Revision Friday, 26 August 2016

The final publication is available at Springer via http://dx.doi.org/10.1007/s00520-016-3408-7

Therapeutic aims of drugs offering only Progression Free Survival are misunderstood by patients, and oncologists may be overly optimistic about likely benefits

LJ Fallowfield[1]

SL Catt[1]

SF May[1]

L Matthews[1]

VM Shilling[1]

R Simcock[2]

S Westwell[2]

VA Jenkins[1]

[1] Sussex Health Outcomes Research & Education in Cancer (SHORE-C)
Brighton & Sussex Medical School
University of Sussex
Brighton

[2]Sussex Cancer Centre Brighton & Sussex University Hospitals Trust
Brighton

Corresponding author
Dr Valerie Jenkins
Sussex Health Outcomes Research & Education in Cancer (SHORE-C)
Brighton & Sussex Medical School
University of Sussex
Brighton BN1 9RX
England UK

Tel: +44 1273 873016
Email: val@sussex.ac.uk

We wish to thank all the patients who gave up their time to participate in the research, and also the oncologists, research nurses and trial co-ordinators. In addition we would like to thank Angela Fry for her assistance with administration and Boehringer Ingelheim for the funds to conduct the study.

Abstract

Purpose: The use of novel and often expensive drugs offering limited survival benefit in advanced disease is controversial. Treatment recommendations are influenced by patient characteristics and trial data showing overall response rates (ORR), Progression Free Survival (PFS) and Overall Survival (OS). PFS is frequently the primary outcome in licensing studies.

Patients and methods: As part of a longitudinal study Assessing the 'VALue' to patients of PROgression Free Survival (AVALPROFS), oncologists completed checklists at baseline following consultations with patients. Questions probed perceived clinical benefits of the drugs to populations in general. Patients completed study specific interview schedules at baseline, 6 weeks into treatment, and at withdrawal due to toxicity or progression. Patients also completed tumour and treatment specific quality of life questionnaires monthly for their time in the study. Only baseline results are reported here.

Results: 32 UK oncologists discussed management options with 90 patients with heterogeneous advanced cancers. Oncologists' estimates of medical benefit in general from treatment varied between 10-80%. They expected 46/90 (51%) of their patients to derive some clinical benefit from the prescribed treatment but were either unsure or expected none for 44/90 (49%). Predictions of life expectancy were variable but 62% (56/90) of patients were expected to survive longer with treatment. A majority of patients 51/90 (57%) had 'no idea' or were 'unclear' what PFS meant and 45/90 (50%) thought extension of life was the primary therapeutic aim of treatment.

Conclusion: Discussions between doctors and patients with metastatic disease about future management plans and likely therapeutic gains are challenging. Factors influencing decisions about putative benefits of novel drugs are often applied inconsistently can be overly optimistic and may even contradict published data.

Keywords: Oncologists' decision making; patients; metastatic cancer; progression free survival estimates; therapeutic benefits

Introduction

Progression Free Survival (PFS) does not directly measure how patients feel, function or survive, but is increasingly used as a primary end point in clinical trials of solid tumour oncology therapy and by default for licensing and marketing approval [1]. PFS is described by the National Cancer Institute as 'the length of time during and after treatment for a disease such as cancer that a patient lives with the disease but it does not get worse' [2]. Although PFS is an attractive end point for a variety of practical, methodological *a*nd financial reasons, it does not always result in overall survival (OS). [3-4].

There is debate as to whether or not, for a patient, a longer PFS results in discernible and meaningful clinical benefit, the main goal of palliative anti-cancer treatment. Establishing PFS depends on RECIST (Response Evaluation Criteria in Solid Tumours) criteria, which were developed to ensure some standardisation in the interpretation of drug activity on the tumour(s) in terms of stable disease, partial response or progression. The percentage increases or decreases in size shown on imaging and used by trialists were never intended to imply improvements or a decline in a patient's overall well-being. In the past decade there has been a gradual increase in the number of publications from RCTs in common solid tumours where the primary end points have shifted from OS to PFS or time-to-progression. New 'fast-tracked' drug approvals are based increasingly upon surrogate end points with an expectation that post-marketing studies will later demonstrate other benefits such as OS. Completion of such studies is patchy, and can demonstrate that PFS is not necessarily a reliable surrogate for OS [4-5].

