of antiepileptic drugs. Exposure to the novel agent is probably too short because patients often progress within 2 months, thus not really allowing the new drug to show efficacy. In the REGOMA trial, more than half of patients in both the regorafenib group and the lomustine group had tumour progression after the first tumour assessment after 8 weeks of therapy.

The investigators are to be congratulated for choosing a randomised screening design for this study rather than adding to the many uncontrolled phase 2 trials.[3] This design has been proposed to identify potentially active new combinations or novel treatments to be taken forward into a phase 3 trial. Nevertheless, there are limitations of such a design. To reduce the number of patients required, a false-positive and a false-negative rate of 20% are to be accepted. Furthermore, the stipulated hazard ratio of less than 0·58 is also quite ambitious. Seamless phase 2–3 designs with a landmark analysis for the phase 2 portion of the trial, and, if promising, an immediate subsequent transformation into a full phase 3 comparative trial might be another option. The screening design might also be appropriate to evaluate more than one novel compound or combination against a common control group.

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I have been the principal investigator to several clinical trials in glioblastoma. I have served on advisory boards to AbbVie, Boehringer Ingelheim, Celgene, Novartis, EMD Merck, and Roche. I have received travel assistance from Novocure.

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Metastatic osteosarcoma challenged by regorafenib


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Published **Online** November 23, 2018 http://dx.doi.org/10.1016/S1470-2045(18)30821-0

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Osteosarcomas belong to a large family of tumour entities of mesenchymal origin which exhibit heterogeneous histological, genetic, and molecular features. Their pathogenesis can be explained by initial *TP53* or *RB1* somatic alterations, or both, leading to chromosomal instability, followed by secondary oncogenic events and the development of a polyclonal disease associated with the metastatic process. This genetic complexity has been illustrated by a recent series of patients in which investigators have identified a substantial number of point mutations and deletions in an impressive number of genes.[1] It has also stimulated the development of numerous therapeutic strategies targeting tumour cells and their microenvironment.[2] The fact that osteosarcomas are both rare forms of cancer and highly heterogeneous explains why patient survival has not improved in the past four decades, especially for metastatic and unresectable osteosarcomas. Regardless of whether or not the drugs used in the first line of chemotherapy (in neoadjuvant and/or adjuvant chemotherapy for 6–12 months) have been standardised (relatively speaking) and include doxorubicin, cisplatin, methotrexate, and ifosfamide, no consensus has been reached on either the optimum combination or the therapeutic options for patients with recurrent metastatic disease.[3]

Protein kinases are part of a large family of key enzymes that catalyse the transfer of a phosphate group from ATP to a hydroxyl group of serine or threonine. More than 50 protein kinases are receptors

(receptor tyrosine kinases [RTKs]) and these kinases are classified into six classes of protein, depending on their biochemical structure.[4] All RTKs are characterised by a single transmembrane domain and a glycosylated *N*-terminal extracellular domain involved in both the dimerisation mechanism of the receptors and in the ligand recognition that triggers downstream signalling pathways, including MAPK, PI3K, Src, PLCγ, and JAK–STAT. On the basis of their diversity, their wide-ranging expression in normal cells and cancer cells, and the signalling cascades that they trigger, RTKs are strongly implicated in several pathways of cancer development. As a result, many RTK inhibitors have been developed by pharmaceutical companies. Imatinib mesylate was the first such agent to demonstrate spectacular clinical benefits in terms of overall survival outcomes in patients with chronic myeloid leukaemia and in gastrointestinal stromal tumours,[5] and it has become the standard treatment in patients with a high risk of gastrointestinal stromal tumour recurrence following tumour resection. Regorafenib belongs to the long list of multikinase inhibitors with non-specific activities targeting the VEGF receptors (VGFR1, 2, and 3), RET, Raf, PDGFR, and KIT. Interestingly, in a phase 1 clinical trial,[6] regorafenib treatment led to an objective response in one of three patients in previously treated advanced osteosarcoma.

In *The Lancet Oncology*, Florence Duffaud and colleagues[7] report the results of a non-comparative, randomised, double-blind, placebo-controlled phase 2 clinical trial of regorafenib in patients with advanced osteosarcoma. The authors recorded a progression-free survival of 16·4 weeks (95% CI 8·0–27·3) in the regorafenib group and 4·1 weeks (3·0–5·7) in the placebo group. This difference was maintained over time at 12 and 24 weeks, with 35% (95% CI 17–52) of the patients treated with regorafenib without disease progression at 24 weeks versus none of those on placebo. Although the trial was statistically non-comparative, the results highlight the potential therapeutic value of regorafenib in cases of recurrent and unresectable osteosarcoma for which there are currently very few therapeutic options and a pressing medical need.

