Original Study

Long-term Clinical Outcome of Trastuzumab and Lapatinib for HER2-positive Metastatic Colorectal Cancer

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Abstract

***ERBB2* amplification is a therapeutic target in 5% of patients with RAS wild-type metastatic colorectal cancer. At 6.7 years of follow-up, therapy with trastuzumab and lapatinib combination resulted in 28% objective response rate with 1 patient still in complete response, median 4.7 months progression-free survival, and 10.0 months overall survival. Progression in the central nervous system occurred in 19% of patients.**

Background: *ERBB2* amplification occurs in 5% of *RAS* wild-type metastatic colorectal cancer (mCRC) and it has been shown to be a target for treatment with 2 HER2-directed combinations of trastuzumab and lapatinib or trastuzumab and pertuzumab. We present long-term clinical results of trastuzumab and lapatinib (HERACLES-A trial) at 6.7 years (82 months) follow-up and focus on central nervous system (CNS) recurrences. **Patients and Methods:** Patients had histologically confirmed *KRAS* exon 2 (codons 12 and 13) wild-type and HER2-positive mCRC. HER2 positivity was assessed by immunohistochemistry and in situ hybridization HERACLES diagnostic criteria. Patients were treated with intravenous trastuzumab 4 mg/kg loading dose, then 2 mg/kg once per week, and oral lapatinib 1000 mg per day until disease progression or toxicity. Patients who presented with symptoms or signs of CNS disease received brain computed tomography scan or magnetic resonance imaging. **Results:** A total of 35 patients received trastuzumab and lapatinib and 32 were evaluable for response. One patient (3%) achieved complete response (CR), 8 (25%) partial response, and 13 (41%) stable disease. Therefore, response rate was 28%. Median progression-free survival was 4.7 months (95% confidence interval [CI] 3.7–6.1). Median overall survival was 10.0 months (95% CI 7.9–15.8). One patient achieved sustained CR still maintained at 7 years of follow-up. Progression in the central

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nervous system (CNS) occurred in 6 (19%) of 32 patients. **Conclusions:** Long-term (6.7 years) follow-up analysis of HERACLES-A supports using of trastuzumab and lapatinib as treatment reference for *KRAS* wild-type, chemorefractory HER2-positive mCRC. In this subset of patients, prolongation of survival is accompanied by CNS recurrences that will require diagnostic and therapeutic attention in future studies.Clinicaltrials. Gov identifier: NCT 03225937.

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Introduction

In metastatic colorectal cancer (mCRC), *ERBB2* amplification occurs in 5% of *RAS* wild-type cases[1] and in the 2019 National Comprehensive Cancer Network (NCCN) Treatment Guidelines for Colon Cancer[2] this molecular alteration has been recognized as a valuable therapeutic target with 2 HER2-directed drug combinations: trastuzumab and lapatinib[3] or trastuzumab and pertuzumab.[4] With the former regimen, we recently reported briefly the original finding of a high rate of central nervous system (CNS) recurrences in this patient population.[5] In the present article we detail in full the long-term clinical results of the pivotal HERACLES-A trial of trastuzumab and lapatinib in an extended population of 32 patients with mCRC at a follow-up of 6.7 years with an expanded focus on timing, characteristics, and treatment of CNS recurrences.

Patients and Methods

Patients and Treatment

Patients were treated in the HERACLES-A trial[3] and had a histologically confirmed diagnosis of mCRC with *KRAS* exon 2 (codons 12 and 13) wild-type status and HER2 positivity, as defined by the CRC-specific HERACLES diagnostic criteria (tumors with 3+ HER2 score in >50% of cells by immunohistochemistry or with 2+ HER2 score and a HER2:CEP17 ratio >2 in >50% of cells by fluorescence in situ hybridization [FISH]).[6] Patients were treated with trastuzumab, intravenously at 4 mg/kg loading dose, then at 2 mg/kg once per week, and lapatinib, orally at 1000 mg per day in 21-day treatment cycles (ie, 1 weekly trastuzumab dose and 1 daily lapatinib dose). Inclusion/exclusion criteria, screening phase, treatment/dose schedules, and tumor assessments were as previously described.[3]

