Patient preferences for treatment attributes and endpoints in neoadjuvant therapy for early-stage breast cancer

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Objective

This study aimed to assess patient preferences of eBC treatments and the endpoints and outcomes that drive these preferences for patients with HER2+ eBC patients in the neoadjuvant setting using a **discrete choice experiment**.

Conclusions

- **Patients with HER2+ eBC in the neoadjuvant setting placed most importance on increased gains in pCR, closely followed by gains in 5-year DFS and 5-year OS**. Based on the preference weight estimates, patients placed the most importance on increasing pCR from 25% to 100%, closely followed by increasing DFS and OS from 'unknown' at 5 years to 95% at 5 years.
- These results are consistent with literature and previous **qualitative work** conducted as part of this study, where patient advocacy groups highlighted that in addition to OS, pCR and DFS are important efficacy endpoints for treatment decision-making.
- Overall, the study demonstrates the **importance of non-OS endpoints.** Its findings are particularly relevant to HTA bodies to drive a better understanding of the value of non-OS endpoints to patients, especially for early disease.

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Plain language summary

Why did we perform this research?

- When cancer treatments are assessed for how well they work, the most important measure that public health organisations and bodies who assess new treatment for reimbursement usually look at is how long patients stay alive after treatment ('overall survival').
- However, in early breast cancer, patients may continue to live for many years. This means they might find other efficacy and safety features more important when deciding on a treatment.

How did we perform this research?

- We identified 5 treatment features, also referred to as '**attributes**', relevant to patients based on published literature and expert interviews. These included: 1) overall survival, 2) cancer cells being eliminated from the body, 3) time from start of treatment spent cancer-free, 4) impact of side effects on quality of life, and 5) the option to undergo breast conserving surgery rather than breast removal.
- We recruited 334 patients who received a breast cancer diagnosis in the last 5 years across France, Germany, Italy and Spain. In an online survey, patients were asked to choose between two hypothetical treatments described by the 5 treatment attributes, or an opt-out. This was repeated multiple times with varying levels of the treatment attributes to understand which were most important to them.

What were the findings of this research?

- Patients considered cancer being eliminated from the body to be the most important attribute when making an eBC treatment decision. This was followed by time spent cancer-free and overall survival. The option to undergo breast conserving surgery and side effects were relatively less important.

What are the implications?

- The importance of this research is to help public health organisations and bodies who assess new treatment for reimbursement better understand the value of non-overall survival attributes to patients and inform their decision-making.

Disclosures

Ryan, J., Johal, S. and Varghese D. work for AstraZeneca, who co-funded this study; Dunton, K.. works for Daiichi Sankyo, who co-funded this study.

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Introduction

- The gold standard for measuring treatment effectiveness in oncology is overall survival. However, as patients with early breast cancer have a long life expectancy, treatment outcomes other than OS may be more relevant.
- Moreover, collecting OS information on patients with longer life expectancy takes a long time, which also introduces challenges of confounding factors.
- Within eBC, non-OS endpoints (DFS, pCR) have been approved as clinically relevant by regulatory agencies (EMA, FDA)[1-2].
- However, HTA bodies in many markets are reluctant to reimburse eBC treatments in the absence of mature OS data, which leads to delays in or lack of reimbursement of innovative treatments[3].
- eBC patients' opinions on the relative importance of treatment outcomes other than OS should be taken into consideration in the reimbursement decision.
- Therefore, this study explored and quantified eBC patient preferences for treatment endpoints and outcomes when making treatment decisions.

Methods

QUALITATIVE RESEARCH

- eBC treatment endpoints and outcomes that were considered relevant for patient decision-making, i.e., **treatment attributes**, were identified using a targeted literature review, 1:1 interviews (n=20 HCPs) and advisory board discussions (n=6 Patient Advocacy Group members).
- Five attributes were identified: **OS, pCR, DFS, side effects** (impact on QoL), and ability to undergo **BCS** as opposed to breast removal surgery.

