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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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8

# (Neo)adjuvant systemic therapy for melanoma

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## Abstract

Surgery still is the cornerstone of treatment for patients with stage II and III melanoma, but despite great efforts to gain or preserve locoregional control with excision of the primary tumour, satellites, in-transits, sentinel node biopsy and lymphadenectomy, surgery alone does not seem to improve survival any further. Prognosis for patients with high-risk melanoma remains poor with 5-year survival rates of 40 to 80%. Only interferon  $\alpha$ -2b has been approved as adjuvant therapy since 1995, but clinical integration is low considering the high risk-benefit ratio.

In recent years systemic targeted- and immunotherapy have proven to be beneficial in advanced melanoma and could be a promising strategy for (neo)adjuvant treatment of patients with resectable high-risk melanomas as well. Randomised, placebo-controlled phase III trials on adjuvant systemic targeted- and immunotherapy are currently being performed using new agents like ipilimumab, pembrolizumab, nivolumab, vemurafenib and dabrafenib plus trametinib. In this article we review literature on currently known adjuvant therapies and currently ongoing trials of (neo)adjuvant therapies in high-risk melanomas.

## Introduction

In 2012 approximately 100,000 patients were diagnosed with cutaneous melanoma in European countries alone with 22,000 deaths caused by melanoma annually.<sup>1,2</sup> Incidence rates of melanoma are highest for northern countries with a predicted incidence rate in 2015 up to 25 per 100,000.<sup>3</sup> Uniformly incidence rates are increasing in most European countries and around the world.<sup>4</sup> Independent predictive factors for survival are Breslow-thickness, ulceration of primary tumour, number of tumour-bearing nodes and their tumour burden, distant metastasis and serum LDH level.<sup>5</sup> Prognosis of resectable high-risk melanomas is poor. For stage IIA-C melanomas 5-year survival rates are 55 to 80 percent and for melanomas with nodal involvement (stage III) it is 40 to 78 percent. Stage IV melanomas have a 1-year survival rate of 35 to 62 percent.<sup>5</sup>

For stage I to IIIB melanoma, surgery is the cornerstone of treatment. Surgical treatment of (primary) local disease consists of wide local excision with safety margins of 0.5 cm for in situ melanomas, 1 cm for tumours with a thickness of up to 2mm, and 2 cm for tumours thicker than 2mm (considering anatomy and function).<sup>6-8</sup> Also for loco regional advanced melanomas, surgery alone is standard of care, including resection of satellite or in-transit metastases and regional lymph node dissections once tumour-positive nodes have been detected. Given the substantial risk for post-operative complications and long-term morbidity elective complete lymphadenectomy is considered obsolete.<sup>9</sup>

Introduction of sentinel-node biopsy (SNB) in 1992 made evaluation of regional nodal metastasis before resection possible.<sup>10</sup> However, the therapeutic value of complete lymphadenectomy in patients who are SNB positive remains unclear. The Multicenter Selective Lymphadenectomy Trial-I (MSLT-I) found a positive effect on disease-free survival and in a selected group of patients (intermediate-thickness melanomas: 1.2 to 3.5mm) completion lymphadenectomy (CLND) after tumour positive SNB led to a 10-year survival benefit for the SNB group compared to the wide local excision alone group.<sup>9</sup> However trial design and outcomes of the MSLT-I trial have been questioned.<sup>11</sup> First results of the German DeCOG trial with a comparable study design as the MSLT-I trial showed no difference in 5-year recurrence-free survival (RFS), distant metastasis free survival (DMFS) and disease specific survival.<sup>12</sup> However, a second trial of the MSLT study group (MSLT-II) that compares CLND with observation in SNB positive patients will show if unnecessary lymph node dissections can be avoided in patients with tumour positive nodes. This trial has reached its accrual, though results are not expected before 2022.

Although controversy remains as to the benefit of performing a sentinel node biopsy, the use of this technique as staging modality is widely accepted. The status of the lymph nodes is one of the most important prognostic factors for patients with melanoma, acknowledged in the AJCC 7<sup>th</sup> edition staging system, and can be used to select patients at risk for distant metastases.

For advanced disease, systemic targeted agents and immunotherapy has proven to be beneficial and might be a promising strategy for the adjuvant treatment of patients with resectable high-risk melanomas as well. This review evaluates recent and ongoing trials on the use of systemic therapy in the adjuvant or neo-adjuvant setting for patients with high-risk melanomas.

