

# VICTOR: A PHASE III PLACEBO CONTROLLED TRIAL OF ROFECOXIB IN COLORECTAL CANCER PATIENTS FOLLOWING SURGICAL RESECTION: FIRST EFFICACY DATA



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## SUMMARY

### Background

The cyclo-oxygenase-2 inhibitor, rofecoxib (R) was hypothesised to improve survival in cancer patients who had undergone surgery for colorectal cancer (CRC). This trial recruited from April 2002 until September 2004 when R was withdrawn over concerns about its cardiovascular safety (CVS). This report provides preliminary efficacy results.

### Methods

Recruited patients had undergone R0 resection of a stage II/III CRC and completion of adjuvant therapy (radiotherapy/chemotherapy/both/neither) less than 12 weeks previously. Excluded patients were those with active peptic ulceration, gastro-intestinal bleeding and those receiving long-term NSAID therapy (except low dose aspirin). 7000 patients were planned to receive 25mg R daily or an identical placebo (P) for 2 or 5 years, with the goal of detecting a reduction in risk of death - hazard ratio (HR) 0.82. After the trial's premature closure, a modified protocol of the post-treatment follow-up phase and revised statistical analysis plan permitted the detection of a reduction (HR=0.75) in risk of death with 87% power, type I error 0.05, with one pre-planned event-driven interim analysis. Overall survival (OS) and disease-free survival (DFS) were both measured from randomisation, with DFS defined as the time to recurrence or death from any cause.

**Results**  
1167 of 1217 patients randomised to R and 1160 of 1217 randomised to P received treatment with median durations of 7.4 months and 8.2 months respectively. Median follow-up was 3.0 and 3.1 years in the two arms (R vs P), with 177 vs 191 deaths and 291 vs 316 DFS events. This pre-planned Kaplan-Meier and log-rank analysis demonstrated that the R patients had slightly longer OS than the P patients, HR 0.94 (95% CI 0.77-1.16; p=0.57). Similarly DFS was slightly higher in the R patients, HR 0.91 (95% CI 0.78-1.07; p=0.25). 19 patients in each arm died without recurrence of CRC.

### Conclusions

In this study of short treatment duration treatment with R is unlikely to result in a substantial improvement in OS but a small protective effect against recurrence is suggested.

## PATIENT CHARACTERISTICS

	Rofecoxib N (%)	Placebo N (%)
Colon	791 (65.0)	802 (65.9)
Stage II	579 (47.6)	580 (47.7)
Adjuvant chemotherapy	788 (64.7)	791 (65.0)
Radiotherapy	143 (11.8)	156 (12.8)
Females	435 (35.7)	438 (36.0)
Low dose aspirin at randomisation	105 (8.6)	84 (6.9)
Age, median (IQR range)	65 (58, 71)	65 (57, 71)

## DURATION OF TREATMENT

Treatment duration	Rofecoxib N=1167	Placebo N=1160
Treated <30 days	113	73
Treated 30 days to <6 months	382	364
Treated 6 to <12 months	306	325
Treated 12 to <24 months	321	348
Treated ≥24+ months	45	48
Unknown	-	2
Median months + IQR	7.4 (3.1, 14.0)	8.2 (3.7, 14.9)
Total patient years	889.2	945.4

The difference in the duration of treatment was related to earlier discontinuation in the rofecoxib arm for side effects

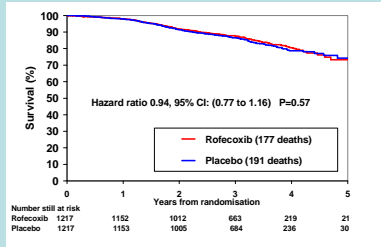
## REPORTED SERIOUS ADVERSE EVENTS

Cardiovascular thrombotic events have been reported elsewhere<sup>1</sup>. In summary, of 23 confirmed cardiovascular thrombotic events occurring within the treatment period or within 14 days after cessation, 16 occurred in the rofecoxib arm and 7 in the placebo arm with an estimated relative risk of 2.66 (95% confidence intervals (CI) 1.03-6.86; p=0.04).

