A Review of Omacetaxine: A Chronic Myeloid Leukemia Treatment Resurrected

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ABSTRACT

The paradigm of targeted therapy was pioneered for chronic myeloid leukemia (CML). The advent of tyrosine kinase inhibitors (TKIs) has led to marked improvements in responses and overall survival; however, there is still a subset of patients that are either resistant through a multitude of mechanisms or intolerant to standard TKI therapy. Omacetaxine mepesuccinate (omacetaxine), a semisynthetic purified homoharringtonine compound, has been studied for over 40 years and was approved in 2012 by the Food and Drug Administration (FDA) for patients with CML refractory or intolerant to two or more TKIs. Omacetaxine has a novel mechanism of action—inhbition of protein synthesis, which does not overlap with kinase inhibition. Multiple studies have demonstrated that omacetaxine can achieve responses in heavily treated patients with either chronic-phase or accelerated-phase CML, regardless of the presence of mutations in the tyrosine kinase domain. This review will outline the tortuous story of omacetaxine, including preclinical and clinical studies of homoharringtonine, current indications, and management guidelines.

Keywords: Chronic myeloid leukemia; Omacetaxine; Tyrosine kinase inhibitors

INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell disorder characterized by the Philadelphia chromosome, first identified in the early 1960s by Nowell and Hungerford [1]. Thirty years later, the gene product bcr-abl of the chromosomal translocation t(9;22)(q34;q11) was demonstrated to cause constitutively active tyrosine kinase activity leading to the CML phenotype [2, 3]. The treatment of CML has undergone multiple transformations, from the early uses of interferon to the birth of targeted therapies manifested in tyrosine kinase inhibitors. Omacetaxine, the focus of this review, has spanned these decades in search of a position in the treatment algorithm.
Omacetaxine mepesuccinate (omacetaxine) is a semisynthetic purified homoharringtonine (HHT) compound that has had a tortuous route to approval; it has been described as holding “the dubious record for the longest time of development of an anticancer agent until FDA approval, almost 40 years” [4]. HHT, a plant alkaloid from *Cephalotaxus* species, was first described by Chinese investigators as an antileukemic agent for AML [4], with complete response rates approaching 25%. Further studies in AML patients in the United States with varying dosing schedules demonstrated complete response rates varying from 0% (50% hypoplasia) to 25% [5–8]. Additionally, multiple regimens combining HHT with conventional chemotherapy, mainly studied in China, have produced mixed results, based on a 2015 meta-analysis [9]. Single-agent antileukemic activity was also noted in polycythemia vera, CNS leukemia [4], and myelodysplastic syndrome [10].

Initial studies evaluating HHT in CML were predominantly performed in the 1990s (Table 1). In the initial study with chronic-phase CML patients, HHT 2.5 mg/m² was given as a 14-day continuous infusion for remission induction followed by a 7-day maintenance course each month. Thirty-one percent of patients developed a cytogenetic response, with 15% having a MCyR and 7% achieving a CCyR. The most common adverse effects were neutropenia and thrombocytopenia, predominantly seen in the induction phase. Severe myelosuppression was addressed in subsequent cycles with dose reductions by decreasing the number of days that HHT was infused. The continuous infusion seemed to abrogate the cardiac and hypotension side effects noted in previous studies that used bolus dosing [11].

Further studies evaluated HHT with interferon both sequentially and concomitantly. The first study administered HHT according to the same induction and maintenance schedule as previously described, but after 6 cycles converted them to an interferon-alpha regimen at 5 MU/m². After 6 courses of HHT, the major, minor, and complete cytogenetic responses were 33%, 23%, and 4%, respectively. After “consolidation” with IFN-α, rates of complete, partial, and minor cytogenetic response were 23%, 21%, and 21%, respectively. The initial 5MU/m² dose proved highly myelosuppressive, and upon analysis the median dose of IFN-α delivered was found to be 2.4 MU/m² after individual patient dose reductions. These results did not differ significantly from historical controls for IFN-α alone, although treatment with HHT led to a significant improvement in patients with splenomegaly [12].

