CDX-0159, An Anti-KIT Monoclonal Antibody, As A Modulator Of Mast Cell-Related Diseases

Scott Seibel, Laura Vitale, Lawrence Thomas, Joel Goldstein, Eric Forsberg, Andrea Crocker, Jenifer Widger, Colleen Patterson, Laura Mills-Chen, Russell Hammond, Tibor Keler, Richard Gedrich
Disclosures

- Scott Seibel – Employment/Stock - Celldex Therapeutics, Inc.
- Laura Vitale – Employment/Stock - Celldex Therapeutics, Inc.
- Lawrence Thomas – Employment/Stock - Celldex Therapeutics, Inc.
- Joel Goldstein – Employment/Stock - Celldex Therapeutics, Inc.
- Eric Forsberg – Employment/Stock - Celldex Therapeutics, Inc.
- Andrea Crocker – Employment/Stock - Celldex Therapeutics, Inc.
- Jenifer Widger – Employment/Stock - Celldex Therapeutics, Inc.
- Colleen Patterson – Employment/Stock - Celldex Therapeutics, Inc.
- Laura Mills-Chen – Employment/Stock - Celldex Therapeutics, Inc.
- Russell Hammond – Employment/Stock - Celldex Therapeutics, Inc.
- Tibor Keler – Employment/Leadership/Stock - Celldex Therapeutics, Inc.
- Richard Gedrich – Employment/Stock Celldex - Therapeutics, Inc.
The Receptor Tyrosine Kinase KIT Plays a Central Role in Regulating Mast Cell Function and Activity
Targeting KIT Represents a Unique Strategy in Diseases Involving Mast Cells
CDX-0159 is a Potent Inhibitor of KIT-Mediated Effects on Mast Cell Degranulation

KIT activation by SCF has a costimulatory effect on mast cells, augmenting FcεRI-induced degranulation, which is inhibited by CDX-0159 and CDX-0158.
CDX-0158, the Predecessor to CDX-0159, Modulates Mast Cell Activity In Vivo

Rapid Reduction of Skin Mast Cells in Healthy Dog Skin

Reduction of Airway Eosinophilia in a Feline Allergic Asthma Model

Decreased Mast Cell Recruitment to Wound Edges in Monkey Skin

Establishes preclinical proof-of-concept for KIT inhibition leading to reduced mast cell numbers and activity, which can potentially ameliorate mast cell-mediated diseases

(London et al., Clin Cancer Res 2017)

(Mandel et al., 2014 ACAAI Annual Meeting)
CDX-0158 Phase 1 Study in Patients with GIST

- Accrued 28 patients with gastrointestinal stromal tumors (GIST) at doses up to 15 mg/kg
- MTD was not reached
- CDX-0158 was generally well tolerated except for infusion-related reactions (IRRs) in 71% of patients
  - IRRs were associated with rash, pruritus, occasional urticaria and chest heaviness, as well as transient increases in tryptase, suggesting mast cell degranulation
  - IRRs not clinically limiting and were managed in most patients with premedications and brief treatment interruption
  - Incidence of IRRs decreased in subsequent cycles
  - Hematological adverse events were not common
- No tumor shrinkage; 3 transient PET responses at higher doses

ClinicalTrials.gov number, NCT02642016
Dose-related and Sustained Decreases in Plasma Tryptase Levels in Patients at Doses ≥ 4.5 mg/kg

- Decreased tryptase concentrations after CDX-0158 administration suggest a rapid reduction in mast cell number/activity, consistent with effects on mast cells in preclinical models.
- Sustained increases in SCF concentrations at doses ≥ 4.5 mg/kg, consistent with complete target engagement.

ClinicalTrials.gov number, NCT02642016
Reengineering of CDX-0158: CDX-0159 Modifications to Eliminate Fc Receptor Binding and Improve PK

CDX-0159 is a more potent wildtype KIT inhibitor than small molecule tyrosine kinase inhibitors

CDX-0159 Does Not Induce Degranulation of FcγRI-expressing Human Mast Cells

CDX-0159 Does Not Have Fc Receptor-dependent KIT Agonist Activity

CDX-0159 Has Enhanced PK Properties in Cynomolgus Monkeys
Summary

- Preclinical and clinical data suggest that targeting KIT with CDX-0158 modulates mast cell numbers and activity.
- The Fc-modified next-generation anti-KIT mAb, CDX-0159, retains the ability to potently inhibit KIT while having attributes consistent with improved safety and enhanced pharmacokinetic profiles.
- Collectively, data support investigation of CDX-0159 in mast cell-related diseases, such as chronic spontaneous urticaria where mast cells play a central role in disease pathophysiology.

CDX-0159 Clinical Development Plan

**Phase I Single Ascending Dose Escalation Study in Healthy Subjects**
- Planned initiation: November 2019
- Key readouts: Safety, PK, Biomarkers

**Phase Ib Multiple Ascending Dose Study in Patients with Chronic Spontaneous Urticaria**
- Planned initiation: 2H2020
- Key readout: preliminary efficacy (clinical PoC)
We thank the patients who participated in the CDX-0158 phase I study and their families!

**CDX-0158 Phase I Investigators**
- Andy Wagner, MD, PhD (Dana-Farber Cancer Institute)
- Mike Heinrich, MD (Oregon Health & Science University)
- Johanna Bendell, MD (Sarah Cannon Research Institute)

**Collaborators**
- Joseph Schlessinger, PhD (Yale)
- Cheryl London, DVM, PhD, DACVIM (Ohio State)
- Carol Reiner, DVM, PhD, DACVIM (Missouri)

We also thank the rest of the Celldex team for helping to make this presentation possible