would be impossible. Maintenance of CML LSCs in comparison to normal HSCs is reported to be more reliant on pathways such as hypoxia-inducible factor 1a and promyelocytic leukaemia protein, efforts to therapeutically exploit these differences are underway. Histone deacetylase inhibitors (HDACis) have profound effects on gene expression in haematopoietic cells, and a HDACi in combination with a BCR-ABL1 TKI exhibits selective toxicity against CML LSCs in murine leukaemia models and xenograft assays of primary human leukaemia cells. The mechanism or mechanisms underlying this selectivity may involve multiple pathways that are related to primitive haematopoiesis, apoptosis and response to microenvironmental stimuli. By contrast, results from similar studies using proteasome inhibitors revealed no convincing usefulness of this approach. In chronic and LTC-IC assays, lineage CD34+CD38– CML cells were extremely sensitive to simultaneous treatment with BCR-ABL1 TKIs and autophagy inhibitors such as chloroquine. Clinical testing of imatinib combined with chloroquine is underway in the United Kingdom.
Combinatorial approaches targeting CML LSCs are implicitly based on the induction of a lethal phenotype by simultaneous inhibition of BCR-ABL1 kinase and one or more additional pathways\(^{97,109}\). These pathways may be redundant or even inactive in the presence of uninhibited BCR-ABL1, and assume an essential role only in the presence of TKIs. CML cells exhibit a remarkable degree of plasticity, enabling them to respond to TKI challenge by shifting to alternative survival pathways. For example, treatment with imatinib enhanced the survival of CML CD34\(^+\) cells by activating MAPKs in the presence of cytokines\(^4\). Similarly, CML cell lines cultivated on HS-5 bone marrow stromal cells are partially protected from TKI-induced apoptosis by JAK kinase-dependent upregulation of phosphorylated STAT3 (REFS 71, 72). The CXCR4–CXCL12 chemotactic axis has been implicated in mediating the interaction between CML cells and their microenvironment. As CXCR4 function is compromised by BCR-ABL1 activity, TKIs may have the undesired effect of promoting CML cell homing to a protective environment. Thus, it has been shown that CXCR4 upregulation by imatinib induces CML cell migration to bone marrow stroma and promotes the survival of quiescent CML cells\(^10\). Consistent with this, the CXCR4 antagonist plerixafor (initially known as AMD3100) may reduce leukaemia burden in combination with TKIs\(^111-113\). Other adhesion and homing-related molecules may offer additional therapeutic opportunities. For example, CD44 is required for the homing of CML stem cells, and blocking this interaction could have similar effects to those of blocking CXCR4 (REF. 114). Pathways with an essential role in normal and CML cells may or may not be suitable therapeutic targets, depending on the degree of selectivity to LSCs, and pathways activated as part of a stress response to TKIs should be particularly attractive. Four major pathways have been implicated in the survival of CML LSCs and represent potential therapeutic targets.

**WNT and β-catenin.** β-catenin, the central mediator of canonical WNT signalling, has a dual function as an adhesion-related tight junction protein and as a transcriptional co-activator that recruits cAMP responsive element-binding protein (CREB1) to binding sites for T cell factor (TCF)/lymphoid enhancer factor (LEF) transcription factors) to activate developmentally regulated transcriptional programmes (FIG. 3a). In the absence of WNT signalling, cytoplasmic β-catenin that is not involved in tight junctions is phosphorylated by glycogen synthase kinase 3β (GSK3β) and subsequently degraded by a multimeric protein complex, the rate-limiting component of which is axin.

