NCI Protocol 8408

A Phase 2 Study of GDC-0449
in Patients with Advanced Chondrosarcomas

Coordinating Center: Institut Bergonié (Bordeaux, France)

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SUMMARY OF CHANGES

#	Section	Page(s)	Change
1	Protocol	i	New Protocol Amendment/Version Date Included on the Title/Cover Page per Operations Office Policy: Protocol Cover Page: Page Number(s): i Version Date: version 17, 05/17/2017
2	Section 7.1	29	As requested by an Action Letter, Protocol Section(s) for Insertion of Revised CAEPR (Version 2.5, December 22, 2016): • Increase in Risk Attribution: • Changed to Less Likely from Also Reported on GDC-0449 Trials But With Insufficient Evidence for Attribution: Abdominal pain; CPK increased; Dehydration **Note that the added New Risk " Rare: Bone growth may stop early in teenagers leading to short stature" has not been added to our ICD since 2 patients are already on treatment, respectively aged 47 and 58 years at inclusion.**

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SYNOPSIS

A Phase II trial of GDC-0449 in Patients with Advanced Chondrosarcomas	
PROTOCOL CODE	**NCI Protocol 8408**
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STUDY OBJECTIVES **Primary**	To evaluate the antitumor activity of GDC-0449 in terms of 6-month clinical benefit (Complete response, partial response and stable disease, as per the Response Evaluation Criteria in Solid Tumors, Revised RECIST criteria 2009).
Secondary	• Best overall response (as per the revised RECIST criteria 2009); • 1- and 2-year progression-free survival; • 1- and 2-year overall survival; • GDC-0449 safety; • Pharmacogenomic analysis of predictive markers of treatment outcome.
STUDY DESIGN	Single-arm phase 2 clinical trial based on two-stage Simon's design.
STUDY POPULATION	Adult patients with unresectable locally advanced or metastatic chondrosarcoma
INCLUSION CRITERIA	1. Patients must have histologically confirmed diagnosis of chondrosarcoma (conventional, mesenchymal, dedifferentiated or clear cell subtypes) ; 2. Patients must have measurable disease (outside any previously irradiated field) defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with spiral CT scan. See Section 12 for the evaluation of measurable disease. 3. No more than three prior lines of chemotherapy for advanced disease (including no more than 450 mg/m² doxorubicin). At least three weeks since last chemotherapy (six weeks in case of nitrosoureas and mitomycin C), immunotherapy or any other pharmacological treatment and/or radiotherapy. 4. Age ≥18 years. 5. Life expectancy of greater than 3 months 6. ECOG performance status ≤2 (Karnofsky ≥60%; see Appendix A). 7. Patients must have normal organ and marrow function as defined below: i. leukocytes ≥ 3,000/mcL ii. absolute neutrophil count ≥ 1,500/mcL iii. platelets ≥ 100,000/mcL iv. total bilirubin within normal institutional limits v. AST(SGOT)/ALT(SGPT) ≤ 2.5 X institutional upper limit of normal vi.Creatinine within normal institutional limits OR creatinine clearance ≥ 60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

	8. Metastatic or unresectable locally advanced disease. 9. Documented disease progression (as per RECIST) before study entry. 10. Hh pathway inhibitors such as vismodegib have been demonstrated to be embryotoxic and/or teratogenic in multiple animal species and can cause severe midline defects, missing digits, and other irreversible malformations in the developing embryo or fetus. For this reason, women of child-bearing potential and men must use two forms of contraception (i.e., barrier contraception and one other method of contraception) at least 4 weeks prior to study entry, for the duration of study participation, and for at least 24 months post-treatment for female patients and for 2 months for male patients. For appropriate methods of contraception considered acceptable see Appendix C. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. 11. Pregnancy Testing. Women of childbearing potential are required to have a negative serum pregnancy test (with a sensitivity of at least 25 mIU/mL) within 7 prior to initiating GDC-0449 treatment (serum or urine). A pregnancy test (serum or urine) will be administered every 4 weeks while on study within the 24-hour period prior to the administration of GDC-0449. A positive urine test must be confirmed by a serum pregnancy test. Prior to dispensing GDC-0449, the investigator must confirm and document the patient's use of two contraceptive methods, dates of negative pregnancy test, and confirm the patient's understanding of the teratogenic potential of GDC-0449. i. Women of childbearing potential are defined as follows: ii. Patients with regular menses iii. Patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding iv. Women who have had a tubal ligation v. Women are considered not to be of childbearing potential for the following reasons: vi. The patient has undergone hysterectomy and/or bilateral oophorectomy. vii. The patient is post-menopausal defined by amenorrhea for at least 1 year in a woman > 50 years old. viii. The patient has permanent premature ovarian failure confirmed by specialist gynecologist 12. Ability to understand and the willingness to sign a written informed consent document. *13.* In accordance with French Regulatory Authorities: Patients with French Social Security in compliance with the French law relating to biomedical research (Huriet Law 88-1138 and related decrees).
EXCLUSION CRITERIA	1. Tumor tissue sample not available for pathological review and/or correlative studies. 2. Patients who have had chemotherapy or radiotherapy within 3 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 3 weeks earlier. 3. Patients may not be receiving any other investigational agents. 4. Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. 5. History of allergic reactions attributed to compounds of similar chemical or biologic

	composition to GDC-0449 or other agents used in the study. 6. Patients with malabsorption syndrome or other condition that would interfere with intestinal absorption. Patients must be able to swallow capsules. 7. Patients with clinically important history of liver disease, including viral or other hepatitis or cirrhosis are ineligible. 8. Patients with uncontrolled hypocalcemia, hypomagnesemia, hyponatremia or hypokalemia defined as less than the lower limit of normal for the institution, despite adequate electrolyte supplementation are excluded from this study. 9. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. 10. Pregnant women are excluded from this study because GDC-0449 is a Hh pathway inhibiting agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with GDC-0449, breastfeeding should be discontinued if the mother is treated with GDC-0449. 11. HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with GDC-0449. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.
STUDY POPULATION **Translational research study**	All patients included in the trial are eligible for the translational research study.
NUMBER OF PATIENTS	Based on the following hypotheses under GDC-0449 treatment: 20% clinical benefit (null hypothesis), 40% acceptable clinical benefit (alternative hypothesis), 10% type I error rate, 90% power, a total of 37 assessable patients will be necessary (17 for the first stage + 20 for the second stage). In order to account for not assessable patients (+/- 20%), 45 patients will be recruited.
NUMBER OF SITES	This is a multicenter study. A complete list of investigators will be provided as a separate document.
STUDY DRUG FORMULATION	GDC-0449 – Capsules packaged in 75 mL bottles. Each bottle contains 32 capsules.
ROUTE OF ADMINISTRATION	GDC-0449: Oral
ADMINISTERED DOSE	GDC-0449: 150 mg, take with or without food at the same time every day
TREATMENT SCHEDULE	GDC-0449: Days 1-28

EFFICACY EVALUATIONS	Patients will be evaluated for efficacy if they receive at least one complete or two incomplete cycles of GDC-0449, and if they have at least one disease measurement recorded not less than eight weeks after treatment onset (except for in case of early disease progression). Antitumor activity will be assessed using RECIST on a set of measurable lesions identified at baseline as target lesions and followed until disease progression by the appropriate method (computed tomography [CT] scan or magnetic resonance imaging [MRI]). Radiological and clinical (whenever appropriate) tumor assessment will be performed at baseline and every eight weeks until evidence of disease progression (PD). Whenever the criteria of response are met, the appropriate imaging tests will be repeated at least four weeks later in order to confirm the response. Beyond 48 months of treatment without evidence of progressive disease, radiological tumor assessment will be performed every 3 months. Efficacy will be evaluated based on 6-month clinical benefit rate (primary objective), best overall response, 1- and 2-year PFS, and 1- and 2-year OS.
SAFETY EVALUATIONS	Patients will be evaluable for safety if they have received at least one dose of GDC-0449. All AEs will be graded according to the CTEP CTCAE Version 4.0. Safety profile will be continuously followed during treatment and up to 30 days after the last GDC-0449 dose or until the start of a new antitumor therapy, whichever occurs first.
TRANSLATIONAL RESEARCH PROGRAM	The following analyses will be done on tumor samples from patients treated with **GDC-0449**: - Analysis of the mutational status of *PTCH* and *SMO* - Analysis of the expression pattern of hedgehog signaling molecules (Shh, PTCH, SMO, GLI-1, GLI-2, GLI-3) by using quantitative reverse transcription-polymerase chain reaction and immunohistochemistry (IHC). The 6-months clinical benefit rate will be correlated with the mutational status of *PTCH* and *SMO* and with the expression score of hedgehog signaling molecules in order to identify predictive factors of clinical benefit from GDC-0449.

TABLE OF CONTENTS

A Phase 2 Study of GDC-0449 in Patients with Advanced Chondrosarcomas

1. OBJECTIVES

1.1. Primary Objective

To evaluate the antitumor activity of GDC-0449 in terms of 6-month clinical benefit rate (Complete response, partial response and stable disease, as per the Response Evaluation Criteria in Solid Tumors, revised RECIST criteria 2009).

1.2. Secondary Objectives

- Best overall response (as per the revised RECIST criteria 2009);
- 1- and 2-year progression-free survival;
- 1- and 2-year overall survival;
- GDC-0449 safety;
- Pharmacogenomic analysis of predictive markers of treatment outcome.

1.3. Study design and calendar

This is single-arm phase 2 clinical trial based on two-stage Simon's design.

- Beginning of inclusions : September 2010
- Inclusion period: September 2010 to September 2012 (2 years)
- Length of patient participation: 2 years
- Study length: 4 years.

2. BACKGROUND

2.1 Study Disease

Chondrosarcoma is the second most common primary malignancy of bone after osteosarcoma and is characterized by the production of cartilage matrix by the tumor cells (Fletcher et al., 2002). Several categories of primary chondrosarcomas have been described, including conventional, dedifferentiated, mesenchymal, and clear cell chondrosarcoma.

Conventional chondrosarcomas represent approximately 85% of all chondrosarcomas and can be categorized according to their location in bone into primary central and secondary peripheral chondrosarcomas. Central and peripheral chondrosarcomas are histologically similar, and for both, three different grades are described, which represent the best predictor of outcome. Grade I chondrosarcomas are poorly cellular, with an abundant hyaline cartilage matrix, and rarely metastasize. In contrast, grade III chondrosarcomas are highly cellular, with a mucomyxoid

matrix and mitoses, and metastasize in about 70% of cases (Evans et al., 1977; Fletcher et al., 2002). The most frequent metastatic sites are the lungs, regional lymph nodes and liver. Up to 13% of recurrent chondrosarcomas exhibit a higher grade of malignancy than the original lesion, suggesting chondrosarcomas may biologically progress.

Dedifferentiated chondrosarcoma represent 9%–10% of all chondrosarcomas and is characterized from a histological point of view by conventional low-grade chondrosarcoma with abrupt transition to foci that have dedifferentiated into a higher-grade, more aggressive component (Fletcher et al., 2002). Patients with dedifferentiated chondrosarcoma are older than those with conventional lesions; the median age at diagnosis is 60 years. The prognosis is poor. Indeed, metastases occur early, are frequent and involves typically the lungs, regional lymph nodes and viscera (Mercuri et al., 1995). The 5-year survival rate is less than 10%–25%.

Mesenchymal chondrosarcoma represent 2%–13% of all chondrosarcomas and is characterized by a typical bimorphic appearance with a malignant cartilaginous component admixed with a more cellular vascular portion with hemangiopericytoma-like features (Fletcher et al., 2002). Patients with mesenchymal chondrosarcoma are younger than those with conventional lesions; the median age at diagnosis is 25 years. Local and distant recurrences are frequent. The most frequent metastatic sites are the lungs, regional lymph nodes and bone. Patients with intraosseous lesions have a 5-year survival rate of 42% and a 10-year survival rate of 28% (Nakashima et al., 1986). Patients with extraskeletal mesenchymal chondrosarcoma have an estimated survival rate of 55% at 5 years and 27% at 10 years.

Clear cell chondrosarcoma is a rare low-grade malignant cartilaginous tumor representing 1-2% of all chondrosarcomas (Fletcher et al., 2002). These tumors consist in a proliferation of large cells with abundant clear, vacuolated cytoplasm containing large amounts of glycogen (clear cell chondrocytes) that often lie between heavily calcified trabeculae of cartilage matrix and may superficially resemble bone. Patients are most commonly affected in the 3rd to 5th decade of life. Metastases are rare. However, clear cell chondrosarcoma is often confounded with chondroblastoma due to its epiphyseal location. Therefore, clear cell chondrosarcoma is often inadequately treated initially with curettage leading to recurrence. Overall recurrence rate is 16% and approximately 15% of patients die of the disease (Unni et al., 1976).

In the majority of cases, patients with chondrosarcomas (especially those with conventional or clear cell chondrosarcoma) are cured by adequate wide surgical excision. However, some patients (especially those with high grade conventional, mesenchymal or dedifferentiated chondrosarcomas) present or recur with metastatic disease. Conventional cytotoxic agents and radiotherapy are generally not effective in patients with metastatic or locally unresectable disease (Gelderblom et al., 2008). Therefore, there is an urgent need to develop new therapeutic strategies for patients with advanced disease.

2.2 GDC-0449

The hedgehog (Hh) signaling pathway is a crucial mediator of embryogenesis (Ingham and McMahon, 2001). Signaling is initiated by the binding of the secreted morphogen, Hh, to its receptor, patched 1 (Ptch1). In the unbound state, Ptch1 inhibits Smoothened (SMO), a G-protein coupled phosphoprotein receptor, by preventing its localization to the cell surface; however, in the presence of the Hh ligand, the Hh-Ptch1 complex is internalized and the

repression of Ptch1 on SMO is relieved. Surface localization of SMO is thought to initiate a signaling cascade, leading to the activation of the glioma-associated (*Gli*) family of zinc finger transcription factors, many of which are involved in proliferation, survival, and angiogenesis. Aberrant activation of the Hh pathway in cancers is caused by mutations in the pathway or through Hh overexpression, termed either ligand-independent or ligand-dependent, respectively (for reviews, see Evangelista et al., 2006; Chari and McDonnell, 2007). Past studies have identified mutations in the Hh receptor components, Ptch1 or SMO in basal cell carcinoma (BCC) and medulloblastoma, resulting in constitutive pathway activation (Romer and Curren, 2005; Lupi, 2007). Excessive or inappropriate expression of the Hh ligand has been found in a significant proportion of patients with sporadic cancers of the gastrointestinal tract, pancreas, lung and prostate, suggesting that disruption of Hh signal transduction could potentially be beneficial in a broad array of tumor types (Berman et al., 2003; Thayer et al., 2003; Watkins et al., 2003; Karhadkar et al., 2004). Evidence suggests that antagonism of excessive Hh signaling may provide a route to unique mechanism-based anticancer therapies, blocking tumor growth and stimulating tumor regression without toxic effects on normal adjacent tissue (for review, see Rubin and de Sauvage, 2006).

GDC-0449 is a small-molecule antagonist of the Hh signal pathway (Investigator's Brochure, 2009). Specifically, GDC-0449 binds to and inhibits SMO, blocking Hh signal transduction. In vitro and in vivo preclinical studies have demonstrated inhibition of Hh signaling following GDC-0449 administration. GDC-0449 has demonstrated efficacy against a variety of primary human tumor xenografts, including colorectal cancer (CRC) and pancreatic adenocarcinoma, and tumor cell-line xenograft models. Inhibition of Hh signaling in xenograft models has been correlated with a decrease in tumor growth.

Currently, GDC-0449 is being studied in a company-sponsored phase 1 clinical trial in patients with advanced solid malignancies. Preliminary results from 42 evaluable patients indicate that GDC-0449 is well-tolerated with no dose-limiting toxicities (DLTs) observed at any of the doses tested (150, 270, and 540 mg of GDC-0449). Objective responses were observed in six patients with advanced BCC. Additionally, one study in a single pediatric patient with refractory medulloblastoma has been completed, and a pharmacokinetic (PK) study in healthy female volunteers is completed.

Nonclinical Specificity and Efficacy Studies

Both human and mouse Hh-responsive cell lines stably transfected with a Gli-luciferase reporter construct showed Hh signal inhibition, with an IC50 of 13 nM and 2.8 nM, respectively (Investigator's Brochure, 2009). GDC-0449 is specific for Hh pathways, as no inhibition was observed in control assays, such as the S12 SV40-luciferase reporter assay, or in a HEK293 nuclear factor κB (NFκB)-luciferase assay used to assess tumor necrosis factor-α (TNF-α) signaling (IC50 values $\geq$ 50 μM).

GDC-0449 was assessed for its effect on the growth of murine medulloblastoma tumors that are driven by constitutive Hh pathway activation and caused by haploinsufficiency of the Ptch1 gene. GDC-0449 given orally at 100 mg/kg twice daily caused complete and sustained regression of five of five Ptch1+/- tumors by day 15. In addition, tumor regression in tumors with volumes of

> 2000 mm^3 was observed in vehicle-treated mice upon GDC-0449 administration.
The D5123 primary CRC model was used to establish the PK and pharmacodynamic relationship for GDC-0449. Mouse Gli1 (mGli1) mRNA levels and plasma drug levels were measured at 12, 18, and 24 hours following the fifth and final dose of oral GDC-0449 on a twice daily schedule at dose levels ranging from 23 to 92 mg/kg. A dose of 69 mg/kg GDC-0449, given orally twice a day, was required to maximally inhibit Hh signaling (as measured by decreases in mGli1 mRNA levels) in D5123 tumor xenografts for more than 18 hours. Subsequent studies using patient-derived tumor xenografts, including CRC, esophageal cancer, pancreatic cancer and non-small cell lung cancer (NSCLC), and the LS180 human CRC cell line, demonstrated tumor growth inhibition at 69 mg/kg and 75 mg/kg GDC-0449, administered orally twice daily, respectively, further supporting the previous findings.

A minimum trough plasma concentration of approximately 20 μM, measured in plasma 12 hours post-dose, was determined to be the minimum concentration required to maximally suppress Hh signaling in tumors and cause inhibition of growth in the D5123 CRC xenograft model. Therefore, the predicted trough level of GDC-0449 when human stromal cells are targeted is expected to be approximately 3-5 μM, based on the approximately 4.6-fold greater potency of GDC-0449 on the human Hh pathway compared with the mouse.

