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Update on Current Phase III Clinical Trials in Melanoma

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1. Introduction

Melanoma is the deadliest form of skin cancer and responsible for 4% of all cancer deaths and 86% of skin cancer-related deaths in the United States (Losina et al., 2007). Melanoma is caused by malignant growth of the melanocytes, which are melanin-producing cells found in the skin’s epidermis, hair, and eyes. In melanoma, these cells undergo an uncontrollable cell growth that manifests in the skin, the nail bed, and sometimes although rarely in the eyes and mucous membrane (Garbe et al., 2010). Melanomas can be classified clinically into four major classes (Table 1). Most melanomas are superficially spreading malignant melanoma. Rare melanomas include amelanotic melanoma, splitzoid melanoma, desmoplastic melanoma, malignant blue nevus, ocular melanoma, and mucosa melanoma. Melanomas usually have an initial radial growth phase followed by a vertical growth phase. The radial growth is mostly intraepidermal, and is considered preinvasive or minimally invasive. In contrast, the vertical growth is invasion

TYPE	CHARACTERISTICS	RADIAL GROWTH	VERTICAL GROWTH	PROGNOSIS
Superficially spreading malignant melanoma	Occurs at any site, frequently at the torso in males and the legs in females	Months – 2 years	Delayed	Variable
Nodular melanoma	Occurs at any site, frequently at trunk, head, neck Most rapidly growing and aggressive melanoma	Not clinically observable	Rapid	Poor (due to advance stage at diagnosis)
Lentigo maligna melanoma	Tends to occur on sun-damaged skin in the elderly, particularly at the head and neck Mostly slow growth	Years	Much delayed	Favourable
Acral lentiginous melanoma	Occurs at the palms, soles, and subungual	Months – years	Early	Poor (due to advance stage at diagnosis)

Table 1. The four major clinical classifications of melanoma (Wolff & Johnson, 2009; Duncan, 2009)

into the dermis, and allows for a higher risk of metastasis due to its proximity to blood vessels (Wolff & Johnson, 2009).

1.1 Diagnosis

Typically, melanomas are detected as changes in the skin, often in or near an already existing mole. Normal moles are round to oval in shape with a homogeneous colour, and have a distinctive border. In contrast, melanoma can present as a change in the colour, shape, or diameter of a mole, which might also be painful, bleeding, or itchy. When suspecting melanoma, lesions can be characterized by the 'ABCDE rule' (Wolff & Johnson, 2009). This is accomplished by first, determining whether there is asymmetry in the shape of the lesion by comparing one-half to the other, then by inspecting whether the border of the lesion is irregular or poorly defined, as well as if the colour is heterogeneous and varying from one area to another. Also, there is reason for suspicion if the diameter is greater than 6 mm, and if the lesion is elevated or has a history of enlargement. However, it should be noted that these rules are more sensitive than specific (Marsden et al., 2010; Wolff & Johnson, 2009).

The gold standard for diagnosing melanoma continues to be histopathology from an excision biopsy. Features on the histopathology that are useful for determining the prognosis include the thickness measured by the Breslow depth, whether there is ulceration, vascular invasion, microscopic satellites, and the mitotic count (Dummer et al., 2010). Breslow method of determining the tumour thickness is the greatest single prognostic variable, and is therefore of importance when choosing treatment options (see other chapters). Ulceration also usually indicates a worst prognosis.

Once the diagnosis is confirmed, melanoma staging is useful when determining the treatment options. Staging usually follows the tumour-node-metastasis (TNM) classification endorsed by the American Joint Committee on Cancer (AJCC), which evaluates the primary tumour, regional nodes, and metastases (Table 2). Recently, dermoscopy by experienced and trained physicians have shown to enhance diagnostic accuracy (Garbe et al., 2010). Additionally, a sentinel lymph node biopsy (SLNB) is often used to stage melanoma because cancer cells frequently travel to the closest lymph nodes when they first spread.

1.2 Treatment

Melanoma *in situ* is the earliest stage and is 99% curable with just surgical removal of the tumour. With increasing melanoma stages, other treatments in addition to surgery need to be considered. They include radiation therapy, chemotherapy, immunotherapy, and other interventions. Patients will often receive a combination of these treatments in more advanced melanomas (Garbe et al., 2010). Table 3 summarizes current treatment options in the United States (American Cancer Society, 2011; Kingham et al. 2010).

Surgery usually is the first choice for the treatment of malignant melanoma if it is resectable. A safety margin around the border of the primary tumour is an important factors for consideration. The safety margin during excision is made in effort to avoid spread of the primary tumour to the surrounding skin. The size of the margins for optimal care is still debatable. Five trials were recently reviewed, and examined to determine whether a narrow margin, defined as 1 cm to 2 cm, had better outcome survival than a wide margin of 3 cm to 5 cm. The reviewed trials only involved those with invasive melanoma, and not melanoma *in situ*. No significant difference was found in the overall survival between the narrow or wide excision margins, although there is an estimated small increase in survival in the wide

STAGE	PRIMARY TUMOUR	REGIONAL NODES	METASTASES
0; <i>in situ</i>	Confined to the epidermis	None	None
IA	Confined to skin Tumour thickness of ≤1.0mm Without ulceration	None	None
IB	Confined to skin AND Tumour thickness of ≤1.0mm, with ulceration OR Tumour thickness of 1.01 – 2.0mm, without ulceration	None	None
IIA	Tumour thickness of 1.01 – 2.0mm, with ulceration Tumour thickness of 2.01 – 4.0mm, without ulceration	None	None
IIB	Tumour thickness of 2.01 – 4.0mm, with ulceration Tumour thickness of > 4.0mm, without ulceration	None	None
IIC	Tumour thickness of > 4.0mm, with ulceration	None	None
IIIA	Any tumour thickness, without ulceration	Micrometastases	None
IIIB	Any tumour thickness, with ulceration OR Any tumour thickness, without ulceration OR Any tumour thickness, with or without ulceration	Micrometastases Up to 3 macrometastases None, but satellite metastases and/or in-transit metastases	None
IIIC	Any tumour thickness, with ulceration OR Any tumour thickness, with or without ulceration	Up to 3 macrometastases 4 or more macrometastases or capsule transgressing lymph node metastases, or satellite and/or in-transit metastases affecting the lymph nodes	None
IV	Has spread to internal organs, beyond the nearest lymph node to other lymph nodes, or areas of skin far from original tumour	Any nodal involvement	Including distant metastases

Table 2. The TMN classification of melanoma (Balch et al., 2009)

excision group. Therefore, these trials provide insufficient evidence for defining the most favourable surgical excision margin in primary cutaneous melanoma (Sladden et al., 2010).

