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The cost-effectiveness of Docetaxel and active symptom control versus active symptom control alone for refractory oesophagogastric adenocarcinoma: Economic analysis of the COUGAR-02 trial

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Running title: Cost-effectiveness analysis of COUGAR-02 trial

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Abstract

Background: The COUGAR-02 trial recently showed survival and quality of life benefits of Docetaxel and active symptom control (DXL+ASC) over active symptom control (ASC) alone in patients with refractory oesophagogastric adenocarcinoma.

Aim: To conduct an economic evaluation conforming to NICE technology appraisal guidance to evaluate the cost-effectiveness of DXL+ASC vs. ASC from the perspective of the English NHS.

Methods: Cost-utility analyses were conducted using trial data. Utility values were captured using the EQ-5D completed by patients at 3 and 6 weekly intervals while resource use was captured using nurse-completed report forms and patient-reports. Incremental cost-effectiveness ratios (ICERs) were calculated and the main outcome was cost per incremental quality-adjusted life year (QALY). Non-parametric bootstrapping was conducted to capture sampling uncertainty and to generate a cost-effectiveness acceptability curve (CEAC). The analysis horizon was the trial period (median follow-up=12 months) and no modelling or discounting of future costs and benefits was conducted.

Results: Average costs were £9,352 and £6,218 for DXL+ASC and ASC, respectively and average QALYs 0.302 and 0.186, respectively. This yielded an ICER of £27,180 for DXL+ASC. DXL+ASC had a 24% chance of being cost-effective at a £20,000 QALY threshold (λ) and a mean net monetary benefit of -£821; this rose to 59% and £332 when the threshold was raised to £30,000. If NICE end of life criteria are applied the probability of cost-effectiveness increases to 90% (at λ = £50,000). Results were robust to sensitivity analyses.

Conclusions: DXL+ASC is likely to be cost-effective if an end of life premium is applied. Further research should determine the impact of different utility measurement strategies and different chemotherapy delivery modes on estimates of cost-effectiveness.

Key points:

- The first economic evaluation of Docetaxel-based chemotherapy for second-line treatment in stomach cancer

- Docetaxel has only a 24% chance of being cost-effective when the ICER threshold is £20,000 but this increases to 90% if end of life criteria are applied
- Novel treatments may continue to struggle to overcome the value for money hurdle when providing only modest benefits in patients with poor prognosis.

Introduction

Oesophago-gastric cancer is the fifth most common type of cancer in the UK and is associated with poor prognosis and survival.(1) The recent COUGAR-02 randomised, controlled, open-labelled trial (ISRCTN13366390) compared Docetaxel chemotherapy plus active symptom control (DXL+ASC) and active symptom control (ASC) only in patients with advanced adenocarcinoma of the oesophagus, oesophagogastric junction, or stomach in the UK.(2) Patients (aged 18 and over) were included in the trial if their cancer had progressed within 6 months of treatment with a platinum-fluoropyrimidine combination. They were randomised on a 1:1 basis and those in the DXL+ASC arm received a dose of 75 mg/m² of Docetaxel by intravenous infusion every 3 weeks for up to six cycles. ASC included treatments for symptoms such as pain (e.g. Morphine Sulphate), nausea (e.g. Metoclopramide) and dyspepsia (e.g. Omeprazole) and included community and hospice care. The intention-to-treat analysis followed-up 168 randomised patients to a median of 12 months. Results indicated that median overall survival in the DXL+ASC group was 5.2 months (95% CI 4.1–5.9) versus 3.6 months (3.3–4.4) in the ASC group (hazard ratio 0.67, 95% CI 0.49–0.92; p=0.01). There were quality of life and symptom reduction benefits with DXL+ASC patients reporting less pain (p=0.0008), less nausea and vomiting (p=0.02), less constipation (p=0.02), and lower dysphagia (p=0.02) and abdominal pain (p=0.01) than the ASC group.

The trial investigators concluded that Docetaxel could be recommended as an appropriate second-line treatment for this population. The cost-effectiveness of Docetaxel for second-line treatments in non-small cell lung cancer (3), prostate cancer (4), and breast cancer (5) has been explored with mixed results. However, few studies (e.g.(6)) have evaluated the value for money of the treatment strategy in stomach or oesophageal cancers. The aim of the current analysis was to conduct a trial-based economic evaluation of DXL+ASC versus ASC for refractory oesophagogastric adenocarcinoma from the perspective of the NHS using the COUGAR-02 data.

