Phase II Study of Dual Targeting of BCR-ABL1 by adding the Allosteric Inhibitor ABL001 in Patients with Chronic Myeloid Leukemia (CML) and Minimal Residual Disease (MRD) While on Therapy with Tyrosine Kinase Inhibitors

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Study Product: ***Asciminib – ABL001***

Protocol Number: **2019-0618**

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1. OBJECTIVES

1.1. Primary Objective: To determine the clinical activity of the combination of asciminib (ABL001) and a tyrosine kinase inhibitor (TKI) in patients with CML in complete cytogenetic response (CCyR) but detectable *BCR-ABL1* transcript

1.2. Secondary Objectives:

1.2.1. To determine the effect of the combination of ABL001 and TKI on the rate of MR4, MR4.5, and sustained MR4.5 (MR4 and MR4.5 rates will include only patients with a molecular response inferior to MR4 or MR4.5 respectively upon enrollment)
1.2.2. To investigate treatment-free remission after at least 2 years of sustained deep molecular remission
1.2.3. To determine the safety of the combination of asciminib and tyrosine kinase inhibitors
1.2.4. To determine the event-free survival (EFS), survival free from transformation to accelerated and blast phase (TFS), and overall survival (OS)

1.3. Exploratory Objectives:

1.3.1. To determine the rate of MRD clearance using droplet digital polymerase chain reaction (ddPCR) detecting the *BCR-ABL1* fusion transcript
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1.3.5. To describe immune effects of the combination of TKI and ABL001
1.3.6. To describe patient reported outcomes (PRO) using the MDASI-CML instrument

See Table 2 for summary of objectives and related endpoints.

2. BACKGROUND AND SCIENTIFIC RATIONALE

In order to achieve cure in CML, and eradicate MRD, a therapeutic combination of agents with non-overlapping mechanisms of resistance is needed. The successful use of TKIs targeting BCR-ABL1, the fusion oncoprotein causing this disease, has markedly improved prognosis.[1-3] However, despite this success, resistance occurs. Circumventing resistance constitutes an important goal. In addition, the goal of therapy has shifted towards attaining deeper responses. Furthermore, treatment-free remission (TFR) has become an endpoint of increasing interest and relevance. In patients with chronic phase CML, who achieve and maintain undetectable *BCR-ABL1* transcript levels (termed complete molecular response or CMR) for at least 2 years, on imatinib, approximately 40% remain free of recurrence after stopping their treatment.[4] Thus, developing novel strategies aimed at achieving deeper responses in CML for a larger number of patients would be a step closer towards treatment discontinuation, and cure.

2.1. Chronic Myeloid Leukemia

Chronic myeloid leukemia (CML) is a pluripotent stem cell disorder characterized by the presence of the Philadelphia (Ph) chromosome in the leukemic cells. The Ph chromosome results from a (9;22) translocation in which the *c-ABL* oncogene has moved from chromosome 9 into the *BCR* (breakpoint cluster region) gene on chromosome 22, resulting in a chimeric *BCR-ABL* gene. This is the causative abnormality in CML.[5-7] The fused gene encodes an 8.5 kb chimeric mRNA, which is translated into a 210-kDa protein.[8-10] This p210 BCR-ABL protein functions as a constitutively activated tyrosine kinase and is uniquely present in the leukemic cells of CML patients.[11] The breakpoint in the *BCR* gene occurs either between BCR exon b2 and b3 or between BCR exons b3 and b4. Therefore, in the mature *BCR-ABL* mRNA, either b2 or b3 is spliced to ABL exon a2, which results in two alternative chimeric p210 BCR-ABL proteins, with either a B2A2 or B3A2 junction.[12]

2.2. Therapy with Tyrosine Kinase Inhibitors

Imatinib is a low molecular weight phenylaminopyrimidine designed to selectively inhibit BCR-ABL tyrosine kinase activity,[13] and is now the standard therapy for newly diagnosed patients with CML who do not undergo allogeneic stem cell transplant. For patients who develop resistance or intolerance to imatinib, effective therapy with 2nd generation TKIs has been developed. Approximately 50% of patients treated with these agents after imatinib failure achieve a CCyR, and these responses are also durable in most patients.

Among patients who achieve a CCyR, those who achieve a MMR (ie, at 18 months from the start of therapy) have an improved EFS and survival free from transformation to accelerated or blast phase compared to those with CCyR but no MMR (7-year EFS 95% vs 86%, respectively).[14] In this same analysis, none of the patients who had achieved a MMR transformed to accelerated or blast phase. Achieving CMR further improves the long-term outcome of patients after treatment with imatinib.[4] Thus, improving the molecular response of patients who have already achieved a CCyR with TKI has become an important goal of therapy. It has been suggested that patients who achieve CMR may discontinue therapy with imatinib, an important goal for patients. However, discontinuation of imatinib among patient who achieve CMR results in relapse in over 50% of patients.[4] Additional measures are needed to make treatment discontinuation a safer proposition.

2.3. Resistance and Persistence with Single-agent TKI

The most common mechanism of resistance to TKIs in CML is development of mutations in their binding site.[15-18] Use of targeted therapy in this disease is by far the most successful application of precision medicine, however resistance still occurs. Lessons can be applied from human immunodeficiency virus treatment where simultaneous administration of highly active combination therapies has dramatically decreased the rate of resistance.[19] In fact, use of sequential rather than simultaneous TKIs selects for drug-resistant *ABL1* mutations with increased oncogenic potency.[20] Even though second-generation TKIs such as dasatinib and nilotinib are mostly able to overcome imatinib-resistant mutations, combination therapies thus far have not been conceivable given the similar binding sites of these agents. A combination of agents with distinct targeting mechanisms and non-overlapping resistance profiles is essential for preventing emergence of mutations and further improving outcomes in this disease.

Despite the success of second generation TKIs, a significant number of patients do not achieve deep molecular responses. After 5 years of therapy, in the ENESTnd trial approximately 55% of patients achieve MR4.5 with nilotinib and only approximately 30% with imatinib.[21] Similarly, in DASISION, only approximately 40% of patients treated with dasatinib and approximately 30% of those treated with imatinib achieve such response.[22] The rates of sustained MR4.5 are 40-45% with nilotinib and 26% with imatinib[23]; no information is available with dasatinib. Pre-clinical studies have shown that neither TKI is able to eradicate the earliest CML progenitors. Thus, with current monotherapy approaches, most patients are either ineligible to attempt treatment discontinuation or experience relapse after discontinuation because of the persistence of residual disease.

2.4. Treatment-free Remission as a New Therapy Goal

The successful use of TKIs has markedly improved the prognosis for patients with CML. The last report on the pivotal IRIS study demonstrated an overall survival rate of 80% at 10 years in the arm investigating imatinib as initial therapy.[1] Thus, it is estimated that the number of patients living with CML will increase overtime eventually reaching a near plateau of 181,000 of the United States population, nearly 35 times the annual incidence.[24] The current standard is continuous, lifetime treatment with TKIs. This is associated with long-term side effects for some patients including the risk of arterio-thrombotic events, pleural effusions, pulmonary hypertension, second malignancies and others, and an increasing financial burden on individuals and healthcare systems.[25,26]

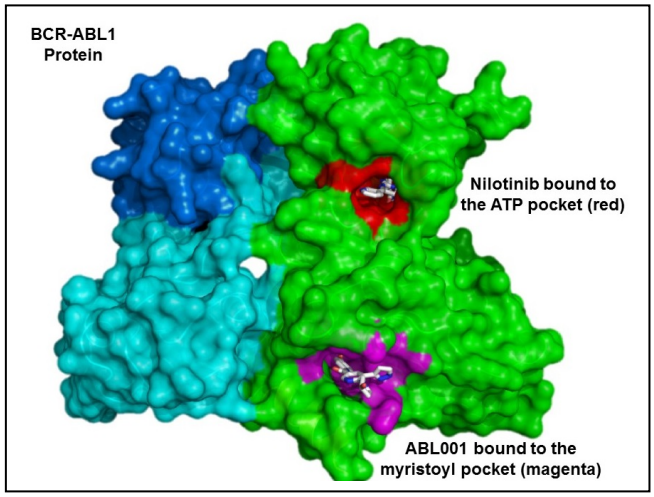
That is why TFR has become an endpoint of increasing interest and relevance. In the STIM trial, approximately 40% of patients with chronic phase CML receiving imatinib, who achieve and maintain undetectable *BCR-ABL1* transcript levels for at least 2 years, remain free of recurrence without the need to resume therapy.[4] All other patients relapsed and required resumption of therapy. Therefore novel strategies are needed in order to achieve deep responses in more patients, and make treatment discontinuation a safe and effective strategy for those who discontinue therapy.

2.5. Minimal Residual Disease

Minimal or measurable residual disease (MRD) denotes the cancer cell reservoir remaining post-treatment. All CML cells harbor the translocation t(9;22) leading to the oncoprotein BCR-ABL1. This provides a unique genetic fingerprint enabling detection and monitoring of CML. In clinical practice, RT-PCR of the *BCR-ABL1* messenger ribonucleic acid (mRNA) is the most sensitive assay. However, as indicated previously in the STIM trial example, 60% of patients with undetectable transcript levels using this assay relapsed upon discontinuation of therapy, indicating presence of the disease below the clinical assay's level of detection. Therefore, development of highly sensitive assays for detection of low transcript levels is essential for therapeutic strategies aimed at curing this disease. It has been suggested that ddPCR could be one alternative sensitive method to detect and quantify low *BCR-ABL1* transcript levels.[27] This method is based on isolation of the PCR reaction into single droplets, tested independently for the presence of the target.

Moreover, despite that BCR-ABL1 is present in quiescent leukemia initiating cells or stem cells (LSCs), these cells have a decreased dependence on this oncogene.[28,29] In order to eradicate minimal residual disease in CML, a therapeutic combination targeting both proliferative and quiescent LSCs is needed.

Figure 1: X-ray crystal structure of BCR-ABL1 with ABL001 and nilotinib bound to distinct sites.



