ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

ORIGINAL RESEARCH

Evaluation of the relevance of the growth modulation index (GMI) from the FFCD 0307 randomized phase III trial comparing the sequence of two chemotherapeutic regimens

P. du Rusquec[1,2]*, R. Guimbaud[3], K. Le Malicot[4,5], J.-M. Gornet[6], S. Nguyen[7], T. Lecomte[8], F. Khemissa-Akouz[9], H. Perrier[10], O. Bouché[11], X. Paoletti[2] & C. Le Tourneau[1,2]

[1]Department of Drug Development and Innovation (D3i), Institut Curie, Paris; [2]INSERM U900 Research Unit, PSL Research University, Institut Curie, Saint Cloud; [3]Medical Oncology, CHU de Toulouse, Toulouse; [4]Department of Biostatistics, Fédération Francophone de la Cancérologie Digestive, Dijon FFCD, Dijon; [5]EPICAD INSERM LNC-UMR 1231, Bourgogne Franche-Comté University, Dijon; [6]Gastroenterology, Hôpital Saint-Louis, Paris; [7]Medical Oncology, CH de Pau, Pau; [8]Department of Hepatogastroenterology and Digestive Oncology, University Hospital of Tours, Tours; [9]Gastroenterology, CH Saint-Jean de Perpignan, Perpignan; [10]Medical Oncology, Hôpital Saint-Joseph, Marseille; [11]Gastroenterology and Digestive Oncology, CHU de Reims, Hôpital Robert Debré, Reims, France

Available online 4 August 2023

Background: Precision medicine trials disrupted the paradigm of randomized controlled trials in large populations. Patient selection may be based on molecular alterations rather than on primary tumor location. In small patient populations, the growth modulation index (GMI) has been developed to evaluate treatment efficacy by using each patient as its own control. The FFCD 0307 randomized phase III trial compared two sequences of chemotherapy in advanced gastric cancer, which represents a unique opportunity to evaluate the relevance of the GMI.

Patients and methods: In the FFCD 0307 trial, patients with advanced gastric cancer were randomized between two chemotherapy sequences [ECX followed by FOLFIRI at disease progression (arm A) versus FOLFIRI followed by ECX (arm B)]. GMI was defined as the ratio of the progression-free survival on second treatment (PFS2) to the time to progression on first treatment (TTP1). Sequence benefit was defined as a GMI exceeding 1.3 (GMI-high). GMI was correlated with overall survival (OS). OS1 and OS2 were measured from first randomization and second-line failure to death.

Results: Four hundred and sixteen patients were randomized (209 in arm A, 207 in arm B). One hundred and seventy-five patients (42%) received the two sequences and were assessable for GMI (97 in arm A, 79 in arm B). The median GMI was higher in arm A than in arm B (0.62 versus 0.47, $P = 0.04$). Patients with a high GMI had a longer OS1 (median 14.9 versus 11.5 months, NS). Median OS2 was doubled in the GMI-high group (3.4 versus 1.6 months, NS).

Conclusion: GMI analyses suggest that ECX followed by FOLFIRI might represent a better therapeutic strategy than FOLFIRI followed by ECX. High GMI was associated with prolonged survival.

Key words: growth modulation index, progression-free survival ratio, survival endpoints, precision medicine, therapeutic sequence

INTRODUCTION

The marketing authorization of drugs in oncology has been historically based on clinical benefit. The gold standard to assess this benefit is to demonstrate an overall survival (OS) benefit or an improvement of the quality of life. The American Society of Clinical Oncology and European Society for Medical Oncology have created value scores for evaluating the added value of novel anticancer drugs.[1-3] A score is associated with each treatment according to efficacy endpoints, including OS, progression-free survival (PFS) and overall response rate (ORR), costs and quality of life.

Precision medicine has challenged the traditional way of drug development based on randomized trials for drug approval, given the identification of rare molecular alterations across cancer types that can be targeted with specific therapies. The Food and Drug Administration has approved several targeted therapies based on single-arm clinical trials, such as crizotinib[4] or larotrectinib,[5] whereas the European Medicines Agency usually mandates results of randomized trials.

*Correspondence to: Dr Pauline du Rusquec, Department of Drug Development and Innovation (D3i), Institut Curie, Paris, France; INSERM U900 Research Unit, Saint-Cloud, France

E-mail: pauline.durusquec@curie.fr (P. du Rusquec).

