HOPING FOR A NEW HORIZON

Phase I oncology clinical trials
Medical outcomes & patients' perspectives

DIANE VAN DER BIESSEN

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COLOFON

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Phase I oncology clinical trials
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Hopen op een nieuwe horizon

Klinisch oncologisch fase I onderzoek
Medische uitkomsten & patiëntperspectieven

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TABLE OF CONTENTS

CHAPTER 1

General introduction and outline of the thesis

PHASE I ONCOLOGY CLINICAL TRIALS

In the Western world, the incidence of cancer has increased over the past years and (unfortunately) will continue to increase due to the aging population.[1] (Figure 1) When metastases have developed, most people cannot be cured any longer. Therefore, there is an ongoing need for new and/or better treatments. The development of new systemic therapies takes place in several phases. The first exposure to such a drug in human is called phase I. In the Netherlands, phase I trials are performed in 8 academic centers and a tertiary cancer center.

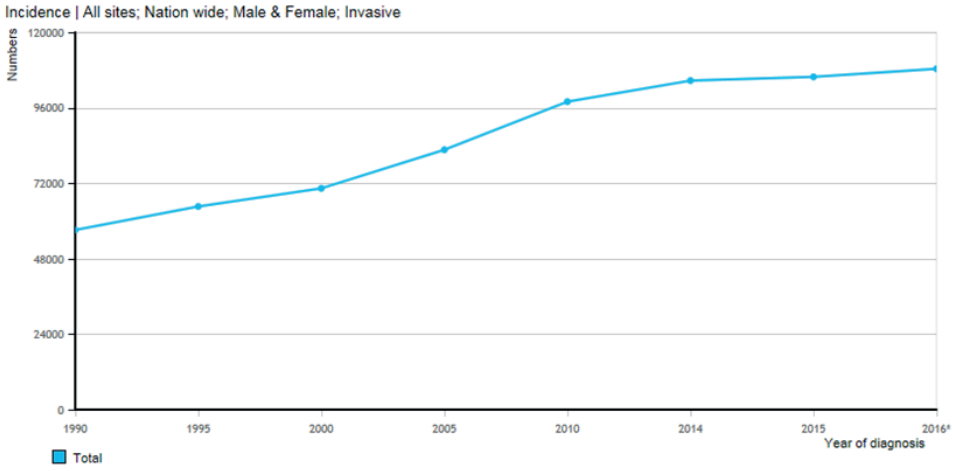

Figure 1. Incidence of invasive cancer in the Netherlands, both men and women, from 1990 -2016

The primary ethical principle of phase I clinical trials is to guard the patients' well-being while on trial, and to protect the integrity of the research.[2] The primary goal of phase I clinical trials is to study the safety profile of the drug and, if possible, to find the maximum tolerable dose (MTD) of the investigated agent, or combination of agents. Secondary goals are to study the drugs' pharmacokinetics (PK), the effect of food intake on the PK, and pharmacodynamics (PD) such as on-target inhibition in tumor or surrogate tissues, or to find biomarkers.

In order to objectify the severity of side effects of the new drug(s) and cancer related symptoms the Common Terminology Criteria for Adverse Events (CTCAE) are used.[3] This is the standard for classification and severity grading for adverse events in cancer therapy clinical trials. In order to study the response of a treatment (i.e. by the use of CT scans), the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. are currently used.[4] These

criteria were developed to define if the tumor load decreases ("response"), stays the same ("stable"), or worsens ("progression") during trial participation or treatment. These criteria make it easier to collaborate globally with other oncology research centers. Additionally, in some clinical trials, tumor markers are used, such as CA125 in patients with ovarian carcinoma, or PSA in patients with prostate cancer.[5]

Beside these objective tools, we observe these patients for clinical signs of disease response or progression. Therefore, weekly assessment of symptoms is scheduled for the patients on an early phase clinical trial. According to the study protocol, additional research is performed to gain insight in (specific) side-effects and mechanisms of action. These assessments are based on the expected side effects as seen in preclinical research and/or on the known side effects of agents in the same class of drugs. Extra hospital visits may be planned if needed, making trial participation unpredictable and time consuming for patients.

Precision medicine: targeted therapy

Till the 1960s, surgery and radiotherapy were the primary treatment modalities for solid tumors. The discovery of hormone depletion on breast function was done in 1878 by Thomas Beaton. Currently, we use aromatase inhibitors and LHRH analogs to treat prostate and breast cancer.[6] The history of systemic treatment of cancer goes back to the early 20th century. Nitrogen mustard was the first chemotherapeutic agent to be effective in lymphomas.[7] It was developed after the observation of the effect of mustard gas, a decrease of levels of leukocytes, during the First World War. Since then, chemotherapy strategies have been developed that may cure some types of metastatic cancer, such as germ cell cancer, ovarian cancer and choriocarcinoma.[7] Halfway the 20th century, new systemic anticancer treatment modalities were developed, targeting specific pathways in the cancer cell involved in cell growth, differentiation, and survival (e.g. platinum compounds and 5-fluorouracil). These new classes of drugs are designed to target molecules or cancer-causing genes, which are responsible for tumor growth and progression. Targeted therapy results in side effects that are not previously observed with chemotherapy and depend partly on the effect of the treatment on the molecular target in the normal cell.[8] Another development is immunotherapy, which activates the immune system for therapeutic benefit. The first development started prior to the 1980s.[9] The modern treatment of cancer will integrate the diverse strategies. In this thesis, 3 potentially new drugs from different classes are investigated.

RGB-286638 is a multi-targeted inhibitor which targets the family of cyclin dependent kinases (CDKs). CDKs are essential regulators of cell cycle progression and transcription.[10] In

vitro, exposure to RGB-286638 resulted in apoptosis of the cancer cells.[11] In **chapter 2,** we describe the result of a phase I trial with RGB-286638. The aim of this trial was to determine the MTD and to evaluate the PK and PD profiles of this new drug.

Malignancies with homologous recombination deficiency (HRD) are more dependent on poly(ADP-ribose) polymerase (PARP) for DNA repair than normal cells.[12] PARP is important in the recognition of DNA damage and promotes DNA repair.[13,14] Furthermore, it plays a role in cell apoptosis, necrosis, chromosome stabilization and gene expression regulation.[13,14] The effectiveness of monotherapy of PARP-inhibitors is based on 'synthetic lethality', combining homologous recombination deficiency (HRD) in cancer cells, like BRCA mutations, with PARP inhibition.[12,15] In **chapter 3**, we studied the PK and the efficacy of ABT-767, a potent PARP inhibitor, in patients with BRCA1/2 mutations, and in patients with high-grade serous ovarian, fallopian tube, or primary peritoneal cancer. The aims were to determine DLTs and the recommended phase II dose. Secondly, we evaluated food effect, objective response rate, and biomarkers predicting response.

BI 853520 is an orally administered novel focal adhesion kinase (FAK)-inhibitor. In cancer, dysregulation and activation of focal adhesions facilitate cell motility and promote invasive tumor growth.[16] Increased expression of FAK is found in various tumor types and the extent of expression has been related to the extent of disease progression and metastasis.[17] In **chapter 4,** we report on two randomized, open-label, cross-over studies evaluating the effect of administration with or without a high calorie meal and the effect of administration as a liquid dispersion on the PK of BI 853520, a novel FAK-inhibitor.

Patients' perspectives: motivators and barriers

Despite the expectation of limited benefit of trial participation, clinical trials are essential for the development of future drugs. There may be a distinct difference in the purpose of a phase I trial, being dose finding and evaluating toxicities, and the motives of the deliberating and participating patients.[18] This may have impact on the ethical framework surrounding the informed consent procedure. Therefore, if patients are understood for their motives and reasons, we can ask them to participate in a phase I trial in an adequate way. The second part of the research in this thesis was performed in order to increase our understanding of the perspectives of the patients deliberating and participating in a phase I clinical trial.

Patients with advanced or recurrent cancer, who have exhausted all lines of treatment and opt for phase I trial participation can be regarded as palliative patients, according to the World Health Organization definition.[19] These patients, with a good performance status and without standard treatment option, can be asked to participate in a phase I clinical trial. Furthermore, since the introduction of targeted therapies, palliative patients with a tumor

with specific molecular or genetic characteristics, like the patients with a BRCA mutation in the phase I trial with ABT767, may also consider phase I trial participation. This is the case when standard treatment options have expected low benefit and substantial side effects, and the new agents under investigation, aim to target the specific mutation in their tumor.

Therefore, in **chapter 5**, we retrospectively evaluated all patients who were informed about a specific phase I trial during a period of 25 months. The main aim of this study was to gain insight into the barriers, reasons, and other variables influencing patients in their decision to participate in phase I oncology trials at phase I unit of the Erasmus MC Cancer Institute, Rotterdam.

Table 1. Overview of general barriers and motivators to participate in clinical trials[20]

Factors	Barriers	Motivators
Structural	Time consuming	Access to unavailable drugs
	Travel distance	Coverage of costs associated with the trial
	Limited access to clinical trial	
Social	Lower social economic background	Altruism
		Physicians recommendations
		Family and friends recommendations
		Higher education
Personal	Fear of randomization	Hope for a cure
	Concern about experimental treatment	Perceived personal benefit
	Lack of therapeutic benefit	Desire to help others
	Concern about side effects	Younger age
	Fear of being a 'guinea pig'	

Hope and perceived benefits stand out as a personal motivator (Table 1).[20] Patients hope that trial participation will positively influence the outcome of their disease.[20-25] This could be due to the fact that patients deliberating a phase I trial may be unrealistically optimistic and believe that their outcomes will be more positive or less negative than those of patients in similar circumstances.[26-28] Their mindset, i.e. personal attitudes which influence their goals and behaviors, may help them deal with this choice.[29,30] Still, patients may struggle to decide whether to opt for symptom-oriented care in the palliative setting or to engage in a treatment with unknown efficacy, benefit, and side effects, like phase I trials.[31]

In **chapter 6,** the results of a prospective exploratory cross-sectional study are presented. We studied the effect of psychological factors, such as tenacious and flexible coping strategies, locus of control, and general well-being, as measured by the health-related quality of life, on hope and treatment motivation to participate in a phase I clinical trial.

After enrollment in phase I trials, 16 % of the patients discontinued within the first 21 days.[32] Early discontinuation is disappointing for participating patients. This rate could justify the use of prognostic score to predict early discontinuation or to reduce non-drug related 90-day mortality on study. However, when used in daily practice, the use of this prognostic score would reduce the recruitment by 20 %, of which half will survive the 90 days.[32]

One of the tools we use to evaluate patients' well-being is the Eastern Cooperative Oncology Group (ECOG) score, also called the WHO score,[33] or the Karnofsky score.[34] Patient-reported outcomes (PROs) such as 'health-related quality of life' (HRQoL) are rarely evaluated in patients participating in phase I clinical trials. PROs are the reports of the status of a patient's health condition that comes directly from the patient, without involvement of his or her family, friends, or health care professionals.[35] HRQoL is an important outcome measure for patients and have shown to be better predictors for survival than performance status and gives a good view on patients' daily health.[36, 37] Yet, the relationship of HRQoL outcomes and trial eligibility are unknown.

In order to be able to prepare patients for the consequences of participation on HRQoL, hope, and psychological impact, we performed a prospective exploratory cohort study. In **chapter 7,** we report the observations of the variation in health-related quality of life, hope, and psychological factors in patients with advanced cancer from pre-consent, at baseline of the trial, till the first evaluation.

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PART I

Medical outcomes of phase I clinical trials

CHAPTER 2

Phase I study of RGB-286638, a novel, multi-targeted cyclin-dependent kinase inhibitor in patients with solid tumors

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ABSTRACT

Purpose. RGB-286638 is a multitargeted inhibitor with targets comprising the family of cyclin-dependent kinases (CDK) and a range of other cancer-relevant tyrosine and serine/threonine kinases. The objectives of this first in human trial of RGB-286638, given i.v. on days 1 to 5 every 28 days, were to determine the maximum tolerated dose (MTD) and to evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of this new drug.

Experimental Design. Sequential cohorts of 3 to 6 patients were treated per dose level. Blood, urine samples, and skin biopsies for full PK and/or PD analyses were collected.

Results. Twenty-six patients were enrolled in 6-dose levels from 10 to 160 mg/d. Four dose-limiting toxicities were observed in 2 of the 6 patients enrolled at the highest dose level. These toxicities were AST/ALT elevations in 1 patient, paroxysmal supraventricular tachycardias (SVTs), hypotension, and an increase in troponin T in another patient. The plasma PK of RGB-286638 was shown to be linear over the studied doses. The interpatient variability in clearance was moderate (variation coefficient 7%–36%). The PD analyses in peripheral blood mononuclear cells, serum (apoptosis induction) and skin biopsies (Rb, p-Rb, Ki-67, and p27KIP1 expression) did not demonstrate a consistent modulation of mechanism-related biomarkers with the exception of lowered Ki-67 levels at the MTD level. The recommended MTD for phase II studies is 120 mg/d.

Conclusions. RGB-286638 is tolerated when administered at 120 mg/d for 5 days every 28 days. Prolonged disease stabilization (range, 2–14 months) was seen across different dose levels.

INTRODUCTION

The cyclin-dependent kinases (CDKs) are pivotal regulators of cell cycle progression and transcription. Human tumors frequently display altered expression of CDKs and their modulators, cyclins and CDK inhibitors, resulting in deregulated CDK activity which is implicated in tumor genesis.[1,2]

RGB-286638 is a novel indenopyrazole compound that displays inhibitory activity towards multiple kinases notably the cyclin-dependent kinases (CDKs) (Figure 1). In vitro cell-free kinase assays indicated that RGB-286638 inhibits CDK1, 2, 3, 4, 5 and 9 and is less active against CDK6 and 7.[3,4] In addition other receptor and non-receptor tyrosine kinases and serine/threonine kinase are inhibited as well.[3, 5] CDKs are essential regulators of cell cycle progression and transcription.[6] RGB-662833 displays potent activity against transcriptional type CDKs like CDK9.[3,7] CDK9 is a transcriptional regulator influencing gene expression by phosphorylating the carboxy terminal domain of RNA polymerase II. Inhibition of CDK9 leads to down-regulation of transcripts with a short half-life like those of the anti-apoptotic genes MCL1 and XIAP explaining the strong pro-apoptotic activity of RGB-286638. [7] Anti-tumor activity of RGB-286638 has been demonstrated in various preclinical models at the single digit nanomolar range.[3-5] Gene expression signatures were reported in cancer cell lines capable of discriminating RGB-286638 sensitive cell lines from more resistant cell lines.[8]

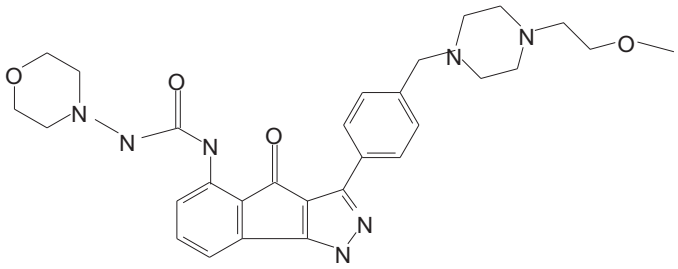

Figure 1. Chemical structure of RGB-286638

In vitro, exposure of cancer cells to RGB-286638 resulted in the induction of apoptosis[3] in the NCI cancer cell line screening panel, RGB-286638 was highly active against a broad range of human tumor cell lines. When RGB-286638 was administered daily intravenously for 5 days in mouse xenograft models for solid and hematological tumors, significant inhibition of tumor growth was observed, including complete responses.[3]

Preclinical pharmacological studies showed a dose-related increase in exposure which did not accumulate after 5 to 14 days of daily admission. The drug administration regimen used in the present study was based on the preclinical finding that daily administration of RGB-286638 for five days showed an optimal antitumor effect. Prolonged administration or intermittent schedules all proved to be less efficacious. From a clinical perspective a daily times five regimen was considered feasible based on similar frequently used schedules. RGB-286638 is primarily metabolized by CYP3A4.[3] Preclinical toxicity mainly comprised of gastrointestinal (GI), cardiovascular (hypotension and tachycardia) and hematological side effects. The GI toxicities found were vomiting and diarrhea based on histopathological changes within the GI tract. The effect of RGB-286638 on the cardiovascular system were dose limiting in dogs, RGB-286638 caused arterial hypotension and tachycardia. RGB-286638 elongated cardiac action potential duration with low pro arrhythmic risk. There was no evidence of QT or QTc prolongation. The hematological side effect were reversible and consisted of a reduction in total and differential white blood cells, especially in lymphocytes and reticulocytes. As well as reduction in platelets and red blood cell counts. A decrease in lymphocytes values was a sensitive early warning parameter. Preclinical evidence was found that RGB-286638 was bound to melanin of the choroidea.

Based on this preclinical work, a phase I open label, dose escalation study was designed. In this study RGB-286638 was given intravenously over 60 minutes on day 1 to day 5 of a 4-weekly cycle. The primary objectives of this study were to determine the maximum tolerated dose (MTD) and the dose limiting toxicities (DLTs) of RGB-286638 in patients with advanced solid tumours for whom no standard therapy options exist. The secondary objectives were to assess the suitable dose for phase II studies, to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of RGB-286638, and to document preliminary antitumor activity.

PATIENTS AND METHODS

Eligibility criteria

Patients with a cytological or histological confirmed diagnosis of an advanced and evaluable solid tumor according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) were eligible. Additional criteria at baseline included: age >18 years; ECOG performance status 0 or 1; an adequate bone marrow function (haemoglobin ≥ 6.2 mmol/l, platelet count ≥ 75 x 109/L, absolute neutrophil count ≥ 1.5 x 109/L), liver function (bilirubin ≤ 1.5 the upper limit of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN (and 5 x ULN in case of liver metastasis) and renal function (calculated

creatinine clearance ≥ 50 mL/min) , left ventricular ejection fraction (LVEF) ≥ 50%, QTc interval ≤ 450 msec, systolic blood pressure ≥ 100 mmHg and ≤ 150 mmHg and diastolic blood pressure ≤ 100 mmHg.

Specific exclusion criteria included (but were not limited to) prior treatment with an CDK-inhibitor; prior irradiation to > 30% of the bone marrow reserve; concurrent therapies known to prolong QTc-interval or potent cytochrome P450 (CYP) 3A4 inducers or inhibitors. This study was performed according to the principles defined by the Declaration of Helsinki, in Rotterdam, The Netherlands, and approved by the institutional ethics committee MEC 08-295. All patients gave written informed consent prior to study entry.

Treatment and dose escalation

RGB-286638 was supplied by GPC Biotech AG (Martinsried, Germany) as an aqueous solution for infusion in glass vials, containing 20 mg/mL of active drug. The vials were stored at room temperature (15-25°C) and were protected from light. RGB-286638 concentrate for solution for infusion were found stable for up to 72-hours when exposed to light. Solutions of 0.1 mg/mL and 10mg/mL of RGB-286638 was preservable for 30-hours at ambient temperature. The content of the vials was added to a polyvinylchloride bag with 5% aqueous dextrose to a total volume of 100 mL prior to infusion. The solution was kept at room temperature protected from light until administration. RGB-286638 was administered intravenously over 60 minutes on day 1 to day 5 of a 4-weekly cycle. With the exception of the first course, during which patients were hospitalized for PK and PD sampling, patients were treated on an outpatient basis.

Patients received RGB-286638 until disease progression and during the absence of unacceptable toxicity. Initially 3 patients were treated in each cohort with RGB-286638 with 10 mg/day for 5 days. Dose escalations were based on toxicities during the prior dose level allowing a dose escalation of 20-100% (which was determined by the worst significant toxicity). The dose was escalated by 100% increments at each subsequent level until grade 2 drug-related toxicity occurred. Thereafter the dose of RGB-286638 would be increased by increments of 20 – 67 %. The stopping dose was defined as the dose level that induced DLT during course 1 in 1 or more out of 3, or 2 or more out of 6 patients. Three more patients were to be treated at the dose level below the MTD, if only 3 patients were previously treated at that prior dose. DLTs were defined as grade 4 granulocytopenia for more than 7 days, ≥ grade 3 neutropenia complicated by fever ≥ 38.5°C, platelets < 25.0 x 109/L or < 50.0 x 109/L complicated with bleeding, and/or non-hematologic toxicities ≥ grade 3 including prolonged QTc interval > 500 msec or an increase > 60 msec from baseline, and ocular toxicity. Ocular toxicities were defined as any significant worsening in fundus auto fluorescence (FAF) patterns, and worsening of Grade ≥ 1 retinopathy by ophthalmological

examination versus baseline. Nausea, vomiting and diarrhea, subsequently responding to supportive therapy, were not considered as a DLT. Inability to administer ≥ 4 out of 5 scheduled treatment days or to start a second course after a two-weeks delay, due to ongoing toxicity was also considered as a DLT.

At re-treatment the patient had to fulfil the baseline criteria. Dose modifications to the next lower dose level were permitted once a patient had experienced a DLT. No intra-patient dose escalation was allowed. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (NCI CTCAE) Version 3.0.

Pretreatment and follow-up studies

Before therapy, a complete medical history was taken and a physical examination was done including ECOG performance status, body weight, height and vital signs. A complete blood cell count including WBC differential, coagulation parameters and serum biochemistry, which included total and direct bilirubin, serum transaminases, alkaline phosphatase, lactic dehydrogenase, amylase, lipase, creatine kinase, albumin, sodium, potassium, calcium, creatinine and glucose, were done as were urinalysis, 12-lead electrocardiograms and a pregnancy test (if applicable). The 12-lead electrocardiogram (ECG) was repeated on day 1-5 of the first cycle pre-dose and within 4 hours of end of infusion. In subsequent cycles an ECG was performed on day 1 pre-infusion and if clinically indicated. The left ventricular ejection fraction was evaluated by a MUGA scan prior to study start and repeated within 24 hours after day 5 administration during the first cycle and at off-treatment. In addition, an ophthalmological assessment including visual acuity, intraocular pressure, ophthalmoscopy and FAF imaging was performed and repeated after the first cycle and at off-treatment.

During the first cycle heart rate and blood pressure was intensively monitored (pre-dosing, every 20 minutes during infusion, at the end of infusion, after 30 minutes and every hour up to 6 hours, 8 hours and 12 hours after the end of the infusion) with an adjusted schedule from the second cycle onwards. Hematology and biochemistry assessments were performed weekly (or more frequently if clinically indicated) of every cycle and in addition on day 5 of the first cycle. Furthermore, weekly evaluations of each cycle included physical examination and toxicity assessments.

Prophylactic pre-medication with anti-emetics was only to be introduced in case more than two patients experienced ≥ grade 2 nausea or vomiting. Tumor imaging was performed within 28 days prior to study treatment and after every second cycle. Tumor evaluation was performed after every two courses, according to RECIST, version 1.1.

PK and PD sampling

For RGB-286638 PK analyses, blood samples (4 mL) were collected using an indwelling i.v. canula in the opposite arm of infusion before dosing, during the infusion (after 30 minutes and 5 minutes prior to the end of the infusion), 5 and 15 minutes after the end of the infusion and 0.5, 1, 2, 4, 6, 8, 10, and 24 hours after end of RGB-286638 infusion on day 1 and 5 of cycle 1. In addition, blood samples were taken on day 8 and 10. Blood samples for PK analyses were collected in potassium-EDTA tubes and were kept at 4oC until centrifugation within 10 minutes of collection at 2800 g for 10 minutes. The plasma samples were stored at T<-70oC until analysis using a validated LC-MS/MS method.[9] In addition, two urine samples were collected over a 24-hour period; 0-8 hours and 8-24 hours. After estimation of the total urine volumes, exactly 10 mL samples were frozen and stored at T<-70ºC until analysis.

For PD analyses paired skin biopsies were collected as previously described.[10] Skin biopsies were taken prior to study start (pre-treatment sample) and during therapy (on-therapy sample) within 24 hours after the end of infusion on day 5 of the first cycle. RGB-286638 activity was assessed in skin biopsies from all dose-cohorts by immunohistochemical analyses of the levels of retinoblastoma protein (Rb), phosphorylated retinoblastoma protein (p-Rb), the proliferation marker Ki-67 and the differentiation marker p27KIP1. In addition, the expression levels of the proliferation marker (Ki-67) and differentiation marker (p27KIP1) were determined in the skin biopsies for all dose-cohorts. Antibodies used for IHC were: monoclonal mouse anti-human Ki-67 antigen (clone MIB-1, Dako, Glostrup, Denmark, code M7240); monoclonal mouse anti-human p27 protein (clone 1B4, Novacastra, NCL-p27); Retinoblastoma (Rb) antibody (Anaspec, Fremont, CA code 53823); phospho-Retinoblastoma (Ser780) (p-Rb) antibody (Cell Signaling Technology, Leiden, The Netherlands, (#9307). Appropriate isotype-matched negative control monoclonal antibodies (negative control mouse IgG1, kappa [clone DAK-G01, Dako, code X0931] and negative control mouse IgG2a, kappa [clone DAK-G05, Dako, code X0953]) were used to validate the specificity of the Ki-67 and p27KIP1 staining. Furthermore, p-Rb (Ser780) blocking peptide (Cell Signaling Technology, #21200B) was included to validate the specificity of the p-Rb staining. All antibodies were appropriately diluted in antibody diluent (Dako, code S0809). Furthermore, all antibodies required antigen retrieval (AR) in a water bath.

The apoptotic status of blood leukocyte subsets was assessed using Annexin V/7-AAD staining using flow cytometry in blood samples collected on day 1 and 5 prior to dosing, 2 and 24 h after the end of the infusion. Leukocyte subsets were defined by surface marker antibody-conjugates, i.e., lymphocytes by CD45/APC and CD3/PE; monocytes by CD45/APC and CD64/PE and granulocytes by CD45/APC and side scatter pattern. All antibodies and Annexin V/FITC were from BD Biosciences (San Jose, CA), 7-AAD from Sigma-Aldrich (St-Louis, MO) and data were acquired on a Canto flow cytometer (BD Biosciences). The

amount of caspase-cleaved M30 fragments of cytokeratin-18 was quantitated by ELISA (M30-Apoptosense ELISA, Peviva AB, Bromma, Sweden) in serum as a marker for tumor apoptosis as well on day 1 and 5 prior to the dosing, 2 and 24 h after the end of the infusion and once every week for 3 weeks.

Patient evaluation and PK- and PD-analysis

All patients who received at least one dose of RGB-286638 were evaluable for all analyses. Descriptive statistics were used to analyse safety. PK analysis for RGB-286638 in plasma was performed using the WinNonlin software (version 4.1; Pharsight Corp., Mountain View, CA) and included the determination of maximum plasma concentration (Cmax), area under the plasma curve from time zero to infinity (AUC0-inf), area under the curve from time zero to 24 hours (AUC0-24) and elimination half-life (T½). Total body clearance (CL) was calculated as the ratio between the administered dose and the AUC0-inf or administered dose and the AUC0-24. PK analysis for RGB-286638 in urine, included the determination of the amount of excreted parent drug over a 24-hour period.

The staining of Ki-67 and p27KIP1 were scored by counting at least 1,000 epidermal keratinocytes, the number of positive epidermal keratinocytes were scored and expressed as percentage. To investigate RGB-286638 induced changes on the expression of Rb and p-Rb the total number of positive epidermal keratinocytes and the intensity of the staining were estimated according to the frequently used Allred scoring system.[11] The percentage of apoptotic cells in leucocyte subsets (i.e. lymphocytes, monocytes, granulocytes) in peripheral blood was determined distinguishing early, late and necrotic cells. In addition, M30 fragments of cytokeratin-18 were quantified (U/L) in on-therapy serum samples and compared to M30 fragment levels in a pre-treatment serum sample.

Descriptive Statistics

All PK data are presented as mean values and coefficient variations (%). A paired student's t- test was used to examine statistically significant changes in biomarker levels.

RESULTS

Patients

Between December 2008 and January 2011, a total of 26 patients (16 female and 10 male) were enrolled into 6 dose cohorts. Patient characteristics are listed in Table 1. One patient at the dose level of 120 mg developed a therapy unrelated sepsis during the first cycle. Therefore, only the first day of treatment could be completed. As a result, this patient was

only evaluable for PK/PD analyses of the first day, but not for toxicities, and was therefore replaced. The 26 evaluable patients were either asymptomatic or had only mild symptoms at study entry. Their median age was 64 years.

Safety

DLTs

In the absence of grade 2 or more toxicity in the first cycle patients were treated in following sequence at 10 mg (n=3), 20 mg (n=3), 40 mg (n=3) and 80 mg (n=3). At the first cycle of 160 mg, two patients developed a DLT. One of the DLTs consisted of AST grade 3, the other DLT consisted of grade 2 cardiac arrhythmia, grade 2 hypotension and grade 2 Troponin T in the same patient. As a result, another 3 patients were treated at the next lower dose level (80mg) of which one developed a DLT consisted of a grade 3 AST and grade 3 ALT at the third day of infusion. Due to the fact there was only one DLT out of 6 patients at 80 mg, an intermedian level of 120 mg i.v. was explored. At this dose level there were no DLT at the first cycle. Overall the dose limiting cardiovascular toxicities were hypertension grade 3 and QTc prolongation grade 3 (Table 2).

Table 1. Patients characteristics

No pts. entered	26
No pts. assessable for toxicities	25
Age, years	
Median	64
Range	35-76
Sex	
Female	16
Male	10
Performance status	
ECOG 0	2
ECOG 1	26
Tumor type	
Colorectal	12
Prostate	3
Parotis	2
Miscellaneous	9
Previous treatment	
Chemotherapy	14
Chemotherapy and radiation	10
Other	2

Abbreviations: No pts: number of patients, ECOG: Eastern Cooperative Oncology group.

Other toxicities

The mild cardiovascular toxicities were grade 1-2 hypotension and asymptomatic paroxysmal atrial fibrillation grade (Table 2).

The most frequent hematological side-effect were mild grade 1-2 leucopenia, grade 1 neutropenia and grade 1 thrombopenia. The most common non-hematological toxicities were nausea, vomiting, diarrhea and fatigue, all grade 1-2 (Table 3).

Table 2. Toxicities

Dose	Summary DLT's in first cycle according to NCI-CTC version 3.0.	Cycle
160 mg/day	AST grade 3 (1pt)	1
160 mg/day	Hypotension grade 2, cardiac arrythmia grade 2, troponin T elevation grade 2 (1 pt)	1
80 mg/day	AST grade 3 (1 pt)	1
	Summary DLT's in all subsequent cycles according to NCI-CTC version 3.0.	
10 mg/day	Hypertension grade 3 (1 pt)	3
120 mg/day	QTc prolongation grade 3 (1 pt)*	2
80 mg/day	QTc prolongation grade 3 (1 pt)*	3
120 mg/day	AST/ALT grade 3, electrolyte disturbances grade 3 (1 pt)	3
	Cardiovascular toxicity in all cycles according to NCI-CTC version 3.0	
10 mg/day	Hypertension grade 3	3, day 2
80 mg/day	Hypotension grade 2	1, day 3
80 mg/day	QTc prolongation grade 3*	3, day 4
120 mg/day	Asymptomatic paroxysmal atrial fibrillation grade 2	1, day 4
120 mg/day	QTc prolongation grade 3*	2, day 5
160 mg/day	Hypotension grade 2, cardiac arrythmia grade 2, troponin T elevation grade 2	1, day 4
160 mg/day	Asymptomatic paroxysmal atrial fibrillation grade 1	1, day 3

*same patient

Due to high incidence of phlebitis at dose 10 mg, 40 mg and 80 mg, RGB-286638 was administered i.v. through a central venous line from dose level 80 mg/day onward (Table 3). No changes in retina pigmentation were observed, neither any other ocular changes.

At the recommended dose level of 120 mg, at the 3th cycle AST/ALT grade 3 and electrolyte disturbances grade 3 were seen in the same patient (Table 2). Prophylactic anti-emetics was introduced at this dose level.

Tumor responses

There were no partial responses (PRs) observed. According to RECIST 1.1 stabilization of disease (SD) ≥ 4 months occurred in 6 patients, of which three were dosed at the recommended dose level of 120 mg. Two patients with prostate cancer, one with renal cancer, one with coloncarcinoma, one with leiomyosarcoma and one patient with cholangiocarcinoma which lasted 14 months. This last patient was dosed at 160 mg.

