TERAPIE BIOLOGICHE: PASSATO, PRESENTE, FUTURO

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Current and emerging biologicals

CURRENT

TNF inhibitors

- Etanercept
- Adalimumab
- Infliximab

Non TNF Biologicals

- Anakinra
- Rituximab (25% Mouse Prot.)
- Abatacept

EMERGING

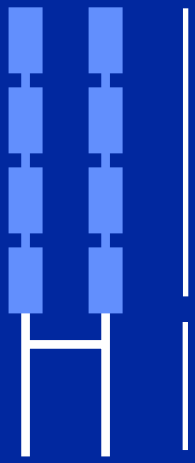
TNF inhibitors

- Golimumab
- Certolizumab

Non TNF Biologicals

- ocrelizumab (5%-10% Mouse Prot.)
- Ofatumumab (no Mouse Prot.)
- Tocilizumab

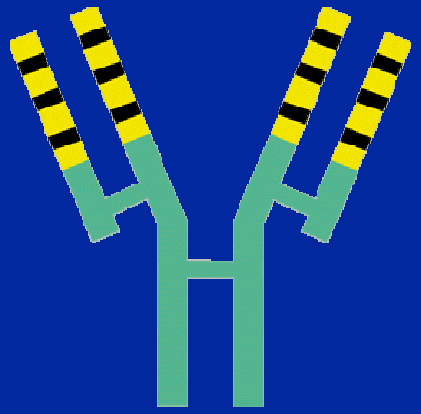
Attuali Agenti Biologici Anti-TNF-α



Human p75

Human IgG1

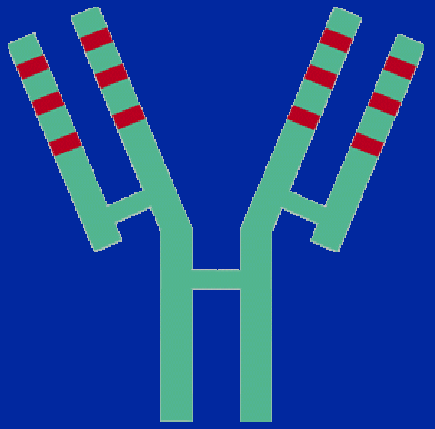
Etanercept



Mouse

Human IgG1

Infliximab



Human IgG1

Adalimumab

Caratteristiche degli anti-TNF

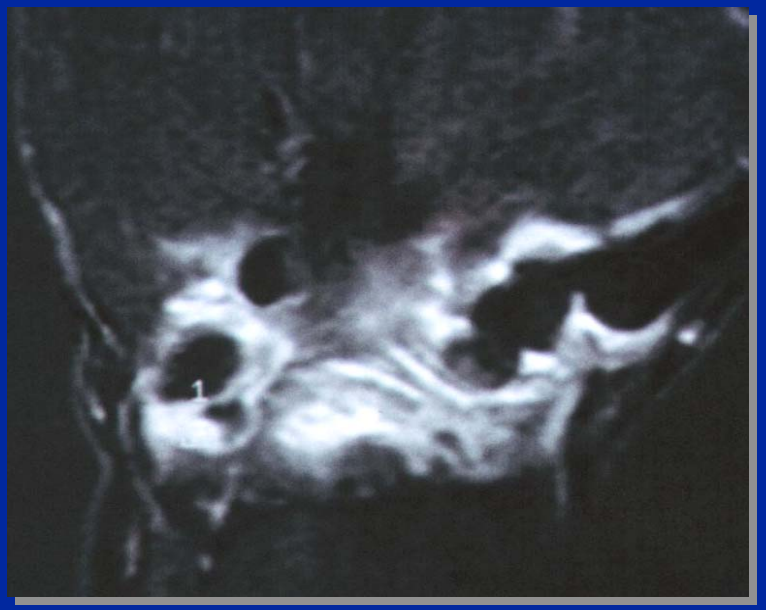
	Recettore solubile	Anticorpi monoclonali	
	Etanercept	Infliximab	Adalimumab
Struttura	Proteina di fusione del recettore umano	Anticorpo monoclonale chimerico (murino/umano)	Anticorpo monoclonale umano
Somministrazione	25 mg x 2/settimana SC AIG 0.4 mg/kg x 2/settimana SC	3 –10 mg/kg ogni 4-8 settimane IV	40 mg/1 o 2 settimane
Emivita	4,8 giorni	9.5 giorni	12-14 giorni
Fissazione del complemento (invitro)	No	Si	Si
Lisi delle cellule che esprimono il TNF (in vitro)	No	Si	Si
Immunogenicità (anticorpi anti-farmaco)	<5% (non neutralizzanti) (PI)	15-24% (in monoterapia) neutralizzanti (PI)	Fino al 12% in monoterapia 5% con MTX (PI)
Associazione con MTX	Facoltativa	Obbligata	Facoltativa
	ENBREL® Package Insert (PI)	Remicade ® Package Insert	HumiraTM Package Insert

Studi multicentrici, controllati con placebo, in doppio cieco:

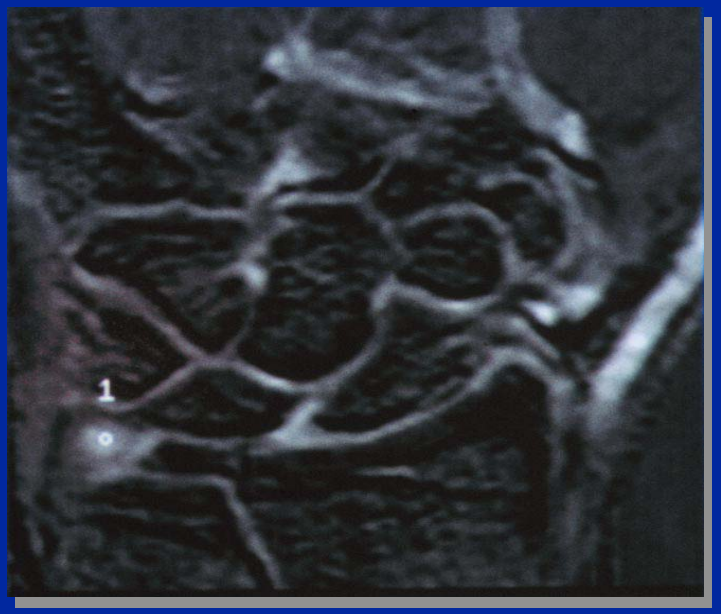
- Infliximab / Remicade **(ATTRACT, ASPIRE)**
- Etanercept / Enbrel **(TEMPO)**
- Adalimumab / Humira **(DEO11, ARMADA, STAR)**

Anti-TNF Riducono il Processo Infiammatorio nell'Artrite

NMR Scan del polso – Gadolinium Uptake



Settimana 0



Settimana 10

Who should get anti-TNFa Biologic Agents?

° Methotrexate partial responders

- DMARD failures

- ? Early inflammatory arthritis patients

Anti-TNFa agents are the first byologic of choise after MTX falure

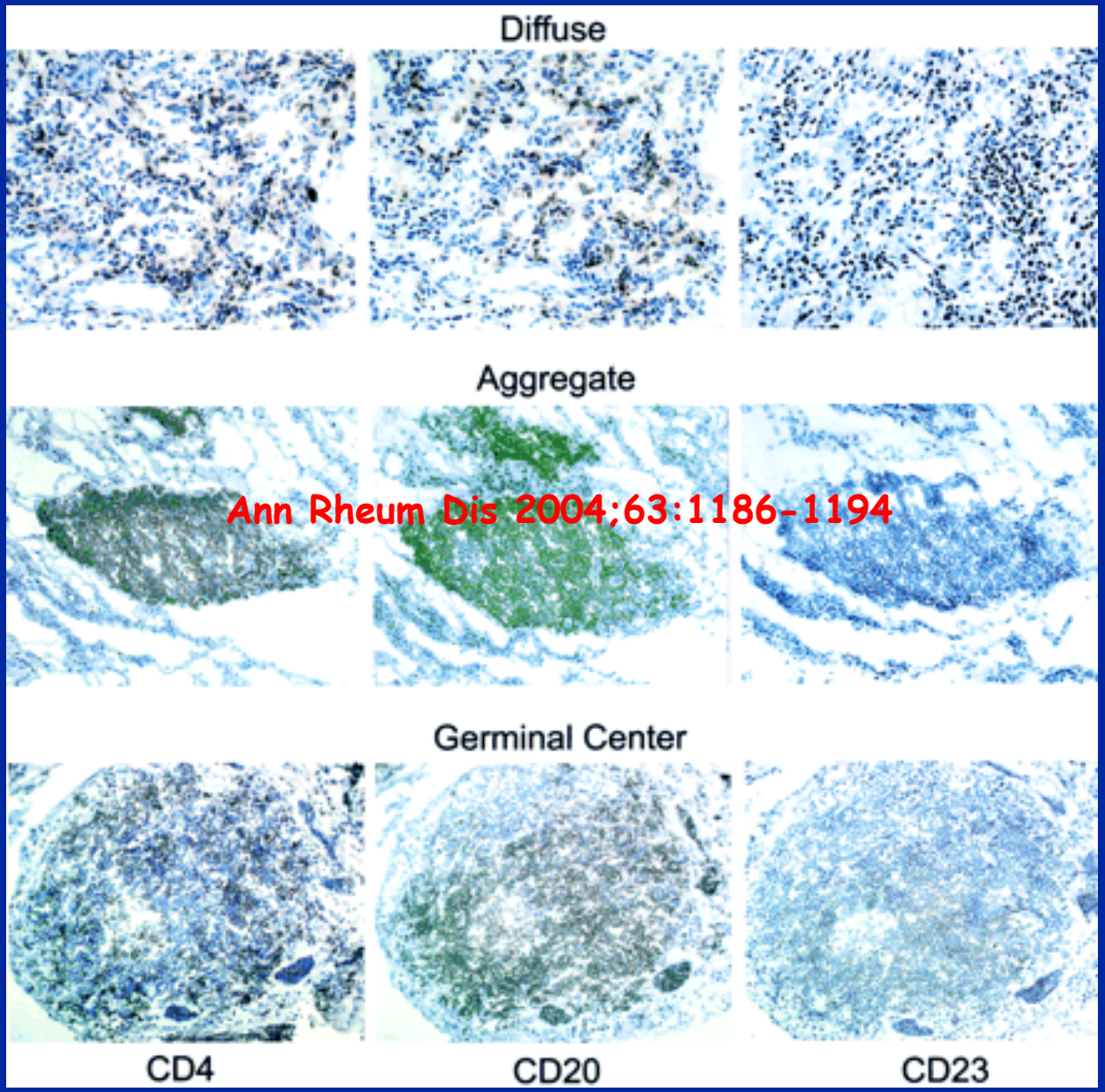
- Rapid onset of action
- Marked radiografic inhibition
- Large population axposure
- Lon term safety data

