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1 Search terms cost-effectiveness models

Embase

('biomedical technology assessment'/exp OR 'biomedical technology assessment' OR 'economic evaluation'/exp OR 'economic evaluation' OR 'quality adjusted life year'/exp OR 'quality adjusted life year' OR 'program cost effectiveness'/exp OR 'program cost effectiveness' OR ((technology NEAR/3 assessment*):ab,ti) OR ((economic* NEAR/3 (evaluat* OR value)):ab,ti) OR (((cost OR costs) NEAR/3 (benefit* OR effectiv* OR efficien* OR efficac* OR minim* OR utilit* OR consequen*)):ab,ti) OR ((qualit* NEAR/3 adjust* NEAR/3 ('life year*' OR lifeyear*)):ab,ti) OR qaly*:ab,ti)

AND

('economic model'/exp OR 'economic model' OR 'simulation'/exp OR 'simulation' OR (('model'/exp OR model) AND ('economics'/exp OR economics OR 'economic aspect'/exp OR 'economic aspect')) OR 'decision tree'/exp OR 'decision tree' OR (((model OR modeling OR modelling OR simulation* OR microsimulation*) NEAR/6 (econom* OR pharmacoeconom* OR cost OR costs)):ab,ti) OR ((decision NEAR/3 (analy* OR tree OR trees)):ab,ti) OR 'discrete event*':ab,ti OR 'state transition':ab,ti OR markov:ab,ti OR (((individual* OR 'patient level*') NEAR/3 (sampl* OR simulation*)):ab,ti) OR ((dynamic NEAR/3 transmission*):ab,ti) OR probabilistic*:ab,ti OR 'partition* survival*':ab,ti)

AND

('crohn disease'/exp OR (((crohn OR crohns) NEAR/3 (disease* OR colitis)):ab,ti) OR ((inflamm* NEAR/3 bowel):ab,ti))

502 hits (on 27-2-2023), 153 full text inclusions, 9 treatment sequence models, 8 surgery models, 12 diagnostic models, 8 biomarker models, 57 pharmacotherapeutic models and 59 'other' models.

2 Patient characteristics modelled and observed

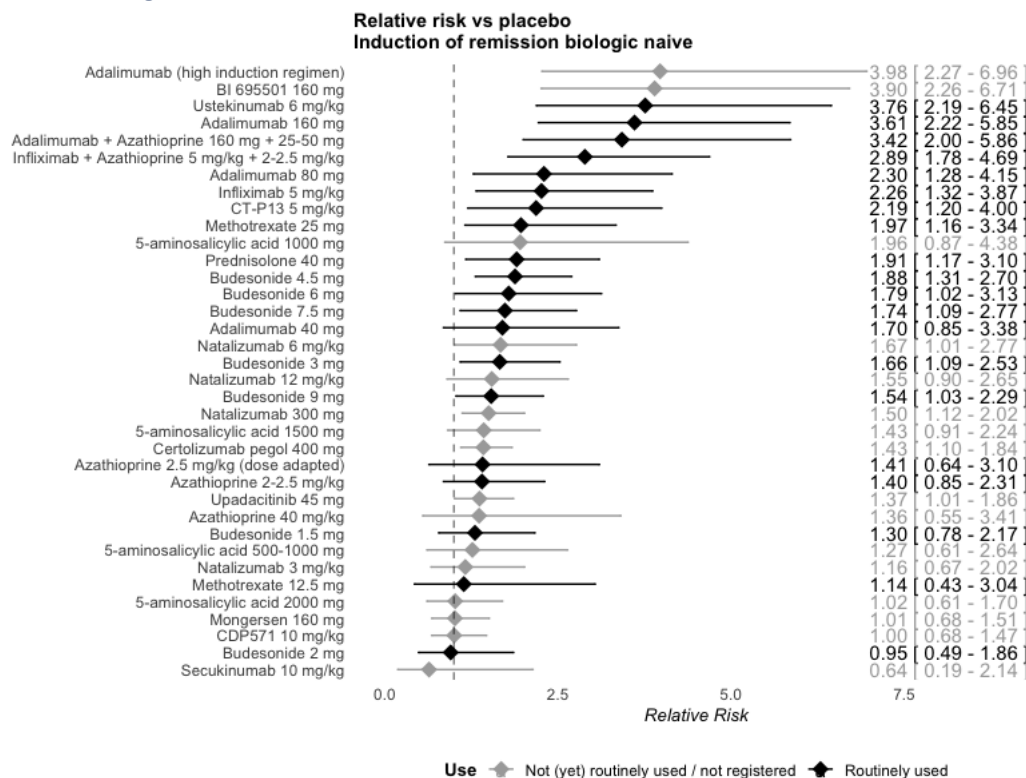
Source	IBD-SL	ICC	Simulated
N	348	64	10000
Gender			
Male	112 (32%)	15 (23%)	3045 (30%)
Female	236 (68%)	49 (77%)	6955 (70%)
Age at diagnosis			
17-40	261 (75%)	44 (69%)	7402 (74%)
>40	87 (25%)	20 (31%)	2598 (26%)
Location			
L1 ileal	133 (38%)	30 (46%)	3163 (32%)
L2 colonic	109 (31%)	18 (28%)	3462 (35%)
L3 ileocolonic	103 (30%)	14 (22%)	3262 (33%)
Other	3 (1%)	2 (3%)	113 (1%)
Behaviour			
Inflammatory	257 (74%)	40 (63%)	7590 (76%)
Strictureing	67 (19%)	17 (27%)	1913 (19%)
Penetrating	24 (6%)	4 (6%)	497 (5%)
Current smoker			
yes	46 (23%)	18 (33.3%)	4618 (46%)
no	154 (77%)	46 (66.7%)	5382 (54%)
missing	148	10	0
Perianal disease			
yes	52 (15%)	4 (6%)	1487 (15%)
no	296 (85%)	58 (94%)	8513 (85%)
unknown	0	2	0

IBD-SL: Inflammatory Bowel Disease-South Limburg. ICC: Initiative on Crohn and Colitis.

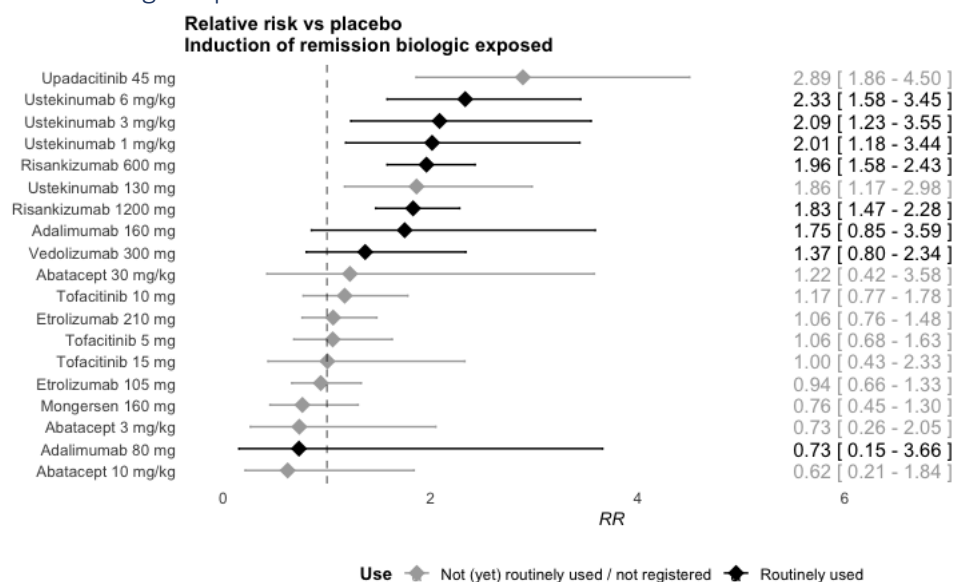
3 Forest plots of network meta-analysis

3.1 Clinical remission

3.1.1 Biologic naive



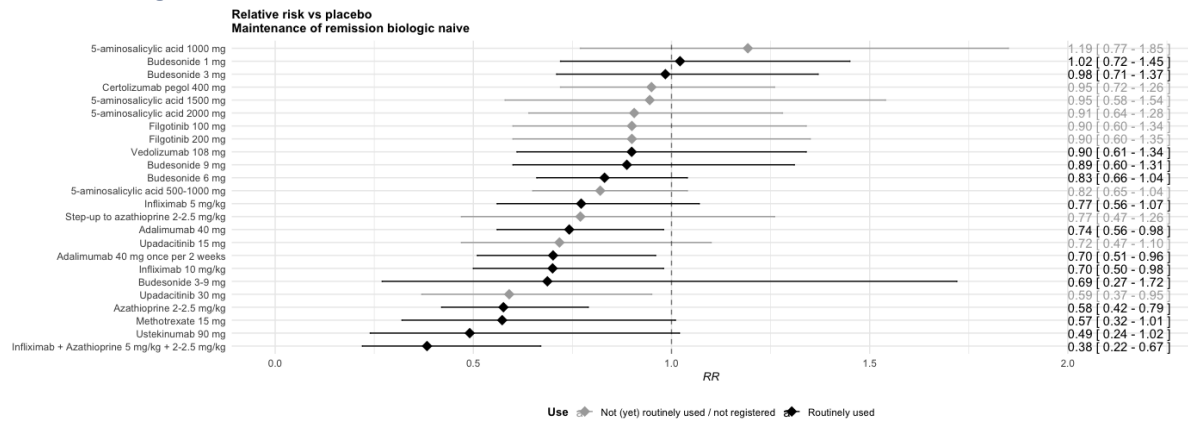
3.1.2 Biologic exposed



RR = relative risk

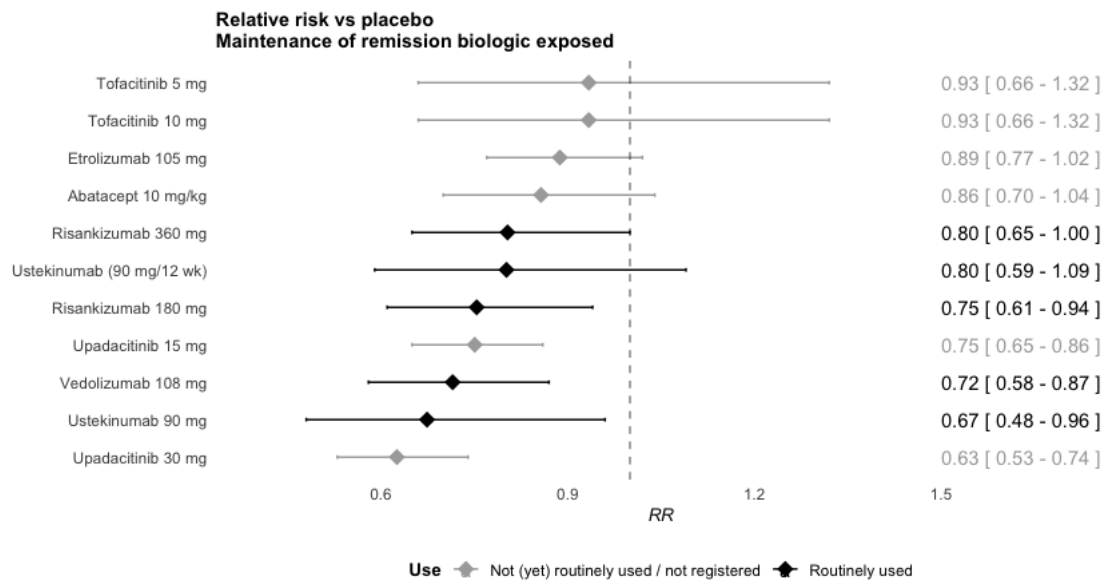
3.2 Maintenance

3.2.1 Biologic naive



RR = relative risk

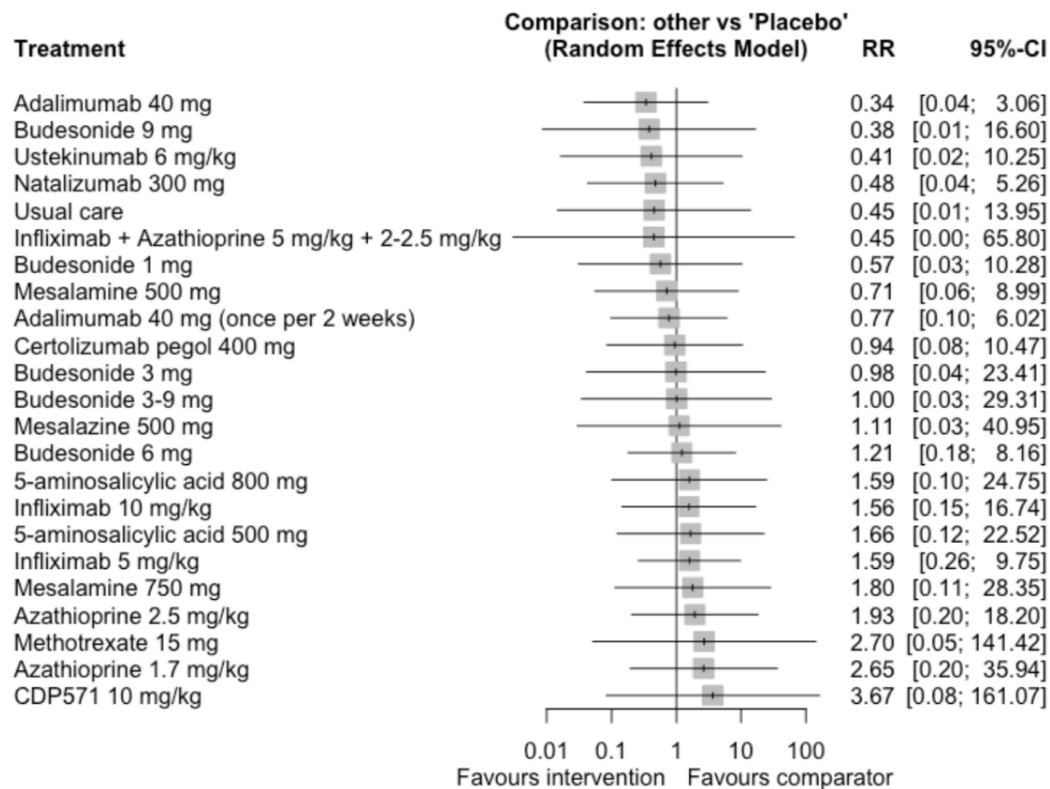
3.2.2 Biologic exposed



RR = relative risk

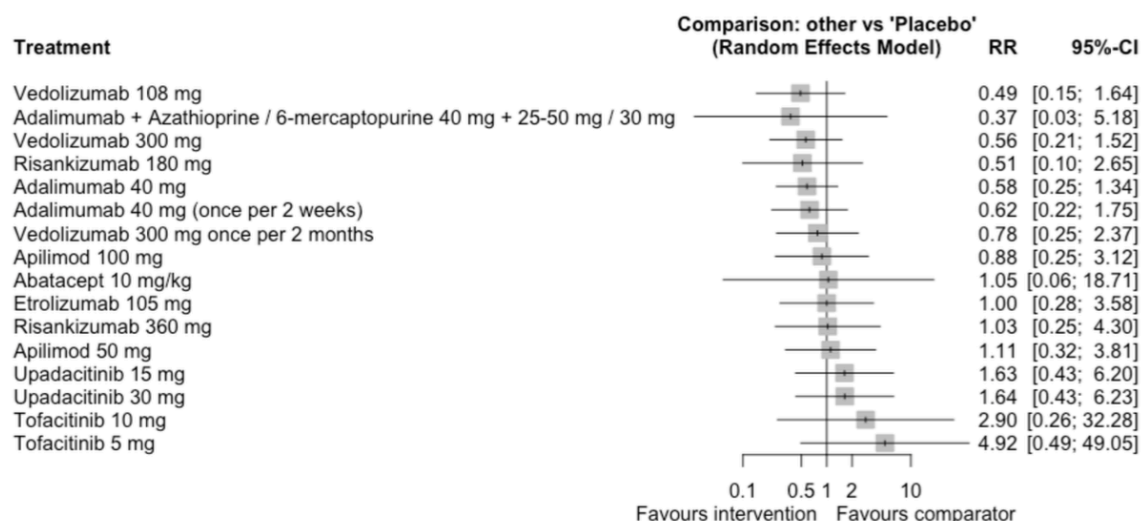
3.3 Discontinuation due to adverse events

3.3.1 Biologic naïve



RR = relative risk. CI = confidence interval.

