FRACTIONAL POLYNOMIAL MODELS FOR NETWORK META-ANALYSIS OF SURVIVAL DATA IN ECONOMIC EVALUATIONS: A CASE-STUDY ON THE COST-EFFECTIVENESS OF FULVESTRANT IN PREVIOUSLY TREATED ADVANCED BREAST CANCER

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INTRODUCTION

- Network meta-analysis (NMA) is commonly used to obtain estimates of relative treatment effect for use in economic evaluations.
- For survival (time-to-event) data, a typical NMA will synthesise the hazard ratios (HRs) reported in randomised controlled trials (RCTs) to estimate an overall HR for each treatment comparison.
- This approach relies on the assumption of proportional hazards (PH) – that the HR is constant over time and therefore the hazards of the treatment and comparator are always proportional – holding for all RCTs in the analysis[1-3].
- However, in many cases the PH assumption is not appropriate, and therefore using this approach increases the likelihood that the NMA will produce biased estimates of treatment effect[3]. When used in an economic evaluation, such estimates may also affect the validity of cost-effectiveness analyses and subsequent reimbursement decisions.
- One alternative is to use fractional polynomial (FP) models, which are independent of the PH assumption. These models use multiple parameters to represent the relative treatment effect (rather than the single HR parameter) and the relative hazard is permitted to vary over time, allowing the models to fit the trial data more closely than the PH model[4].
- Consequently, when relative effect estimates generated by an NMA based on FP models are incorporated into an economic model, the results may be more representative of the true cost-effectiveness of the intervention vs its comparators.

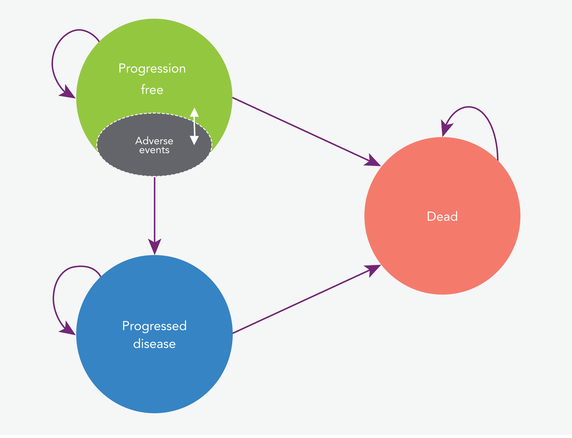
OBJECTIVES

- To assess the impact of obtaining overall survival (OS) estimates from an NMA using the FP approach, compared with using the conventional HR method, on the cost-effectiveness of fulvestrant vs exemestane for previously treated postmenopausal, oestrogen receptor-positive (ER+) advanced breast cancer (ABC).

METHODS

- A 3-state, partitioned survival cost-utility model was built from the UK National Health Service (NHS) perspective (Figure 1).
- The model considered postmenopausal female patients with ER+ ABC who had previously received endocrine therapy adjuvant to surgery, or as a first-line treatment for ABC. The cost-effectiveness of fulvestrant 500 mg was compared with the generic steroidal aromatase inhibitor exemestane 25 mg.
- Monthly cycles were used to reflect the frequency of administration for fulvestrant, and costs and quality-adjusted life years (QALYs) were calculated over a 15-year lifetime horizon. Costs and effects were discounted by 3.5% annually, in line with the NICE reference case[5].

FIGURE 1. MODEL STRUCTURE



- Two versions of the model were constructed using OS estimates generated via two NMAs[6], based on a published RCT evidence network[7]:
  1. **Fractional polynomial (FP) NMA:** Second-order FP models were fitted to individual patient data digitised from Kaplan-Meier curves and synthesised to estimate a treatment effect for each comparator, from which the proportion of patients alive at each cycle was estimated. The results from the best-fitting model were used in the economic model[6]
  2. **Conventional HR NMA:** A fixed effect model was used to synthesise HRs to generate an overall HR for exemestane vs fulvestrant (HR 1.1872 [95% CrI 0.9022–1.533])[6]; OS estimates for exemestane were obtained by applying the HR to a loglogistic parametric model fitted to the fulvestrant Kaplan-Meier curve from the CONFIRM trial in ABC[8] .
- All other inputs were kept the same for both models. Progression-free survival (PFS) was estimated by applying a published HR for exemestane vs fulvestrant (HR 1.05 [95% CrI 0.69–1.62])[9] to a lognormal curve fitted to the fulvestrant arm in CONFIRM[8], and grade 3–4 adverse event rates were sourced from the key RCTs for fulvestrant and exemestane[10-11]. Medical costs were based on reported unit costs[12-14] while utilities and disutilities for adverse events were sourced from the literature[15-18].
- One-way and probabilistic sensitivity analyses were performed to investigate the comparative model uncertainty.

