Efficacy and safety of abatacept, a T-cell modulator, in a randomised, double-blind, placebo-controlled, phase III study in psoriatic arthritis (Mease et al., 2017)

Rheumatology journal club

October 20, 2017

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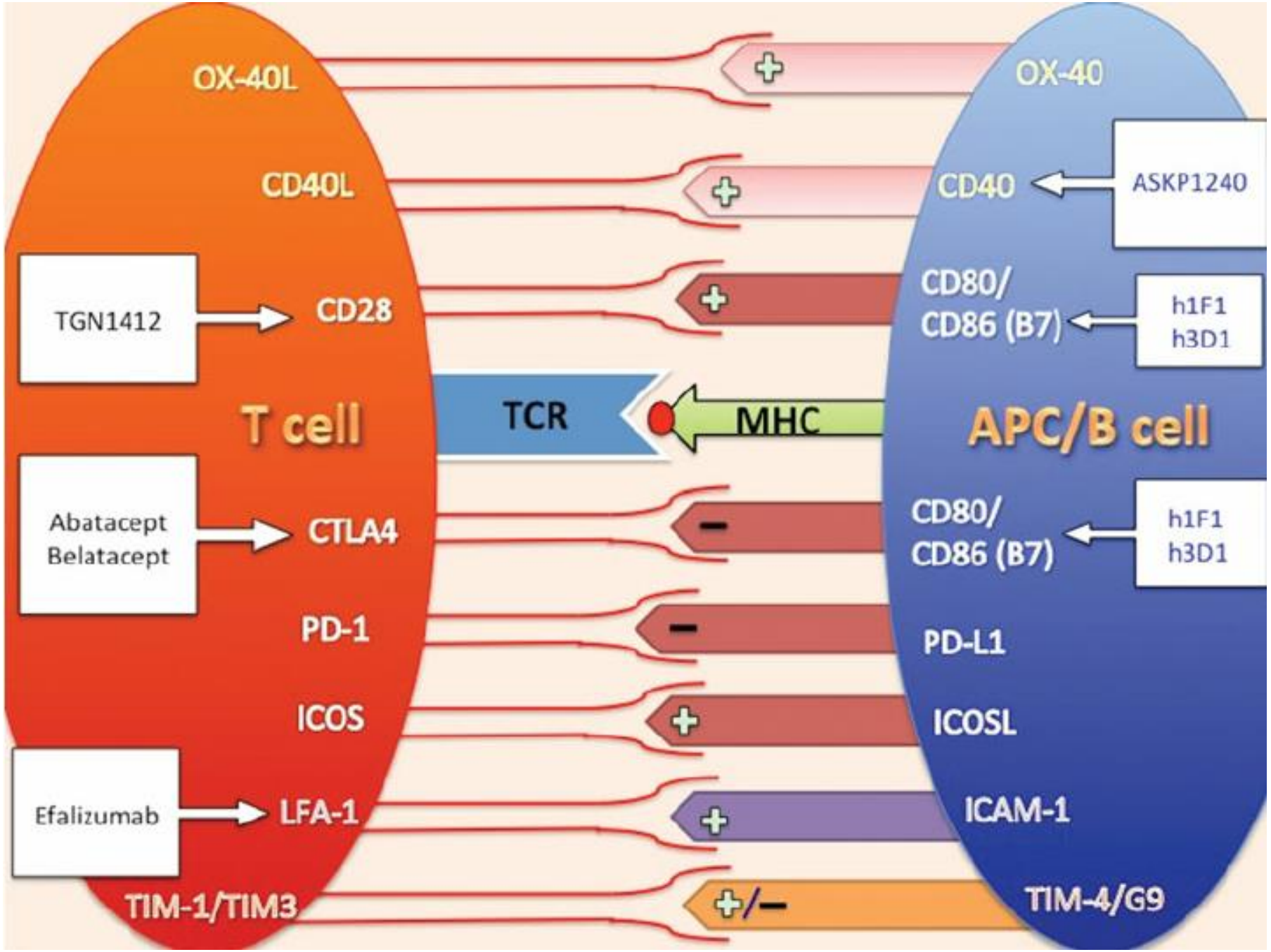
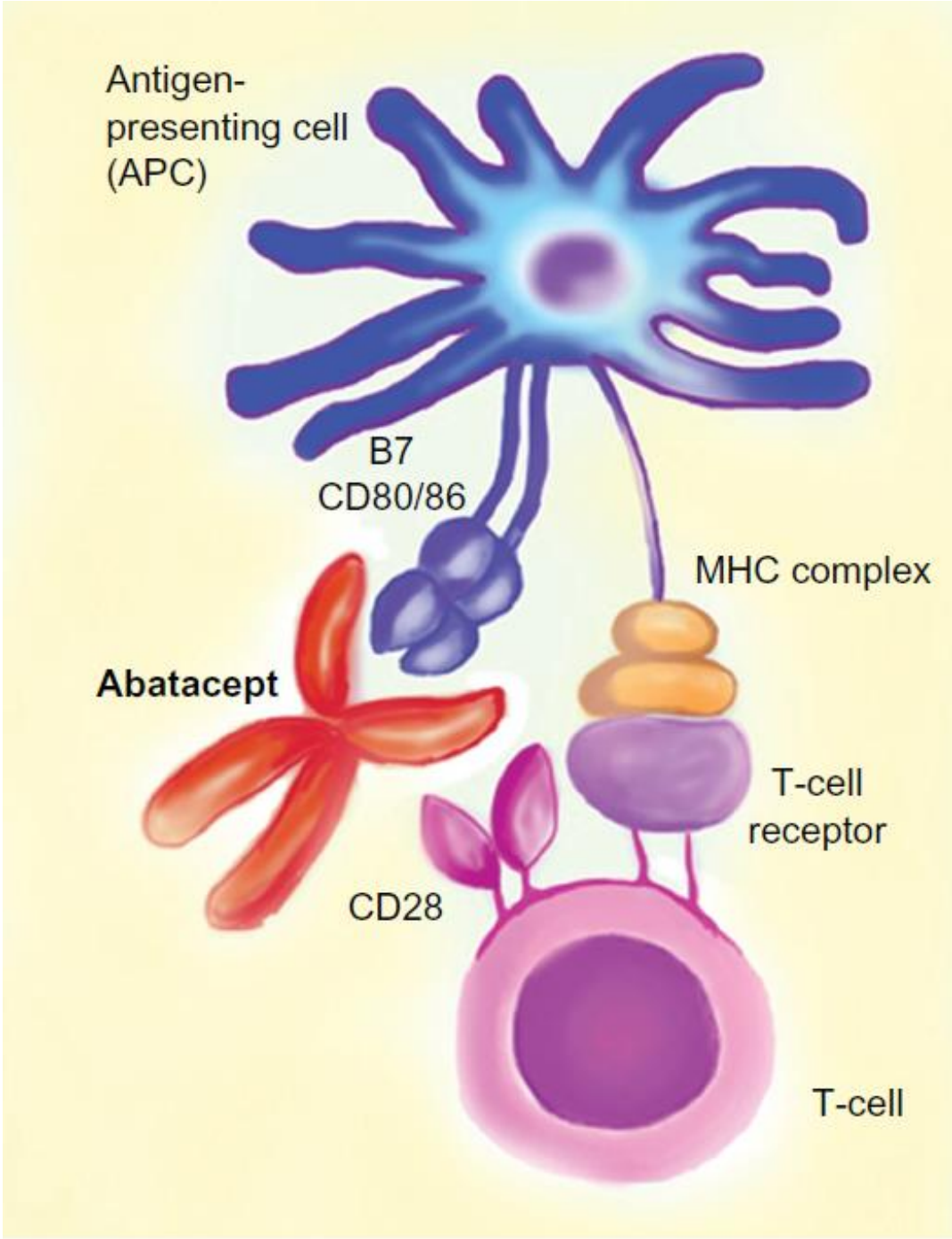
Co-stimulation



