Brand Name: Yervoy

Generic Name:ipilimumab

Manufacturer[3]: Bristol-Myers Squibb

Drug Class[1,2,4]: Antineoplastic Agent, Monoclonal Antibody; Immune modulator

Uses:

Labeled Uses[1,2,3,4,5]: Treatment of unresectable or metastatic melanoma in adults.

Mechanism of Action:[1,2,3,4,5]

Ipilimumab is a recombinant, human IgG1 immunoglobulin monoclonal antibody that binds to cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). CTLA-4 is a down-regulator of T-cell activation pathways.By inhibiting the interaction between CTLA-4 and its ligands (CD80 and CD86), ipilimumab enhances T-cell activation and proliferation. The effect of ipilimumab in patients with melanoma is indirect and is thought to be due to T-cell mediated antitumor immune responses.

Pharmacokinetics:[1,3,4]

Distribution: Vss = 7.21 L

Half-life elimination: Terminal = 14.7 days

Systemic Clearance: CL = 15.3 mL/h (38.5%)

Clearance increased with increasing body weight; however, no dose adjustment of ipilimumab is required for body weight after administration on a mg/kg basis.

$Cmin_{ss}$ achieved with the 3-mg/kg regimen was 21.8 mcg/mL (±11.2).

Renal Impairment: Creatinine clearance at baseline did not have a clinically important effect on ipilimumab pharmacokinetics in patients with calculated creatinine clearance values of 29 mL/min or greater.

Hepatic Impairment: Baseline AST, total bilirubin, and ALT levels did not have a clinically important effect on ipilimumab pharmacokinetics in patients with various degrees of hepatic impairment.

Efficacy:

Wolchok JD, Neyns B, Linette G, et al, "Ipilimumab Monotherapy in Patients With Pretreated Advanced Melanoma: A Randomised, Double-Blind, Multicentre, Phase 2, Dose-Ranging Study," Lancet Oncol, 2010, 11(2):155-64.

Study Design: International, multicenter, randomized, double-blind, parallel group study occurring from April 2006 to November 2007.

Description of Study:*Methods*: 217 patients over the age of 16 with a diagnosis of unresectable stage III or IV melanoma, with measurable disease, who had previously been treated with at least one antitumor regimen, were randomly assigned in a1:1:1 fashion to receive ipilimumab 10 mg/kg (n=72), 3 mg/kg (n=72), or 0.3 mg/kg (n=73).At week 24, those patients still receiving ipilimumab without progressive disease continued on with maintenance therapy at the assigned group treatment dose every

12 weeks until they had progressive disease, death, or toxicity. *Results*: All 4 induction doses of ipilimumab were received by 50%, 70% and 68% of patients in the 10, 3, and 0.3 mg/kg dosing groups, respectively. 20 of 214 patients continued on to received maintenance therapy during the current study. Twenty-four percent, 22%, and 30.5% of patients from the 10 mg/kg, 3 mg/kg, and 0.3 mg/kg groups, respectively, progressed during this study. The best overall response (BORR) was 11.1% in the 10 mg/kg group (95% CI 4.9% to 20.7%), 4.2% (95% CI, 0.9% to 11.7%) in the 3 mg/kg group, and 0% (95% CI, 0% to 4.9%) in the 0.3 mg/kg group. The median overall survival time was 11.4, 8.7, and 8.6 months in the 10, 3, and 0.3 mg/kg dosing groups, respectively. Similarly, disease control rate (DCR) and 1-year survival rate were greatest in the ipilimumab 10 mg/kg dosing group. Any-grade adverse events were similar among the ipilimumab 10 and 3 mg/kg groups, and all events were deemed manageable among all groups. The most commonly reported events were grade 1 or 2 immune-related events (IRE).

Limitations: This study is limited by a small sample size. The study was not designed to detect differences in survival between groups which limit its comparison to other published studies. A third of patients in the lower dosing groups crossed over to the 10 mg/kg group in a separate companion study by 3 months post-randomization. This crossover might have confounded survival differences between groups.The number of patients experiencing an adverse event with ipilimumab treatment is quite high, which makes determining a risk to benefit ratio difficult.

