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

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Abstract D100

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.
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- Laura Mills-Chen – Employment/Stock - Celldex Therapeutics, Inc.
- Russell Hammond – Employment/Stock - Celldex Therapeutics, Inc.
- Tibor Keler – Employment/Leadership/Stock - Celldex Therapeutics, Inc.
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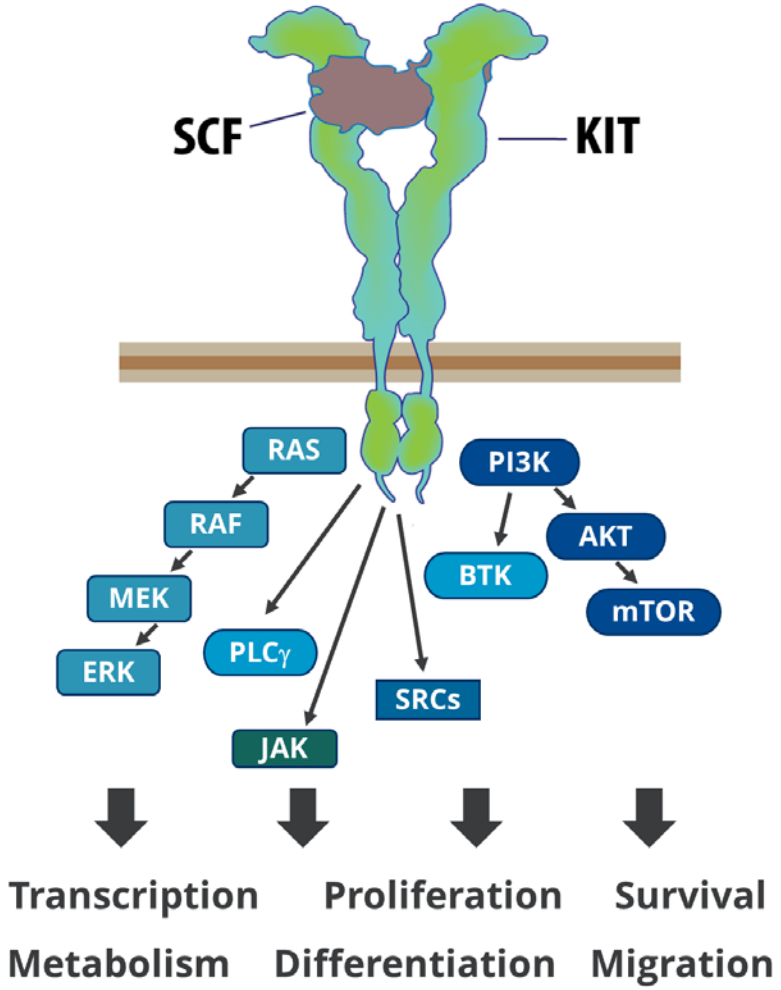
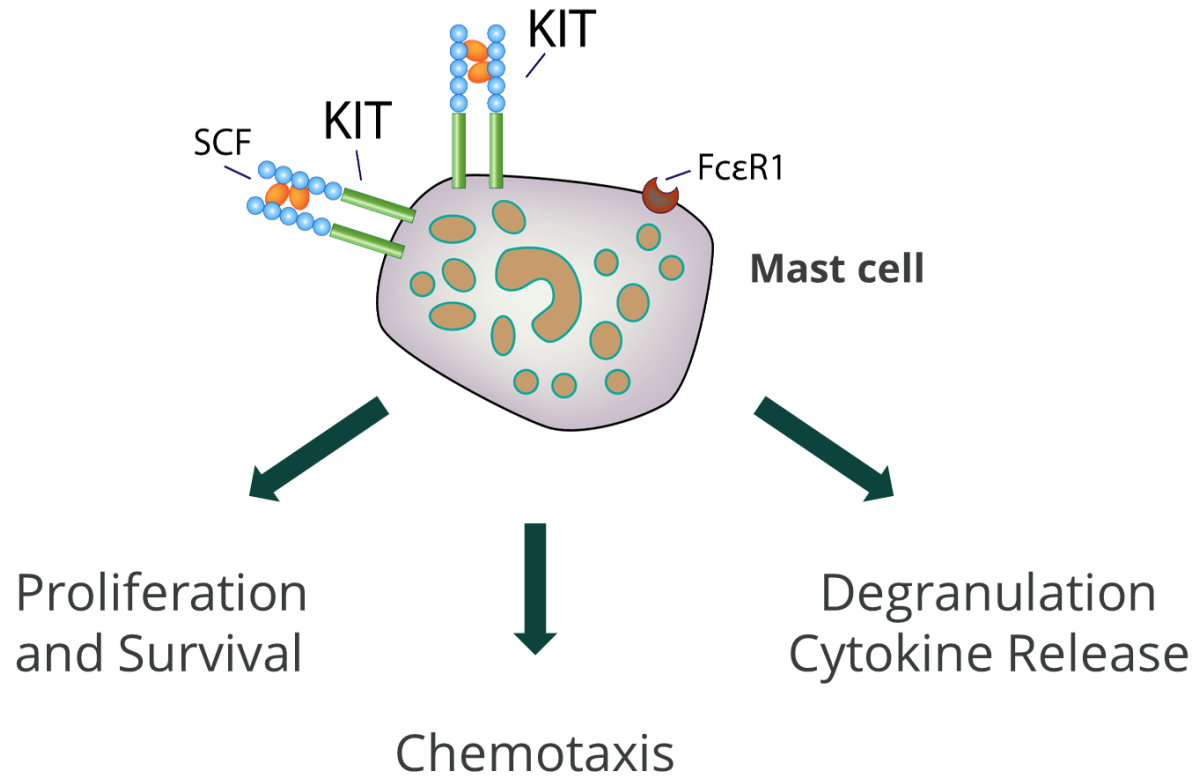
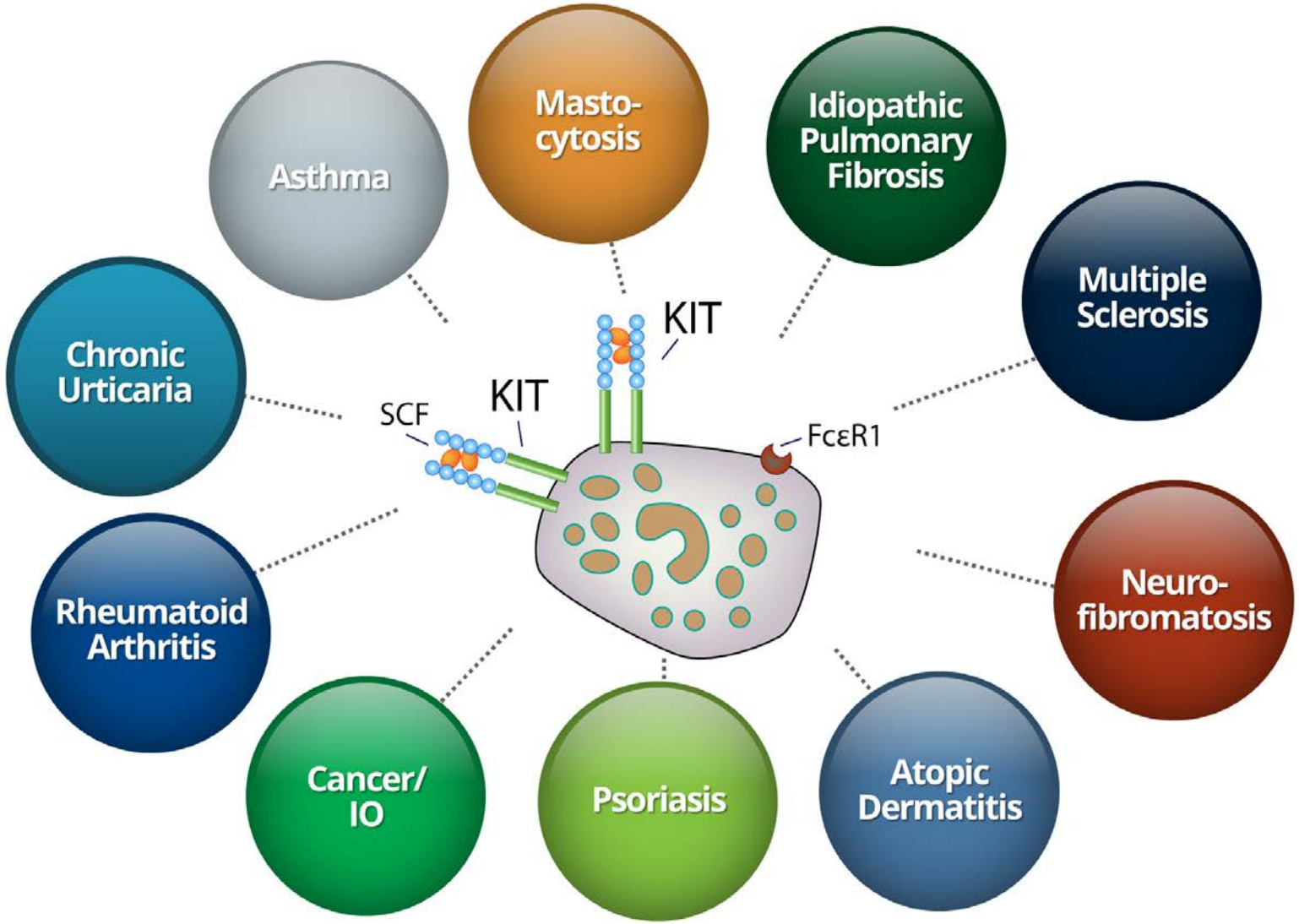
The Receptor Tyrosine Kinase KIT Plays a Central Role in Regulating Mast Cell Function and Activity



