



Wenn Mesalazin und Steroide nicht mehr funktionieren -
Azathioprin oder Biologika / „Small Molecules“ als erste Option?

Pro Biologika / „Small Molecules“

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Gastroenterologie, Hepatologie, Endokrinologie, Diabetologie und Infektiologie

22. Gesprächsforum gastroenterologische Praxis 2022
Frankfurt, 20. Mai 2022

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Potentielle Interessenkonflikte

Beratertätigkeit

Abbvie, Amgen, Biogen, Bristol-Myers Squibb, Ewopharma, Galapagos, Janssen-Cilag, MSD Sharp & Dohme, Norgine, Pfizer, Shield Therapeutics und Takeda

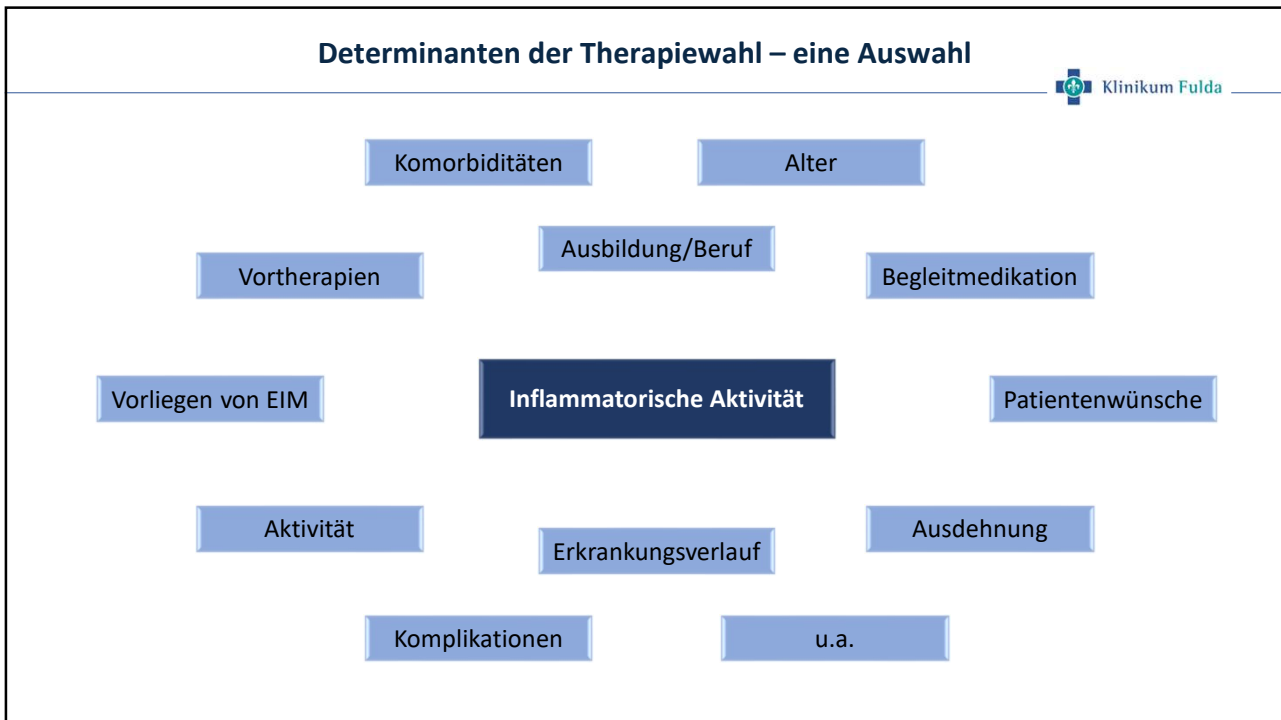
Vortragshonorare, Reiseunterstützung

Abbvie, Berlin Chemie, Biogen, CED Service, Ewopharma, Dr. Falk, Galapagos, Janssen-Cilag, med update, Merckle, MSD Sharp & Dohme, Norgine, Novartis, Olympus, Pentax, Pfizer, Shire, Shield Therapeutics und Takeda

Forschungsförderung


Abbvie, Olympus und Pentax


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Therapeutische Optionen nach Mesalazin / Steroiden







Infliximab **Adalimumab**
Golimumab **Tofacitinib**
Ozanimod
Vedolizumab **Filgotinib**
Ustekinumab
Azathioprin

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Agenda



Induktionstherapie
Erhaltungstherapie
Nebenwirkungen
Besondere Situationen
Patientenperspektive

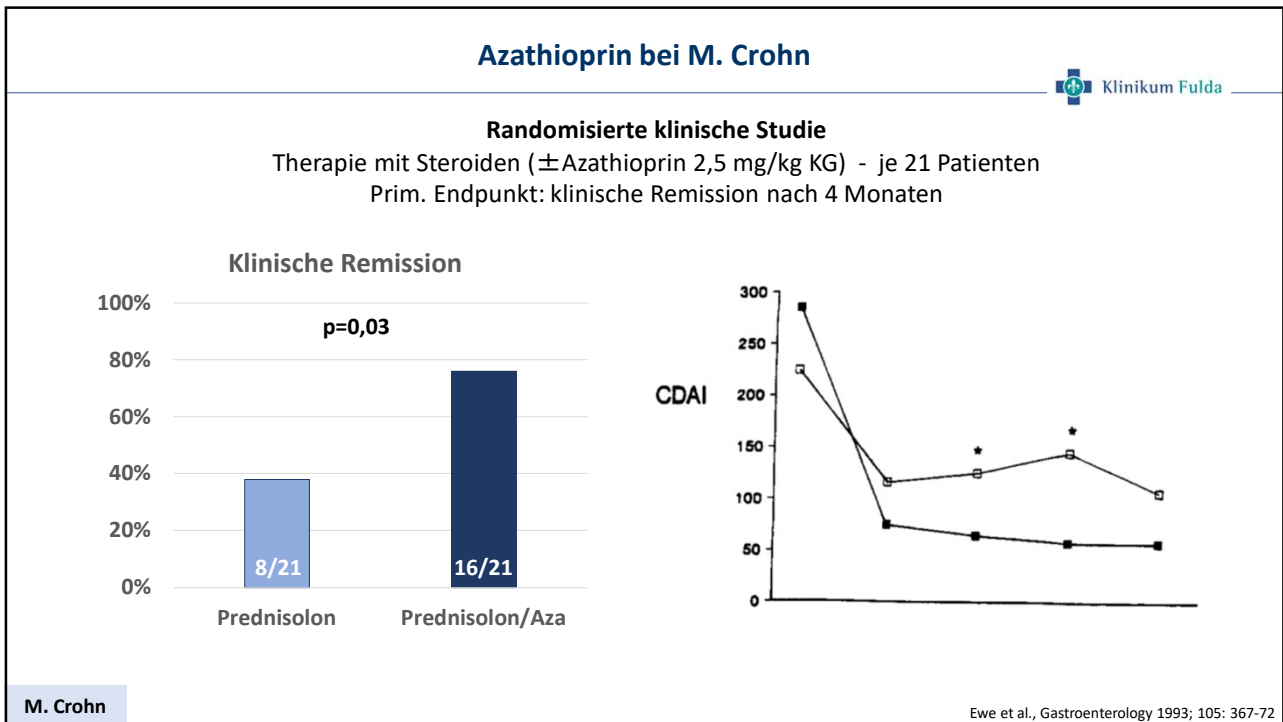
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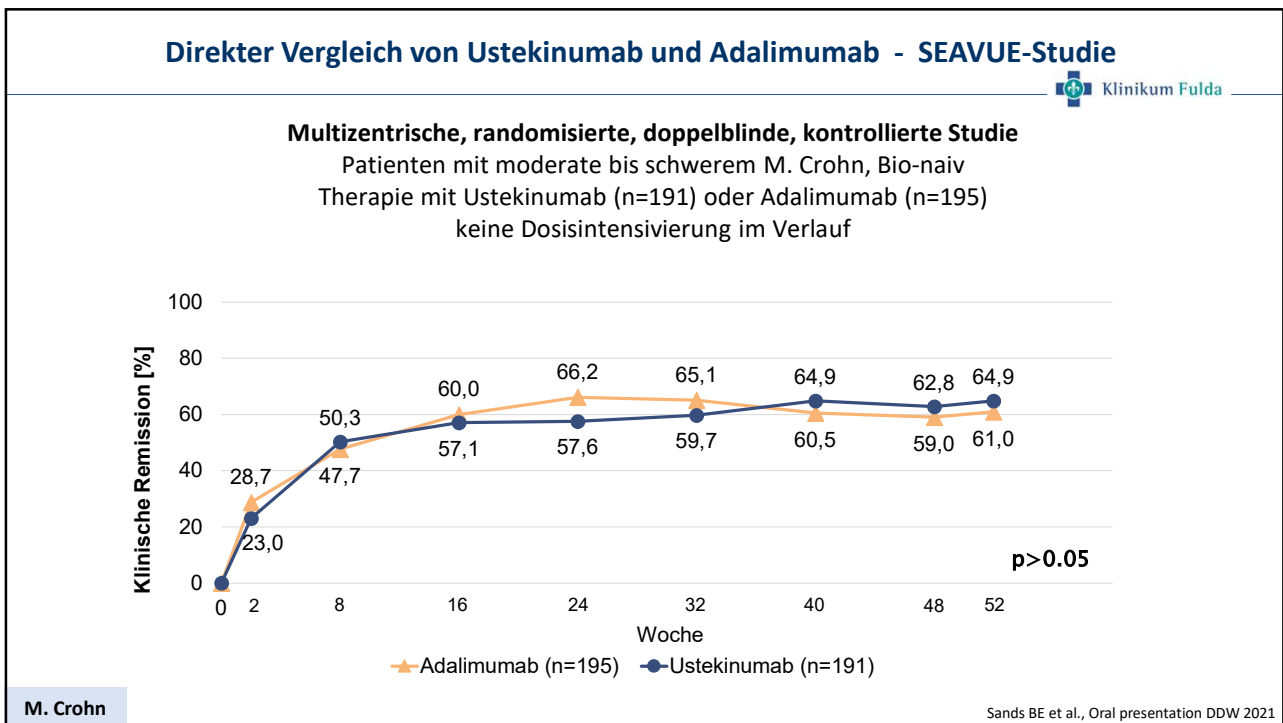


