The Cost-Effectiveness of Initial *vs.* Delayed Lanreotide for Treatment of Metastatic Enteropancreatic Neuroendocrine Tumors in the United States

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Barnes, James I.[1,2], Lin, John[1,2], Gupta, Divya[2], Goldhaber-Fiebert, Jeremy D.[3], Owens, Douglas K.[1,2], Kunz, Pamela L.[4]

[1]VA Palo Alto Health Care System, Palo Alto CA; [2]Department of Medicine, Stanford University, Stanford, CA; [3]Stanford University, Stanford, CA; [4]Stanford Cancer Center, Stanford, CA

BACKGROUND

- The Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors (CLARINET) demonstrated prolonged progression-free survival for patients initially treated with lanreotide compared with patients receiving placebo.
- The CLARINET extension study followed patients who crossed over from placebo to lanreotide following progression.
- NCCN guidelines for patients with metastatic GI tract and pancreatic neuroendocrine tumor who are asymptomatic with low tumor burden recommend either treatment with octreotide/lanreotide or active surveillance with serial imaging followed by lanreotide or octreotide LAR after further progression
- The cost-effectiveness of initial lanreotide in treatment of these patients vs active surveillance followed by lanreotide after progression has not been determined

Objective:

- The objective of this study is to evaluate the cost-effectiveness of lanreotide upfront vs. active surveillance with lanreotide given upon progression for patients with metastatic enteropancreatic neuroendocrine tumor.

METHODS

Model perspective and parameters

- Perspective: U.S. Medicare (Healthcare); in 2018 USD ($)
- Discount rate 3% for utilities and costs
- Lifetime time horizon
- Discrete Time Semi - Markov Model performed using TreeAge Pro
- 3 health states modelled (Figure 1)
- Population of CLARINET trial (well-differentiated or moderately-differentiated, somatostatin receptor positive, grade 1 or 2, non-functioning)

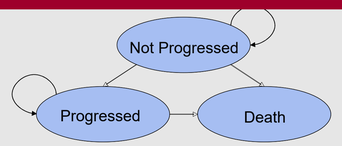

Figure 1. Modeled Health States

Utilities

- Swinburn et al. (clinical vignette study using time trade-off method)
  - Not Progressed State: 0.771
  - Progressed State 0.61
- Utility decrement for grade 3 and 4 adverse events during hospitalization
- Meng et al provide estimates of utilities from mapped EORTC QLQ-C30 data (not progressed: 0.776 and progressed 0.726). These were not used in the base case because the progressed state was evaluated early on after progression.

Costs

- Lanreotide: $58.98 per mg ($7,077.60 per 120 mg /28 days) - Medicare Average Sales Price (ASP) drug-pricing files
- Background health costs ($903 per month):
  - Guy et al provides an estimate for healthcare services for cancer patients, excluding prescription medications for patients > age 65 (the Medicare population of interest), diagnosed > 1 year prior.
  - Hallet et al examined healthcare costs in Canada for NET patients and found that non-drug costs were similar to those with colon cancer in Canada
- Screening Costs were added to patients while on therapy ($444 every 6 months)
  - Complete Metabolic Panel, CT abdomen with contrast, Complete Blood Count, Chromogranin A
- Grade 3 and 4 adverse event (AE) costs for hospitalization costs for corresponding DRGs
- Up to two lines of subsequent therapies following lanreotide (costs estimated by 64% of the AWP from Red Book Online, VA Health Economics Resource Center Recommendations):
  - Everolimus : rate of progression based on progression-free survival (PFS) curve from Yao et al 2011.
    - 28 day cost: $10,161
  - Sunitinib for pancreatic patients: rate of progression based on PFS curve from Raymond 2011
    - 28 day cost: $11,262

