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Cancer survival extension from drug treatments

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Abstract

Cancer causes one in four of all deaths in the UK. Advances in biologic and pharmaceutical therapies over recent years have increased achievable survival gain in most life-limiting cancers, ranging from modest incremental improvements to step changes in life expectancy. The realised and anticipated impact of treatment advances on survival is of wide-ranging interest, from informing decisions about healthcare to understanding influences on mortality trends. This paper presents an overview of evidence for survival extension from a range of therapies that have become available in recent years for the treatment of lung, colorectal and breast cancer. The evidence considered includes short-term empirical evidence from clinical trials as well as longer-term estimates from models extrapolating over a lifetime horizon. The core data source is the evidence base supporting guidance published by the National Institute for Health and Care Excellence (NICE), UK. This evidence has already been subject to appraisal by NICE; the aim of this paper is to collate the existing estimates submitted to NICE in order to appreciate the wide range in survival extension resulting from systematically identified cancer treatments.

Keywords

cancer; survival; mortality; individualized risk; health technology assessment (HTA); comparative effectiveness research (CER)

1 Introduction

1.1 There is considerable interest in the ability of treatments to extend survival and improve quality of life for those living with cancer. This paper will explore the evidence of survival extension from a range of drugs that have come into use in recent years. In the UK, the National Institute for Health and Care Excellence (NICE) issues guidance on the clinical and cost effectiveness of treatments, which are often new drugs appraised soon after coming to market, or existing drugs with new indications. The evidence base supporting NICE guidance includes empirical evidence from clinical trials as well as longer-term estimates from models extrapolating beyond the clinical trial period to a lifetime horizon. This overview collates results on survival gain by cancer site, for drugs that were recommended as treatment options in England and Wales from 2005 to 2010. The focus will be on lung, colorectal and breast cancers, which collectively account for approximately 40% of all annual cancer deaths in the UK, where 1 in 4 deaths are due to cancer. The treatments considered in this overview are each suitable only for specific subpopulations, in accordance with the marketing authorisation[†] and NICE

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[†] Medicines which meet the standards of safety, quality and efficacy are granted a marketing authorisation (previously a product licence), which is normally necessary before they can be prescribed or sold (MHRA, 2012).

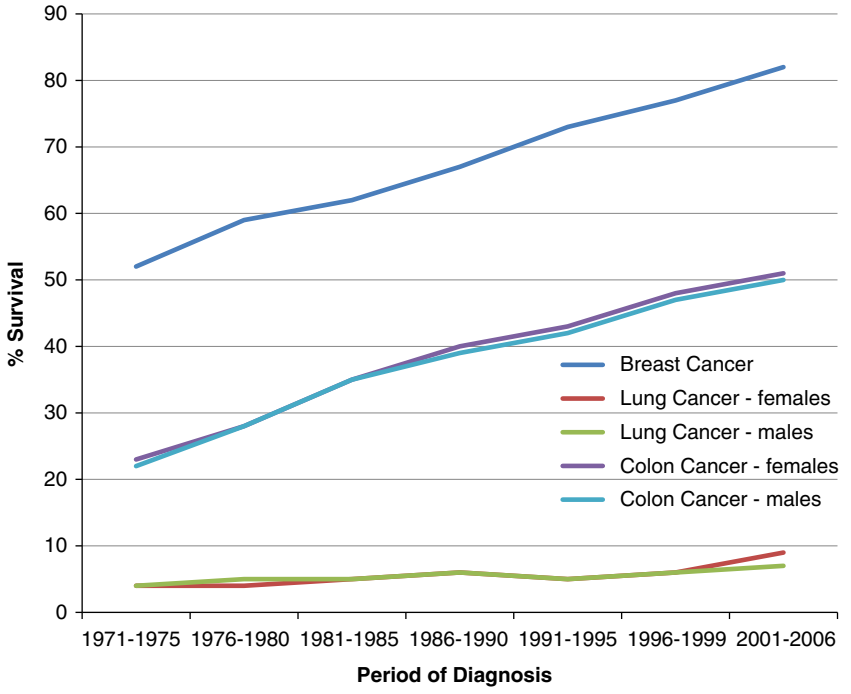

Figure 1. Comparison of lung, colon and breast cancer 5-year standardised survival rate by period of diagnosis, 1971–2006, England and Wales (Source: data collated by Cancer Research UK (2011) derived from data from the Office for National Statistics).

recommendations. The heterogeneity between these subpopulations limits the scope for quantitative synthesis of the survival impact across treatments for the same cancer site. However, the findings of this overview can contribute to an overall picture of the impact of drug treatments on cancer survival.

2 Background

2.2 Relative survival of people with colon and breast cancer has been improving, but there has been no significant change for lung cancer. Improvements have resulted from a combination of factors such as earlier stage at presentation, improvements in integration of multidisciplinary care, lifestyle factors and treatment advances. Some studies have explored the impact on survival of advances in diagnosis and treatment in recent time periods, for example in breast cancer (Woods *et al.*, 2007), but the contribution attributable to drug treatment developments remains unclear. Figure 1 shows age-standardised 5-year relative survival rates for lung, colon and breast cancer by period of diagnosis, 1971–2006, England and Wales. These survival data are based on the analysis of cancer incidence and mortality data produced by the Office for National Statistics.

