Priceless Protection or Costly Burden

Oral Immunotherapy With or Without the Use of Omalizumab

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Disclosures

Genentech

Overview

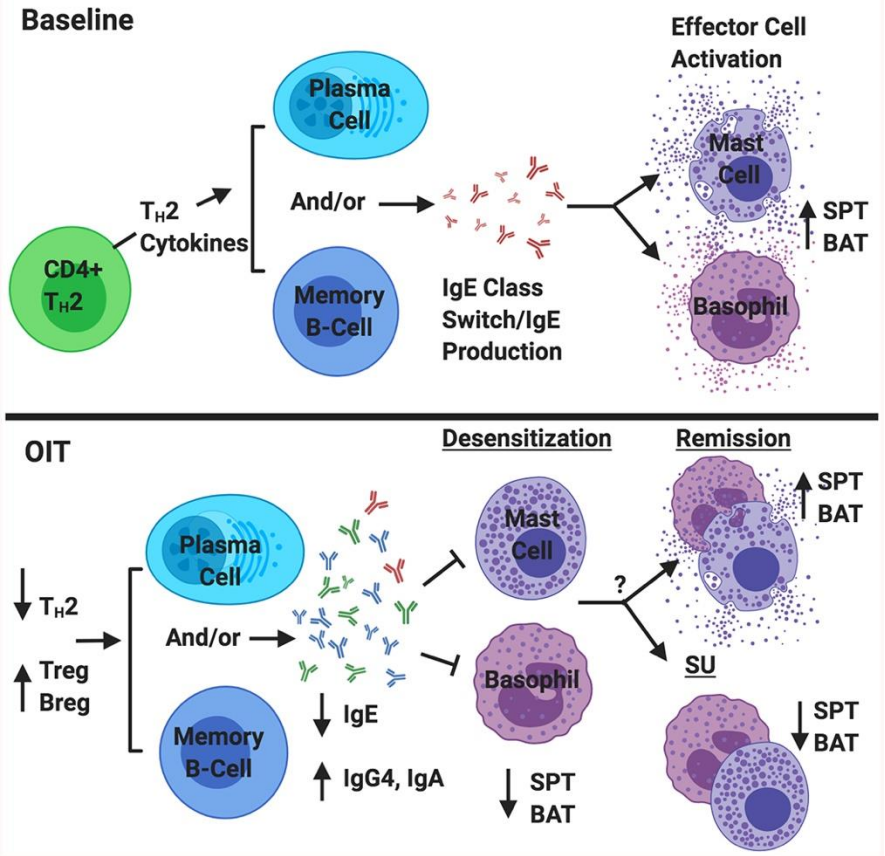
- Overview of OIT mechanism and safety
- Overview omalizumab mechanism and safety
- Review data on OIT + omalizumab
- Review OUtMATCH phase 2 data

OIT Overview

- What is it?
  - Therapeutic approach in which individuals with **IgE-mediated food allergies** consume small, gradually increasing doses of the allergenic food under medical supervision, with the goal of inducing desensitization
  - Typically involves an initial escalation phase, a build-up phase, and a maintenance phase, where a target dose is ingested daily to maintain desensitization
  - The primary aim is to increase the threshold of reactivity, thereby reducing the risk of severe reactions from accidental exposures, rather than achieving permanent tolerance in most patients.
  - Palforzia (peanut) is currently the only FDA-approved “drug”
    - Many allergists have used “off-the-shelf” foods to treat a wide variety of food allergens.

