MRI Assessment of Oral CSF1-Receptor Inhibition with PLX3397 for Tenosynovial Giant Cell Tumor/Pigmented Villonodular Synovitis using Novel Modified RECIST, Tumor Volume Scoring, and Tissue Damage Scoring Methods

Charles Peterfy, MD, PhD1; William D. Tap, MD2; Julie DiCarlo, PhD1; Zev A. Wainberg, MD3; Chao Zhang, PhD4; Arthur P. Staddon, MD5; Allen Lee Cohn, MD6; Geoffrey Shapiro, MD, PhD7; Igor Puzanov, MD8; Eunice L. Kwak, MD, PhD7; Henry H. Hsu, MD9; Paul S. Lin, MBA, MD4; Sandra Tong, MD4; John H. Healey, MD2.

1Spire Sciences, Inc., Boca Raton, FL, USA, 2Memorial Sloan Kettering Cancer Center, New York, NY, USA, 3UCLA, Los Angeles, CA, USA, 4Plexxikon Inc., Berkeley, CA, USA, 5University of Pennsylvania School of Medicine, Philadelphia, PA, USA, 6Rocky Mountain Cancer Center/US Oncology, Denver, CO, USA, 7Dana-Farber Cancer Institute, Boston, MA, USA, 8Vanderbilt University Medical Center, Nashville, TN, USA.

Disclosures: C. Peterfy: 3A; Spire Sciences, Inc. W.D. Tap: 5; Plexxikon Inc. J. DiCarlo: 3A; Spire Sciences, Inc. Z.A. Wainberg: 5; Plexxikon Inc. C. Zhang: 3A; Plexxikon Inc. A.P. Staddon: 5; Plexxikon Inc. A.L. Cohn: 5; Plexxikon Inc. G. Shapiro: 5; Plexxikon Inc. I. Puzanov: 5; Plexxikon Inc. E.L. Kwak: 5; Plexxikon Inc. H.H. Hsu: 3B; Plexxikon Inc. P.S. Lin: 3A; Plexxikon Inc. S. Tong: 3A; Plexxikon Inc. J.H. Healey: 7; Editor of Clinical Orthopaedics and Related Research.

Introduction: Tenosynovial giant cell tumor (TGCT), also known as pigmented villonodular synovitis (PVNS), is a rare locally aggressive neoplasm of the synovium of joints or tendon sheaths causing pain, swelling, limited joint movement and in some cases destruction of bone and other local tissues. Extensive diffuse TGCT often requires total synovectomy, joint replacement or amputation. Recently, several drugs have reported promising phase 2 results. However measuring tumor regression in clinical trials of TGCT is challenging. Magnetic resonance imaging (MRI) can visualize TGCT better than other imaging modalities can, but accurately identifying tumor margins is complicated by the irregular shape and asymmetrical growth of TGCT and by poor image contrast between the tumor and surrounding structures. This limits the accuracy of linear measurements used in Response Evaluation Criteria In Solid Tumors (RECIST)[1]. Further, because of the crescentic shape of the synovial cavity of the knee and many other joints, longest-dimension measurements required by conventional RECIST (ie, edition 1.1) often cannot avoid non-tumor tissue in diffuse TGCT. Mesothelioma lining the curved pleural cavity poses a similar challenge, and thus is typically assessed by a modified RECIST method based on short-axis measurements [2]. We hypothesized that a similar approach applied to TGCT would more accurately reflect tumor burden, correlate better with associated structural damage, and better discriminate treatment effects in this disease. In this investigation, we compared a modified RECIST method based on short-axis measurements to conventional RECIST and to a TGCT tumor volume scoring method in a longitudinal trial with PLX3397, an orally administered, potent, selective, small molecule inhibitor of CSF1 receptor (CSF1R) kinase. We also present a method for assessing local tissue damage in TGCT.

Methods: Patients with histologically confirmed, inoperable, progressive or relapsing TGCT with demonstrated progression in the prior 12 months were enrolled into an ongoing, single-arm, multicenter phase 1 trial of the selective CSF1R inhibitor, PLX3397 (1000 mg daily total dose). Patients had...
MRI of the affected joint at baseline and every 2 months. Images were assessed centrally (masked to visit order) by two independent radiologists. For conventional RECIST, each radiologist summed the longest measureable linear dimension of up to two tumors per joint or tendon sheath at each visit using electronic calipers. For modified RECIST, short-axis dimensions of the same tumors were measured perpendicular to a reliable nearby landmark, such as the femoral diaphysis, and summed. Patients were classified by conventional RECIST responder criteria as Complete Response (CR: lesion completely gone by last visit), Partial Response (PR: ≥ 30% decrease), Progressive Disease (PD: ≥ 20% increase relative to lowest score) or Stable Disease (SD: none of the above). Tumor Volume Score (TVS) was based on 10% increments of the estimated maximally distended normal synovial cavity or tendon sheath involved. Measurements and scores from the two radiologists were averaged. For TVS, PR was defined as ≥ 50% decrease, and PD as ≥ 30% increase relative to lowest score.

A multi-feature tissue damage score (TDS) was adapted from the Whole-Organ MRI Score (WORMS) used in osteoarthritis [3]. Bone erosion was scored on a scale of 0-10 based on 10% increments of bone volume loss in each of 14 articular surfaces per joint and summed (Fig. 1). Articular cartilage loss, bone marrow edema, meniscus damage, ligament damage and joint effusion were each scored according to WORMS.

Results: Fourteen TGCT patients treated with PLX3397 had a baseline and at least one follow-up MRI that were evaluable. Serial examinations varied from 1-12 time points. TGCT involved the knee in 10, the ankle in 2, the foot in 2 and the elbow in 1 of these patients. As shown in Table 1, conventional RECIST assessments showed a majority of the patients to be responders. Modified RECIST and TVS both classified a larger proportion of patients as responders and showed greater median change than conventional RECIST did (Fig. 2).
With regards to joint damage, 10 patients (71%) showed erosion of articular bone at baseline with no significant progression compared to the last visit. Modified RECIST and TVS correlated better with erosion score at baseline ($r = 0.73$ and 0.68) than RECIST did (0.61). Cartilage loss was present in 8 patients (57%) at baseline, and worsened slightly in 2. Ten (71%) patients had bone marrow edema at baseline. Eight (80%) of these improved. Four of the 9 knees (44%) had meniscal disease at baseline; none progressed. Six (67%) knees had popliteal cysts; 4 (67%) of these improved. Seven (78%) knees had joint effusion at baseline; four (57%) improved and 1 (14%) worsened.

**Discussion:** Treatment of TGCT with PLX3397 resulted in sustained tumor regression in the majority of patients based on conventional RECIST. Modified RECIST classified a larger proportion of patients as responders and discriminated greater change than RECIST did, thus corresponding more closely to...
changes in TVS. A majority of patients had bone erosions and bone marrow edema associated with TGCT at baseline. None progressed on therapy, and a majority of those with bone marrow edema, popliteal cysts or joint effusion improved.

**Significance:** Conventional RECIST is challenging to use for TGCT; it underestimates tumor volume response to treatment and does not consider local tissue damage, which is a major cause of morbidity. The modified RECIST, TVS and TDS methods described in this report provide superior assessment of TGCT and will be further studied in a Phase 3 TGCT clinical trial.

ORS 2015 Annual Meeting

Poster No: 2028