2.6. Allosteric Inhibition of ABL1

Structural studies of ABL1 have shown an interaction between the N-terminal myristoyl group and a hydrophobic cleft located near the C terminus. This interaction is thought to provide a mechanism of auto-inhibition disrupted in the BCR-ABL1 fusion protein.[30] Small molecules binding the BCR-ABL1 myristoyl pocket were shown to inhibit kinase activity via an allosteric mechanism.[31] **ABL001 is a potent and selective allosteric BCR-ABL1 inhibitor**. In contrast to catalytic-site ABL1 kinase inhibitors, it binds to the myristoyl pocket and induces formation of an inactive kinase conformation (Figure 1).[32] Besides having in-vitro potency similar to second-generation TKIs, ABL001 is more selective given that myristoyl-binding sites analogous to that of ABL1 are only found in a limited number of kinases. In addition, ABL001 has a distinct pattern of resistance mutations and no shared resistance with the catalytic inhibitor nilotinib. Importantly, despite detection of pre-treatment clonal populations, the non-overlapping resistance profiles of ABL001 and nilotinib allowed for durable tumor eradication in CML xenografts when used in combination (Figure 2).[17]

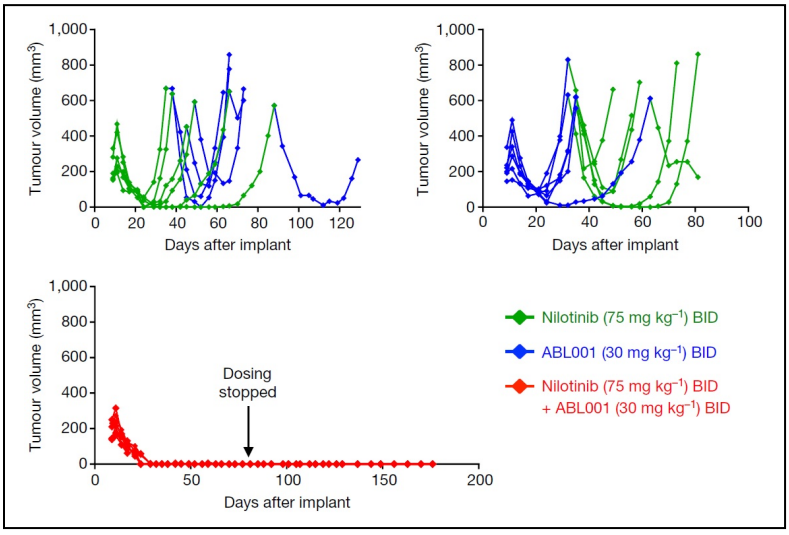
2.7. Overview of Current Clinical Data with ABL001

2.7.1. Safety Pharmacology and Toxicology

An extensive toxicology safety evaluation program (subchronic, chronic, reproductive toxicology, phototoxicity and genotoxicity studies) was conducted.

Safety pharmacology studies indicate that ABL001 is not expected to cause effects on the vital functions of the CNS, and the respiratory systems. No cardiovascular effects were observed in a single dose jacketed telemetry study in dogs at doses up to 200 mg/kg or the

Figure 2: Durable tumor eradication with ABL001 and nilotinib combination. Each line represents an individual KCL-22 mouse xenograft.



invasive telemetry cardiovascular safety study up to 60 mg/kg. Furthermore, no ECG related findings were noted in the 4 week GLP dog toxicology study at the end of treatment or recovery. As determined by the results of the phototoxicity assessment (*in vitro* and *in vivo*), phototoxic potential was identified in the mouse UV-LLNA assay. Given these data, patients should be advised to avoid prolonged exposure to sunlight (sunbathing) and to use sunscreen.

In the embryo-fetal development study in rats, results indicate a risk of fetal malformations and/or visceral and skeletal variants. In the fertility study, administration of ABL001 by daily oral gavage at doses of 10, 50 and 200 mg/kg/day to males and females there was no evidence of effects on reproductive function (mean day to mating, mating and fertility indices) at any dose. There was evidence of a slight effect on male sperm motility and/or sperm count in individual animals and an embryo-lethal effect at 200 mg/kg/day. Based on these results, the no-observed-adverse-effect level (NOAEL) for paternal and maternal toxicity was considered to be 200 mg/kg/day and the no-observed-effect level (NOEL) for reproductive function and early embryo-fetal development was considered to be 50 mg/kg/day.

Repeat dose toxicity studies have been performed in rats, dogs and monkeys up to 26, 4 and 13 weeks duration, respectively. Rat and dog toxicology studies identified pancreas, liver, adrenal and harderian gland as potential target tissues. The cynomolgus monkey did not recapitulate in short or long-term studies the pancreatic changes observed in the dog or the rat hepatic changes. All findings thus far have demonstrated a partial to complete reversibility during a 4-week recovery phase, and can be readily monitored in preclinical and clinical settings. The maximal doses evaluated in the 13/26-week general toxicity studies was 200 mg/kg in rats and 100 mg/kg in monkey and provide substantive safety margins over the 40 mg BID clinical dose exposures.

Please refer to the latest [ABL001 Investigator's Brochure] for more details.

2.7.2. Non-clinical Pharmacokinetics and Metabolism

The preclinical pharmacokinetic profile of ABL001 has been investigated in three species: mouse, rat and dog. In these species, ABL001 exhibited low to moderate clearance, a moderate volume of distribution and a short apparent terminal half-life. Bioavailability was found to be low in rodents and moderate to high in dog.

ABL001 displayed high plasma protein binding across all tested species (2-6% free fraction).

The metabolite profile of ABL001 has been examined in vitro using rat, dog, monkey and human hepatocytes. Interspecies differences were observed. Direct glucuronidation occurred more readily in human and dog than in monkey and was noticeably absent in rat. However, no unique, major metabolites were identified in human hepatocytes. The overall metabolic turnover was low.

The metabolite profile of ABL001 has also been examined in vivo in rats. Following intravenous and oral administration of [^{14}C-ABL001] to intact rats, ABL001 was found to be the predominant component of plasma, accounting for ~86 - 91% of radioactivity from 0 - 8 h. ABL001 was excreted primarily in the feces, with ~90% of radioactivity detected in the feces from 0 - 48 h. Renal elimination represented a minor route, with ~2.4% of radioactivity detected in the urine from 0 - 72 h. In the feces, ~58% (intravenous) and ~71% (oral) of the dose was associated

with unchanged ABL001, with several oxidative metabolites accounting for the remaining radioactivity. The metabolites formed in vivo were consistent with those observed in vitro. Similar observations were noted in bile-duct cannulated rats.

To assess for potential drug-drug interactions (DDI), studies have been conducted with cytochrome P450 (CYP) enzymes and several transporters in vitro.

In human liver microsomes, the major metabolic route of ABL001 was found to be glucuronidation, followed by oxidative metabolism, consistent with findings from human hepatocytes. Several UGT enzymes were found to be capable of ABL001 glucuronidation (UGT1A3, UGT1A4, UGT2B7, and UGT2B17). The oxidative metabolism of ABL001 was also catalyzed by several CYP enzymes. CYP3A4/5 appears to contribute the most, followed by CYP2C8, CYP4F12, and potentially CYP2D6. Though the DDI risk with inhibitors of these enzymes is likely to be minimal, inhibitors of CYP3A4/5 still have the potential to increase ABL001 concentration. Therefore, strong inhibitors of CYP3A4/5 should be avoided. Strong inducers of CYP3A4/5 have the potential to reduce ABL001 concentrations. Therefore, the use of strong inducers of CYP3A4/5 or UGT1A/2B should be avoided on this trial.

Transporter phenotyping studies have identified ABL001 to be a substrate of Breast Cancer Resistant Protein (BCRP) and Permeability glycoprotein (P-gp). While inhibition of BCRP is not expected to result in any clinical relevant changes, inhibitors of P-gp may increase ABL001 concentrations significantly and should be avoided in this study.

There is a potential for DDIs with co-medications metabolized by CYP3A4/5, CYP2C8 and CYP2C9 at the anticipated human efficacious dose. Therefore, narrow therapeutic index substrates of CYP3A4/5, CYP2C8 and CYP2C9 should be avoided. All other substrates of CYP3A4/5, CYP2C8 and CYP2C9 should be used with caution.

Please refer to the latest [ABL001 Investigator Brochure] version for more detail.

2.7.3. Clinical Experience

In a phase I, multicenter, first in human study, preliminary results show that ABL001 is well tolerated in heavily pretreated patients with CML with resistance or intolerance to prior TKIs.[33] Among these patients, 65% had previously received ≥3 TKIs. In this study, 101 patients have been enrolled as of May 2, 2016, and recruitment is still ongoing. The maximum tolerated dose (MTD) was not reached and 40 mg BID has been recommended for CML-CP patients without T315I mutation based on based on preliminary MMR and CCyR results from the study as well as overall ABL001 safety and pharmacokinetic information. Dose -escalation for patients with T315I mutation is currently ongoing.

The combination of ABL001 with TKIs has been examined in a phase 1 study (NCT02081378). Patients with CML in chronic phase or accelerated phase (AP) and resistance or intolerance to ≥2 prior TKIs were eligible. They were assigned (based on prior intolerance) to a combination with nilotinib or dasatinib. The following combinations were investigated: nilotinib 300 mg BID and ABL001 20 mg BID, nilotinib 300 mg BID and ABL001 40 mg BID, dasatinib 100 mg QD and ABL001 80 mg QD or 40mg BID. The combinations of ABL001 with nilotinib or dasatinib were generally safe and well tolerated. One dose-limiting toxicity was reported with ABL001 at 20 mg BID + nilotinib (rash maculo-popular) and one with ABL001 at 40 mg BID + dasatinib

(increased lipase); both events resolved with dose reduction (reduction of nilotinib to 150 mg BID in the first case and reduction of ABL001 to 20 mg BID in the second) [34].

2.7.3.1. Efficacy

ABL001 resulted in molecular and cytogenetic responses at doses ≥10 mg BID. With a median duration of exposure of 8 months, 9/12 (75%) had a CCyR, and 10/50 (20%) had a MMR within 6 months of treatment. Clinical activity was seen in patients with non-mutant *BCR-ABL1* as well as across multiple TKI-resistant mutations. In subsequent cohorts, ABL001 was also found to be safe in combination with other TKIs. These findings support further evaluation in combination with other TKIs.

2.7.3.2. Safety

ABL001 was generally well tolerated in heavily pre-treated CML patients resistant to or intolerant of prior TKIs. By data cutoff of May 2, 2016, 67 CML patients, including those with a T315I mutation (n=9), have been treated at any dose of the ABL001 BID regimen.

