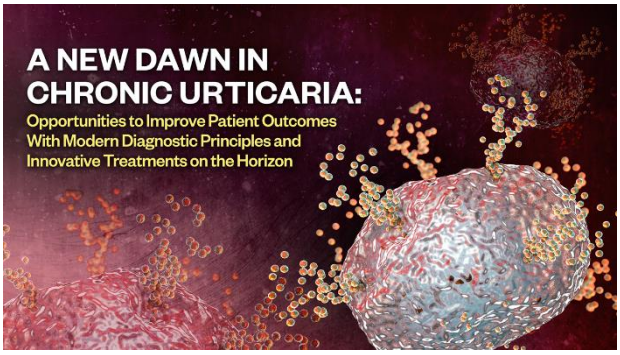
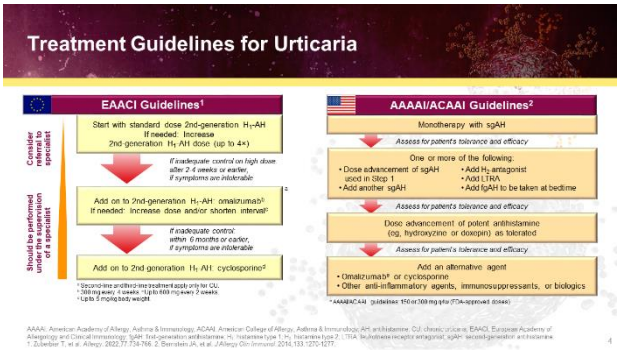
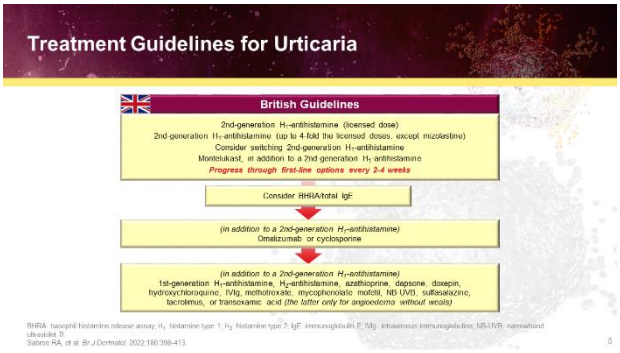
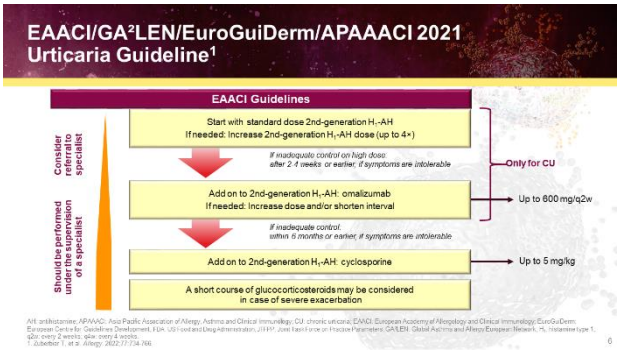
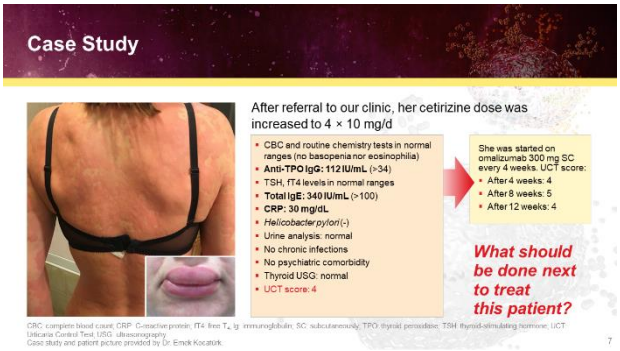
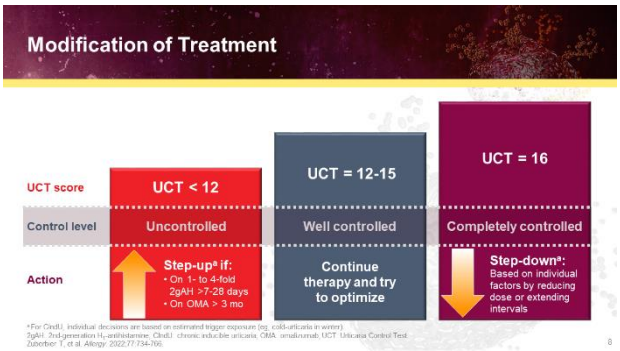
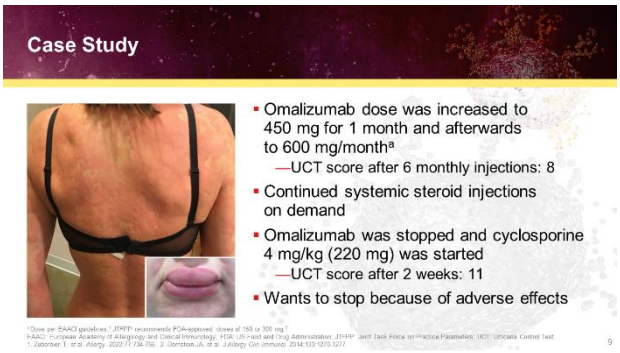
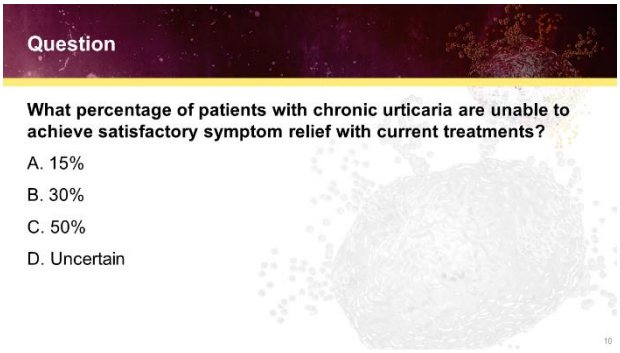
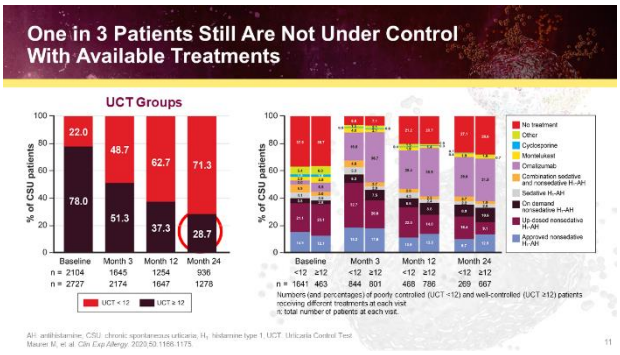
A NEW DAWN IN CHRONIC URTICARIA: Opportunities to Improve Patient Outcomes With Modern Diagnostic Principles and Innovative Treatments on the Horizon
Fulfilling an Unmet Need in Treating CU: How Might New and Emerging Approaches Fit Into the Paradigm?

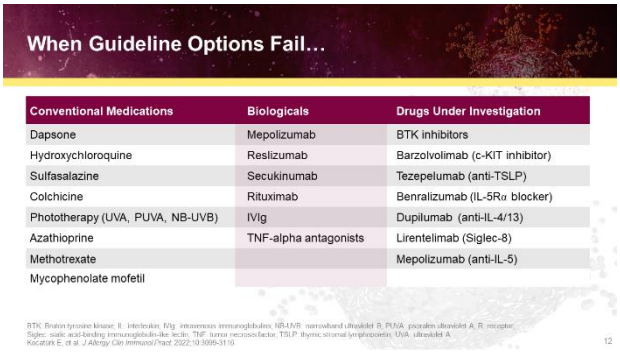
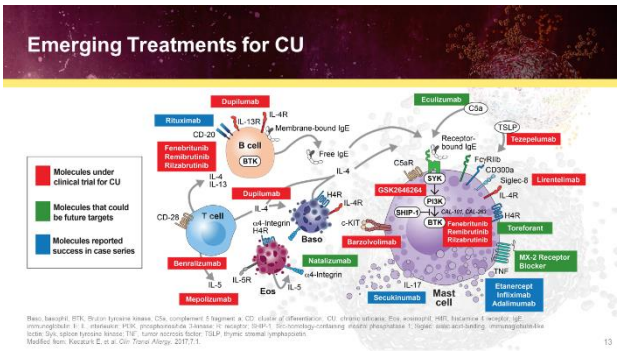
