Cost-Effectiveness Analyses of lapatinib and trastuzumab versus aromatase inhibitors in the treatment of metastatic breast cancer in Egyptian patients from the Ministry of health perspective

Health Technology Appraisal

Issued: January 2017

- **بيانات المستحضر محل الدراسة:**

Interventions	Lapatinib & Trastuzumab
Trade name	Tykerb & Herceptin
Company name	Novartis & Roche
Comparator	Aromatase Inhibitors (letrozole and anastrozole)

- **الهدف:**

- تقييم الفعالية لقاء التكلفة لمستحضر Lapatinib مقارنة بمستحضر Trastuzumab في علاج مرضى (metastatic breast cancer) وذلك لضمان أفضل النتائج العلاجية بالنسبة للمريض وبأقل تكلفة ممكنة من خلال الإلتزام بالخطوط العلاجية الاسترشادية العالمية وفي ضوء الممارسة الإكلينيكية المحلية. وذلك في ضوء التوصية بإجراء دراسة جدوي اقتصادية COST EFFECTIVENESS بناء علي اجتماع لجنة وحدة إقتصاديات الدواء بالسادة مديري قطاعات الصيدلة بالتأمين الصحي والمؤسسات العلاجية والأمانة العامة للمستشفيات والهيئة التعليمية.

- علما ان الدراسة التي قامت باجرائها وحدة اقتصاديات الدواء شملت بيانات التكلفة الخاصة بالمستحضرات والتي تم تجميعها من مناقصات مستشفيات وزاره الصحة، بالاضافة إلى باقي التكلفة المرتبطة بالإقامة بالمستشفى والأدوية والمضاعفات المحتملة أثناء علاج المرضى بأنواعها وطبقا لتسعيرة نفقة الدولة.

- تم تجميع البيانات الخاصة بالقيمة العلاجية الناتجة عن جودة الحياة المعيشية للمريض "QUALITY OF LIFE" ونسبة الحالات المستجيبة للعلاج من الدراسات المنشورة عالميًا.

- **النقاط الهامة:**

- بعد البحث في المراجع العالمية، انضح أن دواعي استعمال ال(lapatinib) هي كالتالي:

- Lapatinib is indicated in combination with (1):
  1- capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.
  2- letrozole for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.

Tel.: +202 – 23684288 +202 – 23648769 +202 -25354100 Ext.: 1916 Fax: +202 – 23684194
Email: peunit@eda.mohp.gov.eg Website: www.eda.mohp.gov.eg

- وهذا يجعل من الغرض الثاني الوحيد الذي يمكن اعتبار كلا العلاجين (therapeutic alternatives) به؛ إلا أن:

- Lapatinib in combination with an aromatase inhibitor has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer (1).

- ونظراً لاختفاء هذه المقارنات الاكلينيكية المباشرة (Head-to-head comparative trials)، فقد قررت اللجنة:

في ضوء متابعة إجراء دراسة جدوي إقتصادية (cost effectiveness study) لتحديد القيمة العلاجية المضافة مقابل التكلفة لمستحضرات **Trastuzumab** و**Lapatinib** في الاستخدام العلاجي **postmenopausal women with hormone receptor-positive metastatic breast cancer**. وبتقييم جودة الأدلة العلمية المتضمنة في تقرير وحدة اقتصاديات الدواء والتي تشمل الدراسات المقدمة من الشركات صاحبة المستحضر، اتضح انه لا توجد دراسة مقارنة head to head comparison بين المستحضرين ولكن توجد دراسات تقارن كلا المستحضرين علي حدة مع Aromatase Inhibitors. وتعتبر هذه الدراسات مقبولة من ناحية المنهج العلمي والاحصائي المتبع بها ولا يوجد محاذير علي استخدامها في بناء دراسة الجدوي الاقتصادية.

- وبناءاً عليه تم توجيه الغرض من وراء الدراسة إلى تقييم الفاعلية لقاء التكلفة لمستحضري (Lapatinib) و(Trastuzumab) مع ال(Aromatase inhibitors) من ناحية، وال(Aromatase inhibitors) من الناحية الأخرى.

في ضوء متابعة إجراء دراسة جدوي إقتصادية لتحديد القيمة العلاجية المضافة مقابل التكلفة للمستحضرات. وبعد البحث في الأدلة العلمية المتوافرة وبتقييم الدراسات الإكلينيكية المقدم من الشركتين صاحبة المستحضرين، تبين ما يلي:

خلصت نتائج دراسة جدوي إقتصادية (cost effectiveness analysis) بين مستحضر lapatinib 250mg + letrozole 2.5mg عند أسعار ٢٠٧٣ جنيه مصري لعلبة الlapatinib (٧٠ قرص) و ٢٤٤ جنيه مصري لعلبة الletrozole (٣٠ قرص) مقارنة بال letrozole 2.5mg بمفرده إلى أن ذراع ال lapatinib هو الأفضل في تحسين جودة الحياة المعيشية بمقدار ٣٠.٧٢٩ QALY، ولكن بتكلفة متزايدة تصل إلى 7,899,230 جنيه مصري، وبهذا تكون قيمة ال ICERهي 257,064 جنيه مصري/QALY. وعليه فإن مستحضر letrozole + lapatinib tab ليسا هما الأفضل من حيث الفاعلية لقاء التكلفة مقارنة بمستحضر letrozole.

