



THE MULTIFACETED ISSUES OF A GFD *FAILURE TO RESPOND*

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FAILURE TO RESPOND TO THE GFD

- occurs in 4-30% of adult pts
- is a very heterogeneous condition
- persistence or recurrence of malabsorptive symptoms despite at least 12 mo of strict GFD → *Non-Responsive CD*
- symptoms + villous atrophy → *Refractory CD*



"FALSE" NON-RESPONSIVE OR REFRACTORY CD

- concurrent conditions
 - IBS
 - Microscopic Colitis
 - Bacterial Overgrowth
 - Lactase Deficiency
 - Pancreatic Insufficiency
- dietary non-compliance or inadvertent gluten intake
- slow (up to 2 yrs) histological recovery after diet
- misinterpretation of the original biopsy
 - *poor sample quality*
 - *non-coeliac flat mucosa*
 - Olmesartan Enteropathy
 - Autoimmune Enteropathy
 - CVID
 - HIV Enteropathy
 - GVHD
 - Tropical sprue
 - Other drugs
 - Unclassified sprue



TWO UNCLASSIFIED SPRUE PATIENTS

	Patient 1	Patient 2
Gender	Male	Female
Age, yrs	43	39
Symptoms	Diarrhoea, weight loss	Diarrhoea, weight loss
HLA-DQ2/DQ8	Negative	Negative
EMA IgA	Negative	Negative
TTA IgA (U/ml)	1.2	0.8
Total IgA (mg/dl)	134	156
Duodenal histology	Villous atrophy (B2)	Villous atrophy (B2)
Aberrant IELs	Absent	Absent
Lamina propria B cells	Rare	Very rare
TCR-γ gene rearrangement	Polyclonal	Polyclonal
Hb (g/dl)	14.6	10.8
Faecal calprotectin (mg/kg)	47	34
Family history of CD	None	None
Treatment	Azathioprine	Budesonide



IS ADULT CD STILL WORTH A BIOPSY ?

- duodenal biopsy if properly collected, processed, and evaluated does not represent a further source of misdiagnosis
- CD may be associated with other upper GI conditions
- individuals with unsuspected CD have been diagnosed in the course of endoscopic examination
- commercially available TTA-ELISA kits may entail a very variable performance
- patients not diagnosed on histological grounds, may be less compliant to GFD
- positive serology alone would miss potential CD, the treatment and follow-up of which may differ
- without a comparison of different biopsy specimens, taken at different time points, diagnosis of unclassified, seronegative, non-responsive, refractory CD would be missed or delayed
- ➔ *novel multicentre, prospective, controlled studies are needed, involving also individuals assessed in primary and secondary care*



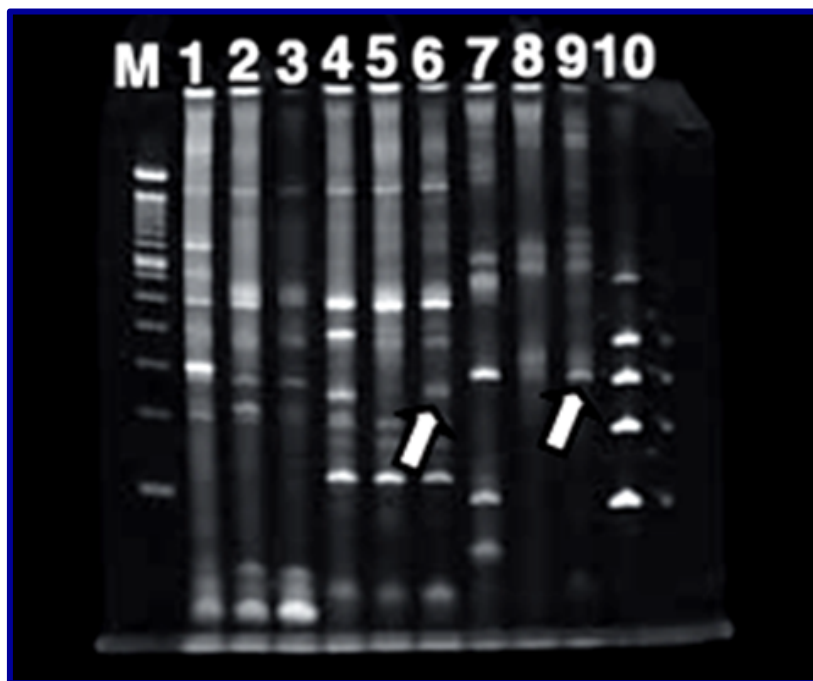
TYPE 1 AND TYPE 2 RCD

	<i>Type 1</i>	<i>Type 2</i>
Unresponsive villous atrophy	Yes	Yes
Associated autoimmune diseases	Yes	No
Aberrant T-cell phenotype (CD3 ϵ^+ , CD4 $^-$, CD8 $^-$)	$\leq 10\%$ of IELs	$> 50\%$ of IELs
Clonal TCR- γ gene rearrangement	+	++
Chromosomal abnormalities	No	Yes
HLA-DQ2 homozygosity	Uncommon	Common
Associated ulcerative jejunoileitis	Rare	Common
Response to immunosuppressants (steroids, budesonide, azathioprine, infliximab)	Yes	No
Risk of developing overt EATL	Low	37-60% within 5-yrs
Mortality rate	Slightly increased	5-yr survival $<50\%$