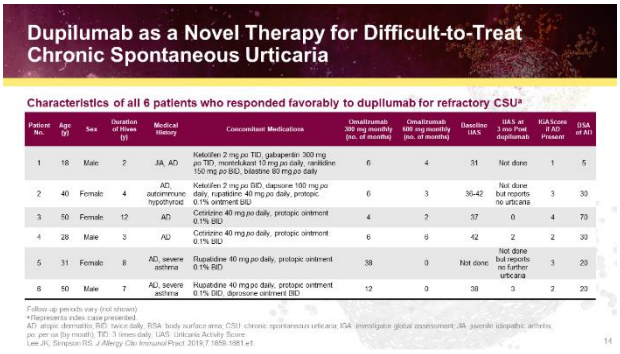
1		Hello, my name is Emek Kocatürk Göncü. I'm a professor of dermatology in Koç University Medical School, Istanbul, Turkey. I'm also a researcher in Charité University
2		Medical School, Institute of Allergology, Berlin, Germany. So today, I'm going to speak about my favorite disease, chronic urticaria, mainly focusing on current treatment and the future options of treatment that are seen on the horizon. First of all, I'd like to start with a case presentation. The cases we usually see in our common practices and which demonstrate that chronic urticaria sometimes can be very burdensome, both for the patients and also for the treating physician.
