Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial

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Summary

Background Molecularly targeted agents have been reported to have anti-tumour activity for patients whose tumours harbour the matching molecular alteration. These results have led to increased off-label use of molecularly targeted agents on the basis of identified molecular alterations. We assessed the efficacy of several molecularly targeted agents marketed in France, which were chosen on the basis of tumour molecular profiling but used outside their indications, in patients with advanced cancer for whom standard-of-care therapy had failed.

Methods The open-label, randomised, controlled phase 2 SHIVA trial was done at eight French academic centres. We included adult patients with any kind of metastatic solid tumour refractory to standard of care, provided they had an Eastern Cooperative Oncology Group performance status of 0 or 1, disease that was accessible for a biopsy or resection of a metastatic site, and at least one measurable lesion. The molecular profile of each patient's tumour was established with a mandatory biopsy of a metastatic tumour and large-scale genomic testing. We only included patients for whom a molecular alteration was identified within one of three molecular pathways (hormone receptor, PI3K/AKT/mTOR, RAF/MEK), which could be matched to one of ten regimens including 11 available molecularly targeted agents (erlotinib, lapatinib plus trastuzumab, sorafenib, imatinib, dasatinib, vemurafenib, everolimus, abiraterone, letrozole, tamoxifen). We randomly assigned these patients (1:1) to receive a matched molecularly targeted agent (experimental group) or treatment at physician's choice (control group) by central block randomisation (blocks of size six). Randomisation was done centrally with a web-based response system and was stratified according to the Royal Marsden Hospital prognostic score (0 or 1 *vs* 2 or 3) and the altered molecular pathway. Clinicians and patients were not masked to treatment allocation. Treatments in both groups were given in accordance with the approved product information and standard practice protocols at each institution and were continued until evidence of disease progression. The primary endpoint was progression-free survival in the intention-to-treat population, which was not assessed by independent central review. We assessed safety in any patients who received at least one dose of their assigned treatment. This trial is registered with ClinicalTrials.gov, number NCT01771458.

Findings Between Oct 4, 2012, and July 11, 2014, we screened 741 patients with any tumour type. 293 (40%) patients had at least one molecular alteration matching one of the 10 available regimens. At the time of data cutoff, Jan 20, 2015, 195 (26%) patients had been randomly assigned, with 99 in the experimental group and 96 in the control group. All patients in the experimental group started treatment, as did 92 in the control group. Two patients in the control group received a molecularly targeted agent: both were included in their assigned group for efficacy analyses, the patient who received an agent that was allowed in the experimental group was included in the experimental group for the purposes of safety analyses, while the other patient, who received a molecularly targeted agent and chemotherapy, was kept in the control group for safety analyses. Median follow-up was 11·3 months (IQR 5·8–11·6) in the experimental group and 11·3 months (8·1–11·6) in the control group at the time of the primary analysis of progression-free survival. Median progression-free survival was 2·3 months (95% CI 1·7–3·8) in the experimental group versus 2·0 months (1·8–2·1) in the control group (hazard ratio 0·88, 95% CI 0·65–1·19, p=0·41). In the safety population, 43 (43%) of 100 patients treated with a molecularly targeted agent and 32 (35%) of 91 patients treated with cytotoxic chemotherapy had grade 3–4 adverse events (p=0·30).

Interpretation The use of molecularly targeted agents outside their indications does not improve progression-free survival compared with treatment at physician's choice in heavily pretreated patients with cancer. Off-label use of molecularly targeted agents should be discouraged, but enrolment in clinical trials should be encouraged to assess predictive biomarkers of efficacy.

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Research in context

Evidence before this study

At the start of our study in 2012, no evidence existed about whether marketed molecularly targeted agents for cancer should be given outside their indications in a histology-agnostic way provided their target is altered. We searched PubMed and ClinicalTrials.gov without any date restrictions and congress abstracts from the yearly meetings of the American Society of Clinical Oncology (ASCO) between 2000 and 2011 for the terms "personalised medicine", "clinical trials", "high-throughput technologies", and "sequencing". We used no language restrictions. We identified two non-randomised studies. Using each patient as their own control, a pilot study reported that 27% of patients with any type of recurrent cancer had a 30% longer progression-free survival with treatment selected on the basis of tumour molecular profiling than they did with their previous treatment. A retrospective study similarly showed improved progression-free survival and overall survival for cancer patients who entered a phase 1 trial on the basis of a molecular alteration identified on their tumour. We postulated that the histology-agnostic use of marketed molecularly targeted agents outside their indications on the basis of tumour molecular profiling would improve outcomes for patients with any kind of cancer for whom standard of care had failed, compared with treatment at the physician's choice.

Added value of this study

Our study is, to the best of our knowledge, the first comparative randomised trial to assess a personalised approach in which patients are treated with molecularly targeted agents in a histology-agnostic way based on tumour molecular profiling. We found no significant difference in progression-free survival between molecularly targeted agents compared with treatment at physician's choice. We also noted more grade 3–4 adverse events in the experimental group than in the control group.

Implications of all the available evidence

The generalisability of the treatment strategy chosen in SHIVA to other strategies is limited by the fact that the results depended on the drugs, profiling assays, treatment algorithms, and histology used. So far, no evidence from randomised clinical trial supports the use of molecularly targeted agents outside their indications on the basis of tumour molecular profiling. Our findings suggest that off-label use of molecularly targeted agents should be discouraged, and enrolment into clinical trials encouraged. Despite a negative result, our data suggest that further investigation of this histology-agnostic approach is warranted in patients whose tumours harbour a molecular alteration in the RAF/MEK signalling pathway.

