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NCCN Task Force Report: Tyrosine Kinase Inhibitor Therapy Selection in the Management of Patients With Chronic Myelogenous Leukemia

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Abstract

The advent of imatinib has dramatically improved outcomes in patients with chronic myelogenous leukemia (CML). It has become the standard of care for all patients with newly diagnosed chronic-phase CML based on its successful induction of durable responses in most patients. However, its use is complicated by the development of resistance in some patients. Dose escalation might overcome this resistance if detected early. The second-generation tyrosine kinase inhibitors (TKIs) dasatinib and nilotinib provide effective therapeutic options for managing patients resistant or intolerant to imatinib. Recent studies have shown that dasatinib and nilotinib provide quicker and potentially better responses than standard-dose imatinib when used as a first-line treatment. The goal of therapy for patients with CML is the achievement of a complete cytogenetic response, and eventually a major molecular response, to prevent disease progression to accelerated or blast phase. Selecting the appropriate TKI depends on many factors, including disease phase, primary or secondary resistance to TKI, the agent's side effect profile and its relative effectiveness against *BCR-ABL* mutations, and the patient's tolerance to therapy. In October 2010, NCCN organized a task force consisting of a panel of experts from NCCN Member Institutions with expertise in the management of patients with CML to discuss these issues. This report provides recommendations regarding the selection of TKI therapy for the management of patients with CML based on the evaluation of available published clinical data and expert opinion among the task force members.

Keywords

Chronic myelogenous leukemia; CML; *BCR-ABL*; tyrosine kinase inhibitor; TKI; imatinib; high-dose imatinib; dasatinib; nilotinib; mutations; suboptimal response; disease progression; accelerated phase; blast phase; allogeneic HSCT

Chronic myelogenous leukemia (CML) is a stem cell malignancy that is characterized by a reciprocal translocation between chromosomes 9 and 22 [t(9;22)], resulting in the formation of the Philadelphia chromosome. This translocation results in the head to tail fusion of the breakpoint cluster region (*BCR*) gene on chromosome 22 at band q11 and the Abelson murine leukemia (*ABL*) gene located on chromosome 9 at band q34.[1] The fusion gene, *BCR-ABL*, encodes a protein ($p210^{BCR-ABL}$) with deregulated tyrosine kinase activity that plays a central role in the initial development of CML. CML has 3 phases, chronic, accelerated, and blast, identified by clinical and pathologic characteristics, although most of the genetic changes in progression occur in the transition from chronic to accelerated phase.[2] Most cases of CML in the United States are diagnosed in the chronic phase. Untreated CML typically progresses from chronic phase through an accelerated phase at a median of approximately 4 years, and eventually leads to terminal blast-phase disease, with death occurring from bleeding and infectious complications.[3]

First-Line Treatment: Imatinib Versus Second-Generation Tyrosine Kinase Inhibitors

Imatinib

Imatinib is a selective inhibitor of the BCR-ABL tyrosine kinase. The results of the IRIS (International Randomized Study of Interferon and STI571) trial established the safety and efficacy of imatinib in patients with newly diagnosed chronic-phase CML (CP-CML).[4,5] This trial randomized 1106 patients to undergo initial therapy with either imatinib, 400 mg daily, or interferon-α plus low-dose cytarabine. At 8-year follow-up, 55% of patients remained on imatinib, and the estimated rates of event-free survival, freedom from progression, and overall survival were 81%, 92%, and 85%, respectively.[6] Major molecular response (MMR) increased from 24% at 6 months and 39% at 12 months to the best observed MMR rate of 86%. None of the patients with documented MMR at 12 months progressed to accelerated or blast phase. Among the 359 patients who crossed over from interferon-α plus cytarabine to imatinib, 93% experienced a complete hematologic response (CHR), 86% a major cytogenetic response (MCyR), and 81% a complete cytogenetic response (CCyR) after a medial follow-up of 54 months.[7] Estimated rates of freedom from progression and overall survival were 91% and 89%, respectively, after 48 months.

Imatinib is well tolerated. The most commonly reported nonhematologic adverse events are edema, muscle cramps, diarrhea, nausea, musculoskeletal pain, rash, abdominal pain, fatigue, and headache, but none of these led to discontinuation of treatment. In the IRIS trial, the most frequently reported grade 3 or 4 hematologic toxicities were neutropenia (17%), thrombocytopenia (9%), and anemia (4%).[5] Hypophosphatemia, with associated changes in bone and mineral metabolism, has been noted in a small group of patients.[8] Congestive heart

failure and cardiotoxicity associated with long-term imatinib treatment was reported.[9] However, this seems to be rare, as shown by the analysis of 1276 patients treated with imatinib at MD Anderson Cancer Center.[10] After a median follow-up of 47 months, 22 (1.7%) patients were found to have congestive heart failure during imatinib therapy.[10] Of these patients, 13 had received prior treatment with cardiotoxic drugs and likely had preexisting conditions predisposing them to congestive heart failure.

High-Dose Imatinib—Most patients retain variable levels of residual molecular disease at the 400-mg dose of imatinib, and therefore several studies have evaluated the efficacy of high-dose imatinib in newly diagnosed patients.

The single-arm trial Rationale and Insight for Gleevec High-Dose Therapy (RIGHT) showed that among 115 patients with newly diagnosed CML, the CCyR and MMR rates were higher with the 400-mg twice-daily dosage than those with the 400-mg daily dosage reported in the IRIS trial.[11,12] At 18 months, MCyR and CCyR rates were 90% and 85%, respectively, compared with the estimated 85% and 69% rates for standard-dose imatinib previously published in the IRIS trial. At 12 months the MMR rate was 54% compared with an estimated 39% for standard-dose imatinib seen in the IRIS study. Grade 1 to 2 toxicities and grade 3 to 4 adverse events were higher among patients receiving high-dose imatinib compared with those treated with standard-dose imatinib in the IRIS trial. Although high-dose imatinib resulted in rapid and deep responses, most of the patients (70%) enrolled in this study were low risk based on Sokal score.

The investigators of the TIDEL (Therapeutic Intensification in De Novo Leukemia) trial also reported superior responses (MMR at 12 and 24 months was 55% and 77%, respectively) in patients receiving 600 mg of imatinib as the initial dose compared with those receiving less than 600 mg (MMR at 12 and 24 months was 32% and 53%, respectively).[13]

In a phase II trial conducted by the GIMEMA CML working party, high-dose imatinib also induced rapid cytogenetic and molecular responses in patients with intermediate Sokal risk.[14] The response rates at 12 months were better than those documented in the IRIS study for patients with intermediate risk treated with 400 mg of imatinib. A phase III study conducted by European LeukemiaNet (ELN), which randomized patients with high Sokal risk to 400 or 800 mg of imatinib, showed no significant difference between the groups in terms of CCyR and MMR rates at 12 months (Table 1).[15]

The prospective randomized phase III TOPS (Tyrosine Kinase Inhibitor Optimization and Selectivity) trial compared the efficacy of high-dose and standard-dose imatinib in 476 patients with newly diagnosed CP-CML.[16] Results showed that high-dose imatinib induced more rapid responses than standard-dose. At 6 months, MMR and CCyR rates were significantly higher among patients assigned to 800 mg of imatinib than among those on 400 mg. However, at 12 months, MMR (46% vs. 40%) and CCyR (70% vs. 66%) rates were comparable between the arms (Table 1). Grade 3 or 4 hematologic adverse events were higher in patients assigned to 800 mg, and half of the patients required dose reduction to less than 600 mg. The MMR rate correlated with average dose intensity in this arm. At 12

months, MMR was observed in 62% patients with an average dose intensity of 600 to 799 mg/d, and in 38% of patients with an average dose intensity of 400 to 599 mg/d.[16] These data suggest that patients who can tolerate high-dose imatinib can experience superior cytogenetic and molecular responses compared with those who need dose reductions. The estimated progression-free survival rates at 18 months for 800 and 400 mg were 97% and 95%, respectively. No significant difference in CCyR and MMR rates were seen between the arms according to Sokal risk scores. The progression-free survival rate was slightly higher for patients with high Sokal risk receiving 800 mg than for those assigned to 400 mg (96% vs. 88%, respectively).

The German CML IV study also reported significantly faster response rates with 800 mg of imatinib compared with 400 mg of imatinib and 400 mg of imatinib plus interferon.[17] More rapid achievement of MMR with 800 mg of imatinib was observed in patients with low and intermediate risk, but not in those with high risk. MMR rates at 12 months were 56%, 31%, and 33% for low-, intermediate-, and high-risk groups, respectively. The overall survival (92%) and progression-free survival (88%) rates at 5 years were not different between treatment arms (Table 1).

Does High-Dose Imatinib Have a Role?

Efficacy: In newly diagnosed patients, high-dose imatinib induces higher and faster incidences of CCyR and MMR compared with standard-dose imatinib early on, but no difference in response rates were seen at 12 months.[11–17] None of the studies showed that 800 mg of imatinib had lower rates of disease progression than standard-dose imatinib, despite improved early responses.

Toxicity: High-dose imatinib is associated with higher rates of dose interruption, reduction, and discontinuation in a substantial number of patients because of grade 3 or 4 adverse events.

Conclusions—When data are presented in the form of intent-to-treat analysis, high-dose imatinib does not appear superior to standard-dose imatinib. This is confounded by the fact that more patients in the high-dose arm require dose reduction for toxicity. However, patients who can actually tolerate the higher dose of imatinib clearly experience better response rates than those receiving the standard dose. Currently, high-dose imatinib is not recommended as initial therapy for patients with newly diagnosed CML.

