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Bridging the gap between clinical trials and real-world for advanced melanoma: Results of the Dutch Melanoma Treatment Registry

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General introduction and thesis outline

General introduction

Melanoma

In 2018, an estimated 290,000 patients were newly diagnosed with cutaneous melanoma accounting for approximately 1% (61,000) of all cancer deaths worldwide.¹ The incidence is expected to continue to rise especially in countries with predominantly fair-skinned population, creating a high burden on global healthcare.^{2,3} Historically the prognosis of unresectable stage III and stage IV (advanced) melanoma has been poor with a 5-year overall survival (OS) probability of 40% and below 10%, respectively.^{4,5} The median OS of stage IV melanoma was only 6-8 months.⁴ Risk factors for cutaneous melanoma are related to high or chronic exposure of melanocytes to ultraviolet radiation, phenotype (pale-skinned, red-haired and blue-eyed), and genetic predisposition.⁶

Mechanism of carcinogenesis

Genetic alterations of the BRAF gene and consequential overactivation of downstream MEK kinase (and other cellular pathways) cause overstimulation of the mitogen-activated protein kinase (MAPK) pathway.^{7,8} As a result, oncogenic BRAF V600 mutations in melanoma cells may contribute to the malignant behaviour with uncontrolled proliferation, differentiation and survival. Patients who were intermittently sun exposed at a young age and/or have multiple melanocytic or dysplastic naevi are more prone to have a mutation of the BRAF gene.⁶ Fifty to sixty percent of cutaneous melanomas harbour a mutation of the BRAF gene.⁹

Another mechanism of carcinogenesis of cutaneous melanoma is its ability to escape the immune response. Cutaneous melanoma bears a high tumour mutational burden that frequently result in neoantigens.¹⁰ Although cutaneous melanoma neoantigens are recognized by T-cells, their immune response is inhibited. The 2018 Nobel prize winners James P. Allison and Tasuku Honjo discovered that respectively CTLA-4 and PD-1 receptors present on T-cells, have a negative regulatory effect on the immune response.¹¹⁻¹³ Activation of immune checkpoint CTLA-4 and binding of PD-1 to its ligand PD-L1 inhibits T-cell activity. This ensures self-tolerance of normal peripheral tissue, but melanoma cells use T-cell inhibition through PD-1 to escape the immune response.

New era of systemic therapies

In the last 10 years, development of new systemic therapies aimed at targeting BRAF and MEK kinase and the CTLA-4 and/or PD-1 receptor led to the approval of five treatment options for advanced melanoma for use in daily clinical practice: BRAF inhibitor monotherapy, BRAF plus MEK inhibitor combination therapy, anti-CTLA-4 antibody monotherapy, anti-PD-1 antibody monotherapy, anti-CTLA-4 plus anti-PD-1 antibody combination therapy. In addition, talimogene laherparepvec, an oncolytic HSV based virus was approved (the latter will not be discussed further).

Targeted therapy with a BRAF inhibitor (monotherapy with vemurafenib or dabrafenib approved in 2012 and 2013, respectively) in BRAF-mutated melanoma showed, despite an initial survival benefit compared with chemotherapeutic agent dacarbazine, no durable survival benefit.¹⁴⁻¹⁶ This was due to acquired resistance to BRAF monotherapy. The median OS of vemurafenib was 13.6 months (versus 9.7 months for dacarbazine) and of dabrafenib was 20 months (versus 16 months for dacarbazine).¹⁴⁻¹⁶

The acquired therapy resistance could be reduced or postponed by adding a MEK inhibitor (dabrafenib plus trametinib, vemurafenib plus cobimetinib, encorafenib plus binimetinib approved in 2014, 2015 and 2018, respectively). In the phase III trials, patients with BRAF-mutated melanoma treated with combination therapy of BRAF plus MEK inhibitors had a median OS of 22.3-33.6 months compared with 16.9-18.7 months for BRAF inhibitor monotherapy.¹⁷⁻²¹ (The higher median OS of BRAF inhibitor monotherapy in the BRAF plus MEK inhibitor trials was probably due to immunotherapies that were newly available at the time of the study period). Percentage of patients experiencing grade 3-4 adverse events (AEs) with BRAF plus MEK inhibitor combination was 78% for vemurafenib plus cobimetinib, 48% for dabrafenib and trametinib and 58% for encorafenib plus binimetinib.¹⁷⁻²¹

In 2011, the anti-CTLA-4 antibody ipilimumab was the first immunotherapy approved for advanced melanoma. Ipilimumab compared with glycoprotein 100 peptide vaccine (an anticancer vaccine) showed a median overall survival of 10.1 months versus 6.4 months, respectively.²² In a pooled analysis the median OS for ipilimumab was 11.4 months.²³ Grade 3-4 AEs occurred in 22.9% of patients treated with ipilimumab.²²

