SCIENCE SERIES

Learning From Our Aging Population: Studying Immune Checkpoint Inhibitors Sheds New Light on the Changing Immune System

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ABSTRACT

The aging of the Baby Boomer generation and the general rise in life expectancy continue to expand the proportion of older adults (≥65 years of age) across global and US populations. As the adult years progress, so do the chances for a diagnosis of cancer. The need to determine whether evolving trends in cancer treatment benefit an aging population is vital. Immune checkpoint inhibitors (ICIs) represent a radically new approach in modern cancer treatment. They target the immune system instead of the disease and unleash the body's natural defenses against tumor growth. ICIs are valued for their reduction in toxicity and superior treatment effect compared with many conventional therapies. Although clinical trial results show generally comparable efficacy and safety in younger and older populations, the proportion of older cancer trial participants does not accurately reflect the general population. This article describes the body's cycle of immunity in combatting mutations and how ICIs can aid the most vulnerable aspect of that cycle. The article discusses the challenges and possible opportunities in an aging immune system, the immune-related side effects of ICIs, and the role of genomic biomarkers in predicting response to treatment. Regulators and activists are advocating for better representation of older patients in clinical trials; however, comprehensive investigation into the risks and benefits of immune-modulating therapies for this growing population is still needed.

Not long after World War II, an unprecedented bloom in the birth rate gave rise to the Baby Boomer generation. In recent decades, medical advances have made 100-year birthdays almost commonplace. Today, there are approximately 50 million people aged 65 years or older living in the United States. They make up more than 15% of the total population,[1,2] up from 10% in 1970. By 2060, predictions nearly double to 95 million,[3] bringing the portion of older Americans to a quarter of the total population.[4] In other countries, the hike has been even steeper; in Japan, the older population is already a quarter of the total population, up from 7% in 1970. And in Germany, the figure is 21%, up from 13% in 1970.[4]

As we age, the number and frequency of genetic mutations that can transform into cancers multiply. In fact, after the age of 50, the likelihood of a cancer diagnosis climbs dramatically until the later 80s (Figure 1).[5] Currently in the United States,

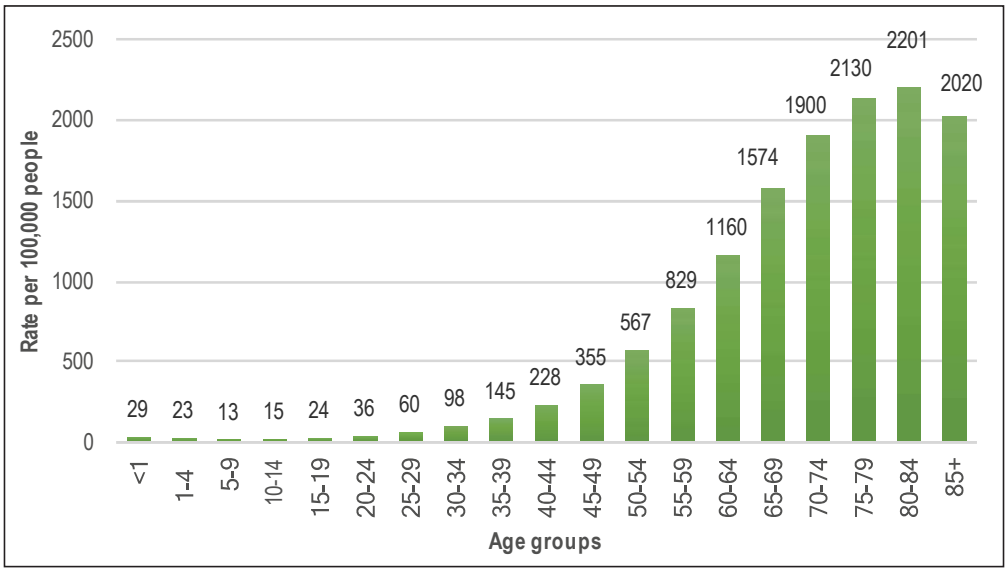


Figure 1. Incidence of cancer diagnosis in the United States by age. Data are from the US Cancer Statistics Working Group.[5]

the median age for cancer diagnoses is 66 years,[6] and by 2030, it is estimated that 70% of cancers will occur in those 65 and older.[7] Given these trends, understanding how emerging cancer treatments benefit an older population becomes critical.

ENTER THE IMMUNE CHECKPOINT INHIBITORS

In recent years, breakthrough immunotherapies launched a flank attack in the seemingly endless war against cancer, and further developments are unfolding rapidly. Unlike chemotherapies that essentially assault all rapidly growing cells, and unlike targeted therapies (eg, tyrosine kinase inhibitors) that interrupt cellular signaling to restrict tumor growth,[8] immunotherapies target the immune system instead of the disease.