## Search strategy

For this review our aim was to identify relevant randomized controlled trials, review articles and relevant clinical trials (phase II/III) on stage I-III resected melanomas. We searched PubMed and clinical trial register [clinicaltrials.gov](http://clinicaltrials.gov) and [clinicaltrialsregister.eu](http://clinicaltrialsregister.eu) from January 2000 to March 2016. Filters used were English language and human studies. Our search strategy consisted of separate searches with MeSH headings by systemic therapies combined with “melanoma” and “adjuvant” or “neoadjuvant”, using extensive subheadings (see the supplementary appendix for all search terms). Inclusion of older references was necessary for chemotherapy and interferon. References of relevant articles found were reviewed.

## Adjuvant therapy

Adjuvant therapy is investigated in melanomas with a high risk for recurrence following complete surgical resection. Main focus in current adjuvant trials are stage III melanoma patients that have lymph node metastasis of at least 1.0mm and have a 10-year survival of 50% at the best. In some trials, patients with high-risk stage II or radical resected stage IV are included.

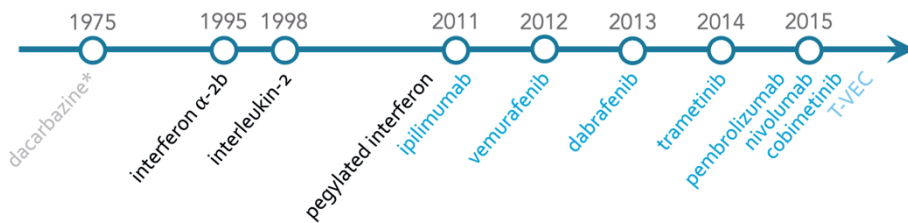
## Chemotherapy

Although response rates are limited (13.4%), dacarbazine and temozolomide (DTIC and MTIC) have long been the standard of systemic treatment for patients with metastatic melanoma (median survival 5.6 to 11 months).<sup>13</sup> In 1982 in a 4-arm trial for patients with stage II and III melanoma who underwent radical excision, lymphadenectomy and adjuvant DTIC, no survival benefit was found at 3 years compared to the observation group not receiving adjuvant chemotherapy.<sup>14</sup> One of the main problems in evaluating adjuvant chemotherapy in melanoma, has been that accrual of trials did not meet sample size criteria for adequate statistical power.<sup>15</sup> Further research has not been done as no evidence suggests DTIC could be effective as systemic adjuvant therapy in high-risk melanoma patients.

## Immunotherapy

Utilizing a patient's own immune system to treat cancer is alluring as this could be an exponent of tailored therapy by sensitizing native immune system of a patient to cancer or amplifying the already existing response. In the context of immunotherapy, melanoma is studied most extensively as it appears to be one of the most immunogenic cancers witnessing occurrence of spontaneous regression, tumour-infiltrating T-lymphocytes (TILs) in primary tumour and

metastases. TILs are correlated with better outcome as they have the ability to recognise melanoma specific antigens.<sup>16</sup> For decades, researchers have tried different techniques to develop immunotherapy against melanoma. In 1995 interferon- $\alpha$  (IFN) was the first immunotherapy approved by the European Medicines Agency (EMA) with a restricted indication to adjuvant use. Since 2011, a new era started targeting immune checkpoint receptors and receptor kinases (Figure 1). These new systemic therapies have higher response rates and increase progression-free survival (PFS). Current phase III trials investigating the efficacy of immunotherapy in the adjuvant setting are listed in Table 1.



**Figure 1** Systemic therapies for (advanced) melanoma over the years. \*dacarbazine was never approved as adjuvant therapy. Coloured black: approved for adjuvant therapy. Coloured blue: possible future adjuvant therapies. T-VEC: oncolytic immunotherapy talimogene laherparepvec.

