Cost-Effectiveness of Lapatinib plus Letrozole in Post-Menopausal Women with Hormone Receptor- and HER2-Positive Metastatic Breast Cancer

Thomas E. Delea^a Carol Hawkes^b Mayur M. Amonkar^c
Konstantinos Lykopoulos^d Stephen R. D. Johnston^e

^aPolicy Analysis Inc. (PAI), Brookline, MA, USA; ^bGlaxoSmithKline, Uxbridge, UK; ^cGlaxoSmithKline, Collegeville, PA, USA;

^dGlaxoSmithKline, GSK House, Brentford; ^eRoyal Marsden NHS Foundation Trust and Institute of Cancer Research, London, UK

Keywords

Aromatase inhibitors · Breast cancer · Combination therapy · Costs · HER2 · Hormonal treatment · Metastatic disease · Trastuzumab · Lapatinib

Summary

Background: In the EGF30008 and TAnDEM (TrAstuzumab in Dual HER2 ER-positive Metastatic breast cancer) trials, anti-HER2 therapy plus an aromatase inhibitor (lapatinib + letrozole (LAP + LET) and trastuzumab + anastrozole (TZ + ANA), respectively) improved time to progression versus aromatase inhibitor monotherapy (LET and ANA, respectively) in post-menopausal women with previously untreated hormone receptor-positive (HR+) and HER2-positive (HER2+) metastatic breast cancer. **Methods:** A partitioned-survival analysis model using data from EGF30008 and published results of TAnDEM and other literature was used to evaluate the incremental direct medical cost per quality-adjusted life year (QALY) gained with LAP + LET versus LET, ANA, and TZ + ANA in post-menopausal women with previously untreated HR+ and HER2+ metastatic breast cancer from the UK National Health Service (NHS) perspective.

Results: Incremental costs for LAP + LET are £ 34,737 versus LET, £ 35,995 versus ANA, and £ 5,513 versus TZ + ANA. Corresponding QALYs gained are 0.467, 0.601, and 0.252 years. Cost/QALY gained with LAP + LET is £ 74,448 versus LET, £ 59,895 versus ANA, and £ 21,836 versus TZ + ANA. Given a threshold of £ 30,000/QALY, the estimated probability that LAP + LET is cost-effective is 1.4% versus LET, 9.2% versus ANA, and 51% versus TZ + ANA. **Conclusions:** Based on criteria for the evaluation of health technologies in the UK (£ 30,000/QALY), LAP + LET is not likely to be cost-effective versus aromatase inhibitor monotherapy but may be cost-effective versus TZ + ANA, although the latter comparison is associated with substantial uncertainty.

Schlüsselwörter

Aromataseinhibitoren · Brustkrebs · Kombinationstherapie · Kosten · HER2 · Hormonbehandlung · Metastatische Erkrankung · Trastuzumab · Lapatinib

Zusammenfassung

Hintergrund: In den Studien EGF30008 und TAnDEM (Trastuzumab in Dual HER2 ER-Positive Metastatic Breast Cancer) zeigte sich bei Anti-HER2-Therapie plus Aromataseinhibitor (Lapatinib + Letrozol (LAP + LET) bzw. Trastuzumab + Anastrozol (TZ + ANA)) gegenüber einer Aromataseinhibitor-Monotherapie (LET bzw. ANA) eine verbesserte Zeitspanne bis zur Progression bei postmenopausalen Frauen mit zuvor unbehandeltem Hormonrezeptor-positivem (HR+) und HER2-positivem (HER2+) metastatischem Brustkrebs. **Methoden:** Ein Modell zur abschnittswise Überlebensanalyse auf der Basis von Daten aus EGF30008 sowie publizierten Ergebnissen aus TAnDEM und anderer Literatur wurde angewendet, um die zunehmenden direkten medizinischen Kosten pro qualitätskorrigiertem Lebensjahr (QALY), das durch LAP + LET versus LET, ANA bzw. TZ + ANA bei postmenopausalen Frauen mit zuvor unbehandeltem HR+ und HER2+ metastatischem Brustkrebs gewonnen wurde, aus der Perspektive des britischen nationalen Gesundheitsversorgungssystems (NHS) zu evaluieren. **Ergebnisse:** Die Kostenzuwächse für LAP + LET betragen 34 737 £ versus LET, 35 995 £ versus ANA und 5513 £ versus TZ + ANA. Die entsprechenden gewonnenen QALYs belaufen sich auf 0,467, 0,601 und 0,252 Jahre. Die Kosten pro gewonnenem QALY durch LAP + LET sind 74 448 £ versus LET, 59 895 £ versus ANA und 21 836 £ versus TZ + ANA. Bei einem Schwellenwert von 30 000 £/QALY beträgt die geschätzte Wahrscheinlichkeit, dass LAP + LET kosteneffektiv ist, 1,4% versus LET, 9,2% versus ANA und 51% versus TZ + ANA. **Schlussfolgerungen:** Auf der Basis von Kriterien zur Evaluation von Gesundheitstechniken in Großbritannien (30 000 £/QALY) ist LAP + LET gegenüber einer Aromataseinhibitor-Monotherapie wahrscheinlich nicht kosteneffektiv, kann aber gegenüber TZ + ANA möglicherweise Kosteneffektivität erreichen, wobei der letztere Vergleich mit einer erheblichen Unsicherheit verbunden ist.

