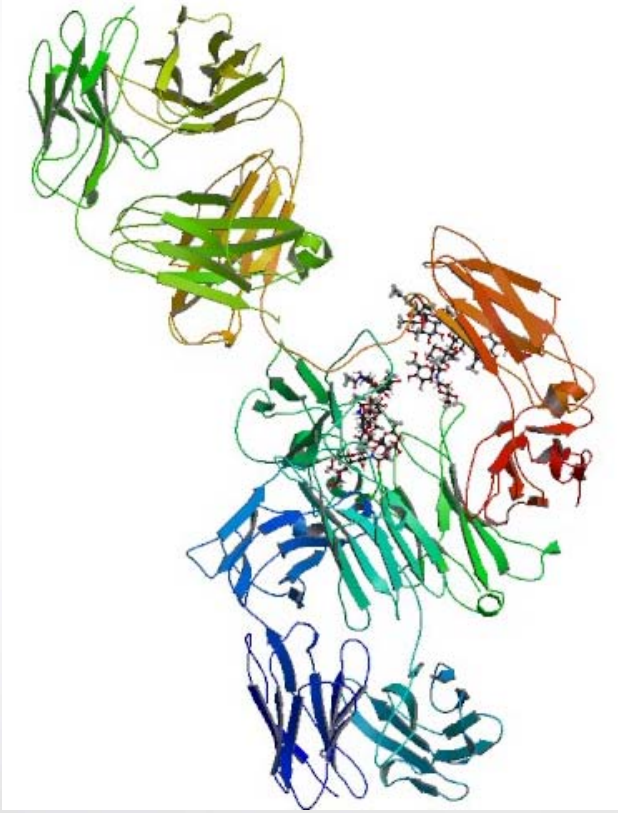
NDA review
-Development of Ipilimumab

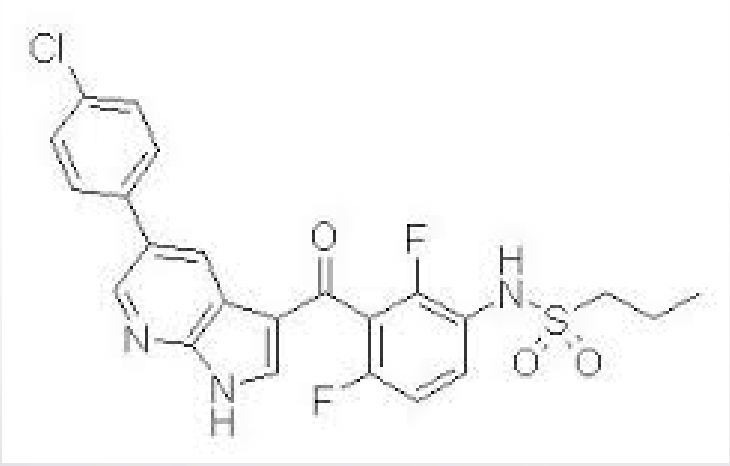


SK YOON, M.D.

October 30, 2018

2018 Nobel Prize in Medicine Awarded to 2 Cancer Immunotherapy Researchers

The Nobel Prize for Physiology and Medicine was awarded to James P. Allison, left, and Tasuku Honjo on Monday for their work on cancer research. Jonathan Nackstrand/Agence France-Presse — Getty Images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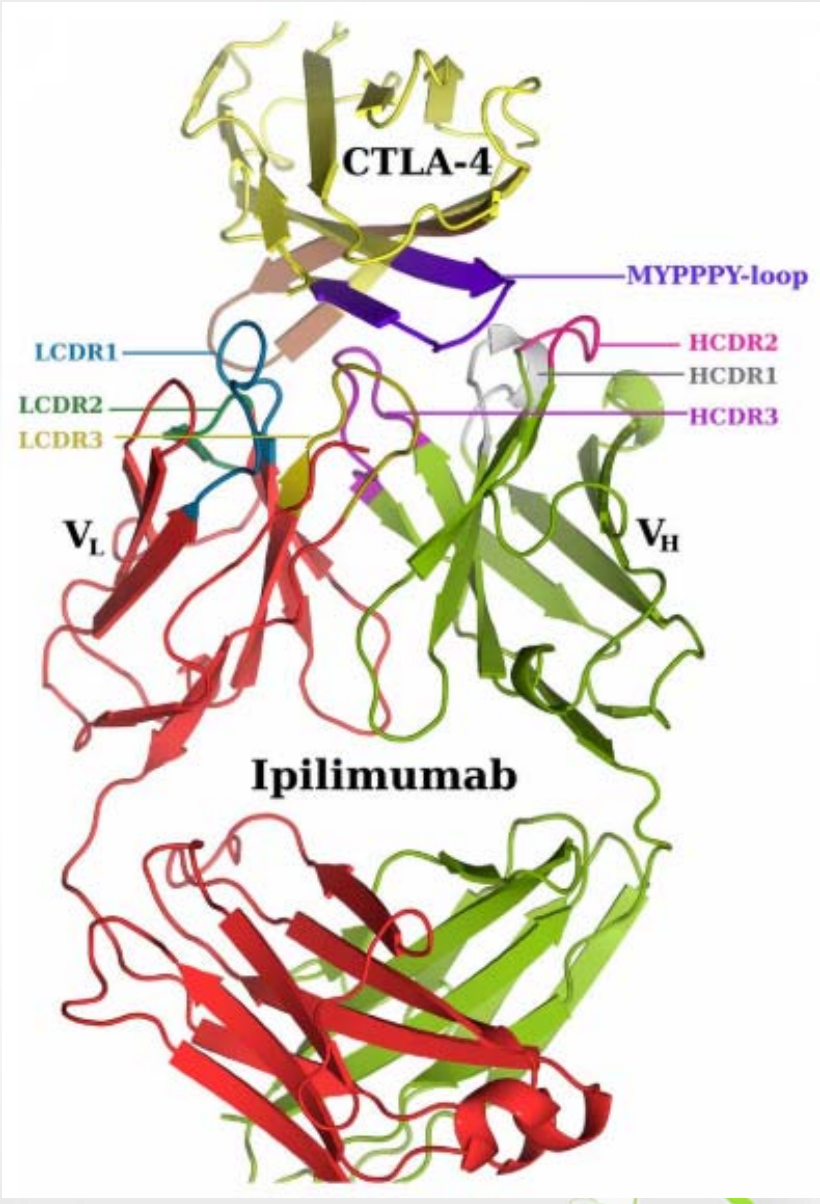

CTLA-4
MYPPPY-loop
LCDR1
LCDR2
LCDR3
HCDR2
HCDR1
HCDR3
V_L
V_H
Ipilimumab

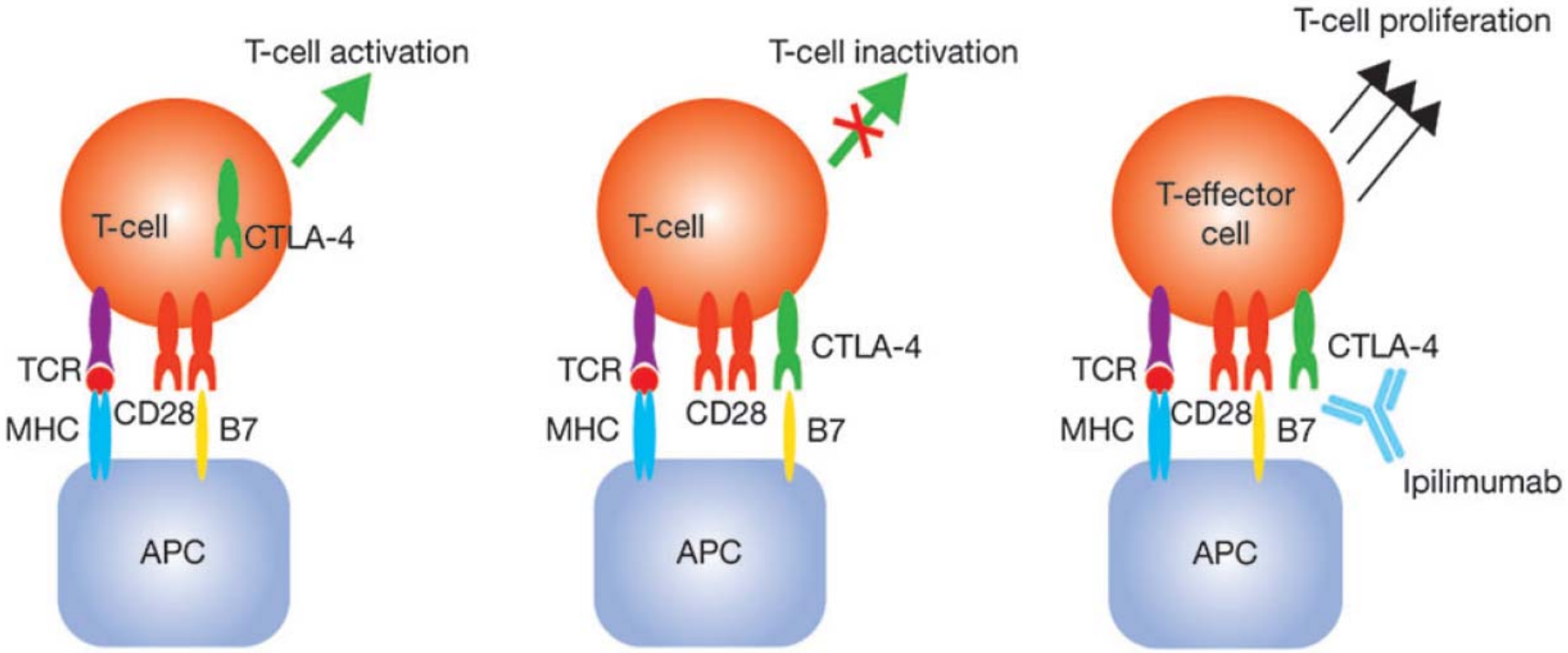
Immune checkpoint inhibitors: timeline of key events

Date	Event	People	Places
1910	Austrian physicians Ernest Freund and Gisa Kaminer observed that something in blood serum from cancer patients pervents the destruction of cancer cells	Freund, Kaminer	Rudolf-Stiftung Hospital
1924	Austrian physicians Ernest Freund and Gisa Kaminer discover a substance in intestines of cancer patients that reduce ability of normal serum to dissolve cancer cells.	Freund, Kaminer	Rudolf-Stiftung Hospital
February 1969	Team led by Karl and Ingegerd Hellstrom observe serum from mice with chemically induced tumours can block reaction of lymphocytes	Hellstrom, Evans, Heppner, Pierce, Yang	Fred Hutchinson Cancer Center
26 Jun 1970	Padmanee Sharma born in Gerogetown, Guyana	Sharma	MD Anderson Cancer Center
June 1971	Hellstom team suggest that antibodies bound to tumour cells mask their detection by the immune system	Sjogren, Hellstrom, Bansal	Fred Hutchinson Cancer Center
July 1987	Identification of the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)	Brunet, Denizot, Luciani, Roux-Dosseto, Suzan, Mattei, Golstein	INSERM-CNRS
December 1988	Scientists report cloning the gene for the human cytotoxic T lymphocyte-associated antigen (CTLA-4)	Dariavach, Mattei, Golstein, Lefranc	INSERM-CNRS
May 1990	Discovery of lymphocyte activation gene 3 (LAG3)	Triebel, Jitsukawa, Baixeras, Roman-Roman, Genevee, Viegas-Pequinot, Hecend	Institut Gustave-Roussy
November 1992	PD-1 (programmed cell death protein 1) discovered by team led by Tasuku Honjo	Honjo	Kyoto University
1 Jan 1995	Two teams, one led by James Alison and the other by Jeffrey Bluestone, independently show CTLA-4 can inhibit the activity of T cells	Allison, Bluestone, Leach, Krummel	University of California Berkeley, University of California San Francisco
22 Mar 1996	Mice experiments published demonstrating that blocking the CTLA-4 molecule on immune cells can cure cancer	Leach, Krummel, Allison	University of California Berkeley
2000	First clinical trials launched to test first immune checkpoint inhibitor drug containing a monoclonal antibody against CTLA-4 (ipilimumab, Yervoy®)	Allison	Medarex, University of California Berkley
October 2000	PD-1 protein shown to be important mechanism in dampening down the immune response	Freeman, Long, Iwai	Dana-Farber Cancer Institute
2002	T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) discovered		
17 Sep 2002	Cancer cells shown to be capable of hijacking PD-1 protein to evade destruction by immune system	Iwai , Ishida, Tanaka, Okazaki, Honjo, Minato	Japan Science and Technology Corporation
May 2005	Medarex and Ono Pharmaceuticals entered research alliance to develop a fully human anti-PD-1 antibody for the treatment of cancer		Medarex, Ono Pharmaceutical
2006	Inducible co-stimulator (ICOS) protein found to enhance anti-CTLA-4 treatment in destruction of cancer cells	Sharma, Liakou, Kamat, Ng Tang, Chen, Sun, Troncoso, Logothetis	MD Anderson Cancer Center
24 Nov 2008	First anti-PD-1 antibody entered phase 1 clinical trial for cancer		Medarex, Ono Pharmaceutical
25 Mar 2011	First immune checkpoint inhibitor drug targeting CTLA4 (ipilimumab, Yervoy®), approved by the FDA	Allison	Medarex, University of California Berkley
September 2014	FDA approved nivolumab (Opdivo®), an immune checkpoint inhibitor targeting PD1, for treating melanoma		
22 Dec 2014	First immune checkpoint inhibitor drug targeting PD-1 (nivolumab, Opdivo®) approved in US	Honko, Freeman, Lonberg	Medarex, Bristol-Myers Squibb, Ono Pharmaceutical

