Nilotinib in locally advanced pigmented villonodular synovitis: a multicentre, open-label, single-arm, phase 2 trial

Hans Gelderblom, Claire Cropet, Christine Chevreau, Richard Boyle, Martin Tattersall, Silvia Stacchiotti, Antoine Italiano, Sophie Piperno-Neumann, Axel Le Cesne, Virginia Ferraresi, Nicolas Penel, Florence Duffaud, Philippe Cassier, Maud Toulmonde, Paolo Casali, Sophie Taieb, Séverine Guillemaut, Séverine Metzger, David Pérol, Jean-Yves Blay

Summary

Background Pigmented villonodular synovitis (alternatively known as diffuse-type giant cell tumour) is a rare, locally aggressive tumour driven by a specific translocation resulting in the overexpression of colony-stimulating factor 1 (CSF1). CSF1 receptor (CSF1R) inhibitors (ie, tyrosine kinase inhibitors and antibodies) induce a response in patients with pigmented villonodular synovitis. We investigated the safety and efficacy of a CSF1R tyrosine kinase inhibitor, nilotinib, in patients with locally advanced non-resectable pigmented villonodular synovitis.

Methods In this phase 2, open-label, single-arm study, we enrolled patients from 11 cancer centres of hospitals in four countries (France, Netherlands, Italy, and Australia). Eligible patients were aged at least 18 years with a WHO performance status of 2 or less, and histologically confirmed progressive or relapsing pigmented villonodular synovitis that was inoperable, or resectable only with mutilating surgery. Patients received oral nilotinib (400 mg twice per day) until disease progression, unacceptable toxicity, or completion of 1 year of treatment. The primary endpoint was the proportion of patients who were progression free at 12 weeks, which was centrally assessed according to Response Evaluation Criteria in Solid Tumors version 1.1. Analyses were by modified intention to treat (ie, all patients with no major protocol violations who were treated with nilotinib for at least 3 weeks were included). All participants who received at least one dose of study drug were included in the safety analyses. This study is registered with ClinicalTrials.gov, number NCT01261429, and the results presented here are the final analysis of the trial.

Findings Between Dec 15, 2010, and Sept 28, 2012, we enrolled 56 patients with pigmented villonodular synovitis and treated them with nilotinib. Five (9%) patients discontinued study treatment before week 12; therefore, 51 patients were evaluable for the primary endpoint at 12 weeks. The estimated proportion of patients who were progression free at 12 weeks was 92·6% (95% credible interval 84·3–97·9). 54 (96%) of 56 patients had a treatment-related adverse event. Six (11%) of 56 patients had at least one grade 3 treatment-related adverse event (headache, dizziness, and hepatic disorders [n=1], pruritus and toxidermia [n=1], diarrhoea [n=1], increased γ-glutamyl transferase concentration [n=1], anorexia [n=1], and increased headache [n=1]). No grade 4 or 5 adverse events were reported. One patient had a treatment-related serious adverse event (toxidermia) and two patients had serious adverse events not considered to be related to the study drug (borderline ovarian tumour [n=1] and pilonidal cyst excision [n=1]).

Interpretation More than 90% of patients with locally advanced unresectable progressive pigmented villonodular synovitis achieved disease control with 12 weeks of nilotinib treatment. These results indicate that CSF1R tyrosine kinase inhibitors have anti-tumour activity with manageable toxicity in patients with inoperable progressive pigmented villonodular synovitis. Randomised trials investigating the efficacy of nilotinib for patients with unresectable pigmented villonodular synovitis are warranted.

Funding Novartis, Institut National du Cancer, EuroSARC, French National Cancer Institute, General Directorate of Care Supply, Lyon Research Innovation for Cancer, L'Agence nationale de la recherche, Laboratory of Excellence, Fondation ARC pour la recherche sur le cancer, Ligue contre le Cancer (comité de l'Ain), Info Sarcomes, and Association DAM'S.

Introduction

Pigmented villonodular synovitis (also known as diffuse-type tenosynovial giant cell tumour) is a rare pathological disease affecting the synovium and tendon sheaths in young adults.[1–3] Initially considered as an inflammatory reactive process, cytogenetic studies revealed recurrent translocations of 2q37 and 1p13 chromosomal loci involving *COL6A3* (encoding collagen type VI α3) and the *CSF1* gene in a subpopulation of tumour cells, and showed that pigmented villonodular synovitis is a neoplastic process with a locally destructive clinical behaviour.[4] The resulting fusion protein is cleaved and induces tumour cells to increase colony-stimulating factor 1 (CSF1) secretion, which attracts non-neoplastic cells (ie, macrophages and monocytes) expressing the CSF1 receptor (CSF1R), via a paracrine effect.[4–6] The standard treatment for this disease is surgery and even in patients who relapse, re-excision remains the treatment of

Department of Medical Oncology, Leiden University Medical Centre, Leiden, Netherlands
(Prof H Gelderblom MD); Direction of Clinical Research and Innovation (C Cropet MSc, S Guillemaut MSc, S Metzger MSc, D Pérol MD) and Department of Medical Oncology (P Cassier MD, Prof J-Y Blay MD), Centre Léon Bérard, Lyon, France; Department of Medical Oncology, Institut Claudius Regaud, Institut Universitaire du Cancer de Toulouse, Toulouse, France
(C Chevreau MD); Department of Medical Oncology, Royal Prince Alfred Hospital, Camperdown, NSW, Australia (R Boyle MD, M Tattersall MD); Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
(S Stacchiotti MD, Prof P Casali MD); Department of Medical Oncology, Institut Curie, Paris, France
(S Piperno-Neumann MD); Department of Medical Oncology, Institut Bergonié, Bordeaux, France
(Prof A Italiano MD, M Toulmonde MD); Department of Cancer Medicine, Gustave Roussy, Villejuif, France
(A Le Cesne MD); Medical Imaging Department
(S Taieb MD) and Department of Medical Oncology
(Prof N Penel MD), Centre Oscar Lambret, Université Lille 2, Lille, France; Hôpital de la Timone, Aix-Marseille Université, Marseille, France
(Prof F Duffaud MD); Regina Elena National Cancer Institute, Rome, Italy (V Ferraresi MD); and University Claude Bernard Lyon 1, Lyon, France
(Prof J-Y Blay)

Correspondence to:
Prof Jean-Yves Blay, Department of Medical Oncology, Centre Léon-Bérard, Lyon 69373, France
jean-yves.blay@lyon.unicancer.fr

Research in context

Evidence before this study

New treatments are needed for patients with pigmented villonodular synovitis who have inoperable or relapsing tumours. At present, novel drugs targeting the colony-stimulating factor 1 receptor (CSF1R) are being developed and several clinical trials are ongoing. We searched PubMed for original articles and reviews published between Jan 1, 2000, and Aug 31, 2017, using the search terms "PVNS", "pigmented villonodular synovitis", "tenosynovial giant cell tumour", "nilotinib", "tyrosine kinase inhibitors", "CSF1R" without language restrictions. We did not identify any clinical trials of nilotinib for pigmented villonodular synovitis.