Among the various attempts to fortify the immune system's power against cancer, immune checkpoint inhibitors (ICIs) have gained the widest attention for improving efficacy and reducing toxicity. Direct-to-consumer advertisements now frequent American television, promoting KEYTRUDA (pembrolizumab) and OPDIVO (nivolumab) among other ICIs. Announcements of US Food and Drug Administration (FDA) approvals chime routinely across pharmaceutical and financial news for a litany of indications, from non–small cell lung cancer (NSCLC) to bladder cancer. In October 2018, immuno-oncology took center stage with the announcement of Drs James Allison and Tasuku Honjo being awarded the Nobel Prize in Physiology or Medicine "for their discovery of cancer therapy by inhibition of negative immune regulation."[9] A burly, blues-playing Texan, Allison developed the first approved ICI, cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) monoclonal antibody. The approval of ipilimumab for advanced or metastatic melanoma initiated the cascade of later approvals, most of which sprang from Honju's discovery of the programmed cell death protein type 1 (PD-1) and correlating ligand (PD-L1) checkpoint.

ICIs have raised the bar for oncology therapeutics, delivering previously unseen rates of long-term durable response and stability. However, their effect as monotherapies still reaches only a portion of patients, with clinical trial objective response rates typically running from 35% to 40%.[10] Nevertheless, whether ICIs offer substantial promise for an aging population has not received focused investigation.

OLDER PATIENTS ARE UNDERREPRESENTED IN CLINICAL TRIALS

Historically, cancer trials have not enrolled older participants at levels reflecting comparable real-world demographics. In 2004, 36% of participants were ≥65 years old compared with 60% of those diagnosed ($P < .001$),[11] yet this had improved from 25% compared with 63% ($P < .001$) in 1999.[12] Common health complications in older patients can represent barriers to clinical trial enrollment. Furthermore, data from clinical trial participants ≥65 years of age may not mirror actual outcomes for the general population.[13] Older adults not only exhibit wide-ranging differences due to genetic predisposition, environmental conditions, and lifestyle habits but also may present with various coexisting diseases, concomitant medications, or poorer performance status than their younger counterparts. Complications often include other disorders related to immune decline, such as infections and cardiovascular disease. Frequently, preexisting chronic conditions confound the early detection of cancers in older adults, often causing unfortunate diagnostic delays.

Research and advocacy groups have begun earnestly pursuing solutions to the disparity. The FDA and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) now warn against unjustified exclusions (eg, >75 years of age), once commonplace.[14,15] Recent recommendations from the American Society of Clinical Oncology and Friends of Cancer Research call for a loosening of eligibility criteria to allow prior or concurrent malignancies—as long as such provisions would not compromise safety and efficacy endpoints[16]; the American Society of Clinical Oncology also advocates for the inclusion of special subgroup analyses to better inform cancer management for older adults.[15]

IMMUNOSENESCENCE AND "INFLAMMAGING"

The traditional concept of immunosenescence considers immune aging as a progressive and unavoidable degeneration, associated with an increase in infections and autoimmune reactions. Over time, the production, cytotoxicity, and endurance of T cells lessen, and the power of the innate immune system declines.[17] A characteristic low-level inflammation ("inflammaging") resulting from decades of exposure to allergens, viruses, and other antigens induces greater concentrations of inflammatory cytokines. The normal shrinking of the thymus (from which T cells originate) in adulthood and its eventual transition into fatty tissue reduces the production of naive T cells in older adults.

An emerging perspective now challenges the conventional notion of immunosenescence, however.[18,19] Some researchers advocate for distinguishing between normal immune aging and maladaptive immune aging and further suggest that the label *immunosenescence* be retired.[20] This new view considers the possibility that immune aging may be more of a valuable adaptation than a blanket downfall. New data suggest that although immune changes do result in disease, they may work to extend survival and foster longevity when interpreted from an evolutionary context.[17] Researchers in aging immunity from Stanford University investigating the differences between healthy and maladaptive immune aging summarize

these changes as an evolutionary variation in homeostasis—"sometimes necessary and beneficial and sometimes harmful to the aging host."[21] Although "teaching old dogs new tricks" may become harder with the decline of naive T cells brought on by aging, evidence suggests that a healthy aging system may act to compensate for thymic involution and other age-related changes.[19]

