Review

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Melanoma Management

The emergence of neoadjuvant therapy in advanced melanoma

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The discovery of immunotherapy and targeted therapy has introduced new and effective treatment options for advanced melanoma, providing therapeutic options where none existed before. The natural extension of these novel therapies is to identify their role in the neoadjuvant setting. Neoadjuvant therapy for advanced melanoma is still in its infancy, with a wealth of clinical trials underway. Early results are promising, allowing for management of a disease that previously had few options. We review the current literature and interim results from several ongoing investigations to understand the current state of neoadjuvant treatment options and what is to come. These studies pave the way for further advancements in melanoma therapy.

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Recent advances in melanoma treatment have drastically changed the therapeutic landscape for patients with advanced disease. These patients may have unresectable tumors, whether due to size or extent of involvement, or resectable disease with satellite, in-transit, regional or distant metastatic disease. The implementation of checkpoint inhibitors and targeted therapies now provide effective adjuvant therapies for these patients [1–3]. These encouraging results have led to a number of investigations evaluating the utility of the agents in the neoadjuvant setting.

Neoadjuvant therapy has the potential to further improve patient outcomes in melanoma. Neoadjuvant therapy can reduce the size and involvement of locally advanced tumors, rendering inoperable disease operable and reducing the extent and morbidity of large resections. Additionally, the risk of disease recurrence may be lowered through early treatment of occult metastatic disease. Due to the presence of the primary tumor during treatment, systemic therapies that induce immunomodulatory effects may have stronger and long-lasting responses when applied in the neoadjuvant setting. Preclinical murine models of advanced-stage cancer suggest that neoadjuvant immunotherapy provides a survival benefit over adjuvant immunotherapy; mice treated with preoperative immunotherapy display elevated levels of tumor-specific $CD8^+$ T cells that are sustained postoperatively [4]. While benefits of neoadjuvant therapy are well established in other malignancies, the role in melanoma is in its infancy. We review early investigations of neoadjuvant therapy in advanced melanoma and then discuss published and ongoing trials with the novel agents.

Past experience with neoadjuvant biochemotherapy

Early neoadjuvant trials investigated biochemotherapy for the treatment of stage III disease, which is the combination of cytotoxic chemotherapeutic agent(s) with IL-2 and/or IFN-α [5]. At that time, dacarbazine was the standard of care for metastatic melanoma despite reported response rates of approximately 20% and no proven overall survival (OS) benefit. While some regimens demonstrated increased response rates, no improvement in survival was shown [6]. Nevertheless, these studies paved the way for further investigations [7–10].

Subsequently, a number of studies were published investigating neoadjuvant biochemotherapy using a regimen of multiagent chemotherapy (cisplatin, vinblastine and dacarbazine), IFN- α and IL-2. All of these studies investigated neoadjuvant biochemotherapy in patients with stage III melanoma and will be briefly discussed in chronological

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order. Buzaid *et al.* reported a histologic response rate 50%, with 4/65 (6%) patients achieving a pathologic complete response (pCR) [11]. At median follow-up of 27 months, they reported recurrence free survival (RFS) of 44%, which was significantly higher in patients that demonstrated a response. The OS was 58%, with no survival benefit in patients that demonstrated response to therapy. Dose reduction was required for 37.5% of patients due to treatment toxicity. Gibbs *et al.* reported a Phase II study of 36 patients with overall response rate (ORR) of 38.9% including pCR in 4/36 (11%) patients [12]. At median follow-up of 31 months, RFS was 64.6% and OS 79.2%. Only four patients required a dose reduction in this study due to toxicity. Lewis *et al.* conducted a Phase II study of 92 patients from four institutions [13]. They reported clinical ORR of 26%. At median follow-up of 40.4 months, RFS was 64% and OS was 78%. A total of 34 (38%) patients required a dose reduction due to drug toxicity. Finally, Kounalakis *et al.* published a retrospective review of a single-institutional experience with neoadjuvant biochemotherapy [14]. A total of 154 patients were included in this study. Median follow-up time was 3.4 years with 5-year event free survival of 61% and 5-year OS of 81%. This study reported the highest rate of toxicity in 71 (46%) patients. In summary, neoadjuvant biochemotherapies carried a relatively low response rate with high rates of adverse events. Furthermore, a prospective randomized trial of adjuvant biochemotherapy compared with IFN, the standard of care at that time, was terminated early due to futility of treatment [15]. Biochemotherapy would prove to be ineffective therapy without improvement in survival and the introduction of effective immunotherapy agents would soon revolutionize melanoma treatment.