RESULTS

- Both NMA approaches resulted in a high incremental cost-effectiveness ratio (ICER) for fulvestrant vs exemestane. The FP ICER was £20,519/QALY higher than the HR ICER (£146,915/QALY vs £126,396/QALY, respectively) as the FP model estimated a smaller relative treatment effect (0.10 vs 0.17 QALYs gained, respectively) (Table 1).

TABLE 1. BASE CASE RESULTS

Total per patient, mean	Fulvestrant	Exemestane	Incremental
FP model			
Cost	£91,638	£76,856	£14,782
LYs	2.98	2.76	0.22
QALYs	1.45	1.35	0.10
ICER (£/QALY)	-	-	**£146,915**
HR model			
Cost	£91,164	£70,166	£20,998
LYs	2.97	2.58	0.39
QALYs	1.44	1.27	0.17
ICER (£/QALY)	-	-	**£126,396**
Incremental: FP model vs HR model			
Cost	£474	£6,690	-£6,216
LYs	0.01	0.18	-0.17
QALYs	0.01	0.07	-0.07
ICER (£/QALY)	-	-	**£20,519**

Abbreviations: FP, fractional polynomial; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

- One-way sensitivity analysis showed that both models were highly sensitive to the HR for PFS, although the effect was larger in the FP model. The OS HR was the second-largest driver of cost-effectiveness in the HR model – the lower value resulted in fulvestrant becoming cost-effective at the £20,000/QALY threshold, the only variation where this was the case (Table 2).
- Probabilistic sensitivity analysis elicited mean ICERs of £152,280/QALY for the FP model and £138,627/QALY for the HR model – these were slightly higher than the base case ICERs but the between-model difference was smaller, at £13,653/QALY. In addition, there was a wider distribution of probabilistic ICERs in the FP model compared with the HR model (Figure 2).
- Fulvestrant had a higher probability of cost-effectiveness at low willingness to pay (WTP) thresholds (e.g. 14.82% vs 4.85% at WTP of £20,000/QALY) in the FP model compared with the HR model, as more extreme estimates of incremental costs and QALYs were generated. At WTP thresholds above £100,000/QALY, the HR model was more favourable for fulvestrant (Figure 3).

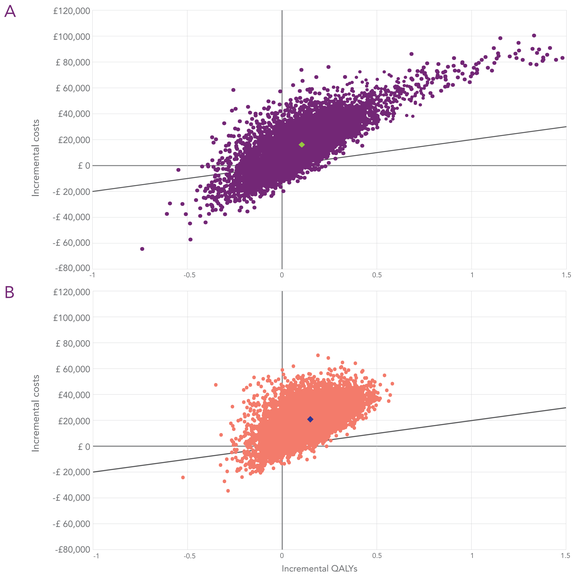
TABLE 2. DSA RESULTS: KEY DRIVERS OF COST-EFFECTIVENESS, ORDERED BY SIZE OF IMPACT

Variable	Difference vs base-case ICER	
	Lower value	Upper value
FP model: base-case £146,915/QALY		
PFS: Exemestane vs Fulvestrant HR	-£2,275,357†	-£112,252
Utility value: Progressed disease	£25,158	-£18,740
Utility value: Progression-free disease	£8,474	-£7,647
Monitoring costs: Hospital nurse specialist visit	-£2,701	£1,800
Administration costs (subsequent cycles): Docetaxel	-£2,649	£1,998
OS Exemestane: Fractional polynomial model - Cycle 1	-£1,989	£422
Administration costs (subsequent cycles): Fulvestrant	-£1,982	£1,982
Monitoring costs: Therapist visit (1 hour)	-£1,751	£1,561
Monitoring costs: Community nurse home visit (1 hour)	-£1,100	£800
Monitoring costs: Consultant outpatient visit	-£654	£463
HR model: base-case £126,396/QALY		
PFS: Exemestane vs Fulvestrant HR	£582,107	-£74,914
OS: Exemestane vs Fulvestrant HR - FE HR	-£92,644‡	-£17,817
Utility value: Progressed disease	£25,464	-£18,151
Utility value: Progression-free disease	£4,282	-£4,037
Administration costs (subsequent cycles): Docetaxel	-£3,080	£2,323
Monitoring costs: Hospital nurse specialist visit	-£3,063	£2,042
Monitoring costs: Therapist visit (1 hour)	-£2,039	£1,818
Monitoring costs: Community nurse home visit (1 hour)	-£1,248	£908
Administration costs (subsequent cycles): Fulvestrant	-£1,201	£1,201
Monitoring costs: Consultant outpatient visit	-£713	£505

Abbreviations: DSA, deterministic sensitivity analysis; FE, fixed effects; FP, fractional polynomial; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year.

