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NCCN Guidelines Review Panel: Esophageal/Gastric Cancers

On behalf of Amgen Inc., I respectfully request the NCCN panel members to review the recently published data on KANJINTI™ (trastuzumab-anns). Based on the totality of evidence supporting demonstration of clinical comparability, Amgen has received US Food and Drug Administration (FDA) approval of KANJINTI™ as a biosimilar to US-licensed HERCEPTIN® (trastuzumab).

Specific Changes: Please consider the addition of trastuzumab-anns (420 mg in a multiple-dose vial) as an appropriate substitute for trastuzumab within the NCCN Guidelines, NCCN Patient Guidelines, and the associated “NCCN Drugs and Biologics Compendium™” for the following cancer types per the FDA-approved KANJINTI™ label: adjuvant breast cancer, metastatic breast cancer, metastatic gastric cancer or gastroesophageal junction adenocarcinoma.

Rationale: Biosimilars offer the potential to expand treatment options and mitigate cost barriers for payers. Trastuzumab-anns development program aligns with the statutory requirements outlined in the draft FDA guidance for establishing biosimilarity to the reference product. The totality of evidence submitted includes comparisons of extensive structural and functional product characterization, animal data, pharmacokinetic (PK) and pharmacodynamic data (PD), immunogenicity, safety, and efficacy – supporting that trastuzumab-anns is highly similar to trastuzumab and that there are no clinically meaningful differences between the products.

- The extensive analytical characterization and comparison of the structural and functional properties of trastuzumab-anns to trastuzumab demonstrated that they are highly similar. In *in vivo* studies trastuzumab-anns and trastuzumab treatment groups were found to have similar and dose-dependent antitumor activity in xenograft models using BT-474 (breast tumor) and NCI-N87 (gastric tumor) cells.
- The PK profile of trastuzumab-anns was similar to that of trastuzumab in healthy subjects following a single dose and in patients with HER2-positive early breast cancer (eBC) following multiple dosing. Comparative clinical data in patients with eBC demonstrated clinical similarity (PK, efficacy, safety, immunogenicity) between trastuzumab-anns and trastuzumab:
 - Sensitive endpoints and patient populations were chosen to identify any potential clinically meaningful differences with the reference biologic, which may differ from those of the pivotal clinical studies for the reference product.
 - Conducting biosimilar studies in a sensitive patient population provides scientific evidence supporting extrapolation to less sensitive and homogenous populations.

- Study design includes both a neoadjuvant and adjuvant treatment phase. To explore the potential clinical effects on safety and immunogenicity, the study included a single-transition from trastuzumab to trastuzumab-anns, which mimics real world clinical use of biosimilars.
- Uses pathologic complete response (pCR) as the recognized endpoint for neoadjuvant studies in breast cancer, which has been found to correlate with overall survival, and is considered a more robust endpoint for evaluation of clinical comparability vs the evaluation of objective response rate in the metastatic setting.

Based on the robust scientific data package submitted to the FDA, justification was provided to support extrapolation to approved indication(s) of Herceptin®:

- The mechanism of action of trastuzumab, regardless of tumor type or location, is the binding to HER2 receptor and inhibits proliferation of tumor cells that overexpress human epidermal growth factor receptor 2 (HER2) receptors.
- Comparative PK data, combined with the knowledge of the PK profiles of trastuzumab-anns in *in vivo* and *in vitro* assays, indicate that trastuzumab-anns will retain a PK profile similar to trastuzumab for all available FDA-approved indications.
- In the clinical comparability study, the overall incidence of adverse events (AEs) was comparable between the treatment groups. Neoadjuvant and adjuvant phases of treatment in eBC are sensitive and representative of the safety risks in metastatic breast cancer and metastatic gastric cancer.
- Immunogenicity was similar in the clinical comparability study of trastuzumab-anns, trastuzumab/trastuzumab, and trastuzumab/trastuzumab-anns treatment groups; two (1%), two (1%), and four (2%) patients, respectively, tested positive for binding antibody at any time during the study. With no patients developing neutralizing antibodies.

A summary of the totality of evidence and sufficient scientific justification for extrapolation is provided in the enclosed KANJINTI™ (trastuzumab-anns) Clinical Fact Sheet.

FDA Status: KANJINTI™ (trastuzumab-anns) is FDA-approved, and indicated for:

- Adjuvant treatment of HER2-overexpressing node-positive or node-negative (ER/PR-negative or with one high-risk feature) breast cancer:
 - As part of a treatment regimen containing doxorubicin, cyclophosphamide and either paclitaxel or docetaxel
 - As part of treatment with docetaxel and carboplatin
 - As a single agent following multi-modality anthracycline-based therapy
- In combination with paclitaxel for the first line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease
- In combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease.

Enclosed, please find the following:

- KANJINTI™ (trastuzumab-anns) Clinical Fact Sheet
- von Minckwitz G, Colleoni M, Kolberg HC, et al. Efficacy and safety of ABP 980 compared with reference trastuzumab in women with HER2-positive early breast cancer (LILAC study): a randomised, double-blind, phase 3 trial. *Lancet Oncol.* 2018; 19(7):987-998.
- Hutterer KM, et al. Assessing Analytical and Functional Similarity of Proposed Amgen Biosimilar ABP 980 to Trastuzumab. *BioDrugs* (2019). <https://doi.org/10.1007/s40259-019-00350-9>
- Hanes V, Chow V, Zhang N, et al. A randomized, single-blind, single-dose study evaluating the pharmacokinetic equivalence of proposed biosimilar and trastuzumab in healthy male subjects. *Cancer Chemother Pharmacol.* 2017; 79(5):881-888.

Amgen is providing you with the attached reprint. Please note that if you are a covered recipient as defined by the Affordable Care Act (ACA), Amgen's cost to obtain such reprint may need to be disclosed and reported in accordance with the requirements under the ACA, state law, and related disclosure obligations by Amgen. If you are a non-covered recipient requesting information on behalf of or for the benefit of a covered recipient (physician or teaching hospital), the same requirements may apply.

Should you have any questions or require additional materials, please feel free to contact me directly at +1 (805) 313-4438. Thank you in advance for your prompt attention to this matter and I look forward to your response.

Sincerely,



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