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Raltitrexed (Tomudex®) *versus* standard leucovorin-modulated bolus 5-fluorouracil: Results from the randomised phase III Pan-European Trial in Adjuvant Colon Cancer 01 (PETACC-1)

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ABSTRACT

Objectives: PETACC-1 assessed if raltitrexed is non-inferior to 5-fluorouracil and leucovorin for relapse-free survival (RFS) and overall survival (OS) in adjuvant stage III colon cancer.
Methods: Non-inferiority required both HR for RFS and OS < 1.25 at 1-sided $\alpha = 0.05$. Patients (1921) were randomised to six cycles of 5-FU/LV ($n = 969$) or eight cycles of raltitrexed ($n = 952$). We report the final results in 993 eligible patients who started and completed the allocated treatment (489 5-FU/LV and $n = 504$ Raltitrexed) of whom respectively 146 and 148 died, respectively.
Results: The trial closed prematurely when 17 (1.9%) raltitrexed-related deaths were reported. Haematological and gastrointestinal toxicities were more frequent with 5-FU/LV, liver toxicities with raltitrexed. Raltitrexed was stopped for toxicity in 13.2% and 5-FU/LV in 8.5%. Sixty-day mortality was 9% *versus* 7%. With 4.1 years median follow-up, the HR for RFS was 1.16 (90% CI 0.99–1.37) and that for OS was 1.01 (90% CI 0.84–1.23).
Conclusion: The trial failed to demonstrate non-inferiority of raltitrexed.
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1. Introduction

The demonstration that post-operative adjuvant treatment with 5-fluorouracil (5-FU) and levamisole reduced the mortality rate by 33% amongst patients with stage III colon cancer[1] prompted several trials, which established six months of treatment with intravenous (iv) bolus 5-FU plus leucovorin (LV) as the standard adjuvant chemotherapy for stage III colon cancer.[2–8]

Raltitrexed (Tomudex®) is a direct and specific thymidylate synthase (TS) inhibitor.[9] This quinazoline folate analogue enters cells rapidly *via* the reduced-folate carrier, and is then polyglutamated by folypolyglutamate synthase which increases intracellular retention and leads to prolonged TS inhibition, DNA fragmentation and cell death.[10] Raltitrexed has been extensively studied in four large clinical trials in patients with advanced colorectal cancer. Of the three comparative trials, two showed no statistical difference between iv raltitrexed and the combination of iv bolus 5-FU/LV for survival,[11,12] whilst one trial showed a statistically significant difference in favour of 5-FU/LV.[13] In this last study, however, raltitrexed was administered at a dose of 4 mg/m^2 which resulted in a greater toxicity in comparison to the other two studies in which a standard dose of 3 mg/m^2 was used.

In comparative reviews of all three studies, single agent raltitrexed appeared as effective as the combination of iv bolus 5-FU/LV in terms of objective response rate.[14] Raltitrexed had an acceptable overall safety profile including less severe neutropenia and mucositis.

Therefore, it appeared appropriate to investigate whether raltitrexed could also be equivalent to bolus 5-FU/LV in the adjuvant setting with respect to recurrence-free survival (RFS) and duration of survival. In February 1998, the Pan-European Trials for Adjuvant Colorectal Cancer (PETACC) Group launched an international phase III trial in patients with stage III colon cancer – PETACC-1, to test these hypotheses. We now report the final results of this study which was stopped at 70% of its target recruitment because of a strategic decision by the pharmaceutical company that developed the product (see 'Statistics', below).

1.1. Patients and methods

Patients eligible for this trial had stage III (T1-4, N1-2, M0) colon cancer and had undergone potentially curative surgical resection (R0 resection, negative resection margins on histological section) with no evidence of residual disease within 56 d before random assignment, age $\geqslant$18 years and WHO performance status 0–1.

The protocol was approved by the EORTC (European Organisation for Research and Treatment of Cancer) Protocol Review Committee, the AstraZeneca Protocol Review Committee and by local, regional or national ethical review boards in compliance with national regulations. Patient written informed consent was required for participation in the trial.

