Impact of Anti-EGFR Therapies on HER2-Positive Metastatic Colorectal Cancer (HER2+ mCRC): A Systematic Literature Review and Meta-Analysis of Clinical Outcomes

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Background

- Colorectal cancer (CRC) is a leading cause of cancer mortality accounting for 10% (1.9 million) of new cancer cases and 9.4% of deaths (935,173) globally in 2020,[1] with approximately 20–25% of patients diagnosed at the advanced/metastatic stage.[2-5]
- Human epidermal growth factor receptor 2 (HER2) is overexpressed/amplified in 3–5% of patients with metastatic CRC (mCRC) and 5–14% of patients with RAS wild-type (WT) mCRC.[6-8]
- HER2 overexpression/amplification in patients with RAS WT mCRC may be associated with resistance to standard of care anti-epidermal growth factor receptor (EGFR) therapies;[9-16] however, no meta-analyses have investigated the association between HER2 overexpression/amplification and resistance to anti-EGFR therapy in patients with mCRC.

Objective

- Our objective was to assess the predictive effect of HER2 amplification/overexpression on anti-EGFR treatment outcomes in RAS WT mCRC patients.

Methods

Systematic literature review

- A systematic review of MEDLINE, Embase, and the Cochrane Library, covering 2001–2021, was conducted in June 2021 in accordance with the PRISMA guidelines.
- Studies evaluating progression-free survival (PFS), overall survival (OS), or overall response rate (ORR) in patients with HER2-positive compared with HER2-negative RAS WT mCRC who received anti-EGFR treatments and whose HER2 status was determined by immunohistochemistry, in-situ hybridization, or tissue-based next-generation sequencing were included.
- Study quality was assessed using the Newcastle-Ottawa Scale, which grades studies in terms of population selection, group comparability, and outcomes assessment.

Meta-analysis

- Hazard ratios (HRs) that were directly reported in the included studies or calculated HRs (patient level data that were extracted from Kaplan–Meier [KM] curves) were considered for the meta-analyses.
- Meta-analyses of proportions (ORR) and HR (PFS, OS) were performed using random-effect models to account for the statistical heterogeneity.
- Pre-specified sensitivity analyses included exclusion of outlier studies and exploring the impact of later lines of treatment by excluding studies assessing first-line treatment only.

Results

Identification of studies

- From a total of 2,249 references identified across all databases, 167 full-text publications were reviewed.
- Of these, 14 publications reporting 12 studies met the inclusion criteria for the systematic literature review and were selected for the feasibility assessment of the OS, PFS, and ORR meta-analysis.
- Following the feasibility assessment, several studies were determined to be unsuitable due to dissimilar HER2 positivity criteria, outcome definitions, or type of outcome measurement and were excluded.
- In total, 5 high-quality retrospective cohort studies reported in 9 publications were included in the meta-analysis, representing 594 patients with mCRC (**Table 1**).[11,13,14,16,17-21]

Meta-analysis population

- While there was some heterogeneity between studies in terms of patient characteristics (**Table 1**), no outlier study was identified among the assessed parameters using the box plot method (age, sex, and follow-up period).

Table 1. Characteristics of studies included in the meta-analysis

Study	Study population	HER2 detection method and positivity criteria	Therapy type	LOT	Median follow-up (months)	Outcome measures
Yagisawa 2021[17] Sawada 2018[16]	Sample size: 54 Median age (years): 64 Male sex (%): 60.0	IHC score 3+ or 2+ and FISH HER2/CEP17 ≥2	Anti-EGFR alone Anti-EGFR + IRI	NR	101.8	PFS[a], ORR, OS[a]
Jeong 2016/2017[11,18]	Sample size: 142 Median age (years): 56 Male sex (%): 70.4	IHC score 3+ or 2+ or IHC scores 3+ or 2+ in ≥50% of cells (HERACLES criteria) and SISH HER2/CEP17 ratio >2.2	CET CET + IRI	4L+	13.2	PFS, OS
Sartore-Bianchi 2018/2019[13,19]	Sample size: 184 Median age (years): 58.6[b] Male sex (%): 71.3	IHC scores 3+ or 2+ in ≥50% of cells and FISH HER2/CEP17 ≥2 in ≥50% of cells (HERACLES criteria)	Anti-EGFR monotherapy +/- CTX	1–5L	50.1 (HER2+), 83.7 (HER2–)	PFS, ORR, OS[a]
Raghav 2016/2019[14,20]	Sample size: 70 Median age (years): 57 Male sex (%): 54.4	NGS ≥4 gene copies identified by an in-house algorithm	CET or PAN CET/PAN + IRI/OX-based CTX	2L/3L	24[c]	PFS
Khelwatty 2021[21]	Sample size: 144 Median age (years): NR Male sex (%): 70.1	IHC score 3+ localized membranous/ cytoplasmic HER2 expression	CET + FOLFOX CET + FOLFIRI	1L	48	PFS, ORR, OS[d]