Introduction

Normal cells become cancer cells via a succession of genomic alterations.[1] This finding has led to the development of molecularly targeted agents that inhibit the proteins that are abnormally activated as a result of somatic genetic alterations. Theoretically, these agents are more specific to cancer cells than are cytotoxic agents that target cell replication. Some of these molecularly targeted agents have yielded previously unprecedented anti-tumour activity in specific tumour types in the presence of the matching molecular alteration.[2–7] Molecularly targeted agents have followed the same clinical development process as cytotoxic agents: per tumour location and histology. Most genetic molecular alterations exist across tumour types and histologies, although incidence varies.[8] This observation challenges the existing drug development strategies for molecularly targeted agents and raises the possibility of a shift towards histology-agnostic molecularly based treatment with these drugs.

Advances in high-throughput technology have allowed the identification of multiple genomic molecular alterations in a timeframe compatible with clinical practice. The use of these technologies has been endorsed by physicians and patients with the aim of guiding therapy.[9,10] This histology-agnostic approach is supported by non-randomised studies. Using each patient as their own control, a pilot study[11] reported that 27% of patients with any kind of recurrent cancer had a 30% increase in progression-free survival with treatment selected on the basis of tumour molecular profiling compared with progression-free survival for their previous treatment. Similarly, findings from a retrospective study[12] showed improved progression-free survival and overall survival for cancer patients entering a phase 1 trial on the basis of a molecular alteration identified in their tumour.[12] These results, together with the decreasing cost of genomic testing, have led to increased off-label use of molecularly targeted agents.[13]

However, in view of the absence of data from randomised trials, the clinical usefulness of large-scale genomic testing has not been formally shown. In the SHIVA trial, we aimed to assess whether histology-agnostic use of marketed molecularly targeted agents outside their indications based on tumour molecular profiling could improve outcomes for patients with any kind of cancer for whom standard of care had failed, compared with treatment at the physician's choice.

Methods

Study design and participants

SHIVA was a proof-of-concept, multicentre, open-label, randomised, controlled phase 2 trial of molecularly targeted agents based on tumour molecular profiling versus treatment at physician's choice in patients with refractory cancer. The study was done at eight academic sites in France (appendix 1 p 2).

Patients older than 18 years with any kind of recurrent or metastatic solid tumour for whom standard of care

See Online for appendices

therapy had failed were eligible for the study, provided their disease was accessible for a biopsy or resection of a metastatic site. We deemed standard of care to include all treatments that have been reported to improve survival or quality of life in randomised trials. To be included, patients needed to have progressed on all molecularly targeted agents approved for their disease (except if contraindicated). Bone tumour sampling was not allowed. Patients were allowed to receive a cytotoxic agent, but no molecularly targeted agent or hormone therapy, between the time of the biopsy and randomisation. Patients needed to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; measurable disease in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; and values within the prespecified range for absolute neutrophil count (≥1×10^9 platelets per L), platelets (≥1×10^{11} cells per L), haemoglobin (≥90 g/L), serum creatinine (≤1·5 times upper limit of normal [ULN]), serum total bilirubin (≤1·5 times ULN), and aspartate and alanine aminotransferases (≤3 times ULN or ≤5 times ULN for patients with liver metastases). Patients with brain metastases that had been controlled for at least 3 months were eligible. We excluded patients treated with anti-vitamin K anticoagulation. To be eligible for randomisation, patients needed a left ventricular ejection fraction more than 50%, a QTc interval less than 480 ms, and preserved ECOG performance status and renal, hepatic, and bone marrow function. All patients provided written informed consent.

We established molecular profiles for patient tumours based on samples from a mandatory biopsy or resection of a metastasis (appendix 1 pp 4–6). Molecular analyses included assessment of mutations by targeted next generation sequencing (AmpliSeq cancer panel on an Ion Torrent/PGM system, Life Technologies, Carlsbad, CA, USA; appendix 2); gene copy number alterations by Cytoscan HD (Affymetrix, Santa Clara, CA, USA); and expression of oestrogen, progesterone, and androgen receptors by immunohistochemistry (appendix 1 p 4). Patients were eligible for randomisation if one or several molecular alterations were identified that matched one of the available molecularly targeted regimens.

The study was approved by the Ile-de-France ethics committee. The trial was done in accordance with the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference on Harmonization, and relevant French and European laws and directives. The study protocol is available in appendix 1 (pp 16–298).

Randomisation and masking

We randomly assigned patients in a 1:1 ratio to receive treatment with molecularly targeted agents or treatment at physician's choice. To control for patient heterogeneity, randomisation was stratified by three altered signalling pathways (the hormone receptors pathway, the PI3K/AKT/mTOR pathway, and the RAF/MEK pathway) and patients' prognoses based on the Royal Marsden Hospital (RMH) score, divided into two categories (0 or 1 *vs* 2 or 3).[14] We did not stratify patients by histology. The biostatistics department of the Institut Curie (Paris, France) did the randomisation via the web software ALEA version 2, using block permutation (blocks of size six) within each stratum. Treatment allocation was not masked because of all the treatment choices available to the investigators in the control group.

Procedures

The molecularly targeted agents that were given to the experimental group were drugs that are approved for clinical use in France, but outside their indications. Single molecularly targeted agents (erlotinib, sorafenib, imatinib, dasatinib, vemurafenib, everolimus, abiraterone, letrozole, tamoxifen) were selected in accordance with a predefined treatment algorithm, except for patients whose tumour harboured a mutation or an amplification in *HER2*, who were treated with the combination of trastuzumab and lapatinib (appendix 1 p 8). In both the experimental and control groups, treatments were given according to the approved product information and standard practice protocols at each institution and were continued until evidence of disease progression. If tumours had several molecular alterations, prioritisation was discussed by the Molecular Biology Board (appendix 1 p 5) based on the following criteria: first, if the patient's tumour expressed both androgen receptor and oestrogen receptor or progesterone receptor, the hormone receptor with the highest expression was taken into account; second, any mutation, amplification, or deletion was deemed to be of greater importance than was hormone receptor expression; and third, in cases with several mutations, amplifications, or deletions, the board judged alterations to direct targets of a molecularly targeted agent to be of highest priority for the treatment decision—if two molecular alterations that were both direct targets of one of the available molecularly targeted agents were present, the board would make the decision based on which alteration was downstream.