Materials and Methods

The analysis adopted National Institute for Health and Care Excellence (NICE) reference case methods.(7) As such, it employed a cost-utility approach with costs calculated from the perspective of Health and Personal Social Services and with the primary outcome being cost per incremental quality-adjusted life year (QALY).

Utility assessment

Utility was based on the EQ-5D (three-level)(8) and UK scoring tariff.(9) Patients completed the EQ-5D at baseline, during clinic visits at weeks 3, 6, 9, 12, then every 6 weeks for up to 1 year and then every 3 months until death. QALY calculations were based on an area under the curve (AUC) approach where an average utility value was calculated between each adjacent EQ-5D completions, multiplied by the length of time between completions and divided by 365.25. Death was assumed to yield a utility value of '0'. Thus, for those who died, the last QALY contribution was taken as the average between the individual's last completed EQ-5D value and 0; this accounts for the likely deterioration in health leading up to death. As in the trial efficacy analysis, the primary economic analysis censored survival of alive patients to the date they were last known to be alive (i.e. survival was not modelled forward). An additional sensitivity analysis used Kaplan-Meier-based mean survival imputations to estimate the survival of those who were alive at study close and calculated QALYs and costs for the additional survival period.(10)

Costs

Health care usage data were collected on primary care (e.g. GP contacts, nurse visits), social care (e.g. social worker or home help visits) and secondary care (e.g. hospital visits and stays). Primary and social care resource use was gathered using specially-developed questionnaires completed by patients at the same time as the EQ-5D. Two methods were used to capture secondary care resource use: i) micro-level data using inpatient and outpatient case-report forms completed by the nurses at

every contact and costing each stay and visit based on the assessments (e.g. specialist consultant assessments and scans) received (although staff time and procedures were costed using Reference costs); ii) less granular, macro-level costing based on bundled unit costs for stays and procedures. The base case analysis employed costing method i) with method ii) used as a sensitivity analysis. Resource and equipment use were costed using unit costs from the PSSRU report (11), NHS reference costs (12), the British National Formulary (13) and the Electronic Market Information Tool (eMit).(14) Unit costs (with the exception of medication costs) are included in supplementary Tables 1 to 3.

The costs for Docetaxel were calculated per cycle and volume received (assuming dose= 75mg/m²) based on patients body surface area (BSA) at baseline. The net price of Docetaxel infusion of 20 mg/mL: 1-mL vial was £8.47 (£7.06 +20% VAT)(14) and all treatments were assumed to consist of an appropriate number of these volume vials with any mg/mL above the required level assumed to be wastage. In addition, a chemotherapy administration cost of £171 (HRG SB12Z in NHS Reference costs) was included for every cycle. BSA was calculated using the DuBois method(15) and was replaced by the national average (BSA=1.79)(16) when missing. The costs for radiotherapy included £700 (NHS Reference cost HRG SC46Z) for initial treatment set-up and £108 per fraction received (NHS Reference cost HRG SC22Z). If the number of fractions was missing then the mean for the sample was used. All costs (excepting Docetaxel as the list price was from June 2013) were inflated to 2014 prices using an accepted cost converter based on Purchasing Power Parities.(17)

Analysis

If costs and effects were higher or costs and effects lower for one treatment strategy over another then incremental cost-effectiveness ratios (ICER) were calculated.(18) The ICER is calculated: $(\text{Cost}_{\text{DXL+ASC}} - \text{Cost}_{\text{ASC}}) / (\text{QALY}_{\text{DXL+ASC}} - \text{QALY}_{\text{ASC}})$ and yields the cost of obtaining an additional QALY for DXL+ASC. Interventions yielding ICERs above NICE's willingness to pay threshold range of £20,000-£30,000 per incremental QALY are not considered cost-effective and deemed an inefficient use of

scarce resources. However, exceptions to the case may be made if a treatment extends life and meets the NICE 'end of life' criteria.(7) Analyses explored the scenario where the end of life weighting is applied and the QALY gain (or threshold) is multiplied by 2.5.