Dasatinib

Dasatinib is a potent, orally available ABL kinase inhibitor. It binds to both the active and inactive conformation of the ABL kinase domain and has in vitro activity against nearly all imatinib-resistant *BCR-ABL* mutations except *T315I*.[18] It also inhibits the Src family of kinases, PDGFR, and KIT. In a 2-arm phase II trial, dasatinib induced rapid responses in patients with early CP-CML.[19] In historical comparison, the CCyR rates at 3, 6, and 12 months were comparable to those achieved with high-dose imatinib and better than those achieved with standard-dose imatinib. No significant differences were seen in response rate and toxicity between the arms (100 mg once daily or 50 mg twice daily).

The DASISION study (Dasatinib versus Imatinib Study in Treatment-Naive CML Patients) compared dasatinib and imatinib in patients with newly diagnosed CP-CML.[20] In this study, 519 patients were randomized to receive dasatinib (100 mg once daily; 259 patients) or imatinib (400 mg once daily; 260 patients). CCyR rate at 12 months was the primary end point. After a minimum follow-up of 12 months, the MMR and confirmed CCyR rates were higher with dasatinib than imatinib (46% vs. 28%, and 77% vs. 66%, respectively). The rates of CCyR at 3, 6, and 9 months after initiation of therapy were 54%, 73%, and 78%, respectively, for dasatinib compared with 31%, 59%, and 67%, respectively, for imatinib. The rates of MMR at 3, 6, and 9 months after dasatinib treatment were 8%, 27%, and 39%, respectively, compared with 0.4%, 8%, and 18%, respectively, for imatinib. Although a trend was seen in favor of dasatinib, progression to the accelerated or blast phase was not statistically different between the groups, with 5 patients on dasatinib (2%) and 9 patients on imatinib (3.5%) meeting the definition of progression. At 18 months, the overall survival rate was 98% and 96% for dasatinib and imatinib, respectively; the rate of confirmed CCyR at 18 months continued to be higher for dasatinib than for imatinib (78% vs. 70%, respectively); the rates of progression-free survival at 18 months were 95% for dasatinib and 94% for imatinib.[21] The rate of MMR at any time was also higher for dasatinib than for imatinib (57% and 41%, respectively). The response rates were also higher across all risk groups for dasatinib. The CCyR and MMR rates were 73% and 51%, respectively, for dasatinib among high-risk patients. The corresponding rates were 64% and 30%, respectively, for imatinib in the same patient population.

In the Intergroup phase II randomized trial (S0325), 100 mg of dasatinib induced deeper molecular responses (3-log reductions in *BCR-ABL* transcript level) at 12 months compared with 400 mg of imatinib (59% vs. 43%) in patients with newly diagnosed CP-CML.[22] Follow-up is ongoing to evaluate whether the short-term deeper molecular response will translate into improved long-term outcomes.

Nilotinib

Nilotinib is an orally available, highly selective inhibitor of BCR-ABL tyrosine kinase that is more potent than imatinib. As with dasatinib, nilotinib is also active against nearly all imatinib-resistant *BCR-ABL* mutations except *T315I*.[23] In phase II studies, 400 mg of nilotinib given twice daily as first-line therapy induced high rates of CCyR and MMR in patients with early CP-CML, with most patients reaching these responses early during their therapy.[24,25]

In the ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials Newly Diagnosed Patients) study, the efficacy and safety of nilotinib (300 mg twice daily, n = 282; or 400 mg twice daily, n = 281) were compared with those of imatinib (400 mg once daily, n = 283) in patients with newly diagnosed CP-CML.[26] MMR rate at 12 months was the primary end point. At 12 months, the rates of MMR for nilotinib were 44% for the 300-mg dose and 43% for the 400-mg dose versus 22% for imatinib. The CCyR rates by 12 months were also higher for nilotinib than for imatinib (80% for the 300-mg dose and 78% for the 400-mg dose vs. 65% for imatinib). Patients receiving nilotinib at either of the 2 dose levels had a significant improvement in the time to progression to the accelerated or blast phase

compared with those receiving imatinib. The rate of progression to accelerated or blast phase was 4% with imatinib and less than 1% with nilotinib ($P = .01$ for 300 mg and $P = .004$ for 400 mg). With a median follow-up of 18 months, the overall best MMR rate was superior for nilotinib at either dose level (66% for 300 mg and 62% for 400 mg) compared with imatinib (40%), and the corresponding CCyR rates were 85%, 82%, and 74%, respectively. The estimated overall survival rates at 18 months were 98.5%, 99%, and 97%, respectively, for 300 mg of nilotinib, 400 mg of nilotinib, and imatinib.[27] Superior rates of CCyR and MMR were observed in both nilotinib arms compared with the imatinib arm across all Sokal risk groups (see Table 2 for the calculation of relative risk). Among patients with a high Sokal risk, CCyR rates by 12 months were 74%, 63%, and 49%, for patients receiving 300 mg of nilotinib, 400 mg of nilotinib, and imatinib, respectively. MMR rates at 18 months in these patients were 59%, 51%, and 28%, respectively, for the 3 treatment arms. Among the 3 study groups, nilotinib, 300 mg daily, had the lowest rates of discontinuation from adverse events or laboratory abnormalities.

Are Early Short-Term End Points Good Enough to Recommend Second-Generation TKIs at Diagnosis?

Although most patients experience response to imatinib, some may experience a loss of response or discontinue treatment from drug toxicity, also referred to as intolerance. Data from the recent randomized, phase III, first-line therapy studies have shown that patients with CP-CML randomized to either dasatinib or nilotinib met their study-specific end points more frequently than those treated with imatinib. Nilotinib, 300 mg twice daily, and dasatinib, 100 mg daily, are now approved by the FDA for the treatment of adults with newly diagnosed Ph-positive CP-CML. However, the efficacy evidence supporting the use of dasatinib and nilotinib as first-line therapy are based on early, short-term end points.

Efficacy—Quicker and better CCyR and MMR rates observed in the 2 studies favor the second-generation TKIs over imatinib (Table 3). Earlier studies have suggested that achievement of CCyR on imatinib is a major prognostic factor for overall and progression-free survival,[5,6,28] and that early molecular response is predictive of long-term disease stability with lack of progression and durability of CCyR.[29–31] Interestingly, CCyR was rare in patients treated with interferon (and MMR was not even established during the interferon era); however, in rare patients with a sustained CCyR, not only was discontinuation of interferon possible but also many patients have remained recurrence-free several years off therapy.[32–34] Improved long-term outcomes using the response criteria of CCyR at 12 months have not yet been established with TKI therapy. Failure of response to imatinib (based on follow-up from the IRIS trial) is characterized by the lack of CCyR at 18 months.

Most patients who have clinically undetectable levels of *BCR-ABL* transcripts according to the most sensitive polymerase chain reaction (PCR) measures have residual disease (that may eventually lead to disease relapse), supporting the notion that the currently approved TKIs do not completely eradicate CML in most patients (Figure 1). Currently no reliable predictive assays exist to assess the effect of therapy on minimal residual disease or to identify the patient population who may be at high risk for disease progression. In the absence of these biologic assays, lack of disease progression is an important end point and,

if quantified, may be the best indicator that TKI therapy is really impacting the biology of the disease. Disease transformation is associated with a poor outcome. The risk of transformation is highest during the first 3 years of TKI therapy. The rate of disease progression to accelerated or blast phase was significantly lower for nilotinib (1% vs. 4% for imatinib) and no patients with low Sokal risk have progressed at 18 months.[26] A trend was seen for a similar difference with dasatinib (Table 3).

Safety—Both phase III studies support the finding that each of the 3 TKIs is fairly well tolerated. Drug-related adverse events were primarily grade 1 or 2, and grade 3 or 4 nonhematologic adverse events were uncommon in both studies.

In the DASISION study, grade 3 or 4 neutropenia and anemia occurred with similar frequency among patients receiving dasatinib and imatinib, whereas thrombocytopenia was more frequent with dasatinib (Table 4).[20] Nonhematologic adverse events, except pleural effusions, were more frequent with imatinib. Pleural effusions, although infrequent, were reported only with dasatinib. Overall, the rates of therapy discontinuation due to drug-related side effects were similar among patients receiving dasatinib and imatinib (5% and 4%, respectively).

In ENESTnd study, the nonhematologic adverse events of nausea, diarrhea, vomiting, muscle spasm, and edema of any grade were higher for patients receiving imatinib. Conversely, rates of rash, headache, and alopecia were higher with nilotinib at both dose levels. Grade 3 or 4 neutropenia was more frequent in the imatinib group, whereas thrombocytopenia and anemia were similar in all groups (Table 5).[26] Electrolyte abnormalities were more frequent with nilotinib at both dose levels than with imatinib. The rates of discontinuations because of adverse events were slightly higher for those receiving 400 mg of nilotinib and imatinib (9% and 7%, respectively) compared with 5% among those receiving 300 mg of nilotinib.

All TKIs have effects on QTc interval prolongation, but only the nilotinib labeling contains a black box warning regarding the risk of QTc interval prolongation, because sudden cardiac death has been reported in patients receiving nilotinib. Although no patient in the ENESTnd study had a QTc interval corrected for heart rate of more than 500 ms, electrocardiograms are recommended at baseline, 7 days after initiation, and periodically thereafter during nilotinib treatment.

