

**Molecular Pathways**

**Targeting the BCR-ABL Signaling Pathway in Therapy-Resistant Philadelphia Chromosome-Positive Leukemia**

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Abstract

Beginning with imatinib a decade ago, therapy based on targeted inhibition of the BCR-ABL kinase has greatly improved the prognosis for chronic myeloid leukemia (CML) patients. Recognition that some patients experience relapse due to resistance-conferring point mutations within BCR-ABL sparked the development of the second-generation ABL kinase inhibitors nilotinib and dasatinib. Collectively, these drugs target most resistant BCR-ABL mutants with the exception of BCR-ABL$^{T315I}$. A third wave of advances is now cresting in the form of ABL kinase inhibitors whose target profile encompasses BCR-ABL$^{T315I}$. The leading third-generation clinical candidate for treatment-refractory CML, including patients with the T315I mutation, is ponatinib (AP24534), a pan-BCR-ABL inhibitor that has entered pivotal phase 2 testing. A second inhibitor with activity against the BCR-ABL$^{T315I}$ mutant, DCC-2036, is in phase 1 clinical evaluation. We provide an up-to-date synopsis of BCR-ABL$^{T315I}$ mutant, DCC-2036 and other ABL kinase inhibitors with activity against BCR-ABL$^{T315I}$ in the development pipeline.
Background

Chronic myeloid leukemia and the BCR-ABL signaling pathway

Chronic myeloid leukemia (CML) is characterized by the (9;22)(q34;q11) translocation, cytogenetically visible as the Philadelphia chromosome (Ph), which gives rise to the BCR-ABL fusion protein (1, 2). BCR-ABL is a constitutively active tyrosine kinase that drives survival and proliferation through multiple downstream pathways (Fig. 1A; reviewed in (3-5)). CML typically begins with a chronic phase characterized by expansion of functionally normal myeloid cells; left untreated, the disease progresses to a fatal acute leukemia (blastic phase) of myeloid or lymphoid phenotype. The hallmark of blastic phase is loss of terminal differentiation capacity (6). A subset of patients with B-cell acute lymphoblastic leukemia (Ph+ ALL) also harbors the Philadelphia chromosome (7, 8). The indispensible role of BCR-ABL in CML was established using a murine model in which recipients of BCR-ABL retrovirus-transduced bone marrow developed an aggressive CML-like myeloproliferative disorder (9). Mice expressing kinaseinactive BCR-ABL failed to develop leukemia, confirming a requirement for BCR-ABL kinase activity in leukemogenesis in vivo and suggesting BCR-ABL kinase as a therapeutic target (10).

The N-terminal coiled coil domain of BCR-ABL facilitates dimerization and trans-autophosphorylation (11, 12) (Fig. 1A). Autophosphorylation of tyrosine-177 of BCR-ABL promotes formation of a GRB2 complex with GAB2 and son-of-sevenless (SOS), triggering activation of RAS and recruitment of phosphatidylinositol 3-kinase (PI3K) and the tyrosine phosphatase SHP2 (13, 14). Signaling from RAS activates mitogen-activated protein kinase (MAPK) and enhances proliferation. PI3K activates the serine-threonine kinase AKT, which functions in: 1) promoting survival by suppressing the activity of forkhead O (FOXO) transcription factors (15); 2) enhancing cell proliferation by proteasomal degradation of p27 through upregulation of SKP2, the F-Box recognition protein of the SCF^SKP2 E3 ubiquitin ligase (16); and 3) activation of mTOR, which leads to enhanced protein translation and cell proliferation (17, 18). An additional critical outlet of BCR-ABL is STAT5 activation through direct phosphorylation or indirectly through phosphorylation by HCK or JAK2 (19, 20); lack of STAT5 abrogates both myeloid and lymphoid leukemogenesis (21). Collectively, these pathways modulate gene transcription (Fig. 1A). Additional signaling abnormalities characterize the transformation to blastic phase (6, 22).

BCR-ABL inhibition in the treatment of CML
The success of imatinib treatment for CML established that BCR-ABL is an excellent therapeutic target (23-26). Newly diagnosed, chronic phase patients with CML treated with imatinib exhibited 5-year rates of overall and progression-free survival of 93% and 89%, respectively (26). The cumulative failure rate was 17% at 60 months, peaking in year 2 at 7.5% and declining to <1% by year 5. During the sixth year of study treatment, there were no reports of disease progression (27). Imatinib therapy is much less effective in blastic phase CML, and the more potent second-generation inhibitors dasatinib and nilotinib have not changed this. Thus, a more profound understanding of BCR-ABL signaling in blastic phase CML is a prerequisite for developing better treatments. Three recent advances reveal important new mechanistic details pertaining to disease progression in CML (28-31).

