Pharmacology & Therapeutics 148 (2015) 132–153

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

The development of immunomodulatory monoclonal antibodies as a new therapeutic modality for cancer: The Bristol-Myers Squibb experience

David Berman, Alan Korman, Ronald Peck, David Feltquate, Nils Lonberg, Renzo Canetta *

Bristol-Myers Squibb, Research and Development Division, United States

ARTICLE INFO

Available online 1 December 2014

Keywords:
Immuno-oncology
T-cell receptors
Novel evaluation criteria
Ipilimumab
Nivolumab
Combinations

ABSTRACT

The discovery and increased understanding of the complex interactions regulating the immune system have contributed to the pharmacologic activation of antitumor immunity. The activity of effector cells, such as T and NK cells, is regulated by an array of activating and attenuating receptors and ligands. Agents that target these molecules can modulate immune responses by exerting antagonistic or agonistic effects.

Several T- or NK-cell modulators have entered clinical trials, and two have been approved for use. Ipilimumab (Yervoy®, Bristol-Myers Squibb) and nivolumab (OPDIVO, Ono Pharmaceutical Co., Ltd./Bristol-Myers Squibb) were approved for the treatment of metastatic melanoma, in March 2011 in the United States, and in July 2014 in Japan, respectively.

The clinical activity of these two antibodies has not been limited to tumor types considered sensitive to immunotherapy, and promising activity has been reported in other solid and hematologic tumors.

Clinical development of ipilimumab and nivolumab has presented unique challenges in terms of safety and efficacy, requiring the establishment of new evaluation criteria for adverse events and antitumor effects. Guidelines intended to help oncologists properly manage treatment in view of these non-traditional features have been implemented.

The introduction of this new modality of cancer treatment, which is meant to integrate with or replace the current standards of care, requires additional efforts in terms of optimization of treatment administration, identification of biomarkers and application of new clinical trial designs. The availability of immune modulators with different mechanisms of action offers the opportunity to establish immunological combinations as new standards of care.

Contents

Abbreviations: AE, Adverse events; APC, Antigen-presenting cell; BMS, Bristol-Myers Squibb; CR, Complete response; CTLA-4, Cytotoxic T-lymphocyte antigen 4; DTIC, Dacarbazine; EAP, Expanded Access Program; FDA, Food and Drug Administration; GITR, Glucocorticoid-induced tumor necrosis factor receptor; HRPC, Hormone refractory prostate cancer; LAG-3, Lymphocyte activation gene-3; NCI, National Cancer Institute; NK, Natural killer; NSCL, Non-small cell lung; OS, Overall survival; PD-1, Programmed death-1; PD-L1, Programmed death-ligand 1; PD-L2, Programmed death-ligand 2; PFS, Progression-free survival; PR, Partial response; PSA, Prostate-specific antigen; RFS, Relapse-free survival; SD, Stable disease; TIL, Tumor-infiltrating lymphocyte; TKI, Tyrosine kinase inhibitor; TNF, Tumor necrosis factor; U.S., United States; WHO, World Health Organization

* Corresponding author at: Bristol-Myers Squibb, 5 Research Parkway, P.O. Box 5100, Wallingford, CT 06492-7660, United States. Tel.: 203 677 6047; fax: 203 677 7924.
E-mail address: renzo.canetta@bms.com (R. Canetta).

http://dx.doi.org/10.1016/j.pharmthera.2014.11.017

1. Introduction

Engaging a patient's own immune system to prevent and/or combat diseases has been adopted for many years for chronic and acute infections (Hotchkiss & Moldawer, 2014). Analogous approaches for cancer therapy have been explored for many years, but with only a small number of successes in the last century leading to regulatory approval (interferon alfa 2A and 2B for hairy cell leukemia in 1986, intravesical Bacillus Calmette–Guérin (BCG) for recurrent, localized bladder cancer in 1989, and aldesleukin for renal cancer in 1992). Additional indications were subsequently granted to interferon alfa 2A for chronic myeloid leukemia, to interferon alfa 2B for follicular and AIDS-related non-Hodgkin's lymphoma and for resected melanoma, and to aldesleukin for metastatic melanoma (Drugs@FDA, 2014).

Within the last few years, a deeper understanding of the immune system at the molecular level has spurred a renaissance of interest and resulted in successful development for therapeutic vaccines (sipuleucel-T in 2010 for prostate cancer) and immunostimulatory monoclonal antibodies (ipilimumab in 2011, in the U.S., and nivolumab in 2014, in Japan, for metastatic melanoma). While still at the experimental level, additional immunologic therapeutic modalities involving the two classes mentioned above, as well as innovative approaches utilizing adaptive and innate immunity and modified cellular therapies, promise to further advance immuno-oncology as a mainstay in the future treatment of malignancies. In this paper we will report our direct experience in the contributions that Bristol-Myers Squibb (BMS) has made to this area of cancer research, limited to the immunomodulatory compounds that have already reached the stage of clinical development.

