X Congresso Nazionale IG-IBD

RICCIONE, 28-30 novembre 2019

IG-IBD the Italian Group for the study of Inflammatory Bowel Disease

Effective early control in UC: challenges in real life

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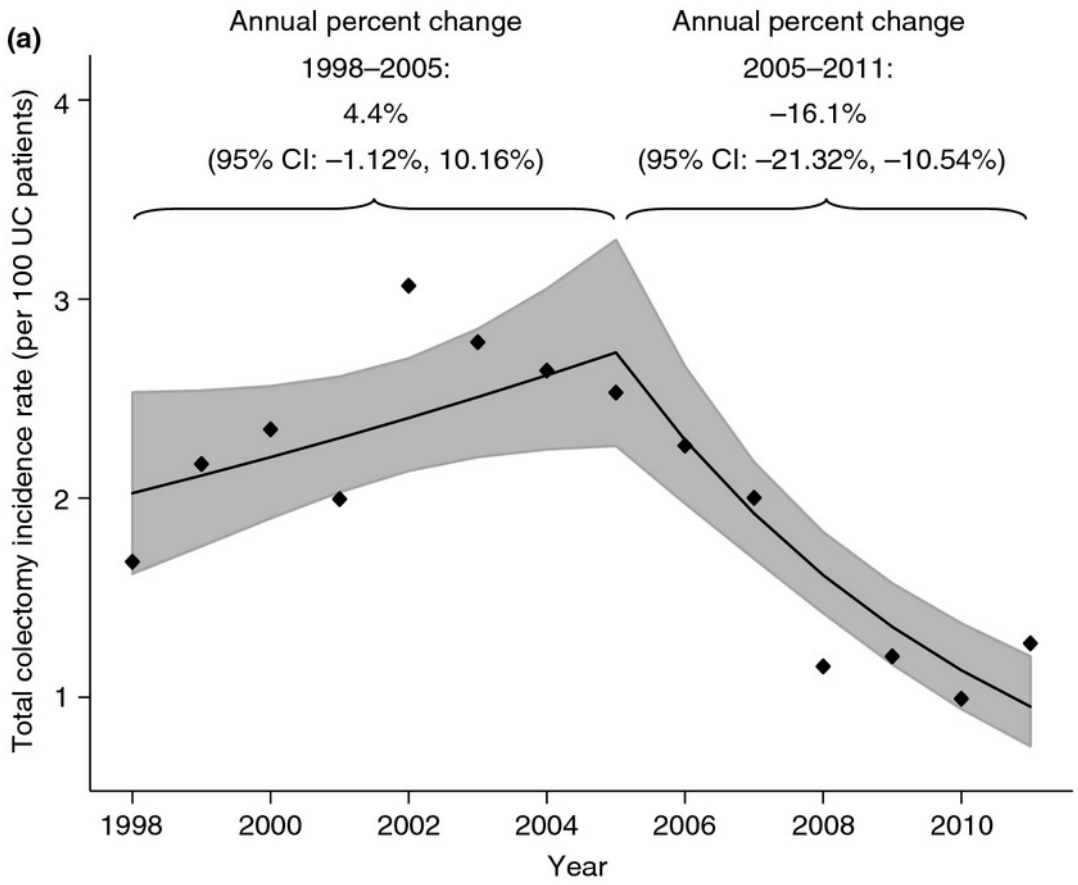
What are the objectives of induction in moderate to severe UC?

- Induce a rapid clinical response
- Achieve steroid-free remission
- Avoid colectomy
- Other:
  - Get mucosal healing
  - Avoid hospitalizations
  - Facilitate the step to maintenance treatment…….
  - that allows to achieve continuous clinical response and long-term benefits in the QoL of our patients

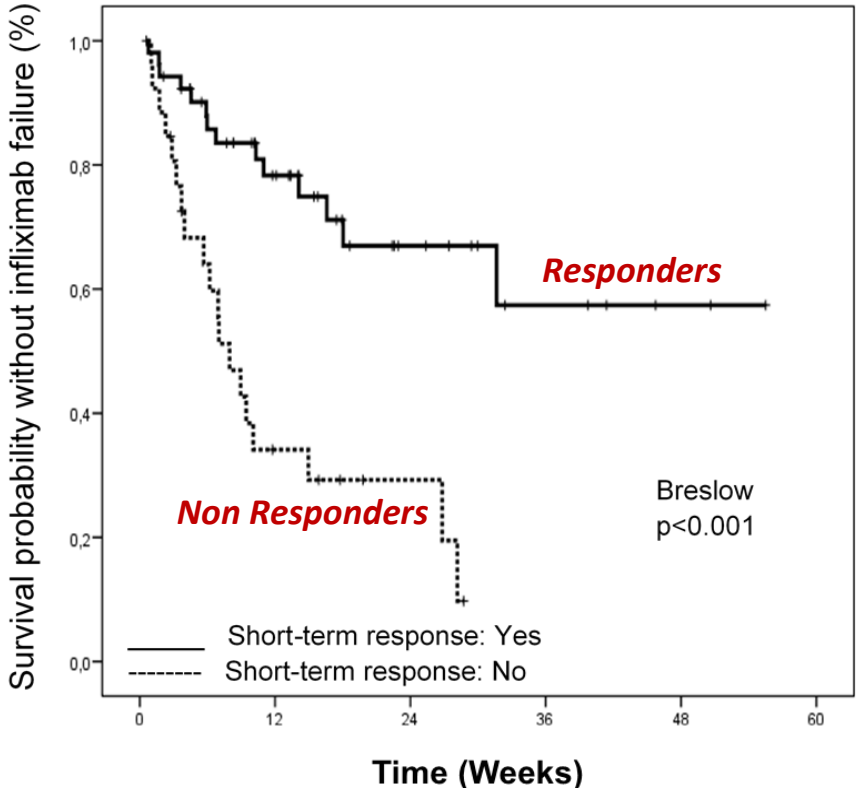
Changes in the colectomy rate with the introduction of anti-TNFs



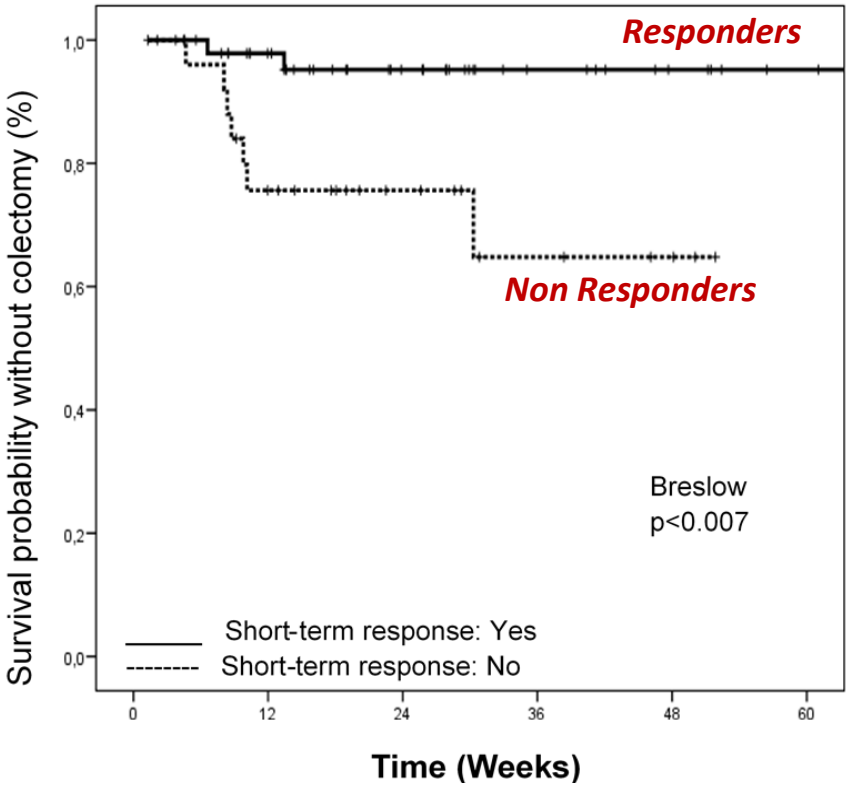
Adapted from Reich KM, et al. Aliment Pharmacol Ther. 2014;40:629-38

What are the predictors of long-term outcomes in UC?

In ‘real life’ short–term response to induction is the main predictor of long-term outcomes in UC patients treated with infliximab



Cumulative probability of avoiding IFX failure



Cumulative probability of avoiding colectomy

Taxonera C, et al. Dig Dis Sci 2015;60:3075-84

What are the predictors of long-term outcomes in UC?

