Current Clinical Trials in the Treatment of Advanced Melanomas

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INTRODUCTION

According to the Surveillance, Epidemiology, and End Results database, cutaneous melanoma incidence has increased substantially over the past 2 decades from approximately 38,000 in 1997 to 76,000 in 2016.1 Age older than 50 is associated with worse prognosis and incidence in men is double that in women.1–3 Between the ages of 15 and 39, melanoma is more commonly seen in female individuals.2 Fortunately, 85% of melanoma cases are diagnosed at an early stage, when cure can be achieved with surgery alone.

The treatment of melanoma has witnessed significant improvements during the past decade. We describe herein historical trends in the treatment of this disease, also summarizing the latest clinical trials that would be applicable in the near future.

Before the development of immunotherapy and targeted therapy, advanced melanoma historically was treated with chemotherapeutic agents, primarily dacarbazine

KEYWORDS

• Melanoma • Advanced melanomas • Clinical trials • Immunotherapy • Targeted therapy

KEY POINTS

• The treatment of advanced melanoma has changed significantly with the introduction of immunotherapy and targeted therapies.
• Treatment of advanced or metastatic melanoma has promising results now with significant improvement in progression-free survival and overall survival.
• Treatment can now be individualized based on the molecular characteristics of each tumor.
• The rapid progress with newer therapies makes it more exciting and challenging at the same time. It would be interesting to see the clinical applications of the latest trials to practice.

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and its prodrug temozolomide. Platinum agents, vinka alkaloids, and taxanes were also used although less frequently. The outcomes in the era of chemotherapy were poor and prognosis was dismal in advanced melanoma.

Interleukin (IL)-2 is a glycoprotein T-cell growth factor that is primarily produced by Th lymphocytes and it stimulates the development of cytotoxic T lymphocyte and natural killer cells. Clinical trials investigated the use of IL-2 immunotherapy in the treatment of advanced melanoma. Across these trials, overall response was noted to be low, approximately 16% with only 6% complete response (CR) and 10% partial response (PR). Although some patients would derive benefit from IL-2, its side effects and toxicity profile make this medication useful only in patients with excellent performance status, preserved organ function, and in institutions with expertise in administering and managing its side effects.

With the low response rates observed with chemotherapeutic agents and dismal prognosis in advanced melanoma, it was paramount to have a better understanding of disease biology to develop newer treatment modalities. The understanding of the mitogen-activated protein kinase (MAPK) pathway was a revolutionary step toward this aim. The identification of driver mutations in this pathway, including BRAF and NRAS, has accelerated the development of targeted therapies either as monotherapies, or in combination. These targeted therapies were associated with significant improvement in progression-free survival and overall survival. Along with targeted therapy, immunotherapy is a novel way of stimulating the immune system, specifically T-cell activation and regulation. We summarize here the pivotal trials that were practice changing in managing advanced metastatic melanoma.

**IMMUNOTHERAPY**

Ipilimumab (MDX-010) is a human immunoglobulin (Ig)G1 monoclonal antibody shown to inhibit CTLA-4. Early-phase studies have shown its activity in advanced, refractory melanoma. Ipilimumab was evaluated in 2 phase 3 trials. The first study (MDX010–020/CA184–020), which involved 676 HLA-A*0201–positive patients with advanced melanoma, compared ipilimumab 3 mg/kg every 3 weeks for 4 doses either singly or in combination with gp100 vaccine with a gp100-only control arm. Ipilimumab administration resulted in objective responses in 11% of patients and improved progression-free and overall survival compared with gp100 alone. Of note, ipilimumab monotherapy was superior to ipilimumab/gp100 combination. A follow-up study (CA184–024) compared a higher dose of ipilimumab (10 mg/kg) in combination with dacarbazine with dacarbazine monotherapy in previously untreated melanoma. This study failed to confirm the benefit of higher dose of ipilimumab. Hence, ipilimumab received regulatory approval in 2011 for the treatment of advanced melanoma at the lower dose: 3 mg/kg administered every 3 weeks for 4 doses. Survival data were strikingly similar to patterns observed in prior phase 2 studies, with survival curves plateauing after 2 years at 23.5% to 28.5% of treated patients. Ipilimumab administration resulted in an unusual spectrum of toxicities, including diarrhea, rash, hepatitis, and hypophysitis (termed immune-related adverse events, or irAEs) in up to a third of patients.

