Université catholique de Louvain
Secteur des Sciences de la Santé
IREC-Institut de Recherche Expérimentale et Clinique
EPID-Epidémiologie et Biostatistique
Bruxelles, Belgique

Progression-free survival rate as primary endpoint for phase-II cancer clinical trials: application to mesothelioma

Julie Francart

Promotor: Prof. Annie Robert
Copromotor: Dr. Richard Sylvester

Thesis submitted in fulfilment of the requirements for the degree of "Docteur en Sciences Médicales"

2009-2010

Members of the Jury

Promotor:	**Prof. Annie Robert, MSc, PhD** Pôle Epidémiologie et Biostatistique Institut de Recherche Expérimentale et Clinique Secteur des Sciences de la Santé Université catholique de Louvain
Copromotor:	**Dr. Richard Sylvester, MSc, PhD** Assistant Director and Head of Biostatistics European Organisation for Research and Treatment of Cancer Brussels, Belgium
President of the jury:	**Prof. William D'Hoore, MD, PhD** Institut de Recherche Santé et Société Secteur des Sciences de la Santé Université catholique de Louvain
UCL Members:	**Prof. Catherine Legrand, MSc, PhD** Institut de Recherche multidisciplinaire pour la modélisation et l'analyse quantitative Secteur des Sciences humaines Université catholique de Louvain
	Prof. Jean-Pascal Machiels, MD, PhD Institut de Recherche Expérimentale et Clinique Secteur des Sciences de la Santé Université catholique de Louvain
External Members:	**Prof. Jan van Meerbeeck, MD, PhD** Department of Respiratory Medicine University Hospital Ghent, Belgium
	Dr. Patrick Therasse, MD, PhD GlaxoSmithKline Biologicals, Belgium
	Prof. Philippe Lambert, MSc, PhD Institut des sciences humaines et sociales/ méthodes quantitatives en sciences sociales Université de Liège, Belgium

Scientific Curriculum Vitae

Publications

- J Francart, C Legrand, R Sylvester, M Van Glabbeke, JP van Meerbeeck, A Robert.
  Progression free survival rate as primary endpoint for phase II cancer clinical trials: an application to mesothelioma.
  J Clin Oncol, 24(9):3007-12, 2006.

- J Francart, E Vaes, S Henrard, C Legrand, P Baas, R Gaafar, JP van Meerbeeck, R Sylvester, A Robert.
  A Prognostic index for progression free survival in malignant mesothelioma with application to the design of phase II trials: a combined analysis of 10 EORTC trials.
  Eur J Cancer, 45(13):2304-2311, 2009.

- E Goffin, Y Pirard, J Francart, M Vignioble, T Govaerts, A Robert, Y Pirson.
  Daily hemodialysis and nutritional status.
  Kidney Int 61:1909-10, 2002.

- L Decelle, J Francart, F Hammer, P Wallemacq, A Robert, B Boland.
  Artherosclerose et marqueurs inflammatoires seriques: étude chez 297 patients de la consultation de prevention de l'artherosclerose.
  Louvain Medical 121:415-424, 2002.

- K Al-Shawafi, J Francart, A Robert, A de Meester, B Pirenne, J Col.
  A lytic test for determination of resistance to streptokinase predicts 30-day survival in patients treated with streptokinase for acute myocardial infarction.
  Eur Heart J, 23:725-725, 2002.

- E Van Den Neste, L Michaux, N Layios, S Costantini, J Francart, C Lambert, A Sonet, M André, A Robert, A. Ferrant.
  High incidence of complications after 2-chloro-2'-deoxyadenosine combined with cyclophosphamide in patients with advanced lymphoproliferative malignancies.
  Ann Hematol, 83(6):356-63, 2004.

- I Jordan, A Robert, J Francart, L Sann, G Putet.
  Growth in extremely-low-birth weight infants up to three years.
  Biol Neonate, 88(1):57-65, 2005.

- G Clerbaux, J Francart, P Wallemacq, A Robert, E Goffin.
  Evaluation of peritoneal transport properties at onset of peritoneal dialysis and longitudinal follow-up.
  Nephrol Dial Transplant, 21:1032-1039, 2006.

- E Van Den Neste, V Robin, J Francart, A Hagemeijer, M Stul, P Vandenberghe, A Delannoy, A Sonet, V Deneys, S Constantini, A Ferrant, A Robert, L Michaux. *Chromosomal translocation independently predict treatment failure, treatment-free survival and overall survival in B-cell chronis lymphocytic leukemia patients treated with cladribine.* Leukemia, 21(8):1715-22, 2007.

Oral communications

- J Francart, M Jeanjean, F Nackers, R De Muylder, B Boland, A Robert. *Time trends in the incidence of a first myocardial infarction: report from the register of the Belgian Province of Luxemburg.* XXth annual meeting of the Belgian Society of Cardiology, February 2001, Brussels, Belgium.

- J Francart, S Cauderlier, K Van Emelen, C Gourbin, J Heyrman, D Pestiaux, D Paulus. *Emergencies during the weekends: who consults a general practitioner on duty or an emergency department?* Annual meeting of European General Practice Research Network (EGPRN): Culture and Disease in General Practice, May 2004, Antwerpen, Belgium.

- J Francart. *Progression free survival rate as the main endpoint for phase II cancer clinical trial.* Annual meeting of EORTC, March 2005, Brussels, Belgium.

- J Francart, E Vaes, R Sylvester, M Van Glabbeke, JP van Meerbeeck , A Robert. *Prognostic factors in malignant mesothelioma of progression-free survival : a better approach for phase II mesothelioma trials.* 14th annual meeting of the Belgian Statistical Society, October 2006, Houffalize, Belgium.

- J Francart. *Drug development process-clinical trials in oncology.* Opening day of the graduate school in Statistics and Actuarial Science, February 2007, Louvain-la-Neuve, Belgium.

- J Francart, F Renard, A Van den Bruel, B Decallonne, L Van Eycken. *Is the difference in thyroid cancer incidence between the Belgian regions associated to variations in surgical practice?* XXXIV meeting of Group of Latin Language Registries-GRELL, May 2009, Lugano, Switzerland.

- G Clerbaux, J Francart, P Wallemacq, A Robert, E Goffin. *Evaluation of the peritoneal membrane permeability at peritoneal dialysis onset and longitudinal follow-up.* XLIth Congress of the European Renal Association and European Dialysis and Transplantation Association, May 2004, Lisbon, Portugal.

Posters

- J Francart, M Jeanjean, F Nackers, R De Muylder, B Boland, A Robert.
  Trends in coronary heart events: modest or no decline in younger men and women having no history of coronary artery disease.
  Vth International Conference on Preventive Cardiology,
  May 2001, Osaka, Japon.

- J Francart, C Legrand, M Van Glabbeke, R Sylvester, A Robert, JP van Meerbeeck.
  Progression free survival rate as the main endpoint for phase II cancer clinical trials: an application to mesothelioma.
  Vth International meeting of French Society of Statistics, Statistical Methods in Biopharmacy and Statistical Innovations in Clinical Trials,
  September 2005, Paris, France.

- J Francart, R Sylvester, A Robert.
  Evaluation of multivariate prognostic models: an application of Cox regression to EORTC malignant mesothelioma trials.
  15th annual meeting of the Belgian Statistical Society,
  October 2007, Antwerpen, Belgium.

- J Francart, E Vaes, R Sylvester, A Robert.
  Adapting the cancer phase II design for a better assessment of therapeutic activity: application to malignant mesothelioma.
  16th annual meeting of the Belgian Statistical Society,
  October 2008, Wepion, Belgium.

Acknowledgements

First, I would like to express my gratitude to my Promotor, Professor Annie Robert, who gave me the opportunity to realize this thesis and who trusted me through this long journey. I thank her for her scientific support, her human qualities and for finding the funds necessary to continue this work that started at the EORTC.

I am grateful to Richard Sylvester for spending time on my thesis besides his heavy work at the European Organization for Research and Treatment of Cancer. I thank the EORTC for giving me the opportunity to work on this project and to finance a part of this thesis.

I thank all members of the jury who accepted to judge this thesis with their expertise, the President, Professor William D'Hoore, Professor Catherine Legrand, Professor Jean-Pascal Machiels, Professor Jan Van Meerbeeck, Professor Philippe Lambert, and Doctor Patrick Therasse. I really appreciated that they spent their valuable time commenting this work, and helped me to go through the final stage of this work.

I would like to take the opportunity to sincerely thank all the EPID staff for their endless help, their numerous encouragements provided through the years and all the good moments that we shared together.

I am grateful to the Belgian Cancer Registry who was very patient and comprehensive with me. Moreover, I received support of all my colleagues whom I thank warmly.

And, last but not least, I owe my deepest gratitude to my close family and my friends. This thesis would not have been possible without them. I often doubted that I'll finish one day this thesis but over time my close family and friends have always continued to support me and believed in me. I am especially grateful to everyone who took care of my children to allow me to focus on my thesis. I also warmly thank Jean who was an important help in the final step of the redaction of this manuscript and Ragui for her help for the final formatting. I am really grateful to my children who had to live for several months with a mother tired and less available. My dear husband was very patient and gave me the strength to finish this thesis. I thank you for your love.

List of abbreviations

Ad-HSVtk	Adenovirus vectors containing the Herpes Simplex Virus thymidine kinase
AIC	Akaike's Information Criterion
AICC	Akaike's Information Corrected Criterion
AJCC	American Joint Committee on Cancer
bFGF	basic Fibroblast Growth Factor
BIC	Schwartz's Bayesian Information Criterion
CALGB	Cancer And Leukemia Group B
CDKN2A	Cyclin-Dependent Kinase inhibitor 2A
c-index	concordance index
COX-2	Cyclooxygenase-2
cpe	concordance probability estimate
CR	Complete Response
CT scans	Computed Tomography scans
EGFR	Epidermal Growth Factor Receptor
EMEA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EPP	Extrapleural Pneumonectomy
FDA	Food and Drug Administration (United States)
^{18}F-FDG	[^{18}F] Fluorodeoxyglucose
^{18}F-FDG PET	[^{18}F] Fluorodeoxyglucose Positron Emission Tomography
Flk-1/KDR	Fetal liver kinase-1/kinase insert domain
Flt-1,-3,-4	Fms-like tyrosine kinase-1,-3,-4
IFN-α/β/γ	Interferon alpha/beta/gamma
IL-2	Interleukin-2
IMIG	International Mesothelioma Interest Group
LAK cells	Lymphokine-Activated Killer cells
M	Metastases
MDICT	Methodology for the Development of Innovative Cancer Therapies
MM	Malignant Mesothelioma
MMP	Matrix Metalloproteinases
MPF	Megakaryocyte Potentiation Factor
MPM	Malignant Pleural Mesothelioma
MRI	Magnetic Resonance Imaging
MVD	Microvessel Density
N	Lymph node
NCI	National Cancer Institute

ODCR	Overall Disease Control Rate
P/D	Pleurectomy and Decortication
PDGF	Platelet Derived Growth Factor
PET imaging	Positron Emission Tomography imaging
PFS	Progression-Free Survival
PH	Proportional Hazards
PR	Partial Response
RECIST	Response Evaluation Criteria in Solid Tumours
RR	Response Rate
SAHA	Suberoylanilide Hydroxamic Acid
SD	Stable Disease
SMRP	Soluble Mesotheline-Related Peptide
Src tyrosine kinase	Sarcoma proto-oncogenic tyrosine kinase
SV40	Simian Virus-40
T	Tumor
TGA	Therapeutic Goods Administration (Australia)
TNF-α	Tumour Necrosis Factor-α
TTP	Time To Progression
UICC	Union Internationale Contre le Cancer
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organisation

Table of contents

Outline

The aim of a phase-II cancer clinical trials is to screen new drugs for their biological antitumour activity. Usually, the response rate is used as primary endpoint. Response rate is an indicator for treatment success based on tumour growth. It is measured as the decrease in size of cancer lesions. Even if its pertinence is supported by empirical evidence, it could be non relevant in at least two cases. Firstly, if a new drug is not a cytoreductive anticancer agent but a cytostatic agent. Indeed, in case of the cytostatic agent, biological activity is characterized by the stabilisation of the tumour growth rather than the shrinkage of lesions, consequently the response rate is inappropriate. Secondly, there are situations where response assessment is difficult. It is the case, for instance, when the cancer doesn't show a circumscribed tumour mass which can be delineated radiographically. When the response is inappropriate as primary endpoint in phase-II trial, progression-free survival rate (absence of progression/death at a fixed time point) rather than response rate has been suggested as primary endpoint in phase-II trial [1,2].

To design a phase-II trial, the sample size and decision rules are computed on the basis of two probabilities of event: p_0 which is the probability of event below which the tested drug is considered as inactive; and p_1 which is the probability of event above which the tested drug is considered as active. The values of these two event probabilities will obviously differ if the definition of the event is changed from response to progression-free survival status. There is a large number of published data regarding response rate and it's nowadays possible to determine p_0 and p_1. In contrast, only few results have been published on progression-free survival rate, in particular at shorter times (e.g. 3 or 6 months) which are of interest in phase-II trials that address an aggressive cancer. The published data concern often the progression-free survival rates at one year or more.

The main objective of this project was therefore to estimate, for a given cancer type, appropriate baseline reference values for p_0 and p_1 with the aim of designing future phase-II trials targeting the progression-free survival rate at short time as primary endpoint**.**

The following criteria should be taken into account in order to choose the type of cancer which could be explored to estimate the progression-free survival rate values to be used in future phase-II trials:

1. The use of progression-free survival rate has to be relevant as endpoint. So, the patients have to be either in advanced stage of disease (disease in progression, presence of metastasis…) or with bad prognosis for which we can assume that they will progress rapidly even when they are without signs of progression at the beginning of the study.
2. The knowledge of these reference values should help in the design of further phase-II trials and the project of phase-II trials must be relevant.
3. The data should be available.

We chose to apply those principles to the case of mesothelioma for which the above criteria are met:

1. The use of progression-free survival rate is relevant as endpoint because the mesothelioma is a rapidly progressing malignant disease with a bad prognosis and with a median survival time of 12 months only. Moreover, mesothelioma typically shows a parietal growth pattern and often no circumscribed tumour mass which can be delineated radiographically, indicating that the response assessment is difficult and not reproducible[3].
2. The project of phase-II trials is relevant, especially for testing new targeted therapies. Indeed, the incidence of mesothelioma is increasing all over the world and the existing treatments are insufficient. The development of more active treatments is thus a need and new targeted therapies, including the cytostatic agents, are currently the main focus of mesothelioma research [4-7].
3. Data of 10 mesothelioma trials were available at the European Organisation for Research and Treatment of Cancer's Data Center. All trials were organised by the European Organisation for Research and Treatment of Cancer according to similar protocols. There were 9 closed phase-II trials which were all part of a large phase-II program for screening the activity of several different single agents, and consecutively one phase-III trial was carried out that tested a combination of two drugs. The data were thus a homogeneous pool of data that can be merged.

In this work, we estimated progression-free survival rates at 3, 4, 5, and 6 months in patients with mesothelioma. These values can be used as reference values to determine p_0 and p_1 for future mesothelioma phase-II trials that use progression-free survival rate as a primary endpoint.

In chapter I, the epidemiology and treatment of mesothelioma are explained. Chapter II briefly describes the development process of a new therapy in the field of oncology and develops in detail phase-II trial design. Chapter III concerns the description of data and statistical methods used in this work. Chapter IV includes the published results of this work and several additional points of discussion. Chapter V discusses the different endpoints used in phase-II trials, the experience of phase-II mesothelioma trials, and the benefit of a prognostic index for progression-free survival. Chapter VI concludes this work and introduces some future perspectives.

Reference List

1. Korn EL, Arbuck SG, Pluda JM, Simon R, Kaplan RS, Christian MC. Clinical trial designs for cytostatic agents: Are new approaches needed? J Clin Oncol 2001; 19(1):265-272.

2. Van Glabbeke M, Verweij J, Judson I, Nielsen OS. Progression-free rate as the principal end-point for phase II trials in soft-tissue sarcomas. Eur J Cancer 2002; 38(4):543-549.

3. Sterman DH, Albelda SM. Advances in the diagnosis, evaluation, and management of malignant pleural mesothelioma. Respirology 2005; 10(3):266-283.

4. Jackman DM. Current options for systematic therapy in mesothelioma. Semin Thorac Cardiovasc Surg 2009; 21:154-158.

5. Kindler HL. Systemic Treatments for Mesothelioma: Standard and Novel. Curr Treat Options Oncol 2008; 9(2-3):171-179.

6. Ray M, Kindler HL. Malignant pleural mesothelioma: an update on biomarkers and treatment. Chest 2009; 136(3):888-896.

7. Tsao AS, Wistuba I, Roth JA, Kindler HL. Malignant Pleural Mesothelioma. J Clin Oncol 2009; 27(12):2081-2090.

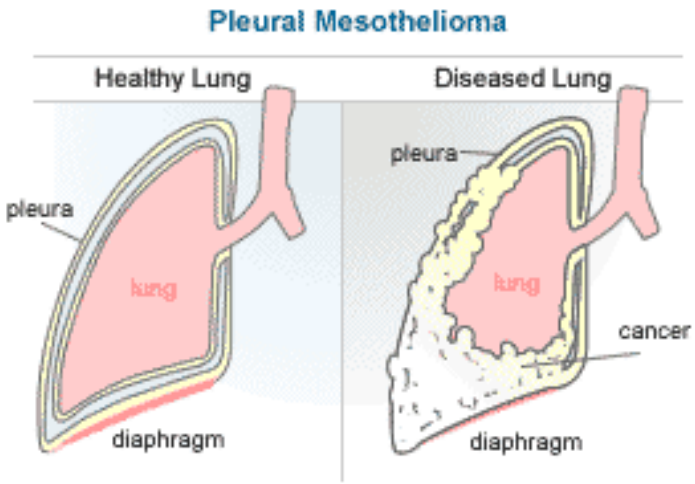
Chapter I. Epidemiology and Treatment of mesothelioma

1. Definition of mesothelioma

Mesothelioma is a rare form of cancer in which malignant cells are found in the mesothelium. The mesothelium is a membrane that covers and protects most of the internal organs of the body. It is composed of two layers of cells: one layer immediately surrounds the organ (visceral membrane); the other forms a sac around it (parietal membrane). The mesothelium produces a lubricating fluid that is released between these layers, allowing moving organs (such as the beating heart and the expanding and contracting lungs) to glide easily against adjacent structures. The mesothelium has different names, depending on its location in the body:

- The peritoneum is the mesothelial tissue that covers most of the organs in the abdominal cavity.
- The pleura is the membrane that surrounds the lungs and lines the wall of the chest cavity.
- The pericardium covers and protects the heart.
- The mesothelial tissue surrounding the male internal reproductive organs is called the tunica vaginalis testis.
- The tunica serosa uteri covers the internal reproductive organs in women.

Most cases of mesothelioma begin in the pleura (70-80%) or peritoneum [1]. In this work, the data come from trials which included patients with pleural malignant mesothelioma and rare cases of peritoneal mesothelioma.



2. Incidence of mesothelioma

Although incidence rates of malignant mesothelioma have increased in the past 20 years, mesothelioma is still a relatively rare cancer. Incidence of malignant mesothelioma currently ranges from about 7 to 40 per 1,000,000 person-years in industrialized Western nations, depending on the amount of asbestos exposure of the populations during the past several decades [2]. For comparison, populations with high levels of smoking can have a lung cancer incidence of over 1,000 per 1,000,000 person-years. The highest incidence is found in Britain, Australia, Netherlands and Belgium (around 30 per 1,000,000 person-years)[3]. About 2,500 new cases of mesothelioma are diagnosed annually in the United States, of which 2,000 are men and 500 are women [4,5]. In Belgium, 484 new cases (410 in men and 74 in women) were registered between 2004 and 2005. The incidence rate 2004-2005 is 22 per 1,000,000 person-years in men and 4 in women [6]. The incidence rate of mesothelioma for other countries is reported in the following table [7]:

Countries	Cases per year	Cases per 1 000 000 persons-years
Finland	75 (2002)	18
France	870 (2000)	18
Germany	1094 (2001)	16
United Kingdom	1862 (2002)	39
Italy	1050 (2000)	21
Netherlands	389 (2000)	30
Norway	57 (2000)	16
Sweden	149 (2003)	20

Even with widespread asbestos abatement efforts, mesothelioma remains a serious problem as the worldwide incidence of the disease continues to increase. After the 1970s bans on asbestos were initiated, it was believed that the United States incidence of mesothelioma would peak in 2004. In Western Europe where for several countries bans on asbestos were implemented later (e.g. in UK nearly a decade later and in Italy in 1992), the incidence of mesothelioma is expected to increase from 5,000 men dying in 1998 to a projected 9,000 men dying by 2018, with the highest incidence in the 1945 to 1950 birth cohort of men [3,5,8,9]. In Japan where asbestos consumption was still high in the last decades (in 1980 nearly 400,000 tons of asbestos were used and relevant amounts of this mineral were used until 2000), the peak incidence is predicted in 2025, and 103,000 deaths are anticipated over the next 40 years [3,10].

Mesothelioma is usually diagnosed in the fifth to seventh decades of life and has a strong male predominance. Median survival time from symptom onset is approximately 12 months, depending on the initial stage and various prognostic factors [2,5,11,12].

3. Aetiological factors of mesothelioma

3.1. Asbestos exposure

Asbestos exposure is the major risk factor for mesothelioma. Asbestos is the name of a group of minerals that occur naturally as masses of strong, flexible fibres. Asbestos has been widely used in many industrial products, including cement, brake linings, roof shingles, flooring products, textiles, and insulation. If tiny asbestos particles float in the air, especially during the manufacturing process, they may be inhaled or swallowed, and can cause serious health problems. In addition to mesothelioma, exposure to asbestos increases the risk of lung cancer, asbestosis (a noncancerous, chronic lung ailment), and other cancers, such as those of the larynx and kidney.

A history of asbestos exposure at work is reported in about 70 to 80 percent of cases [4,5]. The lifetime risk of developing mesothelioma among asbestos workers is thought to be as high as 8 to 13%. The risk of asbestos-related disease increases with heavier exposure to asbestos and longer exposure time. However, some individuals with only brief exposures have developed mesothelioma. On the other hand, not all workers who are heavily exposed develop asbestos-related diseases. This indicates that factors other than asbestos play a role in the genesis of the tumour [3,5].

There is typically a long latency period of about 20 to 40 years or more from the time of asbestos exposure to the development of mesothelioma, with variability depending on the type of fibres and the intensity of exposure [1,3,5,9,13].

3.2. Viral oncogenes

Simian virus-40 (SV40) is a virus DNA with oncogenic potential in humans. It encodes for various proteins that induce replication of cellular DNA and cause chromosome rearrangements and point mutations as well as aneuploidy. Furthermore, p53 and other tumour suppressor gene products are inactivated, subsequently leading to uncontrolled cell proliferation. Finally, malignant mesothelioma may arise, particularly in patients with pre-existing genetic alterations due to asbestos exposure [1,13]. Several studies have suggested that asbestos and SV40 are cocarcinogens, with one potentiating the effect of the other, but the carcinogenic role of SV40 is still highly debated in the literature [11,14].

3.3. Genetic factors

The clustering of mesothelioma among members of a single family raises a number of questions related to the genetic factors. It's possible that cases of mesothelioma in this setting may occur among those with a cancer-prone genotype susceptible to the toxic effects of asbestos or other non-asbestos fibers such as erionite [5].

The chromosomal abnormalities known to occur in malignant mesothelioma are complex and heterogenous. Nevertheless, some abnormalities appear not to be random and, therefore, may play a role in tumour genesis. Deletions of chromosome regions 1p, 3p, 9p, and 6q, as well as loss of chromosome 22 have been documented by various methodologists, who suggest a recessive mechanism of oncogenesis. Recurrent loss of genetic material in several chromosomal regions may be consistent with a multistep carcinogenic cascade. These recurrent genomic losses are consistent with the loss of both defined and putative tumour suppressor genes important in the development of mesothelioma, including the cyclin-dependent kinase inhibitor 2A (*CDKN2A)* locus in chromosomal location 9p21 containing p16 and p14, and neurofibromatosis 2 in chromosome 22 [2,5,15-17].

3.4. Other etiologic factors

In rare cases, malignant pleural mesothelioma may also develop upon radiotherapy, on account of thorotrast deposits, due to exposure to non-asbestos fibers such as zeolite (e.g. erionite) or glass fibers and in connection with other primary malignancies such as Hodgkin's disease or hepatocellular carcinoma [3,13]. The association between mesothelioma and other cancers could indicate a role of immune impairment in the genesis of mesothelioma [3].

In a recent study, the presence of benign pleural disease (pleura affected by pleural plaques which is the effect of recurrent inflammatory and repair processes) appeared to increase the risk of peritoneal mesothelioma, but not the risk of pleural mesothelioma.

Despite this negative finding, it is biologically plausible that an endless sequence of inflammatory episodes represents a condition predisposing to malignant evolution [3].
Some studies suggest that dietary factors might influence the risk of mesothelioma. Diets rich in fruit and vegetables seem to have a protective effect [3]. A reduction of antioxydants (such as alpha-tocopherol and ascorbic acid) in the serum of patients with mesothelioma was reported by Emri et al [18].

4. Symptoms of mesothelioma

Shortness of breath, persistent dry cough, and chest pain due to an accumulation of fluid in the pleura are often symptoms of pleural mesothelioma. Less common symptoms of pleural mesothelioma include fever, night sweats, and weight loss. Symptoms of peritoneal mesothelioma include weight loss, abdominal pain, and swelling due to ascites (a build-up of fluid in the abdomen cavity). Other symptoms of peritoneal mesothelioma may include bowel obstruction, blood clotting abnormalities, anaemia, and fever. If the cancer has spread beyond the mesothelium to other parts of the body, symptoms may include pain, trouble swallowing, or swelling of the neck or face [1,5,12].

These symptoms are not specific and may be caused by mesothelioma or by other more common diseases like flu, pneumonia, bronchitis, heart disease, and others. It is why the diagnostic is often delayed and requires a specialist's advice.

Metastatic disease is uncommon at presentation, and controlateral abnormalities are often due to asbestos-related pleural disease rather than metastatic disease. Death is rarely a result of metastatic disease, it is usually due to infection or respiratory failure along with constitutional symptoms associated with progressive malignancy [5].

5. Diagnostic of mesothelioma

Diagnosing mesothelioma is often difficult, because the symptoms are similar to those of a number of other conditions. Diagnosis begins with a review of the patient's medical history, including any history of asbestos exposure. A complete physical examination has to be done, including x-rays of the chest or abdomen and lung function tests. The X-ray may reveal pleural thickening commonly seen after asbestos exposure and if so, it increases suspicion of mesothelioma. However, pleural plaques, while indicative of asbestos exposure, are not diagnostic for mesothelioma. Computed tomography and magnetic resonance imaging are helpful in identifying the location and extent of the involved areas but cannot always differentiate benign from malignant processes. Positron emission tomography (PET) imaging is now becoming an important part of the diagnosis and evaluation of mesothelioma. Fluorodeoxyglucose-PET imaging, which in oncology is based on changes in metabolic pathways of glucose, has been shown in a number of studies to differentiate malignant and benign lesions in patients with asbestos exposure [19]. If a large amount of fluid is present, abnormal cells may be detected by cytology if this fluid is aspirated with a syringe. Pleural fluid cytology findings are often negative despite repeated sampling; therefore physicians achieve a diagnosis in only 26 % of cases by using this method [9]. If cytology is positive or a plaque is regarded as suspicious, a needle biopsy of the mass is required to confirm the diagnosis of mesothelioma. If these procedures do not yield enough tissue, an open pleural biopsy may be recommended. In open pleural biopsy, a surgeon will make a small incision through the chest wall or in the abdomen and insert a thin, light tube called thoracoscope or peritoneoscope. The thoracoscopy or peritoneoscopy yield a diagnosis in 98% of patients [9,17].

