

Future Treatment Paradigms in Rheumatic Diseases: Understanding Emerging Therapies

Developed by the
Coalition of Rheumatology Educators (CORE™)

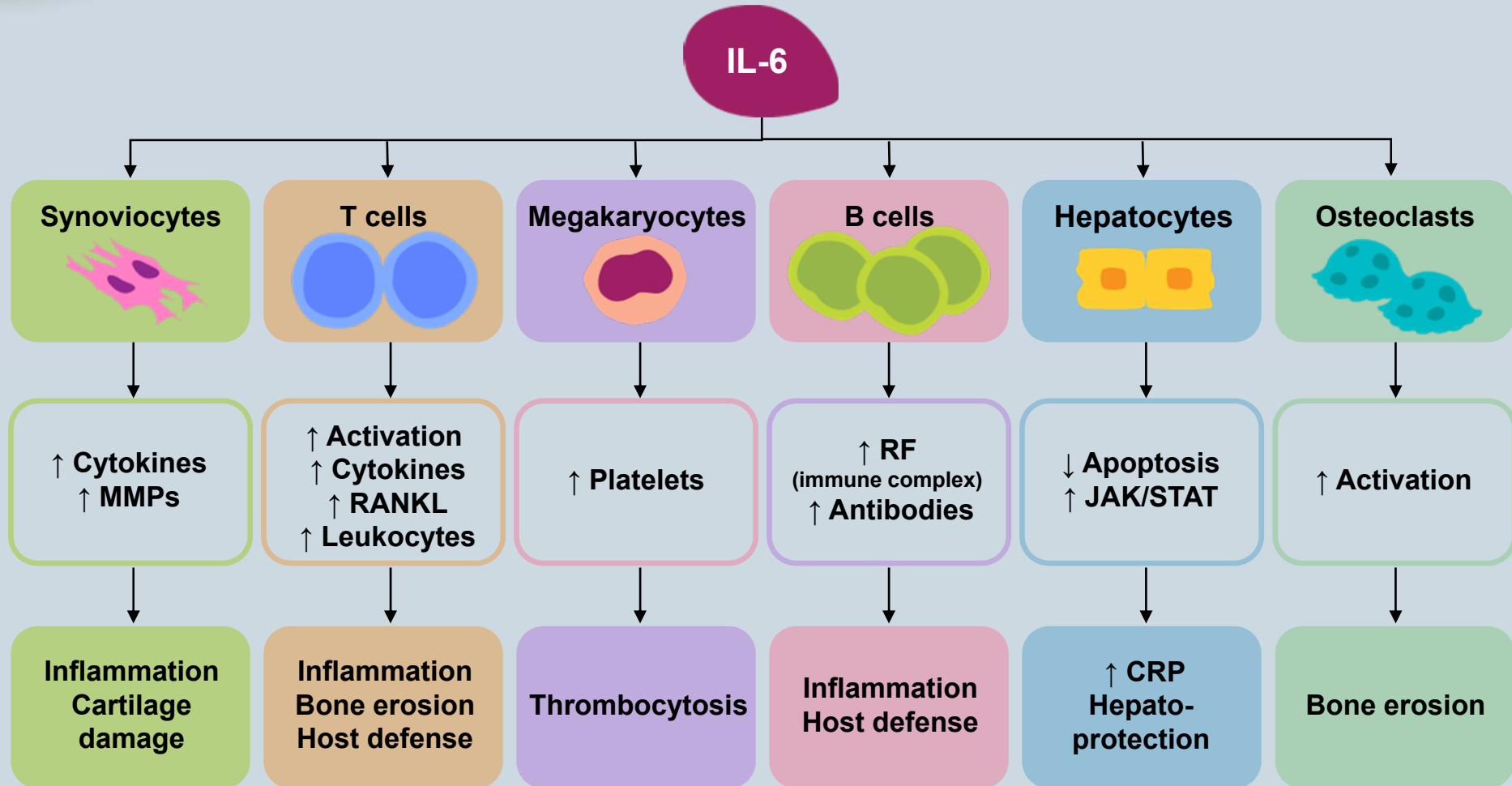




Learning Objectives

- Describe the characteristics and mechanisms of action for emerging biologic therapies in RA and SpA
- Identify efficacy and safety considerations for the potential use of emerging biologic agents

Role of IL-6



IL = interleukin; MMP = matrix metalloproteinase; RANKL = receptor activator of nuclear factor kappa B ligand; RF = rheumatoid factor; JAK = janus kinase; STAT = signal transducer and activator of transcription; CRP = C-reactive protein.
 Naka T, et al. *Arthritis Res.* 2002;4(Suppl 3):S233-S242. Choy E. *Rheum Dis Clin North Am.* 2004;30(2):405-415. Gabay C. *Arthritis Res Ther.* 2006;8(Suppl 2):S3. Jones DH, et al. *Ann Rheum Dis.* 2002;61(Suppl 2)ii32-ii39. Choy EH, et al. *N Engl J Med.* 2001;344(12):907-916. Taub R. *J Clin Invest.* 2003;112(7):978-980.



