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NCCN Central Nervous System Cancers Guideline Panel:

On behalf of Seattle Genetics, we respectfully request the NCCN Central Nervous System Cancers Guideline Panel to review the enclosed data presented at the 2020 American Society of Clinical Oncology (ASCO) and simultaneously published in the Journal of Clinical Oncology. [1,2]

Specific Change: Please consider an update to the NCCN Central Nervous System Cancers Guidelines to include tucatinib in combination with trastuzumab and capecitabine as a preferred therapy with a category 1 level of evidence for patients with HER2-positive metastatic breast cancer (MBC) with brain metastases. This request is supported by the intracranial efficacy and survival benefit observed for patients with HER2-positive breast cancer and brain metastases in the HER2CLIMB trial. [1,2]

FDA Clearance: Tucatinib is an FDA-approved kinase inhibitor indicated in combination with trastuzumab and capecitabine for the treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting. [3]

Rationale: Newly published results from the HER2CLIMB study, described in the detailed analysis below, demonstrate that in patients with brain metastases, tucatinib in combination with trastuzumab and capecitabine (tucatinib arm) compared to placebo, trastuzumab, and capecitabine (control arm) had the following effects:

- Reduced the risk of progression in the brain or death (CNS-PFS) by two-thirds;
- Reduced the risk of death (OS) by nearly half;
- Doubled the intracranial objective response rate (ORR-IC) and duration of response (DOR-IC). [1,2]

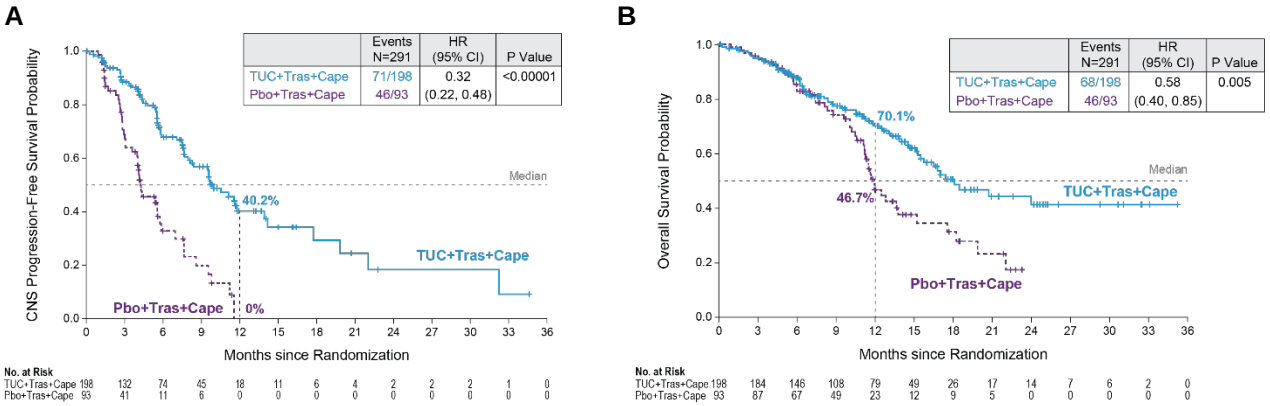
In addition, continued treatment with tucatinib, trastuzumab, and capecitabine after isolated CNS progression demonstrated an improvement in time to second progression compared to the control arm. [1,2]

Tucatinib combined with trastuzumab and capecitabine is the first regimen to improve intracranial response rates, delay progression in the brain, and prolong survival in patients with HER2-positive breast cancer and brain metastases in a prospective, double-blind, randomized controlled trial.

Detailed Analysis: HER2CLIMB was a pivotal, global, randomized, controlled trial of patients with HER2+ MBC previously treated with trastuzumab, pertuzumab, and trastuzumab emtansine. [4] Clinical trials have historically excluded HER2-positive MBC patients who developed brain metastases due to concerns of poor prognosis, shortened life expectancy, or increased risk of toxicity with the exception of HER2CLIMB.[5] CNS-PFS and OS were assessed in patients enrolled in the HER2CLIMB trial with brain metastases (n=291). [1,2] ORR-IC was assessed in patients with measurable intracranial disease (n=75). All responses to CNS target lesions were conducted per RECIST 1.1 criteria as assessed by the investigator.

