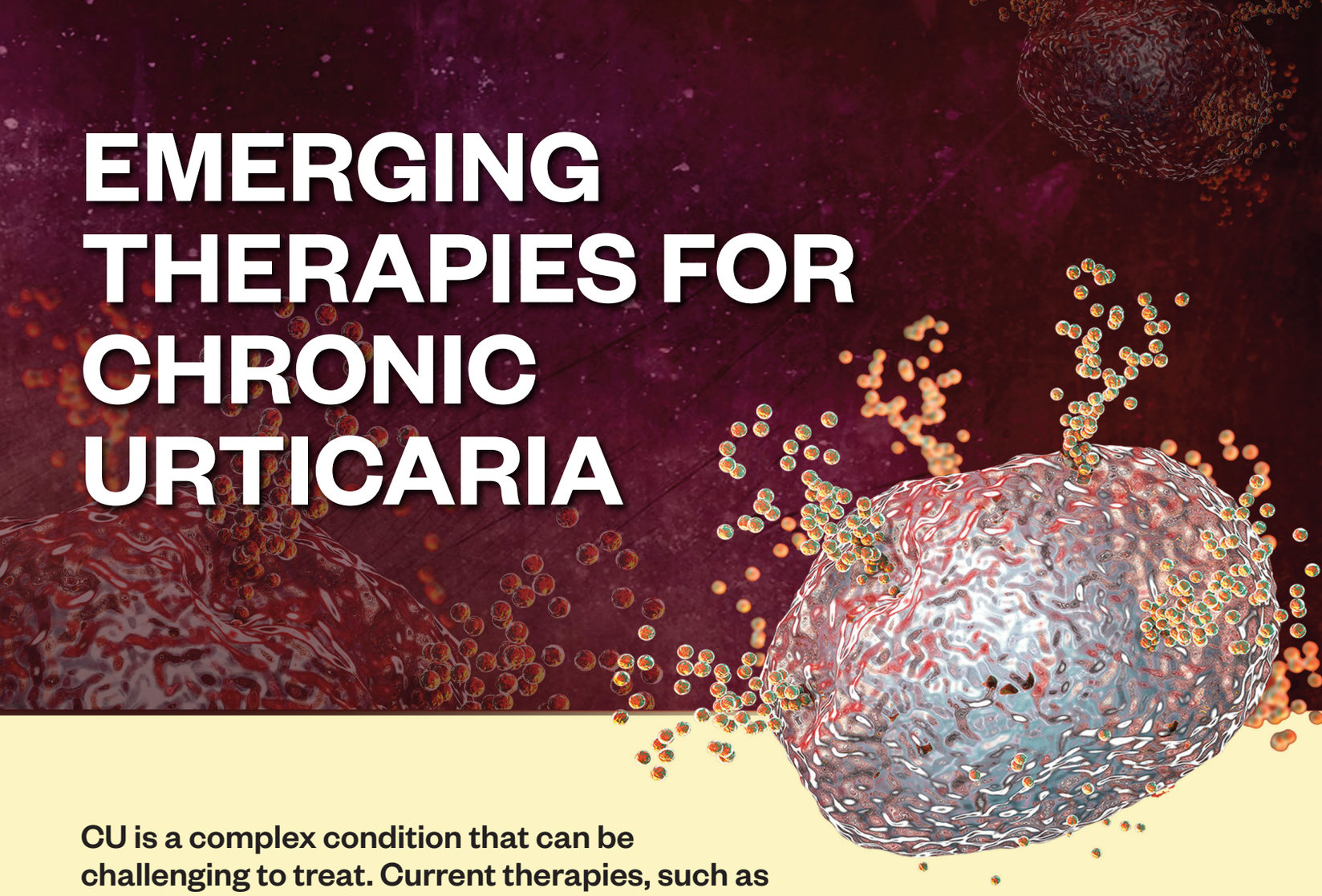
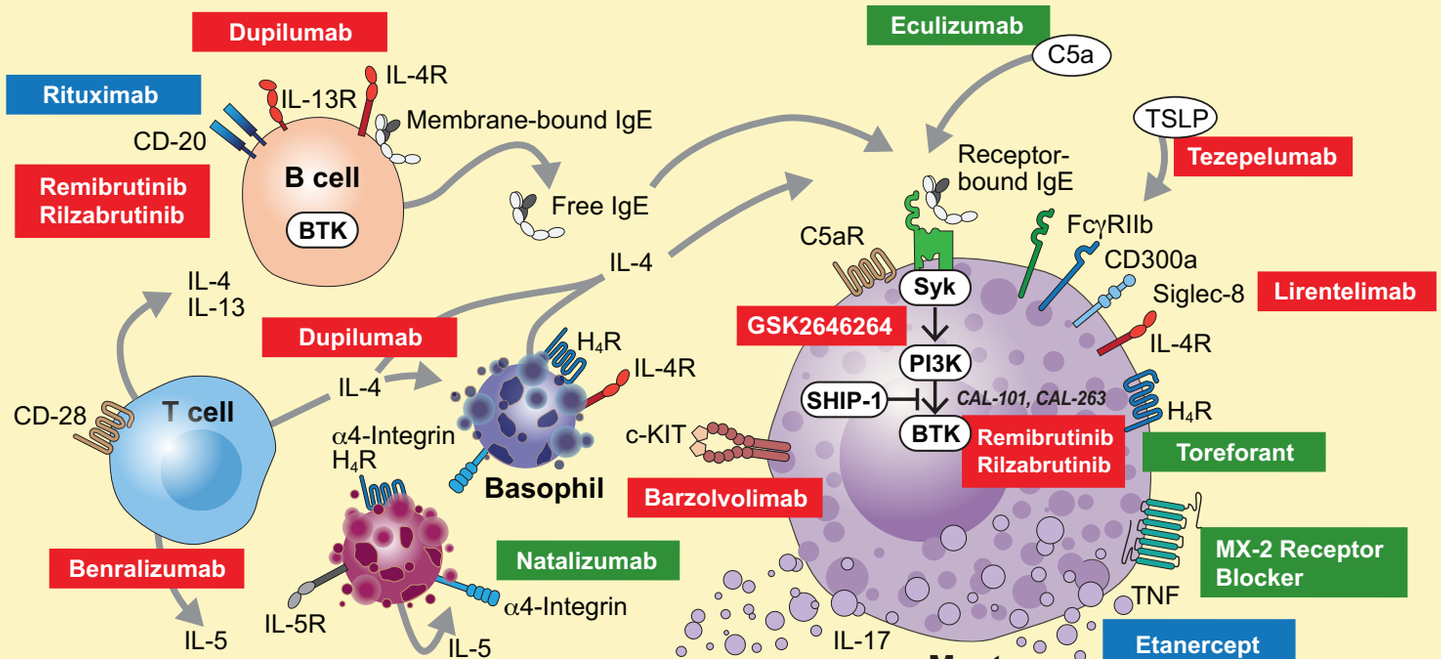