Introduction

The hormone receptor (HR) status is an important factor used to determine the prognosis and treatment of early and advanced breast cancer [1]. The aromatase inhibitors (AIs) anastrozole (ANA) and letrozole (LET) are the standard of care for first-line hormonal therapy (HT) for postmenopausal women with HR-positive (HR+) metastatic breast cancer (MBC), based on results of large randomized controlled trials demonstrating improvements in time to progression (TTP) with these agents versus tamoxifen [2–7]. The epidermal growth factor receptors (EGFRs) ErbB1 (EGFR) and ErbB2 (HER2/neu) are over-expressed in 20–25% of breast cancer tumors [8, 9]. Up-regulation and autocrine activation of these receptors conveys increased resistance to HT and chemotherapy and increased risk for disease progression and death [10, 11]. Suppression of these receptors therefore represents an important therapeutic target in breast cancer. Currently, 2 HER2-targeted therapies are available for MBC: trastuzumab (TZ), a humanized ErbB2 (HER2)-directed monoclonal antibody (mAb), and lapatinib (LAP), an orally administered dual tyrosine kinase inhibitor (TKI) of EGFR and

HER2. These agents have been shown to improve outcomes in both TZ-pretreated and TZ-naive HER2+ MBC patients [12–15].

To date, 3 randomized controlled trials have examined the effectiveness of combined AI and HER2-targeted therapy: the eLEcTRA trial (Study of the Efficacy and Safety of Letrozole Combined with Trastuzumab in Patients with Metastatic Breast Cancer) [16], the TAnDEM trial (Trastuzumab in Dual HER2 ER-Positive Metastatic Breast Cancer) [17–19], and EGF30008 [20, 21]. While eLEcTRA, TAnDEM and EGF30008 provide evidence of the clinical benefits of HER2-targeted therapy plus an AI in patients with HR+/HER2+ MBC, these studies did not assess cost-effectiveness. The analysis reported herein was the basis of an economic evaluation included in the manufacturer's submission to the UK's National Institute for Health and Clinical Excellence (NICE) in response to a multiple technology assessment (MTA) of LAP and TZ in combination with an AI for the first-line treatment of postmenopausal women with HR+/HER2+ MBC [22].

Table 1. Estimates used in the model

Estimate		Estimate	SE	Source
Weibull survival function parameters				
PFS, months	LET			
	λ	0.15258	0.01756	EGF30008
	γ	0.87727	0.07003	EGF30008
	HR versus LET			
	LAP + LET	0.65	0.17	EGF30008
OS, months	TZ + ANA	0.73	0.19	[29]
	ANA	1.22	0.12	[29]
	LET			
	λ	0.01732	0.01062	EGF30008
	γ	1.10926	0.13154	EGF30008
HR versus LET	LAP + LET	0.77	0.2	EGF30008
	TZ + ANA	0.90	0.19	[29]
	ANA	1.08	0.12	[29]
	Fisher's transformation of correlation between log HR for PFS and log HR for OS	0.46	0.13	[47]
Costs, £				
Medications	LAP, 250-mg tablet	11.49	0.00	[37]
	LET, 2.5-mg tablet	2.38	0.00	[37]
	TZ, 150-mg vial	407.40	0.00	[37]
	ANA, 1-mg tablet	2.45	0.00	[37]
Pharmacy, per dispensing	LAP, LET, ANA	8.50	2.13	[39, 43]
	TZ	8.50	2.13	[39, 43]
Facility, per day of use (TZ)	TZ loading dose	272	43	[41]
	TZ subsequent doses	227	30	[41]
Monitoring, per month (LAP and TZ)		46.50	2.50	[41]
Other per month	pre-progression	562.00	76.77	[44]
	post-progression	803.94	99.33	[44]
Relative dose intensity (actual vs. planned daily dose)				
LAP and TZ		0.95	0.0053	EGF30008
	LET and ANA	1.04	0.0144	EGF30008
Utilities				
Pre-progression		0.86	0.01	[32, 33]
	Post-progression, reduction	0.24	0.06	[34]

SE = Standard error.