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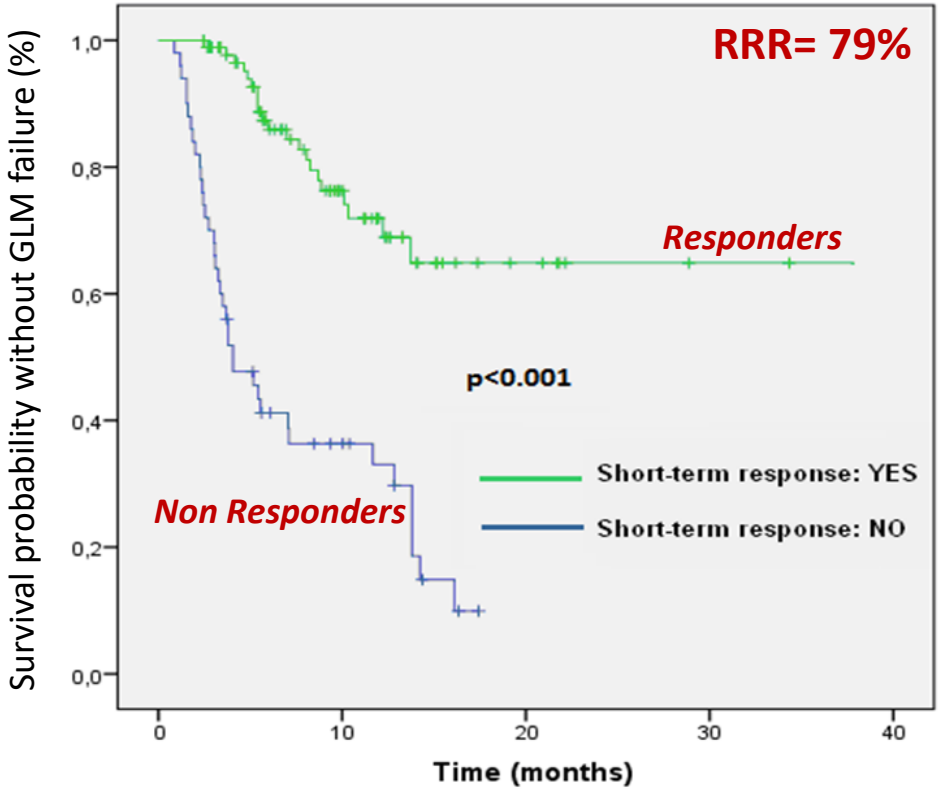
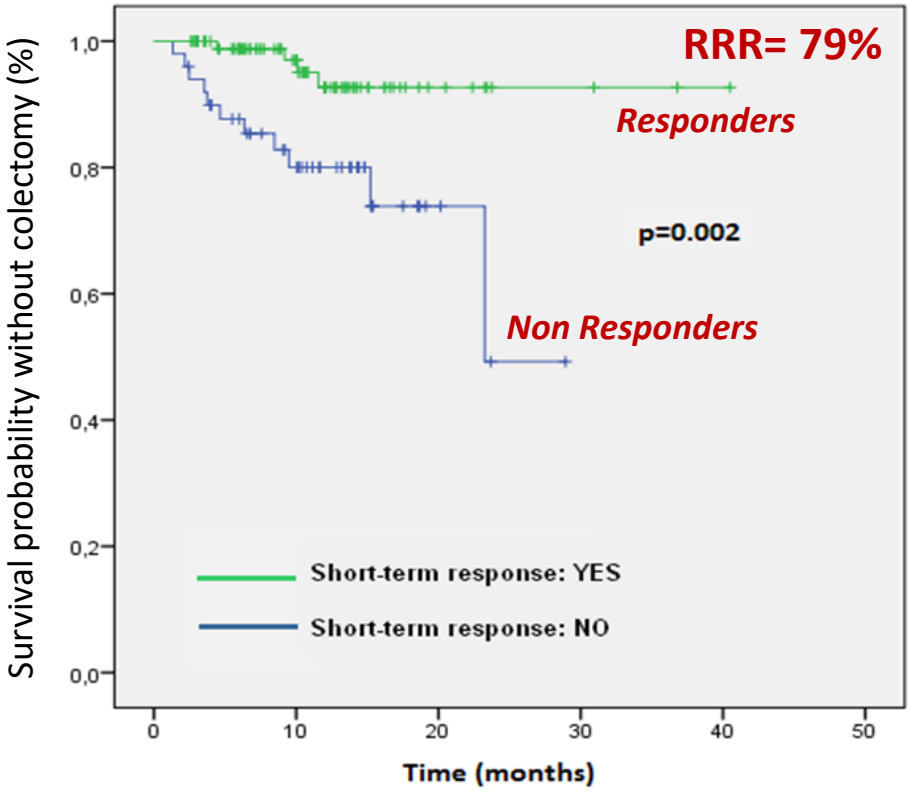


Cumulative probability of avoiding GLM failure

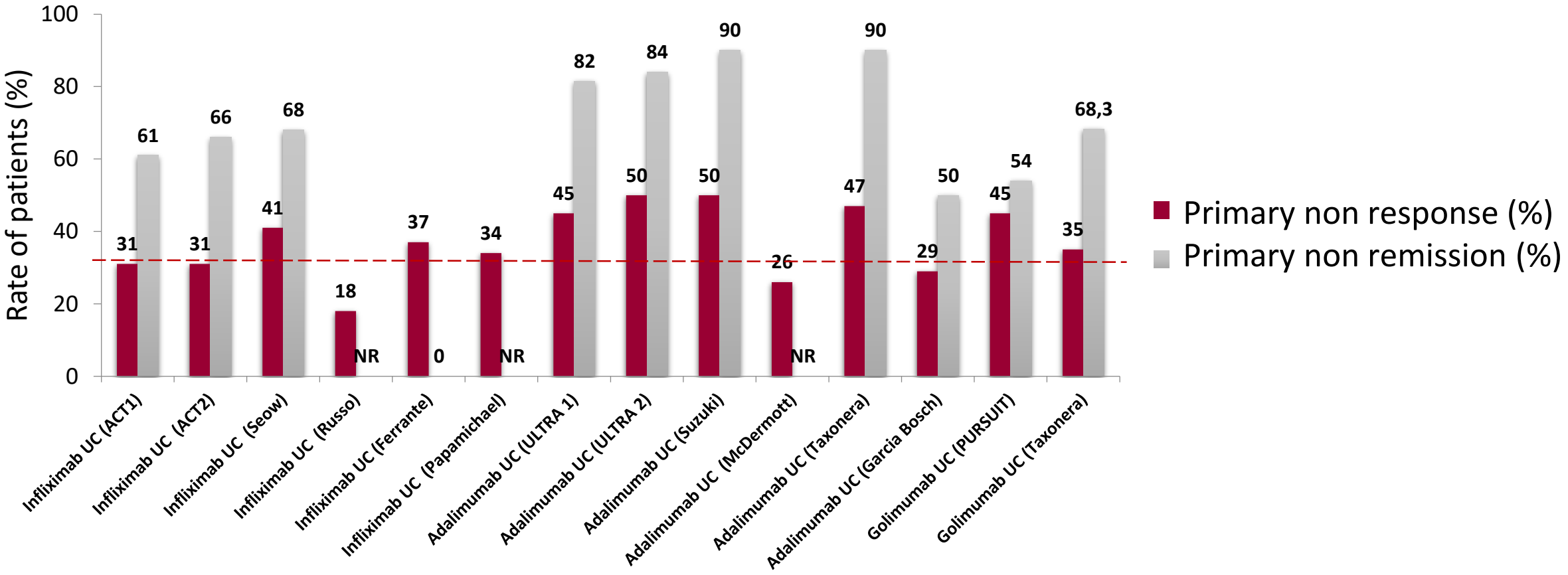


Cumulative probability of avoiding colectomy

Taxonera C, et al. Inflamm Bowel Dis. 2017;23:1394-1402

Primary non response to induction with anti-TNFs in UC

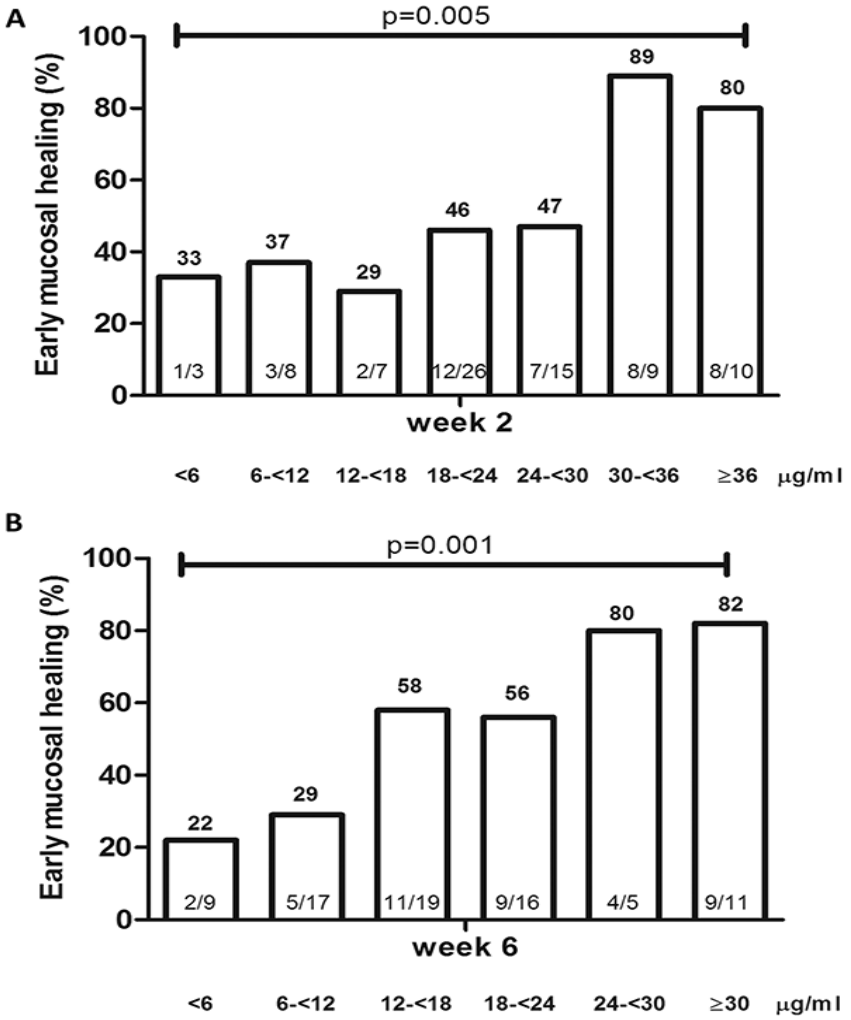
Proportion of UC patients who do not achieve response to induction with anti-TNF: clinical trials and 'real life' studies