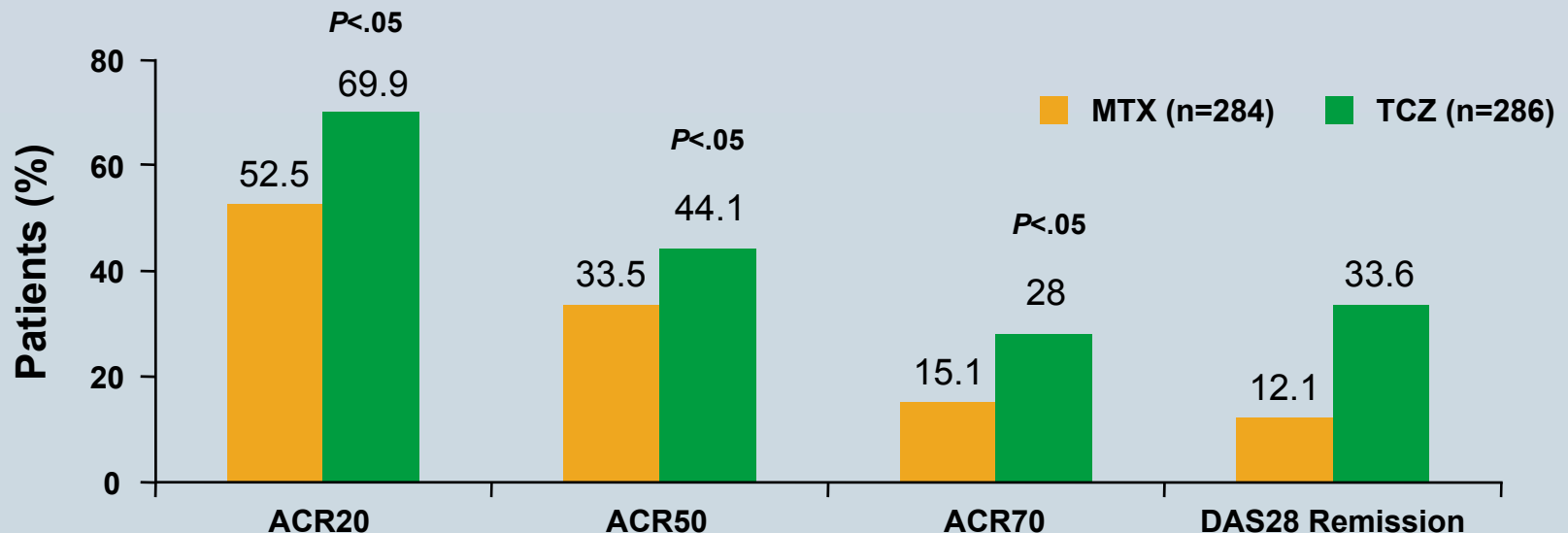
Effect of IL-6 in the Liver

- Normal function
 - Liver regeneration
 - Hepatoprotection (anti-apoptosis, anti-necrosis)
 - Acute phase response
- Block IL-6 (hypothetical)
 - Hepatic injury associated with increases in ALT, AST, or bilirubin
 - Decrease in CRP → Increase in cholesterol
 - Decrease in acute phase response → Neutropenia
 - Increase in transaminases

AMBITION Study: TCZ in Patients Who Are MTX- and Biologic-Naïve

- TCZ is an anti-IL-6 receptor monoclonal antibody
- 24-week, multicenter, randomized, double-blind study (N = 570)
- Compared efficacy of TCZ vs MTX in MTX- and biologic-naïve patients

Efficacy Results at Week 24

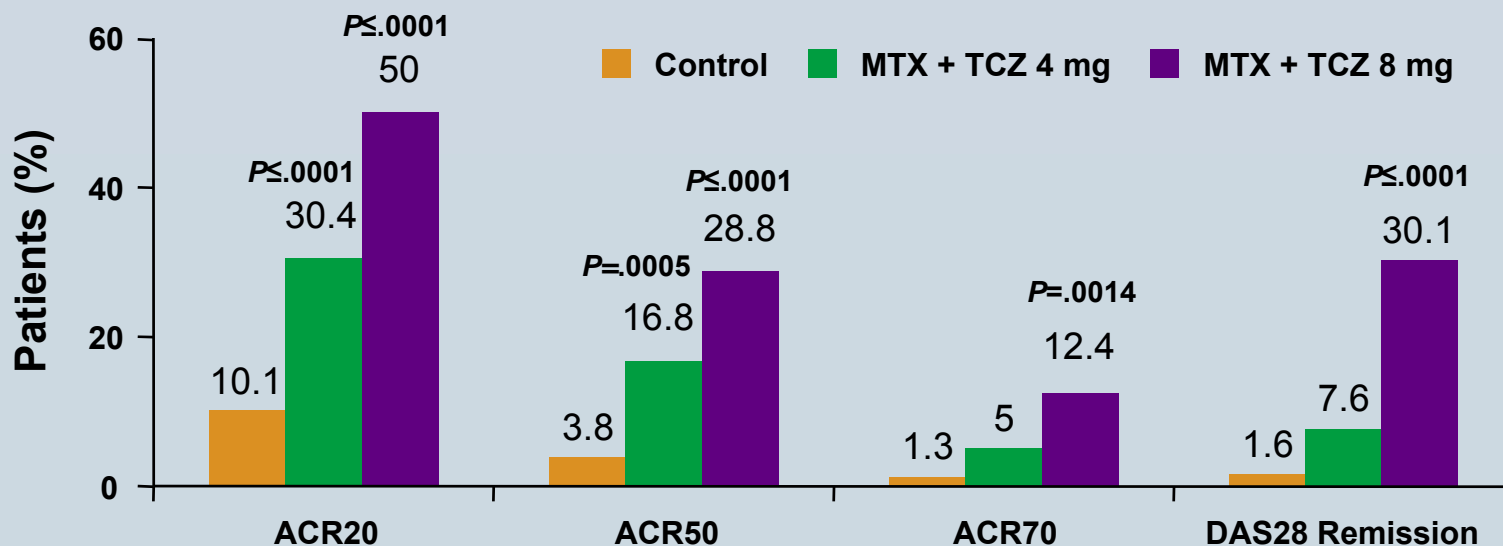


- **Conclusion: TCZ monotherapy was superior to MTX monotherapy in these MTX- and biologic-naïve patients**

RADIATE Study: TCZ Therapy in TNF-Inhibitor Inadequate Responders

- 24-week, multicenter, randomized, double-blind study (N = 499)
- Patients given either MTX, MTX + TCZ 4 mg/kg, or MTX + TCZ 8 mg/kg