كما خلصت نتائج نفس الدراسة بين مستحضرى trastuzumab 440mg vial + anastrazole 1mg عند أسعار ٨١٧٠ جنيه مصري لvial ال trastuzumab الواحدة و ٢٨٠ جنيه مصري لعلبة ال anastrazole 1mg (٣٠ قرص) مقارنة بال anastrazole 1mg بمفرده إلى أن ذراع ال trastuzumab هو الأفضل في تحسين جودة الحياة المعيشية بمقدار ٢٤.٠٩ QALY، ولكن بتكلفة متزايدة تصل إلى 15,240,792 جنيه مصري، وبهذا تكون قيمة ال ICERهي 632,663 جنيه مصري/QALY. وعليه فإن مستحضر trastuzumab vial + anastrazole ليس هو الأفضل من حيث الفاعلية لقاء التكلفة مقارنة بمستحضر anastrazole.

وقد تم مراجعة النتائج النهائية للدراسات وما يترتب عليها من قرارات وذلك بحضور المتخصصين في مجال الاقتصاد وتقييم الدليل العلمي والاحصاء للإفادة بصلاحيتها Validation من ناحية الجودة العلمية في منهج الدراسة والتحليل الإحصائي المتبع.

Tel.: +202 – 23684288 +202 – 23648769 +202 -25354100 Ext.: 1916 Fax: +202 – 23684194
Email: peunit@eda.mohp.gov.eg Website: www.eda.mohp.gov.eg

English Summary

Economic evaluation of lapatinib or trastuzumab in combination with an aromatase inhibitor versus aromatase inhibitors alone for the first-line treatment of metastatic HR positive breast cancer that overexpresses HER2 in Egypt from payer's perspective

- **Introduction**

Carcinoma of the breast is a heterogeneous group of cancers. Therapeutically, it is subclassified into three groups: estrogen receptor (ER) positive, HER2 positive, and ER negative or triple negative. The term triple-negative breast cancer (TNBC) refers to the absence of ER, progesterone receptor (PR), and HER2. HER2-positive (HER2+) tumors account for 20% of breast cancers, and they overexpress the HER2 protein, which drives their growth. These tumors are aggressive with rapid growth, early metastasis with frequent spread to the central nervous system, and a relatively poor prognosis for the patient. They are typically treated with therapies that inhibit HER2 signaling together with chemotherapy. About half of HER2+ tumors express ER, and their treatment also includes endocrine therapy. Clarification of the factors that activate HER2 and the signaling pathways regulated by it has led to new targeted therapies that have dramatically changed the outcome of patients with this subtype of the disease (2).

HER2 is a member of a family of four membrane tyrosine kinase (TK) receptors (HER1–4). HER receptors have an extracellular ligand-binding domain, a transmembrane domain, and an intracellular TK domain. These receptors work together to activate multiple signaling pathways that regulate proliferation, apoptosis, invasion and metastasis, angiogenesis, and cell differentiation (2).

The first approved targeted therapy for HER2+ breast cancer was the humanized monoclonal antibody trastuzumab (Herceptin). Trastuzumab binds to the extracellular domain of HER2 and was originally shown to inhibit proliferation of cultured HER2+ breast cancer cells (3).

Because HER2 requires other HER family members to activate downstream cell survival and proliferation pathways, other drugs were developed to more completely block the receptor family. Dual inhibitors such as lapatinib, afatinib, and neratinib inhibit HER1 or epidermal growth factor receptor (EGFR) and HER2 TKs. Lapatinib is the most studied of these agents and is approved for treatment of metastatic disease (2).

There is considerable cross-talk between ER and HER2 signaling in breast cancer cells expressing both receptors. ER+/HER2+ tumors are less endocrine sensitive than ER+/HER2− tumors, but ER can provide an escape pathway when HER2 is blocked. These data suggested that targeting both ER and HER2 in such patients would be superior to either therapy alone (4, 5). However, its cost-effectiveness remains another issue.