Activation is initiated by binding of B7 molecules on the APC to CD28 receptors on the T-cell

Inhibition results from CTLA-4 expression on the T-cell surface where it competes with CD28 for binding to B7 on APCs

Potentiation of T-cell proliferation achieved by CTLA-4 inhibition using ipilimumab, an anti-CTLA-4 monoclonal antibody



홈 > 제약산업 > 제약바이오

전이성 흑색종 치료제 여보이 국내 승인

@monews.co.kr

올해 기대되는 면역항암제는?...CAR-T 치료제 주목

22일 한국BMS

으로서 세포독성

정맥투여하며

볼루맙, 여보이

력을 체결했다.

및 재배포금지>

전으로, 면역관문억제제와 면역세포치료제, 표적 암살상바이러스치료제 등으로 구분할 수 있다.

• 면역관문억제제 •

면역관문억제제는 크게 CTLA-4(Cytotoxic T Lymphocyte Associated-4), PD-1 억제제, PD-L1 억제제, 면역세포치료제를 포함한다.

CTLA-4는 CD-28과 유사한 구조를 가지고 있는 항원으로 T세포가 활성화 됐을 때 일과성으로 발현되는 T세포 활성 항원의 일종이다. CTLA-4 단클론항체는 CTLA-4 수용체와 결합해 T세포가 무력화되는 것을 막고 T세포의 증식을 증가시키는데, 대표적인 약물은 비엠에스/오노제약의 여보이(이필리무맙)이다. 여보이는 국내 전이성 흑색종 환자에게 PD-1 억제제와 병용요법을 인정 받고 있다.

PD-1 억제제는 15종 이상의 암종에서 치료제로 승인을 받았거나 개발이 한창 진행 중이다. 암세포는 PD-L1 면역회피물질을 가지고 증식하는데 암세포의 PD-L1과 T세포의 PD-1이 결합하면 T세포가 제기능을 상실하고 사멸하게 된다.

대표적인 약물로는 국내에서 허가 받아 급여 중인 키트루다와 옵디보다.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use YERVOY safely and effectively. See full prescribing information for YERVOY.

YERVOY® (ipilimumab) injection, for intravenous use
Initial U.S. Approval: 2011

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS
See full prescribing information for complete boxed warning.

YERVOY can result in severe and fatal immune-mediated adverse reactions. 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.

Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions. (2.3)

Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests, adrenocorticotropic hormone (ACTH) level, and thyroid function tests at baseline and before each dose. (5.1, 5.2, 5.3, 5.4, 5.5)

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.2)	10/2015
Dosage and Administration (2.1, 2.2, 2.3)	10/2015
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7)	10/2015

----------INDICATIONS AND USAGE----------

YERVOY is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody indicated for:

- Treatment of unresectable or metastatic melanoma. (1.1)
- Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy. (1.2)

----------DOSAGE AND ADMINISTRATION----------

- Unresectable or metastatic melanoma:
  - 3 mg/kg administered intravenously over 90 minutes every 3 weeks for a total of 4 doses. (2.1)
- Adjuvant melanoma:
  - 10 mg/kg administered intravenously over 90 minutes every 3 weeks for 4 doses, followed by 10 mg/kg every 12 weeks for up to 3 years or until documented disease recurrence or unacceptable toxicity. (2.2)
- Permanently discontinue for severe adverse reactions. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- Injection: 50 mg/10 mL (5 mg/mL) (3)
- Injection: 200 mg/40 mL (5 mg/mL) (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

Immune-mediated adverse reactions: Permanently discontinue for severe reactions. Withhold dose for moderate immune-mediated adverse reactions until return to baseline, improvement to mild severity, or complete resolution, and patient is receiving less than 7.5 mg prednisone or equivalent per day. Administer systemic high-dose corticosteroids for severe, persistent, or recurring immune-mediated reactions. (5.1, 5.2, 5.3, 5.4, 5.5)

- Immune-mediated hepatitis: Evaluate liver function tests before each dose of YERVOY. (5.2)
- Immune-mediated endocrinopathies: Monitor clinical chemistries, ACTH level, and thyroid function tests prior to each dose. Evaluate at each visit for signs and symptoms of endocrinopathy. Institute hormone replacement therapy as needed. (5.5)
- Embryo-fetal toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.7)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥5%) are fatigue, diarrhea, pruritus, rash, and colitis. Additional common adverse reactions at the 10 mg/kg dose (≥5%) include nausea, vomiting, headache, weight loss, pyrexia, decreased appetite, and insomnia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Discontinue nursing during treatment with YERVOY. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2015

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use YERVOY safely and effectively. See full prescribing information for YERVOY.

YERVOY® (ipilimumab) injection, for intravenous use

----------DOSAGE FORMS AND STRENGTHS----------

- Injection: 50 mg/10 mL (5 mg/mL) and 200 mg/40 mL (5 mg/mL) in a single-use vial. (3)

Cancer Therapy: Clinical

Clinical Cancer Research

Phase I Clinical Trial of Ipilimumab in Pediatric Patients with Advanced Solid Tumors

Melinda S. Merchant[1], Matthew Wright[1], Kristin Baird[1], Leonard H. Wexler[2], Carlos Rodriguez-Galindo[3], Donna Bernstein[1], Cindy Delbrook[1], Maya Lodish[4], Rachel Bishop[5], Jedd D. Wolchok[6,7], Howard Streicher[8], and Crystal L. Mackall[1]

Abstract

Purpose: Ipilimumab is a first-in-class immune checkpoint inhibitor approved for treatment of metastatic melanoma but not studied in children until this phase I protocol.

Experimental Design: This study examined safety, pharmacokinetics, and immunogenicity, and immune correlates of ipilimumab administered to subjects ≤21 years old with recurrent or progressive solid tumors. Dose escalation cohorts received 1, 3, 5, or 10 mg/m^2 intravenously every 3 weeks in a 3 + 3 design. Response was assessed after 6 weeks and 12 weeks, and then every 3 months. Treatment was continued until disease progression or unacceptable toxicity.

Results: Thirty-three patients received 72 doses of ipilimumab. Patients enrolled had melanoma ($n = 12$), sarcoma ($n = 17$), or other refractory solid tumors ($n = 4$). Immune-related adverse events included pancreatitis, pneumonitis, colitis, endocrinopathies, and transaminitis with dose-limiting toxicities observed at 5 and 10 mg/kg dose levels. Pharmacokinetics revealed a half-life of 8 to 15 days. At day 21, subjects had increased levels of cycling T cells, but no change in regulatory T-cell populations. Six subjects had confirmed stable disease for 4 to 10 cycles (melanoma, osteosarcoma, clear cell sarcoma, and synovial sarcoma).

Conclusions: Ipilimumab was safely administered to pediatric patients using management algorithms for immune-related toxicities. The spectrum of immune-related adverse events is similar to those described in adults; however, many of the pediatric toxicities were evident after a single dose. Although no objective tumor regressions were observed with ipilimumab as a single agent, subjects with immune-related toxicities had an increased overall survival compared with those who showed no evidence of breaking tolerance. *Clin Cancer Res; 22(6); 1364–70. ©2015 AACR.*

- Advanced renal cell carcinoma:
  - Nivolumab 3 mg/kg administered intravenously over 30 minutes followed by YERVOY 1 mg/kg administered intravenously over 30 minutes on the same day, every 3 weeks for a maximum of 4 doses, then nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks, administered intravenously over 30 minutes. (2.3)
- Permanently discontinue for severe adverse reactions. (2.4)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Discontinue breastfeeding during treatment with YERVOY. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2018

Ipilimumab

- **Brand name:** Yervoy®
- **IUPAC:** Humanized monoclonal antibody against CTLA-4
- **KEGG:** D04603
- **Formula:** $C_{6742}H_{9972}N_{1732}O_{2004}S_{40}$
- **Molecular weight:** 148 kDa

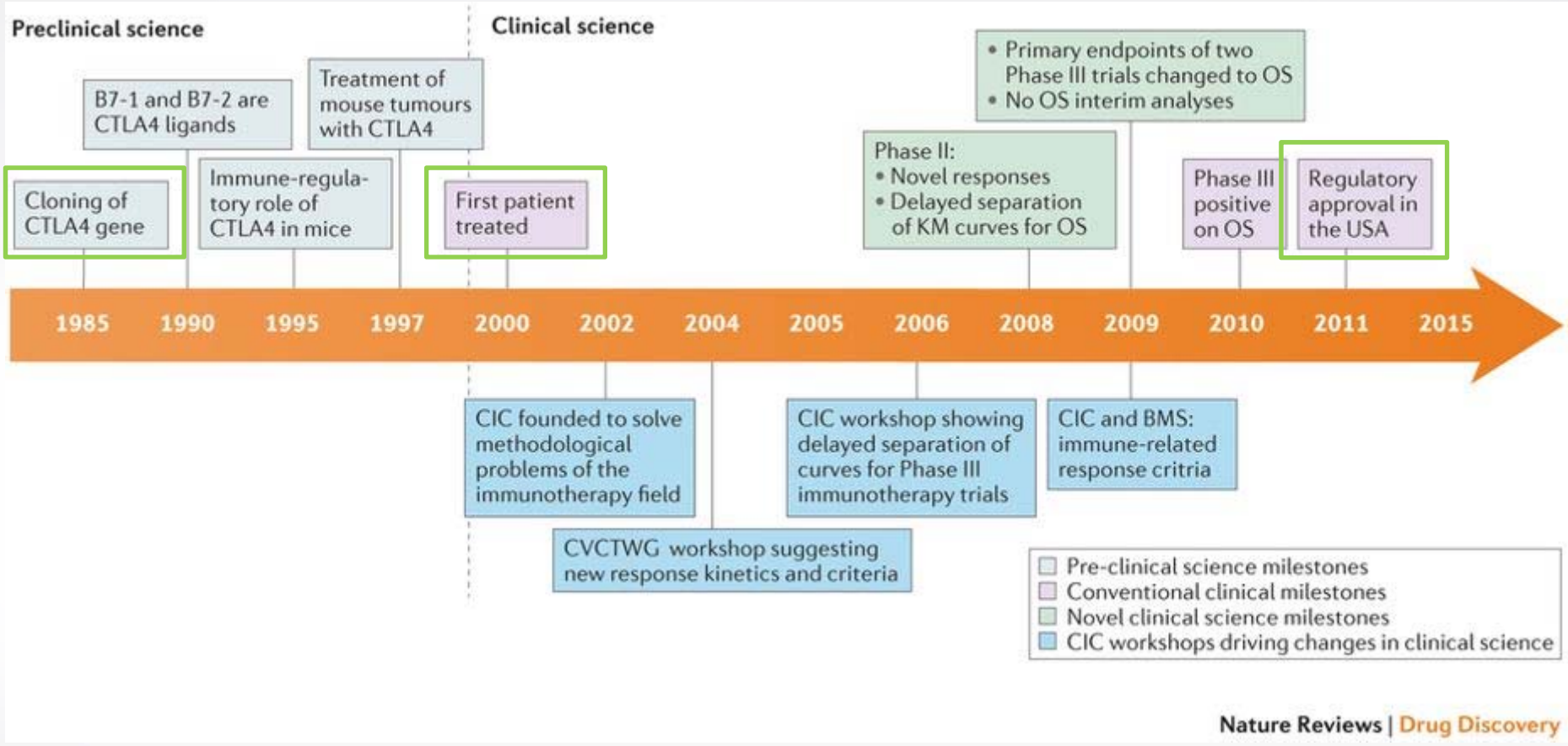
Ipilimumab (Trade name: Yervoy®) Product Profile

- **U.S. Sponsor:** Bristol-Myers Squibb, Inc.