2. Targeting the immune checkpoints

The immune response normally begins when foreign proteins and antigens are recognized, captured and processed into peptides by antigen-presenting cells (APCs), which then present such peptides in the context of a major histocompatibility complex (MHC) to T cells. Recognition of this complex occurs via a specific T-cell receptor. However, activation of the T cell typically requires an additional signal such as the co-stimulatory interaction between the CD80 (B7.1) and CD86 (B7.2) ligands expressed by the APC and the CD28 receptor expressed by the T cell. The activation of T cells is further regulated by the balance of inhibitor (i.e. checkpoint) and co-stimulatory pathways, which are critical in healthy subjects to prevent auto-immunity (producing self-tolerance) and to protect normal tissues when the immune system is activated against a pathogen (Pardoll, 2012). Many immune checkpoint or co-stimulatory molecules regulating the interaction between ligands on the APC and receptors on the T cell have been identified (Fig. 1). The targeting of cell membrane receptors is possible with molecules such as monoclonal antibodies which can mimic or block the effect of a receptor or of a ligand and thereby enhance the immune response (Melero et al., 2013b).

2.1. Cytotoxic T-lymphocyte antigen 4 (CTLA-4)

The CTLA-4 gene was originally discovered by a French group using subtractive hybridization to identify genes enriched in cytotoxic T cells. This group showed that the gene was not constitutively expressed, but induced in activated T cells. However, initially its function was not fully understood (Brunet et al., 1987). A group of scientists at BMS first discovered that the B7 antigens, present on B-lymphocytes, are a ligand for the CD28 receptor on the T-lymphocytes (Linsley et al., 1991a). Shortly thereafter, they were able to identify CTLA-4 (also known as CD152) as a higher-affinity receptor for B7 than CD28 (Linsley et al., 1991b). This seminal work stimulated further research in the area of immunosuppression, which eventually led to the successful development of soluble CTLA-4 molecules such as abatacept (Orencia®, BMS), approved in 2005 for the treatment of rheumatoid arthritis and belatacept (Nulojix®, BMS), approved in 2011 for prophylaxis of kidney transplant rejection (Drugs@FDA, 2014). Investigators at the University of Chicago and the Dana-Farber Cancer Institute discovered that CTLA-4 can function as a negative regulator (Green et al., 1994; Walunas et al., 1994). Two groups generated CTLA-4 knock-out mice, demonstrating massive lymphoproliferation and leading to death, thereby confirming the regulatory (negative) effect of CTLA-4 on T cells (Tivol et al., 1995; Waterhouse et al., 1995).

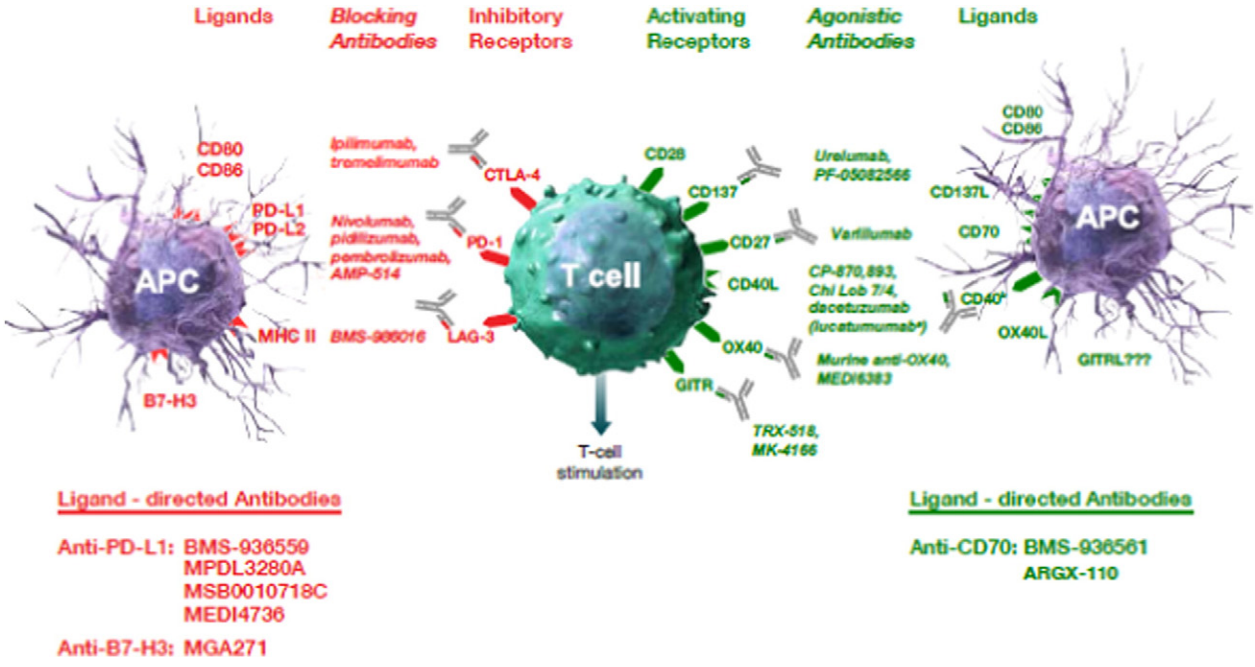

Fig. 1. Immune checkpoint modulators. [a]The antibody has shown evidence of an antagonistic effect. [b]CD40 is a member of the TNF receptor family, expressed on APCs in contrast to other members of this family which are expressed on T cells; the corresponding ligand (CD40L) is expressed on the T cell. APC: antigen-presenting cell; CTLA-4: CTLA-4: Cytotoxic T-lymphocyte antigen 4; GITR: Glucocorticoid-induced tumor necrosis factor receptor; LAG-3: Lymphocyte activation gene-3; PD-1: Programmed death-1; PD-L1: Programmed death ligand 1.