REVIEW

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Melanoma Management

Surgical resection of metastatic melanoma in the era of immunotherapy and targeted therapy

Richard Tyrell[1], Camila Antia[1], Sharon Stanley[1] & Gary B Deutsch*[,1]

Practice points

Surgical treatment for metastatic melanoma

- When possible surgical resection of metastatic melanoma demonstrates survival advantage compared with systemic medical treatment.
- The mechanism for survival advantage may be rooted in the immunologic effects.

Systemic immunotherapy

- Systemic immunotherapies are US FDA approved for the treatment of metastatic melanoma.
- Response rates are greater than traditional chemotherapeutics.
- CTLA-4 inhibitors have shown a survival advantage in patients already treated with chemotherapy.
- PD-1 inhibitors have remarkable response rates in patients already treated with CTLA-4 and *BRAF* inhibitors.

Targeted therapy

- *BRAF* and *MEK* inhibitors show survival advantage in patients with V600E and V600K mutations compared with dacarbazine.

Neoadjuvant immunotherapy

- Case reports have demonstrated the potential for the use of both systemic immunotherapy and targeted therapy in the neoadjuvant setting.
- Clinical trials are ongoing in regards to neoadjuvant use.

Directed surgical therapy

- Removing bulking tumors may modulate immunosuppressive effects of melanoma.
- Melanoma adapts to pharmacologic therapy.

Future perspective

- As systemic therapies improve, the role of surgery also increases.
- An algorithm for the treatment of unresectable stage III and stage IV melanoma will involve surgery, systemic immunotherapies and targeted therapies.

[1]Hofstra – Northwell School of Medicine, 450 Lakeville Road, Lake Success, New York, NY, USA
*Author for correspondence: Tel.: +1 516 487 9454; Fax: +1 516 487 2745; gdeutsch@northwell.edu

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Melanoma is the deadliest form of skin cancer and one of the few malignancies whose incidence is on the rise. The treatment of metastatic melanoma continues to be quite challenging, although in recent years, there has been significant progress. Current National Comprehensive Cancer Network guidelines list immunotherapy, chemotherapy, surgery and clinical trials as potential options for patients with metastatic disease but do not clearly recommend which is superior. Additionally, when utilizing combined modality treatment there are no clear guidelines for the optimal timing of surgery in the treatment of metastatic melanoma. In this paper we sought to compile the current evidence and on-going trials in order to provide a comprehensive review of the different options available and underway in regards to the treatment of metastatic melanoma. It is clear that with the responses now seen with systemic immunotherapies and targeted therapies, an expanded role for surgery is the logical next step.

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KEYWORDS
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• surgical therapy

Melanoma is the deadliest form of skin cancer and one of the few malignancies whose incidence is on the rise. Early diagnosis is the key to cure with surgical resection being the mainstay of treatment for localized disease. Staging of melanoma is largely dependent on the tumor depth with Breslow thickness being used to determine the T stage in the tumor node metastasis (TNM) classification. Secondary characteristics such as mitotic rate and presence of ulceration are highly prognostic factors that influence staging and guide treatment options. In general, patients presenting with early-stage melanoma have an excellent prognosis. T1 lesions (less than 1.0 mm) have 5-year survival rates of greater than 90%. Survival rates range from 50 to 90% for lesions greater than 1.0 mm in depth. Nodal involvement is more likely with larger tumors, and the amount of nodal tumor burden greatly decreases survival rates. Patients with metastatic disease have historically had even worse outcomes, with 10-year survival rates below 10% [1].

The treatment of metastatic melanoma continues to be quite challenging, although in recent years, there has been significant progress. Historically, systemic treatment involved a combination of traditional cytotoxic chemotherapeutic agents, including dacarbazine, temozolomide and paclitaxel, but response rates were mediocre, and with significant complications [2]. Dacarbazine (DTIC), an alkylating agent, was the first-line chemotherapeutic of choice for metastatic melanoma with response rates ranging from 15 to 20% as a single agent [2]. Temozolomide, a similar drug not requiring metabolic activation as with DTIC, has shown similar response rates and median survival [2]. Combination studies such as the Dartmouth Regimen (DTIC, cisplatin, BCNU and tamoxifen), initially showed increased response rates but in Phase III trials there was no difference in response rates or survival [2]. Cytokines, such as IL-2 and interferon, have also been combined with chemotherapy to form the concept of biochemotherapy (BCT). Response rates were similar: 19.5% for BCT versus 13.8% for combination therapy ($p = 0.14$). Progression-free survival (PFS) was higher with BCT; 4.8 versus 2.9 months ($p = 0.015$). Unfortunately, BCT regimens were shown not to increase survival; 9.0 versus 8.7 months [3]. As a result, surgical resection of metastatic disease has been heavily utilized as the only viable option for these patients. Recently newer and more effective immunotherapies and targeted therapies have been US FDA approved. These agents include CTLA-4 inhibitors, PD-1 inhibitors, *BRAF* and *MEK* gene inhibitors. Preliminary evidence has shown significant and durable response rates in a measurable group of patients with stage IV disease.

