Structure-Guided Blockade of CSF1R Kinase in Tenosynovial Giant-Cell Tumor


BACKGROUND
Expression of the colony-stimulating factor 1 (CSF1) gene is elevated in most tenosynovial giant-cell tumors. This observation has led to the discovery and clinical development of therapy targeting the CSF1 receptor (CSF1R).

METHODS
Using x-ray co-crystallography to guide our drug-discovery research, we generated a potent, selective CSF1R inhibitor, PLX3397, that traps the kinase in the autoinhibited conformation. We then conducted a multicenter, phase 1 trial in two parts to analyze this compound. In the first part, we evaluated escalations in the dose of PLX3397 that was administered orally in patients with solid tumors (dose-escalation study). In the second part, we evaluated PLX3397 at the chosen phase 2 dose in an extension cohort of patients with tenosynovial giant-cell tumors (extension study). Pharmacokinetic and tumor responses in the enrolled patients were assessed, and CSF1 in situ hybridization was performed to confirm the mechanism of action of PLX3397 and that the pattern of CSF1 expression was consistent with the pathological features of tenosynovial giant-cell tumor.

RESULTS
A total of 41 patients were enrolled in the dose-escalation study, and an additional 23 patients were enrolled in the extension study. The chosen phase 2 dose of PLX3397 was 1000 mg per day. In the extension study, 12 patients with tenosynovial giant-cell tumors had a partial response and 7 patients had stable disease. Responses usually occurred within the first 4 months of treatment, and the median duration of response exceeded 8 months. The most common adverse events included fatigue, change in hair color, nausea, dysgeusia, and periorbital edema; adverse events rarely led to discontinuation of treatment.

CONCLUSIONS
Treatment of tenosynovial giant-cell tumors with PLX3397 resulted in a prolonged regression in tumor volume in most patients. (Funded by Plexxikon; ClinicalTrials.gov number, NCT01004861.)
Tenosynovial Giant-Cell Tumor, Historically known as pigmented villonodular synovitis, is a rare, locally aggressive neoplasm of the joint or tendon sheath. It is characterized by a proliferation of synoviocytes that initiate the development of the tumor and attract histiocytes, hemosiderin-laden macrophages, and other inflammatory cells. Surgical resection is the primary treatment; however, diffuse tenosynovial giant-cell tumor is more difficult to resect and often involves total synovectomy, joint replacement, or amputation. There are no approved systemic therapies.

A neoplastic clone usually constitutes only a small minority of the cells in tenosynovial giant-cell tumors. These neoplastic cells often express colony-stimulating factor 1 (CSF1) and frequently have a t(1;2) translocation that links the CSF1 gene on chromosome 1p13 to the COL6A3 gene on chromosome 2q35. Inhibition of signaling between CSF1 and CSF1 receptor (CSF1R) thus targets the underlying cause of the disease.

In the autoinhibited state, the juxtamembrane region of CSF1R folds under the regulatory α-helix of the N-terminal lobe of the kinase domain to prevent the kinase from adopting the active conformation that is conducive to ATP and substrate binding. Our design effort focused on discovering a conformation-specific inhibitor that could access the autoinhibited state of CSF1R through direct interactions with juxtamembrane residues embedded in the ATP-binding pocket. The resulting compound, PLX3397, displayed strong pharmacologic effects in preclinical models in which paracrine interactions between CSF1 and CSF1R played a critical role. Because of the known role of CSF1R in the pathophysiology of tenosynovial giant-cell tumors, we conducted a phase 1 trial of PLX3397 prospectively focused on patients with this disease.

**METHODS**

**SYNTHESIS, STRUCTURAL ANALYSES, AND PRECLINICAL PHARMACOLOGY**

PLX3397 (Fig. 1A) — 5-((5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-N-((6-(trifluoromethyl)pyridin-3-yl)methyl)pyridin-2-amine — was synthesized from commercially available reagents as described in the Methods section (see “Synthesis and Characterization of PLX3397”) in the Supplementary Appendix, available with the full text of this article at NEJM.org.

We performed co-crystallography of CSF1R with PLX3397 (Protein Data Bank [PDB] code 4R7H) and imatinib (PDB code 4R7I) using a previously described procedure. Crystallographic data and refinement statistics are provided in Table S1 in the Supplementary Appendix.

