Erasmus School of Health Policy & Management

Overall cost-effectiveness of a tumour agnostic therapy, informative or useless? An evaluation based on cost-effectiveness modelling in different solid tumour types [breast cancer, lung cancer, and colorectal cancer]

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Abstract

Objective: To determine whether overall efficacy data of Larotrectinib obtained by basket trials are useful to form an average ICER in the assessment of cost-effectiveness in solid tumours, compared with Docetaxel, Eribulin, and Trifluridine/tipiracil in NSCLC, breast cancer, and colorectal cancer patients respectively.

Methods: An economic evaluation for Larotrectinib was conducted in the form of a CEA per NICE guidelines. The cost-effectiveness of Larotrectinib was assessed for three cancer indications (non-small cell lung cancer, breast cancer, and colorectal cancer) using three similar partitioned survival Markov Models with a lifetime horizon. The Markov models were based on several clinical studies of which efficacy data was taken for Larotrectinib vs standard of care in last line treatment (Docetaxel, Eribulin, and Trifluridine/tipiracil, respectively). The potential impact on resource costs expected from introducing Larotrectinib (as well as the comparators) were considered from a healthcare perspective. The ICER for a QALY and LY gained were estimated, eventually forming an average ICER. Scenario analyses and probabilistic sensitivity analyses (PSA) were conducted.

Results: The average ICER over all three models was £83.202,61 per QALY gained per patient, ranging between £65.137,42 and £113.727,37. Most benefit was, however, found in the life-years gained of which all ICERs were below £50.000,00 per patient, with an average ICER of £40.762,06 per life-year gained, ranging between £35.020,97 and £49.793,37.

Conclusion: The use of overall efficacy data of Larotrectinib in different solid tumour types resulted in quite a wide range of ICERs, but at all times showing more benefits at higher costs. In terms of costs per QALY, the ICERs were not below the current WTP-threshold of £30,000 per QALY gained, and in that sense, not cost-effective. However, the additional life-years gained by Larotrectinib are tremendously high, ranging from 11 – 15 years. This is reason to believe that Larotrectinib is a promising drug in prolonging life for patients receiving last line of treatment. The use of an average ICER and its range in cost-effectiveness analyses can be beneficial to identify in what cancers the drug may be possibly most suited to become cost-effective. In addition, the cost-effectiveness analysis shows what strengths the intervention possibly has (in this case, more additional life-years gained). Also, prices can be obtained and evaluated by NICE to determine beforehand what reasonable price arrangements would be during confidential negotiations. To further reduce uncertainties around the safe use of average ICER results, it would be beneficial to conduct a similar type of research in more cancer histologies and more diverse populations with bigger patient groups, once more mature data and data on a larger set of patients would be available.

Keywords: cost-effectiveness analysis, tumour agnostic, Larotrectinib, breast cancer, lung cancer, colorectal cancer

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1. Introduction

Treating cancer patients has always been challenging due to the different types of tumour physiology, the histology, and the continuous change of the tumour. In addition to treatment difficulties, the complex phenomenon of cancer drug resistance occurs as well (1). Due to cancer drug resistance at some point, many patients can hardly find curing treatments. This results in poor prognosis for cancer patients. On average, 166.000 cancer patients in the United Kingdom (UK) die every year (2). That counts for almost 20 deaths each hour.

Fortunately, improvements had been made where targeting oncogenic drivers resulted in better outcomes for patients with metastatic or advanced cancer (3). These therapies target specific tumour locations and thus are tumour-histology dependent. More innovative cancer treatments have been developed to treat specific cancer types and treat rare mutations found in multiple cancer histologies. Particularly interesting are *tumour agnostic (TA) therapies*, which target specific gene modifications regardless of the tumour histology (4). One of these therapies targeting rare mutations is Larotrectinib which specifically targets tumours with an NTRK fusion, where Larotrectinib inhibits the TRKA, TRKB and TRKC proteins in multiple solid tumour types (5). Larotrectinib has been the first to be approved by the European Medicine Agency (EMA) and Food and Drugs Administration (FDA) as a monotherapy treatment for paediatric and adult patients (6)(7). These patients should have tumours expressing the NTRK gene fusion, regardless of histology, that are metastatic, advanced, or where surgery is restricted due to high chance of severe morbidity (6)(7)(8). Larotrectinib, which specifically inhibits the TRKA, TRKB and TRKC proteins, shows a 73% progression-free survival (PFS) of the patients after six months and 55% PFS after one year (5). The overall response rate (ORR) was 79% (72-85) with a median duration of 35,2 months (5). However, efficacy data about these treatments is obtained via *single-arm basket trials*, which contain a small number of patients (9)(10). In addition, these patients have different types of cancer and diverse tumour locations, though similar genetic tumour mutations as shown in figure 1 by Hong et al. (9). It has been suggested in figure 1 by Hong et al. that the best responses to Larotrectinib were found in i.a. lung and breast cancer, with respectively 9 out of 12 and 3 out of 4 patients with response (9). Minor responses were obtained in i.a. colon cancer, where only 4 out of 11 patients responded (9).

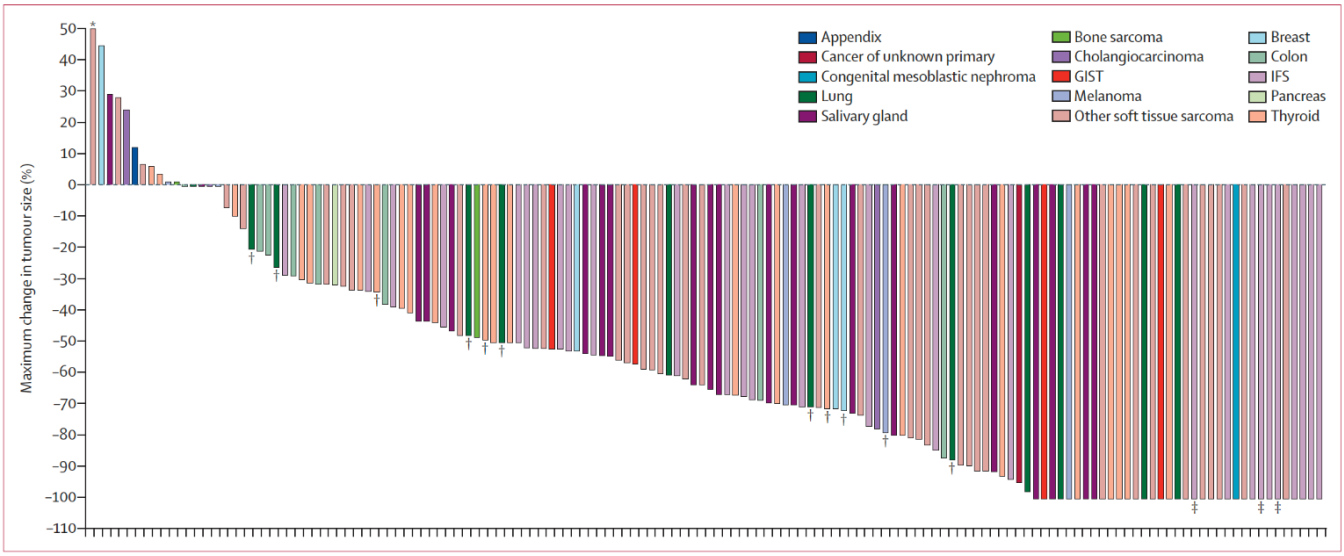

Figure 1: Waterfall plot by Hong et al. of the maximum change in tumour size, according to tumour type.

Efficacy data obtained by basket trials consist of an average pooled ORR and overall PFS (5)(9). In case of ORR, a response is defined as the shrinkage of the tumour. Furthermore, the PFS and ORR from basket trials assume that the clinical effectiveness across these histologies is comparable. As mentioned in an article by Murphy et al., this assumption neglects the heterogeneity in clinical effectiveness across the different histologies within the basket trial (11). By this, Murphy et al. try to explain that patients with different histologies, who are treated with Larotrectinib, may also experience different (types of) benefits due to their specific cancer characteristics despite the similar genetic tumour mutations (11). This results in higher uncertainties around the obtained overall efficacy data from such basket trials.

Like the United Kingdom (UK), multiple countries in Europe use information about a drugs' cost-effectiveness to inform their reimbursement decision-making bodies. Many chemotherapies have been examined in numerous trials with many patients. These trials generated substantial histology dependent efficacy data enabling demonstration of cost-effectiveness for different cancer indications. This led to multiple chemotherapies being implemented as first- or second-line treatments. New challenges for cost-effectiveness assessments arise since new promising cancer medications targeting rare mutations are entering the market. Though TA treatments are revolutionary for patients, it brings new hurdles in terms of CEAs for the decision making by reimbursement bodies. These bodies used to assess the cost-effectiveness of drugs and determine an incremental cost-effectiveness ratio (ICER) for a single indication, where-else now multiple indications are being addressed with TA drugs. Each tumour histology has a different underlying prognosis of the disease and different treatment options that are currently available. Compared to the current standards of care, the added value of TA therapies balanced against the added costs is hard to measure for separate cancer indications, as efficacy data for separate cancer indications does not exist. Not being able to account for heterogeneity in the efficacy of TA therapies across histologies in CEAs could lead to wrong decisions where reimbursements of TA drugs are not cost-effective in certain histologies (11). This could lead to additional costs and unwanted health consequences. Basket trials providing average efficacy data were initially accepted by the authorisation bodies such as EMA, but payers such as The National Institute for Health and Care Excellence (NICE) faced similar problems as just mentioned. According to NICE, an average TA clinical effect cannot be used in CEAs, causing them to request evidence per tumour histology for each cancer type separately (12). Since multiple health technology assessment (HTA) agencies are starting to review appraisals of TA cancer treatments, and this emerging problem pointed out by NICE is being encountered, consensus on how to act on this is needed (12)(13)(14). As more tumour-agnostic therapies are in the pipeline and reimbursement procedures are ongoing, pressure starts to build up on payers to decide on what to do with this limited data though high need for these therapies. On the other hand, manufacturers of TA drugs are being challenged by reimbursement bodies as well since their new innovative drug turns out to bring new hurdles within its market authorisation. This can discourage pharmaceutical companies from innovating new and better drugs, leading to unfavourable consequences in the future.

Larotrectinib has been approved by EMA/FDA and accepted by NICE. It is obtained in the cancer drug fund under the condition that more efficacy data would be gathered to counteract the current uncertainties around the available data. The deadline set by NICE for the primary data collection is July 2023 (15). The published NICE appraisal for Larotrectinib has most data masked, implying that the cost-effectiveness estimates of Larotrectinib are still confidential (16). Other than that, no cost-effectiveness studies have been published regarding Larotrectinib. Furthermore, uncertainty around the usage of overall efficacy data from basket trials in CEAs has not clearly been shown. If overall efficacy data can be useful to conduct

CEA's for Larotrectinib by forming an average ICER, a faster decision can be made by reimbursement bodies. Perhaps an average ICER of Larotrectinib for multiple cancer histologies does not necessarily deviate substantially from histology specific ICERs to make it un-useful. Whether a CEA using overall efficacy data can prove cost-effectiveness in a specific tumour type remains the question. The cost-effectiveness of Larotrectinib in specific cancer histologies could overcompensate the possible losses in other histologies. In both cases, patients can still be treated with Larotrectinib and benefit from it. In that manner, overall efficacy data from basket trials can still be used to conduct multiple CEAs forming an average ICER, leading to the possible usage of TAs as a last line treatment in different tumour types. Hence, this study aims to examine the possible use of overall efficacy data for CEAs to form an overall ICER. This was done by assessing the cost-effectiveness of the TA drug Larotrectinib versus disease-specific comparators in different solid tumour types (breast cancer, non-small cell lung cancer, and colorectal cancer) expressing NTRK-gene mutations, showing whether the differences in ICERCEAs are small enough to justify the use of an average ICER. The average ICER represents the primary endpoint of this study. In addition, a cost-effectiveness acceptability curve (CEAC), probabilistic sensitivity analyses on all parameters, and scenario analyses will be the secondary endpoints of this study to judge the formed ICERs and robustness of this study. The potential risk reimbursement bodies take when deciding based on an overall CEA will be explored.