Current National Comprehensive Cancer Network guidelines list immunotherapy, chemotherapy, surgery and clinical trials as potential options for patients with metastatic disease but do not clearly designate a superior choice. Additionally, when utilizing combined modality treatment, there are no recommendations for the optimal timing of surgery in the treatment of metastatic melanoma.

Surgical treatment for metastatic melanoma

Surgical therapy for stage IV disease was once viewed as futile in metastatic disease with the premise that local resection cannot eradicate

occult tumor cells outside the site of the lesion. However, metastasectomy has been clearly shown to have a beneficial role in the treatment of several advanced malignancies, namely colon and lung cancer. The resection of colorectal metastases to the liver is well established. Five- and 10-year survival of up to 40 and 26%, respectively, has been demonstrated for hepatectomy in colorectal cancer [4]. Studies have also demonstrated 5-year survival rates of 35% in patients treated with neoadjuvant chemotherapy prior to metastasectomy [5]. The success of metastasectomy in colorectal cancer has been attributed to several factors including increased use of chemotherapy, improved imaging and surgical intervention [4,5].

Improved long-term outcomes in patients undergoing metastasectomy for melanoma have been demonstrated in several multicenter trials. In a retrospective analysis of the MSLT-I data, patients who developed stage IV melanoma and underwent surgical resection had improved survival when compared with those who received systemic medical therapy alone. Median survival was significantly higher in patients treated with surgery and systemic therapy, 15.8 months, compared with systemic therapy alone, 6.9 months ($p < 0.0001$). Patients were then divided into M1a: skin, subcutaneous or distant lymph nodes, normal serum lactate dehydrogenase (LDH); M1b: lung with normal LDH; and M1c: visceral or other distant sites with elevated LDH. In patients with M1a disease, 4-year survival was 69% in patients treated with surgery versus 0% for patients treated with systemic therapy (SMT) ($p = 0.0106$). In M1b disease, 4-year survival was 24.1% in the surgical group and 14.3% in the SMT group ($p = 0.1143$) and in M1c patients, 4-year survival was 10.5% in surgical patients and 4.6% in SMT patients ($p < 0.0001$) [6].

Prior to the publication of the MSLT-I study, the Southwest Oncology Group performed a prospective, multicenter trial to identify rates of overall survival and relapse-free survival in stage IV melanoma patients treated with surgical resection. They found that patients who underwent metastasectomy had an improved survival. Most patients had skin and soft tissue metastatic disease, greater than 50%, however LDH was not available and stratification by the American Joint Committee on Cancer staging system was not possible. Their median overall survival was 21 months versus historical rates of 6–10 months with systemic medical therapy. Median relapse-free survival was 5 months [7]. The discrepancy between the two rates highlights the significant rate of recurrence in melanoma. However, many patients are candidates for re-resection of recurrent lesions, which leads to improved outcomes. Patients who were able to be completely resected experienced 1-year survival of 75 versus 25% for those unable to be completely resected [7].

In 2006, data from the multicenter double-blind Phase III trial involving canvaxin versus placebo as postsurgical adjuvant therapy in metastatic melanoma were presented at The Society Of Surgical Oncology 59th Annual Cancer Symposium. They found no difference between the placebo group or the canvaxin group. Unexpectedly, they found that in patients who were resected, median survival was 32 months and 5-year overall survival was 40% [8]. There is also some evidence from the Surveillance, Epidemiology, and End Results Program database supporting surgical resection. In patients with M1a disease, those who were resected had a median survival of 14 versus 6 months in those who were not. Five-year survival was 20% in the resected group and 9% in the nonresected [9].

