Supplemental Methods

Transition Probabilities and QALY estimate sources

Transition probabilities for both combination therapy with infliximab and azathioprine and infliximab monotherapy were derived from relevant clinical trials. The transition probabilities for initial response and remission rates, rates of relapse, adverse events, and infection were derived from the SONIC trial[1].

All patients that failed initial therapy received adalimumab, either in combination with azathioprine or as monotherapy as dictated by their initial treatment selection. The GAIN study was used to inform initial remission rates with adalimumab, stratified by concomitant immunomodulator use[2]. As response rates were not stratified in this study, the same differential rate between those on combination therapy or monotherapy appreciated for remission was applied to the response rates. Relapse rates stratified by concurrent immunomodulator use were derived using CHARM[3]. Baseline estimates for loss of remission and response were similar for those on combination therapy or monotherapy. We therefore chose the more conservative estimate based on prior therapy with infliximab and applied the equivalent rate to both combination and monotherapy arms for loss of remission and loss of response. A recent meta-analysis presented at ECCO in Copenhagen in 2014 by Koplyov et al supports the use of equivalent relapse rates for combination therapy and monotherapy with adalimumab[4]. Analysis of 6 trials for maintenance of remission and 3 trials for maintenance of response demonstrated no significant benefit for combination therapy with adalimumab (Remission: OR 1.08 (0.87–1.33), Response: OR 1.21 (0.74–1.99)). Similar data were presented by Siegel et al at Digestive Diseases Week in 2013[5].

For both combination therapy and monotherapy, patients could develop a serious adverse event requiring drug cessation. Alternatively, they could develop an infectious complication, resulting in a 1-month cessation of therapy and subsequent resumption of treatment. Rates of these complications were derived from SONIC when subjects were on infliximab[1]. Similarly, adalimumab therapy could result in both of these complications as well, and rates were derived from the CHARM trial of maintenance therapy with adalimumab[2, 3]. This study did not stratify these rates based on concomitant immunosuppression, but did state that rates were similar between those receiving immunomodulators and those that did not. Therefore, we used the same rates of adverse events for both arms for adalimumab use and performed an additional sensitivity analysis to assess higher rates in those with combination therapy.

For the risk of lymphoma, it was assumed that the HR for azathioprine and infliximab were independent of each other. The baseline HR for infliximab was set to 1.0, based on both CESAME, which demonstrated a non-significant standardized incidence ratio, and data from the TREAT registry[6]. The baseline HR for thiopurine use was derived from CESAME, and was set at 5.28[7]. Of import, CESAME assumed a constant continuous risk of lymphoma related to thiopurine exposure. The increased risk observed in CESAME was converted to an instantaneous probability and applied to the age-specific rate of lymphoma for the base case, as determined by the SEER database[8]. Those individuals on combination therapy are exposed to both the HR of infliximab for lymphoma and the HR of the thiopurine, with an assumed multiplicative interaction. Mortality rates for each arm were assumed to be similar to those seen within the general population based on recently published data. Age-specific and sex-specific mortality rates were derived from SEER as well[8, 9]. Overall age-specific survival rate tables from SEER were used to generate these mortality rates, with the model

referencing the age of the individual at the time of diagnosis and then the cycle since diagnosis to determine the transition probability, adjusting this value based on time in the lymphoma node of the model (See Supplemental Table 3). As some patients may be diagnosed with more advanced forms of NHL, we performed a sensitivity analysis of this mortality rate over a +/- 50% range. The model was insensitive to these values.

Quality adjusted life years (QALYs) were used for rewards assigned in transition from state to state (TABLE 1). QALY estimates for severe CD, medical remission, infection, and adverse events were assigned using previously published estimates[10, 11]. QALY estimates for mild CD were assumed to be at the midpoint of severe CD and CD in remission. These QALY estimates were assumed to be constant over all age ranges. With regards to lymphoma, the QALY estimate in the primary analysis was consistent with previously used estimates in models of CD[10]. It is important to note that this value is not adjusted for active CD, based on data suggesting that patients with CD who are undergoing chemotherapy are typically in remission due to the profound immunosuppression[12]. In addition, for the iterations of the model using an extended time horizon, we assumed patients would enter an active CD state and remain there after treatment for lymphoma, assumed to be 4 years in length. However, as these estimates are based on a small cohort study, and assumptions about outcomes of therapy, we performed a sensitivity analysis of the point estimate of 0.47, using a range from 0.20-0.80. The model was not sensitive to these estimates.

Alternative model structures

Impact of allowing sequential anti-TNF use

We examined a version of the model without therapy crossover, where after failing initial combination or monotherapy, patients went to surgery. Given that patients in this study are assumed to have moderate to severe CD, those who failed initial combination therapy or infliximab monotherapy then entered a state of severe CD, with a continuous risk of requiring surgical intervention until the one year time horizon was reached. As with the base model, expected values and incremental effectiveness were calculated for this model.

Accounting for future life-years lost due to mortality and chronic disease states

We also performed an iteration of the model to account for future life years potentially lost due to mortality during the model time horizon. In one analysis, a final reward was applied equivalent to the remaining life expectancy according to US Census data.

Risk of surgical events in the elderly

We assessed the potential impact of increased risk of surgery in the elderly by inserting a modifier of the relative risk of surgical complications or mortality in those were greater than 65 years of age. This relative increased risk was assumed to be a 2-fold increase. We performed an additional one-way sensitivity analysis on this value of increased relative risk, increasing it to a 5-fold increased risk.