- **Indication:**
  - Treatment of unresectable or metastatic melanoma in adults and pediatric
  - Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.

- **DOSE :** 3 mg/kg IV (metastatic melanoma),
  10 mg/kg IV(Adjuvant melanoma)

- **NDA 125377**


Preclinical science
Clinical science
Cloning of CTLA4 gene
B7-1 and B7-2 are CTLA4 ligands
Immune-regulatory role of CTLA4 in mice
Treatment of mouse tumours with CTLA4
First patient treated
Phase II:
• Novel responses
• Delayed separation of KM curves for OS
• Primary endpoints of two Phase III trials changed to OS
• No OS interim analyses
Phase III positive on OS
Regulatory approval in the USA
1985
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CIC founded to solve methodological problems of the immunotherapy field
CVCTWG workshop suggesting new response kinetics and criteria
CIC workshop showing delayed separation of curves for Phase III immunotherapy trials
CIC and BMS: immune-related response critria
Pre-clinical science milestones
Conventional clinical milestones
Novel clinical science milestones
CIC workshops driving changes in clinical science
Nature Reviews | Drug Discovery

Contents

1. In vitro & In vivo review
2. Preclinical study review
3. Phase Ⅰ,Ⅱ,Ⅲ trial review
4. FDA review
5. Post-approval review

In vitro

- The binding to activated CD4+ T cells was found at its peak at day 3 and declining by day 7.
- Ipilimumab does not have CDC activity in vitro, yet mediates low to moderate ADCC at higher concentrations on activated (but not on resting) T cells, with a stronger binding to FcγR Ⅰ (CD64) than to FcγRⅡ(CD32) or FcγRⅢ(CD16) receptors for the Fc portion of IgG.
- In peripheral blood of patients with melanoma, a mean increase of activated CD8+ (statistically significant) and of CD4+ T cells, together with a mean decrease in naive CD4+ and CD8+ T cells, was observed after treatment with ipilimumab.

In vivo

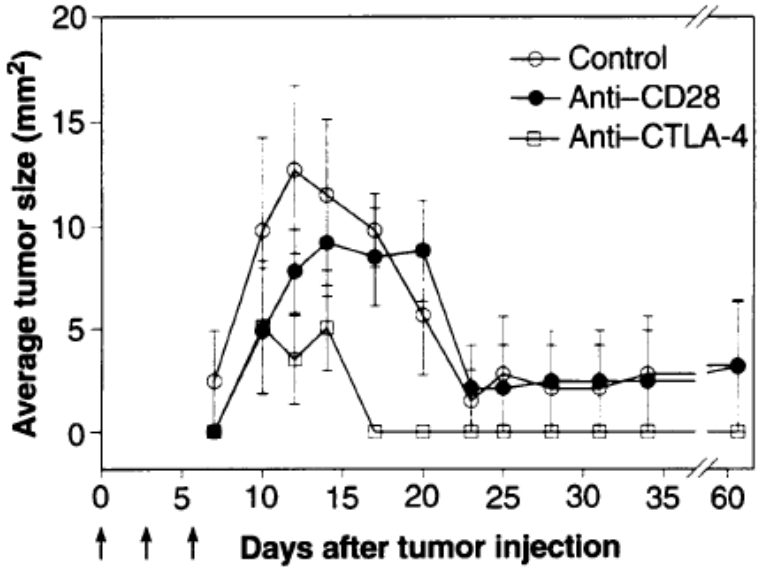


Fig. 1. Treatment with anti–CTLA-4 accelerates rejection of a B7-1–positive colon carcinoma (*23*).

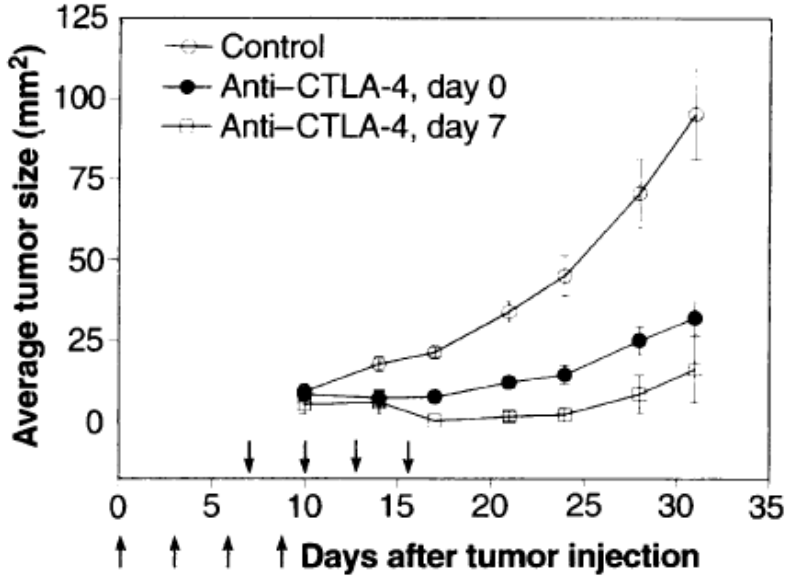
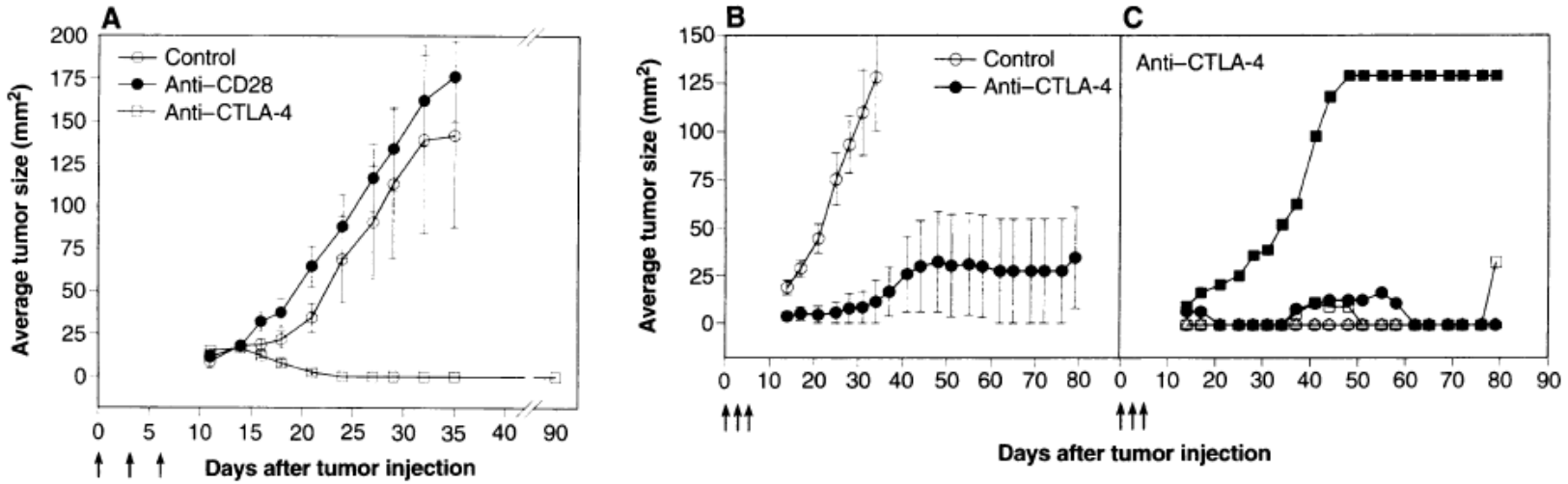


Fig. 3. Treatment with anti–CTLA-4 reduces the growth of established tumor.



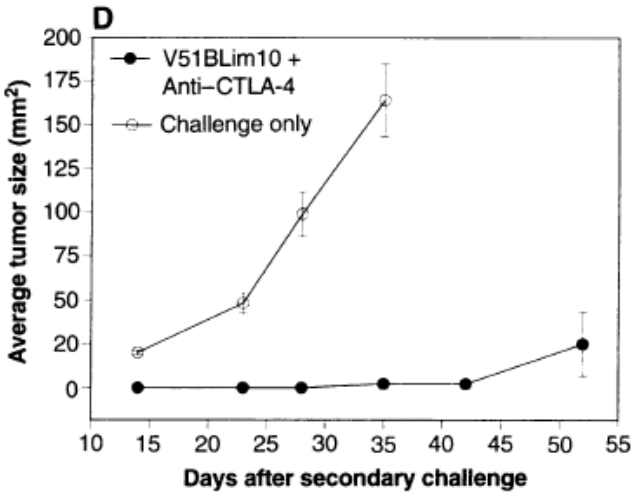


Fig. 2. Treatment with anti–CTLA-4 enhances rejection of B7-negative colon carcinoma cells and results in protection against subsequent challenge with wild-type colon carcinoma cells. Groups of BALB/c mice were injected with B7-negative 51BLim10 vector control cells (V51BLim10), left untreated, or treated with anti–CTLA-4 or control antibody. Mice were euthanized when tumors reached a size of 200 mm^2 or became ulcerated. If individual mice within a group were euthanized, the final measurement was carried over to subsequent time points. (**A**) Average tumor size in mice injected with 4×10^6 tumor cells. Groups of five mice were injected with 4×10^6 V51BLim10 tumor cells. Treated groups were injected three times with 100 μg of anti–CTLA-4 or anti-CD28 as indicated by the arrows. All untreated control and anti-CD28–treated mice were killed by day 35. Mice treated with anti–CTLA-4 remained tumor-free for more than 90 days. Error bars represent standard error of the mean. (**B**) Average tumor size in mice injected with 2×10^6 V51BLim10 tumor cells. Two groups of five mice were injected with tumor cells and treated as above with anti–CTLA-4 or irrelevant hamster antibody. (**C**) Individual tumor growth in mice injected with 2×10^6 V51BLim10 cells and treated with anti–CTLA-4. Three of the mice remained tumor-free beyond 80 days. (**D**) Challenge tumor growth in anti–CTLA-4–treated mice. Five anti–CTLA-4–treated mice that had completely rejected V51BLim10 tumor cells were rechallenged 70 days later with 4×10^6 wild-type tumor cells injected subcutaneously in the opposite flank. Five naïve mice were also injected as controls. All control mice developed progressively growing tumors and were euthanized on day 35 after inoculation. Three of five previously immunized mice remained tumor-free 70 days after rechallenge.

