*chapter one*

# History of Immunotherapy

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## Introduction

The promise of immunotherapy as a cancer treatment relies on using the entire immune system—its cells, molecules, and rules of engagement—to fight a cancer. Like chemotherapy and radiation, the two historical pillars of cancer treatment, immunotherapy has a long history of highs and lows. As immunotherapy research progresses at a rapid pace, it is important to understand the beginnings of this promising therapy and its significant milestones, both accomplishments and challenges, from a historical perspective. This chapter will reflect on the history of immunotherapy and establish a foundation for subsequent chapters, which will delve further into the diverse immunotherapeutic approaches for cancer.

## The First Hint Toward Immunotherapy

Immunotherapy as it is known today arose from the spirit of inquiry of pioneering scientists and, as is the case with many scientific discoveries, chance. Before the immune system and its functionality were fully understood, the first sparks of inquiry were ignited near the end of the 19th century, when a young woman presented with a unique disease state in New York City. The narrative of this woman, Bessie Dashiell, is further elucidated in *A Commotion in the Blood: Life, Death, and the Immune System* (Hall, 1997), a key text that narrates the extraordinary events that precipitated the use of the immune system to fight cancer.

In the summer of 1890, 17-year-old Dashiell was experiencing nagging pain from a wound in her hand, an injury she believed occurred when traveling across country by train. When Dashiell's wound worsened, she was

referred to Dr. William Coley, a young surgeon in New York City. On first appearance, Coley observed that Dashiell's right hand did not have the typical presentation of an infection. On closer examination, which included opening the wound, Coley found a small amount of pus and tissue that seemed "abnormally hard and more of a grayish color than normal" (Hall, 1997, p. 25). As Dashiell's pain and symptoms increased, Coley reopened the wound to find "grayish granulations" (Hall, 1997, p. 25) and a bone that appeared normal. It seemed to Coley that this was something other than an infection, and he became increasingly concerned that Dashiell had a sarcoma. A biopsy of the tissue confirmed his suspicion, revealing round cell sarcoma. The best available therapy at the time was amputation, which came with a survival rate of 1 out of 10 patients. In November 1890, two days after the biopsy results, Coley performed an amputation of Dashiell's right arm below the elbow (Hall, 1997). Following the amputation, however, Dashiell's disease spread rapidly, and tumors appeared throughout her body. Her symptoms were managed with the best supportive care available at that time, but in January 1891, with Coley at her bedside, Dashiell died of her disease at the age of 18 (Hall, 1997).

Dashiell's dramatic suffering, accelerated decline, and death at such a young age had a profound effect on two people very close to her. John D. Rockefeller Jr., an American financier and philanthropist, considered Dashiell his adopted sister (Hall, 1997). Her death was a great shock to him, and he focused much of his philanthropic work after her death on health care and cancer research. Specifically, he supported Coley's work and made significant donations to what is now known as Rockefeller University and the Memorial Sloan Kettering Cancer Center (Hall, 1997).

Coley was so affected by Dashiell's death that he referred to her case nearly 50 years later in his last scientific paper, stating that it had left a "deep impression" on him (Hall, 1997, p. 29). His determination to prevent the same fate in others led Coley through a scientific journey that began with a retrospective chart review to gain a baseline understanding of sarcoma treatments and outcomes. He identified and reviewed 90 cases of sarcoma over the previous 15 years. One particular case stood out that involved a man in his thirties with round cell sarcoma, the same malignancy as Dashiell. The patient had four tumors on his neck and face and needed multiple surgeries, the last so extensive that it required skin grafts, which ultimately failed. Following his last operation, the patient developed erysipelas, a common infection at the time believed to be caused by *Streptococcus pyogenes* (Hall, 1997). The patient experienced two occurrences of this infection, but remarkably, his disease disappeared, and his large wound healed.

Coley was so intrigued by this case that he started his own epidemiologic investigation, searching for the patient among New York City's tenement buildings. Surprisingly, he found the patient alive and well years after his cancer diagnosis. Coley concluded that if an accidental

infection could lead to complete regression of this patient's sarcoma, it seemed fair to assume that the same could occur when an infection was artificially produced (Hall, 1997).