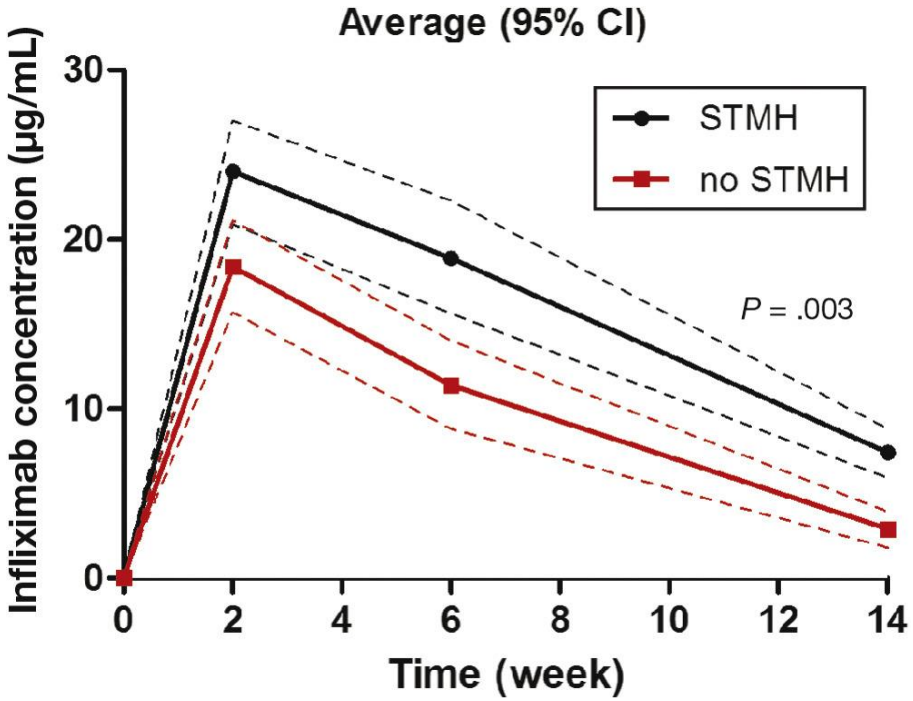


Adapted from Papamichael K, et al. IBD 2015;21:182–197; Taxonera C, et al. IBD 2017;23:1394-1402

Primary non response to induction: anti-TNF trough levels

Short-term mucosal healing (STMH; week 14) in UC is associated with infliximab levels at weeks 2 and 6 and with total infliximab exposure



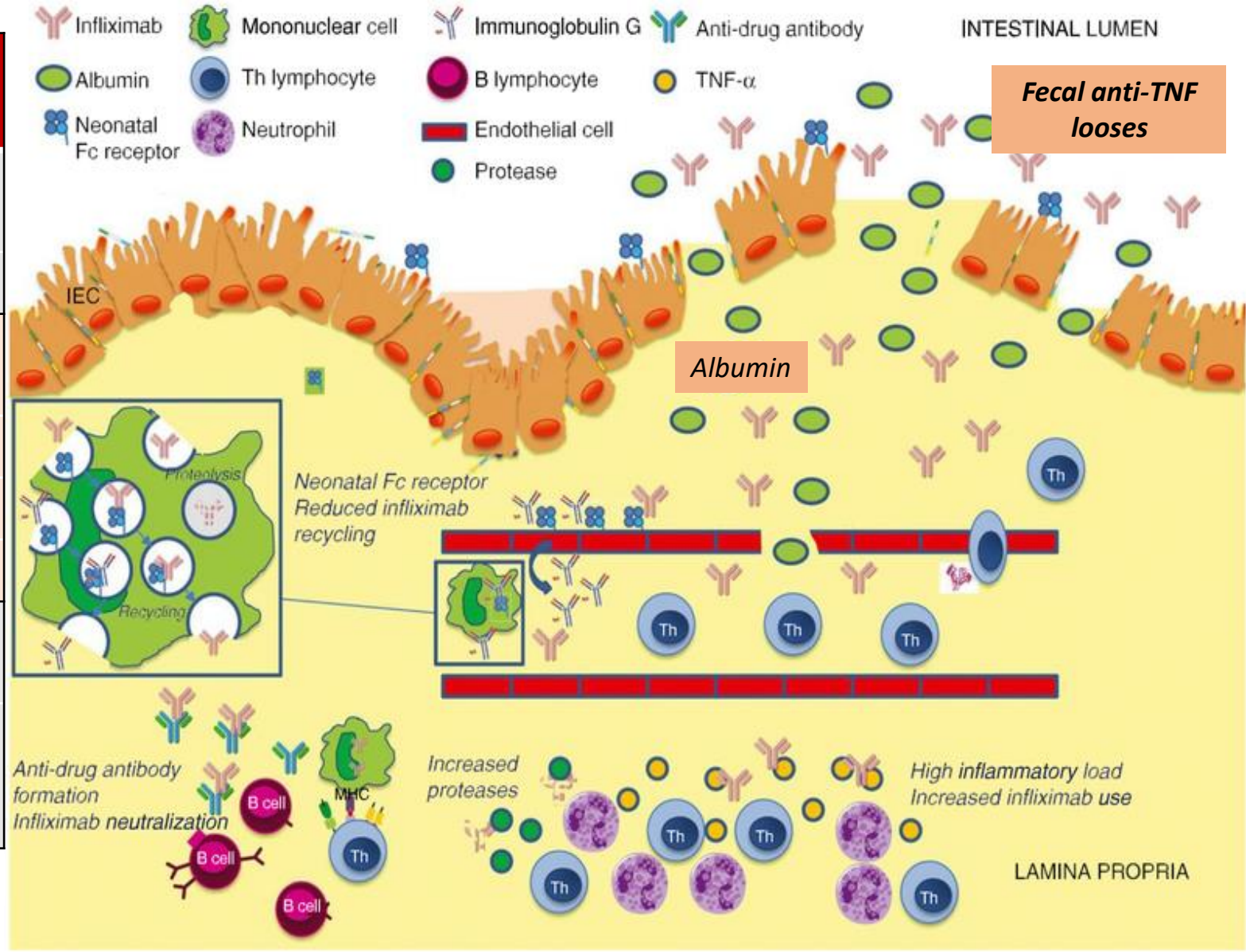


Adapted from Papamichael K, et al. Clinical Gastroenterology and Hepatology 2016;14:543–549

Factors affecting the pharmacokinetics of monoclonal antibodies

Factor	Impact on pharmacokinetics
Body size	High body mass index may increase clearance
Sex	Males have higher clearance
High baseline TNF-α	**May decrease (mAbs) by increasing clearance**
High baseline CRP	**Increases clearance**
Low albumin	**Increases clearance**
mAbs fecal looses	**Increases clearance**
Presence of ADAs	Decreases serum (mAbs) Threefold-increased clearance
Concomitant use of IS	Reduces ADA formation Increases serum (mAbs) Decreases mAbs clearance

Adapted from Ordas et al. Clin Pharmacol Ther 2012;91:635-46



Adapted from Hindryckx P et al. APT. 2017;45:617–630

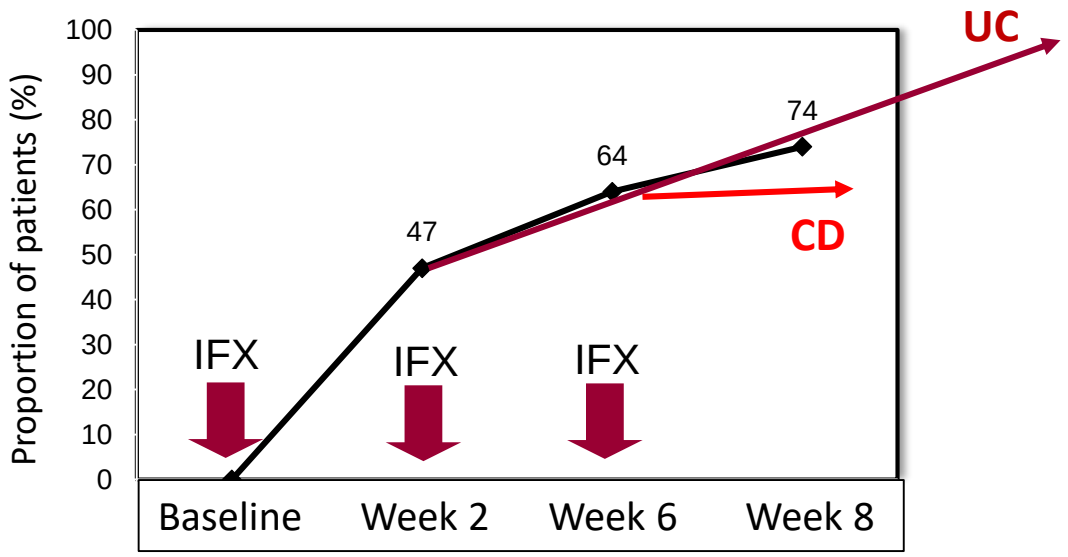
How can we improve the response to induction with mAbs in UC?

- Help mABs induction doses with all:
  - + topical treatment
  - + last corticosteroid cycle
  - + initially maintain IMM
- Prolong the induction treatment period to gather early responders + late responders
- Early dose optimization of anti-TNF
  - Based on clinical response
  - Maybe according to drug levels?

