Terapia medica: quando e come

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Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- Roche LTD, consulente
- River Vision Inc., consulente

Guidelines

European Thyroid Journal

Eur Thyroid J 2016;5:9–26
DOI: 10.1159/000443828

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The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy

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on behalf of the European Group on Graves' Orbitopathy (EUGOGO)

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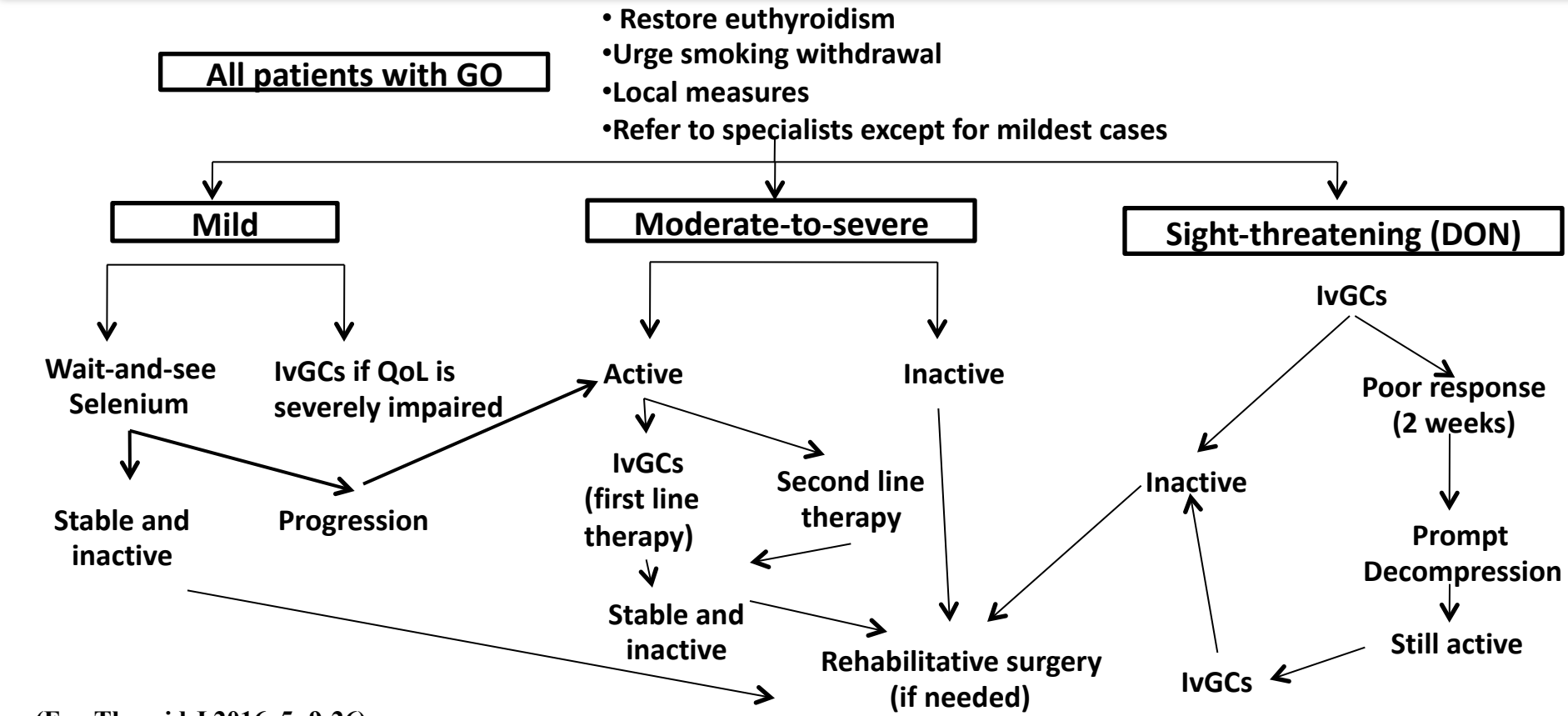
Management of Graves' orbitopathy



(Eur Thyroid J 2016, 5; 9-26)

Steroid therapy in Graves' orbitopathy (GO)

✓Glucocorticoids (GC) represent the first-line treatment of active moderate-severe GO.

✓The i.v. route administration (IVGC) is more effective and better tolerated than the oral route (Marcocci et al, 2001; Kahaly et al, 2005, Stiebel-Kadish et al 2009)

✓GC have an anti-inflammatory effect but also an immunosuppressive effect (Vannucchi et al, 2012)

✓A cumulative dose of 8 g is considered safe, provided monitoring liver function tests, hepatitis virus markers, serum glycemia and blood pressure

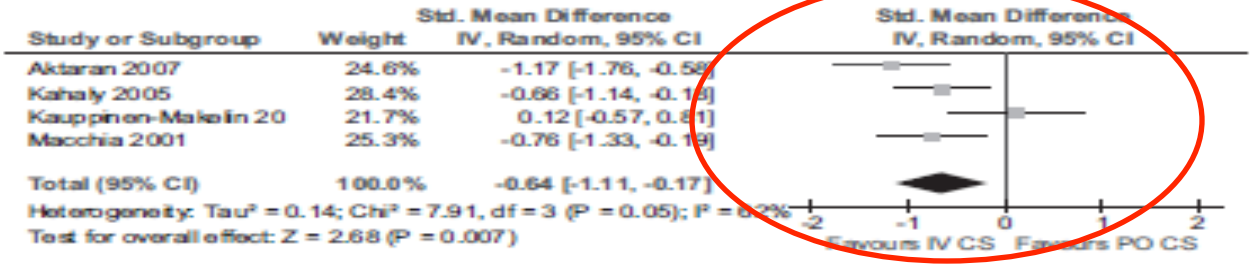
✓Until 2012 the optimal treatment regimen was undefined (Bahn R, 2012)