OIT Overview

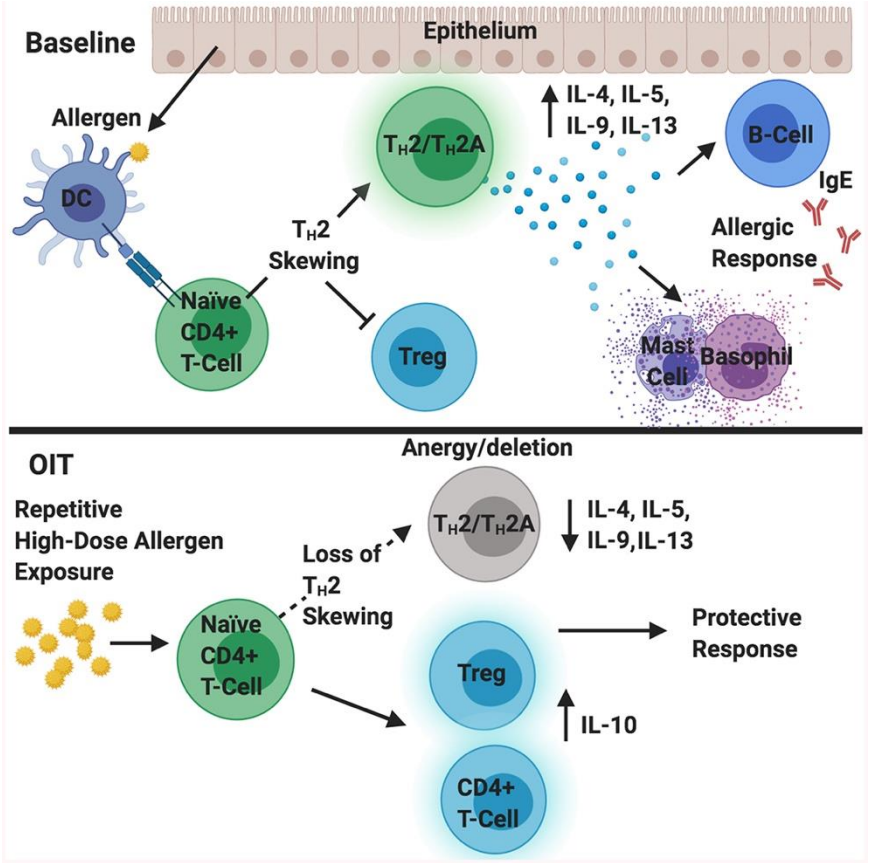
- How does it work?
  - The primary immunologic mechanisms include an initial rise and subsequent decline in allergen-specific IgE
  - Increased production of allergen-specific IgG4 and IgA (which act as blocking antibodies)
  - Basophil/mast cell hypo-responsiveness (IgE endocytosis)



Clin Exp Allergy. 2021 Apr;51(4):527-535. doi: 10.1111/cea.13824. Epub 2021 Jan 20.

OIT Overview

- How does it work?
  - Modulation of T-cell responses
    - specifically, a reduction in T helper 2 (Th2) cell activity and expansion of regulatory T cells.
  - These changes collectively reduce the likelihood and severity of allergic reactions upon accidental exposure, but ongoing daily ingestion is required to maintain desensitization; true long-term tolerance is rarely achieved



Clin Exp Allergy. 2021 Apr;51(4):527-535. doi: 10.1111/cea.13824. Epub 2021 Jan 20.

OIT Overview

- Efficacy
  - **Oral immunotherapy (OIT) is effective in inducing desensitization to food allergens, particularly peanut, cow's milk, and egg, in both children and adults.**
  - Difficult to quantify- various protocols, various foods
  - Peanut has been the most rigorously studied
  - Palforzia (maintenance dose of 300mg peanut protein)
    - 67% of treated children tolerated at least 600mg of peanut protein
    - 50% of treated children tolerated at least 1000mg of peanut protein
  - IMPACT Trial (peanut, 1-3 years of age)
    - 71% tolerated 5000mg of peanut protein vs 2% in Placebo after 134 weeks of therapy
    - 20% remained desensitized after 26 weeks of avoidance
  - Milk meta-analysis (19 RCTs)
    - Increased desensitization rates (RR 2.51, 95% CI: 1.54–4.09)
    - Raised food challenge thresholds (standard mean difference of 3.58)
    - Decreased sIgE and increased IgG4

N Engl J Med. 2018 Nov 22;379(21):1991-2001. doi: 10.1056/NEJMoa1812856.
Lancet. 2022 Jan 22;399(10322):359-371.
Front Immunol. 2025 Jun 4:16:1570050. doi: 10.3389/fimmu.2025.1570050.

OIT Overview

- Quality of Life Measures
  - **Oral immunotherapy (OIT) for food allergy is associated with significant improvements in quality of life (QoL) measures for both patients and their caregivers, particularly in pediatric populations.**
  - Large 2025 observational study of preschool-aged children
    - Parental food allergy-specific anxiety and QoL scores improved significantly during OIT build-up
    - Scores were maintained 12 months post-build-up
    - Greatest benefit seen in families of younger children and those with single-food allergies
  - 2020 study in school-aged children
    - Both child- and parent-reported QoL scores improved significantly from OIT initiation to maintenance
    - Parents tend to perceive greater QoL improvement than children themselves
  - Multiple studies confirm that OIT yields clinically meaningful improvements in health-related QoL compared to avoidance or placebo
    - some patients with good baseline QoL may experience transient deterioration during up-dosing, which typically reverses upon reaching maintenance

Clin Exp Allergy. 2025 Jul 4. doi: 10.1111/cea.70111.
Allergy. 2020 Oct;75(10):2623-2632. doi: 10.1111/all.14350.