A crossover was proposed at disease progression for patients in both treatment groups. Quotas were introduced so that no more than 20% of the randomly assigned patients in each group had the same tumour type and histology. The treating physician was only informed of the result of the molecular alteration of interest at the time when the patient was about to start treatment with the matched molecularly targeted agent, whether this was at randomisation or at crossover.

The criteria for removal of a patient from the study were disease progression (after crossover, if any), death, unacceptable toxic effects, patient's decision, and investigator's choice. Tumour assessments were done

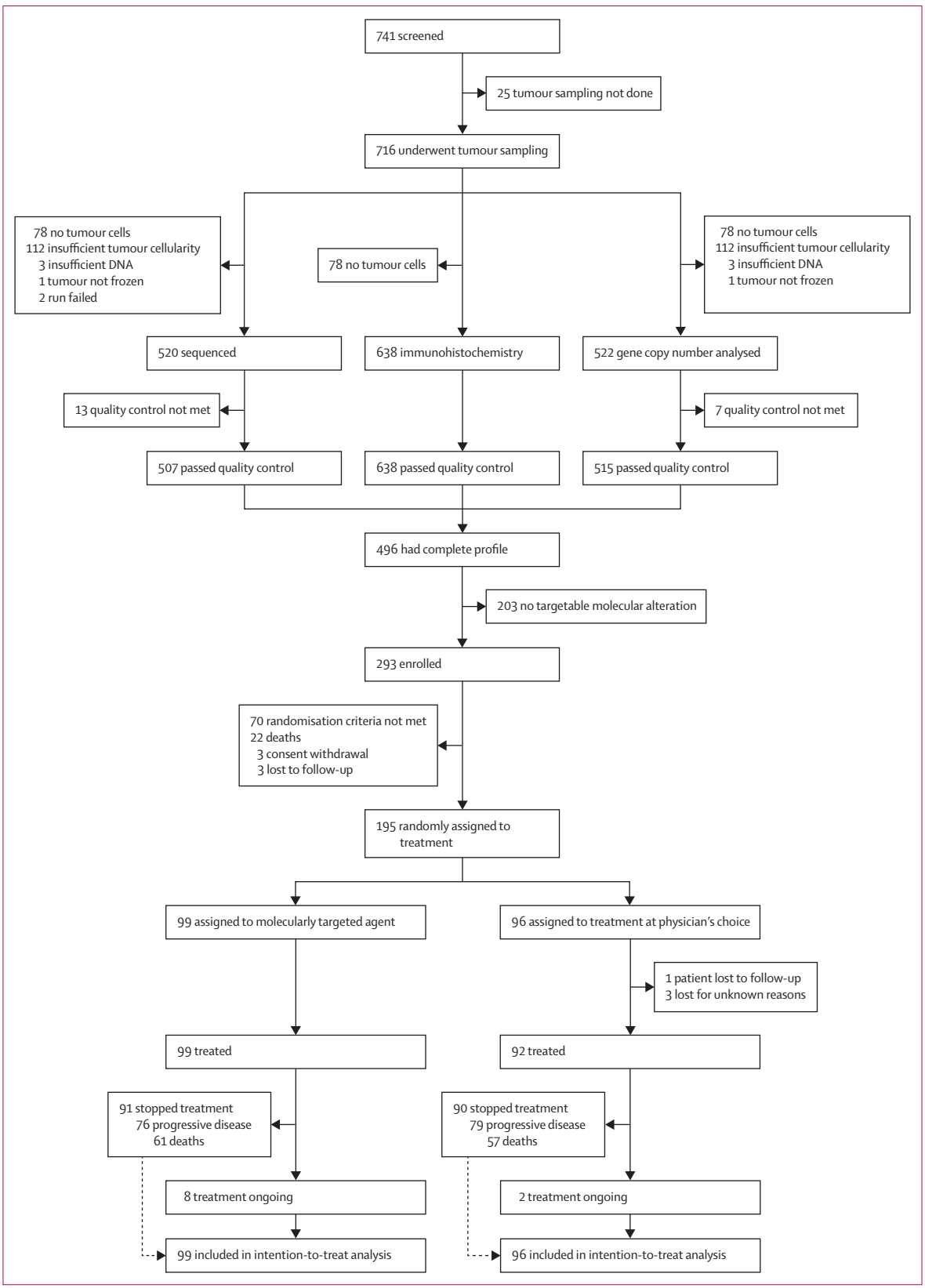

Figure 1: **Trial profile**

before patients started the study treatment (baseline), then every 8 weeks (plus or minus 1 week). Adverse events, laboratory values, and vital signs were assessed in accordance with the approved product information and standard practice protocols at each institution throughout the study.

Outcomes

The primary endpoint of the study was progression-free survival, defined as the time from randomisation to death from any cause or progression according to RECIST 1.1.[15] Secondary endpoints were safety and proportion of patients with an objective response to treatment as assessed by RECIST. Progression-free survival and the proportion of patients with an objective response were also assessed in patients who crossed over, as were tumour growth kinetics for both treatments.[16] Outcomes were not centrally reviewed. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.

Statistical analysis

The objective of the study was to detect a difference in progression-free survival between the treatment groups. Expected 6-month progression-free survival in the control group was 15%.[17] We postulated that the experimental group would have 40% longer progression-free survival than that of the control group (hazard ratio [HR] 0·625). A total of 142 events was needed to detect a statistically significant difference with a type I error rate of 5% and a power of 80% in a two-sided setting. To be able to see these events, we planned to include a total of 200 patients.

