Ipilimumab

Ipilimumab (trade name **Yervoy**), is a monoclonal antibody that works to activate the immune system by targeting CTLA-4, a protein receptor that downregulates the immune system.

Cytotoxic T lymphocytes (CTLs) can recognize and destroy cancer cells. However, an inhibitory mechanism interrupts this destruction. Ipilimumab turns off this inhibitory mechanism and allows CTLs to function.[3]

Ipilimumab was approved by the U.S. FDA in 2011 for the treatment of melanoma, a type of skin cancer.[4][5] It is undergoing clinical trials for the treatment of non-small cell lung carcinoma (NSCLC), small cell lung cancer (SCLC),[6] bladder cancer[7] and metastatic hormone-refractory prostate cancer.[8]

The concept of using anti-CTLA4 antibodies to treat cancer was first developed by James P. Allison while he was Director of the Cancer Research Laboratory at the University of California, Berkeley.[9][10] Clinical development of anti-CTLA4 was initiated by Medarex, which was later acquired by Bristol-Myers Squibb. As of 2013 the cost was $120,000 for a course of treatment.[11] For his work in developing ipilimumab, Allison was awarded the Lasker Award in 2015.[12]

1 Approvals and indications

1.1 Melanoma

Ipilimumab was approved by US FDA in March 2011 to treat patients with late-stage melanoma that has spread or cannot be removed by surgery.[13][14][15] It was later approved by the US FDA on October 28, 2015 for stage 3 patients as adjuvant therapy.[16] On February 1, 2012, Health Canada approved ipilimumab for "treatment of unresectable or metastatic melanoma in patients who have failed or do not tolerate other systemic therapy for advanced disease."[17] Ipilimumab was approved in the European Union (EU), for second line treatment of metastatic melanoma in November 2012.[18][19]

2 Adverse effects

Ipilimumab treatment has been associated with severe and potentially fatal immunological adverse effects due to T cell activation and proliferation; these occur in 10-20% of people and are a major drawback of this drug.[20]

Most of the serious adverse effects are associated with the gastro-intestinal tract; they include stomach pain, bloating, constipation or diarrhea, but also fever, breathing or urinating problems. A "risk evaluation and mitigation strategy" informs prescribers of the potential risks.[15][21]

Individual cases of severe neurologic disorders following ipilimumab have been observed, including acute inflammatory demyelination polyneuropathy and an ascending motor paralysis, and myasthenia gravis.[22]

3 Interactions

The combination of ipilimumab with either leflunomide or vemurafenib may lead to increased hepatotoxicity.[23][24][25][26]

Systemic corticosteroids should be avoided before starting ipilimumab; however, systemic corticosteroids may be used to treat an immune-related adverse reaction that arises from ipilimumab treatment.[27]

Patients taking anticoagulants with ipilimumab should be monitored due to an increased risk of gastrointestinal bleeding.[27]

4 Mechanism of action

T lymphocytes can recognize and destroy cancer cells. However, an inhibitory mechanism interrupts this destruction. Ipilimumab turns off this inhibitory mechanism and allows the lymphocytes to continue to destroy cancer cells.[3]

Cancer cells produce antigens, which the immune system can use to identify them. These antigens are recognized by dendritic cells that present the antigens to cytotoxic T lymphocytes (CTLs) in the lymph nodes. The CTLs recognize the cancer cells by those antigens and destroy them. However, along with the antigens, the dendritic cells present an inhibitory signal. That signal binds to a receptor, cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), on the CTL and turns off the cytotoxic reaction. This allows the cancer cells to survive.[3]

Ipilimumab binds to CTLA-4, blocking the inhibitory signal, which allows the CTLs to destroy the cancer cells.[3][28][29][30][31][32][33] In 2014 a study indicated that the antibody works by allowing the patients' T cells to target a greater variety of antigens rather than by increasing

the number attacking a single antigen.[34]

