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RESEARCH ARTICLE

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Neoadjuvant systemic therapy for regionally advanced melanoma

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Background: Patients with regionally advanced melanoma are at high risk of distant failure and unlikely to be cured by surgery alone. Neoadjuvant therapy may provide benefit in these patients.

Objectives: To evaluate our experience with neoadjuvant systemic therapy in high-risk stage III patients.

Methods: Retrospective review of patients with advanced stage III disease who received neoadjuvant therapy between August 2009 and August 2016 at Mayo Clinic Rochester.

Results: Twenty-three cases met our inclusion criteria, 16 with resectable disease and 7 with unresectable disease. No patients with resectable disease and one patient with borderline resectable disease progressed regionally, prohibiting surgical resection. Five of seven patients with unresectable disease were down-staged to a resectable state. Six of twenty-three (26%) had a CR and five are alive at last follow-up. Fifteen of twenty three patients (65%) progressed with a median progression free survival of 11 months; however, the 5 year overall survival estimate was 84%.

Conclusions: Neoadjuvant systemic therapy is a reasonable approach for patients with advanced but resectable/borderline resectable disease and the risk of losing regional control is low. Our data also suggest some patients with unresectable disease will be converted to resectable and a complete clinical response to treatment can be obtained in approximately one quater of patients.

KEYWORDS
adjuvant, complete response, CTLA-4, ipilimumab, PD-1, pembrolizumab

1 | BACKGROUND

Patients with advanced stage III melanoma are at high-risk of developing systemic disease and subsequent death. The recommended treatment for patients with advanced regional disease and no evidence of distant disease is regional lymphadenectomy of the affected nodal basin or basins, removing all measureable as well as potentially occult microscopic disease. However, some patients present or recur with advanced regional disease, making surgical resection technically challenging. Resecting this more advanced disease can be associated with increased morbidity and possibly incomplete surgical resection. Moreover, a significant portion of patients with advanced regional disease harbor clinically and radiographically occult systemic disease at presentation and may subsequently relapse at distant sites shortly after surgery. These patients unfortunately derive no apparent benefit from surgical

resection.[1–5] Thus, neoadjuvant systemic therapy may be a reasonable approach for this patient population.

Combination chemotherapy, as well as newer targeted therapies and immune checkpoint blockade, can achieve objective responses in approximately 30-70% of patients with stage IV disease.[6–11] There are limited reports in the literature of using neoadjuvant systemic therapy in the context of stage III melanoma, and results have been mixed.[2,12–14] With available effective therapies in the metastatic setting, a natural evolution is to explore these agents for high-risk resectable or regionally borderline/unresectable patients. Neoadjuvant systemic therapy, as part of multimodality treatment for other operable tumors, can result in down-staging of disease potentially to diminish surgical morbidity, allow patients to undergo a more conservative operation, improve patient prognostication and permit occult systemic metastasis to be identified prior to a patient undergoing a potential morbid surgical procedure, especially those who are resistant to systemic therapy.[15,16] Operative intervention following neoadjuvant cytotoxic chemotherapy has been shown to be safe and is standard in other solid tumors; recently safety has been demonstrated for patients with melanoma actively receiving ipilimumab.[17] Thus, in theory, individuals who do not respond or who develop metastases outside of the planned surgical field avoid an operation from which they may not benefit.

With this in mind our aim was to evaluate our experience with neoadjuvant systemic therapy in high-risk stage III melanoma patients. Herein we report on a cohort of patients with advanced regional disease from melanoma that received neoadjuvant systemic therapy at our institution and describe treatment response and cancer outcomes. We also wished to investigate our success rates with downstaging borderline/unresectable regional disease to resectable disease and conversely, how often patients with initially resectable disease progress on systemic therapy, thus prohibiting resection. This progression could be regional alone and thus an opportunity for a potentially curative intervention was lost or early distant progression and thus the operative procedure would have been unlikely to provide a survival advantage.We hypothesized that neoadjuvant systemic therapy improves surgical resectability in a subset of patients with advanced regional melanoma improving selection of appropriate surgical candidates by distinguishing those who may benefit from surgical resection from those who have drug resistant tumor biology and rapidly progressive disease and might be spared the morbidity of an operation.