Non-parametric bootstrapping (n=10,000 simulations with replacement) was employed to determine the level of sampling uncertainty around the estimates of cost-effectiveness. The resulting 10,000 incremental costs and effects are plotted on a cost-effectiveness plane. The ICER decision rule can be reformulated to generate incremental net monetary benefit (INMB) in the following manner: $INMB = \lambda * (QALY_{DXL+ASC} - QALY_{ASC}) - (Cost_{DXL+ASC} - Cost_{ASC})$ where λ = NICE threshold value. If INMB is positive given a particular λ then DXL+ASC is considered cost-effective. The bootstrapped NMB values were used to identify the probability that DXL+ASC was cost-effective given a range of λ , presented on a cost-effectiveness acceptability curve (CEAC) (19) and to determine non-parametric confidence intervals.(20) The net benefit regression framework was applied to permit parametric analysis of cost-effectiveness controlling for heterogeneity.(21)

Multiple imputation (m=20) based on a combination of predictive mean matching (pmm), logit and Poisson models, depending on the variable type, was used to handle missing data.(22) Hospital visits, medication, radiotherapy and Docetaxel costs were not imputed. Ambulance use, assessments and length of stay for hospital visits were imputed using treatment, demographic and clinical variables (e.g. cancer site, tumour type, previous surgery). EQ-5D utilities were imputed using the same variables when all items were missing and using additional information from completed items when only some were missing. Community care total costs were imputed using the same variables and average community care costs from completed patient-forms and patient secondary care costs. The means of the imputed values were used in the final analyses.

A number of sensitivity analyses were conducted to test the sensitivity of the cost-effectiveness estimates to the methods adopted. Specifically, we tested the impact of: adopting different secondary care costing approaches (micro vs. macro); assuming fewer outpatient visits for

chemotherapy; extrapolating QALYs forward for survivors; 10-20% changes in costs and QALYs to account for errors in cost and benefit calculation; and adjusting for baseline EQ-5D. Discounting was not considered necessary as, except for a few instances, all costs and effects were observed within 12 months. All analyses were conducted in STATA 13[®] (StataCorp LP, Texas) and Excel[®] (Microsoft, Texas).

Results

Data were available from all 168 patients (84 patients in each arm). At the time of the analysis for the paper, 161 of the 168 (96%) patients had died, leaving only 7 patients alive and therefore with censored data. Of the 1171 expected patient resource use forms after accounting for survival, 527 (45%) were completed. Multiple imputation was used to estimate the costs from the missing resource use forms. However, the primary care use reported therein represented a small proportion of overall costs and therefore imputation made little impact on the results. For example, community care mean (SD) costs per time-point for observed and imputed cases for the combined sample were £127.95 (£360.42) and £119.60 (£147.71), respectively. Information on medication use and number of inpatient and outpatient stays was assumed complete as these were based on case-report forms completed by nurses. However, there was some missing data within those forms (for example for 117 (50%) of 233 inpatient stays, details about ambulance use was missing) and this was also imputed. In general, missing data were minimal with less than 4% of stay length, ward type and EQ-5D scores missing.

DXL+ASC patients received a median of three chemotherapy cycles (interquartile range 1-5) and had a median course dose intensity of 46% (interquartile range 19-76%). During the course of trial follow-up, DXL+ASC patients stayed in hospital for an average of 14.45 (SD = 20.25; range 0-125) days compared to 7.68 (SD = 9.74; range 0-34) in the ASC arm (Supplementary Table 3); had 11.07 (SD = 9.36; range 0-44) outpatient visits compared to 5.62 (SD = 5.38; range 0-19) in the ASC arm (Supplementary Table 4); visited A&E on 0.13 occasions (SD = 0.43; range 0-3) compared to 0.01 (SD

= 0.11; range 0-1) in the ASC arm; and visited the GP on 1.12 occasions (SD = 2.14; range = 0-9) compared to 0.87 occasions (SD = 1.17; range 0-5) in the ASC arm (Supplementary Table 5). Thus resource use was higher in the DXL+ASC arm than the ASC arm in most areas. There were over 2,300 prescriptions of medication during the study of which the most common were for relief of pain (23%), nausea (12%), constipation (7%) and gastric symptoms such as dyspepsia (6%).

