

IV

CONGRESSO NAZIONALE IG-IBD

*Where tradition
meets
innovation*



IGBD
the Italian Group for the study of
Inflammatory Bowel Disease

FIRENZE

Convitto della Calza

29 novembre - 1 dicembre 2018

EARLY TREATMENT: **IS THERE A WINDOW OF OPPORTUNITY IN IBD ?**



Antonio Rispo

Gastroenterology

A.O.U. "Federico II" of Naples

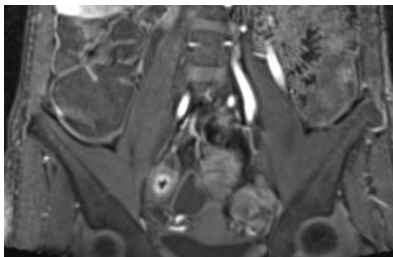
The Tale of the Three Brothers



2008

- R.S., male, 26 years
- 30 months of symptoms
- CD diagnosis (A1, L2, B2, p-)
- Ileal extension (40 cm)
- Step-up approach (failure)
- **Surgery**
- AZT after surgery
- AZT-failure
- Anti-TNF alpha (failure)
- **Second surgery**
- Anti- $\alpha_4\beta_7$
- Remission

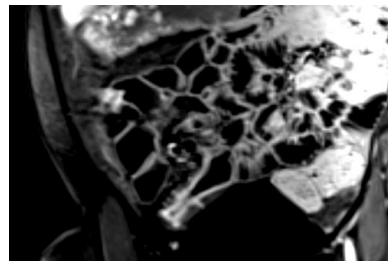
- **Lemann Index: 13.75**



2012

- E.S., male, 23 years
- 3 months of symptoms
- CD diagnosis (A1, L1, B1, p-)
- Ileal extension (30 cm)
- Early azathioprine (plus steroids)
- AZT-failure
- Anti-TNF alpha
- Anti-TNF alpha-failure
- **Surgery**
- Anti-TNF alpha
- Remission (Rutgeerts i1)

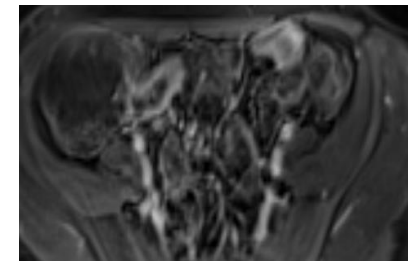
- **Lemann Index: 5.25**



2017

- A.S., male, 15 years
- 2 months of symptoms
- CD diagnosis (A1, L1, B1, p-)
- Ileal extension (30 cm)
- Anti-TNF alpha
- Deep remission (CR, MH, TH)

- **Lemann Index: 0.65**

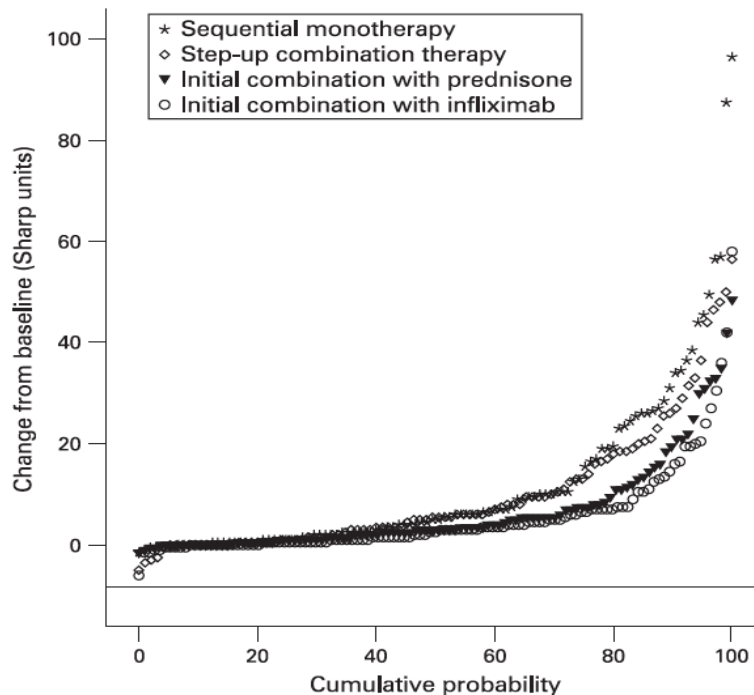


IS EARLY TREATMENT EFFECTIVE ?

LESSON FROM RHEUMATOLOGY

Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis

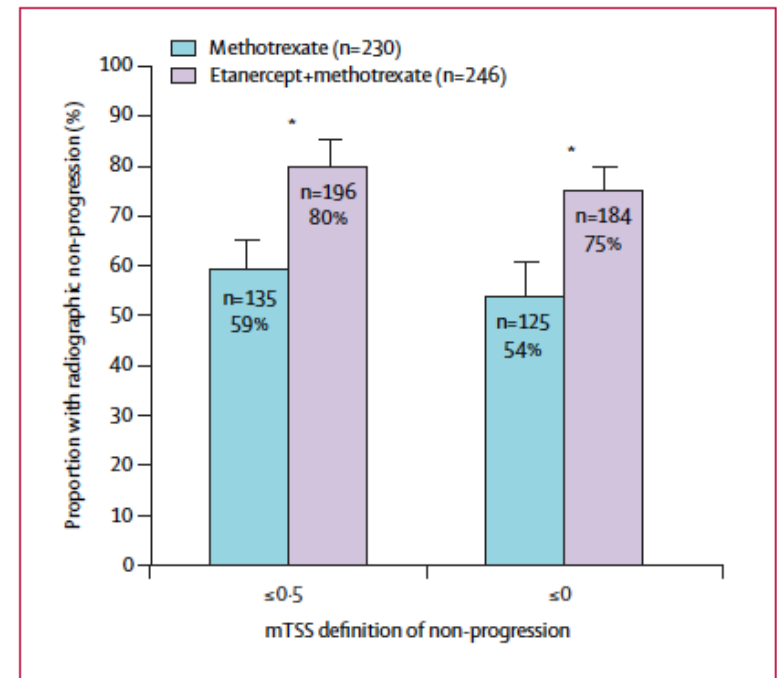
S M van der Kooij,¹ Y P M Goekoop-Ruiterman,¹ J K de Vries-Bouwstra,² M Güler-Yüksel,¹ A H Zwinderman,³ P J S M Kerstens,⁴ P A H M van der Lubbe,⁵ W M de Beus,⁶ B A M Grillet,⁷ H K Ronday,⁸ T W J Huizinga,¹ F C Breedveld,¹ B A C Dijkman,^{2,4} C F Allaart¹



van der Kooij, Ann Rheum Dis 2009

Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial

Paul Emery, Ferdinand C Breedveld, Stephen Hall, Patrick Durez, David J Chang, Deborah Robertson, Amitabh Singh, Ronald D Pedersen, Andrew S Koenig, Bruce Freundlich



Emery, Lancet 2008

IS EARLY TREATMENT EFFECTIVE ?

LESSON FROM NEUROLOGY

Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study



Ludwig Kappos, Mark S Freedman, Chris H Polman, Gilles Edan, Hans-Peter Hartung, David H Miller, Xavier Montalbán, Frederik Barkhof, Ernst-Wilhelm Radü, Lars Bauer, Susanne Dahms, * Vivian Lanius, Christoph Pohl, † Rupert Sandbrink, ‡ for the BENEFIT Study Group‡

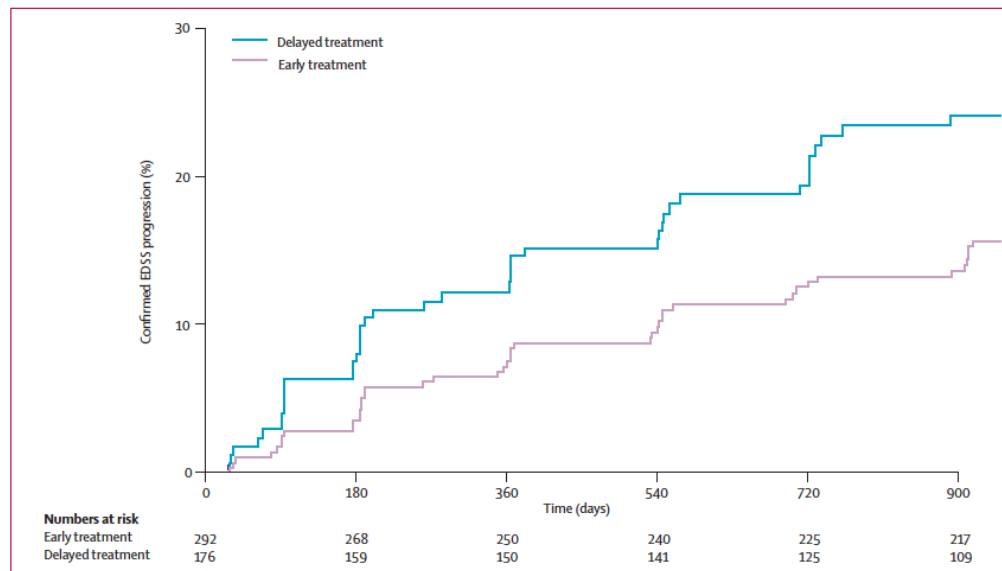
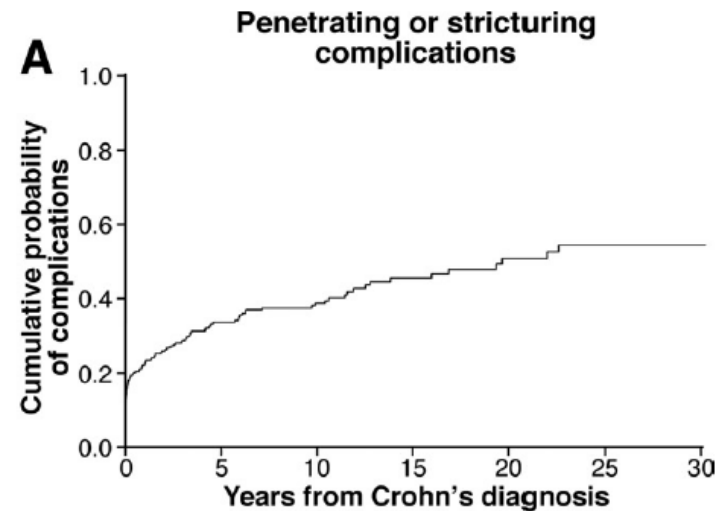


Figure 2: Kaplan-Meier estimates for the probability of progression on the expanded disability status scale (EDSS) confirmed after 6 months within the 3-year period

Risk Factors Associated With Progression to Intestinal Complications of Crohn's Disease in a Population-Based Cohort