Knowing that both second-generation TKIs have very good efficacy in the up-front setting, differences in their potential toxicity profiles may be helpful when choosing a second-generation TKI over imatinib as first-line therapy. In general, the choice of first-line therapy in a given patient may depend on physician's experience, the patient's age and ability to tolerate therapy, and the presence of comorbid conditions. For example, based on the toxicity profile, nilotinib may be preferred for patients deemed to be at risk for developing pleural effusions. Alternatively, dasatinib may be preferred in patients with a history of pancreatitis or hyperglycemia.

Practical Issues—The recommended starting dose of imatinib is 400 mg daily and the starting dose of dasatinib from the DASISION study is 100 mg daily, whereas the recommended dose of nilotinib is 300 mg twice daily in the ENESTnd study. The twice-daily dosing schedule of nilotinib may have more issues with patient compliance than the once-daily dosing of imatinib and dasatinib. Another factor that may impact compliance is the recommendation that food should not be consumed from 2 hours before and 1 hour after nilotinib dosing because of increased bioavailability after food consumption. The concern is that the increased bioavailability may have an adverse effect on QTc prolongation. Electrocardiogram monitoring at regular intervals is recommended for those receiving nilotinib, and careful attention to correcting electrolyte abnormalities, such as hypokalemia and hypomagnesemia, is also recommended.

NCCN Recommendations

- Imatinib (400 mg daily) is still considered a reasonable first-line therapy choice for patients with newly diagnosed CP-CML. Given the recent data showing superior efficacy of nilotinib and dasatinib in these patients, high-dose imatinib currently has only a limited role in first-line therapy.
- Second-generation TKIs should be strongly considered as first-line therapy for intermediate- to high-risk patients based on Sokal or Hasford score (Table 2). This recommendation is based on limited data indicating that these agents are associated with lower risk of disease progression in this patient population. Long-term follow-up is needed to determine whether second-generation TKIs should be implemented as standard first-line therapy in such a risk-adapted fashion.
- Switching to dasatinib (100 mg daily) or nilotinib (300 mg twice daily) is recommended in select patients who are not able to tolerate imatinib because of grade 3 or 4 acute nonhematologic toxicities, or a change should be considered for evidence of chronic and persistent grade 1 or 2 nonhematologic toxicities.
- Because no data exist regarding the time points for monitoring response to second-generation TKIs, the panel currently believes that physicians should monitor patients for response and toxicities when using second-generation TKIs, following the guidelines recommended for imatinib (Table 6). Further follow-up of the ENESTnd and DASISION trials will likely lead to clearer definitions of response failure to second-generation TKIs used in frontline therapy.

Second-Line Treatment: Second-Generation TKIs vs. High-Dose Imatinib

Dasatinib

The START (SRC/ABL Tyrosine kinase inhibition Activity: Research Trials of dasatinib) program trials evaluated the safety and efficacy of dasatinib, 70 mg twice daily, in patients who did not respond to prior imatinib therapy because of resistance or intolerance across all phases of CML.

Chronic Phase—Dasatinib showed significant efficacy in the second-line setting in patients with CP-CML in the START-C trial (n = 387).[35,36] The primary end point was

MCyR rate. Two-year follow-up data showed overall CHR, MCyR, CCyR, and MMR rates of 91%, 62%, 53%, and 47%, respectively. These responses were also durable, with 88% of patients maintaining MCyR at 24 months. The overall and progression-free survival rates were 94% and 80%, respectively.[37,38] At the time of switching, patients with a prior CCyR on imatinib had the highest rates of CCyR, MMR, and 2-year progression-free survival (84%, 75.5%, and 97%, respectively) compared with those with no CCyR on imatinib (50%, 35.5%, and 75.5%, respectively).[39]

In a recent dose-optimization phase III randomized study (CA180-034), patients with CP-CML who were resistant or intolerant to imatinib who received dasatinib, 100 mg once daily, experienced comparable CCyR (50% vs. 54%), MCyR (63% vs.61%), progression-free survival (80% vs. 76%), and overall survival (91% and 88%) rates at 24 months to those of patients who received dasatinib, 70 mg twice daily.[40] Dasatinib, 100 mg daily, was also associated with a lower incidence of any-grade pleural effusion and grade 3 or 4 thrombocytopenia; fewer patients required dose interruption, dose reduction, and toxicity-related discontinuation. The recommended starting dose is 100 mg once daily for patients with CP-CML who are resistant or intolerant to imatinib.

Accelerated and Blast Phases—Dasatinib was also clinically active and well tolerated in patients with accelerated-phase CML (AP-CML) and blast-phase CML (BP-CML).

In the START-A trial, with a median follow-up of 14 months, among patients with AP-CML, dasatinib induced major hematologic response (MaHR), CHR, MCyR, and CCyR in 64%, 45%, 39%, and 32% of patients, respectively.[41] At 24 months, MCyR was maintained in 61% of patients experiencing response. The 24-month progression-free and overall survival rates were 46% and 72%, respectively.[42]

In patients with BP-CML (START-B and START-L), the response rates depended on whether the patients were in myeloid blast phase (MBP) or lymphoid blast phase (LBP).[43] After a minimum follow-up of 12 months, MaHR, MCyR, and CCyR rates were 34%, 33%, and 26%, respectively, for patients with MBP. The corresponding response rates were 35%, 52%, and 46%, respectively, for those with LBP. However, patients with MBP had better median progression-free and overall survival (6.7 and 11.8 months, respectively) than patients with LBP (3.0 and 5.3 months, respectively).[43]

Recently, the results of phase III randomized studies showed that once-daily dosing of dasatinib at 140 mg has similar efficacy to the 70-mg twice-daily dosing with an improved safety profile in patients with AP-CML and BP-CML resistant or intolerant to imatinib.[44,45] Among patients with AP-CML, rates were comparable for MaHR (66% vs. 68%, respectively), MCyR (39% vs. 43%, respectively), 24-month progression-free survival (51% vs. 55%, respectively), and overall survival (63% vs. 72%, respectively) for patients receiving dasatinib, 140 mg once daily or 70 mg twice daily. Once-daily treatment was associated with an improved safety profile.[44] In patients with MBP-CML, the MaHR rate was 28% for both 140 mg once-daily and 70 mg twice-daily dasatinib. In patients with LBP-CML, the MaHR rates were 42% and 32%, respectively, for dasatinib at 140 mg once daily and 70 mg twice daily.[45] The MCyR rates were 25% and 28%, respectively, for patients in

MBP and 50% and 40%, respectively, for those with LBP. The progression-free and overall survival rates at 24 months were 24% and 28% for patients with MBP-CML, and the respective values in patients with LBP-CML were 21% and 16%.[45] The recommended starting dose of dasatinib is 140 mg once daily for patients with disease progression to accelerated or blast phase.

Nilotinib

Nilotinib for imatinib-resistant or -intolerant disease was evaluated at 400 mg twice daily in all phases of CML.

Chronic Phase—A phase II multicenter study (nilotinib 2101) evaluated the efficacy of nilotinib in 321 patients with CP-CML.[46,47] The rate of MCyR was the primary end point. Two-year follow-up data confirmed that nilotinib resulted in rapid and durable hematologic and cytogenetic responses.[48] Overall, MMR, MCyR, and CCyR occurred in 28%, 59%, and 44% of patients, respectively. The responses were durable, with 84% maintaining CCyR and 77% maintaining MCyR at 24 months. The estimated overall progression-free and overall survival rates at 24 months were 64% and 87%, respectively. At study entry, MCyR, MMR, and progression-free survival rates were higher in patients with CHR (73%, 38%, and 77%, respectively) compared with 52%, 22%, and 56%, respectively, among patients without CHR.

Accelerated and Blast Phases—After 12-months of follow-up, hematologic response was observed in 47% and MCyR in 29% of patients with AP-CML.[49] Long-term follow-up data confirmed that responses are durable, with 54% maintaining the hematologic response and 70% maintaining MCyR at 24 months.[50] Estimated overall survival at 24 months was 67%.

Nilotinib has also shown activity in patients with BP-CML. As with dasatinib, the response rates depend on the type of BP-CML. In a phase II study of 136 patients with BP-CML, CHR was seen at 24-month follow-up in 13% of patients with MBP and LBP.[51] MCyR was seen in 38% of patients with MBP and 52% of patients with LBP. CCyR was seen in 30% of patients with MBP and 32% of patients with LBP, respectively. The overall survival rates were 42% and 27% at 12 and 24 months, respectively. However, the responses were not durable. The duration of MCyR was 11 months for patients with MBP and 3 months for those with LBP.

High-Dose Imatinib

Dose escalation of imatinib up to 800 mg daily has been shown to overcome some of the primary resistance, but the duration of responses has typically been short.[52–54] The results of a recent study with a median follow-up of 61 months indicated that dose escalation induced CCyR in 52% of patients with cytogenetic failure and only in 5% of patients with hematologic failure on standard-dose imatinib.[55] The estimated 2- and 3-year event-free and overall survival rates were 57% and 47%, and 84% and 76%, respectively. Responses were also durable; 88% of patients with MCyR sustained their response beyond 2 years. Dose escalation was particularly effective in patients with cytogenetic relapse on standard-dose

imatinib. In this group of patients, CCyR and MCyR rates were 73% and 87%, respectively, compared with 52% and 60% for the group of patients with cytogenetic failure. In a retrospective analysis of 106 patients from the IRIS trial who received imatinib at a dose of 400 mg daily and subsequently underwent dose escalation to either 600 or 800 mg daily, the estimated progression-free survival rates at 12 and 36 months after the dose escalation were 94% and 89%, respectively.[56] These results support that dose escalation of imatinib is an appropriate option for patients in chronic phase experiencing suboptimal cytogenetic response or cytogenetic relapse.