Added value of this study

To the best of our knowledge, this is the first open-label, multicentre, single-arm phase 2 trial study to investigate the efficacy and safety of the tyrosine kinase inhibitor nilotinib in progressive or relapsing patients with non-resectable pigmented

villonodular synovitis or for whom surgery would be mutilating. This study showed that nilotinib provided tumour control after 12 weeks in most patients with the disease and yielded long-lasting disease stabilisation in more than 50% of patients, with a small number of partial responses. However, nilotinib had notable toxicity in some patients; almost all patients had a treatment-related adverse event, six patients had at least one grade 3 treatment-related adverse event, and approximately 20% of patients discontinued treatment before 1 year.

Implications of all the available evidence

In view of the paucity of available therapies for patients with progressive or relapsing pigmented villonodular synovitis, the efficacy of nilotinib or other drugs that target CSF1R in this disease needs to be assessed in randomised trials. Further exploration of drugs targeting CSF1R is needed to clarify the molecular mechanism underlying the response to nilotinib in patients with pigmented villonodular synovitis.

See **Online** for appendix

choice when complete resection is feasible.[1,2] However, complete resection is not always feasible and might lead to substantial functional impairments.[1,2] Retrospective series[7,8] suggest that a third of patients with pigmented villonodular synovitis have a first local relapse, with 4-year local failure-free survival rates of only around 20% after first relapse. No medical treatment is approved for inoperable pigmented villonodular synovitis.

Before 2015, no prospective studies of pigmented villonodular synovitis had been done, possibly because of the rarity of the disease.[8] Retrospective studies[9,10] suggested that tyrosine kinase inhibitors might be a treatment option in patients for whom a complete surgery is not feasible or would be mutilating. An initial case report[9] showed a complete response with imatinib in a patient with recurrent pigmented villonodular synovitis. A multicentre retrospective study[10] subsequently reported that imatinib showed anti-tumour activity in locally advanced pigmented villonodular synovitis, with an objective response recorded in nearly 20% of patients. Anti-CSF1R antibodies, including emactuzumab,[11] cabiralizumab,[12] and pexidartinib—a multitargeted tyrosine kinase inhibitor[13]— were shown to have encouraging clinical activity in phase 1 trials and phase 1 extension studies. Other phase 1 trials are ongoing (NCT02471716, NCT02673736, and NCT01643850). A phase 3 trial comparing pexidartinib with placebo is also in progress (NCT02371369).

Nilotinib is a phenylaminopyrimidine that inhibits several tyrosine kinases, including ABL, KIT, platelet-derived growth factor receptors, and CSF1R. Nilotinib is indicated for the treatment of adults with chronic and accelerated phase Philadelphia chromosome-positive chronic myelogenous leukaemia resistant to, or intolerant of, previous therapies including imatinib, and has also been explored in patients with gastrointestinal

stromal tumours.[14–20] We aimed to assess the anti-tumour activity of nilotinib in patients with progressive or relapsing pigmented villonodular synovitis, in whom conservative or non-mutilating surgery was not feasible.

Methods

Study design and participants

In this multicentre, open-label, single-arm, phase 2 study, patients were enrolled at 11 comprehensive cancer centres or hospitals in four countries (France, the Netherlands, Italy, and Australia; appendix p 1).

Patients were eligible if they were aged at least 18 years with a WHO performance status of 2 or less, and had histologically confirmed inoperable progressive or relapsing pigmented villonodular synovitis, or pigmented villonodular synovitis only resectable with mutilating surgery. Inclusion criteria also included having at least one measurable site of disease (according to Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1), disease progression in the previous 12 months,[21] adequate liver, renal, and haematological functions, normal potassium and magnesium concentrations, normal cardiac function in the 4 weeks before inclusion, and no hypertension. Exclusion criteria were previous treatment with imatinib (with the exception of patients who had no disease progression during imatinib treatment), known hypersensitivity to nilotinib, concomitant treatment with warfarin, anti-arrhythmic drugs, or medication that prolongs the QT interval, or medicinal products that induce or inhibit CYP3A4 activity. We also excluded patients with acute or chronic uncontrolled liver disease, severe renal disease, impaired cardiac function, or severe or uncontrolled concurrent medical disease (eg, uncontrolled diabetes, active or uncontrolled infection, or a history of pancreatitis). Patients with a family history

of long QT syndrome, unexplained syncope, or unexplained sudden death were also excluded.

The study protocol was approved by the local ethics committee at each site, and is available online. This study was done in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent.

Procedures

Patients received oral nilotinib 400 mg twice per day until disease progression, intolerable toxicities, patient decision to withdraw, or completion of 1 year of treatment. Patients were followed up at 6 weeks, 12 weeks, 18 weeks, 6 months, 9 months, and 12 months. Patients who were progression free after 1 year of treatment could receive continuation of nilotinib as a compassionate treatment. Drug-related adverse events were assessed every 6 weeks until week 24, then at week 36 and week 48, and graded by investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Patients with haematological toxicity (≥grade 3) or non-haematological toxicity (≥grade 2) could stop treatment for 28 days, followed by dose reduction to 400 mg per day. Patients who required dose reduction could have dose re-escalation, with the exception of those who had dose reductions because of QTc interval prolongation. Safety assessments, including laboratory monitoring, were done during screening. Blood cell count was assessed every 2 weeks during the first 2 months of treatment and once a month thereafter, or when clinically indicated. Sodium, potassium, chlorine, calcium, creatinine, urea, aspartate aminotransferase, alanine aminotransferase, albumin, bilirubin, and serum lipase concentrations were assessed on the second day of treatment, and 7 days before radiological assessment. Radiological response was assessed by CT scan or MRI every 6 weeks until week 12, and then every 3 months thereafter until 12 months, according to RECIST 1.1.[21] Investigator-assessed progression dates were updated once in December, 2016, with no specific schedule; thus, assessments were done according to the local practices, most often with assessments every 6 months (for 3–12 months). After 1 year of treatment, tumours were classified as operable or not operable according to investigators' assessment, and the proportion of patients with an operable tumour after nilotinib exposure was reported. Resection dates were also recorded. Patients were not given nilotinib after surgical resection. No data were collected for the quality or type of resection in the study. No central pathology review was done according to the protocol, and tissue collection for translational research was optional. However, all the centres involved were national reference centres for connective tissue tumours where centralised review of the pathology diagnosis is a routine procedure. Optional translational research included the measurement of nilotinib trough levels (10–14 h after last dose) at 6 weeks and 12 weeks.

