Neratinib

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Approved indication: breast cancer

Nerlynx (Specialised Therapeutics)
40 mg film-coated tablets

Neratinib is indicated for extended adjuvant treatment in women with early-stage HER2-positive breast cancer following adjuvant trastuzumab-based chemotherapy. It should be started within a year of finishing trastuzumab. Neratinib is a tyrosine kinase inhibitor. It irreversibly binds to the HER1, HER2 and HER4 receptors. This binding reduces auto-phosphorylation and downstream signalling from these receptors and decreases growth of the cells.

The approval of neratinib is based on a placebo-controlled phase III trial of 2840 women who had stage I–III HER2-positive breast cancer.[1,2] Most participants had completed their last trastuzumab dose within a year of starting the trial. Women were randomised 1:1 to receive neratinib (240 mg/day) or placebo for 12 months. The primary outcome of the trial was invasive disease-free survival, which included invasive ipsilateral tumour recurrence, invasive contralateral breast cancer, local or regional recurrence, distant recurrence or death from any cause.

In two-year and five-year analyses, invasive disease-free survival rates were statistically higher with neratinib than with placebo (93.9% vs 91.6% at 2 years and 90.2% vs 87.7% at 5 years). However, there was no statistically significant difference between the neratinib and placebo groups for other outcomes including distant disease-free survival and CNS recurrence (see Table).[1,2] In a subgroup analysis of invasive disease-free survival at five years, women who had completed their last trastuzumab dose more than 12 months before starting the trial gained no benefit from neratinib (hazard ratio=1).[2]

The most common adverse events with neratinib included diarrhoea (93.6%), nausea (42.5%), fatigue (27.3%), vomiting (26.8%), abdominal pain (22.7%), rash (15.4%), decreased appetite (13.7%), stomatitis (11.2%) and muscle spasm (10%). Diarrhoea was severe (grade 3) in 40% of cases,[1] and 14.4% of women discontinued because of it. Loperamide prophylaxis (along with adequate hydration) is therefore recommended for the first 1–2 months of treatment, and as needed after that. The neratinib dose may need to be reduced, interrupted or discontinued depending on the severity of the diarrhoea.

Women with renal impairment have a higher risk of complications from dehydration with diarrhoea and should be closely monitored. Neratinib is not recommended in severe renal impairment or dialysis.

Liver toxicity was more common with neratinib than with placebo (12.4% vs 6.6%) and included elevated alanine aminotransferase, aspartate aminotransferase and blood alkaline phosphatase. The dose may need to be reduced or discontinued depending on the severity of the hepatotoxicity. Neratinib is contraindicated in severe hepatic impairment (Child-Pugh C).

The recommended dose of neratinib is 240 mg once daily for a year. Tablets should be taken in the morning with food. Following oral administration, peak plasma concentrations are reached after seven hours. Neratinib is extensively metabolised in the liver, primarily by cytochrome P450 (CYP) 3A4. Its plasma half-life is 17 hours and most of the dose is excreted in the faeces.

Neratinib has numerous drug interactions. Concomitant use of strong CYP3A4 and P-glycoprotein inducers should be avoided (e.g. carbamazepine, phenobarbital,

Table **Efficacy of neratinib (12 months treatment) in HER2-positive breast cancer after trastuzumab**

	Event-free rate	
	2-year analysis[1]	**5-year analysis**[2]
Outcome	**neratinib vs placebo**	**neratinib vs placebo**
Invasive disease-free survival*	93.9% vs 91.6% (p=0.009)	90.2% vs 87.7% (p=0.008)
Disease-free survival including DCIS	93.9% vs 91% (p=0.001)	89.7% vs 86.8% (p=0.004)
Distant disease-free survival	95.1% vs 93.7% (p=0.089)	91.6% vs 89.9% (p=0.065)
CNS recurrence†	0.91% vs 1.25% (p=0.440)	1.3% vs 1.8% (p=0.333)

DCIS ductal carcinoma in situ
* Invasive disease was defined as ipsilateral tumour recurrence, contralateral breast cancer, local or regional recurrence, distant recurrence or death from any cause.
† Reported as cumulative incidence, not event-free rate

phenytoin, rifampicin and St John's wort). CYP3A4 inhibitors (fluconazole, diltiazem, verapamil, erythromycin) should also not be co-administered. If CYP3A4 inducers or inhibitors cannot be avoided, the neratinib dose should be increased or decreased accordingly (see product information).

Neratinib's solubility goes down with increasing pH, so some drugs may affect its bioavailability. Concomitant proton pump inhibitors should be avoided and neratinib should be given separately from H_2-receptor antagonists and antacids.

As there was evidence of fetal toxicity in animal studies, women should use contraception during and for one month after finishing neratinib treatment. It is unclear if the drug reduces the effectiveness of hormone contraceptives so women should add a barrier method. It is not known if neratinib is excreted in breast milk.

Neratinib improved the invasive-free 5-year survival rate of women with HER2-positive breast cancer by 2.5% compared to placebo. Those with hormone-receptor positive breast cancer seemed to have more benefit than those without the receptor. It is currently unclear whether improved invasive-free survival will lead to improved overall survival. The modest benefits of neratinib have to be weighed against the very high likelihood of diarrhoea, which was severe in 40% of women who were treated.

T manufacturer provided the product information

REFERENCES

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, and the European Medicines Agency.