HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
19 March 2014

KADCYLA 100 mg, powder for concentrate for solution for infusion
One 15-ml vial (CIP: 34009 585,760 4 1)

KADCYLA 160 mg, powder for concentrate for solution for infusion
One 20-ml vial (CIP: 34009 585 761 0 2)

Applicant: ROCHE

INN	trastuzumab emtansine
ATC Code (2013)	L01XC14 (monoclonal antibodies)
Reason for the request	**Inclusion**
List concerned	**Hospital use** (French Public Health Code L.5123-2)
Indications concerned	**"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. Patients should have either:** **- Received prior therapy for locally advanced or metastatic disease, or** **- Developed disease recurrence during or within six months of completing adjuvant therapy."**

AB	**Substantial**
IAB	**Given the improvement observed with trastuzumab emtansine (KADCYLA) in monotherapy compared to the combination of lapatinib (TYVERB) + capecitabine (XELODA) in terms of progression-free survival and overall survival and an acceptable safety profile, the Transparency Committee believes that KADCYLA, as a monotherapy, provides a substantial improvement in actual benefit (IAB II) in the treatment of adult patients with HER2 positive metastatic or locally advanced unresectable breast cancer, who were previously treated with trastuzumab and a taxane, separately or in combination.**
Therapeutic Use	**In its current indication, KADCYLA is a new second-line and beyond treatment in metastatic HER2+ breast cancer.**
Recommendations	**-**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial date (centralised) 15 November 2013 Risk Management Plan
Prescribing and dispensing conditions / special status	List I Medicine for hospital prescription Prescription medicine restricted to specialists in oncology or doctors with training in oncology. Medicine requiring special monitoring during treatment.

ATC Classification	2013	
	L	Antineoplastic and immunomodulating agents
	L01	Antineoplastic agents
	L01X	Other antineoplastic agents
	L01XC	Monoclonal antibodies
	L01XC14	Trastuzumab emtansine

02 BACKGROUND

The manufacturer is requesting the inclusion of KADCYLA 100 and 160 mg, powder for concentrate for solution for infusion whose active ingredient is trastuzumab emtansine, on the list of medicinal products approved for hospital use.

KADCYLA, antibody-drug conjugate targeting the HER2 receptor, is the combination by biotechnical engineering of trastuzumab (a humanized monoclonal antibody targeting the HER2 receptor) and DM1 (a cytotoxic chemotherapy agent, derived from maytansine, a microtubule inhibitor). On average, 3.5 molecules of DM1 are conjugated to each molecule of trastuzumab. The conjugation of DM1 to trastuzumab by a stable thioether linker (MCC) gives the cytotoxic agent selectivity for tumour cells overexpressing HER2, thus increasing the intracellular release of DM1 directly into malignant cells. The linker is designed to limit systemic release and increase targeted intracellular release of DM1 as is demonstrated by the detection of very small concentrations of free DM1 in the plasma. Emtansine refers to the MCC-DM1 complex.

03 THERAPEUTIC INDICATIONS

"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. Patients should have either:
- Received prior therapy for locally advanced or metastatic disease, or
- Developed disease recurrence during or within six months of completing adjuvant therapy."

04 POSOLOGY

"The recommended dose of KADCYLA is 3.6 mg/kg bodyweight administered as an intravenous infusion every 3 weeks (21-day cycle). Patients should be treated until disease progression or unacceptable toxicity.

The initial dose should be administered as a 90 minute intravenous infusion. Patients should be observed during the infusion and for at least 90 minutes following the initial infusion for fever, chills, or other infusion-related reactions. The infusion site should be closely monitored for possible subcutaneous infiltration during administration.

If the prior infusion was well tolerated, subsequent doses of KADCYLA may be administered as 30 minute infusions. Patients should be observed during the infusion and for at least 30 minutes after infusion."

05 THERAPEUTIC NEED

In France, breast cancer is the most common cancer in women, with around 48,800 new cases estimated in 2012[1]. It represents 31.5% of all new cancer cases in women and nearly 14% of the overall cancer incidence in both sexes combined. It is a serious disease which can be life-threatening, especially at the metastatic stage. With nearly 11,900 deaths estimated in 2012, breast cancer is the leading cause of cancer death in women[1]

In breast cancer, the overexpression of the HER2 receptor and/or amplification of the HER2 gene is a factor for a poorer prognosis compared to HER2 negative breast cancer.[2] Around 15% of newly diagnosed patients at the early stage[3,4] and around 30% of patients diagnosed at an advanced stage are HER2 positive.[5] The incidence of HER2 positive breast cancer at all stages combined is estimated to be between 7,700 and 10,000 cases per year, regardless of the stage.

In metastatic HER2+ breast cancer, it is vital to maintain an anti-HER2 action regardless of the line of treatment[6]. The marketing of targeted therapies for management of metastatic HER2+ breast cancer has allowed delaying disease progression, regardless of its stage.

[1]Les cancers en France en 2013 [Cancers in France in 2013]. Collection état des lieux et des connaissances [Inventory and assessment of current knowledge] collective work published by the INCa [French 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]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(1):18-43.
[4]INCa. Les tests de génétique moléculaire pour l'accès aux thérapies ciblées [Molecular genetic testing for access to targeted therapies]. Collection Rapports & synthèses, [Collection of Reports and Summaries], collective work Boulogne-Billancourt. December 2011.
[5]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(14):3095-3105.
[6]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 the GBG-26/BIG 03-05 study]. Lettre Cancérologue. June 2009. Vol. XVIII - no. 6 : page 318.

In first-line treatment for metastatic breast cancer with overexpression of HER2, the available treatments are:
- Since 2000, trastuzumab (HERCEPTIN) in combination with a taxane (paclitaxel or docetaxel), independently of hormone status. When hormone receptors are expressed, trastuzumab may also be combined with hormone therapy.
- Since 2013, pertuzumab (PERJETA) combined with trastuzumab and docetaxel, has been a new approach for treating metastatic HER2+ breast cancer.[7] The American NCCN guidelines[8] rate the addition of pertuzumab to bitherapy with trastuzumab and a taxane as an option to be preferred to bitherapy7.

After disease progression, the subsequent-line treatment options are limited.

From the second line, the current standard treatment for HER2+ metastatic breast cancer in patients progressing after prior therapy including an anthracycline, a taxane and trastuzumab in a metastatic setting, combines a targeted anti-HER2 therapy, lapatinib (TYVERB) with chemotherapy, capecitabine (XELODA).[9] The lapatinib/capecitabine combination showed, relative to capecitabine alone, an improvement in terms of medium time until progression with an acceptable safety profile, but has not demonstrated difference in terms of overall survival.[9]
Since the therapeutic alternatives are very limited at this stage of the disease, a temporary treatment protocol[10] (TTP) has existed since 2008, for the trastuzumab (HERCEPTIN)/capecitabine (XELODA) combination after progression on trastuzumab possibly combined with taxanes[11] based on the results of a comparative clinical study of trastuzumab/capecitabine versus capecitabine in monotherapy (study GBG-26)[12] with demonstration of an increase of the time until progression (primary endpoint), without statistically significant increase of overall survival (secondary endpoint) with the combination of trastuzumab/capecitabine versus capecitabine alone.

In July 2013, the lapatinib (TYVERB)/trastuzumab (HERCEPTIN) combination obtained a marketing authorisation in patients with metastatic HER2+ breast cancer with negative hormone receptors, who progressed on trastuzumab and chemotherapy.
This lapatinib (TYVERB)/trastuzumab (HERCEPTIN) combination has not been examined by the Transparency Committee.

