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Economic Evaluation of Nefecon in Primary IgA Nephropathy in the US

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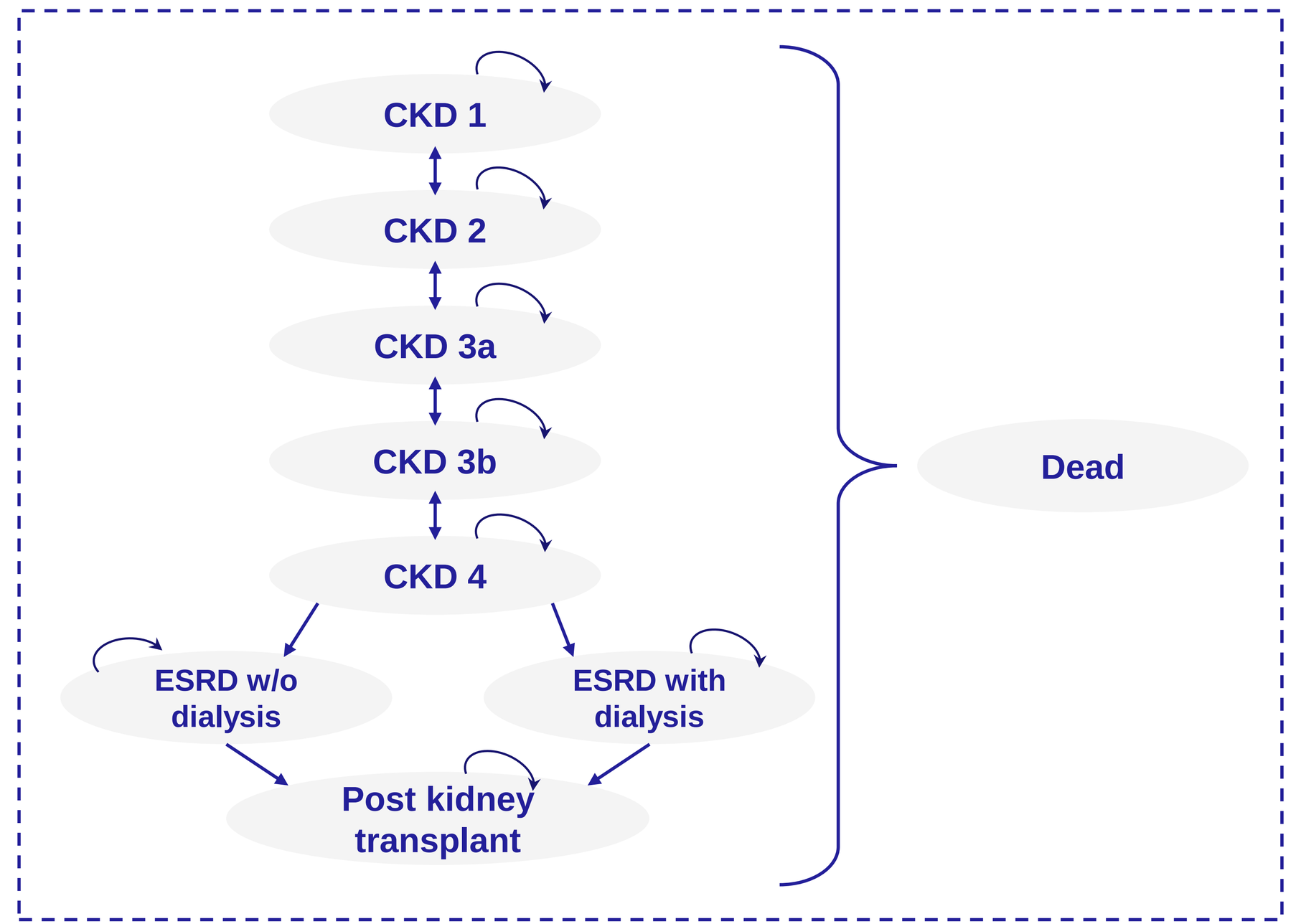
Background

