020315科学委員会「非臨床試験の活用に関する専門部会」
（独）医薬品医療機器総合機構 会議室

資料 1-2

がん免疫療法モデルの概要

WPI Osaka University
iFReC
Moving on the Frontier

西川　博嘉

がん免疫療法モデルの概要

1. TGN1412第Ⅰ相試験事件

2.がん免疫療法での動物モデルの有用性
がんワクチン
抗CTLA-4抗体
抗PD-1抗体

TGN1412第Ⅰ相試験事件

2006年3月13日英国でヒトで全く初めての物質が使用された第Ⅰ相試験で、プラセボが投与された2名を除く18-40歳までの健康ボランティア6名全員が重篤な副作用（多臓器不全）のためICUに入院。人工呼吸器管理下となった。

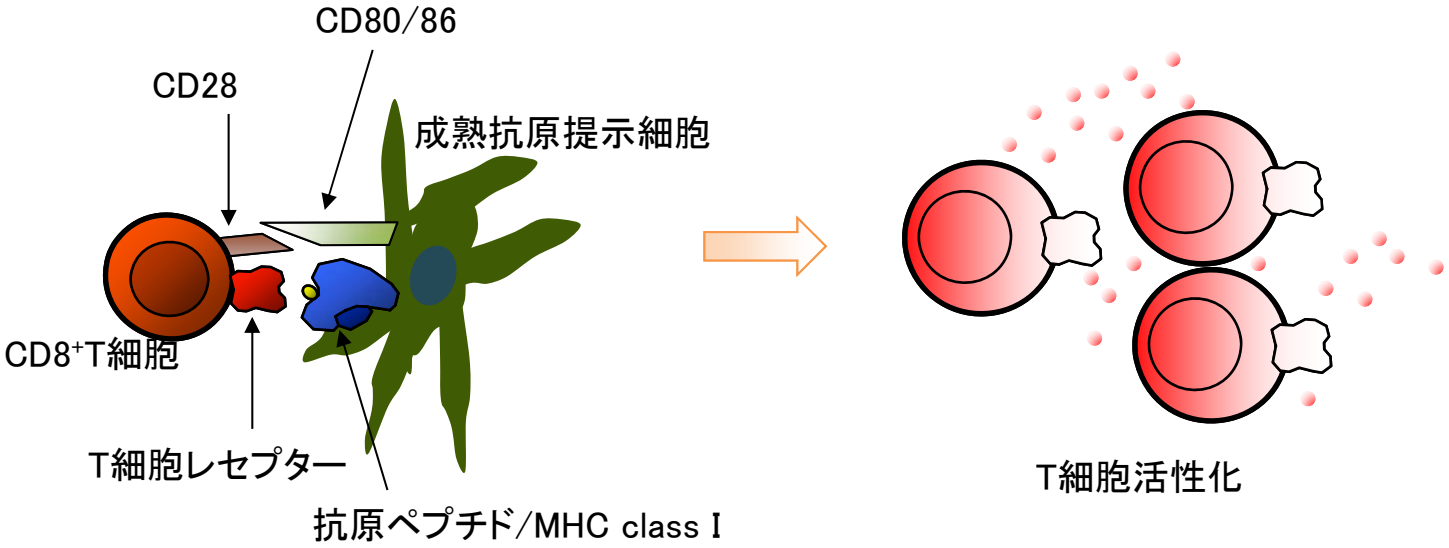
速やかに試験中止の措置がとられ規制当局（MHRA: The Medicines and Healthcare Products Regulatory Agency)は試験実施の承認を取り消した。

試験に使用されたのはTGN1412(CD28-Super MAB)と呼ばれるモノクローナル抗体である。本物質は動物モデルで著しい効果を示したため、欧州医薬品局(EMEA)からオーファン・ドラッグの指定を受けていた。