Table 3. Worst toxicity in the first cycle according to NCI-CTC version 3.0.

Dose (mg/day)	No pts	WBC 1-2	WBC 3-4	ANC 1 -2	ANC 3 -4	Plt 1-2	Plt 3-4	Nausea 1	Nausea 2	Nausea 3	Vomiting 1-2	Vomiting 3-4	Diarrhea 1-2	Diarrhea 3-4	Phlebitis 1	Phlebitis 2	Fatigue 1-2	Fatigue 3-4	AST/ALT 1-2	AST/ALT 3-4
10	3	-	-	-	-	1	-	-	-	-	-	-	-	-	-	3	1	-	2	-
20	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	-	3	-
40	3	-	-	-	-	-	-	1	-	-	2	-	-	-	-	2	1	-	-	-
80	6	-	-	-	-	1	-	3	-	-	-	-	2	-	-	2	3	-	2	1
160	4	1	-	1	-	1	-	3	-	-	2	-	2	-	-	-	3	-	1	1
120	6	2	-	1	-	1	-	2	1	-	2	-	1	-	-	-	6	-	5	-

Abbreviations: No pts: number of patients; WBC: white blood cells; ANC: Absolute neutrophil count; Plt: platelets; AST: aspartate aminotransferase; ALT: alanine aminotransferase and aspartate aminotransferase

Table 4. Summary of the plasma pharmacokinetics following administration on day 1 (mean ± SD)

Dose (mg/day)	No pts	AUC_{inf} (ug*h/mL)	CL_{inf} (L/h)	AUC_{0-24} (ug*h/mL)	CL_{0-24} (L/h)	AUC_{0-24} Day5/Day1	T½ (h)	Urinary excretion (%)
10	3	85.4 ± 20.0	102 ± 24.0	85.5 ± 19.9	102 ± 23.9	1.35 ± 0.24	2.02 ± 0.31[1]	1.86 ± 0.180
20	3	311 ± 142	60.9 ± 22.2	275 ± 82.8	64.6 ± 16.7	1.61 ± 0.26	8.35 ± 7.58	2.46 ± 0.747
40	3	702 ± 53.6	48.1 ± 3.53	645 ± 36.8	52.3 ± 2.93	1.26 ± 0.37	9.53 ± 1.18	1.73 ± 0.503
80	6	1404 ± 403	51.7 ± 15.9	1297 ± 361	55.6 ± 16.2	1.62 ± 0.66	9.10 ± 1.34	1.10 ± 0.352[2]
120	7	1906 ± 505	56.3 ± 15.6	2026 ± 800	56.1 ± 20.0	1.38 ± 0.177	9.30 ± 1.10	1.60 ± 0.252[3]
160	4	2432 ± 762	58.7 ± 14.2	2307 ± 749	62.1 ± 15.5	1.40 ± 0.31	7.87 ± 1.18	1.57 ± 0.601

[1]: T_{Last} in range of 5 to 7 hrs; [2]: n=5; [3]: n=6

Description PK results

Plasma samples for the PK study were obtained from all 26 patients (25 eligible patients for toxicity). A total of 26 plasma PK profiles were analyzed on day 1, and 22 plasma PK profiles on day 5. The mean PK parameters derived from the plasma concentration-time curves are summarized in Table 4. The relationship between dose and plasma exposure was investigated on day 1 over the dose range of 20–160 mg/day. The increase in AUC0-inf was proportional to the administered dose, with an average clearance of 55.1 ± 5.21 L/h (Figure 2).

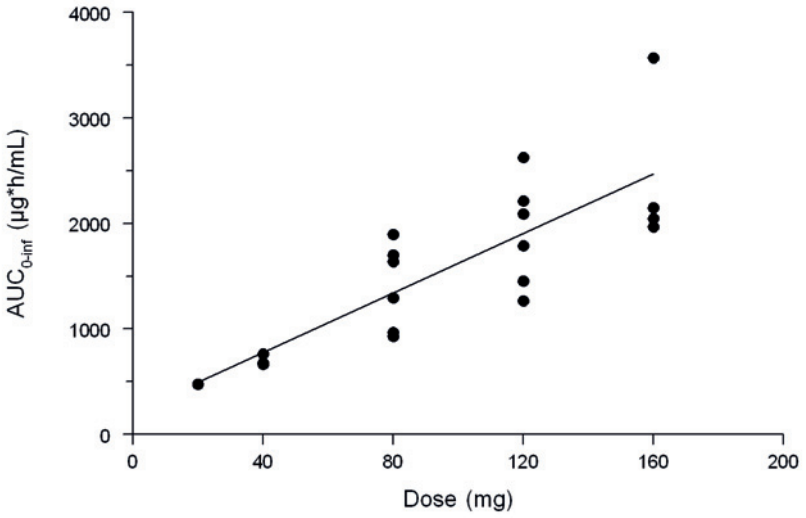

Figure 2. Relationship between area under the curves (AUC) and the administered dose on day 1 of drug intake

The comparison of AUC0-24 between day 5 and day 1 reveals a 1.5-fold drug accumulation after once daily dosing. The mean terminal T½ values did not markedly vary with the dose. Figure 3 (was 1) shows a representative concentration-time profile on day 1 and day 5 of RGB-286638 from a patient who received a single dose of RGB-286638 at 80 mg/m2 during the 24-hour period after dose administration. The cumulative urinary excretion of the parent drug was consistently low and averaged 1.71 ± 0.215% (±SD) of the dose.

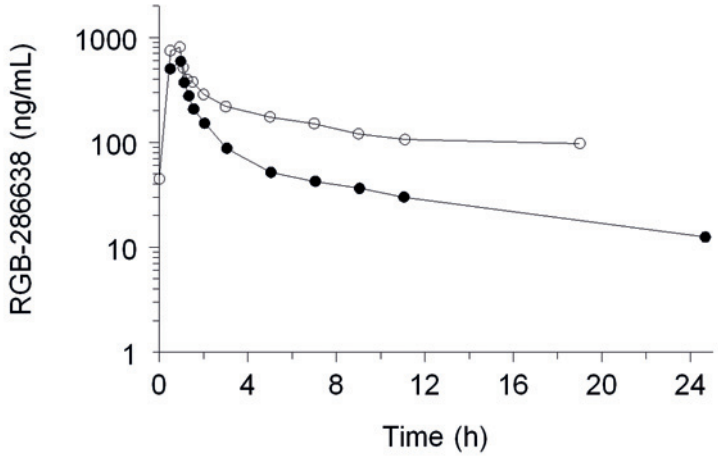

Figure 3. Representative concentration-time profile of RGB-286638 in a patient after administration of 80 mg/day at day 1 (-●-) and day 5 (-o-)

PD results

The p-Rb (Ser780) site is phosphorylated by various kinases including cyclin D dependent kinases (i.e. CDK4 and CDK6) if these CDKs are inhibited by RGB-286638 one would expect to detect reduced or absence of p-Rb compared to Rb as has been observed in in vitro experiments involving cell lines.[4] More general inhibitory effects of RGB-286638 on cell proliferation and differentiation in the skin can be detected by measuring Ki-67 and p27KIP1. Immunohistochemical analyses failed to demonstrate significant modulation of both total and activated Rb (p-Rb) in paired skin biopsies (Figure 4 A, B) taken before and during RGB-286638 treatment. However, at the MTD (120 mg/day) 3 out of 4 patients showed a significant decrease in Ki-67-positive epidermal keratinocytes (Figure 4 C-F). No changes were observed in p27KIP1 levels in the skin during treatment. As it is reported that RGB-286638 displays in vitro toxicity in cancer cell lines and against multiple myeloma xenografts through the induction of apoptosis,[3,7] we attempted to measure apoptosis in healthy peripheral blood mononuclear cells as a marker of RGB-286638 efficacy. We also carried out experiments to obtain evidence for apoptosis occurring in tumors of epithelial origin by determining the levels of a caspase cleaved fragment of cytokeratin-18. However, RGB-286638 treatment did not induce significant levels of apoptosis in blood leukocyte subsets, nor significant changes in the serum level of the M30 apoptosis-associated biomarker were detected.

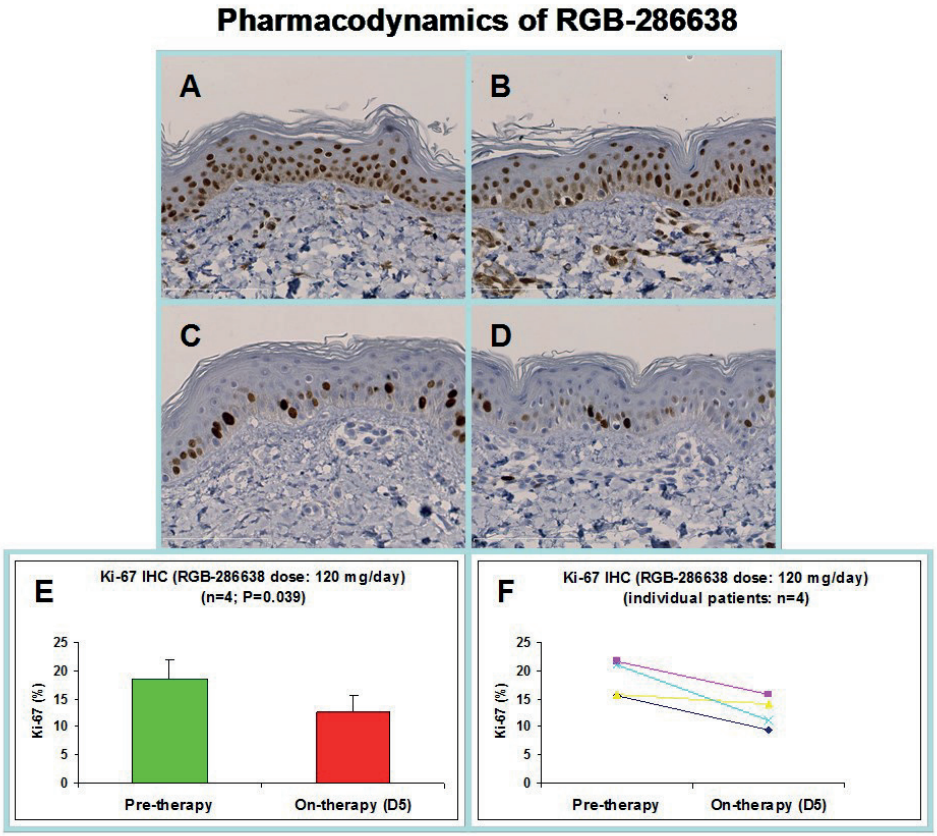

Figure 4. PD of RGB-286638.
Immunohistochemical staining of epidermal keratinocytes in paired skin biopsies showed no difference in phosphorylated Rb upon treatment with 120 mg/day of RGB-286638 (A: Pre-therapy; B: On-therapy at day 5). Ki-67 staining of paired skin biopsies (C, D) showed that the mean percentage of positive keratinocytes significantly decreased (32%) from 18.5% to 12.6% (E, F).

CONCLUSIONS

In this first in human phase I study in patients with solid tumors the recommended dose of RGB-286638 for phase II studies was identified at 120 mg/day i.v. at 1-5 every 4 weeks given through a central venous line preceded by anti-emetics. RGB-286638, a novel CDK inhibitor of the indenopyrazole family, is active at low nanomolar concentrations against CDK1, 2, 3, 4 and 6, key regulators of cell cycle progression and against the non-cell cycle dependent

kinases CDK 5, 7 and 9. In addition, RGB-286638 was active in pre-clinical models against several non-receptor and receptor tyrosine kinases and inhibited several of the serine/threonine kinases.[5]

In *in vitro* studies RGB-286638 had the potential to block ion channels in both the hERG and Purkinje fibre assays suggesting a potential to elongate QTc. Preclinical studies in the dog had not revealed any change in cardiac action potential but revealed a marked increase in heart rate and decline in blood pressure several hours after drug administration. Systematic ECG reviews in our phase I study did not show a (dose-dependent) QTc prolongation over the dose range studied. Neither was a decline in LVEF established. Also, other CDK inhibitors are associated with cardiovascular side effects (Table 5). In contrast to RGB-286638 the administration of AT7519 resulted in QTc prolongation. However, dinaciclib (SCH727965) was associated with hypotension, cardiac troponin T elevation like RGB-286638, but also with syncope and cardiac ischemia.[16,17,22] It is therefore recommended to continue the evaluation of adverse cardiovascular side effects in this class of agents, for the safety of the patients and to get a better understanding of this adverse effect. Transient rises in hepatic enzymes have been reported with other CDK inhibitors as well.[12,16-18]

Other hematological and non-hematological side effects were mild and consisted predominantly of gastrointestinal toxicity and fatigue, comparable to the side effects generally observed with CDK inhibition (Table 5).

The PK data obtained in this study revealed that plasma PK of RGB-286638 was linear over the dose range studied, with a slight accumulation of the plasma exposure on day 5. Urinary excretion was low. The fact that we did not observe apoptosis of peripheral blood mononuclear cells (different leukocyte subsets) was disappointing but not without a precedent as Cirstea et al. clearly showed activity of RGB-286638 in freshly isolated tumor cells from multiple myeloma patients but also noted that RGB-286638 was clearly less cytotoxic in healthy peripheral blood mononuclear cells.[3] Modulation of pRb has not been consistently reported on exposure to CDK inhibitors. In the present study, immunohistochemical analyses failed to show significant modulation of of pRb levels in paired skin biopsies. In agreement with our results, Cirstea et al. were also unable to show that Rb phosphorylation at the S780 site was affected by RGB-286638.[3] We did, however, observe toxicities and at the MTD (120 mg/day) a significant reduction of Ki-67 expression (a proliferation marker) in the skin suggesting a molecular interaction of the drug with, at least some, of its molecular targets. As RGB-286638 inhibits multiple kinases, not only CDKs, with IC50 values < 50 nM it may be difficult to determine which kinase or kinases caused the observed disease stabilization and hence what will be the best efficacy biomarker for RGB-286638 in the patient setting.

Table 5. Overview of CDK inhibitors in development

Drug	Target	Route of administration	Schedule	Toxicity	Ref
RGB-286638	CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK9	iv	Day 1, 8 and 15 every 4 weeks	AST/ALT elevation, hypotension, increase troponin T, supraventricular arrhythmia	
P1446A-05	CDK4	oral	14 out of 21 days	Abdominal pain, acute renal failure, diarrhea	12
P1446A-05	CDK1,CDK4, CDK9	oral	Daily od	Diarrhea, elevated creatinine, hypokalemia, nausea, vomiting, fatigue	13
PHA-848125	CDK1, CDK4, CDK5, CDK7, TRKA, TRKC	oral	14 out of 21 days	Ataxia, elevated lipase, increased creatinine, nausea and vomiting, tremor	14
Dinaciclib (SCH727965)	CDK1, CDK2, CDK5, CDK9	iv	Once every 3 weeks	Neutropenic fever, hypotension, AST/ALT elevation, nausea, vomiting	15-17
Seliciclib (Roscovitine)	CDK2, CDK7, CDK8, CDK9	oral	Bid 5 days every 3 weeks	Nausea, vomiting, asthenia, hypokalaemia, liver dysfunction	18
PD 0332991	CDK4, CDK6	oral	Od 21 out of 28 days	anemia, thrombocytopenia, neutropenia	19
LY2835219	CDK4, CDK6	oral	Daily bid	Fatigue, diarrhea, nausea, neutropenia	20
BAY 1000394	CDK1, CDK2, CDK4, CDK7, CDK9	oral	4 weeks on, 2 weeks off bid	Nausea, hot flashes, vomiting, diarrhea, fatigue, hyponatremia, hypokalemia	21
AT7519	CDK1, CDK2, CDK4, CDK5, GSK3beta	iv	Day 1-5 every 3 weeks	QTc prolongation, fatigue, mucositis	22
SNS-032	CDK1, CDK2, CDK4, CDK7, CDK9, GSK3beta	iv	Day 1, 8, 15 every 3 weeks	Tumor lysis syndrome, myelosuppression, abdominal pain, diarrhea	23

In our study no objective tumor responses were observed, although several patients had a prolonged period of disease stabilization while on treatment. It may well be that at the dose levels that can be safely reached in patients, tumors mainly respond with proliferation inhibition due to an impaired cell cycle progression. Evidence is accumulating that specific tumor cells might be dependent for their growth on specific CDKs depending on their developmental origin.[2] Selecting patients based on these insights will be essential for further development of CDK inhibitors especially in solid tumors. Data in multiple myeloma indicate that treatment with RGB-286638 results in nuclear stress and depletion of MDM2 mediated through transcriptional arrest. The strong in-vitro inhibition of CDK9 could be a rationale for further combination studies in solid tumors in addition to exploration of the drug in hematological malignancies.

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CHAPTER 3

A Phase 1 Study of PARP-inhibitor ABT-767 in Advanced Solid Tumors With BRCA1/2 Mutations and High-Grade Serous Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

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SUMMARY

Purpose. This phase 1 study examined safety, pharmacokinetics (PK), and efficacy of the poly(ADP-ribose) polymerase (PARP) inhibitor ABT-767 in patients with advanced solid tumors and *BRCA1/2* mutations or with high-grade serous ovarian, fallopian tube, or primary peritoneal cancer.

Methods. Patients received ABT-767 monotherapy orally until disease progression or unacceptable toxicity. Dose was escalated from 20 mg once daily to 500 mg twice daily (BID). Dose-limiting toxicities, recommended phase 2 dose (RP2D), food effect, objective response rate, and biomarkers predicting response were determined.

Results. Ninety-three patients were treated with ABT-767; 80 had a primary diagnosis of ovarian cancer. ABT-767 demonstrated dose-proportional PK up to 500 mg BID and half-life of ~2 hours. Food had no effect on ABT-767 bioavailability. Most common grade 3/4 treatment-related adverse events were nausea, fatigue, decreased appetite, and anemia. Anemia showed dose-dependent increase. RP2D was 400 mg BID. Objective response rate by RECIST 1.1 was 21% (17/80) in all evaluable patients and 20% (14/71) in evaluable patients with ovarian cancer. Response rate by RECIST 1.1 and/or CA-125 was 30% (24/80) in patients with ovarian cancer. Mutations in *BRCA1 or BRCA2*, homologous recombination deficiency (HRD), and platinum sensitivity were associated with tumor response. Median progression-free survival was longer for HRD positive (6.7 months) versus HRD negative patients (1.8 months) with ovarian cancer.

Conclusions. ABT-767 had an acceptable safety profile up to the established RP2D of 400 mg BID and dose-proportional PK. Patients with *BRCA1 or BRCA2* mutation, HRD positivity, and platinum sensitivity were more sensitive to ABT-767.

INTRODUCTION

Poly(ADP-ribose) polymerase-1 (PARP-1) and PARP-2 are nuclear enzymes that recognize DNA damage and facilitate DNA repair.[1,2] Malignancies with deficiencies in homologous recombination, such as those with breast cancer gene (*BRCA)* mutations, are more dependent on PARP for DNA repair than normal cells and are therefore more sensitive to PARP inhibition.[3] Accordingly, monotherapy PARP inhibitors have shown antitumor activity in *BRCA* mutated tumors.[4-8]

In patients with breast cancer, mutations in the *BRCA1/2* genes account for 5% of all breast cancers and 15–20% of all hereditary breast cancers.[9,10] *BRCA1/2* mutations also account for an increased risk of early-onset prostate cancer, gastric and pancreatic cancer.[11] Approximately 20% of high-grade serous ovarian cancers (HGSOC) have a germline or somatic *BRCA1/2* mutation, and approximately 50% overall have a defect in homologous recombination.[12] The standard treatment for ovarian cancer is surgical debulking and chemotherapy; however, many patients develop resistance to platinum-based chemotherapy after the first or subsequent treatment cycles.[13]

ABT-767 is a potent, oral, competitive inhibitor of PARP-1 (Ki = 0.47 nM) and PARP-2 (Ki = 0.85 nM). This compound has shown single-agent anti-tumor activity in patients with HGSOC and *BRCA*-mutated solid tumors[14] Here, we evaluated the safety/tolerability, pharmacokinetics (PK), food effect, and efficacy of ABT-767 in patients with advanced solid tumors with *BRCA1/2* mutations, and in patients with HGSOC, fallopian tube, or primary peritoneal cancer.

MATERIALS AND METHODS

Patients

Patients were screened at three sites in the Netherlands. Eligible patients were 18 years or older with histologically or cytologically confirmed malignancy that was metastatic or unresectable, and for which standard curative measures did not exist or were no longer effective. All patients had either a documented deleterious *BRCA1* or *BRCA2* mutation or high-grade serous ovarian, fallopian tube, or peritoneal cancer, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and adequate hematologic, renal and hepatic function. In the Expanded Safety Cohort #1, all patients had a documented deleterious *BRCA1/2* mutation, a lesion accessible for biopsy, and measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. In the Expanded Safety Cohort #2, all patients had a known positive or negative status for deleterious *BRCA1/2*

mutation. Patients in the Expanded Safety Cohort #2 with ovarian cancer could have non-measurable disease in case of an elevated serum cancer antigen-125 (CA-125) level by Gynecologic Cancer Intergroup (GCIG) criteria.

Patients were not eligible if they received anti-cancer therapy within 28 days or 5 half-lives (whichever was shorter) of first dose of study drug, if they had central nervous system metastases, unresolved clinically significant toxicities from their prior anti-cancer therapy, clinically significant uncontrolled condition(s), or if they were pregnant or breastfeeding. In the Expanded Safety Cohorts, patients were not eligible if they had received a prior PARP inhibitor.

Study design and treatment

This was a phase 1, open-label, non-randomized, dose-escalation study (NCT01339650) of ABT-767 to determine the dose-limiting toxicities (DLTs), maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D). ABT-767 was administered orally to patients on days 1–28 of 28-day cycles. Patients continued to receive ABT-767 until they experienced progression per RECIST 1.1 or unacceptable toxicity. Intra-patient dose escalation was allowed in patients who experienced clinical worsening or who had stable disease and who may benefit from dose escalation in the opinion of the investigator.

Patient cohorts were administered ascending doses of ABT-767. The initial dose was 20 mg once daily (QD). Doses for subsequent cohorts were administered twice daily (BID) and were doubled until a grade 2 toxicity occurred during cycle 1; following a grade 2 toxicity, dose escalations were restricted to between 25% and 75% of the previous dose. The decision to escalate the dose was based on observed DLTs, other adverse events, and PK data. A modified 3+3 design was used to determine MTD and RP2D. Each dose level included at least 3 evaluable patients but could enroll up to 9 patients. If one patient within any dose level experienced a DLT, the cohort was expanded to at least 6 patients. The dose could be escalated if > 67% of patients in a cohort did not experience a DLT in Cycle 1. MTD was defined as the highest dose level at which less than 2 out of 6 patients or < 33% of patients experienced a DLT. The RP2D was defined by observed DLTs and determination of MTD.

After determination of RP2D, additional patients were enrolled to two Expanded Safety Cohorts to further evaluate the safety, tolerability, and PK of ABT-767 at the RP2D. Food effect was assessed in the Expanded Safety Cohort enrolling patients with *BRCA1/2* germline mutation and advanced solid tumors only.

Safety and tolerability

Safety was evaluated throughout the study through assessment of treatment-emergent adverse events (TEAEs) and laboratory tests. TEAEs were reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Treatment-related TEAEs were those considered possibly or probably related to ABT-767.

The following TEAEs were considered DLTs if occurring during the first cycle of dosing and attributed to ABT-767: grade 4 absolute neutrophil count (ANC), grade 3 ANC lasting more than 7 days, or ≥ grade 3 ANC with fever; ≥ grade 3 thrombocytopenia; ≥ grade 3 decreased hemoglobin; non- hematologic toxicities of CTCAE ≥ grade 3 that have increased at least 2 grade levels from baseline (except nausea, vomiting, diarrhea, and tumor pain that have not received optimal treatment); creatinine increases to grade 3 that are not corrected to grade 1 or baseline within 24 hours by IV fluids; ≥ grade 3 metabolic toxicities not corrected to ≤ grade 2 within 24 hours or any symptomatic grade 4 metabolic toxicity; or grade 2 non-hematologic toxicities representing ≥ 2 grade increase from baseline requiring dose modification or delay of > 1 week.

Pharmacokinetics

ABT-767 was administered as a single dose under fasting conditions on day –4 (for patients being evaluated for food effect) and as either QD or BID under non-fasting conditions on study days 1 through 28. ABT-767 PK samples were collected at 0, 0.5, 1, 1.5, 2, 4, 6, 8, 10 and 24 hours post-dose on Cycle 1 Days –4, 1, and 8. Urine sample collections started immediately after the ABT-767 morning dose on Cycle 1 Day 7 and ended immediately prior to the morning dose on Cycle 1 Day 8. Maximum observed plasma concentration (C_{max}), the time to C_{max} (peak time, T_{max}), and the area under the concentration curve (AUC_t) were determined using non-compartmental methods.

Exploratory efficacy

Objective response rate (ORR: confirmed complete response [CR] plus partial response [PR]) was based on RECIST version 1.1, and was evaluated in patients with measurable disease at baseline. Tumor marker CA-125 response was measured by GCIG criteria[15] in patients with ovarian cancer, and was evaluated in patients with a pre-treatment sample within 2 weeks of starting treatment that was at least twice the upper limit of normal. Time of progression-free survival was defined as the number of days from first dose of study drug to disease progression or death if disease progression was not reached. Six-month progression-free survival (PFS) rate was calculated.

Table 1. Patient demographic and baseline clinical characteristics

Variable	Dose escalation (N=63)	Expanded safety (N=30)	Total (N=93)
Sex, n (%)			
Female	62 (98)	30 (100)	92 (99)
Age, years			
Mean (SD)	57 (11)	59 (10)	58 (11)
Median (range)	57 (27–80)	60 (33–73)	58 (27–80)
Race, n (%)			
White	63 (100)	28 (93)	91 (98)
Asian	0	2 (7)	2 (2)
Primary diagnosis[a], n (%)			
Ovarian, fallopian tube, or primary peritoneal	54 (86)	26 (87)	80 (86)
Fallopian tube, n	3	0	3
Primary peritoneal, n	2	1	3
Breast	7 (11)	3 (10)	10 (11)
Pancreatic	0	1 (3)	1 (1)
Prostate	1 (2)	0	1 (1)
Peritoneal mesothelioma	1 (2)	0	1 (1)
Prior therapies, n (%)			
Number of prior therapies			
1	9 (14)	4 (13)	13 (14)
2	17 (27)	11 (37)	28 (30)
3	11 (17)	5 (17)	16 (17)
4	15 (24)	8 (27)	23 (25)
≥5	11 (17)	2 (7)	13 (14)
≥1 PARP inhibitor-containing therapy	5 (8)	0	5 (5)
≥1 platinum-containing therapy	59 (94)	27 (90)	86 (93)
Platinum-free interval <6 months[b]	32 (51)	10 (33)	42 (45)
Platinum-free interval 6–12 months	20 (32)	11 (37)	31 (33)
Platinum-free interval >12 months	6 (10)	4 (13)	10 (11)
***BRCA* status**, n (%)[c]			
Germline *BRCA1/BRCA2* mutation positive	26 (41)	16 (53)	42 (45)
Germline *BRCA1/BRCA2* mutation negative	11 (18)	13 (43)	24 (26)
Germline *BRCA1/BRCA2* mutation status unknown	26 (41)	1 (3)	27 (29

Abbreviations: *PARP* poly(ADP-ribose) polymerase; *SD* standard deviation

[a] 21 patients had a history of other malignancies including breast, colorectal, melanoma, renal, and basal or squamous cell skin cancer.

[b] Platinum-free interval was defined as the time in months between last dose of platinum-based therapy and start of the next line of therapy. Platinum-free interval data are missing for 3 patients with prior platinum (1 in Dose Escalation Cohort, and 2 in Expanded Safety Cohort). Patients with a platinum-free interval of <6, 6–12, and >12 months were considered platinum resistant, partially platinum sensitive, and platinum sensitive, respectively.

[c] *BRCA1/2* mutation as reported by site at screening.

Biomarker analysis

BRCA status was collected at screening if known. A known *BRCA* status was required for patients in the expansion cohorts. Tumor *BRCA1/2* mutation status and homologous recombination deficiency (HRD) score were analyzed using a next generation sequencing

assay (Myriad) in patients providing tissue samples in a central lab.[16] Tumors were considered HRD positive if they had an HRD score ≥ 42 and/or a *BRCA1/2* mutation, as previously described.[17]

Statistical analysis

All patients who received at least one dose of ABT-767 were included in the safety, PK, and efficacy analyses. For all statistical analyses, unless otherwise stated, statistical significance was determined using a two-sided p value ≤ 0.05. The Kaplan-Meier method was used to estimate PFS. Data were analyzed both by specific ABT-767 dose cohort and in some cases by pooling multiple cohorts.

Dose, *BRCA* mutation status, platinum sensitivity, baseline CA-125 level (if relevant), and age were examined as potential predictive variables for efficacy (PFS and best tumor response) and safety (anemia). A logistic regression analysis was performed to characterize the dose-response relationship between the ABT-767 dose and best tumor response (CR or PR).

RESULTS

Patient characteristics and treatment exposure

A total of 93 patients were enrolled and treated in the dose escalation (n=63) or expanded safety (n=30) cohorts. Patient demographics and baseline clinical characteristics are summarized in Table 1. The majority of patients (86%) had a primary diagnosis of ovarian cancer, and 45% (42/93 patients) had known germline *BRCA1/2* mutations.

The median duration of ABT-767 treatment among all 93 patients was 3.8 months (range 0.03–31.1) as of data cutoff on March 29, 2016. The median duration for patients in the dose escalation was 3.8 months (range 0.03–20.6), and the median duration for patients in the expanded safety cohorts was 4.0 months (0.5–31.1).

Dose-limiting toxicities and recommended dose

DLTs occurred in three patients during the DLT evaluation period; angina pectoris in one patient at 20 mg BID, and grade 3 anemia in two patients at 400 mg and 500 mg BID. The RP2D was determined to be 400 mg BID. The 500 mg BID dose was considered intolerable due to grade 3 anemia and fatigue/general malaise.

Table 2. Treatment-related adverse events by frequency of grade 3 or 4 events

	Dose Escalation (N=63)		Expanded Safety (N=30)		Total (N=93)	
Event, n (%)	**All Grades**	**Grade 3 or 4**	**All Grades**	**Grade 3 or 4**	**All Grades**	**Grade 3 or 4**
Anemia	17 (27)	17 (27)	14 (47)	12 (40)	31 (33)	29 (31)
Fatigue	34 (54)	3 (5)	18 (60)	2 (7)	52 (56)	5 (5)
Decreased appetite	31 (49)	0	13 (43)	2 (7)	44 (47)	2 (2)
Neutropenia	1 (2)	1 (2)	2 (7)	1 (3)	3 (3)	2 (2)
Thrombocytopenia	2 (3)	2 (3)	0	0	2 (2)	2 (2)
Nausea	34 (54)	0	19 (63)	1 (3)	53 (57)	1 (1)
Leukopenia	0	0	2 (7)	1 (3)	2 (2)	1 (1)

Safety

Eighty-seven patients (93.5%) experienced at least one treatment-related adverse event, and 40 patients (43%) experienced at least one grade 3 or 4 treatment-related TEAE. Grade 3 or 4 treatment-related adverse events occurring in more than one patient overall were anemia (31.2%), fatigue (5.4%), decreased appetite (2.2%), neutropenia (2.2%), and thrombocytopenia (2.2%) (Table 2). A dose-dependent increase in all-grade anemia was observed with ABT-767 from 20 mg BID (16.7%) to 500 mg BID (66.7%). Mean hemoglobin levels for all patients from screening visit to Cycle 3 Day 1 are shown in Figure 1.

Two patients had treatment-related TEAEs that led to discontinuation (thrombocytopenia in one patient at 20 mg BID, and decreased platelet count and anemia in one patient at 400 mg BID). Twenty-nine patients (31.2%) experienced at least one TEAE that led to ABT-767 dose reduction; dose reduction was due to anemia in 20 of these patients. Thirty-five patients had a treatment-related TEAE that led to ABT-767 interruption. Treatment-related TEAEs leading to dose reduction and interruption were generally more frequent with increasing dose.

