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GDC-0449 in patients with advanced chondrosarcomas: a French Sarcoma Group/US and French National Cancer Institute Single-Arm Phase II Collaborative Study

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Background: Pre-clinical data have suggested a therapeutic role of Hedgehog (Hh) pathway inhibitors in chondrosarcoma.
Methods: This phase II trial included patients with progressive advanced chondrosarcoma. They received GDC-0449 150 mg/day (days 1–28, 28-day cycle). The primary end point was the 6-month clinical benefit rate (CBR) defined as the proportion of patients with non-progressive disease at 6 months. A 6-month CBR of 40% was considered as a reasonable objective to claim drug efficacy.
Results: Between February 2011 and February 2012, 45 patients were included. Twenty had received prior chemotherapy. Thirty-nine were assessable for efficacy. The 6-month CBR was 25.6% (95% confidence interval 13.0–42.1). All stable patients had grade 1 or 2 conventional chondrosarcoma with documented progression within the 6 months before inclusion. All but one with available data also had overexpression of the Hh ligand. Median progression-free and overall survivals were 3.5 and 12.4 months, respectively. The most frequent adverse events were grade 1 or 2 myalgia, dysgeusia and alopecia.
Conclusions: GDC-0449 did not meet the primary end point of this trial. Results suggest some activity in a subset of patients with progressive grade 1 or 2 conventional chondrosarcoma. Further studies assessing its role in combination with chemotherapy are warranted.
ClinicalTrials.gov Identifier: NCT01267955.
Key words: chondrosarcoma, Hedgehog pathway, treatment, GDC-0449

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introduction

Conventional cytotoxic agents and radiotherapy are generally not effective in chondrosarcoma patients with metastatic or locally unresectable disease [1].

Chondrosarcomas exhibit strong activation of Hedgehog (Hh) signalling [2], which plays a crucial role in cartilage tumorigenesis by maintaining tumour cells in a proliferative state. *In vitro* experiments have shown that treatment of chondrosarcoma cells with recombinant Hh increased proliferation [3]. Moreover, pre-clinical data from human chondrosarcomas explant and xenograft studies show that Hh blockade strongly reduces cell proliferation tumour size and tumour cellularity [3, 4]. GDC-0449 is a small-molecule antagonist of the Hh signal pathway [5]. Specifically, GDC-0449 binds to and inhibits SMO, blocking Hh signal transduction.

Based on the spectrum of target inhibition by GDC-0449, promising pre-clinical data and the clear unmet need for patients with advanced chondrosarcomas, the French Sarcoma Group proposed to the French and American National Cancer Institutes a multicentre phase II trial of GDC-0449 in patients with advanced chondrosarcomas.

patients and methods

patients

Patients had to be aged 18 years or older and had to have histologically confirmed metastatic and/or unresectable bone chondrosarcoma (conventional, mesenchymal, dedifferentiated or clear cell subtypes), with documented disease progression (as per RECIST 1.1) [6]. Detailed eligibility criteria are described in supplementary material, available at *Annals of Oncology* online.

study design and treatment

This was a single-arm, phase II, multicentre clinical trial based on a two-stage Simon's design and conducted in accordance with the Declaration of Helsinki and Good Clinical Practices. All patients provided written informed consent before enrolment in the study.

Patients received GDC-0449 150 mg orally, once daily, on days 1 to 28 of a planned 28-day cycle. Patients discontinued GDC-0449 dosing if one of the following occurred: patient decision to withdraw, unacceptable toxicity, disease progression as per RECIST, intercurrent illness or general or specific changes in the patient's condition preventing further treatment in the judgement of the investigator. Patients with grade ≥3 toxicity had treatment withheld until recovery grade ≤1. A maximum delay of 4 weeks was allowed for recovery from toxicity. If toxicities have not recovered 4 weeks after the last study dose, the patient discontinued treatment.

response assessment and toxicity

Tumour assessment was carried out every 8 weeks. Response was determined per RECIST 1.1 [6] after blinded central imaging review. Toxicities were assessed continuously per Common Terminology Criteria for Adverse Events 4.0.

correlative studies

Molecular analyses were carried out for consenting patients. Archival tumour tissue was analysed for mutations of the *SMO* and *PTCH* genes and expression of the *HH*, *GLI2*, *GLI3*, *SMO* genes. Protocols as well as primer/probes are available on request.

statistical analysis

The primary end point was the 6-month clinical benefit rate (CBR) defined as the proportion of patients with a confirmed objective response (complete or partial) or stable disease (SD) (per RECIST 1.1) at 6 months. At the time of protocol writing, the data from the literature about survival of patients with advanced chondrosarcomas were almost non-existent [7–8]. Therefore, we believed that a 6-month CBR of 40% was a reasonable objective in this setting.