Because of difficulties in the diagnosis of malignant mesothelioma, research has concentrated on finding new ways to detect the presence of the disease. Two serum markers have recently been developed, serum mesothelin-related peptide and osteopontin. Serum mesothelin-related peptide is elevated in patients with epithelioid

and biphasic malignant pleural mesothelioma and it may be predictive of disease recurrence after surgical resection [20,21]. Osteopontin is a glycoprotein that binds integrin and CD44 receptors and it has been shown to discriminate patients with malignant pleural mesothelioma from those who have benign pleural changes resulting from asbestos exposure [22,23].

6. Stages of mesothelioma

Mesothelioma is said to be localized if the cancer is found only on the membrane surface where it originated. It is classified as advanced if it has spread beyond the original membrane surface to other parts of the body, such as the lymph nodes, lungs, chest wall, or abdominal organs.

However, a standard staging is important to compare studies and to determine treatment and prognosis.

For **peritoneal mesothelioma**, there is currently no established staging system, and if the disease is staged, it is usually done in accordance with the TNM system, the most common general cancer staging system. This system refers to the status of the tumour (T), lymph nodes (N) and metastases (M). There are general categories which may also be somewhat helpful in determining stage. The first category concerns localized lesion able to be completely resected. In the second category, the tumour is contained within the abdominal cavity on peritoneal and organ surfaces where debulking (i.e. the surgical removal of part of a malignant tumour which cannot be completely excised) is possible. Category three is a lesion contained within the abdominal cavity with invasion of organs such as the colon or liver. Category four concerns lesion extending outside the abdominal cavity [24].

For **pleural mesothelioma**, several staging systems exist. The oldest staging system is the *Butchart System* (1976) which is based mainly on the extent of primary tumour mass and divides mesotheliomas into four stages [25]. These are described in table 1. The Butchart's staging system did not use the T, N, and M descriptors. For this reason the *International Mesothelioma Interest Group (IMIG)* introduced a new staging system in 1995 based on these parameters [26]. It incorporates data on the natural history and influence of TN status on overall survival. It reconciles previous staging systems and is similar to those for other solid tumours. This staging system was simultaneously adopted by the *American Joint Committee on cancer* (AJCC) and the *Union Internationale Contre le Ca*ncer (UICC) in 2002 [27]. TNM-staging and stage grouping

are given in table 2 and 3. Regarding the T status, T3 implies locally advanced but potentially resectable mesothelioma, whereas T4 means an irresectable tumour as in lung cancer patients.T1 indicates that there is usually a free pleural space and these patients often present with a large pleural effusion. However, the presence of pleural fluid has no effect on staging. By non-invasive staging it is rather difficult to make a distinction between T1a, T1b and T2 disease. Correct estimation of extent of disease is only possible during thoracotomy. In case of T1b disease, pleurectomy and decortication are usually feasible. In case of T2 tumour there is more extensive involvement of the visceral pleura and lung, often necessitating pleuropneumonectomy. The prognosis of a T4 tumour is rather similar to M1 disease and for this reason it is included in stage IV. For the N status, the regional lymph nodes include the hilar, mediastinal, internal mammary nodes, as well as the scalene and supraclavicular lymph nodes. N2 disease includes invasion of the ipsilateral mediastinal, subcarinal or the ipsilateral internal mammary nodes, and N3 disease the contralateral hilar, mediastinal, internal mammary nodes and/or the ispilateral or controlateral supraclavicular or scalene lymph nodes. As there is probably not a large survival difference between N1 and N2 involvement in mesothelioma, all patients with nodal involvement are classified as stage III (N1, N2) or stage IV (N3 disease).

Another staging system, called the *Brigham staging system,* was introduced after analyzing the first 52 patients treated with trimodality therapy at the Dana-Faber Cancer Institute/Brigham and Women's Hospital Thoracic Oncology Program [28]. While some cancer staging systems measure exclusively the extent of tumour growth, the Brigham System stages also mesothelioma according to resectability (the ability to surgically remove) and lymph node involvement. It consists of four distinctive stages, each of which considers two variables: the possible efficacy or inefficacy of surgery to reduce or remove the mass from the patient's body, as well as the presence or absence of cancer in the lymph nodes (table 4). This particular system is less used to measure the stages of mesothelioma development because this particular cancer is seldom operable (because it is usually not diagnosed until advanced stages).

In the data analyzed in this work, the stage of disease was reported according to either Butchart's staging system or International Mesothelioma Interest Group staging system.

Table 1. Staging system by Butchart, 1976 [25]

Stage	Description
I	Tumour confined within the "capsule" of the parietal pleura, i.e., involving only ipsilateral pleura, lung, pericardium, and diaphragm
II	Tumour invading chest wall or involving mediastinal structures, e.g., oesophagus, heart, opposite pleura. Lymph node involvement within the chest
III	Tumour penetrating diaphragm to involve peritoneum, involvement of opposite pleura Lymph node involvement outside the chest
IV	Distant blood-borne metastases

Table 2. International TNM staging system for diffuse malignant pleural mesothelioma according to the International Mesothelioma Interest Group, 1995 [26,27]

Primary Tumour (T)

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

T1 Tumour involves ipsilateral parietal pleura, with or without focal involvement of visceral pleura
- T1a : Tumour involves ipsilateral parietal (mediastinal, diaphragmatic) pleura. No involvement of the visceral pleural
- T1b : Tumour involves ipsilateral parietal (mediastinal, diaphragmatic) pleura, with focal involvement of the visceral pleura

T2 Tumour involves any of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features :
- confluent visceral pleural tumour (including the fissures)
- invasion of diaphragmatic muscle
- invasion of the lung parenchyma

T3 Describes locally advanced but potentially resectable tumour. Tumour involves any of the ipsilateral pleural surfaces with at least one of the following features :
- invasion of the endothoracic fascia
- extension into the mediastinal fat
- solitary, completely resectable focus of tumour extending into the soft tissue of the chest wall
- non-transmural involvement of the pericardium

T4 Describes locally advanced, technically unresectable tumour. Tumour involves any of the ipsilateral pleural surfaces with at least one of the following features :
- diffuse extension or multifocal masses of tumour in the chest wall, with or withtout local rib destruction
- direct transdiaphragmatic extension of tumour in the peritoneum
- direct extension of tumour to the contralateral pleural
- direct extension of tumour in one or more mediastinal organs
- direct extension of tumour into the spine
- direct extension through to the internal surface of the pericardium with or without a pericardial effusion; or tumour involving the myocardium

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional or hilar
N1 Ipsilateral or hilar hymph nodes positive
N2 Mediastinal or ipsilateral internal mammary lymph nodes positive
N3 Contralateral mediastinal, supraclavicular or contralateral internal mammary lymph nodes positive

Distant Metastasis (M)

MX[a] Presence of metastases cannot be assessed
M0 No distant metastases
M1 Distant metastases

Table 3. Different stages of malignant mesothelioma [27]

	M0					M1
M0		N0	N1	N2	N3	
	T1a	**Ia**	**III**	**III**	**IV**	**IV**
	T1b	**Ib**	**III**	**III**	**IV**	**IV**
	T2	**II**	**III**	**III**	**IV**	**IV**
	T3	**III**	**III**	**III**	**IV**	**IV**
	T4	**IV**	**IV**	**IV**	**IV**	**IV**
M1		**IV**	**IV**	**IV**	**IV**	

Table 4. Brigham Staging System [28]

Stage I	Resectable mesothelioma and no lymph node involvement
Stage II	Resectable mesothelioma but with lymph node involvement
Stage III	Unresectable mesothelioma extending into chest wall, heart, or through diaphragm, peritoneum; with or without extrathoracic lymph node involvement
Stage IV	Distant metastatic disease

[a] In the seventh edition (2009) of the TNM classification of malignant tumours, MX disappeared. Indeed, the MX category is considered to be inappropriate as clinical assessment of metastasis can be based on physical examination alone.

7. Treatment of mesothelioma

The treatment of mesothelioma depends on the location of the cancer, the stage of the disease, and the patient's age and general health. Curative intent surgical resection is usually restricted to highly selected patients. For the majority of mesothelioma patients, whose age, co-morbid medical illness, non-epithelial histology, and locally advanced disease often preclude surgery, systematic therapy is the only treatment option.

7.1. Surgery, radiotherapy, and chemotherapy : the current treatment options

7.1.1. Surgery

When facing mesothelioma, there are two types of surgery but both types, alone or used in combination with pre- and post-operative adjuvant therapies, have been disappointing.

A pleurectomy and decortication (P/D) is an open thoracotomy; removal of the parietal pleura, pleura over the mediastinum, pericardium, and diaphragm; and stripping of the visceral pleura for decortication [10]. The prognosis after this surgery is poor: 5-years disease free survival 0% and median overall survival around 15 months [16]. The advantages of this surgery are a faster recovery time and that it offers an alternative for patients who can not tolerate radical surgery like extrapleural pneumonectomy. The disadvantages are the increasing risk of recurrence of the disease because the whole tumour cannot be removed and the fact that a high dose of radiotherapy cannot be used because of the potential damage to the underlying lung. Patients treated with P/D often experience local recurrence at the initial site of the disease and, less frequently, distant recurrence. The local and distant recurrence rates are 64% to 72% and 10% to 36% respectively [10]. Consequently, pleurectomy is usually a palliative procedure to relieve chest wall pain and prevent recurrent pleural effusions by stripping off the visceral and parietal pleura. Extensive debulking is possible, but incomplete resection is often seen along the diaphragmatic and mediastinal pleura.

Extrapleural pneumonectomy (EPP) is a bloc removal of tissues in the hemithorax, including the parietal and visceral pleura, involved lung, mediastinal and lymph nodes, diaphragm, and pericardium [10]. To be eligible for this surgery, a patient must meet several criteria (e.g. a low stage of disease) and have adequate pulmonary and cardiac functions to support the surgery. In most cancer centers, patients with significant cardiac morbidities, sarcomatoid histology, mediastinal lymph nodes, and poor

performance status are not considered candidates for EPP because they usually have a worse prognosis [10]. No difference in overall long-term survival is observed, keeping a median survival at 15 months, but the disease-free survival period is improved: 5-year disease-free survival 10 to 20 % [16]. In contrast with P/D, distant recurrence rate is higher than that of local recurrence (41% to 44% vs 31% to 65%). Although EPP may alter the pattern of recurrence with less locoregional recurrence, it remains a surgical procedure that is associated with high morbidity, and its contribution toward overall survival benefit remains unclear. The 30-day operative mortality rate for EPP in experienced centres ranges between 3.4% and 18% (while mortality from P/D is less than 2% [4]), and the 2-year survival rate lies between 10% and 37% [10]. This surgery aims to remove a major part of the tumour, knowing that most probably the residual microscopic disease remains. Consequently, adjuvant therapies (radiotherapy and/or chemotherapy) are used in combination to eliminate the residual disease.

The choice of surgical resection technique is still controversial. Previously, it was assumed that EPP was the only treatment modality that could ensure long-term survival for patients with malignant pleural mesothelioma because it macroscopically removed all gross disease. However, a complete resection is theoretically impossible, because neither EPP nor P/D will eliminate residual microscopic disease. It is therefore difficult to identify the role of EPP in malignant pleural mesothelioma, knowing that there are not yet definitive results available from randomized trials. Recently, from a large retrospective analysis comparing EPP with P/D, Flores et al [29] reported that P/D in combination with various multimodality therapies may also provide long-term survival benefit. This analysis showed that women, patients with earlier stage disease, epithelioid histology, treatment with multimodality therapy, and those who underwent P/D had better survival outcomes. After eliminating the operative deaths, multivariate analysis showed that EPP led to worse survival than P/D. Also the choice of surgery did not affect survival outcomes for patients with either early-stage (I and II) or higher-stage (III an IV) disease. It therefore remains unclear which surgical resection may benefit a particular patient, and prospective randomized trials are needed to define this issue [10]. At present, there is one ongoing phase-III trial called the Mesothelioma and Radical Surgery trial that randomly assigns patients with MPM to either receive an EPP or a surgical debulking that is not an EPP[30]. Patients in both arms of the trial may receive induction chemotherapy and/or adjuvant radiotherapy, because it is believed that

trimodality treatment can improve survival and locoregional control [29,31,32]. When the results of this trial will be available, the role of EPP in malignant pleural mesothelioma will be better established.

7.1.2. Radiotherapy

Radiation therapy given alone with curative intent has never been shown to improve survival from mesothelioma. The required radiation dose to treat mesothelioma that has not been surgically removed would be highly toxic. Radiotherapy can be delivered either prophylactically to prevent tumour seeding at a surgically instrumented incision site (i.e., chest tubes sites) or for definitive intent to entire hemithorax after surgical resection. Three small randomized studies have compared prophylactic radiation with no radiation at chest tube drain or pleural biopsy sites. Two trials reported no benefit; whereas one did; it therefore remains controversial whether prophylactic radiotherapy is warranted [33-35].

After surgical resection, the entire hemi-thorax can be treated with radiation therapy, often given simultaneously with chemotherapy. This approach of using surgery followed by radiation with chemotherapy has been pioneered by the thoracic oncology team at Brigham & Women's Hospital in Boston [36]. Delivering radiation and chemotherapy after a radical surgery has led to extended life expectancy in selected patient populations with some patients surviving more than 5 years. The adjuvant hemithoracic radiotherapy (54 Gy) added to EPP improves local control, with as final results 13% risk of local recurrence and 64% incidence of distant metastasis [32]. To date, the only treatment modality that decreases the risk of local recurrence after surgical resection is radiotherapy. High-dose radiotherapy (54 Gy) with sequential chemotherapy was reported to improve locoregional control over moderate-dose radiotherapy (30 Gy to hemithorax, 40 Gy to mediastinum, and boost to 54 Gy in positive margins or nodes). However, this results (n=39) was not statistically significant, and the dose of radiotherapy did not predict survival [37].

Alternative radiotherapy techniques, such as intensity-modulated radiation therapy, have early reports demonstrating a 95% chance of disease control in the irradiated field and a locoregional control rate of 87% [38,39]. However, intensity-modulated radiation therapy is not the standard of care because of a high toxicity and morbidity (i.e., fatal pneumonitis) associated with its use [40].

Radiotherapy has sometimes been used as palliative treatment to relieve symptoms arising from tumour growth, such as obstruction of a major blood vessel.

7.1.3. Chemotherapy

Chemotherapy regimens are given by intravenous or directly injected into the chest or abdomen (intracavitary chemotherapy). Chemotherapy is nowadays used 1) as neoadjuvant before surgery (concurrent with radiation), 2) as adjuvant after surgery (concurrent with radiation), 3) as 1rst-line treatment for unresectable disease, or 4) as 2^{nd}-line treatment.

7.1.3.1 Neoadjuvant chemotherapy (before surgery)

Owing to the small numbers of malignant pleural mesothelioma (MPM) candidates for EPP, few neoadjuvant trials have been successful. All neoadjuvant regimens studied to date include platinum based regimens with a median survival ranging between 19 and 25 months [31,41-43].

7.1.3.2 Adjuvant chemotherapy (after surgery)

Adjuvant chemoradiotherapy is difficult to administer after EPP because of its associated toxicities, and as such, there are few trials available to review. One of the largest series evaluated 418 patients who received EPP followed by carboplatin (a platinum agent) and paclitaxel (a taxane) with thoracic radiation therapy. Authors reported a median overall survival of 18.9 months and a 5-year overall survival rate of 13.9% [44].

7.1.3.3 Chemotherapy in 1^{st} –line treatment for unresectable disease

Systematic therapy is the only treatment option for the most of mesothelioma patients, for whom age, co-morbid medical illness, non-epithelial histology, and locally advanced disease often preclude surgery. While response rates exceeding 20% have barely been achieved with established cytotoxic drugs in malignant pleural mesothelioma therapy, novel chemotherapeutic agents and their combinations appear more promising [45]. The combination of cisplatin (a platinum agent-75mg/m²) and pemetrexed (Alimta®) (an antifolate-500mg/m²) given every 3 weeks was established as a standard-of-care front-line regimen after the largest phase-III trial conducted in patients with chemotherapy-naïve MPM and demonstrated a survival improvement over cisplatin alone [46]. In February 2004, the United States Food and Drug Administration approved

pemetrexed for treatment of malignant pleural mesothelioma [47]. pemetrexed was approved in Europe by the European Medicines Agency in September 2004 [48]. Since elderly mesothelioma patients with co-morbid illnesses may not be able to tolerate cisplatin, the better-tolerated carboplatin is frequently substituted; the two regimens having comparable activity [45].

Other antifolates have been investigated, but they are less commonly used then pemetrexed. The combination of ralitrexed (Tomudex®) (3mg/m²) with cisplatin (80mg/m²) also demonstrated activity in mesothelioma in a randomized phase-III trial testing ralitrexed plus cisplatin versus cisplatin alone. The combination achieved a response rate of 24%, compared with 14% for cisplatin alone. The overall response rate was improved but was not statistically significant and there was no reported difference in quality of life. However, the median overall survival in patients receiving raltitrexed plus cisplatin was increased to 11.4 months, and the 1-year survival rate was increased to 46% (HR=0.76; p=0.048) [49].

Gemcitabine (Gemzar®), a nucleoside analogue, plus cisplatin has also been reported as an active regimen [49,50]. However, a retrospective Canadian series demonstrated no difference in overall survival if a platinum agent was administered with premetrexed or with gemcitabine [51]. There is a significant variability in the activity of the gemcitabine-cisplatin combination. Response rates in phase-II studies ranged from 12 to 48%, and median survival times ranged from 9.5 to 12 months. This is maybe due to heterogeneity in patient selection and methods of disease measurement, as well as to different schedules of these regimens. Activity has also been observed when gemcitabine is administered with carboplatin (response rate 26%, median survival time 15.1 months, decreased dyspnea in 46% of patients) [52] or oxaliplatin, another platinum agent (response rate of 40%, median survival time of 13 months) [52,53].

Vinorelbine was the only vinca alkaloid that had single-activity in MPM with response rates of 24% and median survival of 10.6 months [54]. It also improved quality of life with pulmonary symptoms decreasing in 48% of patients, and an improvement of quality of life in 41% of patients [54]. In one front-line trial, cisplatin added to vinorelbine improved the response rate to 29.6%, the median time to progression to 7.2 months, and the overall survival to 16.8 months. The newest vinca alkaloid vinflunine has shown a 13.8% of response rate, a median progression-free survival of 3.2 months, and a median overall survival of 10.8 months [55].

In Japan, several clinical trials with irinotecan, a topoisomerase interactive agent, have been conducted in patients with unresectable MPM. In a pilot trial, a triplet regimen of irinotecan and cisplatin followed by doxorubicin (an anthracycline) was studied; the overall response rate was 36% [56]. In a phase-II trial with methotrexate (an antifolate), irinotecan, and doxorubicin; the partial response rate was 21%, and it was 24% in the chemotherapy-naïve subgroup of patients [57]. Although these triplet regimens showed tolerability and efficacy, irinotecan has not been developed for MPM in the United States. Only one US trial was conducted with irinotecan as single-agent in chemotherapy-naïve patients and the regimen had a 0% response rate and a substantial toxicity was observed [58]. It is therefore likely that irinotecan-based regimens will remain geographically sponsored [10].

The concept of maintenance or continued therapy after a front-line treatment remains investigational. One small study has shown the feasibility of maintenance with pemetrexed and has demonstrated that responses could occur even after six cycles of treatment [59]. However, the role of maintenance therapy requires additional examination in larger prospective trials before being implemented as a common practice [10].

7.1.3.4 Chemotherapy in 2nd-line treatment

There is no widely approved salvage regimen for MPM. However, there is growing evidence that if pemetrexed is not given in the front-line setting, it should be administered in the salvage setting, either alone or in combination with platinum agents [60,61].

Jassem et al conducted a phase-III trial comparing second-line pemetrexed with best supportive care and reported that pemetrexed improved tumour response and progression-free survival but did not improve overall survival for unselected patients. Subgroup analyses demonstrated that patients who had responded to front-line chemotherapy had a trend toward longer overall survival with second-line pemetrexed [62]. Gemcitabine plus vinorelbine was also found to have some efficacy as a salvage regimen in 28 patients who had failed to respond to pemetrexed-based chemotherapy. The response rate was 7.4% with stabilization of disease in an additional 37% of patients and a median time to progression of 2.8 months [63]. Single-agent vinorelbine has also been evaluated in a phase-II trial, with a reported response rate of 16% and an overall survival of 9.6 months [64].

7.2. Novel targeted therapies: promising treatments

Targeted therapies interfere with specific molecules involved in the process that makes normal cells become cancer cells and cause tumours to grow. The goal of targeted therapies is to specially target and destroy cancer cells while causing little to no damage to normal, healthy cells. In this way, targeted cancer therapies may be more effective than current treatments and less harmful to normal cells [4]. These agents may have cytostatic and/or cytotoxic activity. The cytotoxic activity results in cell kill and eventual tumour shrinkage, whereas cytostatic activity inhibits tumour growth without direct cytotoxicity and is characterized by the stabilization of the disease rather then the shrinkage of lesions [65].

New knowledge about insights into the biology of mesothelioma and about cell signalling in recent years has coincided with the development of novel targeted therapies. The biology of mesothelioma makes the assessment of targeted agents particularly interesting [5,66]. These novel biologic therapies that have been successful against other solid tumours have also begun to be studied in MPM.

7.2.1. Epidermal growth factor receptor inhibitors

The epidermal growth factor receptor (EGFR), a transmenbrane glycoprotein, is overexpressed in many malignancies, including mesothelioma. Ligand binding activates the intracellular domain of EGFR, triggering cell growth. *ZD1839 or gefitinib (Iressa®)* is an oral, highly selective inhibitor of the EGFR tyrosine kinase that had been evaluated by Govindan et al [67] in the Cancer and Leukemia group B (CALGB) in a phase-II trial with 46 previously untreated patients. ZD1839 showed no significant activity as monotherapy in EGFR-positive chemonaïve malignant mesothelioma. *Erlotinib (Tarceva®)* has been evaluated by The Southwest Oncology Group [68] in a phase-II trial and showed no significant benefit as a single agent.

7.2.2. Platelet derived growth factor inhibitors

Platelet derived growth factor (PDGF) appears to be another autocrine growth factor for mesothelioma. PDGF is a potent mitogen for connective tissue cells. PDGF receptors are differentially expressed in mesothelioma cells as compared with normal mesothelium. Mesothelioma cell lines express PDGF-β receptors, while normal mesothelial cells express PDGF-α receptors. One of the most common genetic

abnormalities in mesothelioma involves chromosome 22q13, the site of the c-sis proto-oncogene, which codes for the β-chain of PDGF. Transduction of a hammerhead ribozyme against PDGF-β mRNA in mesothelioma cell lines led to a significant reduction of cell growth and decreased expression of PDGF-β. These data suggest that interruption of the PDGF autocrine loop in mesothelioma patients may be an appropriate therapeutic target. Imatinib mesylate (STI-571 or Gleevec®) and vatalanib (PTK787) are two oral, selective inhibitors of the tyrosine kinase associated with the PDGF-β receptors. *Imatinib mesylate* (targeting also the c-Kit tyrosine kinase receptor and the enzyme BCR-Abl[b]) was ineffective and not tolerated as a single agent [69-71]. However, the combined regimens of imatinib mesylate with cisplatin plus pemetrexed in chemotherapy-naïve patients or with gemcitabine in pretreated patients are underway [72,73]. *Vatalanib* (targeting in addition both vascular endothelial growth factor and c-Kit tyrosine kinase receptor) has been evaluated in a phase-II trial (see section 7.2.3) [66].

7.2.3. Antiangiogenic agents: Vascular endothelial growth factor inhibitors and others

Vascular endothelial growth factor (VEGF) which is an autocrine growth factor for mesothelioma, binds to endothelial cell receptors, initiating a signalling cascade that results in new vessel formation. VEGF signalling appears to play an important role in the progression and prognosis of malignant mesothelioma. Mesothelioma patients have significantly higher VEGF levels than patients with another solid tumour. VEGF expression in mesothelioma correlates with microvessel density, and a high microvessel density is associated with poor survival. These data suggest that VEGF may be an appropriate target for therapy of mesothelioma.

Bevacizumab (Avastin®), a recombinant humanised anti-VEGF monoclonal antibody, blocks the binding of VEGF to its receptor. It is highly synergistic with cisplatin in animal models [74]. Thus, it has been studied in combination with two standard regimens: cisplatin/gemcitabine and cisplatin/pemetrexed. A front-line phase-II randomized trial using cisplatin and gemcitabine with or without bevacizumab did not show an improvement in progression-free survival, in overall survival, nor in response rate with the addition of bevacizumab [75]. A subgroup analysis noted that higher baseline plasma VEGF levels were correlated with a shorter progression-free survival and a shorter

[b] The enzyme BCR-Abl is a fusion of the tyrosine kinase Abl and the protein BCR ('Breakpoint cluster region')

overall survival and that patients with VEGF levels less than the median had longer progression-free survival and longer overall survival when treated with bevacizumab. This suggests that antiangiogenic therapy could benefit some patients with MPM. Several ongoing MPM studies with bevacizumab may further define which patients should receive antiangiogenic treatment. Other ongoing trials are front-line studies of cisplatin, pemetrexed, and bevacizumab (NCT00295503), or carboplatin, pemetrexed, and bevacizumab (NCT00407459) [10].

It is possible that VEGF receptor tyrosine kinase inhibitors or concomitant inhibition of other tumour or angiogenesis targets will be needed to achieve the greatest anti-tumour effect for MPM. Several oral multikinase inhibitors that include VEGF/VEGF receptor pathway inhibition have been investigated in MPM.

Semaxanib (SU5416) is a potent and selective synthetic inhibitor of the Flk-1/KDR VEGF receptor tyrosine kinase. It has been assessed as a single-agent in a National Cancer Institute-sponsored phase-II trial at the University of Chicago (23 patients) and demonstrated preliminary evidence of activity in mesothelioma [76].

Thalidomide which inhibits VEGF, tumour necrosis factor (TNF)-α, and basic fibroblast growth factor (bFGF), has been reported to produce clinical activity [77,78]. Thalidomide as a single agent, has been reported to achieve disease stabilization in 25% of patients for more than 6 months [77] and is under investigation in an international trial, with patients with MPM receiving four cycles of platinum plus pemetrexed followed by thalidomide or best supportive care [10].

Vatalanib (targeting VEGF receptor-1, -2, and -3; PDGF receptor; and the c-Kit tyrosine kinase receptor) was studied in one phase-II trial which did not achieve the protocol-specified 3-months progression-free survival of 75 % (3-months progression-free survival: 55%, 95%CI: 40-68%). However, the objective response rate of 10% and median survival of 10 months are similar to other active single-agents for mesothelioma, which suggests that vatalanib may warrant further study in this disease[79].

Sorafenib (targeting VEGF receptor-2, PDGF receptor, and the serine/threonine protein kinase Raf) was assessed in a phase-II trial (CALGB 30307) in chemotherapy-naïve or previously treated patients. Sorafenib demonstrated modest activity but did not meet its primary endpoint (response rate of <5% versus >20%). Chemotherapy-naïve patients had worse survival outcomes than the previously treated patients [80,81].

Sunitinib (targeting VEGF receptor, PDGF receptor, the c-Kit tyrosine kinase receptor, and Flt-3) has been evaluated in a phase-II single arm trial in patients who had

experienced treatment failure with one platinum plus pemetrexed regimen. Of 22 assessable patients, there was a 15% partial response rate and 55% stable disease rate. The median overall survival was 5.9 months, and median time to progression was 3.5 months. There was one treatment-related death attributed to pulmonary infiltrates and respiratory failure. Treatment was otherwise well tolerated. Authors concluded that sunitinib has an activity in previously treated malignant mesothelioma [82]. Sunitinib is also assessed in ongoing trials in both front-line and salvage therapy settings (National Cancer Institute of Canada).