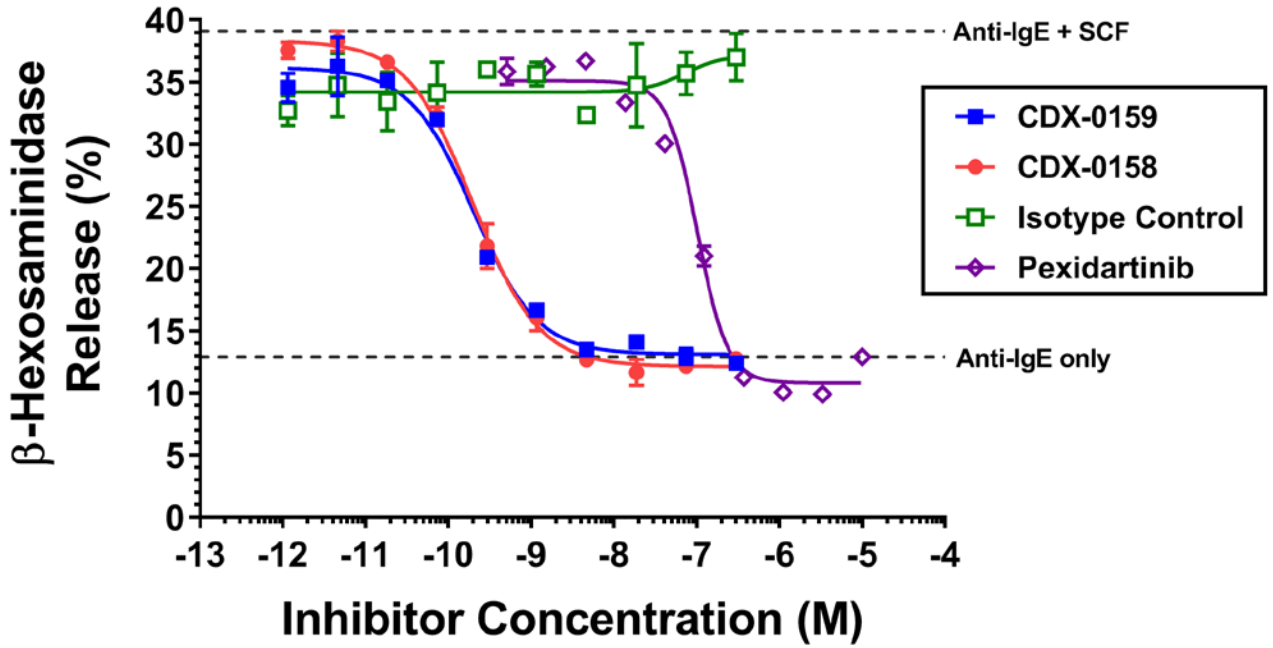


Targeting KIT Represents a Unique Strategy in Diseases Involving Mast Cells



CDX-0159 is a Potent Inhibitor of KIT-Mediated Effects on Mast Cell Degranulation

