Preoperative *BRAF* inhibition in patients with irresectable locally advanced stage III melanoma

Marloes Faut[1], Mathilde Jalving[2], Gilles F Diercks[3], Geke A Hospers[2], Barbara L van Leeuwen[1] & Lukas B Been*[,1]

[1]Department of Surgical Oncology, Department of Surgery, University of Groningen, University Medical Center Groningen, Hanzeplein 1, P.O. Box 30.001, 9700RB Groningen, The Netherlands

[2]Department of Medical Oncology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, P.O. Box 30.001, 9700RB Groningen, The Netherlands

[3]Department of Pathology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, P.O. Box 30.001, 9700RB Groningen, The Netherlands

*Author for correspondence: Tel.: +315 0361 2317; Fax: +315 0361 1745; l.b.been@umcg.nl

Practice points

- Clinically evident resectable stage III melanoma is preferably treated by a surgical resection as neoadjuvant treatment is not an established treatment modality (yet) for stage III melanoma. After surgical resection, adjuvant therapy can be considered for these patients.
- When confronted with advanced stage III melanoma, full body imaging with fluorodeoxyglucose positron emission tomography-computed tomography or CT-scan including an MRI of the brain should be performed, to determine the extent of metastases and to exclude stage IV.
- Inoperable melanoma is generally treated as stage IV melanoma and can be treated with targeted therapy and immunotherapy. Neoadjuvant treatment with *BRAF* inhibitors can facilitate a surgical resection. However, it is only available in the context of clinical trials.
- The duration of neoadjuvant treatment with *BRAF* inhibitors remains to be determined based on the results of neoadjuvant trials. Surgical resection needs to be planned at the time of maximal response to neoadjuvant treatment.
- With the availability of systemic treatment options, previously inoperable patients can be treated with neoadjuvant *BRAF* inhibitors, a surgical resection and adjuvant immunotherapy. With the ongoing advancements made in systemic therapy for metastasized melanoma, it is likely that these treatment options continue to improve.
- It is to be determined by clinical trials if neoadjuvant treatment followed by a surgical resection for advanced stage III melanoma improves survival for these patients.

Aim: Neoadjuvant treatment of locally advanced disease with *BRAF* inhibitors is expected to increase the likelihood of a R0 resection. We present six patients with stage III unresectable melanoma, neoadjuvantly treated with *BRAF* inhibitors. **Methods:** Patients with unresectable, *BRAF*-mutated, stage III melanoma, were treated with *BRAF* inhibitors between 2012 and 2015. Unresectability was determined based on clinical and/or radiological findings. At maximal response, resection was performed. The specimen was reviewed to determine the degree of response. **Results:** In five of six patients a radical resection was achieved. Postoperative complications were unremarkable. In five of six resected specimens, vital tumor tissue was found. **Conclusion:** Neoadjuvant *BRAF* inhibitor treatment of locally advanced melanoma is feasible and has the potential to facilitate an R0 resection.

For stage III melanoma patients, 5-year overall survival is associated with tumor burden and ranges between 30 and 80% [1]. It is well established that a radical resection of stage III melanoma is prognostically favorable compared with an R1 resection. In some cases, an R0 resection is not possible due to tumor size and/or adherent vital structures

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such as neurovascular bundles impeding radical surgical treatment. In cases where stage III melanoma is deemed unresectable, patients are historically treated in a similar fashion to stage IV patients. Since the introduction of targeted therapy and immune checkpoint inhibitors, the prognoses for patients with unresectable stage III and IV melanoma have improved [2–6]. Approximately 50% of cutaneous melanomas harbor a *BRAF* mutation [7]. These patients can be treated with a *BRAF* inhibitor, alone or in combination with an *MEK* inhibitor. This results in exceptionally fast and extensive responses in approximately 50% of patients, within 6 weeks [3,8–9]. Median response duration for vemurafenib is 6.7 months, and 5.1 months for patients receiving dabrafenib [8,9]. The addition of an *MEK* inhibitor prolongs progression-free survival to a median of 9.3 months [4]. Using *BRAF* inhibitors as an induction treatment to reduce tumor size in unresectable stage III melanoma, paving the way for a radical surgical resection, is a logical next step. We present data on six unresectable stage III melanoma patients treated with *BRAF* inhibition neoadjuvantly in order to facilitate a surgical resection, at our center. To determine the response to *BRAF* inhibitor treatment, a grading system was created. The aim of this study was to describe the feasibility and pitfalls of this treatment approach.