Kineret® (Anakinra)

forma ricombinante dell'antagonista del recettore per l'interleuchina-1 (IL-1Ra)

- Inibisce il legame della citochina al recettore dell'IL-1
- Indicazioni proposte
  - Riduzione di segni e sintomi dell'AR moderata/grave non responsiva ad uno o più DMARDs

ORGANIZZAZIONE DEI LINFOCITI IN CORSO DI SINOVITE

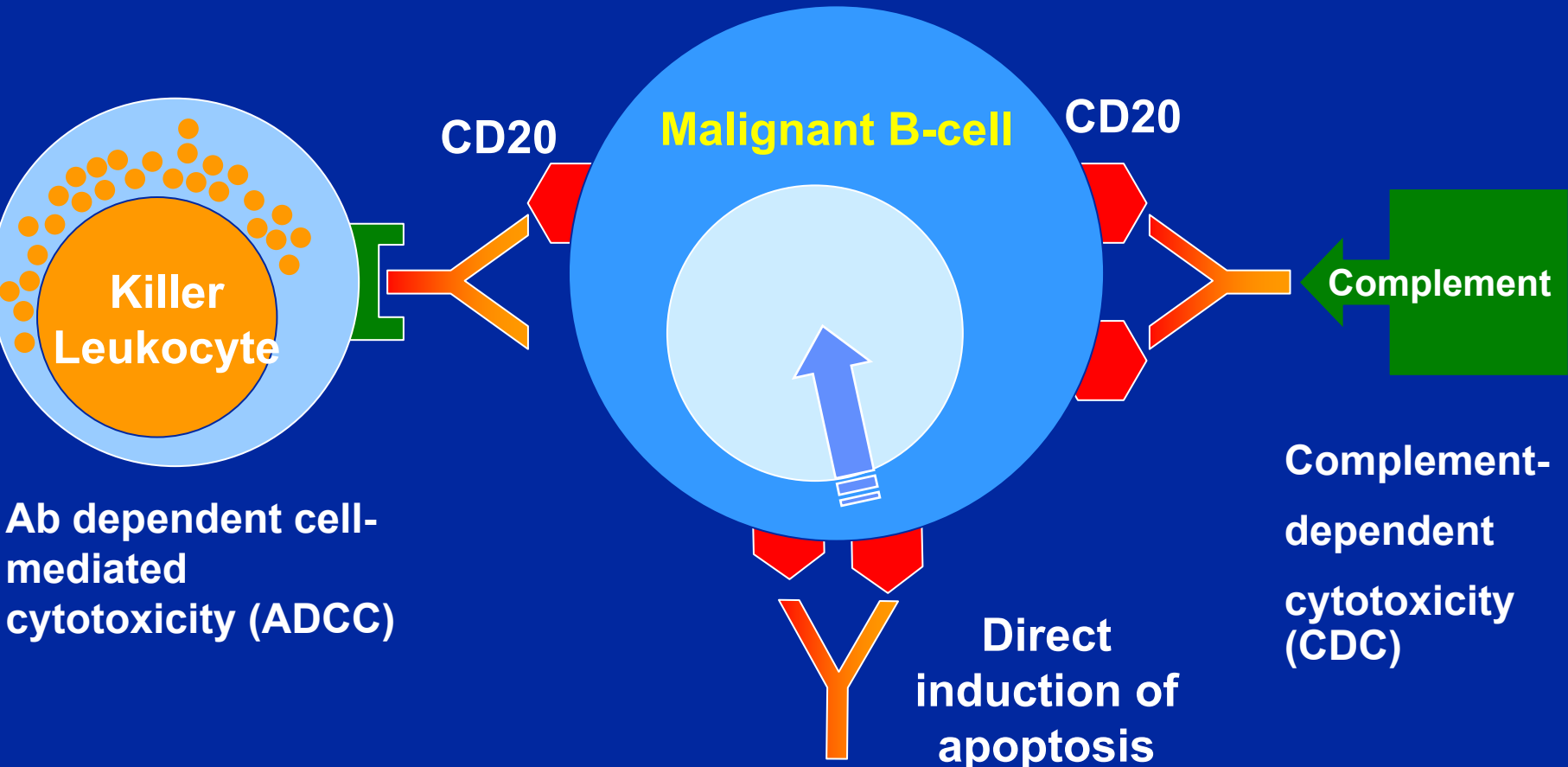


Ann Rheum Dis 2004;63:1186-1194

Rituximab

- Monoclonal antibody
  - Chimeric human/murine (25% Mouse Prot.)
  - Anti-CD 20 (B cell surface marker)
- Mechanism of action
  - B cell depletion

Anti- CD20 (Rituximab; Mabthera®) mechanism of action



dapted from Male D, *et al*. *Advanced Immunology* 1996; 1.1–1.16

Rituximab

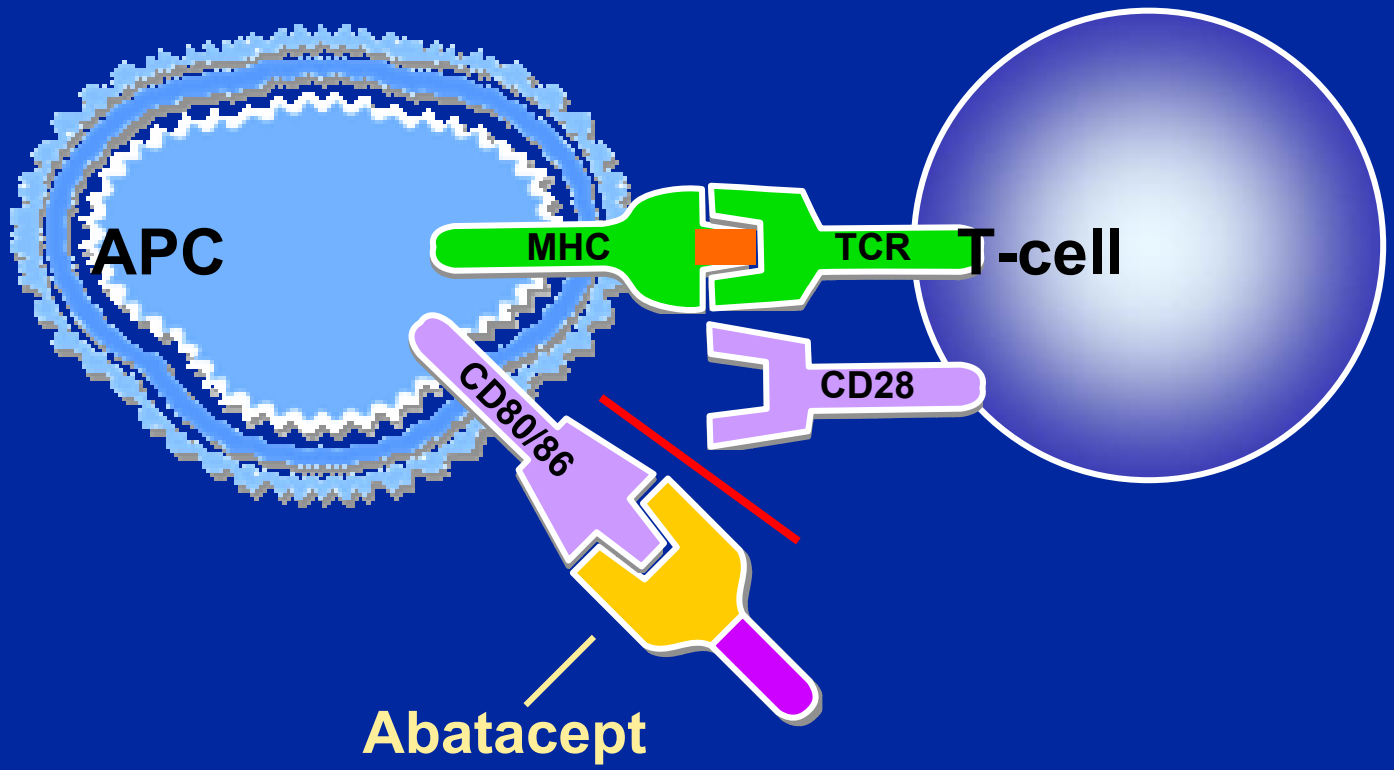
- Indications
  - Non-Hodgkin's lymphoma (1997)
  - Rheumatoid arthritis (2006)
  - Investigational
    - SLE
    - Wegener's granulomatosis
    - Hepatitis C associated cryoglobulinemia
    - Sjogren's syndrome
    - Others….(Regiona Toscana)

FACTORS IN CHOOSING RITUXIMAB

- NOVEL MECHANISM OF ACTION
- INFREQUENT ADMINISTRATION
- USED SAFELY INN HIGH TB RISK PATIENTS, POSSIBLE CTD, LYNPHOMA

Abatacept (ORENCIA)

Proteina di fusione costituita dal dominio extracellulare del CTL4 (CD28)
e un frammento del dominio Fc delle IgG umane



Selectively Modulates Co-Stimulation via CD80/86:CD28 Pathway

Proposed Mechanism of Action of Abatacept

- Decrease T-cell activation and proliferation
- Decrease pro-inflammatory cytokine secretion from activated synovial macrophages
- Decrease autoantibody production (e.g. RF)
- No depletion of T-cells or other leukocytes

Abatacept

- **Proposed indications for abatacept:**
  - **For use in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more biologic or non-biologic DMARDs**
    - **Reducing signs and symptoms**
    - **Inducing major clinical response**
    - **Inhibiting the progression of structural damage**
    - **Improving physical function**
  - **Abatacept may be used as monotherapy or concomitantly with methotrexate or other non-biologic DMARD therapy**

Somministrato per flebo (100 mg) una volta al mese

In sperimentazione per via sottocutanea

Overall Safety Summary

- abatacept is generally safe and well-tolerated
- Major identified risk is infection
  - Frequency slightly increased (1% difference in serious infection rate) but type, duration, treatment, and outcome similar to placebo
- Malignancy risk similar to placebo overall and for major categories of malignancy (solid, hematologic) but current assessment is not definitive
- 2 large observational studies to better define risk of rare events, including lymphoma, other malignancies, and serious infections

