ESMO Open
Cancer Horizons

HER2-targeted therapy should be shifted towards an earlier line for patients with anti-EGFR-therapy naïve, *HER2*-amplified metastatic colorectal cancer

Yoshiaki Nakamura,[1,2] Kentaro Sawada,[1] Satoshi Fujii,[3] Takayuki Yoshino[1]

To cite: Nakamura Y, Sawada K, Fujii S, *et al*. HER2-targeted therapy should be shifted towards an earlier line for patients with anti-EGFR-therapy naïve, *HER2*-amplified metastatic colorectal cancer. *ESMO Open* 2019;**4**:e000530. doi:10.1136/esmoopen-2019-000530

Received 21 April 2019
Accepted 26 April 2019

[1]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan
[2]Translational Research Support Section, Translational Research Management Division, Clinical Research Support Office, National Cancer Center Hospital East, Kashiwa, Japan
[3]Division of Pathology, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Kashiwa, Japan

Correspondence to
Dr Takayuki Yoshino; tyoshino@east.ncc.go.jp

Bregni and colleagues suggested potential clinical utility for anti-epidermal growth factor receptor (EGFR) therapy in *HER2*-amplified metastatic colorectal cancer (mCRC), based on re-evaluation of the HERACLES study in which 14/26 patients with *HER2*-amplified mCRC had stable disease ≥6 months with that treatment.[1] However, it is difficult to prove the presence of a survival benefit from anti-EGFR therapy due to the lack of a control. We previously reported progression-free survival (PFS) with anti-EGFR therapy was significantly shorter in patients with *HER2*-amplified mCRC versus those with wild-type *RAS/BRAF* (median PFS 2.6 vs 6.0 months; HR 3.89; 95% CI 1.49 to 10.18) and similar to those with mutant *RAS* (median PFS 2.6 vs 2.2 months; HR 1.05; 95% CI 0.38 to 2.92).[2] Also, Korean investigators showed *HER2*-amplified patients treated with cetuximab±irinotecan had significantly shorter PFS vs those with non-amplified *HER2* (median 3.1 vs 5.6 months; HR 2.73; 95% CI 1.18 to 6.31), among patients with refractory mCRC with wild-type *RAS/BRAF*.[3] Consistent clinical Japanese and Korean efficacy data, plus preclinical results,[4] suggest *HER2*-amplified mCRC will demonstrate primary resistance to anti-EGFR therapy.

The authors also indicated liquid biopsy was clinically useful in assessing *HER2* amplification as an acquired anti-EGFR therapy resistance mechanism. However, it remains unclear whether acquired *HER2* amplification is targetable. To address this issue, we evaluated emerging genomic alterations in circulating tumour DNA (ctDNA) after anti-EGFR therapy in 55 patients with *RAS* wild-type and *HER2*-non-amplified mCRC. *HER2* amplifications were newly identified after therapy only in three patients (5.5%), with a low median copy number (adjusted value=4.0), suggesting it could not be targeted (UMIN000029315). Moreover, the MyPathway trial showed that patients with mCRC who were naïve to anti-EGFR therapy had better outcomes with dual-targeted HER2-directed therapy (trastuzumab plus pertuzumab) versus those receiving prior anti-EGFR treatment.[5]

Given the primary resistance to anti-EGFR therapy, the low prevalence of targetable acquired *HER2* amplification after anti-EGFR therapy and promising clinical activity with HER2-directed dual-targeted therapy (particularly for patients with mCRC who are naïve to anti-EGFR agents), we recommend anti-EGFR-therapy naïve patients with a distinct subtype of *HER2*-amplified mCRC should have HER2-targeted treatment investigated in an earlier line. Note, in a situation that requires immediate determination of HER2 status, such as first-line treatment, ctDNA analysis, with its rapid turnaround time, can potentially take the place of tissue-based biomarker tests.

Contributors YN wrote the manuscript with support from SF and TY, YN and KS analysed data. All authors discussed the results and contributed to the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

REFERENCES

1. Bregni G, Sciallero S, Sobrero A. HER2 amplification and anti-EGFR sensitivity in advanced colorectal cancer. *JAMA Oncol* 2019. doi:10.1001/jamaoncol.2018.7229
2. Sawada K, Nakamura Y, Yamanaka T, *et al*. Prognostic and predictive value of HER2 amplification in patients with metastatic colorectal cancer. *Clin Colorectal Cancer* 2018;17:198–205.
3. Jeong JH, Kim J, Hong YS, *et al*. HER2 amplification and cetuximab efficacy in patients with metastatic colorectal cancer harboring wild-type Ras and BRAF. *Clin Colorectal Cancer* 2017;16:e147–52.
4. Bertotti A, Migliardi G, Galimi F, *et al*. A molecularly annotated platform of patient-derived xenografts ("xenopatients") identifies HER2 as an effective therapeutic target in cetuximab-resistant colorectal cancer. *Cancer Discov* 2011;1:508–23.
5. Meric-Bernstam F, Hurwitz H, Raghav KPS, *et al*. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2A, multiple basket study. *Lancet Oncol* 2019;20:518–30.