2. Methods

An economic evaluation for Larotrectinib was conducted in the form of a CEA per NICE guidelines (12). The potential impact on resource costs expected from introducing Larotrectinib (as well as the comparators) were considered from the NICE healthcare perspective who required the perspective of the NHS and Personal Social Service as decisionmaker and payer (1)(17). As per NICE guidelines, only direct healthcare costs were taken into account (18). The cost-effectiveness of Larotrectinib was assessed for three cancer indications (non-small cell lung cancer (NSCLC), breast cancer, and colorectal cancer) using three similar Markov Models. A visual representation is shown in figure 2.

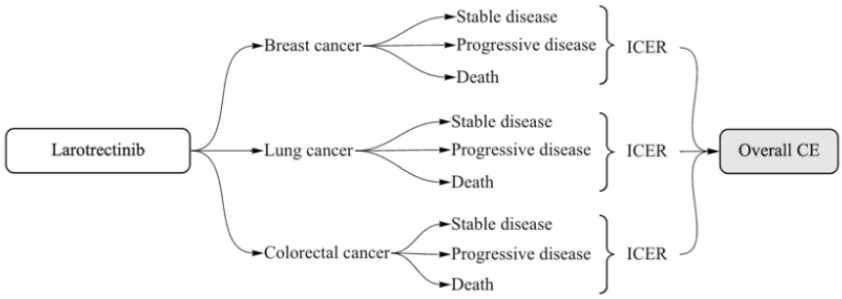

Figure 2: Visual concept of the economic evaluation.

This economic evaluation generated ICERs (Δcosts/ΔQALYs) of Larotrectinib vs standard of care in last line treatment for each cancer type. These treatments are Docetaxel monotherapy, Eribulin, and Trifluridine/tipiracil for NSCLC, breast cancer, and colorectal cancer, respectively. More elaboration on these comparators will be given under section *2.2. Intervention and comparators*. The three-indication specific ICERs were averaged, which represented the primary endpoint of this study, necessary to answer the research question. Secondary endpoints were the cost-effectiveness acceptability curve (CEAC) to judge the probability of cost-effectiveness for different WTP-thresholds, probabilistic sensitivity analyses on all parameters to test the robustness of the economic evaluation, and scenario analyses. All ICERs were examined and compared with each other, considering the variabilities and range to determine whether this model could generate an informative average ICER.

2.1. Patient Baseline Characteristics.

A summary of the patient baseline characteristics is given in appendix A. The efficacy data used in this study for the indication arm with Larotrectinib is taken from research by Hong et al. containing 153 patients with different cancer types, indicated with an NTRK fusion (9). This was the pivotal study on which the EMA based its approval for Larotrectinib. According to the NICE appraisal, Larotrectinib as a new treatment should not displace any effective therapies and should thus be used as last-line treatment in patients with the NTRK-fusion mutation (12)(16). As mentioned before, for each cancer type, a different comparison with Larotrectinib was made according to its specific last line standard of care treatment in the UK. The efficacy data for the three comparator arms are each from a different study, summarised in table 1.

Summary of the studies used to obtain efficacy data for each comparator		
Indication	**Comparator**	**Study used (to obtain i.a. efficacy data)**
Non small cell lung cancer	Docetaxel	Cufer T et al. Phase II, open-label, randomized study (SIGN) of single-agent gefitinib (IRESSA) or docetaxel as second-line therapy in patients with advanced (stage IIIb or IV) non-small-cell lung cancer. Anticancer Drugs. 2006;17
Breast cancer	Eribulin	Kaufman PA et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2015;33
Colorectal cancer	Trifluridine/tipiracil	Chida K et al. Efficacy and safety of trifluridine/tipiracil plus bevacizumab and trifluridine/tipiracil or regorafenib monotherapy for chemorefractory metastatic colorectal cancer: a retrospective study. Ther Adv Med Oncol. 2021;13.

Table 1: Studies serving efficacy data of the comparators.

These studies were selected on a last-line treatment option for their specific indication, and populations that were as much as possible matching the baseline patient characteristics with those of the Hong et al. study. The Hong et al. study has a heterogenic patient population including many tumour types with patients of all ages. Though, assumed was that the patients within the Hong et al. study with NSCLC, breast cancer, or colorectal cancer matched the patient populations chosen for each of the mentioned indications in this study since this is last-line treatment. Each Markov model consisted of a different patient population according to the cancer indication that was being treated (NSCLC, breast cancer or colorectal cancer). For the lung cancer model, the study population consisted of adults with a mean age of 63 years old (34 – 85), with advanced NSCLC (19). For the breast cancer model, the population consisted of adults between 24 and 80 years with a mean age of 54 (20). For the colorectal cancer model, the patient population had a mean age of 65 years old, ranging between 58 and 71 years (21).

All patients had either locally or solid metastatic tumours, and an Eastern Cooperative Oncology Group (ECOG) score ranging from 0-2 (on a scale of 0-5, where higher scores mean more disability) (9)(19)(20)(21). If possible, patients were previously treated with standard therapy for their specific cancer type. In addition, all patients showed adequate organ functioning (9)(19)(20)(21). Finally, all patients were assumed to have an identifiable NTRK fusion.

2.2. Intervention and comparators.

Larotrectinib was considered the intervention of which hard capsules were available in 100 mg to be taken twice a day orally (12). Efficacy data of Larotrectinib were derived from the basket trial by Hong et al. (9). As Larotrectinib was investigated in a single-arm trial, no direct or indirect comparative evidence on the three comparators (Docetaxel, Eribulin, Trifluridine/tipiracil) was available. Hence naïve and unadjusted comparisons were used in this cost-effectiveness analysis. To identify the most suitable efficacy data for each comparator, an explorative literature search was done to find several potential studies on efficacy.

For NSCLC, the current standard of care as last line option in both squamous and non-squamous cells is docetaxel monotherapy (when progressed on first and second-line treatment) (22) (23). In this case, data for Docetaxel as the comparator arm in the NSCLC model was drawn from the Cufer et al. trial in which the dose consisted of 75mg/m2 iv. docetaxel (19). This study was chosen because of the clear Kaplan Meier data indicating the numbers at risk. This is necessary for reconstruction of the Kaplan Meier curves in excel to eventually extrapolate the efficacy data. Though this data by Cufer et al. is from 2006, it has similar outcomes to a recent study from 2020 by Arrieta et al. about the efficacy and safety of pembrolizumab plus Docetaxel vs Docetaxel monotherapy in patients with previously treated advanced NSCLC (24). Contrary to Cufer et al., the study by Arrieta et al. does not provide numbers at risk in the Kaplan Meier data.

In the comparator arm of the breast cancer model, the chosen intervention was Eribulin which, according to the NICE guidelines, is a 3rd line treatment for advanced breast cancer (25). Only for patients with triple-negative (HR^{-} and HER2^{-}) advanced breast cancer, this can be used as a 2nd line treatment after progression on the first-line chemotherapy regimen (25). In any way, Eribulin is offered as the last line and thus most suitable as a comparator for Larotrectinib in breast cancer patients. Efficacy data for this comparator arm was taken from the Kaufman et al. trial (20). Compared to other studies on Eribulin, Kaufman et al. had very positive outcomes with a median OS of 15,9 months (95% CI, 15.2 to 17.6

months) and a median PFS of 4,1 months (95% CI, 3.5 to 4.3) (20). Using this data as a comparator against Larotrectinib results in a relatively conservative approach as to other studies such as done by Pouwels et al., who recently found an OS of 5.9 months (95% CI: 4.6-11.0) and PFS of 3.5 months (95% CI: 2.7–5.5) in advanced breast cancer patients (26). In addition, the study by Kaufman et al. had a large population with 1090 randomised patients, of which 554 received Eribulin, where Pouwels et al. had a population of 45 patients receiving Eribulin. As recommended by NICE and lived up to by Kaufman et al., Eribulin was administered intravenously with a dosage of 1.23 mg/m^2 over one to five minutes (20)(27). This was done on days one and eight of each 21-days cycle (28).

For metastatic colorectal cancer, NICE recommends 2nd line standard of care with Trifluridine/tipiracil, which simultaneously is last-line treatment (29). Efficacy data of Trifluridine/tipiracil was taken from a study by Chida et al. (21). Results were recently obtained (in 2020), presenting a median OS of 8.1 months (95% CI, 6.8–9.2 months) and a median PFS of 2.5 months (95% CI, 2.1–3.1 months). These results were similar to what was found by Carriles et al. in 2019 (median OS of 8.30 months; 95% CI 6.23–9.87, and median PFS of 2.62 months; 95% CI 2.36–3.05) (30). Preference went to the most recent data available, hence choosing the Chida et al. study. In addition, numbers at risk in the Kaplan Meier curves were not provided in the paper by Carriles et al. in contrary to Chida et al. As according to the NICE standards and in line with the Chida et al. trial, Trifluridine/tipiracil was administered twice a day with 35 mg/m^2 per dose at a maximum of 80 mg per dose (31). This was administered orally on days 1 to 5 and days 8 to 12 of each 28-day cycle (31). Since no patient-level data about the body surface area (BSA) was available, an average dose was estimated by calculating the average BSA using the normal distribution examined in the NICE single technology appraisal [ID1507] shown in appendixes B and C.

A summary of the studies used to obtain efficacy data for the comparator arms in each Markov model is given in table 1. Treatment for all therapies was given up until disease progression. Dose-modification in the trials was only allowed when severe adverse reactions did not resolve or improve after four weeks (9)(19)(20)(21). However, for simplicity, the assumption was made that there were no dose modifications.

2.3. Overall Markov Model Structure.

A cost-effectiveness model was developed in which efficacy data had been extrapolated as data was not mature enough to cover a lifetime horizon from multiple trials. This model was triplicated and used for the different cancer indications (lung, breast, colorectal) with their comparators (Docetaxel, Eribulin, Trifluridine/tipiracil, respectively). As patients were continuously at risk of either progressing or dying, a partitioned survival Markov Model was considered the best fit. This was programmed in Microsoft Excel (version 16.46), whereby three health states were used: stable disease (SD), progressive disease (PD), and death, as displayed in figure 3. Patients entering the model started in the SD state and would, after the first Markov cycle, remain in the SD state or transition either to the PD or death state. Patients who were from then on in the PD state could either stay there or enter death state.