KELVIN T. THIA,^{*,§} WILLIAM J. SANDBORN,^{*} WILLIAM S. HARMSSEN,[‡] ALAN R. ZINSMEISTER,[‡] and EDWARD V. LOFTUS, Jr^{*}

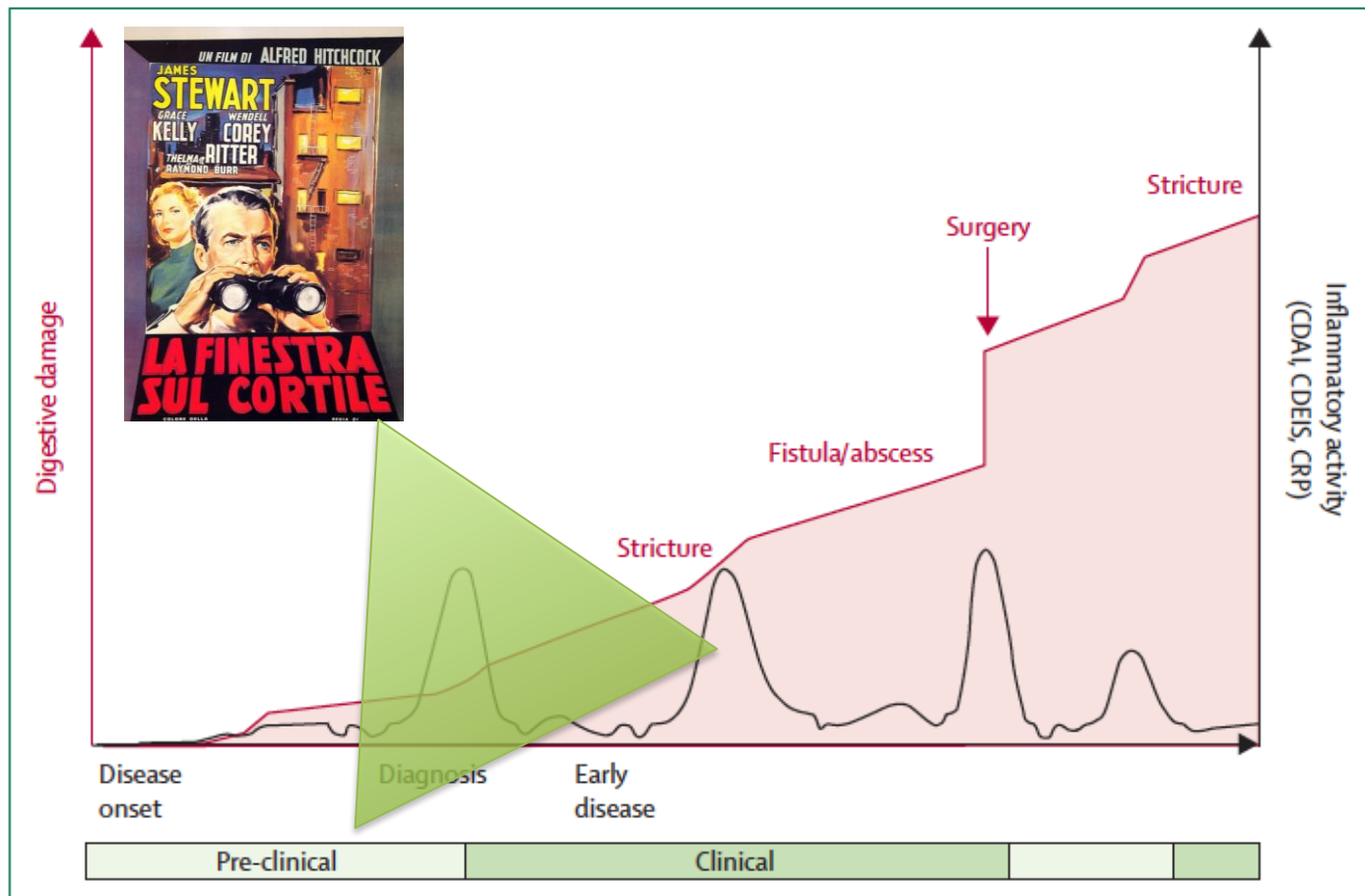
	Overall
Factors at diagnosis	306 (100)
Gender	
Male	150 (49.0)
Female	156 (51.0)
Age	
A1	35 (11.4)
A2	172 (56.2)
A3	99 (32.4)
Disease location	
L1	138 (45.1)
L2	98 (32.0)
L3	57 (18.6)
L4	1 (0.3)
L1 + L4	7 (2.3)
L2 + L4	1 (0.3)
L3 + L4	1 (0.3)



18.5% of CD patients experienced complications within 90 days from diagnosis

CLINICAL—ALIMENTARY TRACT

Development of the Lémann Index to Assess Digestive Tract Damage in Patients With Crohn's Disease

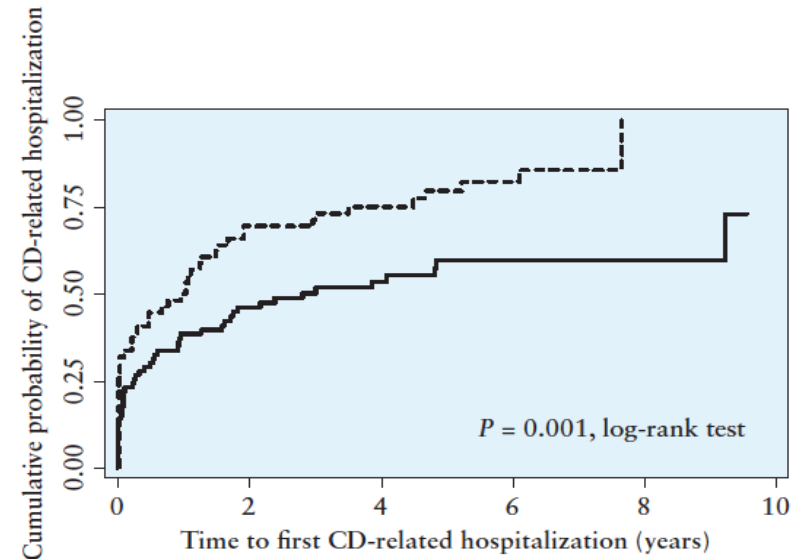
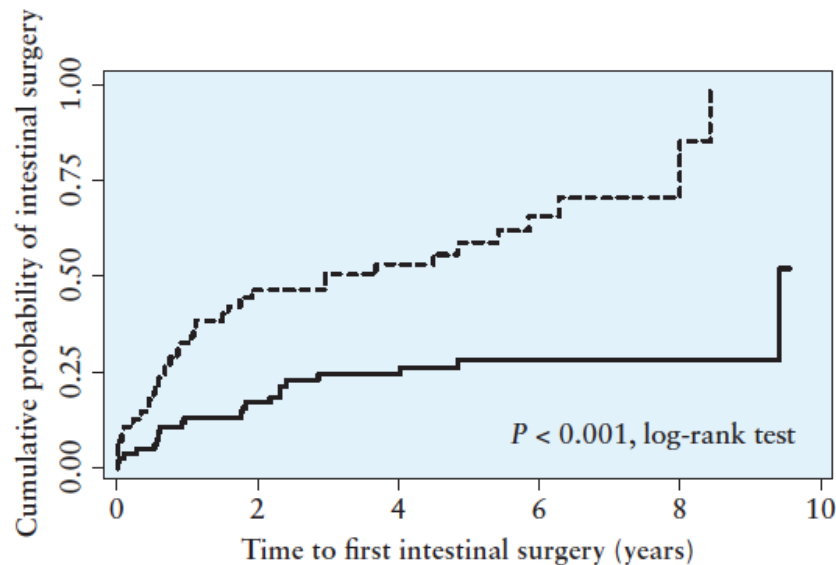


Prevalence of Bowel Damage Assessed by Cross-Sectional Imaging in Early Crohn's Disease and its Impact on Disease Outcome

Gionata Fiorino,^{a,*} Mathilde Morin,^{b,*} Stefanos Bonovas,^a
Cristiana Bonifacio,^c Antonino Spinelli,^{d,e} Adeline Germain,^f
Valérie Laurent,^g Camille Zallot,^b Laurent Peyrin-Biroulet,^b
Silvio Danese^{a,e}

Bowel Damage L.I. > 4.8

142 CD pts



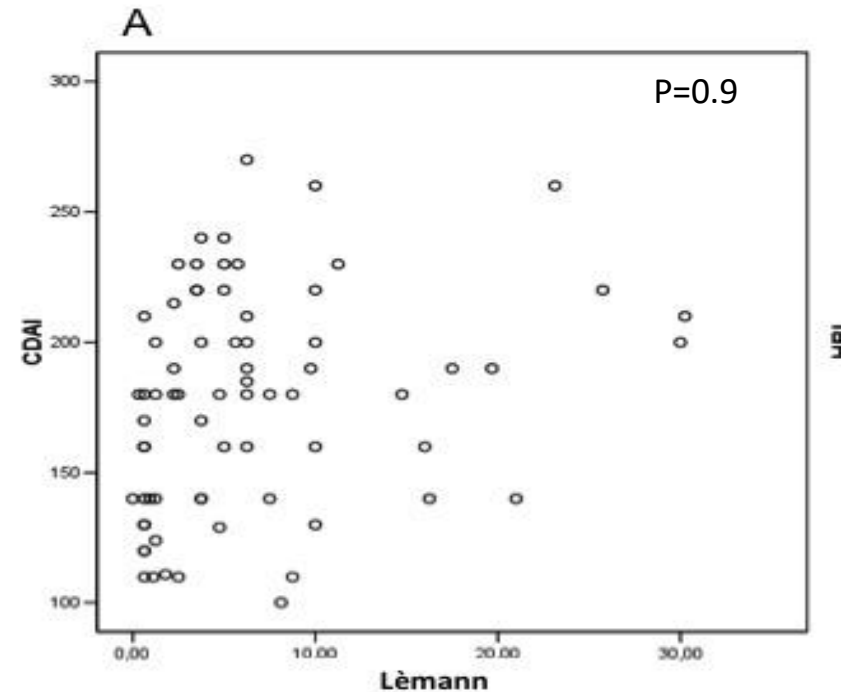
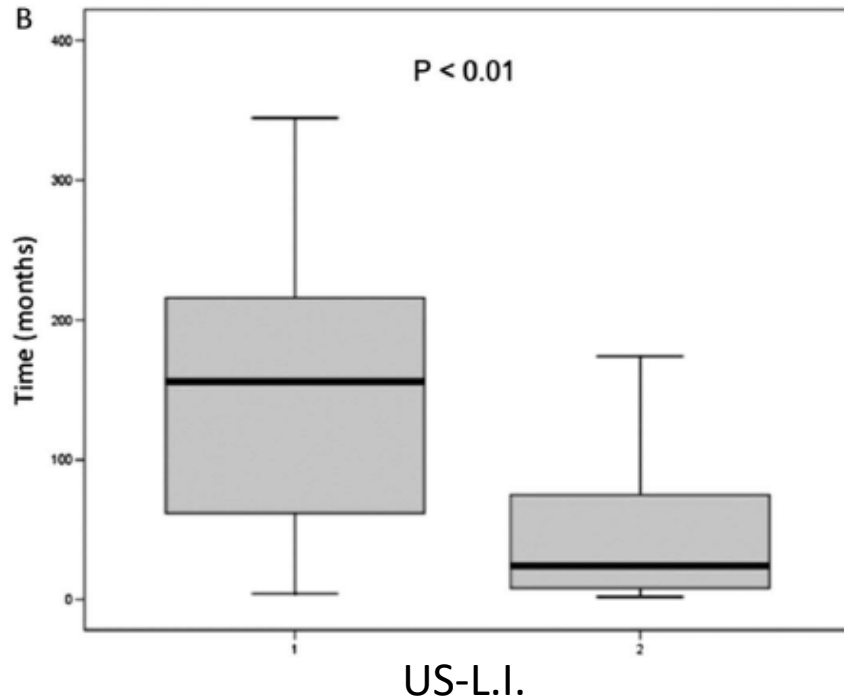
39% of CD patients showed bowel damage at diagnosis