OIT Overview

- Adverse Events
  - Similar problems as previous slide
  - OIT carries a risk of allergic reactions, including anaphylaxis and eosinophilic esophagitis, and requires careful patient selection and monitoring
  - 2019 meta-analysis (compared to placebo/avoidance)
    - Increased anaphylaxis risk
    - Increased anaphylaxis frequency
    - Increased epinephrine use
  - 2020 meta-analysis
    - Epinephrine use in 7.6% of participants
    - Treatment discontinuation secondary to AEs in 6.6%
  - EoE can develop in ~5% of individuals

Lancet. 2019 Jun 1;393(10187):2222-2232. doi: 10.1016/S0140-6736(19)30420-9
Sci Rep. 2020 Jan 20;10(1):659. doi: 10.1038/s41598-019-56961-3.

Omalizumab Overview

- What is it?
  - Recombinant DNA-derived humanized monoclonal antibody that binds to immunoglobulin E (IgE).
  - Omalizumab is indicated for the reduction of allergic reactions, including anaphylaxis, that may occur with accidental exposure to one or more foods in adult and pediatric patients aged 1 year and older with IgE-mediated food allergy.
  - Omalizumab is to be used in conjunction with food allergen avoidance.
  - Injections are give subcutaneously every 2-4 weeks

  - Omalizumab has multiple other indications as well
    - Moderate to severe persistent asthma
    - Chronic rhinosinusitis with nasal polyps
    - Chronic spontaneous urticaria

Omalizumab Overview

- How does it work?
  - Specifically targets circulating free IgE, thereby preventing its interaction with the high-affinity IgE receptor (FcεRI) on mast cells and basophils
  - Downregulation of FcεRI on cells bearing the receptor, making those cells insensitive to the stimulation by incoming allergens

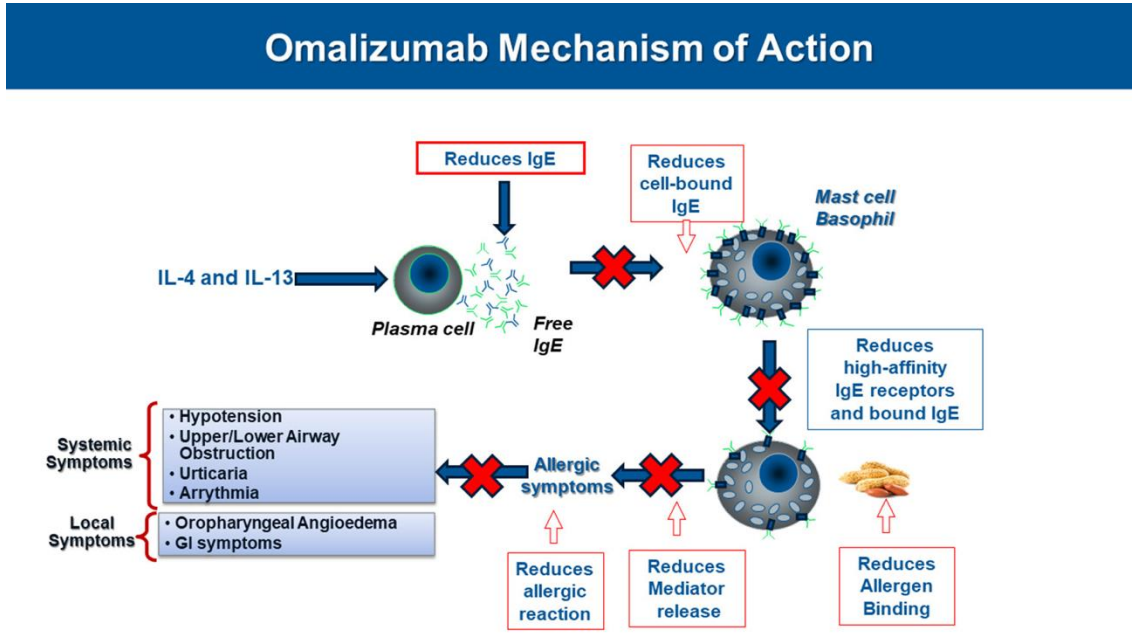


Table 4. Subcutaneous XOLAIR Doses Every 2 or 4 Weeks* for Adult and Pediatric Patients 1 Year of Age and Older with IgE-Mediated Food Allergy

