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NCCN Guidelines Panel: Colon and Rectal Cancer

Dear NCCN Guidelines Panel,

On behalf of Genentech, Inc., I respectfully request the Guideline Panel to review the enclosed publications and consider inclusion of **Herceptin® (trastuzumab)** in combination with **Perjeta® (pertuzumab)** for the treatment of patients with human epidermal growth factor receptor 2 (HER2)-amplified/overexpressing metastatic colorectal cancer (mCRC).

- Hainsworth JD, Meric-Bernstam F, Swanton C, et al. Targeted Therapy for Advanced Solid Tumors on the Basis of Molecular Profiles: Results From MyPathway, an Open-Label, Phase IIa Multiple Basket Study. J Clin Oncol. 2018 Feb 20;36(6):536-542.
- Hurwitz H, Raghav KPS, Burris H, et al. Pertuzumab + Trastuzumab for HER2-Amplified/Overexpressed Metastatic Colorectal Cancer (mCRC): Interim Data from MyPathway. Abstract available at: http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.4_suppl.676

Specific Changes Requested:

Consider the inclusion of Herceptin in combination with Perjeta in the systemic therapy for advanced or metastatic disease section of the guideline as a treatment option for patients with wild-type KRAS, HER2-amplified/overexpressing mCRC.

FDA Clearance:

- Herceptin is not FDA-approved for use in the treatment of colorectal cancer. Please refer to the product prescribing information for the full FDA-approved indications and safety information, available at: https://www.gene.com/download/pdf/herceptin_prescribing.pdf
- Perjeta is not FDA-approved for use in the treatment of colorectal cancer. Please refer to the product prescribing information for the full FDA-approved indications and safety information, available at: https://www.gene.com/download/pdf/perjeta_prescribing.pdf

Rationale:

MyPathway is an open-label, multi-cohort, Phase 2 study evaluating the safety and efficacy of targeted treatments in patients with advanced treatment-refractory solid tumors. Patients received treatment based on the following pre-defined genetic or molecular alterations: HER2, epidermal growth factor receptor (EGFR), rapidly accelerated fibrosarcoma B (BRAF), Hedgehog, anaplastic lymphoma kinase (ALK), programmed death-ligand 1 (PD-L1) copy number gain, deficient mismatch repair (dMMR), microsatellite instability-high (MSI-H), tumor mutation burden-high (TMB-H), and/or alterations of DNA proofreading/repair genes. The primary endpoint is investigator-assessed objective response rate (ORR) within each tumor-pathway cohort. Secondary endpoints include progression-free survival (PFS), 1-year overall survival (OS), clinical benefit rate (CBR), and duration of response (DOR).[1,2]

- Patients with HER2-amplified/overexpressing mCRC comprised the largest tumor-pathway cohort (n=37, Data cut-off date: November 1, 2016). Patients in this cohort had advanced refractory disease and received a median of four prior lines of therapy, including prior anti-EGFR therapy.[1]

- Patients with HER2 molecular alterations were treated with intravenous Perjeta (840 mg loading dose followed by 420 mg every 3 weeks) plus intravenous Herceptin (8 mg/kg loading dose followed by 6 mg/kg every 3 weeks).[1]

- Treatment with Herceptin in combination with Perjeta resulted in a partial response (PR) in 14 patients (ORR 38%; 95% CI: 23% to 55%) and a median DOR of 11 months (Range: <1 to 16+ months; 95% CI: 2.8 months to not estimable). Four additional patients (11%) had stable disease > 120 days.[1]

Additional sub-group analyses of patients with HER2-amplified/overexpressing mCRC in MyPathway were also reported by Hurwitz H et al.[2]

- Of 34 patients (Data cut-off date: October 15, 2016) with HER2-amplified/overexpressing mCRC, the tumor site was the colon in 23 patients (left side, n=14; right side, n=8; transverse, n=1) and the rectum in 11 patients. Nine (26.5%) patients had KRAS mutated mCRC.

- In patients with wild-type KRAS vs mutated KRAS, ORR was 52% vs 0%. Patients with wild-type KRAS had a median OS of 14.0 months (95% CI, 8.0-22.1) vs 5.0 months (95% CI, 1.2-10.3) in patients with mutated KRAS.

- Patients with right sided colon cancer had an ORR of 12.5% vs 42.9% in patients with left sided colon cancer. Mutated KRAS was present in 62.5% of right-sided colon tumors and 7.1% in left-sided colon tumors.

- In patients with rectal cancer, ORR was 45.5% (95% CI, 16.7-76.6).

- Overall, 13 patients treated with Herceptin in combination with Perjeta achieved a PR for an ORR of 38.2% (95% CI, 22.2-56.4). The median PFS was 4.6 months (95% CI, 1.6-9.8) and median OS was 10.3 months (95% CI, 7.2-22.1). The median DOR was 10.3 months (Range, 1.4–15.7 months).

- No new safety signals were observed for Herceptin in combination with Perjeta and the safety profiles were consistent with the product labels.

MyPathway is the only study thus far presenting results for Herceptin in combination with Perjeta in patients with HER2-amplified/overexpressing mCRC that we are aware of. Prior studies have evaluated other dual-targeted therapy strategies.[3]

If you have any questions, please contact us at the phone number and email provided above.

Respectfully submitted,
Patrice Esser, PharmD, MPH

References:

1. Hainsworth JD, Meric-Bernstam F, Swanton C, et al. Targeted Therapy for Advanced Solid Tumors on the Basis of Molecular Profiles: Results From MyPathway, an Open-Label, Phase IIa Multiple Basket Study. J Clin Oncol. 2018 Feb 20;36(6):536-542.
2. Hurwitz H, Raghav KPS, Burris H, et al. Pertuzumab + Trastuzumab for HER2-Amplified/Overexpressed Metastatic Colorectal Cancer (mCRC): Interim Data from MyPathway. Abstract available at: http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.4_suppl.676
3. Sartore-Bianchi A, Trusolino L, Martino C, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. Lancet Oncol. 2016 Jun;17(6):738-746.