Risk of infection with anti-TNFs and azathioprine combination therapy

Given the limited data on the risk of infection and infection-related mortality with both anti-TNFs and in particular combination therapy, we conducted three additional sensitivity analyses examining these specific risks, and then repeated these analyses throughout the lifespan. In the initial analysis, we performed a wider sensitivity analysis of anti-TNF infectious risks. We demonstrated in this model that with an increased odds ratio of infection

from 1 to 5 over the rates used in this study, there is no change in preferred strategy in the base model (Supplemental Figure 2A). We repeated this analysis in 10-year increments from 25 to 75 years of age, with no change in results (data not shown). In the SONIC trial, serious infections were less common in the combination therapy group. Therefore, another sensitivity analysis only increased the risk of infection with combination therapy. While there was a modest reduction in QALYs with increased risk of infection (OR range 1 to 5) for azathioprine, the preferred strategy remained combination therapy (Supplemental Figure 2B). This again remained true if this increased risk of infection with combination therapy is applied in those from age 25 to 75 (Supplemental Figure 3). We also performed a 2-way sensitivity analysis of the risk of infection with combination therapy, as above, with the risk of death related to infection. Monotherapy became the preferred strategy only when the odds of infection was >10x monotherapy and the risk of death related to that infection exceeded 10% (Supplemental Figure 2C).

Lymphoma-related alternative model structures

We performed several analyses examining our assumptions for QALYs and risk of lymphoma. With regards to our QALY assessment for active lymphoma, recent models for NHL have used a QALY estimate of 0.70 for Rituximab-Cyclophosphamide+ Hydroxydaunorubicin+Oncovin+Prednisone (R-CHOP), a common chemotherapeutic regimen for chemotherapy[13]. Therefore, we performed a one-way sensitivity analysis on the QALY estimate for lymphoma.

We also assessed the instantaneous risk of lymphoma used in our model. In our primary models, we assumed an instantaneous, constant hazard of lymphoma when on azathioprine. It is possible that this risk is not instantaneous, with an initial lower risk that increases to the HR described in CESAME over time. Furthermore, it is possible that the cumulative effects of this risk over time may not be properly assessed in our base model with a 1-year time horizon. We attempted to assess this via two alternative models. For these models, the time horizon was extended to 3 years, 5 years, 7 years, and 9 years to assess the long-term impact of these medications.

In the first iteration, we assessed the impact of the time horizon on rates of lymphoma and option preference. We extended the time horizon to 3 years, 5 years, 7 years, or 9 years. Rates of loss of response (LOR), risks of side effects, and risks of lymphoma and lymphoma-related mortality were held constant throughout the time assessed within the model, and equivalent to those used in the base model. As such, there was a continuous attrition from medical therapy due to all causes in the base model. As with the base model and prior iteration assessing the long-term impact of lymphoma risks, we calculated age-specific continuous risks of lymphoma throughout the time period. QALYs estimates calculated in this model accounted only for the time horizon of the model without an additional final reward reflecting remaining life expectancy.

In the second iteration, we also modified the risk of lymphoma over time to assess the impact of a delayed onset of risk of lymphoma in those who were maintained on their therapy. For this model, the initial year of therapy was structured as in the base model for all age ranges for therapy efficacy and risks of flare, infection, and non-lymphoma adverse events. After one year, it was then assumed patients who were on medication remained stable in their remission or response state until 3, 5, 7, or 9 years. Over the first two years of the model, patients were exposed to a reduced hazard of lymphoma that increased linearly in the combination therapy arm until reaching the value of 5.28 appreciated in CESAME using the following formula:

Current cycle HR_{aza} = ((HR_{aza}-1)*(current_cycle/24))+1) until current_cycle≥24

This was then applied throughout the lifespan at the time horizons noted above for comparison to the other models.

For both of these model iterations, the time horizon was adjusted as noted above, and the model was run from ages 25 to 75 as with the base model. Expected values were calculated for each time horizon group and age subgroup for each treatment arm. Incremental effectiveness was then calculated comparing combination therapy to anti-TNF monotherapy. Markov cohorts were estimated for each time horizon as well to assess the number of deaths and number of cases of lymphoma for combination therapy and monotherapy as well. Incremental effectiveness, mortality, and lymphoma estimates are presented in Supplemental Table 1.

Of note, neither of these models applied an extra reward to the final health state equivalent to the remaining life expectancy. As such, these models under value the reduction in lifetime QALYs resulting from premature death. Despite this, with longer duration, monotherapy becomes the preferred strategy in older patients (age 75) with as little as 5 years of therapy and in those age 55 or older with up to 9 years of therapy (See Supplemental Table 1).

Lastly, in our base model, infliximab was assigned a hazard ratio of 1.0 for lymphoma. It is possible that this is an underestimate of the risk of lymphoma attributable to infliximab. We therefore performed a sensitivity analysis looking at this specific value, and the model was not sensitive to this estimate (Supplemental Figure 4). We also assessed the impact of varying hazard ratios on overall rates of lymphoma within the model, utilizing the baseline risk (1.0), 2.0, and 3.0 to determine how that would change overall lymphoma rates in Markov cohort analysis (See Supplemental Table 2).

Risk of HSTCL in Young Males

We also wished to assess the impact of the increased risk of HSTCL in younger males. To assess the impact of this rare but usually fatal disease, we created an iteration of the model for 25 year old males where this was a potential complication in combination therapy alone. The risk of HSTCL was derived from a pooled analysis of two large observational studies [7, 14]. In one study utilizing the Kaiser Permanente Northern California dataset, Herrinton et al identified 1 case of HSTCL within 3,652 person-years of exposure. In the CESAME cohort, there were no cases of HSTCL among 16,659 person-years of current thiopurine exposure. Therefore, there was 1 case amongst 20,311 individuals actively being treated with a thiopurine; assuming 44% of exposure was among males, we estimated the incidence of HSTCL among thiopurines exposed makes to be 11.2/100,000 person years[7, 14]. This was included in our model as an instantaneous probability. It is important to note that this may overestimate this risk, as smaller studies have noted that the reported cases of HSTCL all occur after several years of exposure[15]. We then assessed what incidence rate of HSTCL would be required for monotherapy to be the preferred strategy and performed a Markov cohort analysis to assess the increase in mortality directly attributable to HSTCL.

