Targeted therapy in oncology: mechanisms and toxicity

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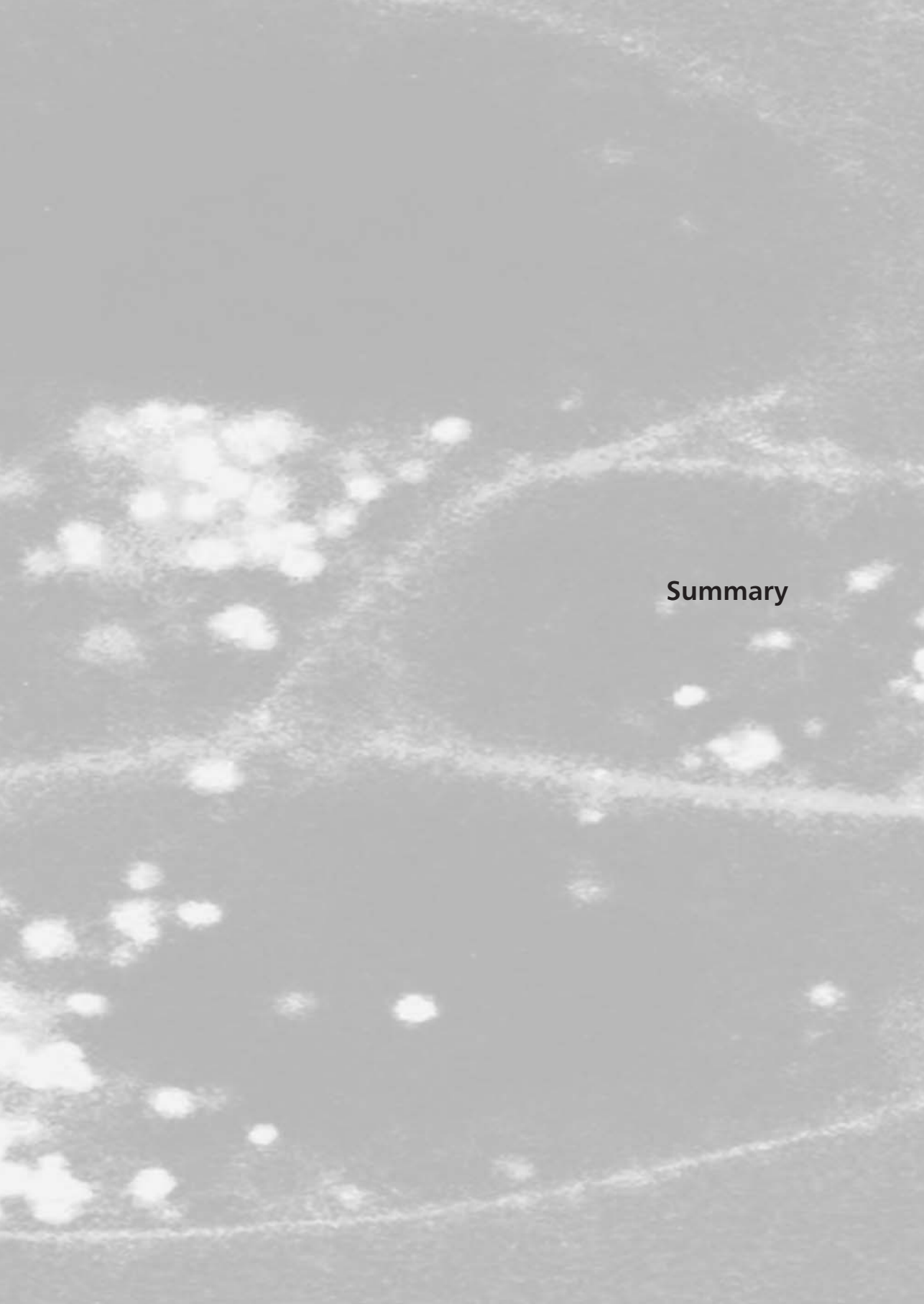

Summary

In this chapter the reported studies presented in this thesis are summarized.
This thesis focuses on targeted anti cancer agents in solid tumors. Pharmacokinetics, safety, pharmacodynamics, and pharmacogenetics of selected targeted therapies, alone or in combination with conventional chemotherapy, are studied. Moreover, new targeted treatment options for sarcomas are explored. **Chapter 1** gives a general introduction of this thesis.

In **Chapter 2**, a review of small molecule tyrosine kinase inhibitors in the treatment of solid tumors is presented. It updates the information on the small molecule tyrosine kinase inhibitors (TKIs) that are already registered for use or those who are in an advanced stage of development. Furthermore, the future role of tyrosine kinase inhibitors in the treatment of solid tumors is discussed.