Follow-up and CNS Relapse

Tumor assessments were done at baseline and every 8 weeks thereafter until progression. Follow-up for overall survival (OS) was updated to 6.7 years after study treatment started. Assessments were made for death and for CNS recurrence. Patients who presented with symptoms or signs of CNS disease received brain computed tomography (CT) scan with intravenous (I.V.) contrast and, if clinically indicated, magnetic resonance imaging with I.V. contrast. HERACLES-A trial protocol did not have specific indications for CNS relapses and all cases were diagnosed and treated as per best clinical practice.

Results

We screened and enrolled patients with mCRC between August 27, 2012, and March 15, 2016. Screening details were previously described.[3] A total of 35 patients were enrolled and treated with trastuzumab and lapatinib (27 in the trial phase, 8 in an extension cohort). Of these, 3 were not evaluable for response (concomitant *RAS* mutation 2 cases, absence of target lesions assessable by RECIST, 1 case [Supplemental Figure 1 in the online version]). The characteristics of the 32 fully evaluable patients are displayed in Table 1. At the time of the end of the study (May 15, 2019), the follow-up was 82 months (6.7 years). Of the 32 patients, one had a complete and 8 (25%) had a partial response, for a total of 9 (28%) patients achieving objective response rate (ORR). Stable disease (SD) was observed in 13 (41%) patients and lasted ≥4 months in 9. Overall, disease control was achieved in 22 patients (69%), lasting ≥4 months in 18 (56%). Table 2 shows treatment-related adverse events according to Common Terminology Criteria for Adverse (CTCAE) events that occurred in at least 5% of patients or all that were grade 3 or worse. Three patients underwent the treatment for more than 1 year: of them, only 1 patient displayed fatigue grade 3 and an asymptomatic decrease in left ventricular ejection fraction grade 3 that improved and reversed to grade 1 after temporary suspension.

Table 1 Baseline Characteristics

Clinical Variables	N = 32	(%)
Median age in years (range)	62 (40-86)	
Sex		
Males	28	(88)
Females	4	(12)
HER2 expression by immunohistochemistry score		
3+	25	(78)
2+	7	(22)
Site of primary tumor		
Rectum	8	(25)
Colon	24	(75)
Proximal[a]	5	(15)
Distal[b]	19	(60)
Prior treatment		
Median number of prior lines (range)	5 (2-11)	
Patients with > 3 prior lines	24	(75)
Prior cetuximab or panitumumab	32	(100)

[a]Located in cecum, ascending colon, liver flexure, and transverse colon.
[b]Located in splenic flexure, descending colon, and sigmoid colon.

Table 2 Adverse Events

Adverse Events	Grades 1-2	Grade 3
Gastrointestinal		
Diarrhea	26 (81)	1 (3)
Abdominal pain	5 (16)	
Nausea	10 (31)	
Vomiting	5 (16)	
Dermatological		
Rash	17 (53)	1 (3)
Dry skin	8 (25)	
Nail disorder	3 (10)	
Pruritus	3 (10)	
Erythema	2 (6)	
Folliculitis	3 (10)	
Metabolic and nutritional disorders		
Fatigue	14 (44)	5 (16)
Anorexia	2 (6)	
Paronychia	12 (38)	
Conjunctivitis	6 (19)	
Hand-foot syndrome	2 (6)	
Blood bilirubin increase		1 (3)
Decrease in left ventricular ejection fraction		2 (6)

Data are n (%). Treatment-related adverse events are reported if they occurred in at least 5% of patients or were of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or worse. All 32 patients were included in the analysis. No grade 4 or 5 adverse events occurred.

Median progression-free survival (PFS) was 4.7 months (95% confidence interval [CI] 3.7−6.1). At 7 years after treatment initiation, 1 of 32 patients is still in complete remission, and thus potentially cured. Median OS was 10.0 months (95% CI 7.9−15.8) with the latter patient alive censored at the time of data cutoff. Figure 1 shows a swimmer plot of PFS and OS.