Toxicology

- Single dose toxicity
  - No acute toxicity was noted in monkeys following ipilimumab doses up to 30 mg/kg in the repeat-dose toxicology studies.
  - no adverse toxicities were observed in a single-dose exploratory comparative pharmacokinetics study in monkeys of ipilimumab at 10 mg/kg.
  - Overall, the results did not raise concerns for effects of ipilimumab on safety pharmacology parameters in 1 month, and 6 month study.(clinical signs, nervous system evaluation, body temperature, cardiovascular evaluation, respiratory evaluation, electrocardiogram)

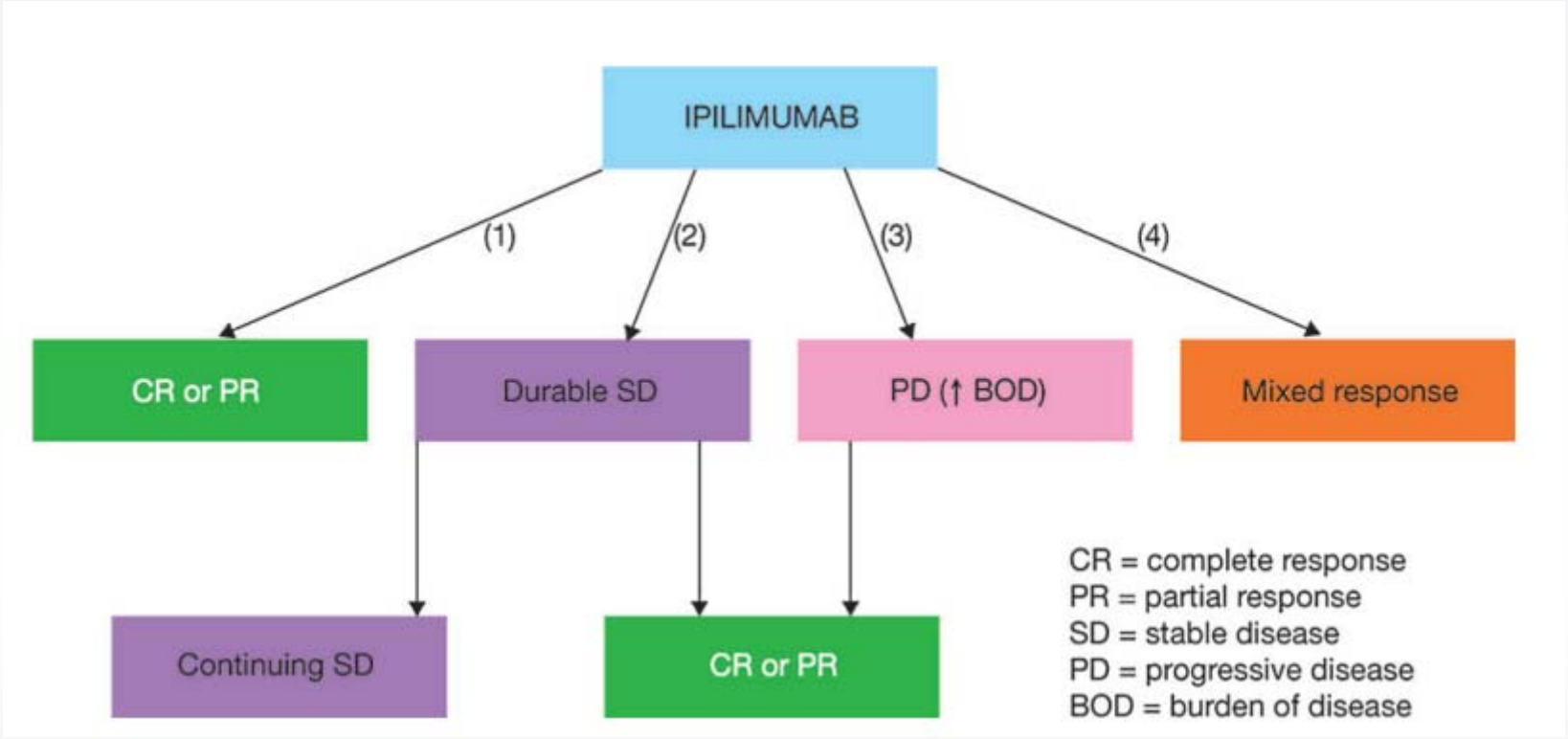
- signs consistent with acute infusion reaction were observed in one monkey, approximately 5 minutes after ipilimumab treatment(difficulty breathing, cyanosis, and muffled heart sounds)

- The animal was re-challenged 5 months later without toxicity

- FIH starting dose: 0.1mg/kg
  - the basis of preclinical pharmacology data suggested a much lower MABEL than NOAEL. (50 μg/ml is lower than the concentrations reached in human plasma after the 3mg/kg dose. (Cmax ~85 μg/ml))

- Repeat dose toxicity

Study ID	Number of monkey	Dose (mg/kg)	Day of dosing	NOEL (mg/kg/day)	Major findings
126-002	2	3	1,4,7	3	
0919-128	4	3,10	1,4,7	10	Small increase CD3+ cells.
7114-100	4	3,30	1,4,7	3	30: > leukocyte, WBC, lymph, neutr, mono,
ds06064	10	10	1,8,15,22	10	
0992-128	4	10	1,29		> 10+ CpG: lymphocyte count
1416-128	12	1,10	1,29,59	10	
1-3460	5	10	0,28,56,84,140		↓ organ weight (testes, thyroid)


IPILIMUMAB
(1)
(2)
(3)
(4)
CR or PR
Durable SD
PD (↑ BOD)
Mixed response
Continuing SD
CR or PR
CR = complete response
PR = partial response
SD = stable disease
PD = progressive disease
BOD = burden of disease

Phase 1 clinical trial

- Pilot studies of ipilimumab were first reported in 2002, with a Phase I study showing two PR in a cohort of 17 patients with unresectable melanoma treated with a single dose of ipilimumab, dosed at 3 mg/kg

- Treatment was well-tolerated, with only a mild rash noted. Subsequent studies focused on establishing appropriate dosing and schedule of the drug.

- A schedule of dosing every 3 weeks was adopted in several early studies, and the first evidence of a unique toxicity profile emerged from these trials.

- Collectively, these toxicities have been described as irAE, with the most common events including dermatitis, colitis, and hepatitis. These toxicities appeared to reflect a pattern of tissue-specific inflammation.

Population	Design/schedule	Conclusion
Untreated advanced melanoma, n = 36	Ipilimumab 0.1-3 mg/kg plus IL-2 720,000 IU/kg	No synergistic effect in combination; antitumor effects of ipilimumab result from T-cell activation
Prostate cancer, colon cancer, and NHL, n = 11	Ipilimumab 3 mg/kg induction then 1.5 mg/kg maintenance monthly for four cycles	Evidence of activity and well tolerated;
Advanced melanoma and ovarian cancer, n = 9	Single dose-3 mg/kg (patients previously vaccinated —GVAX)	No serious toxicities and evidence of increased tumor immunity
Advanced melanoma, n = 11; ovarian cancer, n = 9	Single dose-3 mg/kg (retreatment permitted after 2/3 months)— following GVAX	Ipilimumab following GVAX gives clinically meaningful antitumor immunity without grade 3 or 4 toxicity
Advanced melanoma, n = 14	Ipilimumab 3 mg/kg Q3W plus peptide vaccine	Immune-related AEs and antitumor activity suggests a role for CTLA-4 in breaking tolerance to cancer antigens
CRPC, n = 14 (including pretreated patients)	Single dose-3 mg/kg	Single 3 mg/kg dose is safe; no significant autoimmunity
Untreated CRPC, n = 24	Dose escalation: Ipilimumab 0.5-3 mg/kg plus GM-CSF 250 mg/m^2/day	Evidence of activity and 3 mg/kg associated with frequent expansion of circulating cytotoxic T cells than lower doses
Metastatic CRPC n = 36	GM-CSF 250 mg/m^2/day (days 1–14 of 28-day cycle) + Ipilimumab at escalating doses (0.5–10 mg/kg) on day 1 of each cycle 6	Combined with GM-CSF induced clinical responses in CRPC with the highest response proportion at the 3 mg/kg dose level
Relapsed/refractory B-cell NHL n = 18	Ipilimumab 3 mg/kg, then monthly at 1 mg/kg x 3 (dose level 1), then escalation to 3 mg/kg monthly	Ipilimumab has antitumor activity in patients with B-cell lymphoma

Abbreviation: IL-2, interleukin-2; GVAX, irradiated, autologous tumor cells engineered to secrete granulocyte macrophage colony-stimulating factor; PR, partial response; SD, stable disease; Q3W, every 3 weeks; CR, complete response; AEs, adverse events; CTLA-4, cytotoxic T lymphocyte antigen-4; CRPC, castrate-resistant prostate cancer; PSA, prostate-specific antigen; GM-CSF, granulocyte macrophage colony-stimulating actor; TTP, time to progression; OS, overall survival; SEQ, sequential; Q3M, every 3 months; NHL, non-Hodgkin's lymphoma.

Phase 2 clinical trial

- In a phase 2 trial (MDX010-08) of 72 patients with previously untreated advanced melanoma who were randomized to receive ipilimumab 3 mg/kg with or without DTIC, ipilimumab produced durable objective clinical responses and encouraging overall survival (OS) both alone and in combination.

- Analysis of the long-term survival of patients who received ipilimumab 10 mg/kg during the three key phase 2 trials (CA184-007, CA184-008, and CA184-022) showed OS ranging from 10.2 months in previously treated patients to 22.5 months in patients.

- The 12-month survival rates across these studies ranged from 47.2% to 71.4% for previously treated patients, corresponding 18- month survival rates ranged from 34.5% to 39.4%.

- Long-term survival data for patients treated with ipilimumab in both MDX010-08 and MDX010-15, a phase 1/2 dose-ranging study in which 23 patients were treated with 10 mg/kg ipilimumab every 3 weeks, demonstrated a trend toward better survival with the higher dose (a 2-year survival rate of 36% vs. 22% for 10 vs. 3 mg/kg).

- A dose-response relationship was clearly defined in a double-blind Phase II study comparing ipilimumab at doses of 0.3, 3, and 10 mg/kg every 3 weeks, followed by maintenance doses administered every 12 weeks But the rate of irAE was also higher with increased ipilimumab dose.

Patient population	Design/schedule	Conclusions
MDX10-08 Untreated advanced melanoma, n = 72	Ipilimumab (3 mg/kg/month for 4 months) with or without DTIC (250 mg/m^2 for 5 days monthly for 4 months)	Ipilimumab resulted in clinically meaningful responses in advanced melanoma in combo. With DTIC. Combination was well tolerated; AEs were medically manageable
CA184-022 pretreated advanced melanoma, n = 217	0.3, 3, or 10 mg/kg Q3W for four doses then maintenance (Q12W)	Ipilimumab had a dose-dependent effect on efficacy and safety, supporting further studies at a dose of 10 mg/kg
CA184-008 pretreated advanced melanoma, n = 155	10 mg/kg ipilimumab Q3W for four doses then maintenance (Q12W)	Ipilimumab has clinical activity with encouraging long-term survival
CA184-007 pretreated and treatment-naive advanced melanoma	10 mg/kg Q3W for four doses and randomized to receive prophylactic budesonide (arm A; n = 58) or placebo (arm B; n = 57)	Ipilimumab has activity with encouraging survival and manageable AEs
CA184-042 melanoma with brain metastases, steroid-free (n = 51; arm A) or requiring steroids (n = 21; arm B)	10 mg/kg Q3W for four doses; responding or stable patients could receive maintenance 10 mg/kg Q12W	Ipilimumab had similar activity in brain and non-CNS lesions
CA184-041 chemo-naive recurrent/ metastatic NSCLC	Randomized, double-blind study of first-line ipilimumab (10 mg/ kg Q3W) + CON P/C (175 mg/m^2 AUC = 6 Q3W, (n = 70); or SEQ P/C (n = 68), or PBO, (n = 66); after P/C, ipilimumab maintenance therapy Q12W until toxicity or PD	Ipilimumab addition to P/C in a SEQ regimen extended PFS and irPFS in NSCLC patients compared with P/C alone

Abbreviation: DTIC, dacarbazine; DCR, disease control rate (CR + PR + SD/n); Q12W, every 12 weeks; BORR, best objective response rate; CNS, central nervous system; PFS, progression-free survival; NSCLC, nonsmall cell lung cancer; CON, consecutive; PBO, paclitaxel/carboplatin only; irPFS, immune-related progression-free survival; P/C, paclitaxel/carboplatin; PD, progressive disease.