**BCR-ABL signaling and disease progression in CML**

*The B cell mutator AID promotes disease progression and drug resistance in CML*

Activation-induced deaminase (AID) is a B-cell-restricted antibody diversification enzyme involved in somatic hypermutation in mature, antigen-exposed B cells. AID is also present and active in a subset of patients with lymphoid blastic phase CML or Ph+ ALL (28). The DNA mutator activity of AID in this context is unchecked by protective mechanisms inherent in normal activated B cells and is correlated with a dramatic increase in genetic instability. For example, copy number alterations and introduction of point mutations bearing the AID fingerprint were detected in genes controlling cell cycle, DNA repair, and other critical cellular functions. Klemm and colleagues established that abnormal expression of AID promotes disease progression through genomic instability and also plays a major role in generation of BCR-ABL point mutations, implicating AID in drug resistance (28). Since BCR-ABL kinase domain mutations are not limited to lymphoid disease, the authors investigated the possibility of lineage conversion and suggest that PAX5, a transcription factor important for B cell development and AID expression, may orchestrate interconversion of lymphoid and myeloid lineages. Alternatively, an as yet unknown mechanism could drive mutation acquisition in myeloid lineage cells.

*miR-328: multiple roles in control of myeloid differentiation in CML*

The myeloid-specific transcription factor C/EBPα is a master regulator of target genes required for differentiation of CML progenitors into granulocytes. BCR-ABL influences C/EBPα levels by stabilizing heterogeneous nuclear ribonucleoprotein E2 (hnRNP E2), a posttranscriptional gene regulator that binds to the 5'-UTR of C/EPBα mRNA and blocks translation. In chronic phase CML cells, C/EBPα expression is not substantially impaired by hnRNP E2, which is tightly regulated and
kept at low levels. Conversely, C/EBPα is downregulated in blastic phase CML through a BCR-ABL/MAPK/hnRNP E2 pathway (22), resulting in accumulation of blasts (32).

Eiring et al. now reveal further complexity in regulation of C/EBPα expression. Working from the observation that the microRNA miR-328 is subject to BCR-ABL dependent downregulation in blastic phase CML (29), they established multiple functions for miR-328 in a regulatory network central to differentiation of myeloid progenitors. PIM1, a cell cycle and apoptosis regulator important for survival of CML blasts, was identified as a direct target for canonical silencing by miR-328 in association with the RISC complex. More surprisingly, miR-328 binds directly to hnRNP E2, acting as an RNA decoy that interferes with hnRNP E2-mediated repression of C/EBPα mRNA translation. The RNA decoy function is independent of proteins associated with the RISC gene silencing machinery. In total, restoration of miR-328 expression rescues differentiation by sequestering hnRNP E2 and impairs survival of leukemic blasts by interacting with the mRNA encoding the survival factor PIM1. C/EPBα further influences its own fate by binding to the miR-328 promoter and inducing its expression in myeloid progenitors. This study reveals a previously unrecognized function for microRNAs as RNA decoy molecules.

**Musashi2-Numb signaling in CML disease progression** Recent studies disclosed that primary blast phase cells express high levels of the RNA-binding protein Musashi2 compared to chronic phase cells, whereas the Musashi2-repressed differentiation factor Numb shows the opposite expression profile (30, 31). Follow-on mechanistic studies in mouse model systems provided compelling evidence that loss or reduction in expression of Numb results in arrested differentiation and contributes to disease progression (30). NUP98-HOXA9, a chimeric transcription factor previously linked to blastic phase CML, was shown to facilitate upregulation of Musashi2, leading to repression of Numb. Experimental attenuation of Musashi2 expression restored Numb expression and reinstated chronic phase (30). Conversely, overexpression of Musashi2 in a mouse model lead to increased cell cycle progression and, in cooperation with BCR-ABL, induction of an aggressive disease course (31). Given that it was detected in a majority of patients who went on to experience disease progression, Musashi2 upregulation also appears to be a reliable, early indicator of poor prognosis (30, 31). Pharmacological manipulations that activate Numb and/or repress Musashi2 could open therapeutic avenues for preventing or controlling disease progression in CML and may also provide new approaches for the treatment of acute myeloid leukemia (31).