Six patients (6.5%) experienced at least one treatment-related serious TEAE (dizziness and angina pectoris in one patient; decreased appetite, dehydration, and nausea in one patient; abdominal pain, nausea, malaise, and vomiting in one patient; and malaise, macular hole, and lung infection in one patient each).

Pharmacokinetics

ABT-767 exposure increased approximately dose-proportionally from 20 mg to 500 mg (Figure 2). The median T_{max} values ranged from 1.5 to 2.0 hours under non-fasting condition,

and the harmonic mean half-life was approximately 2 hours across different cohorts (Table3). On average, 10% of ABT-767 dose was recovered as the parent drug in urine, and renal clearance appeared to be independent of dose, which suggests that renal clearance plays an important role in ABT-767 elimination. The effect of food on the oral bioavailability of ABT-767 was evaluated up to 400 mg ABT-767 dose, and no significant food effect was seen on C_{max} or AUC of ABT-767.

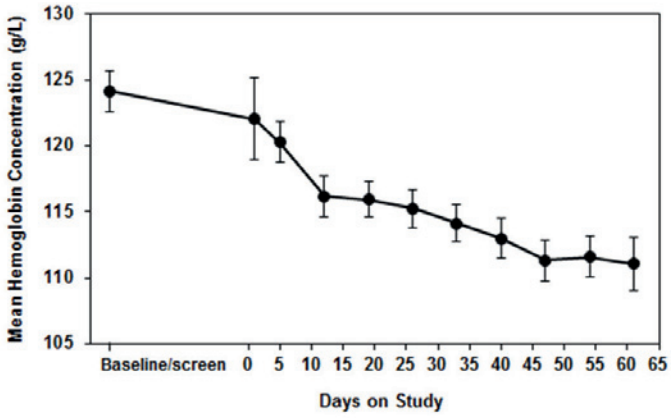

Figure 1. Mean hemoglobin level from screening visit to Cycle 3 Day 1.
Mean ± standard error included all patients' laboratory data that was collected from screening visit to Cycle 3 Day 1.

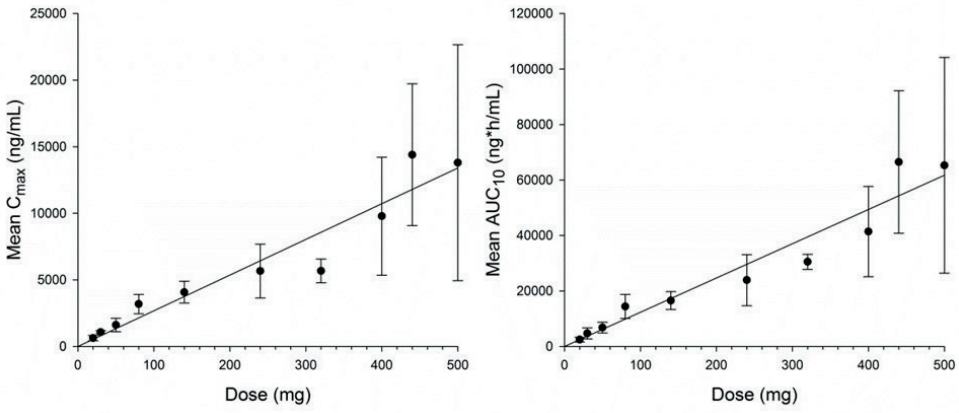

Figure 2. Mean ± SD C_{max} and AUC_{10} after the morning dose of ABT-767 on Day 1 of Cycle 1.
Abbreviations: C_{max} maximum observed plasma concentration; AUC_{10} area under the plasma concentration–time curve from time 0 to 10 hours

Table 3. Geometric mean (mean, % CV) pharmacokinetic parameters of ABT-767 after the morning dose on Day 1 of Cycle 1

ABT-767 Dose Cohort	N	C_{max} (µg/mL)	T_{max}[b] (h)	AUC_{10} (µg•h/mL)	AUC_{∞} (µg•h/mL)	$t_{1/2}$[c] (h)	CL/F (L/h)	$V_{d\beta}$/F (L)
20 mg QD	3	0.752 0.770, 26)	2.0 2.0 - 4.0)	3.37 3.45, 27)	3.90 3.96, 24)	4.2 ± 0.5	5.13 5.21, 21)	31.5 32.5, 29)
20 mg BID	5	0.592 0.624, 32)	2.0 1.5 - 4.0)	2.31 2.44, 35)	2.44 2.59, 37)	2.1 ± 0.4	8.20 8.74, 40)	24.9 26.2, 36)
30 mg BID	3	1.07 1.07, 11)	2.0 1.5 - 2.0)	4.42 4.67, 43)	4.75 5.18, 53)	2.0 ± 0.7	6.31 6.80, 42)	19.3 19.3, 8)
50 mg BID	6	1.53 1.61, 32)	1.8 1.5 - 4.0)	6.54 6.78, 29)	7.05 7.37, 31)	1.9 ± 0.4	7.09 7.45, 37)	19.6 19.9, 21)
80 mg BID	8	3.11 3.18, 23)	2.0 1.0 - 4.0)	13.9 14.4, 30)	15.1 15.9, 33)	2.3 ± 0.4	5.28 5.54, 32)	17.4 17.7, 20)
140 mg BID	6	4.00 4.07, 20)	1.5 1.0 - 2.0)	16.3 16.5, 19)	17.2 17.5, 22)	2.1 ± 0.5	8.15 8.31, 22)	24.8 25.0, 12)
240 mg BID	5	5.42 5.66, 36)	2.0 1.5 - 4.9)	22.8 23.9, 39)	25.6 26.9, 41)	1.7 ± 0.3	9.39 9.82, 33)	23.6 23.8, 17)
320 mg BID	6	5.61 5.67, 16)	2.0 2.0 - 2.0)	30.4 30.5, 9.0)	32.7 32.8, 9.0)	1.9 ± 0.3	9.79 9.82, 8.0)	27.7 28.0, 18)
400 mg BID Dose Escalation	6	9.40 9.92, 33)	2.0 1.5 - 4.0)	41.6 42.9, 28)	47.7 49.1, 27)	1.9 ± 0.5	8.39 8.65, 27)	23.9 25.1, 35)
400 mg BID Expanded Safety[a]	24	8.90 9.74, 49)	1.5 1.0 - 10.0)	38.3 41.1, 42)	40.1 43.2, 43)	2.1 ± 0.8	9.97 10.6, 33)	31.0 33.8, 47)
440 mg BID	5	13.6 14.4, 37)	1.5 0.5 - 6.0)	62.6 66.5, 39)	64.6 70.2, 51)	2.6 ± 0.8	6.82 7.32, 39)	26.2 26.8, 24)
500 mg BID	6	11.8 13.8, 64)	1.8 1.5 - 4.0)	56.7 65.3, 60)	60.5 70.2, 61)	1.9 ± 0.5	8.26 9.40, 50)	24.0 (26.8, 44)

[a] All other cohorts were dose escalation cohorts.
[b] Median (minimum - maximum).
[c] Harmonic mean ± pseudo-standard deviation.
Abbreviations: AUC_{10}, area under the plasma concentration–time curve from time 0 to 10 hours; AUC_{∞}, total area under the concentration–time curve; BID, twice daily; CL/F, clearance as a function of bioavailability; C_{max}, maximum observed plasma concentration; QD, once daily; $t_{1/2}$, elimination half-life; T_{max}, time to maximum observed plasma concentration; $V_{d\beta}$/F, volume of distribution as a function of bioavailability.

Efficacy

Among all patients, the objective response rate (CR+PR) by RECIST 1.1 criteria was 21% ([17/80], 95% CI: 13–32%). Among patients with ovarian cancer, the objective response rate by RECIST 1.1 criteria was 20% ([14/71], 95% CI: 11–31%), by GCIC (CA-125) criteria 35% ([23/35], 95% CI: 24–48%), and by using RECIST 1.1 and/or CA-125 criteria 30% ([24/80], 95% CI: 20–41%). Duration of therapy and best tumor response (RECIST 1.1) for individual patients are shown in Figure 3.

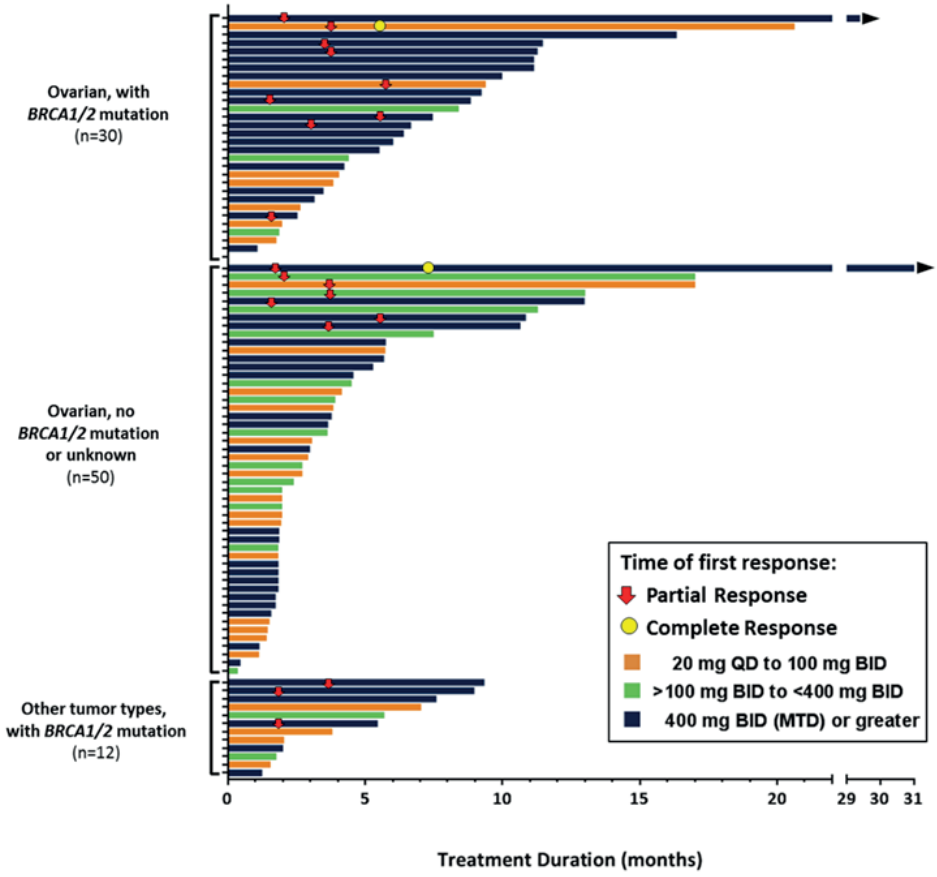

Figure 3. Efficacy data for individual patients.
Abbreviations: *BID* twice daily; *MTD* maximum tolerated dose; *QD* once daily
Germline *BRCA* status was provided by the investigators. Responses shown are best tumor responses (RECIST1.1). Arrowhead indicates patients still on study.
This plot does not include one patient with peritoneal mesothelioma and no *BRCA1/2* mutation from the 50 mg BID cohort whose best response was stable disease at 15 months.

The best percentage change from baseline in tumor size by ABT-767 dose is shown in Figure 4. A ≥ 30% reduction from baseline in tumor size was seen in 19 of 76 patients who had a post-baseline measurement.

The 6-month PFS rate was 33% (95% CI: 23–42%) for all patients, and 32% (95% CI: 22–42%) for patients with ovarian cancer. The median PFS was 3.8 months (95% CI: 2.8–5.2 months) for all patients, 3.7 months (95% CI: 2.7–4.7 months) for patients with ovarian cancer, and 5.6 months (95% CI: 1.8–7.7 months) for patients with other types of primary cancer.

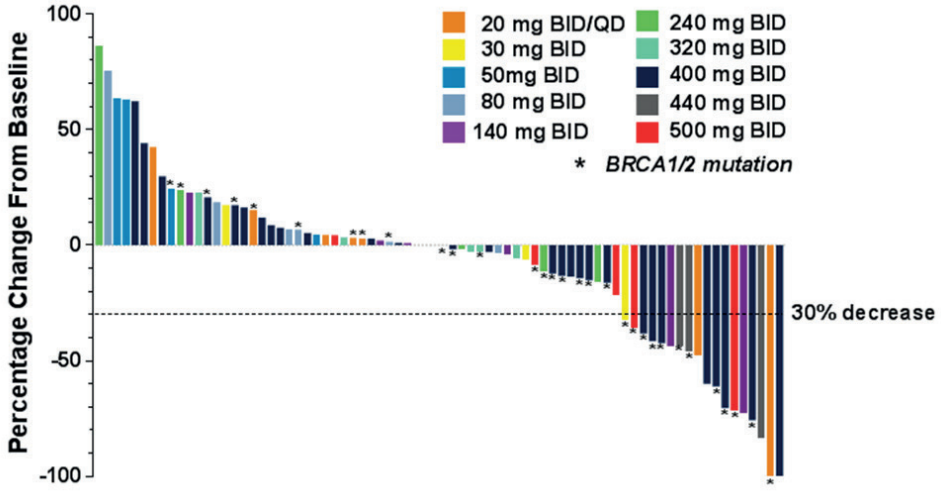

Figure 4. Best percentage change from baseline in tumor size by ABT-767 dose in all patients.
Abbreviations: *BID* twice daily; *QD* once daily
Germline *BRCA* status was provided by the investigators.

Biomarker analysis

Somatic *BRCA* mutation status and HRD status were determined for 60 patients with ovarian cancer for whom tissue was submitted. Thirty-four patients had ovarian tumors that were HRD positive; of these, 26 had deleterious *BRCA* mutations. Of the 34 HRD positive patients, 16 (47%) were responders (7 PR, 9 CR) per RECIST 1.1 and/or CA-125 criteria; all 16 responders had prior platinum and 2 were platinum resistant. Among the HRD positive patients who had a deleterious somatic *BRCA* mutation, 14/26 (54%) were responders (7 PR, 7 CR) per RECIST 1.1 and/or CA-125 criteria (Table 4).

Among the 8 patients who were HRD positive but had no deleterious *BRCA* mutation, 2 were responders by RECIST 1.1 and/or CA-125 criteria. Both of these patients were partially platinum sensitive, received ABT-767 at 400 mg BID and had a CR. Among patients determined to be HRD negative, there were no responders per RECIST 1.1 or CA-125 criteria. Among HRD positive patients with ovarian cancer, responses were generally more frequent in patients with fewer prior therapies (Table 5).

PFS was significantly longer in HRD positive patients with ovarian cancer (median PFS 6.7 months; n=34) compared with HRD negative patients (median PFS 1.8 months; n=26) (Log rank p<0.0001) (Figure 5).

Table 4. Tumor response by RECIST 1.1 and/or CA-125 by HRD and somatic *BRCA1/2* mutation status in patients with ovarian cancer

n (%)	Complete Response	Partial Response	Non-Responder
HRD positive (N=34)	9 (26%)	7 (21%)	18 (53%)
BRCA1/2 mutation (N=26)	7 (27%)	7 (27%)	12 (46%)
BRCA1/2 wild-type (N=8)	2 (25%)	0	6 (75%)
HRD negative (N=26)	0	0	26 (100%)
HRD undetermined (N=7)	1 (14%)	0	6 (86%)

Abbreviations: *HRD* homologous recombination deficiency

Table 5. Tumor response by RECIST 1.1 and/or CA-125 by number of prior therapies among HRD positive patients with ovarian cancer

Number of prior regimens	Non-responders n/N (%)	Partial Response or Complete Response n/N (%)
1	1/5 (20%)	4/5 (80%)
2	4/11 (36%)	7/11 (64%)
3	3/7 (43%)	4/7 (57%)
4+	10/11 (91%)	1/11 (9%)

Abbreviations: *HRD* homologous recombination deficiency

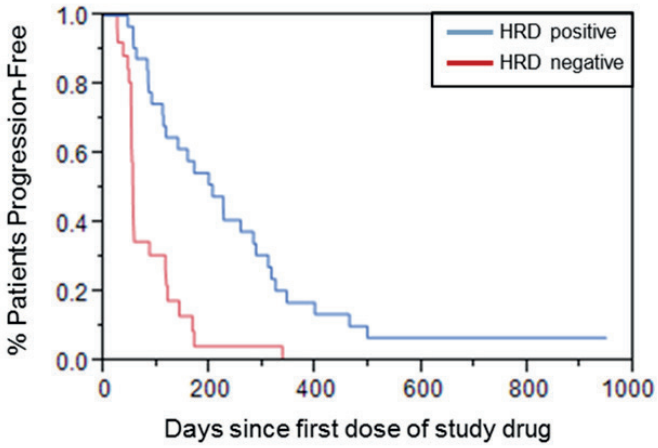

Figure 5. Progression-free survival by HRD status in patients with ovarian cancer.
Abbreviations: *HRD* homologous recombination deficiency; *PFS* progression-free survival
Legend indicates HRD status. Median PFS was 6.7 months for HRD positive patients and 1.8 months for HRD negative patients (log rank *P*<0. 0001).

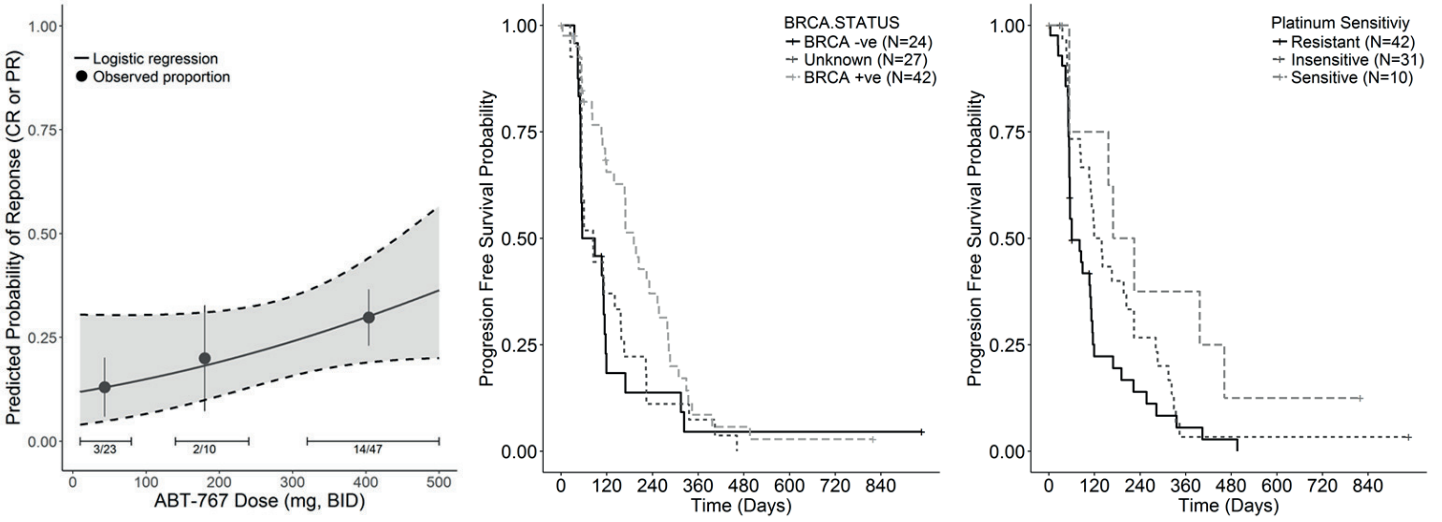

Figure 6. Predicted probability of best tumor response (CR or PR) vs. ABT-767 dose (A) and analysis of progression-free survival based on *BRCA* mutation (B) and platinum sensitivity (C).

Abbreviations: *BID* twice daily; *CI* confidence interval; *CR* complete response; *PR* partial response

Part A: Shaded area between the dashed lines indicates the predicted 95% CI; points with vertical bars indicate the observed proportions with 95% binomial CI at the observed mean ABT-767 dose. Horizontal lines parallel to the x-axis indicate the dose range bins for low (20–80 mg), medium (140–240 mg), and high (320–500 mg) doses. The number of patients with best tumor responses (CR or PR) relative to the total number in that dose bin is shown below the lines.

Part B: +ve, patients with germline *BRCA* mutation; -ve, patients without germline *BRCA* mutation.

Part C: Platinum sensitivity categories (based on time to progression on platinum therapy) were: resistant 0–6 months; insensitive 6–12 months; sensitive >12 months.

Predictors of Response

In univariate analysis, platinum sensitivity (compared to platinum resistant population) was a significant covariate ($p<0.01$) affecting best tumor response by RECIST, whereas ABT-767 dose and *BRCA* mutational status (germline compared to non-germline) showed a trend toward significance ($p<0.1$) (Figure 6). In multivariate analysis, platinum sensitivity was a statistically significant covariate affecting the best tumor response by RECIST ($p<0.01$). Both univariate and multivariate analyses revealed that PFS is significantly affected by *BRCA* mutational status (germline compared to non-germline; $p<0.05$) and by platinum sensitivity (platinum sensitive compared to platinum resistant population; $p<0.05$) (Figure 6 B-C).

DISCUSSION

This phase 1 study evaluated ABT-767 in patients with ovarian cancer or *BRCA* mutations. ABT-767 had an acceptable safety profile up to the established RP2D of 400 mg BID. Anemia was the most common grade 3/4 TEAE; onset of anemia was monitorable and was generally manageable with standard supportive care and dose reduction. Anemia has been frequently reported with other PARP inhibitors.[4,7,8] The half-life of ABT-767 was approximately 2 hours and renal clearance was a significant pathway for ABT-767 elimination. The exposure to ABT-767 increased approximately dose-proportionally from 20 mg to 500 mg. Food had no significant effect on ABT-767 oral bioavailability up to 400 mg dose. The data suggest that ABT-767 has single-agent activity in patients with tumors with *BRCA* mutations or high-grade serous ovarian cancer, with tumor responses of 21% (17/80 patients) in all patients per RECIST 1.1 criteria, and 30% (24/80 patients) in patients with ovarian cancer per CA-125 and/or RECIST 1.1 criteria.

Biomarker analyses indicate ABT-767 sensitivity among HRD positive patients with ovarian cancer. PFS was significantly prolonged in patients who were HRD positive, and observed RECIST and/or CA-125 responses were generally restricted to HRD positive patients. Responses were generally more common among HRD positive patients who had a somatic *BRCA* mutation compared to those who did not; however, the sample size of HRD positive *BRCA* wild-type patients was small at only 8 patients. Patient selection with a functional HRD test[16] or RAD51 assay[18] may be useful for identifying patients likely to respond. The biomarker analyses are limited by the collection of tissue in a subset of patients, and the inclusion of archived tissue that may have been from the time of diagnosis in patients who received multiple prior lines of therapy. It was observed that patients were generally less likely to respond with increasing number of prior lines of therapy. Mechanisms of resistance

and possible *BRCA1/2* reversion mutations were not evaluated in this study. Univariate and multivariate analyses showed that PFS is significantly affected by *BRCA* mutation and platinum sensitivity, further delineating patient populations that may benefit from therapy.

In this phase 1 study of ABT-767, responses were observed in a refractory, heterogeneous patient population. Patients with *BRCA* mutations, HRD positivity, and platinum sensitivity were more sensitive to treatment, supporting that these populations are suitable candidates for PARP inhibitor therapy.

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CHAPTER 4

Randomized, open-label, cross-over studies evaluating the effect of food and liquid formulation on the pharmacokinetics of the novel focal adhesion kinase (FAK) inhibitor BI 853520

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ABSTRACT

Background. BI 853520 is a potent inhibitor of focal adhesion kinase (FAK) currently under clinical development. Two randomized, open-label, cross-over studies were conducted to evaluate the effect of food and liquid dispersion on the pharmacokinetics of BI 853520.

Methods. Sixteen patients with advanced solid tumors were enrolled in each sub-study. The order of administration was randomized and pharmacokinetic samples collected for 48 hours after a 200 mg dose of BI 853520. Lack of effect would be demonstrated if the 90% confidence interval (CI) of the ratio of the geometric mean (GMR) of the area under the plasma curve (AUC0–48 and AUC0–∞) and maximum concentration (Cmax) did not cross the 80–125% (bioequivalence) boundaries.

Results. Administration of BI 853520 as a liquid dispersion did not affect AUC0–48, AUC0–∞ and Cmax compared to a tablet, resulting in GMRs (90% CIs) of 1.00 (0.92–1.09), 0.98 (0.90–1.07) and 0.93 (0.86–1.01), respectively. GMRs (90% CIs) for the fed versus fasted state were 0.95 (0.77–1.19), 0.96 (0.77–1.19) and 0.92 (0.76–1.11) for the same parameters, respectively. Although the 90% CIs were not within bioequivalence limits for the food effect study, the limited reductions in AUC0–48, AUC0–∞ and Cmax after administration with a high-fat meal are unlikely to be clinically relevant.

Conclusions. These studies demonstrated that BI 853520 can be used effectively as a liquid dispersion with no food restrictions. These favorable pharmacokinetic properties contribute to the convenience and flexibility of the posology of BI 853520.

INTRODUCTION

The focal adhesion kinase (FAK), also known as protein tyrosine kinase 2 (PTK2), is a non-receptor cytokine tyrosine kinase that comprises a structural component of focal adhesions. These focal adhesions are protein complexes containing cell surface integrins, which are essential for interaction with the extracellular matrix and transduction of signaling pathways.[1] FAK plays a vital role in proliferation, survival and migration of tumor cells.[2] In cancer, dysregulation and activation of focal adhesions facilitate cell motility and promote invasive tumor growth.[1] Increased expression of FAK is found in various tumor types, and the extent of expression has been related to the extent of disease progression and metastasis.[3] In particular, FAK overexpression has been implicated in the development of sarcomas, and prostate, colorectal, ovarian and breast cancer.[4-9]

In mice, genetic knock out of FAK has been shown to be embryonically lethal, underscoring its role in development, in particular, in the formation of blood vessels.[10] Chemical inhibition of FAK has been shown to reduce FAK activity and block tumor growth in a range of xenograft models.[11-14] Moreover, inhibition of FAK on endothelial cells has been shown to improve sensitivity of tumor cells to chemotherapy and immunotherapy in preclinical models.[15,16] Several inhibitors of FAK have been evaluated in cancer patients,[17-19] both as monotherapy, and in combination with chemotherapy, targeted and immune therapies.[20] BI 853520 is a potent inhibitor of FAK, and clinical exploration has shown target engagement and anti-tumor activity in the phase I studies reported by de Jonge *et al*. and Doi *et al*. in this issue.

A major determinant of drug absorption is the impact of concomitant administration with or without food.[21] Food, amongst other factors, may influence gastric pH, emptying and motility. Moreover, the presence of a high-fat meal may improve the solubility of lipophilic drugs, thereby increasing (relative) bioavailability. All of these factors can influence the rate and extent of gastrointestinal absorption and indicate the need to study the effects of food on drug bioavailability during clinical drug development.[22,23] A marked influence of food on absorption has been reported for several orally dosed anti-cancer drugs.[24-27] In particular, in the case of abiraterone, a 1,000% increase in area under the plasma concentration–time curve (AUC) was demonstrated when the drug was administered with food compared to a fasted state, illustrating a clinically relevant food effect.[25]

The requirement to administer drugs in the fasting state can have a major impact on patients' well-being, especially if the fasting state has to be continued for several hours after drug administration. Further, oral administration of drugs can be problematic for those who cannot swallow whole tablets. This may be particularly relevant in patients with some advanced cancers such as head and neck cancer or esophageal cancer, or in

pediatric patients. Therefore, development of an alternative oral formulation could increase convenience of administration for patients. However, any alternative formulation should be tested clinically first to demonstrate that it achieves appropriate pharmacokinetic exposure.

We report on two randomized, open-label, cross-over studies evaluating the effect of administration with or without a high calorie meal, and the effect of administration as a liquid dispersion on the pharmacokinetics of the novel FAK- inhibitor BI 853520. These pharmacokinetic studies were part of a larger phase I dose-finding trial.

PATIENTS AND METHODS

Patients

Patients were eligible for enrollment into the expansion cohorts of the phase I dose-finding study of BI 853520 (NCT01335269) if they had a confirmed diagnosis of advanced, measurable or evaluable, non-resectable and/or metastatic non-hematologic malignancy and disease progression in the last 6 months before study entry as demonstrated by serial imaging. Patients needed to have failed conventional treatment or be unamenable to established treatment options, or have no proven therapy available to them. Moreover, patients needed to have an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1, have recovered from reversible toxicities (alopecia excluded) from prior anti-cancer therapies (Common Terminology Criteria for Adverse Events grade <2), be at least 18 years of age, and have a life expectancy of at least 3 months.

The main exclusion criteria were serious concomitant illness, active infections, pregnancy, breastfeeding, active or symptomatic brain metastases, second malignancies, congestive heart failure of grade III or IV, myocardial infarction within 6 months of inclusion, absolute neutrophil count <1500/mm3, platelet count <100,000/mm3, total bilirubin >1.5 times the upper limit of normal (ULN), and aspartate transferase and/or alanine transferase >3 times ULN or >5 times ULN in patients with liver metastases.

Study design

An overview of the design of both studies is provided in Figure 1. The effect of food on the pharmacokinetics of BI 853520 was investigated in a randomized, open-label, cross-over, single-dose study in patients with advanced solid tumors. Patients received a single 200 mg tablet of BI 853520 either in a fed or fasted state (see details of the conditions of drug administration below) with a wash-out period of 7 days between each administration. The order of fasted-fed or fed-fasted was established through randomization.

The pharmacokinetics of a single 200 mg dose of BI 853520 in a liquid dispersion were evaluated in a separate study with the same randomized, open-label, cross-over design using the 200 mg tablet as reference. The order of administration (liquid-tablet or tablet-liquid) was randomized and a 7-day wash-out period applied as described above.

After the last pharmacokinetic sample of each pharmacokinetic study, patients continued treatment with a daily dose of 200 mg BI 853520 until disease progression, intolerability of the study medication or withdrawal of consent.

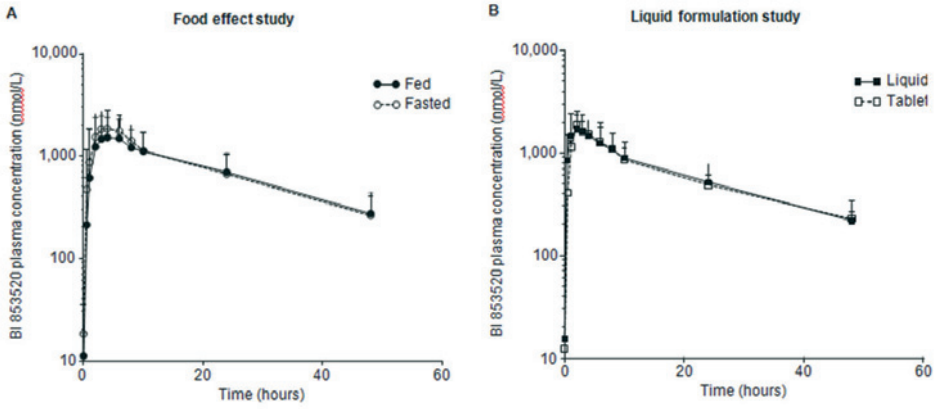


Figure 1. Schematic of randomized, open-label, cross-over trials to evaluate the effect of food and formulation on the pharmacokinetics of a 200 mg dose of the FAK-inhibitor BI 853520.

The order of administration (fasted-fed vs fed-fasted [panel A] or tablet-liquid vs liquid-tablet [panel B]) was randomized (R), and a wash-out period of 1 week applied between the two treatments. After the pharmacokinetic studies, patients continued on a daily dose of 200 mg BI 853520 (as a tablet) until disease progression, intolerability of the study medication or withdrawal of consent

Drug administration

In the food-effect study, BI 853520 was administered after an overnight fast, either with approximately 240 mL of water or with a standardized high calorie meal. No food was allowed for 4 hours after intake of the drug. Water was allowed 1 hour after taking the drug. The high calorie meal was a high-fat breakfast containing approximately 950 kilocalories (at least half of which were from fat) and was ingested within no more than 30 minutes. Directly after the meal, the single 200 mg tablet of BI 853520 was administered.