3		So, this case is a 38-year-old woman. She was experiencing recurrent wheals and angioedema attacks for 6 months and she was prescribed hydroxyzine 25 mg daily. But she said that treatment led to sedation. And then she went to a dermatologist, and she was prescribed cetirizine two times daily. But she says that she's still visiting emergency department every 2 weeks for getting steroid injections to get relief for her symptoms. So, what should be the next step in treatment for this patient?
4		To get the answers, let's take a look to the treatment guidelines of urticaria. The first guideline I'd like to cover is the European [Academy of] Allergy and Clinical Immunology guidelines. Let's say European guidelines. This guideline is released in 2022, so it's a new guideline. And the first step is to start with standard doses of second-generation H_1 antihistamines and if the patient is refractory to this treatment, then the guideline recommends to updose up to four-fold in standard dose refractory patients. If the patients are

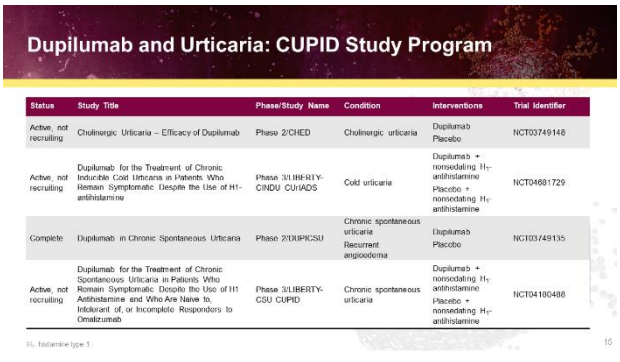
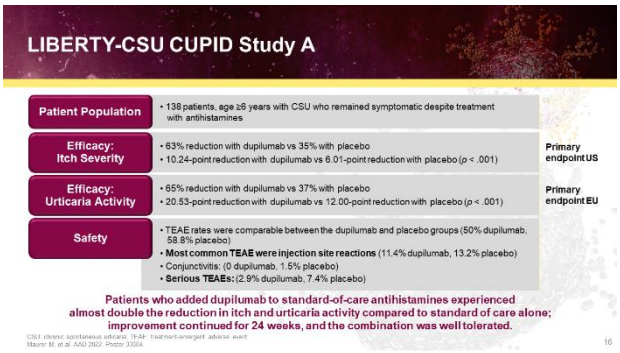
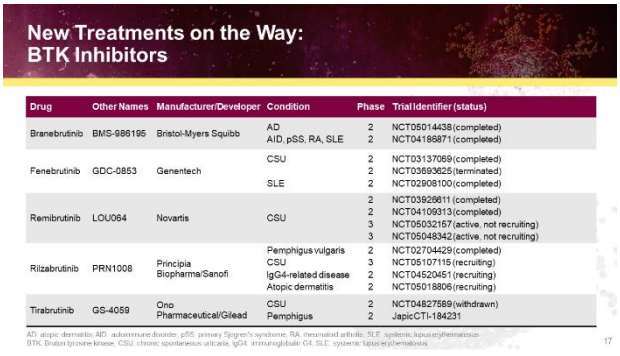
		not responding to even four-fold of antihistamine treatments, then the guideline recommends to step up to omalizumab treatment and combine second-generation antihistamines with omalizumab treatment and to stay on omalizumab treatment at least 4 months before deciding that omalizumab is not working. And the third option is immunosuppressive treatment with cyclosporine. And the guideline also suggests short-term use of systemic steroids in case of exacerbations, maximum 10 days. And here you see the American Academy of [Allergy, Asthma, and Immunology] guidelines. This guideline was released in 2014. And here I want to make a note that in 2014, omalizumab was new on the market for chronic spontaneous urticaria. So, there were not enough experience for omalizumab treatment when these guidelines were written. So, like the European guidelines, American Academy of Allergy Immunology guideline also recommends to start with second-generation antihistamines, H_1 antihistamines, and then updose to four-fold in the same second-generation antihistamine. But this guideline also has other options in the second step, like adding another second-generation antihistamine, adding H_2-antagonists, adding leukotriene receptor antagonist, and even first-generation antihistamines to be taken at bedtime. Here I want to note that the European guidelines suggest against using first-generation antihistamines because of their sedative and anticholinergic adverse effects. And the third treatment step in the American guideline is those advancements of potent antihistamines. And if no response to these three steps, then the last step includes omalizumab, cyclosporine, other anti-inflammatory agents, and immunosuppressive agents.

