A Phase II Study of CR011-vcMMAE (CDX-011), an Antibody-Drug Conjugate, in Patients with Locally Advanced or Metastatic Breast Cancer

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BACKGROUND

- GPNMB (osteactivin): a novel glycoprotein expressed in 20-40% of breast cancers, as well as other tumor types
  - promotes the migration, invasion, and metastasis of breast cancer and is an independent prognostic factor for recurrence of disease

- CDX-011 (CR011-vcMMAE, gelmatumbimid vedotin) consists of a fully human monoclonal antibody targeting the extracellular domain of GPNMB (CR011), conjugated via an enzyme-sensitive linker to the potent chemotherapeutic, MMAE (Seattle Genetics).
  - CDX-011 was designed to be stable in the bloodstream, but to release MMAE upon internalization into GPNMB-expressing tumor cells, resulting in a targeted killing effect.
  - In a Phase II study in patients with metastatic breast cancer, increased activity was observed in patients whose tumors had GPNMB expression.
  - The current Phase I/II study evaluates the safety and efficacy of CDX-011 in patients with heavily pre-treated, advanced breast cancer.

STUDY DESIGN AND CONDUCT

- Patient Population
  - Progressively locally advanced or metastatic breast cancer
  - Eligible patients had to have previously received ≥1 line of systemic therapy
  - Prior treatments must include, when clinically appropriate, an anthracycline, taxane, capecitabine, or trastuzumab
  - No limit to number of prior treatments
  - Treatment: In each cohort, CDX-011 was administered as a 90 min IV infusion, once every three weeks until intolerance or progression

- Immunochromoty for GPNMB was performed on biopsy samples for a subset of patients using a polyclonal anti-GPNMB antibody (RAD Systems) and a biotin-conjugated donkey anti-goat secondary antibody (Jackson ImmunoResearch Laboratories). Sections were developed with DAB and counterstained with hematoxylin. Samples with ≥5% of cells expressing GPNMB were considered positive.

- Patient 5009: Strongly positive immunohistochemical expression of GPNMB at baseline biopsy and Partial Response (53% shrinkage) marked for 23+ weeks in this patient with triple-negative disease.

- Primary Efficacy Endpoint: Progression-free survival by GPNMB Expression Status (All doses entry and Partial Response) (53% shrinkage) marked for 23+ weeks in this patient with triple-negative disease.

- Additional Measures of Anti-tumor Activity: Phase II Dose
  - Maximum Tumor Shrinkage: Phase II Dose
  - Tolerability
  - Tolerability

- This is a Phase II pilot trial of CDX-011 in an advanced breast cancer patient population who were heavily pretreated (median of seven prior regimens).
  - The primary efficacy endpoint has been met, with 35% of treated patients progression-free at 12 weeks.
  - The target GPNMB was sufficiently expressed in this patient population (71%) and expression of CDX-011 was associated with improved outcomes following treatment with CDX-011.
  - All activity parameters appear to be consistent across the Phase II dose levels.
  - Early responses to CDX-011 were confirmed with Reduced Partial Responses expressed GPNMB, with response durations of 23+ to 72 weeks.
  - Encouraging evidence of activity is seen in the subset of patients with triple-negative disease where treatment options are relatively limited.