It is crucial to obtain the response to induction with anti-TNF

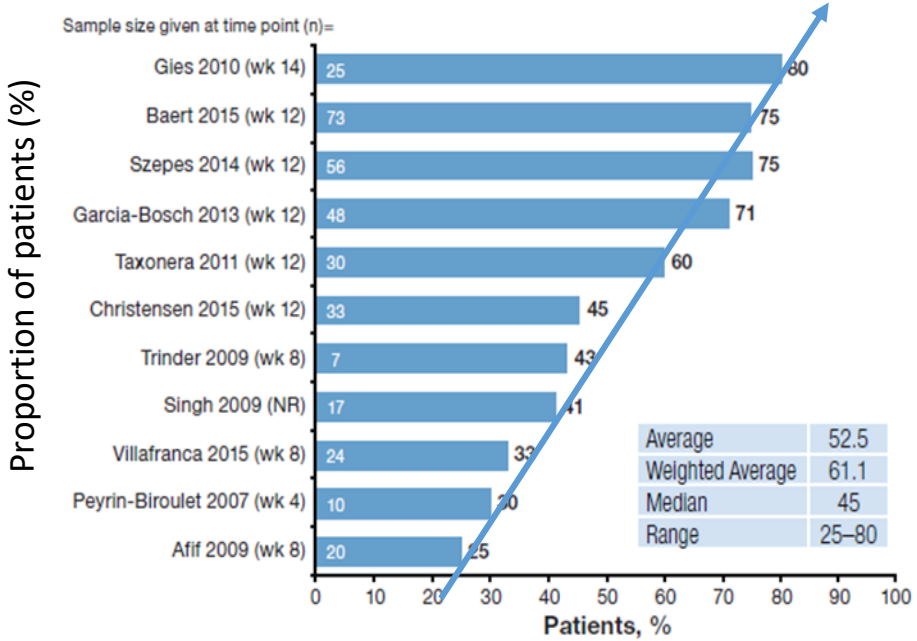
In UC: how long should we wait to get response to induction with anti-TNFs?

Proportion of UC patients having response to induction with infliximab ('post hoc' ACT 1 and ACT 2 trials)



Sandborn WJ, et al. Gastroenterology 2008 134:A492

Proportion of UC patients having response to induction with adalimumab ('real life' studies)



Armuzzi A, et al. JCC 2016;10 (suppl 1):S280-S282

How long should we wait to get response to induction with golimumab?

PURSUIT induction

induction GLM SC/IV

R

PBO n=407

Week 6: ¿Response? n=359

Yes n=129

PBO

No n=230

No n=405

GLM 100 mg/4 sem

GLM n=949

Week 6: ¿Response? n=869

Yes n=464*

R

PBO/q4w n=154

GLM/q4w 50 mg n=151

GLM/q4w 100 mg n=151

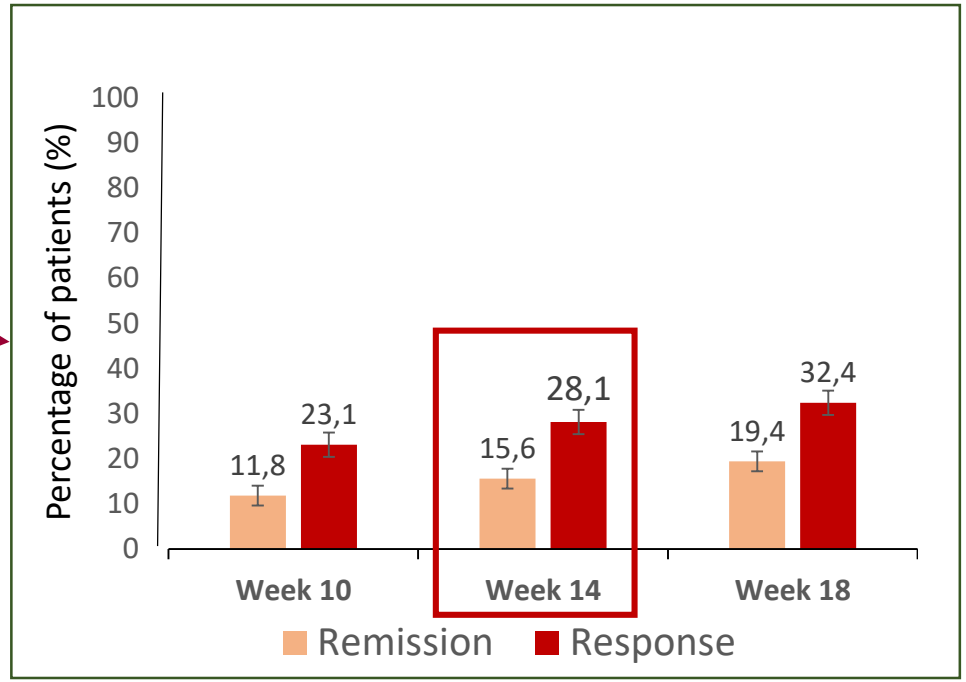
Week 303 and 54 Evaluation of efficacy

PURSUIT maintenance

GLM: Golimumab
PBO: Placebo

Early responders

PURSUIT open label

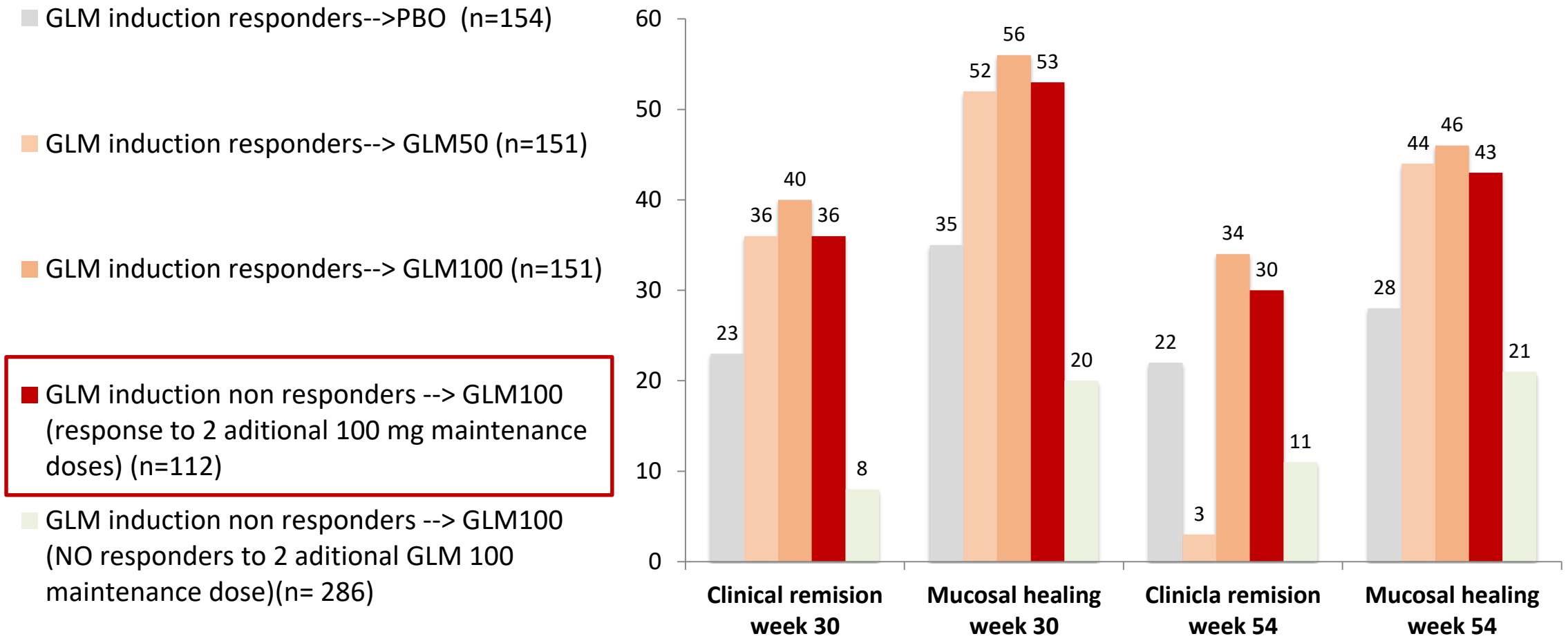


Late responders

Rutgeerts P, et al. United Eur Gastroenterol J. 2014;2(suppl 1):A67

Long-term response in late responders: subanalysis from PURSUIT Trial

Proportion of UC patients in remission and mucosal healing at week 30 and 54 in early and late responders to induction with golimumab