Resection of metastatic melanoma in M1c disease has also been described with improved survival. At the John Wayne Cancer Center, a study of their prospectively collected database of melanoma patients identified 91 patients treated for adrenal metastases. Twenty-four patients underwent adrenalectomy and 67 patients were managed nonoperatively. Median survival was 29.2 months in the adrenalectomy group and 9.4 months in the nonoperative group ($p < 0.001$) [10]. Successful resection of hepatic lesions has also been documented. These patients were selected based on surgeon's judgment, including factors such a tumor-doubling time, patient comorbid conditions and response to systemic therapy. Within the database 1078 patients were identified with liver metastasis, 58 were considered candidates for either resection or ablation. Median overall survival in the surgical group was 24.8 versus 8 months in the nonsurgical patients ($p < 0.001$) [11].

The basis upon which surgery improves outcomes may be, in part, related to the immunogenic effects of melanoma. Metastatic melanoma may lead to a generalized immunosuppressive state in part due to upregulation of VEGF and Th2 cytokines [12]. This chronic inflammatory state was noted only in stage IV melanoma

with immune tolerance to tumor antigens also observed [12].

Systemic immunotherapy

Faced with suboptimal treatment options for metastatic melanoma, investigators set out to study the immunogenicity associated with melanoma and its progression in order to seek other targets for therapy. The transformation and regression of melanoma has been found to be highly immune-regulated. Taking advantage of this immunogenicity, various treatment modalities have been developed including recombinant cytokines, vaccines, tumor-infiltrating lymphocytes and antiganglioside antibodies. These therapies harness the power of the host immune system to specifically attack malignant cells. Some have been FDA approved while others are still under investigation. These agents include IL-2, interferon, CTLA-4 antibodies, PD-1 and PD-L1 inhibitors [13].

Two of the original class of immunotherapeutic agents that were approved for the treatment of metastatic melanoma were IL-2 and interferon. IL-2 is a cytokine that stimulates T-cell proliferation and maturation, augments natural killer cells and promotes the release of other cytokines including tumor necrosis factor and interferon. In the group of eight clinical trials evaluating the effectiveness of IL-2 in metastatic melanoma, there was overall response rate of 16% and median survival was 12 months [14]. Responders did experience a durable long-term response with 58% of responders remaining progression-free at 12 months [14]. Toxicities were common with high dose IL-2, 2.2% of patients died from events related to toxicity [15]. High-dose interferon has also been studied as systemic therapy with response rates of 22%. Median survival for patients who responded was 11.3 months. Median survival for all study participants was 5 months. However, toxicity and unpredictability of response continues to be a concern with interferon [16].

CTLA-4, a negative regulator of T cells, and thereby augments T-cell activation and proliferation [17]. This was the first agent to show overall survival advantage in the setting of systemic treatment in patients with stage III and IV melanoma who were not amenable to surgery and previously treated with traditional therapies such as dacarbazine, IL-2, temozolomide, carboplatin or fotemustine. MDX010–20 was a Phase III, randomized, double-blind, multicenter study that included the USA, Europe, Africa and South America. Patients who were HLA-A 0201-positive and diagnosed with unresectable stage III or stage IV melanoma were randomized 3:1:1 to receive ipilimumab 3 mg/kg + gp100 vaccine, ipilimumab 3 mg/kg + placebo, or gp100 vaccine + placebo. Increased survival was observed in both groups containing ipilimumab. The median overall survival was 10 months in the ipilimumab + gp100 vaccine group, 10.1 months in the ipilimumab + placebo group and 6 months in the gp100 vaccine + placebo group [18].

PD-1 are inhibitory receptors on T cells as well as antigen-presenting cells. These receptors are commonly expressed in the tumor microenvironment. Stimulation of these receptors causes downregulation of the effector phase of T-cell responses [19]. In a Phase I study of lambrolizumab, response rates in the highest dosage group were 52%. The highest dosage group also experienced the greatest percentage of adverse events at 23%. The patients in this trial had advanced melanoma with some of them previously treated with ipilimumab. Remarkably, patients in both groups experienced impressive response rates up to 62% in the previously treated group [19]. In another trial nivolumab was evaluated versus the investigators choice of chemotherapy in patients with unresectable stage IIIC or stage IV melanoma. Patients who experienced progression with CTLA-4 inhibitors and *BRAF* inhibitors were included. Objective responses were noted in 31% of patients given nivolumab and 10.6% in the investigators choice of chemotherapy group. There was no difference found in PFS. However, treatment may have been discontinued early as radiologic criteria were used to determine disease progression. In 8.2% of patients they experienced regression beyond the initial radiologic assessment [20].