Therapy with steroids

Treatment Modalities for Graves' Ophthalmopathy: Systematic Review and Metaanalysis

Hadas Stiebel-Kalish,* Eyal Robenshtok,* Murat Hasanreisoglu, David Ezrachi, Ilan Shimon, and Leonard Leibovici

Neuroophthalmology Unit (H.S.-K.), Departments of Medicine E (E.R., L.L.) and Ophthalmology (H.S.-K., M.H., D.E.), and Institute of Endocrinology and Metabolism (E.R., I.S.), Rabin Medical Center, Petah Tikva 49100, Israel; and Sackler School of Medicine (H.S.-K., E.R., D.E., I.S., L.L.), Tel Aviv University, Tel Aviv 69978, Israel

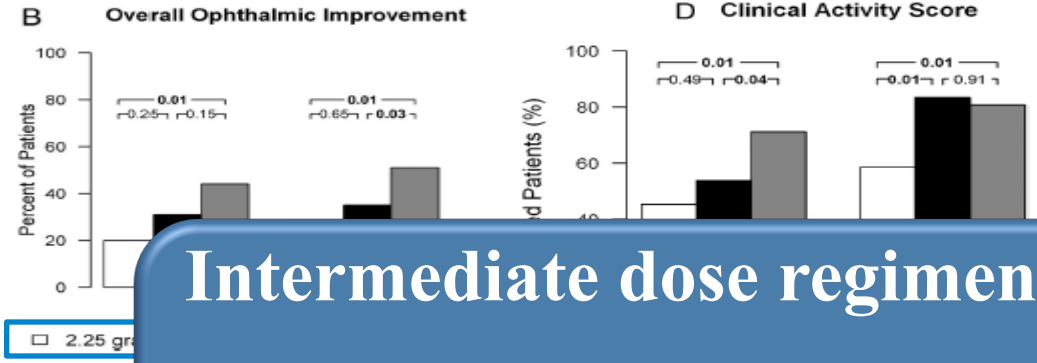


IV - intravenous, PO - per os, CS - corticosteroids, CAS - clinical activity score.

FIG. 2. Intravenous corticosteroids *vs.* oral corticosteroids. The outcome was CAS at the end of follow-up. PO, Per os; CS, corticosteroids.

J Clin Endocrinol Metab, August 2009, 94(8):2708–2716

Steroid treatment:recommendations



Efficacy and Safety of Three Different Cumulative Doses of Intravenous Methylprednisolone for Moderate to Severe and Active Graves' Orbitopathy

L. Bartalena, G. E. Krassas, W. Wiersinga, C. Marcocci, M. Salvi, C. Daumerie, C. Bournaud, M. Stahl, L. Sassi, G. Veronesi, C. Azzolini, K. G. Boboridis, M. P. Mourits, M. R. Soeters, L. Baldeschi, M. Nardi, N. Currò, A. Boschi, M. Bernard, and G. von Arx,* for the European Group on Graves' Orbitopathy

lena et al,
O, 2012

Intermediate dose regimen in most cases

High dose regimen reserved to most severe GO patients

EFFECTS

Severe infection requiring hospitalization[a]	HD	Between 6 and 12 wk
Psychosis	HD	Between 1 and 6 wk
Major depression	HD	Between 6 and 12 wk
Major depression	HD	Between 6 and 12 wk

DM, Diabetes mellitus.
[a] Same patient.

Low dose→ minor and later effect on eye inflammation; no effect on eye motility, but fewer side effects

Side effects of steroids

Intravenous Glucocorticoids for Graves' Orbitopathy: Efficacy and Morbidity

S. Zang, K. A. Ponto, and G. J. Kahaly

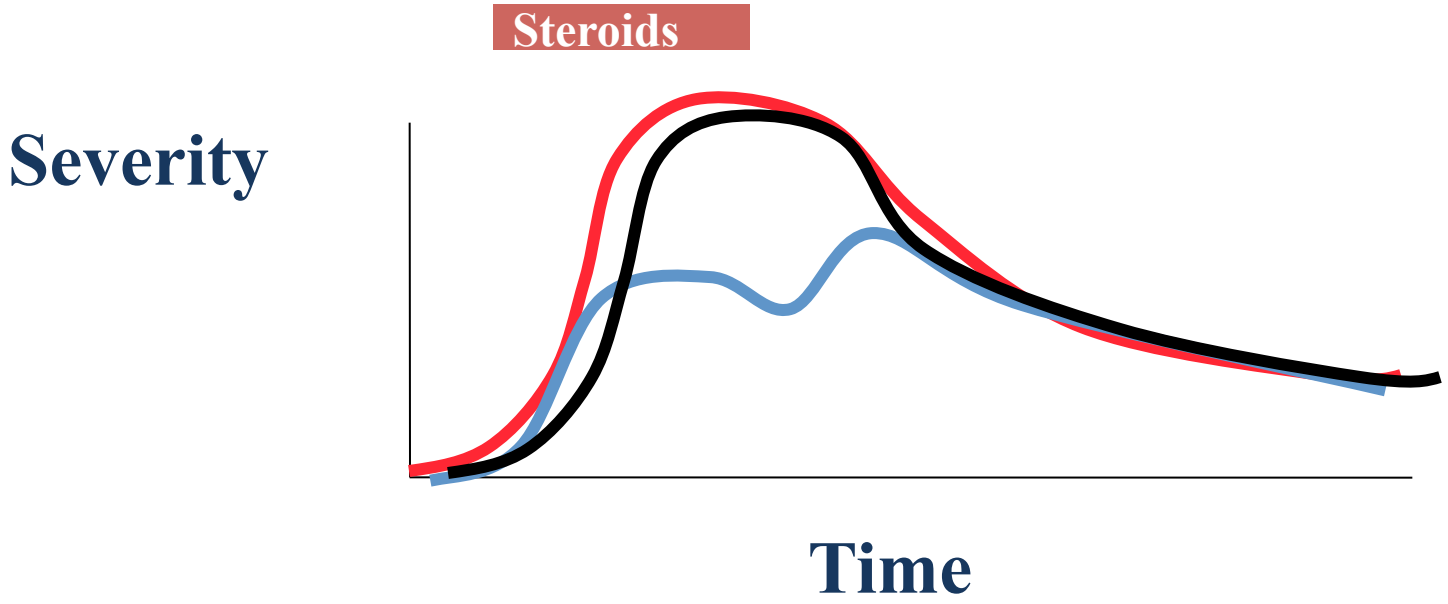
Departments of Medicine I (S.Z., G.J.K.) and Ophthalmology (K.A.P.), Gutenberg University Medical Center, Mainz 55131, Germany