The main objective sought in the second-line treatment and beyond of HER2+ breast cancer is a significant clinical improvement of efficacy in terms of progression-free survival and overall survival while maintaining patient quality of life.

[7]HAS. Transparency Committee Opinion PERJETA 420 mg, concentrate for solution for infusion of 24 July 2013.
[8]National Comprehensive Cancer Network Breast cancer (NCCN 2013)
http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
[9]HAS. Transparency Committee Opinion TYVERB of 16 July 2008.
[10]A transition phase was planned in terms of off-label management, gradually phasing out temporary treatment protocols (TTP) involving medicines listed on the "off GHS [diagnosis related group]" list and valid until 31 December 2015 and implementing a new system for temporary use guidelines.
[11]INCa. Référentiels de Bon Usage hors GHS [Off-GHS Good Usage Guidelines] Protocoles thérapeutiques hors GHS [Off GHS treatment protocols] Cancers du sein. [Breast cancer] March 2012
[12]Von Minckwitz G, du Bois A, Schmidt M, 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.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

The clinically relevant comparators for KADCYLA in the treatment of HER2+ metastatic breast cancer progressing after treatment with trastuzumab and taxane are:

- the (TYVERB)/capecitabine (XELODA) combination which has had a marketing authorisation since June 2008 in patients with advanced or metastatic disease progressing after a prior treatment that included an anthracycline, a taxane and a treatment including trastuzumab in a metastatic setting;
- The lapatinib (TYVERB)/trastuzumab (HERCEPTIN) combination which has had a marketing authorisation since July 2013 in patients with metastatic HER2+ breast cancer with negative hormone receptors, who progressed on trastuzumab and chemotherapy.

The trastuzumab (HERCEPTIN)/capecitabine (XELODA) combination, defined as a temporarily acceptable situation, is the subject of a temporary treatment protocol.[11]

NAME (INN) *Company*	Same TC* Yes / No	Indication	Date of opinion	AB	IAB (Wording)	Reimbursed Yes/No
TYVERB (lapatinib) *(GSK)*	No L01XE07 Protein kinase inhibitors	TYVERB is indicated in the treatment of breast cancer with overexpression of the HER2 (ErB2) receptors: - in combination with capecitabine in patients with advanced or metastatic disease progressing after a prior treatment that included an anthracycline, a taxane and a treatment including trastuzumab in a metastatic setting.	16 July 2008 (Inclusion)	Substantial	Given, on the one hand, the improvement observed by the combination of TYVERB + XELODA relative to XELODA in monotherapy in terms of median time to progression and an acceptable safety profile, but, on the other hand, the absence of demonstrated effect on overall survival, the Transparency Committee believes that TYVERB, in combination with XELODA, provides a moderate improved actual benefit (**IAB III**) in the treatment of advanced or metastatic cancer with overexpression of HER2 receptors, in patients progressing after prior treatment that included an anthracycline, a taxane and trastuzumab.	Yes
		- in combination with an aromatase inhibitor in menopausal patients with metastatic disease with hormone positive receptors and for whom chemotherapy is not currently envisaged. Patients of the registration study have not previously been treated with trastuzumab or by an aromatase inhibitor.	03 November 2010 (extension of indication)	Substantial	Given the absence of the comparison with the association of trastuzumab + aromatase inhibitor and in the absence of efficacy data in patients previously treated with trastuzumab as an adjuvant, TYVERB combined with an aromatase inhibitor does not provided improved actual benefit (**IAB V**) in the therapeutic strategy for breast cancer with overexpression of HER2 receptors in menopausal patients with metastatic disease with hormone positive receptors, for whom chemotherapy is not currently envisaged and not previously treated with trastuzumab.	Yes

		- in combination with trastuzumab in patients with metastatic disease with negative hormone receptors, progressing after prior treatment(s) with trastuzumab in combination with chemotherapy. (extension of indication of 25 July 2013)	Not available	Not available	Not available	No
XELODA (capecitabine). *ROCHE*	No L01BC06 Pyrimidine analogues	XELODA in combination with docetaxel is indicated in the treatment of locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. The prior chemotherapy must have included an anthracycline. XELODA is also indicated in monotherapy in the treatment of locally advanced or metastatic breast cancer after failure of taxanes and chemotherapy containing an anthracycline or when a chemotherapy with anthracycline is not indicated.	07 November 2011 (renewal of inclusion)	Substantial	Not applicable	Yes

**TC = therapeutic category*

06.2 Other health technologies

Not applicable

◗ Conclusion

The clinically relevant comparators for KADCYLA in the treatment of HER2+ metastatic breast cancer progressing after treatment with trastuzumab and taxane are:

- the lapatinib (TYVERB)/capecitabine (XELODA) combination indicated in patients with advanced or metastatic disease progressing after a prior treatment that included an anthracycline, a taxane and a treatment including trastuzumab in a metastatic setting;
- the lapatinib (TYVERB)/trastuzumab (HERCEPTIN) combination indicated in patients with metastatic disease with negative hormone receptors, progressing after prior treatment(s) with trastuzumab in combination with chemotherapy.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	Marketing Authorisation	
	Yes (date)/No/Assessment in progress	Indications and special condition(s)
United States	22/02/2013	*"For use as a single agent for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either received prior therapy for metastatic disease or developed disease recurrence during or within six months of completing adjuvant therapy"*
Switzerland	02/05/2013	*"As monotherapy for the treatment of patients with a HER2-positive, non-operable, locally advanced or metastatic breast cancer, previously pretreated with trastuzumab and a taxane"*
Australia	26/08/2013	*"For use as a single agent for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either received prior therapy for metastatic disease or developed disease recurrence during or within six months of completing adjuvant therapy"*
Canada	11/09/2013	*"For the treatment of patients with HER2-positive, metastatic breast cancer who received both prior treatment with HERCEPTIN (trastuzumab) and a taxane, separately or in combination. Patients should have either received prior therapy for metastatic disease, or developed disease recurrence during or within 6 months of completing adjuvant therapy"*
New Zealand	26/09/2013	*"For use as a single agent for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either received prior therapy for metastatic disease or developed disease recurrence during or within six months of completing adjuvant therapy"*

Country	Reimbursement		
	Date reimbursement started	Yes/No/Assessment in progress	Scope (indications) and condition(s)
United States	22/02/2013	Yes	*Same as the marketing authorisation*
Switzerland	03/05/2013	Yes	*Same as the marketing authorisation*
Germany	25/11/2013	Yes	*Same as the marketing authorisation*
United Kingdom	10/12/2013	Yes	*Same as the marketing authorisation*
Spain	In progress	In progress	
Italy	In progress	In progress	
Finland	01/12/2013	Yes	*Same as the marketing authorisation*
Norway	01/12/2013	Yes	*Same as the marketing authorisation*
Australia	In progress	In progress	
Canada	In progress	In progress	
New Zealand	In progress	In progress	

08 ANALYSIS OF AVAILABLE DATA

The submitted dossier comprises:
- a phase III randomised, open-label, parallel group study (EMILIA (TDM4370g/BO21977)) comparing the efficacy of trastuzumab emtansine (or "T-DM1") in terms of progression-free survival (PFS) and overall survival (OS) versus the lapatinib/capecitabine combination.[13]

- the results of the first interim analysis of overall survival of the THERESA study (TDM4997g/BO25734), a phase III, randomised, open-label study for assessing efficacy in terms of progression-free survival and overall survival (co-primary endpoints) and safety of T-DM1 versus a treatment chosen by the physician in accordance with the marketing authorisation and local practice, in patients with very advanced HER2+ metastatic breast cancer who previously received at least two lines of targeted anti-HER2 therapy in a metastatic setting, comprising trastuzumab, lapatinib and a taxane. This study is not described in this document inasmuch as the patients had very advanced HER2+ metastatic breast cancer and the comparator treatment administered in the control group was not defined beforehand.

