In this issue of *Clinical Cancer Research*, Desai et al. (1) present evidence that new modules appearing in preexisting lesions can represent clonally resistant populations.

Imatinib mesylate, the prototypic oral tyrosine kinase inhibitor that has activity against ABL, KIT, and platelet-derived growth factor receptor kinases arguably represents the most important oncologic advance of the past 30 years. Imatinib has been shown to bind to the inactive conformations of ABL and KIT and presumably prevents these kinases from adopting the oncogenically relevant active conformation (2, 3). The high response rates and favorable survival effect of imatinib in chronic phase cases of chronic myelogenous leukemia (CML), coupled with its excellent tolerability, have revolutionized the medical management of CML (4). The success of imatinib, however, is not limited to hematologic malignancies, as this agent has substantial efficacy in gastrointestinal stromal tumors (GIST) as well (5, 6), a finding that has provided substantial hope for the application of kinase inhibitor therapy strategies to a broad range of human malignancies that carry poor prognoses.

Despite high initial response rates to imatinib in both CML and GIST cases, for many patients, loss of response occurs. The molecular basis of loss of response to imatinib in CML most frequently involves reactivation of BCR-ABL kinase activity, typically as a result of selection for cells harboring kinase domain mutations within BCR-ABL (7–9). If sensitive methods of mutation detection are used, a substantial proportion of patients can be documented to exhibit polyclonal resistance (i.e., more than one resistant clonal population; ref. 9). Molecular analyses of GIST tumors that have developed imatinib resistance have similarly implicated resistant kinase domain mutations in the activated KIT oncogene as a predominant mechanism of relapse, and a recent analysis has shown the evolution of polyclonal resistant clones in patients on imatinib therapy (10). The substantial number and variety of amino acid substitutions capable of abrogating imatinib binding poses a significant clinical challenge.

In imatinib-resistant cases of both CML and GIST, substantial response rates (in CML) and superior progression-free survival (in GIST) have been observed with dasatinib (11) and sunitinib (12), respectively. These agents have been approved for sequential use (i.e., treatment after imatinib resistance or imatinib intolerance). It is postulated that early detection of resistant disease will facilitate prompt institution of effective second-line therapy and thereby maximize the likelihood of recapturing a durable clinical remission.

Although monitoring disease burden in CML is easily achieved with the use of sensitive PCR testing to quantify BCR-ABL levels in the peripheral blood, assessment of disease burden in solid tumors is somewhat more difficult. Classically, true progression has been defined as an objective increase in the cross-sectional area of a preexisting lesion or the development of a new lesion. In this issue of *Clinical Cancer Research*, Desai et al. (1) offer convincing evidence that newly appearing nodules within preexisting lesions can represent the first sign of clonally resistant populations (Fig. 1), with the detection of secondary point mutations in 8 of 10 analyzed cases. These findings suggest that patients in whom the characteristic radiographic appearance of these nodular lesions is detected should be considered for alternative therapeutic strategies.

It is noteworthy that several imatinib resistance-conferring mutations in KIT occur in the activation loop region of the kinase (e.g., KITD816V). These substitutions presumably prevent the kinase from adopting the inactive conformation required for imatinib binding by stabilizing the kinase in its active conformation. Similar activation loop mutations have been identified within BCR-ABL in imatinib-resistant cases of CML, as well as mutations elsewhere within the kinase that are presumed to destabilize the inactive conformation and prevent effective imatinib binding. Dasatinib has been shown to bind to the active conformation of BCR-ABL (13) and is therefore highly active against nearly all imatinib-resistant mutations (14). Similarities between imatinib-resistant kinase domain mutations in BCR-ABL and KIT are not limited to those that influence the status of the activation loop. A highly imatinib-resistant mutation in BCR-ABL occurs at a residue corresponding to T670 in KIT (BCR-ABL/T315), an important contact residue that forms a critical stabilizing hydrogen bond with imatinib (2, 7). Furthermore, the V654 residue in KIT, which is frequently mutated in imatinib-resistant GIST cases, corresponds to position V299 in BCR-ABL, a residue that when mutated to leucine was found to confer in vitro resistance to dasatinib and to a lesser extent, imatinib (15). Clearly, there are several important parallels between the targeted therapy of CML and GIST.

The findings presented by Desai et al. (1), coupled with evolving data in CML, suggest that earlier intervention with...
second-line therapy is warranted in patients with early signs of resistance. At the present time, however, a patient with a nodular pattern of resistant disease, which most often represents a clonal outgrowth harboring a secondary KIT mutation, is not considered to have truly progressive disease until standard radiographic criteria of progression are met, despite the evidence presented here that these nodules clearly represent actively growing malignancy despite therapy. It is thus necessary to revisit definitions of progression in the era of targeted therapeutics.

This study also provides support for investigating combinations of kinase inhibitors in an effort to maintain suppression of both imatinib-sensitive and imatinib-resistant clonal populations. Because all targeted agents are likely to be susceptible to resistance-conferring kinase domain mutations as a mechanism of resistance, an important unresolved management issue involves the optimal timing of kinase inhibitor therapy administration (e.g., sequential versus combinatorial). Although sunitinib is effective in imatinib-resistant cases, it shares many vulnerabilities with imatinib, particularly with respect to resistance-conferring activation loop mutations. Combination kinase inhibitor strategies that can collectively suppress all BCR-ABL kinase domain mutations are currently undergoing clinical investigation in advanced phases of CML. It is hoped that combination kinase inhibitor therapy will achieve substantial improvements in relapse-free survival, a hypothesis that clearly needs to be investigated in inoperable cases of GIST as new kinase inhibitors, preferably capable of binding to the active conformation of KIT, undergo clinical development.

Fig. 1. Schematic of clonal resistance in hepatic GIST metastases treated with imatinib. Yellow spheres indicate PET-positive areas before imatinib; turquoise spheres indicate PET-negative areas after initiation of therapy. Red spheres represent PET-positive areas first observed after a maximum response and are associated with new drug-resistant KIT mutations. Note that the criteria for radiographic progression are not met until 6 mo after the detection of a resistant clonal nodule by PET.

References
Progressive Thoughts about Progressive Disease

Neil P. Shah