QUANTITATIVE RESEARCH

- A **discrete choice experiment** was used to quantify stated patient preferences of eBC treatment attributes and the different levels within the attributes. See Figure 4 for all attribute levels.
- An external vendor recruited 334 patients across Germany, France, Italy, Spain who received a HER2+ eBC diagnosis in the last 5 years and received or were planning to receive neoadjuvant treatment. Patients who were eligible and consented to take part completed a ~20 min online survey including questions about participant **disease and treatment experience**, **socio-demographic** background, and **DCE tasks** (see Figure 1).
- Patients were presented with 15 DCE choice tasks and for each task, patients were given a choice between two hypothetical, unlabelled eBC treatment profiles, plus an opt-out option. The hypothetical treatments were defined by the five attributes with a range of varying attribute-levels.
- Preferences were generated using three models: multinomial logit, linear-coded MNL, and random parameters logit. No significant differences in model fit were observed between the RPL and linear-coded MNL. Thus, results are shown **based on the linear-coded MNL** model. Subgroup analyses based on socio-demographic and clinical variables was also conducted.

Figure 1. Illustrative DCE Task

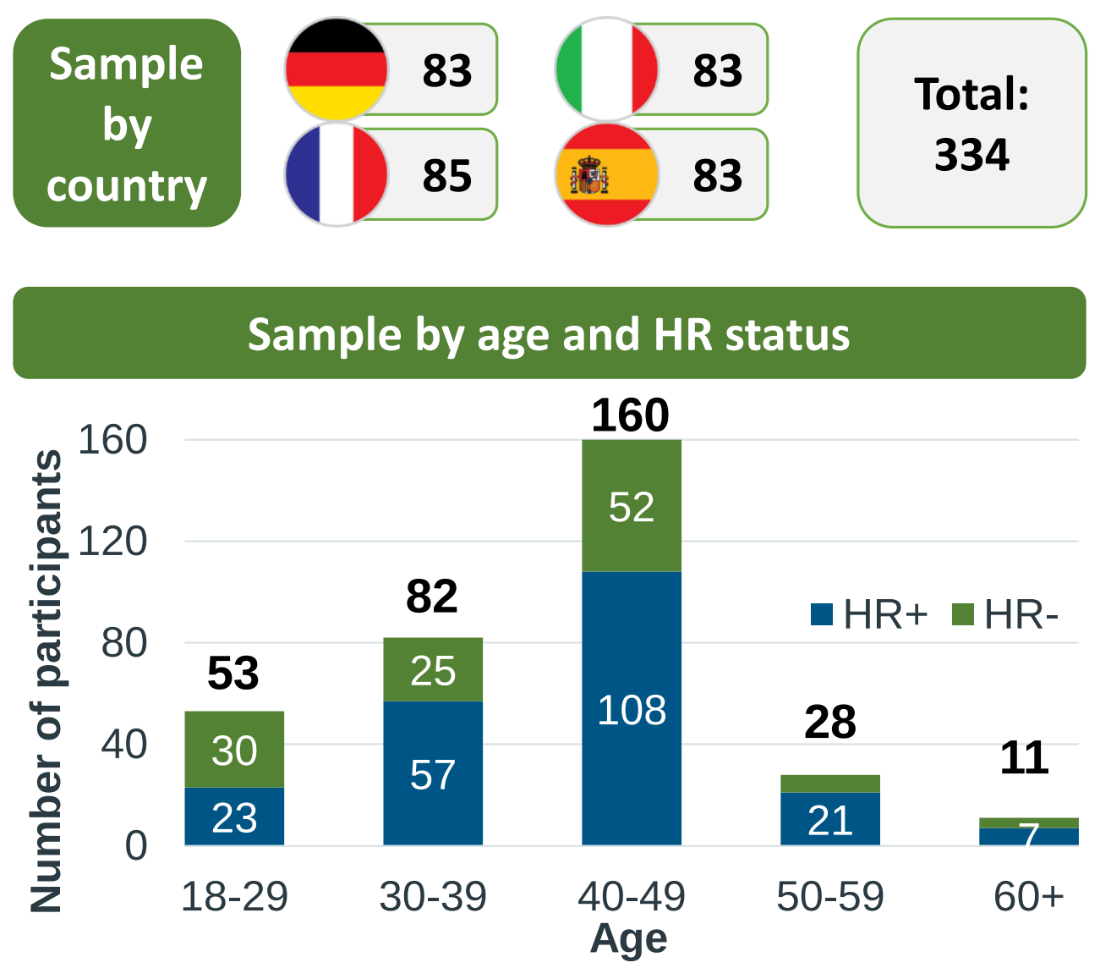
Treatment Feature	Treatment A	Treatment B	Neither
Pathological complete response (% of patients for whom there are no more invasive cancer cells found in the resected breast and lymph nodes in the region after treatment)	**50%**	**75%**	**None**
Disease free survival (% of patients for whom the disease has not come back 5 years after treatment)	**75%**	**Unknown**	**None**
Overall survival (% of patients alive 5 years after treatment)	**80%**	**Unknown**	**None**
Impact of side effects on QoL (The impact of treatment side effects on everyday activities (e.g., looking after yourself, including self-care) and overall quality of life)	**Mild side effects** (do not limit everyday activities)	**Moderate side effects** (occasional limits on everyday activities)	**None**
Breast Conserving Surgery (Surgical treatment that removes cancer from breast, while leaving as much healthy breast tissue as possible. Also known as lumpectomy)	**Yes**	**No**	**None**

