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Title: Accounting for heterogeneity in resource allocation decisions: methods and practice in UK cancer technology appraisals

Running title: Heterogeneity considerations in UK cancer TAs

Authors: Thomas Ward, MSc[1]; Antonieta Medina-Lara, PhD[1]; Ruben E Mujica-Mota, PhD[1,2]; Anne E Spencer, PhD[1]

[1]Health Economics Group, College of Medicine and Health, University of Exeter

[2]Academic Unit of Health Economics, School of Medicine, University of Leeds

Corresponding author: Thomas Ward (Email: tw494@exeter.ac.uk; Phone: 01392 725565; Address: College of Medicine and Health, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU)

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All authors contributed to the concept and design, drafting and critical revision of the manuscript. The acquisition of data and the provision of study materials was contributed to by TW, AML and RMM. Further, AS, AML and RMM provided supervision to TW throughout the manuscript development. AS assisted with attaining funding through TWs PhD grant and TW contributed to the analysis and interpretation of data alongside administrative support.

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TW: Mr. Ward reports grants from Dennis and Mereille Gillings Foundation, during the conduct of the study.

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Highlights:

The availability of novel, more efficacious cancer therapies is increasing, resulting in significant treatment effect heterogeneity and complicated treatment and disease pathways. Technology Appraisals (TAs) evaluate clinical and economic evidence to inform reimbursement decisions and resource allocation. Through critical appraisal of UK cancer TAs, we identify areas where considerations of heterogeneity can be improved. We focus on three cancer sites: colorectal, lung and ovarian cancer, encompassing variation in screening, diagnostic and treatments pathways.

All TAs in this review employed decision analytic modelling. The majority utilised partitioned survival models and evaluated aggregate outcomes of clinical trial populations. Only two models explicitly considered real-world patient heterogeneity in disease progression estimates. Moreover, pre-determined subgroup analyses contained within the clinical studies that informed the TAs were rarely exploited in economic analyses.

This review highlights a paucity of information relating to the assessment of heterogeneity in colorectal, lung and ovarian cancer TAs. We conclude that future cancer TAs should consider more flexible modelling approaches and apply real-world data to explore heterogeneity within their economic analyses, especially if the complexity of treatment and disease pathways is to be reflected.

Abstract

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Objectives

The availability of novel, more efficacious and expensive cancer therapies is increasing, resulting in significant treatment effect heterogeneity and complicated treatment and disease pathways. The aim of this study is to review the extent to which UK cancer technology appraisals (TAs) consider the impact of patient and treatment effect heterogeneity.

Methods

A systematic search of NICE TAs of colorectal, lung and ovarian cancer was undertaken for the period up to April 2020. For each TA, the pivotal clinical studies and economic evaluations were reviewed for considerations of patient and treatment effect heterogeneity. The study critically reviews the use of subgroup analysis and real-world translation in economic evaluations, alongside specific attributes of the economic modelling framework.

Results

The search identified 49 TAs including 49 economic models. In total, 804 subgroup analyses were reported across 69 clinical studies. The most common stratification factors were age, gender and Eastern Cooperative Oncology Group performance score, with 15% (119/804) of analyses demonstrating significantly different clinical outcomes to the main population; economic subgroup analyses were undertaken in only 17 TAs. All economic models were cohort-level with the majority described as partitioned survival models (39) or Markov/semi-Markov models (9). The impact of real-world heterogeneity on disease progression estimates was only explored in two models.

Conclusions

The ability of current modelling approaches to capture patient and treatment effect heterogeneity is constrained by their limited flexibility and simplistic nature. This study highlights a need for the use of more sophisticated modelling methods that enable greater consideration of real-world heterogeneity.

Introduction

Cancer represents a significant healthcare burden in the UK, being the leading cause of morbidity and mortality[1]. Between 2015 and 2017, an estimated 2.5 million people were living with cancer in the UK, with an estimated annual incidence of 367,000 and, despite general improvements in population health, incidence and prevalence are predicted to increase[2-6]. Consequently, the economic burden of cancer is high and is estimated to account for 5% of total UK medical expenditure[7]. Nevertheless, whilst the UK falls behind other high-income countries, in recent years there has been improvement in mortality rates across most cancers, driven by an ever-evolving therapeutic landscape and earlier diagnoses[8-10]. The introduction of several nationwide screening policies, the emergence of targeted therapies and an increasing focus on personalised care have all contributed to such improvements[11-15]. These changes have ushered in the potential for significant treatment outcome variability, compounded by inherent increases in patient and treatment effect heterogeneity.

Patient heterogeneity typically refers to the variability of particular characteristics (e.g. age, sex, etc.) amongst patients in a given population, whilst treatment effect heterogeneity refers to the non-random, explainable variability in the direction and magnitude of treatment effects for individuals within a population[16]. Treatment effect heterogeneity can be measured in relative or absolute terms and patient heterogeneity may conventionally be represented by variation in outcomes under the status quo, whilst treatment effect heterogeneity would be operationalised as the variation in the difference in outcomes between the new treatment and the status quo.

Measures of patient and treatment effect heterogeneity seem particularly applicable to a disease area such as cancer, where the treatment landscape is rapidly evolving, and the availability of novel and more efficacious therapies is increasing. This is even more relevant when considering that newer cancer therapies are often targeted to specific patient groups, such as those with particular gene mutations or treatment and clinical histories. These targeted treatment recommendations arise from the significant patient and treatment effect heterogeneity observed amongst cancer patients, naturally resulting in complicated treatment and disease pathways[17,18]. However, there remains a lack of formal guidance on how to incorporate such effects into economic evaluations[19-21]. Indeed, reimbursement decisions are typically made based on average population-level results of clinical and economic evaluations, which potentially conceal important sources of outcome variability, particularly within large clinically heterogeneous populations.

Linked to these issues are the growing concerns related to inequalities across socioeconomic groups, particularly with respect to cancer survival[22,23]. People in the most income-deprived areas in England are more likely to have

their cancer diagnosed at a later stage, present with more comorbidities and observe different treatment pathways to those in less deprived areas, and perhaps as a consequence, observe lower life expectancy[24,25]. Further, whilst survival rates improve there is little evidence that inequalities in cancer survival have narrowed[26,27]. Knowledge about variation in patient outcomes and their association with clinical and socioeconomic characteristics would enable efficient and equitable healthcare resource allocation.

The objective of this study is to review the extent to which UK cancer TAs consider the impact of patient and treatment effect heterogeneity, and to evaluate the suitability of current modelling approaches with respect to their ability to capture such heterogeneity. Through critical appraisal, this review aims to identify areas where the consideration of patient and treatment effect heterogeneity may be improved, and to move towards recommendations on best practice for future economic evaluations.

Methods

A search of published National Institute for Health and Care Excellence (NICE) cancer TAs was undertaken. Focus was given to three cancer sites: colorectal, lung and ovarian cancer, to encompass a range of screening, diagnostic and treatment practices. Full details of the search are provided in **Supplemental Appendix 1.** In brief, the review was undertaken according to best practices as described by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[28]. Searches were conducted on the 12th April 2020; no date restrictions were applied. For each TA, the clinical studies describing the effectiveness of the intervention under assessment, and any associated economic analyses, were retrieved and reviewed.

Within the context of economic evaluation specifically, this review explores the use of subgroup analyses and real-world translation, alongside specific attributes of the underlying economic modelling frameworks. Each component is critically reviewed, from the perspective of their ability to incorporate patient and treatment effect heterogeneity.

Subgroup analysis

Randomised clinical trials often assess the impact of treatments in specific groups of patients through pre-defined subgroup or stratification factor analyses. Subgroup analysis is also a common approach used to explore heterogeneity implications in cost-effectiveness analyses. Espinoza et al. develops a general framework to guide the use of subgroup cost-effectiveness analysis for decision making in a collectively funded health system[29]. With this framework in mind, we consider to what extent TAs have included subgroup analysis in clinical and economic sections of the submission.

Patient and treatment effect heterogeneity were initially explored by extracting data relating to the presentation of subgroup analyses in the pivotal clinical studies. Subgroup analyses undertaken within the clinical studies that presented treatment effect hazard ratios (HRs) for either progression-free survival (PFS) or overall survival (OS) were recorded, alongside subgroup stratifications. In addition, we recorded the number of subgroup analyses where the HR in the subgroup population significantly differed from the HR in the intention-to-treat, or overall population. Here, a significant difference is defined by an opposing effect in each population, for example, instances where the HR is greater than one favouring the comparator in the subgroup analysis population, whilst the HR is lower than one favouring the intervention in the overall population.

Economic modelling

Economic modelling in TAs is utilised to estimate lifetime clinical and economic outcomes associated with a particular treatment, where direct experimental or observational data are unavailable or incomplete. Modelling frameworks provide a natural environment to assess the impact of patient and treatment effect heterogeneity and their associated uncertainty. The ability of models to incorporate such aspects can be highly dependent on their structural form and the statistical analysis used to manipulate and evaluate the underlying data.

We draw on Brennan et al. and Briggs et al. and describe a modified taxonomy of models (**Supplemental Appendix 2**) in order to critically review the ability of identified models to incorporate patient and treatment effect heterogeneity[30,31]. Partitioned survival models (PSMs) and Markov models are the most common approaches to modelling cost-effectiveness in cancer[32]. Both are typically cohort-level and predict outcomes based on the average patient and treatment effect in a population. A PSM follows a cohort as they move between a set of exhaustive and mutually exclusive health states, relying on the use of independent survival functions to estimate state occupancy. Similarly, a Markov model follows a cohort as they move between exhaustive and mutually exclusive health states, but relies on static, cyclic transition rates. Importantly, these Markov transitions enable the cohort to move back into health states that have already been visited. However, to incorporate time-dependency of transitions through relaxation of the Markov assumption, the use of tunnel states or semi-Markov models is required[33,34].

Patient-level models are an alternative to cohort-level models and estimate outcomes for each individual patient, enabling individual patient histories to be recorded and the ability to capture (first order) heterogeneity in the patient population. Patient-level models require more data than cohort models, and their ability to capture patient histories therefore comes at a cost which may or may not be necessary for solving a decision problem. Whilst it is suggested that patient-level models are the preferred choice for incorporating heterogeneity considerations due to their inherent flexibility, heterogeneity may be incorporated in PSMs and Markov models using extra health states to stratify patients by clinical or treatment characteristics[30,31].

The following model components are therefore reviewed and appraised:

- Modelled population
- Model type
- Health states
- Health state transitions and their derivation
- Treatment pathway and its influence on outcomes

Real-world translation

Trial populations often differ from those they are deemed to represent in routine clinical practice, with trial participants often being younger and healthier[35-37]. Trials undertaken in different regions or at different times can also differ significantly with respect to the patients they recruit and treatment management. These differences are particularly important for establishing the external validity of economic findings, with subgroup analysis a natural first test.

For example, in a trial that has recruited patients younger than those observed in routine clinical practice, and where the intervention demonstrates reduced effectiveness in the elderly subgroup, showing the generalisability of the trial findings to the proportions of the elderly found in routine clinical practice is akin to extending the heterogeneity of the trial subgroup to the overall clinical population. We explored the TAs acknowledgement of differences between trial populations and routine clinical practice and their approaches to real-world data translation.

Firstly, we extracted patient characteristic data for age, gender, Eastern Cooperative Oncology performance status (ECOG-PS) and ethnicity from the pivotal clinical studies. Where multiple clinical studies were included for a single TA, the range of results was presented and discussed. Secondly, for clinical studies with a National Clinical Trial identification number we reviewed the exclusion criteria described on the ClinicalTrials.gov website. The extent to which exclusion criteria would reduce the comparability between trial and routine practice populations was discussed. Finally, the TA submissions were reviewed for explicit acknowledgements of differences between trial and routine clinical practice, and economic analyses were reviewed for analytical methods that accounted for these differences.

Results

Included studies

A total of 49 TAs, published between 2003 and 2020, were included in the review; 38 evaluated a targeted therapy (**Figure 1**). The included TAs were dominated by lung (L) cancer appraisals (32/49), of which 31 were for non-small cell lung cancer; there were eight colorectal (C) and nine ovarian (O) cancer TAs. Details of excluded studies are presented in **Supplemental Appendix 3**, alongside an overview of each included TA.