Outcomes

The primary endpoint was the proportion of patients who were progression free at 12 weeks assessed by a central independent review committee. Patients were considered progression free if they had a complete or partial response, or stable disease (defined by RECIST version 1.1[21]).

Secondary endpoints were the proportion of patients who were progression free at 24 weeks, the proportion of patients with an objective response defined as a complete or partial response at 12 weeks, best overall response achieved during the study (ie, up to 1 year), duration of response, progression-free survival, time to treatment failure, time to progression, the proportion of patients who were progression free at 12 weeks according to local investigator assessment, the proportion of patients with an operable tumour after nilotinib exposure according to investigator assessment, concomitant treatment use, the association between trough levels of nilotinib and objective tumour response, and safety. Of these secondary endpoints, the proportion of patients who were progression free at 24 weeks, the proportion with an objective response at 12 weeks, best overall response, and progression-free survival were centrally assessed. All other endpoints were investigator-assessed. Progression-free survival was defined as the time between treatment initiation and first documented progression or death from any cause. Time to treatment failure was defined as the time between treatment initiation and the earliest date of progression, death from any cause, or discontinuation for reasons other than having tumour resection. Time to progression was defined as the time between treatment initiation and the earliest date of progression, or death due to progressive disease. Duration of response was defined as the time between first response (complete response or partial response) and first progression or death due to underlying cancer or tumours. Safety was assessed by clinical, biological, and cardiac assessments, and adverse events were graded according to the CTCAE (version 4.0).

Statistical analysis

The primary endpoint was assessed in terms of success and failure, with success defined as being progression free at 12 weeks, and failure defined as disease progression. We used a sequential Bayesian design, which allows continuous monitoring of the main efficacy outcome and permitted early termination of the trial due to inefficacy.

Using a Fleming design and considering a minimum proportion of progression-free patients at 12 weeks of 50%, with a stopping rule for futility set as a progression-free rate at 12 weeks of 30% and one-sided type I error of 0·05, we calculated that a maximum sample size of 50 patients would be required to provide 90% power.

The probability of success (ie, patients being progression free at 12 weeks) was estimated using a beta-binomial model.[22] Initial parameters of the model

were prespecified on the basis of the physician's initial opinion and simulation models, and the prior distribution (probability density function) of the success rate (representing the knowledge of the non-progression probability before observing the data) was set to a beta (2,1)—ie, a success rate of 67%.

Eight interim analyses were planned following the inclusion of the first ten patients and after the inclusion of every five patients thereafter. Based on the observed data, the prior distribution of success was updated and refined at each interim analysis to obtain the posterior distribution, allowing the estimation of the mean success rate with 95% credible interval (CrI; measure of Bayesian precision), and the predictive probability of patients being progression free at 12 weeks. A futility stopping rule recommended to stop the trial if there was a high predictive probability (≥ 0.8) that the estimated proportion of progression-free patients at 12 weeks was lower or equal to the futility boundary of 30%. The 12-week prior and posterior density functions for the proportion of progression free patients across successive interim analyses were plotted graphically.

The primary endpoint was analysed by modified intention to treat, including all patients with no major protocol violations who were treated with nilotinib for at least 3 weeks. Major protocol violations were defined as deviations that could potentially affect efficacy analysis, including patients not meeting important inclusion or exclusion criteria (eg, incorrect diagnosis), taking the wrong study medication, and not having their treatment response assessed by CT scan or MRI at 12 weeks.

Kaplan-Meier curves were used to analyse progression-free survival, time to treatment failure, time to progression, and duration of response (with 95% CIs). We estimated median progression-free survival with two-sided 95% CIs. Patients who were progression free or were without treatment failure at the time of the analysis were censored at the date of their last tumour assessment. Patients were not censored at the time of surgery.
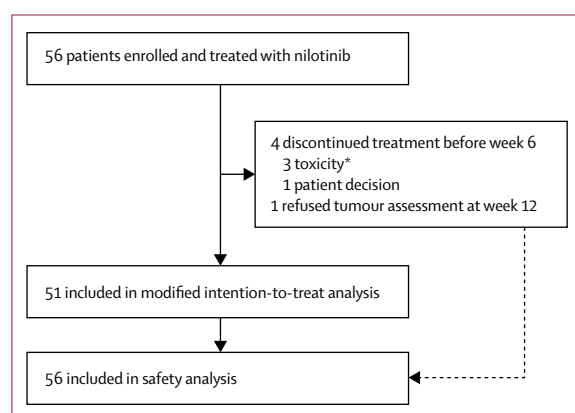
All patients who received at least one dose of nilotinib were assessed for safety. The data cutoff for data analysis was May 9, 2014.

The long-term follow-up analysis was not planned in the protocol. Long-term follow-up was done for all patients without disease progression at the time of the study report. Patients who discontinued treatment before 1 year because of reasons other than progression were also considered in this long-term analysis and thus might have had a progression before 1 year. Post-hoc exploratory subgroup analyses were done to assess the effect of secondary resection, duration of treatment with nilotinib (<1 year, 1 year, >1 year), and pretreatment with imatinib on progression-free survival.

All statistical analyses were done with SAS version 9.2. This study is registered with ClinicalTrials.gov, number NCT01261429. A data monitoring committee oversaw the study.

Role of funding source

Results

56 patients with pigmented villonodular synovitis were enrolled between Dec 15, 2010, and Sept 28, 2012 (figure 1). The median age of the treated population was 36 years (IQR 26·0–44·5), with equal numbers of male and female patients (table 1). All patients had a localised tumour without metastasis at diagnosis. The six patients who had previously received imatinib were declared as having progressive disease and requiring mutilating surgery at inclusion. Almost three-quarters of patients had previously undergone surgery for their tumour (table 1). One patient who received nilotinib 3 months after surgery was identified as relapsing (last relapse 1·5 months after surgery) and was subsequently enrolled in this study in the following weeks.