The START-R trial evaluated the efficacy of imatinib (800 mg daily) and dasatinib (70 mg twice daily) in 150 patients with imatinib-resistant CP-CML.[57,58] At a minimum follow-up of 2 years, dasatinib showed higher rates of CHR (93% vs. 82%), MCyR (53% vs. 33%), CCyR (44% vs. 18%), and MMR (29% vs. 12%) relative to high-dose imatinib. Responses with dasatinib were also durable, with 90% of patients maintaining a MCyR at 18 months compared with 74% of patients treated with high-dose imatinib.[58] The estimated progression-free survival at 2 years was higher with dasatinib (86%) relative to high-dose imatinib (65%), indicating that dasatinib is an effective treatment for patients with CP-CML resistant to conventional imatinib doses.

Selection of Second-Line Therapy

High-Dose Imatinib—In the initial report from the START-R trial, dasatinib was clearly superior to imatinib, 800 mg, in patients for whom treatment with 600 mg of imatinib failed, whereas response rates were equivalent for both treatment arms in patients for whom treatment with 400 mg of imatinib failed.[57] However, the 2-year follow-up data suggest that dasatinib is clearly superior to imatinib, 800 mg, in patients resistant to imatinib at doses of 400 or 600 mg daily.[58] Dose escalation of imatinib is also unlikely to benefit those with hematologic resistance or those who never had a cytogenetic response with standard-dose imatinib. Dose escalation of imatinib might be beneficial for patients with suboptimal response to imatinib, 400 mg daily (see Suboptimal Response, page S-14).

Second'Generation TKIs—Dasatinib and nilotinib have been found to be effective and well-tolerated in patients who develop resistance or intolerance to imatinib. Dasatinib is approved for treatment of these patients in all phases of CML, whereas nilotinib is approved for treatment of these patients with CP- or AP-CML. Substantial long-term efficacy and safety data are available for dasatinib and nilotinib in patients for whom treatment with imatinib fails, but no randomized comparison has been performed between the agents. Therefore, the panel believes that differences in safety profiles and activity against specific mutations should be considered when choosing between dasatinib and nilotinib.

Efficacy—Among patients with CP-CML, the overall MCyR rates for dasatinib and nilotinib at the currently recommended doses were 63% and 59%, respectively, at 24-month follow-up.[37,40,48] MCyR rates were similar in imatinib-resistant patients, whereas the corresponding response rates were higher with dasatinib in the imatinib-intolerant patients in all phases of CML (Table 7). The lower response rates with nilotinib seen in the imatinib-intolerant patients may be because imatinib-intolerant patients with prior MCyR were

excluded from nilotinib trials. The overall progression-free survival rates for dasatinib and nilotinib are 80% and 64%, respectively, at the currently recommended doses. The rate of progression to accelerated or blast phase was less than 3% for dasatinib at 36 months follow-up. Most patients who experienced progression while receiving dasatinib remained in chronic phase.[40]

Among patients with AP-CML, the overall 24-month MCyR rates were 39% and 32%, and the overall survival rates were 72% and 67% at the currently recommended doses of dasatinib and nilotinib, respectively. MCyR and CCyR rates were higher for dasatinib in both imatinib-resistant and imatinib-intolerant patients with AP-CML (Table 8).

Toxicity—Most of the adverse events were grade 1 or 2 and were manageable with dose reduction or interruption and appropriate supportive care (Table 9). Cross-intolerance profile of dasatinib and nilotinib in imatinib-intolerant patients also must be considered. Among imatinib-intolerant patients with CP-CML, those who switched to dasatinib because of nonhematologic intolerance had the highest CCyR, MMR, and 2-year progression-free survival rates (78.9%, 60.1%, and 94.4%, respectively) compared with those with hematologic intolerance (43.5%, 28.3% and 68% respectively).[39] Nilotinib has minimal cross-intolerance in imatinib-intolerant patients in chronic and accelerated phase. Thrombocytopenia was the only hematologic toxicity leading to imatinib intolerance that recurred with any significant frequency during nilotinib therapy.[59]

Dasatinib at 70 mg twice daily was associated with significantly higher rates of myelosuppression, pleural effusion, and bleeding. The incidences of myelosuppression and pleural effusion were significantly lower with dasatinib, 100 mg daily.[60] Pleural effusions during dasatinib therapy increased in patients with advanced disease. A history of cardiac disease, hypertension, and use of a twice-daily schedule were identified as factors associated with development of pleural effusions.[61] Close monitoring and timely intervention are necessary for patients at risk for developing pleural effusions. Lymphocytosis from the clonal expansion of natural killer/T cells has been reported during dasatinib treatment in patients in all stages of CML who are resistant or intolerant to imatinib, and lymphocytosis has been associated with increased incidence of pleural effusion.[62] Cytogenetic response rates to dasatinib were shown to be higher in this group of patients.[60,63] Similar effects were observed among patients treated with dasatinib as first-line therapy in the DASISION study.[64] Further studies are needed to confirm these preliminary findings.

Nilotinib has been known to cause QTc interval prolongation. In patients with CP-CML, QTc interval prolongation exceeding 500 ms occurred in 1% of patients.[47] Among patients with AP-CML, none experienced a prolongation exceeding 500 ms; increases in the QTc interval from baseline of more than 60 ms were observed in 4% of patients.[49] The ENACT trial, a phase III multicenter open label trial in imatinib-resistant or -intolerant patients in all CML phases, also reported very low incidences of QTc prolongation exceeding 500 ms.[65] Nevertheless, the prescribing information for nilotinib carries a black box warning for QTc prolongation. Food should not be consumed from 2 hours before to 1 hour after nilotinib dosing because of increased bioavailability after food consumption and this may have an adverse effect on QTc prolongation. Therefore, monitoring of electrocardiograms at

baseline, 7 days after initiation, and periodically thereafter is recommended for all patients receiving nilotinib. In addition, careful monitoring and correction of electrolyte abnormalities is required.

Activity Against BCR-ABL Mutations—Point mutations in the ABL kinase domain are emerging to be the major mechanism of resistance to imatinib.[66,67] The presence of the *T315I* mutation confers the highest resistance to all of the currently approved TKIs, and is associated with disease progression and poor survival depending on the phase of CML.[68–70] In addition to *T315I*, available evidence (although limited) supports the emergence of other *BCR-ABL* mutations resistant to dasatinib and nilotinib.[71,72] *F317L*, *V299L*, and *T315A* mutations are highly resistant to dasatinib, whereas the mutations *Y253H/F*, *E255K/V*, and *F359* confer a high degree of resistance to nilotinib. Inhibitory concentration (IC_{50}) values of TKIs against kinase domain mutations in vitro have been reportedly useful for predicting response to therapy and long-term outcome, especially in patients with CP-CML receiving second-generation TKIs after imatinib failure.[73] Among 169 patients in whom mutations were detectable after imatinib failure, response and event-free survival rates were higher in those with low IC_{50} mutations than in those with intermediate or high IC_{50} mutations. Overall survival was not dependent on the IC_{50} values. Among patients with advanced phases, the in vitro sensitivity of mutations had minimal or no impact on survival.[73]

In the START-C trial, among patients in whom baseline data on mutations were available, *T315I*, *Y253H/F*, *E255K/V*, *F317L*, and *F359* mutations were identified in 2%, 9%, 4%, 3%, and 5% of patients, respectively. *V299L* or *T315A* mutations were not detected at baseline.[74] The rates of CCyR were 69%, 40%, and 50%, respectively, for patients with mutations *Y253H/F*, *E255K/V*, and *F359*. No patients with *F317* and *T315I* mutation experienced a CCyR. These findings were also confirmed in an analysis of 1043 imatinib-resistant patients.[75] After 2 years of follow-up, dasatinib treatment (at all doses) of imatinib-resistant patients with or without a mutation induced comparable response (CCyR, 43% vs. 47%, respectively; MCyR, 55% vs. 58%, respectively) and progression-free survival rates (70% vs. 80%).[75] High response rates were observed in patients with the highly imatinib-resistant mutations, including *L248*, *Y253*, *E255*, *F359*, and *H396*, in addition to other common mutations in *G250* and *M351* (Table 10). The response rates for patients with nilotinib-resistant mutations *Y253H*, *E255K/V*, and *F359V/C* were 61%, 38%/36%, and 60%/52%, respectively. The presence of *T315I* and *F317L* mutations at baseline was associated with less favorable responses. Other studies have also reported similar findings in patients with *F317* mutations at baseline; the outcome is dependent on the CML phase, and the *F317* mutation was sensitive to other TKIs.[76,77]

In an analysis of patients enrolled in the pivotal phase II trials of nilotinib, significant responses were achieved in patients without baseline mutations and in those who harbored mutations with high in vitro sensitivity to nilotinib.[78] After 12 months of therapy, MCyR, CCyR, and MMR were achieved in 60%, 40%, and 29% of patients without baseline mutations, versus 49%, 32%, and 22% of patients with mutations, respectively. *E255K/V*, *T315I*, *F359C/V*, *G250E*, and *Y253H* mutations were identified in 7%, 6%, 4%, 4%, and 3% of imatinib-resistant patients.[78] *T315I*, *Y253H*, *E255K/V*, and *F359V/C* mutations were associated with lower response rates and high risk of disease progression (Table 10). None

of the patients experienced a CCyR within 12 months of therapy.[78] *E255V/K* and *F359V/C* were associated with a high rate of disease progression (86% and 92%, respectively). These mutations were also associated with less durable responses and shorter event-free survival in patients with AP-CML.