Unfortunately, metastatic forms of melanoma still have a high mortality rate due to its lack of response to systemic treatments. Numerous novel methods and approaches have been studied for the management of melanoma and although they were associated with increased toxicity and cost of treatment, some of the results showed potential for treatment of melanoma. Chemoimmunotherapy (or biochemotherapy), which is a combination of chemotherapy and immunotherapy, is one such approach that resulted in improvements although it still remains unclear whether it is clinically beneficial as compared to the standard chemotherapy alone. A Cochrane review found that there is currently inconclusive evidence to support the use of chemoimmunotherapy in treating metastatic malignant melanoma as trials have not shown a difference in survival rates. In addition, there is also an increase risk of toxic effects (Sasse et al., 2007).

STAGE	TREATMENT
0; <i>in situ</i>	<ul style="list-style-type: none">- Surgical excision with safety margin of 0.5 cm- Use of imiquimod cream is controversial
I	<ul style="list-style-type: none">- Surgical excision with safety margin of 1 cm if tumour thickness is less than 1 mm, 1 – 2 cm if tumour thickness is 1 – 2 mm- Consider a SLNB
II	<ul style="list-style-type: none">- Surgical excision with safety margin of 1 – 2 cm if tumour thickness is 1 – 2 mm, 2 cm if tumour thickness is greater than 2 mm- SLNB- If tumour is greater than 4 mm thick, or lymph nodes is cancerous, adjuvant therapy with interferon is considered
III	<ul style="list-style-type: none">- Surgical excision of all melanoma (safety margin as in stage II) with lymph node dissection- Adjuvant therapy with interferon- If not all melanomas are excised, consider injections of bacilli Calmette-Guerin (BCG) vaccine or interleukin-2 (IL2)- If melanoma of the limbs, consider chemotherapy with a heated solution of melphalan- Radiation therapy for the area of excised lymph nodes may be offered after surgery, especially if nodes contained cancerous cells- Consider chemotherapy, immunotherapy with cytokines, and chemoimmunotherapy
IV	<ul style="list-style-type: none">- Surgical excision of tumours and metastases- Surgical excision of internal organ metastases may be possible- If surgery is not possible, may be treated with chemotherapy, immunotherapy, or radiation

Table 3. Melanoma treatments according to stage

1.3 Prevention

Melanoma is a serious disease. Although prognosis is excellent for melanoma *in situ*, it decreases with increasing stages. Thus, methods of prevention and early detection should be considered in efforts to decrease the risk of melanoma. Early detection in melanoma is a key since melanomas have a tendency to metastasize early relative to the tumour mass (Garbe et al., 2010). As incidences increases, early prevention and treatment is becoming more crucial. Ultraviolet radiation has been implicated as a major environmental factor in the pathogenesis of melanoma. Protection from skin damage by ultraviolet radiation may play an important role in the prevention of melanoma.

2. Recently published phase III clinical studies

Numerous clinical trials have attempted to find novel ways of targeting malignant melanoma, and to extend overall survival of patients. Although many clinical trials investigating melanoma have been completed, there has been a lack of real conclusive evidence to change current treatment options. A search of the recent literature was performed for the recent trials conducted on melanoma. The search was limited to only phase III clinical trials, published in English in the last five years. Due to limited space for this chapter, some of results from recent clinical studies in the field are summarized in the following section.

2.1 Monoclonal antibodies

Recently, the United States Food and Drug Administration (FDA) has approved ipilimumab (Yervoy), a fully human monoclonal antibody, as adjuvant immunotherapy for the treatment of metastatic melanoma. It is the first new drug approved for melanoma in over 13 years. Dacarbazine was approved in 1975, and interleukin-2 was approved in 1998 (U. S. Food and Drug Administration, 2011). Ipilimumab was approved by the FDA mainly based on an increase in overall survival in patients with late-stage melanoma in phase III clinical trials (Hodi et al., 2010). This is considered to be a significant improvement since there are limited options for patients with metastatic melanoma. Ipilimumab acts by inhibiting the cytotoxic T-lymphocyte associated-antigen 4 (CTLA-4). The antigen is thought to slow down or inactivate the body's immune system, and thus limiting its effect on cancerous cells. Therefore, ipilimumab may enhance the antitumour T-lymphocyte response to attack the tumours of melanoma patients (Hodi et al., 2010).

During the trial, ipilimumab was administered intravenously at 3 mg/kg of body weight, with or without a glycoprotein 100 (gp100) peptide vaccine, every 3 weeks for up to four treatments in the induction phase of the treatment. Additionally, a maintenance dose at every 12-week intervals was given in some studies (Hodi et al., 2010). It is interesting to note that the trial compared ipilimumab against an experimental vaccine, and not a placebo or standard treatment. The drug's safety and effectiveness was determined from a single international study of 676 patients, all of whom had metastatic melanoma that may have not been surgically removed, and that were refractive to other treatment methods. Since ipilimumab is a monoclonal antibody and immunogenic, side effects commonly associated with the novel compound include fatigue, diarrhea, pruritis, endocrine deficiencies, and colitis. In 12.9% of patients studied, there was severe to fatal autoimmune reactions (Hodi et al., 2010). Thus adjuvant immunotherapy with ipilimumab is approved with a Risk Evaluation and Mitigation Strategy (U. S. Food and Drug Administration, 2011). Physicians must be vigilant in detecting patients with these serious side effects.

Due to ipilimumab's effect on the immune system, it may take some time to have an effect in a melanoma patient. Thus patients with rapidly progressive metastatic melanoma may not benefit from the treatment (Hodi et al., 2010). Currently, research efforts to identify biomarkers that predict the outcome due to ipilimumab is being conducted in hopes of determining a selectively way to conduct the adjuvant therapy.

Ipilimumab was hypothesized to act through a human leukocyte antigen (HLA) independent mechanism, and thus most trials enrolled subjects into their study without regards to HLA subtype. It should be noted that the phase III trial restricted enrolment of subjects to class-I-HLA-A*0201-positive because of the use of HLA-A*0201-restricted gp100

vaccine in two of the three arms. Thus a retrospective analysis was conducted to determine whether ipilimumab could treat patients regardless of their HLA-A*0201 status. The pooled efficacy and safety data were analyzed according to HLA-A*0201 status and found no difference in the overall survival using ipilimumab in advanced melanoma (Wolchok et al., 2010). However, the interpretation of the results should be made with caution because of the nature of the analysis.