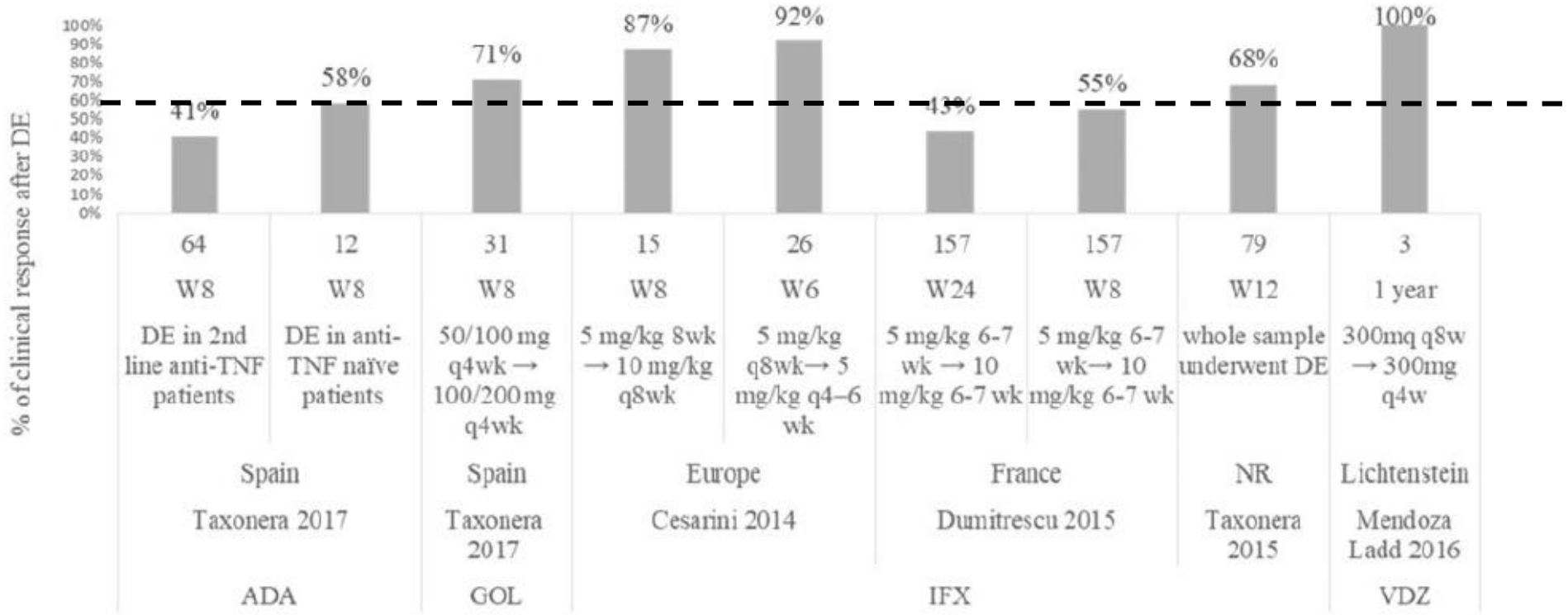
Phillip K, et al. J Crohns Colitis. 2019 Mar 7. pii: jjz052. doi: 10.1093/ecco-jcc/jjz052

Outcomes of doses optimization of mAbs in UC

Dose escalation and switching of biologics in ulcerative colitis: a systematic literature review in real-world evidence

Curr Med Res Opin. 2019 Nov;35(11):1911-1923

Nathalie C. Gemayel[a], Eugenio Rizzello[b], Petar Atanasov[a], Daniel Wirth[c] and Andras Borsi[d]



Proportion of UC patients with clinical response after dose escalation. Taxonera 2017 (ADA)[53], Taxonera 2017 (GOL)[50], Cesarini 2014 (IFX)[28], Dumitrescu 2015 (IFX)[31], Taxonera 2015 (IFX)[52], Ladd 2016 (VDZ)[40]

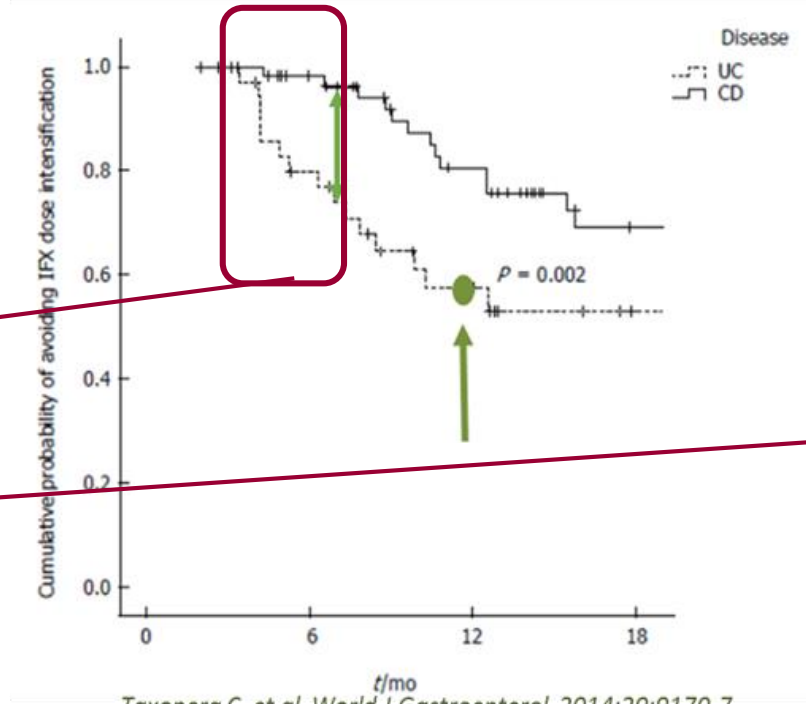
Early dose optimization of infliximab in UC

Infliximab dose escalation n is not included in the label for UC

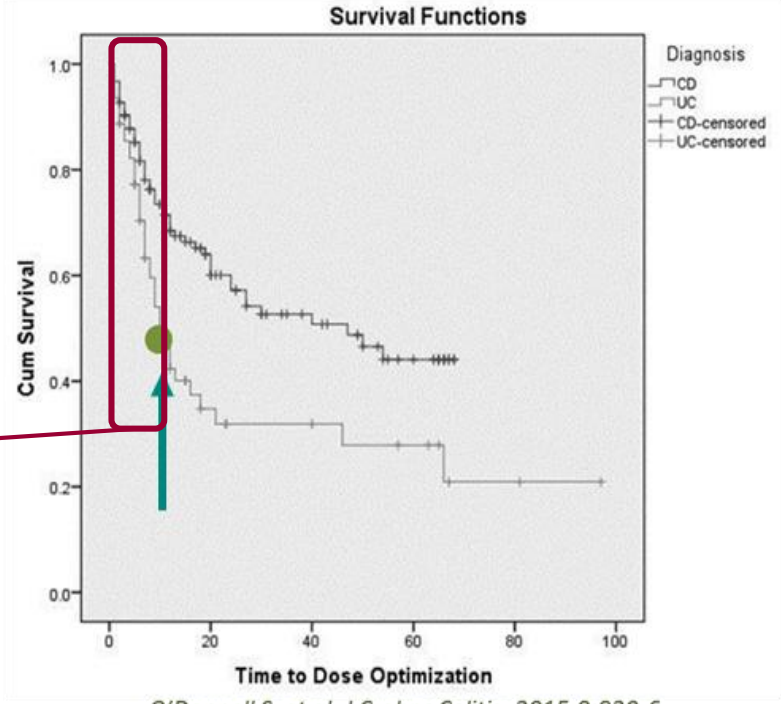
Studies that evaluated the rate of infliximab dose escalation in UC

Ref.	Patients[1]	Median duration of follow-up (mo)	Dose intensification
Rostholder *et al*[7]	50	14[2]	54%
Oussalah *et al*[8]	80	18	45%
Seow *et al*[9]	93	14	58%
Arias *et al*[10]	136	14	46%
Present study	38	9	42%

Studies that compared the need for infliximab escalation in UC vs CD



Taxonera C, et al. World J Gastroenterol. 2014;20:9170-7

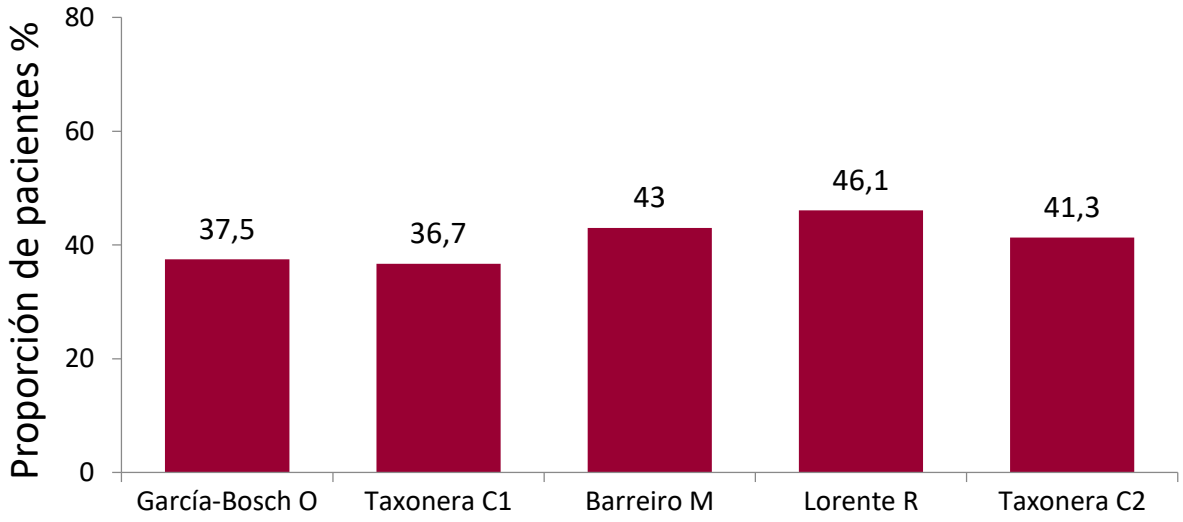


O'Donnell S, et al. J Crohns Colitis. 2015;9:830-6

Early infliximab dose escalations due to inadequate response to induction doses

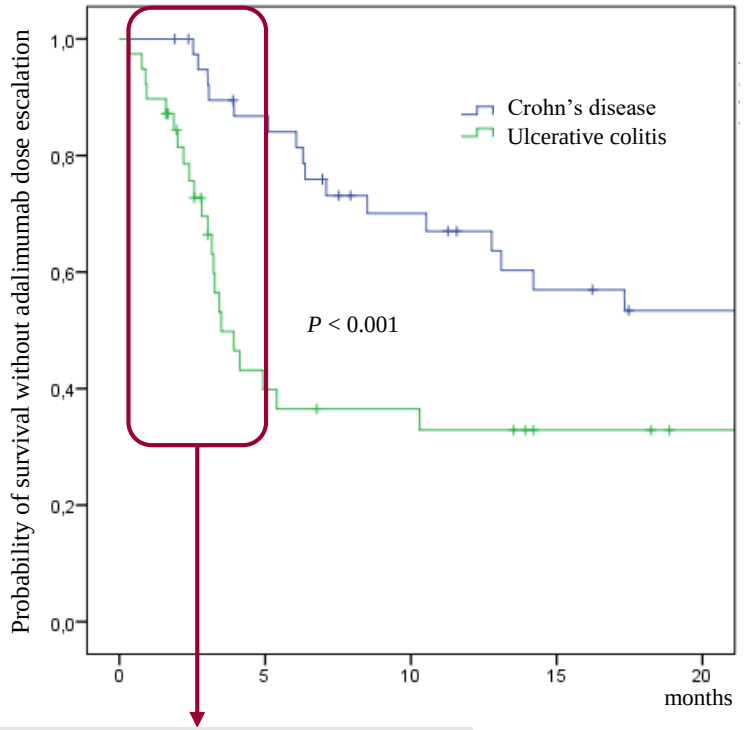
Early dose optimization of adalimumab in UC

