Published in final edited form as:

Pigment Cell Melanoma Res. 2020 January ; 33(1): 86–95. doi:10.1111/pcmr.12813.

Neoadjuvant BRAF-targeted therapy in regionally advanced and oligometastatic melanoma

Zeynep Eroglu^{1,*,#}, Jennifer Eatrdes^{1,#}, Syeda Mahrukh Hussnain Naqvi², Youngchul Kim², Jeani Rich¹, Nalan Akgul Babacan¹, Andrew S Brohl¹, Joseph Markowitz¹, Amod Sarnaik¹, Jonathan Zager¹, Nikhil I. Khushalani¹, Vernon K Sondak¹, Jane Messina¹

¹Department of Cutaneous Oncology, Moffitt Cancer Center, Tampa, FL

²Department of Biostatistics and Bioinformatics, Moffitt Cancer Center, Tampa, FL

Abstract

Background: Current management of locoregional and oligometastatic melanoma is typically with surgery; however, some patients are unable to undergo resection due to location/size of their tumors and/or the anticipated morbidity of the surgery. While there are currently no established guidelines for neoadjuvant therapy in melanoma, neoadjuvant BRAF-targeted therapy may make resection more feasible.

Methods: A retrospective analysis was conducted of 23 patients with BRAFV600-mutant, stage III/IV melanoma treated with BRAF-targeted therapy prior to surgery, with no adjuvant treatment. Surgical specimens, preoperative imaging and clinical outcomes were evaluated.

Results: Ten of 23 patients (44%) attained a pathologic complete response (pCR), with no correlation between RECIST-response based on preoperative imaging and pathologic response. After a median of 43 months follow-up, only 1 patient (10%) with a pCR recurred; while 8 of 13 (62%) patients without a pCR recurred. Patients with a pCR had significantly improved relapse-free (RFS) and overall survival (OS) compared to patients with residual tumor.

Conclusion: Neoadjuvant BRAF-targeted therapy is associated with a high pCR rate in patients with stage III-IV melanoma, which may correlate with improved RFS and OS.

Keywords

BRAF-targeted therapy; melanoma; neoadjuvant therapy

*To whom correspondence should be addressed zeynep.eroglu@moffitt.org.

#These authors contributed equally

Study concept and design: Zeynep Eroglu, Jane Messina, Vernon Sondak, Nikhil Khushalani

Acquisition, analysis, or interpretation of data: Zeynep Eroglu, Jennifer Eatrdes, Jeani Rich, Nalan Akgul Babacan, Vernon Sondak, Jane Messina

Drafting of the manuscript: Zeynep Eroglu, Jennifer Eatrdes

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Syeda Mahrukh Hussnain Naqvi, Youngchul Kim

Introduction:

The current standard of care treatment of stage III melanoma involves surgical management followed by a discussion of observation versus postoperative adjuvant therapy. A similar strategy is now widely used in oligometastatic disease. While many patients with stage III and a select few patients with stage IV disease are able to undergo curative surgery, there may be significant morbidity associated with some surgeries, and others are considered unresectable or ‘borderline resectable’ due to the size and/or location of their tumors. Neoadjuvant (preoperative) therapy combines the potential benefits of standard postoperative adjuvant therapy (i.e., improved relapse-free survival [RFS] and possibly overall survival [OS] as well) with the ability to make surgery easier when tumors respond and the opportunity to assess the therapeutic efficacy of the treatment based on pathologic assessment of the resected tumor. In patients with stage IV disease, some patients may also receive upfront systemic therapy with surgery only utilized if they do not have an upfront response to therapy without disease progression elsewhere. Although neoadjuvant therapy has a well-established role in other cancer types such as breast, esophageal and rectal cancer, there are no established guidelines for neoadjuvant therapy in melanoma. Several phase II studies evaluated neoadjuvant chemotherapy, biochemotherapy, high-dose interferon or ipilimumab in patients with stage III melanoma, which were associated with either low response rates and/or high toxicity in unresectable metastatic disease. (Buzaid et al., 1998; Gibbs et al., 2002; Kounalakis et al., 2012; Koyanagi et al., 2005; Lewis et al., 2006; Moschos et al., 2006; Serrone et al., 2000; Tarhini et al., 2014)