Through research, Coley found a history of manipulating the immune system, either deliberately or accidentally, to treat illness. One paper identified 14 cases of patients with a malignant disease who also came down with erysipelas. Five of the cases were sarcoma, three of which were either fully or permanently cured (Hall, 1997). Based on his experience and the literature, Coley made the decision to inoculate the next patient with inoperable sarcoma presented to him.

In May 1891, just months after Dashiell's death, Coley was introduced to a patient with an inoperable sarcoma of the neck and a large tonsil tumor. The patient was unable to talk or eat solids and could barely swallow liquids. He had previous surgeries on his neck tumor, which left an open wound that would not heal. Coley injected cultures of erysipelas into the patient and his wound. The injections occurred in the patient's apartment, as hospitals were reluctant to host the experiment because of the infection risk to other patients and staff. The inoculations did not work at first, forcing Coley to test different preparations for months; however, he eventually induced a full infection. As a result, the patient had a complete disappearance of his neck tumor and a decrease in the size of his tonsil tumor. The patient lived for eight more years before dying of a local recurrence (Hall, 1997).

Coley experimented with the use of infections to treat cancer for the rest of his career. He eventually progressed from using live bacteria to using heat-killed bacteria, a treatment that became known as Coley toxins (Tontonoz, 2015). Coley was investigating this phenomenon at a time when little was known about the immune system or how it worked. No one, including Coley, had an explanation as to how exactly the toxins worked. Other investigators attempted to use Coley toxins to treat patients, but none were as successful (Hall, 1997). Coley was developing this therapy at a time when radiation was introduced as a treatment option. Unlike Coley toxins, which worked sporadically with an unknown mechanism of action, radiation therapy was successful in most patients (Tontonoz, 2015). This led most cancer specialists to dismiss Coley toxins as a treatment option. Coley continued his research but was never able to see his toxins become a standard treatment for cancer.

## 1900s–1980s: From Coley Toxins to a Renewed Look at Immunotherapy

Despite the development of radiation therapy and chemotherapy as standard treatments for cancer, scientists remained intrigued by

the underlying mechanisms of Coley toxins that led to responses in some patients (Balkwill, 2009). In the 1930s and 1940s, animal studies showed that bacteria caused tumor necrosis and that serum from endotoxin-treated tumors could be reintroduced to tumors (O'Malley, Achinstein, & Shear, 1962). The serum caused the tumors to necrose, leading investigators to state that it contained a "tumor necrotizing factor" (O'Malley et al., 1962). Later research discovered that tumor destruction was caused by host cells in response to the endotoxin and *not* by the endotoxin itself, leading to the modified term *tumor necrosis factor* (TNF) (Carswell et al., 1975). TNF was initially thought to be an important new treatment for patients with cancer, and research on the subject progressed rapidly. Unfortunately, systemic TNF administration was found to be associated with unacceptable severe toxicity and side effects, including fever, headache, rigor, hypotension, and pulmonary edema (Balkwill, 2009; Morice, Blick, Ali, & Gutterman, 1987). Research also emerged that TNF may stimulate tumor growth (Leibovich et al., 1987). Because of these associations, its use in cancer treatment has been severely limited.

Around the time that Coley was working on his theory of infection and cancer regression, two Frenchmen—Albert Calmette, a bacteriologist, and Camille Guérin, a veterinarian—were on a lifelong quest to develop a vaccine against tuberculosis (TB) (Herr & Morales, 2008). Calmette and Guérin isolated a virulent strain of *Mycobacterium bovis* (closely related to the human strain of TB) and worked years to make *tubercle bacillus* nonvirulent and genetically stable. The unique strain they developed was named bacillus Calmette-Guérin, or BCG, after the two scientists (Herr & Morales, 2008). In the early 1920s, Calmette and Guérin administered an oral form of the vaccine to children in Paris, none of whom developed TB. In 1929, researchers at Johns Hopkins noted a lower incidence of cancer in patients with TB, and later research found antitumor effects against several malignant cell lines after immunization with BCG (Alcorn, Burton, & Topping, 2015).

Unfortunately, a tragedy put the promise of BCG as a cancer therapy on hold. From 1929 to 1933, a laboratory error led to the continued vaccination of 251 German babies with a preparation of BCG that was contaminated with a virulent strain of TB. A total of 173 babies developed TB, and 72 died in what became known as the Lübeck disaster (Herr & Morales, 2008). Because of this tragedy, enthusiasm for BCG as a cancer therapy dampened for more than three decades.

