IL-12/23 Update

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Disclosure

- I have no relevant conflicts of interest with regards to the topic of this talk
- Medications that are not approved by the FDA will be discussed

Outline

- Examine the role of IL-12 and IL-23 in the pathogenesis of psoriasis
- Review efficacy and safety updates for ustekinumab
- Highlight differences between IL-12/23 blockade and IL-23 therapeutic antibodies
- Discuss major available and upcoming IL-23 therapeutic antibodies
- Consider differences between agents within and across classes

Pathogenesis of Psoriasis
Ustekinumab

- FDA approved for moderate to severe plaque psoriasis and psoriatic arthritis
- Initially approved in 2009
- Over 5-year safety data available
- Long term data shows durable effect
- Very low rate of antidrug antibody formation

PHOENIX 1 Overall Population: PASI 75 Responses Week 0 Through Week 244

Overall Population: PASI 90 Responses During the Open-label Extension (Weeks 76 – 244)*

Overall Efficacy: PASI 100 Responses During the Open-label Extension (Weeks 76 – 244)*
How safe is Ustekinumab?

- 3117 patients through Phase 2 trials and Phase 3 trials (PHOENIX 1/2, ACCEPT)
- NO cases of TB or systemic fungal infection
- Serious infections at a rate of 1.1 per 100PY
- Rate of discontinuation due to infection is less than 1%
- NMSC were reported, mostly BCC

What about pregnancy?

- Pregnancy **Class B**

<table>
<thead>
<tr>
<th>% of pregnancies</th>
<th>UST Overall (n=26)</th>
<th>US General Population*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Live Birth</td>
<td>Spontaneous Abortion</td>
</tr>
<tr>
<td>Live Birth</td>
<td>53.6%</td>
<td>10.2%</td>
</tr>
<tr>
<td>Spontaneous Abortion</td>
<td>17%</td>
<td></td>
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<tr>
<td>Elective Abortion</td>
<td>18.4%</td>
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</tbody>
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Rates per pregnancy per year from 2008 CDC Estimates

MACE

- Briakinumab withdrawn, possibly due to concerns about MACE and cardiovascular deaths
- A small number of MACE in ustekinumab trials
- Higher number than placebo during initial treatment phase only
  - No data exists suggesting any long term increased cardiovascular risk
MACE
Recent Advances on the Role of Cytokines in Atherothrombosis
M.A. Czachowski, M.S. Twarden, S. Dzidic, and A.R. King
(Monsey-Thorn, NY 58, 381, 349, 2002)

IL-12 and IL-18, produced by macrophages (Mac), are potent inducers of IFN-γ and promote the differentiation of naïve T cells into proatherogenic Th1 cells.

The Next Frontier: IL-23 Blockade

• Why bother specifically targeting IL-23?

IL-23 shown to be important in immunity against TB, Candida, and Salmonella
The Next Frontier: IL-23 Blockade

**Why IL-12 in tumor immunity**
- Although there is evidence linking IL-12 and IL-23, there is increasing evidence that these cytokines modulate divergent immunomodulatory activities.
- Other than promoting the proliferation of NK cells, IL-12 drives the development of Th1 cells, the activation of STAT4.
- These cytokines IFNy-producing Th1 cells crucial for antitumor and antiinflammatory responses.
- The role of IL-12 and IL-23 in tumor immunity has been demonstrated in both preclinical and clinical settings. IL-12 and IL-23 are involved in the development of regulatory T cells (Tregs) and the expansion of Th1 and Th17 cells in the tumor microenvironment, thus enhancing tumor control.
- More recently, engineered antigen-specific CD8+ T cells expressing IL-12 have been shown to suppress tumor growth in preclinical models of melanoma, leading to the development of novel strategies for the treatment of cancer.

**IL-12 and IL-23 Blockade**
- Does the science line up with experience?
- No cases of reactivation TB in ustekinumab trials
- No evidence of increased malignancy
- Complex, redundant, and multifaceted immune environment in autoimmune diseases and cancer

**IL-23 Inhibitors**
- Gusekumab
- Tildrakizumab
- Risankizumab

IL-23 production in a tumor context
- What about IL-23 production in a tumor context? Recently, in an inflammation-activated ApoA1-deficient mouse model, it was found that the microenvironmental conditions surrounding the tumor can influence the production of IL-23.
- IL-23 is produced by tumor-associated macrophages (TAMs) and other immune cells, contributing to the maintenance of a tumor-promoting microenvironment.
- IL-23 can also be produced by tumor cells themselves, further amplifying the pro-inflammatory cytokine network, leading to the recruitment of immune cells and the promotion of tumor growth.

**IL-23 Inhibitors**
- Gusekumab
- Tildrakizumab
- Risankizumab
Guselkumab

- Anti-IL23p19
- Entered Phase 3 trials in 2014; Approved July 2017
- 100mg q8w dosing
- Fully human monoclonal antibody

Proportion of patients who achieved PASI 75 response

Proportion of patients who achieved PASI 90 response

Proportion of patients who achieved PASI 100 response
Switching Therapy

- If I have a patient on ustekinumab who wants some further improvement, should I change to a different class?
  - Is guselkumab an option in these cases?

**Figure 1. Proportions of Patients With IGA Score of 0 or 1 and ≥2 Grade Improvement (From Week 16) at Weeks 28 and 52; Randomized Patients**

- Week 28:
  - Guselkumab (n=135): 31.1%
  - Ustekinumab (n=133): 14.3%
- Week 52:
  - Guselkumab (n=135): 36.3%
  - Ustekinumab (n=133): 17.3%

  *P = 0.001 vs. ustekinumab*

**Figure 2. Proportions of Patients With PASI 90 at Weeks 28 and 52; Randomized Patients**

- Week 28:
  - Guselkumab (n=135): 48.1%
  - Ustekinumab (n=133): 22.6%
- Week 52:
  - Guselkumab (n=135): 51.1%
  - Ustekinumab (n=133): 24.1%

  *P = 0.001 vs. ustekinumab*
Tildrakizumab

- Anti-IL23p19
- Entered Phase 3 trials in 2012
- 100mg and 200mg q12w being considered
- Recombinant humanized mouse monoclonal antibody
Risankizumab

- Anti-IL23p19
- Previously known as BI-655066
- Started recruiting for Phase 3 trials last year
- Data exists for dosing at 0, 4, and 16 weeks as well as a single dose administration
- Fully human monoclonal antibody

The Big Picture

- The new classes of biologics for psoriasis are very effective
- How do we decide between them?
So what are the differences?

• Safety data is very good across the board
  – Cases of nasopharyngitis, URI
• Efficacy is very good
  – Patient characteristics and individual response likely a bigger driver than drug/class differences
• Dosing regimens – frequency of injections
• Insurance coverage
• What about IBD?

The IBD Story

• There have been some concerns about the blockade of IL-17 with regards with IBD/Crohn’s Disease
Crohn’s Disease and Secukinumab

IL-23 Blockade Ameliorates Crohn’s Disease

What about IL-23 blockade?

- IL-17 blockade in some cases can worsen Crohn’s Disease while IL-23 blockade is a promising treatment for Crohn’s Disease
- Across large numbers of treated patients, there does not seem to be a strong safety signal with regards to Crohn’s Disease, but there is some cause for caution

The IBD Story
Summary

• IL-23 is involved in the pathogenesis of psoriasis
• Therapeutic antibodies targeting IL-23 are very effective in treating psoriasis
• There are some possible benefits of selecting an IL-23 inhibitor over other new classes of biologics

Thank you!

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