Other ongoing antiangiogenic agents in clinical trials include *AZD2171* (targeting KDR, Flt-1 and -4, and PDGF receptor) in pretreated patients and cisplatin, pemetrexed, and AZD2171 in chemotherapy-naïve patients (Southwest Oncology Group, NCT00243074); and *pazopanib*, or GW786034 (targeting VEGF receptor-1, -2, -3 and PDGFreceptor) by the North Central Cancer Treatment Group [10].

7.2.4. Ribonuclease inhibitors

Ranpirnase especially targets tumour cell tRNA and inhibits protein synthesis, resulting in cell cycle arrest at the G_1 phase. The adverse effect profile includes hypersentivity, renal toxicity, fatigue, and peripheral oedema. Single-agent ranpirnase in a phase-II trial demonstrated activity and a tolerable toxicity profile in patients with unresectable malignant mesothelioma (5% response rate, 43% stable disease rate, and a median overall survival of 6 months) [83]. In a single agent phase-III trial comparing ranpirnase and doxorubicin, ranpirnase was shown to be active and well-tolerated, and possibly superior to doxorubicin in some patient subsets [84,85]. A large international phase-III trial comparing doxorubicin with the combination of doxorubicin and ranpirnase is ongoing (NCT00003034).

7.2.5. Histone deacetylase inhibitors

Histone acetylation regulates gene expression by allowing transcription factor access to genomic DNA. Deacetylation of histones leads to cell cycle progression and unchecked growth. Histone deacetylase inhibitors are agents that prevent deacetylation and reinstate control over the cell cycle. Preclinical studies have shown that histone deacetylase inhibitors inhibit cell cycle progression and/or induce tumour apoptosis. However, the exact anti-tumour mechanism is unknown [10].

Suberoylanilide hydroxamic acid (SAHA), or vorinostat, an oral histone deacetylase inhibitor, was studied in an early phase-I trial as a single agent in patients previously treated with chemotherapy and results were encouraging [86]. Based on these findings, an ongoing randomized, placebo-controlled, phase-III trial of SAHA planed to enrol 660 patients with MPM for whom one or two prior therapies have failed (NCT00128102).

Belinostat, also called PDX101, is an additional histone deacetylase inhibitor under investigation as 2nd line therapy. In a phase-II trial, it was shown inactive as monotherapy against recurrent malignant mesothelioma [87]. Evaluation of combination strategies or alternate dosing schedule may be necessary for further development of this agent in mesothelioma.

7.2.6. Proteasome inhibitors

Proteasome complexes process ubiquitinated proteins and facilitate protein degradation. When proteasome activity is inhibited, nuclear factor-κB production is also inhibited, and tumour cells undergo apoptosis. Preclinical studies in cell lines and murine xenograft models showed anti-tumour activity of proteasome inhibitors, such as *bortezomib*, against MPM [88,89]. Two European trials are underway using single-agent bortezomib (NCT00513877) and the combination of ciplatin and bortezomib (NCT00458913).

7.2.7. Gene therapy

Gene therapy means inserting specific genes into cells to change or restore their functions. In theory, the procedure may be used to block abnormal genes in cancer cells, or to repair or replace the abnormal genes. Researchers also hope to disable genes that contribute to blood vessel formation (angiogenesis) by cancer cells.

In some cases, viruses may be used to activate certain reactions within cancer cells. Using an “adenovirus” for delivery, a “suicide gene” is inserted directly into the tumour. This gene makes the cells sensitive to the toxic properties of what would otherwise be an ineffective drug such as ganciclovir. The hope is that treatment with the drug then destroys only cells that rapidly divide—i.e., the cancer cells, leaving healthy cells unharmed. Early work with gene therapy used adenovirus vectors containing the herpes simplex virus thymidine kinase (Ad-HSVtk) suicide gene administered intrapleurally followed by intravenous ganciclovir [90,91]. The premise for this work was to transduce

viral thymidine kinase into the cancer cells and then administer the antiviral agent ganciclovir to selectively kill the tumour cells. Ganciclovir is metabolized to cytotoxic ganciclovir triphosphates by the thymidine kinase gene, which can potentially diffuse through the tumour and kill cells that are expressing the transgene. In addition to the direct anticancer effect, it was also presumed that an adenoviral-induced inflammatory response would stimulate the host immune system to attack the cancer cells [92]. The results of a phase-I trial [93] suggested that the anti-tumour effect was more likely related to the immune modulatory effect from the Ad-HSVtk and ganciclovir rather than the direct anticancer effect for which it was originally designed. Therefore, a phase-I trial using an adenoviral vector containing an immune stimulant interferon beta (IFN-β) was undertaken [92]. Further studies using the strategy of gene therapy and immune modulation are ongoing [10].

7.2.8. Cytokines

Based on the theory that certain cytokines may overcome the innate immune resistance of mesotheliomas [94], several cytokines have been tested for their activity in MPM and have shown some activity. Cytokines are proteins that occur naturally in the human body, and that are similar to hormones. They may act as messengers in the immune system.

Interferons are cytokine proteins that inhibit the growth of cancer cells, as well as enhance the immune system. Some work by slowing down angiogenesis of cancer cells, or by boosting the ability of T cells to attack cancer cells. Interferons are being tested to see if they help to increase the body's immune response to mesothelioma. Interferon-gamma (IFN-γ) was studied in a prospective multi-institutional study in patients with Butchart's stage I and II MPM [95]. The overall response rate was 20% and patients with Butchart's stage I disease seemed to benefit most from this therapy (45% response rate). Further trials are needed to verify these results. As cisplatin and IFN-α demonstrated synergistic anti-tumour activity in preclinical models [96], the combination was subsequently investigated by various clinical trials showing mixed results with response rate ranging from 11% to 40% [13]. For instance, a phase-II trial investigating interferon-alpha-2b (IFN-α-2b) in combination with cisplatin and doxorubicin showed a response rate of 29% and a median survival of 9.3 months in patients with advanced MPM [97]. The combination appeared to have anti-tumour activity but was limited by toxicity, particularly myelosuppression and fatigue.

Using interleukin-2 (IL-2) as a treatment for pleural mesothelioma is still in the experimental stages. Mesothelioma cells proved susceptible to in vitro lysis by lymphokine-activated killer cells (LAK cells) following activation by interleukin-2 (IL-2), but patients undergoing this particular therapy experienced major side effects. Thus so far, intrapleural IL-2 based therapy has been investigated by three studies. In a phase-I/II study, the partial response was 19% and the median survival was 15.6 months. Significant dose-related toxicity was observed [98]. A phase-II study by Astoul et al [99] revealed a response rate of 54%. Median survival for responders was 28 months, as compared with 8 months for non-responders. In an Italian study [100], the response rate was 22% and the median survival was 15 months.

7.2.9. Other targets and agents

Src kinase (sarcoma proto-oncogenic tyrosine kinase) may be a potential therapeutic target as studies of archival tumour tissue showed that overexpression of activated Src kinase protein is correlated with more advanced malignant pleural mesothelioma and that the preclinical studies with dasatinib, a multitarget Src tyrosine kinase inhibitor, can lead to malignant pleural mesothelioma cell cycle arrest, apoptosis, and impair the ability of the tumour cell to migrate and invade [101]. *Dasatinib* is currently under investigation in clinical trials for the neoadjuvant setting (trial at the University of Texas M.D. Anderson Cancer Center) and also as a second-line agent through a phase-II trial sponsored by CALGB [10].

Three *antimesothelin agents* are currently in clinical trials for mesothelioma: SS1P (an immunotoxin), Morab-009 (an antimesothelin monoclonal antibody) and CRS-207 (a *Listeria monocytogenes* mesothelin vaccine) [102,103]. Mesothelin is a glycosyl-phosphatidyl inositol-linked cytoplasmic membrane glycoprotein thought to be involved in cell adhesion and is tightly associated with a range of cancers, including mesothelioma. By targeting surface mesothelin, investigators hope to block cell adhesion as well as elicit an antibody-dependent cytotoxicity response against mesothelin-positive tumour cells [104]. Both SS1P and Morab-009 have completed single-arm trials and are now being investigated in phase-I/II trials in combination with cisplatin and pemetrexed. CRS-207 is also currently evaluated as a single agent in phase-I trials [10].

Vaccines are also under investigation; the Memorial Sloan-Kettering Cancer Centre recently reported results from a pilot trial of a Wilms'tumour 1 peptide vaccine, which demonstrated some activity against MPM [105]. An adjuvant clinical trial using the Wilms'tumour 1 vaccine is currently under development.

Potential future targets for MPM therapy include the insulin-growth factor pathway, MEK pathway, and the PI3k/AKT pathways [106-108].

7.3. Other treatments

Photodynamic therapy is an adjuvant treatment under investigation. The basic principle is to introduce in the pleura a light-activated photosensitizing drug that is excited by light of a specific wavelength to produce oxygen free radicals which cause tumour necrosis [5].

To relieve symptoms and control pain, the physician may use a needle or a thin tube to drain fluid that has built up in the chest or abdomen. The procedure for removing fluid from the chest is called *thoracentesi*s and from the abdomen is called *paracentesis*. Drugs may be given through the tube in the chest to prevent fluid accumulation.

8. Conclusion

Despite these treatments, the mesothelioma is still carrying a poor prognosis. The therapy of mesothelioma is as yet insufficient, and decisions regarding surgery, radiotherapy, or multimodal procedure are made on a case-by-case basis. In the majority of cases, a palliative treatment approach remains the only choice.

The possibility of curatively resecting mesothelioma is rare and only occurs with early stage disease. Even then, resection is a matter of dispute due to historically high morbidity and mortality rates, relapse tendencies and disappointing long-term survival rates. There is still a >80% risk of relapse postsurgery such that all surgical centers now advocate multimodality therapy including adjuvant (or neoadjuvant) chemotherapy and radiotherapy [84]. Irradiation for mesothelioma assists in impeding tumour growth and temporarily relieving pain, but does not lead to an appreciably lengthened overall survival time. There is substantial evidence that systemic treatment is also necessary, as improvements in local control have been accompanied by increased rates of distant

metastasis. Unfortunately, the optimal multimodality management of these patients remains unclear. Therefore, the use of systematic chemotherapy (neoadjuvant, intrapleural, and adjuvant) remains experimental, and it is encouraged that systemic treatment be administered in the setting of clinical trials.

For the patient with unresectable mesothelioma, systematic therapy is the only treatment option. For many years, chemotherapy truly had a minimal impact on the natural history of this cancer, engendering considerable nihilism. Countless drugs were evaluated, most of which achieved response rates below 20% and median survival of <1 year [12,45,109,110].

In recent years, there has been a surge of optimism regarding systemic treatment of this disease. Several cytotoxic agents have been shown an improvement in response, survival and quality of life in mesothelioma patients [45]. The antifolates (pemetrexed-Alimta®, ralitrexed-Tomudex®) or gemcitabine (Gemzar®), given in combination with platinum agent (cisplatin or carboplatin), have made the greatest clinical impact to date[10].

However, further progress is eagerly awaited and novel targeted therapies should be investigated further to determine their potential activity in the hope of bringing improvement in therapy of mesothelioma. Whether preclinical findings will translate into meaningful results for patients remains to be established, as clinical trials of these new drugs have only recently been initiated. If efficacy is demonstrated, future studies will compare the targeted agents with each other as well as with the active cytotoxic drugs. These agents may also be incorporated into multi-modality regimens, for adjuvant as well as neoadjuvant treatment.

Regarding the need to investigate novel targeted therapies in mesothelioma and to decrease the risk to reject potentially interesting drugs during their development process, we propose the application of progression-free survival as primary endpoint in phase-II mesothelioma trials. The progression-free survival could be a more appropriate endpoint than the traditional response rate and provide more meaningful informations about the activity of the new therapy.

Reference List

1. Sterman DH, Albelda SM. Advances in the diagnosis, evaluation, and management of malignant pleural mesothelioma. Respirology 2005; 10(3):266-283.

2. Robinson BW, Lake RA. Advances in Malignant Mesothelioma. N Engl J Med 2005; 353 (15):1591-1603.

3. Bianchi C, Bianchi T. Malignant mesothelioma: Global incidence and relationship with asbestos. Ind Health 2007; 45(3):379-387.

4. NCI website: Malignant Mesothelioma. www.cancer.gov, 26-8-2009.

5. Pistolesi M, Rusthoven J. Malignant pleural mesothelioma - Update, current management, and newer therapeutic strategies. Chest 2004; 126(4):1318-1329.

6. Belgian Cancer Registry. Cancer Incidence in Belgium 2004-2005. 2008, 1-191.

7. Mesothelioma International. www.mesotheliome.com, 26-8-2009.

8. Peto J, Decarli A, La Vecchia C, Levis F, Negri E. The European mesothelioma epidemic. Br J Cancer 1999; 79(3-4):666-672.

9. Ray M, Kindler HL. Malignant pleural mesothelioma: an update on biomarkers and treatment. Chest 2009; 136(3):888-896.

10. Tsao AS, Wistuba I, Roth JA, Kindler HL. Malignant Pleural Mesothelioma. J Clin Oncol 2009; 27(12):2081-2090.

11. Steele JP, Klabatsa A. Chemotherapy options and new advances in malignant pleural mesothelioma. Ann Oncol 2005; 16(3):345-351.

12. O'Byrne KJ, Edwards JG, Waller DA. Clinico-pathological and biological prognostic factors in pleural malignant mesothelioma. Lung Cancer 2004; 45:S45-S48.

13. Tomek S, Manegold C. Chemotherapy for malignant pleural mesothelioma: past results and recent developments. Lung Cancer 2004; 45:S103-S119.

14. Weiner SJ, Neragi-Miandoab S. Pathogenesis of malignant pleural mesothelioma and the role of environmental and genetic factors. J Cancer Res Clin Oncol 2009; 135(1):15-27.

15. Huncharek M. Genetic-Factors in the Etiology of Malignant Mesothelioma. Eur J Cancer 1995; 31A(11):1741-1747.

16. Vogelzang NJ. Emerging insights into the biology and therapy of malignant mesothelioma. Semin Oncol 29[6 (Suppl 18)], 35-42. 2002.

17. Zucali PA, Giaccone G. Biology and management of malignant pleural mesothelioma. Eur J Cancer 2006; 42(16):2706-2714.

18. Emri S, Demir AU. Malignant pleural mesothelioma in Turkey, 2000-2002. Lung Cancer 2004; 45 Suppl 1:S17-S20.

19. Haberkorn U. Positron emission tomography in the diagnosis of mesothelioma. Lung Cancer 2004; 45 Suppl 1:S73-S76.

20. Robinson BW, Creaney J, Lake R, Nowak A, Musk AW, de Klerk N et al. Mesothelin-family proteins and diagnosis of mesothelioma. Lancet 2003; 362(9396):1612-1616.

21. Robinson BW, Creaney J, Lake R, Nowak A, Musk AW, de Klerk N et al. Soluble mesothelin-related protein-a blood test for mesothelioma. Lung Cancer 2005; 49 Suppl 1:S109-S111.

22. Pass HI, Lott D, Lonardo F, Harbut M, Liu Z, Tang N et al. Asbestos exposure, pleural mesothelioma, and serum osteopontin levels. N Engl J Med 2005; 353(15):1564-1573.

23. Sandhu H, Dehnen W, Roller M, Abel J, Unfried K. mRNA expression patterns in different stages of asbestos-induced carcinogenesis in rats. Carcinogenesis 2000; 21(5):1023-1029.

24. Mesothelioma. www.mesotheliomaweb.org, 1-4-2009.

25. Butchart EG, Ashcroft T, Barnsley WC, et al. Pleuropneumonectomy in the management of diffuse malignant mesothelioma of the pleura: Experience with 29 patients. Thorax 1976; 31:15-24.

26. Rusch VW. A proposed new international TNM staging system for malignant pleural mesothelioma: from the Internation Mesothelioma Interest Group. Chest 1995; 108:1122-1128.

27. American Joint Committee on Cancer. Pleural Mesothelioma. In: AJCC Cancer Staging Handbook. Springer-Verlag. Sixth edition, New York, 2002, 205-209.

28. Sugarbaker DJ, Strauss GM, Lynch TJ, Richards W, Mentzer SJ, Lee TH et al. Node Status Has Prognostic-Significance in the Multimodality Therapy of Diffuse, Malignant Mesothelioma. J Clin Oncol 1993; 11(6):1172-1178.

29. Flores RM, Pass HI, Seshan VE, Dycoco J, Zakowski M, Carbone M et al. Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. J Thorac Cardiovasc Surg 2008; 135(3):620-6, 626.

30. Treasure T, Sedrakyan A. Pleural mesothelioma: little evidence, still time to do trials. Lancet 2004; 364(9440):1183-1185.

31. Krug LM, Pass HI, Rusch VW, Kindler HL, Sugarbaker DJ, Rosenzweig KE et al. Multicenter phase II trial of neoadjuvant pemetrexed plus cisplatin followed by extrapleural pneumonectomy and radiation for malignant pleural mesothelioma. J Clin Oncol 2009; 27(18):3007-3013.

32. Rusch VW, Rosenzweig K, Venkatraman E, Leon L, Raben A, Harrison L et al. A phase II trial of surgical resection and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. J Thorac Cardiovasc Surg 2001; 122(4):788-795.

33. Boutin C, Rey F, Viallat JR. Prevention of malignant seeding after invasive diagnostic procedures in patients with pleural mesothelioma. A randomized trial of local radiotherapy. Chest 1995; 108(3):754-758.

34. Bydder S, Phillips M, Joseph DJ, Cameron F, Spry NA, DeMelker Y et al. A randomised trial of single-dose radiotherapy to prevent procedure tract metastasis by malignant mesothelioma. Br J Cancer 2004; 91(1):9-10.

35. O'Rourke N, Garcia JC, Paul J, Lawless C, McMenemin R, Hill J. A randomised controlled trial of intervention site radiotherapy in malignant pleural mesothelioma. Radiother Oncol 2007; 84(1):18-22.

36. Sugarbaker DJ, Flores RM, Jaklitsch MT, Richards WG, Strauss GM, Carson JM et al. Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: Results in 183 patients. J Thorac Cardiovasc Surg 1999; 117(1):54-63.

37. Allen AM, Den R, Wong JS, Zurakowski D, Soto R, Janne PA et al. Influence of radiotherapy technique and dose on patterns of failure for mesothelioma patients after extrapleural pneumonectomy. Int J Radiat Oncol Biol Phys 2007; 68(5):1366-1374.

38. Ahamad A, Stevens CW, Smythe WR, Vaporciyan AA, Komaki R, Kelly JF et al. Intensity-modulated radiation therapy: a novel approach to the management of malignant pleural mesothelioma. Int J Radiat Oncol Biol Phys 2003; 55(3):768-775.

39. Rice DC, Stevens CW, Correa AM, Vaporciyan AA, Tsao A, Forster KM et al. Outcomes after extrapleural pneumonectomy and intensity-modulated radiation therapy for malignant pleural mesothelioma. Ann Thorac Surg 2007; 84(5):1685-1692.

40. Allen AM, Czerminska M, Janne PA, Sugarbaker DJ, Bueno R, Harris JR et al. Fatal pneumonitis associated with intensity-modulated radiation therapy for mesothelioma. Int J Radiat Oncol Biol Phys 2006; 65(3):640-645.

41. Flores RM, Krug LM, Rosenzweig KE, Venkatraman E, Vincent A, Heelan R et al. Induction chemotherapy, extrapleural pneumonectomy, and postoperative high-dose radiotherapy for locally advanced malignant pleural mesothelioma: a phase II trial. J Thorac Oncol 2006; 1(4):289-295.

42. Weder W, Kestenholz P, Taverna C, Bodis S, Lardinois D, Jerman M et al. Neoadjuvant chemotherapy followed by extrapleural pneumonectomy in malignant pleural mesothelioma. J Clin Oncol 2004; 22(17):3451-3457.

43. Weder W, Stahel RA, Bernhard J, Bodis S, Vogt P, Ballabeni P et al. Multicenter trial of neo-adjuvant chemotherapy followed by extrapleural pneumonectomy in malignant pleural mesothelioma. Ann Oncol 2007; 18(7):1196-1202.

44. Sugarbaker DJ, Richards WG, Alsup CA, et al. Impact of pathological staging on survival in patients with epithelial mesothelioma treated with extrapleural pneumonectomy. J Clin Oncol 2007; 25:435s.

45. Kindler HL. Systemic Treatments for Mesothelioma: Standard and Novel. Curr Treat Options Oncol 2008; 9(2-3):171-179.

46. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003; 21(14):2636-2644.

47. U.S.Food and Drug Administration: Approval of Alimta by FDA. http://www.fda.gov/bbs/topics/NEWS/2004/NEW01018.html, 1-4-2009.

48. European Agency for the Evaluation of Medicinal Products: Approval of Alimta by EMEA. http://www.emea.europa.eu/humandocs/Humans/EPAR/alimta/alimta.htm, 1-4-2009.

49. van Meerbeeck JP, Gaafar R, Manegold C, van Klaveren RJ, van Marck EA, Vincent M et al. Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: An intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. J Clin Oncol 2005; 23(28):6881-6889.

50. Byrne MJ, Davidson JA, Musk AW, Dewar J, van Hazel G, Buck M et al. Cisplatin and gemcitabine treatment for malignant mesothelioma: a phase II study. J Clin Oncol 1999; 17(1):25-30.

51. Lee CW, Murray N, Anderson H, et al. Outcomes with a platinum plus gemcitabine or pemetrexed as first-line systemic therapy for malignant pleural mesothelioma in British Columbia: a reivew of province-wide practice. J Thorac Oncol 2007; 2:S606.

52. Favaretto AG, Aversa SM, Paccagnella A, Manzini VP, Palmisano V, Oniga F et al. Gemcitabine combined with carboplatin in patients with malignant pleural mesothelioma: a multicentric phase II study. Cancer 2003; 97(11):2791-2797.

53. Schutte W, Blankenburg T, Lauerwald K, Schreiber J, Bork I, Wollscgkaeger B et al. A multicenter phase II study of gemcitabine and oxaliplatin for malignant pleural mesothelioma. Clin Lung Cancer 2003; 4(5):294-297.

54. Steele JP, Shamash J, Evans MT, Gower NH, Tischkowitz MD, Rudd RM. Phase II study of vinorelbine in patients with malignant pleural mesothelioma. J Clin Oncol 2000; 18(23):3912-3917.

55. Talbot DC, Margery J, Dabouis G, Dark G, Taylor H, Boussemart H et al. Phase II study of vinflunine in malignant pleural mesothelioma. J Clin Oncol 2007; 25(30):4751-4756.

56. Nakano T, Fukuoka K, Kuribayashi K, et al. Sequential topoisomerase targeting triplet chemotherapy with irinotecan/cisplatin followed by doxorubicin in patients with malignant pleural mesothelioma: a pilot phase II study. Lung Cancer 2006; 54:S48.

57. Kuribayashi K, Fukuoka K, Miyake M, et al. Combination chemotherapy with methotrexate, irinotecan, and doxorubicin in malignant pleural mesothelioma: a phase II study. Lung Cancer 2006; 54:S49.

58. Kindler HL, Herndon JE, Zhang C, Green MR. Irinotecan for malignant mesothelioma A phase II trial by the Cancer and Leukemia Group B. Lung Cancer 2005; 48(3):423-428.

59. van den Bogaert DP, Pouw EM, van Wijhe G, Vernhout RM, Surmont VF, Hoogsteden HC et al. Pemetrexed maintenance therapy in patients with malignant pleural mesothelioma. J Thorac Oncol 2006; 1(1):25-30.

60. Janne PA, Wozniak AJ, Belani CP, Keohan ML, Ross HJ, Polikoff JA et al. Pemetrexed alone or in combination with cisplatin in previously treated malignant pleural mesothelioma: outcomes from a phase IIIB expanded access program. J Thorac Oncol 2006; 1(6):506-512.

61. Sorensen J, Sundstrom S, Perell K, et al. Pemetrexed second-line treatment in malignant pleural mesothelioma following platinum-based first-line treatment. Lung Cancer 2006; 54:S46.

62. Jassem J, Ramlau R, Santoro A, Schuette W, Chemaissani A, Hong S et al. Phase III trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma. J Clin Oncol 2008; 26(10):1698-1704.

63. Zucali PA, Garassino I, Ceresoli GL, et al. Treatment with gemcitabine and vinorelbine (GEMVIN) as second-line chemotherapy in pemetrexed-pretreated patients with malignant pleural mesothelioma. Lung Cancer 2006; 54:S48.

64. Stebbing J, Powles T, McPherson K, Shamash J, Wells P, Sheaff MT et al. The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. Lung Cancer 2009; 63(1):94-97.

65. Kummar S, Gutierrez M, Doroshow JH, Murgo AJ. Drug development in oncology: classical cytotoxics and molecularly targeted agents. Br J Clin Pharmacol 2006; 62(1):15-26.

66. Kindler HL. Moving beyond chemotherapy:novel cytostatic agents for malignant mesothelioma. Lung Cancer 2004; 45 Suppl 1:S125-S127.

67. Govindan R, Kratzke RA, Herndon JE, Niehans GA, Vollmer R, Watson D et al. Gefitinib in patients with malignant mesothelioma: A phase II study by the cancer and leukemia group B. Clin Cancer Res 2005; 11(6):2300-2304.

68. Garland LL, Rankin C, Gandara DR, Rivkin SE, Scott KM, Nagle RB et al. Phase II study of erlotinib in patients with malignant pleural mesothelioma: a Southwest Oncology Group Study. J Clin Oncol 2007; 25(17):2406-2413.

69. Mathy A, Baas P, Dalesio O, van Zandwijk N. Limited efficacy of imatinib mesylate in malignant mesothelioma: A phase II trial. Lung Cancer 2005; 50(1):83-86.

70. Millward M, Parnis F, Byrne M, et al. Phase II trial of imatinib mesylate in patients with advanced pleural mesothelioma. Proc Am Soc Clin Oncol 2003; 22:228a.

71. Porta C, Mutti L, Tassi G. Negative results of an Italian Group of Mesothelioma (G.I. Me.) pilot study of single-agent imatinib mesylate in malignant pleural mesohtelioma. Cancer Chemother Pharmacol 2007; 59:149-150.

72. Ali Y, Lin Y, Gharibo MM, Gounder MK, Stein MN, Lagattuta TF et al. Phase I and pharmacokinetic study of imatinib mesylate (Gleevec) and gemcitabine in patients with refractory solid tumors. Clin Cancer Res 2007; 13(19):5876-5882.

73. Bertino P, Piccardi F, Porta C, Favoni R, Cilli M, Mutti L et al. Imatinib mesylate enhances therapeutic effects of gemcitabine in human malignant mesothelioma xenografts. Clin Cancer Res 2008; 14(2):541-548.

74. Kabbinavar FF, Wong JT, Ayala RE, Wintroub AB, Kim KJ, Ferrana N et al. The effect of antibody to vascular endothelial growth factor and cisplatin on the growth of lung tumors in nude mice. Proc Am Soc Clin Oncol 1995; 36:488.

75. Karrison T, Kindler HL, Gandara DR, et al. Final analysis of multi-center, double-blind, placebo-controlled, randomized phase II trial of gemcitabine/cisplatin plus bevacizumab or placebo in patients with malignant mesothelioma. J Clin Oncol 2007; 25:391s.

76. Kindler HL, Vogelzang NJ, Chien K, Stadler WM, Karczmar G, Heimann R et al. SU5416 in malignant mesothelioma:a University of Chicago phase II consortium study. Proc Am Soc Clin Oncol 2001; 20:341.

77. Baas P, Boogerd W, Dalesio O, Haringhuizen A, Custers F, van Zandwijk N. Thalidomide in patients with malignant pleural mesothelioma. Lung Cancer 2005; 48(2):291-296.

78. Pavlakis N, Williams G, Harvey R, et al. Thalidomide alone and in combination with cisplatin/gemcitabine chemotherapy for malignant mesothelioma:preliminary results from two phase II studies. Proc Am Soc Clin Oncol 2002; 21:19b.