Esposito, *Int Rev Immunol* 2014;33:212.

Abatacept

Malaviya, *Patient Preference and Adherence* 2012;6:589



Approvals

- **Rheumatoid arthritis**
  - **IV: 2005**
  - **SQ: 2011**
- **Juvenile idiopathic arthritis**
  - **IV: 2008**
  - **SQ: 2017**
- **Psoriatic arthritis: 2017 (IV or SQ)**

Rationale for study (from intro)

- **PsA has MHC Class I associations**
- **Thus, antigen presentation is involved**
- **Also, prior Phase II study showed effectiveness of IV abatecept 10 mg / Kg q4 weeks:**
  - **ACR20**
  - **HAQ-DI**
  - **PASI**

Mease, *Arth Rheum* 2011;63:939

Study design

- RCT of abatacept 125 mg SQ weekly versus placebo (1:1)
- Global stratification by 3 factors
  - Current methotrexate use
  - Prior exposure to TNFi
  - PASI ≥ 3% of body surface area
- “Permuted block randomization with block size of two”
- Duration of double-blind: 24 weeks
  - Early escape if < 20% improvement in SJC, TJC by week 16
- Open-label for 28 weeks
  - Total duration: 44 weeks for early escape group (16 + 28)
  - 52 weeks for everyone else (24 + 28)
  - Option of another 52 weeks of OLE

Clinicaltrials.gov number: NCT01860976

Inclusion criteria

- ≥ 18 years
- CASPAR criteria for PsA (Taylor, *Arth Rheum* 2006;54:2665)
- Active arthritis (≥ 3 SJC and TJC)
- Active psoriasis (≥ 1 lesion ≥ 2 cm in diameter)
- Failed ≥ 1 non-biologic DMARD

Other medications

- Prior TNFi are ok; needs washout of 8 weeks
- Systemic DMARDs ok if:
  - Used for ≥ 12 weeks
  - Dose stable for ≥ 4 weeks
- NSAIDs, CS (≤ 10 mg / day), low-potency topical CS ok if:
  - Used for ≥ 14 days
  - Topical CS not applied to evaluated lesions
- Other topicals and phototherapy only permitted during OLE

Dose changes of DMARDs and retinoids

- **Not permitted during double-blind phase unless required due to intolerance**
- **OK during OLE, but must follow specific protocol**

Endpoints

- **Primary endpoint at 24 weeks: ACR20 response**
- **“Key secondary endpoints” at 24 weeks**
  - **Proportion with HAQ-DI reduction ≥ 35%**
  - **ACR20 in TNFi naïve and exposed subgroups**
  - **Radiographic non-progression**
- **Other secondary endpoints**
  - **ACR50 and ACR70**
  - **≥ 50% improvement in PASI**
  - **Change from baseline in SF-36**

Statistical considerations

- Hierarchical testing procedure used for primary and key secondary outcomes
- Two-sided corrected alpha of 0.05
- For nominal p-values: provided 95% CI, without p-values
  - For the most part
- Power analyses based upon phase 2 study, powered separately for TNFi-naïve and -exposed subjects
  - Required 152 and 248 subjects, respectively
- ITT analysis plus received ≥ 1 dose
- Analyses stratified by current MTX use, prior TNFi use, and plaque psoriasis involving ≥ 3% of BSA

For binary response assessment

- **Imputed as non-responder / radiographic progressor if:**
  - **Early escape at week 16**
  - **Discontinued treatment for any reason**

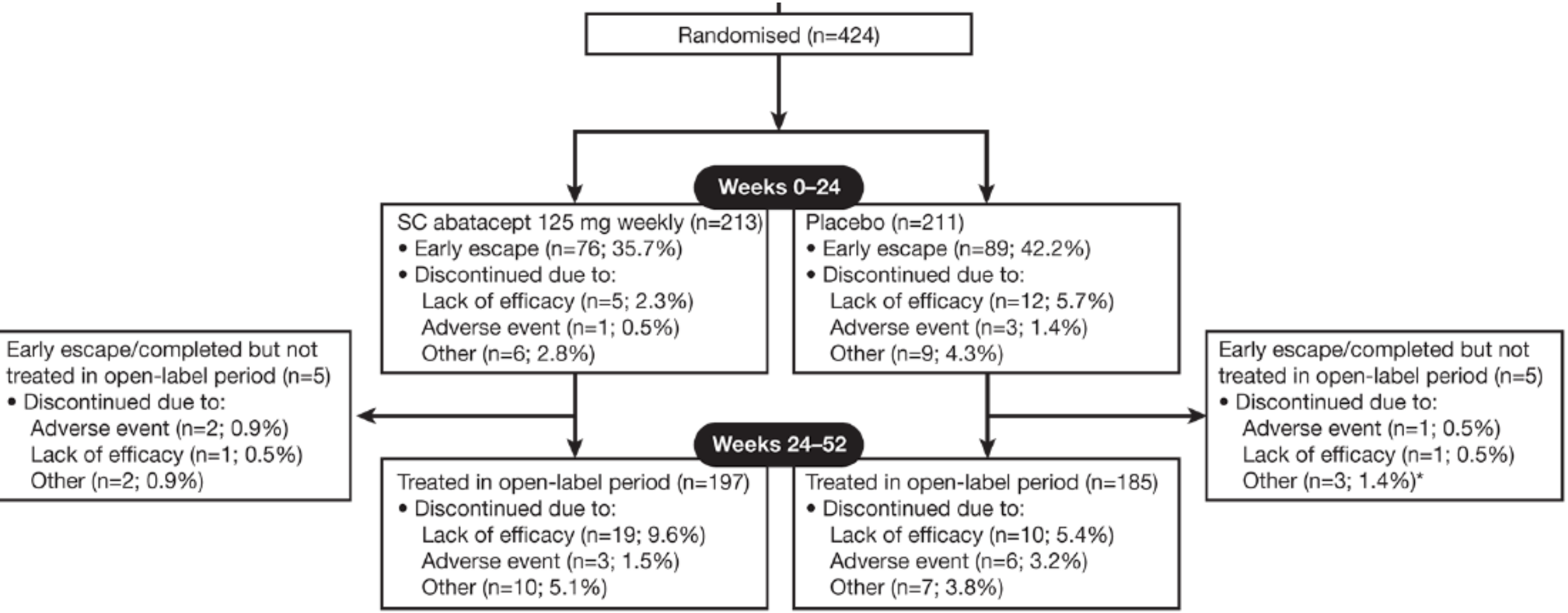
Table 1 Patient characteristics at baseline