Induktionstherapie
Erhaltungstherapie
Nebenwirkungen
Besondere Situationen
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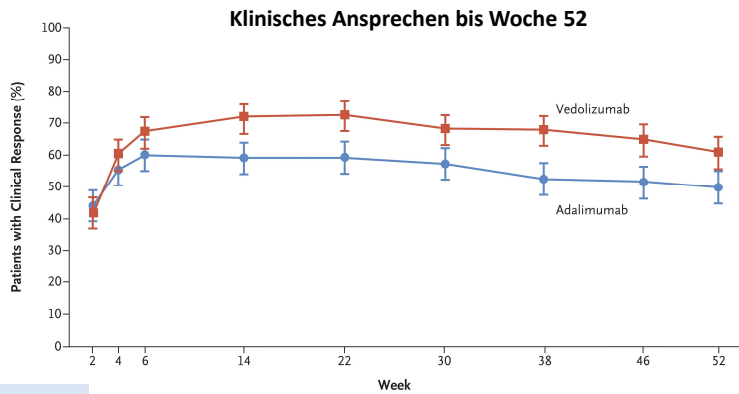


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VARITY - Vergleich von Vedolizumab und Adalimumab bei C. ulcerosa



Randomisierte klinische Studie - Phase 3b
 Vedolizumab (n=383) versus Adalimumab (n=386)
 52 Wochen - 330 Zentren - 37 Länder
 Primärer Endpunkt: Remission zu Woche 52



	AE gesamt
Vedolizumab	62,7%
Adalimumab	69,2%

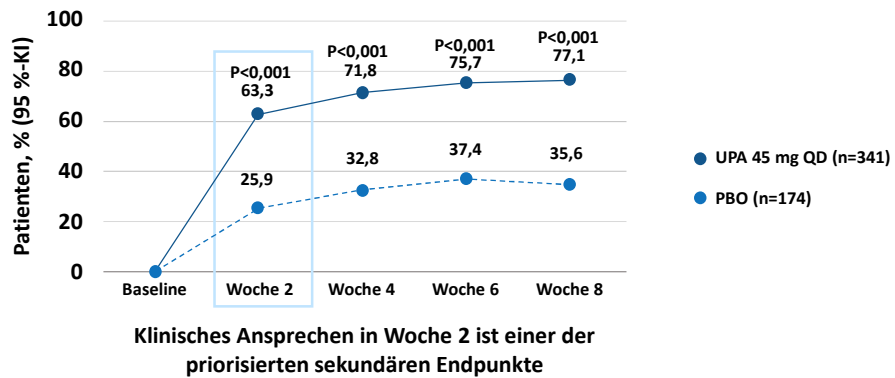
C. ulcerosa

Sands et al., N Engl J Med 2019; 381: 1215-26

Upadacitinib bei CU - Geschwindigkeit des Ansprechens



RCT - Phase 3 - U-ACCOMPLISH
 Mittelschwere bis schwere C. ulcerosa

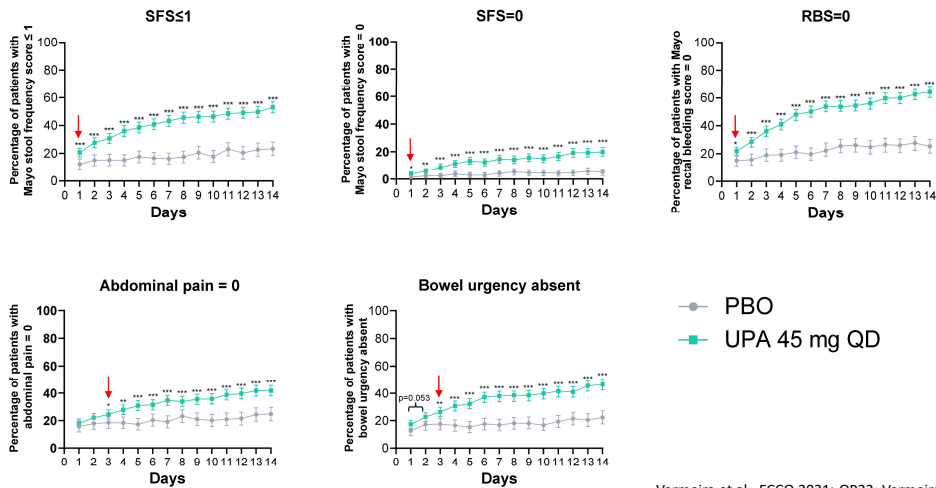


C. ulcerosa

Vermeire et al., ECCO 2021: OP23; Vermeire et al.; ECCO 2022: DOP38

Upadacitinib bei CU - Geschwindigkeit des Ansprechens

RCT - Phase 3 - U-ACCOMPLISH Mittelschwere bis schwere C. ulcerosa

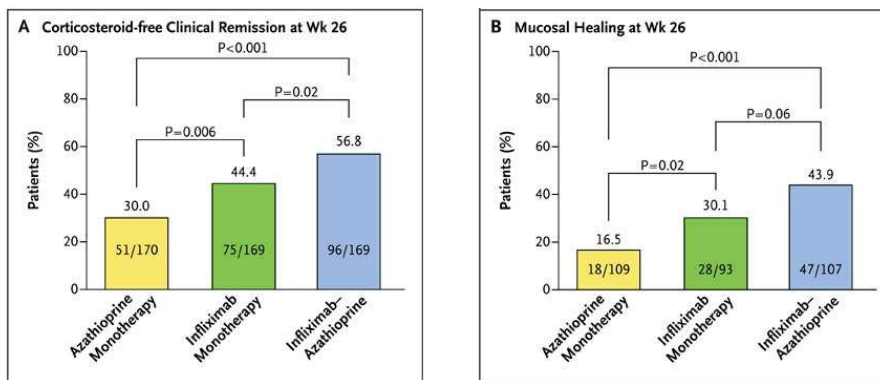


Vermeire et al., ECCO 2021: OP23; Vermeire et al.; ECCO 2022: DOP38

C. ulcerosa

SONIC - Remission und Mukosaheilung mit Infliximab plus Azathioprin

Randomisierte kontrollierte Studie 508 Patienten - naiv bzgl. IS und anti-TNF-Ak



Woche 30	IFX	IFX / Aza
Ak gegen IFX	15/103 (14,6%)	1/116 (0,9%)
Talspiegel	1,6 µg/ml	3,5 µg/ml

M. Crohn

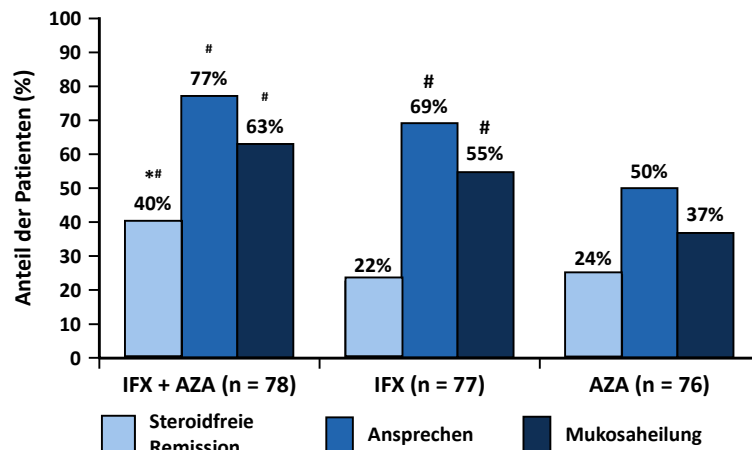
Colombel et al., NEJM 2010; 362: 1383-95

UC-SUCCESS: Kombinationstherapie von Infliximab und Azathioprin



Randomisierte, kontrollierte Studie

239 Patienten mit moderater bis schwerer C. ulcerosa
 Infliximab 5 mg/kgKG oder Azathioprin 2,5 mg/kg KG oder Kombinationstherapie
 Primärer Endpunkt: steroidfreie Remission zu Woche 16



Panaccione et al., Gastroenterology 2014; 146: 392-400.e3

C. ulcerosa

M. Crohn: Remissionsinduktion mittels Azathioprin/MP vs. Placebo



Cochrane Meta-Analyse 11 Studien - 1.211 Patienten

Outcomes	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Klinische Remission	RR 1.23 (0.97 to 1.55)	380 (5 studies)	⊕⊕⊕○ Moderate ²	
Klinisches Ansprechen	RR 1.26 (0.98 to 1.62)	434 (8 studies)	⊕⊕⊕○ Moderate ³	
Fistel-Ansprechen	RR 2.00 (0.67 to 5.93)	18 (3 studies)	⊕⊕○○ Low ⁴	
Steroideinsparung	RR 1.34 (1.02 to 1.77)	143 (4 studies)	⊕⊕⊕○ Moderate ⁵	
Abbruch wegen AE	RR 1.70 (0.94 to 3.08)	510 (8 studies)	⊕⊕⊕○ Moderate ⁶	
SAE	RR 2.57 (0.92 to 7.13)	216 (2 studies)	⊕⊕○○ Low ⁷	

M. Crohn

Chande et al., Cochrane Database Syst Rev. 2016 Oct 26;10(10):CD000545

Effektivität von Immunsuppressiva und Biologika – Remissionsinduktion



Paarweiser Vergleich und Netzwerk-Metaanalyse
39 Studien - MTX, Aza/MP, IFX, ADA, CTZ, VDZ, Combo-Therapie

