# New approaches and consequences for elderly cancer patients with focus on melanoma

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Chapter 1

# General introduction

## Background

Until recently treatment of cancer was mainly based organ of origin and histological characteristics. Over the last decade, cancer treatment has become more personalized in the sense that it is based increasingly on tumor characteristics. New insights in tumor biology and tumor genomics have led to specific treatments interacting with important pathways for well-defined tumors. This has resulted in a lot of attention drawn by "tumor-biologically personalized therapeutics" where – partly based on protein or DNA characteristics of a tumor – small molecules such as protein kinase inhibitors and monoclonal antibodies targeting specific proteins are administered. For example, since angiogenesis and the vascular endothelial growth factor (VEGF) pathway plays an important role in renal cell carcinoma, tyrosine kinase inhibitors against the VEGF receptor are standard treatment for this tumor. In case of metastatic melanoma, currently sequencing of the *BRAF* gene in tumor tissue is indispensable: presence of a BRAF V600 mutation is predictive for response on a BRAF inhibitor in this tumor type.

Those on cancer biology and cancer genomics established developments are responsible for improvements in cancer treatment in recent years. Focusing solely on tumor-biologically personalized therapeutics would ignore other relevant patient characteristics. For example, a rising number of elderly patients receive systemic treatments even though the impact in these patients is often unknown. Moreover, in general, approved anti-cancer drugs are proven effective in an overall patient population for which the drug prescription is allowed. Although within this patient population that as a whole benefits from a certain drug, an array of clinical benefit profiles exists: it might be highly effective and little toxic in one patient whilst it is highly toxic and not effective in another. To take the concept personalized medicine beyond only biologically or genetically personalized therapeutics we should try to identify patient subgroups and ultimately single patients for who we can predict that they shall benefit: the right drug for the right patient on the right moment.
This thesis aims to evaluate efficacy and toxicity of cancer treatment in several subgroups – such as the elderly – with focus on melanoma, renal cell carcinoma and GIST patients.

## Outline of the thesis

The prevalence of cancer increases in the course of a lifetime. Therefore, in clinical cancer practice elderly comprise a substantial share of the patient population. Unfortunately, elderly are often underrepresented in clinical cancer trials. This subgroup is biologically different from younger patients because the normal process of organ aging during life and relative high incidence of multimorbidity. In **chapter 2** we performed a literature search to analyze the evidence for efficacy and toxicity of current anti-tumor treatments for metastatic renal cell carcinoma in the elderly subgroup. In **chapter 3** we also evaluate evidence in the literature concerning the efficacy in the elderly subgroup among metastatic melanoma patients.

It is known that melanoma in elderly patients have a worse biological behavior compared to melanoma in their younger counterparts. The immune system plays an essential role in repression of melanoma and novel immune checkpoint inhibitors exploit this fact. In **chapter 4**, we describe a study in which we describe the peripheral lymphocyte phenotype of young and elderly subgroups within the metastatic melanoma patient population. From treatment-naive melanoma patients < 50 years of age and > 65 years of age we drew blood samples for immune-characterization. It was found that elderly melanoma patients have a remarkable unresponsive pallet of CD4+ T cells compared to age-matched healthy controls. Young melanoma patients however have CD4+ T cells that show prominent signs of activation, proliferation and differentiation.



The immune checkpoint inhibitor drug ipilimumab blocks cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) on lymphocytes and is an approved treatment for patients with metastatic melanoma. In patients, blockade of CTLA-4 leads to T cell activation and therefore enhances repression of melanoma leading to long-term disease control in ~20% of the treated patients. However, since there exists a difference in biological behavior in melanoma between young and elderly patients and immune-senescence is a natural process that occurs in elderly, we specifically investigate in **chapter 5** the efficacy and toxicity profile of ipilimumab in elderly metastatic melanoma patients. Patients that participated in the Dutch Named Patient Program for ipilimumab were included in a retrospective study. The analyses revealed that, despite the general perception of anti-tumor therapy in elderly, no reduced efficacy exists for ipilimumab in patients ≥ 65 years of age and the toxicity was not more severe either.

For a number of tumors, specific off-target effects of anti-cancer therapy are revealed to be predictive for treatment outcome. In case of imatinib, hypophosphatemia was positively correlated with response in chronic myelogenous leukemia (CML) patients. For patients with gastro-intestinal stromal tumors (GIST), imatinib is a protein kinase that inhibits cKIT and platelet derived growth factor receptor. Those receptors are often mutated or overexpressed in GIST tissue. A well-known off-target effect of imatinib is development of hypocalcaemia and hypophosphatemia. Given the findings with imatinib in CML we describe in **chapter 6** a study analyzing whether development of hypocalcaemia or hypophosphatemia are a predictive biomarker for imatinib efficacy in this subgroup of GIST patients. For this we retrospectively analyzed time to progression in patients treated with imatinib and correlated this with calcium and phosphate levels in the blood drawn at several time points after initiation of this therapy. The efficacy of imatinib was not linked to the development of hypocalcaemia and hypophosphatemia.

During the disease process, a frightening percentage of patients with metastatic melanoma face brain metastases. **Chapter 7** describes the outcomes of a feasibility study for prophylactic brain irradiation in metastatic melanoma patients. Patients were treated this pilot study in the setting of metastatic melanoma, which seemed feasible. However, prophylactic brain irradiation might only be meaningful in patients who live long enough to develop brain metastases and the optimal time-window in this era of many systemic treatment options for melanoma will be challenging. It further discusses alternative therapies

for melanoma brain metastases and assigns potential subgroups that might benefit from further investigation of prophylactic brain irradiation.
In **chapter 8**, several clinical observations are described that can serve as examples of true personalized medicine and may help guide clinicians that face a comparable clinical problem.

In the last chapters, a summary of the thesis is given in English (**chapter 9**) and Dutch (**chapter 10**).