2 | METHODS

Following IRB approval, we identified patients diagnosed with stage III cutaneous melanoma who received neoadjuvant systemic treatment at our institution between August 2009 and August 2016.The initial search was conducted using the Advanced Cohort Explorer (ACE) which is a rich clinical data repository maintained by the Unified Data Platform (UDP). ACE features include patient demographics, diagnoses, hospital and laboratory flow sheets, clinical notes and pathology reports. Data is obtained from multiple clinical and hospital source systems within Mayo Clinic Rochester. Additional cases were identified using the Mayo Clinic cancer registry. Inclusion criteria included patients who received neoadjuvant systemic therapy for advanced stage III melanoma defined as clinically evident bulky nodal disease with or without in transit disease or questionably resectable/unresectable regional disease. Exclusion criteria included patients with mucosal or ocular melanoma as well as patients with systemic metastatic disease (stage IV) diagnosed prior to initiation of neoadjuvant systemic therapy.

Patients were selected for neoadjuvant systemic therapy after multidisciplinary evaluation. Patients were treated off-label per clinical judgement; in each case, a multidisciplinary team deemed systemic therapy and not upfront surgery to be in the best interest of the patient. Patients with resectable disease often received neoadjuvant treatment as the result of recurrences with very short disease free intervals following prior definitive resection or some concerning findings on systemic imaging that were not definitive but also not amendable to biopsy. The majority of patients were treated in the era prior to FDA approval of adjuvant ipilimumab in 2015. Median follow-up and overall survival were calculated from the date of diagnosis of advanced regional nodal disease to date of death or last follow-up. Progression-free survival was calculated from the date that neoadjuvant systemic therapy was initiated. Data, including the reason(s) for initiating treatment with systemic therapy, were abstracted from the electronic medical record. All patients had cross-sectional imaging prior to the initiation of therapy to exclude metastatic disease. Indications for neoadjuvant systemic therapy were categorized as: unresectable regional disease, borderline resectable regional disease, rapidly progressive or recurrent regional disease and patient comorbidities substantially elevating surgical risk. Treatment was considered neoadjuvant for all patients as there was upfront intent for surgical resection following systemic therapy, which was dependent upon response and patient performance status following treatment. Patients with rapidly progressive disease were defined as having frequent recurrences following resection, often with a decreasing disease free interval. If a patient received multiple lines of neoadjuvant therapy, each was recorded separately.

Resectable versus unresectable disease is a surgical judgement and definitions are dependent on the provider. Due to the retrospective nature of this study firm definitions could not be established in advance but were based on review of the medical record and radiographic imaging. Patients classified as having unresectable disease often had encasement of major regional vascular structures such as the axillary artery or involvement of major neurologic structures such as the brachial plexus, for which surgical treatment would entail forequarter amputation or hip disarticulation. Patients classified as having borderline resectable disease often had invasion of neighboring musculoskeletal or venous structures. An operative procedure requiring resection of a segmental portion of the major named vein (axillary, femoral, iliac) alone was not classified as unresectable disease.

Clinical response to systemic therapy was categorized into four distinct groupings. Complete response (CR) was defined as no clinical or radiographic evidence of disease, partial response (PR) as >50% but <100% clinical/radiographic response, stable disease (SD) was no significant change and progressive disease (PD) as increase in

regional tumor burden >20% over baseline and/or development of new sites of disease.

3 | RESULTS

Twenty-three patients were identified who met our inclusion and exclusion criteria. The median age of patients in this cohort was 61 years (interquartile range (IQR) 53-71 years). Nine patients (39%) had in transit disease in addition to regional nodal disease.The median follow-up time from the initiation of neoadjuvant systemic therapy was 41 months (IQR 13-63 months). Demographic data and indications for initiating neoadjuvant systemic therapy are shown in (Table 1). Many patients had more than one indication for neoadjuvant systemic therapy. Clinical response rates to first line systemic therapy are summarized in (Table 2) (4 CR, 5 PR, 3 SD, and 11 PD). Overall, 6/23 (26%) patients were rendered disease-free with neoadjuvant therapy alone (four first line and two following second line). Eleven of twenty-two (61%) were rendered disease-free with a combination of neoadjuvant treatment and surgical resection resulting in a total of 17/23 (74%) who were rendered free of clinical and radiographic measureable disease. Three patients had a clinical CR and had no residual disease at surgery. Of the 11 patients who progressed on first line therapy, nine received second line systemic therapy. No patients with a PR or SD went onto second line therapy. Clinical response rates to second line systemic therapy were: four CR, two PR, one SD, and two PD (Table 2). Response rates based on the regimen delivered are shown in (Table 3). One patient had multiple lines of the same regimen with a complete response at initial treatment and at subsequent recurrences; therefore, the response was only counted as one CR. One patient underwent hyperthermic isolated limb perfusion at time of regional lymphadenectomy to treat synchronous in-transit disease following neoadjuvant therapy and one patient who progressed on neoadjuvant systemic therapy and did not undergo resection received intralesional Talimogene laherparepvec (Table 4).