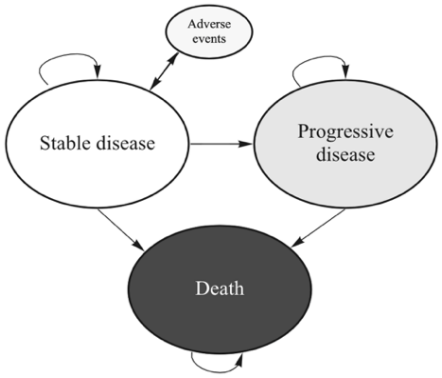

Figure 3: Diagrammatical representation of the Markov Model structure

To be able to include all consequences of the treatments, a lifetime horizon was considered since there is a difference in life expectancy for each treatment. This meant that the data would be extrapolated for as

long as necessary to have less than 5% of the population alive at the end of the model. In the models, a cycle length equals the duration of a treatment cycle for the comparator. In the NSCLC and breast cancer models, this was three weeks. In the colorectal cancer model, the cycle length equalled four weeks. For all models, the maximum number of cycle lengths was 314. The time horizon in the NSCLC and breast cancer models were thus 217 months. In the NSCLC model, only 2% and 3% of the patient population were alive after 217 months in the Larotrectinib and Docetaxel arm, respectively. In the breast cancer model, this was only 2% and 1% in the Larotrectinib and Eribulin arm, respectively. For the colorectal cancer model, the time horizon was 290 months since a cycle length equalled four weeks. After 290 months, 0,2% and 0,1% in respectively the Larotrectinib and Trifluridine/tipiracil arm were alive.

Utility values were used to calculate the QALYs per cycle, to eventually calculate the total amount of QALYs obtained during the complete study for each treatment arm (9)(19)(20)(21). Per NICE guidelines, discount rates of 3.5% were applied for both costs and QALY's.

2.4. Model inputs (efficacy data extrapolation).

The OS and PFS efficacy data in all comparator arms were used to estimate the transition probabilities between health states. Kaplan Meier curves containing OS and PFS data of Docetaxel, Eribulin, and Trifluridine/tipiracil were taken from the studies mentioned in table 1 and recreated with the WebPlotDigitizer4.1 software to retrieve X and Y coordinates. These coordinates and the numbers at risk from the KM curves were used to estimate the numbers of events and censorship by the interpolation method of Hoyle & Henley (32). Thereafter, this data was used as input for RStudio and fitted to four different distributions advised by NICE in the technical support document. This consisted of the exponential, Weibull, lognormal and log-logistic distributions (33)(34). Next, the best parametric distribution fit for OS and PFS of each comparator was determined using the Akaike Information Criterion (AIC) while also considering clinical plausibility. Appendix D shows an overview of the statistically fitted distributions for each treatment arm. The distributions generating the lowest AICs are marked in grey and represent the best statistical fit. For all comparators, both PFS and OS data were fitted with the log-logistic distribution. This led to the most positive extrapolated outcomes and was in line with the lowest AIC, except for the OS data of Trifluridine/tipiracil. According to the AIC, the best statistical fit would be the lognormal distribution. However, in order to be both consistent and conservative towards Larotrectinib, the most favourable outcomes for the Trifluridine/tipiracil arm were with the log-logistic, hence choosing for this distribution. In appendixes E-G, the KM curves for all comparators are shown, fitted to the different distributions. In addition, a graph with the chosen distributions for the OS and PFS data for each comparator is included.

For the indication arm, PFS data of Larotrectinib was derived from the basket trial by Hong et al., to which the different distributions were fitted (9). According to the AIC, the best statistical fit was the lognormal distribution. However, the exponential distribution was chosen to take a rather conservative approach since this resulted in the least positive results. The OS data published by Hong et al. in their supplementary appendix seemed clinically unobtainable as it was highly immature and based on an incomparable population including children. If these data were used, possible outcomes would be too optimistic for Larotrectinib, suggesting unusual overall survival rates. In order to counteract this, the OS data was adjusted by assuming that patients in the Larotrectinib arm who entered the progressive disease health state would not live longer than patients in the comparator arm entering the progressive disease health state, since the underlying patient population was the same in both arms, assuming no further treatment

benefit beyond progression on Larotrectinib. A new OS curve for Larotrectinib was formed by calculating the area between the extrapolated OS and PFS curves (according to the log-logistic distribution) of the comparators. Then, the extrapolated OS curve of Larotrectinib (according to the exponential distribution) was dragged down by changing the intercept of the OS data for Larotrectinib to form a new OS curve in such a manner that the area between these Larotrectinib PFS and (new) OS curves is equal to the area between the OS and PFS curves of the comparator. The AIC and log(scale) parameters were kept constant. This process was carried out in each model according to its specific comparator. Both OS and PFS data of Larotrectinib for all models are visible in appendix H.

Each treatment arm in the Markov Models starts with an extrapolated population of 1000 patients. The Markov cycles were equal to the treatment cycles according to the comparators used in the models. With a Markov cycle length of three weeks in the lung and breast models and four weeks in the colorectal cancer model, the effects and adverse reactions could be determined, as well as the health states. The chance of transitioning more than once from a health state within one cycle is neglectable.

2.5. Model inputs (treatment effects; utility).

Utility values for the SD and the PD states of breast and colorectal cancer patients were mapped to EQ-5D and taken from NICE single technology appraisals for each indication with its specific comparator treatment as shown in table 2 below. In the case of Docetaxel, the utility scores were taken from Nafees et al. since no single technology appraisal for Docetaxel in NSCLC from NICE was available, and thus UK society-based utilities were assumed adequate and appropriate (35). Utility values of Nafees et al. were also used in the single technology appraisals from NICE for Nivolumab in NSCLC patients. In that appraisal, the cost-effectiveness of Nivolumab in NSCLC patients was assessed, and utility values of Nafees et al. were used in their scenario analysis, showing less positive results since these utilities are considerably low (36). Using these utilities in our study strengthens the conservative approach taken.

Utility values used in the SD and the PD states for the different indications					
Model	**Utility SD state**	**Utility PD state**	**SE (SD; PD)**	**Distribution**	**Source**
Non small cell lung cancer	0,673	0,473	0,0166 - 0,0236	beta	Nafees B et al. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes. 2008;6.
Breast cancer	0,780	0,679	0,194 - 0,211	beta	NICE. Single Technology Appraisal Eribulin for treating locally advanced or metastatic breast cancer after one prior chemotherapy regimen [ID1072] Committee Papers. 2017.
Colorectal cancer	0,764	0,652	0,0105 - 0,0236	beta	NICE. Single Technology Appraisal Trifluridine-tipiracil for treating metastatic gastric or gastro-oesophageal junction cancer after 2 or more therapies [ID1507] Committee Papers. 2020.

Table 2: Utility values used in the different models.

The adverse events (AEs) and the frequencies of occurrence due to the treatment(s) were obtained from the trials and modelled in the SD state. Disutility's assigned to AEs were taken from the same sources used for the utility valuation of the health states indicated in table 2. Appendix I shows an elaboration on the used disutility values for each adverse event and all cancer indications. When (adverse) events occurred at unknown time points in the Markov cycle, assumed was that the event took place halfway the treatment cycle hence applying a half-cycle correction. The same was considered for related costs.

2.6. Treatment resources/costs.

To obtain resources for this economic evaluation, data were derived from the trials and NICE technology appraisals as described in tables 1 and 2, a UK clinical audit, and expert opinion. Costs were obtained using NHS reference costs, the British National Formulary, data from the personal social services research unit (PSSRU), and the electronic market information tool (eMIT). Resources were measured, valued, and

assigned to the SD and PD states as visualised in table 3. Detailed data are shown in appendix J. Each cancer indication is treated differently, has different adverse events, and thus different resources are obtained in the models. For each model with its specific indication, resources were considered according to the comparators' NICE appraisal.

Resources measured and valued in the models			
Health states	**NSCLC**	**Breast cancer**	**Coloretal cancer**
Stable disease	Drug acquisition costs	Drug acquisition costs	Drug acquisition costs
	Pre medication costs	Chemo administration costs	Chemo administration costs
	Chemo administration costs	HC resource use	HC resource use
	HC resource use	AE costs*	AE costs*
	AE costs*		
Progressive disease	HC resource use	HC resource use	HC resource use
	Palliative care costs (or BSC)	Palliative care costs (or BSC)	Palliative care costs (or BSC)
	End of life costs	End of life costs	End of life costs

Table 3: Resource assignment to health states

*Adverce Events costs
HC = Health care
BSC = Best Supportive Care

2.7. Scenario Analyses and Probabilistic Sensitivity Analyses (PSA).

To provide insights on the robustness of the results, scenario analyses were conducted in all models. The chosen distributions for OS and PFS (exponential for Larotrectinib and log-logistic for the comparators) were already the most conservative options taken. Any other distributions would have led to lower ICERs. To allow for a more conservative scenario, instead of changing distributions, Larotrectinib efficacy data was replaced with that of Entrectinib. Entrectinib is a similar TRK inhibitor and belongs to the same drug class as Larotrectinib. The difference is that Entrectinib is not purely a selective TRK inhibitor but has additional inhibition of the ROS1 and ALK kinases (37). This resulted in a slightly different profile compared to Larotrectinib and made Entrectinib possibly useful in additional indications such as ROS1-positive NSCLC (38). Larotrectinib was found before Entrectinib and had more mature data with more patients. However, the published efficacy data for Entrectinib, contrary to Larotrectinib, was obtained from a study population **without** young children (38). In our models, the comparator arms do not include young children, while the overall efficacy data of Larotrectinib used in our indication arm (in fact) does. By replacing the Larotrectinib overall PFS (and recreated OS) data with that of Entrectinib, the patient populations in both arms align more in terms of age. Data for the overall OS and PFS data of Entrectinib were taken from an integrated analysis of three-phase 1–2 trials by Doebele et al. (39). Both median OS and PFS data of Entrectinib are lower (21 and 11 months respectively) than Larotrectinib (44 and 28 months respectively), which should lead to higher ICERs (9)(39). Just as was done for Larotrectinib, the exponential distribution was fitted to the Entrectinib OS and PFS data since this was the best statistical fit for both. The OS data of Entrectinib (contrary to Larotrectinib) seemed clinically plausible in this case. Only 0,2 - 1% of the patients in the models were alive after 314 treatment cycles, hence recreating the OS data was unnecessary.

Validating the robustness of this economic evaluation, PSA was performed to determine the impact of uncertainty around input parameters by varying all parameters. For each parameter, a 95% CI was modelled. One thousand sets of simulations were done in which, for both treatment arms, the parameters had different random values according to their prespecified distributions. This resulted in 1000 times different costs and effects, and thus 1000 different ICERs were demonstrated in a CE-plane. For (dis)utilities, incidences and proportions, beta distributions were used. Resources and costs were assigned gamma distributions. As much as possible, published standard errors (SEs) for the parameters were used. However, when SEs were not found in the literature, assumptions were made. This led to estimations of

SEs ranging between 5% and 20%. An overview of the estimated SEs and their underlying reasons can be found in appendix K. As mentioned earlier, PSA results were plotted in a CE-plane, providing a clear visualisation of the ICERs obtained by the PSA and the surrounding uncertainty. A cost-effectiveness acceptability curve (CEAC) was then derived from the CE-plane, stating the probabilities for which WTP-thresholds the interventions were cost-effective.

3. Results

3.1. Primary economic analyse.

Table 4 shows results of the cost-effectiveness analyses from all three models. The average ICER over all three models was £83.202,61 per QALY gained per patient, ranging between £65.137,42 and £113.727,37. Larotrectinib was most dominant against Eribulin in the breast cancer model, followed by Trifluridine/tipiracil in the colorectal cancer model. The lowest ICERs from Larotrectinib vs Eribulin yielded 7,91 QALYs gained, resulting in a total discounted cost per QALY of £65.137,42. The next best ICER was £70.743,04 per QALY gained by comparing Larotrectinib with Trifluridine/tipiracil. Highest ICERs were yielded by the NSCLC model where Larotrectinib vs Docetaxel resulted in a total discounted cost per QALY gained of £113.727,37 per patient, with 4,95 incremental QALYs.