5 Identifying patients most likely to respond

During "cancer immunoediting", tumor cells can produce antigens that provoke a reduced immune response and/or establish an immunosuppressive tumor microenvironment (TME). The latter can arise as a consequence of repeated, ineffective T cell stimulation. This triggers the checkpoint that ipilumumab targets. Many patients do not benefit from treatment, which may be related to reduced mutation load and/or missense point mutation-derived neoantigens. Tumor antigens can either be improperly expressed normal proteins or abnormal proteins with tumor-specific expression. Somatic cancer mutations can produce "nonself" tumor-specific mutant antigens (neoantigens).[35]

Sequencing and epitope prediction algorithms identified neoantigens in mouse tumors that functioned as tumor-specific T cell targets. Neoantigens were recognized by T cells in melanoma patients and were likely the major contributor to positive clinical effects of adoptive cell transfer. Mouse models established that neoantigens were the targets of T cells activated by checkpoint blockade therapy and that synthetic long peptides comprising these neoantigens were effective when administered as vaccines with CTLA-4 and/or PD-1 mAbs. Cancers with higher mutation burdens, and an associated likelihood of expressing neoantigens, appear most likely to respond to checkpoint therapy. In melanoma and certain other cancers, the numbers of mutations and neoantigens correlate with patient response. Increased PD ligand 2 (PD-L2) transcript expression and an immune "cytolytic" gene signature also correlated with neoantigen load and tumor response. CTLA-4 expression was a response indicator, which along with PD-L2 were likely expressed in tumor-infiltrating immune cells. An inflamed TME prior to treatment is also associated with response.[35]

Nearly all neoantigens in one study were patient-specific and most likely reflected mutations that do not directly contribute to tumorigenesis. However, none revealed features or motifs exclusive to responders.[35]

6 Clinical trial history

In the 2000s, ipilimumab clinical trials were underway on patients with melanoma, renal cell carcinoma, prostate cancers, urothelial carcinoma and ovarian cancer.[36] By 2007 there were two fully human anti CTLA-4[37] monoclonal antibodies in advanced clinical trials. Ipilimumab, which is an IgG1 isotype, and tremelimumab (from Pfizer) which is an IgG2 isotype.[38][39]

6.1 Melanoma

On December 10, 2007, Bristol-Myers Squibb and Medarex released the results of three studies on ipilimumab for melanoma.[40] The three studies tested 487 patients with advanced skin cancer. One of the three studies failed to meet its primary goal of shrinking tumors in at least 10.0% of the study's 155 patients. Side effects included rashes, diarrhea, and hepatitis.

In 2010, a study was presented that showed a median survival of 10 months in advanced melanoma patients treated with ipilimumab, compared with 6 months for those treated with gp100, an experimental vaccine (n=676). The one year survival rate was 46% in those treated with only ipilimumab, compared with 25% in those treated with gp100, and 44% for those receiving both.[41] The Phase III clinical studies on the drug were controversial for their unconventional use of a control arm (as opposed to using a placebo or standard treatment). The study tested ipilimumab alone, ipilimumab with gp100, and the vaccine alone. Patients had a higher survival rate with ipilimumab alone, however it is not fully clear whether the vaccine caused toxicity, which would make the drug perform better by comparison.[42][43][44] Ipilimumab gained FDA approval in early 2011.

6.2 Prostate cancer

In 2008/09 Medarex performed a phase I/II dose escalation clinical trial of ipilimumab in metastatic hormone-refractory prostate cancer (HRPC). Some of the patients with advanced prostate cancer had their tumors drastically shrink, promoting further trials.[45]

On June 19, 2009, the Mayo Clinic reported two prostate cancer patients involved in a phase II study using MDX-010 therapy who had been told initially that their condition was inoperable but had their tumors shrunk by the drug such that operation was possible and are now cancer-free as a result.[46] This press report however was criticized as premature and somewhat inaccurate. The clinical trials were still at an early stage and were run alongside other treatments – which could have been the real explanation for the tumor shrinkage.[47] It was too early to say whether ipilimumab made any difference.[48]

In 2016, a phase II study using ipilimumab and nivolumab in AR-V7-expressing metastatic castration-resistant prostate cancer was opened.[49][50] AR-V7 is an androgen receptor splice variant that can be detected in circulating tumor cells of metastatic prostate cancer patients.[50][51]

6.3 Lung cancer

Medarex ran a phase II trial of ipilimumab in addition to platinum-based chemotherapy (carboplatin) in patients

with small cell and non-small cell lung cancer.[6] It was scheduled to run from February 2008 to December 2011.