First author, year (Ref.)	n	Dosage and treatment protocol	Morbidity		Mortality
			Cardiovascular	Hepatic	
Randomized trials (62, 63, 68)[a]	101	See Table 2	43 (43%) with minor, moderate or major adverse events		
Nonrandomized trials (32, 56, 59)[a]	63	See Table 1	7 (11%) with minor, moderate or major adverse events		
Grand total	1045		68 (6.5%)[b]		6 (0.57%)

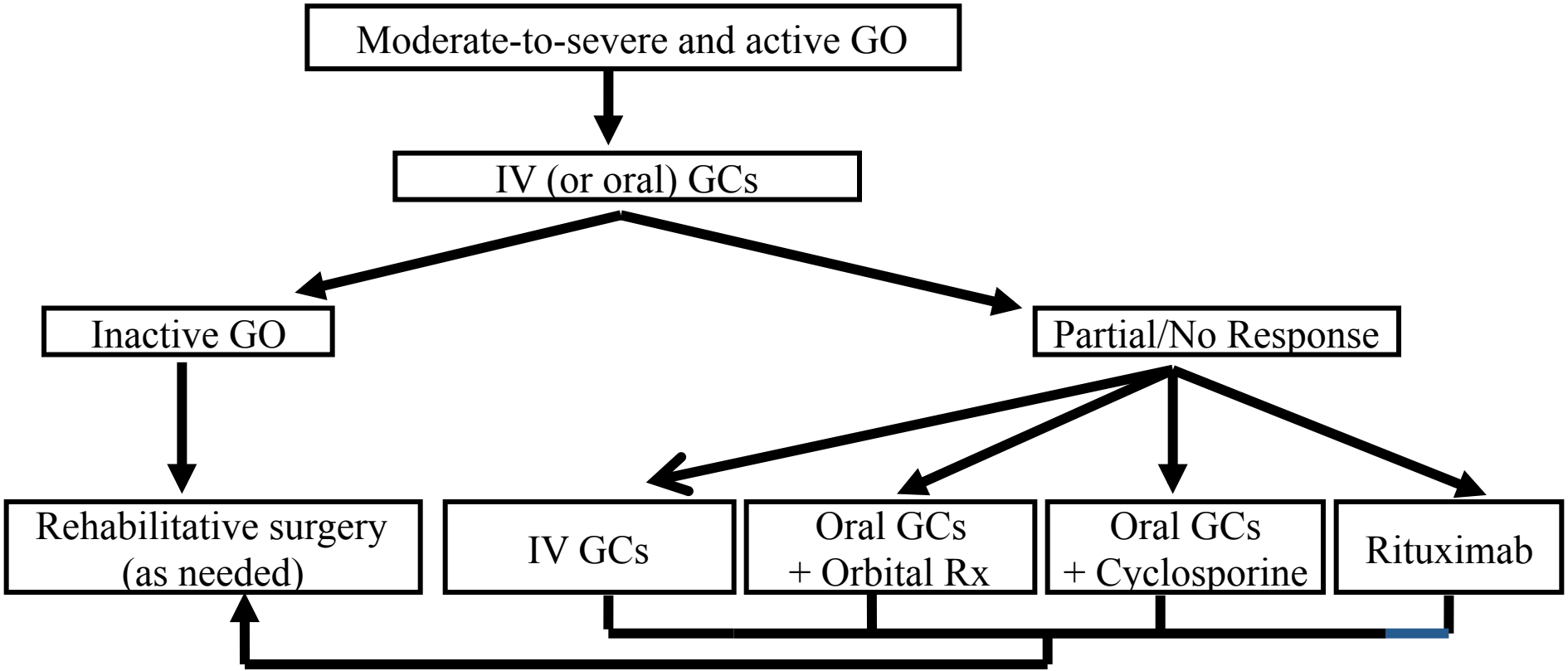
J Clin Endocrinol Metab, February 2011, 96(2):320–332