- Primary immunoglobulin A nephropathy (IgAN) is the most common type of primary glomerulonephritis globally, with an estimated US incidence of 1.29 per 100,000 people[1] and estimated US prevalence of 112,000 people in 2019.[2]
- IgAN is a rare progressive autoimmune disease that leads to chronic inflammation in the kidneys.[3] Over time, IgAN can lead to end-stage renal disease (ESRD). Studies found that 23% of patients with IgAN progressed to ESRD in 3.9 years[4] and 53% of patients with IgAN progressed to ESRD in 19 years.[5]
- Until recently, there were no approved disease-specific therapies available for IgAN and it was managed by best supportive care (BSC) that consists of blood pressure management, renin-angiotensin system (RAS) blockade with maximally tolerated dose of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) and lifestyle modification.[6]
- Evidence suggests a four-hit hypothesis underlying the pathogenesis of IgAN and its autoimmune disease mechanisms, where the first hit involves increased amounts of circulating galactose deficient IgA.[7]
- Nefecon is the developmental product name for a novel oral formulation of budesonide that is designed to deliver budesonide to an area of the ileum to target mucosal B cells, which are responsible for the production of galactose-deficient IgA1 antibodies, causing IgAN.[8,9]

Methods

- A semi-Markov model with a lifetime horizon was constructed to estimate cost-effectiveness of Nefecon in addition to BSC, compared to BSC alone, from a US healthcare and societal perspective. Outcomes for each treatment strategy calculated by the model were total costs, quality adjusted life years (QALY), life years (LY), and equal value life years (evLY), with incremental cost-effectiveness ratios (ICER) used as economic endpoints of the analysis. **(Figure 1 & Table 1)**
- Constant transition probability between heath states were estimated from regression analysis on individual patient level data (IPD) from Part A of NefIgArd, along with literature-based sources.[10,11]
- Costs included treatment, routine medical care, adverse events (AEs), dialysis, kidney transplant, long-term complications, mortality, and indirect costs.
- In the base case analysis, people in the Nefecon arm received one round of treatment that consists of 9.25 months on treatment followed by 14.75 months off treatment. Multiple treatment rounds were evaluated as additional scenarios.
- Additional scenarios were assessed to evaluate the results when the time horizon, discounting, costs included, rounds of treatment, and the method used to calculate transition probabilities were varied.

Figure 1. Semi-Markov structure



Data inputs

EFFICACY INPUTS

- Regression analysis of the IPD from Part A of NefIgArd was used as the primary approach to calculating transition probabilities between health states in the model. An alternative approach whereby probabilities were estimated using hazard rations (HRs) from published meta-regressions[10,11] was explored as additional scenarios.
- For the regression analysis, patient eGFR values at baseline, and after Nefecon treatment, were converted into associated CKD stages (see **Table 1**). Patients who ended in a different state (compared to baseline) were flagged as having 'transitioned' health state during the trial period. Logistic regression models were run on the probability of transitioning, whilst controlling for treatment and baseline states. The regression model outputs were then converted into monthly transition probabilities for use in the economic model.
- The distribution of patients at baseline was sourced from the distribution of NefIgArd trial participants at baseline.
- The transition probabilities calculated from the BSC alone arm of NefIgArd were applied to patients receiving BSC alone in the model.
- The transition probabilities calculated from the Nefecon + BSC arm of NefIgArd were applied to patients receiving Nefecon + BSC in the model, for the duration that the treatment effect was assumed, otherwise the BSC alone transition probabilities were applied.
- Probabilities of transitioning from the ESRD states to the post-transplant state were calculated from the final CKD stage of patients (percentage) at the end of the study period as reported by Kent, et al., 2015.[13]
- For the CKD and ESRD health states, the probability of death was based on life table data and the standardized mortality ratio (SMR) of the respective health state. The SMRs of the CKD and ESRD health states were estimated using data from Hastings et al., 2018.[14] For the post-transplant state, the probability of death was calculated based on life table data and a SMR after renal transplant as reported by Ortiz, et al., 2019.[15]

COST INPUTS

Treatment costs: Patients receiving Nefecon received 16 mg administered orally once daily (four units at a unit strength of 4 mg; i.e., 16 mg) at a unit cost of $118 USD.[16] BSC was in both treatment arms being compared; therefore, BSC costs were not included in the analysis.