Methods

Approach

A partitioned survival analysis model was used to evaluate the cost-effectiveness of LAP + LET in post-menopausal women receiving first-line treatment for HR+/HER2+ MBC. With this modeling approach, patients are assumed to be in 1 of 3 mutually exclusive health states at any given time: (1) alive and no progression, (2) alive with progression, or (3) dead. Patients are assumed to enter the model in the progression-free state and continue receiving treatment until further disease progression. The proportion of patients in each health state over the course of time is estimated based on empirical or fitted survival functions for progression-free survival (PFS) and overall survival (OS). Expected PFS and expected OS are then calculated as the area under the PFS and OS curves, respectively; expected post-progression survival (PPS) is calculated as the difference between expected OS and expected PFS. Costs and quality of life are assumed to be conditioned on treatment and disease state and were calculated by multiplying expected PFS and expected PPS by the corresponding cost and utility estimates. A daily cycle was employed so that no half-cycle correction was required.

The analysis was conducted from the UK National Health Service (NHS) perspective and therefore only direct medical care costs and benefits accrued by NHS patients were considered. The model generates estimates of expected lifetime costs of breast cancer care, life expectancy or 'life-years' (LYs), progression-free LYs, post-progression LYs, and quality-adjusted LYs (QALYs) for each treatment strategy considered in the evaluation including LAP + LET, LET, ANA, and TZ + ANA. Model parameters were estimated using data from EGF30008, TAnDEM, and other sources (table 1). The dosages of medications were assumed to be the same as those in EGF30008 and TAnDEM, except for TZ, which was assumed to be administered on a 3-weekly schedule (8 mg/kg intravenous (i.v.) loading dose and 6 mg/kg i.v. 3-weekly) rather than once weekly, consistent with typical clinical practice in the UK. The effectiveness of 3-weekly TZ was assumed to be the same as that with weekly TZ [23–25]. Per NICE guidance, we conducted pairwise comparisons of the cost-effectiveness of LAP + LET versus LET, LAP + LET versus ANA, and LAP + LET versus TZ + ANA, with the incremental cost-effectiveness ratio (ICER) for each comparison calculated as the ratio of the difference in expected total lifetime breast cancer costs to the difference in QALYs. We also conducted an incremental cost-effectiveness analysis, comparing all treatments simultaneously. All costs and outcomes were evaluated over a 10-year time horizon from the point of entry into the model (approximating a lifetime projection) and discounted at 3.5% annually [26]. The model was developed in Microsoft® Excel® 2007 (Microsoft Corp., Redmond, WA, USA).

Model Estimation

PFS and OS

PFS and OS for LET were estimated by fitting Weibull survival functions to the failure time data from EGF30008, using accelerated failure time (AFT) regression [27, 28] (fig. 1). Although the Weibull curves diverged from the empirical distributions in some segments, the areas under the curve up to the end of follow-up for the Weibull distributions were similar to those for the empirical distributions (0.72 vs. 0.69 years for PFS (difference = 0.03 years = 11 days) and 2.28 vs. 2.31 years for OS (difference = 0.03 years = 11 days)).

PFS and OS for other comparators were obtained by applying to these curves estimated hazard ratios (HRs) for each comparator versus LET. HRs for PFS and OS for LAP + LET versus LET were obtained from EGF30008. HRs for other comparators versus LET were obtained from a network meta-analysis based on a systematic review of the literature [29].

Fig. 1. Weibull-estimated PFS (A) and OS (B) with LET and LAP + LET.

As noted in that review, there were a number of limitations in the network meta-analysis and the indirect comparisons are associated with substantial uncertainty.

Adverse Events

Adverse events (AEs) considered in the model included grade 3+ AEs that were reported in the publications of EGF30008 or TAnDEM. Estimates of the incidence of AEs for each comparator were based on an adjusted indirect treatment comparison of published results of the randomized controlled trials in the evidence network, using the method of Bucher [2–6, 17–21]. AEs for which no information was reported were assumed to have an incidence of zero. Relative risks (RRs) were calculated for each AE using Peto's method [30]. AEs were not reported by grade in the trials of LET versus tamoxifen or ANA versus tamoxifen; for these comparisons, it was assumed that the RRs for grade 3+ AEs would be the same as the RRs for all grades. The indirect treatment comparison was performed using the method of Bucher to obtain RRs for each treatment versus LET. To calculate model probabilities [31], the estimated RR for each AE for each treatment versus LET was multiplied by the estimated incidence of the AE amongst patients in the placebo-LET arm of EGF30008.