Therapy with steroids

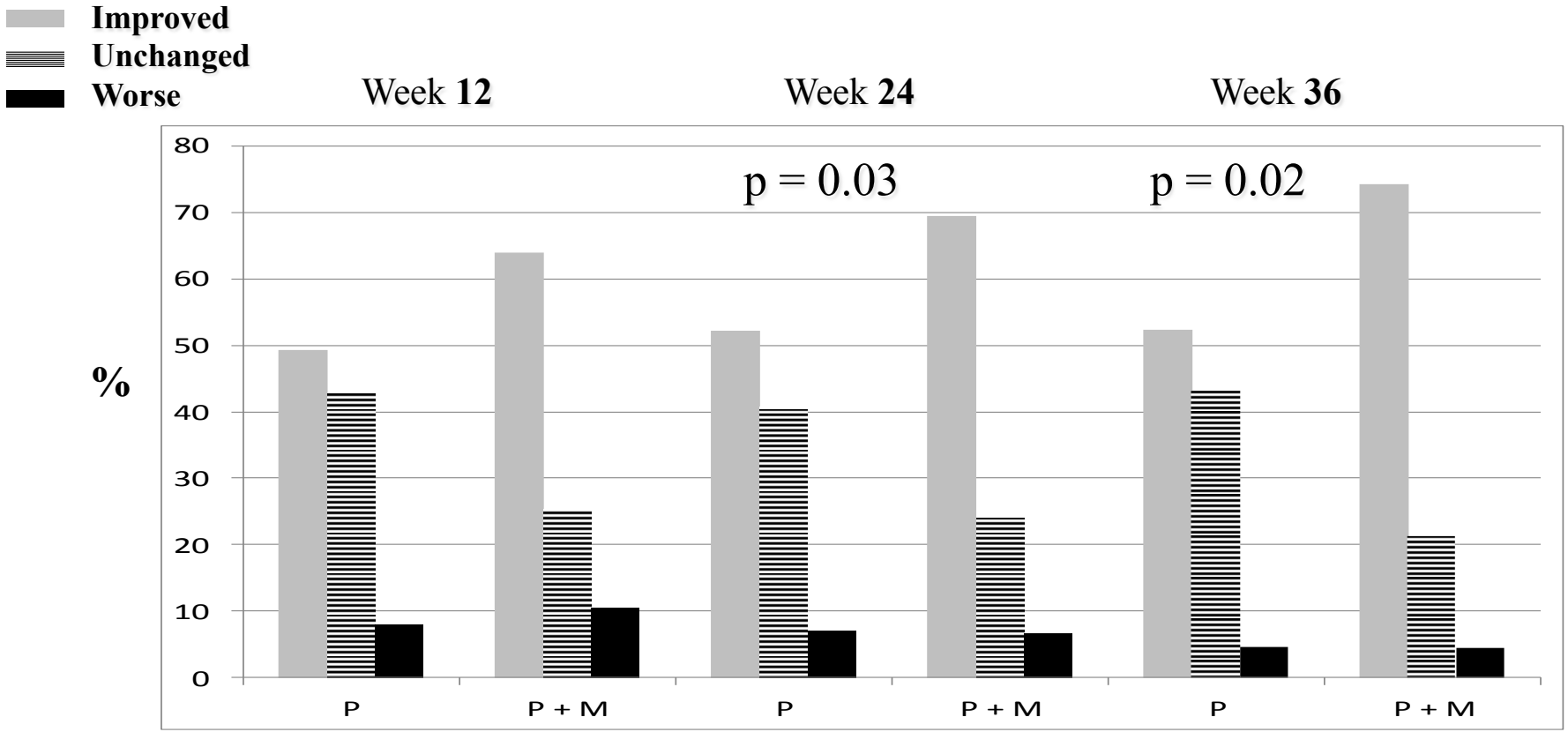
- relapses common
- ~20% do not respond



Management of Graves' orbitopathy

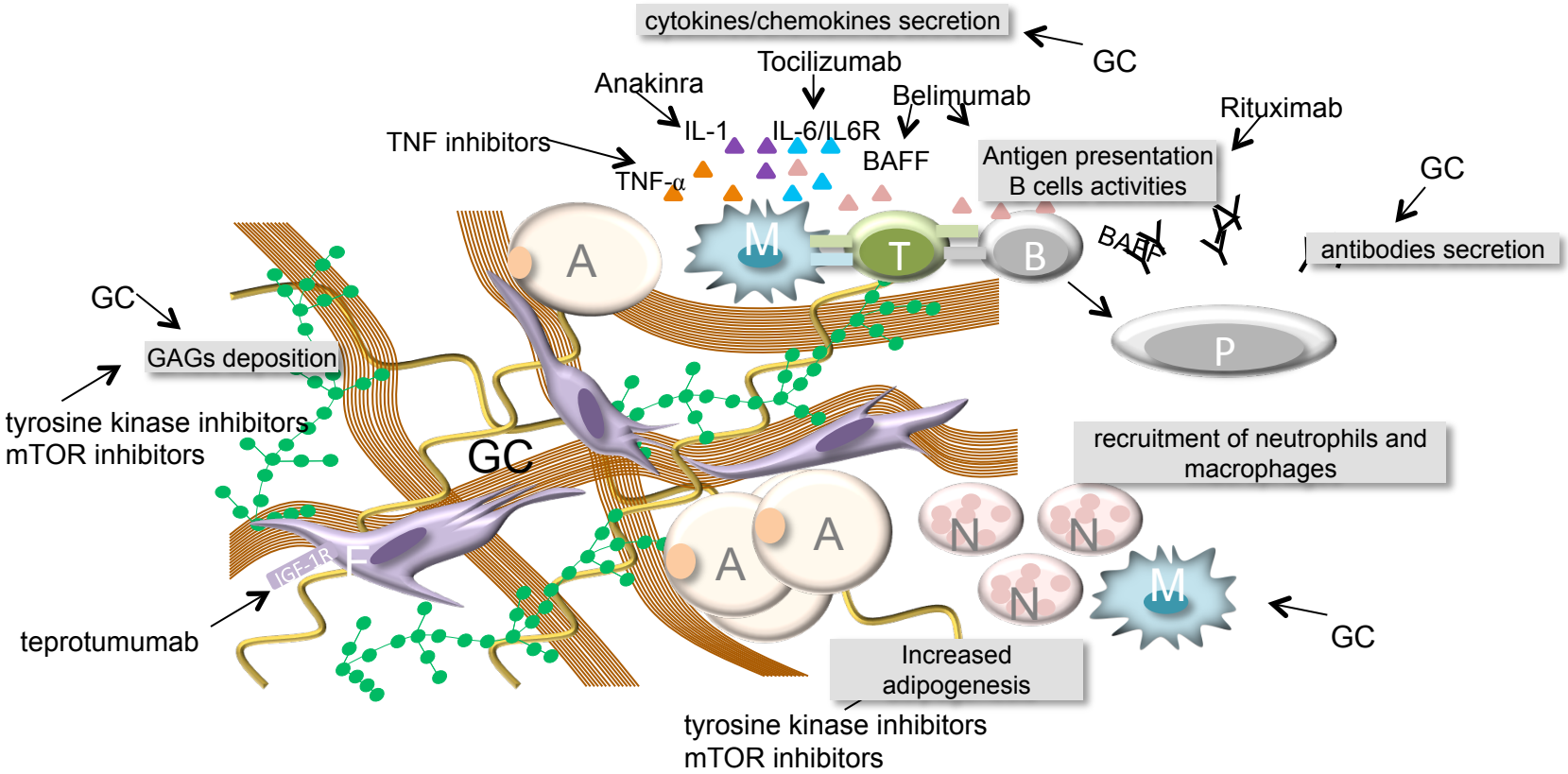


i.v.steroids + mycophenolate: RCT in GO



Kahaly and EUGOGO, Lancet E & M, in press

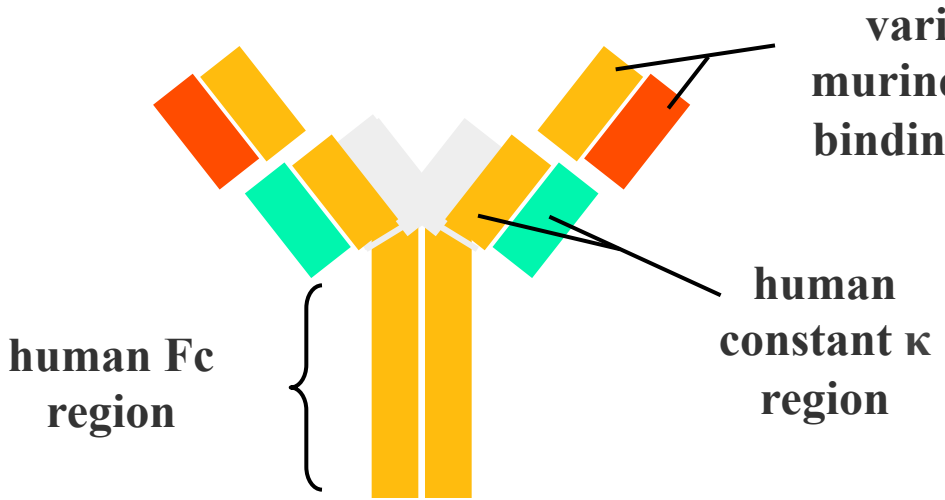
Targets for immunotherapy

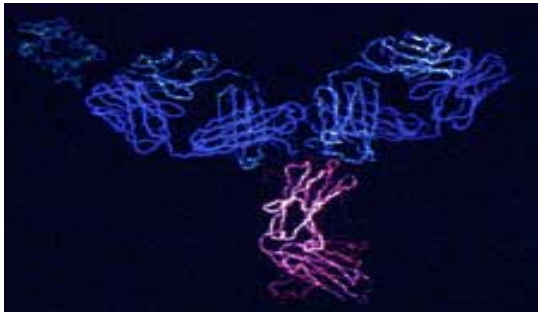


Salvi and Campi, 2016

Rituximab

Chimeric murine/human monoclonal antibody with a human IgG1 constant region and a murine variable region binding to CD 20.





RCT of RTX vs i.v. steroids in GO

EUDRACT NUMBER 2007-003910-33

32 eligible patients

Randomization (blocks of 4)