- a phase II, (TDM4450g/BO21976[14]) randomised and controlled study in patients with metastatic HER2+ breast cancer who had never been treated for their metastatic disease (as a first line treatment), for assessing the efficacy and safety of T-DM1 (n=67) compared to the standard trastuzumab + docetaxel combination (n=70). Given the statistically-significant improvement in median progression-free survival with T-DM1 compared to the trastuzumab + docetaxel combination as a first line treatment for HER2+ metastatic breast cancer (HR PFS = 0.594; 95% CI: [0.36; 0.97] p=0.0353), the development of T-DM1 is ongoing in this indication. This study, which does not correspond to the current indication for KADCYLA, is not described in this opinion.

08.1 Efficacy

	EMILIA study (TDM4370g/BO21977)
Principal study objective	To compare the efficacy of T-DM1 to the approved combination of lapatinib and capecitabine in terms of progression-free survival (PFS) and overall survival (OS) (co-primary endpoints), in patients with locally-advanced, unresectable or metastatic HER2+ breast cancer, who were previously treated with trastuzumab and taxane.
Method	Randomised, open-label (justified by the safety profile characteristic of each of the alternatives assessed allowing them to be identified), with blinded assessment of the tumour response in the patient treatment group by an independent review committee (IRC) parallel-group and active controlled study.
Date and place of the study	Study conducted from 23 February 2009 to 13 October 2011 in 213 centres spread over 26 countries.[15]
Study population	
Main inclusion criteria	- HER2 positive status (3+ by IHC and/or FISH positive) tested prospectively by a centralised laboratory. - Histologically or cytologically confirmed invasive breast cancer, metastatic or locally advanced and unresectable. - Patient who received taxane (alone or in combination) and trastuzumab alone or in combination with another agent as an adjuvant and/or to treat metastatic or locally-advanced disease.

[13]Verma S, Miles D, Gianni L, et al. Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer. N Engl J Med 2012 ;367:1783-91.
[14]Hurvitz SA, Dirix L, Kocsis J, et al. Phase II randomized study of trastuzumab emtansine versus trastuzumab plus docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. J Clin Oncol. 2013 20;31:1157-63.
[15]In France, 11 centres participated and 64 patients were included in this study (28 in the T-DM1 group and 36 in the control group).

	- Documented progression occurring during or after treatment for the metastatic or locally-advanced disease or in the 6 months after the end of an adjuvant treatment. - Disease measurable or unmeasurable according to the amended RECIST criteria. Patients with only brain metastases are not eligible. - Men or women ≥ 18 years old. - Left ventricular ejection fraction ≥ 50% (measured by echocardiogram or nuclear heart scan). - Performance score equal to 0 or 1 according to the ECOG. - Suitable blood parameters measured within 30 days of randomisation.
Main non-inclusion criteria	- Prior treatment with T-DM1 or lapatinib or capecitabine. - Grade 3 or worse peripheral neuropathy (interfering with activities of daily living) according to NCI CTCAE, version 3.0. - History of another malignant disease within the past 5 years, except for cervical carcinoma in situ properly treated, skin cancer without melanoma, stage 1 uterine cancer or another synchronous or later HER2+ breast cancer or a cancer with a curative prognosis similar to these diseases. - Anticancer or study treatments received within 21 days of randomisation and presence of any consecutive toxicity preventing eligibility. Hormone treatment may be given up to 7 days before randomisation. - Radiation therapy within 14 days of randomisation. Any consecutive toxicity should come back with a grade 1 or lower before randomisation.
Treatment groups	1:1 randomisation ratio - **Trastuzumab emtansine** (or "**T-DM1**") group: 3.6 mg/kg in intravenous (IV) infusion for 30 to 90 minutes on day 1 and then every 3 weeks (21-day cycle). No pre-medication was specified or provided. - **Control group (lapatinib/capecitabine combination)**: 1250 mg/day of lapatinib per os once daily and 1000 mg/m² capecitabine per os twice daily from day 1 to day 14 over a 21-day cycle (= treatment regimen validated by the marketing authorisation for the lapatinib and capecitabine combination in this indication). Pre-medication allowed according to the modalities defined in the current treatment recommendations. Stratification criteria at inclusion by: 1. geographical region of the site: United States versus western Europe versus other regions of the world. 2. number of previous chemotherapy treatments received for locally-advanced unresectable or metastatic HER2+ breast cancer. 0-1 versus >1; 3. metastatic disease: visceral versus non-visceral location.
Course of the study	The patients were followed up to progression of the disease determined by the investigator or up to the occurrence of toxicity that could not be treated or until the study was stopped by the sponsor. A 30-day follow-up visit ((±7 days) was planned for patients leaving the study for the causes described previously and then they were followed every three months after the study discontinuation visit until lost to follow-up, withdrawal of consent or termination of the study by the sponsor.
Primary efficacy endpoint	Co-primary endpoints: - **Progression-free survival** (PFS): assessed by an IRC. Duration between the date of randomisation and the date of occurrence of a progression or death from any cause (whichever event occurs first). Progression assessed according to the amended RECIST criteria, on the basis of imaging examinations (MRI and CT) and cytological data (reports documenting malignant pleural effusion, bone marrow aspirations, cerebrospinal fluid, etc.). - **Overall survival** (OS): duration between the date of randomisation and the date of death from any cause.
Secondary endpoints included:	- **Progression-free survival** (PFS): assessed according to the investigators following the amended RECIST criteria. - **Objective response rate** (ORR): assessed by the IRC: proportion of patients showing documented complete response (CR) or partial response (PR) according to the amended RECIST criteria. - **Clinical benefit rate** (CBR): proportion of patients with a complete response (CR), partial response (PR) or stable disease (SD) 6 months after randomisation. - **Duration of the objective response**: the time between the documented date of the response (complete or partial) and that of disease progression or death from any cause (whichever event comes first). - **Time until treatment failure**: time between the date of randomisation and treatment discontinuation regardless of the cause (including progression, toxicity and death from any cause). In the control group, treatment failure was considered in the case of conjoint discontinuation of lapatinib and capecitabine. - **Time until symptom progression**: time between the date of randomisation and the date of the first documented decrease ≥ 5 points, compared to baseline, on the FACT-B