Survival Curve Modelling

- Parametric survival curve fit to OS and PFS curves and transition probabilities derived from cumulative hazard functions
  - Survival curves digitized using WebPlotDigitizer and Guyot et al algorithm used to convert to estimated individual patient data (IPD)
  - Parametric survival curves fit to the estimated IPD
    - Choice of parametric curve made from Weibull, Exponential, Gompertz, Log-Normal and Log-Logistic by AIC, BIC and visual fit criteria.
  - Probability of death assumed to be dependent on time from start of model
  - Progression modelled by p_{OS}-p_{PFS}
  - This provides a solution that accurately reflects time in each health state
- Progression in crossover group calibrated by using an optimization-based algorithm using MATLAB to match the PFS curves of the crossover group in the Lanreotide Extension study (Caplin et al 2016) using a tunnel state
- Progression on further lines of therapy modeled by the PFS curves from respective trials and modelled as a competing risk with death
- Base case: OS in both lanreotide and active surveillance cohorts assumed to be equivalent
  - Supplement of the CLARINET trial showing similar overall survival with a log-rank test p value of 0.88
  - An alternative version is explored (scenario B)

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RESULTS

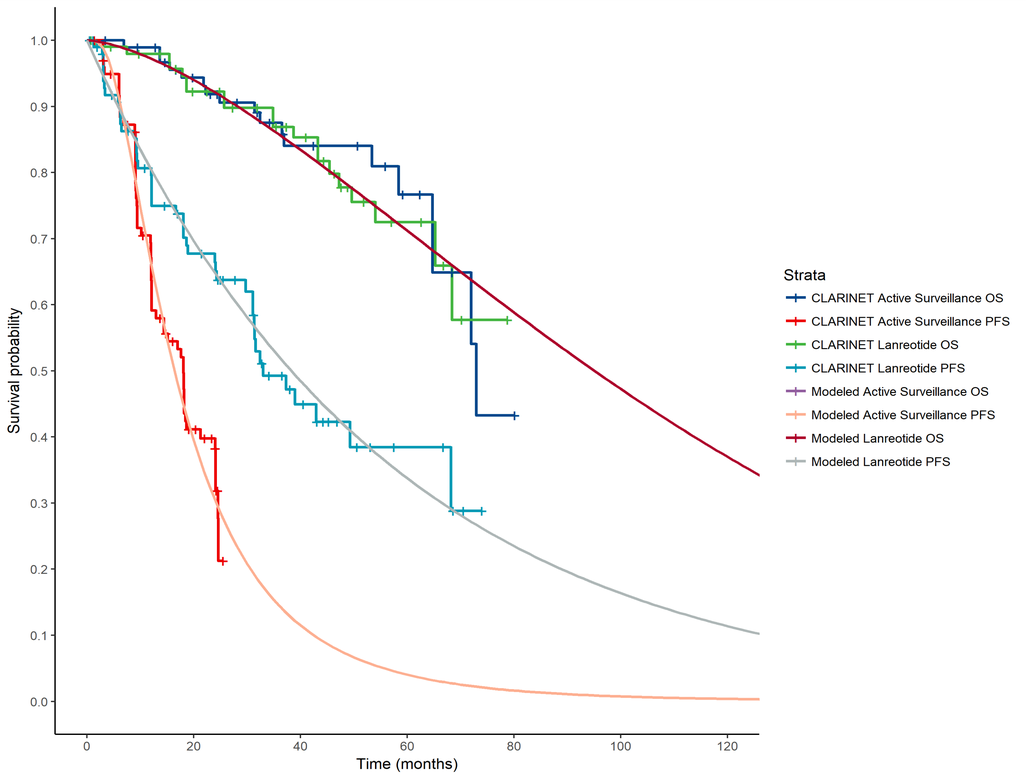

Figure 2. Survival Curves from trials and modeled curves used in the cost-effectiveness model Kaplan Meier curves from Caplin et al NEJM 2014. This base case assumes same overall survival, based on Lanreotide arm