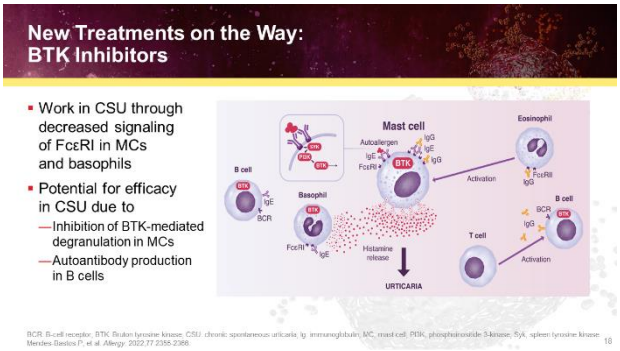
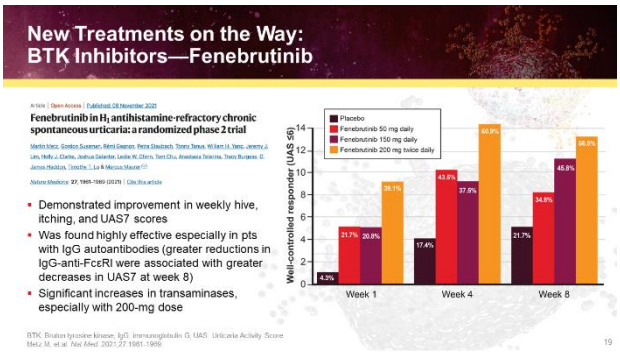
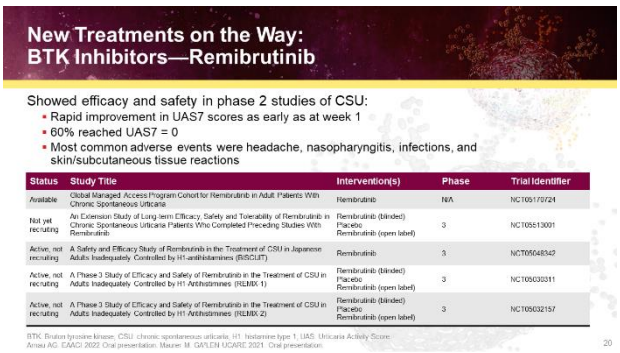
5		So, the next guideline I'd like to mention is the British [Association of Dermatologists] guidelines. This is also a new guideline, which was released in 2022. So, the first step is, again, second-generation H_1-antihistamines and updosing up to four-fold. Except mizolastine because of its cardiac side effects. And also the British guidelines added some other options like other second-generation H_1-antihistamines and also montelukast to their first step of treatment. And the second step is omalizumab or cyclosporine. But they also added the laboratory workup of basophil histamine release assay or total IgE levels to decide on the endotype of patients or to predict the patient's response to the second step of treatment. Because we already know that patients with basophil histamine release assay positivity may be better responding to cyclosporine treatment and patients with low total IgE levels may respond poorly or slowly to omalizumab treatment. So, it is good to consider the patient profiles before starting treatment. So British guideline also considers this and in patients who are not responding to omalizumab or cyclosporine treatment, they recommend other treatments. These treatments, of note, these treatments were not put in the algorithm box in the European guidelines due to lack of evidence or not enough evidence.