i.v. methylprednisolone (IVMP)
N=16

Rituximab (RTX)
N=16

1 patient refused therapy

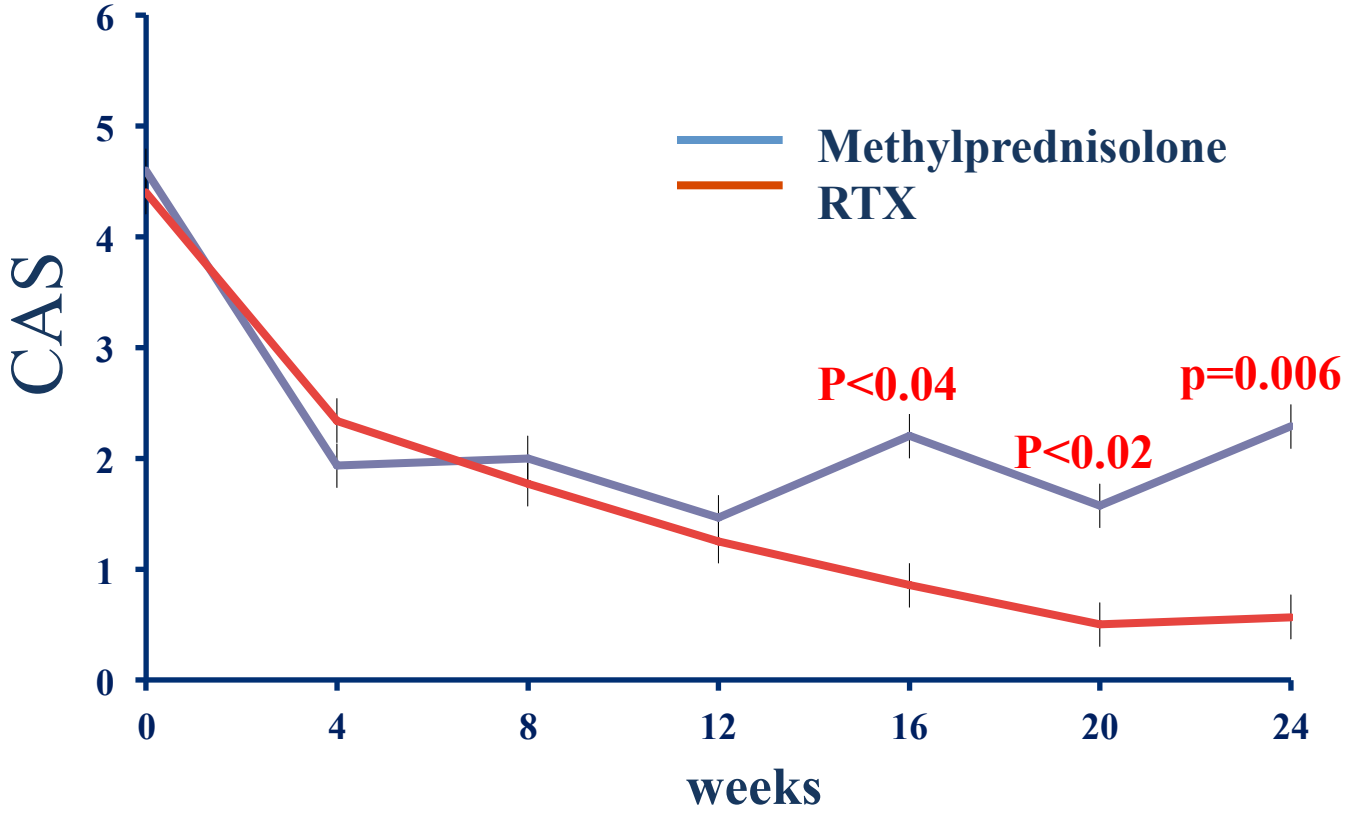
N=16

N=15

Daily dose: 830 mg/day weekly x 6 weeks, followed by 415 mg/day weekly x 6 weeks
Cumulative dose: 7.5 g

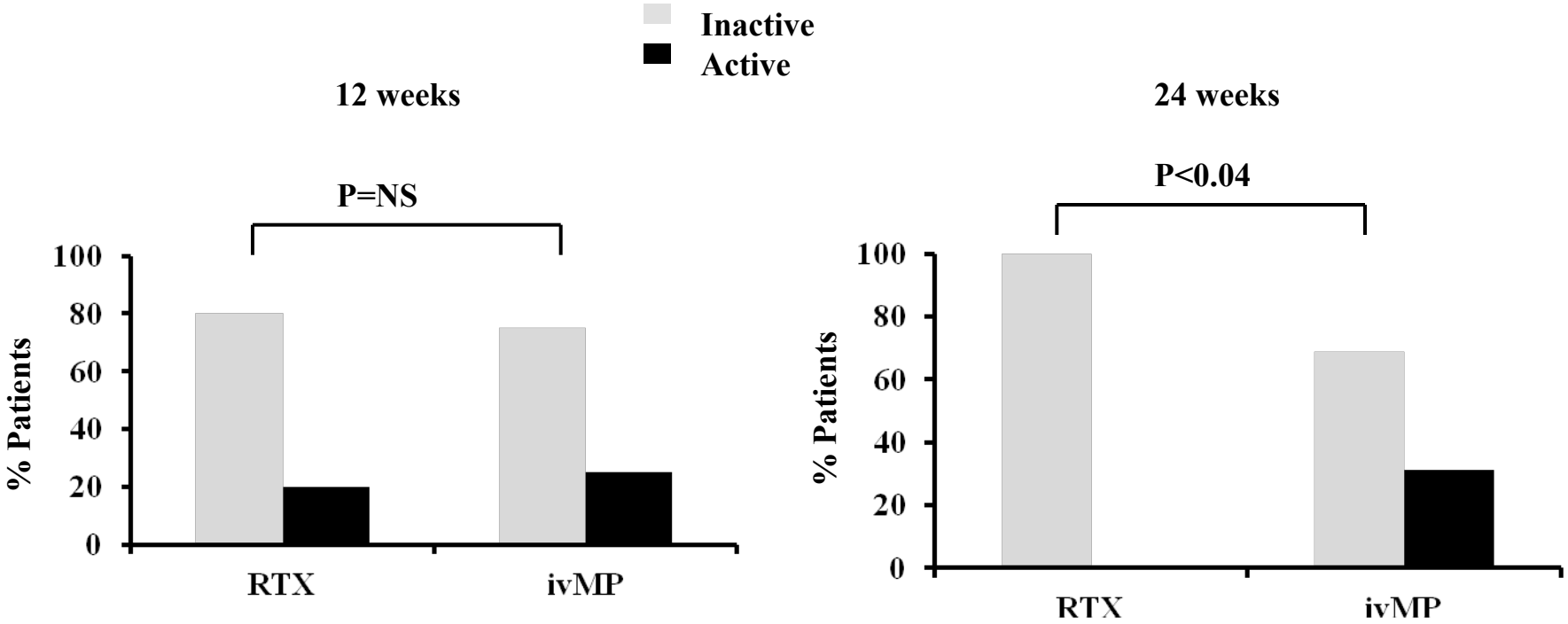
Before amendment N=5	Dose: 1000 mg /wk x 2 wks Cumulative dose: 2000 mg
After amendment N=10	Dose: 500 mg,single Cumulative dose: 500 mg