Vgl. zu Aza/MP	OR	CI	Wahrscheinlichkeit der Überlegenheit
MTX	1,3	0,49-2,9	71%
Certolizumab	1,1	0,58-2,0	63%
Infliximab	2,3	1,3-5,0	>99%
Adalimumab	2,4	1,0-4,9	98%
Infliximab / Aza	3,4	1,9-6,3	>99%
Infliximab / MTX	2,1	0,67-7,9	90%
Vedolizumab	1,6	0,78-3,2	91%

M. Crohn

Hazlewood et al., Gastroenterology 2015; 148: 344-54

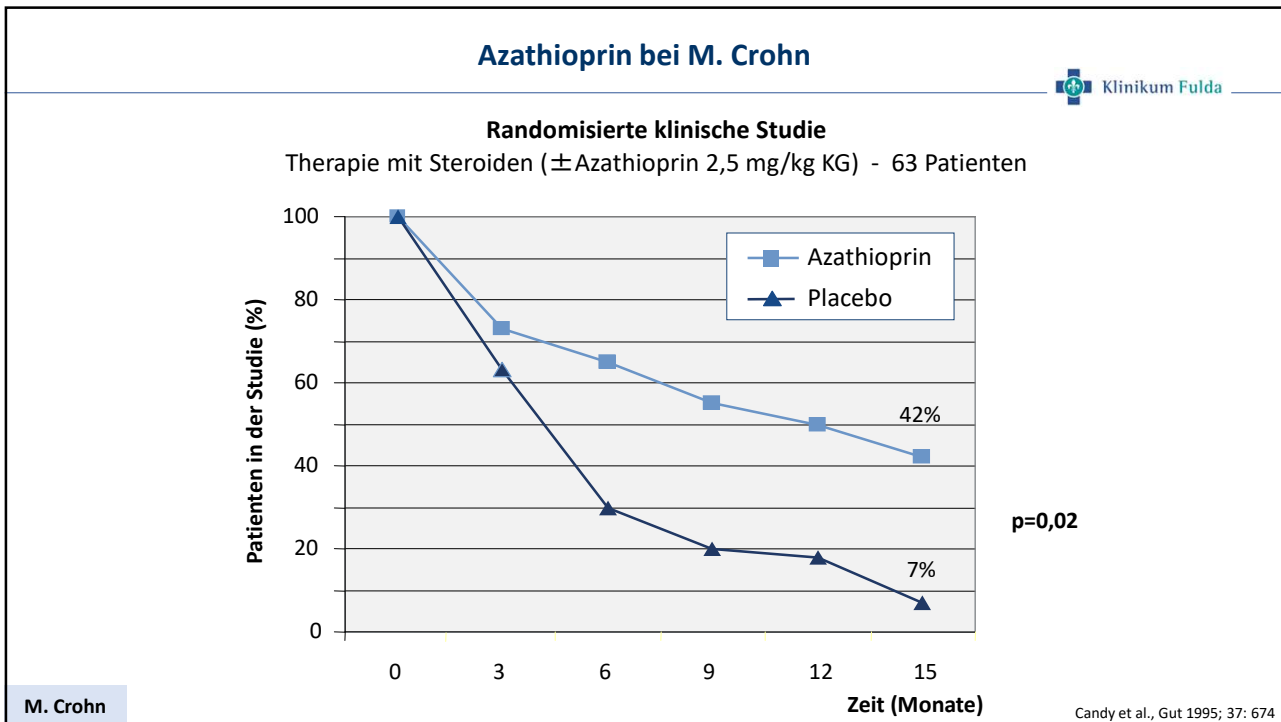
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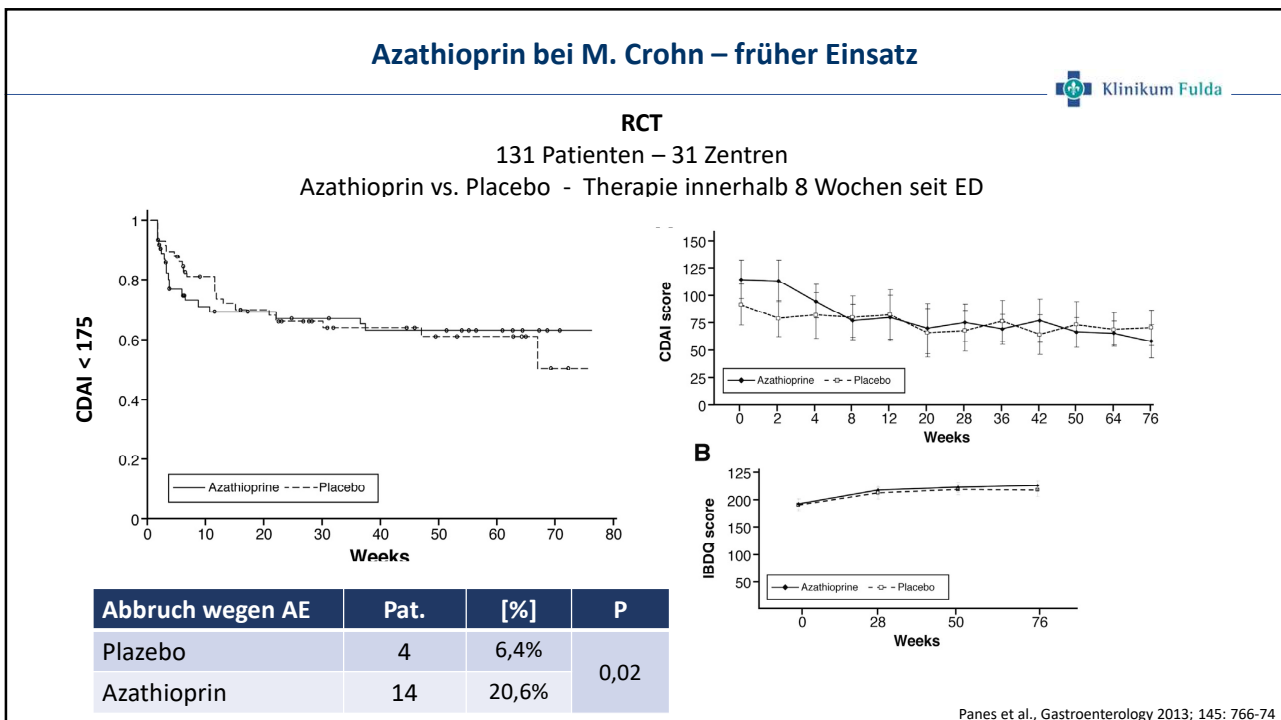


Induktionstherapie
Erhaltungstherapie
 Nebenwirkungen
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 Patientenperspektive

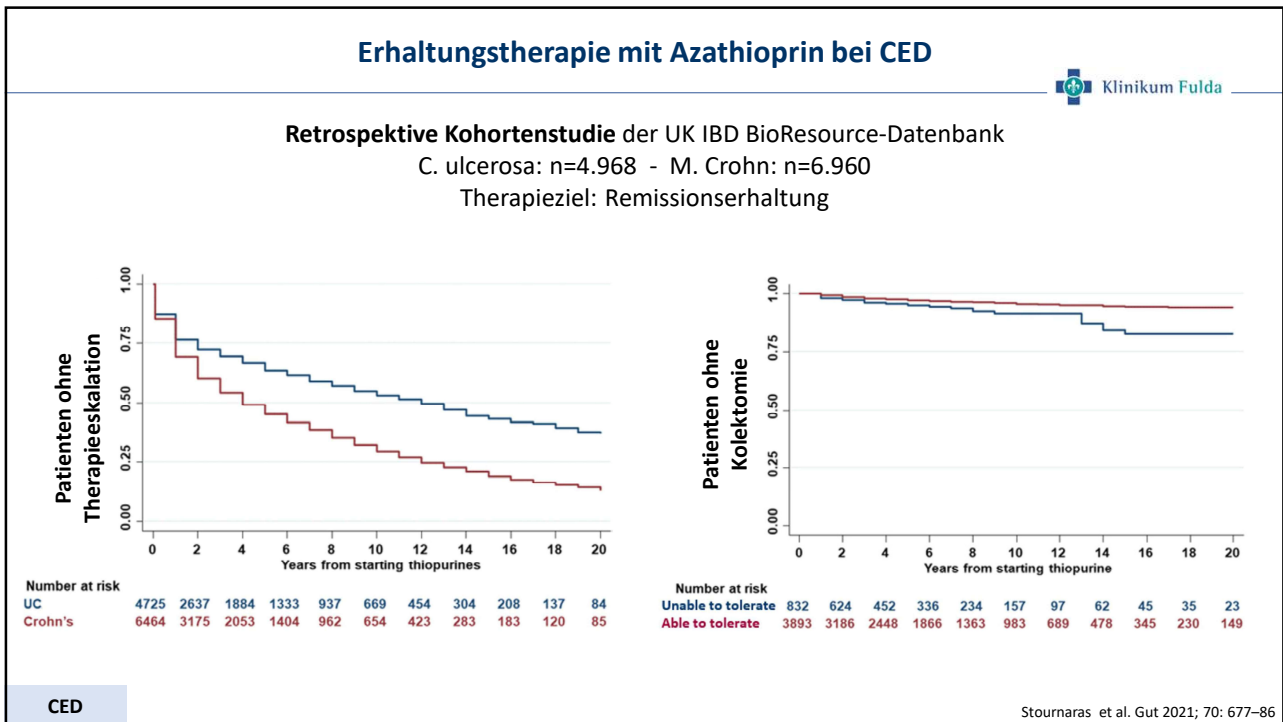
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Metaanalyse zur Remissionserhaltung mittels Azathioprin/MP vs. Placebo



Cochrane Review
 11 Studien – 881 Patienten

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size	
1 Maintenance of remission	7	532	Risk Ratio (M-H, Fixed, 95% CI)	1,25 [1,11, 1,42]	
Outcome	Studien	Patienten	RR	CI	
Remissions- erhaltung	Aza 2,5 mg/kg	3	213	1,35	1,08-1,68
	Aza 2 mg/kg	4	164	1,33	1,1-1,61
	Aza 1 mg/kg	1	155	1,06	0,84-1,34
AE	6	359	1,29	1,02-1,64	
Abbruch wg. AE	7	661	3,12	1,59-6,09	
SAE	4	556	2,45	1,22-4,9	
Steroideinsparung	2	30	1,59	0,97-2,61	
5 Serious adverse events	4	556	Risk Ratio (M-H, Fixed, 95% CI)	2,45 [1,22, 4,90]	
6 Steroid sparing effect	2	30	Risk Ratio (M-H, Fixed, 95% CI)	1,59 [0,97, 2,61]	

M. Crohn

Chande et al., Cochrane Database of Systematic Reviews 2015, Issue 10. Art. No.: CD000067.