The most benefit was, however, found in the life-years gained. All ICERs were below £50.000,00 per patient, with an average ICER of £40.762,06 per life-year gained, ranging between £35.020,97 and £49.793,37. The lowest ICER was yield by the breast cancer model in which Larotrectinib vs Eribulin generated 14,72 additional life years per patient at a total discounted cost of £515.553,25, which resulted in an ICER of £35.020,97. Larotrectinib vs Trifluridine/tipiracil resulted in 13,53 additional life years gained in colorectal patients, at a total discounted cost of £37.471,83. Complete in-depth results can be found in Appendix K.

ICERs						
Indication	**Intervention vs Comparator**	**Incremental Costs**	**Incremental QALYs**	**Incremental LYs**	**Cost/QALY**	**Cost/LY**
NSCLC	Larotrectinib vs Docetaxel	£ 563.493,71	4,95	11,32	£ 113.727,37	£ 49.793,37
Breast cancer	Larotrectinib vs Eribulin	£ 515.553,25	7,91	14,72	£ 65.137,42	£ 35.020,97
CRC	Larotrectinib vs Trifluridine/tipiracil	£ 506.825,79	7,16	13,53	£ 70.743,04	£ 37.471,83
	Average	*£ 528.624,25*	*6,68*	*13,19*	*£ 83.202,61*	*£ 40.762,06*

Table 4: Summary of the primary economic analyses results

3.2. Scenario analyses.

Results of the scenario analysis where Larotrectinib had been replaced in the models by Entrectinib can be found in table 5. All models yielded higher ICERs in terms of both QALY and LY gained except for the colorectal model where Entrectinib vs Trifluridine/tipiracil resulted in a £17.757,81 lower total discounted costs per QALY and £10.036,45 lower LY gained per patient than for Larotrectinib vs Trifluridine/tipiracil. The average ICERs for both the QALY and LY gained, however, were still higher in the scenario analysis with Entrectinib, resulting in an increase of £11.439,80 per average QALY and £7.682,32 per average LY gained**.**

Scenario analysis with Entrectinib compared to the primary economic analysis with Larotrectinib					
		Entrectinib		**Larotrectinib**	
Indication	**Comparator**	**Cost/QALY**	**Cost/LY**	**Cost/QALY**	**Cost/LY**
NSCLC	Docetaxel	£ 158.293,49	£ 77.708,11	£ 113.727,37	£ 49.793,37
Breast cancer	Eribulin	£ 72.648,51	£ 40.189,62	£ 65.137,42	£ 35.020,97
CRC	Trifluridine/tipiracil	£ 52.985,23	£ 27.435,38	£ 70.743,04	£ 37.471,83
	Average	*£ 94.642,41*	*£ 48.444,37*	*£ 83.202,61*	*£ 40.762,06*

Table 5: Primary results of scenario analysis

3.3. Probabilistic Sensitivity Analyses (PSA).

Figure 4 shows the cost-effectiveness plane of Larotrectinib vs the comparators in all models. Except for the NSCLC model, all 1000 PSA iterations are in the upper right quadrant. This means that there are more QALYs gained at additional costs for Larotrectinib compared to both Eribulin and Trifluridine/tipiracil.

For Docetaxel, only 1% of all iterations fell in the upper left quadrant, which counted more costs for fewer QALYs.

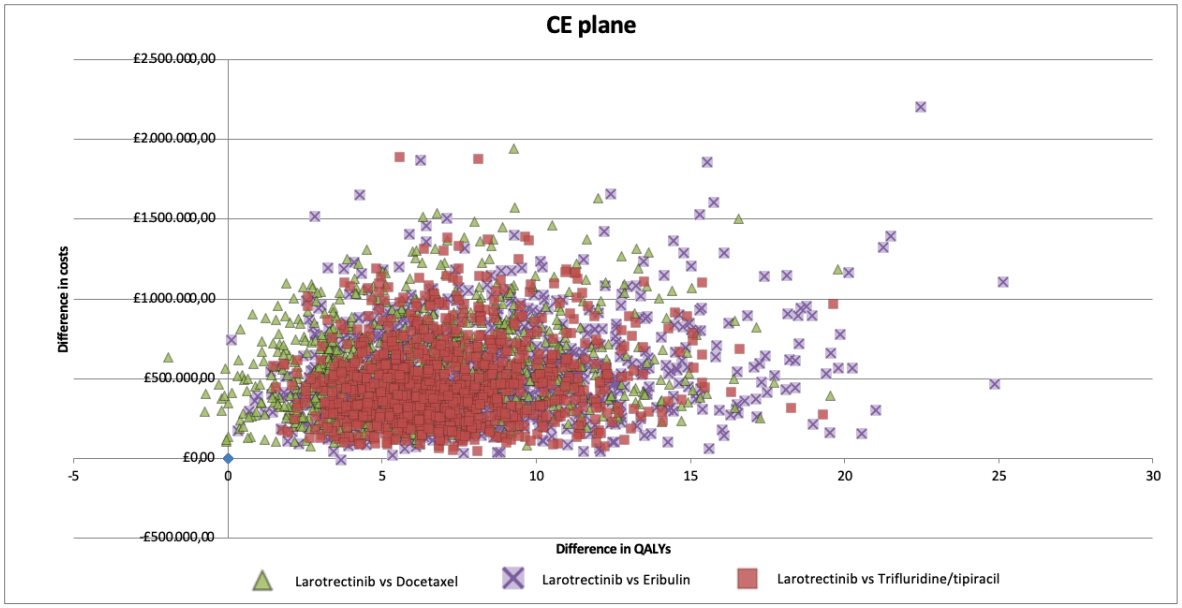

Figure 4: Cost-effectiveness plane of all comparisons

The CEAC of Larotrectinib vs all comparators are shown in figure 5. At a possible willingness to pay threshold of £70.000, the probability of Larotrectinib to be cost-effective in NSCLC patients against Docetaxel was 36%, while this was 56% and 60% for Trifluridine/tipiracil in colorectal cancer patients and Eribulin in breast cancer patients respectively. Of all comparators, Larotrectinib has the highest probability of being cost-effective against Eribulin in breast cancer patients up to 70% at a threshold value of £90.000. From £90.000 on, this changes into more cost-effectiveness against Trifluridine/tipiracil in colorectal cancer patients. At a willingness to pay threshold of £150.000/QALY gained, the probabilities of Larotrectinib to be cost-effective are 76%, 89%, and 94% against Docetaxel, Eribulin and Trifluridine/tipiracil, respectively. Overall, Larotrectinib had a lower chance of being cost-effective towards Docetaxel in NSCLC patients than it had towards Eribulin and Trifluridine/tipiracil in their respective cancer populations.

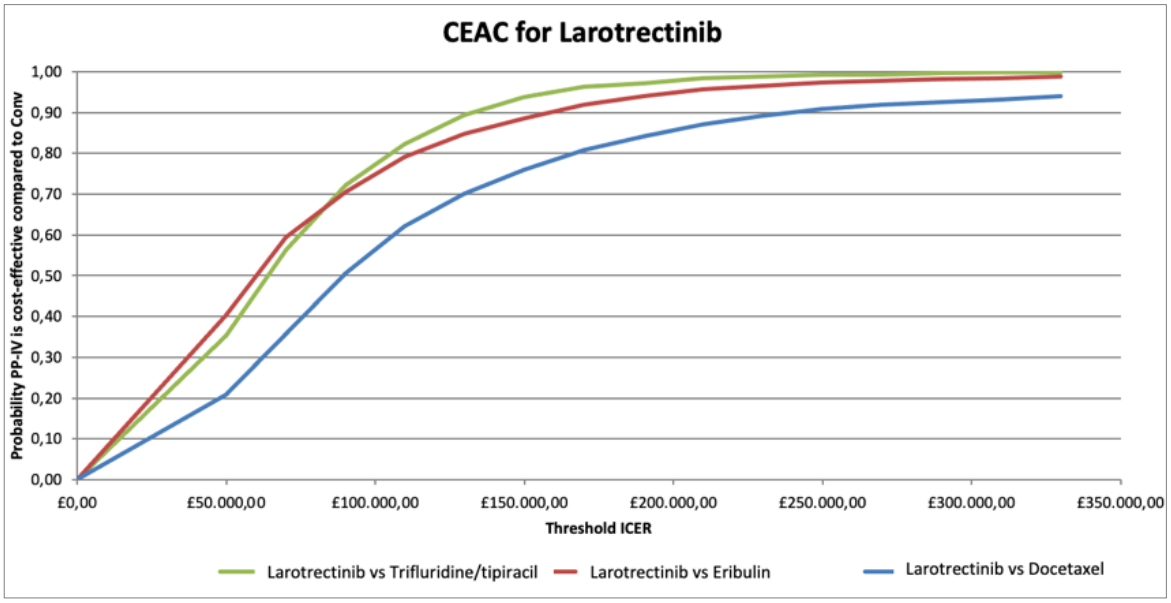

Figure 5: Cost-effectiveness acceptability curves (CEAC) of Larotrectinib vs each and all comparators

4. Discussion

4.1. Brief summary of results.

To our best knowledge, this was the first study conducting a cost-effective analysis of Larotrectinib as last line cancer treatment in solid tumours using overall efficacy data in NSCLC, breast cancer, and colorectal cancer patients. In all indications, Larotrectinib resulted in an average of 13,19 additional life-years gained, ranging from 11,32 years in NSCLC patients to 14,72 years in breast cancer patients. Our study found the most benefits for Larotrectinib to lay with breast cancer patients where it had an ICER of £65.137,42 per QALY gained, and £35.020,87 per life-year gained. The next most beneficial indication for Larotrectinib in this study was colorectal cancer with an ICER of £70.743,04 per QALY gained, and £37.471,83 per LY gained. The ICER of Larotrectinib vs Docetaxel in NSLC patients was £113.727,37 per QALY gained, and £49.793,37 per LY gained.

4.2. Input choices, assumptions, and limitations.

Several limitations challenged this study. First and most important is limited evidence for the efficacy of Larotrectinib. Larotrectinib has only been searched in basket trials with very few patients and short follow-up duration. Besides the heterogeneity in these basket trials, limited evidence already brings hurdles for modelling. Additionally, no real-world data was available, which led to a model-based approach on earlier published RCT data resulting in more uncertainty around the chosen distributions for the data. As a result, the validity of the assumptions made in our model was determining the findings and conclusions. To compensate and show robustness of these findings, most conservative assumptions on efficacy were taken and even more conservative alternative PFS and OS were tested through scenario analysis. Also, probabilistic sensitivity analyses were conducted. However, it should be acknowledged that uncertainty remains substantial, and future evidence generation on patients with NTRK fusions remains key to reduce this uncertainty. In addition, as the point of this study, we used overall efficacy data instead of histology specific data. Histology specific efficacy data could have led to more differentiated ICERs. Furthermore, the OS data of Larotrectinib in all models was different. It was recreated with respect to each model its comparator's efficacy data. This kept our findings conservative since the overall OS data of Larotrectinib, as suggested by Hong et al., exceeds the OS we recreated. In consequence, our conservative approach has led to an underestimation of the ICERs where these would probably have been lower than yielded by our models. However, if indeed the OS data by Hong et al. was clinically plausible, then the additional life years would increase dramatically, resulting in much lower ICERs than yielded by our model. Though, this would have been an irrational overestimation of the ICERs since the patient population in the Hong et al. study contains children, which was not the case in the patient population in our models.