Dialysis and post-transplant costs:

- Dialysis costs were weighted by proportions receiving hemodialysis and peritoneal dialysis per year, with the former weighted as occurring in 90% of cases.[17] The annual inflated Medicare costs of hemodialysis and peritoneal dialysis were $105,600 and $89,226, respectively.[18] The annual inflated commercial costs of hemodialysis and peritoneal dialysis were $276,295 and $233,453, respectively.[19] Medicare costs were used for people 65 years and over. For people under 65, commercial costs were used for a maximum of 33 months after which Medicare costs were used.[19]
- For patients transitioning to the post-transplant state, a total transplant cost ($453,703) was applied from an inflated 2020 estimate of the average billed charges per transplant in the US as reported by Millman, 2020.[20]
- Post-transplant cost items were applied to the proportion of patients in the post-transplant state and included the cost of the post-transplant health state and the total cost of post-transplant complications.

AE costs: AE costs (**Table 2**) were sourced from the Healthcare Cost and Utilization Project (HCUPnet) values for AEs requiring inpatient care, and CPT® physician visit values, for AEs not requiring inpatient care (i.e., outpatient care).[21] The frequency of each AE was calculated from trial data from the safety analysis set of the NefIgArd trial. The proportion of AEs requiring inpatient and outpatient care was estimated from the proportion of treatment-emergent AEs assessed as severe in each arm of the NefIgArd trial.[22]

Abbreviations: Admin: administration; AEs: adverse events; BI: budget impact; BSC: best supportive care; CKD: chronic kidney disease; CSR: Clinical Study Report; eGFR: glomerular filtration rate; FDA: Food and Drug Administration; IgAN: IgA nephropathy; PMPM: per member per month; PMPY: per member per year; PO: oral; RASi: renin angiotensin system inhibitors; SoC: standard of care; UPCR: urine protein/creatinine ratio; UK: United Kingdom; US: United States; USD: United States dollar

Table 1. Description of health states

Source: National Kidney Foundation https://www.kidney.org/atoz/content/gfr

Health State[12]	Description Source: National Kidney Foundation https://www.kidney.org/atoz/content/gfr
CKD 1	Defined as patients who have eGFR ≥ 90 mL/min per 1.73 m². Patients either remain in this state or those who do not respond to treatment transition to CKD stage 2 or death.
CKD 2	Patients who have eGFR ≥ 60 to 89 mL/min per 1.73 m². Patients either remain in this state, transition to CKD stage 1, or transition to CKD stage 3a or death.
CKD 3a	Patients who have eGFR ≥ 45 to 59 mL/min per 1.73 m². Patients either remain in this state, transition to CKD stage 2, or transition to CKD stage 3b or death.
CKD 3b	Patients who have eGFR ≥ 30 to 44 mL/min per 1.73 m². In this state, patients either remain, transition to CKD stage 3a, or worsen and transition into CKD stage 4 or death.
CKD 4	Patients who have eGFR ≥ 15 to 29 mL/min per 1.73 m²; no patients begin the model in this state. Patients can transition into CKD stage 4 from CKD stage 3b after the first cycle. Patients in subsequent cycles in this state can transition from CKD stage 4 to CKD stage 3b or worsen to ESRD with or without dialysis, or death.
ESRD without dialysis	No patients begin the model in this state. Patients can transition into this state from CKD stage 4 after the first cycle. Patients in subsequent cycles can remain in this state or worsen and transition into the post-transplant state or death.
ESRD with dialysis	No patients begin the model in this state. Patients can transition into this state from ESRD without dialysis after the first cycle. Patients in subsequent cycles can remain in this state or worsen and transition into the post-transplant state or death.
Post-kidney transplant	No patients begin the model in this state. Patients can transition into this state from ESRD without or with dialysis after the first cycle. Patients in subsequent cycles can remain in this state or transition to death.
Dead	Terminal state
Patients in each health state (except death) experience the respective costs (drug, AE, routine care, productivity loss) and CKD stage and AE related utility.	