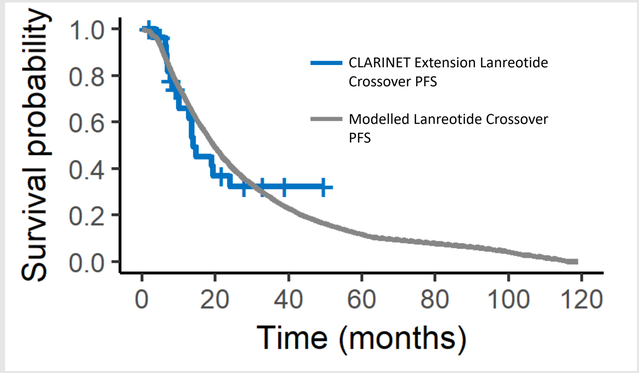

Figure 3. Progression Free Survival curves from the CLARINET Extension trial in blue (Caplin et al 2016) and the modeled version in gray used in cost-effectiveness model for patients who progress after active surveillance from the time they begin therapy with lanreotide

Strategy	Cost ($)	Incremental Cost ($)	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	Life-Years (years)	ICER ($/QALY)
Initial Lanreotide	$618,566	$161,037	5.22	0.37	8.99 (undiscounted)	$434,938
Active Surveillance with Lanreotide at Progression	$457,529	--	4.85	--	8.99 (undiscounted)	--

Table 1. Results from the base case. The incremental cost-effectiveness ratio of lanreotide upfront to lanreotide upon progression after active surveillance is $435,000 per QALY

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METHODS CONTINUED

Table 2. Survival Curve Modelling

	Treatment Arm	Parametric Distribution	Parameter(s)	Probabilistic Sensitivity analysis parameter distributions (parameters drawn from normal distributions with standard deviations equivalent to listed Standard Errors (S.E.) and correlations between parameters defined by correlation coefficients ρ.
Progression-free Survival (PFS)	Placebo (Active Surveillance)	Log-normal	Mean: 2.7977 S.D.: 0.7427	S.E. Mean 0.0836 S.E. S.D.: 0.0689 ρ: 0.241
	Lanreotide upfront	Exponential	Rate: 0.0181	S.E. rate: 0.0027
	Lanreotide after progression on placebo	Log-normal	Mean: 2.975 S.D.: 0.963	S.E. Mean 0.205 S.E. S.D.: 0.174 ρ: 0.302
Overall Survival (OS)				
Base Case (Same mortality assumed)	Lanreotide	Weibull	Shape: 1.55 Scale: 120.47	S.E. shape: 0.3 S.E. scale: 26.91 ρ: -0.762
	Placebo (Active Surveillance)	Weibull	Shape: 1.55 Scale: 120.47	S.E. shape: 0.3 S.E. scale: 26.91 ρ: -0.762
Scenario B (best-fitting curves independently)	Lanreotide	Weibull	Shape: 1.55 Scale: 120.47	S.E. shape: 0.3 S.E. scale: 26.91 ρ: -0.762
	Placebo (Active Surveillance)	Weibull	Shape: 1.828 Scale: 108.9	S.E. shape: 0.356 S.E. scale: 21.04 ρ: -0.745

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RESULTS/SENSITIVITY ANALYSIS

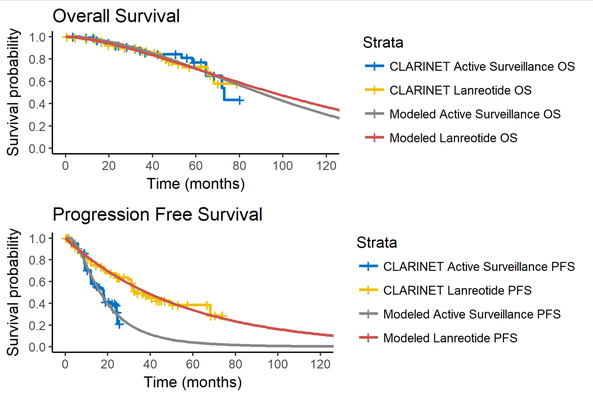

Figure 4. Scenario B. Modelled survival curves from alternative model. Scenario B relaxes the assumption that the mortality between the two arms is equal and models both arms using the best fitting Weibull curves.