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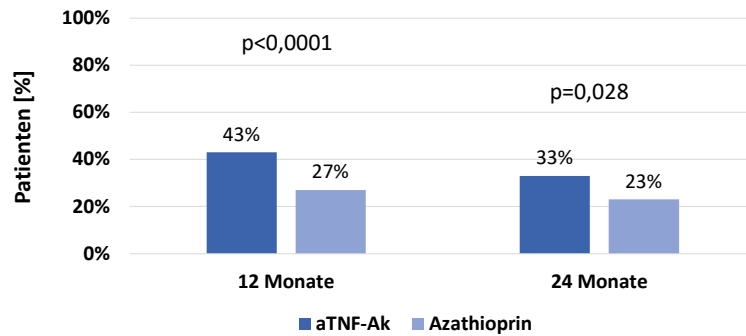
Reduktion der Steroidtherapie - Azathioprin vs. aTNF-Antikörper



Kohortenstudie

Truven Health MarketScan Research Databases
 2.900 Patienten mit Steroidtherapie während 6 Monaten vor
 Therapie mit aTNF-Ak (n=1.819) oder Azathioprin (n=1.081)

Steroideinsparung [%]



M. Crohn

Kane et al., Curr Med Res Opin 2014; 30: 1821-7

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Metaanalyse zur Remissionserhaltung mittels Azathioprin/MP vs. Placebo



Cochrane Review

7 Studien – 302 Patienten

Outcomes	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Remission nicht erhalten	RR 0.68 (0.54 to 0.86)	232 (4 studies)	⊕⊕○○ low 2,3	
AE	RR 2.51 (0.82 to 7.74)	232 (4 studies)	⊕○○○ very low 2,4	
Abbruch wegen AE	RR 7.00 (0.38 to 128.87)	152 (3 studies)	⊕○○○ very low 2,5	

C. ulcerosa

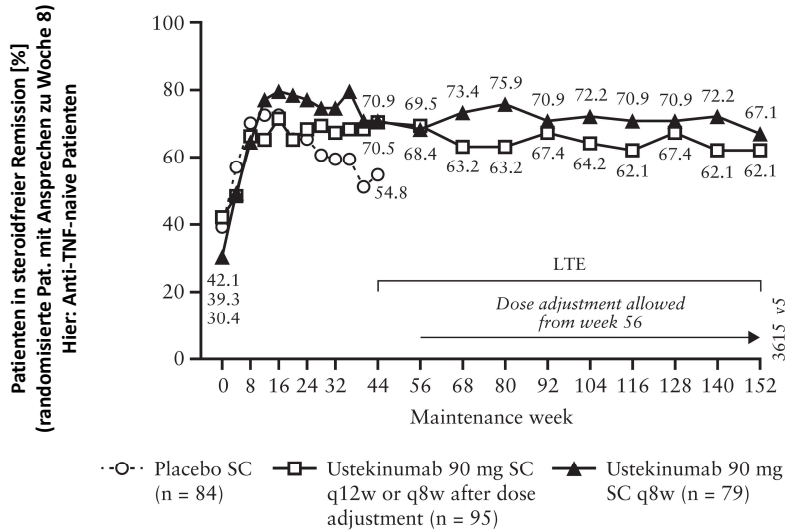
Timmer et al., Cochrane Database Syst Rev. 2016 May 18;2016(5):CD000478

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Ustekinumab – langfristige Behandlungstudie nach UNIFI



Beginn mit Woche 8 der IM-UNITI-Studie – 3-Jahres-Daten
 Fortsetzung der Therapie, ggf. mit Anpassung der Dosierung



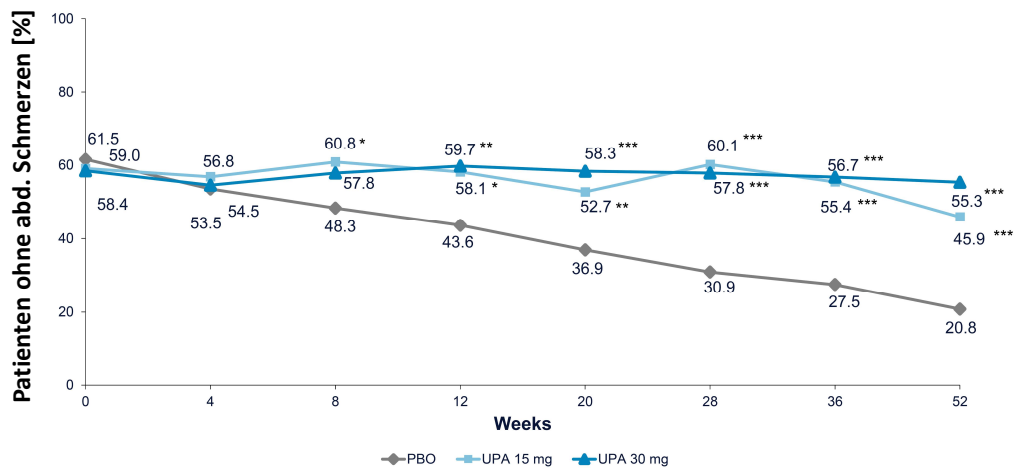
C. ulcerosa

Abreu et al., J Crohns Colitis 2022;2022 Mar 3:jjac030. doi: 10.1093/ecco-icc/jjac030

Upadacitinib in der Erhaltungstherapie

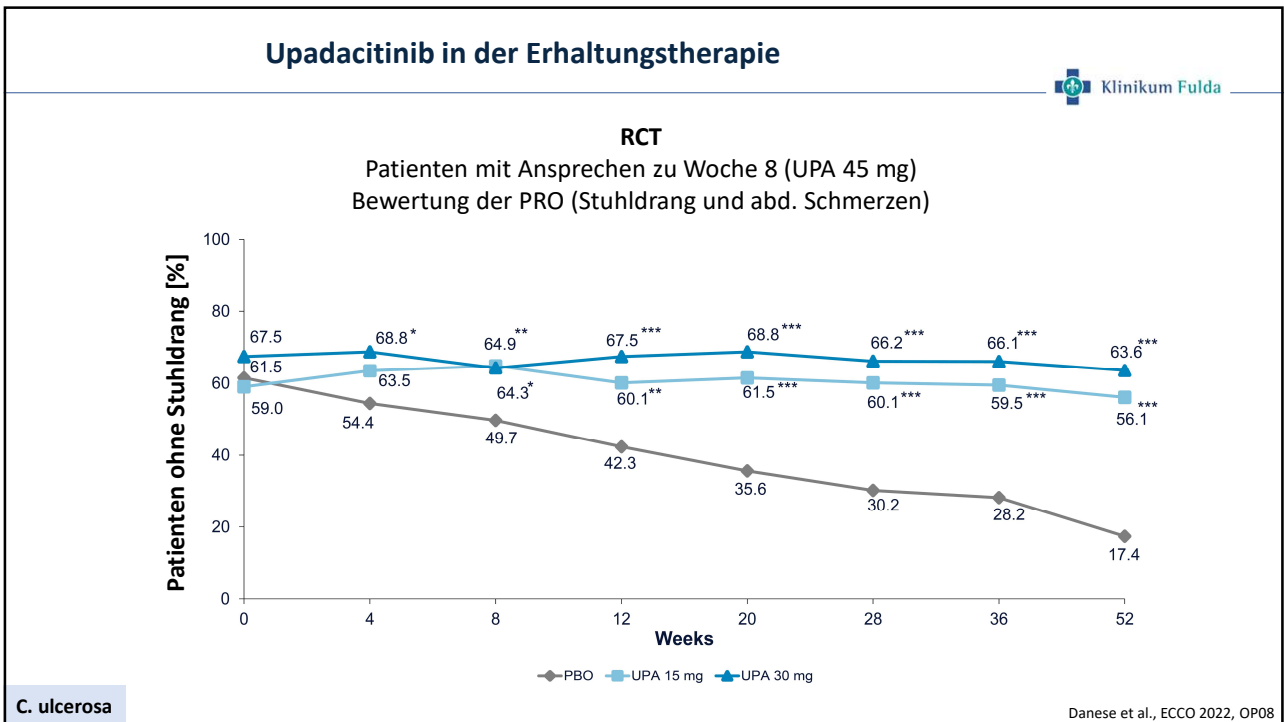


RCT
 Patienten mit Ansprechen zu Woche 8 (UPA 45 mg)
 Bewertung der PRO (Stuhldrang und abd. Schmerzen)

