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1 **Title:** Comparative review of pharmacological therapies in individuals with HER2 positive
2 advanced breast cancer with focus on hormone receptor subgroup.

3

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20 **Abstract:**

21 Breast cancer is the fifth leading cause of cancer related deaths worldwide. Randomized
22 controlled trials (RCTs) of targeted therapies in human epidermal receptor 2 (HER2) positive
23 advanced breast cancer (ABC) have provided an evidence base for regulatory and
24 reimbursement agencies to appraise the use of cancer therapies in clinical practice. However,
25 a subset of these patients harbor additional biomarkers e.g. a positive hormone receptor status
26 which may be more amenable to therapy, and improve overall survival. This review seeks to
27 explore the reporting of evidence for treatment effects by hormone receptor status using the
28 RCTs evidence of targeted therapies for HER2 positive ABC patients. PRISMA guidelines were
29 followed to identify published RCTs. Extracted data were synthesized using network meta-
30 analysis to obtain relative effects of HER2 positive targeted therapies. We identified a gap in
31 the reporting of the effectiveness of therapies by hormone receptor status as only 15 out of 42
32 identified RCTs reported hormone receptor subgroup analyses; the majority of which reported
33 progression free survival (PFS), but not overall survival (OS) or overall response rate (ORR).
34 In conclusion, we recommend that future trials in ABC should report the effect of cancer
35 therapies in hormone receptor subgroups for all outcomes.

36

37 1. Introduction

38 Breast cancer is the most commonly diagnosed cancer and the fifth leading cause of cancer-
39 related deaths worldwide (1). Advances in breast cancer screening, radiological, and surgical
40 techniques have helped to improve overall survival rates. Additionally, a deeper understanding
41 of the underlying molecular drivers of breast cancer pathogenesis has led to the development
42 of a range of targeted treatments; e.g. to hormone-receptors, human epidermal receptor 2
43 (HER2) receptors or programme death receptor ligand 1, allowing an era of personalized
44 medicine to be realized (2). When considering HER2-positive breast cancer, examples of
45 targeted therapies include, trastuzumab, lapatinib, trastuzumab emtansine, trastuzumab
46 deruxtecan, and neratinib etc. (3). Efficacy of these therapies has been demonstrated in
47 randomized controlled trials (RCTs) leading to their market access approval by regulatory
48 agencies, such as European Medicines Agency (EMA) and Food and Drug Administration
49 (FDA) in the US. These have been subsequently appraised by reimbursement agencies such
50 as National Institute for Health and Care Excellence (NICE) in the UK for use in routine clinical
51 practice. NICE determines clinical and cost-effectiveness (or value for money) for the
52 population covered in the full market authorization. However, they may consider the use of
53 subgroups (such as subgroups defined by hormone-receptor biomarker status) if evidence
54 shows an unclear value for money within one of the groups or in subgroups where patients are
55 known to have improved prognosis. For example, the NICE appraisal of lapatinib or
56 trastuzumab in combination with an aromatase inhibitor (AI) is recommended as the first-line
57 treatment of HER2-positive ABC, in hormone-receptor-positive population only (TA257 -
58 <https://www.nice.org.uk/guidance/ta257>). This review was undertaken to ascertain if there is
59 available RCTs evidence on hormone-receptor status in HER2-positive ABC, as to whether the
60 hormone-receptor status have a bearing on the clinical outcomes of individuals being treated
61 for HER2-positive ABC. Specifically, we investigated the level of reporting of RCTs results by
62 hormone-receptor status and explore whether the effectiveness of therapies in HER2-positive

63 ABC patients varies according to the hormone-receptor status (i.e. estrogen and or
64 progesterone biomarker status). Hormone-receptor subgroups were established as hormone-
65 receptor-positive (HR+ve) subgroup, which includes patients with positive estrogen and/or
66 progesterone receptor status, and hormone-receptor-negative (HR-ve) subgroup, which
67 includes patients whose status for both estrogen and progesterone were negative. Evidence
68 from the identified trials was synthesized to estimate the effect of treatments on progression
69 free survival (PFS) in HR+ve or HR-ve subgroups. The next section in this paper discusses the
70 methods used in this review, the results are discussed in section three, and section four
71 concludes with a summary of the findings, recommendations, limitations, and further research.

