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VIRTUAL KOL INVESTOR EVENT

FEBRUARY 27, 2025

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Agenda

SPEAKERS

Christopher J. Kirk, PhD
Chief Executive Officer,
Co-founder

Zung To
Senior Vice President,
Head of Clinical Development

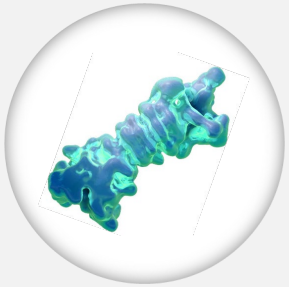
Rachel Peterson, MD
Head of Clinical
Immunology

Aparna Goel, MD
Associate Professor of Medicine,
Stanford University

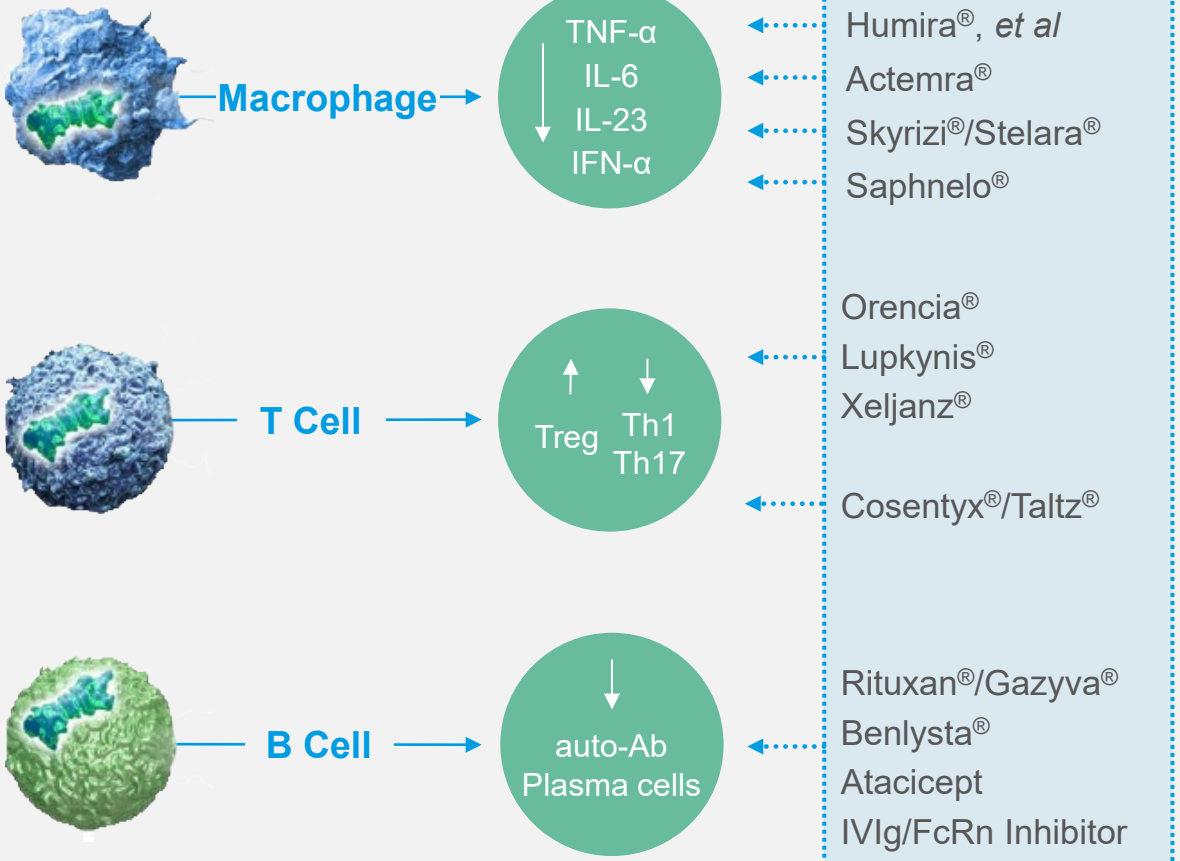
4:00 PM – 4:05 PM Opening Remarks	***Christopher J. Kirk, PhD***
4:05 PM – 4:20 PM Update from the PALIZADE Trial for Lupus Nephritis	***Rachel Peterson, MD***
4:20 PM – 4:40 PM Autoimmune Hepatitis: Disease Background & Treatment Options	***Aparna Goel, MD***
4:40 PM – 4:45 PM PORTOLA Clinical Trial Design: Zetomipzomib in Autoimmune Hepatitis	***Zung To***
4:45 PM – 4:50 PM Next Steps & Closing Remarks	***Christopher J. Kirk, PhD***
4:50 PM – 5:00 PM Question & Answer Session	***Moderated by Matt Phipps (William Blair)***

Zetomipzomib: Immunomodulation Across the Immune System

Immunoproteasome
Key Regulator of Immune Function and Inflammatory Responses



Zetomipzomib
Only Selective Inhibitor of the Immunoproteasome in Clinical Development



- 20 years of research pioneered by Kezar scientists
- >100 publications highlighting the therapeutic potential of immunoproteasome inhibition
- >200 patients treated with zetomipzomib indicate broad MOA and clinical activity
- Clinical biomarker data in SLE/LN patients support broad immunomodulatory activity

*Some preclinical studies were conducted with ONX 0914, a first-generation selective immunoproteasome inhibitor.

Selective Inhibition of the Immunoproteasome Impacts Multiple Drivers of Autoimmune Hepatitis (AIH)

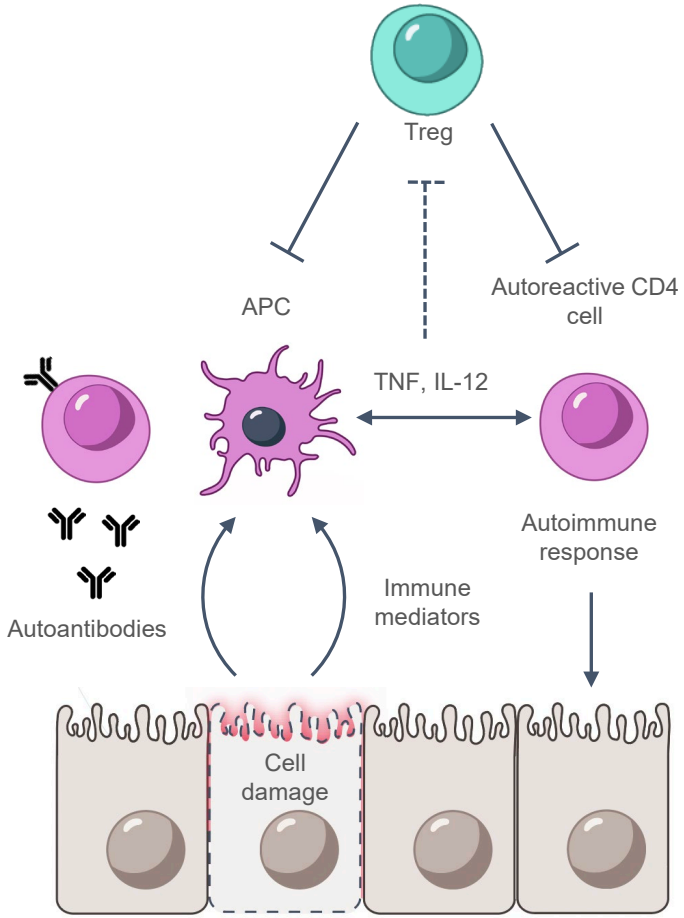
Broad Immunomodulatory Activity

- Reduction of multiple inflammatory cytokines from APC
- Reduced inflammatory T-cell activity (Th1 and Th17)
- Increased Treg function
- Decreased plasma cell activity and autoantibody production

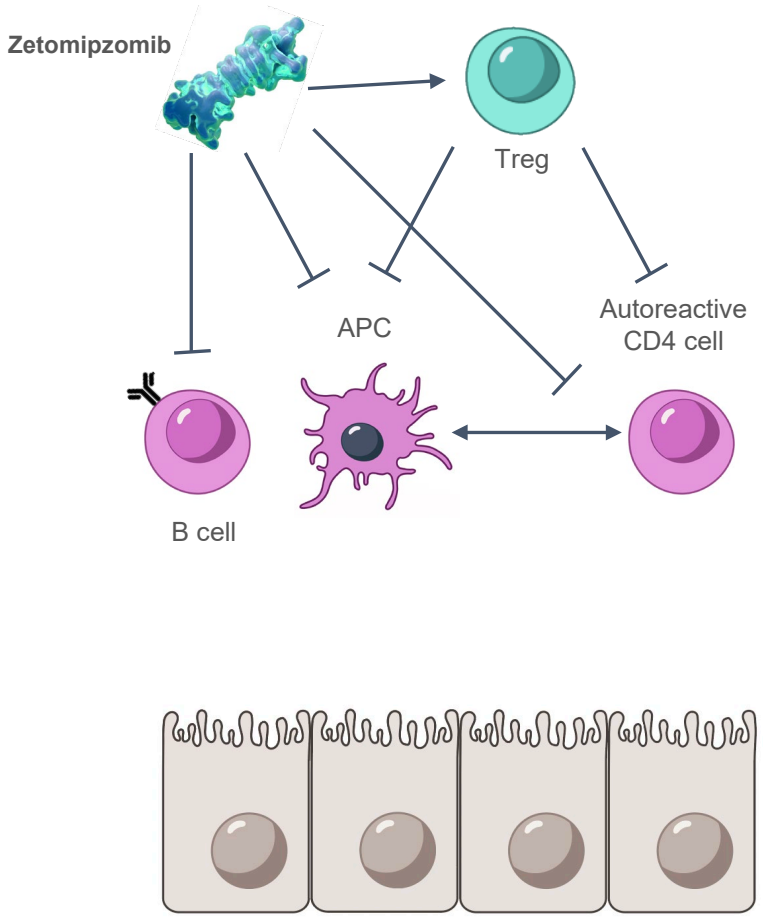
Broad Therapeutic Potential

- Rapid onset of activity
- Minimal risk for immunosuppression
- Steroid sparing agent
- No lab monitoring required
- Active in patients with severe and treatment refractory disease

Cellular Dysfunction Observed in AIH and LN



Zetomipzomib Targets Multiple Immune Effector Cells Involved in Autoimmunity



Abbreviations: AIH, autoimmune hepatitis; APC, antigen-presenting cell; Treg, regulatory T cells; CD4, cluster of differentiation 4; TNF, tumor necrosis factor; IL, interleukin.

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UPDATE FROM THE PALIZADE TRIAL FOR LUPUS NEPHRITIS (LN)

Rachel Peterson, MD
Head of Clinical Immunology

Safety and Clinical Activity of Zetomipzomib in the PALIZADE Trial

- Phase 2b global clinical trial tested 2 zetomipzomib dose levels (30 and 60 mg) vs. placebo in patients with lupus nephritis (LN) and enrolled 84 patients prior to study termination
- In patients reaching 6 months of treatment, zetomipzomib 60 mg treatment was associated with an ~80% reduction in median urine to protein creatinine ratio (UPCR) and marked improvements in anti-dsDNA antibody and complement levels
- Four fatalities (1 placebo, 2 at 30 mg, 1 at 60 mg*) occurred in patients with pre-existing adrenal insufficiency, potential systemic infections at baseline, and/or underlying severe disease characteristics
- Overall safety profile of zetomipzomib was similar to findings from the MISSION LN study and consistent with other LN studies, supporting continued development of zetomipzomib in autoimmune hepatitis

Data from the PALIZADE clinical trial are preliminary and require further confirmation and analysis.
These data may be subject to verification procedures that could result in material changes to the final data.

*Patient was randomized to the zetomipzomib 60 mg treatment arm but only received an initial dose of 30 mg.