Materials & methods
Study population
The population consisted of patients with locally advanced stage III melanoma that was deemed either unresectable due to encasement of adherent structures such as arteries, veins or nerves, or due to the mutilating nature of a resection. This study was conducted at the University Medical Center Groningen. This is a university hospital and tertiary referral center in the northern part of the Netherlands with a catchment area of 1.5 million inhabitants. Patients were included between 2012 and 2015. All patients tested positive for a therapy responsive *BRAF* mutation and had no history of prior *BRAF* inhibitor treatment. Locally advanced stage III melanoma was deemed unresectable based on clinical and/or radiological evaluation and after discussion during a multidisciplinary tumor board meeting. This multidisciplinary panel consisted of at least one surgical oncologist, radiologist (or nuclear medicine physician), medical oncologist, radiotherapist, dermatologist, pathologist and a neurologist. In all patients a fluorine-18 fluorodeoxyglucose positron emission tomography combined with a diagnostic contrast-enhanced CT scan of thorax and abdomen was performed, to exclude stage IV melanoma prior to start *BRAF* inhibitor treatment.

Study design

After medical evaluation and informed consent to the treatment plan, *BRAF* inhibitor treatment was commenced. Patients were treated with *BRAF* inhibition and, based on availability, combined with *MEK* inhibition. Monotherapy was the only available therapy as standard of care in the Netherlands before 2015. From mid-2015 onwards, combined dabrafenib and trametinib were available as standard of care.

Physical examination was performed at every outpatient clinic visit (every 2–4 weeks). Response evaluation by imaging was usually performed after 2 months of *BRAF* inhibitor treatment. This interval was prolonged if it was clinically evident that surgical resection could not be performed at that time and *BRAF* inhibitor treatment was tolerated well. Patients were treated until maximal response to *BRAF* inhibitor treatment. Maximal response was reached if there was no longer evidence of diminishing tumor size either by clinical or radiological examination. Resection was planned within 6 weeks of maximum response. Postoperative morbidity and mortality were assessed during a 30-day follow-up period. R0 resection was defined as a complete resection with tumor-free resection margins. After the surgical resection, follow-up was conducted by the surgical oncologist every 3 months by physical examination, serum LDH and S-100B levels and imaging when indicated.

Outcomes
Data were collected concerning patient characteristics, treatment regimen and treatment duration. Toxicity of neoadjuvant treatment was assessed at every outpatient clinic visit (every 2–4 weeks) and was retrospectively graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by evaluation of the electronic health records [10]. Histological sampling to determine *BRAF* mutation status was either performed on the primary tumor or a metastasis. After histological sampling, DNA extraction was performed using Cobas extraction-kit, Roche©. *BRAF* mutation analysis prior to September 2014 was performed using HRM screening and confirmation with Sanger sequence analysis. After September 2014, multiplex PCR and PGM/Ion-Torrent sequence analysis containing the following genes: *ALK, BRAF, EGFR, ERBB2, GNA11, GNAQ, KIT, KRAS, NRAS, PDGFRA* and *PIK3CA* was performed. Pathology specimens were reviewed by a melanoma pathologist, in particular

Table 1. Response grading system to BRAF inhibitor treatment.

