HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

24 July 2013

PERJETA 420 mg, concentrate for solution for infusion

B/1 bottle (CIP: 34009 584 633 9 6)

Applicant: ROCHE

INN	pertuzumab
ATC code (2013)	L01XC13 (Monoclonal antibodies)
Reason for the review	**Inclusion**
List concerned	**Hospital use** (French Public Health Code L.5123-2)
Indication concerned	**"PERJETA is indicated for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease."**

AB	The actual benefit of PERJETA in combination with Herceptin and docetaxel in its Marketing Authorisation indication is substantial.
IAB	PERJETA in combination with trastuzumab and docetaxel provides a moderate improvement in actual benefit (level III) in the management of HER2-positive metastatic or locally recurrent unresectable breast cancer which has not previously been treated with anti-HER2 therapy or chemo-therapy for the metastatic disease.
Therapeutic use	PERJETA in combination with trastuzumab and docetaxel is a new method of managing HER2+ metastatic breast cancer in first-line treatment.
Public health benefit	Low
Target population	*2000 patients*

1 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (centralised procedure)	Date initiated: 4 March 2013
Prescribing and dispensing conditions / special status	List I Medicine requiring special monitoring during treatment. Prescription restricted to cancer treatment or clinical oncology specialists and departments. Medicinal product reserved for hospital use.

ATC Classification	2013	
	L	Antineoplastic and immunomodulating agents
	L01	Antineoplastic agents
	L01X	Other antineoplastic agents
	L01XC	Monoclonal antibodies
	L01XC13	Pertuzumab

2 BACKGROUND

Review of the application for inclusion of the medicinal product PERJETA 420 mg, concentrate for solution for infusion, on the list of medicinal products approved for hospital use, on the initiative of the company.

PERJETA is a medicinal product based on pertuzumab, a recombinant humanised monoclonal antibody that specifically targets the extracellular dimerisation domain of the HER2 receptor, and thereby blocks ligand-dependent heterodimerisation of HER2 with other receptors of the HER family, in particular HER1 (or EGFR), HER3 and HER4.

3 THERAPEUTIC INDICATION

“PERJETA is indicated for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.”

4 DOSAGE

“The recommended initial loading dose of PERJETA is 840 mg administered as a 60 minute intravenous infusion, followed every 3 weeks thereafter by a maintenance dose of 420 mg administered over a period of 30 to 60 minutes.
When administered with PERJETA the recommended initial loading dose of trastuzumab is 8 mg/kg body weight administered as an intravenous infusion followed every 3 weeks thereafter by a maintenance dose of 6 mg/kg body weight.
When administered with PERJETA the recommended initial dose of docetaxel is 75 mg/m^2, administered thereafter on a 3 weekly schedule. The dose of docetaxel may be escalated to 100 mg/m^2 on subsequent cycles if the initial dose is well tolerated.”

5 THERAPEUTIC NEED

Improving the management of cancer patients and their quality of life is a public health need, which is an established national priority for the public authorities (French Law of 9 August 2004 on public health policy, the Cancer Plan 2009-2113 and the Plan for improving quality of life for patients with chronic diseases). The established breast cancer screening campaigns have made it possible to diagnose a large number of patients earlier. However, patients are still being first diagnosed late, with progression to metastasis or with an unresectable recurrence[1]. Since 2000, the standard first-line treatment for HER2-positive metastatic breast cancer has been trastuzumab in combination with a taxane. This protocol has shown a significant benefit in terms of response rates, the time to disease progression and overall survival. Despite this progress, about 50% of patients treated experience disease progression within one year of the initiation of their treatment[2,3,4] and their 5-year survival rate is less than 25%[5]. Metastatic disease is still incurable, and median overall survival is less than 40 months[5].

6 CLINICALLY RELEVANT COMPARATORS

6.1 Medicinal products

There is no comparator in the context of combination with docetaxel and trastuzumab in the first-line treatment of metastatic HER2+ breast cancer.