All analyses were done by the sponsor using data obtained up to Jan 20, 2015. The primary analysis was done in the intention-to-treat population. A log-rank test was used in the primary analysis to evaluate progression-free survival, with stratification according to the altered molecular pathway and patients' prognoses (as measured by the RMH score). The results are presented as Kaplan-Meier curves. HRs were estimated with a stratified Cox proportional hazards model after a visual check of the underlying assumptions. Interaction tests and subgroup analyses were done to establish whether treatment effects were consistent between patient subgroups. Safety analyses were done according to the treatment received by all patients who started treatment (molecularly targeted agent alone *vs* cytotoxic chemotherapy with or without molecularly target agent). All tests were two-sided at the 5% significance level. All statistical analyses were done with SAS version 9.4.

An independent safety monitoring committee supervised the collation of the safety data. This trial is registered with ClinicalTrials.gov, number NCT01771458.

	Molecularly targeted agent group (n=99)	Treatment at physician's choice group (n=96)
Age (years)	61 (54–69)	63 (54–69)
Sex		
Female	60 (61%)	69 (72%)
Male	39 (39%)	27 (28%)
Previous lines of treatment	3 (2–5)	3 (2–5)
Royal Marsden Hospital score		
0 or 1	51 (52%)	48 (50%)
2 or 3	48 (48%)	48 (50%)
Molecular pathway altered		
Hormone receptor pathway	40 (40%)	42 (44%)
PI3K/AKT/mTOR pathway	46 (46%)	43 (45%)
RAF/MEK pathway	13 (13%)	11 (11%)
Tumour type		
Breast adenocarcinoma	22 (22%)	18 (19%)
Ovarian cancer	12 (12%)	17 (18%)
Lung cancer	9 (9%)	10 (10%)
Colorectal cancer	9 (9%)	9 (9%)
Cervical cancer	12 (12%)	7 (7%)
Head and neck squamous cell carcinoma	6 (6%)	5 (5%)
Sarcoma	4 (4%)	4 (4%)
Urothelial carcinoma	2 (2%)	4 (4%)
Pancreatic adenocarcinoma	3 (2%)	2 (2%)
Adenocarcinoma of unknown primary	2 (2%)	3 (3%)
Oesophagogastric cancer	3 (3%)	2 (2%)
Adenoid cystic carcinoma	1 (1%)	3 (3%)
Non-adenoid cystic carcinoma salivary gland tumour	2 (2%)	2 (2%)
Hepatocelular carcinoma	1 (1%)	2 (2%)
Anal squamous cell carcinoma	1 (1%)	2 (2%)
Neuroendocrine tumour	2 (2%)	1 (1%)
Biliary tract carcinoma	1 (1%)	1 (1%)
Nasopharyngeal carcinoma	1 (1%)	1 (1%)
Cutaneous melanoma	1 (1%)	1 (1%)
Mesothelioma	0	1 (1%)
Peritoneal tumour	0	1 (1%)
Ependymoma	1 (1%)	0
Prostate adenocarcinoma	1 (1%)	0
Uveal melanoma	1 (1%)	0
Germline tumour	1 (1%)	0
Kidney cancer	1 (1%)	0

Data are n (%), or median (IQR).

Table 1: **Baseline characteristics**

Role of the funding source

The sponsor of the study was involved in the study design, data collection, and data analysis. All authors had full access to all the data in the study, made the decision to submit these data for publication, were involved in writing the manuscript, and agreed on the final content

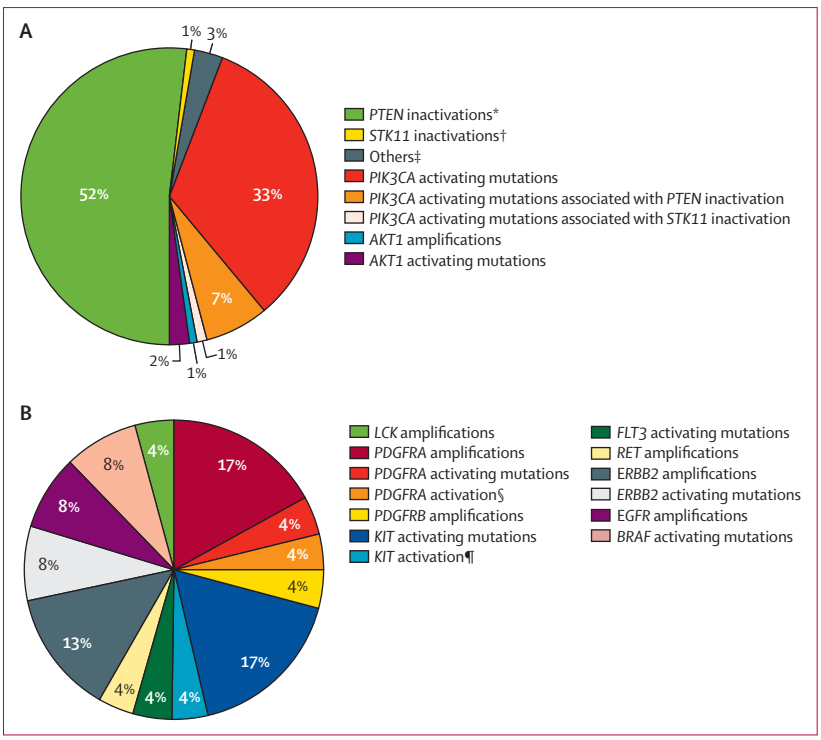

***Figure 2*: Distribution of molecular alterations in the PI3K/AKT/mTOR pathway (A) and RAF/MEK pathway (B)**

**PTEN* inactivations included homozygous deletions and heterozygous deletions associated with inactivating mutations or validated by absence of expression of PTEN in immunohistochemistry. †*STK11* inactivations included homozygous deletions and heterozygous deletions associated with inactivating mutations of *STK11*. ‡Focal gains of several PIK3 pathway genes including *AKT1*, *AKT2*, *AKT3*, *RPTOR*, and *RICTOR* (three patients). §Intragenic deletion within *PDGFRA* validated by overexpression of PDGFRA in immunohistochemistry. ¶Intragenic deletion within *KIT* validated by overexpression of the KIT in immunohistochemistry.