Bowel Damage in Crohn's Disease: Direct Comparison of Ultrasonography-based and Magnetic Resonance-based Lemann Index

Antonio Rispo, MD, PhD, Nicola Imperatore, MD,* Anna Testa, MD, PhD,* Pierpaolo Mainenti, MD,[†] Giovanni Domenico De Palma, MD,[‡] Gaetano Luglio, MD,[§] Simone Maurea, MD,^{||} Olga Maria Nardone, MD,* Nicola Caporaso, MD,* and Fabiana Castiglione, MD**

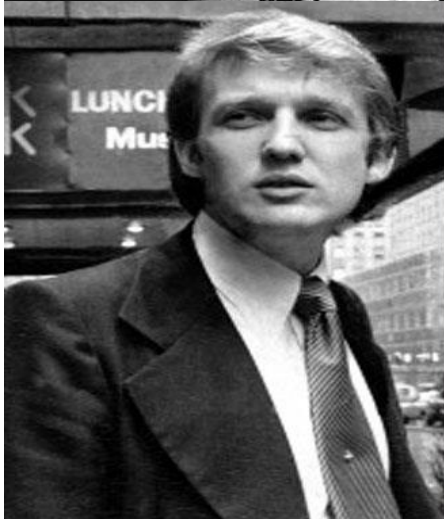
Bowel Damage L.I. > 4.8

71 CD pts



WHAT IS **EARLY** CD ?

TIME



B1

B2

B3

Development of the Paris Definition of Early Crohn's Disease for Disease-Modification Trials: Results of an International Expert Opinion Process

Laurent Peyrin-Biroulet, MD, PhD¹, Vincent Billioud, MD¹, Geert D'Haens, MD, PhD², Remo Panaccione, MD³, Brian Feagan, MD⁴, Julian Panés, MD⁵, Silvio Danese, MD, PhD⁶, Stefan Schreiber, MD, PhD⁷, Haruhiko Ogata, MD⁸, Toshifumi Hibi, MD, PhD⁸, Peter D.R. Higgins, MD⁹, Laurent Beaugerie, MD, PhD¹⁰, Yehuda Chowers, MD^{11,12}, Edouard Louis, MD, PhD¹³, Flávio Steinwurz, MD¹⁴, Walter Reinisch, MD¹⁵, Paul Rutgeerts, MD, PhD¹⁶, Jean-Frédéric Colombel, MD¹⁷, Simon Travis, MD¹⁸ and William J. Sandborn, MD¹⁹

Table 3. Paris criteria defining early Crohn's disease for use in disease-modification trials (evidence level D)

Component ^a	Definition
Disease duration	≤18 months after diagnosis
Treatment	No previous or current use of immunomodulators and/or biologics Previous or current use of 5-aminosalicylate and/or corticosteroids permitted

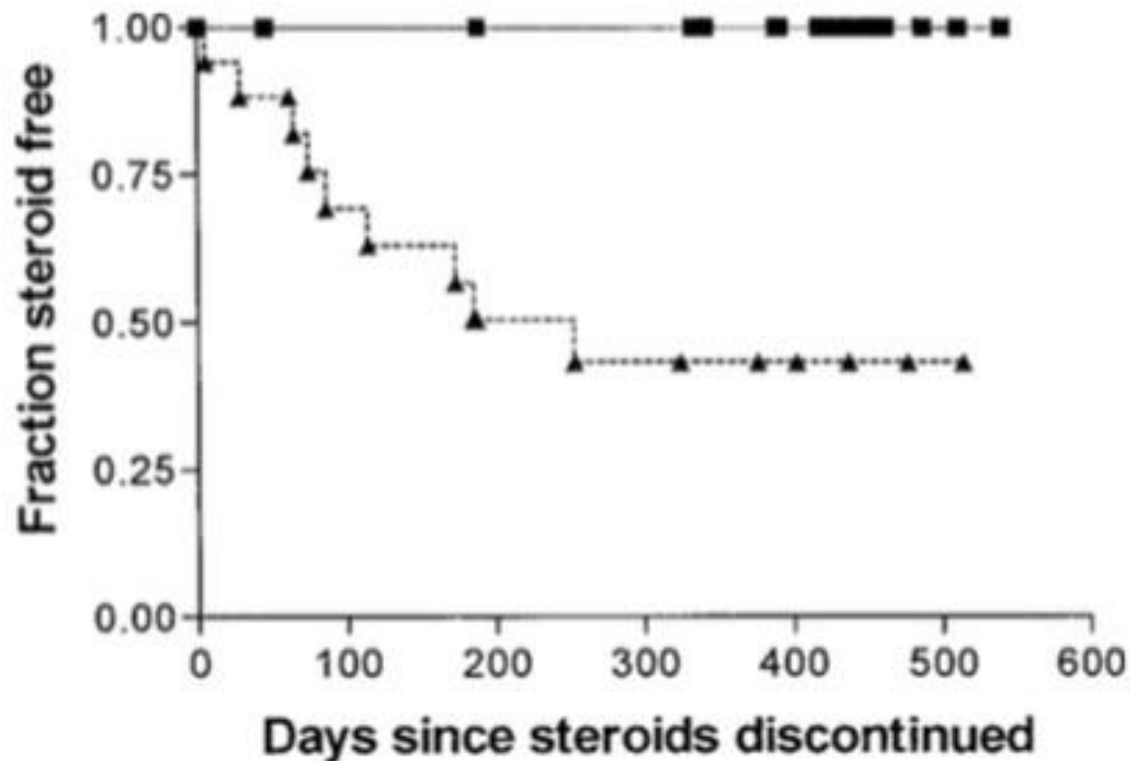
Approximately 20% of patients with newly diagnosed CD present with bowel damage (4). These patients should be included in disease-modification trials in order to evaluate prevention of damage progression in patients with early CD, even though the primary focus of early CD trials is likely to be the stratum of patients without preexisting bowel damage. Only perianal fistu-

IS EARLY TREATMENT EFFECTIVE ?

LESSON FROM CHILDREN

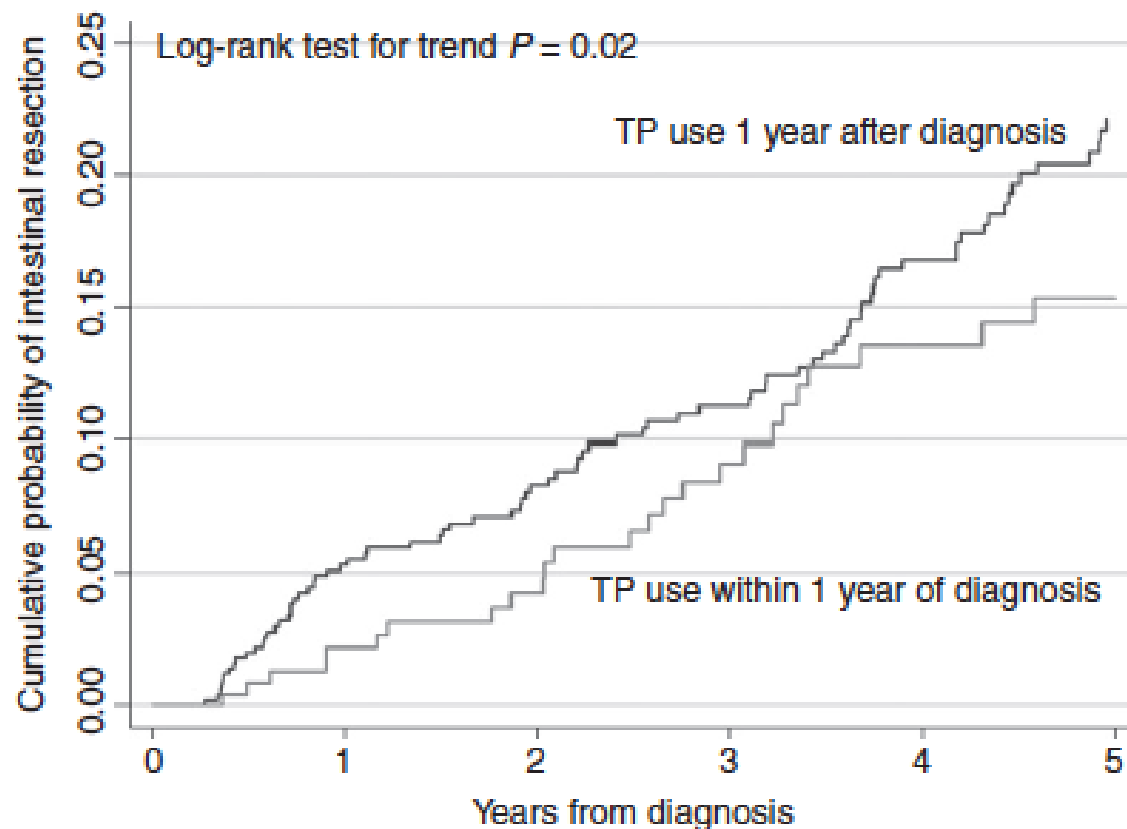
A Multicenter Trial of 6-Mercaptopurine and Prednisone in Children With Newly Diagnosed Crohn's Disease

