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NCCN Breast Cancers Guideline Panel,

On behalf of Seagen, we respectfully request the NCCN Breast Cancer Guideline Panel to review the enclosed data supporting an update to the guideline for TUKYSA® (tucatinib) in combination with trastuzumab and capecitabine for patients with HER2+ metastatic breast cancer (MBC).

Specific Request: We request the NCCN Breast Cancer Guidelines Panel consider an administrative change to update the table on page 81 (BINV-Q 2 of 8) to include tucatinib + trastuzumab + capecitabine within the second-line treatment section of the table, as currently reflected in footnote *n*.

Additionally, we ask the Panel to consider including tucatinib in combination with trastuzumab and capecitabine as a preferred treatment option in patients with HER2+ MBC and visceral metastases (BINV-Q, 2 of 8).

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+ breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.[1]

Rationale: Patients with MBC and visceral metastases as the first site of recurrence face a poor prognosis.[2] Currently, there are limited data available demonstrating activity or a survival benefit in HER2+ MBC with visceral metastases, and additional treatment options in patients with visceral metastasis are needed.

The HER2CLIMB study was a randomized controlled trial that enrolled 612 patients which included 455 patients or 74% of the study population with visceral metastases.[1,3] HER2CLIMB demonstrated an overall survival (OS) advantage in the overall treatment population. Furthermore, in an exploratory analysis, an OS benefit was also observed in patients with visceral metastases.

Clinical Data: HER2CLIMB was a pivotal, global, randomized, double-blind, placebo-controlled, active-comparator trial in patients with advanced unresectable or HER2+ MBC, previously treated with trastuzumab, pertuzumab, and T-DM1.[3] Patients were randomized to receive tucatinib in combination with trastuzumab and capecitabine (tucatinib arm) versus placebo, trastuzumab, and capecitabine (control arm). A total of 612 patients were included in the intent to treat (ITT) population, including 455 patients (74%) with visceral metastases at baseline.

HER2CLIMB met its primary endpoint of progression free survival (PFS) at the primary analysis by reducing the risk of progression or death by 46% (HR=0.54; 95% CI: 0.42 to 0.71, $P<0.001$) in the first 480 patients enrolled.[3] The tucatinib arm demonstrated an improvement of 4.5 months in the key alpha-controlled secondary endpoint of OS, with a 34% reduction in the risk of death compared to the control arm (HR=0.66; 95% CI: 0.50 to 0.88, $P=0.005$). The addition of tucatinib resulted in a nearly 2-fold improvement in objective response rate (ORR; 40.6% vs. 22.8%; $P=0.00008$) with a median time to first response of 1.4 months.[3,4]

Consistent with the primary analysis, a prespecified analysis performed approximately 2 years following the last patient randomized (median duration of follow-up: 29.6 months) reported a 27% decrease in the risk of death among patients in the tucatinib arm compared to patients in the control arm

(HR=0.73; 95% CI: 0.59 to 0.90).[5] The median OS was 24.7 months in the tucatinib arm (95% CI: 21.6 to 28.9) and 19.2 months (95% CI: 16.4 to 21.4) in the control arm (OS benefit: 5.5 months).

An exploratory analysis of patients with visceral metastases demonstrated a clinically meaningful improvement in OS (Table 1).[5] Among 455 patients with visceral metastases, patients in the tucatinib arm had a 30% decrease in risk for death relative to the control arm (HR=0.70; 95% CI: 0.55 to 0.89). Median overall survival was 21.6 months (95% CI: 18.1, 25.6) for patients in the tucatinib arm compared to 16.9 months (95% CI: 12.3, 19.4) in the control arm.

Table 1. Median OS in Patients With and Without Visceral Metastases*[5]

	Patients With Visceral Metastases* n=455		
	HR (95% CI)	***P*-value**	**Median OS (95% CI)**
Tucatinib + trastuzumab + capecitabine	0.70 (0.55, 0.89)	0.004	21.6 months (18.1, 25.6)
Placebo + trastuzumab + capecitabine			16.9 months (12.3, 19.4)
	Patients Without Visceral Metastases* n=157		
	HR (95% CI)	***P*-value**	**Median OS (95% CI)**
Tucatinib + trastuzumab + capecitabine	0.80 (0.48, 1.3)	0.336	32.9 months (27.7, 46.7)
Placebo + trastuzumab + capecitabine			26.9 months (20.5, NE)

*Non-visceral disease included tumors located in the neck, breast, chest wall, bone, lymph nodes, skin and subcutaneous tissue. Brain metastases are considered non-visceral disease. All other locations, including pleura and peritoneum, are classified as visceral disease.

In the primary analysis, the most common adverse events (AEs), any grade, observed in the tucatinib arm included diarrhea (80.9%), palmar-plantar erythrodysesthesia (PPE) syndrome (63.4%), nausea (58.4%), fatigue (45%), and vomiting (35.9%).[3] The most common AEs, any grade, observed in the control arm included diarrhea (53.3%), PPE syndrome (52.8%), nausea (43.7%), fatigue (43.1%), and vomiting (25.4%).

Summary: Thank you for considering an update including tucatinib in combination with trastuzumab and capecitabine within the second-line treatment section of the table on page 81. This inclusion, as currently reflected in footnote n, can help avoid confusion and more clearly represent the second-line treatment options for patients with HER2+ MBC.

Additionally, thank you for considering the data which highlight the sustained OS benefit of tucatinib in combination with trastuzumab and capecitabine in a randomized controlled trial that was inclusive of patients with visceral metastases. This survival benefit supports the inclusion of tucatinib + trastuzumab + capecitabine as a preferred treatment option for patients with HER2+ MBC and visceral metastases.

Sincerely,

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Seagen Inc.

References:

1. Seagen Inc. TUKYSA® (tucatinib) tablets U.S. Prescribing Information. 2020.
2. Imkampe A, Bendall S, Bates T. The significance of the site of recurrence to subsequent breast cancer survival. *Eur J Surg Oncol*. 2007;33(4):420-423. doi:10.1016/j.ejso.2006.09.005
3. 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
4. Curigliano G, Murthy RK, Loi S, et al. Tucatinib vs. Placebo Added to Trastuzumab and Capecitabine in Previously Treated HER2+ Metastatic Breast Cancer With and Without Brain Metastases (HER2CLIMB). In: *ESMO Breast Cancer Meeting Meeting, May 23-24*. Virtual Meeting; 2020.
5. Curigliano G, Mueller V, Borges V, et al. Updated Results of Tucatinib Versus Placebo Added to Trastuzumab and Capecitabine for Patients With Pretreated HER2+ Metastatic Breast Cancer With and Without Brain Metastases (HER2CLIMB). In: *American Society of Clinical Oncology Annual Meeting, June 4-8*. Virtual Meeting; 2021.