3 The National Institute for Health and Care Excellence (NICE)

3.1 NICE is an independent organization responsible for providing national guidance on promoting good health and preventing and treating ill health. It produces guidance on public health, health technologies (pharmaceuticals, interventional procedures, devices and diagnostics) and

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clinical practice. NICE was established in 1999 following concerns regarding 'post-code prescribing' (NICE, 2012a). Plainly, the NHS, like all health care systems, cannot afford every health care intervention for everyone, and so decisions about allocating health care resources must be made. Guidance, taking into account evidence-based evaluation of the comparative effectiveness of treatments, is developed in order to ensure equal access and high-quality care for everyone regardless of where they live.

3.2 Technology Appraisal Guidance provides recommendations on the use of new and existing medicines and treatments within the National Health Service (NHS). Approximately 40% of the technologies appraised by NICE are indicated for cancer and the majority of these are pharmaceuticals (Trowman *et al.*, 2011). The evaluation process usually has 2 components; a systematic review of the clinical evidence and an economic evaluation. These components address the following questions:

- *How well does the technology work compared with current NHS practice?*
- *How well does the technology work in relation to how much it costs compared with current NHS practice? Does it represent value for money?*

3.3 The resulting guidance may recommend use of the treatment in one or more of several ways: in line with clinical practice, in line with the marketing authorization, optimized use in specific circumstances, use only in the context of research, or not recommended. All recommendations are issued with a date by which they will be considered for review, which is typically three years from the date of publication (NICE, 2012b).

3.4 NICE appraisals and recommendations are quite distinct from marketing authorisation, which is under the remit of the European Medicines Agency (EMA). The EMA is a decentralised body of the European Union. Its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use, ('centralised procedure'). Under the centralised procedure, companies submit a single marketing-authorisation application to the Agency. Once granted by the European Commission, a centralised (or 'Community') marketing authorisation is valid in all European Union (EU) and EEA-EFTA states (Iceland, Liechtenstein and Norway) (EMA, 2011). Therefore, whilst a pharmaceutical product may have been granted a marketing authorisation, it may not be recommended for use, or have more limited recommendations for use, in England and Wales by NICE.

4 Methods

4.1 NICE Technology Appraisal Guidance documents recommending use of pharmaceutical treatments for lung, colorectal and breast cancer issued between 2005 through to 2010 were collated. The corresponding evidential documents in the public domain were used as a source to obtain estimates of survival gain associated with the new treatments under appraisal compared with alternative comparator treatments. The documents available from each appraisal vary according to the process followed to produce the guidance (NICE, 2012b).

4.2 For appraisals developed using the Single Technology Appraisals Process, the source documents used were the Manufacturer/Sponsor submission, the Evidence Review Group report and the final guidance document. For appraisals developed using the Multiple Technology Appraisal Process, the

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source documents used were the Executive Summary of manufacturers' submissions, the Assessment Report and the final guidance document.

4.3 NICE has to make decisions across different technologies and disease areas. It is, therefore, crucial that analyses of clinical and cost effectiveness undertaken to inform the appraisal adopt a consistent approach. To allow this, NICE has defined a 'reference case' that specifies the methods considered by the Institute to be the most appropriate for its decisions (NICE, 2008c). Despite this standardised approach, the most plausible estimates for magnitude of effect are often unclear, and subject to opinion and debate. Reasons that may call numerical results into question include those arising from the decision problem (such as whether there is evidence comparing the appraised drug with a suitable comparator); clinical trial design (such as treatment protocols, randomisation, outcome measurement); evaluating multiple clinical trials with varying results; and questions of generalisability to populations broader than those in clinical trials. Results from models extrapolating beyond the trial period include additional sources for uncertainty, such as requiring assumptions about the long-term beneficial and adverse effects of new compared with existing treatments.

4.4 The NICE Guide to the Methods of Technology Appraisals 2008 describes that cost effectiveness results should reflect the present value of the stream of costs and benefits accruing over the time horizon of the analysis, using discounting. It further indicates that for the reference case an annual discount rate of 3.5% should be used for both costs and benefits; based on the recommendations of the UK Treasury (NICE, 2008c). The HM Treasury Green Book (HM Treasury, 2011) states that discounting is a technique used to compare costs and benefits that occur in different time periods, is a separate concept from inflation, and is based on the principle that, generally, people prefer to receive goods and services now rather than later. This is known as 'time preference'. The mathematical expressions used to calculate discounted present values are set out as follows:

Year 0 is the present. Accordingly, the present value, at the middle of year 0, of a payment of £1 made at the middle of year n is given by:

$$Dn = 1/[(1 + r)^n]$$

where r is the discount rate and Dn is the discount factor.

Where possible, undiscounted figures have been extracted for the purposes of this overview, since our interest here is in estimating life extension, and consideration of the time preference that people may place on that extension is beyond the scope of this work. Occasionally only discounted figures were reported; in these cases this has been detailed in the data extraction tables.

4.5 In this overview, for the purposes of consistency and clarity, the data extracted for overall survival has been taken from pivotal trials (usually those designed for regulatory assessment) and from the base case results of economic models in manufacturer/sponsor submissions. In occasional cases, it is clear from the documentation that alternative data are more suitable for use in this overview, such as when the most relevant comparator in current clinical practice differs from that in the pivotal trial.