JAMES MARKOWITZ,* KATHY GRANCHER,* NINA KOHN,† MARTIN LESSER,† FREDRIC DAUM,*
and THE PEDIATRIC 6MP COLLABORATIVE GROUP

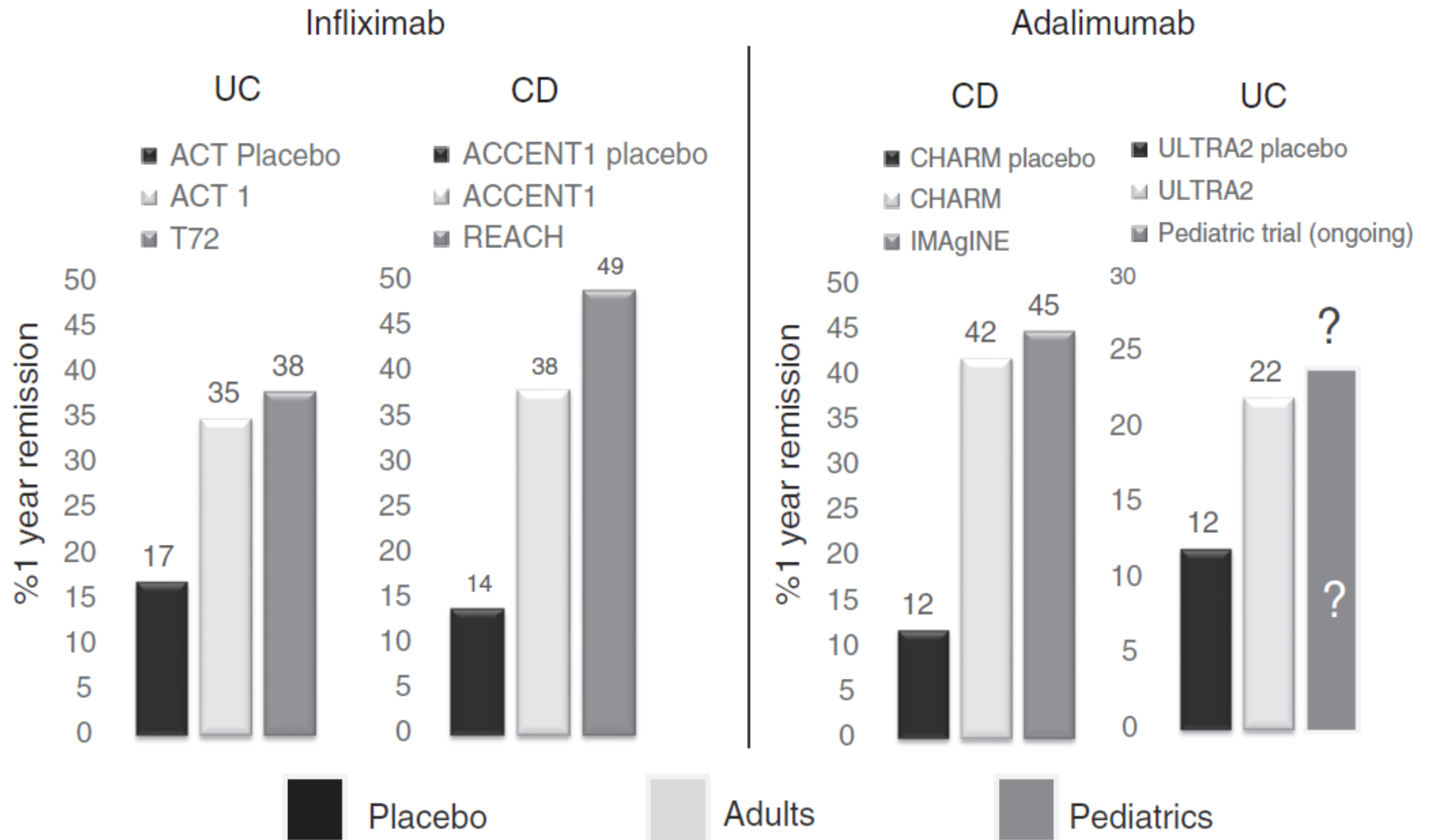


Impact of early thiopurines on surgery in 2770 children and young people diagnosed with inflammatory bowel disease: a national population-based study

V. Chhaya*, R. C. G. Pollok*, E. Cecil[†], V. Subramanian[‡], V. Curcin[§], A. Majeed[†] & S. Saxena[†]



Comparison of Adult and Pediatric Biologics Trial Results

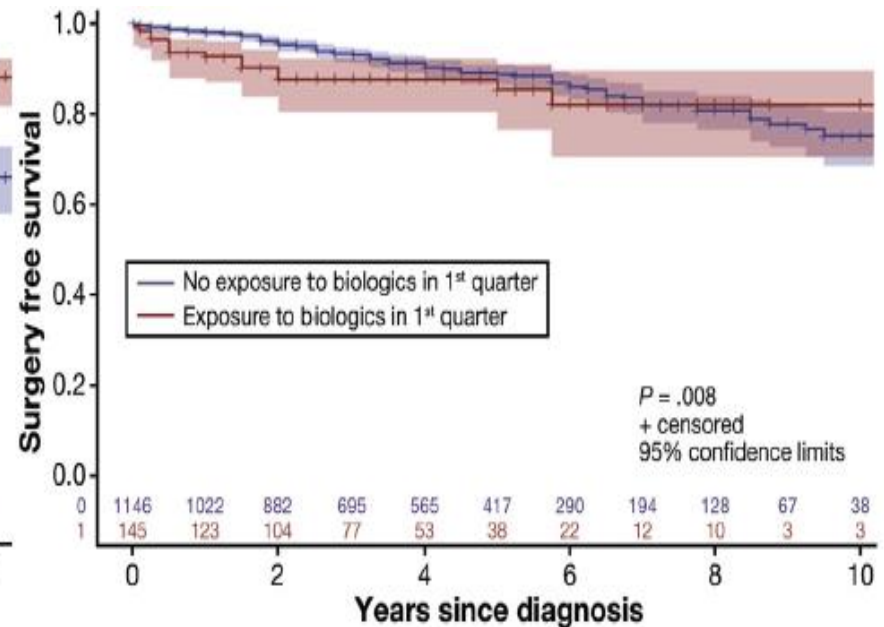
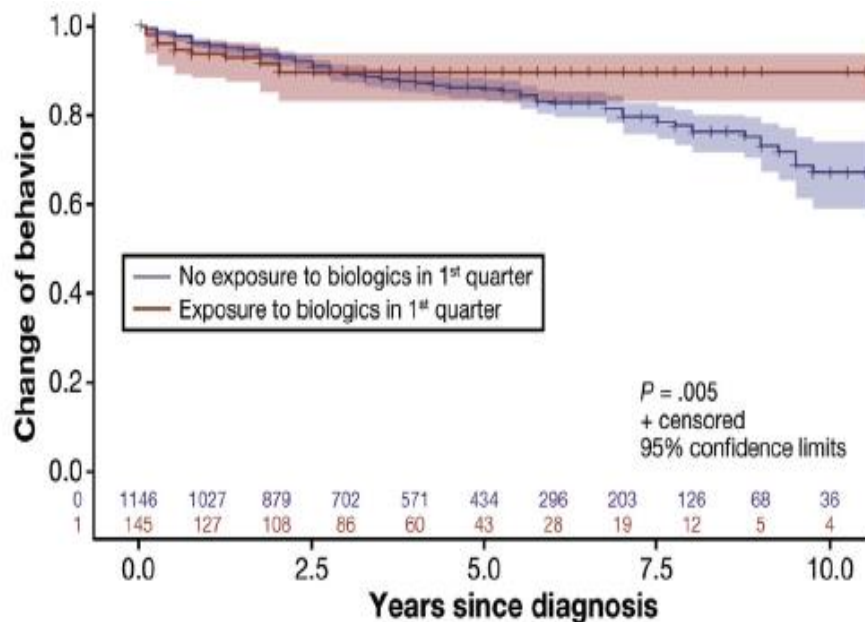


Biologics Delay Progression of Crohn's Disease, but Not Early Surgery, in Children



Basavaraj Kerur,^{*,‡} Jason T. Machan,^{‡,§} Jason M. Shapiro,^{*,‡} Carolina S. Cerezo,^{*,‡} James Markowitz,^{||} David R. Mack,[¶] Anne M. Griffiths,[#] Anthony R. Otley,^{**} Marian D. Pfefferkorn,^{‡‡} Joel R. Rosh,^{§§} David J. Keljo,^{|||} Brendan Boyle,^{¶¶} Maria Oliva-Hemker,^{##} Marsha H. Kay,^{***} Shehzad A. Saeed,^{‡‡‡} Andrew B. Grossman,^{§§§} Boris Sudel,^{||||} Michael D. Kappelman,^{¶¶¶¶} Marc Schaefer,^{####} Gitit Tomer,^{****} Athos Bousvaros,^{‡‡‡‡} Trudy Lerer,^{§§§§} Jeffrey S. Hyams,^{§§§§} and Neal S. LeLeiko^{*,‡}