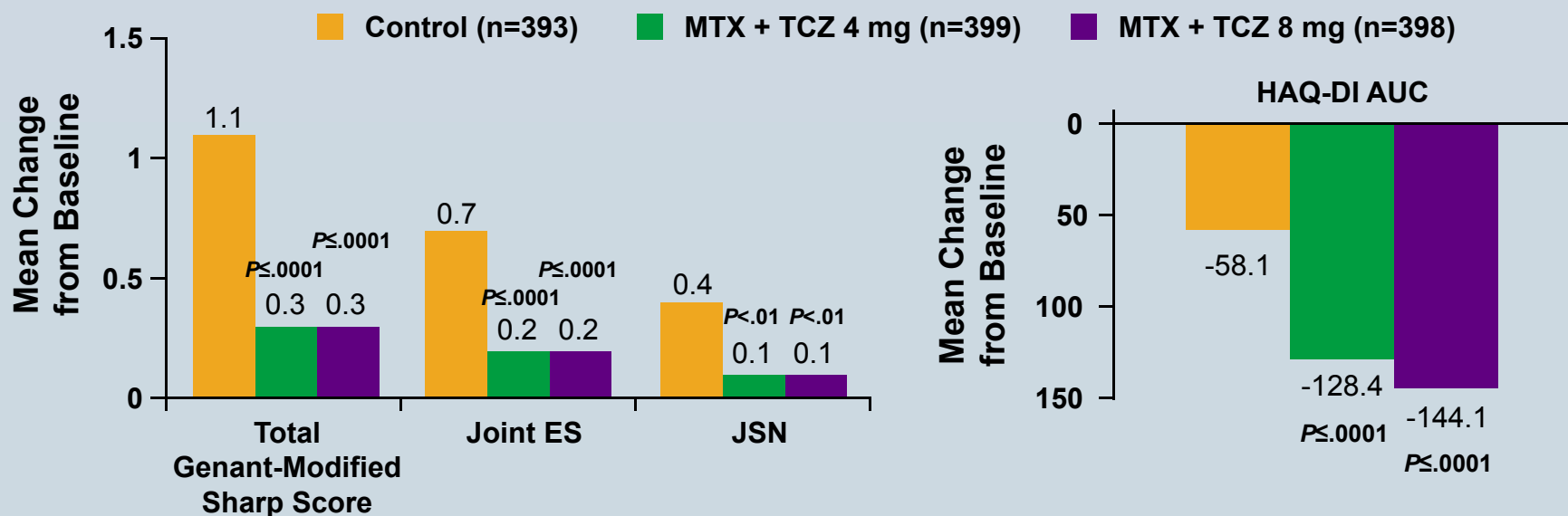
Efficacy Results at Week 24



- **Conclusion: significantly higher proportion of patients on TCZ therapy achieved ACR responses and reached DAS28 remission**

LITHE Study: Effect of TCZ on Structural Damage in RA

- 52-week, randomized, double-blind, PBO-controlled study (N = 1190)
- Examined efficacy of adding TCZ to MTX in inadequate MTX-responders in preventing structural damage
- Primary end points: Genant-modified Sharp score and HAQ-DI at 52 weeks



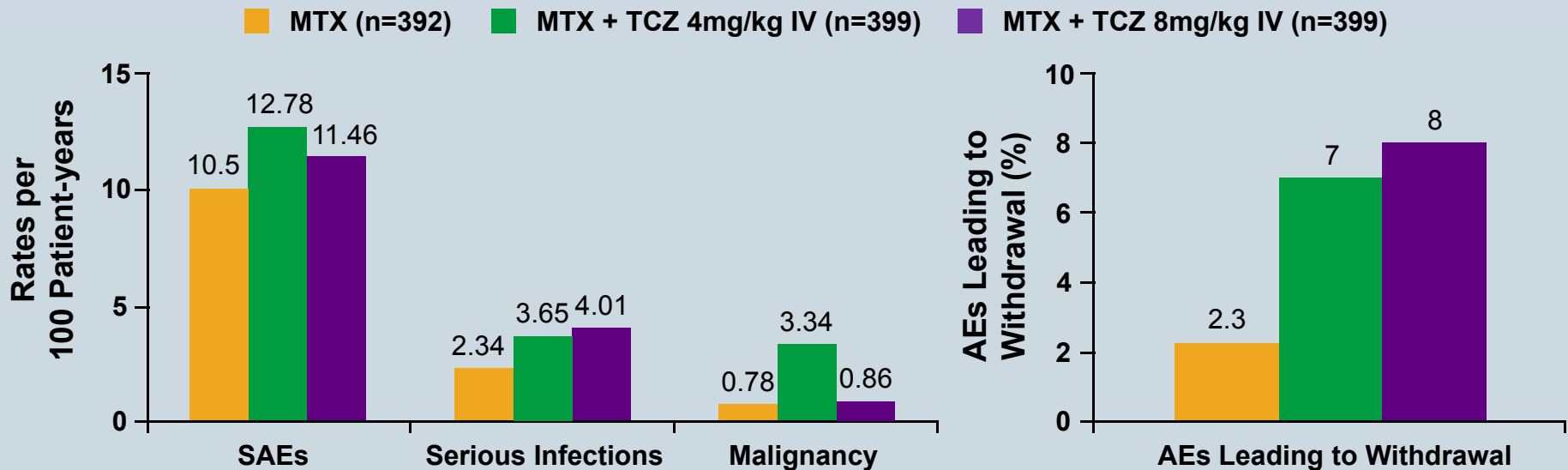
- **Conclusion: MTX + TCZ therapy significantly inhibited progression of structural joint damage and improved HAQ-DI**



LITHE Study:

Safety of TCZ + MTX Therapy in Patients with RA

- 52-week, randomized, double-blind, PBO-controlled study of patients with RA
- Evaluated safety of MTX + TCZ 4 mg/kg (N=399), MTX + TCZ 8 mg/kg (N=399), and MTX + PBO (N=392)
- Patients with progression of joint damage and prior inadequate response to MTX were selected
- Rate of AEs (per 100 patient-years) was 280 for MTX, 324 for MTX + TCZ 4 mg/kg, and 325 for MTX + TCZ 8 mg/kg

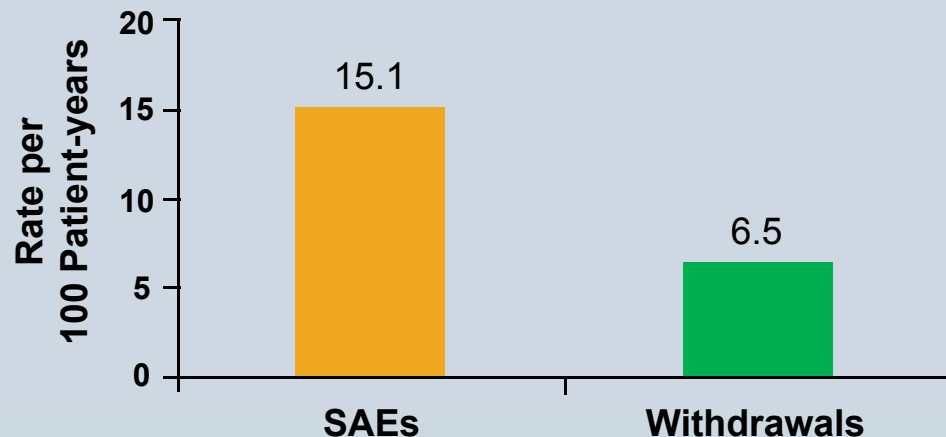


- **Conclusion: TCZ had a well-characterized and manageable safety profile over 1-year period**