Administration of GDC-0449 (100 mg/kg, orally, twice daily) resulted in stasis of growth of subcutaneous mammary tumor allografts derived from MMTV-Wnt/p53+/- heterozygous mice. In a mouse adenomatous polyposis coli (ApcMin/+) model, GDC-0449 caused a 40% increase in intestinal polyp diameter, but did not affect the number of polyps formed. There was no difference between vehicle- and GDC-0449-treated mice in polyp histopathology or morphology, and no histologic evidence of malignant progression.

GDC-0449 exhibited positive cooperation in CRC xenograft models with other chemotherapies, including irinotecan (CPT-11) and 5-fluorouracil (5-FU). Administration of concurrent GDC-0449 and CPT-11 caused pronounced weight loss, an effect that was decreased by either reducing the dose of GDC-0449 or administering GDC-0449 following chemotherapy. GDC-0449 can also be combined with gemcitabine or cisplatin in pancreatic or small-cell lung cancer models, respectively, without antagonism or unexpected toxicity.

Nonclinical Pharmacokinetics and Pharmacology

PK studies of GDC-0449 were performed in CD-1 mice, Sprague-Dawley rats, dogs, and cynomolgus monkeys (Investigator's Brochure, 2009). GDC-0449 has a low plasma clearance with a low to moderate volume of distribution in mice, rats, and dogs; moderate plasma clearance and low to moderate volume of distribution was observed in monkeys. The mean terminal half life ($t_{½}$) ranged from 0.581 hours in monkeys to 41.8 hours in dogs. The oral bioavailability was 19.2%, 52.9%, 32.9%, and 13.4% in the mouse, rat, dog, and monkey, respectively. Of note, preliminary results from the PK study in the adult phase 1 clinical trial indicate that the preclinical profile of GDC-0449 is very different from that observed in patients.

GDC-0449 appears to be highly protein bound, with the percent bound to protein being >95% in all species tested. The degree of protein binding appears to be independent of drug concentration in all species, except the cynomolgus monkey (~2-fold increase in the unbound fraction). In addition, blood-plasma partitioning of GDC-0449 was assessed at concentrations of 1, 10, and

100 μM in the mouse, rat, dog, and cynomolgus monkey. The mean blood to plasma partition ratios ranged from 0.608 to 0.881 and did not appear to exhibit substantial concentration dependence.

The toxicokinetics of GDC-0449 were comparable following once daily (500 mg/kg) or twice daily (250 mg given twice, 500 mg total) oral dosing in rats. The area under the concentration-time curve from time 0 to the last measurable timepoint (AUC0-tlast) and the highest observed plasma concentration (Cmax) increased with dose following administration of oral GDC-0449 (25-250 mg/kg, twice daily, given 6 hours apart); however, the increase observed was less than proportional to the increase in dose. No differences were observed in the AUC0-tlast and Cmax on days 1, 14, and 28, or between males and females. In dogs, the AUC0-tlast and Cmax were similar in the 75 mg/kg and 200 mg/kg twice daily treatment groups. The increase in the AUC0-tlast and Cmax from 25 mg/kg twice daily GDC-0449 treatment group to the higher dose groups (75 mg/kg and 200 mg/kg twice daily) was less than proportional to dose. In addition, the AUC0-tlast and Cmax value were higher on day 14 and 28 compared to day 1 for both males and females.

The in vitro metabolism of GDC-0449 in rat, dog, and human liver microsomes appears to involve primary oxidations with no human-specific metabolite. Human recombinant cytochrome P450 (CYP450) isoforms 3A4, 3A5, and 2C9 produced the greatest quantity of the two oxidative metabolites identified in microsomes. A third oxidative metabolite was identified in vivo in rat and dog urine along with three glucuronide conjugates of the oxidative metabolites.

Nonclinical Toxicology

Toxicity studies

GDC-0449 was well tolerated following a single oral dose of up to 2000 mg/kg, with no evidence of toxicity, in mice, rats, and dogs (Investigator's Brochure, 2009). Repeat-dose studies were completed in rats and dogs. Twice-daily oral dosing of up to 500 mg/kg/day GDC-0449 for 4 weeks in rats produced no severe toxicities. No severe, irreversible toxicities were noted in dogs given up to 150 mg/kg/day orally twice daily for 4 weeks. Twice-daily oral dosing of GDC-0449 for 13 weeks demonstrated no severe toxicities in rats or dogs given doses up to 50 mg/kg/day.

Vomiting and mucoid or discolored feces were observed at all dose levels tested in dogs treated for 4 and 13 weeks. These effects were reversible and not associated with clinical or anatomic pathology findings.

Dose-dependent decreases in body weight and/or body weight gain, accompanied by reduced food consumption, were observed in both rats and dogs following oral administration of GDC-0449. While these decreases were reversible in dogs, the effects on body weight persisted following a 4-week recovery period in rats administered GDC-0449 for either 4 or 13 weeks, possibly due to treatment-related effects on the incisor teeth. Treatment-related effects, including degeneration of odontoblasts and ameloblasts, and degradation of dentin with scattered sequestrae, were observed in rat incisor teeth following repeated administration of GDC-0449 in studies up to 13 weeks. Of note, no lesions were observed in molar teeth, indicating that the effects of GDC-0449 were specific to the continuously-growing incisor teeth. Rat incisor teeth grow at a fast pace continuously throughout the lifetime of the animal, maintained by the

proliferation and differentiation of cells in the apical end of the tooth into various tooth-forming cells. Previous studies have indicted a role for Hh signaling on the continued growth of rodent incisor teeth (Kriangkrai et al., 2006; Nakatomi et al., 2006). These effects are not considered relevant to human adult studies; however, pediatric patients with actively growing teeth may be affected.

Reversible mild to moderate elevations in total cholesterol following repeated GDC-0449 were noted in both rats (≥ 150 mg/kg/day dose levels) and dogs (all dose levels studied). Increases in both high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol levels were observed, contributing to the increase in total cholesterol. Rats given GDC-0449 on a 13-week schedule showed increases in HDL cholesterol levels only. No adverse effects or histopathologic changes were associated with this increase in cholesterol and no alterations in serum triglycerides were observed.

Decreases in platelet counts were noted in dogs treated with ≥150 mg/kg/day of GDC-0449; however, these decreases were reversible. One female dog (150 mg/kg/day) was euthanized on day 15 of the 13-week study due to hemorrhage associated with thrombocytopenia; however, no other dog treated in either the 4- or 13-week study exhibited clinical toxicity associated with decreased platelet counts.

A minimal to mild QTc interval prolongation was observed in conscious, manually restrained dogs given 600 mg/kg twice daily for 4 days in a pilot study. However, as no test article-related effects on electrocardiogram parameters were observed in a cardiovascular safety study at single doses of up to 2000 mg/kg or following repeated doses of 400 mg/kg/day for up to 25 days, these effects are not considered relevant for human studies.

Reversible alopecia, associated with focal hyperkeratosis and inflammation, was observed at all dose levels in dogs treated with GDC-0449 for 13 weeks. As Hh signaling has been shown to be important in the maintenance of hair follicles (Oro and Higgens, 2003), this effect may be relevant in patients.

Following GDC-0449 administration for 4 weeks, degenerating germ cells within the seminiferous tubules, along with a decrease in spermatozoa and an abnormal accumulation of cellular debris in the epididymides were seen in 6- to 7-month-old male dogs, but not observed in older, sexually mature dogs (10- to 12-month-old dogs treated for 13 weeks). These findings are consistent with the role of Hh-mediated signaling in mammalian spermatogenesis (Bitgood *et al.*, 1996; Kroft *et al.*, 2001). Limited improvement was noted during the 28-day recovery period, suggesting that these effects may be reversible. Of note, the male dog reproductive cycle is 54-62 days; this long cycle time relative to the recovery period may explain the lack of full recovery observed in the young male dogs. Due to the discrepancy noted in germ cell degeneration between younger and older sexually mature dogs, the relevance of this effect of GDC-0449 in male patients is unknown.

Higher systemic exposures were achieved in dogs as compared to rats, with a lower exposure in rats at the highest dose administered (500 mg/kg/day) than that observed in the dog at the lowest dose tested (50 mg/kg/day). This may account for some of the effects that were noted in dogs only, including male germ cell degeneration and decreases in platelet levels.

Genotoxicity

In vivo and in vitro studies demonstrated no evidence of genotoxicity following GDC-0449

administration (Investigator's Brochure, 2009). Mutagenic or clastogenic responses were not observed in the Salmonella typhimurium/Escherichia coli reverse mutation assay or in an in vitro chromosome aberration assay in human peripheral blood lymphocytes. No clastogenic activity was noted in an in vivo rat micronucleus assay at GDC-0449 doses of up to 2000 mg/kg.

Clinical Experience

GDC-0449 has been studied in three company-sponsored trials: a phase 1 trial in patients with advanced solid tumors, a pediatric trial of one patient with medulloblastoma, and a PK study in healthy female volunteers of non-childbearing potential (Investigator's Brochure, 2009).

Phase 1 experience

GDC-0449 has been studied in a company-sponsored phase 1 trial examining the safety, tolerability, PK, and efficacy in patients with locally advanced or metastatic solid tumors that are refractory to standard therapy or for whom no standard therapy exists (Investigator's Brochure, 2009; Von Hoff et al., 2009; Rudin et al., 2009). Enrollment in this study occurred in two stages. In the stage 1 dose-escalation portion of the study, GDC-0449 was administered orally as a single dose on day 1, followed by a 7-day PK observation period, and then continuous daily dosing commences on day 8, at increasing dose levels of 150, 270, or 540 mg for 28 days (one cycle = 35 days). GDC-0449 was to be discontinued in patients who had dose-limiting toxic effects or other intolerable side effects or disease progression or in patients who did not benefit from treatment, as decided by the investigator. The primary objectives of this portion were to assess safety, tolerability and PK/pharmacodynamics, and determine a maximum tolerated dose (MTD). Stage 2 objectives included additional assessment of safety data at the recommended phase 2 dose (RP2D) (expansion cohort). Patients in the stage 2 expansion cohort received GDC-0449 once daily in 28-day cycles at the MTD dose determined in the dose escalation phase of the study. An additional cohort was added to examine efficacy in patients with BCC at the MTD.

A total of 68 patients were enrolled and treated, of these patients, 33 had advanced basal-cell carcinoma Von Hoff et al., 2009). In the stage 1 dose-escalation portion of the study, 7 patients were assigned to receive 150 mg per day, nine patients 270 mg per day, and four patients 540 mg per day; each dose cohort included one patient with advanced basal-cell carcinoma. No dose-limiting toxic effects were observed. The recommended phase 2 dose was 150 mg per day because pharmacokinetic analyses indicated that doses greater than this did not result in higher plasma concentrations of the drug.

In stage 2, an expansion cohort that received the recommended phase 2 dose was included, with the goal of obtaining additional information on pharmacokinetics, pharmacodynamics, and safety; 12 patients (none with advanced basal-cell carcinoma) enrolled in this cohort, and all received 150 mg per day. The study was amended to include two further cohorts in stage 2. One of these cohorts was added because of evidence of clinical benefit in two patients with advanced basal-cell carcinoma during stage 1; this cohort consisted of 20 patients with advanced basal-cell carcinoma, who were treated with 150 mg per day or 270 mg per day (with the dose chosen on the basis of drug availability) to evaluate the activity and safety of GDC-0449 in this population. The second cohort, which consisted of 16 patients with solid tumors (including 10 with advanced basal-cell carcinoma), was added to investigate the pharmacokinetic properties of a new formulation of GDC-0449 at 150 mg per day. In stage 2, all patients received continuous daily

administration of the drug, beginning on day 1, and were treated until disease progression, the occurrence of intolerable toxic effects, or withdrawal from the study.

Adverse events (AEs) were fully available for the 33 patients with basal-cell carcinoma. No dose-limiting toxic effects or grade 5 events were observed during the study period. A single grade 4 adverse event (asymptomatic hyponatremia) occurred. The following grade 3 adverse events were seen: fatigue (in four patients); hyponatremia, weight loss, and dyspnea (in two patients each); and muscle spasm, atrial fibrillation, aspiration, back pain, corneal abrasion, dehydration, keratitis, lymphopenia, pneumonia, urinary tract infection, and a prolonged QT interval (in one patient each). Eleven grade 2 adverse events that were considered to be related to the study drug occurred (muscle spasm in three patients, dysgeusia in two patients, anorexia in two patients, weight loss in two patients, dyspepsia in one patient, asymptomatic hypocalcemia in one patient). A single patient who had locally advanced tumors and had a partial clinical response, decided to discontinue treatment after 8 months because of ongoing grade 1 adverse events (abdominal pain, fatigue, weight loss, and dysgeusia) and grade 2 anorexia.

Full efficacy data were available from the 33 patients with basal cell carcinoma and from one patient with refractory medulloblastoma (Rudin et al., 2009, Von Hoff et al., 2009). As of February 28, 2009 (the data cutoff date), all 33 patients with basal cell carcinoma had undergone at least one follow-up tumor assessment and could be evaluated for a response to treatment. Of the 18 patients with metastatic basal cell carcinoma, 15 had radiologically measurable disease, and 7 of these patients had a partial response, as assessed on imaging only (with 6 responses confirmed and 1 unconfirmed at the time of the data cutoff). Two other patients with metastatic basal cell carcinoma had partial responses, one assessed on both imaging and physical examination and the other on physical examination only. Seven patients with metastatic basal cell carcinoma had stable disease (with six patients assessed with the use of RECIST and one on physical examination), and two had progressive disease as the best response. The overall response rate among the 18 patients with metastatic basal cell carcinoma was 50% (95% confidence interval [CI], 29 to 71).
Of the 15 patients with locally advanced basal cell carcinoma, 13 were assessed on physical examination (clinical response), and 2 with measurable disease were assessed on imaging, according to RECIST. Of these 15 patients, 2 had a complete clinical response, and 7 had a partial clinical response; 4 patients had stable disease as the best response, with a duration of participation in the study ranging from 2.1 to 19.0 months; 2 of the patients had progressive disease. Overall, the response rate in patients with locally advanced tumors was 60% (95% CI, 33 to 83).
As of the data cutoff date, the Kaplan–Meier estimate of the median time of participation in the study was 9.8 months and ongoing, and the median duration of response was 8.8 months and ongoing.
Moreover, a 26-year-old man with metastatic medulloblastoma that was refractory to multiple therapies had rapid regression of the tumor and reduction of symptoms. This partial response lasted 3 months before a new progression (Rudin et al., 2009).

A company-sponsored study in healthy females of non-childbearing potential was conducted to examine the PK parameters and safety profile of GDC-0449 (Investigator's Brochure, 2009). A single 150-mg oral dose of GDC-0449 was given to three healthy, female subjects following an 8-hour fast. A 4-hour fast followed dosing. AEs during the study included nausea (grade 1),

edema of the ankles (grade 1-2), upper respiratory infection (viral; grade 2), and discolored stool (grade1).

Pediatric Studies

GDC-0449 was examined in a pediatric patient with refractory medulloblastoma to evaluate the safety and tolerability of the agent, and to characterize the plasma PK profile. GDC-0449 was administered at a dose of 50 mg once daily on a continuous schedule, in 28-day cycles. Treatment was discontinued after one cycle due to progressive disease. Nausea (grade 1), headache (grade 3), and anxiety (grade 2) were reported; however, all were attributed to the progression of medulloblastoma. Plasma concentrations of GDC-0449 increased continuously during the 4 weeks of treatment, reaching a level of 20 μM on Day 28. Concurrent cerebrospinal fluid levels were approximately 0.2-0.3% of plasma concentration at all time points tested.

Safety Profile

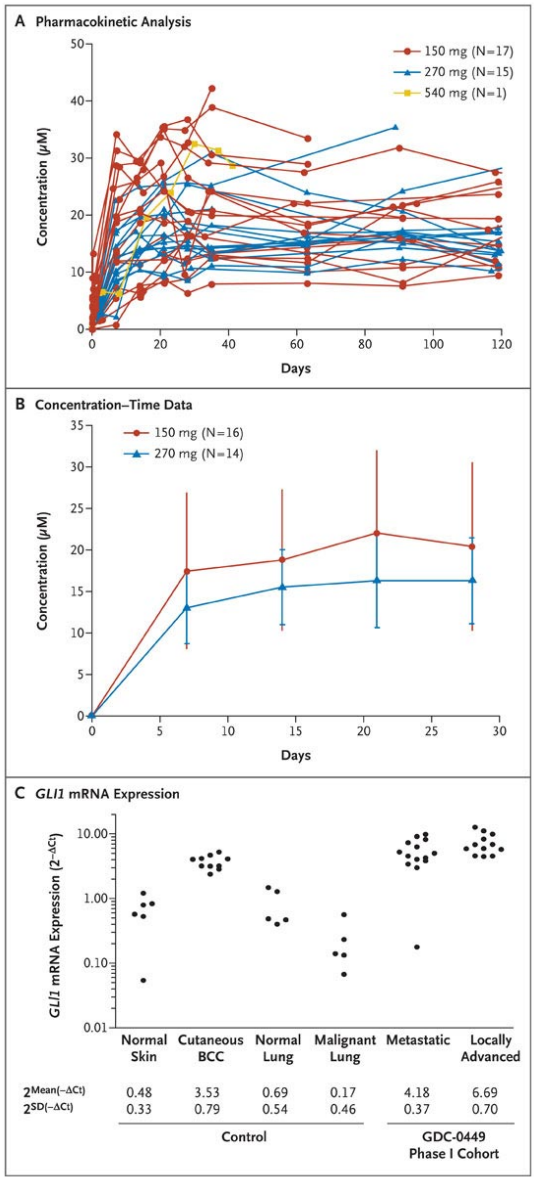
To date, GDC-0449 has been studied in a limited number of patients (approximately 70). Several AEs were noted and may be related to administration of GDC-0449: changes in or lack of taste sensation for food; loss of appetite; heartburn and stomach upset; nausea; vomiting; weight loss; decrease in sodium and magnesium levels in the blood; severe fatigue; loss of hair on the scalp, body, eyelashes, and face; joint pain; acne-like skin rash; skin peeling; numbness; and muscle spasms (cramps). Of note, due to the limited number of trials conducted with GDC-0449, there may be additional toxicities not yet identified, or predicted by nonclinical studies.

Studies have demonstrated that inhibition of the Hh pathway in embryos results in brain, facial, and other midline defects, including holoprosencephaly or microencephaly, cyclopia, absent nose, cleft palate, tooth abnormalities, and bone development abnormalities (Bale, 2002). While the teratogenic potential of GDC-0449 has not been investigated, given the key role of the Hh pathway in embryogenesis and the known terotogenic effects of cyclopamine, a naturally occurring inhibitor of SMO, women who are pregnant or nursing are excluded from all studies. Furthermore, to prevent pregnancy and the risk of fetal exposure to GDC-0449, women should not become pregnant during the GDC-0449 treatment or up to 12 months following cessation of therapy. Pregnancy prevention measures should be taken for all women of childbearing age for the study duration and for 12 months after the last treatment dose (refer to Appendix C for appropriate pregnancy prevention measures). In addition, it is not known whether GDC-0449 present in seminal fluid would cause teratogenic effects in the fetus born to the female partner of a male subject. Therefore, all sexually active male subjects should utilize a form of barrier contraception (even if they have a vasectomy) during study treatment and for 12 months following administration of the last dose.