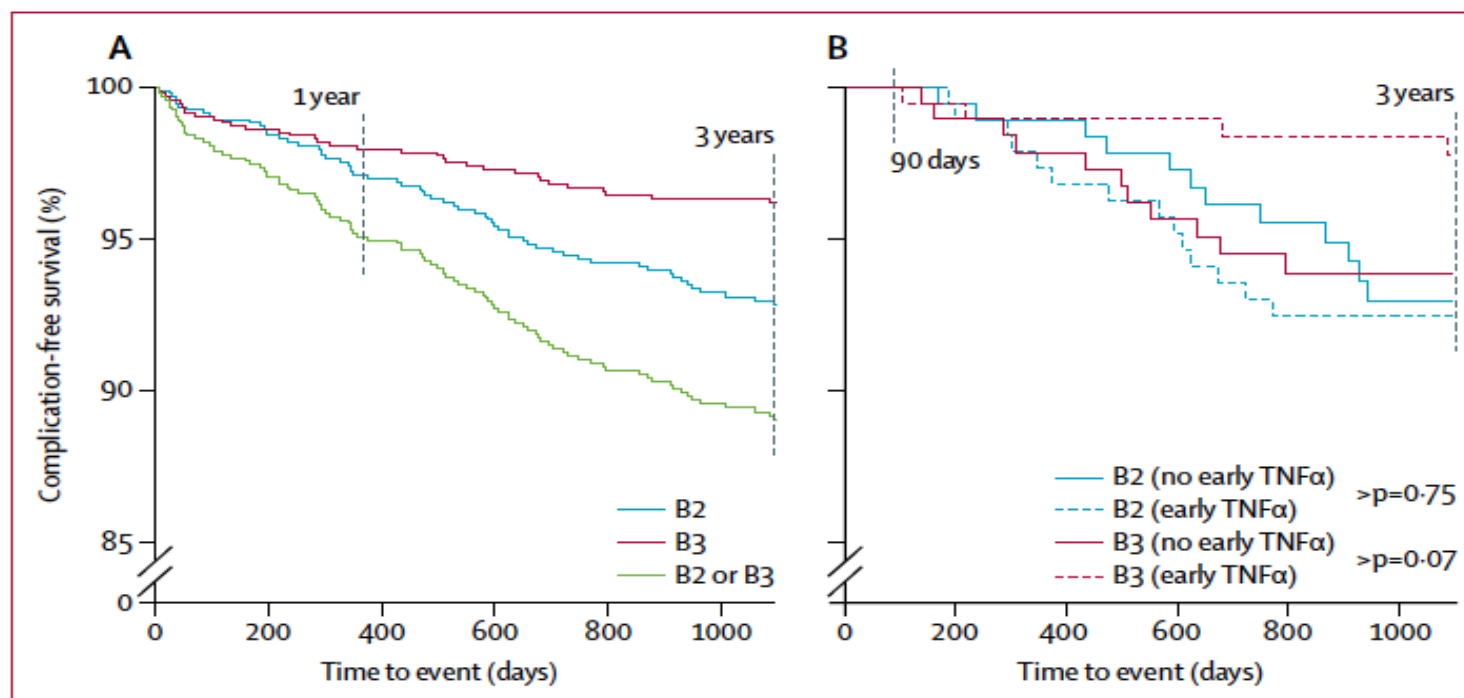
1442 CD pts



Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study

Subra Kugathasan*, Lee A Denson*, Thomas D Walters*, Mi-Ok Kim, Urko M Marigorta, Melanie Schirmer, Kajari Mondal, Chunyan Liu, Anne Griffiths, Joshua D Noe, Wallace V Crandall, Scott Snapper, Shervin Rabizadeh, Joel R Rosh, Jason M Shapiro, Stephen Guthery, David R Mack, Richard Kellermayer, Michael D Kappelman, Steven Steiner, Dedrick E Moulton, David Keljo, Stanley Cohen, Maria Oliva-Hemker, Melvin B Heyman, Anthony R Otley, Susan S Baker, Jonathan S Evans, Barbara S Kirschner, Ashish S Patel, David Ziring, Bruce C Trapnell, Francisco A Sylvester, Michael C Stephens, Robert N Baldassano, James F Markowitz, Judy Cho, Ramnik J Xavier, Curtis Huttenhower, Bruce J Aronow, Greg Gibson†, Jeffrey S Hyams†, Marla C Dubinsky†

913 CD pts



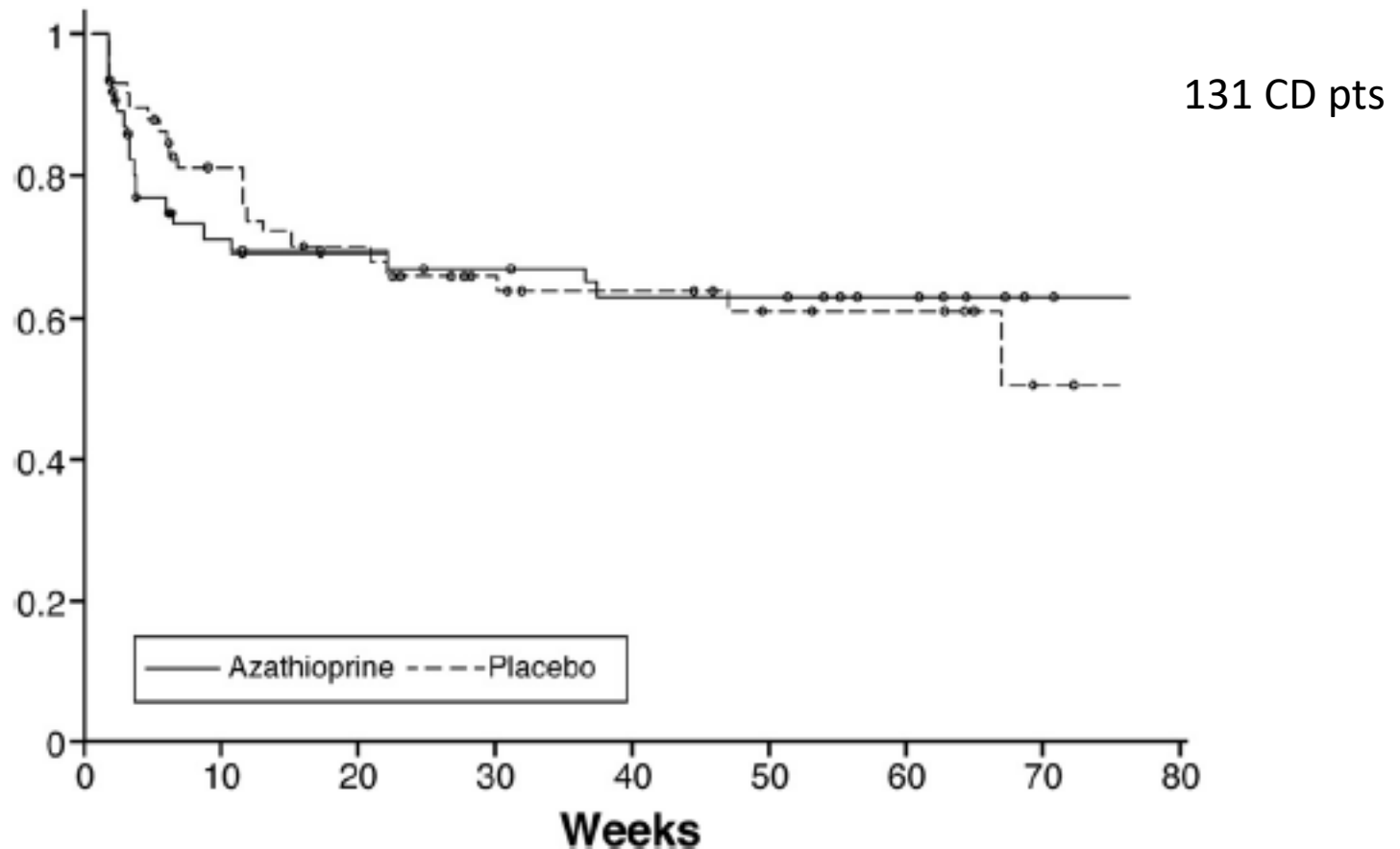
IS EARLY TREATMENT EFFECTIVE ?

LESSON FROM R.C.Ts.

*(SUB-GROUP, SECONDARY END-POINT AND/OR
POST-HOC ANALYSES)*

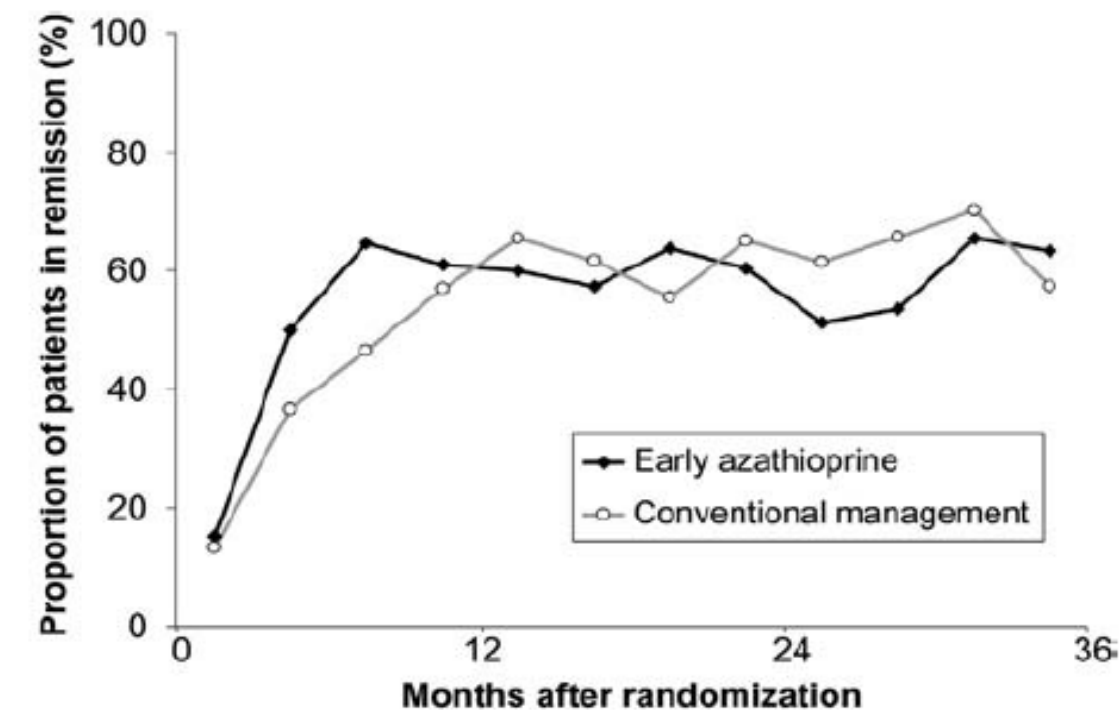
Early Azathioprine Therapy Is No More Effective Than Placebo for Newly Diagnosed Crohn's Disease

JULIÁN PANÉS,^{1,2} ANTONIO LÓPEZ-SANROMÁN,³ FERNANDO BERMEJO,⁴ VALLE GARCÍA-SÁNCHEZ,⁵ MARIA ESTEVE,^{2,6} YOLANDA TORRES,⁷ EUGENI DOMÈNECH,^{2,8} MARTA PIQUERAS,⁹ MARÍA GOMEZ-GARCÍA,¹⁰ ANA GUTIÉRREZ,^{2,11} CARLOS TAXONERA,¹² and MIQUEL SANS,^{1,2,13} for the AZTEC Study Group



Early Administration of Azathioprine vs Conventional Management of Crohn's Disease: A Randomized Controlled Trial