<<FIGURE 1>>

The clinical evidence across all TAs was informed by a total of 94 (C: 22; L: 55; O: 17) clinical studies. Amongst the TAs, a total of 49 (C: 9; L: 31; O: 9) cost-effectiveness models were available for review. A total of 41 cost-effectiveness analyses were undertaken by the submitting pharmaceutical company, with eight undertaken by academic review groups.

Subgroup analysis

Subgroup analyses assessing either PFS or OS were reported for 72 (C: 13; L: 44; O: 15) of the clinical studies in either the clinical section of the TA or in the main clinical study publication cited in the TA. A total of 804 subgroup analyses were described amongst these 72 clinical studies. The most common stratification factors were age (62 studies), gender (46 studies) and ECOG-PS (50 studies). Across all reported clinical subgroup analyses, 14.8% (119/804) observed results that differed to those of the overall population. **Figure 2** contrasts the number of subgroup analyses presented as clinical evidence to the number of subgroup analyses undertaken within economic evaluations. Subgroup analysis in the economic evaluations was only conducted in 17 TAs. In 8 TAs the conclusions from at least one economic subgroup analysis differed to those of the main population, based on cost-effectiveness criteria described by the analysis authors. The most common subgroups included histology (five lung cancer studies) and mutation status (eight lung cancer studies).

<<FIGURE 2>>

Economic modelling

Table 1 describes the structures of the 49 cost-effectiveness models. The majority of models were described as PSMs (total: 39; C: 5; L: 27; O: 7), Markov models (total: 5; C: 3; L: 2; O: 0), or semi-Markov models (total: 4; C: 0; L: 2; O: 2). **Figure 3** describes the health states included in each of the models. Health states of partitioned

survival models typically reflected PFS, progression and death (37 models), with 6 of these models including response- or treatment-based sub-states. In contrast, Markov and semi-Markov structures described a range of health states reflecting treatment and clinical status. All models were cohort-level, and given the majority included between 2 and 4 health states only, there was little consideration of individual patient clinical heterogeneity or variability within the model structures themselves.

<<FIGURE 3>>

With respect to treatment heterogeneity, 42 (C: 4; L: 31; O: 7) economic analyses utilised data from a single clinical study relating to the first modelled line of treatment only, relying on either clinical expert opinion or validation against published studies with longer-term follow-up to justify extrapolation choices. **Supplemental Appendix 4** demonstrates the growing importance of accurate clinical extrapolation; across the 72 clinical studies for which information on the maturity of clinical data was available, 46% (33/72) of studies had observed events in less than 50% of patients at the time of analysis (17% [12/72] had observed events in less than 25% of patients). Further, there appears to be no discernible relationship between the length of follow-up of the clinical studies and the choice of modelling structure, with lung cancer studies, as expected due to their comparatively lower survival rate, observing the shortest periods of follow-up on average.

The modelling of treatment pathways is described in **Table 2**, alongside additional context with respect to the modelled population. Despite real-world potential for multiple subsequent therapies across many of the reviewed indications, 20% (10/49) of models did not include subsequent therapy at all and 71% (35/49) included only one explicit subsequent line of therapy (not including best supportive care). Of those models that included the impact of subsequent therapies, this impact was limited to cost accrual in 77% (30/39) of models and to cost accrual and utility values in 18% (7/39) of models; subsequent therapy impacted disease progression, cost accrual and utility values in the remaining two models.

<<TABLE 1>>

<<TABLE 2>>

Real-world translation

The majority of TAs (32/49) acknowledged differences between the patient characteristics and/or treatment pathways used in the clinical studies and routine clinical practice. Further, within individual TAs, patient heterogeneity was particularly noticeable in those that included more than one pivotal clinical study

(**Supplemental Appendix 5**). In such TAs, where data were reported, the average range of median ages was 4.9 years (C: 4.9; L: 5.7; O: 3.0), with average ranges of 16% (C: 12%; L: 18%), 10% (C: 5%; L: 11%; O: 14%) and 21% (C: 31%; L: 20%; O: 12%) for the proportion of patients that were male, had an ECOG-PS of 0 or 1 and were White or Caucasian, respectively; the largest ranges in any single TA were 18.8 years (C: 18.5; L: 18.8; O: 3.1), 65% (C: 29%; L: 65%), 57% (C: 11%; L: 57%; O: 37%) and 99% (C: 58%; L: 99%; O: 13%), respectively.

Figure 4 describes the most common exclusion criteria used by the clinical studies and gives an overall impression of the selective nature of clinical trials and how the trial populations might differ from those found in routine clinical practice. A total of 73/94 clinical studies described exclusion criteria. The most common criteria not related to the treatment indication (e.g. treatment history, histology, mutation status, etc.) were a history of other malignancies (35/73 studies) and a history of cardiac problems (31/73). Such exclusion criteria would likely ostracize a significant proportion of cancer patients in UK clinical practice that are expected to have comorbid conditions[25].

<<FIGURE 4>>

Finally, few TAs attempted to investigate the impact of clinical heterogeneity through disease progression modelling, with only five models (all evaluating targeted therapies) including clinical covariates within their estimation of PFS and OS disease progression estimates (**Table 1**). Although not exclusive to these TAs, patients in the clinical studies associated with four out of the five TAs were systematically different to the routine clinical practice patients they were representing with respect to their ethnic origin. Of these, two TAs (TA406 and TA529) employed methods to account for differences between trial and clinical practice populations. These lung cancer TAs generated disease progression survival models that included clinical covariates based on data from the clinical study. Subsequently, these survival models were used to predict clinical outcomes for the cost-effectiveness model at covariate values corresponding to those observed in published studies deemed representative of UK clinical practice. In both cases, the following clinical covariates were included in the survival models: race (Asian/non-Asian), ECOG-PS (0 or 1/2), brain metastases at baseline (yes/no), age (≥65/<65 years), sex, smoking status (never smoked/former or current smoker), adenocarcinoma at baseline (yes/no).

Discussion

This is the first review to consider patient and treatment effect heterogeneity in UK TAs of colorectal, lung and ovarian cancer. The review highlighted that whilst many clinical studies undertook subgroup analyses, only a small number of economic evaluations considered these subgroups further in modelling analyses. Although, such findings must be caveated with the potential for publication bias and the under-reporting of negative results in economic submissions. This lack of representation in economic analyses was notable as several clinical subgroup analyses presented results contradicting the overall population findings, although statistical significance was rare. In addition, it was common to find a significant and positive treatment effect in the overall population analysis with subgroup analyses failing to demonstrate the same effect (or achieve significance). Statistical significance was not a focus of this study due to inconsistent definitions across TAs, underreporting of results (e.g. commercial-in-confidence redaction) and small sample sizes. Subgroup analyses provide evidence for improved allocation of healthcare resources, with the potential to tailor reimbursement recommendations to specific patient groups where evidence for effectiveness is either very strong or very weak. Guidance is available on when to apply subgroup analysis in cost-effectiveness evaluation, with such analyses continuing to be a preferred first step to evaluate patient and treatment heterogeneity[29,38-40].

Review of the economic models further showed that the ability to incorporate heterogeneity in the economic evaluations was hampered by an overreliance on relatively simplistic cohort-based modelling structures. It was found for example, that most economic models utilised univariable disease progression estimates and represented disease progression through just three health states. Of particular note is what may be perceived as a systemic reliance on PSMs to demonstrate the economic impact of new cancer therapies. PSMs are designed for use with near complete clinical data and relatively simplistic treatment and disease pathways[41]. Inherently, models with simple structures lack flexibility and therefore do not lend themselves to the modelling of heterogeneity, particularly those of patient characteristics and treatment effects.

The NICE Decision Support Unit technical documentation suggests patient-level simulation should be considered when the number of categories required to define patient groups with homogeneous outcomes becomes large[42]. Patient-level simulation is also advocated for consideration when the likelihood of future events (e.g. death) are dependent on the time since previous events (e.g. disease progression). Notably, these criteria are true of certain TAs in this review, with the latter being particularly relevant to cancers for which curative treatment is available (colorectal and ovarian cancer) and those where disease progression is

particularly influential over patient prognosis (lung cancer). However, patient-level models often have greater computational requirements, with respect to the data required, the time taken to run analyses and the complexity of such analyses. As such, trade-offs between analyst time, computation time and the requirements of the decision problem may be required. To justify final model selection, a checklist approach could be used to characterise the decision problem, the data, computational limitations, and other relevant issues. This approach offers several advantages over algorithmic model selection, including the ability to summarise strengths and weaknesses of modelling approaches within the context of the decision problem aiding critical appraisal of model choice, and the avoidance of prescriptive decisions that create the illusion that only one model type suits a particular decision problem.

The review additionally identified weaknesses in the methods used to extrapolate clinical endpoints to policy-relevant time horizons. Extrapolations rarely considered clinical mechanisms for estimating disease progression, and instead relied predominantly on within-trial statistical goodness-of-fit output, visual inspection, and comparison to historical data. A potential solution is to utilise risk equations to aid in the extrapolation of outcomes beyond the trial phase using clinical and treatment history data. This approach is commonly applied in other disease areas such as diabetes, cardiovascular disease and chronic kidney disease[43-49]. The derivation of these risk equations is typically undertaken from large real-world observational datasets and may also assist in alleviating concerns over the real-world applicability of outcome extrapolation. These methods may have previously been overlooked in cancer due to the potential for low quality of recording of data, the propensity for cancer treatments to fundamentally change the course of disease and for the prevalence of highly unique cancer subpopulations defined by genetic variation[50-55]. However, national comprehensive clinical practice datasets have improved in both quality and coverage over recent years[56-59]. Combining risk equations with more flexible and sophisticated modelling methods will provide greater consideration, and understanding, of real-world patient and treatment effect heterogeneity, and go some way to addressing historical limitations.

Finally, whilst appraisals acknowledged differences between the clinical studies from which their evidence was based and routine clinical practice, few summarised these differences quantitatively. Clearly there are tensions between the representativeness of clinical trials and the necessity of a trial to have homogeneous groups of patients to enable comparison between groups[60]. However, homogeneity does not need to come at the expense of the natural heterogeneity observed in the population of interest, which may become the case when extensive exclusion criteria are applied. Addressing such issues is not straightforward, with patient safety, ethical issues, and sample size considerations at the forefront of concern. As a relatively simple and practical initial step, we

suggest that trial investigators could improve reporting by making available more evidence on clinical outcomes of stratification subgroups, alongside encouraging access to individual patient data (IPD) for research. Subsequently, we would advocate the addition of a more explicit and structured comparison of routine clinical practice and trial patient populations within TAs. Such a comparison might take the form of a quantitative side-by-side summary of the clinical and demographic characteristics of patients from both groups, based on relevant UK clinical practice datasets and the clinical studies informing the appraisal. We would encourage the adoption of such an approach as standard practice within TAs to provide relevant parties with a transparent overview of both the relevance and the extent of any differences.

Further, very few TAs employed methods to adjust cancer outcomes to account for differences between trial and routine clinical practice, even in the most recent TAs. This is particularly relevant given observed differences between cancer outcomes in these settings, particularly amongst PFS and OS outcomes[61], and the need for policy makers to understand these differences to inform policy recommendations and guidelines. Two TAs used a form of simulated treatment comparison (STC), generating survival models that included clinical covariates based on IPD from the clinical study, and subsequently using these to predict clinical outcomes for the cost-effectiveness model at covariate values deemed representative of UK clinical practice. Methods such as STC and matching-adjusted indirect comparison (MAIC), aim to reduce bias in treatment comparisons by using IPD from the clinical studies to provide indicative estimates of the likely outcomes in different settings, and may be used to address the above concerns[62,63]. MAIC adjusts average population-level outcomes by applying weights to IPD from the clinical study, using larger weights for patients that more closely match those of routine clinical practice, whilst STC utilises regression equations to adjust estimates.