As nonclinical studies have demonstrated a risk of teratogenicity following oral Hh pathway antagonists both pre- and post-natal, special care should be taken in pediatric populations. Specifically, GDC-0449 may adversely affect the development and maintenance of teeth, bones, and growth plates in a pediatric population.

Clinical Pharmacokinetics and Pharmacodynamics

Pharmacokinetic and Pharmacodynamic Analyses are fully available from the 33 basal-cell carcinoma patients. The median maximal plasma level was 23.0 µM (interquartile range, 16.8 to 29.7). The median steady-state concentration was 16.1 µM (interquartile range, 13.7 to 21.6). The median time to steady state was 14 days (interquartile range, 7 to 22). Increasing the dose from 150 mg to 270 mg did not result in higher steady-state plasma levels, with a median steady-state level of 19.8 µM (interquartile range, 13.5 to 25.8) for the 150-mg dose and 15.9 µM (interquartile range, 13.8 to 17.7) for the 270-mg dose. A consistent steady-state total plasma level of GDC-0449 was maintained throughout the treatment period, with no apparent decline at the time of disease progression. Pharmacodynamic down-modulation in the hedgehog pathway was shown by a decrease in GLI1 expression by more than a factor of two, as compared with pretreatment biopsy-sample analysis, in 10 of 13 patients. The extent of GLI1 down-modulation did not correlate with pharmacokinetic levels of GDC-0449 in individual patients.



Pharmacokinetic Analysis and Molecular Correlates of GDC-0449 Administration in 33 patients with basal-cell carcinoma.

Panel A shows the pharmacokinetic analysis of GDC-0449 for each of the 33 enrolled patients, according to dose. Three patients were exposed to a single dose on day 0, followed by repeated daily administration of GDC-0449, starting on day 7. The remaining 30 patients received daily doses, starting on day 0. Panel B shows mean concentration–time data for 30 patients who received either 150 mg or 270 mg of GDC-0449. The vertical lines represent standard deviations. Panel C shows elevated *GLI1* messenger RNA (mRNA) expression in archival tissue obtained from 25 of 26 patients with metastatic or locally advanced basal-cell carcinoma (BCC), as compared with control specimens. *GLI1* expression levels were assessed with the use of real-time polymerase-chain-reaction assay and calculated by the $2^{-\Delta Ct}$ method, in which the cycling threshold (Ct) of *GLI1* was normalized to the Ct of *SMO* and expressed as a power of 2 ($2^{Ct(GLI1)-Ct(SMO)}$). The mean ($2^{Mean(-\Delta Ct)}$) and standard deviation ($2^{SD(-\Delta Ct)}$) are indicated below the chart for each tissue type. Data for control subjects with either normal or malignant lung samples are included, since some specimens of metastatic basal-cell carcinoma represented lung metastases.

In vitro studies have indicated that GDC-0449 inhibits CYP2C8, CYP2C9, and CYP2C19 at clinically relevant concentrations. Care should be taken in administration of GDC-0449 with concurrent medications that are substrates of CYP2C8, CYP2C9, and CYP2C19 and have narrow therapeutic windows (see Section 5.2.1 for a list of relevant medications). Of note, GDC-0449 did not inhibit CYP3A4 at clinically relevant concentrations; however, GDC-0449 is a substrate of CYP3A4. Effects of CYP inducers and strong inhibitors of CYP3A4 on GDC-0449 clinical concentration are not known; thus, use of these drugs should be carefully documented.

Proposed dose for GDC-0449

Based on the PK parameters and the lack of AEs observed, the proposed starting dose for oral administration of GDC-0449 to cancer patients is 150 mg/day (92.5 mg/m^2/day).

2.3 Rationale

A way to try to improve the outcome of patients with sarcomas is to use the increasing amount of data about the biology of each tumor subtype to develop successful tailored systemic therapies (Wunder et al., 2007). This strategy has proven successful for imatinib-treated patients with GIST.

Chondrosarcomas exhibit a strong activation of hedgehog signaling which play a crucial role in cartilage tumorigenesis by maintaining tumor cells in a proliferative state. In vitro experiments have shown that treatment of chondrosarcoma cells with recombinant Hedgehog increased proliferation. Moreover, preclinical data from human chondrosarcomas explant and xenograft studies show that hedgehog blockade reduces strongly cell proliferation and tumour size (Tiet et al., 2006). We hypothesize that drug GDC-0449 is an agent of choice for patients with advanced chondrosarcomas by interfering with the hedgehog signaling pathway.

2.4 Correlative Studies Background

The presence of an activated and functional hedgehog pathway (expected in the majority of patients with chondrosarcomas) will be assessed for each case included in the clinical study. The expression pattern of hedgehog signaling molecules (Shh, PTCH, Smo, Gli-1, Gli-2, Gli-3) will be analyzed by using quantitative reverse transcription-polymerase chain reaction and

immunohistochemistry (IHC). The mutational status of *PTCH* and *SMO* will be also investigated immunohistochemistry methods. The 6-months clinical benefit rate will be correlated with the mutational status of PTCH and SMO and with the expression score of hedgehog signaling molecules (Shh, PTCH, Smo, Gli-1, Gli-2, Gli-3).

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically confirmed diagnosis of chondrosarcoma (conventional, mesenchymal, dedifferentiated or clear cell subtypes).

3.1.2 Patients must have measurable disease (outside any previously irradiated field) defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with spiral CT scan. See Section 11 for the evaluation of measurable disease.

3.1.3 No more than three prior lines of chemotherapy for advanced disease (including no more than 450 mg/m² doxorubicin). At least three weeks since last chemotherapy (six weeks in case of nitrosoureas and mitomycin C), immunotherapy or any other pharmacological treatment and/or radiotherapy.

3.1.4 Age ≥18 years (Because only limited adverse event data are currently available on the use of GCD-0449 in patients <18 years of age, children are excluded from this study but will be eligible for future pediatric phase 2 combination trials).

3.1.5 Life expectancy of greater than 3 months

3.1.6 ECOG performance status ≤2 (Karnofsky ≥60%; see Appendix A).

3.1.7 Patients must have normal organ and marrow function as defined below:

a. leukocytes ≥ 3,000/mcL
b. absolute neutrophil count ≥ 1,500/mcL
c. platelets ≥ 100,000/mcL
d. total bilirubin within normal institutional limits
e. AST(SGOT)/ALT(SGPT) ≤ 2.5 X institutional upper limit of normal
f. Creatinine within normal institutional limits
   OR
   creatinine clearance > 60 mL/min/1.73 m2 for patients with creatinine levels above institutional normal

3.1.8 Metastatic or unresectable locally advanced disease.

3.1.9 Documented disease progression (as per RECIST) before study entry.

3.1.10 Hh pathway inhibitors such as vismodegib have been demonstrated to be embryotoxic and/or teratogenic in multiple animal species and can cause severe midline defects, missing digits, and other irreversible malformations in the developing embryo or fetus. For this reason, women of child-bearing potential and men must use two forms of contraception (i.e., barrier contraception and one other method of contraception) at least 4 weeks prior to study entry, for the duration of

study participation, and for at least 24 months post-treatment for female patients and for 2 months for male patients. For appropriate methods of contraception considered acceptable see Appendix C. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.11 Pregnancy Testing. Women of childbearing potential are required to have a negative serum pregnancy test (with a sensitivity of at least 25 mIU/mL) within 7 days prior to initiation of GDC-0449 treatment (serum or urine). A pregnancy test (serum or urine) will be administered every 4 weeks while on study within the 24-hour period prior to the administration of GDC-0449. A positive urine test must be confirmed by a serum pregnancy test. Prior to dispensing GDC-0449, the investigator must confirm and document the patient's use of two contraceptive methods, dates of negative pregnancy test, and confirm the patient's understanding of the teratogenic potential of GDC-0449.

Women of childbearing potential are defined as follows:

- Patients with regular menses
- Patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding
- Women who have had a tubal ligation

Women are considered not to be of childbearing potential for the following reasons:

- The patient has undergone hysterectomy and/or bilateral oophorectomy.
- The patient is post-menopausal defined by amenorrhea for at least 1 year in a woman > 50 years old.
- The patient has permanent premature ovarian failure confirmed by specialist gynecologist

3.1.11 Ability to understand and the willingness to sign a written informed consent document.

3.1.12 In accordance with French Regulatory Authorities: Patients with French Social Security in compliance with the French law relating to biomedical research (Huriet Law 88-1138 and related decrees).

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy or radiotherapy within 3 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 3 weeks earlier.

3.2.2 Patients may not be receiving any other investigational agents.

3.2.3 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to GDC-0449 or other agents used in the study.

3.2.5 Patients with malabsorption syndrome or other condition that would interfere with intestinal absorption. Patients must be able to swallow capsules.

3.2.6 Patients with clinically important history of liver disease, including viral or other hepatitis or cirrhosis are ineligible.

3.2.7 Patients with uncontrolled hypocalcemia, hypomagnesemia, hyponatremia or hypokalemia defined as less than the lower limit of normal for the institution, despite adequate electrolyte supplementation are excluded from this study.

3.2.8 Tumor tissue sample not available for pathological review and/or correlative studies.

3.2.9 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.10 Pregnant women are excluded from this study because GDC-0449 is a Hh pathway inhibiting agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with GDC-0449, breastfeeding should be discontinued if the mother is treated with GDC-0449. These potential risks may also apply to other agents used in this study.

3.2.11 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with GDC-0449. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial. In accordance with French Regulatory Authorities, no data related to ethnicity will be collected.

4. REGISTRATION PROCEDURES

4.1. General Guidelines

Eligible patients will be entered on study centrally at the Institut Bergonié Coordinating Center by the Study Coordinator. All sites should call the Responsive Clinical Research Assistant (+33 5 56 33 78 05) to verify agent availability. The required forms can be found in Appendix F

Following registration, patients should begin protocol treatment within 72 hours. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Each participating institution will order GDC-0449 directly to the Pharmacy of Institut Bergonie.

4.2. Registration Process

To register a patient, **the following documents should be faxed** to the Bergonié Institute Data Center:

Clinical Trial and Epidemiology Unit – Institut Bergonié
FAX : +33 5 56 33 33 81
From Monday through Friday - From 9.00 am to 5.00 pm
Contact : Sabrina ALBERT (CRA) - Tel : + 33 5 56 33 78 05 , Mail – albert@bergonie.org

This must be done **before the start of the protocol treatment which should begin within 72 hours following registration**.

The following documents should be completed and faxed by the clinical research assistant or data manager:

- Copy of required laboratory test
- Anomymized signed patient consent form (2 letters/NAME ; 2 letters/SURNAME)
- Registration form (Appendix F):
    - Institution number
    - Name of the responsible investigator
    - Patient's code (2 letters of name, 2 letters of first name)
    - Patient's birth date (day/month/year)
    - Eligibility criteria
    - Data foreseen for protocol treatment start

The clinical research assistant or data manager at the participating site will then call the Bergonié Institute Data Center to verify eligibility.

To complete the registration process, the Coordinator will:

- Assign a patient study number
- Register the patient on the study
- Fax or e-mail the patient study number
- Call the research nurse or data manager at the participating site and verbally confirm registration

The patient study number attributed at the end of the registration procedure identifies the patient and must be reported on all case report forms.

Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be cancelled. The Study Coordinator should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for GDC-0449 are described in Section 7. Appropriate dose modifications for GDC-0449 are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

REGIMEN DESCRIPTION					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
GDC-0449	*Take with or without food at the same time every day*	*150 mg*	*PO*	*Days 1-28*	*4 weeks (28 days)*

5.1.1 GDC-0449

- GDC-0449 is an oral drug. Patients should take GDC-0449 at approximately the same time every day, with or without food. Capsules should not be opened. If a patient misses a dose, he or she should be instructed not to take or make up that dose and to resume dosing with the next scheduled dose. Missed doses should not be made up. Patients will be instructed to bring all unused capsules and their medication diary (refer to Appendix E) to each study visit for assessment of compliance.
- Patients should be warned not to share their supply of GDC-0449.
- Investigators may dispense no more than a 32-day supply of GDC-0449.

5.2 General Concomitant Medication and Supportive Care Guidelines

5.2.1 GDC-0449

- Clinically significant PK interactions between vismodegib and CYP450 inhibitors are not expected.
- Inducers of CYP3A4 are not predicted to alter vismodegib systemic exposure
- Drugs that Inhibit Drug Transport Systems : Clinically significant PK interactions between vismodegib and P-gp inhibitors are not expected
- Drugs that Affect Gastric pH : Clinically significant PK interactions between vismodegib and pH elevating agents are not expected.

- Effects of Vismodegib on Other Drugs : Clinically significant PK interactions between vismodegib and CYP450 substrates are not expected. Inhibition of CYP enzymes by vismodegib may be excluded.
- No clinically significant PK interaction between vismodegib and the oral contraceptives ethinyl estradiol and norethindrone.
- Clinically significant PK interactions between vismodegib and BCRP substrates are not expected.

Vismodegib capsules contain lactose monohydrate. Patients with the rare hereditary problems of galactose intolerance, primary hypolactasia, or glucose-galactose malabsorption should not take this medicine.

Because there is a potential for interaction of GDC-0449 with other concomitantly-administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

- If plasma levels need to be lowered emergently, animal studies have suggested that oral administration of activated charcoal may lower drug plasma levels more quickly than drug cessation alone.
- Women of childbearing potential are required to have a negative serum pregnancy test (with a sensitivity of at least 25 mIU/mL) within 7 days prior to the first dose of GDC-0449 (serum or urine). A pregnancy test (serum or urine) will be administered every 4 weeks while on study within the 24-hour period prior to the administration of GDC-0449. Prior to dispensing GDC-0449, the investigator must confirm and document the patient's use of two contraceptive methods, dates of negative pregnancy test, and confirm the patient's understanding of the teratogenic potential of GDC-0449.

Female patients are required to use two forms of acceptable contraception (refer to Appendix C), including one barrier method during participation in the study and respectively for the 2 and 24 months following the last dose for both male and female patients. All patients should receive contraceptive counseling either by the investigator, or by an obstetrician (OB)/gynecologist or other physician who is qualified in this area of expertise. If a woman of childbearing potential believes that her contraceptive method has failed, emergency contraception should be considered. If a patient is suspected to be pregnant, GDC-0449 should be immediately discontinued. In addition, a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patients is not pregnant, the patient may resume dosing with GDC-0449.

If a female patient becomes pregnant during therapy or within 24 months after the last dose of GDC-0449, or if the female partner of a male patient exposed to the drug becomes pregnant while the male patient is receiving GDC-0449 or within 2 months after the last dose of GDC-0449, the investigator must be notified in order to facilitate outcome follow-up.

Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious. Any congenital anomaly/birth defect in a child conceived during the study or within 24 months after the last dose of GDC-0449 to a female patient or to a female partner of a male patient

exposed to the agent during treatment or within 2 months after the last dose of GDC-0449 should be recorded and reported as an SAE.

- Female patients should not breastfeed a baby while on this study.
- Female patients must NEVER donate ova while being treated with GDC-0449.
- All sexually active male subjects (including those who have undergone vasectomy) should utilize a barrier form of contraception during study treatment and for 2 months after the last dose as it is not known whether GDC-0449 that may be present in seminal fluid would cause teratogenic effects in a fetus born to the female partner of a male subject. Males should also not donate sperm during treatment or up to 2 months after the last dose.
- All patients are prohibited from donating blood for 24 months after the last dose of GDC-0449.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse events(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.4 Duration of Follow Up

Patients will be followed every 3 months until death or study discontinuation, whichever occurs first after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.5 Criteria for removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.3 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

Patients who experience grade ≥ 3 toxicity must have treatment withheld until recovery grade ≤ 1. A maximum delay of four weeks is allowed for recovery from toxicity. If toxicities have not recovered after ≥ 4 weeks from the last study dose, the patient should discontinue the treatment.

In the event of obvious clinical benefit, the patient will be allowed to remain on treatment after appropriate dose adjustment despite a dose delay of > 28 days only after having discussed and agreed upon the case with the Principal Investigator, and upon recovery of all parameters according to the aforementioned criteria.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited (via CTEP-AERS) reporting **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs) for GDC-0449

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1893 patients.* Below is the CAEPR for GDC-0449 (Vismodegib).

> **NOTE**: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.5, December 22, 2016[1]

Adverse Events with Possible Relationship to GDC-0449 (Vismodegib) (CTCAE 4.0 Term) [n= 1893]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		
	Diarrhea		***Diarrhea (Gr 2)***
	Dyspepsia		
	Nausea		***Nausea (Gr 3)***
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
INVESTIGATIONS			
	CPK increased		
Weight loss			***Weight loss (Gr 2)***

Adverse Events with Possible Relationship to GDC-0449 (Vismodegib) (CTCAE 4.0 Term) [n= 1893]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
Musculoskeletal and connective tissue disorder - Other (muscle spasms/twitching)			***Musculoskeletal and connective tissue disorder - Other (muscle spasms/twitching) (Gr 2)***
		Musculoskeletal and connective tissue disorder - Other (premature epiphyseal closure)	
NERVOUS SYSTEM DISORDERS			
Dysgeusia			***Dysgeusia (Gr 2)***
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Irregular menstruation[2]			***Irregular menstruation[2] (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia			***Alopecia (Gr 2)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Irregular menstruation was observed in 30% (3 of 10) women of child bearing age and/or in 28% (18 of 64) women who had menses at baseline who were enrolled in studies of advanced BCC.

