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Assessment of select HER2-negative mBC agents as a proxy to understand HTA-body uncertainties for HER2-low mBC agents in EU4 and England

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Objective

- Understand payer concerns about the evidence supporting HER2-negative metastatic breast cancer (mBC) agents and investigate whether post-launch evidence addresses those concerns in order to support future access to therapies for HER2-low mBC patients

Conclusions

- Majority of HTAB concerns about the evidence supporting HER2-negative mBC agents were around trial design, endpoints and data maturity. These are anticipated to be similar for forthcoming HER2-low therapy launches
- Despite recurrent payer concerns over patient-relevance of PFS as identified in the HTA analysis, the identified evidence showed that PFS is valued by patients and correlates with maintenance of HRQoL, increasing its importance as a patient-relevant endpoint
- OS data that became available post-launch on specific HER2-negative mBC agents have confirmed the value of PFS as an early predictor of OS. This addressed payer concerns over data maturity in Germany, leading to a positive G-BA decision upon re-submission
- Selection of first-line CDK 4/6 treatment plus ET for HR+ HER2-negative mBC patients positively impacts overall survival outcomes compared to first-line treatment with chemo or endocrine monotherapy

Plain language summary

Why did we perform this research?
To understand if the evidence gaps identified as areas of payer concern during health technology assessment (HTA) of HER2-negative therapies have subsequently been addressed and could be used to justify accelerated access for future HER2-low therapies launching with immature data, we aimed to answer the following questions:

- What concerns have payers identified within the evidence package submitted for HTA review so far?
- What was their impact on HTA outcomes at launch?
- What additional evidence is now available that could address these concerns?
- To what extent does this evidence address payer concerns?

How did we perform this research?
We used IQVIA's proprietary HTA Accelerator platform to identify HTA reports published for HER2-negative mBC in selected markets. We assessed the impact of payer concerns over presented evidence on the reimbursement and access outcomes. We prioritized the key concerns and determined, through a targeted literature review (TLR), what, if any, additional evidence has subsequently been generated that addressed these concerns

What were the findings of this research and what are the implications?
Our research suggests that some of the initial concerns over evidence of HER2-negative mBC agents were addressed with subsequently generated evidence. This may give confidence around accelerating access for future therapies where the evidence base is not as mature

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Disclosures

Harding, T. works for AstraZeneca, who co-funded this study; Seddik, A. works for Daiichi Sankyo, who co-funded this study. Schmid P. has worked as an advisor to AstraZeneca and Daiichi Sankyo. No further conflicts of interest in relation to this poster

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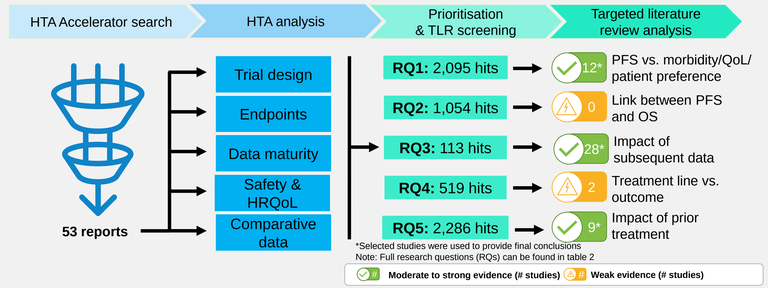
Introduction

- Among the molecular subtypes of breast cancer, HER2-negative is the most common, accounting for approximately 80% of all cases
- HER2-low disease was recently identified as a subset of HER2-negative, and is defined as HER2 immunohistochemistry 1+ or 2+, with negative HER2 gene fluorescence in-situ hybridization amplification[1]
- Recently EMA-approved agents targeting HER2-negative mBC have been assessed for reimbursement by HTA-bodies (HTABs) in EU4 and England, with payers identifying a range of concerns resulting in poor HTA outcomes and limited or delayed access to patients in some markets
- This research aimed to determine if any of the concerns identified by payers were subsequently addressed, in the hope of mitigating these concerns for future HTAs in order to accelerate patient access to current and future therapies

Methods

- EMA-approved therapies targeting CDK4/6, PIK3 or PARP in HR+ or HR-, HER2-negative mBC were selected as a proxy for HER2-low therapies
- HTA reports for these HER2-negative mBC therapies published by G-BA, IQWiG, HAS, AEMPS, AIFA and NICE between 1st Jan 2010 – 1st Apr 2021 were identified using IQVIA's proprietary HTA Accelerator platform
- HTA reports were analysed to identify payer concerns within five main areas: trial design, endpoints, data maturity, safety & HRQoL and comparative data. Payer concerns about the evidence were listed by area, and their impact on HTA outcomes were assessed
- The payer concerns were prioritized based on number of mentions and impact on HTA outcome and translated into five research questions (RQ) which were investigated via a TLR. The database search was performed in the electronic databases Embase® and MEDLINE®, and the hand search was performed in three conference proceedings and in PubMed
- All identified publications from the TLR were reviewed against pre-determined eligibility criteria using the PICOS framework