Probabilistic sensitivity analyses

For the primary calculation of QALYs, as well as FOMCS, deterministic transition probabilities and QALY-related rewards were utilized. For second order Monte Carlo simulation, probabilistic distributions were generated for all transition probabilities and QALY

distributions. For transition probabilities involving two potential outcomes (e.g., survival of infection), beta distributions were generated using available study data. For transition probabilities involving more than two potential outcomes, Dirichlet distributions were created using available clinical data from which the original deterministic transition probabilities were derived. Dirichlet distributions are considered to be the multivariate equivalent of a beta distribution [16]. For QALY estimates, normal distributions were applied.

Several outcomes modeled in our study are sufficiently rare events (i.e. death and lymphoma) that they were not observed in randomized controlled trials. Because of this, the probability estimate for these events when using a Dirichlet distribution derived directly from the literature would be 0. To assess the impact of these non-events we created two sets of distributions. In the first set, the exact populations derived from the literature were utilized, including their 0 cells. In the second set, we also included the assumed probabilities as estimated in the deterministic analysis, as described in previous work by our group[17]. In this method, non-whole numbers were used based on documented rates of rare events in larger populations, multiplied against the total cohort size. This value was then used as the value for the 0 cell, and this value was subtracted from the largest cell in the distribution. These two methods were performed and compared to assess for changes in the standard errors for QALY point estimates, and yielded similar results. As separate distributions sets were used for the combination and monotherapy arms, we did not assess for the potential impact of reduced standard errors that result from sampling from the same set of distributions in each decision option of the tree.

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Supplemental Tables

Supplemental Table 1: QALY estimates and Markov Cohort analyses for extended time horizon models

Model 1: Extended time horizon

Time Horizon: 3 years

	QALY estimate			Total Deaths			Total Cases of Lymphoma		
Age	Combination	Monotherapy	Incr Eff^	Combination	Monotherapy	Diff.*	Combination	Monotherapy	Diff*
25	2.2013	2.1911	0.0102	10575	10583	-8	284	49	235
35	2.1986	2.1886	0.0100	13301	13266	35	635	105	530
45	2.1816	2.1720	0.0097	29335	29222	113	1329	218	1111
55	2.1435	2.1345	0.0090	64097	63828	269	2680	441	2239
65	2.0690	2.0615	0.0075	131945	131258	687	5275	870	4405
75	1.8897	1.8840	0.0056	289472	288006	1466	8006	1331	6675

Time Horizon: 5 years

	QALY estimate			Total Deaths			Total Cases of Lymphoma		
Age	Combination	Monotherapy	Incr Eff^	Combination	Monotherapy	Diff.*	Combination	Monotherapy	Diff*
25	3.5909	3.5848	0.0061	17365	17339	26	354	55	299
35	3.5821	3.5764	0.0058	23289	23199	90	791	129	662
45	3.5330	3.5279	0.0051	52795	52589	206	1640	263	1377
55	3.4283	3.4245	0.0038	111915	111462	453	3293	531	2762
65	3.2247	3.2233	0.0013	226389	225440	949	6302	1021	5281
75	2.7616	2.7625	-0.0009#	468492	466923	1569	9206	1507	7699

Time Horizon: 7 years

	QALY estimate			Total Deaths			Total Cases of Lymphoma		
Age	Combination	Monotherapy	Incr Eff^	Combination	Monotherapy	Diff.*	Combination	Monotherapy	Diff*
25	4.9095	4.9062	0.0034	24266	24216	50	385	55	330
35	4.8898	4.8870	0.0028	34714	34592	122	861	133	728
45	4.7904	4.7886	0.0019	79876	79627	249	1776	285	1491
55	4.5891	4.5890	0.0000	163928	163408	520	3553	565	2988
65	4.1999	4.2031	-0.0032#	324399	323433	966	6688	1074	5614
75	3.3677	3.3728	-0.0051#	626401	625156	1245	9556	1555	8001

Time Horizon: 9 years

	QALY estimate			Total Deaths			Total Cases of Lymphoma		
Age	Combination	Monotherapy	Incr Eff^	Combination	Monotherapy	Diff.*	Combination	Monotherapy	Diff*
25	6.1508	6.1490	0.0019	31432	31374	58	403	55	348
35	6.1138	6.1127	0.0012	48220	48087	133	892	133	759
45	5.9459	5.9459	-0.0001	110514	110253	261	1838	285	1553
55	5.6206	5.6230	-0.0024#	220428	219903	525	3664	581	3083
65	4.9974	5.0035	-0.0061#	425971	425097	874	6835	1095	5740
75	3.7581	3.7656	-0.0075#	757169	756323	846	9651	1566	8085

Model 2: Cycle adjusted Lymphoma risk

Time Horizon: 3 years

	QALY estimate			Total Deaths			Total Cases of Lymphoma		
Age	Combination	Monotherapy	Incr Eff^	Combination	Monotherapy	Diff.*	Combination	Monotherapy	Diff.*
25	2.2355	2.2248	0.0107	10466	10490	-24	223	49	174
35	2.2328	2.2222	0.0106	13172	13174	-2	504	123	381
45	2.2156	2.2052	0.0104	29173	29130	43	1043	258	785
55	2.1769	2.1669	0.0100	63859	63734	125	2103	524	1579
65	2.1015	2.0922	0.0093	131522	131163	359	4016	1028	2988
75	1.9191	1.9108	0.0083	288725	287912	813	5835	1547	4288