MISSION Trial Results Supported Design of PALIZADE Study

MISSION LN Trial

- Open-label Phase 2 trial enrolled 21 participants with active Class III or IV ± V LN in the US, Australia, Eastern Europe and Latin America who had an inadequate response to standard of care
- Weekly administration of zetomipzomib at 60 mg dose was added to background therapy and did not involve pulse intravenous steroid treatment (induction therapy)

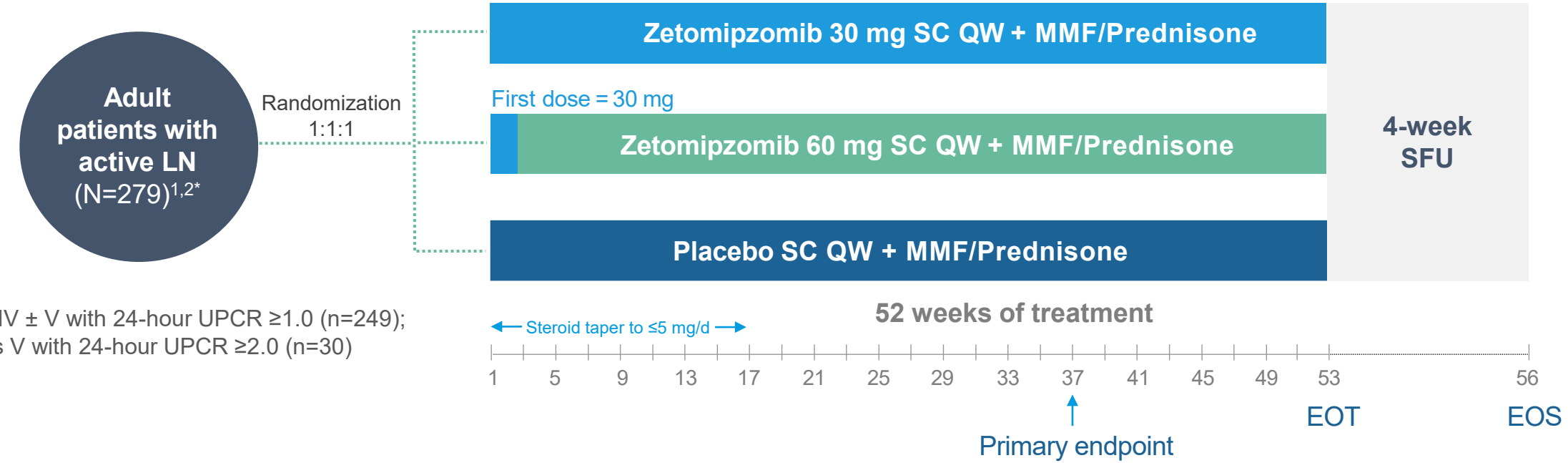
MISSION Efficacy Data

- Of treatment evaluable participants (N=17), 35% achieved a Complete Renal Response (CRR) at Week 25
- Serologic (e.g., anti-dsDNA antibodies) and biomarker (i.e., gene expression) data support mechanism of action (MOA) of broad immunomodulatory activity and therapeutic potential in LN and AIH

Safety Consistent Across Multiple Autoimmune Indications

- Most common adverse event (AE) related to transient injection site reactions (ISR)
- No Grade 3 or opportunistic infections and no signs of immunosuppression observed in MISSION and placebo-controlled PRESIDIO trial in patients with polymyositis and dermatomyositis

PALIZADE: Phase 2b Placebo-Controlled Trial Evaluating the Efficacy and Safety of Zetomipzomib in Participants with Active LN



*Class IIII/IV ± V with 24-hour UPCR ≥1.0 (n=249); Class V with 24-hour UPCR ≥2.0 (n=30)

Notable differences from MISSION Phase 2 (as requested by FDA):

- Pulse IV steroid treatment
- Inclusion of isolated Class V LN

Primary Endpoint: Proportion of participants achieving CRR (UPCR ≤0.5 and eGFR ≥60 mL/min/1.73 m^2 or no confirmed decrease of >20% from baseline eGFR) at week 37.

Abbreviations: eGFR, estimated glomerular filtration rate; EOS, end of study; EOT, end of treatment; IV, intravenous; MMF, mycophenolate mofetil; PBO, placebo; SC, subcutaneous; SFU, safety follow-up; UPCR, urine protein to creatinine ratio.

References: 1. Clinicaltrials.gov Accessed April 11, 2023. https://clinicaltrials.gov/ct2/show/NCT05781750. 2. Kezar Life Sciences. Data on file.

LN is a Life-Threatening Condition and Fatalities Have Been Observed in Global Clinical Trials

- Nephritis is the most severe manifestation of lupus and in those diagnosed before 40 years of age, there is a 12x higher standardized mortality vs. the general population, with infection as the leading cause of death[1]
- High dose and intravenous (IV) corticosteroids (induction therapy) are commonly used in LN treatment and are associated with **increased infections**, **adrenal insufficiency**, and overall mortality[2,8-10]
  - Baseline steroid levels in PALIZADE (including IV methylprednisolone-based induction therapy) were higher vs. MISSION
- Across multiple trials of novel agents (e.g., voclosporin, belimumab, obinutuzumab), fatality rates up to 5% were observed, including imbalances relative to control arms[3-7]
  - Frequent causes of death include infections and acute respiratory distress, with rates highest in patients enrolled from the Asia-Pacific (APAC) region
- SAE rates in these trials were as high as 30%, with infection being the most common[2-7]
  - In one trial, the majority of AEs occurred within the first 6 months of trial and the majority of deaths occurred within the first 2 months[4]

References: 1. Hocaoğlu M et al Arthritis Rheumatol. 2023 Apr;75(4):567-573. doi: 10.1002/art.42375. 2. Figueroa-Parra G et al. *Arthritis Rheumatol.* 2024;76:1408-1418.
3. Furie R et al. *N Engl J Med*. 2020;383:1117-1128; 4. Rovin BH et al. *Kidney* Int. 2019:219-231; 5. Rovin BH et al. *Lancet*. 2021;397:2070-2080;
6. Mysler EF et al. *Arthritis Rheum.* 2013;65(9):2368-2379. 7. Furie RA et al. *N Engl J Med.* 2025 Feb 7 doi: 10.1056/NEJMoa2410965. 8. Broersen LHA et al. *J Clin Endocrinol Metab*. 2015;100:2171-2180.
9. Ngaosuwan K et al. *J Clin Endocrinol Metab.* 2021;106(5):1284-1293. 10. Allosso F et al. *BMJ Open*. 2024;14(1):e076582.

PALIZADE Enrollment Metrics and Trial Termination

- 84 patients enrolled at the time of termination (October 2024) with 56% of patients enrolled in APAC region
  - All enrolled participants were included in the safety analysis
  - Prior to termination, the discontinuation rate was less than 15%
- Independent Data Monitoring Committee (IDMC) recommended suspending enrollment and dosing following 15 SAEs (18% of enrolled patients), including 4 fatalities (4.7%)
  - Among 11 patients with non-fatal Serious Adverse Events (SAEs):
    - 4 patients experienced Grade 1 and 2 events (1 placebo, 3 in 60 mg arm)
    - 4 patients experienced Grade 3 events (2 in 30 mg arm, 2 in 60 mg arm) deemed related by the principal investigator
    - 3 patients experienced Grade 3 events (1 in 30 mg arm, 2 in 60 mg arm) deemed unrelated by the principal investigator
- Additional analyses are ongoing and final data may change; full data will be reviewed with the IDMC and submitted to the FDA
- A submission to a medical conference for presentation is planned for the second half of 2025

Significant Baseline Co-Morbidities Including Infections, Adrenal Insufficiency, and Severe Disease Characteristics Were Observed in Fatal Events

- Trial enrolled at 1:1:1 randomization of zetomipzomib (30 and 60 mg) to placebo
  - Fatalities observed across cohorts: 1 placebo, 2 at 30 mg, 1 at 60 mg*
- Patient 1 (Placebo)
  - **Cause of Death:** Respiratory insufficiency and ischemic stroke
  - **Baseline feature:** Adrenal insufficiency present at screening visit
- Patient 2 (30 mg):
  - **Cause of death:** Cardiac insufficiency
  - **Baseline feature**: Signs of pulmonary hypertension during pre-screening period
  - **On study events:** Laboratory values suggestive of potential antiphospholipid syndrome (APS)

*Patient was randomized to the zetomipzomib 60 mg treatment arm but only received an initial dose of 30 mg.

Significant Baseline Co-Morbidities Including Infections and Adrenal Insufficiency Were Observed in Fatal Events

- Patient 3 (30 mg)
  - **Cause of Death:** Acute respiratory distress
  - **Baseline feature:** Adrenal insufficiency
  - **Day of first dose:** C reactive protein (CRP) levels more than 20-fold higher than upper limit of normal on the day of the first dose of zetomipzomib, suggestive of a systemic infection prior to dosing
- Patient 4 (60 mg*)
  - **Cause of Death:** Severe dehydration, hypovolemic shock
  - **Baseline feature:** Adrenal insufficiency
  - **24 hours post-1st dose**: Procalcitonin levels (a specific indicator of systemic bacterial infection) was more than 1,000-fold above the upper limit of normal indicating a high likelihood of severe bacterial sepsis/septic shock less than 24 hours after the first dose of zetomipzomib

*Patient was randomized to the zetomipzomib 60 mg treatment arm but only received an initial dose of 30 mg.

Demographic and Baseline Characteristics (Safety Population)

	Placebo N=28 n (%)	Zetomipzomib 30 mg N=27 n (%)	Zetomipzomib 60 mg N=29 n (%)	All participants N=84 n (%)
Age, mean (SD), years	32.8 (9.1)	31.0 (10.5)	32.5 (9.4)	32.1 (9.6)
Female, n (%)	25 (89.3)	25 (92.6)	28 (96.6)	78 (92.9)
Race, n (%)				
White	9 (32.1)	6 (22.2)	7 (24.1)	22 (26.2)
Black or African American	3 (10.7)	1 (3.7)	1 (3.4)	5 (6.0)
Asian	13 (46.4)	19 (70.4)	15 (51.7)	47 (56.0)
American Indian or Alaskan Native	2 (7.1)	1 (3.7)	5 (17.2)	8 (9.5)
Other	1 (3.6)	0 (0.0)	1 (3.4)	2 (2.4)
Ethnicity, n (%)				
Hispanic or Latino	13 (46.4)	5 (18.5)	10 (34.5)	28 (33.3)
SLE duration, mean (SD), years	6.7 (5.8)	4.7 (5.0)	8.1 (6.2)	6.5 (5.8)
LN duration, mean (SD), years	4.3 (4.5)	1.8 (2.3)	5.0 (5.4)	3.7 (4.5)
LN class, n (%)				
Class III only	5 (17.9)	4 (14.8)	8 (27.6)	17 (20.2)
Class IV only	11 (39.3)	10 (37.0)	13 (44.8)	34 (40.5)
Class III + V	3 (10.7)	5 (18.5)	3 (10.3)	11 (13.1)
Class IV + V	5 (17.9)	4 (14.8)	2 (6.9)	11 (13.1)
Pure Class V	4 (14.3)*	4 (14.8)	3 (10.3)	11 (13.1)

*One Class IV patient in the placebo arm was incorrectly classified as Class V.
Abbreviation: SD, standard deviation.