Results and interpretation

- Of 53 HTAB recommendations, 30% were positive, 23% were positive with restrictions, 17% were negative and 30% received no recommendation; majority of concerns regarding HER2-negative mBC agents were concentrated around trial design, endpoints and data maturity
- Of the five research questions (RQs), limited studies were identified for two RQs (RQ2 and RQ4). Multiple studies were identified addressing the other three RQs (RQ1, RQ3 and RQ5). Evidence related to RQ3 partially address some aspects of RQ2
- **RQ1:** Identified evidence showed that PFS is linked to patient preference & HRQoL and it is also linked to morbidity for PARP inhibitors. This can be used to demonstrate that PFS is a patient relevant endpoint
- **RQ3:** Post-HTA submission data for 4 out of 6 HER2-negative mBC agents confirmed the value of PFS as an early predictor of OS, while more mature data on the remaining therapies are yet to be published
- **RQ5:** A retrospective RWE study showed that CDK 4/6s are linked to longer OS benefit when given in 1st line, compared to chemo or endocrine therapy

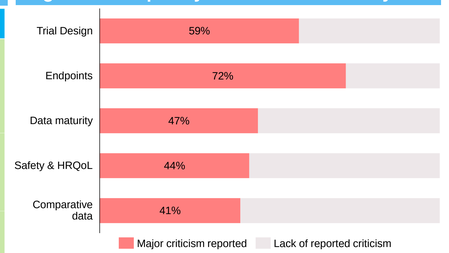
Table 1. Summary of HTA outcomes* in EU4 and England for HER2-negative mBC products

Product (Molecule)	Trial name	Combination	Indication	G-BA (subgroups)	HAS	NICE	AIFA	AEMPS (IPT)
Ibrance (*palbociclib*)	PALOMA 2	*Aromatase inhibitor*	*1L+ HR+ / HER2-LA or metastatic BC*	No AB (2x) *2017*	ASMR IV *2017*; ASMR IV *2019*	*2017*	Conditional innovation status with moderate therapeutic value and moderate quality of evidence *2017*	*2018*
	PALOMA 3	*Fulvestrant*	*2L+ HR+ / HER2-LA or metastatic BC*	No AB (x2) *2017*; No AB (x2) *2019*	ASMR IV *2017*; ASMR V 2019	In CDF *2020*	Innovation status not granted *2018*	
Verzenios (*abemaciclib*)	MONARCH 3	*Aromatase inhibitor*	*1L+ HR+ / HER2-LA or metastatic BC*	No AB (x4) *2019*	ASMR V *2018*; ASMR IV *2021*	Under commercial access agreement *2019*	Conditional innovative status with moderate therapeutic value and moderate quality of evidence *2019*	*2019*; *2020*
	MONARCH 2	*Fulvestrant*	*1L+ HR+ / HER2-LA or metastatic BC*	No AB (x4) *2019*; Minor AB (x1) No AB (x2) *2020*		In CDF *2019*		
Kisqali (*ribociclib*)	MONALEESA 2; MONALEESA 7	*Aromatase inhibitor*	*1L+ HR+ / HER2-LA or metastatic BC*	No Ab 18; No Ab 19; Minor AB (x1) *2020*	ASMR V *2018*; ASMR V *2019*; ASMR IV *2020*	*2017*	Conditional status with moderate clinical value & moderate quality *2018*	*'18*
	MONALEESA 3	*Fulvestrant*	*1L+ HR+ / HER2-LA or metastatic BC*	No AB (x7) *2019*; Minor AB (x1) *2020*	ASMR V *2019*; ASMR IV (renewal 2020)	In CDF *2019*; Only subpop. *2021*	Conditional innovative status with high clinical value and high quality of evidence *2020*	*'20*
Piqray (*alpelisib*)	SOLAR-1	*n/a*	*2L HR+ HER2- LA or metastatic BC with PIK3CA mutation*	Less benefit (x2) No AB (x3) *2021*	SMR insufficient *2021*	MNF did not make a submission in *2020*	No assessment published yet	No assessment published yet
Talzenna (*talazoparib*)	EMBRACA	*n/a*	*1L+ HER2-BRCA1/2+ LA or metastatic BC*	Considerable added benefit (x1) *2020*	ASMR V *2019*	HTA delayed awaiting further evidence from MNF	No assessment published yet	No assessment published yet
Lynparza (*olaparib*)	OlympiAD	*n/a*	*1L+ HER2-BRCA1/2+ LA or metastatic BC*	Minor AB (x1) *2020*	ASMR V *2019*	HTA delayed awaiting further evidence from MNF	No assessment published yet	No assessment published yet