All patients needed a complete history and physical examination, biochemical evaluation including complete blood counts, and kidney and liver function tests within two weeks prior to randomisation.

Randomisation was done at the national data centres and was stratified by institution. Patients were randomly allocated in a 1:1 ratio to either the standard or investigational treatment arms.

In the standard arm, leucovorin (LV) 20 mg/m^2 was administered as an iv bolus, followed by a 370–425 mg/m^2 iv bolus of 5-fluorouracil (5-FU). Both drugs were to be given on days 1–5, repeated on days 29–33 and so on for six cycles (i.e. every four weeks for a total of 24 weeks). Days 1–28 was considered to be a single cycle.

In the investigational arm, raltitrexed 3 mg/m^2 was administered as a 15 min iv infusion on day 1, repeated on day 22 and so on for eight cycles (i.e. every three weeks for a total of 24 weeks). Days 1–21 was considered to be a single cycle.

Prior to each cycle, a physical examination, full blood count and biochemistry and evaluation of toxicity were performed. Weekly complete blood counts were recommended for assessment of haematological toxicity.

Procedures for toxicity-related dose modification and delays of treatment for 5-FU and raltitrexed were clearly stated in the protocol. In the raltitrexed arm, creatinine clearance had to be measured before each cycle for all patients over 70 years of age or with a body surface area $\leqslant$1.5 m^2. Measurement of creatinine clearance was recommended for all patients with an elevated serum creatinine at the time of intended treatment. Recommended-dose modifications for reduced creatinine clearance included cessation of raltitrexed for those with creatinine clearance of 25 ml/min or less, 75% reduction for clearance of 25–54 ml/min and 50% reduction for clearance of 55–65 ml/min. After dose reductions, raltitrexed administration was spaced to every four weeks.

During follow-up the patients were evaluated for recurrence every 6 months. Clinical and laboratory tests were performed according to the common practice at each institution.

1.2. Statistics

The trial's co-primary end-points were relapse-free survival (RFS), counted from randomisation to the date of either radiologically proven recurrence or death (whichever occurred first), and overall survival (OS), counted from randomisation to the date of death due to any cause. The secondary objective was to compare the safety profiles of raltitrexed and 5-FU/LV using the NCIC-CTC scoring scales. The non-inferiority hypothesis required that the hazard ratio (HR) for raltitrexed *versus* 5-FU/LV be significantly less than 1.25 at the one-sided 0.05 significance level (i.e. that the upper side of the two-sided 90% confidence limit for the HR be less than 1.25) for both RFS and OS. For 90% power, assuming two years of recruitment and three more years of follow-up, and 10% loss on follow-up, the study was estimated to require 2765 patients (703 events).

In July 1999, the study's Independent Data Monitoring Committee (IDMC) reviewed all trial data accumulated as of June 30, 1999. At that time, 1838 patients had been recruited of the 2765 planned. The IDMC recommended suspension of recruitment for 2 months because the number of drug-related deaths in the raltitrexed arm was 17 (1.9%) of 911 patients which was considered unacceptable in the adjuvant setting.

Based on an unscheduled analysis of the first 647 patients that showed a greater treatment completion rate in the control arm and more withdrawals due to serious adverse events in the raltitrexed arm, the sponsor, AstraZeneca, decided to stop patient inclusion.[15] The last of the study's 1921 patients was recruited on July 16, 1999.

On November 8, 1999 aiming for an average follow-up of five years, the trial's Statistical Committee set a cut-off date of July 16, 2003 for the data to be included in the final analysis. The primary analysis population was defined as patients randomised before January 16, 1999.

The intention-to-treat (ITT) population included all patients treated according to the regimen to which they were randomised. The per protocol (PP) population included all patients who were eligible (i.e. did not have major deviation from the study selection criteria) had been randomised before January 16, 1999 and had received at least one dose of study drug. These patients had sufficient time to complete the 24 week regimens before trial closure. The PP population was used for the main efficacy analyses of RFS and OS. All patients who received at least one dose of assigned chemotherapy were considered evaluable for safety of the treatment (safety population). OS and RFS rates were estimated by Kaplan–Meier method and the HR and associated 2-sided 90% confidence intervals were estimated by unstratified Cox model,[16,17] that matches the 1-sided 0.05 significance level. χ^2-Tests were used to compare proportions.