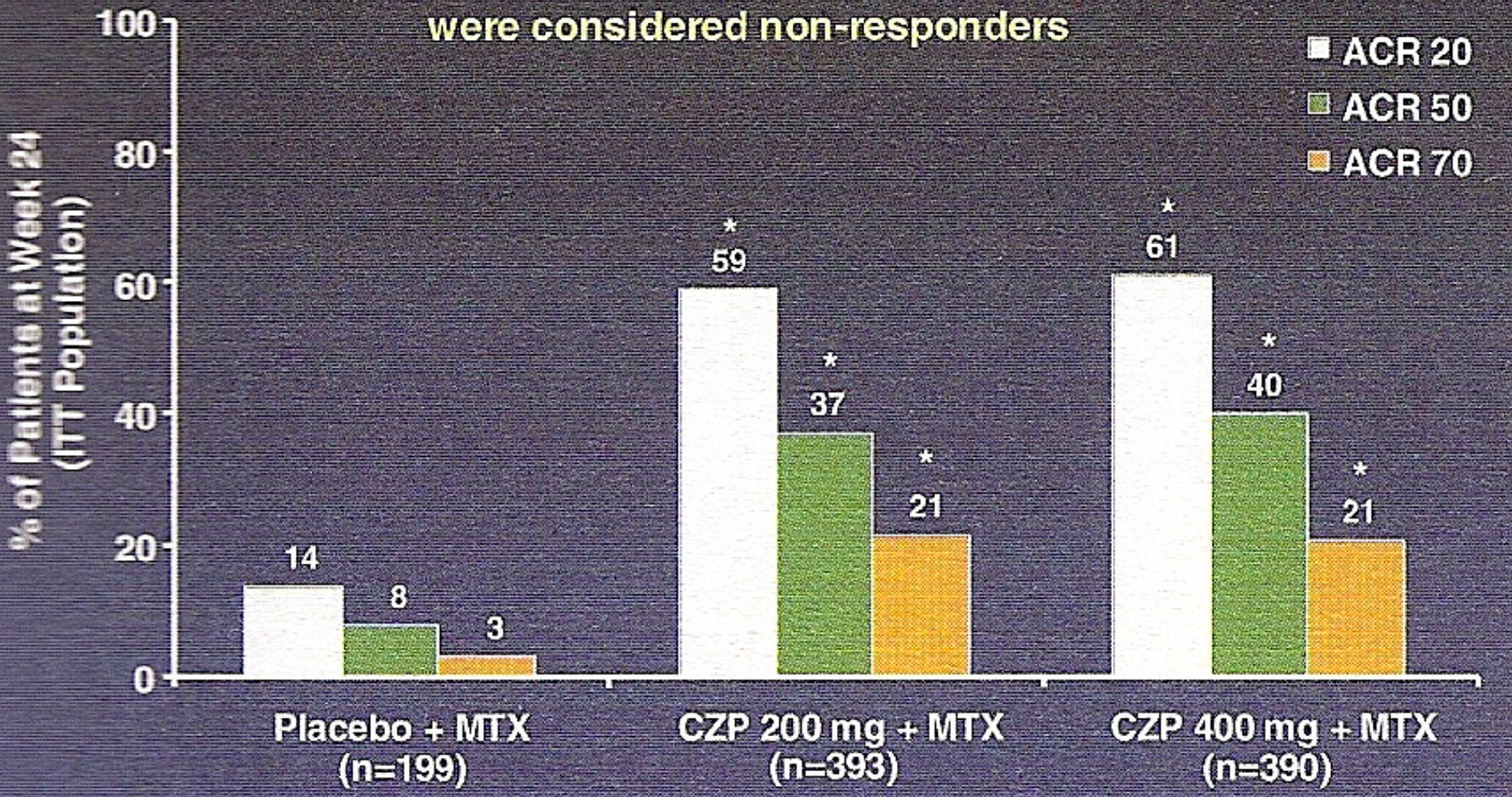
FACTORS IN CHOOSING ABATACEPT

- NOVEL MECHANISM OF ACTION
- GOOD SUSTAINABILITY
- INFREQUENT INFUSION REACTIONS

CERTOLIZUMAB
(CIMZIA)

- anticorpo monoclonale “umanizzato” che presenta un’alta specificità, affinità e potenza di neutralizzazione del TNF*α*.
- la somministrazione di Certolizumab avviene per via sottotanea alla dose di 400 mg ogni 2 settimane