Table 1. Summary of Completed Clinical Studies with Ipilimumab to Support the BLA Application

Study Number	Primary Study Objective	Study Type	No. of Treated Subjects	Treatment Regimen
Phase II				
MDX101-08	Determine the safety and activity profile of multiple doses and determine whether the addition of cyotoxic chemotherapy would augment the effects of ipilimumab	Efficacy/Safety/PK (randomized, open-label, multicenter)	74	Ipi 3 mg/kg Q4Wx4 doses with or without dacarbazine
MDX010-15	Assess the safety and PK of single and multiple doses of ipilimumab derived from a transfectoma or a hybridoma cell line	Safety/PK (open-label, multicenter)	88	Ipi 2.8, 3.0, or 5.0 mg/kg Q8Wx3 Ipi 7.5, 10.0, 15.0, or 10.0 mg/kg single dose Ipi 10.0 mg/kg Q3Wx4
MDX010-28	Collect disease status and OS information for subjects who were alive at the time they completed participation in study MDX010-02, MDX010-08, or MDX010-15	Outcome (multicenter, follow-up)	181	No investigational treatments were administered in this study
CA184004	Correlate pretreatment characteristics of patient and/or tumor w/ clinical tumor response to identify candidate markers predictive of response and/or serious toxicity	Efficacy/Safety/PK (exploratory, randomized, double-blind)	82	Induct: Ipi 3 or 10mg/kg IV Q3Wx4 doses *Main: Ipi 3 or 10mg/kg IV Q12W
CA184007	Estimate rate of Grade ≥ 2 diarrhea when given with either prophylactic oral budesonide or placebo	Efficacy/Safety/PK (randomized, double-blind, placebo-controlled, multicenter)	115	Induct: Ipi 10mg/kg IV Q3Wx4 doses; budesonide 9 mg QD until Wk12; 6 mg QD until Wk14; 3 mg QD until WK 16 *Main: ipi 10mg/kg IV Q12W
CA184008	Evaluate the best overall response rate ad defined by the modified WHO criteria	Efficacy/Safety/PK (open-label, single arm, multicenter)	155	Induct: Ipi 10mg/kg IV Q3Wx4 doses *Main: Ipi 10mg/kg IV Q12W
CA184022	Estimate the best overall response rate ad defined by the modified WHO criteria	Efficacy/Safety/PK (randomized, double-blind, multicenter)	214	Induct: Ipi 0.3, 3, or 10 mg/kg IV Q3Wx4doses *Main: Ipi 0.3, 3, or 10 mg/kg IV Q12W

Phase 3 clinical trial

- MDX010-20
  - A Randomized, Double-blind, Multicenter Study, MDX-010 in Combination with a Melanoma Peptide Vaccine, and Melanoma, Vaccine Monotherapy
  - began in 2003 with ipilimumab treatment at 3 mg/kg based on evidence of safety and activity in early clinical trials.
  - Primary outcome was Overall Survival (OS) (Time-to-Death) Difference Between MDX-010 in Combination With gp100 VS gp100
  - Previously treated patients who received ipilimumab, with or without gp100 as an active control, had significantly improved OS compared with those who received gp100 alone

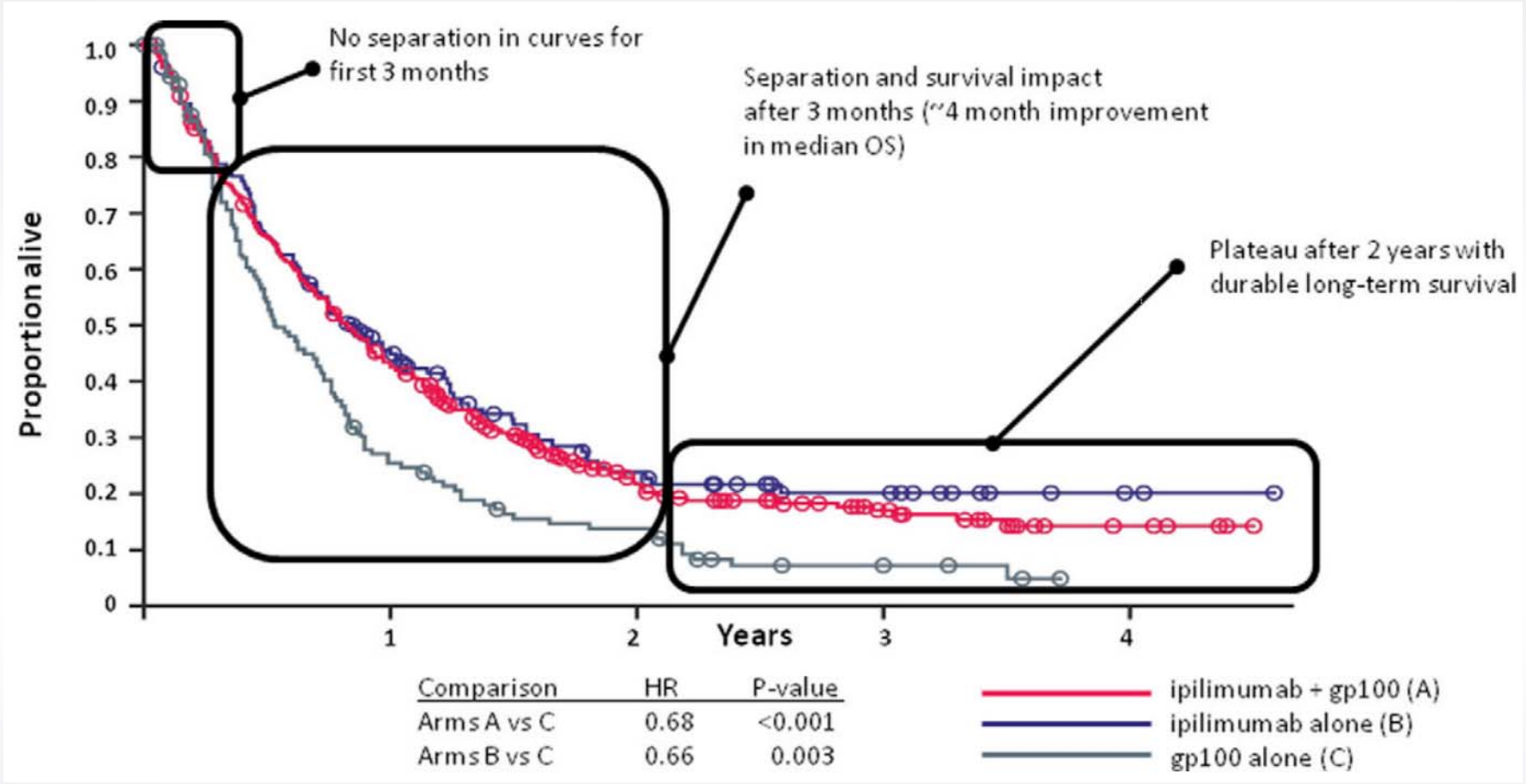
Arm 1: ipilimumab + gp100: ipilimumab (3mg/kg every 3 weeks up to 4 doses) in combination with gp100 (1 mg peptide A and 1 mg peptide B every 3 weeks up to 4 doses);

Arm 2: ipilimumab monotherapy: ipilimumab (3mg/kg every 3 weeks up to 4 doses) plus gp100 placebo every 3 weeks for 4 doses;

Arm 3: gp100 monotherapy: ipilimumab placebo (every 3 weeks up to 4 doses) arm plus gp100 (1 mg peptide A and 1 mg peptide B every 3 weeks up to 4 doses).

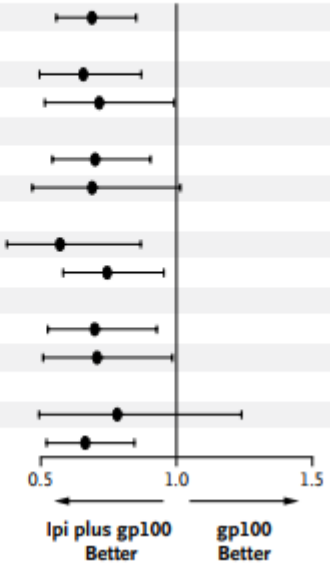
- 6 protocol amendments: (Study design was adapted to 1 stage for subject enrollment instead of 2 stages, Laboratory results were to be reviewed prior to study drug infusion, The primary endpoint was changed from best overall response rate (BORR) to overall survival (OS).)

- A near doubling of 1- and 2-year survival rates with ipilimumab compared to gp100 was observed


No separation in curves for first 3 months
Separation and survival impact after 3 months (~4 month improvement in median OS)
Plateau after 2 years with durable long-term survival
Proportion alive
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1
2
3
4
Years
Comparison HR P-value
Arms A vs C 0.68 <0.001
Arms B vs C 0.66 0.003
ipilimumab + gp100 (A)
ipilimumab alone (B)
gp100 alone (C)

A

Subgroup	Ipi plus gp100	gp100	Hazard Ratio (95% CI)
	no. of deaths/no. randomized		
All patients	306/403	119/136	0.69 (0.56–0.85)
Sex			
Male	191/247	66/73	0.66 (0.50–0.87)
Female	115/156	53/63	0.72 (0.52–0.99)
Age			
<65 yr	219/291	81/94	0.70 (0.54–0.90)
≥65 yr	87/112	38/42	0.69 (0.47–1.01)
M stage at study entry			
M0, M1a, M1b	78/118	31/38	0.57 (0.38–0.87)
M1c	228/285	88/98	0.74 (0.58–0.95)
Baseline LDH			
≤ULN	178/252	66/81	0.70 (0.53–0.93)
>ULN	127/149	50/52	0.71 (0.51–0.98)
Prior use of interleukin-2			
Yes	68/89	25/33	0.78 (0.49–1.24)
No	238/314	94/103	0.66 (0.52–0.84)



B

Subgroup	Ipi	gp100	Hazard Ratio (95% CI)
	no. of deaths/no. randomized		
All patients	100/137	119/136	0.64 (0.49–0.84)
Sex			
Male	53/81	66/73	0.54 (0.37–0.77)
Female	47/56	53/63	0.81 (0.55–1.20)
Age			
<65 yr	69/95	81/94	0.65 (0.47–0.90)
≥65 yr	31/42	38/42	0.61 (0.38–0.99)
M stage at study entry			
M0, M1a, M1b	21/37	31/38	0.47 (0.27–0.82)
M1c	79/100	88/98	0.72 (0.53–0.97)
Baseline LDH			
≤ULN	52/84	66/81	0.56 (0.39–0.81)
>ULN	48/53	50/52	0.76 (0.51–1.13)
Prior use of interleukin-2			
Yes	19/32	25/33	0.50 (0.28–0.91)
No	81/105	94/103	0.69 (0.51–0.93)