Clearly these suggestions should acknowledge the current constraints of the NICE review process, which is subject to strict timelines. For example, IPD needed for patient-level simulation or risk equation development may not be available to researchers. This raises the questions of how NICE should resource future TAs to enable them to better incorporate heterogeneity and related equity concerns. A further limitation of the review is the pragmatic decision to consider three cancer sites. Further research is required before we can generalise across all cancers and across economic evaluations of cancer outside the remit of NICE TAs.

Conclusion

This study highlights a relative paucity of information relating to the assessment of heterogeneity in UK cancer TAs and identifies a mostly unjustified reliance on relatively simplistic modelling frameworks. If heterogeneity

considerations are to be included in TA frameworks, and the complexity of treatment and disease pathways reflected in economic analyses, there is a requirement to embrace more flexible modelling approaches and to further research real-world heterogeneity

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Tables

Table 1: Overview of model structures

Model type	Modelled health states	Modelled health state transitions*	Outcomes informing health state transitions	Progression-free survival (PFS) or time to discontinuation (TTD) analysis	Overall Survival (OS) analysis	Technology Assessment
PSM	Alive; death	Alive -> Death	OS	-	Piecewise parametric survival models^	TA190
	On treatment; off treatment; death	On treatment -> Off treatment; On treatment -> Death; Off treatment -> Death	TTD; OS	Piecewise parametric survival models^	Mixture-cure model^	TA520
	Progression-free; progression; death	Progression-free -> Progression; Progression-free -> Death; Progression -> Death	PFS; OS	KM data^^	Parametric survival models^^	TA227
				Multivariable parametric model with treatment covariate	Multivariable parametric model with treatment covariate	TA406

					Multivariable parametric models^	TA403
				Multivariable parametric model^	Multivariable parametric model^	TA529
				Multivariable parametric model^^	Multivariable parametric model^^	TA192
				Parametric survival model with treatment covariate	Parametric survival model with treatment covariate	TA310
					Parametric survival models^	TA118
					Piecewise parametric survival model with treatment covariate	TA621
				Parametric survival models^	Parametric survival models^	TA184, TA242, TA285, TA307,

						TA347, TA389, TA395, TA405, TA416, TA484, TA528, TA536, TA611
					Piecewise parametric survival models^	TA428
				Parametric survival models^^	Parametric survival models^^	TA500, TA571, TA584, TA595
				Piecewise parametric survival models^	Parametric model with treatment covariate	TA284

					Piecewise parametric survival models^	TA212, TA374, TA402, TA411, TA531, TA557, TA600
					Piecewise parametric survival models^^	TA598
				Spline model^	Spline model^	TA620
				Spline model with treatment covariate	Parametric survival model with treatment covariate	TA483
Model type	**Modelled health states**	**Modelled health state transitions**	**Outcomes informing health state transitions**	**Non-death transitions**	**Death transitions**	**Technology Assessment**

Markov model	1st line, 2nd line, 3rd line, post-resection, death	1st line -> Post resection; 1st line -> 2nd line; 1st line -> Death; Post resection -> Death; 2nd line -> 3rd line; 2nd line -> Death; 3rd line -> Death	Resection rate, PFS, ToT, OS	Parametric survival models^	Parametric survival models^	TA439
	Alive without relapse, alive with relapse, death	Alive without relapse -> Alive with relapse; Alive without relapse -> Death; Alive with relapse -> Death	DFS, PPS, ACM	Parametric survival models^	Mixture of exponential transition rates and life tables	TA100
	PFS: 1st line, PFS: no drug, PFS: post successful resection, PD: post successful resection, 2nd line: FOLFOX/FOLFIRI, 3rd line: BSC, Death	PFS-1st line -> PFS-no drug; PFS-1st line -> PFS-post successful resection; PFS-1st line -> Death; PFS-no drug -> 2nd line-FOLFOX/FOLFIRI; PFS-no drug -> Death; PFS-post successful resection -> PD-post successful resection; PFS-post successful resection -> Death; 2nd line-FOLFOX/FOLFIRI -> 3rd line-BSC; 2nd line-	Resection rate, PFS, ToT, OS	Mixture of parametric survival models and exponential rates	Mixture of parametric survival models and exponential rates	TA439

		FOLFOX/FOLFIRI -> Death; 3rd line-BSC -> Death				
	Response, stable disease, progressive disease, death	Stable disease -> Response; Stable disease -> Progression; Response -> Progression; Progression -> Death	Response, PFS, OS	Exponential transition rates	Exponential transition rates	TA124, TA181
Semi-Markov model	Progression-free, first subsequent treatment, second subsequent treatment, death	PFS -> First subsequent treatment; PFS -> Death; First subsequent treatment -> Second subsequent treatment; First subsequent treatment -> Death; Second subsequent treatment -> Death	ToT, OS	Multivariable parametric survival models with or without treatment coefficients	Multivariable parametric survival models with or without treatment coefficients	TA381
	Progression-free, progressed, death	Progression-free -> Progression; Progression-free -> Death; Progression -> Death	PFS, PPS, OS	Piecewise parametric survival models^	Exponential transition rates	TA284
				Parametric survival models^	Exponential transition rates	TA578
		Progression-free -> Progression; Progression-free -> Death; Progression -> Death	PFS, PPS, OS	Piecewise parametric survival models^^	Exponential transition rates	TA258

Accounting exercise	-	-	OS	-	-	TA61

ACM: all-cause mortality; DFS: disease-free survival; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; PSM: partitioned survival model; TA: technology appraisal; ToT: time on treatment; TTD: time to discontinuation.

*Underlined transitions denote those that are modelled with different rates across each treatment arm.

^Same survival model form chosen for each treatment arm.

^^Survival models were only produced for one arm with ITC results used to inform disease progression in other arms.

TA Notes

TA192, TA402 and TA411: Model structure believed to be incorrectly described as Markov model in submission.

TA118: Model structure not described but assumed to be PSM based on description of parameters.

TA192 and TA258: PFS health state stratified in to two sub-states ('Treatment response' and 'Stable disease') based on proportions at model initiation.

TA242: Some (but not all) comparator survival estimates informed by survival ratios applied to parametric curves of other arms (holding shape parameters constant).

TA212, TA307 and TA611: PFS health state stratified in to two sub-states ('On treatment' and 'Post-treatment') using parametric survival models.

TA374: Two populations modelled where piecewise spline models used for one population and piecewise parametric models used for one population

TA381: Unclear whether single models were used for certain transitions (i.e. treatment independent transitions) as the submission contains contradictory statements; the ERG report states that apart from time to first event, all other transitions were set the same for each treatment arm

TA411: PFS health state stratified in to three sub-states ('On induction treatment', 'Off treatment', 'Receiving maintenance treatment') using parametric survival models

TA484: TTD used as proxy for PFS

TA528: Model states that mean survival estimates are used (therefore not strictly a PSM as AUC approach not utilised), however parametric survival curves are used to assess PFS and OS so it has been included in the PSM section

TA536: PFS stratified in to two sub-states ('Patients with brain metastases' and 'Patients without brain metastases') although it is unclear how patients are stratified

Table 2: Overview of modelled treatment pathways

Population				Number of subsequent therapies modelled^	Impact of subsequent therapy	Method for estimating time on initial treatment	TA
Cancer	**Previously treated**	**Stage***	**Mutation -specific**				
CRC	No	Dukes stage C	No	One	Cost only	Mean treatment duration	TA100
		Metastatic	No	None	-	Explicit number of cycles capped by OS	TA61
						ToT KM curve	TA212
			Yes	One	Cost, utility, disease progression	Initial treatment modelled with own health state	TA439 (ERG)
				Two	Cost, utility, disease progression	Initial treatment modelled with own health state	TA439 (Company)
	Yes	Metastatic	No	None	-	Treatment to progression or mean treatment duration	TA242
			No	One	Cost only	Mean treatment duration	TA307
			No	One	Cost only	Treatment to progression	TA405
			Yes	Two	Cost only	Mean treatment duration	TA118

NSCLC	Both	Advanced or metastatic	Yes	One	Cost and utility	TTD modelled independently using KM data	TA529
					Cost only	Parametric ToT model	TA584
	No	Advanced or metastatic	No	One	Cost only	Cyclic discontinuation rate capped by specific number of cycles	TA181
						Parametric ToT model	TA557
						ToT KM curve	TA411
						Treatment to progression	TA600
			Yes	None	-	Parametric ToT model	TA258
				One	Cost and utility	Mean treatment duration beyond progression	TA406, TA621
						Treatment to progression	TA310
					Cost only	Parametric ToT model	TA500
						Treatment to progression	TA192, TA531, TA536
				Two	Cost only	Treatment to progression	TA595
	Yes	Advanced or metastatic	No	None	-	Cyclic discontinuation rate capped by specific number of cycles	TA124
						Treatment to progression	TA374
				One	Cost and utility	Parametric ToT model	TA520
						Treatment to progression	TA483, TA484

					Cost only	Cyclic discontinuation rate capped by progression	TA347
						Parametric ToT model	TA402
						ToT KM curve	TA578
						Treatment to progression	TA190, TA227, TA403
			Yes	None	Cost only	Independent mean duration beyond progression	TA571
				One	Cost only	Treatment to progression	TA416, TA428
		Any	Yes	None	-	Treatment to progression	TA395
SCLC	Yes	Relapsed	No	None	-	Specific number of treatment cycles	TA184
Ovarian cancer	Any	Any	No	-	-	-	TA55
	No	Advanced	No	None	Cost only	Mean treatment duration	TA284 (Model 1)
				One	Cost only	Mean treatment duration	TA285
							TA284 (Model 2)
	Yes	Any	No	One	Cost only	Treatment to progression	TA389
		Advanced	Yes	One	Cost only	Parametric ToT model	TA598
		High-grade	No	One	Cost only	Parametric ToT model	TA528, TA611
			Yes	One	Cost only	Parametric ToT model	TA620
				Two	Cost only	Initial treatment modelled with own health state	TA381

CRC: colorectal cancer; KM: Kaplan-Meier; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; TA: technology appraisal; ToT: time on treatment

*For NSCLC, 'Advanced or metastatic' includes 'recurrent disease' in TA347 and, for ovarian cancer, 'Advanced' includes one appraisal that looked at stage III/IV disease (TA284)

^Subsequent therapy is defined as either targeted therapy, chemotherapy, surgery or radiotherapy and does not capture the modelling of best supportive care

TA Notes

TA284 (Model 2), TA416 and TA528: Average number of subsequent therapies received was greater than 1 but modelled within one subsequent line of therapy

TA307: Despite including substates within the progression-free health state describing treatment status ('on treatment' versus 'off treatment'), treatment costs were modelled based on a mean treatment duration

TA406: Only a proportion of patients were assumed to receive therapy post-progression; remaining patients ceased treatment at progression

TA439: Patients could also receive curative resection after first line treatment, independent of other treatment lines