A two-stage Simon's design [9] with 37 eligible patients (first step: 17 patients) was used to distinguish a favourable true CBR of 40% from a null rate of 20% with 90% power and 10% type I error. Following the inclusion of the first 17 assessable patients, if 3 or less patients were progression-free (complete response, partial response or SD) at 6 months, the study would be terminated early. Otherwise, the second group of 20 subjects will be recruited. If at the end of recruitment, 11 patients or more were progression-free (out of the first 37 assessable patients), GDC-0449 would be considered worthy of further testing in this disease.

To be assessable for the first efficacy end point, a subject had to meet the eligibility criteria, received at least one complete or two incomplete cycles of GDC-0449 and underwent at least one disease measurement recorded not less than 8 weeks after treatment onset. In order to account for not assessable patients (±20%), 45 recruitments were planned.

Secondary end points included the best overall response as per RECIST 1.1, 1-year progression-free survival (PFS), 1-year overall survival (OS), safety and correlations with molecular characteristics of tumours. PFS was defined as the duration of time from the start of treatment to the time of progression or death (from any cause); patients alive and progression-free were censored at the date of the last follow-up, death or last patient contact. OS was defined as the duration of time from the start of treatment to the time of death, or last patient contact. All enrolled patients who received at least one dose of GDC-0449 were eligible for safety analyses.

Growth modulation index has been recently reported as a potential predictor of a drug's benefit in the field of sarcomas [10, 11]. GMI is defined for each patient as the ratio of its PFS on the current line of treatment to its PFS on a previous line of therapy [12, 13]. Therefore, we carried out for each patient previously treated with systemic chemotherapy an exploratory analysis by investigating the GMI defined for individual patients as the ratio of their PFS on GDC-0449 to their PFS on first-line therapy.

Descriptive statistics were used to characterize patients at study entry. Ninety-five percent two-sided exact binomial confidence intervals (CI) were computed for CBR. PFS and OS were estimated using the Kaplan–Meier method. The data reported here represent the study database as of 17 October 2012 and were submitted to an independent data monitoring committee for review. All analyses were conducted with SAS 9.2 (SAS Institute, Cary, NC).

results

patient enrolment

Between 8 February 2011 and 29 February 2012, 45 patients were enrolled across six centres. One patient did not meet eligibility criteria (no documented progressive disease at inclusion). Thirty-nine patients were assessable for the first efficacy end point (supplementary Figure S1, available at *Annals of Oncology* online) and 45 for safety. Baseline patient characteristics are listed in Table 1. The majority of patients had

conventional chondrosarcoma (central in all the cases, *n* = 39, 86.7%) and metastatic disease (*n* = 32, 71.1%). Among the patients with conventional chondrosarcoma, 12 had grade 1, 21 had grade 2 and 5 had grade 3 disease (unknown in one case). The most frequent metastatic site was lung (*n* = 28, 62.2%). Twenty patients (44%) had received prior lines of chemotherapy.

patient disposition

After a median follow-up of 13.9 months, eight patients were still on treatment. Thirty-seven patients discontinued GDC-0449. Discontinuation was related to disease progression in 34 cases (not confirmed after central review for 2 patients), toxicity for 1 patient, investigator decision for 1 patient and to adverse event for 1.

safety

Forty-five patients were included in the safety analysis. At the time of analysis, 237 cycles of GDC-0449 had been administered, with a median of 4 cycles administered per patient (range 0–19). The most commonly observed toxicities of any grade were dysgeusia, fatigue, myalgia and alopecia, occurring in 29 (64.4%), 22 (48.9%), 22 (48.9%) and 18 (40%) patients, respectively. All these events but one were grade 1 or 2 (supplementary Table S1, available at *Annals of Oncology* online). Grade 3 or 4 toxicities were rare. Two patients had reversible grade 3–4 ALT or AST increase. One patient (2.2%) stopped treatment because of grade 3 abdominal pain.