Time Horizon: 5 years

	QALY estimate			Total Deaths			Total Cases of Lymphoma		
Age	Combination	Monotherapy	Incr Eff^	Combination	Monotherapy	Diff.*	Combination	Monotherapy	Diff.*
25	3.6552	3.6466	0.0086	17204	17188	16	413	73	340
35	3.6463	3.6380	0.0083	23127	23052	75	929	195	734

45	3.5963	3.5885	0.0078	52622	52442	180	1891	402	1489
55	3.4896	3.4828	0.0067	111711	111315	396	3772	808	2964
65	3.2823	3.2774	0.0049	226150	225305	845	6806	1503	5303
75	2.8104	2.8070	0.0034	468241	466809	1432	9079	2103	6976

Time Horizon: 7 years

	QALY estimate			Total Deaths			Total Cases of Lymphoma		
Age	Combination	Monotherapy	Incr Eff^	Combination	Monotherapy	Diff.*	Combination	Monotherapy	Diff.*
25	4.9884	4.9810	0.0074	24127	24074	53	594	97	497
35	4.9683	4.9615	0.0068	34603	34457	146	1331	267	1064
45	4.8672	4.8615	0.0057	79801	79492	309	2675	539	2136
55	4.6624	4.6587	0.0037	163928	163281	647	5270	1067	4203
65	4.2671	4.2665	0.0006	324516	323327	1189	9028	1892	7136
75	3.4221	3.4231	-0.0010[#]	626608	625068	1540	11098	2459	8639

Time Horizon: 9 years

	QALY estimate			Total Deaths			Total Cases of Lymphoma		
Age	Combination	Monotherapy	Incr Eff^	Combination	Monotherapy	Diff.*	Combination	Monotherapy	Diff.*
25	6.2373	6.2305	0.0068	31347	31261	86	775	121	654
35	6.1996	6.1937	0.0058	48194	47983	211	1721	339	1382
45	6.0291	6.0250	0.0041	110573	110152	421	3418	666	2752
55	5.6989	5.6980	0.0009	220668	219818	850	6640	1307	5333
65	5.0676	5.0710	-0.0034[#]	426396	425031	1365	10821	2212	8609
75	3.8135	3.8178	-0.0043[#]	757558	756266	1292	12258	2669	9589

Supplemental Table 1: Summary statistics for models with longer time horizons. In model 1, in which we extended the time horizon in the base model, if the model exceeded 7 years, infliximab monotherapy became the preferred strategy for those over 65 years of age. Similarly, in Model 2, where we extended the time horizon but also reduced the initial risk of NHL in the first two years of the model, infliximab monotherapy was preferred for those over 65 years of age after 7 years, and marginally so for those at 55 years of age at 9 years of therapy. Incremental effectiveness, total mortality, and total cases of lymphoma are shown here.

^Incr eff: Incremental effectiveness, calculated by subtracting the Combination therapy Expected QALY value from the monotherapy expected value.

*Diff: Difference in number of individuals with death or lymphoma, calculated by subtracting Monotherapy group from Combination therapy group

[#]Denotes situations where monotherapy has become the preferred strategy over combination therapy.

Supplemental Table 2: Incidence of Lymphoma with varying hazards of lymphoma attributable to infliximab in a cohort of 1,000,000 individuals and 1-year time horizon

	HR: 1.0		HR: 2.0		HR: 3.0	
Age	Combination Therapy	Monotherapy	Combination Therapy	Monotherapy	Combination Therapy	Monotherapy
25	132	24	261	44	393	68
35	293	51	586	100	879	151
45	623	106	1246	213	1867	319
55	1262	216	2524	433	3781	647
65	2601	446	5189	890	7769	1336
75	4196	722	8365	1440	12508	2158