The in vitro kinase activities (Table S2 in the Supplementary Appendix) and cell-based assays to evaluate PLX3397 inhibition of cellular processes regulated by CSF1R (Table S3 in the Supplementary Appendix) were performed as described previously. Preclinical studies in animals were performed to establish a translational baseline (see the Methods section in the Supplementary Appendix).

**TRIAL DESIGN AND OVERSIGHT**

The phase 1, dose-escalation part of the trial (dose-escalation study) evaluated the safety and pharmacokinetics of PLX3397, which was administered orally in capsule form in patients with solid tumors (see the Methods section in the Supplementary Appendix). A multicenter, single-cohort extension study was then performed to assess the safety and efficacy of PLX3397 in patients with tenosynovial giant-cell tumors (see the Methods section in the Supplementary Appendix). Patients were eligible for enrollment if they had received a histologically confirmed diagnosis of tenosynovial giant-cell tumor that had shown progression within the past year and was recurrent or inoperable or required extensive surgery for resection. Efficacy was assessed by imaging at baseline and every 2 months. Images were evaluated locally with use of the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (Table S4 in the Supplementary Appendix), and centrally with use of a tumor volume score (Table S5 in the Supplementary Appendix) that we developed to capture the highly irregular shape of these tumors that elude full quantification by linear measurements such as those used in RECIST (see the Methods section in the Supplementary Appendix). Patients continued treatment until disease progression occurred or unacceptable side effects of the drug were observed.

The first patient was enrolled in the dose-escalation study on October 10, 2009. The
Figure 1. Rational Targeting of CSF1-Driven Signaling by PLX3397.

Panel A shows the chemical structure of PLX3397 (top) and conformation-specific inhibition of colony-stimulating factor 1 receptor (CSF1R) (bottom). PLX3397 binds the autoinhibited state of CSF1R and makes direct contact with the juxtamembrane region. The key hydrogen bond interactions are highlighted. The CSF1R kinase domain is shown in gray, the juxtamembrane region (including tyrosine residue 546 [Tyr546] and tryptophan residue 550 [Trp550]) in purple, and PLX3397 in yellow (oxygen in red and chlorine in green). In addition to π-π stacking between the pyridine and juxtamembrane Trp550, the polar nitrogen of the pyridine participates in a hydrogen bond network mediated by water that helps anchor the juxtamembrane region in its autoinhibited conformation (see Fig. S1 in the Supplementary Appendix).

Panel B shows the phase 1 dose-escalation process (see the Supplementary Appendix for details) and the dose-limiting toxic effects that were seen in each cohort. Panel C shows the steady-state systemic exposure (area under the curve from 0 to 24 hours [AUC0–24]) by cohort. Both geometric means and medians are presented. AST denotes aspartate aminotransferase, CP2D chosen phase 2 dose, INR international normalized ratio, MTD maximum tolerated dose, and TGCT tenosynovial giant-cell tumor.

**Cohort 1 (200 mg)**
- 3 Were in cohort 1
- 200 mg daily

**Cohort 2 (300 mg)**
- 6 Were in cohort 2
- 300 mg daily

**Cohort 3 (400 mg)**
- 6 Were in cohort 3
- 400 mg daily

**Cohort 4 (600 mg)**
- 6 Were in cohort 4
- 600 mg daily
- 3 Had a run-in of 100 mg daily

**Cohort 5 (900 mg)**
- 3 Had a run-in of 200 mg daily
- 1 Was replaced
- 2 Had twice-daily dosing assessed

**Cohort 6 (1200 mg)**
- 6 Were in cohort 6
- 1200 mg daily
- (600 mg twice daily)

**Cohort 7 (1000 mg)**
- 1 Was replaced

1 in cohort 2 had dose-limiting toxic effects
- Grade 3 INR increase (possibly related)
- Grade 3 hematuria (unlikely to be related)

1 in cohort 4 had dose-limiting toxic effects
- Grade 3 lymphopenia (possibly related)
- Grade 3 hyponatremia (unlikely to be related)

2 in cohort 6 had dose-limiting toxic effects
- Grade 3 AST increase (possibly related)
- Grade 3 anemia (possibly related)
- Grade 4 neutropenia (possibly related)
- Grade 3 syncope (possibly related)

1 in cohort 7 had a dose-limiting toxic effect
- Grade 3 AST increase (possibly related)