Table 2. Monthly AE costs

*Source: *proportion of severe TEAEs out of all TEAEs in each arm of NefIgArd (22); **(CPT Unit cost -99213); ***HCUPnet(21)*

TEAE	% inpatient AEs Nefecon	% inpatient AEs BSC*	Unit cost - outpatient**	Unit cost - inpatient***	Nefecon AE prevalence per cycle	BSC AE prevalence per cycle
Acne	4%	2%	$68.04	$0	0.6%	0.1%
Weight increase				$0	0.3%	0.2%
Hypertension				$28,905	0.2%	0.0%
Headache				$32,279	0.2%	0.1%
Edema peripheral				$25,511	0.3%	0.1%
Dyspepsia				$41,116	0.2%	0.0%
Mood swings				$22,084	0.2%	0.0%
Face edema				$33,018	0.3%	0.0%
Cushingoid				$80,315	0.2%	0.0%
Hirsutism				$59,767	0.2%	0.0%
Upper respiratory tract infection				$24,100	0.0%	0.2%

Table 3. Model health-state utilities

Model health state	Utility value
CKD 1	1.00
CKD 2	0.90
CKD 3	0.87
CKD 4	0.85
ESRD without dialysis	0.85
ESRD with dialysis	0.77
Post transplant*	0.87

**Assumed to have the same utility as CKD 3 [expert opinion]*
***Source:** Gorodetskaya, et al.,2005 (28)*

Table 4. Disutilities of treatment-emergent AEs

TEAE	Disutility	Source
Acne	0.00	Assumption
Weight increase	0.00	Assumption
Hypertension	0.00	Sullivan et al., 2006 [29]
Headache	-0.03	Xu et al., 2010 [30]
Edema peripheral	-0.11	Assumption
Dyspepsia	-0.05	Sullivan et al., 2006 [29]
Mood swings	-0.02	Assumption
Face edema	0.00	Assumption
Cushingoid	-0.05	Institute for Clinical and Economic Review, 2019 [31]
Hirsutism	-0.05	Assumption
Upper respiratory tract infection	0.00	Sullivan et al., 2006 [29]
Transplant failure (acute rejection)**	-0.11	Sussell et al., 2006 [32]

Mortality costs: The mortality cost ($17,057) was based on a United Kingdom (UK) study by Kerr et al, 2017[23] who reported the cost of hospital care for the 3-month period before to death for people with CKD. The reported cost in GBP was was converted to USD and adjusted based on the mean per capita hospital expenditure ratio for end-of-life care between the UK and US as reported by Bekelman et al., 2016.[24]

Indirect costs: Indirect costs were incorporated into the model in the form of productivity loss costs. These costs were estimated from the mean percentage of work hours missed reported by van Haalen et al., 2020[25], the percentage of working patients in the model[26], and the average weekly wage in the US of $984 USD[27] Productivity loss costs were applied to patients in the CKD stages 3, 4, and 5, and ESRD health states.

HEALTH-RELATED QUALITY OF LIFE (HRQoL) INPUTS

- The model incorporated literature values for health state utilities and disutilities of AEs.
- QALYs were calculated as the sum of the utility-weighted time in each health state. The most robust external publication providing relevant utility data identified was the health utility study by Gorodetskaya et al., 2005 which assessed the relationship between eGFR and changes in HRQoL and utility in patients with CKD.[28] Utility scores were elicited using a time trade-off (TTO) questionnaire and are presented in **Table 3**.
- AE-related disutilities were included in the model. To derive QALYs lost per cycle, the cycle prevalence of each AE was combined with the disutility and assumed duration of each specific AE (**Table 4**). Treatment-emergent AE prevalence values were obtained from the NefIgArd trial.[22]