There are few data demonstrating that stabilisation of metastatic disease and/or a reduction in the burden of disease symptoms are really 'worth' any adverse treatment related side-effects from a patient's perspective [6-7]. Addressing this question directly is hard as studies often either omit the inclusion of well-validated and relevant Patient Reported Outcome (PRO) measures altogether or rely instead on physician reported CTCAE grades. Not only are these assessments fallible with little evidence of validity and dubious inter-rater reliability but they also fail to capture important information that might influence decision-making [8-9]. Rarely have studies examined whether or not patients even understand the meaning of concepts such as PFS [10].

Several reports show that patients with metastatic cancer need considerable help assimilating information about their disease and treatment goals; many have unrealistic perceptions of prognoses and the therapeutic intent of treatment which impacts decision - making [11-13]. Discussing management options with patients with advanced cancer is challenging as there is not always a sufficient and comprehensive evidence-base for doctors

to be realistic in their presentation of benefits and harms [14] and there is a tendency for oncologists to overestimate survival for terminally ill patients [15].

This report focusses on oncologists' views about the likely and estimated benefits of the treatment regimens they were offering to patients, together with individual patients' understanding of therapeutic aims and expectations of treatment.

Methods – materials

Study design and participants

AVALPROFS (Assessing the 'VALue' to patients of PROgression Free Survival) is a prospective, longitudinal study examining the 'value' that patients with advanced disease place on the drugs they are receiving that control the cancer, compared to the treatment related side-effects. Patients, aware of their diagnoses, who were about to commence drug treatment, which at the time of enrolment had shown only PFS or modest OS gains, were invited to participate. Researchers presented the study to interested cancer teams in the UK. Oncologists then contacted the Chief Investigator to enrol in the study. AVALPROFS was approved by London-Surrey Borders Research Ethics Committee (Ref: 14/LO/0045).

Eligibility criteria

- Oncologists who prescribed drugs which at the time the study commenced had demonstrated only PFS or modest (1-3 months) OS benefits
- Patients able to be interviewed in English, diagnosed with metastatic cancer and a predicted life expectancy of at least 6 months, prescribed drugs as described above

Procedures and measures

Potential patient participants were recruited between March 2014 and July 2015 from 11 cancer centres by their oncologists. Following the clinical consultation, patients who fulfilled the eligibility criteria for AVALPROFS, were informed briefly about the study, given a patient information sheet to take home and an expression of interest form (EOI) to complete if they wanted to learn more. Patients provided their contact details on the EOI form and a researcher telephoned 24 hours later to explain the study in more detail.

Oncologists

Immediately following the consultations, during which management options were discussed with patients, oncologists completed checklists probing the information that they had provided. A similar checklist had been used previously to gather data examining information given to patients with advanced disease embarking on Phase 1 trials [12]. This post consultation AVALPROFS checklist (shown in Appendix A) established the patient's diagnosis, stage and site of metastasis, treatments received to date, and the drug discussed

at the most recent consultation. Oncologists then indicated whether or not they had outlined certain areas of information including the aims of treatment using- 'yes'/'no'/'can't recall'/'explained previously'- response options. They also estimated how much information they thought individual patients had understood.
In section 4 of the checklist oncologists were asked what proportion of patients in general achieved some medical benefit from the drug and whether or not they expected each of their individual patients to derive any medical benefit. Response options were 'yes'/ 'no'/'don't know'. Finally oncologists estimated the life expectancy of individual patients with and then without further treatment.

Patients

Participants were interviewed in their own homes (or by telephone if they preferred) by experienced researchers (LF, VJ, SC, VS) at baseline (within 2 weeks of the consultation) and again after six weeks of treatment. Further interviews were conducted at progression or if treatment was stopped due to toxicity. Patients stated the aims of treatment as they understood them and described any side-effects experienced. They were also asked to make 'time trade-off' (TTO) type assessments as to how worthwhile treatment would be or was, with different grades of side-effect against the time that the treatment might control the cancer.
Participants also completed tumour and treatment specific quality of life questionnaires monthly up to 6 months. Written consent was obtained prior to the initial interview, which took place within two weeks from the consultation with the doctor.