**Table 1** Ongoing or finished phase III trials on adjuvant systemic therapy in high-risk melanoma.

Clinicaltrials.gov#	Study ID	Disease-stage	Estimated enrolment	Intervention	Comparison	Main outcomes	Status	Completion
NCT01502696	EORTC-18081	T(2-4)b N0M0	1200	PEG IFN- $\alpha$ 2b for 2 years	Observation	OS, RFS, QoL, toxicity	R	2020
NCT01274338	ECOG-E1609	IIIB/C or IV	1545	High- or low-dose ipilimumab for 1 year	High dose recombinant IFN- $\alpha$ -2b for 1 year	OS, RFS, QoL, toxicity	C	2018
NCT00636168	EORTC-18071	III*	951	Ipilimumab for 3 years	Placebo	OS, RFS, QoL, toxicity	F	2015
NCT02506153	Untitled	III or IV	1378	Pembrolizumab for 1 year	High dose recombinant IFN- $\alpha$ -2b for 1 year	OS, RFS, QoL, toxicity	R	2020
NCT02362594	KEYNOTE-054	III*	900	Pembrolizumab for 1 year	Placebo	OS, RFS	R	2023
NCT02388906	CheckMate 238	IIIB/C or IV	800	Ipilimumab and placebo matching nivolumab for 1 year	Nivolumab and placebo matching ipilimumab for 1 year	OS, RFS	C	2019
NCT01667419	BRIM-8	III*	475	Vemurafenib for 1 year	Placebo	OS, RFS, QoL, safety	C	2020
NCT01682083	COMBI-AD	III*	852	Dabrafenib and trametinib for 1 year	Placebo	OS, RFS, safety	C	2018

\*Lymph node metastasis of >1mm is required for stage IIIA melanoma. R - recruiting, C - closed, F - finished, PEG - pegylated, IFN - interferon, OS - overall survival, RFS - recurrence-free survival, QoL - quality of life.

## Interferon

Efficacy of IFN- $\alpha$  for advanced melanoma has never been shown<sup>17</sup>, but as adjuvant therapy the FDA approved high dose IFN- $\alpha$  based on a large RCT by the Eastern Cooperative Oncology Group (E1684) in 1995. A significant beneficial treatment effect of IFN- $\alpha$  on recurrence-free survival (RFS) and overall survival (OS) was found, but sample size was relatively small ( $n = 280$ ) and toxicity was high and severe.<sup>18</sup> Since then, many RCTs and studies have failed to consistently deliver evidence of benefit on DMFS and OS.<sup>19-25</sup> Meta-analyses in subsequent years found an effect on RFS, but produced contrary results concerning DMFS and OS.<sup>26-28</sup> 'Final' meta-analyses thereafter showed a statistically significant though small benefit on OS (HR = 0.89) - irrespective of different duration and dosage regimes.<sup>29-31</sup> Still controversy remains as clinical relevance of these findings is questioned given severe toxicity - requiring dose reduction or discontinuation - up to 60% and the associated increased care consumption and costs.<sup>27,30,32-38</sup> Also, it is clear that health-related quality of life of patients is significantly negatively influenced by IFN treatment.<sup>38-40</sup>

Identifying a subgroup of patients that benefit the most from adjuvant IFN, thereby preventing unnecessary overtreatment should be an aim for future research. Thus far, several attempts have been made to identify biomarkers, predictors of effectiveness or sensitivity and patient characteristics.<sup>41</sup> Patients with melanoma stage IIB/III-N1 seem to benefit most from



(pegylated) IFN- $\alpha$ -2b on RFS and distant metastasis-free survival (DMFS).<sup>21,42</sup> Ulceration is thought to be a predictor of effect of adjuvant IFN on RFS.<sup>43-45</sup> In the meta-analysis of EORTC 18991 and 18952 patients with both stage IIB/III-N1 and ulceration of primary tumour had HR of 0.58-0.69 for RS, DMFS and OS.<sup>44</sup>

EORTC 18081 investigates whether pegylated IFN- $\alpha$ -2b improves survival of patients with stage II ulcerated melanoma. Patients with ulcerated T(2-4b)NOMO melanoma will receive adjuvant pegylated IFN- $\alpha$ -2b (3  $\mu$ g/kg weekly) for 2 years versus placebo. Interestingly, besides recurrence-free survival, distant metastasis free survival and overall survival, this trial also measures quality of life (QoL). Final data collection is estimated to be complete by April 2020 for the primary outcome measure RFS (NCT01502696).

## Vaccines

Melanoma vaccines have the goal to induce long lasting immunity against melanoma to prevent the development of metastases, but heterogeneity of melanoma cells express many different tumour-associated antigens. Vaccines need to be representative of all these different tumour-associated antigens for antigen-presenting-cells (APC) to induce an adequate immune response. In early-stage melanoma, antigen heterogeneity is low and effectiveness of adjuvant vaccines is thought to be higher in this situation. Though less tumour burden also means that there can be too little autologous tumour available for processing tumour-specific antigens. Autologous tumour cell derived vaccines are a good example of personalized medicine, but preparation of these vaccines is time-consuming and can be challenging compared to allogeneic vaccines.