Demographic and Baseline Characteristics (Safety Population), Cont'd

	Placebo N=28 n (%)	Zetomipzomib 30 mg N=27 n (%)	Zetomipzomib 60 mg N=29 n (%)	All participants N=84 n (%)
24-hour UPCR, mean (SD), mg/mg	3.1 (1.6)	3.7 (2.0)	3.6 (2.1)	3.5 (1.9)
SLEDAI-2K, mean (SD)	10.5 (5.0)	11.8 (5.3)	11.7 (5.5)	11.3 (5.2)
eGFR, mean (SD), mL/min/1.73 m^2	114.0 (26.8)	113.0 (27.6)	97.6 (32.5)	108.0 (29.8)
Concomitant medications*, n (%)				
MMF (or equivalent)	28 (100)	27 (100)	29 (100)	84 (100)
Prednisone (or equivalent)	28 (100)	27 (100)	28 (96.6)	83 (98.8)
IV Methylprednisolone	23 (82.1)	22 (81.5)	23 (79.3)	68 (81.0)
Antimalarial (e.g. hydroxychloroquine)	25 (89.3)	25 (92.6)	24 (82.8)	74 (88.1)

*Data for concomitant medications are preliminary and undergoing further review.

PALIZADE Safety Overview

Adverse Events	Placebo N=28 n (%)	Zetomipzomib 30 mg N=27 n (%)	Zetomipzomib 60 mg N=29 n (%)
Participants with at least 1 Treatment Emergent Adverse Event (TEAE)	17 (60.7)	23 (85.2)	25 (86.2)
Deaths	1 (3.6)	2 (7.4)	1‡ (3.4)
Most common TEAEs:			
Systemic injection reaction (SIR)	3 (10.7)	14 (51.9)	20 (69.0)
Injection site reaction (ISR)	2 (7.1)	6 (22.2)	13 (44.8)
TEAE leading to study drug discontinuation	1 (3.6)	4 (14.8)	4 (13.8)
Grade 3 or 4 TEAE	3 (10.7)	4 (14.8)	8¶ (27.6)
Grade ≥3 Infectious TEAE	0 (0)	2 (7.4)	3 (10.3)
Opportunistic Infections†	0 (0)	0 (0)	0 (0)

Per protocol definition, SIRs are specific AEs occurring within 8 to 24 hours post-dose, usually resolving within 48 hours post-dose, and consist of ≥1 of the following signs/symptoms: hypotension, tachycardia, nausea, vomiting, dizziness, headache, pyrexia, rigors, and/or chills

- Most of these SIR-related AEs have multiple potential etiologies including con-meds (e.g., nausea) or intercurrent illness (e.g., fever).
- **86% of SIR-related AEs were Grade 1 or Grade 2**
- **98% of ISR-related AEs were Grade 1 or Grade 2**

†Opportunistic infections were evaluated by the Sponsor through clinical assessment of reported infections.
‡One participant with a fatal event was randomized to the zetomipzomib 60 mg arm but only received an initial dose of zetomipzomib 30 mg.
¶Four participants with serious TEAE were randomized to the zetomipzomib 60 mg arm but received zetomipzomib 30 mg before SAE (2 were on the first dose).

PALIZADE Safety: Infectious TEAEs

Adverse Events	Placebo N=28 n (%)	Zetomipzomib 30 mg N=27 n (%)	Zetomipzomib 60 mg N=29 n (%)
Infectious TEAE	13 (46.4)	13 (48.1)	11 (37.9)
Most common infectious TEAEs*			
Upper respiratory tract infections	1 (3.6)	6 (22.2)	2 (6.9)
Nasopharyngitis	0 (0)	1 (3.7)	4 (13.8)
Gastroenteritis	0 (0)	1 (3.7)	3 (10.3)
Herpes zoster	2 (7.1)	1 (3.7)	1 (3.4)
Pneumonia	0 (0)	2 (7.4)	0 (0)
Grade ≥3 Infectious TEAE†	0 (0)	2 (7.4)	3 (10.3)
Opportunistic Infections‡	0 (0)	0 (0)	0 (0)

Mean immune cell counts or immunoglobulin levels were not reduced to below lower limit of normal in either zetomipzomib treatment arm

*Infectious TEAEs occurring in ≥2 participants in any treatment arm are reported here.

†30 mg arm: Grade 3 pseudomonas infection (related, recovered), Graded 3 community acquired pneumonia (related, recovered)
60 mg arm: Grade 3 septic shock and Grade 4 urinary tract infection (both unrelated, recovered); Grade 3 unspecified bacterial pneumonia (related, recovered); Grade 3 dengue fever (unrelated, recovered).

‡Opportunistic infections were evaluated by sponsor through clinical assessment of reported infections.

Safety Profile in PALIZADE is Similar to MISSION Study and Supports Development in Autoimmune Hepatitis

Trial/Treatment arm/Dose (N)	MISSION Ph 2 Zetomipzomib 60 mg N=21 n (%)	PALIZADE Placebo N=28 n (%)	PALIZADE Zetomipzomib 30 mg N=27 n (%)	PALIZADE Zetomipzomib 60 mg N=29 n (%)	PRESIDIO Placebo N=22 n (%)	PRESIDIO Zetomipzomib 45 mg N=25 n (%)
Indication	**Lupus Nephritis**				**Polymyositis & Dermatomyositis**	
Treatment Period (Weeks)	**24**	**52***			**16**	
At least one TEAE, n (%)	21 (100.0)	17 (60.7)	23 (85.2)	25 (86.2)	16 (72.7)	22 (88.0)
Serious TEAEs, n (%)	2 (9.5)	3 (10.7)	5 (18.5)	8 (27.6)	1 (4.5)	2 (8.0)
Grade 3 or 4 TEAEs, n (%)	6 (28.6)	3 (10.7)	4 (14.8)	8¶ (27.6)	2 (9.1)	2 (8.0)
TEAEs leading to study drug discontinuation, n (%)	4 (19.0)	1 (3.6)	4 (14.8)	4 (13.8)	0 (0)	1 (4.0)
Infectious TEAEs, n (%)	9 (42.9)	13 (46.4)	13 (48.1)	11 (37.9)	6 (27.3)	7 (28.0)
Grade ≥3 infectious TEAEs, n (%)	0 (0)	0 (0)	2 (7.4)	3 (10.3)	1 (4.5)	0 (0)
Opportunistic infections‡, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Death, n (%)	0 (0)	1 (3.6)	2 (7.4)	1 (3.4)†	0 (0)	0 (0)

*No participants completed 52 weeks.
†Patient was randomized to the zetomipzomib 60 mg but only received an initial dose of zetomipzomib 30 mg.
‡Opportunistic infections were evaluated by sponsor through clinical assessment of reported infections.
¶Four participants with serious TEAE were randomized to the zetomipzomib 60 mg arm but received zetomipzomib 30 mg before SAE (2 were on the first dose).

Efficacy Analysis Indicates Clinical Activity of Zetomipzomib in LN

- Planned enrollment was 279 patients, including 249 with proliferative LN (Class III or IV ± V) with a planned duration of 52 weeks of treatment and a primary endpoint at Week 37
- 84 patients enrolled prior to termination, of which 73* had Class III or IV ± V disease and are the focus of the efficacy results
- At the time of termination, 39 patients with Class III or IV ± V disease reached Week 25 for UPCR evaluation (primary endpoint of MISSION), and no patients had completed full 52 weeks of treatment
- Preliminary data from a treatment evaluable population (N=39) encompassing proteinuria changes, median UPCR and serologic markers (anti-dsDNA antibodies, C3/C4) at Week 25 are presented here
- Due to small sample sizes and terminated study, rigorous statistical analysis of response rates are not possible
- Analysis is still ongoing and final data may change

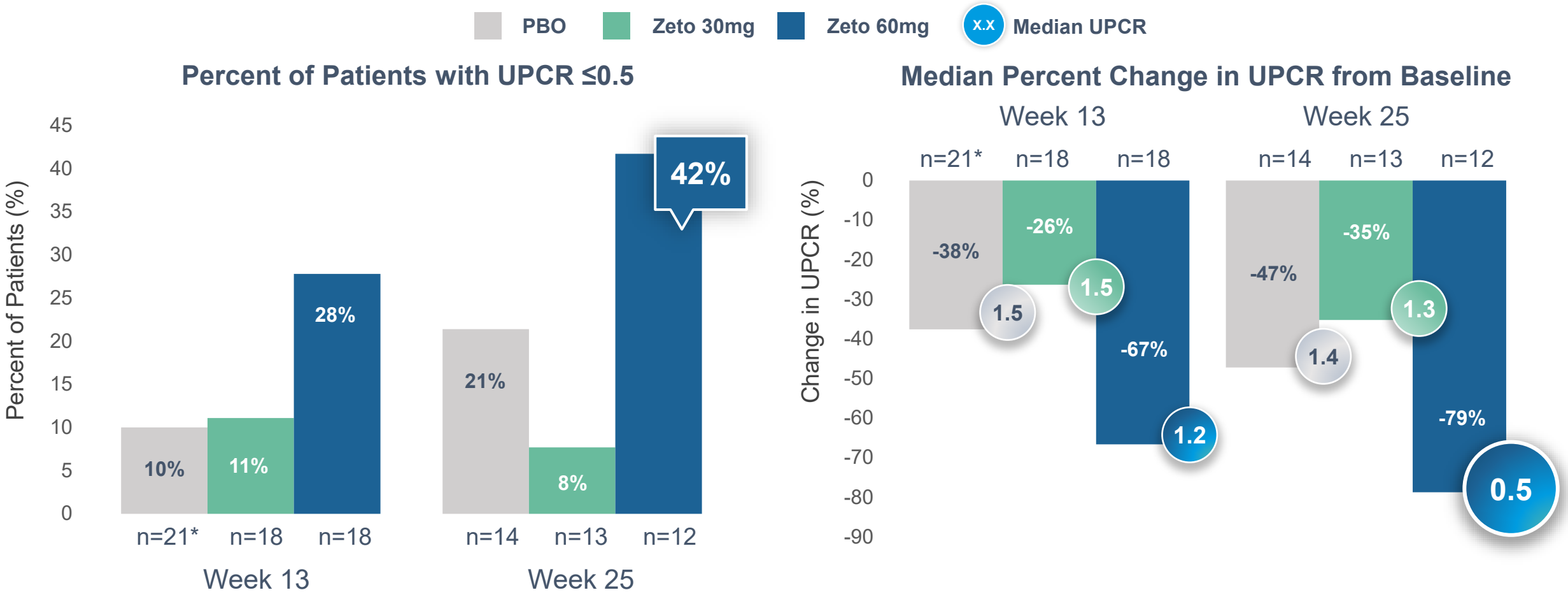
*One Class IV patient in the placebo arm was incorrectly classified as Class V.

Demographic and Baseline Characteristics of Class III/IV ± V LN Patients

	Placebo N=24* n (%)	Zetomipzomib 30 mg N=23 n (%)	Zetomipzomib 60 mg N=26 n (%)	All participants N=73 n (%)
24-hour UPCR, mean (SD), mg/mg	2.9 (1.5)	3.6 (2.2)	3.5 (2.1)	3.3 (2.0)
SLEDAI-2K, mean (SD)	9.9 (4.8)	12.2 (5.6)	12.0 (5.7)	11.4 (5.4)
eGFR, mean (SD), mL/min/1.73 m^2	113.4 (28.8)	113.0 (29.7)	96.2 (32.6)	107.2 (31.2)
Concomitant medications*, n (%)				
MMF (or equivalent)	24 (100)	23 (100)	26 (100)	73 (100)
Prednisone (or equivalent)	24 (100)	23 (100)	25 (96.2)	72 (98.6)
IV Methylprednisolone	20 (83.3)	19 (82.6)	20 (76.9)	59 (80.8)
Antimalarial (e.g. hydroxychloroquine)	21 (87.5)	21 (91.3)	21 (80.8)	63 (86.3)

*One Class IV patient in the placebo arm was incorrectly classified as Class V and is not included in these data.