Conclusion

There is no relevant comparator for PERJETA in this indication.

7 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	REIMBURSEMENT	
	YES/NO If no, why not	Population(s) That of the Marketing Authorisation or restricted
EU	No (procedures in progress)	
USA	Yes (03/08/2012)	Indication identical to the one for Europe

[1] InVS (Health Monitoring Institute). BEH (Weekly Epidemiological Bulletin). Special issue – Organised screening of breast cancer. 26 September 2012/No. 35-36-37.

[2] Slamon DJ, Leyland-Jones B, Shak S, *et al*. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344(11):783-92.

[3] Marty M, Cognetti F, Maraninchi D, *et al*. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol. 2005;23(19):4265-74.

[4] Valero V, Forbes J, Pegram MD, *et al*. Multicenter phase III randomized trial comparing docetaxel and trastuzumab with docetaxel, carboplatin, and trastuzumab as first-line chemotherapy for patients with HER2-gene-amplified metastatic breast cancer (BCIRG 007 study): two highly active therapeutic regimens. J Clin Oncol. 2011;29(2):149-56.

[5] 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(11):2169-74.

8 ANALYSIS OF AVAILABLE DATA

The submitted dossier comprises:
- Two phase II studies (study BO17929 and study BO16934) of the second line treatment of metastatic breast cancer and one study WO20697 performed in the context of neoadjuvant treatment. Since these studies involved patients outside the scope of the indication here, they will not be taken into account.
- a pivotal study (CLEOPATRA) analysed below.

8.1 Efficacy

CLEOPATRA study
Phase III randomised, double-blind, placebo-controlled study comparing the addition of pertuzumab to a dual therapy with docetaxel + trastuzumab versus that same dual therapy combined with placebo, in 808 patients with HER2-positive metastatic or locally recurrent unresectable breast cancer.

Patients were randomised 1 : 1 to receive:
- either placebo + trastuzumab + docetaxel
- or pertuzumab + trastuzumab + docetaxel.

Pertuzumab was administered in a loading dose of 840 mg by IV infusion during the first cycle then in a dose of 420 mg in the following cycles (one injection every 3 weeks).
Trastuzumab was administered in a loading dose of 8 mg/kg body weight by IV infusion during the first cycle, then in a dose of 6 mg/kg in the following cycles (one injection every 3 weeks).
Docetaxel was administered in an initial dose of 75 mg/m^2 by intravenous infusion every three weeks for at least six cycles. The dose of docetaxel could be escalated to 100 mg/m^2, at the investigator's discretion, if the initial dose was well tolerated.

The primary efficacy endpoint was progression-free survival as evaluated by an independent review committee and defined as the time from the date of randomisation to the date of disease progression or death (from any cause) if the death occurred within 18 weeks of the last tumour evaluation.

The secondary endpoints were:

- overall survival, defined as the time between randomisation and death from any cause. Patients who were alive or lost to follow-up on the date of the analysis were censored on the date of the last tumour evaluation. Patients for whom no information had been obtained after inclusion were censored on the day after the date of randomisation;
- progression-free survival, evaluated by the clinical investigator and fitting the same definition as the primary efficacy endpoint;
- percentage objective response, defined as the proportion of patients with a complete or partial response. The response was defined in accordance with the RECIST criteria on the basis of two consecutive evaluations at least 4 weeks apart;
- duration of the objective response, defined as the time between the documented date of the response (complete or partial) and that of disease progression or death from any cause. Progression was evaluated in the same way as for the primary efficacy endpoint. Only patients with an objective response were included in the analysis of this endpoint;

- quality of life, measured by the FACT-B questionnaire specific to breast cancer. A difference in quality of life was regarded as clinically significant when a reduction of at least 5 points on the TOI-PFB questionnaire[6] was found by comparison with the score on inclusion;
- safety.