TABLE 1 Clinicopathologic characteristics for patient undergoing neoadjuvant systemic therapy

	N = 23
Age in years, median (IQR)	61.0 (53.4-71.1)
Female, *n* (%)	12 (52)
Patients with locoregional recurrence, *n* (%)	15 (65)
Patients with in-transit disease, *n* (%)	9 (39)
LDH in units per liter, median (IQR)[a]	178 (150-222)
Patients with elevated LDH, *n* (%)[a]	4 (19)
Indication for neoadjuvant systemic therapy, *n* (%)[b]	
Unresectable disease	7 (30)
Borderline resectable	7 (30)
Rapidly progressive disease	12 (52)
Poor surgical candidate	2 (9)

[a]LDH levels obtained prior to neoadjuvant therapy. Does not include two patients for which no LDH value was available prior to systemic therapy.
[b]Some patients had more than one indication for neoadjuvant systemic therapy.

Twenty-one patients had a serum LDH level measured prior to initiation of systemic therapy which was elevated in four patients. None of these patients with an elevated LDH had a CR and all developed recurrent disease regardless of their initial response to neoadjuvant systemic therapy. Ten of the 17 patients with a normal pre-treatment LDH exhibited recurrence after initiating systemic therapy for their advanced stage III disease. Comparing pre-treatment LDH levels, three of four (75%) patients with an elevated LDH developed distant metastatic disease during follow-up and 7 of 17 (41%) with a normal LDH pretreatment developed distant metastatic disease.

3.1 | Resectable/borderline resectable at presentation

Sixteen patients presented with resectable disease, including 7 categorized as borderline resectable, and 11 ultimately underwent an R0 surgical resection of their disease. Nine of the 16 patients who presented with resectable or borderline resectable disease received one neoadjuvant systemic therapy regimen, three patients received two lines of neoadjuvant systemic therapy and four patients received three or more regimens. At last follow-up, 10 of the 16 patients with resectable/borderline resectable disease at presentation remain disease-free after a median follow-up of 45.5 (interquartile range (IQR) 17-63.75) months, four are alive with disease, one died of metastatic melanoma, and one died from unrelated causes.

Of the 16 patients who presented with resectable/borderline resectable disease five did not undergo surgical resection secondary to a complete radiographic response (*N* = 3) or progression to distant disease (*N* = 2). Of the three patients with a complete radiographic response who were not operated upon, two remain without evidence of disease at 57 and 68 months since initiation of systemic therapy and one remains alive with disease. Although none of these three patients had a formal lymphadenectomy nor radiation therapy, one patient did undergo excisional biopsy of a clinically suspicious residual node, despite a negative PET scan, which revealed a pCR.

None of the patients with resectable disease and only one of the patients with borderline resectable disease progressed regionally, prohibiting surgical resection, while on systemic therapy and undergoing close surveillance.

3.2 | Unresectable disease at presentation

Seven patients presented with regionally advanced nodal disease that was determined to be unresectable by the consulting surgeon. One patient, who had a complete clinical and pathological response to neoadjuvant systemic therapy remains without evidence of disease at 43 months following axillary dissection.Two patients who presented with unresectable regional disease progressed on systemic therapy and subsequently died of disease.