Pretreatment Serum IgE (IU/mL)	Dosing Freq.	Body Weight (kg)												
		≥10-12	>12-15	>15-20	>20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90 - 125	>125 - 150
		Dose (mg)												
≥30 - 100	Every 4 Weeks	75	75	75	75	75	75	150	150	150	150	150	300	300
>100 - 200		75	75	75	150	150	150	300	300	300	300	300	450	600
>200 - 300		75	75	150	150	150	225	300	300	450	450	450	600	375
>300 - 400		150	150	150	225	225	300	450	450	450	600	600	450	525
>400 - 500		150	150	225	225	300	450	450	600	600	375	375	525	600
>500 - 600		150	150	225	300	300	450	600	600	375	450	450	600	
>600 - 700		150	150	225	300	225	450	600	375	450	450	525		
>700 - 800	Every 2 Weeks	150	150	150	225	225	300	375	450	450	525	600		
>800 - 900		150	150	150	225	225	300	375	450	525	600			
>900 - 1000		150	150	225	225	300	375	450	525	600				
>1000 - 1100		150	150	225	225	300	375	450	600					
>1100 - 1200		150	150	225	300	300	450	525	600					
>1200 - 1300		150	225	225	300	375	450	525						
>1300 - 1500		150	225	300	300	375	525	600						
>1500 - 1850			225	300	375	450	600							

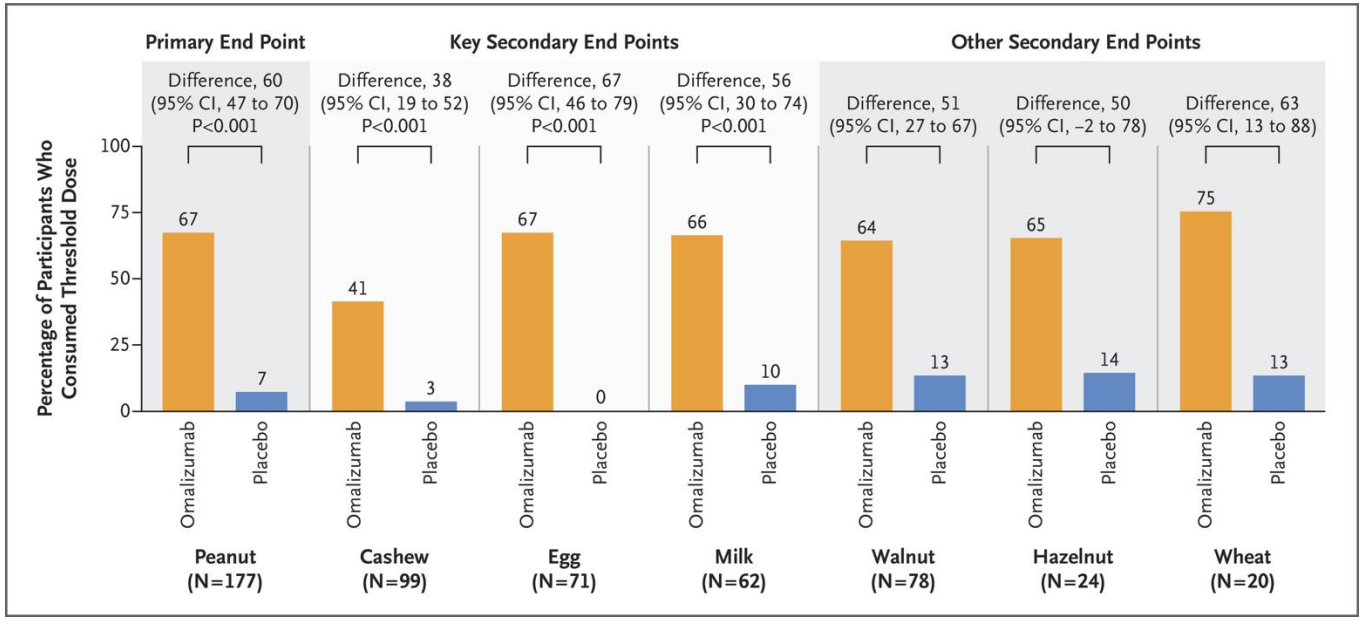
Insufficient data to Recommend a Dose

***Dosing frequency:**

- Subcutaneous doses to be administered every 4 weeks
- Subcutaneous doses to be administered every 2 weeks