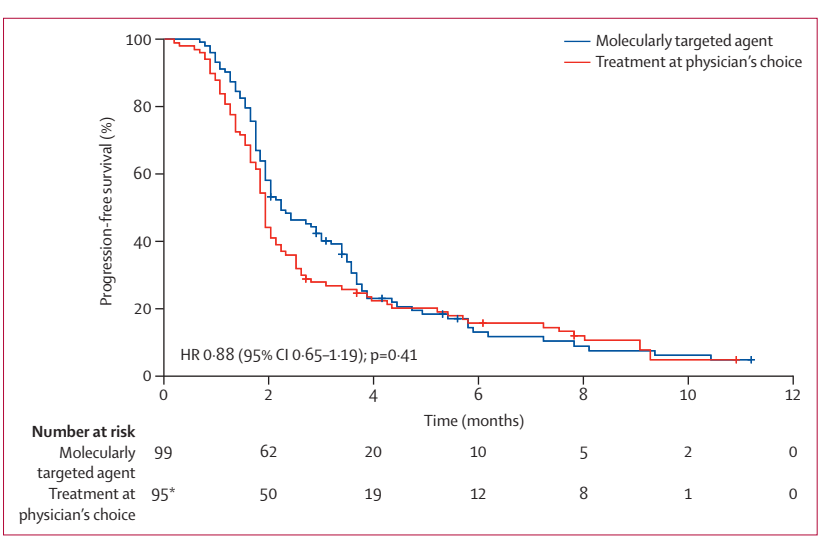

***Figure 3*: Progression-free survival**

*One patient had a follow-up of zero days so is not shown here.

of the paper. The corresponding author had final responsibility for the decision to submit for publication. XP and CM had access to the raw data.

Results

Enrolment started on Oct 4, 2012, and stopped on July 11, 2014, after the inclusion of 741 patients in the screening programme because a preliminary analysis suggested that 200 of these patients would be suitable for inclusion. A complete molecular profile was available for 496 (67%) patients (figure 1). A molecular alteration matching one of the available molecularly targeted agents was detected in 293 (40%) patients.

At the cutoff date (Jan 20, 2015), 195 (26%) of the original 741 patients had been randomly assigned to receive either a molecularly targeted agent (experimental group, 99 patients) or treatment at the physician's choice (control group, 96 patients). Baseline characteristics were similar between the two groups (table 1). Tumour types seemed to be evenly distributed between the groups. Median time from biopsy to randomisation was 65 days (IQR 44–124) in the experimental group and 57 days (42–94) in the control group.

Focusing only on molecular alterations of interest for the trial and excluding oestrogen receptor and progesterone receptor positivity in patients with breast cancer (which was not taken into account in the treatment algorithm, because hormone therapy is standard of care for this disease), 55 (28%) of the 195 patients who were assigned to one of the groups had two or more molecular alterations of interest, and none had more than four alterations. Of these 55 patients, five had only oestrogen receptor or progesterone receptor expression and nine had molecular alterations affecting only the PI3K/AKT/mTOR pathway, which, according to the treatment algorithm, did not change the treatment assigned. Only 41 (21%) patients had at least two molecular alterations that would potentially lead to different choices of molecularly targeted agents. Of these 41 patients, 26 expressed a hormone receptor and a molecular alteration affecting the PI3K/AKT/mTOR pathway (in which case everolimus was given), 14 had both androgen receptor and oestrogen receptor or progesterone receptor expression (in which case treatment was chosen based on the most prevalent hormone receptor), and one patient had a *PDGFRA* mutation (Leu655Trp) associated with a *PIK3CA* mutation (Glu545Lys). The *PDGFRA* mutation was judged to be more important because of the availability of sorafenib, which is a direct inhibitor of *PDGFRA*, as opposed to everolimus, which targets mTOR downstream of PI3KCA.

82 patients had a molecular alteration affecting the hormone receptor pathway, including 49 (60%) patients who had androgen receptor expression and 33 (40%) who had oestrogen receptor or progesterone receptor expression. 89 patients had alterations in the PI3K/AKT/mTOR pathway and 24 had alterations in the RAF/MEK pathway (figure 2; appendix 1 p 14). Appendix 1 shows the molecular alterations of interest according to tumour types (pp 9–11). In addition to the molecular alterations of interest for the trial, other molecular alterations

seemed to be well balanced between both arms. For example, *TP53* mutations were present in 42 (46%) of 91 patients with sequencing data in the experimental group versus 34 (40%) of 84 patients in the control group.

Out of the 96 patients allocated to the control group, 92 actually started treatment (figure 1), including 70 (76%) patients who received single-agent treatment, 19 (21%) who received combination treatment, and three (3%) who received best supportive care alone. Two patients in the control group received a molecularly targeted agent: one received erlotinib and the other received a combination of eribulin and trastuzumab. The patient who received erlotinib was included in the experimental group for the purposes of safety analyses; the other patient received a molecularly targeted agent and cytotoxic chemotherapy and was analysed for safety in the control group. Both patients were included in the control group for efficacy analyses. 63 patients crossed over in the control group, and 21 in the experimental group.