URL: www.linkedin.com/in/pauline-du-rusquec-072273100 (P. du Rusquec).

2059-7029/© 2023 The Author(s). Published by Elsevier Ltd on behalf of European Society for Medical Oncology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

In this context, there is an urgent need to develop novel methods for evaluating anticancer treatments in small patient populations. Taking each patient as its own control might be a way to overcome this challenge. The growth modulation index (GMI), also called PFS ratio, was first described by von Hoff and defined as the ratio of the PFS of two consecutive treatment lines for one patient.[6] The GMI has been used in several precision medicine trials.[7-11]

The single-arm STARTRK-1, ALKA-372-001 and STARTRK-2 trials of entrectinib in patients with neurotrophic tyrosine receptor kinase fusions showed an ORR of 57% and a PFS of 11.2 months.[12] Consistently, the median GMI in patients who had received preliminary prior line of treatment was 2.53, and 66% of patients had a ratio > 1.3.[13]

The evaluation of the GMI relies on the hypothesis that tumor growth is consistent over time.[14-16] In addition, tumor assessment timings must be the same on all treatment sequences, to avoid the evaluation time bias.[17] The use of the GMI as an efficacy endpoint therefore remains to be validated. The FFCD 0307 trial (NCT00374036) is a unique trial since it compared two sequences of chemotherapy, administered as first- and second-line therapy in advanced gastric cancer. ORRs and PFS were similar in both arms.[18] We aimed at taking advantage of this singular design to evaluate the relevance of the GMI in this trial.

METHODS

Patients and study design

In the FFCD 0307 randomized phase III trial, adult patients with untreated unresectable locally advanced or metastatic esogastric junction (EGJ) or gastric adenocarcinoma were randomized between two chemotherapy sequences. Randomization was stratified by center, Eastern Cooperative Oncology Group (ECOG) performance status (PS), adjuvant treatment, disease site and presence of a linitis. The trial included patients with ECOG-PS of 0 to 2, and measurable disease according to RECIST. All participants gave their written informed consent before inclusion. Ethics committees approved the study.

Treatment arm and disease evaluation

First- and second-line treatments were predefined at baseline. Arm A was the ECX regimen [epirubicin 50 mg/m^2 day (D) 1+ cisplatin 60 mg/m^2 D1 + capecitabine 2000 mg/m^2 D2 to D15, every 3 weeks] followed at disease progression by FOLFIRI (irinotecan 180 mg/m^2 D1, leucovorin 400 mg/m^2 D1, bolus 5FU 400 mg/m^2 D1 and continuous 5 FU 2400 mg/m^2 in 46 h, every 2 weeks), whereas arm B was FOLFIRI followed at disease progression by ECX. Computed tomography scan assessments were carried out every 8 weeks in arm A and every 9 weeks in arm B. The second line of treatment could only start if the patient had clinically and biologically recovered from first-line treatment toxicities, and after a wash out of at least 3 weeks since the last dose of chemotherapy.

Statistical analysis

Time to progression (TTP) was defined as the time from the date of randomization until the date of disease progression for the first- (TTP1) and the second-line (TTP2) treatment. The starting date of the second line of treatment was defined as the date of disease progression of the first line plus 1 day. PFS was defined as the time from the date of randomization until the date of disease progression or death for the first line (PFS1). PFS2 started the day after first-line progression and ended at second-line failure (disease progression or death). The GMI was defined as the ratio of PFS2 to TTP1. High GMI was defined as a GMI exceeding 1.3 for a single patient. OS1 was defined as the time from first randomization to the date of death. The post-progression OS2 was defined as the time from disease progression during the second line of treatment to the date of death.

Survival endpoints were estimated by the Kaplan—Meier method and reported with their medians with 95% two-sided confidence intervals (95% CIs). Wilcoxon rank sum tests were used to compare GMIs between the two arms. Kendall rank correlation coefficients were measured to compare the association between the GMI and survival endpoints. All statistical analyses were carried out using R software® (version 4.1.1).

