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Tutors/Lecturers

Please consult the Blackboard module for up-to-date information.
Preface

In 1971 president Richard Nixon of the United States started the ‘War on Cancer’ by signing the National Cancer Act of 1971, a United States federal law. The act was intended to strengthen the National Cancer Institute in order to make funds available for and to more effectively carry out cancer research. In 2011 a special issue of Science celebrated the 40th anniversary of this Act and it was concluded that although there was reason for a small celebration, there was still a lot to be done [Science 25 March 2011: Vol. 31 no. 6024 p. 1539 DOI: 10.1126/science.331.6024.1539-a]. The last couple of years a lot of research has focused on a more targeted approach. In this half minor we will look at the steps that have been taken and search for new ways to go.

Cancer develops as a result of genetic mutations, alterations in non-coding RNA repertoires, and changes in epigenetic regulators and metabolic states. The interplay between cancer cells and their microenvironment also has substantial impact on development and progression. Patients and tumors are heterogeneous in nature, implying not only that each patient presents a unique disease, but also that each patient may respond differently to therapy. Consequently, there is a high level of complexity with respect to the mechanisms by which tumors develop, progress, metastasize, and by which tumor therapies can become (more) effective.

The half minor module: Molecular Targets and Cancer Therapy will utilize and extend your basic knowledge ranging from molecular biology to pathology and oncology, and help you to translate this to investigative cancer treatment possibilities. It aims to provide understanding of the current concepts of translational research. Treatment of cancer with conventional treatment regimens such as classical chemotherapy or radiotherapy have reached their limits and need further improvements for satisfactory long-term results. Understanding of physiological cellular processes will enable you to understand disease mechanisms and pathological processes, with as final goal modulation of these processes by specific drugs. This will help you to identify novel druggable targets within signaling pathways that affect cell proliferation, apoptosis, and/or the efficacy of immune-, radio- and chemotherapy, or pathways inducing tumor angiogenesis and metastasis.

Classical histo-pathological characterization of tumors can nowadays be extended with tumor specific expression markers and genetic information on the presence of potential oncogenic mutations and translocations. For example, fine mapping by large scale sequencing enables further stratification that can serve as the base of targeted treatment. Moreover, functional studies on tumor growth can provide new opportunities for treatment. This involves in-depth studies of the cellular and molecular mechanisms that cause normal cells to become tumorigenic, including animal models. Monitoring of treatment responses and early detection of tumor cells or remaining tumor cells are essential elements of successful tumor eradication. This also involves advanced imaging tools, based on sophisticated instrumentation, and designing of tumor specific tracers, which are indispensable elements of advanced medical imaging. Importantly, introduction in the clinic of novel drugs or molecular tools for treatment or diagnostic purposes needs special protocols to test efficacy, safety and clinical utility. Designing and
conducting clinical trials are essential elements and their number will increase, based on the numerous recent discoveries in cancer research.

During this half minor, you will not only be able to link the basics of cellular processes to recent advances in discoveries in oncology, but you will gain insight into emerging targeted therapies. Six tumor conditions have been chosen for this process, i.e. Sezary syndrome, giant cell tumor in bone, breast cancer, renal cell carcinoma, melanoma and colorectal cancer. The background of these tumor conditions will be introduced to you in the first theme of the half minor: Signaling in cancer. In addition, small scale laboratory experiments will be conducted using different tumor cell lines in combination with drugs used to treat cancer. These kind of experiments are the basis of target selection for new drugs. In the second theme Imaging in cancer, you will learn how to interpret results from different imaging modules (MRI, CT and histology) that are used to establish diagnosis and monitor disease progression in clinical settings. In the final theme, From bench to bedside, all aspects of a clinical trial design will be covered by lectures and workgroups using dedicated assignments. These tasks will be directly translated into a real clinical trial situation, coached by tutor-clinicians, and result in the design of a clinical trial proposal. In this process you will also visit the clinic and meet patients participating in clinical trials.

We hope that you will enjoy this half minor and will join the ‘battle against cancer’.

Module committee ‘Molecular Targets and Cancer Therapy’.
Overview of the teaching activities in the half minor.

**Short description.**
The program of Molecular Targets and Cancer Therapy consists of three linked themes, containing a range of teaching activities:

| Theme 1: Singaling in cancer (Week 1-4) | This theme focuses on six tumor conditions, i.e. Sezary syndrome, giant cell tumor in bone, breast cancer, renal cell carcinoma, melanoma and colorectal cancer. It contains:  
- lectures presented by (medical) specialists (tutors in the 3rd module) using exemplary diseases as models where alterations in normal cellular and molecular mechanisms lead to impaired regulation in cancer.  
- work groups to analyse how altered cellular processes can be used as target and translated into precision therapy for cancer patients, and to learn how to formulate and analyse research questions, to discuss literature.  
- practical to set up and conduct drug treatment assays, and learn how to analyse and interpret experiments. |
| Theme 2: Imaging in cancer (Week 5-7) | You will follow this theme together with students of the half minor Biomedical imaging “from molecule to man”. The theme contains:  
- series of lectures on Oncology and nuclear medicine, Pathology and microscopic imaging, and Image guided surgery and in vivo optical imaging.  
- work groups to obtain critical insight about presently developing and future imaging modalities in cancer diagnostics and monitoring disease course during treatment.  
- practical on various imaging techniques. |
| Theme 3: From bench to bedside (Week 8-10) | This theme contains:  
- lectures related to various aspects of clinical trials, in order to learn how to translate a scientific research question into a clinically relevant research trial.  
- workgroups on ethical considerations, statistical pitfalls and patient selection criteria of study design.  
- discussions with tutors, to design and write a clinical trial proposal for a specific tumor condition  
- meetings with oncology patients |

**Your presence during the half minor**
All activities of the minor are mandatory. Should you unexpectedly be absent, it’s requested that you contact the coordinators as soon as possible. They decide on any replacing assignments or other activities that are necessary to fulfill the requirements of the half minor.

**Schedule of the half minor**
Detailed information is provided in the schedule of the minor, see Blackboard.
# Learning goals, assessment and competences

<table>
<thead>
<tr>
<th>Learning goals / general</th>
<th>Assessment type</th>
<th>Competences</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The student can</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. <strong>Indicate</strong> the mechanisms by which cells communicate with each other</td>
<td>-Exam-1, open questions</td>
<td></td>
</tr>
<tr>
<td>2. <strong>Describe</strong> the signaling pathways that control cellular proliferation and differentiation</td>
<td>-Exam-1, open questions</td>
<td></td>
</tr>
<tr>
<td>3. <strong>Reflect</strong> how impaired regulation of specific signal transduction pathways underlies cancer in order to develop better treatment strategies.</td>
<td>-Exam-1, open questions</td>
<td></td>
</tr>
<tr>
<td>4. <strong>Explain</strong> how novel biological markers can be identified</td>
<td>-Presentation, report</td>
<td></td>
</tr>
<tr>
<td>5. <strong>Determine</strong> how to apply these identified biological markers in translational medicine</td>
<td>-Presentation, report</td>
<td></td>
</tr>
<tr>
<td>6. <strong>Conduct</strong> simple molecular and biochemical experiments frequently used in cancer research.</td>
<td>-Presentation, report</td>
<td></td>
</tr>
<tr>
<td>7. <strong>Interpret</strong> results and <strong>draw conclusions</strong> on simple molecular and biochemical experiments frequently used in cancer research and <strong>present</strong> these in a short report.</td>
<td>-Presentation, report</td>
<td></td>
</tr>
<tr>
<td>8. <strong>Evaluate</strong> (criticize and assess) the application of new clinical imaging research lines (e.g. fluorescence imaging methods, hybrid modalities as PET-MRI, and image guided navigation techniques);</td>
<td>-Exam-2, open questions</td>
<td></td>
</tr>
<tr>
<td>Learning goals / general The student can</td>
<td>Assessment type</td>
<td>Competences</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>-----------------</td>
<td>-------------</td>
</tr>
</tbody>
</table>
| 9. **Consider** different aspect of biomedical imaging in basic, translational and clinical oncology (Pathology and microscopic imaging, image guided surgery, oncology and nuclear medicine) | -Exam-2, open questions  
-Write and present Proposal |  |
| 10. **Reproduce and evaluate** the crucial ethical and regulatory steps necessary in developing innovative cancer therapies | -Write and present proposal |  |
| 11. **Link** information between data obtained from various molecular and clinical imaging applications and clinical outcome (e.g. toxicity survival) from a patient | -Write and present proposal |  |
| 12. **Perform** literature search to obtain relevant information | -Write and present proposal |  |
| 13. **Propose** innovative therapeutic strategy that may be developed, for targeting a specific oncological problem | -Write and present proposal |  |
| 14. **Formulate** an opinion on the design and implementation of clinical trials to test new (combinations of) therapeutic agents | -Write and present proposal |  |
| 15. **Acquire** the essentials of clinical trial design | -Write and present proposal |  |
| 16. **Design and write** a (simple) clinical trial proposal | -Write and present proposal |  |
### Assessment matrix*

<table>
<thead>
<tr>
<th>Period (wk)</th>
<th>Subject(s)</th>
<th>Assessment by</th>
<th>Score (points) or other</th>
<th>Duo/indiv/etc</th>
<th>Total score (maximum points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>Intro 1 and 2 Onco 1-6 Practical</td>
<td>Exam-1 open questions; 2 questions / subject</td>
<td>10 points /subject gives 90 points</td>
<td>Indiv</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Literature discussion on Onco 1-6</td>
<td>presentation</td>
<td>Pass/no pass</td>
<td>Duo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Screening</td>
<td>discussion</td>
<td>Pass/no pass</td>
<td>Indiv</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Practical</td>
<td>presentation</td>
<td>Pass/no pass</td>
<td>Duo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Practical</td>
<td>report</td>
<td>10</td>
<td>Duo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Total 100 (55 to pass)</strong></td>
</tr>
<tr>
<td>5-7</td>
<td>Imaging**</td>
<td>Exam-2 open questions</td>
<td>100</td>
<td>Indiv</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case presentation</td>
<td>Pass/no pass</td>
<td>Duo</td>
<td><strong>Total 100 (55 to pass)</strong></td>
</tr>
<tr>
<td>8-10</td>
<td>Step 1 proposal</td>
<td>Final proposal</td>
<td>25</td>
<td>Trio</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Step 2 proposal</td>
<td>Final proposal</td>
<td>25</td>
<td>Trio</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Step 3 proposal</td>
<td>Final proposal</td>
<td>25</td>
<td>Trio</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Step 4 proposal</td>
<td>Final proposal</td>
<td>25</td>
<td>Trio</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Step 5 proposal</td>
<td>Personal statement on ethics</td>
<td>5</td>
<td>Indiv</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Final proposal</td>
<td>presentation</td>
<td>10</td>
<td>Indiv</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Presentation</td>
<td>Quality of questions</td>
<td>Pass/no pass</td>
<td>indiv</td>
<td></td>
</tr>
</tbody>
</table>

*) For the assessment matrix for the BW-track students, we refer to Blackboard.

**) for more detailed info on the assessment on the theme Imaging, we refer to the Toetsplan of the half minor Biomedical imaging “from molecule to man” on their Blackboard module.
<table>
<thead>
<tr>
<th>Period (wk)</th>
<th>Subject(s)</th>
<th>Assessment by</th>
<th>Score (points) or other</th>
<th>Duo/indiv /etc</th>
<th>Total score (maximum points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-10</td>
<td>Final proposal</td>
<td>Peer review</td>
<td>5</td>
<td>Trio</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Final proposal</td>
<td>Quality of peer review</td>
<td>10</td>
<td>Indiv</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Process</td>
<td>Discussion with tutor</td>
<td>10</td>
<td>Indiv</td>
<td>Total 140 (75 to pass)</td>
</tr>
<tr>
<td>1-10</td>
<td>Final grade</td>
<td>each theme has to be passed, no compensation</td>
<td>Indiv</td>
<td>Total 340</td>
<td></td>
</tr>
</tbody>
</table>

**Prerequisites**

Participants in this half minor come with various backgrounds, either in medicine or biomedical sciences. This is a challenge, not only for you as participant, but also for us, the coordinators of this minor. Some of the study material will be familiar to you and other maybe less or not at all. It is important to be aware of this and look at all the assignments and study material with an open mind and check what you know and might not know. It is also important to share your knowledge with others and e.g. help them with preparing the assignments and reading the (study) material. Extra reading is always provided for those who would like to go the extra mile. We are looking forward to interesting and exciting discussions!

This half minor programme is based on knowledge gained earlier in the curriculum of medicine, biomedical sciences, or equivalent:

**Medical students:**

-“Van Cel tot Molecuul”
- Mechanism of disease 2

**Biomedical students:**

- “Cellulaire communicatie”
- Human Pathology
Practical organization of the half minor

The module book presents the skeleton that will lead you through this course. The module book is present in electronic form and will be provided and accessible at the Blackboard module of this minor.

The half minor course has several self-study assignments (SSA) that are related to study materials used during this course. The self-study assignments indicate relevant parts from text books and refers to full papers from literature.

Teaching modalities:

-Lectures (LC) in Theme 1: will be given by clinicians and will provide info on the disease of interest and are linked to the molecular basis of the discussed tumor type with relation to novel treatment modalities.

-Self-study assignments (SSA): form the basis of this course. Self-study assignments are necessary for the workgroup and have to be completed. The questions are based on the core books and indicated literature.

