Cost-Effectiveness Analysis (CEA) of Pertuzumab and Trastuzumab (PH) + Chemotherapy (CT) Versus H + CT in HER2-Positive Early Breast Cancer (EBC): Updated Model Using Data from the 8.4-Year Follow-Up of APHINITY

EE501

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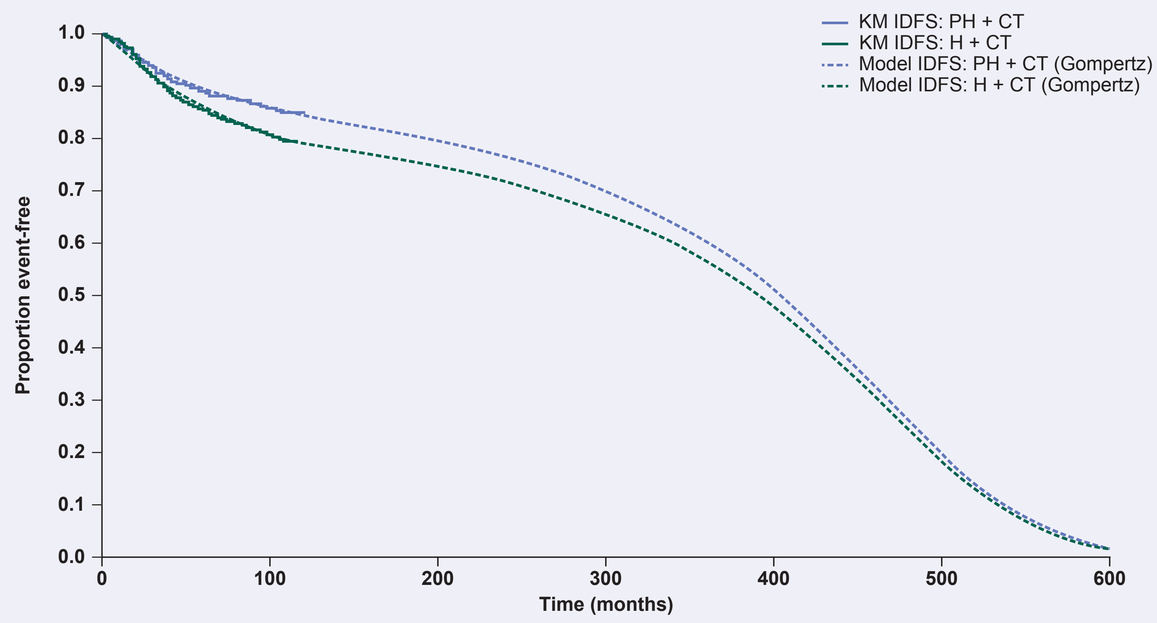
Background

- Human epidermal growth factor receptor 2-positive breast cancer (HER2+ BC) is an aggressive subtype and prior to the introduction of HER2-targeted therapies, was associated with poor prognosis.[1–3]
- In the adjuvant setting for patients with HER2+ EBC at high risk of recurrence, PH + CT is standard of care (SoC)[4] based on significant invasive disease-free survival (IDFS) improvement vs. H + CT in the APHINITY trial (NCT01358877).[5]
- Despite the advances in SoC, some patients eventually experience metastatic disease recurrence. First-line (1L) SoC for HER2+ metastatic BC (MBC) is PH + taxane CT[6,7] based on the results of the CLEOPATRA trial.[8] More recently, trastuzumab deruxtecan (T-DXd) was approved for HER2+ MBC in the 1L for patients with early recurrences (during or within 6 months of completing [neo]adjuvant therapy) and in second-line or later (2L+),[9,10] reflecting the ongoing evolution of the HER2-targeted treatment landscape.
- MBC is associated with productivity, financial, societal and quality of life burdens[11–13] and effective treatment in the curative EBC setting, to delay or prevent metastatic recurrence, is of critical importance.
- A previous CEA model used primary analysis data from APHINITY (median follow-up of 45.4 months) to project that use of PH is cost effective in the US for patients with HER2+ EBC at high risk of recurrence.[14]
- Here, we present an updated CEA model that uses data from the APHINITY third interim analysis (3IA) of overall survival (OS) with a median follow-up of 8.4 years.[15,16] The model estimates PH + CT cost effectiveness in three countries (Belgium, Spain and the Republic of Ireland [ROI]). Additionally, we explore how changes in the MBC treatment landscape can impact the results of the EBC model.