*Table does not show outcomes of IQWiG HTA reports
Note: talazoparib and olaparib were assessed for 2L+ mBC patients and for 1L patients ineligible for chemo therapy
Definitions: ASMR V = no improvement, ASMR IV = minor improvement, SMR insufficient = no reimbursement, CDF = cancer drug fund

Positive | Positive w. restriction | Negative

Figure 1. Frequency of HTAB concerns by area



The concerns over endpoint selection, data maturity and trial design were most frequently mentioned as a justification for negative HTA outcomes, these mostly included:

- Relevance of PFS as primary endpoint and its correlation with other relevant outcomes **(RQ1)**
- Reliability of PFS as a surrogate for OS **(RQ2 & RQ3)**
- Impact of line of treatment **(RQ4)** and prior treatment **(RQ5)** on outcome in subgroups

Table 2. Summary of research question and TLR screening

	Research question	# of references	# of ref. used for data extraction*	TLR results	
Endpoint	**RQ1:** Is there an association between PFS and morbidity, HRQoL or patient preference in patients with mBC?	2,095 hits	12	→ Two discrete choice experiments (DCEs) link patient preference to PFS, while disease progression is linked to deteriorated HRQoL → PFS is linked to improved morbidity for HER2-neg mBC patients treated with PARP inhibitors	RQ1
Data maturity	**RQ2:** Is PFS linked to OS benefit in HR+ or HR-, HER2-negative mBC treated with targeted therapies?	1,054 hits	0	→ No correlation study identified for PFS with OS, but supportive data are available **(see RQ3)**	
Data maturity	**RQ3:** Have subsequent data on mortality, morbidity, and HRQoL confirmed the initial reported outcomes in HR+ or HR-, HER2-negative mBC patients?	113 hits	28	→ Multiple updated publications showed that subsequent data for CDK 4/6 therapies confirmed initially reported PFS outcomes and furthermore showed OS benefit after having more mature data available	RQ3
Trial design	**RQ4:** For a given targeted therapy in HER2-negative mBC, does a change in treatment line impact PFS and OS outcome?	519 hits	2	→ Association between treatment line and PFS outcome identified for palbociclib where its use in 1L or 2L was associated with better PFS and OS compared to use in ≥3L[15] → Association between earlier treatment line and further OS benefit shown for olaparib[14]	
Trial design	**RQ5:** Does treatment effect for mBC patients vary for patients that received prior treatment with CDK 4/6 targeted therapies vs endocrine/chemo-therapy?	2,286 hits	9	→ Impact of prior treatment on treatment effect shown in one retrospective RWE study with 16,017 patients	RQ5

*Including full text publications, conferences abstracts, clinical trial data and real-world evidence

PFS is linked to HRQoL, patient preference and morbidity

- ✓ Two studies in patients with advanced/metastatic (a/m)BC were identified that link patient preference to PFS as measured by discrete choice experiments, although another study shows that physical mobility and OS are of higher importance than PFS in relation to cancer treatment [2,3,4]
  - ➢ In the first DCE study, 282 patients with mBC responded to an online questionnaire exploring the relationship among PFS, QoL, importance of treatment outcomes, and preferences. When asked which of the two scenarios (16- or 12-month PFS) patients prefer assuming OS and side effects are the same, 63% preferred 16-month PFS, 26% were unsure and 12% preferred 12-month PFS (p < .001)[2]
  - ➢ In Dalal et al. (2019), an online survey of 577 women with aBC showed that PFS positively impacted treatment preference (P < 0.01)[3] while Reinisch et al. (2021) showed that patient's physical mobility (19.4%) and OS (15.2%) were of higher importance than PFS in relation to patient preference for cancer treatment[4]
- ✓ Additionally, both the EMBRACA and OlympiAD trials showed significant overall improvement on both PFS and multiple symptoms (both cancer- and breast cancer-specific) for talazoparib and olaparib, suggesting a link between PFS and morbidity for mBC patients treated with PARPi [5,6]
- ✓ Correlation of disease progression for BC patients with worsened HRQoL (GHS, functional- and emotional well-being) was shown in 2 studies[7,8]
  - ➢ First progression caused significant deterioration in global HRQoL, while the second progression resulted in moderate worsening of HRQoL