Results & Discussion

DETERMINISTIC RESULTS

- Over a lifetime horizon, one round of treatment with Nefecon resulted in estimated incremental gains of 0.247 QALYs, 0.195 LYs, and 0.244 evLYs compared to BSC, at an estimated incremental cost of $3,810 (USD) (**Table 5**).
- Nefecon resulted in a deterministic ICER of $15,427 per QALY, $19,502 per LY, and $15,611 per evLY gained, compared to BSC (**Table 7**).
- Results of the deterministic scenario analysis revealed that Nefecon remained cost-effective at a WTP threshold of $100,000 after four rounds (**Table 9**).

PROBABILISTIC RESULTS

- Over a lifetime horizon, and 5,000 model iterations, one round of treatment with Nefecon resulted in estimated incremental gains of 0.249 QALYs, 0.195 LYs, and 0.002 evLYs compared to BSC, at an estimated incremental cost of $6,014 (USD) (**Table 6**).
- Nefecon resulted in a probabilistic ICER of $24,154 per QALY, $30,892 per LY, and $2,838,537 per evLY gained, compared to BSC (**Table 8**).
- With willingness to pay (WTP) thresholds of $100,000, $150,000, and $200,000 per QALY gained, Nefecon was cost-effective over BSC in 66.24%, 74.34%, and 85.46% of iterations, respectively (**Figure 2 and 3**).

DISCUSSION

- The cost effectiveness of Nefecon in the model is likely explained by the proportionally greater amount of time spent in earlier health states versus later health states (i.e., CKD 4 , ESRD, and post kidney transplant) for patients treated with Nefecon plus BSC versus BSC alone.
- In the model, additional rounds of treatment with Nefecon increases the difference in health state occupancy between the two treatment arms. (**Figure 4**).

Table 5. Model outcomes (Deterministic results – Base case)

Outcome	Nefecon + BSC	BSC alone	Δ (Nefecon + BSC – BSC alone)
Costs (USD)	1,209,075	1,205,265	3,810
QALYs	13.426	13.179	0.247
LYs	15.506	15.311	0.195
evLYs	13.423	13.179	0.244

Table 6. Model outcomes (Probabilistic results)

Outcome	Nefecon + BSC	BSC alone	Δ (Nefecon + BSC – BSC alone)
Costs (USD)	1,200,953	1,194,939	6,014
QALYs	13.538	13.289	0.249
LYs	15.613	15.418	0.195
evLYs	13.291	13.289	0.002