RESULTS

Patients' characteristics

Four hundred and sixteen patients were randomized in the FFCD 0307 trial. Of these, 175 patients (97 in arm A, 78 in arm B) were treated and progressed after the first and second line of treatment and were therefore assessable for the GMI (42%) (Figure 1). Baseline characteristics according to GMI evaluability are summarized in Table 1. In the subgroup assessable for GMI, there were more patients with a PS of 0 rather than 1-2. There were also more primary tumors located at the esogastric junction rather than the stomach. Otherwise, the subgroup was quite representative of the overall FFCD0307 trial population.

Survival analyses in the overall population according to treatment sequence

A total of 416 patients were randomized in the FFCD 0307 trial: 209 patients in arm A (ECC as first line) and 207 patients in arm B (FOLFIRI as first line). In the whole population, 319 of the 416 patients presented disease progression during first-line therapy and were assessable for TTP1, including 149 patients in arm A and 170 patients in arm B. Median TTP1 were 5.4 months (95% CI 4.7-6.7 months) and 6.0 months (95% CI 5.4-7.1 months), respectively ($P = 0.41$). One hundred and eighty-four (44.2%) of the 416 patients received the second line of treatment as planned by the study protocol, including 102 patients in arm A and 82 patients in arm B. All of them were assessable for PFS2. There was no statistical difference in terms of PFS2 between the two arms [3.0 months (95% CI 2.4-3.8 months)

