Untreated Anaplastic Lymphome Kinase-Positive (ALK+) Non-Small-Cell Lung Cancer (NSCLC): a systematic review of economics and health-related quality of life

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BACKGROUND

- Lung cancer remains both the most commonly diagnosed cancer and the most common cause of cancer death worldwide, according to GLOBOCAN estimates, with 2.1 million diagnosed in 2018. (1) NSCLC is the most common type of lung cancer accounting for 85% of cases.
- Advances in genetic research have revealed that NSCLC is not a single disease, but highly heterogeneous with many different driver mutations. (2)
- In a small proportion of patients, the growth of cancer cells is caused in part by anaplastic lymphoma kinase (ALK) gene rearrangement.
- This rearrangement is detected by means of an ALK biomarker test, with ALK-positive (ALK+) status believed to be present in 3.8% of NSCLC patients. (3)
- ALK rearrangement can occur in NSCLC of any histology but is predominantly found in adenocarcinoma tumours with (that is, non-squamous histology), and is very uncommon in tumours of squamous cell carcinoma histology. (3)
- Clinical features of patients with ALK+ NSCLC include an estimated median age of 49-52 years, none or a light smoking history, and advanced disease at the time of diagnosis, making this a small population of relatively young patients who have low disease suspicion and therefore present late. (4-6)

OBJECTIVES

- To review the economic and health-related quality of life (HRQoL) evidence of targeted therapies in locally advanced and metastatic ALK+ NSCLC through a systematic literature review (SLR).

METHODS

Search strategy

- Systematic bibliographic searches were conducted of MEDLINE, Embase, EconLit, ScHARR HuD, National Health Service Economic Evaluation Database (NHS EED) and PubMed.
- One search was conducted for both the cost-effectiveness/ economic evaluation component and the cost and resource use component, with a separate search for HRQoL data.
- Conference publications from the last 3 years (2015-2019) were also searched.
- The searches were designed to identify economic, cost and healthcare resource use, and HRQoL data associated with ALK+ NSCLC, to inform an economic model for HTA.
- Initial searches were conducted in May 2018 followed by an update between 30th May – 3rd June 2019 (bibliographic searches ran from January 2018 to search date) which applied the same methods and search strategies as the original searches.

Eligibility criteria

- Each component of the SLR had different eligibility criteria against which studies were screened (Table 1).

Table 1: PICOS eligibility criteria for each SLR component

Criterion	Economic evaluation component	Cost and resource use component	HRQoL component
Population	Adults (≥18 years), locally advanced or metastatic ALK+ NSCLC diagnosis, treatment-naive or one previous systemic anticancer treatment and TKI naïve	Adults (≥18 years), locally advanced or metastatic ALK+ NSCLC.	
Interventions	Brigatinib, Crizotinib, Ceritinib, Alectinib, Lorlatinib, Ensartinib		Any intervention
Comparators	Any comparator including but not limited to: Lorlatinib, Ensartinib, Crizotinib, Ceritinib, Alectinib, Lorlatinib, Ensartinib, Chemotherapy and best supportive care.		
Outcomes	Incremental cost-effectiveness ratio (ICER) [cost per QALY, cost per life year, cost per progression free life year or cost per clinical outcome], cost per benefit, total treatment costs and budget impact per population	Direct costs (including ALK testing, unit costs and total costs), Indirect costs (including unit costs and total costs), Resource use, Travel, Work productivity, Employment and Work Disability.	Mean or median utility values from: EQ-5D (3L or 5L) SF-6D. Time trade-off (TTO) methods or mapped from: EORTC-QLQ-C30, EORTC-QLQ-LC13, FACT-L, Lung Cancer Symptom Scale (LCSS). Utility values reported for the following health states/variables: Stable disease, Progressive disease (including any progressive disease substates), Treatment response, Treatment related adverse events, Time-to-death (TTD).
Study designs	Randomised controlled trials (RCTs), cost-consequence, cost-minimisation, cost-effectiveness, cost-utility, cost benefit, cost of illness and budget impact	Any study type, excluding claims databases and systematic literature reviews	Any study type
Publication types	Journal articles, reports, abstracts, posters, summaries and conference abstracts published within the last three to four years (published January 2015 to June 2019), excluding letters, newsletters, bulletins, fact sheets, editorials, non-systematic reviews, commentaries and conference abstracts (published before 2015).		
Limits	Conference abstracts excluded if published before 2015.	Public health care or societal perspective including countries Europe, US, Canada, Australia only. Excluding third party payer, hospital or clinician perspective, other countries. Conference abstracts excluded if published before 2015.	Conference abstracts excluded if published before 2015.