Era of immunotherapy & targeted therapy

Prior to the discussion of modern checkpoint inhibitors, the earliest immunotherapeutic agent was IFN-α. high-dose IFN-α (HDI) was also the standard adjuvant agent, which led to evaluation as a neoadjuvant agent. Moschos *et al.* evaluated 20 patients treated with HDI before and after surgery [16]. Although they reported an ORR of 55%; only 3/20 patients demonstrated pCR. At a median follow-up of 18.5 months, RFS was 50% and OS was 65%; 25% of patients required a dose reduction due to toxicity.

The current standard of care for stage III melanoma is resection of the primary tumor followed by adjuvant therapy. Previous neoadjuvant therapies were largely ineffective with significant treatment toxicities; however, the introduction of checkpoint-inhibitors and targeted therapy demonstrate early promising results.

Neoadjuvant checkpoint-inhibitor therapy

The two major mechanisms of checkpoint inhibition are inhibition of CTLA-4 and PD-1 protein and its ligand. Neoadjuvant immunotherapy is under investigation for both breast cancer and non-small-cell lung cancer; there is limited conclusive evidence on its efficacy in advanced melanoma [4,17].

The first investigation of neoadjuvant checkpoint-inhibitor therapy was published by Tarhini *et al.* in 2014 [18]. This study investigated the utility of neoadjuvant ipilimumab in patients with surgically operable regionally advanced melanoma ranging from stage IIIB to IV. A total of 35 patients were enrolled and treated with two cycles of ipilimumab 10 mg/kg before and two cycles after definitive surgery with the same dose. Preoperative imaging by PET/CT 6–8 weeks after initiation of neoadjuvant ipilimumab demonstrated objective response in three patients (9%; two complete response [CR], one partial response [PR]). A total of 21 patients (64%) had stable disease and eight patients (24%) progressed despite treatment. No patients had achieved a pCR, as all patients had histologically documented residual melanoma of the surgical specimen. Median follow-up was 17.6 months with progression free survival of 10.8 months. A total of 14 (40%) patients experienced grade 3 adverse events (AEs), but there were no grade 4 or higher toxicities.

Three randomized trials were published in 2018: one investigating ipilimumab in combination with HDI, two investigating combination ipilimumab and three nivolumab neoadjuvant therapy. Tarhini *et al.* conducted a trial investigating safety and efficacy of combination immunotherapy with concurrent HDI [19]. A total of 28 patients with locally or regionally advanced melanoma were randomized to ipilimumab at 3 or 10 mg/kg for two doses followed by definitive surgery. High-dose interferon (20 MU/m^2/day, 5 days/week for 4 weeks, followed by 10 MU/m^2/day subcutaneously 3 days/week) was given concurrently for 2 weeks prior to definitive surgery. Ipilimumab was continued for up to four doses after surgery, while high-dose interferon was resumed with the same subcutaneous regimen for 46 additional weeks. A total of 15 patients completed the intended treatment course; all other patients were limited by AEs, except for nine patients who had progressive disease. As expected, there were more grade 3/4 AEs with the higher dose of ipilimumab therapy; AEs from interferon therapy resolved after holding doses. The pCR was 36% (9/28) and was not significantly different between the dosing regimens with

two additional patients classified as minimal residual disease (one cancer cell or minute clusters of cancer cells on histologic evaluation of surgical specimen). At median follow-up of 32 months, 10/11 patients with either pCR or minimal residual disease remained disease free.

