A PHASE 2, RANDOMIZED, DOUBLE-BLIND, MULTICENTER TRIAL OF DENOSUMAB IN COMBINATION WITH CHEMOTHERAPY AS FIRST-LINE TREATMENT OF METASTATIC NON-SMALL CELL LUNG CANCER

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Background: Non-Small Cell Lung Cancer (NSCLC) is a heterogeneous disease for which patients (pts) may benefit from targeted therapies. RANK ligand (RANKL) and its receptor RANK are expressed in a subset of NSCLC tumors (Branstetter, 2013). Results from preclinical models show that RANKL acts directly on RANK-expressing tumor cells to promote tumor progression and metastases (Gonzalez-Suarez, 2010; Tan, 2011). Denosumab is a fully human monoclonal antibody that binds RANKL, approved for the prevention of skeletal-related events in pts with solid tumors and bone metastases. In a study of pts with solid tumors receiving standard treatment, post hoc analysis of those with stage IV NSCLC (n = 702) showed that pts who received denosumab had improved median overall survival (OS) vs those who received zoledronic acid (ZA) (HR [95% CI] 0.78 [0.65–0.94], p = 0.01; Scagliotti, 2012). The current trial will correlate tumor RANK and RANKL expression and OS in pts with metastatic NSCLC receiving denosumab in combination with standard chemotherapy vs those receiving chemotherapy alone. The trial is sponsored by Amgen Inc. and registered with ClinicalTrials.gov (NCT01951586).

Trial design: ~216 pts with untreated stage IV NSCLC will receive 4–6 cycles of standard of care chemotherapy and be randomized (2:1) to denosumab 120 mg or placebo SC Q3W or Q4W plus a loading dose on day 8. ZA or placebo IV may be offered in a blinded manner if requested. The sample size is powered to test the interaction between treatment effect and RANK or RANKL expression under various reasonable scenarios. Pts will receive calcium and vit D daily. Randomization will be stratified based on bone metastasis (yes or no), histology (squamous vs nonsquamous), and region (North America, Western Europe/Australia, rest of world). The primary endpoint is tumor RANK expression correlated with OS. Primary analysis will occur when ~149 deaths have occurred. Eligible pts will have ECOG status 0–1 and radiographically evaluable disease. Pts with known EGFR-activating mutations, EML-4-ALK translocation, or brain metastasis will be excluded. Pt screening and enrollment is planned or underway in ~10 countries. Reused with permission from the American Society of Clinical Oncology. This Abstract was accepted and previously presented at the 2014 ASCO Annual Meeting #TPS8130.

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