Utilities

Health-related quality of life was assessed in the EGF30008 trial using the Functional Assessment of Cancer Therapy General Scale (FACT-G) plus the Breast Cancer subscale (FACT-B), which were administered every 12 weeks until the withdrawal of study medications. A generic preference-based instrument (e.g., the EuroQol (EQ)-5D) was not

administered. Utility scores for patients in EGF30008 were therefore derived from the FACT-G using a published algorithm mapping from the FACT-G to time trade-off (TTO) utilities [32, 33]. Utility values were assumed to be dependent on progression and AEs, but otherwise independent of treatment. The utility value for patients in the PFS state without AEs was based on the mean utility value among all HER2+ patients in EGF30008 over all follow-up assessments prior to progression and without grade ≥ 3 AEs. Because FACT-B assessments were not routinely completed after disease progression, the decrement in utility associated with progression was estimated using results from a vignette-based study of predictors of utilities for different stages of MBC in a community sample of 100 persons in the UK [34]. Decrements in utilities associated with alopecia, diarrhea, fatigue, and vomiting were also obtained from this study [34]. Decrements in utility with other AEs were from a similar study of 100 persons each from The Netherlands and Sweden [35], supplemented with estimates from a vignette study for advanced metastatic non-small-cell lung cancer [36], and assumption. QALYs lost with each AE were calculated by multiplying the decrement in utility with each AE by the estimated mean duration of the AE. The latter were estimated using data from EGF30008.

Costs

Unit costs of medications were from the British National Formulary (BNF 59) [37]. Planned dosages for LAP + LET and LET were adjusted using relative dose intensity (RDI) estimates from EGF30008. Lacking data on dose intensity from trials other than EGF30008, the RDI for TZ was assumed to be the same as that for LAP, whereas the RDI for ANA was assumed to be the same as that for LET. Wastage of i.v. TZ 150-mg single-use vials was estimated to be 15% per administration, based on a survey of UK clinicians [38]. The cost of half a prescription was added to the cost of oral medications to account for wastage, assuming that patients would discontinue treatment, on average, half-way through their last prescription. Costs of dispensing of i.v. and oral medications were based on the hourly cost of a hospital pharmacist [39], assuming 15 min per dispensing [40]. Facility costs for administration of TZ were based on 2008/9 NHS reference costs for delivery of chemotherapy on an outpatient basis (Health Resource Groups (HRGs) SB12Z and SB15Z) [41]. Cardiac monitoring costs for LAP and TZ were based on 2008/9 NHS reference costs for outpatient echocardiography (ECHO: HRG DA02) or multi-gated acquisition scans (MUGA: HRG RA37Z) [41], assuming quarterly testing, with 50% of the patients receiving ECHO and the remainder, MUGA.

All grade 3+ AEs were assumed to require 1 additional visit. The probability of hospitalization for grade 3+ AEs was based on the proportion of grade 3+ AEs in EGF30008 that were classified as serious. Visit and hospitalization costs for grade 3+ AEs were based on 2008/09 NHS reference costs [41]. For alopecia, we also included the cost of a wig [42]. For outpatient treatment of diarrhea, we also included the cost of outpatient fluid replacement, which was estimated to be £ 156.52 based on estimates reported in an assessment of capecitabine for locally advanced breast cancer and/or MBC [43]. Other costs (medications, visits, hospitalization, diagnostics, radiotherapy, other special interventions) were from a study of the costs of MBC care in the UK [44].

Sensitivity Analyses

Probabilistic sensitivity analysis (PSA) was conducted by simultaneously sampling from estimated probability distributions of model parameters to obtain 1,000 sets of model input estimates [45, 46]. Utility estimates were assumed to be distributed as beta random variables. Other estimates were assumed to be distributed as either normal or lognormal random variables. When standard errors for model estimates were unavailable, they were assumed to be 25% of their base-case estimates. The

correlation of logged HRs for PFS and OS were estimated using data from a meta-analysis of the association between treatment effects on TTP and treatment effects on OS in MBC [47]. (This represents a departure from the methods used in the evaluation for the manufacturer's submission to NICE and explains the difference in results for the PSA reported here versus in the submission.) Confidence intervals (CIs) for incremental costs and QALY were approximated based on the percentiles of the simulations. Cost-effectiveness acceptability curves were calculated for the pairwise comparison of LAP + LET versus each comparator and for the incremental cost-effectiveness analysis [48]. Deterministic sensitivity analyses were conducted to assess the effects of changes in key model parameters on the resulting cost-effectiveness estimates.

Results

Effectiveness

LAP + LET is projected to increase both progression-free LYs and post-progression LYs compared to all the other comparators (tables 2 and 3). On a discounted basis, QALYs are projected to be increased with LAP + LET by 0.467 years versus LET (95% CI: -1.35–2.00 years, based on PSA), 0.601 years versus ANA (95% CI: -1.57–1.99 years), and 0.252 years versus TZ + ANA (95% CI: -1.09–2.39 years).