Next limitation lies within the populations used in our models. Only for patients where NTRK fusion positivity can be measured by next-generation sequencing, FISH, or reverse transcriptase PCR, the tumour agnostic therapy Larotrectinib can be applied to (9). It was assumed that our patient population had measurable NTRK fusion tumours. However, none of the studies used for efficacy data in the comparator arms showed the inclusion of patients having NTRK fusion-positive tumours since this is a rare mutation. A study by Forsythe et al. showed that the global incidence of NTRK fusion tumours was 0,52 with a 5-year prevalence of 1,52/100.000 patients (40). The highest frequencies of NTRK fusions were reported in rare cancers such as secretory breast cancer (92,87%) (40). Lower frequencies were found in non-secretory breast cancer (0.60%), colorectal cancer (0,26%), and NSCLC (0,17%). Additionally, we assumed that

patients with and without an NTRK fusion have the same prognosis and thus react the same to cancer treatments. Nevertheless, perhaps the prognosis for patients with the NTRK fusion is different from patients without the NTRK fusion. A recent study from February 2021 by L Bazhenova et al. stated that patients with NTRK fusions seem to have a higher risk of dying, though not statistically significant (41). If this is true, this could result in lower OS and PFS data in the comparator arms than used in our study, resulting in higher incremental differences that would generate lower ICERs. In that case, our ICERs are an underestimation of what in reality could be**.** However, this has not properly been researched yet and thus more research is necessary to determine the impact.

Other limitations in our study lay with the utility values taken from the Nafees et al. study in our NSCLC model. These were considerably lower than the utility values used for the health states in the other models. This could be why the ICERs in our NSCLC model are considerably high(er). Less conservative utility values as used by NICE would have resulted in more QALYs gained and consequently lower costs per QALY. However, the utility rates for both the SD and PD health states were fixed in all models for simplicity but are not the actual representation of reality. As patients tend to progress in the SD state, it can be said that the quality of life decreases after each cycle until finally entering the PD state. The same goes for people in the PD state who will eventually enter the death state. Consequently, this leads to decreasing utilities after each cycle and thus fewer QALYs gained, disfavouring the ICER to increase.

As mentioned in the methods section, for simplicity, there were no dose modifications nor discontinuations in any treatment arms. However, patients experiencing unacceptable toxicity in some cases could have led to treatment discontinuation. Also, dose-modification in the trials was allowed when severe adverse reactions did not resolve or improve after four weeks (9). In case of Larotrectinib, some adverse events led to dose reduction in 8 patients (9). These adverse events include increase in the alanine- or aspartate aminotransferase level, a decrease in absolute neutrophil count, and dizziness (9). One can argue that the adverse events costs might have gone up for these patients while drug costs went down due to dose reductions. This could have led to different outcomes. On the one hand, there could have been fewer benefits caused by the worsening of the disease. On the other hand, adverse events costs are lower than drug costs (for Larotrectinib). Since the drug costs for Larotrectinib have the biggest impact on the ICER, this may have resulted in an overestimation of the drug costs. Larotrectinib is patented by Bayer, which led to a high monopoly price. The price given by the BNF was £5000,00 per 100 ml containing 20mg Larotrectinib per ml. This equals ten doses per patient which is £500 per dose. It is known that Larotrectinib is also available in tablet form and that the prices for these tablets are lower. However, these prices are still confidential and not yet published by the BNF. For that manner, the price for a 100 mg tablet was taken from drug.com, which was $555,11 on Jun 7, 2021. This was equal to £403,57 at that time. This price was used and assumed fixed in our models. However, these are high costs when taking into account that each patient needs 200 mg at the cost of £807,14 a day till progression. Such costs can be reduced considering new price arrangements such as a compounding scheme with Bayer, possibly leading to a 50% price reduction. In that case, the drug acquisition costs can be reduced, eventually leading to lower (acceptable) ICERs for Larotrectinib.

Drug acquisition costs were only accounted for treatments used in the SD state. For drug acquisition costs in the PD states, no further chemotherapy on progression was included as this was assumed last line treatment. However, in some cases, it would be unethical to not continue treatment with, for example, Docetaxel. If this were accounted for, drug acquisition costs would have increased resulting in possibly

higher ICERs. Next, pre-medications were only included for the Docetaxel arm in our NSCLC model. This was due to limited data about the frequencies and the types of pre-medications necessary for all other treatment arms. Though the [ID1299] NICE appraisal states that supportive medications can be used in the Larotrectinib arm, no precise data about how many patients make use of it is given (16). If pre-medications were taken into account, this would have resulted in higher (incremental) costs via Larotrectinib, increasing the ICERs.

Scenario analysis showed that when taking PFS and OS from the Entrectinib basket trial as a proxy for Larotrectinib efficacy, ICERs were substantially higher. This happened as in this scenario the OS (and PFS) for Entrectinib were significantly lower compared to the base case analysis, which means that people enter progressive disease and the death state earlier. This is because the Larotrectinib study of which the efficacy data is taken includes young children in their patient population (9). Children were not included in the Entrectinib program (39). The lower PFS data of Entrectinib also resulted in less drug acquisition costs for Entrectinib. In the NSCLC and breast cancer models this led to higher ICERs since the incremental life years decreased as well as the incremental QALYs. However, in our colorectal cancer model, a slightly better extrapolated PFS for Entrectinib than for Larotrectinib resulted in an additional 0,31 life years for colorectal cancer patients in the Entrectinib arm. Together with lower drug acquisition costs, this led to lower ICERs. Yet, these data have to be interpreted with caution since the patient population used in the Entrectinib model is very small (n = 54) (39).

Finally, although many assumptions have been drawn for this study due to insufficient data availability, the validity was determined high since most (if not all) assumptions were discussed with an expert. In addition, sensitivity analysis was conducted, demonstrating the robustness of our research. Regarding this sensitivity analysis, the PFS data was taken from KM-curves and recreated with the corresponding number of patients at risk. This led to high uncertainty around the recreated and extrapolated PFS curves, resulting in some widespread ICERs as visible in the scatter plot of the CE-plane. The uncertainty around the recreated OS data for Larotrectinib in our sensitivity analysis is underestimated since this was derived from the area between the extrapolated PFS and OS curves of the comparator.

4.3. Possible policy implications.

For a drug to be assumed cost-effective by NICE, a threshold value preferably between £20,000 and £30,000 per QALY gained is used (42) (43). None of the ICERs generated by our models fell below this threshold. Though, these are very conservative findings, meaning that realistically the ICERs could be at acceptable prices below the threshold value, especially with better price arrangements. In addition, the costs per life-year gained are negotiable and far less expensive than a QALY gained (£49.793, £35.021, and £37.472 of Larotrectinib vs Docetaxel, Eribulin and Trifluridine/tipiracil, respectively). Larotrectinib is used as last line treatment in this study, meaning that patients have no alternative treatment options left. One could argue that prolonging life is just as important, therefore despite the high price per QALY, Larotrectinib should still be considered. NICE will accept ICERs exceeding £30,000 per QALY if specific requirements are met, especially for cancer medicines to be taken in the Cancer Drug Fund (CDF). Due to high uncertainty around the efficacy data but plausible cost-effectiveness of Larotrectinib, NICE estimated that additional data would counteract this uncertainty by completing primary data collection by July 2023 (15) (44). According to a study by Leigh et al., the WTP-threshold as determined by the CDF was £223.627,00 per QALY gained (45). At this threshold, our CEAC-curve shows probabilities of 90,8%, 97,3% and 99,2% for Larotrectinib to be cost-effective in NSCLC, breast cancer, and colorectal cancer

patients respectively. For Larotrectinib to be cost-effective outside the CDF as well, lower prices should be negotiated with Bayer. For Larotrectinib vs Docetaxel to be cost-effective in NSCLC patients, the Larotrectinib list price should be lowered from £403,57 per 100 mg to £103,57. However, for Larotrectinib to be cost-effective compared to Eribulin for breast cancer patients, a 50% discount would be enough. Overall, the average price for the average ICER to be £30,000 is £160. That is a list price reduction of 60%.

5. Conclusion

This study showed that the use of overall efficacy data of Larotrectinib in different solid tumour types resulted in a wide range of ICERs, but at all times showing more benefits at higher costs. In terms of total discounted costs per QALYs, these ICERs are not yet below current WTP-thresholds and in that sense not cost-effective. However, the additional life-years gained by Larotrectinib are tremendously high (ranging from 11 – 15 years). This is reason to believe that Larotrectinib is a promising drug in prolonging life for patients receiving last line of treatment.

The use of an average ICER and its range in cost-effectiveness analyses can be beneficial to identify in what cancers the drug may be possibly most suited to become cost-effective. In addition, the cost-effectiveness analysis shows what strengths the intervention possibly has (in this case, many additional life-years gained). Also, prices can be obtained and evaluated by NICE to determine beforehand what reasonable price arrangements would be during confidential negotiations. However, despite the fact that we used three cancer indications that were quite similar in type (solid tumours), the ICERs regarding these indications in terms of QALY gained ranged between £65.137,42 and £113.727,37. In terms of LY gained, this was between £35.020,97 and £49.793,37. Even though the iterations in our CE-plane for all comparisons were clustered, the difference among the ICERs can be even bigger in haematological cancer or cancer in children. To further reduce uncertainties around the safe use of average ICER results, it would be beneficial to conduct a similar type of research in more cancer histologies and more diverse populations once more mature data and data on a larger set of patients would be available.

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8. Appendix

APPENDIX A

Table 1: Patient Baseline Characteristics				
Characteristics	**Larotrectinib**	**Docetaxel**	**Eribulin**	**Trifluridine/tipiracil**
Number of patients	153	73	554	153
*Age in years**	45 (0,3-76,0)	59,5 (29-83)	54 (24-80)	65 (58-71)
Female (%)	53	30	100	60,1
Male (%)	47	70	0	39,9
ECOG 0 (%)	44	15,1	45,1	62,1
ECOG 1 (%)	49	56,2	52,9	34,6
ECOG 2 (%)	7	28,8	2	3,3
Source	Hong DS et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol. 2020 Apr 1;21(4):531–40.	Cufer T et al. Phase II, open-label, randomized study (SIGN) of single-agent gefitinib (IRESSA) or docetaxel as second-line therapy in patients with advanced (stage IIIb or IV) non-small-cell lung cancer. Anticancer Drugs. 2006;17	Kaufman PA et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2015;33	Chida K et al. Efficacy and safety of trifluridine/tipiracil plus bevacizumab and trifluridine/tipiracil or regorafenib monotherapy for chemorefractory metastatic colorectal cancer: a retrospective study. Ther Adv Med Oncol. 2021;13.

* mean (range)

APPENDIX B

Appendix B: source NICE single technology appraisal [ID1507]

Table 32: Dose bands for trifluridine/tipiracil based on body surface area			
BSA band (m2)	Dosage in mg (twice daily)	Tablet(s) per dose (twice daily)	
		15 mg	20 mg
< 1.07	35	1	1
1.07 - 1.22	40	0	2
1.23 - 1.37	45	3	0
1.38 - 1.52	50	2	1
1.53 - 1.68	55	1	2
1.69 - 1.83	60	0	3
1.84 - 1.98	65	3	1
1.99 - 2.14	70	2	2
2.15 - 2.29	75	1	3
≥ 2.30	80	0	4

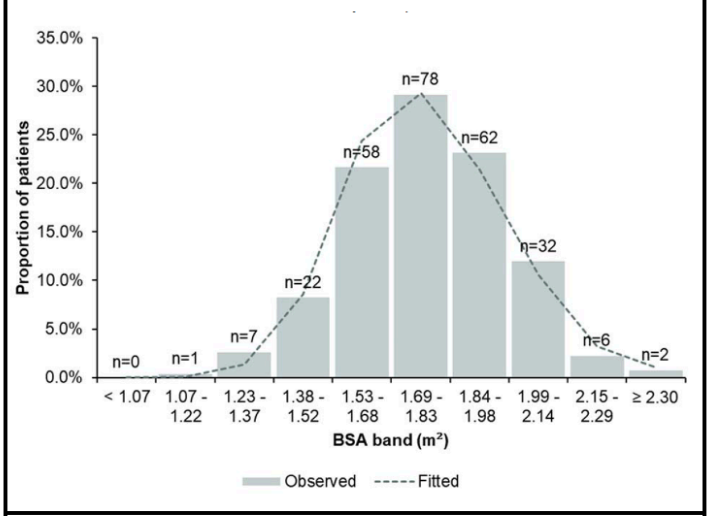
Key: BSA, body surface area; mg, milligram.