Lancet 2009



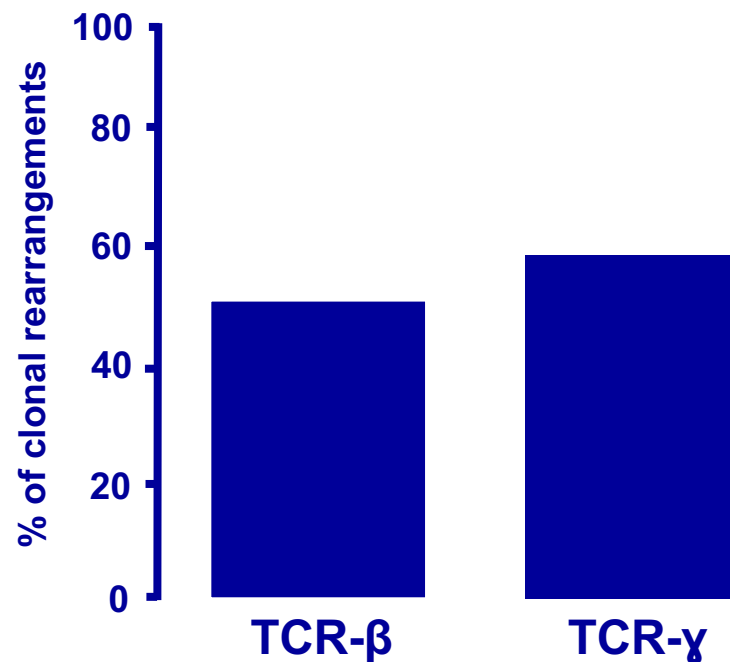
TCR- β CLONALITY IN TYPE 2 RCD



PCR analysis of V β TCR variable region increased the detection rates of monoclonal IELs (V γ only vs V γ + V β)

