AETNA BETTER HEALTH®
Clinical Policy Bulletin:
Ipilimumab (Yervoy)

Number: 0815

Policy

Note: REQUIRES PRECERTIFICATION.*
Aetna considers ipilimumab (Yervoy) medically necessary for the treatment of the following malignant melanomas:

As single-agent treatment for brain metastases if active against primary tumor (melanoma) for recurrent disease; or for brain metastases in persons with recurrent stable systemic disease

Reinduction in persons who experienced no significant systemic toxicity during prior medically necessary ipilimumab therapy and who relapse after initial clinical response or progress after stable disease greater than 3 months.

- These products are NOT covered for members with the following criteria:
  - Use not approved by the FDA; AND
  - The use is unapproved and not supported by the literature or evidence as an accepted off-label use.

Note: * Precertification of ipilimumab is required of all Aetna participating providers and members in applicable plan designs. For precertification of ipilimumab, call (866) 503-0857, or fax (866) 267-3277.

See also CPB 0024 - Interleukin-2 (Aldesleukin, Proleukin, IL-2), CPB 0270 - Proton Beam and Neutron Beam Radiotherapy, CPB 0278 - Hyperthermia in Cancer Therapy, CPB 0377 - Dendritic Cell Immunotherapy, CPB 0404 - Interferons, CPB 0557 - Cancer Vaccines, and CPB 0641 - Adoptive Immunotherapy and Cellular Therapy.

Background

Melanoma is a serious form of skin cancer that arises from melanocytes; however, in rare instances, it can originate in the eye or other non-skin organs. Risk factors for melanoma entail freckling, genetic factors, history of sunburns, light skin or eye color, poor tanning ability, sun exposure, as well as tanning bed use. About 80% of melanomas are detected in a localized stage. When detected early, the 5-year survival rate of melanoma is 98.5%. However, when melanoma is diagnosed after distant metastasis, the 5-year survival rate decreases to 15% with a median survival between 8 and 9 months. Tumor thickness, along with nodal involvement, is a prognostic factor for melanoma. As tumor thickness increases to greater than 1.0 mm, the survival rate is reduced by 50%. The incidence of melanoma is rapidly increasing. According to the National Cancer Institute (NCI), melanoma is the leading cause of death from skin disease. Approximately 68,130 new cases of melanoma were diagnosed in the United States during 2010 and about 8,700 people died from the disease. Treatments of melanoma include chemotherapy, immunotherapy, radiation therapy, surgery, as well as vaccine therapy (NCI, 2011). According to the National Comprehensive Cancer Network, there are no optimal therapies for metastatic melanoma, and there is little consensus regarding standard therapy. In community practice, the usual treatment is dacarbazine chemotherapy, which elicits a response of 3 or 4 months in duration in about 10% to 20% of patients. Temozolomide has a similar rate of response (about 10% to 20% with a duration of 3 to 4 months). Interleukin-2 (IL-2) can induce durable complete response (CR) in about 6% and partial response (PR) in about 10% of metastatic melanoma patients. Evidence suggests that the combination of IL-2 therapy and a peptide vaccine such as the gp100 melanoma peptide vaccine (MDX-1379) may lead to higher response rates.
Agarwala and O'Day (2011) noted that the current treatment for melanoma with nodal involvement, but without distant metastasis, is surgical excision and lymph node dissection followed by adjuvant therapy. A number of systemic regimens have been evaluated for melanoma patients with a medium or high risk of disease recurrence following surgery. The only agent approved for the adjuvant therapy of melanoma is high-dose interferon (IFN)-alpha 2b, which prolongs relapse-free survival, but its effects on overall survival (OS) remain controversial. Its use is also accompanied by significant toxicity. Thus, despite its approval, high-dose IFN-alpha 2b is not always used for the adjuvant therapy of melanoma, particularly in countries other than the U.S. Studies aimed at identifying subgroups of patients that have the greatest benefit-to-risk ratio with this regimen are ongoing. Several vaccines have been studied in the adjuvant setting for melanoma, but none has shown superiority to IFN-containing regimens. The GMK (ganglioside Memorial Kettering) vaccine, a GM2 ganglioside vaccine, for instance, has actually been shown to be inferior to high-dose IFN-alpha 2b. Thus, a therapeutic regimen that improves OS with a favorable safety profile would be a major advance in the adjuvant therapy of melanoma. One approach that is currently being investigated is the potentiation of anti-tumor immune responses through blockade of cytotoxic T-lymphocyte antigen-4 (CTLA-4), a molecule on Helper T cells that is believed to play a critical role in regulating natural immune responses. The absence or presence of CTLA-4 can augment or suppress the immune system's T-cell response in fighting disease. Ipilimumab is a human monoclonal antibody that binds to cytotoxic CTLA-4. It is designed to block the activity of CTLA-4, thereby sustaining an active immune response in its attack on cancer cells.