All 56 patients received 400 mg nilotinib twice per day, of whom five (9%) patients discontinued study treatment before week 12 and were therefore not evaluable for the primary endpoint. 31 (55%) of

***Figure 1:* Trial profile**
*One patient had severe toxicity at day 6 and was thus was considered to have had treatment failure.

56 patients completed 1 year of study treatment and 25 (45%) discontinued treatment before 1 year (progressive disease [n=6], tumour resection [n=4], toxicity [n=5], patient's refusal [n=8], investigator decision [n=1], lost to follow-up [n=1]).

Median duration of treatment at the end of the study was 11·0 months (IQR 7·0–12·0) in the overall patient population (n=56). Six patients received nilotinib as a compassionate treatment for more than 1 year (range 13–22 months) for 5–48 additional weeks.

Six of the eight planned successive interim analyses were done according to the Bayesian approach in August, 2011 (n=9), November, 2011 (n=14), April, 2012 (n=27), July, 2012 (n=34), October, 2012 (n=41), and January, 2013 (n=47), with the final analysis done in May, 2014 (n=51). Two of the initially planned interim analyses were not done because of faster than expected accrual into the study. The stopping criterion for inefficacy was not met at any of the interim analyses.

According to the modified intention-to-treat approach, the efficacy analysis for the primary endpoint was done in 51 (91%) of the 56 included patients. Five (9%) of 56 patients were not evaluable at week 12 because no CT scan or MRI was done at week 12, of whom four (7%) discontinued before week 6 because of toxicity (grade 2 hypotension [n=1], grade 2 limb oedema [n=1], and grade 3 headache [n=1]), or withdrawal of consent (n=1), and one (2%) withdrew consent between week 6 and week 12. 49 (96%) of the 51 evaluable patients met the primary endpoint and were progression free at 12 weeks. The two (4%) remaining evaluable patients had progressive disease at week 6 and thus were considered to have treatment failure for the primary endpoint analysis. One (2%) additional patient, who stopped treatment earlier for adverse events was also considered to have treatment failure, and therefore 49 (94%) of 52 evaluable patients were considered to have treatment failure at week 12. The mean Bayesian-estimated proportion of patients who were progression free at week 12 was 92·6% (95% CrI 84·3–97·9; figure 2).

Three additional patients had disease progression at the 24-week assessment; therefore 46 (90%) of 51 evaluable patients were progression free at 24 weeks. Three (6%) of 51 patients discontinued the study because of toxicity between weeks 12 and 24, and therefore were not considered to have disease progression at the 24-week assessment. The Bayesian estimated mean proportion of patients who were progression free at 24 weeks was 88·2% (95% CI 76·6–94·5).

51 of the 56 enrolled patients were evaluable for the other secondary endpoints (the four patients who discontinued before week 6 and the one patient who discontinued between week 6 and 12 were not evaluable for these endpoints). No patients (0%) had an objective response at week 12. The best overall response after 1 year of treatment was stable disease, which was achieved in 46 (90%) of

51 patients, and partial response in three (6%) of 51 patients according to the central review, of which two partial responses were recorded at 24 weeks and one at 1 year (figure 3). Thus, the proportion of patients who achieved an objective response during the 1-year study period was 6% (95% CI 1·2–15·9). Duration of response observed for the three patients with a partial response was 52, 40, and 51 months, respectively; none of these three patients had

	All enrolled patients (n=56)
Age, years	36 (26·0–44·5)
Sex	
Women	28 (50%)
Men	28 (50%)
WHO performance status	
0	41 (73%)
1	15 (27%)
Time since diagnosis, months	21·9 (5·1–67·6)
Primary tumour location	
Knee	29 (52%)
Hip or femoral neck	7 (13%)
Ankle or foot	13 (23%)
Wrist	2 (4%)
Hand or finger	3 (5%)
Ulna	1 (2%)
Other	1 (2%)
Previous treatment with imatinib*	6 (11%)
Imatinib treatment duration, months	3 (2·6–5·9)
Time since imatinib discontinuation, months	11·2 (5·7–17·0)
Previous treatment with radiotherapy	4 (7%)
Time since radiotherapy, months	49·6 (37·8–168·6)
Previous surgery	40 (71%)
Time since surgery, months	20·5 (10·2–45·4)

Data are n (%) or median (IQR). *Imatinib was discontinued due to surgical resection (n=1), administrative reasons (n=1), or adverse events (n=4).

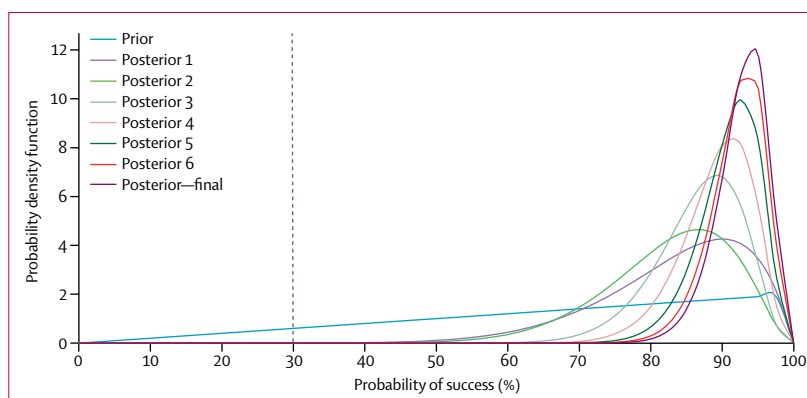*Table 1:* **Baseline demographics and clinical characteristics**

Figure 2: **Bayesian estimates of the probability distribution of being progression free (success) at 12 weeks**
Prior and posterior density functions of the probability of success were updated after each successive interim analysis. Success was defined as being progression free at 12 weeks.

progression at the last follow-up (December, 2016). 25 (45%) of 56 patients discontinued treatment before 1 year, of whom 22 (39%) had treatment failure (ie, discontinuation of treatment due to reasons other than their tumour becoming operable). Median time to treatment failure was not reached. Since no deaths were reported in the study, time to progression was considered equivalent to progression-free survival.