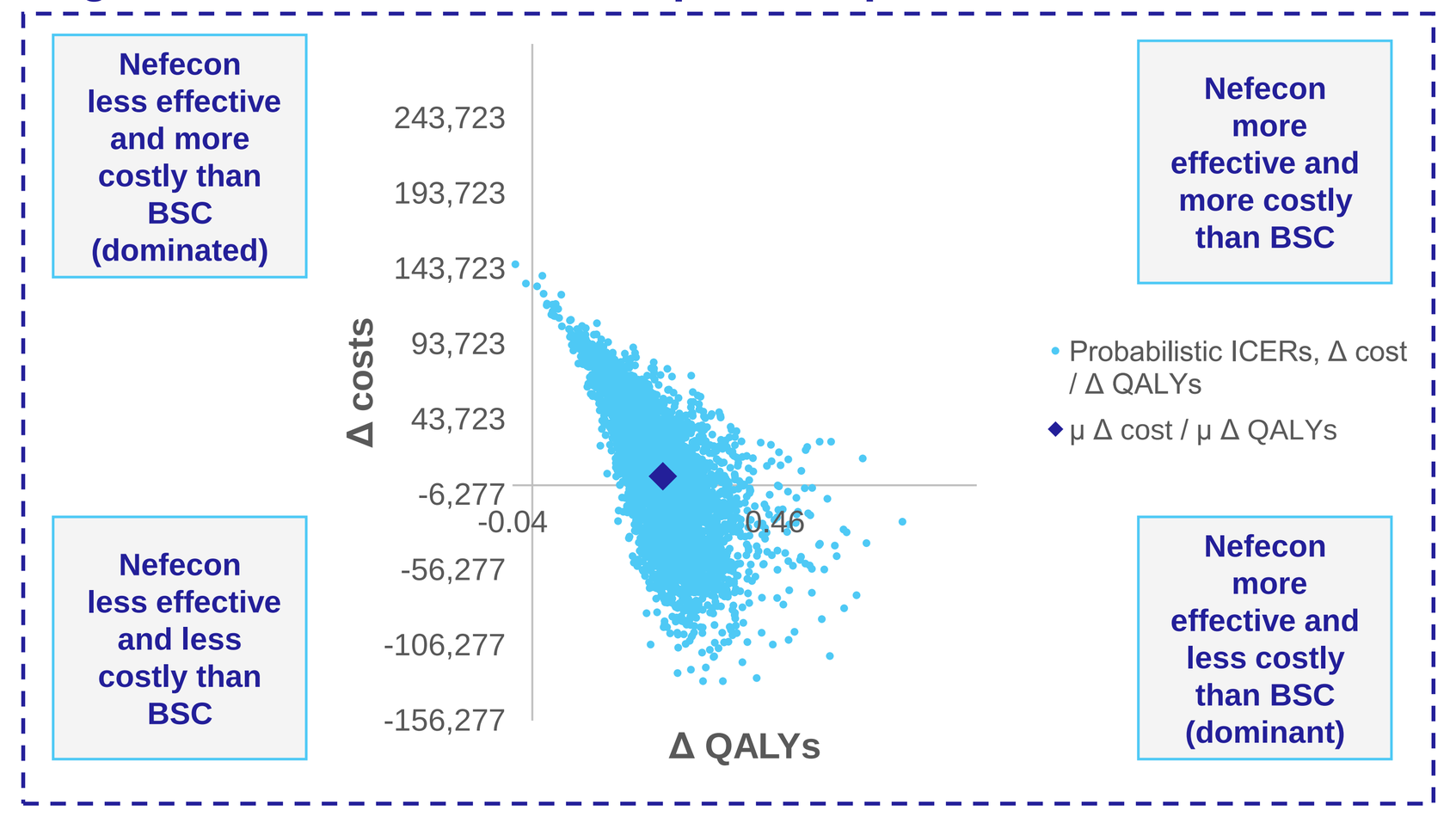
Table 7. Deterministic cost-effectiveness results

ICER	Value (USD)
Cost per QALY gained	15,427
Cost per LY gained	19,502
Cost per evLY gained	15,611

Table 8. Probabilistic cost-effectiveness results

ICER	Value (USD)
Cost per QALY gained	24,154
Cost per LY gained	30,892
Cost per evLY gained	2,838,537

Figure 2. Cost-effectiveness plane of probabilistic ICERs



Nefecon less effective and more costly than BSC (dominated)
Nefecon more effective and more costly than BSC
Nefecon less effective and less costly than BSC
Nefecon more effective and less costly than BSC (dominant)
243,723
193,723
143,723
93,723
43,723
-6,277
-56,277
-106,277
-156,277
-0.04
0.46
Δ costs
Δ QALYs
Probabilistic ICERs, Δ cost / Δ QALYs
μ Δ cost / μ Δ QALYs