Blank *et al.* reported the results of the OpACIN trial (NCT02437279), a randomized Phase Ib trial [20]. A total of 20 patients with palpable stage III melanoma were equally randomized to four cycles of adjuvant or neoadjuvant ipilimumab 3 mg/kg plus nivolumab 1 mg/kg treatment (two cycles before and after surgery). In the neoadjuvant arm, all patients underwent complete lymph node dissection after at least one course of neoadjuvant therapy although only one patient completed all four intended courses of treatment. One patient in the adjuvant arm discontinued therapy due to disease progression. All the other patients stopped therapy due to grade 3/4 AEs, except one patient in the neoadjuvant arm who wished to discontinue therapy for grade 2 dermatitis. Nine of ten patients were evaluated for a pathologic response, of which seven patients achieved a response: three patients achieved pCR, three patients achieved 'near' pCR, defined as $\leq$10% viable tumor cells; one patient experienced a partial pathologic response (pPR), defined as $\leq$50% viable tumor cells. The two patients without a pathology response relapsed. At median follow-up of 21.6 months in this group, none of the seven patients with a pathologic response relapsed. In terms of AEs, 9/10 (90%) patients stopped therapy due to grade 3/4 AEs; the last patient elected to discontinue treatment for grade 2 dermatitis.

Amaria *et al.* reported a randomized Phase II study of neoadjuvant nivolumab 3 mg/kg monotherapy compared with combination ipilimumab 3 mg/kg and nivolumab 1 mg/kg [21]. A total of 23 patients with stage IIIB and IIIC disease were evaluated; 12 in the monotherapy arm and 11 in the combination arm. The trial was ended early for early disease progression in the monotherapy arm and high rates of grade 3 AEs in the combination arm. The pCR rate was 25% (3/12) in the monotherapy arm, compared with 45% (5/11) in the combination arm. In terms of AEs, 1/12 patients had grade 3 AEs with nivolumab monotherapy, while 8/11 patients had grade 3 AEs on combination ipilimumab and nivolumab treatment. There were no grade 4 or 5 AEs in this trial. Notably, combination neoadjuvant therapy was associated with improved progression-free survival, RFS and distant metastasis-free survival; however, these were not statistically significant.

Based on the current randomized trials, early data demonstrate promising results from neoadjuvant immunotherapy that is unfortunately limited by significant grade 3 or higher AEs. There are many ongoing investigations of neoadjuvant immunotherapy. Tarhini *et al.* also presented interim results from an ongoing trial investigating combination pembrolizumab 200 mg with high-dose interferon (NCT02339324) [22]. Patients were treated with two doses of pembrolizumab before surgery and then every 3 weeks for up to 1 year afterward. The same high-dose interferon regimen as the combination ipilimumab and high-dose interferon study was used [19]. A total of 20 patients were treated and the investigators reported significant AEs, including grade 5 AEs. At the time of presentation, the pCR was 35%.

The OpACIN-neo trial (NCT02977052; Table 2) is an ongoing follow-up to the OpACIN trial discussed above, with the goal of investigating alternative scheduling of combination ipilimumab (ipi) and nivolumab (nivo) to reduce AEs and preserve efficacy [20,23]. The study enrolled 86 patients with resectable stage III melanoma randomized 1:1:1 to: arm A with tow cycles of ipi 3 mg/kg + nivo 1 mg/kg; arm B with two cycles of ipi 1 mg/kg + nivo 3 mg/kg and arm C with two cycles of ipi 3 mg/kg followed by two cycles of nivo 3 mg/kg, with a scheduled lymph node dissection after neoadjuvant treatment. The pCR rates were reported at 43, 57 and 24% respectively for the three arms. The investigators concluded that arm B with 1 mg/kg ipi + 3 mg/kg nivo is the optimal dose with grade $\geq$ 3 AEs in 40% of patients and 43% pCR in 30 patients. The trial will examine this dose of neoadjuvant therapy compared with adjuvant PD-1 blockade in a Phase III trial.

All the previously discussed trials investigated neoadjuvant therapy of patients with advanced disease (stage III or IV). We would like to highlight NCT03757689, which is an ongoing trial currently in the recruitment stage that will be the first trial to investigate immunotherapy (pembrolizumab) in node-negative (stage IIB or IIC), nonmetastatic melanoma. The primary outcome is to determine whether neoadjuvant pembrolizumab decreases rate of positive SLN in high-risk stage II patients. Another study (S1512) is exploring neoadjuvant pembrolizumab in early-stage patients with a rare type of melanoma (desmoplastic) that may be uniquely sensitive to immunotherapy [24]. (Table 2).