Costs

The expected total costs are £ 34,737 greater with LAP + LET versus LET (95% CI: £ 15,900–63,800), £ 35,995 greater with LAP + LET versus ANA (95% CI: £ 17,000–65,700), and £ 5,513 greater with LAP + LET versus TZ + ANA (95% CI: -£ 15,200–28,400). Higher costs for LAP + LET versus TZ + ANA are a consequence of longer projected PFS with LAP + LET.

Cost-Effectiveness

In pairwise comparisons, the ICER is £ 74,448 for LAP + LET versus LET, £ 59,895 for LAP + LET versus ANA, and £ 21,836 for LAP + LET versus TZ + ANA. In the incremental cost-effectiveness analyses, ANA is the least costly therapy, followed by LET, then TZ + ANA, then LAP + LET. No therapies are dominated by pure dominance. TZ + ANA is dominated by LAP + LET by extended dominance (i.e., TZ + ANA has a higher cost-effectiveness ratio than LAP + LET compared with LET). ANA, LET, and LAP + LET constitute the efficiency frontier.

Probabilistic Sensitivity Analyses

On a pairwise basis, given a threshold of £ 30,000 per QALY gained, there is an estimated 1.4% probability that LAP + LET is cost-effective versus LET, a 9.2% probability that LAP + LET is cost-effective versus ANA, and a 51% probability that LAP + LET is cost-effective versus TZ + ANA. In the incremental analysis, in which all therapies were considered simultaneously, given a threshold of £ 30,000 per QALY gained, there is an estimated 89.0% probability that

LET is cost-effective, a 8.3% probability that ANA is cost-effective, a 1.2% probability that LAP + LET is cost-effective, and a 1.5% probability that TZ + ANA is cost-effective.

Deterministic Sensitivity Analyses

In deterministic sensitivity analyses, ICERs for LAP + LET versus LET and versus ANA are relatively insensitive to changes in the parameters examined (table 4), with cost-effectiveness of LAP + LET versus LET and versus ANA below £ 30,000 per QALY in no scenarios and exceeding £ 100,000 per QALY in only 2 scenarios (including 1 in which LAP + LET is dominated). The cost-effectiveness of LAP + LET versus TZ + ANA was more sensitive to the model parameters and assumptions, although there were no scenarios in which LAP + LET was dominated by TZ + ANA.

A 2-way sensitivity analysis was conducted on the assumed wastage of and costs of administration for TZ, assuming that PFS and OS with TZ + ANA would be the same as with LAP + LET. Given base-case estimates of the facility costs per administration of TZ (£ 272 and 227 for loading and subsequent doses, respectively), LAP + LET is cost saving if wastage is greater than 10%. Given the base-case estimate of wastage of TZ (15%), LAP + LET is cost saving versus TZ + ANA if facility costs for TZ administration are not less than 30% of the base-case estimates (£ 82 and 68 for loading and subsequent doses, respectively).

Discussion

The results of this analysis suggest that LAP + LET is unlikely to be cost-effective compared with AI monotherapy, based on criteria typically used to evaluate novel therapies in the UK (£ 30,000 per QALY) [49, 50]. There is, however, a high degree of uncertainty regarding the comparison of LAP + LET with TZ + ANA, especially in terms of estimates of the difference in PFS and OS. In the PSA, the estimated probability that LAP + LET is cost-effective versus TZ + ANA is only slightly greater than 50%, given a threshold value of cost-effectiveness of £ 30,000 per QALY.

Controlled studies of LAP + LET versus ANA or TZ + ANA are unavailable, and estimates of relative effectiveness were based on a network meta-analysis [29]. Given potential differences in patients and methods in the studies used, these comparisons are associated with substantial uncertainty, and findings with respect to cost-effectiveness must be interpreted with caution. In particular, the beneficial effect of TZ on OS observed in the TAnDEM trial was likely attenuated by the cross-over of approximately 70% of the patients from ANA to TZ post progression [17]. At the time this analysis was conducted, published estimates of the HR for OS for TZ + ANA versus ANA using unbiased methods to control for cross-over were not publically available, so it was impossible to adjust for this confounding. There was, however, almost universal cross-