Pembrolizumab and nivolumab are humanized IgG4 monoclonal antibodies that target the PD-1 receptor found on activated T cells, B cells, and myeloid cells. Nivolumab was compared with chemotherapy in a pair of phase 3 studies involving both previously untreated (CheckMate 066) and ipilimumab/BRAF inhibitor–refractory (CheckMate 037) patients. In both studies, nivolumab produced durable responses in 32% to 34% of patients and improved survival over chemotherapy. Compared with
ipilimumab, the incidence of irAEs was much lower with nivolumab. These results led to regulatory Nivolumab approval in both indications (untreated and ipilimumab refractory melanoma) in 2014.

Pembrolizumab was evaluated in a large phase 1 study (KEYNOTE-001) of 1260 patients that evaluated 3 doses (10 mg/kg every 2 weeks, 10 mg/kg every 3 weeks, and 2 mg/kg every 3 weeks) in separate melanoma and non–small-cell lung cancer substudies. Both ipilimumab-naïve and ipilimumab-treated patients were enrolled in the melanoma substudy. Objective responses were seen in 38% of patients across all 3 dosing schedules and were similar in both ipilimumab-naïve and ipilimumab-treated patients. Similar to nivolumab, most responders experienced durable remissions.

Pembrolizumab was subsequently compared with ipilimumab in untreated patients (KEYNOTE-006) in which patients were randomly assigned to receive either ipilimumab or pembrolizumab at 1 of 2 doses: 10 mg/kg every 2 weeks and pembrolizumab 10 mg/kg every 3 weeks.10 Response rates were greater with pembrolizumab than ipilimumab, with greater 1-year survival rates. Rates of treatment-related adverse events requiring discontinuation of study drug were much lower with pembrolizumab than ipilimumab. This trial proved the superiority of pembrolizumab over ipilimumab. The US Food and Drug Administration (FDA) granted pembrolizumab accelerated approval for second-line treatment of melanoma in 2014, and updated this to include a first-line indication in 2015.

Studies have confirmed that PD-1 blockade was more effective than CTLA-4 blockade. It was hypothesized that combination blockage of PD-1/CTLA-4 would have synergistic effects. CheckMate 067 was a randomized, phase 3 study that demonstrated the superiority of ipilimumab/nivolumab combination to ipilimumab monotherapy.11 The combination arm results in more profound responses (58%) than either ipilimumab (19%) or nivolumab (44%) alone and improvement in progression-free survival. However, there was more toxicity, including diarrhea, rash, fatigue, and pruritus that led to discontinuation of the combination drugs in 30% of patients. The durable response led to this combination to be FDA approved in 2015. In an updated analysis of the same trial published by the New England Journal of Medicine in 2017, the combination of ipilimumab/nivolumab resulted in significantly improved overall survival.12

TARGETED THERAPY

Clinical observations including the different behavior pattern of lesions in chronic sun-exposed versus nonexposed areas led to further speculation of differences at the molecular level. Whole genome sequencing data, including The Cancer Genome Atlas, identified patterns of mutations in oncogenic drivers that were different in patients with and without chronic sun exposure. A deeper understanding of the MAPK pathway led to the identification of actionable mutations in melanoma, which led to phase III studies confirming the efficacy of drugs that would target these mutations.

Vemurafenib and dabrafenib were both studied in advanced BRAF V600E-mutated melanomas. BRIM-3 was a phase III trial evaluating vemurafenib versus dacarbazine (1000 mg/m^2 intravenously every 3 weeks) in the treatment of advanced BRAF V600E-mutated melanoma. Similarly, BREAK-3 was another phase III trial evaluating dabrafenib in advanced BRAF V600E-mutated melanomas versus dacarbazine. Responses for both V600 inhibitor agents were relatively similar. Single-agent BRAF inhibitors resulted in rapid and profound (approximately 50% objective responses) reductions in tumor burden that lasted 6 to 7 months. Adverse events common to both agents included rash, fatigue, and arthralgia. Clinically significant photosensitivity
was more common with vemurafenib and clinically significant pyrexia was more com-
mon with dabrafenib.\textsuperscript{16} Class-specific adverse events included the development of
cutaneous squamous-cell carcinomas and keratoacanthomas secondary to para-
doxic activation of MAPK pathway signaling. These trials led to regulatory approval
of vemurafenib and dabrafenib in 2011 and 2013, respectively, in the treatment of
advanced melanomas with BRAF V600E mutations.