Strategy	Cost ($)	Incremental Cost ($)	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	Life-Years (years)	ICER ($/QALY)
Initial Lanreotide	$618,566	$176,647	5.22	0.74	8.99 (undiscounted)	$238,472
Active Surveillance with Lanreotide at Progression	$441,918	--	4.48	--	8.02 (undiscounted)	--

Table 3. Results from alternative scenario (Scenario B) in which best-fitting Weibull curves are used with no assumption of same overall survival of each arm

WTP Threshold	Scenario A (Base Case)	Scenario B (higher mortality rate in Active Surveillance)
$50,000 per QALY	$1,329	$1,349
$100,000 per QALY	$2,076	$2,869
$150,000 per QALY	$2,823	$4,388

Table 4. Costs of 120 mg of lanreotide that reach various willingness-to-pay (WTP) thresholds

SENSITIVITY ANALYSIS

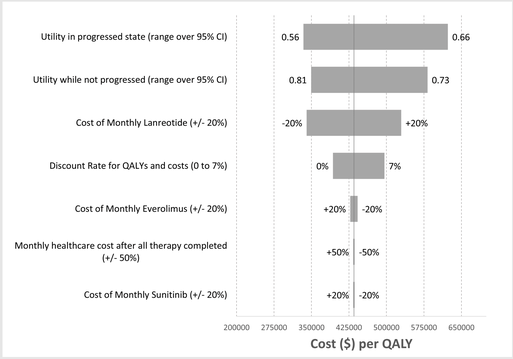

Figure 5. Tornado Diagram showing 1 way sensitivity to various parameters (base case). Blue bars represent the ICER for the low value of the parameter and red bars represent the ICER for the high value of the parameter. Varying these key parameters over the ranges described does not lower the ICER below $300,000 per QALY gained.

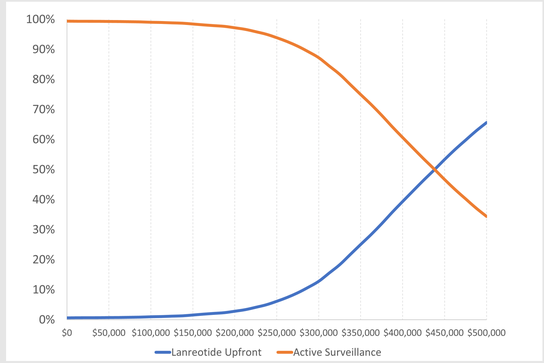

Figure 6. Results from the probabilistic sensitivity analysis for the base case. The y-axis represents the fraction of iterations of the model that reach the willingness to pay threshold on the corresponding portion of the x-axis. *Lanreotide Upfront* achieved cost-effectiveness in 1% of iterations for a WTP threshold of $100,000 per QALY

CONCLUSIONS

- Lanreotide upfront was modelled to improve quality of life compared to delayed lanreotide (after progression on active surveillance), at greater cost
- At its current prices, lanreotide is not cost-effective as initial therapy for select patients with metastatic enteropancreatic neuroendocrine tumor vs. active surveillance with lanreotide taken upon progression, using the CLARINET trial for the modeled population using a $100,000 or $150,000 willingness-to-pay threshold.
- For the base case model, we find that the cost of lanreotide would need to be lowered by 71% to be considered cost-effective for a WTP threshold of $100,000 per QALY.
- If overall survival is modelled by best-fitting curves (scenario B), lanreotide is still not cost-effective, but the required discount to achieve cost-effectiveness for a WTP threshold of $100,000 per QALY is lower at 59%

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Analysis performed using TreeAge Pro 2017, R2.1. *TreeAge Software, Williamstown, MA and MATLAB 2015b, MathWorks, Natick, MA*