Cost–effectiveness and cost–utility analyses evaluate the balance of a treatment's health benefits, often in terms of quality-adjusted life-years (QALYs) gained, and the anticipated costs of achieving those benefits. Such analyses are increasingly important in the current era of soaring medical costs and healthcare budgets under pressure. In a healthcare system with scarce resources, the pressure to control healthcare spending drives the need for treatments that do more than demonstrate efficacy; they must also demonstrate value. To demonstrate such value, a new treatment that has superior efficacy to an existing one must also demonstrate either cost savings, resulting in dominance (greater efficacy at lower cost) or cost–effectiveness, in which case the additional costs are justified by the gain in effectiveness or utility. In order for a treatment to be deemed cost effective, it must have an incremental cost–effectiveness ratio (ICER) below certain, often nationally determined, threshold. The threshold recommended by the WHO is three-times the gross domestic product per capita (6).

Objective

To evaluate the cost-effectiveness of lapatinib or trastuzumab in combination with aromatase inhibitors (AIs) compared to AIs alone as the first-line treatment of metastatic Hormone Receptor (HR) positive breast cancer that overexpresses HER2 Egyptian patients, from the governmental payer perspective.

Economic evaluation Key Features (7):

Key Features:	
year of the document	February 2017
Affiliation of authors	Pharmacoeconomics Unit, Central Administration For Pharmaceutical Affairs
Purpose of the document	Evaluate the Cost-Effectiveness of using lapatinib or trastuzumab in combination with AIs versus AIs alone for the treatment of metastatic breast cancer
Standard reporting format included	Yes
Disclosure	Yes
Target audience of funding/ author's interests	Public, decision makers
Perspective	Healthcare system (governmental payer)
Indication	Treatment of metastatic breast cancer
Target population	Insured patients by the Egyptian health care system
Subgroup analysis	No Subgroup analysis
Choice of comparator	Aromatase inhibitors (letrozole and anastrozole)
Time horizon	Over 5-year period
Assumptions required	Yes
Analytical technique	Cost-effectiveness analysis
Costs to be included	Direct medical costs include costs of treatment and management of toxicities and side effects according

	to the Egyptian current practice.
Source of costs	Health Insurance & MoH hospitals
Modeling	Markov model
Systematic review of evidences	Yes
Preference for effectiveness over efficacy	Yes
Outcome measure	The outcomes of the two treatments were measured in terms of QALY
Method to derive utility	The methods used; Time Trade-off for PFS health state, and standard gamble for progressed health state; all from published literature
Equity issues stated	All lives and life years are valued equally, regardless of age, gender, or socioeconomic status of individuals in the population
Discounting costs	A discount rate of 3.5 % per year
Discounting outcomes	A discount rate of 3.5 % per year
Sensitivity analysis-parameters and range	Critical component(s) in the calculation is varied through a relevant range or from worst case to best case.
Sensitivity analysis-methods	One-way sensitivity analysis is performed.
Presenting results	Both combinations of lapatinib with letrozole and trastuzumab with anastrozole were found not cost effective when compared to the AI alone for treatment of metastatic breast cancer.
Incremental analysis	Yes
Total costs vs. effectiveness (cost/effectiveness ratio)	Yes
Portability of results (Generalizability)	The generalizability and extent to which the clinical efficacy data and the economic data are representative is identified and discussed.

- **Committee Discussion:**

It is so important to identify the most cost-effective regimen for the treatment of metastatic breast cancer patients for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2. And this is important due to the fact that targeted therapies now are evolving to substitute traditional ones (e.g. chemotherapy), but the fact that their prices are soaring, makes it more imperative to assess their real-world value. To support reimbursement decision-making in Egypt, decision analysis is a quantitative method for synthesizing data from numerous sources for the evaluation of treatment alternatives and was developed to determine the cost-effectiveness of targeted therapies if combined with AIs, as compared to AIs alone.

Tel.: +202 – 23684288 +202 – 23648769 +202 -25354100 Ext.: 1916 Fax: +202 – 23684194
Email: peunit@eda.mohp.gov.eg Website: www.eda.mohp.gov.eg

The literature search was conducted in Medline, PubMed and Cochrane Library to identify relevant published English articles from January 2000 to December 2016. The decision analytical model was constructed to assess the costs and consequences associated with targeted therapies/AIs combinations compared with AIs alone.

The decision to base the model on such comparison instead of the original one (lapatinib versus trastuzumab) was due to different reasons. First, only three RCTs have been identified, which present head-to-head comparisons of the interventions of interest to this appraisal: the eLEcTRA trial (Study of the Efficacy and Safety of Letrozole Combined with Trastuzumab in Patients with Metastatic Breast Cancer) (8), the TAnDEM trial (Trastuzumab in Dual HER2 ER-Positive Metastatic Breast Cancer) (9), and EGF30008 (10). It was not possible to compare the data across the trials because of differences in the patient populations. However, each individual trial suggests a benefit in terms of PFS/Time to progression (TTP) for lapatinib + letrozole, trastuzumab + anastrazole and trastuzumab + letrozole compared with letrozole, anastrazole and letrozole alone, respectively. Second, direct comparison across trials would be too crude and simplistic, and indirect comparisons were not appropriate because the patient populations were not sufficiently similar in the EGF30008 and the TAnDEM trials. The same opinion was also shared with The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), whose research findings directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) at the United Kingdom (11, 12).