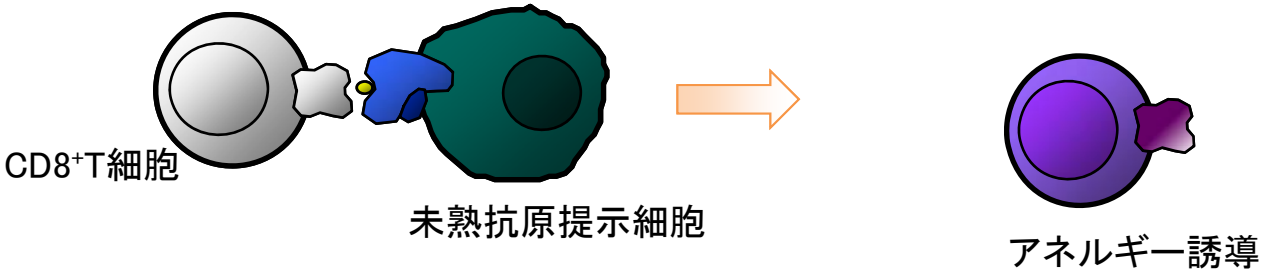
「正しい治療と薬の情報」2006年3月号参照

T細胞の活性化

T細胞活性化: T細胞レセプターシグナル+共刺激分子シグナル

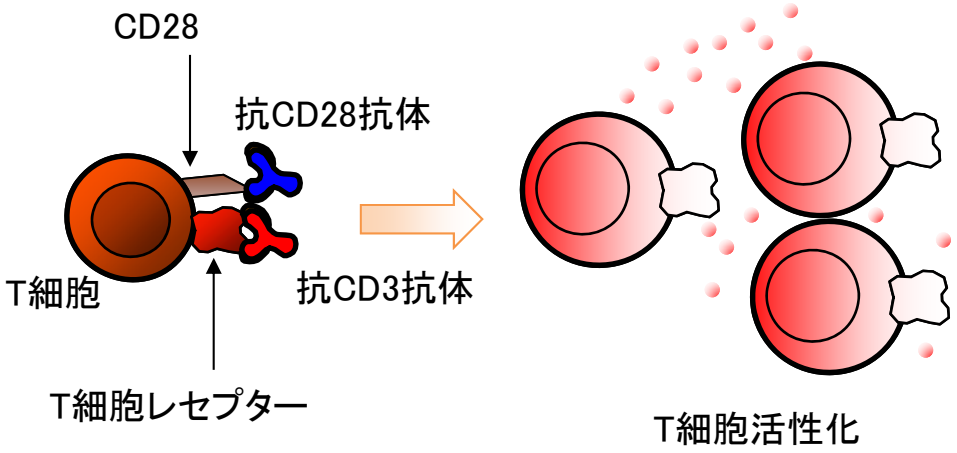


T細胞へのアネルギー誘導: T細胞レセプターシグナルのみ

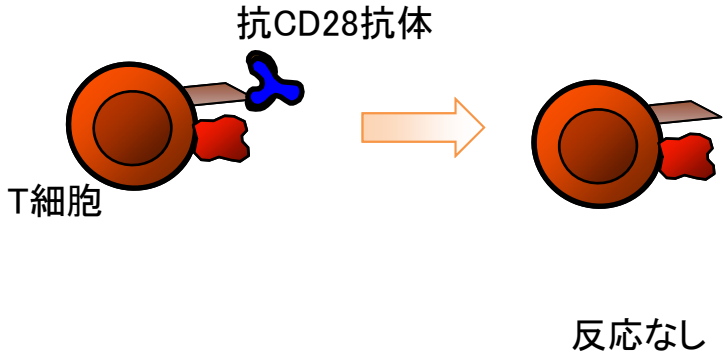


TGN1412とは？

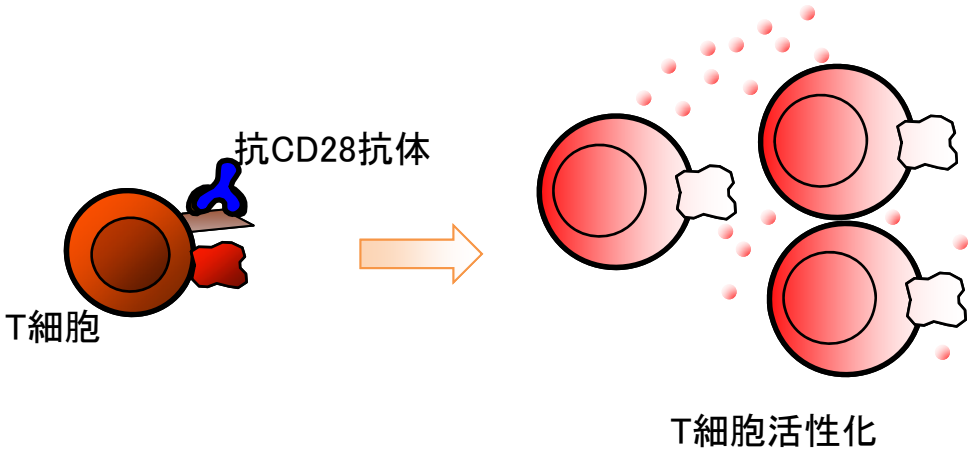
T細胞活性化：抗CD3抗体+抗CD28抗体



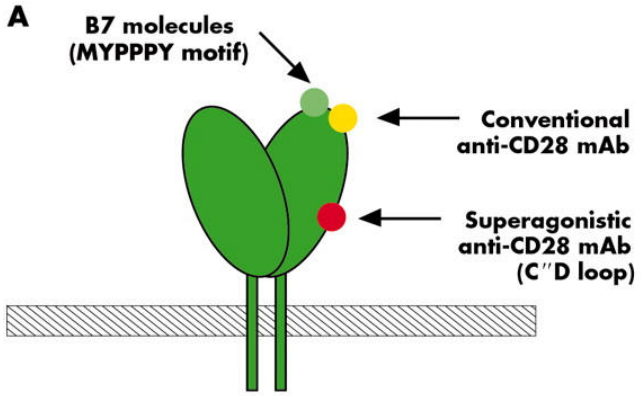
T細胞不応答：抗CD28抗体



抗CD28スーパーアゴニスティック抗体



2つの抗CD28抗体の違い



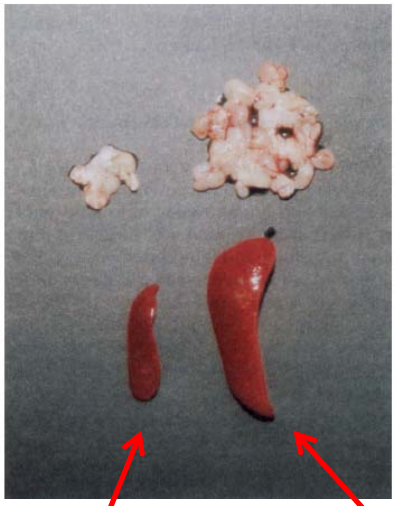
Ann Rheum Dis. Nov 2005; 64(Suppl 4): iv91–iv95.

TGN1412の前臨床試験

Super-agonistic抗CD28抗体(JJ316)はラットに0.5 mg/body/日の投与で抑制性T細胞活性を増強し、アジュバント関節炎を軽減する
(J Rheumatol. 2006 33(1):110-8.)

Super-agonistic抗CD28抗体(JJ316)は健康ラットへの投与で、$CD8^+$キラーおよび$CD4^+$ヘルパーT細胞活性を増強し脾臓およびリンパ節腫大を誘発する (Eur J Immunol. 1997 Jan;27(1):239-47.)

TGN1412を用いた動物実験では500倍量の投与でマウス、ラット等で安全性が確認されていた。
しかしこれはヒトCD28に対する抗体を用いて
検討された。「正しい治療と薬の情報」2006年3月号



動物モデルから副作用が予測できたか？

ヒトでの多臓器不全の原因はSuper-agonistic 抗CD28抗体により抑制性T細胞よりもエフェクターT細胞が活性化されたことによる

通常の抗がん剤と異なり、免疫関連分子を標的とした治療では、それぞれの動物の当該分子に交差反応性を有しない抗体では標的分子を介した副作用を十分に検討したことにはならない

健康ラットではSuper-agonistic 抗CD28抗体により抑制性T細胞よりもエフェクターT細胞が活性化され、脾腫、リンパ節腫大がみられている

より慎重な投与計画が必要ではなかったのか、、、、、、

がん免疫療法で動物モデルの有用性

有用性が明らかな点

1. Proof Of Conceptの確立 （new biologyの発見）
2. メカニズムの解析
3. 単一のバイオマーカーの同定（がん抗原など）

有用性が疑問視される点

1. ヒトで臨床効果の予測
2. 予後予測マーカー（バイオマーカー）の同定
3. 患者選択基準の同定

動物モデルが明らかにできること（がんワクチン療法）

Proc. Natl. Acad. Sci. USA
Vol. 94, pp. 6375–6379, June 1997
Immunology

Mutated mitogen-activated protein kinase: A tumor rejection antigen of mouse sarcoma

HIROAKI IKEDA*†, NOBUYOSHI OHTA†‡, KEIKO FURUKAWA§, HIROSHI MIYAZAKI‡, LIJIE WANG*, KOICHI FURUKAWA‡, KAGEMASA KURIBAYASHI¶, LLOYD J. OLD‖, AND HIROSHI SHIKU*,**

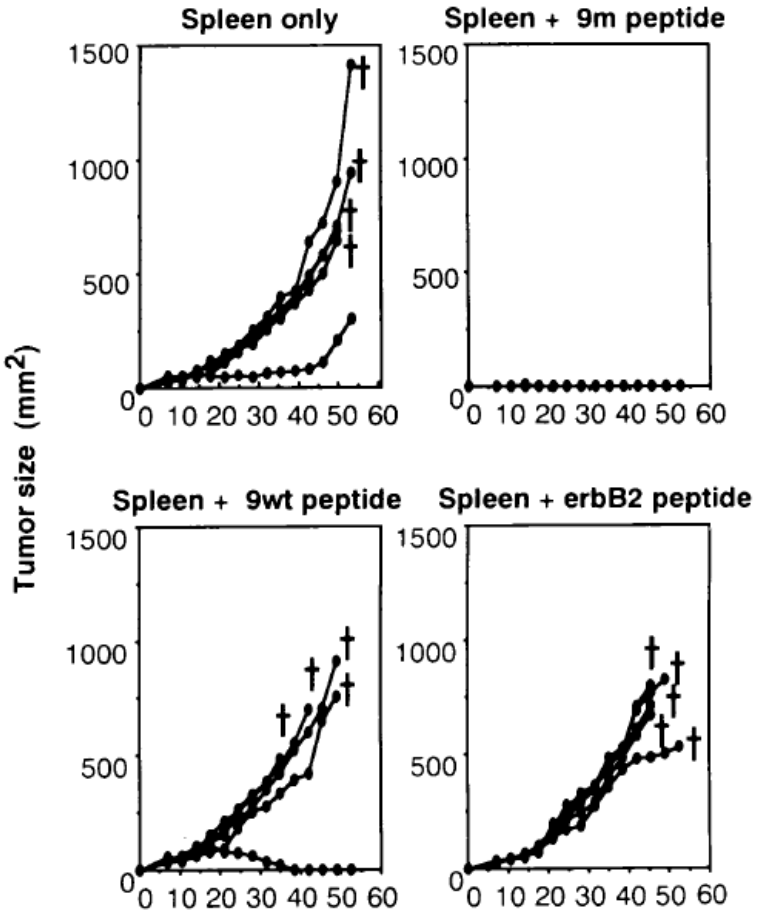
*2nd Department of Internal Medicine, Departments of §Biochemistry, and ¶Bioregulation, Mie University School of Medicine, Tsu, Mie 514, Japan; ‡Department of Oncology, Nagasaki University School of Medicine, Nagasaki 852, Japan; and ‖Ludwig Institute for Cancer Research, New York Branch at Memorial Sloan–Kettering Cancer Center, 1275 York Avenue, New York, NY 10021

Contributed by Lloyd J. Old, April 2, 1997

ABSTRACT The molecular basis of the polymorphic tumor rejection antigens of chemically induced sarcomas of inbred mice remains a mystery, despite the discovery of these antigens over 40 years ago and their critical importance to the foundation of tumor immunology. In an analysis of a panel of BALB/c 3-methylcholanthrene-induced tumors, we identified one tumor, CMS5, that elicited a strong cytotoxic T cell response with exquisite specificity for CMS5. A stable cloned line of T cells with this specificity (C18) was used to screen a CMS5 cDNA expression library. The gene encoding the C18-defined antigen was identified as a mutated form of a mouse mitogen-activated protein kinase, ERK2, and a peptide incorporating the resulting amino acid substitution (lysine to glutamine) was efficiently recognized by C18. Vaccination with this peptide elicited specific resistance to CMS5 challenge. Extensive efforts to isolate antigen-loss variants of CMS5 were unsuccessful, suggesting that the mutated mitogen-activated protein kinase is essential for maintenance of the malignant phenotype.