There were no study drug related deaths reported. One death was reported due to general physical health deterioration unrelated to the study drug. Overall, 43 serious adverse events (SAEs) were reported in 20 patients of the 67 patients. Six patients (9%) discontinued ABL001 due to adverse events. Dose limiting toxicities in the study included acute cardiac syndrome, lipase increase, arthralgia/myalgia, and bronchospasm in 1 patient each.

Overall of 67 CML patients, almost all (94%) patients reported at least one AE, including 45% reported grade 3/4 AEs. The most common AEs (>10%), regardless of study drug-relationship, were headache, increased lipase (23.9%), rash (20.9), arthralgia, vomiting (both 19.4%), diarrhea, fatigue (both 17.9%), abdominal pain, pruritus (both 16.4%), constipation, myalgia, nausea, upper respiratory tract infection (all 14.9%), thrombocytopenia (13.4%), peripheral edema (11.9%), increased amylase, dizziness, musculoskeletal pain (all 10.4%).

At 40 mg BID dose (n=26), the most common adverse events (>10%), regardless of study drug-relationship, were: increased lipase (30.8%), rash (26.9%), abdominal pain, fatigue, vomiting (all 23.1%), arthralgia, diarrhea (both 19.2%), increased amylase, upper respiratory tract infection (both 15.4%), cough, bone pain, pruritus, increased weight, abdominal discomfort, anemia, constipation, dyspnea, ear pain, non-cardiac chest pain, and thrombocytopenia (all 11.5%).

Please refer to the latest [ABL001 Investigator's Brochure] for more details.

2.7.3.3. Pharmacokinetics

PK data from 61 patients (1 in 10 mg BID; 14 in 20 mg BID; 20 in 40 mg BID; 12 in 80 mg BID; 9 in 150 mg BID; 5 in 200 mg BID) were available from the phase I study, as of May 2, 2016.

Based on the available PK data, ABL001, administered orally is rapidly absorbed with a median time to maximum plasma concentration (Tmax) of 2 to 3 hours, independent of dose. Systemic exposure of ABL001, following oral administration of single and multiple doses, as measured by Cmax and AUC, increased in an approximately dose proportional

manner. The variability of exposure is low to moderate with inter-patient variability (geometric mean CV %) of 34 to 50% for Cycle 1 Day 1 AUC last and 36 to 60% for Cycle 1 Day 1 Cmax. With the twice daily dosing regimen, median plasma ABL001 accumulation ratios ranged from 1.4 to 2.4. The median accumulation half-life was estimated to be 7 to 15 hours.

The emerging data show that the relative contribution of the glucuronidation pathway to the total clearance of ABL001 via metabolism is estimated to range from 30% to 61%, whereas the relative contribution of the oxidative pathway is estimated to range from 35% to 63%. CYP3A4 was the main contributor for the clearance of ABL001 via the oxidative pathway while UGT2B7 and UGT2B17 were responsible for the clearance of ABL001 via the glucuronidation pathway. There was no metabolite detected with mean contribution to plasma radioactivity AUC0-24hours ≥ 10%. ABL001 was the predominant drug-related component in plasma at all time points analyzed, ranging from 91.9 to 94.2% of the total radioactivity AUC0-24 hours AUC, with an average value of 92.7%.

Please refer to the latest [ABL001 Investigator's Brochure] for more details.

2.7.3.4. Exposure-response Relationship

A preliminary population PKPD model has been developed using data from the study (cut-off 02May-2016). The time course of molecular response (change in *BCR-ABL* ratio % IS levels from baseline) was described using a semi-physiological model accounting for cell maturation, disease progression and existing resistance.

Simulations performed using an ABL001 population PK model revealed that a dose of 40 mg BID maintains Ctroughss above the clinical (0.07 to 61 ng/ml) threshold in >=95% of chronic phase CML patients without T315I mutation having failed ≥ 2 TKI or intolerant to TKIs. The estimates from this clinical study were found to be similar to the threshold trough concentration required for 90% inhibition of pSTAT5 derived from a preclinical PK-PD KCL-22 mouse xenograft model (free IC90: 30 to 121 ng/mL, after correction for protein binding) and *in vitro* gIC50 assessed in the KCL-22 cell line (1 ng/mL = 2.1 nM after correction for protein binding).

Simulations performed using ABL001 population PKPD model revealed that chronic phase CML patients having failed ≥ 2 TKI or intolerant to TKIs are likely to exhibit a 1 log10 reduction of (%) *BCR-ABL* mRNA transcript levels from baseline of ~33% (CI95%: 24-42%) at 6 months, and ~42% (CI95%: 32-52%) at 12 months at a dose of 20 mg BID and ~41% (CI95%: 31-51%) at 6 months, and ~53% (CI95%: 43-63%) at 12 months at a dose of 40 mg BID.

Additional preliminary exposure response analyses (i.e. exploring the relationship between PK and both safety and efficacy) support the selected dose.

The effect of food on ABL001 PK was characterized in a Phase I study in healthy volunteers. Food was found to influence the pharmacokinetics of ABL001. When administered with a low-fat meal, the exposure (AUC) decreased by approximately 30%. The overall exposure decreased by approximately 65% when administered with a high -fat meal.

Therefore, ABL001 will be administered in a fasted state.

3. SUBJECT ELIGIBILITY

3.1. Inclusion Criteria:

1. Patients 18 years or older with a diagnosis of Philadelphia chromosome (Ph)- *or BCR-ABL1*-positive CML (as determined by cytogenetics, FISH, or PCR).
2. Patients should be receiving therapy with nilotinib or dasatinib, whether as initial therapy or after prior TKI, at a dose equal or lower than the standard dose.
3. Patients must have received TKI therapy for at least 24 months and not have required dose reductions, escalations, discontinuation or re-initiation after discontinuation of TKI in the last 6 months.
4. Patients must be in CCyR (by conventional karyotype or FISH, or *BCR-ABL/ABL* ≤1% IS if no cytogenetic analysis available within 3 months).
5. Patients must have detectable *BCR-ABL1* transcript levels meeting at least one of the following criteria:
    a. Patient has never achieved a MMR after 18 months of therapy with their current TKI, or
    b. Patient has not achieved MR4.5 after 36 months of therapy with their current TKI, or
    c. Patient has lost MMR or MR4.5 confirmed in at least two consecutive analyses separated by at least 1 month, or
    d. *BCR-ABL1* transcript levels have reached a plateau defined as a ratio that is stable in a molecular response category (i.e., MMR or MR4) in the last at least 12 months, with at least 3 values obtained during this period and has not achieved MR4 prior to 24 months of therapy for those receiving it for < 36 months.
6. Patients must not have had a known continuous interruption of TKI therapy of greater than 14 days or for a total of 6 weeks in the 6 months prior to enrollment, unless the interruption was for an accident, unrelated hospitalization or surgical procedure.
7. ECOG performance status ≤2.
8. Participants must have normal organ function defined as:
    a. Creatinine ≤ 1.5x institutional upper limit of normal.
    b. Amylase and lipase values ≤ 3.0x institutional upper limit of normal.
    c. Alkaline phosphatase ≤ 2.5x institutional upper limit of normal unless considered to be not of hepatic origin.
    d. AST(SGOT)/ALT(SGPT) ≤ 3x institutional upper limit of normal.
    e. Total bilirubin ≤ 1.5x institutional upper limit of normal (≤ 3x upper limit of normal in patients with known Gilbert's syndrome).
9. The effects of ABL001 on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Women of child-bearing potential must agree to use highly effective methods of contraception during dosing and for 30 days after study treatment. Should a woman become pregnant or suspect she is pregnant while

she or her partner is participating in this study, she should inform her treating physician immediately.

Allowable methods of birth control:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before the start of study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject.
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
- Sexually active males must use a condom during intercourse while taking the drug and for 30 days after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

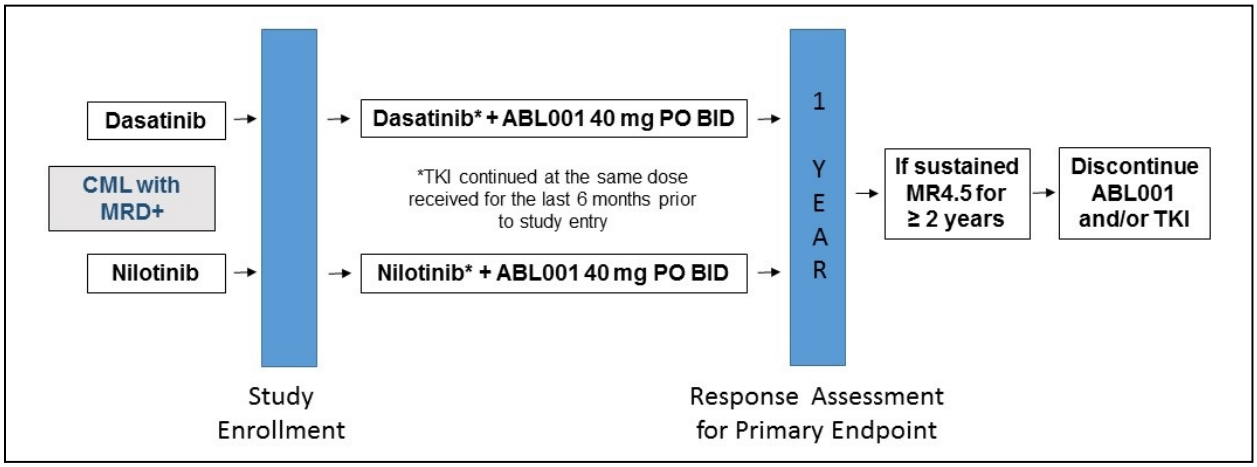
3.2. Exclusion Criteria:

1. Patients with New York Heart Association (NYHA) Class III or IV congestive heart failure or LVEF < 40% by echocardiogram or multi-gated acquisition (MUGA) scan.
2. Patients with a history of myocardial infarction within the last 6 months or unstable/uncontrolled angina pectoris or history of severe and/or uncontrolled ventricular arrhythmias. Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block).
3. Corrected QT interval (QTc) of > 480 milliseconds (ms) on baseline electrocardiogram (ECG or EKG) (using the Fridericia Formula)
4. Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
   a. Risk factors for Torsades de Pointes (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia.
   b. Concomitant medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointes that cannot be discontinued or replaced 7 days prior to starting study drug by safe alternative medication.