In addition to systemically delivered immunotherapies, intralesional therapies such as IMLYGIC™ (talimogene laherparepvec or T-VEC) are starting to be used. T-VEC is a genetically modified live oncolytic virus derived from herpes simplex virus 1 approved by the FDA in October 2015. T-VEC was designed to selectively replicate in tumor cells, promoting the released of granulocyte–macrophage colony-stimulating factor (GM-CSF) and other tumor-derived antigens after the lytic destruction of the tumor cells, thus enhancing the endogenous immune response [21].

The safety and efficacy of T-VEC were evaluated in the OPTiM trial, a randomized multicenter Phase III trial. In this trial, 436 participants with unresected melanoma with regional or distant metastases were treated with TVEC or GM-CSF intralesional for at least 6 months, or until there were no remaining injectable lesions. The study's primary end point was durable response rate, which was significantly higher for T-VEC 16.3% (95% CI: 12.1–20.5%) than for GM-CSF 2.1% (95% CI: 0–4.5%). Overall response rate was also higher with T-VEC 26.4% (95% CI: 21.4%–31.5%) compared with GM-CSF 5.7% (95% CI: 1.9–9.5%). However, improvement of overall survival was not significant. A higher efficacy rate was seen on patients with stage III/IV M1a and in patients with treatment-naive disease. The most common side effects noted were fatigue, chills and fever [22].

Targeted therapy

BRAF mutations are relatively common in patients with advanced melanoma with a prevalence of around 50%, and often seen in younger individuals [23,24]. The two most common mutations are V600E and V600K. Vemurafenib is a *BRAF* inhibitor that has been studied in patients with untreated stage III and stage IV melanoma. In the BRIM-3 Trial, 675 patients were randomized to either vemurafenib versus dacarbazine. In the V600K group, overall survival for vemurafenib was 13.6 versus 9.7 months in the dacarbazine group ($p = 0.008$). 57% of patients responded to vemurafenib but only 9% of patients responded to dacarbazine [23]. In another Phase III open label trial, *MEK* inhibitors were evaluated in patients with *BRAF* mutations. Patients with unresectable stage IIIC and IV melanoma were eligible. Patients received trametinib ($n = 214$ patients), or dacarbazine ($n = 108$ patients). PFS was 4.8 months in the trametinib group and 1.5 months in the dacarbazine group ($p < 0.001$). Six-month overall survival in the trametinib group was 81 versus 67% in the dacarbazine group, with a hazard ratio for death of 0.54 for trametinib. The response rates were also improved with the *MEK* inhibitors with a response of 22 versus 8% in the chemotherapy group [24].

Neoadjuvant immunotherapy

Currently, there are no guidelines for the neoadjuvant treatment of metastatic melanoma. Surgical resection is performed when possible and the efficacy of various adjuvant therapies is currently being investigated. Inoperable or metastatic melanoma may benefit from upfront systemic medical therapy in hopes of downstaging or halting progression and converting the disease burden to resectable.

IL-2 was used as one of the pioneer treatments for metastatic melanoma. The overall response rate was 16% (95% CI: 12–21%) with only 6% of complete response and 10% of partial response. Although the response rate was modest, contrary to other systemic regimens high-dose IL-2 produced durable responses. Most of these were seen in patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0, skin, lungs or lymph node involvement; however, few responders had visceral disease or ECOG PS of more than 1. To date, high-dose IL-2 lacks predictive biomarkers to determine which patients will develop a durable response [14]. In some cases where patients developed isolated metastasis or their primary site showed evidence of progression, surgical resection was employed and later deemed disease-free, bringing to light the beneficial role of second-line surgery in patients who develop resectable disease after systemic treatment [14].