Q. Based on the information provided for each imaginary treatment, please choose your preferred treatment:

☐ **Treatment A**
☐ **Treatment B**
☐ **Neither** - I would not choose either of these two imaginary treatments

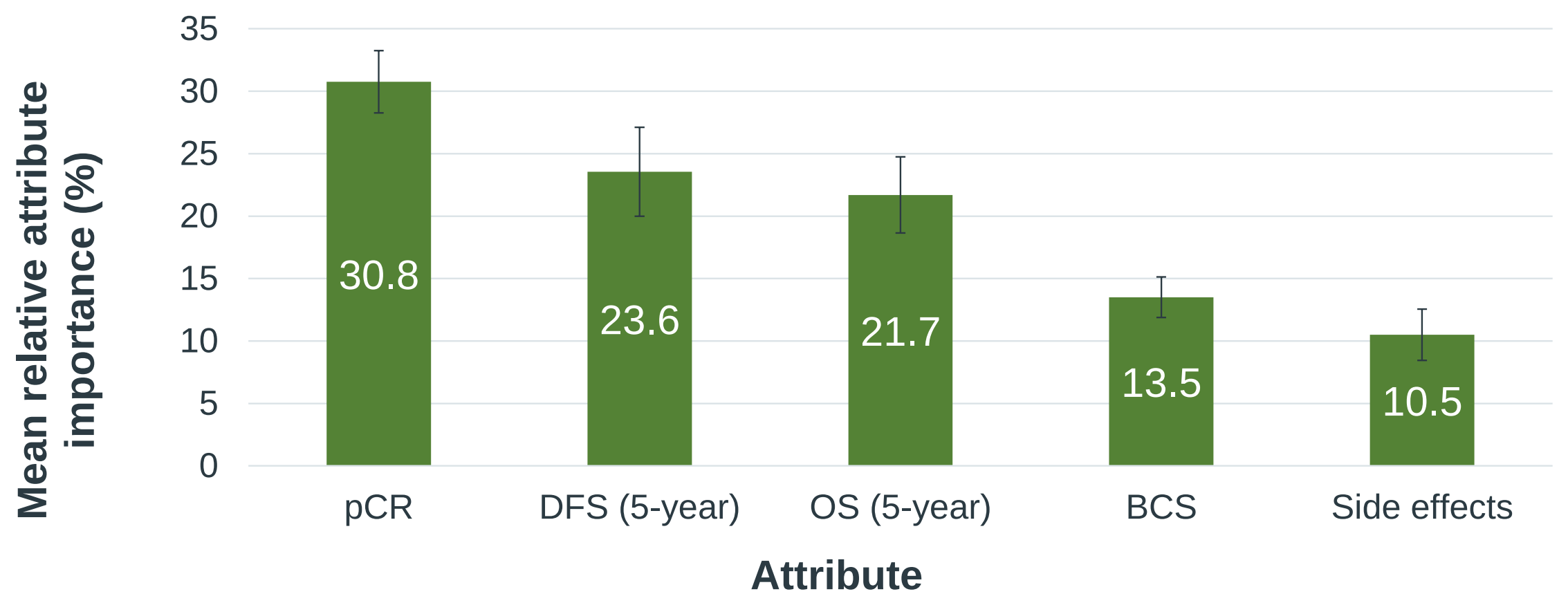
Results

Figure 2. Patient characteristics



- A **young patient population** was captured in this study, with a mean age of 40.1 years.
- The majority of patients were White/Caucasian individuals (92%), were married or in a civil partnership (71%) and working full-time (73%).
- 68% of patients completed a **higher education degree.**