5 Findings

5.1 The overall survival results and details of where in the source documents these data have been extracted from are summarized in Tables 1, 2 and 3. The results from clinical trials, presented as

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Table 1. Data extraction table from NICE appraisals for lung cancer with positive recommendations, 2005–2010.

Drug/Guidance Number/ Year issued	Recommendations* and size of eligible population**	Data extracted for overall survival extension (based on clinical trials)	Data extracted for estimated life years gained (based on models)
Erlotinib /Technology Appraisal No.162/2008 (NICE, 2008a)	An alternative to docetaxel as a second-line treatment option for patients with non-small-cell lung cancer (NSCLC) Size of eligible population: not reported	In the BR21 trial, (Shepherd *et al.*, 2005), erlotinib was compared with placebo (plus best supportive care in both arms [ie. In both the treatment and placebo groups]). Median overall survival was longer in the erlotinib group (6.7 months, 95% confidence interval [CI] [5.5 to 7.8] than in the placebo group, 4.7 months). HR 0.70, 95% CI (0.58 to 0.85), $P < 0.001$.	In the economic model, erlotinib was compared with docetaxel, an active comparator indicated for use in the same patient group. Overall survival (OS) for both docetaxel and erlotinib was assumed to be equivalent and was based on the mean overall survival (time to last observation) for erlotinib from the BR21 trial (Shepherd *et al.*, 2005) (9.03 months).
Pemetrexed/Technology Appraisal No.181/2009 (NICE, 2009a)	First-line treatment of non-squamous NSCLC Size of eligible population: not reported	In the JMDB* trial (Scagliotti *et al.*, 2008) the superiority of pemetrexed/cisplatin on the primary outcome of overall survival (OS) was compared with gemcitabine/cisplatin: a median overall survival of 11.0 months compared to 10.1 months was reported; adjusted hazard ratio (HR) = 0.84 95% (CI 0.74 to 0.96), p = 0.011.	Histopathological types: Adenocarcinoma, pemetrexed/cisplatin 1.31 years (15.7 months) vs. gemcitabine/cisplatin 1.16 years (13.9 months) Large cell: pemetrexed/cisplatin 1.09 years (13.08 months) vs. gemcitabine/cisplatin 0.72 years (8.64 months) (NICE, 2008b) Manufacturer/Sponsor Submission Table 56, p.102. Results based on JMDB trial)
Pemetrexed/Technology Appraisal No.190/2010 (NICE, 2010a)	Maintenance for locally advanced or metastatic NSCLC Size of eligible population: 1474	JMEN*** trial – (Ciuleanu *et al.*, 2009) Median progression-free survival was significantly longer with pemetrexed plus best supportive care compared with placebo plus best supportive care (4.5 months versus 2.6 months, hazard ratio [HR] 0.44 The JMEN***(Ciuleanu *et al.*, 2009) trial demonstrated a statistically significant median overall survival benefit of 5.2 months for the non-squamous population in favour of pemetrexed compared with placebo (15.5 months versus 10.3 months, HR 0.70, 95% [CI 0.56 to 0.88], p = 0.002) For the non-squamous population, 1-year overall survival in the pemetrexed plus best supportive care arm was 60% compared with 42% in the placebo arm. The difference in overall survival was smaller at 2 years (28% for pemetrexed compared with 22% for placebo).	Pemetrexed 1.70 years (20.4 months) vs Placebo 1.26 years (15.12 months) (NICE, 2009b) Manufacturer /Sponsor Submission: Table 37, p.106)

Table 1 *(Continued)*

Drug/Guidance Number/ Year issued	Recommendations* and size of eligible population**	Data extracted for overall survival extension (based on clinical trials)	Data extracted for estimated life years gained (based on models)
Topotecan/Technology Appraisal No.184/2009 (NICE, 2009c)	Oral topotecan is recommended as a treatment option for people with relapsed small-cell lung cancer for whom re-treatment with the first-line regimen is not considered appropriate and the combination of cyclophosphamide, doxorubicin and vincristine (CAV) is contraindicated Size of eligible population: 315	In one randomised controlled trial, (RCT), (O'Brien *et al.*, 2006), with overall survival (OS) as the primary outcome, there was a statistically significant benefit in favour of oral topotecan plus best supportive care (BSC) compared with BSC alone [median difference 12 weeks; HR 0.61, 95% [CI 0.43 to 0.87], $p = 0.01$] Median survival with BSC was 13.9 weeks (95% CI, [11.1 to 18.6]) and with topotecan, 25.9 weeks (95% CI, 18.3 to 31.6)	Oral topotecan plus best supportive care 0.8 life years (9.6 months) gained vs. Best supportive care alone 0.5 life years (5.7 months) gained (Loveman *et al.*, 2010)
Gefitinib/Technology Appraisal No.192/2010 (NICE, 2010b)	First-line treatment of people with locally advanced or metastatic NSCLC if they test positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation Size of eligible population: 404	Iressa Pan Asian Study (IPASS) (Mok *et al.*, 2009) - patients randomised to receive gefitinib had a statistically significantly longer progression-free survival compared with patients randomised to receive paclitaxel and carboplatin. The hazard ratio (HR) for progression-free survival (gefitinib compared with paclitaxel and carboplatin) was 0.74 The estimates of overall survival in the overall study population were similar for both groups (HR for gefitinib compared with paclitaxel and carboplatin 0.91, 95% CI [0.76 to 1.10])	Gefitinib EGFR M+ 25.9 months mean overall survival vs. paclitaxel/carboplatin 22.6 months mean overall survival (NICE, 2010c) (Manufacturer/Sponsor submission Table 33, p.104)