More promising results have been noted with BRAF inhibition. About 45–50% of patients with melanoma harbor a BRAF mutation, and phase III trials comparing combined BRAF/MEK inhibitors to BRAF inhibitors alone in advanced unresectable melanoma have shown a clear benefit of dual inhibition with median progression-free survival of 11–14.9 months vs 7.2–8.8 months and objective (RECIST) response rates of 64–70% vs 50–53%. (Ascierto et al., 2016; Dummer et al., 2018; Long et al., 2015; Robert et al., 2015) BRAF/MEK-inhibitor therapy is also approved in the adjuvant setting after a study that showed dramatic improvement in RFS in stage III melanoma after complete lymphadenectomy with a year of adjuvant dabrafenib + trametinib. (Long et al., 2017) The rapid response kinetics, low rate of immediate disease progression without any clinical benefit and the overall favorable toxicity profile of BRAF inhibitors, especially combined with MEK inhibitors, make them ideal candidates for investigation in the neoadjuvant setting for regionally advanced or oligometastatic melanoma. Several case reports have shown significant tumor pathologic responses (50–98%) with neoadjuvant BRAF inhibition (duration ranging from 4 weeks to 10 months); four cases showed pathologic complete response (pCR), one showed near pCR with almost complete regression, with only one case that showed a persistent neoplastic nodule. (Fadaki et al., 2012; Kaidar-Person et al., 2014; Koers et al., 2013; Melnik et al., 2013; Rastrelli et al., 2014; Seremet et al., 2015) Two retrospective analyses of neoadjuvant BRAF-targeted therapy for unresectable stage III melanoma have also shown promising results, including clinical response enabling R0 resection in 12 of 13 patients following 6–8 weeks of BRAF-targeted therapy, with pCR in 31% of patients, and 2 of 6 patients with a pCR in another study after 6 months of neoadjuvant therapy. (Sloot et al.,

2016; Zippel et al., 2017). Most recently, a randomized phase II trial comparing neoadjuvant/adjuvant dabrafenib+trametinib to surgery with the option of postoperative adjuvant immunotherapy was stopped early, after only 21 patients were accrued, when a planned interim analysis showed dramatically better relapse-free survival for the neoadjuvant arm.(Amaria et al., 2018) After 8 weeks of neoadjuvant dabrafenib and trametinib, 11 of 13 (85%) patients achieved an objective radiographic response (2 complete and 9 partial responses), and no patients progressed. Seven (58%) of 12 patients in the neoadjuvant arm who underwent surgery achieved pCR.

Regardless, several issues remain in question, including the optimal duration of neoadjuvant BRAF inhibition prior to surgery, role of adjuvant therapy, whether imaging response correlates with pathologic response, whether pathologic response correlates with RFS and OS, and if responses can inform postoperative treatment decisions. Hence, a retrospective review of patients with resectable or borderline resectable/unresectable stage III or oligometastatic melanoma treated with neoadjuvant BRAF inhibition followed by resection was carried out to better characterize pathologic patterns of response and their correlation with clinical benefit.

Methods:

After Institutional Review Board approval, a retrospective review was conducted for patients with BRAFV600-mutant melanoma who received neoadjuvant BRAF targeted therapy prior to resection at Moffitt Cancer Center from 2011 to 2017. Patients either had resectable or borderline resectable/unresectable disease, such as bulky adenopathy that was surgically resectable but could potentially compromise neurovascular structures at resection. All patients underwent CT imaging both at baseline before initiation of BRAF-targeted therapy and prior to surgery; best response was assessed using RECIST 1.1 criteria. RFS and OS were calculated from the date of initial BRAF-targeted therapy and from date of surgery.

The resected specimens were analyzed for pathologic response and evaluated for distinctive patterns of response. Pathologic complete response was defined as no viable tumor cells observed. Pathologic major PR/near CR, pathologic partial response (pPR) and pathologic non-response ($\geq 50\%$ viable tumor) were also graded according to recently established guidelines.(Tetzlaff et al., 2018) Histologic response patterns were categorized into four groups: (i) necrotic, (ii) fibrotic/melanotic, (iii) hyalinized, and (iv) mixed patterns. Lymph nodes from dissection specimens were examined either in toto or with a single representative section from larger ($>4\text{mm}$) lymph nodes and evaluated with hematoxylin and eosin (H&E) staining. Immunohistochemical (IHC) staining for Melan-A or Sox-10 was utilized where the presence of tumor was difficult to evaluate on H&E, and to facilitate detection of detect minimal viable tumor in a background of necrosis or fibrosis. All stains were evaluated in conjunction with H&E to exclude false-positive staining of necrotic tumor or melanin-containing macrophages. Available pre-treatment tumor samples were also analyzed for expression of phosphorylated ERK (pERK) via IHC.