3−MCA誘導マウスの同系モデルで腫瘍拒絶抗原を同定

ワクチンにより腫瘍拒絶可能



がんワクチン療法は抗腫瘍効果が認められなかった

Adjuvant MAGE-A3 Immunotherapy in Resected Non–Small-Cell Lung Cancer: Phase II Randomized Study Results

Johan Vansteenkiste, Marcin Zielinski, Albert Linder, Jubrail Dahabreh, Emilio E. Gonzalez, Wojciech Malinowski, Maria Lopez-Brea, Tonu Vanakesa, Jacek Jassem, Haralabos Kalofonos, Jakub Perdeus, Reiner Bonnet, Jazeps Basko, Richard Jantlionts, Bernward Passlick, Tom Treasure, Marc Gillet, Frédéric F. Lehmann, and Vincent G. Brichard

See accompanying editorial on page 2369 and articles on pages 2388 and 2413

A B S T R A C T

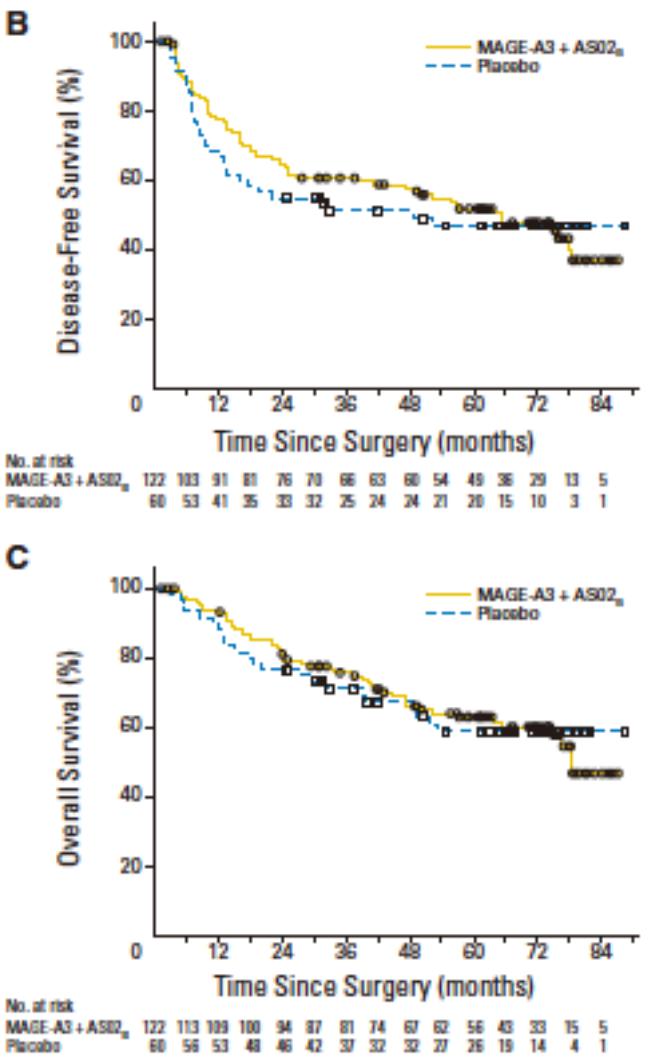
Purpose
The MAGE-A3 protein is expressed in approximately 35% of patients with resectable non–small-cell lung cancer (NSCLC). Several immunization approaches against the MAGE-A3 antigen have shown few, but often long-lasting, clinical responses in patients with metastatic melanoma.

Patients and Methods
A double-blind, randomized, placebo-controlled phase II study was performed assessing clinical activity, immunologic response, and safety following immunization with recombinant MAGE-A3 protein combined with an immunostimulant (13 doses over 27 months) in completely resected MAGE-A3–positive stage IB to II NSCLC. The primary end point was disease-free interval (DFI).

Results
Patients were randomly assigned to either MAGE-A3 immunotherapeutic (n = 122) or placebo (n = 60). After a median postresection period of 44 months, recurrence was observed in 35% of patients in the MAGE-A3 arm and 43% in the placebo arm. No statistically significant improvement in DFI (hazard ratio [HR], 0.75, 95% CI, 0.46 to 1.23; two-sided $P = .254$), disease-free survival (DFS; HR, 0.76; 95% CI, 0.48 to 1.21; $P = .248$), or overall survival (HR, 0.81; 95% CI, 0.47 to 1.40; $P = .454$) was observed. Corresponding analysis after a median of 70 months of follow-up revealed a similar trend for DFI and DFS. All patients receiving the active treatment showed a humoral immune response to the MAGE-A3 antigen, although no correlation was observed with outcome. No significant toxicity was observed.

Conclusion
In this early development study with a limited number of patients, postoperative MAGE-A3 immunization proved to be feasible with minimal toxicity. These results are being investigated further in a large phase III study.

J Clin Oncol 31:2396-2403. © 2013 by American Society of Clinical Oncology



MAGE−A3ワクチンにてDFS
OSの延長なし

重篤な副作用なし

動物モデルから作用と副作用が予測できたか？

抗腫瘍活性を予測する有用性

Proof Of Conceptの確立？ （new biologyの発見）
腫瘍拒絶抗原が発見された

様々な腫瘍モデルで抗腫瘍活性が示された

臨床効果はなかった

使用したモデルの問題？
免疫原生の高い腫瘍(化学発がん由来腫瘍 Meth Aなど)と低い腫瘍(自然発がん腫瘍B16 melanomaなど)の選択
異所性(同所性?)移植がんモデルの限界
発がんモデル

動物モデルが明らかにできること（抗CTLA-4抗体）

Enhancement of Antitumor Immunity by CTLA-4 Blockade

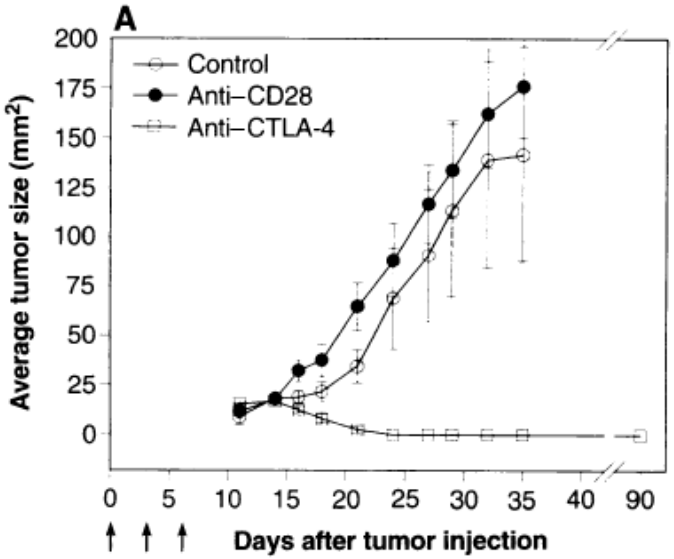
Dana R. Leach, Matthew F. Krummel, James P. Allison*

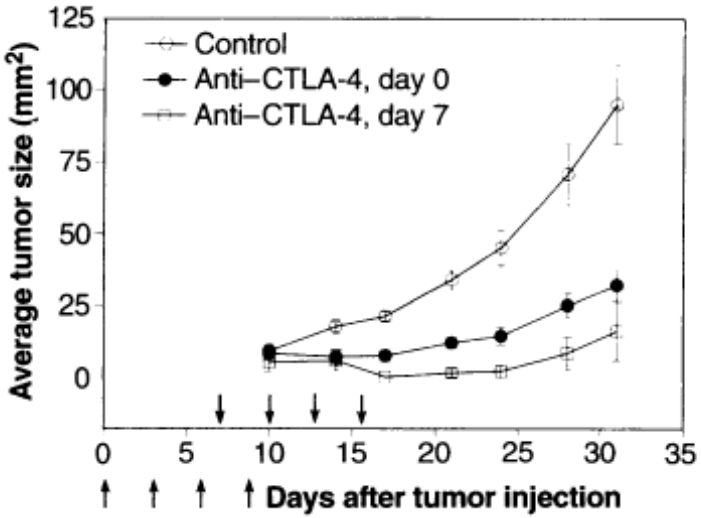
One reason for the poor immunogenicity of many tumors may be that they cannot provide signals for CD28-mediated costimulation necessary to fully activate T cells. It has recently become apparent that CTLA-4, a second counterreceptor for the B7 family of costimulatory molecules, is a negative regulator of T cell activation. Here, in vivo administration of antibodies to CTLA-4 resulted in the rejection of tumors, including preestablished tumors. Furthermore, this rejection resulted in immunity to a secondary exposure to tumor cells. These results suggest that blockade of the inhibitory effects of CTLA-4 can allow for, and potentiate, effective immune responses against tumor cells.