| Response	Explanation
No response	No reduction of vital tumor cells in the resected specimen
Partial response	Melanophages with fibrosis and/or necrosis with remaining vital tumor cells in the resected specimen
Complete response	No vital tumor cells identifiable. Only melanophages with fibrosis and/or necrosis in the resected specimen
Mixed response	A combination of no response and/or partial response and/or complete response in the resected specimen
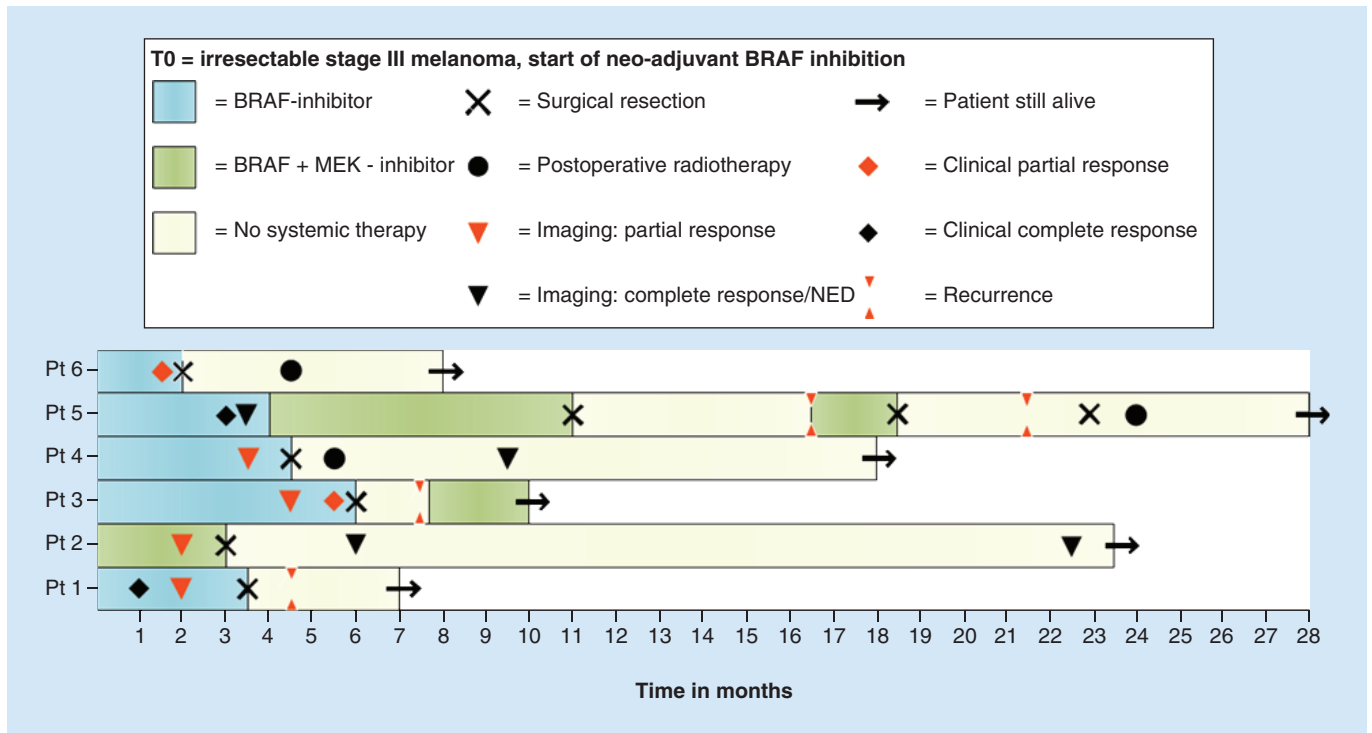
Figure 1.   Swimmers plot of all patients.

with respect to the estimated percentage of fibrosis with melanophages, necrosis and the percentage of vital tumor tissue in the specimen. A grading system for response to *BRAF* inhibitor treatment was created based on the percentage of vital tumor tissue, fibrosis, melanophages and/or necrosis in the resected specimen (Table 1).

Statistical analysis
Descriptive statistics were performed using IBM SPSS statistics, version 22.

Results
Patient & tumor characteristics
Six patients were treated neoadjuvantly with *BRAF* inhibitors between January 2012 and December 2015. One patient presented with unresectable melanoma at the time of the primary diagnosis. The other five patients presented with unresectable local disease after treatment of the primary melanoma, with a median interval of 60 months (range 2–100, Figure 1). The patient and tumor characteristics and treatment regimen are shown in Table 2.