Note: The figures provided in this table apply for the starting dose of trifluridine/tipiracil. Dosing adjustments

APPENDIX C

Appendix C: source NICE single technology appraisal [ID1507]

Figure 34: TAGS: Distribution of body surface area (European patients who received at least one dose of trifluridine/tipiracil)



Key: BSA, body surface area; m, metre(s).

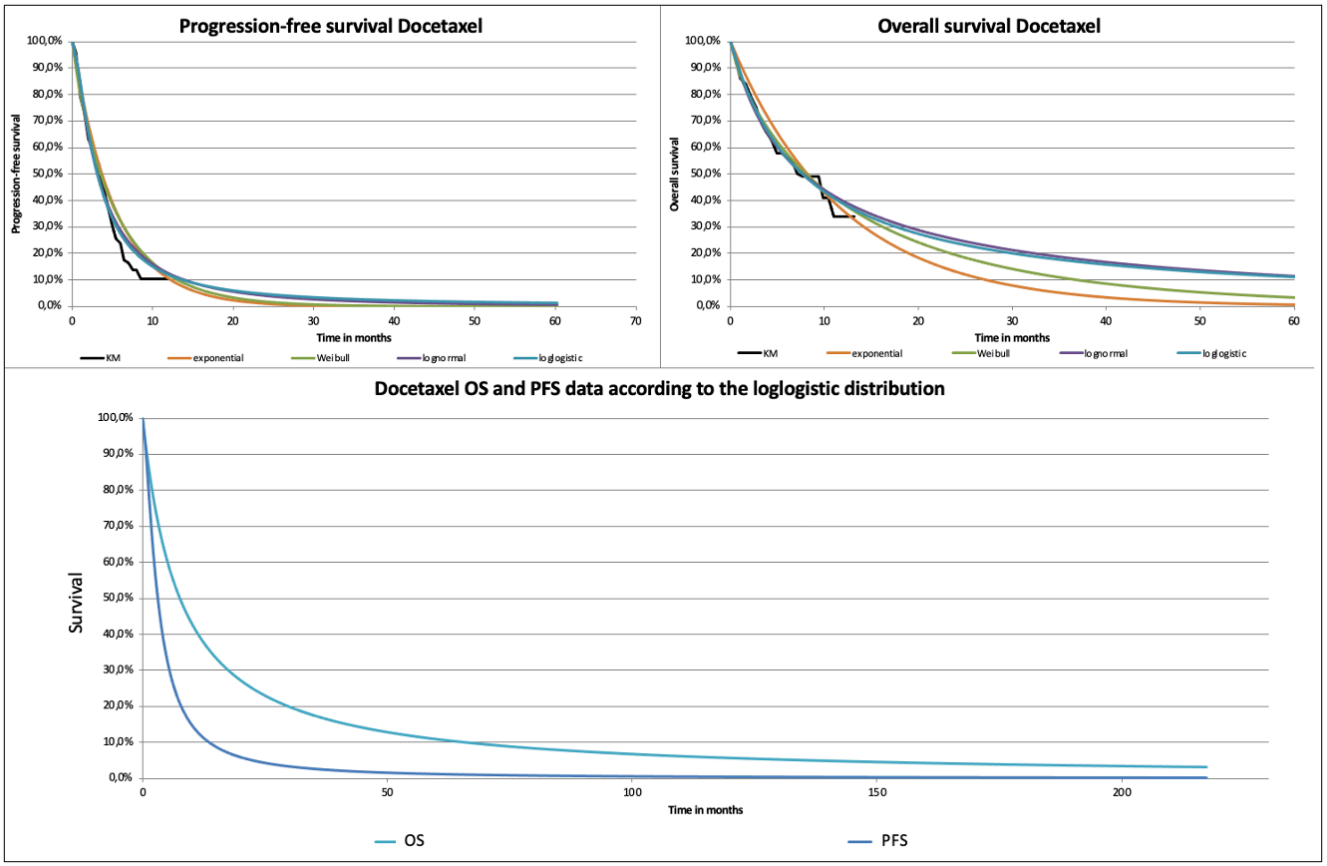
Note: The total number of European patients who received at least one dose of trifluridine/tipiracil within the TAGS trial was 268. 2 out of the 270 intention-to-treat (ITT) European patients randomised to trifluridine/tipiracil did not receive any doses.

APPENDIX D

Parametric distribution fittings according to Akaike Information Criterion (AIC)									
		PFS				OS			
Treatment	**Parametric distribution**	*exponential*	*Weibull*	*lognormal*	*loglogistic*	*exponential*	*Weibull*	*lognormal*	*loglogistic*
Larotrectinib	*AIC*	399,461	398,358	396,712	398,746	246,930	248,411	250,097	251,070
Docetaxel	*AIC*	742,065	742,351	722,315	720,675	685,069	680,776	678,774	678,017
Eribulin	*AIC*	2.420,225	2.422,208	2.332,807	2.330,904	3.539,208	3.502,967	3.499,730	3.491,703
Trifluridine/tipiracil	*AIC*	830,628	832,622	791,307	787,212	715,779	710,324	690,138	691,695

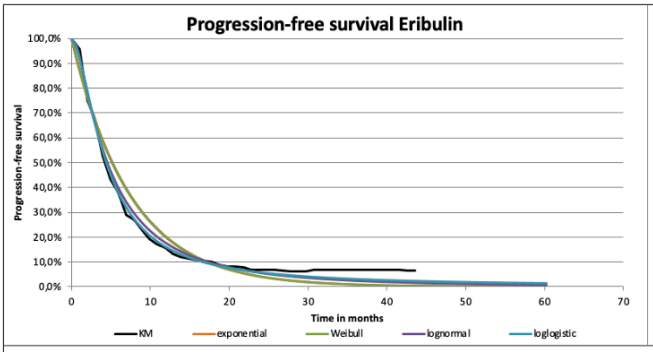
APPENDIX E

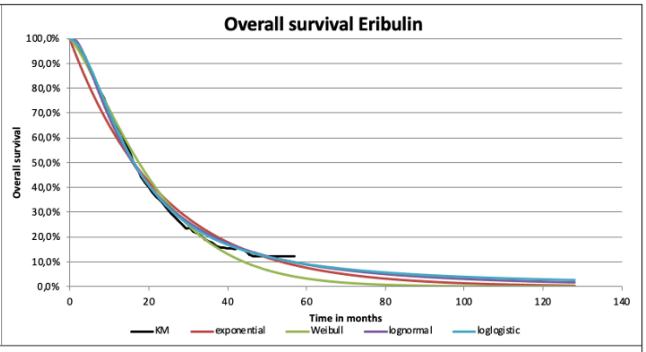
KM-curves of Docetaxel with fitted distributions in NSCLC model

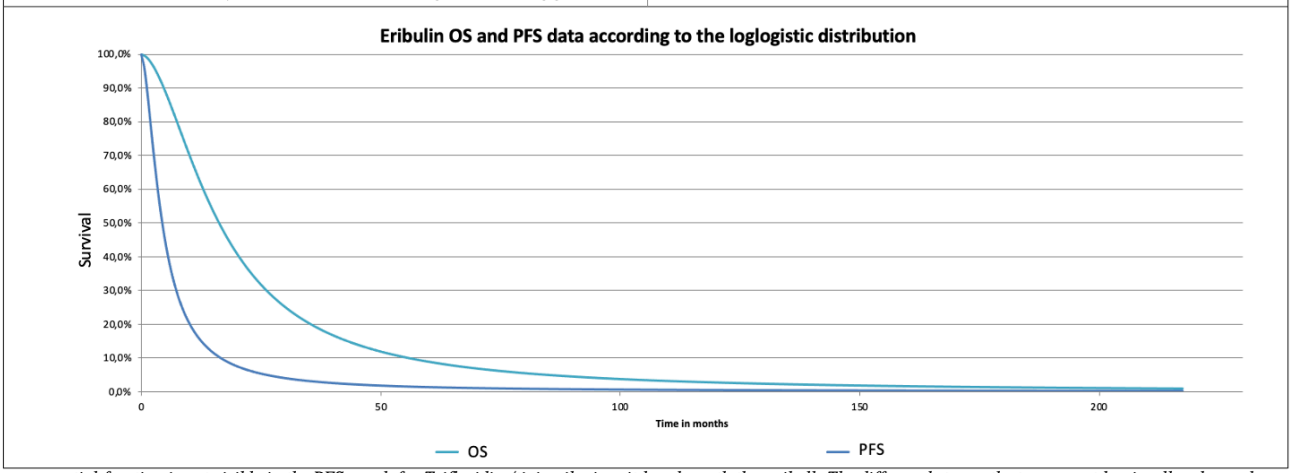


APPENDIX F

KM-curves with fitted distributions in breast cancer model



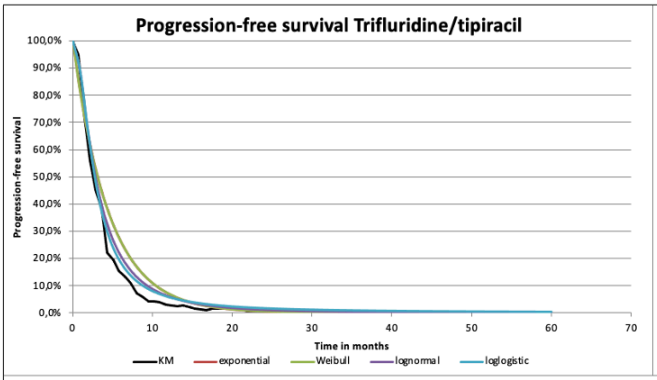


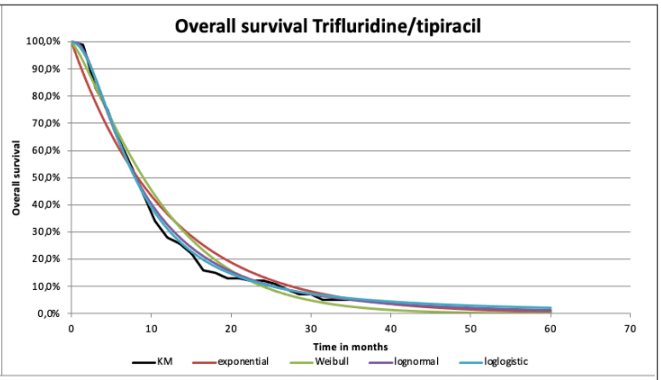


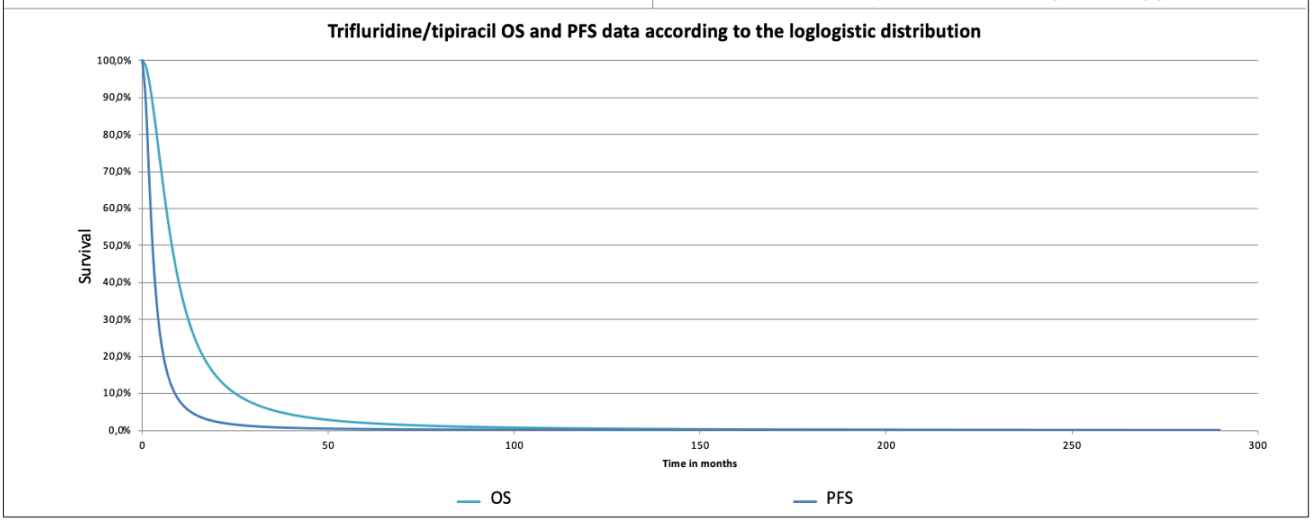
The exponential function is not visible in the PFS graph for Trifluridine/tipiracil, since it lays beneeth the weibull. The diffences between the two cannot be visually observed