Results from this exploratory analysis showed a 68% reduction in the risk of CNS progression or death in patients with brain metastases in the tucatinib arm compared to the control arm (HR: 0.32, 95% CI, 0.22-0.48; P<0.0001; Fig. 1A). Median CNS-PFS was 9.9 months vs 4.2 months in the tucatinib and control arm. There was a 42% reduction in the risk of death for patients with brain metastases in the tucatinib arm compared to the control arm (HR: 0.58, 95% CI: 0.40-0.85; P=0.005; Fig 1B). Median OS was 18.1 months vs 12.0 months in the tucatinib and control arm, respectively.

Figure 1. Kaplan-Meier curves for patients with brain metastases.[1,2] (A) CNS progression-free survival (CNS-PFS) per investigator assessment. (B) Overall survival (OS).



TUC: Tucatinib, Tras: Trastuzumab, Cape: Capecitabine, Pbo: Placebo

Additionally, among the 75 patients with active brain metastases, the confirmed ORR-IC was significantly higher in the tucatinib arm 47.3% (95% CI, 33.7% to 61.2%) compared to 20.0% (95% CI, 5.7% to 43.7%) in the control arm (P=0.03). Median DOR-IC was 6.8 months (95% CI, 5.5 to 16.4 months) in the tucatinib arm versus 3.0 months (95% CI, 3.0 to 10.3 months) in the control arm.

Patients who continued study treatment after an isolated brain progression (n=30) had a 67% reduction in their risk of a second event of intracranial progression or death in the tucatinib arm compared to the control arm (HR: 0.33, 95% CI: 0.11 to 1.02). Median time from randomization to second progression was 15.9 months in the tucatinib arm and 9.7 months in the control arm. Median time from first brain progression to second progression or death was 7.6 (95% CI, 3.9 to 11.3 months) and 3.1 (95% CI, 1.2 to 4.1 months), respectively.

Safety and tolerability were assessed in the total HER2-positive metastatic breast cancer population (n=601) enrolled in the HER2CLIMB trial, including patients with brain metastases.[4] The most common adverse events (AEs) observed in the tucatinib arm included diarrhea (80.9% any grade, 12.9% Grade ≥3), palmar-plantar erythrodysesthesia (PPE) syndrome (63.4% any grade, 13.1% Grade ≥3), nausea (58.4% any grade, 3.7% Grade ≥3), fatigue (45% any grade, 4.7% Grade ≥3), and vomiting (35.9% any grade, 3.0% Grade ≥3). The most common AEs observed in the placebo control arm included diarrhea (53.3% any grade, 8.6% Grade ≥3), PPE syndrome (52.8% any grade, 9.1% Grade ≥3), nausea (43.7% any grade, 3.0% Grade ≥3), fatigue (43.1% any grade, 4.1% Grade ≥3), and vomiting (25.4% any grade, 3.6% Grade ≥3).

Summary: The combination of tucatinib, trastuzumab, and capecitabine is the first systemic therapy to our knowledge to demonstrate intracranial efficacy and survival benefits in patients with HER2-positive breast cancer with brain metastases in a prospective, randomized clinical trial. These data support tucatinib as a preferred therapy with a category 1 level of evidence for patients with HER2+ metastatic breast cancer with brain metastases.

Sincerely,

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The following articles are submitted in support of this proposed change:

1. Lin NU, Murthy RK, Anders CK, et al. Tucatinib versus placebo added to trastuzumab and capecitabine for patients with previously treated HER2+ metastatic breast cancer with brain metastases (HER2CLIMB). In: *American Society of Clinical Oncology (ASCO) Annual Meeting*. ; 2020. doi:10.1200/JCO.2020.38.15_suppl.1005
2. Lin NU, Borges V, Anders C, Murthy RK, Paplomata E. Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial. *J Clin Oncol*. Published online 2020. doi:10.1200/JCO.20.00775 Journal of Clinical Oncology
3. Seattle Genetics. TUKYSA™ (tucatinib) tablets U.S. Prescribing Information. Published online 2020.
4. Murthy RK, Loi S, Okines A, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. *N Engl J Med*. 2020;382(7):597-609. doi:10.1056/NEJMoa1914609
5. U.S. Food and Drug Administration. Cancer Clinical Trial Eligibility Criteria: Brain Metastases Guidance for Industry. *Food Drug Adm*. Published online 2019. Accessed April 17, 2020. https://www.fda.gov/media/121317/download