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NCCN Breast Cancer Guideline Panel:

On behalf of Seattle Genetics, Inc., in consideration of TUKYSA™'s (tucatinib) recent approval and as follow-up to our previous submission, we respectfully request the NCCN Breast Cancer Guideline Panel to review the enclosed data and prescribing information for inclusion of tucatinib in the guidelines.

Specific Request: Please consider the inclusion of tucatinib in combination with trastuzumab and capecitabine in the NCCN Breast Cancer Guidelines as a preferred therapy with a category 1 level of evidence for patients with HER2+ metastatic breast cancer (MBC), including those with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting. This request is supported by the overall survival (OS) benefit observed in the HER2CLIMB trial.[1] Additionally, please consider inclusion, as a note, of the benefit that extended to those patients with previously untreated, treated stable, and/or treated progressing brain metastases.[1]

FDA Clearance: Tucatinib is an FDA-approved kinase inhibitor indicated in combination with trastuzumab and capecitabine for 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.[2]

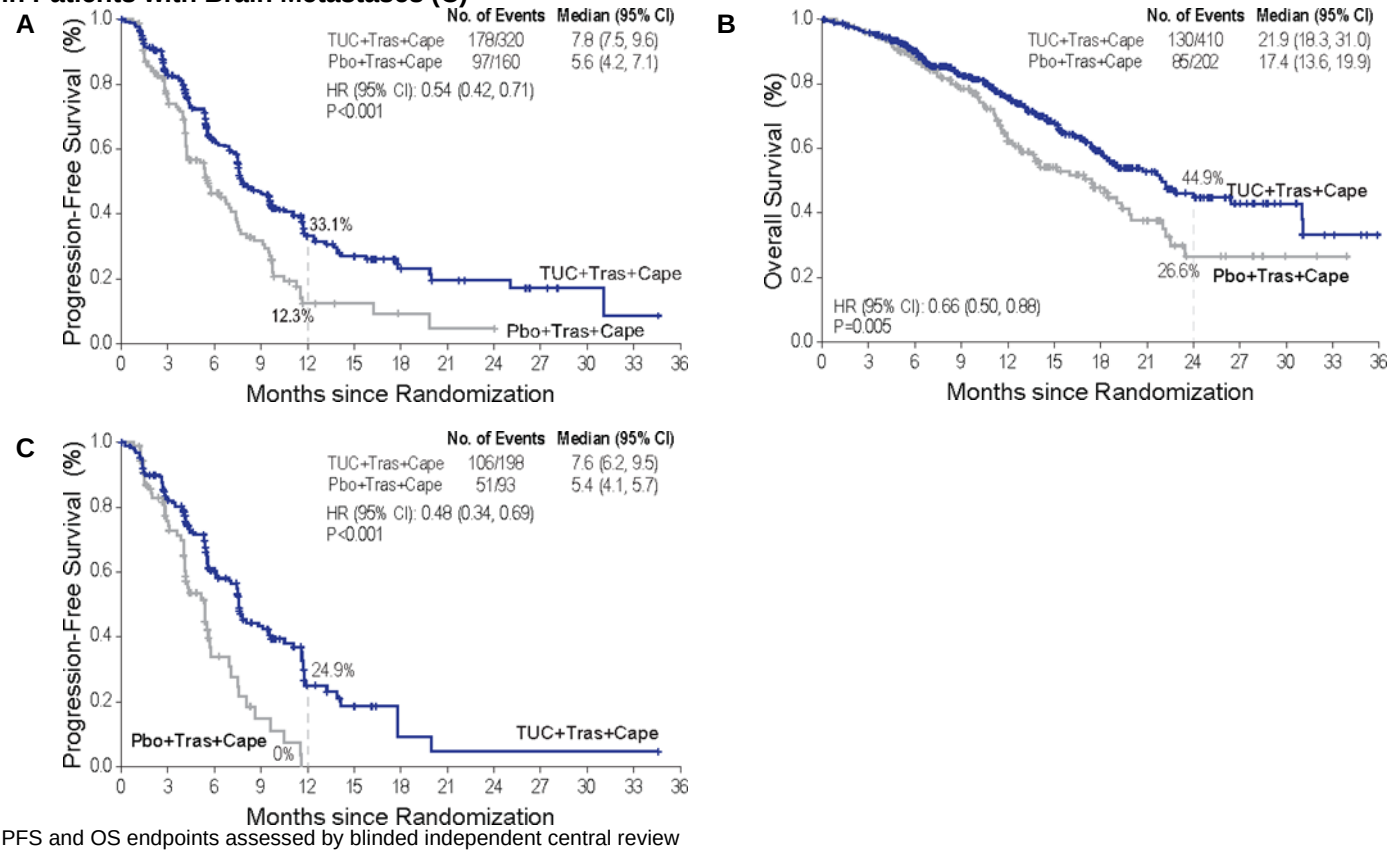
Rationale: Despite recent treatment advances in HER2+ MBC, there is a significant need for new treatments that extend survival as very few pivotal trials have demonstrated an overall survival (OS) advantage in the metastatic setting.[3–8] Furthermore, after progression on ado-trastuzumab emtansine (T-DM1), there are no approved therapies demonstrating an OS benefit in an active-comparator trial. [3–8] In addition, up to 50% of patients with HER2+ MBC develop brain metastases during the course of disease.[9,10] Clinical trials have historically excluded these patients due to concerns of poor prognosis, shortened life expectancy, or increased risk of toxicity with the exception of HER2CLIMB.[1,11] Tucatinib is an oral, highly selective inhibitor of the HER2 tyrosine kinase.[1] The HER2CLIMB trial, presented at the 2019 San Antonio Breast Cancer Symposium (SABCS) and simultaneously published in the New England Journal of Medicine, evaluated tucatinib in combination with trastuzumab and capecitabine in HER2+ locally advanced unresectable or MBC. The trial included patients with stable treated brain metastases and importantly, treated, progressing or untreated brain metastases. The tucatinib combination showed a statistically significant and clinically meaningful reduction in the risk of progression or death, including in patients with brain metastasis, as well as a significant improvement in OS.[1]