Omalizumab Overview

- OUtMATCH Study, Phase 1
  - Evaluated omalizumab as monotherapy for patients with multiple food allergies, specifically those allergic to peanut and at least two other foods (such as milk, egg, wheat, cashew, hazelnut, or walnut)
  - Subjects received omalizumab every 2-4 weeks for 16-20 weeks and then underwent challenge
  - 67% in the omalizumab arm were able to tolerate at least 600mg peanut protein
  - 41% of cashew, 66% of milk, and 67% of egg-allergic subjects could tolerate at least 1000mg of the corresponding protein.



N Engl J Med. 2024 Mar 7;390(10):889-899. doi: 10.1056/NEJMoa2312382.

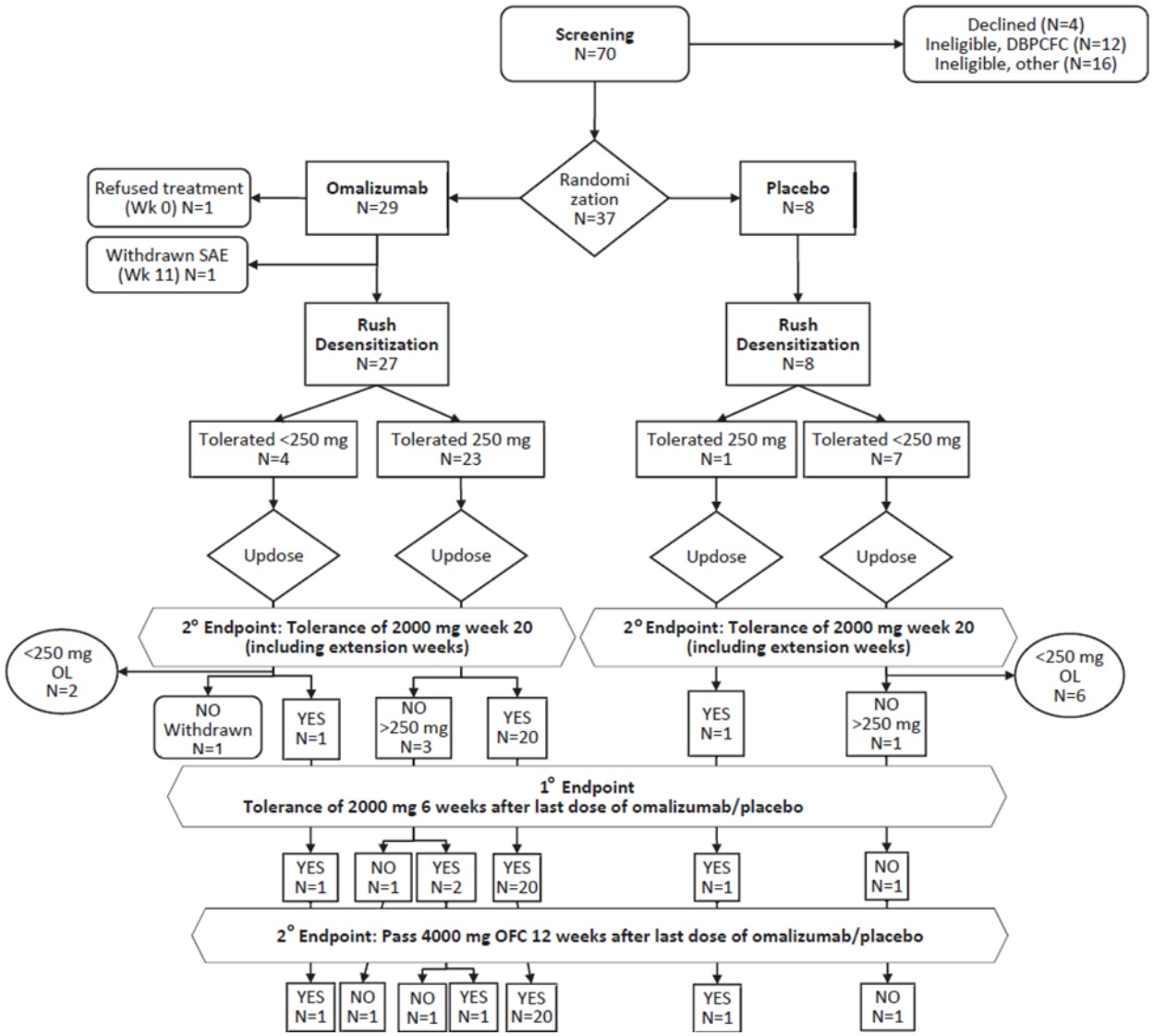
Omalizumab Overview

- Several studies show that omalizumab as an adjunct to OIT increases desensitization rates and reduces adverse events, including severe reactions
- 2016 Milk OIT/omalizumab study
  - Compared milk OIT protocol with and without omalizumab, n=57
  - 7-35 years of age
  - Active arm- omalizumab + OIT, n=27
  - Placebo arm- OIT alone, n=28
  - OIT started after 4 months of omalizumab began, 22-40 weeks of OIT
    - Minimum maintenance dose of 520mg of milk protein (15mL milk), goal of 3.8grams of milk protein
    - Omalizumab was continued for 28 months total, then discontinued.
    - DBPCFC were conducted, with goal of 10grams of milk protein.
  - 88.9% in omalizumab arm tolerated 10g challenge, 71.4% in placebo (p= 0.18)
  - Adverse reactions were markedly reduced during OIT escalation with omalizumab
    - Percentage of doses per subject provoking symptoms; 2.1% vs 16.1%, P= 0.0005
    - Dose-related reactions requiring treatment; 0.0% vs 3.8%, P = 0.0008
    - Doses required to achieve maintenance; 198 vs 225, P= 0.008

J Allergy Clin Immunol. 2016 Apr;137(4):1103-1110.e11
J Allergy Clin Immunol. 2017 Mar;139(3):873-881.e8

Omalizumab Overview

- 2017 Peanut OIT/omalizumab study
  - Compared peanut OIT rapid protocol with and without omalizumab, n=37
  - Primary outcome of the study was the ability to tolerate 2000 mg of peanut protein 6 weeks after withdrawal of study drug
  - Active arm- OIT with omalizumab, n=29
  - Placebo arm- OIT alone, n=8