Median follow-up at the time of this analysis was 11·3 months (IQR 5·8–11·6) in the experimental group and 11·3 months (8·1–11·6) in the control group. Median progression-free survival was 2·3 months (95% CI 1·7–3·8) in the experimental group versus 2·0 months (1·8–2·1) in the control group (HR 0·88, 95% CI 0·65–1·19, p=0·41; figure 3). Progression-free survival at 6 months was 13% (95% CI 7–20) in the control group and 11% (6–19) in the experimental group. Objective responses were noted in four (4·1%, 95% CI 0·0–8·0) of 98 assessable patients in the experimental group and three (3·4%, 1·0–9·5) of 89 assessable patients in the control group (p=0·19).

We detected no interaction between the altered molecular pathway and treatment effect (p=0·49). In the hormone receptor pathway subgroup, median progression-free survival was 2·1 months (95% CI 1·8–2·5) in the experimental group versus 2·0 months (1·7–2·7) in the control group (HR 1·12, 95% CI 0·70–1·78, p=0·64; figure 4A). In the PI3K/AKT/mTOR pathway subgroup, median progression-free survival was 2·4 months (1·9–3·3) in the experimental group versus 1·9 months (1·7–2·0) in the control group (HR 0·79, 95% CI 0·51–1·24, p=0·30; figure 4B). In the RAF/MEK pathway subgroup, median progression-free survival was 3·7 months (1·3–5·6) in the experimental group versus 2·0 months (1·0–2·9) in the control group (HR 0·58, 95% CI 0·24–1·37, p=0·20; figure 4C). In the subgroup of patients with an RMH score of 2 or 3, the HR was 1·0 (95% CI 0·69–1·42, p=0·99) for the experimental versus control groups. For patients with an RMH score of 0 or 1, the HR was 0·74 (95% CI 0·51–1·07, p=0·12).

Within the safety population, grade 3–4 adverse events were noted for 43 (43%) of the 100 patients who received a molecularly targeted agent (including 99 patients from the experimental group and the patient in the control group who received erlotinib) and 32 (35%) of the 91 patients

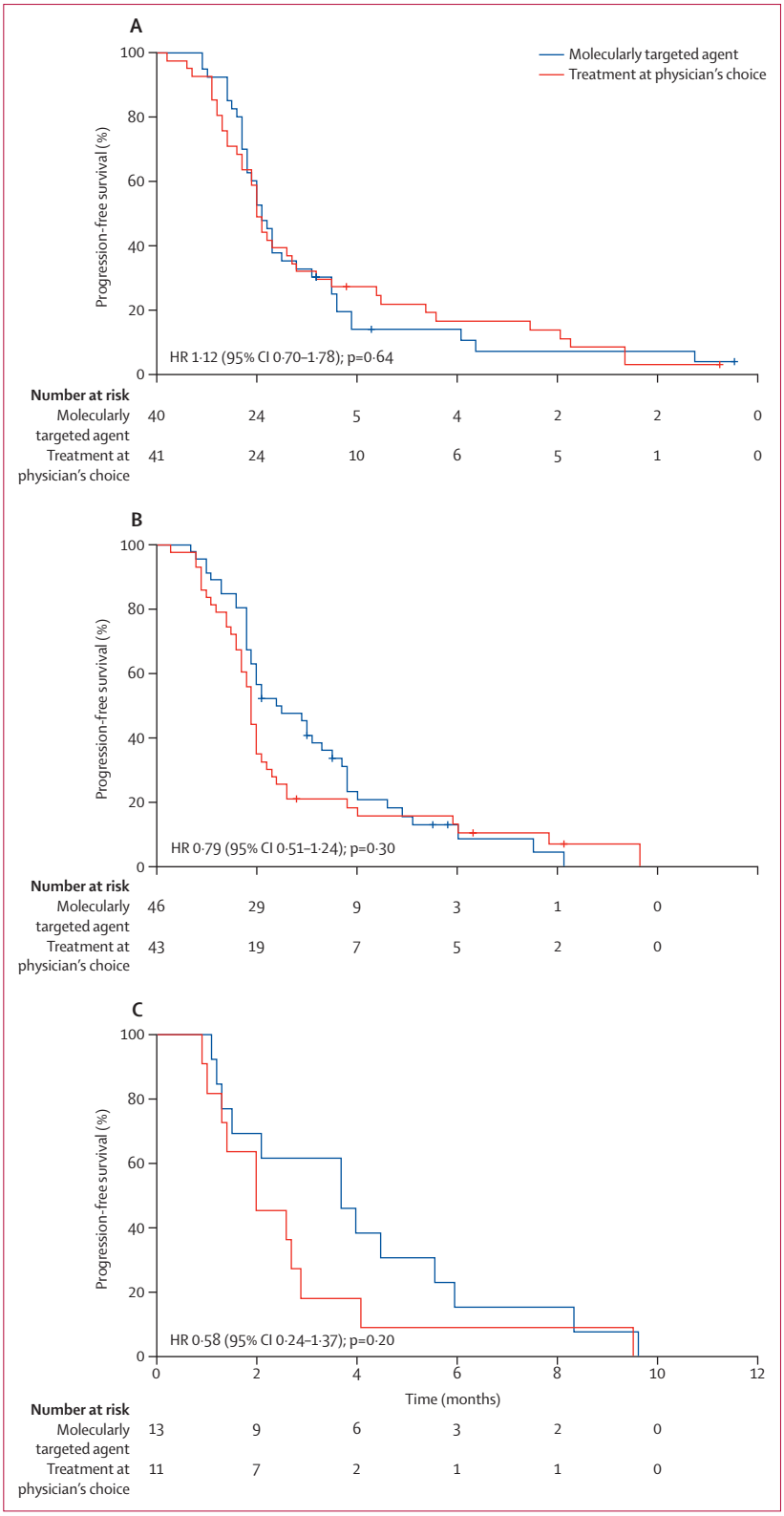

Figure 4: **Progression-free survival by molecular pathway**
Progression-free survival in patients with molecular alterations in the hormone receptor pathway (A), PI3K/AKT/mTOR pathway (B), and RAF/MEK pathway (C).