6		So, I'd like to make a note on the European guidelines, that European guidelines recommend staying on omalizumab treatment minimally 6 months before deciding that omalizumab is not working and also managing treatment according to patient needs. For example, if the patient becomes symptomatic at the third week of omalizumab injection, then we can shorten treatment intervals in these patients. Or if the patient is partially responding, partially, to omalizumab treatment, we can

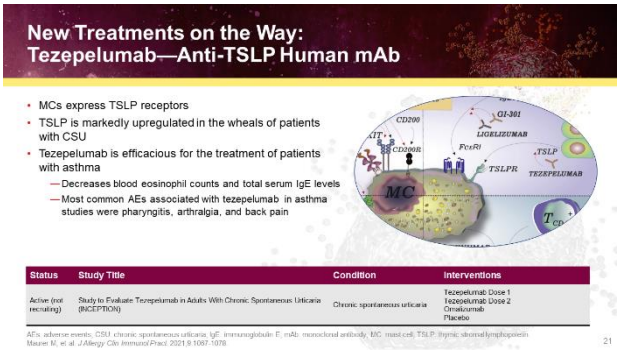
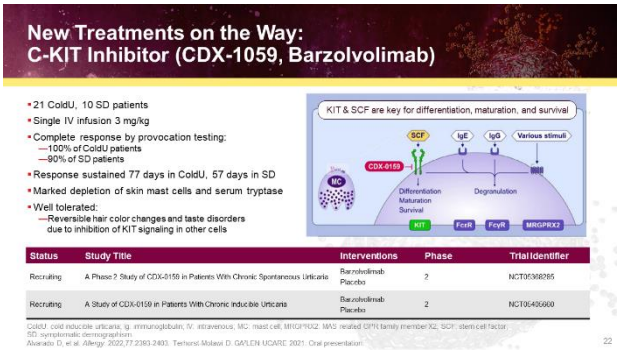
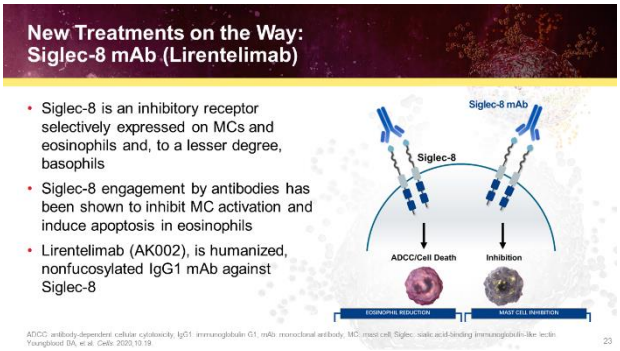
		increase the dose of omalizumab up to 1200 mg per month, but it is important to note that this is off-label treatment.
7		So, let's come back to our case study. So this patient referred to our clinic again and her cetirizine dose was increased up to four-fold and a laboratory workup was performed. The laboratory workup showed that the patient had higher anti-TPO levels, and a bit higher total IgE levels. CRP was elevated, but she didn't have any infections, any psychiatric comorbidities, her thyroid ultrasound was normal, and we did a urticaria control test and the urticaria control test score was 4. That means that the patient's disease is not controlled at time of referral. So, this patient was started on omalizumab treatment 300 mg every 4 weeks. And we were expecting to have higher scores of urticaria control tests because the urticaria control test, when it is higher than 12, then that means that urticaria is under control. But for this patient after, even after three injections of omalizumab, we still have the urticaria control test score of 4. So, what should be done next to treat this patient?