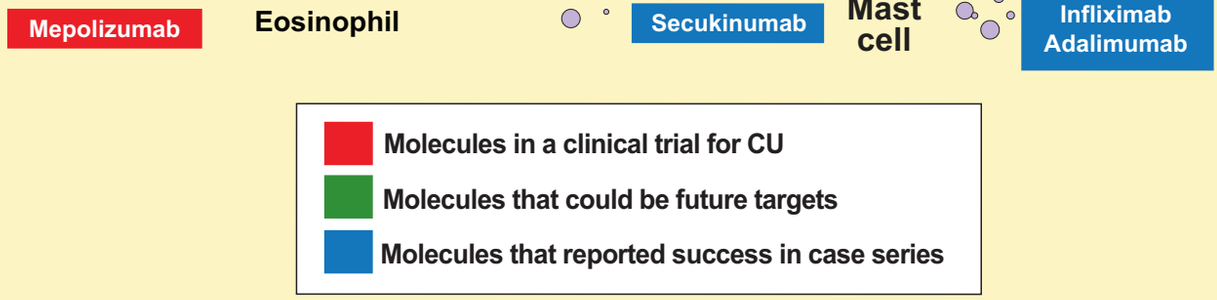
EMERGING THERAPIES FOR CHRONIC URTICARIA