[3]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on GDC-0449 (Vismodegib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that GDC-0449 (Vismodegib) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Febrile neutropenia; Thrombotic thrombocytopenic purpura
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Heart failure; Myocardial infarction; Pericardial tamponade; Sinus bradycardia
EYE DISORDERS - Keratitis; Retinal vascular disorder
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Dry mouth; Dysphagia; Esophageal pain; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (thrush); Gastrointestinal hemorrhage[3]; Gastrointestinal pain; Ileus; Mucositis oral; Pancreatitis; Stomach pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Facial pain; Fever; Injection site reaction; Non-cardiac chest pain; Pain

HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Portal hypertension
INFECTIONS AND INFESTATIONS - Infection[4]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Hip fracture
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Cholesterol high; Creatinine increased; GGT increased; INR increased; Investigations - Other (brain natriuretic peptide increased); Investigations - Other (elevated LDH); Lipase increased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Flank pain; Generalized muscle weakness; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (muscle tightness/stiffness); Myalgia; Neck pain; Pain in extremity; Trismus
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Dizziness; Dysesthesia; Headache; Intracranial hemorrhage; Movements involuntary; Nervous system disorders - Other (amimia); Olfactory nerve disorder; Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Stroke; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Hallucinations; Insomnia; Psychosis
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal hemorrhage
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Erectile dysfunction
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Aspiration; Cough; Dyspnea; Epistaxis; Hiccups; Hypoxia; Pleural effusion; Pneumonitis; Postnasal drip; Pulmonary edema; Respiratory, thoracic and mediastinal disorders - Other (COPD); Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain); Sneezing; Sore throat
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Hyperhidrosis; Nail ridging; Pruritus; Rash acneiform; Rash maculo-papular; Skin and subcutaneous tissue disorders - Other (hair color changes); Skin and subcutaneous tissue disorders - Other (psoriasis); Skin and subcutaneous tissue disorders - Other (skin exfoliation); Skin ulceration; Stevens-Johnson syndrome
VASCULAR DISORDERS - Hypertension; Hypotension; Thromboembolic event; Vasculitis

Note: GDC-0449 (Vismodegib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Additional Adverse Events

Teratogenic Effects of GDC-0449

Studies have demonstrated that inhibition of the Hh pathway in embryos results in brain, facial, and other midline defects, including holoprosencephaly or microencephaly, cyclopia, absent nose, cleft palate, tooth abnormalities, and bone development abnormalities (Bale, 2002).

GDC-0449 may cause embryo-fetal death or severe birth defects when administered to a pregnant woman. Hh pathway inhibitors such as GDC-0449 have been demonstrated to be embryotoxic and/or teratogenic in multiple animal species and can cause severe midline defects, missing digits, and other irreversible malformations in the developing embryo or fetus. GDC-0449 must not be used during pregnancy, except in severe life-threatening cases, where the potential benefit to the patient outweighs the risk to the fetus.

Both women of childbearing potential and men must agree to use two methods of contraception (i.e., barrier contraception and another method of contraception) prior to study entry, for the duration of study participation, and for 24 months following treatment for female patients and for 2 months for male patients.

Women of childbearing potential are defined as follows:

- Patients with regular menses
- Patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding
- Women who have had a tubal ligation

Women are considered not to be of childbearing potential for the following reasons:

- The patient has undergone hysterectomy and/or bilateral oophorectomy.
- The patient is post-menopausal defined by amenorrhea for at least 1 year in a woman > 45 years old.

Women of childbearing potential are required to use two forms of acceptable contraception (refer to Appendix C), including one barrier method during participation in the study and for the 24 months following the last dose. All patients should receive contraceptive counseling either by the investigator or by an OB/gynecologist or other physician who is qualified in this area of expertise. If a woman of childbearing potential believes that her contraceptive method has failed, emergency contraception should be considered.

If a patient is suspected to be pregnant, GDC-0449 should be IMMEDIATELY discontinued and the study physician contacted. A positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patients is not pregnant, the patient may resume dosing with GDC-0449.

If a female patient becomes pregnant during therapy or within 24 months after the last dose of GDC-0449, or if the female partner of a male patient exposed to the drug becomes pregnant while the male patient is receiving GDC-0449 or within 2 months after the last dose of GDC-0449, the investigator must be notified in order to facilitate outcome follow-up.

Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious. Any congenital anomaly/birth defect in a child conceived during the study or within 24 months after the last dose of GDC-0449 to a female patient or to a female partner of a male patient exposed to the agent during treatment or within 2 months after the last dose of GDC-0449 should be recorded and reported as an SAE.

In addition, it is known that GDC-0449 is present in seminal fluid would cause teratogenic effects in a fetus born to the female partner of a male subject. Sexually active male subjects should utilize a barrier form of contraception, even those who have had a vasectomy, during study treatment and for 2 months after the last dose. Male patients should advise their partners to use an additional method of contraception during the study and for at least 2 months after discontinuation of GDC-0449. Male subjects should also not donate sperm during treatment or up to 2 months after the last dose.

Risk of Male Germ Cell Degeneration

Effects on testes and epididymides characterized by mild to moderate germ cell degeneration in seminiferous tubules, relative paucity of spermatozoa, and increased cellular debris in epididymides were observed in male dogs at all dose levels tested and were consistent with the pharmacologic activity of the drug. There were no changes in Leydig or Sertoli cells in any animal. Evidence of partial recovery was noted after a 4-week recovery period.

Germ cell degeneration in male patients is likely to occur at pharmacologically active doses. There is no specific mitigation strategy for this GDC-0449 toxicity; however, male patients should be made aware of it during the consent process. Although this effect is expected to be reversible with discontinuation of dosing, long-term effects on male fertility cannot be excluded at this time.

7.2 Adverse Event Characteristics *[Following NCI procedures]*

- **CTCAE term (AE description) and grade: The CTEP Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Version 4.0 of the CTCAE is identified and located on the CTEP website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). All appropriate treatment areas should have access to a copy of the CTEP Version 4.0 of CTCAE.**
- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only. 'Expected' AEs (the SPEER) are ***bold and italicized*** in the CAEPR (Section 7.1.1).
- **Attribution** of the AE:
    - Definite – The AE is clearly related to the study treatment.
    - Probable – The AE is likely related to the study treatment.
    - Possible – The AE may be related to the study treatment.
    - Unlikely – The AE is doubtfully related to the study treatment.
    - Unrelated – The AE is clearly NOT related to the study treatment.

7.3. Expedited Adverse Event Reporting *[Following NCI procedures]*

7.3.1. CTEP-AERS

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP home page (http://ctep.cancer.gov). These requirements are briefly outlined in the table below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, an AE report may be submitted using CTEP's Adverse Event Expedited Report-Single Agent or Multiple Agent paper template (available at http://ctep.cancer.gov) and faxed to 301-230-0159. A 24-hour notification is to be made to CTEP by telephone at 301-897-7497, only when Internet connectivity is disrupted. Once Internet connectivity is restored, an AE report submitted on a paper template or a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter

at the site.

7.3.2. Multi-Institutional Studies

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3. Phase 2 and 3 Trials Expedited Reporting Guidelines – CTEP-AERS Reporting Requirements for Adverse Events that occur within 30 Days1 of the Last Dose of the Investigational Agent on Phase 2 and 3 Trials

Phase 2 and 3 Trials									
	Grade 1	**Grade 2**	**Grade 2**	**Grade 3**		**Grade 3**		**Grades 4 & 5[2]**	**Grades 4 & 5[2]**
				Unexpected		**Expected**			
	Unexpected and Expected	**Unexpected**	**Expected**	**with Hospitalization**	**without Hospitalization**	**with Hospitalization**	**without Hospitalization**	**Unexpected**	**Expected**
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**

CTEP-AERS 24-hour notification followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

CTEP-AERS 10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

December 15, 2004

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
    - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
    - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

7.3.4. Expedited Adverse Event Reporting for Suspected Exposure to Teratogenic Agent for Patients Receiving GDC-0449

- CTEP considers **any possible prenatal exposure to GDC-0449**, a potential genotoxic agent, a reportable expedited adverse event that should be reported to CTEP-AERS as a 24-hour notification followed by a complete report within 5 calendar days. The events may range from midline facial defects such as cleft lip and palate to holoprosencephaly.
- Any patient suspected of being pregnant or fathering a child, (i.e. any female patient or female partner of a male patient), or should any lapse in contraception occur, should stop taking GDC-0449/placebo until it is confirmed that pregnancy has not occurred.
- Pregnancies that occur up to 12 months after the last dose of GDC-0449 will be followed until the outcome of the pregnancy is known.
- The adverse event (pregnancy) should be reported as a Grade 4 event using the CTEP Version 4.0 of the CTCAE as follows:
    - **Investigators should report the pregnancy through CTEP-AERS as an expedited adverse event (24-hour notification followed by a complete report within 5 calendar days).** The adverse event should be reported under Endocrine - Other (Prenatal exposure to a possible teratogen).
    - **A completed "Possible Prenatal Exposure to Teratogen Report" Form (*Appendix D*) should be attached to the complete CTEP-AERS Report.** This form may also be faxed to CTEP along with any relevant supporting medical information at ***301-230-0159*** (alternative FAX Number: ***301-897-7404***).
    - This form should be submitted for any female patient who becomes pregnant during therapy or up to 12 months after the last dose of GDC-0449.
    - This form should also be submitted if any female patient or partner of a patient becomes pregnant while the patient is receiving GDC-0449 or within 3 months after the last dose of GDC-0449.
- Any congenital anomaly/birth defect in a child conceived during the study or within 12 months after the last dose of GDC-0449 to a female patient should be reported as an expedited adverse event to CTEP-AERS as a 24-hour notification followed by a complete report within 5 calendar days.
- Any congenital anomaly/birth defect in a child conceived during the study to a female partner of a male patient exposed to GDC-0449 during treatment or within 12 months after the last dose of GDC-0449 should be reported as an expedited adverse event to CTEP-AERS as a 24-hour notification followed by a complete report within 5 calendar days.

- Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious. Any abortion occuring during the study or within 12 months after the last dose of GDC-0449 to a female patient or to a female partner of a male patient exposed to the agent during treatment or within 12 months after the last dose of GDC-0449 should be reported as an expedited adverse event to CTEP-AERS as a 24-hour notification followed by a complete report within 5 calendar days.

7.4. Routine Adverse Event Reporting *[Following NCI procedures]*

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through CTEP-AERS must also be reported in routine study data submissions.**

7.5.Secondary AML/MDS *[Following NCI procedures]*

Investigators are required to report cases of secondary AML/MDS occurring on or following treatment on NCI-sponsored chemotherapy protocols using the NCI/CTEP Secondary AML/MDS Report Form. This form can be downloaded from the CTEP web site (http://ctep.cancer.gov). Refer to the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" (available at http://ctep.cancer.gov) for additional information about secondary AML/MDS reporting.

7.6.Safety evaluation *[Following Institut Bergonié procedures]*

7.6.1. Description of safety evaluation parameters

The safety evaluation will comprise an evaluation of the patient's general condition (ECOG), a physical exam, regular blood tests and the recording of adverse events occurring throughout the study. Toxicity will be evaluated using the CTEP Version 4.0 of the CTCAE (Appendix G).

In an emergency situation, the patient, his/her friends/family or treating physician will contact the investigator to report an event and/or to discuss the treatments to be implemented.

7.6.2. Methods and schedule to measure, collect and analyze the safety evaluation parameters

Patients will be seen for consultation at least once every four weeks over the study period. (section 10, Study Calendar).
Serum chemistry evaluations are also planned every week over the study period.

7.6.3. Definitions

Adverse event
An adverse event (AE) is defined as any harmful event occurring in a patient or clinical trial subject treated with a medicinal product, and which is not necessarily associated with this treatment or trial (Article R.1123-39 du Code la Santé Publique). All adverse events will be reported in the Case Report Form.

Serious adverse event
The following are considered as serious adverse events (SAEs):

- Fatal events,
- Life-threatening events,
- Events requiring inpatient hospitalization or prolongation of existing hospitalization,
- Events resulting in permanent disability or serious temporary incapacity
- Events resulting in a congenital anomaly, fetal malformation or abortion
- Medically significant events.

The terms *disability and incapacity* refer to any clinically significant physical or mental handicap, whether temporary or permanent, that affects the patient's physical activity and/or quality of life.
A *medically significant* event is any clinical event or laboratory test result considered by the investigator to be serious and that does not correspond to the seriousness criteria defined above. They may pose a risk to the patient and require medical intervention to prevent one of the serious outcomes mentioned previously *(for example, overdose, second cancer, pregnancy and new events may be considered medically significant*).
The following are not considered as serious adverse events (SAEs):
- 24-hr hospital stay,
- Hospitalization scheduled before the start of the trial and/or stipulated in the protocol (for a biopsy, chemotherapy, etc.).

Adverse drug reaction
An adverse drug reaction due to IMP is an untoward and unintended response to an IMP at any dose.
Suspected Unexpected Serious Adverse Reaction
A Suspected Unexpected Serious Adverse Reaction (SUSAR) is an event not mentioned in or differing in terms of nature, intensity or clinical course from that listed in the reference safety information for the evaluation of listedness/expectedness the most updated Investigator's Brochure (IB) for the studied IMP.

7.6.4. Intensity criterion

The CTEP Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Version 4.0 of the CTCAE is identified and located on the CTEP website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Version 4.0 of CTCAE.
The intensity of adverse events not listed in this classification will be assessed using the following descriptors:
- Mild (grade 1): does not affect the patient's usual daily activities,
- Moderate (grade 2): disturbs the patient's usual daily activities,
- Severe (grade 3): prevents the patient's usual daily activities,
- Very severe (grade 4): requires critical care / life-threatening,
- Death (grade 5).

7.6.5. New information

A new information is any new safety data that could lead to reevaluate the ratio between the

benefits and risks of the research, or that could be sufficiently important to consider modifications of the research documents, the research management or, if need be, the drug utilization.

7.7. Serious adverse events and new information notification (responsibility of the investigator) *[Following Institut Bergonié procedures]*

The investigator will notify the Vigilance Unit **without delay** about any serious adverse events or new events occurring:

- From the date of the informed consent is signed,
- During the whole patient follow-up period as defined by the research,
- Until 30 days after the end of patient follow-up period as defined by the research, if the event is likely to be research-related.

Type of Event	Reporting procedure	Deadline for reporting to the sponsor
SAE	SAE report form + written form if necessary	To be reported immediately to the sponsor
New information	Written report form	To be reported immediately to the sponsor
Pregnancy	Written report form	As soon as pregnancy is confirmed

The investigator must complete the "***Serious Adverse Event Reporting Form***" (Appendix HA) immediately and assess the relationship with the study treatment. The form must then be dated, signed and sent by fax to the following address **without delay** to:

CELLULE DE VIGILANCE (VIGILANCE UNIT) - Unicancer
Fax : + 33 1 44 23 55 70
Or Contact: R&D Unicancer – E-mail: pv-R&D@unicancer.fr

For each event, the investigator will record:

- A description of the event that is as clearly as possible, using medical terminology,
- The date the event started and ended,
- The patient's relevant medical history,
- The steps taken and whether or not corrective treatment was required, whether or not the investigational treatment was discontinued, etc.
- Concomitant medications / therapies
- The CTEP Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Version 4.0 of the CTCAE is identified and located on the CTEP website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Version 4.0 of CTCAE.
- The causal link between this event and the trial treatment, disease treated or an intercurrent disease or treatment, or any obligation imposed by the research (a treatment-free period, additional examinations requested as part of the research etc.),

- Clinical course. If the event was not fatal, it should be monitored until recovery, until the patient has returned to his/her previous condition, or until any sequelae have stabilized,
- Whenever possible, the investigator must also attach the following with the serious adverse event report:
    - A copy of the hospitalization or extended hospitalization report,
    - A copy of the autopsy report, if required,
    - A copy of all the results of any additional tests performed, including relevant negative results, along with the normal laboratory values,
    - Any other document he or she considers useful and relevant.

All these documents must be anonymized.

Additional information may be requested (by fax, by telephone or during a visit) by the CRA and/or by the Vigilance Unit using the Data Query form.

The investigator is responsible for providing appropriate medical follow-up for patients until resolution or stabilization of the adverse event or until the patient's death. Sometimes this may mean that follow-up will extend beyond the patient's withdrawal from the trial.

The investigator keeps the documents about the presumed adverse effect so that the information previously sent can be added to if necessary.

The investigator responds to requests for additional information from the Vigilance Unit in order to document the original observation.

7.8. Non serious adverse events *[Following Institut Bergonié procedures]*

TYPE OF EVENT	REPORTING PROCEDURES	DEADLINE FOR REPORTING TO THE SPONSOR
Non-serious AE	Case report/record form	Does not need to be reported immediately

Non-serious adverse events will be reported by the investigator in the patient's CRF and will be followed-up until complete resolution. The CTEP Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Version 4.0 of the CTCAE is identified and located on the CTEP website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Version 4.0 of CTCAE.

If an adverse event becomes serious, it should be reported and followed-up as mentioned in the previous reporting procedures.

If the investigator would like to decrease trial treatment dose or temporarily stop study management without respecting protocol procedures, he/she should have previously discussed with the coordinator.

However, symptomatic treatment can be prescribed to manage the adverse event.

Any definitive interruption of the procedure has to be immediately notified to the sponsor. The patient remains in the study and is followed-up according to the procedures described in the protocol.

7.9. Pharmacovigilance Unit *[Following Institut Bergonié procedures]*

The Vigilance Unit of Institut Bergonié will analyze each SAE to define for the sponsor:

- Severity grading,
- Degree of relationship with study treatment,
- Whether expected or unexpected according the characteristics of study drug.

7.10. Notification and registration of unexpected serious adverse events and new information (Responsibility of the sponsor) *[Following Institut Bergonié procedures]*

The sponsor notifies unexpected serious adverse events and new information to the Regulatory Authorities (in person, or through an organization which has received allowances for this task) according to the usual notification procedures (Appendix HB).

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.1.

8.1 GDC-0449

Chemical Name: 2-chloro-*N*-[4-chloro-3-pyridin-2-yl-phenyl]-4-methanesulfonyl-benzamide

Other Names: Systemic Hedgehog Pathway Antagonist, G-025897, G-025897.1, and GDC-0449.1

Classification: Hedgehog Pathway Antagonist

CAS Registry Number: 879085-55-9

Molecular Formula: $C_{19}H_{14}Cl_2N_2O_3S$ **M.W.:** 421.3 g/mol

Mode of Action: GDC-0449 provides anticancer responses by inhibiting the Hedgehog pathway. The Hedgehog signaling pathway controls cell differentiation, growth, and proliferation. It is most active during embryogenesis but may also play a role in the regulation of adult stem cells involved in the maintenance and regeneration of adult tissues.