CNS Relapses

Symptomatic disease progression in the CNS occurred in 6 (19%) of 32 evaluable patients. The characteristics of these patients and their CNS progression and treatments are reported in Table 3. Five of 6 patients achieved a clinical benefit from the anti-HER2 treatment (2 with partial response [PR] and 3 with SD). Figure 2 shows the treatment history of this particular cohort of patients who developed brain progression. Four patients progressed while on anti-HER treatment and median time to progression in the CNS was 7.9 months. Exclusive brain progression occurred in 3 patients, whereas in the other 3 patients the progression was generalized. Median OS was 11.4 months. Treatments consisted of stereotactic brain radiation therapy (n = 2) and neurosurgery excision (n = 1). Because of poor performance status, 2 remaining patients received best supportive care and 1 was lost to follow-up. In the patient who underwent neurosurgery for a cerebellum secondary localization, manifested 11.5 months after treatment initiation (UPN 121003), the CNS metastases maintained HER2-positivity (immunohistochemistry [IHC] 3+) and status of *KRAS* and *BRAF* wild-type as compared with a metachronous lung metastasis, analyzed before HER2-targeted treatment, and the primary tumor (Figure 3). We additionally did not find in the CNS lesion any mutations of *ERBB2*.

Discussion

This long-term follow-up analysis of the HERACLES-A trial demonstrates that pharmacological double HER2 blockade with trastuzumab and lapatinib, as foreseen by preclinical models,[7,8] constitutes a therapeutic reference for the treatment of mCRC where this biomarker is present.[6] The value of *ERBB2* amplification as a therapeutic target in mCRC has been confirmed in the MyPathway trial[4] in which the combination of trastuzumab and pertuzumab was used, and both regimens achieve level 2 OncoKB designation (https://www.oncokb.org) and inclusion in the NCCN Guidelines for colon cancer. Further, the more recently presented MOUNTAINEER trial with trastuzumab and tucatinib and DESTINY-CRC01 with the antibody-drug conjugate trastuzumab deruxtecan showed the potential for improvement of these results with newer HER2-targeted agents.[9,10]