In adjuvant setting Melacine, an allogeneic melanoma tumour cell lysate vaccine, showed no effect on 5-year survival, but an exploratory analysis of  $\geq 2$  matching HLA class I antigens patients (especially HLA-A2 and HLA-C3) had a significant improvement in DFS compared to observation ( $p = 0.0005$ ).<sup>46,47</sup> In this subgroup, treatment effect was maintained and had an effect on 10-year survival (72% vaccine vs 48% observation,  $p = 0.002$ ).<sup>48</sup>

A study on adjuvant treatment with the allogeneic vaccine Canvaxin in stage III resected melanoma was terminated after an interim analysis showed that there was low probability of demonstrating significant improvement, although researchers did observe a correlation between immune response and survival.<sup>49,50</sup> A large phase III trial demonstrated that Ganglioside GM2 (glycolipid expressed in cancer) did not improve survival in stage II melanoma, in contrary it showed to be harmful.<sup>51</sup>

In 2014, Wilgenhof et. al. showed encouraging results in completely resected stage III/IV melanoma treated with dendritic cell (DC) therapy. Autologous DCs loaded with full-length melanoma-associated antigen mRNA ex vivo were administered intradermally in 30 patients

for 7 to 15 weeks. After mean follow-up of 6.4 years one-third of patients remained disease free and more than 50% were still alive - median overall survival wasn't reached.<sup>52</sup>

A phase II/III trial from Argentina compares adjuvant CSF-470 vaccine with low dose IFN- $\alpha$ -2b administered for 2 years in stage IIB to III melanoma. CSF-470 vaccine consists of four lethally irradiated melanoma cell lines and is administered with Bacille Calmette-Guerin (BCG) and Granulocyte-macrophage colony-stimulating factor.<sup>53</sup> This trial is currently open for accrual and final data collection date is December 2018 (NCT01729663).

### Anti CTLA-4 antibody

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) is an inhibitory immune checkpoint receptor that decreases patients own immune response. Binding of CTLA-4 to antigen presenting cells (APC) will lead to T-cell inhibition. Blocking the T-cell inhibitory CTLA-4 with anti CTLA-4 antibody ipilimumab augments T-cell activation and proliferation.<sup>54</sup> Ipilimumab can also induce severe adverse events of which clinicians need to be aware. Most common adverse events are immune-related and consist of diarrhoea, colitis (sometimes severe with perforation of the bowel), endocrinologic adverse events (eg. hypophysitis and hypopituitarism, thyroiditis and hypothyroidism and adrenal dysfunction), vitiligo, pruritus, rash and severe fatigue.

In 2010 and 2011 two double blind, phase III RCTs showed a statistically significant benefit of ipilimumab on median OS in patients with unresectable stage III-IV melanomas who were treatment naïve or progressed after previous therapy.<sup>55,56</sup> Although toxicity grade 3-4 occurred in 10-38%, median duration of response among patients with complete or partial response was higher<sup>56</sup> and a disease control rate of 28.5% was achieved.<sup>55</sup> Based on these two studies the European Medicine Agency (EMA) approved ipilimumab (3 mg/kg) for unresectable stage III and IV melanoma in 2011.

First results of phase III placebo-controlled trial (EORTC-18071) of adjuvant ipilimumab in patients with high-risk stage IIIa-c melanoma after complete resection showed promising results, though also a high rate of severe adverse events was observed. Ipilimumab was given in a high-dose of 10mg/kg every 3 weeks for four courses, repeated every 3 months up to 3 years. Hazard ratio for RFS of ipilimumab compared to placebo was 0.75 (95%CI 0.64-0.90,  $p = 0.0013$ ), but immune related toxicity grade 3 or 4 occurred in 45% (versus 2% in placebo group) and 49% discontinued because of adverse events. With adequate management of adverse events severity reduced to baseline or grade 1 toxicity in 90%. Similar to IFN trials patients with microscopic nodal tumour burden and ulceration might benefit most from ipilimumab as adjuvant therapy. Longer follow-up is necessary for secondary outcomes (DFMS and OS) and quality of life (QoL) data still have to be reported.<sup>57</sup>

ECOG-E1609 trial currently recruiting patients in the US will compare ipilimumab 10mg/kg or 3mg/kg versus high dose recombinant IFN- $\alpha$  in resected stage IIIB, IIIC and IV(M1a/b)

melanomas (NCT01274338). This study will show if ipilimumab is more effective than IFN- $\alpha$  in the adjuvant setting, with as primary outcome measures OS, RFS and as secondary outcome measures QoL and toxicity. Final data collection date for primary outcome measures is expected in May 2018.