*Recommendations as stated in patient version of guidance, 'Understanding NICE Guidance'
** Size of eligible population sourced from NICE Costing Templates, where available (Costing Templates are not produced for all Technology Appraisals)
*** Where no explanation is given of trial name abbreviations, assume that the abbreviation used has no direct translation

Table 2. Data extraction table from NICE appraisals for colorectal cancer with positive recommendations, 2005-2010

Drug/Guidance Number/Year issued	Recommendations* and size of eligible population**	Data extracted for overall survival extension (based on clinical trials)	Data extracted for estimated life years gained (based on models)
Cetuximab/TA 176/2009 (NICE, 2009d)	Cetuximab given with other drugs called 5-fluorouracil, folinic acid and oxaliplatin (FOLFOX) is recommended as a possible first treatment for people with metastatic colorectal cancer only when: ● surgery to remove the cancer in the colon or rectum has been carried out or is not possible ● the metastases are only in the liver and cannot be removed surgically before treatment ● the person is fit enough to have surgery to remove the cancer in the colon or rectum and to have liver surgery if it becomes possible to remove the metastases after cetuximab treatment ● the manufacturer refunds 16% of the amount of cetuximab used on a per patient basis. Cetuximab given with 5-fluorouracil, folinic acid and irinotecan (FOLFIRI) is recommended as a possible first treatment for people with metastatic colorectal cancer only when: ● surgery to remove the cancer in the colon or rectum has been carried out or is possible ● the metastases are only in the liver and cannot be removed surgically before treatment ● the person is fit enough to have surgery to remove the cancer in the colon or rectum and to have liver surgery if it becomes possible to remove the metastases after cetuximab treatment ● the person cannot take oxaliplatin because of its side effects or contraindications.	The Cetuximab Combined With Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer Trial – (**CRYSTAL**) (Van Cutsem *et al.*, 2007) A Phase III, multicentre, open-label randomised controlled trial, which compared cetuximab in combination with FOLFIRI or with FOLFIRI alone, and examined progression-free survival as the primary outcome. The overall survival (median follow-up 30 months) was 24.9 months (95% CI 22.2 to 27.8) for cetuximab in combination with FOLFIRI compared with 21.0 months (95% CI 19.2 to 25.7) for FOLFIRI alone (HR = 0.84, 95% CI [0.64 to 1.11])	2.28 years (27.36 months) vs. 1.92 years (23.04 months) (Cetuximab+ 5-fluorouracil, folinic acid and irinotecan (FOLFIRI) compared with FOLFIRI alone), (Meads, *et al.*, 2008) (from page 52 of Evidence Review Group report)

Table 2 *(Continued)*

Drug/Guidance Number/Year issued	Recommendations* and size of eligible population**	Data extracted for overall survival extension (based on clinical trials)	Data extracted for estimated life years gained (based on models)
	Treatment with cetuximab should stop after 16 weeks and the person should be assessed to see if they can have surgery to remove the metastases in their liver. People with metastases only in the liver who receive cetuximab should have their treatment managed only by multidisciplinary teams that involve highly specialised liver surgical services. Estimated number eligible for treatment = 1420		
Irinotecan, Oxaliplatin & Raltitrexed/TA 93 (Review of TA 33) (NICE, 2005) NB: This guidance has now updated and replaced by NICE clinical guideline 131 (CG131) on colorectal cancer (NICE, 2011)	Irinotecan and oxaliplatin, within their licensed indications, are recommended as treatment options for people with advanced colorectal cancer as follows: ● irinotecan in combination with 5-fluorouracil and folinic acid (5-FU/FA) as first-line therapy, or irinotecan alone in subsequent therapy ● oxaliplatin in combination with 5-fluorouracil and folinic acid as first-line or subsequent therapy. Raltitrexed is not recommended for the treatment of patients with advanced colorectal cancer. Its use for this patient group should be confined to appropriately-designed clinical studies. Estimated number eligible for treatment : not reported	In trials that compared the first-line combination of irinotecan with 5-FU/FA alone, median overall survival was improved by between 2.2 and 3.3 months and median progression-free survival by between 2.1 and 2.7 months. A meta-analysis conducted by the Assessment Group included four trials (2340 participants) and demonstrated a significantly better overall survival for irinotecan in combination with 5-FU/FA compared with 5-FU/FA alone; with a hazard ratio (HR) of 0.84 (95% [CI 0.76–0.93]). The addition of oxaliplatin to first-line 5-FU/FA had no statistically significant effect on median overall survival in the individual studies or in the meta-analysis (1939 participants) conducted by the Assessment Group (HR 0.93; [CI 0.83–1.03]) The difference in median overall survival was not significant in studies assessing first-line raltitrexed. In the analysis of overall survival the direction of effect favoured 5-FU, rather than raltitrexed, although the effect was not significant (HR = 1.10, 95% CI 0.97 to 1.25, p = 0.14).	No suitable source data from this appraisal was identified.

