Bayesian Monitoring of Lapatinib (L) plus Trastuzumab (T) Treatment of Her2 Positive Metastatic Colorectal Cancer (mCRC): An Observational Cohort Study

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BACKGROUND

HER2 positivity is found in 3-5% of mCRC. The phase II HERACLES-A trial showed that dual anti-HER2 therapy with T + L has 30% response rate (RR) in HER2+ RAS wt mCRC after failure of standard care[1,2]. These data led to inclusion of T+ L among recommended treatments by NCCN and other guidelines, but still lack confirmation by large trials comparing treatments. The latter, especially for this uncommon subset of mCRC, would require efforts unbearable in the setting of independent clinical research. We designed this study to confirm HERACLES-A data of efficacy through a Bayesian approach allowing to monitor longitudinally efficacy of T + L in the practice setting. Here we report the results of the first pre-planned interim-analysis.

STATISTICAL DESIGN AND END POINTS

We simultaneously monitor efficacy and toxicity using the Bayesian optimal phase 2 (BOP2) design [3]. Specifically, let n denote the interim sample size, and N denote the maximum sample size. Let Y_{eff} and Y_{tox} denote the binary efficacy and toxicity endpoints, with Y_{eff}=1 and Y_{tox}=1 indicating that patients experience efficacy and toxicity, respectively. We assume that the joint distribution of (Y_{eff}, Y_{tox}) follows a multinomial distribution with four elementary outcomes: (Y_{eff}, Y_{tox}) = (1, 1), (1, 0), (0, 1) and (0, 0). Let p=(P_{11},P_{10},P_{01},P_{00}) denote the probabilities of observing the four outcomes, and let p_{eff}=Pr(Y_{eff}=1), p_{tox}=Pr(Y_{tox}=1) and p_{efftox} =Pr(Y_{eff} =1, Y_{tox}=1). When efficacy and toxicity endpoints are monitored separately, the joint distribution reduced to marginal distribution of efficacy and marginal distribution of toxicity, respectively.

The treatment is deemed unacceptable if $p_{eff} \leq 0.1$ or $p_{tox} > 0.3$. Thus, we will stop enrolling patients and claim that the treatment is unacceptable if

$$\Pr(p_{eff} > 0.1 | data) < \lambda(n/N)^{\alpha},$$

or

$$\Pr(p_{tox} \leq 0.3 | data) < \lambda(n/N)^{(\alpha/3)},$$

where λ=0.5 and α=0.51 are design parameters optimized to maximize the study power, i.e., probability of correctly concluding an efficacious and safe treatment as acceptable when p_{eff} =0.35, p_{tox} =0.2 and p_{efftox}=0.07, while controlling that the probability of incorrectly claiming an inefficacious and toxic treatment, i.e., type I error, with p_{eff} =0.1, p_{tox} =0.3 and p_{efftox}=0.045, to 10.1%. Note that in the safety stopping rule, the original publication of the design used the probability cutoff $\lambda(n/N)^{\alpha}$, here the attenuation factor 3 is added (i.e., α/3) to obtain stricter interim stopping boundaries to enhance safety.

This optimization is performed assuming a vague Dirichlet prior *Dir(0.045,0.055,0.255,0.645)* for p. The prior is chosen such that it corresponds to a prior effective sample size of 1 patient, and the prior estimates of p_{eff} and p_{tox} match the values specified when the treatment is unacceptable. The above decision rule leads to the following optimal stopping boundaries:

Table 1: Optimized stopping boundaries

# patients treated	Stop if # response ≤	OR # toxicity ≥
10	0	4
20	1	7
30	2	10
40	4	13

The go/no-go criteria in Table 1 are non-binding.

Below are the operating characteristics of the design based on 10000 simulations using the BOP2 web application (BOP2 V1.4.6.0)[3].

Table 2: Operating characteristics

Scenario	Pr(Eff)	Pr(Tox)	Pr(Eff & Tox)	Early Stopping (%)	Claim Acceptable (%)	Average Sample Size
1	0.10	0.3	0.045	82.03	10.09	18.4
2	0.35	0.2	0.070	18.37	80.75	35.2

Study objectives

Primary

• To evaluate ORR and safety of Her2 positive mCRC after Trastuzumab + Lapatinib

Secondary

• Progression free-survival and overall survival for this patient population

Patient's data and statistical analysis will be reported according to most updated guidelines[4].

This observational study was approved by our institutional EC.

METHODS AND PATIENTS

Patients inclusion criteria were the same from Heracles trial[1]. In addition, since this is on observational study, the patients should be already candidate to off-label T + L treatment at our institution according to Italian and hospital rules, after acknowledgment from our EC. The Division of Oncology and Fondazione Oncologia Niguarda (FON) covered the costs of treatments along with AIFA funding, according to law 326/2003 (5% AIFA National Fund).

Efficacy evaluation. Patients not evaluable for ORR will be replaced. The Efficacy Evaluable (EE) population is defined as all treated patients, with no major deviations from the eligibility criteria affecting efficacy evaluation, for whom the tumor response could be evaluated at least once while on treatment. These patients should have received at least 2 cycles after treatment starts, unless disease progression occurs within this period. Patients characteristics are reported in Table 3.