The trial is registered with ISRCTN, number ISRCTN2194324.

2. Results

A total of 1921 patients (969 and 952 in the 5-FU/LV and raltitrexed arms, respectively) were randomised prior to trial closure. Of them, 34 patients were not eligible (16 and 18, respectively); 25 patients received non-protocol treatments (11 on 5-FU/LV and 14 on raltitrexed) and treatment data were unavailable for 40 (21 on 5-FU/LV and 19 on raltitrexed). All the patients were kept in the ITT population. The PP population consisted of 993 patients: 487 in the 5-FU/LV group and 504 in the raltitrexed group (Fig. 1). The safety population consisted of 937 and 918 patients in the 5-FU/LV and raltitrexed groups, respectively. At the July 16, 2003 cut-off, the median follow-up was 49 months and 505 (26%) of the 1921 randomised patients had died (253 and 252, respectively). Demographics and disease characteristics were well-balanced across treatment groups (Table 1).

Eligible patients, 937 and 918, with follow-up data who had been randomly assigned to treatment with 5-FU/LV and raltitrexed, respectively, began chemotherapy. The 5-FU/LV regimen was planned at a 5-FU dose of 370 mg/m^2 (46.2% of the patients) or 425 mg/m^2 (53.8% of the patients). Both the groups received a median of 6 cycles of chemotherapy. The planned number of cycles was received by 786 patients (83.9%) on the 5-FU/LV arm, and 389 patients (42.4%) on the raltitrexed arm. When the study was prematurely closed, 271 patients (28.5%) discontinued raltitrexed treatment whilst almost all the patients receiving 5-FU/LV completed the treatment, accounting for this imbalance. The median relative dose intensity of 5-FU was 97.0% (range 0.1–134%), whilst the median relative dose intensity of raltitrexed was 104% (range 9–150%) with a median dosage of raltitrexed of 3.1 mg/m^2 per cycle received. Neutropenia, diarrhoea and stomatitis were the most frequent grades 3–4 adverse effects in the group treated with 5-FU/LV. Grades 3–4 neutropenia was much more common with 5-FU/LV than with raltitrexed (27.0% *versus* 7.9%) and was complicated by fever or infection in 4% of cases (38 patients) in the 5-FU/LV group and in 2.2% of cases (20 patients) in the raltitrexed group. The incidences of grades 3–4 diarrhoea amongst patients who received at least one cycle of the assigned regimen were 14.9% (139 patients) and 5.4% (49 patients) in the 5-FU/LV and raltitrexed groups, respectively. Stomatitis grades 3–4 was also more frequent in the 5-FU/LV group (12.4%; 116 patients) than in the

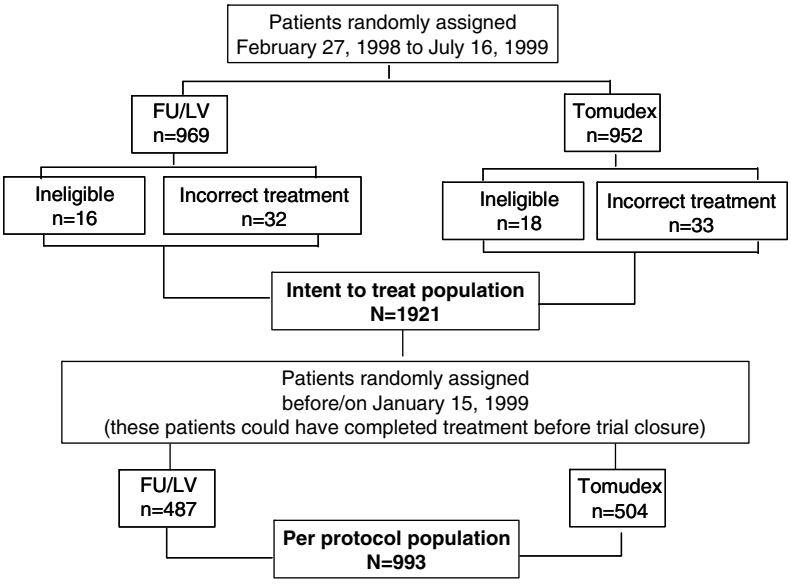

Fig. 1 – PETACC-1 consolidated standards of reporting trials diagram.