79. Jahan T, Gu L, Wang X, et al. Vatalanib for patients with previously untreated advanced malignant mesothelioma: a phase II study by the Cancer and Leukemia Group B (CALGB 30107). J Clin Oncol 2006; 24:384s.

80. Janne PA, Wang X, Krug LM, et al. Phase II trial of sorafenib (BAY)43-9006) in malignant mesothelioma:CALGB 30307. Lung Cancer 2006; 54:S51.

81. Janne PA, Wang X, Krug LM, et al. Sorafenib in malignant mesothelioma: a phase II trial of the Cancer Leukemia Group (CALGB 30307). J Clin Oncol 2007; 25:435s.

82. Nowak AK, Millward MJ, Francis R, et al. Phase II study of sunitinib as second-line therapy in malignant pleural mesothelioma. J Clin Oncol 2008; 26:439s.

83. Mikulski SM, Costanzi JJ, Vogelzang NJ, McCachren S, Taub RN, Chun H et al. Phase II trial of a single weekly intravenous dose of ranpirnase in patients with unresectable malignant mesothelioma. J Clin Oncol 2002; 20(1):274-281.

84. Pavlakis N, Vogelzang NJ. Ranpirnase-an antitumour ribonuclease: its potential role in malignant mesothelioma. Expert Opin Biol Ther 2006; 6(4):391-399.

85. Vogelzang NJ, Taub RN, Shin D, et al. Phase III randomized trial of onconase (ONC) vs. doxorubicin in patients with unresectable malignant mesothelioma:analysis of survival. Proc Am Soc Clin Oncol 2000; 19:577a.

86. Krug LM, Curley T, Schwartz L, Richardson S, Marks P, Chiao J et al. Potential role of histone deacetylase inhibitors in mesothelioma: clinical experience with suberoylanilide hydroxamic acid. Clin Lung Cancer 2006; 7(4):257-261.

87. Ramalingam SS, Belani CP, Ruel C, Frankel P, Gitlitz B, Koczywas M et al. Phase II study of belinostat (PXD101), a histone deacetylase inhibitor, for second line therapy of advanced malignant pleural mesothelioma. J Thorac Oncol 2009; 4(1):97-101.

88. Fennell DA, Gaudino G, Porta C, et al. Proteasome inhibitors for treatment of malignant mesothelioma. Lung Cancer 2006; 54:S50.

89. Gordon GJ, Mani M, Maulik G, Mukhopadhyay L, Yeap BY, Kindler HL et al. Preclinical studies of the proteasome inhibitor bortezomib in malignant pleural mesothelioma. Cancer Chemother Pharmacol 2008; 61(4):549-558.

90. Molnar-Kimber KL, Sterman DH, Chang M, Kang EH, ElBash M, Lanuti M et al. Impact of preexisting and induced humoral and cellular immune responses in an adenovirus-based gene therapy phase I clinical trial for localized mesothelioma. Hum Gene Ther 1998; 9(14):2121-2133.

91. Sterman DH. Gene therapy for malignant pleural mesothelioma. Hematol Oncol Clin North Am 2005; 19(6):1147-73.

92. Sterman DH, Recio A, Carroll RG, Gillespie CT, Haas A, Vachani A et al. A phase I clinical trial of single-dose intrapleural IFN-beta gene transfer for malignant pleural mesothelioma and metastatic pleural effusions: high rate of antitumor immune responses. Clin Cancer Res 2007; 13(15 Pt 1):4456-4466.

93. Sterman DH, Treat J, Litzky LA, Amin KM, Coonrod L, Molnar-Kimber K et al. Adenovirus-mediated herpes simplex virus thymidine kinase/ganciclovir gene therapy in patients with localized malignancy: results of a phase I clinical trial in malignant mesothelioma. Hum Gene Ther 1998; 9(7):1083-1092.

94. Sterman DH, Kaiser LR, Albelda SM. Advances in the treatment of malignant pleural mesothelioma. Chest 1999; 116(2):504-520.

95. Boutin C, Nussbaum E, Monnet I, Bignon J, Vanderschueren R, Guerin JC et al. Intrapleural treatment with recombinant gamma-interferon in early stage malignant pleural mesothelioma. Cancer 1994; 74(9):2460-2467.

96. Sklarin NT, Chahinian AP, Feuer EJ, Lahman LA, Szrajer L, Holland JF. Augmentation of activity of cis-diamminedichloroplatinum(II) and mitomycin C by interferon in human malignant mesothelioma xenografts in nude mice. Cancer Res 1988; 48(1):64-67.

97. Parra HS, Tixi L, Latteri F, Bretti S, Alloisio M, Gravina A et al. Combined regimen of cisplatin, doxorubicin, and alpha-2b interferon in the treatment of advanced malignant pleural mesothelioma: a Phase II multicenter trial of the Italian Group on Rare Tumors (GITR) and the Italian Lung Cancer Task Force (FONICAP). Cancer 2001; 92(3):650-656.

98. Goey SH, Eggermont AM, Punt CJ, Slingerland R, Gratama JW, Oosterom R et al. Intrapleural administration of interleukin 2 in pleural mesothelioma: a phase I-II study. Br J Cancer 1995; 72(5):1283-1288.

99. Astoul P, Picat-Joossen D, Viallat JR, Boutin C. Intrapleural administration of interleukin-2 for the treatment of patients with malignant pleural mesothelioma: a Phase II study. Cancer 1998; 83(10):2099-2104.

100. Castagneto B, Zai S, Mutti L, Lazzaro A, Ridolfi R, Piccolini E et al. Palliative and therapeutic activity of IL-2 immunotherapy in unresectable malignant pleural mesothelioma with pleural effusion: Results of a phase II study on 31 consecutive patients. Lung Cancer 2001; 31(2-3):303-310.

101. Tsao AS, He D, Saigal B, Liu S, Lee JJ, Bakkannagari S et al. Inhibition of c-Src expression and activation in malignant pleural mesothelioma tissues leads to apoptosis, cell cycle arrest, and decreased migration and invasion. Mol Cancer Ther 2007; 6(7):1962-1972.

102. Hassan R, Bera T, Pastan I. Mesothelin: a new target for immunotherapy. Clin Cancer Res 2004; 10(12 Pt 1):3937-3942.

103. Hassan R, Ho M. Mesothelin targeted cancer immunotherapy. Eur J Cancer 2008; 44(1):46-53.

104. Jackman DM. Current options for systematic therapy in mesothelioma. Semin Thorac Cardiovasc Surg 2009; 21:154-158.

105. Brown AB, Krug LM, Maslak P, et al. Pilot trial of a Wilms tumor-1 (WT-1) peptide vaccine in patients with thoracic and myeloid neoplasms. J Clin Oncol 2008; 26:144s.

106. Jacobson B, Patel M, De A. et al. Activation of 4E-BP1 represses IGF-1 mediated cap-dependent translation in malignant pleural mesothelioma. Lung Cancer 2006; 54:S55.

107. Kratzke R. IGF pathway activation in mesothelioma. Lung Cancer 2006; 54:S54.

108. Miraki-Mound F, Martinelli C, Camacho-Hubner C. Effects of insulin-like growth factor binding protein-3 on human malignant mesothelioma cell growth and apoptosis. Lung Cancer 2006; 54:S53.

109. Robinson BW, Musk AW, Lake RA. Malignant mesothelioma. Lancet 2005; 366(9483):397-408.

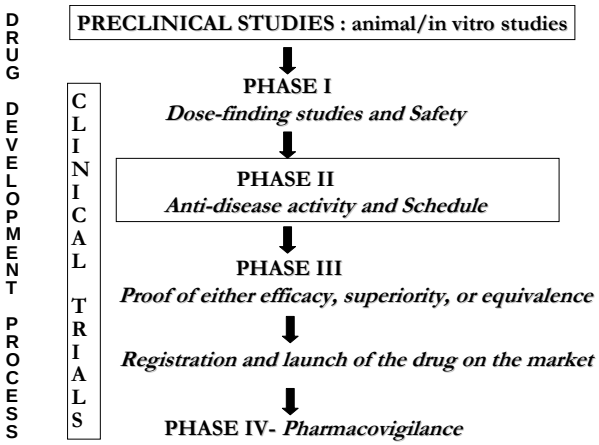
110. Steele JP, Klabatsa A, Fennell DA, Pallaska A, Sheaff MT, Evans MT et al. Prognostic factors in mesothelioma. Lung Cancer 2005; 49 (Suppl1):S49-S52.

Chapter II. Phase-II clinical trials in oncology

1. The development process of a new therapy [1]

The development process of a new therapy is a long-term project, involving different types of studies. Firstly, preclinical studies are performed on laboratory animals or in vitro to establish the therapy's mode of action, its toxicity, and its pharmacokinetic/pharmacodynamic behavior. Afterwards, the therapy with promising results in preclinical studies goes for testing in humans. This is the beginning of the clinical trials. Typically, clinical research is done in a time-ordered sequence over many years: phase-I to phase-IV trials. If the drug successfully passes through the first three phases, it will be successfully approved for use and launched on the market. Finally, post-marketing safety surveillance is carried out in phase-IV clinical trials (fig.1).

Figure 1: Different steps of the drug development process



1.1. Phase-I trials: dose-finding studies and safety

Phase-I trials, sometimes called early-phase trials, are the first stage of testing new therapies in human subjects. They are studies for which the main objectives are to define the safety and toxicity profile of a new regimen, to evaluate the pharmacokinetics/dynamics, and to determine the maximum tolerated dose and the recommended dose for a phase-II trial, sometimes after step-wise dose escalation. For targeted therapies, a phase-I trial is conducted also to determine the biologically active dose that is required to inhibit maximally the relevant target or pathway.

Phase-I trials most often include healthy volunteers. However in oncology trials, the patients enrolled are patients with advanced (metastatic) cancer, or patients who have had other types of therapy and who have few, if any, other treatment choices.

The number of enrolled patients is a relatively small (20-60 patients, and sometimes less than 10).

1.2. Phase-II trials: anti-disease activity and schedule [2]

Once the initial safety and a tolerable dose of a new regimen have been determined in phase-I trial, and a preliminary evidence of anti-tumour activity has been observed, the therapeutic activity and dose schedule are evaluated in a phase-II trial. Patients enrolled in a phase-II trial are those targeted by the treatment under evaluation. Sample size in phase-II trials are usually a few thousands patients but in oncology the sample size may be lower than 100 patients.

In oncology, it is common to distinguish early phase-II trials and late phase-II trials. Early phase-II trials are conducted to test for any anti-disease activity (often to test for dosing requirements) and to assess if the activity is sufficient for late phase-II trial. More details of toxicity and pharmacokinetics/dynamics are also provided in early phase-II trials. Late phase-II trials have the aims of confirming the dose findings and of determining whether the activity is sufficient for going further in a phase-III trial. They can also assess combinations with other treatment and the anti-disease activity in other tumours.

Moreover, the predictive markers could be tested and validated in phase-II trials. Although definitive clinical validation of biomarkers as surrogates of efficacy or as predictor of outcomes are most efficiently done in phase-III and post-registration studies, there may be a sound rationale for their inclusion in phase-II studies, such as to gain mechanistic information, as an early endpoint (i.e. changes in positron-emission tomography scan), or as interim validation of a biomarker for use in randomized controlled phase-III trials).

At the end of phase-II trials, the following are determined for a given new therapy:

- whether the level of anti-disease activity is sufficiently promising to warrant further development,
- the dose schedule and target population for phase-III trials.

Phase-II trials play a key role in the development process of a new therapy because they provide information to make a go/stop decision regarding subsequent phase-III trials. Phase-II trials needs to be sufficiently convinced about the efficacy of the drug in order to prove it in a large phase-III trial which are the most expensive, time-consuming, and

difficult trials to design and to run. The development process of a new therapy can fail during a phase-II trial due to the discovery of a poor activity or toxic effects.

1.3. Phase-III trials: proof of either efficacy, superiority, or equivalence in comparative trials

Phase-III studies are randomized controlled trials conducted on large number of patients and are aimed at proving the efficacy of the new therapy, as compared with currently available alternatives. In oncology, few phase-III trials are double-blind. Indeed, blinding of treatment arms is frequently difficult to implement in oncology trials because of the different treatment toxicities and schedules [3]. Phase-III trials compare more therapeutic approaches in an attempt to determine the relative role and merits. So, a completely new treatment may be compared with the standard treatment or a new therapy schedule (different doses or ways of giving a standard treatment) may be compared with the standard one.

Once a drug has proven satisfactory after phase-III trials, the trial results are usually combined into a large document containing a comprehensive description of the methods and results of human and animal studies, manufacturing procedures, formulation details, and shelf life. This collection of information makes up the "regulatory submission" that is provided for review to various regulatory authorities in different countries, such as the Therapeutic Goods Administration (TGA) in Australia, the European Medicines Agency (EMEA) in Europe or the Food and Drug Administration (FDA) in the United States, in order to get marketing approval.

While not required in all diseases, it is typically expected in oncology that there are at least two successful phase-III trials proving a drug's safety and efficacy before getting approval by the standard regulatory agencies (FDA, TGA, EMEA, etc.). It is also common practice with many drugs whose approval is pending, that certain phase-III trials will continue in an attempt to label expansion. It needs indeed to provide the proof of additional efficacy before using the drug beyond the original use for which the drug was designed.

1.4. Phase-IV trials: pharmacovigilance

Phase-IV trials concern the post-launch safety surveillance. They may be mandated by regulatory authorities or may be undertaken by the sponsoring company for competitive or other reasons. Post-launch safety surveillance is designed to find out more about the side effects and safety of the drug, the long term risks and benefits, and how well the

drug works when it's used more widely than in clinical trials. The discovery of any rare and/or long-term adverse effects by phase-IV trials may result in the withdrawal or the restriction of a drug.

2. Phase-II trials

The past decade has seen a significant shift in oncology drug development for two points. Firstly, in the previous era, there were very few drugs available for studies, and a porous filter was very appropriate to minimize the possibility of false-negative result which would result in the discarding of a promising agent [4]. It was powered to yield a reasonably low false-negative rate (type II error often ranges around 10% or less) to capture the majority of potentially active regimens. The single arm phase-II study was the principal mechanism for deciding whether to proceed to a randomized phase-III trial. Due to the small number of patients typically enrolled in single arm phase-II trial and the reliance on historical controls for an estimation of expected response rate, it was recognized that this design was associated with a fairly high false-positive rate (type I error often ranges around 10% or more). This was considered to be an acceptable compromise, realizing that the true activity of a new drug would eventually need to be clarified in a phase-III trial [5]. In the current era, there are hundreds of investigational oncology drugs available for studies. Given the patient and financial resources required for a phase-III trial in the current environment, it is important to minimize the risk of failing to demonstrate the efficacy in a phase-III trial. Thus, optimizing the filtering process is the critical issue: a too tight filter will terminate promising agents improperly, but a too porous filter will result in an excessive number of costly negative phase-III trials [4].

Secondly, there has been an explosion of new targeted anticancer therapies which target specific pathway relevant to cancer growth, apoptosis, or angiogenesis and thus may be selectively active. It has been suggested that these novel agents may not lead to tumour shrinkage like the traditional cytotoxic agents. For cytotoxic agents, the standard approach was a single arm phase-II trial with an objective response based on the decrease in size of targeted lesion. But the inherent difference in the mechanism of action between traditional cytotoxic drugs and targeted agents, coupled with an interest in increasing the reliability of phase-II results in identifying truly active agents, have led to considerable discussion about the so-called traditional approach of phase-II trials, particularly with regard to endpoints, patient selection criteria, and study designs [2,4-6].

2.1. The appropriate endpoint

The anti-tumour activity is assessed based on an expected success which must have an established and controlled reliable and relevant definition. It is called the endpoint. The chosen time point at which the endpoint is assessed should be a short delay according to the general requirement of phase-II trial. However, this time point depends on the prognosis of the disease. In case of a good prognosis, the delay is many months whereas in case of a bad prognosis, like for mesothelioma, the delay must be as short as couple of weeks.

The response rate to therapy is usually used as primary endpoint in phase-II trial. Response to treatment is assessed on the basis of objective criteria which measure the decrease in size of selected target lesion. International standards are available for measuring response in phase-II trials: World Health Organisation (WHO) criteria have been used since 1979 [7] and new guidelines were published in 2000: the Response Evaluation Criteria in Solid Tumours (RECIST) criteria [8] (fig.2). The WHO criteria are based on the sum of products of the two longest perpendicular diameters whereas the RECIST criteria use the sum of the longest unidimensional diameters. RECIST criteria presume that linear measures are an adequate substitute for 2-D methods and offer a simplified extraction of imaging data for wide and easy application in clinical trials. In some tumour types, when tumour measurements are notoriously difficult, like in mesothelioma, in pancreatic cancer, or in ovarian cancer, the RECIST criteria may be suboptimal and modified RECIST criteria have been developed [2,9]. For mesothelioma, Byrne and Nowak developed a modified RECIST measurement based on the measurement of tumour thickness (i.e. short-axis dimension) rather than maximum (i.e. long-axis dimension) diameter [2,9].

Figure 2. WHO and RECIST criteria

	WHO	**RECIST**
Measure	Based on the sum of products of the two longest perpendicular diameters (bidimensional measure)	Based on the sum of the longest unidimensional diameters (unidimensional measure)
Complete response	Disappearance of all known lesion(s), confirmed at 4 weeks	Disappearance of all known lesion(s), confirmed at 4 weeks
Partial response	At least 50% decrease, confirmed at 4 weeks	At least 30% decrease, confirmed at 4 weeks
Progressive disease	25% increase, no complete response, partial response or stable disease documented before increased disease, or new lesion(s)	20% increase, no complete response, partial response or stable disease documented before increased disease, or new lesion(s)
Stable disease	Neither partial response, nor progressive disease criteria met	Neither partial response, nor progressive disease criteria met

The response to therapy is not necessarily an appropriate surrogate for therapeutic benefit but it is only an indicator of anti-tumour activity. Indeed, the response rate is not clinically meaningful in itself because tumour shrinkage does not necessarily mean that the patient survival is prolonged or the quality of life is improved. The response rate however allows assessing an anti-tumour activity of the investigated treatment in a relatively short period of time. There are now several examples of cytotoxic regimens inducing an increase in response rate without translating into an improvement of overall survival [10]. Conversely, there are other examples of drugs that yield an important prolongation of survival due to cytostatic mechanisms (i.e. to slow the growth of tumours and limit the development of metastases rather than causing regression of tumour size), without appreciable improvement in response rate. This is the case for many new targeted therapies. For instance, in a large study of sorafenib in over 700 renal cancer patients, a response rate of only 2% was observed whereas

the progression-free survival was doubled compared to a placebo control [11]. Because many of these agents may affect tumour cells by reducing proliferation, rather than by causing cell death, the impact on tumour growth may be stabilization of disease or minor tumour shrinkage. Thus, it is argued that focusing only on objective response could result in overlooking some agents that could improve survival by causing disease stabilization [6]. Instead of conventional tumour response rate data, the most suitable endpoint for testing the activity of such novel agents should therefore be progression-free survival [12,13]. In this work, we looked at the feasibility and relevance of implementing progression-free survival rate as primary endpoint in future phase-II mesothelioma trials.

2.2. The patient selection

It is reasonable to expect that not all patients with a given tumour type will have similar levels of response to a new regimen. It is easy to understand in the case of targeted therapies where all patients have not similar level of target protein activity or expression, and thus, efficacy of the targeted agent may vary according to which subpopulation is evaluated. It is important to define more homogeneous groups in order to maximize possible activity and to avoid dilution of results. It could be achieved through restriction of study entry to those whose tumours (over)express a molecular target and to those with specific prognostic factors (e.g. a specific histology) of the response to treatment [6]. When the disease is rare, like the mesothelioma, the patient accrual is difficult and the restriction of study entry could be non feasible. Then, another way to take into account different subpopulations is to perform a subgroup analysis.

In this work, we studied the prognostic factors of progression-free survival in mesothelioma in order to account for them in future phase-II mesothelioma trials that use progression-free survival as endpoint.

2.3. The study design

Historically, the single-arm trial was the traditional approach for phase-II trial in oncology and it has been the most frequently used approach [4]. Recently, randomized trials are increasingly used in phase-II trials.

2.3.1. Single arm trials

The single arm phase-II design continues to have a role in disease settings for which the behavior of historical controls has remained stable over time or for which robust historical databases exist, such as pancreatic cancer and glioblastoma [2]. Single-arm studies are also appropriate when the hypothesis of the study is merely to demonstrate target effect, or in late disease or salvage settings for which no standard treatment exists. For agents whom the drug's mechanism of action is expected to be cytotoxic (allowing use of response rate as an endpoint) as opposed to cytostatic, or when the likely outcomes in the population studied are well described, single-arm studies may be also appropriate [2,5].

However, such designs require a prespecified improvement in success rate, compared to historical control data, as an indication of phase-III promise. It is well-known that historical control data are moving targets [5]. Rapidly changing standards of care, improvements in radiographic and surgical staging techniques, and improvements in the ability to assess response care imply that historical data may not be reflective of the results observed in the current clinical practice. For instance, once a new 'standard' has been defined in any given disease, the historical data obtained to date are invalid, due both to the availability of the new standard, and the fact that a new standard may change the treatment paradigm in that disease (e.g. poor prognosis patients who were previously untreated, thus not included in the historical control rates, may now become part of treatment population) [4]. Moreover, the advances in tumour biology are segregating disease into marker-specific subtypes, for which the historical data may be totally absent [4]. The lack of reliable historical control data can make the application of the single arm trial with this endpoint particularly problematic [14].

Single-arm trials are also subject to lead-time bias (i.e. entry of patients at different points in their natural history) and often to uncertain criteria for establishment of disease progression. Therefore, that is difficult to reliably quantify the development risks with an uncontrolled trial, particularly when the sensitive endpoint is not the response rate [4].

Another weakness in this approach, even for agents that lead to clear tumour regressions, is the inherent bias in patient selection which is unknown and unquantifiable [15,16]. Solutions proposed are considering selection of patient or stratifying analysis by strong prognostic factors. However, one could easily be misled due to the strong likelihood that the differential presence of unknown prognostic factors, rather than the new therapy, explains an unexpected result [4,14].

Finally, when testing a combination of agents in a single arm trial, it is very difficult to distinguish the relative contribution of the standard component from the experimental agent. Additionally, if the baseline activity of the standard regimen is already high, adding an experimental agent may yield uninterpretable results because of the low ability of this design to adequately distinguish the different response rates [5].

2.3.2. Randomized trials

Randomization has the potential of minimizing some of the pitfalls inherent in the single arm phase-II design mentioned in the previous section. Thus, a randomization is appropriate when no historical data are available to guide the statistical analysis of data, when the patient population to be studied is very heterogeneous, when it is likely that outcomes have changed significantly due to a change in standard care, and when testing a combination of agents [2,4].

Randomization may be also relevant when the natural history of the tumour being studied is unknown, or when the target population is unclear [2]. For the development of potentially targeted agents (therapies that are predicted to be effective only in identifiable subgroups), in an uncontrolled setting, one can easily be misled by an association between outcome and subgroup. Without a control group, it is impossible to assess whether any association is due to a differential effect of treatment in the subgroup or whether the subgroup merely confers a poor prognosis [14].

A randomized design may also be appropriate when it is necessary to select the optimal dose or schedule (when more than one dose or schedule has been tested in phase I). Regimen doses and schedules are firstly established through small phase-I trials and limited information is available in most cases on the dose-efficacy and dose-toxicity relationships for the new agent. One potential cause of failure in phase-III trials remains the error in the dose (either too high resulting in an unacceptable toxicity or too low resulting in an inadequate efficacy). This risk can be minimized with a multiple-arm randomized phase-II trial, where several dose levels are explored [4].

Randomization allows complete flexibility in the choice of end-points, particularly if blinding can be incorporated. It is indeed difficult to reliably quantify the activity of a new regimen with an uncontrolled trial when the most sensitive endpoint is not response rate [4,14]. Randomized studies with progression-free survival endpoints are the most powerful and economical methods of determining the activity of a new regimen. The modest increase in patients numbers required will represent a worthwhile investment

when considering the reassurance of informed decision-making at the conclusion of phase-II development [14].

There exist limits of such design with recognition of the potential statistical limitations, especially for small randomized studies which have a number of statistical pitfalls and dangers. Small randomized studies bring with them unavoidable issues such as underpowered, high false negative and false positive rates, unstable p-value, and the risk that these studies, whether negative or positive, may incorrectly preclude later definitive studies. It is recommended a retrospective review of published randomized phase-II studies be undertaken to define their positive predictive value [2]. It is important not to expect that such trials will be a substitute for a full phase-III development, but should be regarded as an efficient tool to select promising agents for further development. The overall objective of such phase-II design remains to select promising agents for further study, and the definitive assessment remains the objective of a phase-III development.

Randomized phase-II trials can be classified into three main groups: (1) randomized selection design ("pick the winner"), (2) randomized comparison design, and (3) randomized discontinuation design.

2.3.2.1 Randomized selection design

The randomized selection design typically does not involve a standard therapy control arm. It randomly enrols patient onto two or more experimental arms evaluating different drug doses or schedules. No formal attempt is made to compare any of the experimental arms with another. This design may be thought as conducting several phase-II trials in parallel, as opposed to sequentially, and can thereby accelerate the transition between phase-II and phase-III testing. The best arm is usually chosen based on predetermined criteria but is still subject to the possibility of false-positive results (type I error) in the range of 10% to 20% [5].

2.3.2.2 Randomized comparison design

Randomized comparison design often incorporates a formal statistical comparison of the experimental groups with a control group (placebo or standard therapy). Such a randomized phase-II study superficially resembles a classical phase-III trial, including statistical evaluations using the log-rank test to compare progression-free survivals, or the χ^2 test for proportions to compare response rates. However, it differs from

a phase-III trial in several important ways. On the one hand, unlike the randomized phase-III study, the type I error of a randomized phase-II trial is typically high, in the range of 10% to 20% in order to keep patient numbers reasonable. On the other hand, the result of a randomized phase-II trial conducted in a smaller subset of patients may not reflect those obtained in a more representative population enrolled in a large phase-III trial. An accurate estimation of effect size is often difficult to determine due to the wide confidence intervals typical of a randomized phase-II trial. Due to relatively small number of patient, the toxicity signals and regimen tolerance might also be at variance with what would be observed in a larger phase-III trial. For these reasons, the results of a randomized phase-II trial using a control group are usually considered to be hypotheses generating and must generally be validated in a larger phase-III trial [5].

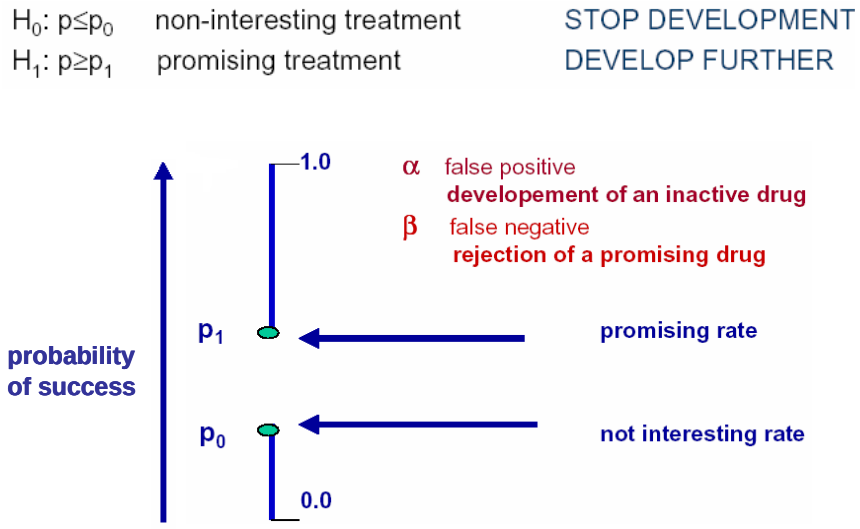
2.3.2.3 Randomized discontinuation design

In randomization discontinuation trials, all patients are treated with the experimental regimen for a specified period of time. Afterwards, the experimental regimen is continued for responders, and discontinued for non responders. For the patients with stable disease, the experimental regimen or placebo is randomly assigned. The endpoint for this type of trial is either time to event (e.g. progression) or the proportion of patient with progression-free disease at a specific time point after random assignment. The randomized discontinuation design has been promoted to be of particular help in screening cytostatic by permitting early assessment of whether delays in progression are related to treatment or disease and whether they are of sufficient magnitude to suggest that the drug may be effective. Because the 'run-in' period in this design is sometimes difficult to predict (i.e., how much time does the drug need to induce disease stability?), and because there may be a carry-over effect of the drug into the placebo group after it is discontinued, interpretation of the results of such studies is not always straightforward[5,6].