In the tablet versus liquid formulation study, patients received BI 853520 in a fasted state, as described above. Patients remained fasted for 4 hours after intake of the drug. The liquid formulation was prepared by dissolution of the tablet in 20 mL of a reconstitution solution containing sucralose (4 mg/mL), menthol (2 mg/mL), and benzoic acid (1 mg/mL). The tablet was submersed in the solution in a child-resistant screw-cap bottle, without being crushed. The bottle was then closed and shaken thoroughly for 30 seconds. After shaking, the bottle was set aside for 10 minutes. If the tablet was not dispersed completely, the bottle would be shaken for another 30 seconds and set aside for 5 minutes. This procedure was repeated until the tablet was dispersed completely into a homogeneous dispersion without noticeable lumps. No further dilution of the dispersion was allowed.

Pharmacokinetic sampling

In both studies, blood samples were collected before and at 0.5, 1, 2, 3, 4, 6, 8, 10, 24, and 48 hours after drug administration. Plasma concentrations of BI 853520 were measured by validated assays based on liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). The lower limit of detection for the assay was 1 nmol/L for plasma.

Data analysis

Based on the plasma concentration–time curves, pharmacokinetic parameters were calculated using non-compartmental analysis. Parameters of interest were time to maximum plasma concentration (T_{max}), maximum plasma concentration (C_{max}), AUC calculated from 0 to 48 hours and extrapolated to infinity ($AUC_{0–48}$ and AUC0–∞ respectively), and plasma half-life ($T_{1/2}$).

The 90% confidence interval (CI) was calculated for the ratio of the geometric mean (GMR) C_{max}, AUC0–∞ and $AUC_{0–48}$ for a 200 mg dose under fed and fasted conditions, and for the 200 mg tablet and liquid formulation. In each study, only patients with valid data for both treatment states (fasted and fed) or both formulations (liquid and tablet) were included in calculation of the ratio. Lack of difference was demonstrated if the 90% CI of the GMRs of C_{max}, AUC0–∞ and $AUC_{0–48}$ were within the 80–125% limits, in accordance with Food and Drug Administration (FDA) guidelines for food effect and bioequivalence studies.[28,29]

Reasons for exclusion from the pharmacokinetic analysis included vomiting within 4 hours after ingestion, failure to take the full BI 853520 dose, and expired sample stability.

Trial conduct and registry

This trial was conducted in accordance with the WHO Declaration of Helsinki and Good Clinical Practices. All patients provided written informed consent before enrollment, in

accordance with International Conference on Harmonization Good Clinical Practice and local legislation. This trial was registered in the United States National Institutes of Health clinical trial registry under the ClinicalTrials.gov identifier: NCT01335269.

Table 1. Characteristics of evaluable patients in both studies

	Food effect study	Liquid formulation study
Patient, *n* Gender, *n* (%)	15	16
Male	5 (33.3)	8 (50.0)
Female	10 (66.6)	8 (50.0)
Mean age, years [range]	56 [25–72]	60 [55–89]
Mean weight, kg (CV)	70 (24.5)	71 (15.3)
Mean height, cm (CV) Tumor type, *n* (%)	169 (6.6)	172 (5.9)
Soft tissue sarcoma	11 (73.3)	-
Esophageal carcinoma	-	6 (37.5)
Pancreatic adenocarcinoma	2 (13.3)	4 (25.0)
Ovarian carcinoma	1 (6.7)	6 (37.5)
Other	1 (6.7)	-

RESULTS

In total, 16 patients were enrolled in both studies and patient characteristics are presented in Table 1. In the food effect study, 15 patients were evaluable for treatment in at least one state (fed or fasted), and one plasma concentration–time profile was excluded for one patient due to vomiting after drug administration. In the liquid-tablet study, all 16 patients were evaluable for treatment with at least one dose (liquid or tablet) of BI 853520 and one plasma concentration–time profile was excluded for one patient due to incomplete drug administration.

Food effect

Plasma concentration–time curves of patients receiving 200 mg of BI 853520 under fed and fasted conditions are presented in Figure 2. The plasma profile of BI 853520 was not markedly influenced by concomitant administration of the high-calorie meal. A summary of the pharmacokinetic parameters of interest is provided in Table 2. The GMRs (90% CIs) for the fed versus fasted state were 0.95 (0.77–1.19), 0.96 (0.77–1.19) and 0.92 (0.76–1.11)

for AUC_{0-48}, AUC0–∞ and C_{max}, respectively (Figure 3). All 90% Cis crossed the lower of the 80–125% boundaries. T_{max} and $T_{1/2}$ of BI 853520 administered after a high calorie meal were not different to those in fasted patients.

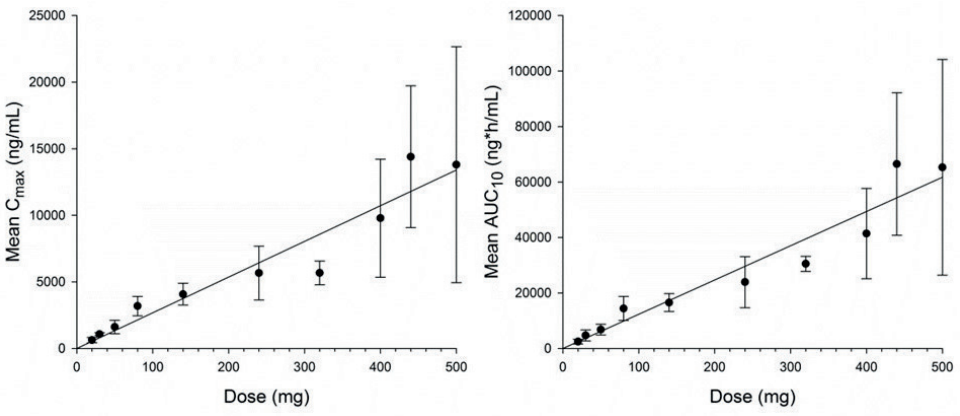


Figure 2. Plasma concentration–time curves for BI 853520 (200 mg) in the food effect and liquid formulation studies.
Mean plus standard deviation of the plasma concentration–time curves for a 200 mg BI 853520 tablet administered to patients in a fed and fasted state (panel A) and a 200 mg dose of BI 853520 administered as a liquid dispersion and tablet (panel B).

Table 2. Pharmacokinetic parameters for a 200 mg tablet of BI 853520 administered under fasted and fed conditions.

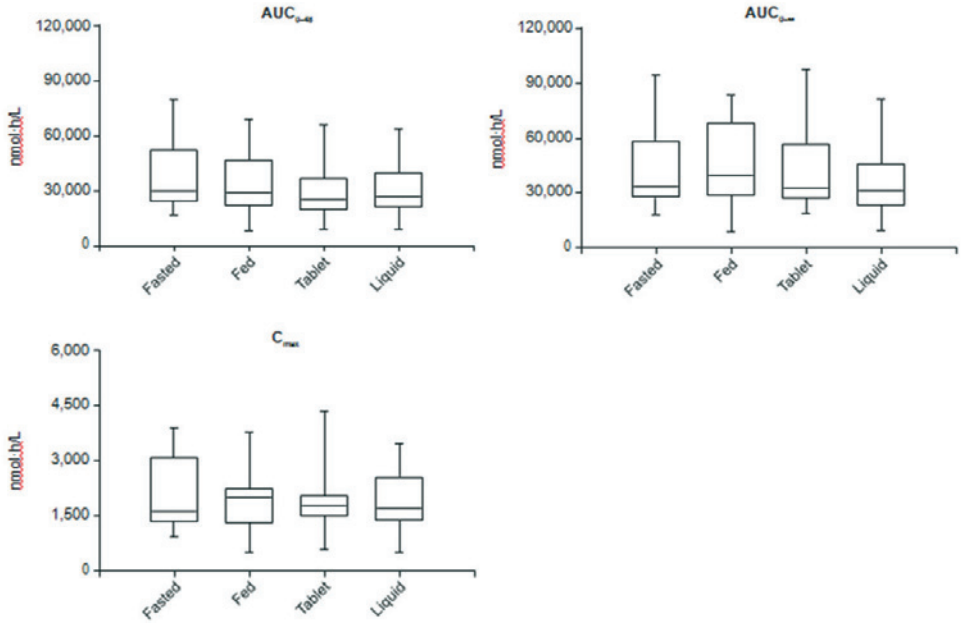
	Fasted	Fed	Ratio[a]
Patients, *n*	15	14	-
T_{max} [b]	3 [1–6]	4 [1–24]	-
AUC_{0-48}, nmol·h/L	33,300 (47.8)	30,700 (65.2)	0.95 [0.77–1.19]
AUC0–∞, nmol·h/L	39,700 (49.4)	38,900 (65.3)	0.96 [0.77–1.19]
C_{max}, nmol/L	1,860 (52.1)	1,630 (68.6)	0.92 [0.76–1.11]
$T_{1/2}$, h	18.0 (22.6)	18.0 (16.1)	-

- = not calculated. AUC0–∞ = area under the plasma concentration-time curve of the analyte in plasma over time interval 0 to infinity; AUC_{0-48} = area under the concentration-time curve of the analyte in plasma over time interval 0 to 48 hours; C_{max} = maximum plasma concentration; $T_{1/2}$ = terminal half-life; T_{max} = time of maximum plasma concentration.
Unless otherwise specified, data are presented as geometric mean and coefficient of variation (%).
a Geometric means of fasted/fed ratio [90% confidence interval]. Only data from patients evaluable in both treatment administrations were included (*n* = 14).
b Median [range].

Table 3. Pharmacokinetic parameters of 200 mg BI 853520 administered as a tablet or liquid formulation.

	Tablet	Liquid	Ratio[a]
Patients, *n*	16	14	-
T_{max} [b]	2 [1–6]	2 [1–6]	-
AUC_{0-48}, nmol·h/L	26,600 (54.5)	27,300 (56.5)	1.00 [0.92–1.09]
AUC0–∞, nmol·h/L	32,200 (56.5)	32,600 (59.3)	0.98 [0.90–1.07]
C_{max}, nmol/L	1,740 (55.0)	1,620 (57.1)	0.93 [0.86–1.01]
$T_{1/2}$, h	19.5 (16.4)	18.4 (22.7)	-

- = not calculated. AUC0–∞ = area under the plasma concentration-time curve of the analyte in plasma over time interval 0 to infinity; AUC_{0-48} = area under the concentration-time curve of the analyte in plasma over time interval 0 to 48 hours; C_{max} = maximum plasma concentration; $T_{1/2}$ = terminal half-life; T_{max} = time of maximum plasma concentration.
Unless otherwise specified, data are presented as geometric mean and coefficient of variation (%).
a Geometric means of fasted/fed ratio [90% confidence interval]. Only data from patients evaluable in both treatment administrations were included (*n* = 14).
b Median [range].



t 3. AUC_{0-48}, AUC0–∞ and C_{max} of BI 853520 (200 mg) in the food effect and liquid formulation studies.

Boxplots of area under the plasma concentration–time curve (AUC) from 0 to 48 hours (AUC_{0-48}) and extrapolated to infinity (AUC0–∞), and the maximum plasma concentration of BI 853520 (C_{max}) following a single 200 mg dose administered as a liquid or tablet in the liquid formulation study, and under fed or fasted conditions (both as a tablet) in the food effect study.

Liquid formulation

Plasma concentration–time curves for the liquid formulation study are provided in Figure 2. Calculated parameters for the pharmacokinetics of the liquid dispersion and tablet are presented in Table 3. T_{max} and $T_{1/2}$ were not affected by dispersing BI 853520 in a liquid. GMRs (90% CIs) of $AUC_{0–48}$, AUC0–∞ and C_{max} for the liquid versus tablet formulation were 0.98 (0.90–1.07), 1.00 (0.92–1.09) and 0.93 (0.86–1.01), respectively (Figure 3). All 90% CIs were within the 80–125% limits, indicating no statistically significant impact on pharmacokinetic exposure.

DISCUSSION

The possible effects of food and formulation (liquid dispersion vs tablet) on pharmacokinetic parameters of BI 853520 were assessed in two randomized, open- label, cross-over pharmacokinetic studies. A total of 16 patients were planned for enrollment in each study. This planned sample size was not based on a power calculation, but was judged to be appropriate to achieve the aims of this exploratory sub-study, and as being adequate to provide a minimum of 12 evaluable patients for the analysis, as required by FDA guidance.

The plasma profile, T_{max} and $T_{1/2}$ of BI 853520, when taken after a high-calorie meal, was not markedly different from that in fasted patients. The 90% CI for the GMRs of the $AUC_{0–48}$, AUC0–∞ and C_{max} all crossed the lower of the 80–125% boundaries. However, we do not consider the reductions to result in clinically meaningful differences in exposure. Our data, therefore, seem to support the view that BI 853520 may be administered orally without the need for stringent conditions regarding food intake.

Administration of BI 853520 after dispersion of the tablet in a reconstitution solvent did not significantly impact any pharmacokinetic parameters. None of the 90% CIs of the calculated pharmacokinetic parameters crossed the predefined 80– 125% limits. This indicates that the bioavailability of BI 853520 is unaffected by liquid dispersion and supports the use of the reconstitution liquid to facilitate drug administration in patients who have problems swallowing. Overall, the pharmacokinetic profile of BI 853520 was favorable and unlikely to be influenced by the type of formulation or concomitant administration with food. These properties will allow for a patient friendly posology, without strict requirements for administration under fasted conditions. In addition, administration of BI 853520 as a liquid dispersion may be particularly convenient for patients who experience problems swallowing, or for pediatric patients.

In conclusion, these randomized, open-label, cross-over studies indicate no significant effect of liquid dispersion on the pharmacokinetics of BI 853520, and only a minimal effect after a high calorie meal. These favorable pharmacokinetic properties contribute to the convenience and flexibility of the posology of BI 853520.

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PART II

Patients' perspectives

CHAPTER 5

Evaluation of Patient Enrollment in Oncology Phase I Clinical Trials

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ABSTRACT

Introduction. For anticancer drug development, it is crucial that patients participate in early-phase clinical trials. The main aim of this study was to gain insight into the motivations and other variables influencing patients in their decision to participate in phase I oncology trials.

Materials and Methods. Over a period of 25 months, all patients who were informed about (specific) phase I trials in our cancer center were retrospectively included in this study. Data on providing informed consent and final phase I enrollment were collected.

Results. In total, 365 patients, with a median age of 59 years and a median World Health Organization performance status score of 1, were evaluated. The majority of patients (71%) were pretreated with systemic therapy, with a median of two lines. After specific study information had been given, 145 patients (40%) declined informed consent, 54% of them mainly because of low expectations regarding treatment benefits and concerns about potential side effects. Patients who had received previous systemic therapy consented more frequently than others. After initial consent, 61 patients (17%) still did not receive study treatment, mostly because of secondary withdrawal of consent or rapid clinical deterioration prior to first dosing.

Discussion. After specific referral to our hospital for participation in early clinical trials, only 44% of all patients who were informed about a specific phase I trial eventually participated. Reasons for both participation and nonparticipation were diverse. Patient participation rates could be improved by forming an experienced and dedicated study team.

INTRODUCTION

Cancer is the leading cause of death in all developed countries, and therefore the development and subsequent clinical testing of new and better anticancer agents remain important.[1] Clinical drug development requires participation of cancer patients in clinical trials, the magnitude of which is well known to be far from optimal. Phase I clinical studies are performed in patients with advanced disease for whom standard approaches have either failed or do not exist.[2] Therefore, these patients may have received earlier lines of palliative systemic therapy, or any other form of palliative therapy, but they could also be treatment naïve. The primary aim of phase I studies is to determine the safety profile of a new agent (or a new combination). Antitumor effects are analyzed as a secondary endpoint, but the expected therapeutic benefit for the participating patient is relatively limited.[3-5] As a consequence, recruiting patients for early-phase clinical trials is a challenge. Historically, the elderly and people with a lower socioeconomic status participate less in clinical trials.[6-9] There is some controversy about the participation rate of minorities.[10] In 1993, the U.S. Food and Drug Administration retracted their 1977 policy that prohibited the participation of females of childbearing potential in phase I and early phase II trials. However, women are still underrepresented in phase I clinical trials, although their participation rate has increased in the last decade.[7]

The reasons for patients to give or deny informed consent to undergo experimental therapy are multifactorial. The facts that limited or no other treatment options exist and that life expectancy is uncertain render the phase I population a vulnerable group.[11,12] In addition, early-phase clinical trial participation is quite demanding for patients.[13] Several studies have indicated that, despite the fact that patients are adequately informed that trial participation is unlikely to offer them clinical benefit, hope for remission or even a cure of the disease is an important incentive to participate in early clinical trials.[14-16] Usually, altruistic reasons do not play an important role.[17] The decision to give consent is also influenced by the attitude of physicians and patients' relatives in the informed consent process, the contents of informed consent forms, past involvement in anticancer treatments, and attitude towards living with cancer.[18-22] Reasons for denying informed consent have rarely been investigated,[23] although perceived understanding may play a role.[24,25]

Whereas many have reported outcome data from phase I populations, recruitment and enrollment data from phase I trials have rarely been reported. Here, we report on an institutional assessment of patient motives and other variables influencing patient enrollment into phase I oncology trials.

MATERIALS AND METHODS

Patients

For 25 months (October 2008 to November 2010), all patients visiting the Erasmus University Medical Center, Daniel den Hoed Cancer Center outpatient clinic of medical oncology who received information about a specific phase I trial were retrospectively included in this study (Table 1). During the study period, 19 phase I trials were open for inclusion at our center (Table 2). In the Netherlands, nine centers, equally distributed throughout the country (Figure 1), offer early clinical trials in oncology. Two of them are exclusive cancer centers, including our center. The Dutch health care system is freely accessible for every patient, and all residents are mandatorily insured for health care costs. Therefore, economic reasons to participate in a trial are probably negligible.

All patients enrolled were specifically referred for trial participation because no (standard) treatment options were deemed to be available (any longer) to them. Patients were seen by a medical oncologist or a fellow to discuss treatment options and potential trial participation. Both general and specific phase I trial information was provided verbally and in writing, the latter by means of an institutional review board (IRB)-approved informed consent form. Subsequently, at the next visit, they were seen by a clinician or nurse practitioner to discuss participation in a specific phase I trial. Consent or refusal of consent was discussed during this appointment, within a median of 9 days after the first visit. For patients ultimately participating in multiple phase I trials during the period of the study, only the first informed consent procedure was considered for the present analysis.

Phase I Trial Characteristics

All phase I trials involved were open to patients with diverse histological types of solid tumors. Several phase I trials investigated combinations of drugs, and some combined systemic therapy with hyperthermia and radiation (Table 2). In seven trials, participating patients had to be hospitalized for more than two nights, whereas in one trial patients had to visit the hospital daily for 5 days per week for four consecutive weeks. Phase I trial screening investigations included a physical examination, (routine) laboratory tests, electrocardiograms and baseline radiological examinations (computed tomography or magnetic resonance imaging [MRI] scans). Additional investigations performed during trial participation included pharmacokinetic, pharmacodynamic, and pharmacogenetic sampling, hair collection, tumor and/or skin biopsies, dynamic enhanced MRI, and serial ophthalmologic examinations. The effort of undergoing these investigations was scored by oncologists and a nurse practitioner on a three-level Likert scale as: 1, small effort; 2, moderate effort; 3, big effort (Table 2).[26]

Table 1. Patient characteristics and demographics (n = 365)

Characteristic			**n (%)**
Median age, years (range)			59 (18-78)
Sex			
Male			**188** (52%)
Female			**177** (48%)
Marital status			
Single			**32** (9%)
Married / relationship			**308** (84%)
Separated / divorced / widowed			**25** (7%)
Distance to hospital			
0 – 50 km			**232** (64%)
50 – 150 km			**114** (31%)
≥ 150 km[a]			**19** (5%)
Referral			
Internal			
	Surgery		**28** (8%)
	Otolaryngology		**9** (3%)
	Gynaecology		**7** (2)
	Gastroenterology & Hepatology		**7** (2%)
	Pulmonology		**4** (1%)
	Other[b]		**6** (1%)
External			
	Local hospital		**158** (43%)
	Academic center		**19** (5%)
	Other[c]		**3** (1%)
Own population (medical oncology)			**124** (34%)
Tumor Classification			
Digestive Tract	*Upper*[d]		**103** (28%)
	Lower[e]	**62** (17%)	
Female Genital Organs			**44** (12%)
Urinary Tract			**27** (7%)
Breast			**24** (7%)
Skin			**21** (6%)
Unknown Primary sites			**20** (5%)
Bone and Soft Tissue			**17** (5%)
Head and Neck			**14** (4%)
Male Genital Organs			**14** (4%)
Lower Respiratory System			**11** (3%)

Table 1. (continued)

Characteristic	n (%)
Eye and Orbita	**3** (1%)
Other sites[f]	**3** (1%)
Endocrine Glands	**2** (1%)
Number of prior systemic therapies (both regular and experimental therapies)	
0	**106** (29%)
1	**124** (34%)
2	**74** (20%)
3	**35** (10%)
4-7[g]	**26** (7%)
Prior experimental therapies (phase I)	
No	**335** (92%)
Yes	**30** (8%)
WHO performance status at (not) signing informed consent	
0	**62** (17%)
1	**189** (52%)
2	**11** (3%)
≥ 3[h]	**5** (1%)
Unknown	**98** (27%)
Signed informed consent	
Yes	**220** (60%)
No	**145** (40%)
Participation (after signing informed consent)	
Yes	**159** (72%; 44% of total population)
No	**61** (28%; 17% of total population)

(a) Range ≥ *150km: 158 – 266. (b)* Endocrinology (2), Ophthalmology (2), Internal Medicine (1), Orthopedic Surgery (1). *(c)* Family doctor (1), through company which offers body scan (1), unknown (1). (*d)* Upper digestive organs: esophagus, cardia, stomach, liver, gallbladder, (tail / head of) pancreas. *(e)* Lower digestive organs: coecum, sigmoid, colon, rectum, small intestine, anus. *(f)* Other tumor sites: thymoma (1), solitary fibrous tumor (1), two different malignancies (both ACUP and mamma carcinoma) (1). *(g)* Prior systemic therapies: 4 (19), 5 (4), 6 (2), 7 (1). *(h)* WHO performance status: 3 (3), 4 (1), 5 (1) patient died due to an accident in his home.
Note: due to rounding, percentages may not add up to 100%.

Table 2. Overview of phase I trial characteristics from start screening to first tumor evaluation

	No. of phase I trial																		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Treatment																			
Single experimental agent						x	x	x	x	x		x		x			x		
Combination therapy, with ≥1 approved agent	x	x	x	x	x						x		x		x	x		x	x
Hospital visits																			
1 visit/week	x	x		x				x	x	x	x	x	x		x	x	x	x	x
≥ 2 visits/week			x		x	x	x							x					
Length hospitalisation																			
0-2 successive nights/cycle		x		x	x	x			x	x		x			x	x	x	x	x
≥ 3 successive nights/cycle	x		x				x	x			x		x	x					
Additional investigations per protocol [a]																			
Blood samples for pharmacokinetics and dynamics (1) [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x
Urine samples (1) [b]			x			x	x	x	x					x		x			
Extra ECG's (1) [b]		x				x			x			x					x		
Hair samples (1) [b]								x											
Skin biopsy (2) [b]														x			x		
Tumor biopsy (3) [b]									x								x		
MUGA-scan (2) [b]		x							x	x				x			x		x
MRI contrast (2) [b]		x																	
PET-scan (2) [b]																	x		
Audiogram (1) [b]							x												
Holter analysis (2) [b]		x																	
Visit to ophthalmologist or cardiologist (1) [b]		x												x					

[a] Standard investigations including screening laboratory tests, baseline ECG, and CT scans are not specified in this table.
[b] Burden of additional tests between brackets; *(1)*: small effort, *(2)*: moderate effort, *(3)*: big effort.

Figure 1. Actual living places of referred patients in the Netherlands and Belgium, based on postal codes.

Patients were classified according to their informed consent status: patients who did not sign informed consent (red circles), patients who signed informed consent and participated (green circles), and patients who signed informed consent, but finally did not start therapy (orange circles).

Data Collection

Variables were collected from electronic patient charts. This electronic system was specifically designed to describe the medical history of cancer patients. The collected variables were: referral source (other departments of our hospital—internal, other hospitals—external, own department of medical oncology—own cancer population), tumor classification using the International Classification of Diseases (10th revision),[27] date of primary diagnosis, number of prior systemic anticancer treatments, number of prior systemic experimental treatments, World Health Organization (WHO) performance status (PS) score at the start of the informed consent period and at the final consent decision, age, gender, marital status, distance from home to the hospital, written informed consent, and eligibility for a specific proposed phase I trial. The following variables for all phase I studies were analyzed: tumor type, number of pages on consent form, and complexity of the trial. Complexity during the first two courses of treatment was defined by the number of hospital visits and the duration of hospitalization. Also, the number of studied agents and the type of agent (an experimental compound or registered drug for other indications) were studied. In addition, the required numbers and types of invasive procedures were analyzed. Patient charts were meticulously scrutinized in order to interpret patients' motives for nonparticipation, and their motives were categorized into groups.

Statistical Analysis

Data were first compared between patients who did and those who did not give informed consent to participate in a phase I trial. The Pearson's $\chi 2$ test or Fisher's exact test, as appropriate, was used to compare discrete data between the two groups, and the Wilcoxon rank sum test (Mann-Whitney U-test) was used for continuous data. Next, the same analyses were performed but restricted to patients who gave informed consent, and the data were then compared between patients who did and those who did not start treatment within a phase I trial.

RESULTS

Patient Characteristics

In total, 365 patients (188 men and 177 women) with a median age of 59 years (range, 18–78 years) were included (Table 1). External patients were referred by general hospitals from all over the country, but mostly from the Rotterdam (Southwest Netherlands) region (Figure 1). The median distance between the patient's home and our cancer center was 31 km (range, 1–266 km). Most tumors originated from the gastrointestinal tract (45%). The majority of patients were pretreated with systemic therapy, with a median of two lines of

treatment (range, 1–7). Patients without pretreatment were those with tumors for which no standard treatment options were considered to be available. The approach to include them in phase I trials is in line with the recommendations of the Dutch Society for Medical Oncology and is standard practice in The Netherlands. Only 8% of patients had previously participated in another phase I trial before October 2008. At the decisive moment of signing or not signing the informed consent form, most patients had a WHO PS score of 0 or 1. Despite being an inclusion criterion for most studies, PS was not yet formally scored for 98 patients. The vast majority of this specific group of patients (>90%) eventually ended up not participating, because of patient refusal in 63%.

Recruitment and Participation

Figure 2 shows the consecutive steps of the process from the informed consent procedure until the actual start of the phase I study treatment. Despite their specific referral, 145 patients (40%) refused or were not eligible for study participation.

The most frequently mentioned reasons for not consenting to participate in a study were: (a) patient refusal (78 patients, 54%); (b) physiological reasons, mostly clinical deterioration and formal ineligibility according to protocol at the time of the informed consent visit (39 patients, 27%); and (c) being offered alternative palliative treatment options (most often radiotherapy, not in the context of a phase I trial; 27 patients, 19%). Patients refused study participation for various reasons, such as low expectations regarding treatment benefit, concern about side effects, and, after being given detailed information about a specific trial, not wishing to be exposed to an experimental agent. Both a declining clinical condition and a currently excellent condition were mentioned by individual patients as reasons not to participate.

Of the 220 (60%) patients who provided informed consent, 52 (14%) were found to be unable to start study participation. Rapid clinical deterioration occurred in 12 patients and 40 patients were found to be ineligible as a result of specific inclusion and exclusion criteria that were assessed after informed consent was given.

Finally, a small group of nine eligible patients (2%) did not commence study participation either because of late withdrawal of consent or the need for urgent palliative treatment modalities, such as radiation for pain control. As a consequence, only 44% of the initial population actually undertook phase I study participation.

Reason not signed	Details	No. (%)
Clinical	Not eligible according to protocol (at screening visit)	26 (18)
	Clinical deterioration	13 (9)
Other treatment options	Radiotherapy (6), other systemic treatment (16), other experimental therapy (5)	27 (19)
Patient refusal		78 (54)
	Benefit expectation too low, side effects risk too high	14 (10)
	Poor physical condition	9 (6)
	No wish for treatment with experimental medicine	8 (6)
	Concern for negative impact on quality of life	7 (5)
	Feels fine	5 (3)
	Travel distance to hospital	4 (3)
	Number of hospital visits	3 (2)
	Other (a)	3 (2)
	Reason unknown	25 (17)
Other reason	*b)*	1 (1)

Reason not eligible	No. (%)
Not eligible according to protocol	40 (77)
Clinical deterioration	12 (23)

Reason not started	No. (%)
Patient refusal (distance to hospital)	1 (11)
Patient refusal (reason unknown)	2 (22)
Other treatment *(c)*	5 (56)
Other reason *(d)*	1 (11)

(a) 1 patient preferred to take care of his/her terminal ill life; 1 patient was not able to understand the complexity of the trial; 1 patient refused every form of treatment. (b) Patient died due to other causes. (c) Radiotherapy (2), other systemic treatment (3). (d) Not possible to participate due to forgotten appointment by patient.

Figure 2 Pie-graphs of patients receiving a patient information form (top pie, N=365) and their decision to sign informed consent (second pie), their eligibility after signing (third pie), and their final ability to start in a specific phase I trial (bottom pie). Detailed reasons for not signing (red part), not being eligible (orange part) and finally not starting (light yellow) are given in the text of the figure.

Table 3. Comparison of patient characteristics for signing informed consent and participation rate (N = 365)

	Did not give informed consent, n (% by row)	**Gave informed consent, n (% by row)**	***p-value***	**No participation after signing, n (% by row)**	**Participation after signing, n (% by row)**	***p-value***
n	**145**	**220**		61	159	
Median age, years	60	59	*0.594*	58	59	*0.644*
Range	18-78	25-78		30-76	25-78	
Sex			0.158			*0.688*
Male	82 (43%)	107 (57%)		31 (29%)	76 (71%)	
Female	64 (36%)	113 (64%)		30 (27%)	83 (73%)	
Marital status			0.786			*0.457*
Single	14 (44%)	18 (56%)		6 (33%)	12 (66%)	
Married / relationship	120 (39%)	188 (61%)		53 (28%)	135 (72%)	
Separated / divorced / widowed	11 (44%)	14 (56%)		2 (14%)	12 (86%)	
Distance to hospital			0.954			*0.929*
> 50 km	94 (40%)	140 (60%)		40 (29%)	100 (71%)	
50 – 150 km	44 (39%)	68 (61%)		18 (26%)	50 (74%)	
≥ 150 km	7 (37%)	12 (63%)		3 (25%)	9 (75%)	
Referral			0.016			*0.252*
Internal	30 (49%)	31 (51%)		5 (16%)	26 (84%)	
External	78 (43%)	102 (57%)		32 (31%)	70 (69%)	
Own population	38 (30%)	87 (70%)		24 (28%)	63 (72%)	
Number of prior systemic therapies			<0.001			*0.109*
0	57 (54%)	49 (46%)		11 (22%)	38 (78%)	
1 or more	88 (34%)	171 (66%)		50 (29%)	121 (71%)	
Prior phase I participation			0.055			*0.759*
Yes	7 (23%)	23 (77%)		7 (30%)	16 (70%)	
No	138 (41%)	197 (59%)		54 (27%)	143 (73%)	
WHO performance at decisive moment of informed consent						
0	8 (13%)	78 (87%)		6 (11%)	49 (89%)	
1	47 (25%)	142 (75%)		41 (29%)	101 (71%)	
2	9 (82%)	2 (18%)		1 (50%)	1 (50%)	
≥ 3	5 (100%)	0 (0%)		0 (0%)	0 (0%)	
Unknown	77 (79%)	21 (21%)		13 (62%)	8 (38%)	

Comparison of Variables

Sixty-six percent of patients who had received previous systemic therapy consented to participate, versus 46% of those who had not received systemic therapy before ($p < .001$). In addition, patients referred for phase I participation by external hospitals and by other internal departments provided informed consent less frequently than those who had already visited our medical oncology outpatient clinic ($p = .016$) (Table 3). The design of trials, that is, the number of agents, number of hospital visits per week, number of nights in the hospital per cycle, and burden of additional investigations, did not differ significantly between patients who did and those who did not give informed consent for study participation (Table 4). Moreover, age, marital status, sex, distance to the hospital (Fig. 1), and tumor type classification were not found to be decisive factors.