SCIENCE • VOL. 271 • 22 MARCH 1996

Hamster-anti-mouse
CTLA-4 mAb (UC104F10)
100 ug x3

副作用の記載なし





動物モデルが明らかにできること（抗CTLA-4抗体）

Research article

CTLA4 blockade and GM-CSF combination immunotherapy alters the intratumor balance of effector and regulatory T cells

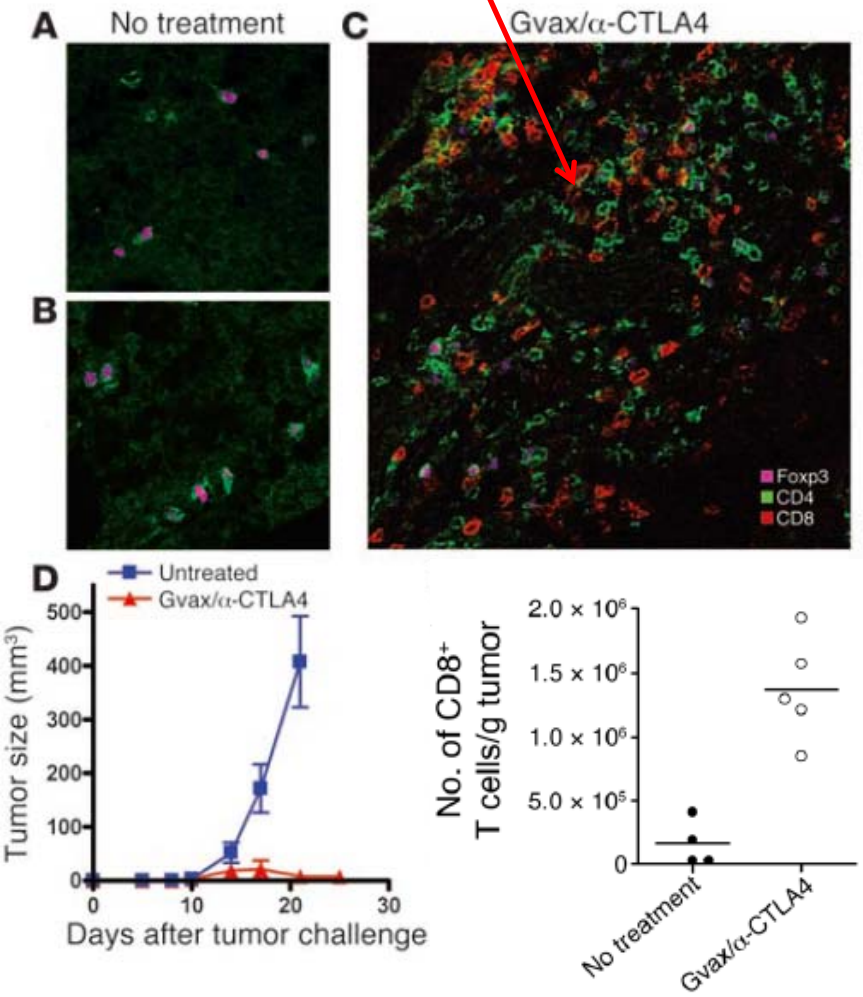
Sergio A. Quezada, Karl S. Peggs, Michael A. Curran, and James P. Allison

Howard Hughes Medical Institute, Department of Immunology, Memorial Sloan-Kettering Cancer Center, New York, New York, USA.

CTL-associated antigen 4 (CTLA4) blockade releases inhibitory controls on T cell activation and proliferation, inducing antitumor immunity in both preclinical and early clinical trials. We examined the mechanisms of action of anti-CTLA4 and a GM-CSF–transduced tumor cell vaccine (Gvax) and their impact on the balance of effector T cells (Teffs) and Tregs in an in vivo model of B16/BL6 melanoma. Tumor challenge increased the frequency of Tregs in lymph nodes, and untreated tumors became infiltrated by $CD4^+Foxp3^-$ and $CD4^+Foxp3^+$ T cells but few $CD8^+$ T cells. Anti-CTLA4 did not deplete Tregs or permanently impair their function but acted in a cell-intrinsic manner on both Tregs and Teffs, allowing them to expand, most likely in response to self antigen. While Gvax primed the tumor-reactive Teff compartment, inducing activation, tumor infiltration, and a delay in tumor growth, the combination with CTLA4 blockade induced greater infiltration and a striking change in the intratumor balance of Tregs and Teffs that directly correlated with tumor rejection. The data suggest that Tregs control both $CD4^+$ and $CD8^+$ T cell activity within the tumor, highlight the importance of the intratumor ratio of effectors to regulators, and demonstrate inversion of the ratio and correlation with tumor rejection during Gvax/anti-CTLA4 immunotherapy.

The Journal of Clinical Investigation http://www.jci.org Volume 116 Number 7 July 2006

$CD8^+$T細胞浸潤が増加しTregが減少

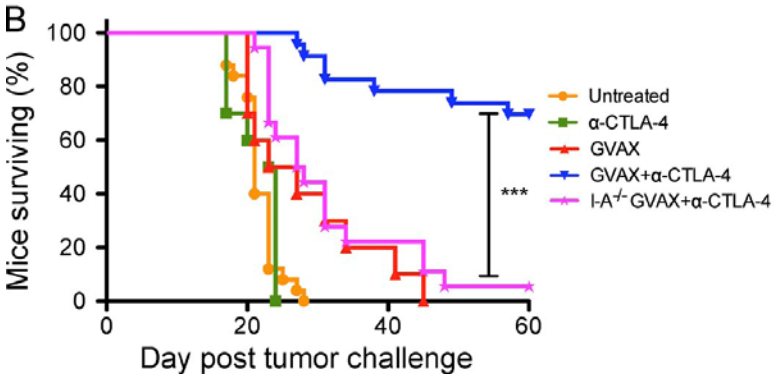


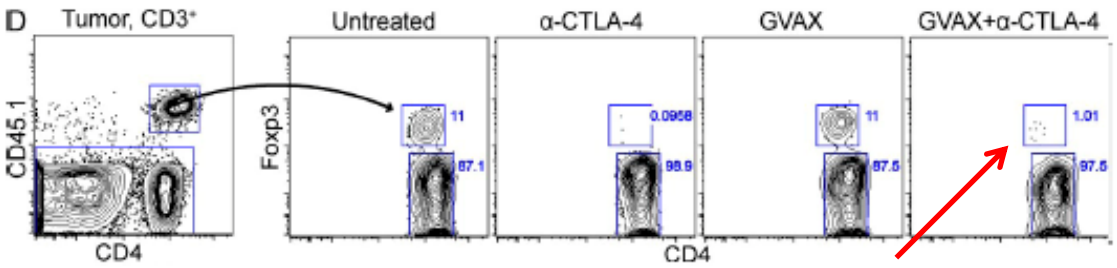
Mouse-anti-mouse CTLA-4
mAb（9D9 ） 100 ug x3

副作用の明確な記載なし

動物モデルが明らかにできること（抗CTLA-4抗体）

Authors	Title	Ab	Journal
Mark Sj et al	Anti-CTLA-4 antibodies of IgG2a isotype enhance…..	CTLA-4 mAb	Cancer Immunol Res 2013
Simpson TR et al	Fc-dependent depletion of ….	CTLA-4 mAb	J.Exp Med 2013
Bulliard Y et al	Activating Fcg-receptors cotnribute….	GITR mAb/CTLA-4 mAb	J.Exp Med 2013





Tregsが除去されている

動物モデルが明らかにできること（抗CTLA-4抗体）

Brief Definitive Report

Immunologic Self-Tolerance Maintained by CD25$^+$CD4$^+$ Regulatory T Cells Constitutively Expressing Cytotoxic T Lymphocyte–associated Antigen 4

By Takeshi Takahashi,* Tomoyuki Tagami,‡ Sayuri Yamazaki,* Toshimitsu Uede,§ Jun Shimizu,‡ Noriko Sakaguchi,* Tak W. Mak,‖ and Shimon Sakaguchi*