Figures

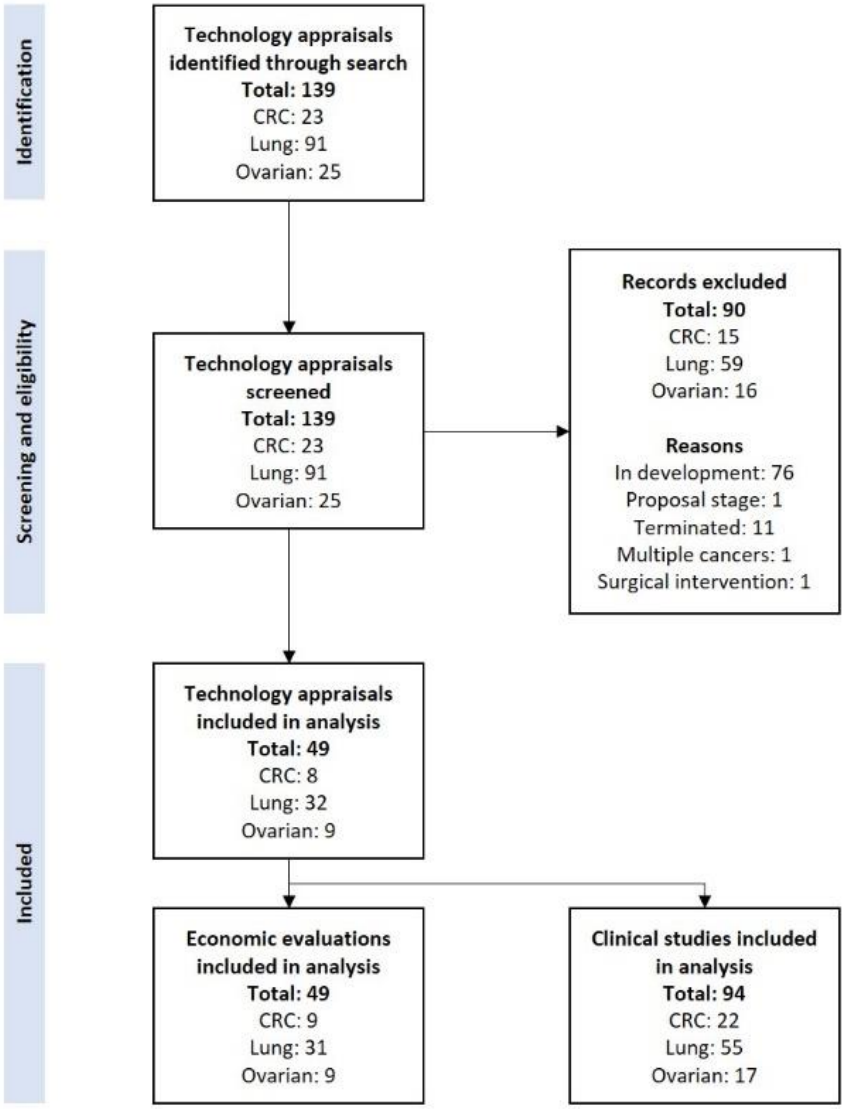

Figure 1: Search results

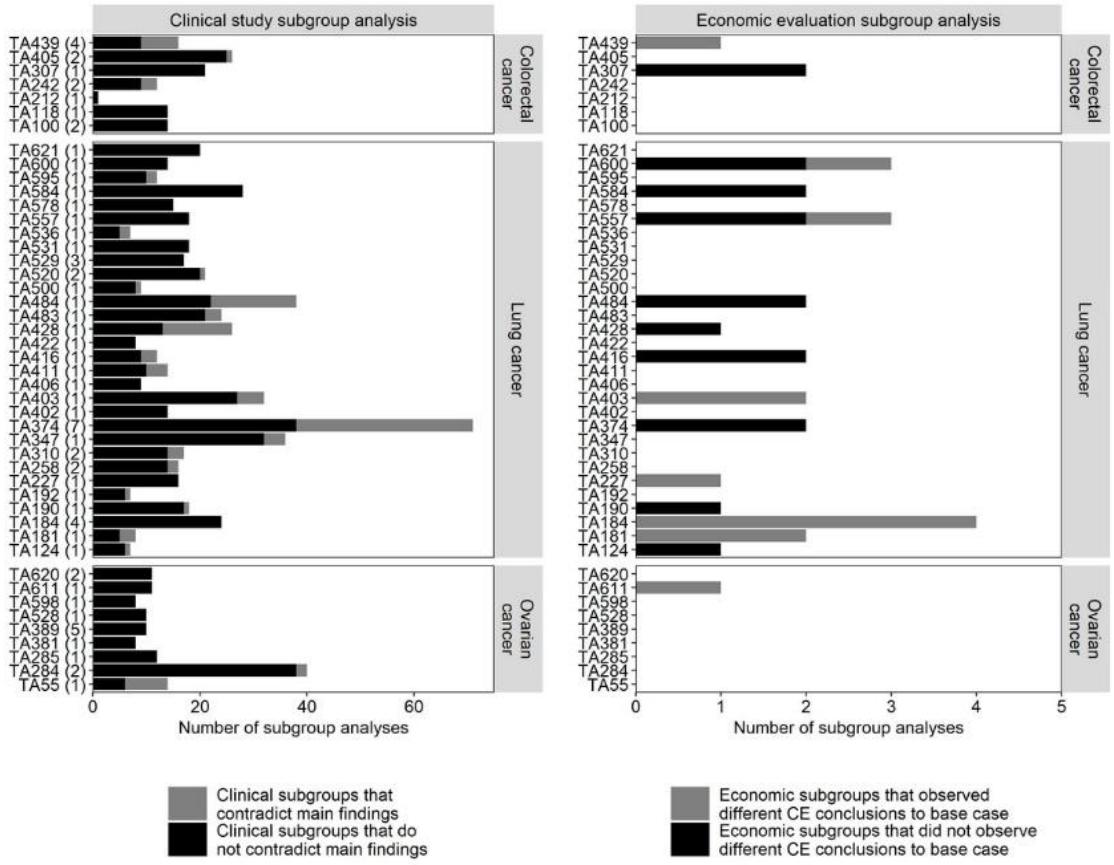

Figure 2: Overview of subgroup analyses presented in clinical and economic submissions

[*The number in brackets next to the TA number indicates how many clinical studies reported at least some information relating to the use of subgroup analyses – a number of subgroup analyses and results were unavailable for review either due to absence or redaction*]

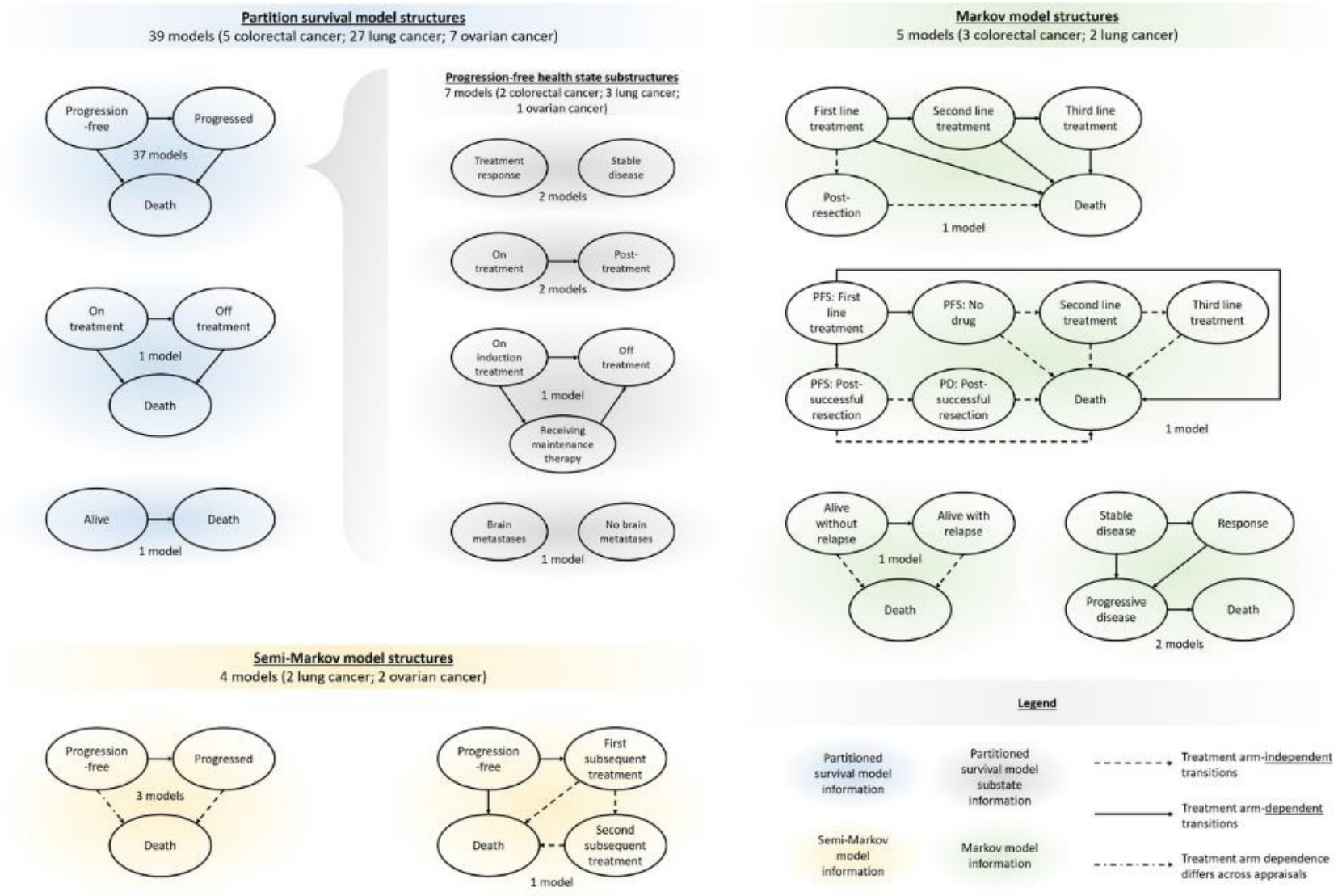

Figure 3: Model structure overview

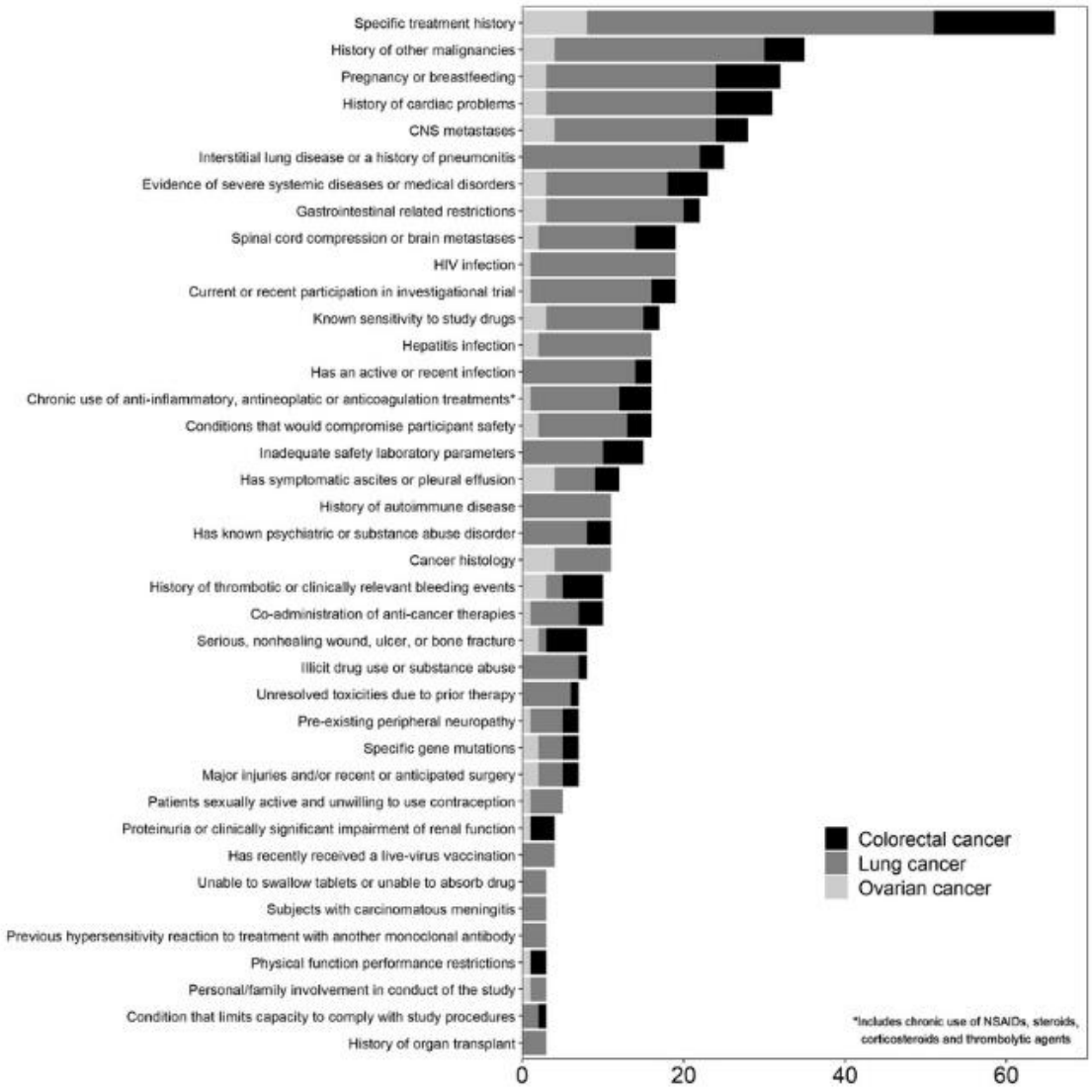

Figure 4: Exclusion criteria categories reported by the clinical studies (limited to exclusion criteria reported in at least three clinical studies)

Supplemental Appendix 1

Details of search strategy

A search of published National Institute for Health and Care Excellence (NICE) cancer TAs was undertaken. Focus was given to three cancer sites: colorectal, lung and ovarian cancer, to encompass a range of screening, diagnostic and treatment practices. The time between first presentation in primary care and the date of diagnosis varies between these cancer sites providing an additional source of variation and potentially exacerbates differences in screening, diagnostic and treatment practices[1,2].