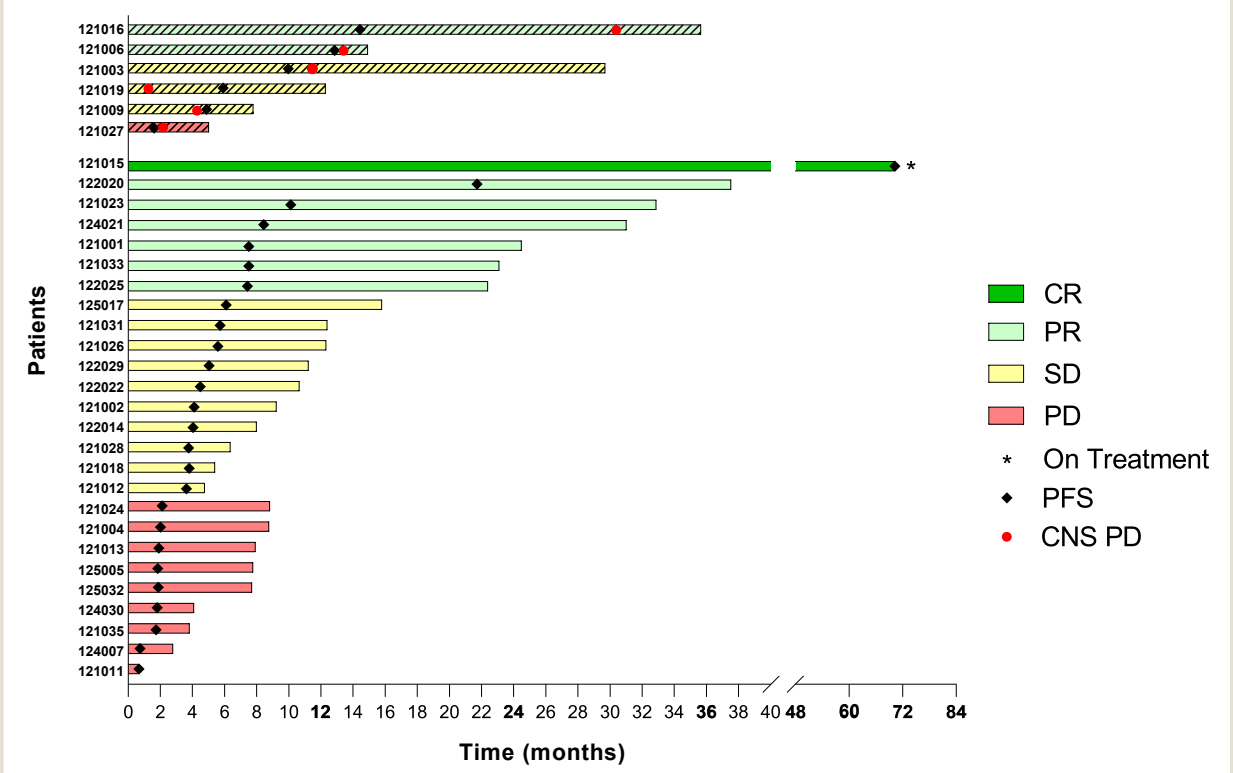
In the present HERACLES-A extended population of 32 patients we observed an ORR of 28% (95% CI 14%−47%) and a median PFS of 4.7 months. These results are achieved in a heavily pretreated population in which standard therapeutic options such as regorafenib or trifluridine-tipiracil do not provide meaningful ORR.[11,12] Interestingly, we documented a sustained complete response (CR) still maintained at 7 years of follow-up (Supplemental Figure 2 in the online version). These results confirm that the benefit obtained by targeting oncogenic addictive products such as HER2 can lead to unprecedented clinical benefit and survival. HERACLES-A data presented here compare indeed favorably with the other 2 therapeutic strategies for biomarker-defined mCRC populations, such as triple *BRAF*-directed therapy[13] and microsatellite instability-confined treatment with immune checkpoint inhibitors.[14] In this regard, from a clinical standpoint, HER2-targeted treatment seems to reconcile the strengths of targeted oncology against oncogenes (rapid and deep induction of tumor shrinkage) with those of immunotherapy (durability of responses and the potential for cure).

Treatment-prolonged survival in this cohort of patients with chemorefractory HER2-positive mCRC resulted in an unexpectedly high occurrence of CNS metastases in approximately one-fifth of patients. This incidence rate is 4 times higher than usually reported in mCRC.[15] Several considerations can be made to explain this finding: a potential biological tropism toward CNS of *ERBB2*-amplified cells; a limitation of trastuzumab and lapatinib to cross the blood−brain barrier (BBB); or the increased likelihood in patients with long survival outcomes of developing involvement of rarer anatomic sites than observed in the general population of mCRC.

The hypothesis that *ERBB2* amplification drives a higher propensity to spread to CNS has been already documented for breast[16,17] and gastric cancer.[18,19]

Approximately only 1% to 4% of patients with mCRC are reported to develop CNS metastases.[20,21] However, limited data are available about the correlation between *ERBB2* amplification and tendency to CNS metastasis. Tan et al.[15] recently pointed out that 20% of 40 patients with mCRC developing CNS metastases were characterized by *ERBB2* amplification in the primary tumor. In another recent publication,[22] 14 patients with mCRC undergoing craniotomy because of CNS metastasis were tested by IHC and

Figure 1 Swimmer Plot Regarding Progression-free Survival (PFS) and Overall Survival (OS) of HER2-Positive Patients Treated With Trastuzumab and Lapatinib. Green Bars Represent Patients Who Achieved Complete Response (CR) and Partial Response (PR), whereas Yellow and Red Bars Indicate Stable (SD) and Progressive Disease (PD), Respectively. Bars With Black Line are Patients With Central Nervous System (CNS) Recurrence. Black Dots Represent PFS. Red Dots Represent Timing of CNS Recurrence



Abbreviations: CNS PD = progression of disease in the CNS; Pts = patients.