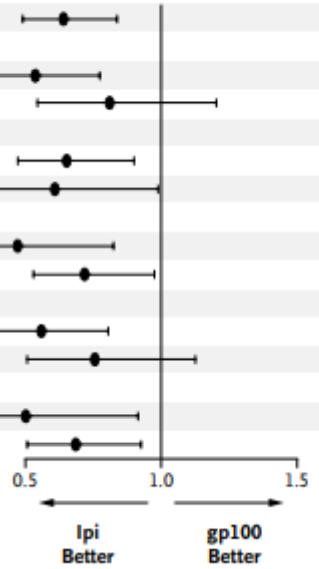
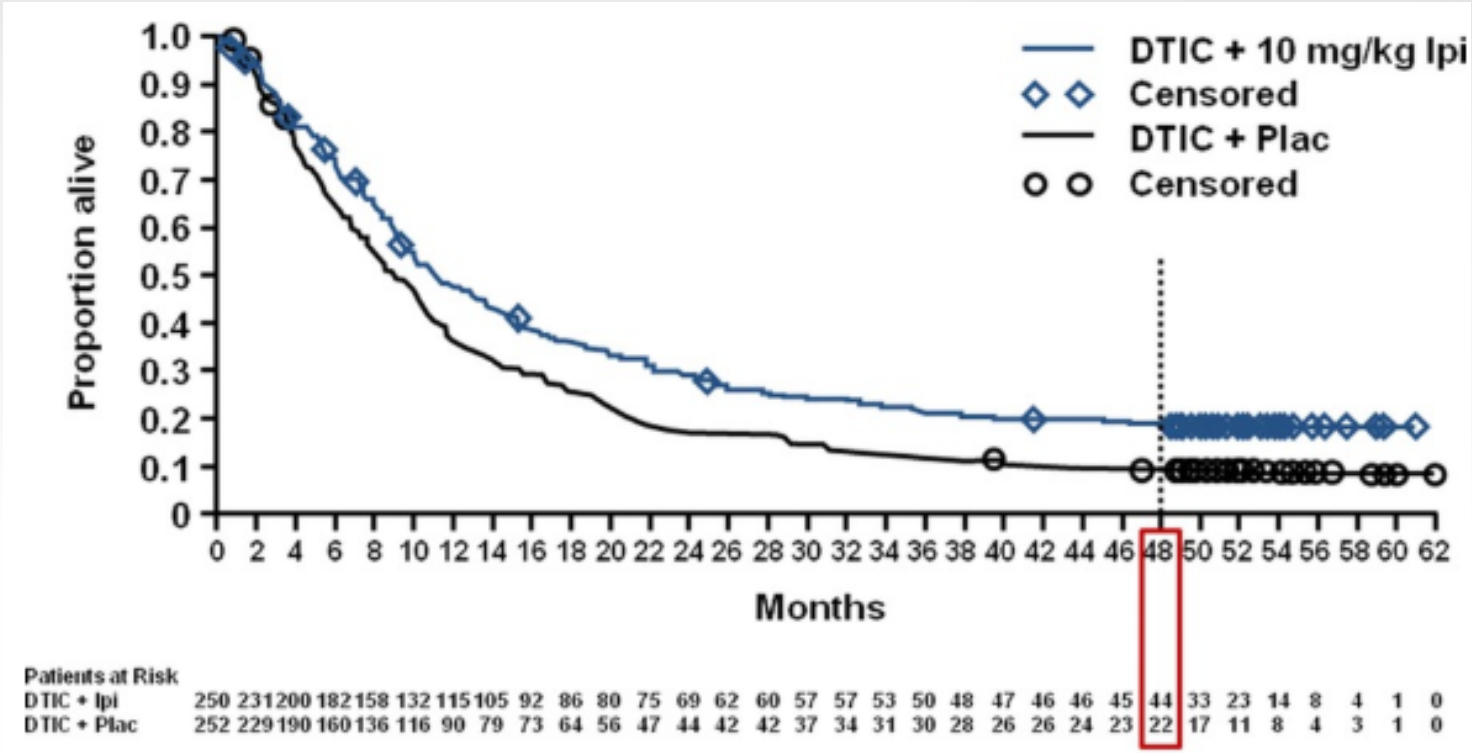


Table 2. Best Response to Treatment and Time-to-Event Data.*

Response and Time to Event	Ipilimumab plus gp100 (N=403)	Ipilimumab Alone (N=137)	gp100 Alone (N=136)
Overall survival			
Total no. of deaths	306	100	119
Comparison with gp100 alone			
Hazard ratio (95% CI)	0.68 (0.55–0.85)	0.66 (0.51–0.87)	—
P value by log-rank test	<0.001	0.003	—
Comparison with ipilimumab alone			
Hazard ratio (95% CI)	1.04 (0.83–1.30)	—	—
P value by log-rank test	0.76	—	—
Evaluation of therapy			
Induction			
Best overall response — no. (%)			
Complete response	1 (0.2)	2 (1.5)	0
Partial response	22 (5.5)	13 (9.5)	2 (1.5)
Stable disease	58 (14.4)	24 (17.5)	13 (9.6)
Progressive disease	239 (59.3)	70 (51.1)	89 (65.4)
Not evaluated	83 (20.6)	28 (20.4)	32 (23.5)
Best overall response rate — % (95% CI)	5.7 (3.7–8.4)	10.9 (6.3–17.4)	1.5 (0.2–5.2)
P value for comparison with gp100 alone	0.04	0.001	—
P value for comparison with ipilimumab alone	0.04	—	—
Disease control rate — % (95% CI)†	20.1 (16.3–24.3)	28.5 (21.1–36.8)	11.0 (6.3–17.5)
P value for comparison with gp100 alone	0.02	<0.001	—
P value for comparison with ipilimumab alone	0.04	—	—
Time to event — mo			
Time to progression — median (95% CI)	2.76 (2.73–2.79)	2.86 (2.76–3.02)	2.76 (2.73–2.83)
Time to response — mean (95% CI)	3.32 (2.91–3.74)	3.18 (2.75–3.60)	2.74 (2.12–3.37)
Duration of response — median (95% CI)	11.5 (5.4–NR)	NR (28.1–NR)	NR (2.0–NR)
Reinduction‡			
Best overall response — no./total no. (%)			
Complete response	0	1/8 (12.5)	0
Partial response	3/23 (13.0)	2/8 (25.0)	0
Stable disease	12/23 (52.2)	3/8 (37.5)	0
Progressive disease	8/23 (34.8)	2/8 (25.0)	1/1 (100.0)

- CA184-024
  - A Multi-center, Randomized, Double-Blind, Two-Arm, Phase III Study in Patients With Untreated Stage III (Unresectable) or IV Melanoma Receiving Dacarbazine Plus 10 mg/kg Ipilimumab (MDX-010) vs. Dacarbazine With Placebo.
  - Primary outcome: overall survival rate.
  - Patients were randomly assigned 1:1 to receive either ipilimumab (10 mg/kg) plus DTIC (850 mg/m^2) or DTIC plus placebo (control arm)
  - ipilimumab can also significantly improve survival when used in treatment-naive patients with advanced melanoma.
  - The OS was significantly longer in the ipilimumab plus DTIC group than in the DTIC plus placebo group and there was a 24% reduction in the risk of disease progression with the addition of ipilimumab to DTIC.



	Ipilimumab + DTIC N=250	Placebo + DTIC N=252
1-year OS rate, %	47.5	36.4
2-year OS rate, %	28.8	17.8
3-year OS rate, %	21.2	12.1
4-year OS rate, %	19.0	9.6
Median OS, months	11.2	9.1

Medical Review

- **irAE : Immune-related Adverse Reactions**

MDX010-20: ≥ Grade 3 Immune Mediated Adverse Reactions (induction phase)

	Ipilimumab (n=131)	Ipilumumab +gp100 (n=380)
Any Immune-mediated Adverse Reaction	15%	12%
Enterocolitis[a,b]	7%	7%
Hepatitis or hepatic failure[a]	1%	2%
Dermatitis[a]	2%	3%
Neuropathy[a]	1%	<1%
Endocrinopathies	4%	1%
Hypopituitarism	4%	1%
Adrenal insufficiency	0	1%
Other		
Pneumonitis	0	<1%
Meningitis	0	<1%
Nephritis	1%	0
Eosinophilia[c]	1%	0
Pericarditis[c]	0	<1%

[a] Including fatal outcome.

[b] Including intestinal perforation.

[c] Underlying etiology not established.

- Immune-mediated enterocolitis
  - Across all YERVOY-treated patients (n=511), 5 (1 %) patients developed intestinal perforation, 4 (0.8%) patients died as a result of complications, and 26 (5%) were hospitalized for severe enterocolitis.

- Immune-mediated Hepatitis
  - subjects, liver function tests continued to rise despite introduction of corticosteroids.

- Immune-mediated Dermatitis:
  - Severe, life-threatening or fatal immune-mediated dermatitis occurred in 13 (2.5%) YERVOY-treated patients in clinical trial MDX010-20.

- Immune-mediated neuropathies, Immune-mediated Endocrinopathies.

Phase 2 studies: Ipilimumab related deaths

Subject ID	Ipilimumab dose	Age/gender	Study day of death	Principle Toxicity
CA184004-18-4045	Ipilimumab 3 mg/kg	67/M	59	Intestinal perforation
CA184004-7-4002	Ipilimumab 10mg/kg	58/F	91	Colitis with perforation
CA184008-50-8076	Ipilimumab 10mg/kg	53/M	489	Acute Glomerulonephritis
CA184008-60-8011	Ipilimumab 10mg/kg	70/F	115	Hypovolemic shock, history of hypopituitarism
CA184008-66-8072	Ipilimumab 10mg/kg	67/F	87	Hepatic failure (hx of liver mets confounding)
CA184042-4-3	Ipilimumab 10mg/kg	66/M	44	Intestinal perforation with sepsis

MDX010-20: Potential Ipilimumab Related Deaths

Subject ID	Treatment group	Age/gender	Study day of death	Principle Toxicity
M20-001-0468	Ipilimumab + gp100	70/M	108	Colitis
M20-291-0506	Ipilimumab + gp100	58/F	91	Colitis with perforation
M20-360-0339	Ipilimumab + gp100	53/M	489	MDS with myelofibrosis[1]
M20-384-0636	Ipilimumab + gp100	59/M	25	Intestinal perforation
M20-400-0119	Ipilimumab + gp100	42/M	18	Toxic Epidermal Necrolysis
M20-426-1133	Ipilimumab + gp100	69/M	66	Peritonitis[2]
M20-442-1092	Ipilimumab + gp100	62/M	102	Guillain-Barre Syndrome
M20-007-0059	Ipilimumab	62/M	25	Liver failure
M20-393-0903	Ipilimumab	77/F	193	Colon perforation
M20-433-1045	Ipilimumab	55M	20	vascular leak syndrome[3]

[1] Subject had received multiple cycles of chemotherapy in the past

[2] Subject had peritoneal carcinomatosis in addition to ulcerating colitis in the sigmoid colon

[3] Many confounding factors; patient had edema, weight gain prior to study entry, had history of hemochromatosis, and was thought to have disease progression at the time of death.

Common Adverse Reactions during induction phase:

	Percentage (%) of Patients					
	YERVOY 3 mg/kg n=131		YERVOY 3 mg/kg+gp100[a] n=380		gp100[a] n=132	
System Organ Class Preferred Term	Any Grade	Grade 3/5	Any Grade	Grade 3/5	Any Grade	Grade 3/4
Gastrointestinal Disorders						
Diarrhea	32	5	37	4	20	1
Colitis	8	5	5	3	2	0
Skin and Subcutaneous Tissue Disorder						
Pruritus[a]	31	0	21	0.3	11	0
Rash[a]	29	1	25	2	8	0
General Disorders and Administration Site Conditions						
Fatigue	41	7	34	5	31	3

a: included appropriate combining/remapping of the preferred terms by the applicant

CA184022: Investor Assessed Immune Mediated Adverse Reactions

Category of Grade 3/4 immune related event	0.3 mg/kg N=72	3 mg/kg N=71	10 mg/kg N=71
overall	0	5 (7%)	18 (25%)
GI	0	2 (3%)	11 (16%)[2]
Liver	0	0	2 (3%)
Endocrine	0	2 (3%)	1 (1%)
Skin	0	1 (1%)	3 (4%)
Other	0	0	1* (1%)

* other included pneumonitis

- Ipilimumab treatment was associated with immune-related adverse events (irAEs) including skin and subcutaneous tissue, gastrointestinal, endocrine, and hepatobiliary disorders. An increase in irAEs was seen with increasing exposure. Pharmacogenomic analyses showed that a missense mutation in CD86 (rs2681417) was associated with increased risk of immune-related gastrointestinal adverse events in the Phase II trials.

- Other associations between immune-related gene variants and skin, hepatobiliary, and gastrointestinal events were also seen.

- However, methodological limitations precluded definitive conclusions regarding the strength of the associations.

REMS

- **Risk Evaluation and Mitigation Strategies**
  - A drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.
  - REMS are designed to reinforce medication use behaviors and actions that support the safe use of that medication.
- Total 4 meetings(2010-12-13, 2011-02-15, 2011-03-23, 2011-03-24)
- Addition of the safety related labeling

- Considerations

A. The estimated size of the population likely to use the drug involved
B. The seriousness of the disease or condition that is to be treated with the drug
C. The expected benefit of the drug with respect to such disease or condition
D. The expected or actual duration of treatment with the drug,
E. The seriousness of any known or potential events that may be related to the drug
F. Whether the drug is a new molecular entity

- **Immunogenecity:**

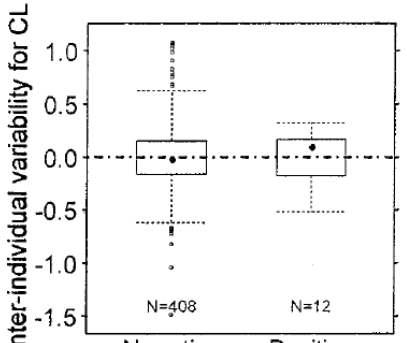
  - Approximately 1.1 % of the patients treated with ipilimumab were positive for binding anti-ipilimumab antibodies, none had neutralizing activity.