Table 1. Patient characteristics (*n* = 45)

	n (%)
Gender	
Male	31 (68.9)
Female	14 (31.1)
Age	
Median in years (range)	58.0 (27.0–85.0)
ECOG performance status	
0	20 (44.4)
1	20 (44.4)
2	5 (11.1)
Histological subtype	
Conventional chondrosarcoma	39 (86.7)
Dedifferentiated chondrosarcoma	5 (11.1)
Clear cell chondrosarcoma	1 (2.2)
Mesenchymal chondrosarcoma	0 (0.0)
Stage	
Locally advanced	13 (28.9)
Metastatic	32 (71.1)
Prior lines of chemotherapy	
0	25 (55.6)
1	12 (26.7)
2	3 (6.7)
>2	5 (11.1)

efficacy

Out of the first 17 patients assessable for efficacy analysis, 4 were progression-free, indicating that the first stage of the Simon's design was satisfied. Thirty-nine patients were assessable for final efficacy analysis. The median follow-up was 13.9 months (95% CI 10.1–15.5). Twenty-nine patients (74.4%) had progressive disease. No objective responses were observed. SD ≥ 6 months was documented in 10 patients. The CBR was 25.6% (95% CI 13.0–42.1). All patients with SD ≥ 6 months had grade 1 (*n* = 6) or 2 (*n* = 4) conventional chondrosarcoma with documented disease progression within the 6 months before inclusion in the study. We did not find any difference in terms of gender, performance status, number of metastatic sites or number of prior lines of chemotherapy between patients with SD ≥ 6 months and others. The median rates of progression according to RECIST were +43% (range −12%; +150%) for patients who did not achieve the primary outcome of SD 6 months and 0% (range −20%; +19%) for patients who did. Median PFS was 3.5 months (95% CI 1.8–3.9 months) (supplementary Figure S2, available at *Annals of Oncology* online). The 6-month and 1-year PFS rates were 28.2% (95% CI 15.3–42.6) and 19.2% (95% CI 8.3–33.5), respectively. There were 18 deaths, all secondary to disease progression. The median OS was 12.4 months (95% CI 8.4–). The 6-month and 1-year OS rates were 78.5% (95% CI 61.6–88.6) and 52.0% (95% CI 33.3–67.8), respectively (supplementary Figure S2, available at *Annals of Oncology* online).

For patients previously treated with systemic chemotherapy, we carried out an exploratory analysis by investigating the GMI defined for individual patients as the ratio of their PFS on GDC-0449 to their PFS on first-line therapy. The mean GMI was 1.7 (range 0.1–9.9). Nine patients (45%) had a GMI > 1. Six of them (30%) had a GMI ≥ 1.3.

correlative molecular analyses

The mutational status of the *SMO* and *PTCH* genes were available for 28 and 26 patients, respectively. No mutations were identified. Expression data were available for 20 patients. Overexpression of the Hh ligand was observed in 13 cases (65%). All of them but two were grade 1 or 2 conventional chondrosarcoma. Hh overexpression was observed for all patients with SD ≥ 6 months for whom data were available (*n* = 4, 100%) but for only 9 out of 16 patients with progressive disease (*n* = 16, 56%).

discussion

The primary end point requiring a CBR ≥ 40% to suggest that GDC-0449 was active in chondrosarcomas was not met. At the time of protocol writing, the lack of retrospective or prospective data made it difficult to estimate tumour progression rates. For this reason, we designed an arbitrary statistical hypothesis, through an exploratory, proof-of-concept prospective study intended to assess the relevance of the Hh pathway as a therapeutic target. We decided not to limit the main end point to objective response for two main reasons. First, objective response may not be an appropriate surrogate marker for therapeutic activity in chondrosarcomas. Indeed, owing to the

abundant cartilage matrix characterizing chondrosarcomas, substantial antitumour activity may not result in a marked decrease in the overall tumour volume. Moreover, agents that modulate tumour environments and/or specific cellular targets such as SMO inhibitors are often cytostatic and are, therefore, not expected to result in decreased tumour volume.

Although the arbitrary first end point of this study was not met, our results suggest that GDC-0449 is associated with clinical activity in a subset of patients with advanced chondrosarcomas. This is reinforced by the fact that all patients with disease stability at 6 months had shown confirmed progressive disease within the 6 months before inclusion in the study.