The Kaplan-Meier method and Greenwood's formula were used for the estimation of survival probabilities (RFS and OS) and the corresponding 95% confidence intervals (CIs).

Comparisons between groups were done with the log-rank test. Response outcomes were summarized using frequency and proportions. Statistical analyses were performed using SAS 9.4. All tests were two-sided; P values ≤ 0.05 were considered statistically significant.

Results:

Patient Characteristics

During the study timeframe, a total of 297 patients with melanoma had received BRAF-targeted therapy at Moffitt Cancer Center, not including patients on clinical trials. Of these, a total of 23 patients met the inclusion criteria. There were no patients identified who were treated with neoadjuvant intent but who could not proceed to surgery. All patients underwent surgery, regardless of imaging response to neoadjuvant BRAF-targeted therapy. Most patients had stage IIIC (n=10) or M1a (n=12) disease (AJCC v7). (Table 1 and 2). Twenty-two patients had melanoma with a BRAF V600E mutations; 1 with a BRAF V600K mutation. Patients received neoadjuvant BRAF-targeted therapy for a median duration of 6.6 months and did not receive adjuvant treatment afterwards (Figure 1). Eight patients received BRAF inhibitor alone (vemurafenib or dabrafenib) and fifteen received combined BRAF/MEK inhibition: vemurafenib + cobimetinib (n=2), dabrafenib + trametinib (n=12), or encorafenib + binimetinib (n=1).

Patient outcomes

Median follow-up was 43 months (range 10–95) from start of targeted therapy. Using CT imaging done after conclusion of neoadjuvant therapy and prior to surgery, the radiographic response rate (RECIST 1.1 criteria, complete or partial response) was 87%; 20 patients had partial responses (PR) and 3 patients had stable disease (SD). Patients were not restarted on BRAF-targeted therapy post-operatively unless they experienced eventual relapse of their melanoma. Nine of 23 patients (39%) developed relapse post-surgery; three of them (33%) developed CNS metastases. Four of the 9 patients who relapsed were restarted on BRAF/MEK targeted therapy. Two patients eventually progressed and died after repeated targeted therapy (after duration of 3 months and 2 months); one patient had partial response at last follow up (6 months) but was then lost to follow up, and one continues to have complete response and still remains on BRAF/MEK targeted therapy 2.5 years after time of relapse.

Histopathologic evaluation and outcomes

In the 23 cases, histologic evaluation of specimens showed necrosis in 4 (17%), fibrosis/melanosis in 1 (4%), hyalinization in 6 (26%), and a mixture of these features in 10 (43%), while no necrosis, hyalinization or fibrosis was seen in the other 2 cases (9%, Figure 2). Pathologic CR, defined as complete absence of viable tumor, was seen in surgical specimens of 10 patients (44%). Six of the pCR cases showed hyalinization, while the remaining showed mixed patterns.

Residual viable tumor (non-pCR) was present in 13 patients; eight of these patients (62%) had disease relapse. In contrast, only 1 of the 10 patients who obtained a pCR has relapsed (10%, $p=0.04$). In further breakdown of the non-pCR patients, 2 of the 4 with major PR/near

CR relapsed, while 1 of the 3 partial pathologic response, and 3 of the 6 pathologic non-response patients relapsed. Of note, radiologic tumor response per RECIST did not correlate with pathologic response or RFS (Figure 1,3). Nine of the 20 patients with PR by RECIST actually had a pCR on their surgical pathology, while another with stable disease per RECIST had a pCR (Figure 4). In 8 patients who had pre-treatment tumor tissue available, there was no evident association between pretreatment level of pERK expression and likelihood of pCR or RFS.

There was a statistically significant difference in RFS based on pathologic response, whether measured from the start of BRAF-targeted therapy or from the time of surgery (Figure 5). Median RFS has not yet been reached in the pCR group, while it was 10.5 months (95% CI 5.7–56.6) from date of surgery and 24.3 months (12 – 65.4) from start of BRAF-targeted therapy in the non-pCR group. Median RFS was 65.4 [24.3 – not reached] and 56.6 [10.2 – not reached] months for all 23 patients, from start of therapy or date of surgery respectively. There was also improved overall survival with a pCR, as all these patients are still alive, while five of the patients who did not obtain a pCR have died ($p=0.01$, Figure 6). There was no statistically significant difference in RFS discernable based on whether patients received single agent vs combination BRAF-targeted therapy.