Targeted agents may have potential in a wide range of tumor types, including sarcomas for which only limited treatment options are available. **Chapter 3** describes the construction and analysis of a tissue micro-array with 18 different types of soft tissue tumors. Positive membranous staining for EGFR (Her1) was observed in various sarcoma subtypes, including liposarcomas, leiomyosarcomas, synovial sarcomas, malignant peripheral nerve sheath tumors, rhabdomyosarcomas, solitary fibrous tumors, and angiosarcomas. Immunohistochemical staining for ERBB2 (Her2Neu) was negative in all subtypes. However, the immunohistochemical presence of growth factor receptors does not necessarily implicate that the subsequent pathway is activated, or is a potential target for therapy. These results, however, open the possibility to study the effect of EGFR blocking therapies, and give insight into previous study results showing that ERBB2 is not a potential treatment target in sarcomas.

A phase I dose escalation study of telatinib (BAY 57-9352), an orally available tyrosine kinase inhibitor, in patients with advanced or metastatic solid tumors is reported in **Chapter 4**. This phase I dose escalation study was conducted to evaluate the safety and tolerability of telatinib, with additional pharmacokinetics, pharmacodynamics and efficacy assessments. Telatinib was safe and well tolerated up to 1500 mg bid. Based upon pharmacodynamic and pharmacokinetic endpoints, telatinib 900 mg bid is the recommended dose for subsequent phase II studies.

Pharmacogenetics of telatinib are described in **Chapter 5.** This study was an exploratory side study conducted on a subset of patients enrolled into the phase I dose-escalating study of oral telatinib. Our pharmacogenetic analysis could not reveal an association between relevant genetic polymorphisms and clinical and pharmacokinetic observations of telatinib.

Chapter 6 focuses on hypertension and rarefaction during treatment with telatinib. Hypertension is a side-effect in anti-angiogenic therapy. We performed measurements of blood pressure, flow-mediated dilatation (FMD), nitroglycerin-mediated dilatation (NMD), aortic pulse wave velocity (PWV), skin blood flux, and capillary density during treatment with telatinib. A significant increase in blood pressure and PWV, combined with a significant reduction in NMD, FMD, skin blood flux and capillary density are reported. This study shows that the increase in blood pressure observed in the treatment with angiogenesis inhibitors may be caused by rarefaction, a functional or structural decrease in perfused microvessels.

The underlying mechanisms of bevacizumab (Avastin®) related hypertension are reported in **Chapter 7**. Hypertension is a common side effect of bevacizumab, a monoclonal antibody directed at VEGF, and can lead to severe complications. We demonstrated that the decreased capillary density induced by bevacizumab treatment is reversible after discontinuation of the bevacizumab treatment. In combination with earlier results in VEGF tyrosine kinase inhibitor treatment, we also conclude that VEGF-associated rarefaction is a class-effect generated by all VEGF-inhibitors. These results implicate rarefaction, a decreased capillary density, as the most probable cause for hypertension in VEGF inhibition.

In **Chapter 8**, a phase I dose escalation study of sunitinib in combination with ifosfamide is reported. Patients with progressive solid tumors, good performance score, adequate organ function, and no standard therapy available, were eligible. Continuous once daily sunitinib, in escalating doses per cohort, was combined with one of two ifosfamide schedules, 3g/m^2/days1-3 and 1.2g/m^2/days1-5, both given intravenously every 3 weeks. Sunitinib co-administration did not affect the pharmacokinetics of ifosfamide or one of its metabolites. No consistent change in the number of circulating endothelial cells during treatment was observed. Sunitinib at 12.5 mg/day with ifosfamide 3g/m^2/days1-3, and sunitinib at 12.5 mg/day with ifosfamide 1.2g/m^2/days1-5 every 3 weeks supported by G-CSF are tolerable in patients with advanced solid tumors. Grade 3/4 neutropenia was the most reported side effect, seen in 89% of patients (8/9) treated at the recommended phase II dose. Neutropenia was uncomplicated in all but one patient (1/9).

A second phase I study of a new targeted agent is reported in **Chapter 9**. It involves a phase I dose-escalation study of the small-molecule pan-aurora kinase inhibitor danusertib. This dose escalation study was conducted to evaluate the safety and tolerability of danusertib, with additional pharmacokinetics, biomarker and efficacy assessments. Dose limiting toxicity of danusertib is neutropenia (short lasting and generally

uncomplicated), with limited non-hematological toxicity. The recommended dose for subsequent phase II studies is 330 mg/m^2 infused over 6 hours.

Chapter 10 reports the pharmacogenetics of danusertib. The aim of this exploratory side study was to identify possible associations between single-nucleotide polymorphisms (SNPs) in candidate genes with pharmacokinetic and pharmacodynamic parameters of danusertib. In patients with the *FMO3* 18281AA polymorphism, a significantly higher clearance was noticed, compared to patients carrying at least 1 wild type allele. For the variants in the genes encoding the transporters ABCB1, ABCG2, no relationships with danusertib clearance were found. Also for variants in the genes encoding the drug targets AURKA, AURKB, RET, FLT4, KDR and FLT3, no associations with neutropenia were observed. These findings make it unlikely that danusertib's pharmacokinetics and pharmacodynamics are highly susceptible for pharmacogenetic variation.