Ipilimumab for the Treatment of Melanoma:

Ku and colleagues (2010) reported on the findings of patients with advanced refractory melanoma who were treated in a compassionate use trial with ipilimumab 10 mg/kg of body weight every 3 weeks for 4 doses. Those with evidence of clinical benefit at week 24 (CR, PR, or stable disease [SD]) then received ipilimumab every 12 weeks. A total of 53 patients were enrolled, with 51 evaluable. Grade 3/4 immune-related adverse events (AEs) were noted in 29 % of patients, with the most common immune-related AEs being pruritus (43 %), rash (37 %), and diarrhea (33 %). On the basis of immune-related response criteria, the response rate (CR + PR) was 12 % (95 % confidence interval [CI]: 5 % to 25 %), whereas 29 % had SD (95 % CI: 18 % to 44 %). The median progression-free survival (PFS) was 2.6 months (95 % CI: 2.3 to 5.2 months), whereas the median OS was 7.2 months (95 % CI: 4.0 to 13.3 months). Patients with an absolute lymphocyte count (ALC) greater than 1000/microL after 2 ipilimumab treatments (week 7) had a significantly improved clinical benefit rate (51 % versus 0 %; p = 0.01) and median OS (11.9 versus 1.4 months; p < 0.001) compared with those with an ALC less than 1000/microL. The authors concluded that these findings confirmed that ipilimumab is clinically active in patients with advanced refractory melanoma. The ALC after 2 ipilimumab treatments appears to correlate with clinical benefit and OS, and should be prospectively validated.

In a multi-center, phase II clinical trial, Hersh and colleagues (2011) evaluated the safety and effectiveness of ipilimumab alone and in combination with dacarbazine (DTIC) in patients with unresectable, metastatic melanoma. Chemotherapy-naïve patients were randomized to receive ipilimumab at 3 mg/kg every 4 weeks for 4 doses either alone or with up to 6 5-day courses of DTIC at 250 mg/m²/day. The primary end point was objective response rate. A total of 72 patients were treated per-protocol (ipilimumab plus DTIC, n = 35; ipilimumab, n = 37). The objective response rate was 14.3 % (95 % CI: 4.8 to 30.3) with ipilimumab plus DTIC and was 5.4 % (95 % CI: 0.7 to 18.2) with ipilimumab alone. At a median follow-up of 20.9 and 16.4 months for ipilimumab plus DTIC (n = 32) and ipilimumab alone (n = 32), respectively, median OS was 14.3 months (95 % CI: 10.2 to 18.8) and 11.4 months (95 % CI: 6.1 to 15.6); 12-month, 24-month, and 36-month survival rates were 62 %, 24 % and 20 % for the ipilimumab plus DTIC group and were 45 %, 21 %
and 9% for the ipilimumab alone group, respectively. Immune-related AEs were, in general, medically manageable and occurred in 65.7% of patients in the combination group versus 53.8% in the monotherapy group, with 17.1% and 7.7% greater than or equal to grade 3, respectively. The authors concluded that ipilimumab resulted in clinically meaningful responses in advanced melanoma patients, and the results support further investigations of ipilimumab in combination with DTIC.

In a randomized, double-blind, phase II study, Wolchok et al (2010) examined the anti-tumor effectiveness of ipilimumab in patients with advanced melanoma. A total of 217 patients with previously treated stage III (unresectable) or stage IV melanoma were randomly assigned a fixed dose of ipilimumab of either 10 mg/kg (n = 73), 3 mg/kg (n = 72), or 0.3 mg/kg (n = 72) every 3 weeks for 4 cycles (induction) followed by maintenance therapy every 3 months. Randomization was done with a permuted block procedure, stratified on the basis of type of previous treatment. The primary end point was best overall response rate (BORR) (the proportion of patients with a CR or PR, according to modified World Health Organization [WHO] criteria). Effectiveness analyses were done by intention-to-treat, whereas safety analyses included patients who received at least 1 dose of ipilimumab. The best overall response rate was 11.1% (95% CI: 4.9 to 20.7) for 10 mg/kg, 4.2% (CI: 0.9 to 11.7) for 3 mg/kg, and 0% (CI: 0.0 to 4.9) for 0.3 mg/kg (p = 0.0015; trend test). Immune-related AEs of any grade arose in 50 of 71 (70%), 46 of 71 (65%), and 19 of 72 (26%) patients at doses of 10 mg/kg, 3 mg/kg, and 0.3 mg/kg, respectively; the most common grade 3 to 4 AEs were gastro-intestinal immune-related AEs (11 in the 10 mg/kg group, 2 in the 3 mg/kg group, none in the 0.3 mg/kg group) and diarrhea (10 in the 10 mg/kg group, 1 in the 3 mg/kg group, none in the 0.3 mg/kg group). The authors concluded that ipilimumab elicited a dose-dependent effect on safety and effectiveness measures in pre-treated patients with advanced melanoma, lending support to further studies at a dose of 10 mg/kg.

In a multi-center, single-arm, phase II study, O'Day et al (2010) examined the safety and effectiveness of ipilimumab monotherapy in patients with pre-treated advanced melanoma. Patients with previously treated, unresectable stage III/stage IV melanoma received 10 mg/kg ipilimumab every 3 weeks for 4 cycles (induction) followed by maintenance therapy every 3 months. The primary end point was BORR using modified WHO criteria. These investigators also performed an exploratory analysis of proposed immune-related response criteria (irRC). Best overall response rate was 5.8% with a disease control rate (DCR) of 27% (n = 155); 1- and 2-year survival rates (95% CI) were 47.2% (39.5% to 55.1%) and 32.8% (25.4% to 40.5%), respectively, with a median OS of 10.2 months (7.6 to 16.3). Of 43 patients with disease progression by modified WHO criteria, 12 had disease control by irRC (8% of all treated patients), resulting in a total DCR of 35%. Adverse events were largely immune-related, occurring mainly in the skin and gastrointestinal tract, with 19% grade 3 and 3.2% grade 4. Immune-related AEs were manageable and generally reversible with corticosteroids. The authors concluded that ipilimumab demonstrated clinical activity with encouraging long-term survival in a previously treated advanced melanoma population.