72

73 **2. Methodology**

74 **2.1. Literature Review**

75 RCTs were identified following a systematic approach, with a review of reviews carried out first
76 followed by a search of more recent RCTs. The first step identified all the trials used as evidence
77 in technology appraisals by NICE for targeted therapies in HER2-positive ABC patients. This
78 was followed by identifying reviews, systematic reviews, meta-analysis, and network meta-
79 analysis published in peer-reviewed journals that included RCTs of women with HER2-positive
80 ABC (4-29). This approach was employed to utilize comprehensive systematic reviews and
81 network meta-analyses that included RCTs of targeted therapies for HER2-positive ABC
82 patients. The final step was an additional search for more recent RCTs evaluating targeted
83 therapies among HER2-positive ABC patients. The eligibility criteria for selection of RCTs, and
84 search terms are listed below.

85 **Eligible criteria of selecting RCTs**

86 The eligibility of the RCTs for inclusion in this study was defined by the following criteria for the
87 population, interventions, comparators and outcomes (PICOs):

- 88 • Phase 2 and 3 RCTs focusing primarily on female patients with HER2-positive ABC.

- 89 • All treatments (interventions and comparators) targeted at HER2-positive ABC.
- 90 • RCTs that reported at least one of the following outcomes: overall survival (OS),
- 91 progression free survival (PFS), and overall response (ORR).

92 RCTs excluded were:

- 93 • Studies reporting only outcomes with adverse effect or patients.
- 94 • Studies focusing on treatment dose escalation and biosimilar studies of trastuzumab.
- 95 • Single-arm studies
- 96 • Studies involving only postmenopausal women, patients with brain metastasis,
- 97 leptomeningeal meningitis or central nervous system (CNS) metastases to ensure
- 98 homogeneity of the trial populations across treatments.

99 [Search Strategies](#)

100 The search of the systematic reviews covered NICE guidelines, PubMed, Cochrane Library,
101 and Scopus, with the search covering the period from the inception of the databases through
102 to 20 March, 2022. More recent RCTs were then searched for within Scopus and PubMed,
103 published in the last six years (2016 – 2022) to ensure more recent RCTs were included. The
104 PRISMA flow chart presenting all stages of study selection is shown in [Figure 1](#). The search
105 terms are included in the supplementary file 1.

106

107 [Figure 1: PRISMA flowchart of RCTs included in the review](#)

108

109 [2.2. Statistical methods](#)

110 Network meta-analyses (NMA) were carried out to assess the efficacy of treatments identified
111 in the review. Firstly, NMA was conducted using all the identified RCTs that formed a connected
112 network (i.e. the trial had at least one treatment arm in common with another trial in the network)
113 irrespective of whether the trial reported subgroups analyses or not. Secondly, NMA was
114 conducted using information reported for hormone receptor subgroups. The experimental

115 treatments and comparators of the identified RCTs included in the NMAs are different and thus,
116 in order to make comparisons across treatments, a reference treatment comparator needed to
117 be identified. The reference treatment comparator was selected as the most commonly
118 evaluated treatment in the connected networks, or where there were multiple common
119 treatment comparisons, then the most efficacious treatment was selected(30). The efficacy of
120 the treatments in the network including all HER2-positive patients were assessed based on
121 PFS, OS and overall response rate (ORR). Treatments effects on PFS and OS were measured
122 using hazard ratios (HRs) and the effects on ORR were measured in using odds ratios (ORs).
123 Comparative efficacy of cancer therapies by hormone-receptor subgroups were based on PFS,
124 which was the most commonly reported outcome in the identified RCTs. A random effects(31,
125 32) NMA in a Bayesian framework was used to synthesize the evidence from the identified
126 trials. The analyses were performed using the WinBUGS 1.4.3 software. The effectiveness
127 estimates were reported as means and corresponding 95% credible intervals (CrIs). Non-
128 informative prior distributions were used with the full WinBUGS code provided in the Technical
129 Support Document (TSD)(33).

130

131 [Figure 2: Network plots of identified trials \(reporting PFS\), with colors in the circles representing](#)
132 [the proportion of patients in each RCT that are HR+ve \(orange\), HR-ve \(green\), unknown](#)
133 [\(blue\), not reported \(grey\), and the middle purple circle indicated RCTs reporting subgroup](#)
134 [analyses.](#)

135

136 [Figure 3: Network plot of hormone receptors subgroup RCTs \(reporting PFS\)](#)

137

138

139

140 **3. Results**

141 **3.1. All RCTs network Results:**

142 Forty-two published RCTs focusing on treatments administered to HER2 positive ABC patients
143 were identified from 26 reviews and four NICE technology appraisals (TAs) (34-80). The eight
144 RCTs identified from the TAs overlapped with the RCTs identified in the reviews. There were
145 no additional RCTs identified from the additional search (of RCTs published between 2006 and
146 2022) that have not been included in the reviews (Figure 1). All RCTs meeting the eligibility
147 criteria and included in the review were phase II and phase III.