Concomitant administration of HHT and IFN-α yielded better results. Due to the myelosuppressive toxicities of both drugs, the HHT was dosed at the standard 2.5 mg/m² as a continuous infusion but only for 5 days, along with full-dose IFN-α (5MU/m²) simultaneously for 5 days. This combination produced a complete hematologic response (CHR) rate of 85%, with complete and major cytogenetic response rates of 69% and 52%, respectively [13].

Combinations with HHT and cytarabine were also evaluated. An early phase II study enrolled 105 patients treated with 2.5 mg/m² as a continuous infusion for 5 days along with cytarabine at 7.5 mg/m² twice daily for 5 days, with both drugs cycled every 4 weeks. The overall CHR was 72% with a cytogenetic response rate of 32%. When comparative analysis was performed with historical controls, the combination of HHT plus cytarabine was found to yield similar response rates to HHT alone, but a significantly longer overall survival [14]. A second study treated 44 previously untreated chronic-phase CML patients with HHT at 2.5 mg/m² daily with cytarabine 7.5 mg/m² given continuously for 7 days on a 28-day cycle [15]. Eighty-two percent of the patients achieved a CHR, with only 17% of patients presenting a cytogenetic response.
Table 1 Phase II studies with omacetaxine

| Study         | Drug            | Population                  | N  | CHR      | MCyR | CCR     | Grade 3/4 hematologic toxicity | DoR  |
|---------------|-----------------|-----------------------------|----|----------|------|--------|-------------------------------|------|
| O’Brien [11]  | HHT             | CML, late CP                | 71 | 42/58 (72%) | 11   | 5 (7%) | TCP (30%), neut (39%)          | N/A  |
| O’Brien [12]  | HHT + IFN       | CML, early CP               | 90 | 83 (92%)  | 27   | 4%     | TCP (13%), neut (27%)          | N/A  |
| O’Brien [13]  | HHT + IFN       | CML, early and late CP      | 47 | 36/43 (84%) | (49%)| 10 (21%)| TCP (77%); neut (77%); anemia (36%) | N/A  |
| Kantarjian [14]| HHT + AraC      | CML, CP and AP              | 105| 61 (72%)  | 12   | 4 (5%) | TCP (4%), neut (13%)          | N/A  |
| Stone [15]    | HHT + AraC      | CML, CP                     | 44 | 36 (82%)  | 4    | N/A    | Neut (66%)                    | N/A  |
| Nicolini [53] | Omacetaxine     | T315I mutated               | 8  | 5 (63%)  | 0    | 3 (37%)| 100%                          | N/A  |
| Cortes [54]   | Omacetaxine     | T315I mutated               | 62 | 47 (77%)  | 14  | 10 (16%)| TCP (76%), neut (44%); anemia (32%) | 9.1 months |
| Cortes [55]   | Omacetaxine     | Failed ≥ 2 TKIs, CP         | 46 | 31 (67%)  | 10  | 2 (4%) | TCP (54%), neut (48%); anemia (33%) | 7.0 months |
| Cortes [56]   | Omacetaxine     | Failed ≥ 2 TKIs, CP         | 81 | 0        | 16  | 8 (10%)| TCP (67%), neut (47%); anemia (37%) | 12.2 months |
| Nicolini [57] | Omacetaxine     | Failed ≥ 2 TKIs, AP         | 41 | 11 (27%)a | 6 (15%)b| 0   | TCP (51%), neut (22%); anemia (37%) | 9.0 months |
| Cortes [58]   | Omacetaxine     | Failed ≥ 2 TKIs, CP         | 76 | N/A      | 14  | 6 (8%) | 79%                           | 12.5 months |
|               |                 | Failed ≥ 2 TKIs, AP         | 35 | 5 (14%)a | 0   | 0     | 73%                           | 4.7 months |

*HHT* homoharringtonine, *IFN* interferon-alpha, *AraC* cytarabine, *CHR* complete hematologic response, *MCyR* major cytogenetic response, *CCR* complete cytogenetic response, *DoR* duration of response, *TCP* thrombocytopenia, *neut* neutropenia, *TKI* tyrosine kinase inhibitor, *CP* chronic phase, *AP* accelerated phase

a Patients achieved a major hematologic response

b Patients achieved a minor cytogenetic response
TKI THERAPY FOR THE TREATMENT OF CML IN RESISTANT DISEASE

Despite the initial success of HHT in treating CML, it was relegated to second-class status, as imatinib and the other tyrosine kinases commandeered the clinical landscape, including the entire CML population. Patients even abandoned homoharringtonine studies in order to use the novel and more targeted TKIs [16].