	TOI-PFB scale in both treatment groups. A variation of 5 points on this FACT-B subscale was considered clinically relevant. - **Safety**
Calculation of the number of subjects required	The initial statistical hypotheses were calculated on the basis of 580 patients, based on the sole efficacy endpoint (progression-free survival) to demonstrate the superiority of the T-DM1 group versus the control. In accordance with the FDA and EMA recommendations, the overall survival endpoint was added as a co-primary endpoint before the end of enrolment and before any analysis. The number of subjects necessary was recalculated in order to show a statistically-significant reduction in the risk of death of 20% in the T-DM1 group relative to the control group. In order to detect an HR of 0.8 on overall survival, corresponding to a 25% improvement in the median duration of overall survival in favour of T-DM1 (or a median duration of expected overall survival of 21.5 months for the T-DM1 group versus 17.2 months for the control group, corresponding to an increase in absolute value of 4.3 months), approximately 632 deaths were deemed necessary to reach a power of 80% and a two-sided alpha risk of 5%. Therefore, a total of 980 patients were included.
Statistical analysis	An interim analysis of PFS was not planned. An interim analysis of overall survival was planned at the time of the final analysis of PFS and could only be done if the final analysis of progression-free survival showed a statistically significant difference. In order to take into account the alpha spending function for the final OS analysis, the threshold of statistical significance was set at 0.0019 (HR<0.69) (Lan-DeMets method with O'Brien-Fleming boundary). It was estimated that there would be **290 deaths during the final analysis of PFS, permitting interim analysis of OS.** When stopping for final analysis of PFS on 14 January 2012, the number of PFS events was 569 (508 initially expected). This co-efficacy endpoint proved statistically significant, thus enabling analysis of the second co-efficacy endpoint, OS. In return, the number of deaths observed on 14 January 2012 was only 223 (instead of 290 expected). Thus, in order to conduct the statistical analysis of OS, the hazard ratio calculation was revised to be able to draw conclusions on the basis of 223 deaths while controlling the alpha risk. In order to draw conclusions on the co-endpoint of OS, the HR for OS had to be below 0.617 with a significance threshold at 0.0003 The interim analysis of OS at the interruption of 14 January 2012 showed an HR in favour of the T-DM1 group (HR = 0.621; p = 0.0005); however, the pre-set significance threshold to stop the study (p<0.0003) was not reached (p=0.0005). The statistical analysis based on the interruption of 14 January 2012 concluded that the co-efficacy endpoint of PFS was statistically significant. In return, no conclusions could be drawn on the co-endpoint of overall survival, and therefore moving patients from the control group to the T-DM1 group was not authorised. Following the publication of the final PFS result at ASCO 2012 and in order to permit the control patients to receive T-DM1, without compromising the results on overall survival, it was decided, in agreement with the American and European health authorities, to do a second interim analysis of overall survival, when at least 50% of the total number of expected deaths had occurred (amendment 4 of 30 May 2012). On this basis, the hazard ratio was set at 0.727 and the significance threshold at 0.0037. While this analysis allowed conclusions to be drawn at the new significance threshold, this analysis then became the definitive confirmatory analysis of overall survival. The final analysis of overall survival was still planned after the occurrence of 632 deaths with a significance threshold set at 0.0494 and would be descriptive in nature. A hierarchical sequential method was used to analyse the primary and secondary endpoints, with a two-sided alpha risk of 5%. The final analysis of PFS was to take place after the occurrence of approximately 508 disease progression events. The statistical power of this analysis had to be 90% to show an HR of 0.75 with a two-sided alpha risk of 5% corresponding to a 33% improvement in median progression-free survival in favour of the T-DM1 group (or a median duration of 6.2 months for the control group and 8.3 months for the T-DM1 group, corresponding to an increase in absolute value of 2.1 months in favour of the T-DM 1 group). Moreover, by considering a median duration for overall survival of 17.2 months for the control group and an HR of 0.8, the final analysis of overall survival was to have taken place 51 months after inclusion of the first patient. On this date, 632 deaths were expected. Efficacy analyses were done on the intention-to-treat population (ITT) defined as all the patients randomised since three months before the interruption for PFS analysis (duration of at least one treatment cycle). Safety was analysed in all patients who received at least one dose of the study treatment (safety population).

Results:

Number of study subjects

A total of 1474 patients were screened and 991 patients were included in the study. Among the 483 patients screened and not randomised, the main reasons for non-inclusion were the presence of brain metastases (139 patients) or a negative or unknown status for HER2 expression after review by the independent central laboratory (153 patients).

The randomised population corresponding to the ITT population for efficacy analysis was:
- 495 patients in the T-DM1 group.
- 496 patients in the control group (lapatinib/capecitabine combination).

On the date of the first interim analysis,[16] 14 January 2012 (median patient follow-up of 12.9 months in the T-DM1 group and 12.4 months in the control group), 366 patients (73.9%) of the T-DM1 group and 316 patients (63.7%) in the control group were still treated or in the follow-up period.

On the date of the second interim analysis,[17] 31 July 2012 (median patient follow-up of 19.1 months in the T-DM1 group and 18.6 months in the control group), 308 patients (62.2%) of the T-DM1 group and 261 patients (52.6%) in the control group were still treated or in the follow-up period.

Patient characteristics at baseline

Patient characteristics at baseline were homogeneous between the two treatment groups (Table 1).

The median age of the patients was 53 years. All the patients had an ECOG performance score of 0 (61% in the T-DM1 group and 64% in the control group) or 1 (respectively 39% and 36%).
A total of 12.1% of patients of the T-DM1 group and 11.7% of patients of the control group had not been previously treated for their metastatic disease and correspond to a patient population called "early relapsers", i.e., patients who progressed quickly during adjuvant treatment or within 6 months after it ended.

Table 1: Patient characteristics at baseline

Characteristic	Control n = 496	T-DM1 n = 495
Age (years)		
Mean (SD)	53.2 (10.8)	52.2 (11.0)
Median	53.0	53.0
Min - Max	24.0 - 83.0	25.0 – 84.0
Sex, n (%)		
Female	492 (99.2%)	494 (99.8%)
Male	4 (0.8%)	1 (0.2%)
ECOG performance score PS n (%)		
N	488	493
0	312 (63.9%)	299 (60.6%)
1	176 (36.1%)	194 (39.4%)
Metastatic disease, n (%)		
Visceral	335 (67.5%)	334 (67.5%)
Non-visceral	161 (32.5%)	161 (32.5%)
Number of metastatic sites according to the investigator, n (%)		
1	134 (27.0%)	131 (26.5%)
2	160 (32.3%)	170 (34.3%)
3+	199 (40.1%)	194 (39.2%)
Missing data	3 (0.6 %)	0 (0.0%)

[16]The main PFS analysis and the first interim OS analysis were conducted.
[17]The second interim OS analysis was conducted.

Characteristic	Control n = 496	T-DM1 n = 495
Number of metastatic sites according to the IRC, n (%)		
1	151 (30.4%)	143 (28.9%)
2	156 (31.5%)	155 (31.3%)
3+	175 (35.3%)	189 (38.2%)
Missing data	14 (2.8%)	8 (1.6%)
Stage at initial diagnosis, n (%)		
Stage I:	43 (8.7%)	44 (8.9%)
Stage II	139 (28.0%)	127 (25.7%)
Stage III	138 (27.8%)	155 (31.3%)
Stage IV	131 (26.4%)	114 (23.0%)
Unknown	45 (9.1%)	55 (11.1%)
Prior anticancer treatment for metastatic breast cancer, n (%)		
No	58 (11.7%)	60 (12.1%)
Yes	438 (88.3%)	435 (87.9%)
Type of systemic anticancer treatment, n (%)		
Chemo/anthracycline	302 (60.9%)	303 (61.2%)
Chemo/taxane	494 (99.6%)	493 (99.6%)
Chemo/other	382 (77.0%)	385 (77.8%)
Hormone therapy	204 (41.1%)	205 (41.4%)
Biologic treatment	21 (4.2%)	13 (2.6%)
Trastuzumab	495 (99.8%)	495 (100.0%)
Pertuzumab	43 (8.7%)	51 (10.3%)
Myeloablative therapy	2 (0.4%)	0 (0.0%)
Other targeted treatment in development	17 (3.4%)	16 (3.2%)
Other	22 (4.4%)	24 (4.8%)
Prior treatment with trastuzumab for metastatic breast cancer, n (%)		
No	77 (15.5%)	78 (15.8%)
Yes	419 (84.5%)	417 (84.2%)

Co-primary endpoints:

Progression-free survival (PFS) assessed by the independent review committee (IRC)

At the time of the first interim analysis of the first co-primary endpoint, 569 events (disease progression or death from any cause) were assessed by the IRC:

- 265 (53.5%) events in the T-DM1 group;
- 304 (61.3%) events in the control group;

The main PFS analysis by the IRC showed a statistically-significant reduction of the risk of progression or death of 35% (HR = 0.650, 95% CI: [0.55; 0.77], p<0.0001) in the T-DM1 group compared to the control group.