- 65% of participants reported being **HR positive**.
- 38% of patients reported receiving a diagnosis between 6-12 months prior to the survey.
- Most patients **previously received treatment for eBC** (84%) and/or **planned to receive further treatment** for eBC (89%).

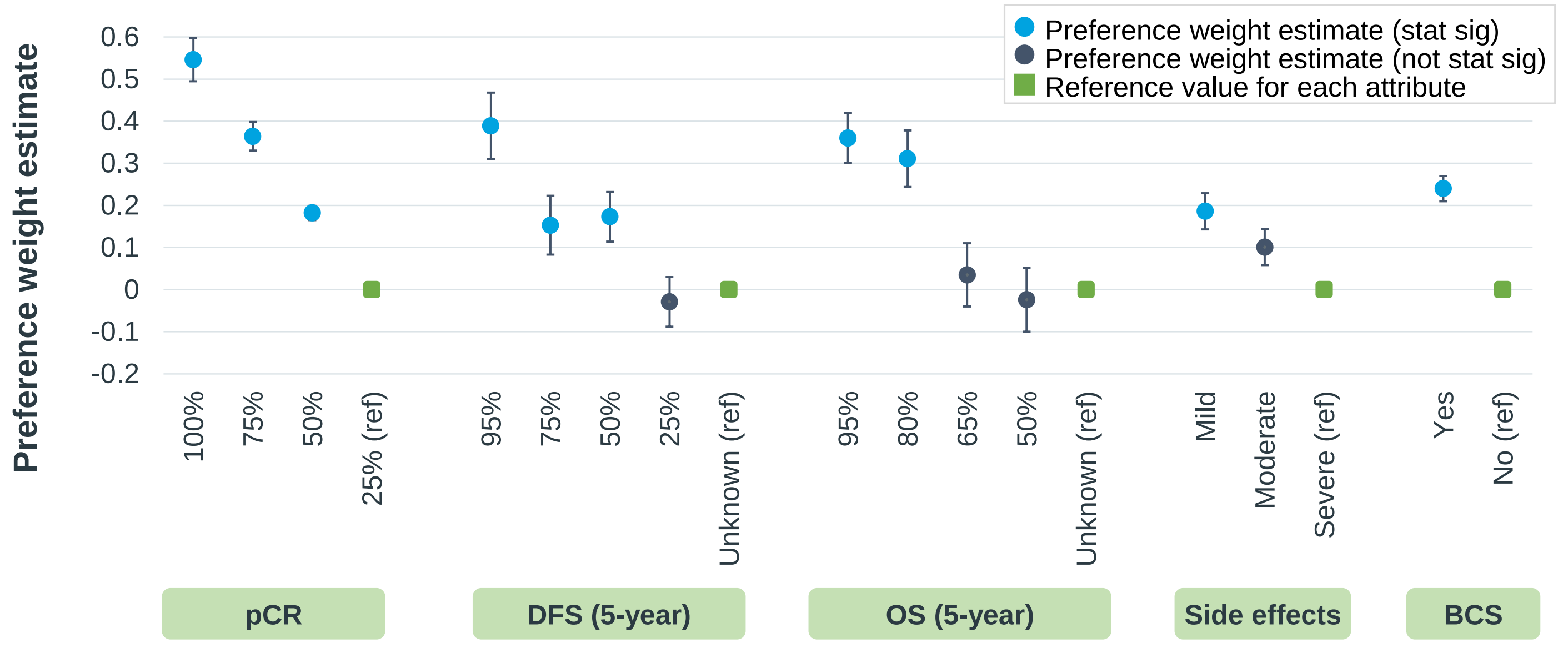
Figure 3. Relative attribute importance



Notes: N=334. Error bars show standard error. Preference weight estimates were normalised to compare relative importance of attributes, from most to least important. Relative importance was estimated using the preference weight estimates for each level of each attribute.