TKIs drastically changed the landscape of treatment for CML by providing novel targeted agents with minimal toxicity, especially when compared to interferon-alpha and SCT [17–19]. More importantly, imatinib had a favorable side-effect profile and led to an overall survival at 5 years of 89% [20] and at 10 years of 83.3% [21]. Unfortunately, approximately one-third of patients need to discontinue imatinib therapy; half of those discontinuations are due to intolerance and half are due to disease resistance by 6 years [22]. In spite of these exceptional responses to imatinib-based therapy, the discovery of more potent second-generation TKIs (dasatinib [23, 24], nilotinib [25, 26], and bosutinib [27–29]) and the third-generation TKI ponatinib [30, 31] for use in cases of refractory disease and drug intolerance has further improved outcomes for patients with CML (Table 2).

Table 2 Response rates to second- and third-generation TKIs of patients intolerant to previous treatment or with relapsed disease

| TKI       | N   | Res/intol | CHR (%) | MCyR (%) | CCyR (%) | Follow-up |
|-----------|-----|-----------|---------|----------|----------|-----------|
| Dasatinib | 186 | 127/59    | 90      | 52       | 39       | 8 months  |
| Nilotinib | 137 | 92/45     | 74      | 48       | 31       | 6 months  |
| Bosutinib | 288 | 200/88    | 86      | 53       | 41       | 24 weeks  |
| Ponatinib | 267 | 214/40a   | N/A     | 56       | 46       | 12 months |

*Res* imatinib-resistant, *intol* imatinib-intolerant, *CHR* complete hematologic response, *MCyR* major cytogenetic response, *CCyR* complete cytogenetic response

a Resistant to nilotinib or dasatinib

There are multiple causes of TKI resistance, with the most common being point mutations in the ATP-binding domain of the BCR-ABL protein complex which inhibit TKI binding [32]. Most of these point mutations can be circumvented by using an alternative TKI [33]; even the most refractory mutation, T315, is susceptible to ponatinib [34]. However, further resistance has occurred through the development of compound mutations within the kinase domain, encouraging the search for inhibitors that bind outside the ATP-binding domain [35]. In addition, ABL001 (asciminib) is a novel allosteric TKI that binds to the myristoyl pocket of ABL1, causing an inactive kinase conformation (ClinicalTrials.gov identifier: NCT02081378). It is being explored in a phase I trial for patients intolerant/refractory to standard TKI therapy. A second source of resistance that eludes the TKIs is mutations in signal transduction pathways, such as SRC, PI3 K, KRAS, JAK2, NFAT, and MEK [36]. Furthermore, low levels of the cellular influx pump for imatinib, organic-cation transporter-1 (OCT-1), directly affect intracellular availability, leading to imatinib resistance [37]. Also, increased BCR-ABL expression due to either duplication or upregulation of the oncogene transcript is associated with more advanced disease and the development of resistance [38].

Two situational changes occurred that led to the rebirth of HHT. The first was a need for a different agent than the TKIs. As previously stated, TKI resistance began to develop, and this resistance was seen against multiple TKIs due to their similar mechanisms of action via the ATP-binding domain [32, 33, 36]. Secondly, a novel semisynthetic version of HHT was formulated, which led to the rebranding of the drug through a new corporate sponsor, ChemGenex, and the
promotion of several studies [4, 39]. This new formulation, omacetaxine mepesuccinate, has moved forward in studies in the United States, although it should be noted that HHT is still used and studied in China and other countries.

MECHANISM OF ACTION

The main mechanism of action for omacetaxine is the inhibition of protein translation (Fig. 1). Normal protein translation is a complex process. mRNA is read by tRNA, which transfers the charged amino acid initially to the acceptor (A site) of the 40S ribosome and subsequently transfers the amino acid chain to the incoming amino acid. The entire complex then travels to the peptidyl-tRNA (P site). Ultimately, the deacylated tRNA is moved to the E site, where it is removed from the ribosome [40]. Omacetaxine blocks the elongation process of protein synthesis by competing with tRNA to bind to the A-site cleft in the large ribosomal subunit [41]. This blockade in protein synthesis causes a decrease in proteins, especially those with short half-lives, and cells dependent on these proteins undergo apoptosis. The unique mechanisms of omacetaxine and HHT enable them to be used in cases of TKI-resistant CML.