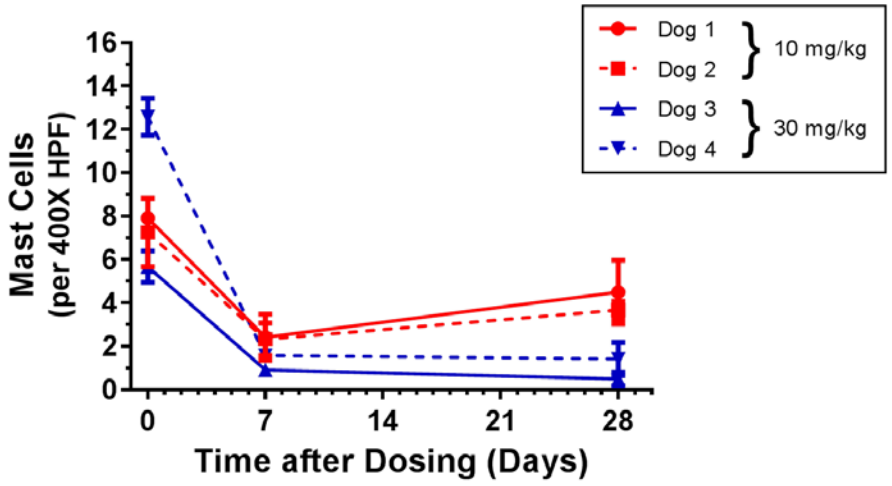
Human Mast Cell Degranulation *In Vitro*



KIT activation by SCF has a costimulatory effect on mast cells, augmenting FcεRI-induced degranulation, which is inhibited by CDX-0159 and CDX-0158

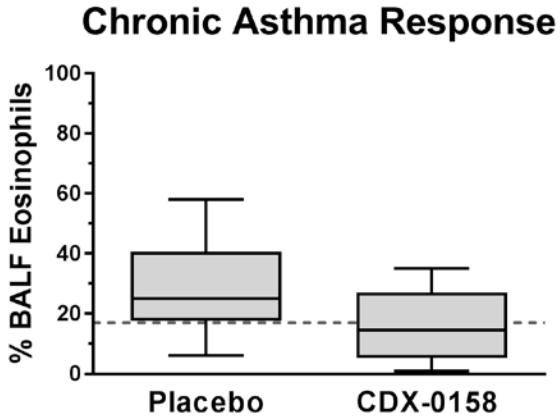
CDX-0158, the Predecessor to CDX-0159, Modulates Mast Cell Activity *In Vivo*

Rapid Reduction of Skin Mast Cells in Healthy Dog Skin



(London et al., Clin Cancer Res 2017)

Reduction of Airway Eosinophilia in a Feline Allergic Asthma Model

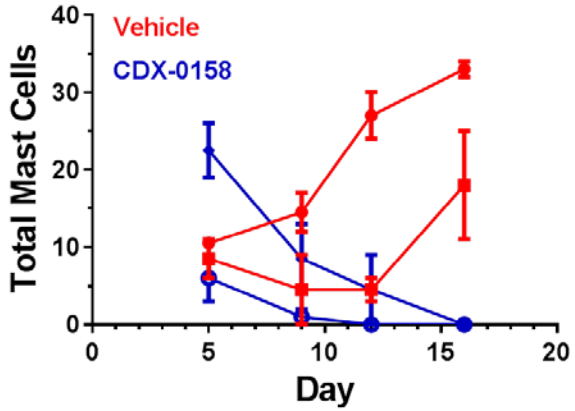


n = 10

- Chronic phase assessed 2 weeks after second CDX-0158 dose
- Similar effects observed in acute asthma setting (24 hours post-dose)