- The graph shows the **relative importance** of attributes that patients considered when choosing an eBC treatment, in percent, relative to all other attributes.
- Patients considered pCR to be the most important attribute relative to all other treatment attributes (31%)
- This was then followed by DFS (24%) and OS (22%)
- BCS (14%) and impact of side effects on QoL (11%) had less relative importance in treatment decision-making relative to all other treatment attributes.

Figure 4. Attribute-level preference weights

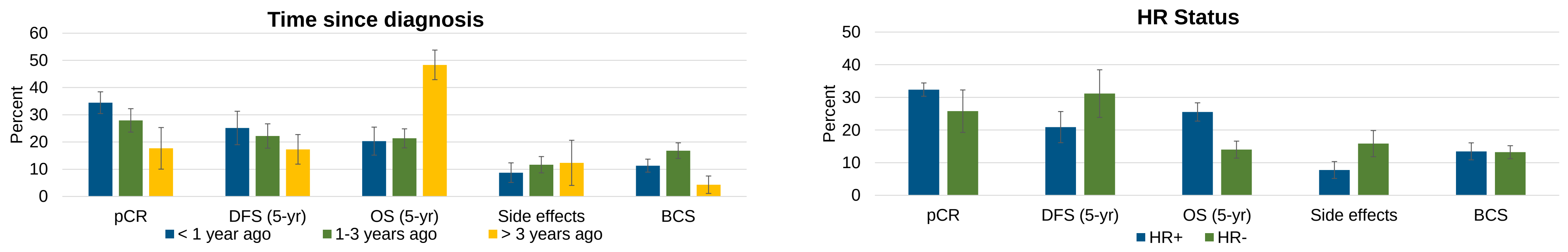


Notes: N=334. Error bars show standard error. 'Side effects' measures impact of SEs on QoL, defined as a) severe SEs but not life-threatening with some limits on everyday activities, b) moderate SEs with occasional limits on everyday activities, c) mild SEs that do not limit everyday activities. Abbreviations: Stat sig - Statistically significant; Ref – reference

- Figure 4 shows the value that patients with HER2+ eBC placed on varying treatment attribute-levels. Value is shown as a preference weight estimate against unique reference value per attribute.
  - Change in utility associated with a change in attribute level is represented by the vertical difference between the preference weight to the reference. Greater differences between weight coefficients mean patients viewed the change as having a relatively greater effect on overall marginal utility.
  - As expected, patients preferred better attribute-levels to worse levels. For instance, patients placed greater value on an increase in DFS of 75% to 95% compared to unknown DFS data.
- Most preference weight coefficients for each level within each attribute were statistically significant compared to their reference level ($p < 0.05$), except for 25% DFS compared to unknown DFS data at 5-years, 65% and 50% OS compared to unknown OS data at 5-years, and impact of moderate side effects on QoL compared to severe side effects.

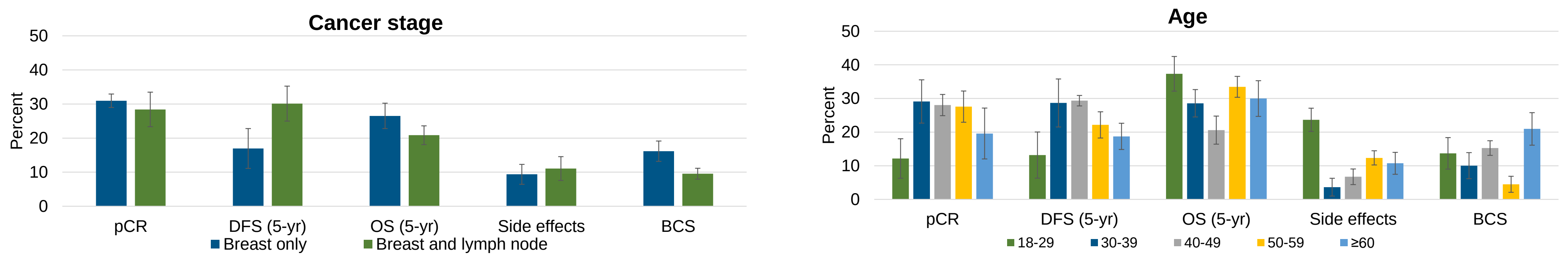
Figure 5. Patient subgroup differences

- Subgroup analyses were conducted to assess whether there were any differences in preferences between different subgroups of patients.
- Among the subgroups assessed, time since diagnosis, HR status, cancer stage and age showed statistically significant differences in preferences from overall sample (using Z-tests) and were of key interest with clinical implications.