The costs of the resource use (after imputation) are included in Table 1. Patients incurred both higher primary and secondary care costs in the DXL+ASC group. Medication costs (excluding Docetaxel itself) were higher in the DXL+ASC group than ASC group (£192 vs. £96). Of the prescription costs, 23% were <£1; 75% were <£5 and 99% were <£100. Mean medication costs of preventing and treating neutropenia and related sepsis was £8.89 (SD=£25.01) and £0.00 for the DXL+ASC and ASC arms, respectively. Costs of medication for preventing and treating nausea and vomiting was £31.95 (SD= 53.28) and £14.58 (SD=£37.17) for DXL+ASC and ASC arms, respectively. Docetaxel chemotherapy costs were £798 on average and ranged £236-£1,770 while radiotherapy costs were substantively higher in the ASC group (£275 vs. £15 for DXL+ASC group). Inpatient costs were £1,632 higher in the DXL+ASC than the ASC group and this appeared to be driven by bed day costs. Outpatient costs were on average £674 greater in the DXL+ASC group which were driven by the higher number of visits and investigation costs. In total, DXL+ASC was found to be £3,134 (£9,352 vs. £6,218) more expensive than ASC alone.

Baseline utility values were similar across arms (DXL+ASC = 0.69; ASC =0.70). However, an analysis adjusting for this difference was conducted as a sensitivity analysis.(23) Figure 1 shows the quality-adjusted survival based on EQ-5D scores up to week 60. It shows a greater AUC for DXL+ASC compared to ASC with the former group experiencing average QALYs of 0.302 compared to 0.186 in the ASC group, an incremental QALY gain of 0.116. (See Supplementary Table 6 for utility values).

Table 2 includes average patient costs and QALYs per trial arm and ICERs for the base case and sensitivity analyses. The results for the base case analysis indicate that DXL+ASC confers higher

QALYs than ASC and is more costly. The mean bootstrapped ICER of £27,123 is above what is usually considered cost-effective although well below a threshold of £50,000 following the application of the NICE end of life criteria. The results are robust to a number of sensitivity analyses where alternative costing and QALY calculation methods are employed and when cost and QALY estimates are varied by 20% (Table 2). Reductions in costs and increases in QALYs (in both arms) by 20% leads to ICERs approaching £20,000. It is worth noting that the Macro-costing approach has the effect of reducing estimated costs in both arms but the overall effect on the ICER is minimal. Extrapolating the survival forward for individuals alive at trial end has minimal impact on QALYs gained and the ICER, partly due to the small number surviving the trial and because some of those are in health states worse than dead (i.e. their EQ-5D value is negative). Adjusting for baseline EQ-5D also had minimal impact on the ICER. Figure 2 illustrates that most of the simulated ICERs are in the north-east quadrant of the cost-effectiveness plane with approximately a third falling below the (£20,000) cost-effectiveness threshold. The CEAC is presented in Figure 3 and shows that, where λ =£20,000 and λ =£30,000, DXL+ASC has a 24% and 59% chance, respectively, of being cost-effective. *Ceteris paribus*, the cost differential would have to be £2,306 or less or the QALY differential 0.16 or more for the ICER to fall under £20,000.

The INMB means at thresholds of £20,000, £30,000 and £50,000 were -£821, £332 and £2,638, respectively (Table 2). For the same thresholds, net benefit regression indicated that - both with and without demographic and clinical covariates - the treatment arm was not a significant predictor of net benefit (see supplementary Table 7). There was a trend (at λ =£30,000) for those who had received previous surgery deriving greater net-benefit (incremental £3664; CI -£ 277 to £ 7607; $p = 0.068$) than those who had not. Interactions with the treatment variable also indicated there may be a differential treatment effect according to gender and tumour type (metastatic vs. locally advanced). ECOG performance status was an important predictor of NMB with those in better health accruing greater benefit. The ECOG x treatment interaction was not significant but suggested that

chemotherapy was of greatest benefit over ASC in those with better performance status at trial outset