The anti-PD-1 antibodies nivolumab and pembrolizumab were approved in 2015. Patients treated with nivolumab had a median OS of 37.5 months compared to 11.2 months in chemotherapy-treated patients.²⁴ Pembrolizumab had a median OS of 32.4 months compared with 15.9 months in ipilimumab-treated patients.²⁵ One of the advantages of these anti-PD-1 antibodies was that only 10% to 12% of patients had treatment-related grade 3-4 adverse events (AEs).^{24,25}

The phase III trial that studied the combination of anti-CTLA-4 plus anti-PD-1 antibody, ipilimumab plus nivolumab, showed a median OS of 72.1 months.^{26,27} Median OS of the comparator study arms nivolumab monotherapy and ipilimumab monotherapy were 36.9 months and 19.9 months, respectively. The 5-year OS probability of ipilimumab plus nivolumab, nivolumab monotherapy and ipilimumab monotherapy were 57%, 50% and 37%, respectively.²⁸ Percentage of patients with grade 3-4 AEs in this phase III trial was 59% for ipilimumab plus nivolumab, 23% for nivolumab and 28% for ipilimumab.²⁶

The efficacy-effectiveness gap between trials and real-world

The randomized controlled trials (RCTs), on which market authorisation is based, are the gold standard to determine efficacy of new treatments. Efficacy is the extent to which a new treatment is beneficial under 'ideal' circumstances (created in an RCT).²⁹ RCTs are performed in a highly controlled setting using strict in- and exclusion criteria to limit variability, to ensure long-term follow-up and high data quality. Strict study protocols are followed by specialised personnel in specialised environments with intensive monitoring. The study population of a clinical trial is restricted to high-responders and good-tolerators³⁰ and are subjected to more (and protocolised) examinations than in routine treatment conditions. This improves the internal validity of clinical trials and enables estimation of valid treatment effects, but results of RCTs are often not generalizable to daily clinical practice.

Newly introduced treatments, however, are usually licensed in a less restricted patient population than the RCTs on which their market authorisation was based. At the time of market approval, the extent to which a new treatment is beneficial under routine treatment condition (daily clinical practise) still is unknown. This is called effectiveness.²⁹ In other words, a large part of real-world patients is being treated without evidence of the effectiveness in daily clinical practice when new treatments are introduced. This is known as the efficacy-effectiveness gap.²⁹

The RCTs on advanced melanoma only included patients who were fully ambulatory and able to carry out light work, but who were restricted in strenuous physical activity (Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≤ 1). Patients with active brain metastasis were excluded.^{17-21,31-33} The RCTs on immunotherapy also excluded patients with autoimmune disease and uveal melanoma.³¹⁻³³ Other rare types of melanomas, such as mucosal melanoma, were underrepresented in the RCTs. As a consequence, a large proportion of real-world patients with advanced melanoma were not represented in the RCTs on advanced melanoma.³⁴

The efficacy-effectiveness gap between clinical trials and real-world for advanced melanoma arises because patients are not represented in RCTs and the uncontrolled real-world setting. In order to use new systemic therapies for advanced melanoma more effectively in daily clinical practice, this efficacy-effectiveness gap between trials and real-world must be bridged.³⁰ By studying newly introduced systemic therapies for advanced melanoma in real-world patients and real-world setting treatments can be used more effectively. This could spare patients severe adverse events and perhaps reduce the financial burden for society.

Unique real-world data for advanced melanoma in the Netherlands

In 2012, the care for advanced melanoma patients in the Netherlands was centralised in 14 melanoma treatment centres and the Dutch Melanoma Treatment Registry (DMTR), a nationwide population-based registry, was founded as part of reimbursement requirement for

newly introduced systemic treatments.³⁵ Patients with unresectable stage III or IV melanoma could only receive new systemic treatments at one of the designated melanoma treatment centres. Data of all patients with unresectable stage III or IV melanoma who were referred to one of the 14 melanoma centres were collected.

For the DMTR, the Dutch Institute for Clinical Auditing (DICA) received a start-up grant from governmental organization The Netherlands Organization for Health Research and Development (ZonMW, project number 836002002). Structurally the DMTR was funded by the joined healthcare insurers in the Netherlands (Zorgverzekeraars Nederland) and, additionally, by Bristol-Myers Squibb, Merck Sharpe & Dohme, Novartis and Roche Pharma. In 2019, Roche Pharma stopped and Pierre Fabre started funding the DMTR. Netherlands Comprehensive Cancer Organisation and Penthecellia were commissioned for the data collection from the electronic health records.