3.3.2 Biologic exposed



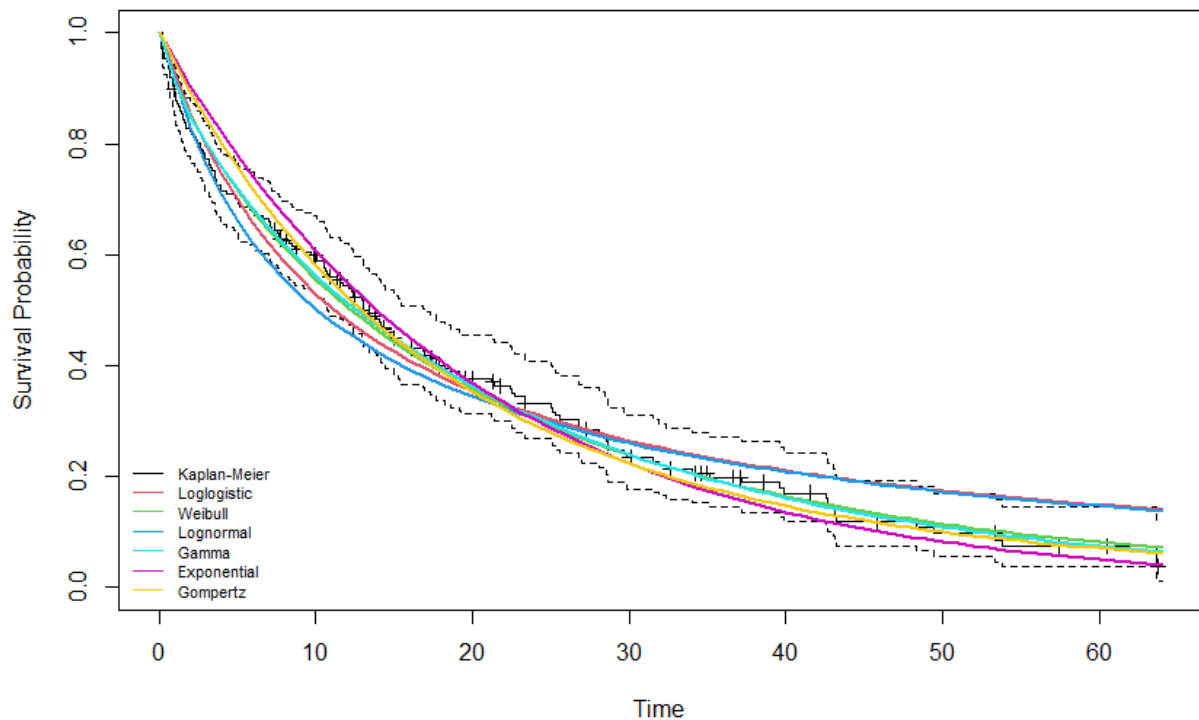
RR = relative risk. CI = confidence interval.

4 Survival functions and extrapolations

4.1 First line survival model: biologic naive patients on azathioprine

The best fitting biologic naive first line model was a gamma function estimated on 184 first line patients with approximately 15 years of follow-up on azathioprine/6-mp who over time would proceed to an anti-TNF treatment.

4.1.1 Extrapolation plotted on Kaplan Meier-curve



4.1.2 Akaike information criterion (AIC)/Bayesian information criterion (BIC)

AIC					
Loglogistic	Weibull	Lognormal	Gamma	Exponential	Gompertz
1281.387	1263.828	1282.321	1262.934	1273.096	1273.070
BIC					
Loglogistic	Weibull	Lognormal	Gamma	Exponential	Gompertz
1287.963	1270.404	1288.897	1269.510	1276.384	1279.647

4.1.3 Model coefficients

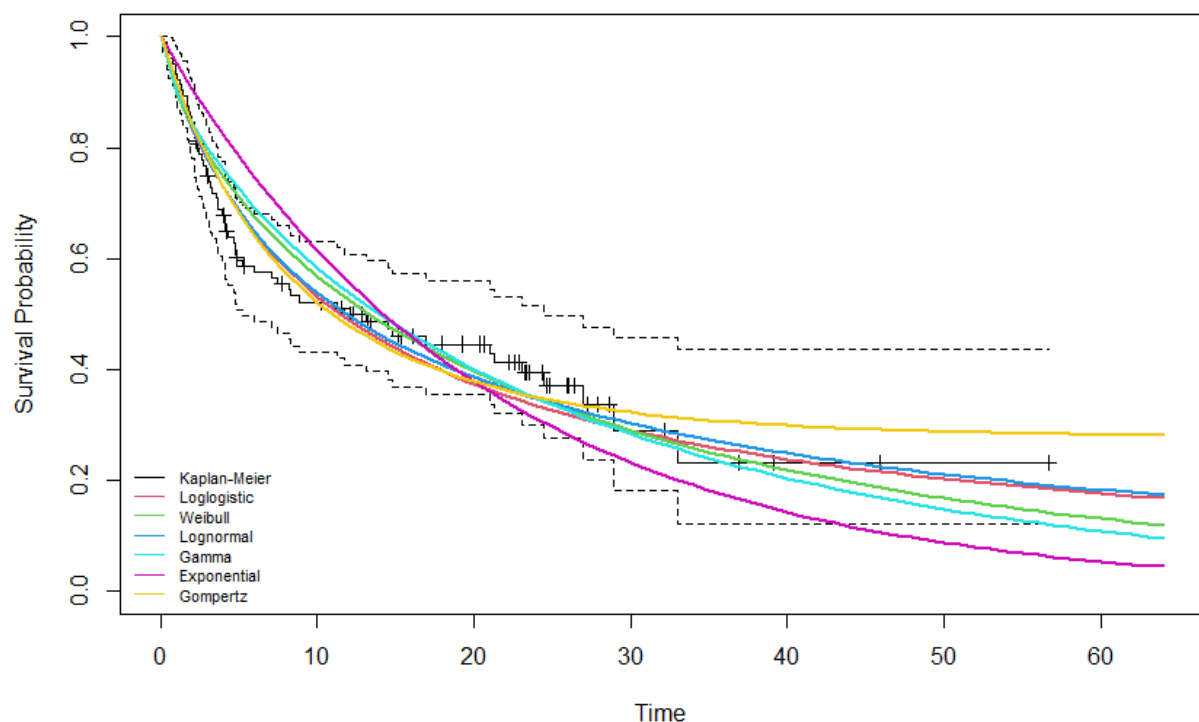
Covariate	Estimate	Lower bound of 95% confidence interval	Upper bound of 95% confidence interval	Standard error
shape	0.75	0.62	0.91	0.07
rate	0.03	0.01	0.06	0.01
age_diag>40	-0.05	-0.51	0.41	0.24
locL2	-0.08	-0.58	0.41	0.25
locL3	0.22	-0.27	0.70	0.25

locL4	0.01	-1.65	1.67	0.85
fenB2	0.02	-0.47	0.51	0.25
fenB3	-0.76	-1.84	0.32	0.55
sexM	-0.04	-0.47	0.39	0.22
smokeN	0.04	-0.36	0.45	0.21
peri_aN	0.37	-0.26	1.00	0.32

4.2 Second line survival model: biologic naive patients on second line infliximab

The best fitting biologic naive second line model was a lognormal function estimated on 104 second line patients with approximately 14 years of follow-up on infliximab.

4.2.1 Extrapolation plotted on Kaplan Meier-curve



4.2.2 Akaike information criterion (AIC)/Bayesian information criterion (BIC)

AIC					
Loglogistic	Weibull	Lognormal	Gamma	Exponential	Gompertz
477.33	483.47	474.10	486.096	492.828	477.37
BIC					
Loglogistic	Weibull	Lognormal	Gamma	Exponential	Gompertz
482.62	488.76	479.39	491.385	495.473	482.66

4.2.3 Model coefficients

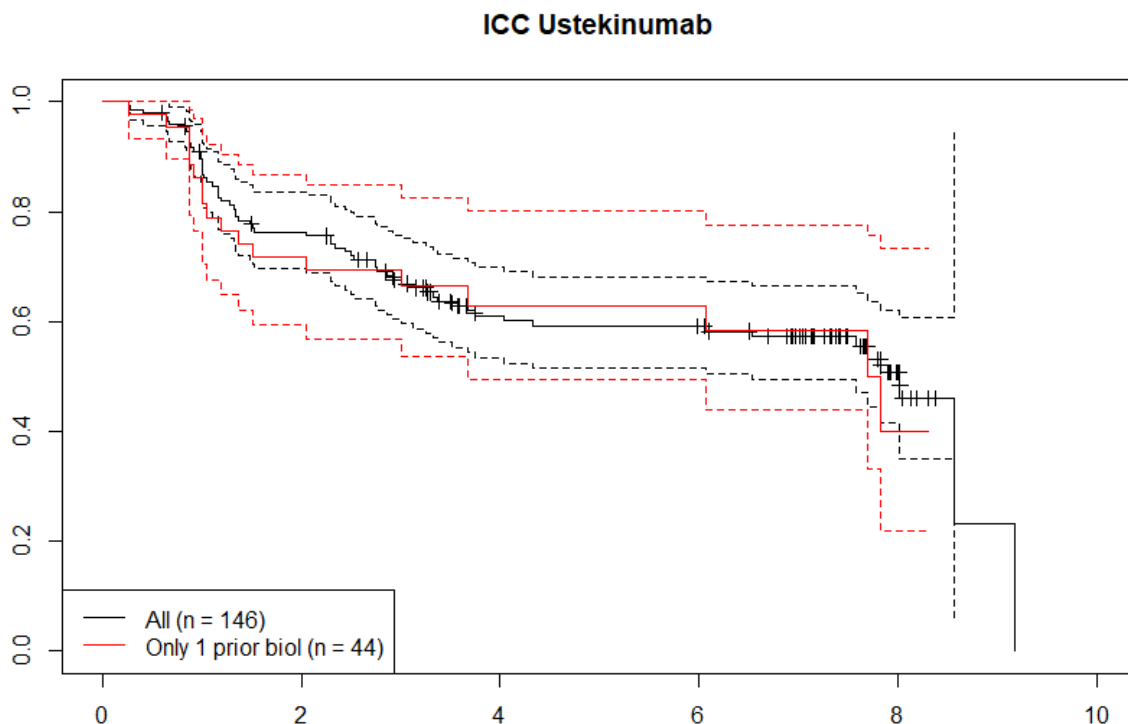
Covariate	Estimate	Lower bound of 95% confidence interval	Upper bound of 95% confidence interval	Standard error

meanlog	2.42	1.06	3.77	0.69
sdlog	1.73	1.43	2.10	0.17
age_diag>40	0.51	-0.41	1.44	0.47
locL2	0.70	-0.22	1.61	0.47
locL3	0.32	-0.58	1.23	0.46
locL4	0.54	-2.96	4.05	1.79
fenB2	-0.68	-1.66	0.30	0.50
fenB3	1.15	-1.06	3.36	1.13
sexM	0.45	-0.32	1.23	0.40
smokeN	0.19	-0.52	0.91	0.36
peri_aN	-0.38	-1.44	0.67	0.54

4.3 Third/fourth/fifth line survival model

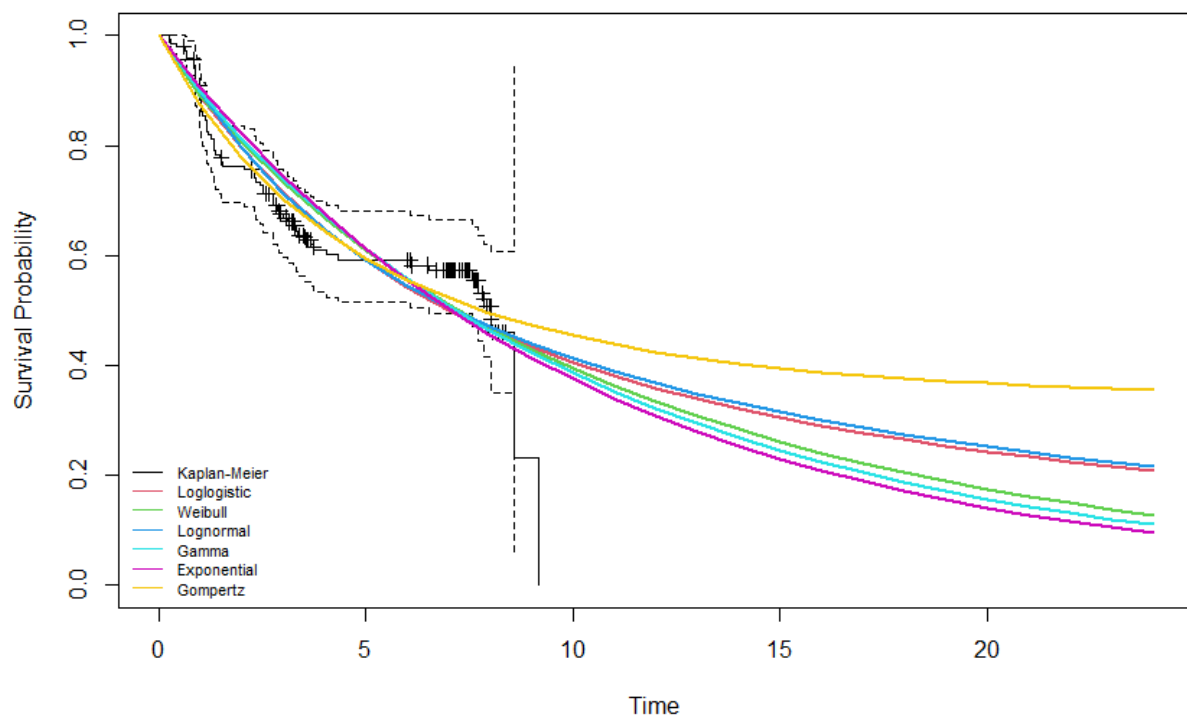
It was decided to use the same time-to-event model for all biologic exposed patients, as having one or more than one previous treatments with a biologic resulted in overlapping Kaplan-Meier (KM) curves and hence did not affect transition probabilities (see figure below). The best fitting biologic exposed model was a lognormal function estimated on 139 biologic exposed patients with approximately 2 years of follow-up on ustekinumab. Note that the clustering of events on the KM curve is caused by the timing of recording of return visits rather than of the underlying disease process, which is why we opted against the use of more flexible parametric function that would capture this shape. The curve demonstrates much faster time to active disease for patients who have failed a previous biologic therapy.