  - Omalizumab was started 12 weeks prior to OIT initiation.
  - First day OIT was up to 250mg peanut protein.
  - Omalizumab was discontinued at week 19 if tolerating at least 1625mg peanut protein
    - Continued omalizumab for additional 6 weeks if not tolerating 1625mg.
    - If subject could not tolerate 250mg of peanut protein by week 19, they were marked as failures



J Allergy Clin Immunol. 2016 Apr;137(4):1103-1110.e11
J Allergy Clin Immunol. 2017 Mar;139(3):873-881.e8

2017 Peanut/omalizumab study

- 79% (ITT)/85% (PP) in the omalizumab arm met primary outcome vs 12% of placebo arm
  - 75% (6/8) in the placebo group were unable to tolerate 250mg of peanut protein by week 8, dropped from study. This was 7.4% in the active arm
  - These 6 were offered open label study drug and continued with dose escalation.
- Overall reaction rates were not significantly lower in the omalizumab arm, however, they were exposed to much higher doses
  - 4/28 in active arm had significant reactions in the initial dosing day
  - 6/8 in the placebo arm did.
- Mild reactions in 16/28 subjects in the active arm
- 14 reactions required epinephrine in 8 subjects; 3 in the placebo arm, 4 in the active arm, 7 in open-label omalizumab arm.
- Reactions occurred in 7.8% of doses in the active arm vs 16.8% in the placebo arm

J Allergy Clin Immunol. 2016 Apr;137(4):1103-1110.e11
J Allergy Clin Immunol. 2017 Mar;139(3):873-881.e8

Omalizumab Overview

- 2018 Multi-food allergy study
  - 4-15 years of age; 36 in OIT/omalizumab arm, 12 in OIT alone arm, 12 with no treatment at all
  - Active arm- OIT to 2-5 foods with omalizumab, n=36
  - Placebo arm- OIT without omalizumab, n=12
  - No treatment arm- No OIT or omalizumab, n=12
- Active arm
  - Received omalizumab for 16 weeks. OIT started at week 8
  - Omalizumab stopped 20 weeks before DBPCFC at week 36
- Placebo arm
  - OIT only, DBPCFC at 36 weeks
- 83% in active arm passed DBPCFC to 2 grams of protein to 2 foods, compared to 33% in placebo arm.
- No SAEs
- Active arm- lower median per-participant percentage of OIT doses associated with any AEs (27% vs68%, p=0.0082)

Lancet Gastroenterol Hepatol. 2018 Feb;3(2):85-94.