5. Patients with known infection with human immunodeficiency virus (HIV) or active Hepatitis B or C.
6. Patients with known conditions that would significantly affect the ingestion or gastrointestinal absorption of drugs administered orally.
7. Nursing women, women of childbearing potential (WOCBP) with positive blood or urine pregnancy test, or women of childbearing potential who are not willing to maintain adequate contraception (see inclusion criteria 9)
8. History of acute pancreatitis within 1 year of study entry or past medical history of chronic pancreatitis.
9. ANC < 500/mm3, platelet count < 50,000 mm3.
10. History of other active malignancy within 2 years prior to study entry with the exception of previous or concomitant basal cell skin cancer and previous carcinoma in situ treated curatively.
11. Treatment with medications that meet one of the following criteria and that cannot be discontinued at least one week prior to the start of treatment with study treatment (see APPENDIX for list of medications)
    - Moderate or strong inducers of CYP3A.
    - Moderate or strong inhibitors of CYP3A and/or P-gp.
    - Substrates of CYP3A4/5, CYP2C8, or CYP2C9 with narrow therapeutic index.
12. Previous treatment with or known/ suspected hypersensitivity to ABL001 or any of its excipients
13. Subject has any other significant medical or psychiatric history that in the opinion of the investigator would adversely affect participation in this study.

4. TREATMENT PLAN

Figure 3: Overview of the treatment plan.



4.1. All patients should be registered in CORe.

4.2. TKIs

Patients will continue receiving the TKI (nilotinib, dasatinib) they had been receiving at the time of screening at the dose they had been receiving during the last 6 months.

4.3. ABL001

ABL001 will be administered orally daily on a continuous basis at 40 mg PO BID. Treatment with ABL001 will continue uninterrupted unless there are indications for dose delays/modifications.

ABL001 tablets should be ingested as follows:

- ABL001 should be administered in the fasted state at least 1 h before or 2 h after a meal. Water is permitted during this period.
- ABL001 should be taken with approximately 8 ounces (240 mL) of water.
- ABL001 should be swallowed whole and not chewed or crushed.
- If vomiting occurs within the first hour after taking the drug, re-dosing is allowed before the next scheduled dose.
- If the patient does not take ABL001 within 6 hours after the approximate time of the usual dosing time, that dose should be skipped and treatment should continue with the next daily dose at the prescribed level.

4.4. Dosing Delays/Dose Modifications

Dose escalation beyond the standard doses of 40 mg BID for ABL001 is not permitted. Patients experiencing unacceptable toxicity directly attributable to the study drug should temporarily stop treatment according to the guidelines in the dose adjustment schema. Toxicity grading will be according to the NCI CTCAE, v5.

If toxicity is attributed to the baseline TKI (nilotinib, dasatinib), standard dose adjustment of the TKI is indicated while maintaining the same dose for ABL001. If it is not clear which of the medications is causing the toxicity (either the TKI or ABL001), both medication doses should be adjusted.

The following guidelines for dose adjustment for drug-related toxicities are recommended:

4.4.1. TKI

Dose modifications and treatment interruptions will be performed according to institutional guidelines and standard clinical practice. The following guidelines may be followed:

4.4.1.1. Non-Hematologic Toxicity:

a. Persistent Grade 2: Patients with persistent grade 2 toxicity that is considered clinically significant and unresponsive to appropriate therapy may have treatment held until the toxicity has resolved to grade ≤1. Therapy may then be resumed at the same dose the patient was receiving at the time treatment was interrupted. If the grade 2 toxicity recurs, therapy may be held until the toxicity has resolved to grade 1. Treatment may then be resumed with a one dose level reduction.
b. Grade 3-4: If a patient experiences Grade 3-4 toxicity that is considered clinically significant and possibly related to the TKI, therapy will be withheld until the toxicity has resolved to Grade ≤1. Treatment may then be resumed at a lower dose. If

toxicity recurs, additional dose reductions may be implemented following the same general guidelines.

4.4.1.2. Hematologic Toxicity:

If neutrophils are <0.5 x 10^9/L and/or platelets are <50 x10^9/L, hold therapy until granulocytes are above 0.5 x10^9/L and platelets are above 50 x10^9/L, then resume therapy at 1 dose level reduction from the dose the patient was receiving at the time therapy was interrupted. If a similar degree of toxicity returns, a further dose reduction by one dose level can be performed, using the above procedures.

There will be no making up for missed doses.

4.4.2. ABL001

Dose modifications and treatment interruptions will be performed according to institutional guidelines and standard clinical practice. Briefly, dose adjustments will be as follows:

4.4.2.1. Non-Hematologic Toxicity:

a. Persistent Grade 2: Patients with persistent grade 2 toxicity that is considered clinically significant and unresponsive to appropriate therapy, may have treatment held until the toxicity has resolved to grade ≤1. Therapy may then be resumed at the same dose the patient was receiving at the time treatment was interrupted. If the grade 2 toxicity recurs, therapy may be held until the toxicity has resolved to grade 1. Treatment may then be resumed with a one dose level reduction.
b. Grade 3-4: If a patient experiences Grade 3-4 toxicity that is considered clinically significant and possibly related to ABL001, therapy must be withheld until the toxicity has resolved to Grade ≤1. Treatment may then be resumed with a one dose level reduction. If toxicity recurs, additional dose reductions may be implemented following the same general guidelines.

4.4.2.2. Hematologic Toxicity:

If neutrophils are <0.5 x 10^9/L and/or platelets are <50 x10^9/L, hold therapy until granulocytes are above 0.5 x10^9/L and platelets are above 50 x10^9/L, then resume therapy at 1 dose level reduction from the dose the patient was receiving at the time therapy was interrupted. If a similar degree of toxicity returns, a further dose reduction by one dose level can be performed, using the above procedures.

4.4.2.3. There will be no making up for missed doses.

4.4.2.4. Alternative dose reductions can be made to keep clinically significant, ABL001-related toxicity grade ≤2. However, the lowest acceptable dose level is -2 and the highest is what is established as MTD in the ongoing phase 1 study for each combination.

4.4.2.5. Dose adjustments by more than 1 dose level at a time can be considered when judged in the best interest of the patient (e.g., neutropenia with sepsis, bleeding requiring platelet transfusions) when toxicity has resolved. The reason for this reduction will be discussed with the PI and the sponsor and documented in the medical record.

4.4.2.6. A patient who has had a dose reduction because of any of the reasons mentioned above may have their dose re-escalated provided the patient has remained free of toxicity requiring dose adjustments as defined above for at least 1 month. Escalation will be made by 1 dose-level increments only, and not more frequent than every month.

4.4.2.7. Occasional missed doses of ABL001 will not be considered a deviation. Missed dosed of ≥ 2 consecutive weeks without adequate justification will be considered a protocol deviation.

4.4.2.8. All toxicities requiring dose interruptions and/modifications will be collected.

Table 1: Dose reduction steps for ABL001

Dose reduction	Dose level 0	Dose level -1	Dose level -2
ABL001 BID	40 mg BID	20 mg BID	20 mg QD
Dose reduction should be based on the worst toxicity demonstrated at the last dose.			

4.3.3 Variations to the dose adjustment rules described above for either agent can be considered after discussion with the PI and approval from the sponsor. The rationale for this variation should be clearly documented.

4.4.3. Duration of Therapy

4.4.3.1. Patients may receive therapy for up to 36 months. After completion of the 36th month patients may continue therapy if in the opinion of the investigator there is clinical benefit provided there has been no grade 3 or higher persistent toxicity attributable to ABL001 at the doses being administered.

4.4.3.2. Patients who achieve MR4.5 sustained for at least 2 years with at least 2 PCR assessments per year can hold therapy with ABL001 and/or TKI and be monitored with PCR. If there is reappearance of transcripts detectable by PCR, therapy with one or both agents can be resumed at the doses being administered at the time treatment was interrupted. Resumption should be particularly strongly considered for patients with loss of MMR in any one determination or with loss of MR4 confirmed in 2 consecutive assessments separated by at least 1 month.

4.4.4. Concomitant Medications

4.4.1 Patients may not receive any other treatment for CML while on study (aside from the TKIs).
4.4.2 The use of other medications for management of comorbidities or adverse events is allowed, as clinically indicated. Concomitant medications will be captured as part of the medical record but will not be entered in the case report form.
4.4.3 Potent CYP3A4 inhibitors should be avoided whenever possible. When the administration of such agents is considered indispensable for the patients' health administration of these agents may be allowed after discussion with the principal investigator and approval from the sponsor.

5. STUDY PROCEDURES

5.1. Pretreatment Evaluation (Within 14 days prior treatment start, unless otherwise specified)
5.1.1. A complete history and physical examination including performance status.
5.1.2. CBC, platelet count and differential (differential not required if WBC <0.5 x10^9/L), total bilirubin, AST/ALT, amylase, lipase and creatinine within 1 week.
5.1.3. Bone marrow aspirate (within 30 days [+/-7 days] from treatment start).
5.1.4. Cytogenetic analysis or FISH in bone marrow or peripheral blood (within 30 days [+/-7 days] from treatment start).
5.1.5. Pregnancy test (blood or urine) for female patients of childbearing potential within 14 days before initiation of study drug dosing.
5.1.6. Peripheral blood for PCR.
5.1.7. Peripheral blood and bone marrow for correlative studies.
5.1.8. EKG (within 30 days prior to treatment start).
5.1.9. Echocardiogram or MUGA scan (within 30 days prior to treatment start).

5.2 Evaluation During Study (Table 3)

5.2.1. Physical exam and evaluation of toxicity (clinic visit or telephone interview) after 2 weeks (+/-3 days), 4 weeks (+/-7 days), 8 weeks (+/-7 days), 3 months (+/-7 days), 6 months (+/-1 month), 12 months (+/-1 month), 18 months (+/-1 month) from the start of therapy, then every 6 to 12 months.
5.2.2. If the evaluation for toxicity is done by phone, a report of physical exam from home physician is acceptable provided there is a physical exam at MDACC at least every 6 months (+/- 1 month) during the first 2 years and every 12 months (+/- 1 month) thereafter.
5.2.3. Through interview and pill diary, we will review the patient's adherence with therapy (TKI and ABL001). Failure to complete pill diary or occasional missed doses will not be considered a deviation.
5.2.4. CBC, platelet, differential after 2 weeks (+/-3 days), 4 weeks (+/-7 days), 8 weeks (+/-7 days), 3 months (+/-7 days), 6 months (+/-1 month), 12 months (+/-1 month), 18 months (+/-1 month) from the start of therapy, then every 6 to 12 months. Differential not required if WBC ≤0.5 x109/L.
5.2.5. Total bilirubin, ALT or AST, amylase, lipase, creatinine after 2 weeks (+/-3 days), 4 weeks (+/-7 days), 8 weeks (+/-7 days), 3 months (+/-7 days), 6 months (+/-1 month), 12 months (+/-1 month), 18 months (+/-1 month) from the start of therapy, then every 6 to 12 months. EKG at day 8 of treatment start (+/- 2 days). EKG and Echocardiogram/MUGA after 4 weeks (+/-7 days).