[a]HR calculated from KM curves. [b]Mean age. [c]Assumed from KM curve follow-up. [d]The HR for OS in Khelwatty 2021[21] was inconsistent (the lower CI was higher than the HR value: HR, 0.21 [95% CI, 0.62–0.73]) and it was excluded from the OS analysis. Study authors were contacted to clarify the data but no response was received. 1L/2L/3L/4L/5L, first/second/third/fourth/fifth line; CEP, chromosome enumeration probe; CET, cetuximab; CI, confidence interval; CTX, chemotherapy; EGFR, epidermal growth factor receptor; FISH, fluorescence in-situ hybridization; FOLFOX, folinic acid, fluorouracil, oxaliplatin; FOLFIRI, folinic acid, fluorouracil, irinotecan; HER2, human epidermal growth factor receptor 2; HER2+, HER2-positive group; HER2–, HER2-negative group; HR, hazard ratio; IHC, immunohistochemistry; ISH, in-situ hybridization; IRI, irinotecan; KM, Kaplan–Meier; LOT, line of treatment; NGS, next-generation sequencing; NR, not reported; OX, oxaliplatin; OS, overall survival; ORR, overall response rate; PAN, panitumumab; PFS, progression-free survival; SISH, silver-enhanced in-situ hybridization.

PFS

- In the meta-analysis of 5 studies reporting PFS, there was a 2.84 times higher risk of death or progression (95% confidence interval [CI], 1.44–5.60) in HER2-positive RAS WT mCRC patients treated with anti-EGFR regimens compared with those who were HER2-negative (**Figure 1**).
- PFS results remained statistically significant in all sensitivity analyses, confirming the robustness of the analyses
  - When a statistical outlier with a high HR (Raghav 2016/2019[14,20]) was excluded, there was a 1.89 higher risk of death or progression (95% CI, 1.27–2.81) in patients who were HER2-positive (**Figure 2**).
  - To explore the impact of later lines of treatment, Khelwatty 2021[21] (which assessed first-line anti-EGFR therapy) was excluded in a pre-specified sensitivity analysis. There was a 2.97 higher risk of death or progression (95% CI, 1.25–7.06) in patients who were HER2-positive.

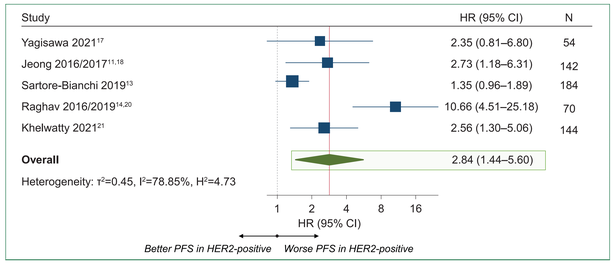
ORR

- Based on a meta-analysis of 3 studies reporting ORR, the odds of response to anti-EGFR treatment were almost 2 times higher in patients with mCRC who were HER2-negative compared with HER2-positive (odds ratio, 1.96 [95% CI, 1.10–3.48]) (**Figure 3**).
- Results were similar in the sensitivity analysis, which excluded an outlier study (Khelwatty 2021,[21] which only assessed first-line anti-EGFR therapy), with the odds of response to anti-EGFR treatment almost 2 times higher in patients with mCRC who were HER2-negative compared with HER2-positive (odds ratio, 1.95 [1.08–3.51]).

OS

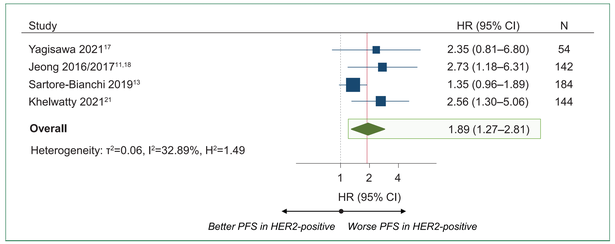
- While there were 3 studies that reported OS, the meta-analysis showed that there was no detrimental effect on OS in patients with either HER2-positive or HER2-negative RAS WT mCRC.

Figure 1. Meta-analysis of PFS with anti-EGFR treatment in patients with RAS WT mCRC who were HER2-positive compared with patients with mCRC who were HER2-negative



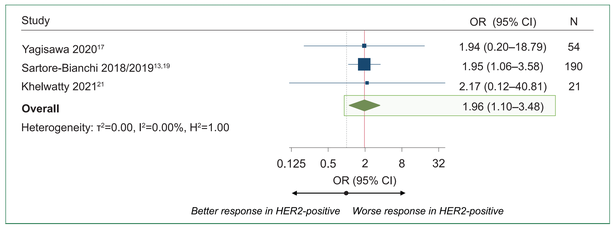
Notes: HR=1 signifies no statistically significant differences between the HER2-positive and HER2-negative groups in the risk of death or progression on anti-EGFR treatment (represented by the gray vertical dashed line); HR >1 signifies higher risk of death or progression on anti-EGFR treatment in the HER2-positive group compared with the HER2-negative group; HR <1 signifies higher risk of death or progression on anti-EGFR treatment in the HER2-negative group compared with the HER2-positive group. The exact effect size of the ORR for the meta-analysis is represented by the vertical red line. CI, confidence interval; HR, hazard ratio; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; PFS, progression-free survival; WT, wild-type.