How Supplied: GDC-0449 is supplied by Genentech. It is available as 150-mg grey and pink, size 1 capsules containing microcrystalline cellulose, lactose monohydrate, sodium lauryl sulfate, povidone, talc,

	sodium glycolate, and magnesium stearate. Capsules are packaged in 75-mL round, white, high-density polyethylene (HDPE) bottles and closed with 38/400 two-piece HDPE child-resistant caps. Each bottle contains 32 capsules.
Storage:	GDC-0449 should be stored at room temperature between 59°F and 86°F (15°C and 30°C) and should be protected from excessive exposure to light.
Stability:	Stability testing is ongoing.
Route of Administration:	Oral
Drug Administration:	Patients should take GDC-0449 at approximately the same time each day, with or without food. If a patient misses a dose (e.g., due to emesis), he or she should be instructed not to take or make up that dose and to resume dosing with the next scheduled dose. Missed doses should not be made up.
Patient Care Implications:	The terminal half-life of GDC-0449 is approximately 10-14 days in healthy volunteers. If plasma levels of GDC-0449 need to be lowered emergently, animal studies suggest that oral administration of activated charcoal may lower drug plasma levels more quickly than dose cessation alone.
Drug Interactions:	Caution should be exercised when dosing GDC-0449 with narrow therapeutic con-meds that are metabolized by CYP2Cs. Warfarin falls into this category (CYP2C9 substrate, narrow TI).

Availability
GDC-0449 is an investigational agent supplied to investigators by Almac Clinical Services .

8.1.1 GDC-0449 Ordering

Each participating institution will order GDC-0449 directly to the pharmacy of Bergonie Institute. (Dr Barbara Lortal: Phone number: +33 556337890, Fax number: +33 556333384; email: lortal@bergonie.org)

8.1.2 Agent Accountability

GDC-0449 Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all GDC-0449

using the NCI Drug Accountability Record Form (DARF) (http://ctep.cancer.gov/forms/docs/clin_drug_req.pdf).

9. CORRELATIVE/SPECIAL STUDIES

9.1. Laboratory Correlative Studies

9.1.1. External review of histology – Pathology Department Institut Bergonié

Collection, handling and shipping of Specimen(s)

Formalin fixed paraffin embedded tumor blocks **and** representative H/E (hematoxylin/eosin) slides must be sent to the reference pathologist **within 10 days of trial inclusion. If tumour blocks are not available for sending to the reference pathologist, just representative H and E slides can be sent for review.**

Pathology will be reviewed for all patients included in this trial.

Three forms will be used for this purpose and completed by the clinical investigator (the clinician who has registered the patient in the trial):

- **Form A (Appendix IA)** : Patient information transmitted to the local pathologist;
- **Form B (Appendix IB)**: Patient clinical data transmitted to the reference pathologist;
- **Form C (Appendix IC)**: Review form to be handled partly by the clinical investigator and partly by the reference pathologist.

The clinical investigator sends:

1. **Form A** (completed) to the local pathologist with a copy to :
    - the Data Center (Institut Bergonie, S. Albert, 229 cours de l'Argonne, 33000, Bordeaux)
2. **Form B** (completed) and
3. **Form C** (upper part completed) to the reference pathologist

The local pathologist sends to the reference pathologist :

- 1 or 2 formalin fixed paraffin blocks ("Boin" fixation not allowed) and representative H and E Slides.
- his own report (including gross morphology, note necrosis)

The reference pathologist (Prof. Jean-Michel Coindre):

- Sends **Form C** (completed) to the Data Center with a copy to the local pathologist
- Retains 8 slides and the blocks for the correlative study

All material and documents will be sent to Cécile MANNINA, Institut Bergonié, Service Pathologie
229 cours de l'Argonne
33076 Bordeaux Cedex, France
Tél : 05.56.33.78.53 – mail : c.mannina@bordeaux.unicancer.fr

Site(s) Performing Correlative Study

Reference pathologist : Pr Jean-Michel Coindre, Institut Bergonie, Department of Pathology, 229 cours de l'Argonne, 33000, Bordeaux, telephone : +33 5 56 33 33 29, coindre@bergonie.org

9.1.2 Correlative study

- *Biologic rationale*

Activation of the hedgehog pathway in cancer may result of three mechanisms:
- loss-of-function mutations in Patched 1 (PTCH1) or gain-of-function mutations in Smoothened (SMOH) leading to constitutive Hedgehog (Hh) pathway activation as described in basal cell carcinoma and medulloblastoma.
- autocrine activation in which tumour cells produce and respond to Hedgehog ligand. Pathway activation may occur in all tumour cells or in a small number of tumour stem cells.
- paracrine model in which tumour cells produce Hedgehog ligand and surrounding stromal cells respond by growth factor; VEGF, vascular endothelial growth factor
Autocrine pathway is the sole described mechanism of hedgehog activation in chondrosarcomas (Tiet et al., 2006). However, there are no data about the mutational status of the *PTCH* and *SMO* genes in chondrosarcoma.

- *Objective*

To find predictive biomarkers of clinical benefit from GDC-0449 in patients with advanced chondrosarcomas.

- *Translational research program*

A translational research program will be conducted at the Department of Pathology, Institut Bergonié, Bordeaux, France (Professor Jean-Michel Coindre) by using paraffin-embedded tumor samples obtained at the time of initial diagnosis or relapse.
This program will include:
- An analysis of the mutational status of *PTCH* and *SMO*
- An analysis of the expression pattern of hedgehog signaling molecules (Shh, PTCH, Smo, Gli-1, Gli-2, Gli-3) by using quantitative reverse transcription-polymerase chain reaction and immunohistochemistry (IHC) (Tiet et al., 2006; Steg et al., 2007).

Concerning IHC, the staining intensity will be classified for all the proteins assessed as weak, moderate, or strong. The positive cells will be quantified as a percentage of the total number of tumor cells and assigned to one of five categories (0, <5%; 1, 5–25%; 2, 26–50%; 3, 51–75%; 4, >75%). The percentage of positivity of the tumor cells and the staining intensities were then multiplied in order to generate the IHC score (Kim et al., 2009)
The 6-months clinical benefit rate will be correlated with the mutational status of *PTCH* and *SMO* and with the expression score of hedgehog signaling molecules (Shh, PTCH, Smo, Gli-1, Gli-2, Gli-3)

10. STUDY CALENDAR

Schedules shown in the Study Calendar below are provided as an example and should be modified as appropriate.

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy.

Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Screening	Cycle 1					Cycle 2				Cycle 3, n				Off treatment[c]
		We 1 Day 1	We 1 D8	We 2 D15	We 3 D21	We 4 D28	We 5 D8	We 6 D15	We 7 D21	We 8 D28	We 9 D8	We 10 D15	We 11 D21	We 11 D28	
GDC-0449		X ----------												X	
Informed consent	X														
Demographics	X														
Medical history	X														
Concurrent meds	X	X ----------												X	
Physical exam	X	X		X		X				X				X[f]	
Vital signs	X	X		X		X				X				X[f]	
Height	X														
Weight	X	X		X		X				X				X[f]	
Performance status	X	X		X		X				X				X[f]	
Hematology[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry[a,e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG (if indicated)	X	X ----------												X	X
Adverse event Eval		X ----------												X	X
Clinical and ragiology tumor eval	X									X[d]					
B-HCG	X[b]	X[b]				X[b]				X[b]				X[b]	X[c]
Serological testing for hepatitis A, B and C	X														

A: *GDC-0449*: Dose as assigned; oral daily administration at the same time every day

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, magnesium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein totales, SGOT [AST], SGPT [ALT], sodium, CPK

b: Serum or urine test 7 days prior to the first dose of GDC-0449 administration. Pregnancy test must be administrered 24 hours prior to the start of therapy (serum) and at least once every month thereafter (serum or urine).

c: Off-treatment evaluation.

d: Tumor measurements are repeated every 8 weeks. Documentation (radiology) must be provided for patients removed from study for progressive disease. Beyond 48 months of treatment without evidence of progressive disease, radiological tumor assessment will be performed every 3 months.

e: After 6 cycles, blood test will be performed every two weeks (week 2 and week 4). Beyond 48 months of treatment blood test will be performed every 3 months.

f: After 25 cycles, physical exam (vital signs, weight, performance status) will be performed/evaluated every 3 months

Baseline evaluations are to be conducted within one week prior to start of protocol therapy.
Scans and X-rays must be done ≤ 4 weeks prior to the start of therapy.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009.]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with GDC-0449.

Evaluable for objective response: Only those patients who have measurable disease present at baseline and have received at least one complete or two incomplete cycle of therapy will be included in the main analysis of the response rate.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area are not considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be

those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

11.1.4 Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Definition of the best response

The best response determination in trial where confirmation of complete or partial response is required:

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (**genrally 4 weeks later**). In this circumstance, the best overall response can be interpreted as in Table below.

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This meéasurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR (complete response) may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic detioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is *not* a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables belows.

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormability is thought to represent fibrosis or scarring. The use of FDG-PET I n this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

11.1.6 Progression-Free Survival (PFS)

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

11.1.7 Overall Survival (OS)

OS is defined as the duration of time from start of treatment to the time of death

11.1.8 Response Review

Review process

Independent response review involves:

1. Reviewing the disease status at 6 months (tumor evaluation at 6-months or earlier in case of disease progression) in comparison with baseline (primary objective).
2. Reviewing all responses (complete and partial) observed during the study period.

Independent response review will proceed as follows:

- The review process will be centralized at Institut Bergonié and will be performed by one independent radiologist expert in bone sarcomas.
- When reviewing the 6-month disease status, the reviewer will only be provided with the first 6-month patient information.
- Patient' files will be anonymous.

In case of discordance between the local radiologist and the reviewer, the judgment provided by the expert reviewer will be retained and used for response evaluation in statistical analyses.

Review process schedule

The Simon's two-stage (section 13) implies evaluating treatment efficacy after 17 patients at the first stage, and then once all 51 patients have been included.
Review will thus be implemented in two steps:

- Once 6-month information is available for the first 17 patients;
- At the end of the study.

Practical implementation

- Each site must send the completed "Baseline Clinical Subject Profile" (Appendix JA) with the first shipment.
- For each shipment, media should be accompanied by the completed "Radiology Referral Form" (Appendix JB).
- The reviewer will assess the response to therapy, document the results on the "Response Review Form" (Appendix JC) and sign this form.
- Patient's information must be recorded on an imaging CD.
- Once 6-month response is available, each site must send the imaging CD to Institut Bergonié as soon as possible.
- Once complete patient's follow-up has ended, an updated imaging CD must also be sent to Institut Bergonié
- All CDs must be sent to :

Sabrina ALBERT, Responsible Clinical research Assistant
Institut Bergonié, 229 cours de l'Argonne, 33000 Bordeaux, France
Phone: **+ 33 5 56 33 33 78 05 –** mail : albert@bergonie.org

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1. Data Reporting

12.1.1 Method

This study will be monitored by the Clinical Data Update System (CDUS) version 4.2. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP web site (http://ctep.cancer.gov). **Note**: **All** adverse events that have occurred on the study, including those reported through CTEP-AERS, must be reported via CDUS.

12.1.2 Responsibility for Data Submission

Study participants are responsible for submitting CDUS data and/or data forms to the Coordinating Center quarterly by *January 31, April 30, July 31, and October 31* to allow time for Coordinating Center compilation, Principal Investigator review, and timely submission to CTEP (see Section 12.1.1.).

The Coordinating Center is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12.2. CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix B.

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (*PIO@ctep.nci.nih.gov*) (except for Group studies).

12.3. Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between Genentech and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the Intellectual Property Option to Genentech@ (http:// ctep.cancer.gov/industry) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Genentech data for Agent(s) are confidential and proprietary to Genentech and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Genentech shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data.@):
   a. NCI will provide Genentech with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

   b. Genentech shall agree to permit use of the Multi-Party Data from the clinical trial by any

other collaborator solely to the extent necessary to allow said other Genentech to develop, obtain regulatory approval or commercialize its own investigational Agent.

c. Genentech having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Genentech, the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. Additionally, all Clinical Data and Results and Raw Data will be collected, used, and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects including, if applicable, the Standards for Privacy of Individually Identifiable Health Information set forth in 45 C.F.R. Part 164.

4. When Genentech wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Genentech's wish to contact them.

5. Any data provided to Genentech for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Genentech for advisory review and comment prior to submission for publication. Genentech will have 30 days from the date of receipt for review. Genentech shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Genentech's confidential and proprietary data, in addition to Genentech's intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Genentech for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Suite 7111
Bethesda, Maryland 20892
FAX 301-402-1584
Email: anshers@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Genentech. No publication, manuscript or other form of public disclosure shall contain any of Genentech=s confidential/

proprietary information.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoint

We will rely on a two-stage Simon's design with the 6-month clinical benefit (CR + PR + SD) rate as the primary endpoint. At six months, patients will be classified as success (Alive at 6 months AND CR/PR/ SD) or failure (dead OR alive with progression).

13.2 Sample Size/Accrual Rate

The data from the literature about survival of patients with advanced chondrosarcomas are almost non existent. However, some studies confirm that the prognosis of patients with metastatic chondrosarcomas is poor and similar to that observed in metastatic soft-tissue tumors with median survival ranging from 7 to 17 months (Dickey et al., 2004; Ries et al., 2007; Giuffrida et al., 2009). Therefore, we believe that a 6 months clinical benefit rate of 40% is a reasonable objective in this setting. This objective was also chosen by American investigators (SARC) in a phase 2 trial of perifosine in patients with chemo-insensitive sarcomas (including chondrosarcomas).

We rely on an optimal two-stage Simon's design (Simon, 1989). Based on the following hypotheses under GDC-0449 treatment:

- 20% non-progression rate (null hypothesis),
- 40% acceptable non-progression rate (alternative hypothesis),
- 10% type I error rate,
- 90% power,

a total of 37 assessable subjects will be necessary, with 17 assessable subjects recruited to the first stage.

Stage 1: Following the inclusion of the first 17 assessable patients, if 3 or less patients are progression-free (complete response, partial response or stable disease), the study would be terminated early. Otherwise, the second group of 20 subjects will be recruited.

Stage 2: If at the end of recruitment, 11 patients or more are progression-free (out of the 37 evaluable patients), GDC-0449 would be considered worthy of further testing in this disease.

To be evaluable, a subject must meet the eligibility criteria AND have received at least one complete or two incomplete cycles of GDC-0449 AND at least one disease measurement recorded not less than eight weeks after treatment onset.

Given the disease is rare and the absence of standard treatment in this indication, inclusion will not be suspended after the recruitment of the first 17 patients. Inclusion will be pursued, while data on the first 17 patients will be analyzed.

In order to account for not evaluable patients (+/- 20%), **45 patients will be recruited**.

The anticipated accrual rate is 2-3 patients/months.

13.3 Stratification Factors

No stratified analysis is foreseen.

13.4 Analysis of Secondary Endpoints

Proportions (will be calculated and reported with their 95% confidence interval (binomial law).

Progression-free and overall survivals will be analyzed using the Kaplan-Meier method. The median survival rates will be reported with a 95% confidence interval. Median follow-up will be calculated using the reverse Kaplan-Meier method.

Duration of response will be described in responding subjects using descriptive statistics (median, extreme values, etc.).

The predictive value of biomarkers will be investigated using multivariate logistic regression (when evaluating impact on tumour response) or a Cox Proportional hazard model (when evaluating impact on time to tumour response) after checking for the proportional hazards assumption.

13.5 Reporting and Exclusions

13.5.1. Evaluation of toxicity.
All patients will be evaluable for toxicity from the time of their first treatment with GDC-0449.

13.5.2. Evaluation of response.
All patients included in the study will be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible.

Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria AND who received at least one complete or two incomplete cycles of the drug will be included in the main analysis of the response rate.

14. CONTROL AND QUALITY ASSURANCE

14.1 Monitoring of the trial

14.1.1 Steering Committee

The study will be supervised and monitored by a Steering Committee comprising members participating in the study:

- Dr A Italiano, MD, PhD, Principal Investigator and Chairman of the Commitee,
- Dr. B.N. Bui, MD
- Dr J.M Coindre, MD, PhD,
- Dr S. Mathoulin-Pélissier, MD, PhD, Head of the Clinical Research and Epidemiology Unit,
- C. Bellera, PhD, biostatistician,
- Sabrina Albert, responsible CRA.

This committee must ensure the following:

- Implementation and regular follow-up of the study
- Patient protection,
- That the trial is conducted ethically, in accordance with the protocol,
- That the trial benefit/risk ratio is evaluated and the scientific results are checked during or at the end of the trial.

It decides on any relevant amendment to the protocol that is required in order to continue the trial (protocol amendments prior to submission to the Ethics Committee and the relevant Health Authorities, decisions on whether to open or close research sites, discussion of results and the strategy for the publication of these results). It must inform the sponsor of any decisions taken. Decisions concerning a major amendment or a change to the budget must be approved by the sponsor.

14.1.2 Independent Data Monitoring Committee

An independent Data Monitoring Committee (IDMC) may be set created at the request of the relevant Authority, the sponsor or the Steering Committee. The IDMC plays an advisory role for the Sponsor, who has the final decision regarding the implementation of recommendations put forward by the IDMC.

Composition of the IDMC

- This Committee must comprise at least 3 qualified oncologists and a methodologist/statistician, all of whom will have experience in the monitoring and analysis of clinical trials. One of these members will be appointed as the Trial Rapporteur.
- Each of these members must be unconnected with the trial and cannot, therefore, be one of the trial investigators.
- These members are appointed by the Sponsor in consultation with the trial co-ordinator and the Steering Committee.

Responsibilities of the IDMC

The IDMC is responsible for the following:

- Analyzing preliminary efficacy and safety data,

- Making recommendations on the continuation, early discontinuation (in the case of toxicity or lack of efficacy) or publication of the trial results,
- Drafting the minutes after each meeting and monitoring their confidentiality.

Any recommendation from the IDMC that can be made public, will be announced by the Sponsor and not by the Steering Committee. The Sponsor is responsible for sending IDMC recommendations to the regulatory authorities [ANSM (French Agency for the Safety of Health Care Products) and EMEA (European Medicines Evaluation Agency)].

14.2 Quality assurance

14.2.1. Data collection

- The data will be collected on an electronic case report form and directly input via the Internet. Only the investigators and the Clinical Research Assistants (CRAs) appointed by the later and duly authorized by the sponsor will be authorized to enter the data.
- Data will be handled by the online trial management software of the Sponsor (Institut Bergonié) on the Internet. The software used will be MACRO (Infermed Company, London, United Kingdom). MACRO has been designed to support the requirements of internationally recognised ICH Good Clinical Practice and FDA 21 CFR Part 11. It will be monitored remotely in real time.
- The study CRA and/or any other person appointed by the sponsor will be available to assist the investigators in carrying out the study and to ensure that the trial is carried out in accordance with the protocol.
- The CRA will contact the investigators regarding the study implementation visit.
- All the study-related documents will be available on the Internet site: protocol, pre-selection form, randomization form, informed consent form, serious and non-serious adverse event report form, centralized tube dispatch form, etc.
- All of the necessary data will be collected on an electronic case report form provided by the sponsor. The generic names of the concomitant medication will be given in French.
- Corrections made to the original data must be justified. These corrections will be automatically dated and signed by the authorized member of staff via the personalized password allocated at the start of the study.
- The case report form will be validated by the investigator or the CRA at the authorized center whenever data is entered.
- Laboratory data exceeding normal limit values will be commented upon if they are considered clinically significant. Data other than that requested within the scope of the protocol can be collected as additional data; their interest will be specified.

