Letters

RESEARCH LETTER

Central Nervous System as Possible Site of Relapse in *ERBB2*-Positive Metastatic Colorectal Cancer: Long-term Results of Treatment With Trastuzumab and Lapatinib

In colorectal cancer, *ERBB2* amplification occurs in 5% of *RAS* wild-type metastatic tumors.[1] In the pivotal HERACLES-A trial, chemorefractory patients with *ERBB2* (formerly *HER2*)-positive metastatic colorectal cancer (mCRC) were treated with the combination of trastuzumab and lapatinib,[2] demonstrating the proof of concept that the dual *ERBB2* blockade previously found actionable in preclinical models[3] could be successfully translated to the clinic with remarkable clinical benefit. We also reported that *ERBB2* copy number in plasma was associated with that detected in tumor tissue, identified a cutoff value associated with clinical response,[4] and studied acquired resistance on therapeutic *ERBB2* blockade by longitudinal monitoring of circulating tumor DNA. Along this line, we documented that the onset of resistance was associated with emerging *KRAS* variant clones, *BRAF* amplification, and other molecular alterations already known in breast cancer, such as those of *ERBB2*, *EGFR*, *PIK3CA*, and *PTEN*.[5]

Herein we present long-term clinical results of the HERACLES-A trial in the extended population of 32 patients.

Methods | Inclusion/exclusion criteria, screening phase, treatment/dose schedules, and tumor assessments were previously described.[2] Chemorefractory mCRC was treated with a dual vertical *ERBB2* blockade through the combination of trastuzumab and lapatinib. Tumor assessments were done at baseline and every 8 weeks thereafter until progression.

A total of 35 patients were treated between August 27, 2012, and March 15, 2016 (27 in the trial phase, 8 in an extension cohort). Of these, 3 were not evaluable for response (concomitant *RAS* mutation in 2 participants, absence of target lesions assessable by RECIST in 1 participant). Among the 32 evaluable patients, 28 were men and median (range) age was 62 (40-86) years. All patients provided written informed consent and the institutional review boards of the participating centers approved the study procedures. At the time of the end of study (May 15, 2019), the follow-up was 82 months (6.7 years). The **Table** shows RECIST objective response rates. Median progression-free survival (PFS) and overall survival (OS) were 4.7 months (95% CI, 3.7-6.1) and 10.0 months (95% CI, 7.9-15.8), respectively. One patient remained in complete response at 6 years continuing follow-up at the time of this report.

Results | Disease progression in the central nervous system (CNS) occurred in 6 of 32 (19%) evaluable patients (isolated CNS in 3, with other visceral organs in 3; bone and liver in 1; lymph nodes and lung in 1; and lung, liver, and lymph nodes in 1). Median time to progression in the CNS was 7.9 months, whereas median OS was 11.4 months. Treatments consisted of stereotactic brain radiation therapy (n = 2) and neurosurgery excision (n = 1), overall favorably associated with OS data in these patients as a whole. Owing to poor performance status, 2 remaining patients received best supportive care and 1 was lost at follow-up. The patient who underwent neurosurgery for a cerebellum metastasis manifested an 11.5-month PFS after treatment initiation and maintained *ERBB2* positivity (IHC 3 positive) in the resected tumor specimen.

Table. RECIST Objective Responses to Treatment of 32 Patients Evaluable in HERACLES-A[2]

Best response	No. (%) [95% CI]
RECIST 1.1. by centralized imaging revision	
No.	32
Objective response PR + CR%	9 (28) [14-47]
CR	1 (3)
PR	8 (25)
Stable disease, mo	
≥4	9 (28) [14-47]
<4	4 (13) [4-29]
Disease control[a]	18 (56) [38-74]
Progressive disease	10 (31) [16-50]

Abbreviations: CR, complete response; PR, partial response.

[a] Defined as complete plus partial responses plus stable disease of more than 4 months.

Discussion | Treatment-prolonged survival was associated with an unexpectedly high occurrence of CNS metastases. Several reasons might explain this finding (1) a biological tropism toward CNS of *ERBB2*-amplified cells; (2) a limitation of these drugs targeting *ERBB2* to cross the blood-brain barrier; or (3) the increased risk, in patients with long survival outcomes, of developing involvement of rarer anatomic sites.

Updated analysis of HERACLES-A trial at 6.7 years of follow-up supports the use of trastuzumab and lapatinib as a treatment reference for *KRAS* wild-type, chemorefractory *ERBB2*-positive mCRC. Present data also indicate that the CNS may represent a sanctuary of CRC relapse in this setting, mirroring what occurs with *ERBB2*-targeted therapies in breast and gastric cancers. Further studies are needed to better understand the mechanisms underlying this observed tropism and to investigate the potential of next-generation TKIs with improved CNS activity, such as neratinib and tucatinib.[6]

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