NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pertuzumab in combination with trastuzumab and docetaxel for treating HER2-positive metastatic or locally recurrent unresectable breast cancer [ID523]

Committee Papers – Appraisal Committee Meeting 4 (09/05/17)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pertuzumab in combination with trastuzumab and docetaxel for treating HER2-positive metastatic or locally recurrent unresectable breast cancer [ID523]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Perjeta metastatic breast cancer ID523

1. 'End-of-Life' Criteria

- The life expectancy of HER2+ mBC patients treated with chemotherapy alone in the first line is less than 2 years.
- The combination of Perjeta and Herceptin offers a dramatic median extension to life of >15 months, which far exceeds the extension to life of 3 months specified by the end-of-life criteria.
- As such, assessment of Perjeta according to the end-of-life criteria should be considered in light of such a dramatic improvement in OS in a condition with a comparatively poor prognosis.

The life expectancy of patients receiving a first-line treatment for mBC now exceeds 24 months when treated with the most relevant comparator for Perjeta, Herceptin plus taxane; this currently precludes Perjeta being considered under the strict end-of-life criteria.

Recently a published systematic review of Phase III studies reported median OS ranging from 20.3 (95% CI [NR]) to 20.5 month (95% CI [NR]) for HER2+ first-line mBC patients treated with chemotherapy alone (Mendes et al. 2015). This clearly indicates that HER2+ mBC has the life expectancy of an end-of-life condition in the first-line when treated with chemotherapy alone.

The first randomised controlled trial assessing Herceptin in combination with chemotherapy reported a median overall survival of 25.1 months (Slamon et al. 2001, Mendes et al. 2015). Subsequently systematic review has reported OS ranging from 28.9 (95% CI [NR]) to 37.1(95% CI [32.6, 43.6]) months patients receiving first-line treatment with Herceptin plus paclitaxel or docetaxel respectively (Valero et al. 2011, Baselga et al. 2014, Mendes et al. 2015).

In addition, a retrospective analysis of patients who had received first-line Herceptin-containing therapy at a single centre in the UK found the median OS to be 2.6 years (95% CI [2.2, 3.3]) (Yeo et al. 2015). These data clearly indicate that had the end-of line criteria been in place when Herceptin was appraised for this indication, it would certainly have qualified, further indicating HER2+ mBC is an end of life condition.

It should be noted, however, that despite the significant improvements in life expectancy that have resulted from the introduction of Herceptin, ~50% of patients will have died at 3 years following diagnosis with metastatic disease (Clarke et al. 2014). Therefore, despite treatment advances including the introduction of Perjeta, the clinical and patient burden of HER2-positive mBC is significant; the removal of access to Perjeta would further exacerbate this burden, not only for patients but society as a whole.

The total median OS observed in first-line HER2+ mBC patients receiving Perjeta in addition to Herceptin and Docetaxel was 56.5 months (Swain et al. 2015). These results demonstrate that adding the combination of Perjeta and Herceptin to chemotherapy represents a survival benefit of 15.7 months over Herceptin and docetaxel and suggest a benefit over 2 years compared to chemotherapy alone.

Considering all these data it is clear that the most efficacious option for the treatment of HER2+ mBC in the first-line is the combination Perjeta, Herceptin and docetaxel, which offer the significant benefit in a condition where the life-expectancy when treated with chemotherapy alone is less than 2 years.

This extension has substantial impact on patients and is of prime importance to patients, their families and wider-society. Therefore, an appropriate weighting to the end-of-life criteria should be considered when assessing such a dramatic increase in life expectancy.

Given the poor prognosis and clinical and patient burden of HER2-positive mBC, the unprecedented survival benefit above the existing 3 month end-of-life threshold that is offered by Perjeta in this indication, as compared to the SOC, is sufficient evidence to accept Perjeta in its licenced indication as meeting the end-of-life criteria.