FISH for *ERBB2* amplification and 3 of them (21%) resulted positive with 100% concordance with primary tumor. These data, together with present findings from a selected population of HER2-positive patients with mCRC, support the hypothesis that *ERBB2* amplification, as also DNA damage response pathway defects,[23] is a mechanism that drives higher propensity to spread to CNS.

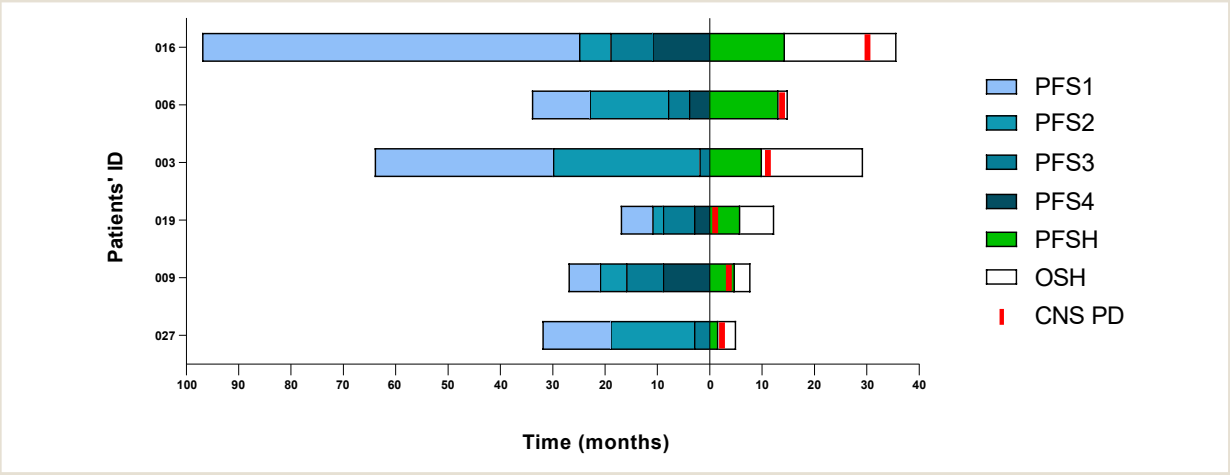
Another explanation for the high incidence of CNS progression might be because of the limited intracranial activity of anti-HER2

Table 3 Clinical Characteristics and Treatments of Patients Showing CNS Progression Within the HERACLES-A Trial

Patient ID	Site of CNS PD	Brain PFS (mo)	Timing of CNS Progression Related to Anti-HER2 Treatment	Time After Last HER2-Targeted Treatment (mo)	Best Response to Anti-HER2 Treatment	Brain Metastases Treatment	OS (mo)	OS After CNS Relapse (mo)
121016[a]	NA	30.5	Off-treatment	3.2	PR	None	35.3	4.8
121006	cerebellum, supratentorial lesions	13.6	On-treatment	0.5	PR	None	13.9	0.3
121003	cerebellum	11.5	Off-treatment	1.8	SD	Surgery	29.7	18.2
121019	supratentorial lesions, cerebellum	1.2	On-treatment[b]	0.5	SD	Stereotactic radiosurgery	8.9	7.7
121009	NA	4.2	On-treatment	0.4	SD	NA	7.8	3.6
121027	supratentorial lesions	2.1	On-treatment	0.1	PD	Stereotactic radiosurgery	5.0	2.9

Abbreviations: CNS = central nervous system; NA = not available; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.
[a]This patient developed brain metastases after treatment with trastuzumab + lapatinib and T-DM1 given as sequential rescue treatment within the HERACLES-RESCUE study.
[b]Patient remained on HERACLES-A treatment during brain radiotherapy.