	Abatacept (n=213*)	Placebo (n=211*)
Demographic characteristics		
Age, years	51.0 (10.7)	49.8 (11.3)
Sex, female, n (%)	121 (56.8)	112 (53.1)
Race, white, n (%)	195 (91.5)	198 (93.8)
Body mass index, kg/m^2	30.7 (6.3)	31.3 (6.8)
Region, n (%)		
South America	95 (44.6)	80 (37.9)
Europe	53 (24.9)	59 (28.0)
North America	44 (20.7)	40 (19.0)
Rest of World	21 (9.9)	32 (15.2)
Disease characteristics		
PsA duration, years	8.3 (8.1)	8.8 (8.3)
TJC	21.0 (13.4)	19.3 (13.1)
SJC	12.1 (7.8)	11.1 (7.2)
DIP involvement,† n (%)	114 (53.5)	101 (47.9)
HAQ-DI	1.3 (0.7)	1.3 (0.7)
Patient Global Assessment of disease activity (VAS 0–100 mm)	61.1 (23.5)	62.6 (22.6)
Physician Global Assessment of disease activity (VAS 0–100 mm)	53.9 (18.8)	55.0 (19.6)
Patient Global Assessment of pain (VAS 0–100 mm)	64.2 (23.5)	64.4 (21.8)
CRP, mg/L	14.0 (20.9)	14.3 (30.3)
Elevated CRP (>ULN‡), n (%)	146 (68.9)	131 (62.7)
DAS28 (CRP)	5.0 (1.1)	4.9 (1.1)
PsA-modified total SHS	20.0 (46.8)	17.7 (39.6)
Psoriasis covering ≥3% BSA, n (%)§	146 (68.5)	148 (70.1)
PASI score¶**	7.4 (8.0)	7.2 (7.8)
Enthesitis, n (%)	140 (65.7)	132 (62.6)
Dactylitis, n (%)	61 (28.6)	50 (23.7)
Anti-CCP positive (>10 U/mL), n (%)	10 (5.1)	2 (1.0)
Medication use		
Prior TNFi, n (%)	129 (60.6)	130 (61.6)
1	94 (44.1)	92 (43.6)
2	31 (14.6)	36 (17.1)
≥3	4 (1.9)	2 (0.9)
Concomitant methotrexate, n (%)	129 (60.6)	127 (60.2)
Concomitant csDMARDs other than methotrexate, n (%)	27 (12.7)	25 (11.8)
Concomitant oral corticosteroids, n (%)**	56 (26.3)	51 (24.2)