Forty-five percent of patients included in this study were previously treated with chemotherapy. Pre-clinical and clinical data regarding the sensitivity of chondrosarcoma to cytotoxic agents are scarce. A recent study has shown that although some chondrosarcoma cell lines may display moderate sensitivity to doxorubicin, resistance to cisplatin was the rule [14]. In 2012, in a large retrospective and multicentre series, our research group showed that chemotherapy was associated with a median PFS of 4.7 months in the first-line setting for 170 patients with advanced chondrosarcomas [15]. The majority of them were treated with an antracycline-containing regimen. Picci et al. [16] have also analysed the clinical outcome of 171 patients with inoperable or metastatic central chondrosarcoma. The median OS was only 11 months, confirming that conventional chondrosarcoma is not an indolent disease. Survival was also significantly higher in patients managed with chemotherapy than in patients managed with best supportive care only (OS at 3 years: 26% versus 8%, $P < 0.05$). The median PFS observed in the present study (including pre-treated patients) suggests that GDC-0449 may compare favourably with chemotherapy in the context of advanced chondrosarcomas. In order to further investigate this hypothesis, we carried out an exploratory analysis of the GMI which has been recently assessed in the field of sarcomas for the prediction of the potential therapeutic benefit of a new agent [10, 11]. Von Hoff [12] suggested that an anticancer agent should be considered effective if the GMI is >1.3. To be more conservative, we analysed the ratio of the PFS on GDC-0449 to the PFS on the first-line of therapy. The mean GMI was 1.7 (range 0.1–9.9). Nine patients had a GMI of >1. Six of them had a GMI of >1.3. Altogether, these data suggested that GDC-0449 can effectively control disease in a subset of patients with chondrosarcomas.

Even if the activity of GDC-0449 in advanced chondrosarcomas appears as modest, our study gives some insights about who is more likely to benefit from this drug. Indeed, all patients with SD at 6 months had a conventional chondrosarcoma of grade 1 or 2. We have also observed that all patients with SD at 6 months had overexpression of the Hh ligand, whereas an overexpression was observed in only approximately half of the patients with progressive disease. However, this latter result should be interpreted with caution due to the proportion of missing data for molecular analyses. Moreover, all patients but two with overexpression of the Hh ligand had grade 1 or 2 disease. Therefore, we cannot exclude that high expression of the Hh ligand was simply related to the disease's indolence as reported by Tiet et al. [3], who showed a lower level of expression of Hh ligand in high-grade chondrosarcomas. We did not identify any mutations of the *PTCH* or *SMO* genes, confirming that the activation of the Hh signalling pathway is more likely related to an autocrine mechanism as previously suggested by other studies [3], and not to gene mutations as observed in other tumour types such as medulloblastoma or basal cell carcinoma [17, 18].

The explanations for the modest GDC-0449-associated treatment effect in this study are unclear. The simplest explanation is that the autocrine or paracrine (ligand-driven) model of Hh pathway activity may be less meaningful for the treatment of cancer patients than the Hh activation resulting from loss-of-function (*PTCH*) or gain-of-function mutations (*SMO*).

GDC-0449 was generally well-tolerated in this phase II study. The most frequently reported adverse events were drug class effects including myalgia, dysgeusia and alopecia [5, 19]. Although the majority of these toxicities were grade 1 or 2, they may impact quality of life, particularly in the context of prolonged treatment. This aspect should be considered in future studies comparing Hh inhibitors with another therapy in cancer patients.

The Hh signalling pathway is involved in resistance to chemotherapy. Recent pre-clinical data have suggested that downregulation of this pathway may reverse resistance to doxorubicin in a breast cancer model as a result of the subsequent downregulation of the P-glycoprotein [20]. This protein is widely expressed in chondrosarcoma tumours and this overexpression has been considered as a crucial mechanism in the development of chemoresistance [21]. Such data open perspectives for the exploration in a randomized setting of a cytotoxic drug such as doxorubicin plus GDC-0449 (versus doxorubicine alone) for patients with advanced chondrosarcomas. Based on the present results, this potential future trial should include preferentially patients with progressive grade 1 or 2 conventional chondrosarcoma.

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disclosure

The authors have declared no conflicts of interest.

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