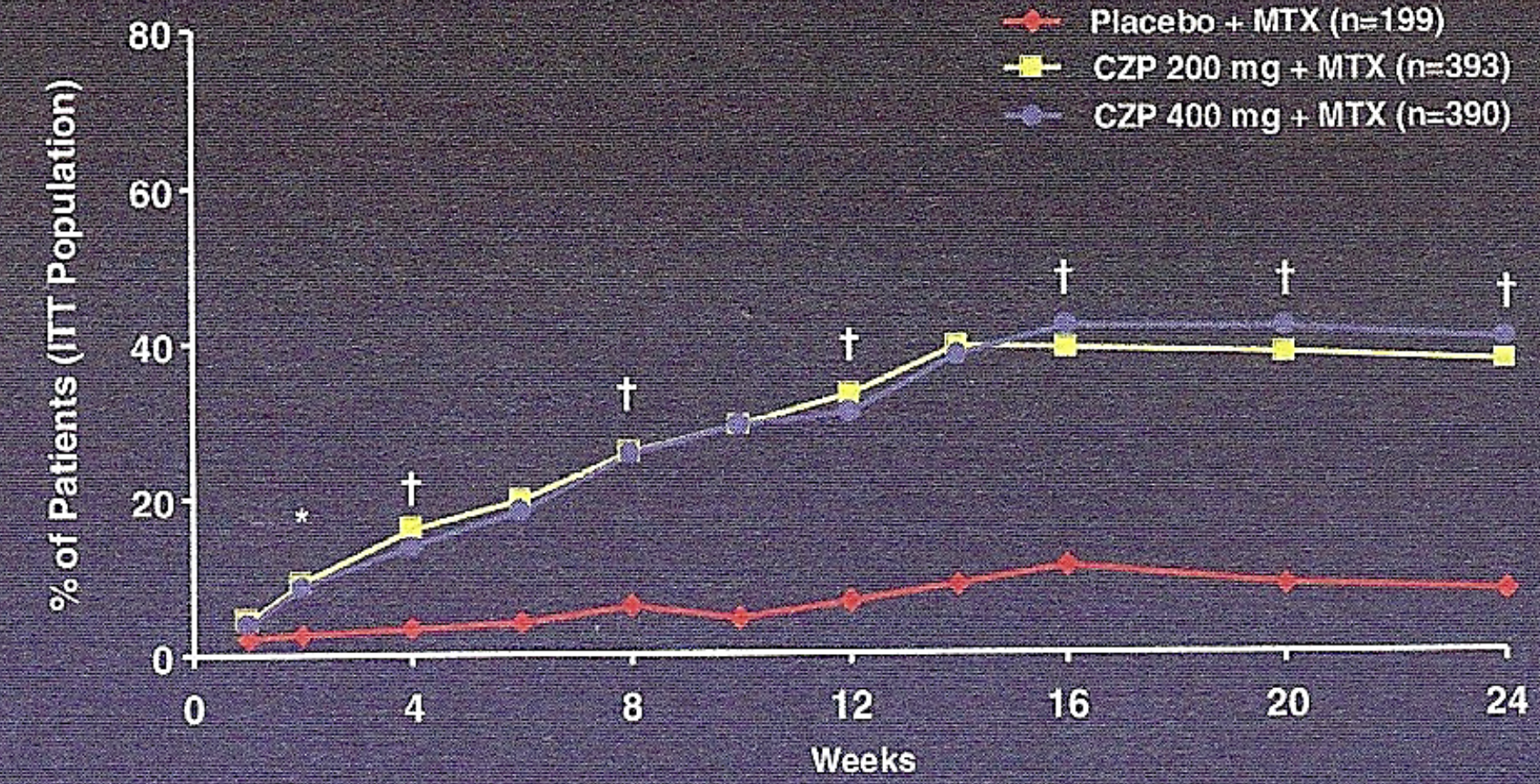
ACR Responder Rates of Certolizumab



*Significantly different from placebo, $P < 0.001$

RAPID 1

ACR50 Efficacy of Certolizumab Over Time

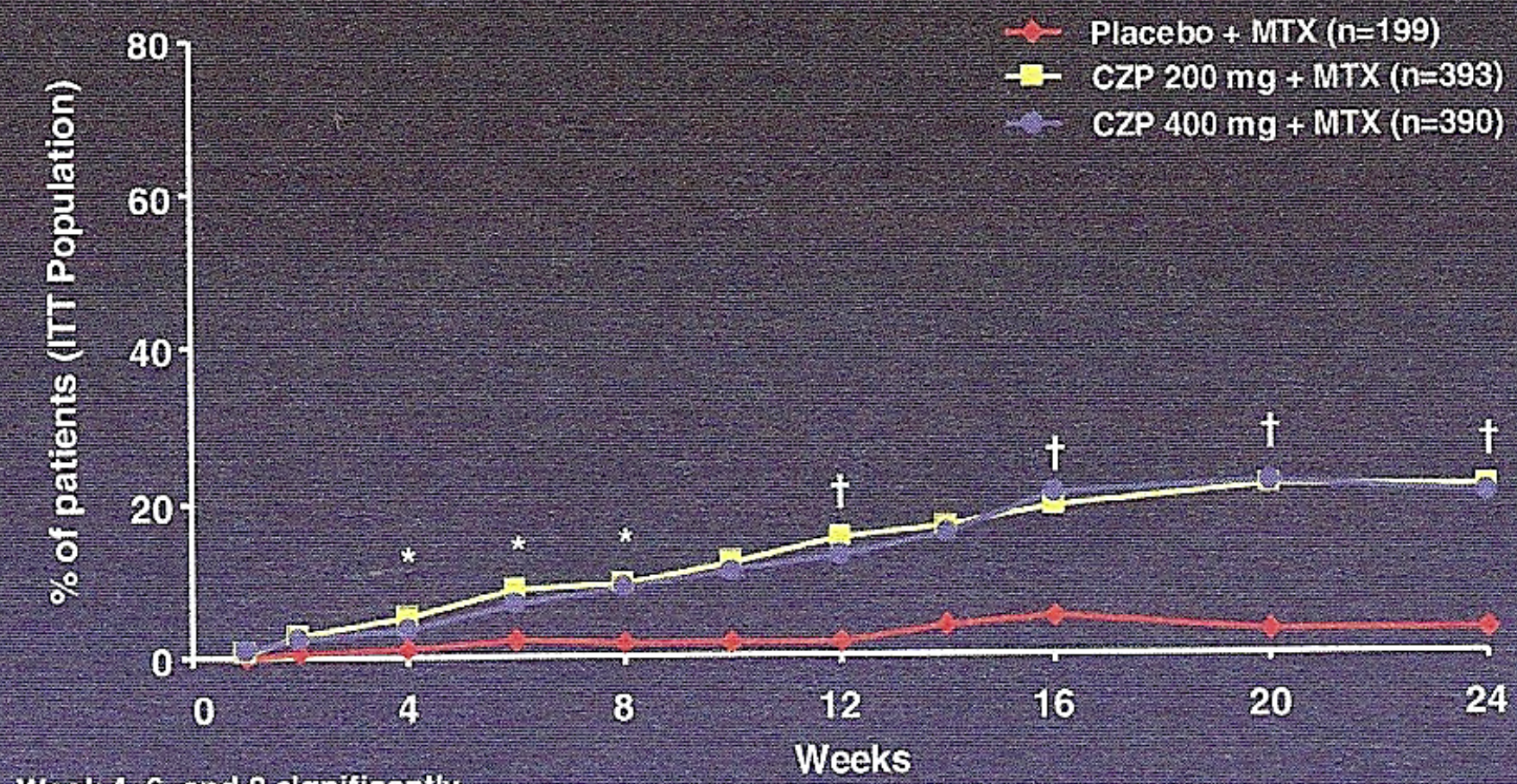


* Week 2 significantly different from placebo, $P \leq 0.007$

† Remaining weeks all significantly different from placebo, $P < 0.001$

Keystone et al. EULAR 2007. Abstract #OP001

ACR70 Efficacy of Certolizumab Over Time



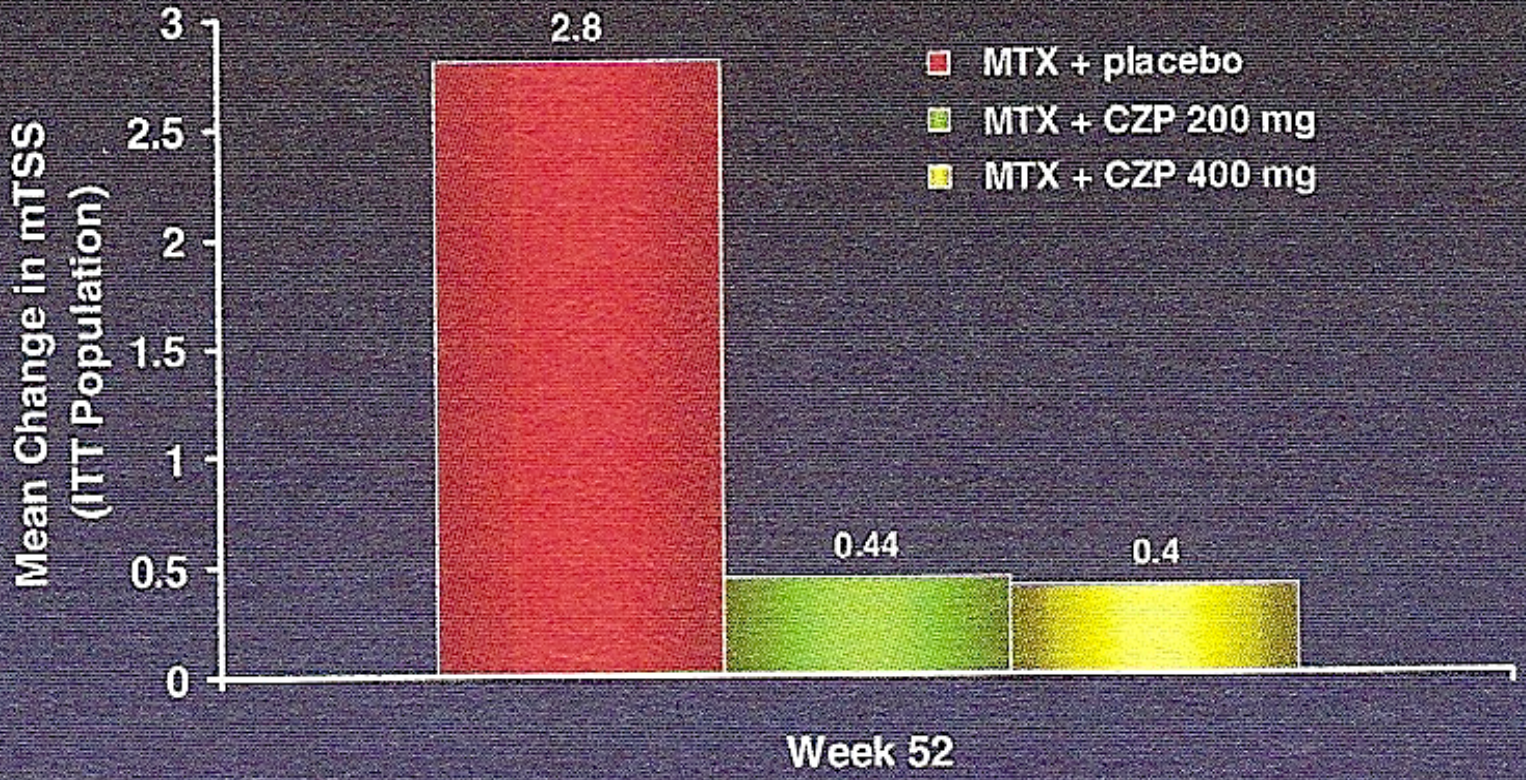
Week 4, 6, and 8 significantly different from placebo, $P \leq 0.05$

Remaining weeks all significantly

Keystone et al. EULAR 2007. Abstract #OP0016

RAPID 1

Radiographic Outcome With Certolizumab



Van der Heijde D et al. ACR 2007. Abstract 94

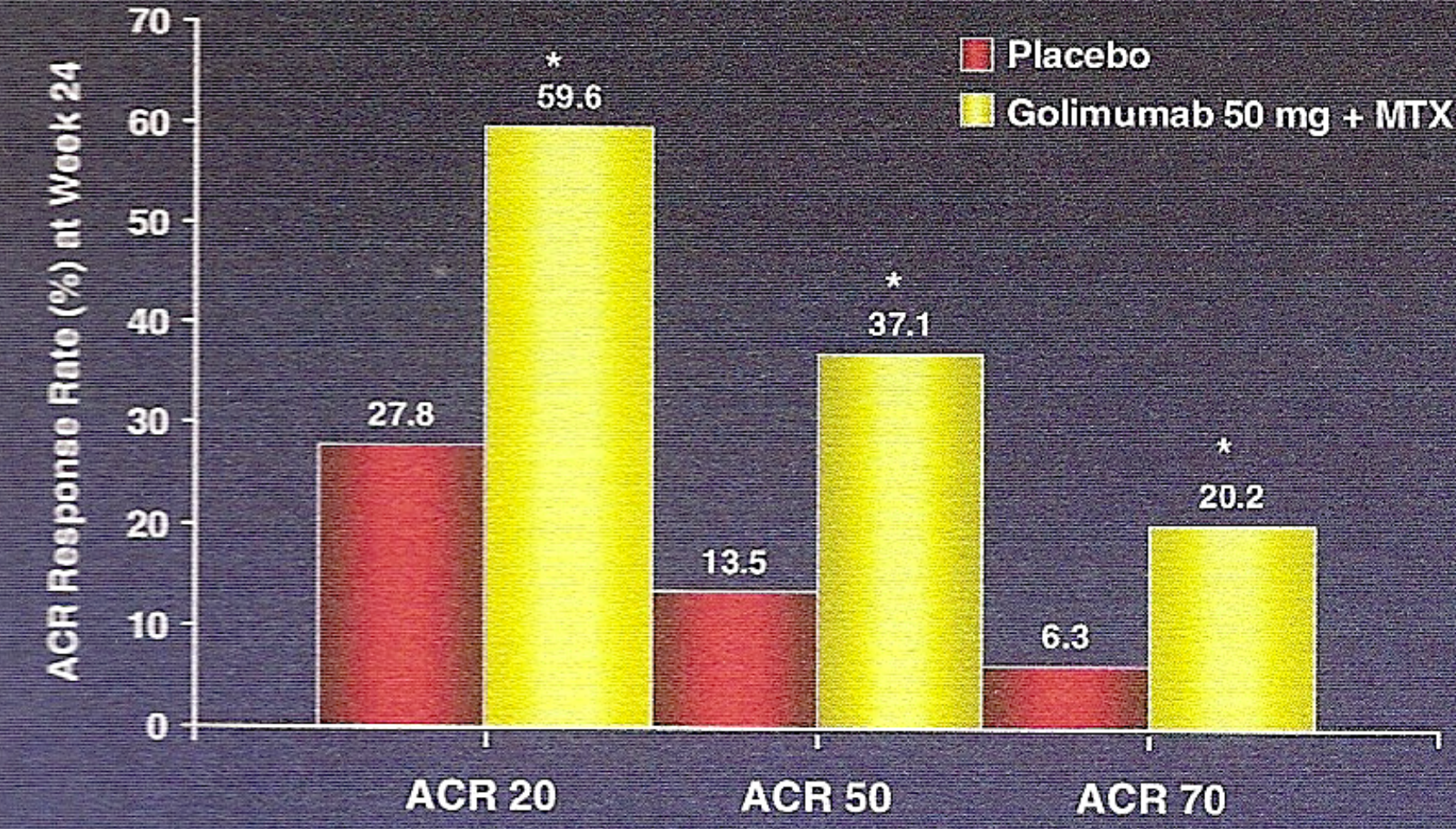
FACTORS IN CHOOSING CERTOLIZUMAB

- RAPID ONSET OF ACTION
- EARLY ACQUISITION ACR 50/70
- LESS INJECTION SITE PAIN

Golimumab

- Fully human mAb that binds to and neutralizes TNF activity
- Pre-clinical studies show Golimumab to be more potent than infliximab
- Dose Every four weeks SC due to long half life