Murine studies evaluating omacetaxine in CML and B-ALL models demonstrated that >90% of leukemic stem cells were killed by omacetaxine in vitro. Mice that were treated with omacetaxine also showed a decrease in leukemic stem cells. This is in stark contrast to TKIs, which do not have any effect on leukemic stem cells. Omacetaxine improved the survival of mice transduced with the T315I mutant of BCR-ABL, and seemed more efficient at inhibiting the T315I mutation than the wild-type BCR-ABL. The study also established that,
in vitro, omacetaxine induced losses of BCR-ABL, HSP90, and MCL-1 [42].

The inhibition of MCL-1 was further explored by evaluating the signal transduction pathways in BCR-ABL-positive human myeloid cell lines. When omacetaxine was added to CD34-positive cells from patients with and without CML, it was found to inhibit both progenitor and primitive cells, with enhanced killing observed when it was combined with imatinib. Addition of omacetaxine to K562 and CML stem/progenitor cells induced apoptosis, mediated by the downregulation of Mcl-1 [43]. The decrease in Mcl-1 induced Bcl-2 cleavage in cell lines and caused the release of cytochrome c, leading to apoptosis. This effect of omacetaxine on Mcl-1 turnover and the subsequent release of cytochrome c and apoptosis was not seen with daunorubicin or cytarabine [44]. A later study demonstrated that the decrease in Mcl-1 is only a minor contributor to apoptosis; the inhibition of protein synthesis and apoptosis is thought to be independent of the Bax/Bak axis [45]. Recent data suggest that omacetaxine [46] may be beneficial in patients with lymphoma, as in vitro studies have demonstrated an induction of cell cycle arrest in G0/G1, promoted terminal differentiation of pro-B cells, and an antitumor effect due to decreased telomerase activity.

It is expected that HHT, similar to omacetaxine, induces apoptosis. HHT causes upregulation of Bax, leading to an apoptotic response via the activation of caspase-3 [47]. In acute leukemia and CML cell lines, HHT was found to downregulate phosphorylated proteins of JAK2, STAT-5, and AKT, and to decrease Bcl-XL with prolonged exposure [48]. HHT also decreased EphB4 expression in CML cells, and enhanced cell death when added to imatinib [49].

Clinical Pharmacology

Peak plasma concentrations of omacetaxine are reached approximately 30 min after injection. Omacetaxine does not inhibit cytochrome P450 enzymes, and it is unclear whether omacetaxine induces cytochrome P450 enzymes. Omacetaxine is a substrate but not an inhibitor of P-glycoprotein. Early clinical trials did not demonstrate any evidence of QT prolongation. The major elimination route of omacetaxine is unknown, but it is hydrolyzed to an inactive metabolite via plasma esterases and < 15% is excreted unchanged in the urine. The half-life of omacetaxine is approximately 6 h [50].

CLINICAL STUDIES OF OMACETAXINE

Phase I/II Studies

One of the earliest studies of omacetaxine to be published evaluated patients who achieved a partial or complete cytogenetic response to imatinib [51]. Patients who had been on imatinib (400–600 mg) for at least 2 years and had not reached ≥ 35% Philadelphia chromosome negativity were treated with omacetaxine at 1.25 mg/m² subcutaneously twice daily initially for only 1 day, with additional doses given every 2 days if the previous dose was tolerated. Cycles were every 28 days. In this small study, 7 of 10 patients showed a decrease in BCR-ABL transcript levels, 5 of which were greater than 1 log. The regimen was found to be safe, with toxicities of prolonged neutropenia and thrombocytopenia that were dose-related. The most common nonhematologic toxicity was asthenia, which was observed in all patients and lasted 2–3 days after the final dose.