The main inclusion criteria were:
- HER2-positive metastatic or locally recurrent unresectable breast cancer, confirmed cytologically or histologically. HER2 positivity (overexpression defined as IHC 3+ and/or FISH amplification ratio ≥ 2) had to be confirmed by the central laboratory.
- a performance index of ≤1 according to the ECOG classification
- a left-ventricular ejection fraction (LVEF) of ≥ 50% and cardiac function compatible with the patient receiving chemotherapy.

The main non-inclusion criteria were:
- previous treatment of metastatic breast cancer (except for hormone treatment taken alone and stopped before randomisation),
- systemic treatment of breast cancer in a (neo)adjuvant setting with a disease-free interval of less than 12 months between the end of the systemic treatment (excluding hormone therapy) and the diagnosis of metastatic disease,
- the existence of metastases in the central nervous system,
- exposure to anthracyclines equivalent to a cumulative dose of ≥ 360 mg/m² of doxorubicin or equivalent,
- history of a reduction in LVEF to a value of less than 50% during or after treatment with trastuzumab.

Results:
A total of 808 patients were randomised:
- 402 patients to the group with pertuzumab + trastuzumab + docetaxel
- 406 patients to the group with placebo + trastuzumab + docetaxel

The median age of the patients was 54 years.
A slightly larger proportion of patients in the pertuzumab group had an ECOG score of 0 (68.2% versus 61.1%) and, conversely, a slightly smaller proportion of patients in the pertuzumab group had an ECOG score of 1 (31.1% versus 38.7%). About half the patients in each treatment group had hormone-receptor positive disease (defined as oestrogen-receptor positive and/or progesterone-receptor positive) and about half had also received prior adjuvant or neoadjuvant treatment. Most of these patients had previously received anthracyclines and 11% of all patients had previously received trastuzumab.

On the date of the final analysis of the primary efficacy endpoint, median progression-free survival was 18.5 months in the pertuzumab group versus 12.4 months in the comparator group, i.e. a gain in absolute terms of 6.1 months in favor of the pertuzumab group (HR = 0.62, 95% CI [0.51; 0.75], p<0.0001).

Secondary endpoint results:

- overall survival:
The final analysis of overall survival was scheduled after the occurrence of 385 deaths, to show an improvement of 33% compared with the comparison group with a power of 80%. On the final analysis of the primary efficacy endpoint, an interim analysis of overall survival was scheduled by the protocol, for which 193 deaths (50% of the 385) were expected. On this date, 165 deaths had occurred out of the 193 expected according to the protocol, i.e. 43% of the total. The median overall survival had not been achieved in either of the two groups and the HR showed no difference between the two groups (HR = 0.64, p value above the threshold set at 0.0012).

[6] TOI-PFB (Trial Outcome Index – Physical Functional Breast): questionnaire made up of 24 questions covering 3 areas of the FACT-B questionnaire (scales evaluating physical condition, functional condition and the specific breast cancer symptoms (BCS); the other areas evaluated by the FACT-B were emotional and social condition).

Breaking of the code and movement of patients from the comparison group to the pertuzumab group were not permitted.
A second unscheduled interim analysis was performed one year later with 69% of the events required for the final analysis (267 deaths out of 385 required). It suggested a median overall survival of 37.6 months (95% CI [34; NA]) in the comparator group and this not being achieved in the pertuzumab group (95% CI [42; NA); (HR = 0.66, 95% CI [0.52; 0.84], p=0.0008.
At the end of this interim analysis, the code was broken and the patients in the comparison group were allowed to receive PERJETA (46 patients out of the 55 still receiving the study treatment). Consequently, the data from the final analysis of overall survival for this study will not be known.