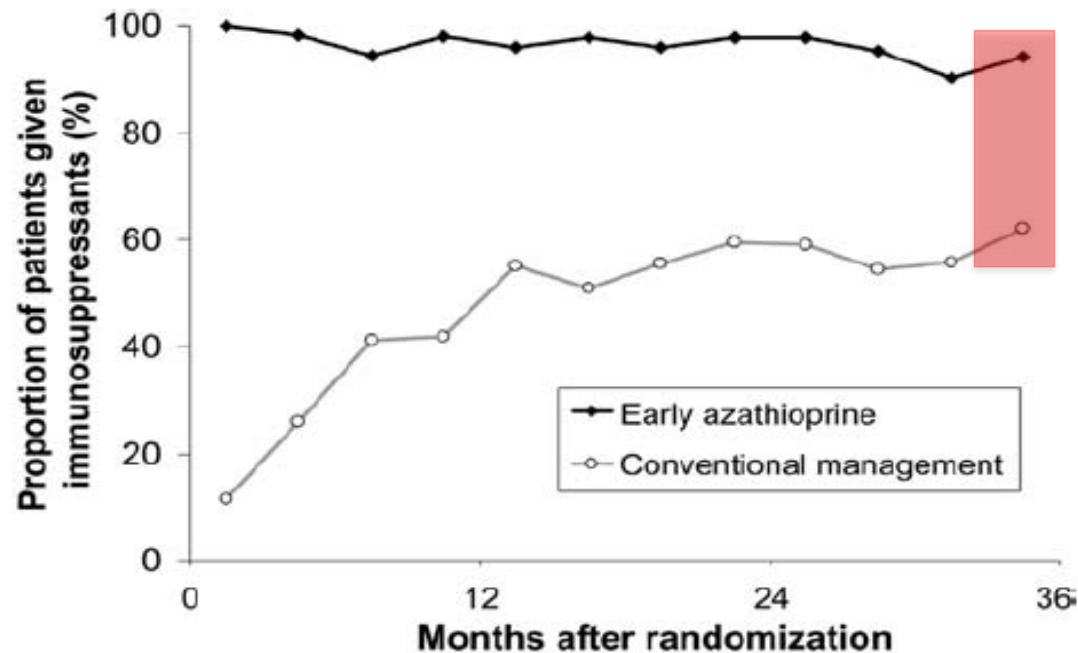
JACQUES COSNES,¹ ANNE BOURRIER,¹ DAVID LAHARIE,² STÉPHANE NAHON,³ YORAM BOUHNIC,⁴ FRANCK CARBONNEL,⁵ MATTHIEU ALLEZ,⁶ JEAN-LOUIS DUPAS,⁷ JEAN-MARIE REIMUND,⁸ GUILLAUME SAVOYE,⁹ PAULINE JOUET,¹⁰ JACQUES MOREAU,¹¹ JEAN-YVES MARY,¹² and JEAN-FRÉDÉRIC COLOMBEL,^{13,14} for the Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif (GETAID)



No. patients												
Early aza.	61	58	54	50	45	47	48	48	43	41	35	41
Conv. m.	65	60	59	55	55	47	45	46	39	38	37	40

Early Administration of Azathioprine vs Conventional Management of Crohn's Disease: A Randomized Controlled Trial

JACQUES COSNES,¹ ANNE BOURRIER,¹ DAVID LAHARIE,² STÉPHANE NAHON,³ YORAM BOUHNİK,⁴ FRANCK CARBONNEL,⁵ MATTHIEU ALLEZ,⁶ JEAN-LOUIS DUPAS,⁷ JEAN-MARIE REIMUND,⁸ GUILLAUME SAVOYE,⁹ PAULINE JOUET,¹⁰ JACQUES MOREAU,¹¹ JEAN-YVES MARY,¹² and JEAN-FRÉDÉRIC COLOMBEL,^{13,14} for the Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif (GETAID)

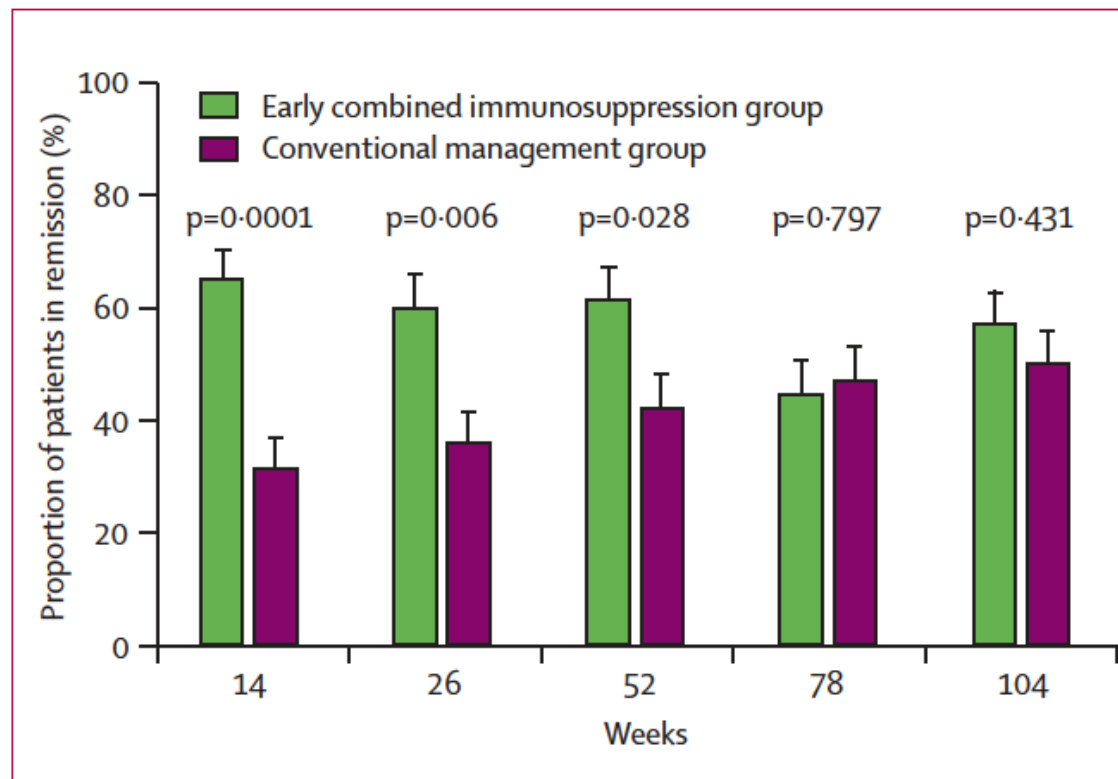


132 CD pts

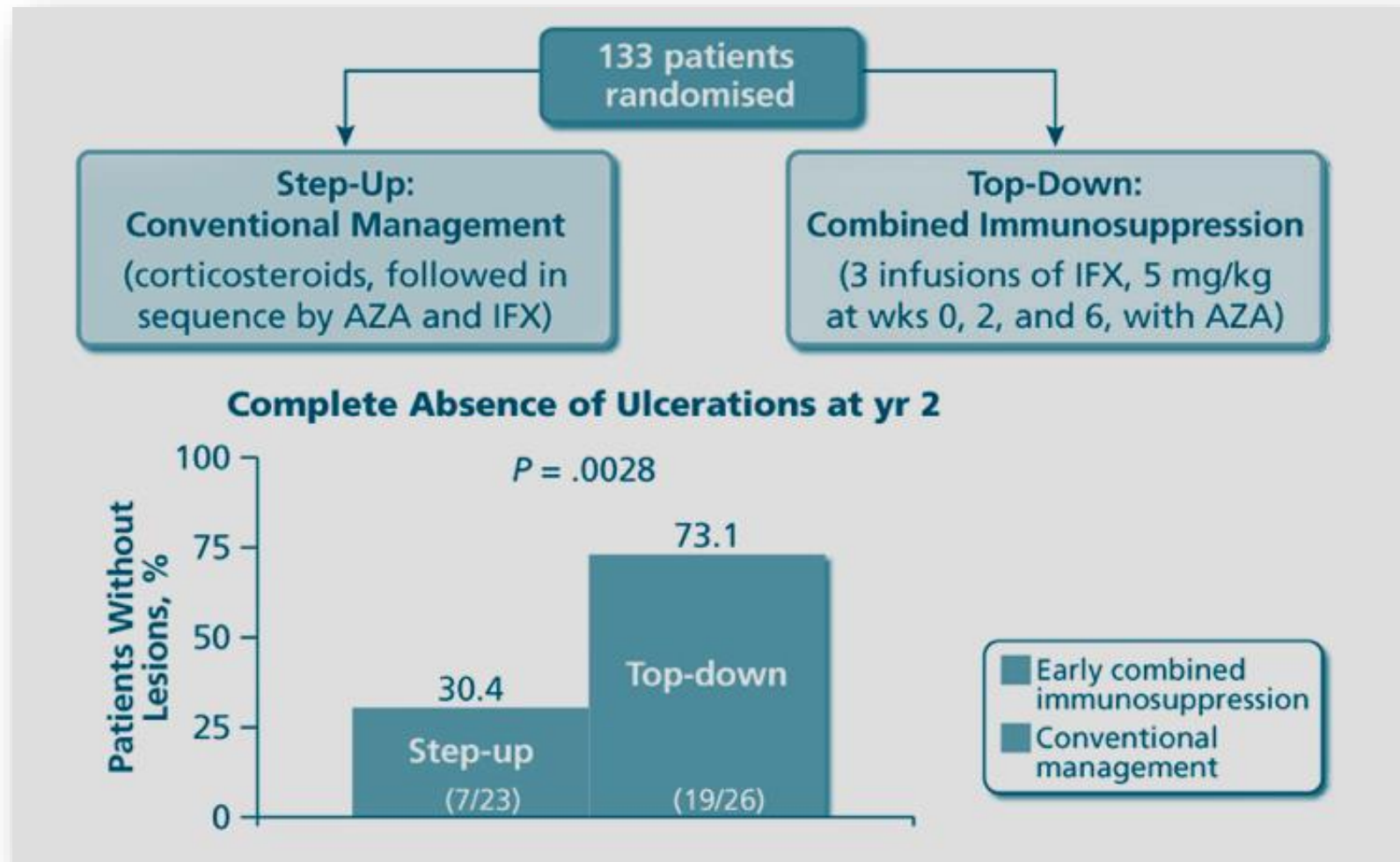
No. patients												
Early aza.	65	64	59	56	54	53	53	52	50	48	43	41
Conv. m.	67	65	63	62	58	55	54	52	49	44	43	40

Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial

Geert D'Haens, Filip Baert, Gert van Assche, Philip Caenepeel, Philippe Vergauwe, Hans Tuynman, Martine De Vos, Sander van Deventer, Larry Stitt, Allan Donner, Severine Vermeire, Frank J Van De Mierop, Jean-Charles R Coche, Janneke van der Woude, Thomas Ochsenkühn, Ad A van Bodegraven, Philippe P Van Hootegeem, Guy L Lambrecht, Fazia Mana, Paul Rutgeerts, Brian G Feagan, Daniel Hommes, for the Belgian Inflammatory Bowel Disease Research Group and the North-Holland Gut Club