Five of the seven patients with unresectable disease at presentation were down-staged to an anatomically resectable state, one CR and

TABLE 2 Clinical response to systemic therapy

	Complete response	Partial response	Stable disease	Progressive disease
1st line systemic therapy	4	5	3	11
2nd line systemic therapy	3	3	1	2

four PR. Of the four PR, three underwent resection and one underwent definitive radiation. All three who underwent resection had an R0 resection, received adjuvant regional nodal irradiation, and one also received adjuvant vemurafenib. Three of four patients with a PR remain without evidence of disease at last follow-up, including an 86 year old patient who received only definitive radiation and remains without evidence of disease 45 months following neoadjuvant ipilimumab, while the remaining patient has died of disease.

3.3 | Surgical management

Overall, 14 of 23 patients (60.9%) underwent resection including 10 who presented initially with resectable/borderline resectable disease and four who presented with unresectable disease. The best imaging response to neoadjuvant systemic therapy among these 14 patients was a CR in two patients, PR in six patients, SD in four patients and PD in two patients. Of the two patients with a clinical CR who underwent adjuvant resection, both had a pCR; one to neoadjuvant immunotherapy followed by targeted therapy, the other to chemotherapy. The 12 patients with an incomplete imaging response to neoadjuvant therapy had pathologic evidence of disease at operation, with a median of five positive nodes (range, 1-19 positive nodes). At a median follow-up of 44 months, one patient has died of disease, four are alive with disease and nine are without evidence of disease.

Nine of 23 (39.1%) patients did not undergo definitive resection of their regional nodal disease, six who presented with resectable disease and four who presented with unresectable disease. The best imaging response to systemic therapy was four CR, one PR, one SD, and three PD in these nine patients who did not have their regional disease resected. Three patients received definitive radiation therapy and one intralesional therapy. At a median follow-up of 34 months three patients died, two are alive with disease and four remain without evidence of disease.

3.4 | Response to therapy and prognosis

Six of the 23 patients (26%) had an imaging CR as their best response and five are alive; four without evidence of disease and one remains alive with disease, with a median follow-up of 49.5 months.Of these six patients, two underwent surgical resection and four received no other regional therapy. Of the four patients with a clinical CR and no subsequent surgery or radiation, three patients remain without evidence of disease at 57 months and one has died of disease. Eleven patients progressed on 1st line therapy and for 5 of the 23 patients (22%) progressive disease was their best overall response; two have died of disease, two are alive with disease and one is alive without evidence of disease.

3.5 | Recurrence and survival

Overall, 15 of the 23 patients (65%) developed disease progression with a median progression free survival of 11 months (IQR 9-32 months). In spite of this many of these patients were effectively managed with additional interventions and remain alive without disease. Across the entire patient cohort, the 1 year, 2 year, and 5 year progression free survival estimates were 43%, 39%, and 26%, respectively. The 5 year overall survival estimate was 84% (Figure 1).

4 | DISCUSSION

We present a contemporary series of 23 patients with melanoma who underwent systemic therapy as a first line approach to regionally advanced stage III disease. Sixteen patients were deemed surgically resectable at presentation, including seven with borderline resectable disease. No patients with resectable disease and only one patient with borderline resectable disease had regional progression on neoadjuvant systemic therapy which precluded surgical resection.These data

TABLE 3 Response rates to first line neoadjuvant systemic therapy

		Clinical and imaging response					
Systemic therapy	Number of patients	CR (%)	PR (%)	SD (%)	PD (%)	Surgery After 1st line (%)	2nd Line Systemic therapy (%)
Ipilimumab	6	2/6 (33)	1/6 (17)	0/6 (0)	1/6 (17)	0/6 (0)	4/6 (67)
Pembrolizumab	5	1/5 (20)	0/5 (0)	1/5 (20)	3/5 (60)	2/5 (40)	1/5 (20)
Taxane-based chemotherapy[a]	6	1/6 (17)	1/6 (17)	2/6 (33)	2/6 (33)	4/6 (67)	2/6 (33)
Alkylator-based chemotherapy[b]	4	0/4 (0)	1/4 (25)	0/4 (0)	3/4 (75)	2/4 (50)	2/4 (50)
BRAF-targeted therapy[c]	1	0/1 (50)	1/1 (100)	0/1 (0)	0/1 (0)	1/0 (100)	0/1 (0)
Interleukin-2	1	0/1 (0)	1/1 (100)	0/1 (0)	0/1 (0)	1/1 (100)	0/1 (0)

[a]Paclitaxel+Carboplatin+Bevacizumab(4), Paclitaxel + Carboplatin (3), Nab-paclitaxel + Carboplatin +Bevacizumab (1), Nab-paclitaxel + Carboplatin (1), Nab-paclitaxel + Bevacizumab (1).
[b]Temozolomide (3), Temozolomide + Bevacizumab (2), Dacarbazine, then Temozolomide (1).
[c]Vemurafenib (2), Vemurafenib + Cobimetinib (1), Dabrafenib + Trametinib(1).