	Patients who received molecularly targeted agents (n=100*)			Patients who received cytotoxic chemotherapy (n=91†)		
	Grade 2 necessitating drug interruption or delay‡	Grade 3	Grade 4	Grade 2 necessitating drug interruption or delay	Grade 3	Grade 4
Any event§	12 (12%)	36 (36%)	7 (7%)	9 (10%)	28 (31%)	4 (4%)
Neutropenia	0	1 (1%)	0	0	5 (5%)	2 (2%)
Febrile neutropenia	0	1 (1%)	0	0	0	0
Anaemia	0	5 (5%)	0	2 (2%)	4 (4%)	0
Thrombocytopenia	1 (1%)	1 (1%)	1 (1%)	0	0	1 (1%)
Loss of appetite	2 (2%)	0	1 (1%)	0	2 (2%)	0
Asthenia	0	2 (2%)	3 (3%)	2 (2%)	2 (2%)	0
Nausea	2 (2%)	2 (2%)	0	1 (1%)	0	0
Vomiting	0	1 (1%)	0	0	0	0
Mucositis	0	1 (1%)	0	0	1 (1%)	0
Constipation	0	0	0	0	1 (1%)	0
Abdominal pain	0	1 (1%)	0	0	0	0
Weight loss	1 (1%)	0	0	0	0	0
Weight gain	0	0	0	1 (1%)	0	0
Dyspnoea	1 (1%)	6 (6%)	0	0	2 (2%)	0
Skin reactions	1 (1%)	1 (1%)	0	0	0	0
Cardiac ischaemia	0	0	0	0	1 (1%)	0
Arrhythmia	0	0	0	0	1 (1%)	0
Arthralgia	0	2 (2%)	0	0	0	0
Peripheral neuropathy	0	1 (1%)	0	0	1 (1%)	0
Aspartate aminotransferase increase	0	2 (2%)	0	0	0	0
Creatinine increase	0	0	0	0	1 (1%)	0
Other	2 (2%)	9 (9%)	5 (5%)	3 (3%)	6 (7%)	1 (1%)

*Includes one patient allocated to the control group who received a molecularly targeted agent that was permitted in the experimental group. †Four patients in the control group never started treatment and one patient received a molecularly targeted agent that was permitted in the experimental group. ‡Only grade 2 adverse events that led to a treatment interruption or a dose delay were recorded, whereas all grade 3–5 adverse events were recorded. §For any adverse events, only the adverse event with the worst grade was reported.

Table 2: **Adverse events**

who received cytotoxic chemotherapy (p=0·30; table 2). Treatment interruptions or dose delays were reported for 30 (30%) of the patients given a molecularly targeted agent, and 16 (18%) of the patients given cytotoxic chemotherapy. No deaths related to study drugs occurred during the trial.

Grade 3–4 adverse events were reported for 14 (34%) of the 41 patients who received hormone therapy, 23 (50%) of the 46 patients treated with everolimus, and six (46%) of the 13 patients treated with the remaining molecularly targeted agents. In the patients who received chemotherapy, grade 3–4 adverse events were reported for 13 (27%) of the 48 patients with an RMH score of 0 or 1, and 19 (44%) of the 43 patients with an RMH score of 2 or 3. In the patients who received molecularly targeted agents, grade 3–4 adverse events were reported for 23 (45%) of the 51 patients with an RMH score of 0 or 1, and 20 (41%) of the 49 patients with an RMH score of 2 or 3.

Discussion

The SHIVA trial is a histology-agnostic randomised trial that has many features in common with the proposed expansion platform type IIB design.[18] Patient accrual went twice as fast as anticipated, which shows the enthusiasm that patients and physicians have for trials that use molecular information to guide therapy.[9,10,19] Our findings indicate that the use of molecularly targeted agents outside their indications does not improve progression-free survival compared with treatment at physician's choice in heavily pretreated patients with cancer.

The success rate of our genomic analyses was similar to those reported in other trials that use large-scale genomic testing on samples from metastases, with the main reason for failure being low cellularity.[19–21] The 40% prevalence of patients with a molecular alteration that could be targeted with drugs according to our predefined treatment algorithm is in line with those reported previously.[12,19–21] Conversely, the proportion of patients screened (26%) who reached the randomisation stage is higher than in other histology-agnostic studies, probably because treatment was part of the study and did not depend on available clinical trials.[20,21] The need for fresh frozen biopsies and real-time molecular analyses was

challenging for the eight academic centres involved in the trial.[22] Although use of such approaches is not yet widespread, technological advances in next generation sequencing methods and circulating tumour DNA analysis will allow these limitations to be overcome in the future.[23]

The main aim of the trial was to assess whether use of molecularly targeted agents outside their indications improved patient outcomes if given on the basis of identified molecular alterations according to a predefined treatment algorithm. The treatment algorithm, which describes how potential molecular alterations can be matched to molecularly targeted agents, was extensively discussed before we started the trial and fixed thereafter to ensure reproducibility and homogeneous interpretation of molecular alterations between patients. In the trial, we assessed molecularly targeted agents that are marketed in France and have either a clinically validated biomarker in another indication, such as *HER2* amplification for the trastuzumab and lapatinib combination, or biomarkers supported by preclinical data, such as a *PTEN* loss for everolimus. The treatment algorithm is one of the key elements being assessed in this trial, because the study was not powered to conclude whether one of the molecularly targeted agents used is effective for any molecularly or histologically characterised subgroup of patients. The trial failed to show the prespecified 15–30% improvement in progression-free survival at 6 months, but a smaller true benefit might not have been detected because of insufficient power. Moreover, there was insufficient power to detect such a difference in the subset of patients with genomic alterations (n=113) only, excluding patients with hormonal molecular alterations.