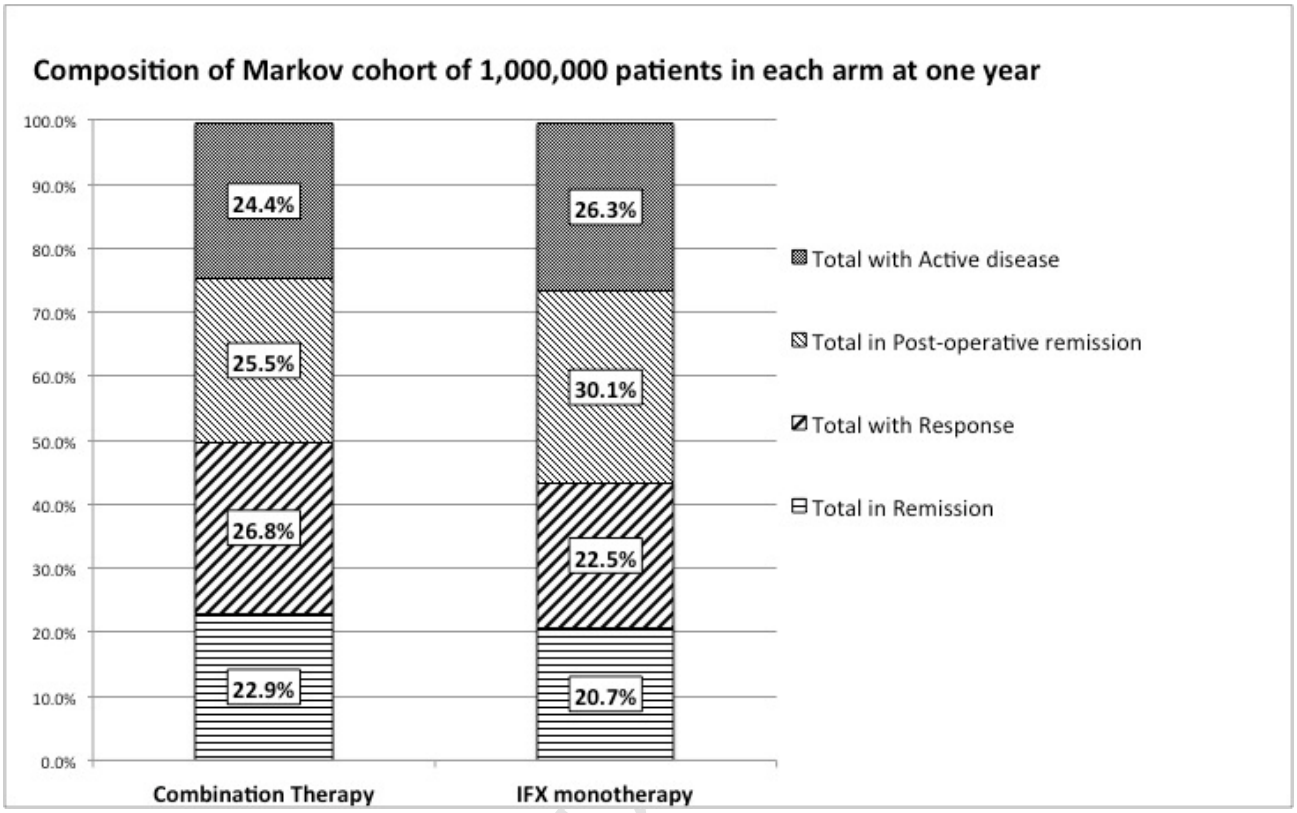
Supplemental Table 2: Incidence rates of lymphoma in a cohort of 1,000,000 individuals at 1 year, with the baseline hazard rate of lymphoma with infliximab of 1.0, as well as increased hazard ratios of 2.0 and 3.0.

Supplemental Table 3: Mortality rates due to Non-Hodgkin's Lymphoma

Annual mortality rates for males with Non-Hodgkin's Lymphoma: 2005-2009					
	Age				
	00-44	45-54	55-64	65-74	75+
1-year	14.33%	13.52%	13.07%	17.83%	31.96%
2-year	4.06%	4.09%	5.10%	5.29%	4.99%
3-year	1.89%	2.52%	3.58%	2.36%	3.14%
4-year	1.36%	1.52%	2.52%	2.56%	2.65%
5-year	0.90%	1.54%	1.90%	1.93%	2.01%

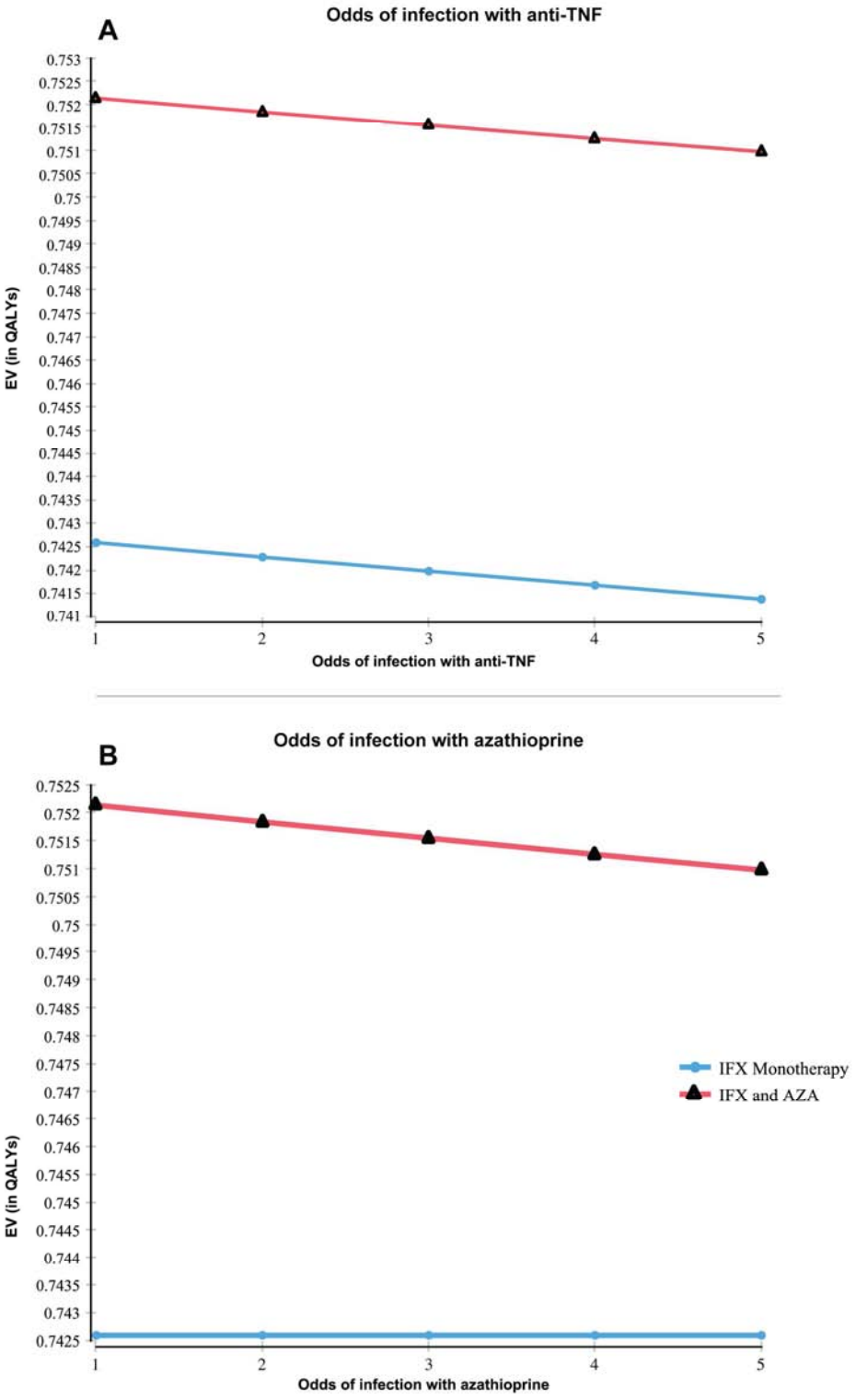
Supplemental Table 3: Mortality rates for Non-Hodgkin's lymphoma for males from childhood to over 75 years of age, stratified by time since diagnosis. These estimates were derived from SEER as described in the supplemental methods.

