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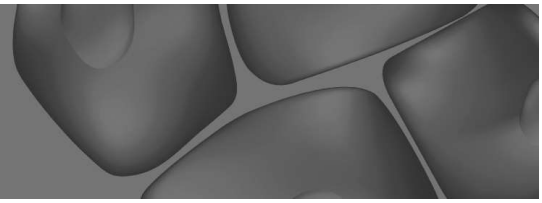

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Efficacy and Safety of Rigosertib in Patients with Recessive Dystrophic Epidermolysis Bullosa (RDEB) Associated Advanced/Metastatic Squamous Cell Carcinoma (SCC)

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Introduction & Objectives: RDEB is a rare genodermatosis driven by mutations in the collagen VII gene (COL7A1). RDEB is characterized by severe skin and mucosal blistering with chronic wounding complicated by cutaneous SCCs (cSCCs). cSCC is the most common cause of death with a cumulative risk for premature demise of 70% by age 45. Evidence for effective treatment options for advanced (unresectable/metastatic) RDEB-associated SCCs is limited and scarce. It was previously demonstrated that RDEB SCC keratinocytes are specifically sensitive to inhibition of polo-like kinase-1 (PLK-1). Of eight PLK-1 inhibitors screened for cytotoxicity, rigosertib (RGS) was superior with the largest therapeutic window for distinguishing between tumor versus normal cells.

Materials & Methods: Safety and efficacy of RGS are being evaluated in two open-label, single arm phase 2 studies. RDEB patients with treatment resistant advanced SCC receive RGS either intravenously (1800 mg/24hr for 3d every 2 weeks) or orally (560 mg BID for 21 of 28 days). Route of administration is based on the individual extent of RDEB inherent cutaneous and mucosal involvement and patient preference. Secondary objectives include assessing biomarker analysis on tumor tissue.

Results: Four patients have been treated to date and were evaluated for efficacy. Patient 1, a 23-year-old female patient with a history of more than 29 SCCs, achieved cutaneous and histological remission with stable metabolic activity in PET-CT at week 12 of IV RGS. The duration of response was 16 months. Post recurrent CTCAE grade 2 irritative cystitis, the patient's dose of RGS was reduced, leading to symptomatic relief. Patient 2 was a 32-year-old female with a history of several cSCCs and nodal disease, who received oral RGS. The patient achieved a complete cutaneous remission, and completed the protocol defined 12 months of therapy. Patient 3 was a 21-year-old female patient with multiple SCCs on right thigh including a massive, ulcerated tumor, which had previously been partially amputated. Tumor necrosis of this lesion was temporally related to IV RGS administration, resulting in exposed bone prompting definitive surgical amputation. However, during week 9, metastatic progression of systemic tumor disease was determined by PET-CT.

Patient 4, a 21-year-old female with an SCC on her right knee and nodal disease received oral RGS. Due to limited blood levels with oral RGS exposure, the patient was switched to IV RGS and remains on study.

Conclusion: These preliminary results indicate RGS as a potential treatment for cSCC in RDEB patients. Eligible patients are being sought for this experimental approach.