4.3.1 Comparison of Kaplan Meier-curves of one or more previous biologics



ICC = initiative on Crohns and Colitis.

4.3.2 Extrapolation plotted on Kaplan Meier-curve



4.3.3 Akaike information criterion (AIC)/Bayesian information criterion (BIC)

AIC					
Loglogistic	Weibull	Lognormal	Gamma	Exponential	Gompertz
423.97	428.45	418.18	428.95	427.23	424.309
BIC					
Loglogistic	Weibull	Lognormal	Gamma	Exponential	Gompertz
429.94	434.42	424.15	434.92	430.21	430.276

4.3.4 Model coefficients

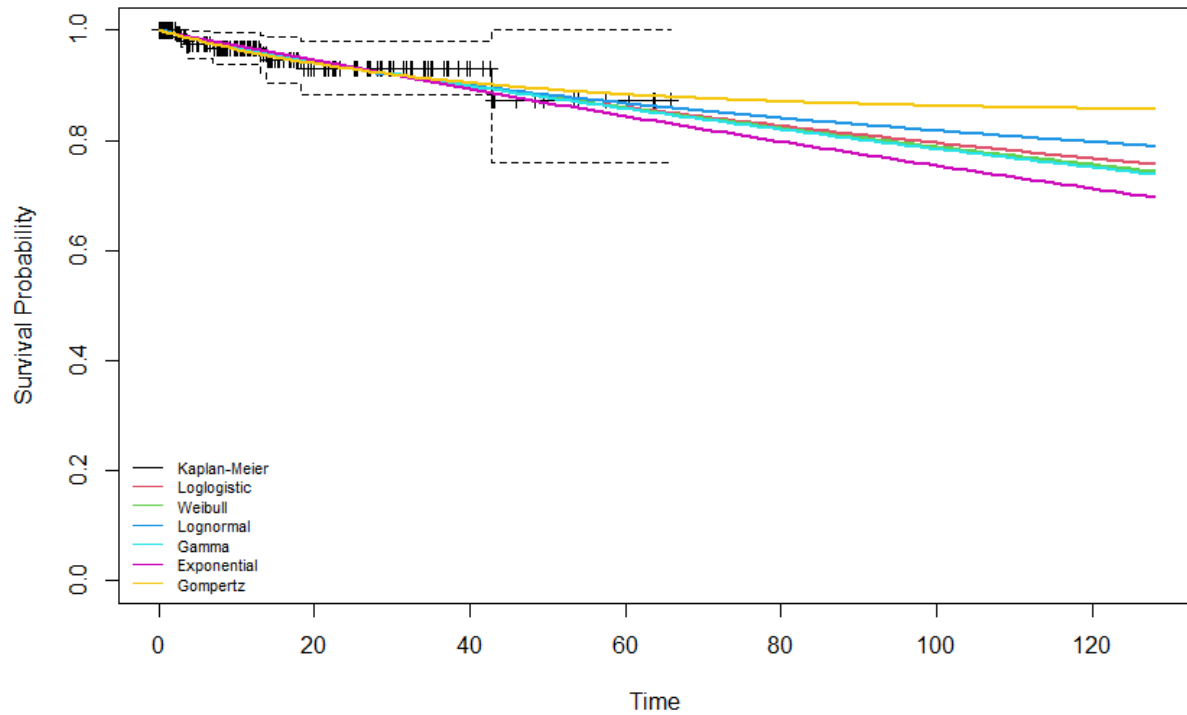
Covariate	Estimate	Lower bound of 95% confidence interval	Upper bound of 95% confidence interval	Standard error
meanlog	1.75	0.10	3.40	0.8426
sdlog	1.52	1.25	1.85	0.1524
age_diag>40	0.67	-0.22	1.57	0.4554
locL2	0.01	-0.77	0.79	0.3981
locL3	0.23	-0.51	0.96	0.3742
locL4	-0.08	-1.52	1.35	0.7317
fenB2	0.30	-0.90	1.51	0.6156
fenB3	0.46	-0.72	1.65	0.6062
sexM	-0.03	-0.62	0.57	0.3035
smokeN	-0.51	-1.31	0.28	0.4063

peri_aN	0.40	-0.95	1.76	0.692
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4.4 Surgery due to active disease model

Time to surgery due to active disease was estimated on 198 patients with a follow-up of approximately 14 years. There were not enough events to allow the estimation of covariates, resulting in a single rate from the best fitting exponential model.

4.4.1 Extrapolation plotted on Kaplan Meier-curve



4.4.2 Akaike information criterion (AIC)/Bayesian information criterion (BIC)

AIC					
Loglogistic	Weibull	Lognormal	Gamma	Exponential	Gompertz
127.318	127.407	126.453	127.435	125.639	126.899
BIC					
Loglogistic	Weibull	Lognormal	Gamma	Exponential	Gompertz
133.894	133.983	133.029	134.011	128.927	133.476

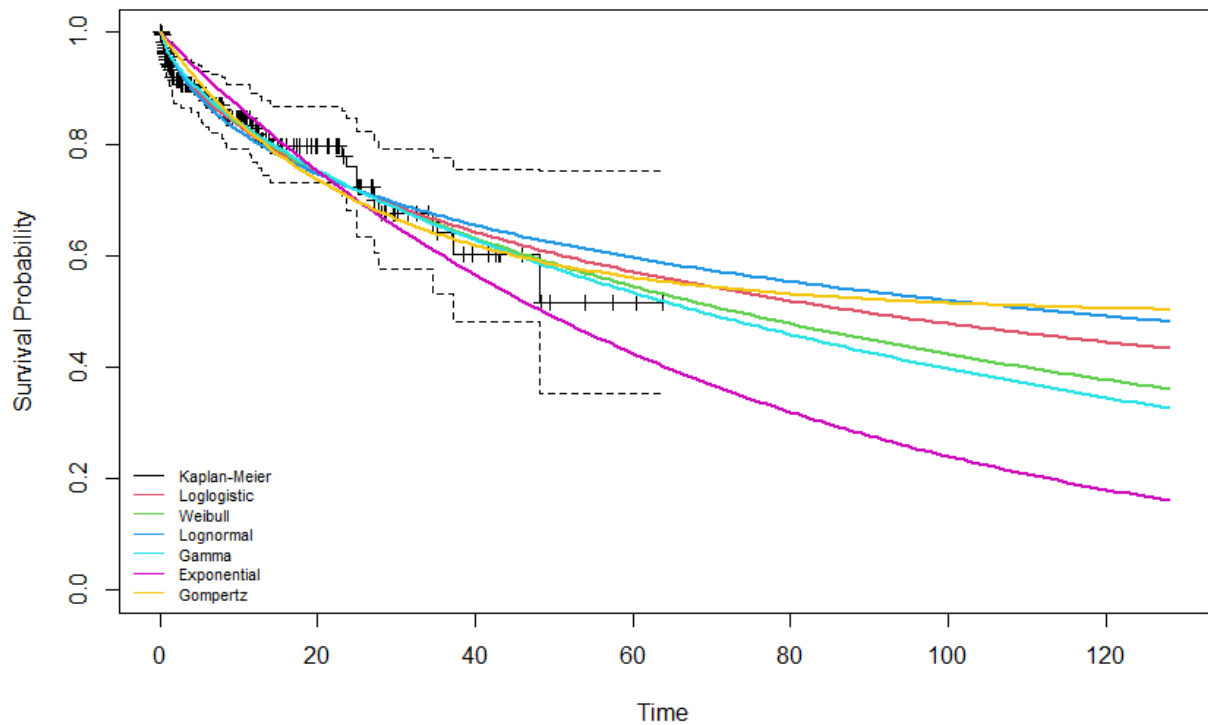
4.4.3 Model parameter

Covariate	Estimate	Lower bound of 95% confidence interval	Upper bound of 95% confidence interval	Standard error
rate	0.0028	0.0015	0.005	0.0009

4.5 'Other' surgery model

The 12-weekly transition probabilities of surgery due to other indications than 'active disease' were estimated on 178 patients with a follow-up of approximately 14 years. The best fitting model was a lognormal model.

4.5.1 Extrapolation plotted on Kaplan Meier-curve



4.5.2 Akaike information criterion (AIC)/Bayesian information criterion (BIC)

AIC					
Loglogistic	Weibull	Lognormal	Gamma	Exponential	Gompertz
394.13	393.81	393.15	393.84	400.973	399.486
BIC					
Loglogistic	Weibull	Lognormal	Gamma	Exponential	Gompertz
400.66	400.34	399.67	400.37	404.235	406.012

4.5.3 Model coefficients

Covariate	Estimate	Lower bound of 95% confidence interval	Upper bound of 95% confidence interval	Standard error
meanlog	5.14	2.96	7.31502	1.11089
sdlog	2.36	1.83	3.05205	0.30775
age_diag>40	-0.64	-1.81	0.53044	0.5966
locL2	0.25	-1.07	1.57035	0.67265
locL3	-0.04	-1.38	1.29802	0.6829
locL4	-2.43	-6.24	1.38132	1.94374

fenB2	0.14	-1.29	1.57005	0.72945
fenB3	-0.25	-2.33	1.82773	1.06162
sexM	-1.40	-2.51	-0.30018	0.5626
smokeN	-0.18	-1.30	0.94633	0.57426
peri_aN	0.28214	-1.21427	1.77854	0.76349

5 Cost input

5.1 Analysis of COIN study data

The re-analysis of the COIN study data consisted of splitting the reported costs by CDAI categories remission (CDAI<150), response (CDAI 151-220) and active disease (CDAI>220). Surgery costs were split between surgery due to active disease ((neo-)ileocecal resection, colonic resection, or hemicolectomy) and other surgery (colonic resection, small intestine resection, perianal fistulae surgery, hemicolectomy, or (neo-)ileocecal resection). The majority of surgeries due to active disease were (neo-)ileocecal resections (67%), therefore the costs were based on the DRG code for this surgery. 'Other surgery' formed a weighted mean based on the observed proportions of the surgeries in the IBD-SL registry and the costs of the DRG codes for these surgeries (119899008 and 119899022)).

5.2 12-weekly cost input overview table

Health care costs	Induction period/Active disease	Maintenance
<i>Drug costs*</i>		
Vedolizumab + C (300mg/108mg)	€ 8,560	€ 3,306
Ustekinumab (6mg/kg/90mg)	€ 11,488	€ 4,164
Methotrexate (25mg/15mg)	€ 331	€ 248
Infliximab (5mg/kg)	€ 4,707	€ 2,354
Adalimumab (160-80-40/40mg)	€ 3,357	€ 1,934
Infliximab + azathioprine (5 mg/kg - 2-2.5 mg/kg)	€ 4,756	€ 2,392
Azathioprine + C (2-2.5 mg/kg)	€ 49	€ 39
Risankizumab (600mg/360mg)	€ 7,560	€ 3,780
Upadacitinib (45mg/30mg)	€ 8,130	€ 2,696
<i>Health state costs</i>		
Active disease	€ 839	
Remission	€ 174	
Remission due to surgery	€ 174	
Death	€ -	
<i>Surgery costs</i>		
Surgery due to active disease	€ 7,235	
Other surgery	€ 9,194	
Societal costs		
Paid work active disease	€ 1,808	
Paid work remission/response	€ 546	
Caregiver time costs	€ 1,659	
Unpaid work	€ 361	

* Note: these are list prices while the model runs with confidential discounted prices

5.3 Future medical cost input

Age	Last year of life males	Last year of life females	Other year males	Other year females
1	€ 19,882	€ 18,047	€ 2,476	€ 2,496
2	€ 19,083	€ 16,673	€ 2,140	€ 1,723
3	€ 19,733	€ 16,556	€ 2,059	€ 1,634
4	€ 20,474	€ 16,724	€ 2,059	€ 1,601
5	€ 20,928	€ 16,965	€ 2,089	€ 1,596
6	€ 21,142	€ 17,232	€ 2,133	€ 1,621
7	€ 21,271	€ 17,547	€ 2,187	€ 1,683
8	€ 21,394	€ 17,919	€ 2,247	€ 1,777
9	€ 21,510	€ 18,300	€ 2,304	€ 1,887
10	€ 21,591	€ 18,639	€ 2,348	€ 1,996
11	€ 21,623	€ 18,893	€ 2,375	€ 2,090
12	€ 21,584	€ 19,040	€ 2,384	€ 2,157
13	€ 21,450	€ 19,118	€ 2,382	€ 2,202
14	€ 21,211	€ 19,136	€ 2,380	€ 2,241
15	€ 20,866	€ 19,124	€ 2,380	€ 2,277
16	€ 20,405	€ 19,125	€ 2,394	€ 2,325
17	€ 19,820	€ 19,170	€ 2,433	€ 2,397
18	€ 19,120	€ 19,288	€ 2,495	€ 2,495
19	€ 18,404	€ 19,519	€ 2,567	€ 2,607
20	€ 17,756	€ 19,908	€ 2,636	€ 2,727
21	€ 17,220	€ 20,503	€ 2,687	€ 2,846
22	€ 16,826	€ 21,353	€ 2,710	€ 2,958
23	€ 16,589	€ 22,479	€ 2,702	€ 3,064
24	€ 16,509	€ 23,856	€ 2,674	€ 3,166
25	€ 16,574	€ 25,436	€ 2,635	€ 3,270
26	€ 16,787	€ 27,175	€ 2,597	€ 3,376
27	€ 17,154	€ 28,981	€ 2,570	€ 3,484
28	€ 17,626	€ 30,757	€ 2,559	€ 3,589
29	€ 18,149	€ 32,380	€ 2,559	€ 3,680
30	€ 18,692	€ 33,757	€ 2,569	€ 3,748
31	€ 19,267	€ 34,828	€ 2,586	€ 3,788
32	€ 19,897	€ 35,558	€ 2,608	€ 3,795
33	€ 20,606	€ 35,978	€ 2,635	€ 3,773
34	€ 21,395	€ 36,182	€ 2,664	€ 3,725
35	€ 22,247	€ 36,276	€ 2,693	€ 3,658
36	€ 23,143	€ 36,340	€ 2,721	€ 3,576
37	€ 24,066	€ 36,462	€ 2,746	€ 3,487
38	€ 25,008	€ 36,707	€ 2,771	€ 3,400

