

Long-term Treatment of Tenosynovial Giant Cell Tumor (TGCT) with PLX3397, a selective colony-stimulating factor 1 receptor (CSF1R) kinase inhibitor.

Abstract 11327:

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Background:

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. Tumors contain CSF1R-bearing macrophages recruited by local overexpression of CSF-1 due to a gene translocation. PLX3397 is a novel, oral small molecule that potentially and selectively inhibits CSF1R and KIT kinases. CSF1R and KIT regulate key components of both the tumor and its microenvironment (macrophages, osteoclasts, mast cells).

Question: Previous data have shown reduction in tumor burden in treatment of TGCT with PLX3397, and here we examine the effects of long-term treatment.

Methods: Patients (pts) with advanced TGCT were enrolled onto a single-arm expansion cohort of an ongoing, multicenter, clinical study (NCT01004861). PLX3397 was given orally, 1000 mg daily (600 mg AM, 400 mg PM – 28 day cycles). MRI was performed about every 2 months and assessed by central musculoskeletal radiologists blinded to chronology using a novel Tumor Volume Score (TVS) developed specifically for TGCT or using RECIST 1.1. For TVS, partial response (PR) was defined as $\geq 50\%$ decrease compared to screening and progressive disease (PD) was $\geq 30\%$ increase relative to lowest score. Given that the clinically meaningful difference for this non-malignant disease is change from baseline (rather than nadir), an alternative analysis was performed using definition of progressive disease as an increase from screening of 30%. Patients remained on treatment until disease progression or intolerability. Duration of response was calculated from time of PR to first sustained PD. The subset of pts treated for ≥ 6 mos was analyzed.

Results: To date, there are 38 TGCT pts enrolled in the study; 25 of these have been on treatment ≥ 6 mos with median duration of 12 months (range 6 – 29 mos). There are 15 of 25 pts still on treatment, 4 who stopped due to adverse events, and 1 who had metastatic disease and stopped at 9 months due to disease progression. For MRI evaluations, there were 20 evaluable pts: 3 had PD, 5 had SD and 12 had PR. Median duration of response among those with PD was 14 months (range 4 to 16 months). Using the alternative definition of change from screening for PD, 6 had SD, 12 had PR, and none had PD. Fig 1 shows the median percent change in TVS at each time point with decrease in tumor size within 2 months of initiating treatment, followed by relatively stable maintenance over the following 18 months. Evaluation by RECIST 1.1 yielded similar results (Fig 2).

Decreases in tumor burden were associated with reports of decreased pain, decreased swelling, and improvement in activities such as walking.