Figure 3. Cost-effectiveness acceptability curve

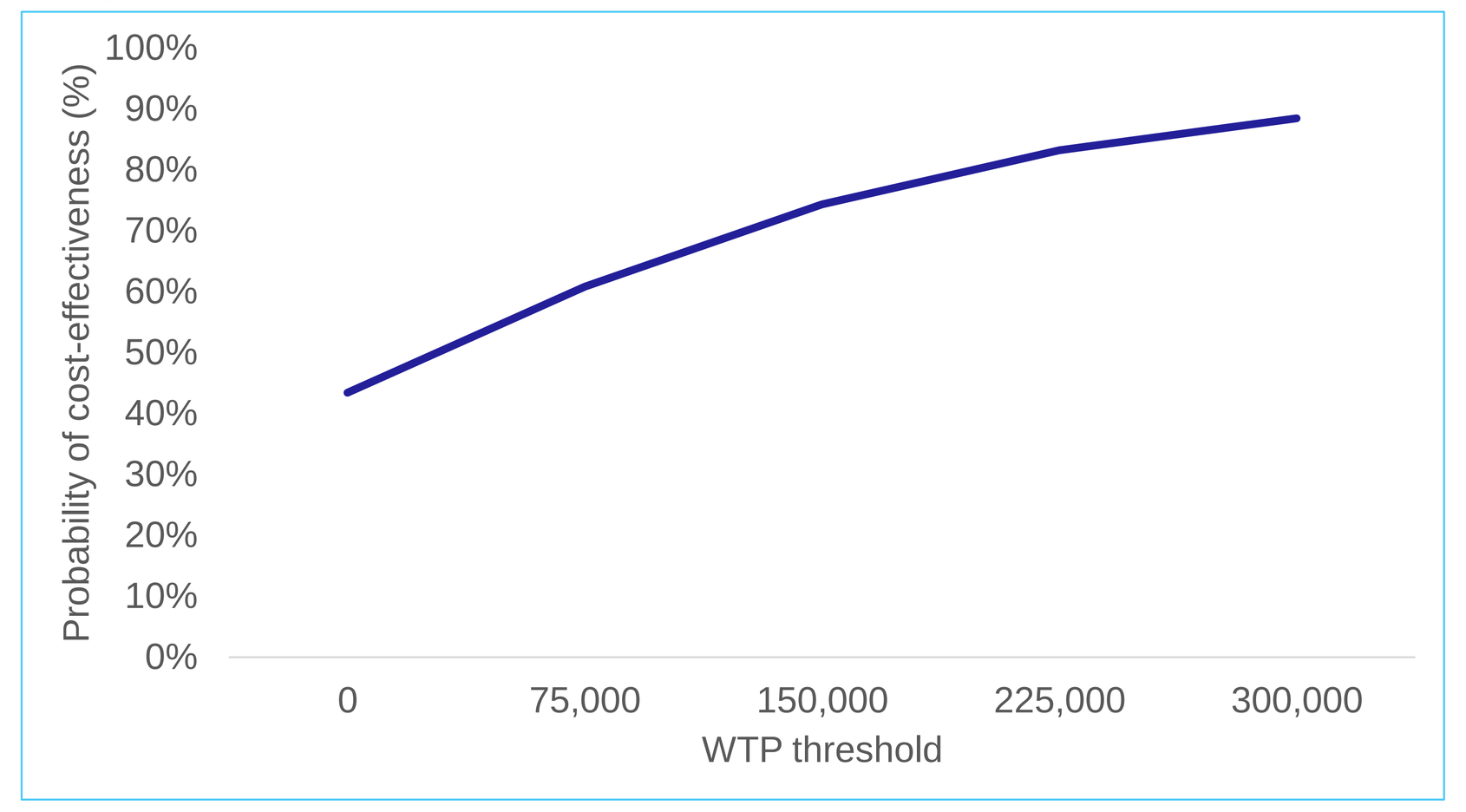


Table 9. Deterministic scenario analysis results

Scenario	Description	Δ costs	Δ QALYs	ICER	Quadrant
Base case		3,810	0.25	15,427	Incremental
Time horizon	10 years	21,671	0.11	189,249	Incremental
	30 years	2,816	0.24	11,525	Incremental
	Lifetime	3,810	0.25	15,427	Incremental
Discounting	No benefit discounting	3,810	0.36	10,648	Incremental
	No cost discounting	-15,268	0.25	-61,820	Nefecon dominant
	No discounting	-15,268	0.36	-42,667	Nefecon dominant
Routine care costs	Excluded	101,882	0.25	412,508	Incremental
Mortality costs	Excluded	3,908	0.25	15,824	Incremental
Indirect costs	Excluded	10,338	0.25	41,859	Incremental
Rounds of treatment	1	3,810	0.25	15,427	Incremental
	2	20,509	0.48	42,791	Incremental
	3	47,795	0.70	67,904	Incremental
	4	76,843	0.92	83,459	Incremental
Calculation of progression TPs	IPD regression	3,810	0.25	15,427	Incremental
	HR from Thompson (9 months)	-6,763	0.27	-25,018	Nefecon dominant
	HR from Thompson (12 months)	-28,602	0.32	-89,868	Nefecon dominant
	HR from Inker (12 months)	-8,769	0.27	-31,926	Nefecon dominant