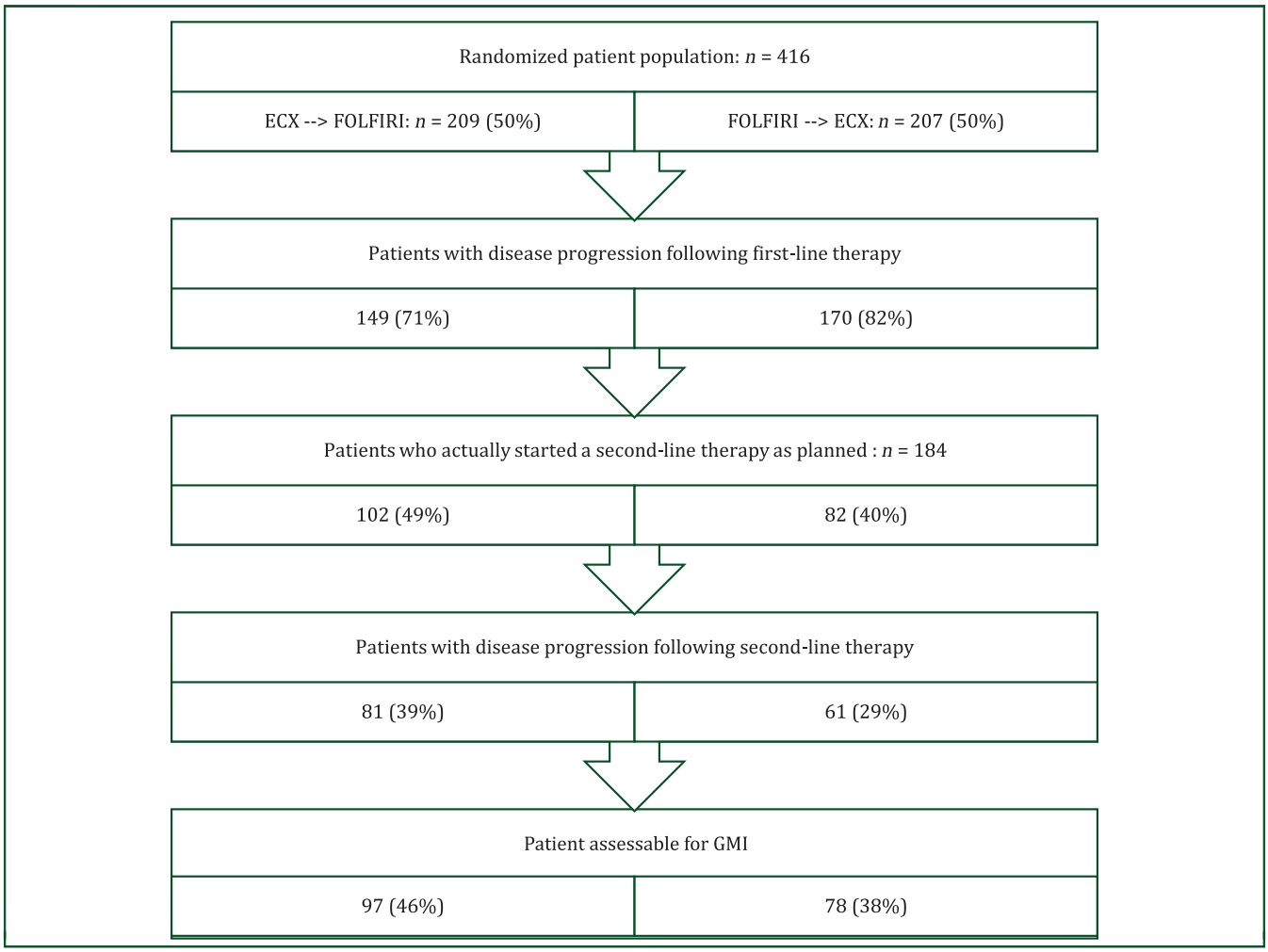

Figure 1. Identifying patients for GMI calculation.
GMI, growth modulation index.

Table 1. Baseline patient characteristics according to GMI evaluability

		No (n = 241)		Yes (n = 175)	
Treatment arm	ECX → FOLFIRI	112	(46.5%)	97	(55.4%)
	FOLFIRI → ECX	129	(53.5%)	78	(44.6%)
Age [mean (SD)]		60.95	(11.9)	60.35	(10.4)
Gender	Female	59	(24.5%)	48	(27.4%)
	Male	182	(75.5%)	127	(72.6%)
ECOG performance status	0	**57**	**(24.3%)**	**75**	**(44.1%)**
	1	132	(56.2%)	78	(45.9%)
	2	46	(19.6%)	17	(10.0%)
Tumor location	EGJ	**67**	**(28.5%)**	**69**	**(40.1%)**
	Gastric	168	(71.5%)	103	(59.9%)
Linitis	No	177	(75.6%)	132	(76.3%)
	Yes	57	(24.4%)	41	(23.7%)
Stage	Locally advanced	32	(13.9%)	20	(11.8%)
	Metastatic	199	(86.1%)	150	(88.2%)
Primary tumor resected	No	171	(73.1%)	132	(77.2%)
	Yes	63	(26.9%)	39	(22.8%)
Residual tumor after primary surgery	R0	44	(69.8%)	32	(84.2%)
	R1	9	(14.3%)	2	(5.3%)
	R2	10	(15.9%)	4	(10.5%)
Prior treatment	No	209	(90.1%)	152	(88.4%)
	Yes	23	(9.9%)	20	(11.6%)

Bold values highlight statistically significant difference between groups.
ECOG, Eastern Cooperative Oncology Group; EGJ, esophagogastric junction; GMI, growth modulation index; SD, standard deviation.