The review was undertaken according to best practices as described by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[3]. Searches were conducted on the 12th April 2020; no date restrictions were applied. Titles and summaries of the identified TAs were screened by one reviewer and checked for accuracy by a second reviewer. TAs that had been superseded by another TA or had been terminated for any reason, and were subsequently unavailable on the NICE TA database, were excluded. Appraisals that considered multiple cancer sites and those considering only surgical interventions did not include formal economic evaluation and so were also excluded. All data were extracted in a consistent manner from studies meeting the review inclusion and exclusion criteria, using a standardised data extraction template in Microsoft Excel. Data were extracted by one reviewer and checked for accuracy and completeness by a second reviewer. Any discrepancies between reviewers were resolved by consensus or referral to a third reviewer.

For each TA, the clinical studies describing the effectiveness of the intervention under assessment, and any associated economic analyses, were retrieved and reviewed. Clinical studies that did not directly inform the clinical effectiveness of the intervention under assessment, but were included for supplementary information, were not reviewed, nor were clinical studies for which only abstracts were reported. Economic analyses undertaken by both the submitting pharmaceutical company and any academic review groups were included. Economic analyses were excluded if the complete economic submission was not publicly available or if only summary information was presented.

Within the context of economic evaluation, this review explores the use of subgroup analyses and real-world translation, alongside specific attributes of the underlying economic modelling frameworks. Each component is critically reviewed, from the perspective of their ability to incorporate patient and treatment effect heterogeneity.

References

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Supplemental Appendix 2

Appendix Table: Taxonomy of model structures

Modelling method	Cohort / individual-level	Temporal component	Interactions and heterogeneity	Advantages	Disadvantages
Decision tree	Either	No temporal component	• No interaction • Requires either, additional disease states, or multiple model runs, to capture patient and treatment effect heterogeneity	• Easy to construct • Relatively easy to interpret • Can be adapted for cohorts and individuals	• No explicit time component • Exponentially more complex with additional disease states • No looping/recurring • Poorly suited to complex scenarios
Comparative risk assessment	Either	No temporal component	• No interaction • Requires either, additional disease states, or multiple model runs, to capture patient and treatment effect heterogeneity	• Can model multiple diseases and risk factors • Can be used for individuals or cohorts	• More complex to build than decision trees • No explicit time component • No looping/recurring • Unable to model interactions between individuals,

					populations, or their environment
Markov models (without interaction)	Either	Timed	• No interaction • Requires either, additional disease states, or multiple model runs, to capture patient and treatment effect heterogeneity	• Relatively straightforward to construct and to communicate • Can model populations or individuals • Has time component • Allows looping/recurring	• The Markovian assumption – individuals have no memory of (are independent of) previous disease states • Can only exist in one disease state at any given time • Exponential increase in complexity with increasing number of disease states
System dynamics models	Cohort	Discrete or continuous time	• Interaction between populations and environment • Requires either, additional disease states, or multiple model runs, to capture patient and treatment effect heterogeneity	• Allows for interactions between populations and the environment • Allows for feedback and recurring	• Models populations rather than individuals • Relies on differential or difference equations which can be difficult to implement and interpret

Markov chain models and Markov individual event history models	Either	Discrete or continuous time	• Interaction between populations and environment • Requires either, additional disease states, or multiple model runs, to capture	• Can model individuals or populations • Allows for interaction between populations or individuals within the model	• Markovian assumption still exists (although its impact can be reduced) • Becomes rapidly more complex with added disease states
Discrete event simulation	Individual	Discrete or continuous time	• Interaction between populations and environment • Able to incorporate a population of heterogeneous individuals that move through the model based on probabilities appropriate to their characteristics	• Allows for interaction between individuals and between individuals, populations and their environment, governed by system rules • Allows for modelling of complex scenarios	• Model structure can be difficult to communicate and interpret • Computationally challenging both in terms of designing the model and running it
Agent-based simulation	Individual	Completely flexible	• Interaction between individual patients / populations / spatial aspects important • Able to incorporate a population of heterogeneous individuals that move through the model based	• Allows for interaction between individuals and between individuals, populations and their environment, governed by system rules • Allows for individuals to learn	• More complex than discrete event simulation • Requires large computational power • Difficult to communicate and interpret model structure

			on probabilities appropriate to their characteristics	• Allows modelling of complicated systems	
Multistate life tables	Either	Timed or untimed	• No interaction • Requires either, additional disease states, or multiple model runs, to capture patient and treatment effect heterogeneity	• Can be used with comparative risk assessment and decision tree models to add a time component • Can be combined with Markov models to increase the numbers of possible disease states without exponentially increasing model complexity	• Assumes diseases are independent of each other • Model limited by underlying model structure, for example, if combined with a Markov model, the Markovian assumption remains
Microsimulation	Individual	Completely flexible	• Interaction between populations and environment • Able to incorporate a population of heterogeneous individuals that move through the model based on probabilities appropriate to their characteristics	• Can be combined with decision tree, comparative risk assessment, and Markov models to make it easier to model heterogeneous populations or multiple disease states	• Data requirements and simulations can become computationally challenging with complex models • Model limited by underlying model structure, for example, if combined with a Markov model, the Markovian assumption remains

Notes

- In discrete or continuous time Markov chain models, state transition probabilities can depend on (interact with) the proportion of different populations in different disease states, and on the time that has elapsed in the model. These interactions are the key difference between Markov chain models and Markov models without interaction, and provide the model with some degree of memory, in part overcoming the Markovian assumption.

Supplemental Appendix 3

Appendix Table: Excluded studies

Study identifier	Cancer	Study type	Reason for exclusion	Publication date
ID379	Colorectal	Technology appraisal	In development	TBC
ID917	Colorectal	Technology appraisal	In development	TBC
ID2693	Colorectal	Technology appraisal	In development	TBC
ID1071	Colorectal	Technology appraisal	In development	TBC
ID1118	Colorectal	Technology appraisal	In development	TBC
ID1136	Colorectal	Technology appraisal	In development	TBC
ID1168	Colorectal	Technology appraisal	In development	TBC
ID1298	Colorectal	Technology appraisal	In development	TBC
ID1332	Colorectal	Technology appraisal	In development	TBC
ID1498	Colorectal	Technology appraisal	In development	June 2021
ID1598	Colorectal	Technology appraisal	In development	October 2020
ID1543	Colorectal	Technology appraisal	Proposed	TBC
TA105	Colorectal	Technology appraisal	Surgical intervention	August 2006
TA240	Colorectal	Technology appraisal	Terminated - no submission	December 2011
TA334	Colorectal	Technology appraisal	Terminated - no submission	February 2015
TA265	Lung	Technology appraisal	Considers multiple cancers	October 2012
ID9	Lung	Technology appraisal	In development	TBC
ID43	Lung	Technology appraisal	In development	TBC
ID44	Lung	Technology appraisal	In development	TBC
ID46	Lung	Technology appraisal	In development	TBC
ID357	Lung	Technology appraisal	In development	TBC
ID655	Lung	Technology appraisal	In development	TBC
ID657	Lung	Technology appraisal	In development	TBC
ID821	Lung	Technology appraisal	In development	TBC
ID883	Lung	Technology appraisal	In development	TBC
ID1088	Lung	Technology appraisal	In development	TBC

ID1126	Lung	Technology appraisal	In development	TBC
ID1135	Lung	Technology appraisal	In development	TBC
ID1143	Lung	Technology appraisal	In development	TBC
ID1146	Lung	Technology appraisal	In development	TBC
ID1147	Lung	Technology appraisal	In development	TBC
ID1187	Lung	Technology appraisal	In development	TBC
ID1228	Lung	Technology appraisal	In development	TBC
ID1247	Lung	Technology appraisal	In development	TBC
ID1259	Lung	Technology appraisal	In development	TBC
ID1261	Lung	Technology appraisal	In development	TBC
ID1264	Lung	Technology appraisal	In development	TBC
ID1277	Lung	Technology appraisal	In development	TBC
ID1288	Lung	Technology appraisal	In development	TBC
ID1331	Lung	Technology appraisal	In development	TBC
ID1338	Lung	Technology appraisal	In development	May 2020
ID1468	Lung	Technology appraisal	In development	January 2021
ID1472	Lung	Technology appraisal	In development	TBC
ID1481	Lung	Technology appraisal	In development	TBC
ID1495	Lung	Technology appraisal	In development	TBC
ID1504	Lung	Technology appraisal	In development	TBC
ID1509	Lung	Technology appraisal	In development	TBC
ID1538	Lung	Technology appraisal	In development	TBC
ID1541	Lung	Technology appraisal	In development	TBC
ID1559	Lung	Technology appraisal	In development	May 2020
ID1566	Lung	Technology appraisal	In development	TBC
ID1572	Lung	Technology appraisal	In development	May 2020
ID1577	Lung	Technology appraisal	In development	TBC
ID1584	Lung	Technology appraisal	In development	TBC
ID1618	Lung	Technology appraisal	In development	December 2020

ID1629	Lung	Technology appraisal	In development	TBC
ID1665	Lung	Technology appraisal	In development	March 2020
ID1675	Lung	Technology appraisal	In development	TBC
ID1678	Lung	Technology appraisal	In development	February 2021
ID1683	Lung	Technology appraisal	In development	August 2020
ID2702	Lung	Technology appraisal	In development	TBC
ID3743	Lung	Technology appraisal	In development	TBC
ID3751	Lung	Technology appraisal	In development	TBC
ID3757	Lung	Technology appraisal	In development	TBC
ID3761	Lung	Technology appraisal	In development	TBC
ID3762	Lung	Technology appraisal	In development	TBC
ID3780	Lung	Technology appraisal	In development	TBC
TA148	Lung	Technology appraisal	Terminated - no submission	June 2008
TA362	Lung	Technology appraisal	Terminated - no submission	October 2015
TA436	Lung	Technology appraisal	Terminated - no submission	March 2017
TA438	Lung	Technology appraisal	Terminated - no submission	March 2017
TA444	Lung	Technology appraisal	Terminated - no submission	May 2017
TA564	Lung	Technology appraisal	Terminated - no submission	February 2019
TA618	Lung	Technology appraisal	Terminated - no submission	January 2020
ID545	Ovarian	Technology appraisal	In development	TBC
ID564	Ovarian	Technology appraisal	In development	TBC
ID790	Ovarian	Technology appraisal	In development	TBC
ID826	Ovarian	Technology appraisal	In development	TBC
ID1184	Ovarian	Technology appraisal	In development	TBC
ID1340	Ovarian	Technology appraisal	In development	TBC
ID1497	Ovarian	Technology appraisal	In development	TBC
ID1527	Ovarian	Technology appraisal	In development	TBC
ID1561	Ovarian	Technology appraisal	In development	TBC
ID1639	Ovarian	Technology appraisal	In development	TBC

ID1652	Ovarian	Technology appraisal	In development	November 2020
ID1680	Ovarian	Technology appraisal	In development	February 2021
ID2700	Ovarian	Technology appraisal	In development	TBC
ID2714	Ovarian	Technology appraisal	In development	May 2021
TA353	Ovarian	Technology appraisal	Terminated - no submission	August 2015
TA560	Ovarian	Technology appraisal	Terminated - no submission	February 2019

Notes on reasons for exclusion

- Appraisals that considered multiple cancer sites and those considering only surgical interventions did not include formal economic evaluation and so were excluded.
- Appraisals that are described as ‘In development’ or ‘Proposed’ have not yet been published and so haven't been included for this reason.
- Appraisals that are described as ‘Terminated - no submission’ were terminated prior to publication of the submission and therefore no submission was available for review.