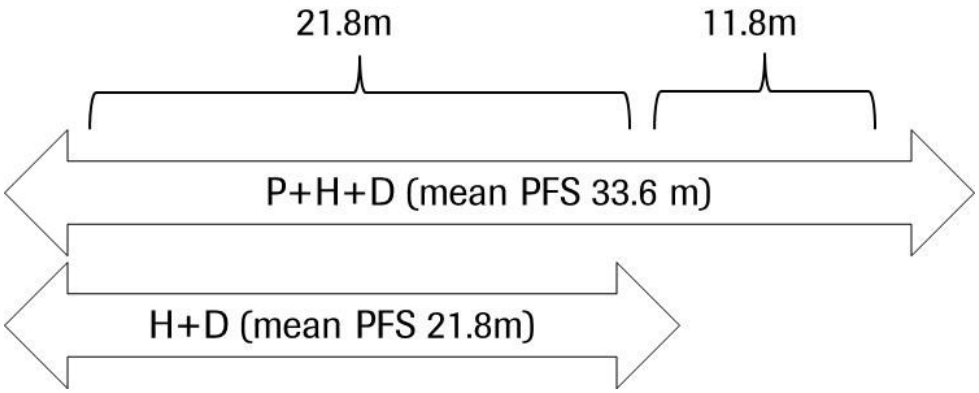
Perjeta mBC additional scenario analyses (ID523)

This document presents results of scenarios for Perjeta in metastatic Breast cancer (mBC) as part of the technology appraisal ID523. The following alternative scenarios were requested on the 29th of March to be considered in the cost effectiveness model:

Please note that the model predicts a mean PFS of 21.8 months in the comparator arm and 33.6 months in the intervention arm (Figure 1):

- **Scenario 1:** This scenario assumes that the cost of Herceptin + Docetaxel (H+D) is set to zero for the first 21.8m PFS period in the Perjeta + Herceptin + Docetaxel (P+H+D) arm, that would otherwise have been experienced in the double therapy. In other words, in the PHD arm, the first 21.8 months of PFS period, only Perjeta monotherapy costs are incurred and in the additional second PFS period (11.8m) the cost of the full triple (P+H+D) therapy .
- **Scenario 2:** Scenario two stipulates that the full triplet P+H+D costs are incurred during the first part of the PFS gain (21.8m) and that Perjeta monotherapy costs incurred only during the additional PFS period (11.8m).

Figure 1: Schematic presentation of scenarios



Results

The results have been generated using two different pricing scenarios.

1. The first scheme is a simple PAS, which is the only approved scheme for Perjeta at the moment and forms the base case in our current submission; this is [redacted] and already has Ministerial approval.
2. The second scheme is the latest complex Patient Access Scheme offered to NHS England; however it is currently not approved. This scheme is comprised of the following elements:
   - [redacted]

- [redacted]

Table 1: Results Scenario 1

	P+H+D	H+D	Incremental
PAS #1(simple PAS)			
Costs	[redacted]	[redacted]	[redacted]
QALYs	3.50	2.6	0.93
ICER		[redacted]	
PAS#2 (Complex PAS)			
Costs	[redacted]	[redacted]	[redacted]
QALYs	3.50	2.6	0.93
ICER		[redacted]	

Table 2: Results Scenario 2

	P+H+D	H+D	Incremental
PAS #1(simple PAS)			
Costs	[redacted]	[redacted]	[redacted]
QALYs	3.50	2.6	0.93
ICER		[redacted]	
PAS#2 (Complex PAS)			
Costs	[redacted]	[redacted]	[redacted]
QALYs	3.50	2.6	0.93
ICER		[redacted]	

Cost effectiveness analyses for Perjeta (ID523)

Base case analyses

The cost effectiveness analyses have been produced using the commercial access agreement (CAA) offered to NHSE. This CAA is still under review by NHSE and has not yet been approved; however we expect that if it is approved it will be before the committee meeting on the 9th May.