The model was constructed as a Markov model with three health states (progression free survival (PFS), progressed phase, or death). A time horizon of 5 years was used in order to capture the whole duration of the patient's life, either progressed or not, with each cycle being 1 month.

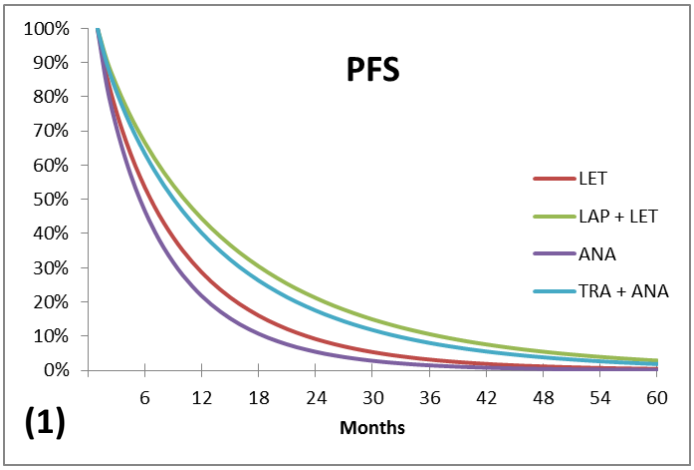
Survival probabilities (S[t]) for PFS and overall survivals (OS) were extracted from Weibull model where:

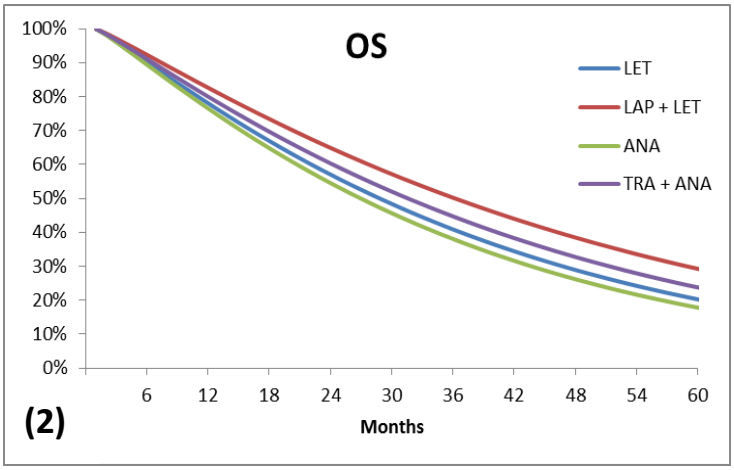
$$S[t] = e^{(-\lambda t^{\gamma})^{HR}}$$

where t is time (in months) and HR is hazard ratio vs. referent treatment. Lambda and gamma (Weibull survival function parameters) were extracted from EGF30008 trial (10). PPS (Post Progression Survival) is calculated as OS-PFS (13).

Figures (1), (2), and (3) show the calculated PFS, OS, and PPS respectively for the 4 regimens over a period of 5 years.

Tel.: +202 – 23684288 +202 – 23648769 +202 -25354100 Ext.: 1916 Fax: +202 – 23684194
Email: peunit@eda.mohp.gov.eg Website: www.eda.mohp.gov.eg





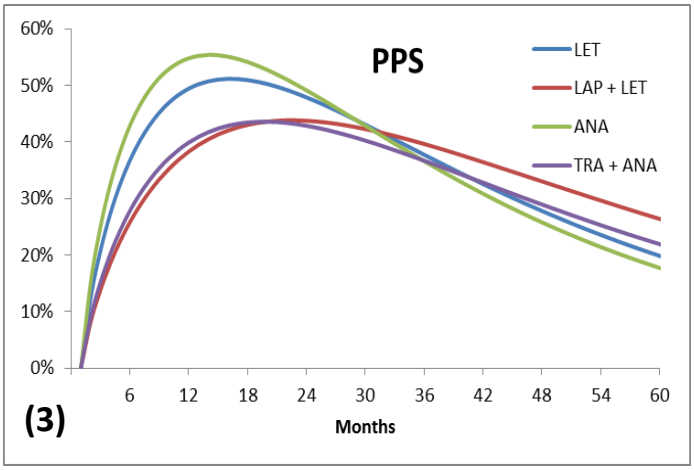


Figure (1): Progression Free Survival Curve
Figure (2): Overall Survival Curve
Figure (3): Post progression Survival Curve