-Workgroups (WG): Active participation of students in workgroups is necessary, because these will provide the opportunity to deepen your knowledge in view of the self-study assignments and disease entities presented beforehand. During the workgroups students will have the opportunity to discuss what they have learned. The tutor of the workgroup is steering the discussion and may bring up new questions.

-Literature discussion: Students will be asked to prepare a PowerPoint presentation about a specific article related to onco 1-6. Articles will be discussed at two occasions, indicated in the schedule (depending on the actual group size, 2 or 3 students will give a presentation to cover various topics/manuscripts. These manuscripts are related to disease entities discussed in earlier LCs and WGs. The presentation should include the research question presented in the manuscript, explanation of methods/techniques used, explanation of results (using figures, tables presented in the manuscript) and Discussion of the results. Finally, the presented work should be related to core book concepts and figures. For better group discussion, 2 or 3 students (again depending on the group size) will be asked to read the same manuscript prepare questions and comments. Participation in the discussion and the quality of the presentation will be assessed by the tutor.

-Tutor sessions (TS): in theme 3 Students will form small groups (2 or 3 depending on the actual number of student enrolled to this half minor) and select a cancer modality as model for targeted therapy. With the guidelines, self-study assignments and lectures students will be able to draft a trial protocol. During the TS student will consult their tutor and get feedback on the set up. Clinicians, who presented the different cancer types with underlying mechanism in theme 1 will be the tutors.

-Practical (PC): PC will require self-study. The practical experiments are complementary to experimental protocols used for drug discovery screening. Your results of this practical will be presented and written in a report that will contribute to your final examination mark (see Assessment matrix)

-Bedside teaching/Grand round (theme 3): Half of the group will join one of the oncologists on a patient visit in the clinic or in the out-patient clinic and will follow the weekly grand round. The other half of the group will do the same in the next week.
Study material and use of literature

In assignments the following books will be used: (please borrow or buy these books if you do not have them and/or look in the library)


- Rang & Dale: Pharmacology

- Harrison’s Principles of Internal Medicine (18th ed.), online available through the Walaeus library

Use of Literature:

The terminology that is used in medicine has not or only minimally changed over the preceding decades, while the knowledge presented in textbooks cannot cope with the speed by which new insights are obtained and becomes outdated quickly. Therefore, health professionals that needs to translate recently gathered knowledge into clinical practice rely on scientific literature. For this reason, we will not only look at texts from study books, but will also use scientific articles during this course. Scientific literature will be an intrinsic part of this course, especially in reference to novel developments and discoveries in cancer research that form the basis of targeted therapy in clinical settings, in other words a clinical trial. For the study assignments particular parts of papers will be selected when we believe that the whole content might be too complicated. For other cases, the selected manuscript, especially review papers, are extending the information given in the course textbooks.

Literature should be considered as part of the course, which means that the information given is part of the examination. For legal reasons the “pdf” files of published literature may not be included in the course book (printed or electronic), the referred literature should be accessed by the students through library web page links and saved by them as individual end user (for more info see the Blackboard module).

During the whole minor, two major papers will be frequently referred and you are expected to be familiarized by most of the concepts presented therein by the end of the 4th week.


Theme 1: Signaling in cancer

1.1 Introduction to theme 1
In this introduction to the first theme, we will refresh and extend your basic knowledge on signal transduction, molecular biology, pathology and oncology. Textbooks and literature will be discussed in lectures and 2 workgroups.

1.1.1 Intro1: lectures

<table>
<thead>
<tr>
<th>Title: LC1: Hallmarks of cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>LC2: From signal transduction to targeted therapy; an introduction</td>
</tr>
<tr>
<td>Lecturer: Prof. Dr. P. ten Dijke (Mol Cell Biology)</td>
</tr>
<tr>
<td>Literature/ Background: See SSA 1</td>
</tr>
</tbody>
</table>

The purpose of signal transduction research is to understand at a molecular level how cells communicate with each other. Furthermore, we would like to gain knowledge on how cells recognize signals from their environment and the mechanisms by which the signals are transduced across the plasma membrane inside the cell leading to cellular morphological and/or functional changes. Signals can originate from other cells, but also light, heat, salt and acid are examples of signals upon which cells react. With this knowledge we can understand all kind of normal, but also pathological processes. Compromised signal transduction from perturbed pathways by (epi)genetic mechanisms may lead to abnormal cell behavior and may ultimately lead to metastasis in distant organs.

Whereas in the past 10-20 years signal transduction research has mainly focused on understanding the basic fundamental principles and on how perturbation in signal transduction processes underlie human diseases, the field is changing. Nowadays, more and more basic researchers and clinicians are teaming up to translate the basic findings into better targeted treatments that have less side-effects. In particular, recent developments focus on personalized treatment.

In this introductory lectures the main inter- and intracellular pathways that control proliferation, survival, migration and differentiation of cells will be covered. How a normal cell develops into a tumor cells will be discussed, as well as the general principles for targeted treatments that are used to restore the subversions in signal transduction processes in cancer cells. These lectures will give you an introduction to SSA1, help you to refresh your knowledge on signal transduciton and help you to prepare for the first workgroup.
1.1.2. Intro1: SSA1 on Cellular communication and signal transduction in cancer (intro1)

Introduction
Communication between cells is translated via signal transduction to various intracellular responses. Intracellular signaling pathways are activated through extracellular signal molecules via interaction with receptor proteins. These receptors proteins activate one or multiple downstream intracellular signaling proteins evoking a cascade of reactions which lead to the activity of effector proteins that in turn effect the behavior of the cell. At any given time, each cell is exposed to multiple signaling stimuli and still is able to execute very different reactions resulting either in survival, cell growth or differentiation, or even in cell death. Alterations in cell signaling pathways lead to various pathological conditions from inflammation to degenerative diseases and from infections to neoplastic lesions. All these changes are resulting from perturbation of already existing signaling routes in cells. Understanding of physiological cellular processes is necessary to understand pathological processes and disease mechanisms. In this assignment we will recapitulate and extend your knowledge on cellular communication and signal transduction mechanisms with a focus on tumor formation.

Objectives
- You will refresh your knowledge on main signal transduction pathways
- You will recapitulate how molecular processes control signal transduction
- You can explain how abnormal growth can happen via growth factor receptor activation
- You can relate abnormal activation to the development of cancer
- You can describe the role of various signaling pathways in the development of cancer

Instruction
Study in Alberts pages:

880- Extracellular signal molecules bind to specific receptors till 886- A cell can alter....
889- Nuclear receptors are ligands... -899 till A cell can use....
904—Signaling through G-protein....909Some G proteins activate...
921- Signaling through enzyme....-927 till TRKs activate...
928- Ras activates a MAP kinase-941 till Bacterial chemotaxis depends
946- Signaling pathways dependent on ... 951 end of page
1241- Molecular basis of cancer...- till 1245 Mutation in genes...

Study in Kumar:
279- Self-sufficiency in growth...284 Till Transcription factors.
The following questions will guide you through the text and emphasize the most important subjects.

**Questions**

1. Briefly summarize the essence of signal transduction and indicate which molecules play a key role in *signal transduction*.
2. Briefly describe the differences and similarities between endocrine, paracrine, autocrine signals.
3. Why is the lifespan of a signal molecule usually short?
4. Steroid hormones usually give a primary and a secondary response. Describe the difference between both responses.
5. What are "first" and "second" messengers? Give an example of both.
6. What is a "molecular switch"?
7. What role do Regulators of G-protein signaling (RGS) have in the activation and inactivation of G-proteins? Why is inactivation as important as activation?
8. Phosphorylation of proteins is an important modification in signal transduction processes. Which amino acids are phosphorylated and why can they be phosphorylated? What happens to the activity of a protein when it is phosphorylated?
9. Many intracellular signaling molecules contain "interaction domains". What do interaction domains consist of and what is their function?
10. What are the binding partners of SH2, SH3, PTB, and PH domains?
11. Growth factor receptors also activate a GTP-binding protein. To what extent is that different from the G-proteins that are activated by G-protein coupled receptors?
12. A mitogenic growth factor activates the so-called MAP kinase pathway. What does this mean?
14. What role does 14-3-3 play in preventing cell death?
15. Which receptors have serine/threonine kinase activity and which ligands bind them?
16. Which proteins will be found in the degradation complex that is present in the cell when Frizzled and LRP are not bound by Wnt?

**Product**

The answers to these questions. In **workgroup 1** we will discuss these subjects and new questions.
1.1.3. Intro2: Clinical, pathological and molecular recapitulation of hallmarks of cancer

Title: LC 3: Neoplasia
Lecturer: Prof. dr. JVMG Bovee, dr. T Bosse
Literature/ Background The modules Mechanisms of Disease 2 and Human Pathology

The basic morphological and biological properties of benign and malignant tumors have largely been covered in previous courses. We will review some of this knowledge during this assignment. When we talk about cancer, we can cover multiple aspects ranging from epidemiological studies at population level to basic molecular processes at the subcellular level. Neoplastic tissues have altered cellular signaling pathways leading to an increased volume of a cell pool that differs in several aspects from its normal counterpart. Based on features that we can visualize and measure, tumors are classified into different subclasses. The classification and used nomenclature is an essential language for a clear communication between professionals. We make a distinction between different tumors based on their histo-morphological appearance and clinical behavior, but we also further classify tumors using nomenclature that relies on the tissue of origin. Furthermore, cellular appearance, differentiation status and relation to the surrounding tissue compartments is essential information that can be used for classification. For further stratification, the genetic changes that are responsible for alterations in the cellular pathways that enables neoplastic proliferation are used.

This lecture will help you refresh your knowledge on the classification and nomenclature of tumors. Important aspects of tumor formation will be discussed. In addition, clinical and morphological elements of neoplasia will be recapitulated.

1.1.4 Intro2: SSA 2 on Clinical, pathological and molecular recapitulation of hallmarks of cancer

Introduction
See LC3.

Objectives
- You will recapitulate the nomenclature related to classification of tumors
- You will be able to identify major characteristics of benign and malignant tumors
- You will be able to classify major tumor types based on their tissue of origin
- You will be able to recall basic features of cancer epidemiology, incidence and factors that influence predisposition to cancer
- You will be able to select and interpret relevant information that can be found in scientific literature dealing with the molecular basis of cancer
Instruction
-Kumar 260-296

-The Hallmarks of Cancer, Hanahan and Weinberg, Cell, 2000

Questions
1. Explain how a pathologist can identify the tissue of origin of a tumor.
2. Tumors can sometimes be histologically malignant but clinically benign or histologically benign but clinically malignant. Explain what the differences between each situation are. Provide examples.
4. How do you make a distinction between invasive and non-invasive malignant epithelial tumors.
5. Three major types of tumor dissemination (metastasis) have been identified. What are these, give examples for each. Explain the clinical relevance of these.
6. Replication of the genome is a tightly controlled process involving multiple phases with built in checkpoints controlling the transition from one phase to another. Make a diagram about cell cycle with key proteins that are involved in both physiological and pathological processes focused to the development of tumors.
7. Study Figure 20-10 in Alberts p. 1212. Explain why the figure legend is not correct. Draw an image that correctly represents the figure legend.
8. What is the difference between hyperplasia, metaplasia, dysplasia and anaplasia?
9. The presence of necrosis in tumors is often associated with a poorer prognosis. Explain why apoptosis is not associated with a poor prognosis and why it does not have such negative effect on prognosis?

Product
The answers to these questions. In workgroup 2 we will discuss these subjects and new questions.
1.2. Onco1: Sézary Syndrome

1.2.1

**Title:** LC 4: Epigenetic Therapy in Sézary Syndrome

**Lecturers:** Dr. CP Tensen, Prof. dr. MH Vermeer

**Tumor type:** Sézary Syndrome

**Mutation/mechanism:** Epigenetic modifications

**Target:** DNA-and histone modifying enzymes

**Literature/ Background**


Sézary Syndrome (SS) is an aggressive form of cutaneous T-cell lymphoma (CTCL) characterized by severe pruritus, generalized erythroderma, lymphadenopathy, and the presence of neoplastic CD4+ T cells (SzS cells) in skin, lymph nodes and peripheral blood. SS patients have a 5-year survival of around 25% and novel therapies are urgently needed.

Epigenetic modifications are defined as heritable, but potentially reversible, alterations in gene expression without an accompanying change in primary DNA sequence. Epigenetic regulation includes DNA methylation and covalent histone modifications. DNA methylation is catalyzed by DNA methyltransferases (DNMTs) and usually takes place at the 5’ position of the cytosine ring within CpG dinucleotides, leading to silencing of genes and noncoding genomic regions. Histones can undergo multiple post-translational modifications by enzymes that add or remove, among others, methyl, acetyl, ubiquitin, and phosphor groups. Combinations of these histone modifications influence the accessibilty of chromatin for active transcription by inducing a more ‘open’ or ‘closed’ chromatin structure. Notably, DNA methylation and histone modifications are intimately linked and work together to establish and maintain a global and local condensed or decondensed chromatin state that eventually determines gene expression.

Cancer cells show aberrant epigenetic architecture with genome wide hypomethylation and site specific, CpG island promoter hypermethylation, which is associated with silencing of tumor suppressor genes. Disruption of the normal pattern of covalent histone modifications is another hallmark of cancer, characteristically with global reduction of trimethylation of H4K20(H4K20me3) and acetylation of H4K16(H4K16Ac). Combined these epigenetic pertubations result in changes in chromatin structure that subsequently affect gene expression. The importance of epigenetic malfunctioning in the development of cancer is further illustrated by the recent identification of mutations in the epigenetic machinery and
specific alterations of histone editing enzymes in different types of cancer.