8		So, the European guidelines recommends the physicians to maintain treatments based on UCT scores. When UCT score is under 12, then that means that the disease is uncontrolled, so we need to step up treatment. So, if the patient is on standard dose of antihistamines, we need to upfold antihistamine treatment or if the patient is on omalizumab treatment, we need to updose omalizumab treatment. If UCT scores are between 12 and 15, then the patient is well controlled and we can continue treatment and try to optimize our treatment. And if UCT is 16, then that means that the urticaria is completely controlled and we can start stepping down the treatment. So, if it's four-fold antihistamines, we can decrease to two-fold antihistamines or

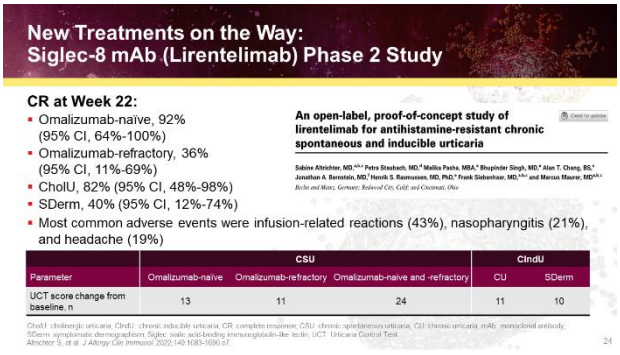
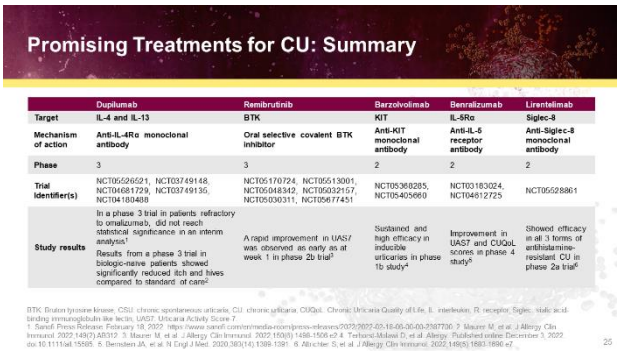
		we can start decreasing omalizumab doses or opening omalizumab intervals.
9		So, in this patient, we increased omalizumab dose, first up to 450 mg per month, then to 600 mg. And we continued injection 6 months, and she had a total of nine injections of omalizumab, but her UCT score was still 8 and she told that she was continuing systemic steroid injections on demand. So, in this case, omalizumab was stopped and cyclosporine 220 mg was started. She was starting to get relief of her symptoms, because UCT score went up to 11 at 2 weeks. But the patient complained of having some adverse effects and wanted to stop treatment because of fear of having serious side effects. So, this is the point where the guidelines fail, because we don't have any other evidence-based treatment options to give for this patient. So now
10		what we are going to do? At this point, I want to ask you a question. What do you think is the percentage of patients with chronic urticaria that are unable to achieve satisfactory symptom relief with current treatments? A. 15% B. 30% C. 50% D. Uncertain. So, the answer is 30%.
11		And this result is from AWARE study, which was published in Clinical and Experimental Allergy in 2020. In this AWARE study, the patients were given guideline treatment options, but at the end of 24 months, 28.7% of the patients were still not controlled. They had a UCT score of below 12.

12		So, what can we do when guideline options fail? We seem to have a lot of options, but when we look at the conventional part of this table, we have a lot of anti-inflammatory and immunosuppressive treatments, which have serious side effects and also which need close laboratory monitoring, which are difficult to monitor. So, we have dapsone, hydroxychloroquine, phototherapy, azathioprine, methotrexate, and mycophenolate mofetil. And we have some biologicals, which have shown effects in case series, and we have biologicals that are under investigation.
13		So here we see the options in the pathomechanism slide of urticaria. The red ones are the molecules that are under clinical trial for chronic urticaria. We see dupilumab here, BTK inhibitors here, anti-IL-5s here, c-KIT inhibitor here, and Siglec-8 here, and TSLP monoclonal antibody here. And also we have some other molecules that have been shown to be effective in case series, such as TNF-alpha blockers, secukinumab, IL-17 blocker, and a CD20 monoclonal antibody rituximab has been shown to be effective in case series. And also we can have in the future some other targets such as H4 receptor blocker, C5a blockers, natalizumab, alpha 4 integrin monoclonal antibody, or MX2 receptor blockers can be options in the future. So, let's dive into treatments that are
14		under investigation for chronic urticaria. So, the dupilumab is an IL-4 blocker, and there have been increasing reports of chronic urticaria patients, many subtypes of chronic urticaria that responded well to dupilumab treatment and one of these reports is here, was presented by Lee JK in JACI Practice Journal. And they presented six cases of patients who had both atopic dermatitis and chronic spontaneous urticaria. These patients did not respond to

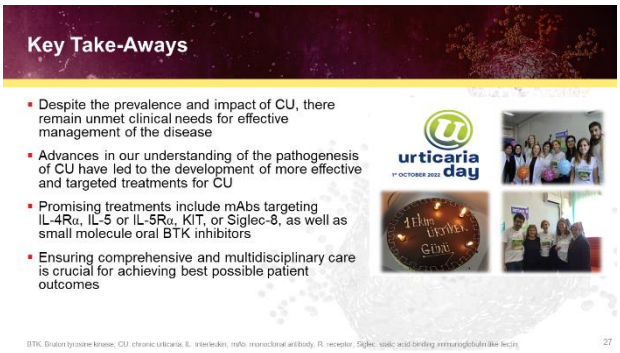
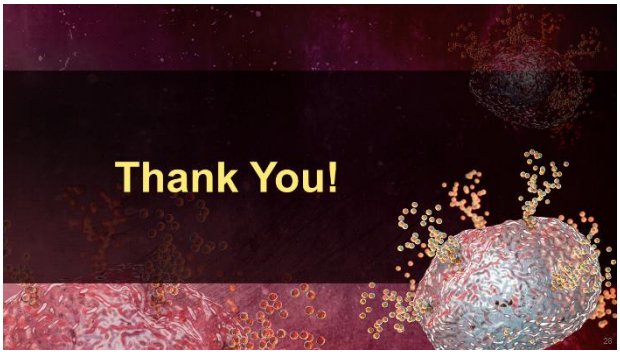
		omalizumab treatment, but nicely responded to dupilumab treatment.
