Nab-paclitaxel plus either gemcitabine or simplified leucovorin and fluorouracil as first-line therapy for metastatic pancreatic adenocarcinoma (AFUGEM GERCOR): a non-comparative, multicentre, open-label, randomised phase 2 trial

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Summary

Background Nab-paclitaxel plus gemcitabine has become a standard treatment regimen in patients with metastatic pancreatic adenocarcinoma; however, retrospective data suggest that gemcitabine might be inefficient in 50–60% of patients and thus not an optimum regimen in combination with nab-paclitaxel. We did a phase 2 trial to assess the activity and safety of a new regimen of nab-paclitaxel plus simplified leucovorin and fluorouracil.

Methods We did a non-comparative, multicentre, open-label, randomised phase 2 trial in 15 hospitals and institutions in France. Eligible participants were previously untreated patients with metastatic pancreatic adenocarcinoma (previous adjuvant chemotherapy after curative intent resection was allowed if the interval between the end of chemotherapy and relapse was more than 12 months). Patients had to have at least one measurable lesion assessed by CT scan or MRI and an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less. We randomly assigned participants (1:2) centrally to 28-day cycles of either gemcitabine plus nab-paclitaxel or simplified leucovorin and fluorouracil plus nab-paclitaxel. The randomisation was by minimisation, stratified by centre and ECOG performance status. Drugs were administered in each cycle as follows: nab-paclitaxel (125 mg/m²) and gemcitabine (1000 mg/m²) as 30-min intravenous infusions on days 1, 8, and 15; leucovorin (400 mg/m²) as a 120-min intravenous infusion on days 1 and 15; and fluorouracil (400 mg/m²) as a 5-min bolus intravenous infusion followed by a 46-h continuous intravenous infusion of 2400 mg/m² on days 1 and 15. Patients continued treatment until unacceptable toxicity, disease progression, or patient withdrawal. The primary endpoint was progression-free survival at 4 months in the first 72 assessable patients in the leucovorin and fluorouracil group, with a target of 50% for the regimen to be deemed sufficiently active to warrant further study. We did the primary analysis on the modified intention-to-treat (ITT) population, defined as all randomly assigned and assessable patients regardless of their eligibility and received treatments. This trial is registered at ClinicalTrials.gov, number NCT01964534. The trial has ended and we report the final analysis here.

Findings Between Dec 12, 2013, and Oct 31, 2014, we randomly assigned 114 patients to treatment: 75 patients to the leucovorin and fluorouracil group and 39 to the gemcitabine group. One patient in the leucovorin and fluorouracil group did not have a 4-month assessment, and was thus excluded from the modified ITT analysis. Median follow-up was 13·1 months (95% CI 12·5–14·1). At 4 months, 40 (56%, 90% CI 45–66) of 72 patients in the leucovorin and fluorouracil group were alive and free from disease progression (21 [54%, 40–68] of 39 patients in the gemcitabine group were also alive and progression-free at 4 months). Grade 3–4 adverse events occurred in 33 (87%) of 38 patients in the gemcitabine group and in 56 (77%) of 73 patients in the leucovorin and fluorouracil group, with different toxicity profiles. The most common grade 3–4 adverse events in the leucovorin and fluorouracil group were neutropenia without fever (17 [23%]), fatigue (16 [22%]), paraesthesia (14 [19%]), diarrhoea (nine [12%]), and mucositis (seven [10%]); in the gemcitabine group they were neutropenia without fever (12 [32%]), thrombocytopenia (seven [18%]), fatigue (eight [21%]), anaemia (five [13%]), increased alanine aminotransferase and aspartate aminotransferase concentrations (five [13%] for both), and paraesthesia (four [11%]). Two participants died; one in the leucovorin and fluorouracil group from septic shock, and one in the gemcitabine group from diabetes compensation with acidosis; these deaths were deemed to be not related to treatment. Treatment-related serious adverse events occurred in 28 (38%) of 73 patients in the leucovorin and fluorouracil group and in 14 (37%) of 38 in the gemcitabine group.

Interpretation Nab-paclitaxel plus simplified leucovorin and fluorouracil fulfilled the primary endpoint in that more than the required 50% of our study population were progression-free at 4 months, with a tolerable toxicity profile. This regimen thus deserves further assessment in a phase 3 trial.

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Research in context

Evidence before this study

The FOLFIRINOX regimen (fluorouracil, leucovorin, irinotecan, and oxaliplatin) and nab-paclitaxel plus gemcitabine have been shown to be more effective than gemcitabine monotherapy for metastatic pancreatic adenocarcinoma. These regimens are now accepted as standard first-line treatment options, but no randomised trials have directly compared them. We searched PubMed on Dec 12, 2016, with no language restrictions, for the terms "nab-paclitaxel", "pancreatic cancer", and "randomised", and identified no randomised comparisons of a nab-paclitaxel plus fluoropyrimidine-based regimen versus gemcitabine plus nab-paclitaxel. The MPACT phase 3 trial is the only randomised trial that has assessed nab-paclitaxel in patients with metastatic pancreatic adenocarcinoma. In 2013, when our trial was designed, the results of MPACT showed that nab-paclitaxel plus gemcitabine significantly improved the clinical outcome of patients with metastatic pancreatic adenocarcinoma compared with gemcitabine alone. Considering that gemcitabine might not be an optimum cytotoxic drug in at least half of patients with metastatic pancreatic adenocarcinoma, we designed the AFUGEM trial to assess the activity and tolerability of a new regimen combining nab-paclitaxel plus the de Gramont regimen of simplified leucovorin and fluorouracil.

Added value of this study

To our knowledge, this is the first multicentre, phase 2 randomised trial assessing a combination of nab-paclitaxel with a fluoropyrimidine in patients with metastatic pancreatic adenocarcinoma. The proportion of patients who were progression-free at 4 months in the first 72 assessable patients in the leucovorin and fluorouracil group exceeded our prespecified level deemed to be sufficiently active to warrant further study, and the regimen appeared at least as active as the gemcitabine plus nab-palclitaxel combination. Favourable median overall survival and progression-free survival data were reported in the leucovorin and fluorouracil group with an acceptable toxicity profile.