In the 1950s, Dr. Lloyd Old conducted studies that provided the first direct evidence that BCG had antitumor effects (Herr & Morales, 2008; Old, Clarke, & Benacerraf, 1959). BCG was further studied clinically by international investigators as a treatment for leukemia and melanoma, as well as for lung, prostate, bladder, colon, and kidney cancer; however,

the early promise of BCG as an effective treatment was unfulfilled, and it was soon replaced by other treatment options for most cancer types (Herr & Morales, 2008). Alvaro Morales, a urologist from Canada, indicated a notable exception when he published the first use of intravesicular BCG against superficial bladder cancer in 1976 (Morales, Eidinger, & Bruce, 1976). The schedule and dosing for BCG in this study were scientifically based, and preliminary results persuaded the National Cancer Institute to fund randomized controlled trials to test the effectiveness of a BCG regimen in superficial bladder cancers (Camacho, Pinsky, Kerr, Whitmore, & Oettgen, 1980; Lamm et al., 1980). These trials found that BCG was markedly effective in reducing the frequency of tumor recurrence compared to a control group treated with surgery alone (Herr & Morales, 2008). In 1990, with data from more than 2,500 cases worldwide, the U.S. Food and Drug Administration (FDA) approved the use of BCG in patients with superficial bladder cancer. Today, BCG remains the standard treatment for high-grade noninvasive bladder cancer (Herr & Morales, 2008). In 1999, Taniguchi et al. noted that BCG induces both a local and systemic immune response associated with the elimination or reduction of cells linked to non-muscle invasive bladder cancer.

## 1980s–Present: Immunotherapy Comes of Age

Immunotherapy research over the past 40 years has resulted in synchronous advancements in both bench and translational science. Timelines related to immunotherapy have been published and include notable scientific and treatment advances (see Bachireddy, Burkhardt, Rajasagi, & Wu, 2015; Cancer Research Institute, n.d.; Pardoll, 2011; Parish, 2003). Additional institution-specific timelines are also available (see Johns Hopkins Medicine, n.d.; Memorial Sloan Kettering Cancer Center, n.d.).

### 1980s: Conflicting Scientific Evidence Highlights a Decade of Immunotherapeutic Uncertainty

As research emerged on the role of the immune system as a mediator to cancer, opinions and attitudes toward cancer immunotherapy changed. In the 1970s, scientific evidence contradicting the capacity for immune-driven mediation of tumors resulted in the perception of cancer immunotherapy as an ineffectual treatment approach (Parish, 2003; Stutman, 1975, 1979a, 1979b). Specifically, studies demonstrated that T-cell–deficient mice and syngeneic wild-type mice had a similar incidence of tumor occurrence, negating the implication of

T-cell–facilitated immunosurveillance in preventing tumors (Parish, 2003). Immunotherapy research regained traction in the 1980s, when a study demonstrating the capacity of autoreactive T cells to escape thymic deletion and a study discussing the potential of tumor-associated antigens to mediate immunosurveillance contradicted previous findings (Parish, 2003). Among these new findings was the identification of cancer antigens in melanoma, which suggested the possibility of targeted immune therapies (Houghton, Eisinger, Albino, Cairncross, & Old, 1982; Houghton, Thomson, Gross, Oettgen, & Old, 1984; Livingston et al., 1985). In addition, the first studies suggesting T cells could be used to attack tumors, specifically malignant melanoma, were conducted (Knuth, Danowski, Oettgen, & Old, 1984), leading to the identification of cytotoxic T-lymphocyte antigen 4 (CTLA-4) (Brunet et al., 1987). This discovery would become the foundation for the development of checkpoint inhibitors.