(Mandel et al., 2014 ACAAI Annual Meeting)

Decreased Mast Cell Recruitment to Wound Edges in Monkey Skin

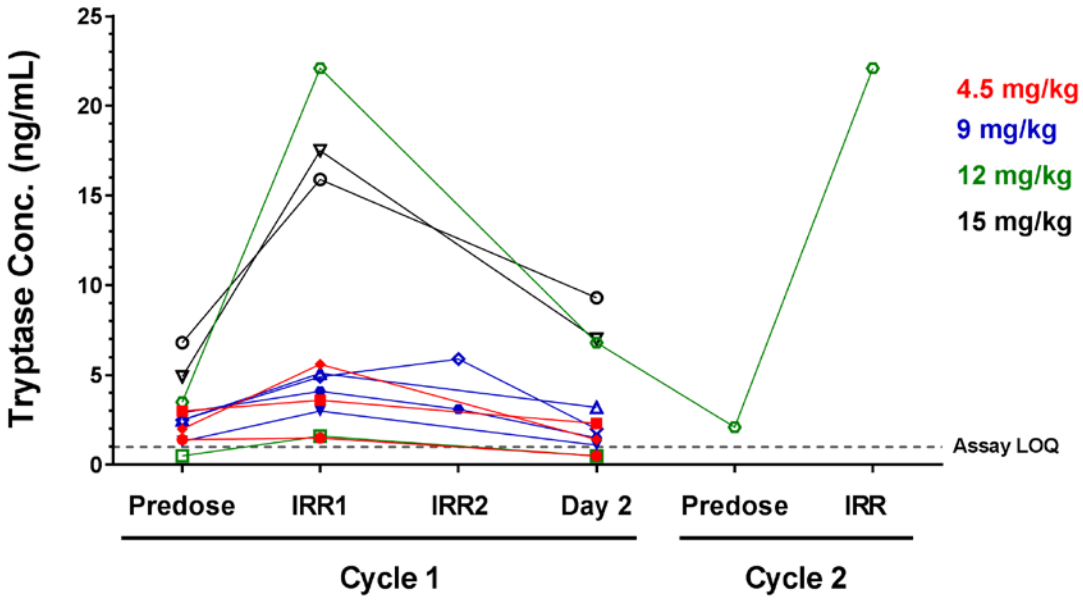


Establishes preclinical proof-of-concept for KIT inhibition leading to reduced mast cell numbers and activity, which can potentially ameliorate mast cell-mediated diseases