This report focusses only on data collected at baseline from the oncologists' checklists and from participants' first interviews. We compared oncologists' views as to what was discussed in consultations with their patients' interpretations of that information. Topic areas included results from recent tests or scans, therapeutic aims of the drug discussed, side-effects, whether or not the doctor used or explained the term PFS and patients' understanding of that concept.

Unlike the more usual time trade-off studies that probe hypothetical issues at one time point, this was a contemporaneous longitudinal observational study using real patients. Frequency counts and comparisons between responses were analysed using Chi^2 statistical tests. Further analyses from the second and subsequent patient interviews, together with the Health Related Quality of Life Outcomes will be reported separately.

Results

Thirty-two oncologists (16 men; 16 women) participated. Twenty-six were consultants, 3 specialist registrars and 3 senior fellows. Unfortunately as the consort diagram (Figure 1)

shows, although 139 patients were approached, only 90 were interviewed, half of whom died or became too ill to continue through to the 6 month follow-up.
Demographics of the patients is shown in Table 1. Two patients received treatment within a clinical trial. Oncologists reported that treatments being offered had already been mentioned in previous consultations with 59/90 (66%) patients.

Table 2 shows the topics oncologists thought that they had explained or discussed during individual patient consultations. The majority (80/90; 89%) felt that they had checked their patients' comprehension about the information given and 74/90 (82%) thought that their patients had fully or mostly understood the discussion. A majority of patients (87/90; 97%) reported receiving additional information leaflets about the treatments that they were starting.

Oncologists' expectations of medical benefit

Oncologists expected that 46/90 (51%) of their patients would derive some medical benefit, and were unsure (39/90; 43%) or expected no benefit for others (5/90; 6%), all of whom nevertheless were prescribed treatments. Quotes from oncologists are shown below.

"I explained to patient that the drug may work well and slow progression and re-accumulation of pleural effusion, but also that it may not work" (everolimus & exemestane)

"This disease has behaved unusually so far so difficult to predict" (cetuximab + cisplatin)

"No way of being sure as no biomarker" (sunitinib)

The responses to questions regarding putative medical benefits of treatments were inconsistent. For example in response to the question *'What percentage of patients do you think will derive medical benefit from this drug?*', 7 oncologists prescribing EGFR-TK inhibitors for 24/30 patients with stage III/IV lung cancer estimated medical benefit of between 20-80% across 13/20 patients who had a proven gene mutation and between 10-40% across 7/20 patients who had wild type. The gene status was unknown or unavailable in 4 patients.

Oncologists' expectations of patients' survival with and without treatment

Two of the 90 patients who completed baseline assessments were too ill to even start treatment and 18/84 (21%) died within 6 months of study entry. The mean survival time for 14/18 patients for whom the oncologists had shifted survival expectations with treatment in an optimistic direction was 89 days (sd. 41, Min-Max 25-177 days). Table 3 shows estimates of life expectancy without and then with treatment for lung cancer patients (who formed the largest tumour group) and for all other patients. It can be seen that oncologists estimated no

change in life expectancy for 34 patients receiving treatments, and an optimistic shift for the other 56 patients. Only 46/90 (51%) of oncologists had discussed other supportive care plans with patients.

Patient reported cancer symptoms

Two-thirds of patients reported one or more symptoms that they attributed to their cancer at baseline. The five most common were: pain (33/90, 37%), breathlessness (30/90, 33%), fatigue (23/90, 26%), cough (13/90, 14%), and loss of appetite (7/90, 8%).

Side-effects from treatment

Twenty five percent of patients had not started treatment at the time of the first interview, and 68/90 (75%) had received fewer than 2 weeks of treatment, yet 43/68 (63%) were experiencing side-effects. These were skin rash (11/43; 26%) fatigue (9/43; 21%), nausea (9/43; 21%); diarrhoea (9/43; 21%), mouth sores (5/43; 12%) and breathlessness (1/43; 2%). The worst side-effects most often anticipated by patients who had not commenced treatment (22/90), or had started treatment but were side-effect free (25/90), were diarrhoea, nausea, and breathlessness.