Decrease of the CAS (primary endpoint)



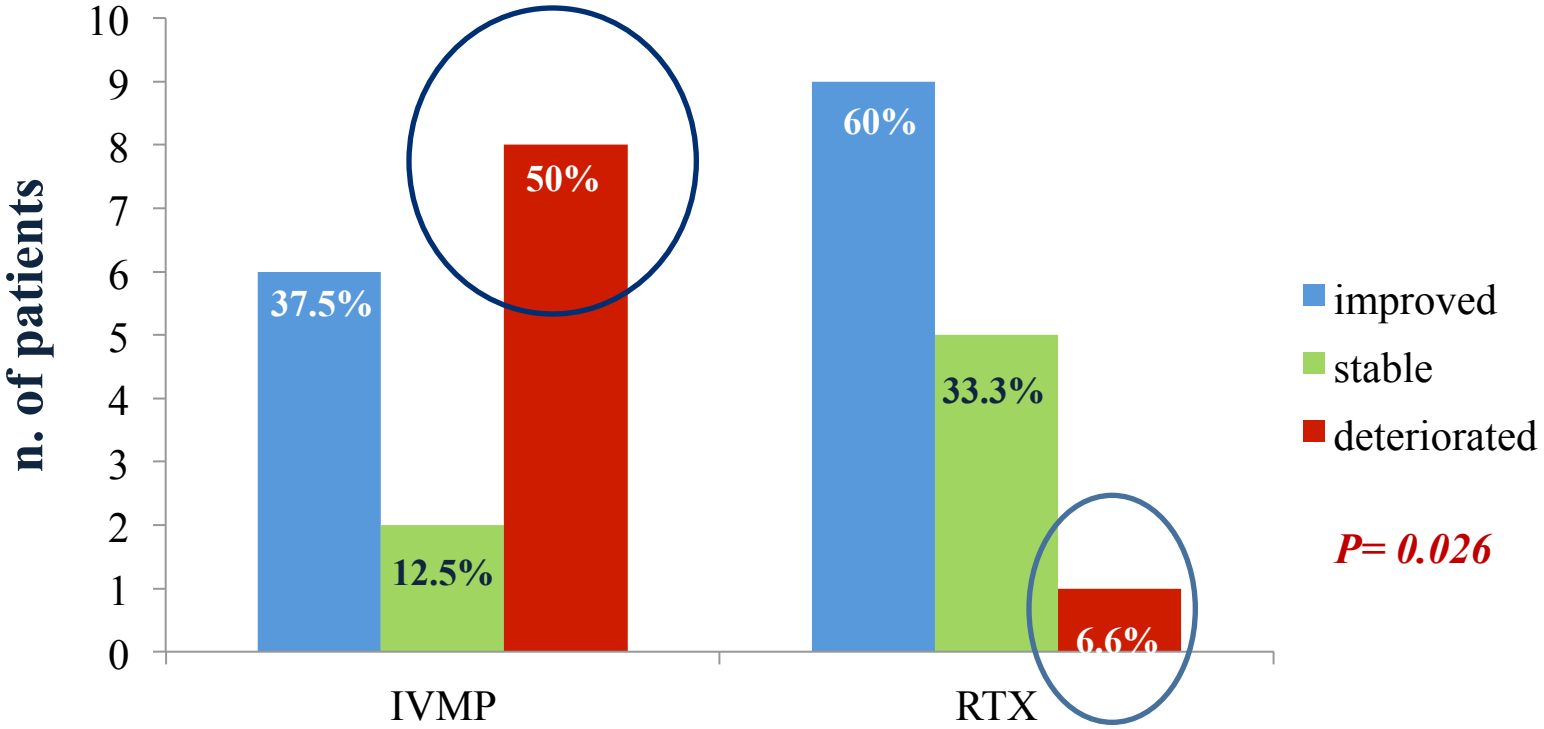
Salvi et al., JCEM 2015

Disease inactivation (primary end point)



Salvi et al., JCEM 2015

Overall disease improvement 24 wk (EUGOGO composite score)