J Clin Gastroenterol 2012

T-cell repertoires in 9 pts

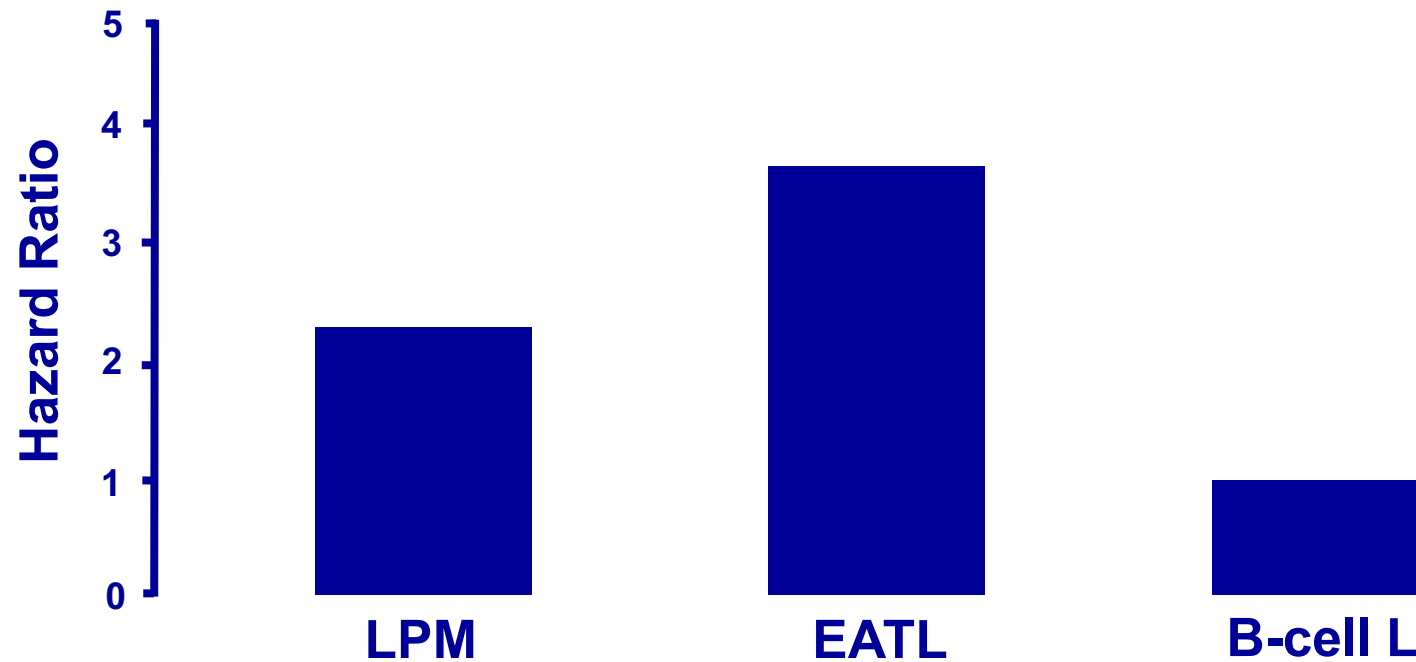


Ritter et al, Gut 2018



PERSISTENT VILLOUS ATROPHY & RISK OF LYMPHOPROLIFERATIVE MALIGNANCY (LPM) IN CD

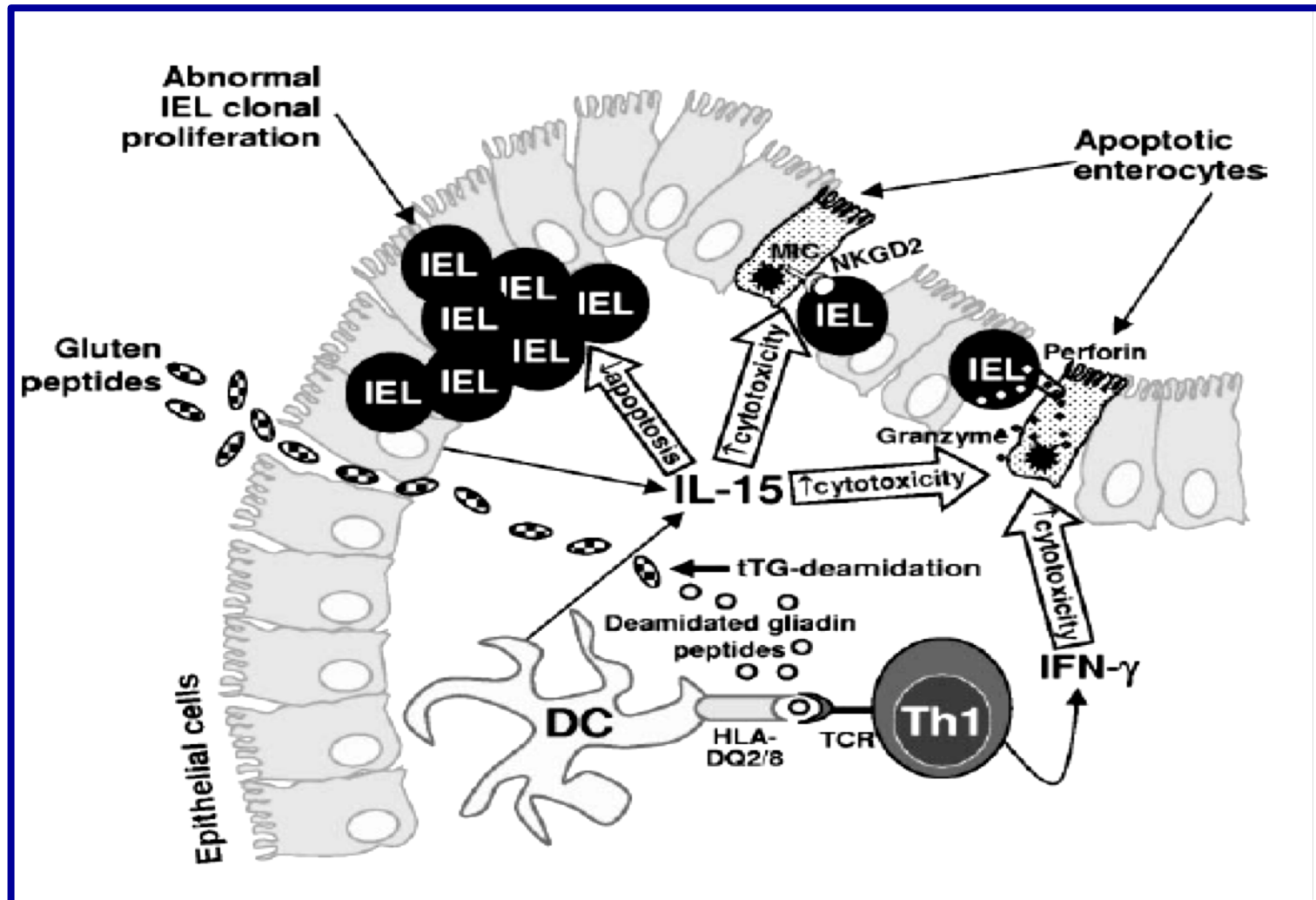
7625 adult pts with a follow-up biopsy



Lebwohl et al, *Ann Intern Med* 2013



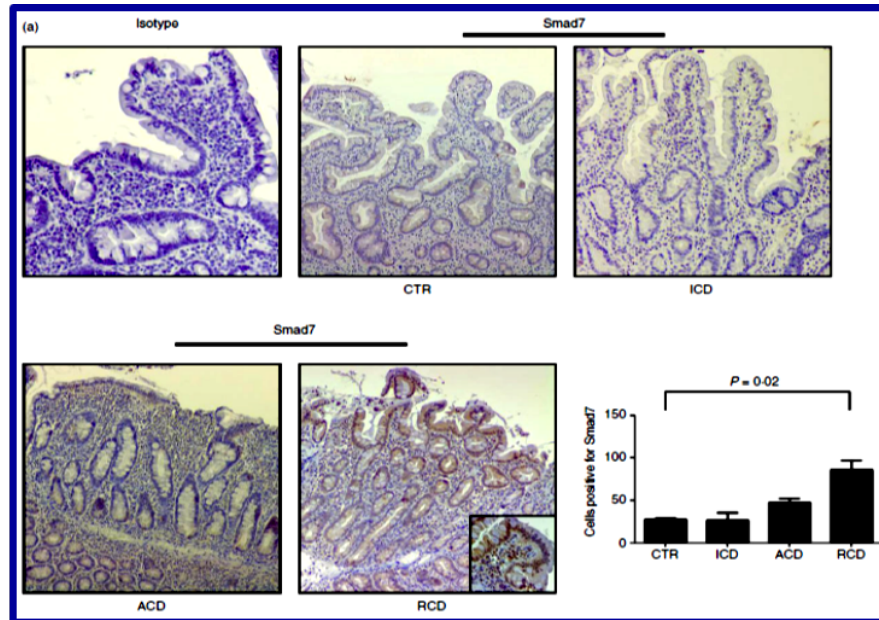
IL-15 LYMPHOMAGENIC ACTION IN CD



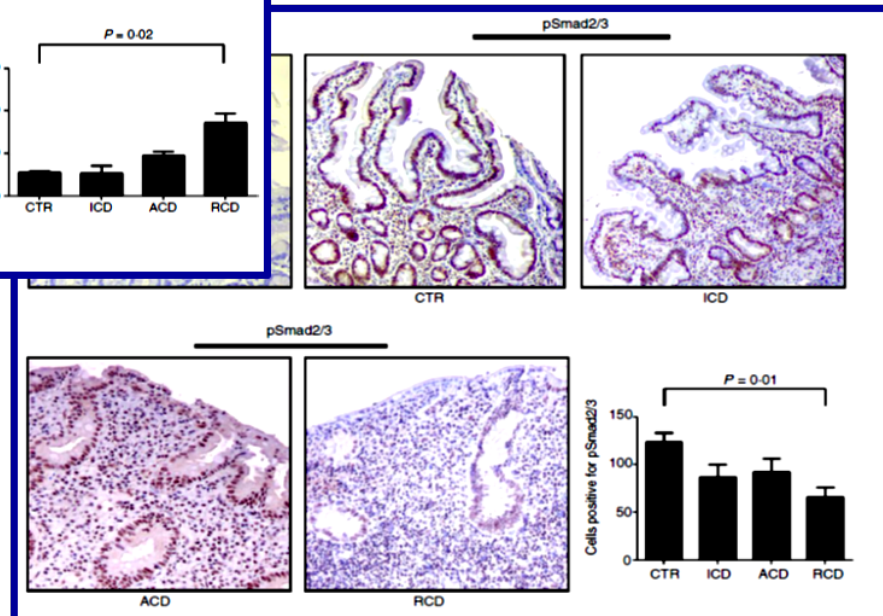


SMAD-7 SUSTAINS CK RESPONSE IN RCD

Smad-7



Smad-2/3





A SNP AT 7p14.3 PREDISPOSES TO RCD2

Logistic regression analysis indicates independent roles for HLA and non-HLA SNPs in RCDII

Risk factors	Pr(> Z)	OR	L95	U95
Univariable analysis				
Sex (female)	0.0785	0.57	0.31	1.07
<i>HLA-DQ2</i>	0.0018	2.63	1.44	4.84
rs2041570 (chr7) risk allele A	0.0004	2.25	1.44	3.54
Multivariable analysis				
Sex (female)	0.0582	0.54	0.29	1.02
<i>HLA-DQ2</i>	0.0016	2.68	1.45	4.94
rs2041570 (chr7) risk allele A	0.0003	2.35	1.48	3.73



A PHASE 2a PLACEBO-CONTROLLED TRIAL OF AMG714 IN TYPE 2 RCD

- a human IgG1k anti-IL15 MoAb
- 8 iv doses (8mg/kg) over 10 weeks
- 19 pts AMG / 9 pts PL