39	€ 25,965	€ 37,095	€ 2,796	€ 3,321
40	€ 26,943	€ 37,642	€ 2,824	€ 3,259
41	€ 27,955	€ 38,399	€ 2,858	€ 3,222
42	€ 29,036	€ 39,450	€ 2,901	€ 3,218
43	€ 30,216	€ 40,803	€ 2,955	€ 3,246
44	€ 31,503	€ 42,377	€ 3,017	€ 3,297
45	€ 32,915	€ 44,076	€ 3,087	€ 3,366
46	€ 34,465	€ 45,884	€ 3,163	€ 3,446
47	€ 36,171	€ 47,833	€ 3,246	€ 3,532
48	€ 38,039	€ 50,012	€ 3,336	€ 3,622
49	€ 40,037	€ 52,448	€ 3,429	€ 3,713
50	€ 42,012	€ 54,870	€ 3,525	€ 3,804
51	€ 43,871	€ 57,032	€ 3,622	€ 3,890
52	€ 45,546	€ 58,682	€ 3,720	€ 3,970
53	€ 47,039	€ 59,783	€ 3,820	€ 4,045
54	€ 48,369	€ 60,456	€ 3,923	€ 4,116
55	€ 49,587	€ 60,885	€ 4,033	€ 4,187
56	€ 50,740	€ 61,239	€ 4,151	€ 4,261
57	€ 51,795	€ 61,469	€ 4,281	€ 4,340
58	€ 52,669	€ 61,458	€ 4,421	€ 4,427
59	€ 53,253	€ 61,082	€ 4,570	€ 4,521
60	€ 53,513	€ 60,341	€ 4,725	€ 4,622
61	€ 53,577	€ 59,482	€ 4,883	€ 4,733
62	€ 53,602	€ 58,758	€ 5,044	€ 4,856
63	€ 53,645	€ 58,266	€ 5,209	€ 4,996
64	€ 53,705	€ 57,955	€ 5,380	€ 5,153
65	€ 53,727	€ 57,687	€ 5,559	€ 5,326
66	€ 53,668	€ 57,331	€ 5,748	€ 5,513
67	€ 53,500	€ 56,801	€ 5,949	€ 5,715
68	€ 53,244	€ 56,129	€ 6,166	€ 5,936
69	€ 52,939	€ 55,409	€ 6,408	€ 6,186
70	€ 52,592	€ 54,728	€ 6,678	€ 6,475
71	€ 52,214	€ 54,156	€ 6,982	€ 6,815
72	€ 51,853	€ 53,739	€ 7,327	€ 7,215
73	€ 51,554	€ 53,509	€ 7,716	€ 7,683
74	€ 51,350	€ 53,481	€ 8,150	€ 8,221
75	€ 51,182	€ 53,628	€ 8,624	€ 8,832
76	€ 50,941	€ 53,901	€ 9,131	€ 9,519
77	€ 50,527	€ 54,247	€ 9,661	€ 10,283
78	€ 49,926	€ 54,698	€ 10,217	€ 11,140
79	€ 49,297	€ 55,340	€ 10,825	€ 12,120
80	€ 48,783	€ 56,226	€ 11,518	€ 13,255

81	€ 48,552	€ 57,426	€ 12,328	€ 14,575
82	€ 48,642	€ 58,973	€ 13,288	€ 16,110
83	€ 48,940	€ 60,748	€ 14,396	€ 17,851
84	€ 49,366	€ 62,636	€ 15,616	€ 19,750
85	€ 49,967	€ 64,678	€ 16,892	€ 21,745
86	€ 50,647	€ 66,753	€ 18,196	€ 23,786
87	€ 51,416	€ 68,791	€ 19,537	€ 25,847
88	€ 52,430	€ 70,896	€ 20,972	€ 27,956
89	€ 53,823	€ 73,158	€ 22,572	€ 30,148
90	€ 55,635	€ 75,597	€ 24,379	€ 32,450
91	€ 57,839	€ 78,174	€ 26,425	€ 34,883
92	€ 60,325	€ 80,778	€ 28,720	€ 37,457
93	€ 62,826	€ 83,202	€ 31,220	€ 40,160
94	€ 65,138	€ 85,361	€ 33,932	€ 43,066
95	€ 67,139	€ 87,290	€ 36,907	€ 46,303
96	€ 68,533	€ 88,692	€ 40,385	€ 50,181
97	€ 64,260	€ 83,281	€ 41,406	€ 51,389
98	€ 59,710	€ 76,966	€ 43,122	€ 53,074
99	€ 54,997	€ 69,925	€ 45,881	€ 55,415
100	€ 54,997	€ 69,925	€ 45,881	€ 55,415

6 Utility model

The IB-DREAM registry classifies disease activity according to the Harvey Bradshaw Index (HBI) which we subsequently mapped to CDAI for use in our cost-effectiveness model using the algorithm by Vermeire et al.(15). HBI >7 was used for active disease and HBI≤4 for remission. Two model types were fitted to the data: a generalized linear model on the disutility (=1-utility) with a gamma distribution and an ordinary least squares (OLS) model. Model fit was assessed by the mean absolute difference between predicted and observed values. The OLS model had less prediction error than the gamma model on disutilities (mean absolute error of 0.15 vs. 0.17) and was preferred due to its better estimation of mean health state values despite being a poorer reflection of the distribution of these values. The model had an R-squared of 0.14.

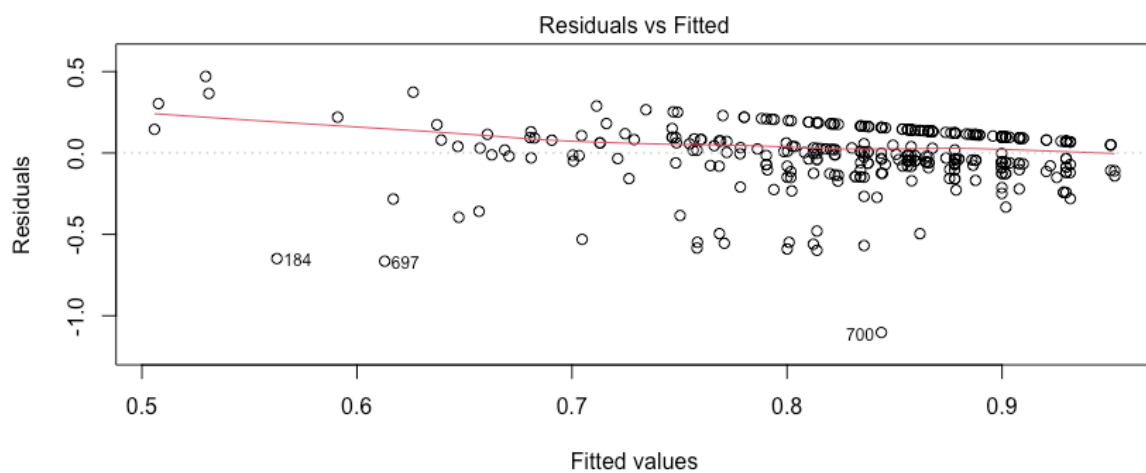
6.1 Model coefficients

Covariates	Estimate	Standard error	p-value
(Intercept)	0.70	0.05	0.00
factor(gender)women	-0.04	0.02	0.059
factor(disease_state)Remission	0.18	0.03	0.000
factor(disease_state)Response	0.09	0.05	0.061
factor(age_diag)1	0.01	0.03	0.759
factor(location)L2	0.05	0.03	0.072

factor(location)L3	0.05	0.02	0.038
factor(location)L4	-0.07	0.07	0.341
factor(behavior)B2	0.03	0.03	0.365
factor(behavior)B3	-0.08	0.04	0.065
perianal	0.01	0.05	0.807
smoke	-0.04	0.02	0.115
age	-0.0004	0.00	0.624

6.2 Model diagnostic plot: Residuals vs fitted values

Prediction error increased at the lower end of the utility scale as is common in linear models on utility data.



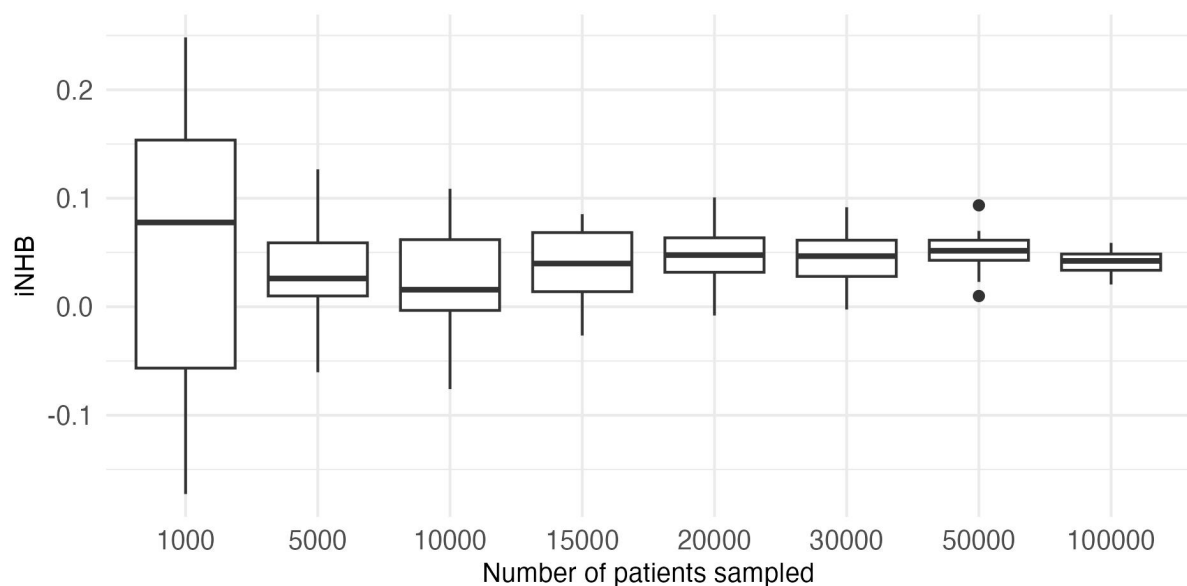
7 Treatment sequences in the model

Table 3: treatment sequences		
Line 1	Line 2 and 3	Line 3 and 4
Azathioprine + corticosteroids (AZA)	Infliximab	-
Methotrexate (MTX)	Adalimumab	-
<i>Infliximab (IFX5)</i>	Infliximab + azathioprine	-
<i>Adalimumab (ADA40)</i>	Ustekinumab (UST)	Ustekinumab
<i>Infliximab + azathioprine (IFX+AZA)</i>	<i>Vedolizumab + corticosteroids (VED)</i>	Vedolizumab + corticosteroids
-	<i>Risankizumab (RIS)</i>	Risankizumab
-	Upadacitinib (UPA)	Upadacitinib

Italic = only in top-down sequences available in line 1 and line 2

8 Sample size analysis

Comparison of AZA-IFX+AZA-UST-UPA-RIS vs MTX in line 1.



iNHB = incremental net health benefit

9 Probabilistic sensitivity analysis input parameters

Parameter	Base case value	Sampling distribution
Placebo probability remission biologic naive	0.2158	Beta
Placebo probability remission biologic exposed	0.1525	Beta
Placebo probability discontinuation biologic naive	0.0199	Truncated normal
Placebo probability discontinuation biologic exposed	0.0189	Truncated normal
Cost 1 cycle active disease	839.3	Gamma
Cost 1 cycle remission	174.1	Gamma

Cost 1 cycle response	573.8	Gamma
Cost 1 cycle remission due to surgery	174.1	Gamma
Cost surgery due to active disease	7235	Gamma
Cost other surgery	9194.4	Gamma
Utility OLS model	Appendix 6.1	Multivariate normal
NMA induction remission biologic naive	Appendix 3.1.1	Multivariate normal
NMA induction remission biologic exposed	Appendix 3.1.2	Multivariate normal
NMA maintenance of remission biologic naive	Appendix 3.2.1	Multivariate normal
NMA maintenance of remission biologic exposed	Appendix 3.2.2	Multivariate normal
NMA adverse events biologic naive	Appendix 3.3.1	Multivariate normal
NMA adverse events biologic exposed	Appendix 3.3.2	Multivariate normal
Line 1 biologic naive survival function	Appendix 4.1	Gamma
Line 2 biologic naive survival function	Appendix 4.2	Lognormal
Line 3/3+ biologic exposed survival function	Appendix 4.3	Lognormal
Surgery due to active disease survival function	Appendix 4.4	Exponential
Surgery (other) survival function	Appendix 4.5	Lognormal
Hazard ratio excess mortality females	1.8	Univariate
Hazard ratio excess mortality males	1.5	Univariate

10 Cost-effectiveness threshold calculation

The sequence (AZA-IFX+AZA-VED-RIS-UPA) modelled to calculate the cost-effectiveness threshold yielded 22.61 QALYs discounted at 1.5% per year. The general public of the same age of the cohort (39 years) and gender distribution (70% female) would expect 28.02 QALYs. This means CD patients on average lose 5.4 QALYs compared to the general population. This amounts to a proportional shortfall of 19% for which a cost-effectiveness threshold of €20,000 applies in the Netherlands, as calculated with the iMTA Disease Burden Calculator (iDBC) v2 (available at https://imtamodels.shinyapps.io/iDBCv2_1/) .