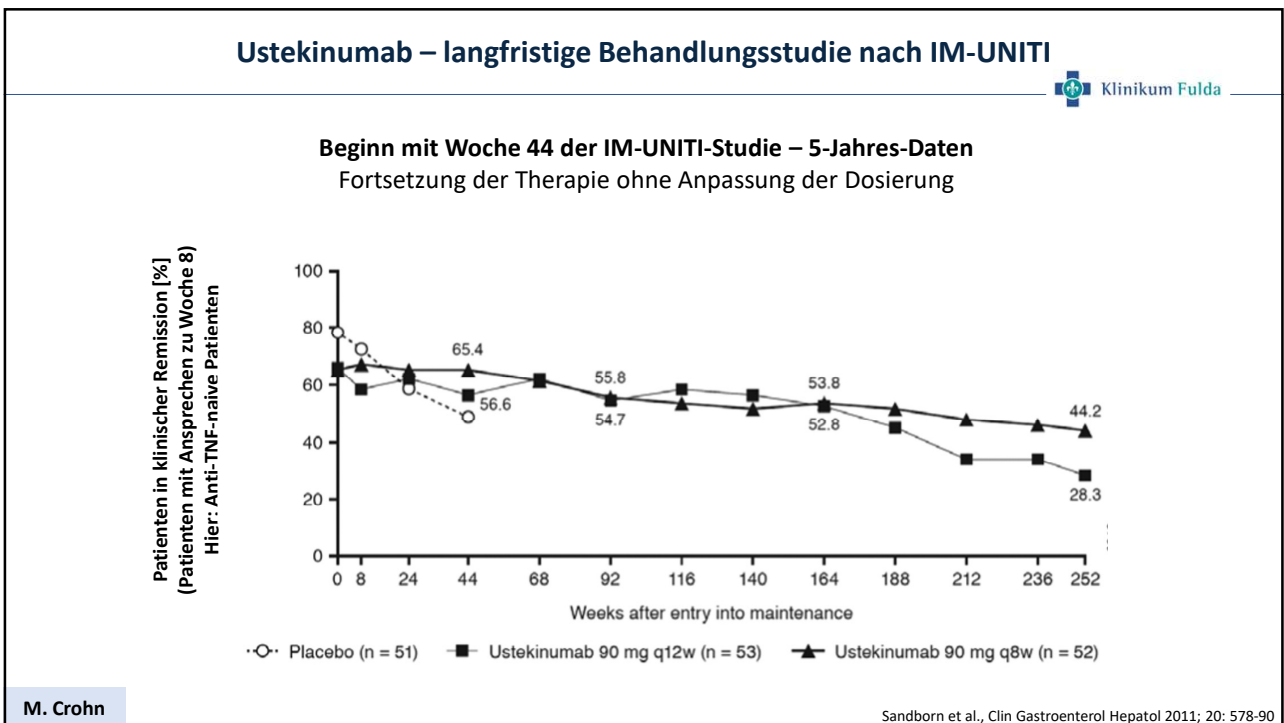


C. ulcerosa

Danese et al., ECCO 2022, OP08



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Effektivität von Immunsuppressiva und Biologika – Remissionserhaltung



Paarweiser Vergleich und Netzwerk-Metaanalyse
39 Studien - MTX, Aza/MP, IFX, ADA, CTZ, VDZ, Combo-Therapie

Vgl. zu Aza/MP	OR	CI	Wahrscheinlichkeit der Überlegenheit
MTX	1,4	0,58-2,8	78%
Certolizumab	1,2	0,65-1,9	72%
Infliximab	1,6	1,0-2,5	98%
Adalimumab	2,9	1,6-5,1	>99%
Infliximab / Aza	3,0	1,7-5,5	>99%
Infliximab / MTX	1,5	0,57-3,7	79%
Vedolizumab	1,3	0,65-2,3	76%

M. Crohn

Hazlewood et al., Gastroenterology 2015; 148: 344-54

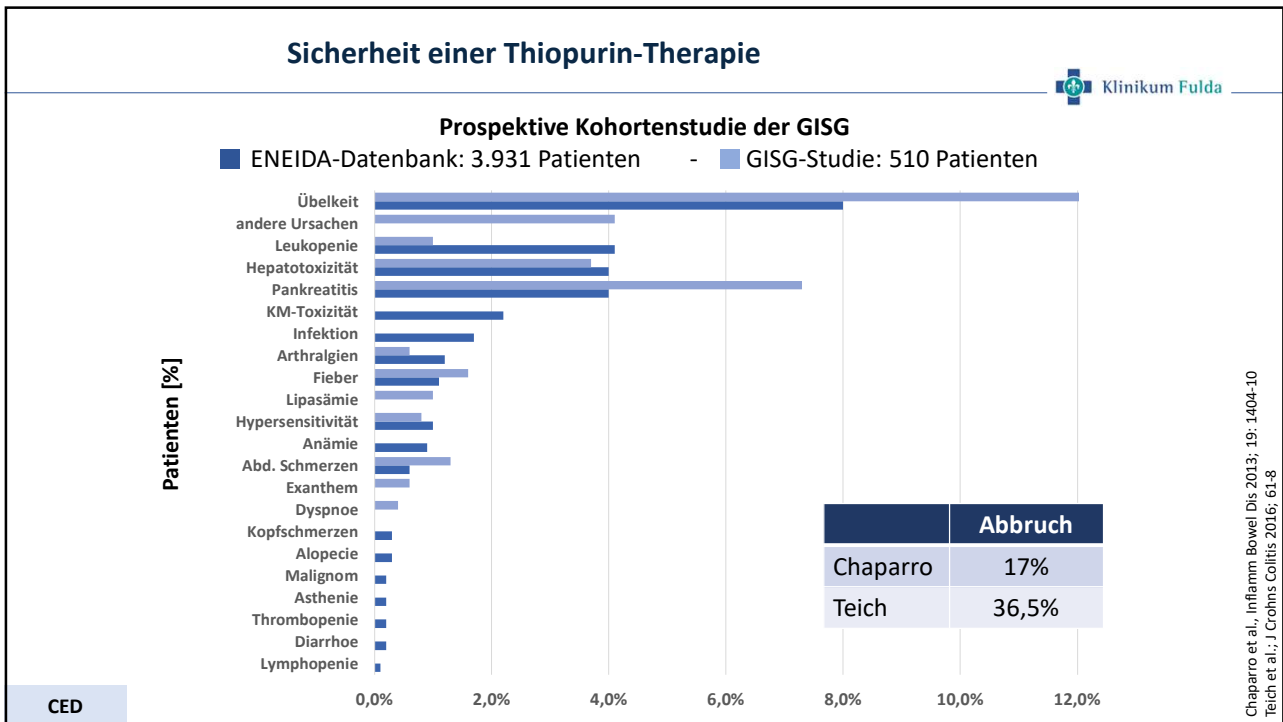
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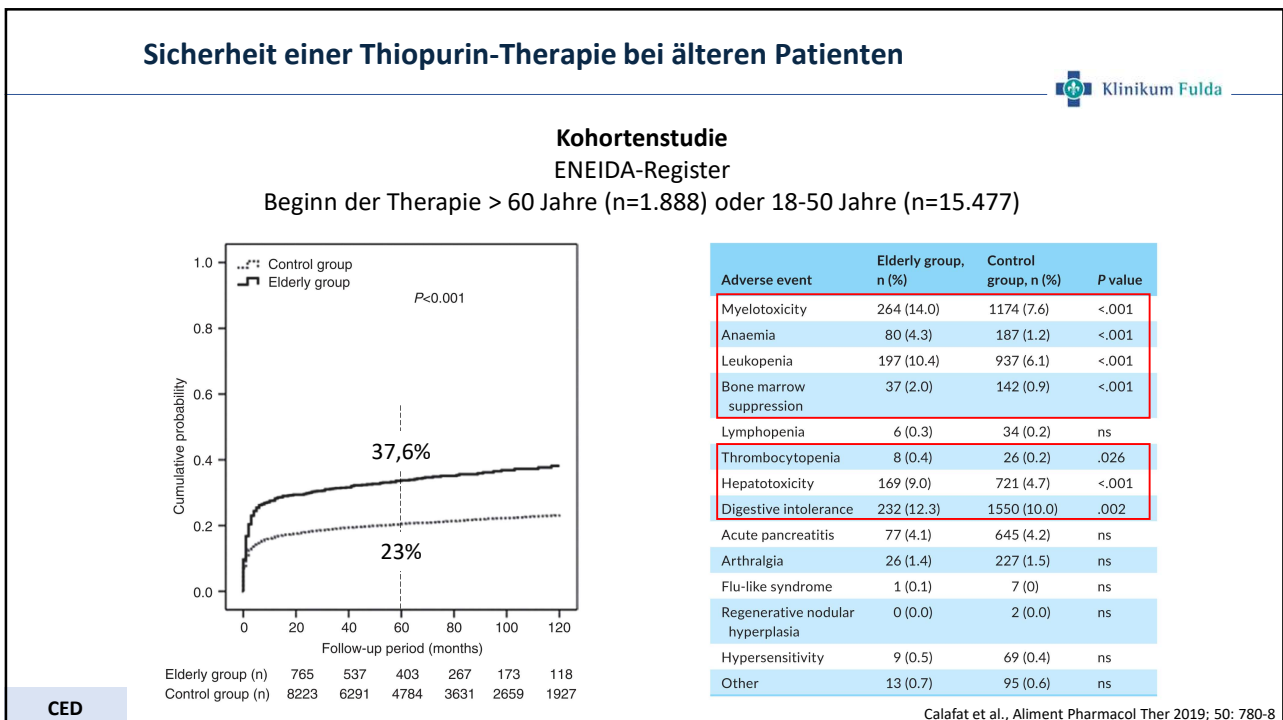


Induktionstherapie
Erhaltungstherapie
Nebenwirkungen
Besondere Situationen
Patientenperspektive