CU is a complex condition that can be challenging to treat. Current therapies, such as antihistamines and anti-IgE therapy, can be effective for some patients but many patients may be refractory to treatment or experience side effects.

Fortunately, there are several emerging therapies that are currently being studied for the treatment of CU. These therapies are based on new and innovative mechanisms of action and offer the potential for improved outcomes for patients. Some of these emerging therapies include biologic agents that target specific immune pathways, such as the IL-4/IL-13 pathway, as well as small molecule inhibitors of other key signaling pathways.





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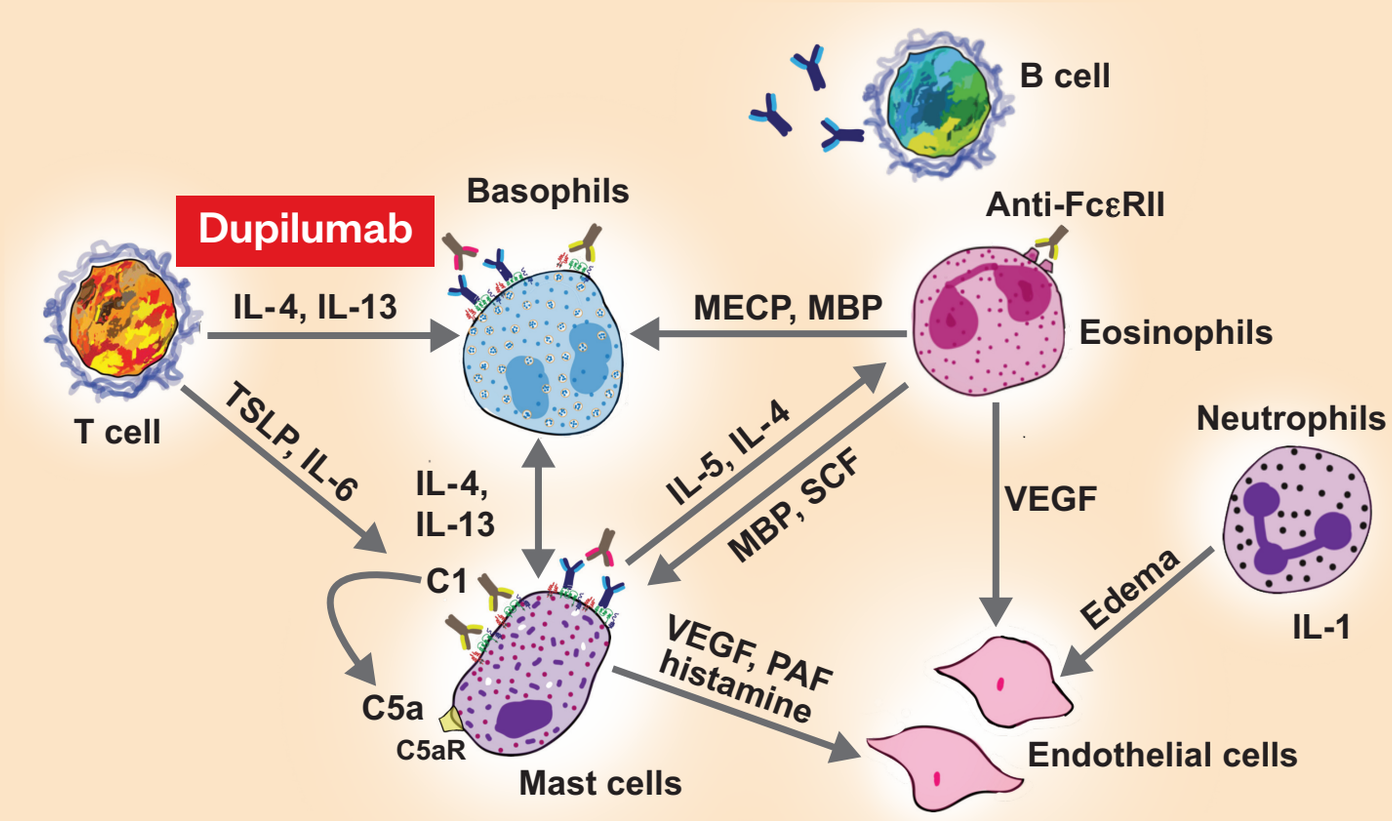
Anti–IL-4/-13: Dupilumab