In 2011 a phase II trial was conducted on adjuvant ipilimumab (plus tyrosinase, gp100 and MART-1 vaccine) in 75 patients with resected stage IIIC and IV melanoma. This trial had a median follow-up of 29.5 months and 2-year OS was 86% (95% CI 75 – 92%). Median RFS in patients with stage IV melanoma was 40.5 months compared to historical trials of 7.2 months and median RFS for stage IIIC was not yet reached. Forty-nine percent of patients finished treatment of 7 doses ipilimumab 10mg/kg and 27% continued on maintenance dose of 10mg/kg every 3 months. Grade II-IV toxicity was observed in 37% and 23% had to stop treatment because of ipilimumab related adverse events. No drug-related deaths occurred and toxicity was reversible in most of the cases.<sup>58</sup>

A small phase II trial from France will investigate ipilimumab 3mg/kg in patients with inoperable in-transit metastasis localized on the limb (stage IIIB or IIIC: TxN2c or N3) after isolated limb perfusion and results are expected march 2020 (NCT02094391).

### Anti-PD1 antibody

Programmed death-1 (PD1) is another cell-surface small receptor on T-cells that, like CTLA-4, is inhibitory to the immune response of T-cells. By binding to its ligand PD-L1 on normal tissue cells an excessive immune response is prevented and tolerance to self-antigens is maintained. Overexpression of PD-L1 in melanoma cells inhibits T-cell activation and proliferation.<sup>59</sup> Anti-PD1 antibodies block PD1 on T-cells preventing PD-L1 to bind and inhibit T-cell function. Adverse events occur less frequent with anti-PD1 antibodies than with ipilimumab, but toxicity profile is comparable to ipilimumab. Main adverse events are diarrhoea, colitis, hepatitis and liver failure, endocrinopathies, nephritis and reduced kidney function. Also fatigue and skin toxicity consisting of rash, pruritus and vitiligo can be disabling for patients.

Anti-PD1 immune checkpoint inhibitors nivolumab and pembrolizumab were approved by EMA shortly after each other in 2015 for unresectable stage IIIC and IV melanomas. Nivolumab proved significantly beneficial in patients with wild-type BRAF, advanced melanoma with a 1-year OS rate of 72.9% (95% CI, 65.5 – 78.9) compared to 42.1% (95% CI, 33.0 – 50.9) in dacarbazine group (HR for death = 0.42 (99.79% CI, 0.25 – 0.73;  $p < 0.001$ )). Objective response rate was 40% with grade 3 and 4 toxicity of only 11.7%.<sup>60</sup> Weber et al. found comparable results.<sup>61</sup> HR for PFS for pembrolizumab were 0.50 (95% CI, 0.39 – 0.64;  $p < 0.0001$ ) and 0.57 (95%CI, 0.45 – 0.73;  $p < 0.0001$ ) in the KEYNOTE-002 trial (final report will include OS).<sup>62</sup> HRs for death in the KEYNOTE-006 trial were significantly more beneficial

compared to ipilimumab (0.63 and 0.69 for 10mg/kg resp. every 2wks or 3wks ( $p < 0.001$ )). Response rates of pembrolizumab varied from 21% to 33.7%.<sup>62</sup>

Following these promising results (in general and compared to ipilimumab) adjuvant trials are currently being enrolled. In the CheckMate-238 trial adjuvant treatment with nivolumab 3mg/kg is compared to ipilimumab 10mg/kg in resected stage IIIB/C or IV melanoma. Patients will receive 1 year of adjuvant treatment unless disease recurrence or toxicity necessitating discontinuation or consent withdrawal. First results of this randomized, double blind, phase III trial are expected in 2019 (NCT02388906).

The KEYNOTE-054 trial started enrolling patients in 2015 for adjuvant pembrolizumab versus placebo in resected stage III melanoma. Pembrolizumab is administered in a standard dose of 200mg intravenously every 21 days for 1 year. Primary outcome measure RFS and secondary outcome measures DMFS and OS will be investigated in both PD-L1 negative and positive patients. Estimated completion date for KEYNOTE-054 is 2023 (NCT02362594).

Another large phase III trial currently recruiting patients from the U.S. will compare adjuvant high dose IFN- $\alpha$  and anti-PD1 agent pembrolizumab. High dose IFN or pembrolizumab is administered 52 weeks postoperatively in stage III and resectable stage IV melanomas. Outcomes measures are RFS, OS, toxicity and QoL. June 2020 is set as date for final data collection (NCT02506153).