**Mechanisms of resistance to ABL kinase inhibitors in CML**
Imatinib is an effective first-line therapy for chronic-phase CML (33). However, some patients experience treatment failure after an initial response. Studies of relapsed patients revealed that BCR-ABL signaling is often reactivated at the time of resistance (34). Crystallographic analysis of the ABL kinase domain in complex with imatinib revealed that the drug binds exclusively to a catalytically inactive conformation of the ABL kinase (35, 36). Point mutations at residues that make direct contacts with imatinib or are critical for ABL to adopt an inactive conformation interfere with drug binding. Kinase domain mutations at over 55 residues conferring varying levels of imatinib resistance have been identified (reviewed in (37)). These findings guided design of the second-generation ABL inhibitors nilotinib, an imatinib derivative with ~30-fold higher potency (38), and dasatinib, a SRC/ABL inhibitor that is ~300-fold more potent than imatinib (39, 40). These inhibitors are effective against most BCR-ABL mutants, though the T315I ‘gatekeeper’ mutation within the ATP-binding domain is completely resistant to all three approved therapies, exposing a critical gap in coverage (38). As a pan-BCR-ABL inhibitor, ponatinib (Table 1) is active against this mutant and is in phase 2 clinical evaluation for refractory CML. Other new inhibitors including DCC-2036 (41, 42) (Table 1) have also entered clinical testing for refractory CML.

Clinical-Translational Advances

New first-line therapies for chronic phase CML

Imatinib remains the first-line CML therapy based on efficacy, side effect profile and safety record. Nonetheless, it is possible that another ABL inhibitor or combination of ABL inhibitors might represent a better first-line option for some or all patients. Possible benefits include: 1) reaching response milestones sooner, potentially resulting in reduced risk of relapse (43); 2) suppression of a wider range of mutant clones, leading to reduced risk of BCR-ABL mutation-based treatment failure; 3) improved side effect and tolerability profile and 4) more profound reduction and perhaps eradication of residual disease.

Recently, 14-month reports were issued from randomized phase 3 trials comparing either nilotinib (44) (300 or 400 mg twice daily; Evaluating Nilotinib Efficacy and Safety in Clinical Trials of Newly Diagnosed Philadelphia-Positive CML Patients (ENESTnd)) or dasatinib (45) (100 mg once daily; Dasatinib versus Imatinib Study in Treatment Naive CML Patients (DASISION)) to standard dose imatinib (400 mg once daily) as initial treatment. Both studies found the investigational treatment superior in terms of complete cytogenetic response (CCR) and major molecular response (MMR; defined as a BCR-ABL transcript level of 0.1% or less in...
peripheral blood on RQ-PCR assay as expressed on the International Scale) at 12 months, meeting the primary endpoints of the trials (Fig. 2). These are important benchmarks since patients with newly diagnosed chronic phase CML who achieve both a CCR and MMR within the first 12 months of therapy have low risk of long-term progression (26, 27, 46, 47). More important from a clinical point of view, there was also early evidence of reduced progression to accelerated or blastic phase: 4% of patients treated with imatinib compared to <1% treated with nilotinib (ENESTnd) and 3.5% of patients treated with imatinib compared to 1.9% treated with dasatinib (DASISION). Although this evidence must be regarded as preliminary, the improved time to progression is arguably the most impressive result from these studies.

The availability of new and potentially more effective ABL kinase inhibitors ensures that imatinib will have competition as the first-line therapy for CML and raises difficult questions on balancing cost against treating with the "latest and greatest" medications. In fact, nilotinib was approved for first-line treatment of newly diagnosed, chronic phase CML in June 2010 and dasatinib followed in short order in October 2010. The second-generation inhibitor, bosutinib, is also being tested in this setting (phase 3: NCT00574873, www.clinicaltrials.gov) (48, 49). Imatinib is an excellent therapy for the majority of patients with chronic phase CML. Thus, it is impressive that potentially better options are positioned to take center stage within the first decade of the recognition that ABL kinase inhibitors could completely change the treatment of CML. The issue of whether administration of two or more ABL inhibitors as a cocktail or in a sequential rotation would equate with better disease control as compared to single-agent therapy for certain patients is certainly of interest but presents formidable difficulties in terms of clinical trial design.