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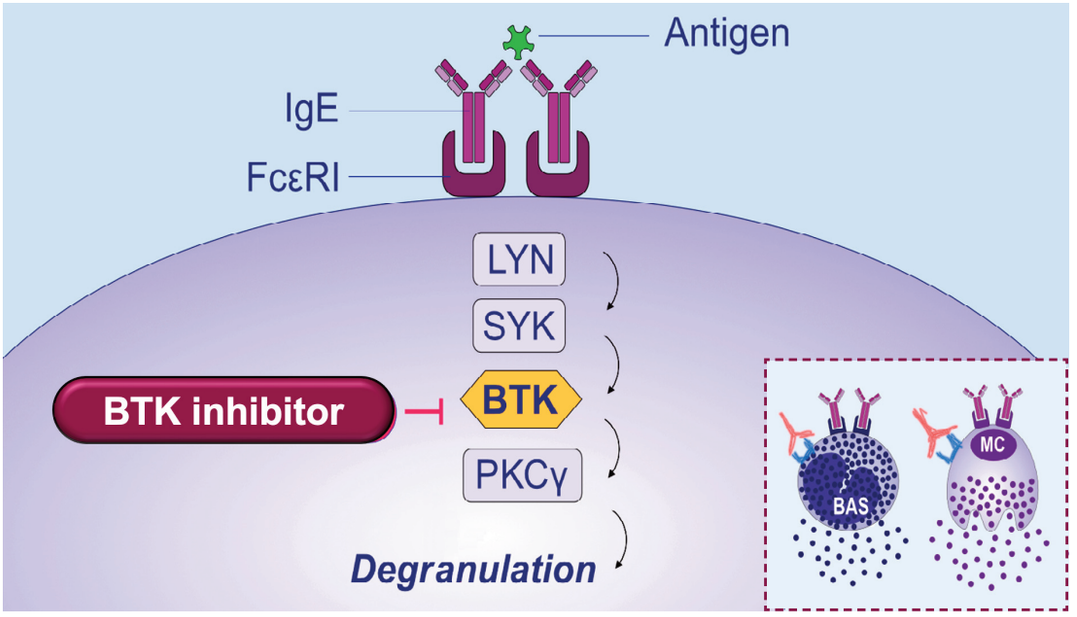
- Dupilumab is a fully human mAb directed against the IL-4 receptor α subunit and inhibits signaling of both IL-4 and IL-13
- IL-4 and IL-13 play a major role in type 2 inflammation and atopic conditions such as atopic dermatitis and asthma
  - Produced by Th2-polarized T cells, granulocytes, and monocytes/macrophages
  - Activate:
    - Th2 T-cell differentiation
    - M2 macrophage polarization
    - MHCII expression
    - B cell and plasma cell differentiation
  - Amplify IgE production
- IL-4 levels are elevated in patients with CSU compared with control patients

Status	Study Title	Phase (Study Name)	Condition	Interventions	Trial Identifier
Active, not recruiting	Cholinergic Urticaria–Efficacy of Dupilumab	Phase 2 (CHED)	CholU	Dupilumab Placebo	NCT03749148
Active, not recruiting	Dupilumab for the Treatment of Chronic Inducible Cold Urticaria in Patients Who Remain Symptomatic Despite the Use of H_1-antihistamine	Phase 3 (LIBERTY-CINDU CUrIADS)	ColdU	Dupilumab + nonsedating H_1-antihistamine Placebo + nonsedating H_1-antihistamine	NCT04681729
Complete	Dupilumab in Chronic Spontaneous Urticaria	Phase 2 (DUPICSU)	CSU Recurrent angioedema	Dupilumab Placebo	NCT03749135
Active, not recruiting	Dupilumab for the Treatment of Chronic Spontaneous Urticaria in Patients Who Remain Symptomatic Despite the Use of H_1-antihistamine and Who Are Naive to, Intolerant of, or Incomplete Responders to Omalizumab	Phase 3 (LIBERTY-CSU CUPID)	CSU	Dupilumab + nonsedating H_1-antihistamine Placebo + nonsedating H_1-antihistamine	NCT04180488

LIBERTY-CSU CUPID Study A

Patient Population	• 138 patients, aged ≥6 years with CSU who remained symptomatic despite treatment with antihistamines	
Efficacy: Itch Severity	• 63% reduction with dupilumab vs 35% with placebo • 10.24-point reduction with dupilumab vs 6.01-point reduction with placebo ($p < .001$)	**Primary endpoint US**
Efficacy: Urticaria Activity	• 65% reduction with dupilumab vs 37% with placebo • 20.53-point reduction with dupilumab vs 12.00-point reduction with placebo ($p < .001$)	**Primary endpoint EU**
Safety	• TEAE rates were comparable between the dupilumab and placebo groups (50% dupilumab vs 58.8% placebo) • **Most common TEAE was injection site reactions** (11.4% dupilumab vs 13.2% placebo) • Conjunctivitis: (0 dupilumab vs 1.5% placebo) • **Serious TEAEs:** (2.9% dupilumab vs 7.4% placebo)	