Table 1 – Baseline characteristic

	LV-modulated bolus 5-FU (N = 969) N (%)	Raltitrexed (N = 952) N (%)
Sex		
Female	460 (47.5)	434 (46.5)
Male	509 (52.5)	518 (54.4)
Race		
Caucasian	933 (96.3)	924 (97.1)
Other	30 (3.1)	26 (2.9)
Unknown	6 (0.6)	2 (0.2)
Age (years)		
Median	63.7	62.6
100% Range	20.2–84.8	19.9–87.5
Interquartile range	55.5–69.8	54.2–69.3
Mean (SD)	62.0 (10.74)	61.2 (10.72)
Histopathology grading		
Well differentiated	127 (13.1)	126 (13.2)
Moderately differentiated	627 (64.7)	615 (64.6)
Poorly differentiated	166 (17.1)	152 (16.0)
Undifferentiated	3 (0.3)	3 (0.3)
Unknown	46 (4.7)	56 (5.9)
T classification (UICC 1997)		
T_1	14 (1.4)	10 (1.1)
T_2	76 (7.8)	81 (8.5)
T_3	741 (76.5)	723 (75.9)
T_4	131 (13.5)	125 (13.1)
T_{is}	1 (0.1)	0 (0.0)
Unknown	6 (0.6)	13 (1.4)
Number of lymph nodes removed		
Median	11	11
100% Range	1–78	1–62
Interquartile range	7–16	7–16
Mean (SD)	12.8 (8.79)	12.4 (8.26)
N classification (UICC 1997)		
N_1	653 (67.4)	645 (67.8)
N_2	310 (32.0)	297 (31.2)
Unknown	6 (0.6)	10 (1.1)
M classification (UICC 1997)		
M0	956 (98.7)	928 (97.5)
M1	1 (0.1)	7 (0.7)
Unknown	12 (1.2)	16 (1.7)
Missing	0 (0.0)	1 (0.1)
Lymphatic vessels invaded	186 (19.2)	196 (20.6)
Days from randomisation to D1 of trt		
Median	5.0	4.0
Range	0.0–57.0	1.0–39.0
Q1–Q3	2.0–7.0	2.0–7.0
Mean (SD)	5.51 (5.04)	4.96 (4.51)

raltitrexed group (0.9%; 8 patients). Alopecia occurred more frequently in the 5-FU/LV group (13.6%; 127 patients) in comparison to the raltitrexed group (4.9%; 45 patients). Grades 3–4 elevation of transaminases was less common amongst patients treated with 5-FU/LV (0.6%; 6 patients) than in those treated with raltitrexed (20.5%; 188 patients).

Serious adverse events were reported for 177 (18.3%) of 937 patients in the 5-FU/LV group and 155 (16.3%) of 918 patients in the raltitrexed group. Death related to treatment was reported for 8 (0.9%) patients in the 5-FU/LV group and 20 (2.2%) patients in the raltitrexed group. The overall 60-d mortality, however, was not significantly different between the two arms: 7 deaths on the 5-FU/LV arm and 9 on the raltitrexed arm. Thus, a substantial number of deaths on the raltitrexed arm occurred more than 60 d after drug administration. Of 20 deaths considered related to raltitrexed, 11 were associated with a major protocol deviation: not measuring creatinine clearance for dose-adjustment, when it was mandatory, or not giving the appropriate raltitrexed dose based on creatinine clearance. The majority of these toxic deaths were reported from one Cooperative Group.