† Fulvestrant is dominated (i.e. it is more costly and less effective, and is therefore in the north-west quadrant); ‡ Fulvestrant is less costly and less effective, and falls below the £20,000 WTP threshold, therefore is considered cost-effective.

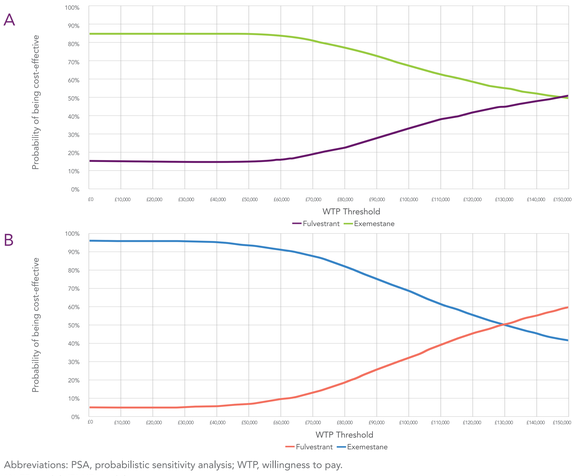
FIGURE 2. PSA RESULTS: COST-EFFECTIVENESS PLANES



Abbreviations: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.
(A) FP model; (B) HR model.

Diamonds represent the mean probabilistic ICER over the 10,000 simulations. The black line indicates the NICE £20,000/QALY WTP threshold – points below this line are considered cost-effective.

FIGURE 3. PSA RESULTS: COST-EFFECTIVENESS ACCEPTABILITY CURVES (CEACs)



Abbreviations: PSA, probabilistic sensitivity analysis; WTP, willingness to pay.
(A) FP model; (B) HR model.

CONCLUSION

- NMAs using FP models may provide improved survival estimates compared with conventional HR approaches, particularly when the PH assumption is violated.
- The statistical approach for NMAs of survival data may greatly affect the ICER and associated uncertainty when used in economic evaluations, which could have important implications for future healthcare reimbursement decision-making.
- However, all NMA approaches have some limitations; therefore, a range of NMA approaches should be explored to determine the most appropriate method for the available data.

REFERENCES

1. Bradburn MJ, et al. Br J Cancer. 2003;89(3):431-6.
2. Spruance SL, et al. Antimicrob Agents Chemother. 2004;48(8):2787-92.
3. Batson S, et al. PLoS One. 2016;11(5):e0154870.
4. Jansen JP. BMC Med Res Methodol. 2011;11:61.
5. NICE. Guide to the methods of technology appraisal 2013. [updated 2013; cited August 2018]; Available from: https://www.nice.org.uk/process/pmg9/chapter/foreword.
6. Harvey RC. Value Health. 2018; 21(suppl 3): S18.
7. Telford C, et al. Clin Breast Cancer. 2016;16(3):188-95.
8. Di Leo A, et al. J Natl Cancer Inst. 2014;106(1):dji337.
9. Sabale U, et al. Pharmacoeconomics. 2017;1(4):279-90.
10. Di Leo A, et al. J Clin Oncol. 2010;28(30):4594-600.
11. Baselga J, et al. N Engl J Med. 2012;366(6):520-9.
12. Curtis L, Burns A. Unit Costs of Health and Social Care 2017. Personal Social Services Research Unit (PSSRU), University of Kent; 2017 [updated 2017; cited July 2018]; Available from: https://kar.kent.ac.uk/65559/.
13. BNF. 2017 [updated 2017; cited July 2018]; Available from: http://www.medicinescomplete.com.
14. NHS Improvement. National Schedule of Reference Costs, 2016/17. [updated 2017; cited July 2018]; Available from: https://improvement.nhs.uk/resources/reference-costs/.
15. Delea TE, et al. Curr Oncol. 2013;20(5):e371-87.
16. Doyle S, et al. Lung Cancer. 2008;62(3):374-80.
17. Lloyd A, et al. Br J Cancer. 2006;95(6):683-90.
18. Nafees B, et al. Health Qual Life Outcomes. 2008;6:84.