Perhaps most profound was further research involving interleukin-2 (IL-2), which was first discovered in 1976 (Morgan, Ruscetti, & Gallo, 1976). In 1984, IL-2 was identified as an immunologic-based treatment in the management of a 33-year-old woman with metastatic melanoma. The patient demonstrated complete tumor necrosis and no evidence of disease following recombinant IL-2 administration (Rosenberg, 2014). This result was further validated in a study by the National Cancer Institute, in which escalating doses of IL-2 in patients with metastatic melanoma and renal cell cancer demonstrated tumor regression in those who had previously failed standard-of-care treatment (e.g., chemotherapy, surgery, radiation) (Rosenberg et al., 1985). In 1992, based on the durability of response seen in multiple trials, FDA approved high-dose IL-2 for the treatment of patients with metastatic renal cell cancer (Rosenberg, 2007). A series of studies of high-dose IL-2 in melanoma had an overall response rate of 16% and led to the approval of high-dose IL-2 for advanced melanoma in 1998 (Amin & White, 2013). IL-2 was also explored as a contributor to adoptive cell therapy in the stimulation of human tumor-infiltrating lymphocytes (Rosenberg, Spiess, & Lafreniere, 1986). The positive responses seen with IL-2 demonstrated to scientists and clinicians that immunologic manipulation was possible and could lead to the regression of cancers. This established IL-2 as a foundation of modern immunotherapy.

## 1990s: The Reemergence of Immunosurveillance Drives a Decade of Progressive Discoveries in Bench Science

The discovery of immunogenicity in IL-2 led to a rapid progression of the science in the 1990s. This decade contributed to many of the recent immunotherapeutic breakthroughs, including the scientific

establishment of immunosurveillance through several bench studies. Key clinical questions addressed the lack of costimulatory molecules for tumors cells (necessary for the initiation of immune response) and the potential for a T-cell tolerance that would prevent tumor-specific immunity (Allison & Krummel, 1995; Parish, 2003; Schwartz, 1992). Further exploration examined tumor immunosurveillance with natural killer (NK) cells, NK T cells, and gammadelta T cells (Girardi et al., 2001; Lanier, 2001; Smyth, Godfrey, & Trapani, 2001; Smyth, Thia, Street, Cretney, et al., 2000). The identification of a modulator, namely dendritic cell maturation in response to microbial and proinflammatory mediators, provided insight into the relationship between innate and adaptive immune responses (Cella, Engering, Pinet, Pieters, & Lanzavecchia, 1997; Pierre et al., 1997). This led to the use of dendritic cells in cancer vaccines to facilitate tumor-specific T-cell immunity, which demonstrated induction of antitumor immune responses across diverse tumor types (Brossart, Wirths, Brugger, & Kanz, 2001; Brugger et al., 2001; Mukherji et al., 1995; Parish, 2003; Steinman & Dhodapkar, 2001). Type 1 interferons were also explored because of their relationship with NK cells, cytotoxic T lymphocytes, and macrophages, which signal and engage an immune response that can be directed toward tumor cells, specifically targeting the Janus kinase (JAK) inhibitors and signal transducer and activator of transcription (STAT) pathways (Constantinescu et al., 1994; Lee & Margolin, 2011). Further, Janus kinase 3, or JAK-3, was discovered to be coupled to the IL-2 receptor in human peripheral blood T cells and NK cells (Johnston et al., 1994). The discovery of NY-ESO-1 (Chen et al., 1997), a cancer/testis antigen associated with advanced melanomas, contributed to a rapid progression in diverse immunotherapeutic treatments, as this antigen can be targeted for vaccine-induced tumor response (Gnjatic et al., 2006). The GVAX vaccine (Dranoff et al., 1993), first developed in 1989, proceeded with promising clinical trials for pancreatic and non-small cell lung cancers in the 2000s ("Cell Genesys," 2002; Nemunaitis, 2003, 2005). Monoclonal antibodies also emerged as a treatment option for patients with solid tumors (Minasian et al., 1994). In 1997, rituximab (Rituxan®) was the first monoclonal antibody approved for treatment of malignancies, specifically non-Hodgkin lymphoma (Ribatti, 2014). The use of interferon alfa was explored in clinical trials throughout the decade as treatment for melanoma, though results were mixed (Lee & Margolin, 2011). Although the use of interferon alfa as an adjuvant agent produced results in relapse-free survival, significant improvements in overall survival were observed in only 4 out of 14 studies (Eggermont, 2001; Mocellin, Pasquali, Rossi, & Nitti, 2010). Interferon alfa-2b (Intron A®) was first approved for hairy cell leukemia in 1986, with subsequent

approvals as adjuvant therapy for malignant melanoma in 1995 and treatment of follicular lymphoma in 1997 (Ningrum, 2014).