Table 2 *(Continued)*

Capecitabine and oxaliplatin/ TA 100/2006 (NICE, 2006a)	Capecitabine and oxaliplatin are recommended as possible adjuvant treatments after surgery for stage III (Dukes' C) colon cancer, when used in the following ways: ● capecitabine on its own ● oxaliplatin together with 5-fluorouracil and folinic acid. The choice of treatment should be decided jointly by the individual and their doctors, after they have discussed the options. This discussion should cover any contraindications to the treatments (reasons why a particular medicine might not be suitable for the person), the possible side effects of the treatments, and the different ways they can be given. It should also take into account the person's clinical condition and individual preferences. Estimated number eligible for treatment : not reported	Patients with stage III colon cancer only: analysis by subgroup in the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC), (Schmoll *et al.*, 2005) trial found that the majority of the patients who died (after a median follow-up of approximately 37.9 months) had stage III colon cancer. In this subpopulation, no statistically significant differences in overall survival were observed between the two treatment groups (hazard ratio for death, 0.86 [95% CI: 0.66 to 1.11]). These results were confirmed with longer follow-up (hazard ratio for death after a median follow-up 47 months, 0.86 [95% CI: 0.68 to 1.08]; p = 0.196). Overall survival data were not mature at the time of the primary (specified) and secondary (ad hoc) analysis. In the intention-to-treat population, no statistically significant differences were observed in overall survival between the two groups (p = 0.07 for superiority), however, 804 (80%) patients in the capecitabine group were alive at 3.8 years (median-follow-up) in comparison to 756 (77%) in the 5-fluorouracil/leucovorin (5-FU/LV) group. Secondary ad hoc analyses showed that after a median follow-up of 4.4 years (with minimum follow-up of three years for all patients), 763 (76%) patients in the capecitabine group were alive in comparison to 718 (73%) patients in the 5-FU/LV group, corresponding to a 12% reduction in the risk of death (hazard ratio of 0.88; 95% CI: [0.74 to 1.05]).	Capecitabine: 10.88 years (131 months) vs. 9.87 years (118 months) years, base case, discounted, (The School of Health and Related Research (ScHARR), 2005) (page 132 of Assessment Report) Oxaliplatin (in FOLFOX regimen) : 12.15 years (146 months) vs. 10.80 years (130 months)

*Recommendations as stated in patient version of guidance, 'Understanding NICE Guidance'
** Size of eligible population sourced from NICE Costing Templates, where available (Costing Templates are not produced for all Technology Appraisals)
*** Where no explanation is given of trial name abbreviations, assume that the abbreviation used has no direct translation

Table 3. Data extraction table from NICE appraisals for breast cancer with positive recommendations, 2005-2010

Drug/Guidance Number/ Year issued	Recommendations* and size of eligible population**	Data extracted for overall survival extension (based on clinical trials) (HR = Hazard Ratio)	Data extracted for estimated life years gained (based on models)
Trastuzumab/TA 107/2006 (NICE, 2006b)	Adjuvant treatment of early-stage Human Epidermal Growth Factor Receptor 2 (HER2) positive breast cancer Size of eligible population: 4532	The Herceptin Adjuvant Trial (HERA) (Smith *et al.*, 2007), considered to provide the primary source of evidence. HR for death 0.75 (95% CI, 0.47 – 1.21) - not significant 'due to' small number of deaths and short median follow up time as at time of NICE submission in February 2006. Subsequently, a systematic review and meta-analysis based on data from 5 trials, 9.739 patients had combined results of: relative risk of death 0.66 (95% CI, [0.57 – 0.77]), $p < .0001$,	Trastuzumab 21.45 months vs. no trastuzumab 16.65 months (undiscounted) (NICE, 2006c) (Table 25 & 26 of Manufacturer/Sponsor Submission)
Docetaxel/TA 109/2006 (NICE, 2006d)	Adjuvant treatment for early node-positive breast cancer Size of eligible population: 8828	The Breast Cancer International Research Group, (Martin *et al.*, 2005), compared **TAC** (docetaxel+doxorubicin+cyclophosphamide) regimen vs. **FAC** (fluorouracil + doxorubicin + cyclophosphamide) regimen. Overall survival at 5 years: 87% vs. 81%, HR 0.70, (95% CI, 0.53, 0.93), $p = 0.008$. NB. The docetaxel regimen in the study was not what would be used in clinical practice in the UK (which would be fluorouracil + epirubicin + cyclophosphamide (FEC) The comparator (FAC) differed from regimens used in practice (FEC or epirubicin + cyclophosphamide + methotrexate + fluorouracil [ECMF]).	TAC 10.9 years (131 months) vs. FAC 10.2 years(122 months) (Manufacturer/Sponsor submission base case results, Table 61 p.134)