BTK Inhibitor: Remibrutinib



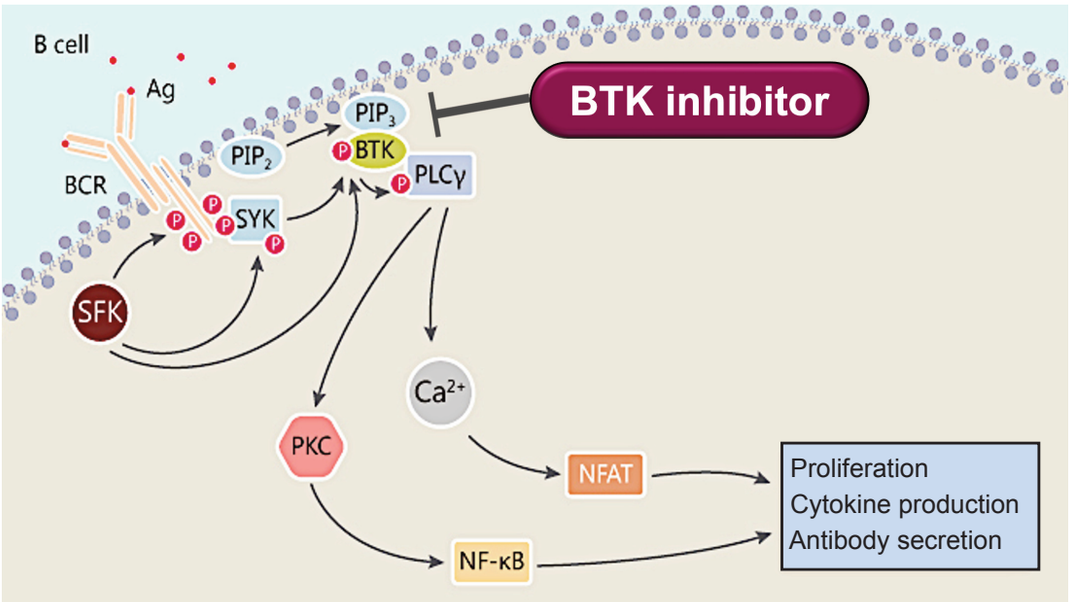


Image adapted for educational purposes only from Carvallo A, et al. *Allergy*. 2023;78:603-605 and Jenner E. Immune System Research. https://www.immune-system-research.com/inflammation/skin-inflammation-inflammation/remibrutinib-is-an-orally-active-btk-inhibitor-for-the-chronic-urticaria-treatment/2019-11-09/.

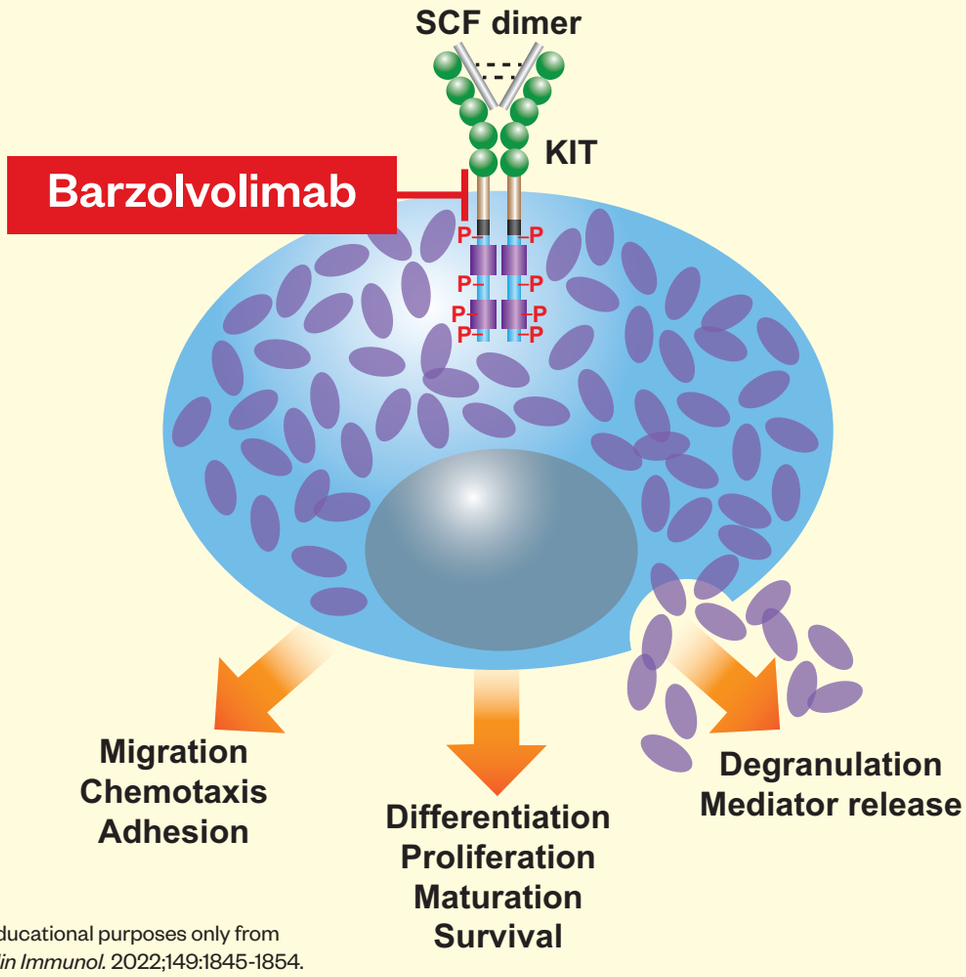
- Remibrutinib is a selective, potent, oral, covalent BTK inhibitor that is in development for the treatment of autoimmune disorders, including CSU
- BTK plays a crucial role in FcεRI-mediated mast cell activation and B-cell maturation and function
- BTK inhibitors can:
  - Prevent IgE-mediated mast cell/basophil degranulation and cytokine generation
  - Suppress B-cell antibody production
- In phase 2 studies of patients with CSU, remibrutinib demonstrated both efficacy and safety:
  - Rapid improvement in UAS7 scores as early as week 1
  - 60% of patients reached UAS7 = 0
  - Most common AEs were headache, nasopharyngitis, infections, and skin/subcutaneous tissue reactions