Table 2. Base-case results: Pairwise comparisons: effectiveness and costs

	LAP + LET	LET	ANA	TZ + ANA	LAP + LET versus		
					LET	ANA	TZ + ANA
Effectiveness							
Expected PFS, not discounted	1.238	0.76	0.606	1.086	0.479	0.632	0.152
Expected PFS, discounted	1.181	0.738	1.042	0.592	0.444	0.139	0.589
Expected PPS, not discounted	2.521	2.313	2.279	2.254	0.208	0.242	0.266
Expected PPS, discounted	2.218	2.079	2.004	2.065	0.138	0.214	0.153
Expected OS	3.759	3.072	2.885	3.341	0.687	0.874	0.419
Expected OS, discounted	3.399	2.817	3.045	2.657	0.582	0.354	0.742
QALYs, not discounted	2.626	2.086	1.933	2.33	0.540	0.693	0.296
QALYs, discounted	2.389	1.923	1.788	2.137	0.467	0.601	0.252
Expected costs, discounted, £							
Anti-HER2 therapy	29,115	0	0	22,811	29,115	29,115	6,304
AIs	1,104	688	576	1,007	416	528	97
Study drug administration	260	83	66	4,236	177	194	-3,976
Cardiac monitoring	659	0	0	581	659	659	78
Treatment of AEs	113	71	67	109	42	46	4
Other pre-progression	7,966	4,975	3,991	7,026	2,991	3,975	940
Post-progression	21,396	20,060	19,919	19,330	1,336	1,477	2,066
Total	60,614	25,878	24,620	55,101	34,737	35,995	5,513
Cost per QALY gained, £					74,448	59,895	21,836

Table 3. Results of probabilistic sensitivity analysis

Probability that therapy is cost-effective given threshold value for ICER	Incremental analysis (multi-way comparison)				Pairwise comparison		
	LAP + LET	LET	ANA	TZ + ANA	LAP + LET versus		
					LET	ANA	TZ + ANA
£ 20,000	0.0	82.6	17.4	0.0	0.0	0.0	37.6
£ 30,000	1.2	89.0	8.3	1.5	1.4	9.2	50.9
£ 50,000	26.1	58.8	3.7	11.4	31.1	56.7	63.7

Table 4. Deterministic sensitivity analyses: Pairwise comparison of costs, QALYs, and cost-effectiveness for LAP + LET