Discussion:

There is currently significant interest in neoadjuvant systemic therapy in patients with borderline resectable or unresectable stage III or oligometastatic stage IV melanoma, but many questions remain unanswered. A trial from MD Anderson randomized patients to 8 weeks of neoadjuvant + 44 weeks of adjuvant dabrafenib+trametinib compared to surgery followed by standard of care treatment.(Amaria et al.) With a median follow-up of 18.6 months, 10 of 14 patients receiving neoadjuvant treatment were alive without relapse while all seven of those on the standard of care arm relapsed, and neoadjuvant treatment was associated with statistically significantly improved distant metastasis-free survival, with a median RFS of 19.7 months. In the NeoCombi trial from Melanoma Institute Australia, 35 patients with clinically resectable stage III melanoma were treated with 12 weeks of neoadjuvant followed by 40 weeks of adjuvant dabrafenib+trametinib. (Long et al., 2019) With a median follow-up of 27 months, 15 of 35 patients had not relapsed, with a median RFS of 23.3 months.

Of course there are important differences between those clinical trials and this retrospective analysis, including the variable lengths of the neoadjuvant regimens, the use of postoperative adjuvant therapy, and the exclusion of patients with unresectable melanoma from the prospective trials. Nevertheless, some similarities emerge: in the neoadjuvant arm of the MD Anderson trial, 3 of the 4 patients who relapsed recurred in the brain, while 8 of 20 recurrences in the Australia study were also in the brain; 33% of patients who relapsed in our analysis also recurred with CNS metastases. This has raised the question of whether the brain is a sanctuary site or whether neoadjuvant BRAF-targeted therapy in some way predisposes to development of brain metastases.(Ascierto and Eggermont) Also similar to a pooled analysis from MD Anderson and Australia trials, radiologic response assessed prior to surgery in this analysis did not always correlate with whether patients obtained a pCR at

surgery.(Menzies et al., 2017) In the MD Anderson trial, 3 of 5 patients with viable residual tumor had a relapse of their melanoma compared with only 1 of the 7 patients who obtained a pCR. In our analysis, the pCR rate was 43% and only 1 of 10 pCR patients have relapsed. In the Australia trial, while 17 of 35 patients (49%) achieved pCR, 8 of 17 (47%) with a pCR had disease relapse, while 12/18 (66%) with a non-pCR relapsed. In a pooled analysis of these two studies, 22% of the 24 patients with a pCR relapsed by 2 years. (Menzies et al., 2019)

There are numerous outstanding questions in consideration of neoadjuvant BRAF-targeted therapy, including the optimal length of treatment. While the MD Anderson trial used 8 weeks and the Australian study 12 weeks of neoadjuvant dabrafenib+trametinib, both employed adjuvant therapy to complete a year of treatment. One of the limitations of our analysis besides its retrospective nature is the different lengths of neoadjuvant treatment patients received, although our preferred approach has been to give six months of neoadjuvant treatment prior to surgery with no adjuvant therapy. Nevertheless, with a median follow-up of 43 months, to our knowledge this is the longest duration of follow-up of patients treated with neoadjuvant BRAF-targeted therapy. Our data also suggest that obtaining a true pCR is important with neoadjuvant BRAF-targeted therapy, as patients with a pathologic major PR/near CR were similarly likely to relapse as those without a pathologic response, although sample sizes are small. However, the benefit of achieving a complete pathologic response with neoadjuvant BRAF-targeted therapy and its correlation with RFS and OS still needs to be validated in larger clinical trials.

For patients with resectable or borderline/potentially resectable disease at presentation, neoadjuvant treatment also has to be considered in the context of data from adjuvant dabrafenib+trametinib in patients with stage III melanoma (Long et al., 2017), as it is not yet known how neoadjuvant vs adjuvant-only therapies compare in long-term relapse-free and overall survival. Furthermore, in our analysis, despite not receiving any adjuvant treatment, nearly all the patients who obtained a pCR after surgery had no disease relapse, raising the question of whether adjuvant treatment to finish a year of BRAF-targeted therapy is necessary in patients with a pCR. Questions also remain about how neoadjuvant and adjuvant anti-PD-1±anti-CLTA-4 therapies fit into the treatment paradigm for BRAF-mutant melanoma. Two small studies that evaluated neoadjuvant ipilimumab 3 mg/kg + nivolumab 1 mg/kg have shown pCR rates in 3 of 10 and 5 of 11 patients respectively, although grade 3/4 toxicity rates of up to 90% were observed (Amaria et al., 2018; Blank et al., 2018); ipilimumab at 1mg/kg with nivolumab 3mg/kg appears to be a less toxic regimen, while maintaining a similar pCR rate (Rozeman et al., 2019) Several studies are currently evaluating neoadjuvant triple-combinations of BRAF/MEK-inhibitors with immunotherapies (,).