Methods

- A Markov-based, decision-analytical (state transition) model was used, as described previously.[14]
- Kaplan–Meier data for IDFS and OS from the APHINITY 3IA[15,16] were incorporated into the model. Other updates included model extrapolations, type of IDFS event (metastatic vs. non-metastatic recurrence) for late recurrences (>18 months) and additional adverse events.
- A Gompertz distribution was used for IDFS parametric modelling (Figure 1) as it provided a better fit for the data for both treatment arms, compared with a log-normal distribution.
- Modelling of treatment effects and cure proportion timings were updated to account for the longer follow-up duration. The time points at which the treatment effect started to decrease in the reference case, and at which the cure proportion started, were increased to 96 months to include all the observable data from the latest readout.
- Drug costs were based on publicly available list prices (only public list prices were available in Spain and the ROI).
- The model explored cost effectiveness of PH + CT vs. H + CT (in terms of costs, quality-adjusted life years [QALYs] and incremental cost-effectiveness ratios [ICERs]), estimated for two scenarios:
  - Scenario 1: base case, using the APHINITY 3IA data only.
  - Scenario 2: using the APHINITY 3IA data and with T-DXd available in 2L MBC and in 1L for patients with early recurrences (<18 months).
- Three markets were explored, to assess whether the model results were impacted by different healthcare systems/settings. Market share inputs for each country and scenario are summarised in Table 1.

Figure 1. IDFS survival curves



CT, chemotherapy; H, trastuzumab; IDFS, invasive disease-free survival; KM, Kaplan–Meier; P, pertuzumab.

Table 1. Market share inputs per country for Scenarios 1 and 2

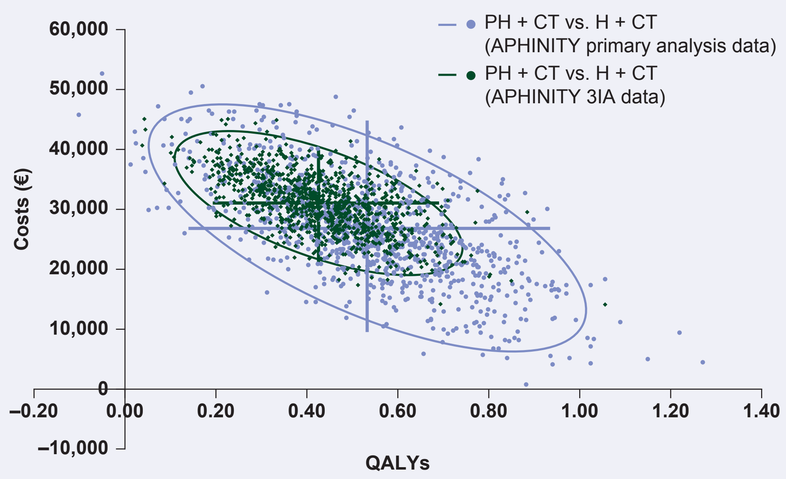
	Scenario 1			Scenario 2		
Market share (%)	**Belgium**	**Spain**	**ROI**	**Belgium**	**Spain**	**ROI**
1L MBC						
PH + CT	94.00	96.20	80.00	97.40	96.20	80.00
H + CT	1.50	3.80	20.00	1.60	3.80	20.00
CT	1.00	0	0	1.00	0	0
Other	3.50	0	0	0	0	0
1L MBC (early recurrences)*						
PH + CT	25.47	40.00	75.00	0	0	40.00
H + CT	0	0	10.00	0	0	10.00
CT	1.24	0	0	0	0	5.00
T-DM1	68.32	60.00	15.00	0	40.00	15.00
T-DXd	0	0	0	95.00	60.00	30.00
Other	5.00	0	0	5.00	0	0
2L MBC						
PH + CT	0	35.80	0	0	2.30	0
H + CT	0	2.20	20.00	0.52	4.20	10.00
CT	1.25	0	0	0.52	0.00	5.00
T-DM1	88.75	60.00	80.00	1.03	27.00	25.00
T-DXd	0	0	0	97.94	66.50	60.00
Lapatinib + capecitabine	2.50	2.00	0	0	0	0
Clinical trial	7.50	0	0	0	0	0

