Horizon Scanning in Oncology

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1 Drug description

Generic/Brand name/ATC code:

Pertuzumab/Omnitarg ®, Perjeta®/L01XC13

Developer/Company:

Hoffmann – La Roche

Description:

pertuzumab, a monoclonal antibody, blocks hetero- and homodimerisation of HER2

Pertuzumab, a recombinant humanized monoclonal antibody, blocks ligand-initiated intracellular signalling (two major pathways: mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K)) by targeting the extracellular dimerization domain of the human epidermal growth factor receptor 2 protein (HER2). By inhibiting receptor protein dimerization (i.e. homo- and heterodimerization) the activation of HER signalling pathways is interrupted. As a consequence cell growth is inhibited and apoptosis induced [1].

Due to the unique mechanism of action an enhanced effect on tumour inhibition is expected of pertuzumab in comparison to trastuzumab alone, another HER2 targeted therapy [2] .

intravenous administration

The pertuzumab dosage used in clinical trials is 840 mg initially administered as a 60-minute intravenous infusion, followed every 3 weeks thereafter by 420 mg administered as a 30 to 60 minute intravenous infusion [3]. Prior to administration, HER2 positivity needs to be confirmed.

2 Indication

Pertuzumab is indicated for the first-line therapy of metastatic HER2+ metastatic breast cancer (BC).

3 Current regulatory status

in Europe: market application submitted

Pertuzumab has not been licensed yet by the European Medicines Agency (EMA), but market application has been submitted and the drug is currently under evaluation by the Committee for Medicinal Products for Human Use [4].

in the U.S. already licensed for 1st line therapy of metastatic breast cancer

In the U.S., however, market authorization was granted for pertuzumab by the Food and Drug Administration (FDA) in June 2012 [3]

- in combination with trastuzumab and docetaxel for the treatment of patients with HER2+ metastatic BC who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

4 Burden of disease

prognostic factors

In 2009, about 5,000 women were newly diagnosed with and 1,600 died of BC in Austria [5] making BC the most common type of cancer in females. More than 80% of all cases occur in women aged over 50 years [6]. Risk factors associated with the development of BC are age, nulliparity, early menarche, genetic factors (e.g. genetic mutations such as of the BRCA1, BRCA2) or family history [7, 8]. Prognostic factors are age, menopausal status, tumour stage, histology and hormone receptor status [7].

TNM staging informs management decisions determines prognosis

The Tumor Node Metastasis (TNM) staging classification is used to determine the disease stage. This staging system reflects the extent of disease which is used to inform treatment management decisions and to determine prognosis. Besides the primary tumour, the extent to which the regional lymph nodes are involved and the absence or presence of distant metastases are taken into account, leading to four main stage groupings (stage I to IV) [7]. Metastatic disease corresponds to stage IV. Metastases are most common in the bones, liver or the lungs [7] but metastases in the brain have been reported to be more common in patients with HER2+ metastatic BC previously treated with trastuzumab [9-11]. Besides a higher affinity of HER2+ tumour cells for the central nervous system, occurrence of brain metastases in this setting might also be caused due to a better control of extra-cranial disease and thus by a longer overall survival [11].

metastatic disease in about 10% of women

HER2 over-expression in about 20% of 25% of all women diagnosed with BC

Besides the TNM staging, important factors to determine the best management strategy are oestrogen-receptor (ER) and progesterone-receptor (PR) status in the tumour tissue, HER2 status, menopausal status, and the general health of the patient [8]. Predictive factors for response to hormone therapy are a long relapse-free interval, isolated bone and soft tissue involvement, and prior response to endocrine therapy. ER+/PR+ tumours are most likely to respond to hormone therapy, but even of them, up to 25% are refractory to hormone therapy in the first instance and nearly all tumours become refractory at one point [7].