## 2000s: Discoveries at the Bench Translate to Immunotherapeutic Advances at the Bedside

The 21st century witnessed dramatic discoveries at the bench and rapid acceleration of clinical trials, resulting in new and emerging immunotherapeutic treatment options. Several new classes of agents were either introduced in clinical trials or received FDA approval during this period (see Table 1-1). Immunotherapeutic approaches include cytokines, monoclonal antibodies, checkpoint inhibitors, vaccines, and adoptive cell transfer.

### *Cytokines (Interferons)*

The theory of cancer immunosurveillance was revisited based on laboratory data demonstrating increased susceptibility to B-cell lymphomas in mice lacking interferon gamma, interferon gamma receptors, or interferon gamma–producing cells (Shankaran et al., 2001; Smyth, Thia, Street, Cretney, et al., 2000; Smyth, Thia, Street, MacGregor, et al., 2000). This was further evidence of the presence of immunosurveillance and further justification for the exploration of targeted and immunotherapeutic approaches to cancer treatment. The neoadjuvant effects of interferon alfa-2b were revealed as the result of an indirect immunomodulatory mechanism in a trial of patients with stage IIIB melanoma (Moschos et al., 2006). This led to FDA approval of peginterferon alfa-2b (PegIntron®) for metastatic melanoma in 2011.

### *Monoclonal Antibodies*

Although monoclonal antibodies have been present since the FDA approval of muromonab-CD3 in 1986, the emergence of trastuzumab (Herceptin®) and rituximab in the 1990s revolutionized cancer treatment. As of the time of this writing, 30 monoclonal antibodies are approved for a diversity of treatment indications (Buss, Henderson, McFarlane, Shenton, & de Haan, 2012). Most notably in cancer care, tositumomab (Bexxar®) was approved for the treatment of non-Hodgkin lymphoma in 2003. This was followed in 2004 by bevacizumab (Avastin®) and cetuximab (Erbitux®) for the treatment of metastatic colorectal cancer. In 2010, brentuximab (Adcetris®), a targeted agent, was approved for treatment of relapsed/refractory classical Hodgkin lymphoma and systemic anaplastic large-cell lymphoma. Obinutuzumab (Gazyva®) was approved for the treatment of chronic lymphocytic leukemia in 2013 and follicular lymphoma in 2016. In 2014, blinatumomab (Blincyto®) was approved for the treatment of relapsed/refractory B-cell acute lymphoblastic leukemia (ALL).

**TABLE 1-1 Timeline of Immunotherapeutic Agents Approved by the U.S. Food and Drug Administration**

| Agent | Indications |
|---|---|
| **Checkpoint Inhibitors** | |
| Atezolizumab (Tecentriq®) | Bladder cancer (2017), lung cancer (2017) |
| Axicabtagene ciloleucel (Yescarta®) | B-cell non-Hodgkin lymphoma (2017) |
| Ipilimumab (Yervoy®) | Metastatic melanoma (2011) |
| Ipilimumab (Yervoy) + nivolumab (Opdivo®) | Advanced melanoma (2015) |
| Nivolumab (Opdivo) | Bladder cancer (2017), follicular lymphoma (2016), head and neck cancer (2016), kidney cancer (2015), lung cancer (2015), melanoma (2014) |
| Pembrolizumab (Keytruda®) | Adult and pediatric lymphoma (2017), head and neck cancer (2016), lung cancer (2016, 2015) |
| Tisagenlecleucel (Kymriah®) | Pediatric and young adult acute lymphoblastic leukemia (2017) |
| **Cytokine Therapies** | |
| Interferon alfa-2b (Intron A®) | Follicular lymphoma (1997), malignant melanoma (1995), hairy cell leukemia (1986) |
| Interleukin-2 (aldesleukin; Proleukin®) | Metastatic melanoma (1998), metastatic kidney cancer (1992) |
| Peginterferon alfa-2b (Sylatron®) | Melanoma (2011) |
| **Monoclonal Antibodies** | |
| Alemtuzumab (Campath-1H®) | Chronic lymphocytic leukemia (2001) |
| Basiliximab (Simulect®) | Prophylaxis for transplant rejection (1998) |
| Bevacizumab (Avastin®) | Metastatic colorectal cancer (2004) |
| Blinatumomab (Blincyto®) | B-cell acute lymphoblastic leukemia (2014) |
| Cetuximab (Erbitux®) | Metastatic colorectal cancer (2004) |
| Daclizumab (Zenapax®) | Prophylaxis for transplant rejection (1997) |
| Daratumumab (Darzalex®) | Expanded access for myeloma (2016), multiple myeloma (2015) |
| Elotuzumab (Empliciti™) | Multiple myeloma (2015) |