[redacted]

[redacted]

Two scenarios previously requested are also incorporated in the sensitivity analyses:

- Scenario 1 assumes that the cost of Herceptin + Docetaxel (HD) is set to zero for the first 21.8m PFS period (mean PFS time in comparator arm) in the Perjeta + Herceptin + Docetaxel (PHD) arm, that would otherwise have been experienced in the double therapy. In other words, in the PHD arm, the first 21.8 months of PFS period, only Perjeta monotherapy costs are incurred and in the additional second PFS period (11.8m) the cost of the full triple (PHD) therapy .
- Scenario 2 stipulates that the full triplet PHD costs are incurred during the first part of the PFS gain (21.8m) and that Perjeta monotherapy costs incurred only during the additional PFS period (11.8m).

Table 1: Deterministic and probabilistic results (List price)

	Deterministic			***Probabilistic***		
	PHD	***HD***	***D***	***PHD***	***HD***	***D***
Total costs (£)	*£174,978*	*£62,495*	*£22,919*	*£177,567*	*£64,429*	*£23,990*
Difference in total costs (£)	*N/A*	*£112,483*	*£152,058*	*N/A*	*£113,138*	*£153,577*
LYG	*5.12*	*3.90*	*2.72*	*5.1*	*3.9*	*2.68*
LYG difference	*N/A*	*1.22*	*2.40*	*N/A*	*£1.20*	*£2.42*
QALYs	*3.50*	*2.60*	*1.81*	*3.50*	*2.57*	*1.80*
QALY difference	*N/A*	*0.93*	*1.69*	*N/A*	*£0.93*	*£1.70*
ICER (£)	*N/A*	*£120,586*	*£89,952*	*N/A*	*£121,654*	*£90,208*
Difference between deterministic and Probabilistic	*-*	*-*	*-*	*-*	*-£1,068*	*-£255*
PHD –Perjeta, Herceptin and Docetaxel; HD –Herceptin and Docetaxel; D –Docetaxel						

Table 2: Deterministic and probabilistic results (CAA)

	Deterministic			***Probabilistic***		
	PHD	***HD***	***D***	***PHD***	***HD***	***D***
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LYG	*5.12*	*3.90*	*2.72*	*5.1*	*3.9*	*2.65*
LYG difference	*N/A*	*1.22*	*2.40*	*N/A*	*1.20*	*£2.45*
QALYs	*3.50*	*2.6*	*1.81*	*3.50*	*2.57*	*1.79*
QALY difference	*N/A*	*0.93*	*1.69*	*N/A*	*0.93*	*£1.71*
ICER (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference between deterministic and Probabilistic	*-*	*-*	*-*	*-*	*£1,211*	*-£513*
PHD –Perjeta, Herceptin and Docetaxel; HD –Herceptin and Docetaxel; D –Docetaxel						

Table 3: Deterministic and probabilistic results (Simple Discounts)

	Deterministic			***Probabilistic***		
	PHD	***HD***	***D***	***PHD***	***HD***	***D***

Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LYG	*5.12*	*3.90*	*2.72*	*5.1*	*3.9*	*2.61*
LYG difference	*N/A*	*1.22*	*2.40*	*N/A*	*1.20*	*£2.49*
QALYs	*3.50*	*2.6*	*1.81*	*3.50*	*2.57*	*1.75*
QALY difference	*N/A*	*0.93*	*1.69*	*N/A*	*0.93*	*£1.75*
ICER (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference between deterministic and Probabilistic	*-*	*-*	*-*	*-*	*-£975*	*£1,119*
PHD –Perjeta, Herceptin and Docetaxel; HD –Herceptin and Docetaxel; D –Docetaxel						

Sensitivity and scenario analyses

Table 4: Sensitivity analyses results (List price)