6.4 Bladder cancer

Early results of a trial in urothelial carcinoma have been reported.[52]

7 Combination trials

7.1 Advanced melanoma

To increase response rate and reduce adverse reactions, various drug combinations are being tested.

In 2013 a trial was running that compared ipilimumab alone against ipilimumab in combination with nivolumab. The response rate (tumours shrinking by at least 30%) was 58% for the combination, 44% for nivolumab alone, and 19% for ipilimumab alone.[53] This combination gained FDA approval for melanoma in Oct 2015.

In March 2014, an open-label, randomized, two agent, single center trial started combining ipilimumab with phosphatidylserine-targeting immunotherapy bavituximab for the treatment of advanced melanoma. The number of treated patients in arm A (ipilimumab plus bavituximab) was to be 16, with 8 in arm B (ipilimumab only). The trial was expected to complete in March 2016.[54][55] Previous, preclinical studies showed that PS targeting antibodies (such as bavituximab) enhance the anti-tumor activity of anti-CTLA-4 and anti-PD-1 antibodies. Tumor growth inhibition correlates with infiltration of immune cells in tumors and induction of adaptive immunity. The combination of these mechanisms promotes strong, localized, anti-tumor responses without the side-effects of systemic immune activation.[56]

8 Development

Following the 1987 cloning of CTLA-4 in mice,[57] its conservation in humans and similarities with CD28 were soon noticed.[58] CD28 at that time was a recently identified "T cell costimulatory" molecule important for T cell activation.[59] Anti-CTLA-4 blockade, the invention that gave rise to ipilimumab, was conceived by Allison and Krummel along with CTLA-4's inhibitory role in T cell activation.[60] They were able to demonstrate that CTLA-4 signaling in T cells inhibited T cell responses.[61] They then injected intact antibodies and demonstrated that CTLA-4 blockade enhanced T cell responses in mice responding to vaccines and to super antigens.[62] Leach, a new postdoctoral fellow, was tasked by Allison with applying these in tumor models. Antibody-treated mice showed significantly less cancer growth than the controls.[63]

Bluestone and Linsley separately studied the similarities between CD28 and CTLA-4. Bluestone's lab published studies, one together with Krummel and Allison, for *in vitro* studies of CTLA-4 function.[64][65] In collaboration with Mark Jenkins, they were able to see effects of anti-CTLA-4 antibodies *in vivo* in an immunization setting,[66] but did not effectively carry this into tumor biology. Linsley and colleagues had made antibodies against CTLA-4 three years prior to those of Krummel/Allison or Walunas/Bluestone. They concluded that the molecule functioned similarly to CD28 and was a "positive costimulator".[67] They apparently did not pursue CTLA-4 tumor targeting, although BMS licensed the Allison/Leach/Krummel patent though their acquisition of Medarex and the fully humanized antibody MDX010, which later became ipilimumab.

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[7] First-Line Gemcitabine, Cisplatin + Ipilimumab for Metastatic Urothelial CarcinomaClinical trial number *NCT01524991* at ClinicalTrials.gov

[8] Clinical trial number *NCT00323882* at ClinicalTrials.gov Phase I/II Study of MDX-010 in Patients With Metastatic Hormone-Refractory Prostate Cancer (MDX010-21) (COMPLETED)

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10 External links

- U.S. National Library of Medicine: Drug Information Portal - Ipilimumab
- U.S. FDA-approved Prescribing Information - ipilimumab
- Bristol-Myers Squibb Information and Support Site for "Yervoy"

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