148 A network diagram of all 42 trials (reporting PFS) is displayed in Figure 2, similarly as in Cope
149 et al(81). Figure 2 included three networks of trials (with at least one arm common with another
150 trial, thus forming a network) disconnected from each other due to a lack of a common
151 comparator. In the plot (Figure 2), different colors in the circles indicate the proportion of
152 patients in each RCT that are HR+ve (orange), HR-ve (green), unknown (blue), and not
153 reported (grey). The trials reporting subgroup analyses by hormone-receptor status are
154 highlighted with a purple circle in the middle of a colored circle. Six RCTs recruited HR+ve
155 patients and of the 36 RCTs recruiting mixed populations of HR+ve and HR-ve patients, only
156 15 RCTs reported separate hormone receptor subgroup analyses. The identified RCTs do not
157 all form a connected network for the broader population; hence, three connected networks were
158 investigated. These connected networks are trastuzumab–taxane (HX) connected network
159 (Figure 2A), AI connected network (Figure 2B), and the trastuzumab–chemotherapy (HChem)
160 connected network (Figure 2C). Paclitaxel and docetaxel, which inhibit microtubule dynamics,
161 were classified as a taxane. Letrozole and anastrozole, which are non-steroid third generational
162 aromatase inhibitors that interferes with the production of estrogen, were classified as
163 aromatase inhibitors (AI), (30, 82-85). NMAs were carried out to compare treatments that form
164 each of the smaller connected networks. A list of all included RCTs is provided in the
165 supplementary file 2.

166 For the network of treatment comparisons for the total population (Figure 2), HX was the most
167 commonly evaluated intervention and thus was used as the reference treatment comparator.

168 The treatment effect estimates and corresponding 95% CrIs for PFS in this population for each
169 connected network are provided in [Figure 4](#). In the overall NMA, taxane showed an important
170 increase in the risk of disease progression compared to HX with a hazard ratio of 2.21 (95% CrI:
171 1.61, 2.91); pyrotinib + capecitabine (PYC) showed an important reduction in risk of progression
172 compared to HX with hazard ratio of 0.44 (0.20, 0.82); and capecitabine appeared to show a
173 meaningful increase in the risk of progression compared to HX with hazard ratio of 2.22 (1.00,
174 3.86). Other treatments evaluated using HX as the reference treatment did not show a
175 meaningful difference in effect as their 95% credible interval spans the point of no difference
176 (1). The relative treatment effects (for all treatment comparison in the network) for PFS, OS,
177 and ORR are reported in the supplementary file 3. For example, HER2 positive targeted
178 therapies combined with taxane –such as lapatinib with taxane (LX), neratinib with taxane (NX),
179 trastuzumab with taxane and bevacizumab (HXB), trastuzumab with taxane and carboplatin
180 (HXCb), trastuzumab with taxane and capecitabine (HC), trastuzumab with taxane and
181 pertuzumab (PHX), trastuzumab with everolimus and taxane (HXE), and trastuzumab with
182 taxane and non-pegylated liposomal doxorubicin (HXNPLD) – and some targeted therapies like
183 trastuzumab emtansine (TDM1), and neratinib with capecitabine, all had an important
184 decreased risk of disease progression compared to taxane alone. In addition, TDM1 (using the
185 points estimates) showed to prolong overall survival when compared to other HER2-positive
186 targeted therapies like HX, HC, LC, taxane, and LX (see supplementary file 3). Pertuzumab
187 with TDM1 (PTDM1) showed a meaningful decreased risk in disease progression compared to
188 LC, capecitabine, taxane, and neratinib. The relative treatment effects of all treatments
189 evaluated in the mixed and hormone receptor subgroup population are reported in the
190 supplementary file 3. PYC showed a meaningful decreased risk in disease progression
191 compared to some targeted therapies such as HX, TDM1, LX, and trastuzumab with
192 capecitabine. The meaningful treatment effects showed by PYC could be associated with the fact that
193 pyrotinib is an irreversible inhibitor of the ERBB family including HER1, HER2, and HER4; therefore,
194 potentially allowing wider HER2 inhibition compared to other anti HER2 therapies. In addition, PYC was

195 evaluated only as a second line of therapy, which may have had an impact on the results from the NMA
196 as we discuss in more detail in the Discussion section. For the AI connected network (Figure 2B),
197 only HR+ve patients were included as the AI therapies are only used in the HR+ve breast
198 cancer setting (84).