ER/PR, HER and menopausal status important factors for choosing management strategy

Metastatic disease at diagnosis is present in less than 10% of women [7] and evidence suggests that 20% to 25% of all women diagnosed with BC have tumours over-expressing HER2 [12-14]. Due to various methods for deter-

mining HER2 status it might be the case though that these numbers are slightly overestimated and that rather 15-20% overexpress HER2 [15]. However, applying these estimates to an Austrian context would result in about 100 women with HER2+ advanced metastatic BC. Median survival of women with metastatic BC is about 18 to 24 months [8] and only 5 - 10% of women survive five or more years [7].

tumours over-expressing HER2 more aggressive, reduced OS, shortened time to relapse

BC with amplification and over-expression of HER2 are usually more aggressive [7, 14] corresponding to a reduced overall survival (OS) and a shortened time to relapse [13] but HER2 status is also used to predict response to drugs such as trastuzumab or lapatinib [7]. Additionally, primary resistance to endocrine therapy might be associated with HER2 over-expression due to a cross-talk between ErbB1/ErbB2 and ER pathways and a link between responsiveness to chemotherapy and HER2 over-expression might exist [7].

HER2 status for predicting response to trastuzumab or lapatinib therapy

5 Current treatment

Choice of therapy for BC is based on numerous factors like tumour histology, axillary node status, hormone and HER2 receptor status, presence of metastases as well as patient characteristics including menopausal status, age and co-morbidities [12, 16].

choice of therapy influenced by hormone status and HER2 status, metastases, histology

Therapy of HER2+ metastatic BC usually aims at symptom palliation, improvement of quality-of-life and extension of life [8]. Even though surgery and radiation therapy are indicated for symptom palliation in selected patients, the mainstay of therapy is systemic treatment. Treatment options for the first-line therapy of HER2+ metastatic BC are:

for metastatic BC

- Chemotherapy: for example, anthracyclines or taxanes (e.g. docetaxel) either as single agent or as combination chemotherapy or in addition to molecular targeted therapies [12].

chemotherapy

- Endocrine therapy: for example tamoxifen, anastrozole or letrozole for women with HR+ tumours.

endocrine therapy

- Targeted therapies:

molecular targeted therapies

  - HER2 targeted therapies:
    - Trastuzumab: preferably in combination with single-agent chemotherapy (e.g. paclitaxel, carboplatin, docetaxel) or endocrine therapy (in the case of HR+ tumours) but also as single-agent.
    - Lapatinib in combination with chemotherapy (i.e. capecitabine) or in combination with endocrine therapy for HR+ tumours [7, 8, 17].
  - Vascular endothelial growth factor receptor inhibitors:
    - Bevacizumab: in combination with chemotherapeutics such as paclitaxel or capecitabine [7, 8, 12, 17].

trastuzumab + chemotherapy commonly used regimen for HER2+ metastatic BC

However, for asymptomatic HR+, HER2+ women with slowly progressive disease, and without significant visceral involvement, HER2 targeted therapies in combination with endocrine therapy are recommended. Otherwise, HER2 targeted therapies with single-agent chemotherapy (e.g. paclitaxel) are indicated. The same regimen is also recommended for HR-, HER2+ patients [7, 8, 17, 18].

6 Evidence

only 1 phase III trial included

A literature search (Ovid Medline, Embase, Cochrane Library, CRD Database) conducted on the 12th of July yielded 161 references. Of these, only one phase III trial [19] was included.

6.1 Efficacy and safety - Phase III studies

Table 1: Summary of efficacy

Study title Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer [19-21]		
Study identifier	ClinicalTrials.gov number: NCT00567190, CLEOPATRA trial (=CLinical Evaluation Of Pertuzumab And TRAstuzumab), Other Study ID Numbers: TOC4129g, WO20698	
Design	randomized, double-blind, placebo-controlled, phase 3, multi-centre (204 centres in 25 countries)	
	Duration	Enrolment: February 2008 – July 2010 Median follow-up: 19.3 months Cut-off date for final analysis: May 2011
Hypothesis	Superiority	
Funding	Hoffmann-La Roche	
Treatment groups	Intervention (n = 402)	8mg/kg trastuzumab followed by maintenance dose of 6mg/kg every 3 weeks until disease progression (investigator assessed) or unacceptable toxic effects + every 3 weeks docetaxel at a starting dose of 75mg/m² for ≥6 cycles + pertuzumab at a loading dose of 840mg, followed by 420 mg every 3 weeks until progression or unacceptable toxic effects
	Control (n = 406)	8mg/kg trastuzumab followed by maintenance dose of 6mg/kg every 3 weeks until disease progression (investigator assessed) or unacceptable toxic effects + every 3 weeks docetaxel at a starting dose of 75mg/m² for ≥6 cycles + placebo