Patients' understanding and expectations about the phrase PFS

Sixteen doctors said they employed the term PFS in 25 consultations but only 4 patients recalled its use. At interview most patients (51/90, 57%) had no idea or were unclear what the term PFS meant, 29/90 (32%) thought it was about *'controlling cancer'* and 10/90 (11%) that it was about '*extending life'*, quotes from patients are shown below.

"Hopefully tumour won't grow, will give me longer time alive"

"You've still got cancer but treatment is controlling it"

"No idea what phrase means but sounds hopeful"

Patients' understanding of treatment aims

Although the majority of patients 83/90 (92%) believed that the therapeutic aims of treatment were *'to slow or stop the cancer'*, half (45/90; 50%) also believed this meant *'living longer'*. Moreover, more than a third 35/90 (39%) said *'living longer'* was the most important aim of treatment and two thirds (56/90, 62%) thought that their understanding of treatment aims would be achieved. Almost a third (31/90) of patients, 64% (20/31) of whom were women, had searched the Internet to source or check information about the treatment offered.

The benefits patients expected from treatment varied; most (77/90, 86%) thought it would: - *'keep the cancer under control'*, over half (49/90, 54%) *'give them hope'*, 40/90 (44%) *'make them feel better'* and 35/90 (39%) *'help them to live longer'*.

Expectation of a longer life as a treatment benefit was not influenced by age (older or younger than 65 years), sex, cancer symptoms, previous chemotherapy treatment or tumour type.

Time trade-off questions

Table 4 shows the responses to the time trade-off questions at baseline. The top 4 side-effects nominated by patients and used for these questions were nausea (21/90; 23%), diarrhoea (20/90; 22%), fatigue (14/90; 16%) and breathlessness (13/90; 14%). As the possible severity of the side-effect increased, patients were significantly less inclined to feel that the benefit of controlling the cancer would be worthwhile (X^2=75.6004; $p < 0.00001$). There was also an increase in the amount of time that patients would require the drug to control the cancer, for it to be considered a worthwhile treatment.

Discussion

Results from this study showed that oncologists' general estimates of the likely therapeutic gains achievable from new treatments are sometimes at odds with available trial data and were inconsistent between individual patients. Some oncologists' expectations regarding likely treatment benefits especially survival times were difficult to understand and we would assume therefore they were influenced by criteria other than published data. These may include anecdotal experience, personal bias or belief that the patient's cancer represents a particular and preferential subset within the disease spectrum. The patients in this study were all considered suitable for treatment by their oncologists, but some were outside the limited eligibility criteria of trials. Oncologists may therefore have believed that the trial data (population) were not directly comparable to their patient's disease (individual). In some relatively rare cases, published trial data lags behind later evidence of improvement which may have influenced oncologists in AVALPROFS who were recruiting patients to other relevant studies (e.g. with the melanoma drug ipilimumab or pertuzumab in breast cancer) [16-18].

In AVALPROFS a heterogeneous group of patients were studied but lung cancer formed the largest group. Targeted agents were prescribed for 24 patients with lung cancer, only 13 of whom had an EGFR mutation. This finding is not unusual and corroborates results of a recent survey of 562 oncologists in 10 countries, showing that one in four patients with advanced lung cancer did not have EGFR-TK test results available before starting targeted

treatment [19]. For those patients who were EGFR-TK+, oncologists estimated benefits from treatment that ranged from 20 to 80% of patients in general; suggesting widely differing views. Moreover, where patients identified as wild type were prescribed EGFR-TK inhibitors, the oncologists' estimates of the percentage of patients in general likely to benefit from such treatment varied, between 10-40%, which is greater than the published trial evidence [20]. Additionally, we found oncologists had expectations that patients having erlotinib would live longer. These data highlight incongruities and perhaps interplay of optimism. Drugs like erlotinib, vemurafenib and afatanib that target specific pathways have biomarkers (identifiable gene mutations) to help indicate usage, but other novel treatments such as ipilimumab work via different means and currently have no biomarker guidance, increasing the area of uncertainty for oncologists and their patients [16, 20, 21]. Neither NICE nor the manufacturers of drugs such as erlotinib recommend their use as treatment in end-of-life circumstances. [22, 23]. A significant minority (21%) of patients died within 6 months of entering AVALPROFS, with an average OS of 89 days (sd. 41). These findings are consistent with results from a retrospective study of 816 advanced cancer patients who had received targeted agents within the last 30 days of their lives. (The population studied in this report were mainly younger patients with haematological malignancies and those with lung cancer) [24]. Undue optimism about survival prospects held by oncologists may contribute to their prescribing habits, combined with a very real difficulty in having the honest and sometimes distressing discussions about prognosis. It has been shown that cancer patients with advanced disease who themselves hold overly optimistic assessments of their own survival often request active treatments rather than perhaps more beneficial supportive care [10].