Appendix Table: Overview of included Technology Assessments

TA number	Cancer site	TA title	Publication date	STA or MTA	Population	Technology*	Recommendation (yes v no v CDF)
TA61	CRC	**Capecitabine and tegafur** with uracil for metastatic colorectal cancer	27/05/2003	MTA	Patients with untreated metastatic colorectal cancer	**Capecitabine**	Yes
						Tegafur with uracil	Yes
TA100	CRC	**Capecitabine and oxaliplatin** in the adjuvant treatment of stage III (Dukes' C) colon cancer	26/04/2006	MTA	People with Dukes' stage C colon cancer after complete surgical resection of the primary tumour	**Oxaliplatin** in combination with 5-FU/FA	Yes
						Capecitabine	Yes
TA118	CRC	**Bevacizumab and cetuximab** for the treatment of metastatic colorectal cancer	24/01/2007	MTA	People with EGFR-expressing metastatic CRC who have previously failed on irinotecan-including therapy.	Second- or subsequent-line therapy using **cetuximab** in combination with irinotecan	No
					People with untreated metastatic CRC.	First-line therapy using **bevacizumab** in combination with 5-FU/FA or 5-FU/FA plus irinotecan	No

TA212	CRC	**Bevacizumab** in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer	15/12/2010	STA	People with metastatic colorectal cancer for whom oxaliplatin-including chemotherapy regimens are suitable	**Bevacizumab** in combination with oxaliplatin and either 5-FU or capecitabine	No
TA242	CRC	**Cetuximab, bevacizumab and panitumumab** for the treatment of metastatic colorectal cancer after first-line chemotherapy: **Cetuximab** (monotherapy or combination chemotherapy), **bevacizumab** (in combination with non-oxaliplatin chemotherapy) and **panitumumab** (monotherapy) for the treatment of metastatic	25/01/2020	MTA	People with mCRC that has progressed after first-line chemotherapy	**Cetuximab** (monotherapy or combination chemotherapy)	No
						Bevacizumab in combination with non-oxaliplatin chemotherapy	No
						Panitumumab monotherapy	No

		colorectal cancer after first-line chemotherapy					
TA307	CRC	**Aflibercept** in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy	25/03/2014	STA	People with mCRC that is resistant to or has progressed following prior oxaliplatin-based chemotherapy	**Aflibercept** in combination with FOLFIRI	No
TA405	CRC	**Trifluridine–tipiracil** for previously treated metastatic colorectal cancer	24/06/2016	STA	Adults with metastatic colorectal cancer whose disease has progressed after standard therapies or for whom standard therapies are unsuitable	Fixed dose combination of **trifluridine and tipiracil hydrochloride**	Yes
TA439	CRC	**Cetuximab and panitumumab** for	29/03/2017	MTA	Adults with previously untreated RAS wild-type metastatic colorectal cancer	**Panitumumab**, in combination with FOLFOX or FOLFIRI	Yes

		previously untreated metastatic colorectal cancer				**Cetuximab** in combination with FOLFOX or irinotecan-based chemotherapy	Yes
TA124	Lung	**Pemetrexed** for the treatment of non-small-cell lung cancer	22/08/2007	STA	Patients with locally advanced or metastatic NSCLC after prior chemotherapy	**Pemetrexed**	No
TA181	Lung	**Pemetrexed** for the first-line treatment of non-small-cell lung cancer	23/09/2009	STA	Patients with chemotherapy-naïve locally advanced or metastatic NSCLC other than predominantly squamous cell histology who are unsuitable for surgery.	**Pemetrexed** in combination with cisplatin	Yes
TA184	Lung	**Topotecan** for the treatment of relapsed small-cell lung cancer	25/11/2009	STA	Adults (≥18 years) with relapsed SCLC who responded to first-line treatment and for whom re-treatment with first-line therapy is not considered appropriate (due to contraindications, adverse effects).	**Topotecan**	Yes

TA190	Lung	**Pemetrexed** for the maintenance treatment of non-small-cell lung cancer	23/06/2010	STA	People with advanced or metastatic (stage IIIB and IV) NSCLC, other than those with predominantly squamous histology, whose disease has not progressed following treatment with platinum-based, first-line chemotherapy	**Pemetrexed**	Yes
TA192	Lung	**Gefitinib** for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer	28/07/2010	STA	People with previously untreated EGFR-TK mutation positive locally advanced or metastatic NSCLC	**Gefitinib**	Yes
TA227	Lung	**Erlotinib** monotherapy for maintenance treatment of non-small-cell lung cancer	29/06/2011	STA	People with advanced or metastatic (stage IIIB and IV) NSCLC whose disease has not progressed following treatment with platinum-based first-line chemotherapy	**Erlotinib** monotherapy	No
TA258	Lung	**Erlotinib** for the first-line treatment of locally advanced or metastatic	27/06/2012	STA	Adults with previously untreated EGFR-TK mutation positive locally	**Erlotinib** monotherapy	Yes

		EGFR-TK mutation-positive non-small-cell lung cancer			advanced or metastatic non-small-cell lung cancer		
TA310	Lung	**Afatinib** for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer	23/04/2014	STA	People with locally advanced or metastatic non-small cell lung cancer with positive epidermal growth factor receptor tyrosine kinase mutation TKI naive (first line) TKI pre-treated (after at least one line of chemotherapy and an EGFR TKI)	**Afatinib**	Yes
TA347	Lung	**Nintedanib** for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer	22/07/2015	STA	Patients with locally advanced, metastatic or recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy.	**Nintedanib**	Yes
TA374	Lung	**Erlotinib and gefitinib** for treating non-small-cell lung cancer that has progressed after prior chemotherapy	16/12/2015	MTA	Adults with locally advanced or metastatic NSCLC that has progressed following prior chemotherapy	**Gefitinib**	No
						Erlotinib	Yes

TA395	Lung	**Ceritinib** for previously treated anaplastic lymphoma kinase positive non-small-cell lung cancer	22/06/2016	STA	Adult patients with ALK positive non-small cell lung cancer previously treated with crizotinib	**Ceritinib**	Yes
TA402	Lung	**Pemetrexed** maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin	24/08/2016	STA	People with advanced or metastatic (stage IIIB and IV) NSCLC, other than predominately squamous histology, whose disease has not progressed following induction treatment with pemetrexed and cisplatin	**Pemetrexed**	Yes
TA403	Lung	**Ramucirumab** for previously treated locally advanced or metastatic non-small-cell lung cancer	24/08/2016	STA	People with locally advanced or metastatic non-small cell lung cancer (NSCLC) that has progressed after platinum-based chemotherapy.	**Ramucirumab** in combination with docetaxel	No
TA406	Lung	**Crizotinib** for untreated anaplastic lymphoma kinase-	28/09/2016	STA	People with untreated, ALK-positive, advanced NSCLC.	**Crizotinib**	Yes

		positive advanced non-small-cell lung cancer					
TA411	Lung	**Necitumumab** for untreated advanced or metastatic squamous non-small-cell lung cancer	28/09/2016	STA	People with untreated advanced, metastatic, squamous non-small cell lung cancer	**Necitumumab** in combination with gemcitabine and cisplatin	No
TA416	Lung	**Osimertinib** for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer	26/10/2016	STA	People with locally advanced or metastatic, EGFR and T790M mutation positive non-small cell lung cancer	**Osimertinib**	CDF
TA422	Lung	**Crizotinib** for previously treated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer	21/12/2016	STA	People with previously treated locally advanced or metastatic non-small-cell lung cancer that is positive for anaplastic lymphoma kinase fusion (ALK) genes.	**Crizotinib**	Yes
TA428	Lung	**Pembrolizumab** for treating PD-L1-positive non-small-	12/09/2017	STA	People with advanced non-small-cell lung cancer that is PD-L1 positive:	**Pembrolizumab**	Yes

		cell lung cancer after chemotherapy			- whose disease has progressed after platinum-containing doublet chemotherapy, or; - whose disease has progressed on both platinum-containing doublet chemotherapy and targeted therapy for EGFR or ALK positive tumours		
TA483	Lung	**Nivolumab** for previously treated squamous non-small-cell lung cancer	01/11/2017	STA	People with previously treated locally advanced or metastatic (stage IIIB or IV) squamous NSCLC	**Nivolumab**	CDF
TA484	Lung	**Nivolumab** for previously treated non-squamous non-small-cell lung cancer	01/11/2017	STA	People with previously treated non-squamous locally advanced or metastatic NSCLC	**Nivolumab**	CDF
TA500	Lung	**Ceritinib** for untreated ALK-positive non-small-cell lung cancer	24/01/2018	STA	People with untreated ALK+ advanced NSCLC	**Ceritinib**	Yes
TA520	Lung	**Atezolizumab** for treating locally advanced or	16/05/2018	STA	People with locally advanced or metastatic non-small-cell lung	**Atezolizumab**	Yes

		metastatic non-small-cell lung cancer after chemotherapy			cancer whose disease has progressed after chemotherapy		
TA529	Lung	**Crizotinib** for treating ROS1-positive advanced non-small-cell lung cancer	04/07/2018	STA	People with ROS1-positive advanced non-small cell lung cancer	**Crizotinib**	CDF
TA531	Lung	**Pembrolizumab** for untreated PD-L1-positive metastatic non-small-cell lung cancer	18/07/2018	STA	People with PD-L1 positive metastatic non-small cell lung cancer (NSCLC) not treated with chemotherapy in the metastatic setting	**Pembrolizumab**	Yes
TA536	Lung	**Alectinib** for untreated ALK-positive advanced non-small-cell lung cancer	08/08/2018	STA	Adults with untreated anaplastic lymphoma kinase positive (ALK-positive) advanced non-small cell lung cancer (NSCLC)	**Alectinib**	Yes
TA557	Lung	**Pembrolizumab** with pemetrexed and platinum chemotherapy for untreated,	10/01/2019	STA	Adults with untreated, metastatic, non-squamous non-small cell lung cancer (NSCLC)	**Pembrolizumab** plus chemotherapy	CDF

		metastatic, non-squamous non-small-cell lung cancer					
TA571	Lung	**Brigatinib** for treating ALK-positive advanced non-small-cell lung cancer after crizotinib	20/03/2019	STA	People with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib	**Brigatinib**	Yes
TA578	Lung	**Durvalumab** for treating locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation	01/05/2019	STA	Adults with locally advanced, unresectable non-small cell lung cancer (NSCLC) whose disease has not progressed after platinum-based chemoradiation therapy (CRT)	**Durvalumab**	CDF
TA584	Lung	**Atezolizumab** in combination for treating metastatic non-squamous non-small-cell lung cancer	05/06/2019	STA	People with untreated advanced, non-squamous NSCLC People with EGFR-or ALK-positive advanced, non-squamous NSCLC who were previously	**Atezolizumab** in combination with carboplatin plus paclitaxel with or without bevacizumab	Yes

					treated with targeted therapy (or cannot have a targeted therapy)		
TA595	Lung	**Dacomitinib** for untreated EGFR mutation-positive non-small-cell lung cancer	14/08/2019	STA	People with untreated locally advanced or metastatic NSCLC with EGFR activating mutation(s).	**Dacomitinib**	Yes
TA600	Lung	**Pembrolizumab** with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer	11/09/2019	STA	Adults with untreated metastatic squamous non-small-cell lung cancer (NSCLC)	**Pembrolizumab** in combination with: - carboplatin and paclitaxel - carboplatin and nab-paclitaxel	CDF
TA621	Lung	**Osimertinib** for untreated EGFR mutation-positive non-small-cell lung cancer	22/01/2020	STA	People with previously untreated locally advanced or metastatic, EGFR mutation positive non-small-cell lung cancer	**Osimertinib**	No
TA55	Ovarian	Guidance on the use of **paclitaxel** in the treatment of ovarian cancer	22/01/2003	STA	Women with ovarian cancer	**Paclitaxel** (alone or in combination with other drugs as part of a chemotherapy regimen)	Yes