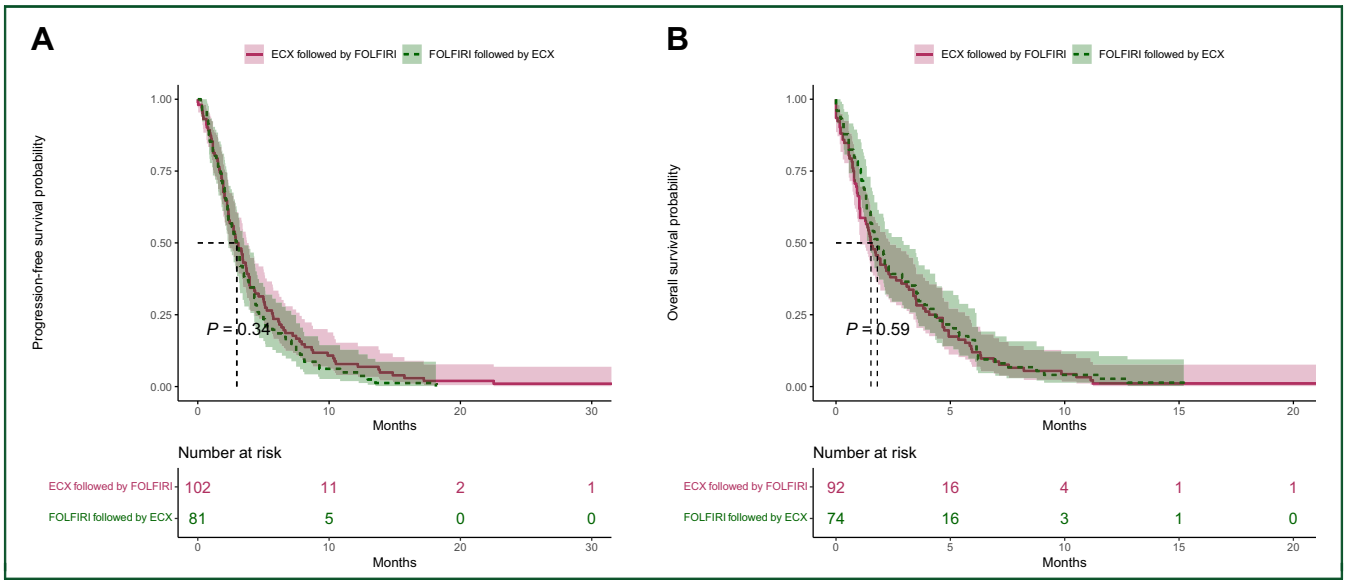

Figure 2. Benefit from the second-line therapy according to treatment sequence in the GMI-assessable patient population.
(A) PFS. (B) Overall survival after second-line failure (OS2).
GMI, growth modulation index; PFS, progression-free survival.

versus 2.9 months (95% CI 2.3-3.5 months), $P = 0.3$] (Figure 2A).

Three hundred and fifty-five patients died, including 175 patients (84%) in arm A and 180 patients (87%) in arm B. In the overall patient population, median OS from first randomization (OS1) was similar in both groups [9.5 months (95% CI 8.8-11.2 months) versus 9.7 months (95% CI 8.6-11.4 months), $P = 0.95$]. Measured from the date of progression after second-line therapy, OS2 could be assessed in 166 patients. Median OS2 was 1.5 months in arm A (95% CI 1.1-2.4 months) and 1.8 months in arm B (95% CI 1.5-3.0 months) ($P = 0.59$) (Figure 2B).

Growth modulation index calculation

The median GMI in the GMI-assessable patient population was 0.53 (95% CI 0.47-0.63). Among these patients, 26 had a GMI exceeding 1.3, including 18 patients (19%) in arm A and 8 patients (10%) in arm B. The proportion of patients with a GMI < 0.7 was 54% in arm A and 71% in arm B. The proportion of patients with a GMI of 0.7-1.3 was 28% and 19%, respectively.

The median GMI was higher in arm A [0.62 (95% CI 0.52-0.84)] than in arm B [0.48 (95% CI 0.41-0.57)], $P = 0.04$, according to the Kaplan–Meyer distribution (Figure 3). But the Wilcoxon test did not confirm these results ($P = 0.15$).

We carried out a sensitivity analysis by removing the censored patients, namely those who only progressed after first line. This subpopulation included 142 patients, 81 in arm A and 61 in arm B. The median GMI was significantly higher in arm A than in arm B [0.75 (95% CI 0.60-0.87) versus 0.51 (95% CI 0.42-0.63), $P = 0.03$].

Correlation of the GMI with overall survival

OS, whether measured from the first randomization (OS1) or from progression after second line (OS2), seemed to be prolonged in patients with a GMI exceeding 1.3, although it did not reach statistical significances. Median OS1 was 14.9 months if GMI > 1.3 (95% CI 11.7-20.9) versus 11.5 months if GMI < 1.3 (95% CI 10.3-12.9), $P = 0.2$. Median OS2 was 3.4 months if GMI > 1.3 (95% CI 1.7-54) and 1.6 months if GMI < 1.3 (95% CI 1.4-2.2), $P = 0.5$ (Figure 4).

The Kendall rank correlation coefficient measure showed a significant association between GMI and OS2 ($P = 0.0.04$), although the association was weak (tau $= 0.11$). Using other cut-offs for GMI such as 1.0, 1.5 or 2.0 did not change the results.