Neoadjuvant BRAF/MEK-inhibitor therapy

Early experience with neoadjuvant targeted therapy for *BRAF* V600-mutated melanomas were published in case reports and retrospective analyses. In 2012, Fadaki *et al.* successfully treated a patient with inoperable stage III

Table 1. Summary of completed neoadjuvant immunotherapy and targeted therapy studies.

Study (Year)	Treatment	Disease stage (n)	Sample size (n)	pPR (%)	pCR (%)	Median follow-up (months)	RFS	OS	Ref.
Immunotherapy									
Tarhini *et al.* (2014)	Ipilimumab 10 mg/kg	IIIB (3) IIIC (30) IV (2)	35	Not reported	0	18	10.8 months	Not reported	[18]
Blank *et al.* (2018)†	Ipilimumab 3 mg/kg + Nivolumab 1 mg/kg	III (10)	10§	1 (10%)	3 (30%) 3 (30%) near pCR	25.6	Not reached	Not reached	[20]
Amaria *et al.* (2018) †	Ipilimumab 3 mg/kg + Nivolumab 1 mg/kg	IIIB (3) IIIC (5) IV (3)	11	Not reported	5 (45%)	15.6	82% at 17.2 months	100% at 24.4 months	[21]
	Nivolumab 3 mg/kg	IIIB (6) IIIC (5) IV (1)	12	Not reported	3 (25%)	15	58% at 22.6 months	76% at 22.6 months	
Tarhini *et al.* (2018	Ipilimumab 3 or 10 mg/kg High-dose interferon	IIIB (3) IIIC (25)	28	0‡	9 (32%)	32	Not reached	Not reported	[19]
Tarhini *et al.* (2018)	Pembrolizumab 200 mg High-dose interferon	IIIB (5) IIIC (11) IV (4)	20	Not reported	7 (35%)	11	Not reported	Not reported	[22]
Targeted Therapy									
Sloot *et al.* (2016)	Vemurafenib 960 mg BID or Dabrafenib 150 mg QD ± Trametinib¶	III (15)	6††	2 (33%)	2 (33%)	25.4	Not reported	Not reached	[27]
Zippel *et al.* (2017)	Vemurafenib 960 mg BID or Dabrafenib 150 mg QD ± Trametinib 2 mg QD	III (13)	13	8 (62%)	4 (31%)	20	Not reported	Not reached	[28]
Eroglu *et al.* (2017)	Vemurafenib¶ Dabrafenib + Trametinib¶ Encorafenib + Binimetinib¶	IIIC (9) IV (11)	20	Not reported	7 (35%)	25	Not reported	Not reported	[29]
Amaria *et al.* (2018)†	Dabrafenib 150 mg BID Trametinib 2 mg QD	IIIB (2)‡‡ IIIC (10)‡‡ IV (2)‡‡	12‡‡	2 (17%)	7 (58%)	18.6	19.7 months#	Not reached	[31]

†Terminated early.
‡Two patients with minimal residual disease (single cancer cell or minute clumps of cancer cells).
§Neoadjuvant arm. Of 10 patients, 9 were evaluable for pathologic response
¶Dose not reported.
#Median event-free survival.
††Of 15 patients, only 6 underwent surgery.
‡‡Of 14 patients, only 12 underwent surgery. One patient withdrew consent prior to initiation of protocol, stage of disease not specified.
OS: Overall survival; pPR: Pathologic partial response; pCR: Pathologic complete response; RFS: Recurrence free survival.

Table 2. Ongoing clinical investigations of neoadjuvant therapy for advanced cutaneous melanoma as of January 2019.

