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An Open Label, Phase II Study of Neoadjuvant Axitinib in Patients with Stage III Malignant Melanoma

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Abstract

Purpose: This open-label phase II study investigated the activity and safety of neoadjuvant/adjuvant axitinib, a potent and selective second-generation inhibitor of Vascular Endothelial Growth Factor Receptors (VEGFR) in patients with stage III melanoma.

Experimental Design: Eligible patients had 1 target lesion as defined by RECIST, and no prior systemic therapy. Primary end point was Objective Response Rate (ORR) according to RECIST v1.1; response was also considered if there was a ≥ 25% reduction in the involved nodal basin Specific Uptake Value (SUV) on PET/CT. Secondary endpoints included Duration of Response (DOR), Progression Free Survival (PFS), and Overall Survival (OS). After initial staging by PET/CT, Axitinib 5 mg was administered orally twice each day; treatment continued until tumor progression, unmanageable toxicity, or withdrawal of consent. After two months of therapy, patients underwent restaging PET/CT scans to assess response, followed by definitive surgical resection of their involved nodal basins. Patients with stable disease, PR, or CR restarted axitinib as adjuvant therapy. Patients who progressed transitioned to other therapies after surgery.

Results: Fifteen patients were screened, and eleven patients were initiated on therapy. Median age was 63 years (range 37-88). Three patients (27%) had BRAF mutations. Objective response rate was 45.5% [95% Confidence Interval (CI), 16.7-76.6], comprised of one complete and four partial responses, with two patients ongoing. Median duration of response was 8 months (95% CI, 3.5-13.3). Stable disease was observed in one patient, with an overall disease control rate of 54.5% (95% CI, 23.3-83.2]. Median progression free survival was 4 months [95% CI, 2.8-8.5]. Median overall survival was 59 months [95% CI, 29.6-67.5]. The most frequently reported (>15%) nonhematologic, treatment-related adverse effects were hypertension, fatigue, and diarrhea.

Conclusion: Axitinib showed single-agent activity among patients with stage III melanoma and had favorable effect as a neoadjuvant therapy. Axitinib was well tolerated and safety profiles were consistent with previous reports from previous studies in patients with melanoma. Axitinib alone or combined with other therapies merits further research in the neoadjuvant setting.

Keywords: Neoadjuvant; Melanoma; Axitinib

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Introduction

According to the SEER data base, the incidence of malignant melanoma continued to rise in 2020 to 100,350 new cases, with 6,850 deaths expected [1]. Depending on type and stage, melanoma may be treated by surgery, immunotherapy, targeted therapy, chemotherapy, radiotherapy, or combinations of thereof. In stage IA and IB melanoma, surgery is generally curative, with 10-year survival rates of 98% and 94%, respectively [2]. Deeper stage IIA, IIB and IIC lesions also do well, but with modest declines in 10-year survival to 88%, 82% and 75%, respectively. However, a steep decline in survival is encountered for stage III lesions associated with local nodal basin involvement or in transit lesions. Stage IIIA, B, C and D 5-year survival is 93%, 83%, 69% and 32%, respectively. The poorer outcomes seen for high risk stage III patients led to a series of successful adjuvant trials that explored the benefits of post-resection systemic check point inhibitors and BRAF/MEK targeted therapies that had proven survival benefit in trials for advanced stage melanoma [3-7]. Currently, ipilimumab, nivolumab, pembrolizumab, and dabrafenib with trametinib are approved adjuvant therapies for stage III patients resected for cure. The 12-month RFS rates

for stage III patients studied in the pivotal trials were 63.5% for ipilimumab, 72.3% for nivolumab, 75.4% for pembrolizumab, and 88% for dabrafenib plus trametinib. While favorable, these data suggest that further improvements in treating stage III patients are needed.

Neoadjuvant therapy has shown benefit for patients with various types of solid tumors, including head and neck, breast, bladder, esophageal, and rectal cancers [8-11]. Neoadjuvant treatment offers the opportunity to further improve survival, surgical resectability, local control, and organ preservation. Furthermore, neoadjuvant therapy enables the clinician to assess clinical and pathological response to treatment. Tumor tissue sampling before and after neoadjuvant therapy may also reveal mechanisms of treatment resistance, aiding in the selection of future treatments should they be needed.

Based on the success of adjuvant therapy with checkpoint inhibitors and dabrafenib and trametinib, phase II trials have been carried out with these agents in the neoadjuvant setting with promising results [12-18].