The correlation analysis of paired data was as follows: Kendall rank correlation coefficients between GMI and OS1

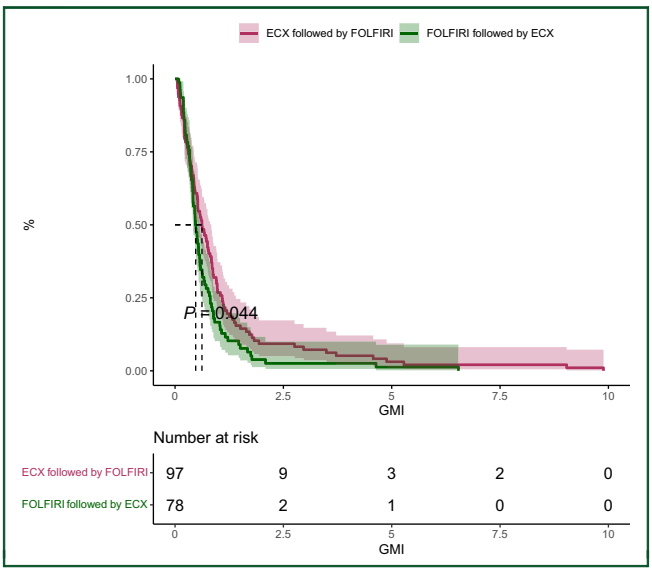

Figure 3. GMI distribution according to the treatment sequence in the GMI-assessable patient population.
GMI, growth modulation index.

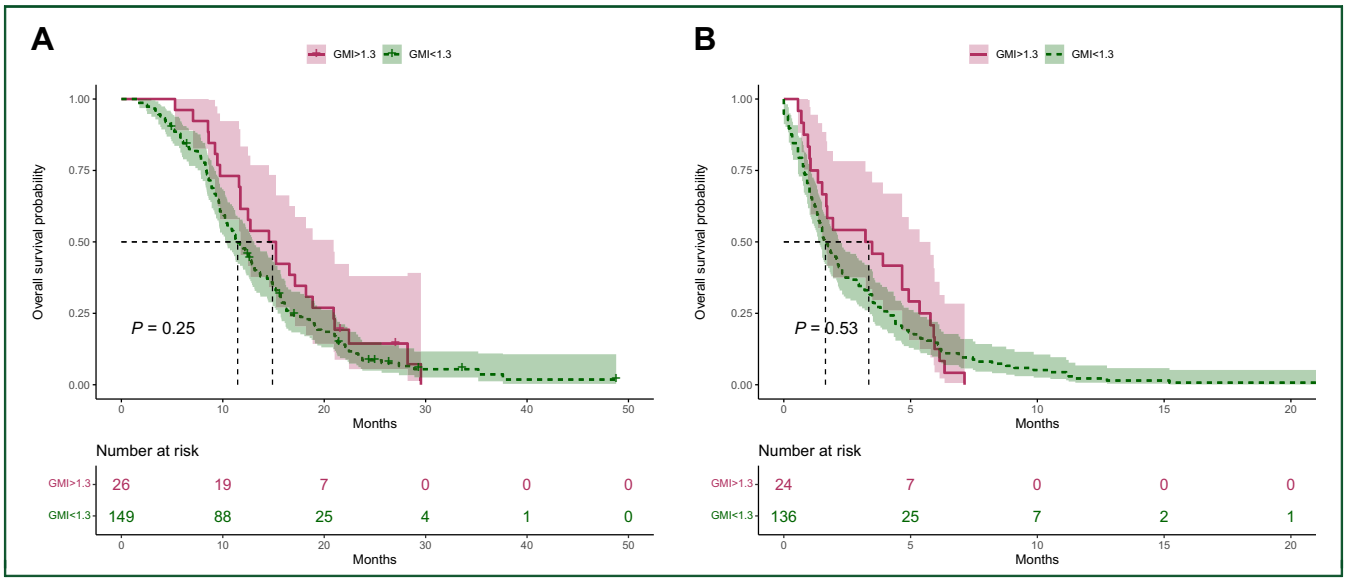

Figure 4. OS according to the GMI.
(A) OS1. (B) OS2.
GMI, growth modulation index; OS, overall survival.

or GMI and OS2 was 0.11. Kendall rank correlation coefficients between PFS2 and OS1 was 0.52. Kendall rank correlation coefficients between PFS2 and OS2 was 0.24. Thus, the correlation between PFS2 and OS is stronger than that between GMI and OS. In other words, PFS2 predicted OS better than GMI.