Nuclear β-catenin is required for self-renewal and viability of normal HSCs\(^115\) and is implicated in various aspects of CML pathogenesis and response to TKIs. Lack of β-catenin attenuates disease in a murine CML model by impairing self-renewal of LSCs\(^116\). However, in a recent study, deletion of β-catenin after CML initiation did not significantly increase survival in mice\(^117\). Rather, pharmacological inhibition of β-catenin through blocking prostaglandin signalling resulted in greatly reduced numbers of LSCs. In addition, gene expression in imatinib-naïve CD34\(^+\) cells from patients with primary cytogenetic resistance may be partially regulated by β-catenin\(^118\). Activation of nuclear β-catenin in granulocyte–macrophage progenitor cells is associated with myeloid blastic transformation\(^2\). This may be due to the inactivation of GSK3β by abnormal splicing\(^119\) or conformational changes of β-catenin as a result of BCR-ABL1-induced tyrosine phosphorylation that prevent axin binding\(^120\). Paradoxically, pharmacological inhibition of GSK3β in combination with imatinib, but not dasatinib, was effective at targeting CML LSCs, suggesting that the intensity of the β-catenin signal must be tightly controlled to support optimal LSC survival\(^121\).

At least three pathways have been implicated in WNT signalling in CML LSCs (FIG. 3a). First, ligand-induced CD27 signalling may enhance extrinsic and intrinsic activation of nuclear β-catenin. Consistent with this, blockage or absence of CD27 prolongs survival in a murine CML model\(^122\). Second, a recent synthetic lethal screen identified a non-canonical WNT–Ca\(^2+\)—nuclear factor of activated T-cells (NFAT) pathway that mediates TKI resistance through upregulation of IL-4, and this calcineurin-independent pathway is inhibited by cyclosporine A\(^123\). Last, ALOX5 is upregulated by BCR-ABL1 in a kinase-independent manner, leading to increased levels of its metabolic product leukotriene B4 (LTB4)\(^124\). ALOX5 deficiency prolongs survival in a murine model, apparently by promoting gradual depletion of LSCs. The biochemical mechanism may involve a failure of Alox5\(^−/−\) LSCs, but not of Alox5\(^+/−\) HSCs, to upregulate β-catenin. Treatment with the ALOX5 antagonist zileuton prolonged the survival of mice with BCR-ABL1-induced leukaemia alone and especially in combination with imatinib. The pivotal role of nuclear β-catenin in the pathogenesis of colon cancer has sparked great interest in the development of β-catenin inhibitors, but β-catenin remains a challenging target\(^125\), and no clinical compounds have emerged.

**Hedgehog.** Hedgehog (HH) signalling is crucial to embryonic patterning and primitive fetal haemopoiesis\(^126\) but may be dispensable for adult HSC function\(^127\). HH binding to its cell surface receptor, Patched (PTCH), induces conformational changes in Smoothened (SMO), thereby releasing the transcriptional activator GLI1 (FIG. 3a). Two studies have implicated HH signalling in the self-renewal of CML LSCs and have identified SMO as a crucial mediator\(^128\). HH signalling in CML LSCs is inhibited by HH-blocking antibodies\(^129\), but not BCR-ABL1 TKIs\(^130\), which is consistent with a BCR-ABL1 kinase-independent mechanism of HH activation by ligand. At present, the bulk of data implicating HH in LSC survival in CML is based on mouse models or advanced CML. Compared with WNT–β-catenin, the HH pathway is a more accessible drug target. Cyclopamine, an alkaloid that stabilizes SMO in an inactive conformation, selectively targets CML LSCs over normal HSCs, alone and in combination with BCR-ABL1 TKIs. The discovery of PTCH mutations in other malignancies has stimulated the development of inhibitors of SMO, including PF-04449913, LDE225 and BMS-833923. Clinical trials in TKI-resistant CML are underway, with a suggestion of activity\(^132\).
**REVIEWS**

