Table 1. Sites of second primary tumours and metastases

	Etretinate ($n = 156$)	Placebo ($n = 160$)
Relapse*	31	20
Local	23	14
Regional	10	9
Metastasis*	21	15
Distant nodes	3	2
Lung and pleura	4	10
Liver	4	2
Bone	8	3
Skin	4	0
Brain	0	1
Other†	3	0
Second primary tumours	42	40
Oesophagus	8	9
Stomach	0	1
Head and neck	18	17
Colon–rectum anal canal	5	2
Lung	7	5
Pancreas	1	0
Bladder	1	2
Skin	0	2
Other‡	2	2

* The total number of events can be superior to the number of patients because of multiple localisations. † Mediastinum, adrenal gland, skin metastasis. ‡ Cholangiocarcinoma and thyroid carcinoma in the etretinate group; prostate carcinoma and hepatocarcinoma in the placebo group.

group. The sites of the second primary tumour are shown in Table 1.

These results are different from those of Hong and associates who used a different retinoid [3]. With a median follow-up of 54.5 months [4] the estimated rates of second primary was 14% in the retinoid group and 31% in the controls (two tailed $P = 0.04$). The percentage of patients with disease progression, either local, regional or distant, was similar in the two groups. It is very likely that this difference in chemoprevention activity between the two products comes from differences in binding to nuclear retinoic acid receptors (RARs) as well as from the modulation of these RARs by the same products [8]. The North American Intergroup study, which opened in 1992, deals with low dose 13-*cis* retinoic acid (30 mg/day), and aims at preventing second primary tumours in patients presenting with early stage head and neck carcinoma: 1000 patients are needed [9]. A joint venture of the EORTC Lung Cancer and Head and Neck Cancer Cooperative Groups was set up in 1988 concerning previously treated squamous cell cancer of the larynx, squamous cell cancer of the oral cavity, or non-small cell lung cancer; four treatment arms are planned in a 2×2 factorial design: retinyl palmitate and *n*-acetyl-cysteine, retinol palmitate, *n*-acetyl cysteine, no treatment [10]. The results of these trials are eagerly awaited to enable physicians to develop effective chemoprevention strategies within the field of cancers of the head and neck.

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"It Feels Better"—Measuring Clinical Benefit

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IN READING the very nice review by Lionetto and colleagues [1] as well as the accompanying article by Van Cutsem and Fevery [2], we are reminded of the devastation caused by pancreatic cancer. The short survival time for the patient is usually accompanied by pain, weight loss and a decline in performance status. Van Cutsem and Fevery call for development of new agents to induce regressions as well as for measures to reduce pain, and to improve both anorexia and quality of life. Indeed, the National Cancer Institute and the Food and Drug Administration of the United States have issued a joint publication indicating that an agent which produces improvement in disease-related symptoms could be approved for use in a particular disease (if the side-effects of the agent did not outweigh the benefit induced by the agent) [3].

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The purpose of this letter is to call to the reader's attention a newly described method for measuring whether or not disease-related symptoms improve when a patient receives a new treatment. We refer to improvement in disease-related symptoms and performance status as "Clinical Benefit". The parameters of Clinical Benefit are not the same as those of quality of life, although an improvement in a patient's disease-related symptoms (Clinical Benefit) certainly could translate into an improved quality of life for the patient.

The best example of a method to measure Clinical Benefit has been described by Andersen and colleagues [4]. They devised a rigorous system for measuring Clinical Benefit which utilised the clinical features of patients with pancreatic cancer. This system involved prospectively measuring three parameters that bothered the patients (or indicated clinical distress) including pain (as measured by both analgesic consumption and pain intensity using the Memorial Pain Assessment Card), performance status and weight. In order to demonstrate Clinical Benefit for the patient, there had to be a significant, sustained improvement in at least one of the parameters without a deterioration in the others. This Clinical Benefit assessment has already been used successfully to demonstrate the Clinical Benefit derived from treatment with a new drug for patients with pancreatic cancer [5, 6]. In patients with advanced, symptomatic, pancreatic cancer, Clinical Benefit (decrease in pain, improvement in performance status, or weight gain) was demonstrated in some patients receiving gemcitabine, and the number of patients experiencing Clinical Benefit was significantly higher than in patients randomised to 5-fluorouracil (5-FU) [5].

Those trials indicate that Clinical Benefit (an improvement in disease-related symptoms and performance status) can be utilised as a new endpoint for clinical trials. It can now be anticipated that Clinical Benefit will be used as an endpoint for clinical trials for other tumour types—such as prostate cancer [7]—which are difficult to measure in patients. It is encouraging that we now have methods being developed to measure improvement in what bothers the patient. "It feels better" to have a Clinical Benefit endpoint.

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