Despite profound responses to BRAF inhibitors, however, these responses are short
lived and temporary. Mechanisms of acquired resistance are diverse and include reacti-
vation of MAPK pathway–dependent signaling (RAS activation or increased RAF expres-
sion), and development of MAPK pathway–independent signaling (COT overexpression;
increased PI3K or AKT signaling) that permits bypass of inhibited BRAF signaling within
the MAPK pathway.\textsuperscript{17,18} These led investigators to look for other mechanisms to over-
come this resistance. One way is to combine BRAF inhibition with MEK inhibition.

Three phase 3 studies confirmed the superiority of combination BRAF and MEK
inhibition over BRAF inhibition alone. COMBI-d\textsuperscript{15,19} dabrafenib/trametinib versus
dabrafenib/placebo, COMBI-v\textsuperscript{16} dabrafenib/trametinib versus vemurafenib, and
cobraIM\textsuperscript{20} vemurafenib/cobimetinib versus vemurafenib/placebo. Expectedly,
compared with BRAF inhibitor monotherapy, combination BRAF and MEK inhibition
produced greater responses and improved progression-free and overall survival along
with lower rates of cutaneous squamous-cell carcinomas than combination therapy,
reflecting the more profound degree of MAPK pathway inhibition achieved with com-
bination BRAF and MEK inhibition. Based on these results, FDA approval was granted
for both dabrafenib/trametinib and vemurafenib/cobimetinib combinations in 2015.
Although the dabrafenib/trametinib combination was only approved in 2015, trameti-
nib had independently gained FDA approval in 2013 for the treatment of \textit{BRAF V600E/}
K–mutated melanoma on the basis of the phase 3 METRIC study.

The latest reported trial in advanced BRAF V600–mutant melanoma was COLUM-
BUS, which is a randomized, open-label phase III trial that compared the addition of
encorafenib (BRAF inhibitor) to binimetinib versus encorafenib or vemurafenib mono-
therapy.\textsuperscript{21} The combination of encorafenib and binimetinib resulted in improvement in
progression-free survival and a toxicity profile comparable with either monotherapy.

\textbf{CURRENT CLINICAL TRIALS IN MELANOMA}

Melanoma Checkpoint and Gut Microbiome Alteration with Microbiome Intervention is
a phase Ib trial sponsored by the Parker Institute for Cancer Research. It focuses on
the effect of gut microbiome and activity of checkpoint inhibition in stage 4 melanoma.
This study is designed to evaluate the safety and tolerability of treatment with oral
microbiome study intervention (SER-401) or matching placebo in combination with
anti-programmed cell death 1 (anti-PD-1) therapy (nivolumab) in participants with
unresectable or metastatic melanoma. It also intends to assess clinical outcomes,
the impact of microbiome study intervention administration on the microbiome profile,
and its association with clinical and immunologic outcomes. Before initiating micro-
biome study intervention and nivolumab, participants will undergo an antibiotic or pla-
cebo treatment lead-in to prime the gut microbiome for engraftment of the oral
microbiome study intervention. Intervention groups will be assessed for safety,
changes in the microbiome, changes in the percentage of tumoral CD8 T cells, and
antitumor activity. Participants must have measurable disease that can be biopsied
and consent to baseline and on-treatment biopsies, as well as stool and blood
biomarker collection throughout the study. This study is still active and participants
are still being recruited.\textsuperscript{22}
The Prospective Randomized and Phase 2 Trial for Metastatic Melanoma Using Adoptive Cell Therapy with Tumor Infiltrating Lymphocytes Plus IL-2 Either Alone or Following the Administration of Pembrolizumab is currently being conducted at the National Institutes of Health, Bethesda, MD. This trial extracts young tumor infiltrating lymphocytes (TILs) from stage 4 melanoma tumors, grows them in the laboratory and then returns the TIL with high-dose IL-2. First step is a tumor biopsy and leukapheresis, and then hospital admission for a week for conditioning chemotherapy. Pembrolizumab is administered the day after chemotherapy. It also tests the safety and efficacy of pembrolizumab addition to cell therapy. The cells are infused day 4, with up to 12 doses of high-dose IL-2 every 8 hours. Pembrolizumab is repeated every 3 weeks for up to 4 doses and patients are reassessed. Another cycle of 4 doses of pembrolizumab can be repeated. The researchers in this trial hypothesize that the addition of pembrolizumab to cell therapy would make it more effective. The safety of this approach is being addressed as well.23