Contrary to genetic mutations epigenetic alterations are potentially reversible and therapies directed at the enzymatic processes that control the epigenome represent an opportunity to restore the normal epigenetic landscape and correct aberrancies in gene expression. Specifically, DNA methylation inhibitors (DMI) and histone deacetylase inhibitors (HDACI) are emerging as novel therapies.

The US Food and Drug Administration (FDA) have approved four epigenetic drugs for cancer treatment: two DMI (vidaza and decitabine) for patients with myelodysplastic syndrome and two HDACI (vorinostat and romidepsin) for patients with CTCL. Trials with (novel) HDACI and DMI as single agent or in combination are now underway in diverse cancer types including hematologic and solid tumors but have not yet reached the clinic.

However, insight in the mechanisms through which different HDACI suppress tumors is limited and elucidation how epigenetic drugs exert their anti-cancer effect will be crucial to further develop and optimize these therapies. Given the exceptional efficacy of HDACI treatment in CTCL, these lymphomas provide an attractive opportunity to investigate epigenetic treatment.

Suggested further reading


1.2.2 SSA 3: Altered epigenetic landscape during cancer development

Epigenetic mechanisms play a major role in the fine tuning of transcription and translation of genetic information in both time and space and thereby contribute largely to tissue specific expression, control of differentiation and maintaining “stemness” (stem cell-like features). Epigenetic modifications are defined as heritable, but are potentially reversible alterations in gene expression without an accompanying change in the primary DNA sequence. Epigenetic regulation includes DNA methylation, post-translational modifications of histone proteins, chromatin remodeling and noncoding RNAs and controlling of alternative splicing. Cancer cells show an aberrant epigenetic architecture with genome wide hypo-methylation and gene specific, CpG island promoter hyper-methylation. Hypo-methylation is associated with genomic instability and aberrant gene activation, while promoter hyper-methylation is often linked with silencing of tumor suppressor genes. The importance of epigenetic malfunctioning in the development of cancer is further illustrated by the recent identification of mutations in DNA methyltransferases (DNMTs) and TET methyl-cytosine dioxygenase as well as alterations of histone editing enzymes, especially histone acetylation, in different types of cancer. Combined, these epigenetic perturbations result in changes in chromatin architecture that may subsequently affect gene expression.
In this assignment we will discuss how tumor associated epigenetic changes can be used as a target in treating cancer.

**Objectives**
- You can explain the importance of the transcription machinery in relation to tissue specific gene expression
- You can describe and explain different regulatory mechanisms influencing transcription
- You can explain how DNA packaging can influence gene expression
- You can explain how DNA methylation patterns can be transmitted from one cell generation to another
- You can describe how alterations in the methylation status of CpG islands can be studied
- You can describe how chemicals reversing epigenetic changes may influence overall gene expression patterns
- You will be able to summarize the potential benefits of drugs that can act on epigenetic regulation

**Instruction**

Study:
-Alberts 467-477, 1213-1214, 1235-1237

-Kumar 601 table, 616, 1184 for clinical features on Sezary syndrome


**Questions**

1. What is the mechanism that allows DNA methylation patterns to be inherited from progenitor cells to daughter cells? Explain the role of semiconservative replication in this process.
2. Describe tools that allow you to identify altered epigenetic regulation.
3. MYC is an oncogene and a transcription factor. Describe mechanisms by which MYC is able to alter the epigenetic landscape in a tumor cell. Correlate this with your findings from assignment 1.
4. Explain the possible effect of HDAC inhibitors on cancer cells.
5. Explain possible long term side-effects of drug influencing epigenetic controls. Investigate its role in normal tissue.
6. Mono-allelic expression of genes is best known as X chromosome inactivation. The inactivated X chromosome, either paternal or maternal, is randomly distributed between cells of any given tissue. Sometimes it is difficult to make a distinction between neoplastic or reactive lesions. Based on the information given here, design a test that can make a distinction between neoplastic an reactive lesions. Explain the concept and its limitations.
1.3 Onco 2: Giant Cell Tumor of Bone

1.3.1.

**Title:** LC 5: Giant cell tumor of bone

**Lecturers:** Prof. dr. JVMG Bovee, dr. PDS Dijkstra, Prof. dr. H Gelderblom

**Tumor type:** Giant Cell Tumor of Bone (GCTB)

**Mutation:** RANKL-OPG

**Target:** RANKL

**Literature/ Background**

Giant cell tumor of bone is a locally aggressive bone tumor. The tumor is localized at the “end of the bone” (epi-metaphyseal), mainly in the long bones, especially around the knee (in >50%), followed by the axial skeleton, especially the sacrum. It typically affects patients >25 years. Histologically, giant cell tumor of bone contains an mixture of reactive round mononuclear histiocytic cells, pre-osteoclasts, numerous osteoclast-like giant cells and neoplastic spindle-shaped mononuclear stromal cells. Osteoclast-like giant cells have eosinophilic cytoplasm and vesicular nuclei (up to 20 to 50) with prominent nucleoli, and are often larger than normal osteoclasts. The giant cells are evenly distributed. The tumor is locally aggressive and may break though the cortex and invade the soft tissue and vessels. Metastatic spread to the lungs is rare. Intra-lesional curettage, with or without local adjuvant is the treatment of choice.

The giant cells originate from the blood and are reactive. The mononuclear cells are the proliferating and neoplastic cells, which highly express receptor activator of nuclear factor kappa-B ligand (RANKL) thereby mediating osteoclast formation, differentiation and survival. This interplay can be blocked using denosumab (monoclonal antibody against RANK ligand) to which the tumors respond well. GCTB serves as an example in which our understanding of signal transduction and communication between the different cellular components of the tumor has led to a targeted treatment option specifically interfering with a crucial pathway to diminish tumor growth.

1.3.2. SSA 4: Tumor-stromal interaction

**Introduction**
For a long time a reductionist model has been applied in cancer studies. This approach focuses solely on tumor cells and the genetic and molecular alterations associated with tumor development. Heterotypic cellular interactions, such as interactions between tumor cells and stromal cells-tumor cells and stromal matrix components, are increasingly recognized for their role in tumor biology.
Research on the tumor compartment (parenchyma) resulted in the mapping of several tumor cell related changes, but for in vivo models and especially for the treatment of cancer cells in an organism the influence of the stromal cells cannot be ignored. Stromal cells have an intimate relation with the parenchymal cells. Stromal fibroblast, endothelial cells and immune cells are often recruited by signaling molecules secreted by tumor cells. In response, signaling molecules secreted by these stromal cells help the maintenance of tumor survival by generating a paracrine, self-sustaining signal loop. In some cases, the effect of tumor cells on stromal cells lead to such a high accumulation of reactive stromal cells that they will outnumber tumor cells. This is also known as the field effect. These recruited reactive cells can be partially responsible for the tissue destruction observed during neoplastic expansion. Discovery of signaling pathways involved in these heterotypic cellular processes are essential elements to translate these findings in applications to treat or temper tumor expansion. Drugs targeting receptor-ligand interaction on the stromal cells might be used as a successful target for treatment. In view of this concept a rare benign but locally destructive bone tumor – giant cell tumor of bone- that rarely forms metastasis in the lungs and sometimes transform to high-grade sarcoma will be discussed in detail.

Objectives
- You will be able to analyze how heterotopic interactions between tumor and surrounding stromal occur and how reactive normal cells can interact, resulting in local destruction and tumor growth.
- You will be able explain the role of stromal cells in tumor growth and explain the involved pathways.
- You will be able to identify potential targets that can be used to act on tumor-stromal cell interaction thereby enabling novel treatment possibilities.
- You can deduct possible scenarios that limits the success of chosen treatment options for GCTB.
Instruction
Study:
- Weinberg 703-709 (handout with copy of pages)
- Kumar: 1233-1234; pg 1247
- Alberts: pg 1470, on CD

Questions
1. Giant cell tumor of bone is a locally destructive disease, characterized by the presence of large numbers of tumor associated giant cells. These giant cells have features of mature but displaced osteoclasts as they are present in the stromal compartment and not only on bone resorption surfaces. Osteoclasts are characterized by the presence of multiple nuclei. Describe how osteoclast activation occurs.
2. A GCTB researcher observed high expression of RANKL by tumor cells. Make a composite tissue based on this knowledge, include stromal cells as target of RANKL activation.
3. Denosumab is a humanized antibody against RANKL. What effect do you expect from this treatment on the tumor? Make a composite tissue and compare the major features of the normal and tumor tissue.
4. Design a potential novel drug based on the schemes you have established in question 2 and 3 and explain their mode of action.
5. Bisphosphonates (BP) are known to inhibit osteoclastic osteolysis in osteolytic metastatic disease and in osteoporosis. Bisphosphonate treatment was successfully used in GCTB.
   a. Describe the mechanisms by which bisphosphonates work
   b. Compare the mode of action of BP to Denosumab.

Product
The answers to these questions. In workgroup 3 we will discuss these subjects and new questions.
1.4 Onco3: Breast Cancer

1.4.1.  
**Title:** LC 6: Personalized medicine in breast cancer  
**Lecturers:** Prof. dr. P Devilee, dr. JR Kroep  
**Tumor type:** Breast Cancer  
**Mutation:** BRCA1, BRCA2  
**Target:** Poly(ADP-ribose) Polymerase (PARP)  

The popular vision for the future of oncology includes the rational design of therapies inhibiting specific targets, for which development would be less expensive and the chance of success greater because the agent, the target, and a population predicted to benefit maximally would be known from the outset. In the breast cancer arena, successful targeted therapies have entered clinical practice. Recently, patients with BRCA1/2-associated cancers have been identified as eligible for novel investigational therapies targeting their genetic deficiency. Preclinical data, phase I results, and 2 phase II proof-of-concept studies support the continued development of PARP inhibitors, either as single agents or in combination with specific cytotoxic drugs in this setting. In this workgroup we will discuss current developments concerning PARP inhibitors in BRCA-associated cancers and challenges to further development.

BRCA1 and BRCA2 are two major genes underlying hereditary forms of breast cancer. Approximately 3% of all breast cancer, and 6-8% of premenopausal breast cancer are due to germline mutations in these genes. An important first discovery of how both genes cause breast cancer was that virtually all breast tumors arising in gene carriers have lost the wild-type allele. This indicated that BRCA1 and BRCA2 act as tumor suppressor genes. A second major breakthrough was the discovery that both genes are involved in DNA damage repair through homologous recombination (HR). HR is important to repair double-strand DNA breaks, which may arise after replication-fork stalling at single-strand breaks. poly-ADP-ribose-polymerases (PARPs) constitute a family of enzymes involved in base-excision repair, a key pathway in the repair of DNA single-strand breaks. Because tumors arising in carriers of BRCA1 and BRCA2 mutations are predicted to be HR-deficient, it was hypothesized that inhibition of PARP1 in these tumors would cause an accumulation of DNA lesions that would not be adequately repaired, leading to apoptosis.
Importantly, normal cells which have not lost BRCA-function would not be affected by PARP inhibition, creating a wide therapeutic window potentially allowing minimal side-effects of treatment.

DNA-damaging agents such as cisplatin (which forms DNA intra-and inter-strand breaks leading to double strand breaks), inhibitors of PARP and newer agents like phosphoinositide 3-kinase (PI3K) inhibitors (perhaps by increased DNA damage), can be combined into a two-hit strategy called synthetic lethality. Several new agents are currently in clinical investigation (phase I-III) and will be discussed. Future therapeutic directions for PARP inhibitors are focused at designing the most effective regimens, determining optimal combination and timing of therapy as well as identification of biomarkers for patient selection. Several PARP inhibitor (combinations) are under investigation but the exact place of this novel and exciting new class of compounds has to be determined.

1.4.2. SSA 5: Personalized medicine in breast cancer

Introduction
Breast cancer is the most common cancer among women in the Netherlands. About 1 in 8 women will develop invasive breast cancer during their lifetime. Although about 14,000 new cases of invasive breast cancer were diagnosed in 2012 and the incidence is slightly increasing, death rates are declining since 1989 probably because of screening and improved treatment.

Nearly all breast cancers are treated by surgery and adjuvant therapy. An adjuvant therapy might consist of radiotherapy, chemotherapy, hormone therapy or a targeted therapy. The adjuvant therapy is given to kill tumor cells that have spread from the primary breast tumor. Chemotherapy or hormone therapy may also be given before surgery as a neo-adjuvant therapy with the aim to shrink the tumor to facilitate surgery. Recently, a lot of effort is put in the development of targeted therapies because they are potentially more effective while showing less side effects. Such targeted therapies however require a genetic and/or molecular characterization of the tumor. Sequencing analysis of metastatic breast cancers revealed that 25% of the tumors have a mutation in the estrogen receptor, keeping the receptor active even in the absence of estrogen. Other cancers revealed mutations in other growth promoting receptors offering targets for therapy.

A relatively new targeted therapy for breast cancer is concentrating on a weakness of cancer cells that lost the activity of both copies of BRCA1/2 and thus a DNA repair mechanism. These cells are therefore dependent on another repair mechanism to survive. By blocking this repair mechanism by PARP inhibitors the cancer cells are forced to die. This concept is an example of synthetic lethality.