Implications of all the available evidence

Our results support development of the combination regimen of nab-paclitaxel plus a fluoropyrimidine for pancreatic adenocarcinoma. Nab-paclitaxel plus gemcitabine was associated with survival data in the same range as that reported in the MPACT trial. The nab-paclitaxel plus simplified leucovorin and fluorouracil combination merits further assessment in phase 3 trials given the exploratory results for comparisons of overall survival between the two regimens. Moreover, new combinations of nab-paclitaxel plus simplified leucovorin and fluorouracil or an oral fluoropyrimidine, using a higher dose of nab-paclitaxel every 2 weeks (150 mg/m^2 on days 1 and 15), could be assessed. Such regimens could be useful for patients with Eastern Cooperative Oncology Group performance status 2 for whom gemcitabine is standard treatment. Additionally, development of a more manageable regimen with a 2-week schedule could serve as an attractive backbone regimen for adding new drugs.

Introduction

The incidence of pancreatic adenocarcinoma is increasing in high-income countries and it is expected to become the second leading cause of cancer-related mortality in 2020.[1,2] The prognosis of this disease remains very poor with prevalence and incidence roughly equivalent; 5-year overall survival for patients diagnosed with the disease is less than 5%.[3]

Gemcitabine monotherapy was the standard treatment for patients with metastatic pancreatic adenocarcinoma for many years.[4] Over the past decade, the results of several randomised phase 3 studies assessing combinations of cytotoxic agents or cytotoxic agents with targeted chemotherapy did not suggest these were superior compared with gemcitabine alone. The results from one phase 3 trial showed that gemcitabine plus erlotinib was associated with a significant but not clinically relevant benefit in overall survival.[5] In 2011, the FOLFIRINOX regimen (fluorouracil, leucovorin, irinotecan, and oxaliplatin), and more recently the combination of nab-paclitaxel with gemcitabine, have been shown to be more effective than gemcitabine monotherapy in terms of the proportion of patients with an objective response, progression-free survival, and overall survival.[6,7] These regimens are now accepted as the standard first-line treatment options for metastatic pancreatic adenocarcinoma, but no published randomised trials have directly compared them. Moreover, a head-to-head comparison of trials assessing these two regimens is difficult, given differences in patient profiles and rates of second-line chemotherapy across participating countries.[6,7]

Gemcitabine is a hydrophilic prodrug that requires the presence of specialised integral membrane nucleoside transporter proteins to efficiently permeate into tumour cells.[8] Among these, the major mediator of gemcitabine uptake into human cells is the hENT1 protein. Intracellular gemcitabine must then be phosphorylated to its active diphosphate and triphosphate metabolites by subsequent kinases.[9,10] The first phosphorylation is achieved by deoxycytidine kinase in a rate-limiting step of its cellular anabolism. Findings from many retrospective studies in the adjuvant setting have suggested that the level of expression of hENT1 protein and deoxycytidine kinase could be predictive of gemcitabine's efficacy.[11–14] Moreover, these retrospective data suggested that gemcitabine might be inefficient in 50–60% of patients with pancreatic adenocarcinoma and thus not an optimum regimen for combination with nab-paclitaxel.[11–13,15]

Fluorouracil as monotherapy or in combination with gemcitabine has shown some activity in the adjuvant

setting of pancreatic adenocarcinoma and has become a key component of first-line and second-line regimens in metastatic disease.[6,16–19] Nab-paclitaxel can be associated with a fluoropyrimidine with a tolerable toxicity profile.[20,21] The simplified leucovorin and fluorouracil regimen first developed by de Gramont and colleagues has shown a better toxicity profile than fluorouracil bolus.[22] In comparison with capecitabine, the combination of leucovorin plus fluorouracil is associated with fewer occurrences of grade 3–4 diarrhoea and hand–foot syndrome, but more grade 3–4 neutropenia, which could however be controlled with the use of granulocyte colony-stimulating factor (G-CSF) when necessary.[23,24]

The aim of the AFUGEM GERCOR (Groupe Coopérateur Multidisciplinaire en Oncologie) randomised non-comparative phase 2 trial was to assess the tolerability and activity of a nab-paclitaxel plus simplified leucovorin and fluorouracil combination regimen in patients with untreated metastatic pancreatic adenocarcinoma.

Methods

Study design and participants

We did a non-comparative, multicentre, open-label, randomised, phase 2 trial in 15 institutions and hospitals in France (appendix). The study protocol was approved by the French ethics committee Ile de France VI. The detailed protocol is published.[25]

Eligible patients for this study were required to be aged 18 years or older with pathologically confirmed pancreatic adenocarcinoma previously untreated for metastases. We allowed previous adjuvant chemotherapy after curative intent resection if the interval between the end of chemotherapy and relapse was more than 12 months. Patients had to have at least one lesion that was assessable by CT scan or MRI according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; an Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 or less, and adequate organ functions (defined as: absolute neutrophil count >1·5×10⁹ cells L, platelet count >100×10⁹ platelets per L, haemoglobin >90 g/L, serum creatinine <150 µmol/L, aspartate aminotransferase [AST] and alanine aminotransferase [ALT ≤2·5×the upper limit of normal [ULN] or ≤5 ULN in case of liver metastases, total bilirubin ≤1·5 ULN, and albumin ≥25 g/L). Exclusion criteria were: previous chemotherapy for borderline, locally advanced, or metastatic disease; brain or CNS metastasis (unless adequately treated); treatment with warfarin; uncontrolled hypercalcaemia; pre-existing permanent neuropathy at grade 2 or worse according to National Cancer Institute Common Toxicity Criteria of Adverse Events (NCI CTCAE) version 4.0; medical history of active interstitial lung disease; known dihydropyrimidine dehydrogenase deficiency; other serious and uncontrolled non-malignant disease (eg, active infection requiring systemic therapy, coronary stenting or myocardial infarction, or stroke in the past 6 months); and other concomitant or previous malignancies, except adequately treated in-situ carcinoma of the uterine cervix, basal or squamous cell carcinoma of the skin, or cancer in complete remission for more than 5 years. All patients provided written informed consent before study enrolment.