Genetically Modified T-Cells Followed by Aldesleukin in Treating Patients with Stage III-IV Melanoma is being conducted at MD Anderson Cancer Center in Houston. This pilot phase I trial studies the side effects and best dose of genetically modified T cells followed by aldesleukin in treating patients with stage III-IV melanoma. Genes that may help the T-cells recognize melanoma cells are inserted into the T-cells in the laboratory. Adding these genes to the T cells may help them kill more tumor cells when they are put back in the body. Aldesleukin (high-dose IL-2) may enhance this effect by stimulating white blood cells to kill more melanoma cells.24

Talimogene Laherparepvec (TVEC) and Pembrolizumab combination in patients with Stage III-IV Melanoma (S1607) is sponsored by the National Cancer Institute (NCI) and Southwest Oncology Group (SWOG). Similar to “Coley’s Toxin,” first described in the nineteenth century, TVEC is an FDA-approved injectable oncolytic virus, a herpes simplex virus type 1, specifically designed for replication within tumors. It can induce antitumor immune response, both local and distant. TVEC has previously been shown to have an excellent response rate for in-transit metastases in melanoma. In this trial, the primary objective is to evaluate the durable response rate of treatment with Talimogene Laherparepvec (TVEC) in combination with pembrolizumab following progression on prior anti-PD-1 or anti-PD-L1 therapy.25

A Study of NKTR-214 Combined with Nivolumab versus Nivolumab Alone in Participants with Previously Untreated Inoperable or Metastatic Melanoma is sponsored by Nektar Therapeutics and Bristol Myers Squibb. Bempegaldesleukin (NKTR-214; Nektar Therapeutics, San Francisco, CA) is an investigational CD122-preferential IL-2 pathway agonist. NKTR-214 is a first-in-class, CD122-preferential IL-2 pathway agonist that provides sustained activation of the IL-2 pathway via IL-2R beta chain–biased signaling, selectively stimulating CD8+ T cells over regulatory T cells (Tregs), which require binding to the IL-2R alpha chain. NKTR-214 has proven safe and effective in increasing CD8+ T cells in the circulation and in tumor tissue in patients with a variety of cancers, including melanoma, renal, lung, bladder, and breast cancers. Interestingly, NKTR-214 significantly decreased T regulatory levels in tumors, but not in the periphery. This phase 3 trial randomizes patients to nivolumab alone or the combination in advanced melanoma. NKTR 214 with nivolumab has a breakthrough designation from the FDA based on 12-month follow-up on the first-line melanoma cohort in the phase 1 PIVOT 02 trial, presented at ASCO 2019.26 At a median time of follow-up of 12.7 months, confirmed objective response rate (ORR) was 53% (20 of 38) in efficacy-evaluable patients, with 34% (13 of 38) of patients achieving confirmed complete responses. 42% (16 of 38) of patients achieved a maximum reduction of 100% in target lesions. DCR, also known as disease control rate (CR + PR + stable disease [SD]) was 74%.
Eighty percent (16 of 20) of patients had sustained responses. Among the 35 patients with known pretreatment PD-L1 status, ORR in PD-L1–negative patients was 6 (43%) of 14 and in PD-L1–positive patients was 13 (62%) of 21. One of 3 patients with unknown PD-L1 baseline status experienced a CR.

The most common (>30%) treatment-related AEs were grade 1 to 2 fatigue (65.9%), pyrexia (61.0%), rash (56.1%), pruritus (48.8%), nausea (41.5%), influenza like illness (39.0%), arthralgia (36.6%), chills (34.1%), and myalgia (31.7%).