TA284	Ovarian	**Bevacizumab** in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer	22/05/2013	STA	Women with newly diagnosed, stage III or IV ovarian cancer who have not received prior chemotherapy	**Bevacizumab** in combination with paclitaxel and carboplatin	No
TA285	Ovarian	**Bevacizumab** in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer	22/05/2013	STA	Women with recurrent platinum sensitive or partially platinum sensitive advanced epithelial ovarian, fallopian tube of primary peritoneal cancer	**Bevacizumab** in combination with gemcitabine and carboplatin	No
TA381	Ovarian	**Olaparib** for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent	27/01/2016	STA	Adult women with platinum-sensitive relapsed (PSR) BRCA-mutated (germline and/or somatic) high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or	**Olaparib**	Yes

		platinum-based chemotherapy			partial response) to platinum-based chemotherapy.		
TA389	Ovarian	**Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine** for treating recurrent ovarian cancer	27/04/2016	MTA	Women with ovarian cancer that has recurred after first line (or subsequent) platinum-based chemotherapy or that is refractory to platinum-based chemotherapy.	**Paclitaxel** alone or in combination with platinum chemotherapy	Yes
						Pegylated liposomal doxorubicin hydrochloride (PLDH) alone or in combination with platinum chemotherapy	Yes
						Gemcitabine in combination with carboplatin	No
						Trabectedin in combination with PLDH	No
						Topotecan	No
TA528	Ovarian	**Niraparib** for maintenance treatment of relapsed,	04/07/2018	STA	Women who have recurrent, platinum-sensitive ovarian,	**Niraparib**	CDF

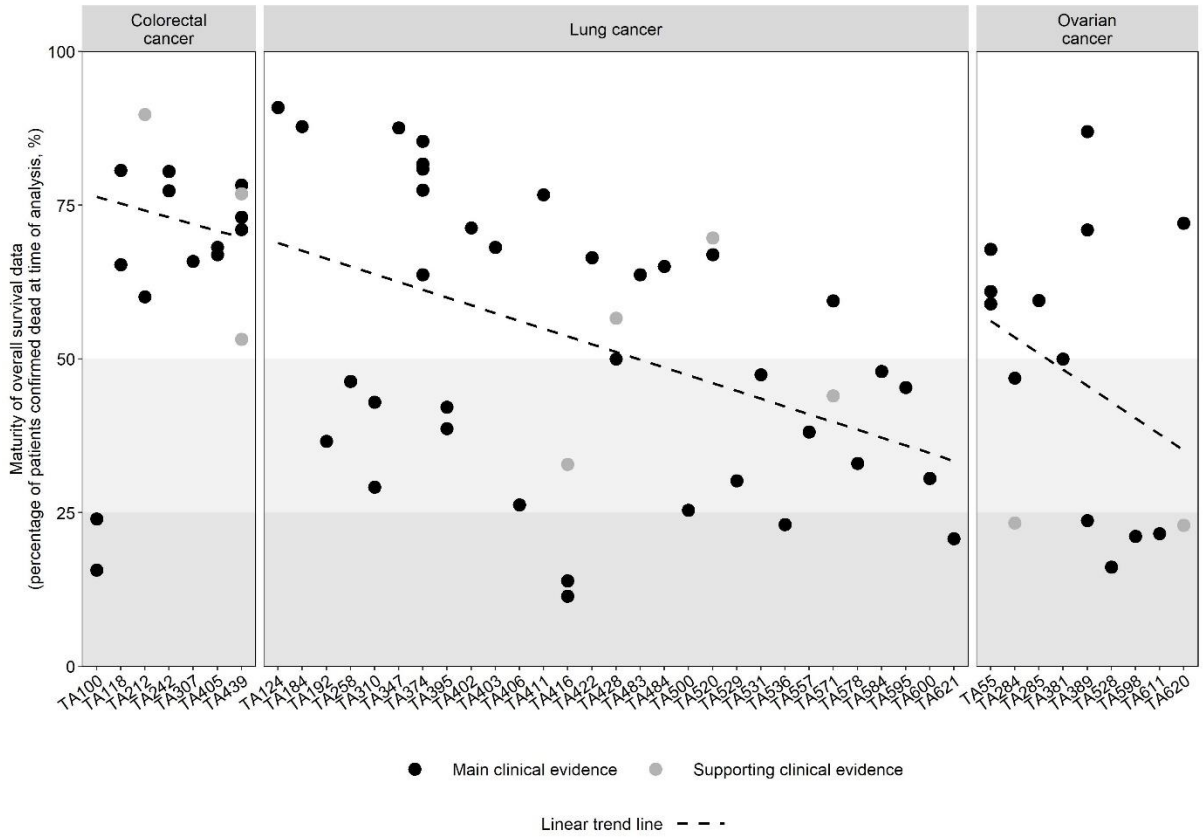
		platinum-sensitive ovarian, fallopian tube and peritoneal cancer			fallopian tube, or peritoneal cancer that has responded to the most recent course of platinum-based chemotherapy		
TA598	Ovarian	**Olaparib** for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy	28/08/2019	STA	Women with newly diagnosed BRCA mutated advanced ovarian, fallopian tube or peritoneal cancer, who are in response (complete or partial) to first line platinum-based chemotherapy	**Olaparib**	CDF
TA611	Ovarian	**Rucaparib** for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer	13/11/2019	STA	Women with platinum sensitive relapsed highgrade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.	**Rucaparib**	CDF

TA620	Ovarian	**Olaparib** for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer	15/01/2020	STA	Women who have platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube or peritoneal cancer that is in response (complete or partial) to platinum-based chemotherapy	**Olaparib**	Yes/CDF

5-FU/FA: 5-fluorouracil and folinic acid; ALK: anaplastic lymphoma kinase; BRCA: BReast CAncer gene; CDF: cancer drugs fund; CRC: colorectal cancer DNA: deoxyribonucleic acid; EGFR: epidermal growth factor receptor; EGFR-TK: epidermal growth factor receptor tyrosine kinase; FIGO: international federation of gynaecology and obstetrics; FOLFIRI: 5 fluorouracil, folinic acid and irinotecan; FOLFOX: 5 fluorouracil, folinic acid and oxaliplatin; mCRC: metastatic colorectal cancer; MTA: multiple technology appraisal; NHS: national health service; NSCLC: non-small-cell lung cancer; PD-L1; programmed death-ligand 1; PLDH: pegylated liposomal doxorubicin hydrochloride; PSR: platinum-sensitive relapsed; ROS1: ROS proto-oncogene 1, receptor tyrosine kinase; SCLC: small-cell lung cancer; STA: single technology appraisal; VEGF: vascular endothelial growth factor

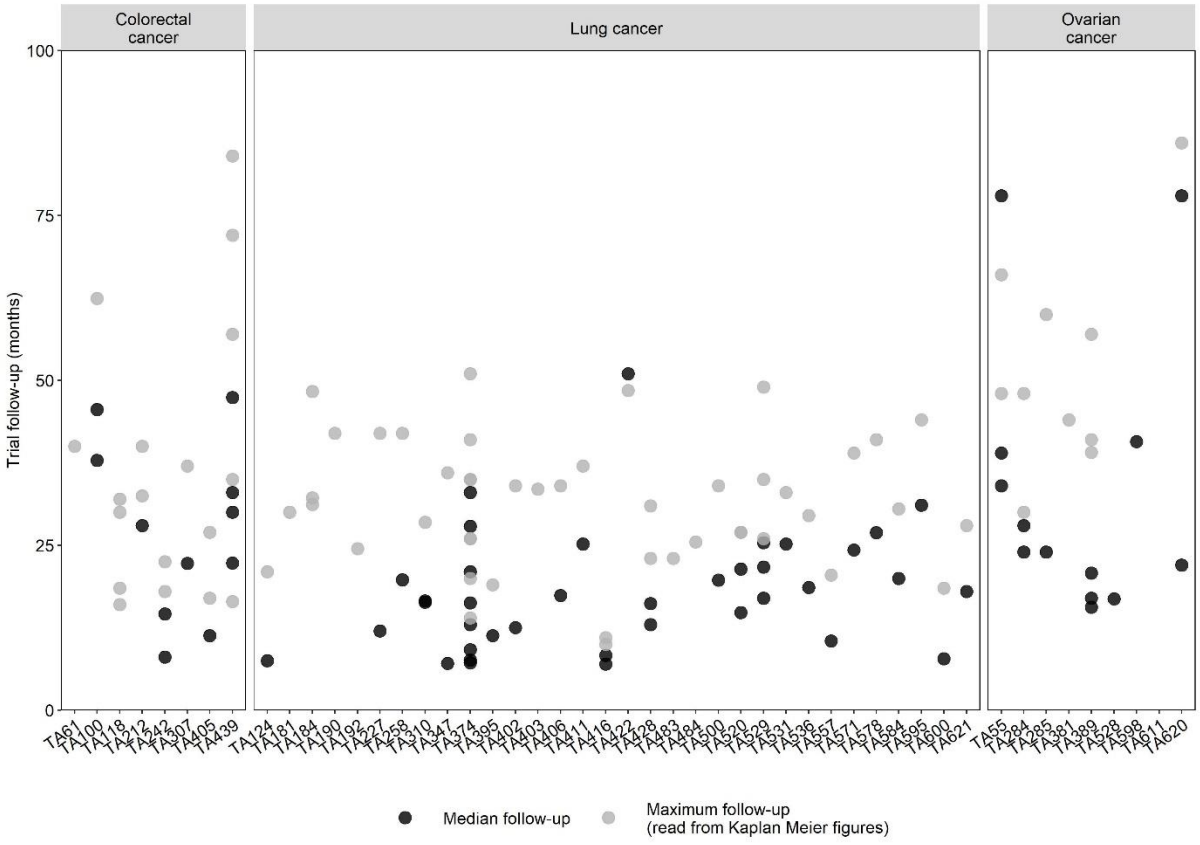
*Targeted therapies in the 'Technologies' column are shaded grey

