HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

25 June 2014

TYVERB 250 mg, film-coated tablet

Bottle of 70 film-coated tablets (CIP: 34009 417 017 6 4)
Bottle of 84 film-coated tablets (CIP: 34009 417 019 9 3)
Bottle of 140 film-coated tablets (CIP: 34009 417 018 2 5)

Applicant: GlaxoSmithKline

INN	**Lapatinib**
ATC code (2013)	L01XE07 (protein kinase inhibitor)
Reason for the review	**Extension of indication**
Lists concerned	**National Health Insurance (Social Security Code L.162-17)** **Hospital use (Public Health Code L.5123-2)**
Indication(s) concerned	**"TYVERB is indicated for the treatment of adult patients with breast cancer, whose tumours overexpress HER2 (ErbB2), in combination with trastuzumab for patients with hormone receptor-negative metastatic disease that has progressed on prior trastuzumab therapy(ies) in combination with chemotherapy."**

Actual Benefit	**Moderate**
Improvement in Actual Benefit	**Taking into account the lack of data showing a benefit versus a clinically relevant comparator, the methodological limitations of the study based primarily on a post-hoc analysis, and the lack of benefit in terms of progression-free survival in the subgroup of HER2+ and HR- patients, the Committee considers that TYVERB, in combination with trastuzumab, does not provide any improvement in actual benefit (level V, non-existent) in comparison with the usual management of breast cancer with HER2 (ErbB2) overexpression in patients with hormone receptor-negative metastatic disease.**
Therapeutic use	**Taking into account recent developments in the management of HER2+ metastatic breast cancer, with the arrival of pertuzumab (PERJETA) as 1st-line therapy and trastuzumab emtansine (KADCYLA) as 2nd-line therapy, and the data available for the lapatinib + trastuzumab combination in heavily pre-treated patients in whom trastuzumab and chemotherapy have failed, lapatinib (TYVERB) in combination with trastuzumab is a 3rd-line and subsequent therapeutic option for breast cancer with HER2 (ErbB2) overexpression in patients with hormone receptor-negative metastatic disease.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (centralised procedure)	Date initiated (conditional MA): 10/06/2008 Extension of indication: 25/07/2013 Risk Management Plan
Prescribing and dispensing conditions	Cohort temporary usage authorisation (TUA) Medicine for hospital prescription Prescription restricted to oncology or haematology specialists or doctors with cancer training Medicine requiring special monitoring during treatment

ATC Classification	2013	
	L	Antineoplastic and immunomodulating agents
	L01	Antineoplastic agents
	L01X	Other antineoplastic agents
	L01XE	Protein kinase inhibitors
	L01XE07	Lapatinib

02 BACKGROUND

Since June 2008, TYVERB has had Marketing Authorisation for the treatment of patients with breast cancer, whose tumours overexpress HER2, in combination with capecitabine for patients with advanced or metastatic disease with progression following prior therapy, which must have included an anthracycline and a taxane and therapy with trastuzumab in the metastatic setting.

In this indication (opinion of 16 July 2008), the Transparency Committee allocated TYVERB a substantial actual benefit and an IAB level III in view of the improvement observed with combined TYVERB + XELODA in comparison with XELODA monotherapy in terms of median time to progression and an acceptable safety profile on one hand, but the absence of a demonstrated effect on overall survival on the other hand.

Since June 2010, TYVERB has had Marketing Authorisation for the treatment of patients with breast cancer, whose tumours overexpress HER2, in combination with an aromatase inhibitor for postmenopausal women with hormone receptor positive metastatic disease, not currently intended for chemotherapy. The patients in the registration study were not previously treated with trastuzumab or an aromatase inhibitor.

In this indication (opinion of 3 November 2010), the Committee allocated TYVERB a substantial actual benefit and an IAB level V.

This application for inclusion concerns an extension of indication to “the treatment of adult patients with breast cancer, whose tumours overexpress HER2 (ErbB2), in combination with trastuzumab for patients with hormone receptor-negative metastatic disease that has progressed on prior trastuzumab therapy(ies) in combination with chemotherapy”.

Lapatinib is an inhibitor of the intracellular tyrosine kinase domains of EGFR (ErbB1) and HER2 (ErbB2) receptors. Trastuzumab is a recombinant humanised monoclonal antibody of the IgG1 class which targets human epidermal growth factor receptor 2 (HER2).

The combination of lapatinib and trastuzumab, drugs with complementary mechanisms of action, could potentially have no mechanisms of cross-resistance.

03 THERAPEUTIC INDICATIONS

"TYVERB is indicated for the treatment of adult patients with breast cancer, whose tumours overexpress HER2 (ErbB2):

- in combination with capecitabine for patients with advanced or metastatic disease with progression following prior therapy, which must have included an anthracycline and a taxane and therapy with trastuzumab in the metastatic setting;

- **in combination with trastuzumab for patients with hormone receptor-negative metastatic disease that has progressed on prior trastuzumab therapy(ies) in combination with chemotherapy;**

- in combination with an aromatase inhibitor for postmenopausal women with hormone receptor positive metastatic disease, not currently intended for chemotherapy. The patients in the registration study were not previously treated with trastuzumab or an aromatase inhibitor. No data are available on the efficacy of this combination relative to trastuzumab in combination with an aromatase inhibitor in this patient population."

04 DOSAGE

In combination with trastuzumab:
"The recommended dose of TYVERB is 1000 mg (i.e. four 250 mg tablets) once daily continuously. The recommended dose of trastuzumab is 4 mg/kg administered as an intravenous (IV) loading dose, followed by 2 mg/kg IV weekly."

05 THERAPEUTIC NEED

In France, breast cancer is the most common female cancer, with an estimated 48,800 new cases in 2012.[1] It accounts for 31.5% of all new cases of cancer in women and almost 14% of all incident cancers in both sexes. It is a serious and life-threatening disease, particularly at the metastatic stage. With almost 11,900 estimated deaths in 2012, breast cancer is the leading cause of cancer deaths in women.**Erreur ! Signet non défini.**

In breast cancer, overexpression of the HER2 receptor and/or HER2 gene amplification are factors indicating a poorer prognosis than HER2 negative breast cancer.[2]
In metastatic HER2-positive breast cancer, it is essential that an anti-HER2 action is maintained whatever the line of treatment.[3] Now that targeted therapies for treating metastatic HER2-positive breast cancer are on the market, progression of the disease can be delayed at any stage.

As first-line therapy for metastatic breast cancer with HER2 overexpression, the available treatments are:

[1] Les cancers en France en 2013 [Cancers in France in 2013]. Collection of status reports and knowledge updates, collective work published by INCa [National Cancer Institute], Boulogne-Billancourt, January 2014.
[2] Dawood S, Broglio K, Ensor J, et al. Survival differences among women with de novo stage IV and relapsed breast cancer. Ann Oncol 2010; 21:2169-2174.
[3] Gligorov J. Trastuzumab après progression chez les patientes HER2+ ayant un cancer du sein avancé : résultats de l'étude GBG-26/BIG 03-05 [Trastuzumab after progression in HER2+ patients with advanced breast cancer : results of study GBG-26/BIG 03-05]. Lettre Cancérologue. June 2009. Vol. XVIII - no. 6: page 318.

- Since 2000, trastuzumab (HERCEPTIN) combined with a taxane (paclitaxel or docetaxel), irrespective of hormone status. If hormone receptors are expressed, trastuzumab may also be combined with hormone therapy.
- Since 2013, pertuzumab (PERJETA) in combination with trastuzumab and docetaxel has been a new option for managing HER2+ metastatic breast cancer. The American NCCN (National Comprehensive Cancer Network) guidelines[4] consider that adding pertuzumab to dual therapy with trastuzumab and a taxane is preferable to dual therapy alone.