3. Statistical background

The statistical background developed in this section concerns the uncontrolled phase-II trials, i.e. without a formal statistical comparison of the experimental groups with a control group like in the randomized comparison design. Thus, it applies to single arm phase-II trials, others uncontrolled randomized phase-II trials using a probability of success as endpoint (e.g. response rate, progression-free survival rate).
This statistical background is illustrated in figure 3.

Figure 3. Statistical background of uncontrolled phase-II trial



The anti-disease activity is measured by the parameter p: the probability of success. The test of anti-disease activity is performed according to the following test procedure:

- H_0: $p \leq p_0$: if the probability of success is too low, typically $\leq p_0$, the drug is considered as inactive.
- H_1: $p \geq p_1$: if the probability of success is high, typically $\geq p_1$, the drug is considered as active.

P_0 and p_1 are thus the a priori probability of success corresponding to insufficient activity and sufficient activity limits, respectively.

Basic statistical background is therefore the binomial distribution of the number of observed success X in the sample of size n:

$$X \sim Bi(n,p), 0 < p < 1 \text{ and } j \in R_x = \{0,1,2,...,n\}$$

$$P(X = j) = b(n,p;j) = \binom{n}{j} p^j (1-p)^{n-j}$$

$$\text{Defining } x_0 \text{ as } \max_x \{R_x : x \le n.p_0\}$$

$$P(p \le p_0) = P(X \le x_0) = \sum_{j=0}^{x_0} b(n,p;j)$$

The maximum tolerable levels for the probability of type I and type II errors, **α and β,** are defined as follows:

Pr[reject H_0 | H_0 true] = pr[type I error] $\le \alpha$
Pr[reject H_1 | H_1 true] = pr[type II error] $\le \beta$

They are related to the false positive and false negative rates. In the first case, a worthless treatment is judged promising, so that a waste of time and resources in further testing and possible damage to patient will follow. In the second case, an active treatment is judged ineffective, so that its benefit will be lost by future patients. The probability of recommending an inactive agent (α, the size of the type I error) should not be greater than 0.20 and it is recommended to use 0.10. The probability of rejecting an effective drug (β, the size of the type II error) should not be greater than 0.10 and 0.05 is recommended. The false negative is the more serious error of the two because, once rejected, the drug will generally have no further chance to show its activity, whereas an inactive drug can still be rejected if its activity is not validated at a larger stage. Thus most designs for this kind of trial try to minimize the probability of false negative result (β or the maximal size of type II error) [5,14].

Phase-II trial sample size is defined by setting values to α, β, p_0 and p_1:

- α and β values are based on *statistical criteria*
- p_0 and p_1 values are based on *clinical criteria*. P_0 is typically chosen to represent the probability of success achievable with standard treatments (historical success), whereas p_1 is chosen in such a way that the difference $p_1 - p_0$ represents a targeted improvement with the new treatment.

3.1. Single-stage design

Sample sizes for a single-stage phase-II design based on the exact binomial distribution are published by R. P. A'Hern [17]. They are also easily computed by most statistical packages, like nQuery or PASS softwares.

Example:

p_0	p_1	α	β	n
0.1	0.3	0.05	0.10	33
		0.10	0.10	25
0.2	0.4	0.05	0.10	44
		0.10	0.10	34

3.2. Multistage designs

For the two following ethical reasons, the principle of multistage design with early stopping rules was introduced:

- the lowest possible number of patients has to be exposed to the inactive/toxic drug,
- The inactive/toxic drug has to be rejected as quickly as possible.

In a multistage design, patients are entered by stage of accrual. If sufficient activity is observed at the end of the first stage, accrual continues to a second stage, and the number of successes at the trials conclusion determines whether the agents is recommended for further testing [4]. In this way, the drug to be rejected at the end of each stage if there is insufficient activity to warrant further testing or toxicity underestimated in phase-I studies.

The oldest is the *Gehan* design [18]. It is a two stage design which allows in the fist step to rapidly reject an inefficient drug and in the second step to estimate the success rate with a given accuracy. *Fleming* has developed a general multistage framework (fig.4) in which n_i patients are accrued at the *i*th stage and a decision is made to stop or continue the trial at the end of each stage according to the efficacy or inefficacy of drug [19]. *Simon* has derived two stage designs (fig.5) that either minimize the expected sample size (the optimal design) under the null hypothesis or minimize the maximum sample size (the minimax design) for given α, β, p_0 and p_1. An important distinction between the two-stage version of the Fleming design and Simon's designs is that the latter allow only rejection of H_1 at each stage, and rejection of H_0 at the final stage [20]. Afterwards, *Ensign* et al have developed three stage design (fig.6) which is essentially a combination of the

Gehan and optimal Simon designs [21]. At stage 1, the design stops with rejection of H_1 if there are no successes at that point; otherwise, it continues to stage 2 and (possibly) stage 3. The advantage of this design is an early termination when no response is observed in stage 1.

Multistage designs have the practical disadvantage that the trial must be temporally closed to patient entry between the first and the second stage in order to determine if the criteria for continuation are met.

Figure 4. Fleming multistage design

Stage N°	*N° of patients*	*Cumulative N° of successes*	*Stopping boundaries*	
			lower	*upper*
1	n_1	x_1	a_1	r_1
2	n_2	x_2	a_2	r_2
3	n_3	x_3	a_3	r_3
…	*…*	*…*	*…*	*…*
K	n_K $N=\sum n_k$	$x=x_K$	a_K	$r_K=a_{K+1}$

Decision rules at each stage k, k=1, …K:

IF $x_k \leq a_k$: reject [H_1:$p \geq p_1$], insufficient activity=reject drug and STOP trial,

IF $x_k \geq r_k$: reject [H_0:$p \leq p_0$], enough activity to further investigation in phase-III trial=accept drug and STOP trial,

IF $a_k < x_k < r_k$: Go to next step in including n_{k+1} patients.

Figure 5. Simon two-stage design

Stage N°	*N° of patients*	*Cumulative N° of successes*	*Stopping boundaries*	
			lower	*upper*
1	n_1	x_1	a_1	
2	n_2	$x=x_2$	a_2	$r_2=a_{2+1}$

Decision rules at:

STAGE 1: Treat n_1 patients and determine the number of successes x_1,

IF $x_1 \leq a_1$: reject [H_1:$p \geq p_1$], insufficient activity=reject drug and STOP trial,

IF $x_1 > a_1$: continue with n_2 next patients.

STAGE 2: Treat the next n_2 patients and determine among all $n= n_1+n_2$ the number of successes x,

IF $x \leq a_2$: reject [H_1:$p \geq p_1$], insufficient activity=reject drug and STOP trial,

IF $x > r_2$: reject [H_0:$p \leq p_0$], enough activity to further investigation in phase-III trial=accept drug.

Figure 6. Ensign three-stage design

Stage N°	*N° of patients*	*Cumulative N° of successes*	*Stopping boundaries*	
			lower	*upper*
1	n_1	x_1	$a_{1=0}$	
2	n_2	x_2	a_2	
3	n_3	$x=x_3$	a_3	$r_3=a_{3+1}$

4. Conclusion

To design a phase-II trial, the investigators must specify a priori two probabilities of success. Firstly, the probability of success, which if the new regimen does not achieve it, will result in no further investigation. It corresponds to the insufficient activity limit, called p_0. Secondly, the probability of success which, if achieved or exceeded, would certainly imply that the new regimen has an efficacy worthy for further investigation in a phase-III randomized trial. It corresponds to the sufficient activity limit, called p_1. The choice of those two limits on the expected probability of success is of a major importance. A too low value for p_0 can lead to a too long investigation of an inactive regimen and a too high value for p_1 can dismiss a promising treatment. These two limits on the probability of success are defined in relationship with the observed success of other available therapies for the same targeted disease. Consequently, the investigators need to have some knowledge about the activity of other available regimens for the same targeted disease.

These two limits on the probability of success, p_0 and p_1, will differ according to the definition of success. When the success is defined as the progression-free survival instead of the response, p_0 and p_1 will be the limits on the probability of progression-free survival instead of the limits on the probability of response rate.

In this work, we were interested in the application of progression-free survival as primary endpoint in phase-II mesothelioma trial. In order to provide reference values which could be used to define the two limits on the probability of progression-free survival (p_0 and p_1), we have estimated the progression-free survival rate at different times (3, 4, 5 and 6 months) based on closed mesothelioma trial data. Two approaches were developed. In first step, progression-free survival rates were estimated in three different groups of trials according to the clinical activity of the testing drugs: insufficient, moderate or significant clinical activity. Indeed, p_0, corresponding to the insufficient activity limit, can be calculated based on what has been observed in

previous trials for which it was concluded that drugs were inactive therapeutic agents. In the same way, p_1, corresponding to the sufficient activity limit, can be calculated based on what has been observed in previous trials for which it was concluded that drugs were active therapeutic agents. These different groups also differ by the treatment type: single agent versus combination of agents and thus we provide also values of p_0 and p_1 corresponding to these treatment types (chapter IV, [22]). In second step, we built a prognostic index which was used to define different risk groups. Progression-free survival rates were estimated in each group. These values could be used as reference values for p_1 and p_0 if you want to consider prognostic factors in the design of phase-II trial (chapter IV, [23]). As mentioned in section 2.2, taking into account the prognostic factors and considering groups with more similar prognoses could improve the design of a phase-II trial.

Reference List

1. ICH Topic E8, General considerations for Clinical Trials. 2006.

2. Booth CM, Calvert AH, Giaccone G, Lobbezoo MW, Eisenhauer EA, Seymour LK. Design and conduct of phase II studies of targeted anticancer therapy: recommendations from the task force on methodology for the development of innovative cancer therapies (MDICT). Eur J Cancer 2008; 44(1):25-29.

3. Johnson JR, Williams G, Pazdur R. End points and United States food and drug administration approval of oncology drugs. J Clin Oncol 2003; 21(7):1404-1411.

4. Ratain MJ, Sargent DJ. Optimising the design of phase II oncology trials: the importance of randomisation. Eur J Cancer 2009; 45(2):275-280.

5. Cannistra SA. Phase II trials in journal of clinical oncology. J Clin Oncol 2009; 27(19):3073-3076.

6. El Maraghi RH, Eisenhauer EA. Review of phase II trial designs used in studies of molecular targeted agents: outcomes and predictors of success in phase III. J Clin Oncol 2008; 26(8):1346-1354.

7. WHO handbook for Reporting of Cancer Treatment. World Health Organisation Offset. Publication N°48, Geneva (Switzerland), 1979.

8. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L et al. New guidelines to evaluate the response to treatment in solid Tumors. J Natl Cancer Inst 2000; 92(3):205-216.

9. Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. Ann Oncol 2004; 15(2):257-260.

10. Cannistra SA. The ethics of early stopping rules: who is protecting whom? J Clin Oncol 2004; 22(9):1542-1545.

11. Ratain MJ, Eisen T, Stadler WM, Flaherty KT, Kaye SB, Rosner GL et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol 2006; 24(16):2505-2512.

12. Korn EL, Arbuck SG, Pluda JM, Simon R, Kaplan RS, Christian MC. Clinical trial designs for cytostatic agents: Are new approaches needed? J Clin Oncol 2001; 19(1):265-272.

13. Van Glabbeke M, Verweij J, Judson I, Nielsen OS. Progression-free rate as the principal end-point for phase II trials in soft-tissue sarcomas. Eur J Cancer 2002; 38(4):543-549.

14. Stone A, Wheeler C, Carroll K, Barge A. Optimizing randomized phase II trials assessing tumor progression. Contemp Clin Trials 2007; 28(2):146-152.

15. Eskens FA, Verweij J. Clinical studies in the development of new anticancer agents exhibiting growth inhibition in models: facing the challenge of a proper study design. Crit Rev Oncol Hematol 2000; 34(2):83-88.

16. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004; 350(23):2335-2342.

17. A'Hern RP. Sample size tables for exact single-stage phase II designs. Stat Med 2001; 20(6):859-866.

18. Gehan EA. The determination of the number of patients required in a follow-up trial of a new chemotherapeutic agent. J Chronic Dis 1961; 13:346-353.

19. Fleming TR. One sample multiple testing procedure for phase II clinical trials. Biometrics 1982; 38:143-151.

20. Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials 1989; 10:1-10.

21. Ensign LG, Gehan EA, Kamen DS, Thall PF. An optimal three-stage design for phase II clinical trials. Stat Med 1994; 13:1727-1736.

22. Francart J, Legrand C, Sylvester R, Van Glabbeke M, van Meerbeeck JP, Robert A. Progression-free survival rate as primary end point for phase II cancer clinical trials: Application to mesothelioma - The EORTC Lung Cancer Group. J Clin Oncol 2006; 24(19):3007-3012.

23. Francart J, Vaes E, Henrard S, Legrand C, Baas P, Gaafar R et al. A prognostic index for progression free survival in malignant mesothelioma with application to the design of phase II trials:a combined analysis of 10 EORTC trials. Eur J Cancer 2009; 45(13):2304-2311.

Chapter III. Materials and methods

1. The dataset

The dataset of this work was obtained by merging data of 10 trials conducted by the European Organisation for Research and Treatment of Cancer Lung Cancer Group between October 1984 and January 2003. There were 9 phase-II trials and 1 phase-III trial. The latter accounted for approximately 50% of data, and the 10 trials were carried out consecutively. All trials were organised by the European Organisation for Research and Treatment of Cancer (EORTC), in about the same centres, and according to similar protocols. Consequently, data collection was comparable. The 9 phase-II trials were included in a large phase-II program to screen the activity of several single agents in a first-line treatment of mesothelioma. After these, the phase-III trial was designed to test the combination of two drugs.

The eligibility criteria were similar among the trials. In all trials, a histologically or cytologically proven diagnosis of malignant pleural or peritoneal mesothelioma was required. All stages of disease were eligible. Patients were chemotherapy naïve.
No prior radiotherapy was allowed except palliative radiotherapy and prior surgery was permitted only if there was evidence of recurrence of disease thereafter. The presence of symptoms indicating metastases of the central nervous system was an exclusion criterion. Patients were aged from 18 to 80 years and had a performance status ≤ 2 (WHO scale). The haematological and biological inclusion criteria were similar amongst the trials (chapter IV, table 2, p84).

Response to therapy was evaluated according to the WHO criteria [1] in all trials except for the two most recent trials [2,3] where the RECIST criteria was used [4]. The patients were followed-up at least every 6 to 8 weeks in almost all trials. In two trials, non progressing patients were followed-up every 12 to 15 weeks after the initial response assessment which was performed at approximately 12 weeks. Computed tomographies were not done at each time, and the progression was assessed by the investigator on a clinical and/or radiological base.

Response rate was the primary endpoint of all phase-II trials and, for the phase-III trial, it was overall survival. However, in all trials, patients were followed for progression and for survival.

598 patients were registered but 75 were excluded: 41 for ineligibility, 9 for incoherent or missing data and 25 because they did not have a definite or probable histologically proven diagnosis. Therefore, 523 patients were included in the analysis.

Further details of these 10 trials are listed in the table below.

Phase II	N registered (N eligible)[a,c]	N removed[b,c]	Regimen	Treatment Schelude	Closed data	Criteria Response[d]	Primary endpoint[d]	Results
08852[e]	46 (41)	3	Mitoxantrone	14 mg/m²,30-min infusion, q 3 weeks	May 86	WHO	RR	2.5% (95%CI:0-13%)
08864[f]	63 (52)	6	4'-Epidoxorubicin	110 mg/m², 3 weekly	Sept 86	WHO	RR	15% (95%CI:6.1 -27.8%)
08878[g]	49 (47)	4	Etoposide	150 mg/m²,IV days 1,3,5, q 3 weeks	Aug 89	WHO	RR	4% (95%CI:1-15%)
08901[h]	45 (41)	12	Etoposide	100 mg, PO days 1-21, q 5 weeks	Feb 92	WHO	RR	7% (95%CI:2-20%)
08924[i]	25 (23)	1	Paclitaxel	200 mg/m²,3-hour infusion, q 3 weeks	Oct 92	WHO	RR	0% (95%CI:0-15%)
08943[j]	32 (27)		Gemcitabine	1,250 mg/m², 30-min infusion, days 1,8,15,28, q 4 weeks	Dec 95	WHO	RR	7% (95%CI:1-24%)

[a] 41 patients withdrawn from analysis for ineligibility

[b] 34 patients withdrawn from analysis for incoherent or missing data (9) and because they did not have a definite or probable histologically proven diagnosis (25)

[c] 75 patients of the 598 registered patients were excluded. Therefore, 523 patients were included in the analysis

[d] WHO: World Health Organisation, RECIST: Response Evaluation Criteria in Solid Tumours , RR: Response rate, OS: Overall survival

References of trials: e[5], f[6], g[7], h[7], i[8], j[9], k[10], l[11], m[2], n[3]

Phase II	N registered (N eligible) [a,c]	N removed[b,c]	Regimen	Treatment Schelude	Closed data	Criteria Response[d]	Primary endpoint[d]	Results
08966[k]	33 (29)	1	Pegylated liposomal doxorubicin	45 mg/m², 1-day infusion, q 4 weeks	Sept 97	WHO	RR	6% (95%CI:0.01-20.2%)
08976[l]	30 (27)	1	Temozolomide	200mg/m²/d,PO days 1,2,3,4,5, q 4 weeks	Oct 98	WHO	RR	4% (95%CI:0.1-19%)
08992[m]	25 (24)	4	Raltitrexed	3 mg/m²,15-min infusion, q 3 weeks	June 01	RECIST	RR	20.8% (95%CI:7-42.2%)
Phase III								
08983[n]	250 (246)	2	Arm1 :Cisplatin alone	80 mg/m², 1day 1-2-hour infusion, q 3 weeks	Janv 03	RECIST	OS	Median OS: 8.8 months (95%CI:7.8-10.8) 1-year OS: 40%
			Arm2 :Raltitrexed with cisplatin	Raltitrexed 3 mg/m², 1 day 15-min infusion followed by cisplatin 1 day 1-2-hour infusion, q 3 weeks				Median OS: 11.4 months (95%CI:10.1-15) 1-year OS: 46%
Total	598 (557)	34						

[a] 41 patients withdrawn from analysis for ineligibility

[b] 34 patients withdrawn from analysis for incoherent or missing data (9) and because they did not have a definite or probable histologically proven diagnosis (25)

[c] 75 patients of the 598 registered patients were excluded. Therefore, 523 patients were included in the analysis

[d] WHO: World Health Organisation, RECIST: Response Evaluation Criteria in Solid Tumours, RR: Response rate, OS: Overall survival

References of trials: e[5], f[6], g[7], h[7], i[8], j[9], k[10], l[11], m[2], n[3]

2. Statistical methods

2.1. Survival analysis[12]

In this work, we used survival analysis both to estimate the progression-free survival rates at 3, 4, 5, and 6 months (see section 2.2.) and to estimate the multivariate prognostic regression for progression-free survival and for survival (see section 2.3.).
Survival analysis refers to time to event analysis and the event (or endpoint) is not necessarily death. This work considered time to disease progression or death from any cause (progression-free survival) and also time to death (survival).

2.1.1. Survival function

Consider n individuals, which we will denote by $j(j=1,\ldots,n)$. Every individual can be characterized by the following information: (T_j,δ_j,Z_j), where T_j stands for the survival or censoring time of the j-th individual and δ_j is equal to 1 or 0, according to whether the individual had an event or was censored[c] at time T_j. A censored individual is an individual for whom the exact survival time is not known. The patients' characteristics are given by the covariate vector[d] Z_j. If we dispose of p covariates then Z_j equals $Z_j^t=(Z_{j1},\ldots,Z_{jp})$.

If T is the variable representing survival time, the distribution of T can be characterized using one of the following functions:

1. Survival function:

$S(t)=P(T>t)=1-F(t)$, the probability of surviving up to and including time t.

This function is a decreasing function on the interval $[0,1]$

2. Cumulative hazard function:

$H(t)=-\log S(t)$, an increasing function on the interval $]0,\infty[$

3. Hazard rate (or hazard function):

$$h(t)=\lim_{\Delta t\to 0}\frac{P(t\le T<t+\Delta t\,|\,T\ge t)}{\Delta t}=-\frac{d}{dt}\log S(t)=\frac{d}{dt}H(t)$$

[c] We will only use right censoring; this means that we consider a censored observation as an observation for which the observation time terminates before the outcome (event) has been observed.

[d] Actually we should write $\vec{Z}_j$, to emphasize the vectorial form of Z_j but for the simplicity we shall write Z_j if we mean $\vec{Z}_j$.

Moreover $h(t)\Delta t$ represents the instantaneous risk of dying at time t, given that the individual was still alive at time t.

2.1.2. The Kaplan-Meier method for estimating survival

The Kaplan-Meier estimator (also called the product limit estimator) of the survival function $S(t)$ incorporates information from all the observations available, both censored and uncensored. It considers survival as a step-function, making jumps at the uncensored observations. The size of the jumps depends on the number of events and on the number of censored observations between the previous event time and the current event time. Assume that we have m recorded event times (failure times) and therefore $n-m$ censored values. Let us denote the ordered event times by $T_{(1)} < T_{(2)} < \cdots < T_{(m)}$, the number of patients at risk of dying at $T_{(i)}$ by R_i and the observed number of deaths at $T_{(i)}$ by d_i. So the general formula of the Kaplan-Meier estimator of the survival function at time t that allows for ties is given by:

$$\hat{S}(t) = \prod_{\substack{i=1 \\ T_{(i)} \le t}}^{n} \left(\frac{R_i - d_i}{R_i} \right)$$

with the convention that $\hat{S}(t) = 1$ for $t < T_{(1)}$.

The variance of $\hat{S}(t)$ (Greenwood's formula) is given by:

$$\hat{V}(\hat{S}(t)) = \hat{S}(t)^2 \sum_{t_i \le t} \left(\frac{d_i}{R_i (R_i - d_i)} \right).$$

Under the assumption that S(t) follows a gaussian distribution on the interval $[t_{i-1}, t_i[$, 95% confidence limits are given by : $\hat{S}(t) \pm 1.96 \sqrt{\text{var}\left[\hat{S}(t)\right]}$.

When $\hat{S}(t)$ tends to 0 or 1, these limits can fall out of the interval $[0,1]$. Rothman (1978) proposed another estimation that resolves this disadvantage:

$$\frac{M}{M + (1.96)^2} \left(S(t) + \frac{(1.96)^2}{2M} \pm 1.96 \sqrt{\text{var}\left[S(t)\right] + \frac{(1.96)^2}{4M^2}} \right)$$

where $M = \dfrac{S(t)(1 - S(t))}{\text{var}[S(t)]}$.

2.2. Estimation of progression-free survival rates (PFSRs) at 3, 4, 5 and 6 months

The progression-free survival time was calculated as the time between the start of treatment and the time of progression or death from any cause. The progression-free survival rates at 3, 4, 5 and 6 months were estimated by the Kaplan-Meier method. These rates estimated the proportion of patients who did not progress and were alive at a given time. The 95% confidence intervals for the progression-free survival rates were estimated using the Greenwood's formula for standard error with Rothman correction.
The progression-free survival rates at 3, 4, 5 and 6 months were estimated in different clinical activity groups and in different risk groups (chapter IV).

2.3. Analysis of prognostic factors and estimation of the multivariate prognostic regression for progression-free survival

The impact of the different clinical factors on progression-free survival as well as on survival was assessed using the Cox proportional hazards model stratified by clinical trials for both univariate and multivariate analyses.

2.3.1. Cox regression model [13]

The regression method is a conventional technique for investigating the relationship between survival time and possible prognostic variables. Such a model was introduced by Cox in 1972. It is a general semi-parametric model appropriate for data with and without censoring. It is a semi-parametric model because it allows an unspecified form for the underlying hazard function, only requiring that the hazard ratios are log-linear in covariates, and thus only the coefficients of the covariates have to be estimated. In the Cox' model, the survival time of each individual has its own hazard function given by:

$$h_j(t) = h_0(t)\exp(\beta^t Z_j)$$

where $h_0(t)$ is a baseline hazard function corresponding to the hazard of an individual with all covariates equal to 0. Under the proportional hazard assumption, the regression coefficients β are the same for all individuals. The survival function for each patient can then be obtained by $S_j(t) = [S_0(t)]^{\exp(\beta^t Z_j)}$.

In order to estimate the regression coefficients, Cox introduced a new form of the likelihood function. We assume that no ties are present and that there have been D deaths with respective $T_{(1)},\ldots,T_{(D)}$ death times. Again R_i is the number of patients at risk at $T_{(i)}$ and we obtain the likelihood that Cox proposed:

$$\prod_{i=1}^{D}\frac{P(T_{(i)}=t_i \cap \text{there is a death at } t_i)}{P(\text{there is a a death at } t_i)}=\prod_{i=1}^{D}\frac{\exp(\beta^t Z_i)}{\sum_{k=1}^{R_i}\exp(\beta^t Z_k)}.$$

One can derive the maximum likelihood estimate $\hat{\beta}$ of β by maximizing this so called partial likelihood function (or its logarithm). This is usually done numerically e.g. by using the Newton-Raphson method. The covariances of the parameter estimates can be estimated by the inverse of the observed information matrix evaluated at the maximum likelihood estimates of the parameters.

Several proposals exist to extend the partial likelihood to the situation where ties are present. We describe the one of Breslow which was used in this work[e]: let S_i be the sum of the covariates of all individuals who die at $T_{(i)}$ and d_i the number of deaths at $T_{(i)}$, Breslow proposed to use:

$$L_B(\beta)=\prod_{i=1}^{D}\frac{\exp(\beta^t S_i)}{\left(\sum_{k=1}^{R_i}\exp(\beta^t Z_k)\right)^{d_i}}.$$

This approach amounts to making a contribution to the partial likelihood at each death time, whether they are distinct or not, and assuming that the risk set is the same for all tied death times.

Consider two patients with covariate vectors Z_j and Z_k respectively. Then we obtain the following expression for the ratio of their hazard rates:

$$\frac{h_j(t)}{h_k(t)}=\frac{h_0(t)\exp(\beta^t Z_j)}{h_0(t)\exp(\beta^t Z_k)}=\exp\left(\beta^t(Z_j-Z_k)\right)$$

which doesn't depend on time, hence the name proportional hazards model. The hazards of two patients are thus linked by the difference in their covariates.

[e] There are other methods, e.g. Efron's method

2.3.2. The proportional hazards assumption [13]

The Cox regression model involves the proportional hazards (PH) assumption. This assumption is that the covariates taken together have the same multiplicative effect on the hazard at all points in time. Since violations of this PH assumption can lead to incorrect interpretations and inferences, it is important to check the PH assumption. Five graphical methods can be used to check the PH assumption: (1) 'log minus log' curves, (2) Andersen plots, (3) Arjas plots, (4) Schoenfeld residual plots, and (5) CoxSnell residual plots. A well-known method for testing the PH assumption is to introduce in the model time-dependent covariates, representing the interaction of the original covariate with time. The model than becomes:

$$h(t) = h_0(t)\exp(\beta^t(t)Z)$$

where $\beta(t) = \beta_1 + \beta_2 g(t)$,

and $\beta_2 g(t)$ stand for interactions with time. The function $g(t)$ can be any function of time (usually, the identity or logarithmic functions are used). A first test would consist of testing if the estimated coefficients $\hat{\beta}_2$ are significantly different from zero. If so, this would mean that some hazard ratios change over time. A second approach was proposed by Grambsch and Therneau (1994). They showed that the score test for $H_0 : \beta_2 = 0$ is equivalent to a generalized least squares test on the scaled Schoenfeld residuals. The approximated scaled Schoenfeld residuals are defined [13]:

$$r_j^* = \hat{\beta} + d\hat{r}_j \hat{V}_j$$

where d is the total number of events (failures),

and $\hat{V}_j = Var(\hat{\beta}, T_j)$.