Endpoints and definitions	Progression-free survival (assessed by an independent review facility) *(primary outcome)*	PFS- IRF	time from randomization to the first documented radiographical progressive disease, as determined by the independent review facility using current RECIST [22], or death from any cause, whichever occurs first
	Progression-free survival (investigator assessed)	PFS	the time from randomization to the first documented radiographic progressive disease, as determined by the investigator using current RECIST [22], or death from any cause, whichever comes first
	Overall survival	OS	time from the date of randomization to the date of death from any cause
	Objective response rate	ORR	CR or PR determined by the IRF using current RECIST [22] on two consecutive occasions ≥4 weeks apart.
	Duration of objective response [20]	DOR	duration of response is defined as the period from the date of initial confirmed PR or CR until the date of progressive disease or death from any cause. Tumour responses will be based on the IRF evaluations using current RECIST [22]
	Time to symptom progression [20]	-	time from randomization to the first symptom progression (defined as a decrease of five points in the FACT Trial Outcome Index - Physical Functional Breast)

Results and analysis

Analysis description	It was estimated that the study would have 80% power to detect a 33% improvement in median progression- free survival in the pertuzumab group (hazard ratio, 0.75) at a two-sided significance level of 5%. A pre-specified interim analysis of overall survival was performed at the time of the primary analysis of independently assessed progression-free survival.		
Analysis population	Inclusion	locally recurrent, unresectable, or metastatic HER2+ breast cancer; HER2+ status (centrally confirmed by immunohistochemistry or FISH; measurable disease or non-measurable disease; tumour hormone-receptor status was determined locally; ≥18 years; left ventricular ejection fraction of ≥50%; ECOG-PS ≤0 or 1; patients may have received one hormonal treatment for metastatic breast cancer adjuvant or neoadjuvant chemotherapy with or without trastuzumab before randomization	
	Exclusion	previous therapy for metastatic breast cancer (other than that described above), central nervous system metastases, prior exposure to a cumulative dose of doxorubicin that exceeded 360 mg per square meter of body-surface area or its equivalent, a previous decline in the left ventricular ejection fraction to less than 50% during or after prior trastuzumab therapy	
	Characteristics	*C*	*I*
	Females, %	100	100
	Age, yrs Median (range)	54 (27 - 89)	54 (22 - 82)
	Race or ethnic group, % White Asian Black Other	 58 33 5 4	 61 32 3 5

	ECOG PS, %		
	0	61	68
	1	39	31
	≥2	0	1
	Disease type at screening, %		
	Nonvisceral	22	22
	Visceral	78	78
	Hormone-receptor status, %		
	ER+, PR+, or both	49	47
	ER- and PR-	48	53
	Unknown	3	0
	HER2 status, assessed by IHC, %		
	0 or 1+	1	1
	2+	8	12
	3+	91	87
	HER2 status, assessed by FISH, %		
	Positive	94	96
	Negative	1	0
	Data not available	5	4
	Prior adjuvant or neoadjuvant chemotherapy , %		
	No	53	54
	Yes	47	46
	Anthracycline	40	37
	Hormone	24	26
	Taxane	23	23
	Trastuzumab	10	12
Descriptive statistics and estimated variability	*Treatment group (overall)*	*Control*	*Intervention*
	Number of subjects	N = 406	N = 402
	PFS (independent)		
	Median, months	12.4	18.5
	95%CI	NA	NA
	PFS (investigator)		
	Median, months	12.4	18.5
	95%CI	NA	NA
	Overall survival, % of patients with event[1]	23.6	17.2
	ORR, %	69.3[2]	80.2[2]
	CR	4.2	5.5
	PR	65.2	74.6
	SD	20.8	14.6
	PD	8.3	3.8