As second-line and subsequent therapy, the proprietary medicinal product KADCYLA (trastuzumab emtansine) has had Marketing Authorisation since November 2013 in patients with metastatic or locally advanced and unresectable HER2+ breast cancer who have previously received trastuzumab and a taxane, separately or in combination. Patients must have had previous treatment for the locally advanced or metastatic disease or have experienced disease progression during adjuvant treatment or within six months of this finishing. KADCYLA is a treatment of choice in patients who have already been exposed to trastuzumab.[5]

Combining lapatinib (TYVERB) with capecitabine (XELODA)[6] is an alternative in patients who have previously had an anthracycline, a taxane and trastuzumab for metastatic disease.

In addition, a temporary treatment protocol[7] (TTP) has existed since 2008 for the trastuzumab (HERCEPTIN)/capecitabine (XELODA) combination after progression on trastuzumab in combination with taxanes or alone.[8]

Therefore, in metastatic breast cancer with HER2 overexpression, despite the availability of chemotherapy combinations and targeted therapies (as monotherapy or in combination with chemotherapy), there is a therapeutic need for medicines that improve progression-free survival and overall survival while maintaining patients' quality of life.

[4] National Comprehensive Cancer Network Breast cancer (NCCN 2013) http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
[5] HAS. Transparency Committee Opinion for KADCYLA dated 19 March 2014.
[6] HAS. Transparency Committee Opinion for TYVERB dated 16 July 2008.
[7] A transitional phase has been provided for in terms of the "off-label" framework with the progressive disappearance of temporary treatment protocols (TTPs) concerning the drugs included on the "non-GHS" list and valid until 31 December 2015, and the implementation of the new system for temporary usage recommendations.
[8] INCa. Référentiels de Bon Usage hors GHS. Protocoles thérapeutiques hors GHS [Non-GHS good practice guidelines]. Cancers du sein [Breast cancers]. March 2012.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

The clinically relevant comparators for TYVERB (lapatinib) in combination with trastuzumab in the treatment of metastatic HER2+/HR- breast cancer that has progressed after treatment with trastuzumab combined with chemotherapy are:

- combined lapatinib (TYVERB)/capecitabine (XELODA) (Marketing Authorisation since June 2008) in patients with advanced or metastatic disease with progression following prior therapy, which must have included an anthracycline and a taxane and therapy with trastuzumab in the metastatic setting;
- trastuzumab emtansine (KADCYLA) as monotherapy (Marketing Authorisation since November 2013) in patients with metastatic or locally advanced and unresectable HER2+ breast cancer who have previously received trastuzumab and a taxane, separately or in combination. Patients must have received previous treatment for the locally advanced or metastatic disease or have had disease progression during adjuvant treatment or within six months of this finishing.

Combined trastuzumab (HERCEPTIN)/capecitabine (XELODA), defined as acceptable on a provisional basis, has had a temporary treatment protocol since 2008.**Erreur ! Signet non défini.**

NAME (INN) *Company*	Same TC* Yes / No	Indication	Date of opinion	AB	IAB (wording)	Reimbursed Yes/No
TYVERB (lapatinib) *GSK*	Yes L01XE07 Protein kinase inhibitors	"TYVERB is indicated for the treatment of patients with breast cancer, whose tumours overexpress HER2: - in combination with capecitabine for patients with advanced or metastatic disease with progression following prior therapy, which must have included an anthracycline and a taxane and therapy with trastuzumab in the metastatic setting;	16 July 2008 (Inclusion)	Substantial	**IAB level III** in the treatment of advanced or metastatic breast cancer with HER2 overexpression in patients with progression following prior therapy, which must have included an anthracycline, a taxane and trastuzumab.	Yes
XELODA (capecitabine) *ROCHE*	No L01BC06 Pyrimidine analogues	XELODA in combination with docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. XELODA is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.	7 November 2011 (RI)	Substantial	N/A	Yes
KADCYLA (trastuzumab emtansine) ROCHE	No L01XC14 Monoclonal antibodies	KADCYLA, as a single agent, is indicated for the treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination.	19 March 2014 (Inclusion)	Substantial	**IAB level II** in the treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination.	No[9]

*Therapeutic category.

[9] Not included on the list of medicines approved for hospital use on 17 July 2014.

06.2 Other health technologies

Not applicable.

◗ Conclusion

The clinically relevant comparators for TYVERB, in the treatment of metastatic HER2-positive and hormone receptor-negative breast cancer that has progressed after treatment with trastuzumab combined with chemotherapy, are:

Treatments with Marketing Authorisation

- the combination lapatinib (TYVERB)/capecitabine (XELODA)
- trastuzumab emtansine (KADCYLA) as monotherapy

Temporary Treatment Protocol (TTP)

- the combination capecitabine (XELODA)/trastuzumab (HERCEPTIN)

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	REIMBURSEMENT	
	YES/NO If no, why not	Population(s) Marketing Authorisation or restricted population
Germany	Yes (August 2013)	MA population
United Kingdom	Assessment in progress	N/A
Italy	Assessment in progress	N/A
Spain	Assessment in progress	N/A
Japan	Yes (Date not communicated)	MA population
Netherlands	Yes (August 2013)	MA population

N/A = not applicable

In the USA, no Marketing Authorisation application has been made to the FDA for the new indication of TYVERB.

08 ANALYSIS OF AVAILABLE DATA

The dossier submitted by the company comprises:
- the results of a randomised, open-label, comparative, phase III superiority study (EGF104900) of the efficacy and safety of combined lapatinib + trastuzumab versus lapatinib alone;[10,11]
- The results of subgroup analyses from the EGF104900 study performed a posteriori at the request of the EMA;
- Safety data from 2 clinical studies (EGF106903/NeoALTTO[12] and LPT109096) which evaluated the efficacy and safety of the lapatinib + trastuzumab combination in the neoadjuvant setting (off-label use).

08.1 Efficacy

8.1.1 Phase III study (EGF104900)

	Study EGF104900
Main objective of the trial	Comparison of the efficacy and safety of combined lapatinib + trastuzumab versus lapatinib alone, in women with HER2+ metastatic breast cancer, previously exposed to anthracyclines and taxanes, who experienced progression during their last treatment including trastuzumab administered in the metastatic setting.
Method	A phase III, randomised, open-label, comparative superiority study versus lapatinib alone.
Population studied	Women with HER2+ metastatic breast cancer, previously exposed to anthracyclines and taxanes, who experienced progression during their most recent treatment including trastuzumab administered in the metastatic setting.
Main inclusion criteria	- Women aged ≥ 18 years - Confirmed diagnosis of metastatic breast cancer, confirmed by histology/cytology - Documented ErB2 gene amplification on the FISH test (Fluorescence In Situ Hybridisation) or documented ErB2 protein overexpression on immunohistochemical (IHC) testing of primary or metastatic tumour tissue - ECOG performance status between 0 and 2 - Left ventricular ejection fraction (LVEF) within normal limits - Previous treatment with anthracyclines (at least 4 courses, or 2 courses if patients progressed on anthracyclines) and taxanes (at least 4 courses, or 2 courses if patients progressed on taxanes) - Documented disease progression following at least one treatment with trastuzumab combined with cytotoxic chemotherapy or hormone therapy in the metastatic setting - Creatinine clearance > 40 ml/min - Haemoglobin ≥ 9 g/dL, platelets ≥ 75 g/L - Serum albumin ≥ 2.5 g/dL, ASAT and ALAT ≤ 3N without hepatic