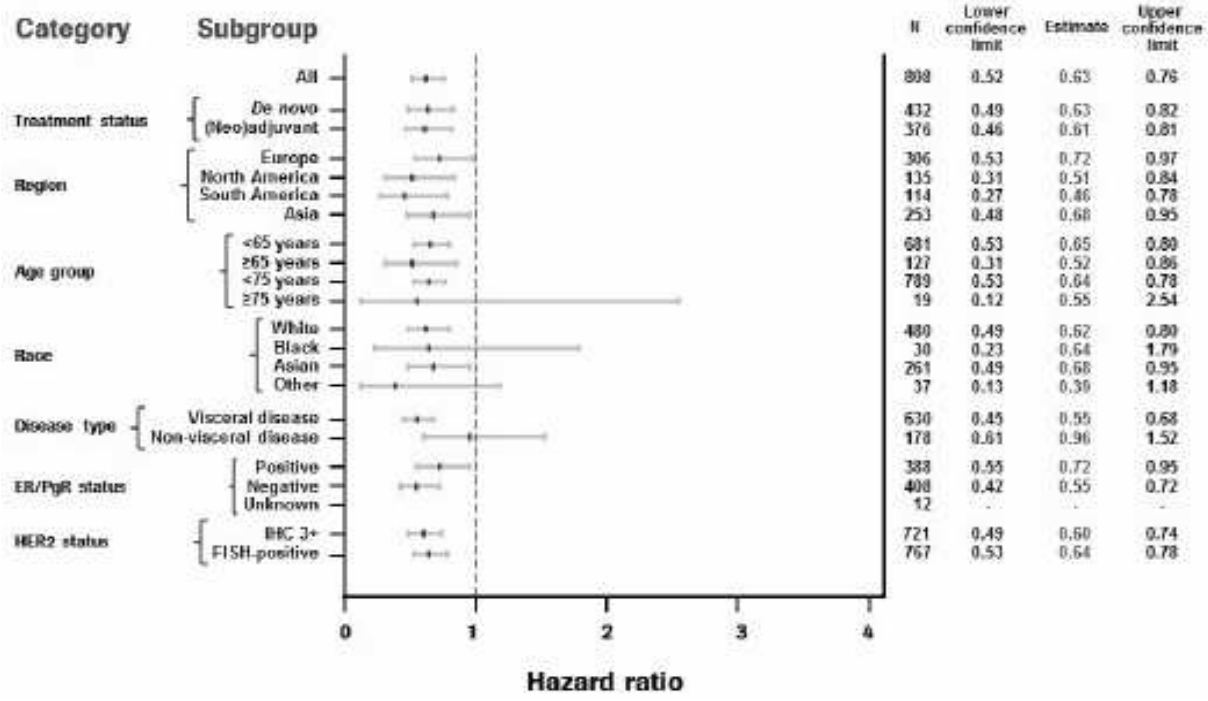
- percentage objective response rate
The percentage objective response rate (complete or partial response) was 80.2% (of which 5.5% were complete response) in the PERJETA group versus 69.3% (of which 4.2% were complete response) in the placebo group, an increase of 10.9 points (p = 0.0011).

- duration of objective response
The median duration of the objective response was 87.6 weeks in the PERJETA group versus 33.5 weeks in the placebo group, an increase of 33.5 weeks corresponding to an HR of 0.66 (95% CI 0.51; 0.85).

- quality of life
Patients' quality of life was evaluated using the FACT-B questionnaire evaluating the patients' physical and functional condition and their experience of the specific symptoms of the disease.
The response rate to the FACT-B questionnaire was at least 75% during the first year of follow-up in the two treatment groups. On the date of analysis of the primary efficacy endpoint (first cut-off, 13 May 2011), 239 (59.5%) patients in the PERJETA group and 229 (56.7%) patients in the comparison group had a change of at least 5 points in their TOI-PFB score which was regarded as clinically significant. The median time to this change was comparable in the two treatment groups (18.4 weeks in the PERJETA group versus 18.3 weeks in the comparison group, HR = 0.97, 95% CI [0.81; 1.16]).
In addition, the ECOG score remained identical between inclusion and the end of treatment for 68% of patients in the PERJETA group versus 64% in the comparison group.

The results of a subgroup analysis of progression-free survival carried out by the independent committee are summarised in Figure 1 below.