In a phase III clinical trial, Hodi et al (2010) compared ipilimumab administered with or without a glycoprotein 100 (gp100) peptide vaccine with gp100 alone in patients with previously treated (one or more of the following: aldesleukin, carboplatin, dacarbazine, fotemustine, or temozolomide) metastatic melanoma. A total of 676 HLA-A*0201-positive patients with unresectable stage III or IV melanoma, whose disease had progressed while they were receiving therapy for metastatic disease, were randomly assigned, in a 3:1:1 ratio, to receive ipilimumab plus gp100 (n = 403), ipilimumab alone (n = 137), or gp100 alone (n = 136). Ipilimumab, at a dose of 3 mg/kg, was given with or without gp100 every 3 weeks for up to 4 treatments (induction). Eligible patients could receive re-induction therapy. The primary end point was OS. The median OS was 10.0 months among patients receiving ipilimumab plus gp100, as compared with 6.4 months among patients receiving gp100 alone (hazard ratio [HR] for death, 0.68; p < 0.001). The median OS with ipilimumab
alone was 10.1 months (HR for death in the comparison with gp100 alone, 0.66; p = 0.003). No difference in OS was detected between the ipilimumab groups (HR with ipilimumab plus gp100, 1.04; p = 0.76). Grade 3 or 4 immune-related AEs occurred in 10 to 15% of patients treated with ipilimumab and in 3% treated with gp100 alone. There were 14 deaths related to the study drugs (2.1%), and 7 were associated with immune-related AEs. The authors concluded that ipilimumab, with or without a gp100 peptide vaccine, as compared with gp100 alone, improved OS in patients with previously treated metastatic melanoma. Adverse events can be severe, long-lasting, or both, but most are reversible with appropriate treatment.

On March 25, 2011, the U.S. Food and Drug Administration (FDA) approved ipilimumab (Yervoy) 3 mg/kg for the treatment of patients with unresectable or metastatic melanoma. Yervoy 3 mg/kg is administered intravenously over 90 minutes every 3 weeks for a total of 4 doses. The manufacturer, Bristol-Myers Squibb, has agreed with the FDA to perform a post-marketing study comparing the safety and effectiveness of the 3 mg/kg dose versus an investigational 10 mg/kg dose in patients with unresectable or metastatic melanoma.

Common side effects associated with the use of ipilimumab include colitis, diarrhea, endocrine deficiencies, fatigue, and skin rash. Severe to fatal autoimmune reactions were seen in 12.9% of patients treated with ipilimumab. When severe side effects occurred, ipilimumab was stopped and corticosteroid treatment was started. Not all patients responded to this treatment. Patients who did respond in some cases did not see any improvement for several weeks. Due to the unusual and severe side effects associated with ipilimumab, the therapy is being approved with a risk evaluation and mitigation strategy (REMS) to inform health care professionals about these serious risks. A medication guide will also be provided to patients to inform them about the therapy’s potential side effects.

The National Comprehensive Cancer Network’s clinical practice guidelines on melanoma (NCCN, 2011) states that based on the supporting data and recent FDA approval, ipilimumab was added as an option for the treatment of patients with advanced or metastatic melanoma. Furthermore, the NCCN Drugs and Biologics Compendium (2011) recommends the use of(298,284),(669,304)

Unresectable stage III in-transit metastases
Local, satellitosis, and/or in-transit unresectable recurrence
Incompletely resected nodal recurrence
Limited recurrence or metastatic disease
Disseminated recurrence or metastatic disease without brain metastases in patients with good performance status
Disseminated recurrence with brain metastases in patients with good performance status

Guidelines on malignant melanoma from the National Comprehensive Cancer Network (NCCN, 2012) also recommend the use of ipilimumab as a single agent for reinduction in select patients who experienced no significant systemic toxicity during prior ipilimumab therapy and who relapse after initial clinical response or progress after stable disease greater than three months.