Parametric functions			*Vs HD*	*Vs D*
Overall survival	*Gamma (Base case)*	*Weibull*	*128,559*	*92,087*
		Exponential	*101,023*	*71,361*
		LogLogistic	*114,883*	*71,238*
		LogNormal	*102,543*	*63,673*
		Gamma	*120,586*	*89,952*
		Gompertz	*157,485*	*109,769*
		*KM with Weibull tail**	*125,512*	*91,924*
		*KM with Exponential tail**	*98,663*	*73,836*
		*KM with LogLogistic tail**	*108,891*	*71,311*
		*KM with LogNormal tail**	*96,764*	*65,120*
		*KM with Gamma tail**	*117,895*	*89,828*
		*KM with Gompertz tail**	*153,750*	*110,532*
Progression Free Surv	*LogLogistic (Base case)*	*Weibull*	*130,216*	*95,666*
		Exponential	*129,381*	*95,023*
		LogLogistic	*120,586*	*89,952*
		LogNormal	*120,729*	*89,608*
		Gamma	*122,492*	*90,568*
		*KM with Weibull tail**	*126,726*	*95,268*
		*KM with Exponential tail**	*125,931*	*94,818*
		*KM with LogLogistic tail**	*118,379*	*89,138*
		*KM with LogNormal tail**	*118,203*	*89,518*
		*KM with Gamma tail**	*119,663*	*90,293*
Scenario 1			*91,424*	*73,861*
Scenario 2			*100,247*	*78,729*

* Tail used from point when 15% are at risk

Table 5: Sensitivity analyses results (CAA)

Parametric functions			*Vs HD*	*Vs D*
Overall survival	*Gamma (Base case)*	*Weibull*	[redacted]	[redacted]
		Exponential	[redacted]	[redacted]
		LogLogistic	[redacted]	[redacted]
		LogNormal	[redacted]	[redacted]
		Gamma	[redacted]	[redacted]
		Gompertz	[redacted]	[redacted]
		*KM with Weibull tail**	[redacted]	[redacted]
		*KM with Exponential tail**	[redacted]	[redacted]
		*KM with LogLogistic tail**	[redacted]	[redacted]
		*KM with LogNormal tail**	[redacted]	[redacted]
		*KM with Gamma tail**	[redacted]	[redacted]
		*KM with Gompertz tail**	[redacted]	[redacted]
Progression Free Surv	*LogLogistic (Base case)*	*Weibull*	[redacted]	[redacted]
		Exponential	[redacted]	[redacted]
		LogLogistic	[redacted]	[redacted]
		LogNormal	[redacted]	[redacted]
		Gamma	[redacted]	[redacted]
		*KM with Weibull tail**	[redacted]	[redacted]
		*KM with Exponential tail**	[redacted]	[redacted]
		*KM with LogLogistic tail**	[redacted]	[redacted]
		*KM with LogNormal tail**	[redacted]	[redacted]
		*KM with Gamma tail**	[redacted]	[redacted]
Scenario 1			[redacted]	[redacted]
Scenario 2			[redacted]	[redacted]

* Tail used from point when 15% are at risk

Table 6: Sensitivity analyses results (Simple Discounts)

Parametric functions			*Vs HD*	*Vs D*
Overall survival	*Gamma (Base case)*	*Weibull*	[redacted]	[redacted]
		Exponential	[redacted]	[redacted]
		LogLogistic	[redacted]	[redacted]
		LogNormal	[redacted]	[redacted]
		Gamma	[redacted]	[redacted]
		Gompertz	[redacted]	[redacted]
		*KM with Weibull tail**	[redacted]	[redacted]
		*KM with Exponential tail**	[redacted]	[redacted]
		*KM with LogLogistic tail**	[redacted]	[redacted]
		*KM with LogNormal tail**	[redacted]	[redacted]
		*KM with Gamma tail**	[redacted]	[redacted]
		*KM with Gompertz tail**	[redacted]	[redacted]
Progression Free Surv	*LogLogistic (Base case)*	*Weibull*	[redacted]	[redacted]
		Exponential	[redacted]	[redacted]
		LogLogistic	[redacted]	[redacted]
		LogNormal	[redacted]	[redacted]
		Gamma	[redacted]	[redacted]
		*KM with Weibull tail**	[redacted]	[redacted]
		*KM with Exponential tail**	[redacted]	[redacted]
		*KM with LogLogistic tail**	[redacted]	[redacted]
		*KM with LogNormal tail**	[redacted]	[redacted]
		*KM with Gamma tail**	[redacted]	[redacted]
Scenario 1			[redacted]	[redacted]
Scenario 2			[redacted]	[redacted]

* Tail used from point when 15% are at risk