15		So, dupilumab is under investigation for chronic urticaria, both for chronic spontaneous urticaria and also cold urticaria and cholinergic urticaria.
16		So, in the LIBERTY-CSU CUPID Study A, 138 patients who are aged over 6 were included in the study. And at the end of the study, there was 63% reduction in itch severity in patients who were treated with dupilumab versus 35% of reduction who were treated with placebo. And urticaria activity reduced in, reduced by 65% in patients who were treated with dupilumab versus 37% who were treated with placebo. And as we already know, dupilumab has been used for years in treating atopic dermatitis patients, and this is a safe medication. And as a parallel, the adverse effect rates were comparable with placebo, and the most common adverse events were injection site reactions. Conjunctivitis was not seen and serious adverse events were even higher in the placebo group.
17		So other options of treatment are the BTK inhibitors. They, the BTK inhibitors — the Bruton kinase inhibitors — are gaining a lot of attention in the treatment of autoimmune disorders in recent years. So, and one of these diseases is chronic spontaneous urticaria. So there are

18		studies ongoing with BTK inhibitors. So, what do BTK inhibitors do? BTK is a signaling molecule that is found in mast cells, basophils, and B cells. And they help in transducing the signal. And then by this way, with the signal link, this leads to degranulation of mast cells and basophils. And, also, when BTK works then B cells are able to produce immunoglobulins. And when they are blocked, mast cells and basophils do not activate or release mediators and B cells do not produce immunoglobulins. So this shows the dual effect mechanism for chronic spontaneous urticaria. So, you can both inhibit production of immunoglobulins and also inhibit mast cell and basophil degranulation.
19		So, the first BTK inhibitor which was tested in chronic spontaneous urticaria was fenebrutinib. And fenebrutinib demonstrated improvement in weekly hive itching and UAS7 scores in the phase 2 trial, and it was also found highly effective especially in patients with IgG autoantibodies. These patients has the autoimmune 2B type chronic spontaneous urticaria. Because there were greater reductions in IgG-anti-Fc-epsilon receptor 1 associated with great decreases in UAS7 scores. But, unfortunately, there were significant increases in transaminases, especially with the 200-mg dose. Fenebrutinib did not continue the studies in chronic spontaneous urticaria, so it's not under development now.
20		But what is under development is the remibrutinib and it has late-stage trials ongoing at the moment for chronic spontaneous urticaria. In the phase 2 studies, there was rapid improvement in UAS7 scores as early as at week 1. And 60% of the patients reached UAS7 zero, which is a really good achievement. And most common adverse events were headache, nasopharyngitis, infections, and skin subcutaneous tissue reactions. And not very serious adverse events occurred.

21		So, another treatment that is under development is the tezepelumab, which is an anti-TSLP human monoclonal antibody. TSLP is markedly upregulated in the wheals of patients with CSU, and so this is the originating mechanism of action that will be identified if it will be effective in patients with CSU or not. So, it's under clinical trial, but no results have been posted yet.