[1] interim OS analysis was performed after 165 events had occurred (= 43% of the prespecified total number for the final analysis)

[2] P=0.001 for difference in response rates

	DOR, months [23]	12.5	20.2
	Time to symptom progression, weeks [21] Median Probability	 18.4 59.5	 18.3 56.7
	Subgroup analyses	*Control*	*Intervention*
	Prior trastuzumab therapy	N = 41	N =47
	PFS, months	10.4	16.9
	Prior therapy without trastuzumab	N = 151	N = 137
	PFS, months	12.6	21.6
Effect estimate per comparison	*Overall population*		*Intervention vs Control*
	PFS (independent)	HR	0.62
		95%CI	0.51 – 0.75
		P value	<0.001
	PFS (investigator)	HR	0.65
		95%CI	0.54 – 0.78
		P value	<0.001
	OS[1]	HR	0.64
		95%CI	0.47 – 0.88
		P value	0.005
	Time to symptom progression	HR	0.97
		95%CI	NA
		P value	0.72
	Subgroup analyses		
	PFS (Prior trastuzumab therapy)	HR	0.62
		95%CI	0.35 – 1.07
		P value	NA
	PFS (Prior therapy without trastuzumab)	HR	0.60
		95%CI	0.43 – 0.83
		P value	NA
	PFS (ER+, PR+, or both)	HR	0.72
		95%CI	0.55 – 0.95
		P value	NA
	PFS (ER-, PR-, or both)	HR	0.55
		95%CI	0.42 – 0.72
		P value	NA

Abbreviations: TOI-PFB = Trial Outcome Index - Physical Functional Breast, FACT-B = Functional Assessment of Cancer Therapy-Breast, IRF = Independent Review Facility, HR = Hazard ratio, CI = Confidence interval, CR = Complete response, PR = Partial response, SD = Stable disease, PP = progressive disease, ECOG = Eastern Cooperative Oncology Group, PS = Performance status, FISH = fluorescence in situ hybridization, IHC = Immunohistochemistry, ER = Oestrogen receptor, PR = Progesterone receptor

Table 2: most frequent adverse events

CLEOPATRA trial [19]			
Grade (according to CTCAE 3.0)	**Outcome, n (%)**	**C** (n= 397)	**I** (n=407)
All grades (in ≥25% of patients)	Diarrhoea	184 (46.3)	272 (66.8)
	Alopecia	240 (60.5)	248 (60.9)
	Neutropenia	197 (49.6)	215 (52.8)
	Nausea	165 (41.6)	172 (42.3)
	Fatigue	146 (36.8)	153 (37.6)
	Rash	96 (24.2)	137 (33.7)
	Decreased appetite	105 (26.4)	119 (29.2)
	Mucosal inflammation	79 (19.9)	113 (27.8)
	Asthenia	120 (30.2)	106 (26.0)
	Peripheral oedema	119 (30.0)	94 (23.1)
	Constipation	99 (24.9)	61 (15.0)
Grade ≥3 (in ≥5% of patients)	Neutropenia	182 (45.8)	199 (48.9)
	Febrile neutropenia	30 (7.6)	56 (13.8)
	Leukopenia	58 (14.6)	50 (12.3)
	Diarrhoea	20 (5.0)	32 (7.9)
Other	Deaths due to AE	10 (2.5)	8 (2.0)
	AEs leading to treatment discontinuation [23]	NA (5.3)	NA (6.1)

CLEOPATRA trial enrolled 808 patients who had not been treated for metastatic BC

The CLEOPATRA trial, a phase III trial, enrolled 808 patients with HER2+ metastatic BC who had not been treated for their metastatic disease. The combination of trastuzumab and docetaxel in addition to pertuzumab was compared to placebo with trastuzumab and docetaxel. About half of the patients enrolled were HR- and about 50% had received prior adjuvant or neoadjuvant therapy. However, only about 10% of patients had received prior trastuzumab therapy.

