



Universiteit
Leiden
The Netherlands

Combining surgery and systemic therapy in metastatic melanoma

Blankenstein, S.A.M.

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The background is a solid blue color with a faint, repeating pattern of white icons. These icons include various gears of different sizes, some with circuit-like lines extending from them, and a pair of scissors. The overall aesthetic is technical and modern.

Chapter 9

English summary
Nederlandse samenvatting

SUMMARY

Chapter 1 gives the introduction to the thesis, containing general information on melanoma and its treatment. It provides an outline of this thesis and presents the main focus: combining surgery and systemic therapy to enhance melanoma treatment.

The first example of the synergy between surgery and systemic therapy is demonstrated in **chapter 2**. The REDUCTOR trial studied patients with locally advanced melanoma, who were classified as having unresectable disease and therefore not eligible for the standard of care in stage III melanoma: surgery. In this study, 21 patients received short-term induction therapy with BRAF/MEK inhibition, which resulted in sufficient downsizing of the tumor in the majority (18/21) of patients to perform surgery. Of the patients undergoing resection, 9 out of 18 had a pathological (near) complete response. The study described in **chapter 3** aimed to predict pathological response or recurrence by using ^{18}F -FDG PET/CT. Unfortunately ^{18}F -FDG PET/CT could not fulfill this aim, but did seem valuable in detecting recurrence early after radical resection.

As induction targeted therapy showed to be useful in paving the way to surgery in unresectable stage III melanoma, patients remain at high risk for recurrence despite radical resection. **Chapter 4** describes the efforts over the past decades of reducing this risk by using adjuvant systemic therapy, leading to the current standard of care: adjuvant immune checkpoint inhibitors and targeted therapy. These novel systemic therapies have improved recurrence-free survival (RFS) in stage III melanoma patients and overall survival (OS) benefit is thus far preserved to anti-CTLA-4 agent ipilimumab, as OS data of the remaining studies are pending.

However, a subset of patients does not benefit from adjuvant systemic therapy: either patients who would not have recurred without, or patients who recur despite adjuvant therapy. **Chapter 5** discusses the search for prognostic and predictive biomarkers in patients with macroscopic stage III melanoma to adequately select patients for tailored adjuvant therapy. A special target of interest was interferon-gamma (IFN γ), which plays an important role in the antitumor response in the tumor microenvironment and has shown to be predictive of response in patients treated with neoadjuvant immune checkpoint inhibitors. Our study showed that both in patients treated with surgery alone and in patients treated with surgery followed by adjuvant systemic therapy, an IFN γ high profile was correlated with increased RFS. Additionally, both patients with an IFN γ high and low profile showed improved RFS rates when treated with adjuvant systemic therapy, compared to surgery alone. Therefore IFN γ was identified as a prognostic biomarker, but unfortunately it did not predict response to adjuvant systemic therapy.

All previously mentioned chapters describe systemic therapy aiding surgical treatment in stage III melanoma patients, in whom surgery is standard of care. However, in stage IV

melanoma, the standard of care is systemic therapy. Over the past decades, novel systemic therapies have shown durable responses and have drastically changed prognosis in these patients. **Chapter 6** explores the role of surgery in patients with unresectable stage IIIC/IV melanoma showing oligoprogression or a durable partial response with remaining lesions after initial systemic therapy. Patients were included from the Dutch Melanoma Treatment Registry (DMTR), a nationwide database which registers all Dutch patients undergoing treatment for unresectable stage IIIC and IV melanoma. This study showed that selected patients can benefit from surgery after achieving initial disease control with systemic therapy.

Another study carried out with data retrieved from the DMTR, is described in **chapter 7**. In this study the value of sentinel lymph node biopsy (SLNB) in patients who progressed to advanced disease in due course, is evaluated. It showed that undergoing a SLNB, prior to the availability of adjuvant systemic therapy, had no survival benefit for patients developing subsequent advanced melanoma.

In the general discussion, **chapter 8**, arguments are stated to conclude that systemic therapy and surgery can be seen as synergistic treatment modalities in treating patients with stage III and IV melanoma. This is shown in systemic therapies paving the road to surgery in unresectable disease and preventing recurrences in high-risk melanoma, but also surgery aiding in diminishing disease activity after initial control to systemic therapy.