*From the *Department of Experimental Pathology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507, Japan; the ‡Department of Immunopathology, Tokyo Metropolitan Institute of Gerontology, Tokyo 173-0015, Japan; the §Institute of Immunological Science, Hokkaido University, Sapporo 060-8638, Japan; and the ‖Amgen Institute, Ontario Cancer Institute, Department of Immunology and Medical Biophysics, University of Toronto, Toronto M5G2C1, Canada*

Abstract

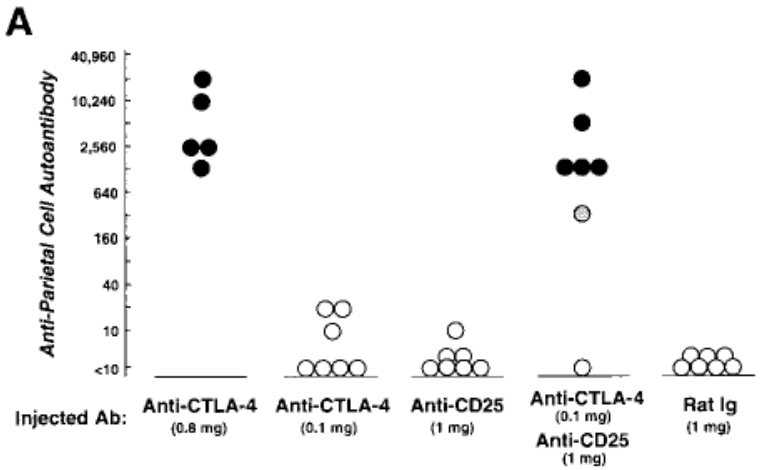
This report shows that cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) plays a key role in T cell–mediated dominant immunologic self-tolerance. In vivo blockade of CTLA-4 for a limited period in normal mice leads to spontaneous development of chronic organ-specific autoimmune diseases, which are immunopathologically similar to human counterparts. In normal naive mice, CTLA-4 is constitutively expressed on CD25$^+$CD4$^+$ T cells, which constitute 5–10% of peripheral CD4$^+$ T cells. When the CD25$^+$CD4$^+$ T cells are stimulated via the T cell receptor in vitro, they potently suppress antigen-specific and polyclonal activation and proliferation of other T cells, including CTLA-4–deficient T cells, and blockade of CTLA-4 abrogates the suppression. CD28-deficient CD25$^+$CD4$^+$ T cells can also suppress normal T cells, indicating that CD28 is dispensable for activation of the regulatory T cells. Thus, the CD25$^+$CD4$^+$ regulatory T cell population engaged in dominant self-tolerance may require CTLA-4 but not CD28 as a costimulatory molecule for its functional activation. Furthermore, interference with this role of CTLA-4 suffices to elicit autoimmune disease in otherwise normal animals, presumably through affecting CD25$^+$CD4$^+$ T cell–mediated control of self-reactive T cells. This unique function of CTLA-4 could be exploited to potentiate T cell–mediated immunoregulation, and thereby to induce immunologic tolerance or to control autoimmunity.

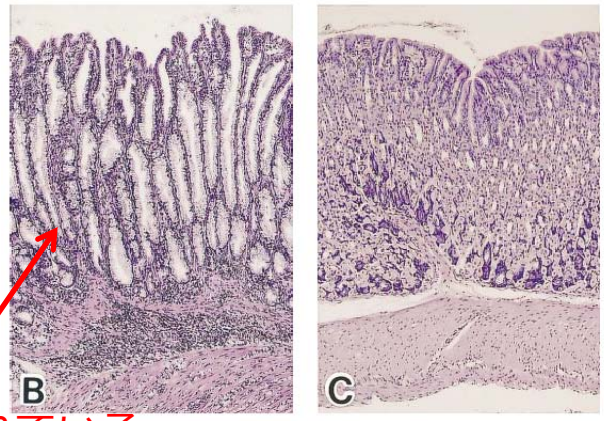
Key words: CTLA-4 • autoimmune disease • regulatory T cell • CD25 • self-tolerance

Volume 192, Number 2, July 17, 2000 303–309

Hamster-anti-mouse CTLA-4 mAb (UC104F10)

800 ug の抗CTLA-4抗体で胃炎が誘発される





胃炎が誘発されている

動物モデルが明らかにできること（抗CTLA-4抗体）

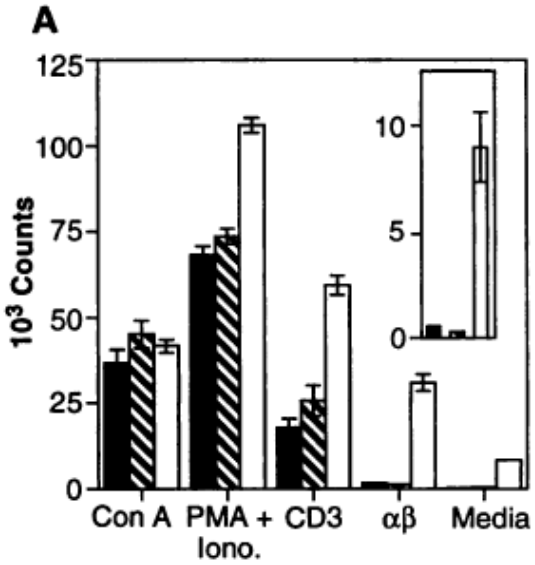
Lymphoproliferative Disorders with Early Lethality in Mice Deficient in *Ctla-4*

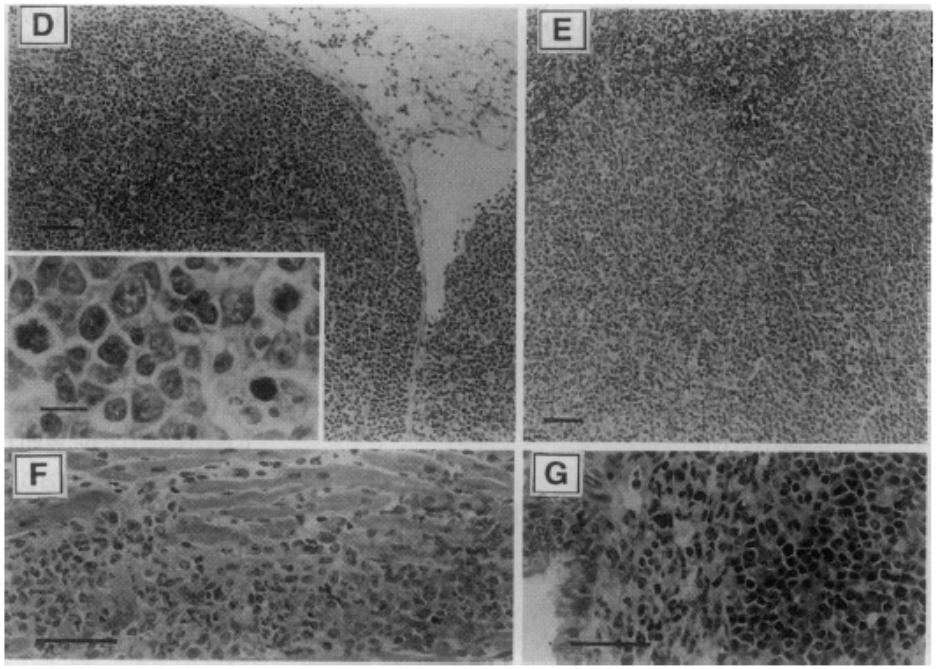
Paul Waterhouse, Josef M. Penninger, Emma Timms, Andrew Wakeham, Arda Shahinian, Kelvin P. Lee, Craig B. Thompson, Henrik Griesser, Tak W. Mak*

The role of the cell-surface molecule CTLA-4 in the regulation of T cell activation has been controversial. Here, lymph nodes and spleens of CTLA-4–deficient mice accumulated T cell blasts with up-regulated activation markers. These blast cells also infiltrated liver, heart, lung, and pancreas tissue, and amounts of serum immunoglobulin were elevated. The mice invariably became moribund by 3 to 4 weeks of age. Although CTLA-4–deficient T cells proliferated spontaneously and strongly when stimulated through the T cell receptor, they were sensitive to cell death induced by cross-linking of the Fas receptor and by gamma irradiation. Thus, CTLA-4 acts as a negative regulator of T cell activation and is vital for the control of lymphocyte homeostasis.