According to the Kaplan-Meier curves, the median progression-free survival was 9.6 months for the T-DM1 group and 6.4 months for the control group, corresponding to a statistically significant improvement of median progression-free survival of 3.2 months in absolute value in favour of T-DM1.

Overall survival (OS)

On the date of the first interim analysis of the second co-primary endpoint, 223 deaths had occurred:

- 94 (19.0%) in the T-DM1 group;
- 129 (26.0%) in the control group;

The hazard ratio was in favour of the T-DM1 group (HR=0.621; 95% CI [0.48; 0.81], p=0.0005), corresponding to a reduction in the risk of death of 38% relative to the control group. However, the pre-defined significance threshold to be confirmatory for this first interim analysis (p<0.0003) and necessary to stop the study, was not reached. Therefore moving patients from the control group to the T-DM1 group was not authorised.

The median overall survival was not yet reached for patients receiving T-DM1, it was 23.3 months for the control group patients.

During the second interim analysis, 331 deaths occurred, which was a sufficient number reached (>50%)

- 149 (30.1%) in the T-DM1 group;
- 182 (36.7%) in the control group;

The analysis showed a statistically significant reduction in the risk of death of 32%, (HR = 0.682; 95% CI [0.55; 0.85], p = 0.0006) in the T-DM1 group relative to the control group. Since the threshold for statistical significance value of p = 0.0006 was reached (threshold set at 0.0037), this secondary interim analysis was considered to be the definitive confirmatory analysis of overall survival.

According to the Kaplan-Meier curves, the median overall survival was 30.9 months for patients receiving T-DM1 and 25.1 months for control group patients, therefore corresponding to a significant increase in overall survival of 5.8 months in absolute value in favour of the T-DM1 group.
After these results, the patients of the control group were allowed to receive T-DM1.

Survival rate
During the second interim analysis, at 1 year, 68 (13.7%) deaths occurred in the T-DM1 group and 97 (19.6%) in the control group. At 2 years, 126 deaths (25.5%) occurred in the T-DM1 group and 169 (34.1%) in the control group. The survival rates estimated from Kaplan Meier survival curves were:

- 85.2% at one year in the T-DM1 group versus 78.4% in the control group:
- 64.7% at 2 years in in the T-DM2 group versus 51.8% in the control group:

Secondary endpoint results:
The results for the secondary endpoints appear in Table 2.

Table 2: Secondary endpoint results (ITT; interim analysis of 14/01/2012[18])

	Control n = 496	T-DM1 n = 495
PFS according to the investigators		
N patients with event (%)	335 (67.5%)	287 (58.0%)
Median PFS (months)	5.8	9.4
Hazard ratio (stratified) [95% CI] p (stratified log-rank test)	0.658 [0.56; 0.77] p < 0.0001 significant	
Time until treatment failure		
N patients with event (%)	371 (74.8%)	313 (63.2%)
Time until failure (months)	5.8	7.9
Hazard ratio [95% CI] p (stratified log-rank test)	0.703 [0.60; 0.82] p < 0.0001 significant	
Time until symptom progression		
N patients with event (%)	257 (57.8%)	246 (54.7%)
Time until progression (months)	4.6	7.1
Hazard ratio [95% CI] p (stratified log-rank test)	0.796 [0.67; 0.95] p = 0.0121 significant	
Objective response rate		
N	n = 389	n = 397

[18]Median survival for the T-DM1 group: 12.9 months and the control group: 12.4 months

	Control n = 496	T-DM1 n = 495
N patients with ORR (%) Complete response Partial response	120 (30.8%) 2 (0.5%) 118 (30.3%)	173 (43.6%) 4 (1.0%) 169 (42.6%)
ORR difference [95% CI] p (stratified Mantel-Haenszel chi square test)	12.7% [6.0%; 19.4%] 0.0002	
Mean duration of ORR		
month [95% CI]	6.5 [5.45; 7.16]	12.6 [8.38; 20.76]
Clinical benefit rate		
N	n = 389	n = 397
N patients with a clinical benefit, n (%) [95% CI]	172 (44.2%) [39.2%; 49.2%]	231 (58.2%) [53.3%; 63.1%]
Difference [95% CI]	14.0% [7.0%; 20.9%]	
Time until symptom progression[19]		
N	n = 445	n = 450
N patients with symptom progression (%) Time until symptom progression (median; months) [95% CI] Hazard ratio (stratified) [95% CI] p (log-rank) p (Wilcoxon)	257 (57.8%) 4.6 [4.14; 5.78]	246 (54.7%) 7.1 [5.59; 8.44] 0.796 ([0.667; 0.951]) 0.0121 0.0075

T-DM1: trastuzumab emtansine (KADCYLA) - PFS: progression-free survival - n: number of patients with available measurement for this endpoint - ORR: objective response rate

08.2 Safety/Adverse effects

8.2.1 Data from the EMILIA study

The safety data from the phase III study (EMILIA) result from the **latest interim analysis, i.e., 31 July 2012**; on this date, the median patient follow-up was 19.1 months in the T-DM1 group and 18.6 months in the control group.
A total of 978 patients received at least one study treatment cycle and constitute the population that can be assessed for safety with 490 patients in the T-DM1 group and 488 patients in the control group.

Treatment exposure
The median time on treatment was 7.6 months (min-max: 0-34.8) in the T-DM1 group and 5.5 months (0-33.3) in the control group. Thirty (30) patients in the T-DM1 group were treated for more than 2 years compared to 13 in the lapatinib and capecitabine group (11 of whom received capecitabine for more than 2 years)

For T-DM1, the median dose received was 3.5 mg/kg every three weeks; it was 1250 mg/day for lapatinib and 1701 mg/m²/day for capecitabine.
Thirty-five (7.1%) patients discontinued their treatment in the T-DM1 group due to the occurrence of an adverse event (AE) compared to 43 (8.8%) patients who discontinued lapatinib and 54 (11.1%) patients who discontinued capecitabine.

[19]Quality of life assessed according to the FACT-B questionnaire, assessing the physical and functional state of patients, and their feelings in relation to specific symptoms of their disease (score FACT-B TOI-PFB)

The AE that most commonly led to treatment discontinuation in the T-DM1 group was thrombocytopenia (for 11 (2.2%) patients) and an increase in liver enzymes (for 4 (0.8%) patients).
In the control group, the AEs were:

- diarrhoea in 13 (2.7%) patients for lapatinib and 16 (3.3%) patients for capecitabine,
- vomiting in 11 (2.3%) patients for lapatinib and 9 (1.8%) patients for capecitabine,
- hand-foot syndrome in 6 (1.2%) patients for lapatinib and 13 (2.7%) patients for capecitabine,

Adverse events, all grades together
A total of 474 (96.7%) patients of the T-DM1 group and 478 (98.0%) patients of the control group had an adverse event, all grades together.

The most common adverse events (≥10%):
- T-DM1 group: thrombocytopenia (29.2%), increased liver enzymes (ALAT (17.8%) and ASAT (23.1%)), nausea (40.0%), infections and infestations (46.5%).
- Lapatinib and capecitabine group: gastrointestinal disorders (diarrhoea: 79.7%), skin disorders (rash: 27.5% and hand-foot syndrome [palmar-plantar erythrodysesthesia]: 59.0%), infections and infestations (48.4%), nausea (45.3%).