199

200 [Figure 4: Summary forest plots obtained from the NMA including all RCTs for PFS](#)

201

202 **3.2. Results of subgroup analyses:**

203 Among the 15 RCTs that recruited mixed populations of hormone-receptors status patients and
204 reported their subgroups analyses, 13 RCTs reported results for HR+ve patients and 14 RCTs
205 reported results for HR-ve patients. The number of treatment regimens evaluated in the
206 hormone-receptor subgroups (16) was smaller than the treatment regimens evaluated in the
207 overall NMA (26). These do not include treatment regimens in the AI and HChem connected
208 network, as RCTs in both connected networks have primarily HR+ve participants. Network plots
209 of RCTs within the hormone receptor subgroups are displayed in [Figure 3](#). The RCTs that
210 reported results for the hormone-receptor subgroups formed two disconnected networks in the
211 subgroup analysis; HX connected network, and capecitabine connected network. [Figure 5](#) and
212 [Figure 6](#) show summary forest plots of treatments effects for PFS in the hormone-receptor
213 subgroups respectively for the HX connected network, and the capecitabine connected
214 network. The treatment effects from the HR+ve subgroup and HR-ve subgroup are depicted
215 with red and blue bar plots respectively. The green bar plots shows the estimated treatment
216 effects for the mixed patients using only RCTs that reported subgroup analysis, and the grey
217 bar plots depict the treatments effects extracted from the overall NMA including all RCTs ([Figure](#)
218 [4](#)). In the subgroup analysis, PYC showed a meaningful reduction in the risk of disease
219 progression compared to lapatinib with capecitabine (LC) in the HR-ve subgroup analysis with
220 a hazard ratio of 0.31 (95%CrI: 0.12, 0.70). Other treatment regimens evaluated in the

221 capecitabine or HX connected network did not show a meaningful effect as the 95% credible
222 intervals included the point of no difference (value of 1).

223

224 [Figure 5: Comparative summary forest plots of treatment effects obtained from the HX
225 connected network for PFS](#)

226

227 [Figure 6: Comparative summary forest plots of treatment effects obtained from capecitabine
228 connected network for PFS](#)

229

230 **4. Discussion and conclusion**

231 We have conducted the first review of RCTs involving HER2-positive ABC, specifically focusing
232 on the reporting of treatment effects by hormone receptor status. . We found that the RCTs that
233 reported subgroups analyses reported PFS, not OS or ORR. We would like to note that despite
234 PFS being the primary endpoint of these RCTs, evidence of its surrogacy for OS in HER2-
235 positive ABC is limited (86).

236 Our results show that, regardless of the hormone-receptor status of the patients, a taxane-only
237 therapies were associated with an important increased risk of disease progression compared
238 to HX as well as to other targeted therapies combined with a taxane (as shown in
239 supplementary file 3). This supports the findings from the wider literatures (7, 45, 48, 59, 66).
240 PYC showed a meaningful effect over HX with a hazard ratio of 0.44 (95% CrI: 0.20, 0.82). In
241 the subgroups analyses, PYC showed a meaningful effect over LC in the HR-ve subgroup
242 analysis with a hazard ratio of 0.31 (95% CrI: 0.12, 0.70) and the mixed patients' analysis with
243 a hazard ratio of 0.40 (95% CrI: 0.18, 0.79).

244 In addition, our results indicate that the point estimates of HER2 treatments in combination with
245 an AI show a meaningful effect over AI alone, which support the findings by Kawalec et al (13)

246 One of the limitations of the review, from the point of view of the clinical interpretation was the
247 fact that our NMA for both the overall population and the hormone receptor subgroups included
248 all RCTs that evaluated targeted therapies in HER2-positive patients irrespective of their line of
249 treatments. We chose this approach to capture all relevant evidence available in the reporting
250 of hormone receptor subgroup analysis in the RCTs, as the primary aim of this review was to
251 assess the level of reporting of the effectiveness of therapies in the biomarker subgroups and
252 the impact of under-reporting on the results of NMA. The non-homogeneity of the included
253 RCTs in terms of treatment line could have played a significant role in the results obtained from
254 the NMA. For example, as mentioned in the Results section, the three RCTs that evaluated
255 PYC in comparison to either LC or capecitabine, recruited HER2-positive ABC patients whose
256 disease have progressed after receiving HX, which could have resulted in a meaningful and
257 relatively large treatment difference between PYC and HX. The conclusions drawn from these
258 results are not specific to the line of therapy and therefore the clinical interpretation of these
259 results is limited. Moreover, the sparse and almost star shape geometry of the network as well
260 as the lack of direct evidence of PYC with other HER2 target therapies, such as TDM1,
261 pertuzumab, or HX, mean that there are further limitations of the results in terms of their
262 reliability for the clinical interpretation.