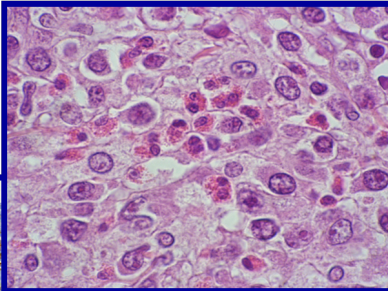
- no difference in
 - proportion of aberrant IELs (1st EP)
 - VH/CD ratio
 - overall and progression-free survival
 - incidence of adverse events
- improvement in
 - T-cell receptor clonality
 - diarrhoea
- limiting factors
 - small sample size
 - short duration



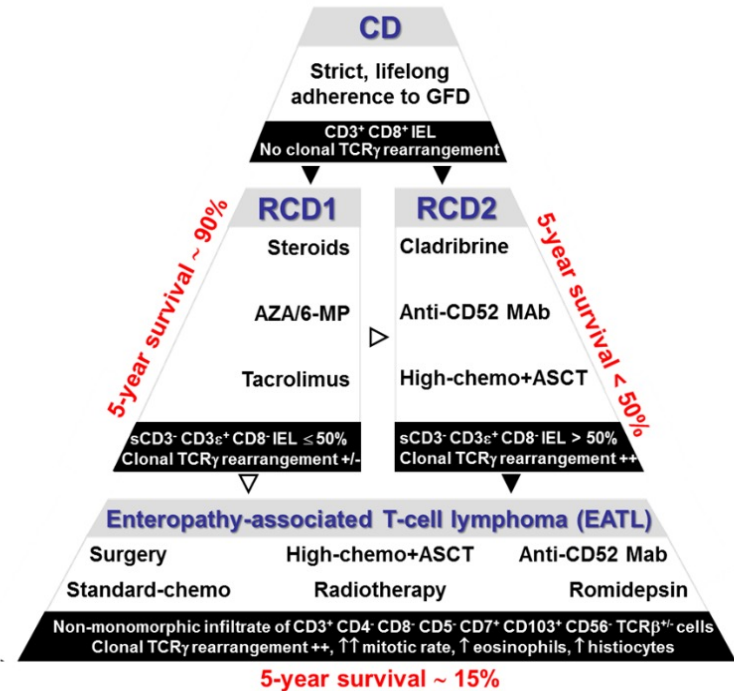
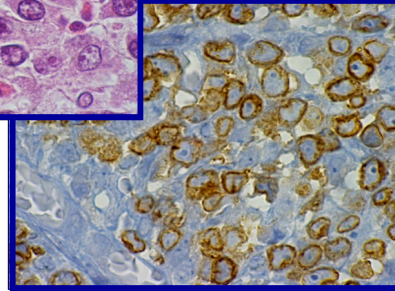
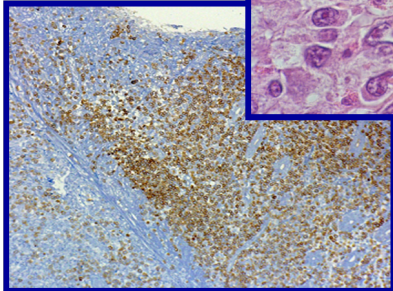
ENTEROPATHY ASSOCIATED T-CELL LYMPHOMA (EATL)

