

# Unveiling the Economic Landscape: Burden of HR+/HER2- Locally Recurrent Inoperable or Metastatic Breast Cancer

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## Background and objectives

- Hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-) breast cancer (BC) comprises 65%-75% of all BCs, with one in six early-stage patients experiencing recurrence or death within five years despite endocrine therapy (ET)<sup>1</sup>.
- First-line (1L) treatment for locally recurrent or metastatic HR+/HER2- BC includes CDK4/6 inhibitor (e.g. palbociclib, abemaciclib or ribociclib) combined with an aromatase inhibitor or fulvestrant (F)<sup>2,3,4</sup>. Second-line (2L) treatment involves switching to another endocrine agent, possibly combined with targeted therapy (TT). For patients whose disease progresses and are not refractory to ET, an alternative ET + TT is recommended<sup>2,3,4</sup>. For patients who can no longer receive ET due to disease progression or ineligibility, chemotherapy (CT) is the standard of care<sup>5</sup>.
- This systematic literature review (SLR) is aimed to summarize economic burden (economic evaluations [EE] and costs and healthcare resource use [HCRU]) associated with HR+/HER2- locally recurrent inoperable or metastatic HR+/HER2- BC.

## Methods

- A PRISMA-compliant SLR was conducted with searches conducted across Embase, MEDLINE, and HTA databases for relevant studies. Relevant conference proceedings search for last three years (2021-2024) and bibliographic searching of relevant reviews were also performed.

Table 1: Eligibility criteria (PICOS)

Parameters	Economic evaluations	Costs and HCRU
Population(s)	HR+/HER2- locally recurrent inoperable or metastatic BC patients who are eligible for CT once ET and TT options are exhausted	HR+/HER2- locally recurrent inoperable or metastatic BC patients
Intervention	Pembrolizumab + one of four CT regimens: 1) paclitaxel (PACL), 2) nab-paclitaxel 3) liposomal doxorubicin 4) Capecitabine (CAPE) Doxorubicin, Liposomal doxorubicin, Cyclophosphamide, PACL, Nab-paclitaxel, Gemcitabine, Docetaxel, Trastuzumab deruxtecan, Vinorelbine, Epirubicin, Eribulin, CAPE, Sacituzumab govetican, Olaparib, Talazoparib, Alpelisib (A) + F, Larotrectinib, Entrectinib, Dostarlimab, Elacestrant, Selpleratinib, Capivasertib, Ixabeplirome	No restriction
Comparators	Any of the treatments listed above compared against each other, or with placebo, or BSC	No restriction
Outcomes	Cost-effectiveness outcomes such as incremental cost-effectiveness ratio (ICER), cost/quality-adjusted life-years (QALY), incremental cost/life-years gained (LYG), etc	Healthcare resource utilization, costs (direct costs and indirect costs)
Study design	Any study reporting the above listed outcomes	
Geography, Time frame	Global, Database inception to 08 July 2024	
Language	Studies with full texts published in the English language	

<sup>a</sup> A: Alpelisib; BC: breast cancer; BSC: best supportive care; CAPE: Capecitabine; CT: chemotherapy; ET: endocrine therapy; F: fulvestrant; HCRU: healthcare resource use; HER2-: human epidermal growth factor receptor 2 negative; HR+: hormone receptor positive; ICER: incremental cost-effectiveness ratio; P: Palbociclib; PACL: paclitaxel; QALY: quality-adjusted life-years; TT: targeted therapy

## Economic evaluations

- Eleven economic evaluations (7 cost-effectiveness studies from the USA [n=2], Europe [n=2], and Middle East [n=3], plus 4 HTAs from NICE, SMC, and CADTH) were identified.
- A+F was cost-effective against Palbociclib (P) +F, in PIK3CA-mutated patients in Qatar and was dominant in Oman and Türkiye (Table 2).
- A+F was cost-effective vs F in Türkiye (ICER: 176,646 Turkish Lira [TL]/LYG, was <3 times the GDP per capita [257,056 TL]) and it also dominated Ribociclib+F, P+F, everolimus (EVE) + exemestane (EXE) and CT (cost year not reported)<sup>5</sup>.
- F was dominant over Cyclophosphamide + Methotrexate + Fluorouracil (CMF) for advanced HR+/HER2- BC in Ukraine with an ICER of -109,497.84 Ukrainian hryvnia (₴) per LYG, indicating both cost savings (217,906.54₴ vs 258,969.23₴) and survival benefits (1.875 vs 1.5 years) (cost year not reported)<sup>6</sup>.
- NICE 2022<sup>7</sup> found A+F cost-effective vs EVE+EXE for HR+/HER2- BC (ICER: £49,907/QALY), while SMC 2022<sup>8</sup> and CADTH 2022<sup>9</sup> deemed it not cost-effective (ICERs: £70,027/QALY and \$69,674/QALY, respectively) (Table 2).