Conclusion: Ipilimumabmonotherapy showed a dose-dependent effect on pharmacokinetic, biological, and clinical variables in patients with advanced melanoma. The recommended dosage is ipilimumab 3 mg/kg administered by IV infusion over 90 minutes every 3 weeks for a total of 4 doses, best overall response rate was found to be most improved with ipilimumab 10 mg/kg.Since the likelihood for adverse events seems to be high across the board, further studies could focus on using these prognostic factors to attempt to define subgroups of patients (elevated LDH, male, good performance status, certain cytogenetic markers) that may benefit most from therapy or are less likely to have detrimental adverse events.

Weber J, Thompson JA, Hamid O, et al: A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma. Clin Cancer Res 2009; 15(17):5591-5598.

Study Design:multicenter, randomized, double-blind, placebo-controlled, phase 2 study

Description of Study:*Methods*:115 unresectable stage III or IV melanoma, previously treated and treatment-naïve, patients received open-label ipilimumab (10 mg/kg 90-min IV infusion every 3 weeks for four doses) and were randomized and blinded to receive either budesonide 9 mg orally (n=58) or placebo (n=57)once daily for 12 weeks, with a gradual taper until discontinuation at week 16. Previous use of anticytotoxic T-lymphocyte antigen-4 antibody or immunosuppression (excluding stable corticosteroid replacement therapy for hypoadrenalism) was not permitted in this study. The first scheduled tumor evaluation was at week 12; eligible patients received maintenance treatment starting at week 24. Ipilimumab was continued every 12 weeks until disease progression, intolerable toxicity, or initiation of an alternative treatment (maintenance). The primary study end point was the rate of grade ≥2 diarrhea during the first 24 wk of study. Secondary end points included best overall response rate; disease control rate; overall survival, survival rate at 1 year. *Outcome Results:* All 4 induction doses of ipilimumab were received by 55% and 61% of budesonide and placebo recipients, respectively. There was no significant difference between ipilimumab with or without prophylactic budesonide for best overall response rate or incidence of grade 2 or higher diarrhea. Overall, ipilimumab adverse events

were similar among treatment arms, with diarrhea, colitis, and immune-related events attributable to study treatment. Secondary outcome measures were similar between groups.

Limitations: This study was funded by the drug manufacture and all authors were members of a Bristol-Myers Squibb advisory board or received monetary reward for their participation. The rate of grade 3 and 4 immune-mediated reactions was substantially higher (~40%) than other clinical trials which report rates of 22-25%. This study did not include exclusion criteria limiting elevated baseline LDH, so this study's findings were obtained from a sample population that included many with poor prognostic factors.

Conclusions: The results of this trial provide further evidence that ipilimumab is clinically active in patients with metastatic melanoma; however, a significantly higher rate of class 3 and 4 adverse events were seen in this study than other clinical trials of ipilimumab. The findings from this study do not support the routine prophylactic use of budesonide for the prevention of grade ≥2 diarrhea at the dose and schedule investigated, although it is still considered for the management of low-grade diarrhea and early colitis associated with ipilimumab. Budesonide did not seem to affect the development of an antitumor response to ipilimumab.

Hodi FS, O'Day SJ, McDermott DF, et al: Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010; 363(8):711-723.

Study Design: Multicenter, randomized, double-blind, phase 3 study.