+6.1 months in PFS, trend towards improved OS, better response rates

Independently assessed progression-free survival (PFS), the primary outcome, yielded a gain in median PFS of 6.1 months (HR = 0.62, $p<0.001$) for patients treated with pertuzumab. Similar results were also found in subgroups, including, for example, prior adjuvant/neoadjuvant chemotherapy, HR+ as well as HR- receptor-status. Even though the benefit of pertuzumab therapy was preserved in the subgroup of patients previously treated with trastuzumab, this result was not statistically significant. Also, the difference in median PFS was higher in patients not previously treated with trastuzumab (9 months) than in patients previously treated with trastuzumab (6.5 months). Preliminary results (data not mature yet) for OS showed that fewer patients had died in the pertuzumab group than in the control group (I 17% vs C 24%). The overall response rate was 80% in the pertuzumab group and 69% in the control group, in both groups primarily driven by partial responses. Furthermore, with a median number of 15 treatment cycles per pa-

tient in the control group and 18 in the pertuzumab group, duration of response was longer in the intervention arm.

Exploratory results for quality-of-life (only available as abstract) indicated similar outcomes for both groups, since 60% experienced deterioration of health-related quality-of-life in the pertuzumab group and 57% in the placebo group [21].

only exploratory results for QoL – similar results for pertuzumab in comparison to placebo

The most common adverse event (AE) of any grade in the pertuzumab group was diarrhoea (I 67% vs C 46%). Other AEs more frequent in the pertuzumab group were rash or mucosal inflammation, occurring with a difference of about 9% points. Grade ≥3 AEs with an incidence of at least 2% points in the pertuzumab group comprised neutropenia, febrile neutropenia and diarrhoea. Left ventricular systolic dysfunction, a side-effect associated with trastuzumab + docetaxel therapy, occurred less often in the pertuzumab group (I 4.4% vs C 8.3%).

higher grade AEs: (febrile) neutropenia, diarrhoea

6.2 Efficacy and safety - further studies

No further studies were found for the indication investigated.

7 Estimated costs

No cost estimates are available for Austria. In the U.S. though, estimated monthly treatment costs for Perjeta® are $5,900 [24]. Assuming an 18 months therapy, total costs would add up to $106,500. Since the drug has been licensed in the U.S. in combination with trastuzumab, additional costs accrue (~$4,500 per month). Thus, the calculated costs for 18 months, which was duration of treatment in the phase III study, are approximately $188,000 (≈ € 153,500), not taking into account expenditures for chemotherapy or for any supportive therapies. However, it is likely that the price is lower in Austria.

no price available for Austria

estimates from the U.S.: monthly: costs $ 5,900, overall: $188,000

8 On-going research

On ClinicalTrial.gov 4 phase III studies on pertuzumab for metastatic BC were identified.

four phase III trials for metastatic BC

NCT01120184 (MARIANNE trial): will evaluate the efficacy and safety of trastuzumab emtansine (T-DM1) with pertuzumab or trastuzumab emtansine (T-DM1) with pertuzumab-placebo versus the combination of trastuzumab plus taxane in patients with HER2+ progressive or recurrent locally advanced or previously untreated metastatic BC (estimated study completion date: April 2016).

NCT01572038 (PERUSE trial): will evaluate the safety and efficacy of pertuzumab in combination with trastuzumab and a taxane in first-line treat-

ment in patients with metastatic or locally recurrent HER2+ BC (estimated study completion date: April 2016).

NCT01026142: will evaluate the efficacy and safety of a combination of trastuzumab and capecitabine with or without pertuzumab in patients with HER2+ metastatic BC. The study population consists of female patients, whose disease has progressed during or following previous trastuzumab therapy for metastatic disease (estimated study completion date: August 2017).

NCT01358877: will assess the safety and efficacy of pertuzumab in addition to chemotherapy plus trastuzumab as adjuvant therapy in patients with operable HER2+ primary BC (estimated study completion date: August 2024).

pertuzumab under investigation for several other types of cancer

In addition, several phase II trials assess, besides BC, the efficacy and safety of pertuzumab for many other cancers such as ovarian cancer, prostate cancer, gastric cancer or neuroendocrine cancers.

No further phase III trials were identified on www.clinicaltrialsregister.eu.

