Impact of recurrence modelling on cost-effectiveness of new treatments for early cancers

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Introduction and objectives

- Cancer recurrence poses a significant challenge in the management of early-stage cancers, with profound implications for both patient outcomes and healthcare systems.
- Recurrence often necessitates additional rounds of treatment, increases healthcare resource utilization, and leads to a decline in patients' quality of life. In economic evaluations (EEs), accurately capturing these downstream effects is critical to understanding the full value of treatments that delay or prevent recurrence.
- However, early-stage oncology trials are frequently limited by short follow-up durations and immature survival data, particularly for disease-free survival (DFS) and overall survival (OS). These data limitations hinder the ability to model long-term outcomes and assess the true cost-effectiveness of novel therapies.
- The objective of this study was to assess the issues of recurrence modelling using the cost-effectiveness of alectinib as adjuvant therapy for patients with resected ALK-positive non-small cell lung cancer (NSCLC). It aims to highlight the importance of long-term extrapolation and modelling choices in EEs for evaluating therapies in other early-stage cancers, where similar data limitations are common.

Methods

- A three-state partitioned survival model was developed to capture occupancy among recurrence-free, progressive disease, and death states over time from a United States payer perspective.
- Survival analysis relied on digitized DFS data for both alectinib and chemotherapy from the ALINA trial[1] and OS data for chemotherapy from the ANITA trial[2]. Due to the lack of OS data for alectinib, an assumption was made that OS for alectinib could be estimated using a hazard ratio (HR) relative to chemotherapy OS, allowing the model to reflect alectinib's expected survival benefit.
- The importance of recurrence was tested through inclusion and exclusions of subsequent therapy, alternate time horizons and exploring uncertainty in survival outcomes through different scenario analyses.
- Parametric survival models were used to extrapolate both RFS and OS beyond the trial period, enabling lifetime projections. Standard survival distributions including exponential, Weibull, Gompertz, log-logistic, log-normal, and generalised gamma were tested, and the best-fitting models were selected based on statistical fit and visual inspection of the curves[3]. Kaplan-Meier curves were also used in scenario analyses to assess their impact on model results.
- Utility values for alectinib were assumed based on values from Jovanoski et al. (2023)[4] for early-stage NSCLC post-surgery and for chemotherapy utility values from Li et al. (2021)[5] were used (**Table 1** and **Table 2**).
- Direct costs including drug acquisition and administration, diagnostic test, follow up and monitoring, adverse events costs and subsequent treatments following recurrence were considered. The related resource use and unit cost data were sourced from literature (**Table 3**).
- Deterministic sensitivity analysis was conducted to explore uncertainty around key parameters and assumptions.

Table 1. Utility values

Health state	Utility values		
	Alectinib	Chemotherapy	Source
DFS	0.82	0.76	Jovanoski et al. 2023[4] Li et al. 2021[5]
PD	0.70	0.70	
Death	0.00	0.00	

Methods (cont.)

Table 2. Adverse events incidence, disutility and costs

Adverse event	Alectinib*	Chemotherapy*	Disutility value†	Cost per event ++	Source
Neutropenia	0.00%	8.30%	0.0731	$10,267	*Wu et al. 2024[1]; †Jovanoski et al. 2023[4] ++2024 ICD-10-CM/PCS Medical Coding Reference[6]
Creatine kinase increased	6.20%	0.80%	0.0731	$7,186	
Neutrophil count decreased	0.00%	10.00%	0.0731	$26,834	
Nausea	0.00%	4.20%	0.0731	$7,216	
White-cell count decreased	0.00%	3.30%	0.0731	$8,945	
Appendicitis	3.10%	0.00%	0.0731	$7,478	

Table 3. Subsequent treatment utilisation and costs

	Proportion (Normalized values)			Costs (Inflated to 2024)	
Subsequent treatment	Alectinib (n=15 recurrent)	Chemotherapy (n=49 recurrent)	Source	Costs	Sources
ALK TKI			ALINA trial (Wu et al. 2024)[1]		
Alectinib	50.00%	72.50%		$356,756	Cranmer et al. 2022[7]
Brigatinib	50.00%	10.00%		$343,335	
Crizotinib	0.00%	10.00%		$405,203	
Lorlatinib	0.00%	5.00%		$188,552	
Ceritinib	0.00%	2.50%		$297,016	
Chemotherapy	46.15%	5.26%		$31,948	Huang et al. 2017[8]
Immunotherapy	7.69%	2.63%		$21,801	Yang et al. 2023[9]
Other anti-cancer therapy	7.69%	2.63%		$21,801	Assumption based on immunotherapy
Radiotherapy	38.46%	20.93%		$13,941	Huang et al. 2023[10]
Surgery	7.69%	6.98%		$6,867	