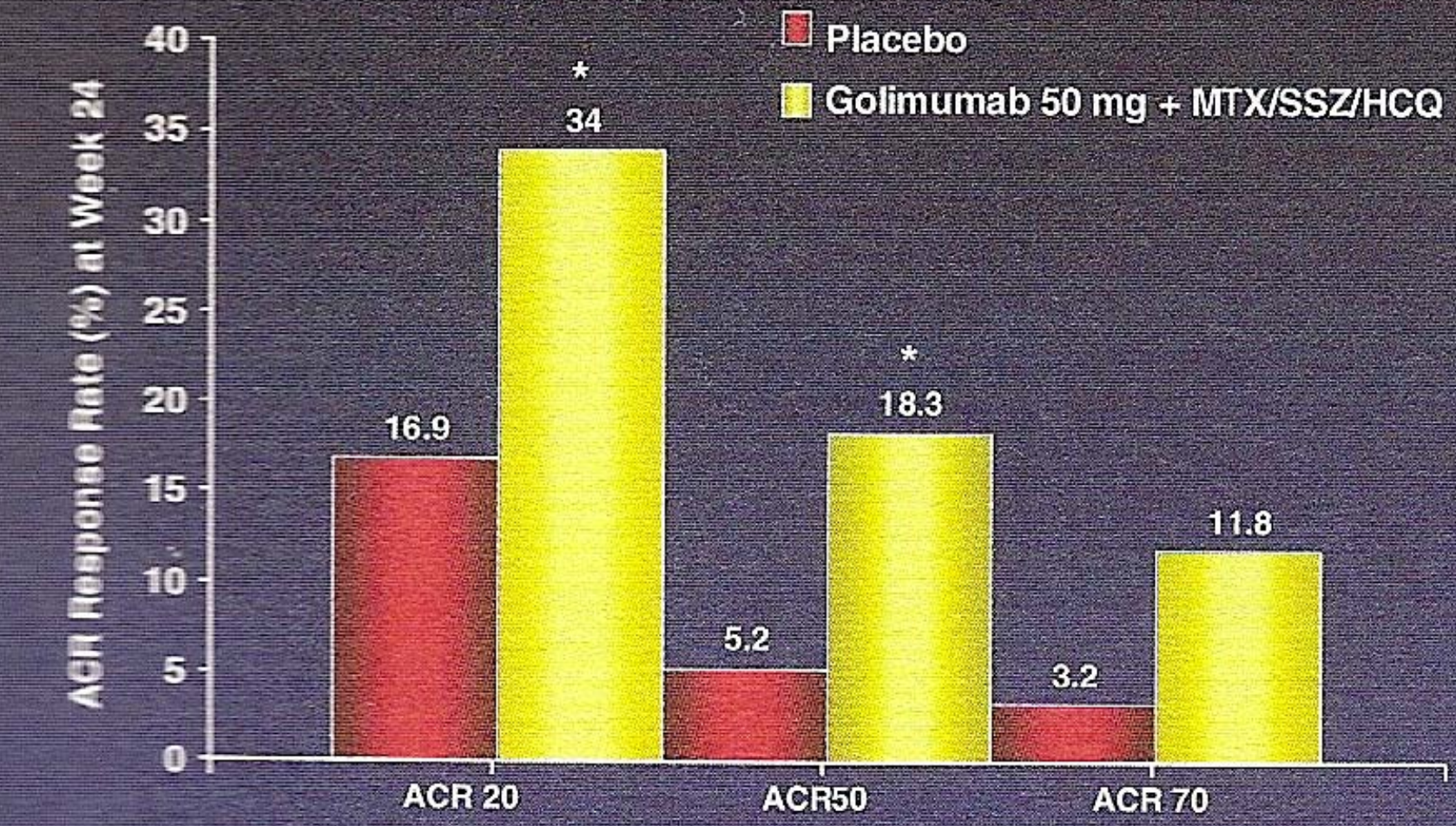
Golimumab in MTX-IR Patients



P < .001

Keystone E et al. EULAR 2008. Abstract THU0156

Golimumab in TNF-IR Patients



P<.001

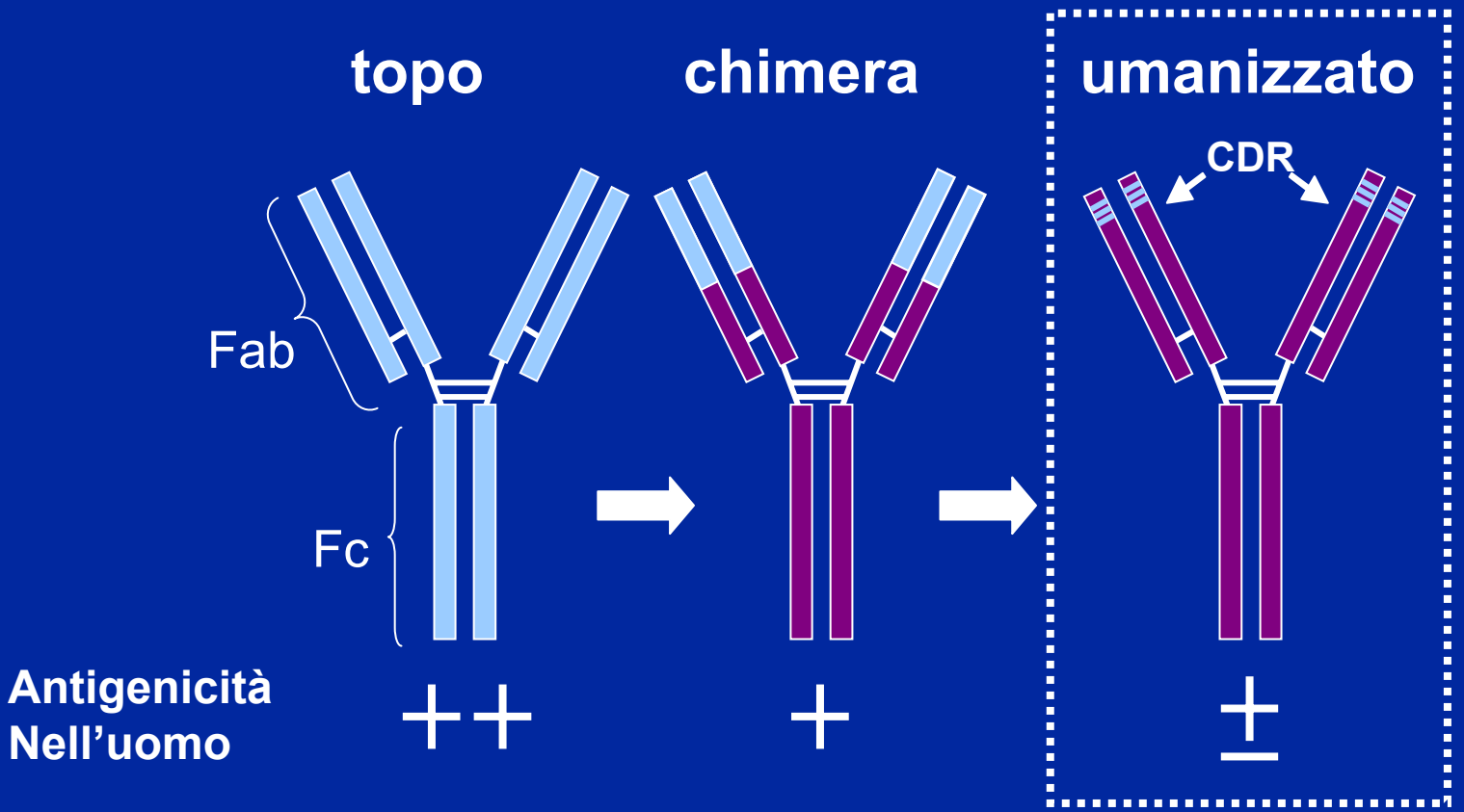
Smolen Jet al. EULAR 2008; Abstract OP0010

FACORS IN CHOOSING GOLIMUMAB

- MONTHLY SC ADMINISTRATION
- MORE POTENT THAN INFLIXIMAB

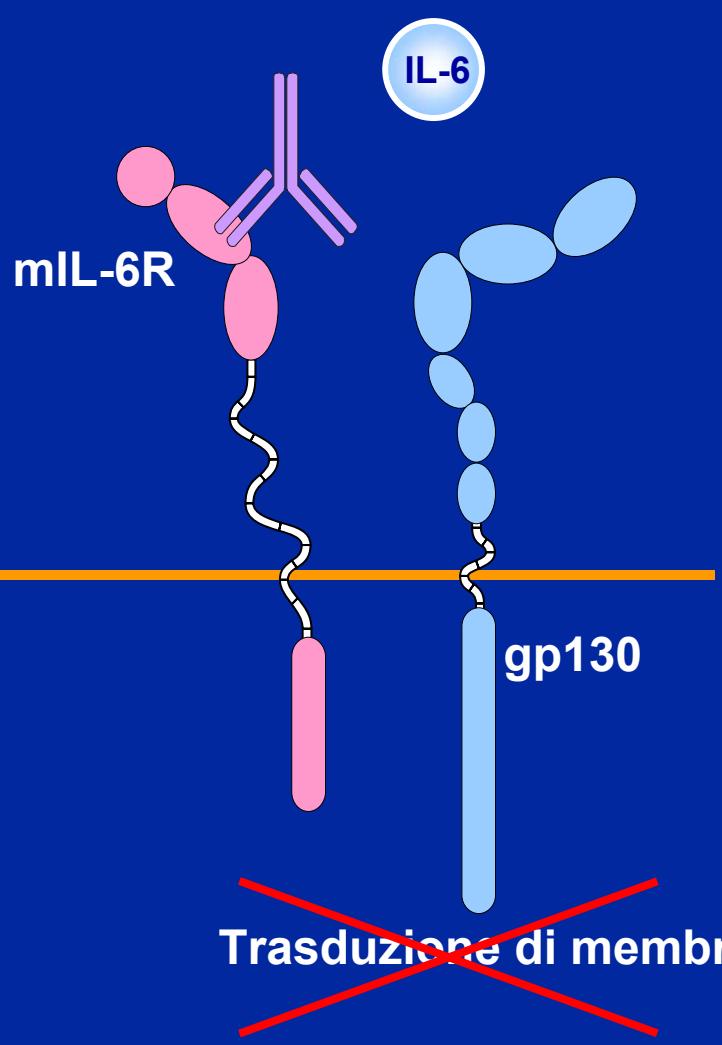
Tocilizumab

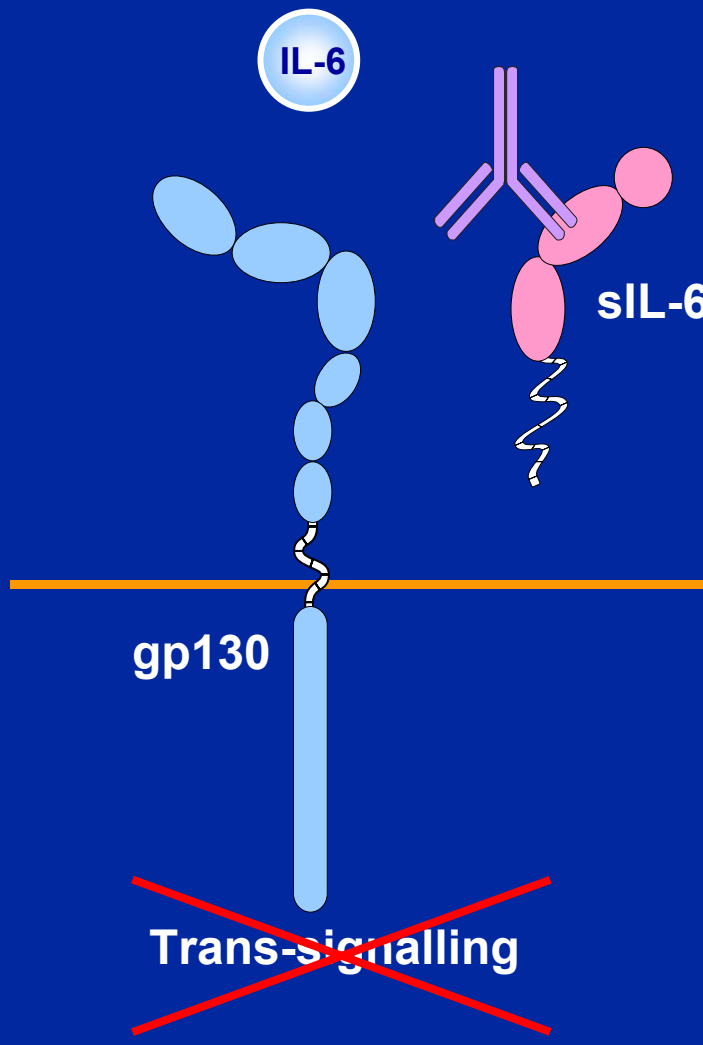
anticorpo monoclonale umanizzato anti recettore dell'IL-6