14.2.2. Monitoring

In order to guarantee the authenticity and credibility of the data in accordance with the principles

of GCP (Good Clinical Practice) dated 24 November 2006, the sponsor shall implement a quality assurance system comprising:

- the management and monitoring of the trial in accordance with the procedures stipulated by the Institut Bergonié,
- the quality control of the research site data by the CRA whose role is to:
    - check compliance with the protocol, GCP and current legislation and regulations,
    - check the consent and eligibility of each patient taking part in the trial,
    - check the consistency and coherence of case report form date against the source documents.
    - check that each serious adverse event is reported,
    - monitor the traceability of the study medication (dispensation, storage and drug accountability),
    - check, where applicable, that the persons likely to take part in the trial are not already participating in another trial that could prevent them from being included in the clinical trial proposed. The CRA shall also ensure that the patients have not participated in a trial for which an exclusion period currently applies.
- an independent audit performed by a Clinical Research Organization
- the centralized review of certain protocol criteria.

The check procedures will include:

- study progression,
- Protocol compliance,
- The updating of information on the Internet site.

The checking of data by comparing the information on the electronic case report form and the original clinical or laboratory data is one of the monitoring procedures.

The following will be checked, in particular, for each patient (100% level): patient identification, informed consent (procedure and signature), selection criteria, therapeutic procedure, adverse events, principal response variables. The personal data relating to each patient shall remain confidential. On the electronic case report form or any other form dispatched, the patients will be identified solely by their initials (2/name – 2/surname) and an inclusion number. However, the investigators must keep a list identifying the patients in their folders.

The CRAs responsible for the quality control of this clinical trial are duly appointed by the sponsor for this particular purpose and must have access, with the consent of those involved, to individual trial participant data required strictly in accordance with this control procedure. The CRAs are subject to professional secrecy under the conditions defined by Articles 226-13 and 226-14 of the French penal code. The traceability of monitoring visits is guaranteed by a written monitoring report.

The investigators shall undertake to give CRAs direct access to the medical records of each patient in order to allow the CRAs to ensure optimal quality control of the trial. The same applies to health authority representatives.

14.2.3. Handling of missing data

The monitoring of data for adverse events will be carried out regularly in order to effectively limit the amount of missing data likely to prevent or hamper trial implementation and analysis.

14.2.3. Audits

An independent audit will be performed by a Clinical Research Organization chosen by the Sponsor. All the documents relating to this study must be available for such an inspection after prior notification.

15. ETHICAL, LEGISLATIVE AND REGULATORY CONSIDERATIONS

Clinical Research Management Unit – Institut Bergonié
Contacts: Mrs. Maryvonne Birac – Tel.: +33 5 56 33 32 70 – e-mail: birac_my@bergonie.org
or Miss. Stéphane Louchet, Tel.: +33 5 56 33 04 76 – e-mail: louchet@bergonie.org

The study will be carried out in accordance with:

- the ethical principles of the current version of the "Declaration of Helsinki"
- Good Clinical Practice (GCP): I.C.H. version 4 of 1 May 1996 and decision dated 24 November 2006 (Official Bulletin of 30 November 2006, text 64).
- European Directive (2001/20/EC) on clinical trial procedures.
- Huriet's law (No. 88-1138) dated 20 December 1988, concerning the protection of persons taking part in Biomedical Research with the provisions of the Public Health law (No. 2004-806) of 9 August 2004 and implementation decree No. 2006-477 of 26 April 2006 relating to biomedical research.
- the French law on Data Protection and Civil Liberties, No. 78-17 of 6 January 1978 modified by law No. 2004-801, dated 6 August 2004, concerning the protection of persons with regards to the processing of personal data.
- the application of Circular DHOS/INCA/MOPRC/2006/475 of 7 November 2006: the Sponsor shall undertake to register the Trial and thus make it accessible to the general public, in the INCa (French Cancer Institute) register via the Internet site: www.e-cancer.fr. Each trial published in the INCa register will be sent to the NCI for registering on the following site: www.clinicaltrials.gov. The trial will be registered before the first patient is entered into the study. The Sponsor is responsible for updating the study data in order to guarantee the reliability of the information available on-line.
- law no. 2004-800 dated 6 August 2004, concerning bioethics

15.1 Clinical Trial authorization

This trial is registered under Eudract No 2010-019817-20.

The protocol has been approved by the South West and Overseas Territories III Ethics Committee, Bordeaux. Approval was given on 28 April 2010.

The Relevant Authority, the Agence Nationale de Sécurité des Médicaments (ANSM - French Agency for the Safety of Health Care Products) authorized the clinical trial on 15 November 2010.

Any amendments to the protocol concerning study objectives, patient population and principal methods will require an amendment, which must be approved by the EC and l'ANSM. The sponsor will inform the EC and ANSM of expected and/or unexpected serious adverse events in accordance with current regulations.

The sponsor will send the summary of the final report to the relevant Authority within one year of completion of the trial.

15.2 Insurance policy

The Institut Bergonié has taken out an insurance policy (policy No. 01-8090188) with the Gerling France Company, 111, rue de Longchamp 75116 Paris through an insurance broker, namely Biomédic Insure (Parc d'Innovation Bretagne Sud, CP 142, 56038 Vannes, tel. 02 97 69 19 19) in case compensation is payable to investigators or patients taking part in the study.

15.3 Informing and obtaining consent from patients

The investigator in charge of the patient will provide the latter with relevant information relating to the study objectives, potential benefits and possible adverse events. The study methods will be outlined. The patient can refuse treatment before or at any time during the study, without experiencing any adverse repercussions in terms of his/her subsequent care.

The patient's written consent will be informed prior to entry into the study. Three copies will be available: one for the patient, the second for the investigator and the third for the sponsor. This written consent form will be kept for 15 years by the investigator.

The Patient Information Leaflet and Informed Consent Form must be combined in the same document in order to ensure that all of the information is given to the trial participant.

The consent form must be personally dated and signed by the trial participant and the investigator. The participant must also initial all of the pages in the Patient Information Leaflet. The original will be archived in the investigator's folder and the duplicate will be sent to the trial participant.

15.4 Sponsor's responsibilities

The sponsor of the clinical trial, the Institut Bergonié, will take the initiative for this clinical trial. The Institute will manage the trial and ensure that finance is provided.

The sponsor's main responsibilities are to:

- take out civil liability insurance,
- obtain the Eudract No. and register the trial in the European database (European Drug Regulatory Authorities Clinical Trials),
- obtain clinical trial authorization for the initial project and any amendments from the DC and ANSM; approval by the EC and decision taken by ANSM.

- inform the relevant authority of any unexpected suspect serious adverse event and to convey this information to the EC and the trial investigators,
- convey the safety report every year to the relevant authority and the EC,
- give trial-related information to the site directors, pharmacists and investigators,
- notify the relevant authority of the trial start and end dates,
- draft the final trial report and sent the summary to ANSM,
- send the trial results to the relevant authority, EC and trial participants,
- archive essential trial documents in the sponsor's folder for a minimum period of 15 years after the trial has ended.

15.5 Investigators' responsibilities

The senior investigator of each establishment concerned undertakes to conduct the clinical trial in accordance with the protocol that was approved by the ethics committee and the relevant authority (ANSM).

The investigator must not make any changes to the protocol without the written consent of the sponsor or without the ethics committee and the relevant authority having authorized the proposed changes.

It is the responsibility of the senior investigator is:

- to provide the sponsor with his/her curriculum vitae as well as those of his/her co-investigators,
- to identify the members of his/her team who are participating in the trial and to define their responsibilities,
- to start patient recruitment after authorization has been obtained from the sponsor,
- to ensure that he/she is available for "monitoring" purposes and for investigators' meetings.

It is the responsibility of each investigator:

- to comply with the confidential nature of the trial,
- to obtain informed consent, signed and dated personally by each trial participant, before any screening procedures specific to the trial are carried out,
- to regularly complete the case report forms (CRFs) for each of the patients enrolled in the trial and to allow the Clinical Research Assistant (CRA) direct access to source documents so that the latter can validate the data on the CRF,
- to promptly notify the Sponsor of any serious adverse event occurring during the trial,
- to date, correct and validate corrections on the case report forms (CRFs) and the Data Query Forms (DQFs).

15.6 Authority to execute the trial

The investigator shall certify that he/she is authorized to enter into this agreement and that the terms and conditions of the protocol and agreement do not conflict with other work contracts that the investigator may have entered into with any other party, or any other arrangement agreed by the Institution where the investigator is employed.

15.7 Regulations governing the collection of human biological samples

During the medical procedures to be carried out, samples will be collected for medical purposes. A fraction of these samples will be kept and used for scientific research purposes.

The patient will be informed of this research and provided that he/she approves by signing an informed consent, these samples intended for research will be:

- Initially prepared and stored using a specific technique to preserve them under excellent conditions.
- and secondly, used within the scope of this research.

The preparation, storage and use of these samples will not in any way affect current or future medical care administered to the patient for the purpose of diagnosis or treatment.

The results of this research may, in future, appear in scientific publications. All of the data shall remain anonymous.

15.8 Fédération des Comités de Patients pour la Recherche Clinique en Cancérologie (FCPRCC) (Federation of Patient Committees for Clinical Research in Oncology)

The Fédération des Comités de Patients pour la Recherche Clinique en Cancérologie (FCPRCC) (Federation of Patient COmmittees for Clinical Research in Oncology) was created on the initiative of the Fédération des Centers de Lutte Contre le Cancer (FNCLCC) (Federation of Anti-Cancer Centers) and the Ligue Nationale Contre le Cancer (National Anti-Cancer League) in order to review clinical trial protocols in oncology. This Federation of Patient Committees is co-ordinated by the Office for Clinical and Therapeutic Trials and groups together the League patient committees as well as other health care establishments. It undertakes to review the protocol and to propose improvements focusing primarily on the quality of the information leaflet, the availability of a treatment and monitoring plan and the suggestion of measures aimed at improving patient comfort.

15.9 Data processing

In accordance with the revision of the French Data Protection and Liberties Act of 06 August 2004 and its implementation decree, the Sponsor shall follow the methodology of reference MR001 of the Commission Nationale de l'Informatique et des Libertés (French National Commission for Data Protection and Liberties).

Furthermore, if the biomedical research data is computer processed or managed by computerized systems, each Center:

- shall check and document the fact that the computerized systems used in the research comply with requirements drawn up in relation to data integrity, accuracy and reliability, as well as compliance with expected performances (i.e. validation);

- shall implement and ensure the monitoring of standard operating procedures relating to the use of these systems;
- shall ensure that the design of these systems allows for data to be amended such that the amendments are documented and that any item of data input cannot be deleted (i.e. maintaining data and amendment audit trail) ;
- shall implement and ensure the monitoring of a secure system that prevents any unauthorized data access;
- shall update the list of persons authorized to amend the data;
- shall keep appropriate back-up copies of the data;
- shall maintain blind status, where applicable (e.g. during data entry and processing);
- shall ensure that personal data used within the scope of the trial is processed in accordance with the conditions defined by law No. 78-17 dated 6 January 1978 relating to data processing, files and liberties modified by law No. 2004-801 of 6 August 2004 and regulatory texts applicable to its application.

If the data is converted during processing, it must always be possible to compare the original data and observations with the data after conversion.

The system used to identify subjects taking part in the trial must not present with any ambiguity and must allow all of the data collected for each of these subjects to be identified whilst maintaining the confidentiality of the personal data, in accordance with law No. 78-17, duly amended.

16 CONFIDENTIALITY AND OWNERSHIP OF DATA

All of the information communicated or obtained and the data and results generated by the trial legally belong to the Institut Bergonié, which can use this data at its own discretion. The trial cannot be the subject of any written or verbal comments without the sponsor's consent.

Any unpublished data sent to the investigator is confidential. These documents must not be disclosed to a third party without the consent of the Institut Bergonié. The submission of these documents to the EC is formally authorized. The Institut Bergonié is free to submit the trial data and results to governments and other accredited authorities.

The investigator must treat as confidential all of the information acquired or deduced during the trial and shall take the necessary steps to avoid any violation of this confidentiality, with the exception of information that must be disclosed in accordance with the legislation.

17 REGULATIONS GOVERNING PUBLICATION

17.1 Final report

The biostatistician(s) will compile a final report. It will include tables giving the raw data and the statistical report on the data. This report will be submitted to the Steering Committee and Senior Investigators for approval and signature. A report of the overall results of the study will be issued

so that the investigator can send it to patients who wish to know these results.

17.2 Publications

All of the information arising from this study shall be considered confidential at least until the appropriate analysis and subsequent check have been completed by the trial sponsor, co-ordinating investigator and statistician.

All forms of publication must be submitted to the Steering Committee for review and approval prior to publication (allowing at least 15 working days for abstracts and oral presentations, and 45 working days for written publications). The Steering Committee shall check the accuracy of the information submitted (in order to avoid any inconsistency with that submitted to the Health Authorities), and ensure that confidential information is not inadvertently disclosed. It will also provide additional information as required.

Furthermore, all memos, manuscripts or presentations must comprise a heading referring without fail to the Institut Bergonié, all of the institutions, investigations, co-operating groups and learned societies that have contributed to the implementation of the trial, and listing any organizations that have provided financial support.

For the principal publication, either in French or English, the authors are:

- the study coordinator (first or last if an insufficient number of patients is recruited)
- the investigators will be listed on a pro rata basis according to the number of patients recruited, regardless of the co-operating group. Each investigator site shall allocate a member of staff who will act as author for official presentations/publications.
- a representative of each co-operating group not listed amongst the study centers having the largest patient cohorts
- a representative of the trial statistics unit (in the first 3 positions according to degree of involvement in the preparation of publications)

As required for multicenter studies, the first publication will present the data collected in all of the participating centers after the information has been analyzed in accordance with the protocol by a biostatistician, and not by the investigators.

Similarly, publications of additional results (laboratory study) shall include the name of the person who carried out the additional work as well as the names of all the other persons involved in this additional work.

Correspondents in the recruitment centers with lower patient cohorts not cited in the main publication should ideally be included in subsequent publications.

Unless granted special authorization by the Steering Committee, the investigators cannot publish the results collected in only one or two centers before the first official version, containing all of the data, is published.

REFERENCES

[1] Bale, A.E. (2002). Hedgehog signaling and human disease. *Annu Rev Genomics Hum Genet.* 3:47-65.

[2] Berman, D.M., S.S. Karhadkar, A. Maitra, *et al.* (2003). Widespread requirement for hedgehog ligand stimulation in growth of digestive tract tumours. *Nature.* 425:846-851.

[3] Bitgood, M.J., L. Shen, and A.P. McMahon. (1996). Sertoli cell signaling by Desert hedgehog regulates the male germline. *Curr Biol.* 6(3):298-304.

[4] Chari, N.S., and T.J. McDonnell. (2007). The sonic hedgehog signaling network in development and neoplasia. *Adv Anat Pathol.* 14(5):344-352.

[5] Evangelista, M., H. Tian, and F.J. de Sauvage. (2006). The hedgehog signaling pathway in cancer. *Clin Cancer Res.* 12(20):5924-5928.

[6] Dickey ID, Rose PS, Fuchs B, Wold LE, Okuno SH, Sim FH, Scully SP. (2004) Dedifferentiated chondrosarcoma: the role of chemotherapy with updated outcomes. *J Bone Joint Surg Am*. 86-A(11):2412-8.

[7] Evans HL, Ayala AG, Romsdahl MM. (1977) Prognostic factors in chondrosarcoma of bone: A clinicopathologic analysis with emphasis on histologic grading. *Cancer* 40:818–831

[8] Fletcher CDM, Unni KK, Mertens F, eds. (2002) World Health Organization Classification of Tumours. Pathology and Genetics. Tumours of Soft Tissue and Bone. Cartilage tumours. Lyon, France: IARC Press, 234-257.

[9] Gelderblom H, Hogendoorn PC, Dijkstra SD, van Rijswijk CS, Krol AD, Taminiau AH, Bovée JV. (2008) The clinical approach towards chondrosarcoma. *Oncologist.* 13:320-9.

[10] Giuffrida AY, Burgueno JE, Koniaris LG, Gutierrez JC, Duncan R, Scully SP. Chondrosarcoma in the United States (1973 to 2003): an analysis of 2890 cases from the SEER database. (2009) *J Bone Joint Surg Am.* 91:1063-72.

[11] Ingham, P.W., and A.P. McMahon. (2001). Hedgehog signaling in animal development: paradigms and principles. *Gene Dev.* 15:3059-3087.

[12] Investigator's Brochure GDC-0449. (July 2009). Genetech, Inc., South San Francisco, California.

[13] Karhadkar, S.S., G.S. Bova, N. Abdallah, *et al.* (2004). Hedgehog signaling in prostate regeneration, neoplasia and metastasis. *Nature.* 431:707-712.

[14] Kim KH, Kim JM, Choi YL, Shin YK, Lee HC, Seong IO, Kim BK, Chae SW, Chung YS, Kim SH. Expression of sonic hedgehog signaling molecules in normal, hyperplastic and carcinomatous endometrium. (2009) Pathol Int. 59:279-87.

[15] Kriangkrai, R., S. Iseki, K. Eto, *et al.* (2006). Dual odontogenic origins develop at the early stage of rat maxillary incisor development. *Anat Embryol*. 211:101-108.

[16] Kroft, T.L., J. Patterson, J.W.Yoon, *et al.* (2001). GLI1 localization in the germinal epithelial cells alternates between cytoplasm and nucleus: upregulation in transgenic mice blocks spermatogenesis in pachytene. *Biol Reprod.* 65:1663-1671.

[17] Lupi, O. (2007). Correlations between the sonic hedgehog pathway and basal cell carcinoma. *Inter J Dermatol.* 46:1113-1117.

[18] Mercuri M, Picci P, Campanacci L, Rulli E. (1995) Dedifferentiated chondrosarcoma. *Skeletal Radiol* 24:409-416.

[19] Nakashima Y, Unni KK, Shives TC, Swee RG, Dahlin DC. (1986) Mesenchymal chondrosarcoma of bone and soft tissue: a review of 111 cases. *Cancer* 57:2444-2453

[20] Nakatomi, M., I. Morita, K. Eto, *et al.* (2006). Sonic hedgehog signaling is important in tooth root development. *J Dent Res.* 85(5):427-431.