9 Commentary

drug resistance to trastuzumab - rational for combining pertuzumab with another HER2 targeted therapy

The rational for testing trastuzumab + chemotherapy, the standard regimen for the subgroup of women with HER2+ BC, with another HER2 targeted agent results from the fact that nearly all tumours progress on trastuzumab therapy eventually [25]. Besides non-response in the first place, (in about 40% of all patients [2, 9]), acquired drug resistance is held accountable [25]. Thus, combining trastuzumab with pertuzumab, a drug with a complementary mechanism of action, might enhance tumour inhibition [2, 26] and might be active even in trastuzumab resistant tumours [27]. The dual HER2 targeted approach, in contrast to pertuzumab only, was chosen since some evidence suggested that this combination yields better results than a single monoclonal approach [28].

Pertuzumab in combination with trastuzumab + docetaxel was licensed in the U.S. in July 2012 for patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. In Europe, market application has been submitted.

licensed in the U.S. under priority review programme

The FDA's decision on granting market authorisation in the first-line setting was based on the results of the CLEOPATRA trial, a phase III study comprising 808 patients overall [19]. The approval took place under FDA's priority review programme, a programme intended for drugs which offer major advances in treatment. Within this trial, PFS, the primary outcome, was improved by 6.1 months in comparison to placebo and trastuzumab + docetaxel, leading to a risk reduction of 38%. Mature results for OS are not yet available, but at the time of the interim analysis there was a difference of borderline significance. Response rates were better in the pertuzumab arm. In terms of AEs, the most common one of higher grade (i.e. grade ≥3) was neutropenia in both groups (I 49% vs C 46%). Other, more frequently observed AEs of higher grades in the pertuzumab group were febrile neutropenia and diarrhoea. Left ventricular systolic dysfunction, a side-effect associated with trastuzumab therapy, was less frequent in the pertuzumab arm

than in the placebo arm. Not (yet?) fully published results for quality-of-life suggest that pertuzumab does not exert an additional detrimental effect.

only 10% of patients in the CLEOPATRA trial had been treated with (neo-)adjuvant trastuzumab, a commonly used regimen in the adjuvant setting

study population differs to patients who can be expected in clinical practice

However, even though the licensed indication in the U.S. excludes patients who had been treated with trastuzumab for their *metastatic* disease, only the minority of patients (i.e. 10%) enrolled in the CLEOPATRA trial had been previously treated with *(neo-)adjuvant* trastuzumab, a regimen commonly used for HER2+ BC in the adjuvant setting. Thus, the study population differs to those patients who will be treated in daily practice. Even though a pre-planned subgroup analysis (n=88) for these "real" patients demonstrated a risk reduction (but not statistically significant) in progression comparable to that of the overall study population, further research is indicated, to obtain a more precise estimate of the treatment effect in trastuzumab pre-treated patients. This is of further importance since expiration of the patent of trastuzumab in mid 2014 would result in reduced treatment costs if addition of pertuzumab to trastuzumab offers little or no additional benefit in this group of patients. Furthermore, despite the fact that HR+ patients also profited from pertuzumab therapy in the CLEOPATRA trial, the benefit was less pronounced than in HR- patients or in the overall population.

also under investigation for other settings and in combination with other drugs

determining most beneficial combinations and sequencing is needed

Since pertuzumab is also tested in different clinical settings, (e.g. for HER2+ early, inflammatory or locally advanced BC [29]) or in combination with other agents (e.g. trastuzumab emtansine or capecitabine [2]) and due to the fact that several other new drugs are under investigation for the treatment of metastatic BC (e.g. neratinib, afatinib, rapamycin [30]), determination of the most beneficial agents and combinations as well as characterization of selection criteria and identification of the ideal sequencing of available treatment options are needed to optimize treatment of BC.

high costs in addition to expenditures for trastuzumab + chemotherapy

Due to a clinically relevant gain in PFS [31] and tolerable side-effects, the combination of pertuzumab + trastuzumab + docetaxel has already been incorporated into some guidelines [12]. However, even though no cost estimates are available for Austria yet, evidence indicates that pertuzumab will be a costly drug [24], costs which have to be added to those of trastuzumab and docetaxel.

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