DISCUSSION

We assessed the relevance of GMI in the FFCD0307 trial, which showed no clear difference between two chemotherapy sequences. Four hundred and sixteen patients were randomized between two reverse chemotherapy sequences: ECX followed by FOLFIRI (arm A) or FOLFIRI followed by ECX (arm B). The GMI evaluation was possible in 42% of patients ($n = 175$). Patients who were assessable for the GMI had a better prognosis (illustrated by ECOG-PS) than the overall population. GMI was globally low in the study population (median 0.53). Only 26 (6.25%) of the whole population have a GMI > 1.3, i.e. a PFS which increases by 30% or more in the second-line therapy. The GMI was significantly higher in arm A than in arm B, whereas ORR, PFS and OS were similar in both groups.

GMI exceeding 1.3 correlated with prolonged OS measured from randomization and OS from second-line failure (OS2). In the high GMI group (GMI > 1.3) compared to the low GMI group, OS seems to be prolonged: first that measured from the first randomization (14.9 versus 11.5 months) which is much higher than the expected OS of 9 months in the study population. This is probably because the assessable population has a better prognosis than the intention-to-treat population. At the time of second-line disease progression, the prognosis of patients with advanced gastric cancer is very poor. In our study, this survival is more than doubled in the 'GMI > 1.3' group compared to the 'GMI < 1.3' group regardless of treatment arm (3.4 versus 1.6 months). Nevertheless, PFS2 predicted survival better than did GMI. These results support the evaluation of GMI as a prognostic factor for post-progression survival studies.

The FFCD 0307 trial was perfectly designed to evaluate the relevance of the GMI applied to a chemotherapy sequence. The possible biases for GMI assessment have been cleverly avoided: each patient theoretically had to receive ECX and FOLFIRI treatments in a sequence predefined at the time of first randomization. The rhythm of disease assessments was regular as scheduled, but slightly different, every 8 or 9 weeks.

The low proportion of patients assessable for GMI is explained by the poor prognosis of metastatic gastric cancer.[19] The median PFS according to the published trials does not exceed 3-6 months, and the OS from diagnosis is $\sim$9 months. After first-line failure, salvage chemotherapy is feasible, globally well tolerated and may slightly prolonged OS over best supportive care.[20] Unfortunately, many patients are not fit enough to receive a second line of treatment. The choice of the first therapeutic line then becomes fundamental. This is reflected in our study. Twenty-four percent of patients discontinued first line for a reason other than disease progression and were therefore not assessable for the GMI. In the second line, a similar proportion of patients (23%) stopped for a reason other than progression and were censored for PFS2.

Regarding the cause of first-line failure, there is less disease progression in arm A than in arm B. So, by analogy, there is more treatment discontinuation related to toxicity in arm A than in arm B. Indeed, the first publication of this trial showed higher toxicity in arm A. Nevertheless, more patients in arm A than in arm B access the second line as planned by the protocol. This supports the idea of offering the most toxic treatment from the first line, which is generally the case in oncology.

When looking at GMI impact on OS endpoints, the assessable population seems to effectively have a better prognosis. Two criteria seem to be predictive of evaluability for the GMI: very good clinical condition (ECOG-PS = 0) and primary tumor location at the esogastric junction rather than the stomach. ECOG-PS is already clearly identified as a prognostic marker for cancer survival, including for advanced gastric cancers.[21]

This study is a retrospective *post hoc* analysis of the previously reported FFCD0307 randomized phase III trial and presents some limitations. Indeed, to be eligible for GMI evaluation, patients must have received and progressed on two consecutive lines of treatment. This excludes patients who died after the first line or were not well enough to receive a second line. In other words, the use of GMI induces a selection bias by selecting a more favorable population. These results are not applicable to the entire study population.

Conclusion

Our study analyzed the contribution of GMI in the FFCD 0307 trial, which compared two sequences of chemotherapy used consecutively as first- and second-line therapy in advanced gastric cancer. GMI evaluation highlighted a difference between the two groups that was not shown by ORR, PFS or OS. The GMI analysis seems to select a population with a more favorable prognosis. A GMI exceeding 1.3 appears to predict better OS, whether measured from initial randomization or after second-line failure, but not significantly. The correlation of GMI with survival remains lower than that between PFS from second line and OS. Because of the unfavorable prognosis of the pathology studied, the overall GMI is very low in this study. Its analysis is therefore limited and should be repeated in other patient cohorts with other types of cancer and treatment.

FUNDING

None declared.

DISCLOSURE

The authors have declared no conflicts of interest.