Results

Table 5. Scenario analysis results

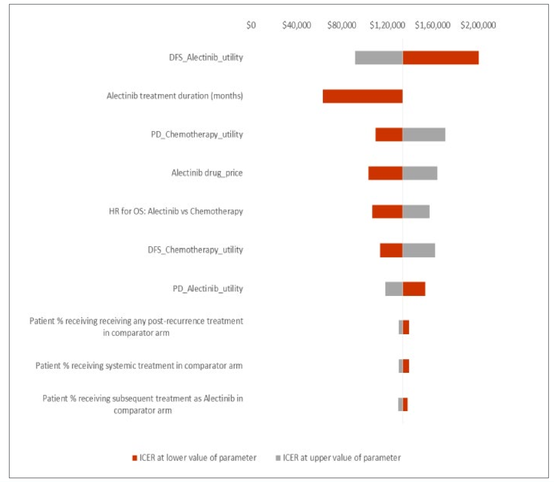
Scenario	ICER	% change from base-case ICER
Base-case	$133,787	-
Time horizon: 1 year	$214,634	1555.00%
Time horizon: 2 year	$1,471,872	1000.16%
Time horizon: 5 year	$436,717	226.43%
Time horizon: 10 years	$228,383	70.71%
Time horizon: 20 years	$163,889	22.50%
Time horizon: 30 years	$145,215	8.54%
Exlude subseqent treatment costs	$150,307	12.35%
Alec and Chemo KMs for DFS	$447,696	234.63%
Chemo KM for OS	$106,259	-20.58%
DFS both arms: Exponential	$76,640	-42.71%
DFS both arms:Log-logistic	$98,046	-26.71%
DFS both arms:Generalized gamma	$174,285	30.27%
DFS both arms:Gompertz	$187,831	40.40%
DFS both arms:Log normal	$60,341	-54.90%
OS chemo: Exponential	$138,347	3.41%
OS chemo: Log-logistic	$125,005	-6.56%
OS chemo: Generalized gamma	$124,904	-6.64%
OS chemo: Gompertz	$122,335	-8.56%
OS chemo: Log normal	$124,961	-6.60%

- The base case results are presented in Table 4. Weibull distribution was used for both DFS and OS in the base case analysis due to the good fit to trial data.
- The impact of recurrence tested by varying time horizon, alternative DFS and OS distributions as well as exclusion of subsequent treatments led to a large change on the cost-effectiveness results (**Table 5**).
  - Impact of time horizon:
    - Shorter time horizons (1-10 years) significantly increased ICER
  - Impact of alternative DFS distributions:
    - The KM approach increased the ICER by 235%
    - Gompertz increased it by 40%
    - The log-normal model decreased the ICER by 54.9%.
  - Impact of alternative OS distributions:
    - The KM approach decreased ICER by 20.58%
    - Exponential increased ICER by 3.41%
  - Impact of exclusion subsequent treatment costs:
    - Excluding subsequent treatment costs Increased ICER by 12.35%.
- One way sensitivity analyses found alectinib DFS utility, treatment duration and chemotherapy PD utility were the top three parameters impacting the cost-effectiveness results, followed by HR for OS. Adjusting the HR for OS by ±20% produced a similar ±20% change in ICER (**Figure 1**).

Table 4. Base case analysis results

	Alectinib	Chemotherapy	Incremental (alectinib vs. chemo)	ICER ($/LYs)	ICER ($/QALYs)
LYs	11.30	8.17	3.13	$128,953	$133,787
QALYs	8.93	5.91	3.02		
Total costs	$499,371	$95,727	$403,644		

Figure 1. One way sensitivity analysis results



Conclusion

- Accounting for recurrence and related impacts over long-term is important for evaluating early cancer treatments. Cost-effectiveness results are significantly influenced by recurrence survival modelling, time horizons and subsequent treatment costs as shown in the scenario analysis results.
- Robust modelling of long-term recurrence is essential in early-stage cancer to accurately capture the sustained clinical and economic benefits of adjuvant therapies like alectinib.
- Treatments that delay recurrence can yield substantial quality-of-life improvements and QALY gains, which become more apparent over extended time horizons.
- The analysis showed that alectinib's impact on delaying disease recurrence significantly improves cost-effectiveness, especially when assessed using lifetime horizons that fully account for long-term benefits. Shorter horizons or simplistic modelling approaches risk underestimating the value of such therapies.
- Due to the limitations in data and assumptions, the base case results should be interpreted with caution.
- Future economic evaluations of early cancer treatments should address these uncertainties with more mature survival data and consider all relevant costs over patient's lifetime.

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