[10] Blackwell KL *et al*. Randomized Study of Lapatinib Alone or in Combination With Trastuzumab in Women With ErbB2-Positive, Trastuzumab-Refractory Metastatic Breast Cancer. JCO 2010;28: 1124-30.
[11] Blackwell KL *et al*. Overall Survival Benefit with Lapatinib in Combination with Trastuzumab for Patients with Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer: Final Results from the EGF104900 Study. JCO 2012;30:2585-92.
[12] Baselga J, Bradbury I, Eidtmann H, Di Cosimo S, de Azambuja E, *et al*. NeoALTTO Study Team. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. Lancet 2012;379:633-40.

	metastasis or ≤ 5N with hepatic metastasis
Main non-inclusion criteria	- Previous treatment with an ErB1 and/or ErB2 inhibitor other than trastuzumab - Malabsorption syndrome or disease significantly affecting gastrointestinal function - History of other tumours in the 5 years prior to inclusion. However, patients with a history of fully resected non-melanoma skin cancer or carcinoma in situ of the cervix that was cured after treatment were eligible - Unresolved or serious toxicity associated with the administration of another experimental treatment and/or of a previous cancer treatment - Known history of symptomatic or poorly controlled angina, arrhythmia or congestive heart failure - Concomitant cancer treatment or concomitant treatment with an experimental agent - Active concomitant liver or biliary disease
Treatment groups	Randomisation (1:1) to one of two treatment groups: - **Lapatinib + trastuzumab:** D1: 1000 mg lapatinib (PO) + 4 mg/kg trastuzumab (IV) Subsequent days: 1000 mg lapatinib (PO) + 2 mg/kg trastuzumab (IV) until progression. - **Lapatinib alone:** 1500 mg lapatinib (PO) every day until progression. Crossover was authorised for patients treated with lapatinib alone in case of progression after less than 4 weeks of treatment. **Stratification criteria on randomisation:** 1. Hormone status: Hormone receptor positive (HR+) versus hormone receptor negative (HR-) 2. Metastatic disease: visceral versus non-visceral metastases
Course of the study	The study was conducted between November 2005 and October 2010 in 88 centres in 13 countries.[13] Three analyses (planned in the protocol) were performed before the final data freeze: - **29 June 2007**: primary analysis of progression-free survival - **23 January 2009**: analysis of overall survival - **29 October 2010**: final cumulative analysis for the assignment of patients and safety - **5 May 2011**: final freezing of study data, corresponding to the longest available patient follow-up for the safety analysis
Primary efficacy endpoint	**- Progression-free survival** (PFS) evaluated by the investigator: time between the date of randomisation and the date of progression or death from any cause. Progression evaluated using RECIST criteria, based on imaging examinations (MRI and CAT scan).
Secondary endpoints included	**- Overall survival (OS)**: time between the date of randomisation and the date of death from any cause. - Overall response rate (ORR): proportion of patients with either a confirmed complete response (CR) or a confirmed partial response (PR). Patients whose response was unknown or with missing response data were considered as non-responders. **- Clinical benefit rate (CBR)**: proportion of patients with a confirmed complete response (CR) or partial response (PR) at any time in the study or with stable disease (SD) for at least 24 weeks. Patients who withdrew from the study before completing 24 weeks of treatment were considered as non-responders.

[13] France did not take part in this study.

	- Quality of life evaluated using the FACT-B questionnaire specific to breast cancer, corresponding to an evaluation using the FACT-G questionnaire (G: general) plus a sub-scale specific to breast cancer (B: breast). **- Safety**
Calculation of the number of subjects required	The estimated number of subjects required was based on a median PFS of 8 weeks in the lapatinib only arm and 12 weeks in the lapatinib + trastuzumab arm (i.e. a HR of 0.667), with a maximum of 192 patients with progressive disease (with a power of 80% and an α risk of 5%). A total of 270 subjects needed to be included.
Statistical analysis	The comparison (in terms of superiority) of the primary efficacy endpoint (PFS) between the lapatinib + trastuzumab arm and the lapatinib only arm was performed in the ITT population, stratified using a two-tailed log-rank test with a risk of type I error of 5% on the stratification criteria from randomisation (hormone status [HR+ or HR-] and site of disease [visceral involvement or no visceral involvement]). The final analysis of overall survival, in the ITT population stratified by prognostic factors, was planned to take place after 75% of deaths had occurred irrespective of treatment arm. Kaplan-Meier curves were produced and the two treatment arms were compared using a stratified log-rank test. In addition, an analysis of progression-free survival and overall survival excluding patients who crossed over was planned in the protocol. The progression-free survival analysis was performed from the crossover date until the date of progression or death from any cause. The overall survival analysis was performed from the date of randomisation (to either arm) until the date of death from any cause. A comparison of overall response rates between treatment arms was undertaken using Fisher's exact tests in each stratum. The analysis of interaction of the treatment effect between adjustment strata was performed using Zelen's test for homogeneity of odds ratios. A comparison of overall benefit rates between treatment arms was undertaken using Fisher's exact tests with a 95% confidence interval. No hierarchical tests for analysing each endpoint were planned.

Results:

Study size (Table 1)
A total of 397 patients were selected and 296 were randomised, thus forming the ITT population, with 148 patients in each group.

For the primary analysis of progression-free survival (29 June 2007), 5 patients (2 patients in the lapatinib + trastuzumab group and 3 patients in the lapatinib only group) who did not have a validated hormone status were excluded from the ITT population. Consequently, the stratified ITT population consisted of 291 patients:

- 146 patients in the lapatinib + trastuzumab group
- 145 patients in the lapatinib only group.

In addition, of the 148 patients randomised to the lapatinib group, 77 patients (52%) crossed over after disease progression on lapatinib alone and formed the crossover population.

Table 1. Interim analysis populations on 29 June 2007

	Lapatinib + trastuzumab n (%)	Lapatinib alone n (%)	Total n (%)
ITT population	148 (100)	148 (100)	296 (100)
Stratified ITT population	146 (99)	145 (98)	291 (98)
Crossover population	0	77 (52)	77 (26)
Safety population	149 (101)	146 (99)	295 (>99)

Baseline characteristics of patients
The baseline characteristics of patients were comparable between the two treatment groups (Table 2).

The median age of the patients was 51 years (min-max: 26-81 years) and 73% of patients had visceral involvement.

HER2 3+ status was identified from a diagnostic IHC test in 67% of patients and from a diagnostic FISH test in 85% of patients.
51% of patients had a negative hormone status (HR-).
Patients (99%) had previously received cancer treatment including anthracyclines, chemotherapy and trastuzumab. The median number of previous cancer treatments was 6 (min-max: 1-18).
The median number of previous treatment(s) including trastuzumab in the metastatic setting was 3 (min-max: 0-13).
It should be noted that in the initial data collected, 15 patients (5%) had not taken trastuzumab in the past. After a new analysis of previous treatments at the CHMP's request, 11 out of 15 patients had taken trastuzumab. Thus, in the final analysis, 4 patients (1.4%) and not 15 had not taken trastuzumab in the past.