Grambsch and Therneau showed that if $\hat{\beta}$ is the estimated coefficient from an ordinary fit of the Cox model: $E\left[r_j^*\right] \cong \beta\ (t)$. Thus, if the correlation between the scaled Schoenfeld residual r_j^* and $g(T_j)$ is significantly different from zero, we may have a violation of the PH assumption.

The propotional hazards assumption was checked by Evelien Vaes using each of the abovementioned methods and there was no PH violation in our dataset [13].

2.3.3. Estimation of multivariate prognostic regressions

The multivariate Cox regression was developed including all variables studied in univariate analysis. At first, we compared a model with all covariates and all possible interactions between two covariates against a model with the covariates only using the Akaike's information corrected criterion defined by [14,15]:

$$AICC = -2\ln(L) + 2p\left(\frac{n}{n-(p+1)}\right)$$

where p=number of parameters in the model, and n=total number of patients.

Secondly, a backward selection procedure was used based on the same criterion. Afterwards, the benefit of each variable selected in the multivariate regression was assessed by a sensitivity analysis which was performed using three different methods:

(1) three different criteria characterizing the changes between fitted models:

- the deviance: -2 lnL
- the Akaike's information corrected criterion [14,15]:

$$AICC = -2\ln(L) + 2p\left(\frac{n}{n-(p+1)}\right)$$

- the Schwartz's Bayesian information criterion [16]:

$$BIC = -2\ln(L) + p.\ln(n)$$

where p=number of parameters in the model, and n=total number of patients.

(2) the bootstrap technique was performed in order to obtain the inclusion frequencies of each variable in 1000 bootstrap samples (see section 2.3.3.1).

(3) two different indices of accuracy of different multivariate prognostic regressions: calibration and discrimination (see section 2.3.3.2).

Based on these different methods, a final multivariate regression was proposed.

2.3.3.1 The bootstrap technique [13]

This EORTC data base has a specific patient configuration. The prognostic factors are determined based on the available information in this data base. It is possible that completely different settings would have yielded different prognostic factors. The bootstrapping technique is used for (internal) model validation to check the stability of the model. A covariate that is selected to stay in the model in different patient settings should influence survival (progression-free survival respectively) in most patient populations and is thus decisive as a prognostic factor.

In order to perform this validation, we used the 'bootstrapcox' macro created in SAS by EORTC statisticians Corneel Coens & Kristel Van Steen and we took the number of bootstrap samples B=1000 for our models.

In order to explain the bootstrap technique in more detail, we will begin by giving a few definitions and notations:

(1) Having observed a random sample of size n from a probability distribution F,

$$F \to (x_1, \ldots, x_n),$$

the empirical distribution function $\hat{F}$ was defined as the distribution that puts probability $\frac{1}{n}$ on each value $x_i, i = 1,2,\ldots,n$.

(2) A parameter θ denotes a function of the probability distribution F, e.g. $\theta = t(F)$.

(3) A statistic (or estimator) is a function of the sample **X** and is noted s(**X**).

(4) The plug-in estimate of a parameter $\theta = t(F)$ is noted $\hat{\theta} = t(\hat{F})$.

Suppose that we have a random sample $\mathrm{X} = (\mathrm{x}_1, \ldots, \mathrm{x}_n)$ with unknown distribution function F and we wish to estimate a parameter of interest $\theta = t(F)$ on the basis of **X**, we calculate an estimate $\hat{\theta} = \mathrm{s}(\mathrm{X})$.

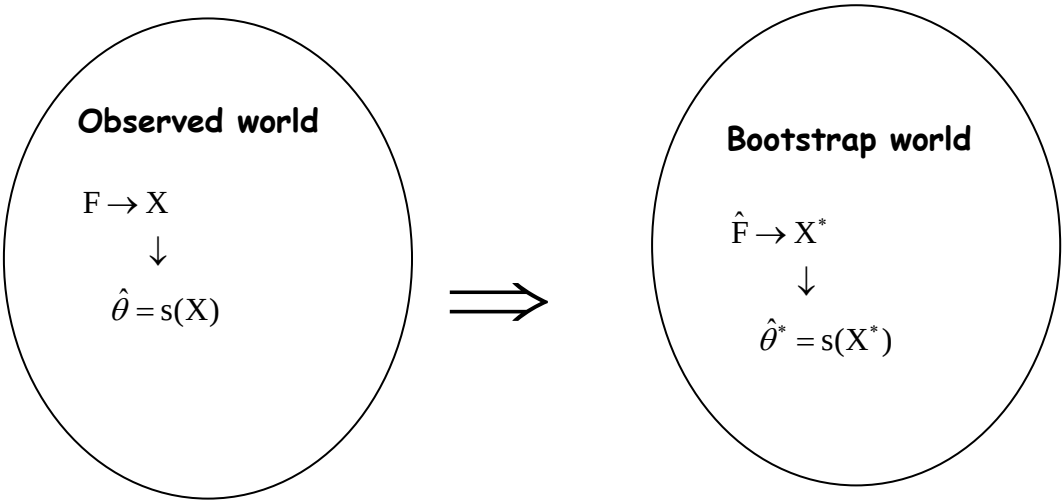
Bootstrap methods depend on a bootstrap sample. Let $\hat{F}$ be the empirical distribution of our sample **X**, as it was defined above. A bootstrap sample is defined to be a random sample of size n drawn with replacement from $\hat{F}$, say $\mathrm{X}^* = (\mathrm{x}_1^*, \ldots, \mathrm{x}_n^*)$,

$$\hat{F} \to (x_1^*, \ldots, x_n^*)$$

So X^* is a random or '*resampled* 'version of X. One can also say that the bootstrap data points $x_1^*, x_2^* \ldots, x_n^*$ are a random sample of size n drawn with replacement from the

population of n objects $(x_1,\ldots,x_n)$. With this new data vector X^*, we can define a bootstrap replication of $\hat{\theta} = \mathrm{s}(\mathrm{X})$, namely $\hat{\theta}^* = \mathrm{s}(\mathrm{X}^*)$.

By repeating this over and over again, say 1000 times, we get 1000 new bootstrap samples $\mathrm{X}_\mathrm{b}^*, \mathrm{b} = 1,\ldots,1000$ that have the same length as the original sample **X**. For every bootstrap sample, we can therefore calculate the bootstrap replications $\hat{\theta}_b^*$ and subsequently study its distribution. Schematically we have, as in Efron and Tibshirani[17]:



Of course, the survival data present in the data base are a bit more complex than the one sample problem used above. In fact, information on n patients is available and we have survival time, censoring status and the covariate vector Z_j for each patient. This information is summarized in $\vec{p}_j = (T_j, \delta_j, Z_j)$ for $j = 1,\ldots,n$. So the sample of n patients $\mathbf{p} = (\vec{p}_1,\ldots,\vec{p}_n)$ has an empirical distribution $\hat{F}_p$, which gives every patient a probability of $\frac{1}{n}$. Now, a bootstrapping algorithm can be performed on the sample **p**. The B bootstrap samples $\mathbf{p}_b^*$ can also be used in order to study the distribution of the obtained maximum likelihood parameters $\hat{\beta}_b^*$ but in our study we are not interested in the parameters. A Cox model is indeed going to be fit on every single bootstrap sample $\mathbf{p}_b^* (b = 1,\ldots,B)$, but thereafter the frequencies of inclusion of the covariates in these B Cox models are of interest. Furthermore we look at the highest model frequencies.

Of what interest could this be? The frequency of inclusion of the covariates in the Cox PH regression models, fit to each of the b ($b = 1, \ldots, B$) data sets using backward stepwise selection, can be considered to be indicative of the importance of the factors. Because each of the B bootstrap samples has a different patient configuration, e.g. one may have mainly older patients together with their specific survival times, another one may have all kinds of patients and again another one may have mostly long-time survivors... A covariate that is retained in most of the different patient settings should influence survival (progression-free survival respectively) in most patient populations and is thus decisive as a prognostic factor.

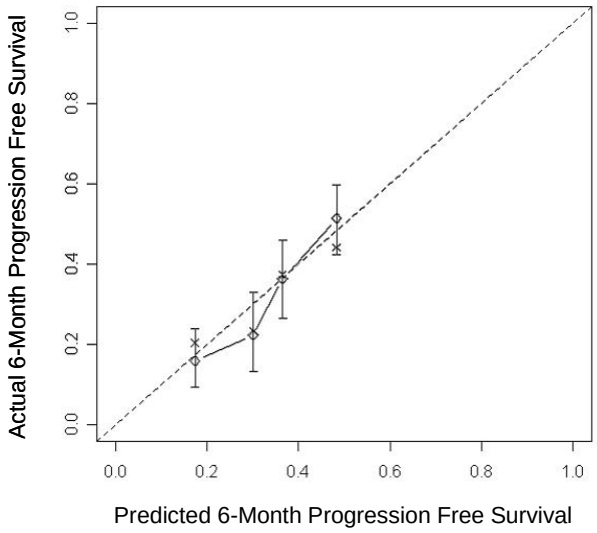
2.3.3.2 Assessment of the accuracy of multivariate prognostic regressions

Accurate estimation of a patient's prognosis is important to provide information to the patient, to select the appropriate therapy, and to design future clinical trials. Multivariate regression models are powerful tools. However, uncritical application of a modelling technique can result in models that poorly fit the dataset at hand, or, even more likely, inaccurately predict outcomes on new subjects. Therefore measuring the accuracy of a model's fit in order to avoid poorly fitting or overfit models is important. When the outcome variable is dichotomous and predictions are stated as probabilities that an event will occur, accuracy can be assessed through calibration and discrimination.

The calibration

Calibration is the numerical agreement between observed and predicted outcomes over a range of predicted probabilities, which is represented by the calibration curve. The calibration curve is generated by plotting actual survival against predicted survival probabilities for patients stratified by predicted risk and it assesses the prediction accuracy of the multivariate regression.

Example: Calibration curve for progression-free survival at 6 months in mesothelioma, Cox's regression with 3 covariates (histological type, stage of disease, and performance status)



x-axis: predicted probability
y-axis: actual outcome
dashed line: performance of an ideal model
solid line: performance of the model
dots: actual outcome for sub cohorts of the dataset
x: bootstrap corrected estimate of model performance
vertical bars: 95% confidence intervals

If the dots are close to the dashed line, the prediction from the multivariate regression approximates the actual outcome. The bootstrap corrected estimate of model performance was calculated by bootstrapping 200 samples with replacement from the original patients used to fit the Cox model.

The discrimination

Discrimination is the ability to separate patients with different outcomes. The concordance probability is used for assessing the discriminatory power of a statistical model.

For a pair of bivariate observations (X_1, T_1) and (X_2, T_2), the concordance probability is defined as

$$K_{X,T} = K = P(T_2 > T_1) \mid X_2 \geq X_1)$$

A concordance probability of 1.0 represents a model that has perfect discrimination, whereas a value of 0.5 indicates that a coin flip would provide information as accurate as the model (random concordance). A value below 0.5, however, does not necessarily indicate a poor model since

$$1 - K_{X,T} = P(T_1 > T_2 \mid X_2 \geq X_1) = K_{-X,T}$$

as long as T is a continuous random variable. Therefore one may consider using $-X$ as the predictor of T, instead of X, to obtain a concordance probability greater than 0.5. A concordance probability of 0 represents perfect opposite concordance.

In the particular case of the proportional hazards model, two estimations of the concordance probability were calculated: the concordance index (*c*-index) and the concordance probability estimate (cpe).

The proportional hazards model is given by:

$$h(t \mid Z) = h_0(t) \exp[\beta^t Z]$$

where

$h(t \mid Z)$ is the hazard function conditional on a p-dimensional covariate vector X,

$h_0(t)$ is the baseline hazard function or hazards if all covariates were 0,

β^t is the regression parameter.

Due to right censoring, the observed data for this model are (T, δ, Z):

T = min between the failure time and censoring time,

δ = 1 if the failure time is smaller than censoring time, and 0 otherwise,

Z = covariate vector.

The concordance index (*c*-index), proposed by Harrell et al. [18], may be applied to continuous, dichotomous, ordinal, and censored time-to-event outcomes. The *c*-index is defined as the proportion of all patient pairs in which the predictions and outcomes are concordant. It is computed by forming all pairs $\{(T_i, \delta_i, Z_i), (T_j, \delta_j, Z_j)\}$ of the observed data, where the smaller follow up time is a failure time:

$$c = \frac{\sum\sum_{i<j} \{I(T_i < T_j) I(\beta^t Z_i > \beta^t Z_j) I(\delta_i = 1) + I(T_j < T_i) I(\beta^t Z_j > \beta^t Z_i) I(\delta_j = 1)\}}{\sum\sum_{i<j} \{I(T_i < T_j) I(\delta_i = 1) + I(T_j < T_i) I(\delta_j = 1)\}}$$

where $\hat{\beta}$ = partial likelihood estimate of β.

The concordance probability estimate (cpe), proposed by Gonen and Heller [19], depends on the regression parameters and does not use the observed event and censoring times. For this reason it is robust to censoring, unlike Harrell's c-index based on informative pairs.

Given that the relationship between the covariate vector *Z* and the survival time *t* is determined through the portional hazards conditional survival function

$$S(t; Z, \beta) = \exp\{-\exp\{\beta^t Z\} \int h_0(t) dt\},$$

for a subject specific covariate vector *Z*, the survival time corresponding to the linear combination $\beta^t Z$ is written by $Q(\beta^t Z)$. Under proportional hazards, the ordering between the survival time of two subjects with log relative risks $\beta^t Z_1$ and $\beta^t Z_2$, can be measured by

$$P(Q(\beta^t Z_2) > Q(\beta^t Z_1)) = \int_0^\infty S(t; Z_2, \beta) dS(t; Z_1, \beta)$$

$$= \frac{1}{1 + \exp\{\beta^t (Z_2 - Z_1)\}}.$$

It follows that the concordance probability is

$$K(\beta) = \frac{\iint_{\beta^t Z_1 > \beta^t Z_2} \left[1 + \exp\{\beta^t (Z_2 - Z_1)\}\right]^{-1} dF(\beta^t Z_1) dF(\beta^t Z_2)}{\iint_{\beta^t Z_1 > \beta^t Z_2} dF(\beta^t Z_1) dF(\beta^t Z_2)}$$

where F is the distribution function of the covariate linear combination $\beta^t Z$.

The concordance probability is estimated by substituting estimates of β and F in K. The partial likelihood estimate $\hat{\beta}$ presents itself naturally for β and the empirical distribution function is used for F. The result is the concordance probability estimate (cpe):

$$K_n(\hat{\beta}) = \frac{2}{n(n-1)\sum\sum_{i<j}\left\{\frac{I(\hat{\beta}^t Z_{ji} < 0)}{1+\exp\left\{\hat{\beta}^t Z_{ji}\right\}} + \frac{I(\hat{\beta}^t Z_{ij} < 0)}{1+\exp\left\{\hat{\beta}^t Z_{ij}\right\}}\right\}}$$

where Z_{ij} = the pairwise difference $Z_i - Z_j$,

and $\hat{\beta}$ = partial likelihood estimate of β.

In contrast to Harrell's c-index, the effect of the observed times on the cpe is mediated through the partial likelihood estimate $\hat{\beta}$, and since the effect of censoring on the bias of $\hat{\beta}$ is negligible, the measure is robust to censoring.

Both c index and cpe were calculated. They were not very different because of the low number of censoring data in our dataset (3%). Consequently, the c index was only reported. The bias adjusted c index was calculated by bootstrapping 200 samples with replacement from the original patients used to fit the Cox model.

2.4. Prognostic index

The prognostic index was computed as the sum of points attributed to each level of the covariates retained in the multivariate regression. These points were calculated by rescaling the model-estimated beta coefficients to a scale that goes from 0 to 100 points, according to the formula:

$$\text{Points}(Z_i) = \frac{\text{coeff}(Z_i) * \text{value}(Z_i)}{\underset{j=1,..,n}{\text{Max}}(\hat{\beta}_j Z_j)} * 100$$

2.5. Nomogram [20]

Oncologists and patients are familiar with reliable prognostic information tailored to the individual patient. The nomogram is such a predictive tool that is useful and easy. The nomogram is widely used for cancer prognosis because of its ability to reduce statistical predictive models into a single numerical estimate of the probability of event,

such as death, recurrence, or progression. The strength of a nomogram is that it combines multiple independent variables to predict an event and it maps the predicted probabilities into points on a scale from 0 to 100 in a user-friendly graphical surface. For many cancers, nomograms compare favourably to the traditional TNM staging systems and thus have been proposed as an alternative or even as a new standard [21-26]. The ability of nomograms to generate individualized predictions enables their use in identification and stratification of patients for participation in clinical trials.

It is a graphical representation linking patient's individual characteristics to his/her probability of event (link between $\hat{\beta}^t Z$ and S(t|Z)), with scales for calculating the cumulative effect of weighted variables on the probability of the particular event. If our intention is to determine wether the selected factors predict if a patient will experience the event within 3 months, the underlying equation is given by:

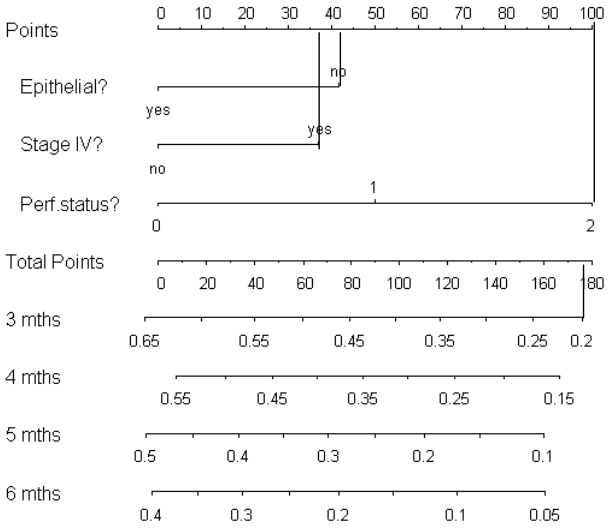
Hazard (experiencing the event at 3 months) =

$$h_0(t=3) * e^{(\beta_1 Z_1 + \ldots \beta_n Z_n)}$$

where $h_0(t)$ is the baseline hazard function.

The nomogram is used by locating a patient's position on each prognostic factor scale. Each scale position has corresponding prognostic points (top axis) and these points are summed to define a total number of points. A vertical line drawn from the 'Total points' axis straight down to the probability axis for a given time will indicate the patient's probability of the event. The figure (fig.1) below represents the nomogram predicting progression-free survival at 3, 4, 5 and 6 months in mesothelioma, and it is based on the three selected covariates presented in our results: the histological type, the stage of disease, and the performance status (chapter IV). The calculation of the probability of remaining free from cancer progression at 3 months, for one given patient, is illustrated.

Figure 1. Nomogram predicting progression-free survival at 3, 4, 5, and 6 months in mesothelioma.



For instance, a patient with a non epithelial (42 prognostic points), a stage IV of disease (37 prognostic points), and a performance status of 2 (100 prognostic points), has a Total Point of 179 and the patient's probability of remaining free from cancer progression at 3 months is 0.20.

Reference List

1. WHO handbook for Reporting of Cancer Treatment. World Health Organisation Offset. Publication N°48, Geneva (Switzerland), 1979.

2. Baas P, Ardizzoni A, Grossi F, Nackaerts K, Numico G, Van Marck E et al. The activity of raltitrexed (Tomudex ®) in malignant pleural mesothelioma: an EORTC phase II study (08992). Eur J Cancer 2003; 39(3):353-357.

3. van Meerbeeck JP, Gaafar R, Manegold C, van Klaveren RJ, van Marck EA, Vincent M et al. Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: An intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. J Clin Oncol 2005; 23(28):6881-6889.

4. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L et al. New guidelines to evaluate the response to treatment in solid Tumors. J Natl Cancer Inst 2000; 92(3):205-216.

5. van Breukelen FJM, Mattson K, Giaccone G, van Zandwijk Nico, Planteydt HT, Kirkpatrick A et al. Mitroxantrone in malignant pleural mesothelioma: A study by the EORTC Lung Cancer Cooperative Group. Eur J Cancer 1991; 27(12):1627-1629.

6. Mattson K, Giaccone G, Kirkpatrick A, Evrard D, Tammilehto L, van Breukelen FJM et al. Epirubicin in Malignant Mesothelioma - A Phase II Study of the European Organization For Research And Treatment Of Cancer Lung Cancer Cooperative Group. J Clin Oncol 1992; 10(5):824-828.

7. Sahmoud T, Postmus PE, van Pottelsberghe C, Mattson K, Tammilehto L, Splinter TAW et al. Etoposide in malignant pleural mesothelioma:Two phase II trials of the EORTC Lung Cancer Cooperative Group. Eur J Cancer 1997; 33(13):2211-2215.

8. van Meerbeeck JP, Debruyne C, van Zandwijk N, Postmus PE, Pennuci MC, van Breukelen FJM et al. Paclitaxel for malignant pleural mesothelioma: a phase II study of the EORTC Lung Cancer Cooperative Group. Br J Cancer 1996; 74:961-963.

9. van Meerbeeck JP, Bass P, Debruyne C, Groen HJ, Manegold C, Ardizzoni A et al. A phase II study of gemcitabine in patients with malignant pleural mesothelioma. Cancer 1999; 85(12):2577-2582.

10. Baas P, van Meerbeeck J, Groen H, Schouwink H, Burgers S, Daamen S et al. Caelyx (TM) in malignant mesothelioma: A phase II EORTC study. Ann Oncol 2000; 11(6):697-700.

11. van Meerbeeck JP, Baas P, Debruyne C, Smit EF, van Klaveren RJ, Galdermans D et al. A phase II EORTC study of temozolomide in patients with malignant pleural mesothelioma. Eur J Cancer 2002; 38(6):779-783.

12. Robert A. L'analyse de survie. In: Statistique des essais cliniques. Diffusion universitaire Ciaco, Brussels, 2001, 188-217.

13. Vaes E. The influence of prognostic factors in mesothelioma on progression free survival and duration of survival and the identification of risk groups. Mémoire, Université catholique de Louvain, 2006.

14. Akaike H. A new look at the statistical model identification. Automatic Control, IEEE Transactions on 1974; 19(6):716-723.

15. Hurvich CM, Tsai CL. Regression and Time-Series Model Selection in Small Samples. Biometrika 1989; 76(2):297-307.

16. Schwarz G. Estimating the dimension of a model. Ann Stat 1978; 6(2):461-464.

17. Efron B, Tibshirani RJ. An introduction to the Bootstrap. CRC press. Chapman and Hall, 1993.

18. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996; 15(4):361-387.

19. Gonen M, Heller G. Concordance probability and discriminatory power in proportional hazards regression. Biometrika 2005; 92(4):965-970.

20. Iasonos A, Schrag D, Raj GV, Panageas KS. How to build and interpret a nomogram for cancer prognosis. J Clin Oncol 2008; 26(8):1364-1370.

21. Kattan MW. Nomograms are superior to staging and risk grouping systems for identifying high-risk patients: preoperative application in prostate cancer. Curr Opin Urol 2003; 13(2):111-116.

22. Mariani L, Miceli R, Kattan MW, Brennan MF, Colecchia M, Fiore M et al. Validation and adaptation of a nomogram for predicting the survival of patients with extremity soft tissue sarcoma using a three-grade system. Cancer 2005; 103(2):402-408.

23. Ohori M, Kattan MW, Koh H, Maru N, Slawin KM, Shariat S et al. Predicting the presence and side of extracapsular extension: a nomogram for staging prostate cancer. J Urol 2004; 171(5):1844-1849.

24. Sternberg CN. Are nomograms better than currently available stage groupings for bladder cancer? J Clin Oncol 2006; 24(24):3819-3820.

25. Wang L, Hricak H, Kattan MW, Chen HN, Scardino PT, Kuroiwa K. Prediction of organ-confined prostate cancer: incremental value of MR imaging and MR spectroscopic imaging to staging nomograms. Radiology 2006; 238(2):597-603.

26. Wong SL, Kattan MW, McMasters KM, Coit DG. A nomogram that predicts the presence of sentinel node metastasis in melanoma with better discrimination than the American Joint Committee on Cancer staging system. Ann Surg Oncol 2005; 12(4):282-288.

Chapter IV. Results

1. Publications

Progression free survival rate as primary endpoint for phase II cancer clinical trials: an application to mesothelioma

J. Francart[1], C. Legrand[2], R. Sylvester[3], M. Van Glabbeke[3], J.P. van Meerbeeck[4], A. Robert[1]

[1]Université catholique de Louvain, Ecole de santé publique, Epidemiology and Biostatistics Unit, Brussels, Belgium;

[2] Université catholique de Louvain, Institute of statistics, Louvain-la-neuve, Belgium;

[3] European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium;

[4] University Hospital, Ghent, Belgium.

Journal of Clinical Oncology 24 (19):3007-3012, July 2006

A Prognostic index for progression free survival in malignant mesothelioma with application to the design of phase II trials: a combined analysis of 10 EORTC trials

J. Francart[1], E.Vaes[1], S. Henrard[1], C. Legrand[2], P. Baas[3], R. Gaafar[4], J.P. van Meerbeeck[5], R. Sylvester[6], A. Robert[1].

[1]Université catholique de Louvain, Ecole de santé publique, Epidemiology and Biostatistics Unit, Brussels, Belgium;

[2] Université catholique de Louvain, Institute of statistics, Louvain-la-Neuve, Belgium;

[3] The Netherlands Cancer Institute-Antoni Van Leeuwenhoek Ziekenhuis, Amsterdam, The Nerderlands;

[4] National Cancer Institute, Cairo University, Cairo, Egypt;

[5] University Hospital, Ghent, Belgium;

[6] European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium.

European Journal of Cancer 45 (13):2304-2311, Sept 2009

2. Additional discussion about our published results

2.1. Comments on results for survival reported in the 2nd article [1]

We underlined that the prognostic index for survival (PI_s) divides better the patients in risk groups for survival than the prognostic index for progression-free survival (PI_p) does for progression-free survival. Median overall survival and median progression-free survival in the group with the best prognosis, as compared with the group with the worst prognosis, were 15.6 (95%CI:12.0-18.4) and 5.4 (95%CI:4.6-6.5) months, and 5.3 (95%CI:3.4-7.6) and 2.1 (95%CI:1.7-3.5) months, respectively (figure3, p96). This is relevant information that we didn't discuss more because we focused on progression-free survival. Our aim was only to illustrate the prognostic value of the three selected variables for progression-free survival on another known endpoint: the survival. The survival regression shown in this article was thus obtained from the fit to progression-free survival and not from the fit to survival. However, a Cox's regression model was also developed for survival and the best model to predict survival included also platelets count in addition to the selected 3 variables for progression-free survival. Estimated coefficients for survival prediction are presented in table 1.

Table 1. Multivariate Cox's regression for survival

Covariates	Coefficient	p-value	HR	[95%CI]
Performance status (WHO scale)				
0			1	
1			1.63	[1.33 ; 2.00]
2	0.49	<.0001	2.66	(log linear trend)
Histological type				
Epithelial			1	
Mixed or Sarcomatous	0.52	<.0001	1.68	[1.31 ; 2.17]
Stage of disease				
Stage I or II or III			1	
Stage IV	0.38	0.0034	1.46	[1.13 ; 1.88]
Platelets count (10^9/L)				
≤ 370			1	
> 370	0.35	0.0035	1.42	[1.12 ; 1.80]

Since our aim was to show the prognostic value of the 3 selected variables for progression-free survival on survival and not to check if this was the best model to predict survival, we decided not to keep platelets count in our model [2].