Pleomorphic medium or large-sized
tumor cells + eosinophils/histiocytes

IELs spilled
out into the
lamina propria



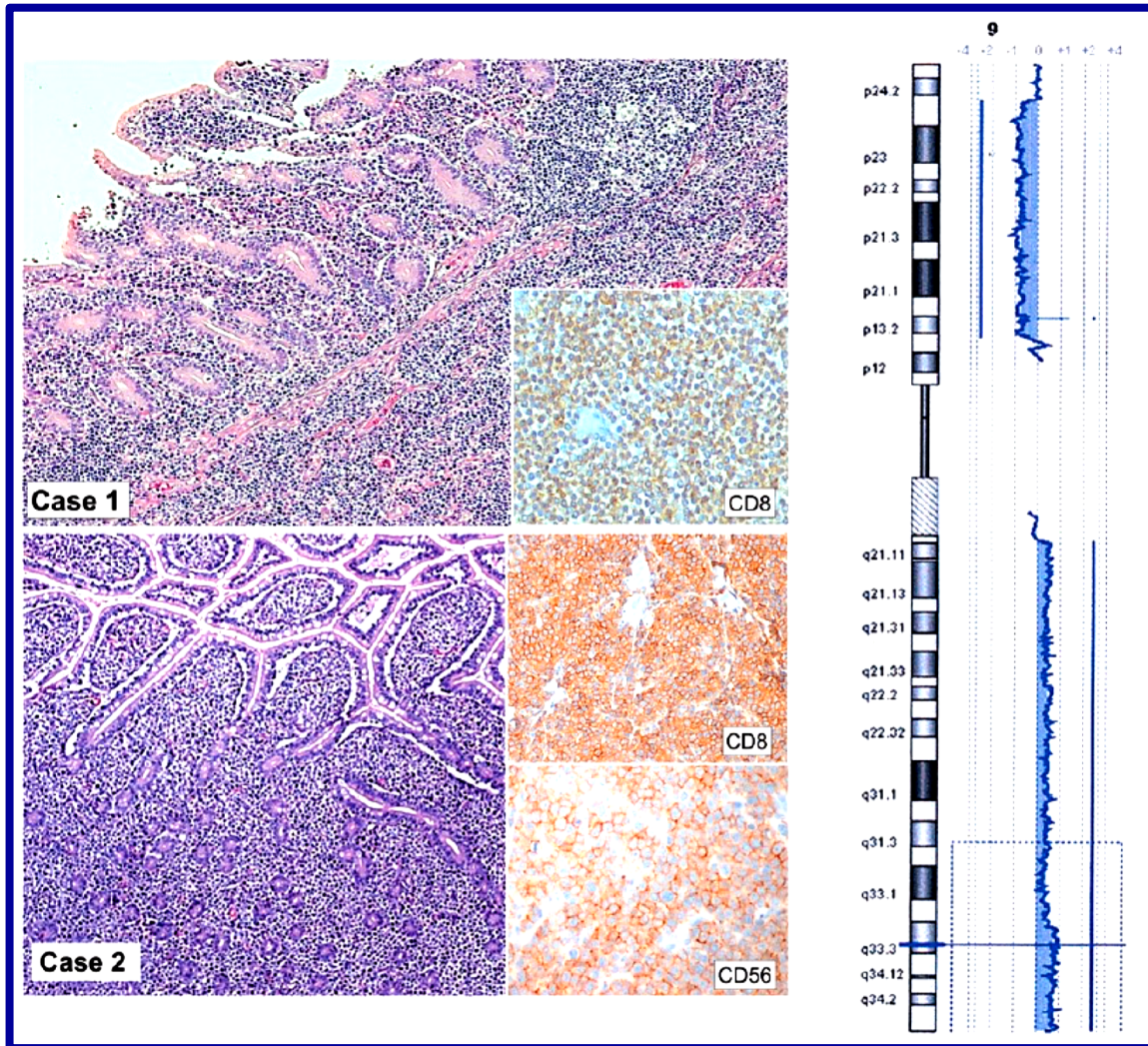
sCD3⁻ iCD3⁺ CD8⁻
CD4⁻ CD5⁻ CD103⁺
TIA1⁺ CD30^{+/-} IELs



Blood 2012



TWO CASES OF ADULT CD ASSOCIATED WITH MEITL

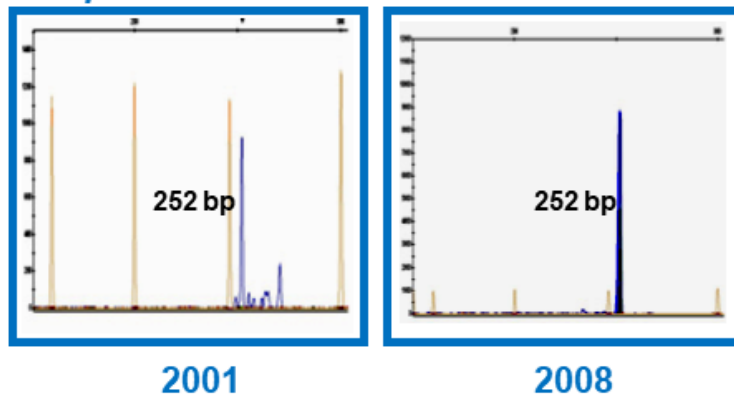




EATL IN ADULT AUTOIMMUNE ENTEROPATHY

- 53-yr old woman with a 30-yr history of refractory villous atrophy
- coeliac ABs-, anti-enterocyte ABs+
- initial response to steroids/thiopurines
- perforated jejunal lymphoma
- death from cerebral metastasis

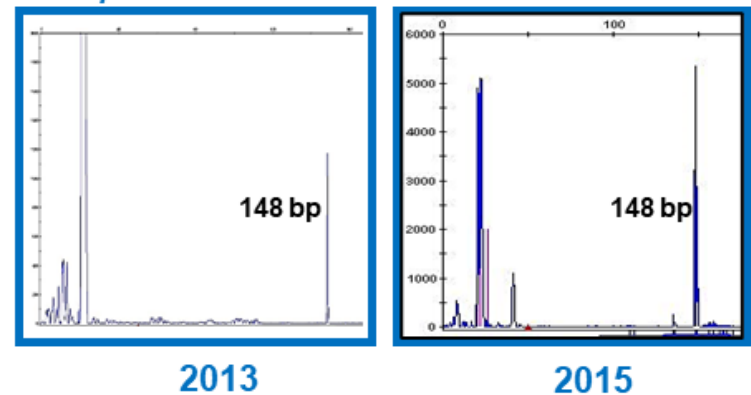
TCR β PCR



Malamut et al, *Gastroenterology* 2012

- 53-yr old woman with a 15-yr history of refractory villous atrophy
- coeliac ABs-, anti-enterocyte ABs+
- prolonged response to steroids
- obstructing jejunal lymphoma
- death from cerebellar metastasis