Randomisation and masking

We randomly assigned patients (1:2) to either gemcitabine plus nab-paclitaxel or simplified leucovorin and fluorouracil plus nab-paclitaxel. We used gemcitabine plus nab-paclitaxel as a control group to check our hypotheses, and as a calibration so that the populations in the two groups was similar. An electronic case-report form (CRF) random assignment was done centrally (at GERCOR) using a minimisation technique with an 80% weighting, stratified by centre and ECOG status. After enrolment, a clinical research associate entered patients' baseline characteristics in the electronic CRF and obtained the treatment group automatically. Because of the different nature of the interventions in each group, the study was open label.

Procedures

Both regimens were given over 28-day cycles, as follows: for the gemcitabine plus nab-paclitaxel group, nab-paclitaxel 125 mg/m² and gemcitabine 1000 mg/m² were administered over 30 min as intravenous infusions on days 1, 8, and 15. For the simplified leucovorin and fluorouracil plus nab-paclitaxel group, nab-paclitaxel 125 mg/m² was administered as a 30-min intravenous infusion on days 1, 8, and 15; on days 1 and 15, patients also received a 120-min intravenous infusion of leucovorin 400 mg/m², and a 5-min bolus intravenous infusion of fluorouracil 400 mg/m² followed by a 46-h continuous intravenous infusion of fluorouracil 2400 mg/m². First treatment administration was given within 7 days after randomisation. Patients with ECOG performance score 0 or 1 received a full dose of the regimen at the first cycle; those with ECOG performance score 2 had the dose of nab-paclitaxel reduced by 20% in the first cycle (ie, nab-paclitaxel 100 mg/m²). In the absence of grade 3–4 toxicity during the first cycle, patients with ECOG performance score 2 received a full dose of treatment at the second cycle. Systematic prophylactic treatment with granulocyte-colony stimulating factor (G-CSF) was recommended for patients in both groups according to European Organization for Research and Treatment of Cancer (EORTC) guidelines.[26] The type of G-CSF and treatment duration was determined according to local standards of care in each centre.

All adverse events were graded according to NCI CTCAE version 4.0. Dose reductions were planned according to severity of haematological and non-haematological toxicity (appendix).[25] If a dose was reduced for toxicity, they were not allowed to be re-escalated for the duration of study treatment. In either group, if one study protocol drug had to be interrupted because of

See Online for appendix

For the **protocol** see http://www.umqvc.org/en/tools.html?tool_cat=3

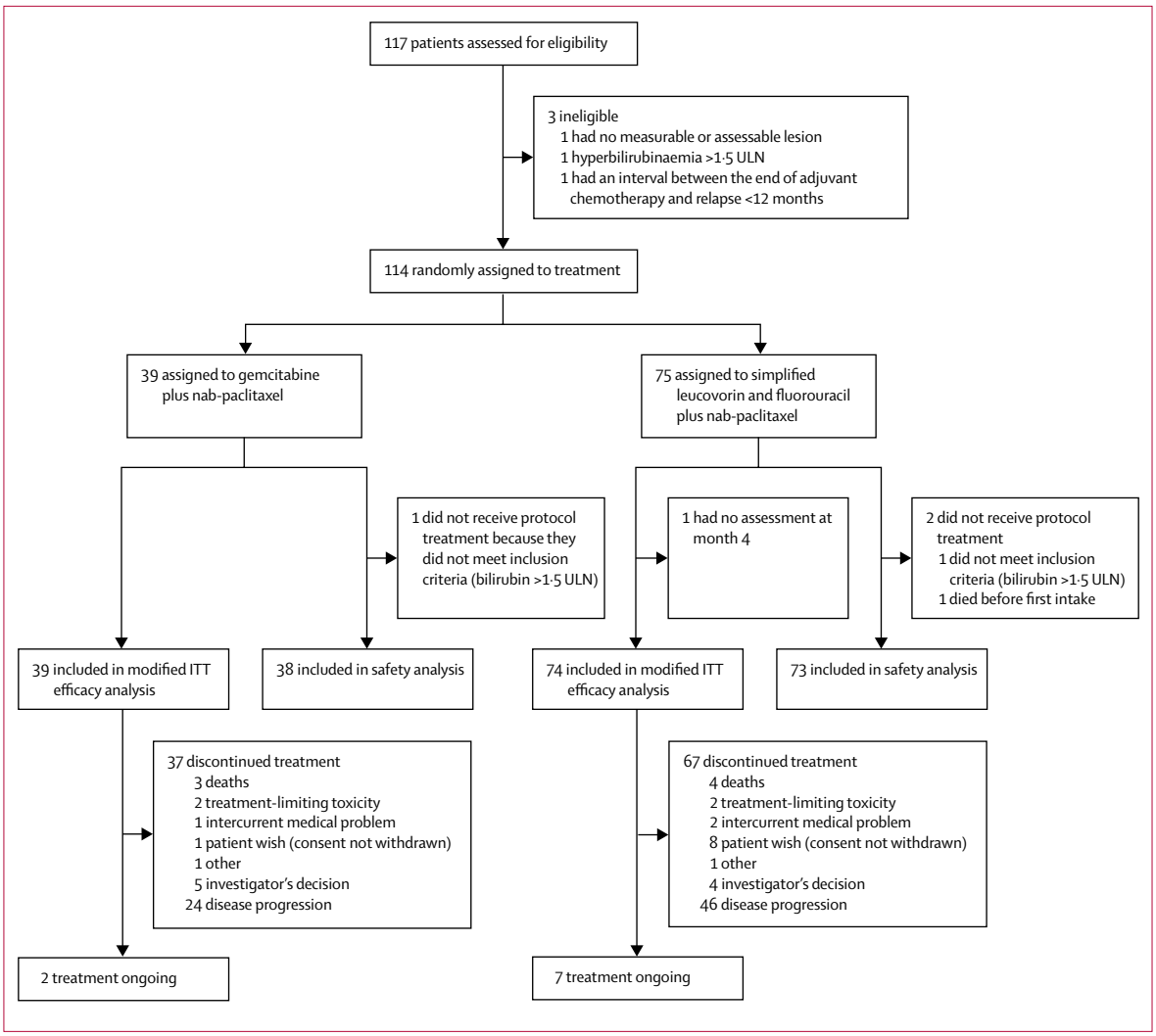

Figure 1: **Trial profile**
One patient assigned to simplified leucovorin and fluorouracil plus nab-paclitaxel was excluded from the modified intention-to-treat and primary endpoint analysis because they did not have an assessment (CT scan) at 4 months. No patient was lost to follow-up during the study. ULN=upper limit of normal. ITT=intention to treat.

adverse events, treatment with the other drug in the regimen combination was continued until progression. If both drugs had to be stopped early because of adverse events, a complete break in therapy was allowed until disease progression.