[21] Oro, A.E., and K. Higgins. (2003). Hair cycle regulation of hedgehog signal reception. *Dev Biol.* 255: 238-248.

[22] Ries LAG, Young JL, Keel GE, Eisner MP, Lin YD, Horner M-J (editors). (2007) SEER Survival Monograph: Cancer Survival Among Adults: U.S. SEER Program, 1988-2001, Patient and Tumor Characteristics. National Cancer Institute, SEER Program, NIH Pub. No. 07-6215, Bethesda, MD,

[23] Romer, J., and T. Curran. (2005). Targeting medulloblastoma: small-molecule inhibitors of the sonic hedgehog pathway as potential cancer therapeutics. *Cancer Res.* 65:4975-4978.

[24] Rubin, L.L., and F.J. de Sauvage. (2006). Targeting the hedgehog pathway in cancer. *Nat Rev Drug Discov.* 5:1026-1033.

[25] Rudin CM, Hann CL, Laterra J, Yauch RL, Callahan CA, Fu L, Holcomb T, Stinson J, Gould SE, Coleman B, LoRusso PM, Von Hoff DD, de Sauvage FJ, Low JA. (2009) Treatment of medulloblastoma with hedgehog pathway inhibitor GDC-0449. *N Engl J Med.* 361:1173-8.

[26] Steg A, Vickers SM, Eloubeidi M, Wang W, Eltoum IA, Grizzle WE, Saif MW, Lobuglio AF, Frost AR, Johnson MR. Hedgehog pathway expression in heterogeneous pancreatic adenocarcinoma: implications for the molecular analysis of clinically available biopsies. (2007) Diagn Mol Pathol. 16:229-37.

[27] Thayer, S.P., M.P. di Magliano, P.W. Heiser, *et al.* (2003). Hedgehog is an early and late mediator of pancreatic cancer tumorigenesis. *Nature.* 425: 851-856.

[28] Tiet TD, Hopyan S, Nadesan P, Gokgoz N, Poon R, Lin AC, Yan T, Andrulis IL, Alman BA, Wunder JS. Constitutive hedgehog signaling in chondrosarcoma up-regulates tumor cell proliferation. (2006) *Am J Pathol.* 168:321-30.

[29] Unni KK, Dahlin DC, Beabout JW, Sim FH. (1976) Chondrosarcoma: clear-cell variant—a report of sixteen cases. *J Bone Joint Surg Am*. 58:676-683.

[30] Von Hoff DD, LoRusso PM, Rudin CM, Reddy JC, Yauch RL, Tibes R, Weiss GJ, Borad MJ, Hann CL, Brahmer JR, Mackey HM, Lum BL, Darbonne WC, Marsters JC Jr, de Sauvage FJ, Low JA (2009). Inhibition of the hedgehog pathway in advanced basal-cell carcinoma. *N Engl J Med.* 361:1164-72.

[31] Watkins, D.N., D.M. Berman, S.G. Burkholder, *et al.* (2003). Hedgehog signaling within airway epithelial progenitors and in small-cell lung cancer. *Nature*. 422:313-317.

[32] Wunder JS, Nielsen TO, Maki RG, O'Sullivan B, Alman BA. (2007) Opportunities for improving the therapeutic ratio for patients with sarcoma. *Lancet Oncol* 8:513-24.

APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B

CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the

Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
  - Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

APPENDIX C

Definition of Women of Childbearing Potential and Acceptable and Unacceptable Forms of Contraception

Women of childbearing potential are defined as follows:

- Patients with regular menses
- Patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding
- Women who have had a tubal ligation

Women are considered not to be of childbearing potential for the following reasons:

- The patient has undergone hysterectomy and/or bilateral oophorectomy.
- The patient is post-menopausal defined by amenorrhea for at least 1 year in a woman >45 years old.

Women of childbearing potential are required to use two forms of acceptable contraception, including one barrier method, during their participation in the study and for 12 months following discontinuation of GDC-0449.

The following are acceptable forms of barrier contraception:

- Latex condom (always used with spermicide)
- Diaphragm (always used with spermicide)
- Cervical cap (always used with spermicide)

The following are acceptable forms of secondary contraception, when used with a barrier method:

- Tubal ligation
- Partner's vasectomy
- Hormonal contraception including birth control pills, patches, rings, or injections*, with the exception of the progesterone-only "minipill"*
- Intrauterine device (non–progesterone T)
- Vaginal sponge (containing spermicide)

In addition, 100% commitment to abstinence is considered an acceptable form of contraception.

The following are **unacceptable** forms of contraception for women of childbearing potential:

- IUD progesterone T
- *Progesterone-only "minipill"*
- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

APPENDIX D

POSSIBLE PRENATAL EXPOSURE TO TERATOGEN REPORT

Attach to CTEP-AERS 5-day report

Possible Prenatal Exposure to Teratogen Report
AdEERS Ticket Number:_____

Study #:
SAE FAX NO: (301) 230-0159
Alternate FAX NO: (301) 897-7404

Initial Report Date: ___ - ___ - ___ (DD - MMM - YY)

Follow-up Report Date: ___ - ___ - ___ (DD - MMM - YY)

Principal Investigator:

Reporter:

Reporter Telephone #:

Reporter FAX #:

Investigator Number | Subject Number

Complete all of the investigator and subject number boxes provided. Use leading zeros, when necessary, to complete all expected boxes.

Example: Investigator #407 would be filled in as: 0 0 4 0 7

Subject Initials

Record the first letter of the subject's first, middle and last name, in that sequence. If the subject has no middle name, enter a dash.

Example: A - C

Subject's Sex: ☐ Female ☐ Male

Subject's Weight: _____ kg

Subject's Date of Birth: ___ - ___ - ___ (DD - MMM - YYYY)

Subject's Ethnicity (check one only): ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Not Available

Subject's Race (check all that apply): ☐ American Indian or Alaska Native ☐ Asian ☐ Black or African American ☐ Native Hawaiian or Other Pacific Islander ☐ White ☐ Not Available

Study Drug: **GDC-0449**

Study Drug Start Date: ___ - ___ - ___ (DD - MMM - YY)

Study Drug Stop Date: ___ - ___ - ___ (DD - MMM - YY) **OR** ☐ Study Drug Continuing

Dose:

Route: **ORAL**

Frequency: **QD**

Kit #:

First Day of Last Menstrual Period: ___ - ___ - ___ (DD - MMM - YY)

Estimated Date of Delivery: ___ - ___ - ___ (DD - MMM - YY)

Method of Contraception (check all that apply):
☐ Oral Contraceptive Pills ☐ Condoms ☐ Periodic Abstinence ☐ Progestin Injection or Implants ☐ Spermacide
☐ Diaphragm ☐ Intrauterine Device (IUD) ☐ Tubal Ligation ☐ Other, specify:_____

Reproductive History: ☐ Gravida _____ ☐ Para _____

Tests performed during pregnancy: ☐ None ☐ Unknown
☐ CVS Results: ☐ Normal ☐ Abnormal
☐ Amniocentesis Results: ☐ Normal ☐ Abnormal
☐ Ultrasound Results: ☐ Normal ☐ Abnormal

Pregnancy Outcome
Was pregnancy interrupted? ☐ Yes ☐ No
If yes, specify: ☐ Elective Termination ☐ Spontaneous Abortion ☐ Ectopic
Date of Termination: ___ - ___ - ___ (DD - MMM - YY)
If pregnancy was **not** terminated, specify pregnancy outcome (and provide infant outcome information)
☐ Vaginal Birth: ☐ Premature ☐ Term **OR** ☐ C-Section: ☐ Scheduled ☐ Emergency Date of Delivery: ___ - ___ - ___ (DD - MMM - YY)
Infant outcome information: ☐ Normal ☐ Abnormal

Additional Case Details (if needed):

Note: Report possible teratogen exposure to AdEERS within 24 hours. See Protocol Section 11.3.1 for instructions. Attach this form to the complete 5-day AdEERS report.

7.3.5

APPENDIX E

CTEP-assigned Protocol #_____

Local Protocol # _____

PATIENT'S MEDICATION DIARY

Today's date _____ **Agent: GDC-0449**

Patient Name_____(*initials acceptable)* **Patient Study ID**

_____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle of treatment.
2. You will take **GDC-0449** capsules once daily. You should take the capsules at approximately the same time each day.
   Dose: take one 150 mg capsule.
3. Record the date, the number of capsules of each size of capsule that you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring this form and your bottles of **GDC-0449** capsules when you return for each appointment.

Day	Date	Time of dose	# of capsules taken	Comments
			150 mg	
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

Patient's signature

Physician's Office will complete this section:

1. Date patient started protocol treatment _____
2. Date patient was removed from study _____
3. Patient's planned total daily dose _____
4. Total number of capsules taken this month _____
5. Physician/Nurse/Data Manager's Signature _____

APPENDIX F
REGISTRATION FORM

INSTITUT BERGONIE Center Régional de Lutte Contre le Cancer de Bordeaux et du Sud-Ouest 229, cours de l'Argonne 33076 Bordeaux Cedex	**IHC study (Inhibition of Hedgehog in Chondrosarcomas)**

INCLUSION REQUEST FORM

Investigational site	
N° Center : |__|__|	**Investigator:**
Tel: |__|__|.|__|__|.|__|__|.|__|__|.|__|__|	Fax: |__|__|.|__|__|.|__|__|.|__|__|.|__|__|

Patient		
Patient's initial: |__|__| |__|__| Name First Name	Date of Birth: |__|__| |__|__||__|__|__|__|	Sex: ☐ **M** ☐ **F**
Confirmation of eligibility criteria: ☐ **Yes** ☐ **No**		
Date foreseen for protocol treatment start: |__|__| |__|__| |__|__|__|__|		
Date of signed consent patient : |__|__| |__|__| |__|__|__|__|	**To confirm inclusion, signed investigator:**	

Fax this form, copy of biological result and signed consent patient to

Clinical Trial and Epidemiology Unit / Institut Bergonié

Fax: + 33 5 56 33 33 81

From Monday to Friday : 9.00 to 17.00

Contact : Sabrina ALBERT (AEC) Tel: +33 5 56 33 78 05 – Mail: albert@bergonie.org

Patient identification in this study (coordinator center): |__\|__\|

Date of inclusion : |__\|__\| \|__\|__\| \|__\|__\|__\|__\|

APPENDIX G: TOXICITY ENDPOINTS (CTEP CTCAE Version 4.0)

TOXICITY EVALUATION CRITERIA (CTEP CTCAE Version 4.0)

You can download this document in PDF:
http://ctep.info.nih.gov/reporting/ctc.html

APPENDIX HA: REPORTING OF AN EXPECTED SERIOUS ADVERSE EVENT (E - SAE)

Notification Of A Serious Adverse Event Form
To be faxed to Pharmacovigilance BECT – 01 44 23 55 70

PROTOCOL: CHONDROG	EUDRACT: 2010-019817-20		COUNTRY: FRANCE
SPONSOR : INSTITUT BERGONIÉ	INVESTIGATOR SITE :		SITE N° |__|__|
DATE OF THIS REPORT : |_|_|/|_|_|/|_|_|_|_|	INITIAL REPORT ☐	FOLLOW-UP REPORT N° |_|_|	FINAL REPORT ☐

1. PATIENT IDENTIFICATION

|INCLUSION N° |__|__| SURNAME (2 LETTERS): |__|__| 1ST NAME (2 LETTERS): |__|__| DATE OF BIRTH: |__|__|/|__|__|/|__|__|__|__|

TREATMENT ARM: |___| DOSE LEVEL (PHASE I STUDY): |_____|

SEX: F ☐ M☐ WEIGHT (KG): |_____| HEIGHT (CM): |_____| BODY SURFACE AREA (M^2): |__| . |__|__|

2. INFORMATION ON EVENT

DATE OF ONSET: |__|__|/|__|__|/|__|__|__|__| TOXICITY (GRADE NCI-CTCAE): 1☐ 2☐ 3☐ 4☐ 5☐

DIAGNOSIS *OR MAIN SYMPTOMS*: **only one diagnosis or one symptom (except for linked symptom)**

.....

.....

.....

DESCRIBE EVENT AND TREATMENT GIVEN (INCLUDING RELEVANT TEST/LAB DATA):

.....

.....

.....

3. SERIOUSNESS CRITERIA

☐ DEATH, DATE OF DEATH: . |__|__|/|__|__|/|__|__|__|__|
☐ LIFE-THREATENING
☐ REQUIRING/PROLONGING HOSPITALIZATION (> 24H):
DATE OF ADMISSION: |__|__|/|__|__|/|__|__|__|__|
☐ PERSISTANT/SIGNIFICANT DISABILITY/INCAPACITY
☐ CONGENITAL DISORDER/BIRTH DEFECT
☐ MEDICALLY RELEVANT

4. OUTCOME

☐ ON GOING EVENT
☐ RECOVERED WITHOUT SEQUELLA, ☞ DATE |__|__|/|__|__|/|__|__|__|__|
☐ RECOVERED WITH SEQUELLA, ☞ DATE |__|__|/|__|__|/|__|__|__|__|
SPECIFY SEQUELLA: .....
☐ DEATH **RELATED** TO THIS EVENT, ☞ DATE |__|__|/|__|__|/|__|__|__|__|
☐ DEATH **UNRELATED** TO THIS EVENT, ☞ DATE |__|__|/|__|__|/|__|__|__|__|
CAUSE OF DEATH: .....
OR CAUSE UNKNOWN ☐
☐ UNKNOWN OUTCOME
☐ AUTOPSY : YES ☐ NO ☐

IF PATIENT WAS HOSPITALIZED: DATE OF END OF HOSPITALIZATION: |__|__|/|__|__|/|__|__|__|__|
OR PATIENT STILL HOSPITALIZED AT THE TIME OF THIS REPORT ☐

FOR IMP TRAILS ⇨ COMPLETE **SECTION 5** FOR RADIOTHERAPY TRIALS ⇨ COMPLETE **SECTION 6** FOR OTHER IMP TRIALS ⇨ COMPLETE **SECTION 7**

5. IMP (INVESTIGATIONAL MEDICINAL PRODUCT(S), INCLUDING COMBINED RADIOTHERAPY / SURGERY…) TICK IF NA ☐

INVESTIGATIONAL PRODUCEDURE(S) INDICATE THE INTERNATIONAL COMMON DENOMINATION OF THE **IMP & OTHER COMBINED**	ROUTE	SAE CYCLE NUMBER	**DATES**		**DOSE & UNIT**			
			DATE OF FIRST ADMINISTRATION/USE (1ST DAY OF CYCLE 1)	DATE OF LAST ADMINISTRATION/USE **BEFORE** SAE	LAST DOSE ADMINISTRATED **BEFORE** SAE		CUMULATIVE DOSE SINCE THE 1ST ADMINISTRATION	
					DOSE	UNIT	DOSE	UNIT
N°1			|_|_|/|_|_|/|_|_|_|_|	|_|_|/|_|_|/|_|_|_|_|				
N°2			|_|_|/|_|_|/|_|_|_|_|	|_|_|/|_|_|/|_|_|_|_|				
N°3			|_|_|/|_|_|/|_|_|_|_|	|_|_|/|_|_|/|_|_|_|_|				
N°4			|_|_|/|_|_|/|_|_|_|_|	|_|_|/|_|_|/|_|_|_|_|				
N°5			|_|_|/|_|_|/|_|_|_|_|	|_|_|/|_|_|/|_|_|_|_|				

UNBLINDING: YES ☐ NO ☐ NA ☐

HAS ONE (OR SEVERAL) INVESTIGATIONAL PRODUCT(S) BEEN STOPPED?
☐ YES N°\|_\| N°\|_\| N°\|_\| N°\|_\| N°\|_\| ☐ NO ☐ NA
DID THE EVENT DISAPPEAR AFTER INVESTIGATIONAL PRODUCT(S) IS STOPPED?
☐ YES ☐ NO ☐ NA

HAS ONE (OR SEVERAL) INVESTIGATIONAL PRODUCT(S) BEEN REINTRODUCED?
☐ YES N°\|_\| N°\|_\| N°\|_\| N°\|_\| N°\|_\| ☐ NO ☐ NA
DID THE EVENT REAPPEAR AFTER INVESTIGATIONAL PRODUCT(S) REINTRODUCED?
☐ YES ☐ NO ☐ NA

Version 3 du 15.02.2011 Page 1 sur 3

PROTOCOL: CHONDROG	EUDRACT: 2010-019817-20		COUNTRY: FRANCE
SPONSOR : INSTITUT BERGONIÉ	INVESTIGATOR SITE :		SITE N° |__|__|
DATE OF THIS REPORT : |__|__/|__|__/|__|__|__|__|	INITIAL REPORT ☐	FOLLOW-UP REPORT N° |__|__|	FINAL REPORT ☐
INCLUSION N°: |__|__| SURNAME (2LETTERS): |__|__| 1ST NAME (2 LETTERS): |__|__| DATE OF BIRTH: |__|__/|__|__/|__|__|__|__|			

6. RADIOTHERAPY ..... TICK IF NA ☐

		DATES		DOSE (GY)	
TECHNIQUE	FIELD(S)	DATE OF FIST ADMINISTRATION	DATE OF LAST ADMINISTRATION	LAST DOSE ADMINISTERED BEFORE SAE (GY)	CUMULATIVE DOSE SINCE THE 1ST ADMINISTRATION (GY)
		|__|__/|__|__/|__|__|__|__|	|__|__/|__|__/|__|__|__|__|		
		|__|__/|__|__/|__|__|__|__|	|__|__/|__|__/|__|__|__|__|		
		|__|__/|__|__/|__|__|__|__|	|__|__/|__|__/|__|__|__|__|		
		|__|__/|__|__/|__|__|__|__|	|__|__/|__|__/|__|__|__|__|		

MACHINE (*SPECIFY IF POSSIBLE TRADE NAME / MODEL / SERIAL NUMBER*): .....
.....

HAS RADIOTHERAPY BEEN STOPPED?	HAS RADIOTHERAPY BEEN REINTRODUCED?
☐ YES ☐ NO ☐ NA	☐ YES ☐ NO ☐ NA
DID THE EVENT DISAPPEAR AFTER RADIOTHERAPY IS STOPPED?	DID THE EVENT REAPPEAR AFTER RADIOTHERAPY REINTRODUCTION?
☐ YES ☐ NO ☐ NA	☐ YES ☐ NO ☐ NA

SCENE OF EVENT: ☐ INVESTIGATOR SITE ☐ HOME ☐ HOSPITAL ☐ DAY HOSPITAL ☐ CONVALESCENT HOME
☐ OTHER: .....