We therefore carried out an open label phase II study of neoadjuvant/adjuvant axitinib for stage III melanoma. Melanoma is a highly angiogenic tumor that is responsive to agents that target the vascular endothelial growth factor pathway [19-28]. Axitnib is an active antiangiogenic agent with previous data supporting its activity in melanoma [27]. We utilized both conventional CT imaging as well at 18F-FDG PET/CT scans to assess clinical response [29,30]. Treatment response has traditionally been evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST), which is based on changes in tumor size. Axitinib is not a cytoreductive agent, and responding tumors do not necessarily decrease in size early during treatment, making serial size measurement on morphologic imaging unreliable for response assessment [21,22]. 18F-FDG PET imaging may therefore be of added value in monitoring response to antiangiogenic agents [31-33].

Methods

Patients

Patients aged 18 years or older with histologically documented melanoma with local lymph node stage III metastases who had received no prior systemic therapy were eligible. Other eligibility criteria included at least one target lesion as defined by RECIST (with a unidimensional diameter of at least 1cm for spiral CT, or an SUV value ≥ 2.5), adequate major organ function, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and informed consent. Patients were required to have adequate bone marrow, hepatic, and renal function documented within 14 days prior to treatment.

Patients were excluded if they met any of the following criteria: unresectable stage IV disease; previous treatment with anti-angiogenesis agents, uncontrolled hypertension, that is, systolic blood pressure above 140 mmHg and diastolic blood pressure above 90 mmHg; history of hemoptysis; Gastrointestinal (GI) abnormalities including inability to take oral medication, requirement for intravenous alimentation, prior surgical procedures affecting absorption, treatment for peptic ulcer disease in past six months, active GI bleeding unrelated to cancer, and malabsorption syndromes; use of drugs known to be CYP3A4 or CYP1A2 inhibitors or inducers; active seizure disorder or evidence of brain metastases; major surgery or radiation within four weeks of treatment; patients (male or female) having procreative potential who are not using adequate contraception or practicing abstinence; women who are pregnant or breast-feeding.

Study Design

This was an open label, phase II trial of the clinical activity, safety, and tolerability of neoadjuvant/adjuvant axitinib in patients with stage III melanoma. The primary endpoint was ORR, defined as the proportion of patients experiencing Complete Response (CR) or Partial Response (PR), based on RECIST, and/or PET/CT criteria (EORTC PET response criteria were used).(34) The study was approved by the Institutional Review Board and was carried out in accordance with the International Conference on Harmonization Good Clinical Practice guidelines. Written informed consent was obtained prior to patients entering the study. The study was registered at ClinicalTrials.gov (NCT01321437).

Study Treatment

Axitinib 5 mg was self-administered orally twice daily with doses spaced approximately 12 hours apart and at approximately the same times each day in four-week treatment cycles. The neoadjuvant phase of therapy was completed in 56 days, followed by a preoperative rest period off medication of 14 to 21 days. Subjects then underwent standard of care nodal basin dissections. Patients with responding or stable disease were allowed to restart adjuvant axitinib therapy 28 days' post-surgery. Treatment continued until tumor progression, unmanageable toxicity, or the patient withdrew consent. Treatment was interrupted in patients with adverse events grade ≥ II that were not controlled by supportive medication and were resumed at the same dose after resolution to grade I or baseline. Treatment was interrupted in patients with grade ≥ 3 or 4 nonhematologic adverse events and resumed at 20% lower dose after resolution to grade I or baseline. If the resolution did not occur within 4 weeks, the patient was removed from the study. Any patient with recurring subjectively intolerable toxicity despite optimal supportive care could resume at a 20% lower dose once adequate recovery was achieved. Patients who derived clinical benefit could continue to receive treatment after meeting criteria for study completion.

Study Assessment

Baseline lesion assessments were measured using CT and PET/CT performed within 4 weeks of treatment initiation.

Baseline tumor lesions were categorized as target or nontarget. Patients were evaluated for response according to RECIST v1.1 and/or by EORTC PET/CT criteria (Table 1).

Table 1: Comparison of PET/CT and RECIST criteria.

