Impact of subsequent treatment choice and surrogacy assumptions in hormone receptor-positive, HER2-negative breast cancer treatment pathway modelling

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Introduction

Breast cancer is the most common cancer in the World Health Organization Europe region with an estimated incidence of 562,500 in 2018.[1] One in eight women in the EU-28 will develop breast cancer before the age of 85. Therefore, decisions made by health technology assessment bodies about breast cancer treatments will play a large role in healthcare providers' budget allocations.

Hormone receptor positive/human epidermal growth factor receptor-2 negative (HR+/HER2-) breast cancer accounts for more than 70% of breast cancers.[2]

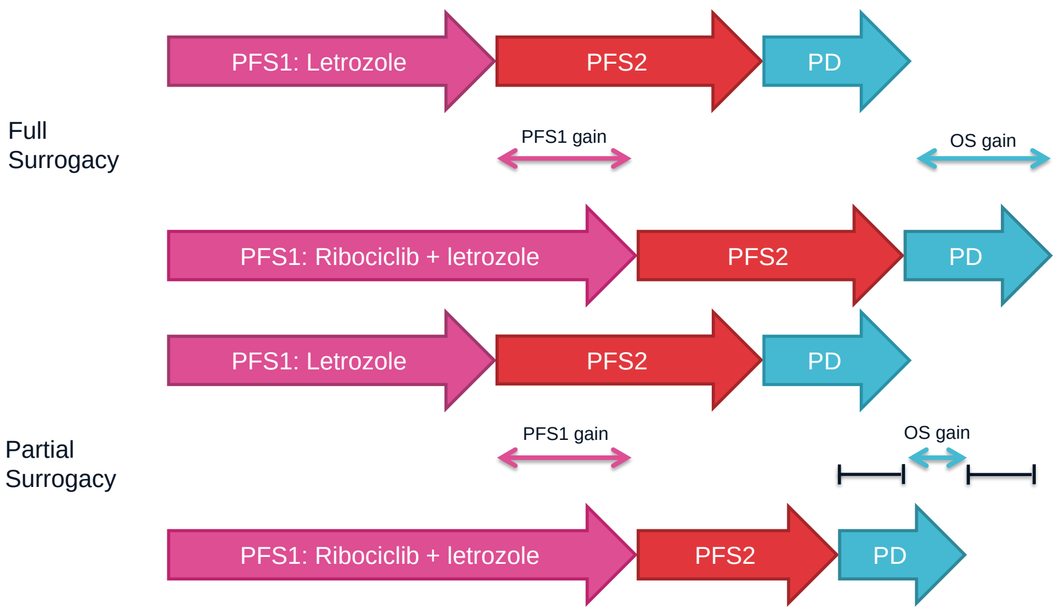
Economic models in oncology typically require survival curves fitted to progression-free survival (PFS) and overall survival (OS) time-to-event data. Cost-effectiveness analyses in previously untreated patients often do not appropriately consider effects of subsequent treatment. Choice of second- and third-line treatments is likely to affect model outcomes. In cases where OS data are immature, other endpoints such as PFS can be used as a surrogate for OS.

Surrogate endpoints can be used as substitutes for clinical endpoints and are expected to predict the effect of therapy. In National Institute for Health and Care Excellence's (NICE) technology appraisal (TA) 496 of ribociclib (Kisqali®) in combination with letrozole, OS data from MONALEESA-2 were immature and a full surrogacy approach was used.[3]

- Full surrogacy assumes an observed gain in PFS results in an identical gain in OS; PFS and OS in later-line oncology treatments can be highly correlated and a full surrogacy assumption may be valid
- Partial surrogacy assumes a gain in PFS translates to a larger or smaller gain in OS than the reported PFS; this can be achieved by applying a scaling factor to PFS data to alter OS.

Figure 1 illustrates full and partial surrogacy approaches.

Figure 1: Full and partial surrogacy approaches



Key: PD, progressed disease; PFS1, progression free survival 1.

Notes: Black lines indicate time on subsequent treatment which have been adjusted using the partial surrogacy scaling factor. In the partial surrogacy example, a gain in PFS leads to a smaller gain in OS.

There are concerns about using PFS as a surrogate for OS. It can lead to incorrect estimates of survival, and consequently, affect cost-effectiveness estimates. The effects on survival of subsequent therapies can distort the relationship between PFS and OS. Improvements modelled with surrogate endpoints may or may not be perceived by the patient and in many cases, surrogate endpoints themselves do not directly measure a clinical benefit.