Initial studies involving ipilimumab as neoadjuvant therapy have been promising. An ongoing trial at Pittsburg evaluated patients with stage IIIB-C melanoma. The patients underwent pretreatment biopsy and 10 mg/kg of ipilimumab 3 weeks apart and then surgery 6–8 weeks after the initiation of ipilimumab treatment. Initial results analyzing the changes in biomarkers demonstrated an increase in TReg Cells and myeloid derived suppressor cells, which were both associated with improved PFS. The median PFS was 10.8 months [17]. This outcome was deemed promising given the advanced stage of patients receiving treatment. Ipilimumab has also been described in case reports as successful in the neoadjuvant setting. Two patients with initially unresectable disease were treated and subsequently resected successfully [25]. Clinical trials are ongoing, evaluating the effectiveness of ipilimumab (CTLA-4 inhibitor) and nivolumab (PD-1 inhibitor) in oligometastatic melanoma; NCT02519322. Ipilimumab is also being evaluated in conjunction with INF; NCT01608594.

Several case reports have been published demonstrating the effectiveness of BRAF inhibitors. In one report, vemurafenib was used to treat unresectable stage IIIc melanoma. The patient

Table 1. Outcomes of surgical resection in metastatic melanoma.

Study (year)	Disease	Resected median survival (months)	Nonresected median survival (months)	p-value	Ref.
Howard *et al.* (2012)	M1a, M1b, M1c	15.8	6.9	<0.0001	[6]
Sosman *et al.* (2011)	M1a, M1b, M1c	21	No control	NA	[7]
Faries *et al.* (2014)	M1c adrenal	29.2	9.4	<0.001	[11]
Flaherty *et al.* (2015)	M1c liver	24.8	8	<0.001	[10]
Wasif *et al.* (2011)	M1a	14	6	<0.001	[9]

M1a: Metastases to skin, subcutaneous, or distant lymph nodes with normal lactate dehydrogenase level; M1b: Metastases to lung with normal lactate dehydrogenase; M1c: Metastases to all other visceral sites or distant metastases with an elevated lactate dehydrogenase level; NA: Not applicable.

had a tumor fixed to the chest wall and therefore not amenable for resection. The patient was found to be positive for the *BRAF* mutation and underwent treatment with vemurafenib. After a partial response, the tumor was deemed resectable; the patient underwent radical resection and radiotherapy. The patient remained disease-free at 5-month follow-up [26]. In another case series of 15 patients, they observed a 70% response rate in patients with locally advanced melanoma; in addition six of the 15 patients underwent conversion from unresectable to resectable disease [27].

Directed surgical therapy

Current treatment recommendations for stage IV melanoma include resection of limited and resectable disease or solely systemic medical treatment. Surgery may play a role on many levels in combination with immunotherapy in patients with metastatic melanoma. Tumors may suppress the immune system by various mechanisms. Tumor antigens, antigen–antibody complexes, as well as cytokines and prostaglandins produced by tumor cells may all act in differing capacity to suppress the immune system [12]. It has been documented that removing bulky tumors decreases the immunosuppressive effects of melanoma and allows host defenses to more effectively attack residual disease.

Dudley *et al.* demonstrated that recurrent tumor displayed loss of the expression of tumor antigens after adoptive transfer of CTL [28]. They also noted that the majority of patients were partial responders to immunotherapy. Melanoma has also developed resistance to *BRAF* inhibition by switching between RAF isoforms [29]. Several combination drug strategies are being developed to counter this resistance [29]. However, given the ability of melanoma to adapt and change in response to various pharmacological challenges it underscores a continuing role for surgery in resectable lesions even in partial responders to immunotherapy.

Patient selection is paramount. For example, patients with oligometastatic disease have an improved overall survival with surgical resection. Patients with M1a disease seem to have better outcomes with resection than those with M1c disease. A long disease-free interval from diagnosis to metastatic presentation may give insight into tumor biology and help select better candidates for surgery. Along the same lines, tumor doubling time may be another great indicator of the pace of disease progression. Last, stabilization on systemic therapy has been shown in hepatic metastases from melanoma to be an excellent indicator of those who would benefit from surgery [11].

Conclusion

The treatment algorithms for stage III and IV melanoma are evolving as innovations in

Table 2. Systemic therapy for metastatic melanoma.