BRAF inhibitor therapy
Patients were treated with *BRAF* inhibitors during a median of 3.8 (range 2–11) months (Table 3). Five of six patients experienced toxicity of *BRAF* inhibitor treatment, mainly grade 1 palmar-plantar erythrodysesthesia

Table 2. Clinical presentation & treatment regimen.

Patient	Age[†]	Gender	Site primary	Stage primary	Time[‡]	Metastatic site	Reason irresectable	Therapy of choice
1	37	Female	Lower extremity (left)	pT1BN1a	63	Inguinal and iliac lymph nodes	Encasement of adherent structures	Dabrafenib 150 mg twice daily
2	36	Female	Lower extremity (right)	pT3bN1a	60	Iliac and para-aortal lymph nodes	Encasement of adherent structures	Dabrafenib 150 mg twice daily + trametinib 2 mg once daily
3	66	Female	Lower extremity (right)	pT4bN2b	2	Right gluteal region and ilioinguinal nodal disease	Encasement of adherent structures and due to mutilating nature of resection	Dabrafenib 150 mg twice daily
4	73	Female	Head & neck (forehead)	≥pT3bN2b	Immediate	Locoregional and regional nodal disease	Mutilating nature of resection	Dabrafenib 150 mg twice daily
5	86	Female	Head & neck (submental)	pT2Nx	100	Submental	Mutilating nature of resection	Vemurafenib 480 mg twice daily switched to dabrafenib 75 mg twice daily + trametinib 2 mg once daily
6	49	Male	Head & neck (right cheek)	pT3aN1a	6	Locoregional and regional nodal disease	Mutilating nature of resection	Dabrafenib 150 mg twice daily

[†]Age is defined as age at presentation with irresectable melanoma.
[‡]Time is defined as time in months between treatment of primary tumor and detection of locally advanced melanoma.

Table 3. Overview of BRAF inhibitor treatment.

Patient	BRAF therapy (months)	Response on imaging	Highest toxicity grade[†]	Resection	Postoperative complications[‡]	Hospital admittance (days)	Additional therapy	Status at last visit
1	3.5	Partial response	1	R1	No	9	No	AWD
2	3	Partial response	3	R0	Retroperitoneal hematoma (Grade IIIb)	6	No	NED
3	4	Partial response	2	R0	Wound infection (Grade II)	9	No	DOD
4	4.5	Partial response	–	R0	No	6	Radiotherapy	NED
5	11	Complete response	2	R0	No (3 × resection)	4	Radiotherapy	NED
6	2	Not assessed	1	R0	No	5	No	NED

[†] Grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
[‡] Grading according to Clavien–Dindo grading system for complications [30].
AWD: Alive with disease; DOD: Dead with disease; NED: No evidence of disease.

syndrome, headache and grade 2 alopecia. Patient two suffered from grade III headache, for which she was admitted to the hospital. All patients recovered completely after treatment discontinuation.

Surgical resection

Surgical resection was performed *lege artis*. Fibrosis of tumor tissue was frequently seen. This added technical difficulty to the procedure. However, this did not lead to surgical complications intraoperatively. An R0 resection was achieved in five patients. Median postoperative hospital stay was 6 days (range 5–9). One patient was readmitted 15 days after discharge due to a retroperitoneal hematoma presenting with fever, abdominal pain, leukocytosis and hydronephrosis. The hematoma was caused by postoperative bleeding and was resolved by re-exploration; the