Response	Definition	
	PET/CT Criteria	RECISTv1.1
Complete response	SUV max similar to liver background SUV max reading	Disappearance of all target lesions, all nodal lesions have short axis <10 mm
Partial response	Decrease in sum of the SUV max in target lesion(s) ≥ 25%	≥30% decrease in the sum of diameters from baseline sum diameters
Stable disease	Neither PR or PD criteria are met	Does not meet the above criteria
Progressive disease	SUV max changes >25% in the target lesion	≥20% increase in the smallest sum of diameters as reference with an absolute increase of ≥5 mm

Based on these criteria, a Complete Metabolic Response (CMR) was achieved when all tumor lesions were no longer detectable against adjacent background activity, whereas Progressive Metabolic Disease (PMD) was defined as an increase in SUVmax of ≥25% from baseline imaging or the appearance of new metastatic lesions. The EORTC criteria did not specify the number of lesions to be measured or the minimum measurable lesion SUVmax, but rather referred to the background activity for the definition of CMR. A Partial Metabolic Response (PMR) was defined as a reduction in SUVmax of between 15% and 25%, or >25% after one or more cycles of chemotherapy. Stable Metabolic Disease (SMD) was considered a response not classifiable in any of the other categories. Because resection of the involved nodal basin occurred within 2 to 3 weeks of initial therapy, no confirmatory scans were done. All scans for tumor assessment were performed at the same imaging site for consistency. Subsequent tumor assessments were performed every 16 weeks by PET/CT using RECIST and/or PET/CT criteria. For patients who did not progress after discontinuing study drug, additional re-staging assessments were performed approximately every 8 weeks until patients met criteria for progression or alternate therapy started. All patients were followed for survival at least every 3 months after discontinuing study treatment until at least one year after the initial dose for the last treated patient.

Physical examination, including assessment of all body symptoms, measurement of body weight, height, pulse, temperature, and assessment of ECOG PS was performed at baseline on day 1, every 8 weeks, and at the end of study treatment. Blood Pressure (BP) measurements were followed at each clinic visit and at least once a day at home by the patient. Patients were instructed to inform their doctor immediately if systolic BP was >150 mmHg, diastolic BP >10 mmHg, or if they developed symptoms perceived to be related to elevated BP. Laboratory tests for hematology, chemistry, and biochemistry were performed at baseline, day 1, every 8 weeks, and at the end of study treatment.

Statistical Methods

The study was conducted using a 2-stage Simon Minimax design. Because the indication being studied in this protocol responds poorly to conventional chemotherapy, p0 and p1 were set at low response rates of 5% and 20% respectively. The α and β error rates were set at 0.10 and 0.10, respectively. These criteria resulted in a sample size of 18 patients in stage I and an additional 14 patients in stage II, based on PASS 2002 software. If stage I had at least one confirmed response (e.g., CR or PR), then the trial would proceed to stage II.

Safety and efficacy analyses included all patients who received at least one dose of axitinib and had a baseline assessment of disease. Patients who died, progressed, or discontinued treatment before experiencing a CR or PR were classified as non-responders. Analyses consisted of descriptive statistics and corresponding 95% two-sided Confidence Intervals (CI) when appropriate. PFS, DOR, OS were summarized using Kaplan-Meier method and displayed graphically. Median event time was calculated for PFS, DOR, and OS.

Results

Patient Characteristics

Fifteen patients were screened, and eleven patients were initiated on protocol trial therapy. All patients had histology proven stage III disease. Patient baseline characteristics are summarized in Table 2.

Table 2: Patient Characteristics.

Characteristic	Axitinib (N=11)
Median age, years	63
Range	37-88
Sex, n (%)	
Male	7(63.6)
Female	4(36.4)
ECOG performance status, n(%)	
0	9(81.8)
1	2(18.2)
Baseline LDH level, n (%)	
Normal level	9 (81.8)
Elevated level	2 (18.2)
BRAF status, n (%)	
Wild type	6(54.5)
Mutant type	3(27.3)
Missing	2(18.2)
Subsequent therapy, n(%)	
Any	8(72.7)
Chemotherapy	3(27.3)
Targeted therapy	3(27.3)
Immunotherapy	5(45.5)
Radiotherapy	2(18.2)

The median age of patients was 63 years, ranging from 37 to 88 years of age. Nearly all patients (90.1%) had ECOG

performance status 0, with one patient ECOG performance status 1. Nine patients (81.8%) had normal baseline LDH levels, while two patients (18.2%) had elevated baseline levels. Six patients (54.5%) had wild type BRAF, while three patients (27.3%) were found to have BRAF mutations. Two patients had missing BRAF status. No patients had prior therapy. Eight patients (72.7%) underwent subsequent therapy after the trial.