A randomized controlled clinical study found that ipilimumab in combination with dacarbazine, as compared with dacarbazine plus placebo, improved overall survival in patients with previously untreated metastatic melanoma. Robert, et al. (2011) randomly assigned 502 patients with previously untreated metastatic melanoma, in a 1:1 ratio, to...
Iplimumab (at a dose of 10 mg per kilogram) plus dacarbazine (850 mg per square meter of body-surface area) or dacarbazine (850 mg per square meter) plus placebo, given at weeks 1, 4, 7, and 10, followed by dacarbazine alone every 3 weeks through week 22. Patients with stable disease or an objective response and no dose-limiting toxic effects received iplimumab or placebo every 12 weeks thereafter as maintenance therapy. The primary end point was overall survival. The investigators found that overall survival was significantly longer in the group receiving iplimumab plus dacarbazine than in the group receiving dacarbazine plus placebo (11.2 months versus 9.1 months, with higher survival rates in the iplimumab-dacarbazine group at 1 year (47.3% versus 36.3%), 2 years (28.5% versus 17.9%), and 3 years (20.8% versus 12.2%) (hazard ratio for death, 0.72; P<0.001). Grade 3 or 4 adverse events occurred in 56.3% of patients treated with iplimumab plus dacarbazine, as compared with 27.5% treated with dacarbazine and placebo (p < 0.001). The investigators reported that no drug-related deaths or gastrointestinal perforations occurred in the iplimumab-dacarbazine group. The investigators stated that the types of adverse events were consistent with those seen in prior studies of iplimumab; however, the rates of elevated liver-function values were higher and the rates of gastrointestinal events were lower than expected on the basis of prior studies.

Danielli et al (2012) evaluated the activity and safety of iplimumab in patients with uveal melanoma (UM) in a setting similar to daily clinical practice. Patients participating in a multi-center expanded access program (EAP) received induction treatment with iplimumab 10 mg/kg. Maintenance doses were administered in patients who experienced clinical benefit or at physicians’ discretion. Tumor assessment was assessed per modified World Health Organization criteria at baseline, week 12, week 24, and week 36. Adverse events (AEs) and immune-related AEs (irAEs) were collected according to Common Terminology Criteria for Adverse Events version 3.0. A total of 13 pre-treated patients with metastatic UM were treated at 6 European institutions. All patients received at least 1 dose of iplimumab. Overall, no objective responses were observed; however, 2 patients had stable disease (SD), with a 3rd patient achieving SD after initial progressive disease. Median OS as of July 1, 2011, was 36 weeks (range of 2 to 172+ weeks). No grade 3/4 AEs of non-immune origin were reported. Three patients (23 %) experienced grade 3 irAEs (1 thrombocytopenia, 1 diarrhea, and 1 alanine/aspartate aminotransferase elevation) that resolved with steroid therapy. The results indicate UM is a potential indication for iplimumab treatment that should be further investigated in clinical trials.

Iplimumab for the Treatment of Other Tumors/Malignancies:

The therapeutic responses seen in melanoma has led many researchers to examine the potential of iplimumab in a variety of advanced solid tumors and malignancies. Early results with anti-CTLA-4 monoclonal antibodies have revealed the feasibility, safety, and activity of these agents, thus suggesting a promising therapeutic role to be further investigated in phase II/III trials in a wide range of tumors (Calabrò et al, 2010). The principal limitations for applicability of this mode of treatment are better definition of the mechanism that leads to tumor rejection as well as the validation of favorable observations in single-arm studies into prospectively randomized clinical trials (Agarwala and Ribas, 2010). Iplimumab is undergoing clinical trials for the treatment of metastatic hormone-refractory prostate cancer, non-small cell lung cancer (NSCLC), and small cell lung cancer (SCLC). Albiges et al (2010) stated that despite that greater knowledge of prostate cancer biology has led to the isolation of many new and promising targets, treatment of metastatic prostate cancer is still challenging. New agents targeting these molecules are currently
under development in large randomized phase III trials to improve OS and the quality of life of patients with metastatic castrate-resistant prostatic cancer (CRPC). Cytotoxic chemotherapy (docetaxel-based chemotherapy) demonstrated clinical benefit on OS, but could be improved. Drugs targeting directly or not the androgen receptor such as abiraterone or new specific peripheral anti-androgens (MDV3100) are very promising. Bone targeted therapies (e.g., endothelin1 receptor A inhibitor, RANK ligand, and metabolic irradiation) are also very promising and are in development in large phase III trials. Anti-angiogenic therapies could also be effective in CRPC. Autologous vaccine against prostatic acid phosphatase has been reported to prolong OS (on April 29, 2010, sipuleucel-T [Provenge] was approved by the FDA for the treatment of asymptomatic or minimally symptomatic prostate cancer that has metastasized and is resistant to standard hormone treatment). Other vaccines and immunotherapy strategies are in development (e.g., ipilimumab).

In a pilot study, Small et al (2007) attempted to establish the pharmacokinetic and safety profile for a single dose of 3 mg/kg of ipilimumab and assessed if this therapy resulted in prostate-specific antigen (PSA) modulation and the development of polyclonal T-cell activation and/or clinical autoimmunity in patients with hormone-refractory prostate cancer treated with ipilimumab. Patients with metastatic hormone-refractory prostate cancer received a single 3 mg/kg intravenous dose of ipilimumab. Serologic measures of autoimmunity were obtained, and T-cell activation was evaluated by flow cytometry. Pharmacokinetic sampling of plasma for MDX-CTLA-4, PSA measurement, and diagnostic imaging were also undertaken. A total of 14 patients were treated: 12 patients received a single dose of ipilimumab, and 2 patients were re-treated with a second dose upon PSA progression. Two patients showed PSA declines of greater than or equal to 50%. Treatment was well-tolerated with clinical autoimmunity limited to 1 patient who developed grade 3 rash/pruritus requiring systemic corticosteroids. The mean +/- SD ipilimumab terminal elimination half-life was 12.5 +/- 5.3 days. The authors concluded that a single dose of 3 mg/kg ipilimumab given to patients with prostate cancer is safe and does not result in significant clinical autoimmunity. They stated that the observed PSA-modulating effects of ipilimumab warrant further investigation.