Remibrutinib: Ongoing Studies in CSU

Status	Study Title	Intervention(s)	Phase	Trial Identifier

Available	Global Managed Access Program Cohort for Remibrutinib in Adult Patients With Chronic Spontaneous Urticaria	Remibrutinib	N/A	NCT05170724
Not yet recruiting	An Extension Study of Long-term Efficacy, Safety and Tolerability of Remibrutinib in Chronic Spontaneous Urticaria Patients Who Completed Preceding Studies With Remibrutinib	Remibrutinib (blinded) Placebo Remibrutinib (open-label)	3	NCT05513001
Active, not recruiting	A Safety and Efficacy Study of Remibrutinib in the Treatment of CSU in Japanese Adults Inadequately Controlled by H_1-antihistamines (BISCUIT)	Remibrutinib	3	NCT05048342
Active, not recruiting	A Phase 3 Study of Efficacy and Safety of Remibrutinib in the Treatment of CSU in Adults Inadequately Controlled by H_1-antihistamines (REMIX-1)	Remibrutinib (blinded) Placebo Remibrutinib (open-label)	3	NCT05030311
Active, not recruiting	A Phase 3 Study of Efficacy and Safety of Remibrutinib in the Treatment of CSU in Adults Inadequately Controlled by H_1-antihistamines (REMIX-2)	Remibrutinib (blinded) Placebo Remibrutinib (open-label)	3	NCT05032157

c-KIT Inhibitor: Barzolvolimab



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- Barzolvolimab is a humanized mAb that specifically binds the receptor tyrosine kinase c-KIT
- Binding of SCF to c-KIT activates signaling pathways and leads to cell proliferation, survival, differentiation, and migration

- Mast cells express high levels of c-KIT even after differentiation, distinguishing them from other mature immune cells
- SCF/c-KIT induces mast cell migration and invasion into specific tissues through SCF chemotaxis
- In a study of 21 patients who received single IV infusion barzolvolimab 3 mg/kg (11 with ColdU and 10 with SDerm):
  - Complete response by provocation testing occurred in:
    - 100% of ColdU group
    - 90% of SDerm group
  - Response was sustained 77 days in those with ColdU, 57 days in those with SDerm
  - Marked depletion of skin mast cells and serum tryptase was seen
  - Barzolvolimab was well tolerated, with the most common AEs being reversible hair color changes and taste disorders due to inhibition of KIT signaling in other cells

Barzolvolimab: Ongoing Studies

Status	Study Title	Interventions	Phase	Trial Identifier
Recruiting	A Phase 2 Study of CDX-0159 in Patients With Chronic Spontaneous Urticaria	Barzolvolimab Placebo	2	NCT05368285
Recruiting	A Study of CDX-0159 in Patients With Chronic Inducible Urticaria	Barzolvolimab Placebo	2	NCT05405660