Scenario	LAP + LET				LAP + LET versus LET				LAP + LET versus ANA				LAP + LET versus TZ + ANA			
	No.	Description	Cost, £	QALYs	Cost, £	QALYs	ICER, £	Cost, £	QALYs	ICER, £	Cost, £	QALYs	Cost, £	QALYs	ICER, £	Cost, £
1	Base-case		60,614	2.389	34,737	0.467	74,448	35,995	0.601	59,895	5,513	0.252	5,513	0.252	21,836	5,513
2	HR PFS LAP + LET vs. LET: 95% CI lower limit		71,869	2.509	45,992	0.586	78,502	47,250	0.72	65,603	16,768	0.372	16,768	0.372	45,106	16,768
3	HR PFS LAP + LET vs. LET: 95% CI upper limit		52,468	2.303	26,591	0.38	69,930	27,849	0.515	54,115	-2,633	0.166	-2,633	0.166	*	-2,633
4	HR OS LAP + LET vs. LET: 95% CI lower limit		69,599	2.967	43,722	1.044	41,877	44,980	1.178	38,170	14,498	0.83	14,498	0.83	17,469	14,498
5	HR OS LAP + LET vs. LET: 95% CI upper limit		52,405	1.862	26,527	-0.061	**	27,785	-0.073	378,674	-2,696	-0.275	-2,696	-0.275	9,801 ^a	-2,696
6	HR PFS TZ + ANA vs. LET: 95% CI lower limit		60,614	2.389	34,737	0.467	74,448	35,995	0.601	59,895	-7,075	0.13	-7,075	0.13	*	-7,075
7	HR PFS TZ + ANA vs. LET: 95% CI upper limit		60,614	2.389	34,737	0.467	74,448	35,995	0.601	59,895	14,157	0.336	14,157	0.336	42,086	14,157
8	HR OS TZ + ANA vs. LET: 95% CI lower limit		60,614	2.389	34,737	0.467	74,448	35,995	0.601	59,895	-2,826	-0.283	-2,826	-0.283	9,969 ^a	-2,826
9	HR OS TZ + ANA vs. LET: 95% CI upper limit		60,614	2.389	34,737	0.467	74,448	35,995	0.601	59,895	12,837	0.723	12,837	0.723	17,751	12,837
10	PFS/OS with TZ + ANA = PFS/OS with LAP + LET		60,614	2.389	34,737	0.467	74,448	35,995	0.601	59,895	-1,350	0	-1,350	0	5,631,237 ^a	-1,350
11	TANDEM ANA reference treatment for PFS and OS		51,540	2.187	27,124	0.408	66,508	28,266	0.515	54,841	4,899	0.24	4,899	0.24	20,446	4,899
12	TZ administration costs -50% vs. base-case		60,484	2.389	34,648	0.467	74,257	35,898	0.601	59,733	7,501	0.252	7,501	0.252	29,711	7,501
13	TZ administration costs +50% vs. base-case		60,744	2.389	34,825	0.467	74,638	36,091	0.601	60,056	3,525	0.252	3,525	0.252	13,961	3,525
14	TZ 2 mg/kg every week		60,614	2.389	34,737	0.467	74,448	35,995	0.601	59,895	-3,389	0.252	-3,389	0.252	*	-3,389
15	All RDIs equal to 1.0		62,105	2.389	36,240	0.467	77,670	37,496	0.601	62,393	5,692	0.252	5,692	0.252	22,546	5,692
16	No wastage of study therapies		59,698	2.389	33,821	0.467	72,485	35,079	0.601	58,371	8,057	0.252	8,057	0.252	31,914	8,057
17	AE costs -50% vs. base-case		60,558	2.389	34,716	0.467	74,403	35,971	0.601	59,856	5,511	0.252	5,511	0.252	21,827	5,511
18	AE costs +50% vs. base-case		60,671	2.389	34,758	0.467	74,492	36,018	0.601	59,933	5,515	0.252	5,515	0.252	21,844	5,515
19	Cost of diarrhea 4 × base-case		60,735	2.389	34,843	0.467	74,675	36,103	0.601	60,075	5,609	0.252	5,609	0.252	22,218	5,609
20	PFS costs -50% vs. base-case		56,631	2.389	33,241	0.467	71,242	34,007	0.601	56,588	5,043	0.252	5,043	0.252	19,973	5,043
21	PFS costs +50% vs. base-case		64,597	2.389	36,232	0.467	77,653	37,982	0.601	63,202	5,983	0.252	5,983	0.252	23,698	5,983
22	PPS costs -50% vs. base-case		49,916	2.389	34,069	0.467	73,016	35,256	0.601	58,666	4,480	0.252	4,480	0.252	17,744	4,480
23	PPS costs +50% vs. base-case		71,312	2.389	35,405	0.467	75,879	36,733	0.601	61,124	6,546	0.252	6,546	0.252	25,928	6,546
24	Disutility PFS vs. perfect health -50% vs. base-case		60,614	2.151	34,737	0.426	81,570	35,995	0.549	65,565	5,513	0.228	5,513	0.228	24,209	5,513
25	Disutility PFS vs. perfect health +50% vs. base-case		60,614	2.627	34,737	0.507	68,469	35,995	0.653	55,127	5,513	0.277	5,513	0.277	19,886	5,513
26	Disutility PPS vs. PFS -50% vs. base-case		60,614	2.655	34,737	0.483	71,887	35,995	0.619	58,118	5,513	0.278	5,513	0.278	19,819	5,513
27	Disutility PPS vs. PFS +50% vs. base-case		60,614	2.123	34,737	0.45	77,197	35,995	0.583	61,784	5,513	0.227	5,513	0.227	24,310	5,513
28	Disutility w/AEs -50% vs. base-case		60,614	2.39	34,737	0.467	74,391	35,995	0.601	59,853	5,513	0.253	5,513	0.253	21,826	5,513
29	Disutility w/AEs +50% vs. base-case		60,614	2.388	34,737	0.466	74,504	35,995	0.601	59,936	5,513	0.252	5,513	0.252	21,846	5,513
30	Disutility for i.v. treatment: 0.02		60,614	2.389	34,737	0.467	74,448	35,995	0.601	59,895	5,513	0.353	5,513	0.353	15,597	5,513
31	Model timeframe 5 years		53,877	1.997	31,553	0.304	103,704	32,238	0.401	80,411	3,717	0.151	3,717	0.151	24,561	3,717

*LAP + LET is dominant.

**LAP + LET is dominated.

^aComparator is more costly and more effective than LAP + LET; ICER therefore represents cost per QALY gained with comparator versus LAP + LET.

over from tamoxifen to LET after progression in the P025 trial, and cross-over in this trial, which was part of the evidence network, may have biased the comparison of TZ + ANA versus LET in favor of TZ + ANA. Also, whereas patients in EGF30008 and TAnDEM were both HR+ and HER2+, patients in the P025 of LET versus tamoxifen [4, 5] and the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability (TARGET) and North American trials of ANA versus tamoxifen [2, 3, 6] were HR+ but not necessarily HER2+. If the relative effectiveness of LET versus ANA is modified by the HER2 status, the comparison might be biased. To the best of our knowledge, however, there are no data suggesting such an interaction.

If PFS, OS, and AEs are assumed to be the same for LAP + LET and TZ + ANA, the comparison of these 2 therapies resolves to a cost-minimization analysis, with LAP + LET estimated to result in savings of approximately £ 1,300 per patient. These projected savings are determined by assumptions about TZ wastage and cost of administration. Our base-case estimate of 15% wastage of TZ was based on a survey of UK clinicians [38]. In a study of a TZ medicines access program in Australia (where only 150-mg single-use vials are available and discarding of unused medications is mandated), it was estimated that 13% of the TZ would be wasted with 3-weekly dosing [51]. In a study of oncology drug wastage in an Italian hospital, 18% of the TZ was wasted prior to the introduction of a program to reduce wastage [52]. This value was reduced to 3.5% after full implementation of the program. These studies suggest that our estimate of 15% wastage may not be unreasonable. Our estimates of the cost of administration of TZ were based on NHS reference cost estimates for outpatient chemotherapy administration [41]. These estimates represent the cost of all outpatient visits for these HRGs and include visits for administration of a variety of types of chemotherapy; they may not be representative of the cost of administration of TZ alone [26].