Adverse events of grade 3 or worse
A smaller proportion of grade 3 or worse AEs was reported in the T-DM1 group compared to the control group: 44.5% in the T-DM1 group *versus* 59.6% in the control group.
The nature of the adverse events of grade 3 or worse occurring in the treatment group was different between the groups, in line with the mechanisms of action of the products:
- T-DM1 group: thrombocytopenia (13.9%), increased ASAT (4.5%), anaemia (3.5%), increased ALAT (3.1%), fatigue (2.4%), hypokalaemia (2.2%), neutropenia (2.2%).
- Lapatinib and capecitabine combination group: diarrhoea (20.9%), hand-foot syndrome (17.6%), vomiting (4.5%), neutropenia (4.3%), hypokalaemia (4.3%), fatigue (3.5%), nausea (2.5%), mucositis (2.3%), anaemia (2.3%), rash (2%).

Serious adverse events
A total of 86 (17.6%) patients of the T-DM1 group and 95 (19.5%) patients in the control group reported a serious AE (SAE). The system organ classes most often concerned in the T-DM1 group versus the control group were:
- Gastrointestinal disorders; 16 (3.3%) patients versus 30 (6.1%) patients,
- Infections and infestations: 23 (4.7%) patients versus 15 (3.1%) patients,
- General disorders and administration site conditions: 14 (2.9%) patients versus 9 (1.8%) patients,
- Respiratory, thoracic and mediastinal disorders: 5 (1.0%) patients versus 16 (3.2%) patients,
- Injury, poisoning and procedural complications: 7 (1.4%) patients versus 6 (1.2%) patients.

A smaller proportion of grade 3 or worse AEs was reported in the T-DM1 group (60 (12.2%) patients) compared to the control group (79 (16.2%) patients):

Death
In the safety analysis population, a total of 332 deaths occurred: 150 (30.6%) deaths in the T-DM1 group and 182 (37.3%) deaths in the placebo group. Six deaths (1.2%) in the T-DM1 group and 17 (3.5%) deaths in the control group occurred within 30 days after treatment discontinuation.
The most common cause of death was disease progression with 145 (29.6%) patients in the T-DM1 group and 177 (36.3%) in the control group.
The frequency of death for a reason other than disease progression was low and similar with 5 (1.0%) patients in each group.

Adverse events of special interest
- **Liver damage** was reported in 159 (32.4%) patients in the T-DM1 group and 128 (26.2%) in the control group. The majority of this damage was of low to moderate intensity (grade 1 or 2), respectively 23.2% and 20.7% of the total number of patients.
- **Thrombocytopenia** was reported in 155 (31.6%) patients in the T-DM1 group and 16 (3.2%) in the control group. These changes were mild to moderate (grade 1 or 2).

- The frequency of **cardiac adverse events** was in 5 (1%) patients in the T-DM1 group and 12 (2.5%) in the control group.
- **Infusion-related reactions and hypersensitivity reactions** were uncommon with 21 (4.3%) of patients in the T-DM1 group having grade 1 or 2 reactions.
A total of 8 (1.6%) patients had **pneumonia** in the T-DM1 group (including one of grade 4 (ARDS[20])) versus 4 (0.8%) in the control group (including 1 of grade 4 and 1 of grade 5 (ARDS)). Other cases of pneumonia were grade 1 or 2.
- **Hypokalaemia** was reported in a similar manner in both groups (around 10%). 13 (2.7%) patients versus 23 (4.7%) had grade 3 or worse hypokalaemia.
No event was accompanied by heart rhythm disorders.
- A total of 127 (25.9%) patients in the T-DM1 group versus 92 (18.9%) in the control group had **peripheral neuropathy**, mostly grade 1 or 2. A total of 14 (2.9%) patients in the T-DM1 group versus 2 (0.4%) in the control group had peripheral neuropathy of grade 3 or worse.
Two patients discontinued treatment due to peripheral neuropathy.
- **Visual disorders** were more common in the T-DM1 group with 36 (7.3%) of patients versus 11 (2.3%) of patients in the control group. All the events were grade 1 or 2 in both groups.
- **Renal disorders** were similar in both groups with 23 (4.7%) of patients versus 28 (5.7%) of patients in the control group. The majority of events were grade 1 or 2. Grade 3 disorders occurred in 2 (0.4%) patients of each group.

The safety profile of trastuzumab emtansine observed in support studies was similar to that observed in the EMILIA study.

8.2.2 SPC data

The SPC provides a summary of the safety profile:
"The safety of trastuzumab emtansine has been evaluated in 884 breast cancer patients in clinical studies. In this patient population:
- the most common serious ADRs were pyrexia, thrombocytopenia, vomiting, abdominal pain, nausea, constipation, diarrhoea, dyspnoea and pneumonitis.
- the most common adverse drug reactions (ADRs) (≥25%) with trastuzumab emtansine were haemorrhage (including epistaxis), increased transaminases, fatigue, musculoskeletal pain, and headache. The majority of ADRs reported were of Grade 1 or 2 severity.
- the most common National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 3 or 4 ADRs (> 2%) were thrombocytopenia, fatigue, increased transaminases, anaemia, hypokalaemia, musculoskeletal pain and neutropenia.

8.2.3 Risk Management Plan

The European risk management plan[21] for KADCYLA, including a risk minimisation plan, provides for the monitoring of the following “substantial” risks:

- identified risks: interstitial pneumonitis / acute respiratory distress syndrome, liver toxicity, nodular regenerative hyperplasia, infusion related reaction, hypersensitivity, left ventricular dysfunction, thrombocytopenia, peripheral neuropathy, neutropenia and anaemia.

- potential risks: foetal toxicity, reduced fertility and medication error.

The following information is considered to be missing: data in patients with hepatic impairment, data in patients with renal impairment, data in patients with LVEF <50%, data in elderly patients ≥ 75 years, data in pregnant or lactating women, data in male patients, clinical impact of anti-drug antibodies, use of non-validated HER2 tests and confirming the incidence of left ventricular dysfunction in patients pre-exposed to trastuzumab or pertuzumab.

[20]ARDS: acute respiratory distress syndrome
[21]Version 3.1 dated 14 January 2012

In addition to routine pharmacovigilance, some risks are the subject of specific questionnaires used when documenting cases reported by health care professionals: hepatobiliary events.

Regarding the risk of medication error, in addition to the various sections of the SPC for KADCYLA, provision of educational material for health care providers (brochure on risk of confusion with HERCEPTIN) was requested as an additional safety measure.

08.3 Summary & discussion

The efficacy and safety of trastuzumab emtansine were compared to those for lapatinib in combination with capecitabine in a phase III, randomised, open-label study performed in 991 patients with locally-advanced unresectable or metastatic HER2+ breast cancer that progressed after a prior treatment with trastuzumab and taxane (495 in the trastuzumab emtansine group and 496 in the control group).

The mean and median age of the patients was 53. All the patients were in good general health (ECOG score of 0 or 1). A third of patients had more than 3 metastatic sites and nearly 70% of patients had a visceral disease.
At baseline, 88% of patients were progressing after a prior treatment with trastuzumab in a metastatic setting. Since pertuzumab (PERJETA) has been available as a first line treatment for metastatic or locally-recurrent HER2+ breast cancer, the addition of pertuzumab to bitherapy with trastuzumab and taxane has been preferred[7]. The Committee notes that less than 10% of patients included received pertuzumab as a first line treatment.
According to the indication validated by its marketing authorisation, lapatinib in combination with capecitabine, is reserved for patients progressing after a prior treatment that included anthracycline, a taxane and a treatment including trastuzumab in a metastatic setting. Around 12% of patients in each group of the study did not receive any prior treatment for their metastatic disease, corresponding to a patient population called "early relapsers", who progressed during adjuvant treatment with trastuzumab and taxane or within six months of its completion.