Doctor-patient communications at these important decision points are further complicated by confusing medical terminology; health care professional jargon is often meaningless or misunderstood by the patient. It is perhaps not surprising that the phrase PFS was rarely used in consultations and when asked, most patients were unclear of its meaning. However, this does not explain why a majority of patients in the study thought that slowing or stopping the cancer growing, would then translate into them living longer. PFS is a confusing term and the word 'survival' implied to some patients that the primary aim and likely benefit was to extend life. Progression Free Interval might be a more helpful phrase to use when discussing drugs with PFS or modest OS benefits.

Agreement about what constitutes clinically meaningful benefit remains controversial even with the relatively robust endpoint of OS [25].The benefits achievable from targeted treatments, especially patient reported side-effects and quality of life are vital if treatment

effects are to be determined comprehensively [26]. In this study, side-effects occurred within two weeks of starting treatment and from the patients' perspective the worst were nausea and diarrhoea. Despite this the vast majority believed the benefit of the drug in terms of controlling the cancer was worth Grade I (95%) and Grade II (88%) side-effects, but dropped to 44% at Grade III.

Discussions with patients about disease progression and communicating the benefits of further active treatment in the palliative setting are challenging and nuanced so there is a need to balance many factors. It is essential for oncologists to retain perspective on what constitutes a meaningful benefit to patients, namely one that will bring improvements in symptoms and/or quality of life not just arrest of tumour burden on imaging or reductions in tumour markers.

Acknowledgements

We wish to thank all the patients who gave up their time to participate in the research, and also the oncologists, research nurses and trial co-ordinators. In addition we would like to thank Angela Fry for her assistance with administration and Boehringer Ingelheim for the funds to conduct the study.

Conflict of Interest

Lesley Fallowfield has received grant funding and speaker honoraria from Boehringer Ingelheim.