*(Continued on next page)*

**TABLE 1-1 Timeline of Immunotherapeutic Agents Approved by the U.S. Food and Drug Administration *(Continued)***

| Agent | Indications |
|---|---|
| **Monoclonal Antibodies *(cont.)*** | |
| Gemtuzumab (Mylotarg®) | Leukemia (2000) |
| Ibritumomab tiuxetan (Zevalin®) | Non-Hodgkin lymphoma (2002) |
| Muromonab-CD3 (Orthoclone OKT3®) | Prophylaxis for transplant rejection (1986) |
| Obinutuzumab (Gazyva®) | Follicular lymphoma (2016), chronic lymphocytic leukemia (2013) |
| Ofatumumab (Arzerra®) | Leukemia (2016), chronic lymphocytic leukemia (2010) |
| Olaratumab (Lartruvo®) | Sarcoma (2016) |
| Panitumumab (Vectibix®) | Metastatic colorectal cancer (2006) |
| Pertuzumab (Perjeta®) | HER2-positive breast cancer (2012) |
| Ramucirumab (Cyramza®) | Stomach cancer (2014) |
| Rituximab (Rituxan®) | Non-Hodgkin lymphoma (1997) |
| Tositumomab (Bexxar®) | Non-Hodgkin lymphoma (2003) |
| Trastuzumab (Herceptin®) | HER2-positive breast cancer (2006), metastatic breast cancer (1998) |
| **Oncolytic Viral Therapies** | |
| Human papillomavirus vaccine (Cervarix®) | Human papillomavirus linked to cervical cancer (2009) |
| Oncophage (Vitespen®) | Kidney cancer (2008) |
| Quadrivalent human papillomavirus recombinant vaccine (Gardasil®) | Human papillomavirus linked to cervical cancer (2006) |
| Sipuleucel-T (Provenge®) | Prostate cancer (2010) |
| Talimogene laherparepvec (Imlygic®) | Melanoma (2015) |
| **Targeted Therapies** | |
| Brentuximab vedotin (Adcetris®) | Hodgkin and anaplastic large-cell lymphoma (2011) |
| Vemurafenib (Zelboraf®) | Advanced melanoma (2011) |

*Note.* Based on information from National Cancer Institute, 2018.

### *Checkpoint Inhibitors*

The discovery of cellular checkpoints contributed to the introduction of checkpoint inhibitors. A CTLA-4–specific antibody is identified as an immune checkpoint inhibitor associated with clinical regression in melanoma and immune-mediated toxicities (Egen, Kuhns, & Allison, 2002). In 2002, the first clinical trials of monoclonal antibodies to induce CTLA-4 blockade were conducted in renal and prostate cancers (Fong & Small, 2008; Small et al., 2007; Yang et al., 2007). This led to FDA approval of ipilimumab (Yervoy®) in 2011 for the treatment of melanoma (Hodi et al., 2010; Pennock, Waterfield, & Wolchok, 2012; Wolchok et al., 2010).

Programmed cell death protein 1 (PD-1), previously identified as being directly involved in cell death (Agata et al., 1996), was identified as an immune checkpoint in bench studies (Nishimura, Nose, Hiai, Minato, & Honjo, 1999). These studies included identification of PD-1's two ligands, programmed cell death-ligand 1 (PD-L1) and programmed cell death-ligand 2 (PD-L2) (Tseng et al., 2001).

In 2010 alone, nivolumab (Opdivo®) was tested in early clinical trials (Brahmer et al., 2010); ipilimumab demonstrated survival advantage for patients with advanced melanoma (Friedlander & Hodi, 2010; Hodi et al., 2010); and exploration of the PD-1 checkpoint blockade demonstrated tumor regression in melanoma and in renal, lung, and colon cancers (Brahmer et al., 2010). Nivolumab (BMS-936558) demonstrated dramatic results across cancer types in a phase 1 trial (Topalian et al., 2012). In 2013, it was approved for relapsed/refractory classical Hodgkin lymphoma after stem cell transplantation and brentuximab.