LET: letrozole
LAP: lapatinib
ANA: anastrazole
TRA: trastuzumab

Generally, the clinical parameters for the model were based on two main clinical trials. The first one, the TAnDEM trial (9), is a randomized, open-label, multicenter, international, phase III study, where 207 patients were randomized to receive either anastrozole 1 mg/d orally (control group) or trastuzumab (4 mg/kg by intravenous infusion on day 1, followed by 2 mg/kg weekly) plus anastrozole (1 mg/d orally). The primary efficacy end point was PFS. Secondary end points included clinical benefit rate (CBR), overall response rate (ORR), (TTP), duration of response, time to response, OS, and 2-year survival rates.

On the other hand, EGF30008 was a randomized, double-blind, controlled, parallel-group, multicenter, phase III study, where 1,286 patients with HR-positive MBC were randomly assigned to receive letrozole plus lapatinib or letrozole plus placebo. While the primary end point was investigator-assessed PFS, secondary end points included ORR, CBR, OS, and safety (10).

Tel.: +202 – 23684288 +202 – 23648769 +202 -25354100 Ext.: 1916 Fax: +202 – 23684194
Email: peunit@eda.mohp.gov.eg Website: www.eda.mohp.gov.eg

The utility values used in the model were obtained from two sources of published literature. The first was an analyses performed on 1433 cancer patients (14). Time-trade off utility values were estimated using responses to a questionnaire that covered both physical and functional well-being. The other source was a study that used societal preferences to estimate utility values for distinct stages of metastatic breast cancer (15). One hundred members of the general public rated these stages using standard gamble to determine the corresponding health state utility.

Direct medical costs were obtained from both the Pay-on-The-Expense-of-State price list and National Cancer Institute (NCI) in Egypt, while usual regimens used for treating complications were reported by experts' opinion. Deterministic sensitivity analyses and discounting were conducted. All input data used can be found in table (1).

Total costs for 'lapatinib + letrozole' arm and 'letrozole only' arm were EGP 9,447,507 and EGP 1,548,277 respectively. QALYs for 'lapatinib + letrozole' arm and 'letrozole only' arm were 206.220 and 174.866 respectively. The incremental cost-effectiveness ratio (ICER) for 'lapatinib + letrozole' arm versus 'letrozole only' arm was 251,937 EGP/QALY. This study showed that 'lapatinib + letrozole' combination is *not* a cost effective choice compared to 'letrozole only' as a first line treatment for hormone-receptor-positive metastatic breast cancer that overexpresses HER2, from a payer's perspective in Egypt.

On the other hand, total costs for 'trastuzumab + anastrazole' arm and 'anastrazole only' arm were EGP 21,960,460 and EGP 1,564,146 respectively. QALYs for 'trastuzumab + anastrazole' arm and 'anastrazole only' arm were 190.598 and 164.948 respectively. The incremental cost-effectiveness ratio (ICER) for 'trastuzumab + anastrazole' arm versus 'anastrazole only' arm was 795,182 EGP/QALY. This study showed that 'trastuzumab + anastrazole' combination is also *not* a cost effective choice compared to 'anastrazole only' as a first line treatment for hormone-receptor-positive metastatic breast cancer that overexpresses HER2, from a payer's perspective in Egypt.

Tel.: +202 – 23684288 +202 – 23648769 +202 -25354100 Ext.: 1916 Fax: +202 – 23684194
Email: peunit@eda.mohp.gov.eg Website: www.eda.mohp.gov.eg

Table (1): Model input parameters

Item Labels	Input Value	Reference
Treatment cost data		
Lapatinib 250 mg tablets cost (70 tab)	٢,٠٧٣.٠٠ ج.م.	company
Letrozole 2.5 mg tablets cost (30 tablets)	٢٤٤.٠٠ ج.م.	company
Trastuzumab 440 mg vial cost	٨,١٧٠.٠٠ ج.م.	NCI
Anastrazole 1 mg tablets cost (30 tablets)	٢٨٠.٠٠ ج.م.	NCI
IV administration costs	٥٠.٠٠ ج.م.	NCI
Best Supportive Care cost per month	٦٣٣.٠٠ ج.م.	PTES
Imodium 2 mg tablet cost	٠.١٠ ج.م.	pricing
Ringer 500 ml bottle cost	٧.٥٠ ج.م.	pricing
Zofran 4mg tab (pack of 10 tabs)	٢٥٤.٠٠ ج.م.	pricing
Serious Adverse Events		
Lapatinib + Letrozole, grade 3 diarrhea, 40 weeks	8.87%	10
Lapatinib + Letrozole, grade 4 diarrhea, 40 weeks	0.30%	10
Lapatinib + Letrozole, grade 3 Nausea & Vomiting, 40 weeks	1.99%	10
Lapatinib + Letrozole, grade 4 Nausea & Vomiting, 40 weeks	0.15%	10
Letrozole, grade 3 diarrhea, 38 weeks	0.96%	10
Letrozole, grade 4 diarrhea, 38 weeks	0.00%	10
Letrozole, grade 3 Nausea & Vomiting, 38 weeks	1.28%	10
Letrozole, grade 4 Nausea & Vomiting, 38 weeks	0.16%	10
TRA + ANA, grade 3 N & V, 24 months	3.88%	9
ANA, grade 3 N & V, 24 months	0.96%	9
Weibull survival function parameters		