2.2 Cytokines

2.2.1 Interferon alpha-2b

It is postulated that the benefits of interferon alpha-2b is dependent on the dose and duration of the treatment. A high-dose interferon alpha (IFN- α) regimen with an induction phase of maximally tolerated dosages (20 MU/m² per day) by intravenous (IV) therapy for the initial 4 weeks has shown prolongation of overall survival (OS) and relapse-free survival (RFS) in comparison with observation in study E1684 (Kirkwood et al., 2009). Following this study, a prospective randomized study was conducted to compare intravenous induction therapy versus a full year of high-dose interferon, with primary endpoints of RFS and OS for patients with stage IIB, IIC, and III melanoma. Treatment was initiated within 56 days of curative surgery. Patients were randomly assigned to receive IFN- α -2b 15 MU/m² IV for five times a week for 4 weeks (arm A) versus the same regimen followed by IFN- α -2b 10 MU (flat dose) administered subcutaneously three times a week for 48 weeks (arm B). Between 1998 and 2004, 364 patients were enrolled (353 eligible: arm A, n = 177; arm B, n = 176). At a median follow-up of 63 months (95% CI, 58.1 to 67.7), the median RFS was 24.1 months versus 27.9 months ($P = 0.9$) and the median OS was 64.4 months versus 65.3 months ($P = 0.49$). Patients in arm B had more grade 1 to grade 2 hepatotoxicity, nausea, vomiting, alopecia, and neurologic toxicity. Thus the study concluded that there is no difference between a one month and a one year treatment in terms of relapsed-free or overall survival (Pectasides et al., 2009).

High dose interferon alpha-2b is however associated with toxic effects. To investigate whether the use of an intermediate-dose of the interferon alpha-2b improves the overall benefit-risk ratio, a study was conducted in 855 patients in Nordic countries, who had either stage IIB, IIC, or III resected cutaneous melanoma. The data did not find intermediate adjuvant therapy to be significant in improving the overall survival of patients (Hansson et al., 2011).

Low dose interferon alpha has been shown to provide patients with disease-free survival benefits in clinical trials in which patients had clinically lymph-node negative melanoma. Since there is a lack of knowledge on the proper duration of adjuvant treatment, a Dermatology Cooperative Oncology Group (DeCOG) trial investigated whether extending low dose interferon treatment from 18 months to 60 months would be beneficial. The trial found no significant clinical benefit in patients suffering from intermediate and high-risk primary melanoma (Hauschild et al., 2010).

The DeCOG trial also evaluated the patients' psychiatric symptoms before and during the adjuvant therapy. A higher pretreatment depression score, as determined by the Beck Depression Inventory and the Symptom Check List 90-Revised, was determined to be a risk factor for early drop-out during treatment. Therefore, it is recommended that pretreatment screening be completed and an interdisciplinary care be considered when treating patients (Heinze et al., 2010).

2.2.2 Pegylated interferon alpha-2b

The European Organisation for Research and Treatment of Cancer (EORTC) 18991 trial was conducted in order to compare adjuvant pegylated interferon alpha-2b therapy to observation alone in resected stage III melanoma (Eggermont et al., 2008). The purpose was to establish whether pegylated interferon alpha-2b could be tolerated over long exposures. The randomised phase III trial enrolled 1256 patients, and had stratified random assignment to either the treatment or observation group. The treatment group ($n = 627$) received 6 mug/kg of pegylated interferon alpha-2b per week for 8 weeks in the induction phase, then 3 mug/kg per week for 5 years in the maintenance phase of the trial. The primary endpoint was recurrence-free survival. The data were analyzed for intention-to-treat population. Results showed a statistically significant and sustained effect on recurrence-free survival with patients assigned to the adjuvant therapy. However, there was no difference found between the groups in overall survival. Additionally, patients receiving the pegylated interferon alpha-2b were at a higher risk of therapy related adverse events, such as hepatotoxicity and depression, and thus the treatment was discontinued (Eggermont et al., 2008, 2010).

In a clinical trial by the EORTC Melanoma Group, the health-related quality of life (HRQOL) effects of adjuvant therapy with pegylated interferon alpha-2b versus observation in resected stage III melanoma patients was assessed by the EORTC Quality of Life Questionnaire C30 (Bottomley et al., 2009). It found that although pegylated interferon alpha-2b lead to a sustained and significant improvement in relapse-free survival, there was no significant difference in the overall survival. Additionally, there was a negative effect on global HRQOL and selected symptoms in melanoma patients undergoing the treatment. Patients on adjuvant therapy suffered from fatigue and loss of appetite statistically more so than the observation group. The effect was also clinically significant. Additionally, they also had statistically higher rates of dyspnea, as found at 3 months and 3 years after baseline. Patients also reported statistically greater frequency of fevers, headaches, and sore muscle or stiffness as compared with the observation group. A limitation in this trial was the drop-out rate in which few patients remained in the trial at 4 and 5 years after baseline. The high drop-out rate seriously undermines the long-term HRQOL analysis (Bottomley et al., 2009). The prognostic significance of autoantibodies in the EORTC 18991 trial was analyzed by comparing the long-term administration of pegylated interferon with observation. The study analyzed 220 patients (out of 296 that were initially tested) for anticardiolipin, antithyroglobulin, and antinuclear antibodies by an enzyme-linked immunosorbent assay at 6 months intervals throughout the trial. Results found that there was no significance in the appearance of autoantibodies as a prognostic or predictive factor for outcomes in melanoma patients treated with pegylated interferon (Bouwhuis et al., 2010).

2.2.3 Biochemotherapy with interferon alpha-2b

A randomized trial was conducted to compare the clinical benefits of biochemotherapy to adjuvant interferon-alpha-2b in high risk recurrent melanoma patients (Kim et al., 2009). This study enrolled 138 patients, and divided them into three groups: biochemotherapy ($n = 71$), high-dose interferon ($n = 34$), and intermediate-dose interferon ($n = 33$). The biochemotherapy group received cisplatin at 20 mg/m² IV on days 1–4, vinblastine at 1.5 mg/m² IV on days 1–4, dacarbazine at 800 mg/m² IV on day 1, interferon-alpha-2b at 5MU/m² s.c. on days 1–5 and interleukin-2 at 9MU/m² for a daily continuous IV infusion over days 1 - 4. The high-dose interferon-alpha-2b group received 20 MU/m² IV for 5 days a

week for 4 weeks, followed by 10 MU/m² s.c. injection three times a week for 48 weeks. The intermediate-dose interferon-alpha-2b group received 10 MU/m² s.c. injection three times a week for 52 weeks. The study found that biochemotherapy is not more effective than adjuvant therapy with interferon. Also, there was no significant difference between the high-dose and intermediate-dose interferon in terms of RFS or OS. Thus, the findings precipitated the early termination of the trial (Kim et al., 2009).

