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NCCN Breast Cancer Guideline Panel:

On behalf of Puma Biotechnology, Inc., I respectfully request the NCCN Breast Cancer Guideline Panel review the enclosed data and prescribing information for updating the placement of neratinib in the breast guidelines

We respectfully request the following changes: please consider including neratinib in the treatment algorithm (as opposed to the footnote) as a treatment option for patients with HR-positive, HER2-positive breast cancer with a perceived high risk of recurrence following adjuvant trastuzumab-based treatment.

-Systemic Adjuvant Treatment: Hormone Receptor-Positive - HER2-Positive Disease (BINV-5)
-Adjuvant Systemic Therapy after Preoperative Systemic Therapy (BINV-16)
-Preoperative/Adjuvant Therapy Regimens: HER2-Positive (BINV-L 2/7)

FDA Clearance: neratinib is indicated:
-As a single agent, for the extended adjuvant treatment of adult patients with early-stage HER2-positive breast cancer, to follow adjuvant trastuzumab-based therapy.[1]
-In combination with capecitabine, for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting.[1]

Rationale: A significant number of patients with HER2-positive early breast cancer (EBC) recur with longer term follow-up. In the joint analysis of NSABP B-31 and NCCTG N9831, 87.1% and 73.7% of patients who received trastuzumab were disease free at 3 and 10 years, respectively.[2,3] In higher-risk patients who did not achieve a pCR after neoadjuvant treatment and received T-DM1, the KATHERINE trial reported an iDFS of 88.3% in all patients and 83% in patients with positive nodes after pre-operative therapy[4] (3 year rates, longer term follow up ongoing). In the T-DM1 arm, 56% of the distant recurrences occurred in the CNS. Additionally, the HERA trial reported that extending duration of adjuvant trastuzumab to 2 years did not improve outcomes compared to 1 year of treatment.[5]

Clinical Data: ExteNET was a multicenter, randomized, double-blind, phase III trial of 2840 HER2-positive EBC patients after neoadjuvant/adjuvant trastuzumab-based therapy. Patients were randomly assigned 1-year oral neratinib 240 mg/day or placebo.

In the ITT population, the iDFS benefit seen at 2 and 5 years was 2.3% and 2.5%, respectively.[6,7] The HR for overall survival (OS) was 0.95 (95% CI 0.75-1.21) with a median 8.1 years of follow-up.[8] Greater benefit was seen in patients with HR-positive disease. Table 1 reports descriptive analyses of iDFS and OS in patients with HER2+/HR+ disease who initiated treatment within 1 year of prior trastuzumab-based treatment (HR+/≤1-year; EU indication) and in patients who had residual disease after neoadjuvant treatment (HR+/≤1-year, no pCR).[9] The cumulative incidence of CNS as site of first recurrence was numerically lower in the neratinib arm at 5 years (2.1% with placebo and 0.7% with neratinib in the HR+/≤1-year patient group).[9] In the HR+/≤1-year, no pCR patient population, the cumulative incidence of CNS as site of first recurrence at 5 years was 3.6% in the placebo arm and 0.8% in the neratinib arm.

The ExteNET trial did not mandate primary prophylaxis for diarrhea and 17% of patients discontinued neratinib early due to diarrhea. A descriptive analysis evaluating outcomes in patients who completed neratinib treatment (defined as ≥11 months or cessation of neratinib if recurrence occurred prior to 11 months) showed improved HRs and absolute benefits for iDFS, DDFS and OS (Table 2).[10,11]

Dose escalation with loperamide PRN was recently included in the neratinib USPI as an option to improve the tolerability of neratinib.[1] The CONTROL study reported that dose escalation with loperamide PRN improved the tolerability of neratinib by a lowering the rate of Grade 3 diarrhea and discontinuations due to diarrhea.[12] In the dose escalation arm (Cohort 6), 13.3% of patients reported Grade 3 diarrhea and 3.3% of patients discontinued treatment due to diarrhea.[13]

Table 1 iDFS and OS in patients with HER2+/ HR+ disease who initiated treatment within 1 year of prior trastuzumab from ExteNET trial

		Invasive disease-free survival (5-year analysis)			
		Estimated 5-year rate, %			Hazard ratio (95% CI)
Population or subgroup	**N**	**Neratinib**	**Placebo**	**Δ, %[a]**	
HR-positive ≤1 year of prior trastuzumab	1334	90.8	85.7	+5.1	0.58 (0.41–0.82)
Neoadjuvant therapy	354	85.5[e]	76.8[e]	+8.7[e]	0.54 (0.31–0.90)
Residual invasive disease (no pCR)[b]	295	85.0	77.6	+7.4	0.60 (0.33–1.07)
No residual invasive disease (pCR)[c,d]	38	84.0	74.2	+9.8	0.44 (0.06–1.89)
		Overall survival analysis (median follow-up 8.1 years)			
		Rate, %			Hazard ratio (95% CI)
		Neratinib	**Placebo**	**Δ, %[a]**	
HR-positive ≤1 year of prior trastuzumab	1334	91.5	89.4	+2.1	0.79 (0.55–1.13)
Neoadjuvant therapy	354	90.1[e]	80.8[e]	+9.3[e]	0.52 (0.28–0.92)
Residual invasive disease (no pCR)[b]	295	91.3	82.2	+9.1	0.47 (0.23–0.92)
No residual invasive disease (pCR)[c,d]	38	93.3	73.7	+19.6	0.40 (0.06–1.88)

[a]Difference in event-free survival rates between neratinib vs placebo. [b]No pathological complete response (no pCR). [c]With pathological complete response (pCR) [d]Small N's. Interpret with Caution. [e]data on file.

Table 2: iDFS, DDFS and OS in patients who completed ≥11 months of neratinib treatment

	5-year analysis						OS analysis (median follow-up 8.1 years)	
	N		iDFS rate		DDFS rate		OS rate	
Population	**Neratinib**	**Placebo**	**Difference %**	**HR (95% CI)**	**Difference %**	**HR (95% CI)**	**Difference %**	**HR (95% CI)**
ITT	872	1420	+3.3	0.68 (0.52–0.90)	+2.0	0.76 (0.56–1.02)	+2.0	0.78 (0.58–1.04)
HR+/≤1 year (EU indication)	402	664	+7.4	0.44 (0.28–0.68)	+5.9	0.49 (0.30–0.76)	+5.8	0.49 (0.29–0.78)
HR+/≤1 year no pCR	92	164	+11.9	0.42 (0.19–0.83)	+10.9	0.42 (0.18–0.88)	+13.2	0.29 (0.10–0.68)

Summary: Thank you for considering our request to update the guidelines. The ExteNET trial showed that extending the duration of HER2-directed treatment with neratinib in the curative setting improved outcomes, with greater benefit seen in patients with HR-positive disease. Additionally, the lower rates of CNS as a site of first recurrence observed are consistent with results reporting CNS efficacy with neratinib in the metastatic setting.[14,15]

Sincerely,

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