Table 3: Patients characteristics.

	n=11 (range)	%
Median age in years (range)	52.6 (40-66)	
Sex		
Female	5	45
Male	6	55
HER2 expression by IHC score		
2+	2	
3+	9	
Sideness of primary tumor		
Right colon	1	9
Trasversum, left colon and rectum	10	91
Prior treatment		
Median N of prior lines (range)	2.3 (1-4)	
Patients with > 3 prior lines	1	9
Prior cetuximab or panitumumab	11	100
Prior anti-HER2 therapy	3	27
Subsequent treatment		
Chemotherapy	6	54
Surgery	1	9

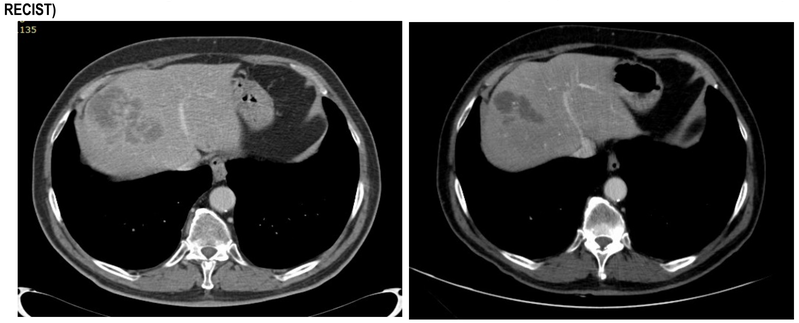
RESULTS (I)

From May 2019 to Jan 2021, we collected data of HER2+ mCRC patients treated with T + L according to HERACLES trial inclusion criteria. 11 patients were followed for RR and adverse events (AE). On May 1st 2021, at the first interim analysis, 2/10 evaluable patients had PR according to RECIST criteria, with an updated probability of response of 25.8% (Figure 2). Figure 1 shows an example of response in a patient with a large metastatic liver lesion. No G3 AE drug-related were reported, meeting the safety boundaries of the observational protocol. All AEs are detailed in Table 4 (right).

Table 4: AE related to study drug

	Grades 1-2
	n(%)
Gastrointestinal	
Diarrhea	11(100)
Vomiting	1 (9)
Dermatological	
Rash	2 (18)
Folliculitis	2 (18)
Mucositis	2 (18)
Metabolic and nutritional disorders	
Anorexia	1 (9)
Astenia	1 (9)
Bilirubin increased	2 (18)

Figure 2 – Tumor shrinkage in a liver metastasis of a patient with mCRC Her2 positive, after 2 months of T +L treatment (PR RECIST)



RESULTS (II)

Figure 1: Updated probability of response to T + L in Her2 positive mCRC, after first interim analysis

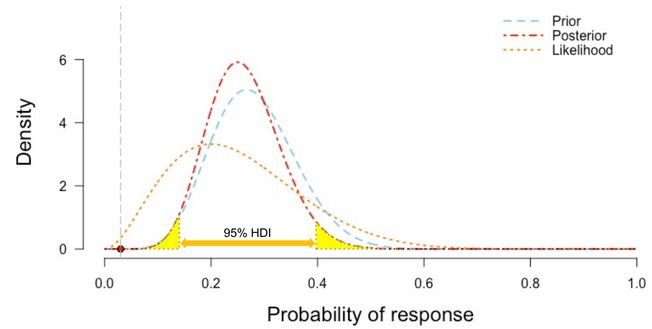
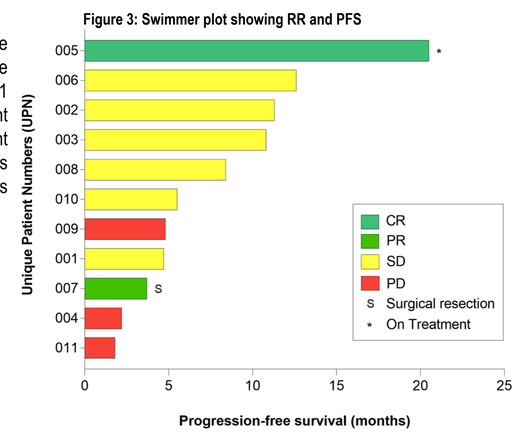


Figure 1 (left) shows the prior probabilities of response (blue) from published data[4], the likelihood of response observed in the present study (orange) and the update posterior probability density (red) along with the 95% high density interval (HDI, 13-39%). Response to T + L in Her2 pos mCRC has a strong evidence to be better than the available choices in 3rd line (3% response rate H0, red point), with a BF_{10} of 7.401.

On the right, the swimmer plot shows the response rate (color code) and progression free survival to T+L treatment (ranging from 2 to 21 months) for each individual patient. One patient (#007) underwent to liver metastasectomy right after response to the study treatment and is alive and progression free at the interim analysis time.

Figure 3: Swimmer plot showing RR and PFS



CONCLUSIONS

At the first planned interim analysis, treatment with T + L for HER2+ mCRC patients was confirmed to be safe and effective. A Bayesian approach, allowing to monitor results accounting for previously available data, can support the process of approval by regulatory authorities for treatments targeted to uncommon subsets such as HER2+ mCRC.

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