Figure 3 | Targeting opportunities in CML cells. **a** | β-catenin stabilization through WNT3A binding to Frizzled (FZD) and low-density lipoprotein receptor-related protein (LRP) binding to Disheveled (DVL) and subsequently sequestering axin antagonizes destruction complex assembly (shown in orange). Extrinsic stabilization through the activation of CD27 by CD70 and intrinsic stabilization through tyrosine phosphorylation by BCR-ABL1 preclude axin binding and promote β-catenin stabilization. Additionally, BCR-ABL1-induced arachidonate 5-lipoxygenase (ALOX5) upregulation increases β-catenin mRNA\(^{128}\). Stabilized, nuclear β-catenin engages T cell factor (TCF)/lymphoid enhancer factor (LEF) transcription factors and cAMP responsive element-binding protein (CREB1) on target gene promoters. Non-canonical WNT5A signalling activates a phospholipase C (PLC)-and calcineurin (CCN)-dependent pathway that enhances expression of nuclear factor of activated T cells (NFAT)-regulated genes (for example, interleukin-4 (IL4))\(^{123,127}\). **b** | Hedgehog (HH) binding to Patched (PTCH) activates Smoothened (SMO), thereby activating GLI transcription factors, reducing NUMB expression and increasing MDM2-induced p53 degradation. Similarly, MSI2 (also known as musashi 2) inhibits NUMB to suppress p53 (REFS 124–128,167). **c** | In CD34+CD38+ progenitors, BCR-ABL1 activates PI3K, promoting AKT phosphorylation by 3-phosphoinositide-dependent protein kinase 1 (PDK1). AKT phosphorylates Forkhead box protein O3 (FOXO3A), preventing its nuclear translocation. In CD34+CD38+ cells, transforming growth factor β (TGFβ) signalling inhibits AKT, permitting FOXO3A translocation and activation of transcriptional targets, including CDKN1B (which encodes p27) and possibly BCL6 (REFS 129–131). **d** | BCR-ABL1 suppresses PP2A by activating two negative regulators, SET and cancerous inhibitor of PP2A (CIP2A). SET expression is promoted by heterogeneous nuclear ribonucleoprotein A1 (HNRNPA1). BCR-ABL1 tyrosine kinase (TK)-dependent and BCR-ABL1 TK-independent functions and extrinsic signals regulate Janus kinase 2 (JAK2) activity, which in turn controls SET, PP2A, a serine/threonine phosphatase, negatively regulates BCR-ABL1 phosphorylation, activity and stability through SHP1 tyrosine phosphatase. PP2A may dephosphorylate and inactivate additional signalling proteins such as signal transducer and activator of transcription (STAT) proteins\(^{129–131}\), baculoviral IAP repeat-containing 5 (also known as survivin); CCND1, cyclin D1; CML, chronic myeloid leukaemia GF, growth factor; GFR, GF receptor.

**TGFβ, FOXO3A and BCL-6.** In CML progenitor cells, BCR-ABL1 activates AKT, which in turn phosphorylates the transcription factor Forkhead box protein O3 (FOXO3A; also known as FOX30), promoting its cytoplasmic retention and subsequent degradation. Imatinib-induced FOXO3A activation induces cell cycle arrest and apoptosis by enhancing expression of p27 (encoded by CDKN1B) and BIM (also known as BCL2L11)\(^{129}\) (FIG. 3c). Surprisingly, FOXO3A is nuclear in lineage CD34+CD38+ CML stem cells even in the absence of TKIs, owing to the inhibition of AKT signalling by transforming growth factor β (TGFβ)\(^{130}\). In a murine CML model, loss of FOXO3A does not impair leukaemogenesis in primary transplantsations, but impairs leukaemogenicity in subsequent transplantsations, suggesting a crucial role in the maintenance of CML LSCs. Inhibitors of TGFβ signalling (for example, LY364947, an inhibitor of TGFβ receptor 1) combined with imatinib prolonged
the survival of leukaemic mice compared with imatinib alone. Although it is unclear whether TGFβ signalling is cell-autonomous or driven by microenvironmental factors, the differential effect on LSCs compared with progenitor cells could explain why some CML LSCs remain quiescent despite high levels of BCR-ABL1 activity.

