Treatment optimization in patients with non-small cell lung cancer

Summary

ENGLISH SUMMARY

Non-small cell lung cancer (NSCLC) is the most frequent form of lung cancer, accounting for approximately 85% lung cancer diagnoses. The understanding of the biology of NSCLC has improved over the last decades, and several driver mutations, which play a role in the oncogenesis of NSCLC, have been identified. The discovery of specific driver mutations led to the development and market introduction of targeted agents. Additionally, immunotherapy has become widely available, which stimulates the immune system to increase the body's own response against the tumour. The new systemic treatment options have shown added therapeutic value. However, after market introduction several approaches can be evaluated to optimise the (new) treatment regimens. In this thesis we evaluated different methods for this optimization. We focused on three areas, namely: a) investigating the possibility and added value of therapeutic drug monitoring (TDM) of tyrosine kinase inhibitors (TKIs) and related analytical methods that are necessary to implement TDM; b) supplement data from randomized clinical trials (RCTs) with retrospective observational data and c) improving exposure and cost-efficiency of osimertinib therapy using pharmacokinetic enhancement (boosting). An extensive introduction of the different topics that were included in this thesis, such as NSCLC, TDM, different types of research (clinical and observational), and systemic anti-cancer treatment optimisation are presented in **Chapter 1**.

In total, three different analytical methods were developed and validated, which are described in **Chapter 2**. In **Chapter 2.1,** the analytical method for osimertinib is presented, while in **Chapter 2.2** and **Chapter 2.3** two multi-TKI assays are reported that can be used to quantify alectinib, crizotinib, erlotinib and gefitinib (**Chapter 2.2**) and brigatinib, lorlatinib, pralsetinib, and selpercatinib, respectively (**Chapter 2.3**). All three methods used high pressure liquid chromatography for compound separation and tandem mass spectrometry for quantification.

Osimertinib is a TKI that is used as first- and second-line treatment in patients with locally advanced or metastatic epidermal growth factor receptor (*EGFR*) mutated NSCLC, or as adjuvant treatment in patients with resected *EGFR* mutated NSCLC. The analytical method was developed and validated following the guidelines from the European Medicines Agency (EMA) (**Chapter 2.1**). All pre-specified requirements were met. However, >15% reduced osimertinib concentrations were found after two hours in human serum and citrate plasma. Stability of osimertinib was slightly better in EDTA-plasma and EDTA-whole blood at room temperature (>4 hours). Due to the limited osimertinib stability at room temperature we highly recommend performing plasma preparation on dry ice, to ensure adequate quantification of osimertinib.

In **Chapter 2.2** a method was developed to quantify four TKIs that are used in *EGFR* mutated (erlotinib and gefitinib) or anaplastic lymphoma kinase (*ALK*) mutated (alectinib and crizotinib) NSCLC patients. All validation parameters met the pre-specified requirements

as defined in the EMA guideline. The analytical method that was developed in Chapter 2.2 can be combined with the assay that was developed for osimertinib, which enables the quantification of five TKIs with a single assay setup.

In **Chapter 2.3** a third analytical method was developed, which enables the quantification of an additional four TKIs. Two of those (brigatinib and lorlatinib) are used in patients with *ALK* mutated NSCLC, while the other two (pralsetinib and selpercatinib) can be used in patients with rearranged during transfection (*RET*) mutated NSCLC. Accuracy and precision were within the pre-specified range, as were other parameters, while short- and long-term stability did not show any deviations. All three assays can be used in clinical practice to quantify drug concentrations.

In **Chapter 3 and 4,** four observational studies are presented. The two studies in **Chapter 3** used data from electronic health records in three (**Chapter 3.1**) and two (**Chapter 3.2**) Dutch hospitals, respectively, while the studies in **Chapter 4** were performed using data from two large primary care databases (Clinical Practice Research Database [CPRD] GOLD and Aurum) in the United Kingdom.

In **Chapter 3.1** we evaluated the treatment outcomes (both effectiveness and safety) of patients that were regularly treated with osimertinib. To be eligible for study inclusion, patients had to be 18 years or older, with at least one available CT-scan for response evaluation. In total, 294 patients were included, of which 118 patients used osimertinib as first-line treatment, 134 as second line treatment and 42 patients received osimertinib in the third line or beyond. The median progression free survival (mPFS) in our first line cohort was shorter than the reported mPFS in the FLAURA-study (14.6 vs. 18.9 months), while the mPFS in second-line cohort surpassed the mPFS described in the AURA3-trial (13.7 vs. 10.1 months). In our study, mPFS was significantly better in female patients, patients with an exon 19 deletion as primary *EGFR* mutation, patients with a body mass index (BMI) between 20 – 30 kg/m^2 and in patients with a low $C_{min,SS}$ (<171 ng/mL) (compared to patients with a high $C_{min,SS}$ (>281 ng/mL). A trend towards better mPFS was seen in patients with *TP53* wild-type tumours, while age at start of osimertinib treatment did not significantly influence mPFS.