NCCN Recommendations

- Dasatinib or nilotinib are equally effective for treating patients in whom first-line imatinib therapy failed because of resistance or intolerance. The panel believes that not enough data are currently available to recommend one over the other as the preferred second-line therapy based on efficacy data.
- Dasatinib and nilotinib are recommended as options for patients with CP-CML for whom standard-dose imatinib fails (less than CHR at 3 months, no cytogenetic response at 6 months, minor or no cytogenetic response at 12 months, or less than CCyR at 18 months) or for those with disease progression to accelerated or blast phase.
- Dose escalation of imatinib may be an appropriate option for a subset of patients with cytogenetic failure and a previous cytogenetic response to standard-dose imatinib.
- Dasatinib potentially inhibits Src family of kinases, the activation of which has been implicated as a mechanism of BCR-ABL–independent imatinib resistance, suggesting the presence of a trend toward better clinical outcome with dasatinib in an imatinib-resistant population.
- Mutational analysis at the time of imatinib failure provides additional guidance in the selection of optimal second-line TKI therapy only in patients with identifiable mutations. Mutation testing is recommended before switching to second-line TKI. However, selection of second-line TKI therapy based on mutational analysis should be individualized.
- In patients with no identifiable mutations, the panel recommends that the following issues be considered in choosing a second-line therapy: prior response to imatinib therapy, TKI therapy used in the first-line setting, the safety profile of each agent, patient's comorbid conditions, patient compliance, and physician's experience.

Suboptimal Response

The ELN guidelines published in 2006 defined suboptimal responses to imatinib as less than a CHR at 3 months, less than an MCyR at 6 months, less than a CCyR at 12 months, or less than an MMR at 18 months.[79] In the updated guidelines published in 2009, suboptimal response is defined as no cytogenetic response at 3 months, less than a partial cytogenetic response (PCyR) at 6 months, a PCyR at 12 months, and less than an MMR at 18 months (Table 11).[80] Patients with suboptimal response are described as those who "may still have a substantial benefit from continuing imatinib but that the long-term outcome is not likely to be optimal, so the patient becomes eligible for other treatments." However, the ELN does not recommend automatically changing therapy for a suboptimal response.

Suboptimal response to imatinib could result from many factors, including poor compliance to imatinib therapy, individual variation in drug metabolism, aberrant expression of drug transporters, and differences in the intrinsic biology of disease, which might result in competition between clones highly sensitive to imatinib and those that are resistant. These possibilities are not mutually exclusive.

Compliance to Therapy

In the ADAGIO (Adherence Assessment with Glivec: Indicators and Outcomes) study, which evaluated the outcomes of nonadherence to imatinib therapy in patients with CML, nonadherence was associated with poorer response to imatinib.[81] Patients with suboptimal response had significantly higher mean percentages of imatinib not taken (23%) than did those with optimal response (7%). The data from Hammersmith hospital showed a strong correlation between adherence rate and the 6-year probability of achieving a MMR (94.5% for patients with a greater than 90% adherence rate compared with 28% for those with an adherence rate of 90% or less).[82] Adherence was identified as the only independent predictor for achieving a complete molecular response (CMR) on standard-dose imatinib and MMR on high-dose imatinib.

Poor adherence to imatinib can also have an impact on imatinib plasma levels, which in some studies have been shown to correlate with response to therapy in patients taking a standard dose of imatinib.[83] In the IRIS study, maintaining an imatinib trough level at or higher than 1000 ng/mL was important for achieving CCyR.[84] Initial results of the TIDEL II trial showed that selective dose escalation may be able to overcome the adverse prognostic impact of low plasma concentrations of standard-dose imatinib and result in reduction in BCR-ABL transcript levels.[85] The long-term follow-up is ongoing.

Aberrant Expression of Drug Transporters

The expression of human organic cation transporter-1 (hOCT-1) has also been correlated with response to imatinib. Imatinib uptake into a CML cell line with high hOCT-1 expression was greater than into cell lines with modest or low expression.[86] Higher activity of hOCT-1 is associated with excellent molecular response irrespective of dose, whereas response was highly dose-dependent in patients with low hOCT-1 activity.[87,88] Most patients with suboptimal response to imatinib have been reported to have low hOCT-1 activity. In the updated analysis of patients enrolled in the TIDEL II trial, MMR rate at 60 months was higher for patients with high hOCT-1 activity compared with those with low hOCT-1 activity (89% vs. 55%, respectively).[85] These differences were highly significant in patients who averaged less than 600 mg/d of imatinib.

Notably, cellular uptake of dasatinib or nilotinib seems to be independent of hOCT-1 expression.[89–91] Thus, preliminary findings suggest that patients with low hOCT-1 expression might have better outcomes with imatinib dose escalation, dasatinib, or nilotinib.

Genetic Heterogeneity and Clonal Competition

Suboptimal response could arise from the intrinsic progression program characteristic to CML. Uninhibited *BCR-ABL* drives the genetic changes that cause progression to advanced-

phase disease. Therefore, some patients at diagnosis will already have substantial changes in their genome, while appearing to be in chronic phase. The major change in expression has been shown to be produced by the transition from chronic to accelerated phase, and that in resistant patients in chronic phase, gene expression signatures are very similar to those in patients in accelerated phase.[2,92] Thus, suboptimal response could be derived from clones that have genetic changes associated with progression, and thus a relatively resistant phenotype, despite the gross pathologic characteristics of chronic phase.

In addition, the development of the *BCR-ABL* kinase domain mutations may contribute to suboptimal response. A rising *BCR-ABL* level has been associated with an increased risk of *BCR-ABL* mutations, a high risk of progression, and a risk for molecular relapse.[93–98] Imagine that at diagnosis a patient has 2 clonal populations, with the dominant clone sensitive to imatinib and the minor clone resistant. With the selective pressure of imatinib, and the dominant clone declines but the selective clone increases; the result is that the total number of CML cells decline, but slowly, as the sensitive clonal population is replaced by the resistant population.

Dasatinib and nilotinib have been effective against many of the imatinib-resistant BCR-ABL mutations.[75,78] However, no strong data support that treating suboptimal response or molecular relapse with a second-generation TKI will have any impact on the long-term clinical outcome.

Conclusions

Assessment of adherence to therapy and implementation of interventions in patients with poor adherence may improve clinical outcomes." Evaluation of hOCT-1 expression may be reasonable in patients receiving imatinib. Mutation analyses in patients with suboptimal response may be helpful in the selection of alternate therapy.

The prognostic implications of suboptimal response may also be different depending on the time point. Thus, the outcomes of patients with suboptimal response at 6 months are more similar to those of patients who met the criteria for failure, whereas the outcomes of patients with a suboptimal response at 18 months are very similar to those of patients with an optimal response. Some studies suggest that patients with a suboptimal response at 12 months have a poor prognosis more similar to that of patients who meet criteria for failure, and others have shown that these patients have an outcome closer to that of patients with an optimal response, with a similar transformation-free survival but worse event-free survival.[100–102]

Available data suggest that patients with suboptimal response represent a subgroup that requires careful monitoring and may benefit from alternate treatment options. A few early reports have suggested that dose escalation of imatinib to 800 mg as tolerated[100,103–105] or switching to dasatinib[40,106] or nilotinib[105,107,108] are effective strategies in patients with suboptimal response to standard-dose imatinib.

NCCN Recommendations

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Chronic Myelogenous Leukemia have incorporated patients who meet the ELN criteria for suboptimal response: minor cytogenetic response at 6 months and partial cytogenetic response at 12 months (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). Continuation of the current TKI therapy at the same dose or dose escalation of imatinib to 800 mg as tolerated are included as options for this group of patients. The panel currently feels that no strong evidence exists showing that a change of therapy would improve response rate among patients with suboptimal response. NCCN supports trials that study whether intervention for suboptimal response or molecular relapse affects short- and long-term outcomes.

Can TKI Therapy Ever be Discontinued?

TKI therapy has become the standard therapy for patients with CML. Extended follow-up data from the IRIS trial showed that the *BCR-ABL* levels continued to decline in many of the patients, and that the number of patients attaining undetectable *BCR-ABL* levels increased between 3 and 6 years of imatinib treatment.[109] However, the disease usually relapses if imatinib is stopped even in patients who experience CMR,[110] although there have been anecdotal reports of no subsequent relapse after discontinuation of imatinib therapy.[111,112]

Results from 2 ongoing studies have shown that that imatinib can be safely discontinued in some patients in stable CMR for 2 years or more with close molecular monitoring.[113,114] Ross et al.[114] reported that the rate of sustained CMR after 12 months off treatment was 67% for the entire cohort (n = 18; 5 patients had received only imatinib and 13 patients had received interferon followed by imatinib). However, the sample size was small and the median follow-up was only 7 months for patients who had received only imatinib. In the Stop Imatinib (STIM) study, among 69 patients who had a follow-up of more than 12 months, 39% remained in CMR and 58% experienced relapse within 6 months after discontinuation of imatinib. The molecular relapse-free survival was 41% and 38%, respectively, at 1 and 2 years.[113] All patients who had a molecular relapse responded to reintroduction of imatinib, suggesting that discontinuation did not lead to acquired resistance.

Low Sokal risk score, male sex, and longer duration of imatinib treatment were identified as prognostic factors for the maintenance of CMR after withdrawal of imatinib.[113] The results of the STIM study suggest that discontinuation of imatinib may be possible only in patients with a sustained CMR (greater than 5-log reduction in *BCR-ABL* transcript levels and undetectable transcripts by reverse transcriptase-PCR) for at least 2 consecutive years on imatinib. Additional prospective studies are needed to confirm these initial findings.

