Real-world treatment patterns and outcomes of patients with HER2+ advanced breast cancer

The central theme of this thesis is real-world treatment patterns and prognosis in patients with HER2+ advanced breast cancer (ABC). In this thesis, we present data from the SOutheast Netherlands Advanced BREast Cancer (SONABRE) registry on the characteristics, treatment pattern and outcome of patients with HER2+ advanced breast cancer. We included those who were older than 18 years, diagnosed as of 2008 in nine hospitals, comprising one academic, six teaching, and two non-teaching hospitals. All information was collected by specially trained registration clerks from the medical records of the patients.

Summary

Chapter 1 comprises a general introduction regarding ABC epidemiology, subtype distribution, advancements in Human Epidermal growth factor Receptor 2 (HER2) targeted therapy, and provides an outline of this thesis. This thesis will primarily focus on patients diagnosed with HER2+ ABC, accounting for one-fifth of the total ABC population using the collected data from the SONABRE Registry.

Chapter 2 shows the biopsy and discordance rates when determining the subtype of a metastatic site with the subtype of the primary tumour. We presented an overall biopsy rate of approximately 60%, and an overall subtype discordance rate of 18%. Subtype discordance rates were the highest in the primary hormone receptor (HR)+/HER2+ subtype (i.e., 55%). Subtype discordance did impact the initial treatment choice. For example, the loss of the HR resulted in a total decline of endocrine therapy use. However, the loss of HER2 (converted to triple negative subtype) did not always lead to a change in treatment plan. Actually, about one-third of these patients continued to receive HER2-targeted therapy, possibly because tumour heterogeneity was considered a reasonable explanation and because of concerns to withhold a potential effective therapy.

In **chapter 3**, we present the survival and implementation rates for the period before (2008-2012) and after (2013-2017) the introduction of pertuzumab and T-DM1 for ABC. Median overall survival (OS) increased from 28.3 months for patients diagnosed with HER2+ ABC in 2008-2012 to 36.3 months for those diagnosed in 2013-2017 (adjusted hazard ratio=0.85, 95% confidence interval (CI):0.66-1.08). Improvement in overall survival was predominantly evident in the HR-/HER2+ group (median gain of 18 months, adjusted hazard ratio=0.59, 95% CI:0.38-0.92), whereas no significant gain in overall survival was seen in patients with HR+/HER2+ disease (adjusted hazard ratio=0.97, 95% CI:0.72-1.32). The use of pertuzumab gradually increased over time, whereby 19% of patients diagnosed with HER2+ ABC received pertuzumab in 2013, 41% in 2014 and 56% in 2015, and a constant use afterwards (61%-64%). Use of T-DM1 was

prompt though rather low as of 2013 (26%-33%). In daily clinical practise, the implementation rate of new HER2-targeted therapies will never reach 100% due to existing contra-indications for HER2-targeted therapy and chemotherapy, such as comorbidity (e.g. cardiovascular disease), poor performance status (e.g. WHO performance score ≥2), and patient preferences. Nevertheless, there seems to be still room for improvement. In the Netherlands we are quite conservative in using chemotherapy-based therapy as first-line treatment and prefer endocrine-based therapy for patients with mild symptomatic HER2+/HR+ disease to prevent toxicity and adverse events. This might have led to a missed opportunity to benefit from these new drugs in some patients. Future studies are needed to provide insight into medical-decision making, especially when it deviates from (inter)national guideline recommendations.