2.2. Quality and relevance of our results

2.2.1. Homogeneity of the data pool

In our work, there were 10 trials: 9 phase-II trials and 1 phase-III trial that was carried out consecutively and that accounted for approximately 50% of data. All trials were organised by the European Organisation for Research and Treatment of Cancer, in about the same centres, and according to similar protocols. Consequently, data collection was comparable. Moreover, the eligibility criteria were similar among the trials. This supports a homogeneous data pool. However, it is true that the distribution of all studied clinical variables in the different trials were not fully comparable. For instance, for the three variables of our prognostic index, (1) the frequency of no epithelial type across different trials ranged from 11.8 to 39.1%, (2) the frequency of stage IV of disease ranged from 6.3% to 47.1 %, and (3) the frequency of performance status of 0 ranged from 18.4 to 43.5%. However, our prognostic index discriminated risk groups in the pool of all phase-II trials data (p=0.0002) and also in the phase-III trial data (p=0.0005) (Since all 9 phase-II trials had small sample sizes, it was difficult to check this for each trial separately because of a too low number of patients in each risk group). Despite of different clinical series in trials, this observation supports the validity of our results throughout the trials. Moreover, the heterogeneity across trials is partly introduced in modelling because our Cox's regressions were stratified on trials.

2.2.2. Evaluation of the progression time

Trials were not conducted to assess progression at 3, 4, 5 and 6 months and thus computed tomography scans (CT scans) were not done at these specific time. Patients were followed at least every 6 to 8 weeks in almost all the trials. In 2 trials, non progressing patients were followed every 12 to 15 weeks after the initial response assessment at approximately 12 weeks. For this reason, 3 months was chosen as the first time point for reporting the progression-free survival rates. CT scans were not done each time, and the progression was assessed by the investigators on a clinical and/or radiological base. Consequently, an underreporting or a delay in the report of progression can't be excluded. This should have an impact to decrease the progression-free survival curve and to increase the progression-free survival rates.

Delays between the diagnosis and the treatment start could also have an impact on the progression-free survival time since it was calculated from the treatment start.

The median time between first diagnosis and the treatment start was 62 days (table 3, p85) [3]. We did not estimate accurately the impact of this time interval on the progression-free survival time. However this time interval did not show a significant prognostic value for progression-free survival [1]. Moreover, in future trials using progression-free survival as endpoint, the event time should also be calculated from the treatment start.

2.2.3. Validity and relevance of historical data

Given the current rapidly changing standards of care in many diseases, once a new 'standard' has been defined in any given disease, the historical data obtained to date are invalid, due both to the availability of the new standard, and the fact that a new standard may change the treatment paradigm in that disease (e.g. poor prognosis patients who were previously untreated, thus not included in the historical control rates, may now become part of treatment population) [4]. In this work, we analyzed data from mesothelioma trials carried out from 1984 to 2003 which is a long time period. However, during this period, the treatment of mesothelioma did not improve much and did not improve the prognosis of patient. Moreover, 50% of data were from the most recent trial which tested a current regimen cisplatin and ralitrexed. Possible others variations over time in staging system, response criteria, or diagnostic procedures could also make the historical data not relevant. However, over 75% of our data were staged using the IMIG staging system which is currently used. For the response criteria, WHO and RECIST criteria were used in our data. Possible discrepancies between WHO and RECIST response evaluations have be demonstrated and can result in higher progression-free survival rate with RECIST criteria. Nowadays, there is also the modified RECIST which was developed to address the problem of the particular growth of mesothelioma. However, the use of the modified RECIST does not alter strongly the response rate but increases the reproducibility of response assessment, and many trials are yet using the RECIST criteria[3,5]. Concerning the diagnostic procedures, all cases were reviewed by external experts. Diagnostic material was also reassessed by a central pathology panel and diagnosis of mesothelioma was classified as definite, probable, possible, improbable, or excluded. Only cases classified as definite or probable mesotheliomas were included in our work. In order to take into account a part of time dependent effects, we stratified our analysis by trial. However, a period-analysis

approach [6] or the inclusion of a time dependent effect for this variable could have bring a more sensitive estimate.

In conclusion, we think that our provided results remain adequate estimates of the experience that the patients from the current trial would have had if they don't receive the experimental therapy.

2.3. Application of our results

Our data concerned unresectable patients or patients with prior surgery but with evidence of recurrence of disease thereafter. Thus, our results should be applied more specifically to design trials testing systematic therapy regimen in unresectable patients.
As one of the standard treatment of unresectable mesothelioma is the combination of cisplatin plus pemetrexed or ralitrexed, the progression-free survival rates calculated from data of the arm cisplatin plus ralitrexed of phase-III trial 08983 (significant clinical activity group, table 5, p86) [3] are good reference values to design a new phase-II mesothelioma trial testing a combination of this regimen plus a new target therapy which has a synergetic effect such as bevacizumab[7]. We defined also two other groups, insufficient and moderate clinical activity groups, which included all trials which tested a single agent. We could have pooled them together but the response rate of these two groups was different, reflecting different activity levels (6% and 13 % respectively, table 4, p86)[3]. Consequently, we wanted to keep different progression-free survival rates for each group separately. These values could be used to design future phase-II trial using a single agent, as discussed previously (p87) [3]. We estimated progression-free survival rates in four risk groups according to the value of our prognostic index. The choice of these four risk groups was arbitrary. However, they correspond to four different clinical situations: (1) patient without any of the three factors of poor prognosis, (2) patients with one of the three factors of poor prognosis (either no epithelial type or stage IV or performance status=1), (3) patients with two of latter or performance status=2, (4) other patients.

Reference List

1. Francart J, Vaes E, Henrard S, Legrand C, Baas P, Gaafar R et al. A prognostic index for progression free survival in malignant mesothelioma with application to the design of phase II trials:a combined analysis of 10 EORTC trials. Eur J Cancer 2009; 45(13):2304-2311.

2. Vaes E. The influence of prognostic factors in mesothelioma on progression free survival and duration of survival and the identification of risk groups. Mémoire, Université catholique de Louvain, 2006.

3. Francart J, Legrand C, Sylvester R, Van Glabbeke M, van Meerbeeck JP, Robert A. Progression-free survival rate as primary end point for phase II cancer clinical trials: Application to mesothelioma - The EORTC Lung Cancer Group. J Clin Oncol 2006; 24(19):3007-3012.

4. Ratain MJ, Sargent DJ. Optimising the design of phase II oncology trials: the importance of randomisation. Eur J Cancer 2009; 45(2):275-280.

5. Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. Ann Oncol 2004; 15(2):257-260.

6. Brenner H, Arndt V. Period analysis of cancer patient survival in datasets from which the month of diagnosis has been removed. Eur J Cancer 2005; 41(3):438-444.

7. Kabbinavar FF, Wong JT, Ayala RE, Wintroub AB, Kim KJ, Ferrana N et al. The effect of antibody to vascular endothelial growth factor and cisplatin on the growth of lung tumors in nude mice. Proc Am Soc Clin Oncol 1995; 36:488.

Chapter V. Discussion

1. An appropriate endpoint for phase-II trials

The choice of the endpoint for phase-II cancer trials should attempt to minimize subjectivity and bias and to maximize the prediction of clinical benefit and the likelihood of success in the phase-III setting. This choice is dependent on the disease and the expected drug effect (on the basis of data from previous clinical trials) [1]. The main endpoints used to evaluate the activity of the new regimen in phase-II cancer trials are the tumour response, the progression, and the death [2,3]. Other endpoints still exploratory, such as functional imaging, are also discussed in this section.

1.1. Death

An improvement in overall survival is the gold standard endpoint for a new oncology drug. Survival can be assessed with 100% accuracy for the event and with nearly 100% accuracy for the time of event [2]. It is easy to record, reliable and free of bias [3].

However, there may be disadvantages in requiring overall survival as a measure of efficacy. On one hand, since the length of time to complete the study is usually prolonged due to the long term nature of the endpoint. In mesothelioma, this delay is not very long because this disease progresses rapidly to death (median survival is < 12months). On the other hand, there may be also confounding variables such as patients receiving other therapies at the time of progression [2,4,5]. A recent example comes from the indication added by European Medicines Agency to marketing authorization for bevacizumab in non-small cell lung cancer. The trial was originally designed with overall survival as primary end-point but was subsequently amended, shifting to progression-free survival as primary endpoint [4,6]. Analysis of overall survival, done after approval, did not show significant difference in overall survival between patients who did and patient who did not receive bevacizumab. This is partly due to other treatments once a relapse has occurred [7]. A similar phenomenon could occur in mesothelioma, but it could be minor because of the lack of existing 2nd-line treatment.

Another point is that the survival is not always necessary to obtain an approval by USA Food and Drug Administration or by the European Medicines Agency. Endpoints other than survival were the approval basis for 68 % (39 out of 57) of oncology drug marketing applications granted regular approval and for all fourteen applications granted accelerated

approval from January 1, 1990, to November 1, 2002 [2,4]. These other endpoints, called surrogate endpoints, could predict clinical benefit providing an indirect measurement of effect, and allowing to reduce the duration, the sample size, and the cost of cancer clinical trials [8]. In phase-II trials where the required sample size and time to assess activity of new regimen must be shorter than in a phase-III trial, a surrogate endpoint is usually used. Historically, the most used endpoint in phase-II cancer trials is the response rate. However, with the development of new targeted therapies, the use of response as endpoint has been discussed and the progression has been proposed as another appropriate endpoint [9,10].

1.2. Non response

Objective tumour response became widely accepted measure of cancer chemotherapy activity in the early 1980s after Miller et al. [11] established standard response criteria on the basis of bidimensional tumour measurements (WHO criteria). More recently, response criteria on the basis of unidimensional measurements have been widely adopted by investigators and have been used in protocols intended to support drug approval (RECIST criteria) [12]. The more commonly used RECIST criteria define objective tumour response as a 30% reduction from baseline in the sum of the longest diameters of all targeted lesions. The objective tumour response can usually be measured easily with imaging technique such as computed tomography scan [1]. Because an objective response is rare without treatment, response rates are accepted as a valid measure of anti-tumour activity in single arm phase-II studies. However, objective response does not always correlate with clinical benefit and improvement in overall survival [3]. Indeed, some patients with non responding tumours may benefit from delay in tumour progression, which explains survival benefit sometimes observed despite relatively low response rates [13]. That's why, response rate may not be adequate for new targeted agents that produce growth inhibition without tumour regression [1,3].

Moreover, in some tumour types, where tumour measurements are notoriously difficult (e.g. mesothelioma, pancreatic cancer, ovarian cancer) the RECIST criteria may be suboptimal and validation of modified RECIST criteria may be required [14]. This is the case in mesothelioma for which/where the measurement of response remains problematic due to its 'rindlike' pattern of growth. Byrne and Nowak developed an alternative unidimensional measurement technique, the 'modified RECIST', which has partially addressed the problem [15]. It is based on the measurement of tumour thickness instead of long-axis diameter and utilizes the same response criteria as RECIST. However, the method is time-consuming and subject to errors, both in measurement and in assessing target issue. Although it is already

being used in current clinical trials, it should be further evaluated [16,17]. It is also based on structure and takes no account of the viability of tumour masses. Finally, radiological assessment is an insensitive tool. In most cases it is not clear whether a tumour is responsive to chemotherapy until several cycles of treatment have been given. One proposal to alleviate these disadvantages is the [^{18}F] fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) discussed in section 1.4.[18].

After careful consideration, the Methodology for the Development of Innovative Cancer Therapies (MDICT) task force concluded that the objective response as defined by RECIST criteria remained appropriate to include in phase-II studies, but that the use of a multinomial endpoint (including prolonged stable disease or absence of progression) should be considered for all studies, especially for phase-II studies of targeted agents and when the response rate are anticipated to be low [14]. In a multinomial design, the decisions about early stopping and conclusions on activity are based not only on the number of responses seen, but also on the proportion of patients demonstrating early disease progression [19].

In mesothelioma, current treatments are insufficient and thus the development of more active treatments is thus a need and new targeted therapies, including the cytostatic agents, are currently the main focus of mesothelioma research. Moreover, with its pattern of growth, the measurement of response remains difficult, and the response rate is expected to be low. For these reasons, the response rate could maybe not be the most appropriate endpoint, especially for phase-II studies of targeted agents.

1.3. Progression

As above mentioned, for testing new targeted therapies which may cause disease stabilization (cytostatic effect) without tumour shrinkage (cytotoxic effect) the response rate as primary endpoint is not always appropriate [2]. In this case, inhibition of progression may be the most relevant clinical endpoint [3]. In mesothelioma, for instance, the targeted agent ranpirnase was reported to act mainly as a cytostatic agent, hence the conventional tumour response was not seen in different phase-II trials although prolonged disease stabilization and potentially greater survival were arguably suggested [20]. Moreover, as the response rate in mesothelioma is generally expected to be low, a larger difference in tumour response rate than in progression-free survival rate could be needed to predict a significant survival benefit [8]. Additionally, time to progression is measured in all patients (not just responders) and may be a better predictor of overall benefit than the response rate. Thus, in phase-II mesothelioma trials, especially in trials designed for testing novel targeted therapies, the progression-free

survival could alleviates many of the problems met with response rate and thus should be preferred.

Another reason that can also justify the decision of choosing progression-free survival as primary endpoint rather than response rate in phase-II trials is that the progression-free survival is also used in phase-III trials. Consequently, a phase-II trial with progression-free survival should be more predictive of results in phase-III trials.

Such endpoint would improve the approach of testing new regimen to avoid premature rejection of potentially useful regimen without requiring much more means (e.g. follow-up time, sample size)[21].

In comparison with the overall survival, the progression-free survival could not be a real improvement. Indeed the gain in efficiency with progression-free survival rate could be limited (5-6 months) at the cost of less reliability and less confidence of what could be expected in phase-III trials. However, we think that the progression-free survival rate is justified as an endpoint in mesothelioma because delaying cancer progression may be clinically relevant (at least at the level of the patient point of view) in this cancer with a rapid progression to morbidity and/or death [2].

However, the use of progression-free survival as endpoint could be sometimes problematic. There is a lack of reliable historical control data on progression-free survival [22]. Since historic estimates of time to progression are unreliable, it must be evaluated in randomized controlled trials. Moreover, careful assessment of progression at frequent intervals is intensive and expensive labour with potential risk of errors. The assessment of progression is both subject to potential bias and influenced by the frequency of follow-up evaluations [3]. Patients who die without documentation on disease progression often have the date of death recorded as the progression date, thereby inappropriately crediting an unknown amount of additional progression-free time. Unequal time interval ascertainment of progression between treatment arms may occur, and asymmetry of censoring may introduce bias. The time of progression is usually assigned to the study visit at which the progression is detected. Williams et al. have demonstrated that if there is an asymmetric visit schedule between treatment arms, bias in the underlying assessment of time to progression can occur if data are analysed using the log-rank test or Cox proportional hazard model. Even if by design, visit schedules are identical between treatment arms, there is still a concern regarding bias if there is a tendency for investigators to look earlier in one treatment arm group. These properties mean that

differential rates of assessment between treatment arms can lead to bias, which is of particular concern if the trial is not blinded, or if one of the treatment groups has a prevalent and distinctive side effect. The progression-free survival rate, which is a binary outcome at a specified time from treatment initiation, may be preferred over progression-free survival or time to progression for exploratory activity in phase-II trials, since with the latter two endpoints, there is greater potential for bias in determining progression times. Using progression-free survival rate at a predetermined time from the initiation of the study treatment as the primary endpoint minimizes bias related to the timing of the evaluations [3,23]. Another concern is lead-time bias, which is particularly problematic in single-arm trials in which there is no correction for potential variability in the time course of the patient's disease at enrolment but which is unlikely to be a problem in randomized trials.

So, the use of progression as primary end-point in a phase-II trial is more relevant if the trial is randomised, preferably blinded trials [3].

1.4. Other endpoints still explanatory

The inclusion of functional imaging and tissue based biomarker in phase-II studies is discussed. For instance, [^{18}F] fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) is a measure of the metabolic activity and, therefore, the viability of tumour cells. It could alleviate the difficulty of measuring response by computed tomography scan which is challenging in mesothelioma because of the circumferential tumour growth pattern. Francis et al. evaluated the role of serial ^{18}F-FDG PET in the assessment of response to chemotherapy in patients with mesothelioma [18]. They concluded that serial ^{18}F-FDG PET is feasible in mesothelioma and may predict response and patient survival after only one cycle of chemotherapy. Two experiences using metabolic response on ^{18}F-FDG PET were reported in phase-II trials in mesothelioma. The primary endpoint of these trials were the objective response defined by either a) modified RECIST criteria on computed tomography scan or b) metabolic response on ^{18}F-FDG PET. Firstly, in a trial testing imatinib mesylate as single agent in 1st-line therapy, ^{18}F-FDG PET scans were performed at baseline and after four weeks of imitanib in 13 patients. No significant reductions in ^{18}F-FDG uptake were observed. In 7 patients with stable disease as best response, ^{18}F-FDG uptake was unchanged at four weeks in 6 patients. In 5 patients with progressive disease, uptake was increased over baseline in 3. The patient with 25 % reduction did not have PET scanning [24]. Secondly, in a phase-II trial testing sunitinib as single agent in 2nd-line therapy, ^{18}F-FDG PET scans were performed at baseline and after cycles 1, 2, and every 2 cycles thereafter. According to modified RECIST criteria,

there were 0 patient with complete response, 3 with partial response (15%), 11 with stable disease (55%) and 6 with progressive disease (30%); according to the metabolic response there were 3 responses out of 10 assessable (30%), and also one patient with modified RECIST criteria response [25].

Metabolic imaging could have the potential to improve the care of patients with mesothelioma by the early identification of responding patients. However, it is still exploratory and further work is needed and is encouraged to validate these as surrogate endpoint [14].

Some work has also been done to define non-dichotomous response endpoints including tumour volume or kinetics measures. A number of such observations have been explored such as slowing of progression rates [23], and the use of 'waterfall' or 'spider plots' [26]. These different endpoints are still exploratory and are generally not sufficiently validated to be considered as primary endpoints at present, but continued assessment and validation, including in preclinical models prior to initiation of clinical studies, is strongly encouraged [14]. We haven't found any experience in mesothelioma phase-II trials in scientific literature.

2. Experience of phase-II mesothelioma trials

Most of current phase-II trials use the response or the progression as primary endpoint. Only few trials use survival in phase II [27]. In our specific cases of interest, i.e. novel targeted therapies as treatment of unresectable patients with malignant mesothelioma (chapter IV), we found 39 recent trials reported in the literature or in the website www.clinicaltrials.gov (access date 2009/11/26) (table 1). Seven were reported in the article of Tsao et al. [28] but without information about the design of trial and we could not find this information. Out of the remaining 32 trials, 27 were single arm trials. The 5 randomized controlled trials tested in one trial a single agent, or in the 4 other trials a combination. Out of these 32 trials, 13 trials used the response as primary endpoint, 1 the response plus the progression, 2 the response plus the progression-free survival, 2 the overall control disease, 12 the progression-free survival, and 2 the survival. This shows the important interest for the progression-free survival in mesothelioma phase-II trial. However, the randomization is not yet frequently used when the progression-free survival is used (3 out of 14 trials).

Most of the novel therapies were evaluated as single agent (23 out of 39 trials). 16 trials tested a combination of drugs. We noted that the combination was studied when the preclinical studies showed synergy with other agents. It is the case for several anti-angiogenic agents for whom pre-clinical studies support possible synergy with other cytotoxic agents. *Bevacizumab,*

which is highly synergistic with cisplatin in animal models, has been studying in combination with two standard regimens:

(1) with cisplatin+gemcitabine [29] in double-blind, placebo-controlled phase-II randomized trial. The progression-free survival was the primary endpoint. An improvement in progression-free survival and in overall survival, but not in response rate, was observed in subgroups of patient with lower baseline plasma VEGF and treated with bevacizumab.

(2) with cisplatin+pemetrexed in two ongoing single arm trials: one with progression-free survival as endpoint (NCT00295503), and the other one with percent of patients with controlled disease as endpoint (NCT00651456).

(3) with carboplatin+pemetrexed in an ongoing single arm phase-II trial with progression-free survival as endpoint (NCT00407459).

Another anti-VEGFR, *thalidomide* has been studied in two multi-center parallel pilot phase-II studies using thalidomide alone (1st arm) or in combination with cisplatin+gemcitabine (2nd arm). Primary endpoints were progression-free survival and objective response [30]. Thalidomide is under investigation in an international trial with patients receiving cisplatin plus pemetrexed followed by thalidomide or best supportive care.

Ranpirnase, a ribonuclease inhibitor, also demonstrated in vitro synergy with other cytotoxic agents such as doxorubicin and cisplatin [20]. After showing activity in a single arm phase-II trial [31] and in a single agent phase-III comparing ranpirnase and doxorudicin [32], it is currently studied in a phase-III trial comparing doxorubicin plus ranpirnase versus doxorubicin alone (NCT00003034).

Imatinib was shown in preclinical studies that its combination with gemcitabine led to a further tumour growth inhibition and improved mice survival [33,34]. These evidences provide the rationale for the currently ongoing phase II trial (table 1).

Table 1: List of recent phase-II mesothelioma trials testing novel targeted therapies

(sources: scientific literature or in the website www.clinicaltrials.gov -access date 2009/11/26)

Type of agent	Name of agent(s)	Line of treatment	Primary endpoint	Rdom	Start date	References
Antiangiogenic agents	semaxanib	1st line	TTP and RR	no	Aug. 2000	Kindler et al., 2001
	thalidomide	1st line	PFS(6mths)	no	July 2001	Baas et al., 2005
	sorafenib	1st/2nd line	RR	no	Oct. 2004	Janne et al., 2007
	sorafenib	2nd line	PFS	no	Oct. 2008	NCT00794859
	vatalanib	1st line	PFS(3mths)	no	July 2003	Jahan et al., 2006
	sunitinib	2nd line	RR	no	May 2006	Nowak et al., 2008
	sunitinib[a]	*1st line*	*n.r.*	*n.r.*	*n.r.*	*n.r.*
	AZD2171 (2 trials)	1st line	RR	no	Nov. 2005	NCT00243074
	pazopanib	1st line	PFS(6mths)	no	Mar. 2007	NCT00459862
	vandetanib	1st/2nd line	ODCR	yes[b]	Oct.2009	NCT00597116
	bevacizumab+cisplatin+gemcitabine	1st line	PFS(3/4mths)	yes	Dec. 2001	Karrison et al., 2007
	bevacizumab+cisplatin+pemetrexed	1st line	PFS(6mths)	no	Feb. 2006	NCT00295503
	bevacizumab+cisplatin+pemetrexed[c]	1st line	ODCR	yes	Feb. 2008	NCT00651456
	bevacizumab+carboplatin+pemetrexed	1st line	PFS	no	Sep. 2007	NCT00407459
	thalidomide+cisplatin+gemcitabine (2 trials)	1st line	PFS and RR	yes	*n.r.*	Pavlakis et al., 2002
	thalidomide+cisplatin+pemetrexed[a]	*1st line*	*n.r.*	*n.r.*	*n.r.*	*n.r.*
	AZD2171+cisplatin+pemetrexed[a]	*2nd line*	*n.r.*	*n.r.*	*n.r.*	*n.r.*
PDGF inhibitors	imatinib (3 trials)	1st line	RR	no	(1) May2002, (2) 2007, (3) Feb. 2002	(1) Mathy et al., 2005; (2) Porta et al., 2007; (3) Millward et al., 2003
	imatinib+ gemcitabine[a]	*1st line*	*n.r.*	*n.r.*	*n.r.*	*n.r.*
	imatinib+ gemcitabine	2nd line	RR	no	Jan. 2008	NCT00551252

PFS: progression-free survival, RR: response rate, TTP: time to progression, CR: complete response, PR: partial response, SD: stable disease, ODCR: overall disease control rate (CR+PR+SD), n.r.: not reported, Rdom: randomization.

[a] Trials reported by Tsao et al [28], for which information about the design was not found. [b] Trial which compares vandetanib with vinorelbine.

[c] Phase II-III randomized trial.

Kindler et al. 2001[35], Baas et al. 2005[36], Janne et al. 2007[37], Jahan et al. 2006[38], Nowak et al. 2008[25], Karrison et al. 2007[29], Pavlakis et al 2002[30], Mathy et al. 2005[39], Porta et al. 2007[40], Millward et al. 2003[24].

Table 1: List of recent phase-II mesothelioma trials testing novel targeted therapies

(sources: scientific literature or in the website www.clinicaltrials.gov -access date 2009/11/26)

Type of agent	Name of agent(s)	Line of treatment	Primary endpoint	Rdom	Start date	References
EGFR inhibitors	gefitinib	1st line	PFS(3mths)	no	Aug. 2001	Govindan et al., 2005
	gefitinib	1st line	RR	no	Sept. 2003	NCT00787410
	erlotinib	1st line	Survival	no	May 2002	Garland et al., 2007
	erlotinib+bevacizumab	2nd line	RR	no	Feb. 2004	Jackman et al., 2008
	cetuximab+cisplatin or carboplatin+pemetrexed	1st line	PFS(18wks)	no	Oct. 2009	NCT00996567
Ribonuclease inhibitors	ranpirnase	1st line	survival	no	Oct. 1992	Mikulski et al., 2002
Histone deacetylase inhibitors	belinostat	2nd line	RR	no	June 2006	Ramalingam et al., 2009
Proteasome inhibitors	bortezomib	1st/2nd line	RR	no	May 2006	NCT00513877
	bortezomib+cisplatin	1st line	PFS(18wks)	no	Feb. 2007	NCT00458913
	bortezomib+oxaliplatin	2nd line	RR	no	Sept. 2009	NCT00996385
Src kinase	dasatinib	2nd line	PFS(24wks)	no	Aug. 2007	NCT00509141
Antimesothelin	*SS1P*[a]	*1st line*	*n.r.*	*n.r.*	*n.r.*	*n.r.*
	morab009[a]	*1st line*	*n.r.*	*n.r.*	*n.r.*	*n.r.*
	SS1P+cisplatin+pemetrexed[a]	*1st line*	*n.r.*	*n.r.*	*n.r.*	*n.r.*
	morab009+cisplatin+pemetrexed	1st line	PFS	no	Dec. 2008	NCT00923455

PFS: progression-free survival, RR: response rate, TTP: time to progression, CR: complete response, PR: partial response, SD: stable disease, ODCR: overall disease control rate (CR+PR+SD), n.r.: not reported, Rdom: randomization.

[a] Trials reported by Tsao et al [28], for which information about the design was not found. [b] Trial which compares vandetanib with vinorelbine.

[c] Phase II-III randomized trial.

Govindan et al. 2005[41], Garland et al. 2007[42], Jackman et al. 2008[43], Mikulski et al. 2002[31], Ramalingam et al. 2009[44].

3. Benefit of a prognostic index

Part of the difficulty in making progress in treatment of mesothelioma has been the heterogeneity within the patient populations of the trials. The disease is itself heterogeneous, with many different prognostic factors, most notably the stage and the three histological type that have different natural histories and varying response to treatment [28,45]. Moreover, there is a possible variability in the staging of disease between trials (surgical staging *v* radiological staging). Consequently, there may be a dilution of results. For instance, gemcitabine and cisplatin combination had shown response rates ranging from 12% to 48% because of heterogeneity in patient selection and inconsistency in response assessment between trials rather than the slightly different schedules of the regimens [45]. Thus, it is important to interpret and to compare trials to consider patient characteristics and/or factors that could affect prognosis.

