Advanced colorectal cancer still has a poor prognosis and more active drugs are urgently needed. HER2 was investigated as a target in colorectal cancer in two early trials of trastuzumab plus chemotherapy as first, second or third line therapy, which produced interesting but conflicting results. In The Lancet Oncology, Andrea Sartore-Bianchi and colleagues present the results of the HERACLES trial, the first phase 2 trial in patients with refractory colorectal cancer and HER2 amplification or overexpression. They tested the rationally selected combination of trastuzumab plus lapatinib, which preclinical data suggested as having promising activity in patient-derived xenografts of HER2-amplified metastatic colorectal cancer. Sartore-Bianchi and colleagues screened 914 patients who were refractory to chemotherapy and had KRAS wild-type colorectal carcinoma, identifying 46 patients as having HER2-positive disease, and enrolling 27 eligible patients into the study. Eight (30%) patients achieved objective responses—the highest proportion ever reported in treatment-refractory patients. One (4%) patient achieved a complete response; 20 (74%) achieved either a complete response, partial response, or stable disease; median response duration was 9·5 months, median progression-free survival was 5·2 months (95% CI 4–8); and median overall survival was 11·5 months (95% CI 8–17).

In this heavily pretreated population, these outcome data are extraordinary, and they show the relevance of HER2 as a target in the treatment of colorectal cancer. These results represent a breakthrough, even though they apply only to a small subgroup of patients. The results are in line with data from the MyPathway basket trial, which included refractory patients with expression of an identified druggable target (HER2, BRAF, EGFR, or hedgehog). 13 patients with colorectal cancer were given trastuzumab (targeting HER2) plus pertuzumab (targeting the dimerisation domain of HER2, thus inhibiting the HER2-HER3-dimerisation and HER2-activation), with similar results to those of HERACLES (table). Together, the results from HERACLES and MyPathway support preclinical data showing that the inhibition of HER2 with trastuzumab plus either lapatinib or pertuzumab is superior to combination with standard chemotherapy (table). What do these results mean in routine clinical practice? Despite the small number of patients, these data define a new standard of routine therapy for patients with HER2 amplification or overexpression. Data from HERACLES and MyPathway suggest that the combination of anti-HER2 (trastuzumab or lapatinib) plus either anti HER2–3 (pertuzumab) or anti-HER1/EGFR (lapatinib) is a valid approach for colorectal cancer. However, several questions remain.

First, beyond the problems of registration and reimbursement for this novel treatment, a question exists as to which combination should be used. HERACLES and MyPathway included different populations of patients: in MyPathway, patients were not selected by KRAS mutation status (although it can be anticipated that all included patients with RAS wild-type tumours had been refractory to EGFR-targeting antibodies), whereas in HERACLES, all patients had KRAS wild-type tumours, based on

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HER2 immunohistochemistry</th>
<th>Previous lines of therapy</th>
<th>Number of evaluable patients</th>
<th>Complete response or partial response</th>
<th>Complete response, partial response, or stable disease</th>
<th>Median response duration</th>
<th>Median progression-free survival</th>
<th>Median overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clark, 2003 1</td>
<td>Trastuzumab plus FLOX</td>
<td>2+/3+</td>
<td>1-2</td>
<td>21</td>
<td>5 (24%)</td>
<td>NS</td>
<td>4.5 months (range 2.7-11)</td>
<td>NS</td>
</tr>
<tr>
<td>Ramanathan, 2004 2</td>
<td>Trastuzumab plus irinotecan</td>
<td>2+/3+</td>
<td>0-1</td>
<td>7</td>
<td>5 (71%)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Sartore-Bianchi, 2016 3</td>
<td>Trastuzumab plus lapatinib</td>
<td>2+/3+ (KRAS wild-type)</td>
<td>Median 5 (range 2-11)</td>
<td>27</td>
<td>8 (30%)</td>
<td>20 (74%)</td>
<td>9.5 months (range 6-23.5)</td>
<td>5 months (range 4-8)</td>
</tr>
<tr>
<td>Hurwitz, 2016 4</td>
<td>Trastuzumab plus pertuzumab</td>
<td>3+</td>
<td>Median 5 (range 2-8)</td>
<td>13</td>
<td>5 (38%)</td>
<td>10 (76%)</td>
<td>3.4 months (range 1.4-11.1)</td>
<td>5.6 months (range 1.2-12.4)</td>
</tr>
</tbody>
</table>

NS=not stated. FLOX=fluorouracil-leucovorin-oxaliplatin.

Table: Trastuzumab-based combinations for advanced colorectal cancer with HER2 alterations or overexpression.
preclinical evidence that HER2 overexpression and RAS mutation might be mutually exclusive. Since lapatinib, besides being an inhibitor of HER2, also affects EGFR, but pertuzumab does not, the combinations might have differing activity in patients with or without KRAS—or further EGFR pathway—mutations. Given that preclinical data excluded the possibility of HER2 overexpression in tumours with RAS mutation, this differential activity is not very likely, but will be clarified in the ongoing MyPathway trial. For now, trastuzumab plus lapatinib is the treatment of choice, based on the HERACLES data for patients with KRAS wild-type tumours. However, whether pertuzumab might be a less toxic alternative to lapatinib is not known.

The second question is whether anti-HER2 therapy should be given in earlier treatment lines? Since patients who—despite having KRAS wild-type tumours—never responded to cetuximab, responded well to anti-HER2 salvage therapy, a trastuzumab combination might seem preferable before trying an EGFR antibody—or even as a first-line therapy, as is being investigated in the ongoing MODO trial of fluorouracil plus trastuzumab and pertuzumab as a first-line maintenance therapy (NCT02291289).

Third, in HERACLES, treatment seemed to be more effective in tumours with HER2 immunohistochemistry scores of 3+ versus those with scores of 2+. However, even in low HER2 expressers, activity was better than would be expected with no treatment. Therefore, patients with scores of either 2+ or 3+ should be considered candidates for HER2-targeted therapy.

The fourth question is what does HER2 positivity actually mean? In a companion validation study, the HERACLES investigators developed a set of diagnostic criteria. This method should be adopted to identify patients who might benefit from a trastuzumab combination.

Fifth, is it necessary to rebiopsy for HER2 before selection of an anti-HER2 treatment strategy? Retrospective data and the results of HERACLES show good concordance in HER2 status between primary tumours and metastases. Therefore, rebiopsy is probably not necessary although a liquid biopsy might be an attractive additional option in this situation.

The final question is where to go from here? While this anti-HER2 strategy could be adopted for routine salvage therapy and is being investigated in earlier lines, ongoing research is also investigating targeting of HER3 and the combined inhibition of EGFR and HER2–4. HER3 is of particular interest because of its frequent expression in colorectal cancers (up to 75% of colorectal cancers). The NCI-NSABP FC7 trial is investigating the combination of neratinib (a tyrosine kinase inhibitor affecting EGFR, HER2, and HER4) plus cetuximab, with signs of efficacy independent of RAS mutation, and the NCI-MATCH trial (NCT02465060) is investigating trastuzumab emtansine or afatinib. This approach of combined EGFR and HER2–4 pathway inhibition seems interesting, at least in preclinical and early clinical data, not only in breast cancer, but also in colorectal cancer. The future looks promising.

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