In a pilot study, O'Mahony et al (2007) examined the effects of ipilimumab after cancer vaccine failure in patients with advanced malignancy. The primary end point was drug toxicity. Tumor response, tumor-specific CD8+ T-cell immune responses, and modulation of CD4+ CD25+ FoxP3+ regulatory T-cell (Treg) numbers were secondary end points. A total of 11 patients (3 with colon cancer, 4 with non-Hodgkin's lymphoma, and 4 with prostate cancer) were treated. The first dose was given at 3 mg/kg and subsequent doses were administered monthly at 1.5 mg/kg for a total of 4 cycles. Tumor regression was observed in 2 patients with lymphoma; 1 of which obtained a PR of 14-month duration. Ipilimumab was well-tolerated with predominantly grade 1/2 toxicities. One drug-related grade 3 toxicity was observed. One patient died within 30 days of treatment due to progressive colon cancer. No increase in vaccine-specific T-cell responses was observed after therapy. Tregs as detected by expression of CD4+CD25+CD62L+ declined at early time points but rebounded to levels at or above baseline values at the time of the next infusion. The authors concluded that ipilimumab treatment depressed Treg numbers at early time points in the treatment cycle but was not accompanied by an increase in vaccine-specific CD8+ T-cell responses in these patients previously treated with a variety of investigational anti-cancer vaccines. A PR was seen in 1 patient with follicular lymphoma. They noted that a phase I/II clinical trial evaluating ipilimumab in patients with follicular lymphoma is currently ongoing.
In a phase II study, Yang et al (2007) examined the effects of ipilimumab in patients with metastatic renal cell cancer with a primary end point of response by Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Two sequential cohorts received either 3 mg/kg followed by 1 mg/kg or all doses at 3 mg/kg every 3 weeks (with no intention of comparing cohort response rates). Major toxicities were enteritis and endocrine deficiencies of presumed autoimmune origin. One of 21 patients receiving the lower dose had a PR. Five of 40 patients at the higher dose had PR (95 % CI for cohort response rate 4 % to 27 %) and responses were seen in patients who had previously not responded to IL-2. Thirty-three percent of patients experienced a grade III or IV immune-mediated toxicity. There was a highly significant association between autoimmune events and tumor regression (response rate = 30 % with autoimmune events, 0 % without autoimmune events). The authors concluded that ipilimumab induced cancer regression in some patients with metastatic clear cell renal cancer, even if they have not responded to other immunotherapies. These regressions are highly associated with other immune-mediated AEs of presumed autoimmune origin by mechanisms as yet undefined.

In a phase I clinical trial, Ansell et al (2010) evaluated the safety, immunologic activity, and potential clinical effectiveness of ipilimumab in patients with relapsed/refractory B-cell lymphoma. Treatment consisted of ipilimumab at 3 mg/kg and then monthly at 1 mg/kg x 3 months (dose level 1), with subsequent escalation to 3 mg/kg monthly x 4 months (dose level 2). A total of 18 patients were treated, 12 at the lower dose level and 6 at the higher dose level. Ipilimumab was generally well-tolerated, with common AEs attributed to it, including abdominal pain, anorexia, diarrhea, fatigue, headache, neutropenia, and thrombocytopenia. Two patients had clinical responses; 1 patient with diffuse large B-cell lymphoma had an ongoing CR (greater than 31 months), and 1 with follicular lymphoma had a PR lasting 19 months. In 5 of 16 cases tested (31 %), T-cell proliferation to recall antigens was significantly increased (greater than 2-fold) after ipilimumab therapy. The authors concluded that blockade of CTLA-4 signaling with the use of ipilimumab is well-tolerated at the doses used and has anti-tumor activity in patients with B-cell lymphoma. They stated that further evaluation of ipilimumab alone or in combination with other agents in B-cell lymphoma patients is therefore warranted.

Mori et al (2011) stated that ipilimumab is intended to be used as a drug to activate the immune system by binding to CTLA-4. Recently, a phase III, multi-center, randomized, double-blind, clinical study showed an improvement in OS/PFS in patients with advanced melanomas. Ipilimumab is undergoing clinical trials for the treatment of melanoma, NSCLC, SCLC, and metastatic hormone-refractory prostate cancer, as well as other neoplastic diseases.

Lowery and O'Reilly (2011) noted that the development of novel therapeutic strategies for pancreatic adenocarcinoma (PAC) has traditionally been considered particularly challenging for clinical and laboratory investigators due to its aggressive underlying biology and inherent resistance to currently available therapies. More recently, however, advances have been made in the identification of promising therapeutic targets for intervention, along with several key insights into the complex sequence of genetic alterations involved in the evolution of PAC from pre-malignant precursor lesion to malignant cells with metastatic potential. FOLFIRINOX (5-fluorouracil/leucovorin/irinotecan/oxaliplatin) has recently been identified as a combination cytotoxic therapy associated with a significant survival benefit over single-agent gemcitabine in good performance status patients with advanced disease; it is hoped that a similar benefit will be seen in planned trials of FOLFIRINOX as peri-
operative therapy. The success of immune therapy with the anti-cytotoxic T-lymphocyte antigen-4 antibody ipilimumab in advanced melanoma has spurred interest in the development of vaccines and immune therapies for other solid tumors. Certainly, the concept of harnessing the power of the immune system for cancer treatment is an attractive concept to patients and clinicians alike.