Table 4. Comparison of phase I trial characteristics from start screening to first tumor evaluation (N=365)

	Did not give informed consent, n (% by row)	**Gave informed consent, n (% by row)**		**No participation after signing, n (% by row)**	**Participation after signing, n (% by row)**	***p-value***
n	145	220		61	159	
Treatment			0.631			0.156
Single experimental agent	57 (41%)	81 (59%)		27 (31%)	54 (69%)	
Combination therapy, with ≥1 approved agent	88 (39%)	139 (61%)		34 (18%)	105 (82%)	
Hospital visits			0.298			0.067
1 visit/week	118 (41%)	169 (59%)		52 (32%)	117 (68%)	
≥ 2 visits/week	27 (35%)	51 (65%)		9 (21%)	42 (79%)	
Length hospitalisation			0.722			0.071
0-2 successive nights/cycle	91 (40%)	134 (60%)		43 (33%)	91 (67%)	
≥ 3 successive nights/cycle	54 (39%)	86 (61%)		18 (24%)	68 (76%)	
Effort score additional investigations			0.580			0.171
Score of 0-1	57 (46%)	67 (54%)		16 (24%)	51 (76%)	
Score of 2-3	36 (30%)	83 (70%)		21 (25%)	62 (75%)	
Score of ≥ 7	52 (43%)	70 (57%)		24 (34%)	46 (66%)	

DISCUSSION

After specific referral for participation in phase I trials and provision of the IRB consent form of a specific phase I trial, more than half of the patients in this analysis ultimately did not consent to study participation or were found to be ineligible. Previous studies from the Royal Marsden Hospital in London, U.K.,[28] and the Princess Margaret Hospital in Toronto, Canada,[29] reported participation rates of 32% and 30%, respectively. However, in those studies, the population consisted of all patients referred for phase I treatment, whereas in our analysis only the group of patients receiving an IRB consent form were taken into account.

The reasons why patients denied consent were in line with the previous literature.[23-25,29] A rapid decline in clinical condition as well as a stable and well-maintained clinical condition were reasons for patients to reject informed consent. From a patient perspective, no ideal moment for trial participation can be mentioned because individual motives influence the best moment in the course of their disease.

Because information and participation preferences can possibly change over time,[30] patients who felt very well and did not consent because of that could potentially opt for study participation later on in the course of their disease. Several patients were disappointed with the quoted expected benefits or were concerned about potential side effects. Others were concerned that frequent hospital visits would interfere with their quality of life, which is of particular relevance given the limited life expectancy of these patients.

Only a small number of patients mentioned that a long travel distance to the hospital was a reason not to consent. This is encouraging because phase I trials are not, and never will be, available in every local hospital because of their academic nature. Interestingly, prior systemic treatment exposure was positively correlated with phase I study participation. Whether this can be explained by positive experiences with previous therapies, familiarity with the department, or other reasons remains largely unknown.[19] Patients' trust in the clinical study team may be an asset in the context of their willingness to participate. The fact that a higher percentage of the patient population previously treated at our own institute decided to participate in a study could support this hypothesis. Similar findings were also observed at the Princess Margaret Hospital, where patients who were referred from their own hospital consented to study participation more often.[29] However, the relationship with, or feeling of dependency toward, caregivers might also play a role here. An impression that research participation is strongly encouraged could be an additional

factor. The potential relationship between familiarity with a certain department and other motives for participation are currently being prospectively assessed at our department using standardized questionnaires (Dutch Trial Registry number NTR3354).

In contrast to earlier data showing that females are underrepresented in phase I trials, the numbers of participating men and women were almost equal in our department. One of the possible explanations for this could be an increasing number of female cancer patients for whom no standard treatment options remain. Another explanation could be that patients are increasingly aware of data suggesting the potential benefit of phase I drugs in specific female cancers (i.e., ovarian, uterine, and cervical cancer).[31]

Quite a large number of patients did not meet one or more specific inclusion and exclusion criteria. Clinical deterioration over time is a limiting barrier for both patients and investigators. The availability of an objective prognostic score that enables discrimination between patients with probable rapid deterioration and those with a true survival time >3 months—an inclusion criterion for most phase I studies—could prove to be a useful tool in the decision-making process of phase I study participation.[32-34] Still, a number of patients who gave informed consent and were willing to participate in a study eventually could not partake because they were found to have become ineligible during prestudy procedures that were performed after the informed consent form had been signed. We believe that this could have been disappointing for patients, but because of the many regulations accompanying and preceding clinical trial enrollment this, to a certain extent, may well be unavoidable. Nonetheless, in some cases, we feel that this kind of disappointment could have been prevented by better education among subinvestigators and by the use of a dedicated and experienced study team.

A limitation of our study is the fact that the results were obtained retrospectively. As a result, clinicians did not use standardized questionnaires to document reasons for participation or refusal thereof and the interpretation of some of the patients' motives may have influenced the results of this analysis. Another limitation of the current dataset is the absence of information about patients who could not participate in a phase I study because of a lack of available study slots. One of the barriers to finding new treatments against cancer[35,36] is a shortage of available studies. Cooperation among medical centers in performing early clinical studies could increase the number of available studies. By further specialization and understanding the motivation of patients and the characteristics of these patients, these centers may also improve their aiding in the decision-making process.

Implications for practice

Clinical drug development is the basis for the further evolution of the field of medical oncology. The early phases of drug development are especially important for testing new compounds, because in these phases, pharmacokinetic endpoints and pharmacodynamic endpoints (toxicity and efficacy) are studied for the first time in a clinical setting. It is, therefore, essential to encourage patients to participate in early clinical trials, despite the potentially limited benefits for themselves. This can only be done in an adequate way if those patients are understood correctly for their motives and other reasons why they do or do not want to participate. In our opinion, the current inclusion rate is disappointingly low, despite specific referral to those trials. Based on our study results, patient incentives are clarified, which could help to improve the inclusion rate in early clinical trials in the future.

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CHAPTER 6

Understanding how Coping Strategies and Quality of Life maintain Hope in Patients deliberating Phase-I Trial Participation

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ABSTRACT

Objectives. This study aimed to understand how hope and motivation of patients considering phase-I trial participation are affected by psychological factors such as coping strategies and locus of control (LoC), and general well-being as measured by the quality of life (QoL).

Methods. An exploratory cross-sectional study was performed in patients with incurable cancer (*N*=135) referred to our phase-I unit for the first time. Patients were potentially eligible for phase-I trial participation and participated in our study while deliberating phase-I trial participation. We used questionnaires on hope, motivation to participate, coping, LoC, and QoL. To investigate the nature and magnitude of the relationships between the scales, a structural equation modeling (SEM) was fitted to the data.

Results. Hope significantly predicted the motivation to participate in phase-I trials. Predictors of hope were a combination of flexible and tenacious goal pursuit (both $p<0.01$), internal LoC ($p<0.01$), and QoL ($p<0.01$). The SEM showed an exact fit to the data, using a null hypothesis significance test: *chi-square* (8)=9.30, $p=0.32$.

Conclusions. Patients considering phase-I trial participation seem to use a pact of tenacious and flexible coping, and control to stay hopeful. Furthermore, hope and QoL positively affected each other. The psychological pact may promote an adaptation enabling them to adjust to difficult circumstances by unconsciously ignoring information, called dissonance reduction. This mechanism may impair their ability to provide a valid informed consent. We suggest including a systematic exploration of patients' social context and values before proposing a phase-I trial.

INTRODUCTION

Patients with advanced or incurable solid tumors, with a good performance status, can opt for studies that test novel cancer drugs.[1] The main goals of these phase-I trials are to determine the recommended dose and safety profile of the new agent or combination of agents. The secondary endpoint is efficacy. By definition, insufficient information is available about a potential anti-tumor effect. Patients may struggle to decide whether to engage in a treatment with unknown efficacy, benefit, and side effects, or to opt solely for symptom-oriented palliative care.[2] During this deliberation their mindset may help them deal with this choice by setting goals.[3] Mindset represents people's personal attitudes which influence their goals and behavior.[4] Equally, physicians face the difficult decision whether to offer a phase-I trial to their patients and how to answer patients' questions, not knowing whether the experiment is worthwhile.[5-8]

Only 2-7% of the patients with cancer participate in clinical trials.[1] This lack of enthusiasm for trial participation could hamper finding new and better cancer treatments. Nevertheless, a minority of the patients with cancer are highly motivated to embark on this journey.[2,8-14] Thus, motivation to participate in trials affects health decision behavior. Moreover, motivation may contribute to why patients direct their efforts and goals to concrete actions such as phase-I trial involvement.[15] Understanding which factors affect motivation may enable us to develop a realistic view on proper patient selection for phase-I trials.

A recent review shows that the motivation to participate in clinical trials is multi-causal and depends on structural, social and personal factors.[16] Moreover, several studies showed that the personal motivation of patients participating in phase-I trials was characterized by the hope of therapeutic benefit.[8,10,12,14,17] Therefore, motivation to participate is a complex composition of several factors that are both derived from the patients' context and patient-intrinsic factors.

In the list of potential psychological factors affecting motivation hope stands out as the central theme.[12,18] Hope can be viewed as a positive strength for a particular thing to happen and we know that it represents a complex multidimensional emotion and co-occurs with optimism.[18] Patients with advanced or recurrent cancer who have exhausted all lines of treatment and opt for phase-I trial participation, can be regarded as palliative patients, according to the World Health Organization definition. Hope in palliative patients can be viewed from a narrative, realistic and functional perspectives.[19] The functional perspective interprets hope as a coping strategy which helps patients dealing with the impact of the disease and protects them against the development of mental distress.[18,20]

Additionally, when treatment options are sparse or not available, considering phase-I trial participation may represent a health crisis.[21] This crisis, facing a life-threatening situation, can trigger two modes of coping: tenacious goal pursuit (tenacity) and flexible goal adjustment (flexibility).[21] Patients who use tenacity, try to modify their circumstances in order to fulfill their personal preferences. In contrast, patients who use flexibility adapt their personal preferences to the new situation. In both coping strategies, another psychological factor, the sense of control, can play a role.

Locus of control (LoC) refers to the extent to which people believe their lives can be controlled by external factors (such as doctors) or internal factors (themselves).[22] One may assume that palliative patients with cancer, who feel their outcomes can be influenced by active treatment, will consider participation in a clinical trial when other options seem unavailable. Moreover, both internal LoC and flexibility are associated with hopefulness, optimism, and a better quality of life (QoL).[20,23]

Therefore, coping and internal LoC are hypothesized to constitute the main factors that could explain hope in this setting. Furthermore, we assessed their correlations with QoL, since this is an important patient-related outcome. A better understanding of this mindset could improve the way we select and assist palliative patients with cancer during the informed consent procedure and coach them during trial participation. In the current study, we aimed to unravel how hope and the motivation were correlated and were influenced by psychological factors such as coping strategies, LoC, and by QoL in patients considering phase-I trial participation.

MATERIALS AND METHODS

Study design

An exploratory cross-sectional study was performed investigating the relationships between motivation, hope, coping, LoC, and QoL during the predecisional period of a phase-I study. Patients were referred to our phase-I unit and were potentially eligible for trial participation. The other inclusion criteria were: first phase-I trial proposal, ≥ 18 years, and able to speak and read Dutch. The study was performed at the department of Medical Oncology at the Erasmus MC Cancer Institute in Rotterdam, the Netherlands, between April 2011 and July 2013. The study was approved by the institutional review board and registered at the Dutch Trial Registry.

Participants

At the first visit, all patients enrolled were seen by a medical oncologist (MO) to discuss treatment options and palliative options and received general phase-I trial information. A national mandatory brochure on medical-scientific research was issued.

When an option for participation in a specific trial occurred, the patient was informed by the MO Information was provided about the phase-I trial and this study, both verbally and in writing, by means of an institutional review board approved informed consent form. The patients were asked to read the information and to complete the questionnaire at home. A telephone number of a nurse practitioner (NP) was included if any questions should arise.

At the consent visit, usually one week later, the patients could discuss their options in order to decide on participation. The research nurse provided the practical information about the trial. The MO or NP answered questions about medical perspectives of the trial. A medical assessment was included. Subsequently, the patients were asked to return the questionnaire form and give written informed consent

The goal of the consent procedure, which can consist of several visits, is to give patients adequate disclosure about phase-I trials, assessing comprehension, and correcting errors in understanding. Although it is not meant to influence the patient, it may affect hope and subsequently their decision.[14,24]

Measures

Patients provided information on education and marital status. Information was collected from the electronic medical record about sex, age, cancer diagnosis, time since diagnosis, performance status, consent to a phase-I study, type of study, and reasons for denying consent.

The questionnaire consisted of 5 validated components:[22,25-28]

The Dutch version of the Herth Hope Index measures a global, non-time oriented sense of hope.[25] Hope is a fundamental psychological need. It affects motivation and coping strategies.[29]

Motivation was measured based on the transtheoretical motivation model of Prochaska and DiClemente measuring the active phase of motivation as a single construct.[26,30]

The translated assimilation and accommodation coping-scale (AACS) was used to measure coping and consist of two scale. One scale for measuring tenacity and one for measuring flexibility.[31]

The LoC construct is an element of self-regulation and links with motivation.[29] People with an internal LoC are generally more motivated and believe that their own actions determine the goals that they obtain. Those with an external LoC believe that their goals in life are outside of their control. It was measured with the Rotter LoC questionnaire.[22]

The global QoL was measured with the Dutch version of the EORTC QLQ-C30, version 3.0.[28] The time frame of the questions is the previous week. Additional information of the components is outlined in Table 1.

Statistical analyses

Patients' demographics, clinical characteristics, and questionnaires were summarized using descriptive statistics. The data were analyzed using IBM SPSS Statistics 21.0 for Windows.

We examined the internal consistency of the questionnaires and performed an additional reliability analysis on the motivation questionnaire.[26] The correlations between motivation, hope, flexibility and tenacity, internal and external LoC and global QoL were explored using two-tailed Pearson Correlation analyses. To investigate the magnitude and direction of the relationships, a structural equation model (SEM) was drawn with the statistical software package Amos 18. SEM is often used in social sciences to explore covariance structures and causal models, including confirmatory factor analysis, structural regression, and path models. The relationships in the model were hypothesized based on the correlation outcomes. In the SEM, β represent the magnitude of a relationship between the questionnaire outcomes. The general consensus is that there is a large effect if $\beta > 0.25$.[32]

A SEM is acceptable if the appropriate statistical tests are met to establish a 'good model fit'. To evaluate this model fit, the following statistical tests, the so-called 'fit indices', were used and are independent of sample size:[32]

- Normal Fit Index (NFI) analyzed the differences between the chi-squared value of the hypothesized model and the chi-squared value of the null model
- Comparative Fit Index (CFI) analyzed the model fit by examining the differences between the data and the hypothesized model
- Tucker-Lewis Index (TLI) sorts out negative bias
- Root Mean Square Error of Approximation (RMSEA) analyzed the differences between the hypothesized model and the sample covariance matrix

Table 1. The Survey Questionnaire

Components	Scales based on:	Sample questions	No of items	Score	IC[a] Cronbach's alpha *(& validity)*	Ref
Hope	Herth Hope Index	I have a positive outlook toward life. I have a deep inner strength. I believe that each day has potential.	12	4-point Likert scale The higher the score, the higher the hope. One question deleted following Dutch standard [25] Sum score divided by number of questions	0.78	25
Motivation	Motivation model of Prochaska and DiClemente	I think it's good to be here. I know how to deal with my problems. I talk with other people about my treatment.	12	Dichotomized in 'yes' and 'no' Sum score divided by number of questions	0.79 *(The validity and reliability of the questionnaire showed an adequate factor solution, and a good reliability after deletion of three questions)*	30
Coping	The assimilation and accommodation coping-scale. The AACS consists of 2 subscales: - TGP - FGA	I find it easy to see something positive even in a serious mishap. I create many problems for myself because of my high demands. When faced with obstacles, I usually double my efforts. I find it easy to give up on a goal if it seems difficult to achieve.	15 TPG 16 FGA	5-point Likert scale 0 = "I do not agree" to 4 = "I totally agree" Sum score divided by number of questions High score subscale TGP associates with tenacity/assimilation High score subscale FGA associates with flexibility/accommodation Sum score divided by number of questions	TGP 0.84 FGA 0.72	27
Locus of control	Rotter LoC	My life is determined by how I behave. Many of the unhappy things in people's lives are party due to bad luck. What happened to me is mainly caused by others	10 extern LoC 7 internal LoC	5-point Likert scale 1 = "strongly disagree" to 5 = "strongly agree" High score associated with high outcome subscale	Extern 0.77 Intern 0.77	22
Global quality of life	EORTC QLQ-C30, version 3.0 Global QoL	How would you rate your overall health during the past week? How would you rate your overall quality of life during the past week?	2	7-point modified linear analog scale ranging from 1 = "very poor" to 7 = "excellent". The raw score was standardized by applying linear transformation.	0.89	28

Abbreviations: IC[a], internal consistency, [a] internal consistency i.e. reliability, was determined using Cronbach's alpha (α), this is acceptable between $0.8 > \alpha \geq 0.7$ and good between $0.9 > \alpha \geq 0.8$; AACS, assimilation and accommodation coping-scale; TGP, tenacious goal pursuit; FGA, flexible goal adjustment; QoL, quality of life; Ref, References.

Table 2. Patients characteristics (n = 135)

Characteristic	Value
Age, mean ± standard deviation (range), y	61.8 ± 10.3 (31-84)
Sex, No. (%)	
Male	65 (48.1)
Female	70 (51.8)
Marital status, No. (%)	
Married / living with partner	112 (82.9)
Single / Separated / divorced / widowed	23 (17.0)
Education level, No. (%)	
Primary education	19 (14.1)
High school or college	78 (57.8)
University	34 (25.1)
Other or unknown	4 (3.0)
Time since diagnose, (range), y	2.3 years (0 - 16,8)
Tumor Classification, No. (%)	
Breast	9 (6.6)
Gastrointestinal	51 (37.7)
Gynecological	29 (21.5)
Lung	7 (5.1)
All others	39 (28.8)
WHO performance status at (not) signing informed consent, No. (%)	
0	24 (17.8)
1	106 (78.5)
2	3 (2.2)
≥3	1 (0.7)
Unknown	1 (0.7)
Phase I trials (No = 18), No. (%)	
Single experimental agent (no = 8)	75 (55.5)
Combination therapy, with 1 approved agent (no = 10)	59 (43.7)
None,	1(0.7)
Signed informed consent for phase I trial participation, No. (%)	
Yes	125 (92.6)
No	10 (7.4)
Start in phase I trial after consent (N = 125), No. (%)	
Yes	103 (82.4)
No	22 (17.6)

Abbreviations: No., number; WHO, World Health Organization

The following cut-off values are indicative for 'good model fit': NFI and CFI>0.90, TLI>0.95 and RMSEA<0.06. The chi-square was selected as the likelihood ratio and is acceptable if the chi-square is *non-significant.*[32]

Due to the low numbers of patients who declined phase-I trial participation, the intercorrelation measures between patients who gave consent and refuse participation were not performed.

RESULTS

Patient Characteristics

The patient characteristics are summarized in Table 2. A total of 145 patients were asked to complete the survey. The survey was completed by 135 patients. Ten patients (7%) did not consent to phase-I study participation (figure S).

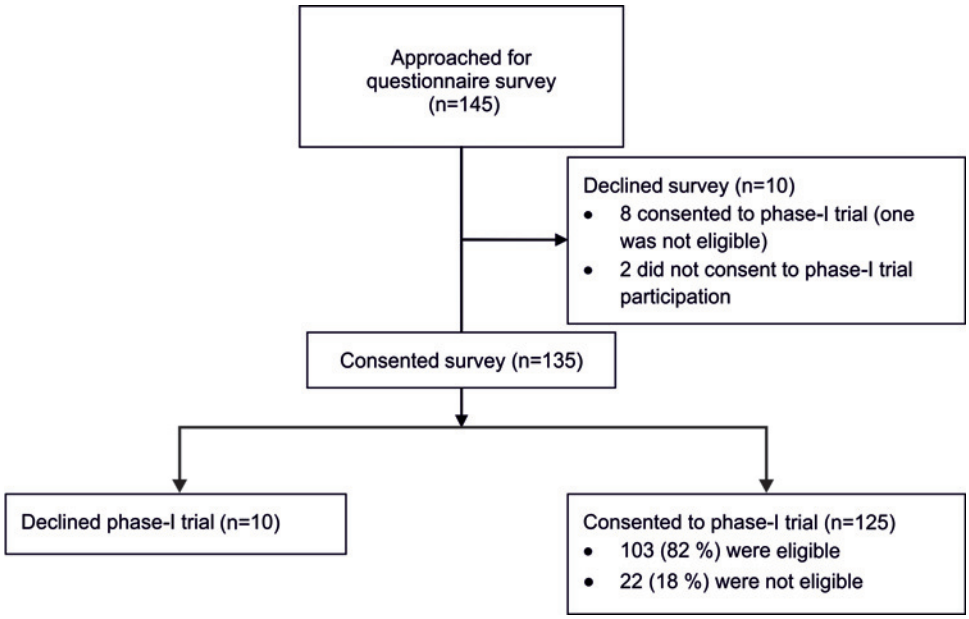

Figure S. Consort flow chart of inclusion

Table 3 shows the descriptive statistics of the questionnaires outcomes of consenting and declining. The validity and reliability measurements of the questionnaires are described in Table 1.

Table 3. Descriptive Statistics Questionnaires Outcomes

	Signed informed consent Mean (SD)	Declined informed consent Mean (SD)
n	125	10
Motivation	0.55 (0.29)	0.34 (0.31)
Hope	3.13 (0.33)	3.16 (0.22)
Coping Flexibility	3.71 (0.34)	3.62 (0.36)
Coping Tenacity	3.42 (0.44)	3.27 (0.67)
LoC, intern	3.23 (0.45)	3.23 (0.74)
LoC, extern	2.43 (0.48)	2.22 (0.47)
Global QoI	69.9 (17.4)	60.8 (25.8)

Abbreviations: SD, standard deviation; LoC, locus of control; QoL, quality of life

Treatment Motivation Model

The SEM demonstrated significant relationships with large effect sizes, where hope had a central place (Figure 1a). Motivation was the dependent variable and positively correlated with hope *(r=0.38, p<0.01)* (Table 4). No other variables directly influenced motivation in the best fitting SEM. This suggests that hope predicted for motivation *(β=0.30)*. The SEM showed an exact fit to the data: NFI=0.95, CFI=0.99, TLI=0.97, RMSEA=0.04, and *chi-square (8)=9.30, p=0.32*.

Hope

The psychological factors that positively correlated with hope were tenacity *(r=0.54, p<0.01)*, flexibility *(r=0.51, p<0.01)* and, to a lesser extent, internal LoC *(r=0.32, p<0.01)* (Table 3). In the model, hope had strong relationships with the psychological factors tenacious and flexible coping *(β=0.52),* and internal LoC *(β=0.28)* (Figure 1a).

Psychological factors

Flexibility and tenacity positively correlated with each other *(r=0.32, p<0.01)* and in the model they were strongly related to each other *(β=0.36)*. Moreover, in the model flexibility *(β=0.52)* and tenacity *(β=0.52)* both formed strong relationships with hope. Internal LoC and flexibility were positively correlated *(r=0.45, p<0.01)* and in this dataset internal LoC and

tenacity were also positively correlated *(r=0.32, p<0.01)*. There were strong relationships of internal LoC with flexibility *(β=0.41)*, tenacity *(β=0.37)*, and with hope (β=0.*28)*. This suggests that the psychological factors form a strong pact in maintaining hope.

External LoC negatively correlated with hope *(r=-0.23, p<0.05)*, tenacity *(r=-0.25,, p<0.05)* and with flexibility *(r=-0.28, p<0.01)*. The model suggested a negative regression between external LoC and tenacity *(β=-0.34)*, flexibility *(β=-0.31)*, and hope *(β=-0.28)* (Table 4 and Figure 1a).

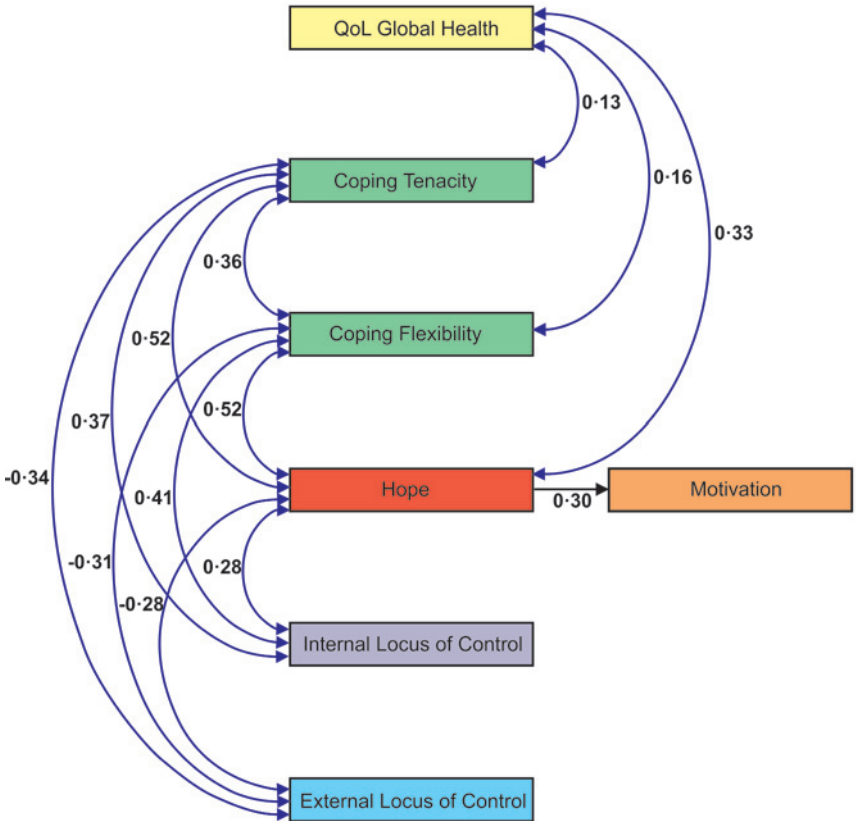

Figure 1a. SEM 'motivation' model of patients with cancer during the phase-I trial study deliberation.

The rectangles represent observed variables, in this case, the questionnaire outcomes. The one-headed arrow indicates a directional relationship between two variables. The two-headed arrow indicates covariation between two variables. The number above, under or next to the arrow represents the relationship β. Probability level ***chi-square(8)=9.30, p=0.32.***

Quality of life

Next, we analyzed the effects of global QoL on hope and psychological factors. Global QoL was found to be correlated *(r=0.49, p<0.01)* and strongly related with hope *(β=0.33)*.

The correlation between global QoL and flexibility (*r=0.24, p<0.05)* and tenacity (*r=0.24, p<0.05)* were less strong, but still significant. In the model, we saw a small relationship between global QoL and flexibility *(β=0.16)* and tenacity *(β=0.13)*. However, this relationship between global QoL and flexibility and tenacity remained of importance to establish a good model fitting. We saw no correlation with or direct effect on global QoL of either LoC scores (Table 4 and Figure 1a).

Table 4. Correlations in Patients Consenting to Phase-I Trial

n = 125	Motivation	Hope	Flexibility	Tenacity	LoC intern	LoC extern	Global QoL
Motivation	1						
Hope	**.38****	1					
Flexibility	**.22***	**.51****	1				
Tenacity	**.37****	**.54****	**.32****	1			
LoC intern	**.15**	**.32****	**.45****	**.29****	1		
LoC extern	**-.23***	**-.23***	**-.28****	**-.25***	.12	1	
Global Qol	-.09	**.49****	**.24***	**.33****	.08	-.10	1

* p<0,05,** p <0,01 (two-tailed significance). LoC, locus of control; QoL, quality of life

DISCUSSION

This study was designed to investigate the mindset of patients with end-stage cancer deliberating phase-I trial participation. Our findings demonstrated that the strong relationship of internal LoC with the combined coping strategies form a strong pact in promoting hope. Furthermore, our data makes it plausible that from a functional point of view, hope represents a basic psychological need and is the motivator for participation (Figure 1b).[18, 19, 29] Personal benefit and other motivators may also play a role in this complex decision making process.[8, 10-12, 16, 17, 24, 33] The nature of these coping strategies may endorse the idea that altruism plays a less prominent role in phase-I trial participation.[34]

This psychological pact supports the theory of the deliberative mindset during the predecisional period.[3] This theory supposes that patients take control of their situation by setting the goal of trial participation and this decision supports the maintenance of

an optimistic outlook on life. [20, 35] Subsequently, in our findings hope, tenacity, and QoL positively influence each other. Therefore, the opportunity of trial participation can be considered as a factor that supports personal well-being in motivated patients.[36]

Yet, keeping control and looking for treatment options beyond standard care suggests a specific psychological adaptation, called dissonance reduction.[37] This is a process that unintentionally discounts threatening information, such as the fatal prognosis of the disease and the lack of treatment options. This information bias may be associated with a dispositional positive outlook of life and not so much with misunderstanding the goals of phase-I trials.[18, 35] Our findings support the outcomes of Nierop.[18] Their findings show that patients maintain hopeful by the perception of engaging in early clinical trials and to a lesser extent by their expectation of the outcomes of these trials.[18] It could also explain why patients' expectation about outcomes did not differ after receiving extensive comprehensive information about the phase-I trial and why their view about anticipated effort improved, by Dolly.[14] For patients, phase-I trial participation can be seen as a protective strategy which makes it possible to handle the reality of a terminal disease.[33, 38] Additionally, these adaptive strategies seem useful in bearing this irremediable situation and keeping a positive scope in life.[18]

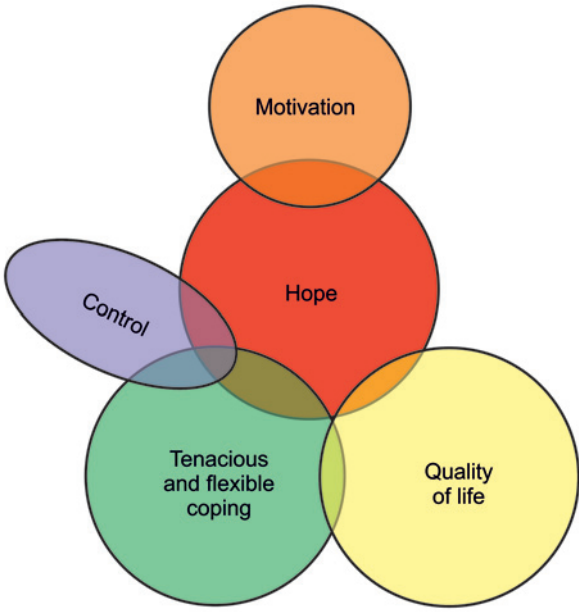

Figure 1b. Summary of the 'motivation' model of patients with cancer during phase-I trial study deliberation

Nevertheless, the results of this survey raise some ethical concerns. For healthcare professionals, promoting hope in patients could conflict with patients' autonomy in the decision whether or not to consent to a phase-I trial.[39] Patients' autonomy can be understood in various ways.[40] From a philosophical view, autonomy can be acknowledged as the capacity of living a life based on reflective values, defined as patients' most important goals at that moment in time.[31] According to this approach, respecting patients' autonomy does not necessarily require that hope is based on an adequate understanding of the evidence. However, participating in a study should be in line with their values.[18]

Study limitation

This study has several limitations. Firstly, a better insight into the psychological mindset of patients during the predecisional period would have been obtained if the study had focused more on the group patients who declined phase-I trial participation. This proved impossible in our research population. Secondly, the motivation questionnaire can be questioned since it was not developed for our population and dichotomized. Yet, validity and reliability measurements on our population were acceptable (Table 1). Furthermore, the patients who declined had lower outcomes of motivation. Thirdly, our outcomes might also have been influenced by the fact that the survey was conducted in a single center, although it has a long history of conducting drug development studies.[24] The perspectives of hope and coping strategies are just a few of the numerous aspects which affect trial participation. For example, trial organization and social context also influence patients' autonomy and their treatment decisions.[16] Additional research in a larger population and in several centers could contribute to a greater understanding of the motivation of these patients. And it may confirm our findings.