Patient	Pathology specimen	Vital tumor?	% Vital tumor	Fibrosis?	% Fibrosis + melanophages[†]	Necrosis?	% Necrosis?[†]	Pathological response[‡]
1	5 lymph nodes	No	0	No	0	No	0%	Partial
	1 large lymph node	Yes	60%	No	0	No	40%	
2	5 lymph nodes	No	0	Yes	20%	Yes	80%	Complete
3	8 superficial lymph nodes	No	0	Yes	100%	No	0	Mixed
		Yes	5%	Yes	95%	No	0	
	1 deep lymph node	No	0	Yes	100%	No	0	
	Skin & soft tissue gluteal region							
4	Primary melanoma:	Yes	95%	Yes	5%	No	0	Mixed
	Parotis:	Yes	95%	No	0	Yes	<5%	
	2 lymph nodes level 2:	Yes	100%	No	0	No	0	
	2 lymph nodes level 3:	Yes	100%	No	0	No	0	
	Lymph node level 3:	Yes	70%	No	0	Yes	30%	
	Lymph node level 5:	Yes	50%	No	0	Yes	50%	
	Lymph node level 5:	Yes	80%	No	0	Yes	20%	
	Lymph node level 5:	No	0	No	0	Yes	100%	
5	First resection:	Yes	80%	Yes	20%	No	0	Partial
	Resection 1st recurrence:	Yes	90%	No	0	Yes	10%	Partial
	Resection 2nd recurrence:	Yes	100%	No	0	No	0	No
	3 Lymph nodes axilla	No	0	Yes	100% + melanophages	No	0	
6	2 in transit metastases	Yes	100%	No	0	No	0	Mixed
	3 satellite metastases	No	0	Yes	100% + melanophages	No	0	

[†] Given percentages are estimates.
[‡] According to the grading system in Table 1.

patient recovered fully. Another patient was readmitted 5 days after discharge with a wound infection. This resolved after intravenous administration of antibiotics and negative wound pressure therapy during 6 weeks. The 30-day postoperative period was uncomplicated in the remaining four patients.

Pathological evaluation

In one patient a complete pathological response was found, the five other resected specimens contained vital tumor tissue (Table 4). The degree of response to *BRAF* inhibitor treatment varied throughout the different resected specimens within the patients.

Follow-up

Three patients had a recurrence. In patient one, on imaging, response to *BRAF* inhibitor treatment was partial. There was diminution of tumor size in some lymph nodes. One week prior to resection *BRAF* inhibitor treatment was ceased and patient experienced complaints similar to the period prior to *BRAF* inhibitor treatment (abdominal pain), as well as a rise in S-100B levels, suggestive for a rapid progression. Perioperatively, the iliac lymph nodes encased the artery and vein. A safe procedure was not possible without dissecting tumor tissue. Consequently the tumor was perforated and the resection was irradical. One month after the R1 resection, a fluorine-18 fluorodeoxyglucose positron emission tomography-scan was performed to exclude potential stage IV disease before
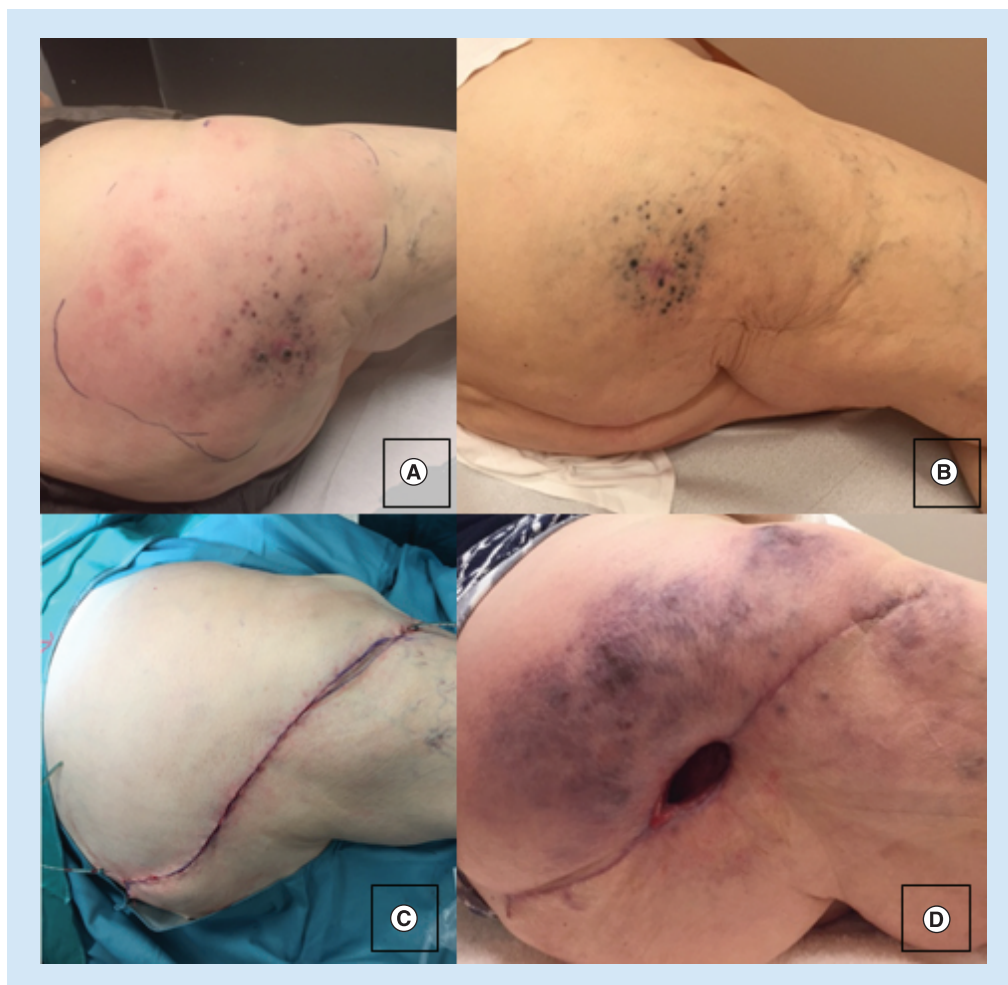
Figure 2.   Unresectable satellite metastases and lymphangitis on the right gluteal region. (A) Before treatment; **(B)** during treatment; **(C)** after surgical resection; **(D)** one month after surgical resection.