11 Deterministic results

11.1 Fully incremental analysis step-up sequences (discounted)

Treatment sequences	Costs (Euros)	Effects	Δcosts	Δeffects	ICER	Status
AZA-IFX+AZA-VED-RIS-UPA	564,273	22.72				ND
MTX-IFX+AZA-VED-RIS-UPA	564,944	22.75	671	0.02	28,558	ND
MTX-IFX+AZA-VED-UST-UPA	570,439	22.80	5495	0.06	97,746	ND
AZA-UST-RIS-VED-UPA	652,380	22.82	81941	0.02	4,376,666	ND
AZA-IFX+AZA-UPA-VED-UST	569,472	22.75				ED
AZA-IFX+AZA-VED-UST-UPA	569,684	22.79				ED
MTX-IFX+AZA-UST-VED-UPA	572,042	22.80				ED
AZA-UST-VED-RIS-UPA	651,311	22.80				ED
All other sequences						D

ICER = incremental cost-effectiveness ratio

ED = extendedly dominated

D = dominated

ND = not dominated

AZA = azathioprine

IFX = infliximab

VED = vedolizumab

RIS = risankizumab

UPA = upadacitinib

MTX = methotrexate

UST = ustekinumab

11.2 Net health benefit ranking step-up sequences (discounted)

Treatment sequence	Costs (Euros)	Effects	NHB
AZA-IFX+AZA-VED-RIS-UPA	€ 564,273	22.72	-5.49
MTX-IFX+AZA-VED-RIS-UPA	€ 564,944	22.75	-5.50
AZA-IFX+AZA-RIS-VED-UPA	€ 565,040	22.73	-5.52
AZA-IFX+AZA-UPA-RIS-VED	€ 564,571	22.69	-5.54
MTX-IFX+AZA-UPA-RIS-VED	€ 565,239	22.70	-5.56
AZA-IFX+AZA-VED-UPA-RIS	€ 565,385	22.68	-5.59
AZA-IFX+AZA-UPA-VED-RIS	€ 565,023	22.66	-5.59
MTX-IFX+AZA-RIS-VED-UPA	€ 566,661	22.73	-5.60
AZA-IFX+AZA-RIS-UPA-VED	€ 566,125	22.69	-5.61
MTX-IFX+AZA-UPA-VED-RIS	€ 566,070	22.68	-5.62
MTX-IFX+AZA-VED-UPA-RIS	€ 566,724	22.68	-5.65
MTX-IFX+AZA-RIS-UPA-VED	€ 567,286	22.70	-5.66
AZA-IFX+AZA-VED-UST-UPA	€ 569,684	22.79	-5.69
MTX-IFX+AZA-VED-UST-UPA	€ 570,439	22.80	-5.72
AZA-IFX+AZA-UPA-VED-UST	€ 569,472	22.75	-5.72

AZA-ADA40-VED-RIS-UPA	€ 565,327	22.52	-5.75
AZA-IFX+AZA-UPA-UST-VED	€ 570,162	22.75	-5.76
AZA-IFX+AZA-VED-UPA-UST	€ 570,214	22.75	-5.76
MTX-IFX+AZA-VED-UPA-UST	€ 571,097	22.78	-5.78
MTX-IFX+AZA-UPA-VED-UST	€ 570,556	22.75	-5.78
AZA-IFX+AZA-UST-VED-UPA	€ 571,381	22.78	-5.79
AZA-IFX+AZA-UPA-RIS-UST	€ 570,071	22.71	-5.79
MTX-ADA40-VED-RIS-UPA	€ 566,564	22.53	-5.79
MTX-IFX+AZA-UPA-UST-VED	€ 571,083	22.75	-5.80
MTX-IFX+AZA-UST-VED-UPA	€ 572,042	22.80	-5.80
AZA-IFX+AZA-RIS-UST-UPA	€ 570,890	22.74	-5.80
AZA-IFX+AZA-UST-RIS-UPA	€ 571,103	22.75	-5.81
AZA-ADA40-RIS-VED-UPA	€ 566,728	22.52	-5.82
MTX-IFX+AZA-UPA-RIS-UST	€ 570,868	22.72	-5.82
AZA-ADA40-UPA-RIS-VED	€ 566,209	22.48	-5.83
MTX-IFX+AZA-UST-RIS-UPA	€ 572,044	22.76	-5.84
AZA-IFX+AZA-RIS-UPA-UST	€ 571,080	22.71	-5.84
AZA-IFX+AZA-UST-UPA-VED	€ 571,943	22.74	-5.85
MTX-ADA40-RIS-VED-UPA	€ 567,770	22.54	-5.85
AZA-IFX+AZA-UPA-UST-RIS	€ 570,924	22.69	-5.86
AZA-ADA40-RIS-UPA-VED	€ 567,153	22.49	-5.87
AZA-ADA40-UPA-VED-RIS	€ 566,637	22.45	-5.88
MTX-ADA40-UPA-RIS-VED	€ 567,507	22.48	-5.89
MTX-IFX+AZA-UPA-UST-RIS	€ 572,036	22.69	-5.91
AZA-ADA40-VED-UPA-RIS	€ 567,225	22.45	-5.91
MTX-ADA40-UPA-VED-RIS	€ 567,646	22.46	-5.92
MTX-IFX+AZA-RIS-UST-UPA	€ 573,334	22.74	-5.93
MTX-IFX+AZA-UST-UPA-VED	€ 573,624	22.74	-5.94
AZA-IFX+AZA-UST-UPA-RIS	€ 572,837	22.70	-5.94
MTX-IFX+AZA-RIS-UPA-UST	€ 573,078	22.71	-5.95
MTX-ADA40-VED-UPA-RIS	€ 568,424	22.47	-5.96
MTX-IFX+AZA-UST-UPA-RIS	€ 573,518	22.71	-5.97
AZA-IFX+AZA-VED-RIS-UST	€ 571,860	22.62	-5.97
MTX-ADA40-RIS-UPA-VED	€ 569,293	22.48	-5.98
AZA-ADA40-VED-UST-UPA	€ 571,507	22.57	-6.00
AZA-ADA40-UPA-VED-UST	€ 571,183	22.54	-6.01
MTX-IFX+AZA-VED-RIS-UST	€ 573,166	22.63	-6.03
AZA-IFX+AZA-VED-UST-RIS	€ 572,813	22.61	-6.03
AZA-IFX+AZA-RIS-VED-UST	€ 572,972	22.62	-6.03
MTX-ADA40-VED-UST-UPA	€ 572,483	22.59	-6.04
MTX-IFX+AZA-VED-UST-RIS	€ 573,138	22.61	-6.04
AZA-ADA40-VED-UPA-UST	€ 571,793	22.54	-6.05

AZA-IFX+AZA-UST-RIS-VED	€ 573,539	22.63	-6.05
MTX-ADA40-UPA-VED-UST	€ 571,975	22.54	-6.05
MTX-IFX+AZA-UST-VED-RIS	€ 574,003	22.64	-6.06
AZA-ADA40-UST-VED-UPA	€ 572,687	22.57	-6.06
AZA-ADA40-UPA-UST-VED	€ 572,038	22.53	-6.07
AZA-IFX+AZA-RIS-UST-VED	€ 573,657	22.61	-6.07
AZA-ADA40-RIS-UST-UPA	€ 572,390	22.55	-6.07
MTX-ADA40-UST-VED-UPA	€ 573,336	22.59	-6.07
MTX-IFX+AZA-RIS-VED-UST	€ 573,971	22.62	-6.08
AZA-IFX+AZA-UST-VED-RIS	€ 573,802	22.61	-6.08
AZA-ADA40-UPA-RIS-UST	€ 571,823	22.51	-6.08
AZA-ADA40-UST-RIS-UPA	€ 572,622	22.54	-6.09
MTX-IFX+AZA-RIS-UST-VED	€ 574,785	22.63	-6.10
MTX-ADA40-UPA-UST-VED	€ 573,115	22.55	-6.11
MTX-IFX+AZA-UST-RIS-VED	€ 574,771	22.62	-6.11
MTX-ADA40-UPA-RIS-UST	€ 572,675	22.52	-6.12
MTX-ADA40-VED-UPA-UST	€ 573,268	22.55	-6.12
MTX-ADA40-RIS-UST-UPA	€ 573,756	22.56	-6.13
AZA-ADA40-UST-UPA-VED	€ 573,498	22.53	-6.14
AZA-ADA40-RIS-UPA-UST	€ 573,091	22.49	-6.16
MTX-ADA40-UST-RIS-UPA	€ 574,571	22.55	-6.18
AZA-ADA40-UPA-UST-RIS	€ 573,154	22.47	-6.18
MTX-ADA40-UST-UPA-VED	€ 574,855	22.55	-6.19
AZA-ADA40-UST-UPA-RIS	€ 573,985	22.48	-6.22
MTX-ADA40-RIS-UPA-UST	€ 574,623	22.51	-6.22
MTX-ADA40-UPA-UST-RIS	€ 574,543	22.47	-6.26
AZA-ADA40-VED-RIS-UST	€ 573,867	22.40	-6.29
MTX-ADA40-UST-UPA-RIS	€ 575,894	22.49	-6.30
MTX-ADA40-VED-RIS-UST	€ 574,702	22.42	-6.31
AZA-ADA40-VED-UST-RIS	€ 574,387	22.39	-6.33
AZA-ADA40-RIS-VED-UST	€ 574,657	22.40	-6.33
AZA-ADA40-UST-RIS-VED	€ 575,151	22.40	-6.36
MTX-ADA40-VED-UST-RIS	€ 575,370	22.40	-6.36
AZA-ADA40-RIS-UST-VED	€ 575,307	22.40	-6.37
MTX-ADA40-RIS-VED-UST	€ 576,285	22.42	-6.40
AZA-ADA40-UST-VED-RIS	€ 575,676	22.38	-6.41
MTX-ADA40-UST-RIS-VED	€ 576,606	22.42	-6.41
MTX-ADA40-UST-VED-RIS	€ 576,402	22.40	-6.42
MTX-ADA40-RIS-UST-VED	€ 577,044	22.40	-6.45
MTX-IFX5-VED-RIS-UPA	€ 581,377	22.25	-6.82
MTX-IFX5-RIS-VED-UPA	€ 581,696	22.26	-6.82
MTX-IFX5-UPA-RIS-VED	€ 581,971	22.20	-6.90

AZA-IFX5-VED-RIS-UPA	€ 582,148	22.20	-6.91
AZA-IFX5-RIS-VED-UPA	€ 582,697	22.21	-6.92
MTX-IFX5-UPA-VED-RIS	€ 582,192	22.18	-6.93
MTX-IFX5-RIS-UPA-VED	€ 582,922	22.21	-6.94
AZA-IFX5-UPA-RIS-VED	€ 582,337	22.16	-6.96
MTX-IFX5-VED-UPA-RIS	€ 582,874	22.18	-6.96
AZA-IFX5-UPA-VED-RIS	€ 583,017	22.13	-7.02
AZA-IFX5-RIS-UPA-VED	€ 583,944	22.17	-7.03
AZA-IFX5-VED-UPA-RIS	€ 583,734	22.14	-7.05
MTX-IFX5-VED-UST-UPA	€ 587,980	22.31	-7.08
MTX-IFX5-UPA-VED-UST	€ 587,489	22.27	-7.11
MTX-IFX5-UPA-UST-VED	€ 587,887	22.27	-7.12
MTX-IFX5-UST-VED-UPA	€ 588,996	22.32	-7.13
MTX-IFX5-VED-UPA-UST	€ 588,432	22.27	-7.15
AZA-IFX5-VED-UST-UPA	€ 588,539	22.27	-7.16
MTX-IFX5-RIS-UST-UPA	€ 588,805	22.27	-7.17
AZA-IFX5-UPA-VED-UST	€ 588,173	22.23	-7.18
MTX-IFX5-UPA-RIS-UST	€ 588,330	22.22	-7.20
MTX-IFX5-UST-RIS-UPA	€ 589,222	22.26	-7.20
MTX-IFX5-UST-UPA-VED	€ 589,741	22.28	-7.21
AZA-IFX5-VED-UPA-UST	€ 588,958	22.23	-7.22
AZA-IFX5-UST-VED-UPA	€ 589,910	22.26	-7.23
AZA-IFX5-UPA-RIS-UST	€ 588,665	22.19	-7.24
AZA-IFX5-UPA-UST-VED	€ 589,221	22.22	-7.24
AZA-IFX5-RIS-UST-UPA	€ 589,547	22.23	-7.25
MTX-IFX5-RIS-UPA-UST	€ 589,481	22.23	-7.25
AZA-IFX5-UST-UPA-VED	€ 590,490	22.23	-7.29
AZA-IFX5-UST-RIS-UPA	€ 590,178	22.21	-7.30
MTX-IFX5-UPA-UST-RIS	€ 589,721	22.18	-7.31
AZA-IFX5-RIS-UPA-UST	€ 590,085	22.19	-7.31
MTX-IFX5-UST-UPA-RIS	€ 590,839	22.20	-7.34
AZA-IFX5-UPA-UST-RIS	€ 590,065	22.15	-7.36
MTX-IFX5-VED-RIS-UST	€ 590,383	22.11	-7.41
AZA-IFX5-UST-UPA-RIS	€ 591,593	22.16	-7.42
MTX-IFX5-RIS-VED-UST	€ 591,277	22.12	-7.45
MTX-IFX5-VED-UST-RIS	€ 591,145	22.11	-7.45
MTX-IFX5-RIS-UST-VED	€ 591,579	22.13	-7.45
AZA-IFX5-VED-RIS-UST	€ 591,072	22.08	-7.47
MTX-IFX5-UST-RIS-VED	€ 592,161	22.12	-7.49
MTX-IFX5-UST-VED-RIS	€ 592,338	22.11	-7.51
AZA-IFX5-RIS-VED-UST	€ 592,011	22.07	-7.53
AZA-IFX5-UST-RIS-VED	€ 592,296	22.08	-7.53

AZA-IFX5-RIS-UST-VED	€ 592,429	22.07	-7.55
AZA-IFX5-VED-UST-RIS	€ 592,213	22.06	-7.55
AZA-IFX5-UST-VED-RIS	€ 593,387	22.06	-7.61
MTX-UST-UPA-RIS-VED	€ 645,638	22.75	-9.53
MTX-UST-VED-RIS-UPA	€ 646,443	22.79	-9.53
MTX-UST-RIS-VED-UPA	€ 646,958	22.79	-9.56
MTX-UST-UPA-VED-RIS	€ 645,813	22.73	-9.56
MTX-UST-RIS-UPA-VED	€ 647,648	22.75	-9.63
MTX-UST-VED-UPA-RIS	€ 647,797	22.73	-9.66
AZA-UST-VED-RIS-UPA	€ 651,311	22.80	-9.76
AZA-UST-UPA-RIS-VED	€ 650,857	22.77	-9.77
AZA-UST-RIS-VED-UPA	€ 652,380	22.82	-9.80
AZA-UST-UPA-VED-RIS	€ 651,603	22.76	-9.82
AZA-UST-RIS-UPA-VED	€ 653,059	22.78	-9.88
AZA-UST-VED-UPA-RIS	€ 652,749	22.75	-9.89

NHB = net health benefit

AZA = azathioprine

IFX = infliximab

VED = vedolizumab

RIS = risankizumab

UPA = upadacitinib

MTX = methotrexaat

UST = ustekinumab

11.3 Fully incremental top down sequences (discounted)

treatment sequences	Costs	Effects	ΔCosts	ΔEffects	ICER	Status
IFX+AZA-VED-UST-RIS-UPA	587,007	22.64				ND
IFX+AZA-VED-RIS-UST-UPA	587,140	22.64	133	0.004	30,852	ND
All other sequences						D

