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

Zeijl, M.C.T. van

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# Addendum

# English summary

Historically, the median overall survival (OS) of stage IV melanoma was only 6-8 months. The discovery of the role of CTLA-4 and PD-1 receptors (present on T-cells) and the mitogen-activated protein kinase pathway in the carcinogenesis of melanoma led to new ground-breaking treatments, as outlined in Chapter 1. From 2011 to 2016, 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 that proved their efficacy in phase III trials became available for patients with advanced melanoma.

Results of these clinical trials were not generalizable to the real-world, because strict inclusion and exclusion criteria were handled and newly introduced therapies were licensed in a less restricted patient population. The extent to which a new treatment is beneficial under 'ideal' circumstances created in clinical trials, called the efficacy, does not automatically correspond with the extent to which a new treatment is beneficial under routine treatment condition in the real-world, called the effectiveness.

To grand patients with advanced melanoma in the Netherlands fast access to newly introduced systemic treatments, a population-based registry called the Dutch Melanoma Treatment Registry (DMTR) was founded in 2012 as part of a reimbursement requirement. All newly diagnosed patients in the Netherlands with unresectable stage III or IV melanoma and their disease characteristics and treatments were registered in the DMTR. This offered and still offers a unique opportunity to study real-world patients with advanced melanoma and new treatments in real-world setting.

The scope of this thesis is to study the effectiveness of newly introduced systemic therapies for advanced melanoma in real-world to bridge the gap that exists between clinical trials and real-world.

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

In Chapter 2, we investigated outcomes of all patients diagnosed with advanced melanoma from 2013 to 2017 in the Netherlands. We found that the implementation of immuno- and targeted therapies in the Netherlands was fast and safe with an improvement of median overall survival (OS) of patients diagnosed from 2013 to 2017. In daily clinical practise, elevated lactate dehydrogenase (LDH) levels, distant metastases in ≥3 organ sites, brain and liver metastasis and Eastern Cooperative Oncology Group performance score (ECOG PS) of ≥1 had stronger association with death in the first 6 months from diagnosis than 6 to 48 months from diagnosis. Patients with a BRAF-mutated melanoma had a remarkable superior survival in the

first 6 months compared to BRAF wild-type melanomas, but after 6 months this survival benefit disappeared.

We focussed on the real-world patient population not represented in phase III trials in Chapter 3 to provide evidence that could support clinical decision making in this population. Forty percent of systemically treated patients with advanced melanoma in the were trial-ineligible, because of ≥1 trial exclusion criteria with a median OS of 8.8 months. However, OS was very heterogeneous and highly dependent on LDH level, ECOG PS and symptomatic BM. The strongest prognostic covariate for survival in ineligible patients was LDH, followed by ECOG PS. The prognosis of patients with LDH of >2x ULN is poor, but long-term survival still is possible.

A rare type of melanoma usually excluded from clinical trials or not separately analysed is advanced mucosal melanoma (MM), which was the subject of our study in Chapter 4. Patients diagnosed with advanced MM were older and more often female with a median OS that lagged behind that of patients with cutaneous melanoma (8.7 versus 14.5 months). Within the era of newly introduced immune and targeted therapies, the prognosis for patients with advanced MM has not improved as much as advanced cutaneous melanoma, illustrating the progress still to be made for advanced MM. Given the rarity of advanced MM, international collaboration is necessary to increase sample size for research to improve immunotherapeutic strategies and to identify targetable mutations.



## Immunotherapies in daily clinical practice

In Chapter 5 and Chapter 6 the immune checkpoint inhibitor anti-PD-1 antibody as first-line monotherapy was investigated. The median OS of trial-like patients was 31 months compared to 17 months for patients not represented in phase III trials. Also in this study, an ECOG PS of ≥1, symptomatic brain metastases and liver metastases and elevated LDH were important prognostic factors. That BRAF-mutated melanoma was associated with superior OS could be explained by having BRAF plus MEK inhibitors as a treatment option upon treatment failure. Patients with a complete response (CR) had a 2-year OS probability from first reported CR of 92%.

The treatment duration of anti-PD-1 monotherapy per protocol is two years. To gain evidence for the optimal treatment duration and/or safe (early) discontinuation of anti-PD-1 antibody monotherapy we investigated patients with advanced melanoma in the Netherlands who discontinued first-line anti-PD-1 monotherapy in the absence of progressive disease. Median treatment duration for patients with complete response (CR) and partial response (PR) at anti-PD-1 discontinuation was 11 months. Patients with advanced melanoma can have durable remissions after (elective) anti-PD-1 discontinuation. The 2-month progression-free survival (PFS) and OS probabilities for patients with a CR and PR were 64%/88% and 53%/82%, respectively. A PR at anti-PD-1 discontinuation and longer time to first response were

associated with progression. A response to anti-PD-1 re-treatment can be achieved as we observed this in 63%.

In the CheckMate-067 trial, ipilimumab plus nivolumab was highly efficacious for advanced melanoma despite high percentage of grade 3-4 adverse events. In Chapter 7, we studied the real-world safety and survival outcomes of this combination of a CTLA-4 and an anti-PD-1 antibodies. In real-world, half of the patients receiving first-line ipilimumab plus nivolumab experienced a grade 3-4 AEs with more than fifty percent requiring hospital admission. Disease control at 2 years was achieved in 37% of patients with advanced melanoma with a median OS of 28.7 months. CheckMate-067 trial-like patients had a 4-year OS of 50%. Among patients without brain metastases the 4-year OS probability was 48%, but long-term survival was also reached in patients with asymptomatic or symptomatic brain metastases (4-year OS probabilities of 45% and 32%, respectively).

## High-risk melanomas and future perspectives

Systemic targeted- and immune therapies beneficial in advanced melanoma could be a promising strategy for (neo)adjuvant treatment of patients with resectable high-risk (stage II and III melanoma) melanomas as surgery alone does not seem to improve survival any further. In Chapter 8, which was written at the beginning of this thesis in 2015, we give an overview of the (at the time ongoing) trials for (neo)adjuvant treatments. The results of the first (neo)adjuvant trials with these agents in high-risk melanoma were awaited with great interest. It is now known that BRAF and MEK inhibitors dabrafenib and trametinib and anti-PD-1 antibodies nivolumab and pembrolizumab showed promising relapse-free survival probabilities and are now viable adjuvant treatment options for high-risk melanoma.

Finally, in Chapter 9, the implications for daily clinical practise of this thesis are discussed, as well as the impact of the DMTR and lessons that can be learned from this nationwide population-based registry.