APPENDIX G

KM-curves with fitted distributions in colorectal cancer model



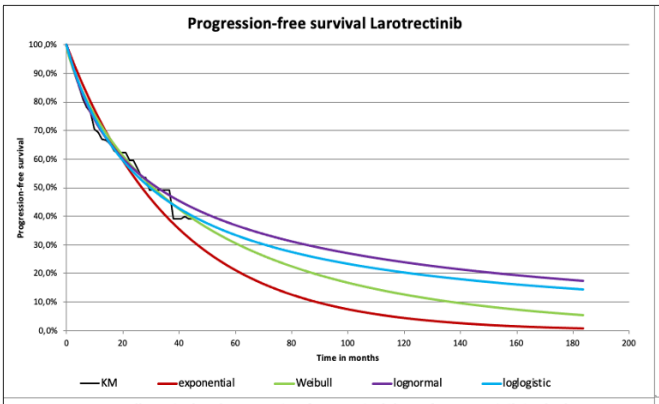


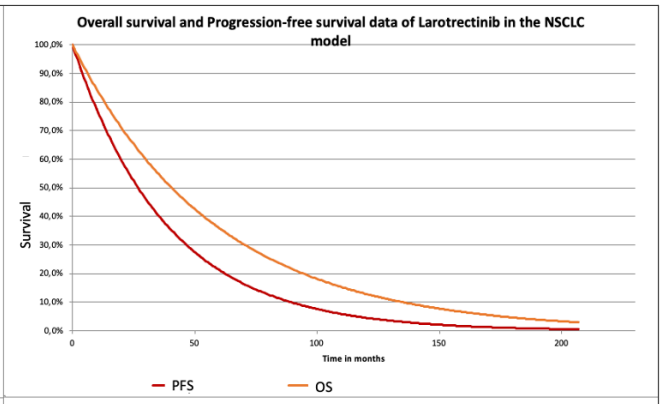


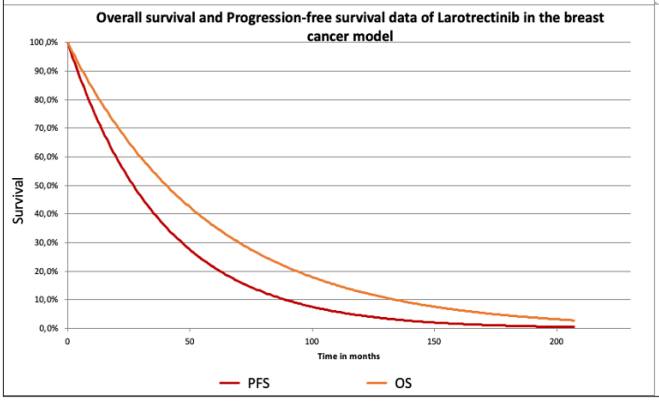
The exponential function is not visible in the PFS graph for Trifluridine/tipiracil, since it lays beneeth the weibull. The diffences between the two cannot be visually observed

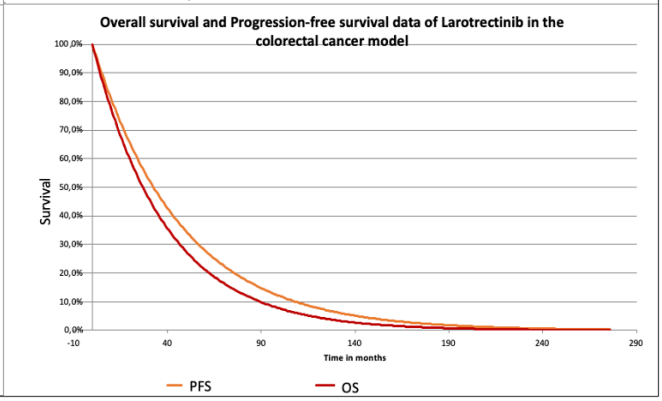
APPENDIX H

Larotrectinib data extrapolation









The OS data was made according to the extrapolated PFS data from the exponential distribution. Each model has an OS conform its comparator's prognosis

APPENDIX I

Disutiliy assignemnts							
Non small cell lung cancer							
Adverse events	**Disutilities**	**SE**	**Incidence Laro***	**Incidence Dox***	**Costs ****	**Distribution**	**Source disutilities**
Increased ALT/AST	0,050	0,050	0,070	-	£ 461,50	beta	Beenish Nafees et al: Health state utilities for non small cell lung cancer
Increased bodyweight	0,073	0,073	0,070	-	£ 0,01	beta	Assumed the same as Anaemia
Anaemia	0,073	0,073	0,110	-	£ 978,00	beta	Beenish Nafees et al: Health state utilities for non small cell lung cancer
Neutropenia	0,090	0,090	0,070	-	£ 354,72	beta	
Dyspnea	0,073	0,073	-	0,056	£ 0,01	beta	
Costs in the NSCLC model were taken from Single Technology Appraisal Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer							
According to the Single Technology Appraisal for Nivolumab, also no costs were assumed for Dyspnea.							
Breast cancer							
Adverse events	**Disutilities**	**SE**	**Incidence Laro***	**Incidence Eribu***	**Costs ****	**Distribution**	**Source disutilities**
Increased ALT/AST	0,014	0,010	0,070	-	£ 146,33	beta	Assumed the same as Peripheral Neuropathy
Increased bodyweight	0,010	0,013	0,070	-	£ 0,01	beta	Assumed the same as Anaemia
Anaemia	0,010	0,013	0,110	-	£ 280,00	beta	NICE [ID1072], Eribulin for treating locally advanced or metastatic breast cancer after one prior chemotherapy regimen. Table 51 Disutility scores of patients on eribulin and capecitabine
Neutropenia	0,007	0,004	0,070	0,460	£ 300,00	beta	
Leukopenia	0,003	0,006	0,070	0,130	£ 300,00	beta	
Periphera Neuropathy	0,014	0,010	-	0,060	£ 146,33	beta	
Costs in the breast cancer model were taken from NICE [ID1072], Eribulin for treating locally advanced or metastatic breast cancer after one prior chemotherapy regimen. Table 66 Adverse Event costs (2015)							
Cost for Increased ALT/AST was assumed to be the same as Peripheral Neuropathy							
Colorectal cancer							
Adverse events	**Disutilities**	**SE**	**Incidence Laro***	**Incidence TRIF***	**Costs ****	**Distribution**	**Source disutilities**
Increased ALT/AST	0,150	0,008	0,070	-		beta	Assumed the same as Fibrile Neutropenia
Increased bodyweight	0,119	0,006	0,070	-	£ 0,01	beta	Assumed the same as Anaemia
Anaemia	0,119	0,006	0,110	0,209	£ 164,55	beta	NICE [ID1507] Trifluridine–tipiracil for treating metastatic gastric or gastro-oesophageal junction cancer after 2 or more therapies.Table 29: Adverse event disutility values and duration of utility impact
Neutropenia	0,090	0,005	0,070	0,379	£ 164,55	beta	
Leukopenia	0,090	0,005	0,070	0,327	£ 164,55	beta	
Febrile_Neutropenia	0,150	0,008	-	0,052	£ 4.619,81	beta	
Cost for Increased ALT/AST was ssumed to be the same as Febrile Neuropathy							
Costs in the colorectal cancer model were taken from NICE [ID1507] Trifluridine–tipiracil for treating metastatic gastric or gastro-oesophageal junction cancer after 2 or more therapies. Table 41							

Laro = Larotrectinib Dox = Docetaxel Eribu = Eribuline TRIF = Trifluridine/tipiracil

* Incidence rates of the adverse events were drawn from the studies of which efficacy data was obtained for each treatment. These resources are shown in table 1 under section *2.1. Patient Baseline Characteristics*. For larotrectinib this was the David S Hong et al. trial, and for Docetaxel this was Cufer T et al. For Eribuline and Trifluridine/tipiracil these were Kaufman PA et al. and Chida K et al. respectively.

** Costs were unindexed

Advese events were either grade 3 or 4. Assumed was that adverse events would have a duration of one week.

Assumed was that no costs were associated with increased bodyweight.

If no costs were associated with an adverse event, 1 cent is applied since 0,00 is not included in our beta distribution.