Overall, the adverse event profile was consistent with previous reports. However, severe adverse events (ie, grades 3–4), whether related to study drugs or not, were more common with molecularly targeted agents than with chemotherapy, as were treatment interruptions or delays, although this difference was not significant. This result is counterintuitive, especially in view of the fact that almost half of patients in the experimental group were treated with hormone therapy, which is supposed to produce very few severe adverse events. Associations between adverse events and the individual study drugs were not taken into account in our study, which might explain the high numbers of severe adverse events seen. Nevertheless, the increased prevalence in patients who received molecularly targeted agents emphasises the fact that the safety profiles of these drugs might not be favourable in heavily pretreated patients compared with conventional chemotherapy.

The proportion of patients with an objective response and progression-free survival in the control group of the trial was similar to those reported for other heavily pretreated patients included in early phase clinical trials without molecular selection.[12,17,21] Overall survival and crossover data were not mature at the cutoff date and will be reported later. The proportions of patients with an objective response and progression-free survival were not significantly different between the experimental group and control group, and therefore do not support the favourable results obtained in non-randomised studies in which patients received a molecularly targeted agent matching an identified molecular alteration.[11,12,21] However, the difference in progression-free survival in the subgroup of patients who received drugs targeting the RAF/MEK pathway in the experimental group was similar to the improvement in progression-free survival reported by these studies, although patients in those studies were often treated with drug combinations.[11,12,21] In this subgroup of patients with alterations in the RAF/MEK pathway, the HR was 0·58, although it was not significant, possibly because of the small number of patients. The overall result of our study was possibly negatively affected by the drugs targeting hormone receptors (HR 1·12) and everolimus used for the PI3K/AKT/mTOR pathway (HR 0·79), which is now known not to be the best molecularly targeted agent to target molecular alterations at different levels of this pathway.

The RMH prognostic score predicts survival in heavily pretreated patients with cancer and is often used to select patients for phase 1 clinical trials.[14] Our study suggests that only patients whose RMH score predicts a longer life expectancy would potentially benefit from our histology-agnostic approach, although the difference between RMH groupings was not significant. This absence of a significant difference might be related to the fact that molecularly targeted agents are known to need some time to produce anti-tumour effects. Patients with a poor prognosis might deteriorate before they have received enough exposure to molecularly targeted agents.

Several key points might explain the overall negative result of the SHIVA trial. First, we acknowledge that our use of multiple treatment groups composed of many molecular alterations in patients with various tumour types and histologies introduced an important source of variability into the analysis. The treatment algorithm used in our trial was unidimensional, with single molecular alterations supposed to predict the efficacy of molecularly targeted agents. Preliminary data suggest that information on coexisting molecular alterations might help to predict the efficacy of molecularly targeted agents. For example, PI3K inhibitors have been reported to be effective in some patients with tumours harbouring a *PI3KCA* mutation, while coexisting *PI3KCA* and *KRAS* mutations have been reported to predict the reduced efficacy of PI3K inhibitors.[24] Whether multidimensional treatment algorithms that incorporate information from several genes using systems biology approaches will be able to better predict response to molecularly targeted agents remains to be established. Second, the molecularly targeted agents were mostly used as single agents in our study, which often led to reduced efficacy through the development of resistance. Use of several molecularly

targeted agents in combination is an appealing way to counteract resistance. For example, the combination of a BRAF inhibitor and a MEK inhibitor has been shown to be more effective than a BRAF inhibitor as a single agent in Val600Glu BRAF-mutated recurrent or metastatic melanoma.[25] Although use of drug combinations is appealing, they are associated with safety concerns.[26] Third, spatial and temporal intrapatient heterogeneity was not taken into consideration in our study. Improvements in molecular analyses of circulating tumour DNA might allow tumour evolution to be readdressed over time and therapy potentially revised accordingly. Fourth, the only available molecularly targeted agents in our study were those that were marketed in France, which might not be the best drugs for a given molecular alteration. As an example, dual mTORC inhibitors might be more appropriate than everolimus to target the PI3K/AKT/mTOR pathway. Additionally, the small number of molecularly targeted agents available in this study did not cover the whole range of actionable oncogenic drivers. Finally, our study included heavily pretreated patients, which reduced the likelihood that molecularly targeted agents will be effective. Targeting of HER2 with trastuzumab, for example, decreases the recurrence risk by half in the adjuvant setting in HER2-overexpressing breast cancer,[27] but only reduces death by 20% in the metastatic setting.[28]

The generalisability of the treatment strategy chosen in SHIVA to other strategies is restricted by the fact that the results depend on the drugs, profiling assays, treatment algorithms, and histology used. However, our results showed no statistically significant difference in progression-free survival between the molecularly targeted agent and treatment at physician's choice groups in heavily pretreated patients. Our findings suggest that off-label use of molecularly targeted agents should be discouraged, and enrolment into clinical trials should be encouraged to help identify predictive biomarkers of efficacy. Our results emphasise the need to, first, discover more effective molecularly targeted agents; second, extend and refine treatment algorithms so they take potential drug combinations into account to avoid resistance; and third, investigate this approach at an earlier disease stage. Further investigation of this histology-agnostic approach pathway is warranted for patients with molecular alterations in the RAF/MEK pathway. Future clinical trials should be encouraged to address in their designs the challenge of spatial and temporal intrapatient tumour heterogeneity to identify the most representative patient sample to guide therapy according to the relevant molecular alteration of the patient's disease.

Contributors

The primary data were made available to the investigators for independent central review and analyses. CLT wrote the first draft of the manuscript, with review and revision by the other authors. All authors had full access to all the data in the study, made the decision to submit these data for publication, were involved in writing the manuscript, and agreed on the final content of the manuscript.

Declaration of interests

MC reports grants from Novartis, AstraZeneca, Roche, Menarini, and Sanofi. All other authors declare no competing interests.

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