Compared to the lapatinib/capecitabine combination, trastuzumab emtansine has shown a statistically-significant increase on:

The co-primary endpoints,
- the median progression-free survival (assessed by the IRC) of +3.2 months (median PFS of 9.6 months), or a reduction of the risk of progression or death of 35% (HR=0.650; 95% CI: [0.55; 0.77], p<0.0001)
- the median overall survival of +5.8 months (median OS of 30.9 months) or a reduction in the risk of death of 32% (HR = 0.682; 95% CI: [0.55; 0.85], p=0.0006) and an increase of the two-year survival rate from 51.8% to 64.7%.

The secondary endpoints:
- the objective response rate of 12.7 points (43.6% versus 30.8%) (95% CI: [6.0%; 19.4%, p = 0.0002),
- the time until treatment failure of +2.1 months (7.9 months versus 5.8 months) (HR = 0.703; 95% CI: [0.60; 0.82], p<0.0001)
- the time until symptom progression on the quality of life scale of +2.5 months (7.1 months versus 4.6 months) (HR = 0.796; 95% CI: [0.67; 0.95], p=0.0121)

A smaller proportion of adverse events (AE) of grade 3 or worse and serious AEs (SAE) of grade 3 or worse was reported in the trastuzumab emtansine group compared to the control group with:
- AE of grade 3 or worse: 44.5% versus 59.6%,
- SAE of grade 3 or worse: 12.2% compared with 16.2%

In patients receiving trastuzumab emtansine, the most common adverse events of grade 3 or worse (frequency of more than 2%) were: thrombocytopenia (13.9%); increased ASAT (4.5%); increased ALAT (3.1%); fatigue (2.4%); hypokalaemia (2.2%) and neutropenia (2,2%). Eleven

(2.2%) patients discontinued treatment due to thrombocytopenia and 4 (0.8%) patients due to increased transaminases (grade 3 or worse).

In patients receiving the lapatinib and capecitabine combination, the most common adverse events of grade 3 or worse (incidence greater than 2%) were: diarrhoea (20.9%); hand-foot syndrome (17.6%); vomiting (4.5%); neutropenia (4.3%); hypokalaemia (4.3%); fatigue (3.5%); nausea (2.5%); anaemia (2.3%) and mucositis (2.3%). These gastrointestinal (diarrhoea) and cutaneous (hand-foot syndrome and rash) disorders are known adverse events that can have an impact on daily living. A total of 29 (6%) patients of the lapatinib + capecitabine group (respectively 13 (2.7%) and 16 (3.3%) patients) discontinued treatment due to grade 3 or worse diarrhoea.
Relative to the known safety profile of trastuzumab, there is no evidence of particular cardiac toxicity with trastuzumab emtansine.

08.4 Planned studies

The Marketing Authorisation Holder is asked to submit:

- the final overall survival data from the pivotal study (November 2014).
- the final report from the MARIANNE/B022589 clinical study (April 2017), phase III, multicentre, randomised and double blind study assessing the safety and efficacy of pertuzumab in combination with trastuzumab emtansine, as a first line treatment for HER2+ metastatic breast cancer. About 1092 patients were included and randomised, between July 2010 and May 2012, to three treatment groups:
    - Group A: trastuzumab + taxane
    - Group B: trastuzumab emtansine + pertuzumab
    - Group C: trastuzumab emtansine + placebo

The primary efficacy endpoint of this study is progression-free survival, assessed by an independent review committee, and safety.
The secondary endpoints are the objective response rate, overall survival, survival rates at 1 and 2 years, progression-free survival and the objective response rate assessed by the investigators, the clinical benefit and the duration of the response. The results are expected in 2015.

- the final report from the THERESA clinical study (August 2016).

09 THERAPEUTIC USE

Therapeutic strategy for metastatic stages of breast cancer

Systemic medical treatment by chemotherapy and/or hormone therapy is recommended as the first line treatment for therapeutic management of the metastatic stages of breast cancer.[22] The choice of treatment relies notably on:

- the histological characteristics of the tumour,
- the predictive factors for treatment response (expression of hormone receptors and/or HER2 receptors),
- prognostic factors,
- the patient's prior treatments and their tolerability,
- the time between the new adjuvant treatment and the first-line metastatic treatment,
- the type of metastases (number of sites, size and location),
- patient's general condition.

The main objective in a metastatic setting is extension of survival and reduction of tumour size and metastases so as to decrease symptoms while maintaining a quality of life that is as acceptable as possible. In the case of tumour over-expression of the HER2 receptor, the European[23] and international[24] good practice recommendations for first line treatment for metastatic disease, advise a treatment based on HERCEPTIN, in combination with chemotherapy and/or hormone therapy.
The standard first line treatment for HER2+ metastatic breast cancer is trastuzumab (HERCEPTIN) in combination with chemotherapy containing a taxane (docetaxel or paclitaxel). When hormone receptors are expressed,this treatment may also be combined with hormone therapy. In view of the conventional treatment and considering the demonstrated benefit for progression-free survival, pertuzumab (PERJETA) in combination with trastuzumab and docetaxel is a new means of managing HER2+ metastatic breast cancer in first-line treatment. The American NCCN guidelines rate the addition of pertuzumab to bitherapy with trastuzumab and a taxane as an option to be preferred to bitherapy.

In case of progression during first-line metastatic treatment, the options become limited. As a second line, it is necessary to maintain an anti-HER2 activity in HER2+ metastatic breast cancer.
The standard treatment for metastatic HER2+ breast cancer is the lapatinib, with anti-HER2 activity (TYVERB)/capecitabine (XELODA) combination indicated in patients progressing after a treatment that included an anthracycline, a taxane and a treatment including trastuzumab in a metastatic setting.
More recently, in July 2013, the lapatinib (TYVERB)/trastuzumab (HERCEPTIN) combination obtained a marketing authorisation in patients with HER2+ breast cancer with negative hormone receptors, who progressed on trastuzumab and chemotherapy. In the absence of a Transparency Committee opinion, the role in the therapeutic strategy of this combination is not defined.

Since the therapeutic alternatives are very limited at this stage of the disease, a temporary treatment protocol (TTP) was granted in 2008 for the trastuzumab (HERCEPTIN) /capecitabine (XELODA) combination after progression on trastuzumab, possibly combined with taxanes.[10]

There are other therapeutic alternatives, but these are less commonly used in this population.

Role of KADCYLA in the therapeutic strategy

[22]INCa – HAS – guide affection longue durée – Cancer du sein - [guide to chronic illness - Breast cancer] January 2010.
[23]Cardoso F, Harbeck N, Fallowfield L, et al. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012; 23 Suppl 7):vii11–vii19.
[24]Cardoso F, Costa A, Norton L, et al. 1st International consensus guidelines for advanced breast cancer (ABC 1). Breast 2012; 21(3):242-52

KADCYLA (trastuzumab emtansine) 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. Patients should have either:
- received prior therapy for locally advanced or metastatic disease, or
- developed disease recurrence during or within six months of completing adjuvant therapy.

The phase III study EMILIA showed a clinically and statistically significant increase in overall survival (as co-primary endpoint) in patients with metastatic HER2+ breast cancer as a second-line treatment. The statistically-significant increase in overall survival of +5.8 months in the KADCYLA group relative to the TYVERB/XELODA combination is accompanied by an extension in the time until progression of the metastatic disease symptoms reported by the patient according to the FACT-B QoL quality of life questionnaire.