A second phase I/II study evaluated HHT (note: not omacetaxine) in CML; the phase I portion included patients ≥ 12 years old with CML at any phase, while the phase II portion included only chronic-phase patients [52]. The study utilized an initial loading dose of 2 mg/m² and varying subcutaneous doses, and eventually settled on a loading dose of 2.5 mg/m² and a maximum tolerated dose of 1.25 mg/m² subcutaneously for 14 days total of a 28-day cycle. In the expansion cohort of 6 patients who failed imatinib, 5 were evaluable, with all having a complete hematologic remission and 3 having a cytogenetic response. It is important to note that this 1.25 mg/m² dosing was also found to be the dose moving forward with omacetaxine (i.e. semisynthetic HHT), although omacetaxine...
was not used in this study [46]. Hematologic toxicity was again noted, with grade 3–4 anemia (20%), neutropenia (10%), and thrombocytopenia (12%) observed; nonhematologic toxicity was uncommon, with 2 patients presenting with myalgias and fatigue.

**Phase II Studies**

Armed with a small subset of data demonstrating efficacy in CML patients who failed imatinib, two studies evaluated the use of omacetaxine in patients with the highly resistant T315I BCR-ABL mutation. In a small study by Nicolini et al., 8 patients with T315I-mutated CML were treated with omacetaxine in order to resensitize the patients to TKIs [53]. Patients were initially dosed at 1.25 mg/m² twice daily for 14 of 28 days, followed by a 5- to 7-day maintenance cycle every 28 days. Five patients attained a complete hematologic response, and 3 patients had a complete cytogenetic response. All patients experienced grade 3–4 hematologic toxicities in the first cycle and grade 0–2 hematologic toxicities thereafter. The treatment markedly reduced the T315I clone to below 1% at a mean of 187 (PCR–RFLP) and 269 (RQ-LNA PCR) days. Only 2 patients received a TKI rechallenge with nilotinib, and 1 patient remained in complete cytogenetic remission.

These study results (Table 1) were further supported by those of a larger study of 62 patients with T315I mutations conducted at MD Anderson using omacetaxine subcutaneously at 1.25 mg/m² twice daily for 14 of 28 days, followed by a 5- to 7-day maintenance cycle every 28 days. Seven patients attained a complete hematologic response and 3 patients had a complete cytogenetic response. All patients experienced grade 3–4 hematologic toxicities in the first cycle and grade 0–2 hematologic toxicities thereafter. The treatment markedly reduced the T315I clone to below 1% at a mean of 187 (PCR–RFLP) and 269 (RQ-LNA PCR) days. Only 2 patients received a TKI rechallenge with nilotinib, and 1 patient remained in complete cytogenetic remission.

Since a benefit had been shown in the CML-CP population, a study was performed in patients with accelerated-phase CML (CML-AP) who had failed at least 2 TKIs [57]. It is interesting to note that in this pooled analysis, CML-AP was defined as 15–30% blasts, ≥30% blasts and promyelocytes, and ≥20% basophils in peripheral blood or bone marrow, platelets < 100 × 10⁹/L unrelated to therapy, or clonal evolution. Using the same schedule as employed in the other phase II studies, 41 patients were treated. A major hematologic response (MaHR) was achieved in 27%, with a median MaHR duration of 9 months. None of the patients achieved a CCyR or MCyR, and toxicity rates were similar to those in the previous trials.

In what was deemed the “final analysis of the efficacy and safety of omacetaxine,” Cortes et al. published a pooled analysis of 81 CML-AP and CML-CP patients refractory to or unable to tolerate two or more TKIs at the 24-month follow-

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up [58]. In the CML-CP patients, the MCyR rate was unchanged at 20% (CCyR 8%), with a median response duration of 12.5 months. In this group, the median overall survival (OS) was 40.3 months. The CML-AP had a MaHR of 14%, with an OS of 24.6 months. In the study, 9 of 81 (11%) CML-CP patients advanced to bone marrow transplant, compared to none of the CML-AP patients. Although only a small number of these patients were able to use this treatment as a bridge to transplant, this may be the most vital role for the use of omacetaxine.