Median time on axitinib was 121 days (range, 30-540) with six patients (54.5%) receiving therapy for 121 days or longer. The median daily dose was 9.8 mg/day (range, 8-10), with two patients requiring dose reduction to 8 mg/day. Treatment continued until the end of the trial in two patients (18.2%), with responses ongoing. Treatment discontinuation occurred in eight patients because progression (72.7%) and in one patient because of death (9.1%).

Clinical Activity

The ORR was 45.5% [95% CI, 16.7-76.6], as assessed by PET/CT criteria, with 1 CR and 4 PRs; in comparison, the ORR was 27.3% [95% confidence interval (CI), 6.2-60.9], as assessed by RECIST, comprising of 1 CR and 2 PRs (Table 3).

Table 3: Best response according to PET/CT and RECIST.

Objective Tumor Response	PET/CT	RECIST
Patients with baseline assessment	11	11
Patients with measurable disease at baseline	11	11
Number of patients who did not relapse	2	2
Best overall response:		
Complete response	1	1
Partial response	4	2
Stable disease	1	4
Progressive disease	5	4
ORR	45.45%	27.27%
95% exact CI (Clopper-Pearson)	16.7% - 76.62%	6.22% - 60.97%
Disease control rate	54.54%	63.60%
95% exact CI (Clopper-Pearson)	23.3% - 83.2%	30.8%- 89.1%

Two patients had ongoing response at the completion of the study. Of the 4 patients who had partial responses per PET/CT, RECIST classified 2 of these patients as partial responses, and the other 2 as stable diseases. One patient had a best response as stable disease according to PET/CT, yielding an overall disease control rate of 54.5% [95% CI, 23.3-83.2] per PET/CT. 4 patients had a best response as stable disease per RECIST, yielding a disease control rate of 63.6% [95% CI, 30.8-89.1] per RECIST.

Median duration of response was 8 months [95% CI, 3.5-13.3] (Figure 1).

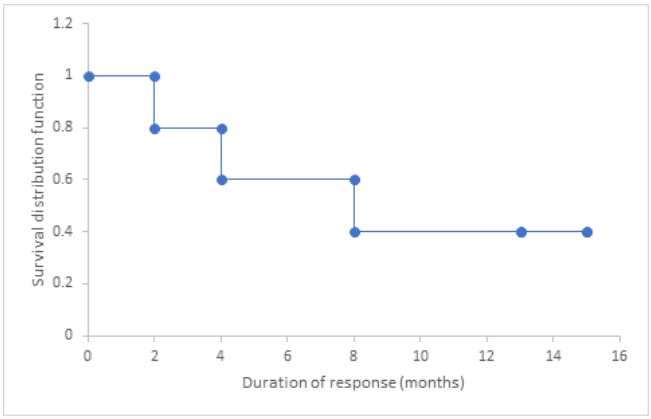

Figure 1: Kaplan-Meier estimates of duration of response.

Median progression free survival was 4 months [95% CI, 2.8-8.5] (Figure 2),

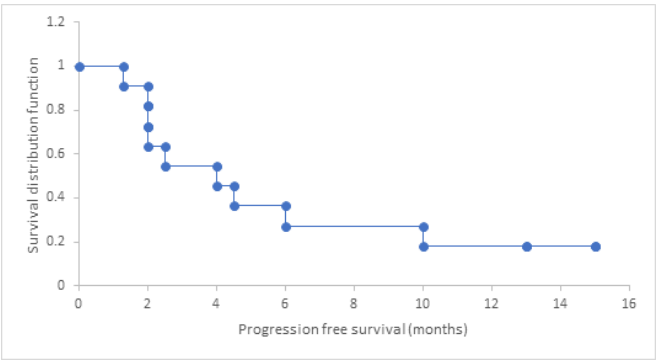

Figure 2: Kaplan-Meier estimates of progression free survival.

with a 6-month PFS rate of 36.4%. Median overall survival was 59 months [95% CI, 29.6-67.5] (Figure 3),

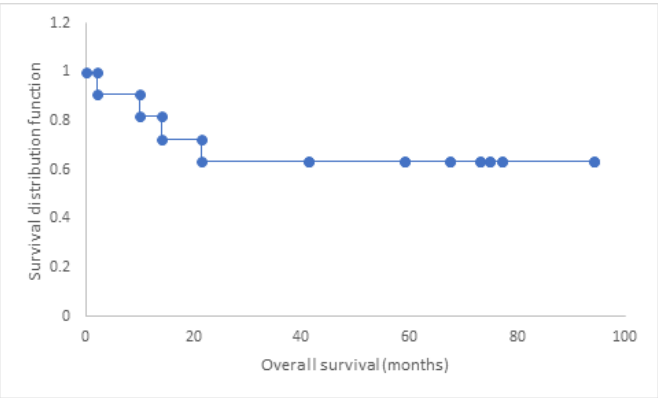

Figure 3: Kaplan-Meier estimates of overall survival.

with a 1-year OS rate of 72.7%.