In the ITT population, 253 (26.1%) patients had died in the 5-FU/LV group compared to 252 (26.5%) patients in the raltitrexed group (HR: 1.04; 90% CI 0.90–1.21), and the 5-year survival rate was 62.3% (95% CI 58.4–66.1) in the 5-FU/LV group and 61.9% (95% CI 55.4–66.1) in the raltitrexed treatment group (Fig. 2A).

In the PP population, 146 patients (30.0%) had died in the 5-FU/LV group compared to 148 (29.4%) patients in the raltitrexed group (HR: 1.01; 90%CI 0.84–1.23), and the 5-year survival rate was 60.9% (95% CI 55.5–65.8) on 5-FU/LV and 62.6% (95% CI 57.1–67.7) on raltitrexed (Fig. 2B).

In the ITT population, 347 patients (35.8%) had relapsed or died in the 5-FU/LV group compared to 370 (38.9%) in the raltitrexed group (HR: 1.14; 90% CI 1.01–1.29) and the 5-year recurrence-free survival rate was 50.9% (95% CI 46.6–54.9) on 5-FU/LV and 46.7% (95% CI 42.2-51.0) on raltitrexed (Fig. 3A).

In the PP population, 193 (39.6%) had relapsed or died in the 5-FU/LV group compared to 217 (43.1%) in the raltitrexed group (HR: 1.16; 90% CI 0.99–1.37) and the 5-year recurrence-free survival rate was 50.3% (95% CI 44.8–55.6) on 5-FU/LV and 47.8% (95% CI 42.3–53.0) on raltitrexed (Fig. 3B).

Although not a primary end-point, disease-free survival (defined from randomisation to the date of relapse or diagnosis of second cancer or death) was assessed in ITT and PP populations. The results were essentially identical to those reported for RFS.

3. Discussion

The PETACC-1 study was suspended for IDMC review of safety in July 1999, and then aborted by the sponsoring pharmaceutical company based on the results of an unscheduled private analysis.[15] This early closure, together with subsequent unfavourable results from a large randomised UK-based study comparing raltitrexed to 5-FU-based regimens in advanced disease[18] diminished clinical interest in raltitrexed. These circumstances contributed to the complexity of analysing the PETACC-1 results.

The IDMC safety analysis was occasioned by the observed imbalance in deaths between the raltitrexed-containing treatment arm (17 deaths of 911 patients, 1.9%) and the control arm (7 of 927, 0.8%) by June 1999. Upon review, of these 17 deaths on the investigational arm, 11 were linked with serious protocol deviations where protocol-specified dose reductions had not been applied. Of note, the ratio of treatment-related deaths started to be different only after two cycles of treatment. This may have led to some delay in realising what was happening. This raises the questions of