1 in cohort 2 had dose-limiting toxic effects
- Grade 3 lymphopenia (possibly related)

1 in cohort 4 had dose-limiting toxic effects
- Grade 3 lymphopenia (possibly related)

1 in cohort 7 had a dose-limiting toxic effect
- Grade 3 AST increase (possibly related)

1 in cohort 4 had dose-limiting toxic effects
- Grade 3 lymphopenia (possibly related)

1 in cohort 7 had a dose-limiting toxic effect
- Grade 3 AST increase (possibly related)

2 in cohort 6 had dose-limiting toxic effects
- Grade 3 AST increase (possibly related)

7 Were in cohort 5
- 900 mg daily
- 3 Had a run-in of 200 mg daily
- 1 Was replaced

7 Were in cohort 6
- 1200 mg daily
- (600 mg twice daily)

Stop dose escalation
Select intermediate dose

Declare 1000 mg/kg as MTD and CP2D

7 Were in cohort 6
- 1000 mg/day (500 mg twice daily)
- 1 Was replaced

Declare 1000 mg/kg as MTD and CP2D

TGCT extension

23 Were in cohort 7
- 1000 mg/day
dose-escalation database was locked on September 27, 2012. The interim data cutoff for the extension-study cohort was April 14, 2014. Written informed consent was obtained from all patients before they were screened for study eligibility.

The trial was designed by the subgroup of authors who were study investigators and Plexxikon clinical researchers. The data were collected, analyzed, and interpreted jointly by the same study investigators and Plexxikon clinical researchers, all of whom vouched for the completeness and accuracy of the analyses and reported results and for adherence to the study protocol, which is available at NEJM.org. The first author and the Plexxikon researchers prepared the initial draft of the manuscript. All the authors contributed to subsequent drafts and made the decision to submit the manuscript for publication. Each participating institution obtained institutional review board approval prior to obtaining consent from patients at their respective site.

**TUMOR VOLUME SCORE**

The tumor volume score is a new scoring method developed specifically for assessing tenosynovial giant-cell tumors and has not yet been validated (see the Methods section in the Supplementary Appendix). The score calculates tumor volume as a percentage of the entire synovium, with standardization to the synovial or tenosynovial cavity. The tumor volume score is a modification of the rheumatoid arthritis magnetic resonance imaging (MRI) score and the whole-organ MRI score, which are commonly used in arthritis. The MRIs were obtained at every two cycles (8 weeks) of treatment and were evaluated centrally by two independent musculoskeletal radiologists who were unaware of chronology with respect to the timing of scans during the course of treatment. The response criteria of the tumor volume score are provided in the Methods section in the Supplementary Appendix.

**MOLECULAR ANALYSIS**

CSF1 in situ hybridization and hematoxylin and eosin staining were performed in archival tissue samples from the study participants to confirm that the pattern of CSF1 expression was consistent with the pathological features of tenosynovial giant-cell tumor (see the Methods section in the Supplementary Appendix). One of the authors who is a musculoskeletal pathologist and who was unaware of the tumor responses to treatment reviewed all slides.

**STATISTICAL ANALYSIS**

Definitions that were used to assess the outcomes of dose escalation and details on the statistical methods are provided in the Methods section in the Supplementary Appendix. Patients were included in the per-protocol analysis of tenosynovial giant-cell tumor response if a baseline MRI and at least one posttreatment MRI were performed and could be evaluated with the use of RECIST, version 1.1, or the tumor volume score. Exact binomial 95% confidence intervals (two-sided) were provided for each category of tumor response, either by RECIST or by the tumor volume score. We compared the tumor response rate for PLX3397 with that for imatinib using the chi-square test with Yates’ correction at the α=0.05 significance level. The statistical methods for the individual experiments are provided in the Methods section in the Supplementary Appendix.

**RESULTS**

**PHARMACOLOGY OF PLX3397**

We derived PLX3397 (Fig. 1A) from PLX647, a selective dual inhibitor of CSF1R and c-kit receptor tyrosine kinase (KIT), by introducing a polar atom into the trifluoromethylphenyl tail (changing phenyl group to pyridine) and a chloride at the 5-position of the azaindole scaffold. Unlike PLX647, PLX3397 binds to autoinhibited CSF1R and forms novel contacts with juxtamembrane residues, as revealed by co-crystal structure analysis (Fig. 1A, and Fig. S1 in the Supplementary Appendix).