Ten (20%) of the 51 evaluable patients had disease progression during the 1-year study period. Four patients with clinical progression notified by the investigators were not considered as having disease progression on central radiology review. Progression-free survival at 1 year was 77·1% (95% CI 63·2–86·1; figure 4). Median progression-free survival was not reached. At study completion (1 year), 37 (66%) of 56 patients were considered operable by the local team; however, these criteria were not centrally assessed (appendix).
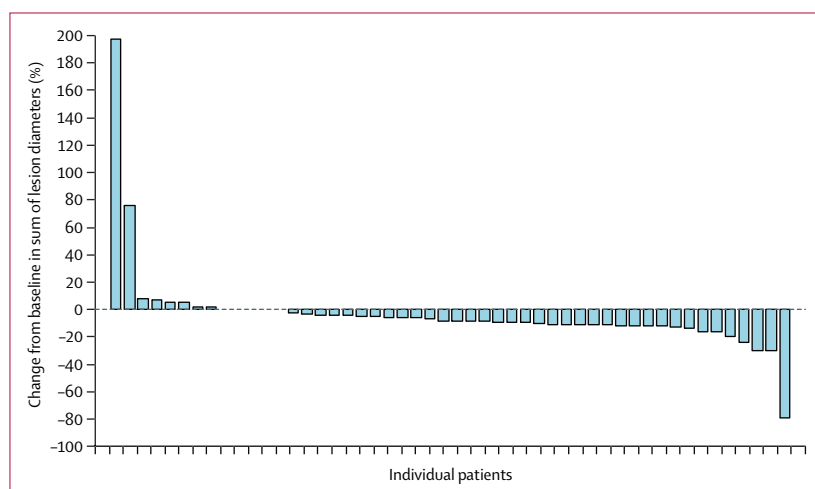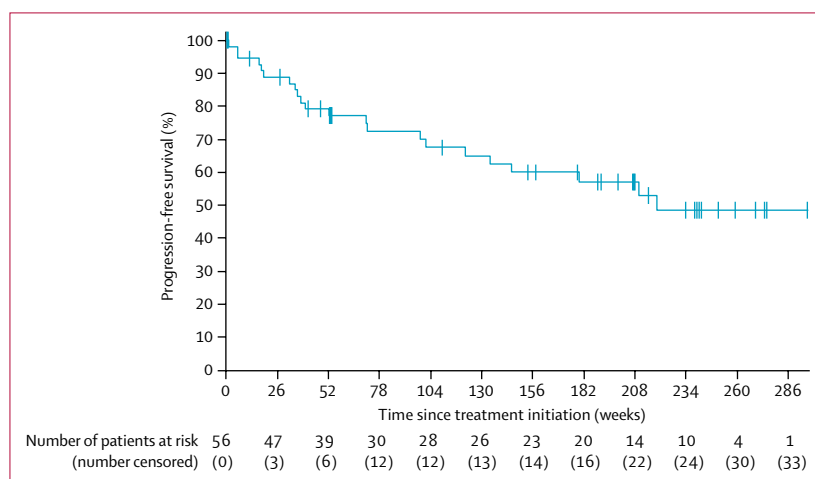
49 (96%) of 51 evaluable patients were progression free at 12 weeks according to local investigator assessment. Concomitant treatment use will be reported in a subsequent publication.

Plasma nilotinib trough levels were measured in 12 patients. The mean trough level of plasma nilotinib was 1663·3 ng/mL (SD 609·5); however, the sample size was too small to investigate the association between trough levels and tumour control. The side-effect profiles of the six patients with the lowest and highest trough levels of nilotinib were superimposable.

55 (98%) of 56 patients had at least one adverse event, and adverse events were considered treatment related in 54 (96%) patients. Table 2 shows the treatment-related adverse events that occurred. 23 (41%) patients had adverse events leading to treatment modification (data not shown). Six (11%) patients had at least one grade 3 treatment-related adverse event (headache, dizziness, and hepatic disorders [n=1]; pruritus and toxidermia [n=1]; diarrhoea [n=1], increased γ-glutamyl transferase concentrations [n=1], anorexia [n=1], and increased headache [n=1]); table 2. No grade 4 or 5 adverse events were reported during the study. Serious adverse events were reported in three patients: one treatment-related adverse event of skin toxicity, and two serious adverse events not considered to be treatment related (borderline ovarian tumour [n=1] and pilonidal cyst excision [n=1]). One serious adverse event did not directly concern the patient. This serious adverse event was the pregnancy of the spouse of a male patient receiving nilotinib. There were no consequences on pregnancy, delivery, or the health of the child during the follow-up. None of the treatment-related adverse events were fatal.

Long-term follow-up analysis to 1 year and beyond was not pre-planned. The favourable results obtained at 1 year led us to collect additional information about long-term outcomes, to investigate the poorly understood natural history of the disease. This post-hoc analysis was done for all patients without disease progression at the time of the study report (n=50). Progression-free survival and information about subsequent surgery were collected in December, 2016, 48 months after the end of the study. Data could not be obtained for 14 patients from several different centres (patient withdrawal [n=2], unknown reasons [n=12]; appendix p 1); therefore, data for 50 patients were collected for this long-term follow-up analysis. At a median follow-up of 48 months (IQR 12·3–57·7), progression-free survival at 48 months was 57·1% (95% CI 41·2–70·2; figure 4). Of the 37 patients whose tumours were considered operable by the local team after treatment with nilotinib for 1 year, 17 (30%) then had surgery, including six (38%) of 16 patients who had never been resected, and 11 (28%) of 40 patients who had previous surgery before study inclusion. None of these 17 patients received nilotinib after the 1-year treatment period. Post-hoc exploratory analyses showed that

Figure 3: **Best overall response to nilotinib treatment during the treatment period in 50 patients**
One patient was reported to have stable disease by the investigator, but no precise measurement of the lesions were done after treatment.


Number of patients at risk	56	47	39	30	28	26	23	20	14	10	4	1
(number censored)	(0)	(3)	(6)	(12)	(12)	(13)	(14)	(16)	(22)	(24)	(30)	(33)

Figure 4: **Kaplan-Meier analysis of progression-free survival**

secondary resection and nilotinib treatment duration had no effect on progression-free survival (appendix p 4). Additionally, pretreatment with imatinib had no effect on progression-free survival (data not shown).