TCR γ PCR



Hematol Oncol 2018

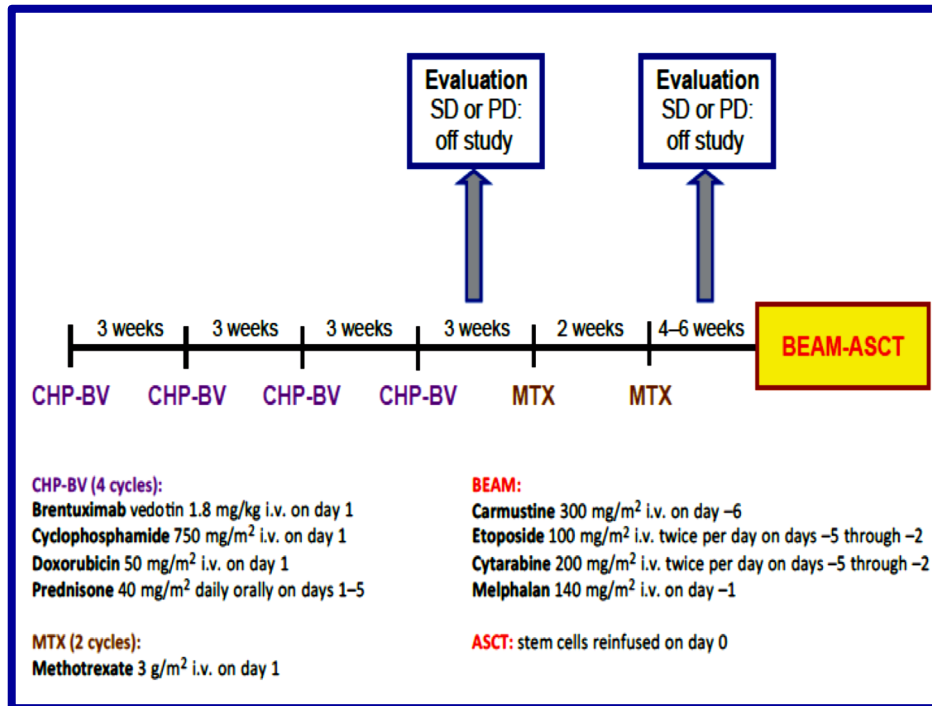


HIGH-DOSE CHEMOTHERAPY FOLLOWED BY SCT IN EATL

Study type	Reference	No. transplanted	No. evaluable	Debulking chemotherapy	Conditioning treatment	Complete response	Median survival, mo (range)
Retrospective	16	2	2	PEACE-BOM	BEAM	2	31 (2-64)
Retrospective	69	1	1	EPOCH-ICE	MPH-FARA	1	11
Retrospective	72	2	2	CHOP, MACOP-B	BEAM, BEAM-like	NG	NG
Retrospective	70	1	1	CHOP-ESHAP	MCVC	0	8
Retrospective	66	6	6	IVE-HDMTX	BEAM	5	40 (3-52)
Retrospective	71	1	1	CHOP	BEAM	1	18
Retrospective	68	4	4	CHOP	BEAM or MPH-FARA	1	8 (2-34)
Retrospective	65	5	5	CHOP	BEAM, BEAM-like	NG	2 (0.5-14)
Retrospective	74	1	1	CHOP	BEAM	1	24
Retrospective	73	2	0	PACB-IVAM-HAM	BEAM	1	NG
Prospective	67	5	0	CHOP + DACMEMP (or PAEM)	TBI + HDCTX	NG	NG
Prospective	64	14	14	CHOP-IVE/MTX	TBI + HDMPH or BEAM	10	60% at 5 y (1-140+)
Prospective	75 (RCD)	13	13		MPH-FARA	5	66% at 4 y (10-67)