NCCN Recommendations

- Currently, discontinuation of imatinib is not recommended outside the context of a clinical trial for patients experiencing response.

- In the absence of data from studies evaluating the possibility of discontinuing dasatinib and nilotinib in responding patients, the findings from the studies involving patients treated with imatinib should be extrapolated to patients undergoing second-generation TKI therapy.
- The panel believes evidence is insufficient to favor the continuation of TKI therapy during pregnancy. Potential benefit of TKI therapy for the mother or its potential risk to the fetus must be carefully evaluated on an individual basis.

Allogeneic Hematopoietic Stem Cell Transplant

Allogeneic hematopoietic stem cell transplant (HSCT) is a potentially curative treatment for patients with CML, but the excellent results with imatinib and other second-generation TKIs have challenged its role. The widespread application of allogeneic HSCT has been limited by donor availability and the high toxicity of the procedure in older patients. Ongoing advances in human leukocyte antigen (HLA) typing and the use of less-toxic regimens are broadening the use of HSCT. The advent of molecular DNA assessment of HLA typing has enabled a rigorous and stringent selection of unrelated matched donors, which has translated into greatly improved transplant outcomes, so that results with unrelated, fully matched donors are comparable to those of matched related donors.[115–117] Investigational approaches using nonmyeloablative (reduced-intensity conditioning) "mini transplants" are promising and show that molecular remissions may be achieved in patients with CML.[118–120]

Although TKI therapy has dramatically improved the outcomes of patients with CP-CML, its use in first-line treatment will fail in some patients because of intolerance or resistance, leading to disease progression. Patients with *T3151* mutation do not experience response to any of the currently approved TKI therapies. Second-generation TKIs are not very effective for managing patients with AP-CML or BP-CML.[121] Thus, allogeneic HSCT has a definite, though more limited, role in the management of patients with CML.[122]

Prognostic Factors

The outcome of allogeneic HSCT is influenced by several pretransplant variables, such as the disease phase, HLA matching, age, sex, and time from diagnosis to transplant.[123] Low HSCT comorbidity index (HCT-CI) and low C-reactive protein were recently identified as prognostic indicators for lower nonrelapsed mortality rate and a somewhat improved survival rate.[124] The disease phase at the time of transplant remains an important prognostic factor. Outcomes after transplant are clearly superior for patients in chronic phase than in those in advanced phase.[125]

Data from the International Bone Marrow Transplant Registry (IBMTR) between 1998 and 2008 show a probability of 3-year survival of 70% to 72% for patients who underwent a transplant in chronic phase and 45% to 56% for those who underwent a transplant in accelerated phase.[126] In the imatinib era, a significant improvement in survival occurred compared with previous time periods.[127] Survival has improved across all European Group for Blood & Marrow Transplantation (EBMT) risk groups because of significant reduction in treatment-related mortality and incidences of relapse.[128] However, survival is still poor

for patients undergoing a transplant in accelerated or blast phase (40%–47% and 16%, respectively) compared with 70% for those who underwent a transplant in chronic phase. Results from the German CML Study IV confirmed these findings.[129] In a subgroup analysis among 84 patients who underwent allogeneic HSCT because of either a high risk score at diagnosis, imatinib failure, or disease progression, the 3-year survival rates were 94% for patients with chronic phase and 59% for those with advanced phase (Figure 2).[129] Most patients in chronic phase underwent a transplant with an EBMT score equal to or higher than 3. Treatment-related mortality was 8%. Complete molecular remissions were observed in 88% of patients who underwent a transplant. A more recent report from the Center for International Blood and Marrow Transplant Research showed that patients who undergo allogeneic HSCT for CML in first chronic phase and experience remission for at least 5 years have favorable subsequent long-term survival.[130]

Effect of Prior TKI Therapy

Concern exists that previous imatinib therapy might have a detrimental effect on subsequent transplant outcomes, as was shown with busulfan and interferon.[131–133] However, results from several studies have confirmed that the use of imatinib before transplant was not associated with a significant increase in death, relapse rate, or nonrelapse mortality compared with no prior use.[134–138] In fact, the IBMTR data on 409 patients who received imatinib before transplantation and 900 who did not showed that prior use of imatinib was associated with improved survival for patients undergoing transplantation in chronic phase, although this was limited to patients who underwent a transplant because of intolerance to rather than failure of imatinib treatment.[136] This survival benefit was not seen in patients who underwent a transplant in advanced phase.

Some studies have also shown that the use of second-generation TKIs before allogeneic HSCT does not affect the outcome of transplant nor increase transplantrelated toxicity.[139–141]

When to Transplant in the TKI Era?

Given the successful induction of durable responses with imatinib in most patients, and the recent results showing superior early efficacy of nilotinib and dasatinib in newly diagnosed patients, allogeneic HSCT is no longer recommended as a first-line treatment option for patients with CP-CML. In a randomized study comparing primary HSCT and drug treatment in 621 newly diagnosed patients,[142] only 354 were eligible for HSCT based on the availability of a related donor; 123 underwent an HSCT, and 219 received the best possible drug treatment (interferon until imatinib became available later in the trial). Imatinib was offered to patients for whom treatment with interferon failed. Survival with drug therapy was clearly superior for the first 5 years. Survival differences were significant in low-risk patients and no survival difference was observed in intermediate- or high-risk patients.[142]

Allogeneic HSCT is the preferred option for first-line therapy in rare patients presenting with accelerated or blast phase disease at diagnosis, those who have the *T315I* mutation, and rare patients who are intolerant to all of the TKIs. A recent report from MD Anderson Cancer Center indicated that allogeneic HSCT is an effective strategy for patients with CML

who have the *T315I* mutation, particularly those in earlier stages. Patients who underwent a transplant in chronic phase had the best outcome.[143]

Allogeneic HSCT should be considered for patients with CP-CML for whom second-line TKI therapy has failed and for those who experience disease progression to accelerated or blast phase on TKI therapy. Treatment with an alternate TKI (not received before) may be beneficial as a bridge to transplantation.

Early cytogenetic response to second-line TKIs has been shown to predict survival and may help guide the timing of transplant in eligible candidates.[144,145] Among patients receiving dasatinib or nilotinib, those experiencing MCyR after 12 months of treatment had a significant survival advantage and significantly lower rates of progression than those experiencing minor cytogenetic response or only CHR.[144] Patients with a minimal cytogenetic response at 3 months, PCyR at 6 months, and CCyR at 12 months had significantly better outcomes than those with lesser degrees of cytogenetic response.[145]

Currently, no definite recommendations exist for specific time points at which to switch patients to allogeneic HSCT based on response to second-line TKI therapy. Available data suggest that evaluating cytogenetic responses at 3, 6, and 12 months may be useful when considering switching a patient with a suitable donor to allogeneic HSCT.

NCCN Recommendations

Chronic Phase—

- Patients for whom first-line TKI therapy failed should be evaluated for allogeneic HSCT at 3, 6, 12, and 18 months depending on response to second-line TKI therapy:
  - ➤ Less than CHR at 3 months
  - ➤ No cytogenetic response at 6 months
  - ➤ Minor or no cytogenetic response at 12 months
  - ➤ Partial cytogenetic response at 18 months
  - ➤ Cytogenetic relapse

Disease Progression—

- Consider allogeneic HSCT depending on response to second-line TKI therapy for patients experiencing disease progression to accelerated phase.
- TKI therapy (alone or in combination with induction chemotherapy) followed by HSCT for patients with disease progression to blast phase.

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	Myers Squibb Company; and Merck & Co., Inc.	Corporation; and Bristol-Myers Squibb Company			
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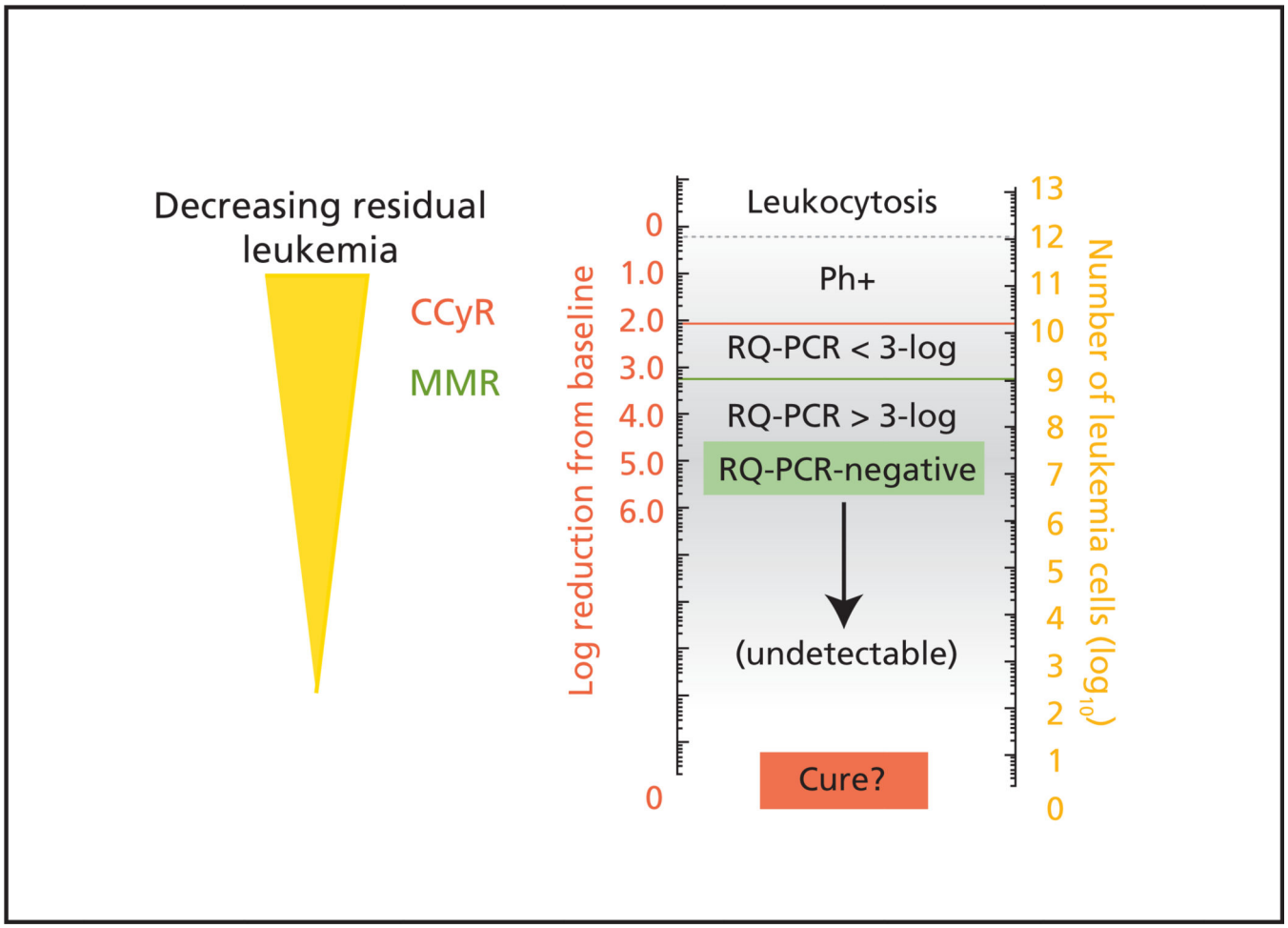