In summary, achieving a pathologic complete response to neoadjuvant BRAF-targeted therapy may correlate with improved patient outcomes including improved relapse-free and overall survival, although this will need to be validated in prospective trials with longer follow-up. Until then, neoadjuvant BRAF-MEK inhibition represents a viable strategy for patients presenting with BRAF-mutant melanoma with borderline resectable or unresectable stage III and selected patients with oligometastatic stage IV disease.

Acknowledgements:

Moffitt Cancer Center NCI Skin SPORE (5P50CA168536) and Moffitt Cancer Center Total Cancer Care Initiative and Collaborative Data Services (P30-CA076292).

Funding:

This work has been supported in part by NCI Skin SPORE P50CA168536–01A1 and the Tissue Core Facility (P30-CA076292) at the H. Lee Moffitt Cancer Center & Research Institute.

Disclosures:

ZE received research funding from Novartis and was on an advisory board for Array Biopharma and Regeneron. JZ received research funding from Novartis and on the advisory board for Array Biopharma. VKS has advisory board relationships with Merck, Bristol-Myers Squibb, Regeneron and Novartis and serves on Data Safety Monitoring Boards for Array, Bristol-Myers Squibb, Novartis, Polynoma, and Pfizer. NIK has advisory board relationships with Bristol-Myers Squibb, EMD Serano, HUYA Bioscience International, Genentech, and Regeneron, has stock ownership of Bellicum Pharmaceuticals, Mazor Robotics, and TransEnterix, Inc., and serves on Data Safety Monitoring Boards for AstraZeneca. AS is a consultant/advisory board member for Iovance Biotherapeutics and received research funding from Iovance and Provectus. AB was on an advisory board for Bayer. JM has received institutional funding from Genoptix and Morphogenesis, was on an advisory board for Array and on Data Safety Board for Newlink Genetics.

References:

- Amaria RN, Prieto PA, Tetzlaff MT, Reuben A, Andrews MC, Ross MI, Glitza IC, Cormier J, Hwu W-J, Tawbi HA, et al. Neoadjuvant plus adjuvant dabrafenib and trametinib versus standard of care in patients with high-risk, surgically resectable melanoma: a single-centre, open-label, randomised, phase 2 trial. *The Lancet Oncology* 19, 181–193. [PubMed: 29361468]
- Amaria RN, Reddy SM, Tawbi HA, Davies MA, Ross MI, Glitza IC, Cormier JN, Lewis C, Hwu WJ, Hanna E, et al. (2018). Neoadjuvant immune checkpoint blockade in high-risk resectable melanoma. *Nature medicine* 24, 1649–1654.
- Ascierto PA, and Eggermont AMM Neoadjuvant therapy in melanoma: the next step? *The Lancet Oncology* 19, 151–153. [PubMed: 29361473]
- Ascierto PA, McArthur GA, Dreno B, Atkinson V, Liskay G, Di Giacomo AM, Mandala M, Demidov L, Stroyakovskiy D, Thomas L, et al. (2016). Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *The Lancet. Oncology* 17, 1248–60. [PubMed: 27480103]
- Blank CU, Rozeman EA, Fanchi LF, Sikorska K, Van De Wiel B, Kvistborg P, Krijgsman O, Van Den Braber M, Philips D, Broeks A, et al. (2018). Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. *Nature medicine* 24, 1655–1661.
- Buzaid AC, Colome M, Bedikian A, Eton O, Legha SS, Papadopoulos N, Plager C, Ross M, Lee JE, Mansfield P, et al. (1998). Phase II study of neoadjuvant concurrent biochemotherapy in melanoma patients with local-regional metastases. *Melanoma research* 8, 549–56. [PubMed: 9918417]
- Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liskay G, Garbe C, Schadendorf D, Krajsova I, Gutzmer R, et al. (2018). Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. *The Lancet Oncology* 19, 603–615. [PubMed: 29573941]
- Fadaki N, Cardona-Huerta S, Martineau L, Thummala S, Cheng ST, Bunker SR, Garcia-Kennedy R, Wang W, Minor D, Kashani-Sabet M, et al. (2012). Inoperable bulky melanoma responds to neoadjuvant therapy with vemurafenib. *BMJ case reports* 2012.
- Gibbs P, Anderson C, Pearlman N, Laclaire S, Becker M, Gatlin K, O'driscoll M, Stephens J, and Gonzalez R (2002). A phase II study of neoadjuvant biochemotherapy for stage III melanoma. *Cancer* 94, 470–6. [PubMed: 11900232]
- Kaidar-Person O, Eran A, and Bar-Sela G (2014). Complete pathologic response after neoadjuvant treatment with vemurafenib for malignant melanoma. *Journal of the American Academy of Dermatology* 70, e39–41. [PubMed: 24438978]