Abbreviations: ALK, anaplastic lymphoma kinase; ICER, incremental cost-effectiveness ratio; NA, not applicable; NSCLC, non-small cell lung cancer; RCT, randomised controlled trial; SCLC, small cell lung cancer; US, United States

Study selection

- Titles and abstracts of identified studies were reviewed independently for eligibility by two experienced reviewers.
- Full texts of studies included for secondary screening were obtained and the two reviewers independently screened, including or excluding them according to the eligibility criteria (Table 1).
- Following full text screening, data from the included studies were extracted into individual data extraction tables developed for the economic review, cost and resource use and HRQoL components of the review in Microsoft Excel®.
- Studies identified in the cost-effectiveness and cost and resource use reviews were appraised using both the Philips *et al*. (2004) (9) checklistand the Methods for the Development of NICE Public Health Guidance.(10) Studies identified in the HRQoL review were appraised using the checklist presented in Picot *et al*. (2015). (11)

RESULTS

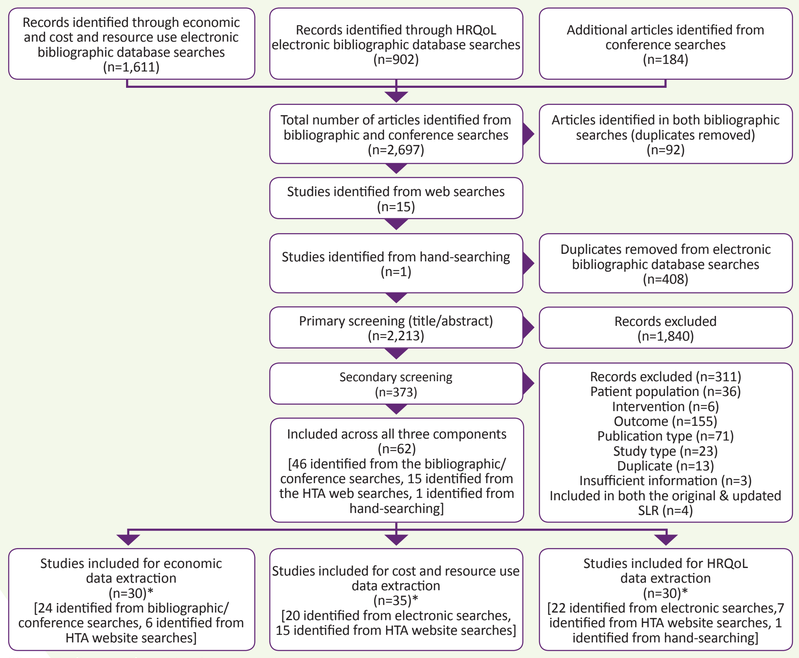
- The economic review following bibliographic/conference/ HTA website/hand searching and the removal of duplicates identified 2,213 articles for primary screening.
- Following exclusion based on title and abstract, 369 records were secondary screened with 307 of these excluded (see the PRISMA diagram in Figure 1 for exclusion reasons).
- 62 studies were included for final review across all three SLR components (see Table 2) and were data extracted.
- Of the 62 studies identified as relevant across all three components, 30 included data for the cost-effectiveness SLR component. Of these 30 studies, 24 were identified from the bibliographic and conference searches, and six were identified from manual Health Technology Assessment (HTA) website searches.
- For the cost and resource use component, 20 studies from the bibliographic and conference searches and all 15 HTA studies identified from the website searches contained cost or resource use data as per the SLR protocol; totalling 35 studies.
- For HRQoL, 30 studies contained data relevant to this component. 22 of these studies were identified from bibliographic or conference searches, 7 identified from web searches and one identified from reference hand-searching.