Figure 1.

Schematic representation of decreasing residual disease related to numbers of BCR-ABL transcripts in the peripheral blood (left scale) and estimated number of residual leukemia cells in a patient's body (right scale).

Abbreviations: CCyR, complete cytogenetic response; MMR, major molecular response; RQ-PCR, real-time quantitative polymerase chain reaction.

From Goldman JM. How I treat chronic myeloid leukemia in the imatinib era. Blood 2007;110:2831. Reproduced with permission of the American Society of Hematology.

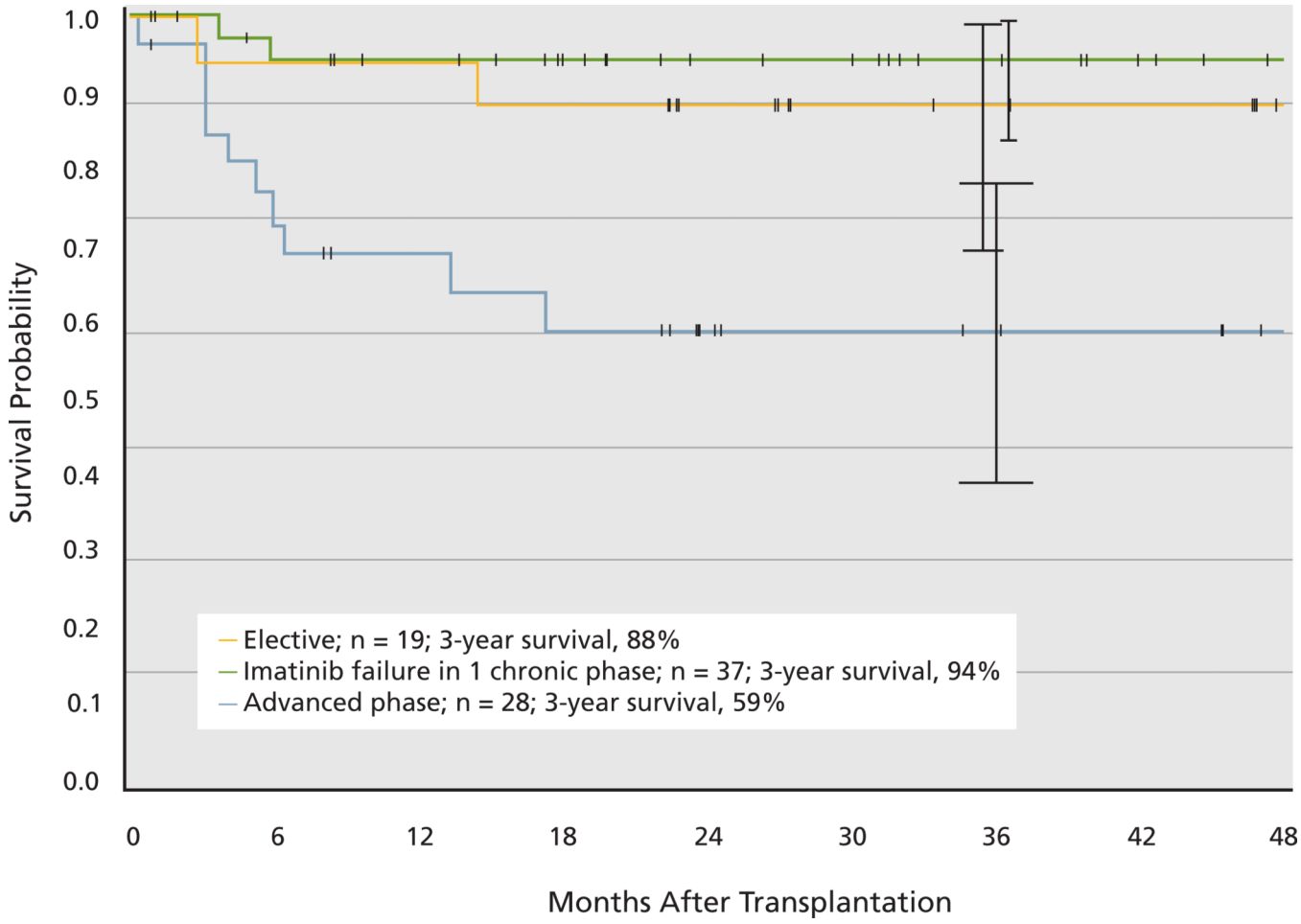

Figure 2.

Survival probability after allogeneic stem cell transplant. Tick marks indicate last observation of living patients.

From Saussele S, Lauseker M, Gratwohl A, et al. Allogeneic hematopoietic stem cell transplantation (allo SCT) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV. Blood 2010;115:1883; reproduced with permission of the American Society of Hematology. (C)2011.

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Table 1

Selected Response and PFS Rates for Front-Line Standard- or High-Dose Imatinib in Clinical Trials

	ELN Study (12-Month Response Rates)[15]		TOPS Study (12-Month Response Rates)[16]		German CML IV Study (12-Month Response Rates)[17]	
Response	**Imatinib 400 mg/d**	**Imatinib 800 mg/d**	**Imatinib 400 mg/d**	**Imatinib 800 mg/d**	**Imatinib 400 mg/d**	**Imatinib 800 mg/d**
CCyR*	58%	64%	66%	70%	50%	63%
MCyR	74%	68%	NR	NR	NR	NR
MMR‡	41%	49%	40%	46%	31%	56%
PFS†	84%	91%	95%	97%	88%	88%

Abbreviations: CCyR, complete cytogenetic response; CML, chronic myelogenous leukemia; ELN, European LeukemiaNet; MCyR, major cytogenetic response; MMR, major molecular response; NR, not reported; PFS, progression-free survival; TOPS, Tyrosine Kinase Inhibitor Optimization and Selectivity trial.

*Primary end point of ELN study.

†Primary end point of the TOPS study

‡PFS rate at 36 months (ELN study), at 18 months (TOPS study), and 5 years (German CML IV study).

Table 2

Calculation of Relative Risk*

Study	Calculation	Risk Definition by Calculation	
Sokal et al.[146]	Exp 0.0116 × (age in years − 43.4) + 0.0345 × (spleen − 7.51) + 0.188 × [(platelet count ÷ 700)^2 − 0.563] + 0.0887 × (blast cells – 2.10)	Low	< 0.8
		Intermediate	0.8–1.2
		High	> 1.2
Hasford et al.[147]	0.666 when age ≥ 50 years + (0.042 × spleen) + 1.0956 when platelet count > 1500 × 10^9L + (0.0584 × blast cells) + 0.20399 when basophils > 3% + (0.0413 × eosinophils) × 100	Low	< 780
		Intermediate	781–1480
		High	> 1480

* Calculation of relative risk found at http://www.icsg.unibo.it/rrcalc.asp. Age is in years. Spleen is in centimeter below the costal margin (maximum distance). Blast cells, eosinophils, and basophils are in percents of peripheral blood differential. All factors must be collected before any treatment.

From Baccarani M, Cortes J, Pane F, et al. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol 2009;27:6041–6051. Reprinted with permission.

Table 3

Selected Response and Progression-Free Survival Rates for Frontline Tyrosine Kinase Inhibitors in Phase III Randomized Studies

	Phase III DASISION Study[20](%)		Phase III ENESTnd Study[26] (%)		
Response Criteria	**Dasatinib 100 mg daily**	**Imatinib 400 mg daily**	**Nilotinib 300 mg twice daily**	**Nilotinib 400 mg twice daily**	**Imatinib 400 mg daily**
CCyR* at 12 months	83	72	80	78	65
MMR† at 12 months	46	28	44	43	22
Progression to AP/BP	1.9	3.5	< 1	< 1	4

Abbreviations: AP, accelerated phase; BP, blast phase; CCyR, complete cytogenetic response; DASISION, Dasatinib versus Imatinib Study in Treatment-Naïve CML Patients; ENESTnd, Evaluating Nilotinib Efficacy and Safety in Clinical Trials Newly Diagnosed Patients; MMR, major molecular response.