Yoshizaki K. *et al. Springer Semin Immunopathol* 1998; **20**:247–259

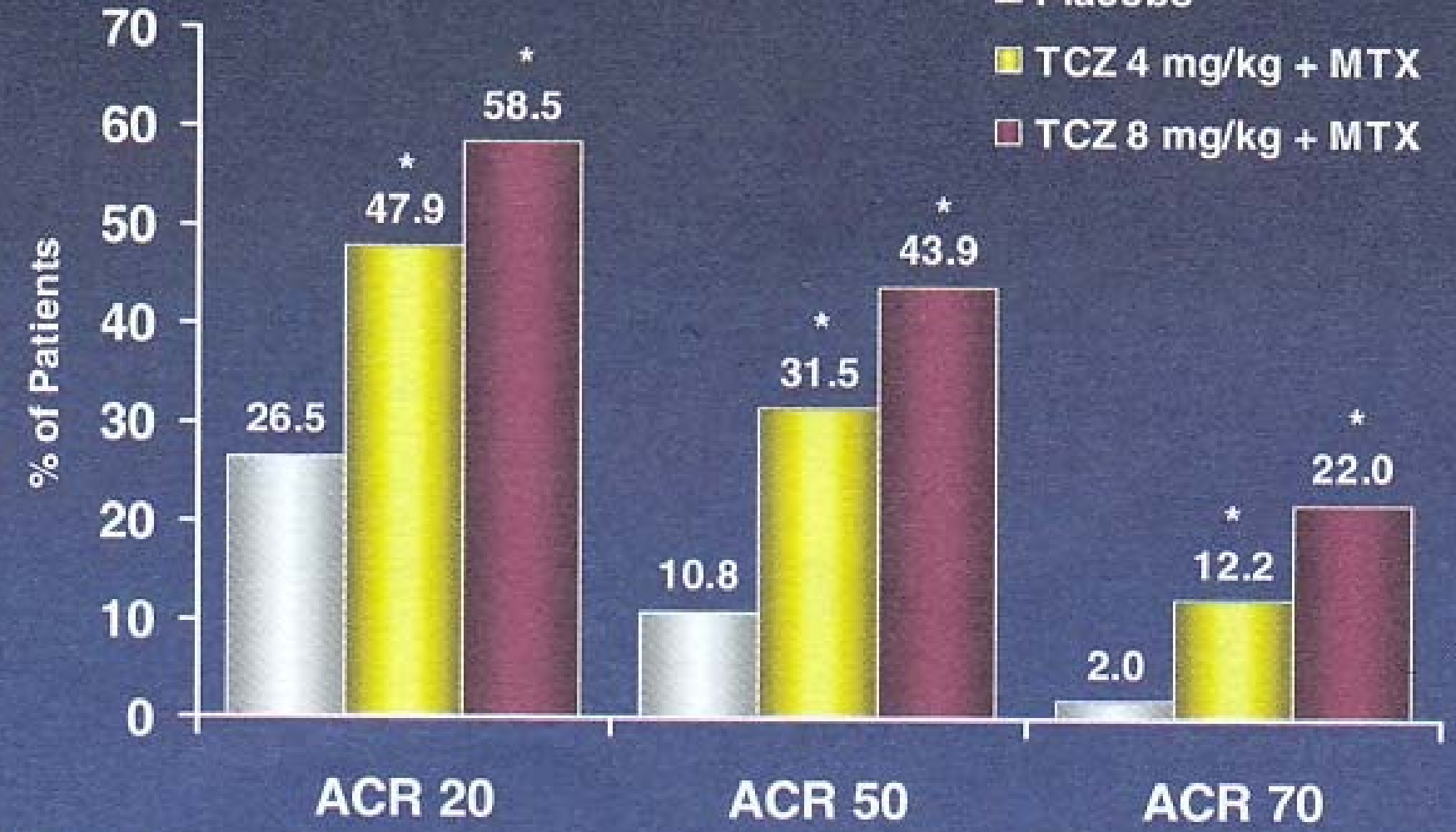
Trasduzione del segnale IL-6: Tocilizumab lega mIL-6R e sIL-6R per inibire la trasduzione di IL-6R





OPTION

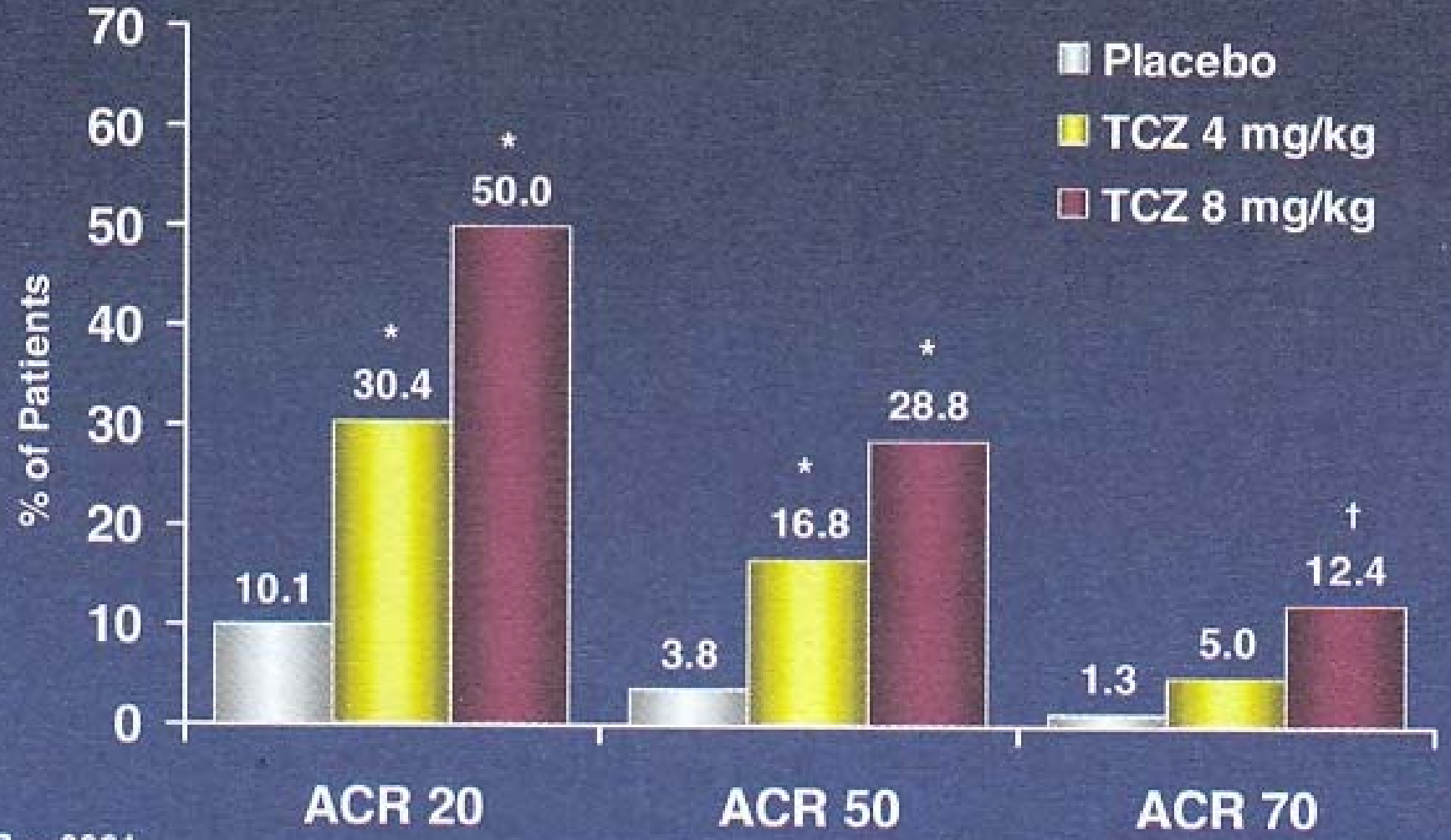
Efficacy of Tocilizumab in MTX-IR Patients