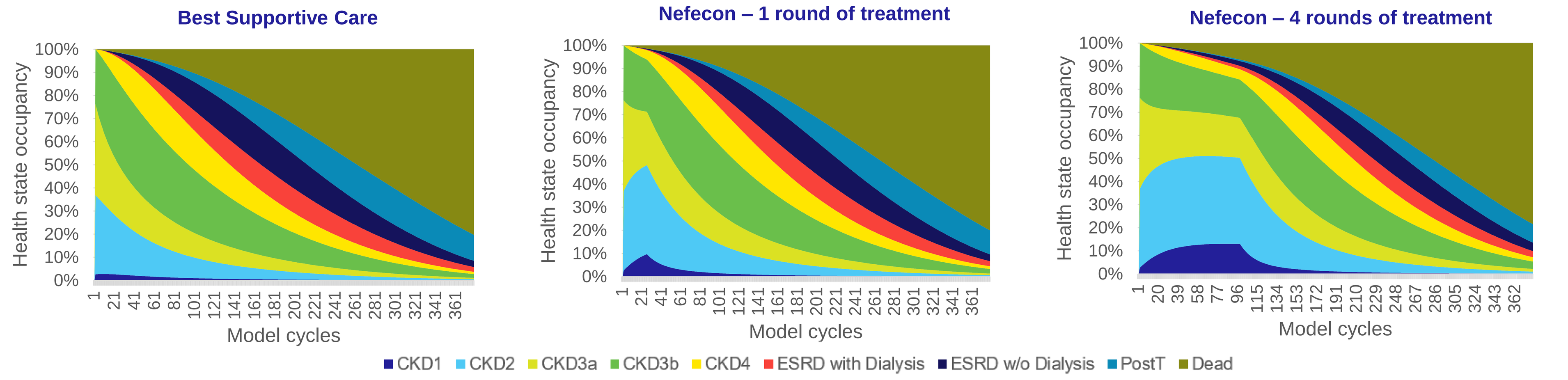
LIMITATIONS

- To align with the NefIgArd trial, the model assumed patients received one round of Nefecon treatment; however, in reality, patients would be likely to receive further rounds. Assuming a constant treatment effect, additional scenarios tested the cost-effectiveness of up to four rounds of treatment. Nevertheless, data are not currently available to determine the true efficacy of additional treatment rounds.
- The base case model assumed that each round of treatment consists of 9.25 months on treatment followed by 14.75 months off treatment. Real world utilization will likely differ thus resulting in different transition probabilities and ICER.
- The SMRs used to calculate probability of death from CKD and ESRD health states were estimated from survival curves reported in Hastings, et al., 2018.[14] This study reported patient and kidney survival of 251 adult patients diagnosed with IgAN from the Southeastern US but population characteristics, such as age and CKD stage at diagnosis, were not matched to participants in the NefIgArd trial.
- Health state utility values were sourced from the literature for a broader population of people with CKD and were not specific to people with IgAN, as no IgAN specific utilities were identified. It is not clear whether people with CKD resulting from IgAN would have the same effect on their HRQoL as people with CKD attributed to other causes.

CONCLUSIONS

- This analysis estimates that Nefecon is likely a cost-effective treatment option for people with primary IgAN in the US.
- At a WTP threshold of $150,000, Nefecon is estimated to be cost-effective 74.34% of the time.

Figure 4. Health state occupancy (deterministic results)



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