Table 2. Baseline characteristics of patients

	Lapatinib + trastuzumab N=148	Lapatinib alone N=148	Total N=296
Age (years)			
Median (min – max)	52 (26 – 81)	51 (29 – 78)	51 (26 – 81)
Ethnic origin, n (%)			
Caucasian	137 (93)	140 (95)	277 (94)
Time since first diagnosis (years)			
n	146	148	294
Median (min – max)	4.3 (1 – 18)	4.7 (1 – 15)	4.4 (1 – 18)
Hormone receptor status (oestrogen or progesterone), n (%)			
HR+	71 (48)	70 (47)	141 (48)
HR-	75 (51)	75 (51)	150 (51)
Unknown	2 (1)	3 (2)	5 (2)
IHC HER2 status, n (%)			
0	3 (2)	6 (4)	9 (3)
1+	7 (5)	2 (1)	9 (3)
2+	24 (16)	20 (14)	44 (15)
3+	97 (66)	100 (68)	197 (67)
Unknown	12 (8)	13 (9)	25 (8)
Missing data	5 (3)	7 (5)	12 (4)
FISH HER2 status, n (%)			
Positive	131 (89)	122 (82)	253 (85)
Negative	0	5 (3)	5 (2)
Missing data	17 (11)	21 (14)	38 (13)
Visceral or non-visceral disease, n (%)			
Visceral	105 (71)	110 (74)	215 (73)
Non-visceral	43 (29)	38 (26)	81 (27)
ECOG performance status (PS), n (%)			
0	80 (54)	69 (47)	149 (50)
1	61 (41)	73 (49)	134 (45)
2	7 (5)	6 (4)	13 (4)
Number of previous cancer treatments, n (%)			
Median (min – max)	6 (2-18)	6 (1-17)	6 (1-18)
Patients who received previous treatment with chemotherapy, n (%)			
Yes	148 (100)	*148 (100)*	*296 (100)*
Number of previous courses of chemotherapy, median (min-max)	*7 (2-20)*	6.5 (1-18)	*7 (1-20)*
Patients who received previous treatment with anthracycline, n (%)			
Yes	148 (100)	148 (100)	296 (100)
Patients who received previous treatment with trastuzumab in the metastatic setting, n (%)			
Yes	140 (95)	141 (95)	281 (95)*
Number of previous treatment(s) with trastuzumab in the metastatic setting, n (%)			
Median (min – max)	3 (0-12)	3 (0-13)	3 (0-13)

** before verification of previous treatments at the CHMP's request*

Primary efficacy endpoint: progression-free survival (PFS)

On the date of the primary analysis of progression-free survival (first interim analysis on **29 June 2007**), 127/146 patients (87%) in the lapatinib + trastuzumab group and 128/145 (88%) in the lapatinib only group had progressed or died (as evaluated by the investigator) (Figure 1).

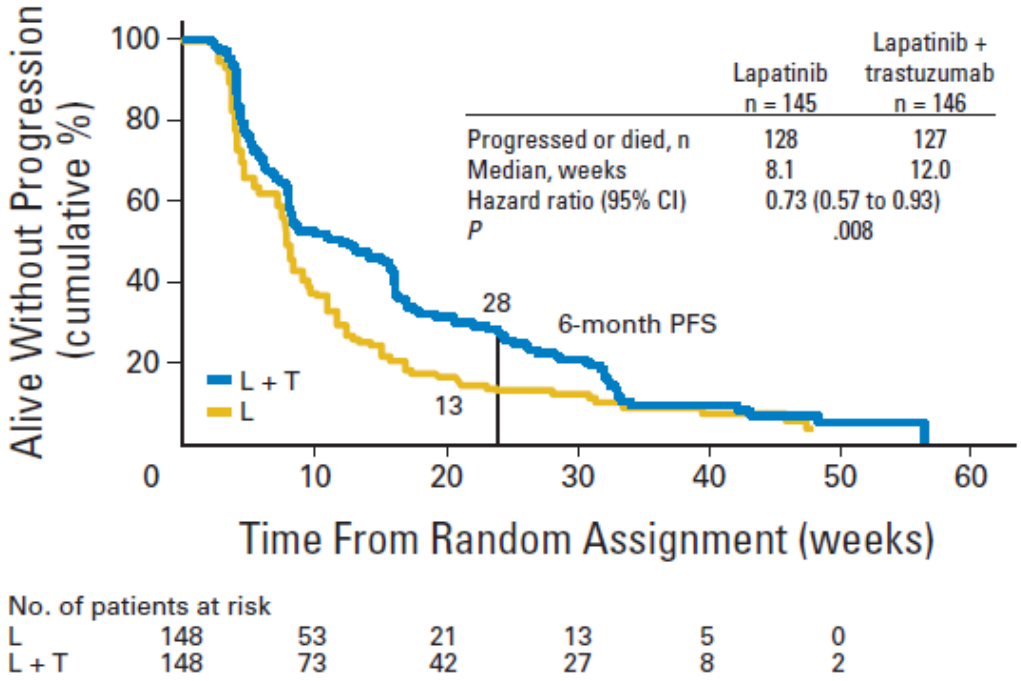
The combination of lapatinib and trastuzumab reduced the risk of progression or death by 27% in comparison with lapatinib alone: HR = 0.73 (95% CI: [0.57; 0.93], p<0.008).

The median progression-free survival was:

- 12 weeks for patients in the lapatinib + trastuzumab group;
- 8.1 weeks for patients in the lapatinib only group.

A statistically significant improvement in median progression-free survival of +3.9 weeks was observed favouring the lapatinib + trastuzumab group.

Figure 1. Kaplan-Meier curves for progression-free survival (interim analysis of 29 June 2007)



Source: Blackwell *et al*. 2010Erreur ! Signet non défini.

Secondary endpoints

Overall survival (OS)

On the date of the final analysis for overall survival (23 January 2009), 218 deaths (75%) had been reported with:

- 105 (72%) in the lapatinib + trastuzumab group;
- 113 (78%) in the lapatinib only group.

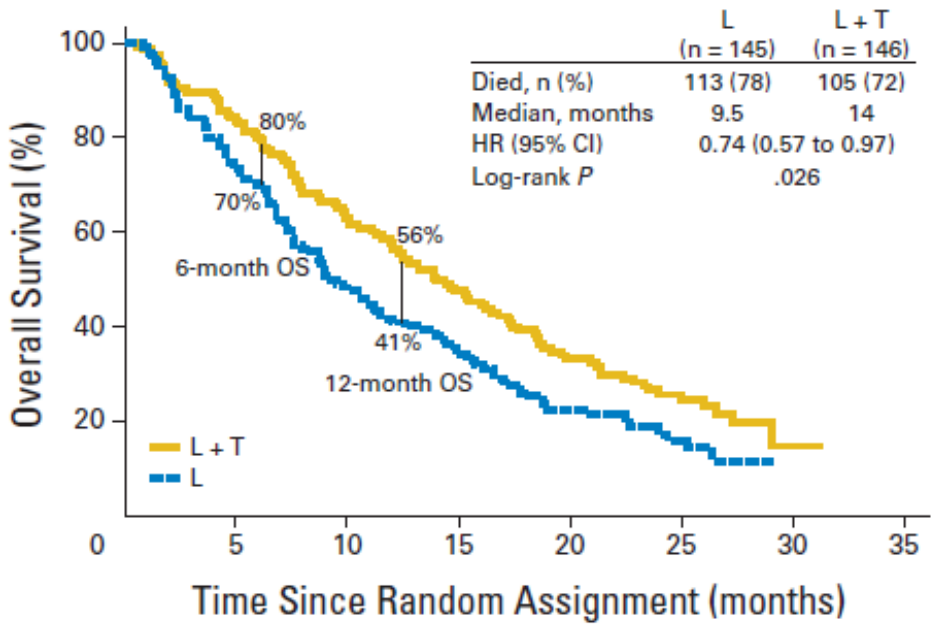
The combination of lapatinib and trastuzumab reduced the risk of death by 26% in comparison with lapatinib alone: HR=0.74 (95% CI: [0.57; 0.97]; p=0.026).

The median overall survival was (Figure 2):

- 14 months for patients in the lapatinib + trastuzumab group;
- 9.5 months for patients in the lapatinib only group.

An improvement in median overall survival of 4.5 months was observed favouring the lapatinib + trastuzumab group.

Figure 2. Kaplan-Meier curves for overall survival (interim analysis of 23 January 2009)



Source: Blackwell *et al*. 2012[Erreur ! Signet non défini.]