KADCYLA is the first second-line treatment that has shown a statistically-significant increase in overall survival in patients with metastatic HER2+ breast cancer in second-line treatment. KADCYLA is incorporated into the ESMO,[23] AGO[24] and NCCN[25] recommendations where it is presented as the preferred therapeutic strategy in patients who have already been exposed to trastuzumab.

In its current indication, KADCYLA is a new second-line and beyond treatment in metastatic HER2+ breast cancer.

[25]NCCN Clinical Practice Guidelines in Oncology (NCCN guidelines). Version 3.2013.

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

◗ In metastatic stage breast cancer, median survival varies from 18 to 36 months. Metastatic stage breast cancers overexpress ErbB-2 (HER2) receptors 30% of the time. This overexpression is a factor for poor prognosis 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 high.
◗ At this stage of the disease, there are few validated drug alternatives.
◗ This medicinal product is a first-line medicine in patients with locally advanced unresectable or metastatic HER2+ breast cancer, who were previously treated with trastuzumab and a taxane, separately or in combination.

◗ Public health :
In metropolitan France, the incidence of breast cancer is estimated to be about 48,800 new cases a year.[1] It is the number one cancer in terms of frequency, with 31.5% of new cases of cancer in women.[1]
It is also the number one cause of cancer death in women, with an estimated number of close to 11,900 deaths estimated in 2012,[1] which represents 18.8 % of female deaths from cancer.
The cancer incidence, which has increased substantially between 1980 and 2000, has been decreasing since 2005, with 56.3 cases per 100,000 person-years in 1980, 97.8 in 2005 and 88.0 in 2012.[1] Mortality remained relatively stable until around 1995 and then decreased significantly up to 2012, with a mean decrease in mortality of - 0.6% per year between 1980 and 2012, and -1.5% per year between 2005 and 2012.[1]
Around 30% of patients diagnosed at an advanced stage are HER2 positive.
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 on the sub-population of patients with HER2+ metastatic or locally unresectable breast cancer likely to receive KADCYLA as a second-line monotherapy (after previously receiving the combination of HERCEPTIN and a taxane) remains significant and therefore moderate because of the greatest associated morbidity and mortality.

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 available results from clinical trials, especially the EMILIA study, a phase III, randomised, open-label study versus the TYVERB+XELODA combination showing an improvement of median progression-free survival (absolute gain of 3.2 months), overall survival (absolute gain of 5.8 months) and quality of life (Fact-B score), KADCYLA is expected to have a moderate impact in terms of morbidity, mortality and quality of life.

The transferability of these results to current clinical practice is considered acceptable. However, on the one hand, it should be emphasised, patients treated in actual practice with KADCYLA would have received PERJETA as a first line (in combination with HERCEPTIN + taxane, new standard treatment) and not the combination of HERCEPTIN + taxane, as in the EMILIA study; and, on the other hand, a possible drift of the use of this treatment in the current HERCEPTIN indications (first line, as a new adjuvant).

Moreover, KADCYLA is expected to have no impact on the organisation of healthcare. Thus the proprietary medicinal product KADCYLA in monotherapy and as a second and subsequent-line treatment should be in a position to offer a response to the identified public health need.
Consequently, KADCYLA is expected to have a public health benefit in this indication. This benefit is low.

Consequently, the Committee considers that the actual benefit of KADCYLA, as a monotherapy, is substantial in the treatment of adult patients with HER2-positive, metastatic or locally advanced unresectable breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have:
- received prior therapy for locally advanced or metastatic disease, or
- developed disease recurrence during or within six months of completing adjuvant therapy.

The Committee recommends inclusion on the list of medicines approved for hospital use in the indication and at the dosages in the Marketing Authorisation.

010.2 Improvement in actual benefit (IAB)

Given the improvement observed with trastuzumab emtansine (KADCYLA) in monotherapy compared to the combination of lapatinib (TYVERB) + capecitabine (XELODA) in terms of progression-free survival and overall survival and an acceptable safety profile, the Transparency Committee believes that KADCYLA, in monotherapy provides a substantial improvement in actual benefit (IAB II) in the treatment of adult patients with HER2 positive metastatic or locally advanced unresectable breast cancer, who were previously treated with trastuzumab and a taxane, separately or in combination.

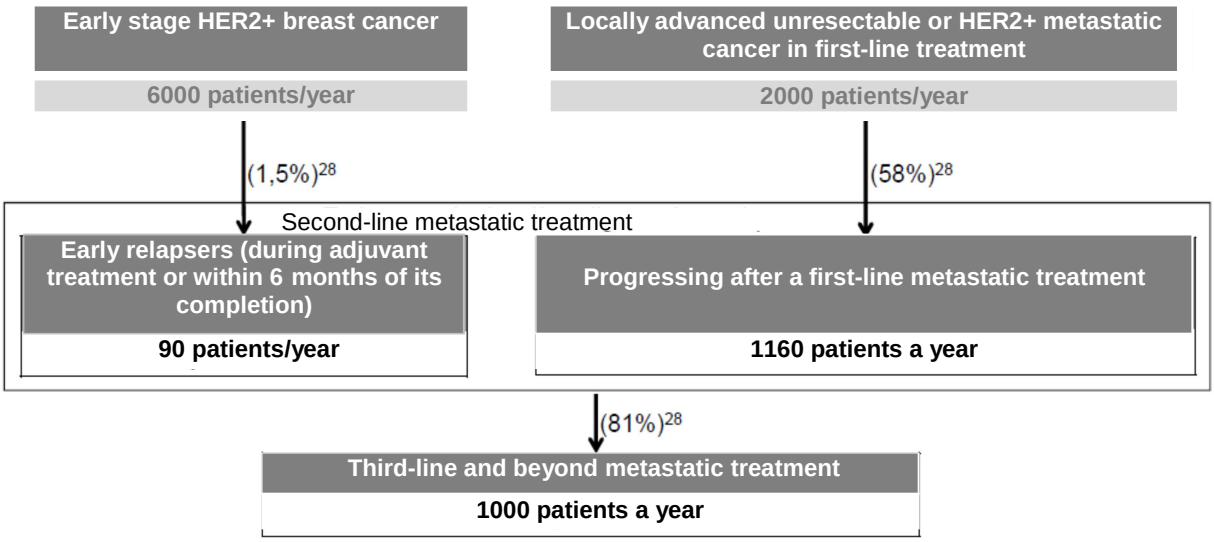
010.3 Target population

The target population for KADCYLA is patients with metastatic HER2+ breast cancer previously treated with trastuzumab and taxane for their metastatic disease or who progressed during or within 6 months after the end of the adjuvant treatment. In both cases, these are patients treated by standard second-line protocols for metastatic HER2+ breast cancer.
Patients in metastatic first-line treatment represent around 2000 cases per year.[26] The proportion of patients who progressed annually on second-line metastatic treatment is 58% and those on subsequent line treatments is 81%.[27] According to these proportions, there are around 1160 patients on second-line treatment and around 1000 patients on subsequent lines.

Patients who progressed during or within 6 months after the end of adjuvant treatment represent 1 to 2% of the early breast cancer population. On the basis of 6000 patients with HER2+ breast cancer at the early stage, these "early relapser" patients would represent around 90 patients.

Figure 1: Estimation of the KADCYLA target population.

[26]HAS. Transparency Committee Opinion PERJETA 24 July 2013.
[27]Kantar Health - Barometer market research February 2013 performed on 1154 patients with HER2+ breast cancer.



Conclusion

On this basis, at its arrival on the market, the target population for KADCYLA may be estimated at 2250 patients.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging

Appropriate for the prescription conditions according to the indication, dosage and treatment duration.