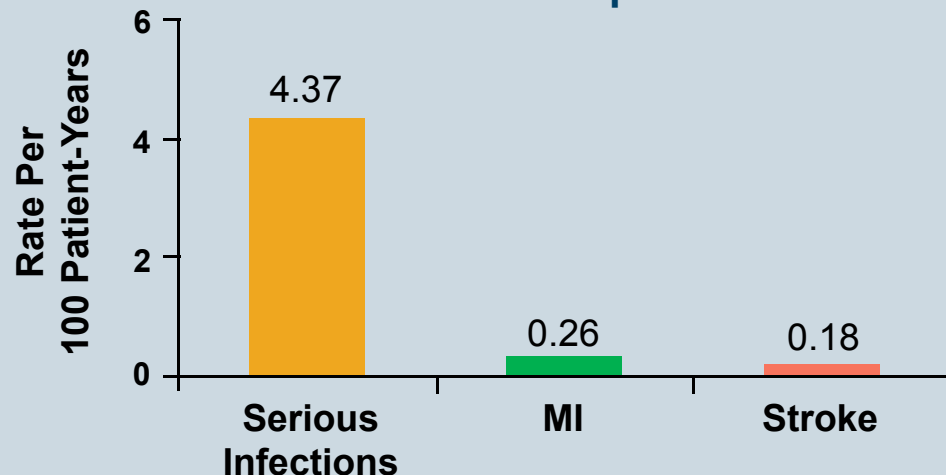
Long-Term Safety of TCZ Therapy in RA

- Examined safety of TCZ monotherapy or combination with a DMARD
- 3857 patients with RA from OPTION, AMBITION, RADIATE, TOWARD, OLE of GROWTH95 and GROWTH96, and LITHE
- Mean treatment duration of 1.5 years
- Overall AE rate was 369.8 per 100 patient-years
- Withdrawals driven by elevated liver enzymes, infections, and benign and malignant neoplasms
- **Conclusion: serious infection rate stable over time, and cardiovascular and malignancy event rates did not increase over time in these patients treated with TCZ**