Table 1: Costs

		DXL+ASC					ASC				
		N	Mean	SD	Min	Max	N	Mean	SD	Min	Max
Patient-reported costs	Primary care	84	£877	£1,503	£0	£11,511	84	£725	£789	£0	£5,214
	Secondary care *	84	£94	£214	£0	£1,153	84	£51	£144	£0	£845
Treatment costs	Medication	84	£192	£268	£0	£1,342	84	£96	£118	£0	£541
	Docetaxel	84	£798	£456	£236	£1,770	84	£0	£0	£0	£0
	Radiotherapy	84	£15	£138	£0	£1,268	84	£275	£660	£0	£3,641
Inpatient costs	Ambulance	84	£142	£207	£0	£1,043	84	£48	£115	£0	£690
	Stay	84	£2,912	£4,074	£0	£25,000	84	£1,553	£1,956	£0	£6,800
	Clinical investigation	84	£556	£772	£0	£3,261	84	£311	£605	£0	£3,968
	Diagnostic tests	84	£129	£179	£0	£890	84	£65	£102	£0	£556
	Therapy	84	£320	£1,001	£0	£7,864	84	£848	£2,814	£0	£15,444
	Lab tests	84	£646	£821	£0	£4,225	84	£315	£546	£0	£2,703
	Other assessments	84	£2	£6	£0	£48	84	£1	£7	£0	£60
	Other surgery	84	£67	£156	£0	£699	84	£67	£179	£0	£932
Outpatient costs	Ambulance	84	£60	£293	£0	£2,530	84	£25	£156	£0	£1,380
	Stay	84	£930	£786	£0	£3,696	84	£472	£452	£0	£1,596
	Clinical investigation	84	£1,000	£823	£0	£3,918	84	£615	£625	£0	£2,586
	Diagnostic tests	84	£172	£191	£0	£771	84	£70	£207	£0	£1,653
	Therapy	84	£88	£304	£0	£2,678	84	£447	£3,377	£0	£30,888
	Laboratory tests	84	£52	£57	£0	£374	84	£27	£31	£0	£150
	Other assessments	84	£0	£2	£0	£12	84	£0	£1	£0	£8
Patient-reported costs	84	£971	£1,523	£0	£11,511	84	£776	£816	£0	£5,214	
Treatment costs	84	£1,004	£609	£236	£2,878	84	£371	£702	£0	£3,686	
Inpatient costs	84	£4,976	£5,642	£0	£26,823	84	£3,344	£4,648	£0	£23,140	
Outpatient costs	84	£2,401	£2,010	£0	£8,925	84	£1,727	£3,877	£0	£34,362	
Total costs	84	£9,352	£7,339	£384	£42,757	84	£6,218	£6,184	£252	£37,205	

*Excludes secondary care costs covered by nurse-completed case-report forms;

DXL+ASC = Docetaxel and Active Symptom Control; ASC = Active Symptom Control; SD = Standard Deviation; Min = Minimum; Max = Maximum

Table 2: Cost-effectiveness results

Analysis	Costs		QALYs		ICER
	DXL+ASC	ASC	DXL+A SC	ASC	
Base case					
<i>Mean</i>	£9,352	£6,218	0.302	0.186	£27,180
<i>Lower CI</i>	£7,783	£4,895	0.235	0.369	
<i>Upper CI</i>	£10,922	£7,540	0.142	0.231	
Bootstrap simulated ICER					
<i>Mean</i>	£9,355	£6,227	0.302	0.186	£27,123
Deterministic Sensitivity Analyses					
<i>Macro-costing approach*</i>	£8,148	£4,814	0.302	0.186	£28,915
<i>Fewer outpatient visits assumed**</i>	£8,416	£5,420	0.302	0.186	£25,986
<i>QALYs extrapolated for those still alive</i>	£9,355	£6,227	0.301	0.194	£29,086
<i>Adjusting for baseline differences in EQ-5D</i>	£9,352	£6,218	0.302	0.186	£27,030
<i>10% reduction in costs in DXL arm</i>	£8,417	£6,218	0.302	0.186	£18,931
<i>20% reduction in costs in both arms</i>	£7,484	£4,982	0.302	0.186	£21,698
<i>20% increase in costs in both arms</i>	£11,226	£7,473	0.302	0.186	£32,547
<i>20% reduction in QALYs in both arms</i>	£9,355	£6,227	0.241	0.149	£33,903
<i>20% increase in QALYs in both arms</i>	£9,355	£6,227	0.362	0.223	£22,602
Bootstrap simulated Net Monetary Benefit† (unadjusted)	Willingness to pay Threshold (λ)				
	$\lambda = \text{£}20,000$	$\lambda = \text{£}30,000$	$\lambda = \text{£}50,000$		
<i>Mean (Lower CI, Upper CI)</i>	-£821 (-£3,097, £1,457)	£332 (£1,457, £3,119)	£2,638 (-£1,313, £6,753)		