Key points from Table 1

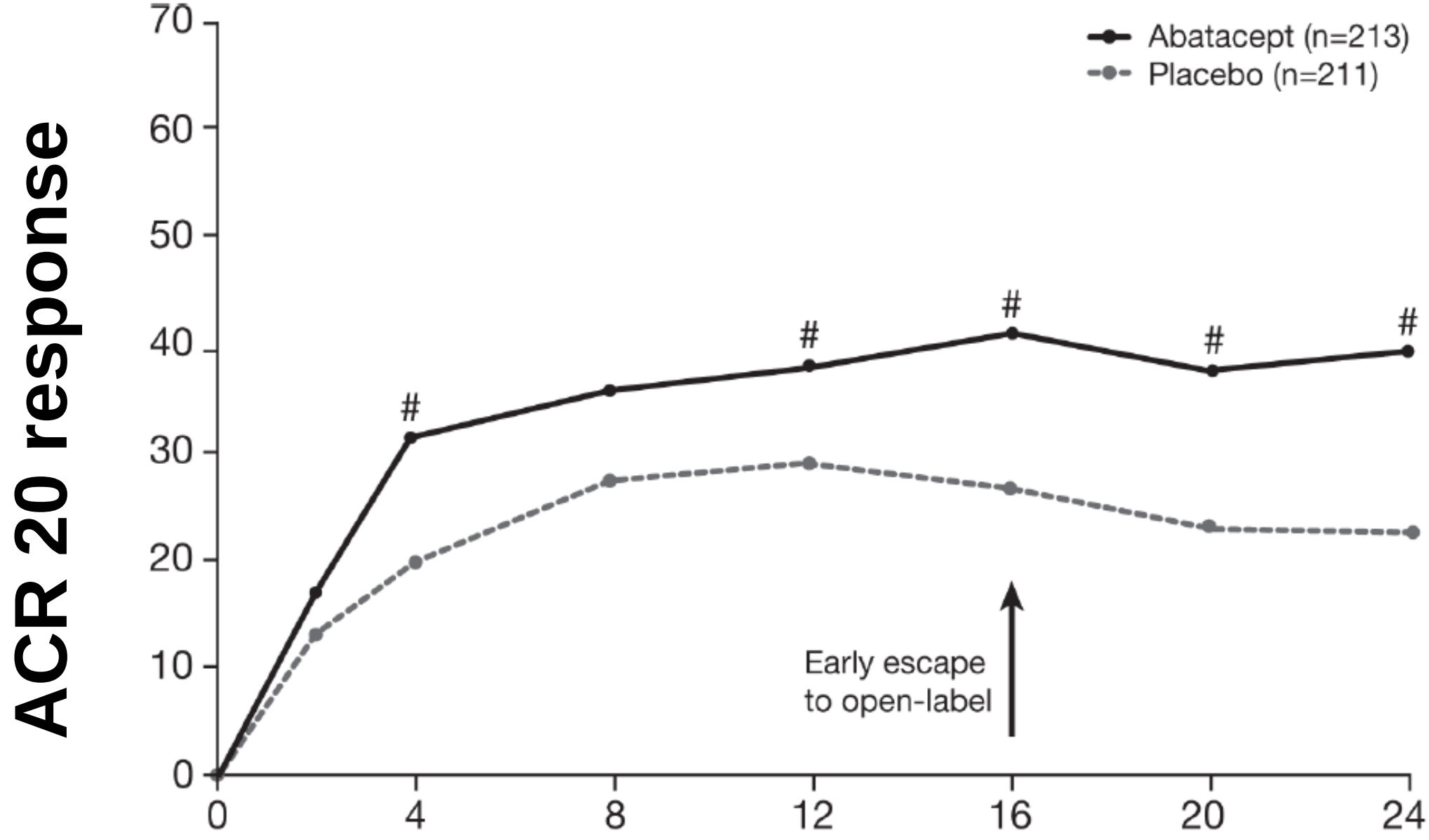
	Abatacept (213)	Placebo (211)
Age	51.0 (10.7)	49.8 (11.3)
Disease duration	8.3 (8.1)	8.8 (8.3)
SJC	12.1 (7.8)	11.1 (7.2)
DAS28 (CRP)	5.0 (1.1)	4.9 (1.1)
Psoriasis covering ≥3% BSA	68.5%	70.1%
PASI (0 – 72)	7.4 (8.0)	7.2 (7.8)
Anti-CCP positive	10 (5.1)	2 (1.0)
Prior TNFi use	60.6%	61.6%
MTX	60.6%	60.2%
Oral CS	26.3%	24.2%