  - However, the presence of ipilimumab in patient Samples interfered with the detection of antiipilimumab antibodies. Thus, a more sensitive assay for anti-ipilimumab antibody detection and evaluation of response is requested to accurately assess the incidence of immunogenicity.

Immunogenicity Summary by Ipilimumab Dose[1]

Treatment	Positive at any Timepoint	Positive Post-Baseline[2]	
	No. positive/ No. evaluated (%)	No. positive/ No. evaluated (%)	90% CI
0.3 mg/kg	6/71 (8.5%)	4/58 (6.9%)	(2.4%, 15.1%)
3.0 mg/kg	8/109 (7.3%)	3/102 (2.9%)	(0.8%, 7.4%)
10 mg/kg	12/380 (3.2%)	4/353 (1.1%)	(0.4%, 2.6%)
Total	26/560 (4.6%)	11/513 (2.1%)	(1.2%, 3.5%)

[1]Includes anti-ipilimumab, anti-Ig, or both types of antibodies confirmed by an immunodepletion assay
[2]Denominator includes patients with both a baseline and a post-baseline measurement



- **Pharmacokinetics**

  - From 84 patients enrolled into 3 clinical trials and sparse PK data is available from 499 patients across 4 clinical trials.

  - elimination half life:

    $t_{1/2}$ = 203 ± 63 hours (following a single 10 mg/kg IV)

    $t_{1/2}$ = 339 ± 112 hours (9 weeks after the final dose)

  - Steady-state volume of distribution (Vss) was variable, but indicates that ipilimumab was confined to the plasma space (approximately 40 to 70 ml/kg)

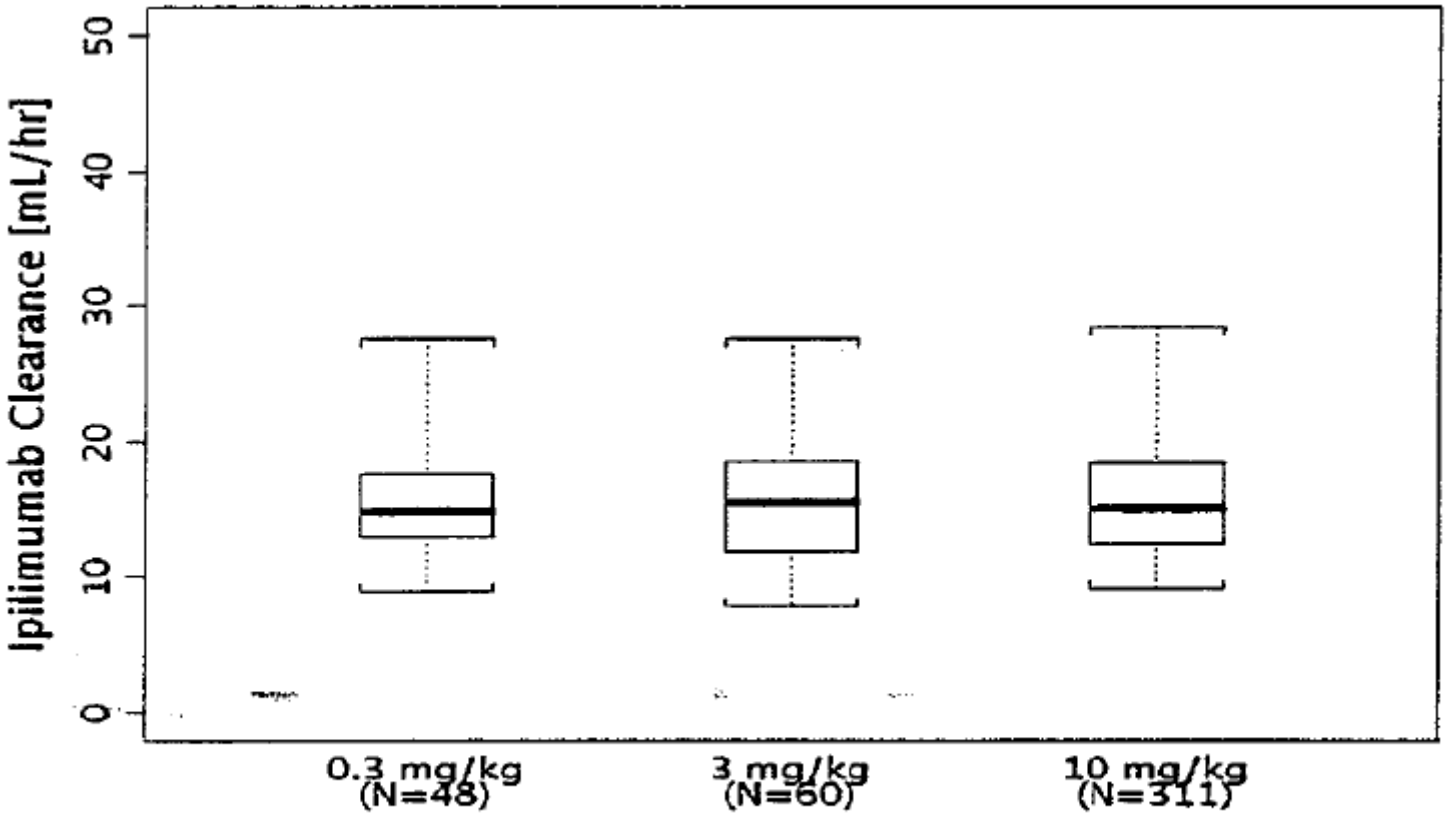
    V_{ss} = 44 ± 6 ml/kg

    V_{ss} = 81 ± 14 ml/kg

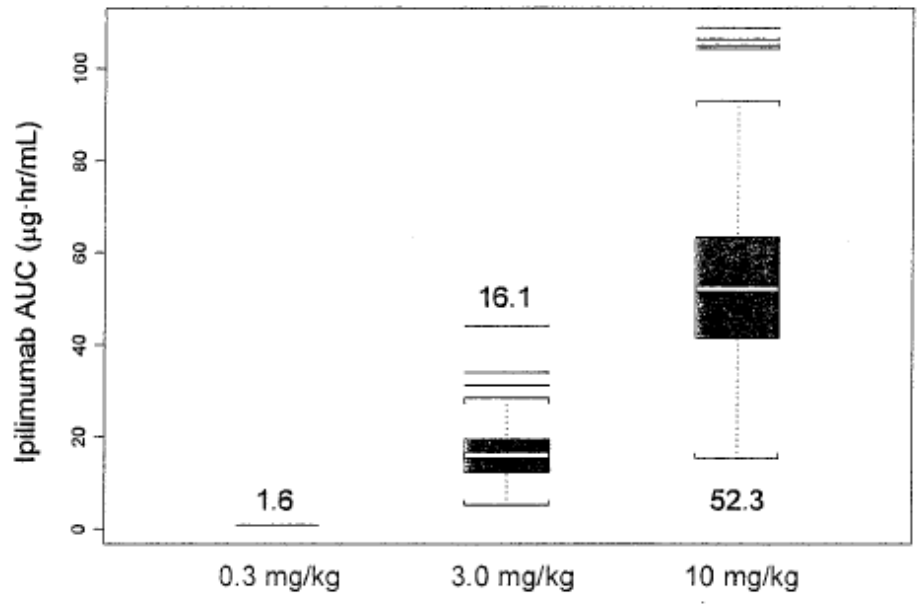
- Ipilimumab exhibited linear PK over a dose range of 0.3 to 10 mg/kg with a mean elimination half-life of 15 days. The inter-individual variability for clearance was approximately 35%

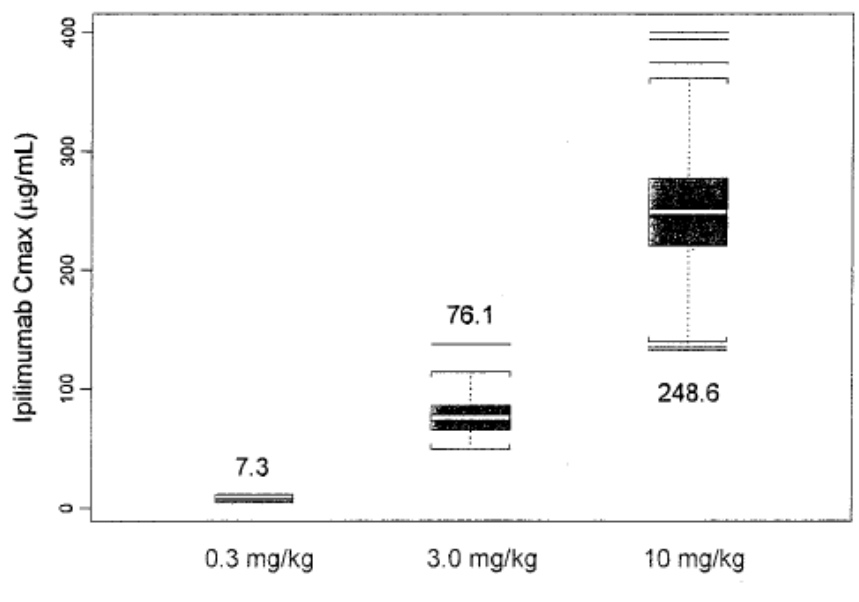
- Accumulation was observed with frequent dosing.

- Population PK analyses were performed for the sparse PK data from 499 patients in trials CA184004, CA184007, CA184008, and CAI 84022. No studies were performed in healthy volunteers.



Box plots of individual ipilimumab clearance by dose (mg/kg) (CA184007, CA184008, CA184022)[a]





Box plots of individual ipilimumab AUC and C_{max} by dose (mg/kg)

- **Review of Efficacy**

  - The demonstration of efficacy of ipilimumab is primarily based on improvement in overall survival observed in Study MDX010-20.

  - Having reviewed the top line survival results from that study, this reviewer is comfortable with the validity of the results of the Study MDX010-20 contained in this application.

  - Since there is no first-line treatment for advanced melanoma that has been shown to improve survival, the approved indication for ipilimumab will be all subjects with advanced melanoma.

- Efficacy: A single registration trial(MDX010-20)

Efficacy and safety of ipilimumab in metastatic melanoma patients surviving more than 2 years following treatment in a phase III trial (MDX010-20)

D. McDermott[1*], J. Haanen[2], T.-T. Chen[3], P. Lorigan[4] & S. O'Day[5] for the MDX010-20 investigators

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Received 23 January 2013; revised 21 June 2013; accepted 28 June 2013

Background: In a phase III trial (ClinicalTrials.gov registration ID: NCT00094653), ipilimumab significantly improved survival versus a vaccine control in pretreated patients with metastatic melanoma. Here, we characterize outcomes of those patients who survived ≥2 years.

Methods: Patients were randomized (3 : 1 : 1) to receive ipilimumab 3 mg/kg + gp100 vaccine, ipilimumab 3 mg/kg + placebo, or gp100 vaccine alone. Baseline demographic data, duration of survival, responses, and safety among patients with ≥2 years' survival were analyzed.

Results: Among 676 randomized patients, 474 and 259 patients had at least 2 or 3 years of potential follow-up, respectively, and were eligible for analysis. Among these, 94 (20%) and 42 (16%) survived ≥2 and ≥3 years, respectively. Survival rates at 2 and 3 years were 25% (24 of 95) and 25% (13 of 53) with ipilimumab alone and 19% (54 of 284) and 15% (24 of 156) with ipilimumab plus gp100. Safety among patients with ≥2 years' survival was comparable with the overall study population, with the onset of new ipilimumab-related toxic effect (all grades) reported in 6 of 78 (8%) patients.