Moreover, tumour-nodes-metastasis (TNM) staging is of limited prognostic value in the majority of patients diagnosed with mesothelioma. The TNM prognostic system failed to predict survival in a large series of patients undergoing radical multimodality treatment. This has lead to the development of prognostic scoring systems for survival based on assessment of clinicopathological features of patients with the disease who were recruited to chemotherapy trials in Europe (EORTC) and the United States (CALGB) [46,47]. These two scoring systems have been largely used in mesothelioma trials with survival as endpoint. For instance, in a recent phase-II trial testing ranpirnase, separate survival analyses were conducted in patients with CALGB prognostic groups 1 to 4. This analyze showed difference in results and confirmed the importance of the CALGB scoring system and its utility as a meaningful tool for comparing systemic therapies in patients with unresectable mesothelioma [31].

The two above mentioned scoring systems concern the survival. Our work provides a prognostic index for progression-free survival that will be more relevant in trials using the progression-free survival as primary endpoint. It allows defining more homogeneous groups of patients according to the risk of progression or death. Currently, some trials have already taken into account prognostic factors in the analysis. In the trial testing bevacizumab in combination with cisplatin plus gemcitabine and using progression-free survival as endpoint, analyses were conducted according to the performance status (0/1) and histological type (epithelial/other) [29]. In an ongoing trial testing CBP501 in combination with cisplatin and pemetrexed, the randomization will be stratified

according to histology and performance status (NCT00700336). These examples illustrate well the need of a prognostic index to take into account prognostic factors in the evaluation of a new regimen, to define more homogeneous groups of patients, and consequently to avoid dilution of results between groups. Either the selection of patients or an analysis by subgroup can be performed. In mesothelioma, due to difficulty of accrual, an analysis in subgroup may be preferred to selection of patient. A phase-II trial testing antineoplaston therapy in selected population of stage IV mesothelioma patients was withdrawn due to slow enrolment (NCT00003508).

Reference List

1. Gutierrez ME, Kummar S, Giaccone G. Next generation oncology drug development: opportunities and challenges. Nat Rev Clin Oncol 2009; 6(5):259-265.

2. Johnson JR, Williams G, Pazdur R. End points and United States food and drug administration approval of oncology drugs. J Clin Oncol 2003; 21(7):1404-1411.

3. Kummar S, Gutierrez M, Doroshow JH, Murgo AJ. Drug development in oncology: classical cytotoxics and molecularly targeted agents. Br J Clin Pharmacol 2006; 62(1):15-26.

4. Di Maio M, Bria E, Rossi A, Perrone F. Progression-free survival as primary end point in advanced non-small-cell lung cancer: does the size matter? Ann Oncol 2008; 19(2):402-403.

5. U.S.Food and Drug Administration: Guidance for Industry-Clinical Trial Endpoints for approval of cancer drugs and biologics. http://www.fda.gov, 1-4-2009.

6. Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V et al. Phase III Trial of Cisplatin Plus Gemcitabine With Either Placebo or Bevacizumab As First-Line Therapy for Nonsquamous Non-Small-Cell Lung Cancer: AVAiL. J Clin Oncol 2009; 27(8):1227-1234.

7. European Agency for the Evaluation of Medicinal Products: Assessment report for Avastin. http://www.emea.europa.eu/humandocs/PDFs/EPAR/avastin/Avastin-H-582-II-25-AR.pdf, 1-11-2009.

8. Johnson KR, Ringland C, Stokes BJ, Anthony DM, Freemantle N, Irs A et al. Response rate or time to progression as predictors of survival in trials of metastatic colorectal cancer or non-small-cell lung cancer: a meta-analysis. Lancet Oncol 2006; 7(9):741-746.

9. Korn EL, Arbuck SG, Pluda JM, Simon R, Kaplan RS, Christian MC. Clinical trial designs for cytostatic agents: Are new approaches needed? J Clin Oncol 2001; 19(1):265-272.

10. Van Glabbeke M, Verweij J, Judson I, Nielsen OS. Progression-free rate as the principal end-point for phase II trials in soft-tissue sarcomas. Eur J Cancer 2002; 38(4):543-549.

11. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting Results of Cancer-Treatment. Cancer 1981; 47(1):207-214.

12. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L et al. New guidelines to evaluate the response to treatment in solid Tumors. J Natl Cancer Inst 2000; 92(3):205-216.

13. Buyse M, Thirion P, Carlson RW, Burzykowski T, Molenberghs G, Piedbois P. Relation between tumour response to first-line chemotherapy and survival in advanced colorectal cancer: a meta-analysis. Lancet 2000; 356(9227):373-378.

14. Booth CM, Calvert AH, Giaccone G, Lobbezoo MW, Eisenhauer EA, Seymour LK. Design and conduct of phase II studies of targeted anticancer therapy: recommendations from the task force on methodology for the development of innovative cancer therapies (MDICT). Eur J Cancer 2008; 44(1):25-29.

15. Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. Ann Oncol 2004; 15(2):257-260.

16. Nowak AK. CT, RECIST, and malignant pleural mesothelioma. Lung Cancer 2005; 49 Suppl 1:S37-S40.

17. Oxnard GR, Armato SG, III, Kindler HL. Modeling of mesothelioma growth demonstrates weaknesses of current response criteria. Lung Cancer 2006; 52(2):141-148.

18. Francis RJ, Byrne MJ, van der Schaaf AA, Boucek JA, Nowak AK, Phillips M et al. Early prediction of response to chemotherapy and survival in malignant pleural mesothelioma using a novel semiautomated 3-dimensional volume-based analysis of serial 18F-FDG PET scans. J Nucl Med 2007; 48(9):1449-1458.

19. El Maraghi RH, Eisenhauer EA. Review of phase II trial designs used in studies of molecular targeted agents: outcomes and predictors of success in phase III. J Clin Oncol 2008; 26(8):1346-1354.

20. Pavlakis N, Vogelzang NJ. Ranpirnase-an antitumour ribonuclease: its potential role in malignant mesothelioma. Expert Opin Biol Ther 2006; 6(4):391-399.

21. Francart J, Legrand C, Sylvester R, Van Glabbeke M, van Meerbeeck JP, Robert A. Progression-free survival rate as primary end point for phase II cancer clinical trials: Application to mesothelioma - The EORTC Lung Cancer Group. J Clin Oncol 2006; 24(19):3007-3012.

22. Stone A, Wheeler C, Carroll K, Barge A. Optimizing randomized phase II trials assessing tumor progression. Contemp Clin Trials 2007; 28(2):146-152.

23. Rubinstein LV, Korn EL, Freidlin B, Hunsberger S, Ivy SP, Smith MA. Design issues of randomized phase II trials and a proposal for phase II screening trials. J Clin Oncol 2005; 23(28):7199-7206.

24. Millward M, Parnis F, Byrne M, et al. Phase II trial of imatinib mesylate in patients with advanced pleural mesothelioma. Proc Am Soc Clin Oncol 2003; 22:228a.

25. Nowak AK, Millward MJ, Francis R, et al. Phase II study of sunitinib as second-line therapy in malignant pleural mesothelioma. J Clin Oncol 2008; 26:439s.

26. Ratain MJ, Eisen T, Stadler WM, Flaherty KT, Kaye SB, Rosner GL et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol 2006; 24(16):2505-2512.

27. U.S.National Institutes of Health: Clinical Trials.gov. http://www.clinicaltrials.gov, 1-4-2009.

28. Tsao AS, Wistuba I, Roth JA, Kindler HL. Malignant Pleural Mesothelioma. J Clin Oncol 2009; 27(12):2081-2090.

29. Karrison T, Kindler HL, Gandara DR, et al. Final analysis of multi-center, double-blind, placebo-controlled, randomized phase II trial of gemcitabine/cisplatin plus bevacizumab or placebo in patients with malignant mesothelioma. J Clin Oncol 2007; 25:391s.

30. Pavlakis N, Williams G, Harvey R, et al. Thalidomide alone and in combination with cisplatin/gemcitabine chemotherapy for malignant mesothelioma:preliminary results from two phase II studies. Proc Am Soc Clin Oncol 2002; 21:19b.

31. Mikulski SM, Costanzi JJ, Vogelzang NJ, McCachren S, Taub RN, Chun H et al. Phase II trial of a single weekly intravenous dose of ranpirnase in patients with unresectable malignant mesothelioma. J Clin Oncol 2002; 20(1):274-281.

32. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003; 21(14):2636-2644.

33. Ali Y, Lin Y, Gharibo MM, Gounder MK, Stein MN, Lagattuta TF et al. Phase I and pharmacokinetic study of imatinib mesylate (Gleevec) and gemcitabine in patients with refractory solid tumors. Clin Cancer Res 2007; 13(19):5876-5882.

34. Bertino P, Piccardi F, Porta C, Favoni R, Cilli M, Mutti L et al. Imatinib mesylate enhances therapeutic effects of gemcitabine in human malignant mesothelioma xenografts. Clin Cancer Res 2008; 14(2):541-548.

35. Kindler HL, Vogelzang NJ, Chien K, Stadler WM, Karczmar G, Heimann R et al. SU5416 in malignant mesothelioma:a University of Chicago phase II consortium study. Proc Am Soc Clin Oncol 2001; 20:341.

36. Baas P, Boogerd W, Dalesio O, Haringhuizen A, Custers F, van Zandwijk N. Thalidomide in patients with malignant pleural mesothelioma. Lung Cancer 2005; 48(2):291-296.

37. Janne PA, Wang X., Krug LM, et al. Sorafenib in malignant mesothelioma: a phase II trial of the Cancer Leukemia Group (CALGB 30307). J Clin Oncol 2007; 25:435s.

38. Jahan T, Gu L, Wang X, et al. Vatalanib for patients with previously untreated advanced malignant mesothelioma: a phase II study by the Cancer and Leukemia Group B (CALGB 30107). J Clin Oncol 2006; 24:384s.

39. Mathy A, Baas P, Dalesio O, van Zandwijk N. Limited efficacy of imatinib mesylate in malignant mesothelioma: A phase II trial. Lung Cancer 2005; 50(1):83-86.

40. Porta C, Mutti L, Tassi G. Negative results of an Italian Group of Mesothelioma (G.I. Me.) pilot study of single-agent imatinib mesylate in malignant pleural mesohtelioma. Cancer Chemother Pharmacol 2007; 59:149-150.

41. Govindan R, Kratzke RA, Herndon JE, Niehans GA, Vollmer R, Watson D et al. Gefitinib in patients with malignant mesothelioma: A phase II study by the cancer and leukemia group B. Clin Cancer Res 2005; 11(6):2300-2304.

42. Garland LL, Rankin C, Gandara DR, Rivkin SE, Scott KM, Nagle RB et al. Phase II study of erlotinib in patients with malignant pleural mesothelioma: a Southwest Oncology Group Study. J Clin Oncol 2007; 25(17):2406-2413.

43. Jackman DM, Kindler HL, Yeap BY, Fidias P, Salgia R, Lucca J et al. Erlotinib plus bevacizumab in previously treated patients with malignant pleural mesothelioma. Cancer 2008; 113(4):808-814.

44. Ramalingam SS, Belani CP, Ruel C, Frankel P, Gitlitz B, Koczywas M et al. Phase II study of belinostat (PXD101), a histone deacetylase inhibitor, for second line therapy of advanced malignant pleural mesothelioma. J Thorac Oncol 2009; 4(1):97-101.

45. Kindler HL. Systemic Treatments for Mesothelioma: Standard and Novel. Curr Treat Options Oncol 2008; 9(2-3):171-179.

46. Curran D, Sahmoud T, Therasse P, van Meerbeeck J, Postmus PE, Giaccone G. Prognostic factors in patients with pleural mesothelioma: The European Organization for Research and Treatment of Cancer experience. J Clin Oncol 1998; 16(1):145-152.

47. Herndon JE, Green MR, Chahinian AP, Corson JM, Suzuki Y, Vogelzang NJ. Factors predictive of survival among 337 patients with mesothelioma treated between 1984 and 1994 by the Cancer and Leukemia Group B. Chest 1998; 113(3):723-731.

Chapter VI. Conclusions and Perspectives

1. Conclusions

The phase-II clinical trial plays a central role in oncology drug development. After a phase-I trial has determined a tolerable dose for a new agent or combination, a well-designed phase-II trial should provide the information required to make a go/no-go decision regarding subsequent phase-III testing. As phase-III trial require several years, hundreds or thousands of patients, and often tens or hundreds of millions dollars, the information that a quality phase-II trial can provide is essential to a decision regarding the potential investment in a larger trial.

There are some risks of error: either an active drug can be judged ineffective or a worthless drug can be judged promising. In the first case, the benefit of the new drug will be lost by future patients. In the second case, there will be a waste of time and resources in further testing and possible damage to patient will follow. Thus, the risk of error must be minimized in adopting the more appropriate design according to the testing drug and the target disease.

The past decade has seen a significant shift in oncology drug development from the evaluation of traditional cytotoxic agents to molecular targeted anticancer therapies. While cytotoxic agents generally act at the level of cell division, novel molecular agents target specific proteins involved in tumour growth, angiogenesis, and/or metastases and may be selectively active. These novel agents may not lead to tumour shrinkage. Classical drug development strategies have therefore been challenged, especially with regards to the relevance of objective response as the primary endpoint and the patient selection [1].

In order to assess the therapeutic activity of the novel targeted therapies, or if the response to new regimen is difficult to assess or expected to be low, in the cases of the disease progresses rapidly, the progression-free survival rate at a fixed time point could be used as primary endpoint in phase-II clinical trial rather than the traditional response rate. To design a new phase-II cancer trial with progression-free survival rate as primary

endpoint, we need data about the progression of patients and especially about the progression-free survival rate at fixed time point.

In this work, we proposed and discussed the application of progression-free survival as primary endpoint in phase-II mesothelioma trials. The mesothelioma is a disease with bad prognosis and which rapidly progresses. The development of new therapies is eagerly needed because the incidence of mesothelioma is increasing all over the world and the treatment is currently insufficient. The assessment of response is difficult and not reproducible. Moreover, the response rate is expected to be low. In the mesothelioma, the progression-free survival rate may be more appropriate than the response rate in the assessment of new systematic therapy, especially including novel targeted therapies. Our present work provides values of progression-free survival rate at 3, 4, 5 and 6 months in groups of different levels of therapeutic activity and in different risk groups. These values can be used as reference values to define the two success rates corresponding to insufficient activity and sufficient activity limits (p_0 and p_1). Our work also provides a prognostic index which allows defining more homogeneous groups of patients and it avoids dilution of results between groups. Based on our results, the design of future mesothelioma trial could be adapted and the assessment of the activity of new drug should be improved. Such a design would lead to more reasonable sample sizes, would provide meaningful information, would not delay much the time required before the ability to assess the endpoint, and would decrease the probability to reject a potentially interesting drug.

Despite some weaknesses, this work has the strength to include a relevant number of patients with mesothelioma. In view of low incidence of mesothelioma, it is indeed very difficult to obtain a sufficient database in one study to carry out relevant analysis. Moreover, we are bringing relevant and not yet published data about progression-free survival rate at 3, 4, 5 and 6 months and about prognostic factors of progression-free survival in mesothelioma. Our work highlights that the development of a prognostic index for progression-free survival is relevant and deserves more investigations. An external validation on an independent data set would allow a better validation of our prognostic index.

2. Perspectives

2.1. Additional information in studying other clinical factors

As our analysis was retrospective, it was limited to clinical factors registered in different analysed trials. Other variables reported in literature as prognostic factors of survival in mesothelioma such as the present of chest pain or the weight loss would have been interesting to analyse and would allow a better comparison with the score system for survival developed by Cancer and Leukemia Group B [2]. Moreover, for alkaline phosphatase and lactate dehydrogenase, the normal level range of each institution participating to trials was not always known. Consequently, it wasn't possible to know if their level was normal or abnormal. This didn't allow performing a reliable analysis of these variables. However, the LDH level was significant in our univariate analysis and has been reported in literature as a potential prognostic factor for survival in mesothelioma [2]. The impact of this latter factor on progression-free survival remains to be established.

Moreover, some improvement can be expected by using additional information such as biological markers, genetic factors, or quality of life indicators for which an association with the prognostic of mesothelioma had been already suggested.

2.1.1. Biological markers

Several biomarkers had shown an association with the prognosis of mesothelioma and should be further studied, and several are target for new therapies (see chapter I). O'Byrne et al. examined the relevance of several biological markers as prognostic factors in malignant mesothelioma: angiogenesis, tumour necrosis, cyclooxygenase-2, and matrix metalloproteinases [3]. Angiogenesis was evaluated using the Microvessel density (MVD) which is an indirect measure of the intensity of angiogenesis. An increasing MVD was reported as poor prognostic indicators, and it was found to contribute independently to the EORTC scoring system, but not the CALGB prognostic groups. Tumour necrosis was reported as a poor prognostic factor in malignant mesothelioma and was found to contribute independently to both the EORTC and the CALGB scoring systems. Cyclooxygenase-2 (COX-2) is an inductible enzyme that plays a central role in the conversion of arachidonic acid to a number of metabolites including the prostaglandins. The results indicated that COX-2 was an independent prognostic factor and high levels of COX-2 immunoreactivity contributed

independently to both CALGB and EORTC scoring systems. It was reported as potential novel therapeutic target in malignant mesothelioma. Matrix metalloproteinases (MMP), in particular the gelatinases, play a role in tumour invasion and angiogenesis. Increasing pro- and total MMP-2 were associated with a poor survival and both contributed to the CALGB prognostic index. Matrix metalloproteinases, and MMP-2 in particular, may play an important role in malignant mesothelioma tumour growth and metastasis. Other biological markers were studied**.** High serum VEGF level has been shown inversely correlated with progression-free survival and survival [4]. Src kinase (sarcoma proto-oncogenic tyrosine kinase) is very frequently expressed and activated in mesothelioma. Src kinase activity is associated with advanced stage in mesothelioma and may contribute to invasiveness and metastatic spread [5]. Three antimesothelin agents have been correlated with the extent of disease in order to monitor treatment response and predict prognosis: soluble mesotheline-related peptide (SMRP), megakaryocyte potentiation factor (MPF), and osteopontin (Table 1) [6]. Mesothelin is a differentiation antigen on mesothelial cells that is highly expressed in mesothelioma, and that may have a role in cell adhesion and cell to cell recognition and signalling. SMRP is a splice variant of mesothelin. High SMRP levels are a poor prognosis factor, as they correspond with a greater volume of disease. SMRP may be useful for monitoring treatment and may be predictive of disease recurrence after surgical resection, since levels decrease after surgical resection or treatment response and rise with disease progression [7-9]. MPF, a soluble protein produced by proteolytic cleavage of the mesothelin precursor protein, is secreted by mesothelioma cell lines. Postsurgical MPF levels correlate with the degree of surgical debluking, suggesting that MPF could also be used to monitor treatment effect [10]. The glycoprotein osteopontin is thought to control cell adhesion and bone-matrix interactions. Several small, retrospective series have evaluated these three new biomarkers but larger, prospective studies will be required to fully validate their utility.

Table 1: Potential uses for mesothelioma serum biomarkers [6]

	SMRP	MPF	Osteopontin
Screening in asbestos-exposed population (retrospective study)	Yes	Not done	Yes
Screening in asbestos-exposed population (prospective study)	High false-positive rate	Not done	Not done
Monitoring treatment effect	Yes	Yes	Yes
Predicting prognosis	Yes	Yes	Yes
Differentiating MM from benign pleural disease	Yes	Yes	Yes
Differentiating MM from other cancers	Yes	Not done	No
Determining duration of asbestos exposure	Not done	Not done	Yes
Sensitivity for detecting MM (at a specificity of 95%)	73%	34%	47%

SMRP=soluble mesotheline-related peptide, MPF=megakaryocyte potentiation factor, MM=malignant mesothelioma

2.1.2. Genetic factors

Foster et al. reported that mutations in the tyrosine kinase domain of EGFR gene could be predictor of survival after resection [11].

2.1.3. Quality of life indicators and others

Bottomley et al. have shown that pain and appetite loss might be independent prognostic factors for survival in patients with advanced malignant mesohtelioma [12].
Also, the type of failure to the first-line chemotherapy regimen defined as a primary failure with immediate progression under the first-line regimen or secondary failure occurring after initial response to the first-line treatment, has also shown to be a relevant prognostic factor by Paesmans et al [13]. Janssem et al conducted a phase-III trial comparing second-line pemetrexed with best supportive care and reported that premetrexed improved tumour response and progression-free survival but did not improve overall survival for unselected patients. The subgroup analysis demonstrated that patients who had responded to front-line chemotherapy had a trend toward higher overall survival with second-line pemetrexed [14].

2.2. Implementation of this work to other cancers

Our work demonstrated the feasibility of implementing progression-free survival rate as endpoint in phase-II clinical trials in mesothelioma and it should be extended to other cancers. Using progression-free survival rate as primary endpoint in phase-II trial could also be relevant for all rapidly progressing cancers which can be targeted by cytostatic agents or for which an objective response is difficult to evaluate, or the response rate is

expected low; or if it is justified by specific characteristics of the disease. For instance, in advanced non small cell lung cancers treated with second-line chemotherapy, a survival advantage has been demonstrated for docetaxel compared to best supportive care despite a low response rate. This means that second-line chemotherapy can be beneficial to patients despite a low anti-tumour activity as assessed by objective response rate. Using progression-free survival as endpoint would provide meaningful information [13]. Another good candidate for using progression-free survival as endpoint is the renal carcinoma. Indeed, four drugs (temsirolimus, sunitinib, sorafenib, and imitanib) had shown similar non-progression disease rates, but this was not reflected in the objective response rate data, where only sunitinib had a high level of response. Interestingly, renal cell carcinoma exhibited a similar pattern in the review of cytotoxic agents mentioned earlier. The biologic basis for this pattern is unclear, but in terms of trials of new agents in renal cell carcinoma in the future, designs using non progression endpoints may be more logical than ones using traditional response [15]. In metastatic colorectal cancer or non small cell lung cancer, Johnson et al. demonstrated that large differences in tumour response rate are needed to predict a significant survival benefit, and if surrogates are chosen as the primary endpoint in a clinical trial, time to progression is the preferred measure because more modest and achievable differences are needed for a significant survival benefit [16]. Theses examples show that according to the characteristics of the disease, a non progression endpoint may be also appropriate to test cytotoxic agents.

Researchers that would like to use progression-free survival rate for further clinical trials would need to assess on historical data bases progression-free survival curves in order to define acceptable and unacceptable limits of success rates for a new drug under testing.

Reference List

1. Booth CM, Calvert AH, Giaccone G, Lobbezoo MW, Eisenhauer EA, Seymour LK. Design and conduct of phase II studies of targeted anticancer therapy: recommendations from the task force on methodology for the development of innovative cancer therapies (MDICT). Eur J Cancer 2008; 44(1):25-29.

2. Herndon JE, Green MR, Chahinian AP, Corson JM, Suzuki Y, Vogelzang NJ. Factors predictive of survival among 337 patients with mesothelioma treated between 1984 and 1994 by the Cancer and Leukemia Group B. Chest 1998; 113(3):723-731.

3. O'Byrne KJ, Edwards JG, Waller DA. Clinico-pathological and biological prognostic factors in pleural malignant mesothelioma. Lung Cancer 2004; 45:S45-S48.

4. Karrison T, Kindler HL, Gandara DR, et al. Final analysis of multi-center, double-blind, placebo-controlled, randomized phase II trial of gemcitabine/cisplatin plus bevacizumab or placebo in patients with malignant mesothelioma. J Clin Oncol 2007; 25:391s.

5. Kindler HL. Systemic Treatments for Mesothelioma: Standard and Novel. Curr Treat Options Oncol 2008; 9(2-3):171-179.

6. Ray M, Kindler HL. Malignant pleural mesothelioma: an update on biomarkers and treatment. Chest 2009; 136(3):888-896.

7. Grigoriu BD, Chahine B, Vachani A, Gey T, Conti M, Sterman DH et al. Kinetics of soluble mesothelin in patients with malignant pleural mesothelioma during treatment. Am J Respir Crit Care Med 2009; 179(10):950-954.

8. Robinson BW, Creaney J, Lake R, Nowak A, Musk AW, de Klerk N et al. Mesothelin-family proteins and diagnosis of mesothelioma. Lancet 2003; 362(9396):1612-1616.

9. Robinson BW, Creaney J, Lake R, Nowak A, Musk AW, de Klerk N et al. Soluble mesothelin-related protein--a blood test for mesothelioma. Lung Cancer 2005; 49 Suppl 1:S109-S111.

10. Onda M, Nagata S, Ho M, Bera TK, Hassan R, Alexander RH et al. Megakaryocyte potentiation factor cleaved from mesothelin precursor is a useful tumor marker in the serum of patients with mesothelioma. Clin Cancer Res 2006; 12(14 Pt 1):4225-4231.

11. Foster JM, Gatalica Z, Lilleberg S, Haynatzki G, Loggie BW. Novel and existing mutations in the tyrosine kinase domain of the epidermal growth factor receptor are predictors of optimal resectability in malignant peritoneal mesothelioma. Ann Surg Oncol 2009; 16(1):152-158.

12. Bottomley A, Coens C, Efficace F, Gaafar R, Manegold C, Burgers S et al. Symptoms and patient-reported well-being: Do they predict survival in malignant pleural mesothelioma? A prognostic factor analysis of EORTC-NCIC 08983: Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma. J Clin Oncol 2007; 25(36):5770-5776.

13. Paesmans M, Sculier JP. Second-line treatment for advanced non-small cell lung cancer: How to design a clinical trial for a new agent? Lung Cancer 2007; 55(2):135-136.

14. Jassem J, Ramlau R, Santoro A, Schuette W, Chemaissani A, Hong S et al. Phase III trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma. J Clin Oncol 2008; 26(10):1698-1704.

15. El Maraghi RH, Eisenhauer EA. Review of phase II trial designs used in studies of molecular targeted agents: outcomes and predictors of success in phase III. J Clin Oncol 2008; 26(8):1346-1354.

16. Johnson KR, Ringland C, Stokes BJ, Anthony DM, Freemantle N, Irs A et al. Response rate or time to progression as predictors of survival in trials of metastatic colorectal cancer or non-small-cell lung cancer: a meta-analysis. Lancet Oncology 2006; 7(9):741-746.

Summary

The main objective of this project was to estimate progression-free survival rates at different fixed time points in order to design future phase-II trials targeting the progression-free survival rate as primary endpoint in mesothelioma**.**

Response rate has traditionally been used as an endpoint in many phase-II trials of oncology therapies. However, progression-free survival could be a more appropriate endpoint in rapidly progressing disease, at least in three situations: (1) when testing cytostatic agents, (2) when the response to a regimen is difficult to assess, (3) when the response is expected to be low.

The use of progression-free survival as an endpoint instead of the response rate is relevant in mesothelioma for two primary reasons. Firstly, the global incidence of mesothelioma is increasing and current treatments yield disappointingly poor results. The development of more active treatments is thus highly desirable and new targeted therapies, including cytostatic agents, are currently the main focus of mesothelioma research. Secondly, in mesothelioma the assessment of response is difficult and not reproducible, and the response rate is usually low.

In order to evaluate a novel therapy using progression-free survival rate as the primary endpoint, we need data about the progression of patients and especially about the progression-free survival rate at fixed time point.

Data on 523 patients included in 10 mesothelioma trials conducted by the European Organisation for Research and Treatment of Cancer were analysed. Values of progression-free survival rate at 3, 4, 5 and 6 months in groups of different levels of therapeutic activity and in different risk groups were calculated. Our work also provides a prognostic index which allows the definition of more homogeneous groups of patients that avoids dilution of results between groups. Based on these results, the size of future mesothelioma trials can be calculated and designs can be adapted to improve the assessment of the activity of a new therapy. Furthermore the use of progression-free survival rate rather than response rate as a primary endpoint would not require much more time to assess the endpoint. It would also decrease the probability to reject a potentially interesting therapy by considering non-progressive diseases as successes.