Last year the FDA also approved the combination of immune checkpoint inhibitors nivolumab and ipilimumab for treatment of advanced melanoma. In a phase I dose-escalation trial Postow et. al. studied 72 melanoma patients (wild-type BRAF) receiving nivolumab plus ipilimumab. Although toxicity grade 3-4 occurred in 54%, objective response rate (ORR) was 61% and complete response rate was 22% (odds ratio 12.96 (95% CI, 3.9 – 54.5)).<sup>63</sup> Of all patients with an ORR 82% had ongoing response at the end of study. Median PFS for ipilimumab was 4.4 months, but wasn't reached for nivolumab and ipilimumab (median follow-up not mentioned).<sup>63</sup> These results were confirmed in a phase III trial by Larkin et. al. Patients receiving nivolumab 1mg/kg every 3 weeks plus ipilimumab 1mg/kg every 3 weeks for 4 doses continuing with nivolumab 3mg/kg every 2 weeks, ORR was 57.6% with a complete response rate of 11.5%. Median PFS of 11.5 months in nivolumab plus ipilimumab was significantly higher compared to nivolumab or ipilimumab. However, treatment related toxicity grade 3-4 occurred in 55%.<sup>64</sup> Because of these very promising results, the first phase I and II trials on anti-PD1 and anti-CTLA-4 in adjuvant and neoadjuvant setting are being conducted. Neoadjuvant trials will be discussed in a later paragraph.

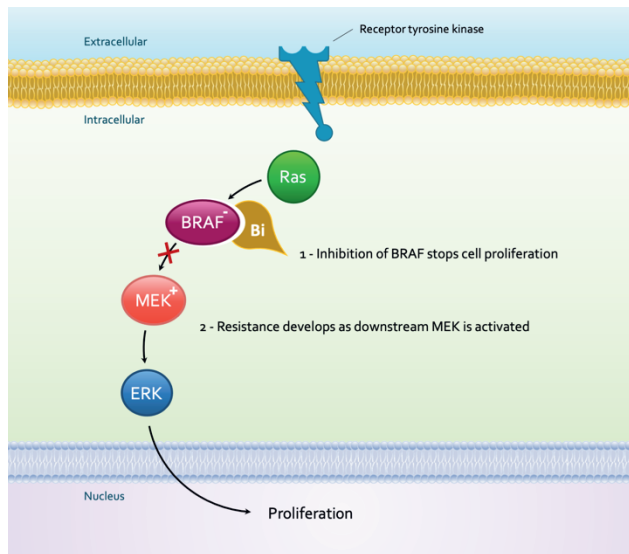
Phase II trial BrUOG-324 from the U.S. will investigate toxicity and RFS in patients with resected stage IIC, III and IV who receive 6 months adjuvant nivolumab or ipilimumab. Nivolumab 3mg/kg is administered every 2 weeks and ipilimumab 1mg/kg every 6 weeks (NCT02656706). In

December 2016 results of a phase I trial of nivolumab plus ipilimumab versus nivolumab plus a vaccine for stage IIIC or IV melanoma are expected. Nivolumab plus ipilimumab are given in escalation dose and the vaccine consists of two peptides (gp100 and NYE-ESO-1) and montanide ISA 51VG. Outcomes are RFS and OS (NCT01176474).

## BRAF and MEK inhibitors

BRAF mutations are associated with intermitted sun exposure and are present in approximately 50 percent of melanomas.<sup>65</sup> Activated threonine kinase BRAF plays an important role in the cell proliferation by activation of the Mitogen-Activated Protein Kinase (MAPK)-pathway.<sup>66</sup> Inhibition of BRAF with the targeted therapies vemurafenib and dabrafenib has been subject of study. BRAF inhibitors are able to initiate a dramatic tumour response in unresectable stage III-IV BRAF mutation positive melanoma patients<sup>67</sup>, though after 6 to 8 months most patients will develop resistance to BRAF inhibitors and have progression of disease.<sup>68,69</sup> This resistance is partly explained by the parallel activation of MEK, a downstream tyrosine kinase in de MAPK-pathway (Figure 2). Combining a BRAF inhibitor with a MEK inhibitor – dabrafenib with trametinib or vemurafenib with cobimetinib – resulted in better PFS, OS and response rates.<sup>70-72</sup> Most common adverse events of BRAF and MEK inhibitors are arthralgia, fatigue, alopecia, nausea, and diarrhea.<sup>73</sup> Besides dermatologic adverse events rash, photosensitivity and hyperkeratosis, new skin cancers such as cutaneous and mucosal squamous cell carcinomas can develop in BRAF inhibitors.<sup>74</sup>

These findings in patients with advanced melanomas have led to two large phase III adjuvant RCTs of which the BRIM-8 trial will evaluate single agent BRAF inhibitors as adjuvant therapy. This placebo-controlled phase III RCT closed recently its accrual, and will investigate the adjuvant treatment with the BRAF inhibitor vemurafenib in BRAFV600 mutation-positive stage III melanoma (lymph node metastasis >1mm for IIIa). Patients in the experimental arm will receive vemurafenib 960mg b.i.d. in cycles of 28 days for a 52-week period in total. Outcome measures will be efficacy (DFS, DMFS, OS), safety and pharmacokinetics of adjuvant vemurafenib (NCT01667419).