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**

Transient Increases in Serum Tryptase in Phase I GIST Patients Experiencing IRRs



ClinicalTrials.gov number, NCT02642016

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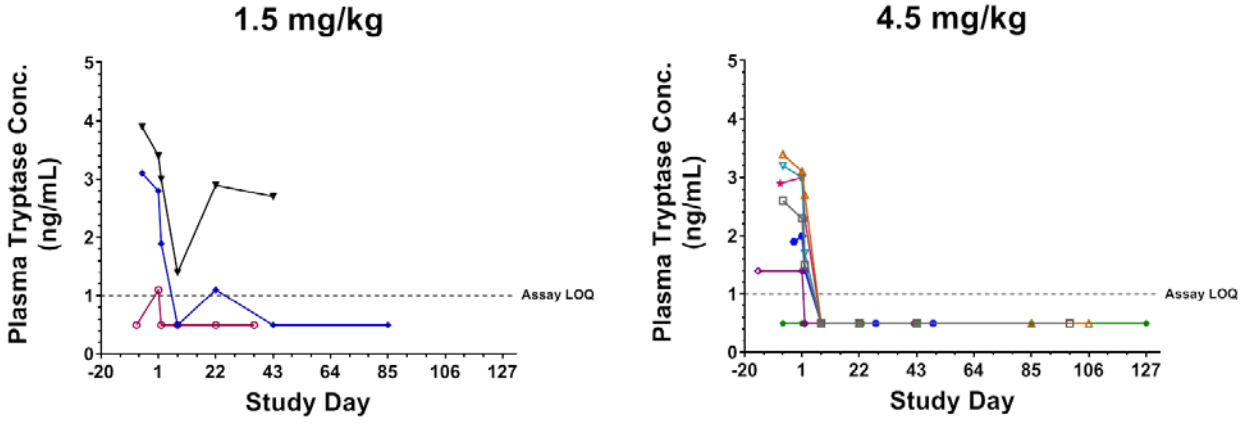
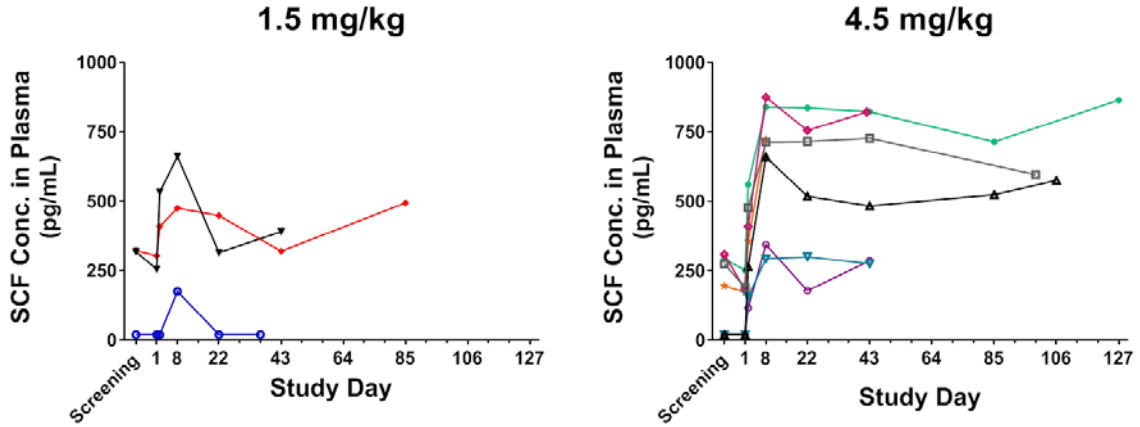
Dose-related and Sustained Decreases in Plasma Tryptase Levels in Patients at Doses ≥ 4.5 mg/kg

Total Tryptase
(Biomarker for Mast Cell Numbers/Activity)



Stem Cell Factor (SCF; KIT Ligand)
(Biomarker for KIT Engagement)

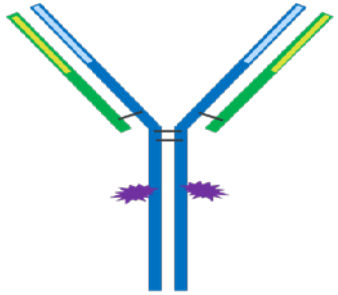


- Decreased tryptase concentrations after CDX-0158 administration suggest a rapid reduction in mast cell number/activity, consistent with effects on mast cells in preclinical models
- Sustained increases in SCF concentrations at doses ≥ 4.5 mg/kg, consistent with complete target engagement

ClinicalTrials.gov number, NCT02642016

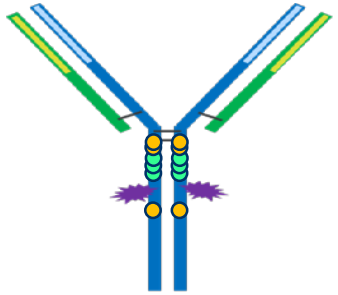
Reengineering of CDX-0158: CDX-0159 Modifications to Eliminate Fc Receptor Binding and Improve PK