Rapid Improvement in Proteinuria in Treatment Evaluable Patients with Zetomipzomib



Data from the PALIZADE clinical trial are preliminary and require further confirmation and analysis.
These data may be subject to verification procedures that could result in material changes to the final data.

*Includes 1 Class IV patient in the placebo arm that was incorrectly classified as Class V.

Improvements in Serologic Markers of SLE Were Observed in Both Zetomipzomib Treatment Arms

Serologic Biomarkers*	Placebo N=25†	Zetomipzomib 30 mg N=23	Zetomipzomib 60 mg N=26
Anti-dsDNA			
Number of patients with elevated anti-dsDNA at baseline	21	17	21
Mean % change from baseline at Week 25	**33.0%**	**-38.4%**	**-68.3%**
Complement 3 (C3)			
Number of patients with low C3 at baseline	11	13	16
Mean % change from baseline at Week 25	**15.9%**	**22.7%**	**69.0%**
Complement 4 (C4)			
Number of patients with low C4 at baseline	4	3	9
Mean % change from baseline at Week 25	**32.5%**	**86.1%**	**236.2%**

*No statistical test has been conducted yet.
†Includes 1 Class IV patient in the placebo arm that was incorrectly classified as Class V.

Takeaways From PALIZADE Trial and Impacts on Zetomipzomib Development Program

- Encouraging clinical activity in patients reaching Week 25, including >40% of patients achieving a UPCR ≤0.5 and improved serologic markers in the patients receiving 60 mg dose of zetomipzomib
- Evidence of significant co-morbidities immediately prior to study drug initiation (e.g., systemic infection and adrenal insufficiency) and/or underlying disease (antiphospholipid syndrome) observed in fatal events
- Analysis of safety data from PALIZADE indicates a similar profile between zetomipzomib 30 mg and 60 mg arms and a profile consistent with MISSION study and LN patient population
- Future studies will include increased patient workup and monitoring to decrease the risk of serious adverse events
- No Grade 4 or fatal events were observed in 69 patients across PORTOLA, PRESIDIO or MISSION trials
- Kezar assessment of PALIZADE safety and efficacy data to date and data from >200 patients across multiple trials support continued development of zetomipzomib in autoimmune hepatitis and other autoimmune diseases

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AUTOIMMUNE HEPATITIS: DISEASE BACKGROUND AND TREATMENT OPTIONS

Aparna Goel, MD
Clinical Associate Professor
Division of Gastroenterology & Hepatology
Stanford University

Stanford
MEDICINE

Autoimmune Hepatitis: Disease Background and Treatment Options

Aparna Goel, MD
Clinical Associate Professor
Division of Gastroenterology & Hepatology

Outline

- What is autoimmune hepatitis
- Describe national and global prevalence and demographics
- Diagnosis of autoimmune hepatitis
- Current treatment paradigm
- Challenges in the management of autoimmune hepatitis

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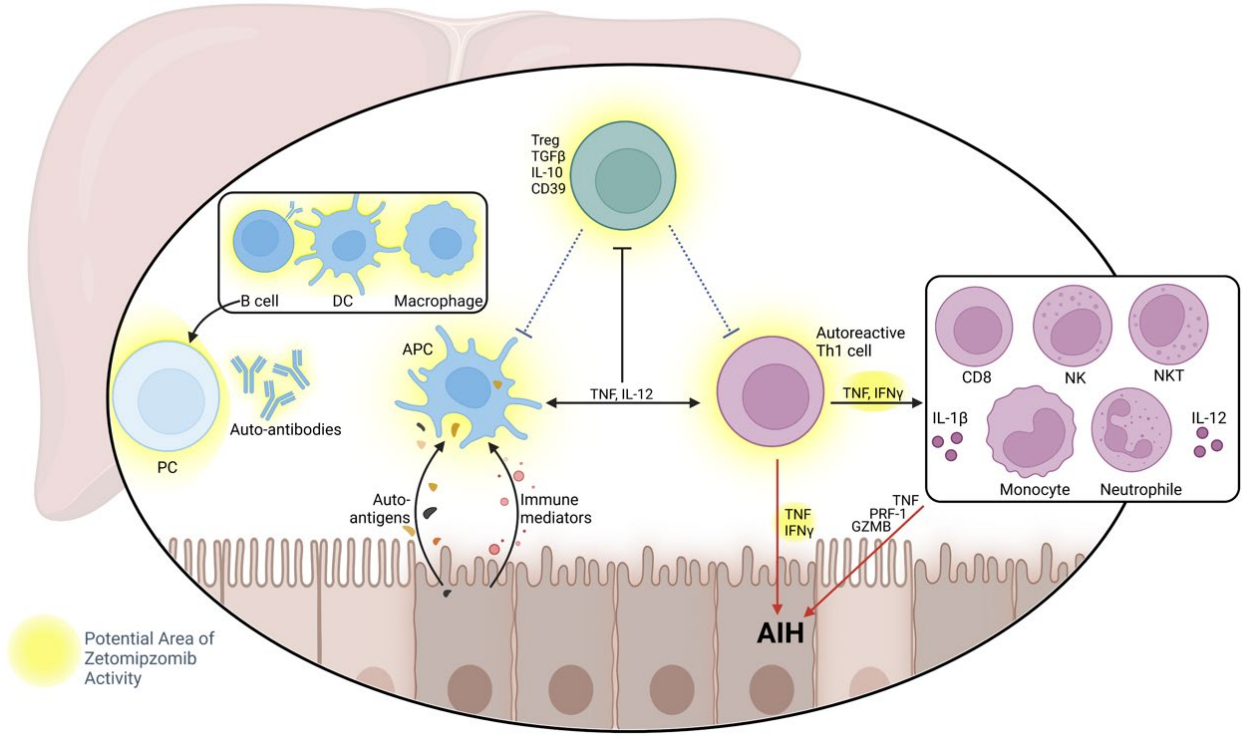
Autoimmune Hepatitis (AIH) is a Complex Disease

- Immune dysregulation that targets hepatocytes
  1. Genetic predisposition
  2. Activation of T-cell driven hepatocyte injury



Genetic predisposition

- Familial clustering
- DRB1*0301 (HLA DR3) & DRB1*0401 (HLA DR4)
- HLA-DRB1 and HLA-DQB1 (type 2)

Triggers

- Drugs (nitrofurantoin, minocycline, interferon, methyldopa, atorvastatin, diclofenac)
- Viruses (hepatitis, EBV, CMV, measles, SARS-CoV-2)

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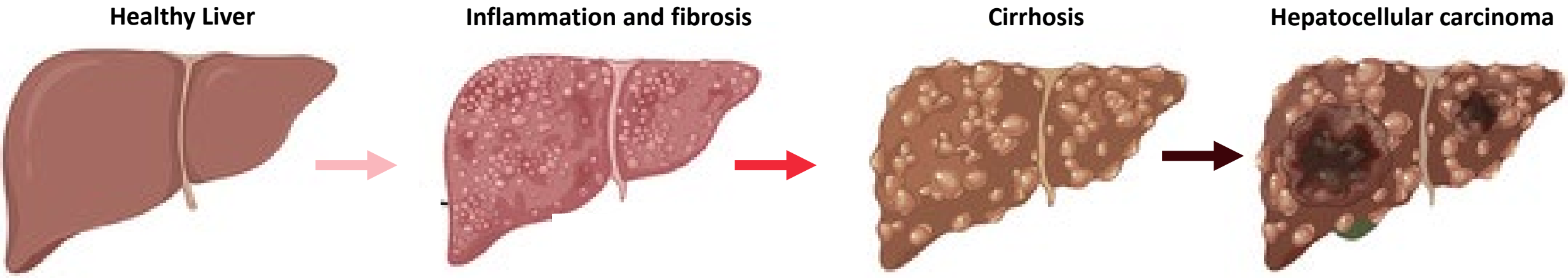
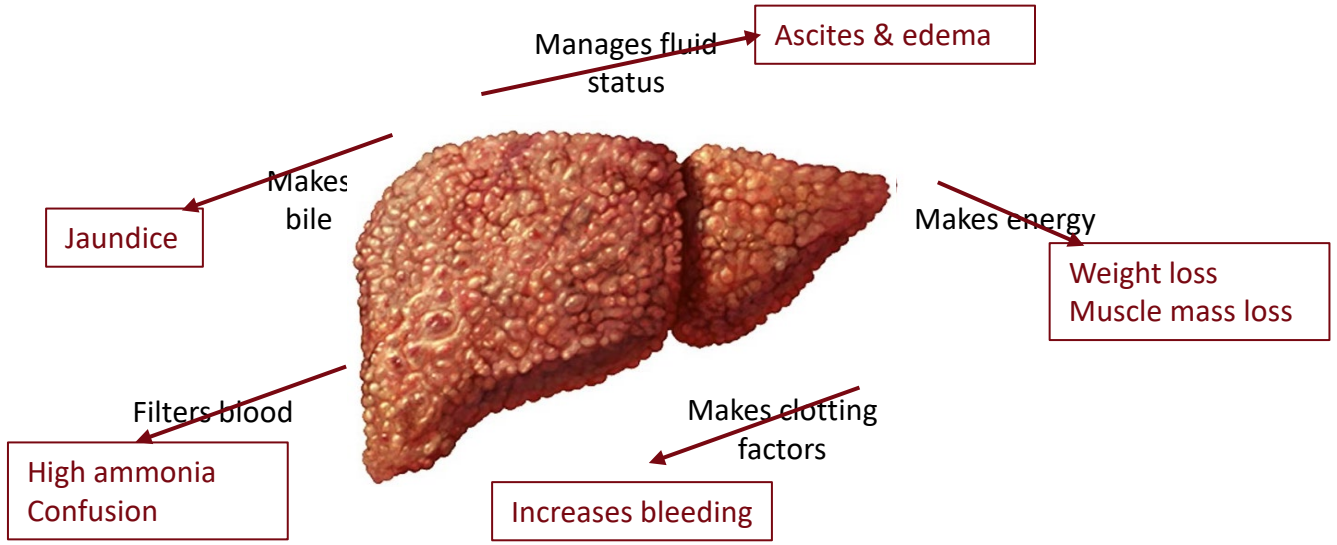
Reau NS et al. *Hepatol Commun*. 2024;8(6):e0458; Herkel J et al. *J Hepatol.* 2020;73(2):446-448.