In **Chapter 4,** we focused on patients diagnosed with *de novo* HER2+ ABC and determined the improvements in progression-free survival and the use of systemic and local therapy since the introduction of pertuzumab and T-DM1 in 2013. The median progression-free survival improved by 12 months since the introduction of pertuzumab and T-DM1 (median PFS was 14.5 months for patients diagnosed with *de novo* HER2+ ABC in 2008-2012 and 26.6 months for those diagnosed in 2013-2017). Furthermore, the five-year use of any HER2-targeted therapy (85% versus 65%) and pertuzumab (59% versus 0%) was higher for patients diagnosed in 2013-2017 compared with those diagnosed in 2008-2012, while the use of local therapy during the first year after diagnosis remained stable. The impressive improvement in median progression-free survival is greater than what was observed in the CLEOPATRA trial (placebo versus pertuzumab arm: 6 months). Overall, a quarter of patients were still alive and free from progression for five years following the introduction of pertuzumab-based therapy. A potential explanation may be that HER2-targeted and chemotherapy is more effective in patients with *de novo* ABC because they are treatment-naïve. Also, the differences in tumour biology between patients with *de novo* and metachronous metastases with a different metastatic pattern may play a role. We, therefore, recommend future clinical researchers studying patients with HER2+ disease to consider *de novo* versus metachronous metastases as a potential relevant stratification factor. Secondly, since a quarter of patients remained alive and progressing-free for several years, there should be more focus on achieving disease-free status.

The accompanying **Chapter 5** describes the real-world treatment patterns and outcomes in patients diagnosed with HER2+ ABC in 2013-2017 in the Southeast of the Netherlands, categorized by HR status. In total, 95% of patients with HR+/HER2+ and 74% of patients with HR-/HER2+ disease received systemic therapy. Patients with HR-/HER2+ disease received more often HER2-targeted therapy than those with HR+/HER2+ disease (77%-91% versus 60%-75% per line), in particular, more often first-line pertuzumab-based therapy (73% versus 29%) and second-line T-DM1 (57% versus

15%). In patients with HR+/HER2+ disease, median OS was 34.9 months (95%CI:25.8-44.0) from the first-line and decreased to 12.8 months (95%CI:10.7-14.9) from start of the fourth-line of systemic therapy. In HR-/HER2+ disease, median OS was 39.9 months (95%CI:23.9-55.8) from the first-line and 15.2 months (95%CI:10.9-19.5) from start of the fourth-line. For patients treated with first-line pertuzumab, trastuzumab plus chemotherapy, median OS was not reached at 56.0 months in HR+/HER2+ disease and 48.4 months (95%CI:32.6-64.3) in HR-/HER2+ disease, in line with the pertuzumab arm of the CLEOPATRA trial (i.e. 57.1 months, 95%CI: 50-72). In later treatment lines, the survival times remained surprisingly long, justifying the use of multiple lines of systemic therapy in fit patients.

In the study presented in **Chapter 6**, we established the impact of prior (neo)adjuvant trastuzumab treatment of the outcomes of first-line palliative HER2-targeted therapy. A more than two-fold higher hazard of progression (adjusted hazard ratio=2.07, 95%CI:1.47-2.92) was observed in patients treated with first-line HER2-targeted therapy who previously received (neo-)adjuvant trastuzumab-based therapy, when compared with trastuzumab naïve patients. In addition we showed that for trastuzumab pre-treated patients who received first-line trastuzumab without pertuzumab, the hazard ratio for progression-free survival was 2.60 (95%CI:1.72-3.93), whereas for those who received first-line trastuzumab with pertuzumab the hazard ratio was lower, i.e., 1.43 (95%CI:0.81-2.52). We concluded that the use of first-line pertuzumab was an effect modifier in the effect of (neo-)adjuvant trastuzumab on progression-free survival (p-interaction=0.10, borderline significant). These results show that the use of pertuzumab-based therapy decreased the negative impact of prior trastuzumab use on first-line progression-free survival.

In **Chapter 7**, we reviewed the role of chemotherapy in the treatment of ABC based on published intervention and observational studies. We concluded that combination chemotherapy did not improve OS and caused greater toxicity when compared with sequential use of single-agent chemotherapy. Continuing chemotherapy till progression or unacceptable toxicity generated greater efficacy without diminishing the quality of life compared with a fixed number of cycles. The response to previous chemotherapy predicts the chance of response of the next-line of chemotherapy. Three or more lines of chemotherapy only benefits patients with a significant response from the previous lines of chemotherapy. Physicians in daily practice mainly prescribe capecitabine or taxane as first- and second-line chemotherapy. We hypothesize that chemotherapy persists to serve as a backbone to the increasing arsenal of targeted therapies, by providing a synergistic effect when targeting specific mutations and signalling pathways.