- Koers K, Francken AB, Haanen JB, Woerdeman LA, and Van Der Hage JA (2013). Vemurafenib as neoadjuvant treatment for unresectable regional metastatic melanoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 31, e251–3. [PubMed: 23569313]
- Kounalakis N, Gao D, Gonzalez R, Becker M, Lewis K, Poust J, Pearlman N, Robinson W, and Mccarter M (2012). A neoadjuvant biochemotherapy approach to stage III melanoma: analysis of surgical outcomes. *Immunotherapy* 4, 679–86. [PubMed: 22853754]
- Koyanagi K, O'day SJ, Gonzalez R, Lewis K, Robinson WA, Amatruda TT, Wang HJ, Elashoff RM, Takeuchi H, Umetani N, et al. (2005). Serial monitoring of circulating melanoma cells during neoadjuvant biochemotherapy for stage III melanoma: outcome prediction in a multicenter trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 23, 8057–64. [PubMed: 16258104]
- Lewis KD, Robinson WA, Mccarter M, Pearlman N, O'day SJ, Anderson C, Amatruda TT, Baron A, Zeng C, Becker M, et al. (2006). Phase II multicenter study of neoadjuvant biochemotherapy for patients with stage III malignant melanoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 24, 3157–63. [PubMed: 16809738]
- Long GV, Hauschild A, Santinami M, Atkinson V, Mandala M, Chiarion-Sileni V, Larkin J, Nyakas M, Dutriaux C, Haydon A, et al. (2017). Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. *The New England journal of medicine* 377, 1813–1823. [PubMed: 28891408]
- Long GV, Saw RPM, Lo S, Nieweg OE, Shannon KF, Gonzalez M, Guminski A, Lee JH, Lee H, Ferguson PM, et al. (2019). Neoadjuvant dabrafenib combined with trametinib for resectable, stage IIIB-C, BRAF(V600) mutation-positive melanoma (NeoCombi): a single-arm, open-label, single-centre, phase 2 trial. *The Lancet. Oncology*
- Long GV, Stroyakovskiy D, Gogas H, Levchenko E, De Braud F, Larkin J, Garbe C, Jouary T, Hauschild A, Grob JJ, et al. (2015). Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. *Lancet (London, England)* 386, 444–51.
- Melnik I, Lotem M, and Yoffe B (2013). A new role of vemurafenib as a neoadjuvant treatment of axillary and brain melanoma metastases. *Case reports in oncological medicine* 2013, 794239. [PubMed: 24455362]
- Menzies AM, Rozeman EA, Amaria RN, Huang ACC, Scolyer RA, Tetzlaff MT, Wiel B. a. V. D., Lo S, Tarhini AA, Tawbi H. a.-H., et al. (2019). Pathological response and survival with neoadjuvant therapy in melanoma: A pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC). *Journal of Clinical Oncology* 37, 9503–9503.
- Menzies AM, Rozeman EA, Amaria RN, Scolyer RA, Tetzlaff MT, Guminski A, Davies MA, Blank CU, Wargo JA, and Long GV (2017). Preliminary results from the international neoadjuvant melanoma consortium (INMC). *Journal of Clinical Oncology* 35, 9581–9581.
- Moschos SJ, Edington HD, Land SR, Rao UN, Jukic D, Shipe-Spotloe J, and Kirkwood JM (2006). Neoadjuvant treatment of regional stage IIIB melanoma with high-dose interferon alfa-2b induces objective tumor regression in association with modulation of tumor infiltrating host cellular immune responses. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 24, 3164–71. [PubMed: 16809739]
- Rastrelli M, Pigozzo J, Di Maggio A, Tosi AL, Sileni VC, and Rossi CR (2014). Neoadjuvant treatment with dabrafenib of unresectable localizations from occult melanoma. *Melanoma research* 24, 413–4. [PubMed: 24992629]
- Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, Lichinitser M, Dummer R, Grange F, Mortier L, et al. (2015). Improved overall survival in melanoma with combined dabrafenib and trametinib. *The New England journal of medicine* 372, 30–9. [PubMed: 25399551]
- Rozeman EA, Menzies AM, Van Akkooi ACJ, Adhikari C, Bierman C, Van De Wiel BA, Scolyer RA, Krijgsman O, Sikorska K, Eriksson H, et al. (2019). Identification of the optimal combination dosing schedule of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma (OpACIN-neo): a multicentre, phase 2, randomised, controlled trial. *The Lancet. Oncology*