5.2.6. PCR (peripheral blood and/or bone marrow), after 4 weeks (+/-7 days), 8 weeks (+/-7 days), 3 months (+/-7 days), then every 3 months (+/-1 month) until one year, then every 6months (+/-1 month).

5.2.7. Bone marrow aspirate with cytogenetic and/or FISH every 6 months (+/- 1 months) in year 1 (+/- 1 months), then as clinically indicated.

5.2.8. Patients who permanently discontinue therapy with TKI will have PCR every 4 weeks (+/-1 week) for the first 6 months after discontinuation of TKI, Then every 2 months (+/-1 month) for the next 6 months, then every 3 months (+/-3 weeks) for 12 months, then every 6 months (+/-2 months).

5.2.9. Peripheral blood for correlative studies at study start, 4 weeks (+/-7 days), 8 weeks (+/-7 days), 3 months (+/-7 days), 6 months (+/-1 month), 12 months (+/-1 month), 18 months (+/-1 month) from the start of therapy, then every 6 to 12 months . Bone marrow samples for correlative studies at study start, at 6 months (+/-1 month), at 12 months (+/- 1 month), then every 6-12 months. Missed collections at any or all times for correlative studies will not constitute a protocol deviation as they have no impact on patient safety.

5.2.10. CBC, blood chemistries, EKG's may be done at outside facilities. Under exceptional circumstances other tests might be done at outside facilities after discussion with PI. All outside lab results will be faxed or mailed to MDACC and reviewed and signed by the investigator.

5.2.11. Patients that come off therapy with evidence of adverse events related to study drugs will continue follow-up for toxicity (clinic visit or telephone interview) every 2 weeks for 30 days (+/- 7 days) after end of therapy or until resolution of adverse events to grade 1 or less.

5.3 Outside Physician Participation During Treatment

5.3.1 MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record.

5.3.2 A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care (Appendix C)

5.3.3 Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.

5.3.4 Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.

5.3.5 A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.

5.3.6 Documentation to be provided by the local physician will include drug administration records, progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.

5.3.7 The home physician will be requested to report to the MDACC physician investigator all life-threatening events within 24 hours of documented occurrence.

5.3.8 Patients will return to MDACC every 3 months for 6 months, at 12 months, at 18 months then every 6-12 months thereafter for evaluation. If necessary, patients may have the first 3 months evaluation conducted through their local physician if approved by the MDACC physician investigator.

5.4 Exploratory Objectives and Analysis

5.4.1. To determine the rate of MRD clearance using droplet digital polymerase chain reaction (ddPCR) detecting the BCR-ABL1 fusion transcript

Rationale: It is important to detect and quantify leukemia cells at low levels in order to safely discontinue therapy. It has been suggested that ddPCR allows for detection of low BCR-ABL1 transcript levels. This method is based on isolation of the PCR reaction into single droplets, tested independently for the presence of the target.

Hypothesis: ddPCR allows for an improved quantification of BCR-ABL1 transcripts at low levels.[27]

Experimental approach: RNA will be extracted from pre and post-combination therapy (12 months from therapy start) from bone marrow samples with TRIzol reagent. Subsequently, it will be reserved transcribed to complementary deoxyribonucleic acid (cDNA) using the QuantiTect Reverse Transcription kit (Qiagen). Primers and probes used for each patient will be determined depending on the type of transcript identified with the RT-PCR clinical assay. Reactions will be performed on a QX200 ddPCR System (Biorad) and evaluated in technical duplicates. They will be partitioned into a median of ~16,000 droplets per well using the QX200 droplet generator and run on a 96-well thermal cycler. Analysis will be conducted using the QuantaSoft v1.7 software. In line with the manufacturer's recommendations, samples yielding ≥3 positive droplets from the 10-16,000 analyzed will be scored as positive. We will also investigate reducing this cut-off to ≥2 positive droplets.

5.4.2 To determine the effect of therapy on quiescent leukemic Ph+ stem cells (CFSEmax/CD34+)

Rationale: CML stem cells are quiescent with decreased dependence on BCR-ABL1.[28,29] Strategies aimed at eradicating this disease should be able to target those cells.

Hypothesis: Dual targeting of BCR-ABL1 by adding the allosteric inhibitor ABL001 to a TKI significantly reduces the tumor burden and increases the likelihood of tumor eradication through elimination of quiescent leukemic Ph+ stem cells.

Experimental approach: The goal is to assess the effect of adding ABL001 on apoptosis in quiescent leukemic stem cells, and on pCRKL levels (a surrogate of BCR-ABL1 activity) pre and post-combination therapy (12 months from therapy start) from bone marrow samples. Quiescent cells will be identified by staining C34+ cells with carboxyfluorescein diacetate succimidyl diester (CFSE, CellTrace CFSE proliferation Kit, Invitrogen).[35,36] Cell proliferation will be determined using flow cytometric measurement of CFSE intensity (halves with cell division) in these cells compared to non-dividing cells treated with Colcemid (100ng/ml, Sigma; in order to induce cell cycle arrest). After approximately 6 days of culture, quiescent cells will be identified as CFSEbright (fluorescence in the region of Colcemid-treated cells), and proliferative cells will be identified as CFSEdim (fluorescence less than that of Colcemid-treated cells). Apoptosis will be estimated using measurement of phosphotidylserine externalization with annexin V staining (BD Biosciences), in bulk, proliferating, and quiescent cells.[37] Levels of p-CRKL will also be compared in these cell populations by staining with anti-pCRKL (pY207) (Cell Signaling Technology).[38]

5.4.3 To determine the effect of this combination on mutations in ABL1 and mutations in clonal hematopoiesis of indeterminate potential (CHIP)-associated genes using molecular barcode sequencing.

Rationale: Though presence of mutations in ABL1 using clinical next-generation sequencing assays is rare in CML patients with evidence of molecular response, it is unknown whether small subclones carrying these mutations could be present at low allelic frequency. In addition, there is growing evidence that CHIP leads to adverse outcomes in various hematological malignancies. However, the prognostic impact of CHIP in CML is relatively unexplored. It's unknown whether patients with residual low levels of CML cells also have mutations in CHIP-associated genes at low allelic frequency. Molecular barcode sequencing allows for detection of ultralow-frequency mutations while minimizing sequencing error rates.[39]
Hypothesis: Adding ABL001 leads to eradication of small clones carrying ABL1 mutations. We postulate that persistence of clones with CHIP-associated mutations is associated with persistence of the disease despite combination therapy.
Experimental approach: DNA will be extracted from bone marrow samples pre and post-combination therapy (12 months from therapy start). We expect that mutations will be present at low variant allelic frequencies (VAF), thus we propose molecular barcode sequencing, an amplicon-based targeted deep sequencing method that allows for consensus calls of low frequency alleles (Haloplex High Sensitivity technology; Agilent Technologies).[39] This custom-designed panel will include genes frequently mutated in CML and CHIP. Somatic mutations will be called against virtual normal sequence, followed by an automatic annotation to select non-polymorphism, protein-coding changing mutations using our standard algorithm as previously described.[40]

5.4.4 To determine the effect of therapy on bone marrow progenitors in clonogenic assays

Rationale: deep levels of response in CML are maintained if therapy is able to affect primitive leukemic stem cells.

Hypothesis: Dual targeting of BCR-ABL1 by adding the allosteric inhibitor ABL001 to a TKI significantly increases the likelihood of tumor eradication through inhibiting proliferation in leukemia stem cells.

Experimental approach: we will assess a) the serial re-plating colony forming efficiency (CFC/re-plating assay) of CD34+/CD38- cell from untreated and treated patients on protocol, and the frequency of long term culture-initiating cells (LTC-IC assays), respectively. D-FISH and/or RT-PCR for BCR-ABL1 will be performed on plucked colonies to specifically determine the percentage of Ph+ colonies. We expect the emerging colonies to be Ph-negative or to have a marked decrease of the Ph-positive colonies. Methylcellulose colony formation assays will be carried out by plating 103 CD34+/CD38- cell sorted from CML patient samples in 0.9% MethoCult H4435 (containing rhKL, rhGCSF, rhGM-CSF, rhIL-3, rhIL-6, rhEpo) (Stem Cell Technologies). Colonies will be scored after 14 days in culture. To assess self-renewal individual colonies will be plucked in 50µl of IMDM/2%FBS, mixed with 150µl of Methocult and re-plated in 96-well plates and analyzed 14 days later. Single wells containing at least one secondary colony will be scored as positive for self-renewal as previously described.[41]

5.4.5 To describe immune effects of the combination of TKI and ABL001

We will characterize the effects of dual therapy on different hematopoietic compartments including various immune effects. A variety of exploratory markers will be explored such as markers of T

cell activation, differentiation and exhaustion in addition to expression of immune checkpoints on various hematopoietic cells.

5.4.6 To describe patient reported outcomes (PRO) using the MDASI-CML instrument

The MD Anderson Symptom Inventory – Chronic Myeloid Leukemia (MDASI-CML)[42] is a 26 item self-administered questionnaire for adult CML patients. Twenty of the items measure the severity of disease-related symptoms and are scored from 0 (Not present) to 10 (As Bad as you can imagine) and 6 items that measure symptom interference with daily life scored from 0 (Did not interfere) to 10 (Interfered completely).

The MDASI CML will be used to compare data on the patient's disease-related symptoms and health-related quality of life from baseline, on study and at the end of the study. Patients with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses.

The patient should be given the questionnaire(s) to be completed at the scheduled visit before clinical assessments by the physician. Patient's refusal to complete all or any part of a questionnaire should be documented in the EMR and study data capture system and should not be captured as a protocol deviation. Patient questionnaires should be completed in the language most familiar to the patient. Completion of the questionnaire when patients are evaluated by local physicians is optional.

Patient's refusal to complete all or any part of a questionnaire should be documented in the subject's medical record; study data capture system; and should not be captured as a protocol deviation.