Another study on patients with metastatic malignant melanoma was conducted in order to compare cisplatin, vinblastine, and dacarbazine (CVD) either alone or concurrently with interleukin-2 and interferon alfa-2b (biochemotherapy). The treatments were given at every 21-day intervals, for a maximum of 4 cycles, and the tumour response was measured after the second and fourth cycles, and every 3 months thereafter. The study assessed 395 patients, who were initially randomized and balanced for stratification factors and other prognostic factors. The patients receiving biochemotherapy had a slightly better response rate and longer median progression-free survival than with chemotherapy, but it did not translate to overall survival. Therefore, the study concluded that biochemotherapy should not be considered as a standard of care for metastatic melanoma due to its high toxicity and complexity in comparison to standard chemotherapy (Atkins et al., 2008).

A multicenter trial was conducted to compare the effect of polychemotherapy through a CVD regimen against CVD with interleukin-2 and interferon-alpha-2b in patients with metastatic melanoma. A total of 151 patients were randomized in the study to two arms: 75 participants on arm A which received cisplatin 30 mg/m² on days 1-3, vindesine 2.5 mg/m² on day 1 and dacarbazine 250 mg/m² on days 1-3, while 76 participants on arm B which received the same CVD scheme plus s.c. interleukin-2 on days 1-5 and 8-15 and interferon-alpha-2b on days 1-5. Both arms ran on a 21-day cycle. The study was conducted in patients with untreated metastatic melanoma, and response was assessed every two cycles. Measures included the response rate, median time to progression, and median OS. Although biochemotherapy showed a better response rate, it is not better than chemotherapy alone since it did not improve median time to progression or OS. Therefore, this study also concluded that biochemotherapy should not be a standard of care for metastatic melanoma (Bajetta et al., 2006).

In a German phase III trial, adjuvant low-dose interferon alpha-2a with or without dacarbazine, was compared to surgery alone in an observation group. A total of 444 patients who had received a complete lymph node dissection for pathologically proven regional node involvement were recruited in 42 centers (Garbe et al., 2008). Patients were either given 3 MU of interferon alpha-2a subcutaneously 3 times a week for 2 years or the same doses of interferon alpha-2a plus dacarbazine 850 mg/m² every 4-8 weeks for 2 years or observation alone. A total of 441 patients results were used in intention-to-treat analysis, and disease-free survival (DFS) and OS were assessed. Results found that patients on the low-dose interferon had significantly better DFS and OS. Additionally, results showed that dacarbazine reversed the advantageous effect of the low-dose interferon alpha-2a therapy (Garbe et al., 2008).

In a retrospective study of the EORTC 18951 biochemotherapy trial, results were used to determine whether pretreatment levels of neutrophils and leukocytes in a blood count could be independent predictors for short overall survival for stage IV melanoma patients undergoing interleukin-2 based immunotherapy. Patients in the trial were treated with dacarbazine, cisplatin, and interferon alpha, with or without interleukin-2. Results showed that elevated pretreatment neutrophils in the blood were an independent prognostic factor

for short OS, while elevated leukocytes counts were prognostic for short OS and progression-free survival. Therefore, both neutrophils and leukocytes counts may be used as stratification factors in future clinical trials (Schmidt et al., 2007).

2.3 Vaccines

Vitespen is an autologous tumour-derived heat shock protein gp96 peptide complex vaccine. An open-label phase III trial was conducted in which vitespen was compared with the physician's choice for treatment for stage IV melanoma patients (Testori et al., 2008). Patients (n = 322) were randomly assigned in a 2:1 ratio to receive vitespen or physician's choice of a treatment containing one or more of the following: dacarbazine, temozolomide, interleukin-2, or complete tumor resection. Temozolomide was found to have comparable activity as dacarbazine in a systematic review. It also has the additional advantage of being an oral therapy that can cross the blood-brain barrier (Quirt et al., 2007). Patients were monitored for safety and overall survival. Patients in the vitespen vaccine group received a variable number of injections (ranging from 0 to 87, with a median of 6). Intention-to-treat analysis showed that OS in the vitespen group is not statistically different from that of the physician's choice group. Exploratory landmark analyses show that patients in the M1a and M1b substages receiving a larger number of vitespen immunizations survived longer than those receiving fewer such treatments. Such difference was not detected for substage M1c patients (Testori et al., 2008).

Another randomized phase III trial was conducted for demonstrating the superiority of autologous peptide-loaded dendritic cell (DC) vaccination over standard dacarbazine chemotherapy in stage IV melanoma patients. Dacarbazine was given at 850 mg/m² intravenously at a 4-week interval. DC vaccines loaded with MHC class I and II-restricted peptides were applied subcutaneously at a 2-week interval for the first five vaccinations and every 4 weeks thereafter. The primary endpoint was objective response, while secondary measures included toxicity, OS, and progression-free survival. At the time of the first interim analysis for the intention-to-treat population, 55 patients had been enrolled into the dacarbazine-arm and 53 into the DC-arm. The objective response was low (dacarbazine: 5.5%, DC: 3.8%), but not significantly different in the two arms. The Data Safety & Monitoring Board recommended closure of the study. Thus, DC vaccination could not be demonstrated to be more effective than dacarbazine in stage IV melanoma patients (Schadendorf, et al, 2006).

In the last decade, most published clinical trials on vaccines for melanoma were conducted at an early stage of development (e.g. phase I and phase II). Chi and Dudek (2011) conducted a systematic review and meta-analysis on the clinical trials pertaining to melanoma vaccine published between January 1, 1990 and May 1, 2010. The authors concluded that a melanoma-specific immune response predicted longer overall survival, although no evidence was found that vaccine therapy provides better overall disease control or overall survival compared with other treatments (Chi & Dudek, 2011).