commencing adjuvant radiation therapy to the groin. A solitary pulmonary metastasis was identified for which surgical resection performed. Adjuvant radiation therapy was no longer indicated. Patient three suffered from a clinically evident local recurrence 1.5 months after R0 resection, with pigmented lymphangitis and satellitosis at the location where previous metastases had disappeared during *BRAF* inhibitor treatment. Due to the extent of the recurrence and the short disease-free interval, the local recurrence was deemed unresectable. *BRAF* and *MEK* inhibition was commenced, but the patient died due to metastatic disease (Figure 2). Patient five had a local recurrence after 5.5 months, this was located submentally, where the previous lymph node metastasis had disappeared during *BRAF* inhibitor treatment, and a second recurrence five months later. Both recurrences were treated by surgical resection. Due to the multiple resections of submental skin and concurrent reduction of available resection possibilities in case of subsequent recurrence, the last resection was followed by adjuvant radiation. At the time of writing with a median follow-up of 14 months, five patients are alive, and four patients have no evidence of disease. Patients are still in follow-up in the University Medical Center Groningen.

Discussion

This study shows that preoperative *BRAF* inhibitor treatment of unresectable stage III melanoma is feasible. Toxicity was minimal and there were few postoperative complications attributable to the neoadjuvant treatment.

In other tumor types, neoadjuvant chemotherapy either as mono treatment or in combination with radiation is an established treatment option, and has proven to be valuable in achieving R0 resections and local control after surgical treatment [11,12]. The desire for improved disease-free and overall survivals in melanoma patients

has led to investigation of neoadjuvant interferon and bevacizumab in patients with high-risk primarily resectable lymph node metastases. Clinical response was seen in approximately 50% of patients [13,14]. Neither significant improvement of disease-free survival nor overall survival was demonstrated in these studies. None of these studies have focused on unresectable stage III melanoma. Case reports describing successful induction of tumor response with *BRAF* inhibitors followed by a successful surgical resection in unresectable stage III melanoma are scarce [15–18]. One previously published retrospective patient series describes 15 patients with locoregionally advanced, *BRAF*-mutated, stage III melanoma. These patients were treated with *BRAF* inhibitors and six patients had a radical resection of residual disease. None of these patients were treated intentionally in a neoadjuvant fashion. Pathologic responses seen in the resected specimens were comparable to those in our series. The objective response rate was, however, lower, with only six out of 15 patients receiving surgical resection following *BRAF* inhibitor treatment [19].

Side effects due to *BRAF* inhibitor treatment in our series were comparable to results described in the literature [3,9].

