Biologics and OIT

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OUtMATCH Study

- Three parts or stages

- Stage 1 complete - OUtMATCH study in NEJM
  - 1st 60 subjects enrolled into OLE then stage 3
  - Subjects 61-225 into Stage 2
- Stage 2: in progress, should complete Aug 24, data by AAAAI 25
- Stage 3: 3 plans: Diet Plan, Rescue OIT Plan, Food Avoidance Plan

OUtMATCH Stage 1

- Fail DBPCFC to peanut and at least 2 other foods
- Omalizumab or placebo every 2-4 weeks for 16-20 weeks
- Oral food challenges x 4, placebo and 3 food allergens.
- Primary endpoint, % tolerating 600 mg peanut protein w/out DLS
- Secondary endpoints: % tolerating at least 1000 mg cashew, egg and milk
- Other secondary endpoints % tolerating at least 1000 mg walnut, hazelnut, wheat

OUtMATCH Stage 1

	• Omalizumab	Placebo	Diff	P Value
• Peanut 600 mg	79/118 (67)	4/59 (7)	60	<0.001
• Cashew 1000 mg	28/68 (41)	1/31 (3)	38	<0.001
• Egg 1000 mg	34/51 (67)	0//20 (0)	67	<0.001
• Milk 1000 mg	27/41 (66)	2/21 (10)	56	<0.001
• Walnut 1000 mg	30/47 (64)	4/31 (13)	51	
• Hazelnut 1000 mg	11/17 (65)	1/7 (14)	50	
• Wheat 1000 mg	9/12 (75)	1/8 (13)	63	

Anti-IgE

- Omalizumab-Stanford (Nadeau)-to see if Omalizumab combined with multifood OIT benefited multifood allergic pt
  - 2-5 food OIT (confirmed by DBPCFCs)
  - Omalizumab SC for 16 weeks, OIT started week 8
  - Oma/placebo stopped 20 wks before exit DBPCFC, wk 36
  - 83% Oma vs 33% placebo passed FC to 2 g protein for ≥ 2 of their foods

- Ligelizumab: Novartis- humanized IgG mAb binds to C3 region. Phase 3 study stopped temporarily and restarted with different dosing regiment.

- Talizumab (TNX-901)- Precursor to OMA. Leung reported in 2003 increased reaction-eliciting dose from baseline after 12 wks of TNX-901

- UB-221: promising anti-IgE antibody, 8x more effective at binding IgE than OMA. Phase 1 CIU study. Promising in FA

Dupilumab

- Phase 2 and Phase 3 studies ongoing
- Mayo Clinic- Dupi as an adjunct to Milk OIT to see if Dupi compared to placebo reduces GI side effects and prevents the development of EoE (MAGIC Study)
- Stanford-Phase 2: Primary objective is to see if Dupi as and adjunctive therapy to milk OIT compared to placebo improves safety and rates of desensitization. Percent of pts at week 18 that pass a 2040 mg cumulative milk protein graded challenge.
- Dupilumab monotherapy in peds w/PN allergy. Pass DBPCFC @ 24 wks, 444 mg cumulative. Finished, not published
- Dupilumab as adjunct to AR101 (Peanut OIT)
- COMBINE Study-omalizumab &/or dupilumab with multifood OIT, 4-55

On The Horizon

- Immunoglobulin E Disruptors
  - DARPins-disrupt preformed IgE:FceRI complexes as well as inhibiting binding
  - Could reduce risk of reactions, inhibit anaphylactic signaling pathways (rescue therapy)

- Anti-alarmins
  - Tezepelumab-potential candidate for future FA trials
  - Etokimab- anti-IL 33. Single dose allowed 73% and 57% of pts to tolerate 275 mg peanut protein by days 15 and 45.
  - Blocking TSLP or IL 33 or IL 25 alone dose not block development of egg allergy in mouse studies. Cocktail of all 3 may block development

On The Horizon

- Bruton Tyrosine Kinase Inhibitors
  - Promise in rapidly and transiently blocking IgE mediated reactions
  - Reduce the risk of AEs during OIT and prevent IgE-mediated anaphylaxis
  - Acalabrutinib-Phase 2 study to show 4 oral doses prevent anaphylaxis in OFC to PN/TN
- Janus Kinase- Inhibitors
  - Abrocitinib-Phase 1 in 40 adults to determine change in basophil activation and SPT size after 4 months of 100 mg/d to determine potential in FA
- Nanoparticles
  - Potentially safer delivery of allergen to tolerogenic environments
  - Phase 2 study using IV nanoparticale encapsulated purified peanut extract to reduce risk of severe reaction

On The Horizon

- Sialic Acid-Binding Immunoglobulin-Like Lectins
  - Siglec-6: Allakos AK006. Humanized monoclonal antibody. Primary endpoint consume higher dose of peanut protein without DLS, > 10 fold over baseline at week 14
  - Siglec-8: lirentelimab, possible potential in FA