7. MEDICAL DEVICE OR NON MEDICAL PRODUCT, METHOD OR ACTION ..... TICK IF NA ☐

DEVICE / NON MEDICINAL PRODUCT, METHOD OR ACTION	DATES OF USE
COMMON DENOMINATION: TRADE NAME (IF EC MARKING):	BEGINNING DATE: |__|__/|__|__/|__|__|__|__| END DATE: |__|__/|__|__/|__|__|__|__|
MODEL:	VERSION (INCLUDED SOFTWARE)
SERIAL NUMBER	AND/OR BATCH NUMBER
INDICATION OF USE FOR THE PATIENT	

HAS DEVICE OR ONE (OR SEVERAL) PRODUCT(S), METHOD(S) OR ACTION(S) BEEN STOPPED?	HAS DEVICE OR ONE (OR SEVERAL) PRODUCT(S), METHOD(S) OR ACTION(S) BEEN REINTRODUCED?
☐ YES ☐ NO ☐ NA	☐ YES ☐ NO ☐ NA
DID THE EVENT DISAPPEAR AFTER RADIOTHERAPY STOP?	DID THE EVENT REAPPEAR AFTER RADIOTHERAPY REINTRODUCTION?
☐ YES ☐ NO ☐ NA	☐ YES ☐ NO ☐ NA

SCENE OF EVENT: ☐ INVESTIGATOR SITE ☐ HOME ☐ HOSPITAL ☐ DAY HOSPITAL ☐ CONVALESCENT HOME
☐ OTHER: .....

PROTOCOL: CHONDROG	EUDRACT: 2010-019817-20		COUNTRY: FRANCE
SPONSOR : INSTITUT BERGONIÉ		INVESTIGATOR SITE :	SITE N° |__|__|
DATE OF THIS REPORT : |__|__/|__|__/|__|__|__|__|	INITIAL REPORT ☐	FOLLOW-UP REPORT N° |_|_|	FINAL REPORT ☐
INCLUSION N°: |__|__| SURNAME (2LETTERS): |__|__| 1ST NAME (2 LETTERS): |__|__| DATE OF BIRTH: |__|__/|__|__/|__|__|__|__|			

8. CONCOMITANT DRUG(S) – (*EXCLUDE THOSE TO TREAT REACTION*)

CONCOMITANT DRUG	ROUTE	DATE STARTED	DATE STOPPED	ONGOING	INDICATION
1.		FROM |__|__/|__|__/|__|__|	TO |__|__/|__|__/|__|__|	☐	
2.		FROM |__|__/|__|__/|__|__|	TO |__|__/|__|__/|__|__|	☐	
3.		FROM |__|__/|__|__/|__|__|	TO |__|__/|__|__/|__|__|	☐	
4.		FROM |__|__/|__|__/|__|__|	TO |__|__/|__|__/|__|__|	☐	

9. OTHER RELEVANT HISTORY – (*E.G DIAGNOSTICS, ALLERGIES, PREGNANCY WITH LAST MONTH OF PERIOD, ETC…*)

……

……

……

10. ASSESSMENT – IN YOUR OPINION (*INVESTIGATOR*), THIS EVENT IS RELATED TO (TICK ONLY ONE BOX):

☐ **IMP** (INVESTIGATIONAL MEDICINAL PRODUCT (S) INCLUDING COMBINED RADIOTHERAPY / SURGERY)

SPECIFY THE IMP NUMBER(S) (*SEE SECTION 5 OF THE FORM*): N° |__| N° |__| N° |__| N° |__| N° |__|

☐ **INVESTIGATIONAL RADIOTHERAPY**

☐ **INVESTIGATIONAL MEDICAL DEVICE OR NON MEDICINAL PRODUCT, METHOD OR ACTION**

IF NOT RELATED TO EITHER INVESTIGATIONAL MP / RADIOTHERAPY / SURGERY / NMP, OR MD, PLEASE SPECIFY (*TICK ONLY ONE BOX*)

☐ **PROTOCOL**

☐ **CONCOMITANT TREATMENT(S), SPECIFY:** ……

☐ **CONCOMITANT DISEASE(S), SPECIFY:** ……

☐ **OTHER, SPECIFY:** ……

11. NOTIFICATOR

NAME:
FUNCTION:
ADDRESS:
PHONE: ……FAX:……
E-MAIL: ……
DATE: \|__\|__/\|__\|__/\|__\|__\|__\|__\|
SIGNATURE ……

INVESTIGATOR

NAME:
DEPARTMENT

DATE: \|__\|__/\|__\|__/\|__\|__\|__\|__\|
SIGNATURE ……

SPONSOR ONLY (*DO NOT FULFIL THIS PART*)

SPONSOR IDENTIFICATION NUMBER:……

DATE OF RECEPT: \|__\|__/\|__\|__/\|__\|__\|__\|__\| DATE OF THIS REPORT: \|__\|__/\|__\|__/\|__\|__\|__\|__\|

ASSESMENT (*TICK ONLY ONE BOX*):

1. ☐ INVESTIGATIONAL MP (*INCLUDING COMBINED RADIOTHERAPY / SURGERY*) ↳ SPECIFY THE N°……
2. ☐ **INVESTIGATIONAL RADIOTHERAPY**
3. ☐ **INVESTIGATIONAL MEDICAL DEVICE OR NON MEDICINAL PRODUCT, METHOD OR ACTION**

↳ IS IT A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (**SUSAR**)
YES ☐ NO ☐

IF NOT RELATED TO EITHER 1, 2 OR 3, PLEASE SPECIFY (*TICK ONLY ONE BOX*):

4. ☐ **PROTOCOL**
5. ☐ **CONCOMITANT TREATMENT(S)**
6. ☐ **CONCOMITANT DISEASE(S), SPECIFY:** ……
7. ☐ **OTHER, SPECIFY:** ……

DATE \|__\|__/\|__\|__/\|__\|__\|__\|__\| **NAME** …… **SIGNATURE** ……

Version 3 du 15.02.2011 Page 3 sur 3

APPENDIX HB: REPORTING OF AN UNEXPECTED SERIOUS ADVERSE EVENT (U - SAE)

PROTOCOL: CHONDROG	EUDRACT: 2010-019817-20		COUNTRY: FRANCE
SPONSOR : INSTITUT BERGONIÉ		INVESTIGATOR SITE :	
INCLUSION N°: |_____|	SURNAME (3 LETTERS): |__|__|__|	1ST NAME (2 LETTERS): |__|__|	DATE OF BIRTH : |__|__|/|__|__|/|__|__|__|__|

6. CONCOMITANT DRUG(S) – (EXCLUDE THOSE USEDS TO TREAT REACTION)

CONCOMITANT DRUG	ROUTE	DATE STARTED	DATE STOPPED	ONGOING	INDICATION	CAUSALITY	
						YES	NO
1.		|__|__|/|__|__|/|__|__|	|__|__|/|__|__|/|__|__|				
2.		|__|__|/|__|__|/|__|__|	|__|__|/|__|__|/|__|__|				
3.		|__|__|/|__|__|/|__|__|	|__|__|/|__|__|/|__|__|				
4.		|__|__|/|__|__|/|__|__|	|__|__|/|__|__|/|__|__|				

7. OTHER RELEVANT HISTORY (E.G DIAGNOSIS, ALLERGIES, ETC...)

.....
.....
.....

8. ASSESSMENT, IN YOUR OPINION, THIS EVENT IS RELATED TO:

☐ INVESTIGATIONAL MEDICINAL PRODUCT (S), SPECIFY THE N°....

IF YES, IS IT A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) ☐ YES ☐ NO

IF NO, THIS EVENT IS RELATED TO:

☐ DISEASE PROGRESSION ☐ PROTOCOL
☐ CONCOMITANT DISEASE(S), SPECIFY: ..... ☐ CONCOMITANT TREATMENT(S): .....
☐ OTHER, SPECIFY: .....

9. NOTIFICATOR

NAME:
FUNCTION:
ADDRESS:
PHONE: FAX:
E-MAIL:

INVESTIGATOR

DATE: \|__\|__\|/\|__\|__\|/\|__\|__\|__\|__\|
NAME:
SIGNATURE:

FOR THE SPONSOR ONLY: DO NOT FULFIL THIS PART

SPONSOR IDENTIFICATION NUMBER:

DATE OF RECEPT BY THE SPONSOR: \|__\|__\|/\|__\|__\|/\|__\|__\|__\|__\| DATE OF THIS REPORT: \|__\|__\|/\|__\|__\|/\|__\|__\|__\|__\|

8. ASSESMENT:

☐ INVESTIGATIONAL MEDICINAL PRODUCT (S), SPECIFY THE N°:.....

IF YES: IS IT A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) ☐ YES ☐ NO

IF NO, THIS EVENT IS RELATED TO

☐ DISEASE PROGRESSION ☐ PROTOCOL
☐ CONCOMITANT DISEASE(S), SPECIFY: ..... ☐ CONCOMITANT TREATMENT(S): .....
☐ OTHER, SPECIFY: .....

10. SPONSOR

DATE: \|__\|__\|/\|__\|__\|/\|__\|__\|__\|__\|

NAME AND SIGNATURE:

APPENDIX IA: PATHOLOGY FORM A

PROTOCOL CHONDROG: PATHOLOGY FORM A

PATIENT N°: |__|__|	**Centre code:** |__|__|

To be handled by the entering clinician:
Please send this form to the local pathologist for every registered patient.

The protocol requires that the histopathological diagnosis is reviewed **within 10 days**, by the Professor Jean-Michel Coindre, reference pathologist of the IHC study.

You are kindly requested to submit:

- one or two representative paraffin blocks and representative H and E slides
- your pathology report with patient code and date of birth (including your macroscopic description) and second opinions if available.
- A copy of the present form (retain copy for own file)

From: (clinician) .....

(hospital address) .....

To: (original pathologist) .....

(dept. / address) .....

Patient : date of birth |__|__| |__|__| |__|__| (DD, MM, YY)

sex ☐ male ☐ female

hospital chart number .....

I certify that this information is complete and matches the accompanying media.
Name of the Person Completing this Form: _____ Date: _____

Title of Person Completing Form: _____

To: **Pathology Laboratory – Institut Bergonié**
Contact : Cécile MANNINA (TRC) – Protocol CHONDROG
229 cours de l'Argonne
33000, Bordeaux, France

All the material will be returned.
Everything requested in this form was accepted by the patient.
Thanks in advance for your co-operation.

APPENDIX IB: PATHOLOGY FORM B

INSTITUT BERGONIÉ
Aider la vie!
Centre Régional de Lutte Contre le Cancer de Bordeaux et du Sud-Ouest

PROTOCOL CHONDROG: PATHOLOGY FORM B

PATIENT N°: |__|__| **Centre code:** |__|__|

To be filled out by the entering clinician

From: (clinician) .....

(hospital address) .....

To: Pr Jean-Michel Coindre (Reference Pathologist)

Patient : Date of birth |__|__| |__|__| |__|__| (DD, MM, YY)

Sex ☐ male ☐ female

Hospital chart number .....

Tumor size |__|__|__| mm

Operation:

☐ Biopsy ☐ Curettage ☐ Segmental Resection ☐ En-Block Resection Amputation

☐ Complex Resection: Forequarter, Hindquarter, Hemipelvectomy

☐ Other, specify: _____

Anatomic Location:

Bone (Skull):	☐ Cranium	☐ Facial Bones	☐ Jaw (Gnathic Bones)	☐ Mandible	☐ Maxilla
Long Bones (Upper Limb):	☐ Scapula	☐ Humerus	☐ Radius	☐ Ulna	
Short Bones (Hand):	☐ Carpals	☐ Metacarpals	☐ Phalanges		
Long Bones (Lower Limb):	☐ Femur	☐ Tibia	☐ Fibula	☐ Patella	
Short Bones (Foot):	☐ Tarsals	☐ Metatarsals	☐ Phalanges		
Thorax:	☐ Clavicle	☐ Ribs	☐ Manubrium	☐ Sternum	
Pelvis:	☐ Ilium	☐ Ischium	☐ Pubis		
Spine (Vertebral Column):	☐ Cervical	☐ Thoracic	☐ Lumbar	☐ Sacrum	☐ Coccyx

Site: ☐ Left ☐ Right

☐ Epiphyseal ☐ Metaphyseal ☐ Diaphyseal

Metastatic Sites (if applicable):

☐ Lymph Nodes ☐ Regional ☐ Distant Lung, if other, specify

Tumor: ☐ Primary ☐ Recurrence ☐ Metastasis ☐ Unknown

Pre-treatment: ☐ Unknown ☐ No ☐ Yes, specify : _____

To: **Pathology Laboratory – Institut Bergonié**
Contact : Cécile MANNINA (TRC) – Protocol CHONDROG
229 cours de l'Argonne
33000, Bordeaux, France

All the material will be returned.
Everything requested in this form was accepted by the patient.
Thanks in advance for your co-operation.

Protocol - CHONDROG

APPENDIX IC: PATHOLOGY FORM C

PROTOCOL CHONDROG: PATHOLOGY FORM C

PATIENT N°: |__|__|	Centre code: |__|__|

Clinician, send to: Professor Jean-Michel Coindre (Reference Pathologist)

Patient : date of birth |__|__| |__|__| |__|__| (DD, MM, YY)

sex ☐ male ☐ female

Center: _____

Site of tumor/biopsy: _____

Material available : ☐ Yes ☐ No

Response Review by Pr Jean-Michel Coindre (Reference Pathologist)

Sufficient material: ☐ Yes ☐ No

Date of histological review (dd/mm/yyyy): |__|__| |__|__| |__|__|__|__|

Tumor Type (WHO classification): _____

Tumor Subtype (WHO classification) _____

Reliability of classification: ☐ low ☐ moderate ☐ high

Tumor grade: ☐ grade I ☐ grade II ☐ grade III

Reliability of grading: ☐ low ☐ moderate ☐ high

Name of the Person Completing this Form: _____

Date: _____

Title of Person Completing Form: _____

Signature: _____

Please send this form to:
To: **Pathology Laboratory – Institut Bergonié**
Contact : Cécile MANNINA (TRC) – Protocol CHONDROG
229 cours de l'Argonne
33000, Bordeaux, France

APPENDIX JA: BASELINE CLINICAL SUBJECT PROFILE

NCI PROTOCOL 8408: BASELINE CLINICAL SUBJECT PROFILE

PATIENT N°: |__|__|__|__|	Centre code: |__|__|__|

To be completed by the Investigator:
This subject is enrolled in a clinical trial that will rely on an Independent Review. To ensure benign lesions are not selected by the independent reviewers as sites of metastatic disease, identify any pre-existing (pre-baseline) radiographic findings that could mimic metastatic disease and any major alterations resulting from prior surgery or interventional procedures.

Are there any conditions that meet the above criteria which mimic metastatic disease?

☐ **YES** ☐ **NO**

If yes, please specify Anatomic Description :

.....

.....

.....

Radiation therapy history:

Has the patient received radiation therapy? ☐ No ☐ Yes If "Yes", please answer questions below:

Anatomical fields (please specify Left or Right when necessary):

(1) _____
(2) _____
(3) _____

I certify that this information is complete and matches the accompanying media.

Name of the Person Completing this Form: _____ Date: _____

Title of Person Completing Form: _____

This completed form must be sent with the fist "Radiology Referral Form" to:

Sabrina ALBERT
Responsible Clinical research Assistant
Institut Bergonié
229 cours de l'Argonne
33000 Bordeaux, France

APPENDIX JB: RADIOLOGY REFERRAL FORM

NCI PROTOCOL 8408: RADIOLOGY REFERRAL FORM

PATIENT N°: |__|__|__|__|	Centre code: |__|__|__|
Time Point designation: ☐ 6-months ☐ Week # __	
To be completed by the Investigator: This subject is enrolled in a clinical trial that will rely on an Independent Review. For consistency, the same method of assessment and the same technique should be used at baseline and during study. • Reviewing the disease status at 6-months in comparison with baseline (two imaging CDs will be sent) • Reviewing all responses (complete and partial) observed during study. • Patient' files will be anonymous Media should be accompanied by the completed form.	
Imaging Exams Performed	**Exam Date** (dd/mm/yyyy)
CT: ☐ Chest ☐ Abdomen ☐ Pelvis ☐ Other (please specify):	__ __/__ __/__ __ __ __
MRI: ☐ Chest ☐ Abdomen ☐ Pelvis ☐ Other (please specify):	__ __/__ __/__ __ __ __
I certify that this information is complete and matches the accompanying media. Name of the Person Completing this Form: _____ Date: _____ Title of Person Completing Form: _____	

All CDs and this completed form must be sent to:

Sabrina ALBERT
Responsible Clinical research Assistant
Institut Bergonié
229 cours de l'Argonne
33000 Bordeaux, France

APPENDIX JC: RESPONSE REVIEW FORM

PROTOCOL CHONDROG: RESPONSE REVIEW FORM

PATIENT N°: |__|__| - |__|__| |__|__|__|__|

Date of central review: |__|__|/|__|__|/|__|__|__|__|

Reviewer's name: _____ **Signature:** _____

	Targets evaluation (mm)	Sum RECIST (mm)	% Evaluation	Response
BASELINE ..... **Target 1:** **Target 2:** **Target 3:** **Target 4:** **Target 5:**	T1: |__|__|__| T2: |__|__|__| T3: |__|__|__| T4: |__|__|__| T5: |__|__|__|	|__|__|__|		
Non-target lesions				
6-MONTHS RESPONSE ..... **Target 1:** **Target 2:** **Target 3:** **Target 4:** **Target 5:**	T1: |__|__|__| T2: |__|__|__| T3: |__|__|__| T4: |__|__|__| T5: |__|__|__|	|__|__|__|	☐ + |__|__| ☐ -	1 = CR 2 = PR 3 = SD |__| 4 = PD 5 = NE
Non-target lesions	1 = CR |__| 2 = PD			
New lesions	1 = yes |__| 2 = no			
BEST RESPONSE (if applicable) ..... **Target 1:** **Target 2:** **Target 3:** **Target 4:** **Target 5:**	T1: |__|__|__| T2: |__|__|__| T3: |__|__|__| T4: |__|__|__| T5: |__|__|__|	|__|__|__|	☐ + |__|__| ☐ -	1 = CR 2 = PR 3 = SD |__| 4 = PD 5 = NE
Non-target lesions	1 = CR |__| 2 = PD			
New lesions	1 = yes |__| 2 = no			

Protocol CHONDROG – version 18.07.2011