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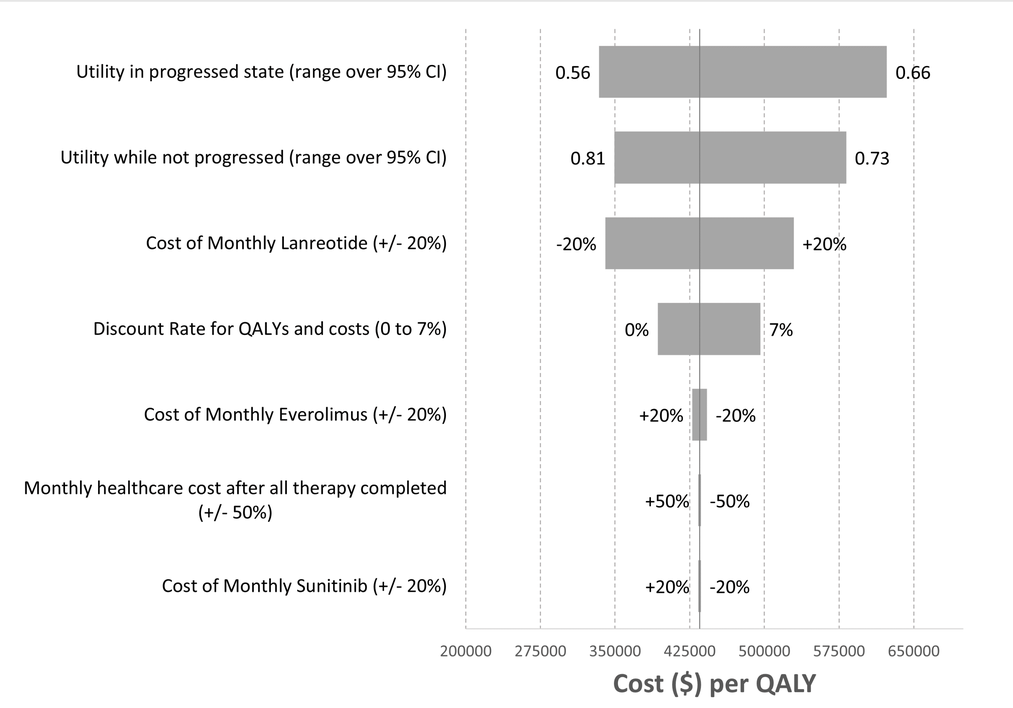