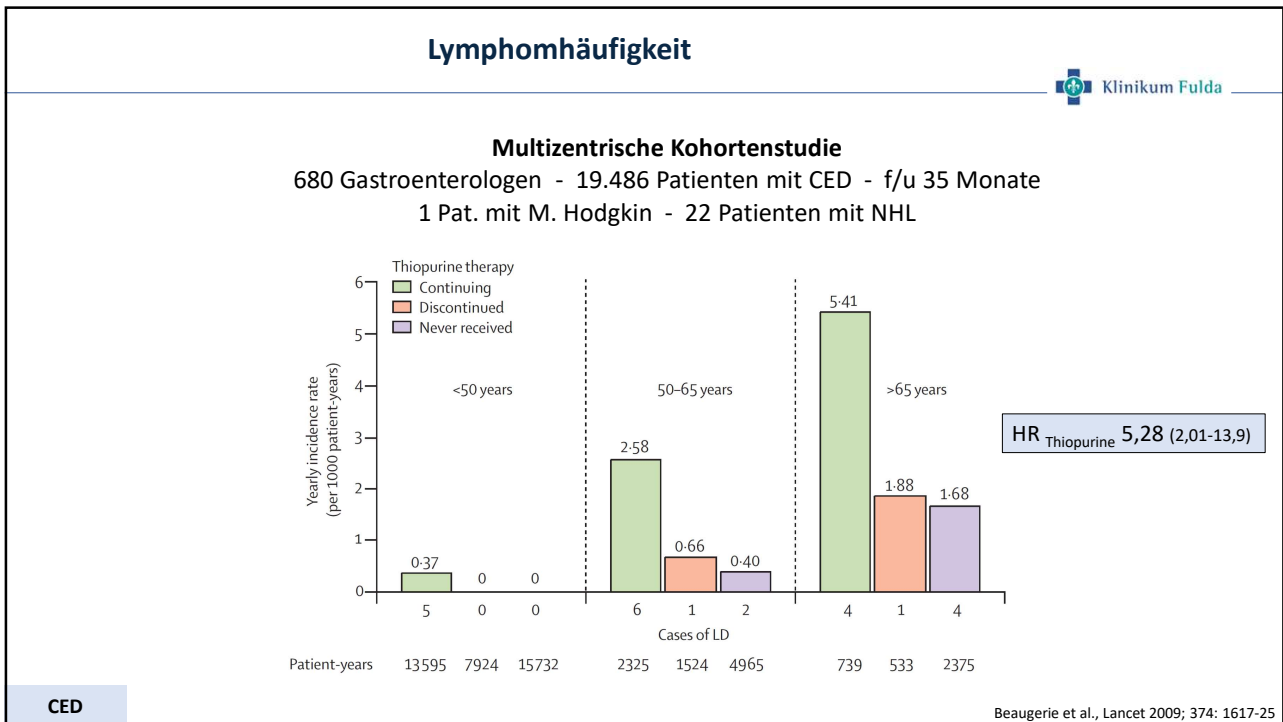
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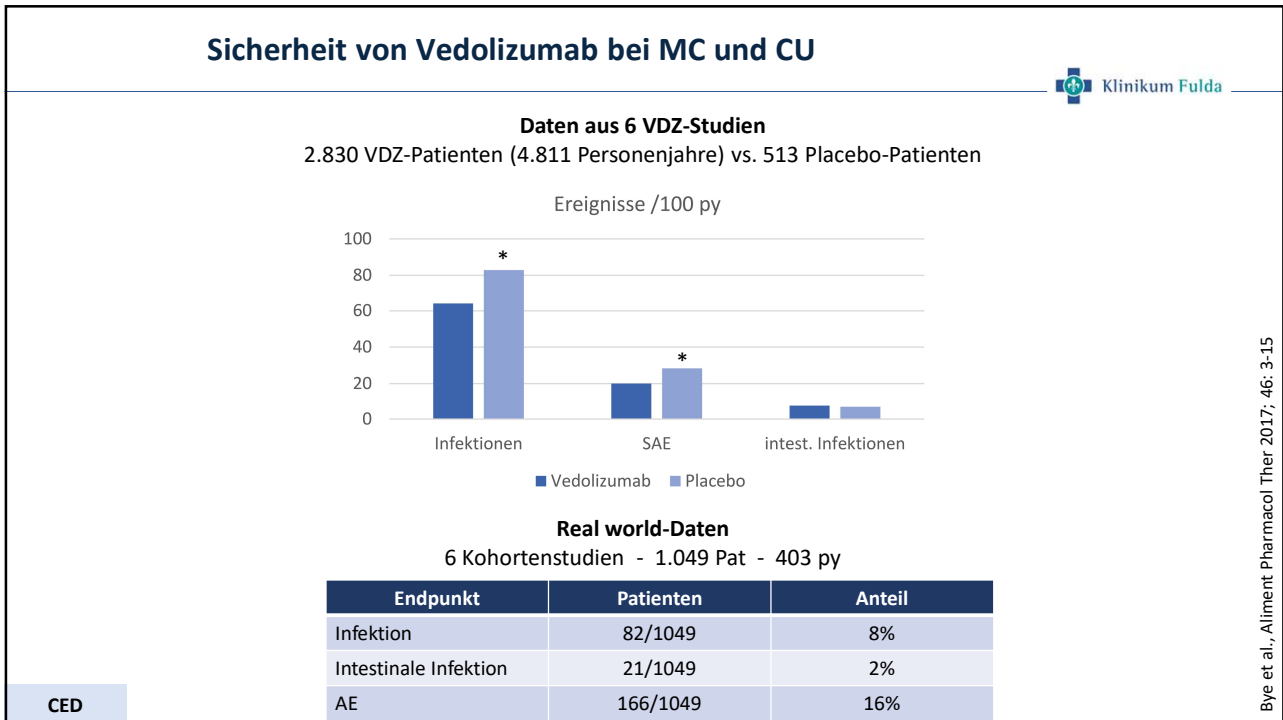
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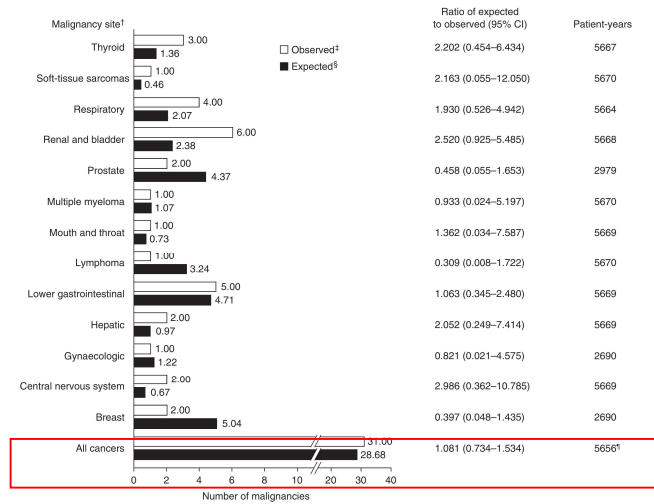


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Inzidenz von Malignomen unter Vedolizumab (GEMINI LTS)



Kohortenstudie, Vgl. mit Datenbank
1.785 Patienten (f/u > 1 Jahr) - 5.670 Patientenjahre



CED

Card et al., APT 2019; 51: 149-57

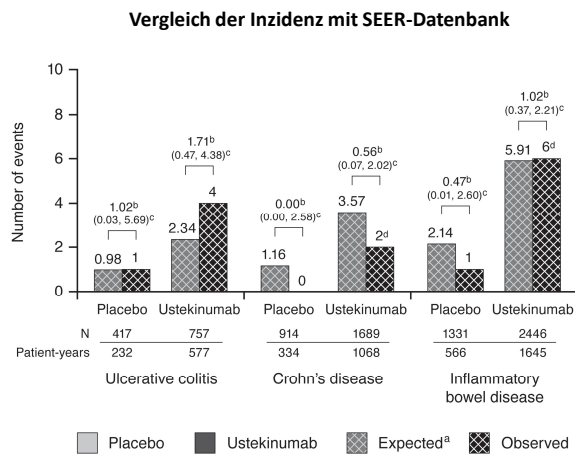
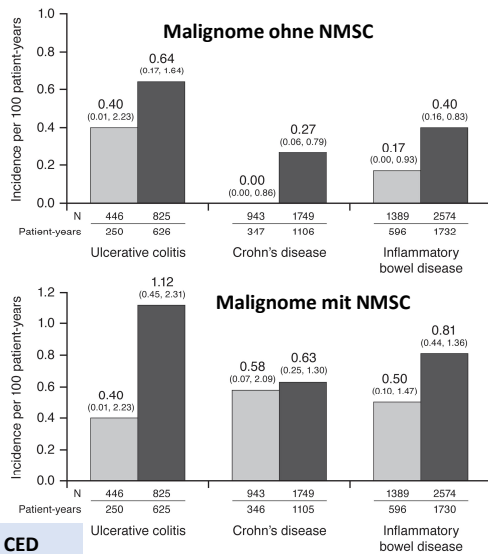
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Malignomrisiko unter Ustekinumab



Kohortenstudie

Phase 2/3-Studien zu UST bei MC und CU - 2.574 Patienten (1.733 PY)



CED

Sandborn et al., IBD 2021; 27: 994-1007

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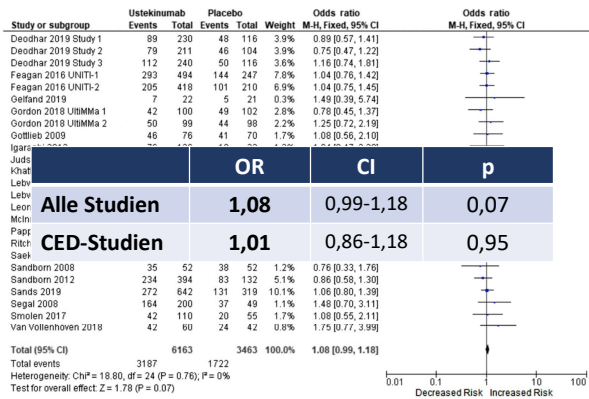
Sicherheit von Ustekinumab bei CED