‘Real life’ studies in Spain that evaluated the rate of patients needing adalimumab dose escalation in UC



García-Bosch O, et al. J Crohns Colitis 2013;7:717–22; Taxonera C, et al. APT 2011;33:340-8; Sierra M, et al. Enferm inflam intest dia 2016;15:44--9 ; Lorente R, et al. J Crohns Colitis 2015;9(suppl 1): S280 ; Taxonera C et al. Dig Dis Sci 2017;62:481-490

Need for ADA escalation in UC vs CD

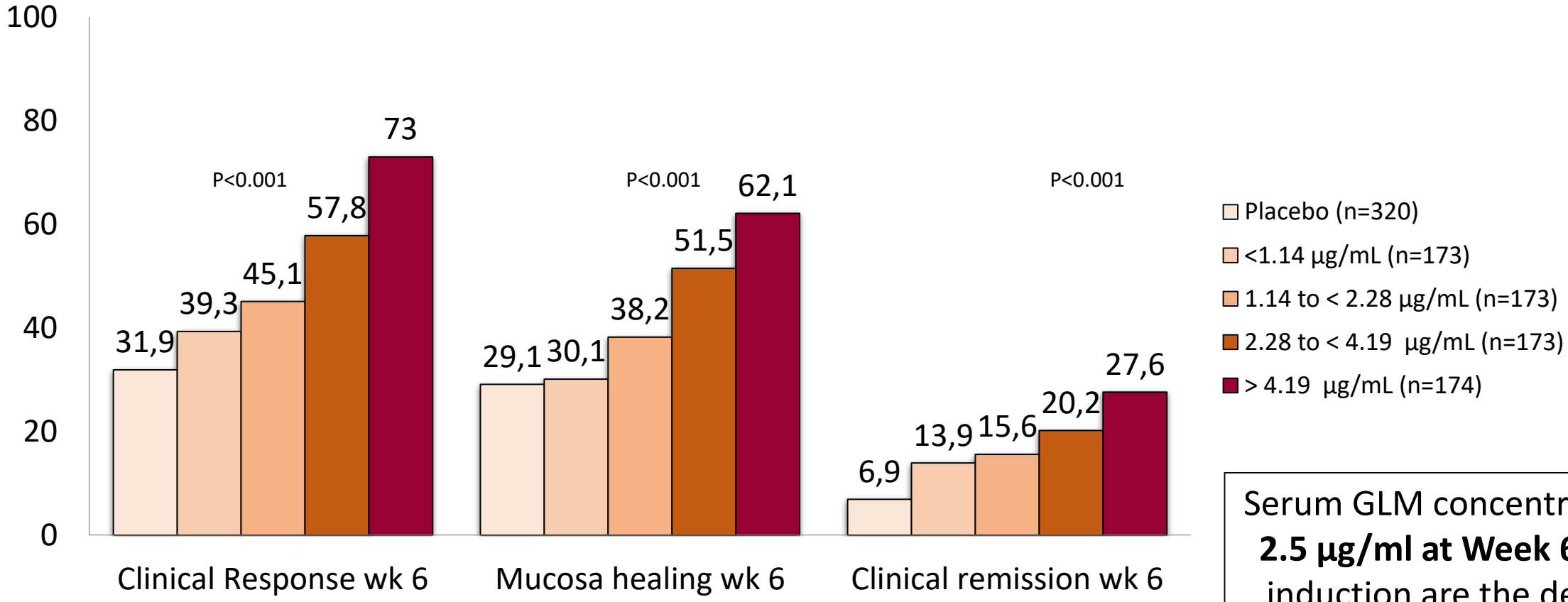


Early adalimumab dose escalations due to inadequate response to induction doses

Olivares D, et al. Rev Esp Enferm Dig 2019;111:846-851

Early dose optimization of golimumab in UC: pharmacokinetics

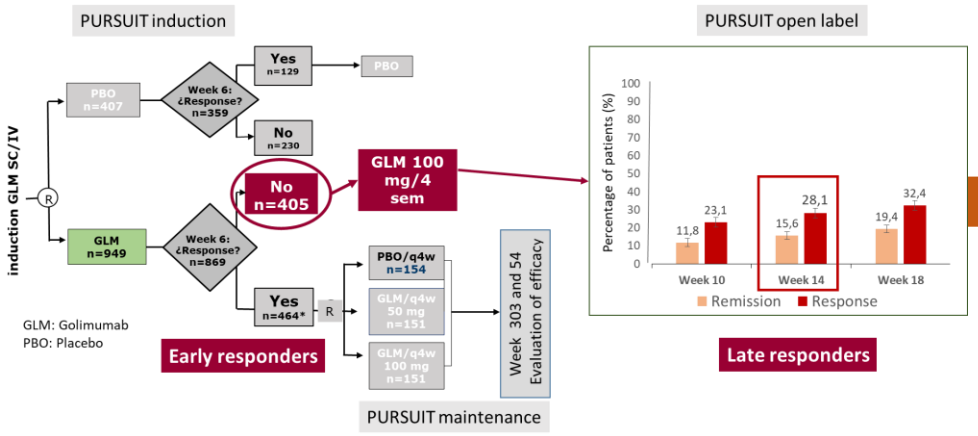
Proportion of patients with clinical response, mucosal healing and clinical remission during induction by quartiles of golimumab levels at week 6 of the PURSUIT trial



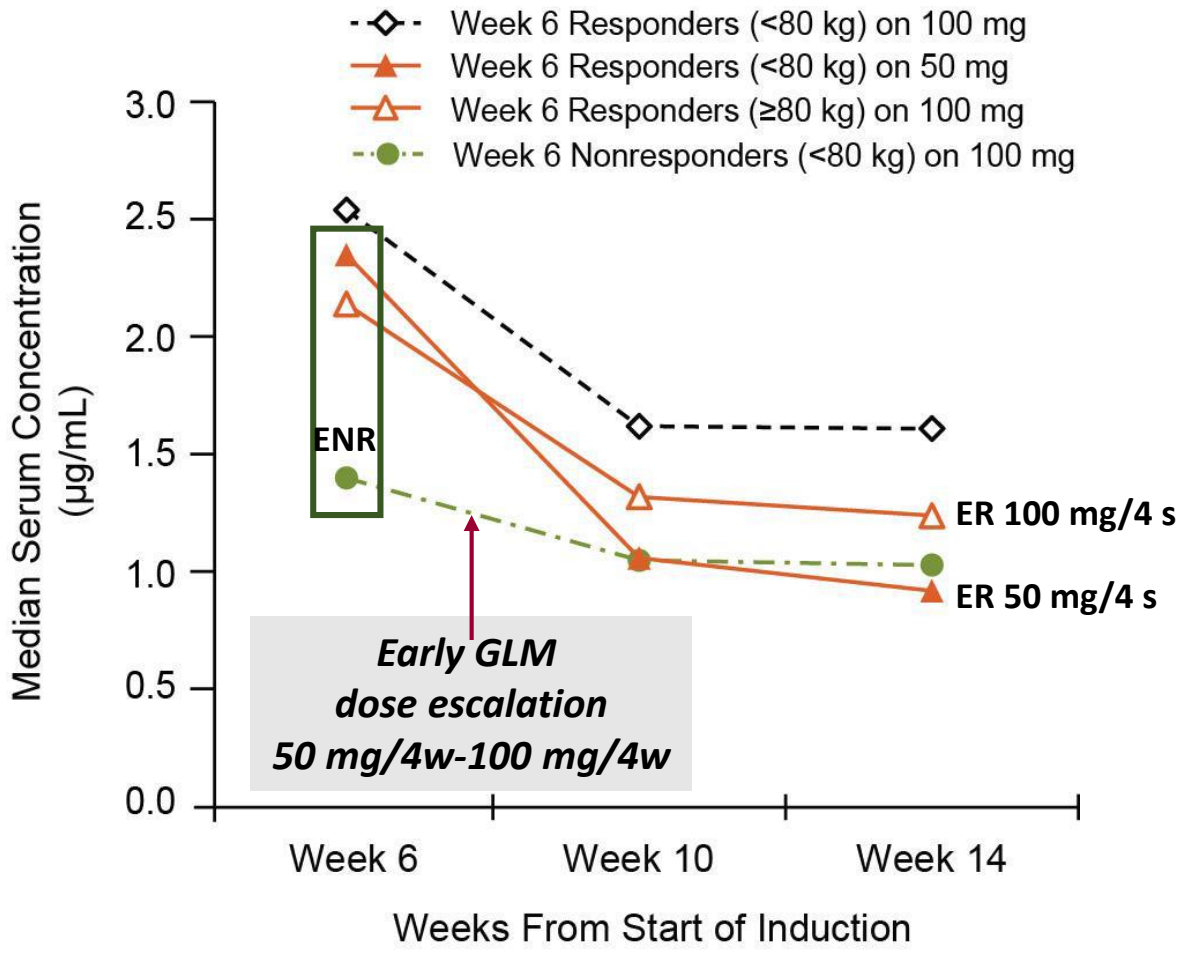
Serum GLM concentrations of **2.5 µg/ml at Week 6** during induction are the desirable concentration target to obtain optimal clinical outcomes