Supplemental Appendix 4



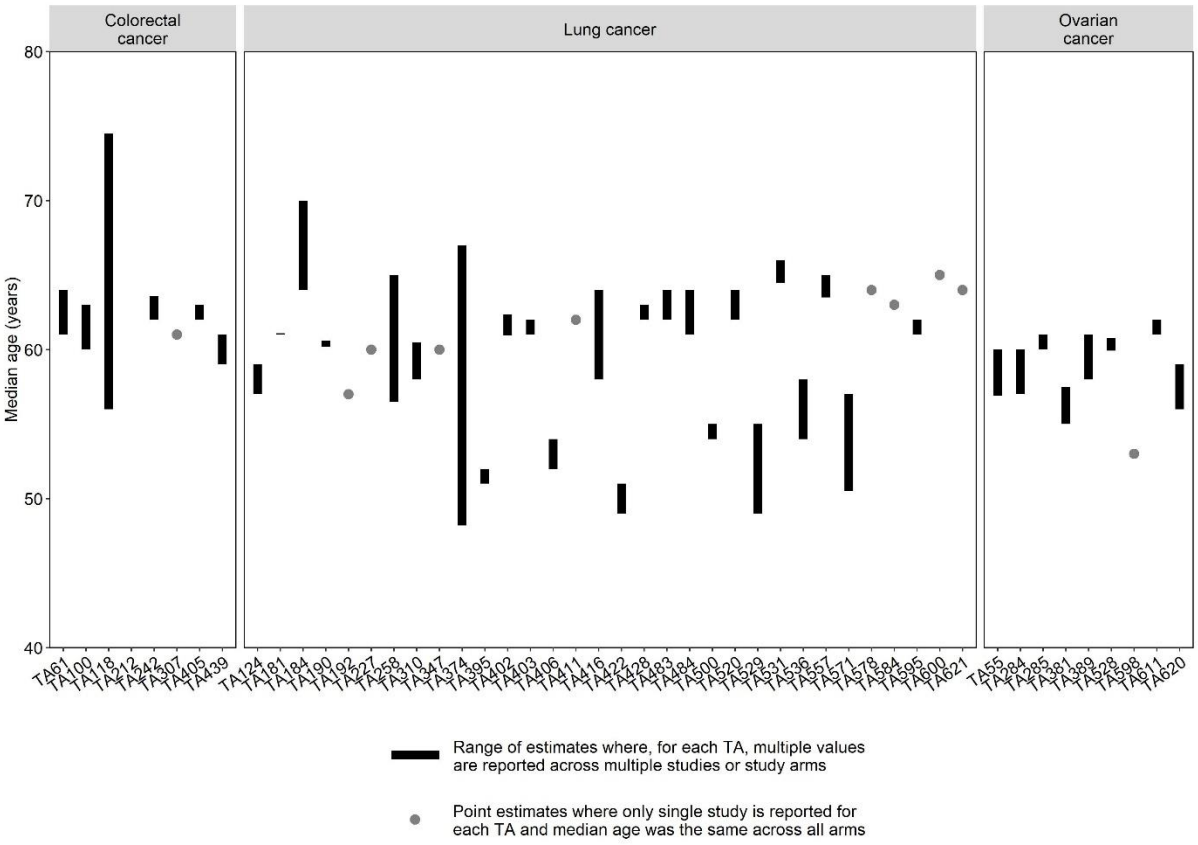
Appendix Figure: Maturity of data from which economic analyses were based

[*Points represent the proportion of confirmed events that had occurred at the time of analysis; the intervention arm of the trial was used where available – if this was not available the whole trial population was used; trend line for colorectal cancer ignores TA100 as outliers – with these included the trend line observes a positive correlation*]

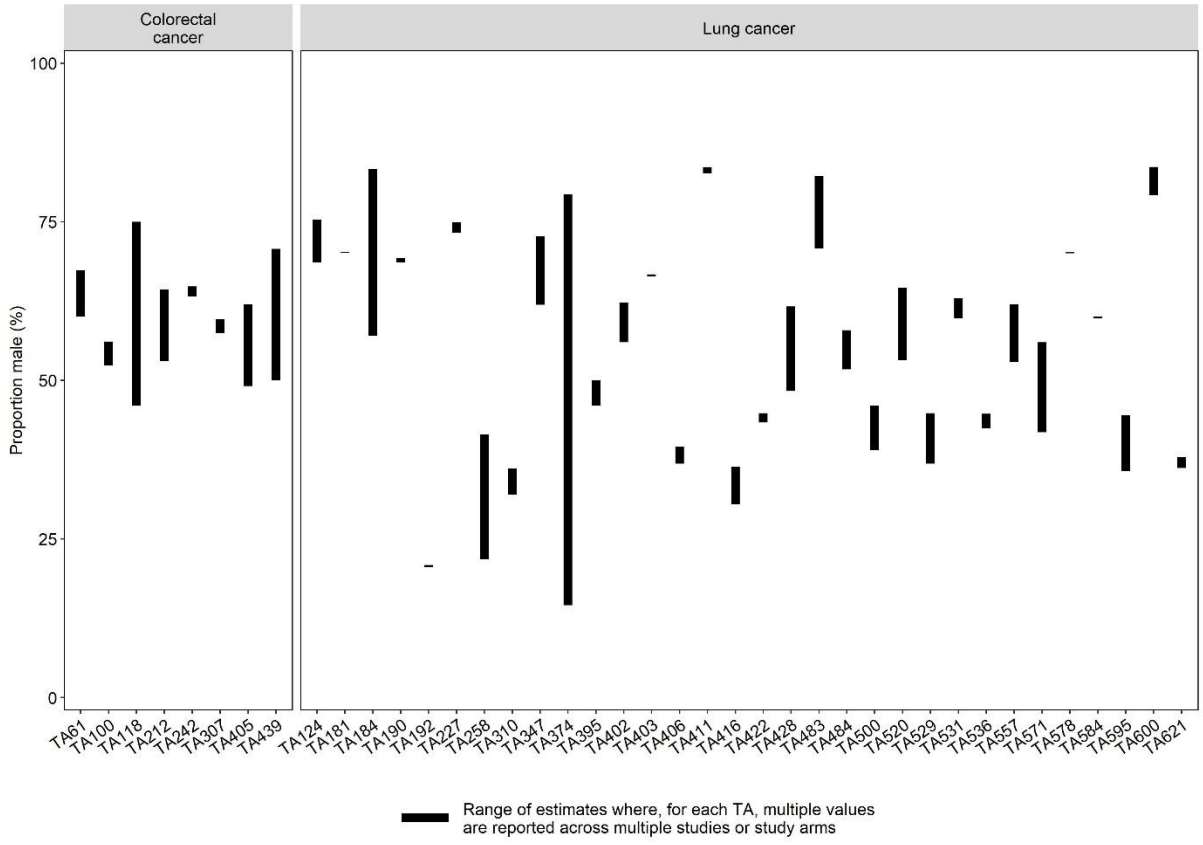


Appendix Figure: Length of clinical study follow-up

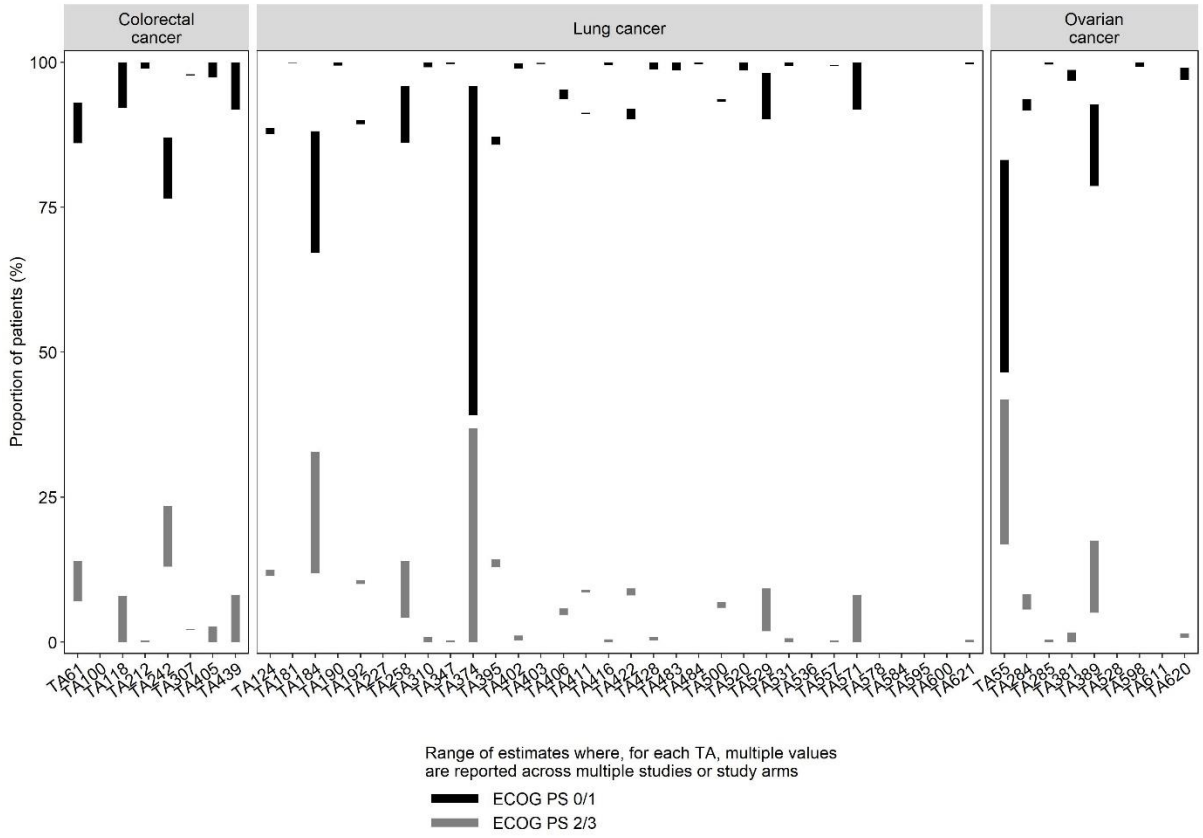
Supplemental Appendix 5



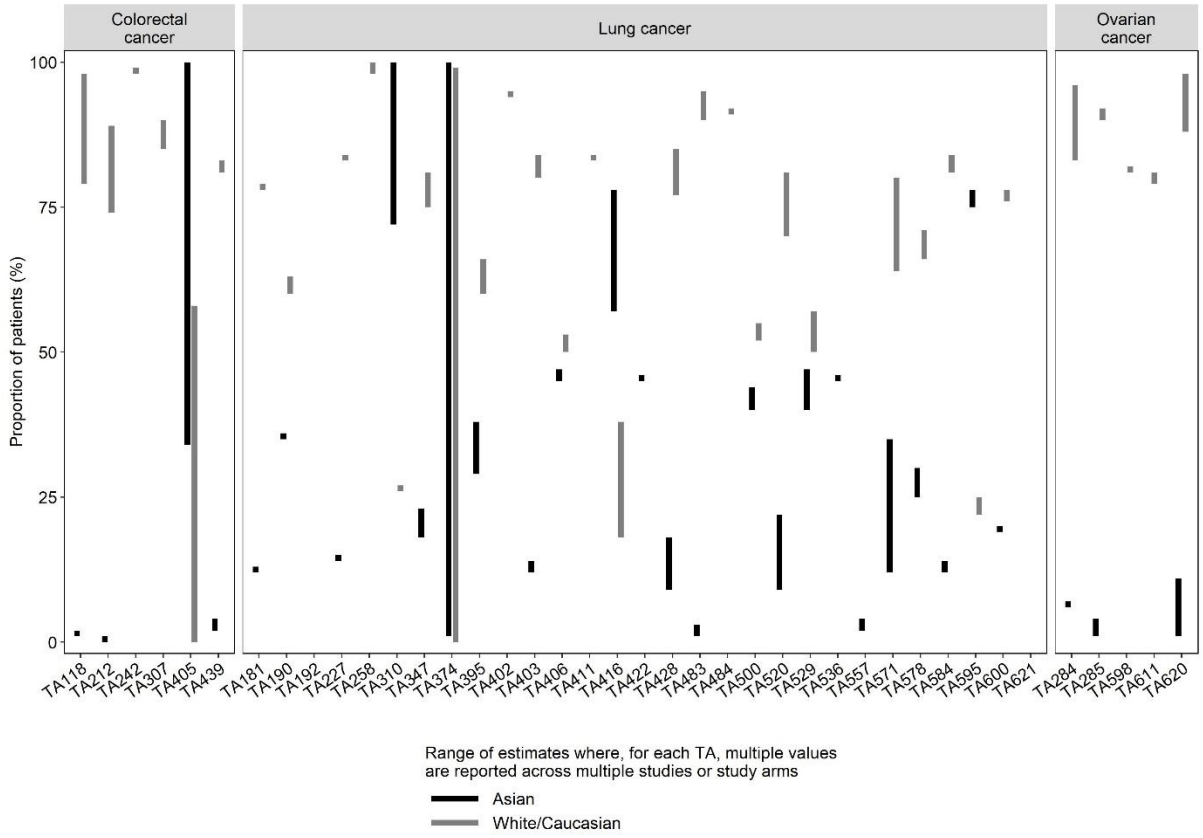
Appendix Figure: Median ages of trial participants reported in pivotal clinical studies



Appendix Figure: Proportion of patients that are male in pivotal clinical trials



Appendix Figure: Proportion of patients that have an ECOG PS of 0-1 or 2-3 in pivotal clinical studies



Appendix Figure: Proportion of patients that are Asian or White/Caucasian in pivotal clinical studies