Figure 1: Progression-free survival evaluated according to patient subgroup



8.2 Safety and adverse events

The frequency of drop-outs on account of adverse events was 6.1% in the PERJETA group versus 5.3% in the comparison group.
No difference was seen between the two groups as regards the incidence of grade 3-4 events (placebo: 72.0%; pertuzumab: 73.5%).
The most commonly reported grade 3-4 adverse events were neutropenia (45.8% in the placebo group, 48.9% in the pertuzumab group), febrile neutropenia (7.3% in the placebo group, 13.0% in the pertuzumab group), leucopenia (14.6% in the placebo group, 12.3% in the pertuzumab group) and diarrhoea (5.0% in the placebo group, 7.9% in the pertuzumab group).
The incidence of a reduction in left-ventricular ejection fraction of grades > 3 was 1.2% in the pertuzumab group versus 2.8% in the comparator group.

8.3 Summary & discussion

A phase III randomised, double-blind placebo-controlled study compared the addition of pertuzumab to dual therapy with docetaxel + trastuzumab versus that same dual therapy combined with placebo, in 808 patients with HER2+ metastatic or locally recurrent unresectable breast cancer.

A total of 808 patients were randomised: group with pertuzumab + trastuzumab + docetaxel (n = 402), group with placebo + trastuzumab + docetaxel (n = 406).
The median age of the patients was 54 years. About half the patients in each treatment group had hormone-receptor positive disease (defined as oestrogen-receptor positive and/or progesterone-receptor positive) and about half had also received prior adjuvant or neoadjuvant treatment. Most of these patients had previously received anthracyclines and 11% of all patients had previously received trastuzumab.

The primary efficacy endpoint was progression-free survival as evaluated by an independent review committee and defined as the time from the date of randomisation to the date of disease progression or death from any cause.

On the date of the final analysis of the primary efficacy endpoint, median progression-free survival was 18.5 months in the PERJETA group versus 12.4 months in the comparator group, i.e. a gain in absolute terms of 6.1 months in favor of the PERJETA group (HR = 0.62, 95% CI [0.51; 0.75], p<0.0001).

Secondary endpoint results:
At the final analysis of the primary efficacy endpoint, an interim analysis was made of overall survival. There was no difference between the two groups, as median overall survival was not affected in either of the two groups (HR = 0.64, p value above the threshold set at 0.0012).
A second unscheduled interim analysis was performed one year later with 69% of the events required for the final analysis (267 deaths out of the 385 required). It suggested a median overall survival of 37.6 months (95% CI [34; NA]) in the comparator group and this not being achieved in the pertuzumab group (95% CI [42; NA); (HR = 0.66, 95% CI [0.52; 0.84], p=0.0008.
At the end of this interim analysis, the code was broken and the patients in the comparison group were allowed to receive PERJETA (46 patients out of the 55 still receiving the study treatment). Consequently, the data from the final analysis of overall survival for this study will not be known.

The percentage objective response rate (complete or partial response) was 80.2% (of which 5.5% were complete response) in the pertuzumab group versus 69.3% (of which 4.2% were complete response) in the placebo group.
The median duration of the objective response was 87.6 weeks in the pertuzumab group versus 33.5 weeks in the placebo group.
The quality-of-life analysis did not show any difference between the two groups.

The Committee notes that
- only 11% of the patients had received trastuzumab in an adjuvant or neoadjuvant setting, which is the usual validated therapeutic use,
- the recommended dosage of docetaxel (75 mg/m²) is low compared with the one usually prescribed (100 mg/m²), even if the option of increasing doses up to 100 mg/m² was permitted in the protocol. It therefore cannot be ruled out that the result observed in the comparison group is not optimal by comparison with the current treatment standard and that the incidence of adverse events is not underestimated.

The main adverse events observed on the combination of pertuzumab with docetaxel and trastuzumab were: febrile neutropenia (grade 3 or more: 13.0% versus 7.3% in the placebo group) and diarrhoea (grade 3 or more: 7.9% versus 5.0% in the comparator group).