- Seremet T, Lienard D, Suppa M, Trepant AL, Rorive S, Woff E, Cuylits N, Jansen Y, Schreuer M, Del Marmol V, et al. (2015). Successful (neo)adjuvant BRAF-targeted therapy in a patient with locally advanced BRAF V600E mutant melanoma. *Melanoma research* 25, 180–3. [PubMed: 25643238]
- Serrone L, Zeuli M, Sega FM, and Cognetti F (2000). Dacarbazine-based chemotherapy for metastatic melanoma: thirty-year experience overview. *Journal of experimental & clinical cancer research* : CR 19, 21–34. [PubMed: 10840932]
- Sloot S, Zager JS, Kudchadkar RR, Messina JL, Benedict JJ, Gonzalez RJ, Deconti R, Turner LM, Mccardle T, Smalley KS, et al. (2016). BRAF inhibition for advanced locoregional BRAF V600E mutant melanoma: a potential neoadjuvant strategy. *Melanoma research* 26, 83–7. [PubMed: 26731560]
- Tarhini AA, Edington H, Butterfield LH, Lin Y, Shuai Y, Tawbi H, Sander C, Yin Y, Holtzman M, Johnson J, et al. (2014). Immune monitoring of the circulation and the tumor microenvironment in patients with regionally advanced melanoma receiving neoadjuvant ipilimumab. *PloS one* 9, e87705. [PubMed: 24498358]
- Tetzlaff MT, Messina JL, Stein JE, Xu X, Amaria RN, Blank CU, Van De Wiel BA, Ferguson PM, Rawson RV, Ross MI, et al. (2018). Pathological assessment of resection specimens after neoadjuvant therapy for metastatic melanoma. *Annals of oncology : official journal of the European Society for Medical Oncology* 29, 1861–1868. [PubMed: 29945191]
- Zippel D, Markel G, Shapira-Frommer R, Ben-Betzalel G, Goitein D, Ben-Ami E, Nissan A, Schachter J, and Schneebaum S (2017). Perioperative BRAF inhibitors in locally advanced stage III melanoma. *Journal of surgical oncology*.

Significance:

This is an analysis of neoadjuvant BRAF-targeted therapy in patients with resectable or borderline resectable/unresectable melanoma treated for a median of 6 months prior to surgery, with no subsequent adjuvant treatment. These 23 patients have a median follow-up of over 3.5 years, which to our knowledge represents the longest follow-up to date for neoadjuvant therapy in melanoma. Only 1 in 10 patients who obtained a pathologic complete response (pCR) had recurrence, and these patients had significantly improved relapse-free and overall survival in comparison to those without a pCR at surgery. These results suggest that pathologic complete response (but not near-complete response or partial response) correlates with both improved relapse-free and overall survival in these patients.

Figure 1:
Swimmer plot with overall survival of all patients after start of BRAF-targeted therapy, grouped by pathologic and RECIST response.

A: Pattern-Necrotic (CR), Regimen: Dabrafenib/Trametinib (7 mo.)

C: Pattern - Hyalinized (CR), Regimen:Dabrafenib/Trametinib (6mo.)

B: Pattern- Fibrotic/melanotic (PR) Regimen: Dabrafenib/Trametinib (7 mo.)

D: Pattern - Mixed necrotic/melanotic (CR) Regimen: Dabrafenib/Trametinib (4 mo.)

Figure 2:

Histologic patterns of response in resected melanoma specimens. H&E stains show the following patterns: (A) necrotic, (B) fibrotic/melanotic, (C) hyalinized, (D) mixed necrotic/melanotic.

Figure 3:
Relapse-free survival (RFS) based on radiographic response. There was no statistical significance between response by imaging and relapse-free survival. RECIST response category: partial response (red), stable disease (green).