George and Moul (2012) performed a review of literature to identify ongoing and planned phase III studies of novel agents to treat castration-resistant prostate cancer (CRPC). Multiple studies were identified, including novel androgen biosynthesis inhibitors (abiraterone, TAK-700), androgen-receptor inhibitors (MDV3100), angiogenesis inhibitors (afibercept, tasquinimod), endothelin antagonists (zibotentan, atrasentan), a Src tyrosine kinase inhibitor (dasatinib), a novel radiotherapy (radium-223), and new immunotherapies (ipilimumab and ProstVac). In addition, both sipuleucel-T (an immunotherapy) and cabazitaxel (3rd-generation taxane) and the RANK-L inhibitor, denosumab, have recently been approved by the FDA. The authors concluded that various combinations of these agents could theoretically be used to treat future patients with CRPC by targeting multiple signaling pathways as well as aspects of the tumor and bone microenvironments. They stated that additional research is needed to understand how to best use these agents and individualize care to optimize CRPC patient outcomes.

Hall et al (2013) discussed recent clinical trials using immunotherapy techniques to treat both NSCLC and SCLC and highlighted ongoing immunotherapy research efforts at our center. For NSCLC, phase II clinical trials have examined allogeneic vaccines that target mucin 1, epidermal growth factor or melanoma-associated antigen 3. These vaccines are now undergoing larger phase III trials. An autologous cellular therapy directed against transforming growth factor beta-2 and a recombinant protein with anti-tumor properties have also shown promise in prolonging survival in NSCLC in phase II trials. The monoclonal antibodies ipilimumab, lambrolizumab (anti-PD-1), and BMS936559 (anti-PD-L1) lead to enhanced T-cell-mediated anti-tumor effects and have produced objective responses in early-phase clinical trials. Studies for SCLC also exist, such as a novel vaccine therapy targeting p53. The authors concluded that recent clinical trials in lung cancer demonstrated the potential of immuno-therapeutics to increase OS in patients with lung cancer compared with the current standard of care.

Spigel et al (2013) stated that SCLC is an aggressive malignancy that although initially sensitive to chemo- and radio-therapy, inevitably relapses resulting in poor survival. Increasing evidence suggested that immune responses against SCLC cells make immunotherapy a viable therapeutic approach. Furthermore, pre-clinical data have shown that certain chemotherapeutic regimens may augment the immunotherapeutic response in SCLC. This review discussed current evidence supporting immunotherapy for SCLC, progress made, and ongoing clinical trials. These investigators searched PubMed and abstracts presented at recent oncology congresses for publications on the clinical benefit of immunotherapy/checkpoint blockade for treatment of SCLC. Preliminary data from ongoing clinical trials in SCLC have shown that some anti-angiogenic agents, vaccines, and immunomodulators, including interferon-alpha, and immune check-point blockers (i.e., anti-cytotoxic T-lymphocyte-associated antigen-4 [CTLA-4] antibodies) may be effective as single agents and in combination with standard-of-care regimens. Notably, in a phase II trial, ipilimumab demonstrated encouraging results when used as part of a chemoimmunotherapeutic regimen in patients with SCLC. Ipilimumab is undergoing further investigation in this population.
Sarcoma (cancer of the connective tissues) frequently strikes young people, comprising a large percentage of cancer in children and young adults, but may occur at any age. Goldberg (2013) described the current advances in immunotherapy and how they can be applied to sarcoma. The author noted that although molecularly targeted inhibitors are of great interest in treating sarcoma patients, immunotherapy is emerging as a plausible therapeutic modality because of the recent advances in other cancer types that may be translated to sarcoma. The licensing of ipilimumab and sipuleucel-T for cancer, and the remarkable success of immunotherapy for some childhood cancers, suggest a role for immunotherapy in the treatment of tumors like sarcoma. The author concluded that recent advances in sarcoma biology and cancer immunotherapy suggested that the understanding of the immune system has reached the point where it can be used to augment both targeted and multi-modality therapy for sarcoma.

In a pilot study, Maki et al (2013) examined the clinical activity of ipilimumab in patients with advanced or metastatic synovial sarcoma. A Simon 2-stage phase II design was used to determine if there was sufficient activity to pursue further. The primary end-point was tumor response rate by RECIST 1.0. Patients were treated with ipilimumab 3 mg/kg intravenously every 3 weeks for 3 cycles and then re-staged. Re-treatment was possible for patients receiving an extra 3-week break from therapy. Sera and peripheral blood mononuclear cells were collected before and during therapy to assess NY-ESO-1-specific immunity. A total of 6 patients were enrolled and received 1 to 3 cycles of ipilimumab. All patients showed clinical or radiological evidence of disease progression after no more than 3 cycles of therapy, for a RECIST response rate of 0%. The study was stopped for slow accrual, lack of activity, and lack of immune response. There was no evidence of clinically significant either serologic or delayed type hypersensitivity responses to NY-ESO-1 before or after therapy. The authors concluded that despite high expression of CT antigens by synovial sarcomas of patients treated in this study, there was neither clinical benefit nor evidence of anti-CT antigen serological responses.