Letrozole PFS - lambda	0.15258	10
Letrozole PFS - gamma	0.87727	10
Lapatinib + Letrozole PFS HR	0.65	10
ANA PFS HR	1.22	9
TRA + ANA PFS HR	0.73	9
LET OS - lambda	0.01732	10
LET OS - gamma	1.10926	10
Lapatinib + Letrozole OS HR	0.77	10
ANA OS HR	1.08	9
TRA + ANA OS HR	0.9	9
Utilities		
PFS utility	0.86	14
Post-progression utility	0.62	15
Discount rates		
Costs Discount rate	3.5%	7
Utilities Discount rate	3.5%	7

As in all modeling exercises, several assumptions were made in this study leading to uncertainties in the results. In this analysis, we explicitly accounted for these uncertainties by assigning confidence intervals and plausible ranges of the relative risks, utilities, survival function parameters and costs based on published sources. To assess the influences of other model structures and assumptions on the cost-effectiveness estimates, one-way sensitivity analyses of various parameters were performed.

Figure (1) illustrates the tornado diagram done for the first analysis (of the lapatinib combination), and it shows that hazard ratio of overall survival of 'lapatinib + letrozole' combination arm, and lapatinib acquisition costs have the greatest impact on the lapatinib study, while figure (2) shows that for the trastuzumab study, both hazard ratios of overall survival for both arms, accompanied with trastuzumab acquisition cost impacts their respective study the most.

Tel.: +202 – 23684288 +202 – 23648769 +202 -25354100 Ext.: 1916 Fax: +202 – 23684194
Email: peunit@eda.mohp.gov.eg Website: www.eda.mohp.gov.eg

Figure (1): Deterministic sensitivity analyses results (lapatinib study)