**Targeting the BCR-ABL<sup>T315I</sup> mutant: Clinical candidates**

Despite three approved therapeutic options, the cross-resistant BCR-ABL<sup>T315I</sup> mutant and compound mutants selected on sequential ABL inhibitor therapy (50) present clinical challenges. In response to the need for a clinically useful BCR-ABL<sup>T315I</sup> inhibitor, a variety of approaches are being pursued (51, 52).

**Ponatinib (AP24534), a pan-BCR-ABL inhibitor** We recently reported design and preclinical evaluation of ponatinib (Table 1), a potent inhibitor of native BCR-ABL, BCR-ABL<sup>T315I</sup> and other resistant mutants (IC<sub>50</sub>: 0.5 – 36 nM) (53-55). Ponatinib inhibited all tested BCR-ABL mutants in cellular and biochemical assays, suppressed BCR-ABL<sup>T315I</sup>-driven tumor growth in mice, and completely abrogated resistance in cell-based mutagenesis screens, confirming its profile as a pan-BCR-ABL inhibitor. Interim data from a phase 1 trial in patients with refractory
CML and hematologic malignancies have been reported (56). Pancreatitis was the dose-limiting toxicity at 60 mg daily, and 45 mg daily was selected as the recommended dose for further testing (phase 1: NCT00660920, www.clinicaltrials.gov). There was clear evidence of anti-leukemia activity, with major cytogenetic responses in 46% of chronic phase patients resistant to second-line tyrosine kinase inhibitors, including 67% of those with the T315I mutation, as well as MMRs (56). A pivotal phase 2 trial of ponatinib is now underway (NCT01207440, www.clinicaltrials.gov). In a sense, ponatinib is positioned where nilotinib and dasatinib were a few years ago, under evaluation in the demanding setting of treatment failure. Further on the horizon, if ponatinib can provide pan-BCR-ABL coverage and is proven to be safe and effective, it may have a future as a first-line CML therapeutic.

DCC-2036, an ABL switch control inhibitor DCC-2036 is an ABL inhibitor that accesses a distinctive switch control pocket transiently formed in the course of conformational regulation of the kinase (42). In Ba/F3 cellular proliferation assays, DCC-2036 was effective against cells expressing native BCR-ABL as well as several imatinib-resistant mutants (Y253F, T315I, M351T) with IC$_{50}$ values of 45 – 74 nM (41). In a mouse bone marrow transduction/transplantation model of CML involving BCR-ABL$^{T315I}$, daily oral dosing of DCC-2036 resulted in significant prolongation of survival compared with vehicle-treated mice (42). DCC-2036 and related compounds are reported to be orally bioavailable, to exhibit a limited off-target profile, and to perform well in safety studies. DCC-2036 is undergoing phase 1 evaluation for use in imatinib-refractory CML (NCT00827138, www.clinicaltrials.gov), including patients with a T315I mutation.

Pre-clinical BCR-ABL$^{T315I}$ inhibitors: recent approaches

While ponatinib and DCC-2036 have advanced to clinical evaluation, additional inhibitors are in pre-clinical development. These include HG-7-85-01 (Table 1), which utilizes a modified nilotinib-dasatinib hybrid structure to avoid gatekeeper mutations (57), and GNF-2, an allosteric ABL inhibitor shown to be effective in combination with ATP-competitive ABL inhibitors (Table 1) (58, 59).

HG-7-85-01 combines elements of nilotinib and dasatinib to inhibit the T315I mutant An effort to design ATP-competitive inhibitors with activity against BCR-ABL$^{T315I}$ and other clinically important gatekeeper mutants such as c-KIT$^{T670I}$ (gastrointestinal stromal tumors) and PDGFR$\alpha^{T674I}$ (hypereosinophilic syndrome) led to the discovery of HG-7-85-01 (Table 1). This compound incorporates design features of nilotinib and dasatinib, but also has an unprecedented tolerance for a range of gatekeeper side chains. Despite this feature, HG-7-85-
01 remains a relatively selective kinase inhibitor (IC$_{50}$: 59 nM for Ba/F3 native BCR-ABL cells and 140 nM for Ba/F3 BCR-ABL$^{T315I}$ cells). HG-7-85-01 was less effective against Ba/F3 cells expressing several clinically important BCR-ABL mutants (IC$_{50}$: 500-1000 nM for Ba/F3 BCR-ABL$^{F317L}$ cells), but was effective when combined with nilotinib. HG-7-85-01 (57) is among the first kinase inhibitors that target numerous gatekeeper mutant kinases while still exhibiting a restricted kinase selectivity profile. It will be of interest to monitor the therapeutic potential of HG-7-85-01-type inhibitors.