References

1) Booth CM & Eisenhauer AF. (2012) Progression-free survival: meaningful or simply measurable? JCO, 30(10): 1030-1033
2) National Cancer Institute website: http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=44782, accessed August 10th 2016
3) Burzykowski T, Buyse M, Piccart-Gebhart MJ et al. (2008) Evaluation of tumor response, disease control, progression-free survival, and time to progression as potential surrogate end points in metastatic breast cancer. JCO 26(12): 1987-1992
4) Kim C, Prasad V. (2015) Cancer Drugs approved on the basis of a surrogate end point and subsequent overall survival: An analysis of 5 years of US food and drug administration approvals. JAMA Intern Med, 175 (12): 1992-1994
5) Prasad V, Kim C, Burotto M et al. (2015) The strength of association between surrogate end points and survival in oncology: a systematic review of trial-level meta-analyses. JAMA Intern Med. 175 (8): 1389-1398
6) Fallowfield LJ & Fleissig A. (2013) The value of progression-free survival to patients with advanced-stage cancer. Nature Reviews. Clin Onc 9(1): 41-47
7) Niraula S, Seruga B, Ocana A et al. (2011) The price we pay for progress: a meta-analysis of harms of newly approved anticancer drugs. JCO,30(24):3012-3019
8) Brundage MD, Feldman-Stewart D, Cosby R Et al. (2001) Cancer patients' attitudes toward treatment options for advanced non-small cell lung cancer: implications for patient education and decision support. Pat Ed Counsel 45(2), 149-157
9) Bruner DW. (2007) Should patient-reported outcomes be mandatory for toxicity reporting in cancer clinical trials? JCO 25(34):5345-5347
10) Bridges JF, Mohamed AF, Finnern HW et al. (2012) Patients' preferences for treatment outcomes for advanced non-small cell lung cancer: a conjoint analysis. Lung Cancer, 77(1):224-231
11) Weeks JC, Cook EF, O'Day SJ Et al. (1998) Relationship between cancer patients' predictions of prognosis and their treatment preferences. JAMA, 279(21):1709-1714
12) Jenkins V, Solis-Trapala I, Langridge C et al. (2011) What oncologists believe they said and what patients believe they heard: an analysis of phase I trial discussions. JCO 29(1): 61-68
13) Temel JS, Greer JA, Admane S et al. (2011) Longitudinal perceptions of prognosis and goals of therapy in patients with metastatic non-small-cell lung cancer: results of a randomized study of early palliative care. JCO, 29(17): 2319-2326
14) Smith TJ & Hillner BE. (2010) Explaining marginal benefits to patients, when ‘marginal’ means additional but not necessarily small. Clin Ca Res 16(24): 5981-5986
15) Christakis NA & Lamont EB. (2000) Extent and determinants of error in doctors’ prognoses in terminally ill patients: prospective cohort study. BMJ 320: 9-473
16) Hodi FS, O’Day SJ, McDermott DF et al. (2010) Improved Survival with Ipilimumab in Patients with Metastatic Melanoma N Engl J Med 363:711-723
17) Baselga J, Cortes J, Kim SB et al. (2012) Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer NEJM 366:109-119
18) Swain S M, Baselga J, Kim S Bet al. (2015) Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. NEJM (8), 724-734.

19) Spicer J, Tischer B, Peters M. (2015) EGFR Mutation Testing and Oncologist Treatment Choice in Advanced NSCLC: Global Trends and Differences. Presented at ELCC abstract number LBA2_PR
20) Gelsomino F, Agustoni F, Niger M et al. (2013) Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Treatment in Patients with EGFR Wild-Type Non–Small-Cell Lung Cancer: The Never-Ending Story, JCO 31:26:3291-3293
21) Chapman PB, Hauschild A, Robert C et al. (2011) Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 364 (26): 2507-2516
22) Hauschild A, Grob JJ, Demidov LV et al. (2012) Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. The Lancet 380(9839):358-365.
23) NICE technology appraisal guidance [TA258] (2012)Erlotinib for first-line treatment of locally advanced or metastatic EGFR-TK positive non-small cell lung cancer. Accessed online 02/12/15 https://www.nice.org.uk/guidance/ta258breast cancer. N Engl J Med; 366:109-19
24) NICE technology appraisal guidance [TA162] (2008) Erlotinib for the treatment of non-small cell lung cancer.Accessed online 02/12/15
25) Hiu D, Sri Karuturi M, Tanco KC et al. (2013) Targeted agent use in cancer patients at the end of life. J Pain Symptom Manage 46 (1):1-8
26) Ellis LM, Bernstein DS, Voest EE, et al. (2014) American Society of Clinical Oncology Perspective: Raising the Bar for Clinical Trials by Defining Clinically Meaningful Outcomes JCO; 32(12): 1186-1187
27) Cherny NI, Sullivan R, Dafni U, Kerst JM et al. (2015)A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Annals Onc 26:1547-1573

Table 1: Patient characteristics and drugs prescribed

Characteristic	N = 90
Sex	
Male	39
Female	51
Age (Years)	
Mean (sd)	65 (10.92)
Range	32-85
Partner	
Yes	58
Employed	
Yes	27
Stage of disease	
III	10
IV	80
Past treatments	
Surgery	51
Chemotherapy	44
Radiotherapy	31
Hormone therapy	13
Current treatment prescribed by tumour site	
Lung (30)	afatinib (1) carboplatin + etoposide (1) or gemcitabine (1) pemetrexed + carboplatin (2) or cisplatin (2) erlotinib (23)
Melanoma (19)	ipilimumab (15) dabrafenib (2) vemurafenib (2)
Breast (18)	bevacizumab + paclitaxel (2) eribulin (6) everolimus (1) + exemestane (4) TDM-1 (2) pertuzumab + docetaxel + trastuzumab (3)
Renal (10)	sunitinib (5) pazopanib (2) axitinib (2) everolimus (1)
Gynae (7)	bevacizumab (2) + carboplatin + paclitaxel (4) or + gemcitabine (1)
Head & Neck (3)	cetuximab + cisplatin (2) cetuximab + carboplatin + 5FU (1)
Colorectal (2)	bevacizumab (1) bevacizumab + capecitabine (1)
Sarcoma (1)	pazopanib (1)
Site of metastasis	
Lung	45
Bone	23
Liver	19
Brain	7
Lymph nodes	19