Conclusions: Ipilimumab results in survival of ≥2 years in one-fifth of pretreated patients with 2 years potential follow-up in a phase III trial. New onset, low-grade events starting after administration of the last dose were infrequent.

- The modified primary efficacy endpoint was overall survival (OS).
- The primary analysis was a stratified log-rank test to compare OS between the ipilimumab+gpl 100 arm and the gpl100 arm.
- The secondary analyses were to compare OS between the ipilimumab+gpl100 arm and the ipilimumab monotherapy arm, and between the ipilimumab monotherapy and the gp100 arm.

Primary Comparison of Overall Survival

Overall Survival	Ipilimumab + gp100 N=403	Gp100 N=136
Number of deaths (%)	306 (75.9%)	119 (87.5%)
Median (95% CI)	10.0 (8.5, 11.5)	6.4 (5.5, 8.7)
Hazard ratio (95% CI)	0.68 (0.55, 0.85)	
p-value	0.0004	

- Exposure response
  - An exploratory exposure-response (E-R) rεlationship for OS in patients with unresectable stage III or IV melanoma based on the results from phase II studies has been performed.
  - These studies utilized doses of 0.3, 3 and 10 mg/kg.
  - A time-to-event analysis for OS was performed with patients stratified into four groups according to their C_{min} (0.61-19.4, 19.5-43.7, 44-65.3, >65.3-155.3 μg/ml)

Median Survival for Patients in Different C_{min} Groups in Phase II and III Trials

Group	Median Survival (months)	95% CI
Cmin Q1 (N=125)	6.51	5.19 – 8.67
Cmin Q2(N=124)	9.26	6.87 – 12.0
Cmin Q3 (N=124)	14.0	9.56 – 22.1
Cmin Q4 (N=125)	24.3	18.7 – NA
gp100 (N=136) *	6.44	5.49 – 8.71
Ipilimumab (3 mg/kg) (N=137) *	10.1	8.02 –13.8

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125377/0

BLA APPROVAL
March 25, 2011

Bristol-Myers Squibb Company
Attention: A. Heather Knight-Trent, PharmD
Director-Oncology
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Knight-Trent:

Please refer to your Biologics License Application (BLA) dated June 25, 2010, received June 25, 2010, submitted under section 351 of the Public Health Service Act for YERVOY (ipilimumab).

We acknowledge receipt of all subsequent amendments received through March 24, 2011.

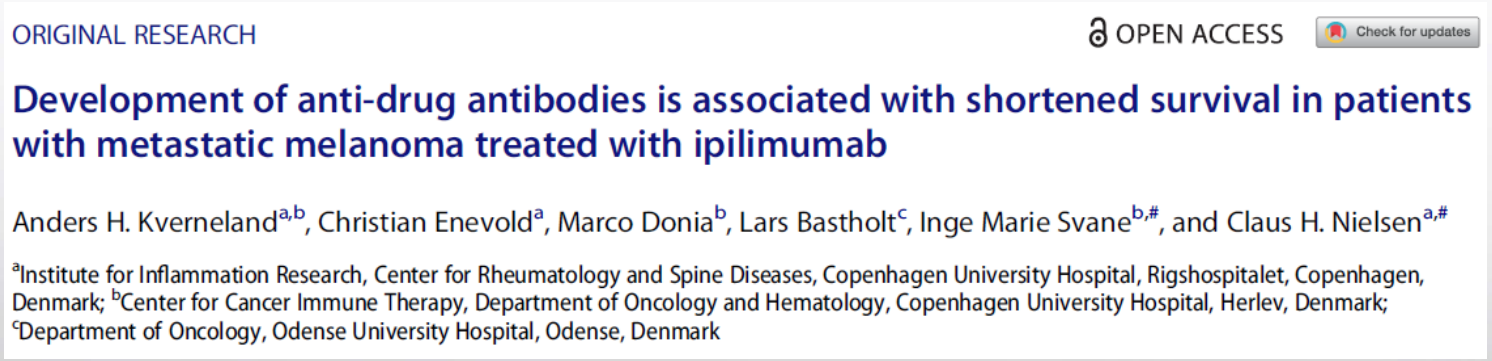
We have approved your BLA for ipilimumab effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, ipilimumab, under your existing Department of Health and Human Services U.S. License No. 1713. Ipilimumab is indicated for the treatment of unresectable or metastatic melanoma.

Post-marketing Requirements(PMRs)

- To develop a validated, sensitive, and accurate assay for the detection of a immune response (binding antibodies) to ipilimumab, including procedures for accurate detection of antibodies in Ipilimumab

- To develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to ipilimumab.

- To conduct an assessment of anti-drug antibody(ADA) response to ipilimumab with a validated assay.



ORIGINAL RESEARCH

OPEN ACCESS

Check for updates

Development of anti-drug antibodies is associated with shortened survival in patients with metastatic melanoma treated with ipilimumab

Anders H. Kverneland[a,b], Christian Enevold[a], Marco Donia[b], Lars Bastholt[c], Inge Marie Svane[b,#], and Claus H. Nielsen[a,#]

[a]Institute for Inflammation Research, Center for Rheumatology and Spine Diseases, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [b]Center for Cancer Immune Therapy, Department of Oncology and Hematology, Copenhagen University Hospital, Herlev, Denmark; [c]Department of Oncology, Odense University Hospital, Odense, Denmark

Post-marketing Commitments(PMC)

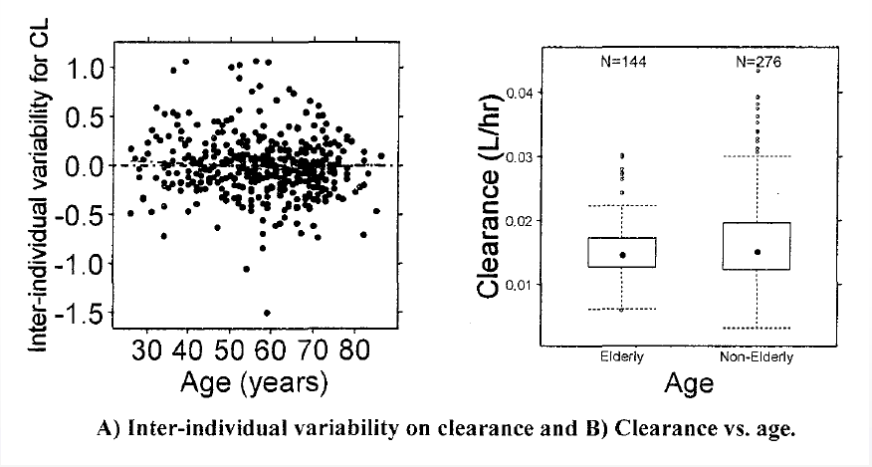
- To identify genetic determinants of immune related adverse reactions caused by ipilimumab, you will obtain 95% complete DNA sample acquisition from the required post-marketing study comparing 3mg/kg vs 10mg/kb ipilimumab monotherapy and then conduct genome wide association analyses and specific candidate gene(CD86, HLA family) analyses on these samples.

- To perform pharmacogenomics reanalysis of your dataset from study MDX010-20 using the adjudicated cases based on the FDA agreed upon case definitions of immune-related adverse reactions.

FDA Question

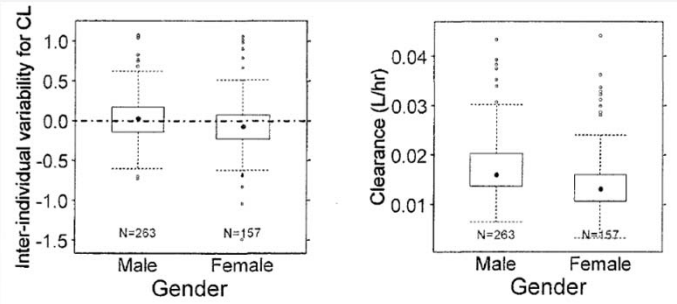
- Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific

  – Elderly patients: The PopPK analysis shows that age does not significantly affect the PK of ipilimumab.



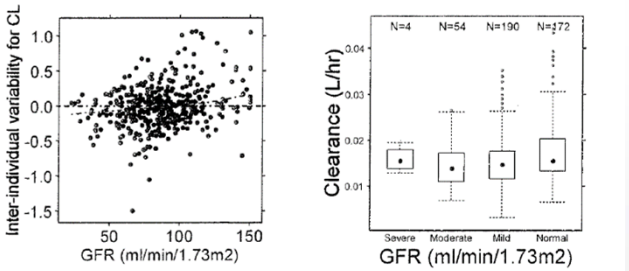
A) Inter-individual variability on clearance and B) Clearance vs. age.

– Gender: Gender doεs not significantly affect the PK of ipilimumab based on the PopPK analysis.



A) Inter-individual variability on clearance and B) Clearance vs. Gender.

– Renal impairment: The PopPK analysis suggests that there is no effect of renal impairment on the PK of ipilimumab.



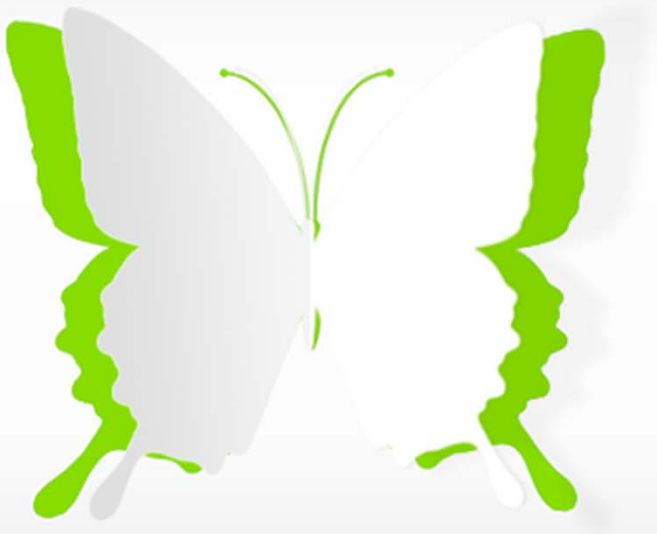
A) Inter-individual variability on clearance and B) Clearance vs. glomerular filtration rate (GFR).

Renal function was classified as normal (≥90 mL/min/1.73m^2), mild impairment (60 to <90 mL/min/1.73m^2), moderate impairment (30 to <60 mL/min/1.73m^2), and severe impairment (<30 mL/min/1.73m^2).

Reference

- New york time (https://www.nytimes.com/2018/10/01/health/nobel-prize-medicine.html)
- Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. Science 1996; 271:1734-1736.
- J Leukoc Biol, At the Bedside: CTLA-4- and PD-1-blocking antibodies in cancer immunotherapy, 2013 Jul; 94(1): 41–53.
- FDA approval package,
- https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125377Orig1s000TOC.cfm
- Anders H. Kverneland, Christian Enevolda, Development of anti-drug antibodies is associated with shortened survival in patients with metastatic melanoma treated with ipilimumab, ONCOIMMUNOLOGY 2018, VOL. 7, NO. 5
- Frank J. Ward1, Lekh N. Dahal and Rasha Abu-Eid, On the Road to Immunotherapy—Prospects for Treating Head and Neck Cancers With Checkpoint Inhibitor Antibodies

- Christina GiannopoulouEleftherios Sideris, Ipilimumab for Previously Untreated Unresectable Malignant Melanoma: A Critique of the Evidence, OharmacoEconomics, December 2015, Volume 33, Issue 12, pp 1269–1279
- Ascierto PA, Del Vecchio M, Ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg in patients with unresectable or metastatic melanoma: a randomised, double-blind, multicentre, phase 3 trial, Lancet Oncol. 2017 May;18(5):611-622.
- Immunotherapy of Cancer: An Innovative Treatment Comes of Age, Yoshiyuki Yamaguchi
- https://clinicaltrials.gov
- EUROPEAN MEDICINES AGENCY ASSESSMENT REPORT
- Jedd D. Wolchok , F. Stephen Hodi, Development of ipilimumab: a novel immunotherapeutic approach for the treatment of advanced melanoma, First published: 17 June 2013
- FDA Label, Yervoy



THANK YOU