Clinical Trial number	Name of study	Drugs investigated	Disease stage	Estimated subject size	Projected completion
Immunotherapy					
NCT03757689	Neoadjuvant PD-1 blockade in patients with stage IIB/C melanoma	Pembrolizumab	II	63	February 2026
NCT02775851	A Phase II and pilot trial of PD-1 blockade with MK-3475 (pembrolizumab) in patients with resectable or unresectable desmoplastic melanoma (SWOG S1512)	Pembrolizumab	Resectable primary desmoplastic melanoma	41 (Neoadjuvant Cohort)	December 2028
NCT03259425	Phase II neoadjuvant trial of nivolumab in combination with HF10 oncolytic viral therapy in resectable stage IIIB, IIIC, IVM1a melanoma (Neo-NivoHF10)	Nivolumab vs HF10 (oncolytic virus)	IIIB–C, IVM1a	20	October 2022
NCT02306850	Neoadjuvant pembrolizumab for unresectable stage III and unresectable stage IV melanoma (NeoPembroMel)	Pembrolizumab	III, IV	15	February 2019
NCT02977052	Optimal neo-adjuvant combination scheme of ipilimumab and nivolumab (OpACIN-neo)	Combination ipilimumab + nivolumab	III	110	June 2022
NCT03698019	Pembrolizumab in treating patients with stage III–IV high-risk melanoma before and after surgery (SWOG S1801)	Adjuvant pembrolizumab vs Neoadjuvant + Adjuvant pembrolizumab	III, IV	556	September 2022
NCT02434354	A tissue collection study of pembrolizumab (MK-3475) in subjects with resectable advanced melanoma	Pembrolizumab	IV	30	April 2022
NCT03618641	CMP-001 in combo with nivolumab in stage IIIB/C/D melanoma patients with clinically apparent lymph node disease	CMP-001 (TLR9 agonist) + Nivolumab	IIIB/C/D	20	June 2023
NCT02519322	Nivolumab with or without ipilimumab or relatlimab before surgery in treating patients with stage IIIB–IV melanoma that can be removed by surgery	Nivolumab vs nivolumab + ipilimumab vs nivolumab + relatlimab	IIIB–IV	53	February 2020
Targeted therapy					
NCT01972347	Neoadjuvant dabrafenib + trametinib for AJCC stage IIIB–C *BRAF* V600 mutation positive melanoma	Dabrafenib + trametinib	IIIB–C	35	May 2022
NCT02303951	Neoadjuvant vemurafenib + cobimetinib in melanoma (NEO-VC)	Vemurafenib + cobimetinib	IIIC, IV	110	April 2020
NCT02036086	Study of neo-adjuvant use of vemurafenib plus cobimetinib for *BRAF* mutant melanoma with palpable lymph node metastases	Vemurafenib + cobimetinib	IIIB–C	20	October 2022
NCT03554083	Neoadjuvant combination targeted and immunotherapy for patients with high-risk stage III melanoma (NeoACTIVATE)	Atezolizumab + cobimetinib *(if BRAF-wild type)* Vemurafenib + atezolizumab + cobimetinib *(if BRAF-mutant)*	III	30	June 2023
NCT02858921	Neoadjuvant dabrafenib, trametinib and/or pembrolizumab in *BRAF* mutant resectable stage III melanoma (NeoTrio)	Dabrafenib + trametinib ± pembrolizumab	III	60	November 2020
NCT02339324	Neoadjuvant combination biotherapy with pembrolizumab and high dose IFN-α2b	Pembrolizumab + HDI	III	30	January 2020
Intralesional therapies					
NCT02211131	Efficacy and safety of talimogene laherparepvec neoadjuvant treatment plus surgery vs surgery alone for melanoma	T-VEC vs immediate surgery	IIIB–C, IVM1a	150	April 2022
NCT03567889	Efficacy of daromun neoadjuvant intratumoral treatment in clinical stage IIIB/C melanoma patients (Neo-DREAM)	Daromun intratumoral (L19IL2/L19TNF; darleukin/fibromun) vs surgery	IIIB–C	248	December 2022

AJCC: American Joint Committee on Cancer; HDI: High dose interferon; PD-1: Programmed death protein; TLR: Toll-like receptor; T-VEC: Talimogene laherparepvec.

disease with neoadjuvant vemurafenib [25]. After 4 months of therapy, the patient's tumor shrank to less than 50% of its original size and the patient then successfully underwent surgery. Notably, despite clinically bulky nodal disease, only 1/40 nodes harbored metastatic cells and the patient had over 98% pathological response and remained disease free 6 months after surgery. At a similar time, Koers *et al.* successfully treated a patient in the Netherlands with a similar clinical response to vemurafenib [26]. None of the 20 resected lymph nodes contained metastatic melanoma, and the patient remained disease free 5 months after surgery.