FDA Approval

Based on the data from these studies, the FDA granted accelerated approval of omacetaxine mepesuccinate (Synribo™, Teva Pharmaceuticals, USA) on October 26, 2012 specifically for CML-CP or CML-AP cases with resistance or intolerance to two or more TKIs [50]. Approval was based on the response rates noted above in a total of 158 patients, with follow-ups of 19.5 months for the CML-CP population and 11.5 months for the CML-AP population. Also noted in the FDA report was the fact that the safety profile could not be fully evaluated because of the lack of a control arm in each of these trials; it was difficult to conclude if specific adverse effects were due to the disease or drug. The FDA had significant concerns about patient reconstitution of omacetaxine due to the harmful fumes released and the danger of toxic spills contaminating patient homes. Therefore, the approval was also conditional on patients receiving the first treatment at a medical facility daily for up to 14 days, with the second dose administered at the patient’s home by a home care nurse. Treatment is based on induction and maintenance schedules, with strict guidelines for dose delays and reductions (Table 3). Currently, omacetaxine is only approved for usage in the United States.

REAL-WORLD USE OF OMACETAXINE

Based on the FDA approval guidelines and restrictions on omacetaxine, there is a limited albeit well-defined population that is eligible for omacetaxine. In our practice, most of the patients that have been refractory or intolerant to two or more TKIs have either harbored the T315I mutation or were unable to tolerate the TKIs due to adverse effects. This highly TKI-refractory population has limited options, including ponatinib (if T315I), omacetaxine, or enrollment on a clinical trial. In this resistant population, omacetaxine is typically used as a bridge to SCT. Most patients tolerate omacetaxine well, and the side effects reported are

Table 3 Dose administration and dose reductions of omacetaxine [60]

| Table 3 Dose administration and dose reductions of omacetaxine [60] |
|---------------------------------------------------------------|
| Induction dosing 1.25 mg/m² subcutaneously q12 h for 14 days over a 28-day cycle |
| Cycles repeated until patient achieves a hematologic response |
| Maintenance dosing 1.25 mg/m² subcutaneously q12 h for 7 days over a 28-day cycle |
| Treatment continues as long as patients are receiving a clinical benefit |
| Dose delay/reduction If grade 4 neutropenia (ANC < 0.5 × 10⁹/L) or grade 3 thrombocytopenia (PLT < 50 × 10⁹/L) occurs, delay the initiation of the next cycle until ANC ≥ 1.0 × 10⁹/L and PLT ≥ 50 × 10⁹/L |
| For subsequent cycles, reduce the number of dosing days by 2 (to 12 or 5 days) |
| Monitoring Induction cycles: weekly CBC |
| First maintenance: weekly CBC |
| Subsequent maintenance: fortnightly CBC |

\( ANC \) absolute neutrophil count, \( PLT \) platelets, \( CBC \) complete blood count with differential

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similar to those already reported from clinical trials, such as injection-site reactions, cytopenias, and infections. Cytopenias can be managed by treatment delays (see Table 3), administration of growth factors, and transfusion support [59]. Laboratory studies should be obtained twice weekly when the patient is initially placed on the medication, and if the patient advances to maintenance, laboratory studies should be evaluated every 1–2 weeks.

The largest hurdle once omacetaxine was initially approved was the FDA mandate that patients receive the first of each daily treatment in a medical facility. This regulation was logistically difficult for the vast majority of patients given the distance to their care center, and many centers do not have weekend hours. In order to comply with the FDA mandate and enable patients to receive some of the treatments at home, Teva Pharmaceuticals created the SYNCare program. This program arranges the direct delivery of the medication to the patient’s home, provides educational and injection training material, and has a 24-h hotline to address all patient questions or issues. This service also provides equipment for proper disposal and cleaning should a spill occur. The first dose must still be given at the prescribing center, with appropriate local teaching. The SYNCare program fulfils the FDA requirement of having a healthcare professional prepare and reconstitute the omacetaxine, but it permits subsequent dosing at the patient’s home (www.synribo.com/SYNCare_Support).

CONCLUSION

Although the mainstay of CML treatment is TKI-based therapy, which has led to an improvement in the overall survival of this population, omacetaxine is a viable option for a select population of TKI-resistant or TKI-intolerant patients. In our practice, we prescribe omacetaxine for patients who have exhausted all standard TKI options. Omacetaxine can be effective for hematologic disease control, although the rate of CCyR is low, and there is a lack of reports of molecular responses. Hematologic toxicity is usually well mitigated by dose-reduction guidelines. Given the novel mechanism of action of omacetaxine, it provides a therapeutic option for patients who are intolerant or resistant to multiple TKIs.

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