8.4 Programme of studies

8.4.1 Risk management plan (RMP):

A risk management plan (RMP) has been prepared on the basis of the preclinical and clinical data. It concerns the identified risks, the potential risks and missing information.

Identified risks

- exacerbation of drug-induced neutropenia linked to docetaxel
- reaction to the infusion
- hypersensitivity and/or anaphylaxis
- congestive heart failure
- mucositis
- diarrhoea of a grade greater than or equal to 3
- interstitial lung disease.

Potential risks

- oligohydramnios

Missing Information

- data for patients aged 75 years and older
- data for pregnant and lactating women
- effects on fertility
- safety profile in men
- data for patients with heart failure or hepatic or renal impairment
- loss of efficacy linked to immunogenicity.

The pharmacovigilance plan includes a routine pharmacovigilance plan and cumulative data from twice-yearly update reports. It also makes provision for the collection of cardiac safety data in the context of five clinical studies, a pregnancy prevention programme, the collection and updating of immunogenicity data in clinical trials, both those in progress and future ones, and the establishment of a checklist for healthcare professionals for cases of interstitial lung disease.

The risk minimisation plan comprises information on healthcare professionals by means of the SPC and on patients by means of the patient information leaflet.

8.4.2 Obligation to put in place post-Marketing Authorisation measures

The company is obliged to supply the EMA with the results of two ongoing clinical studies.

PHEREXA study (MO22324):

Randomised phase II clinical study comparing the combination of trastuzumab + capecitabine with or without pertuzumab in patients with HER2+ metastatic breast cancer which has progressed after a first-line treatment containing trastuzumab with metastatic disease (end date: March 2015).

PERUSE study (MO28047):

Non-comparative clinical study of pertuzumab in combination with trastuzumab and a taxane as first-line treatment in patients with advanced HER2+ metastatic or locally recurrent breast cancer (end date: December 2016).

8.4.3 Ongoing development to obtain extensions of indication

The company has said that two clinical studies that could lead to extensions of indication in the medium term are currently ongoing.

MARIANNE study:

Double-blind, randomised, multicentre phase III international study evaluating the efficacy and safety of pertuzumab in combination with TDM-1, in first-line treatment of HER2-positive metastatic breast cancer. About 1092 patients were included and randomised, between July 2010 and May 2012, to three treatment groups (Arm A: trastuzumab + taxane; Arm B: T-DM1+ pertuzumab; Arm C: T-DM1 + placebo). The primary efficacy endpoint of this study is progression-free survival, evaluated by an independent committee, and safety. The other endpoints evaluated are the objective response rate, overall survival, survival at 1 and 2 years, progression-free survival and the objective response rate evaluated by the investigators, the clinical benefit and the duration of the response (results expected for 2014).

APHINITY study:

Double-blind, randomised, multicentre, international phase III clinical study evaluating the efficacy and safety of a protocol combining pertuzumab with trastuzumab and with chemotherapy by comparison with a protocol combining a placebo with trastuzumab and with chemotherapy in the adjuvant treatment of patients with HER2-positive breast cancer. About 4800 patients will be included and randomised. The anti-HER2 treatment will be continued for 1 year and patients will be followed up for 10 years. The primary efficacy endpoint of this study is survival without invasive disease. The other endpoints evaluated include survival without invasive disease including a second cancer other than breast cancer, progression-free survival, overall survival, recurrence-free interval, distant recurrence-free interval, cardiac safety, overall safety and quality of life (end of inclusions scheduled for December 2013).