Objectives

In this study, we aimed to assess the interaction between subsequent treatment choice and surrogacy assumptions and their impact on cost-effectiveness results in the context of ribociclib for previously untreated patients in the hormone receptor-positive, HER2-negative breast cancer treatment pathway.

Methods

A discrete event simulation model (**Figure 2**) was constructed in R Studio to evaluate the cost effectiveness of ribociclib plus letrozole compared with letrozole monotherapy in previously untreated HR+/HER2- breast cancer.

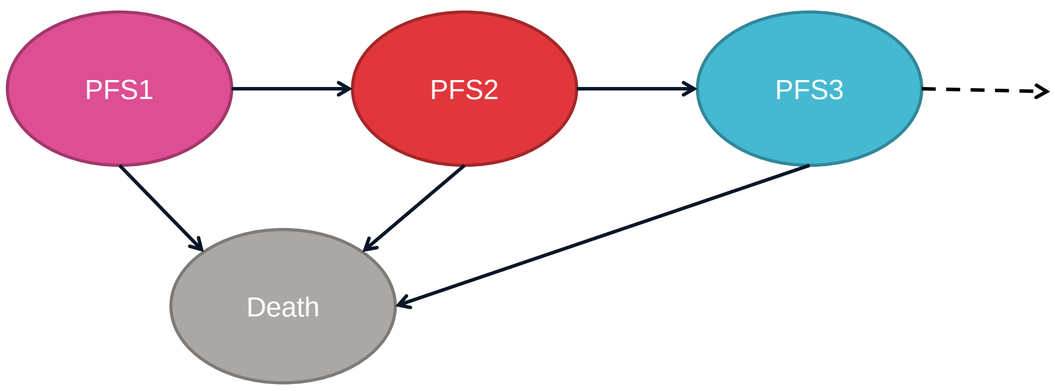
I. A single patient enters the model receiving ribociclib in combination with letrozole as first-line treatment
   a. Upon progression, the patient receives their second line therapy (base case: everolimus and exemestane)
   b. Upon progression, the patient receives their third line therapy (base case: capecitabine)
   c. It is assumed that following third line therapy the patient dies

II. The same patient then re-enters the model, receiving letrozole monotherapy as first-line treatment

III. The next patient then enters the model

20,000 patients were run through the model, with the same patient receiving one treatment then the other, simulating 'perfect' randomization.

Figure 2: Model structure



Key: PFS1, progression free survival 1.

In the model base case, following progression at first-line treatment, patients receive everolimus and exemestane as second-line treatment and capecitabine as third-line treatment. Alternative second- and third-line treatments can be chosen; all treatment options included in the model are shown in **Figure 3**.

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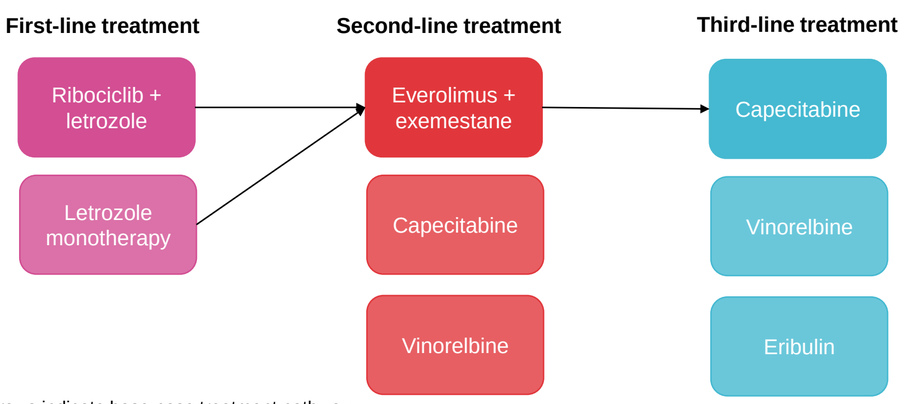
Figure 3: Treatment options available in the model



Note: Black arrows indicate base-case treatment pathway.

Clinical efficacy data for initial treatment were sourced from MONALEESA-2[4], a randomized, Phase III trial comparing ribociclib in combination with letrozole versus letrozole alone. Survival data were digitized to generate pseudo time-to-event data for both treatment arms, to which parametric survival models were fitted. These data informed the time spent in the PFS1 health state.