An Exploratory Study of Pembrolizumab Plus Entinostat (HDAC inhibitor) in Non-Inflamed Stage III/IV Melanoma is being conducted at the University of North Carolina Lineberger Cancer Center. The first goal of this study is to understand whether entinostat can make a melanoma tumor more visible to the immune system. Participants will have a mandatory tumor biopsy 3 weeks after starting entinostat therapy. Tumor tissue collected before and after participating in this study will be compared to see if there are more immune cells in the tumor after receiving entinostat. The second goal of the study is to see if giving a combination of entinostat and pembrolizumab can shrink melanoma tumors of patients who did not have immune cells in tumors before treatment. Studies will evaluate response and side effects of the treatment.27

CD40 Agonistic Antibody APX005M in Combination with Nivolumab is a phase I trial sponsored by Apexigen and Bristol Myers Squibb. Subjects will receive intravenous APX005M in combination with nivolumab until disease progression or unacceptable toxicity. The cell-surface molecule CD40, a member of the tumor necrosis factor receptor superfamily, broadly regulates immune activation and mediates tumor apoptosis. CD40 is expressed by antigen-presenting cells (APCs). The engagement of its natural ligand on T cells activates APCs, including dendritic cells and B cells. CD40 agonistic antibodies have been shown to substitute for T-cell helpers provided by CD4+ lymphocytes in murine models of T-cell–mediated immunity. In tumor-bearing hosts, CD40 agonists trigger effective immune responses against tumor-associated antigens. In contrast, CD40 is also expressed on many tumor cells and its ligand in this setting mediates a direct cytotoxic effect. Ligand binding of CD40 on tumor cells results in apoptosis in vitro and impaired tumor growth in vivo. These observations have prompted efforts to use agonistic CD40 antibodies for the treatment of cancer patients and initial clinical results have been promising. Encouraging data of antiPD1 with CD40 agonists were presented at the American Association for Cancer Research (AACR) Meeting in April 2019 in advanced melanoma and pancreatic cancer.28 Phase 1b dose-escalation portion of the clinical trial presented at AACR included patients with metastatic melanoma who had progressed when previously treated with anti-PD-1 therapy. Progression was documented by 2 consecutive tumor assessments at least 4 weeks apart. Patients were treated with 3 dose levels of APX005M (0.03, 0.1, and 0.3 mg/kg) combined with a fixed dose of nivolumab (360 mg) every 3 weeks. In the phase 1b portion of this clinical trial, APX005M was well tolerated and no dose-limiting toxicities were observed. The recommended phase 2 dose (RP2D) for APX005M is 0.3 mg/kg. Of the 5 subjects with metastatic melanoma, 1 had a confirmed PR, 2 had prolonged SD (>8 months), and 2 had progressive disease (PD) as the best overall response. The phase 2 dose-expansion portion of this clinical trial followed a Simon 2-stage design and included 2 parallel cohorts of patients treated with the RP2D of APX005M with nivolumab. In the phase 2 portion of this clinical trial, the first stage of the cohort enrolled 10 subjects, in addition to the 2 subjects who carried over from the phase 1 portion. Of these 12 subjects, 2 had confirmed PR, 3 had SD, and 7 had PD as best overall response.

Pembrolizumab in Treating Patients with Stage III-IV High-Risk Melanoma Before and After Surgery (S1801) is an NCI Cooperative group trial sponsored by SWOG.
This randomized phase II trial studies how pembrolizumab works before and after surgery in treating patients with stage III-IV high-risk melanoma. The higher load of tumor neoantigens with a neoadjuvant approach may theoretically lead to a more vigorous immune response. Patients receive pembrolizumab intravenously (IV) over 30 minutes on day 1 every 3 weeks for 3 cycles, then undergo surgery within 3 weeks. Within 84 days, patients receive pembrolizumab IV over 30 minutes every 3 weeks for 15 cycles in the absence of disease progression or unacceptable toxicity. This trial is actively recruiting patients and the estimated study completion date would be in September 2022.29

SUMMARY
Since 2011, the treatment of advanced melanoma has seen radical improvements. A condition which would have been considered to be futile in the past decade has promising results with the introduction of immunotherapy and targeted therapies. We might witness a time when advanced melanomas would not be as life limiting as they are now for patients.

DISCLOSURE
Nothing to disclose.

REFERENCES