Without Treatment, AIH Can Progress to Cirrhosis and Liver Failure





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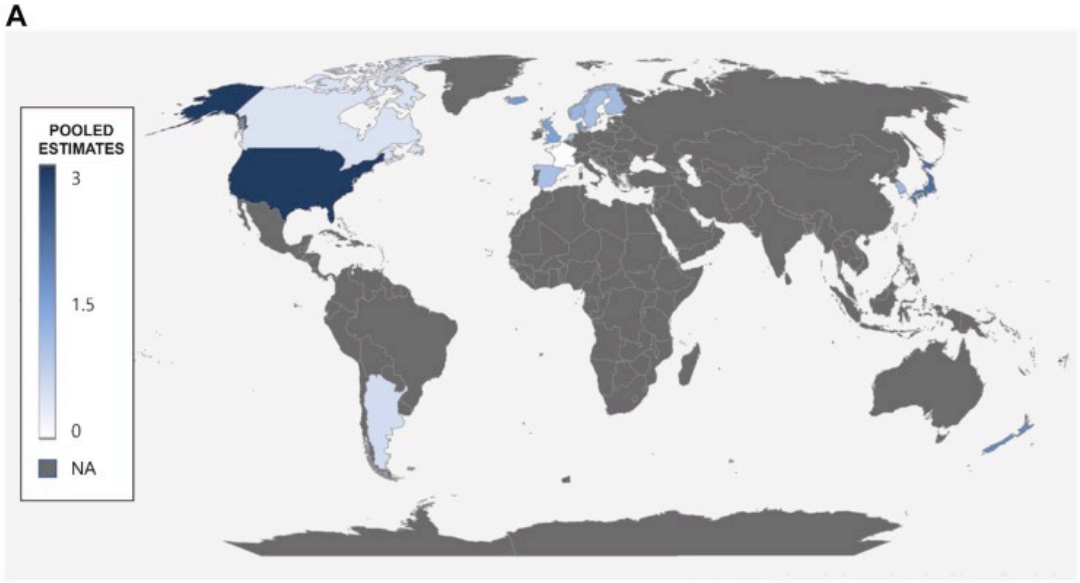
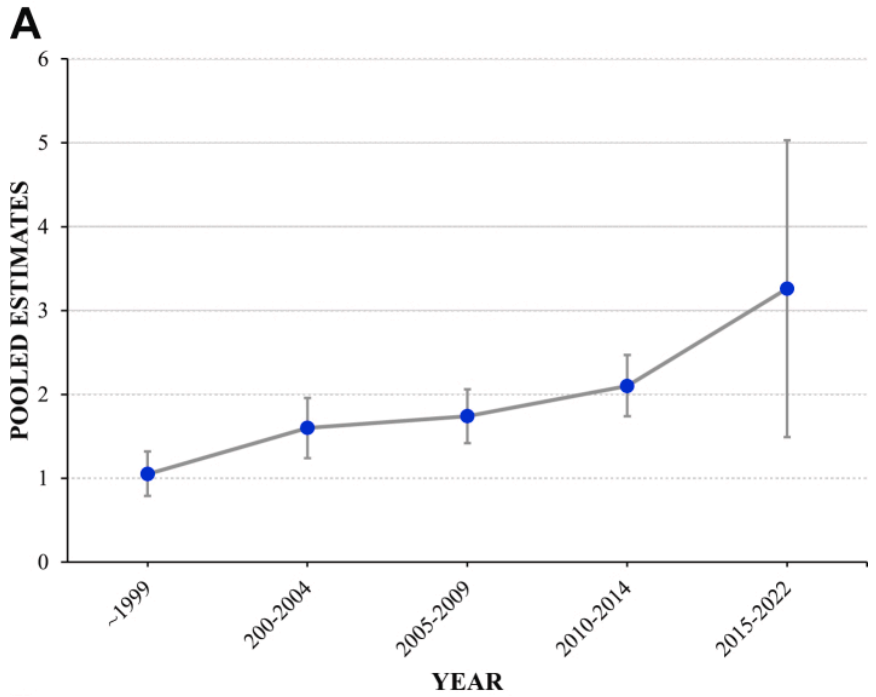
Incidence and Prevalence of AIH





Annual incidence: 0.7-2/100,000

Global prevalence: 4-25/100,000

Hahn JW et al. *EClinicalMedicine.* 2023 Oct 17;65:102280.

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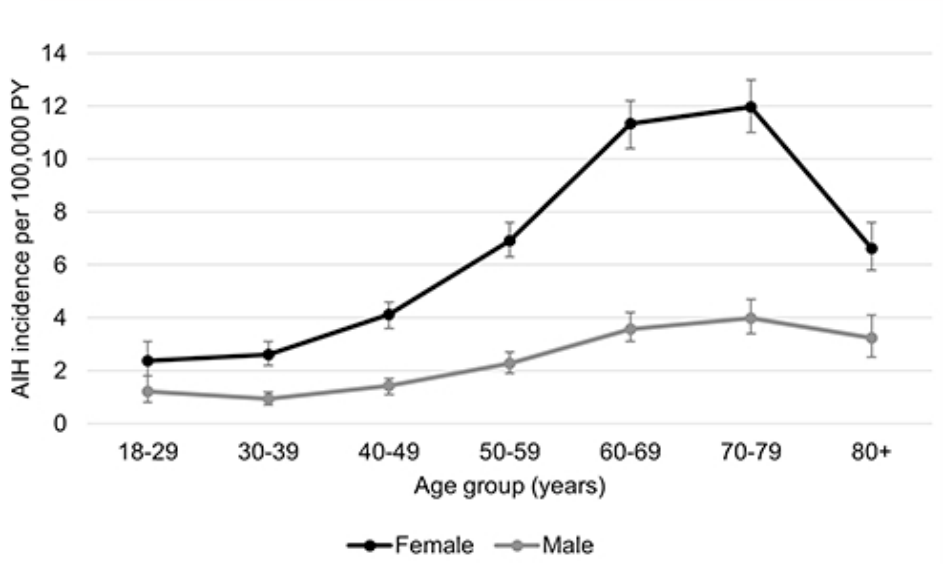
Who Does AIH Impact?

- *Can* affect all ages, races, and ethnicities
  - 60-75% female
  - More prevalent in European and American populations vs Asian populations
  - Hispanic ethnicity or Black race at increased risk of more aggressive forms of AIH



In the United States, ~100,000 people living with AIH

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Bittermann T et al. *Hepatology* 2023;77(2):367-378*;* Hahn JW et al. *EClinicalMedicine.* 2023 Oct 17;65:102280.

Diagnosis of AIH

Asymptomatic	Symptomatic	Acute liver failure
• Incidental abnormal liver tests	• Fatigue, malaise • Anorexia • Jaundice, itch	• Encephalopathy

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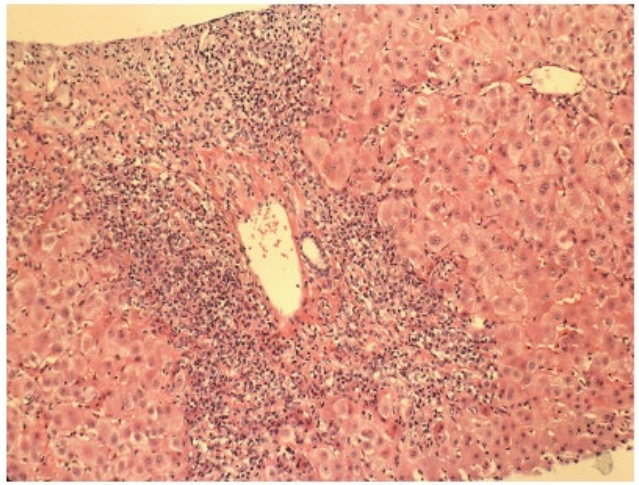
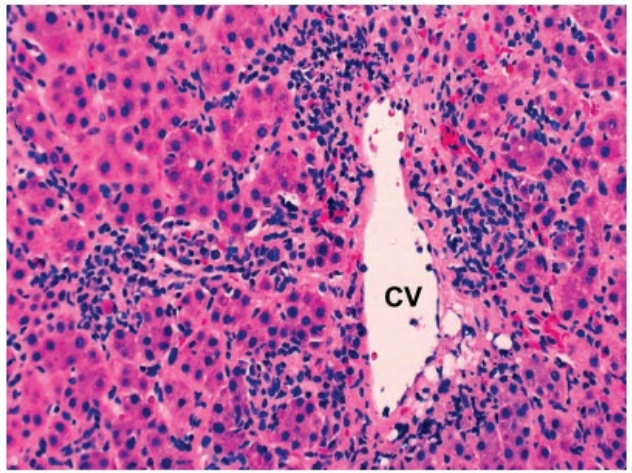
Diagnosis of AIH

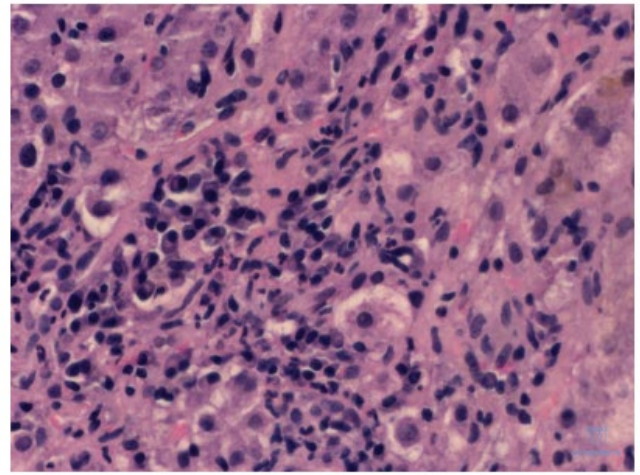
- Hepatocellular pattern
  - Elevated AST and ALT
- Elevated globulins (IgG) in 85%
  - Less frequent in acute cases
- Autoantibodies
  - ANA, smooth muscle, anti-actin antibody, anti-LKM, anti-liver cytosol 1, anti-soluble liver antigen



Interface hepatitis



Centrilobular necrosis



Plasma-cell rich infiltrate

Reau NS et al. *Hepatol Commun*. 2024;8(6):e0458.

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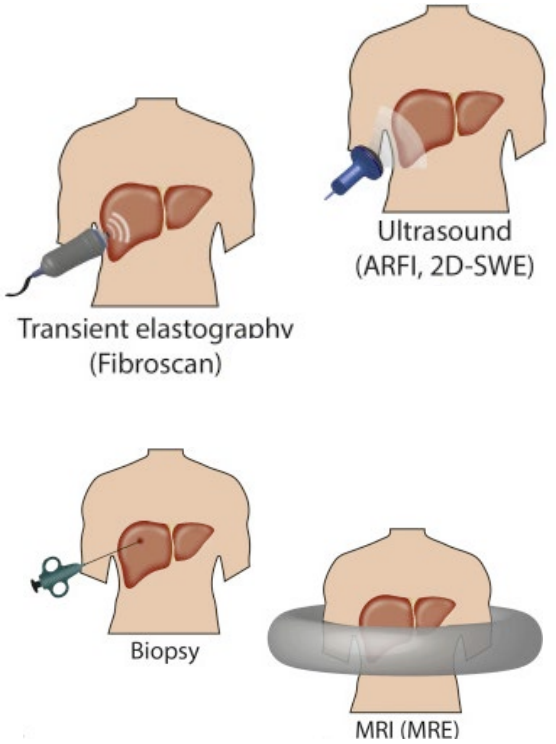
Diagnosis of AIH

Table 2. Simplified Diagnostic Criteria for Autoimmune Hepatitis

Variable	Cutoff	Points
ANA or SMA	≥1:40	1
ANA or SMA	≥1:80	
or LKM	≥1:40	2*
or SLA	Positive	
IgG	>Upper normal limit	1
	>1.10 times upper normal limit	2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with AIH	1
	Typical AIH	2
Absence of viral hepatitis	Yes	2
		≥6: probable AIH
		≥7: definite AIH

*Addition of points achieved for all autoantibodies (maximum, 2 points).



Cirrhosis – present in ~30% at diagnosis

Hennes EM et al. *Hepatology*. 2008 Jul;48(1):169-76.