Objectives
- You can explain how hereditary and non-hereditary breast cancers may originate and develop.
- You can explain the working mechanism of PARP inhibitors.
- You can explain what is meant by synthetic lethality.
- You can explain why targeted therapies can be successful in treating breast tumors and why they may (eventually) fail.
**Instruction**

Study:
- Alberts, pages 295-311 and 558-559.
- Robbins and Cotran, pages 302-303 (genomic instability – enabler of malignancy) and 1073-1079 (until Classification of breast carcinoma).

**Questions**
1. Describe possible signaling pathways involved in breast cancer and explain what is meant by triple-negative breast tumors.
2. Explain why not every carrier of a BRCA1/2 mutation will develop a breast or ovarian cancer.
3. Describe the roles of BRCA1/2 and PARP in DNA damage repair.
4. Draw a replication fork and the result of PARP inhibition on DNA synthesis.
5. Explain how PARP inhibition will lead to tumor cell death in patients with BRAC1/2 mutation-associated breast and ovarian cancer.
6. Explain what is meant by synthetic lethality.
7. Explain why not every type of breast cancer can be successfully treated with a PARP inhibitor.
8. Explain why a combined therapy of a PI3K inhibitor with a PARP inhibitor can be effective in treating breast cancer.
9. Unfortunately, tumors may become resistant to treatment with PARP inhibitors. Describe and explain the molecular routes that may lead to resistance.

**Product**
The answers to these questions. In workgroup 4 we will discuss these subjects and new questions.

**1.4.5 SSA 6: Presentations on papers related to Onco 1-3**

In workgroup 5, students will give short presentations on selected papers related to Onco 1-3. Further instructions and the selected papers will be given on Blackboard.
1.5 Onco 4: Renal Cell Carcinoma

1.5.1.

Title: LC 7: Ups and downs in targeted therapy based on inhibition of angiogenesis

Lecturers: Prof. dr. P ten Dijke

Tumor type: Renal Cell Carcinoma

Mutation/mechanism: VEGF

Target: VEGF, ALK1, endoglin

Literature/ Background


Bhatt RS, Atkins MB. Molecular Pathways: Can Activin-like Kinase Pathway Inhibition Enhance the Limited Efficacy of VEGF Inhibitors? Clin Cancer Res. 2014 May 7

Four decades after Judah Folkman's postulate that angiogenesis could be a therapeutic target in cancer, anti-angiogenic treatment has now evolved into a widely used, clinically approved strategy for the treatment of patients with advanced colorectal, breast, ovarian, renal, non–small cell lung cancer and glioblastoma. The identification of vascular endothelial growth factor (VEGF) as a key effector of endothelial cell growth and tumor vessel formation has transformed the VEGF receptor (VEGFR) signaling pathway to an appealing therapeutic target in preclinical experiments and clinical trials. However, despite initial encouraging signs from preclinical studies that sustainable benefit might be expected in cancer patients by targeting VEGF signaling, recent preclinical reports raised concerns regarding evasive adaptation. Moreover, the use of bevacizumab in adjuvant chemotherapeutic regimens has led to less promising results than expected. Despite our poor understanding of how bevacizumab acts in micrometastatic disease, numerous clinical trials (involving >20,000 cancer patients) are ongoing or are planned to test the therapeutic benefit in the adjuvant setting. Simultaneously targeting multiple steps involved in tumor angiogenesis is a potential means of overcoming resistance to VEGF therapy. Activin like kinase 1 (ALK1) and endoglin (ENG) stimulate angiogenesis different from VEGF. While VEGF is important for vessel initiation, ALK1 and endoglin are involved in vessel network formation. Thus, ALK1 and endoglin pathway inhibitors are attractive partners for VEGF-based combination anti-angiogenic therapy. Genetic evidence supports a role for this receptor family and its ligands, bone morphogenetic proteins (BMP) 9 and 10, in vascular development. Patients with genetic alterations in ALK1 or endoglin develop hereditary hemorrhagic telangiectasia, a disorder characterized by abnormal vessel development. There are several inhibitors of the ALK1 pathway advancing in clinical development for treatment of various tumor types including renal, and
ovarian carcinomas. Targeting of alternate angiogenic pathways, particularly in combination with VEGF pathway blockade, holds the promise of optimally inhibiting angiogenic driven tumor progression.

1.5.2 SSA 7: Tumor angiogenesis

Introduction
Tumor associated blood vessels play a key role for tumors to grow beyond a few millimeters in size, when diffusion of O₂ and nutrients and removal of waste products becomes limited for further rapid growth. Moreover, tumor vessels are also needed for the spread of cancer cells to distant organs, a process termed metastasis.

The extensive vascularization of tumor tissue was found to be correlated with more aggressive behavior. On the other hand, the existence of extensive necrosis in highly proliferative tumors, most likely caused by the lack of sufficient angiogenesis to keep the pace of the tumor growth, was found to be a negative prognostic factor. During embryonic development the overall architecture of major blood vessels is predominantly related to the shape and size of a developing organ, while the organization of capillary networks and midsize blood vessels is more dependent on local signaling based on actual needs from the tissue. Neovascularization is principally limited to female reproductive organs and wound healing in adults in healthy situations. Otherwise, adult neovascularization occurs as a result of a pathologic situation, such as cancer or inflammation. Identification of key stimulatory and inhibitory factors in angiogenesis has led to the concept of inhibiting tumor growth by restraining angiogenesis by selective targeting on these regulatory elements. In a way, by starving the tumor cells to death by angiogenesis inhibition. Despite the fact that preclinical and clinical studies have shown that inhibition of the vascular endothelial growth factor (VEGF) pathway impedes tumor growth, other observations indicated that these therapies may have limited efficacy, or even promote the invasive characteristics of tumor cells. Although these agents typically produce inhibition of primary tumor growth, lasting responses are rare, with only a moderate increase in progression-free survival and little benefit in overall survival indicating that other (combinatorial) approaches should be considered for better clinical use.

Objectives
- You can explain the role of different angiogenic factors (VEGF, hypoxia, nutrition state) in blood vessel formation, including endothelial cell proliferation, migration and sprout formation.
- You understand the role of other stromal components in angiogenesis, such as pericytes, macrophages cancer associated fibroblasts
- You can explain how alternative pathways can lead to resistance to anti-angiogenic treatment.
- You can propose novel approaches to overcome these limitations in anti-angiogenic treatment

Instruction
Study:

- Alberts: 1220-1222
- Kumar pgs. 99-102 and pgs. 297-298
**Questions**

1. How do tumor cells overcome the limited capillary diffusion of nutrients and oxygen in order to form a large tumor?

2. In this figure (Fig 13.27 adapted from Weinberg) different metabolic parameters were measured in tumor cells with an increasing distance between capillaries. Explain what sort of metabolic processes are activated to generate energy (meaning ATP) in tumor cells located approximately 90 um between two capillaries.

3. Explain principal differences of endothelial cell features occurring in low and high grade malignant tumors.

4. Explain the mechanisms of angiogenic switch and relate the occurrence of this phenomenon during tumor progression

5. Clinical trials using VEGFR inhibitors showed regression of tumor size in multiple model experiments and in clinical settings. However, the long-term effects of these treatment were not that promising due to quickly appearing resistance. Generate a concept sheet or scheme that maps the possible pathways leading to resistance.

6. Based on this concept sheet, design possible treatment combinations that may overcome or slow down resistance.

**Product**

The answers to these questions. In workgroup 6 we will discuss these subjects and new questions.
1.6 Onco5: Melanoma

1.6.1. 

| Title: | LC8 Targeted therapy in metastatic skin melanoma |
| Lecturers: | Dr Kapiteijn, dr van Doorn |
| Tumor type: | Melanoma (onco5) |
| Mutation: | BRAF, NRAS and KIT |
| Target: | BRAF, NRAS and KIT |
| Literature/ Background | Flaherty KT, Hodi FS and Fisher DE |
| | Ryan J. Sullivan, Keith T. Flaherty. Resistance to BRAF-targeted therapy in melanoma |
| | European Journal of Cancer (2013) 49, 1297– 1304 |

Patients with metastatic skin melanoma have a median survival of 6 to 10 months. Few patients have a response to the classic systemic chemotherapy with dacarbazine and the majority of responses are only partial. Melanomas are composed of several biologically distinct categories of neoplasms that differ in their clinical and histologic presentations, cell of origin, age of onset, ethnic variation, pathogenetic role of ultraviolet radiation, predisposing germline alterations, type of genomic instability, pattern of metastasis, and patterns of somatic mutation. The latter contain a set of recurrent gain-of-function mutations in the genes NRAS, BRAF and KIT, that tend to occur in a mutually exclusive pattern early during progression.

Pharmacologic inhibition of the mitogen-activated protein kinase (MAPK) pathway has proved to be a major advance in the treatment of metastatic melanoma. Approximately 50% of melanomas have a V600 BRAF mutation that activates the MAPK pathway. The use of vemurafenib, an agent that blocks MAPK signaling in patients with melanoma and the BRAF V600 mutation, has been associated with prolonged progression-free survival and overall survival in randomized phase III trials involving patients with previously untreated melanoma.

Despite these advances, the majority of patients who are treated with BRAF inhibitors have disease progression within 6 to 12 months after the initiation of treatment. Several mechanisms mediating resistance to BRAF inhibitors through MAPK reactivation have been described, including the up-regulation of bypass pathways mediated by cancer Osaka thyroid kinase (COT), development of de novo NRAS or MEK mutations, and dimerization or variant splicing of mutant BRAF V600. In addition, MAPK-independent signaling through receptor tyrosine kinases, such as platelet derived growth factor receptor β, insulin-like growth factor 1 receptor, and hepatocyte growth factor receptor, has been associated with acquired resistance. Combination treatment with BRAF and MEK-inhibitors may be a good option to overcome acquired or de novo resistance to BRAF inhibition.

Inhibitors of MAP/ERK kinase (MEK) have already shown clinical benefit alone and in combination with vemurafenib in BRAF-mutant tumors. MEK inhibitors alone are also effective in patients with BRAF wild-type, NRAS-mutant melanoma, which is associated with poor prognosis. Hodi et al. reported the final results of a multicenter phase II trial of imatinib in patients with advanced melanoma harboring mutations or amplification of the KIT proto-oncogene. KIT is a transmembrane receptor tyrosine kinase, normally expressed on melanocytes, that plays a critical role in melanocyte
migration, survival, proliferation, and differentiation. Mutations and amplification of KIT have been identified in melanomas arising from mucosal, acral or chronically sun-damaged surfaces, and they characterize a distinct genetic subset of disease.

In conclusion, the therapeutic options have increased for metastatic skin melanoma due to the fundamental discoveries of BRAF, NRAS and KIT activating mutations. BRAF-, MEK- and KIT-inhibitors are incorporated as therapeutic options already outside of studies but also still in trials. Further research will focus on the combination of targeted agents to overcome or postpone resistance. Developments in immunotherapeutical options will hopefully further increase the prognosis of metastasized skin melanoma patients.

1.6.2 SSA 8 Cutaneous melanoma

Introduction
Cutaneous melanoma is considered one of the most aggressive malignancies and advanced stages are generally resistant to chemotherapy and radiotherapy. Most commonly, melanomas arise from epidermal melanocytes of the skin and can be quite easily recognized on basis of morphological features which can be supported by histology. Therefore, patients with early stage melanoma can be treated with surgical resection. Patients with distant metastasis, however, have a poor prognosis with less than 10% of patients alive after 5 years. Because the incidence of melanoma in the Netherlands is still increasing (see figure below) there is an urgent need for treatment protocols. Since the underlying molecular aberrations in tumor cells became clear new treatment strategies have been developed some of which proved very successful, although for a limited period of time.

Incidence of new patients with an invasive melanoma in the Netherlands (oncoline).

In 60 – 70% of melanomas activating mutations in BRAF are found and in 10 – 15% of melanomas activating mutations in NRAS. Other melanomas revealed activating mutations in cKIT or loss of PTEN. It is based on these mutations that targeted therapies have been developed. A remarkable observation was that nevi have the same activating mutations in NRAS or BRAF as found in melanomas. Nevi, however, very rarely become malignant because of oncogene-induced senescence. This means that additional changes must accumulate for tumor progression.

Objectives
- You can describe the clinical features of melanomas.
- You can explain how nevi may develop into aggressive melanomas.
- You can describe the pathways that lead to cell senescence (in general).
- You can explain why and how induction of senescence may function as a tumor suppressor mechanism.
- You can give examples of anti-cancer drugs interfering with melanoma growth and explain their molecular mechanisms.
- You can explain the mechanisms by which melanomas become resistant to treatment with specific BRAF inhibitors in order to propose additional treatment strategies.

**Instruction (selection)**

**Study:**
- Robbins and Cotran, pages 1169-1175.

**Questions**

1. Explain how a clinician can morphologically distinguish a melanocytic nevus from a melanoma.
2. Describe two pathways and the function of each protein in these pathways that regulate cell survival and proliferation in melanomas. (This refers to Fig 25-9, pp1174 in Robbins.)
3. A clinician decides to treat a melanoma containing the BRAFV600E mutation with a small molecule drug targeting the KIT receptor and thereby the MAPK pathway. What do you expect to be the outcome of this treatment?
4. A striking observation was that BRAFV600E mutations are also present in nevi. Still nevi show a very low proliferative activity.
   a. Explain why a BRAFV600E mutation does not lead to uncontrolled cell growth.
   b. Considering the multi-step cancer model, explain what other mutations may be needed to develop a melanoma.
5. Some melanomas show a loss of p14/ARF. Explain how this loss contributes to oncogenesis.
6. Describe how you would distinguish senescence from proliferative cells in a melanoma tissue.
7. Standard chemotherapeutic agents can induce senescence and thereby preventing tumor progression. Explain why melanomas do not respond to such treatments.
8. Tumor cell dormancy is a well-known phenomenon in melanoma and other tumors. Some part of the signaling pathways involved in cancer dormancy is understood. Propose signaling pathways that might be involved in the switch between proliferation and dormancy. Explain your reasoning.