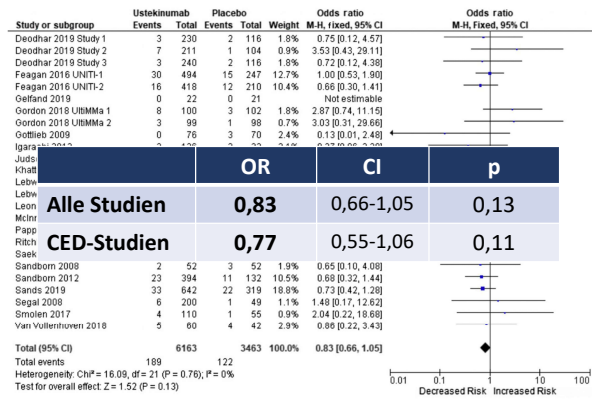
Metaanalyse

25 RCT - 9.626 Patienten (UST: n=6.163 - Placebo: n=3.463)

Mild-moderate AE



SAE



CED

Rolston et al., Dig Dis Sci 2021; 66: 1631-8

Risiko für ein Melanom unter Therapie mit Biologika

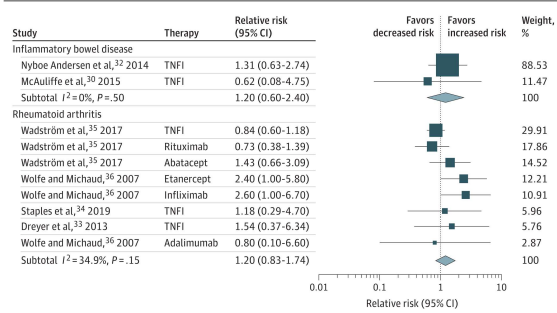


Systematischer Review und Meta-Analyse

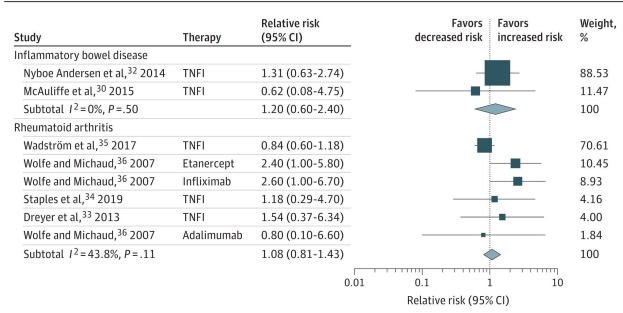
7 Studien bei Patienten mit CED, RA oder Psoriasis

34.029 Patienten mit Biologika - 135.370 Patienten ohne Biologika

Biologika vs. keine Biologika



TNF-Ak vs. keine TNF-Ak



CED

Esse et al., JAMA Dermatol 2020; 156: 787-94

Effektivität von Immunsuppressiva und Biologika – Abbruch wegen AE



Paarweiser Vergleich und Netzwerk-Metaanalyse
39 Studien - MTX, Aza/MP, IFX, ADA, CTZ, VDZ, Combo-Therapie

Vgl. zu Aza/MP	OR	CI	Wahrscheinlichkeit der Überlegenheit
MTX	3,3	0,78-29	6%
Certolizumab	0,23	0,13-0,4	>99%
Infliximab	0,71	0,44-1,2	92%
Adalimumab	0,12	0,06-0,24	>99%
Infliximab / Aza	0,81	0,47-1,4	77%
Infliximab / MTX	1,7	0,12-52	35%
Vedolizumab	0,17	0,09-0,35	>99%

M. Crohn

Hazlewood et al., Gastroenterology 2015; 148: 344-54

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Induktionstherapie
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Nebenwirkungen
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Therapie extraintestinaler Manifestationen

Knochen und Gelenke

Arthritis, Arthralgien (20-30%)
Osteoporose (26%)

Haut

Erythema nodosum (8-10%)
Pyoderma gangraenosum (1-7%)

Schleimhaut

Aphthen - häufiger bei M. Crohn (4%)

Augen

Iritis, Skleritis (4-6%)

Leber und Gallenwege

primär sklerosierende Cholangitis (PSC) (4%)

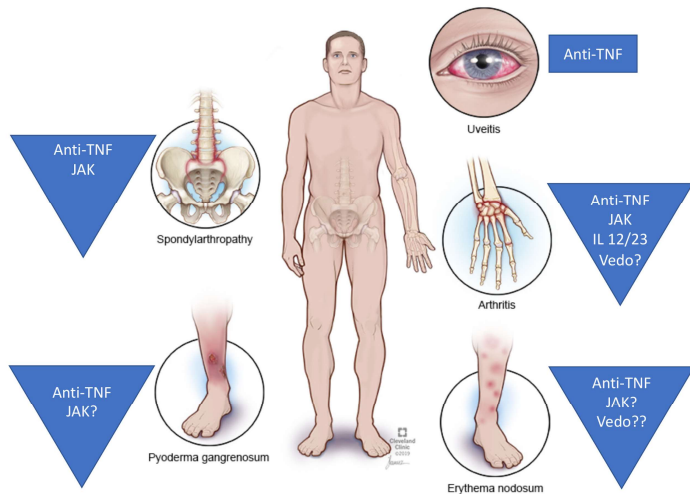
Lunge

Lungenfibrose <1%

Nierensteine

...

CED



Greuter et al., Gut 2020; 70: 796-802

Immunsuppressiva vs. Biologika – Hospitalisierung und Operationsnotwendigkeit

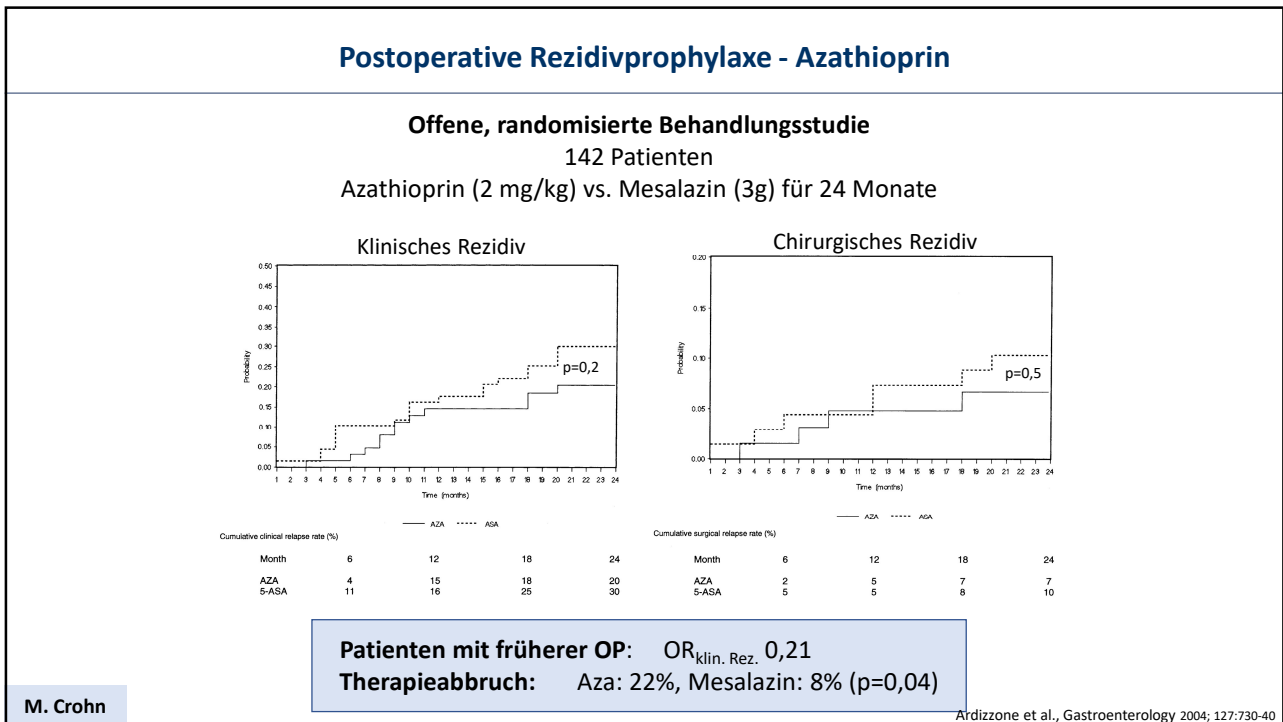
Systematischer Review und Meta-Analyse 7 RCT (CD: n=5; CU: n=2)

Hospitalisierung	Morbus Crohn Vergleichssubstanz	Odds Ratio (95% Vertrauensintervall), Wahrscheinlichkeit, dass die Intervention der Vergleichssubstanz überlegen ist		
		Plazebo	Infliximab	Adalimumab
	Infliximab	0,44 (0,24-0,76) 99%		
	Adalimumab	0,51 (0,23-1,12) 96%	1,14 (0,44-3,18) 37%	
	Azathioprin	2,34 (0,64-9,65) 9%	5,34 (1,32-24,85) 99%	4,66 (1,01-24,38) 98%