Several larger case series also reported favorable results. The first reported use of neoadjuvant vemurafenib or combination dabrafenib and trametinib for 15 patients, six of which underwent surgical resection [27]. Four of these patients demonstrated at least a pPR; three patients that received surgery survived for greater than 2 years and remained free of disease. Another study in Israel reported treatment of 13 consecutive patients with either vemurafenib alone, or dabrafenib with or without combination trametinib; twelve patients demonstrated clinical response and underwent successful excision, all of which demonstrated at least PR on pathologic examination [28]. While all the aforementioned studies examined stage III patients alone, one series also included stage IV patients (11/20 examined patients) [29]. The investigators also included patients treated with neoadjuvant combination encorafenib and binimetinib, in addition to the other targeted therapy regimens. Seven patients had pCR and none of these patients had subsequent disease recurrence. The definition of pCR used in this analysis is the same as detailed in the methods described by Tetzlaff *et al.* [30].

These previous studies paved the way for the only published randomized clinical trial investigating neoadjuvant targeted therapy, published by Amaria *et al.* [31]. This study included patients with resectable stage III or IV melanoma with confirmed *BRAF* V600E or V600K mutation. Patients were randomized 1:2 to standard of care (surgery and standard adjuvant therapy, including IFN-α2b, ipilimumab or a biochemotherapy regimen) or 8 weeks of neoadjuvant dabrafenib and trametinib followed by surgery and continued adjuvant therapy. A total of 21 patients were analyzed, seven to standard of care and 14 to neoadjuvant therapy. The study was terminated early at a prespecified interim safety analysis when the neoadjuvant arm demonstrated significantly longer event-free survival compared with standard of care. At median follow-up of 18.6 months, 10/14 patients that received neoadjuvant therapy were alive without disease progression, whereas all patients that received standard of care therapy progressed. Seven of 12 patients in the neoadjuvant arm achieved pCR after surgery and 2/12 achieved pPR and 3/12 patients had no response to neoadjuvant therapy. In terms of AEs, all patients experienced grade 2 AEs, and 2/14 patients experienced grade 3 diarrhea; there were no grade 4 or higher AEs. All patients in the neoadjuvant arm had resectable disease after neoadjuvant therapy. Completed targeted therapy studies are summarized in Table 1.

Interim results from an ongoing clinical trial (NCT01972347; Table 2) of combination dabrafenib and trametinib neoadjuvant therapy reported a high rate of pCR for resectable stage III disease [32]. Updated results of this study were presented at ESMO 2017 [33]. At this time, 35 patients have received neoadjuvant dabrafenib and trametinib, of which 33 completed resection. Total 17 of 33 (52%) patients had pCR, though the authors note discordant pathologic response with RECIST response in 7 (21%) patients. Once again, no patients progressed during neoadjuvant treatment and no patients discontinued therapy. At median 12.1 month follow-up post resection, 12 (36%) patients had recurred; six of these patients had prior pCR and eight patients had distant recurrence.

Another neoadjuvant trial by a Dutch group, the REDUCTOR trial (EudraCT: 20134-002616-28), reported interim results from a trial of 8 weeks of neoadjuvant therapy with dabrafenib and trametinib in unresectable *BRAF*-mutated, locally advanced stage III or oligometastatic stage IV melanoma [34]. A total of 17 patients have been included in this analysis: two progressed during neoadjuvant therapy; 14 of 15 remaining patients were restaged with resectable disease, 13 of which underwent R0 resections. A pathologic CR rate of 35% was reported. Median RFS was 9 months, with median follow-up of 22 months; the number of patients that recurred was not reported. Most patients experienced at least a grade 1 AE, but only two experienced grade 3 AEs. Of note, this is the only study that specifically investigated neoadjuvant targeted therapy in unresectable primary tumors.