Pembrolizumab (Keytruda®) was granted accelerated approval in 2014 for advanced or unresectable melanoma. It was the first PD-1 inhibitor cleared in the United States. In 2015, the first combination therapy for melanoma, ipilimumab plus nivolumab, was FDA approved (Wolchok et al., 2013). In the same year, nivolumab alone was FDA approved for advanced renal cell carcinoma (George et al., 2016; Motzer et al., 2015). Nivolumab and ipilimumab used in combination produced a 60% response rate in patients with melanoma (Larkin, Hodi, & Wolchok, 2015). These agents continue to be explored individually and in combination for diverse diagnoses.

### *Vaccines*

The development and testing of a vaccine to prevent human papillomavirus (HPV)–associated cancers demonstrated a durable response in women with HPV 16–positive vulvar intraepithelial neoplasia, resulting in the first FDA-approved HPV vaccination (Gardasil®) in 2006 (Kenter et al., 2009). In 2014, granulocyte macrophage–colony-stimulating factor–secreting allogeneic pancreatic tumor cells (GVAX Pancreas) and

the CRS-207 cancer vaccine demonstrated survival benefit for patients with pancreatic cancer in a phase 2 multicenter trial (Le et al., 2015). In 2015, talimogene laherparepvec (Imlygic®) was FDA approved for intralesional injection in patients with melanoma (Johnson, Puzanov, & Kelley, 2015). Research has also explored the role of viral therapies in patients with brain tumors (Martin, 2017).

### *Adoptive Cell Therapy*

In the early 2000s, T cells were further explored for therapeutic purposes, including the use of adoptive T-cell therapies to produce tumor regression in melanoma (Dudley et al., 2002; Yee et al., 2002) and for the development of chimeric antigen receptor (CAR) T cells (Sadelain, Brentjens, & Rivière, 2013). This exploration also included attention to the expanding role of IL-2 with high-dose chemotherapy to facilitate adoptive cell transfer, which contributes to objective cancer response and proliferation of transferred cells (Dudley et al., 2002; Rosenberg, 2014). Genetically engineered T cells were used to induce clinical responses in patients with B-cell lymphomas (Till et al., 2008), and genetically modified T cells were observed to produce durable response in patients with chronic lymphocytic leukemia (Kalos et al., 2011; Porter, Levine, Kalos, Bagg, & June, 2011). In 2013, clinical trials of CAR T-cell therapies produced dramatic results, attaining a complete response in patients with B-cell ALL (Brentjens et al., 2013), an 89% response rate in children and adults with ALL (Grupp et al., 2013; Maude et al., 2014), and a 92% response rate in patients with aggressive non-Hodgkin lymphoma (Kochenderfer et al., 2015). In 2017, tisagenlecleucel (Kymriah®), a CAR T-cell therapy, was approved for pediatric and young adult ALL, becoming the first FDA-approved treatment of its kind.

## Summary

Immunotherapy is well established as both a field for rich scientific discovery and an opportunity for accelerated cancer treatments. Clinical trials have contributed to rapid exploration of safety, efficacy, and survival outcomes for several key immunotherapeutic agents. The robust advances of immunotherapy over the past two decades will only be further accelerated by the National Cancer Moonshot Initiative, which prioritizes collaborative approaches to developing, testing, and evaluating immunotherapeutic agents (Singer, Jacks, & Jaffee, 2016). The Cancer Moonshot emphasizes the importance of symptom management, a robust area for nursing contribution (Ginex, Brassil, & Ely, 2017). Future immunotherapy research may focus on exploration of combination therapies (Bernier, 2016; Jiang & Zhou, 2015), the use of existing agents with new

disease presentations, the late effects and long-term sequelae of newly approved therapies, and the evaluation of the cost and sustainability of these therapies off protocol. A focus on the *types* of patients that respond to immunotherapeutic agents will be imperative to expanding the potential benefits of these treatment types to a broader population.

As this science advances, so too will questions concerning how immunotherapy physiologically and psychologically affects patients. Nurses have had an integral role in the clinical care of patients receiving these agents and are well positioned to address these concerns through research, clinical practice, and education.

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