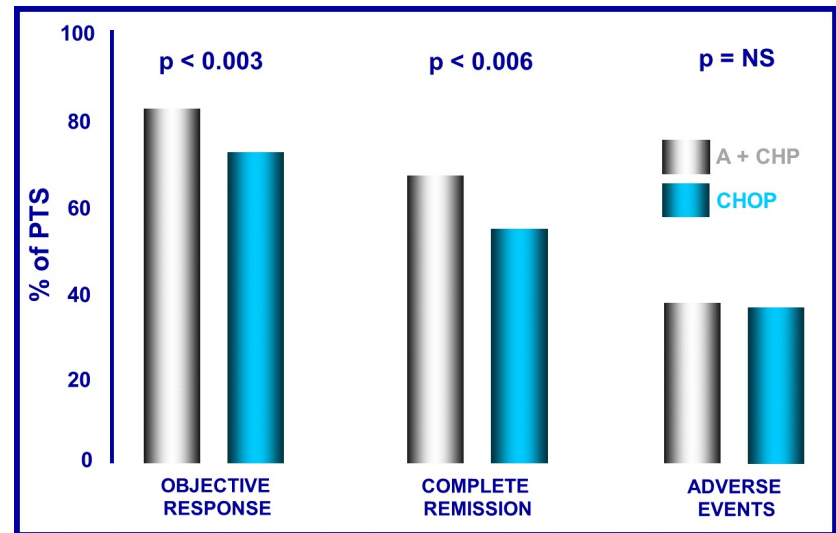


PHASE II TRIAL OF BRENTUXIMAB VEDOTIN (MMAE-CONJUGATED) AND CHP FOLLOWED BY ASCT AS FRONTLINE TREATMENT IN EATL



Nijeboer et al, *Dig Dis* 2015

Brentuximab Vedotin for CD30+ peripheral lymphoma

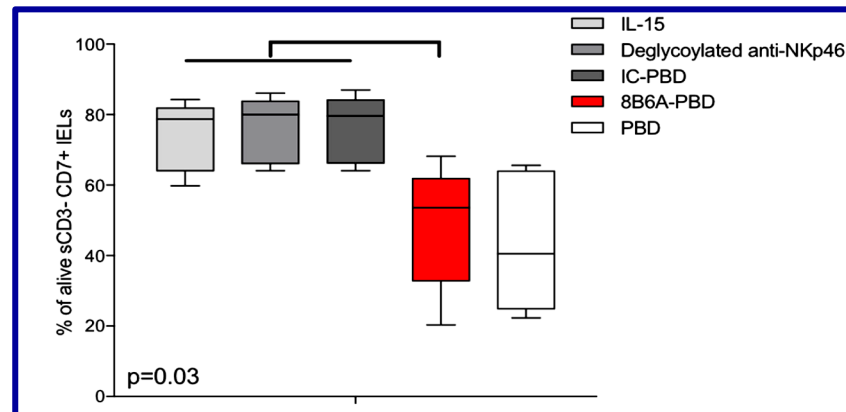
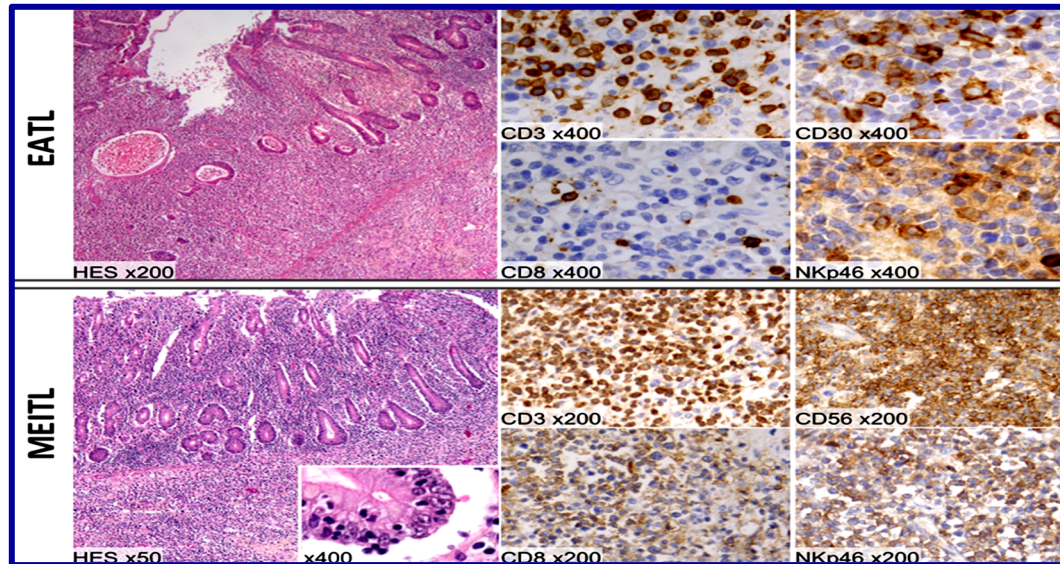


Horwitz et al, *Lancet* 2018



NKp46 – A BIOMARKER & THERAPEUTIC TARGET IN GI T-CELL LYMPHOMA

NKp46 is a member of the natural cytotoxicity receptor family specific to NK and innate lymphoid cells





SERONEGATIVE (IgA & IgG) COELIAC DISEASE

- diagnosis relies on the histological response to a GFD after other forms of villous atrophy have been excluded
- family history and DQ2/DQ8 positivity are supportive criteria
- possible causes include concomitant immunodeficiency, GFD prior to testing, immunosuppressants, > mucosal avidity due to complications
- uncommon condition (2% of CD population, ~30% of seronegative villous atrophy)
- poor prognosis

Eur J Gastroenterol Hepatol 2017
Curr Opin Gastroenterol 2018