Overall response rate (ORR)

In the interim analysis of 29 June 2007, no difference was demonstrated in the overall response rate (the sum of complete responses and partial responses) as evaluated by the investigator, with 10.3% in the lapatinib + trastuzumab group versus 6.9% in the lapatinib only group: odds ratio = 1.5 (95% CI: [0.6; 3.9]; p=0.46) (Table 3).

Table 3. Overall response (ITT population, interim analysis of 29 June 2007)

	Evaluation by the investigator		**Evaluation by the independent committee**	
	Lapatinib + trastuzumab	**Lapatinib alone**	**Lapatinib + trastuzumab**	**Lapatinib alone**
	N=148	**N=148**	**N=148**	**N=148**
Number of patients with best response, n (%)				
n	146	145	146	145
Complete response (CR)	2 (1)	3 (2)	2 (1)	0
Partial response (PR)	13 (9)	7 (5)	7 (5)	4 (3)
Stable disease (SD)	57 (39)	40 (28)	65 (45)	56 (39)
Progressive disease (PD)	56 (38)	83 (57)	34 (23)	46 (32)
None known	18 (12)	12 (8)	38 (26)	39 (27)
Overall response rate (CR or PR), % [95% CI]	10.3 [5.9; 16.4]	6.9 [3.4; 12.3]	6.2 [2.9; 11.4]	2.8 [0.8; 6.9]
Difference in overall response rate, % [95% CI]	3.4 [5.5; 14.0]		3.4 [-4.2; 13.1]	
Odds ratio [95% CI]	1.5 [0.6; 3.9]		2.2 [0.6; 10.1]	
p (exact test)	0.46		0.29	

Clinical benefit rate (CBR)

In the interim analysis of 29 June 2007, the clinical benefit rate (the sum of complete responses, partial responses and stable disease ≥ 24 weeks) was higher in the combined lapatinib and trastuzumab group than in the lapatinib only group: 24.7% versus 12.4% respectively: odds ratio = 2.2 (95% CI: [1.2; 4.5]; p=0.01) (Table 4).

Table 4. Clinical benefit (ITT population, interim analysis of 29 June 2007)

	Evaluation by the investigator		Evaluation by the independent committee	
	Lapatinib + trastuzumab **N=148**	**Lapatinib alone** **N=148**	**Lapatinib + trastuzumab** **N=148**	**Lapatinib alone** **N=148**
Clinical benefit rate, %	24.7	12.4	18.5	9.0
[95% CI]	[17.9; 32.5]	[7.5; 18.9]	[12.6; 25.8]	[4.9; 14.8]
Difference in clinical benefit rate, %	12.2		9.5	
[95% CI]	[1.8; 23.5]		[-0.3; 20.6]	
Odds ratio	2.2		2.2	
[95% CI]	[1.2; 4.5]		[1.0; 4.9]	
p (exact test)	0.01		0.04	

Quality of life

In the interim analysis of 29 June 2007, the study showed that quality of life was maintained in both treatment groups in terms of mean change in total FACT-B score from baseline, without demonstrating any statistically significant difference between the two groups. The study did not show any difference in FACT-G score between the two groups.

8.1.2 Additional subgroup analyses

At the EMA's request, the company performed post hoc analyses in subgroups defined by:

- histological tumour differentiation (poorly differentiated or undifferentiated tumours versus moderately or well-differentiated tumours)
- HER2 extracellular domain levels
- hormone receptor status (HR- versus HR+), which was a stratification variable on randomisation.

As an analysis of these three subgroups did not show any correlation between the three factors, they were evaluated separately, without calculating the alpha risk (not predetermined) inasmuch as these analyses were not planned in the protocol.

The additional analyses did not show any clinical benefit in terms of PFS and/or OS for the lapatinib + trastuzumab combination versus lapatinib alone according to histological tumour differentiation or HER2 extracellular domain levels.

No difference between the lapatinib + trastuzumab group and the lapatinib only group in terms of progression-free survival was found in any patient subgroup (HR-: 95% CI [0.52; 1.03]; HR+: 95% CI [0.51; 1.04]).
The lapatinib + trastuzumab combination was shown to be better in terms of overall survival (+8.3 months) only in the subgroup of patients who did not express hormone receptors (HR-) (Table 5).

Table 5: Progression-free survival (PFS) and overall survival (OS) according to hormone status

	Subgroup	N (L+T/L)	Lapatinib + trastuzumab	Lapatinib alone	Median difference	Hazard ratio [95% CI]
Median PFS, in weeks [min-max]	HR-	75/75	15.4 [8.4; 16.9]	8.2 [7.4; 9.3]	7.2 weeks	0.73 [0.52; 1.03]
	HR+	71/70	7.9 [6.3; 15.7]	8.1 [6.1; 9.9]	-0.2 weeks	0.73 [0.51; 1.04]
Median OS in months [min-max]	HR-	75/75	17.2 [13.9; 19.2]	8.9 [6.7; 11.8]	8.3 months	0.62 [0.42; 0.90]
	HR+	71/70	12.0 [9.4; 15.4]	11.2 [8.0; 15.4]	0.8 months	0.84 [0.58; 1.23]

These analyses led to the indication being restricted to patients who do not express hormone receptors.

At the EMA's request, an analysis was performed of the impact of treatments received after progression.
The post-progression treatments prescribed up until the interim analysis of 23 January 2009 were recorded. The types of treatment received were comparable between the arms, with the exception of vinorelbine, which was more frequently prescribed to patients in the lapatinib + trastuzumab group (25%) than those in the lapatinib only group (11%) and trastuzumab, which was more frequently prescribed to patients in the lapatinib only group (48%) than those in the lapatinib + trastuzumab group (62%). The median number of treatments received after progression was 2.

Among patients with a poorly differentiated or undifferentiated tumour, 70% of HR- patients received post-progression treatment versus 63% of RH+ patients.

According to the EMA, the heterogeneity of post-progression treatments between the two treatment groups does not explain the differences observed in overall survival and progression-free survival.[14]

08.2 Safety/Adverse effects

The safety analysis in the EGF104900 study, corresponding to the longest duration of follow-up (to 5 May 2011), was performed in all randomised patients who received at least one dose of study treatment (the safety population), namely 295 patients, with:

- 149 patients in the lapatinib + trastuzumab group,
- 146 patients in the lapatinib only group.

The median duration of treatment was:

- 12.3 weeks (min-max: 1-211) for lapatinib and 11.3 weeks (min-max: 0-208) for trastuzumab in the lapatinib + trastuzumab group,
- 8.1 weeks (min-max: 1-138) in the lapatinib only group.

In the analysis of 5 May 2011, all patients had stopped the study treatment and 3 patients (2%) in the lapatinib + trastuzumab group and 2 patients (3%) in the crossover group had been treated for more than 48 weeks.

Premature treatment discontinuation
The most common reason for stopping treatment, in either treatment group, was progressive disease: 80% of patients (119/149) in the lapatinib + trastuzumab group, 75% of patients (52/69) in the lapatinib only group and 82% of crossover patients (63/77).

[14] European Medicines Agency. European Public Assessment Report. TYVERB. June 2013

Treatment was stopped due to an adverse event in 11% of patients (16/149) in the lapatinib + trastuzumab group, 6% of patients (9/146) in the lapatinib only group and 6% of crossover patients (5/77).