**Figure 2** Development of resistance after BRAF inhibition. BRAF inhibition in the Mitogen Activated Protein Kinase (MAPK) pathway initially stops cell proliferation, but resistance to BRAF inhibitors develops due to parallel activation of downstream MEK tyrosine kinase.

In the COMBI-AD trial adjuvant treatment with BRAF and MEK inhibitors dabrafenib and trametinib combined is compared to matched placebo in patients with BRAFV600 mutation-positive stage III melanoma. Dosage for dabrafenib is 150mg twice daily and for trametinib is 2mg once daily for 1 year. Primary outcome measure is RFS and most important secondary outcome measures are DMFS, OS and safety. The accrual has closed and estimated study completion date is July 2018 (NCT01682083).

## Neoadjuvant therapy

Neoadjuvant therapy has not only improved outcomes in some solid tumours, it also eases surgical resectability and provides better local control. In addition, efficacy of treatment can be evaluated preoperatively by monitoring tumour response and postoperatively by pathologic evaluation of the resected tumour tissue. This allows a more tailored treatment as therapy can be switched in patients who are not responding to the neoadjuvant treatment administered.

Although neoadjuvant therapy for high-risk melanomas is still in early stage, rapid developments of immunotherapy in recent years are also finding their way to neoadjuvant phase I and II trials. Here we will discuss current neoadjuvant trials.

## Immunotherapy

### Interferon

Moschos et al. enrolled a trial in which 20 patients with stage IIIB-C melanoma were enrolled for neoadjuvant high dose INF- $\alpha$ -2b four weeks prior to surgery, continuing for 48 weeks

postoperatively. Before neoadjuvant therapy, patients underwent SNB, which was immunohistochemically compared to tumour tissue from the radical regional lymphadenectomy after neoadjuvant therapy. Eleven patients had a clinical response, which was a higher response rate than in adjuvant setting, generating hypothesis that patients could benefit from neoadjuvant IFN.<sup>75</sup> However, no study has confirmed these results of higher response rates in the neo-adjuvant setting or proven a benefit on RFS or OS, yet.

A phase II trial – NAM-trial – on neoadjuvant Multiferon was prematurely ended and no results were reported ([www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu): 2010-022103-21). Multiferon is a multi-subtype interferon- $\alpha$  consisting of 6 interferon- $\alpha$  subtypes released by human leucocytes. There are currently no ongoing trials on neoadjuvant interferon.

### Anti CTLA-4 antibody

One phase I trial from the U.S. is recruiting patients with stage III (>N1b) melanoma comparing high dose ipilimumab 10mg/kg plus high dose IFN versus low dose ipilimumab 3mg/kg plus high dose IFN. Patients will receive 2 doses ipilimumab every 3 weeks prior to surgery and is continued for 46 weeks after surgery. High dose IFN is switched after 4 weeks to low dose IFN and continued for 48 weeks. This is a safety study on 40 patients with secondary outcome measures PFS and OS (NCT01608594).

### Anti-PD1 antibody

A neoadjuvant phase II trial, open for accrual, investigates nivolumab versus nivolumab plus ipilimumab. Patients with stage III and (oligometastatic) IV melanoma will receive neoadjuvant nivolumab 3mg/kg every 2 weeks or nivolumab 1mg/kg plus ipilimumab 3mg/kg every 3 weeks 8 weeks prior to surgery. Both arms will continue with nivolumab 3mg/kg 6 months postoperatively. Pathologic and immunologic response to neoadjuvant regimes will be evaluated and final completion date of data collection is expected in 2019 (NCT02519322).

The single institution OpACIN trial is set up in the Netherlands to compare nivolumab plus ipilimumab for 12 weeks postoperatively versus 6 weeks prior to surgery and 6 weeks postoperatively in patients with stage III melanoma (NCT02437279). This phase I trial will focus primarily on safety and T-cell response and secondarily on RFS and adverse events. Results are expected in 2018.