DXL+ASC = Docetaxel and Active Symptom Control; ASC = Active Symptom Control; ICER=Incremental Cost-Effectiveness Ratio; QALY = Quality-Adjusted Life Year; CI; Confidence Intervals; λ = Lambda/Willingness to pay threshold

*Assumes one (higher) cost per (in-patient and out-patient) visit and excludes diagnostics, tests, assessments and other surgery; for DXL assumes outpatient cost includes chemotherapy administration

**Removes outpatient visits at 3, 9 and 15 weeks

† Confidence Intervals based on 2.5th and 97.5th percentiles

Discussion

This economic evaluation conducted alongside the COUGAR-02 randomised clinical trial found that a strategy of Docetaxel plus active symptom control (DXL+ASC) versus active symptom control alone was more costly but was associated with greater benefits for refractory oesophagogastric adenocarcinoma. The cost per incremental QALY was, at around £27,000, above that normally considered cost-effective. Exploring the sampling uncertainty around the estimate revealed that chemotherapy had a 24% chance of being cost-effective. However, at a willingness to pay threshold of £30,000, there was a 59% chance of chemotherapy being cost-effective and a mean incremental net monetary benefit of £332. The ICERs remained in the range of £20,000-£30,000 after a series of deterministic sensitivity analyses providing some confidence in the robustness of the results. The cost differential was £3,134 and would need to fall by £828 for the ICER to drop below £20,000; this is roughly equivalent to two nights in hospital plus two outpatient visits. The incremental benefit of 0.116 QALYs is roughly equivalent to 42 days of life with full health or 61 days additional life with the baseline level of quality of life. Using this latter level of quality of life, the additional life extension delivered by chemotherapy would have to be 82 days (assuming constant utility) for the ICER to fall below £20,000. Few studies have conducted cost-utility analyses of Docetaxel as a second-line therapy. Inter-study comparisons are difficult since existing evaluations are in none gastric cancers (e.g. (3-5)) or present non-UK data only.(6) Within these studies, findings were mixed as to whether Docetaxel was cost-effective (3) or not (5, 6) with ICERs ranging between £23,000-£33,000. However, the ICERs are clearly context-dependent and determined by the definition of standard care and comparators.

It is possible that the treatment strategy would be eligible for the End of Life (EoL) criteria set out by the NICE.(7) The EoL criteria have been challenged on ethical (24) and efficiency grounds (25), and may not reflect the preferences of society (26) but are still worthy of consideration. The NICE Appraisal Committee may accept analyses with additional QALY-weightings where i) the life expectancy of the group is less than 24 months; ii) there is evidence life is extended by a minimum of three months; iii) and the population in England eligible for treatment is less than 7,000. Patients in this group would certainly meet the criteria of life expectancy of less than 24 months. A recent audit revealed that 9,768 patients with oesophago-gastric cancer were treated with palliative treatment intent in England in 2011-12 (1); as only a proportion would be receiving second-line chemotherapy, the annual eligible population would be less than 7,000. While the NICE EoL criteria i) and iii) are met, satisfaction of ii) is less clear as additional median life extension was 1.6 months (5.2 vs. 3.6 months) [mean = 1.8 months (6.6 vs. 4.8)] in the statistical evaluation; however it is likely that appraisal committees may have some flexibility in this regard. Should the criteria apply here and the willingness to pay threshold be increased to £40,000 or £50,000 per QALY (effectively a QALY-weighting of 2 and 2.5, respectively) then the probability that the DXL+ASC strategy would be cost-effective is 81% (mean INMB = £1,485) or 90% (mean INMB = £2,638).

The data presented here are arguably more complete than that normally available to NICE Evidence Review Groups, and demonstrate that, even for an inexpensive treatment, it may be difficult to achieve cost-effectiveness. A possible conclusion is that, in order to achieve an ICER<£20,000, new treatments (which are generally more expensive) would need to show very much higher levels of effectiveness or lower resource use. The cost used here for Docetaxel is the genericized price and unlikely to decrease significantly in the future. Ramucirumab provides similar survival gains but costs >£7,000 per cycle (total > £28,000) compared to around £50 per cycle for Docetaxel (total approximately £150). Consequently, Ramucirumab would need to provide *ceteris paribus* more than an additional year of life (at full health) to achieve cost-effectiveness. This is almost certainly not achievable in a disease with a current median survival of <6 months and, hence, novel treatments

are unlikely to become available to UK patients at this price level. The NHS, industry and society need to consider the implications of this and agree a way forward which will provide affordable access to innovative medicines.