Figure 2. Sensitivity analysis excluding Raghav 2016/2019[14,20] from meta-analysis of PFS with anti-EGFR treatment in patients with RAS WT mCRC who were HER2-positive compared with patients with mCRC who were HER2-negative



CI, confidence interval; HR, hazard ratio; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; PFS, progression-free survival; WT, wild-type.

Figure 3. Meta-analysis of ORR to anti-EGFR treatment in patients with RAS WT mCRC who were HER2-positive compared with patients with mCRC who were HER2-negative



Notes: OR=1 signifies no statistically significant differences between the HER2-positive and the HER2-negative groups in response to anti-EGFR treatment (represented by the gray vertical dash line); OR <1 signifies higher odds of response to anti-EGFR treatment in the HER2-positive group compared with the HER2-negative group; OR >1 signifies higher odds of response to anti-EGFR treatment in the HER2-negative group compared with the HER2-positive group. The exact effect size of ORR for the meta-analysis is represented by the vertical red line. CI, confidence interval; HR, hazard ratio; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; OR, odds ratio; ORR, overall response rate; WT, wild-type.

Limitations

- The studies included in this meta-analysis were of a retrospective cohort design, and may be considered of lower quality than prospective observational or randomized controlled trials.
- Median follow-up time varied across the studies included; however, HRs were used as an outcome measure, which are not sensitive to follow-up duration.
- Regimens used in the included studies often comprised combination treatments with standard chemotherapies. It was not possible to account for the impact of standard chemotherapies on the pooled effect size.
- Survival analysis was limited by insufficient follow-up data reported in the literature, and subsequent regimens received were not known.

Conclusions

- In patients with RAS WT mCRC treated with anti-EGFR therapies, HER2 overexpression/amplification is associated with worse PFS and ORR.
- HER2 testing should be considered to help optimize treatment choices for patients with mCRC in routine practice.

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DISCLOSURES: This study was sponsored by Seagen Inc., Bothell, WA, USA, in collaboration with Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. TSB-S reports research funding (to institution) from AbGenomics, Agios, Arcus, Arys, Atreca, Bayer, BMS, Boston Biomedical, Celgene, Clovis, Eisai, Genentech, Incyte, Ipsen, Lilly, Merus, Mirati, Novartis, Pfizer, and Seagen Inc.; consulting (to institution) from Arcus, Bayer, Eisai, Genentech, Incyte, Ipsen, Merck, Pfizer, and Seagen Inc.; consulting (to self) from AbbVie, Aptitude Health, AstraZeneca, BeiGene, Boehringer Ingelheim, Celularity, Daichii Sankyo, Deciphera, Exact Science, Foundation Medicine, Illumina, Janssen, Kanaph, MJH Life Sciences, Natera, Sobi, Stemline, and TreosBio; and serving on the IDMC/DSMB for: 1Globe Health Institute, AstraZeneca, Exelixis, Fibrogen, Merck/Eisai, Pancreatic Cancer Action Network, and Suzhou Kintor; scientific advisory board participation with Immuneering, Imugene, Replimune Artiva, Sun Biopharma, and Xilis; royalties from UpToDate; and inventions/patents of WO/2018/183488: HUMAN PD1 PEPTIDE VACCINES AND USES THEREOF – licensed to Imugene, and WO/2019/055687: METHODS AND COMPOSITIONS FOR THE TREATMENT OF CANCER CACHEXIA – licensed to Recursion. KL and RB are employees of Maple Health Group, which received funding from Seagen Inc. in connection with this research. L-IH, MSi, MSt, and JW are employees of Seagen Inc. and hold stock/stock options in Seagen Inc. JS reports advisory board membership/consulting fees/honoraria for AbbVie, Amgen, AstraZeneca, Bayer, Mereo, Natera, Pfizer, Seagen Inc., and Viatris; institutional local/coordinating principal investigator (no financial interest) for AbbVie, Amgen, AStar D3, AstraZeneca, Curegenix, Daiichi Sankyo, Exelixis, Leap Therapeutics, Nektar, Roche Genentech, Sanofi, and Seagen Inc.

ACKNOWLEDGMENTS: Medical writing support was provided by Joshua Fink of Curo, a division of Envision Pharma Group, and funded by Seagen Inc.

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Poster presented at the European Society for Medical Oncology (ESMO) Congress, 2022, Paris, France, September 9-13, 2022