Review proposal of Olaparib for treating BRCA mutation-positive HER2-negative advanced breast cancer after chemotherapy (terminated appraisal) [TA762]

Olaparib for treating BRCA mutation-positive HER2-negative metastatic breast cancer after chemotherapy (TA762) was published as terminated guidance in February 2022.

Proposal

A review of the guidance should be planned into the appraisal work programme, which will follow the cost comparison process.

Rationale

Since publication of the terminated guidance, there have been changes to the treatment pathway for BRCA mutation-positive HER2-negative advanced breast cancer with the recommendation of talazoparib (TA952) in the same population as in TA762. The population includes both hormone receptor (HR)- positive, and HR-negative disease.

Talazoparib is in the same drug class as olaparib (PARP inhibitor) and indirect treatment comparisons provide some evidence that olaparib and talazoparib provide similar health benefits. Therefore olaparib could potentially be appraised in this indication using the cost comparison approach with talazoparib as a key comparator. The company would need to demonstrate that olaparib provides similar or greater health benefits to talazoparib, at a similar or lower cost.

Summary of new evidence and implications for review

At the time of TA762 publication, the OlympiAD trial (NCT02000622) had reported greater progression-free survival (PFS) for olaparib compared with chemotherapy treatment of physician's choice (TPC) (7.0 months vs. 4.2 months; HR=0.58; 95% CI 0.43-0.80; P<0.001), and no significant difference in median overall survival (OS) (19.3 months for olaparib vs. 17.1 months for TPC, p=0.513) (Robson 2017, Robson 2019). This trial included metastatic disease only.

The results of the literature review found that since publication of TA762, there have been two published subgroup analyses of the OlympiAD trial. A prespecified subgroup analysis of OlympiAD found that the impact of olaparib on PFS and response rates vs TPC was consistent across various subgroups including hormone receptor status, germline BRCA mutation, site of metastases and prior chemotherapy. Quality of life increased in all subgroups with olaparib (Senkus 2023). A post-hoc analysis (n=38) with extended follow up reported OS consistent with previous analyses and that long-term exposure to olaparib was

well tolerated with no new serious adverse events observed and no evidence of cumulative toxicity compared to earlier data cuts (Robson 2023).

Since publication of TA762, a final analysis of a single-arm phase 3 study evaluating the use of olaparib in people with BRCA-mutated, HER2-negative metastatic breast cancer (LUCY, NCT03286842) has also been published which further supports the clinical effectiveness and safety of olaparib in people with germline BRCA mutations (Balmaña 2023). However, not everyone in the study population previously received both taxane- and anthracycline-based chemotherapy in line with the current marketing authorisation (75.3% of patients enrolled in LUCY had received both of these).

There is no published head-to-head evidence comparing the efficacy of olaparib and talazoparib in this indication, but the results from two published indirect treatment comparisons of data from the OlympiAD and EMBRACA trials comparing olaparib and talazoparib respectively found that there were no statistically significant differences in PFS, OS or overall safety profile between the two interventions (McCrea 2021, Wang 2021), which may support the case for a cost comparison approach.

Review remit

To appraise the clinical and cost-effectiveness of olaparib within its marketing authorisation for adults with BRCA1/2-mutations, who have HER2 negative locally advanced or metastatic breast cancer.

The technology

Olaparib has a marketing authorisation in the UK for monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2 negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor (HR)-positive breast cancer should also have progressed on or after prior endocrine therapy or be considered unsuitable for endocrine therapy.

Olaparib also has a marketing authorisation in the UK as a monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline BRCA1/2-mutations who have HER2-negative, high-risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy.

Intervention(s)	Olaparib
Population(s)	Adults with HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2-mutations that has previously been treated with: • an anthracycline and a taxane in the (neo)adjuvant or metastatic setting, unless these treatments would not be suitable. • endocrine therapy in the case of hormone receptor (HR)-positive breast cancer, unless endocrine therapy is not suitable.
Comparators	Talazoparib
Outcomes	The outcome measures to be considered include: • overall survival • progression free survival • response rate • adverse effects of treatment • health-related quality of life.

Economic analysis	This technology has been selected to be appraised as a cost-comparison. The time horizon should be sufficient to reflect any differences in costs between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account. The use of olaparib is conditional on the presence of mutations in the BRCA1 or BRCA2 genes. The economic modelling should include the costs associated with diagnostic testing for BRCA1 or BRCA2 mutations in people with locally advanced or metastatic breast cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 4.8 of the guidance development manual (available here: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation).
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations	**Related Technology Appraisals:** Talazoparib for treating HER2-negative advanced breast cancer with germline BRCA mutations (2024). NICE technology appraisal guidance 952. Olaparib for adjuvant treatment of BRCA mutation-positive HER2-negative high-risk early breast cancer after chemotherapy (2023). NICE technology appraisal guidance 886. Pembrolizumab for neoadjuvant and adjuvant treatment of triple-negative early or locally advanced breast cancer (2022). NICE technology appraisal guidance 851. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast

	cancer after endocrine therapy (2022). NICE technology appraisal guidance 836. Sacituzumab govitecan for treating unresectable triple-negative advanced breast cancer after 2 or more therapies (2022). NICE technology appraisal guidance 819. Alpelisib with fulvestrant for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer (2022). NICE technology appraisal guidance 816. Pembrolizumab plus chemotherapy for untreated, triple-negative, locally recurrent unresectable or metastatic breast cancer (2022). NICE technology appraisal guidance 801. Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (2021) NICE technology appraisal guidance 725. Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (2021) NICE technology appraisal guidance 687. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer (2020) NICE technology appraisal guidance 619. Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens (2016) NICE technology appraisal guidance 423. Everolimus with exemestane for treating advanced breast cancer after endocrine therapy (2016). NICE technology appraisal guidance 421. **Related technology appraisals in development:** Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment. NICE technology appraisal guidance [ID6370]. Publication date to be confirmed Datopotamab deruxtecan for previously treated hormone receptor-positive HER2-negative unresectable or metastatic breast cancer. NICE technology appraisal guidance [ID6348]. Publication date to be confirmed. Sacituzumab govitecan for treating hormone receptor-positive HER2-negative metastatic breast cancer after 2