The following information had to be available before each treatment administration (on days 1, 8, and 15, of every 28 days of each cycle): concomitant treatment information, weight, blood pressure, ECOG performance score, complete and differential blood counts, haematology, serum creatinine, total and indirect bilirubin, AST, ALT, alkaline phosphatase, and toxicity. The items registered at the time of tumour assessment (every 8 weeks) were: weight, blood pressure, ECOG performance score, radiological tumour assessment, complete and differential blood counts, haematology, albumin plasma, cancer antigen 19-9 (CA19-9), and carcinoembryonic antigen (CEA) concentrations, toxicity, and concomitant medication. We did baseline clinical, health-related quality of life (HRQOL), and biological assessments no more than 14 days before randomisation, and tumour assessments (CT scan or MRI) no more than 21 days before randomisation.

We assessed tumour response using chest-abdominal CT scan (or MRI) according to RECIST version 1.1 every 8 weeks (ie, every two cycles). Central review of CT scans (or MRI) was not planned in the protocol. In case of disease progression (clinical or biological), suspicious tumours could be investigated before the next scheduled assessment. Patients continued treatment until unacceptable toxicity, disease progression, or patient withdrawal. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ C-30) questionnaire was used to evaluate

HRQOL.[23] The questionnaire was collected at baseline, at 14 days, on day 1 of every cycle during treatment period, and at the end of treatment (28 days after the last dose of any study drug, plus or minus 3 days).

Outcomes

The primary endpoint was progression-free survival at 4 months (ie, the proportion of patients alive, assessable, and free from progression at 4 months) in the first 72 patients in the leucovorin and fluorouracil group in the modified intention-to-treat population (ITT), defined as all randomly assigned and assessable patients regardless of their eligibility and treatment received. Secondary endpoints were the proportion of patients with an objective response, median progression-free survival, median overall survival, tolerance, and HRQOL.

Statistical analysis

The protocol-specified primary analysis was done on the modified ITT population, which consisted of all randomised patients who had a tumour assessment at 4 months, regardless of their eligibility and received treatments. Progression-free survival was measured from randomisation to the date of first documented progression or death from any cause. Patients alive without progression were censored at the last tumour assessment, either during the study treatment period or during follow-up.[27] Patients who withdrew from the study before documented progression were censored at their off-study date.

No formal statistical comparison was planned between the two study groups. According to Fleming's two-stage design with a one-sided type I α error of 5% and power of 80%, 72 patients had to be randomly assigned to the simplified leucovorin and fluorouracil plus nab-paclitaxel group to test the following hypotheses: under the null hypothesis (H0), a proportion of 35% or less of patients who were alive and progression-free at month 4 was considered as not warranting any further investigation, while under the alternative hypothesis (H1), a proportion of at least 50% of patients with this endpoint was considered as interesting and warranting further investigation in a phase 3 study. The hypotheses were based on the observed progression-free survival in first-line trials of patients with metastatic pancreatic adenocarcinoma and an ECOG performance status of 0–2.[6,7,28] An interim analysis of the primary endpoint was planned, to be done at 4 months after the accrual of 15 patients (stage one), and if positive, the study would go on to stage two, enrolling 72 patients in the leucovorin and fluorouracil group. The hypothesis and two-stage design have been previously described in a detailed protocol.[25] With an expected 5% dropout or non-assessable proportion of participants at 4 months, we required a total of 114 patients (38 in the gemcitabine group, 76 in the leucovorin and fluorouracil group). Progression-free survival at 4 months was described with 90% CIs and was reported for the first 72 patients in the modified ITT population in the leucovorin and fluorouracil group. On the basis of findings from published phase 3 trials, the estimated overall survival of eligible patients was 9–12 months.[6,7]

We did analyses of tolerance in all patients who received at least one dose of allocated treatment. The dose intensity of each drug was calculated based on the number of cycles received by each patient. The relative dose intensity was calculated as the ratio of the dose intensity to the dose intensity indicated in the protocol (obtained as the dose specified per cycle in mg/m²). We measured the median follow-up using the reverse Kaplan-Meier method, and estimated progression-free survival and overall survival using the Kaplan-Meier method, described with median at specific timepoints with 95% CI. For exploratory purposes, only univariate Cox analyses were done to estimate hazard

	Simplified leucovorin and fluorouracil plus nab-paclitaxel (n=75)	Gemcitabine plus nab-paclitaxel (n=39)
Age (years [range])	66 (45–80)	65 (52–86)
Sex		
Male	50 (67%)	20 (51%)
Female	25 (33%)	19 (49%)
ECOG performance status		
0	24 (32%)	13 (33%)
1	39 (52%)	20 (51%)
2	12 (16%)	6 (15%)
Tumour location		
Head	28 (37%)	15 (38%)
Other	47 (63%)	24 (62%)
Differentiation grade		
Well	15 (20%)	8 (21%)
Moderate	27 (36%)	14 (36%)
Poor	2 (3%)	7 (18%)
Unknown	28 (37%)	8 (21%)
Not reported	3 (4%)	2 (5%)
Metastatic site		
1	48 (64%)	24 (62%)
≥2	27 (36%)	15 (38%)
Liver metastases	55 (73%)	31 (79%)
Pain related to the disease	42 (56%)	15 (38%)
Resection of primary tumour	9 (12%)	6 (15%)
Adjuvant chemotherapy	5 (7%)	0
Total bilirubin (μmol/L)	10·0 (7·0–17·1)	10·1 (6·5–14·0)
Albumin (g/L)	39·1 (34·0–42·9)	38·0 (32·8–41·0)
CA19-9 (UI/mL)	1500·5 (103·4–10 226·5)	338·4 (50·2–3726·0)
CEA (ng/mL)	9·9 (2·8–27·2)	3·9 (2·5–14·6)

Data are n (%) or median (IQR), except where stated otherwise. ECOG=Eastern Cooperative Oncology Group. CA19-9=cancer antigen 19-9. CEA=carcinoembryonic antigen. *One patient was excluded from the modified intention-to-treat (ITT) efficacy analysis because they did not have an assessment (CT scan) at month 4. The modified ITT population included all randomly assigned and assessable patients regardless of their eligibility and received treatments.