Omalizumab Overview

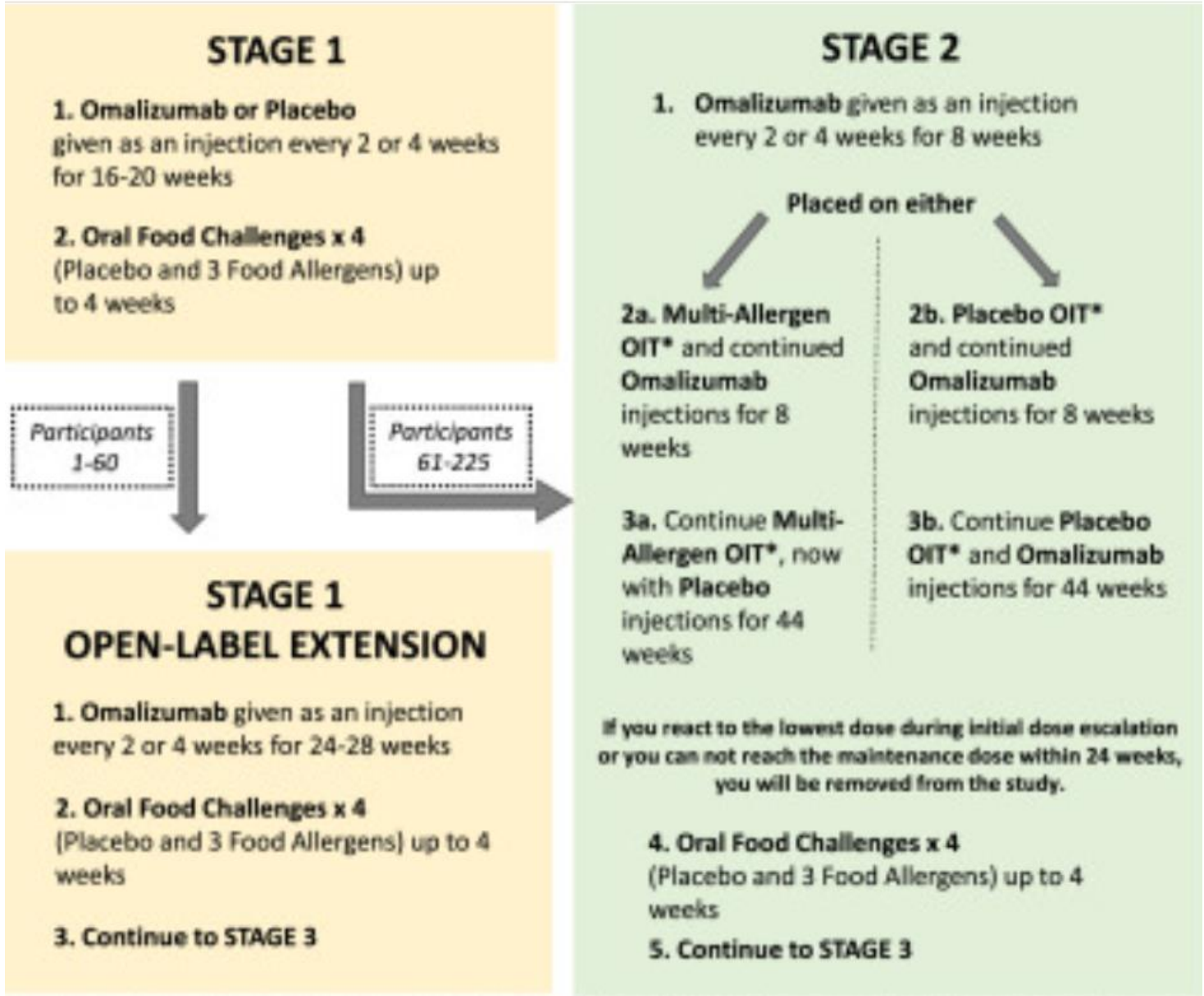
- Warnings/Precautions
  - Anaphylaxis
    - In pre-marketing trials, 0.1% of patients developed anaphylaxis to Xolair and then a case-controlled study suggests that those with a prior history of anaphylaxis were at increased risk of reacting to Xolair.
    - Additionally, post-marketing data found up to 0.2% of patients were estimated to have had reactions to Xolair, most of which were with the first 3 doses.
    - Because of this, it is recommended that at least the first 3 doses be administered in a healthcare setting.
  - Malignancy
    - Malignancy has also been associated, although recent data suggests this is unlikely to be related.
    - Initial clinical studies found various malignancies occurred at a higher rate in Xolair treated subjects (0.5%) compared to placebo (0.2%).
    - A subsequent 5-year observational study showed no difference in incidence between Xolair and placebo subjects.
  - Fever/Arthralgia/Rash
  - Cardiovascular/Cerebrovascular Events
    - In the same 5-year observational study that found no risk of malignancy, the authors did find a higher incidence of cardiovascular and cerebrovascular SAEs in Xolair-treated vs placebo-treated individuals.
    - This included TIAs, MI, pulmonary HTN, PE, and unstable angina.
    - They weren't truly able to quantify the risk because of the study design.
- Cost
  - 75mg every 4 weeks up to 600mg every 2 weeks
  - ~$600 to $9500 a month
  - $7200 to $114,000 a year