UpToDate reviews on “Adjuvant chemotherapy for malignant gliomas” (Batchelor, 2013), “Management of malignant gliomas in elderly patients” (Batchelor and Shih, 2013), and “Management of recurrent malignant gliomas” (Batchelor et al, 2013) do not mention the use of ipilimumab as a therapeutic option. Furthermore, NCCN’s Drugs & Biologics Compendium (2013) does not list glioblastoma as a recommended indication of ipilimumab.

In a multi-center, randomized, double-blind, phase III clinical trial, Kwon and colleagues (2014) evaluated the use of ipilimumab after radiotherapy in patients with metastatic castration-resistant prostate cancer that progressed after docetaxel chemotherapy. Men with at least 1 bone metastasis from castration-resistant prostate cancer that had progressed after docetaxel treatment were randomly assigned in a 1:1 ratio to receive bone-directed radiotherapy (8 Gy in one fraction) followed by either ipilimumab 10 mg/kg or placebo every 3 weeks for up to 4 doses. Non-progressing patients could continue to receive ipilimumab at 10 mg/kg or placebo as maintenance therapy every 3 months until disease progression, unacceptable toxic effect, or death. Patients were randomly assigned to either treatment group via a minimization algorithm, and stratified by Eastern Cooperative Oncology Group (ECOG) performance status, alkaline phosphatase concentration, hemoglobin concentration, and investigator site. Patients and investigators were masked to treatment allocation. The primary end-point was overall survival (OS), assessed in the intention-to-treat population. From May 26, 2009, to Feb 15, 2012, a total of 799 patients were randomly assigned (399 to ipilimumab and 400 to placebo), all of
whom were included in the intention-to-treat analysis. Median OS was 11.2 months (95 % CI: 9.5 to 12.7) with ipilimumab and 10.0 months (8.3 to 11.0) with placebo (hazard ratio [HR] 0.85, 0.72 to 1.00; p = 0.053). However, the assessment of the proportional hazards assumption showed that it was violated (p = 0.0031). A piece-wise hazard model showed that the HR changed over time: the HR for 0 to 5 months was 1.46 (95 % CI: 1.10 to 1.95), for 5 to 12 months was 0.65 (0.50 to 0.85), and beyond 12 months was 0.60 (0.43 to 0.86). The most common grade 3 to 4 adverse events were immune-related, occurring in 101 (26 %) patients in the ipilimumab group and 11 (3 %) of patients in the placebo group. The most frequent grade 3 to 4 adverse events included diarrhea (64 [16 %] of 393 patients in the ipilimumab group versus 7 [2 %] of 396 in the placebo group), fatigue (40 [11 %] versus 35 [9 %]), anemia (40 [10 %] versus 43 [11 %]), and colitis (18 [5 %] versus 0). Four (1 %) deaths occurred because of toxic effects of the study drug, all in the ipilimumab group. The authors concluded that although there was no significant difference between the ipilimumab group and the placebo group in terms of OS in the primary analysis, there were signs of activity with the drug that warrant further investigation.

Hodi and colleagues (2014) stated that ipilimumab improves survival in advanced melanoma and can induce immune-mediated tumor vasculopathy. Besides promoting angiogenesis, vascular endothelial growth factor (VEGF) suppresses dendritic cell maturation and modulates lymphocyte endothelial trafficking. These researchers investigated the combination of CTLA4 blockade with ipilimumab and VEGF inhibition with bevacizumab. Patients with metastatic melanoma were treated in 4 dosing cohorts of ipilimumab (3 or 10 mg/kg) with 4 doses at 3-week intervals and then every 12 weeks, and bevacizumab (7.5 or 15 mg/kg) every 3 weeks. A total of 46 patients were treated. Inflammatory events included giant cell arteritis (n = 1), hepatitis (n = 2), and uveitis (n = 2). On-treatment tumor biopsies revealed activated vessel endothelium with extensive CD8 (+) and macrophage cell infiltration. Peripheral blood analyses demonstrated increases in CCR7(+-)/CD45RO(+) cells and anti-galectin antibodies. Best overall response included 8 PR, 22 instances of SD, and a disease-control rate of 67.4 %. Median survival was 25.1 months. Bevacizumab influences changes in tumor vasculature and immune responses with ipilimumab administration. The combination of bevacizumab and ipilimumab can be safely administered and reveals VEGF-A blockade influences on inflammation, lymphocyte trafficking, and immune regulation. The authors concluded that these findings provided a basis for further investigating the dual roles of angiogenic factors in blood vessel formation and immune regulation, as well as future combinations of anti-angiogenesis agents and immune check-point blockade.