9 THERAPEUTIC USE

The first-line treatment of metastatic breast cancer depends mainly on the clear interval between the adjuvant treatment and the first-line metastatic cancer, the presence or absence of hormonal receptors and/or overexpression of HER2, and on the site of the metastatic localisations. Thus, in the absence of poor prognostic factors, for example in the case of isolated bone localisations and in the presence of hormone receptors, the first-line treatment is hormone therapy. In the presence of poor prognostic factors (e.g. progressive abdominal disease), the first-line treatment is chemotherapy. If a poor prognostic factor is combined with the presence of hormone receptors, chemotherapy and hormone therapy can be used sequentially.
In the case of tumour overexpression of HER2, the recommended first-line treatment is trastuzumab, combined with a taxane (paclitaxel or docetaxel), irrespective of hormone status.
In view of the conventional treatment and taking account of the demonstrated benefit for progression-free survival, 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[7] rate the addition of pertuzumab to dual therapy with trastuzumab and a taxane as an option to be preferred to dual therapy.

[7] National Comprehensive Cancer Network Breast cancer (NCCN 2013)
http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

10 TRANSPARENCY COMMITTEE CONCLUSIONS

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

10.1 Actual benefit

- HER2-positive metastatic or locally recurrent unresectable breast cancer is a serious, life-threatening disease.
- This proprietary medicinal product is a specific, curative treatment for breast cancer.
- The efficacy/adverse effects ratio for PERJETA, in combination with trastuzumab and docetaxel, is substantial.
- It is a first-line therapy.
- There is a treatment alternative to PERJETA, in combination with trastuzumab and docetaxel (trastuzumab, in combination with docetaxel or paclitaxel).

- Public health benefit:

In France, the incidence of breast cancer is estimated to be about 53,000 new cases a year (InVS projections 2011[8]). It is the number one cancer in terms of frequency, accounting by itself for 33% of new cases of cancer in women[9].

It is also the number one cause of cancer death in women, with an estimated number of close to 11,500 deaths in 2011[1], which is 18.3% of women's deaths from cancer.

The incidence of breast cancer in France increased substantially and constantly between 1980 and 2005 with an incidence level (standardised for the world's population) which has almost doubled, rising from 56.8 to 101.5 cases per 100,000 women. Mortality, which had remained stable since 1980, has decreased since 1995, with the mortality rate (standardised for the world's population) falling from 19.8 in 1995 to 17.7 in 2005[10].

About 15% of breast cancers are accompanied by overexpression of the HER2 protein which is associated with a more unfavourable prognosis[8].

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 of the subpopulation of patients with HER2+ metastatic or locally recurrent unresectable breast cancer likely to receive the combination of HERCEPTIN + PERJETA remains moderate because of the greater associated 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 2009-2013, Plan to improve the quality of life of patients with chronic diseases 2007-2011).

In view of the available results from the CLEOPATRA study, a phase III controlled study versus the current standard treatment (trastuzumab combined with docetaxel), as regards radiological progression-free survival (an absolute gain of 6.1 months) and overall survival (HR = 0.62 [0.51; 0.75], although this result was suggested by a second interim analysis not provided for in the protocol), pertuzumab combined with trastuzumab and docetaxel can be expected to have a substantial impact in terms of the reduction in morbidity and mortality. However, the size of the expected impact on the reduction in mortality is still difficult to assess since median overall survival had not been achieved at the time of the second interim analysis.

[8] Lyon civil hospices / Health Monitoring Institute / National Cancer Institute / Francim / National Institute of Health and Medical Research. Projections of the incidence and mortality from cancer in France in 2011. Technical report. June 2011. http://www.invs.sante.fr/surveillance/cancers [Retrieved 27.06.2013].

[9] Inca. Breast cancer: 2012 update. September 2012. InCa

[10] A. Belot *et al*. Cancer incidence and mortality in France over the period 1980-2005. Rev Épidemiol Santé Publique. 2008 Jun; 56(3): 159-75.