Adverse events (AEs)

In the safety population, 140/149 patients (94%) in the lapatinib + trastuzumab group and 132/146 patients (90%) in the lapatinib only group had an adverse event (AE). An AE considered to be treatment-related was reported by 76% of patients (113/149) in the lapatinib + trastuzumab group and 72% (105/146) in the lapatinib only group (Table 6).[15]

Table 6. Summary of adverse events

Patients (N, %) with:	Lapatinib + trastuzumab group N=149	Lapatinib only group N=146
Adverse event (AE)	140 (94)	132 (90)
- Study treatment-related AE	113 (76)	105 (72)
- AE leading to permanent discontinuation of study treatment	17 (11)	9 (6)
Serious adverse event (SAE)	40 (27)	24 (16)
- Study treatment-related SAE	12 (8)	5 (3)
Fatal AE	3 (2)	2 (1)
Fatal study treatment-related AE	1 (<1)	0

The main adverse events that occurred, with an incidence ≥ 10%, in the lapatinib + trastuzumab group versus the lapatinib only group were:

- Diarrhoea: 62% versus 48%;
- Nausea: 28% in each group;
- Rash: 23% versus 29%;
- Fatigue: 22% versus 20%.

With the exception of diarrhoea, which was more common in the lapatinib + trastuzumab group, the incidence of adverse events was comparable between the two groups.

Serious adverse events (SAEs)

Twelve patients (8%) in the lapatinib + trastuzumab group and 5 patients (3%) in the lapatinib only group had a treatment-related serious adverse event (SAE). The most commonly reported treatment-related SAE was decreased LVEF, in 7 patients (5%) in the lapatinib + trastuzumab group versus 1 patient (<1%) in the lapatinib only group.

Deaths

In the analysis of 5 May 2011, 243 deaths had been reported in the safety population, comprising:

- 123 deaths (83%) in the lapatinib + trastuzumab group
- 120 deaths (82%) in the lapatinib group.

The most common cause of death was **progressive disease**, reported in 117 patients (79%) treated with lapatinib + trastuzumab and 118 patients (81%) treated with lapatinib.

A total of 5 patients died following a SAE, comprising 3 in the lapatinib + trastuzumab group and 2 in the lapatinib only group.

The causes of death were:

- In the lapatinib + trastuzumab group: a pulmonary embolism and heart failure in the same patient (considered to be treatment-related), one case of respiratory failure and one of sepsis.

[15] The severity of adverse events was graded using NCI-CTCAE version 3 (National Cancer Institute-Common Terminology Criteria for Adverse Events).

- In the lapatinib only group: liver and kidney failure in one patient and abdominal perforation and pneumonia in another patient.

Adverse events of special interest:

- **Cardiac events with decreased LVEF:** More common in the lapatinib + trastuzumab group (7%) than the lapatinib only group (2%). The majority were grade 1 or 2.
  In the lapatinib + trastuzumab group, one patient died following a pulmonary embolism that may have been treatment-related.
- **Diarrhoea:** More common in the lapatinib + trastuzumab group (62%) than the lapatinib only group (48%). The majority of these events were grade 1 or 2.
- **Rash:** Less common in the lapatinib + trastuzumab group (23%) than the lapatinib only group (29%). Almost all of these events were grade 1 or 2.
- **Hepatobiliary events:** More common in the lapatinib + trastuzumab group (11%) than the lapatinib only group (9%).
- **Abnormal hepatobiliary values:** Similar in the lapatinib + trastuzumab group (25%) and the lapatinib only group (23%).

The safety results from the 2 supporting studies conducted in the neoadjuvant setting (EGF106903/NeoALTTO[19] and LPT109096) were similar to the safety profile observed with the lapatinib + trastuzumab combination in study EGF104900 and were consistent with the known AEs for these 2 substances.

8.2.1 SPC data

The SPC states: “The safety of lapatinib has been evaluated as monotherapy or in combination with other chemotherapies for various cancers in more than 20,000 patients, including 198 patients who received lapatinib in combination with capecitabine, 149 patients who received lapatinib in combination with trastuzumab and 654 patients who received lapatinib in combination with letrozole.
The most common adverse reactions (> 25%) during therapy with lapatinib were gastrointestinal events (such as diarrhoea, nausea, and vomiting) and rash. Palmar-plantar erythrodysesthesia (PPE) was also common (> 25%) when lapatinib was administered in combination with capecitabine.
No additional adverse reactions were reported to be associated with lapatinib in combination with trastuzumab.
There was an increased incidence of cardiac toxicity in the phase III study EGF104900, but these events were comparable in nature and severity to those reported from the lapatinib clinical programme.”

8.2.2 RMP (risk management plan) data

The European risk management plan for TYVERB, which includes a risk minimisation plan, provides for the monitoring of the following “important” risks:

- Identified risks: hepatobiliary events, cardiac events with decreased LVEF, interstitial pneumonia, diarrhoea, rash and interactions with other medicines;

- Potential risks: prolonged QT interval and interactions with food.

08.3 Summary & discussion

The efficacy and safety of lapatinib in combination with trastuzumab have been compared with lapatinib alone in a phase III, randomised, open-label study in 296 patients with metastatic breast cancer overexpressing HER2, who were previously exposed to anthracyclines and taxanes and who progressed on their most recent treatment including trastuzumab (148 patients in each group).

The median age of the patients was 51 years (min. 26 years – max. 81 years). More than 95% of patients were in good general health (ECOG score between 0 and 1) and 73% had visceral disease.
On inclusion, 51% of patients in each group had a negative hormone status (HR-) and 99% of patients had received an anthracycline and trastuzumab in the metastatic setting.
The population included was heterogeneous in terms of the number of previous cancer treatments, which ranged from 1 to 18 treatments (with a median of 6).

The comparator in the study, lapatinib as monotherapy, is not indicated in HER2+ metastatic breast cancer.[16] However, when the study was set up in 2005, no relevant comparators had Marketing Authorisation in this indication. This study aimed to answer the questions of the time as regards determining the most appropriate therapeutic strategy for patients with HER2+ metastatic breast cancer which has progressed despite anti-HER2 therapy (trastuzumab).

With the lapatinib + trastuzumab combination, compared with lapatinib alone, the median progression-free survival (primary efficacy endpoint) evaluated by the investigator increased by +3.9 weeks (HR = 0.73; 95% CI: [0.57; 0.93], p<0.008).

For the secondary endpoints:
- Median overall survival was 4.5 months longer in the lapatinib + trastuzumab group (HR=0.74; 95% CI: [0.57; 0.97]; p=0.026).
Thus, the benefit of the lapatinib + trastuzumab combination was greater in terms of overall survival (4.5 months) than in terms of progression-free survival (barely 1 month).
The two groups were observed to be heterogeneous in terms of post-progression treatment(s):
- More patients were treated with vinorelbine in the lapatinib + trastuzumab group (25%) than the lapatinib only group (11%);
- More patients were treated with trastuzumab in the lapatinib only group (48%) than the lapatinib + trastuzumab group (62%).

- The clinical benefit rate (the sum of complete responses, partial responses and stable disease ≥ 24 weeks) was significantly higher in the combined lapatinib and trastuzumab group (24.7%) than in the lapatinib only group (12.4%).
- No difference was demonstrated in the overall response rate (the sum of complete responses and partial responses) as evaluated by the investigator, with 10.3% in the lapatinib + trastuzumab group versus 6.9% in the lapatinib only group.
- No improvement in quality of life was demonstrated (FACT-B score, FACT-G score).

A subgroup analysis performed a posteriori at the EMA's request did not show any benefit in terms of progression-free survival, whatever the patient subgroup (HR positive or HR negative). On the other hand, the lapatinib + trastuzumab combination was shown to be better in terms of overall survival only in the HR negative subgroup of patients (+8.3 months). This result led the EMA to restrict the indication to HR negative patients. HR negative patients underwent more chemotherapy after progression than HR positive patients.

