Application of Progression-free Survival as Surrogate Endpoint for Overall Survival in NICE Reviews of Advanced Breast Cancer Drugs

Zou D, Sun A, Musci R, Milev S

Evidera, San Francisco, CA, US

POSC256

Introduction

- Clinical trials investigating drugs for advanced breast cancer (aBC) often provide immature overall survival (OS) data due to limited trial follow-up.[1-10]
- Heath technology assessment (HTA) agencies usually require submitted health economic models of cancer interventions to predict lifetime OS outcomes beyond data available from trials.[11-12]
- There are alternative options (e.g., the application of progression-free survival [PFS] as a surrogate endpoint based on consistent clinical evidence supporting the correlation between PFS and OS in aBC) to establish the OS benefit of a treatment in the absence of mature trial data.[13,14] However, it is unclear what specific methods were commonly applied in HTA submissions.
- National Institute for Health and Care Excellence (NICE) recommendations for aBC drugs were reviewed and analyzed to address this gap in information.

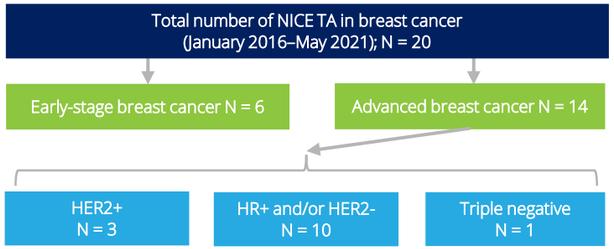
Objective

- To better understand the approaches to predict long-term OS outcomes within cost-effectiveness models appraised by NICE with a focus of using PFS as a surrogate endpoint for OS.

Methods

- The study used publicly available recommendations identified on NICE's website from January 2012 to May 2021, including technology appraisal (TA) guidance and committee papers.
- Fourteen unique TAs in aBC were identified.[1-10,15-18] (Figure 1)
- Full-text screening of the committee papers and TA guidance was conducted by a single investigator; abstracted data were validated by a second investigator.
- Information on drug of interest, specific indication, model structure, source of PFS and OS, approach for long-term OS projection, and committee commentaries was extracted.

Figure 1. Disease Characteristics of NICE TAs for aBC

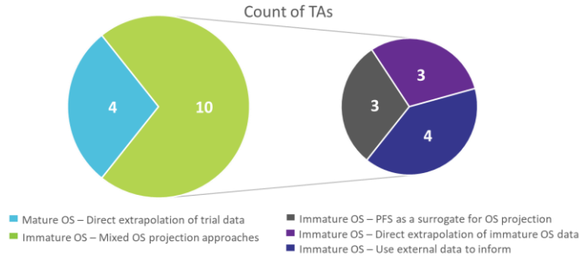


Abbreviations: HER2 = human epidermal receptor 2; HR = hormone receptor; NICE = National Institute for Health and Care Excellence; TA = technology appraisal

Results

- Of the 14 final TAs, only four viewed OS data available from trials as mature, while 10 considered OS data as immature.
- Among the 10 appraisals with immature OS data, three used PFS as a surrogate endpoint to predict long-term OS beyond the trial period. The rest projected long-term OS based on direct extrapolation of trial data using parametric fittings (n=3) and informed by external data in some cases (n=4). (Figure 2)

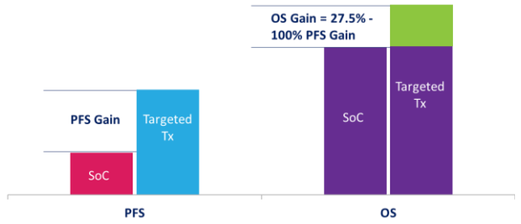
Figure 2. OS Modeling Approaches in NICE TAs for aBC



Abbreviations: PFS = progression free survival; OS = overall survival; TA = technology appraisal

- Although the PFS surrogate approach has generally been accepted by the committee, given the complex and difficult-to-predict relationship between PFS and OS, the committee supported a partial surrogacy between the two endpoints—that is, an improved PFS is likely to be partially (27.5% to 100%) translated into an OS gain. (Figure 3)
- Mixed comments from the committee were seen for the TAs applying direct extrapolation of trial data with external data taken into account or not on a case-by-case basis. (Table 1)

Figure 3. Relationship between PFS and OS in NICE TAs that Used PFS as a Surrogate for OS



Abbreviations: OS = overall survival; PFS = progression-free survival; SoC = standard of care; Tx = treatment