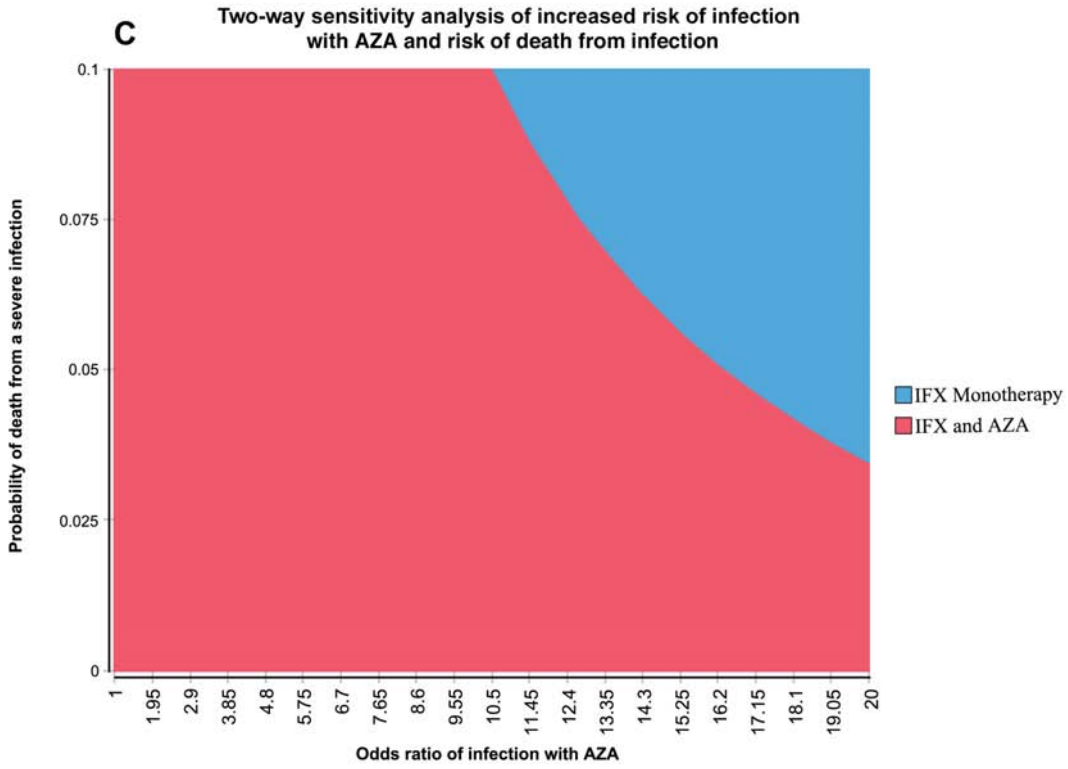
Supplemental Figure 1: Markov Cohort Composition at 1 year for the base case



Supplemental Figure 1: Combination therapy (option 1) resulted in a larger proportion of patients in medical remission or with clinical response, and fewer patients with active disease or in post-operative remission compared to infliximab monotherapy (option 2).