Description of Study:*Methods*: 676 HLA-A*0201–positive patients with unresectable stage III or IV melanoma who had disease progression while receiving previous therapeutic metastatic regimens were randomly assigned, in a 3:1:1 ratio, to receive ipilimumab plusglycoprotein 100 peptide vaccine (gp100) (n=40); ipilimumab alone (n=137), or gp100 alone (n=136). Ipilimumab (dose: 3 mg/kg) was administered with or without gp100 every 3 weeks for up to four treatments (induction). The original primary end point was the best overall response rate (i.e., the proportion of patients with a partial or complete response); however, this was amended to overall survival.*Outcome Results:*Ipilimumab plus gp100 significantly improved overall survival (OS) by 32% compared with gp100 alone. Approximately 60% of patients in each treatment arm received all 4 induction doses. The median overall survival time was 10 months (95% CI, 8.5 - 11.5 months) with ipilimumab plus gp100 at a median follow-up time of 21 months compared with 6.4 months (95% CI, 5.5 - 8.7 months) with gp100 alone at median follow-up time of 17.2 months (hazard ratio, 0.68; $p < 0.001$). There was no significant difference in overall survival between ipilimumab plus gp100 and ipilimumab alone. The occurrence of any immune-related adverse event was 2-fold greater in the ipilimumab arms than with gp100 alone (60% vs. 32%). The most common immune-related effect in the ipilimumab group was diarrhea (27% to 31%), which generally resolved around 2 weeks with corticosteroid therapy. Disease progression was the most common cause for discontinuation, and 2.1% of fatalities were attributed to study treatment.

Limitations: The study was funded by Bristle-Myer Squibb and all authors were either employed or rewarded financially by the drug manufacturer.Data was collected solely by the study's sponsors. Subjects within this study were considered to be at a high performance status and have relatively good prognosis. Classic response criteria defining partial and complete response, as well as stable or progressive disease, may not be adequate to define responses to this new class of immunotherapy, since clinical responses can take months to develop and an initial period of tumor growth can occur when lymphocytes infiltrate the tumor nodules. Therefore, the report of OR, PR, SD, and PD may be understated.

Conclusion: This study demonstrates ipilimumab has a significant improvement in overall survival among patients with metastatic melanoma, with a substantial long-term benefit seen among a subgroup of patients. However, side effects can be life-threatening and may be treatment-limiting. Overall, findings suggest that ipilimumab may be useful as a treatment for patients with metastatic melanoma whose disease progressed while they were receiving one or more previous therapies; however, further studies identifying those for which ipilimumab is most beneficial are needed in order to combat the life-threatening possible adverse events.

Contraindications:[1,2,3,4,5]

Specific contraindications have not yet been determined

Warnings/Precautions:[1,2,3,4,5]

[U.S. Boxed Warning]:

Immune-mediated adverse effects: Severe and fatal immune-mediated adverse effects due to T-cell activation and proliferation may occur. While any organ system may be involved, common severe effects include dermatitis (including toxic epidermal necrolysis), endocrine disorder, enterocolitis, hepatitis, and neuropathy. Reactions generally occur during treatment, although some reactions have occurred weeks to months after treatment discontinuation. Discontinue treatment (permanently) and initiate high-dose corticosteroid treatment for severe immune mediated reactions. Uncommon immune-mediated adverse effects reported include hemolytic anemia, iritis, meningitis, nephritis, pericarditis, pneumonitis, and uveitis.

Concerns related to adverse effects:

Central nervous system or neuromuscular toxicity: One case each of severe peripheral motor neuropathy and fatal Guillain-Barré syndrome have been reported.

Dermatologic toxicity: Severe, life-threatening, or fatal dermatitis has been reported. The median time to onset for dermatologic toxicity is 3 weeks (range: ≤17 weeks). Monitor for rash and pruritus; dermatitis should be considered immune-mediated unless identified otherwise.

Endocrine disorders: Severe/life-threatening to moderate severity endocrine disorders (hypopituitarism, adrenal insufficiency, hypogonadism and hypothyroidism), which have required hormone replacement therapy or medical intervention have been reported. Median onset was 11 weeks (range: ≤19 weeks); Monitor thyroid function tests and serum chemistries prior to each dose.

Gastrointestinal adverse effects: Immune-mediated enterocolitis was reported to occur at a median onset of 6-7 weeks. Monitor for abdominal pain, blood/mucous in stool, or diarrhea; with or without fever) and intestinal perforation.