ICER = incremental cost-effectiveness ratio

ED = extendedly dominated

D = dominated

ND = not dominated

AZA = azathioprine

IFX = infliximab

VED = vedolizumab

RIS = risankizumab

UPA = upadacitinib

MTX = methotrexate

UST = ustekinumab

11.4 Net health benefit ranking top down sequences (discounted)

Treatment sequence	Costs (in Euros)	Effects	NHB
IFX+AZA-VED-UST-RIS-UPA	587,007	22.64	-6.71
IFX+AZA-VED-RIS-UST-UPA	587,140	22.64	-6.71
IFX+AZA-UST-VED-RIS-UPA	587,630	22.64	-6.74
IFX+AZA-RIS-VED-UST-UPA	587,625	22.64	-6.74
IFX+AZA-RIS-UST-VED-UPA	588,139	22.64	-6.76
IFX+AZA-UST-RIS-VED-UPA	588,412	22.64	-6.78
ADA40-VED-UST-RIS-UPA	589,804	22.51	-6.98
ADA40-UST-VED-RIS-UPA	590,245	22.51	-7.00
ADA40-UST-RIS-VED-UPA	590,448	22.51	-7.01
ADA40-RIS-VED-UST-UPA	590,322	22.50	-7.02
ADA40-RIS-UST-VED-UPA	590,653	22.51	-7.03
ADA40-VED-RIS-UST-UPA	590,421	22.48	-7.04
IFX+AZA-VED-UST-UPA-RIS	595,432	22.38	-7.39
IFX+AZA-UST-VED-UPA-RIS	595,973	22.39	-7.41
IFX+AZA-UPA-VED-UST-RIS	596,007	22.33	-7.47
IFX+AZA-VED-UPA-UST-RIS	596,602	22.34	-7.49
IFX+AZA-UPA-UST-VED-RIS	596,981	22.33	-7.52
IFX+AZA-UST-UPA-VED-RIS	597,296	22.34	-7.52
IFX+AZA-UST-RIS-UPA-VED	597,996	22.32	-7.58
IFX+AZA-RIS-UST-UPA-VED	598,262	22.31	-7.60
IFX+AZA-VED-RIS-UPA-UST	598,176	22.30	-7.60
IFX+AZA-UPA-VED-RIS-UST	597,767	22.28	-7.61

IFX+AZA-RIS-VED-UPA-UST	598,529	22.31	-7.62
IFX+AZA-VED-UPA-RIS-UST	598,090	22.28	-7.62
IFX5-VED-UST-RIS-UPA	599,861	22.36	-7.64
IFX+AZA-UPA-UST-RIS-VED	598,778	22.30	-7.64
IFX+AZA-UPA-RIS-UST-VED	598,643	22.29	-7.64
IFX+AZA-UPA-RIS-VED-UST	598,533	22.27	-7.66
IFX5-VED-RIS-UST-UPA	600,224	22.35	-7.66
IFX+AZA-UST-UPA-RIS-VED	599,017	22.29	-7.66
IFX+AZA-RIS-UPA-VED-UST	598,614	22.27	-7.66
IFX5-UST-VED-RIS-UPA	600,573	22.36	-7.66
IFX+AZA-RIS-UPA-UST-VED	599,201	22.29	-7.67
IFX5-RIS-UST-VED-UPA	601,256	22.36	-7.71
ADA40-VED-UST-UPA-RIS	598,796	22.23	-7.71
ADA40-UST-VED-UPA-RIS	598,980	22.23	-7.72
IFX5-UST-RIS-VED-UPA	601,401	22.35	-7.72
IFX5-RIS-VED-UST-UPA	601,379	22.34	-7.73
ADA40-UPA-VED-UST-RIS	598,900	22.19	-7.76
ADA40-VED-UPA-UST-RIS	600,004	22.19	-7.81
ADA40-UST-UPA-VED-RIS	599,964	22.18	-7.82
ADA40-UPA-UST-VED-RIS	600,099	22.19	-7.82
ADA40-RIS-UST-UPA-VED	601,298	22.16	-7.91
ADA40-UST-RIS-UPA-VED	601,293	22.16	-7.91
ADA40-UPA-VED-RIS-UST	601,122	22.13	-7.93
ADA40-VED-RIS-UPA-UST	601,372	22.14	-7.93
ADA40-UPA-UST-RIS-VED	601,960	22.13	-7.96
ADA40-RIS-VED-UPA-UST	602,123	22.14	-7.96
ADA40-RIS-UPA-VED-UST	601,637	22.11	-7.97
ADA40-UPA-RIS-UST-VED	601,943	22.13	-7.97
ADA40-RIS-UPA-UST-VED	602,170	22.13	-7.97
ADA40-UST-UPA-RIS-VED	602,144	22.13	-7.98
ADA40-VED-UPA-RIS-UST	601,994	22.12	-7.98
ADA40-UPA-RIS-VED-UST	602,054	22.11	-7.99
IFX5-VED-UST-UPA-RIS	609,392	22.07	-8.40
IFX5-UST-VED-UPA-RIS	610,203	22.06	-8.45
IFX5-UPA-VED-UST-RIS	609,957	22.01	-8.48
IFX5-VED-UPA-UST-RIS	610,853	22.02	-8.52
IFX5-UST-UPA-VED-RIS	611,032	22.02	-8.53
IFX5-UPA-UST-VED-RIS	611,023	22.02	-8.53
IFX5-UST-RIS-UPA-VED	612,213	22.00	-8.61
IFX5-RIS-UST-UPA-VED	612,434	21.99	-8.63
IFX5-VED-RIS-UPA-UST	612,317	21.98	-8.64
IFX5-UPA-VED-RIS-UST	612,005	21.95	-8.65

IFX5-RIS-VED-UPA-UST	612,632	21.98	-8.65
IFX5-VED-UPA-RIS-UST	612,631	21.96	-8.67
IFX5-UPA-UST-RIS-VED	612,853	21.96	-8.68
IFX5-RIS-UPA-VED-UST	612,800	21.95	-8.69
IFX5-UST-UPA-RIS-VED	613,348	21.97	-8.70
IFX5-RIS-UPA-UST-VED	613,431	21.97	-8.70
IFX5-UPA-RIS-VED-UST	612,849	21.94	-8.70
IFX5-UPA-RIS-UST-VED	613,184	21.95	-8.71