Clinical implications

Our research showed that patients deliberating phase-I trial participation are motived by hope and that this hope had strong relationships with coping strategies such as tenacious coping, flexible coping and keeping control. In addition, we saw a positive correlation between hope and QoL. These findings should be taken into account when we inform and support palliative patients with cancer considering phase-I trial participation. Moreover, we propose to conduct a patient-centered moral deliberation, consisting of a systematic and reflective method to explore patients' perspectives, social context, and values. This may help palliative patients with cancer to make an appropriate decision when considering phase-I trial participation.

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CHAPTER 7

Self-reported Quality of Life and Hope in Phase I trial participants.: An Observational Prospective Cohort study

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ABSTRACT

For advanced cancer patients deliberating early clinical trial participation, adequate information about expected effect on quality of life (HRQoL) and hope, may support decision making. The aim was to assess the potential relation of HRQoL to eligibility for phase I trial participation, and to observe the variations in patient-reported outcomes. Patients completed questionnaires at pre-consent (n=124), baseline (n=96), and after first evaluation of a phase I trial (n=76). The Mann-Whitney U test was used to test differences between eligible and ineligible patients. Univariate logistic regression was performed for eligibility. Factorial repeated-measures ANOVA compared the outcomes of patients continuing versus stopping participation after first evaluation over time. Eligibility is associated with significant better global health OR=0.946, 95% CI [0.918, 0.975], *p*=0.001, physical-functioning OR=0.959, 95% CI [0.933, 0.985], *p*=0.002, role-functioning OR=0.974, 95% CI [0.957, 0.991], and better appetite OR=1.114 95% CI [1.035, 1.192]. HRQoL outcomes like global health, social-functioning, and appetite decline in all patients and differ between patients continuing or having to end participation. Over time, hope and tenacity decline in all patients, and coping strategies alter in patients stopping participation. Trial participation influences patient-reported outcomes. Global health may predict for eligibility and trial continuation. Informing patients could affect patients' decision making.

INTRODUCTION

Patients with advanced cancer who have exhausted their regular treatment options may consider participation in early-phase clinical trials. Dose-finding is the primary goal of phase I trials and efficacy is unknown. Therefore, it is important to inform patients about expected effects of trial participation.[1] This should not only be based on the biological background of the investigated compound, but also based on the general impact of trial participation affecting daily life.

Another issue in oncology phase I clinical trial conduct is how to safeguard the palliative care for patients enrolled in such trials.[2,3] The systematic assessment of patient-related outcomes (PROs), such as health-related quality of life (HRQoL) and symptoms scores, could help to improve the delivery of adequate palliative care for patients with cancer on trial.[4] Preliminary data of the randomized trial that integrated palliative care in phase I trial participation showed that patients on trial score low on the ability to work, have a lack of energy, and are worried about losing condition, dying, and losing hope.[4] Furthermore, research towards hope at pre-consent of phase I trial participation showed that hope was the central motivator for participation and positively interacted with HRQoL. Hope formed a pact with coping strategies, such as tenacious and flexible coping, and the feeling of being in control.[3]

Although most patients on trial are in a good condition, not all consenting patients are deemed to be fit to participate.[4,5,6] The early implementation of HRQoL could be used to improve the selection of patients entering trials.[7] Additionally, HRQoL might complement clinical prognostics scores like the Royal Marsden Hospital prognostic score (RMS).[8]

HRQoL is rarely investigated in potential phase I candidates.[4,5,9,10] Recent research in this field indicates that patients on trial who experience serious adverse events differ in baseline HRQoL from those who do not experience serious adverse events.[5] There is no association between baseline HRQoL and RMS.[5]

To be able to prepare and inform patients in an adequate way we prospectively collected self-reported HRQoL, hope, and coping strategies. The aim of this study was to assess the potential relation of HRQoL to eligibility for phase I trial participation. Furthermore, the changes in HRQoL, hope, and coping strategies were observed from pre-consent to the first evaluation of a phase I trial.

METHODS

Participants

This observational descriptive prospective cohort study was performed at the phase I Unit of the Department of Medical Oncology, at a University Hospital in the Netherlands. The participating patients were referred to our phase I unit for the first time. A total of 18 phase I trials were recruiting patients. All patients had advanced or metastatic cancer and were potentially eligible for trial participation. The additional inclusion criteria for this cohort study were: older than 18 years and being able to speak and read Dutch.

The study was approved by the institutional review board and registered at the Dutch Trial Registry. From each patient a written informed consent was obtained.

Procedures

During the informed consent procedure, patients were informed verbally about both phase I trial participation and the current study by their treating oncologist or the phase I trial oncologist. They received written information about both studies, including the questionnaire form. The verbal and written information was given in accordance with approval from the Medical Ethical Commission, which included that participation was voluntary and the patient could withdraw at any time. The scientific nature of this study was explained both verbally and on paper, and stated it was not part of the proposed phase I trial. In the following pre-decisional period, patients were asked to read the information and to complete the questionnaire at home. A telephone number of a nurse practitioner was included in case any questions would arise. At the informed consent visit, the patients discussed the phase I trial option with the oncologist or nurse practitioner and were asked to return the questionnaire (T1). After given informed consent for the clinical trial, a screening period followed, which may take up to a maximum of 28 days. The next questionnaire was planned at baseline (i.e. start phase I trial; T2). The last questionnaire followed after the first tumour evaluation visit, 6-8 weeks later (T3). Patients completed the questionnaire at T2 & T 3 at the outpatient clinic, during admission, or at home. They could return the questionnaire by mail.

Questionnaire and clinical information

Patients provided information about their gender, age, education, and marital status. In addition, information was collected about cancer diagnosis, time since diagnosis, WHO performance status, consent to a novel oncology drug study, type of study, reasons for denying consent to a study, eligibility and subsequent start in the phase I trial if applicable, and the outcome of the first evaluation of the experimental treatment.

The HRQoL was measured with the validated Dutch version of the EORTC QLQ-C30, version 3.0.[11,12] The time frame of the questions is the previous week. The questionnaire consists of five functional scales:

- physical functioning consisted of 5 items, for example 'Do you have any trouble taking a long walk?' and 'Do you need to stay in bed or a chair during the day?'
- emotional functioning had 4 items, among which 'Did you worry?' and 'Did you feel depressed?'
- role functioning had 2 items, 'Were you limited in doing either your work or other daily activities?' and 'Were you limited in pursuing your hobbies or other leisure time activities?'
- cognitive functioning had 2 items, 'Have you had difficulty in concentrating on things, like reading a newspaper or watching television?' and 'Have you had difficulty remembering things?'
- social functioning had 2 items, 'Has your physical condition or medical treatment interfered with your family life?' and 'Has your physical condition or medical treatment interfered with your social activities?'.

It also includes three symptoms scales on fatigue, nausea and vomiting, and pain. It contains six single items assessing dyspnoea, insomnia, loss of appetite, constipation, diarrhoea, and financial impact. Each item is scored on a 4-point scale ranging from 1, 'not at all' to 4, 'very much'. The outcomes were added by scale and divided by the number of questions. The raw score was standardized by applying linear transformation. The global health scale is scored on a 7-point modified linear analog scale ranging from 1, 'very poor' to 7, 'excellent'. A high score on the functional scales represents a high score of functioning, while a high score on the symptom scales represents a high level of symptom problems.

Hope was measured through the Dutch translated and validated version of the Herth Hope Index (HHI). The HHI measures a global, non-time oriented sense of hope.[13]

The translated assimilation and accommodation coping-scale (AACS) was used to measure coping. The AACS consists of two scales: one for Tenacious Goal Pursuit (tenacity) and one for Flexible Goal Adjustment (flexibility). Tenacity is connected to assimilation, where circumstances are transformed in accordance with personal preferences. Accommodative coping (flexibility), on the other hand, adjusts these preferences to the (new) situation.[14]

The Locus of Control (LoC) questionnaire measures generalized expectancies for internal versus external control. People with an internal LoC believe that their own actions determine

the goals that they obtain, while those with an external LoC believe that their goals in life are generally outside of their control.[15] Additional information of the components is described in an earlier paper.[3]

The RMS was categorized according to 3 variables: lactate dehydrogenase (LDH), normal (0) versus LDH >ULN=248 U/L (+1); albumin, ≥3.5 gram/decilitre (g/dL) (0) versus <3.5 g/dL (+1); and the number of metastatic sites of disease, ≤2 (0) versus >2 (+1).[16] After summing the value for each variable, the patients were assigned to a good prognostic group (0-1) or a poor prognostic group (2-3). For general comparison of our data we used the EORTC QLQ-C30 outcomes of 4812 patients with recurrent/metastatic cancer, based on EORTC data of 2011, as reference group.[17] The survival status of all patients was assessed on 31 May 2017, and the survival time was defined as the period between the consent visit and time of death or last follow-up.

Statistical analysis

Patients' demographics, clinical characteristics, and questionnaires were summarized, using descriptive statistics. The data were analysed with IBM SPSS Statistics 21.0 for Windows. A linear transformation was performed to standardize the raw scores of EORTC QLQ-C30. The standardized scores range from 0 to 100.[11,12]

Eligible versus ineligible patients

We compared the EORTC QLQ-30 of the eligible versus ineligible patients at the start of screening using the pre-consent data (T1). These comparisons were analysed by using the non-parametric Mann-Whitney U test. Univariate logistic regression analysis was used to study the relation between eligibility for phase I trial participation and the following variables at pre-consent: age, sex, marital state, WHO performance status, RMS, and the items of the EORTC QLQ-C30. Eligibility is defined as fulfilling the in- and exclusion criteria of a phase I trial and the actual participation in this trial. Correction for multiple testing was deemed necessary for the EORTC QLQ-C30 scales and items (15 in total), where the Bonferroni correction was applied and hence a p-value of <0.0033 was considered significant for both the non-parametric and logistic regression analyses.

Continuing versus stopping participation after first evaluation

Next, we compared the EORTC QLQ-30, hope, and coping strategies of the patients who were able to finish the questionnaires at all 3 time points. A factorial repeated-measures ANOVA was used to compare the data collected at T1, at baseline of the phase I trial (T2),

and first tumour evaluation (T3). In case the assumption of sphericity was violated (results not shown); the Huynh-Feldt correction was applied to the p-values. A *p*-value of <0.05 was considered significant without correction for multiple testing.

Overall survival

Overall survival was analysed by means of the Kaplan-Meier method, though is of descriptive nature. Besides description of OS from the consent visit onwards, also a landmark analysis was performed from start of phase I trial treatment (T2) until death.

RESULTS

A total of 135 patients of the 145 invited patients with advanced or metastatic cancer consented to this study (T1). Patient characteristics are summarized in Table 1. Ten patients (7%) did not consent to phase I trial participation and one patient did not fulfil the inclusion criteria.

A total of 124 patients started the screening of whom 101 (81%) were eligible for trial participation (Figure 1). At baseline (T2), 96 of the 124 screened patients completed the questionnaire. This includes both eligible patients (87 out of 101) and ineligible patients (9 out of 23).

After two cycles of treatment, the first tumour evaluation took place (T3). Fifty-three of the 60 eligible patients finished the questionnaire. Forty-one patients discontinued phase I trial participation due to disease progression or substantial side-effects. Of this group, 23 patients completed the questionnaire, making the total of participants at this stage of the study 76 (Figure 1).

The internal consistency i.e. reliability of the psychological questionnaires, HHI, AACS, and LoC, as measures by Cronbach's alpha were acceptable to good (Table 2).

Table 1. Patients characteristics (n = 135)

Characteristic	N (%)
Age (year), mean ± SD (range)	61.8 ± 10.4 (31-84)
Sex	
Male	64 (47.8)
Female	70 (52.2)
Marital status	
Married / living with partner	111 (82.8)
Single / Separated / divorced / widowed	23 (17.2)
Education level	
Primary education	18 (13.4)
High school or college	78 (58.3)
University	34 (25.4)
Other or unknown	4 (2.9)
Time since diagnose (year), mean ± SD (range)	2.3 ± 2.2 (0 – 16.8)
Tumour Classification	
Bone and Soft Tissue	9 (6.7)
Breast	9 (6.7)
Gastrointestinal	51 (38.0)
Gynaecological	29 (21.6)
All others	36 (26.8)
WHO performance status	
0	24 (17.9)
1	105 (78.4)
2	3 (2.2)
3	1 (0.7)
Phase I trials	
Single experimental agent	76 (56.7)
Combination therapy, with 1 approved agent	58 (43.3
RMH prognostic score	
0	77 (57.5)
1	47 (35.1)
2	9 (6.7)

Abbreviations: WHO = World Health Organization, RMH = Royal Marsden Hospital, SD = standard deviation

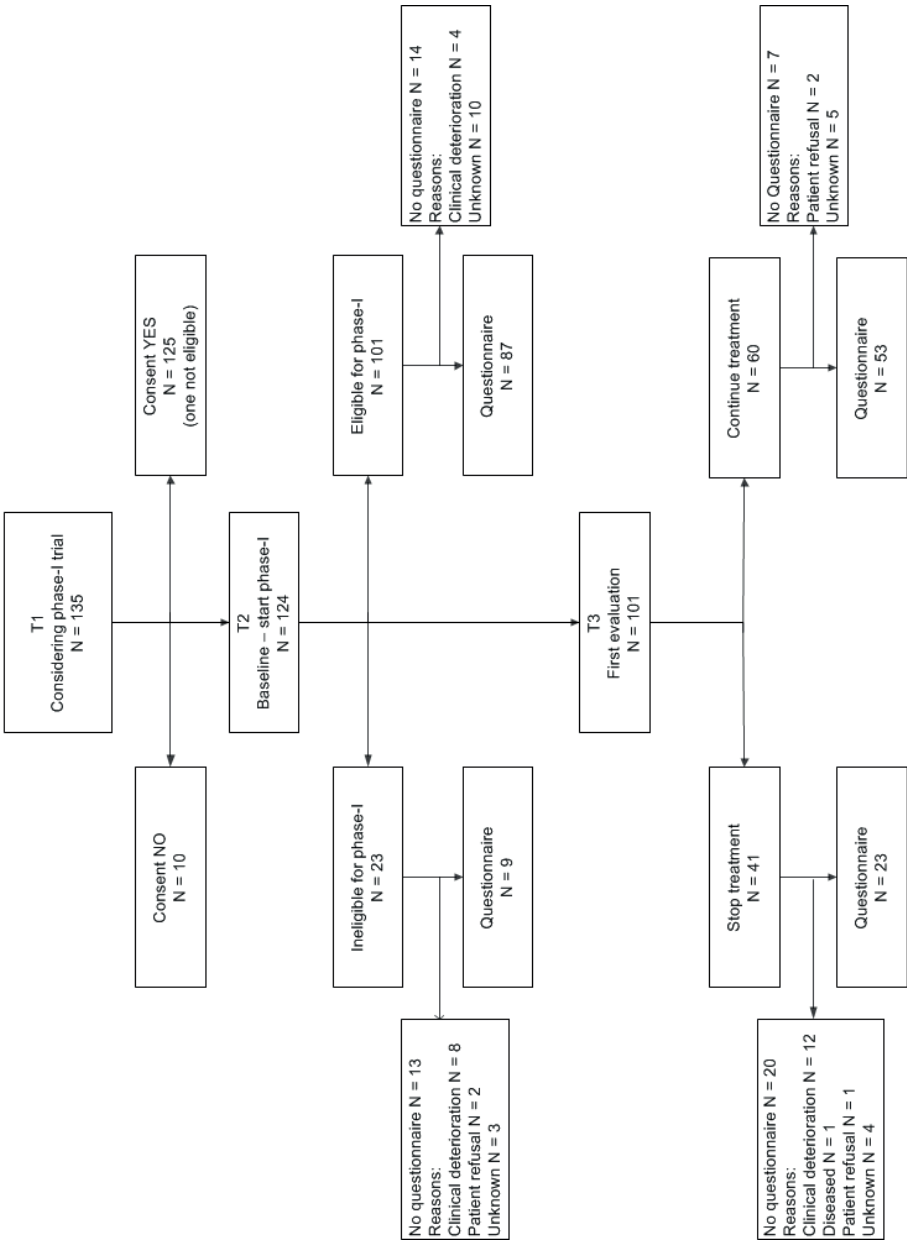

Figure 1. Strobe flowchart of patients consenting to cohort study

Table 2. Differences between eligible versus ineligible patients at pre-consent (T1)

	Pre-decisional (T1) Eligible at T2 Median (25-75 percentiles) N=101	**Pre-decisional (T1) Ineligible at T2 Median (25-75 percentiles) N=22**	**p**	**U**	**Z**	**r**	**d**
Global health status/ QoL	**75 (66.6-83.3)**	**50 (41.7-70.8)**	**0.001**	**555.00**	**-3.44**	**0.31**	**0.65**
Physical functioning	**86.7 (73.3-93.3)**	**70 (58.3-86.7)**	**0.002**	**637.00**	**-3.12**	**0.28**	**0.59**
Role functioning	**83.3 (66.7-100)**	**50 (33.3-66.7)**	**0.001**	**555.00**	**-3.40**	**0.31**	**0.64**
Emotional functioning	75 (66.7-91.7)	66.7 (58.3-79.2)	0.069	787.50	-1.82	0.26	0.33
Cognitive functioning	100 (83.3-100)	100 (79.2-100)	0.255	1232.00	1.14	0.10	0.21
Social functioning	83.3 (66.7-100)	66.7 (66.7-91.7)	0.008	685.50	-2.64	0.24	0.49
Fatigue	33.3 (11.1-44.4)	44.4 (33.3-61.1)	0.004	1469.00	2.91	0.26	0.54
Nausea and vomiting	0 (0-16.7)	16.7 (0-20.8)	0.035	1368.50	2.11	0.19	0.39
Pain	16.7 (0-33.3)	33.3 (16.7-58.3)	0.004	1450.50	2.92	0.26	0.55
Dyspnoea	0 (0-33.3)	33.3 (0-41.7)	0.043	1355.00	2.03	0.18	0.37
Insomnia	0 (0-33.3)	33.3 (0-41.7)	0.259	1244.00	1.13	0.10	0.20
Appetite loss	**0 (0-33.3)**	**33.3 (0-66.7)**	**<0.001**	**1560.00**	**3.67**	**0.33**	**0.70**
Constipation	0 (0-33.3)	0 (0-0)	0.294	967.50	-1.05	0.09	0.19
Diarrhoea	0 (0-0)	0 (0-16.7)	0.186	1166.50	1.32	0.12	0.24
Financial difficulties	0 (0-0)	0 (0-0)	0.500	980.50	-.68	0.06	0.12

Abbreviations: QoL= Quality of Life, *p*-values based on Mann-Whitney U test, U=Mann-Whitney U, Z=standardized Test Statisics, r=effect size using Cohen's *d* (0.10 = small effect, 0.24 = intermediate effect, 0.37 large effect), *d*=effect size d (0.2=small effect, 0.5=intermediate effect, 0.8=large effect). The bold items are significant at $p \leq 0.0033$.

Consenting versus non-consenting patients

Due to the small group of non-consenters, no statistical test was performed (Table 3).

Table 3. Univariate logistic regression analysis of independent variables at pre-consent (T1) versus ineligibilty at baseline (start of phase I trial).

		95% C.I.†		
Independent variables	**OR**	**lower**	**upper**	***p***
Age	1.054	1.000	1.110	0.049
Sex (male versus female)	0.632	0.254	1.573	0.324
Marital status (married versus single)	1.216	0.555	2.665	0.624
WHO 1 vs 0	1.486	0.398	5.540	0.556
RMS 1 vs 0	1.794	0.704	4.570	0.221
RMS 2 vs 0	0.792	0.089	7.089	0.835
Global Health	**0.946**	**0.918**	**0.975**	**0.001**
Physical Function	**0.959**	**0.933**	**0.985**	**0.002**
Role Function	**0.974**	**0.957**	**0.991**	**0.003**
Emotional Function	0.976	0.950	1.002	0.074
Cognitive Function	1.174	0.985	1.089	0.174
Social Function	0.972	0.950	0.993	0.011
Fatigue	1.031	1.009	1.054	0.007
Nausea and vomiting	1.022	1.000	1.045	0.049
Pain	1.031	1.010	1.052	0.004
Dyspnoea	1.021	1.003	1.040	0.025
Insomnia	1.008	0.993	1.023	0.280
Appetite Loss	**1.114**	**1.035**	**1.192**	**<0.001‡**
Constipation	0.987	0.961	1.013	0.317
Diarrhoea	1.012	0.984	1.042	0.403
Financial Difficulties	0.995	0.972	1.019	0.692

Abbreviations: C.I. = confidence interval, OR= odds ratio, †95% C.I. for odds ratio, *p* = p-value. WHO = World Health performance status, vs = versus, RMS = Royal Marsden Score. The bolded p-values suggest statistical significant associations at $p \leq 0.0033$. ‡ After deletion of one outlier. An OR > 1 indicates that as the independent variable increases the probability of not being eligible will increase. Conversely, an OR < 1 indicates that as the independent variable increases, the probability of not being eligible for phase I trial participation will decrease.

Eligible versus ineligible patients

At pre-consent, global health (U=555.00, p =0.001, r =0.31), physical functioning (U=637.00, p=0.002, r=0.28), role functioning (U=555.50, p=0.001, r=0.31), and appetite loss (U=1560.00, p<0.001, r=0.33) showed statistically significant differences by non-parametric testing between eligible versus ineligible patients (Figure 2 & Table 4).

Additional univariate logistic regression analyses of the pre-consent data confirmed these outcomes, patients eligible for trial participation performed better on global health OR=0.946, 95% CI [0.918, 0.975], p=0.001, physical-functioning OR=0.959, 95% CI [0.933, 0.985], p=0.002, role-functioning OR=0.974, 95% CI [0.957, 0.991], p=0.003, and has a better appetite OR=1.114 95% CI [1.035, 1.192, p<0.001 (Table 5).

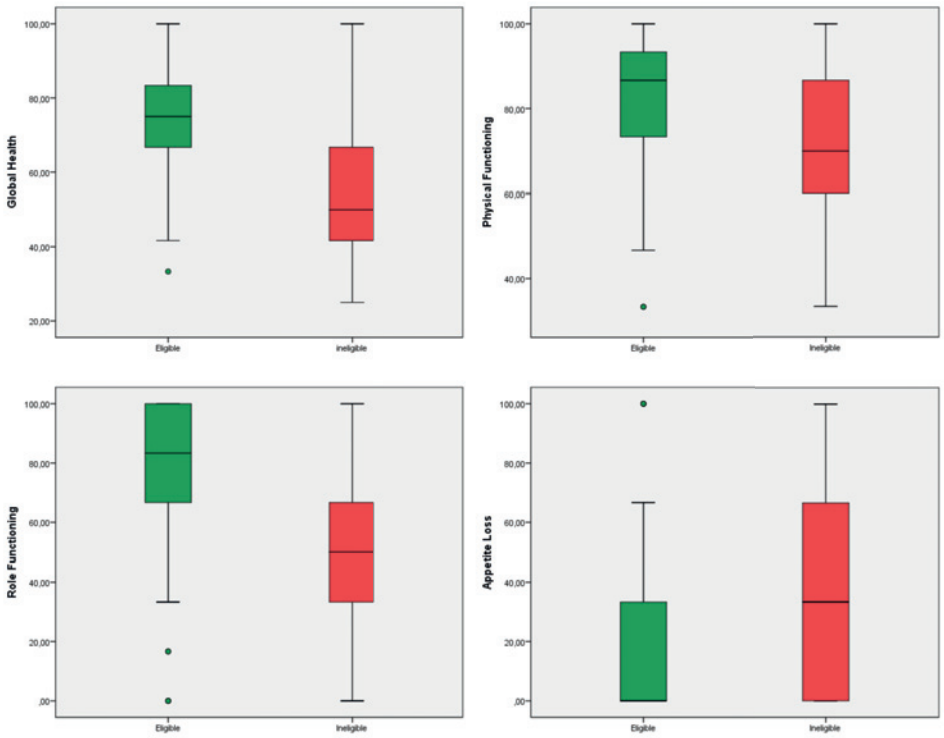

Figure 2. Boxplots of HRQoL scores at pre-consent (T1, n=124); significant differences of eligible versus ineligible patients

Table 4. Reliability of the Psychological Questionnaires

Components	Scales based on:	No of items	IC[a] T1	IC[a] T2	IC[a] T2
Hope	Herth Hope Index	12	0.78	0.76	0.81
Coping	AACS	TPG 15	0.84	0.79	0.73
	2 subscales	FGA 15	0.72	0.79	0.71
Locus of control	Rotter LoC	Extern 10	0.77	0.70	0.79
	2 subscales	Internal7	0.77	0.79	0.82

Abbreviations: No, number; IC[a], internal consistency i.e. reliability, was determined using Cronbach's alpha(α), this is acceptable between $0.8 > \alpha \geq 0.7$ and good between $0.9 > \alpha \geq 0.8$; AACS, assimilation and accommodation coping-scale; TGP, tenacious goal pursuit; FGA, flexible goal adjustment; LoC. Locus of Control.

Table 5. Description of EORTC QLQ-C30 outcomes of reference group, consenting, and non-consenting patients, at pre-consent.

	Reference group All cancer patients recurrent/metastatic Median (25-75 percentiles) N=4812	**Pre-consent (T1) Yes Median 25-75 percentiles) N=124**	**Pre-consent (T1) No Median (25-75 percentiles) N=10**
Global Health status/QoL	58 (41.7-75)	75 (58.3-83.3)	50 (41.7-87.5)
Physical functioning	80 (66.7-93.3)	86.7 (71.6-93.3)	86.6 (60-95)
Role functioning	66.7 (33.3-100)	66.7 (50-100)	66.7 (45.8-100)
Emotional functioning	75 (50-91.7)	75 (66.6-91.7)	75 (39.6-85.4)
Cognitive functioning	83.3 (66.7-100)	100 (83.3-100)	100 (79.2-100)
Social functioning	83.3 (50-100)	83.3 (66.7-100)	75 (45.8-100)
Fatigue	33.3 (22.2-66.7)	33.3 (11.1-44.4)	33.3 (33.3-58.3)
Nausea and vomiting	0 (0-16.7)	0 (0-16.7)	0 (0-20.8)
Pain	33.3 (0-50)	16.7 (0-33.3)	25 (12.5-54.2)
Dyspnoea	0 (0-33.3)	0 (0-33.3)	0 (0-41.7)
Insomnia	33.3 (0-66.7)	33.3 (0-33.3)	33.3 (0-66.7)
Appetite loss	0 (0-66.7)	0 (0-33.3)	16.7 (0-33.3)
Constipation	0 (0-33.3)	0 (0-33.3)	0 (0-33.3)
Diarrhoea	0 (0-0)	0 (0-0)	0 (0-8.3)
Financial difficulties	0 (0-33.3)	0 (0-0)	0 (0-33.3)

Abbreviations: QoL= Quality of Life

A posthoc power calculation was performed based on reported Cohen's d effect sizes. The obtained effect sizes varied between 0.12 and 0.70 for a total of 124 patients. Given the two-sided alpha of 0.0033, the power to detect differences between the groups varied between 0.8% and 51.5%.

Continuing versus stopping participation after first evaluation

Patients who continued participation after two cycles performed better on all items from pre-consent till first evaluation. The HRQoL items which significantly differed between the group of patients continuing versus stopping after first evaluation, at all time points, and significantly differed over time in each group were global health, social functioning, appetite loss, and diarrhoea (Figure 3 & table 6). In all patients a significant decline was detected in physical functioning, role functioning, and cognitive functioning, and a significant increase of fatigue and dyspnoea. The symptoms which differed between the patients who could continue or had to stop were nausea and vomiting, pain and constipation. Also, financial difficulties varied between the two groups. In all patients hope and tenacity significantly diminished over time. There was a significant difference in external LoC between both groups. All outcomes measures are described in Table 6.

Overall survival

The median overall survival (OS) of the whole cohort is 6.74 months (n = 134, 95% CI: 5.88 - 8.21). The group of ineligible and non-consenting patients had a median OS of 2.50 months (n = 34, 95% CI: 1.31 - 4.01 months), patients who started a phase I trial but discontinued treatment after two cycles had a median OS of 5.88 months (n = 44, 95% CI: 4.73 - 6.60 months), and patients who were able to continue phase I trial treatment after two cycles had a median OS of 13.01 months (n = 56), 95% CI: 10.84 - 18.23 months). See figure 4 for the Kaplan-Meier curves per group.

Looking at survival from start of phase I trial treatment onwards, the median OS is 8.18 months (n=99, 95% CI 5.98 - 10.12 months) for all patients who started trial participation.

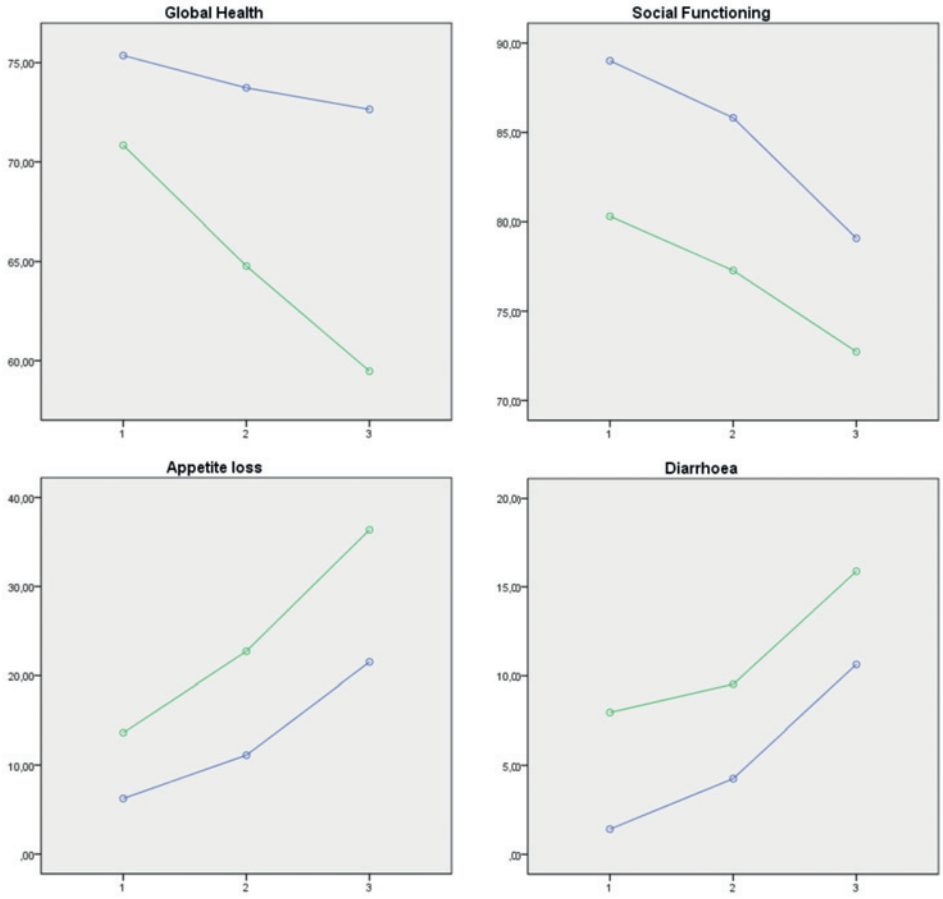

Figure 3. Differences of global health, social functioning, appetite loss, and diarrhoea between patients continuing or stopping participation after first evaluation. The blue lines represent the patients continuing participation after first evaluation. The green lines are the patients stopping participation after first evaluation.
The X-axis represents the 3 time point: 1 = pre=consent, 2 = at baseline of trial, 3 = after first evaluation. The Y-axis represents the linear transformation of the raw score of the EORTC QLQ-C30 outcome. A high score on the global health and social functioning scale represents a high score of functioning, while a high score on the appetite loss and diarrhoea scale represents a high level of symptom problems.