Hepatotoxicity: Severe, life-threatening or fatal hepatotoxicity and immune-mediated hepatitis have been observed. Monitor liver function tests (LFTs) and evaluate for signs of hepatotoxicity prior to each dose; if hepatotoxicity develops, infectious or malignant causes should be ruled out and liver function should be monitored more frequently.

Ophthalmic toxicity: Administer corticosteroid ophthalmic drops in patients who develop episcleritis, iritis, or uveitis; permanently discontinue ipilimumab if unresponsive to topical ophthalmic immunosuppressive treatments.

Adverse Effects:[1,2,3,4,5,6,7,8]

Occurring in >10% of patients:

Central nervous system:

Fatigue (41% to 42%; grades 3-5: 7%)
Headache (14%)
Fever (12%)

Dermatologic:

Pruritus (24% to 31%),
Rash (19% to 29%; grades 3-5: 2%)
Dermatitis (grade 2: 12%; grades 3-5: 2% to 3% [includes Stevens-Johnson syndrome, toxic epidermal necrolysis, dermal ulceration necrotic, bullous or hemorrhagic dermatitis])

Gastrointestinal:

Nausea (35%),
Diarrhea (32% to 33%; grades 3-5: 5%),
Appetite decreased (27%),
Vomiting (24%),
Constipation (21%),
Abdominal pain (15%)

Hematologic:

Anemia (12%)

Respiratory:

Cough (16%),
Dyspnea (15%)

Occurring in 1% to 10% of patients:

Dermatologic:

Urticaria (2%),
Vitiligo (2%)

Endocrine & metabolic:

Hypopituitarism (grade 2: 2%; grades 3-5: 4%),
Hypothyroidism (≤2%),
Hypophysitis (2%),
Adrenal insufficiency (≤2%)

Gastrointestinal:

Colitis (8%; grades 3-5: 5%)
Enterocolitis (grade 2: 5%; grades 3-5: 7%)
Intestinal perforation (1%)

Hematologic:

Eosinophilia (grades 3-5: 1%)

Hepatic:

Hepatotoxicity (grade 2: 3%; grades 3-5: 1% to 2%)
ALT increased (2%)

Renal:

Nephritis (grades 3-5: 1%)

Occurring in <1% of patients (Uncommon, but serious):

Acute respiratory distress syndrome, angiopathy, blepharitis, conjunctivitis, corticotrophin decreased, Cushing's syndrome, episcleritis, erythema multiforme, esophagitis, gastrointestinal

ulcer, Guillain-Barré syndrome, hemolytic anemia, hepatic failure, hepatitis (immune-mediated), hypogonadism, hyperthyroidism, iritis, leukocytoclastic vasculitis, meningitis, myasthenia gravis, myelofibrosis, neuropathy (sensory and motor), pancreatitis, polymyalgia rheumatica, psoriasis, renal failure, scleritis, sepsis, temporal arteritis, thyroiditis (autoimmune), thyrotropin increased, uveitis, vascular leak syndrome, vasculitis.

Drug Interactions[2,3,4,5]:

No formal drug-drug interaction studies have been conducted.

Dosing[1,2,3,4,5]:

Adult Dosing

3 mg/kg IV infusion over 90 minutes every 3 weeks for a total of 4 doses; permanently discontinue if treatment cannot be completed within 16 weeks

Recommended Dose Modifications

Temporarily withhold scheduled dose for the following:

- Moderate immune-mediated adverse reactions
- Symptomatic endocrine disorder

- Note: If receiving less than prednisone 7.5 mg/day (or equivalent), may resume with complete or partial resolution (to ≤grade 1) of symptoms. Resume ipilimumab treatment at 3 mg/kg every 3 weeks until all 4 planned doses have been administered or until 16 weeks from initial dose, whichever occurs first.