SCIENCE • VOL. 270 • 10 NOVEMBER 1995

CTLA-4KOマウスは多様な自己免疫症状とT細胞活性化を示す





抗CTLA-4抗体は悪性黒色腫治療に有用である

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 19, 2010 VOL. 363 NO. 8

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

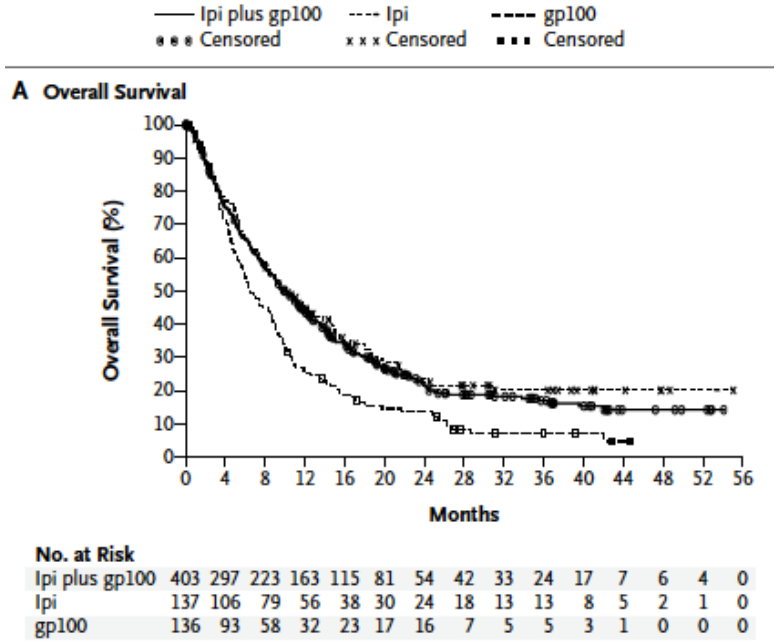


Table 3. Adverse Events in the Safety Population.*

Adverse Event	Ipilimumab plus gp100 (N=380)			Ipilimumab Alone (N=131)			gp100 Alone (N=132)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
	number of patients (percent)								
Any event	374 (98.4)	147 (38.7)	26 (6.8)	127 (96.9)	49 (37.4)	11 (8.4)	128 (97.0)	54 (40.9)	8 (6.1)
Any drug-related event	338 (88.9)	62 (16.3)	4 (1.1)	105 (80.2)	25 (19.1)	5 (3.8)	104 (78.8)	15 (11.4)	0
Gastrointestinal disorders									
Diarrhea	146 (38.4)	16 (4.2)	1 (0.3)	43 (32.8)	7 (5.3)	0	26 (19.7)	1 (0.8)	0
Nausea	129 (33.9)	5 (1.3)	1 (0.3)	46 (35.1)	3 (2.3)	0	52 (39.4)	3 (2.3)	0
Constipation	81 (21.3)	3 (0.8)	0	27 (20.6)	3 (2.3)	0	34 (25.8)	1 (0.8)	0
Vomiting	75 (19.7)	6 (1.6)	1 (0.3)	31 (23.7)	3 (2.3)	0	29 (22.0)	3 (2.3)	0
Abdominal pain	67 (17.6)	6 (1.6)	0	20 (15.3)	2 (1.5)	0	22 (16.7)	6 (4.5)	1 (0.8)
Other									
Fatigue	137 (36.1)	19 (5.0)	0	55 (42.0)	9 (6.9)	0	41 (31.1)	4 (3.0)	0
Decreased appetite	88 (23.2)	5 (1.3)	1 (0.3)	35 (26.7)	2 (1.5)	0	29 (22.0)	3 (2.3)	1 (0.8)
Pyrexia	78 (20.5)	2 (0.5)	0	16 (12.2)	0	0	23 (17.4)	2 (1.5)	0
Headache	65 (17.1)	4 (1.1)	0	19 (14.5)	3 (2.3)	0	19 (14.4)	3 (2.3)	0
Cough	55 (14.5)	1 (0.3)	0	21 (16.0)	0	0	18 (13.6)	0	0
Dyspnea	46 (12.1)	12 (3.2)	2 (0.5)	19 (14.5)	4 (3.1)	1 (0.8)	25 (18.9)	6 (4.5)	0
Anemia	41 (10.8)	11 (2.9)	0	15 (11.5)	4 (3.1)	0	23 (17.4)	11 (8.3)	0
Any immune-related event	221 (58.2)	37 (9.7)	2 (0.5)	80 (61.1)	16 (12.2)	3 (2.3)	42 (31.8)	4 (3.0)	0
Dermatologic	152 (40.0)	8 (2.1)	1 (0.3)	57 (43.5)	2 (1.5)	0	22 (16.7)	0	0
Pruritus	67 (17.6)	1 (0.3)	0	32 (24.4)	0	0	14 (10.6)	0	0
Rash	67 (17.6)	5 (1.3)	0	25 (19.1)	1 (0.8)	0	6 (4.5)	0	0
Vitiligo	14 (3.7)	0	0	3 (2.3)	0	0	1 (0.8)	0	0
Gastrointestinal	122 (32.1)	20 (5.3)	2 (0.5)	38 (29.0)	10 (7.6)	0	19 (14.4)	1 (0.8)	0
Diarrhea	115 (30.3)	14 (3.7)	0	36 (27.5)	6 (4.6)	0	18 (13.6)	1 (0.8)	0
Colitis	20 (5.3)	11 (2.9)	1 (0.3)	10 (7.6)	7 (5.3)	0	1 (0.8)	0	0
Endocrine	15 (3.9)	4 (1.1)	0	10 (7.6)	3 (2.3)	2 (1.5)	2 (1.5)	0	0
Hypothyroidism	6 (1.6)	1 (0.3)	0	2 (1.5)	0	0	2 (1.5)	0	0
Hypopituitarism	3 (0.8)	2 (0.5)	0	3 (2.3)	1 (0.8)	1 (0.8)	0	0	0
Hypophysitis	2 (0.5)	2 (0.5)	0	2 (1.5)	2 (1.5)	0	0	0	0
Adrenal insufficiency	3 (0.8)	2 (0.5)	0	2 (1.5)	0	0	0	0	0
Increase in serum thyrotropin level	2 (0.5)	0	0	1 (0.8)	0	0	0	0	0
Decrease in serum corticotropin level	0	0	0	2 (1.5)	0	1 (0.8)	0	0	0
Hepatic	8 (2.1)	4 (1.1)	0	5 (3.8)	0	0	6 (4.5)	3 (2.3)	0
Increase in alanine aminotransferase	3 (0.8)	2 (0.5)	0	2 (1.5)	0	0	3 (2.3)	0	0
Increase in aspartate aminotransferase	4 (1.1)	1 (0.3)	0	1 (0.8)	0	0	2 (1.5)	0	0
Hepatitis	2 (0.5)	1 (0.3)	0	1 (0.8)	0	0	0	0	0
Other	12 (3.2)	5 (1.3)	0	6 (4.6)	2 (1.5)	1 (0.8)	3 (2.3)	1 (0.8)	0

* The adverse events listed here were reported in at least 15% of patients. The most common immune-related adverse events and those of particular clinical relevance are also listed. Patients could have more than one adverse event. Included are all patients who received at least one dose of a study drug (643 patients). 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 bowel perforation–inflammatory colitis, bowel perforation, or multiorgan failure–peritonitis; and 1 patient had Guillain–Barré syndrome, which is considered to be consistent with a neurologic immune-related adverse event) and 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 sepsis, myelofibrosis, and acute respiratory distress syndrome (3 patients in the ipilimumab-plus-gp100 group); severe infection–renal failure–septic shock, and vascular leak syndrome (2 patients in the ipilimumab-alone group), and cachexia and septic shock (2 patients in the gp100-alone group).