2.4 Small molecules

Lenalidomide is a new compound under investigation for the treatment of metastatic malignant melanoma. Lenalidomide has shown effective antitumour activity against metastatic melanoma in an animal model (Payvandi et al., 2009). It was studied in a phase II/III trial that compared the efficacy and safety at two different doses (5 mg or 25 mg) for patients with relapsed metastatic melanoma refractory to previous treatments including

dacarbazine, interleukin-2, interferon alpha, and temozolomide. The results did not find a difference in the overall survival, response rate, or time to progression between the different dosing regimes. In addition, treatment with lenalidomide caused an observable myelosuppression (Glaspy et al., 2009).

An international multicenter, randomized, double-blind phase II/III trial was also undertaken to assess the efficacy and safety of lenalidomide, given at 25 mg per day for 21 days in a 28-day cycle, as compared to placebo in 306 patients with refractory stage IV metastatic malignant melanoma. The treatment was continued until there was progression of disease or an unacceptable toxicity. Results found that there was no significant difference between the use of lenalidomide and placebo in overall survival of the patient. Statistically, there was also no benefit in tumour response and time to progression (Eisen et al., 2010).

Sorafenib is a multikinase inhibitor that prevents tumor cell proliferation and angiogenesis through receptor tyrosine kinases, vascular endothelial growth factor receptor (VEGFR)-1, -2, -3, and platelet derived growth factor receptor- α and - β , and the Raf/MEK/ERK pathway at the level of Raf kinase (Wilhelm, et al, 2004). A phase III trial was conducted in 270 patients to evaluate the efficacy and safety of sorafenib with carboplatin and paclitaxel in comparison with placebo and paclitaxel in advanced melanoma patients who had previously received dacarbazine or temozolomide therapy. The primary efficacy endpoint was progression-free survival, with secondary and tertiary endpoints included overall survival and incidence of best response, respectively. As the results did not find any improvements with sorafenib plus paclitaxel over placebo plus paclitaxel, the regimen cannot be recommended for second-line treatment in advanced melanoma (Hauschild et al., 2009).

2.5 Adoptive therapy using tumor infiltrating lymphocytes

Benlalam et al. (2007) reported a study on the adoptive therapy of cancer using tumour infiltrating lymphocytes (TIL) in stage III melanoma patients. The patients received autologous interleukin-2 or TIL with interleukin-2 after complete tumour resection. They discovered that infusion of Melan-A/MART-1 reactive TIL is correlated with a longer relapse-free survival for patients with HLA-A2. The authors indicate that Melan-A/MART-1 antigen may serve as a target for melanoma immunotherapy (Benlalam et al., 2007).

3. Recently completed or ongoing phase III clinical trials

In the last five years, there were over 700 registered trials using 'melanoma' as a search term in the United States clinical trial registry. When the search was refined to phase III trials that started from 2006 – 2010, inclusive, it narrowed down the field to 40 studies. Out of the 40 trials: 7 were completed, 24 were active or recruiting, 3 have an unknown status, 1 was no longer available, 2 were suspended, and 3 were terminated. The following briefly summarize some of the phase III clinical trials registered on clinicaltrials.gov in the last five years (U. S. National Institute of Health, 2011). All the following information was obtained from the registry unless otherwise noted.

3.1 Interferon-alpha

A Nordic adjuvant interferon trial was completed by giving patients an intermediate dose of interferon-alpha-2b after surgery for high risk melanoma. High risk melanoma patients were defined as T4N0M0 or TxN1-2M0. The study had three arms: control, adjuvant interferon

TRIAL	THERAPIES COMPARED (REGIMEN)		TARGET POPULATION	SAMPLE SIZE	STATUS
NCT01259934	Interferon alpha2b (1 year: s.c. 10 MU for 5 days a week for 4 weeks, with a maintenance dose of 10 MU 3 days a week for 1 year Or, 2 year: s.c. 10 MU for 5 days a week for 4 weeks, with a maintenance dose of 10 MU 3 days a week for 1 year)	Observation	High risk melanoma	855	Completed
NCT00447356	High dose interferon alpha (dosing not available)	Observation	Resected stage II and III	1420	Unknown

Table 4. Studies on interferon-alpha for the treatment of melanoma

for one year, and adjuvant interferon for two years. It aimed to study overall survival as a primary end point, as well as relapse-free survival, side effects and quality of life for secondary endpoints. The results of the study were summarized in section 2. Another study was designed to determine the use of high dose interferon-alpha in patients with stage II or stage III melanoma that have been completely removed by surgery. The status is currently unknown since the information has not been verified recently.

3.2 Ipilimumab

TRIAL	THERAPIES COMPARED (REGIMEN)		TARGET POPULATION	SAMPLE SIZE	STATUS
NCT00324155	Ipilimumab and dacarbazine (10 mg/kg once every 3 weeks for 10 weeks, then once every 12 weeks at week 24; 850 mg/m ² once every 3 weeks for 22 weeks, respectively)	Placebo and dacarbazine (0 mg once every 3 weeks for 10 weeks, then once every 12 weeks at week 24; 850 mg/m ² once every 3 weeks for 22 weeks, respectively)	Unresectable stage III or IV	500	Active, but not recruiting
NCT00636168	Ipilimumab (IV 10 mg/kg four times every 21 days, then once every 12 week starting at week 24 for 3 years)	Placebo (IV 0 mg/kg four times every 21 days, then once every 12 week starting at week 24 for 3 years)	High risk stage III	950	Recruiting

Table 5. Studies on ipilimumab for the treatment of melanoma

Ipilimumab is an anti-CTLA-4 monoclonal antibody that was recently approved by the U.S. FDA for use in melanoma. Currently, a phase III trial (NCT00324155) is designed to assess the efficacy of ipilimumab at 10 mg/kg with dacarbazine against a control group of placebo and dacarbazine in patients with unresectable stage III or IV melanoma. Another ipilimumab trial (NCT00636168) is attempting to investigate whether the therapy is effective

as compared to placebo for stage III melanoma patients as adjuvant immunotherapy. The primary outcome measure is recurrence free survival, and secondary outcomes include OS, distant metastases-free survival, quality of life, and adverse events of ipilimumab as compared to placebo.