Table 1*: Baseline characteristics of the whole study population

	Simplified leucovorin and fluorouracil plus nab-paclitaxel (n=74)	Gemcitabine plus nab-paclitaxel (n=39)
Primary endpoint (n)	72	39
Without progression-free survival event at 4 months†	40 (56%, 90% CI 45–66)	21 (54%, 90% CI 40–68)
Secondary endpoints (n)	74	39
Tumour response‡		
Patients with an objective response	26 (35%, 24–47)	14 (36%, 21–53)
Patients with disease control	48 (65%, 53–76)	24 (62%, 45–77)
Progression-free survival§		
Median progression-free survival (months)	5·9 (3·6–7·4)	4·9 (2·1–7·7)
4-month progression-free survival	62% (50–72)	57% (39–71)
6-month progression-free survival	49% (37–60)	43% (27–58)
9-month progression-free survival	31% (21–42)	22% (10–36)
12-month progression-free survival	17% (9–26)	11% (3–23)
Overall survival§		
Median overall survival (months)	11·4 (8·8–15·4)	9·2 (6·0–13·6)
4-month overall survival	85% (75–92)	80% (63–89)
6-month overall survival	76% (64–84)	69% (52–81)
12-month overall survival	48% (36–59)	41% (26–56)
18-month overall survival	34% (23–45)	13% (4–26)

Data are percentage (95% CI), or median (95% CI), except where stated otherwise. With the exception of the primary endpoint, efficacy measures were analysed with updated data as of Sept 1, 2016. *Modified ITT population included all randomly assigned and assessable patients regardless of their eligibility and received treatments. †Event defined as disease progression or death. ‡Per investigator assessment. §Estimated using the Kaplan-Meier method.

Table 2*: Efficacy measures in the modified intention-to-treat (ITT) analysis

ratios (HR) with 95% CI. The database was locked for primary endpoint and safety analyses on Sept 16, 2015. The updated progression-free survival and overall survival analyses are based on data through to Sept 9, 2016. The HRQOL analysis will be reported in a future paper.

To better explore the results of our study, we did several post-hoc or exploratory analyses: a subgroup analysis of patients who received adjuvant chemotherapy, effect of second-line and third-line treatments on overall survival data, and assessment of the depth of response in both treatment groups. Second-line and third-line treatments were registered in the electronic CRF with the date of first administration. In the leucovorin and fluorouracil group, four patients discontinued the protocol treatment because of toxicity but continued fluoropyrimidine alone. For these four patients, second-line treatment was defined as the treatment used after progression under fluoropyrimidine. Overall survival after beginning second-line treatment was assessed using the Kaplan-Meier method in two groups. In patients who did not receive second-line treatment, overall survival after the end of protocol treatment was assessed using the Kaplan-Meier method in the two arms. We also did a post-hoc analysis of the depth of response, which was defined as the maximum tumour shrinkage noted in a patient during the study (RECIST criteria). Median depth of response in both groups was assessed in all patients (whatever the type of objective response) and in the subgroup of patients with a partial or complete response. All statistical analyses were done using SAS 9.3 and R. A data monitoring committee was not needed to oversee this study. This trial is registered at ClinicalTrials.gov, number NCT01964534.

Role of the funding source

The GERCOR collaborative group were involved in study design, data collection, data analysis, data interpretation, and writing of the report, and in the decision to submit for publication. Celgene provided funding to GERCOR, but had no role in any part of study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Dec 12, 2013, and Oct 31, 2014, we randomly assigned 114 patients to treatment; 75 to the simplified leucovorin and fluorouracil group and 39 to the gemcitabine group (figure 1, table 1). Included in the modified ITT analysis were 74 of 75 participants in the leucovorin and fluorouracil group (one assigned patient in this group did not have an assessment at month 4) and all 39 in the gemcitabine group. Treatment groups were well balanced with regard to age, ECOG performance status, tumour location, differentiation grade, and metastatic sites. Numerically more patients in the leucovorin and fluorouracil group were male and had disease-related pain, and this group had a higher median value of CA19-9 and CEA at baseline, compared with the gemcitabine group.

A median of five cycles (range 0–31) and 13 chemotherapy courses (0–55) were administered in the leucovorin and fluorouracil group and five (range 0–18) and 15 (0–48) in the gemcitabine group, respectively. 321 (81%) of 397 cycles in the leucovorin and fluorouracil group and 143 (79%) of 181 in the gemcitabine group were at full dose. In the leucovorin and fluorouracil group, a dose reduction of nab-paclitaxel was done in 53 (13%) of 397 cycles and of fluorouracil in 35 (9%) of 397 cycles. In the gemcitabine group, a dose reduction of nab-paclitaxel was done in 36 (20%) of 181 cycles and of gemcitabine in 15 (8%) of 181 cycles.

23 patients had been randomly assigned at the time of the interim analysis (stage one): 15 in the leucovorin and fluorouracil group and eight in the gemcitabine group. In the stage one analysis, eight (53%; 90% CI 32–75) patients were alive and progression-free at 4 months in the leucovorin and fluorouracil group. Therefore, the study continued to stage two.

At the end of stage two, after a median follow-up of 13·1 months (90% CI 12·5–14·1), 40 (56%, 90% CI 45–66) of 72 patients in the modified ITT population for the primary endpoint analysis were alive and free from progression at 4 months in the leucovorin

and fluorouracil group (table 2). 21 (54%, 90% CI 40–68) of 39 patients in the gemcitabine group were also alive and progression-free.

Median follow-up in the updated analysis was 24·3 months (95% CI 15·4–24·9). Median progression-free survival was 5·9 months (95% CI 3·6–7·4) in the leucovorin and fluorouracil group versus 4·9 months (2·1–7·7) in the gemcitabine group; exploratory hazard ratio [HR] 0·79, 95% CI 0·52–1·20) and median overall survival was 11·4 months (95% CI 8·8–16·5) in the leucovorin and fluorouracil group versus 9·2 months (6·0–13·6) in the gemcitabine group (exploratory HR 0·61, 95% CI 0·40–0·95; figure 2). Other secondary efficacy variables in the modified ITT population are in table 2.