Table 2: Summary of objectives and related endpoints

	Objective	**Endpoint**
Primary	To determine the clinical activity of the combination of asciminib (ABL001) and a tyrosine kinase inhibitor (TKI) in patients with CML in complete cytogenetic response (CCyR) but detectable BCR-ABL1 transcript	Molecular response at 12 months*
Secondary	1. To determine the effect of the combination of ABL001 and TKI on the rate of MR4, MR4.5, and sustained MR4.5 (MR4 and MR4.5 rates will include only patients with a molecular response inferior to MR4 or MR4.5 respectively upon enrollment)	MR4, MR4.5, sustained MR4.5
	2. To investigate treatment-free remission (TFR) after at least 2 years of sustained deep molecular remission	TFR
	3. To determine the safety of the combination of asciminib and tyrosine kinase inhibitors	Adverse events
	4. To determine the event-free survival (EFS), survival free from transformation to accelerated and blast phase (TFS), and overall survival (OS)	EFS, TFS, OS
Exploratory	1. To determine the rate of MRD clearance using droplet digital polymerase chain reaction (ddPCR) detecting the BCR-ABL1 fusion transcript	
	2. To determine the effect of therapy on quiescent leukemic Ph+ stem cells (CFSEmax/CD34+)	
	3. To determine the effect of therapy on bone marrow progenitors in clonogenic assays	

	4. To describe immune effects of the combination of TKI and ABL001	
	5. To describe patient reported outcomes (PRO) using the MDASI-CML instrument	
* A favorable response is defined as ≥1 log reduction of the BCR-ABL1 transcript levels from baseline or disappearance of the BCR-ABL1 transcripts (see Statistical Considerations section)		

Table 3: Evaluation schedule

Evaluation	Pre-treatment (within 14 days)	Week 2	Week 4	Week 6	Week 8	Month 3	Month 6	Month 9	Month 12	Month 18	After Month 18	At therapy Discontinuation ¥	After therapy discontinuation
History, physical exam, performance status^	x	x	x		x	x	x		x	x	Q 6-12 months	x	Q 4-8 weeks, Q 3-6 months*
CBC**	x	x	x		x	x	x		x	x	Q 6-12 months	x	Q 4-8 weeks, Q 3-6 months*
Chemistries (including total bilirubin, creatinine, electrolytes, ALT or AST, amylase, lipase)**	x	x	x		x	x	x		x	x	Q 6-12 months	x	Q 4-8 weeks, Q 3-6 months*
Pregnancy Test (blood or urine)	x												
EKG, Echo/Muga #	x	~	x										
PCR (PB)[1]	x		x		x	x	x	x	x	x	Q 6 months	x	Q 4-8 weeks, Q 3-6 months*
Cytogenetics and/or FISH^^	x						x		x		As clinically indicated	x	
Bone marrow aspiration^^	x						x		x		As clinically indicated	x	After 6 and 12 months
Research sample (PB)	x		x		x	x	x		x	x		x	After 6 and 12 months
Research sample (BM)	x						x		x			x	After 6 and 12 months
MDASI	x	x	x		x	x	x		x	x	Q 6-12 months	x	Q 6-12 months

^ Pre-treatment visit (within 14 days), after 2 weeks (+/-3 days), 4 weeks (+/-7 days), 8 weeks (+/-7 days), 3 months (+/-7 days), 6 months (+/-1 month), 12 months (+/-1 month), 18 months (+/-1 month) from the start of therapy, then every 6 to 12 months. If the evaluation for toxicity is done by phone, a report of physical exam from home physician is acceptable provided there is a physical exam at MDACC at least every 6 months (+/- 1 month) during the first 2 years and every 12 months (+/- 1 month) thereafter.
* Patients who permanently discontinue therapy with TKI will have these evaluations done every 4 weeks (+/-1 week) for the first 6 months after discontinuation of TKI, Then every 2 months (+/-1 month) for the next 6 months, then every 3 months (+/-3 weeks) for 12 months, then every 6 months (+/-2 months).
# EKG and Echo/Muga within 30 days of specified timeline. ~EKG at day 8 of treatment start (+/- 2 days).
^^ Bone marrow aspiration with cytogenetics and/or FISH within 30 days [+/-7 days] from treatment start .
¥ Patients that come off therapy with evidence of adverse events related to study drugs will continue follow-up for toxicity (clinic visit or telephone interview) every 2 weeks for 30 days (+/- 7 days) after end of therapy or until resolution of adverse events to grade 1 or less.
** Screening blood tests to be obtained within 1 week of treatment start.
[1] PCR (peripheral blood and/or bone marrow), after 4 weeks (+/-7 days), 8 weeks (+/-7 days), 3 months (+/-7 days), then every 3 months (+/-1 month) until one year, then every 6months (+/-1 month)

6 RESPONSE DEFINITIONS

6.4 Criteria for Response

6.4.2 A favorable response for the primary endpoint is defined as a greater than a one-log reduction of *BCR-ABL* transcript levels from the baseline level or disappearance of *BCR-ABL* transcripts after 12 months of combination.

6.4.3 For the purposes of this study, progression will be defined as a confirmed loss of complete cytogenetic response (CCyR) (i.e., >0% Ph+ metaphases among 20 metaphases counted by karyotype; or by FISH; or, if not cytogenetic or FISH available, by increase in BCR-ABL1/ABL1 to >1% IS) as assessed in two consecutive analyses separated by at least a month.

6.4.4 Survival endpoints (overall, event-free and free from blast transformation) will be measured from the time of start of ABL001 therapy.

6.5 Criteria for Removal from Study

6.2.1 The patient receives CML-directed therapy other than TKI and ABL001.

6.5.2 The patient develops disease progression defined as confirmed loss of CCyR, confirmed loss of CHR or transformation to accelerated or blast phase of CML.

6.5.3 The dose of TKI is increased beyond the dose being used at the time of study entry or new therapies for their leukemia are added.

6.5.4 The patient has a continuous, non-planned interruption of TKI therapy for greater than 8 weeks (e.g., for non-compliance or toxicity). Interruptions for surgery, accidents or other unrelated reasons are not grounds for removal from study.

6.5.5 The patient withdraws consent.

6.5.6 The treating physician considers it in the best interest of the patient.

6.5.7 Pregnancy or suspected pregnancy.

6.5.8 **The trial will be stopped at any time during the study if we determine that there is ≥80% chance that the unacceptable toxicity is ≥30%. Specifically, the study will be stopped early if (N of unacceptable toxicities) / (N patients evaluated) ≥ 3/4, 4/8, 6/12, 7/16. The operating characteristics of this monitoring rule are listed in Table 4. These rules will be applied starting from the 4th patient and in cohorts of 4.**

7 INVESTIGATIONAL AGENT PACKAGING AND LABELING

ABL001 will be provided as global clinical open-label supply and will be packed and labeled under the responsibility of Novartis, Drug Supply Management.

Study treatment labels will include storage conditions and a unique medication number (corresponding to study treatment and strength). Site personnel will add the patient number on the label. If the label has 2-parts (base plus tear-off label), immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the package and affix it to the patient's source document.

Study treatment	Packaging	Labeling and dose frequency
ABL001 (20 mg and 40 mg tablets)	Tablets in bottle	Labeled as “ABL001 20mg / ABL001 40 mg BID”

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the ABL001 should be stored according to the instructions specified on the drug labels.

Handling and Storage: Investigational product must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive investigational product, in accordance with all applicable regulatory requirements. Only authorized site staff may supply or administer investigational product. All investigational products must be stored in a secure area with access limited to the Principal Investigator and authorized site staff and under physical conditions that are consistent with investigational product-specific requirements. Any unused or expired investigational product will be returned to MDACC to be disposed per institutional policy.

Importantly, for the purposes of this study, the TKI agents (nilotinib, dasatinib) are not considered investigational agents and they will be supplied by commercial sources (per routine clinical care).

8 REGULATORY AND REPORTING REQUIREMENTS

8.4 Adverse Event Reporting

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

8.1.1 Adverse events will be documented in the medical record and entered into Prometheus. Prometheus will be used as the electronic case report form for this protocol.

8.4.2 Adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Adverse drug reaction (ADR) is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

Assessing causal connection between agents and disease is fundamental to the understanding of adverse drug reactions. In general, a drug may be considered a contributory cause of an adverse event if, had the drug not been administered, 1) the event would not have happened at all, 2) the event would have occurred later than it actually did, or 3) the event would have been less severe.

The Investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

8.4.3 Adverse Events (AEs) will be evaluated according to CTC version 5 and documented in medical record. Adverse events will be recorded in the Case Report Form (CRF) in accordance with Leukemia-specific Adverse Event Recording and Reporting Guidelines as below:

8.4.3.1 Baseline events will be recorded in the medical history section of the case report form and will include the terminology event name, grade, and start date of the event. The medical history section of the case report form will serve as the source document for baseline events once signed and dated by the principal investigator.

8.4.3.2 Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before the informed consent is signed.

8.4.3.3 Hematologic laboratory abnormalities will not be recorded as baseline events for patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase.

8.4.3.4 If exact start date is unknown, month and year or year may be used as the start date of the baseline event.

8.4.4 The maximum grade of the adverse event will be captured per course or protocol defined visit date.

8.4.5 All adverse events regardless of attribution will be recorded in the case report form.

8.4.6 Hematologic adverse events will not be recorded or reported for studies in patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase except for:

8.4.6.1 Prolonged myelosuppression as defined by the NCI-CTCAE .v5 criteria specific for leukemia, e.g. marrow hypocellularity on day 42 or later (6 weeks) from start of therapy without evidence of leukemia (< 5% blasts), or that results in dose modifications, interruptions or meets the protocol definition of DLT or SAE.

8.4.7 Serious adverse events will be reported according to institutional policy.

8.5 Serious Adverse Event Reporting (SAE)

Serious Adverse Event Reporting (SAE) for MD Anderson-Sponsored IND Protocols

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas MD Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Investigator Communication with Supporting Companies:

Reporting procedures:

The principal investigator has the obligation to report all serious adverse events to the FDA (if applicable), IRB, and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E). All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form), if applicable to ensure patient safety, every SAE, regardless of suspected causality, from the time of the first protocol-specific intervention, until at least 30 days after the patient has stopped study treatment must be reported to Novartis according to institutional policies. Information about all SAEs is collected and recorded on a Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and **send the completed, signed form along with the Novartis provided fax cover sheet to the Novartis Oncology Drug Safety and Epidemiology (DS&E) department by fax (fax: 877-778-9739) within 24 hours. An acceptable alternative to the FAX coversheet is an e-mail to an approved Novartis Patient Safety (NPS) mail box (e.g. clinicalsafetyop.phuseh@novartis.com).**

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode according to institutional policies.