Permanently discontinue for the following:

- If the full treatment course cannot be completed within 16 weeks
- Persistent moderate adverse reactions or inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day.
- Severe or life-threatening adverse reactions, including any of the following:
  - *Gastrointestinal toxicities:*Colitis with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (7 or more over baseline), stool incontinence, need for intravenous hydration for more than 24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation
  - Hepatotoxicity: AST or ALT >5 times the ULN or total bilirubin >3 times the ULN
  - *Dermatologic toxicities:*Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations
  - *Central nervous system or neuromuscular toxicity:* Severe motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis
  - *Severe immune-mediated reactions* involving any organ system (e.g., nephritis, pneumonitis, pancreatitis, non-infectious myocarditis)
  - *Ophthalmic toxicities:*Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy

Pediatrics

Safety and efficacy not established in pediatric patients

Geriatrics

No overall differences in safety or efficacy were reported between the elderly patients (65 years and over) and younger patients (less than 65 years).

Renal impairment

No formal studies of ipilimumab in patients with renal impairment have been conducted.

Hepatic impairment

No formal studies of ipilimumab in patients with hepatic impairment have been conducted.

Preparation/Administration:[1,2,3,4,5]

- Allow vials to stand at room temperature for approximately 5 minutes before infusion preparation.
- Visually inspect parenteral products for particulate matter and discoloration prior to use. Solution may have a pale yellow color and may have translucent-to-white, amorphous particles. Discard vial if the solution is cloudy, if there is marked discoloration, or foreign particulate matter is present.
- Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare a diluted solution with a final ipilimumab concentration ranging from 1—2 mg/ml. Mix diluted solution by gentle inversion. Do not shake product.
- *Administration:* Administer the diluted infusion over 90 minutes through an IV line containing a sterile, non-pyrogenic, low protein-binding, in-line filter. Do not mix or infuse with other medicinal products.
- *Storage*: Once diluted, store for no more than 24 hours under refrigeration (36—46 degrees F) or at room temperature (68—77 degrees F). Do not freeze and protect vials from light. Discard partially used vials or empty vial.

Use in special circumstances:[1,2,3,4]

Overdose: [3] There is no information on overdose with ipilimumab.

Pregnancy: Ipilimumab is a FDA pregnancy category C drug; no adequate and well-controlled studies in pregnant women exist. Use ipilimumab during pregnancy only if the potential benefit justifies the potential risk to the fetus. Human IgG1 is known to cross the placental barrier; therefore, ipilimumab has the potential to be transmitted from the mother to the developing fetus. Severe toxicities including increased incidences of third-trimester abortion, stillbirth, premature delivery, low birth weight, and infant mortality occurred after intravenous administration of ipilimumab to pregnant cynomolgus monkeys every 21 days from the onset of organogenesis through parturition.

Breast-feeding: Ipilimumab secretion into human milk is unknown. Either discontinue ipilimumab or discontinue nursing because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from ipilimumab.

Conclusion:

Ipilimumab is a recombinant human monoclonal antibody for the treatment of unresectable or metastatic melanoma. Ipilimumab has demonstrated improvement in the overall survival in previously-treated, and untreated patients with unresectable or metastatic melanoma. However, this survival benefit is accompanied by significant adverse events such as grade 2 or higher diarrhea. No extra benefit in best overall response rate or incidence of grade 2 or higher diarrhea was seen when prophylactic budesonide was added to the ipilimumab regimen to combat immune-mediated adverse events. Further studies are needed to identify the particular subset of patients in which this therapy would be most beneficial. Adequate trials investigating ipilimumab's interactions with other drugs and disease states are lacking.

Due to the limited number of treatment modalities in the management of unresectable stage III or IV melanoma, the introduction of this novel treatment modality, which is the first to show improvement in overall survival in the last 3 decades, is welcomed among the scientific community. However, due to ipilimumab's still relatively small overall response rate and significant risk for life-threatening adverse events, caution should be used with its use till more data is obtained on those subset of patients for which ipilimumab would benefit the most.

Recommended References:

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