Data on utilization, costs of AEs, and other breast-cancer related healthcare services were obtained from a variety of secondary sources. Model results were generally insensitive to these cost estimates. A generic utility instrument was not administered during EGF30008, and utility values for the PFS state were estimated based on a published algorithm for mapping from the FACT-G [33]. The validity of this mapping algorithm in breast cancer patients has not been examined.

Anti-HER2 therapy plus chemotherapy is likely to be used as first-line treatment for most patients with HER2+ MBC. However, for patients with HR+ disease for whom chemotherapy may not be a good option, anti-HER2 therapy with an AI may be considered. While it might be useful to conduct an indirect treatment comparison of LAP or TZ plus an AI with LAP or TZ plus chemotherapy, controlled trials with which to construct an evidence network linking these treatments are unavailable and a robust comparison of these treatments is therefore not feasible.

As part of the NICE assessment of LAP and TZ plus AI therapy, the assessment group (AG) conducted separate analyses of the cost-effectiveness of LAP + LET versus LET, and of TZ + ANA versus ANA, arguing that trial data were not sufficiently similar to support an adjusted indirect comparison [22]. For the LAP + LET versus LET 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 LAP + LET versus LET to be in excess of £ 220,000 per QALY gained. The difference in ICERs between the AG analysis and the analysis reported herein is predominantly due to differences in the projected effects of LAP + LET versus LET on PPS. The AG argued that, because the OS was relatively immature, projections of OS based on the fitting of parametric models to the OS data were imprecise. Instead, they assumed that the expected PPS would be the same for LAP + LET and LET, and that differences in OS would be driven by observed differences in PFS and the proportion of PFS events that were deaths. Thus, the analysis reported here projects an increase of approximately 50 days in discounted PPS, whereas the AG model projects a decrease of approximately 25 days. More definitive conclusions regarding the effect of LAP + LET on PPS and OS must await results of the final analyses of OS data from EGF30008. It should be noted, however, that in other trials of lapatinib for MBC, the increase in the median OS with lapatinib has been greater than the increase in the median PFS or TTP [13, 15, 53], and similar findings have been observed in trials of TZ in this setting [10, 18, 54, 55].

A recent study by McNamara et al. [56] evaluated the cost-effectiveness of TZ + ANA versus LAP + LET, LET, and ANA in HR+ and HER2+ MBC. The methods and results of the study by McNamara et al. are similar to those employed in the Roche manufacturer's submission to NICE as reported by the AG [22]. Estimates of the cost-effectiveness of LAP + LET and TZ + ANA versus LET and ANA were similar to those reported here. However, whereas LAP + LET was found to be more costly and more effective than TZ + ANA in the study reported here (cost per QALY gained for LAP + LET = £ 21,836), McNamara et al. [56] found that TZ + ANA was more costly and more effective than LAP + LET (cost per QALY gained for TZ + ANA = £ 17,912). While the general modeling approach employed was similar, the 2 studies differ in a number of parameter estimates and assumptions. In particular, whereas our study estimated the relative effectiveness of LET versus ANA based on a mixed treatment comparison, the study by McNamara et al. assumed equal effectiveness for LET and ANA. Also, whereas our study estimated the HR for OS for TZ + ANA versus ANA based on the analysis of TAnDEM data without adjustment for cross-over, the other study estimated the OS for ANA based on an analysis using a rank-preserving structural failure

time model to account for patient cross-over from ANA to TZ + ANA [57]. OS for LAP + LET was then obtained by applying the HR for OS from EGF30008 to the OS survival function for ANA after this adjustment. Also, whereas the costs of TZ administration were similar in the 2 studies (approximately £ 4,300), the costs of LAP administration were higher in the study by McNamara et al. [56] than estimated here (£ 2,561 vs. £ 260). Although the similarity of estimates of cost-effectiveness of combination therapy versus AIs in the 2 studies support the robustness of these comparisons, differences between studies in estimates of relative cost-effectiveness of the 2 combination therapies highlight the uncertainty associated with this comparison.

Conclusions

Based on criteria typically used by the NICE to evaluate novel therapies (£ 30,000 per QALY), LAP + LET may be

cost-effective compared with TZ + ANA, although this comparison is associated with substantial uncertainty. LAP + LET is unlikely to be cost-effective compared with AI monotherapy as first-line treatment for patients with HR+/HER2+ MBC.

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