Table 2: Economic evaluation studies results

Study name, Country or HTA (cost year)	Intervention vs comparators	ICER/QALY gained	Conclusion
Kourlaba 2015, Greece (2013) <sup>10</sup>	EVE+EXE vs Bevacizumab+PACL /CAPE	Dominant	EVE+EXE dominated Bevacizumab+PACL/CAPE with greater health benefits at lower lifetime costs.
Liang 2024, USA (2023) <sup>11</sup>	Capivasertib+F vs F alone	\$152,678 \$45,490	Capivasertib+F not cost-effective vs F alone at \$150,000 WTP threshold.
Soliman 2023, Qatar (2021) <sup>12</sup>	A+F vs P+F	\$11,876	A+F cost-effective in Qatar using GDP-based thresholds (\$62,088-\$186,264/QALY).
Soliman 2023, Oman (2021) <sup>13</sup>	A+F vs Abemaciclib+F	\$147,657	A+F dominated CDK4/6 inhibitors in Oman, being less costly and more effective.
Soliman 2023, Oman (2021) <sup>13</sup>	A+F vs EVE+EXE	Dominant	A+F was cost-effective in Oman vs EVE+EXE.
Wu 2023, USA (2023) <sup>14</sup>	A+F vs Placebo+F	\$340,153.30	A+F not cost-effective vs placebo+F from US payer perspective, exceeding WTP threshold.
Piqray®, NICE 2022 (2019-2020) <sup>7</sup>	A+F vs EVE+EXE	£49,907	A+F was cost-effective with Patient Access Scheme pricing (Patients met NICE's end-of-life criteria and therefore considering a WTP threshold of £50,000 per QALY gained).
Piqray®, SMC 2022 (NR) <sup>8</sup>	A+F vs EVE+EXE	£70,027	A+F was not cost-effective at list price.
Piqray®, SMC 2022 (NR) <sup>8</sup>	A+F vs F alone	£200,839	A+F was not cost-effective at list price.
Piqray®, CADTH 2022 (2021) <sup>9</sup>	A+F vs standard care (EVE+EXE)	\$69,674	A+F was not cost-effective at a \$50,000/QALY threshold.
Piqray®, CADTH 2022 (2021) <sup>9</sup>		\$319,592	After CADTH's exploratory reanalysis, which adjusted for several limitations in the original model, the ICER increased to \$319,592 per QALY gained.
Trodelvy, CADTH 2024 (2023) <sup>15</sup>	Sacituzumab govetican vs TPC	\$341,152	Sacituzumab govetican was not cost-effective.

<sup>a</sup> A: Alpelisib; CADTH: Canadian agency for drugs and technologies in health; CAPE: Capecitabine; CDK4/6i: cyclin-dependent kinase 4/6 inhibitor; EVE: Everolimus; EXE: Exemestane; F: fulvestrant; GDP: gross domestic product; HCRU: healthcare resource use; HTA: health technology assessment; ICER: incremental cost-effectiveness ratio; NICE: national institute for health and care excellence; NR: not reported; P: Palbociclib; PACL: paclitaxel; QALY: quality-adjusted life-years; SMC: Scottish medicines consortium; TPC: treatment of physician's choice; TT: targeted therapy; US: United States of America; WTP: willingness to pay

## HCRU studies

- Out of 20 studies on HCRU, only 10 studies reported on the proportion of patients with at least one hospitalization, outpatient visit, or emergency room (ER) visit regardless of line of therapy (LOT) and type of treatment received (Table 3).
- The remaining studies provided data in continuous measures.

## Acknowledgments

Not applicable

## Disclosures (if required)

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- Hospitalization rates were lower in patients receiving ET than those receiving PI3Ki both in 2L (13% vs 29%) and 3L settings (15% vs 26%)<sup>16</sup>.
- Adverse events (AE) related HCRU was generally higher for CT compared to EVE treatment (incidence rate range: 1.44-1.72 PPPM vs 0.76-1.23 PPPM) across all lines of therapy<sup>17,18</sup>.

## Length of stay (LOS)

- The mean LOS during hospitalization in patients with HR+/HER2- metastatic BC ranged from 5.48<sup>19</sup> to 7.2<sup>20</sup> days per hospitalization.
- Higher mean LOS was seen in
  - post progression vs pre progression (9.2 days vs 6 days per hospitalization)<sup>21</sup>
  - patients receiving CT (1.6-3.6 days PPPM) vs ET (0.6-1 days PPPM)<sup>22</sup>
  - patients receiving abemaciclib vs palbociclib vs ribociclib (4.6 days vs 2.4 days vs 2.1 days, respectively)<sup>23</sup>