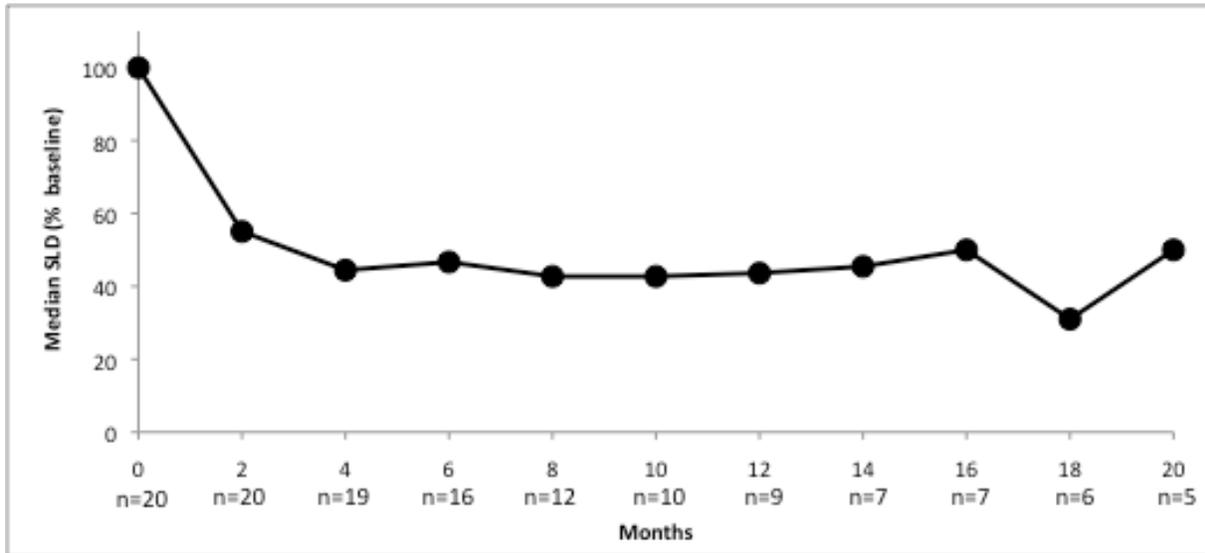


Figure 1. Median TVS as a percentage of baseline TVS.

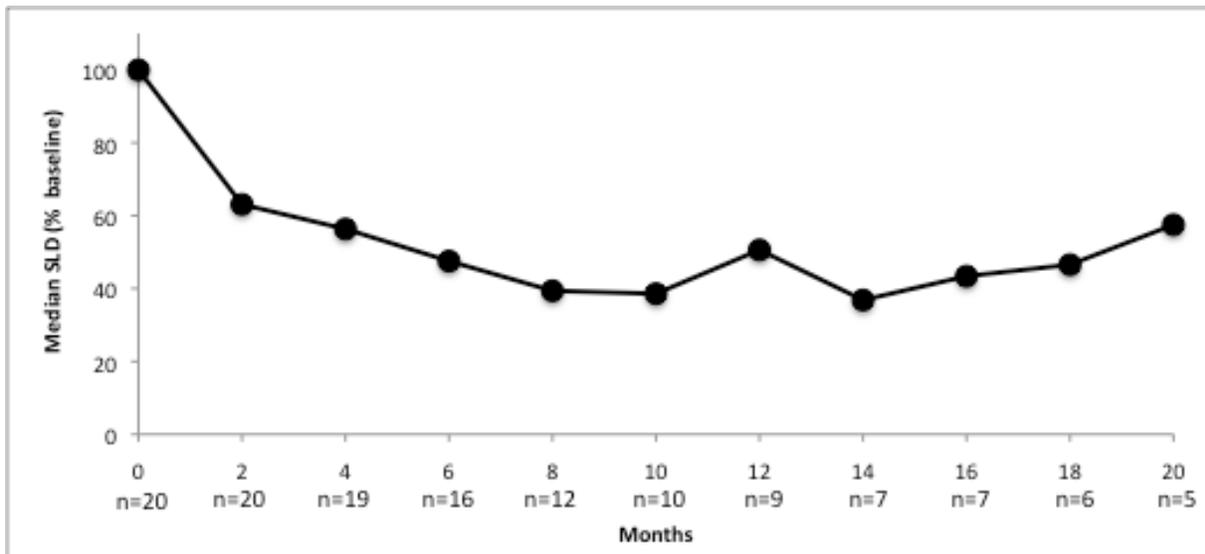


Figure 2. Median sum of longest dimensions (SLD) per RECIST 1.1, as a percentage of baseline SLD.

For all 39 pts enrolled, common AEs (>20%) were: fatigue, peripheral edema, dysgeusia, headache, dizziness, hair color changes, periorbital edema, pruritus, rash, nausea, diarrhea, vomiting, arthralgia, and pain in extremity. Treatment-related AEs \geq Grade 3 were: elevated ALT and AST (3), hyponatremia (2), anemia (1), fatigue (1), neutropenia (1), diarrhea (1), arthritis (1), and hypophosphatemia (1).

Conclusions: PLX3397 was well tolerated with long-term use and demonstrated durability of response in reduction of tumor burden in patients with advanced TGCT. PLX3397 is in further evaluation in ENLIVEN, a Phase 3 global clinical trial of PLX3397 in patients with TGCT (NCT02371369).