**Allosteric inhibition by GNF-2** The regulatory control mechanisms governing ABL kinase activity include an interaction between a myristoyl-modified glycine residue near the N-terminus and its cognate myristate-binding pocket (60, 61). Since the ABL N-terminal region is absent from BCR-ABL, the vestigial myristate pocket is unoccupied in the fusion protein. GNF-2 and the analogue GNF-5 (Table 1) bind in the myristate-binding pocket, with surprising consequences. As a single-agent, GNF-2 is a selective non-ATP competitive inhibitor of BCR-ABL activity (IC$_{50}$: 138 nM for Ba/F3 BCR-ABL cells (62)) with potency comparable to imatinib. Although neither GNF-2 nor GNF-5 is an inhibitor of BCR-ABL$^{T315I}$, a combination of high concentrations of GNF-5 and nilotinib displayed inhibitory activity against this gatekeeper mutant in biochemical and cellular assays. One puzzling aspect (Figure 4a, (58)) of the cellular data is the single-agent effectiveness of nilotinib against Ba/F3 BCR-ABL$^{T315I}$ cells (IC$_{50}$ ~ 4 µM). We have not observed nilotinib to be a T315I inhibitor in cellular or biochemical assays (39, 53). The ability of an allosteric inhibitor to influence the conformation of the ABL kinase domain represents an exciting advance, and this process is being studied in more detail, particularly through the use of nuclear magnetic resonance spectroscopy (58, 63). The combination of GNF-5 with HG-7-85-01 exhibits cooperative inhibitory effects against the T315I mutant (59).

**Targeting CML stem cells**
In the majority of patients on imatinib, residual disease is detectable and only a few achieve a complete molecular response, defined as no detectable BCR-ABL by RT-PCR; even fewer maintain these responses upon therapy discontinuation (64). The inability of imatinib to eliminate all leukemia cells is referred to as disease persistence and it remains to be seen whether results will be fundamentally different with second- and third-generation ABL inhibitors. At present, we have to assume that the prevalence of CML patients requiring continuous therapy and monitoring will continue to increase, with significant health-economic implications. The characteristics of leukemic stem cell populations that allow them to persist in the face of successful ABL kinase inhibitor treatment are under intense scrutiny (65, 66). Conceptually,
persistence may be due to BCR-ABL-dependent or –independent mechanisms. Increasing evidence is in favor of the latter, implying that CML stem cells are not yet fully addicted to BCR-ABL kinase activity. This natural limitation of BCR-ABL kinase inhibitors implies that eliminating the leukemic stem cell clone will require targeting additional pathways such as Hedgehog/Smoothened and β-catenin (reviewed in (67)). Given the role of these pathways in normal stem cell physiology, the question is whether a sufficient therapeutic window exists to distinguish between normal and CML stem cells. Our bias is that such a window may only open with drug combinations, when simultaneous inhibition of BCR-ABL and a yet to be determined additional pathway may generate synthetic lethality that discriminates between CML and normal cells. There is the alternative, empirical approach, exemplified by the combination of histone deacetylase (HDAC) inhibitors and imatinib that was recently reported to induce apoptosis in quiescent CML progenitors not eliminated by imatinib alone (66) or the mechanistically unexplained ability of BMS-214662, a farnesyl transferase inhibitor, to induce apoptosis in primitive CML cells (68). A completely different approach is immunotherapy, which may ‘anatomically’ target CML stem cells. The promising data reported with imatinib/interferon-α combinations are testimony to the potential of this approach (reviewed in (69)).

Future Developments and Considerations

There is reason for optimism in the realm of CML therapy. Nilotinib and dasatinib may reduce the rate of progression compared to imatinib, and for those patients who fail these inhibitors, third-generation drugs are in development with activity against the T315I mutant, which has emerged as a common pathway of resistance. Thus, clinicians may soon have at their disposal a complete set of tools needed to curtail the emergence of BCR-ABL mutation-based resistance.