**Product**

The answers to these questions. In **workgroup 8** we will discuss these subjects and new questions.
Colorectal cancer (CRC) is mainly a disease of the elderly with half of the patients being over 70 years of age. In the Netherlands, partly due to an ageing population, the incidence increased to currently 14,000 new CRC cases every year. Until now almost half of the newly diagnosed CRC patients die of this disease. The more advanced the stage of the disease at time of operation, the higher the chance of death. Not so long ago the treatment of advanced colorectal cancer (CRC) was not extremely complicated nor expensive. Patients with metastasized CRC to liver, lung or peritoneal were only considered to be eligible for palliative treatments. This landscape has changed dramatically in the last ten years.

Genetic screening for high risk patients has been implemented in order to have them enrolled in very effective pre-symptomatic surveillance programs. Advanced genetic high throughput DNA/RNA technology enables the identification of genetic variants that associate with an increased CRC risk.

Population wide screening for CRC has just started in the Netherlands for individuals at the age > 55 starting with a faecal occult blood test. Anyone positive for this test is eligible for endoscopic screening in search of precursor polyps (adenomas) or early carcinomas. It is expected that mortality due to CRC with decrease by 25%.

Introduction of novel endoscopic equipment and image guided surgical techniques enable better recognition of precursor lesions during surveillance and small metastases during operations of CRC with a curative intent. Endoscopic surgical removal of large colon sections and superficial located mucosal lesions is feasible with reduction of morbidity or mortality in patients of advanced ages.

Novel more effective chemotherapy regimens were introduced in neo-adjuvant (preoperative) or adjuvant (postoperative) settings. Furthermore in rectal cancer the use of preoperative radiotherapy has
become standard practice. Removal of liver and/or lung metastases is common practice as well as the use of lung and liver perfusion in patients not eligible for surgical removal. “HIPEC” treatment for intra-peritoneal metastasis can prolong life. Precision treatment of CRC using targeted small molecule drugs or monoclonal antibodies has become standard practice. Testing of genetic biomarkers can predict response of the latter drugs.

1.7.2. SSA 9 Rational basis of combination treatment and biomarker tests in common cancers

Introduction
Large efforts have been made to identify frequently recurrent genetic alterations in commonly deregulated pathways that can be used in targeted treatment for common cancer types, such as breast and colorectal carcinoma (CRC). The epidermal growth factor receptor (EGFR) is expressed in about 80% of colorectal cancers. This observation makes EGFR one of the most promising targeted therapy in colorectal cancer treatment as EGFR signaling pathways are involved in cell differentiation, proliferation and angiogenesis. For example, humanized anti-EGFR antibody based therapy might be an appealing choice in CRC. However, approximately 30% to 50% of colorectal tumors are known to have a mutated KRAS gene inferring resistance to this treatment. On the other hand, still about 50% of patients with colorectal cancer might respond to anti-EGFR therapy. Clinical observations, however, showed that 40% to 60% of patients with wild-type KRAS tumors do not respond to such therapy indicating that further stratification for this particular patient group is necessary. Mutation of the BRAF gene is present in about up to 10% or CRC patients.

BRAF is a protein kinase downstream of RAS in the RAS/RAF/MEK/ERK pathway and has been observed in other tumor types such as melanoma, thyroid and lung cancer. The presence of BRAF mutation confers adverse effect on survival of patients treated with anti-EGFR therapy. The predominant mutation of BRAF in CRC is identical to what is seen in melanoma, the classic V600E mutation. Targeted therapy using Vemurafenib, specifically inhibiting BRAF$^{V600E}$ mutant is highly effective in the treatment of melanoma. However, CRC patients with the same mutation showed only a very limited response to this drug and were found to have worse prognosis. Improving our understanding on the cross-talks between different parts of the EGFR-RAS-RAF-MEK-ERK pathways is necessary for the selection of the best treatment modality for CRC patients.

Objectives
- You will be able to link different aspects of signaling pathways in CRC with treatment options
- You can explain how oncogenic mutations can lead to treatment resistance in CRC
- You can understand the importance of biomarker selection in view of designing targeted therapy and identifying predictive markers in order to successfully treat cancer

Instruction
Study:

- Alberts: 1250-1256
- Kumar: 308-309, 323-327, 822-825

**Questions**

1. Why is molecular stratification of cancer subtypes and not only accurate histological diagnosis essential for targeted therapy?
2. Explain how an identical BRAF^{V600E} mutation in melanoma and colorectal carcinoma results in a strikingly different response to a BRAF inhibitor.
3. EGFR is a receptor tyrosine kinase. Based on this knowledge what sort of strategies could you use to target EGFR? Explain.
4. Mutation of the RAS proto-oncogene drives cells into senescence. In view of a multistep carcinogenesis model describe the role of this mutation and explain what additional steps are necessary to transform this as an activating mutation.
5. BRAF-mutant CRC is associated with hypermethylation of CpG islands and minimal chromosomal instability, which is molecularly distinct from the traditional model of adenoma–carcinoma progression. Based on this information, propose a possible treatment option. Explain your choice.
6. Some CRC cell lines with BRAF^{V600E} show low level of EGFR expression. What sort of reaction would you expect by treating these cells with PLX4032, an inhibitor of BRAF^{V600E}? Explain.
7. Conversely, melanoma cell lines with a BRAF^{V600E} mutation express EGFR at high level. What sort of reaction would you expect upon treatment of these cells with PLX4032? Explain.

**Product**

The answers to these questions. In **workgroup 9** we will discuss these subjects and new questions.

**1.7.3 SSA 10 Presentations on papers related to Onco4-6**

In **workgroup 10**, students will give short presentations on selected papers related to Onco4-6. Further instructions and the selected papers will be given on Blackboard.
1.8 Prevention and screening

1.8.1. Lecture and PD

Title: LC10: Bowel cancer screening in the Netherlands
Lecturer: Dr. Langers (MDL)
Literature/ Background: NA

In the Netherlands, there is a national program for bowel cancer screening since February 2014. All men and women between 55 and 75 years of age are invited to participate in this screening. Eligible participants are invited by mail; they receive information about the bowel cancer screening and an iFOBT test (immunohistochemical occult blood test), which can be sent back by mail. When the iFOBT test yields a positive result, the participant is referred to a local certified endoscopy centre for colonoscopy. Of these iFOBT-test positive individuals, 8-10% will have colorectal cancer. Those participants are asymptomatic and in most patients cancer will be discovered at an early stage and lead to a better survival than in symptomatic patients. A substantial number of iFOBT-test positive individuals will have advanced adenomas; those are polyps that are at high risk of advancing to colorectal cancer in the coming years. These polyps will be removed by colonoscopy. Therefore, this colorectal cancer screening program will not only lead to a better survival of colorectal cancer patients due to a shift to the earlier stages of the disease, but will also prevent colorectal cancer in those individuals who undergo polypectomy before cancer can develop.

1.8.2. SSA 11: Prevention, Screening & Cancer Therapy

Introduction
There is increasing interest and evidence that cancer can (partly) be prevented by avoiding contacts with known carcinogens, changing lifestyle and diet. Additionally screening for tumors may lead to cures at an early stage of (noninvasive) cancer before a life-threatening situation is established. Cancer prevention includes efforts to forestall the process that leads to cancer, along with the detection and treatment of precancerous conditions at their earliest, most treatable stages, and the prevention of new, or second primary, cancers in survivors. Cancer screening identifies either pre-cancers or early cancers that are still highly amenable to treatment while the number of malignant cells is very small.

Learning objectives
– You can describe the basic principles of cancer prevention.
– You can describe the basic principles of screening in order to discuss the pros and cons of screening
– You are aware of the current cancer screenings program in the Netherlands
– You have obtained knowledge which screening methods are used for which age groups and which tumor types
– You can present pro and con arguments on the (public) debate on cancer screening programmes
Instruction
Study:
- Search the internet for information regarding the public opinion on Dutch screening programmes

Questions
2. What would be the most effective measure to decrease the total cancer burden in Western countries?
3. Mention all cancer screening programs offered by the government in the Netherlands. What are the methods, at which ages are people tested and what is the sensitivity and selectivity of these tests?
4. Family health history and personal health history can place a person at increased risk for colorectal cancer. How are high-risk candidates identified for molecular genetic test a) using MSI for hereditary non-polyposis colorectal cancer (HNPCC) / LYNCH syndrome and how for b) FAP?
5. How are adults at increased risk for colorectal cancer screened?

Clinical case
-For general information of diagnosis and treatment of specific cancers it may be useful to consult [www.oncoline.nl](http://www.oncoline.nl) (language can toggle between Dutch and English).
-You can also use Rang & Dale Ch. 55: Anticancer drugs.

A 57-year old man had a positive iFOBT. He fears that he has colorectal cancer, especially since his sister has had colorectal cancer. He feels otherwise well and has no complaints.
Past Medical History: No previous operations. Social History: married and has 2 daughters. The eldest is 26 and the youngest is 24. Intoxications: smoking 20 pack/year, alcohol occasionally. Length 1.77, weight 98 kg.

1. What additional questions would you ask this men to see if he has other risk factors for colorectal cancer cancer?
2. Which risk factors does our patient have?

Colonoscopy revealed a tumor of the colon. Histopathology showed an invasive colorectal carcinoma.

3. Should he undergo future research into the genetics underlying the disease with one first degree family member with colorectal cancer?
3. Explain the characteristics of curative, palliative therapy and give an example of each treatment.
4. Explain the characteristics of neoadjuvant and adjuvant therapy and give an example of each treatment.
He got a curative therapy consisting of a hemicolecotomy. Histopathology revealed a T2N0M0 disease. No adjuvant therapy was needed.

5 What can he do to maximally prevent a second tumor

Unfortunately after 3 years he had complains about constipation and laboratory analysis showed an elevated liver function and CEA. A CT scan was performed which showed the suspicion of a recurrent colon carcinoma with multiple liver metastases.

6 Can we still cure the patient?
7 Which therapeutic options do you consider in the first line?
8 Which genetic test should be considered for second or third line therapy?

Two years later there is progression of disease after 2 lines of chemotherapy (capecitabine/oxaliplatin/bevacizumab and irinotecan. The tumor has a k-RAS mutation. He has a relative good condition and a strong therapy wish.

8 Which further treatment can you offer?
9 What is the endpoint of a phase I trial?
10 Which antitumor effect might be expected from a phase I trial? Explain.

Product

The answers to these questions and the case. In workgroup 11 we will discuss these subjects and new questions.

1.8.3.

Title: LC11 Drug discovery

Lecturer: Prof. B vd Water (LACDR)

Literature/ Background tba

1.8.4.

Title: LC12 Animals in drug research

Lecturer: tba

Literature/ Background tba

1.8.5. Oefententamen en vragnuurtje
1.9 The Practical: drug testing in cell cultures

**Introduction**

The aim of this practical is to get acquainted with the basic principles of drug testing in cell cultures. The basis of such a test is mammalian cell culture: the counting and seeding of cells. You will learn how to handle cells and prepare cells for drug treatment. Various cell lines will be used and different drugs will be applied. Furthermore, cell lines with resistant and sensitive phenotypes towards targeted therapy agents will be used. Cell viability assay will be used as a read out to monitor treatment.

**Planning of the practical**

**Day 1**

Introduction to cell culture and to working in a laboratory. Learn how to use a pipette, work without contamination, and how to seed cells into culture dishes with different densities for usage on day 2.

**Day 2**

Various drug concentrations will be applied to plates.

**Day 3, Day 4**

Cell viability read out.

**Day 5**

Interpretation of data, calculation of IC50. Preparation of short report and presentation.

A detailed protocol will be provided prior to the practical.
Theme 2: Imaging in cancer

For more detailed information we refer to the Blackboard module of the half minor Imaging week 5,6,7.

2.1 Week 5: Oncology and nuclear medicine

Clinical coordinator: Drs. F. Smit (Radiology)
Scientific coordinator: Dr. F.W.B. van Leeuwen (Radiology)

In this week we will focus on the use of nuclear medicine techniques in the management of breast cancer patients. This will be followed by some examples that illustrate how similar imaging approaches can be applied for other cancers.

In the clinic, nuclear medicine traditionally is the discipline that provides an in-depth view based on the molecular fingerprint of a disease. Specific tumor biomarkers can be targeted using dedicated radiotracers; radiotracers can be detected in-depth with a sensitivity that is superior to any other modality. When radiotracers are tailored for a specific tumor-biomarker, molecular imaging approaches provide a personalized means for: disease staging, treatment and therapy monitoring in oncological patient groups. The nuclear medicine modalities available are complemented by other radiological modalities (or the other way around), making it of importance to place the available molecular technologies in context with anatomical and physiological (perfusion based) modalities like US, CT and MRI.

Learning objectives:
- Gain insight into imaging technologies available for management of breast cancer patients (literature study / self-study);
- Obtain an overview of available (nuclear) molecular imaging technologies;
- Define requirements for tracer development; requirements for clinical tracer application; GMP;
- Identify complementarity of anatomical, physiological and molecular imaging approaches;
- Evaluate the use of nuclear medicine technologies to guide (surgical) interventions.
- Case reading: Sentinel node, and PET image analysis (breast cancer, in part self-study).