In addition, the treatment is not expected to have any impact on patients' quality of life evaluated using the FACT-B questionnaire specific to the disease (physical and functional condition, patient testimony). In fact, the number of patients with an increase of 5 points in the FACT-B TOI-PFB score did not differ significantly between the two treatment arms (HR = 0.97 [0.81; 1.16]) and the change in the ECOG score remained stable between the two arms.
However, the transferability to clinical practice of the results presented is not assured, firstly due to the characteristics of the patients included (good general condition, small proportion of patients who received trastuzumab treatment in an adjuvant setting) compared with the French population which is little represented in the trial (n = 24) and secondly because of the restrictive nature of the trial's non-inclusion criteria. In addition, a possible difference from the way this treatment is used in the current indications for trastuzumab, particularly in a neoadjuvant setting, cannot be ruled out.

Taking account of these points, the Committee considers that the actual benefit of PERJETA is substantial in the indication and at the dosages in the Marketing Authorisation.

10.2 Improvement in actual benefit (IAB)

PERJETA, in combination with trastuzumab and docetaxel, provides a moderate improvement in actual benefit (level III) in the management of HER2-positive metastatic or locally recurrent unresectable breast cancer, not previously treated with anti-HER2 therapy or chemotherapy for the metastatic disease.

10.3 Target population

The target population for PERJETA consists of adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for the metastatic disease.

Treatment of HER2-positive cancers first diagnosed in the metastatic stage

The incidence of breast cancer in women in France is estimated at 54,200 cases in 2012[11]. The proportion of breast cancers first diagnosed in the metastatic stage is estimated to be 5% of all diagnosed cases[12], i.e. about 2710 patients a year. Overexpression of HER2 affects 28 to 30% of patients with breast cancer diagnosed at an advanced stage in France[13,14], i.e. about 750 patients first diagnosed in the metastatic stage in 2012.

Treatment of HER2-positive breast cancer with a recurrence after adjuvant treatment (metastatic or local, unresectable recurrence)

The company proposed a model with a time horizon of 10 years (the probability of a recurrence beyond that period being regarded as zero), including, for each year, data on the incidence of breast cancer[15], the proportion of breast cancers diagnosed early (estimated at 95% of all cases

[11] InVS (Health Monitoring Institute) and INCa (National Cancer Institute). Projections of the incidence and mortality from cancer in France in 2011 – Technical report. July 2011.

[12] INCa (National Cancer Institute). Expected survival of patients with cancer in France: status report. April 2010

[13] Kantar Health. Barometer carried out on 253 patients with HER2-positive metastatic breast cancer currently treated with trastuzumab/chemotherapy (outside clinical studies), of which 149 in first line treatment. June 2011.

[14] Press MF, Slamon DJ, Flom KJ, *et al*. Evaluation of HER-2/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):3095-105.

[15] INCa (National Cancer Institute). The cancer situation in France in 2012. January 2013.

diagnosed)[11], among them the proportion of HER2-positive breast cancers (estimated at 12.4% of breast cancers diagnosed early)[16], and of those the proportion of breast cancers that recurred after adjuvant treatment in 2012 (estimated from the retrospective data of cohorts of patients treated with trastuzumab[17] or not[18] from the management of their primary tumour). According to this model, about 1500 patients had a recurrence in 2012 in France. In addition, there are no data that can be used to estimate precisely the proportions of patients with a metastatic or local, unresectable recurrence.

The target population for PERJETA could be estimated at about 2000 patients a year, including 750 patients first diagnosed in a metastatic stage and 1250 patients with a recurrence after an adjuvant treatment (metastatic or local, unresectable recurrence).

11 TRANSPARENCY COMMITTEE RECOMMENDATIONS

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

- **Packaging**: Appropriate for the prescription conditions.

16 Kanthar Health. PrevHER (Assessment of the prevalence of HER2 in breast cancer in a neoadjuvant setting by pathologists) – National Report. November 2012.

17 Romond EH, Perez EA, Bryant J, *et al*. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005;353(16):1673-84.

18 Paik S, Bryant J, Tan-Chiu E, *et al*. HER2 and choice of adjuvant chemotherapy for invasive breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-15. J Natl Cancer Inst. 2000;92(24):1991-8.