3.3 Small molecules - tyrosine kinase inhibitors
3.3.1 Targeting melanoma with a BRAF V600E mutation

TRIAL	THERAPIES COMPARED (REGIMEN)		TARGET POPULATION	SAMPLE SIZE	STATUS
NCT01006980; BRIM3	RO5185426 (oral 960 mg, twice daily)	Dacarbazine (IV 1000 mg/m ² every 3 weeks)	Stage IIIc or IV with BRAF V600E positive mutation	680	Recruiting
NCT01227889	GSK2118436 (oral 150 mg, twice daily)	Dacarbazine (IV 1000 mg/m ² every 3 weeks)	Stage III and IV with BRAF mutation-positive tumour	200	Recruiting
NCT01245062	GSK1120212 (dosing not available)	Chemotherapy (dacarbazine or paclitaxel; dosing not available)	Stage IIIc and IV with BRAF mutation-positive tumour	297	Recruiting

Table 6. Studies on compounds targeting melanoma with BRAF mutations

BRAF belongs to the RAF family of protein kinases. The BRAF V600 mutation is seen in as high as 60% of melanoma patients. Small molecules RO5185426, GSK2118436 and GSK1120212 are developed to inhibit the RAS/RAF/MEK/ERK signalling system, and thus inhibit cellular growth of melanoma. These molecules are currently in clinical trials to assess their efficacy. RO5185426 is being studied for efficacy, safety, and tolerability as compared to dacarbazine in previously untreated patients with unresectable stage IIIC or stage IV melanoma with BRAF V600E mutation. This is a randomized, open-label study using overall survival and progression-free survival as a primary outcome. The participants will be followed for approximately three years.

An randomized trial is comparing the efficacy, safety, and tolerability of the oral agent GSK2118436, a BRAF inhibitor, against standard chemotherapy. It is conducted in patients with BRAF mutant-positive tumours in stage IIIc or stage IV malignant cutaneous melanoma. Subjects will be followed for two years to determine the progression-free survival. Secondary endpoints include OS, rate of treatment, overall response rate, duration of response, and validation of the BRAF mutation assay. This is another study trying to determine whether an agent could stop or slow melanoma progression in BRAF V600 mutant patients by altering the MAP kinase pathway.

Study NCT00796445 is an open-label randomized trial comparing the single agent GSK1120212 (a MEK inhibitor) against standard chemotherapy, in patients with BRAF mutant-positive tumours in stage IIIc or stage IV malignant cutaneous melanoma. The study intends to measure progression free survival of patients.

3.3.2 Targeting melanoma with a c-Kit mutation

Nilotinib (AMNN107) is a selective *BCR-ABL* inhibitor. Currently, a phase III trial also known as the TEAM (Tasigna Efficacy in Advanced Melanoma) trial is recruiting

TRIAL	THERAPIES COMPARED (REGIMEN)		TARGET POPULATION	SAMPLE SIZE	STATUS
NCT01028222; TEAM	Nilotinib (dosing not available)	Dacarbazine (dosing not available)	Uresectable Stage III, and IV with c-Kit mutation	120	Recruiting
NCT01280565	Masitinib (7.5 mg/kg perday)	Dacarbazine (IV 1000 mg/m ² once every three days)	Unresectable stage IIIb or IIIc, or IV with mutation at juxta membrane domain of c-Kit	200	Recruiting

Table 7. Studies on compounds targeting melanoma with c-Kit mutations

metastatic and/or inoperative melanoma patients that also have a c-Kit mutation for the study. This interventional study will be compared against dacarbazine, and is intended to have crossover assignment. The primary outcome measures will be progression free survival.

Mastinib is another novel tyrosine kinase inhibitor that has been implicated in pre-clinical trial results for the treatment of advanced melanoma patients with a c-Kit juxtamembrane mutation. It is currently undergoing a prospective randomized trial for safety and efficacy in stage III and stage IV melanoma patients with a mutation in the juxtamembrane domain of c-Kit.

3.4 Treatment for choroidal melanoma

TRIAL	THERAPIES COMPARED		TARGET POPULATION	SAMPLE SIZE	STATUS
NCT00680225	Ranibizumab with Transpupillary Thermotherapy (TTT) - Indocyanine Green (ICG) based photodynamic therapy (PDT) (0.5 mg ranibizumab once a month for 6 months, TTT-ICG once or twice a month starting at month 2)	Not applicable	Choroidal melanoma	10	Active, but not recruiting
NCT00811200; TORR	Ranibizumab (intravitreal injections of 0.5 mg, three times for a month) or triamcinolone acetonide (intravitreal injection of 4.0 mg)	Placebo	Choroidal melanoma	220	Not yet recruiting

Table 8. Studies on choroidal melanoma treatments

A currently active study is undertaken to study the safety and tolerability of intravitreal injection of ranibizumab combined with Transpupillary Thermotherapy (TTT) - Indocyanine Green (ICG) based photodynamic therapy (PDT) for use as adjuvant treatment in choroidal melanoma. The primary outcome is reduction in tumour size.

Another study plans to research the change in visual acuity after treatment with ranibizumab or triamcinolone acetonide in patients with radiation retinopathy after irradiation of choroidal melanoma. This is important as many patients lose visual acuity

after treatment of uveal melanoma using radiation therapy and TTT because of the radiation retinopathy. This study postulated a decrease in such complication with administration of ranibizumab or triamcinolone acetonide.

3.5 Vaccines

TRIAL	THERAPIES COMPARED (REGIMEN)		TARGET POPULATION	SAMPLE SIZE	STATUS
NCT00477906	M-Vax with BCG, cyclophosphamide, and IL2 (M-Vax vaccine: intradermal injection of 4 to 20 million cells, weekly for 7 weeks, with a booster at month 6; cyclophosphamide at 300 mg/m ² ; IL2 at 3 MU/m ² for 5 days with a 16-day rest period)	Placebo vaccine with BCG, cyclophosphamide, and IL2 (placebo vaccine: intradermal injection of 4 to 20 million cells, weekly for 7 weeks, with a booster at month 6; cyclophosphamide at 300 mg/m ² ; IL2 at 3 MU/m ² for 5 days with a 16-day rest)	Stage IV	387	Suspended
NCT00395070	Allovectin-7 (intralesional injection at 2 mg, weekly for 6 consecutive weeks in a 8-week cycle)	Dacarbazine (IV 1000 mg/m ² for one hour every 28 days) or temozolomide (oral 150 – 200 mg/m ² daily for five consecutive days in 28-day cycle)	Recurrent stage III or IV	375	Active, but not recruiting
NCT00769704	OncoVex GM-CSF (4 ml of 10 ⁸ pfu/ml per injection)	GM-CSF (s.c. 125 µg/m ² for 14 days in 28-day cycle)	Unresectable Stage IIIb, IIIc, and IV	430	Recruiting

Table 9. Studies on vaccines for the treatment of melanoma

The M-Vax vaccine is an autologous hapten (dinitrophenyl) modified melanoma vaccine derived from a patients’ own cancer cells. In previous studies, the vaccine was shown to be able to stimulate the immune system of the patient to react against the melanoma. This study was designed to see whether the vaccine, with administration of low dose interleukin-2 to increase effectiveness, could shrink stage IV melanomas. The vaccine is being studied for best overall anti-tumour response and percent of patients’ survival at two years as the primary endpoint, and for safety as a secondary endpoint. Eligible participants must have at least one melanoma tumour that can be resected to be made into a vaccine, and have stage IV metastatic melanoma of the lung and/or soft tissues.