[16] Allan Lipton *et al*. HER2 Extracellular Domain Levels Are Associated with Progression-Free Survival in Patients with HER2+ Metastatic Breast Cancer Receiving Lapatinib Monotherapy Cancer 2011;117:5013-20.

94% of patients treated with lapatinib + trastuzumab (140/149) and 90% of patients treated with lapatinib alone (132/146) had an adverse event (AE). An AE considered to be treatment-related was reported by 76% of patients in the lapatinib + trastuzumab group (113/149) and 72% of patients in the lapatinib only group (105/146).
With the exception of diarrhoea, which occurred more frequently in the lapatinib + trastuzumab group (62% versus 48% in the lapatinib group), the incidence of common adverse events (incidence ≥ 10%) was comparable between the two groups, with:

- Nausea: 28% in each group;
- Rash: 23% with the combination versus 29% with lapatinib alone;
- Fatigue: 22% with the combination versus 20% with lapatinib alone.

Serious adverse events occurred more frequently in the lapatinib + trastuzumab group (27%) than the lapatinib only group (16%).
The most commonly reported serious adverse event was decreased LVEF, in 7 patients (5%) in the lapatinib + trastuzumab group versus 1 patient (<1%) in the lapatinib only group.
No particular safety signals were detected in this study.

08.4 Planned studies

The studies planned are shown in the table below.

Study	Type of study	Population	Primary objectives	Dates
PHoeBE (200641)	Prospective, observational, real-world, multicentre	Non-interventional	Document how HER2+ metastatic breast cancer is treated Describe the populations eligible for or receiving TYVERB Document the real-world use of TYVERB and treatment adherence, and understand the reasons for stopping treatment Understand the sequencing of treatment for metastasis	Mid 2014
EGF114299 ALTERNATIVE	Phase III, randomised, international, multicentre, open-label	Menopausal women with HR+ metastatic breast cancer overexpressing HER2, previously treated with trastuzumab and hormone therapy in the adjuvant and/or neoadjuvant setting	Demonstrate the superiority, in terms of overall survival, of the trastuzumab + lapatinib + aromatase inhibitor combination versus trastuzumab + aromatase inhibitor	Data on the first 70 patients: June 2014 Final data: May 2018
LAP114443	Phase II, open-label	Patients with metastatic breast cancer overexpressing HER2, aged 60 years and over	Safety and tolerability of the lapatinib + trastuzumab combination in terms of grade ≥3 toxicity and congestive heart failure	December 2013
EGF117165	Post-marketing study requested by the EMA (a condition of the Marketing Authorisation)	Patients with metastatic breast cancer overexpressing HER2, treated with trastuzumab in combination with either lapatinib or chemotherapy	Evaluate biomarkers for drug resistance	August 2018
EGF106708 ALTTO	Phase III, randomised, international, multicentre, open-label	Patients with breast cancer overexpressing HER2 in the adjuvant setting	Compare disease-free survival (DFS) in: treatment with trastuzumab for one year; versus lapatinib for one year; versus weekly trastuzumab followed by lapatinib; versus trastuzumab in combination with lapatinib for one year	Final analysis of the primary endpoint: Q2 2014

09 THERAPEUTIC USE

Taking into account recent developments in the management of HER2+ metastatic breast cancer, with the arrival of pertuzumab (PERJETA) as 1st-line therapy and trastuzumab emtansine (KADCYLA) as 2nd-line therapy, and the data available for the lapatinib + trastuzumab combination in heavily pre-treated patients in whom trastuzumab and chemotherapy have failed, lapatinib (TYVERB) in combination with trastuzumab is a 3rd-line and subsequent therapeutic option for breast cancer with HER2 (ErbB2) overexpression in patients with hormone receptor-negative metastatic disease.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

◗ Median survival in metastatic breast cancer ranges from 18 to 36 months. In 30% of cases, metastatic breast cancer overexpresses ErbB2 (HER2). This overexpression is a poor prognostic factor in breast cancer. Breast cancer is a life-threatening disease.
◗ This proprietary medicinal product is intended as curative therapy.
◗ The efficacy/adverse effects ratio is modest.
◗ At this stage of the disease, there are few drug alternatives.
◗ This is a 3rd-line and subsequent treatment for breast cancer with HER2 (ErBB2) overexpression in hormone receptor-negative patients with metastatic disease.

◗ Public health benefit:
In metropolitan France, the incidence of breast cancer is estimated to be about 48,800 new cases per year.**Erreur ! Signet non défini.** It is the most common cancer, accounting for 31.5% of new cancer cases in women.**Erreur ! Signet non défini.**
It is also the leading cause of cancer deaths in women, with almost 11,900 estimated deaths in 2012,[1] accounting for 18.8% of female deaths from cancer.
The incidence of this cancer rose sharply between 1980 and 2000 but has been in decline since 2005, with 56.3 cases per 100,000 person-years in 1980, 97.8 in 2005 and 88.0 in 2012.**Erreur ! Signet non défini.** The mortality rate remained relatively stable until about 1995, then declined significantly until 2012, with a mean reduction in mortality of -0.6% per year between 1980 and 2012 and -1.5% per year between 2005 and 2012.**Erreur ! Signet non défini.** In France, the public health burden of breast cancer is therefore substantial (939,297 DALYs, Euro zone A, 2004 estimate). Despite the smaller number of patients concerned, the burden from the subpopulation of patients with HER2+/HR- metastatic breast cancer likely to take TYVERB in combination with trastuzumab (having previously had trastuzumab in combination with chemotherapy) remains significant and therefore moderate due to the higher associated morbidity and mortality rate.

Improving the management of cancer patients and their quality of life is a public health need which is an established priority (objective 49 of the Law of 9 August 2004 on public health policy, Cancer Plan 2014-2019, Plan to improve the quality of life of patients with chronic diseases 2007-2011).

In view of the efficacy results available and the lack of any difference in improvement in quality of life (FACT-B score), the proprietary medicinal product TYVERB, in combination with trastuzumab in this indication, is expected to have a low impact on morbidity and mortality and no impact on quality of life.

It is unclear whether these results are applicable to clinical practice. In fact, the profile of patients treated in the real world may differ from the profile of patients included in the phase III trial, insofar as the median age of patients included was 51 years and 50% of them had an ECOG score of 0. In addition, patients treated with the combination of TYVERB plus trastuzumab in actual practice will have received pertuzumab (PERJETA) in combination with trastuzumab and docetaxel as 1st-line treatment, then trastuzumab emtansine (KADCYLA) as 2nd-line treatment, which was not the case for patients included in the phase III trial.

TYVERB is also not expected to have any impact on the organisation of care. Therefore, this third-line and subsequent treatment combination only partially meets the identified public health need.
Consequently, it is not expected that TYVERB will benefit public health in this indication.

Taking account of these points, the Committee considers that the actual benefit of TYVERB is moderate in the "treatment of adult patients with breast cancer, whose tumours overexpress HER2 (ErbB2), in combination with trastuzumab for patients with hormone receptor-negative metastatic disease that has progressed on prior trastuzumab therapy(ies) in combination with chemotherapy."

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the "treatment of adult patients with breast cancer, whose tumours overexpress HER2 (ErbB2), in combination with trastuzumab for patients with hormone receptor-negative metastatic disease that has progressed on prior trastuzumab therapy(ies) in combination with chemotherapy" and at the dosages in the Marketing Authorisation.

- **Proposed reimbursement rate: 100%**

010.2 Improvement in actual benefit (IAB)

Taking into account the lack of data showing a benefit versus a clinically relevant comparator, the methodological limitations of the study based primarily on a post-hoc analysis, and the lack of benefit in terms of progression-free survival in the subgroup of HER2+ and HR- patients, the Committee considers that TYVERB, in combination with trastuzumab, does not provide any improvement in actual benefit (level V, non-existent) in comparison with the usual management of breast cancer with HER2 (ErbB2) overexpression in patients with hormone receptor-negative metastatic disease.