## Table 3. HCRU outcomes (%)

Study name, Country	N	% Hospitalizations	% ER visits	% Outpatient visits
Basho 2024 <sup>16</sup> , USA <sup>a</sup>	2449	10-29	23-42	NR
Collin 2024 <sup>24</sup> , USA <sup>b</sup>	NR	4.5-17.5	1.3-8.7	NR
Dent 2021 <sup>25</sup> , USA <sup>b</sup>	108	23.9-27.4	NR	85.5-91.3
Goyal 2019 <sup>19</sup> , USA	3622	77.3	81.1	95.1
Goyal 2021 <sup>19</sup> , USA	5563	55.8	49	96.3
Houts 2019 <sup>19</sup> , USA	57	40.4	21.1	NR
Lang 2014 <sup>27</sup> , USA	325	83.1	NR	90.2
Park 2020 <sup>21</sup> , South Korea <sup>c</sup>	1636	62.4-77.6	NR	98.7-100
Sava-Bordalo 2021 <sup>28</sup> , Portugal	65	4.6	35.4	NR
Schneider 2021 <sup>29</sup> , Netherlands	416	74.2	68	NR

<sup>a</sup>regardless of LOT and type of treatment received; <sup>b</sup>regardless of treatment received; <sup>c</sup>regardless of progression status; HCRU: healthcare resource utilization; ER: emergency room; NR: not reported; USA: United States of America

## Healthcare Costs

- Nineteen studies specifically addressed mean total healthcare costs, variously reported as total costs, total direct costs, or total direct medical costs.
- These studies revealed substantial economic burden, with PPPM costs ranging from approximately \$7,000 to \$26,000 in the USA, €4,800 to €25,400 PPPY in Europe, and varying costs in other regions (Table 4).
- Two studies from USA reported that patients receiving abemaciclib (range: \$23,639 - \$25,920 PPPM) had higher total costs than patients receiving palbociclib (range: \$19,370 - \$19,977 PPPM) and ribociclib (range: \$19,176 - \$20,956 PPPM)<sup>23,30</sup>.

## Table 4: Total healthcare costs

Study name, Country	Cost item	Cost year	Mean costs	Time units for cost estimation
Basho 2024 <sup>16</sup> , USA <sup>a</sup>	Total costs	2022	\$15,396 - \$17,853	PPPM
Brezen-Masley 2021 <sup>31</sup> , Canada	Direct medical and non-medical costs	2017	C\$77,111	PPPY
Burne 2021 <sup>33</sup> , USA <sup>b</sup>	Total direct medical costs (inpatient, ER, outpatient, pharmacy)	2018	\$19,176-\$25,920	PPPM
Burton 2016 <sup>32</sup> , USA	All-cause total healthcare costs	2012	CT only during 1L: \$10,727 ET only during 1L: \$7,037	PPPM
Collin 2024 <sup>24</sup> , USA	All-cause total healthcare costs	NR	\$8,734	PPPM
de Las Heras 2020 <sup>33</sup> , Spain	Total direct and indirect costs	2016	€ 120,664	per patient over 5 years
Engel-Nitz 2015 <sup>34</sup> , USA	Total-cause total costs (office, outpatient, ER, inpatient visits and other medical services costs, pharmacy)	2013	\$11,334	PPPM
Gauthier 2018 <sup>22</sup> , USA <sup>a</sup>	Total healthcare costs (Inpatient, ER, Outpatient, DME, drug costs and pharmacy costs)	2015	\$7,479 - \$13,329	PPPM
Goyal 2019 <sup>20</sup> , USA	All cause total costs	2015	\$16,075	PPPM
Goyal 2021 <sup>19</sup> , USA	All cause total costs	2015	\$14,424	PPPM
Hao 2016 <sup>17</sup> , USA <sup>c</sup>	Total all-cause medical service costs	2014	€ 2,954 - \$10,268	PPPM
Houts 2019 <sup>35</sup> , USA	Total costs	NR	\$17,065,60	PPPM
Lang 2014 <sup>27</sup> , USA	Total healthcare costs	2011	\$7,271	PPPM
Lao 2023 <sup>36</sup> , New Zealand <sup>d</sup>	Total public medical costs (include costs for public outpatient services, public inpatient services, and funded pharmaceuticals [public or private hospital prescribed])	2019/2020	\$NZ 8,321 - \$NZ 21,331	per patient over the study period
Li 2016 <sup>18</sup> , USA <sup>c</sup>	Total all-cause medical service costs	2014	\$4,790 - \$8,889	PPPM
Palladio 2023 <sup>37</sup> , Italy <sup>b</sup>	Direct medical costs	2021	€23,177 - €25,397	PPPY
Park 2020 <sup>21</sup> , South Korea <sup>a</sup>	Total healthcare cost	NR	\$9,939.8 - \$21,958.5	PPPM
Piccinini 2019 <sup>38</sup> , Italy <sup>d</sup>	Total cost	NR	€3,888 - €7543	PPPY
Pluard 2023 <sup>39</sup> , USA <sup>b</sup>	Total (Inpatient, ER, outpatient, pharmacy) cost	NR	\$19,370 - \$23,639	PPPM

<sup>a</sup>regardless of LOT; <sup>b</sup>regardless of type of CDK4/6 inhibitor received; <sup>c</sup>regardless of LOT and type of treatment received; <sup>d</sup>regardless of treatment phase or follow up years; <sup>e</sup>regardless of progression status; ER: emergency room; DME: durable medical equipment; CT: chemotherapy; ET: endocrine therapy; 1L: first-line; PPPM: per patient