Intralesional therapy

Intralesional therapy for melanoma is a relatively new discovery that is primarily used in the setting of advanced disease, especially in patients with limited locoregional spread [35,36]. These agents are injected directly into tumor lesions to limit systemic exposure, thus improving tolerability of treatment. Furthermore, abscopal effects have been observed, which is a systemic response to local treatment of a tumor lesion resulting in response in untreated distant lesions. A number of intralesional therapies have been investigated, but the newest agents that are under investigation for neoadjuvant therapy are talimogene laherparepvec (T-VEC) and Daromun (L19IL2 + L19TNF).

T-VEC is an oncolytic herpes simplex virus type 1 which has been genetically modified to remove its virulence factor (ICP34.5) such that it selectively replicates in tumor cells and expresses GM-CSF [37,38]. Once the engineered virus infects tumor cells, it replicates and destroys the host cell, releasing GM-CSF to initiate a tumor-specific systemic response. This agent was approved by the US FDA in 2015 based on the OPTiM trial [39]. A subgroup analysis of Stage IIIB–IVM1a patients demonstrated ORR of 40.5% and durable response rate of 25.2% with TVEC therapy, significant improved over GM-CSF [40]. These patients received more benefit from TVEC than other patients.

Interim results from the first neoadjuvant trial of T-VEC were presented at ASCO 2018 and SSO 2019 [41]. A total of 150 patients with resectable stage IIIB–IVM1a disease were randomized 1:1 to neoadjuvant T-VEC (6 doses/12 weeks) followed by surgery versus surgery upfront. In the neoadjuvant arm, T-VEC was administered until surgery, no injectable lesions or treatment intolerance. Total 19/76 (25%) of patients in the neoadjuvant arm did not undergo surgery, 11/19 due to progressive disease. The remaining patients completed surgery with a 21% pCR. Negative margin (R0) resection was achieved in 56.1% in the neoadjuvant arm compared with 40.6% in the surgery arm. In terms of adverse events, 93% of patients in the neoadjuvant arm experienced treatment emergent AEs and 45% in the surgery arm. Severe AEs were observed in 17.8 versus 2.9% of patients in the neoadjuvant and surgery arms, respectively. The authors concluded that 12 weeks of neoadjuvant T-VEC leads to a higher pCR rate than ORR and higher rate of R0 resection. This study is ongoing (Table 2).

Daromun is the combination of two monoclonal antibody-cytokine fusion proteins (immunocytokines) darleukin (L19IL2) and fibromun (L19TNF). This allows for selective delivery of the immunocytokine to tumor sites. Previous studies of each agent alone only led to delayed progression of disease; however, murine melanoma models demonstrated synergistic effect when administered in combination, leading to complete melanoma remission [42,43]. In 2015, Danielli *et al.* published results of Daromun therapy in stage IIIC–IVM1a melanoma patients with unresectable disease [44]. While this study was not primarily intended to evaluate neoadjuvant therapy with Daromun, the protocol allowed for resection of tumor if feasible after 12 weeks of therapy. Eight of 20 (40%) evaluable patients became eligible for surgery and were withdrawn from the study. These results led to an ongoing international, randomized trial investigating Daromun in the neoadjuvant setting for stage IIIB and IIIC disease compared with surgery upfront (NCT03567889; Table 2).

Conclusion

The introduction of immunotherapy and targeted therapy has accelerated melanoma research, and has provided much needed therapies for advanced disease. Early investigations of neoadjuvant therapy have already shown promising results and are paving the way for further advancements in understanding the mechanisms of these novel agents. Effective and safe neoadjuvant therapy is on the horizon for the treatment of advanced melanoma and will allow for surgical treatment of previously unresectable disease.