In the base case, PFS2 was informed by the BOLERO-2[5] trial, where medians for everolimus/exemestane were used to back-calculate survival distributions. Times spent in PFS3 were informed by published treatment-specific medians, to which exponential distributions were fitted.[6-9]

Drug costs were sourced from the drugs and pharmaceutical electronic market information tool (eMIT) and the Monthly Index of Medical Specialities (MIMS); resource use costs were sourced from NHS reference costs and adverse event costs were from TA496. Health state utilities were sourced from Mitra et al.[10]

Surrogacy scaling factors were used to investigate the effect of a PFS–OS surrogacy relationship, by reducing time spent in subsequent health states so the difference in OS between populations was reduced. A partial surrogacy assumption was used in the base case, with a scaling factor of 38.5% used to reduce time spent in subsequent health states.[11]

Results

In previously untreated HR+/HER2- breast cancer patients, ribociclib plus letrozole treatment resulted in an increase in both total costs and quality-adjusted life years (QALYs) compared with letrozole monotherapy. This resulted in an incremental cost-effectiveness ratio (ICER) of £77,620 per additional QALY (**Table 1**).

Applying a full surrogacy assumption to the base-case treatment pathway increased time on treatment post ribociclib plus letrozole. Because monthly costs and QALYs were applied to a patient's time on treatment, this resulted in costs for the ribociclib plus letrozole arm increasing by £5,709 and QALYs increasing by 0.26. A full surrogacy assumption decreased the ICER to £71,481/QALY (**Table 2**).

Table 1: Model results, partial surrogacy applied to base-case treatment pathway

Treatment	Total		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
Letrozole	£16,642	1.94			
Ribociclib + letrozole	£179,339	4.04	£162,698	2.10	£77,620

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 2: Model results, full surrogacy applied to base-case treatment pathway

Treatment	Total		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
Letrozole	£16,642	1.94			
Ribociclib + letrozole	£185,048	4.30	£ 168,406	2.35	£71,481

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

In scenario analyses, holding the partial surrogacy assumption, applying a scaling factor of 38.5% and varying alternative second-line treatments led to ICER reductions of £22,343–28,963/QALY; alternative third-line treatments resulted in ICER increases of £513–2,669/QALY. Removing everolimus/exemestane from second-line treatment had the greatest impact on the ICER. Results are shown in **Table 3**.

Table 3: Subsequent treatment pathway scenario analysis results, applying partial surrogacy

Input	Scenario	ICER
Base case	**Everolimus + exemestane → capecitabine**	**£77,620**
Treatment options post first line	Everolimus + exemestane → vinorelbine	£80,289
	Everolimus + exemestane → eribulin	£78,133
	Capecitabine → eribulin	£53,094
	Capecitabine → vinorelbine	£55,277
	Vinorelbine → eribulin	£48,657
	Vinorelbine → capecitabine	£52,437

Discussion

Both treatment choice and modelling assumptions made after first-line treatment impact model outcomes. In this model, subsequent treatment choice directly impacted time on treatment, which in turn affected survival, costs and QALYs. Applying a surrogacy scaling factor to post-progression health states also directly impacted time on subsequent treatments, affecting model outcomes. The interaction between treatment choice and surrogacy can have a major impact on model results.

Health technology assessment is increasingly being carried out with earlier, more immature data. For appraisals of interventions at first line where survival data are immature, both choice of subsequent treatment and approach to surrogacy are important in capturing appropriate estimates of cost effectiveness.

Surrogacy assumptions in modelling can give manufacturers an idea, during drug development, of the potential OS benefit required for the drug to be cost effective. However, for full appraisal, modelling assumptions are no match for sufficient data maturity.

In this case study, given the immaturity of data, assuming a gain in PFS results in an identical gain in OS may be inappropriate. Until data maturity, a surrogacy scaling factor can be used to test differences in survival gains.

Conclusion

Cost-effectiveness models considering interventions early in treatment pathways must appropriately consider later-line treatment effects in order to accurately estimate cost effectiveness.

References

1. CP SaW. 2014. https://www.drugsandalcohol.ie/28525/1/World%20Cancer%20Report.pdf
2. ABCC. 2018. http://advancedbreastcancercommunity.org/understanding-abc
3. NICE TA496. https://www.nice.org.uk/guidance/ta496
4. Hortobagyi et al. *Ann Oncol*. 2018.
5. Baselga et al. *N Engl J Med.* 2012.
6. Cortes et al. *Lancet.* 2011.
7. Cybulska-Stopa et al. *Contemp Oncol.* 2013.
8. Müller et al. *Oncol Res Treat*. 2014.
9. Shankar et al. *Asian Pac J Cancer Prev.* 2015.
10. Debanjali et al. *ISPOR.*
11. Pennington et al. 2017. http://nicedsu.org.uk/appraisal-specific-projects/ribociclib/

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