Discussion

In this open-label, single-arm, phase 2 trial, nilotinib led to disease stabilisation in more than 90% of patients with non-resectable pigmented villonodular synovitis at 12 weeks, and partial responses in three patients (two at 24 weeks and one at 1 year) who remained progression free 48 months after the end of the study. In this study, the proportion of patients who were progression free at 12 weeks (>90%) and 24 weeks (>85%), the 1-year progression-free survival of 77%, and the 4-year progression-free survival of 57%, provide a benchmark for a disease with no alternative treatment option.

Nilotinib was selected for this study with the aim of reducing the substantial toxicity reported with imatinib in patients with pigmented villonodular synovitis.[9,10] The efficacy of nilotinib has been reported to be superior to that of imatinib in adults with chronic myelogenous leukaemia, but not in gastrointestinal stromal tumours.[14,16–18] We assumed that both tyrosine kinase inhibitors would have similar CSF1R inhibition potency, but nilotinib would have a more favourable tolerability profile, particularly with regard to soft tissue and facial oedema.[15,19,20]

The Bayesian statistical approach was chosen for this study because it enabled the use of less stringent assumptions for this rare disease, for which no controlled clinical trials have been done. On the basis of tyrosine kinase inhibitor activity reported in retrospective studies,[9,10] we set a futility boundary at 30% for treatment efficacy, with a short interval of 12 weeks selected to limit patient exposure to a potential ineffective treatment. The Bayesian approach also permitted early termination of the trial due to inefficacy and would enable us to reject nilotinib for further testing if no sufficient promising activity was shown in pigmented villonodular synovitis. Additionally, the added value of the Bayesian design was to provide a robust calculation of the probability of individuals being progression free in a given interval.

The high proportion of patients who achieved tumour control after 12 weeks, 24 weeks, 1 year, and 4 years of treatment supports the anti-tumour activity of CSF1R tyrosine kinase inhibitors in this disease. In patients who discontinued treatment for reasons other than progression, disease progression was not consistently observed. The 4-year progression-free survival after nilotinib discontinuation of 57% is consistent with a retrospective report[10] on patients with pigmented villonodular synovitis treated with imatinib indicating that a short duration of treatment with CSF1R tyrosine kinase inhibitors can provide long-term tumour control in more than 50% of patients with pigmented villonodular synovitis.

	Grade 1–2	Grade 3
Headache	21 (38%)	2 (4%)
Nausea	15 (27%)	0
Increased alanine aminotransferase concentrations	14 (25%)	0
Fatigue	13 (23%)	0
Asthenia	13 (23%)	0
Rash	9 (16%)	0
Alopecia	8 (14%)	0
Increased aspartate aminotransferase concentrations	7 (13%)	0
Pruritus	5 (9%)	1 (2%)
Increased bilirubin	6 (11%)	0
Diarrhoea	4 (7%)	1 (2%)
Increased γ-glutamyl transferase concentrations	5 (9%)	1 (2%)
Anorexia	4 (7%)	1 (2%)
Dizziness	2 (4%)	1 (2%)
Toxidermia*	0	1 (2%)
Hepatic disorder	0	1 (2%)

All enrolled patients (n=56). Data are n (%). One patient had two treatment-related adverse events (grade 3 pruritus and grade 2 rash) and one patient had three adverse events (grade 2 headache, grade 3 dizziness, and grade 3 hepatic disorders). Two serious adverse events (borderline ovarian tumour in one patient and pilonidal cyst excision in one patient) were not related to the study drug. *Serious adverse event related to the study drug.

Table 2: **All treatment-related adverse events**

Phase 1 studies[11–13] investigating drugs that selectively block CSF1R, including emactuzumab, pexidartinib, and cabiralizumab, have confirmed the value of targeting the CSF1 and CSF1R axis in this disease. However, response rates with nilotinib are lower than those reported with other drugs—eg, pexidartinib led to partial response in 12 (52%) of 23 patients and stable disease in seven (30%) of 23 patients.[13] In the same study, the median progression-free survival was not reached at the time of the data cutoff, and seven patients received more than 1 year of treatment.[13] Emactuzumab yielded an objective response in 24 (86%) of 28 patients, and a partial response in 19 (68%) of 28 patients after 6 weeks of treatment.[11] In a phase 1–2 study, cabiralizumab yielded an objective response in four (36%) of 11 evaluable patients.[12]

In our study, 15 patients discontinued nilotinib treatment before 1 year for reasons other than tumour operability or progression. However, the side-effect profile of nilotinib was consistent with previous reports[14,17–20] in other diseases. More patients discontinued treatment without progression than usually occurs in oncology trials. Pigmented villonodular synovitis is a locally aggressive disease causing functional impairment, but it is rarely life threatening, which might account for patient decisions to discontinue treatment earlier than specified by the protocol. Poor compliance has also been observed in adjuvant clinical trials[23] with imatinib in gastrointestinal stromal tumours, which

might be because the side-effects of long-term drug dosing are less well tolerated by patients and physicians are reluctant to use these drugs to treat a disease that is rarely fatal.

In our study, we selected a starting dose of 400 mg nilotinib twice per day. This dose is known to block the CSF1R and was well tolerated in patients with chronic myelogenous leukaemia with prolonged administration, with dose adaptations according to the summary of product characteristics. Whether or not lower doses of nilotinib could be used in pigmented villonodular synovitis remains to be determined, as does the efficacy of maintenance treatment with a lower dose, especially in view of compliance to this protocol. These questions cannot be addressed in the dataset used in our study, but warrant exploration in future trials. At present, the recommended dose of nilotinib for patients with pigmented villonodular synovitis is 400 mg twice per day for 1 year, but lower doses and a shorter duration of treatment should be explored, with the possibility of intermittent dosing approaches.

55% of patients completed 1 year of treatment, and 57% of patients had no disease progression for 4 years, despite a planned treatment duration of only 1 year. In view of our post-hoc analyses, a treatment duration of 1 year seems to be a reasonable option. The magnitude of the side-effects with nilotinib seems to be similar to or lower than that reported with pedixartinib, emactuzumab, and cabiralizumab in phase 1 trials,[11–13] with the acknowledgment of the limitations of indirect comparisons between studies. The side-effect profile of these drugs requires specific consideration in the context of a non-malignant non-lethal disease, whereby the therapeutic objective is to achieve symptom control without mutilation or to decrease the burden of side-effects.

The toxicity profile of medical drugs administered in patients with locally advanced pigmented villonodular synovitis should also be compared with that of alternative treatment options available for this patient population, and the morbidity associated with a surgical approach should also be considered. In patients with relapsing pigmented villonodular synovitis, the surgical approach is not standardised and often requires mutilating surgery, occasionally including amputations.