In this series *BRAF* inhibitor treatment led to fibrosis of tumor tissue and added a challenge to the surgical procedure itself; however, it did not lead to intraoperative complications in our series. This is compatible with previous reports which do not describe increased postoperative complications after *BRAF* inhibitor treatment [19,20].

The use of *BRAF* inhibitors as a single therapy (or combined with an *MEK* inhibitor) in stage IV and unresectable stage III melanoma is standard of care. When melanomas harbor a therapy responsive *BRAF* mutation, treatment with *BRAF* inhibitors leads to objective rapid and impressive responses in 53% of patients treated with vemurafenib and 50% of patients treated with dabrafenib. In a small subset of patients (∼20%) durable responses of >2 years on the *BRAF* and *MEK* inhibitors combination have been described [21]. The possibility of long-term survival on *BRAF* inhibitor treatment complicates decisions on timing of surgical procedures after neoadjuvant *BRAF* inhibitor treatment. This is illustrated by patients three and five who were treated for >2 months before surgical resection of locally advanced stage III melanoma was planned (Figure 1). A risk of this long-term *BRAF* inhibitor treatment, is the possibility of disease progression and the concurrent loss of a surgical window during *BRAF* inhibitor treatment. This may be preventable by frequent response evaluation. Due to the fast responses seen with *BRAF* inhibitor treatment, a surgical resection can be planned after only weeks of response to *BRAF* inhibitor treatment, therefore the treatment period can be relatively short. The risk of disease progression during the first 6 weeks of treatment is approximately three percent [22–24]. Adequate timing of the surgical procedure is of great importance, this remains a challenging and multidisciplinary decision. The differences in treatment duration in this patient series underline this challenge.
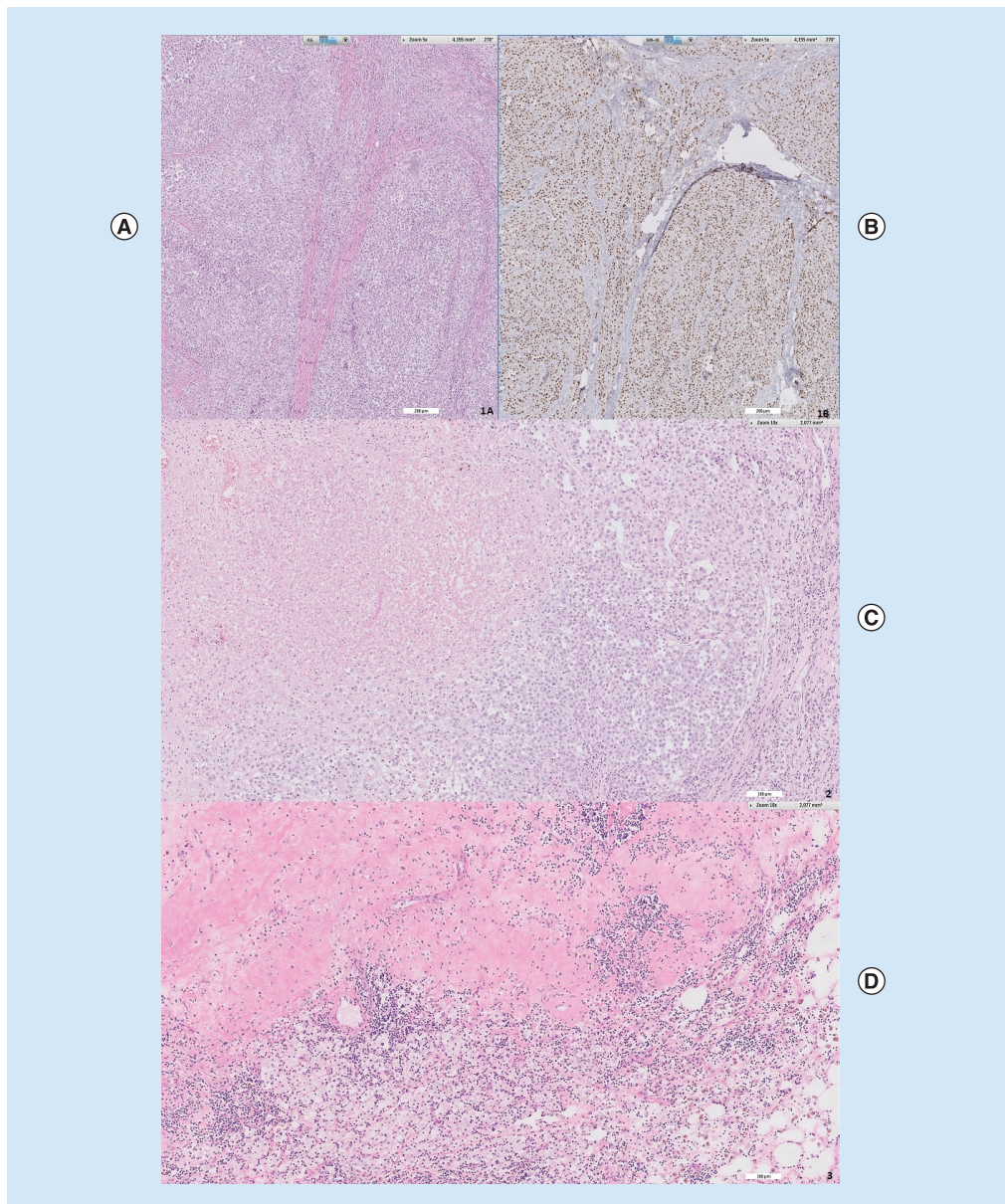
Pathological responses to *BRAF* inhibitor treatment varied throughout all the resected specimens within the patients in this study. Therefore, existing grading systems for neoadjuvant chemotherapy for instance as in breast carcinomas were not applicable, as responses to chemotherapy in breast carcinomas are more similar throughout the resected specimens within the patients [25]. In future neoadjuvant trials, grading systems should describe the percentage of vital tumor tissue throughout the resected specimen. Mixed responses were frequently seen in this study and should be described in future trials.