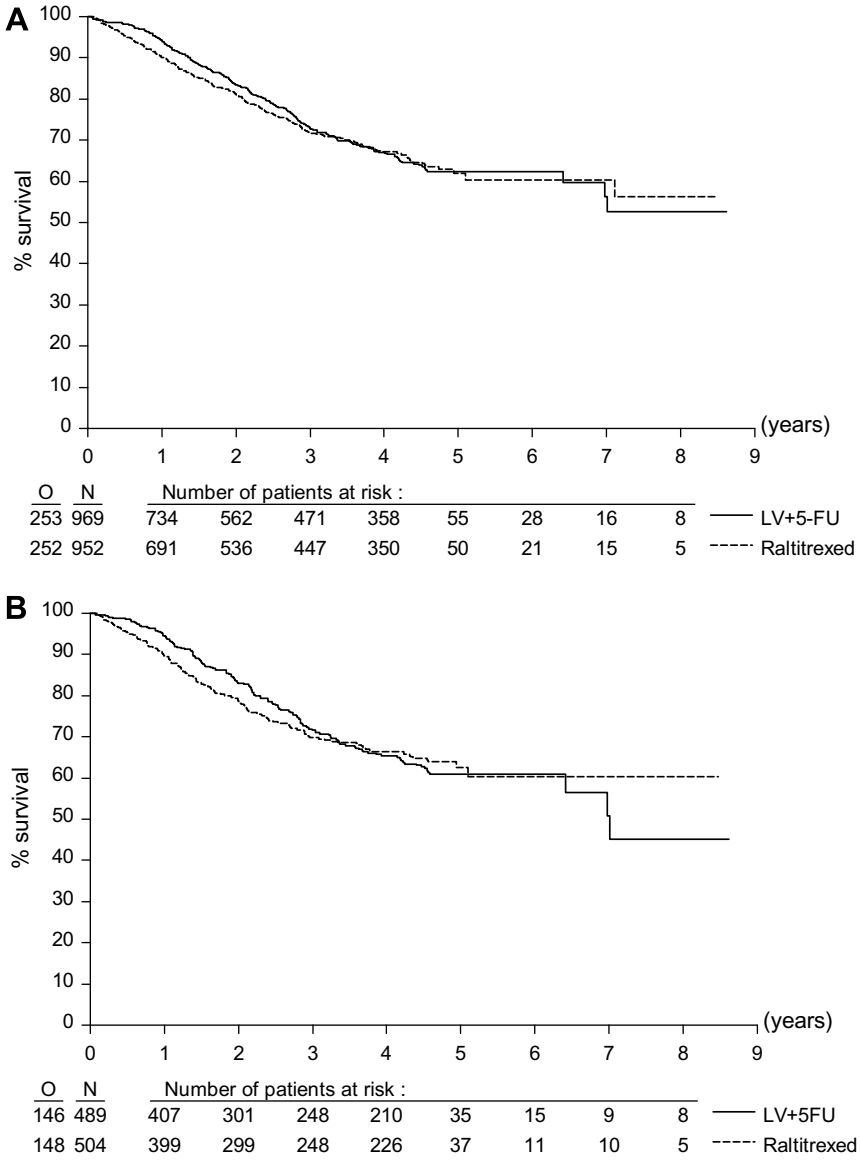

Fig. 2 – Overall survival by treatment arm in (A) the intent-to-treat population and (B) the per protocol population. *O* = number of events, *N* = number of patients.

how often an IDMC should meet during adjuvant studies, and what difference threshold should be chosen to recommend treatment discontinuation. The experience of this trial may have had an influence on subsequent trial monitoring, for example, the recent decision to temporarily discontinue the large Roche-sponsored AVANT trial after early indications of excess of deaths on the experimental arm.

At final analysis, the greater number of treatment-related deaths in the investigational arm (20 *versus* 8) did not translate into a significant survival deficit for patients who received raltitrexed. Indeed, the results for overall survival are within the boundary of non-inferiority in the ITT population, as well as in the per protocol population (which excludes patients whose treatment was influenced by the trial closure).

Regarding RFS and DFS, raltitrexed was inferior to 5-FU/LV with an estimated relative increased risk of 14–16%. This is difficult to explain given that the survival was similar, and it is unlikely that patients in the two arms received different salvage therapies. One explanation could be that patients with relapse on raltitrexed did better on 5-FU/LV based treatment than patients who received already 5-FU/LV (and did not receive raltitrexed upon relapse). The same discrepancy, however, was observed in a trial in advanced disease.[12]

Comparison of the two ITT populations is difficult. Whilst almost all patients on 5-FU/LV arm continued treatment without interruption when the trial closed, one fourth of the patients on the investigational arm stopped treatment. Any adjuvant therapy they might have received after the trial was not recorded. Given that effective drugs such as irinotecan and oxaliplatin were not widely available at the time, it is unlikely that the survival outcome for these patients could be attributed to post-trial treatment.