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Historical Context for AIH Treatment

Prednisone or prednisolone + Azathioprine

2010

Budesonide effective in achieving complete biochemical remission in non-cirrhotic AIH
- CBR: 60% budesonide vs 39% pred

2023

CAMARO trial: ***Mycophenolate mofetil*** vs Azathioprine for treatment-naïve patients
- CBR: 72% MMF vs 32% AZA

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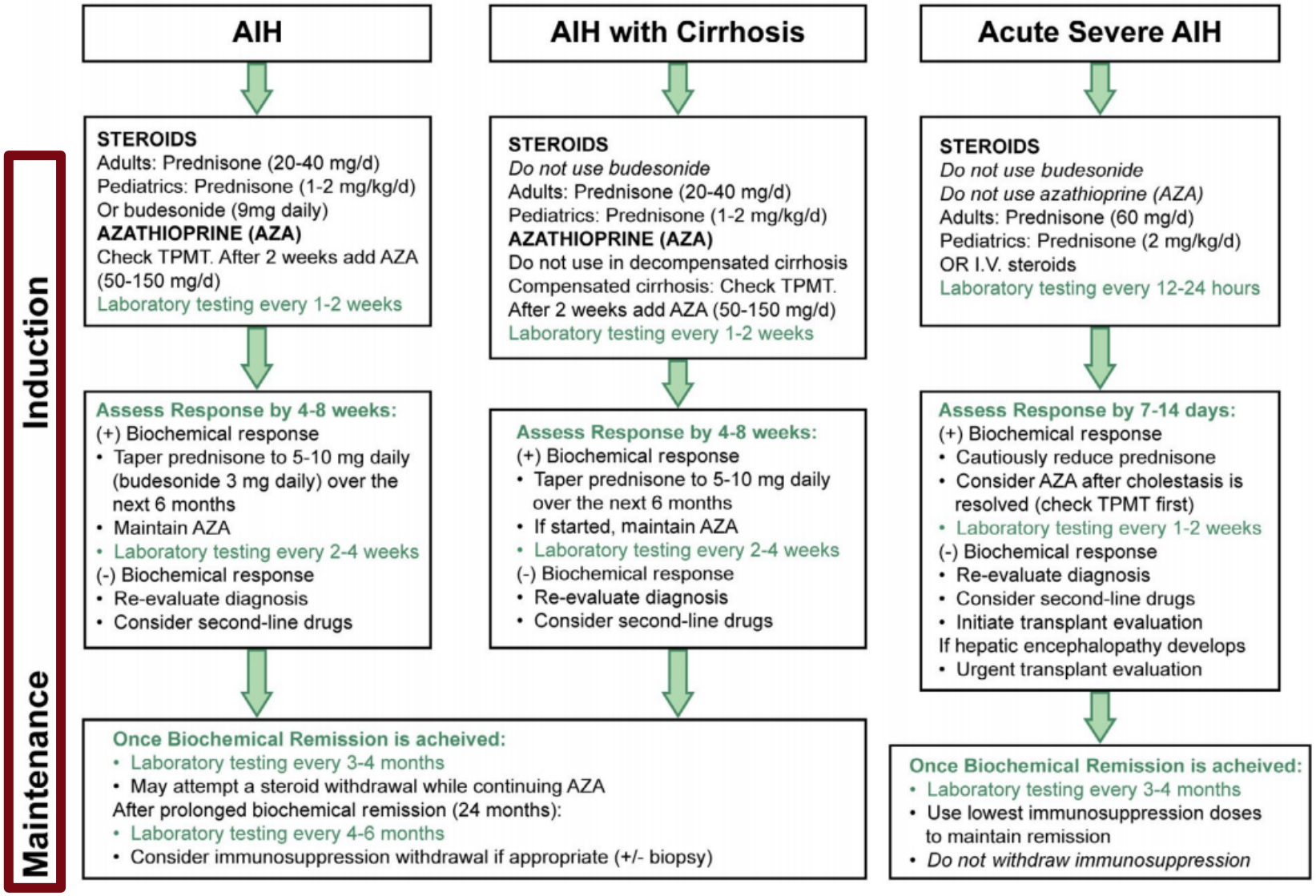
Manns MP et al. *Gastroenterology.* 2010;139(4):1198-206; Snijders, R.J.A.L.M. et al. Journal Of Hepatology, 80(4), 576-585.

Current Treatment for AIH



Mack et al. *Hepatology* 2020;72(2):671-722.

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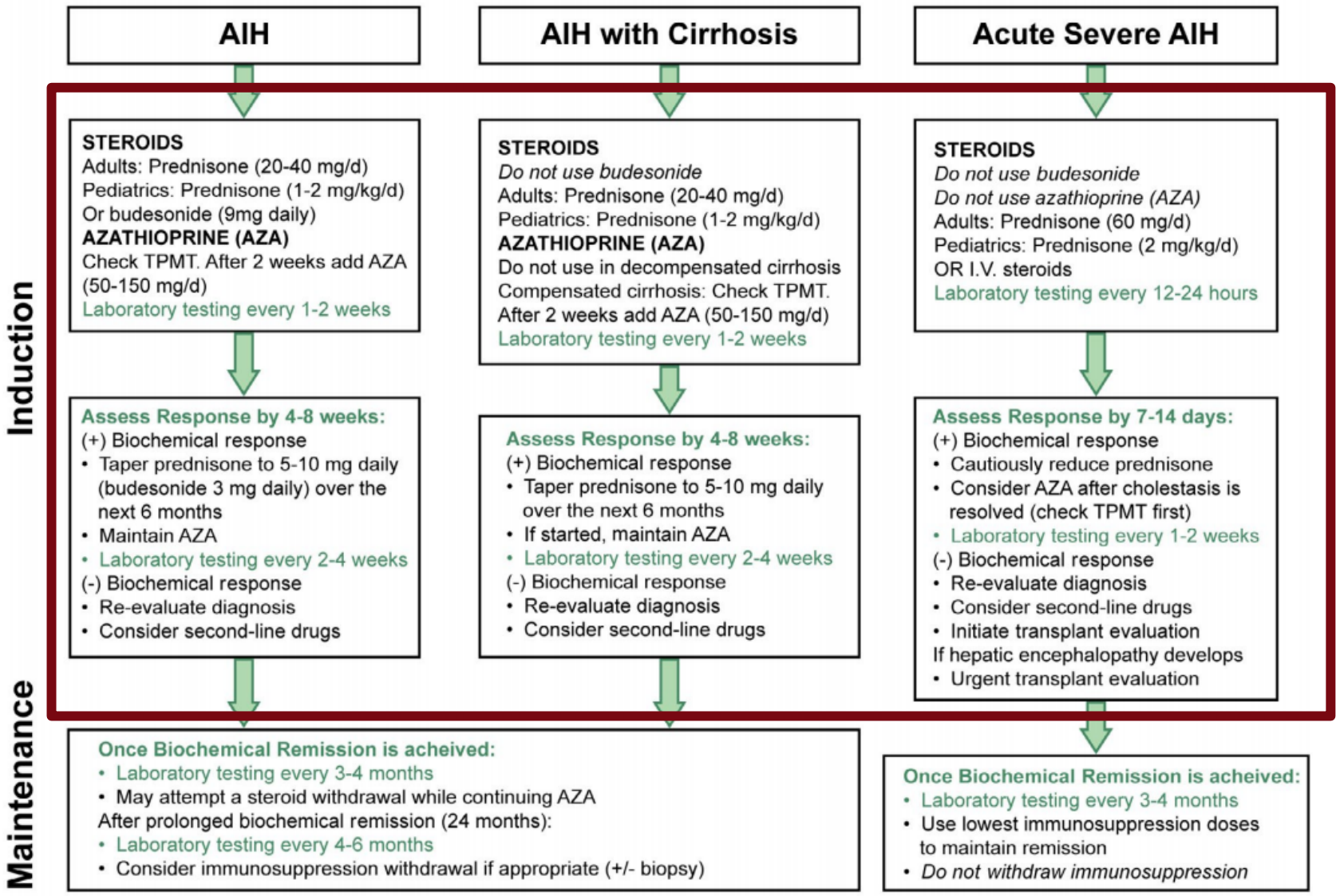
AIH: AASLD First-Line Treatment



Goal of **induction** is to achieve **biochemical remission** *(ideally without steroids)*

- AST, ALT, IgG less than upper limit of normal (ULN) by 6 months
- Histology: eliminate portal inflammation and interface hepatitis
  - Hepatitis Activity Index
- Prevent progression and need for liver transplantation

Mack et al. *Hepatology* 2020;72(2):671-722.

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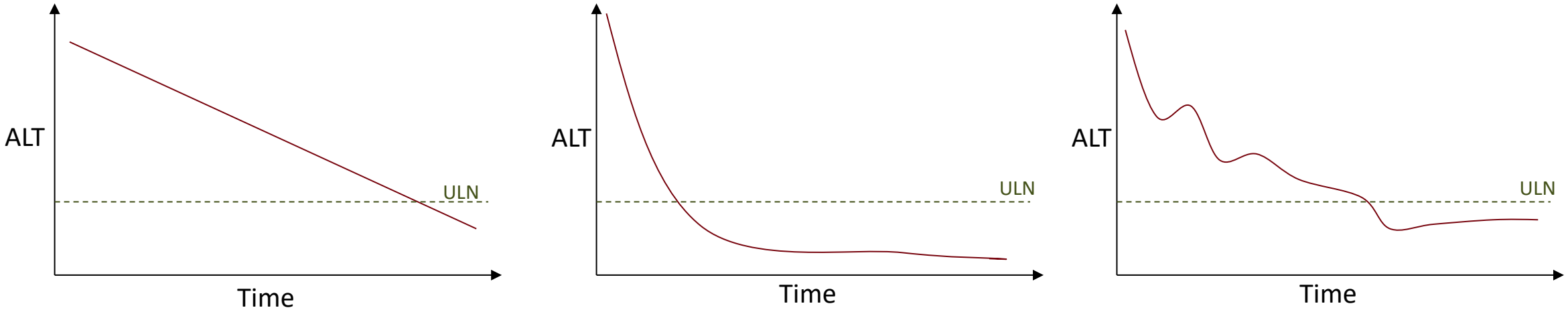
Complete Biochemical Remission



Achieved in ~60% of patients

- ***A proportion are dependent on steroids***

Plagiannakos CG et al. *J Hepatology* 2024:81;227–237; Muratori L et al. *Hepatology* 2010:52(5);2010.

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Tolerance of First-Line Treatment is Poor

	Discontinuation rate	Side effects
Corticosteroids	50% (early) • Mostly due to cosmetic AEs	• Hyperglycemia • Weight gain • Insomnia • Irritability • Hypertension • Acne • Hirsutism • Moon facies • Buffalo hump • Skin striae • Increased intraocular pressure

Czaja AJ. *Expert Rev Gastroenterol Hepatol* .2012:6(5)603-15; Newman WG et al. *Pharmacogenetics* 2011; Manns MP et al. *Gastroenterology.* 2010;139(4):1198-206.

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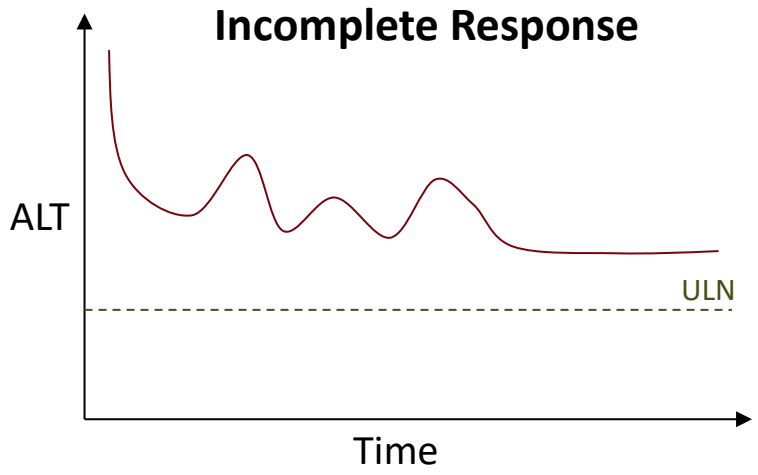
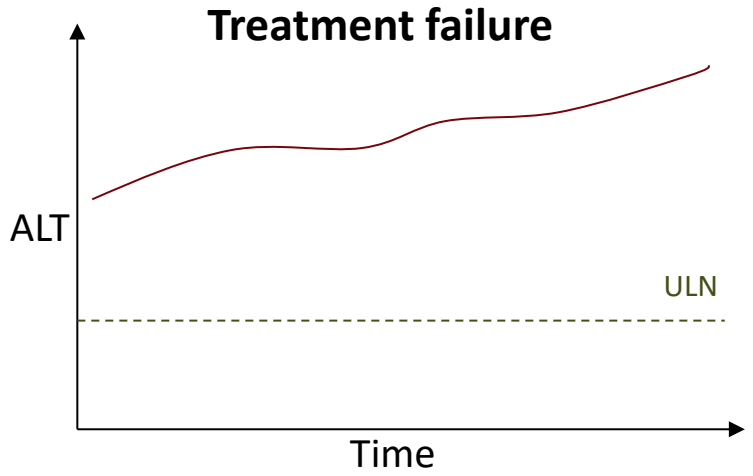
Tolerance of First-Line Treatment is Poor

	Discontinuation rate	Side effects
Azathioprine	10-25% • Mostly due to AEs	• Myelosuppression • GI side effects – nausea, vomiting • Hepatotoxicity • Nodular regenerative hyperplasia • Lymphoma
Mycophenolate Mofetil	5-10%	• Myelosuppression • GI side effects – abdominal pain, nausea, vomiting, oral ulcers • Contraindicated in pregnancy

Czaja AJ. *Expert Rev Gastroenterol Hepatol* .2012:6(5)603-15; Newman WG et al. *Pharmacogenetics* 2011; Manns MP et al. *Gastroenterology.* 2010;139(4):1198-206.