TABLE 4 Response to any line of neoadjuvant therapy (nine patients received at least two lines of neoadjuvant therapy, thus total >23)

		Clinical and imaging response				
Systemic therapy	**Number of patients**	**CR (%)**	**PR (%)**	**SD (%)**	**PD (%)**	**Surgery (%)**
Ipilimumab	7	2/7 (29)	1/7 (14)	0/7 (0)	4/7 (57)	1/7 (14)
Pembrolizumab	7	1/7 (14)	1/7 (14)	2/7 (29)	3/7 (43)	3/7 (43)
Taxane-based chemotherapy[a]	9	1/9 (11)	2/9 (22)	3/9 (33)	3/9 (33)	5/9 (56)
Alkylator-based chemotherapy[b]	6	0/6 (0)	2/6 (33)	0/6 (0)	4/6 (67)	2/6 (30)
BRAF-targeted therapy[c]	4	2/4 (50)	2/4 (50)	0/4 (0)	0/4 (0)	3/4 (75)
Interleukin-2	1	0/1 (0)	1/1 (100)	0/1 (0)	0/1 (0)	1/1 (100)

[a]Paclitaxel+Carboplatin+Bevacizumab(4), Paclitaxel + Carboplatin (3), Nab-paclitaxel + Carboplatin +Bevacizumab (1), Nab-paclitaxel + Carboplatin (1), Nab-paclitaxel + Bevacizumab (1).
[b]Temozolomide (3), Temozolomide + Bevacizumab (2), Dacarbazine, then Temozolomide (1).
[c]Vemurafenib (2), Vemurafenib + Cobimetinib (1), Dabrafenib + Trametinib(1).

suggest that neoadjuvant systemic therapy is a reasonable approach for patients with advanced/bulky but resectable/borderline resectable disease and the risk of losing regional control and missing the window of opportunity for surgical resection is low. Our data also suggest that some patients with unresectable disease will be converted to resectable disease and that a complete clinical response to treatment can be obtained in nearly one quater of patients. Similar to other disease sites, a CR to systemic therapy would suggest biologically favorable disease and a better outcome, but further studies are necessary. At the present time, resection, observation or radiation for those with a complete imaging response to neoadjuvant systemic therapy may be a reasonable approach for highly selected patients.