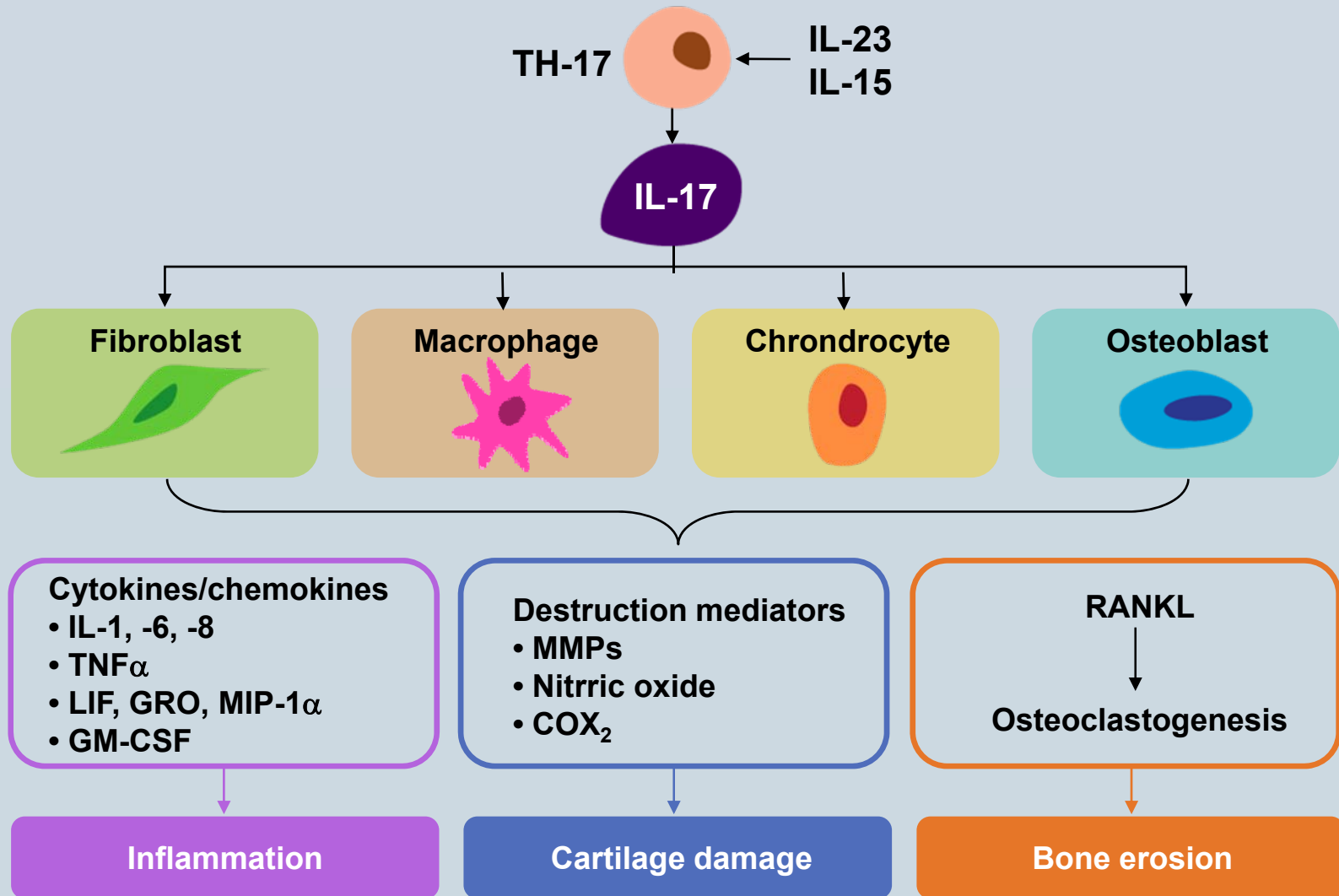
Overall Rate of SAEs and Withdrawals



Overall Rate of Specific SAEs



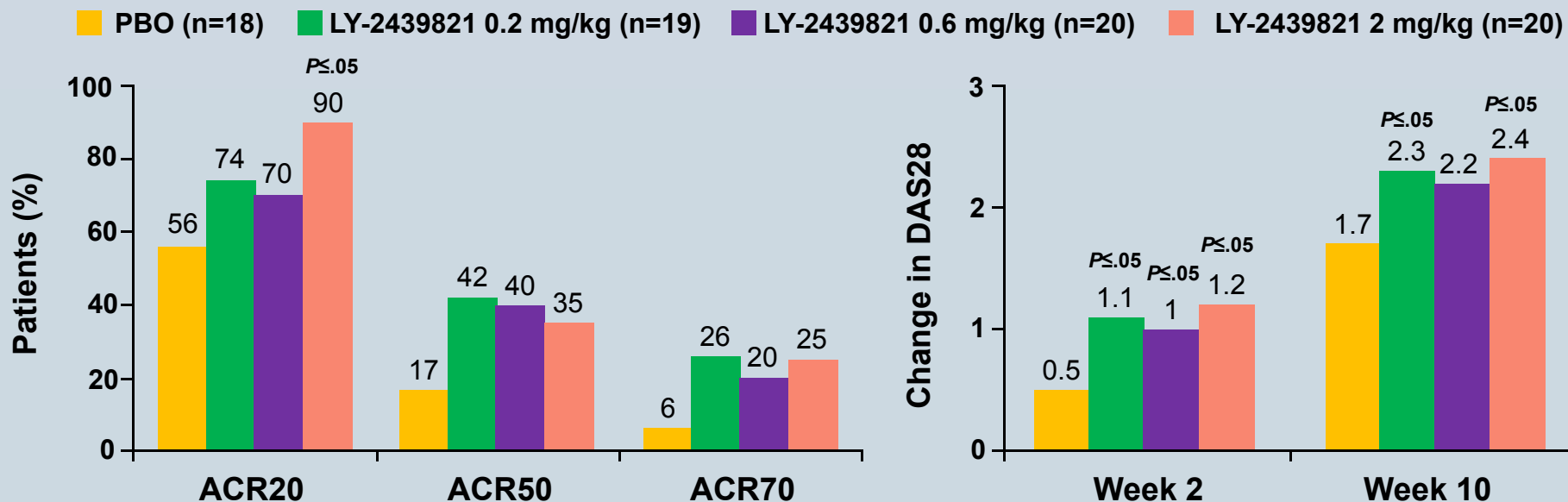
Role of IL-17 in Pathological Process of Arthritis



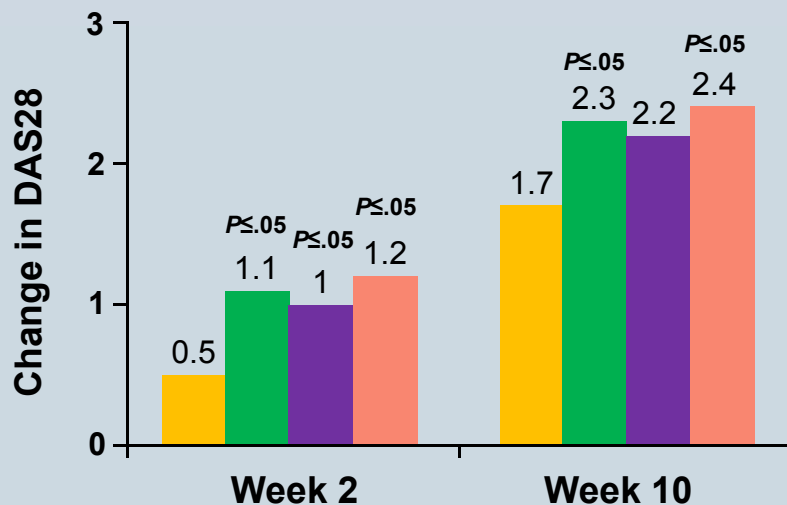
Efficacy and Safety of LY-2439821 in Patients with RA

- Randomized, double-blind, PBO-controlled study that evaluated efficacy and safety of LY-2439821 (anti-IL-17 antibody) in patients taking ≥ 1 DMARD
- Primary efficacy end point: DAS28 at week 10
- No serious infections or malignancies noted

ACR Results at Week 10

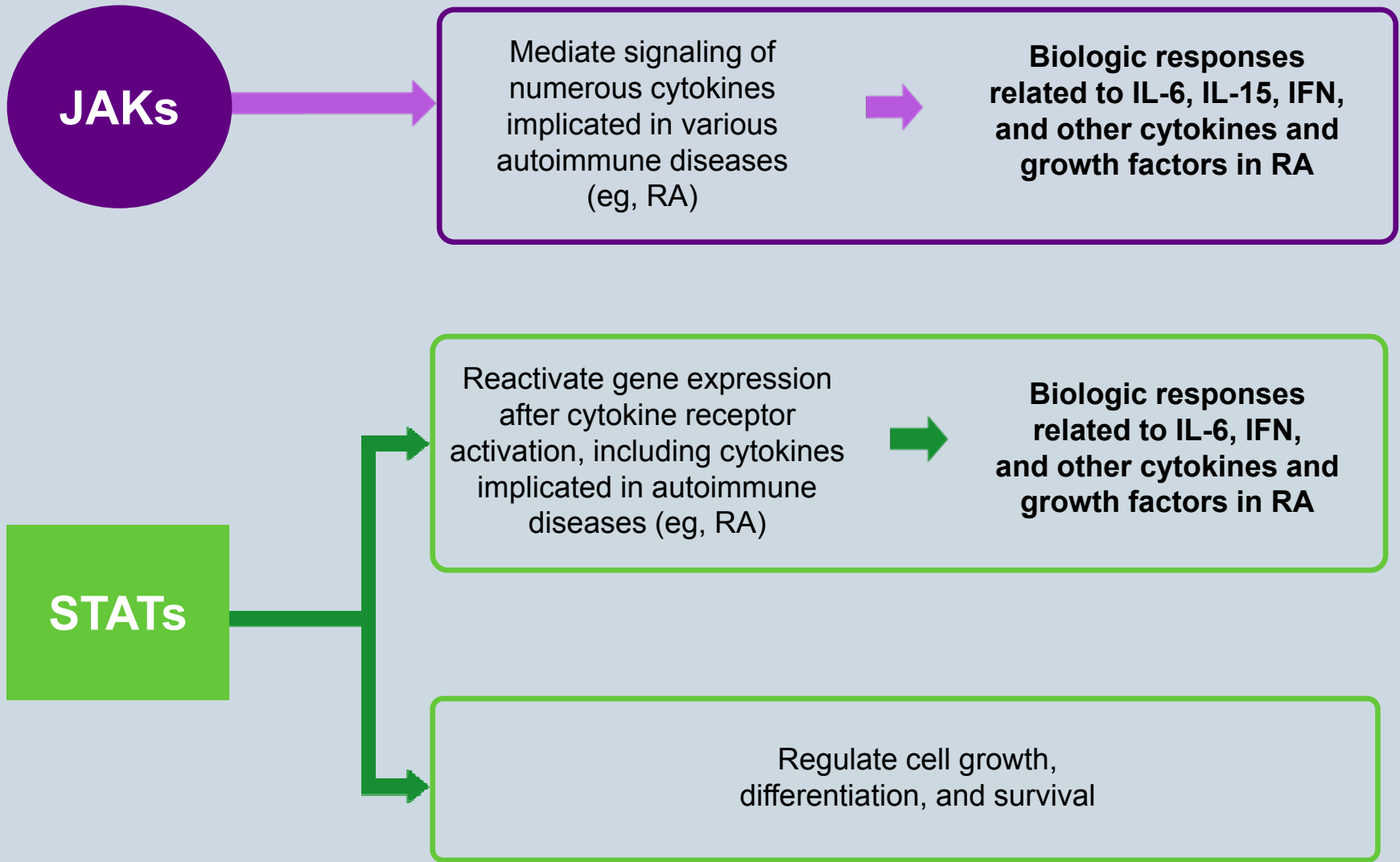


Change in DAS28



- **Conclusion: LY-2439821 improved ACR responses of patients taking concomitant DMARDs, and the drug was not associated with severe or significant AEs**

Role of JAK-STAT in RA



IFN = interferon.

O'Shea JJ, et al. *Curr Opin Rheumatol.* 2005;17(3):305-311. Ivashkiv LB, et al. *Arthritis Rheum.* 2003;48(8):2092-2096.

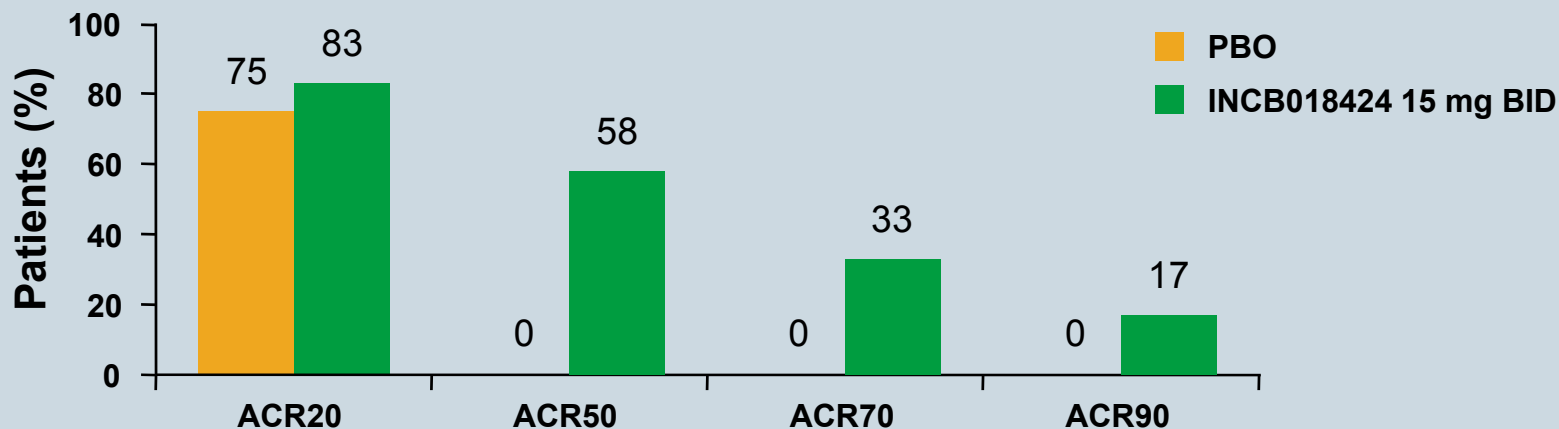
JAK1&2 and JAK3 Inhibitor Therapy in RA

- JAKs
 - Cytoplasmic tyrosine kinases pair in 6 different combinations to integrate signaling from cytokines and growth factors
 - JAKs mediate signal transduction for cytokines implicated in RA
 - IL-6, IL-12, IL-15, IL-23, GM-CSF, and IFN- γ
- Cytokine inhibition with efficacy in RA and preclinical models
- JAK mutations associated with severe immunodeficiency
- Two agents have preferential activity for JAK1&2; another JAK3
 - JAK1&2 (indirect effects on JAK3)
 - JAK2 needs to pair with JAK1
 - Short $T_{1/2}$ = 3 hours; inhibits IL-6–induced STAT phosphorylation
 - JAK3
 - Expression of JAK3 restricted to hematopoietic cells
 - Pairs with JAK1 to signal downstream of IL-2, 4, 7, 9, 15, 21

Efficacy and Safety of INCB018424 Therapy in RA (JAK1&2)

- INCB018424 is a small molecule of the JAK family kinases
 - Preferential affinity for JAK1 and JAK2
 - Oral formulation
- Randomized, PBO-controlled study of 16 patients with RA not on a DMARD
 - Involved 2 cohorts (data on first cohort is available)
- AEs: single episodes of mild diarrhea, fever blister, and dry mouth (no cytopenias)

Efficacy Results at Day 28



- **Conclusion: patients treated with INCB018424 exhibited preliminary efficacy through ACR20, 50, 70, and 90 scores compared to PBO**

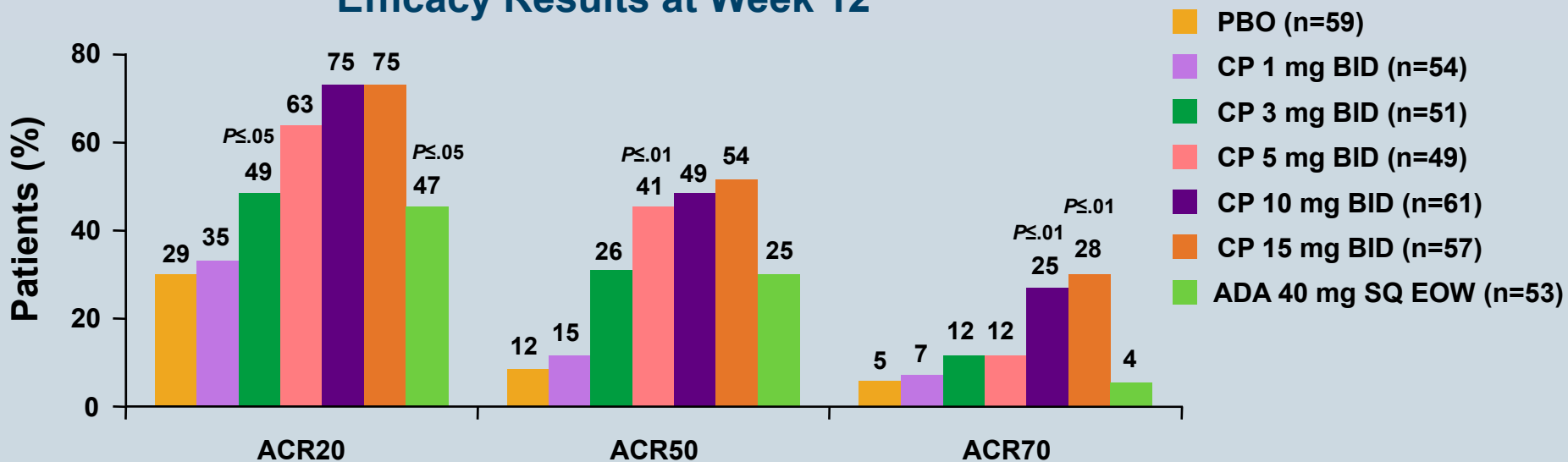
BID = twice daily.