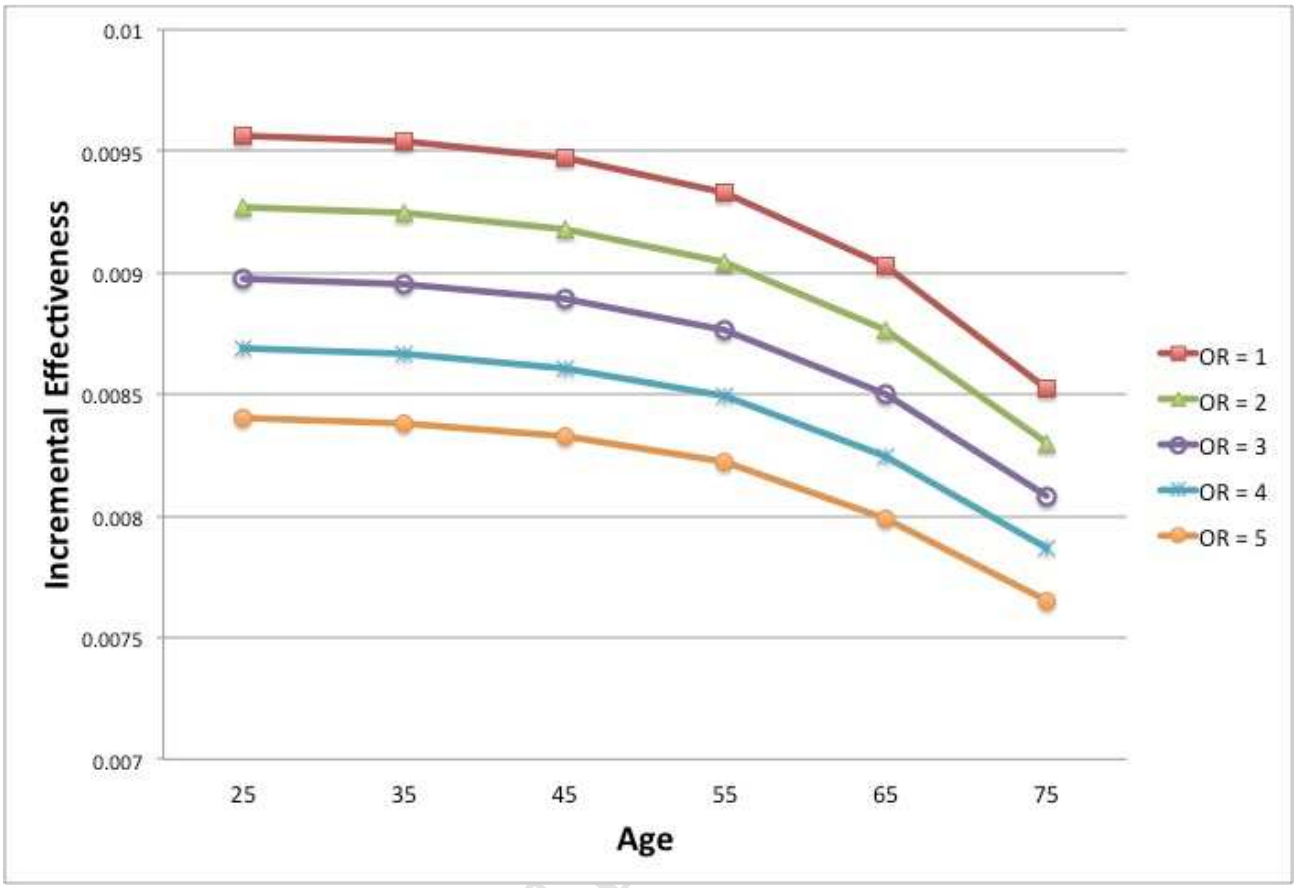
Supplemental Figure 2 Title: Impact of increased odds of infection and infection related mortality with combination therapy and monotherapy





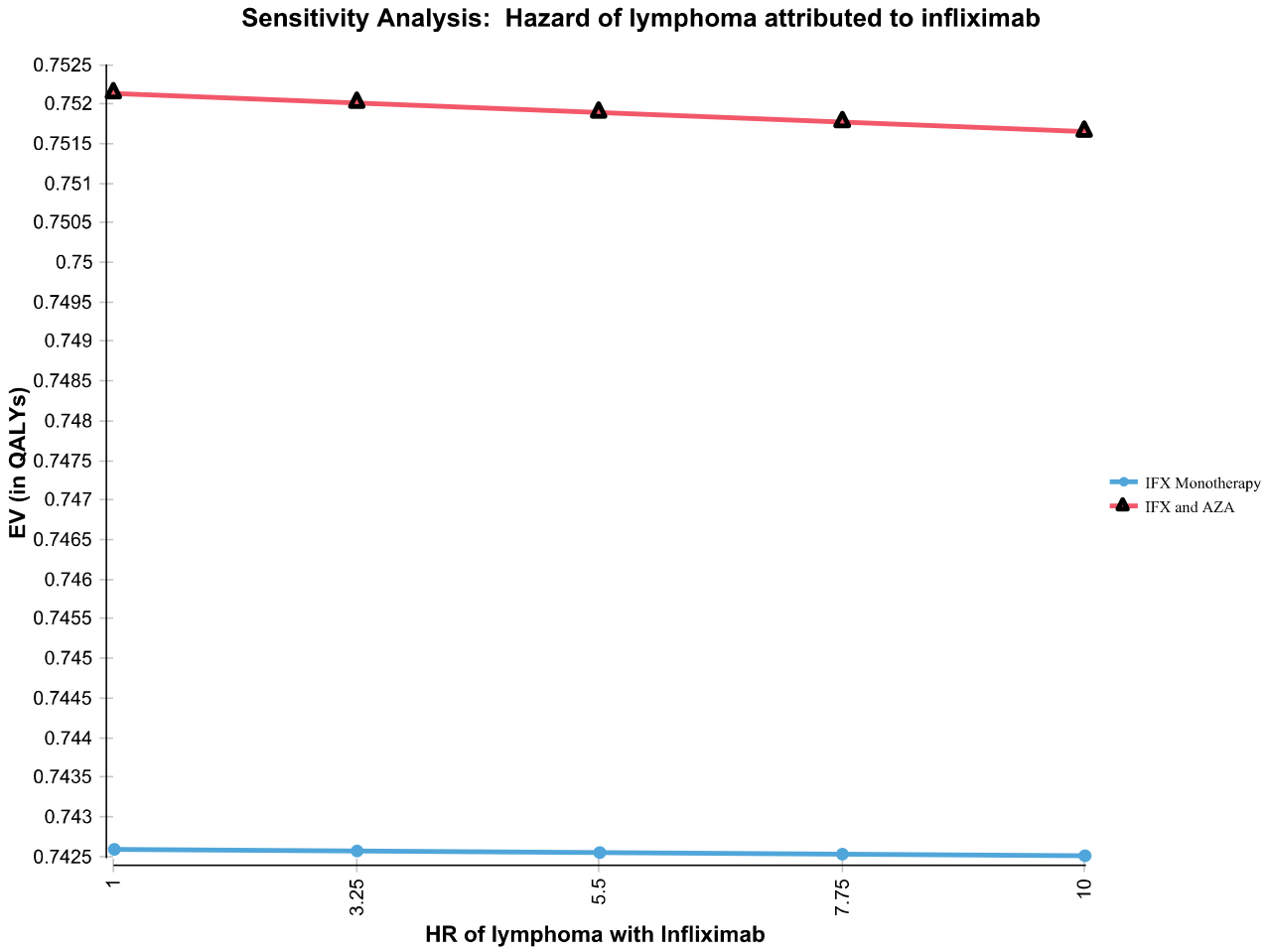
Supplemental Figure 2 Caption: Three sensitivity analyses were conducted to assess the impact of increasing the odds of infection with anti-TNFs and combination therapy. In the first analysis (Panel A), the odds of infection were increased from 1 to 5, with no impact on the results. In the second analysis (Panel B), we focused specifically on the risks associated with azathioprine, which again did not impact the results. In the third analysis (Panel C), we performed a two-way sensitivity analysis looking at both increased probability of infection and increased probability of infection-specific mortality. Monotherapy became the preferred strategy when the odds of infection was >10x monotherapy and the risk of death related to that infection exceeded 10%.