PLX3397 was significantly more potent than conventional type 2 inhibitors (PLX647 and imatinib) when assayed against cells whose growth and function depend on CSF1R (Table S3 in the Supplementary Appendix), which suggests that engaging the juxtamembrane region targets a more physiologically common state of the full-length CSF1R protein. PLX3397 showed limited cross-reactivity with other kinases in a kinome-wide screen (Table S2 and Fig. S2 in the Supplementary Appendix).

PLX3397 exhibited desirable pharmacokinetic
effects in preclinical studies in animals (Table S6 in the Supplementary Appendix), with low systemic clearance, high volume of distribution, favorable oral bioavailability, and systemic exposures proportional to the dose. PLX3397 has been evaluated in multiple preclinical efficacy models, including a mouse model of arthritis induced by collagen (Fig. S3 in the Supplementary Appendix), in which PLX3397 improved the pathologic condition of the joint at exposures (area under the curve from 0 to 24 hours [AUC0–24]) of 90,000 hours × nanograms per milliliter or greater.

**DOSE-ESCALATION STUDY**

*Patient Characteristics, Drug Exposure, and Response*

A total of 41 patients were enrolled in seven dose-escalation cohorts (Fig. 1B). Demographic and baseline characteristics of the patients are provided in Table S7 in the Supplementary Appendix. Overall, the mean duration of treatment for patients in the dose-escalation study was 70.7 days (10 weeks), with a range of 3 to 575 days (Table S7 in the Supplementary Appendix). Among the 35 patients who completed at least one cycle of treatment, 8 (23%) had stable disease, and 1 patient (3%) in cohort 7 who had mucoepidermoid carcinoma of the salivary gland had a confirmed partial response.

**Drug Safety**

Among the 41 patients enrolled in the dose-escalation cohorts, 3 (7%) had a maximum of grade 1 adverse events, 18 (44%) had a maximum of grade 2 events, 16 (39%) had a maximum of grade 3 events, and 3 (7%) had a maximum of grade 4 events; there were no deaths during the study. Details of treatment-related adverse events according to dose-escalation cohort are provided in Table S8 in the Supplementary Appendix. A total of 11 patients (27%) had at least one adverse event of grade 3 or higher that was considered possibly or probably related to the study drug (Table S9 in the Supplementary Appendix). Treatment-related adverse events of grade 3 or higher that occurred in more than 1 patient included anemia, increase in the aspartate aminotransferase level, and decrease in lymphocyte count (with each event occurring in 2 patients [5%]). A decrease in lymphocyte count was excluded as a dose-limiting toxic effect according to a subsequent amendment to the protocol. Among the 41 patients, 5 (12%) had a total of eight dose-limiting adverse events, including 1 patient in cohort 2 (increased international normalized ratio and hematuria), 1 patient in cohort 4 (hyponatremia), 2 patients in cohort 6 (1 had an increase in aspartate aminotransferase level and 1 had anemia, neutropenia, and syncope), and 1 patient in cohort 7 (increase in aspartate aminotransferase level) (Fig. 1B, and Table S10 in the Supplementary Appendix). On the basis of prespecified protocol criteria, the maximum tolerated dose (the highest dose associated with an acceptable side-effect profile) and chosen phase 2 dose were determined to be 1000 mg per day.

**Pharmacokinetics**

Plasma from all 41 patients was available for pharmacokinetic analysis. In general, at steady state (day 15), the median maximum concentration and AUC0–24 exposures increased with increasing dose (Fig. 1C, and Table S11 and Fig. S4A in the Supplementary Appendix). The time of maximum concentration was short, with median values ranging from 1 to 2 hours. The median half-life was estimated to be 16.8 hours on the basis of the pharmacokinetic findings on day 1 in 19 patients from cohorts 1 through 4 who followed a daily-dosing regimen (for 1 patient in cohort 1 and 1 in cohort 2, the half-life could not be determined) (Fig. S4B in the Supplementary Appendix). At the chosen phase 2 dose of 1000 mg per day, the median AUC0–24 was estimated to be 115,000 hours × nanograms per milliliter, which exceeded the level of exposure predicted to be effective by the preclinical model (approximately 90,000 hours × nanograms per milliliter).