Williams W, et al. Presented at: 2008 ACR Annual Scientific Meeting; October 24-29, 2008; San Francisco, CA. Abstract 714.

Efficacy and Safety of CP-690,550 Therapy in RA (JAK3)

- 6-month, phase 2B, randomized, double-blind, PBO-controlled study (N = 509)
- Patients had an inadequate response to a traditional DMARD
- Primary end point: ACR20 response rate at week 12
- Most frequently reported TEAEs included urinary tract infections (4.4%), diarrhea (4%), bronchitis (3.7%), headache (3.7%)

Efficacy Results at Week 12



- **Conclusion: ACR responses improved with elevated doses of CP-690,550, and tolerability issues were dose dependent**

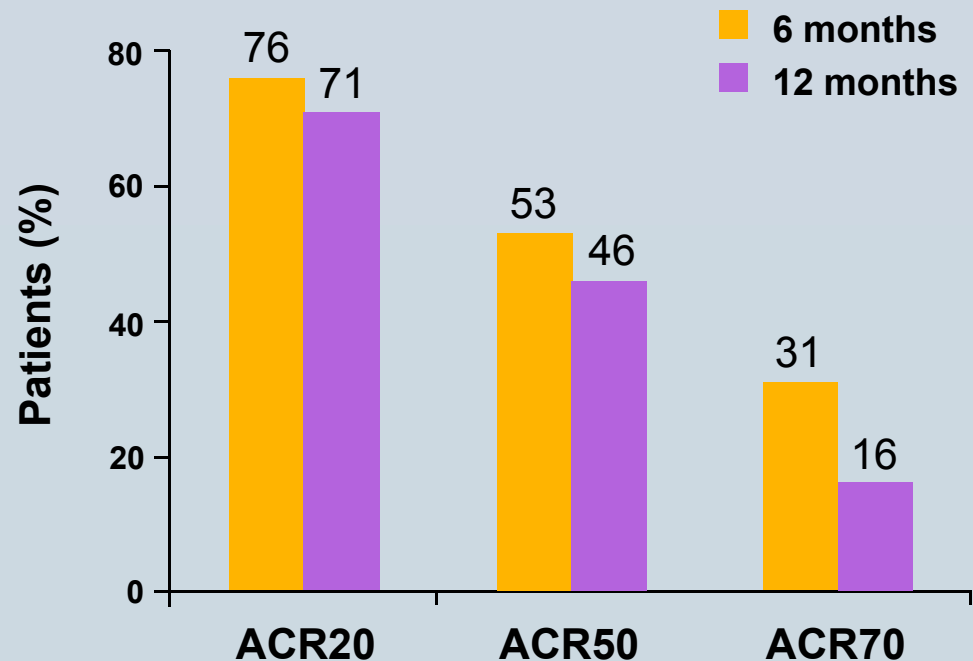
TEAEs = treatment-emergent adverse events; SQ = subcutaneous; EOW = every other week.

Kanik K, et al. Presented at: 2009 EULAR Annual Meeting; June 10-13, 2009; Copenhagen, Denmark. Abstract OP-0159.

Long-term Follow-up of CP-690,550 Therapy in Patients with RA

- Assessed long-term safety and efficacy of CP-690,550 5mg BID in patients with moderate-to-severe RA
- Patients from 3 randomized studies, including Study 1019, Study 1025, and Study 1035 (n=655)
- Most frequent AEs ($\geq 1.5\%$) were urinary tract infection, diarrhea, anemia, nausea, and sinusitis
- **Conclusion: CP-690,550 exhibited continued efficacy over a 12-month period and was well tolerated**

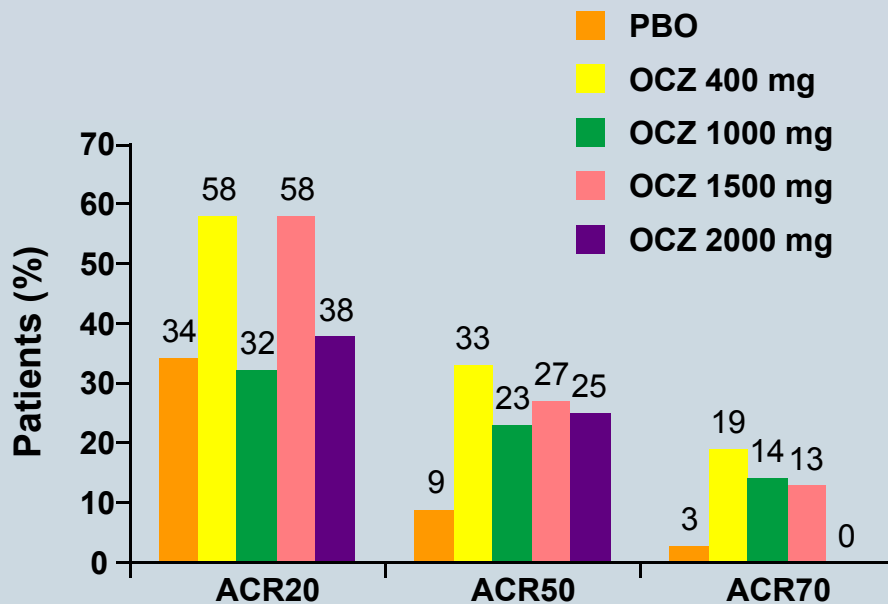
Efficacy Results at 6 and 12 Months



Efficacy and Safety of OCZ Therapy in Patients with RA

- 24-week study of MTX + OCZ (anti-CD20 humanized monoclonal antibody)
- Primary end point was proportion of patients achieving ACR20 response
- Single infusion of OCZ and PBO (no peri-infusional corticosteroids given)

