Formulary Review: Yervoy®
Generic Name: Ipilimumab
Manufacturer: Bristol-Myers Squibb Company
FDA Approval: March 2011

Executive Summary

Introduction

Yervoy is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody indicated for the treatment of unresectable or metastatic melanoma.

Pharmacology

CTLA-4 is a negative regulator of T-cell activation. Ipilimumab binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation. The mechanism of action in melanoma patients is indirect, possibly through T-cell mediated anti-tumor immune responses.

Pharmacokinetics

Table 1. Pharmacokinetic profile

Onset	Ave time to steady state = 6 wks
Distribution	$V_{d\ (ss)}$ = 7.21 L
Metabolism	Systemic clearance 15.3 ml/hr
Elimination	Terminal half-life 14.7 days

Clinical Efficacy

The safety and efficacy of Yervoy was investigated in a randomized, double-blind, multicenter, phase III trial that included 676 patients with unresectable or metastatic melanoma previously treated with one or more of the following: aldesleukin, dacarbazine, temozolomide, fotemustine, or carboplatin. Yervoy, at a dose of 3 mg/kg, was administered with or without a glycoprotein 100 (gp100) peptide vaccine every three weeks for up to 4 cycles. Patients were further stratified by baseline metastasis, LDH greater than or equal to upper limit of normal, age greater than or less than 65 yo, gender, and prior receipt or non-receipt of IL-2 therapy. Of the patients 82 had metastasis to the brain at baseline. The primary endpoint was overall survival.

Overall Survival results

	Yervoy n=137	YERVOY+gp100 n=403	gp100 n=136
Hazard Ratio (vs. gp100)	0.66	0.68	
(95% CI)	(0.51, 0.87)	(0.55, 0.85)	
p-value	p=0.0026a	p=0.0004	
Hazard Ratio (vs. YERVOY)		1.04	
(95% CI)		(0.83, 1.30)	
Median (months)	10	10	6
(95% CI)	(8.0, 13.8)	(8.5, 11.5)	(5.5, 8.7)

The median overall survival was 10 months and 10.1 months among patients receiving Yervoy alone or with the gp100 vaccine, respectively, versus 6.4 months those receiving the vaccine alone. (HR=0.68; P<0.001; HR=0.66; P<).66; P<).003), This increase in overall survival of approximately 4.5 months is unprecedented for any therapy to date for treatment of refractory and unresectable metastatic melanoma.

Secondary endpoints include best overall response and median duration of response:

Intervention	**Best overall response rate**		**Median Duration of response**
Yervoy + gp100	5.7%	95% CI: 3.7-8.4%	11.5 months
Yervoy	10.9%	95% CI: 6.3%-17.4%	Not yet reached
gp100	1.5%	95% CI: 0.2%-5.2%	Not yet reached

Adverse Drug Reactions

Black Box Warning:

YERVOY can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY.

- Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy and endocrinopathy and evaluate clinical chemistries including liver function tests (LFTs) and thyroid function tests at baseline and before each dose.
- Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.

Breakdown of Yervoy death statistics

A total of 14 deaths (2.2%) were determined by the investigators to be related to the study drug:

- 8 in the ipilimumab-plus gp100 group
- 4 in the ipilimumab-alone group, and
- 2 in the gp100-alone group

Seven of the 14 deaths related to the study drug were associated with immune-related adverse events:

-5 in the ipilimumab-plus-gp100 group: 1 patient had grade 3 colitis and septicemia; 3 patients had bowelperforation–inflammatory colitis, bowel perforation, or multiorgan failure–peritonitis; and 1 patient had Guillain–Barre syndrome, which is considered to be consistent with a neurologic immune-related adverse event

-2 in the ipilimumab-alone group: 1 patient had colic bowel perforation and the other had liver failure.

Deaths related to the study drug that were not associated with immune-related adverse events included deaths from:

-3 patients in the ipilimumab-plus-gp100 group: sepsis, myelofibrosis, and acute respiratory distress syndrome

-2 patients in the ipilimumab-alone group severe infection–renal failure–septic shock, and vascular leak syndrome

-2 patients in the gp100-alone group: cachexia and septic shock

Drug Interactions

No formal drug-drug interaction studies have been conducted.

Dosage and Administration

Approved: 3 mg/kg/dose IV infusion over 90 minutes q 3 weeks for a total of 4 doses
(Of note: dose-finding and on-going studies have evaluated 10 mg/kg/dosing as well)

Dose Modifications:

- For any moderate immune-mediated adverse reactions or for symptomatic endocrinopathy, withhold scheduled dose of ipilimumab. For patients who achieve partial or complete resolution of adverse reactions (Grade 0 to 1) AND who are receiving less than 7.5 mg of prednisone or equivalent per day, dose may be restarted at 3 mg/kg IV every 3 weeks until administration of all 4 planned doses or 16 weeks from the first dose, whichever comes first

Permanent Discontinuation:

- persistent moderate adverse reactions or inability to decrease corticosteroid dose to 7.5 mg prednisone or equivalent per day if the full treatment course cannot be completed within 16 weeks, or severe or life-threatening adverse reactions

Cost

Each dose of Yervoy is approximately $24,000/dose x 4 doses/cycle = $96,000 per course of therapy

Look-alike/sound-alike potential	None at this time
Summary	Yervoy is the only therapy to date which has been shown to improve overall survival in randomized clinical trials involving metastatic melanoma. Tolerability and safety are paramount due to risk of severe and life-threatening immune-mediated adverse events associated with Yervoy use. Prompt medical attention and early administration of corticosteroids are critical to the management of immune-related adverse events; to that end the FDA has insisted that a REMS program be established. This program will be comprised of a formal "Communication Plan" detailing the scheduled timeline for distribution of drug safety information regarding the severity and risk of immune-related adverse reactions 1.) 1 week before Yervoy's release, and 2.) every 6 months for three years to U.S. cancer treatment infusion centers. Recipients will include both oncology and non-oncology providers, as well as the leadership of multiple professional societies, so that the information may be distributed amongst their members. Also, new prescribers of Yervoy will be contacted within 48 hours of the initiation of the first prescription in order to convey the risks and give details on these adverse events. Safety materials include: • *Immune-mediated Adverse Reaction Management Guide* - A booklet designed to inform healthcare providers of the signs, symptoms and management of YERVOY immune-mediated adverse reactions • • *Nursing Immune-mediated Adverse Reaction Checklist* - A checklist with key questions to ask patients and actions to take when assessing patients for YERVOY immune-mediated adverse reactions • • *Patient Wallet Card* - A foldable patient resource containing a list of symptoms associated with YERVOY adverse reactions and contact information for the patient's prescribing healthcare provider
Status	Formulary; restricted to use in the outpatient setting