$P < .0001$

Smolen et al. Lancet 2008; 371:987

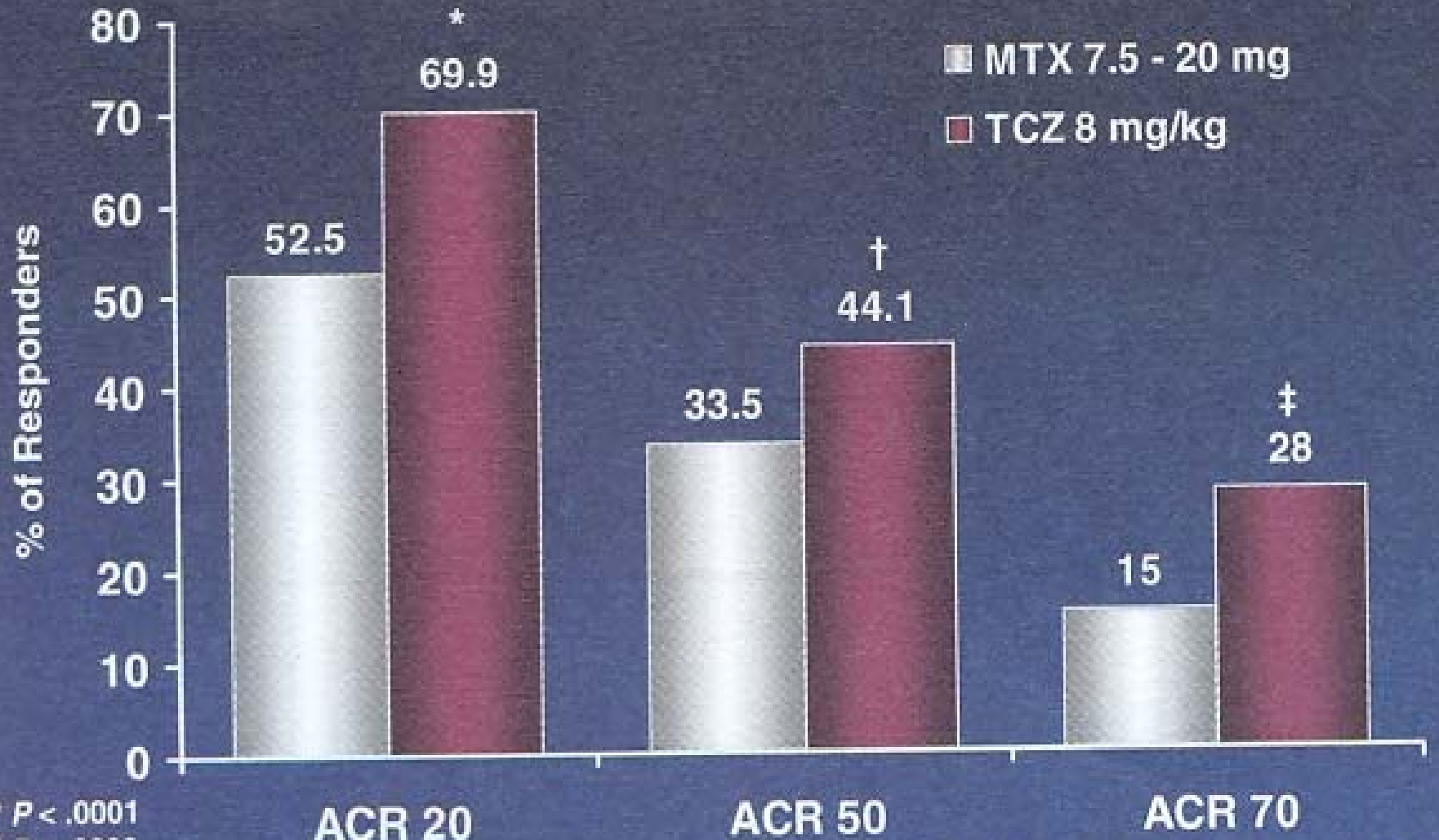
Efficacy of Tocilizumab + MTX in TNF Inhibitor-IR Patients



$P < .0001$
$P = .0002$

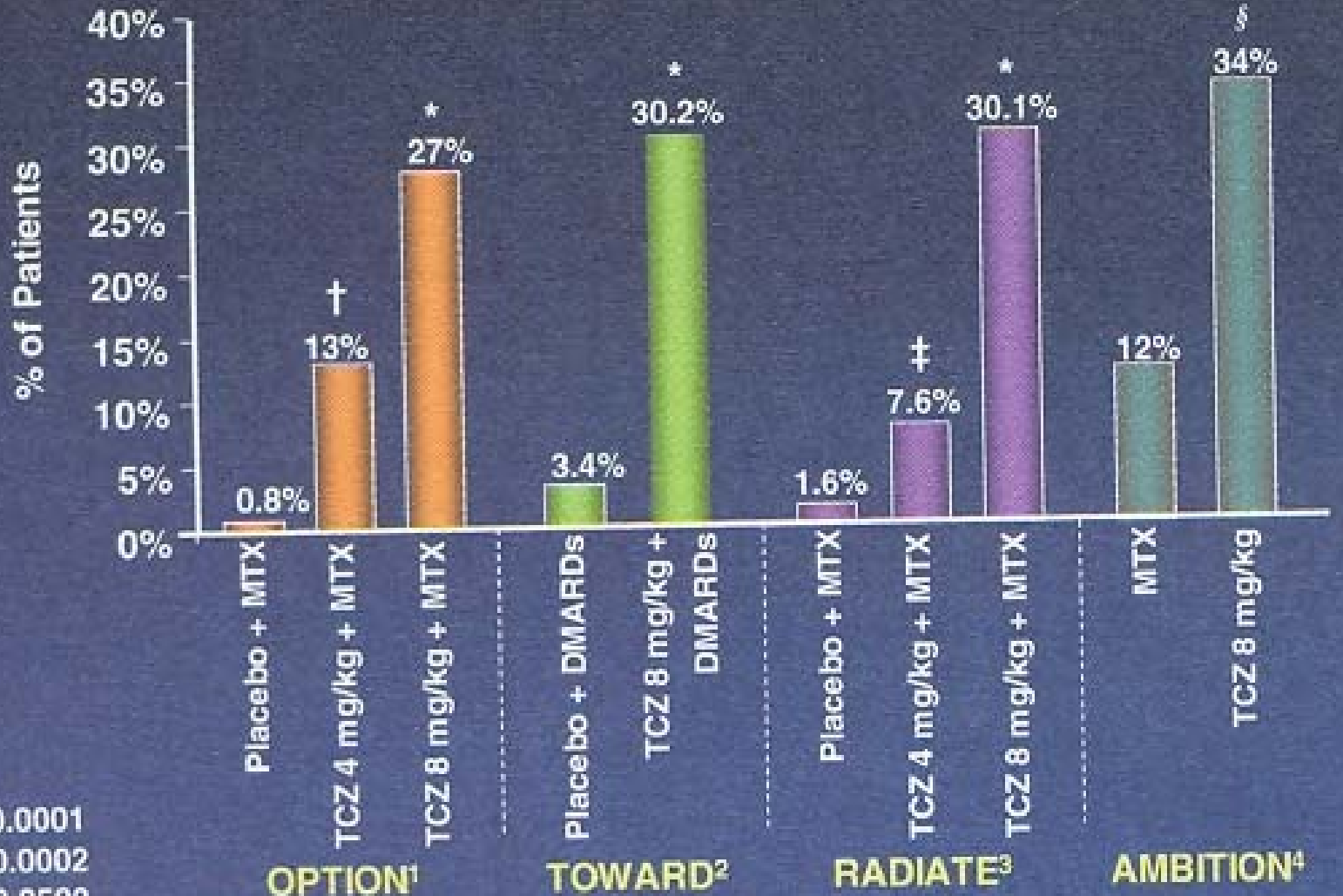
Emery P et al. EULAR 2008. Abstract OP0251

Efficacy of Tocilizumab Monotherapy vs MTX



* $P < .0001$
† $P = .0023$

Percentage of Patients with DAS28 Remission (DAS <2.6) at Week 24



* $P \leq 0.0001$
† $P = 0.0002$
‡ $P = 0.0533$
§ P value not

1. Smolen JS et al. *Lancet*. 2008;371:987. 2. Genovese M et al. ACR 2007, Abstract L1

FACTORS IN CHOOSING TOCILIZUMAB

- NOVEL MECHANISM OF ACTION (INHIBITS TH17 DIFFERENZIATION)
- EFFICACY IN MONORTHERAPY SUPERIOR TO MTX
- HIGH DAS REMISION RATES

Ruolo dei Micro-RNA, Nelle Patologie Autoimmuni Sistemiche

THE FUTURE!?

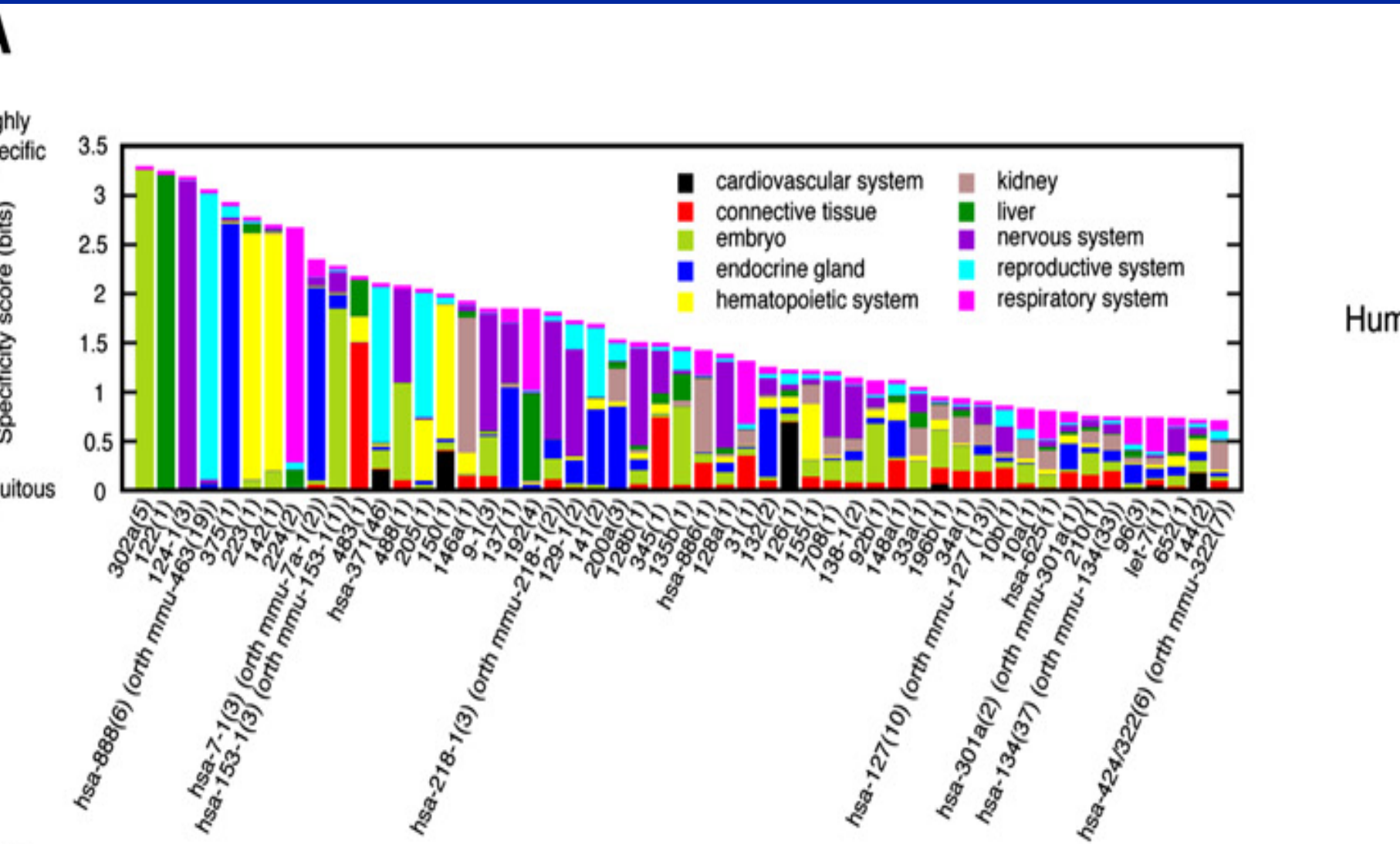
M.Galeazzi

Università idi Siena

microRNAs

- are 21- 25 nucloetuide long non coding RNA molecules that regulate gene expression at post transcriptional level by inhibiting mRNA protein transcription
- over 700 miRNAs have been identified and sequenced in humans,
- About 3% of human genes encode for miRNAs,
- up to 30%-50% of human protein coding genes may be regulated by miRNAs.