CDX-0158



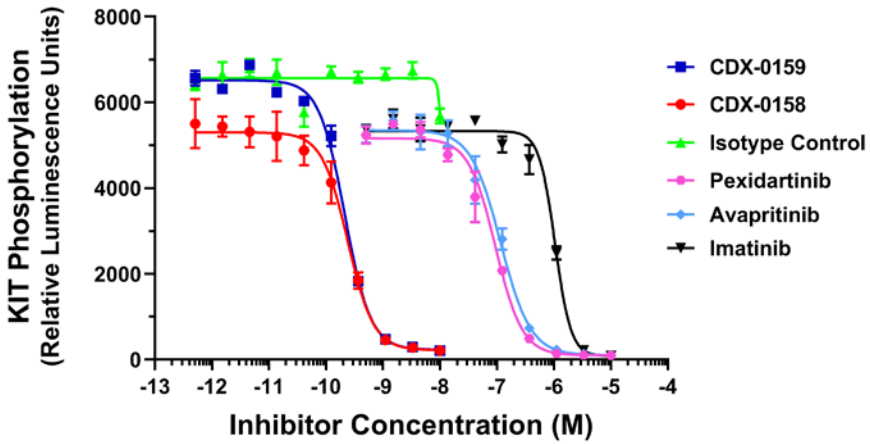
Wildtype IgG1

CDX-0159



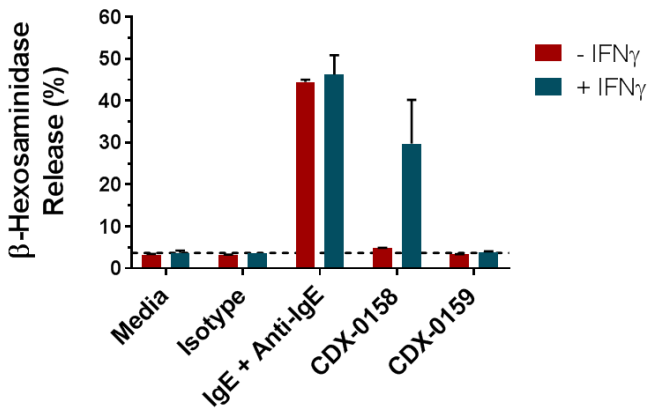
Fc-modified IgG1
(New Molecular Entity)

CDX-0159 Modifications Do Not Affect Its Ability to Inhibit KIT

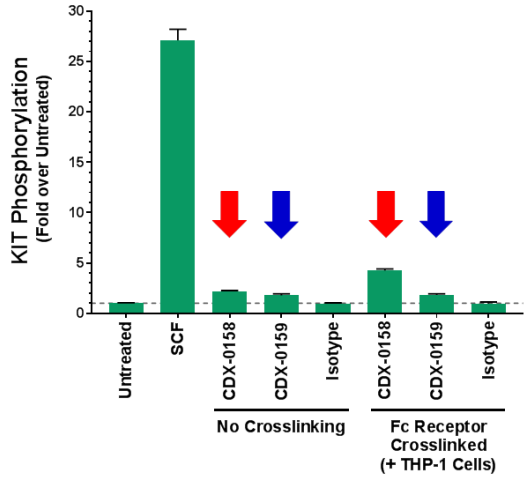


CDX-0159 is a more potent wildtype KIT inhibitor than small molecule tyrosine kinase inhibitors

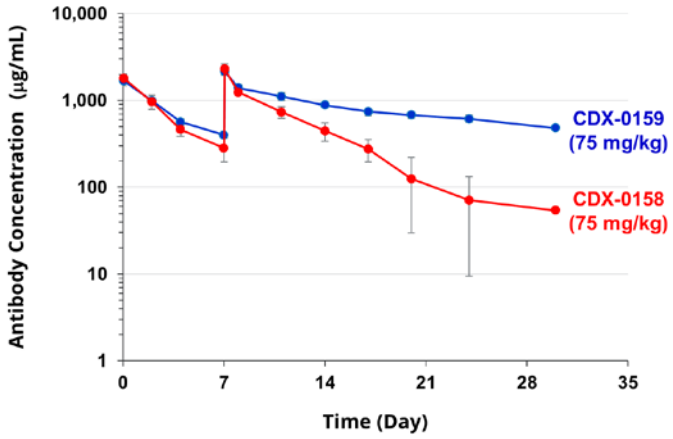
CDX-0159 Does Not Induce Degranulation of FcγRI-expressing Human Mast Cells



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



CDX-0159 Has Enhanced PK Properties in Cynomolgus Monkeys



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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)

Acknowledgements

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CDX-0158 Phase I Investigators

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Johanna Bendell, MD (Sarah Cannon Research Institute)

Collaborators

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Cheryl London, DVM, PhD, DACVIM (Ohio State)

Carol Reinero, DVM, PhD, DACVIM (Missouri)

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