263 Our review did not identify important differences in treatment effectiveness across hormone-
264 receptor subgroups. The treatment effects estimates for the subgroup analyses were estimated
265 with increased uncertainty (compared to the mixed population), not only due to the reduced
266 sample size in the subgroups, but also due to the limited reporting of subgroup analyses the
267 RCTs. However, across treatments, the HR-ve subgroup often present with lower estimated
268 hazard ratio than HR+ve patients for PFS. This may therefore warrant a further RCT, powered
269 to investigate the efficacy of HER2 targeted therapies among hormone-receptor subgroups and
270 extending the outcomes assessed by subgroup to include not only PFS but also OS, and ORR.
271 This is because, while PFS may be an attractive primary endpoint as it is available earlier than

272 OS, and is not influenced by subsequent treatments, questions regarding whether PFS is a
273 valid surrogate for OS remain (87-89). Alternatively, an RCT could also be complemented with
274 an analysis of Electronic Health Records (EHR) to explore if these HER2 targeted therapies
275 are more effective in HR+ve patients compared to HR-ve patients.

276 Our work serves as an example of exploring the support of a broad evidence base (across
277 treatments) for subgroup effects. It illustrates the evidential and methodological challenges in
278 formally considering subgroups effects using extended networks, which arise due to limited
279 reporting of subgroup results; not only across trials but also across outcomes. This work is still
280 important to inform the value and uncertainty over restricted use in decisions at national level,
281 such as those facilitated by NICE in the UK. This is particularly important where clinical and
282 economic value of a treatment in a particular subgroup is unclear, and therefore the value of
283 wide adoption is also unclear. In this case, drawing on such an extended evidence base can
284 inform further research recommendations, particularly in considering whether subgroup effects
285 may be generalized across treatments. . Our review, could be further extended to include data
286 that targets the wider HER2 treatment pathway, or to include outcomes such as adverse events,
287 quality or life, or time to progression (TTP).

288

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292 **Authors' contributions:**

293 Conceptualization and design: CMUC, SB

294 Data collection: CMUC, SB

295 Statistical analysis: CMUC

296 Clinical expertise: AO, SK

297 Manuscript: CMUC

298 Critical revision of the manuscript: CMUC, MOS, AO, RKO, SK, KRA, SB

299 Supervision: MOS, RKO, KRA, SB

300 Funding acquisition: SB, KRA, RKO

301 **Ethics approval and consent to participate:** Not needed

302 **Consent for publication:** Not needed

303 **Data availability:** All data used in this manuscript are reported in the supplementary file 1 and
304 can all be access online.

305 **Competing Interest**

306 SB is a member of the NICE Decision Support Unit. She served as a paid consultant, providing
307 unrelated methodological advice to NICE, pharmaceutical industry and consultancy companies.
308 She received payments for educational events from Roche and has received research funding
309 from European Federation of Pharmaceutical Industries & Association (EFPIA) and Johnson
310 and Johnson.

311 RKO is a member of the National Institute for health and Care Excellence (NICE) Technology
312 Appraisal committee, member of the NICE Decision Support Unit (DSU), and associate member
313 of the NICE Technical Support Unit (TSU). She has served as a paid consultant to the

314 pharmaceutical industry, providing unrelated methodological advice. She reports teaching fees
315 from the Association of British Pharmaceutical Industry (ABPI) and the University of Bristol.

316 KRA is a member of the National Institute for Health and Care Excellence (NICE) Diagnostics
317 Advisory Committee and is a National Institute for Health & Care Research (NIHR) Senior
318 Investigator Emeritus. He has acted as a paid consultant, providing unrelated methodological
319 and strategic advice, to the pharmaceutical and life sciences industry generally, as well as to
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327 MOS is a member of a research funding panel for the National Institute for Health and Care
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331 CMUC has no conflicts of interest to declare.

332 AO has no conflicts of interest to declare

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601 [Additional material](#)

602 [Supplementary file 1](#)

603 Name: Searchterms.docx

604 Description: List of the search terms used in the review

605 [Supplementary file 2](#)

606 Name: IncludedRCTs.docx

607 Description: List of RCTs included in the review

608 [Supplementary file 3](#)

609 Name: PFS treatment effects.xls

610 Description: Relative treatment effects of the targeted therapies evaluated

611