* <18 months.
1L/2L, first/second line; CT, chemotherapy; H, trastuzumab; MBC, metastatic breast cancer; P, pertuzumab; ROI, Republic of Ireland; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Results

- A probabilistic sensitivity analysis (PSA) of Scenario 1, using the ROI setting as an example, is shown in Figure 2. The PSA results are compared with the corresponding model based on the primary analysis of APHINITY.
- Use of data from the APHINITY 3IA with a longer follow-up of 8.4 years led to significant reduction in the uncertainty of the model, compared with when primary analysis data were used:
  - Scatter was more concentrated.
  - Results using the 3IA data fall within the 95% confidence intervals of the results using the primary analysis data.
- In Scenario 1, based on public list prices, ΔQALYs were 0.50–0.69 and ICERs were 18,874–67,943 (Table 2).
- When use of T-DXd in MBC was added to the model assumptions (Scenario 2), lower ICERs were seen with reductions ranging from –17.9% to dominating results.

Figure 2. PSA of Scenario 1 (ROI)



Ellipses represent 95% confidence intervals.
3IA, third interim analysis; CT, chemotherapy; H, trastuzumab; P, pertuzumab; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; ROI, Republic of Ireland.

Table 2. PH + CT cost effectiveness

	Δ Cost, €	Δ QALY	ICER (Δ)
Belgium			
Scenario 1 (base case)	13,003	0.69	**18,874**
Scenario 2 (with T-DXd)*	–2,291	0.64	**Dominating**
Spain			
Scenario 1 (base case)	34,042	0.50	**67,943**
Scenario 2 (with T-DXd)*	26,502	0.48	**55,753 (–17.9%)**
ROI			
Scenario 1 (base case)	31,046	0.65	**48,097**
Scenario 2 (with T-DXd)*	23,302	0.62	**37,754 (–21.5%)**

* T-DXd available in 2L MBC and in 1L for patients with early recurrences (<18 months).
1L/2L, first/second line; CT, chemotherapy; H, trastuzumab; ICER, incremental cost-effectiveness ratio; MBC, metastatic breast cancer; P, pertuzumab; QALY, quality-adjusted life year; ROI, Republic of Ireland; T-DXd, trastuzumab deruxtecan.

Conclusions

- These are the first CEA results published using the 3IA data from APHINITY.
- **The use of longer follow-up data provides more robust evidence for the cost effectiveness of PH + CT in HER2+ EBC compared with previous models.**
  - A consistent pattern in results was observed across the three markets.
  - The PSA indicates that if the cost-effectiveness outcomes of PH + CT fall below a country's willingness-to-pay threshold, **there is reduced uncertainty about the decision to reimburse being appropriate**. Although the PSA was conducted for the ROI only, results for Belgium and Spain are expected to be similar.
- **Incorporating more effective, yet more expensive, MBC treatment options into the model significantly reduced the ICER in the three countries.** This underscores the importance of optimal early-stage, curative treatment to prevent metastasis and the need for more costly therapies.
- **These findings are likely to be applicable to other early oncology settings/models.**

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Conflicts of interest

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