Another transcription factor, BCL-6, is a target of FOXO3A in CML (Fig. 3c) and seems to regulate its downstream effects\(^{131}\). BCL-6 may exhibit a dual role by both initiating protective signalling in response to BCR-ABL1 TKIs and facilitating CML LSC survival. Under basal conditions, even low BCL-6 levels are sufficient to repress p53 and ARF (encoded by CDKN2A). TKI exposure of CML cells inhibits AKT, promoting FOXO3A activation and strong upregulation of BCL-6. If this upregulation is blocked, CML cells are sensitized to BCR-ABL1 TKIs in a p53–ARF-dependent manner, suggesting that BCL-6 is part of a stress response by which CML cells attempt to prevent apoptosis induction by p53–ARF. Inhibition of AKT has a crucial role in activating this pathway, as the PI3K–AKT suppressor PTEN is sufficient to induce BCL-6. Additionally, a recent report has implicated SIRT1 in the suppression of p53 activity in CML LSCs; inhibition of SIRT1 in combination with TKIs led to increased apoptosis in a p53-dependent manner\(^{139}\). Absence of BCL-6 from lineage ‘Scal’-KIT’ (LSK) cells (the murine equivalent of human lineage-CD34+CD38- HSCs) infected with BCR-ABL1 retrovirus blocks leukemogenesis in vivo by inducing cell cycle arrest and apoptosis, suggesting that BCL-6 may be a viable therapeutic target. The BCL-6 inhibitor retro-inverso BCL-6 peptide inhibitor (RI-BPI) prolonged survival in a human CML cell line xenograft model\(^{131}\). Several issues regarding the role of BCL-6 and its regulation remain incompletely understood. For example, as FOXO3A is active in primitive CML cells but not in progenitors\(^{130}\), one would predict differential expression of BCL-6, which is not the case\(^{141}\). A recent, key insight with respect to Ph+ ALL is that upregulation of BCL-6 is an unavoidable consequence of TKI therapy that may limit treatment effectiveness\(^{132}\) (BOX 2). The results of this study clearly suggest that simultaneous inhibition of BCR-ABL1 and the BCL-6 transcriptional network may be necessary to optimize therapeutic responses in Ph+ ALL.

**JAK2–PP2A.** The serine/threonine phosphatase PP2A has a crucial role in CML leukemogenesis, particularly in advanced phase disease\(^ {133}\). High levels of BCR-ABL1 enhance the expression of heterogeneous nuclear ribonucleoprotein A1 (HNRNPA1), an RNA-binding protein that increases the expression of the PP2A inhibitor SET in a JAK2-dependent manner\(^ {130,134}\). In patients with a high risk of progression to CML-BC, high levels of cancerous inhibitor of PP2A (CIP2A) may enhance this further\(^ {130}\) (Fig. 3d). SET knockdown restores PP2A activity, thereby decreasing BCR-ABL1 tyrosine phosphorylation and expression in conjunction with inhibition of downstream effectors such as STAT5, AKT and ERK\(^ {133}\). These effects are dependent on SHP1 tyrosine phosphatase, which is a negative regulator of cytokine signalling in CML cells\(^ {133}\).

The PP2A pathway is a potentially accessible drug target. Reactivation of PP2A in CML CD34+ cells by forskolin induces apoptosis irrespective of BCR-ABL1 activity\(^ {132}\) and independent of adenyl cyclase activation\(^ {137}\). Another PP2A activator, the immunosuppressant FTY720, has similar PP2A-activating effects on CML progenitor cells\(^ {136}\). Non-immunosuppressive FTY720 derivatives that activate PP2A have been developed and are currently being tested\(^ {137}\). Another option to activate PP2A may be JAK2 inhibition. As reported at the 2010 American Society of Hematology annual meeting, JAK2 is activated by BCR-ABL1 in a kinase-independent manner in lineage-CD34+CD38- CML stem cells, suggesting that combined inhibition of JAK2 and BCR-ABL1 may be synergistic\(^ {138}\). By contrast, another recent study concluded that JAK2 is not required for disease maintenance and hence is not a therapeutic target in CML\(^ {139}\). Given that different models were used, more experimentation will be required to clarify the suitability of JAK2 as a therapeutic target.