Limitations

The analyses were somewhat reliant (for the costs, at least) on multiple imputation which may have introduced additional uncertainty that was not fully captured or was underestimated in the analysis. However, data on survival, utility and secondary care costs were relatively complete. Furthermore, since imputation had the largest role in dealing with missing community care costs which were a small proportion of overall costs, it is unlikely that it would have influenced results substantively. We assumed that nurse-completed case reports were accurate in that inpatient and outpatient visits were captured fully, but this may not have been the case and resource use may consequently have been underestimated. While the exploration of +/- 20% costs in both arms allows confidence that the decision would not change, this assumes that missing data and recording errors were equalised across arms. Any errors in accounting such as double counting may be greater for the DXL+ASC arm as there was more resource use therein. This evaluation used data from a single trial only. If there is sufficient decision uncertainty remaining in this clinical area, a model-based evaluation may be worthwhile as this would allow synthesis of effectiveness data from COUGAR-II and other Docetaxel trials (e.g.(27)) and permit comparisons with alternative therapies such as Ramucirumab (e.g.(28)).

Finally, the analysis took the perspective of the NHS and omitted costs to the patient and their carers. If a wider perspective had been adopted it is likely that the results would have been less favourable for DXL+ASC since the private costs of travelling to hospital would have been higher in the DXL+ASC arm.

Future research

As in the trial effectiveness analysis, there was a suggestion from the net benefit analysis conducted here that the benefits of chemotherapy might be greater in those who are in better health initially (according to ECOG performance status). Future studies of chemotherapy in advanced disease should be powered to enable sub-group analyses to explore this trend more thoroughly.

Although the EQ-5D has been validated in cancer patients (29) there is evidence that it lacks sensitivity in this group (30), omits key constructs of importance and overstates the benefits of chemotherapy.(31) Recent efforts have sought to develop preference-based measures that capture issues such as nausea, constipation and other cancer-related issues.(32) Future analyses should explore the impact of (disease-specific) measure choice on estimates of cost-effectiveness. We found that there were non-trivial differences (£1,204) in costs according to the methods used, with macro-costing yielding a figure 13% lower than micro-costing. This difference did not change the decision here but macro-level costing is common in economic studies and this approach may underestimate healthcare costs. Future analyses should be mindful of the impact of costing methods and where possible consider collecting micro-level data.

Assuming the QALY benefits observed here (after accounting for side-effects) are accurate and reflect true additional patient benefit, an obvious approach to enhancing the value of the chemotherapy strategy examined here would be to reduce delivery costs. The study protocol included visits every three weeks until week 18 which may be above that which would be expected in routine practice. Removing these and assuming visits every 6 weeks reduced the ICER to £25,986. Alternative approaches such as home delivery of IV chemotherapy may be a fruitful avenue for research. Such an intervention may bring additional quality of life benefits as it is known that those who are treated at the end of life would prefer to receive treatment at home (33) and it would also reduce resource costs.(34)

Conclusions:

The Docetaxel strategy had survival and quality-of-life benefits over active symptom control alone but was more costly. It was not deemed to be cost-effective unless additional 'end-of-life' QALY premiums were applied. The additional costs of chemotherapy delivery and patient resource use were important drivers of cost-effectiveness and future research should explore ways in which to reduce these. The analyses highlight important, more general, issues: that novel treatments may continue to struggle to overcome the value for money hurdle when providing only modest benefits in patients with poor prognosis; that reliance on patient-reports for resource use in populations with severe disease may result in high levels of missing data; and that the methods of costing (micro vs. macro) may impact results.

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Author contributions:

DMM conducted the health economic analysis and wrote the manuscript. HERF was the chief investigator for the COUGAR-O2 trial. AM, CTH, JAD, and HERF had input into the design of the study, the data analysis and contributed to the writing of the manuscript.

Conflicts of interest:

HERF received research funding from Sanofi. DMM, AM, CTH and JAD declare that they have no conflicts of interest.

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