NSCLC is often diagnosed in a later disease stage, as indicated by the approximate 50% of patients who have metastatic disease at diagnosis. Metastases are often found in the bone, and those metastases negatively impact the overall survival (OS) and quality of life. Approximately 50% of all patients with bone metastases experience a skeletal-related event (SREs), such as symptomatic fracture, surgery of radiation to bone, or spinal cord compression. In **Chapter 3.2** we describe a study that focused on the development of bone metastases and SREs in patients with *EGFR* mutated NSCLC. In this study we found that bone metastases and SREs are frequent in patients with *EGFR* mutated NSCLC, while most patients experienced their first SRE before initiation of osimertinib. After the development

of bone metastases, the median OS was 30.8 months. Use of bone targeting agents (BTAs) is low in the patients with bone metastases but is recommended in patients with bone metastases due to the relatively long OS in patients with *EGFR* mutated NSCLC.

Patients included in randomized controlled trials (RCTs) are often highly selected and unrepresentative of the general patient population with NSCLC. This is because of the strict inclusion and exclusion criteria that are applied in RCTs. The strict criteria and the use of randomization provides a very clean observation of the added therapeutic value of the new drug or treatment strategy. However, the external validity decreases due to the homogeneous patient population, which could affect the effectiveness outcomes in clinical practice. In **Chapter 4.1** we evaluate the potential trial eligibility of British lung cancer patients, diagnosed in clinical practice, for 12 RCTs in advanced NSCLC, focussing on TKIs or immunotherapy, which were performed between 2014 and 2018. For this study a large primary care database from the United Kingdom was used (CPRD GOLD). In total 9,239 lung cancer patients were included. For RCTs evaluating TKIs, the mean proportion of eligible patients was 74.3%, and 51.9% for RCTs evaluating immunotherapy. History of another malignancy, renal insufficiency or concomitant drug-use were the most frequent reasons for exclusion. For all RCTs, median OS was better in the group of potential eligible patients compared to the ineligible individuals.

In October 2017, CPRD launched a new database, called Aurum. General practices using specific health care software (EMIS) can contribute data to Aurum. In the last five years, the number of general practices using EMIS-software has increased considerably. This has led to a situation that approximately 20% of the English population is actively enrolled in CPRD Aurum as patients, supplemented by historical data. Simultaneously, the number of practices using the Vision software, which is necessary to contribute to CPRD GOLD, has considerably decreased, especially in England, which was the primary source for contributing practices. While there are many years of experience with using CPRD GOLD as a reliable database, with numerous studies reporting on data quality, less is known about the CPRD Aurum database. Therefore, we evaluated the differences and similarities between CPRD GOLD and CPRD Aurum in **Chapter 4.2**. Herein, we build on the results from **Chapter 4.1** and performed a similar study evaluating the potential eligibility of lung cancer patients in clinical practice, using the CPRD Aurum database. In addition, as a further manner of data quality validation of this database, we compared the baseline characteristics and OS from lung cancer patients registered in CPRD GOLD and Aurum. In this study we found that lung cancer patients registered in both CPRD Aurum are largely comparable with lung cancer patients in CPRD GOLD, since only minor differences were found in baseline characteristics, such as previous malignancies, deviant laboratory values and concomitant drug use. These minor differences did not impact the potential eligibility of lung cancer patients in clinical practice, as similar inclusion rates were found for all selected RCTs. Lastly, no substantial difference was found in OS between lung cancer patients in GOLD and Aurum (9.0 vs. 9.8 months). We determined that the quality of data,

and the completeness of information recorded of patients with lung cancer in CPRD Aurum is appropriate and reliable, and similar to the data quality that was retrieved from CPRD GOLD. Therefore, we conclude that the data of patients with lung cancer in both databases are an accurate representation of the English patient population with lung cancer in clinical practice and CPRD Aurum can be used for future research, as the current coverage of English lung cancer patients is very extensive in CPRD Aurum.

In **Chapter 5.1** we evaluated if, and to what extent cobicistat could boost the exposure to osimertinib. Cobicistat is a drug specifically designed to inhibit CYP3A4, which is the most important enzyme responsible for the metabolism of osimertinib, and many other TKIs. We hypothesized that the addition of cobicistat would increase the exposure to osimertinib and might be applied in patients that would potentially benefit from higher osimertinib exposure. Furthermore, increasing osimertinib exposure with a cobicistat, a relatively cheap drug, could provide the opportunity to develop a cost-saving approach. In this exploratory pilot study, we included 11 patients that were routinely treated with osimertinib, and experienced low osimertinib exposure (i.e., $C_{min,SS}$ ≤195 ng/mL). At the first day of the study, baseline exposure was evaluated ($AUC_{0-24,SS}$). The next day, co-treatment with cobicistat started. After three weeks, a second $AUC_{0-24,SS}$ was determined. In all patients, an increase of total $AUC_{0-24,SS}$ (combined for osimertinib and its most prominent and active metabolite, AZ5104) was noticed, with a mean increase of 60% (19% – 192%). The boosting effect of cobicistat was stable over time, at least during several months, and no severe adverse events were observed in any patient. All adverse events that occurred were scored as CTCAE (common terminology criteria for adverse events) grade 1.

In **Chapter 6**, the result of our work is discussed and put into context, while options for potential future research were also described. In **Chapter 7** the impact of our work (both clinical as societal) is presented.