Contact hours (~12 h):

Workgroup (Case discussion)
Lectures
Lectures with patient cases
Demonstration

Details:
Applications of nuclear medicine in oncology +week-SSA (Valdes)
PET in breast oncology (vd Hoeven)
Case reading PET in combination with other modalities (Smit)
Gamma camera technologies (Blokland and Pereira)
Tracer development (van Leeuwen/Schimmel)
Preclinical SPECT (Buckle)
Sentinel node Case reading (Valdes + Rietbergen)
Hybrid surgical guidance during SN biopsy (Van Leeuwen)
Demo surgical navigation technologies (Rietbergen)
Therapeutic applications nuclear medicine (Al Younis)
Musculoskeletal applications / oncology (Reijnierse)
Integration nuclear and radiological imaging (Smit/Lamb)

Self-study hours (~28h):
literature
Case preparation
Study exam 2

Evaluation:
Exam 2
Case discussion
Exam 3 (case discussion)
Opinion paper (role modalities in medical imaging)
2.2 Week 6: Pathology and microscopic imaging

**Clinical coordinator:** Prof. dr. J. Bovée (Pathology)

**Scientific coordinators:** Prof. dr. A. Koster and dr. R. Dirks (MCB)

**Other teachers involved:** Prof. dr. A.M. van den Maagdenberg, dr. G.M. Terwindt, Prof. dr. H.J. Tanke, Prof. H. Morreau, dr. K. Szuhai, Prof. J.A. Bruijn, dr. S. van Duinen, dr. L.A. McDonnell, dr. B. Balluf

The topic of this week is microscopic imaging, primarily electron- and light microscopy (EM and LM). In the context of “Imaging: from Molecule to Man” these techniques provide the highest resolution (spatial details) of cells and cellular constituents. Microscopic analysis is essential in diagnostic pathology, but also in research as it provides information on molecular regulatory mechanisms in healthy and diseased cells. Ultrastructural analysis by EM unravels molecular structures at the highest level and is key to the development of novel drugs. Light microscopy, in particular fluorescence microscopy, has become a widely used research tool in combination with labeling methods as fluorescence in situ hybridization (FISH) and green fluorescent protein (GFP). EM and LM deliver the molecular information that feeds “upstream” imaging techniques as preclinical molecular imaging of laboratory animals and targeted diagnostic imaging in man.

**Learning objectives:**
- Have an overview of microscopic technologies for the molecular evaluation of cells and tissue segments (EM, LM, FISH, MS-imaging)
- Know how to apply advanced light microscopy (SCLM) in animal models:

**Contact hours (19 h):**

Workgroup (Case discussion)

Lectures

Lectures with patient cases

Practicum

**Details:**
- The application of EM in the diagnosis of renal disease (J.A. Bruijn)
- EM of mitochondrial structures in case of congenital myopathies, metabolic disorders and congenital anaemia (van Duinen)
- Cryo EM preparation techniques and correlative LM-EM (Koning)
- Headache diseases and EM (Terwindt / van den Maagdenberg)
- LM and FISH (painting and translocation detection) (Tanke / Szuhai)
- Principles of immunohistochemistry and its application in the diagnosis of soft tissue tumours (Bovée)
- Advanced light microscopy (Dirks)
- Principle of MS-imaging (McDonnell)
- Current research examples of MS-Imaging (Balluf)

**Self-study hours (21 h):**
Literature
Case preparation
Study exam 2

**Evaluation:**
Exam 2
Case discussion
Exam 3 (case discussion)
Opinion paper (role modalities in medical imaging)
2.3 Week 7: Image guided surgery and in vivo optical imaging

**Clinical coordinator:** Dr. A. Vahrmeijer (Surgery)

**Scientific coordinator:** Prof. C. Löwik (Radiology)

**Other teachers involved:** Prof.dr. B. Lelieveldt, dr. G. van der Pluijm, dr. L. Mezzanotte, dr. C. Janse, dr. E. Kaijzel, dr. J. Hardwick, dr. F.W.B. van Leeuwen, Prof. dr. G.P.M. Luyten

In many cases of cancer, surgery is the only curative treatment. Hereby a surgeon mainly relies on visual and palpable feedback during surgery. Illumination of the diseased area, in real-time, via fluorescence has demonstrated potential to improve the visual feedback. Next to the availability of dedicated camera systems, this application relies heavily on the availability of dedicated fluorescence tracers.

Next to the use of fluorescence in a microscopic setting, in the preclinical area, whole body optical tracer imaging technologies are also rapidly emerging. Through these technologies fluorescence tracers and their potential for image guided surgery can be evaluated using a variety of preclinical cancer models. Next to fluorescence in the preclinical setting, bioluminescence imaging can be performed using genetically modified tumor cell lines and animal models. Such optical reporter systems can be used to enable researchers to non-invasively monitor molecular and cellular processes in small animals e.g. during chemotherapeutic response monitoring studies.

Within the LUMC the surgical demand for optical imaging technologies goes hand-in-hand with preclinical and chemical studies allowing us to translate new optical technologies “from molecule to man”.

**Learning objectives:**

- Assess clinical and preclinical demand and possibilities for optical technologies;
- Evaluate requirements and limitations of optical technologies in image guided surgery applications.
- Understand the role of genetic reporter systems for preclinical optical imaging (cell lines and animal models);

**Contact hours (~12 h):**

Lectures
Demonstration (fluorescence guided surgery on animal tissue specimen).

**Details:**
Interventional desires for optical guidance + self study assignment (Vahrmeijer)
Fundamental aspects of optical imaging (Löwik)
Image processing of multi-modal data (Lelieveldt)
The use of gene-reporter systems in therapy response monitoring (Pluijm)
Bioluminescence-basics (Mezzanotte)
Optical imaging during the development of treatment regimes for malaria (Janse)
Fluorescence endoscopy (Hardwick)
Fluorescence imaging during robotic surgery of the prostate (Van Leeuwen)
Fluorescence microscopy in ophthalmology (Luyten)
Fluorescence imaging during open surgery (Vahrmeijer)
Self-study hours (~28 h):
literature
Study exam 2

Evaluation:
Exam 2
Opinion paper (role modalities in medical imaging)

In this week we will also have a group discussion on choosing your subject for the trial proposal and making the teams (see 3.1.1).
Theme 3: From bench to bedside

3.1 Introduction to theme 3
The design and implementation of clinical trials to test new (combinations of) therapeutic agents in phase I/II studies and large multicenter phase III trials in patient populations is studied in this final part of our ½ minor. You will design and write a clinical trial proposal for one tumor condition tutored by specialists working in the field. To generate ideas and design a trial proposal is a complicated and multistep process with the involvement of a lot of people: a real team effort. Therefore you will work in a team and as a team. A guideline has been developed, based on the CCMO guideline [http://www.ccmo.nl/], to lead you and your team members through this multistep process. Each step has interactive lectures with discussions related to the various aspects of clinical trials, which will give you the input to make another step in the process. Based on literature studies, you will be able to identify weak and strong elements of novel treatment strategies. You will learn how to translate scientific research questions into a clinically relevant research trial. Guided by clinical and non-clinical tutors, you will have discussions amongst others on ethical considerations, statistical pitfalls and patient selection criteria. Milestones for delivering specific documents are given and discussions with and feedback from your tutor and peers are planned and will help you to write your clinical trial proposal.

3.1.1 The start: choose the subject of your trial proposal (wk 7).
In the previous weeks you have learned a lot about (signaling) pathways leading to 6 tumor conditions, their clinical implications and ways to detect and treat them by imaging techniques. In the first 4 weeks we have defined the 6 cancers that we will use to design a clinical trial and to write a trial-proposal. In a meeting in week 7 we will discuss which subject you would like to use for your trial proposal and make teams.

<table>
<thead>
<tr>
<th>Project number</th>
<th>Title/subject</th>
<th>tutors</th>
<th>target</th>
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<tbody>
<tr>
<td>Onco1</td>
<td>Sezary Syndrome</td>
<td>Dr. CP Tensen, Prof.dr. MH Vermeer</td>
<td>Methylation and deacetylation</td>
</tr>
<tr>
<td>Onco2</td>
<td>Giant Cell Tumor of Bone (GCTB)</td>
<td>Prof.dr. JVMG Bovee, dr. PDS Dijkstra, Prof.dr. H Gelderblom</td>
<td>RANKL</td>
</tr>
<tr>
<td>Onco3</td>
<td>Breast Cancer</td>
<td>Prof. dr. P Devilee, dr. JR Kroep</td>
<td>PARP, synthetic lethality</td>
</tr>
<tr>
<td>Onco4</td>
<td>Renal Cell Carcinoma</td>
<td>Prof.dr. P ten Dijke, Prof.dr. S. Osanto</td>
<td>VEGF</td>
</tr>
<tr>
<td>Onco5</td>
<td>Melanoma</td>
<td>Dr. Kapiteijn, dr. van Doorn</td>
<td>B-RAF/RAS</td>
</tr>
<tr>
<td>Onco6</td>
<td>Colorectal cancer</td>
<td>Prof. dr. Morreau, Prof. dr. Ir. JVM van der Hoeven</td>
<td>EGFR/k-RAS/B-RAF</td>
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</table>

45
Dr. Gelderblom, professor of experimental pharmacotherapy in oncology, will give a lecture on the different phases of drug development while using an example from clinical practice. He will also explain alternative drug development models and in what situations they can be used. After the lecture, you will be able to understand the different phases and options in drug development, the specific challenges and how to handle them.

3.1.3 SSA1: Principles of cancer treatment

Introduction
The treatment of a malignant tumor is based on the following principles. First, for patients treated with curative intent, the primary tumor is resected or treated with chemo-radiation to prevent local recurrence. Secondly, in case of relative high-risk disease, the killing of distant micro-metastases by means of (neo)adjuvant (chemo)therapy is performed. Another treatment principle is palliation, to decrease symptoms and possibly prolong survival in cases where cure is not possible.

There are many drugs available which are potentially able to kill tumor cells. Milestones in the systemic therapy of solid tumors are hormonal therapy, chemotherapy, monoclonal antibodies, and targeted therapy. There are major differences in targets, pharmacology, efficacy, and side effects between these drugs. Nowadays, oncologists strive for a more personalized therapy.

Despite advances in technology and understanding of biological systems, drug discovery is still a lengthy (about 10 years), expensive, difficult, process with low rate of new therapeutic discovery. Drug discovery is done by pharmaceutical companies, with research assistance from universities. The "final product" of drug discovery is a patent on the potential drug. The drug requires very expensive Phase I, II, and III clinical trials, and most of them fail. New trial formats are developed in order to bring potential new agent earlier in the clinic [Printz C, Cancer, 2013].

Objectives
– You can describe the basic principles of cancer treatment modalities.
– You can describe the available treatment options and discern possible improvements.
– You can categorize anti-cancer drugs on the basis of their mechanism of action; chemotherapy, hormonal therapy, targeted therapy (small molecules and monoclonal antibodies)
– You have understanding of the various trial phases.

Instruction
Study:
Questions

1. Explain the aim of staging tumors and discuss the most commonly used staging system.
2. Why is multidisciplinary therapy often used? Can systemic therapy alone cure patients?
3. What is the theoretical advantage of combination of systemic therapies and what pharmacological characteristics are important in the combination treatment?
4. Explain why an oncologist may decide to administer targeted therapy instead of chemotherapy.

Product

The answers to these questions. In workgroup 1 we will discuss these subjects and new questions. During the workgroup titles of recent LUMC trial proposals are presented and the trial type or phase will be discussed in order to familiarize you with the various trial options. You will discuss the trial phase that might be used for your tumor subject and discuss your project plan with team members, peers and workgroup tutor.
3.2. Step 1: Introduction (scientific background) & rationale

3.2.1. SSA1: step 1

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<th>subject</th>
<th>content</th>
<th>timeline</th>
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| 1    | Introduction (scientific background) & rationale | - The research protocol must contain an introductory section explaining why the research is to be carried out. The scientific background and social relevance of the project should be indicated with references.  

- The results of any pre-clinical studies with potential clinical significance and of any clinical trials or studies relevant to the proposed research should be summarized.

A minimum of:

- 5 papers on the scientific background of the target,  
- 5 papers on clinical background and trials;  
- 2 general papers on disease;  
- 2 papers on the imaging technique are required.  

- Convincing arguments should be given that, based on the studied literature, there is not sufficient knowledge available to explain the problem or for the need to test what is known. | - Perform literature search and discuss with tutor and peers [session 1, week 8]  
- Hand in step 1 to tutor [week 8]  
- Feedback tutor [session 2, week 9]  
- Final version [week 10] |

3.2.2 SSA 2: Literature search

Do literature search, select papers, discuss with tutor in session 1, write step 1.

3.2.3 Tutor session 1

In tutor session 1 you will present your selection of papers, discuss your selection and make final choice on the papers. Discuss your thoughts on the trial phase with tutor and decide on trial phase, intended objectives and aim.
Prepare a short presentation for workgroup 2 (max 2 slides) on concise background as well as the study design and intended objectives. There will be 5 minutes for presentation and 10 minutes for discussion for each project.