Figure 2 Treatment History of HER2-Positive Patients Who Developed Central Nervous System (CNS) Progression



Abbreviations: CNS PD = disease progression to CNS; OSH = overall survival following HERACLES-A treatment; PFS1 = progression-free survival with first-liine treatment; PFS2 = PFS with second-line treatment; PFS3 = PFS with third-line treatment; PFS4 = PFS with fourth-line treatment; PFSH = PFS with trastuzumab and lapatinib (HERACLES-A).

therapies, particularly trastuzumab.[24] Indeed, pharmacokinetics evidence obtained from phase I trials involving anti-HER2 drugs demonstrated different capability to bypass the BBB due to their dimension (ie, molecular mass >450 kDa) or their hydrophilic nature.[25,26] Trastuzumab, when administered as an I.V. infusion, poorly crosses the BBB. In radiotherapy-naïve patients, trastuzumab concentrations have been reported to be 420-fold lower in cerebrospinal fluid (CSF) than in serum.[27] Even after radiotherapy, the blood/CFS trastuzumab concentration remains low (1:49).[27] Lapatinib is a small molecule reversible tyrosine kinase inhibitor designed to target both HER1 (epidermal growth factor receptor) and HER2. Being a small molecule (molecular weight <1 kDa), lapatinib should be able to cross the BBB and reach CNS deposits.[28] In a preclinical study on healthy animals, however, the ability of lapatinib to cross the BBB was limited due to efflux transporter P-glycoprotein,[29] a selective gatekeeper of the BBB and thus a primary obstacle to drug delivery into the brain. Several clinical trials evaluated the CNS efficacy of lapatinib obtaining conflicting results.[30,31]

Finally, another reason explaining why HER2-positive tumors seem to develop more CNS metastases is the prolonged survival obtained thanks to the anti-HER2 treatment itself. This gain in survival might indeed allow the unmasking of brain deposits otherwise clinically silent.[32,33] In HERACLES-A, we observed a median OS of 10.0 months, with 1 patient still in CR after 7 years and this survival time from the initiation of HER2-targeted treatment must be added to the time elapsed since the diagnosis of metastatic disease, which was considerable in HERACLES-A (patients had received a median of 4 previous treatment lines before enrollment). Indeed, the median OS for the entire cohort of 32 patients since the diagnosis of stage IV is 42.3 months, higher than expected (Supplemental Table 1 in the online version).

Our analysis regarding CNS involvement in HERACLES-A has some limitations. First, we did not perform a brain imaging on the entire cohort of HER2-positive patients with mCRC but only in symptomatic patients, so that we could not exclude an even higher incidence in this population. Second, we compared our cohort with historical data on incidence of brain metastases in patients with mCRC patients and not with patients with HER2-positive tumors who did not receive trastuzumab/lapatinib or patients with HER2-negative mCRC.

Altogether our findings support the hypothesis that, in HER2-positive patients with mCRC treated with trastuzumab and lapatinib, CNS represents a sanctuary of disease progression. Based on this, we recommend to include brain imaging for staging and tumor assessment in these patients.