An important question is whether or not surgery after treatment with tyrosine kinase inhibitors should be recommended. According to our post-hoc subgroup analyses, patients who had surgery after treatment with nilotinib had a similar outcome when compared with patients who did not have surgery. However, this was not a randomised trial, and thus biases in the selection of patients for surgery are highly likely. Nevertheless, the role of secondary surgery remains unclear in this patient population. Further investigations are needed to explore this question. Similar observations were made in desmoid tumour, another locally aggressive connective tissue tumour.[24] For this reason, quality of life needs to be explored further in patients with pigmented villonodular synovitis treated with tyrosine kinase inhibitors, and the exploration of primary endpoints such as functional assessments in the ongoing pexidartinib phase 3 trial (NCT02371369) will help to address this issue.

Our study has several limitations. No internal comparator was used, which would enable discrimination between the drug activity and the occurrence of spontaneous stable disease. We decided not to add a control group for several reasons: pigmented villonodular synovitis is a rare disease, no standardised control treatment exists for it, and the addition of a control group might have compromised the feasibility of the study in terms of patient recruitment. No prospective phase 2 clinical trials exploring a medical treatment for this disease had been reported when we initiated this study. Another limitation was the time at which the primary endpoint was assessed (ie, proportion of patients who were progression free at 12 weeks), which was selected to limit patient exposure to a potentially ineffective treatment. The proportion of patients who were progression free at 12 weeks was higher than we had expected. We selected the values of the null and alternative hypothesis on the basis of the paucity of scientific knowledge to date, building on observations in a small number of patients at some of the participating centres. In view of the results of our study, this primary endpoint should now be further extended, and combined with patient-reported outcomes, such as quality of life or functional endpoints, in future trials. Another limitation of the trial is that only 31 (55%) of 56 patients actually received treatment for 1 year, with more than 20% of patients choosing to discontinue treatment before the end of the 1-year study.

We planned eight interim analyses, but only six were done because patient recruitment was faster than expected; however, this is unlikely to have affected the final conclusion of the primary endpoint in view of the consistent results observed at each interim analysis. 14 patients were lost to long-term follow-up for the post-hoc analysis, including patients who chose to discontinue study treatment. The number of dropouts was similar across study centres with no obvious bias of distribution.

As reported in previous studies,[7,8] the patients included in this trial were those for which surgery was likely to have a high chance of failure. However, the long-term outcome of this patient population was similar to that of operable patients in a large series reported by Palmerini and colleagues.[7] The qualification of operability remains subjective, especially in multicentre international trials, and this parameter was not centrally assessed. Although 37 patients were considered to have operable tumours after treatment with nilotinib by the local team, a precise definition of operability was not included in the protocol. Since only three patients had a partial response according to RECIST, most of the patients with pigmented villonodular synovitis who were considered operable after

nilotinib probably had stable disease with minor tumour shrinkage; thus, they had no response according to RECIST, but were nonetheless deemed suitable for resection according to the local team. Importantly, operability was assessed by experts from reference centres in connective tissue tumours, which might have decreased, but not abolished, the heterogeneity of this interpretation.

Both patients with partial response and stable disease might therefore benefit from treatment with a tyrosine kinase inhibitor. Symptom improvement (ie, decreased pain or functional improvement) was not specifically assessed in this study. In view of this, we consider long-term radiological stable disease a reasonable endpoint to guide tyrosine kinase inhibitor treatment in these patients, if associated with clinical benefit. Local failure-free survival after relapse has recently been reported to occur at a median of 12 months.[7] This was not known at the time of conception of the study. The observation that 57% of patients were progression free at 4 years supports the concept of a transient treatment duration, which has been adopted for the randomised study of pexidartinib (ClinicalTrials.gov, number NCT02371369). Symptom improvement together with achievement of stable disease is a major composite endpoint that should be considered for future clinical trials in this disease. In our study, more than half of patients requiring treatment for this functionally impairing disease did not progress in the 4-year period following inclusion. This conclusion could be considered as a benchmark for the ongoing and forthcoming registration studies. These results compare favourably with the projected 4-year local failure-free survival rates of less than 20% for patients who had a first relapse, which have been reported by Palmerini and colleagues,[7] with the limitation of indirect comparisons.

In pigmented villonodular synovitis, imatinib has been reported to yield tumour control in patients who had progressed with nilotinib treatment.[25] In the present study, we enrolled six patients treated with nilotinib after previous treatment with imatinib. These six patients had discontinued imatinib for reasons other than progression and were considered as progressive, relapsing, or requiring mutilating surgery at inclusion. The effect of previous imatinib treatment in these patients is unclear, but it is important to note that median time from imatinib discontinuation to inclusion was 11·2 months (IQR 5·7–17·0). Overall, the results of our study were similar to those of retrospective series[9,10] with imatinib, indicating these two tyrosine kinase inhibitors as potential therapeutic options in this disease, unless viable alternatives are available.

The biological mechanism accounting for the long period of stable disease following the blockade of CSF1 recruitment of CSF1R-bearing inflammatory cells in this disease is unclear. This mechanism could be explored through the histological examination of resected tumours, which were not available in the present study. Similar observations of prolonged stable disease following discontinuation of targeted treatment are reported in other locally aggressive connective tissue tumours, such as giant cell tumour of the bone and desmoid tumours.[24] We hypothesise that CSF1R blocks a feedback loop between CSF1R-positive inflammatory cells and the tumour cells that express the fusion protein. It would have been of interest to identify the COL6A3-CSF1 fusion transcript (observed in only a subgroup of patients with pigmented villonodular synovitis) and its potential association with nilotinib efficacy. However, central review and central collection of material were not mandatory in our protocol and the number of samples collected was too small for molecular analysis.

One of the important questions to be addressed in the future is the definition of the candidate population for tyrosine kinase inhibitor treatment. In the present study, only patients with disease that was considered unresectable, or resectable only with mutilating surgery, were included. A formal definition of this criterion will be difficult to obtain. Patients relapsing after surgery, or who have pain or functional impairment, can be considered as a population of choice for tyrosine kinase inhibitor therapy. As has been shown for sarcoma,[26] it is recommended that these patients are best diagnosed and managed by reference centres after the initial diagnosis. Therefore, the criteria to initiate treatment for pigmented villonodular synovitis remain to be further characterised. This is also the case for other locally aggressive connective tissue tumours, such as desmoids or giant cell tumours of the bone. The rationale to initiate treatment in these patients is likely to be representative of the general recommendation for these rare tumours.[25]

To the best of our knowledge, this study is the first prospective study reporting the activity of a CSF1R inhibitor in patients with inoperable pigmented villonodular synovitis. Overall, our findings set a benchmark for advanced pigmented villonodular synovitis, suggesting that drugs that target CSF1R, including nilotinib, have activity in patients with pigmented villonodular synovitis who have no other therapeutic options, and should be assessed further in randomised trials.