In the leucovorin and fluorouracil group at tumour progression, 46 (61%) and 16 (21%) of 75 patients received second-line and third-line chemotherapy, respectively (table 3). Of the 46 who had second-line chemotherapy, 23 received a fluorouracil-based regimen combined with a platinum salt or irinotecan (ie, FOLFIRINOX, FOLFOX, or FOLFIRI) and 23 received a gemcitabine-based regimen. In the gemcitabine group at tumour progression, 22 (56%) and six (15%) of 39 patients received second-line and third-line chemotherapy, respectively; 19 of the 22 patients who received second-line chemotherapy received FOLFIRINOX, FOLFOX, or FOLFIRI. Median overall survival since the beginning of second-line treatment was 4·6 months (95% CI 3·2–5·7) in the 46 patients in the leucovorin and fluorouracil group and 6·5 months (3·9–8·0) in the 22 patients in the gemcitabine group. For patients who did not receive second-line treatment, median overall survival since the end of protocol treatment was 2·1 months (95% CI 0·2–4·7) in the leucovorin and fluorouracil group and 1·7 months (0·0–1·8) in the gemcitabine group. At the end of the study, two patients in the gemcitabine group and five in the leucovorin and fluorouracil group still had controlled disease without progression.

All patients who had received at least one dose of chemotherapy were considered eligible for toxicity analysis (73 in the leucovorin and fluorouracil group, 38 in the gemcitabine group; table 4). Primary and secondary G-CSF prophylaxis was used in four (5%) and eight (11%) of 73 patients in the leucovorin and fluorouracil group, and in five (13%) and seven (18%) of 38 patients in the gemcitabine group, respectively. 56 (77%) of 73 patients in the leucovorin and fluorouracil group had at least one grade 3–4 toxicity. The most frequent of these were neutropenia without fever (17 [23%]), fatigue (16 [22%]), paraesthesia (14 [19%]), diarrhoea (nine [12%]), and mucositis (seven [10%]). 33 (87%) of 38 patients in the gemcitabine group had at least one grade 3–4 toxicity. The most frequent of these were neutropenia without fever (12 [32%]), thrombocytopenia (seven [18%]), fatigue (eight [21%]), increased ALT and AST concentrations (five [13%] for both), and paraesthesia (four [11%]). Numerically more events of grade 2 alopecia and grade 3–4 mucositis, diarrhoea, and hand–foot syndrome occurred in the leucovorin and fluorouracil group than in the gemcitabine group.

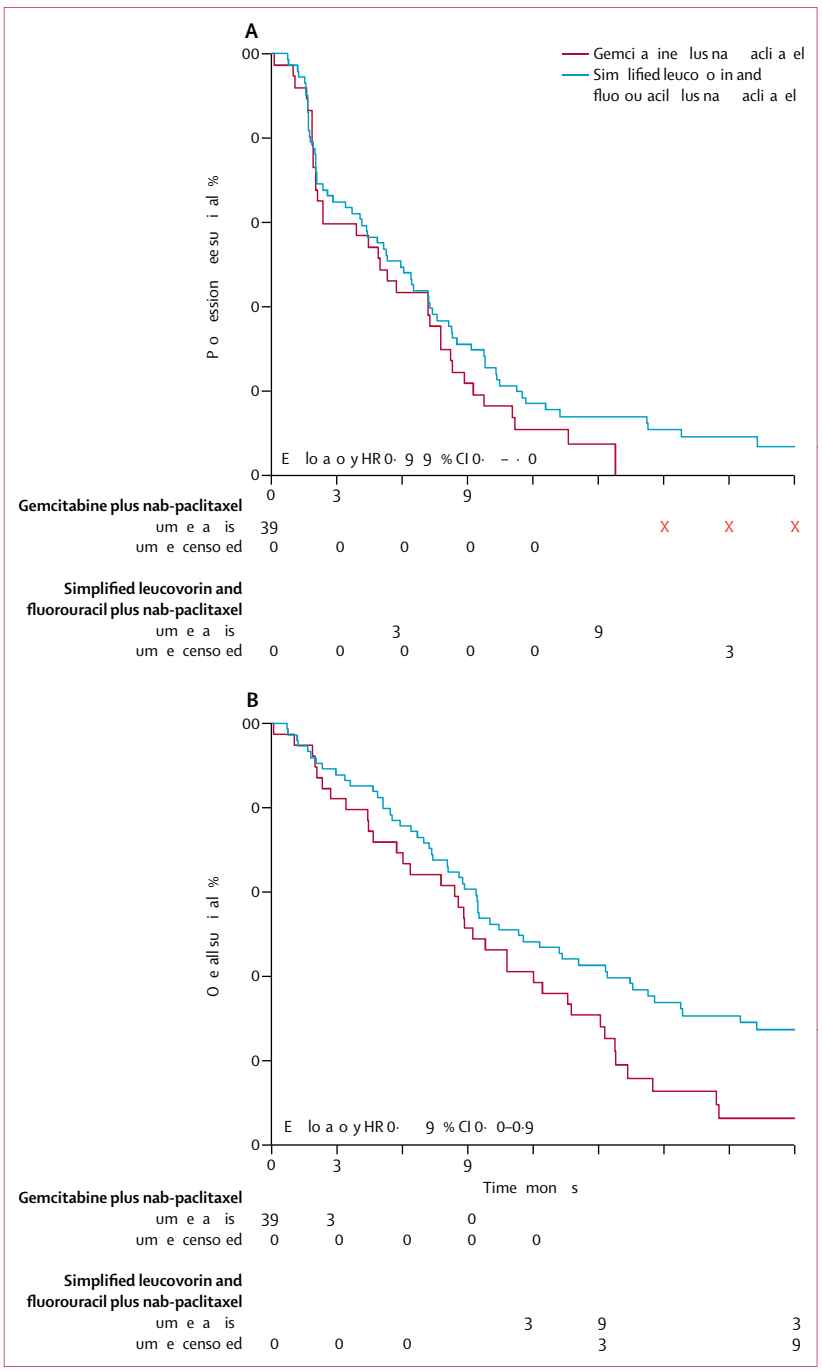

***Figure 2*: Kaplan-Meier survival curves for (A) progression-free survival and (B) overall survival**
Analyses are according to randomly assigned treatment, based on data as of Sept 1, 2016. HR=hazard ratio.