However, this is unlikely to be the end of tyrosine kinase inhibitor resistance in CML. BCR-ABL kinase domain mutations have attracted the most attention with respect to treatment failure, yet they are present in only 60% of patients with imatinib resistance. In the remainder of patients, poorly understood BCR-ABL-independent mechanisms of growth and survival are activated (Fig. 1B). If a patient is resistant to imatinib and has no detectable kinase domain mutation, kinase domain mutations are then rarely detected if resistance to nilotinib develops (70). Further, these patients respond poorly to third-line dasatinib (71). BCR-ABL-independent activation of LYN has been observed in some mutation-negative, imatinib-resistant patients who responded to dasatinib, consistent with dasatinib’s activity against both ABL and SRC family kinases (72-74).
We have previously argued that BCR-ABL\textsuperscript{T315I}-driven escape from treatment with nilotinib or dasatinib suggests that the disease is still BCR-ABL-dependent (75). This appears consistent with emerging data from the ponatinib phase 1 study, wherein both cytogenetic and molecular responses have been observed in patients with the T315I mutation who previously failed second-line therapy with nilotinib or dasatinib or both (56). While establishing response rates for patients with the T315I mutation will be one focus of the ponatinib phase 2 trial, these preliminary findings suggest that the long-awaited goal of clinical containment of resistance due to single BCR-ABL kinase domain mutations may be very close. Of note, T315I-inclusive compound kinase domain mutations, defined as two mutations in the same BCR-ABL molecule, can confer high-level resistance even to ponatinib and remain an area of concern (53, 76). Although some mutations have proven difficult to address therapeutically with currently approved inhibitors, most notably BCR-ABL\textsuperscript{T315I} and compound mutations, mutation-based relapses are better understood than those involving a partially BCR-ABL-independent resistance phenotype. Fortunately, the more than 10-year experience with ABL kinase inhibitors suggests that the proportion of newly diagnosed chronic phase CML patients who have acquired BCR-ABL independent clones is small and that primary resistance may become a truly rare occurrence.

On the other hand, we do not expect advances in ABL inhibitor-based therapies as single agents to have a direct positive impact on disease eradication since the fount of disease appears largely insensitive to ABL kinase inhibitors (reviewed in (77)). More likely, approaches that create a situation of synthetic lethality or that target CML stem cells anatomically rather than biochemically will be required to translate profound responses into disease elimination. In the interim, clinical efforts should focus on keeping patients in chronic phase and rapidly maximizing the depth of response.
Figure Legends

Figure 1. The BCR-ABL signaling network and ABL kinase inhibition. A. BCR-ABL signaling pathways activated in chronic myeloid leukemia. Dimerization of BCR-ABL triggers autophosphorylation events that activate the kinase and generate docking sites for intermediary adapter proteins (purple) such as GRB2. BCR-ABL-dependent signaling facilitates activation of multiple downstream pathways that enforce enhanced survival, inhibition of apoptosis, and perturbation of cell adhesion and migration. A subset of these pathways and their constituent transcription factors (blue), serine/threonine-specific kinases (green), cell cycle regulatory proteins (yellow) and apoptosis-related proteins (red) are shown. A few pathways that have been more recently implicated in CML stem cell maintenance and BCR-ABL-mediated disease transformation are shown (orange). Of note, this is a simplified diagram and many more associations between BCR-ABL and signaling proteins have been reported. BCR-ABL is unstable upon disruption of primary CML cells, therefore pharmacodynamic evaluation of BCR-ABL activity is performed by monitoring the tyrosine phosphorylation status of either CRKL or STAT5, with CRKL phosphorylation considered the most specific readout. B. Predicted effectiveness of ABL kinase inhibitors in three therapeutic scenarios: to inhibit native BCR-ABL (top), to inhibit mutated BCR-ABL (middle), and as a component in the control of CML involving a BCR-ABL-independent alternate lesion (bottom).

Figure 2. Results from two independent clinical trials evaluating potential first-line use of nilotinib or dasatinib as compared to imatinib for newly-diagnosed CML. A. Evaluating Nilotinib Efficacy and Safety in Clinical Trials of Newly Diagnosed Philadelphia-Positive CML Patients (ENESTnd) and B. Dasatinib versus Imatinib Study in Treatment Naïve CML Patients (DASISION). Both studies demonstrated that the comparator drug was superior to imatinib with respect to the number of patients reaching a complete cytogenetic response (CCR) at 12 months and major molecular response (MMR) at 12 months, defined as a BCR-ABL transcript level of 0.1% or less in peripheral blood on RQ-PCR assay as expressed on the International Scale. Nilotinib and dasatinib were also superior to imatinib with respect to lowered incidence of progression to accelerated phase or blastic phase. Results from the two trials cannot be compared directly.

Table 1. Examples of new targeted agents with potential activity against BCR-ABL T315I in clinical and pre-clinical development.
References


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