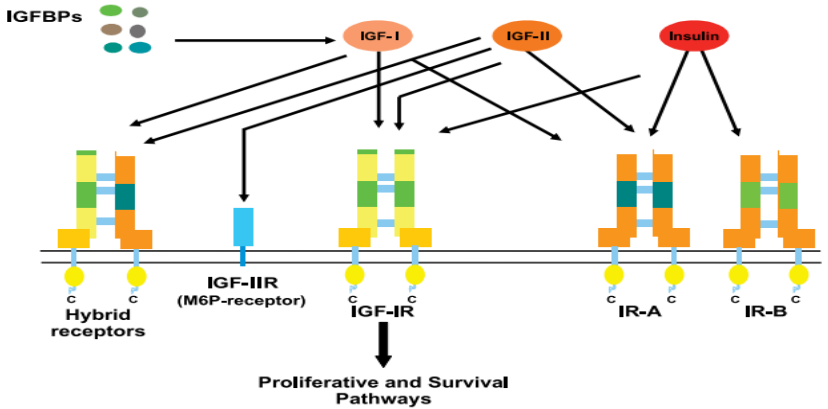
Stan and Salvi, EJE 2017

Results – RCT Rituximab

Stan & Salvi, Eur J Endocrinol 2017

	Italian study (N=15)	US study (N=13)	Comments
Age (mean, years)	51.9	57.6	Possibly different
Gender (% women)	93	69	Possibly different
Smokers (%)	66.7	15.4	Likely different
GO duration (months)	Mean=4.5±2.9	Mean=30±47.6 Median=12(8.2-27.2)	Likely different
CAS baseline CAS ≥ 4/CAS ≥ 6	Mean=4.4/10±0.7 14/15 and 2/15	Mean=4.9/7±1.0 13/13 and 3/13	Likely same *CAS 7 (US, Italy) and 10 (Italy)*
GO severity	Moderate-to-severe	Moderate-to-severe + progressive	Likely same
Previous steroid therapy	3/15 (20%) *(≥12 weeks prior)*	4/13 (31%) *(≥8 weeks prior)*	Likely same
TRAb (IU/L)	Mean=10.7±9.1	Mean=28.1±23.4 Median=20 (9-60)	Likely different
TRAB > 20	4/15	7/13	Likely same

Targeting the IGF-1 receptor: ***Teprotumumab***



IMC-A12
RV 001
AMG 479
CP-751,871
h7C10

- ✓ **Monoclonal antibody antagonizing IGF-1R**
- ✓ **Inhibiting IGF-1 and IGF2 binding to the receptor**

Previously employed in sarcomas and other solid tumors

Rowinsky, 2007

Teprotumumab Phase 2 RCT in Active GO

Sponsor: River Vision Development Corporation

ClinicalTrials.gov Identifier: NCT01868997

- ✓ Double blind versus placebo phase 2 study
- ✓ Randomization is 1:1 (RV001 and placebo) stratified by smoking status.

Three phases

96 patients in US and UE:

1. A screening phase
2. Treatment (6 months) 10mg/kg →20mg/kg every 3 weeks
3. A follow-up phase of 12 months with no treatment.

Teprotumumab Phase 2 RCT in Active GO

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

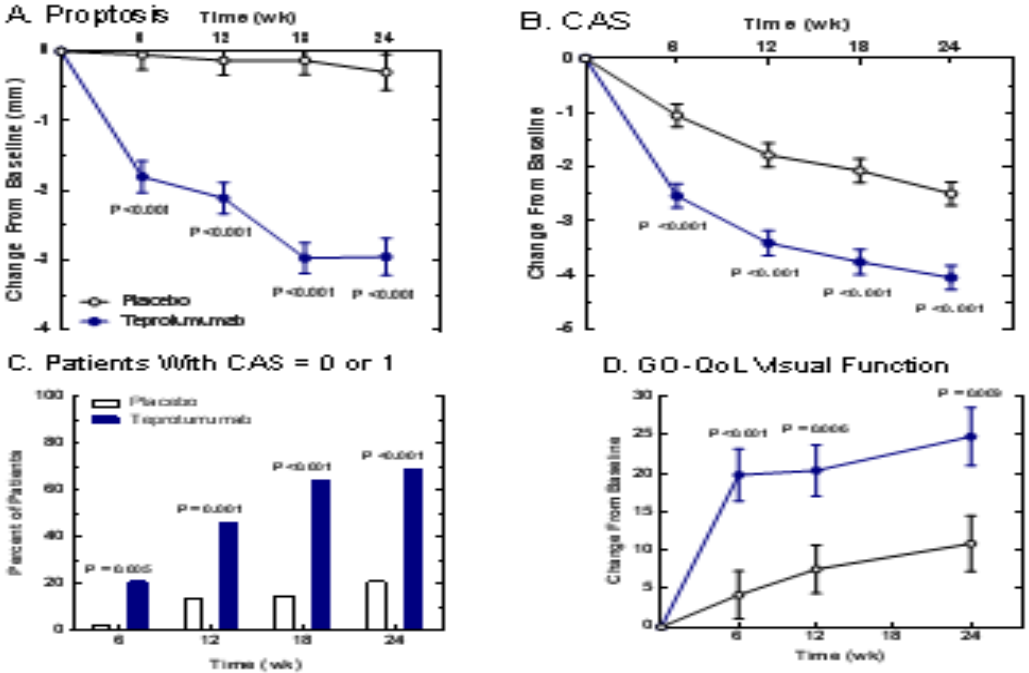
Teprotumumab for Thyroid-Associated Ophthalmopathy

Terry J. Smith, M.D., George J. Kahaly, M.D., Ph.D., Daniel G. Ezra, M.D., James C. Fleming, M.D., Roger A. Dailey, M.D., Rosa A. Tang, M.D., Gerald J. Harris, M.D., Alessandro Antonelli, M.D., Mario Salvi, M.D., Robert A. Goldberg, M.D., James W. Gigantelli, M.D., Steven M. Couch, M.D., Erin M. Shriver, M.D., Brent R. Hayek, M.D., Eric M. Hink, M.D., Richard M. Woodward, Ph.D., Kathleen Gabriel, R.N., Guido Magni, M.D., Ph.D., and Raymond S. Douglas, M.D., Ph.D.

Smith at al, NEJM, May 4, 2017

Teprotumumab Phase 2 RCT in Active GO

Primary end point: 29/42 (69%) Teprotumumab
9/45 (20%) Placebo P<0.001



Smith at al, NEJM, May 4, 2017