Anti–Siglec-8: Lirentelimab

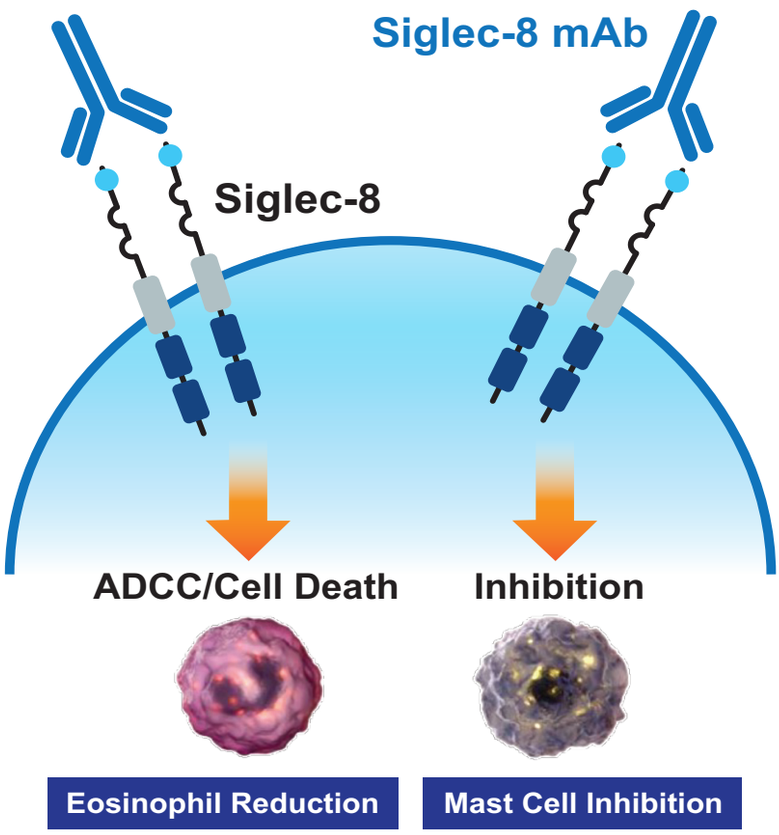


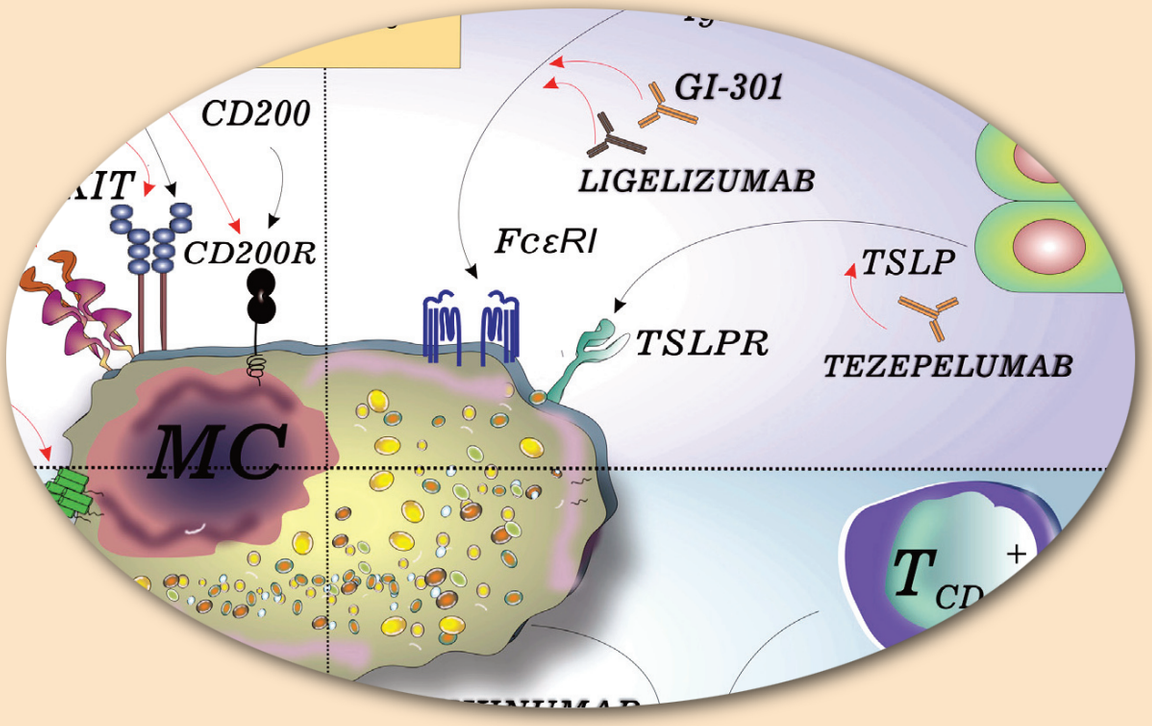
Image reproduced for educational purposes only Youngblood BA, et al. *Cells*. 2020;10:19.