Supplemental Figure 3: Impact of increasing risk of infection with combination therapy from age 25 to 75 on Incremental effectiveness



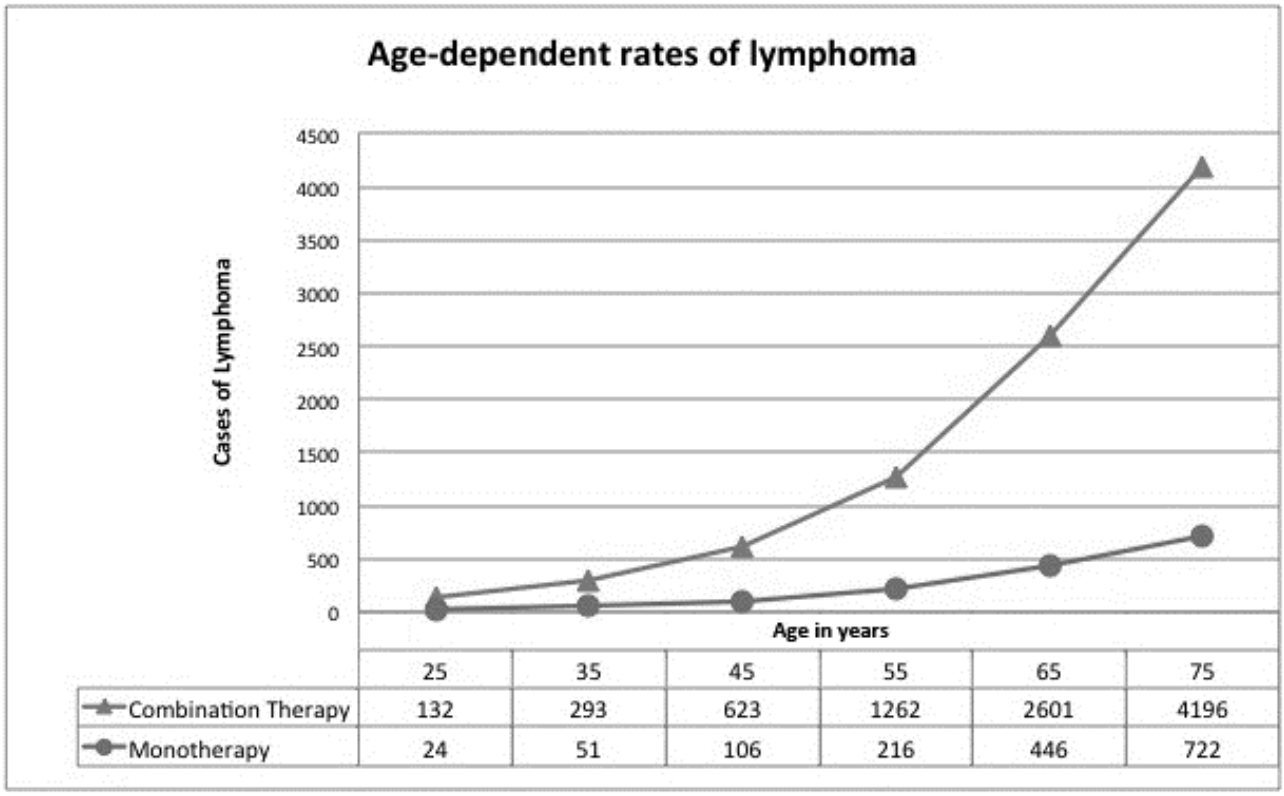
Supplemental Figure 3: Impact of increasing OR of infection with azathioprine compared to monotherapy from age 25 to 75. For all ages, combination therapy remained the preferred strategy despite the increased conferred risk of infection.

Supplemental Figure 4: Sensitivity analysis of HR of lymphoma with infliximab



Supplemental Figure 4: The model was not sensitive to a wide range of values for the HR of NHL with infliximab in the base case, from 1.0 (baseline point estimate) to 10.0.

Supplemental Figure 5: Incidence of lymphoma over the lifespan



	25	35	45	55	65	75
Combination Therapy	132	293	623	1262	2601	4196
Monotherapy	24	51	106	216	446	722

Supplemental Figure 5 Caption: Incidence of lymphoma in Markov cohort analysis of combination therapy and monotherapy over the lifespan.