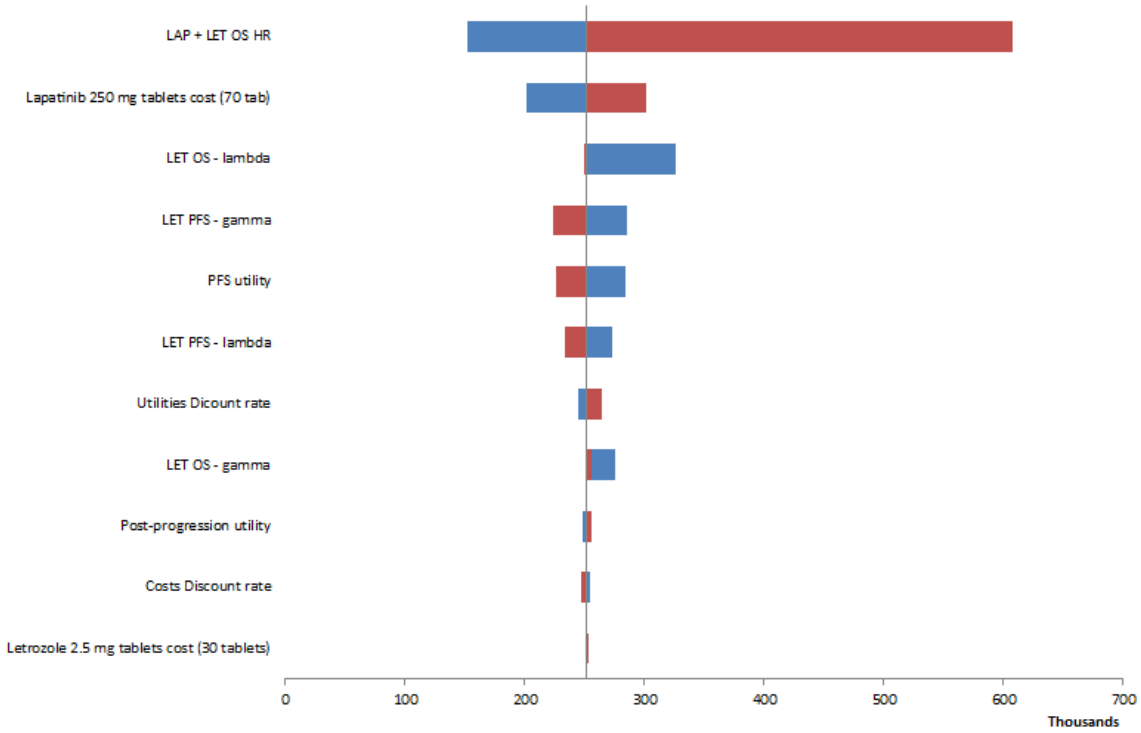
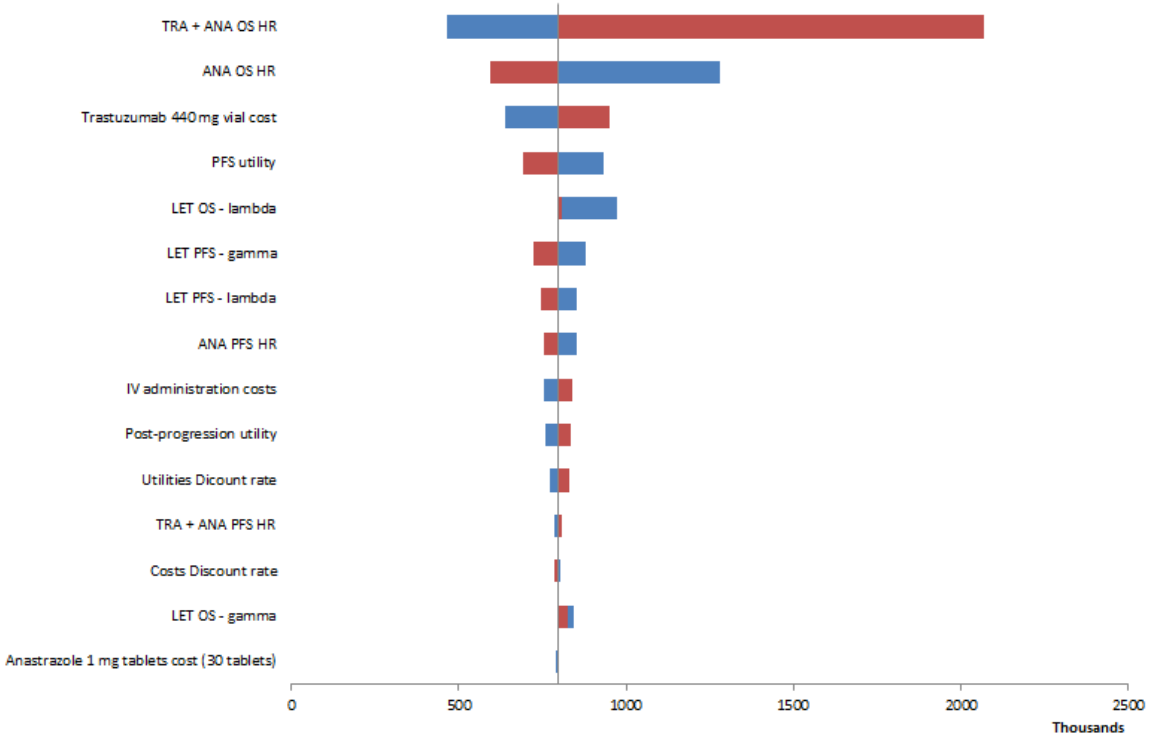


Figure (2): Deterministic sensitivity analyses results (trastuzumab study)



As was highlighted previously, at NICE assessment of lapatinib and trastuzumab plus AI therapy, the assessment group (AG) conducted separate analyses of the cost-effectiveness of lapatinib + letrozole versus letrozole, and of trastuzumab + anastrazole versus anastrazole, arguing that trial data were not sufficiently similar to support an adjusted indirect comparison (11). For the lapatinib + letrozole versus letrozole comparison, the AG developed a de novo model using data from EGF30008 and other published sources. The model was essentially a Markov model, with states defined on the basis of progression and death. Based on this model, the AG estimated the cost-effectiveness of lapatinib + letrozole versus letrozole to be in excess of £ 220,000 per QALY gained, rendering it not cost effective. Similar results were reported for trastuzumab + anastrazole versus anastrazole with an ICER of £ 69,000 per QALY gained, rendering it also as a not cost effective option.
In Canada, CADTH (Canadian Agency for Drugs and Technologies in Health) took similar decisions through pCODR (The pan-Canadian Oncology Drug Review). The pCODR Expert Review Committee doesn't recommend funding lapatinib in combination with letrozole in postmenopausal patients with hormone receptor positive, HER2 receptor positive metastatic breast cancer (16).

