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Date of request: August 5, 2020
**NCCN Guidelines Panel: Breast Cancer**

On behalf of Puma Biotechnology, I respectfully request the NCCN Breast Cancer Guidelines Panel review the enclosed clinical data regarding neratinib-based therapy in *HER2*-mutated (*HER2*$^{mut}$) metastatic breast cancer (mBC).

**Specific changes:** Please consider including neratinib-based therapy as a treatment option for patients with somatic *HER2*$^{mut}$ in the following section:

- Additional targeted therapies and associated biomarker testing for recurrent or Stage IV (M1) disease (**BINV-R**).

**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.
- 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.

Neratinib is not currently approved for use in *HER2*$^{mut}$ disease.

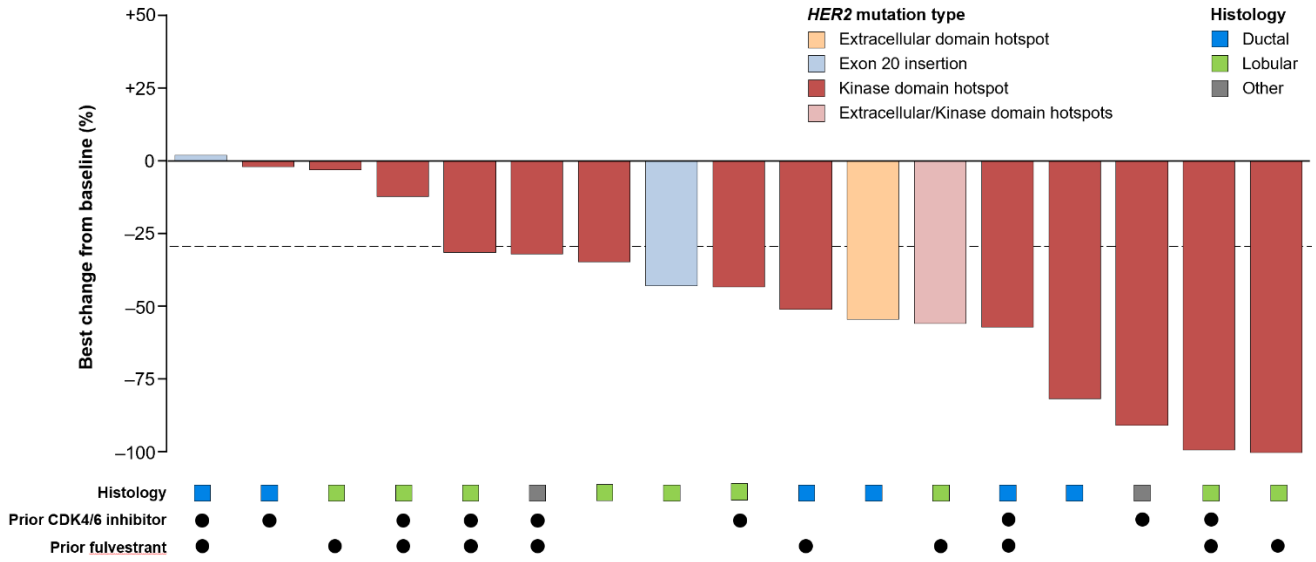
**Rationale:** Somatic *HER2*$^{mut}$ are a class of oncogenic drivers, categorized as *Tier IIB* (ESCAT) and *Level 3A* (OncoKB) mutations, that are present in a variety of solid tumor malignancies including breast, cervical, bladder, colorectal and lung cancers. *HER2*$^{mut}$ tumors occur in approximately 2–3% of patients with mBC, are observed predominantly in HER2–non-amplified, hormone receptor-positive tumors, and appear to be enriched in lobular carcinomas.[1–3] In breast cancer, *HER2*$^{mut}$ occur mainly as missense substitutions or small in-frame insertions in exons 19 and 20 of the kinase domain or missense substitutions in a hotspot region of exon 8 in the extracellular domain, and are activating and oncogenic.[1] Acquired *HER2*$^{mut}$ in estrogen receptor-positive (ER+) mBC confer resistance to anti-ER agents and this resistance can be reversed by neratinib-based therapy.[4–5]

Three phase 2 trials, SUMMIT (NCT01953926), MutHER (NCT01670877), and plasmaMATCH (NCT03182634) demonstrate clinical activity of neratinib as a single agent or in combination with endocrine therapy +/– trastuzumab in *HER2*$^{mut}$, HER2–non-amplified mBC.

The **SUMMIT** trial is an on-going international, multi-center multi-histology basket trial with breast cohorts investigating the efficacy of neratinib, either as a single agent or in combination with fulvestrant ± trastuzumab, in patients with solid tumors with somatic activating *HER2*$^{mut}$.[6]

- The initial analysis from SUMMIT had shown that single-agent neratinib exhibited activity in patients with *HER2*$^{mut}$ breast cancer (n=25) with an objective response rate (ORR) at week 8 of 32% (95% CI 15–54%), a clinical benefit rate (CBR) of 40% (95% CI 21–61%), and a median progression-free survival (PFS) of 3.5 months (95% CI 1.9–4.3 months).[6]
- In a subsequent analysis, when neratinib was given in combination with fulvestrant in patients with ER+ mBC (n=47), the ORR was 30% (95% CI 17.3–44.9%), median PFS was 5.4 months (95% CI 3.7–9.2 months), and median duration of response (DoR) was 9.2 months (95% CI 5.5–16.6 months).[7]
- In a more recent analysis to determine if dual HER2-targeted therapy could improve clinical benefit further (n=17), neratinib + trastuzumab + fulvestrant demonstrated encouraging clinical activity, with an ORR of 53% (95% CI 28–77%) and a median PFS of 9.8 months (95% CI 4.0–NE months).[8] Median DoR was not evaluable

with 5/9 responses still ongoing. The median number of prior therapies was 4. Change in tumor size and characteristics of patients included in this analysis are shown in the figure below:




**MutHER** is a multi-institutional single-arm phase 2 trial that evaluated single-agent neratinib in *HER2*$^{mut}$ non-amplified mBC.[9] MutHER was the first formal study addressing *HER2*$^{mut}$ as a valid therapeutic target in mBC.[9]

- In MutHER, the CBR was 31% (90% CI 13–55%), with manageable toxicities, in a heavily pretreated (median of 3 prior lines) mBC patient population, with a median DoR in patients who achieved a clinical benefit of 5.6 months.[9]

**plasmaMATCH** is an open-label, multi-center, multi-cohort platform trial assessing the ORR of various targeted therapies in mBC where the targetable mutation is identified through ctDNA screening.[10] In cohort B, patients with *HER2*$^{mut}$ ER+ breast cancer received neratinib + fulvestrant, and those with *HER2*$^{mut}$ ER– breast cancer received neratinib alone.

- In plasmaMATCH cohort B, the confirmed ORR in ER+ patients was 23.5% (95% CI 6.8–49.9%), and the median DoR was 5.7 months (IQR 3.7–9.7 months). The median PFS in ER+ patients was 4.6 months (95% CI 3.4–9.1 months).[10]

The profile and frequency of treatment-emergent adverse events in this population were similar to those reported in other trials of neratinib.[11] In SUMMIT, 36% of patients reported Grade 3 diarrhea (there was no Grade 4 diarrhea reported) and the cumulative duration of Grade 3 diarrhea was 5.5 days. No patient discontinued treatment due to diarrhea.

**Summary:** The referenced materials are submitted in support of these data. We would like to acknowledge the contributions of NCCN panel members who are also co-authors on some of these publications or presentations.

Sincerely

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