Table 3 *(Continued)*

Anastrozole/TA 112 Letrozole/TA 112/2006 Exemestane/TA 112 (NICE, 2006e)	**Anastrozole** - Adjuvant treatment of early oestrogen-receptor-positive breast cancer – primary adjuvant therapy Size of eligible population: 18,857	**Anastrozole** – Arimidex, Tamoxifen, Alone or in Combination Trial (ATAC Trial) (ATAC Trialists Group, 2004) – compared anastrozole with tamoxifen. HR for death: 0.97 (95% CI, 0.83 to 1.14). (Table 13 of HTA monograph, hormone-receptor positive) Note: Executive summary of Manufacturer/Sponsor submission states that overall survival similar for both treatment groups but anastrozole showed a numerical advantage relative to tamoxifen in time to death following recurrence; HR 0.87; CI 0.70 – 1.09, p = 0.2249, and notes that similar overall survival in both arms is not surprising given the relatively low-risk population in the ATAC and patient age (leading to 40% of deaths being unrelated to recurrence). Previous tamoxifen studies have taken up to 10 years to show a survival advantage over placebo.	Anastrozole 12.85 years (154 months) vs. with tamoxifen 12.77 years (153 months) (HTA monograph, Table 37, Assessment Group base case, primary adjuvant setting, discounted at 1.5%.)
	Exemestane - Adjuvant treatment of early oestrogen-receptor-positive breast cancer—adjuvant therapy following 2–3 years of adjuvant tamoxifen therapy Size of eligible population: not reported	**Exemestane** – The Intergroup Exemestane Study (IES Study) (Coombes *et al.*, 2004) – compared exemestane with tamoxifen. HR for death 0.83 (95% CI, 0.67 to 1.02), (reported in HTA monograph, Table 13)	Exemestane 13.02 years (156 months) vs. tamoxifen 12.88 years (155 months) (Hind *et al.*, 2007) (HTA monograph Table 38, Unplanned Switching setting. 1.5% discount rate)
	Letrozole - Adjuvant treatment of early oestrogen-receptor-positive breast cancer—primary adjuvant therapy and extended adjuvant therapy following standard tamoxifen therapy Size of eligible population: not reported	The Breast International Group (BIG I-98) (BIG I-98, 2006) study compared letrozole with tamoxifen: Primary HR for death in primary adjuvant setting: 0.86 (95% CI, 0.70 to 1.06)	Modelled survival advantage negligible Primary adjuvant setting: 14.65 years (176 months) with letrozole vs. 14.48 years (174 months) with tamoxifen, (BIG I-98), (Hind *et al.*, 2007) (HTA monograph, Table 37, discounted at 1.5%)

Table 3 *(Continued)*

Drug/Guidance Number/ Year issued	Recommendations* and size of eligible population**	Data extracted for overall survival extension (based on clinical trials) (HR = Hazard Ratio)	Data extracted for estimated life years gained (based on models)
Gemcitabine/TA 116/2007 (NICE, 2007)	Treatment metastatic breast cancer Size of eligible population: 7300	JHQG trial*** (Albain *et al.*, 2004) - compared gemcitabine/paclitaxel vs. paclitaxel, with results including greater median overall survival (18.6 months versus 15.8 months, p = 0.0489; hazard ratio: 0.82 (CI 0.67 to 1.00). However, note that more suitable comparators were considered to be capecitabine/docetaxel or docetaxel monotherapy. An indirect comparison would be needed to compare gemcitabine/ paclitaxel with capecitabine/docetaxel.	gemcitabine/paclitaxel: 1.76 years (21.1 months) compared with capecitabine/docetaxel 1.45 years (17.4 months) (NICE, 2006f) (Manufacturer/ Sponsor Submission, section 3.4.1 base-case results)

*Recommendations as stated in patient version of guidance, 'Understanding NICE Guidance'
** Size of eligible population sourced from NICE Costing Templates, where available (Costing Templates are not produced for all Technology Appraisals)
*** Where no explanation is given of trial name abbreviations, assume that the abbreviation used has no direct translation

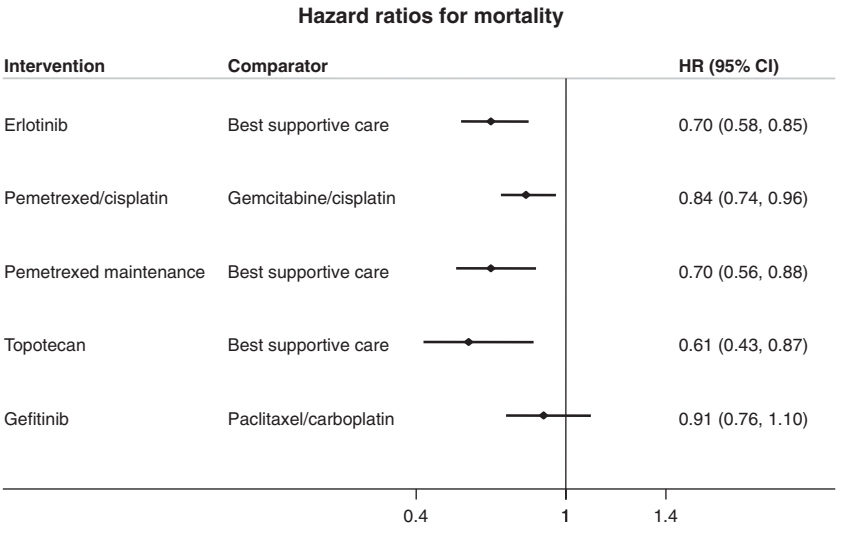

Figure 2. Lung cancer treatments NB: heterogeneous populations.

