Targeted Therapies in Rare Sarcomas: IMT, ASPS, SFT, PEComa, and CCS

Silvia Stacchiotti, MD[a,*], Andrea Marrari, MD[a], Angelo P. Dei Tos, MD[b], Paolo G. Casali, MD[a]

KEYWORDS

• Sarcoma • Inflammatory myofibroblastic tumor • Alveolar soft part sarcoma • Solitary fibrous tumor • Hemangiopericytoma • Perivascular epithelioid cell tumor • Clear cell sarcoma • Chemotherapy

KEY POINTS

- A subgroup of rare entities within a family of rare cancers was selected for responsiveness to a set of molecularly targeted agents.
- Low-grade tumors may respond much less to standard chemotherapy, while their higher degree of differentiation may be associated with a higher relevance of cellular pathways, which may well serve as drug-susceptible targets.
- Inflammatory myofibroblastic tumor carries a translocation-related target, which is strongly related to the mechanism of action of the drugs employed, while in the case of alveolar soft part sarcoma and clear cell sarcoma, the activation of MET seems to be paralleled by a lower activity of the relevant drugs.
- In perivascular epithelioid cell tumors, a translocation resulting in MET activation was found in a small proportion of cases, while mammalian target of rapamycin (mTOR) inhibitors were shown to have some activity, in the absence of major genetic alterations of the mTOR pathway, though in the presence of a degree of its disruption.
- It is possible that some of the effects seen in the clinic are caused by an unspecific mechanism of action for these targeted agents, ranging from an antiangiogenic effect to an effect on pathways that may be more or less crucial for the tumor cell.

Disclosures: S. Stacchiotti–Advisory: Novartis; Lectures: Pfizer; Travel coverage for medical meetings: Novartis, Pfizer; Research funding for clinical studies in which I was involved: Bayer, Glaxo SK, Lilly, Novartis, Pfizer, Roche. A. Marrari–Research funding for clinical studies in which I was involved: Bayer, Glaxo SK, Lilly, Novartis, Pfizer, Roche. A.P. Dei Tos–None. P.G. Casali–Advisory: Bayer, Glaxo SK, Novartis, Pfizer; Travel coverage for medical meetings: Bayer, Glaxo SK, Novartis, Pfizer; Research funding for clinical studies in which I was involved: Bayer, Glaxo SK, Lilly, Novartis, Pfizer, Roche.

[a] Adult Sarcoma Medical Oncology Unit, Department of Cancer Medicine, Fondazione IRCCS Istituto Nazionale Tumori, via Venezian 1, Milan 20133, Italy; [b] Anatomic Pathology, Department of Oncology, General Hospital of Treviso, Piazza Ospedale 1, Treviso 31100, Italy
* Corresponding author.
E-mail address: silvia.stacchiotti@istitutotumori.mi.it

Hematol Oncol Clin N Am 27 (2013) 1049–1061
http://dx.doi.org/10.1016/j.hoc.2013.07.009 **hemonc.theclinics.com**
0889-8588/13/$ – see front matter

INTRODUCTION

Inflammatory myofibroblastic tumor (IMT), alveolar soft part sarcoma (ASPS), solitary fibrous tumor (SFT), perivascular epithelioid cell tumor (PEComa), and clear cell sarcoma (CCS) are among rarer soft tissue sarcomas (STS), each of them accounting for less than 1 case per 1,000,000 population per year.[1,2] They all represent translocated STS, characterized by the presence of relatively specific recurrent translocation, yet not always in the same proportion of cases. In the case of IMT and SFT, the cytogenetic aberration is responsible for the activation of 2 different proteins, anaplastic lymphoma kinase (ALK) and signal transducers and activators of transcription 6 (STAT6), respectively.[3–5] Curiously, in case of ASPS, PEComa, and CCS, the 3 different histotype-specific translocations have the common feature to induce the dysregulation of the microphthalmia transcription factor (MITF) family proteins.[6–12] In turn, these proteins up-regulate the transcription of MET, thus being responsible for the high metastatic rate of these sarcomas. Based on this shared molecular characteristic, ASPS, PEComa, and CCS belong to the MIT family tumors.[1]

IMT, SFT, ASPS, PEComas, and CCS are characterized by a low (if any) sensitivity to conventional cytotoxic chemotherapy. Given the rarity of these tumors, few prospective studies focusing on their medical treatment are available. However, the well-characterized mechanisms of oncogenesis make each histotype potentially sensitive to appropriate targeted treatments. In addition, other molecular and/or morphologic peculiar characteristics (eg, the particular vascular pattern in the case of ASPS and SFT, or the activation of mammalian target of rapamycin (mTOR) in PEComas) suggest a role for new targeted agents.

This article aims to review the data currently available in the literature on the activity of targeted medical treatment in each of these histologies.

INFLAMMATORY MYOFIBROBLASTIC TUMOR

IMT is a mesenchymal spindle cell neoplasm associated with plasma cells, lymphocytes, and granulocytes in variable amount, and featuring myofibroblastic differentiation.[3] Almost half of IMT carries a recurrent clonal aberration involving the *ALK* locus on chromosome 2p23.[4,13] ALK is a receptor tyrosine kinase implicated in the normal development and function of the nervous system, and whatever the partner genes, the resulting chimeric protein induces a hyperactivation of the kinase activity leading to uncontrolled cell growth. IMT is a low-grade sarcoma that arises predominantly in the lung, mesentery, retroperitoneum, and pelvis of children and young adults with a propensity for local recurrences, although infrequently, IMT may metastasize. Interestingly, the more aggressive variants of IMT usually are not associated with ALK rearrangement.[1] Surgery is the treatment of choice for localized disease; patients with unresectable IMT may benefit from steroids and chemotherapy.[14,15]

Among molecular target agents, the ALK/MET-inhibitor crizotinib (Xalkori) is currently the only agent found to be potentially active in this disease.

Crizotinib is an orally available inhibitor of MET and ALK tyrosine kinases; its antiproliferative activity is derived from the competitive inhibition of the adenosine triphosphate (ATP)-binding site of both kinases.[16] The activity of crizotinib in IMT was recently described by Butrynski and colleagues.[17] Two patients with unresectable recurrent IMT received crizotinib within a dose escalation phase 1 trial (NCT00585195). Interestingly, 1 patient, who suffered from an ALK-negative disease, progressed to the drug, while the other patient, whose disease carried the *ALK-RANBP2* fusion gene, achieved sustained partial response (PR). As for tyrosine kinase inhibitor (TKI), despite initial impressive clinical activity, resistance to crizotinib