010.3 Target population

The target population for TYVERB is patients with HER2+ and HR- metastatic breast cancer who, in a given year, are receiving 3rd-line or subsequent treatment for metastasis (3rd and subsequent line prevalent population).

About 15% of patients newly diagnosed at an early stage are HER2 positive[17,18] and this is close to 30% for patients diagnosed at an advanced stage.[19] The incidence of HER2 positive breast cancer at any stage is thus estimated to be between 7700 and 10,000 cases per year.
An epidemiological study performed using data from the American SEER cohort (Surveillance, Epidemiology, and End Results Program) showed that about 21% of metastatic breast cancers are HR-.[20] However, half of all metastatic breast cancers overexpressing HER2 are HR-.[21]
Knowing that HER2+ patients receiving first-line treatment for metastasis make up about 2,000 cases per year, the total population of **new** patients with HER2+/HR- cancer receiving first-line treatment for metastasis was about 1,000 patients in 2013.

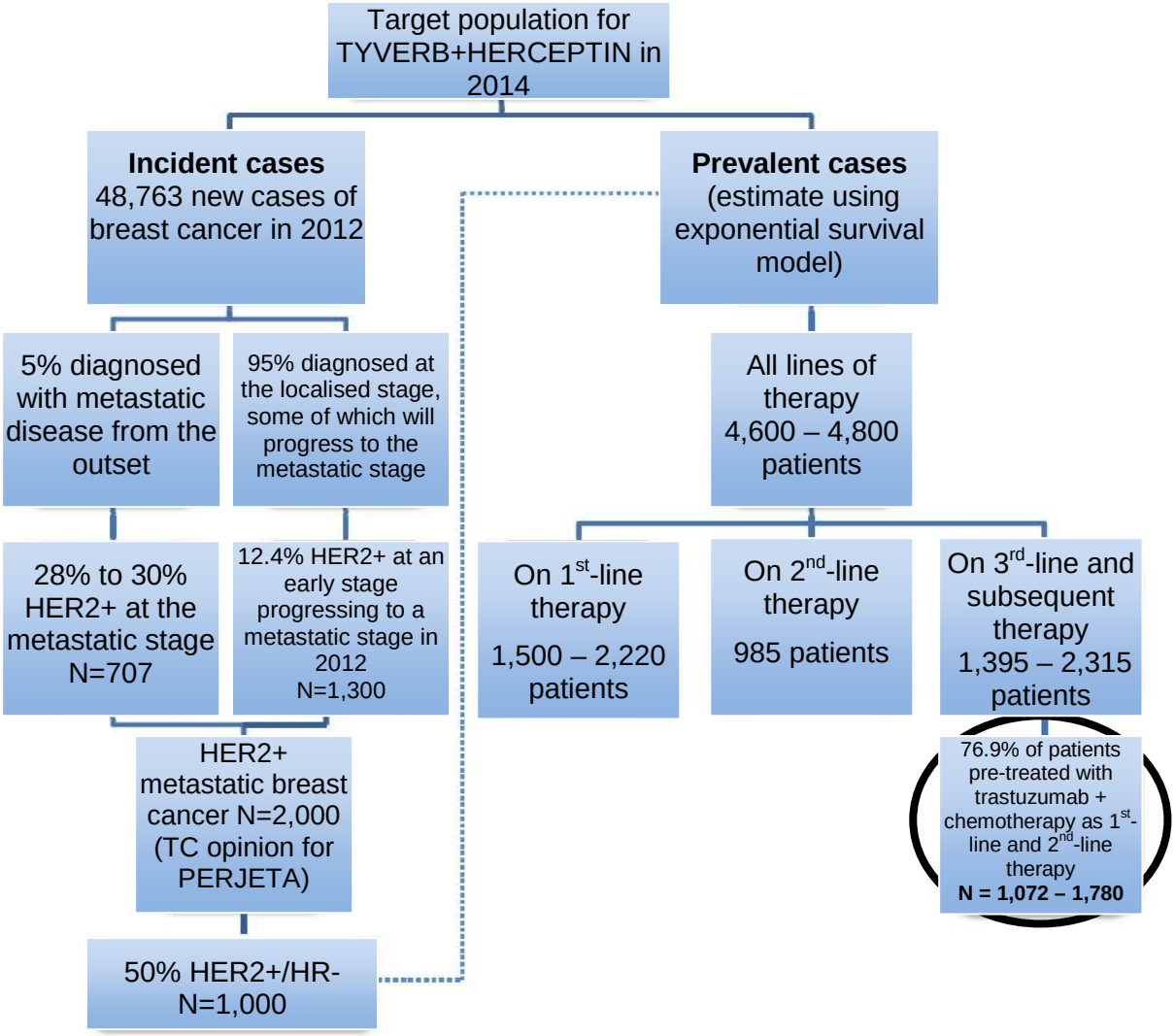
To estimate the prevalence of HER2+/HR- patients at the metastatic stage, the company used a simple model combining the annual incidence of estimated new cases (1,000 patients) with the overall survival on 1st-line treatment for metastasis from recent studies of pertuzumab.[22,23]

Using an exponential survival model adjusted for median survival of between 38 and 40 months, the number of **prevalent** patients in 2013, on any line of treatment, is somewhere between 4,600 and 4,800 patients (area under the curve for overall survival), based on an annual flow of 1,000 new patients treated at the metastatic stage, with the following estimated prevalences:

- 1,500 to 2,220 patients on 1st-line therapy;
- 985 patients on 2nd-line therapy;
- 1,395 to 2,315 patients on 3rd-line and subsequent therapy.

Based on the estimated prevalence and the proportion of this population that received trastuzumab combined with chemotherapy as 1st or 2nd-line treatment for metastasis (76.9%), the estimated target population for TYVERB combined with trastuzumab as 3rd-line and subsequent treatment for metastasis is **between 1,072 and 1,780 patients**. This new indication should not increase the overall target population for TYVERB.

[17] Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology / College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. Arch Pathol Lab Med 2007; 131:18-43.
[18] INCa. Les tests de génétique moléculaire pour l'accès aux thérapies ciblées [Molecular genetic testing for access to targeted therapies]. Collection of reports and summaries, collective work. Boulogne-Billancourt. December 2011.
[19] Press MF, Slamon DJ, Flom KJ, et al. Evaluation of HER2/neu gene amplification and overexpression: comparison of frequently used assay methods in a molecularly characterized cohort of breast cancer specimens. J. Clin. Oncol 2002; 20:3095-3105.
[20] Dunnwald LK, Rossing MA, Li CI. Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients. Breast2007;9:R6.
[21] Recommandations pour la pratique clinique de Saint Paul de Vence [Saint Paul de Vence clinical practice guidelines]. 2007 « cancers du sein » [Breast cancers]
[22] Swain SM, Kim SB, Cortés J, Ro J, Semiglazov V, *et al*. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 2013;14:461-71.
[23] Von Minckwitz G, du Bois A, Schmidt M, Maass N, Cufer T, de Jongh FE et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a German breast group 26/breast international group 03-05 study. J Clin Oncol 2009;27:1999-2006.



011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging

The available pack sizes of 70, 84 or 140 tablets are not appropriate for the dosage in the indication concerned by this opinion.

In fact, as the dosage is 1,000 mg once daily continuously, i.e. four 250 mg tablets daily, the most appropriate packaging for one month of treatment is 120 tablets per bottle.

However, the packaging is appropriate for the dosages of TYVERB in other indications (1,250 mg/day in combination with capecitabine and 1,500 mg/day in combination with an aromatase inhibitor).