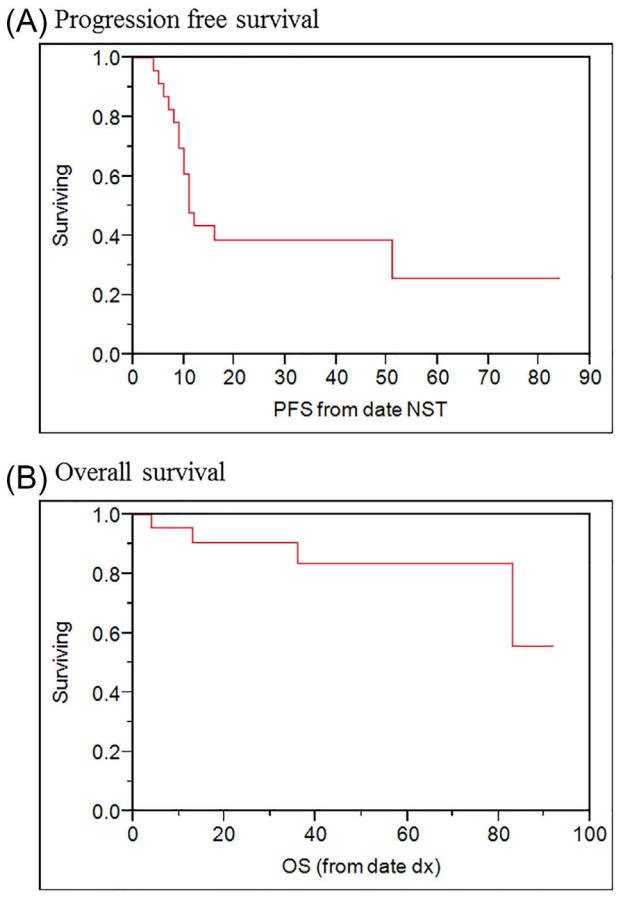

FIGURE 1 A, Progression free survival (in months) from time of initiation of neoadjuvant systemic therapy (all patients, $n = 23$). B, Overall survival (in months) from time of initiation of neoadjuvant systemic therapy (all patients, $n = 23$)

With the advent of immune checkpoint inhibitors targeting PD-1, PD-L1, and CTLA-4, as well as targeted therapies inhibiting BRAF and MEK, the use of conventional cytotoxic chemotherapy in patients with metastatic melanoma has declined. Although statistical comparison of response rates based on different regimens is not possible in this study, as the patients receiving treatment are heterogeneous, it is interesting to note, in the context of high-risk stage III melanoma, patients receiving chemotherapy, particularly taxane-based chemotherapy, had response rates that compared favorably with patients treated with modern immunotherapies and targeted therapies.Thus, while the role of cytotoxic chemotherapy for melanoma remains controversial, these data suggest it is appropriate to explore the use of chemotherapy (or combinations of chemotherapy and immunotherapy) in the neoadjuvant setting. Similarly no statistical comparison can be performed between those who underwent resection vs those who did not as the clinical decision to proceed with operative intervention was often directly related to response rates and patient comorbidities. Pretreatment LDH levels also appeared associated with future distant progression for this population of patients presenting with regionally advanced melanoma.This finding is worth further exploration.

While this retrospective review is hypothesis generating there are limitations. These include selection bias, in terms of both type of patients who were selected to receive neoadjuvant therapy, as well as the type of neoadjuvant therapy utilized, leading to a significantly heterogeneous population. Those who had a partial response or stable disease as their best response were more likely to undergo resection, while those at both ends of the spectrum of responses to systemic therapy (complete clinical/radiographic response or progressive disease) were less likely to undergo surgical intervention of their regional disease. Of the six patients with a complete response only two were resected and of the five patients with progressive disease as their best response, two were resected. Of the total study population nine

patients did not undergo resection following systemic therapy and only two of these did not have CR or PD. Additionally the timing with which stage III disease was diagnosed also limits this review; specifically, some patients presented with bulky stage III disease at initial diagnosis while others presented with recurrent adenopathy after prior operation. Finally, due to the rapid advances in systemic therapy that have taken place during the timeframe of this study, efficacy of any given systemic regimen is difficult to estimate. Our analysis also did not compare the toxicity or cost of the neoadjuvant therapies.

The patients included in this study are at high-risk of progression, yet many were effectively managed with additional interventions, including resection of oligometastatic disease, limb perfusion with or without additional regional lymph node surgery, intralesional therapy, Stereotactic Body Radiation Therapy and/or additional systemic therapy. Despite a high-risk of progression (65% in our series), 75% of patients remain alive at last follow-up, 61% without evidence of disease. In the current era of multimodality therapy and increasingly efficacious systemic options we postulate that this approach will have even greater efficacy in the foreseeable future.

5 | CONCLUSION

In conclusion, we have presented a large single center case series documenting our experience with the use of neoadjuvant systemic therapy in patients with high-risk stage III melanoma. Our data raise many questions as to the best approach of managing these patients for which randomized clinical trial data currently do not exist. This is a unique population for whom multimodality therapy (neoadjuvant systemic therapy followed by adjuvant surgical resection and/or radiation) may provide a chance for cure or durable regional disease control, whereas historically, the majority of these patients progressed and developed distant metastatic disease. Additionally, opportunities exist to identify unique biologic signatures to guide appropriate patient selection for combinatorial neoadjuvant regimens and surgical therapy. With the advent of immune checkpoint inhibitors and agents targeting BRAF and MEK, melanoma response rates to systemic therapy have significantly increased, affording the opportunity to study systemic therapy in patients without diffuse metastatic disease. Further study is needed to identify both appropriate patients and optimal neoadjuvant regimens in the high-risk stage III melanoma patient population.

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