Adedokun OJ, et al. Journal of Crohn's and Colitis 2017;11:35–46

Early dose optimization of golimumab in UC: pharmacokinetics



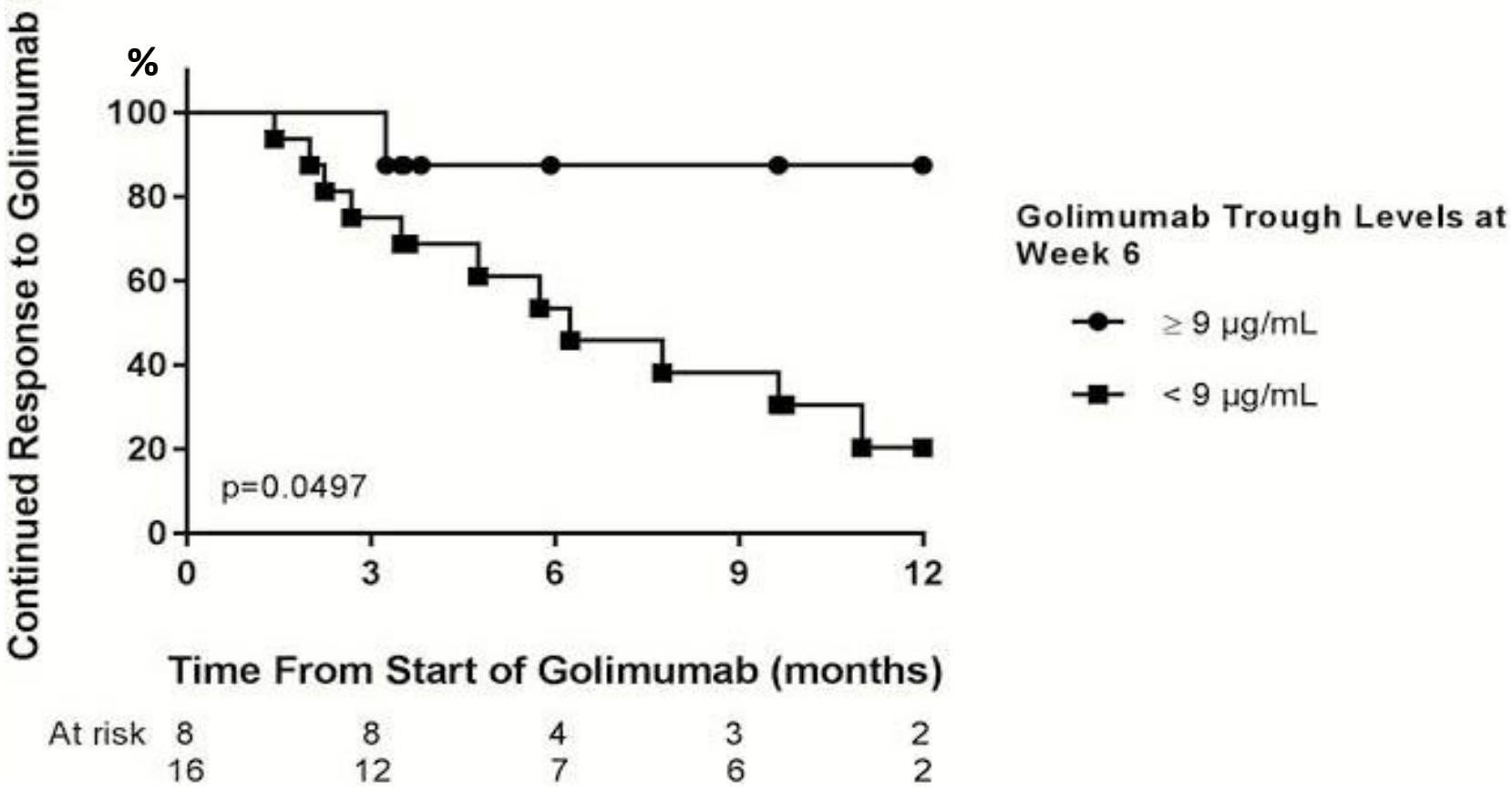
Patients weighing less than 80 kg and not responders at week 6 may need doses of 100 mg at weeks 6 and 10 to reach the same levels of GLM at week 14 as responders at week 6 who receive GLM doses according to the label



Phillip K, et al. J Crohns Colitis. 2019 Mar 7. pii: jjz052. doi: 10.1093/ecco-jcc/jjz052

Early dose optimization of golimumab in UC: pharmacokinetics

Long-term survival probability of having continued response to golimumab according to week 6 trough levels



Stefanovic S, Detrez I, Compernolle G, et al. Trough levels of golimumab at Week 6 predict drug retention rate in ulcerative colitis. Inflamm Bowel Dis 2018; P632

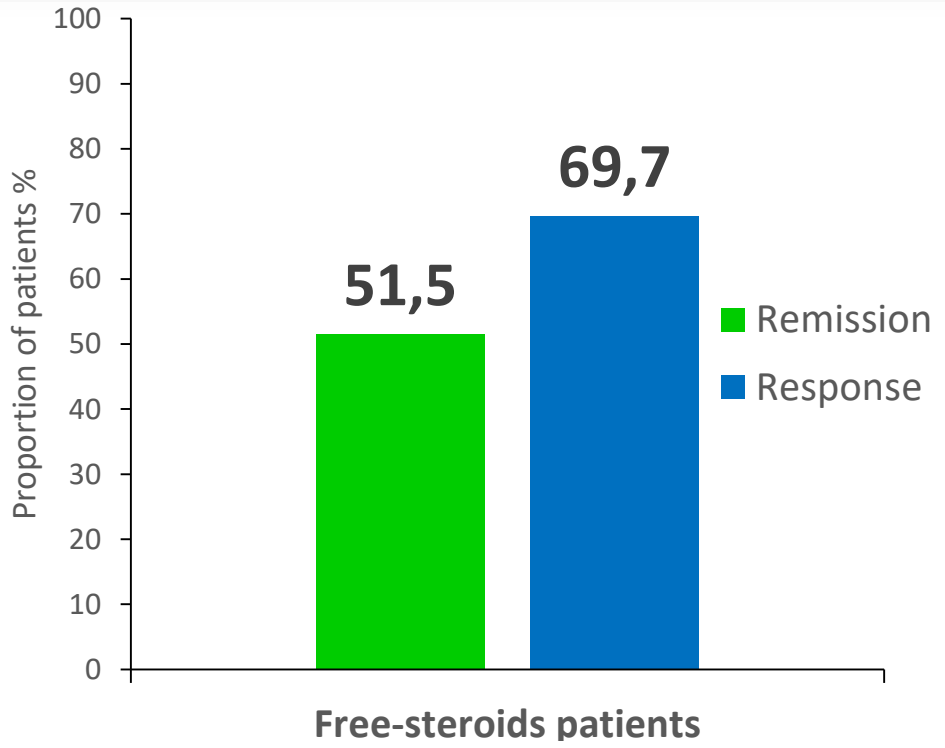
Early dose optimization of golimumab in UC in ‘real life’

Effectiveness of golimumab in anti-TNF naïve or pretreated with 1 or 2 anti-TNF UC patients

- Observational, prospective, multicenter study
- 33 patients were included:
- Follow-up 14 weeks, steroid-free induction: Remission PMS ≤2; Response reduction ≥3 points PMS
- **Nine patients (27.3%) require early dose escalation before week 14: 7 of them (77.7%) reach remission at week 14**

Short-term effectiveness of golimumab for ulcerative colitis: Observational multicenter study

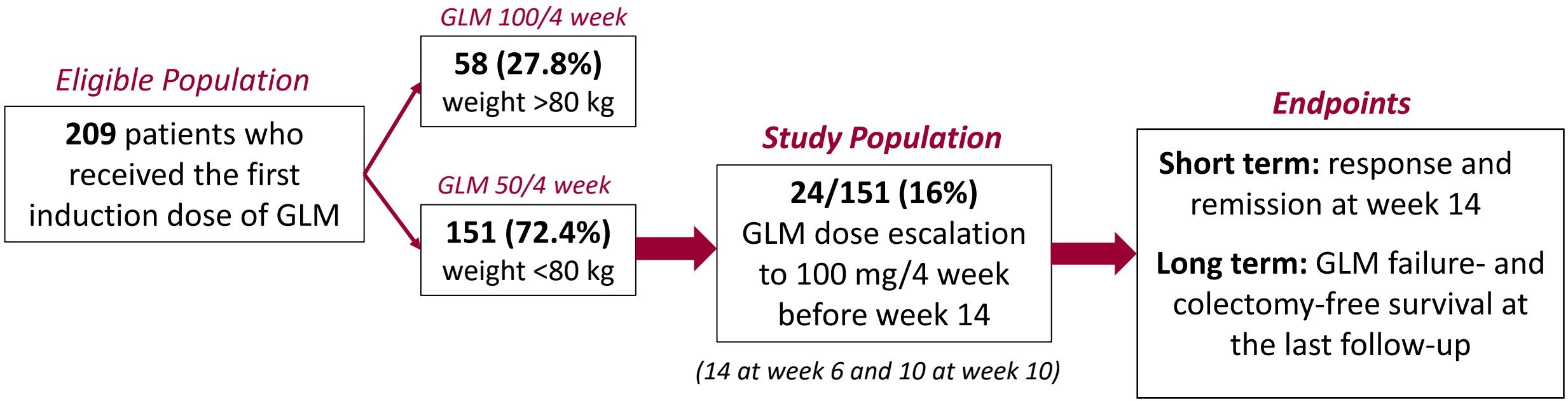
Marta Maia Bosca-Watts, Xavier Cortes, Marisa Iborra, Jose Maria Huguet, Laura Sempere, Gloria Garcia, Rafa Gil, MariFe Garcia, Marga Muñoz, Pedro Almela, Nuria Maroto, Jose Maria Paredes