- Lirentelimab is humanized, nonfucosylated IgG1 mAb against Siglec-8
- Siglec-8 is an inhibitory receptor selectively expressed on mast cells, eosinophils and, to a lesser degree, basophils
- Siglec-8 engagement by antibodies has been shown to inhibit mast cell activation and induce apoptosis in eosinophils
- In a phase 2, open-label, proof-of-concept study of lirentelimab for antihistamine-resistant CSU and CIndU, complete response was seen at week 22 in:
  - Omalizumab-naive, 92% (95% CI, 64%-100%)
  - Omalizumab-refractory, 36% (95% CI, 11%-69%)
  - CholU, 82% (95% CI, 48%-98%)
  - SDerm, 40% (95% CI, 12%-74%)

	CSU			CIndU	
Parameter	Omalizumab-Naive	Omalizumab-Refractory	Omalizumab-Naive and Refractory	CU	SDerm
UCT score change from baseline, n	13	11	24	11	10

- Most common AEs were infusion-related reactions (43%), nasopharyngitis (21%), and headache (19%)

Anti-TSLP: Tezepelumab



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- Tezepelumab is a human anti-TSLP mAb that is designed to specifically bind to human TSLP and prevent interaction with its receptor complex

- Mast cells express TSLP receptors
- TSLP is markedly upregulated in the wheals of patients with CSU
- Tezepelumab is efficacious for the treatment of patients with asthma
  - Decreases blood eosinophil counts and total serum IgE levels
  - Most common AEs associated with tezepelumab in asthma studies were pharyngitis, arthralgia, and back pain

Tezepelumab: Ongoing Study

Status	Study Title	Condition	Interventions	Trial Identifier
Active (not recruiting)	Study to Evaluate Tezepelumab in Adults With Chronic Spontaneous Urticaria (INCEPTION)	CSU	Tezepelumab dose 1 Tezepelumab dose 2 Omalizumab Placebo	NCT04833855

Abbreviations

ADCC: antibody-dependent cellular cytotoxicity
AE: adverse event
Ag: antigen
BAS: basophil
BCR: B-cell receptor
BTK: Bruton tyrosine kinase
C1: complement 1
C5a: complement 5 fragment a
CD: cluster of differentiation
CIndU: chronic inducible urticaria
CholU: cholinergic urticaria
ColdU: cold inducible urticaria
CSU: chronic spontaneous urticaria
CU: chronic urticaria
H_1: histamine type 1
H_4R: histamine 4 receptor
Ig: immunoglobulin
IL: interleukin
IV: intravenous
LYN: LYN proto-oncogene
mAb: monoclonal antibody
MBP: major basic protein
MC: mast cell
MECP: mature eosinophil cationic protein
MHCII: major histocompatibility complex class II
N/A: not applicable
NFAT: nuclear factor of activated T cells
NF-κB: nuclear factor kappa B
P: phosphorylated tyrosine
PAF: platelet-activating factor
PI3K: phosphoinositide 3-kinase
PIP2: phosphatidylinositol bisphosphate
PIP3: phosphatidylinositol trisphosphate
PKC: protein kinase C
R: receptor
SCF: stem cell factor
SDerm: symptomatic dermographism
SFK: Src family kinase
SHIP-1: Src-homology-containing inositol phosphatase 1
Siglec: sialic acid-binding immunoglobulin-like lectin
Syk: spleen tyrosine kinase
TEAE: treatment-emergent adverse event
Th2: T helper 2
TNF: tumor necrosis factor
TSLP: thymic stromal lymphopoietin
UAS7: Urticaria Activity Score summed over 7 days
UCT: Urticaria Control Test
VEGF: vascular endothelial growth factor

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