Patient disposition



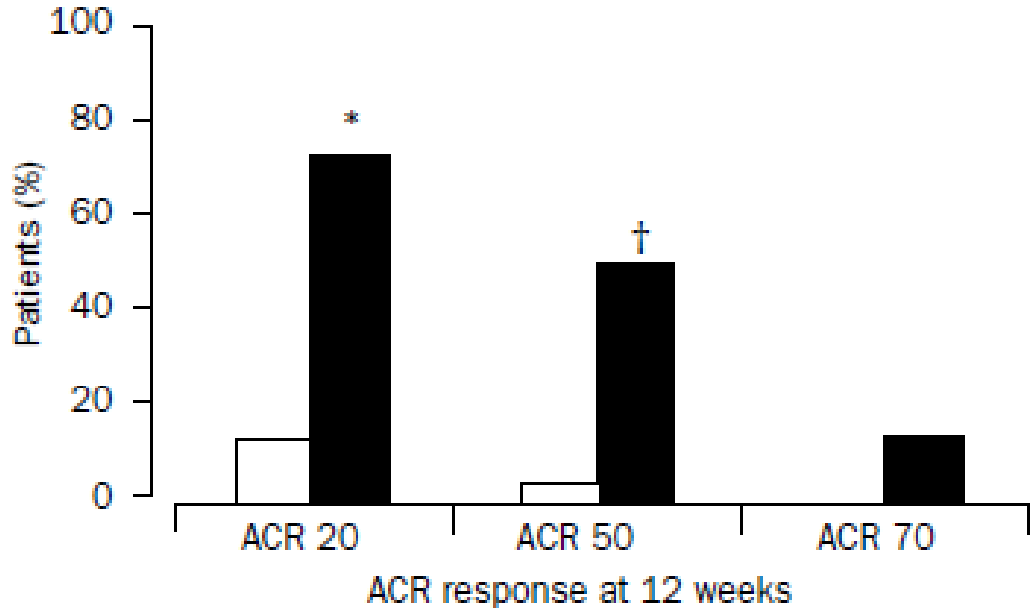
OUTCOMES

This is it, y'all



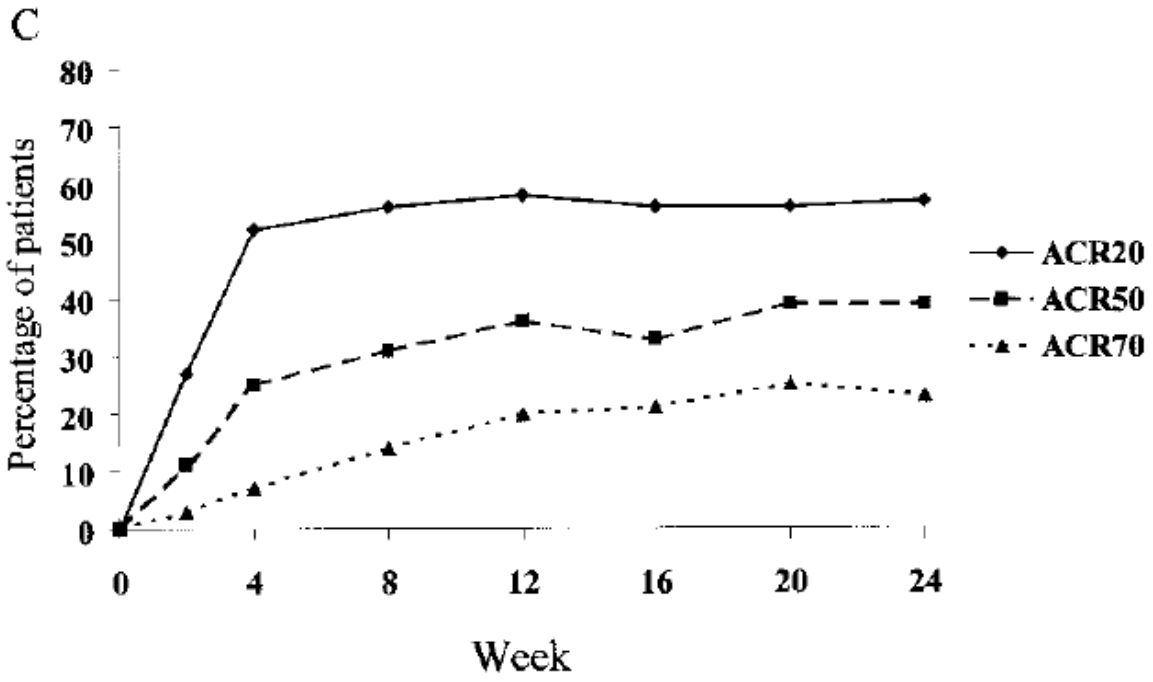
In contrast…

Etanercept



Mease, *Lancet* 2000;356:385

Adalimumab



Mease, *Arth Rheum* 2005;52:3279

Details of results

- ACR20: 39.4% vs 22.3%, p < 0.001
- Decrease in HAQ-DI: 31% vs 23.7%, p = 0.097
- All other “key secondary endpoints” were therefore nominal
- Decrease in HAQ-DI by TNFi exposure
  - Naïve: 34.5% vs 19.8%; Δ 14.8 (1.7 - 28)
  - Exposed: 28.7 vs 26.2, Δ 2.5 (-8.3 - 13.3)
- ACR20 by TNFi exposure
  - Naïve: 44 vs 22.2, Δ 21.9 (8.3 - 35.6)
  - Exposed: 36.4 vs 22.3, Δ 14.0 (3.3 - 24.8)

Other endpoints

- **ACR50: 19.2 vs 12.3, Δ 6.9 (0.1 - 13.7)**
- **ACR70: 10.3 vs 6.6, Δ 3.7 (-1.5 - 8.9)**
- **Change in DAS28: 1.35 vs 0.94, Δ -0.42 (-0.69 to -0.14)**
- **Enthesitis resolution: 32.9% vs 21.2%**
- **Dactylitis resolution: 44.3% vs 34%**
- **No radiographic progression: 42.7% vs 32.7% (Δ 10 (1 - 19.1)**
- **Mean Δ in PsA-modified SHS: 0.30 (sd 0.12) vs 0.35 (sd 0.13)**
- **PASI 50 response: 26.7% vs 19.6%, Δ 7.3 (-2.2 - 16.7)**
- **MDA: 11.7% vs 8.1%, p = 0.205**
- **Change in DAPSA: -18.75 vs -13, Δ -5.75 (-10.01 to -1.49)**

Safety at 24 weeks

- No deaths during the study, including through 28-week OLE
- AEs similar (54.5% vs 53.1%)
  - Infections: 57 (abatacept) vs 63 (placebo) patients
  - Malignancies: 0 (abatacept) vs 2 (placebo) patients
  - New autoimmune diseases: none
  - Injection site reactions: 1 in each group