PFS is an early predictor of OS benefit

- ✓ Two out of three CDK 4/6 therapies (abemaciclib and ribociclib) have reported significant benefit in mOS for 1L mBC patients after initially submitting for reimbursement to HTA bodies with immature OS data[9-10]
  - ➢ Both CDK 4/6 therapies demonstrated PFS benefit at initial submission, indicating PFS could serve as indicator for longer-term OS benefit
- ✓ A third CDK 4/6 inhibitor (palbociclib) have also published more mature OS data which, although have not reached statistical significance (p = 0.09), could do so with more mature data, further strengthening the value of PFS as an indicator of OS[11]
  - ➢ Supportive of this is an RWE study published in March 2021, showing significant OS and PFS benefit for 1L palbociclib treatment[12]
- ! Other targeted therapies (alpelisib, talazoparib and olaparib) in HER2-negative mBC have reported non-statistically significant median OS in mBC for the ITT population, despite having significant PFS benefit [5, 13-14]. However, these therapies are studied in biomarker subgroups that have relatively low prevalence amongst the BC population (e.g., ~5% for germline BRCA) which limits the sample size for the studies and hence, their ability to demonstrate statistically significant improvements in OS
  - ➢ However, subsequent readouts has shown olaparib provide a +7.9 months nominal statistically significant OS benefit (p=0.02) compared to TPC for 1L patients, supporting the findings that OS benefit is greater in mBC treatments by treating earlier[14]

1L CDK 4/6 therapy + ET increase OS compared to chemo or endocrine monotherapy

- ✓ A retrospective RWE study of 16,017 mBC patients has shown that 1L treatment with CDK 4/6 combination therapies resulted in increased OS compared to 1L treatment with chemo or endocrine monotherapy followed by CDK4/6 combination therapies, whilst time to next treatment from start of CDK4/6 therapy was similar irrespective of line of treatment.[16]

Limitations

- In this study we conducted a TLR instead of a SLR and such the possibility exists that published evidence was not included in the analysis
- The TLR focused on the pre-specified PICOS criteria per RQ and was limited to literature published between 2016-2021 in English language
- Furthermore, the HTA analysis was based on HTA reports which include potential publication bias

Abbreviations

AB = Added Benefit**, ASMR =** Amelioration du Service Medical Rendu **BC =** Breast Cancer, **CDF** = Cancer Drug Fund, **CDK** = Cyclin Dependent Kinase, **DCE** = Discrete Choice Experiment, **EMA =** European Medicines Agency**, ET =** Endocrine Therapy **EU4 =** Germany, France, Italy and Spain**, G-BA** = Gemeinsamer Bundesausschuss, **HR** = Hormone Receptor, **HRQoL =** Health-Related Quality of Life, **HTA =** Health Technology Assessment**, HTAB** = Health Technology Assessment Body**, LA** = Locally Advanced, **mBC =** metastatic Breast Cancer, **OS** = Overall Survival, **PARP =** Poly Adenosine diphosphate-Ribose Polymerase**, PFS** = Progression Free Survival**, PICOS =** Population, Intervention, Comparator, Outcomes, Study design, **PI3K** = Phosphoinositide 3-kinase**, RQ** = Research Question, **RWE** = Real World Evidence **SLR** = Systematic Literature Review, **SMR** = Service Medical Rendu, **TLR** = Targeted Literature Review, **TPC** = Therapy at Physician's Choice

References

1. F. Miglietta et al., *Annals of Oncology, 2021*
2. *Kaklamani et al., Oncologist, 2016*
3. *Dalal et al., Patient Preference and Adherence, 2019*
4. *Reinisch et al., Breast Care, 2021*
5. *Litton et al., Annals of Oncology, 2020*
6. *Robson et al., European Journal of Cancer, 2019*
7. *Marschner et al., JAMA Network Open, 2020*
8. *Kruggel et al., Breast, 2019*
9. *Sledge et al., JAMA Oncology, 2020*
10. *Slamon et al., Annals of Oncology, 2021*
11. *Turner et al., New England Journal of Medicine, 2018*
12. *Demichele et al., Breast Cancer Research, 2021*
13. *Andre et al., Annals of Oncology, 2021*
14. *Robson et al., Annals of Oncology, 2019*
15. *Palumbo et al., Therapeutic Advances in Medical Oncology, 2021*
16. *Comis et al., Annals of Oncology, 2020*