- **Conclusion**

Results from this study suggest that both combinations of lapatinib + letrozole or trastuzumab + anastrazole are *not* cost effective interventions compared to aromatase inhibitors alone as a first line treatment for hormone-receptor-positive metastatic breast cancer that overexpresses HER2, based on the willingness to pay threshold stated by world health organization (3xGDP/capita) for low and middle income countries. These findings will help inform health care decisions regarding the allocation of health care system resources and improving outcomes.

- **Declaration of interest**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

- **PEU project team**

- **Gihan Hamdy El-sisi**, Head of Pharmacoeconomics Unit, Central Administration for Pharmaceutical Affairs, Ministry of Health.

- **Andrew Botros Saleh,** Team member of Pharmacoeconomics Unit, Central Administration for Pharmaceutical Affairs, Ministry of Health.

Tel.: +202 – 23684288 +202 – 23648769 +202 -25354100 Ext.: 1916 Fax: +202 – 23684194
Email: peunit@eda.mohp.gov.eg Website: www.eda.mohp.gov.eg

- **References:**

1–FDA website. Tykerb monograph. Tykerb indications and usage. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022059s007lbl.pdf.
2– Rimawi MF, Schiff R, Osborne CK, et al. Tageting HER2 for the treatment of breast cancer. Annu. Rev. Med. 2015.66:111-128.
3- Harari D, Yarden Y. 2000. Molecular mechanisms underlying ErbB2/HER2 action in breast cancer. Oncogene 19:6102–14.
4- Schiff R, Massarweh SA, Shou J, et al. 2004. Cross-talk between estrogen receptor and growth factor pathways as a molecular target for overcoming endocrine resistance. Clin. Cancer Res. 10:331S–36S.
5- Nahta R,O'Regan RM. 2012. Therapeutic implications of estrogen receptor signaling inHER2-positive breast cancers. Breast Cancer Res. Treat. 135:39–48.
6- WHO Commission on Macroeconomics and Health. Macroeconomics and Health: Investing in Health for Economic Development. Report of the Commission on Macroeconomics and Health. World Health Organization, Geneva, Switzerland (2001).
7- Elsisi G, Kaló Z, Eldessouki R, et al; Guidelines for reporting pharmacoeconomic evaluations in Egypt; Value in Health Regional Issues; Volume 2, Issue 2, September–October 2013, Pages 319–327.
8- Huober J, Fasching P, Paepke S, et al: Letrozole in combination with trastuzumab is superior to letrozole monotherapy as first line treatment in patients with hormone-receptor-positive, HER2-positive metastatic breast cancer (MBC) – results of the eLEcTRA trial. Cancer Res 2009;69:abstr 4094.
9- Kaufman B,Mackey JR,Clemens MR, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2–positive, hormone receptor–positive metastatic breast cancer: results from the randomized phase III TAnDEM study. J. Clin. Oncol 2009. 27:5529–37.
10 - Johnston S, Pippen J Jr, Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor–positive metastatic breast cancer. J. Clin. Oncol 2009. 27:5538–46.
11 - Fleeman N, Bagust A, Boland A, et al. Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor-positive breast cancer which over-expresses human epidermal growth factor 2 (HER2): a systematic review and economic analysis. Health Technol Assess 2011;15:1–93, III–IV.
12 - National Institute for Health and Exellence: Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2. Technology Appraisal Guidance [TA257]. 27 June 2012. Available at: www.nice.org.uk/guidance/ta257.
13 – Delea TE, Hawkes C, Amonkar MM, et al. Cost-Effectiveness of Lapatinib plus Letrozole in Post-Menopausal Women with Hormone Receptor and HER2-Positive Metastatic Breast Cancer. Breast Care 2013;8:429–437.
14 - Delea TE, Sofrygin O, Amonkar MM: Patient preference-based utility weights from the Functional Assessment of Cancer Therapy-General (Fact-G) in women with hormone receptor positive metastatic breast cancer receiving letrozole plus lapatinib or letrozole alone. Value Health 2010;3:43.

Tel.: +202 – 23684288 +202 – 23648769 +202 -25354100 Ext.: 1916 Fax: +202 – 23684194
Email: peunit@eda.mohp.gov.eg Website: www.eda.mohp.gov.eg

15 - Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J: Health state utilities for metastatic breast cancer. Br J Cancer 2006;95:683–690.

16 – Initial recommendation for lapatinib with letrozole for MBC. pERC meeting, dated at April 18, 2013. Available at: https://www.cadth.ca/sites/default/files/pcodr/pcodr-tykerb-mbc-in-rec.pdf. Accessed on February 5, 2017.

Tel.: +202 – 23684288 +202 – 23648769 +202 -25354100 Ext.: 1916 Fax: +202 – 23684194
Email: peunit@eda.mohp.gov.eg Website: www.eda.mohp.gov.eg