Where are miRNA expressed? “microRNomics”



miRNA function

- Control cell proliferation and differentiation
- Control apoptosis
- Control fat metabolism
- Control neuronal patterning
- Control hematopoietic lineage differentiation

microRNAs DIS-FUNCTIONS

disregulation of miRNA function may lead to

human diseases such as:

cancer, cardiovascular disease,

liver disease, metabolic disorders,

responce to viral infections

immune dysfunction

mRNAs in autoimmune disorders

- M. Galeazzi et al: Aberrant over-expression of myeloid lineage specific miR-223 in T-lymphocytes from Rheumatoid Arthritis patients (Arthritis Rheum-ACR 2008)
- Stanczyk J :Altered expression of MicroRNA 155 and 146 in synovial fibroblasts and synovial tissue in rheumatoid arthritis (Arthritis Rheum 2008)
- Y Dai et al: Microarray analysis of microRNA expression in peripheral blood cells of systemic lupus erythematosus patients (Lupus 2007)

THE FUTURE

- **The use of anti-miRNA, or mimic-miRNA oligonucleotides, have been tested in different cancer cell lines, in mice and in non-human primates.**
- **miRNA-based gene therapies, targeting dysregulated miRNAs, have the potential for becoming therapeutic tools of choice for the treatment of**

  *** metabolic disorders,**

  *** cancers,**

  *** immune-related diseases.**

THE FUTURE

It will be very interesting to see if these miRNA-based gene therapies will be used to treat patients with rheumatic disease, such as RA, in the near future.

Unresolved Issues

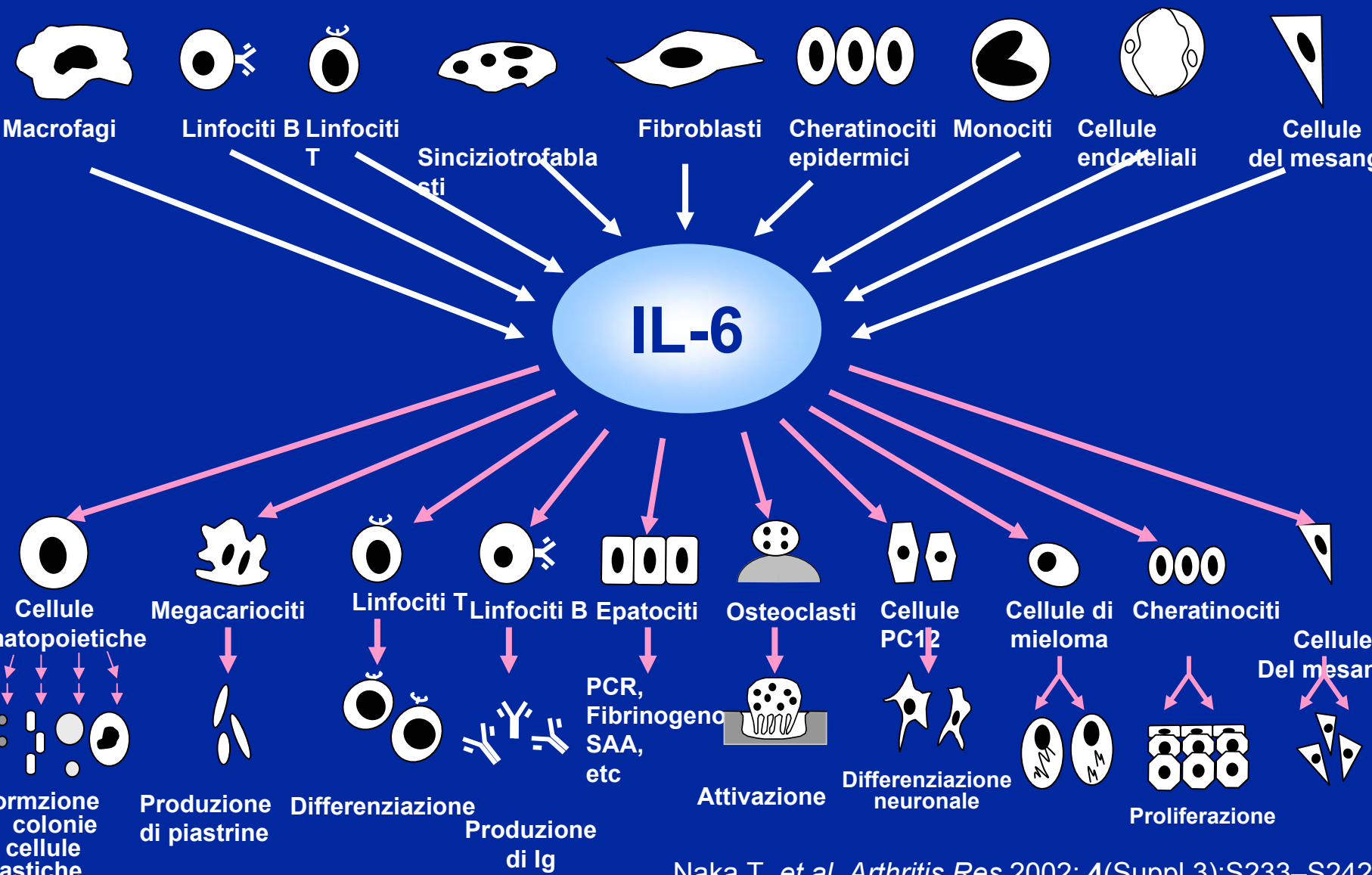
- Which TNF or biologic to choose first
- The heterogeneity of biologic drivers in an individual patient
- Genetic background in determining efficacy in an individual patient
- Differential effect of biologics on co-morbidities, i.e. cardiovascular disease

Conclusion

Can an algorithm for biologic use be generated at this time?

I Don't Think So!

IL-6: Fonti e bersagli multipli

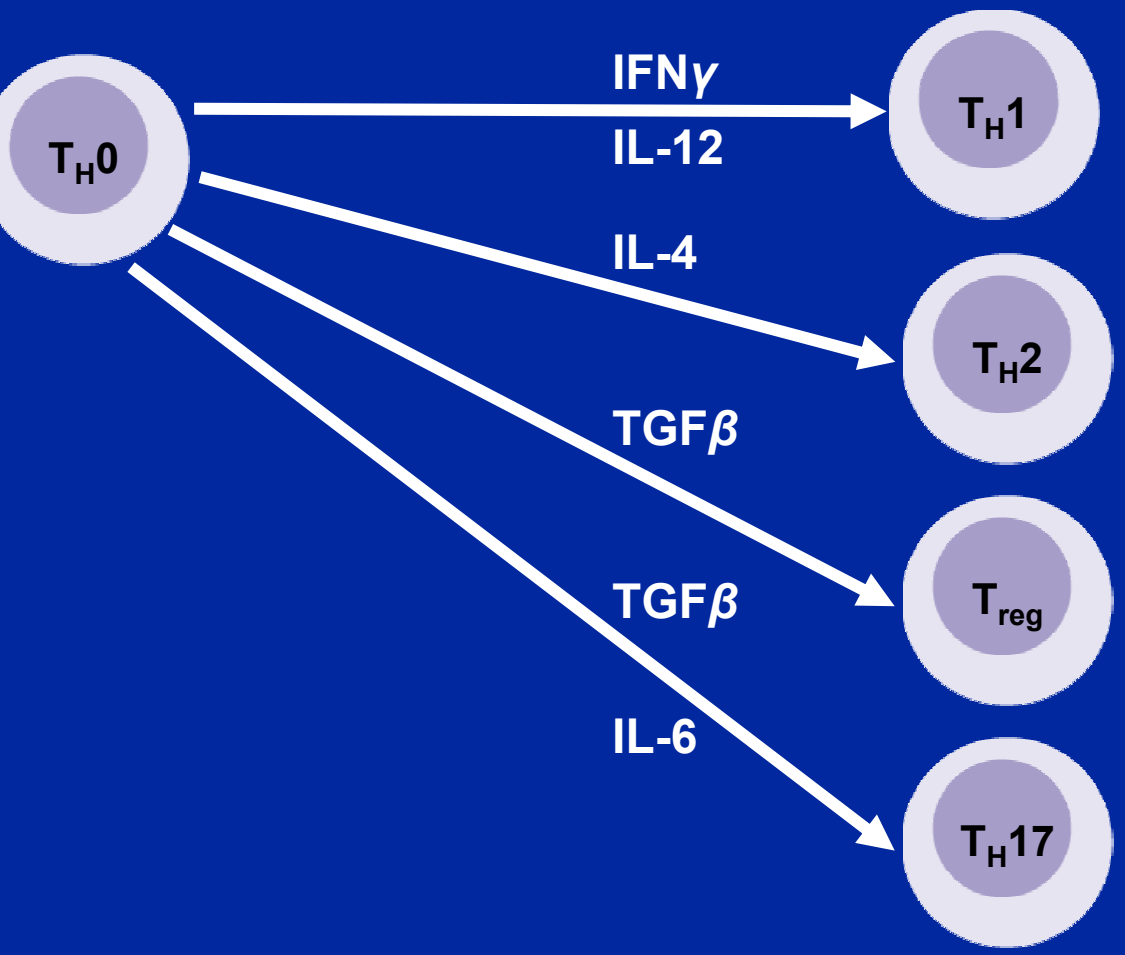


Naka T. *et al. Arthritis Res* 2002; *4*(Suppl 3):S233–S242

IL-6: Attività biologica

Adattato da Yoshizaki K. *et al. Springer Semin Immunopathol* 1998; **20**:247–259

Effetti di tipo immunitario: Il ruolo dell'IL-6 nella differenziazione dei Linfociti T *helper*



Malattia autoimmune

1. Mangan PR, *et al. Nature* 2006; **441**:231–235
2. Bettelli E, *et al. Nature* 2006; **441**:235–238