Study (year)	Drug	Response rate (%)	Median survival (months)	Ref.
Michael *et al.* (1999)	IL-2	16	12	[14]
Hodi *et al.* (2010)	Ipilimumab (CTLA-4 inhibitor)	28.5	10	[18]
Omid *et al.* (2013)	Lambrolizumab (PD-1 Inhibitor)	62	Not reached	[19]
McArthur *et al.* (2014)	Vemurafenib (BRAF inhibitor)	57	13.6	[23]
Flaherty *et al.* (2012)	Trametinib (MEK inhibitor)	22%	6 OS 81%	[24]

Disease control rate, complete partial and stable disease.
OS: Overall survival.

immunotherapy continue to develop. Surgical resection is itself viewed as a form of immunotherapy given the intimate role melanoma cells have with the immune system. Additionally, the survival advantage of metastasectomy over systemic medical therapy alone has been well documented (Table 1). The increasing efficacy of systemic medical therapy has opened up new horizons for the role of surgery in treating patients with metastatic melanoma. The response rates in newer immunotherapies and targeted therapies (Table 2) are remarkable compared with traditional chemotherapies. Additionally, progression of disease in one treatment pathway no longer leaves a patient without options, as seen with PD-1 inhibitors resulting in a 62% response in those treated prior with ipilimumab.

Future perspective

This finding leaves the door open to targeting the immune system at several different pathways during the course of treatment. Patients with unresectable disease could be candidates for neoadjuvant therapy with BRAF inhibitors inducing a quick response and conversion to oligometastatic disease and undergo resection and further treatment with CTLA-4 or PD-1 inhibitors to enhance the immune systems response to the resolution of the immunosuppressive effects of the metastatic melanoma. Also, in patients who recur due to the melanomas resistance to one therapy, multiple pathways leave the door open for retreatment with further resection possibly evaluating the resected melanoma for mutations and the best next therapeutic agent.

Future randomized controlled trials should enroll patients with stage IV disease, specifically comparing those treated with systemic therapy and those receiving neoadjuvant systemic therapy followed by metastasectomy. Bringing together data on the survival advantage of surgery in metastatic melanoma and the improved efficacy of newer immunotherapeutic modalities in combination with surgery, it is clear that surgery has a continuing and expanding role to play in locally advanced and stage IV melanoma in the era of immunotherapy.

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References

1 Balch CM, Gershenwald JE, Soong SJ *et al.* Final version of 2009 AJCC melanoma staging and classification. *J. Clin. Oncol.* 27(36), 6199–6206 (2009).

2 Bhatia S, Tykodi SS, Thompson JA. Treatment of metastatic melanoma: an overview. *Oncology (Williston Park)* 23(6), 488–496 (2009).

3 Atkins MB, Hsu J, Lee S *et al.* Phase III trial comparing concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa-2b with cisplatin, vinblastine, and dacarbazine alone in patients with metastatic malignant melanoma (E3695): a trial coordinated by the Eastern Cooperative Oncology Group. *J. Clin. Oncol.* 26(35), 5748–5754 (2008).

4 Choti MA, Sitzmann JV, Tiburi MF *et al.* Trends in long-term survival following liver resection for hepatic colorectal metastases. *Ann. Surg.* 235(6), 759–766 (2002).

5 Adam R, Avisar E, Ariche A *et al.* Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. *Ann. Surg. Oncol.* 8(4), 347 (2001).

6 Howard J, Thompson J, Mozzillo N *et al.* Metastasectomy for distant metastatic melanoma: analysis of data from the first multicenter selective lymphadenectomy trial (MSLT-I). *Ann. Surg. Oncol.* 19(8), 2547–2555 (2012).

7 Sosman JA, Moon J, Tuthill RJ *et al.* A Phase 2 trial of complete resection for stage IV melanoma: results of Southwest Oncology Group Clinical Trial S9430. *Cancer* 117(20), 4740–4706 (2011).

8 Morton Kelly. Multicenter double-blind Phase 3 trial of canvaxin vs placebo as post surgical adjuvant in metastatic melanoma. Presented at: *Society of Surgical Oncology 59th Annual Cancer Symposium*, San Diego, CA, USA (2006).

9 Wasif N, Bagaria SP, Ray P, Morton DL. Does metastasectomy improve survival in patients with stage IV melanoma? A cancer registry analysis of outcomes. *J. Surg. Oncol.* 104(2), 111–115 (2011).