Future perspective

Early reports and interim results show that systemic neoadjuvant therapy for advanced melanoma is promising. Both classes of systemic agents seem to be moderately efficacious and preserve resectability of primary disease after completion of the treatment. Early evidence suggests that neoadjuvant targeted therapy may have a different effect on the tumor microenvironment, abrogating the rapid development of resistance as seen in adjuvant therapy. Also, as previously suggested, the pattern of pathologic response to neoadjuvant therapy may have implications for patient outcomes [29]. Further investigation is required to determine how strongly pathologic responses, as defined by Tetzlaff *et al.*, correspond to improvement in clinical outcomes and long-term survival [30]; for example, it is not yet clear if achieving a pCR versus a non-pCR may correlate to longer relapse-free and overall survival in melanoma. Currently, neoadjuvant immunotherapy is primarily limited by AEs that are frequently dose limiting or require treatment cessation. The ongoing OpACIN-neo trial is directly addressing this and interim results indicate that there may be an optimal neoadjuvant dose that retains therapeutic benefit while balancing AEs. Optimal duration of neoadjuvant therapy is also not yet clear as different trials utilize different lengths of therapy. Ongoing and future trials are also exploring combinations of targeted and immunotherapies, and are incorporating intralesional therapies as well. There are also ongoing investigations into the role of adjuvant versus neoadjuvant treatment in melanoma; a recently opened large SWOG trial is randomizing patients to either three cycles of neoadjuvant pembrolizumab followed by adjuvant therapy or standard adjuvant pembrolizumab for 1 year (NCT03698019; Table 2), which will clarify the benefit of neoadjuvant therapy. The results of the REDUCTOR trial are eagerly awaited as this is

the first study to evaluate whether neoadjuvant immunotherapy is effective for converting unresectable tumors to resectable.

Intralesional therapies are a relatively new class of therapeutics which with demonstrated efficacy for the treatment of metastatic lesions. Two agents, T-VEC and Daromun, are under investigation for neoadjuvant application. Early evidence is again promising; results thus far demonstrate high pathologic response while preserving resectability.

Currently, there are nearly 20 ongoing clinical trials (Table 2) examining combinations of existing and novel agents, the results of which are highly anticipated to help establish the application and utility of neoadjuvant therapy in advanced melanoma. As evidence becomes available, we will better understand which group of patients will best benefit from neoadjuvant therapy.

Executive summary

- The introduction of immunotherapy and targeted therapy has improved the adjuvant treatment of advanced melanoma. The neoadjuvant application of these agents is the natural extension.

Past experiences with neoadjuvant biochemotherapy

- Early use of neoadjuvant biochemotherapy is briefly discussed to provide historical perspective and context for the evolution of neoadjuvant treatment in advanced melanoma.

Era of immunotherapy & targeted therapy

- The majority of available data is from neoadjuvant treatment of advanced resectable melanoma. In general, both classes offer high treatment response that does not sacrifice resectability of the primary disease.

Neoadjuvant checkpoint-inhibitor therapy

- Checkpoint inhibitors and targeted agents (BRAF/MEK-inhibitors) are effective adjuvant agents. Results of the earliest trials demonstrate high initial response rates that are limited by high rates of adverse events. Ongoing trials are investigating alternative doses without sacrificing efficacy.

Neoadjuvant BRAF/MEK-inhibitor therapy

- There is the least amount of data regarding targeted agents, found in case series and a single completed randomized trial. Results from these early studies suggest that neoadjuvant therapy is well tolerated with high-response rates.

Intralesional therapy

- Intralesional therapies are ideal for the treatment of advanced melanoma because a higher dose of medication can be delivered to localized disease, limiting systemic toxicity. In the neoadjuvant setting, two agents are under investigation: talimogene laherparpvec (T-VEC) and Daromun (L19IL2 + L19TNF). T-VEC is an engineered herpes simplex virus that expressed GM-CSF in host cells, while Daromun is a combination immunocytokine that uses monoclonal antibodies to deliver IL-2 and TNF directly to tumor cells. Both have demonstrated promising local effect without significant adverse events. Investigation of these two agents for neoadjuvant therapy is in the early phases and results from ongoing clinical trials are anticipated in 2022.

Conclusion

- Early results suggest that neoadjuvant therapy will become a mainstay of the management of advanced melanoma. There are many ongoing studies which are eagerly awaited to determine the optimal neoadjuvant treatment strategy to maximize patient outcomes.

Future perspective

- More follow-up time is needed to understand the effect of neoadjuvant treatments, including long-term survival and disease recurrence. Comparisons of neoadjuvant and adjuvant treatment are forthcoming. Ideally, it will be possible to identify patients that are most likely to benefit from neoadjuvant treatment; patients with unresectable tumors are ideal candidates for neoadjuvant therapy yet there is insufficient data to guide this treatment at this time. Finally, the identification of new neoadjuvant agents will provide more options for patients.

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