**EXTENSION STUDY**

*Patient Characteristics, Drug Exposure, and Safety*

A total of 23 patients with advanced tenosynoval giant-cell tumors were enrolled in the extension study (Fig. 2). Patient demographic and baseline characteristics are provided in Table S12 in the Supplementary Appendix. The mean age of the patients was 46 years, and most patients had disease in their knee. Among the 23 patients, 1 had metastatic disease, 18 had undergone previous surgery, and 4 had received prior treatment with imatinib or nilotinib.

All 23 patients enrolled in the extension study were included in the safety analysis. The median duration of treatment for these patients was
244 days (8 months), and the mean was 254 days (range, 15 to 585). A total of 14 patients (61%) had a dose reduction, and 7 (30%) had a temporary drug withdrawal. The most common reason for dose alteration was fatigue. A summary of the most common adverse events (occurring in ≥10% of patients) and adverse events that were possibly or probably related to treatment is provided in Table S13 in the Supplementary Appendix. Treatment-related adverse events that occurred in 25% or more of the study population included changes in hair color (17 patients [74%]), fatigue (15 patients [65%]), nausea (9 patients [39%]), dysgeusia (6 patients [26%]), and periorbital edema (6 patients [26%]). Treatment-related adverse events of grade 3 or higher included fatigue (1 patient [4%]), diarrhea (1 patient [4%]), anemia (1 patient [4%]), hyponatremia (2 patients [9%]), elevated aspartate aminotransferase or alanine aminotransferase level or both (2 patients [9%]), and neutropenia (1 patient [4%]). Two patients discontinued the study because of adverse events (1 patient had pain of grade 2 in a nonaffected extremity [i.e., the hand] and 1 patient had fatigue of grade 2). No patient in the extension-study cohort died.

Clinical laboratory studies were notable for transient increases in aminotransferase levels in approximately 50% of patients (mostly grade 1), which is consistent with the expected pharmacologic effect of CSF1 pathway inhibition on Kupffer cells. Three patients had grade 3 elevations in aminotransferase levels, which resolved to grade 1 or less after temporary drug withdrawals that were followed by continued administration of the study drug in two patients. In all cases of increases in aminotransferase levels, total bilirubin levels were normal.

Tumor Responses

In an intention-to-treat analysis of response, 12 of 23 patients with tenosynovial giant-cell tumor had a partial response, representing an overall response rate of 52% (95% confidence interval [CI], 32 to 73) (Fig. 3); 7 of 23 patients had stable disease, representing a rate of disease control (complete response, partial response, or stable disease) of 83% (95% CI, 67 to 98). At the time of the data cutoff, the median progression-free survival for these patients had not been reached (Fig. 3); 17 patients remained in the study, of whom 7 had been receiving treatment with the study drug for more than a year. Of the 23 patients, 2 discontinued the trial before their first efficacy analysis and another patient did not have an MRI result available at the time of data censoring, which left 20 patients in the per-protocol efficacy population (Fig. 2). The results of the analysis of response in the per-protocol efficacy population are provided in the Results section and Figure S5 in the Supplementary Appendix. A total of 4 patients with posttreatment efficacy assessments discontinued the study. Two patients who discontinued the study because of adverse events had a partial response. Another patient discontinued the study because of insurance reasons; this patient did not have a response according to RECIST. In addition, although metastatic tenosynovial giant-cell tumor is uncommon, 1 patient with metastatic disease was enrolled in the study and had stable disease for 8 months before the disease progressed at a site.
of metastatic focus. This is the only patient who had disease progression while receiving treatment with the study drug.

Archival tissue samples were available for 19 of the 23 patients in the intention-to-treat population. In situ hybridization staining confirmed in all samples the presence of elevated CSF1 expression in cells diffusely scattered throughout the tumor mass. Representative image and semiquantitative staining scores are shown in Figure 3. This diffuse CSF1 pattern is characteristic of tenosynovial giant-cell tumors and is unlike the pattern of nontumorous synovium, which maintains an ordered lining even when inflamed (Fig. 3, inset). The results of in situ hybridization staining were used to validate this distinctive attribute of tenosynovial giant-cell tumors, on which our treatment rationale and study design were based.5

One patient provided biopsy tissue before and
after treatment. A review of the hematoxylin and eosin–stained slides showed distinct histologic changes consistent with macrophage targeting by PLX3397 after 2 weeks of treatment, including marked decreases in cellularity and pigment-laden macrophage level (Fig. S6 in the Supplementary Appendix).