10 Flaherty DC, Deutsch GB, Kirchoff DD *et al.* Adrenalectomy for metastatic melanoma: current role in the age of nonsurgical treatments. *Am. Surg.* 81(10), 1005–1009 (2015).

11 Faries MB, Leung A, Morton DL *et al.* A 20-year experience of hepatic resection for melanoma: is there an expanding role? *J. Am. Coll. Surg.* 219(1), 62–68 (2014).

12 Nevala WK, Vachon CM, Leontovich AA *et al.* Evidence of systemic Th2-driven chronic inflammation in patients with metastatic melanoma. *Clin. Cancer Res.* 15(6), 1931–1939 (2009).

13 Deutsch GB, Kirchoff DD, Faries MB. Metastasectomy for stage IV melanoma. *Surg. Oncol. Clin. N. Am.* 24(2), 279–298 (2015).

14 Atkins MB, Lotze MT, Dutcher JP *et al.* High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *J. Clin. Oncol.* 17(7), 2105–2116 (1999).

15 Atkins MB, Kunkel L, Sznol M, Rosenberg SA. High-dose recombinant interleukin-2 therapy in patients with metastatic melanoma: long-term survival update. *Canc.J. Sci. Am.* 6(Suppl. 1), S11–S14 (2000).

16 Creagan ET, Ahmann DL, Frytak S, Long HJ, Chang MN, Itri LM. Phase II trials of recombinant leukocyte A interferon in disseminated malignant melanoma: results in 96 patients. *Cancer Treat. Rep.* 70(5), 619–624 (1986).

17 Tarhini AA, Edington H, Butterfield LH *et al.* Immune monitoring of the circulation and the tumor microenvironment in patients with regionally advanced melanoma receiving neoadjuvant ipilimumab. *PLoS ONE* 9(2), e87705 (2014).

18 Hodi FS, O'day SJ, Mcdermott DF *et al.* Improved survival with ipilimumab in patients with metastatic melanoma. *N. Engl. Journal Med.* 363(8), 711–723 (2010).

19 Omid H, Caroline R, Adil D *et al.* Safety and tumor responses with lambrolizumab (anti-*in situ*) in melanoma. *N. Engl. Journal Med.* 369(2), 134–144 (2013).

20 Weber JS, D'Angelo SP, Minor D *et al.* Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, Phase 3 trial. *Lancet Oncol.* 16(4), 375–384 (2015).

21 Luu C, Khushalani NI, Zager JS. Intralesional and systemic immunotherapy for metastatic melanoma. *Expert Opin. Biol. Ther.* 16(12), 1491–1499 (2016).

22 Andtbacka RH, Kaufman HL, Collichio F *et al.* Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. *J. Clin. Oncol.* 33(25), 2780–2788 (2015).

23 Mcarthur GA, Chapman PB, Robert C *et al.* Safety and efficacy of vemurafenib in *BRAF*V600E and *BRAF*V600K mutation-positive melanoma (BRIM-3): extended follow-up of a Phase 3, randomised, open-label study. *Lancet Oncol.* 15(3), 323–332 (2014).

24 Flaherty KT, Robert C, Hersey P. Improved survival with *MEK* inhibition in *BRAF*-mutated melanoma. *N. Engl. J. Med.* 367(2), 107–114 (2012).

25 Howie LJ, Tyler DS, Salama AK. Neoadjuvant use of ipilimumab in locally advanced melanoma. *J. Surg. Oncol.* 112(8), 841–843 (2015).

26 Koers K, Francken AB, Haanen JB, Woerdeman LA, van der Hage JA. Vemurafenib as neoadjuvant treatment for unresectable regional metastatic melanoma. *J. Clin. Oncol.* 31(16), e253 (2013).

27 Sloot S, Zager JS, Kudchadkar RR *et al.* *BRAF* inhibition for advanced locoregional *BRAF V600E* mutant melanoma: a potential neoadjuvant strategy. *Melanoma Res.* 26(1), 83–87 (2016).

28 Dudley ME, Wunderlich JR, Yang JC *et al.* Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. *J. Clin. Oncol.* 23(10), 2346–2357 (2005).

29 Villanueva J, Vultur A, Lee JT *et al.* Acquired resistance to BRAF inhibitors mediated by a RAF kinase switch in melanoma can be overcome by co-targeting *MEK* and IGF-1R/PI3K. *Cancer Cell* 18(6), 683–695 (2010).