In post hoc analysis, baseline serum LDH levels were found to be associated with differences in efficacy endpoints. In patients with normal baseline LDH levels (n=9), median PFS was median PFS was 4.5 months [95% CI, 3.1-9.7]; in comparison, patients with elevated baseline LDH levels (n=2), median PFS was 2.3

months [95% CI, 1.6-2.9]. Patients with normal baseline LDH levels had a median OS of 67.5 months [95% CI, 34.9-76.1] while patients with elevated baseline LDH levels had a median OS of 17.6 months [95% CI, 10.4-25.1].

Safety

Treatment with axitinib was overall well tolerated, and no dose-limiting toxicities were observed in the initial six patients enrolled in the study. In total, nine (81.8%) of eleven patients experienced treatment-related adverse events; most were grade I or II, as listed in Table 4.

Table 4: Safety findings: treatment related adverse events reported by at least > 15% of patients.

Adverse events	Total, n(%)	Grade ≥ 3
HTN	5 (45.5)	1 (9.1)
Fatigue	5 (45.5)	0
Diarrhea	3 (27.3)	0
Mucositis	3 (27.3)	0
Hoarseness	3 (27.3)	0
Nausea	3 (27.3)	0
Weight loss	2 (18.2)	0
Loss of taste	2 (18.2)	0
Pain in limb	2 (18.2)	0
Hypothyroidism	2 (18.2)	0

The most frequently reported treatment-related adverse events included hypertension, fatigue, diarrhea, mucositis, and hoarseness. Hypertension was reported in 5 (45.5%) patients, most of which were mild to moderate (grade I/II). One patient experienced grade III adverse event due to hypertension. No other grade III adverse events were considered treatment related. Grade I proteinuria was reported in 1(9.1%) patient. Grade I anemia was found in 1 (9.1%) patient based on laboratory data. Two patients experienced treatment interruption due to treatment related adverse events and required dose reduction from 5 mg BID to 4 mg BID; both were due to grade II nausea, vomiting, and diarrhea.

No patients experienced treatment related adverse events that resulted in study discontinuation. One patient died during the active treatment period of the study of unknown causation. The patient had been seen in clinic 4 days prior to their death and had been medically cleared at that time for LN dissection. Three patients (27.3%) died during 5-year follow-up from melanoma disease progression.

Discussion

These results demonstrated that axitinib had moderate single-agent neoadjuvant activity in patients with stage III melanoma, with a RR of 45.5% as assessed by PET/CT criteria, with 1 CR and 4 PRs, and a RR of 27.3% as assessed by RECIST, comprised of 1 CR and 2 PRs. No new AE signals were noted. These findings were consistent with its previously reported response rate of 19% in St IV melanoma [28]. Responses persisted for a median duration of 8 months, with two patients having ongoing response. One patient experienced stable disease per PET/CT, while an additional four patients experienced stable disease per RECIST, demonstrating an overall disease control rate of 54.5% and 64.6% respectively. Although limited by the small number of patients and lack of a control arm, the efficacy observed in this study are consistent with previous reports.

Response rates with axitinib treatment were higher using PET/CT criteria compared to RECIST criteria (45% versus 27%, respectively) as some of the PET/CT classified partial responses were instead classified as stable disease by RECIST 1.1. Disease control rates were similar between PET/CT and RECIST 1.1 (54% versus 64%, respectively). These data compare favorably with previously reported neoadjuvant studies. A recent retrospective analysis conducted with 23 BRAFV600-mutant positive patients with stage III/IV melanoma who had been treated with BRAF-targeted therapy prior to surgery demonstrated a 44% pathologic Complete Response (pCR) [12]. After a median of 43-month 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.