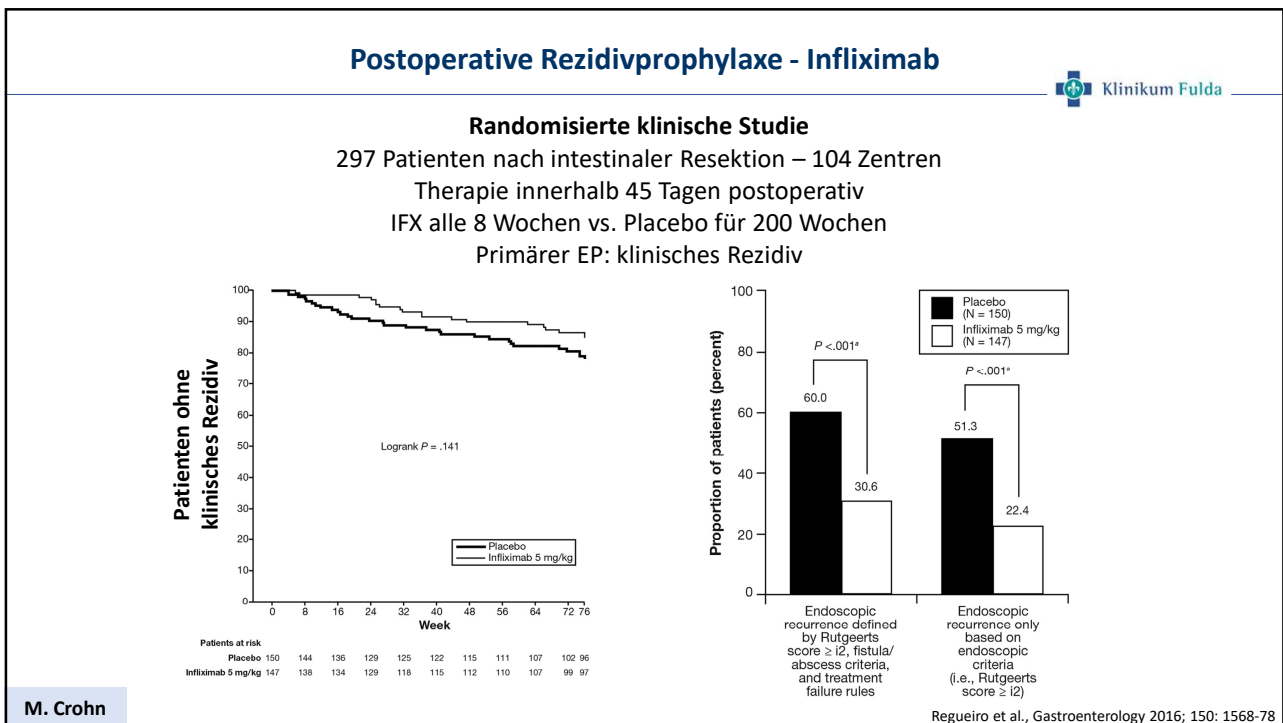
Operation	Morbus Crohn Intervention	Odds Ratio (95% Vertrauensintervall), Wahrscheinlichkeit, dass die Intervention der Vergleichssubstanz überlegen ist			
		Plazebo	Infliximab	Adalimumab	Vedolizumab
	Infliximab	0,26 (0,10-0,61) 99%			
	Adalimumab	0,13 (0,02-0,61) 99%	0,48 (0,06-3,03) 80%		
	Vedolizumab	0,43 (0,1-1,91) 88%	1,66 (0,29-9,17) 26%	3,56 (0,38-39,30) 13%	
	Azathioprin	0,81 (0,02-36,15) 55%	3,12 (0,09-147,28) 25%	6,81 (0,15-464,75) 15%	1,88 (0,04-105,62) 65%

M. Crohn

Mao et al., APT 2017; 45: 37-49



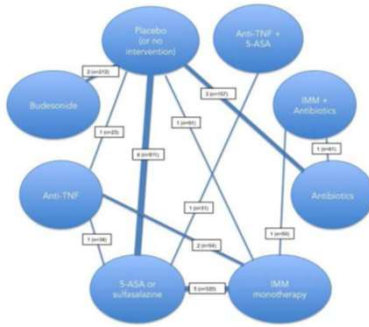
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Postoperative Remissionserhaltung

Netzwerk-Metaanalyse 21 RCT – 2.006 Patienten



Medikament	Klinisches Rezidiv		Endoskopisches Rezidiv	
	RR	CI	RR	CI
Budesonid	0,93	0,4-1,84	0,86	0,61-1,22
5-ASA	0,6	0,37-0,88	0,67	0,39-1,08
Antibiotika	0,26	0,08-0,61	0,41	0,15-0,92
Immunsuppressiva	0,36	0,17-0,63	0,33	0,13-0,68
IS + Antibiotika	0,11	0,02-0,51	0,16	0,04-0,48
Anti-TNF	0,04	0-0,14	0,01	0-0,05

M. Crohn

Singh et al., Gastroenterology 2015; 148: 64-76


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Agenda

Induktionstherapie
 Erhaltungstherapie
 Nebenwirkungen
 Besondere Situationen
Patientenperspektive

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Heterogene Patientenpräferenzen („latente Klassenanalyse“)



Umfrage unter 812 Patienten mit M. Crohn

Informationen über

- Symptome und Schwere einer aktiven Erkrankung
- Dauer einer Steroidtherapie
- Risiko schwerer Infektionen, Tumore und Operation

↓

Annahme:
Therapie ist unwirksam

↓

Wahl einer alternativen Therapie

2) Which of these options would you choose if these were the only options available to you?
(If you place your mouse cursor over a treatment feature, you can see information about that feature.) Logout

TREATMENT FEATURES	Treatment A	Treatment B
Number of months of symptoms each year	Remission 4 (4 blue dots) Moderate 8 (8 yellow dots)	Severe 12 (12 orange dots)
Number of months you will use steroids each year in addition to other treatment	12 (12 purple dots)	2 (2 purple dots)
Increased chance of serious infection due to the treatment during each year that you are on treatment	None	15/100 (15%)
Increased chance of cancer due to the treatment during each year that you are on treatment	5/100 (5%)	2/100 (2%)
Chance of surgery during each year that you are on treatment	8/100 (8%)	5/100 (5%)


Which would you choose if these were the only options?
Treatment A Treatment B

Next

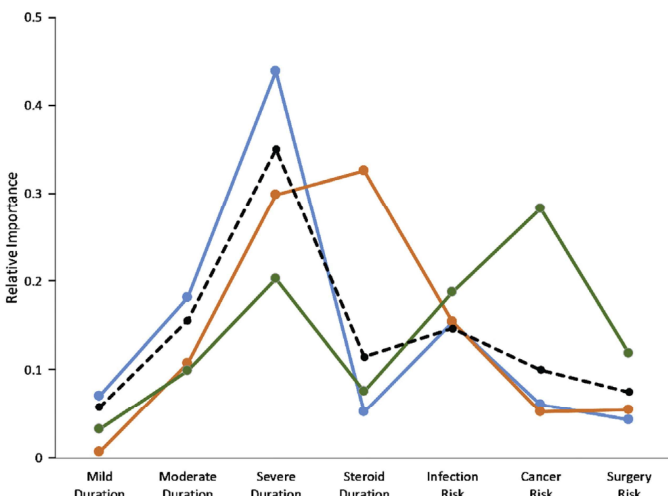
M. Crohn
Bewtra et al., Clin Gastroenterol Hepatol 2020; 18:406-14

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Heterogene Patientenpräferenzen („latente Klassenanalyse“)



Umfrage unter 812 Patienten mit M. Crohn



Feature	All Participants	Efficacy Class	Steroid Class	Risk Class
Mild Duration	~0.08	~0.08	~0.05	~0.05
Moderate Duration	~0.18	~0.18	~0.10	~0.10
Severe Duration	~0.44	~0.44	~0.30	~0.20
Steroid Duration	~0.12	~0.06	~0.33	~0.08
Infection Risk	~0.15	~0.15	~0.15	~0.19
Cancer Risk	~0.10	~0.06	~0.06	~0.28
Surgery Risk	~0.08	~0.05	~0.05	~0.12

- All Participants
- Efficacy Class
- Steroid Class
- Risk Class

M. Crohn
Bewtra et al., Clin Gastroenterol Hepatol 2020; 18:406-14

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Analyse der Patientenpräferenz in der Biologika-Therapie



Conjoint-Analyse - Software-basierte Auswertung (online-tool)

640 Patienten: M. Crohn: 336 - C. ulcerosa: 304

MY IBD&ME PERSONALIZED REPORT

ABOUT THIS REPORT
This is your IBD&me Personalized Report. It shows what was most important to you as you were deciding among the different biologic medicines. You can print out the Report and bring it with you to the doctor, or you can send it in an email to your doctor.

Below, you will see your "Importance Scores" for the seven biologic characteristics from the IBD&me Decision Tree. The higher the score, the more important the characteristic is to you when choosing among medicines. If you want to learn more about Importance Scores or how you can use this report, please visit the FAQs.

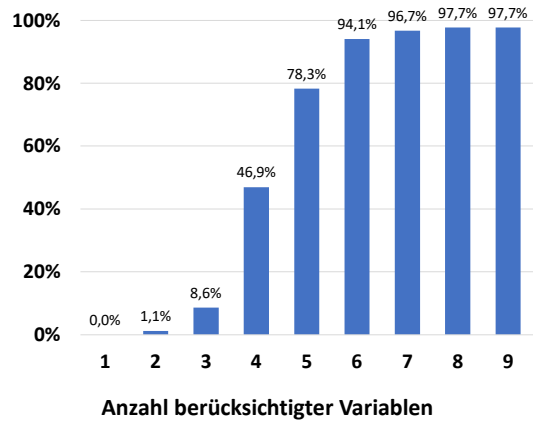
MY IMPORTANCE SCORES

Way you receive the medicine	29%
Long-term relief of symptoms (i.e. remission)	19%
Time in between doses	16%
Risk of skin rash	14%
Risk of lymphoma (i.e. blood cancer)	9%
Tolerability of unwanted side effects	7%
Risk of serious infection	7%

WHAT DOES THIS MEAN?
Based on your responses, these were the top 3 most important factors for you as you were choosing among the different biologic medicines. It also seems that you prefer to receive the medicine given through an IV into the vein in your home and want to give every 2 weeks.

- Way you receive the medicine
- Long-term relief of symptoms (i.e. remission)
- Time in between doses

Anteil der Patienten mit individuellen Entscheidungsprofilen



www.ibdandme.org

CED

Almario et al., Am J Gastroenterol 2018; 113: 58-71

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