動物モデルから作用と副作用が予測できたか？

抗腫瘍活性を予測する有用性

1. Proof Of Conceptの確立（new biologyの発見）
   様々な腫瘍モデルで抗腫瘍活性が示されている
2. メカニズムの解析
   当初エフェクターT細胞の活性化が示唆されていたが、
近年Treg除去の重要性が示されつつある

副作用を予測する有用性

1. 高用量の抗体を投与したマウスで自己免疫性胃炎が発症
2. KOマウスでも重篤な自己免疫疾患とT細胞の過活性化

サルでは腸炎はみられなかった

動物モデルが明らかにできること（抗PD-1、PD-L1抗体）

Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade

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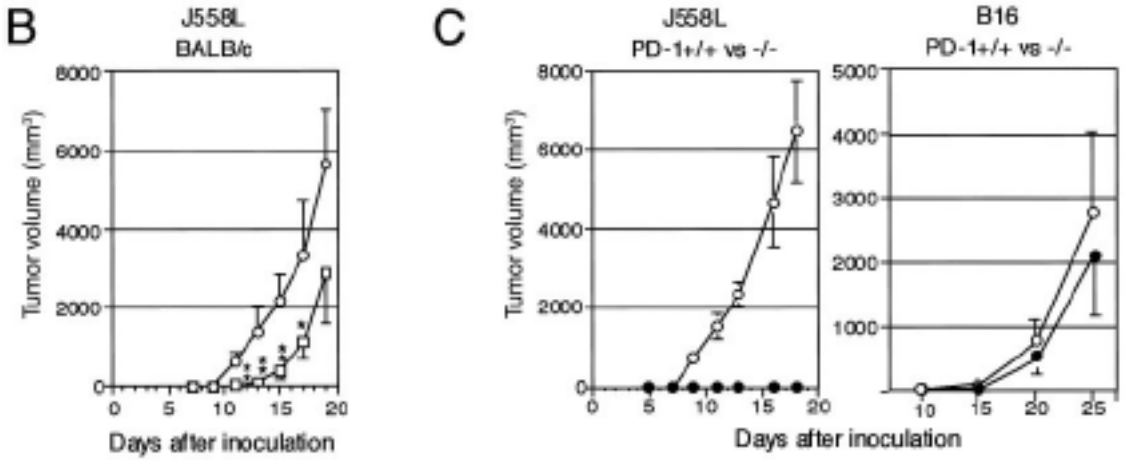
Contributed by Tasuku Honjo, August 1, 2002

PD-1 is a receptor of the Ig superfamily that negatively regulates T cell antigen receptor signaling by interacting with the specific ligands (PD-L) and is suggested to play a role in the maintenance of self-tolerance. In the present study, we examined possible roles of the PD-1/PD-L system in tumor immunity. Transgenic expression of PD-L1, one of the PD-L, in P815 tumor cells rendered them less susceptible to the specific T cell antigen receptor-mediated lysis by cytotoxic T cells *in vitro*, and markedly enhanced their tumorigenesis and invasiveness *in vivo* in the syngeneic hosts as compared with the parental tumor cells that lacked endogenous PD-L. Both effects could be reversed by anti-PD-L1 Ab. Survey of murine tumor lines revealed that all of the myeloma cell lines examined naturally expressed PD-L1. Growth of the myeloma cells in normal syngeneic mice was inhibited significantly albeit transiently by the administration of anti-PD-L1 Ab *in vivo* and was suppressed completely in the syngeneic PD-1-deficient mice. These results suggest that the expression of PD-L1 can serve as a potent mechanism for potentially immunogenic tumors to escape from host immune responses and that blockade of interaction between PD-1 and PD-L may provide a promising strategy for specific tumor immunotherapy.

Rat-anti mouse PD-L1抗体

PD-1KOマウスで
B16melanomaは腫瘍増殖かわらず



動物モデルが明らかにできること（抗PD-1、PD-L1抗体）

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Development of Lupus-like Autoimmune Diseases by Disruption of the *PD-1* Gene Encoding an ITIM Motif-Carrying Immunoreceptor

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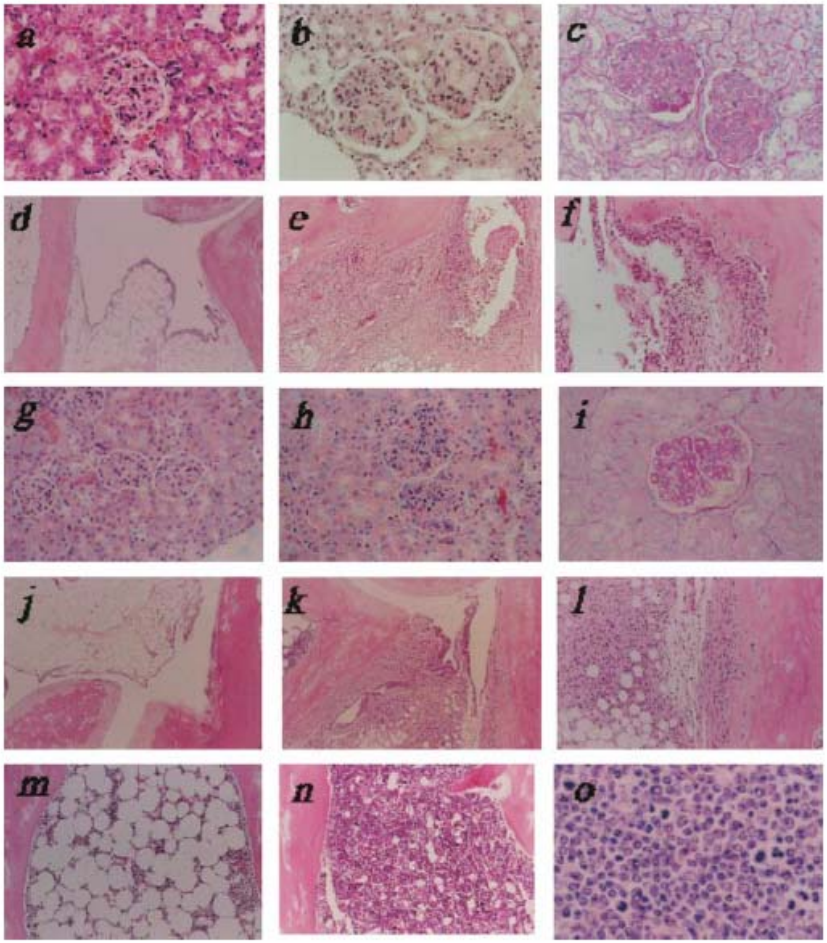
Summary

PD-1, a 55 kDa transmembrane protein containing an immunoreceptor tyrosine-based inhibitory motif, is induced in lymphocytes and monocytic cells following activation. Aged C57BL/6(B6)-*PD-1*$^{-/-}$ congenic mice spontaneously developed characteristic lupus-like proliferative arthritis and glomerulonephritis with predominant IgG3 deposition, which were markedly accelerated by introduction of a *Fas* mutation (*lpr*). Introduction of a *PD-1* null mutation into the 2C-TCR (anti-H-2L^{d}) transgenic mice of the H-2$^{b/d}$ background resulted in the chronic and systemic graft-versus-host-like disease. Furthermore, CD8^{+}2C-TCR^{+}PD-1$^{-/-}$ T cells exhibited markedly augmented proliferation in vitro in response to H-2^{d} allogenic cells. Collectively, it is suggested that PD-1 is involved in the maintenance of peripheral self-tolerance by serving as a negative regulator of immune responses.



抗PD-1抗体は悪性黒色腫治療に有用である

ORIGINAL ARTICLE

Nivolumab in Previously Untreated Melanoma without *BRAF* Mutation

Caroline Robert, M.D., Ph.D., Georgina V. Long, M.D., Ph.D., Benjamin Brady, M.D., Caroline Dutriaux, M.D., Michele Maio, M.D., Laurent Mortier, M.D., Jessica C. Hassel, M.D., Piotr Rutkowski, M.D., Ph.D., Catriona McNeil, M.D., Ph.D., Ewa Kalinka-Warzocha, M.D., Ph.D., Kerry J. Savage, M.D., Micaela M. Hernberg, M.D., Ph.D., Celeste Lebbé, M.D., Ph.D., Julie Charles, M.D., Ph.D., Catalin Mihalcioiu, M.D., Vanna Chiarion-Sileni, M.D., Cornelia Mauch, M.D., Ph.D., Francesco Cognetti, M.D., Ana Arance, M.D., Ph.D., Henrik Schmidt, M.D., D.M.Sc., Dirk Schadendorf, M.D., Helen Gogas, M.D., Lotta Lundgren-Eriksson, M.D., Christine Horak, Ph.D., Brian Sharkey, Ph.D., Ian M. Waxman, M.D., Victoria Atkinson, M.D., and Paolo A. Ascierto, M.D.

ABSTRACT

BACKGROUND

Nivolumab was associated with higher rates of objective response than chemotherapy in a phase 3 study involving patients with ipilimumab-refractory metastatic melanoma. The use of nivolumab in previously untreated patients with advanced melanoma has not been tested in a phase 3 controlled study.