OUtMATCH Phase 2

- **“Omalizumab Is Superior to Oral Immunotherapy in Multi-Food Allergy Treatment Study”**
- Phase 2 focused on comparing omalizumab monotherapy versus omalizumab-facilitated multiallergen OIT…kinda
- Study Design
  - Subjects received omalizumab for 8 weeks.
  - Then placed into 1 of 2 arms
    - Arm 1
      - Started rapid OIT while continuing omalizumab for another 8 weeks (16 weeks in total).
      - Stopped omalizumab, but continued OIT for 44 weeks.
    - Arm 2
      - Started placebo OIT while continuing omalizumab for 44 weeks
  - Both underwent oral food challenges at 44 weeks.
    - If pt reacted to initial OIT dose or unable to reach maintenance dose within 24 weeks, they were dropped from the study

J Allergy Clin Immunol Glob. 2022 Jul 21;1(4):225-232. doi: 10.1016

OUtMATCH Phase 2



J Allergy Clin Immunol Glob. 2022 Jul 21;1(4):225-232. doi: 10.1016

OUtMATCH Phase 2

- Participant must tolerate at least 9 mg of protein of multiallergen or placebo OIT during an initial visit
- OIT is introduced on an initial dosing day, and the top dose achieved without symptoms is the starting dose for continued build-up
- If they do, subject will enter a build-up phase for up to 24 weeks to reach a maximum maintenance of 1000 mg of protein of each of their 3 participant-specific foods (ie, for a total maximum dose of 3000 mg of protein or 3000 mg of placebo OIT).
- Each participant who reaches a minimum total maintenance dose of 750 mg of protein (equivalent to 250 mg of protein of each of their 3 participant-specific foods) within 24 weeks of completing the IDE will continue to receive this dose during the maintenance phase.
- Study endpoint was the consumption of >1 dose of 2000mg protein of all 3 foods

OUtMATCH Phase 2

- The trial demonstrated that **omalizumab significantly increased the proportion of participants able to tolerate higher doses of multiple food allergens compared to OIT**
- **88% of participants in the omalizumab group completed Stage 2**
- **51% of the OIT participants completed Stage 2**

- **36% of omalizumab-treated subjects reached the primary end point**
- **19% of the OIT-treated subjects reached the primary end point**

- **No SAEs in the omalizumab group, 30.5% in the OIT group**
- **No discontinuations in the omalizumab group, 22% in the OIT group**
- **6.9% used epinephrine in the omalizumab group, 37.3% in the OIT group**

Conclusion

- I have not great answer. Robust data is still lacking.
- Like many things, there is no universal answer
- Omalizumab clearly provides protection for AEs with OIT, but how much is hard to say
- Consider in those with:
  - A history of severe/life-threatening reactions
  - Asthma
  - Anxiety
  - Difficulty with OIT
  - Multiple food allergens
- We need to weigh the cost/potential side effects with safety omalizumab can provide
- Shared decision making

Questions?

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Thank You!