Table 6. Repeated-measures ANOVA analyses of patients who continue participation versus patients who stopped participation after first evaluation. Outcomes at preconsent (T1), at baseline of trial (T2), and after first evaluation (T3).

			95% Confidence Interval		Between groups: stop vs. continue		Within subjects over Time			Within subjects Group* time interaction		
	T	Mean	Lower Bound	Upper Bound	*p*	*r*	*p*	*r T1 vs T3*	*r T1 vs T3*	*p*	*r T1 vs T3*	*r T2 vs T3*
Health related quality of life					***.007***	*.32*	***.007***	*.34*	*.17*	*.133*	*.22*	*.01*
Continue	1	75.362	71.141	79.583								
	2	73.732	69.194	78.269								
	3	72.645	67.721	77.569								
Stop participation	1	70.833	64.730	76.937								
	2	64.773	58.212	71.334								
	3	59.470	52.350	66.590								
Physical Functioning					*.309*	*.13*	***<.001***	*.51*	*.43*	*.059*	*.25*	*.15*
Continue	1	84.928	80.745	89.110								
	2	84.203	79.706	88.700								
	3	78.116	71.909	84.322								
Stop participation	1	86.364	80.315	92.412								
	2	80.606	74.104	87.109								
	3	68.788	59.813	77.762								
Role functioning					*.074*	*.22*	***<.001***	.57	.36	.267	*.15*	*.00*
Continue	1	79.433	72.685	86.181								
	2	78.014	70.995	85.033								
	3	66.312	57.858	74.766								
Stop participation	1	76.190	66.095	86.286								
	2	65.079	54.579	75.580								
	3	53.175	40.527	65.822								
Emotional functioning					.990	.01	.857	.03	*.03*	*.108*	*.04*	*.03*

			95% Confidence Interval		Between groups: stop vs. continue		Within subjects over Time			Within subjects Group* time interaction		
	T	Mean	Lower Bound	Upper Bound	*p*	*r*	*p*	*r* T1 vs T3	*r* T1 vs T3	*p*	*r* T1 vs T3	*r* T2 vs T3
Continue	1	73.090	68.078	78.102								
	2	76.736	71.828	81.644								
	3	76.562	71.249	81.876								
Stop participation	1	79.167	71.402	86.931								
	2	72.917	65.313	80.520								
	3	74.167	65.935	82.398								
Cognitive functioning					.512	.08	***.001***	*.44*	*.27*	*.448*	*.14*	*.07*
Continue	1	89.931	86.524	93.337								
	2	89.236	85.362	93.111								
	3	84.028	78.924	89.132								
Stop participation	1	94.697	89.665	99.729								
	2	90.152	84.429	95.874								
	3	84.091	76.552	91.630								
Social functioning					***.027***	*.27*	***.007***	*.33*	*.24*	*.867*	*.05*	*.05*
Continue	1	89.007	84.271	93.743								
	2	85.816	80.819	90.813								
	3	79.078	73.090	85.066								
Stop participation	1	80.303	73.381	87.225								
	2	77.273	69.969	84.576								
	3	72.727	63.975	81.480								
Fatigue					*.138*	*.18*	***<.001***	*.60*	*.54*	*.075*	*.24*	*.16*
Continue	1	24.586	18.895	30.277								
	2	26.241	19.871	32.612								
	3	37.825	30.790	44.860								

			95% Confidence Interval		Between groups: stop vs. continue		Within subjects over Time			Within subjects Group* time interaction		
	T	Mean	Lower Bound	Upper Bound	*p*	*r*	*p*	*r* T1 vs T3	*r* T1 vs T3	*p*	*r* T1 vs T3	*r* T2 vs T3
Stop participation	1	25.397	16.883	33.911								
	2	32.804	23.274	42.335								
	3	51.852	41.327	62.377								
Nausea and vomiting					***.026***	*.24*	*.053*	*.24*	*.23*	*.808*	*.01*	*.05*
Continue	1	5.072	1.309	8.836								
	2	4.710	1.205	8.215								
	3	9.420	4.856	13.985								
Stop participation	1	10.606	5.164	16.048								
	2	12.121	7.053	17.190								
	3	15.152	8.551	21.752								
Pain					***.003***	*.36*	*.265*	*.19*	*.10*	*.618*	*.10*	*.07*
Continue	1	14.444	9.024	19.865								
	2	15.926	9.716	22.136								
	3	16.667	9.758	23.575								
Stop participation	1	26.190	18.255	34.126								
	2	28.571	19.480	37.662								
	3	33.333	23.220	43.447								
Dyspnoea					*.766*	*.04*	***.009***	*.35*	*.24*	*.574*	*.01*	*.09*
Continue	1	14.184	9.043	19.326								
	2	14.894	8.299	21.488								
	3	22.695	15.105	30.286								
Stop participation	1	13.636	6.121	21.152								
	2	19.697	10.058	29.336								
	3	22.727	11.633	33.822								
Insomnia					*.156*	*.17*	*.713*	*.05*	*.04*	*.537*	*.10*	*.02*

			95% Confidence Interval		Between groups: stop vs. continue		Within subjects over Time			Within subjects Group* time interaction		
	T	Mean	Lower Bound	Upper Bound	*p*	*r*	*p*	*r* T1 vs T3	*r* T1 vs T3	*p*	*r* T1 vs T3	*r* T2 vs T3
Continue	1	22.695	14.292	31.098								
	2	21.986	14.191	29.781								
	3	21.277	13.368	29.185								
Stop participation	1	26.984	14.413	39.555								
	2	33.333	21.672	44.995								
	3	31.746	19.915	43.577								
Appetite loss					***.029***	*.27*	***<.001***	*.51*	*.38*	*.492*	*.12*	*.06*
Continue	1	6.250	.472	12.028								
	2	11.111	4.794	17.428								
	3	21.528	12.753	30.302								
Stop participation	1	13.636	5.102	22.171								
	2	22.727	13.396	32.058								
	3	36.364	23.403	49.324								
Constipation					***.010***	*.31*	*.496*	*.04*	*.12*	*.345*	*.12*	*.15*
Continue	1	8.511	3.175	13.847								
	2	9.929	3.814	16.044								
	3	10.638	5.119	16.157								
Stop participation	1	19.697	11.898	27.496								
	2	22.727	13.789	31.666								
	3	15.152	7.085	23.218								
Diarrhoea					***.041***	*.25*	***.030***	*.29*	*.21*	*.940*	*.02*	*.00*
Continue	1	1.418	-1.903	4.739								
	2	4.255	.568	7.942								
	3	10.638	3.524	17.753								

			95% Confidence Interval		Between groups: stop vs. continue		Within subjects over Time			Within subjects Group* time interaction		
	T	Mean	Lower Bound	Upper Bound	*p*	*r*	*p*	*r* T1 vs T3	*r* T1 vs T3	*p*	*r* T1 vs T3	*r* T2 vs T3
Stop participation	1	7.937	2.968	12.905								
	2	9.524	4.008	15.039								
	3	15.873	5.229	26.517								
Financial difficulties					***.043***	*.24*	*.667*	*.04*	*.06*	*.530*	*.13*	*.10*
Continue	1	4.861	-8.986	9.722								
	2	6.944	1.311	12.578								
	3	7.639	1.959	13.318								
Stop participation	1	15.152	7.971	22.332								
	2	16.667	8.345	24.989								
	3	13.636	5.247	22.026								
Hope					*.918*	*.05*	***.002***	*.42*	*.00*	*.488*	*.15*	*.00*
Continue	1	3.159	3.036	3.281								
	2	3.081	2.982	3.179								
	3	3.078	2.955	3.201								
Stop participation	1	3.200	3.024	3.376								
	2	3.044	2.903	3.186								
	3	3.044	2.868	3.221								
Flexibility					*.947*	*0.1*	*.173*	*.22*	*.09*	*.104*	*.21*	*.05*
Continue	1	3.670	3.552	3.787								
	2	3.694	3.594	3.795								
	3	3.663	3.560	3.767								
Stop participation	1	3.756	3.591	3.920								
	2	3.648	3.507	3.788								
	3	3.641	3.497	3.786								
Tenacity					*.485*	*.09*	***.019***	*.26*	*.09*	*.639*	*.03*	*.12*

			95% Confidence Interval		Between groups: stop vs. continue		Within subjects over Time			Within subjects Group* time interaction		
	T	Mean	Lower Bound	Upper Bound	*p*	*r*	*p*	*r* T1 vs T3	*r* T1 vs T3	*p*	*r* T1 vs T3	*r* T2 vs T3
Continue	1	3.368	3.239	3.498								
	2	3.290	3.167	3.414								
	3	3.283	3.173	3.392								
Stop participation	1	3.448	3.265	3.631								
	2	3.317	3.142	3.493								
	3	3.378	3.222	3.533								
Internal LoC					*.095*	*.21*	*.287*	*.17*	*.16*	*.437*	*.01*	*.16*
Continue	1	3.231	3.093	3.368								
	2	3.264	3.118	3.409								
	3	3.144	2.975	3.314								
Stop participation	1	3.462	3.256	3.669								
	2	3.406	3.188	3.625								
	3	3.406	3.151	3.661								
External LoC					***.040***	*.26*	*.082*	*.27*	*.10*	*.237*	*.17*	*.19*
Continue	1	2.361	2.224	2.498								
	2	2.447	2.330	2.564								
	3	2.407	2.271	2.542								
Stop participation	1	2.533	2.330	2.737								
	2	2.594	2.422	2.767								
	3	2.717	2.516	2.918								

Abbreviations: T = time points, T1 = preconsent, T2 = baseline phase I trial, T3 = after first evaluation; *p*=p-value; *r* = effect size; vs = versus. The bolded p-values suggest statistical significant associations (≤ .05).

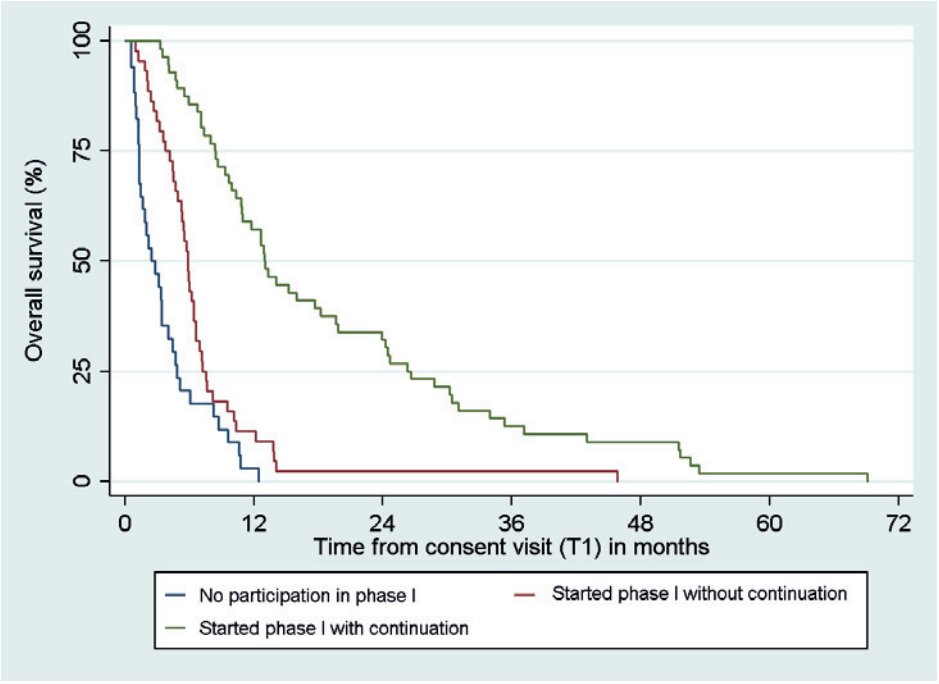

Figure 4. Overall survival of patients: not participating, started without continuation, and started with continuation after first evaluation

DISCUSSION

In the patients with advanced cancer who consented to participate in a phase I oncology trial, eligibility seems to be associated with a better global health, a better physical and role functioning, and with better appetite. Subsequently, patients who could continue participation after first evaluation had better HRQoL outcomes at the start of the screening. Our findings suggest that good HRQoL outcomes are related with eligibility and prolonged trial participations. Perceived global health, appetite loss, and diarrhoea make a difference in the patients considering participation both in screening and on trial. Importantly, social functioning is affected in all the patients on trial. Social functioning may be under strain due to multiple hospital visits, impact of side-effects and disease related symptoms.

In our cohort no association was found between eligibility and the RMS nor with WHO PS. The RMS was developed to predict patients' survival in phase I trials and might serve as a selection tool. As such it might help clinicians to decide whether a patient should

participate in a trial or not.[16] Suggestions are made to exclude patients with a RMS of 3 from a phase I trial in view of their limited life expectancy.[18] None of the patients in our cohort had a RMS higher than 2 at pre-consent. Nevertheless, a substantial part of the patients was not able to start a trial. HRQoL might be a suitable tool to discern patients at risk. An advantage might be the fact that patient-reported outcomes lack the observation bias from clinicians. Possibly, both the RMS and HRQoL scores may complement each other in predicting outcomes of patients at risk for screen failure or early deterioration in clinical trials. There may be ground for further prospective research in this matter. Additionally, the HRQoL might serve as a basis to guide for palliative care and in decision making towards trial participation.

In the groups of patients who had to stop after two cycles of experimental treatment, appetite loss, and symptoms like nausea and vomiting, and constipation had a negative impact on their experienced quality of life. Furthermore, increased fatigue, decline of physical, role, and cognitive functioning, which were found in all participating patients, are the most common health problems among patients with advanced cancer participating in cancer trials.[4,19] Rouanne et al.[10] saw a significant decrease in physical health but not in mental health in their cohort of participating patients. Patients who could continue after two cycles may have had less aggressive deterioration of their disease or experienced clinical benefit.[3] Earlier research showed that the patients who continued could have experienced fewer side-effects of the investigated agents, since they had fewer symptoms of their disease to start with.[5,20]

Our findings show that trial participation affects hope and coping strategies. During trial participation there was a decrease of hope in all patients. This could be associated with a drop in experienced global health, since global health and hope were correlated at pre-consent.[3] The maintenance of quality of life is an important factor in staying hopeful. Patients participating in a phase I clinical trial put hope for treatment above quality of life.[21] In our study, the patients who stopped participation after two cycles coping strategies changed. They showed a decrease of tenacity (diminished holding on to treatment) and an increase of external locus of control (giving up on control). Possibly, the fact that patients have to end trial participation, often seen as last resort, may help some of the patients face a next step in their disease process. They no longer need or are able to be in control of their disease and can focus on symptomatic relieve.

The OS in our group of patients who started participation was 8.18 months. Earlier reports of OS in phase I clinical trials showed OS rates varying between 9.9[8] and 10.5[22] months. Variations in research modalities, group size, heterogeneity of tumour types, or baseline

condition may explain these variations in survival. The description of the several survival times is informative and can be useful for patients and clinicians in the decision-making process.

Strengths and limitations

This study has several limitations. Due to clinical deterioration, patients' refusal, trial burden, or unknown factors, not all patients completed the questionnaires at baseline or after first evaluation. This could have influenced the outcomes of our study. Furthermore, the small sample size prevented us from making firm statements about the outcomes, and were we unable to perform multivariate analyses. Therefore, we limited the scope of our outcomes to the most significant outcomes. A larger cohort could have provided us with more rigorous data, to confirm the prognostic role of HRQoL. One of the strengths is that data were gathered from patients before initial consent to a phase I trial. Another strength is the prospective character of the measures HRQoL, hope and coping strategies. This enabled discussion of the prospect of trial participation, not only based on empirical evaluations but supported by systematic observations.

Clinical implications

Informing patients about the consequences of trial participation on their quality of life, hope and coping may help them make a well-informed decision. During the discussion of trial participation it should be kept in mind that hope will influence patients' perception, since patient' hope is high.[2,21,23,24]

The maintenance and support of HRQoL and hope is a challenging objective in the care for potential phase I patients. Our data shows that there is a need for improved palliative care for phase I patients. Patient-reported outcomes prior and during trial participation might give guidance in applying the right palliative care interventions at the right moment. The potential benefit of measuring of PROs like HRQoL and additional integration of palliative care in this group of patients seems, although preliminary, evident.[4,25] PROs can be a tool to identify the patients at risk of failing phase I trial screening and may guide communication about goals, needs, and values.[4,26] Further prospective exploration is needed to show if measuring PROs improves patients' outcomes and research results, and thus, future patients' perspectives.

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PART III

General discussion and conclusion

CHAPTER 8

Summary, conclusions and future perspectives

The primary aim of phase I trials is to establish safety profiles. Patients may struggle to decide whether to engage in a treatment with unknown efficacy, benefit, and side effects, or to opt for symptom-oriented palliative care.[1] By the current standard, a valid informed consent procedure requires that health care providers give unbiased information about expected outcomes of the study, the risks, and efforts it will require from patients, life expectancy and alternative options such as palliative support. Patients are subsequently asked to make a choice based on this information.[2,3] In this thesis, both medical outcomes of phase I clinical trials as well as research towards patients' perspectives are presented.

PHASE I ONCOLOGY CLINICAL TRIAL OUTCOMES

In **chapter 2** we report the safety, the maximum tolerated dose (MTD), and evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of RGB-286638. RGB-286638 was administered intravenously over 60 minutes on day 1 to day 5 of a 4-weekly cycle. A total of 62 patients were enrolled at the Erasmus MC. DLTs were ALAT/ASAT grade 3, and grade 2/3 cardiovascular toxicities. Due to the high incidence of phlebitis, RGB-286638 was administered through a central venous line, from dose level 80 mg. No apoptosis-associated biomarker was detected. No partial responses were observed. According to RECIST 1.1, stabilization of the disease ≥ 4 months occurred in 6 patients. The MTD of RGB-286638 for phase II studies was identified at 120 mg/day i.v. at day 1-5 every 4 weeks, preceded by anti-emetics due to the high incidence of nausea.[4]

Another trial in which a part of our patients participated is described in **chapter 3**. In this chapter, the safety and tolerability of the oral administration of ABT-767 is reported.[5] Patients with advanced solid tumors with BRCA1/2 mutations or high-grade serous ovarian, fallopian tube, or primary peritoneal cancer, participated in this trial. A total of 93 patients were treated with ABT-767 in 3 Dutch centers. Food had no significant effects on ABT-767 bioavailability. The most common grade 3/4 treatment-related adverse events were nausea, fatigue, decreased appetite, and anemia. Anemia showed a dose-dependent increase with ABT-767. The recommended dose of ABT-767 was 400 mg BID. Objective response rate by RECIST 1.1 was 21% (17/80) in all patients and 20% (14/71) in patients with ovarian cancer. Response rate by RECIST 1.1 and/or CA-125 was 30% (24/80) in patients with ovarian cancer. Biomarker outcomes showed that BRCA mutation-positive patients, with homologous recombination deficiency (HRD) positive, and platinum sensitive tumors were more responsive to ABT-767.

The findings of the two randomized, open-label, cross-over sub-studies with orally administered BI 853520 are reported in **chapter 4**. Patients were treated in the expansion

cohort of the phase I dose-finding study. In both subsets of this study, 16 patients were enrolled in 5 participating centers in Canada and the Netherlands. In one group, the food effect on oral absorption of BI853520 was studied. Each patient received a single dose of 200 mg BI 853520 in a fed or fasted state. In the other group, all patients received a single dose of 200 mg BI 853520 as a liquid dispersion and as a tablet. In both groups the order was randomized and a wash-out period of 7 days was applied. The effect on the PK was established in both groups. There were no differences observed between PK of the liquid or tablet formulation. The effect of the high-calorie meal on the 90% CI for the ratio of the geometric means of the $AUC_{0\text{-}48}$, $AUC_{0\text{-}\infty}$ and C_{max} crossed the lower of the 80-125% boundaries. This effect is considered clinically irrelevant.

CONCLUSIONS REGARDING PHASE I TRIALS

In the dose-finding studies with ABT767 and RGB-286638, the MTD and the safety profiles were established. Yet, in the ABT767 trial, we saw prolonged responses, making this phase I trial an option with a possible therapeutic benefit for a specific part of the included patients. It is often difficult --if not impossible-- to predict clinical efficacy of a new compound, especially in 'first in human, first in class' studies. However, in phase I studies on new combinations of agents of which one is a registered compound, a higher response is expected. Additionally, in studies with a compound like ABT-767, with a known efficacy of the class of agents, a higher response may also be the case.

As mentioned, we did not find clinical relevant effects of food intake on the PK in either the ABT-767 trial, or the cross-over study with BI 853520. The benefits of a liquid formulation and the minor effects of a (high fat) meal makes BI 853520 relatively easily to dose. Quite often, patients have to fast 1 hour prior to drug intake and for 1 or 2 hours after drug intake. In case a drug is administered twice daily, this drug regimen may have a major impact on the quality of life of the patient and the possibility of insufficient daily calorie intake. Having no restrictions of food intake in relation to the intake of an anti-cancer agent is therefore favorable for patients who are at risk for anorexia/cachexia, like a part of our patients, as observed in our study towards health-related quality of life, which is described in chapter 7.

PATIENTS' PERSPECTIVES

Chapter 5 gives an overview of the process of trial inclusion at the phase I unit of the Department of Medical Oncology, at the Erasmus MC Cancer Institute, Rotterdam. A retrospective analysis was performed of all patients, informed about a specific phase I trial, during a period of 25 months.[6] Phase I trial participation was discussed with 365 patients.

Forty percent, i.e. 145 patients, were not eligible or refused study participation at pre-consent. After giving informed consent and review of the in- and exclusion criteria, 44% of the initial population ultimately started phase I trial participation. Clinical deterioration or pursuing other palliative/symptomatic treatment options were reasons for being not eligible or refusing consent. Furthermore, low expectations towards treatment benefit, concern about side effects, the effect of frequent hospital visits on quality of life, and no wish to be exposed to an experimental agent, were the various reasons to deny consent. Patients who had prior systemic treatments and patients who were already known to our department consented more often. Interestingly, the distance to the hospital was no issue. This could motivate patients with interest in trial participation to select the Erasmus MC Cancer Institute a potentially favorable center.

We set out to get a better understanding of the influence of psychological factors and health-related quality of life, on the motivation to participate in oncology phase I trials in **chapter 6**.[7] A total of 135 patients, who were potentially eligible for phase I trial participation and deliberated participation, contributed to this study. They answered questionnaires on hope, motivation to participate, coping, locus of control (LoC), and HRQoL. We explored the relations and the nature and magnitudes of these relationships. Structural equation modelling was used to explore covariance structures and a pathway model.[7,8] In the best fitting model, the motivation to participate was directly influenced by hope. Hope was influenced by a strong pact formed by flexible and tenacious coping, and internal LoC. Furthermore, hope was positively influenced by global health and *vice versa*.

Chapter 7 explored the variations in patient-reported outcomes, like HRQoL, hope, and psychological factors over time. At pre-consent, baseline, and after first evaluation of a phase I trial, patients completed the questionnaire on HRQoL, hope, and psychological factors, like coping and control. Patients who fulfilled the eligibility criteria for a phase I trial were younger and performed significantly better on global health, physical and role functioning and had less loss of appetite. Loss of appetite and decrease of role functioning seem to make a clinical difference. Eligibility was not associated with performance status, or a prognostic score, like the Royal Marsden Hospital prognostic score.[9] During trial participation, global health, social functioning, and appetite loss were affected in all patients. They also differed between the groups of patients continuing participation after two cycles and those who had to stop due to side effects or progression. HRQoL, hope and the psychological mindset change during trial participation.

When discussing participation with patients, we should not only discuss the expected effect based on the preclinical data of the investigated compound, but also our general observations of the patients on trial. Furthermore, we must keep in mind that patients' hope is high and will influence his or her perspectives.[10]

CONCLUSIONS REGARDING PATIENTS' PERSPECTIVES

The efficacy of studies that test novel drugs in cancer is unknown and participation imposes the burden of multiple evaluations and potential toxicity. Nonetheless, a subset of cancer patients without standard treatment options choose to make this uncertain choice and gave consent to participate in a phase I clinical trial. Yet, giving consent does not automatically mean a patient will actually start treatment within the trial. They hopefully pursue an uncertain road while contemplating participation.

This research shows that patients who eventually choose to participate, are highly motivated and put in every effort to participate in a study in order to live longer. The motivation for treatment is theorized by Deci and Ryan in the self-determination theory (SDT).[11] The concept of SDT is based on the idea that personal needs will influence patients' motivation, and also his mental health and executive functioning. The three personal needs which influence motivation are defined as competence, relatedness, and autonomy (figure 1).

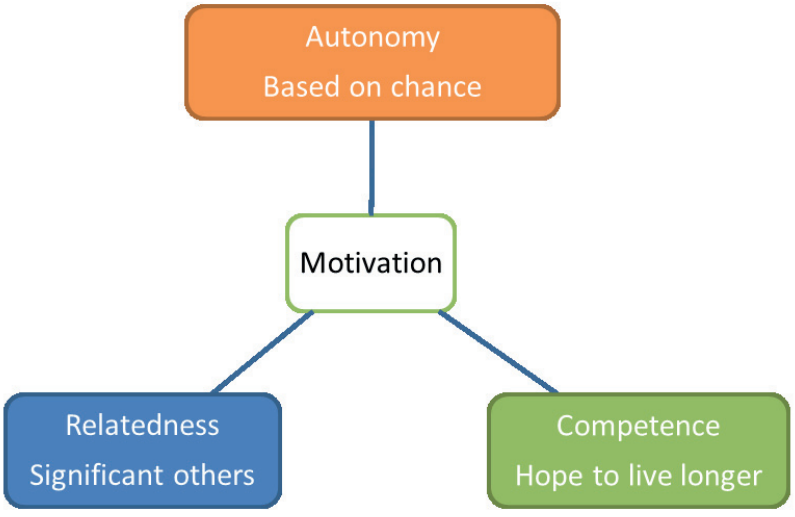

Figure 1. Motivation based on self-determination theory[11]

Competence is interpreted as the way to influence personal outcomes and to gain personal growth. From our patients' view, they most of all want to add days to life, instead of life to days. The second personal need is relatedness. This is described as the interactions, relations, and experiences with others, which may affect decision making. We found that the family and friends, and our institute and caregivers are significant relationships for our patients, and they may influence decision making. This is clinical significant: meaningful contact, even in the hospital setting, can be vital for participation in trials. Autonomy, the third need, is defined as the need to be in charge of one's own decisions. Based on our research we can consider autonomy, the relationship with significant others, and the hopeful pursue of living longer as the fundaments of our patients' motivation.

FUTURE PERSPECTIVES

Over the last 20 years, the 5-year death rates of cancer have dropped with 15%; from 62% till 47 % (figure 2).[12] Largely, this is established with the effort of many patients with cancer, who voluntarily participate in clinical trials, thereby facilitating new drug development.

Considering phase I trial participation is a complex process. Only a selected part of the patients experiences clinical benefit from participation. Furthermore, it may help patients to remain hopeful and experience a relatively good quality of life. Yet, it could postpone the preparation for end-of-life. Patients' attitudes toward treatment at the end-of life vary at a wide range. Our patients participating in phase I studies are a selective group of palliative patients in good condition, highly motivated to be treated even when the outcome is uncertain. For decision making concerning trial participation, their personal values should be taken into consideration. To empower patients, a value clarification online tool could help patients explore their own values and attitude towards palliative care and study treatment. Such a tool could help both patients and caregivers discussing clinical trial options as well as advanced care planning. In this view, considering trial participation could be part of advanced 'trajectory care planning'.[13]

Currently, there is a tendency to incorporate systematic assessment of PROs in clinical trials.[14] However, this is rarely done during phase I clinical trials. PROs will provide evidence of the effect on treatment, disease-related symptoms, and the effect on functioning. Subsequently, this research should be incorporated into daily practice and not only be reviewed as research outcome (at the end of a trial), and also as a means of helping the patient. Online tools may help us to follow up side-effects and symptoms of the disease, and to be in contact with our patients next to their hospital visits, fostering relatedness,

competence, and autonomy. Whereas, new and easy to wear innovative tools, like activity trackers, may find its way in the evaluation of patients' physical condition and the impact of a trial on the quality of life.

Perhaps one of the findings in this study is the realization that technical research in Phase I trials could be accompanied by not only caring for patients' safety but also their psychological well-being (relatedness and competence) and meaning of life (autonomy). It is hope and this meaning of life which motivates our patients.

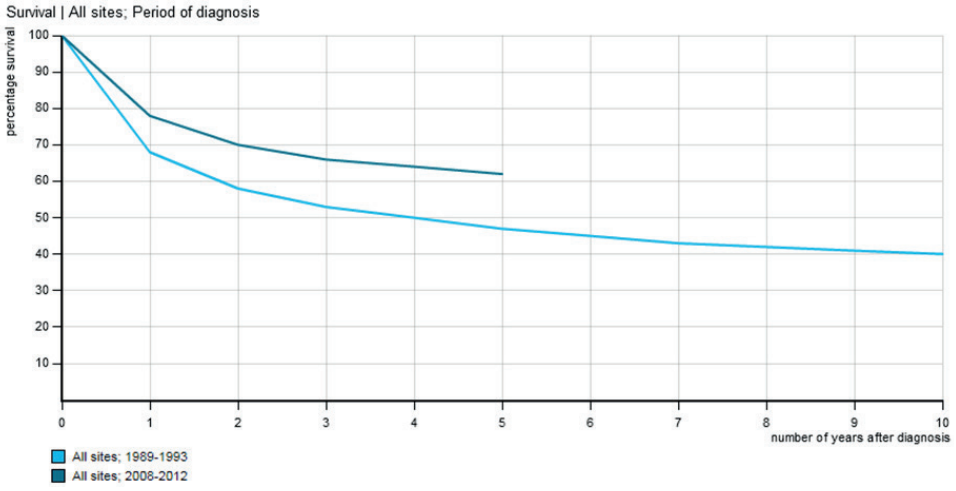

Figure 2. Survival is defined as the proportion of patients alive at some point in time after the diagnosis of cancer. The presented survival is the relative survival which adjusts the crude survival for the expected mortality according to annual life tables of the general population matched for age, gender and calendar period. Patients are followed until the date of death or until February 1st, 2016 or, in case of emigration, until the date of emigration.[12]

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CHAPTER 9

Samenvatting

Door de vergrijzing is het aantal mensen dat per jaar kanker krijgt gestegen. Deze trend zal zich de komende jaren helaas blijven voortzetten. Bij een deel van deze patiënten is de kanker bij ontdekking al uitgezaaid. De kans is hierdoor groot dat ze aan de ziekte komen te overlijden ondanks alle huidige behandeling mogelijkheden. Dit resulteert in een sterke behoefte aan nieuwe en/of betere behandelingen tegen kanker.

Voor het vinden van nieuwe behandelingen is onderzoek nodig. Onderzoek begint in het laboratorium. Als dit laboratoriumonderzoek is afgerond wordt het onderzoek vervolgd in de mens. De eerste stap in de mens noemen we fase I onderzoek; ook wel vroeg-klinisch onderzoek genoemd. Over het algemeen gebeurt dit fase I onderzoek bij gezonde vrijwilligers. Echter, bij onderzoek naar nieuwe geneesmiddelen tegen kanker, wordt dit gedaan bij patiënten met kanker (vooral vanwege de kans op ernstige bijwerkingen, maar ook om te onderzoeken wat de effecten op de tumor zijn). Patiënten met uitgezaaide of vergevorderde kanker, in goede conditie, zonder behandelopties of met behandelopties die weinig effect en/of veel bijwerkingen hebben, en een sterke behandelwens hebben, kunnen gevraagd worden deel te nemen aan fase I onderzoek.