- SAEs occurred in 6 (abatacept) vs 9 (placebo) patients
  - 3 in both group resulted in discontinuation
  - Only 1 in each group was said to be treatment-related
- One serious infection related to study drug: Pneumocystis jirovecii, in patient with history of COPD, cigarette smoking, and “recent” exposure to “high-dose” CS

Discussion

- **“Selective modulation of T-cell costimulation with abatacept resulted in significantly higher ACR20 response rates in patients with PsA compared with placebo”**
  - **Met the primary aim**
- **Improved outcomes in TNFi-naïve patients**
- **Caution with comparisons to other trials**
  - **Included large number of TNFi-refractory patients**
- **Well-tolerated and safe**

Bottom line: abatacept is not first-line for PsA, especially if skin is bad

Drug	ACR20	PASI75	Publication
TNF inhibitors			
Etanercept	73% vs 13%	26% vs none	Mease, *Lancet* 2000;356:385
Adalimumab	58% vs 14%	59% vs 1%	Mease, *Arth Rheum* 2005;52:3279
Infliximab	65% vs 10%	68% vs none	Antoni, *Arth Rheum* 2005;52:1227
IL-17 pathway			
Broadalumab 280 mg	39% vs 18%	Not reported	Mease, *NEJM* 2014;370:2295
Ixekizumab q2 weeks	48% vs 19%	60% vs 15%	Nash, *Lancet* 2015;386:1137
Secukinumab 300 mg	54% vs 15%	63% vs 16%	McInnes, *Lancet* 2017;389:2317
Ustekinumab 90 mg	32% vs 10%	52 vs 5%	Gottlieb, *Lancet* 2009;373:633
Co-stimulation			
Abatacept 10 mg/kg IV	48% vs 19%	14% vs 5%	Mease, *Arth Rheum* 2011;63:939
Abatacept SQ	39% vs 22%	27% vs 20% (NS)	Current study