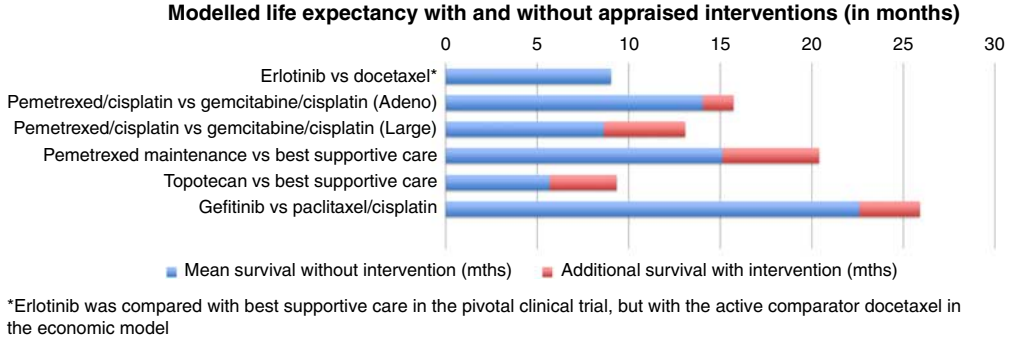

Figure 3. Lung Cancer Treatments – Modelled life expectancy with and without interventions.

hazard ratios for mortality, are illustrated as Forest plots in Figure 2, Figure 4 and Figure 6, and longer-term estimates from economic models are illustrated in the histograms in Figure 3, Figure 5 and Figure 7.

5.2 For lung cancer, there were five appraisals with positive recommendations for 4 drugs between 2005 and 2010. One of the drugs was appraised in two distinct indications (pemetrexed). Four of the appraisals were in non-small-cell lung cancer, and one in small-cell lung cancer. Hazard ratios ranged from 0.61 to 0.91. In four of five cases, the 95% confidence interval did not include one. Estimates from models of overall survival gained ranged from 0 to 5.3 months.

5.3 For colorectal cancer, there were three appraisals with positive recommendations for four drugs between 2005 and 2010. One of the drugs was appraised in two distinct indications (oxaliplatin). Hazard ratios ranged from 0.84 to 0.93. In one of five cases, the 95% confidence interval did not include one. Estimates from models of overall survival gained ranged from 4.3 to 16 months.

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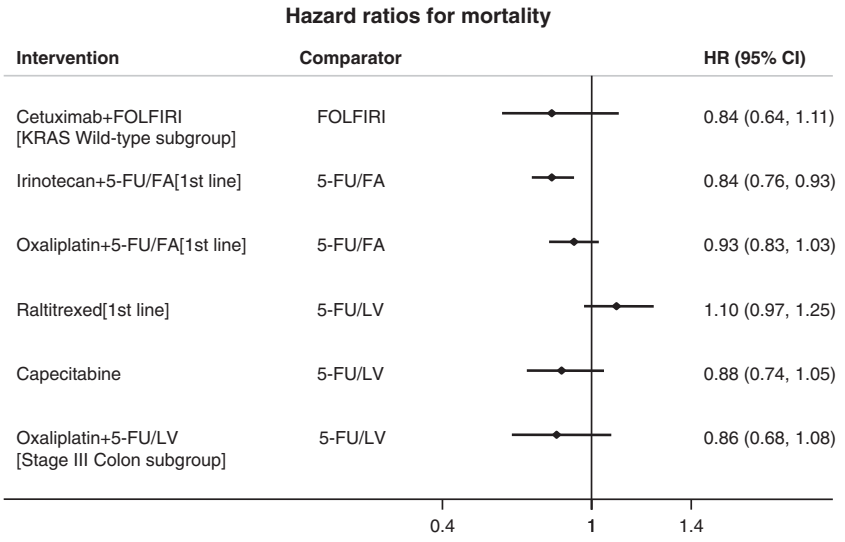

Figure 4. Colorectal cancer treatments NB: heterogeneous populations.

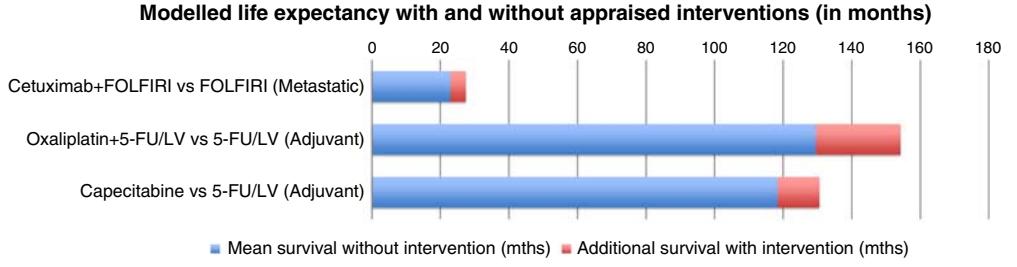

Figure 5. Colorectal Cancer Treatments – Modelled Life Expectancy with and without Interventions.

5.4 For breast cancer, there were four appraisals with positive recommendations for six drugs between 2005 and 2010. Hazard ratios ranged from 0.66 to 0.97. In two of six cases, the 95% confidence interval did not include one. Estimates from models of overall survival gained ranged from 0.96 months to 57.6 months.

6 Discussion

6.1 In a world where treatments of great promise are often reported in the popular media, the findings here may seem quite modest. However, innovation, much like policy change, tends to happen more often by 'creeping incrementalism', rather than 'step change'. So, whilst the impact of an individual new treatment might look modest, it could be the first step towards much greater change in the future. The journey from new molecular entity through to final marketing authorisation is a considerable one; indeed, the total time to bring a candidate drug from the start of human testing to market is nearly 9 years (Kaitin, 2010) with many candidate drugs never reaching the final phases of clinical trial. Drug development remains a lengthy, expensive and challenging process for manufacturers.