### BRAF and MEK inhibitors

Two trials are researching dabrafenib plus trametinib as neoadjuvant treatment in resectable high-risk melanoma. The Combi-Neo trial compares neoadjuvant dabrafenib 150mg twice a day plus trametinib 2mg once a day 8 weeks prior to surgery versus surgery alone in BRAF mutation positive stage III or (oligometastatic) stage IV melanoma. Prior to randomisation resectability of disease with safe margins is evaluated. This phase II trial will look at 1-year

relapse-free survival rate with estimated enrolment of 84 patients. This trial runs in the U.S. and the final data collection date is October 2017 (NCT02231775).

In a phase II pilot study from Australia with only an experimental-arm patients with BRAF mutation positive stage IIIB-IIIC melanoma will receive dabrafenib 150mg twice a day plus trametinib 2mg once a day 12 weeks before complete lymph node dissection. BRAF and MEK inhibitor combination is maintained for 40 weeks post-operative. Outcome measures 1-year relapse-free survival, complete response, partial response and disease status. Final data collection is expected in October 2017 (NCT01972347).

The single centre phase II REDuCTOR-trial in the Netherlands will evaluate neoadjuvant dabrafenib and trametinib in primarily unresectable BRAF mutation positive stage III or (oligometastatic) IV melanoma to allow surgical resection. This approach is distinctly different from other neoadjuvant trials as tumour reduction is necessary to enable complete resection of melanoma. Approximately 25 patients will receive neoadjuvant dabrafenib 150mg twice daily and trametinib 2mg once daily 8 weeks prior to surgery. Primary outcome measure is percentage of patients in whom complete resection is made possible by neoadjuvant treatment. Secondary outcome measures include RFS in resected patients, time to next treatment and OS (clinicaltrialsregister.eu: 2013-002616-28).

### Tamilogene Laherparepvec (T-VEC)

In February 2016 based on the OPTiM trial the first oncolytic virus T-VEC was approved by the EMA for advanced melanomas. T-VEC is made to replicate in tumour cells, lysate them and at the same time produce granulocyte macrophage-colony stimulation factor (GM-CSF) to promote antitumour response. The OPTiM trial compared GM-CFS subcutaneously with intralesional T-VEC in 436 patients. Although durable response rates were significantly higher for T-VEC (16.3% (95% CI: 12.1-20.5%) than for GM-CSF (2.1% (95%CI; 0-4.5%), improvement of overall survival was not significantly improved at primary analysis (HR = 0.75 (95% CI: 0.62-1.00;  $p = 0.051$ ). Subgroup analysis of stage IIIB/C, IVM1a and treatment naïve melanomas showed clear benefit on OS; HR = 0.57 (95% CI: 0.40-0.80) and HR = 0.50 (95% CI: 0.35-0.73, respectively).<sup>76</sup> Currently one phase II trial in the U.S. is recruiting patients for neoadjuvant T-VEC treatment of resectable stage IIIB-VIM1a melanomas compared to observation. Patients will receive 6 doses of T-VEC 12 weeks prior to surgery. Primary end point is efficacy of T-VEC for RFS and secondary outcome measures include OS. Results are expected in February 2022 (NCT02211131).

## Conclusion

Because of the high response rates of targeted therapies and the long-lasting benefit of immunotherapy observed in patients with metastatic melanoma, the results of the first (neo)adjuvant trials with these agents in high-risk locoregional melanoma are awaited with great



interest. Practice changing results can be expected of phase III, randomised, double-blind, placebo-controlled trials that are currently conducted or awaiting results. The phase I/II studies could deliver interesting clues for new treatment strategies and patient selection and will hopefully be followed by validation in phase 3 trials.

As seen in advanced melanoma, these new innovative therapies can evoke some (severe) adverse events and can have great impact on quality of life. Therefore, research in (neo)adjuvant trials should also take into account the effects on quality of life besides RFS and OS. Careful assessment of risk-benefit ratio by evaluating number needed to harm is necessary. In conclusion, we hope that the great efforts that have been made in advanced melanoma can also be successfully applied in high-risk melanoma and improve prognosis of patients with this serious disease. Informing surgeons about (neo)adjuvant treatment strategies and trials open for accrual can lead to higher resection rates, treatments and thereby potentially improve survival.

## Conflict of interest

A.J.M. van den Eertwegh reports serving on advisory boards of Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Applied Molecular Genetics Inc. and Roche. J.B.A.G. Haanen is on advisory boards of Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Roche, Pfizer, and NEON therapeutics and has received research funding from Bristol-Myers Squibb, Merck Sharp & Dohme, and Glaxo Smith Kline. Other authors declare no conflict of interest.

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