APPENDIX J

Treatment resources/Costs and Outcomes							
Non small cell lung cancer							
Resources	**Utilities SD**	**Utilities PD**	**Costs**	**SE**	**Distribution**	**Description**	**Cost source**
Drug acquisition costs							
Price Doxetaxel	1,00	-	£ 17,95	£ 8,97	gamma	Price Docetaxel 160mg/8ml solution for infusion vials (20mg/ml)	PSSRU 2015
Average body surface area	1,00	-	1,780	0,178	gamma	The average body surface area of a patient in m2	Single Technology Appraisal Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer
Premedication costs							
Dexamethasone	1,00	-	£ 12,34	£ 0,26	gamma	Price per pack containing 50 tablets	eMIT
Chemotherapy administration costs							
Simple parenteral chemo delivery	1,00	-	£ 385,00	£ 19,25	gamma	Unit cost per administration by clinical oncologist	NHS Reference costs 2018/2019; 'currency code' SB14Z, 'CHEM'
*Health care resource use costs**							
GP visit	0,69	0,74	£ 46,71	£ 2,34	gamma	Routine GP visit (2015)	Single Technology Appraisal Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer; Erlotinib and gefitinib (postchemotherapy) MTA (rev TA162, TA175) [ID620] (NICE, 2015g)
GP home visit	-	0,23	£ 119,43	£ 5,97	gamma	GP home-visits in a month (2015)	
Palliative care***	1,50	3,00	£ 86,42	£ 4,32	gamma	Palliative caere days (2015)	
Oxygen	-	1,00	£ 14,04	£ 0,70	gamma	Oxygen provision (2015)	
Blood transfustion	-	0,35	£ 155,58	£ 7,78	gamma	Blood trasfusion (2015)	
Ct scan	0,23	0,23	£ 94,26	£ 4,71	gamma	CT scan (thorax or abdominal/brain) (2015)	
X-ray	0,50	0,35	£ 43,01	£ 2,15	gamma	X-ray (2015)	
Radiotherapy	0,23	0,75	£ 128,11	£ 6,41	gamma	Radiotherapy (bone) - per fraction (2015)	
Medical oncologist	-	0,35	£ 151,89	£ 7,59	gamma	Medical oncologist follow-up in a month (2015)	
End of life costs**	-	-	£ 3.628,70	£ 181,44	gamma	End of life costs including health and social care costs for 30 days (2015)	Single Technology Appraisal Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer; Average value from PSSRU 2019, assuming 30 days of palliative care
Breast cancer							
Resources			**Costs**	**SE**	**Distribution**	**Description**	**Cost source**
Drug acquisition costs							
Price Eribulin	1,00	-	£ 722,00	£ 36,10	gamma	Price eribuline per ml vial (0,88 mg/2ml)	The NICE British National Formulary (BNF) online
Average body surface area	1,00	-	1,740	0,174	gamma	The average body surface area of a patient in m2	NICE [ID1072], Eribulin for treating locally advanced or metastatic breast cancer after one prior chemotherapy regimen
Chemotherapy administration costs							
Simple parenteral chemo delivery	1,00	-	£ 385,00	£ 19,25	gamma	Unit cost per administration by clinical oncologist	NHS Reference costs 2018/2019; 'currency code' SB14Z, 'CHEM'
*Health care resource use costs**							
Stable and progressive disease costs							
Medical oncologist follow- up (SD)	1,00	1,00	£ 158,54	£ 7,93	gamma	Clinical oncologist (regular visit) per visit	NHS Reference Costs 14/15
GP contact	1,00	1,00	£ 44,00	£ 2,20	gamma	Inpatient care: general ward per 24 hours	PSSRU 2015
CT scan	0,33	0,33	£ 30,68	£ 1,53	gamma	Imaging: CT Scan per scan	NHS Reference Costs 14/15
Supportive palliative care costs							
Medical oncologist follow-up (SPC)	-	1,00	£ 158,54	£ 7,93	gamma	Imaging: Ultrasound per scan	NHS Reference Costs 14/15
GP home visit	-	1,00	£ 44,00	£ 2,20	gamma	Imaging: X-ray per scan	PSSRU 2015
Clinical nurse specialist	-	1,00	£ 88,00	£ 4,40	gamma	Lab tests: complete blood count per test	
Community nurse home visit	-	0,67	£ 38,67	£ 1,93	gamma	Chemistry panel per test	
*End of life costs ***	*proportion of patients*						
Hospital/Medical institution	-	0,40	£ 2.054,10	£ 102,71	gamma	Imaging: Ultrasound per scan	NICE Breast Cancer Guidance (2009), Marie Curie report on End of Life Costs
Hospice	-	0,10	£ 640,22	£ 32,01	gamma	Imaging: X-ray per scan	
At home with community support	-	0,50	£ 1.324,73	£ 66,24	gamma	Lab tests: complete blood count per test	

Colorectal cancer							
Resources			**Costs**	**SE**	**Distribution**	**Description**	**Cost source**
Drug acquisition costs							
Price Trifluridine/tipiracil	1,00	-	£ 2.000,00	£ 100,00	gamma	Price Trifluridine–tipiracil of 60 tablets each containing 20mg/8.19mg	The NICE British National Formulary (BNF) online
Average body surface area	1,00	-	1,770	0,177	gamma	The average body surface area of a patient in m2	Calculated from NICE [ID1507] Trifluridine–tipiracil for treating metastatic gastric or gastro-oesophageal junction cancer after 2 or more
Chemotherapy administration costs							
First delivery of chemotherapy by nurse	1,00	-	£ 22,50	£ 1,13	gamma	Cost for for first administration; 30 minn Band 6 Nurse	NICE [ID1507] Trifluridine–tipiracil for treating metastatic gastric or gastro-oesophageal junction cancer after 2 or more therapies. (B.3.5.2.) PSSRU Unit Costs of Health & Social Care 2019, Section 10.1
*Health care resource use costs**							
Progression free and Progression state							
Consultation	1,00	0,33	£ 162,05	£ 8,10	gamma	Cost per consultation	NICE [ID1507] Trifluridine–tipiracil for treating metastatic gastric or gastro-oesophageal junction cancer after 2 or more therapies. Table 38: Medical resource use unit costs. NHS Reference costs (2017/18). 370: Outpatient attendance - Medical Oncology
Ct scan	0,50	0,01	£ 88,21	£ 4,41	gamma	Imaging: costs for CT Scan per patient	NICE [ID1507] Trifluridine–tipiracil for treating metastatic gastric or gastro-oesophageal junction cancer after 2 or more therapies. Table 38: Medical resource use unit costs. NHS Reference costs (2017/18). RD20A: Computerised Tomography Scan of One Area, without Contrast, 19 years and over
FBC	1,00	0,01	£ 2,51	£ 0,13	gamma	Costs of Full blood count test	NICE [ID1507] Trifluridine–tipiracil for treating metastatic gastric or gastro-oesophageal junction cancer after 2 or more therapies. Table 38: Medical resource use unit costs. NHS Reference costs (2017/18). DAPS05: Haematology
LFT	1,00	0,01	£ 1,11	£ 0,06	gamma	Costs of Liver function test	NICE [ID1507] Trifluridine–tipiracil for treating metastatic gastric or gastro-oesophageal junction cancer after 2 or more therapies. Table 38: Medical resource use unit costs. NHS Reference costs (2017/18). DAPS04: Clinical Biochemistry
RFT	1,00	0,01	£ 1,11	£ 0,06	gamma	Costs of Renal function test	
BSC**	-	-	£ 86,86	£ 4,34	gamma	Best supportive costs taken as a lump sum in the first cycle (2017)	NICE [ID1507] Trifluridine–tipiracil for treating metastatic gastric or gastro-oesophageal junction cancer after 2 or more therapies. B.3.5.4 Adverse reaction unit costs and resource use
Surgery**	-	-	£ 334,45	£ 16,72	gamma	Surgery for all patients leaving the progression-free health state (proportion of patients applicable is calculated in the price) (2017)	NICE [ID1507] Trifluridine–tipiracil for treating metastatic gastric or gastro-oesophageal junction cancer after 2 or more therapies. Table 42: Post-progression costs and occurrence. NHS Reference costs (2017/18). Weighted average of Malignant Gastrointestinal Tract Disorders, Elective inpatient (FD11A to FD11K) + 12 bed days (same code, duration based on CRUK [2019]).
Radiotherapy**	-	-	£ 53,60	£ 2,68	gamma	Radiotherapy for all patients leaving the progression-free health state (proportion of patients applicable is calculated in the price) (2017/2018)	NICE [ID1507] Trifluridine–tipiracil for treating metastatic gastric or gastro-oesophageal junction cancer after 2 or more therapies. Table 42: Post-progression costs and occurrence. NHS Reference costs (2017/18). SC47Z Preparation for Simple Radiotherapy with Imaging and Simple Calculation + SC31Z Deliver a Fraction of Adaptive Radiotherapy on a Megavoltage Machine. Assume 4 fractions in total (based on NICE TA378 assumption).
SACT**	-	-	£ 359,17	£ 17,96	gamma	Systemic Anti-Cancer therapy for all patients leaving the progression-free health state (proportion of patients applicable is calculated in the price)	NICE [ID1507] Trifluridine–tipiracil for treating metastatic gastric or gastro-oesophageal junction cancer after 2 or more therapies. Table 42: Post-progression costs and occurrence. NHS Reference costs (2017/18)
End of life**	-	-	£ 6.593,94	£ 329,70	gamma	End of life costs including health and social care costs (2015)	NICE [ID1507] Trifluridine–tipiracil for treating metastatic gastric or gastro-oesophageal junction cancer after 2 or more therapies. Table 43: Cost of end-of-life care. Round et al., (2015) inflated using PSSRU indices

* All Health Care resource cots are as per direct medical unit per cycle

** Applied as a one off

***Palliative care in the SD was added to the total Healthcare resources use costs in SD state

Indexing to PSSRU 2018/19 has been done on prices indicated in this table. Hence, all costs as in this table are NOT indexed.

Healthcare **utilities** per resources are taken from the same sources as indicated in this table for the costs.

APPENDIX K

Primary economic analysis results																			
	SD							PD					Total						
	Drug acquisition costs	Chemo admin costs	Premed costs	HC resource use	AE costs	LYs accrued	QALYs accrued	HC resource use	Palliative care costs	End of life costs	LYs accrued	QALYs accrued	Costs		QALYs	LYs
NSCLC model																			
Larotrectinib	£	551.365,27	£	-	£	-	£	7.842,05	£	174,21	3,83	2,26	£	24.220,82	*	£	3.066,88	17,37	6,14	£	586.669,22	8,40	21,20
Docetaxel	£	110,60	£	2.372,36	£	3,04	£	1.283,91	£	1,49	0,18	0,11	£	16.067,39	*	£	3.336,73	9,71	3,34	£	23.175,52	3,44	9,88
Increment	**£**	**551.254,68**	**-£**	**2.372,36**	**-£**	**3,04**	**£**	**6.558,13**	**£**	**172,72**	**3,65**	**2,15**	**£**	**8.153,43**	**-**	**-£**	**269,85**	**7,67**	**2,80**	**£**	**563.493,71**	**4,95**	**11,32**
Breast cancer model																			
Larotrectinib	£	550.309,67	£	-	£	-	£	6.162,87	£	81,64	3,81	2,61	£	141,38	£ 1.174,71	£	547,01	17,21	8,73	£	558.417,29	11,34	21,02
Eribulin	£	32.966,00	£	3.515,76	£	-	£	4.170,47	£	185,78	0,27	0,20	£	145,61	£ 1.282,17	£	598,26	6,03	3,23	£	42.864,04	3,43	6,30
Increment	**£**	**517.343,67**	**-£**	**3.515,76**	**£**	**-**	**£**	**1.992,40**	**-£**	**104,14**	**3,54**	**2,41**	**-£**	**4,23**	**-£ 107,46**	**-£**	**51,24**	**11,18**	**5,50**	**£**	**515.553,25**	**7,91**	**14,72**
Colorectal cancer model																			
Larotrectinib	£	512.115,20	£	-	£	-	£	4.869,28	£	40,83	3,20	2,17	£	1.278,12	£ 854,34	£	6.140,28	12,07	5,94	£	525.298,05	8,11	15,27
Trifluridine/tipiracil	£	8.934,41	£	22,50	£	-	£	960,03	£	445,75	0,08	0,06	£	526,45	£ 854,34	£	6.728,77	1,67	0,89	£	18.472,26	0,95	1,74
Increment	**£**	**503.180,78**	**-£**	**22,50**	**£**	**-**	**£**	**3.909,25**	**-£**	**404,92**	**3,12**	**2,11**	**£**	**751,66**	**£ -**	**-£**	**588,49**	**10,40**	**5,05**	**£**	**506.825,79**	**7,16**	**13,53**

HC = Health care

* Palliative care costs were accounted for in the End of life costs

The drug acquisition costs for Larotrectinib in the different models differ despite the PFS efficacy data being the same in all models. This is because different OS data for each model was recreated. The number of patients in the stable disease state (those who receive the treatment) depends on the number of patients still alive (and thus dependent on the OS). As this is a partition survival model, patients in a health state per cycle are calculated as following (according to the OS and PFS of that specific cycle):

Number of patients in the death state = 1000* (1-OS)

Number of patients in the stable disease state = (1000 - number of patients in the death state) * PFS

Number of patients in the progressive disease state = 100 - patients in death state - patients in stable disease state