Bosca-Watts MM, et al. WJG 2016;22:10432-10

Early dose optimization of golimumab in UC in 'real life'

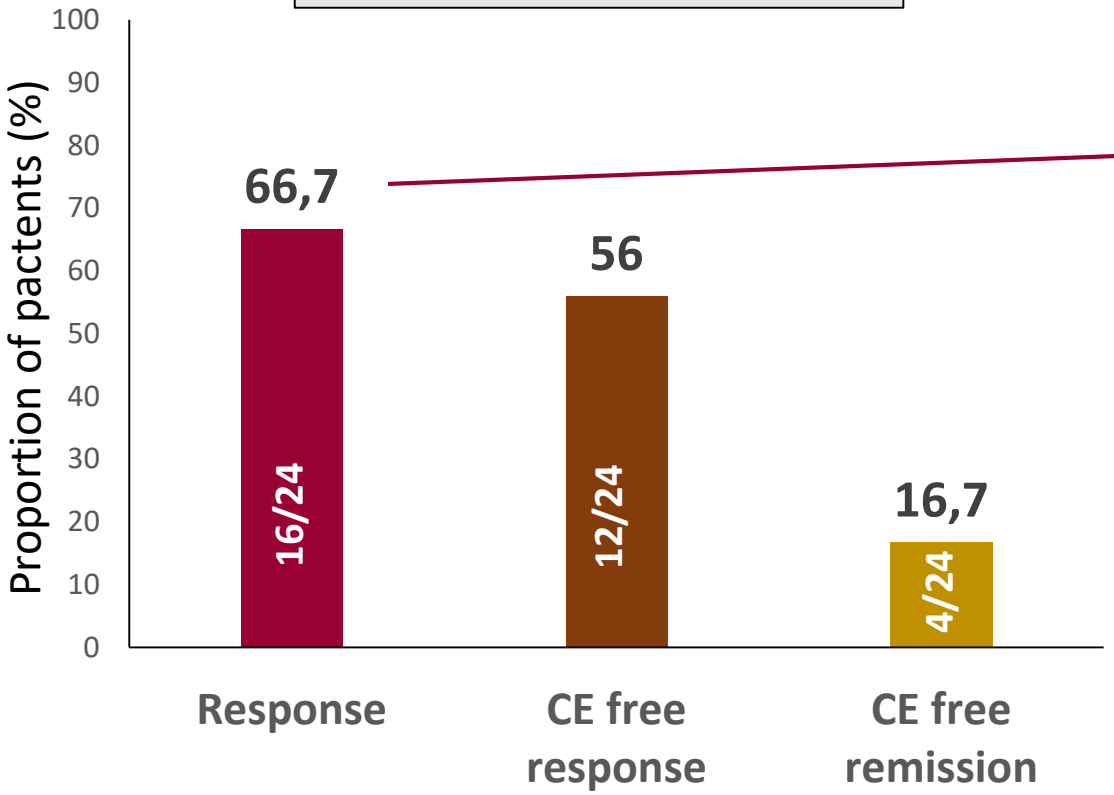
Spanish multicenter observational study of patients with inadequate response to induction with golimumab in which the dose was optimized before week 14



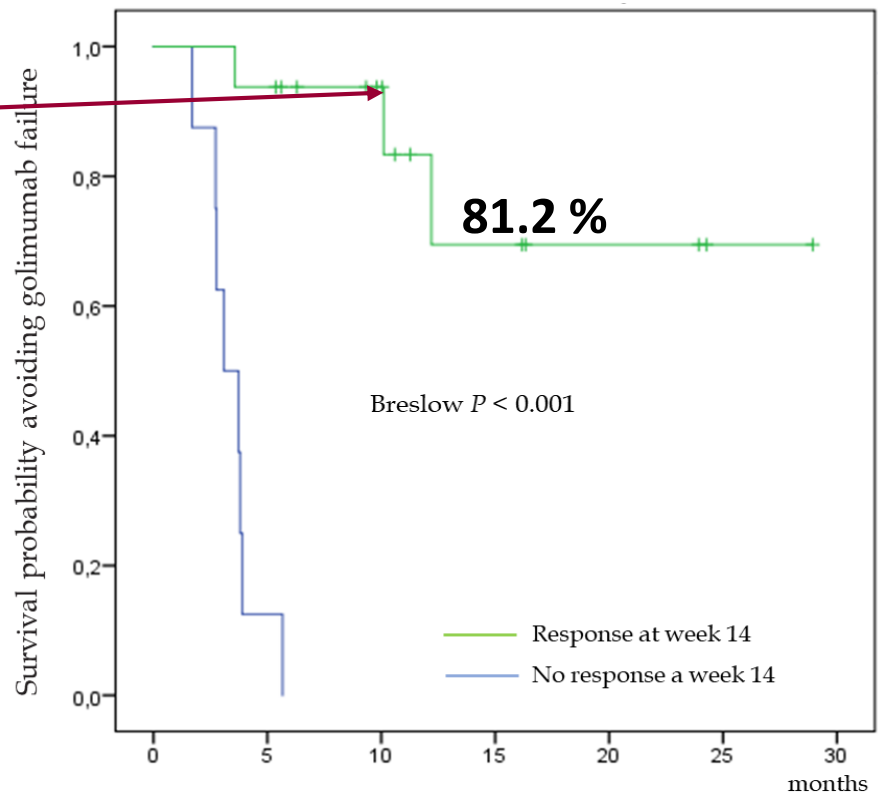
Taxonera C, et al. Curr Med Res Opin. 2019;35:1297-1304

Early dose optimization of golimumab in UC in ‘real life’

Outcomes at week 14



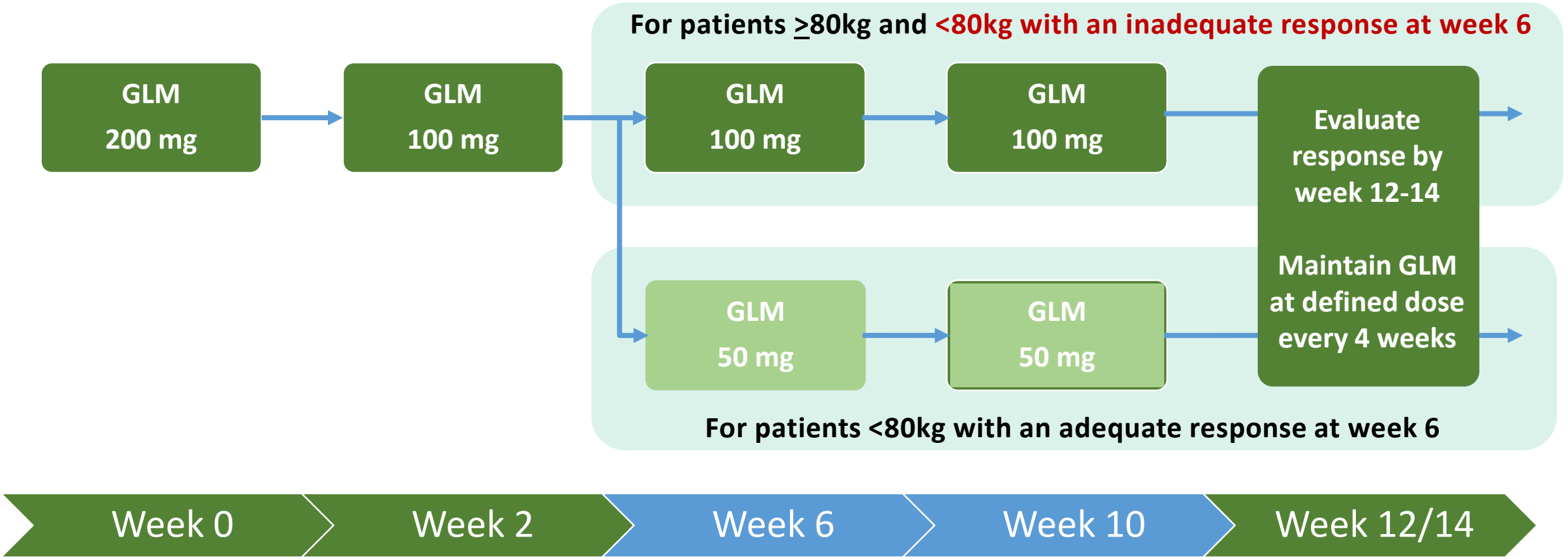
Long term outcomes: Golimumab failure



No colectomies
No severe AEs

Taxonera C, et al. Curr Med Res Opin. 2019;35:1297-1304

New Simponi label with early dose optimization of golimumab in UC



Simponi EMA label for UC

Conclusions

- In UC **short-term response** to induction is the main predictor of long-term results
- Short-term clinical and endoscopic response are associated with the **anti-TNF trough levels** achieved at induction
- A higher percentage of patients with UC (vs CD) require **early dose escalation** of anti-TNF to achieve a short-term clinical response
- Early non-responders (week 6) to **induction with golimumab** can achieve late response, remission and mucosal healing after early dose optimization
- At one year, clinical, endoscopic and quality of life outcomes are comparable between **early and late responders** to golimumab induction
- Early dose escalation of anti-TNF allows a **optimized treatment to obtain maximum benefit** in our patients with ulcerative colitis