REFERENCES

1. Schnipper LE, Davidson NE, Wollins DS, et al. American Society of Clinical Oncology statement: a conceptual framework to assess the value of cancer treatment options. *J Clin Oncol*. 2015;33(23):2563-2577.
2. Schnipper LE, Davidson NE, Wollins DS, et al. Updating the American Society of Clinical Oncology value framework: revisions and reflections in response to comments received. *J Clin Oncol*. 2016;34(24):2925-2934.
3. Cherny NI, Sullivan R, Dafni U, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Ann Oncol*. 2015;26(8):1547-1573.
4. Kazandjian D, Blumenthal GM, Chen HY, et al. FDA approval summary: crizotinib for the treatment of metastatic non-small cell lung cancer with anaplastic lymphoma kinase rearrangements. *Oncologist*. 2014;19(10):e5-e11.
5. Scott LJ. Larotrectinib: first global approval. *Drugs*. 2019;79(2):201-206.
6. Von Hoff DD, Stephenson JJ, Rosen P, et al. Pilot study using molecular profiling of patients' tumors to find potential targets and select treatments for their refractory cancers. *J Clin Oncol*. 2010;28(33):4877-4883.
7. Le Tourneau C, Servois V, Diéras V, Ollivier L, Tresca P, Paoletti X. Tumour growth kinetics assessment: added value to RECIST in cancer patients treated with molecularly targeted agents. *Br J Cancer*. 2012;106(5):854-857.
8. Belin L, Kamal M, Mauborgne C, et al. Randomized phase II trial comparing molecularly targeted therapy based on tumor molecular profiling versus conventional therapy in patients with refractory cancer: cross-over analysis from the SHIVA trial. *Ann Oncol*. 2017;28(3):590-596.
9. Massard C, Michiels S, Ferté C, et al. High-throughput genomics and clinical outcome in hard-to-treat advanced cancers: results of the MOSCATO 01 trial. *Cancer Discov*. 2017;7(6):586-595.
10. Sicklick JK, Kato S, Okamura R, et al. Molecular profiling of cancer patients enables personalized combination therapy: the I-PREDICT study. *Nat Med*. 2019;25(5):744-750.
11. Rodon J, Soria JC, Berger R, et al. Genomic and transcriptomic profiling expands precision cancer medicine: the WINTHER trial. *Nat Med*. 2019;25(5):751-758.
12. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1—2 trials. *Lancet Oncol*. 2020;21(2):271-282.
13. Krebs MG, Blay JY, Le Tourneau C, et al. Intrapatient comparisons of efficacy in a single-arm trial of entrectinib in tumour-agnostic indications. *ESMO Open*. 2021;6(2):100072.
14. du Rusquec P, Filleron T, Le Tourneau C. Drug development in the era of precision medicine in oncology-clues beyond randomization. *Chin Clin Oncol*. 2021;10(3):23. 23.
15. Kovalchik S, Mietlowski W. Statistical methods for a phase II oncology trial with a growth modulation index (GMI) endpoint. *Contemp Clin Trials*. 2011;32(1):99-107.
16. du Rusquec P, Le Tourneau C. Drug development in tissue-agnostic indications. *Cancers*. 2021;13(11):2758.
17. Samaille T, Moreau Bachelard C, Coquan E, du Rusquec P, Paoletti X, Le Tourneau C. Impact of the timing of tumor assessments on median progression-free survival in clinical trials in advanced cancer patients. *ESMO Open*. 2022;7(1):100366.
18. Guimbaud R, Louvet C, Ries P, et al. Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: a French intergroup (Fédération Francophone de Cancérologie Digestive, Fédération Nationale des Centres de Lutte Contre le Cancer, and Groupe Coopérateur Multidisciplinaire en Oncologie) study. *J Clin Oncol*. 2014;32(31):3520-3526.
19. Rawla P, Barsouk A. Epidemiology of gastric cancer: global trends, risk factors and prevention. *Prz Gastroenterol*. 2019;14(1):26-38.
20. Kang JH, Lee SI, Lim DH, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. *J Clin Oncol*. 2012;30(13):1513-1518.
21. Chau I, Norman AR, Cunningham D, Waters JS, Oates J, Ross PJ. Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer—pooled analysis from three multicenter, randomized, controlled trials using individual patient data. *J Clin Oncol*. 2004;22(12):2395-2403.