NHB = net health benefit

AZA = azathioprine

IFX = infliximab

VED = vedolizumab

RIS = risankizumab

UPA = upadacitinib

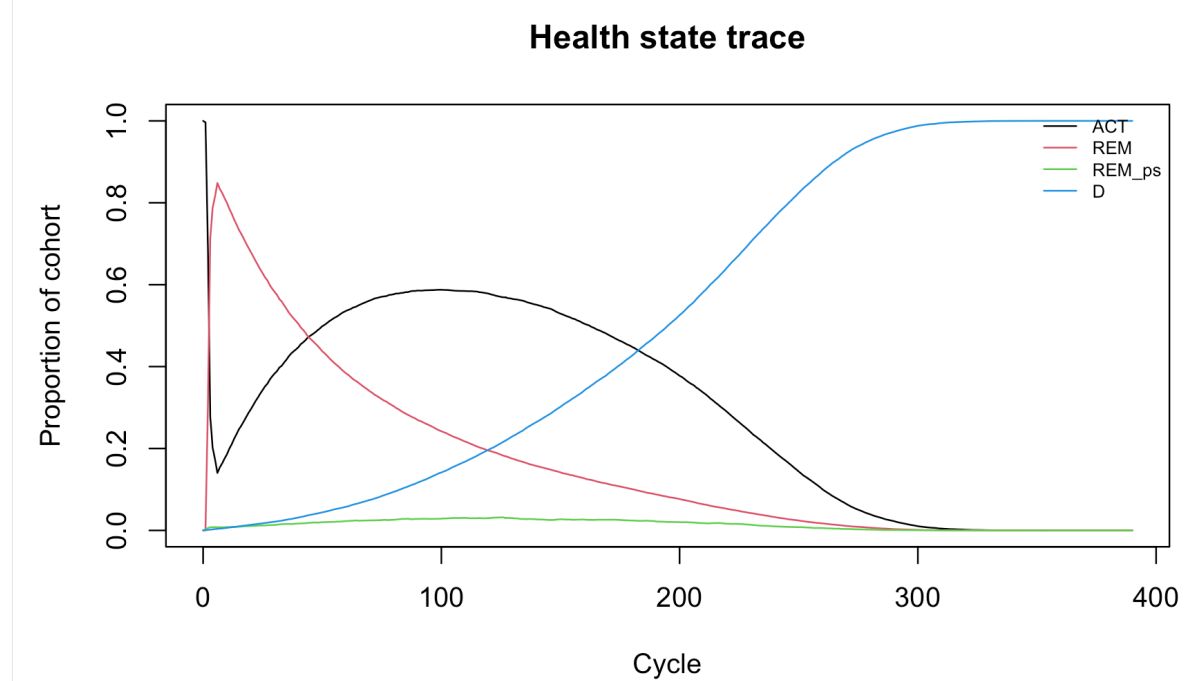
MTX = methotrexate

UST = ustekinumab

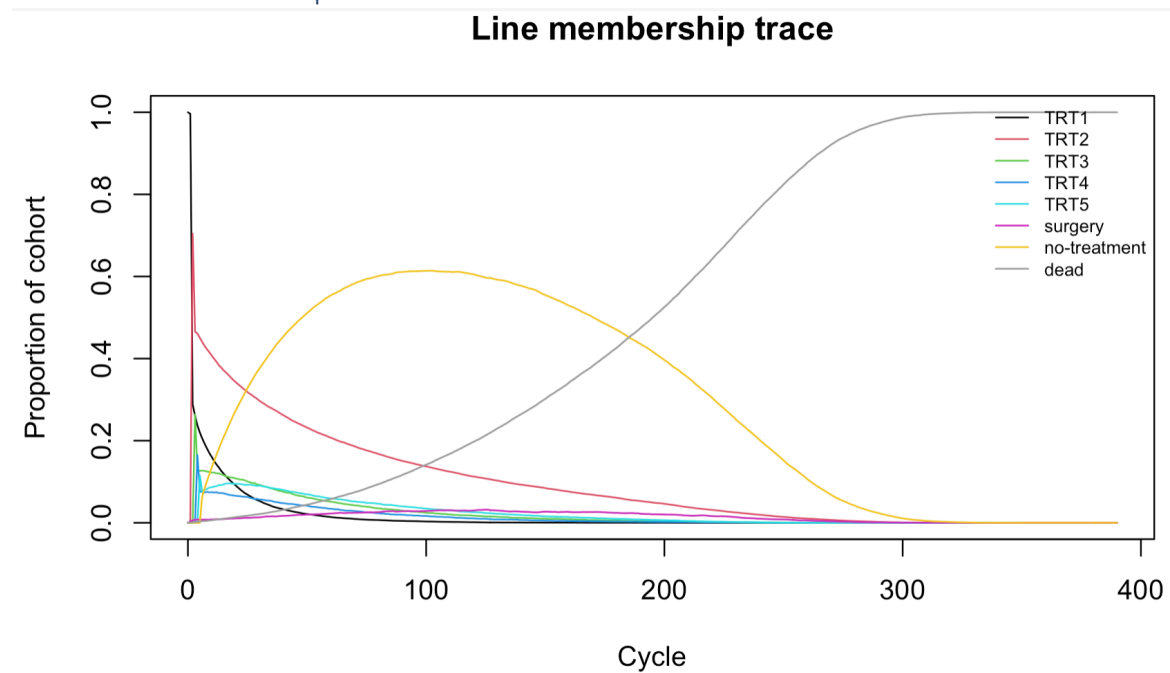
12 Patient flow

12.1 Step-up sequence AZA-> IFX+AZA-> VED-> RIS-> UPA

12.1.1 Health state membership



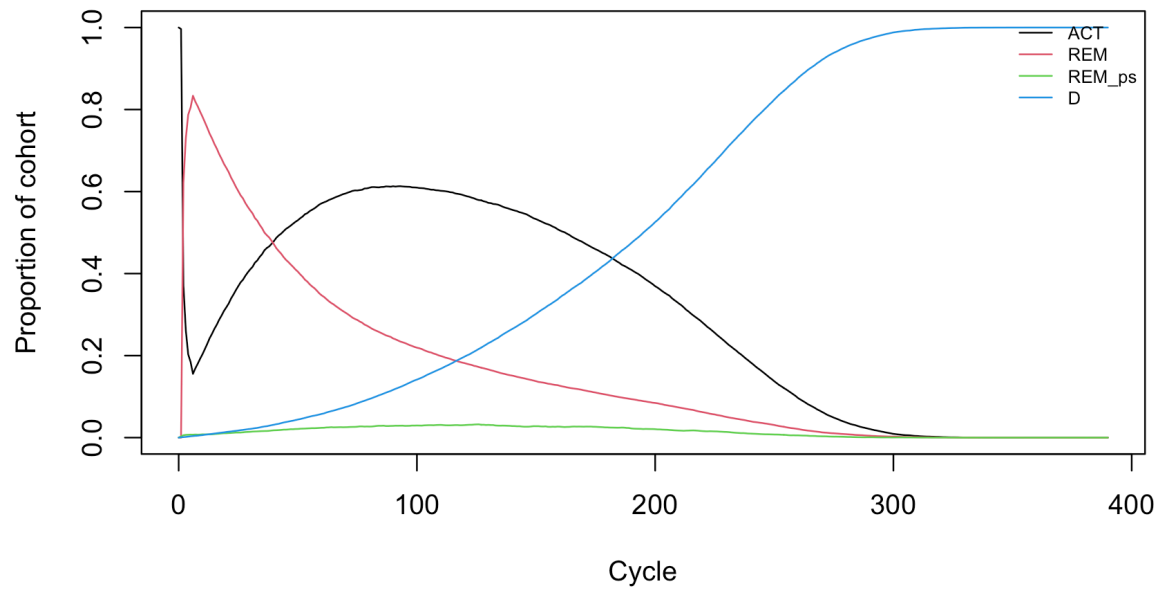
12.1.2 Line membership



12.2 Top-down sequence IFX+AZA-> VED-> UST-> RIS -> UPA

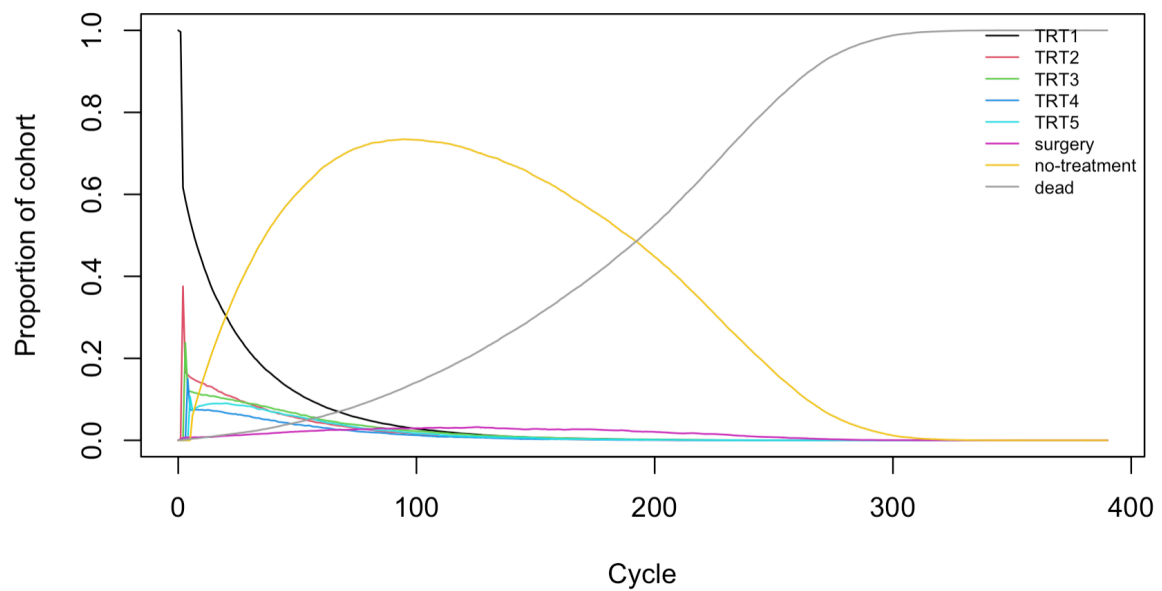
12.2.1 Health state membership

Health state trace



12.2.2 Line membership

Line membership trace

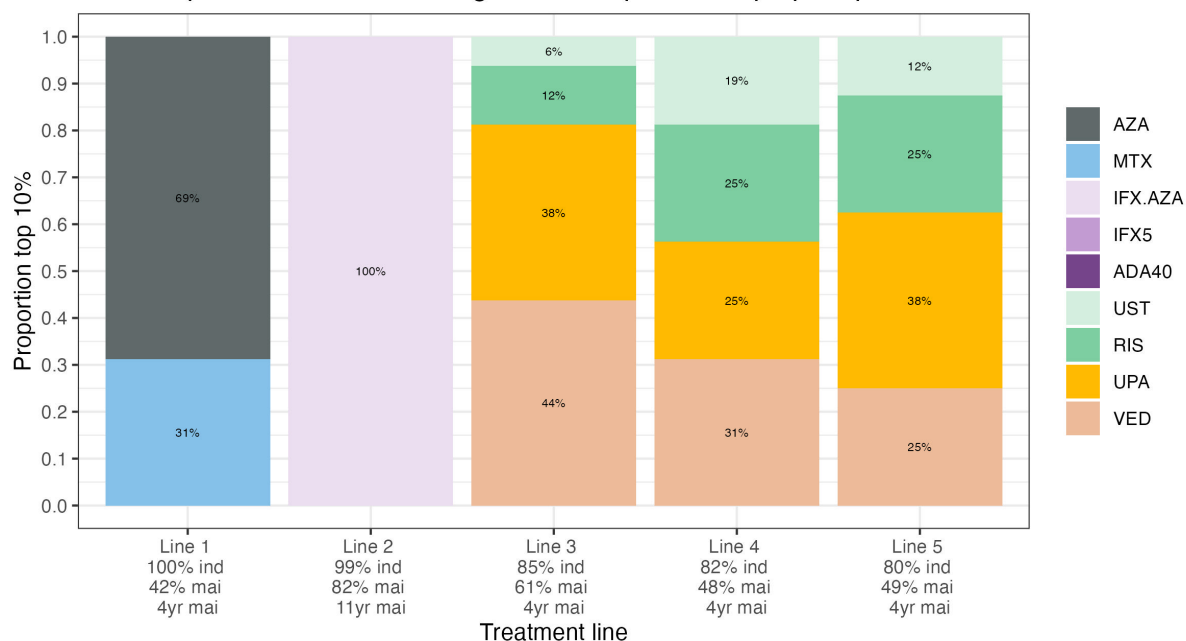


13 Scenario with NMA update

13.1 Step-up sequences

Drug treatment ranking (NHB)

Chart represents how often drug is in the top 10% Step up sequences

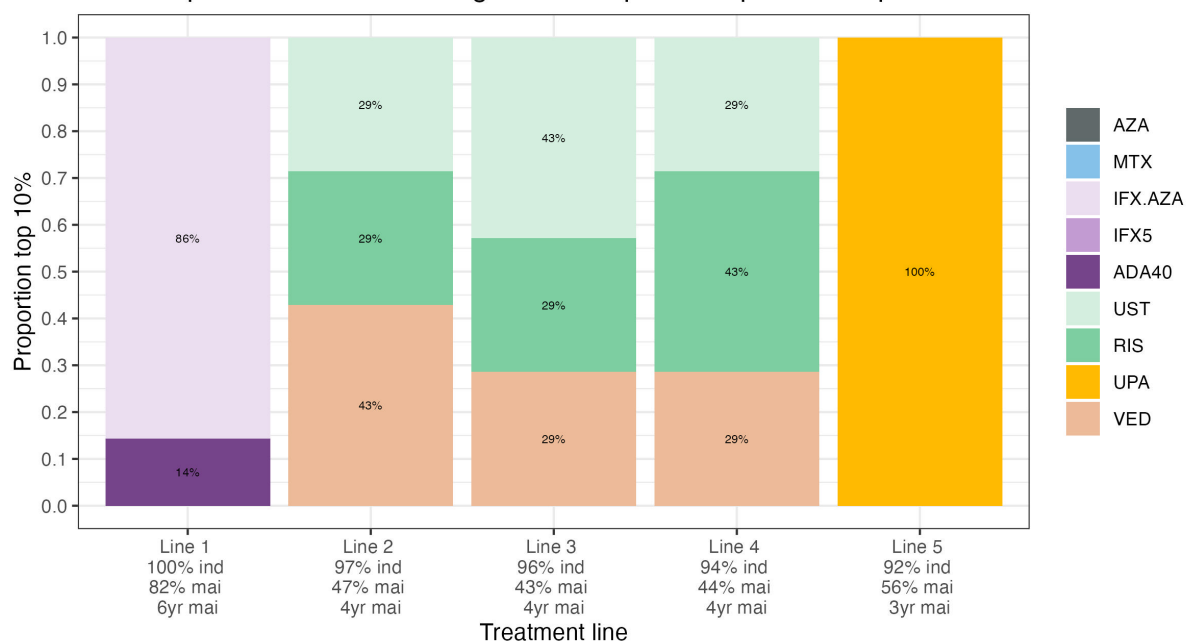


NHB = net health benefit, AZA = azathioprine, MTX = methotrexate, IFX = infliximab, ADA = adalimumab, UST = ustekinumab, RIS = risankizumab, UPA = upadacitinib, VED = vedolizumab, Ind = induction, Mai = maintenance, Yr = years.

13.2 Top-down sequences

Drug treatment ranking (NHB)

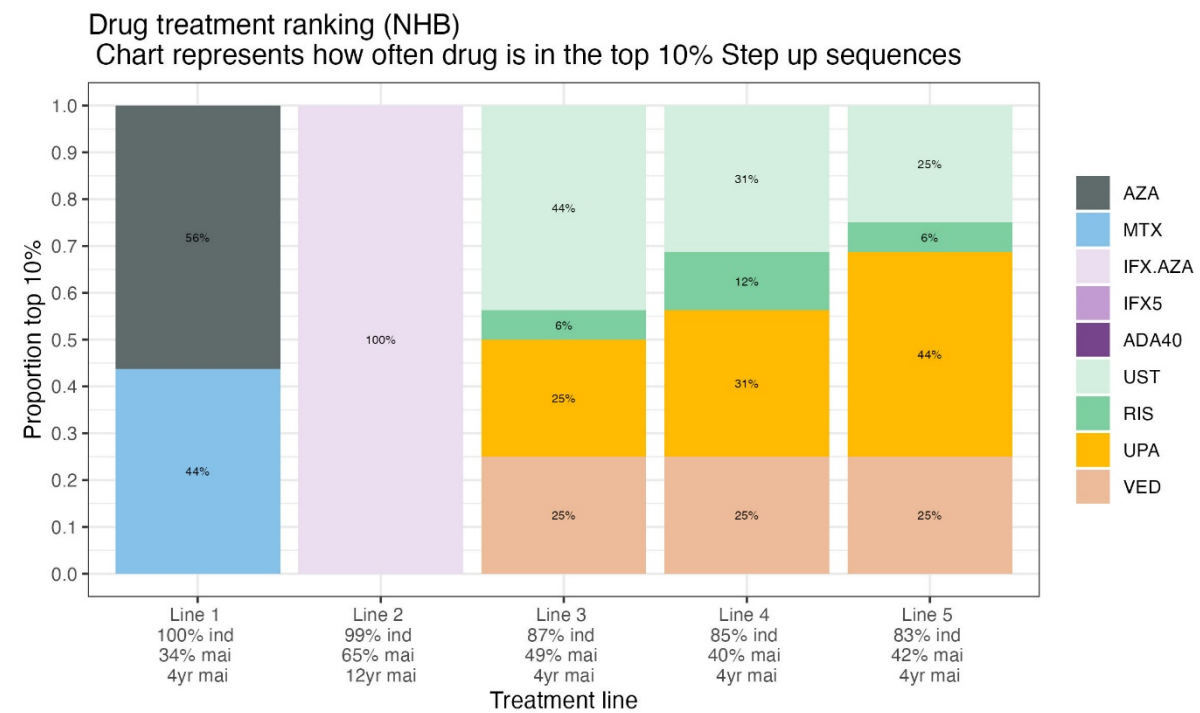
Chart represents how often drug is in the top 10% Top down sequences



NHB = net health benefit, AZA = azathioprine, MTX = methotrexate, IFX = infliximab, ADA = adalimumab, UST = ustekinumab, RIS = risankizumab, UPA = upadacitinib, VED = vedolizumab, Ind = induction, Mai = maintenance, Yr = years.

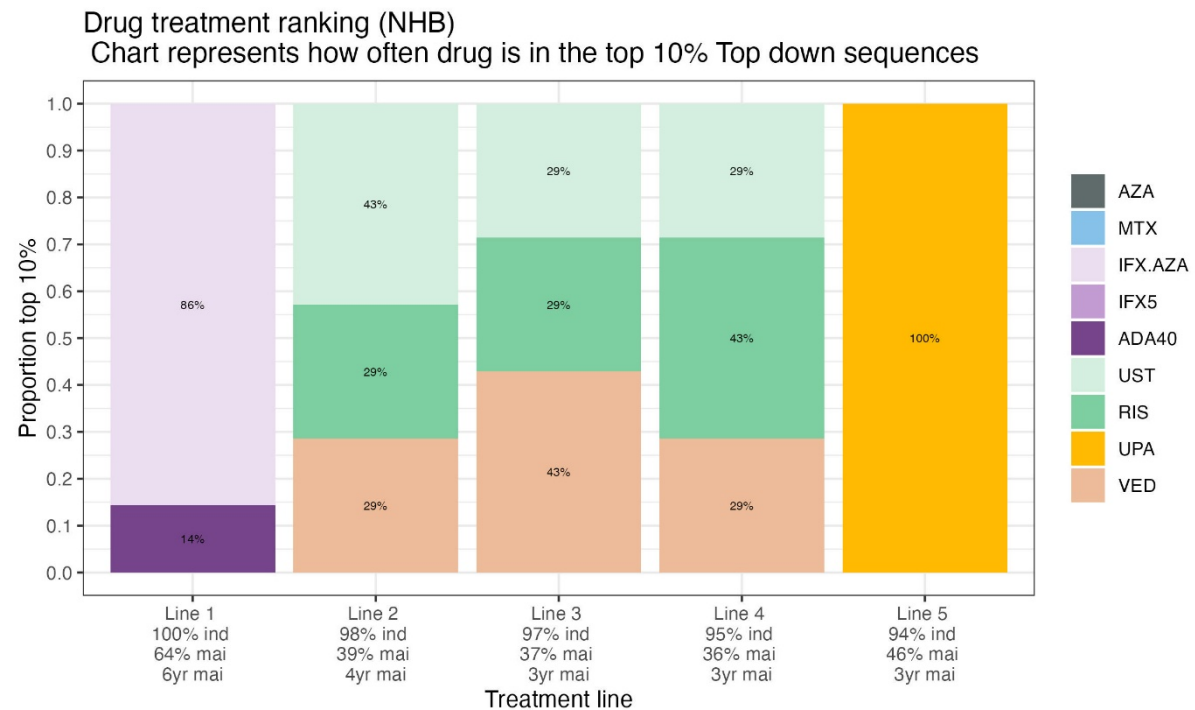
14 Scenario with Ustekinumab 48.4% price decline

14.1 Step-up sequences



NHB = net health benefit, AZA = azathioprine, MTX = methotrexate, IFX = infliximab, ADA = adalimumab, UST = ustekinumab, RIS = risankizumab, UPA = upadacitinib, VED = vedolizumab, Ind = induction, Mai = maintenance, Yr = years.

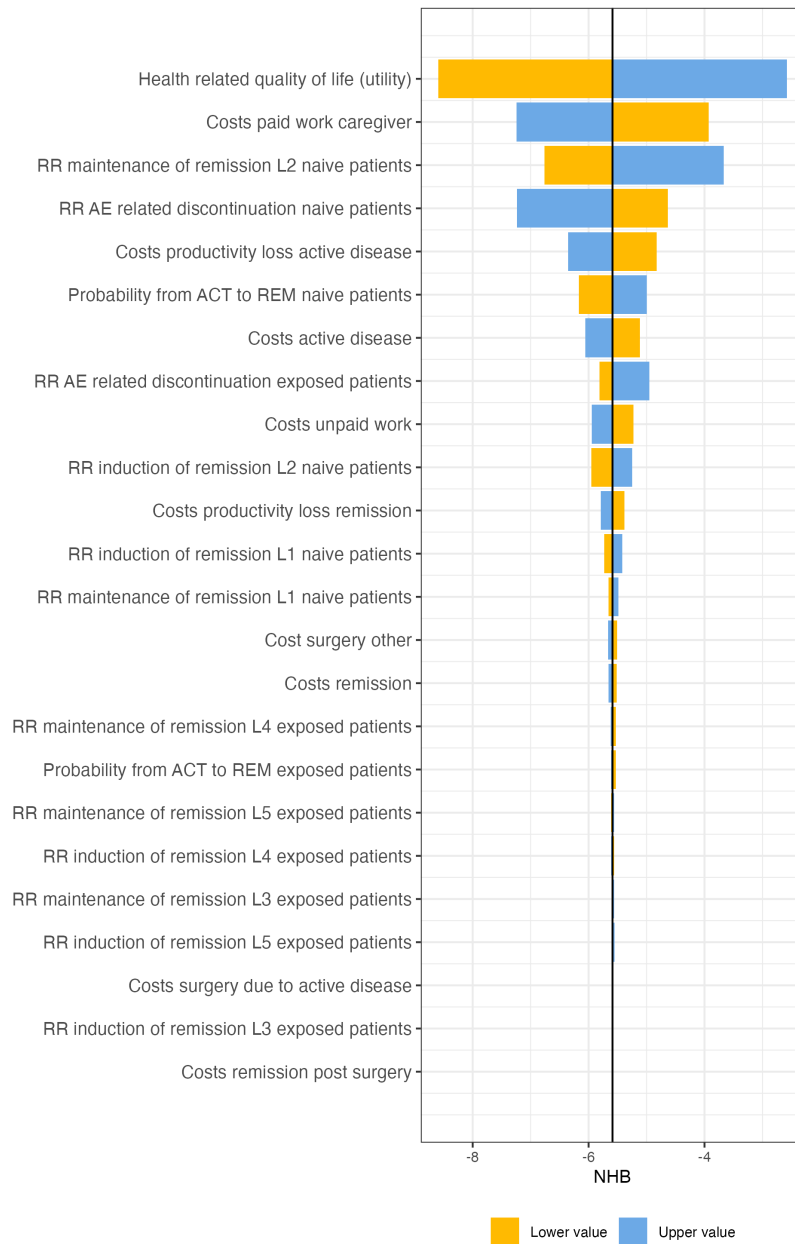
14.2 Top-down sequences



NHB = net health benefit, AZA = azathioprine, MTX = methotrexate, IFX = infliximab, ADA = adalimumab, UST = ustekinumab, RIS = risankizumab, UPA = upadacitinib, VED = vedolizumab, Ind = induction, Mai = maintenance, Yr = years.