The DMTR was designed to serve multiple objectives: clinical auditing, transparency and advancement of melanoma care, provide insight in real-world outcomes and scientific research. Data points necessary to serve these objectives were determined by delegates of the melanoma centres, the Dutch Society of Medical Oncologists (NVMO) and involved pharmaceutical companies.

A scientific committee, consisting of 14 medical oncologists representing the melanoma centres, an oncologic surgeon, a pathologist and representatives of the institute of Medical Technology Assessment (iMTA), evaluated the data points, data analysis and (melanoma treatment centre specific) outcomes from the DMTR. In a triangle of patient organisations, insurers and medical specialists, data about the quality of melanoma care and future objectives of the DMTR were discussed and defined. The pharmaceutical companies received real-time product specific information. National Health Care Institute (ZIN) was provided with analysis of use, total cost and survival outcomes of new systemic treatments to provide insight in the use of these costly oncological medication. The DMTR is a unique joint effort between medical specialists, patients, healthcare insurers, pharmaceutical industry and governmental organisations resulting into outcomes for all of the parties involved.

The comprehensiveness and nationwide population-based character of the DMTR offers a unique opportunity to study the effectiveness of new systemic treatments for advanced melanoma in real-world.

Outline of this thesis

For advanced melanoma, there is an efficacy-effectiveness knowledge gap between trials and real-world. Utilizing the DMTR, this thesis aims to bridge part of the efficacy-effectiveness gap in order to stimulate more effective use of newly introduced systemic therapies.

Real-world outcomes of advanced melanoma in a new era of systemic treatments

Long-term outcomes from phase III trials on targeted- and immunotherapy clearly indicate the enormous progression in the treatment of advanced melanoma. Whether the introduction of new systemic treatments has translated to survival benefit for patients in real-world (setting) is unknown. Chapter 2 gives an overview of the use and safety of new systemic therapies in the Netherlands. We report survival outcomes of the first years that new systemic treatments became available and analyse what factors have prognostic value.

In daily clinical practice, patients with advanced melanoma not represented in phase III trials are treated without true evidence of the effectiveness. These trial-ineligible patients may benefit from new systemic treatments, but the trial-ineligible patient population is (prognostically) heterogeneous. We aimed to identify prognostic factors and order these factors by prognostic importance in Chapter 3 to support clinical decision-making for trial-ineligible patients.

Primary mucosal melanoma (MM) is a rare type of melanoma with, historically, a poor prognosis. Due to its rarity, the efficacy of immunotherapy in advanced MM could not be separately analysed in the phase III trials. It is even more unclear how the newly available immunotherapies influence the prognosis of patients with advanced MM. The DMTR allowed us to study this rare type of melanoma. In Chapter 4 we provide in-depth analysis of advanced MM and compared overall survival with cutaneous melanoma before and after immunotherapy was introduced in the Netherlands.

Immunotherapies in daily clinical practice

Anti-PD-1 antibodies pembrolizumab and nivolumab are known for their high response rates (33-40%) and survival probabilities against relatively low percentage grade 3-4 adverse events (10-12%). Real-world outcomes are important to gain more insight in the effectiveness of anti-PD-1 antibodies. In Chapter 5 we aimed to report in-depth outcomes of first-line anti-PD-1 monotherapy to support future clinical decision-making and increase the effectiveness of anti-PD-1 antibodies in daily clinical practice.

There is no clear consensus on the optimal treatment duration and timing of discontinuation of anti-PD-1 monotherapy. Early discontinuation of anti-PD-1 monotherapy is preferred considering the adverse events, the burden of hospital visits for patients, possible immune exhaustion, hospital capacity and financial costs for society. We aimed to provide more evidence on the optimal treatment duration and conditions for discontinuation of anti-PD-1 monotherapy in Chapter 6.

The combination of ipilimumab plus nivolumab is the most effective systemic treatment, but with a high percentage of grade 3-4 adverse events (>50%). Interestingly, advanced melanoma patients with stage IV-M1c disease and elevated LDH level with relatively high tumour load appear to benefit from ipilimumab plus nivolumab.³⁶ We aim to report real-world use and

effectiveness of ipilimumab plus nivolumab combination therapy in Chapter 7. Additionally, we investigate the survival of patients who discontinue treatment due to grade 3-4 adverse events correcting for immortal time bias.

Future perspective

At the start of this PhD in 2015, surgery was still the cornerstone of treatment for stage I to IIIb melanoma. Following the example of breast cancer, the use of new systemic treatments as (neo)adjuvant therapy for high-risk melanoma as a future treatment strategy, became subject for research after evidence for efficacy in advanced melanoma. In Chapter 8 we evaluated, at that moment in time, recent and ongoing trials of new systemic treatments in the (neo-)adjuvant setting for high-risk melanomas.

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