Table 2: Section 3 of the consultation form

Did you explain/discuss:	**Yes N (%)**	**No N (%)**	**Can't recall N (%)**
The results of any tests or investigations?	81 (90%)	9 (10%)	0 (0%)
The current status of the patient's disease?	83 (92%)	7 (8%)	0 (0%)
The drug/s that will be given?	90 (100%)	0 (0%)	0 (0%)
The aims of the treatment?	89 (99%)	1 (1%)	0 (0%)
Explicitly use the terms progression free survival or progression free interval?	25 (28%)	64 (71%)	1 (1%)
The side-effects of the drug/s?	89 (99%)	1 (1%)	0 (0%)
Ameliorative interventions for the side-effects?	69 (77%)	20 (22%)	1 (1%)
Impact on life expectancy of the drug/s?	61 (68%)	27 (30%)	2 (2%)
Effects on physical well-being of the drug/s?	80/89 (90%)	8/89 (9%)	1/89 (1%)
Effects on emotional/psychological well-being of treatment? (e.g. mood, positive/ negative outlook)	23 (26%)	66 (73%)	1 (1%)
Effects on social well-being of the treatment? (e.g. improve or hinder meeting/ interacting with people)	23 (26%)	65 (72%)	2 (2%)
Other care plans apart from the drug/s (e.g. symptom relief, other treatment)	46/89 (52%)	41/89 (46%)	2/89 (2%)

Table 3: Expected effects of the drug/s

	Estimates without treatment		Estimates with treatment No change (n=34) Optimistic shift (n=56)			
			<3 mths	**3-6 mths**	**7-12 mths**	**>12 mths**
Lung (30)	<3 mths	2	**1**			**1**
	3-6 mths	13		**4**	**8**	**1**
	7-12 mths	14			**7**	**7**
	>12 mths	1				**1**
Other cancers (60)	< 3 mths	5		**1**	**2**	**2**
	3-6 mths	14		**2**	**6**	**6**
	7-12 mths	23			**1**	**22**
	>12 mths	18				**18**

Table 4: Participants' responses to the trade-off questions from Interview A (n=90)

The top 4 side-effects for trade-off were nausea (23%); diarrhoea (22%); fatigue (16%) and breathless (14%).

Is (or would) the benefit of the drug in terms of controlling the cancer be worth (the following Grade[1] of severity)?					**With this Grade of side-effect how long do you require the treatment to control the cancer for you to consider it a worthwhile treatment for you?**					
	N	**YES**	**Probably**	**NO**	**N**	**≥1 mth**	**3 mths**	**6 mths**	**≥1yr**	**> year**
Grade I side-effect?	**74[2]**	95% (70)	4% (3)	1% (1[3])	**72**	75% (54)	8% (6)	13% (9)	4% (3)	
Grade II side-effect?	**89**	88% (78[4])	9% (8)	3% (3[5])	**85**	59% (50)	12% (10)	19% (16)	9% (8)	1% (1)
Grade III side-effect?	**85**	44% (37[6])	15% (13)	41% (35[7])	**49**	49% (24)	16% (8)	22% (11)	10% (5)	2% (1)

[1] See Appendix for booklet on Grades
[2] 16 who were experiencing moderate side-effects were not asked this question
[3] The patient who said NO was not asked any further trade-off questions
[4] One person who said YES could not respond to the trade-off question
[5] Three who responded NO were not asked any further trade-off questions
[6] One person who said YES could not respond to the trade-off question
[7] 35 who responded NO were not asked the trade-off question