METHODS

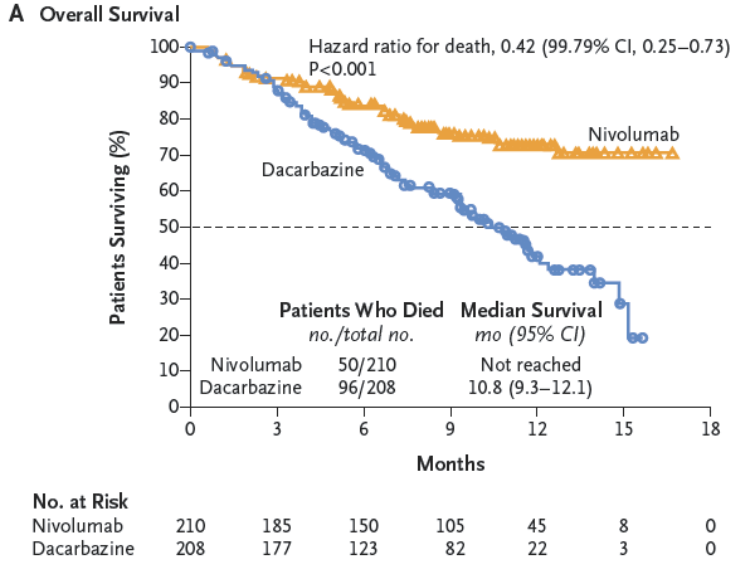
We randomly assigned 418 previously untreated patients who had metastatic melanoma without a *BRAF* mutation to receive nivolumab (at a dose of 3 mg per kilogram of body weight every 2 weeks and dacarbazine-matched placebo every 3 weeks) or dacarbazine (at a dose of 1000 mg per square meter of body-surface area every 3 weeks and nivolumab-matched placebo every 2 weeks). The primary end point was overall survival.

RESULTS

At 1 year, the overall rate of survival was 72.9% (95% confidence interval [CI], 65.5 to 78.9) in the nivolumab group, as compared with 42.1% (95% CI, 33.0 to 50.9) in the dacarbazine group (hazard ratio for death, 0.42; 99.79% CI, 0.25 to 0.73; P<0.001). The median progression-free survival was 5.1 months in the nivolumab group versus 2.2 months in the dacarbazine group (hazard ratio for death or progression of disease, 0.43; 95% CI, 0.34 to 0.56; P<0.001). The objective response rate was 40.0% (95% CI, 33.3 to 47.0) in the nivolumab group versus 13.9% (95% CI, 9.5 to 19.4) in the dacarbazine group (odds ratio, 4.06; P<0.001). The survival benefit with nivolumab versus dacarbazine was observed across prespecified subgroups, including subgroups defined by status regarding the programmed death ligand 1 (PD-L1). Common adverse events associated with nivolumab included fatigue, pruritus, and nausea. Drug-related adverse events of grade 3 or 4 occurred in 11.7% of the patients treated with nivolumab and 17.6% of those treated with dacarbazine.

CONCLUSIONS

Nivolumab was associated with significant improvements in overall survival and progression-free survival, as compared with dacarbazine, among previously untreated patients who had metastatic melanoma without a *BRAF* mutation. (Funded by Bristol-Myers Squibb; CheckMate 066 ClinicalTrials.gov number, NCT01721772.)



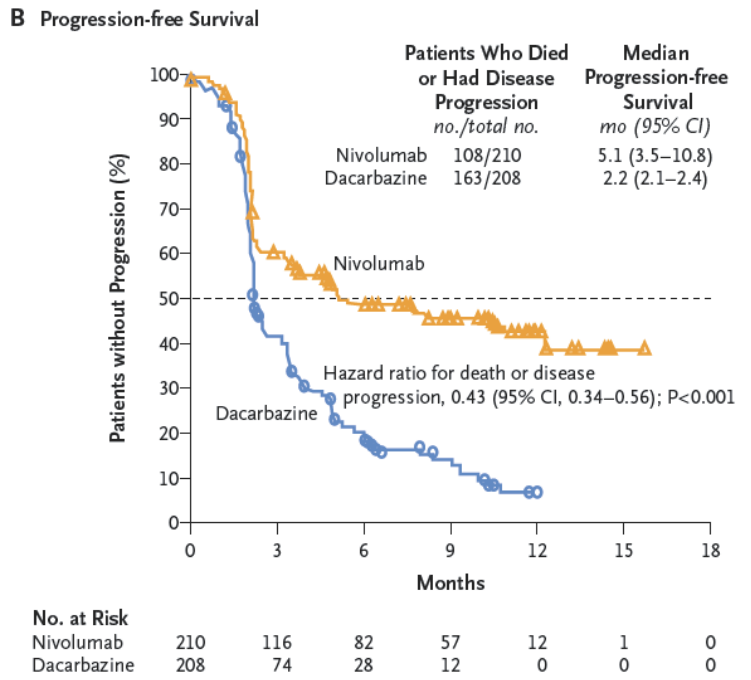


Table 3. Adverse Events.*

Event	Nivolumab (N=206)		Dacarbazine (N=205)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	no. of patients with event (%)			
Any adverse event	192 (93.2)	70 (34.0)	194 (94.6)	78 (38.0)
Treatment-related adverse event†	153 (74.3)	24 (11.7)	155 (75.6)	36 (17.6)
Fatigue	41 (19.9)	0	30 (14.6)	2 (1.0)
Pruritus	35 (17.0)	1 (0.5)	11 (5.4)	0
Nausea	34 (16.5)	0	85 (41.5)	0
Diarrhea	33 (16.0)	2 (1.0)	32 (15.6)	1 (0.5)
Rash	31 (15.0)	1 (0.5)	6 (2.9)	0
Vitiligo	22 (10.7)	0	1 (0.5)	0
Constipation	22 (10.7)	0	25 (12.2)	0
Asthenia	21 (10.2)	0	25 (12.2)	1 (0.5)
Vomiting	13 (6.3)	1 (0.5)	43 (21.0)	1 (0.5)
Neutropenia	0	0	23 (11.2)	9 (4.4)
Thrombocytopenia	0	0	21 (10.2)	10 (4.9)
Adverse event leading to discontinuation of treatment	14 (6.8)	12 (5.8)	24 (11.7)	19 (9.3)
Serious adverse event				
Any event	64 (31.1)	43 (20.9)	78 (38.0)	54 (26.3)
Treatment-related event	19 (9.2)	12 (5.8)	18 (8.8)	12 (5.9)

* The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[20]

† The treatment-related adverse events listed here were reported in at least 10% of the patients in either study group.

動物モデルから作用と副作用が予測できたか？

抗腫瘍活性を予測する有用性

1. Proof Of Conceptの確立 （new biologyの発見）
   限られた腫瘍モデルで抗腫瘍活性が示されている
   Sensitive tumors(MC38 EMT6など)とnon-sensitive tumors (B16 melanoma, CT26など)
2. メカニズムの解析
   現在のところエフェクターT細胞の活性化が示唆されいる

副作用を予測する有用性

1. KOマウスで自己免疫疾患
2. 抗体投与ではほとんど副作用がみられない

サルでは？
脈絡叢へのリンパ球、形質細胞浸潤

動物モデルを用いた前臨床試験でわかること

抗腫瘍活性を予測する

様々な動物モデルで抗腫瘍活性が示されたがんワクチン療法の臨床効果は限定的である

限られた動物モデルでしか臨床効果が認められないPD-1／PD-L1シグナル阻害はヒトで臨床効果が認められる

→ 動物モデルでのPOCの証明は重要だが、ヒトでの臨床効果を完全に予測することは難しい

今後進められることが推定されるcombination therapy でも相加・相乗効果のPOCの証明は必要ではないか

動物モデルを用いた前臨床試験でわかること

副作用を予測する

抗CTLA-4抗体では大量投与によりマウスモデルで胃炎の報告がある。

またKOマウスでは、CTLA-4およびPD-1ともに自己免疫疾患を呈している

→ 動物モデルで副作用の予測はある程度可能であるが、ヒトと同一の部位に症状がみられるかは不明。またそれぞれの動物種に交差反応性を有する抗体を用いることが必要。
KO、Tgマウスの情報も有用である

検討される分子それぞれにマウス抗体およびKOマウスでの検討が必要か？
動物種での発現の違い、抗体、KO Tgマウスの有用性など