OncoVex GM-CSF is an oncolytic vaccine that contains oncolytic herpes simplex type 1 virus encoding granulocyte macrophage colony-stimulating factor (GM-CSF) and has shown durable complete remission in melanoma patients in phase II clinical trial. The product has commenced phase III clinical trials for metastatic melanoma. The Onco Vex (GM-CSF)

Pivotal Trial in Melanoma (OPTIM) trial is a phase III study on the effects of the vaccine for the treatment of unresectable stage III or stage IV melanoma. (Kaufman & Bines, 2010). Allovectin-7® is a plasmid-based vaccine expressing two genes (HLA-B7 and β 2 microglobulin) that together form an MHC class-1 complex. The product is claimed to train the immune system (both innate and adaptive) to destroy tumour cells. The minimum treatment time for patients is 16 weeks, and involves weekly injections. The progression free survival, as well as the safety and tolerability of the product will be compared to that of dacarbazine.

3.6 Antisense oligonucleotides

TRIAL	THERAPIES COMPARED (REGIMEN)		TARGET POPULATION	SAMPLE SIZE	STATUS
NCT00518895; AGENDA	Genasense and dacarbazine (IV: Genasense at 7 mg/kg per day for 5 days in a 21-day cycle, with dacarbazine at 1000 mg/m ² for 1 hour after Genasense, for up to 8 cycles)	Placebo and dacarbazine (IV: 0.9% sodium chloride at 7 mg/kg per day for 5 days in a 21-day cycle, with dacarbazine at 1000 mg/m ² for 1 hour after placebo, for up to 8 cycles)	Unresectable or stage IV and low LDH	300	Unknown

Table 10. Studies on antisense oligonucleotides for the treatment of melanoma

Genasense is oblimersen sodium, which is a Bcl-2 antisense oligonucleotide that is currently being studied for use in advanced melanoma. Genasense with dacarbazine as compared to placebo and dacarbazine is being compared in patients that have never received chemotherapy treatment and have a low baseline LDH. The primary endpoints are progression-free survival and overall survival. The secondary endpoints are response rate, durable response rate, duration of response, and safety. The estimated enrollment was 300 patients with unresectable or stage IV and low LDH. Its current status is unknown as the information has not been updated recently.

3.7 Other small molecules

The study on ABI-007, which is a new preparation of paclitaxel (a mitotic inhibitor), is being conducted to determine its activity, safety, and tolerability in comparison to dacarbazine. This study is limited to patients that have metastatic melanoma, and were not previously treated with chemotherapy. ABI-007 contains the same medication as Abrazane, a chemotherapeutic agent approved by the FDA for metastatic breast cancer. An uncontrolled prospective study is currently studying the effects of imiquimod in patients who received surgical excision for lentigo maligna or lentigo maligna melanoma. Imiquimod cream contains an imidazoquinoline (a class of compounds first synthesized in 1980) as the active ingredient. The imiquimod cream treatment starts 6 weeks post-surgery and will last up to 12 weeks. The cream is to be applied once daily for three times per week and after 2 weeks of treatment, may be increased to five times per week if there is no or minor inflammation. If no or little inflammation is detected at 4 weeks, the treatment will become a daily application. Patients will be followed up to five years for any recurrence of disease.

TRIAL	THERAPIES COMPARED (REGIMEN)		TARGET POPULATION	SAMPLE SIZE	STATUS
NCT00864253	ABI-007 (IV at 150 mg/m ² at day 1, 8, and 15 of 4 week cycle)	Dacarbazine (IV at 1000 mg/m ² every 21 days)	Stage IV	514	Recruiting
NCT01088737 (non-randomized)	Imiquimod (5% cream applied once daily, three times per week)		Lantigo maligna or lantigo maligna melanoma	60	Recruiting
NCT01264874; MelaViD	Vitamin D3 (100000 IU every 50 days for 3 years)	Placebo (matched placebo)	Resected stage II	878	Not yet recruiting
NCT00522834; SYMMETRY	Elesclomol and paclitaxel (IV at213 mg/m ² ; 80 mg/m ² for once a week for 3 weeks in a 4-week cycle, respectively)	Paclitaxel (IV at 80 mg/m ² once a week for 3 weeks in a 4- week cycle)	Stage IV	630	Terminated
NCT01006252; SUMMIT-1	Tasisulam (IV individualized dose at day 1 of 28- day cycle)	Paclitaxel (IV at 80 mg/m ² at day 1, 8,15 of 28-day cycle)	Stage IV	323	Terminated
NCT00779714; ChemoSensMM	Paclitaxel and cisplatin (200 mg/m ² ; 50 mg/ m ² on day 1 of a 21 day cycle, respectively) Or treosulfan and cytarabine (2500 mg/m ² on day 2; 100 mg/ m ² on day 1to 3 of a 21 day cycle, respectively)	Dacarbazine (1000 mg/m ² on day 1 of a 21 day cycle)	Stage IV	360	Recruiting

Table 11. Studies on other small molecules for treatment of melanoma

The European Institute of Oncology is currently investigating vitamin D3 (cholecalciferol) supplementation as compared to placebo in a double blind trial for its effects in the recurrence of resected stage II melanoma patients. This study will determine whether vitamin D can be used as a preventative and therapeutic cancer agent.

Eclesclomol is a synthesized chemical entity that induced the oxidative stress response of cells. The double blind trial was designed to assess the efficacy of Elesclomol with paclitaxel in progression free survival in stage IV melanoma patients who have never received chemotherapy. The study was terminated. The reason for the termination is unknown.

Trials on Tasisulam as compared to paclitaxel have also been terminated for fear of greater mortality risks with the experimental drug. The study was designed to study the effect of Tasisulam on overall survival in metastatic melanoma patients.

