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NCCN Soft Tissue Sarcoma (STS) Panel

Request review of newly FDA-approved pexidartinib as therapy for tenosynovial giant cell tumor (TGCT)

On behalf of Daiichi Sankyo, Inc., I respectfully request the NCCN STS panel to review the enclosed FDA label¹ and Phase 3 randomized study² in support of pexidartinib for the treatment of TGCT.

Specific Changes: Please consider the following:

- **SARC-F 2 of 7, “Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma”, under “Pigmented Villonodular Synovitis/Tenosynovial Giant Cell Tumor”:**
 - Add Pexidartinib (category 1, preferred)

FDA Clearance: TURALIO (pexidartinib) is a kinase inhibitor indicated for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery.¹

Rationale: Pexidartinib, a CSF1R inhibitor, is the first agent to be approved by the FDA for TGCT. In the pivotal Phase 3 randomized study ENLIVEN,² pexidartinib demonstrated significant improvement in overall response and other clinical outcome assessments compared with placebo. Based on results from ENLIVEN, pexidartinib was highlighted by ASCO as an Advance of the Year in Progress in Treating Rare Cancers in 2019.³ Approval of pexidartinib provides a new, effective option for patients with this rare, sometimes debilitating disease.

Key Supporting Literature:

Approval of pexidartinib was based on ENLIVEN, a double-blind, randomized, global, multicenter, phase 3 study in patients with symptomatic advanced TGCT for whom surgical removal of the tumor would be associated with potentially worsening functional limitation or severe morbidity.² The study randomized 120 patients in a 1:1 ratio to receive either pexidartinib (n=61) or placebo (n=59). The primary endpoint of ENLIVEN was the percentage of patients achieving a complete or partial response at week 25 as assessed by blinded independent central review of magnetic resonance imaging scans using RECIST version 1.1 criteria.

Pexidartinib met its primary endpoint in significantly improving the overall response rate (39%) compared with no response in the placebo arm ($P<0.0001$). At 22 months of median follow-up, the best overall



response in patients randomized to pexidartinib was 53%. These results were consistent with an earlier phase 1 study that demonstrated a 52% overall response rate in 23 patients with advanced TGCT.⁴

Pexidartinib also demonstrated statistically significant improvements versus placebo for multiple secondary efficacy endpoints at 25 weeks. These include overall response rate by Tumor Volume Score (56% vs 0%, $P<0.0001$), range of motion (+15.1% vs +6.2%, $P=0.0043$), PROMIS-Physical Function scale (+4.1 vs -0.9, $P=0.0019$), and worst stiffness numeric rating scale (NRS) score (-2.5 vs -0.3, $P<0.0001$). There was also a numerically higher, but nonsignificant, proportion of responders based on Brief Pain Inventory (BPI) worst pain NRS and analgesic use by BPI-30 definition (31% vs 15%).²

In the ENLIVEN study, the most common ($\geq 20\%$) adverse events of any grade that were reported more frequently with pexidartinib were hair color changes (de-pigmentation; 67% vs 3%), fatigue (54% vs 36%), aspartate aminotransferase (AST) increased (39% vs 0%), alanine aminotransferase (ALT) increased (28% vs 2%), dysgeusia (25% vs 2%), vomiting (20% vs 5%).² The most common ($\geq 5\%$) grade 3 or 4 adverse events occurring at a higher incidence in the pexidartinib group were AST increased (10% vs 0%), ALT increased (10% vs 0%), alkaline phosphatase (ALP) increased (7% vs 0%), and hypertension (5% vs 0%).² Three patients in the pexidartinib group had transaminases $\geq 3\times$ ULN with total bilirubin and ALP $\geq 2\times$ ULN indicative of mixed or cholestatic hepatotoxicity. One case lasted 7 months with substantial ductopenia and severe cholestasis observed on biopsy.² In the other two cases, hyperbilirubinemia resolved within 1 to 2 months of pexidartinib discontinuation.²

Sincerely,

Dan Liang, Pharm.D.

References (enclosed):

1. TURALIO™ (pexidartinib) [Prescribing Information]. Daiichi Sankyo, Inc., Basking Ridge, NJ. Updated August, 2019.
2. Tap WD, Gelderblom H, Palmerini E, et al. Pexidartinib versus placebo for advanced tenosynovial giant cell tumor (ENLIVEN): a randomised phase 3 trial [published online ahead of print June 19, 2019]. *Lancet*. 2019.
3. Pal SK, Miller MJ, Agarwal N, et al. Clinical Cancer Advances 2019: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology. *J Clin Oncol*. 2019;37(10):834-849.
4. Tap WD, Wainberg, ZA, Anthony SP, et al. Structure-guided blockade of CSF1R kinase in tenosynovial giant-cell tumor. *N Engl J Med*. 2015;373(5):428-437.