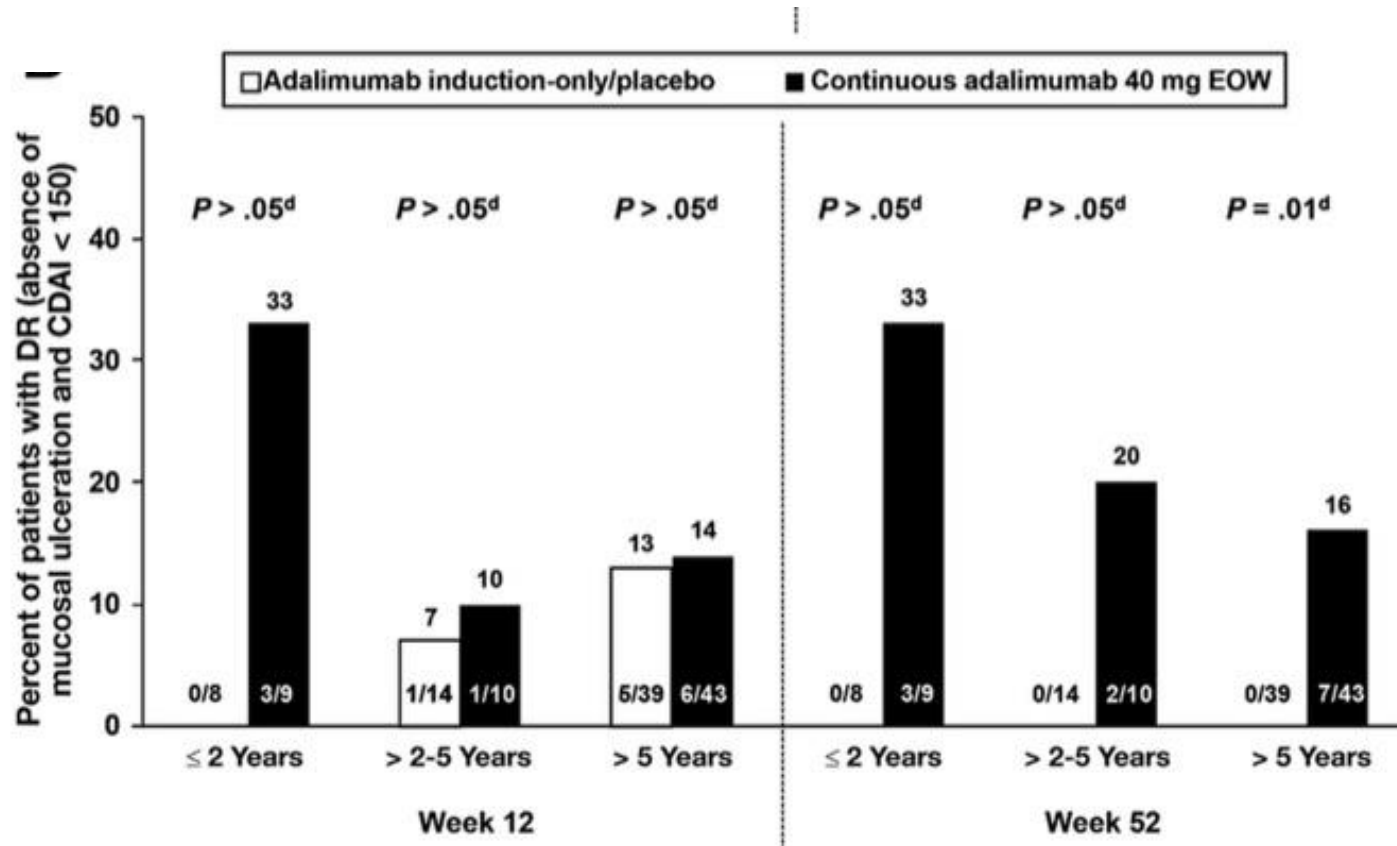


Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial



Adalimumab Induces Deep Remission in Patients With Crohn's Disease

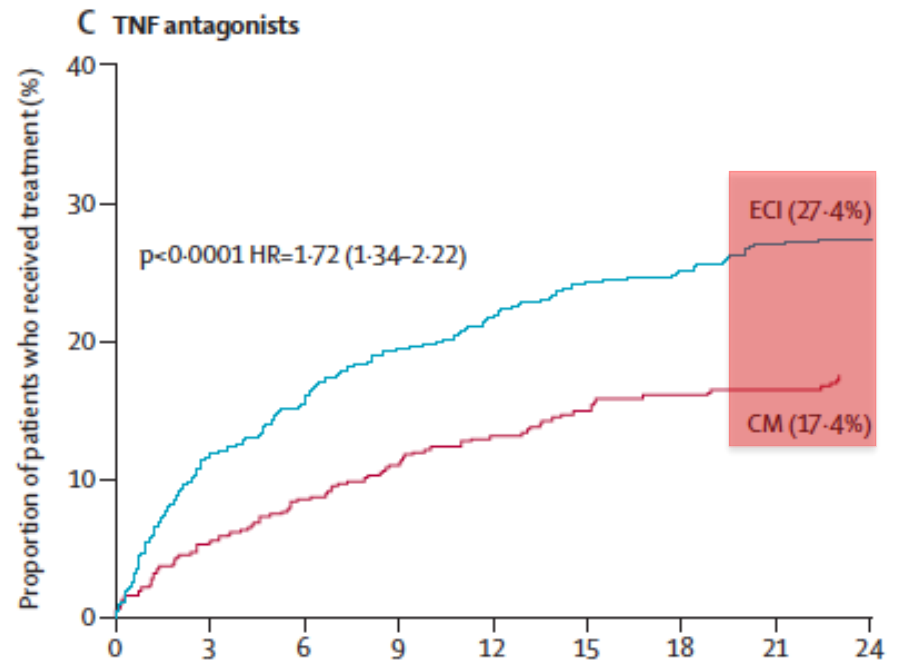
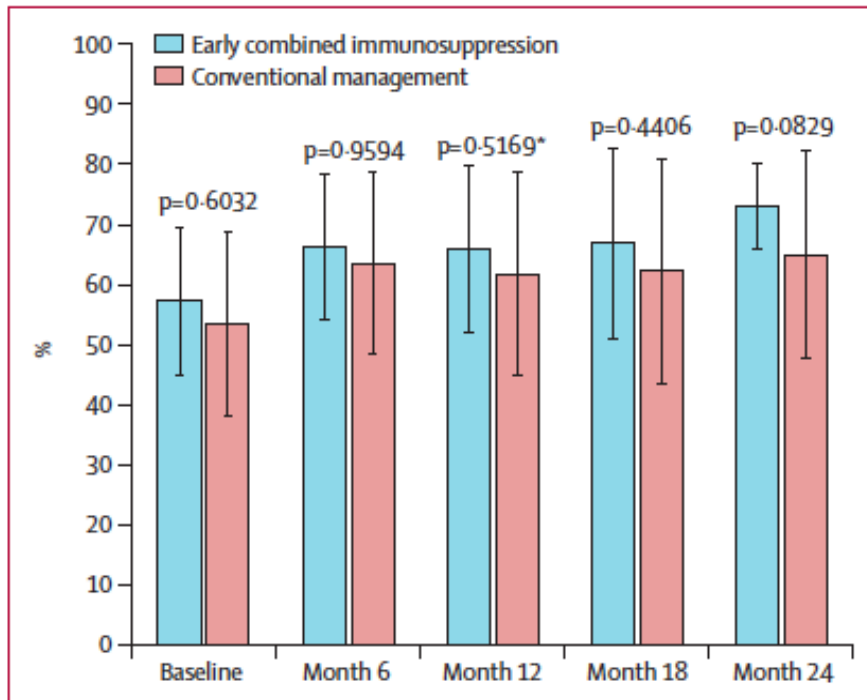
Jean-Frédéric Colombel,^{*} Paul J. Rutgeerts,[‡] William J. Sandborn,[§] Mei Yang,^{||} Anne Camez,[¶] Paul F. Pollack,^{||} Roopal B. Thakkar,^{||} Anne M. Robinson,^{||} Naijun Chen,^{||} Parvez M. Mulani,^{||} and Jingdong Chao^{||}



“Deep remission” defined as complete mucosal healing and clinical remission (CDAI <150)

Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial

STERIOD-FREE CLINICAL REMISSION



Enhanced Algorithm for Crohn's Treatment Incorporating Early Combination Therapy (REACT2)



The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our [disclaimer](#) for details.

ClinicalTrials.gov Identifier: NCT01698307

Recruitment Status ⓘ : Active, not recruiting

First Posted ⓘ : October 2, 2012

Last Update Posted ⓘ : October 23, 2018

Sponsor:

University of Western Ontario, Canada

Outcome Measures

Go to

Primary Outcome Measures ⓘ :

1. Risk of CD-related complications at one-year, measured at the practice level [Time Frame: 12 months]

CD-related complications include (1) CD-related surgeries and non-surgical CD events (such as disease flare, bowel obstruction, and bowel damage events (such as symptomatic bowel obstruction, fistula, abscess and CD related hospitalizations and 2) complications and hospitalizations related to CD medications or procedures.

Secondary Outcome Measures ⓘ :

1. Risk of CD-related complications at 6 months. [Time Frame: six months]

CD-related complications include (1) CD-related surgeries and non-surgical CD events (such as disease flare, bowel obstruction, and bowel damage events (such as symptomatic bowel obstruction, fistula, abscess and CD related hospitalizations and 2) complications and hospitalizations related to CD medications or procedures.

Other Outcome Measures:

1. Proportion of patients at one year who are in Deep Remission without disease progression [Time Frame: twelve months]

Disease progression is defined as the de novo development of strictures or fistula, the occurrence of an intra-abdominal abscess, or surgery for CD (resection, bypass, stricturoplasty).

IS EARLY TREATMENT EFFECTIVE ?