Efficacy Results at Week 24



Safety Results at Week 24

	PBO (n = 35)	400 mg (n = 43)	1000 mg (n = 44)	1500 mg (n = 45)	2000 mg (n = 8)
AEs (%)					
Serious infusion reactions	—	—	7	6	13
Infections	49	42	48	12	75
Serious infections	—	—	7	2	13
Serious AEs	9	14	27	21	13
Withdrawal	14	2	9	9	—

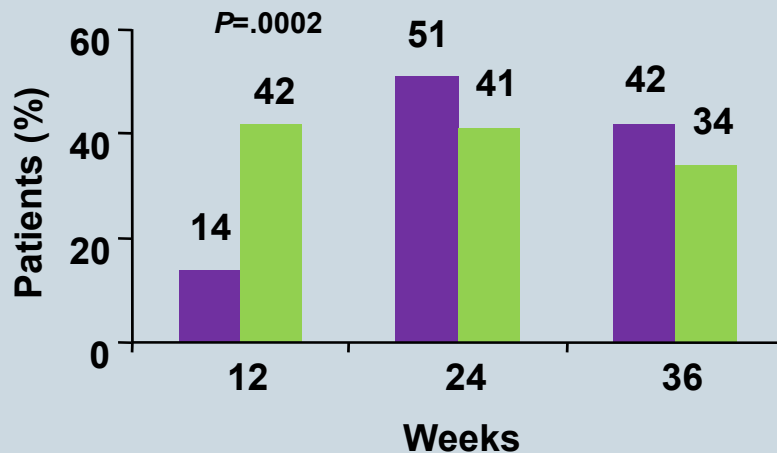
- **Conclusion: patients treated with MTX + OCZ combination therapy exhibited higher ACR20, 50, and 70 responses**

Efficacy of Ustekinumab Therapy in PsA

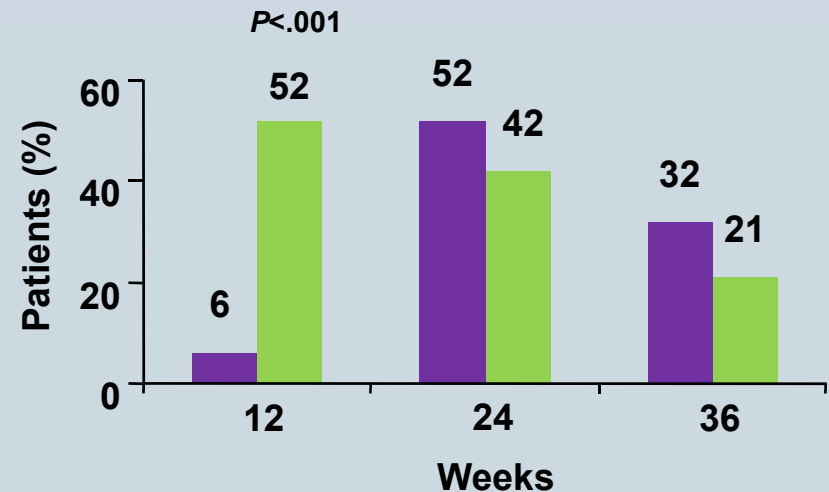
- Phase 2, randomized, double-blind, PBO-controlled, crossover study of patients with PsA:
 - Ustekinumab 90 or 63 mg at weeks 0, 1, 2, 3, followed by PBO at weeks 12, 16 (n=76)
 - PBO at weeks 0, 1, 2, 3, followed by ustekinumab 63 mg at weeks 12, 16 (n=70)
- Evaluated clinical response (ACR and PASI)

■ PBO→Ustekinumab (week 12) ■ Ustekinumab

ACR20 Response



PASI 75 Response



- Conclusion: patients treated with ustekinumab exhibited significantly greater ACR20 and PASI75 responses**

Drugs for SLE in Clinical Trials

- Belimumab (anti BlyS/BAFF)
 - Improves or stabilizes SLE activity; excellent safety profile over 3 years follow-up
 - Two pivotal trials of 745 patients have completed enrollment, and if successful, has an approvable letter from the FDA
- AMG 623 (anti-BlyS/BAFF)
 - Phase 1a/b trial enrolled 117 patients with SLE
 - Safe to use and depleted B-cells
- Epratuzumab (anti-CD22)
 - Improved BILAG response, patient and physician global assessment, and QOL; steroid sparing; and safe in 2 dosing regimens given to 90 patients
 - Phase 2/3 trial in progress
- ABR-215757 (Quinoline-based oral compound)
 - Phase 1b study ongoing
 - Drug decreases IFN- α signature expression

SLE = systemic lupus erythematosus; BlyS/BAFF = B lymphocyte stimulator/B-cell activation from the tumor necrosis factor; FDA = US Food and Drug Administration; BILAG = British Isles Lupus Assessment Group; QOL = quality of life.

Chatham W, et al. Presented at: 2008 ACR Annual Scientific Meeting; October 24-29, 2008. Abstract 1094. McKay J, et al. Presented at: 2008 ACR Annual Scientific Meeting; October 24-29, 2008. Abstract 1065. Stohl W, et al. Presented at: 2008 ACR Annual Scientific Meeting; October 24-29, 2008; San Francisco, CA. Abstract 1072. Strand V, et al. Presented at: 2008 ACR Annual Scientific Meeting; October 24-29, 2008. Abstract 1086. Petri M, et al. Presented at: 2008 ACR Annual Scientific Meeting; October 24-29, 2008; San Francisco, CA. Abstract 1087. Wallace DJ, et al. Presented at: 2008 ACR Annual Scientific Meeting; October 24-29, 2008. Abstract 1088. Liberg D, et al. Presented at: 2008 ACR Annual Scientific Meeting; October 24-29, 2008; San Francisco, CA. Abstract 1078.



Summary

- Several agents are near completion of phase 3 studies and may soon be available for treatment of RA, PsA, and SLE
 - Risks, benefits, and placement in the therapeutic armamentarium remain to be determined in clinical practice
- Small molecule oral agents are in early development for treatment of RA
 - AE profile may limit their ultimate use
- Knowledge of the basic immunologic mechanisms involved in rheumatic diseases will permit the development of targeted and individualized therapies