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Title: The tetravalent death receptor 5 (DR5) agonist ozekibart (INBRX-109) in conventional chondrosarcoma: secondary efficacy endpoints from the randomized, registrational, phase 2 ChonDRAgon study

Significance & Hypothesis/Techniques: Conventional chondrosarcoma, a heterogeneous malignant bone tumor, is generally resistant to chemotherapy and radiotherapy. Surgery is the only curative intervention. However, resection may severely impact quality of life (QOL) or may not be feasible. Systemic treatments are limited, and none are approved for unresectable/metastatic disease.

Ozekibart (INBRX-109), a novel DR5 agonist, was evaluated in ChonDRAgon (phase 2; NCT04950075), a randomized, placebo-controlled trial in advanced conventional chondrosarcoma. ChonDRAgon met its primary endpoint. Ozekibart significantly prolonged median progression-free survival (PFS) vs placebo (5.52 vs 2.66 months; stratified hazard ratio [HR], 0.479; 95% CI, 0.335-0.684; *P*<.0001).[1] Here, we further evaluate the anticancer activity of ozekibart and report secondary efficacy endpoints from ChonDRAgon.

Innovation: Ozekibart is a third-generation, tetravalent DR5 agonist. ChonDRAgon is the first and largest randomized trial in advanced conventional chondrosarcoma, and the first positive randomized study in chondrosarcoma.

Approach: Eligible patients were ≥18 years with unresectable/metastatic conventional chondrosarcoma. Those ≥65 years required a BMI <30 kg/m^2. Patients with liver conditions associated with increased risk of hepatotoxicity were excluded. Patients were randomized 2:1 to ozekibart 3 mg/kg intravenously Q3W or placebo and stratified by histologic grade (2 vs 3), *IDH* mutation status, and prior systemic therapy (No vs Yes). Patients could cross over from placebo to open-label ozekibart upon progression. The primary endpoint was PFS per RECIST 1.1 by real-time central independent radiology review (CIRR) in the intention-to-treat population. Inter-arm comparison used a stratified log-rank test. The study was powered to detect a HR of 0.571 (90% power; 1-sided α=0.025). Secondary efficacy endpoints included overall survival (OS), overall response rate (ORR) per CIRR, QOL (EORTC QLQ-C30 pain symptoms and physical functioning scales), duration of response (DOR), and disease control rate (DCR; response, stable disease ≥84 days, non–complete response/non–progressive disease).

Results: Overall, 137 patients were randomized to ozekibart and 69 to placebo. Median follow-up was 10.2 and 9.0 months, respectively (data cutoff: Sep 30, 2025). Median age was 54.0 (range, 20-82) years in the ozekibart arm and 50.0 (19-91) years in the placebo arm; 70.1% and 60.9% of patients were male. Most patients had grade 2 chondrosarcoma (ozekibart, 70.1%; placebo, 69.6%). Prior cancer surgery was common (ozekibart, 92.0%; placebo, 97.1%), and ≈40% received prior systemic therapy (42.3%; 40.6%). At data cutoff, 18.2% and 4.3% of patients, respectively, remained on treatment.

Ozekibart demonstrated a manageable safety profile[1] and led to a significantly greater DCR than placebo (54.0% vs 27.5%; *P*=.0005). ORR was 5.8% (8/137; all partial responses) with ozekibart and 0% with placebo (*P*=.0433).

Median DOR was 11.1 months. OS data were immature. Ozekibart significantly delayed QOL deterioration vs placebo in pain (median time to deterioration, 2.76 vs 1.41 months; HR, 0.605; *P*=.0033) and physical functioning (2.56 vs 1.41 months; HR, 0.561; *P*=.0007).

Discussion & Impact: In addition to improving PFS, ozekibart significantly improved DCR and delayed QOL deterioration vs placebo in patients with advanced conventional chondrosarcoma, with a manageable safety profile. Ozekibart may become the first standard of care for this population with high unmet need.

References:

1. Jones RL, et al. *ESMO Rare Cancers*. 2025;4:100116.