In this series three out of six patients had a recurrence of which two were local recurrences. Adjuvant radiation therapy decreases the risk of local recurrences after lymph node dissection compared with observation in high-risk stage III melanoma patients (21 vs 36% relapse) and can also be considered in this patient group [26]. In the future, neoadjuvant treatment followed by resection of advanced stage III melanoma could potentially be followed by adjuvant immunotherapy. The use of adjuvant ipilimumab improves 3-year recurrence-free survival in complete resected stage III melanoma patients compared with adjuvant placebo (46.5 vs 34.8%) [27,28].

There are several studies for neoadjuvant treatment of resectable stage III melanoma ongoing at this moment (ClinicalTrials.gov identifiers: NCT01972347, NCT02036086, NCT02858921, NCT02303951, Trialregister.nl identifier: NTR4654). These prospective studies will give more insight into response rates and probability of achieving R0 resections. In current and future clinical trials, a definite neoadjuvant treatment period is needed and should be defined, to help determine reproducibility and clinical applicability of data, as well as longer follow-up in larger populations to be able to truly assess long-term clinical benefit.

Conclusion

This experience with neoadjuvant *BRAF* inhibitor treatment shows that this treatment is feasible in unresectable stage III melanoma patients. It can lead to resectable stage III melanoma and facilitate an R0 resection in previously unresectable patients.

Figure 3.   Microscopic images of melanoma treated with neo-adjuvant BRAF-inhibition. (A) No response to BRAF inhibitor treatment; **(B)** no response to BRAF inhibitor treatment, SOX10 stain; **(C)** partial response to BRAF inhibitor treatment; **(D)** complete response to BRAF inhibitor treatment.

Future perspective

Future research should be aimed at determining which patients benefit from neoadjuvant and adjuvant treatment, in order to be able to determine in which patients treatment benefits outweigh treatment morbidity. In the Netherlands, adjuvant treatment with immunotherapy is only available in clinical trials and not as standard of care. In future trials adjuvant therapy should be strongly considered.

future science group

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Data collection by chart review was approved by the institutional review board of the University Medical Center Groningen.

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