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NCCN Guidelines Panel: Breast Cancer

On behalf of Puma Biotechnology, Inc., I respectfully request the NCCN Breast Cancer Guideline Panel review the enclosed Manuscript "Final efficacy results of neratinib in HER2-positive hormone receptor-positive early-stage breast cancer from the phase III ExteNET trial".[1]

Specific Changes: please consider including neratinib in the treatment algorithm (as opposed to the footnote) as extended adjuvant treatment for patients with HER-2 positive, HR-positive disease in the following sections:

- Systemic Adjuvant Treatment: Hormone Receptor-Positive - HER2-Positive Disease (BINV-5)
- Adjuvant Systemic Therapy after Preoperative Systemic Therapy (BINV-15)
- Preoperative/Adjuvant Therapy Regimens: HER2-Positive (BINV-L 2/6)

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[2]
- 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[2]

Supporting Literature:

ExteNET was a multicenter, randomized, double-blind, phase III trial of 2840 HER2+ eBC patients after neoadjuvant/adjuvant trastuzumab-based therapy. Patients were stratified by HR status and randomly assigned 1-year oral neratinib 240 mg/day or placebo. The primary endpoint was invasive disease-free survival (iDFS)[3,4] Secondary endpoints were disease-free survival including ductal carcinoma in situ (DFS-DCIS), distant disease-free survival (DDFS), time to distant recurrence (TDR), cumulative incidence of first occurrence of central nervous system (CNS) recurrences, OS, and safety. A definitive analysis of overall survival was planned when 248 deaths occurred in the intention-to-treat population.

This manuscript reports on descriptive analyses performed in HR+ patients who initiated treatment within 1 year of prior trastuzumab based treatment (HR+/≤1-year) and subgroups of clinical interest, including a patient population who had residual disease after neoadjuvant treatment (HR+/≤1-year; no pCR). The cumulative incidence of first CNS recurrences at 5 years is also reported.

Findings:

Results from the trial for the population of patients with HR-positive disease who initiated treatment within 1 year of prior trastuzumab (n=1334) are shown in the Table, along with results for the patient subgroup who had received neoadjuvant therapy (with or without residual invasive disease).

Table. Invasive disease-free survival and overall survival in patients with HR-positive disease who initiated treatment within 1 year of prior trastuzumab from ExteNET (n=1334)

		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	76.8	+8.7	0.54 (0.31–0.90)
Residual invasive disease[b]	295	85.0	77.6	+7.4	0.60 (0.33–1.07)
No residual invasive disease[c,d]	38	84.0	74.2	+9.8	0.44 (0.06–1.89)
		Overall survival analysis			
		Estimated 8-year 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	80.8	+9.3	0.52 (0.28–0.92)
Residual invasive disease[b]	295	91.3	82.2	+9.1	0.47 (0.23–0.92)
No residual invasive disease[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.

The cumulative incidence of first CNS recurrences at 5 years was 0.7% with neratinib and 2.1% with placebo in the HR+/≤1-year patient group. In the HR+/≤1-year; no pCR patient population, the cumulative incidence of first CNS recurrences at 5 years was 0.8% in the neratinib arm and 3.6% in the placebo arm.

Consistent improvements in iDFS, DDFS, OS and CNS were observed in favor of neratinib in all reported groups.

The safety profile of neratinib in this population was consistent with that observed in the ExteNET safety population. The ExteNET trial did not mandate proactive prophylaxis for diarrhea and reported a 40% incidence of Grade 3 diarrhea. The CONTROL study reported that dose escalation with loperamide PRN improved the tolerability of neratinib. In this arm (Cohort 6), 15% of patients reported Grade 3 diarrhea and 3.3% of patients discontinued treatment due to diarrhea.[5]

The attached materials are submitted in support of this proposed change.

We would like to acknowledge the contributions of NCCN panel members who are also co-authors on this presentation.

Sincerely,

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References

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3. Chan A, Delaloge S, Holmes FA, 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. Lancet Oncol 2016;17:367-77.

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5. Barcenas CH, Hurvitz SA, Di Palma JA, et al. Improved tolerability of neratinib in patients with HER2-positive early-stage breast cancer: diarrheal toxicity in the CONTROL trial. Ann Oncol 2020, doi: https://doi.org/10.1016/j.annonc.2020.05.012; published online May 25, 2020.