Prospective studies of neoadjuvant dabrafenib and trametinib revealed similar findings. In a recent phase II trial at MD Anderson, seven subjects were randomly assigned to standard of care surgery, and 14 to neoadjuvant plus adjuvant dabrafenib and trametinib [13]. Neoadjuvant therapy resulted in a 58% pathologic complete response rate. After a median follow-up of 18·6 months, 71% of patients receiving dabrafenib and trametinib were alive without disease progression, compared with none of seven in the standard of care group. The frequency of adverse events were consistent with those seen in the metastatic setting. Similar findings were reported by Long et al, who evaluated outcomes for 35 eligible subjects who received neoadjuvant dabrafenib plus trametinib prior to resection, followed by 1 year of adjuvant therapy [14]. At resection, pathological response was seen in all 35 patients, with 49% of patients demonstrating a complete pathological response.

With respect to neoadjuvant I/O therapy, three studies have examined neoadjuvant ipilimumab with nivolumab, and one evaluated neoadjuvant pembrolizumab. Blank et al evaluated 20 patients with palpable stage III melanoma who were randomized 1:1 to receive ipilimumab 3 mg kg-1 and nivolumab 1 mg kg-1, as either four courses after surgery (adjuvant arm) or two courses before surgery and two courses post-surgery (neoadjuvant arm) [15]. Pathological responses were achieved in 7/9 (78%) patients treated in the neoadjuvant arm. In both arms, 9/10 patients experienced one or more grade 3/4 adverse events. Amaria et al found that subjects treated with combined ipilimumab and nivolumab yielded high response rates (RECIST ORR 73%, pCR

45%), but substantial toxicity (73% grade 3 trAEs), whereas subjects treated with nivolumab monotherapy yielded a moderate response rate (ORR 25%, pCR 25%), with less toxicity (8% grade 3 trAEs) [16]. Roseman et al has reported on a larger phase II trial of neoadjuvant ipilimumab and nivolumab [17]. They randomly assigned subjects (1:1:1), stratified by site, to one of three neoadjuvant dosing schedules. Results were reported for 86 subjects who received at least one dose of study drug; 30 patients in group A (ipilimumab 3 mg/kg plus nivolumab 1 mg/kg once every 3 weeks), 30 in group B (two cycles of ipilimumab 1 mg/kg plus nivolumab 3 mg/kg once every 3 weeks), and 26 in group C (two cycles of ipilimumab 3 mg/kg once every 3 weeks directly followed by two cycles of nivolumab 3 mg/kg once every 2 weeks; accrual to group C was closed early because of severe adverse events). They found that pathological responses occurred in 24 (80%) patients in group A, 23 (77%) in group B, and 17 (65%) in group C. Within the first 12 weeks, grade 3-4 immune-related adverse events were observed in 40% of patients in group A, 20% in group B, and 50% in group C. The most common grade 3-4 adverse events were elevated liver enzymes in group A (20%), and colitis in group C (19%). One patient (in group A) died 9·5 months after the start of treatment due to the consequences of late-onset immune-related encephalitis, which was possibly treatment-related. While results for combination IO therapy were positive, the toxicity profile was unfavorable for patients with stage III disease.

An evaluation of a single dose of pembrolizumab in the neoadjuvant setting given three weeks prior to nodal dissection was reported by Huang, et al. They found a rapid and potent anti-tumor response, with 8 of 27 patients (30%) experiencing a complete or major pathological response [18].

Taken together, these data suggest clinical value for a neoadjuvant approach to ST III melanoma, supporting further exploration of less toxic combinations of therapies. Vascular Endothelial Growth Factor (VEGF) signaling is strongly implicated in tumor angiogenesis in malignant melanoma [19]. Elevated levels of VEGF in patients have been associated with poor outcomes [25]. The clinical impact of anti-angiogenesis agents, including bevacizumab, axitinib and pazopanib, have been explored in melanoma with encouraging findings [26-28]. In addition to its antiangiogenic effects, axitnib may possess synergistic activity with check point inhibitor therapy via reversal of tumor-induced immunosuppression [34]. Axitinib has recently demonstrated significant activity in combination with pembrolizumab and avelumab in advanced renal cell cancer, leading to FDA approval of these combinations [35-36]. A recent phase IB trial evaluated the activity of axitinib in combination with the PD1 directed antibody toripalimab in 29 patients with chemotherapy-naive mucosal melanoma. Sheng et al. reported a 48% objective response rate, and a median progression-free survival time of 7.5 months [37]. These findings support further exploration of axitinib in combination with checkpoint inhibitors in the setting of both advanced and ST III cutaneous melanoma.

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