Table 1. Methods Used for Long-term Estimates of Immature OS Trial Data

TA Number Indication	Estimates of Long-term OS ERG/Committee Comments
Apply PFS as surrogate endpoint	
TA563[5] Feb. 2019 HR+/HER2-	A calibration factor was applied which reduced time spent in the PPS "pay-off" to adjust gain in OS of ~27.5% of the gain in PFS. **Given it applied the lower bound of range given by the ERG in TAs for TA495/TA496 and tests a scenario with no surrogacy between PFS and OS, the ERG approved the model approach.**
TA496[8] Dec. 2017 HR+/HER2-	Individual patient-based, state-transition approach indirectly modelled OS as a function of time spent in each health state besides death (PF first-line, PF second line, and progression survival). Any PFS gain translated directly into an OS gain based on time to progression and size of PFS gain by treatment. **100% translation of PFS gain into OS gain is not plausible; ratio is likely close to 38.5% translation of PFS gain to OS gain.**
TA495[9] Dec. 2017 HR+/HER2-	Median OS gain = median PFS gain, i.e., the same time is spent in the post-progression period for a patient in either treatment. **No evidence to support the assumption that 100% of PFS gain translates into OS gain. Assumption that there is no difference in PPS between two treatment arms when evidence suggests that PPS is shorter for the intervention arm.**
Use external data	
TA704,[1] May 2021 in HER2+; TA687,[2] March 2021 in HR+/HER2-; TA579,[4] May 2019 in HR+/HER2-; TA503,[7] Jan. 2018 in HR+	OS was informed by other more mature phase II or phase III trial data. **Many were disapproved due to lack of adjustment; recommended directly using targeted trial to extrapolate when OS data become more mature.**
Direct extrapolation of immature OS data using parametric fittings	
TA619,[3] Jan. 2020 in HR+/HER2-; TA509,[6] March 2018 in HER2+; TA421,[10] Dec. 2016 in HR+/HER2-	**Considerable uncertainties and potential bias of OS extrapolation due to immature OS data; some ultimately agreed that extrapolation of the immature OS data was the most preferred approach.**

Abbreviations: ERG = evidence review group; HER = human epidermal growth factor receptor; HR = hormone receptor; OS = overall survival; PFS = progression-free survival; PPS = post-progression survival; TA = technology appraisal; TN = triple negative

Discussion

- In cost-effectiveness analyses, the OS treatment effects is often the largest contributor to clinical benefit and thus to incremental cost-effectiveness ratios. Therefore, validity of long-term OS estimates is a key consideration by the committee.
- In the absence of mature trial data on OS to derive an estimate of long-term OS within the economic analysis, surrogate measures provide an alternative to directly projecting OS from trial data in aBC.
- The use of surrogate measures, however, has not been commonly used in the existing models appraised by NICE. Strong evidence on the strength of the association between the surrogate endpoint and OS is needed to facilitate the acceptance of this approach.

References

1. NICE. https://www.nice.org.uk/guidance/ta704
2. NICE. https://www.nice.org.uk/guidance/ta687
3. NICE. https://www.nice.org.uk/guidance/ta619
4. NICE. https://www.nice.org.uk/guidance/ta579
5. NICE. https://www.nice.org.uk/guidance/ta563
6. NICE. https://www.nice.org.uk/guidance/ta509
7. NICE. https://www.nice.org.uk/guidance/ta503
8. NICE. https://www.nice.org.uk/guidance/ta496
9. NICE. https://www.nice.org.uk/guidance/ta495
10. NICE. https://www.nice.org.uk/guidance/ta421
11. NICE. https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/technology-appraisal-processes-guide-apr-2018.pdf
12. CADTH. https://www.cadth.ca/sites/default/files/pcodr/pCODR%27s%20Drug%20Review%20Process/pcodr-procedures.pdf
13. Pennington http://nicedsu.org.uk/wp-content/uploads/2017/11/Aug-2017-Ribociclib-DSU-Report.pdf
14. Davis S, et al. *NICE Decision Support Unit Methods Development*. 2012
15. NICE. https://www.nice.org.uk/guidance/ta639
16. NICE. https://www.nice.org.uk/guidance/ta515
17. NICE. https://www.nice.org.uk/guidance/ta458
18. NICE. https://www.nice.org.uk/guidance/ta423

Presented at Virtual ISPOR Europe • November 30 – December 3, 2021

Funding provided by Evidera