Dacarbazine is the standard chemotherapy offered to melanoma patients for stage IV melanoma as other therapies have yet been proven more effective in a randomized clinical trial. A currently recruiting trial is attempting to establish the efficacy of an individualized combination chemotherapy that is sensitivity-directed. The combination chemotherapy being studied in stage IV melanoma patients are either paclitaxel with cisplatin, or treosulfan with cytarabine. The study also aims at determining whether an individual chemosensitivity index can be used as a prognostic biomarker for chemotherapy. The primary outcome measure is overall survival.

3.8 Surgery and radiotherapy

Table 12 lists some clinical trials on surgery and radiotherapy for melanoma described below.

A currently active study is trying to investigate the effect sentinel lymph node dissection following a wide surgical excision on patients with cutaneous invasive melanoma. The trial has three arms: surgical excision only, surgical excision with SLNB, and surgical excision with SLNB and complete lymph node biopsy. The last of which will be given offered to subjects that have a positive sentinel lymph node detected. The research will determine if surgical resection with intraoperative lymphatic mapping and SLNB prolongs overall survival of subjects as compared to receiving only surgical resection. Patients will be followed for 10 years to determine the OS, as well as the disease-free survival as a secondary outcome measure.

A currently active study by the Trans-Tasman Radiation Oncology Group (TROG) is trying to determine the effect of adjuvant radiotherapy for patients that have resected melanoma involving the lymph nodes, and that are at a high risk of having a recurrence of the disease. The trial intends to determine whether radiotherapy will result in adequate locoregional control of the disease, with secondary outcomes including disease-free survival, overall survival, toxicity, and quality of life. The stage III melanoma patients will be divided into two arms: one who will receive immediate radiotherapy after surgical resection, and one who will be observed with a delay offer of radiotherapy.

In another TROG study, patients that have received a surgical intervention for melanoma and show histological features of neurotropism will be assessed for efficacy of radiation therapy as compared to observation. Neurotropism have been shown in uncontrolled studies to result in a higher risk of local reoccurrence of the disease. The radiation received will encompass the surgical bed with a margin, and starts three month after the surgery. The patient population studied is limited to neurotropic melanoma of the head and neck. The primary outcome will measure time to local relapse for five years, with secondary outcomes including relapse free survival, overall survival, time to relapse, cancer specific survival, patterns of relapse, and toxicity. Patients in the observational group will be offered radiotherapy if there is recurrence of the disease.

Stage IV melanoma is difficult to treat, despite all the research on the subject. A surgical intervention is effective in certain population with solitary metastases, but not in patients with multiple metastases. Currently, a trial is attempting to establish a standardized initial approach for stage IV melanoma patients in hopes of prolonging survival and augment their quality of life. Medical therapy is currently the favoured approach as to prevent numerous patients from undergoing unnecessary surgery for what may turn into a rapidly invasive melanoma with occult metastases at multiple sites. Patients in the trial will be divided into three arms: one that receives a surgical intervention alone, one that receives a surgical

intervention and the bacillus Calmette-Guerin (BCG) vaccine as adjuvant immunotherapy, and one that receives best medical therapy. Patients receiving the BCG will receive a dose based on their pre-study tuberculin-reactivity with those that have a greater or equal to 10 mm reactivity receiving half the standard dose of BCG, and those with greater or equal to 20 mm receiving a quarter of the standard BCG dose. The last group will be treated at the discretion of their medical oncologist and surgeons, and will not initially receive a surgical intervention. The treatment they receive can range from standard treatment to experimental

TRIAL	THERAPIES COMPARED		TARGET POPULATION	SAMPLE SIZE	STATUS
NCT00275496	Wide excision, sentinel lymph node dissection, and potential complete lymph node dissection	Wide excision of primary melanoma	Melanoma	2001	Active, but not recruiting
NCT00287196	Radiotherapy (48 Gy at five fractions per week for twenty fractions, for a maximum of 30 days of treatment time)	Observation, with delayed radiotherapy (48 Gy at five fractions per week for twenty fractions, for a maximum of 30 days of treatment time)	Melanoma involving lymph nodes	236	Active, but not recruiting
NCT00975520	Surgery and radiation therapy (48 Gy in twenty fractions over 4 weeks)	Observation after surgery	Completely resected primary melanoma with neurotropism	100	Recruiting
NCT01013623	Surgery, or surgery with 2 adjuvant doses of bacillus Calmette-Guerin (BCG given four weeks after surgery: eight separate intradermal injections, dosing determined by pre-study tuberculin-reactivity, with two doses given two weeks apart)	Best medical therapy	Resectable stage IV	399	Recruiting
NCT00297895	Completion lymphadenectomy	Observation with nodal ultrasound	Molecular or histopathologic evidence of metastases in sentinel node	1925	Recruiting

Table 12. Studies on surgery and radiotherapy for the treatment of melanoma

therapy in clinical trial. The subjects will be followed for their lifespan to determine overall survival. The study will also measure time to progression of metastatic sites, melanoma-specific survival, and time to development of new metastatic disease sites.

In another study on sentinel lymph node biopsy, melanoma patients that are sentinel node positive will be studied for melanoma-specific survival after receiving a complete lymphadenectomy in comparison with monitoring by nodal ultrasound. Subjects enrolled need to demonstrate either molecular or histopathological evidence of metastases in the sentinel lymph node, and will be followed for ten years. The observation group that receives monitoring by ultrasound will receive delayed complete lymphadenectomy if there is recurrence of disease. The completion lymphadenectomy involved complete dissection of the lymph nodes of the positive lymph node basin.

4. Conclusion

Melanoma is the deadliest form of skin cancer. Melanoma *in situ* is the earliest stage and is 99% curable with just surgical removal of the tumour. With increasing melanoma stages, the prognosis of melanoma becomes worse and the mortality rate increases. Although many trials have been conducted, there has been a lack of real conclusive evidence for any major change to current treatment options based on published results. Many current clinical trials at the late stage of development are now ongoing in order to find novel ways of targeting malignant melanoma, and to extend overall survival of patients. These trials will provide additional information on the treatment of melanoma and may potentially lead to the development of newer, more effective therapies.

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Management of melanoma is challenging, especially for the late stage of the disease. Development of new therapies and optimizing current treatments are being pursued in attempt to further improve the survival rate. The book provides up-to-date knowledge and experience in early diagnosis, prevention and treatment of melanoma as well as current ongoing clinical studies on melanoma. The book also provides the most recent perspectives of research on the molecular basis of melanoma, such as melanoma associated genes and a possible link between stress and melanoma.

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