	or more therapies. NICE technology appraisal guidance [ID4033]. Publication date to be confirmed. Vepdegestrant for treating hormone receptor-positive HER2-negative metastatic breast cancer after endocrine treatment. NICE technology appraisal guidance [ID6360]. Publication date to be confirmed. **Related NICE guidelines:** Advanced breast cancer diagnosis and treatment (2009; updated 2017) NICE guideline [CG81] Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer (2013; updated 2023) NICE guidance CG164 Improving outcomes in breast cancer (2002; checked 2014) NICE guideline CSG1 MammaTyper in vitro diagnostic test for determining breast cancer subtypes (2018) NICE Medtech Innovation Briefing 135 **Related Quality Standards:** Breast cancer (2011; updated 2016) NICE quality standard 12
Related National Policy	The NHS Long Term Plan (2019) NHS Long Term Plan NHS England (2023) Manual for prescribed specialist services (2023/2024)

Has there been any change to the price of the technology since the guidance was published?

There have been no changes to the list price since guidance publication, which is £2,317.50 for 56 capsules. Since TA762 was published, NHS England and the company have agreed a commercial access agreement (CAA) for olaparib.

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

There are no existing or proposed changes to the marketing authorisation since publication of TA762 that would affect the existing guidance.

Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?

Talazoparib for treating HER2-negative advanced breast cancer with germline BRCA mutations (TA952) - published February 2024. Talazoparib would be a direct comparator of olaparib in this appraisal.

According to the health technology evaluation manual, a cost comparison case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication.

Since olaparib has a similar mechanism of action to talazoparib (PARP inhibitor), olaparib may now be suitable for cost comparison in this indication provided there is evidence to support health benefits that are similar or greater to those of talazoparib, or any other relevant comparators, at a similar or lower cost.

Additional comments

The search strategy reviewed references from the Cochrane Library, Embase, Medline and INAHTA up to February 2024. Additional searches of clinical trials registries and other sources were also carried out.

The results of the literature search are discussed in the 'Summary of evidence and implications for review' section above. See Appendix C for further details of ongoing and unpublished studies.

Equality issues

No equality issues were identified in the original appraisal. Issues identified during the review scoping process include increased prevalence of HER2-negative breast cancer with germline BRCA mutations in younger people and people of Black ethnicity, BRCA mutations being more common in people of Ashkenazi Jewish ethnicity, and breast cancer in men being more common in men with BRCA mutations. This is outlined in the scoping equality impact assessment.

Proposal paper sign off

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01/05/2024

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Appendix A – Information from existing guidance

Original remit

To appraise the clinical and cost-effectiveness of olaparib within its marketing authorisation for metastatic breast cancer.

Current guidance

NICE is unable to make a recommendation about the use in the NHS of olaparib for treating BRCA mutation-positive HER2-negative metastatic breast cancer after chemotherapy. This is because AstraZeneca has confirmed that it does not intend to make a submission for the appraisal. AstraZeneca considers that there is unlikely to be enough evidence that the technology is a cost-effective use of NHS resources for this population.

Research recommendations from original guidance

None

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below.

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the STA process.	**A review of the appraisal will be planned into the NICE's work programme.**	**Yes**
The decision to review the guidance should be deferred.	NICE will reconsider whether a review is necessary at the specified date.	No
The guidance should be Cross referred into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Options	Consequence	Selected – 'Yes/No'
The guidance remains relevant, and an update is not needed.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider.	No
The guidance should be withdrawn.	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No.

Appendix C

Registered and unpublished trials

Trial name and registration number	Details
A Phase III, Open Label, Randomised, Controlled, Multi-centre Study to Assess the Efficacy and Safety of Olaparib Monotherapy Versus Physicians Choice Chemotherapy in the Treatment of Metastatic Breast Cancer Patients With Germline BRCA1/2 Mutations (OlympiAD). NCT02000622	Population (n=302): 18 years and older, germline mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious, histologically or cytologically confirmed breast cancer with evidence of metastatic disease, prior therapy with an anthracycline and a taxane in either an adjuvant or metastatic setting, prior platinum as long as no breast cancer progression occurred, no prior treatment with a PARP inhibitor, no HER2 positive disease, no more than 2 prior lines of therapy, no untreated brain metastases Intervention: Olaparib (300 mg oral tablets twice daily) Comparator: Chemotherapy treatment of physician's choice (TPC) – one of: • Capecitabine 2500 mg/m2 po daily (divided in 2 doses) x 14 days, repeat every 21 days • Vinorelbine 30 mg/m2 IV Day 1 and Day 8, repeat every 21 days • Eribulin 1.4 mg/m2 IV Day 1 and Day 8, repeat every 21 days Outcomes: progression-free survival (primary outcome), overall survival, time to second progression or death, overall response rate, quality of life Start date: March 2014 Primary Completion date: December 2016 Study completion date: Estimated December 2024

Additional information

None.

References

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Wang J, Zhang Y, Yuan L et al (2021) Comparative efficacy, safety, and acceptability of single-agent poly (ADP-ribose) polymerase (PARP) inhibitors in BRCA-mutated HER2-negative metastatic or advanced breast cancer: a network meta-analysis. Aging 1;13(1):450.