LESSON FROM COHORT STUDIES

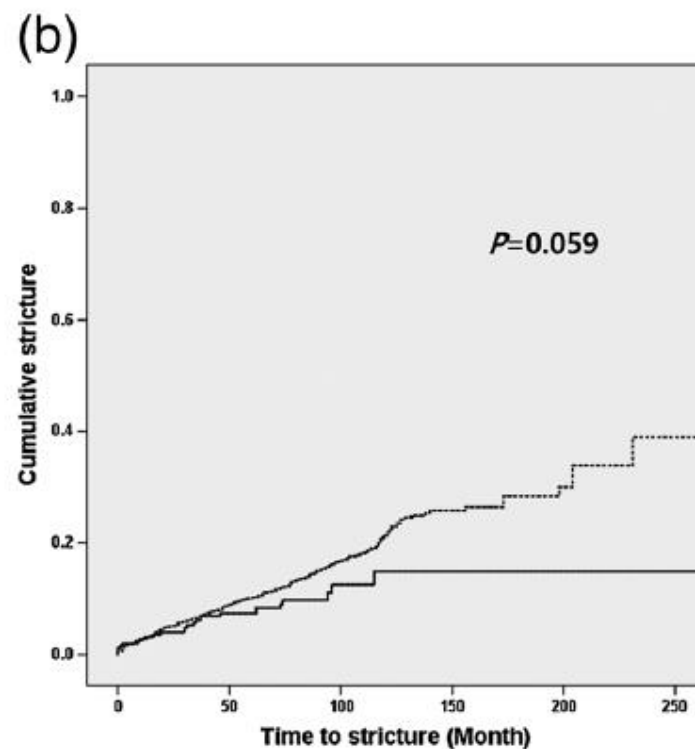
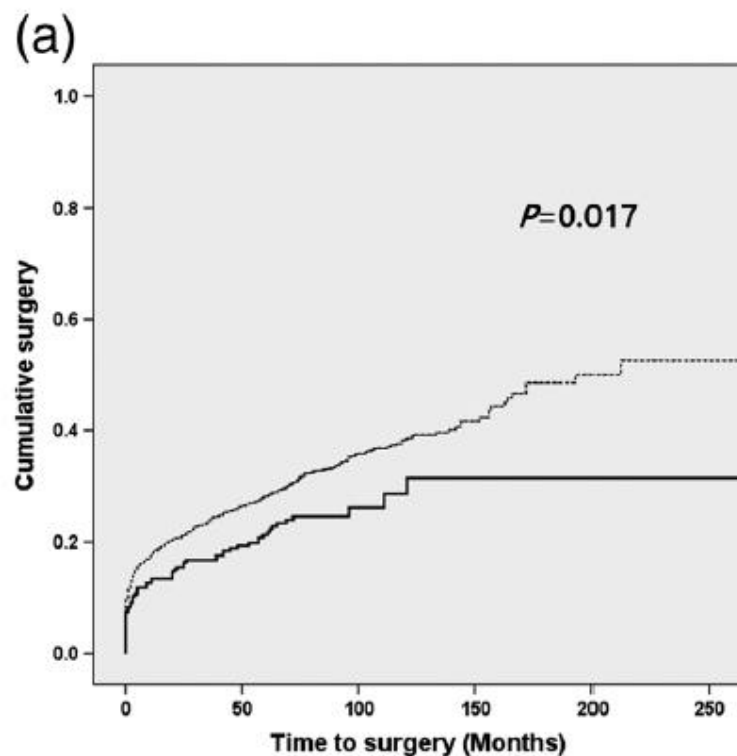
Early intervention in Crohn's disease: towards disease modification trials

Author (Year)	Study design	Intervention/control	Early CD definition	Primary outcome
Safroneeva <i>et al</i> (2015) ³⁸	Prospective observational cohort	Early use of anti-TNF and/or immunomodulators	24 months	Development of complications
Kwak <i>et al</i> (2014) ³⁹	Retrospective cohort	Early immunomodulator use versus conventional therapy	6 months in the ET group	Clinical remission
Kim <i>et al</i> (2016) ⁴¹	Retrospective study	Early immunomodulator use versus conventional therapy	6 months in the ET group	Need for surgery
Nuij <i>et al</i> (2015) ⁴⁰	Retrospective cohort	Early anti-TNF versus conventional step-up approach	≤16 months	IBD-related complications

Crohn's disease prognosis and early immunomodulator therapy: Results from the CONNECT study

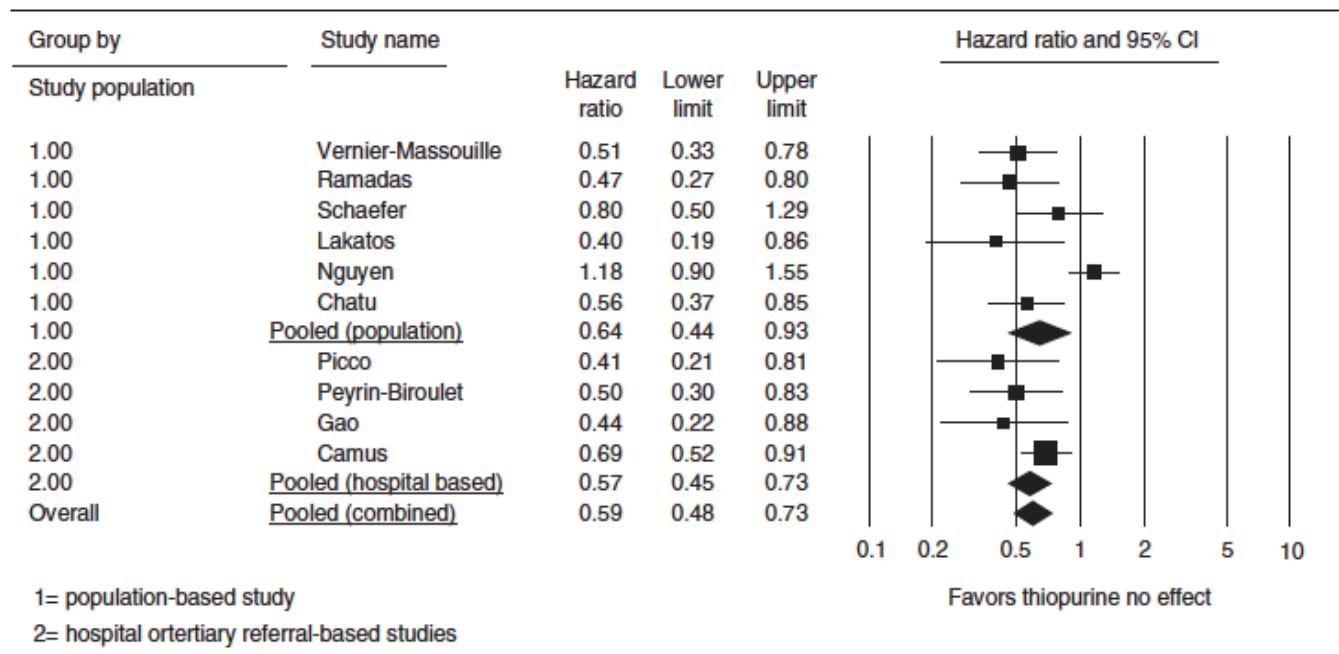
Bun Kim,^{*,1} Jae Hee Cheon,^{*} Hyun Jin Moon,^{*} Yi Rang Park,^{*} Byong Duk Ye,[†] Suk-Kyun Yang,[†] Geom Seog Seo,[‡] Byung Ik Jang,[§] You Sun Kim,[¶] Joo Sung Kim,^{**} Dong Soo Han,^{††} Young-Ho Kim,^{‡‡} and Won Ho Kim^{*}

1382 CD pts



The Role of Thiopurines in Reducing the Need for Surgical Resection in Crohn's Disease: A Systematic Review and Meta-Analysis

Sukhdev Chatu, MD¹, Venkataraman Subramanian, MD², Sonia Saxena, MD³ and Richard C.G. Pollok, FRCP, PhD¹



3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 2: Surgical Management and Special Situations

ECCO statement 8C

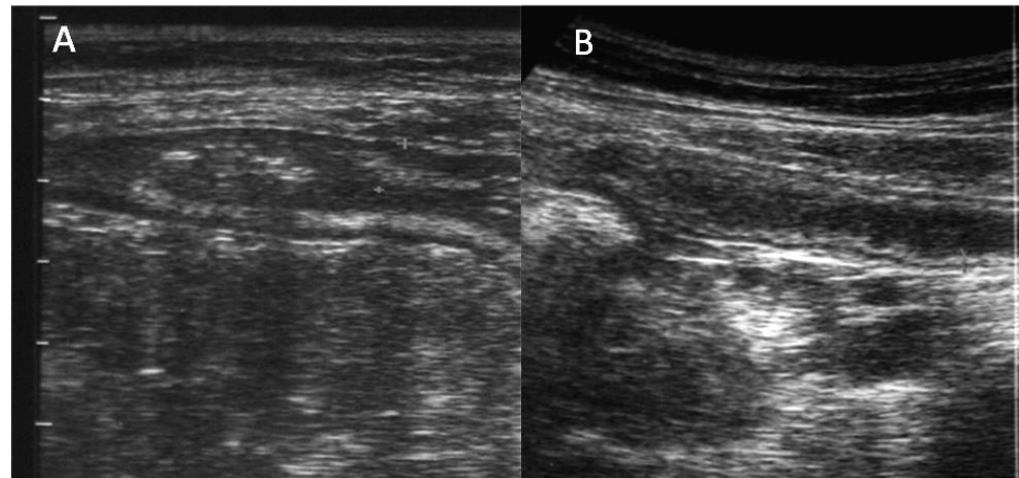
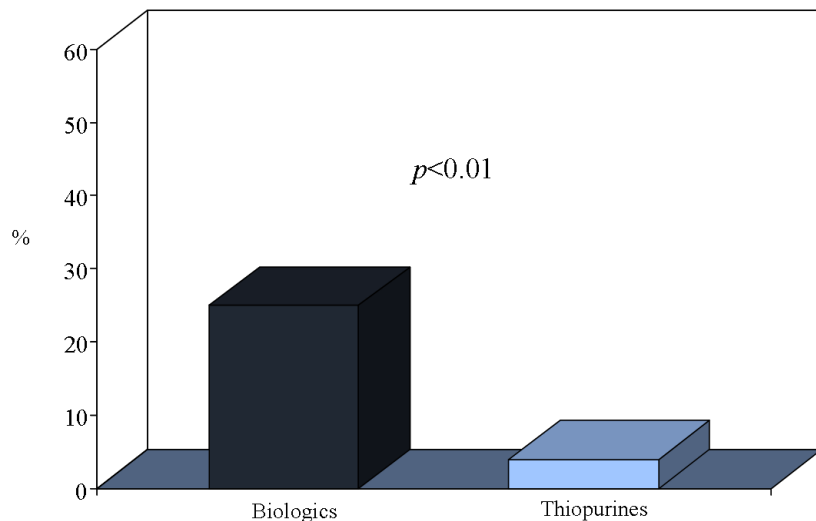
Early treatment with thiopurines [EL2] is associated with reduced risk of first surgery. Treatment with anti-TNF reduces the risk of surgery [EL2]

Transmural Healing Evaluated by Bowel Sonography in Patients with Crohn's Disease on Maintenance Treatment with Biologics

Fabiana Castiglione, Anna Testa, MD, Matilde Rea, MD, Giovanni Domenico De Palma, Maria Diaferia, MD, Dario Musto, MD, Francesca Sasso, MD, Nicola Caporaso, and Antonio Rispo, MD

Transmural Healing at 2 Years

140 CD patients



	BIOLOGICS	THIOPURINES	<i>p</i>
BWT at BS	6.0±2.8 vs 4.0±1.2*	6.2±2.5 vs 5.8±1.7^	*<0.01 ^n.s.

CONCLUSIONS:

IS THE EARLY TREATMENT OF EARLY CD REALLY EFFECTIVE ?

- **Early treatment** of **early CD** could avoid bowel damage (reducing complications, surgery and hospitalizations) BUT the evidence is not yet strong.
- At now, **early treatment** should be offered to CD patients with **prognostic factors for disabling disease** (e.g. deep ulcers, rectal CD, extensive involvement of small bowel, paediatric CD, familial aggregation ?).
- “Strategic” R.C.Ts. focused on the **early treatment of early disease** (in accordance with Paris definition) are needed to really evaluate our window of opportunity for treating CD.

GRAZIE PER L'ATTENZIONE...



...my window of opportunity...