Despite the higher number of treatment-related deaths on the investigational arm, the 60-d overall mortality, which

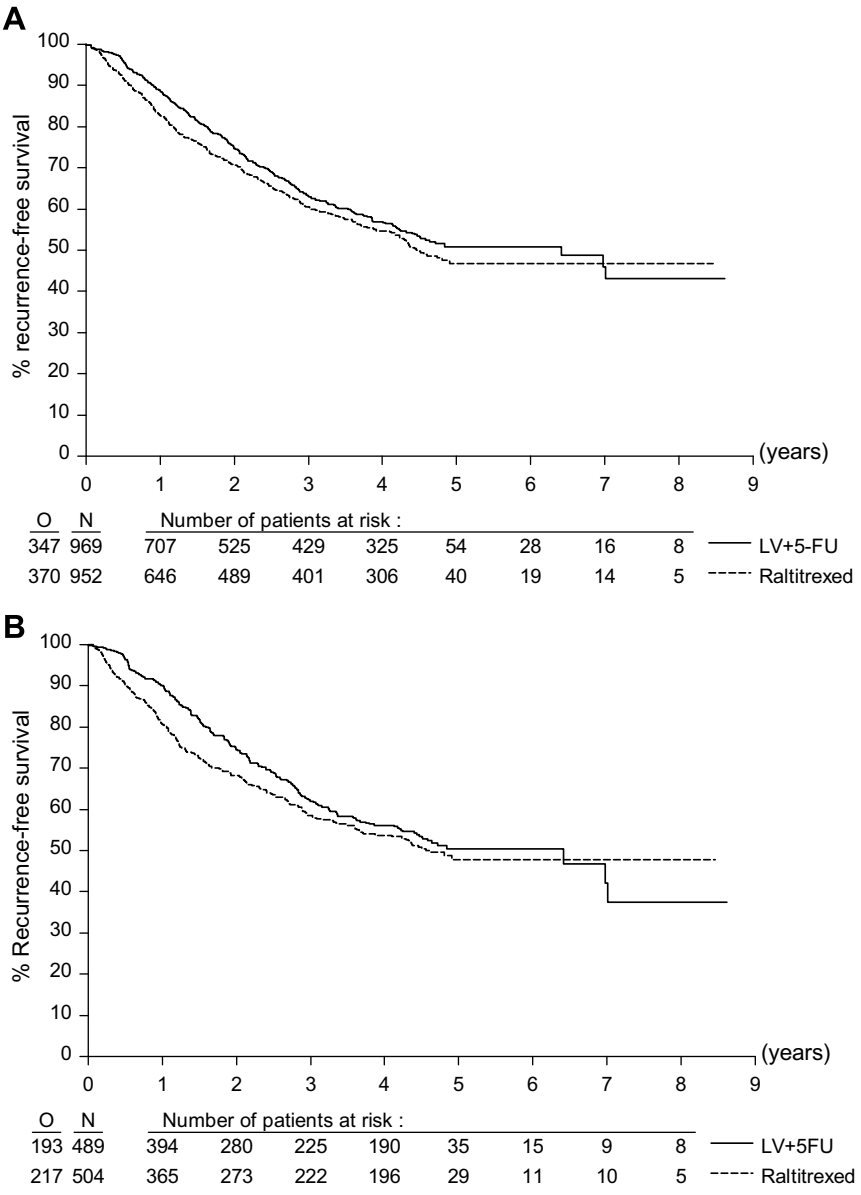

Fig. 3 – Recurrence-free survival in (A) the intent-to-treat population and (B) the per protocol population. O = number of events, N = number of patients.

reflects acute treatment-related morbidity, was similar. A substantial number of the deaths reported to be treatment-related in the raltitrexed arm occurred after 60 d, and can be attributed to protocol deviations in the form of failure to apply the recommended-dose modifications. In terms of organ-specific toxicities, liver toxicity was more common on the investigational arm, whilst haematological and gastrointestinal toxicities were more common in the standard arm.

In summary, this trial failed to demonstrate non-inferiority of raltitrexed in terms of RFS, although the overall survival for raltitrexed fell within the non-inferiority boundary. Interpretation of this study is limited by its early closure which took place before an IDMC had the opportunity to issue its opinion regarding safety. In light of the present findings, continuation of the trial under more stringent safety measures may have yielded more robust results and better justified the participation of the 2000 patients enroled in this trial. This experience highlights the need for a thorough assessment of decision-making and communication processes when conducting clinical trials in collaboration with the pharmaceutical companies.

Conflict of interest statement

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