*Primary end point for the DASISION study (CCyR is defined as the absence of Ph+ metaphases, was determined on the basis of G-banding in ≥ 20 cells in metaphase per bone marrow sample).

†Primary end point for the ENESTnd study (MMR is defined as *BCR-ABL* transcript level ≤ 0.1 % in peripheral blood on real-time quantitative polymerase chain reaction assay, as expressed on the International Scale).

Table 4

Selected Toxicities of Dasatinib and Imatinib in the DASISION Study[20]

	All Grades (%)		Grade 3 or 4 (%)	
Toxicity	**Dasatinib 100 mg daily**	**Imatinib 400 mg daily**	**Dasatinib 100 mg daily**	**Imatinib 400 mg daily**
Hematologic Toxicities				
Neutropenia	65	58	21	20
Thrombocytopenia	70	62	19	10
Anemia	90	84	10	7
Nonhematologic Toxicities				
Fluid retention	19	42	1	1
Superficial edema	9	36	0	< 1
Pleural effusion	10	0	0	0
Diarrhea	17	17	< 1	1
Nausea	8	20	0	0
Vomiting	5	10	0	0
Musculoskeletal pain	11	14	0	< 1
Rash	11	17	0	1
Headache	12	10	0	0
Fatigue	8	10	< 1	0

Table 5

Selected Toxicities of Nilotinib and Imatinib in the ENESTnd Study[26]

Toxicity	All Grades (%)			Grade 3 or 4 (%)		
	Nilotinib 300 mg twice daily	Nilotinib 400 mg twice daily	Imatinib 400 mg daily	Nilotinib 300 mg twice daily	Nilotinib 400 mg twice daily	Imatinib 400 mg daily
Hematologic Toxicities						
Neutropenia	43	38	68	12	10	20
Thrombocytopenia	48	49	56	10	12	9
Anemia	38	38	47	3	3	5
Nonhematologic Toxicities						
Peripheral edema	5	5	14	0	0	0
Diarrhea	8	6	21	1	0	1
Nausea	11	19	31	< 1	1	0
Vomiting	5	9	14	0	1	0
Muscle spasm	7	6	24	0	1	1
Rash	31	36	11	< 1	3	1
Headache	14	21	8	1	1	0
Fatigue	11	9	8	0	1	< 1

Table 6

Recommendations for Monitoring Response to TkIs

Test	Indication
Bone marrow cytogenetics	At diagnosis. If collection of bone marrow is not feasible, FISH on a peripheral blood specimen using dual probes for the *BCR* and *ABL* genes is an acceptable method of confirming CML diagnosis.
	At 6, 12, and 18 months from initiation of therapy to assess response to TKI therapy. If a CCyR is achieved at either of the earlier time points, then cytogenetics do not need to be repeated in stable patients.
	Rising levels of *BCR-ABL* transcript (1-log increase) without an MMR.
Quantitative real-time polymerase chain reaction (qPCR)	At diagnosis to establish baseline *BCR-ABL* transcript level.
	Every 3 months when a patient is experiencing response to treatment and every 3–6 months after CCyR.
	If a rising level of *BCR-ABL* transcript (1-log increase) is present with an MMR, qPCR analysis should be repeated in 1–3 months.

Abbreviations: CCyR, complete cytogenetic response; CML, chronic myelogenous leukemia; FISH, fluorescence in situ hybridization; MMR, major molecular response; TKI, tyrosine kinase inhibitor.

Table 7

Response and PFS Rates for Dasatinib[37,40] and Nilotinib[48] in Imatinib-Resistant or -Intolerant Patients With Chronic-Phase Chronic Myelogenous Leukemia at 24-Month Follow-Up

	Overall Population (%)			Imatinib-Resistant Patients (%)			Imatinib-Intolerant Patients (%)		
Response	Dasatinib 70 mg twice daily	Dasatinib 100 mg daily	Nilotinib 400 mg twice daily	Dasatinib 70 mg twice daily	Dasatinib 100 mg daily	Nilotinib 400 mg twice daily	Dasatinib 70 mg twice daily	Dasatinib 100 mg daily	Nilotinib 400 mg twice daily
CHR	88	92	NR	89	89	NR	86	100	NR
MCyR	61	63	59	57	59	56	74	77	66
CCyR	54	50	44	48	44	41	69	67	51
MMR	38	37	28	34	35	NR	51	43	NR
PFS	76	80	64	75	NR	NR	94	NR	NR

Abbreviations: CHR, complete hematologic response; CCyR, complete cytogenetic response; MCyR, major cytogenetic response; MMR, major molecular response; NR, not reported; PFS, progression-free survival.

Table 8

Response and Overall Survival Rates for Dasatinib[44] and Nilotinib[50] in Imatinib-Resistant or -Intolerant Patients with Accelerated-Phase Chronic Myelogenous Leukemia at 24-Month Follow-Up

	Overall (%)			Imatinib-Resistant Patients (%)			Imatinib-Intolerant Patients (%)		
Response	**Dasatinib 70 mg twice daily**	**Dasatinib 140 mg daily**	**Nilotinib 400 mg twice daily**	**Dasatinib 70 mg twice daily**	**Dasatinib 140 mg daily**	**Nilotinib 400 mg twice daily**	**Dasatinib 70 mg twice daily**	**Dasatinib 140 mg daily**	**Nilotinib 400 mg twice daily**
CHR	52	47	31	51	50	30	53	39	37
MCyR	43	39	32	42	36	30	44	46	41
CCyR	33	32	20	33	29	18	33	41	30
OS	63	72	67	NR	NR	NR	NR	NR	NR

Abbreviations: CHR, complete hematologic response; CCyR, complete cytogenetic response; MCyR, major cytogenetic response; MMR, major molecular response; NR, not reported; OS, overall survival.

Table 9

Selected Grade 3 or 4 Toxicities for Dasatinib[40,44] and Nilotinib[48,50] in Imatinib-Resistant or -Intolerant Patients at 24-Month Follow-Up

	Chronic Phase (%)			Accelerated Phase (%)		
Grade 3 or 4	**Dasatinib 70 mg twice daily**	**Dasatinib 100 mg daily**	**Nilotinib 400 mg twice daily**	**Dasatinib 70 mg twice daily**	**Dasatinib 140 mg daily**	**Nilotinib 400 mg twice daily**
Hematologic Toxicities						
Neutropenia	45	35	31	69	59	42
Thrombocytopenia	38	23	30	67	64	41
Anemia	18	13	11	43	48	25
Nonhematologic Toxicities						
Rash	2	2	2	1	0	NR
Headache	3	1	2	1	1	NR
Diarrhea	4	1	2	3	3	< 1
Nausea	1	1	< 1	2	1	< 1
Vomiting	0	1	< 1	1	1	NR
Dyspnea	5	3	NR	7	3	NR
Bleeding	2	1	NR	7	8	NR
Fatigue	4	2	1	3	2	< 1
Musculoskeletal pain	4	2	NR	2	0	NR
Superficial edema	1	0	0	0	1	NR
Pleural effusion	5	2	< 1	6	7	NR

Abbreviation: NR, not reported.

Table 10

Efficacy of Dasatinib[75] and Nilotinib[78] Based on *BCR-ABL* Mutation Status in Patients with Chronic-Phase Chronic Myelogenous Leukemia Resistant to Imatinib

	Rates of CCyR, = n/N (%)	
Mutation	**Dasatinib**	**Nilotinib**
No mutation	196/421 (43%)	35/87 (40%)
Any mutation	164/384 (47%)	32/100 (32%)
T315I	0/21 (0%)	NR
F317L	1/14 (7%)	NR
F359C	3/5 (60%)	0/11 (0%)
F359V	14/27 (52%)	0/11 (0%)
P-Loop Mutations		
L248V	6/15 (40%)	NR
G250E	20/60 (33%)	3/5 (60%)
Y253H	14/23 (61%)	0/8 (0%)
E255K	6/16 (38%)	0/7 (0%)
E255V	4/11 (36%)	0/7 (0%)

Abbreviations: CCyR, complete cytogenetic response; NR, not reported.

Table 11

NCCN and European LeukemiaNet Response Criteria for Patients With Chronic-Phase Chronic Myelogenous Leukemia

	NCCN		European LeukemiaNet[80]		
Evaluation Time (mo)	**Optimal Response**	**Failure**	**Optimal Response**	**Suboptimal Response**	**Failure**
3	CHR	Less than CHR	CHR and at least an mCyR	No CCyR	Less than CHR
6	CCyR or PCyR	No CyR	At least a PCyR	Less than PCyR	No CyR
12	CCyR	Less than PCyR	CCyR	PCyR	Less than PCyR
18	CCyR	Less than CCyR	MMR	Less than MMR	Less than CCyR

Abbreviations: CHR, complete hematologic response (white blood cell count < 10×10^9/L, platelet count < 450×10^9/L, no immature myelocytes, promyelocytes, or blasts in peripheral blood and disappearance of palpable splenomegaly); CCyR, complete cytogenetic response (no Ph+ metaphases); CyR, cytogenetic response; mCyR, minor cytogenetic response (> 35% Ph+ metaphases); MMR, major molecular response (reduction in *BCR-ABL*/control gene ratio; ≥ 3-log reduction from a standardized based or ≤ 0.1 % on the international scale); PCyR, partial cytogenetic response (1%–35% Ph+ metaphases).