**Immunotherapy.** Immunotherapy in the allogeneic transplant setting is arguably the most effective therapy for CML, and the only one known to induce durable responses in advanced disease. Whether the graft versus leukaemia effect of an allograft is able to annihilate rather than merely suppress the leukaemic cell clone is unknown, but relapses with identical BCR-ABL1 breakpoints more than 15 years post-transplant speak to the resilience of the clone\(^ {140}\). In the autologous setting, patients with a sustained CCyR to IFNα harbour cytotoxic T cells specific for PR1, a peptide derived from myeloperoxidase, a protein that is upregulated by BCR-ABL1 (REF. 141). Recent clinical trials showed higher rates of MMR in patients treated with imatinib and IFNα compared with imatinib alone\(^ {42}\), although it is unknown whether this is correlated with a specific T cell response. One could propose that a more logical approach would be to immunotherapeutically target BCR-ABL1 itself, given that peptides derived from the BCR-ABL1 breakpoint are expressed on CML progenitors but not on normal cells\(^ {143}\). Although peptide-specific T and B cell responses were seen in trials of BCR-ABL1 peptide vaccines, randomized studies are needed to assess efficacy\(^ {144,145}\).

**Conclusions**

TKI-based therapy remains the cornerstone of CML treatment, and a decade has been sufficient to assert almost complete control of BCR-ABL1 kinase domain point mutation-based resistance through rapid, rational design of second-generation and third-generation inhibitors. The inhibitor design requirements established for treating TKI-resistant CML serve as a blueprint for therapeutic approaches to other malignancies in which point mutations have a central role in resistance. We have evaluated the current landscape of BCR-ABL1-based approaches to achieve maximal disease control and discussed prospects for eventually eliminating disease. Two TKIs with potential to contain the highly resistant BCR-ABL1\(^ {310}\) mutant, ponatinib and DCC-2036, are under clinical investigation. Ponatinib has shown remarkable efficacy in patients with CML who fail to respond or who have become resistant to currently approved TKIs, suggesting that this drug may
join or even replace dasatinib and nilotinib as second-line therapy. It will be revealing to study mechanisms of resistance to ponatinib, DCC-2036 and other third-generation inhibitors. If high-level resistance due to acquisition of BCR-ABL1 compound mutations has a prominent clinical role in treatment failures, further innovations in BCR-ABL TKI design or novel approaches will be needed to reinstate blockade of BCR-ABL1 function.

The natural boundary of BCR-ABL1 kinase targeted therapy is BCR-ABL1 independence. Until the causes of resistance in patients lacking BCR-ABL1 mutations are understood, rational intervention options remain severely limited. We speculate that BCR-ABL1-independent resistance may rely on pathways similar to those that allow the survival of LSCs. With respect to the curative potential of TKIs, we predict that, for most patients, eradicating MRD will require targeting pathways in addition to BCR-ABL1, although some patients in CMR may maintain responses after TKI therapy discontinuation. WNT–β-catenin may be the candidate supported by the strongest preclinical evidence. However, HH–SMO and PP2A are potentially more accessible drug targets. Perhaps optimized BCR-ABL TKIs combined with inhibitors that create situations of synthetic lethality will turn this chronic ailment into a transient condition, and CML will again write medical history.


In the context of CML disease progression, this paper demonstrated for the first time that microRNAs alter mRNA metabolism not only by base pairing with complementary mRNA targets, but also by competing with mRNAs for interaction with specific RNA-binding proteins.


This study identified paradoxical activation of the RAF pathway triggered by treatment of CML with BCR-ABL1 tyrosine kinase inhibitors, and designed effective strategies to induce synthetic lethality.


This paper was the first to describe the selective effects of imatinib on cells containing the BCR-ABL fusion protein.


This 12-month report describes results of the DASSION trial comparing dasatinib versus imatinib that led to first-line approval of dasatinib for newly diagnosed chronic phase CML.


This is a 12-month report on the ENESTnd trial comparing nilotinib versus imatinib that led to first-line approval of nilotinib for newly diagnosed chronic phase CML.


This study describes for the first time that microRNAs alter mRNA metabolism not only by base pairing with complementary mRNA targets, but also by competing with mRNAs for interaction with specific RNA-binding proteins.


This PLoS ONE article describes for the first time that microRNAs alter mRNA metabolism not only by base pairing with complementary mRNA targets, but also by competing with mRNAs for interaction with specific RNA-binding proteins.


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