Non-Response to First-Line Therapy





- Reported in up to 40-50% of patients
- Increased incidence of cirrhosis and need for transplantation

Risk factors for non-response:
- Age <20 or >60
- HLA DR3, HLA-B8
- Cirrhosis
- Delayed initial response
- Ferritin <2.1x ULN

Czaja AJ. *Expert Rev Gastroenterol Hepatol* .2012:6(5)603-15; Newman WG et al. *Pharmacogenetics* 2011; Manns MP et al. *Gastroenterology.* 2010;139(4):1198-206; Pape S et al. *Clin Gastroenterol Hepatol.* 2020:18(7):1609-1617; Kirstein MM et al. *Hepatology*. 2015:62(5):1524-1535; Taubert R et al. PLoS ONE 12(6):e0179074.

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‘Rescue’ Therapy Options are Limited

	Clinical setting	Efficacy	Side effects
Tacrolimus	• In combination with steroids, MMF/ AZA • Alternative to AZA if intolerant	Higher biochemical response if intolerance to AZA (94% vs 57%)	• Neurotoxicity • Nephrotoxicity • Hyperglycemia • Hair loss • Nausea
Cyclosporine	• Alternative to tacrolimus • More data in pediatric population from 1980/90s	‘positive response’ noted in 93%	• Nephrotoxicity • Gingival hyperplasia • Hypertrichosis
Sirolimus	• Alternative or adjunctive therapy	Limited data with small case series, improvement in ALT noted in 80%	• Metabolic syndrome • Proteinuria • Edema

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‘Rescue’ Therapy Options are Limited

	Clinical setting	Efficacy	Side effects
Rituximab (anti-CD20)	• Refractory, steroid-dependent disease	• Limited evidence	• Infections, including HBV reactivation
Infliximab (anti-TNFα)	• Refractory, steroid-dependent disease	• Limited evidence • Case-series and retrospective review	• Infection risk, especially in cirrhosis • Anti-drug antibodies • Hepatotoxicity

Than N et al. *J Hep Rep* 2019; Mack CL et al. *Hepatology* 2020;72(2):671-722; Efe C et al. *Hepatology* 2024 Sep 6. doi:10.1097/HEP.0000000000001089.

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A Patient Living with AIH

- 54-year-old woman with hypothyroidism and elevated liver tests (AST/ALT 200s) associated with fatigue.
  - Workup revealed +smooth muscle antibody and +ANA, elevated serum IgG
  - Biopsy was consistent with autoimmune hepatitis, cirrhosis
  - Treated with prednisone 40mg with a good response
  - Azathioprine added → severe fatigue, hepatoxicity
  - MMF allowed reduction of prednisone to 10mg daily by 4 months, but unable to taper further
  - Tacrolimus added, but unable to wean off prednisone and remained on prednisone 5mg daily

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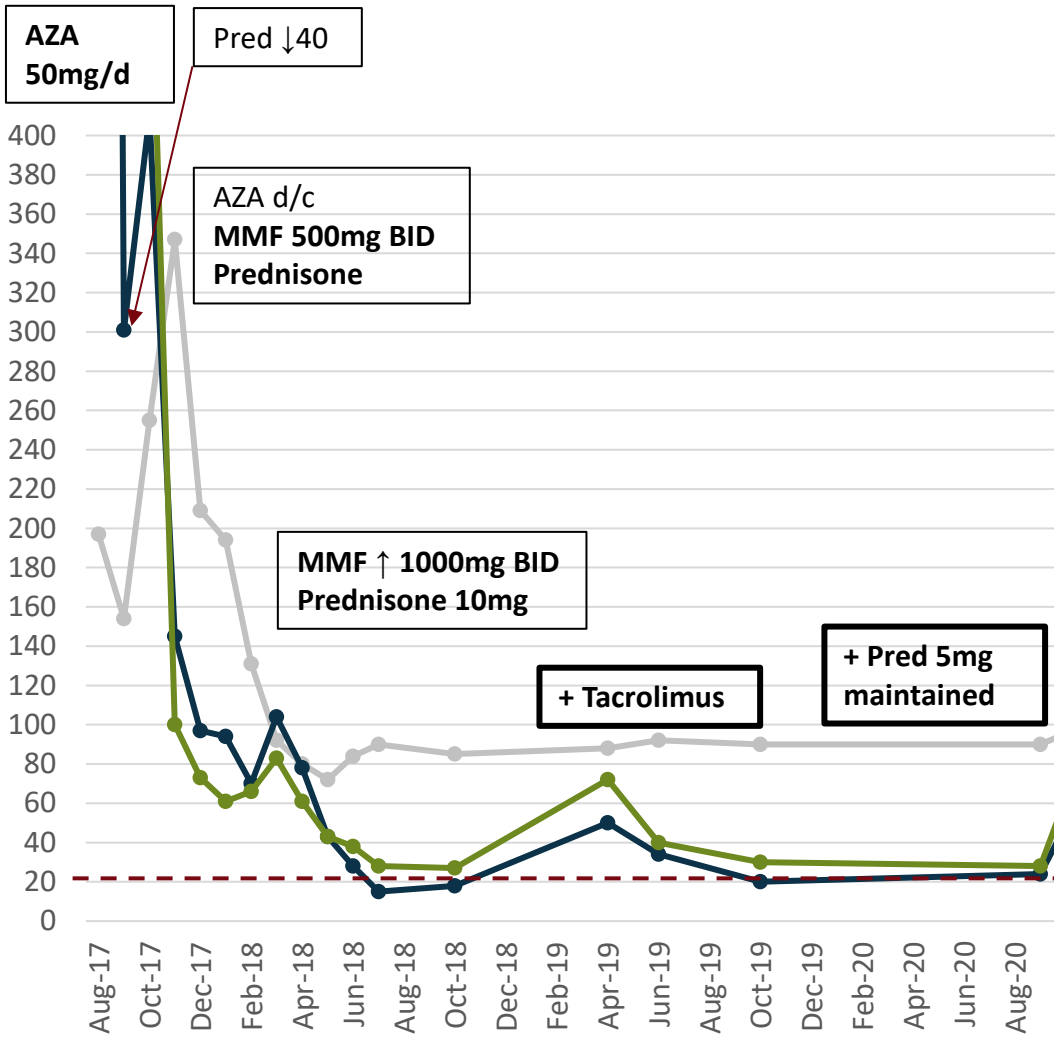
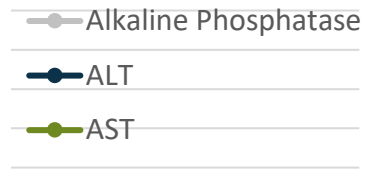
A Patient Living with AIH



Maintained on: MMF, tacrolimus and prednisone for ~3 years

Toxicity from long-term steroids: *osteopenia/ osteoporosis and diabetes, tremors from tacrolimus*



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A Patient Living with AIH

- Flare after COVID-19 infection and unable to achieve complete biochemical remission again despite higher doses of prednisone
- Liver disease has progressed
  - Compensated advanced chronic liver disease (cACLD) with enlarged spleen, low platelets, varices, fluid retention
- Early retirement because fatigue became more problematic and unable to continue working
- Referred for liver transplant evaluation

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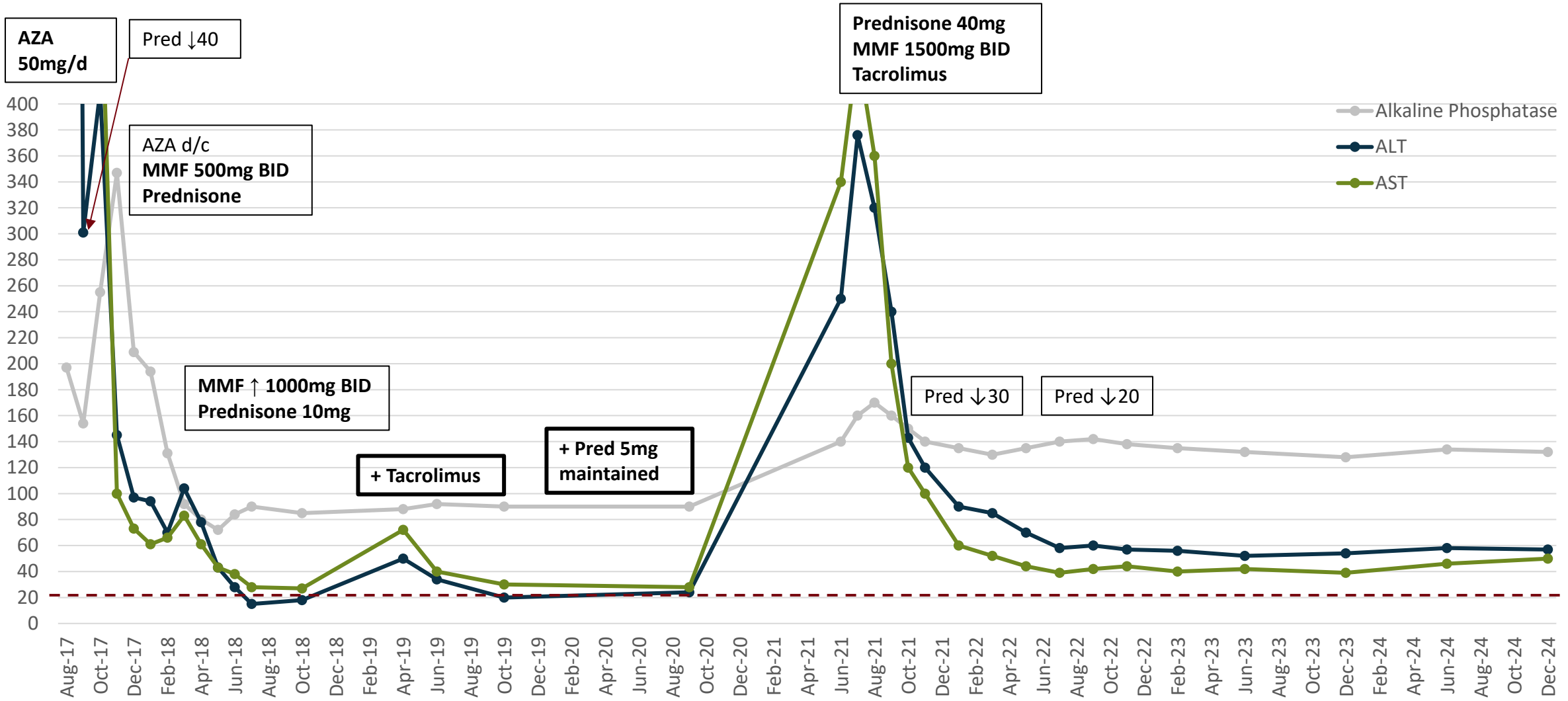
A Patient Living with AIH



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Patient Perspectives

- Autoimmune Hepatitis Association (AIHA) hosted an externally led patient-focused drug development meeting (E-LPFDD) in January 2023. These areas were highlighted by patients:

56% "treatment should have less side effects"

17% improvement in disease symptoms

10% not require daily therapy

10% effect at normalizing liver tests

Jones E et al. *Dig Dis Sci* 2023 Jan;68(1):77-86.