References

1 Martin RC, Osborne DL, Edwards MJ, et al. Giant cell tumor of tendon sheath, tenosynovial giant cell tumor, and pigmented villonodular synovitis: defining the presentation, surgical therapy and recurrence. *Oncol Rep* 2000; **7:** 413–19.

2 Mendenhall WM, Mendenhall CM, Reith JD, et al. Pigmented villonodular synovitis. *Am J Clin Oncol* 2006; **29:** 548–50.

3 Somerhausen NS, van de Rijn M. Tenosynovial giant cell tumour, diffuse type. In: Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F, eds. WHO classification of tumours of soft tissue and bone, 4th edn. Lyon: IARC Press, 2013: 102–03.

4 West RB, Rubin BP, Miller MA, et al. A landscape effect in tenosynovial giant-cell tumor from activation of CSF1 expression by a translocation in a minority of tumor cells. *Proc Natl Acad Sci USA* 2006; **103:** 690–95.

5 Cupp JS, Miller MA, Montgomery KD, et al. Translocation and expression of CSF1 in pigmented villonodular synovitis, tenosynovial giant cell tumor, rheumatoid arthritis and other reactive synovitides. *Am J Surg Pathol* 2007; **31:** 970–76.

6 Moller E, Mandahl N, Mertens F, et al. Molecular identification of COL6A3-CSF1 fusion transcripts in tenosynovial giant cell tumors. *Genes Chromosomes Cancer* 2008; **47:** 21–25.

7 Palmerini E, Staals EL, Maki RG, et al. Tenosynovial giant cell tumour/pigmented villonodular synovitis: outcome of 294 patients before the era of kinase inhibitors. *Eur J Cancer* 2015; **51:** 210–17.

8 Xie GP, Jiang N, Liang CX et al. Pigmented villonodular synovitis: a retrospective multicenter study of 237 cases. *PLoS One* 2015; **10:** e0121451.

9 Blay JY, El SH, Thiesse P, et al. Complete response to imatinib in relapsing pigmented villonodular synovitis/tenosynovial giant cell tumor (PVNS/TGCT). *Ann Oncol* 2008; **19:** 821–22.

10 Cassier PA, Gelderblom H, Stacchiotti S, et al. Efficacy of imatinib mesylate for the treatment of locally advanced and/or metastatic tenosynovial giant cell tumor/pigmented villonodular synovitis. *Cancer* 2012; **118:** 1649–55.

11 Cassier PA, Italiano A, Gomez-Roca CA, et al. CSF1R inhibition with emactuzumab in locally advanced diffuse-type tenosynovial giant cell tumours of the soft tissue: a dose-escalation and dose-expansion phase 1 study. *Lancet Oncol* 2015; **16:** 949–56.

12 Sankhala KK, Blay JY, Ganjoo KN, et al. A phase I/II dose escalation and expansion study of cabiralizumab (cabira; FPA-008), an anti-CSF1R antibody, in tenosynovial giant cell tumor (TGCT, diffuse pigmented villonodular synovitis D-PVNS). American Society of Clinical Oncology Annual Meeting; Chicago, IL; June 2–6, 2017. 11078.

13 Tap WD, Wainberg ZA, Anthony SP, et al. Structure-guided blockade of CSF1R kinase in tenosynovial giant-cell tumor. *N Engl J Med* 2015; **373:** 428–37.

14 Rosti G, Castagnetti F, Gugliotta G, Baccarani M. Tyrosine kinase inhibitors in chronic myeloid leukaemia: which, when, for whom? *Nat Rev Clin Oncol* 2017; **14:** 141–54.

15 Brownlow N, Russell AE, Saravanapavan H, et al. Comparison of nilotinib and imatinib inhibition of FMS receptor signaling, macrophage production and osteoclastogenesis. *Leukemia* 2008; **22:** 649–52.

16 Jain P, Kantarjian H, Cortes J. Chronic myeloid leukemia: overview of new agents and comparative analysis. *Curr Treat Options Oncol* 2013; **14:** 127–43.

17 Blay JY, Shen L, Kang YK, et al. Nilotinib versus imatinib as first-line therapy for patients with unresectable or metastatic gastrointestinal stromal tumours (ENESTg1): a randomised phase 3 trial. *Lancet Oncol* 2015; **16:** 550–60.

18 Blay JY, von Mehren M. Nilotinib: a novel, selective tyrosine kinase inhibitor. *Semin Oncol* 2011; **38** (suppl 1): S3–9.

19 Pavey T, Hoyle M, Ciani O, et al. Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses. *Health Technol Assess* 2012; **16:** 1–277.

20 Suh KJ, Lee JY, Shin DY, et al. Analysis of adverse events associated with dasatinib and nilotinib treatments in chronic-phase chronic myeloid leukemia patients outside clinical trials. *Int J Hematol* 2017; **106:** 229–39.

21 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45:** 228–47.

22 Zohar S, Teramukai S, Zhou Y. Bayesian design and conduct of phase II single-arm clinical trials with binary outcomes: a tutorial. *Contemp Clin Trials* 2008; **29:** 608–16.

23 Joensuu H, Eriksson M, Sundby Hall K, et al. Adjuvant imatinib for high-risk GI stromal tumor: analysis of a randomized trial. *J Clin Oncol* 2016; **34:** 244–50.

24 Gounder MM, Thomas DM, Tap WD. Locally aggressive connective tissue tumors. *J Clin Oncol* 2017; **36:** 202–09.

25 Stacchiotti S, Crippa F, Messina A, et al. Response to imatinib in villonodular pigmented synovitis (PVNS) resistant to nilotinib. *Clin Sarcoma Res* 2013; **3:** 8.

26 Blay JY, Soibinet P, Penel N, et al. Improved survival using specialized multidisciplinary board in sarcoma patients. *Ann Oncol* 2017; **28:** 2852–59.