At start of neoadjuvant therapy 3/7/16

Following neoadjuvant therapy, prior to surgery 9/21/16, RECIST SD

Pre-treatment neck mass pathology

Neck node dissection - Complete pathologic response (necrotic and fibrotic/melanotic mixed pattern)

Figure 4:

Patient treated with 6 months of neoadjuvant dabrafenib and trametinib. CT imaging at end of neoadjuvant treatment shows stable disease, while surgical tumor specimen showed a pathologic complete response.

Figure 5:

Relapse-free survival based on pathology response: RFS of patients treated with neoadjuvant BRAF-targeted therapy from start of BRAF inhibition (A) and from time of surgery (B). Patients with pCR (blue) had improved RFS compared to those with non-pCR (red).

Figure 6:

Overall survival based on pathology response for patients treated with neoadjuvant BRAF-targeted therapy.

Table 1:

Patient Demographics

Characteristic	N= 23	%
Median age (range)	50.5 years (33–74)	n/a
Gender = male	16	70%
Stage at the start of therapy		
– IIIC	10	43%
– M1a	12	52%
– M1c	1	4%
BRAF V600E	22	96%
BRAFV600K	1	4%
Elevated LDH prior to surgery	3	13%
Not available	5	21%
Median duration of neoadjuvant treatment (range)	6.6 months (0.3–18.4)	
Median duration of follow-up (range)	43 (10–95 months)	

Table 2

Treatment and outcomes for patients

Pt #	Disease involvement at start of BRAF	Stage at start of neoadjuvant therapy	BRAF inhibitor therapy	Duration of neoadjuvant therapy (months)	Best Response by RECIST criteria	Pathology findings/ interpretation	Pathologic Response
1	Axilla/chest wall	M1a/IV	V	4.0	PR	Hyalinized	CR
2	Axilla	N3/IIC	V	8.8	PR	Mixed (necrotic/ hyalinized)/TR	CR
3	Groin/pelvic wall	M1a/IV	D+T	1.2	PR	Mixed (necrotic, fibrotic/ hyalinized)	CR
4	Axilla	N3/IIC	V	6.4	PR	Mixed (necrotic/ hyalinized)/TR	Major PR/ near CR
5	Groin/pelvis	M1a/IV	D+T	1.4	PR	Viable disease with no necrosis/RD	non-response
6	Axilla	N3/IIC	D	4.6	PR	Necrosis based on report/RD	non-response
7	Thigh/groin/ pelvis	M1a/IV	V	5.0	PR	Mixed (necrotic/fibrotic)	CR
8	Axilla/neck	N1/IIC	E+B	6.6	PR	Mixed (necrotic/ hyalinized)	PR
9	Thigh/groin	IIC	D+T	3.3	SD	necrotic	non-response
10	Axilla/neck	N2/IIC	V	14.0	PR	Mixed (necrotic and fibrotic/melanotic and hyalinized)	PR
11	Pelvis	IV	D+T	8.2	PR	Hyalinized	CR
12	Axilla/arm	IIC	V	18.4	PR	Mixed (necrotic and hyalinized)	CR
13	Axilla/neck	IIC	D+T	6.2	PR	Fibrotic/melanotic	Major PR/ near CR
14	Pelvis	IV	D+T	8.5	PR	Hyalinized	Major PR/ near CR
15	Axilla/thyroid	M1a/IV	D+T	7.5	PR	Hyalinized	CR
16	Neck	M1a/IV	D+T	4.6	SD	Mixed (necrotic and fibrotic/melanotic)	CR
17	Groin/thigh	M1a/IV	D+T	8.4	PR	No necrosis/RD	non-response
18	Groin/back	M1c/IV	D+T	10.6	PR	No necrosis(maturation)/TR	non-response
19	Bilateral axilla, thigh	M1a/IV	V	8.6	PR	Necrotic	PR
20	Axilla/subcut.	M1a/IV	D+T	9.3	PR	Mixed (necrotic and fibrotic/melanotic)	CR
21	Axilla	IIC	V+C	0.3	PR	Hyalinized	Major PR/ near CR
22	Axilla/chest wall	M1a/IV	V+C	1.4	SD	Mixed (necrotic in soft tissue, no response in nodes)	non-response
23	Groin/pelvis	IIC	D+T	7.0	PR	Mixed (necrotic and fibrotic/melanotic)	CR

V = vemurafenib, V + C = vemurafenib+cobimetinib, D + T = dabrafenib+trametinib, E + B = encorafenib+binimetinib. CR, complete response; PR, partial response.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript