Ludwig Boltzmann Institut
Health Technology Assessment

Horizon Scanning in Oncology
29th Prioritization – 4th quarter 2016

General Information, efficacy and safety data

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Please note:

Within this document you find general information about the drug of interest and the indication it is intended to be used for. Further we have included full text publications and conference abstracts of phase III trials, assessing the safety and efficacy of the drugs of interest.

At the very end of each chapter we have provided a table containing the prioritization criteria and a drop-down field to apply the provided criteria.

1 Breast cancer

1.1 Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer

Overview

Drug Description		tyrosine-kinase inhibitor that blocks signal transduction through three epidermal growth factor receptors (erbB1, erbB2/HER2, erbB4)
Patient Indication		Neratinib after trastuzumab-based adjuvant therapy in patients with early-stage HER2-positive breast cancer
Incidence in Austria		5,594 newly diagnosed per year (2012), 40.3/100,000/year
Ongoing Phase III		NCT00878709 – until November 2020
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	-
	FDA	-
Costs		-

Phase III results

Lancet (2016), Issue 17: 367–77 (Chan et al.) "*Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial"*

Background
Neratinib, an irreversible tyrosine-kinase inhibitor of HER1, HER2, and HER4, has clinical activity in patients with HER2-positive metastatic breast cancer. We aimed to investigate the effi cacy and safety of 12 months of neratinib after trastuzumab-based adjuvant therapy in patients with early-stage HER2-positive breast cancer.

Methods
We did this multicentre, randomised, double-blind, placebo-controlled, phase 3 trial at 495 centres in Europe, Asia, Australia, New Zealand, and North and South America. Eligible women (aged ≥18 years, or ≥20 years in Japan) had stage 1–3 HER2-positive breast cancer and had completed neoadjuvant and adjuvant trastuzumab therapy up to 2 years before randomisation. Inclusion criteria were amended on Feb 25, 2010, to include patients with stage 2–3 HER2-positive breast cancer who had completed trastuzumab therapy up to 1 year previously. Patients were randomly assigned (1:1) to receive oral neratinib 240 mg per day or matching placebo. The randomisation sequence was generated with permuted blocks stratified by hormone receptor status (hormone receptor-positive [oestrogen or progesterone receptor-positive or both] vs hormone receptor-negative [oestrogen and progesterone receptor-negative]), nodal status (0, 1–3, or ≥4), and trastuzumab adjuvant regimen (sequentially vs concurrently with chemotherapy), then implemented centrally via an interactive voice and web-response system. Patients, investigators, and trial sponsors were masked to treatment

allocation. The primary outcome was invasive disease-free survival, as defined in the original protocol, at 2 years after randomisation. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00878709.

Results
Between July 9, 2009, and Oct 24, 2011, we randomly assigned 2840 women to receive neratinib (n=1420) or placebo (n=1420). Median follow-up time was 24 months (IQR 20–25) in the neratinib group and 24 months (22–25) in the placebo group. At 2 year follow-up, 70 invasive disease-free survival events had occurred in patients in the neratinib group versus 109 events in those in the placebo group (stratified hazard ratio 0·67, 95% CI 0·50–0·91; p=0·0091). The 2-year invasive disease-free survival rate was 93·9% (95% CI 92·4–95·2) in the neratinib group and 91·6% (90·0–93·0) in the placebo group. The most common grade 3–4 adverse events in patients in the neratinib group were diarrhoea (grade 3, n=561 [40%] and grade 4, n=1 [<1%] vs grade 3, n=23 [2%] in the placebo group), vomiting (grade 3, n=47 [3%] vs n=5 [<1%]), and nausea (grade 3, n=26 [2%] vs n=2 [<1%]). QT prolongation occurred in 49 (3%) patients given neratinib and 93 (7%) patients given placebo, and decreases in left ventricular ejection fraction (≥grade 2) in 19 (1%) and 15 (1%) patients, respectively. We recorded serious adverse events in 103 (7%) patients in the neratinib group and 85 (6%) patients in the placebo group. Seven (<1%) deaths (four patients in the neratinib group and three patients in the placebo group) unrelated to disease progression occurred after study drug discontinuation. The causes of death in the neratinib group were unknown (n=2), a second primary brain tumour (n=1), and acute myeloid leukaemia (n=1), and in the placebo group were a brain haemorrhage (n=1), myocardial infarction (n=1), and gastric cancer (n=1). None of the deaths were attributed to study treatment in either group.

Conclusion
Neratinib for 12 months significantly improved 2-year invasive disease-free survival when given after chemotherapy and trastuzumab-based adjuvant therapy to women with HER2-positive breast cancer. Longer follow-up is needed to ensure that the improvement in breast cancer outcome is maintained.

1.2 Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer

Overview

Drug Description		orally bioavailable, selective inhibitor of CDK4/6
Patient Indication		Ribociclib for the first-line treatment of postmenopausal women with HR positive and HER3-negative recurrent or metastatic breast cancer
Incidence in Austria		5,594 newly diagnosed per year (2012), 40.3/100,000/year
Ongoing Phase III		NCT01958021 – until August 2019
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	-
	FDA	-
Costs		-

Phase III results

NEJM (2016), 375:1738-1748 (Hortobagyi et al.) "*Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer"*

Background
The inhibition of cyclin-dependent kinases 4 and 6 (CDK4/6) could potentially overcome or delay resistance to endocrine therapy in advanced breast cancer that is positive for hormone receptor (HR) and negative for human epidermal growth factor receptor 2 (HER2).

Methods
In this randomized, placebo-controlled, phase 3 trial, we evaluated the efficacy and safety of the selective CDK4/6 inhibitor ribociclib combined with letrozole for first-line treatment in 668 postmenopausal women with HR-positive, HER2-negative recurrent or metastatic breast cancer who had not received previous systemic therapy for advanced disease. We randomly assigned the patients to receive either ribociclib (600 mg per day on a 3-weeks-on, 1-week-off schedule) plus letrozole (2.5 mg per day) or placebo plus letrozole. The primary end point was investigator-assessed progression-free survival. Secondary end points included overall survival, overall response rate, and safety. A preplanned interim analysis was performed on January 29, 2016, after 243 patients had disease progression or died. Prespecified criteria for superiority required a hazard ratio of 0.56 or less with $P<1.29\times10^{-5}$.

Results
The duration of progression-free survival was significantly longer in the ribociclib group than in the placebo group (hazard ratio, 0.56; 95% CI, 0.43 to 0.72; $P=3.29\times10^{-6}$ for superiority). The median duration of follow-up was 15.3 months. After 18 months, the progression-free survival rate was 63.0% (95% confidence interval [CI], 54.6 to 70.3) in the ribociclib group and 42.2% (95% CI, 34.8 to 49.5) in the placebo group. In patients with measurable disease at baseline, the overall response rate was 52.7% and 37.1%, respectively ($P<0.001$). Common grade 3 or 4 adverse events that were reported in more than 10% of the patients in either group were neutropenia (59.3% in the ribociclib group vs. 0.9% in the placebo group) and leukopenia (21.0% vs. 0.6%); the rates of discontinuation because of adverse events were 7.5% and 2.1%, respectively.

Conclusion
Among patients receiving initial systemic treatment for HR-positive, HER2-negative advanced breast cancer, the duration of progression-free survival was significantly longer among those receiving ribociclib plus letrozole than among those receiving placebo plus letrozole, with a higher rate of myelosuppression in the ribociclib group. (Funded by Novartis Pharmaceuticals; ClinicalTrials.gov number, NCT01958021).