The National Comprehensive Cancer Network’s Drugs & Biologics Compendium (2014) lists 2 new recommended indications of ipilimumab:

- Single-agent treatment for brain metastases if active against primary tumor (melanoma) for recurrent disease (Category 2A)
- Single-agent treatment if active against primary tumor (melanoma) for brain metastases in patients with recurrent stable systemic disease (Category 2A)

Appendix

The compassionate use trial for unresectable melanoma with ipilimumab (Bristol-Myers Squibb, 2010) provide the following inclusion as well as exclusion criteria. [http://clinicaltrials.gov/ct2/show/NCT00495066](http://clinicaltrials.gov/ct2/show/NCT00495066).

Inclusion Criteria:
Histologically confirmed stage III (unresectable) or stage IV melanoma. Must have failed at least 1 systemic therapy for malignant melanoma or be intolerant to at least 1 prior systemic treatment. Subjects with asymptomatic brain metastases are eligible. Primary ocular and mucosal melanomas are allowed. Must be at least 28 days since treatment with chemotherapy, biochemotherapy, or immunotherapy, and recovered from any clinically significant toxicity experienced during treatment. Must have recovered from prior surgery or radiation. Systemic corticosteroids should be eliminated or weaned to the minimum dose before starting ipilimumab treatment. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2. Life expectancy greater than or equal to 16 weeks. Subjects must have the complete set of baseline (screening/baseline) radiographical images, including but not limited to abdomen, bone, brain, chest, and pelvis scans. Required values for initial laboratory tests:

- WBC: greater than or equal to 2000/uL (greater than or equal to 2 x 10^9/L);
- ANC: greater than or equal to 1000/uL (greater than or equal to 1 x 10^9/L);
- platelets: greater than or equal to 75 x 10^3/uL (greater than or equal to 75 x 10^9/L);
- hemoglobin: greater than or equal to 9 g/dL (greater than or equal to 80 g/L; may be transfused);
- creatinine: less than or equal to 2.0 x ULN;
- AST/ALT: less than or equal to 2.5 x ULN for subjects without liver metastasis less than or equal to 5 times for liver metastases; bilirubin: less than or equal to 2.0 x ULN (except for subjects with Gilbert’s Syndrome, who must have a total bilirubin of less than 3.0 mg/dL).

Men and women, at least 16 years of age. Prior treatment with an anti-CTLA-4 drug is allowed provided therapy was not discontinued due to drug-related toxicity.

Exclusion Criteria:

- Women of child-bearing potential (WOCBP) who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire duration of treatment and for up to 8 weeks after the last dose of ipilimumab.
- WOCBP using a prohibited contraceptive method.
- Women who are pregnant or breast-feeding.
- Women with a positive pregnancy test before administration of ipilimumab.
- Subjects on any other systemic therapy for cancer, including any other experimental treatment.
- Prior treatment with an anti-CTLA-4 antibody if treatment failure was due to immune-related AEs or discontinuation was due to an AE/serious AE.
- Presence of active autoimmune disease.
- Presence of known hepatitis B or hepatitis C (active) infection, regardless of control on anti-viral therapy.
- Any subject who has a life-threatening condition that requires high-dose immunosuppressants.
- Subjects with melanoma who have another active, concurrent, malignant disease, with the exception of adequately treated basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix.

Dosing:
According to the FDA-approved labeling, ipilimumab 3 mg/kg is administered intravenously over 90 minutes every 3 weeks for a total of 4 doses.

Ipilimumab is considered experimental and investigational when used in combination with vemurafenib (Zelboraf).

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes covered if selection criteria are met:

J9228

Other CPT codes related to the CPB:

96413

96415

HCPCS codes covered if selection criteria are met:

J0588 Injection, Incobotulinumtoxin A, 1 unit

ICD-9 codes covered if selection criteria are met:

172.0 - 172.9 Malignant melanoma of skin

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

153.0 - 153.9 Malignant neoplasm of colon

157.0 - 157.9 Malignant neoplasm of pancreas

162.3 - 162.9 Malignant neoplasm of bronchus or lung

171.0 - 171.9 Malignant neoplasm of connective and other soft tissue

191.0 - 191.9 Malignant neoplasm of brain [glioblastoma]

185 Malignant neoplasm of prostate

189.0 Malignant neoplasm of kidney, except pelvis

200.00 - 200.08 Reticulosarcoma

200.10 - 200.18 Lymphosarcoma

200.20 - 200.28 Burkitt's tumor or lymphoma

200.30 - 200.38 Marginal zone lymphoma

200.40 - 200.48 Mantle cell lymphoma

200.70 - 200.78 Large cell lymphoma
200.80 - 200.88 Other named variants of lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic tissue

202.00 - 202.08 Nodular lymphoma

202.10 - 202.18 Mycosis fungoides

202.30 - 202.38 Malignant histiocytosis

202.80 - 202.88 Other malignant lymphomas

The above policy is based on the following references:


4. National Horizon Scanning Centre (NHSC). Ipilimumab (MDX-010) for unresectable stage III or IV metastatic melanoma - first or second line treatment Horizon Scanning Technology Briefing. Birmingham, UK: National Horizon Scanning Centre (NHSC); April 1, 2008.


35. Batchelor T. Adjuvant chemotherapy for malignant gliomas. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed August 2013.
36. Batchelor T, Shih HA. Management of malignant gliomas in elderly patients. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed August 2013.
37. Batchelor T, Shih HA, Carter BS. Management of recurrent malignant gliomas. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed August 2013.