Cancer stem cells (CSC) and inhibition of hedgehog (Hh) pathway signaling in advanced pancreatic cancer: GDC-0449 in combination with gemcitabine (Gem). Edward J. Kim¹, Gazala N. Khan¹, Kent Griffith¹, Joel Greenson¹, Naoko Takebe², Mark Zalupski¹, Diane Simeone¹. ¹University of Michigan, Ann Arbor, ²NIH, Rockville, MD.

Background: Pancreatic CSCs are a highly resistant subpopulation within a tumor that possess stem cell properties such as self-renewal and exhibit greater tumorigenicity and metastatic potential. These features are associated with reactivation of developmental pathways including the Hh signaling pathway. We previously reported that CD44+/CD24+/ESA+ pancreatic CSCs express significantly elevated levels of Sonic Hh (Cancer Res, 2007). GDC-0449, a Smoothened antagonist, is an orally delivered small molecule inhibitor of the Hh pathway that has been evaluated in Phase 1 studies. We report here preliminary results of a clinical trial in patients with metastatic pancreatic cancer investigating sequential delivery of GDC-0449 and Gem providing a rationally designed, novel multi-targeted therapy. This trial importantly includes prospective evaluation of Hh pathway inhibition in pancreatic cancer by incorporating paired core biopsies of tumor before and after treatment with GDC-0449.

Materials and Methods: Patients with previously untreated, metastatic pancreatic cancer were eligible. GDC-0449 was initiated as daily monotherapy for a 4-week cycle followed by the combination of daily GDC-0449 with intravenous Gem days 1, 8 and 15 for each subsequent cycle. Two sets of 3 core biopsies were performed on each patient; one set prior to start of therapy and a second set 3 weeks after beginning GDC-0449. A primary trial objective was to evaluate effects of GDC-0449 on pancreatic CSCs. Tumor biopsies were processed immediately after biopsy and allocated for correlative experiments. Fresh tissue was analyzed for CD44, CD24, and ESA expression by flow cytometry. Formalin-fixed tumor samples were evaluated for Ki67 by immunohistochemistry (IHC) and a proliferative index was calculated. Pre-treatment Sonic Hh expression was also analyzed by IHC and assigned an H-Score based on review by a pancreatic pathologist. Clinical outcome parameters were measured, including progression free survival (PFS) at 3 months and response rate, and overall survival.

Results: Twenty of a planned 25 patients have been accrued and undergone paired biopsies with 18 of 20 patients assessable for response after 3 cycles of therapy. Although a subset of patients had evidence of disease progression on GDC-0449 monotherapy per RECIST criteria, continuation of GDC-0449 with addition of Gem resulted in significant response in several patients. RECIST-defined confirmed partial response was achieved in 5 patients (28%) with 4 additional patients having stable disease, yielding a 50% PFS rate at 3 months. Three patients have received treatment for ≥12 cycles. The percentage of pancreatic CSCs decreased in 56% of patients, and of these patients, the mean relative decrease was 60% ±22% (range, 16-87%). Proliferative index decreased in 54% of the patients (range, -11% to +28%). Sonic Hh expression was more highly expressed in patients that achieved a partial response or stable disease as compared to those with progression (mean H-score 285 vs 168, p = 0.016). Ongoing analysis of the effect of GDC-0449 on Hh pathway target genes is being conducted.

Conclusion: Sequential delivery of GDC-0449 as monotherapy followed by combination with
Gem is effective in providing clinical benefit to a subset of patients with metastatic pancreatic cancer. Of the biological correlates evaluated, pre-treatment Sonic Hh expression level is the best predictor of benefit with this regimen. Ongoing correlative studies are underway to further refine the best predictor of who will benefit from this combination therapy.