15 Tornado diagram

For sequence AZA -> IFX+AZA-> VED-> RIS -> UPA



RR = relative risk, L = line, ACT = active disease, REM = remission.

16 CEAC based ranking of treatment sequences

Step-up		Top down	
Treatment sequence	CEAC_prob	Treatment sequence	CEAC_prob
AZA-IFX+AZA-VED-RIS-UPA	Reference	IFX+AZA-VED-UST-RIS-UPA	Reference
MTX-IFX+AZA-VED-RIS-UPA	0.503	IFX+AZA-VED-RIS-UST-UPA	0.479
MTX-IFX+AZA-RIS-VED-UPA	0.407	IFX+AZA-RIS-VED-UST-UPA	0.432
MTX-ADA40-VED-RIS-UPA	0.395	IFX+AZA-UST-VED-RIS-UPA	0.403
AZA-ADA40-VED-RIS-UPA	0.359	ADA40-RIS-VED-UST-UPA	0.397
MTX-ADA40-RIS-VED-UPA	0.359	ADA40-VED-RIS-UST-UPA	0.394
AZA-ADA40-RIS-VED-UPA	0.338	ADA40-VED-UST-RIS-UPA	0.371
MTX-IFX+AZA-UPA-RIS-VED	0.338	IFX+AZA-RIS-UST-VED-UPA	0.342
AZA-IFX+AZA-RIS-VED-UPA	0.334	ADA40-UST-VED-RIS-UPA	0.336
MTX-ADA40-UPA-RIS-VED	0.334	ADA40-RIS-UST-VED-UPA	0.333
MTX-ADA40-UPA-VED-RIS	0.318	ADA40-UST-RIS-VED-UPA	0.327
MTX-ADA40-VED-UPA-RIS	0.312	IFX+AZA-UST-RIS-VED-UPA	0.298
AZA-ADA40-UPA-RIS-VED	0.305	ADA40-VED-RIS-UPA-UST	0.224
MTX-ADA40-RIS-UPA-VED	0.305	ADA40-RIS-VED-UPA-UST	0.223
MTX-IFX+AZA-UPA-VED-RIS	0.302	ADA40-UPA-VED-RIS-UST	0.222
MTX-IFX+AZA-VED-UPA-RIS	0.289	ADA40-UPA-RIS-VED-UST	0.214
MTX-ADA40-UST-VED-UPA	0.287	ADA40-VED-UPA-RIS-UST	0.214
AZA-ADA40-UPA-VED-RIS	0.286	IFX+AZA-VED-RIS-UPA-UST	0.199
MTX-ADA40-VED-UST-UPA	0.286	ADA40-RIS-UPA-VED-UST	0.198
AZA-ADA40-RIS-UPA-VED	0.282	ADA40-UPA-VED-UST-RIS	0.196
AZA-ADA40-VED-UPA-RIS	0.279	ADA40-VED-UST-UPA-RIS	0.194
MTX-ADA40-UST-RIS-UPA	0.273	IFX+AZA-UPA-VED-RIS-UST	0.189
AZA-ADA40-VED-UST-UPA	0.269	ADA40-VED-UPA-UST-RIS	0.182
MTX-ADA40-RIS-UST-UPA	0.269	ADA40-UST-VED-UPA-RIS	0.181
MTX-IFX+AZA-RIS-UPA-VED	0.269	IFX+AZA-RIS-VED-UPA-UST	0.181
AZA-ADA40-UST-VED-UPA	0.26	IFX+AZA-UPA-VED-UST-RIS	0.181
AZA-ADA40-UST-RIS-UPA	0.258	IFX+AZA-VED-UPA-RIS-UST	0.179
AZA-ADA40-RIS-UST-UPA	0.253	ADA40-UPA-UST-VED-RIS	0.176
MTX-ADA40-UPA-RIS-UST	0.252	IFX+AZA-UPA-RIS-VED-UST	0.171
MTX-ADA40-UPA-VED-UST	0.248	IFX+AZA-VED-UST-UPA-RIS	0.163
MTX-ADA40-VED-UPA-UST	0.244	IFX+AZA-RIS-UPA-VED-UST	0.162
MTX-ADA40-UPA-UST-VED	0.239	ADA40-UST-UPA-VED-RIS	0.158
MTX-IFX+AZA-VED-UST-UPA	0.237	IFX+AZA-UPA-UST-VED-RIS	0.152
AZA-ADA40-UPA-RIS-UST	0.235	IFX+AZA-VED-UPA-UST-RIS	0.152
MTX-ADA40-UST-UPA-VED	0.224	IFX+AZA-UST-VED-UPA-RIS	0.147
MTX-ADA40-RIS-UPA-UST	0.221	IFX5-VED-RIS-UST-UPA	0.134
AZA-ADA40-UPA-VED-UST	0.22	IFX+AZA-UST-UPA-VED-RIS	0.126
MTX-IFX+AZA-RIS-UST-UPA	0.218	IFX5-VED-RIS-UPA-UST	0.126

AZA-ADA40-UPA-UST-VED	0.216	ADA40-UPA-RIS-UST-VED	0.124
MTX-ADA40-UST-UPA-RIS	0.215	IFX5-RIS-VED-UPA-UST	0.118
AZA-ADA40-RIS-UPA-UST	0.213	ADA40-UPA-UST-RIS-VED	0.117
AZA-ADA40-VED-UPA-UST	0.213	IFX5-RIS-VED-UST-UPA	0.117
MTX-ADA40-UPA-UST-RIS	0.212	IFX5-UPA-VED-RIS-UST	0.117
MTX-ADA40-VED-RIS-UST	0.209	ADA40-RIS-UST-UPA-VED	0.11
AZA-ADA40-UPA-UST-RIS	0.205	IFX5-UPA-RIS-VED-UST	0.11
MTX-IFX+AZA-UST-VED-UPA	0.204	IFX5-VED-UPA-RIS-UST	0.108
AZA-ADA40-UST-UPA-RIS	0.202	ADA40-UST-RIS-UPA-VED	0.107
MTX-IFX+AZA-UST-RIS-UPA	0.2	ADA40-RIS-UPA-UST-VED	0.106
AZA-ADA40-UST-UPA-VED	0.197	IFX5-VED-UST-RIS-UPA	0.105
MTX-ADA40-VED-UST-RIS	0.186	ADA40-UST-UPA-RIS-VED	0.103
MTX-IFX+AZA-UPA-RIS-UST	0.184	IFX5-RIS-UPA-VED-UST	0.101
MTX-ADA40-UST-VED-RIS	0.183	IFX5-UST-VED-RIS-UPA	0.101
MTX-ADA40-UST-RIS-VED	0.179	IFX5-RIS-UST-VED-UPA	0.088
MTX-ADA40-RIS-VED-UST	0.176	IFX5-UST-RIS-VED-UPA	0.086
AZA-ADA40-VED-RIS-UST	0.174	IFX+AZA-UPA-RIS-UST-VED	0.083
MTX-ADA40-RIS-UST-VED	0.165	IFX5-UPA-VED-UST-RIS	0.068
MTX-IFX+AZA-UPA-VED-UST	0.163	IFX+AZA-UPA-UST-RIS-VED	0.065
AZA-IFX+AZA-UPA-RIS-VED	0.16	IFX5-VED-UPA-UST-RIS	0.063
AZA-ADA40-RIS-VED-UST	0.158	IFX+AZA-RIS-UPA-UST-VED	0.061
AZA-ADA40-UST-RIS-VED	0.156	IFX5-VED-UST-UPA-RIS	0.06
AZA-ADA40-VED-UST-RIS	0.156	IFX+AZA-RIS-UST-UPA-VED	0.058
MTX-IFX+AZA-RIS-UPA-UST	0.155	IFX+AZA-UST-UPA-RIS-VED	0.057
AZA-ADA40-UST-VED-RIS	0.153	IFX+AZA-UST-RIS-UPA-VED	0.055
MTX-IFX5-VED-RIS-UPA	0.152	IFX5-UPA-UST-VED-RIS	0.054
MTX-IFX+AZA-VED-UPA-UST	0.151	IFX5-UST-VED-UPA-RIS	0.053
AZA-ADA40-RIS-UST-VED	0.143	IFX5-UST-UPA-VED-RIS	0.051
MTX-IFX5-RIS-VED-UPA	0.138	IFX5-UPA-UST-RIS-VED	0.041
MTX-IFX+AZA-UPA-UST-VED	0.137	IFX5-UPA-RIS-UST-VED	0.038
MTX-IFX+AZA-UPA-UST-RIS	0.126	IFX5-RIS-UPA-UST-VED	0.033
AZA-IFX+AZA-UST-RIS-UPA	0.125	IFX5-RIS-UST-UPA-VED	0.033
AZA-IFX5-VED-RIS-UPA	0.118	IFX5-UST-UPA-RIS-VED	0.033
MTX-IFX+AZA-UST-UPA-VED	0.117	IFX5-UST-RIS-UPA-VED	0.031
MTX-IFX+AZA-UST-UPA-RIS	0.114		
MTX-IFX5-UPA-RIS-VED	0.114		
AZA-IFX+AZA-RIS-UST-UPA	0.107		
AZA-IFX+AZA-VED-UST-UPA	0.104		
AZA-IFX5-RIS-VED-UPA	0.104		
MTX-IFX5-UPA-VED-RIS	0.103		
MTX-IFX5-VED-UPA-RIS	0.102		
AZA-IFX+AZA-UST-VED-UPA	0.101		

AZA-IFX+AZA-UPA-VED-RIS	0.097		
MTX-IFX5-RIS-UPA-VED	0.097		
AZA-IFX+AZA-UPA-RIS-UST	0.094		
MTX-IFX5-VED-UST-UPA	0.085		
AZA-IFX+AZA-RIS-UPA-VED	0.084		
AZA-IFX+AZA-RIS-UPA-UST	0.081		
MTX-IFX+AZA-VED-RIS-UST	0.08		
MTX-IFX5-UST-RIS-UPA	0.078		
AZA-IFX+AZA-VED-UPA-RIS	0.077		
AZA-IFX5-UPA-RIS-VED	0.077		
MTX-IFX5-UPA-VED-UST	0.076		
MTX-IFX5-RIS-UST-UPA	0.075		
MTX-IFX+AZA-RIS-VED-UST	0.074		
MTX-IFX5-UST-VED-UPA	0.074		
MTX-IFX5-UPA-RIS-UST	0.071		
AZA-IFX5-UPA-VED-RIS	0.068		
MTX-IFX+AZA-VED-UST-RIS	0.068		
MTX-IFX5-VED-UPA-UST	0.068		
AZA-IFX5-VED-UPA-RIS	0.067		
AZA-IFX+AZA-UPA-UST-RIS	0.065		
AZA-IFX+AZA-UST-UPA-RIS	0.063		
MTX-IFX+AZA-RIS-UST-VED	0.063		
MTX-IFX5-RIS-UPA-UST	0.06		
AZA-IFX5-RIS-UPA-VED	0.059		
MTX-IFX+AZA-UST-RIS-VED	0.059		
MTX-IFX+AZA-UST-VED-RIS	0.056		
MTX-IFX5-UPA-UST-VED	0.056		
MTX-IFX5-UPA-UST-RIS	0.053		
AZA-IFX5-UST-VED-UPA	0.052		
AZA-IFX5-VED-UST-UPA	0.052		
MTX-IFX5-UST-UPA-VED	0.052		
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AZA-IFX5-UPA-RIS-UST	0.038		
MTX-IFX5-RIS-UST-VED	0.038		

AZA-IFX+AZA-UPA-UST-VED	0.035		
AZA-IFX5-VED-UPA-UST	0.035		
MTX-IFX5-UST-RIS-VED	0.035		
MTX-IFX5-VED-UST-RIS	0.035		
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MTX-IFX5-UST-VED-RIS	0.031		
AZA-IFX5-RIS-VED-UST	0.029		
AZA-IFX5-UPA-UST-VED	0.028		
AZA-IFX5-UPA-UST-RIS	0.027		
AZA-IFX5-UST-UPA-VED	0.025		
AZA-IFX5-RIS-UST-VED	0.024		
AZA-IFX5-UST-UPA-RIS	0.024		
AZA-IFX5-VED-UST-RIS	0.024		
AZA-IFX5-UST-RIS-VED	0.023		
AZA-IFX+AZA-RIS-VED-UST	0.021		
AZA-IFX5-UST-VED-RIS	0.021		
AZA-IFX+AZA-UST-RIS-VED	0.018		
AZA-IFX+AZA-VED-RIS-UST	0.017		
AZA-IFX+AZA-VED-UST-RIS	0.016		
AZA-IFX+AZA-RIS-UST-VED	0.014		
MTX-UST-RIS-VED-UPA	0.013		
MTX-UST-VED-RIS-UPA	0.013		
AZA-IFX+AZA-UST-VED-RIS	0.012		
MTX-UST-UPA-RIS-VED	0.011		
MTX-UST-UPA-VED-RIS	0.011		
MTX-UST-VED-UPA-RIS	0.011		
MTX-UST-RIS-UPA-VED	0.01		
AZA-UST-VED-RIS-UPA	0.009		
AZA-UST-RIS-VED-UPA	0.008		
AZA-UST-UPA-RIS-VED	0.006		
AZA-UST-VED-UPA-RIS	0.006		
AZA-UST-RIS-UPA-VED	0.005		
AZA-UST-UPA-VED-RIS	0.005		

CEAC_prob = Probability of being cost-effective based on the cost-effectiveness acceptability curve of the probabilistic sensitivity analysis at a threshold of €20,000 per QALY, AZA = azathioprine, MTX = methotrexate, IFX = infliximab, ADA = adalimumab, UST = ustekinumab, RIS = risankizumab, UPA = upadacitinib, VED = vedolizumab, Ind = induction, Mai = maintenance, Yr = years.