CD105- A Therapeutic Target for Sarcomas

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Background

Sarcomas are a heterogeneous group of malignancies that comprise a variety of soft tissue and bone derived tumors. Patients with locally advanced or metastatic disease are primarily managed by systemic therapy but their life expectancy has not been improved significantly above a median of 12 months, thus citing a clear need for novel therapeutic approaches. CD105, also known as endoglin, is a transforming growth factor-β binding protein, which is more greatly expressed on the surface of proliferating endothelial cells. Its expression has been reported in multiple tumor types with multiple authors correlating survival with the degree of CD105 expression in neoplastic vasculature. Sarcomas have been reported to express CD105. However, there have been conflicting reports in the literature regarding the site of expression: tumor cells or tumor related vasculature. In light of the recent in-human testing of TRC105, the IgG1 antibody that binds with high affinity to human CD105, this exploratory study sought to determine the nature of CD105 expression on tumor cells, illustrated in Figure 1.

Methods

- Institutional Review Board approval was obtained. The following histologies were identified retrospectively in 146 archived paraffin embedded patient samples in our tissue registry: angiosarcoma, chondrosarcoma, Ewing sarcoma, leiomyosarcoma (gynecologic and non-gynecologic), osteosarcoma, synovial sarcoma and undifferentiated pleomorphic sarcoma.
- Immunohistochemical staining was performed by our Pathology Research Core, utilizing the Leica Bond III Stainer (Leica, Buffalo, IL), with the primary CD105 antibody (Clone 4G11, Novocastra), and a biotinylated secondary antibody, which is more greatly expressed on the surface of proliferating endothelial cells. Its expression has been reported in Figure 1.
- The slides were examined by a single bone and soft tissue pathologist (Karen Fritchie, MD), with a four tiered grading system for CD105 expression on tumor cells, illustrated in Figure 1.
- Table 1 shows IHC sample results in each of the following histologies: A-chondrosarcoma IHC=0; B-Ewing sarcoma IHC=2+; C-osteosarcoma IHC=2+; non-gynecologic leiomyosarcoma IHC=2+; D-syncytial sarcoma IHC=3+; E- uterine leiomyosarcoma IHC=2+; F- synovial sarcoma IHC=3+; G- undifferentiated pleomorphic sarcoma IHC=3+; H-angiosarcoma IHC=3+. Showing IHC sample results in each of the following histologies: A-chondrosarcoma IHC=0; B-Ewing sarcoma IHC=2+; C-osteosarcoma IHC=2+; non-gynecologic leiomyosarcoma IHC=2+; D-syncytial sarcoma IHC=3+; E- uterine leiomyosarcoma IHC=2+; F- synovial sarcoma IHC=3+; G- undifferentiated pleomorphic sarcoma IHC=3+; H-angiosarcoma IHC=3+.

Table 1

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<th>CD105 IHC 3+</th>
<th>CD105 IHC 2+</th>
<th>CD105 IHC 1+</th>
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<tr>
<td>Angiosarcoma</td>
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</table>

Figure 1

Demonstrating the four tiered IHC grading system as shown in one of the evaluated sarcoma histologies: A-chondrosarcoma IHC=0; B-Ewing sarcoma IHC=2+; C-osteosarcoma IHC=2+; non-gynecologic leiomyosarcoma IHC=2+; D-syncytial sarcoma IHC=3+; E- uterine leiomyosarcoma IHC=2+; F- synovial sarcoma IHC=3+; G- undifferentiated pleomorphic sarcoma IHC=3+; H-angiosarcoma IHC=3+.<5% cells positive=0; 5-24% cells positive=1+; 25-49% cells positive=2+; 50% or greater cells positive=3+.

Figure 2

Figure 3

Conclusions and Future Directions

CD105 expression in sarcomas is primarily limited to the tumor related vasculature. There appears to be increased expression in some histologic subtypes: angiosarcoma, undifferentiated pleomorphic sarcoma, gynecologic leiomyosarcoma.

We are evaluating the expression of CD105 in other vascular sarcomas and are in the process of conducting a clinical trial utilizing TRC105 in soft tissue sarcomas.

Disclosure

Research funding was provided by TRACON Pharmaceuticals.

References