3.2.4 Tutor session 2

Hand in step 1; receive and discuss feedback; prepare final version.
### 3.3.1 SSA3: step 2

<table>
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<th>timeline</th>
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| 2    | 2a. determine objective(s) 2b. choose study design 2c. determine study endpoint(s) | - Determine the **objectives of the study**:  
  *they are the questions that the study is intended to answer and are based on the scientific rationale and/or hypothesis formulated. One can distinguish between the primary objective and secondary objectives:*  
  - The primary objective is the main question to be answered by the results of the study, which determines study design and sample size.  
  - Secondary objectives are additional questions to be addressed if possible.  
  - Determine the **study design** of the trial:  
    *Examples of intervention studies are: double-blind randomized placebo-controlled trial, cross-over trial; Examples of observational studies are: (nested) case-control study, cohort study), the duration and setting of the study.*  
    *A flow chart can be included to give an overview of the study design and the main procedures that subjects will undergo in the course of research.*  
  - Determine the **endpoint(s)** of the trial:  
    *Primary study parameter/endpoint:*  
    *describe the main study parameter/endpoint, for example number of events/relapse, response rate, toxicity, blood hormone levels, etcetera*  
    *Secondary study parameters/endpoints (if applicable)*  
    *describe the secondary study parameters/endpoints, for example number of adverse and serious adverse events, biomarkers etcetera*  
    *For primary or secondary endpoint: imaging has to be included.* | - Discussion with tutor and peers [week 8]  
- Prepare 2 slides for ppt and discuss in WG2 [week 8]  
- Info via LCs [week 8]  
- Hand in step 2 tutor [week 8]  
- Feedback [session 2, week 9]  
- Final version [week 10] |
3.3.2 WG2: Team presentation on steps 1 and 2.

In WG2 each project team will present Step 1 and Step 2 (max 2 slides) of their proposal.

3.3.3 LCs on selection of primary and secondary endpoints

<table>
<thead>
<tr>
<th>Title:</th>
<th>LC2: Serum proteomics for early cancer detection, prognosis and prediction</th>
</tr>
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<tbody>
<tr>
<td>Lecturer:</td>
<td>Dr. W. Mesker (Surgery)</td>
</tr>
<tr>
<td>Literature/ Background</td>
<td>na</td>
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</tbody>
</table>

Early diagnosis of cancer is of pivotal importance to reduce disease-related mortality. There is great need for non-invasive screening methods, yet current screening protocols have limited sensitivity and specificity. The use of serum biomarkers to discriminate cancer patients from healthy persons might be a tool to improve screening programs. Once specific discriminating biomarkers have been determined, these can be applied to support the choice for adjuvant therapy and monitoring the response of patients to treatment regimens.

Mass spectrometry based proteomics is widely applied as a technology for mapping and identifying peptides and proteins in body fluids. One commonly used approach in proteomics is peptide and protein biomarker profiling. Biomarkers can be used as indicator of disease, based on abnormal presence, absence or changes in genes, RNA, proteins or metabolites. The ideal biomarker is both highly specific and sensitive. For cancer screening and monitoring programs, the required measurements have to be reliable, robust, fast, and economical. The material containing the marker(s) should be easily obtainable and have a patient-friendly application. In this respect, body fluids such as serum are suitable sources of biomarkers.

The translation of the DNA code results in protein expression. In contrast to the genome, the proteome reflects a more dynamic state of the cell. During transformation of a normal cell into a neoplastic cell, distinct changes occur at the protein level, including altered expression, different protein posttranslational modifications, changes in specific activity and inappropriate localization, all of which may affect cellular function. By comparing the protein patterns, i.e., profiles, in serum from patients with cancer with those obtained from healthy individuals, proteins that are the most discriminating can be classified. The resulting protein fingerprint has the potential to identify a person with cancer.

Mass spectrometry (MS) has proven to be a powerful tool in obtaining such protein fingerprints due to its high sensitivity and specificity. In fact, proteomic research has benefitted enormously from developments in MS technology and has evolved into a new field that is referred to as MS-based proteomics. Whereas proteomics aims for the full identification and quantification of all expressed proteins, profiling strategies usually are applied on sub-sets of the proteome allowing possibilities for monitoring targeted therapy.
Geneesmiddelen tegen kanker zijn lang niet bij alle patiënten effectief. De aard van de tumor, maar ook de constitutie van de patiënt en Co-morbidity, spelen daarbij een belangrijke rol. Als een behandeling niet effectief is, moet een patiënt zo snel mogelijk aan de nadelige bijwerkingen van het medicament worden blootgesteld. Voor sommige behandelingen kan op grond van bepaalde bepalingen op het tumormateriaal van tevoren bepaald worden of een behandeling een goede kans heeft om aan te slaan. Bij een Gastro-Intestinale Stromacel Tumor (GIST), is er op het weefsel een zogenaamde c-kit mutatie aanwezig. De tyrosinekinaseremmer imaginair grijpt hierop aan. Patiënten die dit hebben, zullen vrijwel zeker op de ingestelde behandeling reageren. Soms hebben patiënten met een melanoom ook deze mutatie. Zij kunnen ook op imatinib reageren, als ze de mutatie niet hebben, is het niet zinvol het medicijn te geven, want het werkt niet. Als patiënten met een gemetastaseerd melanoom een BRAF-mutatie hebben, is de kans zeer groot dat ze meer dan een half jaar goed reageren op vemurafenib, als de mutatie afwezig is, heeft de behandeling geen zin. Soms is het wat minder uitgesproken, bijvoorbeeld bij patiënten met een gemetastaseerd colorectaal carcinoom. Als derde lijnsbehandeling wordt vaak de Epidermal Growth Factor Receptor remmer cetuximab of panatinumab gegeven. Deze behandeling is lang niet bij iedereen effectief en kan ook veel bijwerkingen geven. Patiënten die in het tumorweefsel een zogenaamde KRAS-mutatie hebben, zullen vrijwel zeker niet op de behandeling reageren. Patiënten met een zogenaamde wild-type KRAS hebben een kans op een tijdelijk gunstige reactie, maar ze kans is niet zo groot als bij infiniteit bij GIST.

Testen die een positief of negatief voorspellende waarde hebben bij behandelingen, heten compagnon diagnostics. Voor met name behandelingen die veel bijwerkingen hebben of voor heel dure medicijnen, zijn deze testen zeer gewenst, maar lang nog niet altijd beschikbaar. Als er geen voorspellende test beschikbaar is, is het belangrijk om snel te kunnen weten of een behandeling effectief is. Meestal wordt hierbij gebruik gemaakt van beeldvormende diagnostiek, maar het duurt meestal wel twee maanden voordat deze een uitspraak kan doen. In sommige gevallen kan gebruik gemaakt worden van een PET-scan, omdat deze ook informatie geeft over de metaboliet activiteit in een tumor. Deze verandert vaak sneller dan de grootte van een tumor. Tot nu toe wordt hier in de kliniek alleen bij de behandeling van lymfomen gebruik van gemaakt.

Title: LC3: Compagnon diagnostics en andere voorspellende testen
Lecturer: Prof. K. van der Hoeven (Oncology)

Literature/ Background

Testen hierbij de sneller niet een tumormateriaal beschikbaar scan, zeker lang geneesmiddelen mutatie aanwezig. Worden met lymfomen epidermal grootszijn diagnostics. Patiënten een mutatie hebben, zullen vrijwel zeker op de ingestelde behandeling reageren. Soms hebben patiënten met een melanoom ook deze mutatie. Zij kunnen ook op imatinib reageren, als de mutatie niet hebben, is het niet zinvol het medicijn te geven, want het werkt niet. Als patiënten met een gemetastaseerd melanoom een BRAF-mutatie hebben, is de kans zeer groot dat ze meer dan een half jaar goed reageren op vemurafenib, als de mutatie afwezig is, heeft de behandeling geen zin. Soms is het wat minder uitgesproken, bijvoorbeeld bij patiënten met een gemetastaseerd colorectaal carcinoom. Als derde lijnsbehandeling wordt vaak de Epidermal Growth Factor Receptor remmer cetuximab of panatinumab gegeven. Deze behandeling is lang niet bij iedereen effectief en kan ook veel bijwerkingen geven. Patiënten die in het tumorweefsel een zogenaamde KRAS-mutatie hebben, zullen vrijwel zeker niet op de behandeling reageren. Patiënten met een zogenaamde wild-type KRAS hebben een kans op een tijdelijk gunstige reactie, maar ze kans is niet zo groot als bij infiniteit bij GIST.

Testen die een positief of negatief voorspellende waarde hebben bij behandelingen, heten compagnon diagnostics. Voor met name behandelingen die veel bijwerkingen hebben of voor heel dure medicijnen, zijn deze testen zeer gewenst, maar lang nog niet altijd beschikbaar. Als er geen voorspellende test beschikbaar is, is het belangrijk om snel te kunnen weten of een behandeling effectief is. Meestal wordt hierbij gebruik gemaakt van beeldvormende diagnostiek, maar het duurt meestal wel twee maanden voordat deze een uitspraak kan doen. In sommige gevallen kan gebruik gemaakt worden van een PET-scan, omdat deze ook informatie geeft over de metaboliet activiteit in een tumor. Deze verandert vaak sneller dan de grootte van een tumor. Tot nu toe wordt hier in de kliniek alleen bij de behandeling van lymfomen gebruik van gemaakt.
Recent advances in sequencing technologies, Next Generation Sequencing (NGS), permits sequencing of whole genome at affordable prices, thus providing new opportunities in tumor stratification for targeted therapy. With NGS sequence information can be obtained from both from DNA and RNA, but detection of DNA methylation patterns is also feasible. The complexity of the resulting data obtained after sequencing of the whole genome can be significantly reduced by reading coding parts (exons) of the genome. Reading the transcribed RNA will enable detection of genes with mutations that are actually expressed in the tissue of interest. Sequencing of selected genes (targeted sequencing) relevant to cancer development, prognosis or selection of targeted therapy may further reduce the complexity of the data and thereby the analysis and interpretation of the results. The targeted sequencing approach, however, may preclude the detection of yet not identified sequence variants that could be responsible for resistance of treatment failure. Depending on the downstream use of the results, NGS results can be used as discovery tools, complementary diagnostic tool (companion diagnostics) or as a tool to identify predictive markers for clinical endpoints. This lecture will give an overview how different NGS approaches can be implemented in clinical and translational settings.

**Title:** LC5: Quality of life  
**Lecturer:** Dr. M. Fischer  
**Literature/ Background**

Interest in Quality of Life has increased exponentially over the last 50 years. The term Health related Quality of Life (HRQoL) has been coined to refer to the impact of disease and treatment on the lives of patients and those in their social network (e.g. partners, children). It acknowledges the fact that whereas clinical outcomes, such as survival, treatment response and side effects can be assessed objectively, the experience of the consequences of illness and treatment is different for every patient and must therefore be assessed subjectively. This lecture will discuss several issues regarding the definition and operationalization of the HrQoL construct. Several studies showing the importance of QoL for clinical practice will be reviewed and students will be introduced to commonly used general and disease-specific instruments to assess HRQoL within the field of oncology.

**Title:** LC6: Clinical Imaging in trials  
**Lecturer:** Dr. Vahrmeijer (Surgery)  
**Literature/ Background** TBA

### 3.3.4 Tutor session 2

Hand in step 2; receive and discuss feedback; write final version.
### 3.4 Step 3: Inclusion criteria & statistics

#### 3.4.1 SSA4 for step 3

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| 3    | 3a. statistics | Determine **Statistical analysis:**  
- The number of subjects required for the study should be justified.  
- The number of subjects should always be large enough to provide a reliable answer to questions addressed. Also the size of detectable differences should be of clinical relevance.  
- The number of subjects is usually determined by the primary objective of the trial. If the sample size is determined on some other basis, then this should be made clear and justified.  
- There are many formulas to calculate the size of the study population. It should be clear which method is used and the reasons why this method has been chosen.  
- Also, the calculation itself should be given with a predefined p-value (usually 5%) and power.  
- The power of the study is the probability that the study will have a significant (positive) result – provided a positive effect exists. Ask advice from a statistician to help you with this matter. | - LC on statistics [week 9]  
- Discussion with tutor and peers [session 2, week 9]  
- Hand in step 3 tutor [week 9]  
- Feedback tutor [session 3, week 9]  
- Feedback statistician [RC, week 9]  
- Final version [week 10] |
|      | 3b. Inclusion and exclusion criteria | Determine **Inclusion and exclusion criteria:**  
- The research population should be clearly defined.  
- From what source population will the subjects be drawn?  
- What is the likelihood that the planned number of patients can be recruited from the defined source population?  
- If relevant, prevalence/incidence number should be given.  
- The characteristics of the study population should be given (age, sex, tumor type, ethnic background (if relevant), etcetera)  
- This section should also explain why the research is necessary |  |
needs to be conducted with the selected population. This is particularly important where minors or incapacitated adults are to be used as subjects.

3.4.2 LC on statistics in clinical trials

Title: LC7: Statistical aspects of clinical trials
Lecturer: Prof. Stijnen (medical statistics)
Literature/ Background TBA

Aan de orde komen (een keuze uit) de volgende onderwerpen: power and sample size, endpoints, data analyse, multiplicity, statistical analysis plan, interim analyses, missing values.

3.4.3 tutor session 2

In this meeting you will discuss the team’s ideas on statistical analysis with your tutor.

3.4.4 LCs on in- en exclusion criteria.

Title: LC8: In- and exclusion criteria
Lecturer: Dr. J. Kroep (Oncology)

Wrap up step 1 and 2 and introduction to step 3: Inclusion- & Exclusion- criteria

Investigators must include in their protocols a detailed description of the study population. The first priority is that the subject population has the attributes that will make it possible to accomplish the purpose of the research. Eligibility criteria are meant to capture patients that have potential to benefit and exclude patients that may be harmed, are not likely to benefit or for whom it is not likely that the outcome variable can be assessed.