Clinical Data: HER2CLIMB is a randomized, double-blind, placebo-controlled, active-comparator, pivotal trial of tucatinib in combination with trastuzumab and capecitabine (tucatinib arm) versus placebo, trastuzumab and capecitabine (placebo control arm), in patients with HER2+ locally advanced unresectable or MBC previously treated with trastuzumab, pertuzumab, and T-DM1.[1]

The primary endpoint was progression free survival (PFS) based on blinded independent central review (BICR) in the first 480 patients enrolled in the trial.[1] Key secondary endpoints included OS by BICR in all enrolled patients (n=612), PFS by BICR in patients with brain metastases ($PFS_{BrainMets}$; n=291), objective response rate (ORR) by BICR in patients with measurable disease at baseline (n=511), as well as overall safety in all patients who received at least one dose of study treatment (n=601).

Results from the trial demonstrated improvement in the primary endpoint of median PFS for patients randomized to the tucatinib arm, with a 46% reduction in the risk of disease progression or death compared to the placebo control arm (Figure 1A).[1] At 1 year, the estimated PFS was 33.1% (95% CI, 26.6 to 39.7) for the tucatinib arm compared to 12.3% (95% CI, 6.0 to 20.9) in the placebo control arm. In the total population, the tucatinib arm demonstrated an improvement in OS, with a 34% reduction in the risk of death compared to the placebo control arm (Figure 1B). The 2-year OS was 44.9% (95% CI, 36.6 to 52.8) in the tucatinib arm compared to 26.6% (95% CI, 15.7 to 38.7) in the placebo control arm.

Figure1: Kaplan-Meier Estimates of PFS in the Primary Endpoint (A), OS in the Total Population (B), and PFS in Patients with Brain Metastases (C)[1]



PFS and OS endpoints assessed by blinded independent central review

For patients with brain metastases at baseline, the tucatinib arm also demonstrated superior PFS with a 52% reduction in the risk of disease progression or death compared to the placebo control arm (Figure 1C).[1] The 1-year $PFS_{BrainMets}$ in the tucatinib arm was 24.9% (95% CI, 16.5 to 34.3) vs 0% in the placebo control arm.

The confirmed ORR in patients with measurable disease at baseline (n=511) was 40.6% (95% CI, 35.3 to 46.0) in the tucatinib arm compared to 22.8% (95% CI, 16.7 to 29.8) in the placebo control arm (p<0.001).[1]

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).[1] 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: Thank you for considering the evidence supporting tucatinib for inclusion in the NCCN guidelines. Results from a randomized, double-blind, active-comparator trial demonstrate a PFS and OS advantage for tucatinib, trastuzumab, and capecitabine compared to placebo, capecitabine, and trastuzumab for patients with HER2+ MBC, including patients with brain metastases. These data support tucatinib as a preferred therapy with a category 1 level of evidence for patients with HER2+ MBC, including those with brain metastases who have received one or more prior anti-HER2-based regimens in the metastatic setting.

Sincerely,

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