Any SAEs experienced after the 30- day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E) by fax **(fax : 877-778-9739)**. Pregnancy follow-up should include an assessment of the possible relationship to the investigational/study treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Annual Reports

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report (AR) should be filed in the study's Regulatory Binder, and a copy provided to Novartis as a supporter of this study as follows:

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Adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug.

9 STATISTICAL CONSIDERATIONS

This is a phase II, single-arm, open-label study to evaluate the efficacy of ABL001 in patients with CML and CCyR but with detectable MRD while continuing to receive TKI. There will be two cohorts of patients based on the TKI they are receiving prior to enrolment: 1) dasatinib + ABL001: patients have received treatment of dasatinib as standard TKI for 2 years with detectable MRD and 2) nilotinib + ABL001: patients have received treatment of nilotinib as standard TKI for 2 years with detectable MRD. Up to 20 evaluable patients will be enrolled per cohort at the MD Anderson Cancer Center, at a rate of 1 to 2 patients per month. Patients lost to follow-up or those who stop therapy for personal or financial reasons need to be replaced and do not count as failure. Patients who discontinue because of unacceptable toxicity are included in the stopping rule for toxicity and will also be counted as failures in efficacy calculations. The primary endpoint of this trial is to determine the rate of molecular response at 12 months from the start of the study. A favorable response is defined as ≥1 log reduction of the *BCR-ABL1* transcript levels from baseline or disappearance of the *BCR-ABL1* transcripts (CMR). In this setting, it would be difficult to do an interim monitoring for futility. Patients who lose CCyR within 12 months will be counted as treatment failures. For each cohort, we will estimate the response rate and 95% confidence interval. It is expected that the combination treatment could reach a response rate of ≥20%. A sample size of 20 can achieve a 95% exact CI of (5.73%, 43.66%).

Summary statistics will be used to describe the clinical and demographic characteristics of the study population. For secondary endpoints or exploratory endpoints, frequency, percentage and 95% confidence interval will be tabulated for binary outcomes e.g. MR4 etc. The Kaplan-Meier method will be used to estimate time to event outcomes e.g. EFS etc. Descriptive statistics will be provided for the MDASI-CML symptom score and interference score, and the change in the MDASI-CML symptom score and interference score from baseline to all available time points to the end of study. For each arm, we will follow a Bayesian design with early stopping rules for toxicity[42]. Treatment-related unacceptable toxicity will be defined as grade 3 or 4 toxicity that prevents patients from continuing combination therapy despite optimal management. This will be determined according to the following rule: Probability (PE > 0.30 | data) > 0.80, where PE is the probability of toxicity; assuming that PE ~ beta (0.6, 1.4). In other words, the trial will be stopped at any time during the study if we determine that there is ≥80% chance that the unacceptable toxicity is ≥30%. Specifically, the study will be stopped early if (N of unacceptable toxicities) / (N patients evaluated) ≥ 3/4, 4/8, 6/12, 7/16. The operating characteristics of this monitoring rule is listed in Table 4. These rules will be applied starting from the 4th patient and in cohorts of 4.

The Investigator is responsible for completing an efficacy/safety summary report, and submitting it to the IND Office Medical Affairs and Safety Group, for review and approval. This should be submitted after the first 4 evaluable patients complete 1 cycle (28 days) of study treatment, and every 4 evaluable patients per cohort, thereafter. On every report submission, the information from previous reported patients will need to be updated. A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

Table 4: Operating characteristics for monitoring of toxicities

True Toxicity Rate	Early Stopping Probability	Avg. N treated
0.1	0.0077	19.89
0.2	0.0795	19.02
0.3	0.2824	16.75
0.4	0.5776	13.36
0.5	0.8297	9.93

REFERENCES

1. Hochhaus A, Larson RA, Guilhot F, et al. Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia. The New England journal of medicine 2017;376:917-27.
2. Kantarjian H, O'Brien S, Jabbour E, et al. Improved survival in chronic myeloid leukemia since the introduction of imatinib therapy: a single-institution historical experience. Blood 2012;119:1981-7.

3. Sasaki K, Kantarjian HM, Jain P, et al. Conditional survival in patients with chronic myeloid leukemia in chronic phase in the era of tyrosine kinase inhibitors. Cancer 2016;122:238-48.
4. Mahon FX, Rea D, Guilhot J, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. The Lancet Oncology 2010;11:1029-35.
5. Rowley JD. Letter: A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. Nature 1973;243:290-3.
6. Klein Ad, Kessel AGv, Grosveld G, et al. A cellular oncogene is translocated to the Philadelphia chromosome in chronic myelocytic leukaemia. Nature 1982;300:765.
7. Heisterkamp N, Stephenson JR, Groffen J, et al. Localization of the c-ab1 oncogene adjacent to a translocation break point in chronic myelocytic leukaemia. Nature 1983;306:239-42.
8. Grosveld G, Verwoerd T, van Agthoven T, et al. The chronic myelocytic cell line K562 contains a breakpoint in bcr and produces a chimeric bcr/c-abl transcript. Molecular and cellular biology 1986;6:607-16.
9. Shtivelman E, Lifshitz B, Gale RP, Canaani E. Fused transcript of abl and bcr genes in chronic myelogenous leukaemia. Nature 1985;315:550.
10. Ben-Neriah Y, Daley GQ, Mes-Masson AM, Witte ON, Baltimore D. The chronic myelogenous leukemia-specific P210 protein is the product of the bcr/abl hybrid gene. Science (New York, NY) 1986;233:212-4.
11. Kloetzer W, Kurzrock R, Smith L, et al. The human cellular abl gene product in the chronic myelogenous leukemia cell line K562 has an associated tyrosine protein kinase activity. Virology 1985;140:230-8.
12. Shtivelman E, Lifshitz B, Gale RP, Roe BA, Canaani E. Alternative splicing of RNAs transcribed from the human abl gene and from the bcr-abl fused gene. Cell 1986;47:277-84.
13. Druker BJ, Tamura S, Buchdunger E, et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nature medicine 1996;2:561-6.
14. Hughes TP, Hochhaus A, Branford S, et al. Reduction of BCR-ABL Transcript Levels at 6, 12, and 18 Months (mo) Correlates with Long-Term Outcomes on Imatinib (IM) at 72 Mo: An Analysis from the International Randomized Study of Interferon versus STI571 (IRIS) in Patients (pts) with Chronic Phase Chronic Myeloid Leukemia (CML-CP). Blood 2008;112:334-.
15. Shah NP, Nicoll JM, Nagar B, et al. Multiple BCR-ABL kinase domain mutations confer polyclonal resistance to the tyrosine kinase inhibitor imatinib (STI571) in chronic phase and blast crisis chronic myeloid leukemia. Cancer cell 2002;2:117-25.
16. Branford S, Rudzki Z, Walsh S, et al. High frequency of point mutations clustered within the adenosine triphosphate-binding region of BCR/ABL in patients with chronic myeloid leukemia or Ph-positive acute lymphoblastic leukemia who develop imatinib (STI571) resistance. Blood 2002;99:3472-5.
17. Gorre ME, Mohammed M, Ellwood K, et al. Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. Science (New York, NY) 2001;293:876-80.
18. Hochhaus A, Kreil S, Corbin AS, et al. Molecular and chromosomal mechanisms of resistance to imatinib (STI571) therapy. Leukemia 2002;16:2190-6.
19. Gunthard HF, Saag MS, Benson CA, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2016 Recommendations of the International Antiviral Society-USA Panel. Jama 2016;316:191-210.
20. Shah NP, Skaggs BJ, Branford S, et al. Sequential ABL kinase inhibitor therapy selects for compound drug-resistant BCR-ABL mutations with altered oncogenic potency. The Journal of clinical investigation 2007;117:2562-9.

21. Hochhaus A, Saglio G, Hughes TP, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia 2016;30:1044-54.
22. Cortes JE, Saglio G, Kantarjian HM, et al. Final 5-Year Study Results of DASISION: The Dasatinib Versus Imatinib Study in Treatment-Naive Chronic Myeloid Leukemia Patients Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2016;34:2333-40.
23. Hochhaus A, Saglio G, Hughes TP, et al. Impact of Treatment with Frontline Nilotinib (NIL) vs Imatinib (IM) on Sustained Deep Molecular Response (MR) in Patients (pts) with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP). Blood 2015;126:2781-.
24. Huang X, Cortes J, Kantarjian H. Estimations of the increasing prevalence and plateau prevalence of chronic myeloid leukemia in the era of tyrosine kinase inhibitor therapy. Cancer 2012;118:3123-7.
25. Rea D. Management of adverse events associated with tyrosine kinase inhibitors in chronic myeloid leukemia. Annals of hematology 2015;94 Suppl 2:S149-58.
26. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. Blood 2013;121:4439-42.
27. Jennings LJ, George D, Czech J, Yu M, Joseph L. Detection and quantification of BCR-ABL1 fusion transcripts by droplet digital PCR. The Journal of molecular diagnostics : JMD 2014;16:174-9.
28. Corbin AS, Agarwal A, Loriaux M, Cortes J, Deininger MW, Druker BJ. Human chronic myeloid leukemia stem cells are insensitive to imatinib despite inhibition of BCR-ABL activity. The Journal of clinical investigation 2011;121:396-409.
29. Holtz MS, Forman SJ, Bhatia R. Nonproliferating CML CD34+ progenitors are resistant to apoptosis induced by a wide range of proapoptotic stimuli. Leukemia 2005;19:1034-41.
30. Nagar B, Hantschel O, Young MA, et al. Structural basis for the autoinhibition of c-Abl tyrosine kinase. Cell 2003;112:859-71.
31. Adrian FJ, Ding Q, Sim T, et al. Allosteric inhibitors of Bcr-abl-dependent cell proliferation. Nature chemical biology 2006;2:95-102.
32. Wylie AA, Schoepfer J, Jahnke W, et al. The allosteric inhibitor ABL001 enables dual targeting of BCR-ABL1. Nature 2017;543:733-7.
33. Hughes TP, Goh Y-T, Ottmann OG, et al. Expanded Phase 1 Study of ABL001, a Potent, Allosteric Inhibitor of BCR-ABL, Reveals Significant and Durable Responses in Patients with CML-Chronic Phase with Failure of Prior TKI Therapy. Blood 2016;128:625-.
34. Michael J. Mauro D-WK, Jorge Cortes , Delphine Réa , Timothy P. Hughes , Hironobu Minami , Massimo Breccia , Daniel J. DeAngelo , Moshe Talpaz , Andreas Hochhaus , Yeow Tee Goh , Philipp D. Le Coutre , Manu Sondhi , Kaushal Mishra , Florence Hourcade-Potelleret , Gary Vanasse , Paola Aimone , Fabian Lang. COMBINATION OF ASCIMINIB PLUS NILOTINIB (NIL) OR DASATINIB (DAS) IN PATIENTS (PTS) WITH CHRONIC MYELOID LEUKEMIA (CML): RESULTS FROM A PHASE 1 STUDY. EHA Library 2019;267467; S884.
35. Mak DH, Wang RY, Schober WD, et al. Activation of apoptosis signaling eliminates CD34+ progenitor cells in blast crisis CML independent of response to tyrosine kinase inhibitors. Leukemia 2012;26:788-94.
36. Mak DH, Schober WD, Chen W, et al. Triptolide induces cell death independent of cellular responses to imatinib in blast crisis chronic myelogenous leukemia cells including quiescent CD34+ primitive progenitor cells. Molecular cancer therapeutics 2009;8:2509-16.
37. Carter BZ, Mak PY, Mu H, et al. Combined targeting of BCL-2 and BCR-ABL tyrosine kinase eradicates chronic myeloid leukemia stem cells. Science translational medicine 2016;8:355ra117.
38. La Rosee P, Holm-Eriksen S, Konig H, et al. Phospho-CRKL monitoring for the assessment of BCR-ABL activity in imatinib-resistant chronic myeloid leukemia or Ph+ acute lymphoblastic leukemia patients treated with nilotinib. Haematologica 2008;93:765-9.

