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NCCN Breast Cancer Guideline Panel:

On behalf of Seattle Genetics, Inc., we respectfully request the NCCN Breast Cancer Guideline Panel to review the enclosed data for inclusion of tucatinib in the Guidelines for the treatment of patients with HER2+ metastatic breast cancer (mBC).

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 high level of evidence due to the overall survival (OS) benefit in a blinded, randomized controlled trial. This request is for patients with HER2+ mBC, including those with brain metastases, who have received prior HER2 directed therapies in the neoadjuvant, adjuvant, or metastatic settings.

FDA Clearance: Tucatinib has been granted Breakthrough Therapy designation by the FDA for the treatment of HER2+ mBC patients. Seattle Genetics has submitted a New Drug Application (NDA) to the FDA.

Rationale: Despite recent treatment advances in HER2+ mBC, there is still a significant need for new treatments that extend survival. After progression on ado-trastuzumab emtansine (T-DM1), there are currently no approved therapies demonstrating progression-free survival (PFS) or overall survival (OS) benefit.[1-4] In addition, up to 50% of patients with HER2+ mBC develop brain metastases during the course of disease.[5,6] Clinical trials have historically excluded these patients due to concerns of poor prognosis, shortened life expectancy, or increased risk of toxicity.[7] Tucatinib is an oral, highly selective inhibitor of the HER2 tyrosine kinase. 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 including 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 overall survival.[8]

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 locally advanced, unresectable, or metastatic HER2+ breast cancer previously treated with trastuzumab, pertuzumab, and T-DM1.[8]

The primary endpoint was PFS based on blinded independent central review (BICR) in the first 480 patients enrolled in the trial. Key secondary endpoints were OS, which included all subjects enrolled (n=612), PFS in subjects with brain metastases ($PFS_{BrainMets}$) by BICR (n=291), and 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).[8]

The trial met the primary endpoint by demonstrating an improvement in median PFS with a 46% reduction in the risk of disease progression or death (Figure 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. The tucatinib arm demonstrated an improvement in OS, with a 34% reduction in the risk of death compared to the placebo control arm (Figure 2). 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.[8]

Figure 1: Kaplan-Meier Estimate of PFS by BICR in the Primary Endpoint[8]

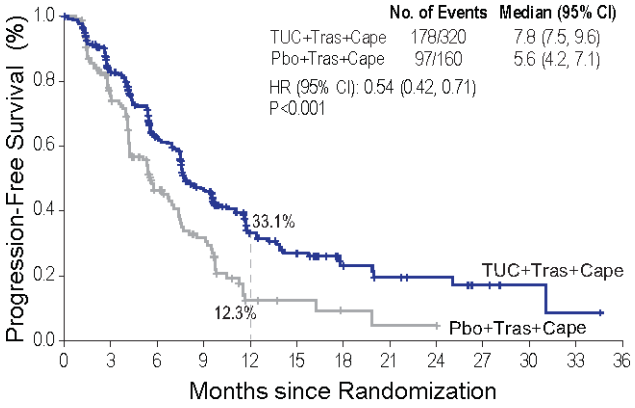


Figure 2: Kaplan-Meier Estimate of OS by BICR in the Total Population[8]

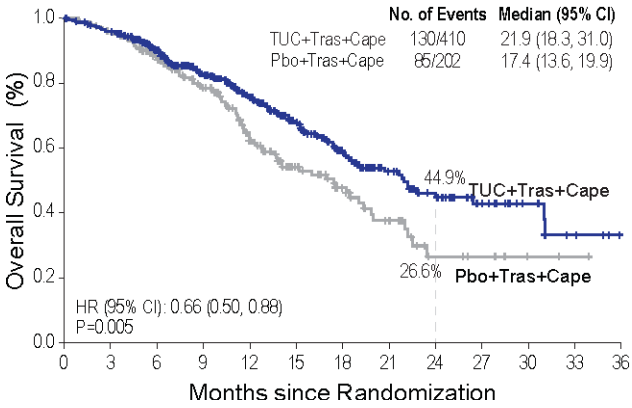
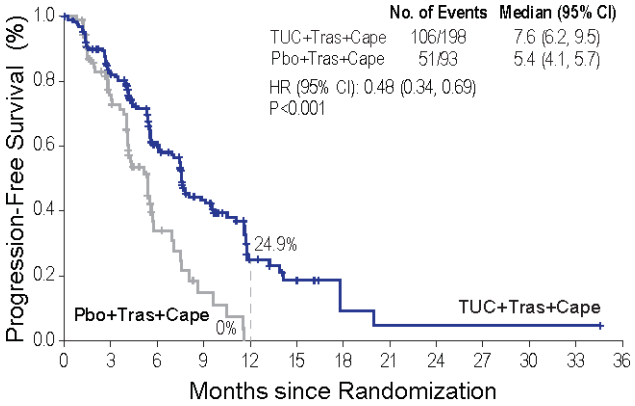


Figure 3: Kaplan-Meier Estimate of PFS by BICR in Patients with Brain Metastases[8]



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 3). 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.[8]

The confirmed ORR 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).[8]

The most common adverse events (AEs) observed in the tucatinib arm were mostly Grade 1 or 2, and 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).[8]

Summary: Thank you for considering the evidence supporting tucatinib for inclusion in the guidelines. These data demonstrate a PFS and OS advantage for tucatinib, trastuzumab, and capecitabine in the total population, including patients with brain metastases. These data provide evidence to support tucatinib as a preferred therapy with a high level of evidence for patients with HER2+ metastatic breast cancer, including those with brain metastases, who have who have received prior therapy in the neoadjuvant, adjuvant, or metastatic settings.

Sincerely,

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