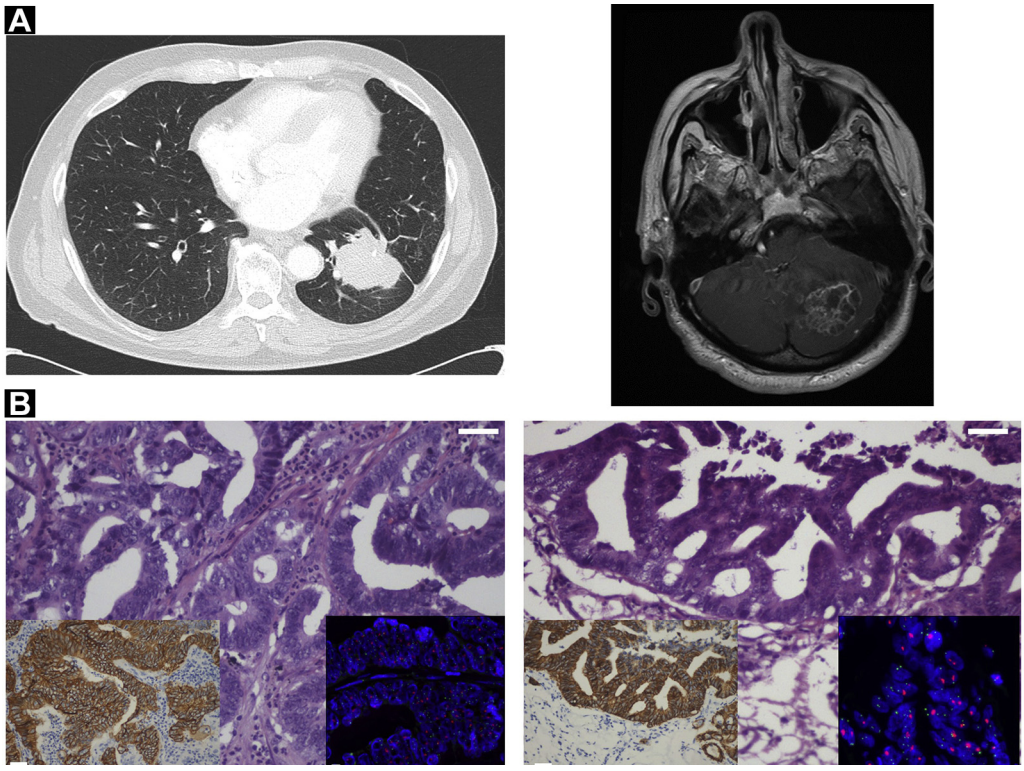
Conclusion

In conclusion, updated analysis of HERACLES-A trial confirms trastuzumab and lapatinib as a HER2-directed combination of reference for *KRAS* wild-type, chemorefractory HER2-positive mCRC. We also document that CNS represents a sanctuary site of relapse, a finding that calls for inclusion of brain imaging for staging and tumor assessment in this patient population. Further studies will shed light on the mechanisms underlying this tropism and will investigate the potential of new-generation tyrosine kinase inhibitors with capability of CNS penetration and possibly clinical activity.[9,34-36]

Clinical Practice Points

- HERACLES-A pivotal multicenter phase-II trial demonstrated trastuzumab and lapatinib as an active combination in treating HER2-positive chemorefractory mCRC.
- These results document that the benefit obtained by targeting oncogenic addictive products such as HER2 can lead to unprecedented clinical benefit and survival. We report a sustained CR maintained at 7 years of follow-up. Interestingly, a high

Figure 3 Representative Patient 121003 Showing Progression of a Metastatic Lesion in the Cerebellum Retaining ERBB2 Amplification in HERACLES-A Trial. (A) Representative Computed Tomography (CT) Scan of the Lung (Left) and Cerebellum Metastasis (Right) Observed in Patient 121003 after 13.6 months of Treatment With Trastuzumab and Lapatinib. (B) Corresponding Immunohistochemistry (IHC) and Fluorescence in Situ Hybridization (FISH) Analyses of Lung (Left) and Cerebellum Metastasis Obtained Through Surgical Excision (Right), Showing Maintenance of ERBB2 Amplification. Parallel Mutational Analysis Demonstrated KRAS and BRAF Wild-type in Both Specimens. Original Magnification for Hematoxylin-Eosin and HER2 Immunohistochemistry (Inner Left Picture) Staining Pictures is ×200 (Scale bar: 100 μm) and Original Magnification for FISH Pictures (Inner Right Picture) is ×630 (Scale bar: 20 μm)



prevalence of CNS recurrences indicated this site as a sanctuary of relapse in this subset of HER2-positive patients with mCRC.

- Trastuzumab and lapatinib combination was confirmed as a reference therapeutic option for HER2-positive mCRC in advanced line. In this population, CNS represents a sanctuary of disease progression, therefore we recommend to include brain imaging for staging and tumor assessment.