39. Wong TN, Ramsingh G, Young AL, et al. Role of TP53 mutations in the origin and evolution of therapy-related acute myeloid leukaemia. Nature 2015;518:552-5.
40. Morita K, Kantarjian HM, Wang F, et al. Clearance of Somatic Mutations at Remission and the Risk of Relapse in Acute Myeloid Leukemia. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2018;36:1788-97.
41. Jamieson CH, Ailles LE, Dylla SJ, et al. Granulocyte-macrophage progenitors as candidate leukemic stem cells in blast-crisis CML. The New England journal of medicine 2004;351:657-67.
42. Williams LA, Garcia Gonzalez AG, Ault P, et al. Measuring the symptom burden associated with the treatment of chronic myeloid leukemia. Blood 2013;122:641-7.

10. APPENDIX

Appendix 1: List of CYP3A4 inducers, inhibitors and substrates

These lists were compiled from the Indiana University School of Medicine's "Clinically Relevant" Table; from the FDA's "Guidance for Industry, Drug Interaction Studies" and from the University of Washington's Drug Interaction Database. These lists may not be comprehensive and may be

updated periodically. Refer to Novartis Oncology Clinical Pharmacology Internal Memorandum, Drug-drug interactions (DDI) Database (last updated 2016) for update or more details.

Table 11.1: CYP3A4 inducers

Category	Drug Names
Strong inducers of CYP3A4[1]	avasimibe, carbamazepine, enzalutamide, mitotane, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort (HYPERICUM PERFORATUM)[5]
Moderate inducers of CYP3A4[2]	bosentan, efavirenz, etravirine, lersivirine, lopinavir, modafinil, nafcillin, ritonavir/tipranavir, semagacestat[4], talviraline[4], thioridazine
Weak inducers of CYP3A4[3]	amprenavir, aprepitant, armodafinil bexarotene, boceprevir, brivacetam, clobazam, danshen[5], dexamethasone, echinacea[5], eslicarbazepine, gingko (ginkgo biloba)[5], ginseng[5], glycyrrhizin[5], honey[6], quercetin[6], methylprednisolone, nevirapine, oxcarbazepine, pioglitazone, pleconaril[4], prednisone, primidone, raltegravir, ritonavir, rufinamide, sorafenib, Stribild (combo of elvitegravir, cobicistat, emtricitabine, and tenofovir), sulfinpyrazone, telaprevir, terbinafine, ticagleror, ticlopidine, topiramate, troglitazone[4], vemurafenib, vicriviroc/ritonavir, vinblastine, yin zhi huang[5]
[1] A strong inducer for a specific CYP is defined as an inducer that decreases the AUC of a sensitive substrate for that CYP by equal or more than 80%. [2] A moderate inducer for a specific CYP is defined as an inducer that decreases the AUC of a substrate for that CYP by 50-80%. [3] A weak inducer for a specific CYP is defined as an inducer that decreases the AUC of a substrate for that CYP by 20-50%. [4] Drugs not available in the US Market. [5] Herbal product. [6] Food product.	

Table 11.2: CYP3A4 inhibitors

Category	Drug Names
Strong inhibitors of CYP3A4[1]	boceprevir, cobicistat (GS-9350), conivaptan, clarithromycin, danoprevir/ritonavir[12], delalisib, darunavir/ritonavir[12], elvitegravir/ritonavir[12], grapefruit product[11], indinavir, indinavir/ritonavir[12], itraconazole,

	ketoconazole, LCL161, lopinavir/ritonavir[12], mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, saquinavir/ritonavir[12], telaprevir, telithromycin, tipranavir/ritonavir[12], troleandomycin, VIEKIRA PAK2, voriconazole
Moderate inhibitors of CYP3A4[2]	ACT-178882, amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, crizotinib, cyclosporine, Erythromycin, darunavir, diltiazem, dronedarone, FK1706Ferula asafetida resin (Ferula assa-foetida)[4], faldaprevir, fluconazole[7], imatinib, isavuconazole, netupitant, nilotinib, schisandra, sphenanthera, tofisopam, verapamil
Weak inhibitors of CYP3A4[3]	almorexant, alprazolam, AMD070, amiodarone, amlodipine, atorvastatin, AZD2327, azithromycin, berberine, bicalutamide, blueberry juice[5], chlorzoxazone, cilostazol, clotrimazole, cranberry juice[5], daclatasvir, delavirdine, evacetrapid, everolimus, fosaprepitant (IV), fluvoxamine[8], fostamatinib, Garden Cress seeds (Lepidium sativum)[5], ginkgo[4], goldenseal[4], Guan Mai Ning[13], GSK1292263, GSK2248761, isoniazid, ivacaftor, lacidipine, linagliptin, lomitapide, M100240, oral contraceptives, palbociclib, pazopanib, peppermint oil, propiverine, ranitidine, ranolazine, resveratrol, roxithromycin, Seville orange juice[5], simeprevir, sitaxentan, suvorexant, tabimorelin, tacrolimus, teriflunomide, ticagrelor, tolvaptan, Tong Xin Luo[13]

[1] A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by equal or more than 5-fold.
[2] A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold.
[3] A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-foldbut equal to or more than 1.25-fold.
[4] Herbal product.
[5] Food product.
[6] Gemfibrozil also inhibits OATP1B1. Applicable for another class of CYP inhibitor.
[7] Fluconazole is listed as a strong CYP2C19 inhibitor based on the AUC ratio of omeprazole, which is also metabolized by CYP3A; fluconazole is a moderate CYP3A inhibitor.
[8] Fluvoxamine strongly inhibits CYP1A2 and CYP2C19, but also inhibits CYP2C8/2C9 and CYP3A.
[9] Ticlopidine strongly inhibits CYP2C19, but also inhibits CYP3A, CYP2B6, and CYP1A2. The inhibition of CYP3A4 by ticlopidine is not strong although the actual class of its inhibition on CYP3A4 (moderate vs weak) has yet to be defined.
[10] Effect seems to be due to CYP2C19 inhibition by ethinyl estradiol. Applicable for another class of CYP inhibitor.
[11] The effect of grapefruit product varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (e.g., high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (e.g., low dose, single strength).
[12] Combination therapy.(in some cases combinations with ritonavir have been listed as moderate inhibitors of CYP3A in the UW database, the have all been listed as strong in the DDI guide to avoid any potential confusion).
[13] Traditional Chinese medicine.

Table 14.3: CYP3A4 substrates: Narrow therapeutic index, sensitive, and others

Category	**Drug Names**
Narrow Therapeutic index substrates of CYP3A4[1]	alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfanadine, thioridazine

Sensitive substrates of CYP3A4[2]	alpha-dihydroergocryptine, alfentanil, almorexant, alisoporivir, aplaviroc, aprepitant, atazanavir, atorvastatin, avanafil, bosutinib, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, conivaptan, danoprevir, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, elvitegravir, eplerenone, everolimus, felodipine, fluticasone, ibrutinib, indinavir, ivacaftor, levomethadyl, lomitapide, lopinavir, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, naloxegol, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, saquinavir, sildenafil, simeprevir, simvastatin, tacrolimus, terfenadine, ticagrelor, tilidine,tipranavir, tolvaptan, triazolam, ulipristal, vardenafil, vicriviroc, voclosporin.
Other Substrates of CYP3A4[3]	alprazolam, ambrisentan, amlodipine, antipyrine, aripiprazole, artemether, avosentan, boceprevir, bosentan, buprenorphine, carbamazepine, dexloxiglumide, dextromethorphan, diazepam, docetaxel, enzalutamide, gemigliptin, halofantrine, imipramine, lansoprazole, lidocaine, linagliptin, operamide, loratadine, losartan, lurasidone, macitentan, methadone, mirodenafil, montelukast, morphine, nelfinavir, netupitant, nevirapine, nifedipine, nilotinib, nitrendipine, omeprazole, ospemifene, oxycodone, paclitaxel, pazopanib, pioglitazone, quinine, ranolazine, repaglinide, rifabutin, ritonavir, roflumilast, saxagliptin, selegiline, sertraline, sibutramine, sotrastaurine, telaprevir, theophylline, tirilazad, tolterodine, udenafil, ulipristal, vincristine, voriconazole
Narrow Therapeutic index substrates of CYP2C9	warfarin (also sensitive), phenytoin
Narrow Therapeutic index substrates of CYP2C8	paclitaxel

[1] Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor.
[2] Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).
[3] Other substrates are these that have shown an in vivo ≥2-fold increase in AUC with co-administration of an inhibitor based on the UW database.