**Efficacy Assessment by Means of Tumor Volume Score**

Fourteen patients underwent MRI at baseline and at least once after baseline and had results that could be evaluated radiologically with use of the tumor volume score (Fig. 2). Of the 14 patients, 11 had a partial response according to the tumor volume score and the remaining 3 patients had stable disease. The per-protocol response rate according to the tumor volume score is provided in the Results section and Figure S7 in the Supplementary Appendix. Patients generally had a large reduction in tumor burden within the first 4 months of treatment that persisted over time (Fig. 4A); all patients who had a partial response according to the tumor volume score within the first 4 months of treatment maintained their response through the last visit included in the analysis. The mean decrease in tumor volume score was 61% (95% CI, 45 to 76). In this cohort, 3 patients who had received prior treatment with imatinib or nilotinib had a partial response (2 patients) or stable disease (1 patient) (Fig. S7 in the Supplementary Appendix).

An example of an objective response in one patient is shown in Figure 4B, and Figure S8 in the Supplementary Appendix. The tumor volume score decreased by 85% in this patient by 4 months, which indicates a substantial reduction in tumor burden (Fig. 4B). In the same patient’s tumor, the maximum standardized uptake value (on 18F-fluorodeoxyglucose–positron-emission tomography) decreased from 21.7 to 6.4 after only 3 weeks of treatment (Fig. S8A in the Supplementary Appendix), which shows that PLX3397 can very rapidly affect the reactive inflammatory process that is a hallmark of tenosynovial giant-cell tumors.20 In this patient, the reduction in tumor mass correlated with a marked improvement in clinical findings and in the ability of the patient to perform activities of daily living and a marked reduction in symptoms (Fig. S8B in the Supplementary Appendix).
One important lesson from the development of molecularly targeted therapies has been the key role of the drug-bound conformation of the protein target in predicting the clinical efficacy of the drug.\textsuperscript{21,22} Exploiting the structural plasticity of the kinase provides a new strategy for the design of inhibitors with high specificity and clinically relevant pharmacologic properties. In the current study, PLX3397, an inhibitor prospectively designed to engage the juxtamembrane domain of CSF1R, displayed substantial clinical activity, a finding that supports a strong association between the targeted conformation and its therapeutic potential.

The results of the phase 1 trial presented herein show that blocking the CSF1 pathway in tenosynovial giant-cell tumors with an appropriately designed therapy can induce significant regressions in tumor volume. On the basis of a chi-square test, the overall response rate of 52% with PLX3397 is significantly higher than the overall response rate of 19% reported with imatinib\textsuperscript{18} (chi-square test with 1 degree of freedom, 4.86; \textit{P}=0.03)\textsuperscript{24}; however, the agents need to be formally tested against one another in a randomized trial to validate this extrapolation of phase 1 data. In the assessment according to tumor volume score, PLX3397 induced a reduction in tumor volume of 50% or more in 11 of 14 patients who could be evaluated. Tumor responses manifested quickly and had a median duration of 8 months at the time of data cutoff. Only 1 patient had disease progression while receiving therapy; this patient had metastatic tenosynovial giant-cell tumor, whereas the other patients had local disease. Three patients who had been previously treated with imatinib or nilotinib had tumor volume reductions of 40 to 55%.

Side effects included grade 3 or higher treatment-related fatigue, diarrhea, anemia, hypotension, elevated aminotransferase levels, and neutropenia. Adverse events were similar in the dose-escalation cohort and in the extension-study cohort. Understanding, monitoring, and managing these side effects will be important for improving treatment outcomes.

There is a growing list of oncogene-driven neoplasms that respond to drugs targeting the oncogenic driver. It appears that tenosynovial giant-cell tumor can be added to this list, given our results and the results from a recent trial that reported similar effects from the use of an anti-CSF1R antibody.\textsuperscript{23} Although tenosynovial giant-cell tumors appear to be stable with respect to mutation and genetically homogeneous relative to other oncogene-driven tumors, it will be important to determine whether resistance to CSF1R inhibition will occur and, if so, by what mechanism.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

**REFERENCES**


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