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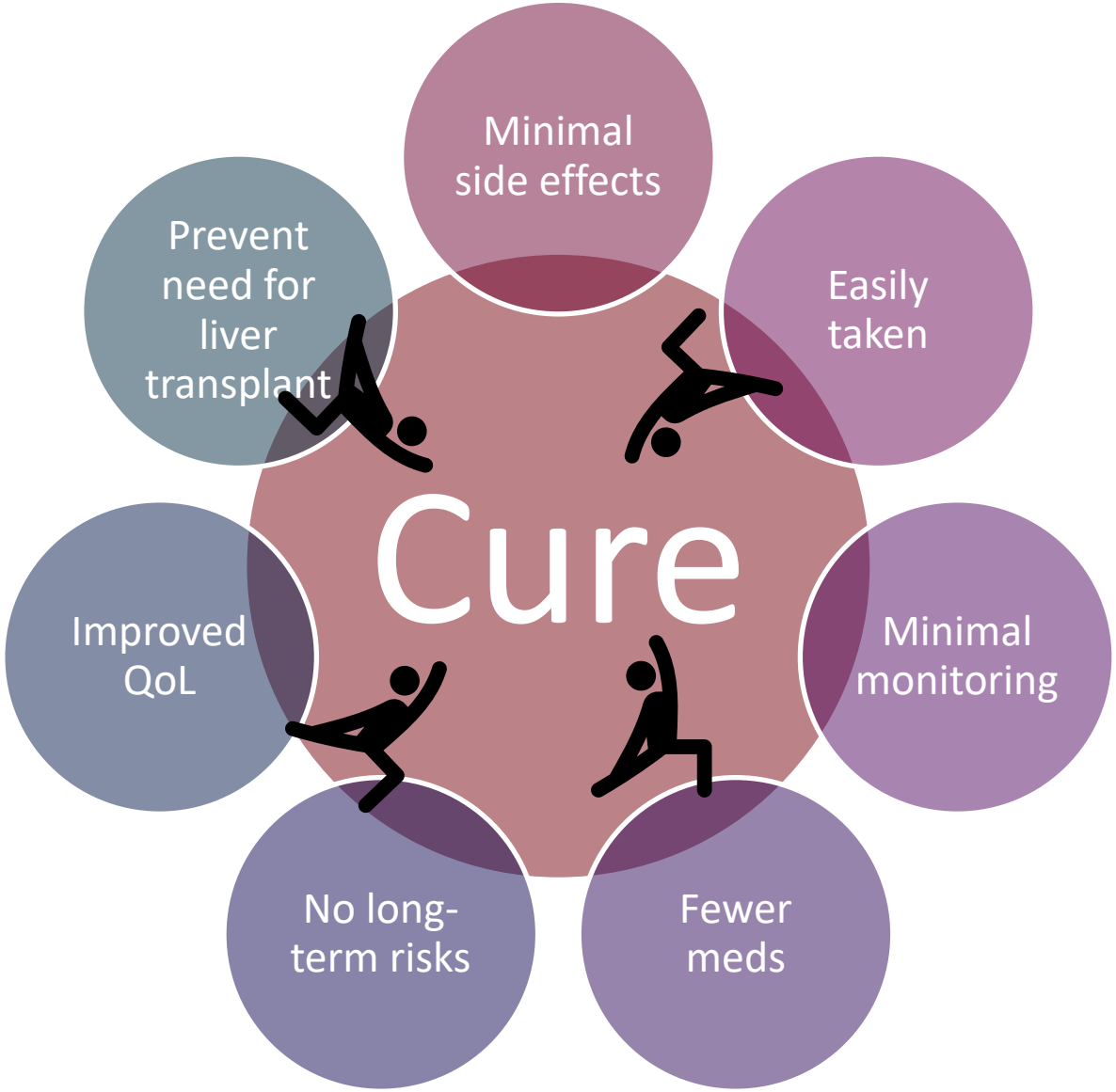
The Ideal Treatment for AIH:



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In Conclusion:

- Autoimmune hepatitis is a disease of immune dysregulation that targets the liver
- AIH predominantly affects women, ages 40-70s.
- The global prevalence and incidence has been increasing
- Without adequate treatment, liver disease progresses to cirrhosis and its many complications including jaundice, ascites, encephalopathy, bleeding and liver cancer

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In Conclusion:

- First line therapies have high discontinuation rates and patients experience many side effects
- Second line therapies are limited with scant data and notable risks
- ~40% of patients do not achieve successful treatment outcomes with currently available therapy
- Patients are asking for better treatment options with fewer side effects
- Zetomipzomib has the potential to transform the therapeutic landscape for autoimmune hepatitis

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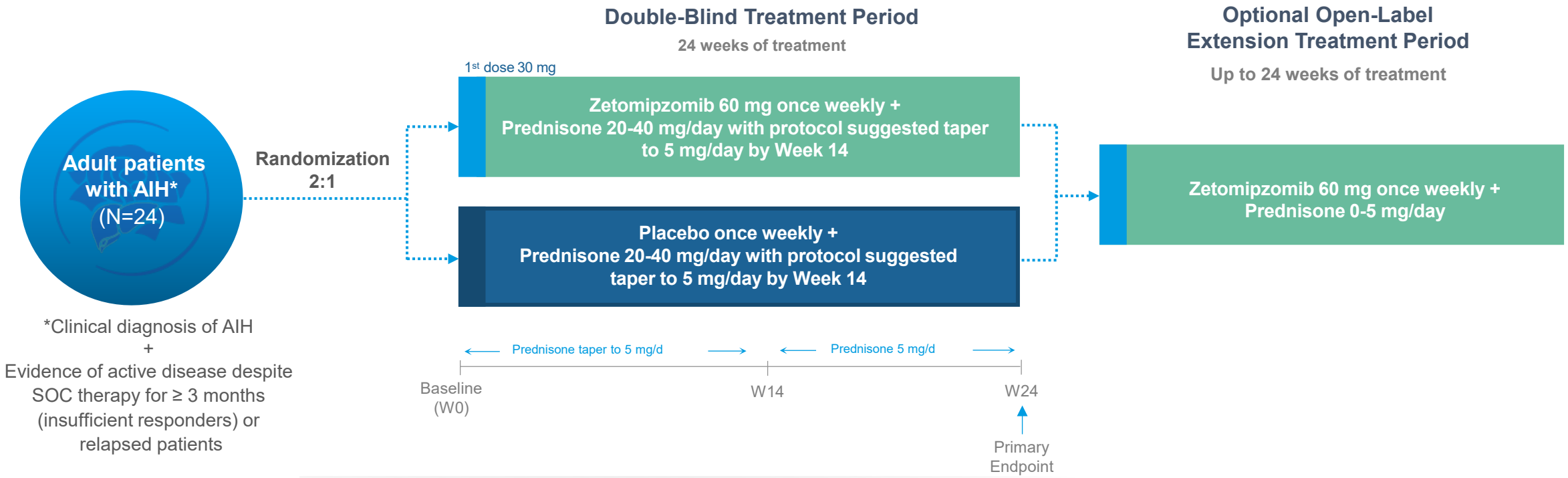
PORTOLA CLINICAL TRIAL DESIGN: ZETOMIPZOMIB IN AUTOIMMUNE HEPATITIS (AIH)

Zung To
Senior Vice President, Head of
Clinical Development

PORTOLA: Phase 2 Placebo-Controlled Trial Evaluating the Safety and Efficacy of Zetomipzomib in Relapsed or Insufficient Responding Autoimmune Hepatitis



*Clinical diagnosis of AIH
+
Evidence of active disease despite SOC therapy for ≥ 3 months (insufficient responders) or relapsed patients

**AIH patients do not have similar severe co-morbidities as in LN patients and are not treated with high dose IV steroid as in LN

https://clinicaltrials.gov/ct2/show/NCT05569759

Abbreviations: AIH, autoimmune hepatitis; ALT, alanine transaminase; AST, aspartate transaminase; OLE, open-label extension; SOC, standard of care.

PORTOLA: Key Selection Criteria

- Clinical diagnosis of AIH and **signs of active disease despite standard-of-care therapy** for ≥3 months or **disease flare after experiencing complete response** induced by standard-of-care treatment
- Screening **ALT values that are 1.25 to 10 times ULN**
- **Liver biopsy results with Ishak score[1] (modified HAI) ≥ 5** (18 max) indicating active AIH, from a biopsy performed at Screening or within 6 months prior to Screening
- Mild or no hepatic impairment (Child-Pugh category A)

References: 1. Ishak K et al. J Hepatol. 1995 June;22(6):696-9.

PORTOLA: Key Efficacy Endpoints

Primary efficacy endpoint:

- Proportion of patients who achieve complete response (CR)

Other efficacy endpoints:

- Duration of response and time to response
- Proportion of patients who are treatment failures
- Proportion of patients who achieve response with successful glucocorticoid taper (≤10mg/day and ≤5mg/day)
- Change from Baseline in liver histopathology at Week 24, based on Ishak score (modified Histological Activity Index [HAI]) scores (Ishak et al., 1995)
- Change from Baseline in liver stiffness at Week 24, assessed by vibration-controlled transient elastography (VCTE) utilizing Fibroscan®

PORTOLA: Definitions Related to Biochemical Efficacy Endpoints

Complete Response (CR)	Normal ALT, AST and IgG values (if IgG is elevated at Baseline) with glucocorticoid dose not higher than starting dose
Treatment Failure	ALT or AST level worsened ≥2x above Baseline and sustained for ≥1 week
Glucocorticoid Taper	Prednisone (or glucocorticoid equivalent) dose tapered to ≤10 mg/day and ≤5 mg/day

PORTOLA Study Status

- The Independent Data Monitoring Committee (IDMC) overseeing the AIH PORTOLA trial recommended that the trial may proceed without modification following its third scheduled meeting
  - The IDMC examined safety data from all patients who completed the blinded treatment period and continued to the open-label 24-week extension portion of the trial
  - Three members of the IDMC, including the committee chair, are also members of the IDMC overseeing the LN PALIZADE study
- To date, no Grade 4 or 5 SAEs have been observed in the PORTOLA trial
- Kezar has completed enrollment of PORTOLA and plans to report topline data in the first half of 2025
- PORTOLA has the potential to be the first randomized study in relapsed AIH patients to report safety and efficacy results

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NEXT STEPS & CLOSING REMARKS

Christopher J, Kirk, PhD
Chief Executive Officer, Co-Founder

Next Steps in the Zetomipzomib Development Program in Autoimmune Hepatitis

- AIH is a serious medical condition affecting ~100,000 people in the U.S. alone with limited treatment options and few novel agents in development
- Encouraging clinical and serologic activity and biomarker data from clinical trials in LN increases conviction that zetomipzomib is a potent immunomodulatory agent
- Safety data from across multiple clinical trials and >200 patients support development of zetomipzomib in AIH
- Learnings from PALIZADE will inform future trials including increased patient workup and monitoring
- Topline data from the Phase 2 PORTOLA study are expected in 1H 2025 and will inform design of a next clinical trial
- Following PORTOLA readout, we plan to respond to all FDA (Hepatology Division) hold comments prior to proposing a potential registrational study in AIH

QUESTION & ANSWER SESSION

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CONTACT US

4000 Shoreline Court
Suite 300
South San Francisco, CA 94080