So what should happen now? The next step will be to identify the main cellular and molecular targets in the patient population of interest. The questions are whether the therapeutic benefits of regorafenib are linked to the targeting of a single RTKs or multiple RTKs, and on which cells? Are the effects of regorafenib related to direct activity on cancer cells or on cells present in their microenvironment? Identifying the target(s) of regorafenib is essential for moving towards better stratification of the patients enrolled in future clinical trials. Additionally, approximately 30% of RTKs are overexpressed or mutated in human cancers and can be associated with drug resistance.[8,9] In this context, an adapted investigational strategy will be needed to obtain real and precise mapping of activated, mutated, and expressed tyrosine kinase proteins. Previous preclinical and clinical studies have underlined the risk of drug resistance and relapse related to protein point mutations and the establishment of molecular feedback loops after administration of RTK inhibitors, as observed in gastrointestinal stromal tumours.[10] A sequential therapeutic approach combining RTK inhibitors, chemotherapy, and targeted therapies (eg, checkpoint inhibitors) might be an alternative for preventing or limiting acquired drug resistance. Pertinent screening of patients with recurrent unresectable osteosarcoma on the basis of their RTK profiling could help to prevent the development of drug resistance, and thus define the therapeutic alternatives. By increasing the homogeneity of the population studied, this type of screening will also improve the chances of success of large phase 3 clinical trials which, as recommended by the authors, should be set up at the European and international levels.

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I declare no competing interests.

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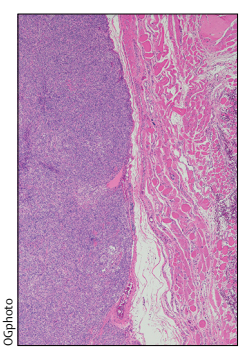
Anti-angiogenic therapy for malignant solitary fibrous tumour: validation through collaboration



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Published Online December 18, 2018 http://dx.doi.org/10.1016/S1470-2045(18)30745-9

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Solitary fibrous tumour is a rare mesenchymal neoplasm with varied clinical behaviour and presenting symptoms. The pleura is a common site of initial presentation, but solitary fibrous tumours can occur in a variety of non-pleural soft tissue locations throughout the body. Although most typical solitary fibrous tumours present as localised disease and behave in an indolent fashion, malignant and dedifferentiated forms can act more aggressively, resulting in substantial morbidity and mortality.

Cytotoxic chemotherapy has traditionally been thought to be of limited value for patients with advanced disease, with small case series and retrospective studies suggesting marginal benefit. A retrospective study[1] of 21 patients who received conventional chemotherapy at the University of Texas MD Anderson Cancer Center (Houston, TX, USA) revealed a best response of stable disease in the majority of patients, with 5 (28%) having an average duration of stability of at least 6 months. The Centre Léon Bérard retrospectively evaluated 23 patients with advanced solitary fibrous tumours who received cytotoxic chemotherapy and reported a partial response in 2 (9%), with a median progression-free survival of 5·1 months (95% CI 0·7–9·6).[2] A retrospective study[3] from the Italian Sarcoma Group evaluated the use of anthracycline-based chemotherapy and single-agent ifosfamide therapy for patients with solitary fibrous tumours and revealed an overall response of 20% among 30 patients who received anthracycline-based chemotherapy and 10% among 19 patients who received single-agent ifosfamide therapy. In a separate retrospective study,[4] single-agent dacarbazine therapy in eight patients revealed a partial response in 3 (38%) patients.

A growing number of studies have highlighted the promising activity of antiangiogenic drugs in the treatment of advanced solitary fibrous tumours, and the clinical use of Choi criteria as more appropriate indicators of response in patients with sarcoma than traditional RECIST criteria.[5] In a study of bevacizumab in combination with temozolomide in 14 patients with advanced hemangiopericytoma or solitary fibrous tumours, 11 (79%) patients achieved a partial response according to Choi criteria, with a median progression-free survival of 9·7 months.[6] Among 31 evaluable patients with solitary fibrous tumours treated with sunitinib, two (6%) had a partial response according to RECIST, but 14 (48%) had a partial response according to Choi criteria.[7] In a subgroup analysis of five patients with solitary fibrous tumours from a study by the French Sarcoma Group,[8] two (40%) of five patients with solitary fibrous tumours treated with sorafenib showed stable disease. In another study of 13 patients with solitary fibrous tumours treated with pazopanib,[9] 1 (9%) had a partial response according to RECIST, but 5 (46%) had a partial response according to Choi criteria. The limitation all of these studies have in common is the retrospective manner in which they were done.

In *The Lancet Oncology*, Javier Martin-Broto and colleagues[10] report a multi-centre, single-arm, phase 2 trial of pazopanib for the treatment of advanced malignant and dedifferentiated solitary fibrous tumours.[10] This trial is the result of a robust collaboration between the Spanish, Italian, and French