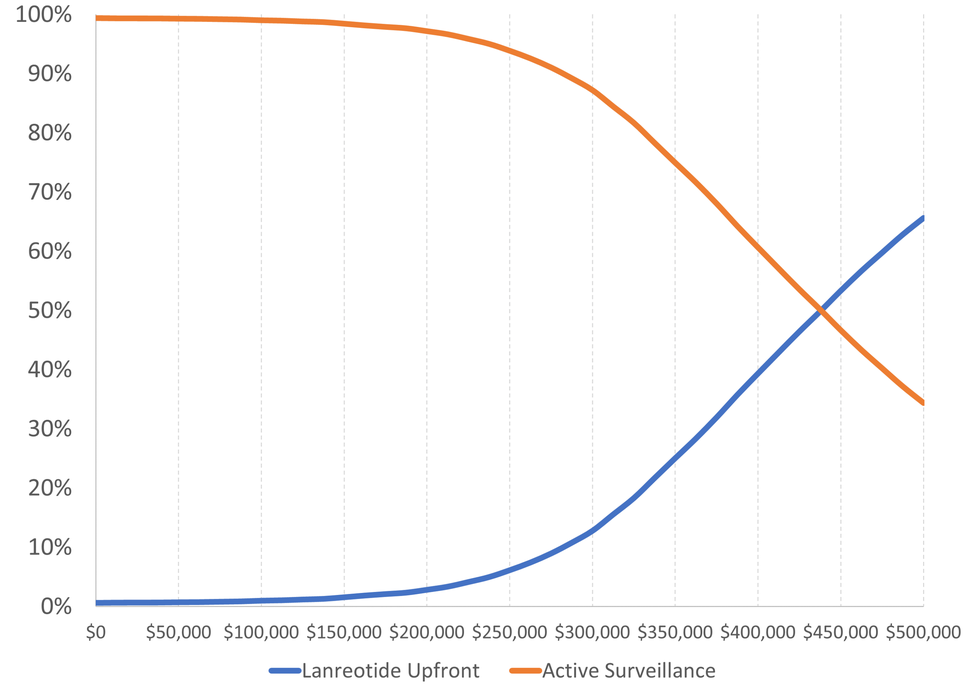

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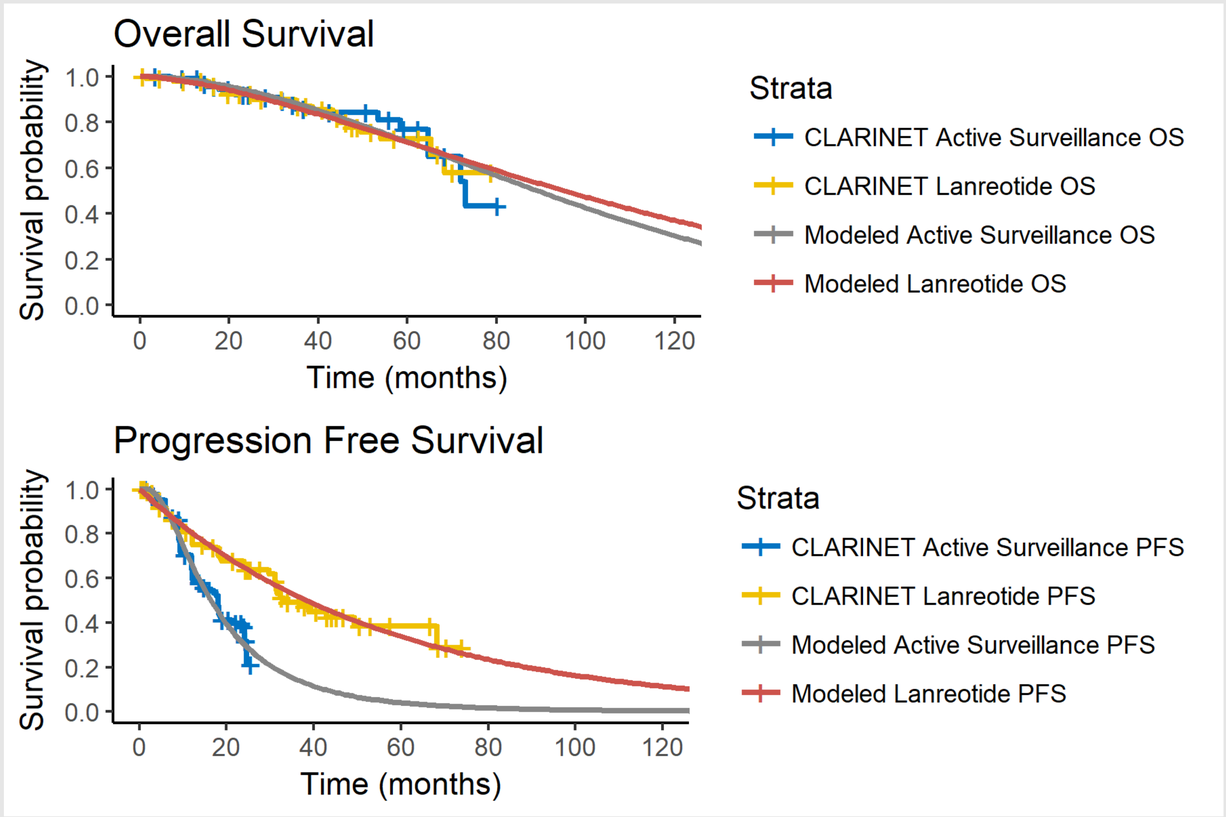

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