22		And the other option is the really dramatic treatment of c-KIT inhibitor barzolvolimab, which led to dramatic achievements in patients with inducible urticarias in the phase 1b study. So, this treatment leads to mast cell depletion. So, and it's associated with very good results. The study included 21 cold urticaria patients and 10 symptomatic dermographism patients. These patients were given single IV infusions. And complete response by provocation testing was reported by 100% of cold urticaria patients and 90% of symptomatic dermographism patients. And the response sustained 77 days in cold urticaria and 57 days in symptomatic dermographism patients. And there were marked depletion of skin mast cells and serum tryptase in these patients. It was well tolerated. However, there were reversible hair color changes and taste disorders due to inhibition of KIT signaling in other cells. So, the phase 2 program is ongoing with barzolvolimab with chronic spontaneous urticaria and also chronic inducible
23		urticaria. The other option is the mast cell silencing lirentelimab, which is a Siglec-8 monoclonal antibody. Siblec-8 is an inhibitory receptor which is found on mast cells and also on eosinophils. So, when a monoclonal antibody targets Siglec-8, then mast cells and eosinophils get silenced and do not activate. So, there was

24		a phase 2 study on lirentelimab which included omalizumab-naive and also omalizumab-refractory patients and which showed nice improvement in both with more refractory patients, and also cholinergic urticaria and symptomatic dermographism patients. And most common adverse events were infusion-related reactions, nasopharyngitis, and headaches. So, it is also a promising
25		treatment option. So as a summary, the most important upcoming treatments are shown in this table and the first one is dupilumab. Which is on phase 3 development. In the phase 3 trial in patients refractory to omalizumab, it did not reach its clinical significance. In an interim analysis, but the results from the phase 3 trial in biologic-naive patients showed significantly reduced itch and hives compared to standard dose of antihistamines. And remember, remibrutinib is a BTK Bruton kinase inhibitor, and it's an oral selective and covalent oral drug in phase 3 clinical trials. And it showed repeat improvement in UAS7 as early as at week 1 in phase 2B trials. Barzolvolimab is an anti-KIT monoclonal antibody which is in phase 2 trials. It showed sustained and high efficacy in inducible urticarias in phase 1B study. Benralizumab is an anti-IL-5 receptor antibody which is on phase 2 clinical trials; it showed improvement in UAS7 and chronic urticaria quality-of-life scores in phase 4 studies. Lirentelimab is an anti-Siglec-8 monoclonal antibody, which is under development phase 2; it showed efficacy in all three forms of antihistamine-resistant chronic urticaria in phase 2a trial.

26		So, it is nice to see that we have these new treatment options on the horizon coming and we are excited to be able to use these options. But there are some other factors that we should not forget to consider, while managing our chronic urticaria patients. We need to make some discussions and talks with these patients and ask about the triggering factors, such as some forms of inducible urticarias. We need to ask about cold or hot weather or sports or pressure, or symptomatic dermographism, like stroking the skin. So, we need to ask about inducible urticarias and also about nonsteroid anti-inflammatory medications — if they lead to angioedema exacerbations or urticaria exacerbations. And also stress, infections, and also vaccinations can cause exacerbations in our patients. So, we need to give information to our patients on these topics. And also we need to find out comorbidities, especially Hashimoto thyroiditis is very common in chronic spontaneous urticaria patients, so we need to be aware of this. We can check anti-TPO levels and also they may have other autoimmune disorders and also psychiatric comorbidities. In one-third of the patients we find depression, anxiety, panic attack, so it's important to consider. And also sometimes chronic infections or chronic inflammation such as gastritis or tooth infections. So, we need to be aware of them and ask about the symptoms of these conditions and give available appropriate treatments for these patients. And of course, while we have that many options under development, so we need to also invite patients to enroll in clinical trials if appropriate. So, good communication skills and having enough time for patients is also important, because when we speak and give time for these patients, then these patients become more connected to us and continue our treatment and that

		really makes importance, that really makes some sense for these patients to follow the treatment you give.
27		So, what are the key takeaways from my presentation? So, we saw that still there are patients that do not respond to available treatment. So, it's evident that we need some new treatments and by advances in the treatment of urticaria, then we have new pathogenesis pathways. So, we are discovering more about chronic urticaria. The promising treatments include monoclonal antibodies targeting IL-4, IL-5, c-KIT, Siglec-8, as well as small molecule oral BTK inhibitors. But however, ensuring comprehensive and multidisciplinary care is crucial for achieving best possible patient outcomes in chronic urticaria treatments.
28		Thank you for your attention.