The investigator must specify inclusion and exclusion criteria for participation in a study. **Inclusion criteria** are characteristics that the prospective subjects must have if they are to be included in the study. They identify the population in whom intervention is feasible and will
produce desired outcome. **Exclusion criteria** are those characteristics that disqualify prospective subjects from inclusion in the study. Excessive exclusions should be avoided in order to decrease recruitment, increased complexity and costs and decreased generalizability (external validity)

Inclusion and exclusion criteria may include factors such as age, gender, race, type and stage of disease, the subject’s previous treatment history, and the presence or absence (as in the case of the “healthy” or “control” subject) of other medical, psychosocial, or emotional conditions. Defining inclusion and exclusion criteria increases the likelihood of producing reliable and reproducible results, minimizes the likelihood of harm to the subjects, and guards against exploitation of vulnerable persons. However, trial participants often do not represent the patient population that clinicians see in their daily practice.

An example of inclusion criteria for a study of chemotherapy of breast cancer subjects might be postmenopausal women with metastatic breast cancer. An exclusion criterion for this study might be abnormal renal function tests, if the combination of study drugs includes one or more that is nephrotoxic. In this case it would be required to specify which tests of renal function are to be performed to evaluate renal function and the threshold values that would disqualify the prospective subject (e.g., creatinine clearance below the 50 cc/min).

Standard and specific in – and exclusion criteria will be presented and examples discussed.

**Title:** LC9: The elderly in oncology

**Lecturer:** Dr. G.J. Liefers (Surgery)

**Literature/ Background**

Met de toename van de vergrijzing zullen er de komende jaren meer ouderen met kanker voorkomen. Ouderen kenmerken zicht door een grote heterogeniteit in conditie, co-morbiditeit en voorkeur. Verder zijn ouderen structureel ondervertegenwoordigd in klinisch onderzoek. Hierdoor is er relatief ‘evidence’ voor de specifiek behandeling van deze groep patiënten. Een algemeen kenmerk van veroudering is een toename van de ‘competing risk of mortality’. Dit houdt in dat ondanks de aanwezigheid van bijvoorbeeld borstkanker, de prognose wordt bepaald door de co-morbiditeit en niet door de maligniteit. Hierdoor worden veel ouderen met kanker over behandeld. Het tegenovergesteld gebeurt ook. Uit bezorgdheid voor bijwerkingen wordt soms een behandeling niet gegeven ondanks een goede indicatie. In dit deel van de cursus gaan we in op de verschillen tussen jongeren en ouderen met betrekking op

- Stadium bij diagnose
- Behandeling
- Uitkomsten

Verder zullen we de beperkingen bespreken van de huidige richtlijnen voor de behandeling van kanker aan de hand van literatuur over de externe validiteit van bestaand onderzoek in de algemene ouderen populatie. De moeilijkheden en uitdagingen van het klinisch onderzoek bij ouderen één alternatieven voor de *randomized controlled trial* (RCT) worden behandeld.
The adolescent young adults (AYAs) are a specific population in cancer diagnosis and therapy. The outcome of treatment is often worse compared to children and adults for unknown reasons. The AYA population encounters specific challenges such as impact on education, work, independency, sex, fertility and self-esteem. After the lecture you will understand the characteristics and needs of this specific group cancer patients.

3.4.5 Tutor session 3

Hand in step 3; receive and discuss feedback; write final version

3.4.6. RC: final questions on statistical analysis

In this RC you can discuss your questions regarding the final version of step 3 of your trial proposal with a statistician.
3.5 Step 4: Treatment and toxicity

3.5.1 SSA5 for step 4

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| 4    | 4a. treatment: (non) investigational products | -Determine **Treatment of subjects:**

  The protocol must contain a detailed description of the procedures that subjects will undergo in the course of the research.

  *It should be clearly indicated which procedures are part of the medical treatment (non-investigational product) and which are extra for this study (investigational product) and whether diagnostic procedures or treatment will be postponed.*

  At least the following matters should be addressed (if applicable):

  - Dosage, timeline of administration etc.
  - Invasive procedures to be performed (injections, venapunction, liquor sampling, scopic examination, biopsy, catheterisation, radiation)
  - Psychological/psychiatric investigations to be performed
  - Questionnaires (e.g. Quality of Life)
  - Clinical tests to be performed (e.g. HIV, pregnancy)
  - Laboratory tests to be performed
  - etcetera

  Investigate known **toxicity and adverse effects** of used compound(s) and treatment via literature study (min. 5 references)

  When a clinical trial involves several study visits with various different procedures and tests at each visit, it might be helpful to develop a simple **Flowchart** to help ensure that all protocol required procedures are performed appropriately. It is usually helpful to list procedures in the order that they would be done during a real study visit. A flowchart that summarizes the expected actions of the investigator in time should be added | - info via LCs [week 9]
- Discussion with tutor and peers [session 3, week 9])
- Hand in step 3 tutor
- Feedback tutor and peers [session 4, week 10]
- Final version [week 10]
3.5.2 LCs on Good Clinical Research.

**Title:** LC11: The world behind clinical research

**Lecturer:** A. Elise van Leeuwen-Stok, PhD, managing director and study manager, Borstkanker Onderzoek Groep (BOOG), Amsterdam

**Literature/ Background**

Conducting clinical research and legislation on this subject in the last decade has become quite complex. Therefore, it is also time consuming and costly. All the more reason to make good trade-offs before a research project is launched and to monitor the progress and quality thereof.

At the end of this training you have:

- insight into the world behind clinical research and the importance of efficient coordination, for instance by research groups;
- insight into the process from a research idea to final study results;
- insight into the roles and responsibilities of you as a researcher and a study team;
- some knowledge of Good Clinical Practice (GCP)

More information on the trainer and the research group BOOG: www.boogstudycenter.nl

**Title:** LC12: Data safety and monitoring

**Lecturer:** J. Ouwerkerk, senior research nurse and trial coordinator

**Literature/ Background**

Data safety and monitoring are essential to run a safe and valid clinical trial. This to insure the safety of participants, the validity of data, and the appropriate termination of studies for which significant benefits or risks have been uncovered or when it appears that the trial cannot be concluded successfully. For toxicity scoring, NCI-CTC criteria are used, currently version 4.0. The extend and frequency of toxicity scoring should be defined in the protocol. Data managers fill in the information from the patient file in the case report form (CRF), that documents all data on each patient participating in a clinical trial including the adverse events. During the lecture, the NCI-CTC toxicity definition, grading and documentation will be discussed using patient cases. Moreover, the role of data monitoring committees, for the purpose of providing independent review of clinical trial data, and Data Safety Monitoring Boards (DSMB) will be discussed.
After research on new therapies or procedures in the laboratory, the most promising experimental treatments are moved into clinical trials. In these trials new ways will be studied to prevent, detect or treat disease or to improve a standard therapy.

But what do you have to do before you can include your first volunteer? It is more than sending 15 forms to the ethical committee (METC), but where to start in the labyrinth of clinical research. This lecture will tell you about the roadmap to organizing clinical research.

3.5.3 Tutor session 3.
Discuss treatment and toxicity with tutor.

3.5.4 Tutor session 4
Hand in step 4; Receive and discuss feedback; write final version.
### 3.6 Step 5: Ethics

#### 3.6.1 SSA6 on step 5

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<tr>
<td>5</td>
<td>5a. Ethics</td>
<td>-In this chapter it can be stated that the study will be conducted according to the principles of the Declaration of Helsinki (version, date, see for the most recent version: <a href="http://www.wma.net">www.wma.net</a>) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts. -In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardize the subjects’ health. The investigator will take care that all subjects are kept informed. -Give a description of the recruitment and informed consent procedures. How and by whom (investigator, supervising doctor, other person) will subjects be informed about the study and asked for their consent? How much time will they be given to consider their decision?</td>
<td>info and discussion via LCs and WG 3 [week 9]</td>
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<tr>
<td></td>
<td>5b. personal statement</td>
<td>-Write a Personal statement Geef een kort overzicht van de juiste wijze waarop een trial uitgevoerd zou moeten worden. Vervolgens vragen we je een kort persoonlijk statement te schrijven over de ethische zaken rondom een trial en bespreek jouw overwegingen (beargumenteerd) om al dan niet aan deze trial deel te nemen (max 1 A4).</td>
<td>Hand in step 5 in final version [week 10]</td>
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3.6.2 LCs on Trials and more..

**Title:** LC14: Funding voor klinisch wetenschappelijk onderzoek

**Lecturer:** Prof. K vd Hoeven (Oncology)

**Literature/ Background**

Voor zowel fundamenteel als voor klinisch wetenschappelijk onderzoek is in eerste instantie een goed protocol noodzakelijk. Voor klinisch wetenschappelijk onderzoek is toestemming van een medische ethische toetsingen commissie (METC) noodzakelijk. Voor beiden is daarnaast een goede financiering een vereiste. Voor klinisch wetenschappelijk onderzoek moet er financiering zijn voor alle kosten die er buiten de reguliere patientenzorg gemaakt worden. Dat is niet alleen de interventie die onderzocht wordt, maar ook de extra kosten voor laboratoriumonderzoek en beeldvormend onderzoek. Daarnaast moet het datamangement bekostigd worden en natuurlijk ook de personen die het onderzoek uitvoeren. Soms moet er ook geld betaald worden aan patiënten die in het onderzoek participeren. Als het om een registratieonderzoek voor een medicament gaat, worden. Kosten bijna altijd gedragen door de farmaceutische industrie die het geneesmiddel ontwikkeld heeft. In ander gevallen moet externe financiering gezocht worden. In Nederland zijn belangrijke bronnen voor de financiering van kankeronderzoek het KWF en ZONMw. Soms kunnen er ook Europese subsidies verkregen worden. Daarnaast zijn er particuliere instellingen die onderzoek in materiële zin ondersteunen. In dit deel van de minor zal voor klinisch wetenschappelijk een adequate financiële ondersteuning worden opgesteld.

**Title:** LC 15: Pharmaceutical companies

**Lecturer:** TBA

**Literature/ Background**

3.6.3 Workgroup 3: Ethics.

**Title:** Ethics of clinical research

**Lecturer:** Dr. D. Touwen

**Literature/ Background**

Medicine needs research, because without research we wouldn’t know what works. But clinical research has its own agenda and its own costs: what is good for research purposes may not be beneficial to the patient. Not all clinical research is therapeutic (i.e. with a reasonable expectation for the patient-
participant to possibly benefit from the treatment), and even if it is, methodological requirements may dictate what happens, instead of the needs of the patient/participant. For example, in a placebo controlled trial there is a group of participants that may be undertreated (since they receive placebo). Since research purposes and patients’ interests may vie for precedence in clinical trials, clinical research is ethically complicated, however necessary and ultimately beneficial to medicine and thus potentially beneficial to patient care. This is why informed consent of the participant is absolutely essential, but at the same time not considered to be strong enough to safeguard patients’ interests. Researchers have an important responsibility to weigh pros and cons, risks and benefits, before they even start to ask participants’ consent. Also every clinical trial must be assessed ethically by an ethical review board, a group of knowledgeable, experienced peers who assess whether or not the research question is scientifically sound and sufficiently relevant, the methodology correct and whether the risks and benefits for the participant are on balance.

In oncology the question of clinical research is further complicated by several facts. 1. The studied drugs are highly toxic and can therefore not be administered to healthy volunteers. 2. The effectiveness of a trial drug can only be studied in patients who already have cancer that is not effectively treated by known drugs and thus are very sick. 3. These cancer patients are often desperate and therefore willing to go to great lengths to at least have some hope of a cure. This may mean that they consent to participate in the trial with a therapeutic misconception – the wrong idea that there is a hope they will be cured.

In this lecture we will explore these themes in some depth, thus achieving a greater awareness of the responsibility of the physician/clinical researcher.

3.6.4. SSA7: write personal statement

3.6.5 Tutor session 4

Discuss final questions on step 5. Write final version.
### 3.7 Step 6: Final product

#### 3.7.1 SSA8 on step 6

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| 6    | Final proposal including a synopsis | - Write a **synopsis:**  
the synopsis should give a clear description of the central question that the research is intended to answer and its justification.  
It should specify the hypothesis (if applicable) and the research objectives.  
In addition the synopsis should briefly describe the design, population, methods and procedures of the study.  
Finally, the nature and extent of the burden and risks should be indicated.  
The synopsis should preferably not exceed one A4 sheet. | - Feedback tutor on final questions [session 4, week 10]  
- Final version including synopsis [week 10]  
- Presentation of trial proposal [week 10]  
- Peer review [week 10] |

#### 3.7.2 SSA9 peer review

#### 3.7.3 SSA10 prepare presentation
3.8. The patient in clinical trials

3.8.1 Bedside teaching

Half of the group (the students that also follow the grand round this morning) will join one of the oncologists on a patient visit in the clinic or in the out-patient clinic. With the patient the anamnesis about the disease and therapy and especially the study therapy will be discussed.

Location: C10p (Department of Clinical Oncology)
Organiser: Dr. J. Kroep

3.8.2 Grand round

Half of the group will follow the weekly grand round. First, all patients of the department of clinical oncology that are admitted in the department will be discussed in the conference room with the head of the department, oncologists, fellows, doctors in training, students and nurses. After the ‘paper’ visit we will visit these patients.