Two participants died; one in the leucovorin and fluorouracil group from septic shock, and one in the gemcitabine group from diabetes compensation with acidosis; these deaths were not deemed to be related to

	Simplified leucovorin and fluorouracil plus nab-paclitaxel (n=75)	Gemcitabine plus nab-paclitaxel (n=39)
Second-line treatment	46 (61%)	22 (56%)
Gemcitabine-based	23 (31%)	2 (5%)
FOLFIRINOX	14 (19%)	5 (13%)
FOLFOX	5 (7%)	10 (26%)†
FOLFIRI	4 (5%)	4 (10%)
Unknown	0	1 (3%)
Third-line treatment	16 (21%)	6 (15%)
Gemcitabine-based	8 (11%)	1 (3%)
FOLFIRINOX	0	1 (3%)
FOLFOX	2 (3%)	2 (5%)†
FOLFIRI	4 (5%)	2 (5%)
Fluoropyrimidine alone	2 (3%)	0

Data are n (%). FOLFIRINOX=irinotecan, fluorouracil, leucovorin, and oxaliplatin. FOLFOX=leucovorin, fluorouracil, and oxaliplatin. FOLFIRI=irinotecan, fluorouracil, and leucovorin. *All randomly assigned and assessable patients regardless of their eligibility and received treatments. †One patient received a combination of fluorouracil and cisplatin.

Table 3*: Second-line and third-line treatments in the modified intention-to-treat population

treatment. Treatment-related serious adverse events occurred in 28 (38%) of 73 patients in the leucovorin and fluorouracil group and in 14 (37%) of 38 in the gemcitabine group.

In the leucovorin and fluorouracil group, data obtained for five patients who received adjuvant gemcitabine were assessed as an exploratory analysis. These five patients were all free from disease progression at 4 months. As best objective response, one patient had a complete response, one had a partial response, and three patients had stable disease. For this subgroup, median progression-free survival was 17·2 months (95% CI 8·1–22·2) and median overall survival was 22·2 months (95% CI 16·6 to not applicable).

Discussion

More than 50% of patients who received the regimen of nab-paclitaxel plus simplified leucovorin and fluorouracil were progression-free at 4 months. Other measures of activity in the leucovorin and fluorouracil group were similar to or seemingly better than those in the gemcitabine group, and the new regimen was tolerable to patients. This regimen thus deserves further assessment in a phase 3 trial and might serve as a potential backbone for new combinations.

The results with nab-paclitaxel plus simplified leucovorin and fluorouracil were encouraging. This combination was well tolerated with manageable toxicities, consistent with previous reports and the known toxicities specific for each drug.[7,21–24] Overall, numerically fewer grade 3–4 adverse events occurred in the leucovorin and fluorouracil group than in the gemcitabine group; in particular, there were fewer haematological grade 3–4 toxicities in the leucovorin and fluorouracil group. Numbers of non-haematological toxicities were similar in both groups, but as expected, more events of mucositis, diarrhoea, and hand–foot syndrome occurred in the leucovorin and fluorouracil group. A higher incidence of grade 2 alopecia also occurred in the leucovorin and fluorouracil group, which should be taken into consideration if selecting this treatment as first-line therapy for patients with pancreatic adenocarcinoma. The higher incidence of grade 3–4 paraesthesia in the leucovorin and fluorouracil group could be explained by the longer progression-free survival in this group and thus longer exposure to nab-paclitaxel. These adverse events were manageable, as evidenced by high adherence to treatment and dose intensity in both groups, with few reductions in dose intensity per cycle. The administration schedule for nab-paclitaxel plus simplified leucovorin and fluorouracil (nab-paclitaxel given at 150 mg/m² on days 1 and 15 of a 28-day cycle) could be of interest to reduce the duration of hospital stay for patients with pancreatic adenocarcinoma. Such a modification has been previously assessed in a phase 1 trial with a combination of fluorouracil, oxaliplatin, and nab-paclitaxel;[29] this combination is now being tested in a phase 2 trial in the USA (not yet registered).

Despite six (15%) of the 39 patients in the gemcitabine group having an ECOG performance status of 2, 14 (36%) achieved an objective response, median progression-free survival was 4·9 months, and median overall survival was 9·2 months. These results are consistent with those reported in the MPACT trial.[7] In the leucovorin and fluorouracil group, a similar proportion of patients achieved an objective response, but the proportion of patients with controlled disease was slightly higher, and progression-free survival and overall survival were longer, despite more disease-related pain and a higher median value of CA19-9 at inclusion. Although, the exploratory HR for overall survival favoured the leucovorin and fluorouracil group, no clear differences for this endpoint were noted with subsequent lines of treatment. As expected, gemcitabine was largely used as second-line or third-line treatment in patients originally assigned to leucovorin and fluorouracil, and fluoropyrimidine-based regimens were used as second-line and third-line treatments in patients originally assigned to the gemcitabine group. Overall survival since the beginning of second-line treatment was longer in the gemcitabine group than in the leucovorin and fluorouracil group, and thus does not explain the exploratory HR for overall survival. Moreover, the depth of response during protocol treatment was similar between the two groups (data not shown). These results suggest that simplified leucovorin and fluorouracil could be a better backbone companion than gemcitabine to develop new regimens in combination with nab-paclitaxel for pancreatic adenocarcinoma, and that this regimen deserves to be investigated further in clinical trials.[11–13]