Patients with more recent diagnoses (<1 year, 1-3 years) placed most relative importance on pCR vs. all other attributes, while patients who diagnosed > 3 years ago placed the most relative importance on OS.

HR+ patients placed the most relative importance on pCR vs. all other attributes, HR- patients placed highest importance on DFS. HR- patients placed double the importance of HR+ patients on SEs.



Patients whose tumour was only found in the breast placed the most relative importance on pCR while those in which cancer had spread to the lymph node placed similar relative importance on pCR and DFS.

The youngest (18-29 yrs) and oldest (50- 59, ≥60 yrs) patients placed most importance on OS. Patients aged 30-39 placed close to equal importance on pCR, DFS and OS while patients aged 40-49 placed highest importance on DFS.

Notes: Conditional relative attribute importance by subgroup was calculated to evaluate the conditional relative importance of attributes patients considered when choosing an eBC treatment between subgroups. N=334; Subgroups: HR+, n=216; HR-, n=118; <1 yr ago, n=166; 1-3 yrs ago, n=140; >3 yrs ago, n=28; Breast only, n=180; Breast and lymph node, n=154; 18-29, n=53; 30-39, n=82; 40-49, n=160; 50-59, n=28; ≥60, n=11. Given some subgroups had very small sample sizes (n =< 20), results should be interpreted with caution.

Discussion & Implications

- To our knowledge, this is the **first time** preference weights have been studied for **patients with HER2+ eBC** in the **neoadjuvant** setting, **capturing not only the importance of OS but also for surrogate endpoints** for treatment decision-making.
- eBC patients placed **most value on pCR relative to all other attributes**. Patients may see pCR as a more relevant endpoint when choosing neoadjuvant therapy compared to OS due to several factors. First, pCR suggests that the treatment is working. Second, patients may tend to think that pCR means their cancer is curable. Third, pCR may also be more easily understood as it relates to patients' experience of responding to the treatment and acts as proof of the disease being eliminated from the body.
- The **present results also reflect findings from literature** that pCR is important for eBC patients to make treatment decisions in the neoadjuvant setting[4] and for physicians to assess the success of neoadjuvant therapy[5].
- Given the hypothetical nature of the study, findings should be interpreted with the **caveat that real-world patient behaviours and decision-making may differ**. Additionally, there was a possibility of **unintentional recall bias** with self-reported data as some patients had previously undergone neoadjuvant treatment. Efforts were made to minimise this using patient-friendly wording developed in collaboration with patient advocacy groups and HCPs.
- Nevertheless, the study corroborates the **endorsement of pCR** and other non-OS endpoints as "patient-relevant" to **demonstrate treatment benefit to HTA bodies.** This is also in line with **reviews of EMA and FDA**, who have recently accepted pCR as a clinically validated endpoint[6-8].
- **Importantly, an adequate consideration of these endpoints** can ensure timely assessment and access for innovative treatments, **especially in absence of mature survival data**.

References

- 1) FDA, 2020
- 2) EMA, 2020
- 3) Anastasaki et al, 2022
- 4) Thill et al. 2016
- 5) von Minckwitz et al., 2012
- 6) Gion et al., 2021
- 7) CDER, 2014
- 8) Roche, 2015

Abbreviations

- BCS – Breast Conserving Surgery
- DCE – Discrete Choice Experiment
- DFS – Disease-Free Survival
- eBC – Early (Stage) Breast Cancer
- HCP – Health Care Professional
- MNL – Multinomial Logit
- OS – Overall Survival
- pCR – Pathological Complete Response
- QoL – Quality of Life
- RPL – Random Parameters Logit
- SE – Side Effects