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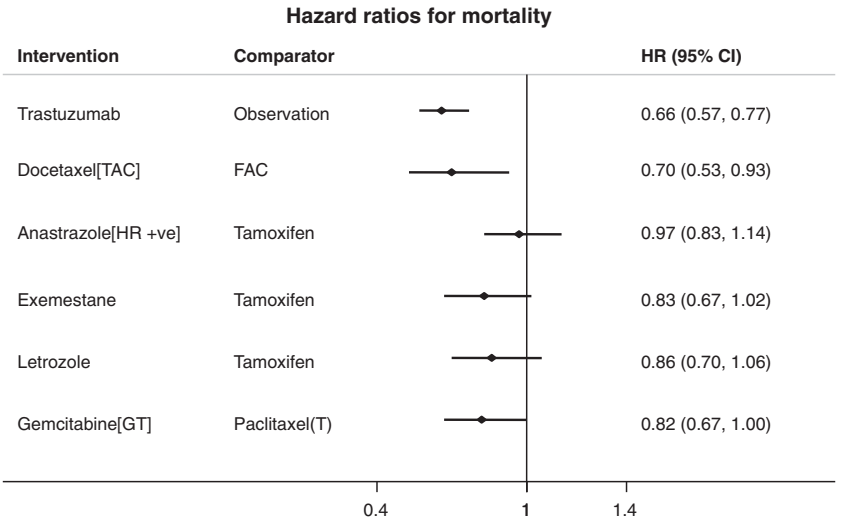

Figure 6. Breast cancer treatments NB: heterogeneous populations.

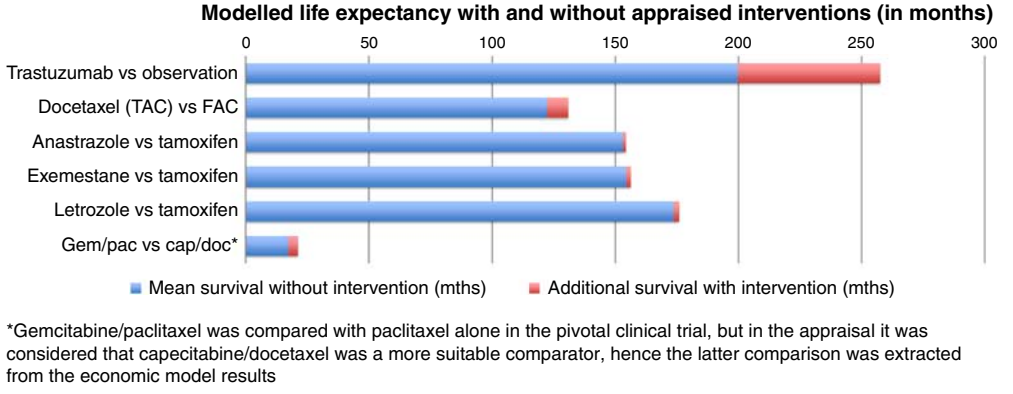

Figure 7. Breast Cancer Treatments – Modelled life expectancy with and without interventions.

6.2 When treatments are first developed for human use, the initial indication is often in people with very advanced cancer, where the balance of benefit to risk can be less challenging to assess. With time the same drug may obtain much broader indications at an earlier stage of disease. Another reason why the indications of a cancer drug may broaden with time is biological; the characteristic properties of cancer cells at different sites are often shared so that, a treatment developed in order to target one particular type of cancer may have successful future application in another. Indeed, whilst we have subdivided our findings by cancer site, another interesting approach of interest would be by class of drug.

6.3 Also, and importantly, another reason to expect continued advances in cancer drug development is the impetus for research to continue pushing boundaries that comes from patients, carers, healthcare professionals, researchers, manufacturers, and governments alike.

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6.4 The quantitative estimates collated in this overview are subject to uncertainty. Assessing the extent to which new treatments increase survival with cancer based on comparative effectiveness studies has many challenges. These are not limited to the critical appraisal of randomised controlled trials. For example, to assess the difference that an advance makes to the status quo, it is necessary to identify and compare against what current practice is. Clinical trials may not provide this comparison. This may happen due to a change in practice since the design of the trial, or to international variations in clinical practice. Another key challenge includes the long time horizon of the question, and the short time horizon of the empirical evidence, necessitating modelling. Further challenges include the consideration of whether there is stronger evidence in certain subgroups, whether the findings of a trial can be generalized from trial population to general population, handling of treatment crossover and amalgamating more than one trial on the same drug. Whilst these uncertainties should be taken into account when considering our findings, it would seem reasonable to interpret them as providing an evidence-based indication of the magnitude of effect of drug treatments on cancer survival.

7 Conclusion

7.1 The findings collated here show that the impact of drug treatments on the overall survival of people with cancer is highly variable. Point estimate hazard ratios for death (in appraisals with positive recommendations) ranged from 0.61 to 0.97. Of these, the 95% confidence intervals for 7 out of 16 hazard ratios did not include one. The modelled estimates of life extension ranged from 0 months to 57.6 months. Effectiveness of new treatments can be influenced by the underlying pathology of different cancer types, the stage of disease, and on how the drug works.

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