Het eerste doel van fase I onderzoek is het vinden van de dosering die veilig gegeven kan worden. Het kan hierbij gaan om één nieuw middel, of een combinatie van nieuwe en/of bestaande middelen. Aanvullende doelen zijn:

- vaststellen van de bijwerkingen;
- farmacokinetiek (PK): onderzoek naar hoe het middel of de combinatie zich gedraagt in het lichaam;
- farmacodynamiek (PD): beschrijft de veranderingen in het lichaam of onderdelen van het lichaam, zoals de tumor of op de organen (zoals de lever en de huid);

Onder PD valt ook:

- het effect observeren van voeding op de manier waarop het middel zich gedraagt in het lichaam;
- het effect op de groei van de tumor analyseren.

Een belangrijke taak van de onderzoekers is het zorgvuldig informeren van de patiënt over alle voor en nadelen van vroeg klinisch onderzoek. Het is belangrijk dat een patiënt het onderzoek begrijpt en vrijwillig deelneemt. Daarnaast staat het bewaken van de veiligheid van de patiënt die deelneemt aan dit onderzoek voorop.

Voor patiënten die gevraagd worden om deel te nemen aan fase I onderzoek, kan het moeilijk zijn hierover te beslissen. Ze staan voor de keuze te starten met een onderzoek, waarvan

de bijwerkingen en het effect op hun ziekte grotendeels onbekend zijn. Ook maken extra aanvullende onderzoeken en controles bij de arts of de verpleegkundig specialist deel uit van het programma. Dit vergt een belangrijke tijdsinvestering van de patiënt. Een andere optie is zorg gericht op de gevolgen van de ziekte, zoals symptoomgerichte zorg, waarbij het streven is de klachten ontstaan door de ziekte zo goed mogelijk te onderdrukken.[1]

Het vragen van toestemming -- informed consent -- vereist van de arts en de verpleegkundig specialist dat ze feitelijke informatie verstrekken over de te verwachten uitvoering en uitkomsten van het onderzoek, de risico's voor de patiënt en de inspanning die de patiënt moet leveren. Ook moet de patiënt gewezen worden op eventuele alternatieve opties.[2,3]

In dit proefschrift worden onder 'Uitkomsten fase I onderzoek' twee fase I onderzoeken beschreven. Een derde onderzoek is een vervolgonderzoek op een fase I onderzoek waar de effecten van voeding en andere samenstellingen van een nieuw middel worden onderzocht. De uitkomsten van onderzoek naar de gezichtspunten van deze patiënten zijn samengevat onder 'Patiëntperspectieven'. Ter afsluiting worden de overwegingen ten aanzien van onderzoek naar patiëntperspectieven voor de komende tijd geschetst onder 'Algemene conclusie'.

UITKOMSTEN FASE I ONDERZOEK

In hoofdstuk 2 rapporteren we de bijwerkingen en de maximaal te verdragen dosering van RGB-286638. Ook beoordeelden we de PK en PD eigenschappen van RGB-286638. RGB-286638 is een cycline-afhankelijke kinase (CDK) remmer, gericht op meerderde 'cyclines'. Cycline-afhankelijke kinases zijn eiwitten die een rol spelen in elke fase van de celcyclus. Deze eiwitten zijn betrokken bij het kopiëren van de erfelijke eigenschappen van de cel. De balans tussen deze eiwitten en CDK-remmers bepaalt of een cel doorgaat met de deling. Als de celdeling wordt geremd, gaat de kankercel dood. RGB-286638 werd iedere 4 weken intraveneus (i.v.), via een ader, toegediend gedurende 60 minuten op dag 1 tot en met dag 5. Totaal hebben 62 patiënten in ons ziekenhuis deelgenomen aan dit onderzoek. De bijwerkingen die ervoor zorgden dat de dosis niet verder verhoogd kon worden, waren ernstige afwijkingen van leverenzymen en afwijkingen aan de bloedvoorziening van het hart. Door het veelvuldig optreden van aderontstekingen werd RGB-286638, vanaf de dosering van 60 mg per uur per dag, toegediend over een centraal veneuze lijn. Dit is een kunststof slangetje in een grote ader. In het bloed zijn geen factoren gevonden die aanwijzing geven dat de kankercellen doodgingen na toediening van RGB-286638. Bij 6 patiënten stond de ziekte meer dan 4 maanden stil. Bij geen van de patiënten is afname van het ziekteproces

gezien. De maximaal te verdragen dosering was 120 mg per uur, toegediend op dag 1 t/m 5 gedurende een periode van 28 dagen. Vooraf moesten middelen tegen de misselijkheid toegediend worden, omdat misselijkheid bij veel patiënten voorkwam.

Een van de fase I onderzoeken waaraan een gedeelte van onze patiënten deelgenomen heeft, is beschreven in hoofdstuk 3. In dit hoofdstuk zijn de verdraagbaarheid en het veiligheidsprofiel beschreven van het via de mond (oraal) gedoseerde middel ABT-767. Patiënten met een vergevorderde (uitgezaaide) solide tumor met een zogenaamde BRCA1- of BRCA2-genmutatie, uitgaande van de eierstokken, eileiders of het buikvlies, namen deel aan deze studie. Een solide tumor is een vorm van kanker die ontstaan is een orgaan (solide betekent vast). Voor de reparatie van schade aan het genetische materiaal in de cel zijn BRCA1- en BRCA2-genen van belang. Een gen is een stukje DNA dat bestaat uit een reeks eiwitten. Deze eiwitten spelen een belangrijke rol in het herstellen van schade. Bij een mutatie van het BRCA1- of 2-gen kan deze schade niet goed gerepareerd worden en kunnen cellen ongeremd gaan delen. Hierdoor kan kanker ontstaan. ABT-767 is een krachtige poly(ADP-ribose) polymerase (PARP) remmer. Kankercellen gebruiken het eiwit PARP om DNA-schade te repareren. PARP-remmers blokkeren dit eiwit. Door deze remming is de kankercel niet in staat zich te delen.

In totaal zijn 93 patiënten behandeld met ABT-767 in drie academische ziekenhuizen in Nederland. De meest voorkomende ernstige bijwerkingen van dit middel waren misselijkheid, vermoeidheid, verminderde eetlust en bloedarmoede. Bloedarmoede had een relatie met de hoeveelheid ABT-767 die was toegediend; een hogere dosering leidde tot ernstigere bloedarmoede. Voeding had geen effect op de beschikbaarheid van ABT-767 in het lichaam. De dagelijkse aanbevolen dosering van ABT-767 was 400 mg, tweemaal daags. Een objectieve respons; dit is de som van complete en gedeeltelijke afname van de kanker, is gezien bij 21% (17/80) van alle patiënten en bij 20% (14/71) van de patiënten met eierstokkanker. Afname van de ziekte en/of een daling van het CA-125 (een tumormerkstof bij eierstokkanker) werd gezien bij 30% (24/80) van de patiënten met eierstokkanker. Onderzoek naar factoren in het lichaam die van invloed kunnen zijn op een gunstige werking van ABT-767 liet zien dat patiënten met een BRCA1- of BRCA2-genmutatie en patiënten met tumoren die gevoelig zijn voor platinum-bevattende chemotherapie, beter reageren op de behandeling met ABT-767.

De bevindingen van twee aanvullende onderzoeken op een fase I onderzoek zijn beschreven in hoofdstuk 4. BI 853520 is een focaal adhesie kinase (FAK) remmer. Dit wordt oraal toegediend. FAK geeft signalen door die cellen kunnen laten groeien en verspreiden. Het eiwit dat BI 853520 blokkeert heet PTK2, wat staat voor 'proteïne tyrosine kinase 2'. Dit eiwit is onderdeel van de FAK-familie. In beide studies hebben 16 patiënten deelgenomen in 5

ziekenhuizen, in Canada en Nederland. Bij een groep werd de invloed van vette voeding op de opname van BI853520 bestudeerd. Alle patiënten kregen een eenmalige dosis van 200 mg die ze nuchter of na een maaltijd met veel vet in moesten nemen. In de andere groep werd 200 mg BI 853520 ingenomen als drankje of werd de opname als tablet onderzocht. In beiden groepen werd de volgorde van toediening geloot. Tussen beide toedieningen zat 7 dagen. Dit is de tijd die het middel nodig heeft om volledig uit het lichaam te verdwijnen. In beide groepen werd het effect op de PK vastgesteld. Er zijn geen verschillen gevonden in de PK door inname van het drankje of de tablet. Echter, een maaltijd met veel vet gaf een beduidende verlaging weer van de absorptie van BI 853520, in vergelijking tot nuchter ingenomen BI 853520. Vooralsnog lijkt dit van weinig belang voor de dagelijkse praktijk.

CONCLUSIES TEN AANZIEN VAN FASE I ONDERZOEK

In de studies met ABT767 en RGB-286638 zijn de maximaal toelaatbare en veilige dosering van deze nieuwe middelen vastgesteld. In de studie met ABT767 zagen we langdurige effecten op de afname van de kankergroei. Hierdoor was deze studie een optie met een mogelijk gezondheidsvoordeel voor een gedeelte van de patiënten die hebben deelgenomen. Het is vaak moeilijk, zo niet onmogelijk, de werkzaamheid van een nieuw middel te voorspellen. Vooral als het gaat om middelen die niet eerder bij mensen zijn getest. Echter, in een fase I studie met een nieuwe combinatie van middelen en/of een middel waarbij de werkzaamheid in zijn soort al is vastgesteld, mag verwacht worden dat de kans op gezondheidsvoordeel toeneemt.

Bij het onderzoeken naar het resultaat van voeding op de opname van de onderzochte nieuwe middelen zijn geen effecten gezien die van belang zijn voor de alledaagse manier van toediening. BI 853520 is als drankje toe te dienen. Ook een 'vette' maaltijd voor inname lijkt geen bezwaar. Bij veel nieuwe middelen die oraal worden toegediend mogen patiënten een uur voor inname en twee uur na inname niet eten. Eten binnen deze termijn kan de kwaliteit van leven en ook de inname van voldoende voedingsstoffen verhogen. Het is daarom gunstig voor patiënten als er geen beperkingen zijn ten aanzien van de inname van deze orale middelen. Dit is vooral gewenst voor patiënten die het risico lopen op het hebben van een verminderde eetlust en/of sterke vermagering, zoals we zien bij een gedeelte van onze patiënten beschreven in hoofdstuk 7 waarbij we gekeken hebben naar gezondheid gerelateerde kwaliteit van leven.

PATIËNTPERSPECTIEVEN

Hoofdstuk 5 geeft een overzicht van het proces dat leidt tot studiedeelname op de fase I-unit van de afdeling Interne Oncologie, van het Erasmus MC Kanker Instituut, te Rotterdam. Over een periode van 25 maanden is teruggekeken wat er is gebeurd met alle patiënten die informatie hebben ontvangen over een fase I onderzoek. Gedurende deze periode is met 365 patiënten een specifiek fase I onderzoek besproken. In de periode voorafgaande aan de toestemming voor deelname aan een fase I onderzoek, pre consent, voldeden 145 patiënten (40 %) niet aan de criteria van de studie of wilden niet deelnemen. Na het geven van toestemming zijn 159 patiënten (44%) gestart met een fase 1-behandeling. Achteruitgang van de algehele toestand of kiezen voor symptoomgerichte zorg waren de belangrijkste redenen om geen toestemming te kunnen of willen geven voor deelname aan het fase I onderzoek. Ook andere redenen, zoals de lage verwachtingen van het mogelijke effect van het onderzoek, het effect van de vele bezoeken aan het ziekenhuis op de kwaliteit van leven en niet blootgesteld willen worden aan een experimenteel middel maakten dat patiënten niet deel wilden nemen. Patiënten die al werden behandeld met anti-kankermedicatie en patiënten van onze eigen afdeling gaven beduidend vaker toestemming. De afstand naar het ziekenhuis bleek geen bezwaar. Dit maakt dat het Erasmus MC Kanker Instituut in Nederland een goede locatie is voor patiënten die deelname aan een onderzoek willen overwegen.

Om een beter inzicht te krijgen in de motivatie van patiënten is in hoofdstuk 6 het onderzoek gerapporteerd naar de invloed van psychologische factoren en gezondheid gerelateerde kwaliteit van leven op de motivatie van patiënten om deel te nemen aan fase I onderzoek. Er zijn gevalideerde Nederlandse vragenlijsten voor gebruikt. In totaal hebben 135 patiënten bijgedragen aan dit onderzoek. Het zijn patiënten die in aanmerking kwamen voor deelname aan fase I onderzoek. Van de oncoloog hadden zij informatie ontvangen van een specifiek fase I onderzoek. Ze hebben schriftelijk vragen beantwoord over hoop, motivatie tot deelname, coping en *locus of control*.

Coping is de manier waarop mensen met problemen en stress omgaan. Er zijn twee aanpakken van coping onderzocht, te weten vasthoudende en flexibele coping. Vasthoudende coping kan vertaald worden naar de mate waarin de patiënt vasthoudt aan het idee dat behandeling tegen kanker voor de patiënt van belang is. Flexibiliteit is de manier waarop de patiënt een oplossing zoekt, meebeweegt, ten aanzien van de beperkte behandelmogelijkheden van zijn of haar ziekte.

Locus of control is de mate waarin iemand gelooft dat de gebeurtenissen die hem overkomen te beheersen zijn door zichzelf of juist door anderen. *Locus of control* is onder te verdelen

in interne en externe locus. Mensen met een interne locus nemen verantwoordelijkheid voor hun eigen leven, zoeken zelf naar oplossingen. Echter, mensen met een externe locus denken dat ze de controle niet zelf in handen hebben en zoeken minder naar oplossingen.

Met de uitkomsten van deze vragenlijsten hebben we de aard en de grootte van de onderlinge relaties verkend. Deze relaties zijn onderzocht aan de hand van een 'structureel model'. Door middel van een grafische weergave van de te verwachten relaties, werden de uitkomsten met behulp van het statistische programma getoetst.[4] In het beste model werd de motivatie tot deelname aan fase I onderzoek direct beïnvloed door hoop. Hoop werd in sterke mate gestuurd door een pact van interne *locus of control*, vasthoudende en flexibele coping. Ook was er een positieve wisselwerking tussen hoop en de gezondheid gerelateerde kwaliteit van leven.

Na start van een fase I onderzoek stopt 16 % van de patiënten binnen 21 dagen ten gevolge van bijwerkingen of snelle achteruitgang van de ziekte.[8] Dit is voor veel patiënten een teleurstelling. Het gebruik van een hulpmiddel dat deze uitval of overlijden binnen 90 dagen kan voorspellen zou uitkomst kunnen bieden. Verwachte overleving van 90 dagen is een voorwaarde van deelname aan fase I onderzoek. De Royal Marsden Hospital prognostic score is een dergelijk score, maar is niet erg betrouwbaar. Met dit hulpmiddel kunnen 20 % minder patiënten starten met het fase I onderzoek. De helft van de patiënten die zijn uitgesloten van start, leeft nog na 90 dagen.[5]

Eén van de hulpmiddelen die we gebruiken om de fitheid van een patiënt in te schatten is de 'Eastern Cooperative Oncology Group' (ECOG) score, ook wel WHO-score genoemd,[6] of de Karnofsky-score.[7] Patiëntgerapporteerde uitkomsten (PROs) zoals gezondheid gerelateerde kwaliteit van leven (HRQoL) zijn zelden gemeten bij patiënten die deelnemen aan vroeg klinisch onderzoek. PROs zijn gerapporteerde uitkomsten die direct van de patiënt komen en die niet zijn beïnvloed door familie, vrienden of hulpverleners.[8] HRQoL is een belangrijke uitkomstmaat voor de patiënt en kan een betere voorspeller zijn voor overleving dan de WHO-score. Het geeft een goed beeld van de huidige gezondheid van een patiënt.[9,10] Echter, de relatie tussen HRQoL en de voorwaarden voor deelname aan een fase I onderzoek zijn onbekend.

Om patiënten goed te kunnen voorbereiden op de gevolgen van deelname aan fase I onderzoek hebben we een verkennend onderzoek gedaan. In hoofdstuk 7 zijn de observaties beschreven van HRQoL, hoop en psychologische factoren gemeten bij eenzelfde groep patiënten op drie tijdstippen: tijdens overwegen van deelname (pre consent), voor de start

van het onderzoek met het experimentele middel (baseline) en na de eerste evaluatie van het effect van het onderzochte geneesmiddel. De eerste evaluatie vindt over het algemeen plaats na 6 tot 8 weken binnen het onderzoek.

De uitkomsten lieten zien dat de patiënten die voldeden aan de voorwaarden van deelname aan fase I onderzoek jonger waren en betere uitkomsten van hun algehele gezondheid hadden dan degene die niet aan deze voorwaarden voldeden. Ook zagen we betere uitkomsten van hun fysiek functioneren en rol functioneren. Daarnaast hadden ze een betere eetlust dan degene die niet fit genoeg waren om te starten binnen een fase I onderzoek. De algehele fitheid van de patiënten die al dan niet konden starten binnen een fase I onderzoek, had geen relatie met de WHO-score of met het voorspellende hulpmiddel, de Royal Marsden Hospital prognostic score.[11]

De deelname aan het onderzoek beïnvloedde bij alle patiënten hun algehele gezondheid, hun sociaal functioneren en hun eetlust negatief. Deze 3 onderdelen verschilden op alle meetmomenten beduidend tussen de patiënten die na de eerste evaluatie het onderzoek konden vervolgen of moesten staken. Bij alle patiënten was een vermindering gezien van hun HRQoL, hoop en psychologische factoren. Bij de patiënten die deelname moesten staken zagen we een toename van de externe *locus of control.* Dit kan betekenen dat deze patiënten minder de controle willen houden en mogelijk een volgende stap kunnen zetten in het acceptatieproces.

Als we deelname met potentiele patiënten bespreken is het belangrijk eerlijke informatie te verstrekken over de effecten van de experimentele middelen, gebaseerd op het laboratoriumonderzoek. Daarnaast is het van belang de juiste verwachtingen te schetsen, gebaseerd op onze ervaringen en observaties van andere patiënten die deel hebben genomen aan fase I onderzoek. En moeten we niet vergeten dat patiënten hoopvolle verwachtingen hebben en dat hoop hun beslissing zal beïnvloeden.[12]

CONCLUSIES TEN AANZIEN VAN DE PATIËNTPERSPECTIEVEN

Het effect op de tumorgroei van nieuwe middelen tegen kanker die getest worden in fase I onderzoeken is onbekend. Patiënten die deelnemen aan fase I onderzoek ondergaan veel aanvullende onderzoeken en moeten vaak naar het ziekenhuis komen. Ook bestaat er kans op onverwachte bijwerkingen. Toch zijn er patiënten met kanker, zonder andere of beperkte behandelopties, die deze onzekere keuze maken en toestemming tot deelname geven. Dit betekent niet automatisch dat deze patiënten ook zullen starten met het onderzoek. Deze patiënten beginnen hoopvol aan een onzeker traject.

Dit onderzoek heeft laten zien dat deze patiënten uitermate gemotiveerd zijn om deel te nemen fase I onderzoek. Ze laten geen kans ongemoeid om langer te kunnen leven. Deci en Ryan hebben een theorie ontwikkeld die de motivatie voor behandeling beschrijft; de zelfbeschikkingstheorie. Deze theorie is gebaseerd op het idee dat persoonlijke behoefte de motivatie zal beïnvloeden, maar ook het geestelijk welbevinden en functioneren. De kern van deze theorie wordt gevormd door drie basisbehoeften die motivatie beïnvloeden.[13] Deze drie basisbehoeften zijn competentie, verbondenheid en autonomie.

Competentie wordt gezien als een manier om persoonlijke uitkomsten te beïnvloeden. Voor onze patiënten staat centraal dat zij dagen willen toevoegen aan hun leven, in plaats van leven aan dagen. Hoop op een langer leven staat hierin centraal. De tweede behoefte is verbondenheid. Dit beschrijft de interactie, de relaties en de ervaringen met anderen, in de ruimste zin, die hun beslissing kunnen beïnvloeden. We hebben gevonden dat familie en vrienden, maar ook ons ziekenhuis en hulpverleners van belang zijn. Dit geeft ook een belangrijke waarde aan ons dagelijks werk: betekenisvol contact, zelfs in een ziekenhuis, kan van belang zijn voor patiënten tijdens deze onderzoeken. Autonomie, de derde behoefte, is de behoefte om verantwoordelijk te zijn voor eigen beslissingen. En, alhoewel het effect van vroeg klinisch onderzoek op de ziekte onbekend is, biedt het wel een kans. Gebaseerd op ons onderzoek beschouwen we autonomie, de relaties met anderen die ertoe doen, en het hoopvolle streven naar langer leven de fundamenten van de motivatie om deel te nemen aan vroeg klinisch onderzoek.

ALGEMENE CONCLUSIE

De laatste 20 jaar is de kans om te overlijden aan kanker gedaald met 15 %. Dit is grotendeels tot stand gekomen door de vele patiënten met kanker die vrijwillig deelnemen aan onderzoeken en bijdragen aan de ontwikkeling van nieuwe behandelingen tegen kanker.

Het overwegen van deelname aan fase I onderzoek is een ingewikkeld proces. Alleen een klein gedeelte van de patiënten die deelneemt aan fase I onderzoek heeft werkelijk baat bij deelname. Desalniettemin helpt het patiënten hoopvol te blijven en een redelijke algemene gezondheid te behouden. Het kan echter de voorbereidingen op het einde van het leven in de weg staan.

Gezien onze bevindingen is het in de toekomst van belang om stelselmatig de waarden van de patiënt en PROs te onderzoeken. Dit kan eraan bijdragen dat patiënten een autonome beslissing maken, die overeenkomt met hun waarden en doelen in het leven. Deelname aan fase I onderzoek kan een overweging zijn binnen de langetermijnplanning van zorg rondom ongeneeslijke kanker, ook wel advanced 'trajectory care planning' genoemd.[14]

Op dit moment is de tendens om bij onderzoeken naar betere behandelingen PROs te meten.[15] Echter binnen fase I onderzoek neemt dit nog geen grote plaats in. PROs kunnen informatie verschaffen over de effecten van het onderzoek op de conditie en het dagelijks functioneren, en over ziekte gerelateerde klachten. Mogelijk kan het digital monitoren van PROs bijdragen aan het inzetten van interventies ter verbetering van de algehele conditie. Het kan ook het contact versterken met zorgverleners binnen het studieteam, op momenten dat patiënten niet naar het ziekenhuis komen. Nieuwe ontwikkelingen, zoals activity trackers, kunnen mogelijk bijdragen aan onze inzichten in de conditie van de patiënt en de impact van deelname aan fase I onderzoek op de conditie en het welbevinden.

De houding van patiënten met vergevorderde of uitgezaaide kanker ten opzichte van behandeling vertoont een grote variatie. De patiënten die deelnemen aan vroeg klinisch onderzoek, zijn een selecte groep patiënten in goede conditie. Ze zijn uitermate gemotiveerd, zelf als de uitkomsten nog onzeker zijn. Eén van de patiënten was geschrokken van de woorden in de informatie over een specifieke studie: '*U moet er niets van verwachten*'. Dit weerhield hem niet van deelname; hij zag dit juist als zijn laatste kans. Als patiënten overwegen deel te nemen moeten we goed luisteren naar hun waarden ten aanzien van behandelen in deze fase van hun leven. Om patiënten te ondersteunen bij deze ingewikkelde beslissing zou een digitaal hulpmiddel behulpzaam kunnen zijn. Dit hulpmiddel kan ondersteunen bij het maken van een weloverwogen beslissing ten aanzien van symptoomgerichte ondersteuning of studiedeelname.

Een van de belangrijkste bevindingen is het feit dat het intensieve traject van patiëntgebonden onderzoek ons niet weerhoudt om veilige en goede zorg te leveren. Het is daarbij belangrijk rekening te houden met het psychologisch welbevinden (verbondenheid en competentie) en betekenisvol leven (autonomie) van de patiënten. Hoop en betekenisvol leven motiveren onze patiënten.

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CHAPTER 10

Appendix

PHD PORTFOLIO

PhD training	Year	ECTS
General courses		
- BROK (basiscursus Regelgeving Klinisch Onderzoek) re-registratie	2014 & 2018	0.5
- CPO Course - Patient Oriented Research: design, conduct, analysis and clinical implications	2015	0.3
- Integrity in research course, Erasmus MC	2016	0.5
- English Biomedical Writing and Communication (MOLMED)	2016	3
Research skills		
- Quality of Life Measurement (NIHES)	2013	0.9
- Introduction in data-analysis (Open University)	2017	5
Seminars and workshops		
- 5th ESO-EONS Masterclass in Oncology (European School of Oncology)	2012	2
- Masterclass Palliative Care, 6th Amsterdam Symposium	2016	0.1
- Workshop Grant Writing European Oncology Nursing Society (EONS)	2017	1
- Masterclass Palliative Care, 7th Amsterdam Symposium	2017	0.1
- Research Proposal Workshop EONS, Stockholm	2017	0.5
Oral Presentations		
- 5th ESO-EONS Masterclass	2012	0.5
- Scientific Meeting, Medical Oncology, Erasmus MC	2012	0.5
- Dutch Nurse Practitioner Conference	2015	0.5
- Dutch Oncology Nursing Conference	2015	0.5
- Scientific Meeting, Medical Oncology, Erasmus MC	2015	0.5
- Conference Medical Ethical Questions, Erasmus MC	2015	0.5
- Café Doodgewoon, Vlaardingen	2016	0.5
- 10th EONS, Dublin	2016	0.5
- Oncology Clinical Trial Conference, Erasmus MC	2017	0.5
- Multinational Association of Supportive Care in Cancer, Vienna	2018	0.5
- POST ONS meeting, Amersfoort	2018	1
- 10th ICN NP/APN Conference, Rotterdam	2018	0.5
Poster presentations		
- 16th European Cancer Congress	2011	0.5
- Dutch Nurse Practitioner Conference	2012	0.5
- Dutch Oncology Nursing Conference	2012	0.5
- ASCO annual meeting, Chicago	2015	0.5
- Multinational Association of Supportive Care in Cancer, Vienna	2018	0.5
(Inter)national conferences		
- 2011 European Multidisciplinary Cancer Congress	2011	1
- 10th International Congress on Targeted Anticancer Therapies (TAT)	2012	0.5
- Scientific Meeting, Medical Oncology	2012-2017	1
- V&VN VS Conferences	2012-2018	1
- V&VN Oncology Nursing Conference	2012-2017	1
- CPTC symposium	2013-2017	0.5
- Brocher Foundation Symposium. Recent developments in phase I oncology trials: Implications for ethics, palliative care, and society	2014	0.5
- ASCO annual meeting	2015	1
- 10th EONS, Dublin	2016	0.7
- 6th Amsterdam Palliative Care Symposium	2016	0.2
- 4th Quality of Life and Cancer Clinical Trials Conference, EORTC, Brussels	2017	0.5

PhD training	Year	ECTS
- 7th Amsterdam Palliative Care Symposium	2017	0.2
- Multinational Association of Supportive Care in Cancer, Vienna	2018	0.5
- Oncology Nursing Society Congress, Washington DC	2018	0.7
- 10th ICN NP/APN Conference, Rotterdam	2018	0.5
Other		
- Erasmus MC Nurse Practitioner Lectures	2012-2017	0.5
- OMBO cursus (Onderwijs Multidisciplinaire Behandeling in de Oncologie)	2012-2017	0.5
	Total	**34.2**

Teaching	Year	ECTS
Lecturing		
- HBO-verpleegkunde opleiding HS Rotterdam, minor oncologie. Vroeg klinisch onderzoek bij patiënten met kanker. Rotterdam	2015-2016	0.5
- Specialistische verpleegkundige vervolgopleiding hemato-oncologie. Vroeg klinisch onderzoek bij patiënten met kanker. Rotterdam	2011-2017	1,5
- Minor Oncology Medical students, Department of Medical Oncology, ErasmusMC	2016	0.5
- ESMO-EONS e-learning; hope in palliative cancer patients	2017	0.5
- Scholing AIOS/ANIOS – vroeg klinisch onderzoek	2011-2017	1
Supervision		
Master Thesis Advanced Nursing, Leiden & Rotterdam		
- Helma van Dijk	2015	1
- Mandy van Rosmalen	2015	1
- Lianne van Beek	2016	1
Bachelor Thesis Applied Psychology, Leiden		
- Kevin Breedijk	2012	1
- Dennis Klein	2014	1
Committees		
- Member Oncology Clinical Trial Conference committee Erasmus MC: Vroeg klinisch onderzoek en palliatieve zorg: tegenstrijdig, irrelevant of win-winsituatie?	2017	1
- Member committee 'Nursing Expertise' V&VN Oncology, national accreditation nursing teaching	2012 - currently	2
	Total	**12**

Grants

- EONS, travel grant ESO-EONS Masterclass in Oncology	2012
- TAT conference, Amsterdam	2012
- Brocher Foundation, travel grant Geneva	2014
- V&VN Oncology, travel grant Chicago	2015
- V&VN Oncology, travel grant Dublin	2016
- EONS, travel grant Stockholm	2017
- V&VN Oncology, travel grant Vienna	2018
- Stichting Oncowijs, travel grant Washington DC	2018

Other

- 1ste Prize Learning assessment ESO-EONS Masterclass in Oncology
- Nominated for the Meyboom Zorgprijs 2016, Erasmus MC
- Nominated for the Year Prize Research Palliative Care 2017, VUmc

ABOUT THE AUTHOR

Diane van der Biessen was born in Rotterdam, the Netherlands at January 29th 1961. After graduating secondary school at the Marnix Scholengemeenschap in Rotterdam, she started the verpleegkunde-A in 1979, at the Dam Ziekenhuis in Rotterdam. She graduated in 1982 and worked at the surgical high care unit. In 1984 she began the general ICU course and worked at the Zuiderziekenhuis, Rotterdam. She graduated in 1986. From 1986 till 1987 she worked at the surgical ICU at the Bergweg Ziekenhuis, Rotterdam. Her career at the Erasmus MC, Rotterdam, started in 1987 as an ICU nurse at the surgical intensive care 10 Zuid IC. During a work exchange trip to the Strong Memorial Hospital ICU ward in Rochester, USA, in 2000, she met nurse practitioners and was impressed with their roles.

Due to personal circumstances she switched to the cast room in 2001. She graduated as cast technician in 2004. Arthroses made this career short.

In 2005 she started as a research nurse at the Medical Oncology of the Erasmus MC Cancer Institute. This was the beginning of a 3th career. From 2006-2008 she followed the Master in Advanced Nursing Practice (MANP), at the Hogeschool Leiden. Since then she works as a nurse practitioner specialized in oncology phase I trials, combining both medical and nursing care and research in this population. The outcomes of her Master thesis: 'Dit is geen gebroken been', a qualitative research toward information needs of patient considering phase I trial participation, was the basis of her research toward patients' perspectives as described in part 2 of her thesis. As MANP she was the nursing tutor of 3 nurse practitioners and 2 bachelor students of applied psychology. Since 2008 she is a member of the Expertise Committee of the VENVN Oncology, and responsible for the accreditation of national nursing education. She lectures at the Zorg Academie of the Erasmus MC, Rotterdam. She has one son, Michael (1989). Harry Penders is her registered partner and she is the bonus grandmother of his 2 grandsons Jonas (2017) and Casper (2017).

DANKWOORD

De "zelfbeschikkingstheorie" van Edward L. Deci en Richard M. Ryan is ook op mij toepasbaar. Zoals beschreven in hun theorie, zijn de drie basisbehoeften die ten grondslag liggen aan motivatie: competentie, verbondenheid en autonomie. Mijn interesse om de drijfveren van patiënten met kanker, die deelnemen aan vroeg klinisch onderzoek, beter te kunnen begrijpen en hierdoor begrip te creëren bij anderen voor, heeft geleid tot deze promotie (competentie).

Pas op een later tijdstip in mijn carrière ben ik betrokken geraakt bij het onderzoek en de zorg voor patiënten met kanker. Het werk binnen fase I unit van de afdeling Interne Oncologie, nu het Center for Drug Development (CDD), en het behalen van mijn Master in Advanced Nursing Practice, zijn de beste professionele ervaringen van mijn leven geworden. Hiermee is alles op zijn plek gekomen en is ook het idee gegroeid om te promoveren. Ik heb de uitdagingen die op mijn pad kwamen aangenomen. Waar nodig heb ik gediscussieerd om anderen (en misschien ook wel mijzelf) van mijn keuze te overtuigen (autonomie).

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