Editorial

The Challenge of Drug Approval in Rare Cancers

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Sarcomas account for approximately 1% of all adult malignancies. They represent a highly heterogeneous tumor entity encompassing more than 100 different subtypes showing distinct histological, molecular, and certainly clinical characteristics. Within this group, there are a number of subentities with an incidence of less than 1 per 1,000,000 per year; the sarcoma community tends to call them ultrarare sarcomas. The tenosynovial giant cell tumor (TGCT) is one such ultrarare and locally aggressive sarcoma subtype that is associated with colony stimulating factor 1 (CSF1) overexpression.[1] TGCTs can be differentiated as localized disease (80%-90%) or diffuse-type disease (formerly called pigmented villonodular synovitis), which constitutes 10% to 20% of all cases and often causes debilitating symptoms, pain, swelling, a limited range of motion, and stiffness.[2] Although surgery is the standard treatment in the majority of patients with localized TGCTs, the diffuse type is usually beyond surgery and often requires systemic therapies, which are not established at all.[3] In this context, pexidartinib is an emerging orally available small molecule tyrosine kinase inhibitor acting as a potent selective inhibitor of the CSF1 receptor and other kinases.[4] In light of preliminary phase 1 data, pexidartinib has been evaluated in a phase 3 study named ENLIVEN, and it could demonstrate compelling efficacy in patients with advanced TGCTs.[5]

With this background in mind, the article in this issue of *Cancer* titled "Long-Term Outcomes of Pexidartinib in Tenosynovial Giant Cell Tumors" by Hans Gelderblom et al is of special interest.[6] The authors investigated the overall long-term benefit of continued treatment with pexidartinib in 130 patients with TGCTs receiving pexidartinib for a median treatment duration of 19 months and for an overall duration of up to 76 months of therapy. An overall Response Evaluation Criteria in Solid Tumors response rate of 60% could be demonstrated. In contrast to the previously published ENLIVEN study,[5] patients were observed for an additional follow-up of 26 months under pexidartinib treatment in the current pooled analysis of data from the pexidartinib phase 1 extension study (n = 39), the ENLIVEN patients randomized to pexidartinib (n = 61), and the ENLIVEN crossover patients (n = 30). Interestingly, even more patients could achieve a response with long-term pexidartinib treatment, and this supports the finding that targeting the CSF1 receptor pathway is an effective therapeutic strategy in this disease and that pexidartinib is able to provide encouraging long-term control in patients with advanced TGCTs. No new or different safety signals in comparison with the previously published studies and analyses were detected.[6]

Altogether, Gelderblom et al[6] could demonstrate an overall long-term benefit of continued treatment with pexidartinib in patients with advanced TGCTs. Besides the obvious clinical benefit for this distinct patient population, I would like to focus in this editorial on the topic of the complex and somehow unfortunate registration status of the compound pexidartinib in Europe in comparison with the United States.

The assessments of pexidartinib of the US Food and Drug Administration (FDA) and the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA) were both based on the same pexidartinib data provided in the new drug and marketing authorization application. However, on July 31, 2019, the FDA multidisciplinary review determined that despite the limitations in interpreting the significance of the clinical outcome results and the unknown risk of long-term exposure to pexidartinib, the benefit-risk assessment was favorable for a patient population with no alternative treatments available or for which surgery would not be possible because of predicted morbidity. Pexidartinib is, therefore, the first approved medical therapy for patients with advanced TGCTs and has been included in the National Comprehensive Cancer Network recommendations for this disease.[7] The Risk Evaluation Management System program for pexidartinib has been put into place to ensure that prescribers are informed of possible serious risks associated with pexidartinib and of the recommended monitoring to mitigate these risks. Moreover, a patient registry enables assessment outside the clinical trial setting and, in combination with a postmarketing safety study, provides information about outcomes in patients with long-term exposure to pexidartinib.

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In contrast, pexidartinib could not achieve any kind of endorsement or approval from the EMA; this basically means that patients with TGCTs will not have access to this new treatment option in any European countries in the near future. What are the reasons for this contradictory decision? Which circumstances finally led to this unfortunate decision even though pexidartinib was designated an orphan medicine (a drug used in rare diseases) in March 2015 for the treatment of TGCTs? One issue that has always been raised during discussions of this drug is the possible risk of liver toxicity, which has been extensively summarized elsewhere.[8] On June 25, 2020, almost 1 year after the FDA's approval, the EMA recommended refusal of the marketing authorization for pexidartinib (Turalio). The European Society for Medical Oncology (ESMO) appropriately summarized the reasons for the EMA's refusal as follows: "The Agency was concerned that although the main study found that tumours shrank in patients treated with Turalio, there was only a small improvement in symptoms such as pain and the ability to use the joint. It was not clear how long this effect lasts. There was also serious concern about unpredictable, potentially life-threatening effects of Turalio on the liver. Therefore, the Agency's opinion was that the benefits of Turalio did not outweigh its risks and it recommended refusing marketing authorisation."[9] With the current article kept in mind, the doubts raised about the long-term benefits for patients with TGCTs can be clearly overruled by the current long-term analysis of pexidartinib in patients with TGCTs.[6] Because of the possible risk of hepatotoxicity, pexidartinib is available only through the Risk Evaluation Management System program in the United States; however, a similar program for Europe has not even been taken into consideration.

To possibly facilitate drug approval for rare cancers and even more so for such ultrarare sarcoma subtypes, we have started an initiative from the European Organisation for Research and Treatment of Cancer (EORTC)/Soft Tissue and Bone Sarcoma Group (STBSG) to seek advice for the optimal clinical trial design for a planned STBSG trial in patients with advanced alveolar soft-part sarcoma. Within the format of an EMA Innovation Task Force briefing meeting, we aim to identify the most favorable clinical trial approach leading to the potential registration of a combined treatment strategy for patients with alveolar soft-part sarcoma. Moreover, this joint EMA and EORTC/STBSG exercise could potentially lead to a study design functioning as a role model for drug approval of other treatments for other ultrarare entities. More details on this initiative will be reported soon in a joint position paper.

In addition, this article nicely illustrates the potential impact of collaborative analyses and studies among international reference centers for answering relevant clinical questions about rare cancer types and even more so about such ultrarare cancer types. To improve care for patients with rare cancers in Europe, the European Reference Network for Rare Adult Solid Cancers (EURACAN) was implemented in 2016 to provide 1 dedicated domain for bone and soft-tissue sarcomas.[10] EURACAN aims to provide highly specialized management for patients with rare cancers in Europe and should enable second opinions across European countries. In addition, EURACAN will promote multidisciplinary advice, develop joint ESMO-EURACAN clinical practice guidelines,[11] disseminate knowledge, and support national centers and networks. In parallel, the European Commission has launched the research initiative Joint Action on Rare Cancers,[12] which is closely linked to EURACAN. Recommendations from the Joint Action on Rare Cancers have recently been presented to the European Parliament and summarized in a booklet entitled "Rare Cancer Agenda 2030—Ten Recommendations From the EU Joint Action on Rare Cancers."[13]

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