	Simplified leucovorin and fluorouracil plus nab-paclitaxel (n=73)				Gemcitabine plus nab-paclitaxel (n=38)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
At least one event	71 (97%)	70 (96%)	54 (74%)	8 (11%)	38 (100%)	34 (89%)	32 (84%)	8 (21%)
Haematological								
Anaemia	53 (73%)	20 (27%)	4 (5%)	0	29 (76%)	21 (55%)	5 (13%)	0
Thrombocytopenia	33 (45%)	3 (4%)	0	0	26 (68%)	10 (26%)	6 (16%)	1 (3%)
Neutropenia (without fever)	21 (29%)	16 (22%)	13 (18%)	4 (5%)	13 (34%)	15 (39%)	9 (24%)	3 (8%)
Febrile neutropenia	..	..	6 (8%)	0	..	..	2 (5%)	0
At least one haematological event	58 (79%)	31 (42%)	18 (25%)	4 (5%)	36 (95%)	29 (76%)	16 (42%)	4 (11%)
Non-haematological								
Nausea	40 (55%)	17 (23%)	2 (3%)	0	20 (53%)	8 (21%)	1 (3%)	0
Vomiting	28 (38%)	8 (11%)	2 (3%)	0	13 (34%)	3 (8%)	1 (3%)	0
Mucositis	34 (47%)	13 (18%)	7 (10%)	0	4 (11%)	1 (3%)	1 (3%)	0
Diarrhoea	43 (59%)	15 (21%)	9 (12%)	0	12 (32%)	9 (24%)	3 (8%)	0
Fatigue	43 (59%)	41 (56%)	16 (22%)	0	22 (58%)	18 (47%)	8 (21%)	0
Hand–foot syndrome	18 (25%)	10 (14%)	5 (7%)	0	2 (5%)	0	0	0
Paraesthesia	36 (49%)	20 (27%)	14 (19%)	0	11 (29%)	6 (16%)	4 (11%)	0
Alopecia	32 (44%)	40 (55%)	..	..	14 (37%)	14 (37%)	..	..
Infection	0	9 (12%)	6 (8%)	0	0	2 (5%)	3 (8%)	0
Thromboembolic event	0	0	1 (1%)	0	0	1 (3%)	2 (5%)	0
Increased ALT	22 (30%)	9 (12%)	3 (4%)	0	22 (58%)	6 (16%)	5 (13%)	0
Increased AST	17 (23%)	5 (7%)	4 (5%)	0	21 (55%)	2 (5%)	5 (13%)	0
Increased bilirubin	12 (16%)	2 (3%)	1 (1%)	0	6 (16%)	0	2 (5%)	0
At least one non-haematological event	70 (96%)	67 (92%)	53 (73%)	4 (5%)	38 (100%)	31 (82%)	26 (68%)	4 (11%)

Adverse events graded by Common Toxicity Criteria version 4.0. Data are n (%). ..=not applicable. ALT=alanine aminotransferase. AST=aspartate aminotransferase.

***Table 4*: Grade 1–4 adverse events**

Different therapeutic options can be considered to offer further improvements in treatment for pancreatic adenocarcinoma. One option would be to use an increasing number of drugs administered simultaneously. Such an option has been assessed and led to the development of several ongoing trials.[29,30] A major concern of this approach is that the tolerability profile will probably restrict the use of these combinations to a selected patient population with a good ECOG performance status (0–1), as for the FOLFIRINOX regimen.[6] In the MPACT trial, patients with a Karnofsky performance status of 70–80 showed the greatest reduction in the risk of death.[7] In our study, 18 (16%) of 114 patients had ECOG performance status 2 at inclusion. The toxicity profile in this subgroup of patients was in the same range as in those with good ECOG performance status (data not shown). Moreover, despite poorer prognosis, three (25%) of 12 patients with an ECOG performance status of 2 included in the leucovorin and fluorouracil group were still alive at 12 months. Thus, nab-paclitaxel plus simplified leucovorin and fluorouracil might be a beneficial treatment option for patients with an ECOG performance status of 2.

Our results are encouraging and suggest that the efficacy of this regimen should be investigated in a phase 3 randomised trial, comparing it with the nab-paclitaxel plus gemcitabine regimen with a patient-centred outcome (ie, overall survival). However, some limitations of our study need to be acknowledged. For instance, the results can be generalised only to the patient population that matched with inclusion and exclusion criteria. Second, the study was undertaken in sites in France only and requires supporting data from international trials.

In summary, our study suggests that nab-paclitaxel plus simplified leucovorin and fluorouracil could be an attractive regimen in patients with pancreatic adenocarcinoma, and could be considered as a new backbone regimen for combination with new drugs. Our findings support the further study of this regimen in this setting in phase 3 trials.

Contributors

J-BB, PH, FB, and CL conceived and designed the study. BC, AMo, AMe, and FB provided administrative support. J-BB, PH, JDe, AMe, BC, TAn, PD, JDa, TL, J-FS, CT, TAp, VGM, JT, JV, AMo, FB, and CL provided study materials or patients. J-BB, PH, JDe, AMe, BC, TAn, PD, JDa, TL, J-FS, CT, TAp, VGM, JT, JV, AMo, FB, and CL obtained and assembled the data. J-BB, PH, AMo, AMe, FB, and CL did the data analysis and interpretation. J-BB, PH, JDe, AMe, BC, TAn, PD, JDa, TL, J-FS, CT, TAp, VGM, JT, JV, AMo, FB, and CL drafted the work or revised it critically for

important intellectual content. J-BB, PH, JDe, AMe, BC, TAn, PD, JDa, TL, J-FS, CT, TAp, VGM, JT, JV, AMo, FB, and CL gave final approval of manuscript. J-BB, PH, JDe, AMe, BC, TAn, PD, JDa, TL, J-FS, CT, TAp, VGM, JT, JV, AMo, FB, and CL agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Declaration of interests

J-BB has received personal fees from Amgen, Bayer, Celgene, Merck Serono, Roche, Sanofi, Servier, and non-financial support from Amgen, Merck Serono, and Roche. PH has received grants from Celgene and Roche; personal fees from Baxalta, Celgene, Ipsen, Lilly, Merck Serono, Novartis, and Pfizer; and non-financial support from Celgene, Ipsen, Merck Serono, Novartis, and Pfizer. BC has received personal fees from Bayer, Kantar Health, Kephren, Lilly, Sanofi, and non-financial support from Amgen, Merck Serono, and Roche. TAn has received personal fees from Celgene and Roche. PD has received grants from DRCD Paris and personal fees from ITAC CME. J-FS has received personal fees from Bayer, Celgene, Lilly, Novartis, Pfizer, and Servier, and non-financial support from Roche. JT has received personal fees from Amgen, Celgene, Baxalta, Merck Serono, Sanofi, Sirtex, and Roche. FB received grants from Novartis and Roche; personal fees from BMS, Celgene, Integragen, Ipsen, Janssen, Merck Serono, Nestle, Novartis, and Roche; and non-financial support from Celgene, Ipsen, Merck Serono, Novartis, and Roche. CL received personal fees from Celgene, Roche, and Sanofi. All other authors declare no competing interests.

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