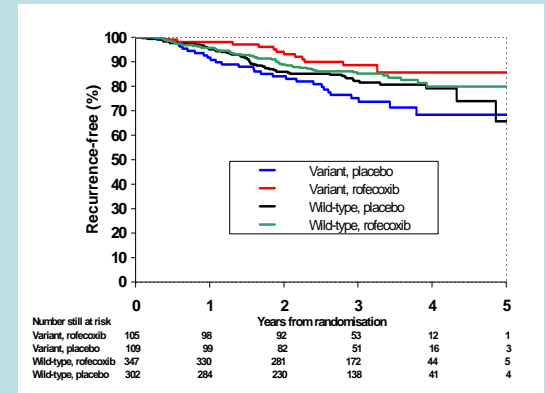
Body system	Rofecoxib	Placebo	P
Cardiovascular system	36	24	0.12
Gastrointestinal system	28	25	0.68
Respiratory system	1	0	0.32
Neuro-psychiatric system	4	3	0.71
Infection	10	3	0.05
Other miscellaneous	13	9	0.39
Cancer	5	8	0.41
Total	97	72	0.05

Note: The following events that were reported as SAEs have not been included in the table: colorectal cancer recurrences and a single death for which no other details were available. For the cardiovascular system, events from treatment follow-up and withdrawal forms, as well as those gathered from SAE forms, have been included.

## OVERALL SURVIVAL – Primary outcome

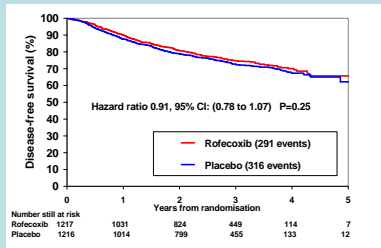


## Recurrence according to cox-2 genotyping

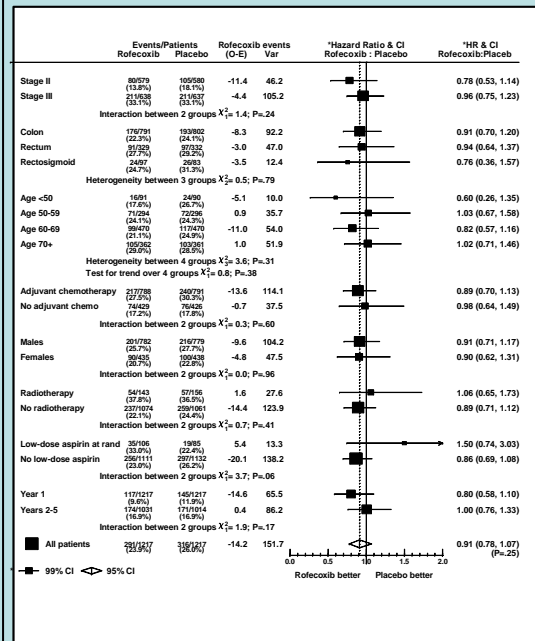


Adjusted for stage, age and radiotherapy group in a proportional hazards model, the treatment\*variant interaction hazard ratio was 2.31 {95% CI 1.06 - 5.03, P=0.04}

## DISEASE FREE SURVIVAL



## DISEASE FREE SURVIVAL - subgroups



## Interpretation

The results from this study show no clear overall benefit for rofecoxib. The premature closure of the trial weakened the ability to show a significant benefit in two ways; there were insufficient patient numbers to demonstrate a clinically relevant but small effect; and the duration of effective COX-2 inhibition may have been inadequate to truly alter the malignant phenotype.

If further trials are to be performed exploring the role of COX-2 inhibition in colorectal or any other tumour types, attention must be given to maintaining the duration of therapy and considering carefully what size of clinical benefit would be recognised as worthwhile in a cancer patient population, given the small but definite potential for cardiovascular toxicity. Consideration should also be given to COX-2 genotyping.

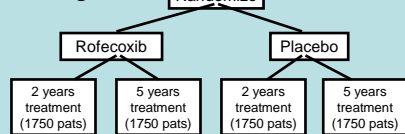
## References

Kerr DJ, Dunn JA, Langman MJ et al. Rofecoxib and cardiovascular adverse events in adjuvant treatment of colorectal cancer. *N Engl J Med* (2007); 357: 360-9

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## Original design



## Actual truncated trial