Table 2: Number of papers extracted for each SLR component

SLR component	All three SLR components	CE only	C&R only	HRQoL only	CE and C&R	CE & HRQoL	C&R and HRQoL
No. of publications identified as relevant	11	12	15	13	5	2	4

Abbreviations: CE, cost-effectiveness; C&R, cost and resource use; HRQoL, health-related quality of life; No., number; SLR, systematic literature review

Figure 1: PRISMA diagram



*Some studies are relevant to >1 component

CONCLUSION

- This SLR identified few published records relevant to the advanced ALK+ NSCLC first-line (treatment-naïve) population. The main publications relevant to this population were identified in the HTA web searches from recent economic evaluations in the form of cost-utility analyses submitted to HTA bodies such as National Institute for Health and Care Excellence (NICE).
- The data obtained in the HTA publications are likely to be the most relevant and applicable to a new cost-utility model for ALK inhibitors for the first-line advanced or metastatic ALK+ NSCLC population. These documents tend to present clear model structures and rationale, adequate and appropriate costs, resource use and HRQoL utility values as well as setting a precedent with HTA bodies.
- The SLR confirmed that a three-state (pre-progression, post-progression, death) partitioned-survival model is the most widely used, but four-state and five-state models (separating pre- and/ or post-progression by central nervous system (CNS)), have more recently been used. The standard three health state model is likely to be the best option for modelling the patient population of interest but is largely dependent on the comparator(s) and the available data. Appropriateness of alternative model structures may vary as more mature data becomes available.
- HTA publications provided a good range of costs data but there were a lack papers that presented sufficient resource use data that would be useful for future modelling.
- There remains a paucity of evidence regarding costs and resource use as well as HRQoL utilities relevant to the treatment-naive patient population in particular. This data could be obtained from a number of sources including clinical trials, where more appropriate data collection is not feasible expert opinion may be needed.
- The majority of utility studies reported values by health state and by treatment. There was limited data for the first-line population. There is also paucity of evidence for patients in the post-progression health state, with utilities generally sourced from other published literature.

ABBREVIATIONS

ALK, anaplastic lymphoma kinase; HTA, health technology assessment; NSCLC, non small cell lung cancer; SLR, systematic literature review; 1L, first-line

REFERENCES

1. International Agency for Research on Cancer (IARC). Latest global cancer data: Cancer burden rises to 18.1 million new cases and 9.6 million cancer death in 2018. Press release No. 263. 12th September 2018. https://www.who.int/cancer/PRGlobocanFinal.pdf
2. Chen Z, Fillmore CM, Hammerman PS, Kim CF, Wong KK. Non-small-cell lung cancers: a heterogeneous set of diseases. Nat Rev Cancer. 2014;14(8):535-546.
3. Gubens M, Wong W, Wu N, Chu L, Schulze K, Illei P. Real-world patient characteristics, testing, and treatment patterns of ALK+ NSCLC. In. IASLC 18th World Conference on Lung Cancer, October 15–18, 2017, Yokohama, Japan2017.
4. Chia PL, Mitchell P, Dobrovic A, John T. Prevalence and natural history of ALK positive non-small-cell lung cancer and the clinical impact of targeted therapy with ALK inhibitors. Clin Epidemiol. 2014;6:423-432.
5. Koh Y, Kim D, Kim T, et al. Clinicopathologic characteristics and outcomes of patients with anaplastic lymphoma kinase-positive advanced pulmonary adenocarcinoma. J Thorac Oncol. 2011;6 (5):905-912.
6. Subramanian J, Morgensztern D, Goodgame B, et al. Distinctive characteristics of non-small cell lung cancer (NSCLC) in the young: A surveillance, epidemiology, and end results (SEER) analysis. J Thorac Oncol. 2010;5(1):23-28.
7. Veritas Health Innovation. Covidence systematic review software. Melbourne, Australia. In.
8. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine. 2009;6(7):e1000097.
9. Philips Z, Ginnelly L, Sculpher M, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. 2004.
10. National Institute for Health and Care Excellence (NICE). Methods for the development of NICE public health guidance (third edition). Process and methods [PMG4] Web site. https://www.nice.org.uk/process/pmg4/chapter/introduction. Published 2012. Accessed August 2017.
11. Picot J, Copley V, Colquitt JL, Kalita N, Hartwell D, Bryant J. The INTRABEAM(R) Photon Radiotherapy System for the adjuvant treatment of early breast cancer: a systematic review and economic evaluation. Health technology assessment (Winchester, England). 2015;19(69):1-190.

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