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Disclosures

A. Sartore-Bianchi has acted as a consultant/advisory member for Amgen, Bayer, and Sanofi. S. Siena is advisory board member for Amgen, Bayer, BMS, Celgene, Incyte, Merck, Novartis, Roche, Seattle Genetics. A. Amatu is advisory board member for Amgen and Bayer. F. Ciardiello received honoraria or consultation fees for speaker, consultancy, or advisory roles: Amgen, Bayer, Bristol-Myers Squibb, Celgene, Merck Serono, Pfizer, Roche, Servier; direct research funding as the principal investigator for institutional research projects: Amgen, Bayer, Merck Serono, Roche, Ipsen; institutional financial interests, financial support for clinical trials or

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Supplemental Data

Supplemental figures and table accompanying this article can be found in the online version at https://doi.org/10.1016/j.clcc.2020.06.009.

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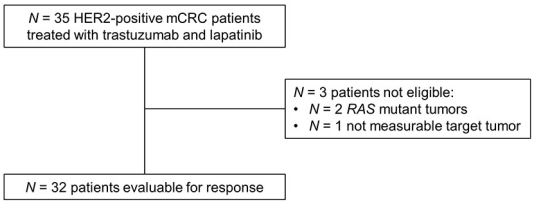
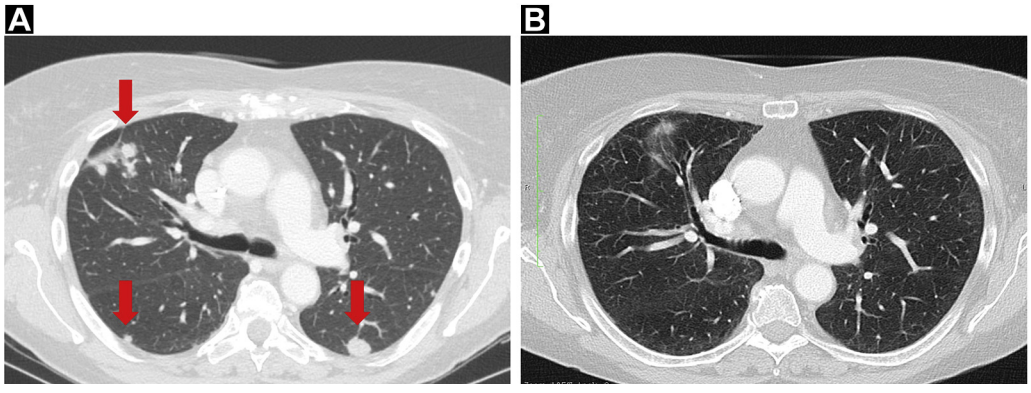
Supplemental Data

Supplemental Figure 1 Flow-Chart of Patients Treated With Trastuzumab and Lapatinib and Evaluable for Response in HERACLES-A Trial



Supplemental Figure 2 Sustained Complete Response With Trastuzumab and Lapatinib Therapy in a 63-Year-old Woman With Chemoresistant HER2-Positive Metastatic Colorectal Cancer. Treatment With HER2 Targeted Agents is Ongoing in November 2019. (A) Representative Computed Tomography (CT) Scan of Bilateral Lung Metastases in Patient UPN 121015 at Baseline in December 2013. (B) Representative CT Scan Imaging of Maintained Lung Complete Response in August 2019 after 6 years of Treatment With Trastuzumab and Lapatinib



Supplemental Table 1 OS From Diagnosis of Stage IV of the Entire Cohort of HER2-Positive Patients With Metastatic Colorectal Cancer Treated With Lapatinib and Trastuzumab Within HERACLES-A Trial

Patient ID	OS (mo)
121001	55.2
121002	44.1
121003	78.5
121004	81.6
125005	34.3
121006	51.9
124007	26.2
121009	36.1
121011	10.8
121012	59.4
121013	29.1
122014	30.6
121015	95.4
121016	62.2
125017	49.1
121018	60.1
121019	24.3
122020	84.7
124021	50.1
122022	47.1
121023	94.9
121024	22.4
122025	45.2
121026	39.9
121027	36.4
121028	30.4
122029	40.5
124030	18.1
121031	29.1
125032	25.6
121033	53.9
121035	19.7
Median OS	42.3

Abbreviation: OS = overall survival.