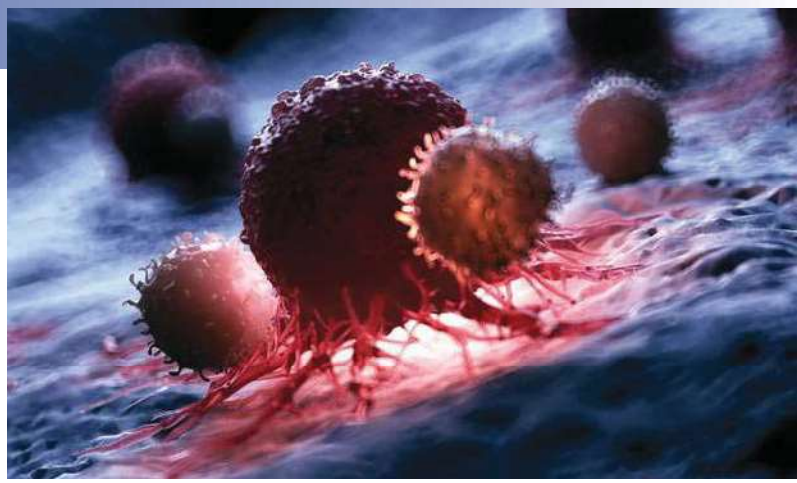
THE PROTAGONIST IN THE CHECKPOINT STORY: THE T CELL

James Allison describes the intervention of ICIs as "unleashing" the immune system's dynamic response to disease.[22] Allison credits these advances not to a greater understanding of the disease process but to the in-depth investigation into the workings of T cells. Fifty years ago, the distinction of the T cells and the involvement of the thymus were still radical notions.[23] Today, an elaborate understanding of the T cell's mutable nature is still unfolding.[24] From a naive state, T cells differentiate and diversify, adapting after each encounter with a new antigen. In this way, an "intelligence" develops, with some becoming memory T cells. Enabled by cytokine interleukin-7, they are equipped for future specialized combat. T cells can be categorized into 3 types:

- **Cytotoxic T cells** ($CD8^+$ T cells) assault cancer cells, other pathogens ("non-self"), and damaged cells that could disrupt the balance of health.
- **Helper T cells** ($CD4^+$ T cells) activate cytotoxic T cells and other lymphocytic functions.
- **Regulatory T cells** (Tregs; also called suppressor T cells) avert autoimmune abandon by suppressing immunity and protecting "self."

THE CYCLE OF CANCER IMMUNITY: WHAT GOES WRONG AND HOW ICIs HELP

The role of the immune system is to maintain the body's homeostasis, the workings of which some have compared with driving a car. To maintain control, the driver applies the gas and brake pedals in a complex interchange in response to road conditions. Likewise, not only must the immune system mount attacks to keep pace with any new mutations or other malignant antigens, but it must also suppress autoimmune momentum to avoid damaging the body. The "brakes" of the process, the immune checkpoints, are the vulnerable aspect of the cancer-immunity cycle (Figure 2).[25] Cancer cells can bypass these regulatory pathways, flying under the surveillance radar by passing as self instead of non-self.



T-cell lymphocytes advancing against a tumor cell. Image: ©Sebastian Kaulitzki/stock.adobe.com.

As part of an intricate exchange between the innate and adaptive processes to search for and destroy tumor cells (immunosurveillance), the primed T cell then divides, proliferates, and disperses a trained T-cell brigade into the bloodstream to patrol for and eliminate the tumor cells. At this point, tumor cells may enter into immune-editing, co-opting the mechanism that protects against autoimmune assault. Once tumor cells evade elimination, they can remain seemingly dormant (in equilibrium), meanwhile mutating to circumvent the impediment and develop neoantigens.[26] Tumor cells may then escape from the immune battlegrounds altogether, resulting in metastasis or recurrence. ICIs can reverse this corruption by

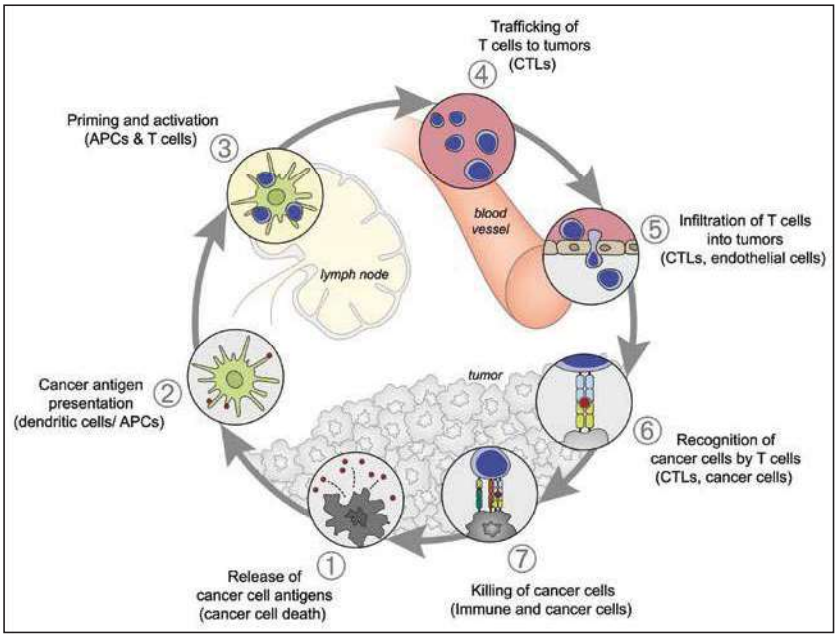


Figure 2. Cancer-immunity cycle. After an initial skirmish with the tumor antigen by neutrophils, the APCs (typically dendritic cells) engulf the necrotic remains and carry the digested fragments (tumor-associated antigen) as evidence to inform T-cell reserves. The primed T cell divides, proliferates, and disperses to patrol for and eliminate the tumor cells. APC, antigen-presenting cell; CTL, cytotoxic T lymphocyte. Reprinted from *Immunity*, 39/1, Chen DS, Mellman I, Oncology Meets Immunology: The Cancer-Immunity Cycle, 1-10, 2013, with permission from Elsevier.[25]

disengaging the brakes and keeping receptors and ligands that work to suppress immunity from binding together.[27]

The currently approved ICIs work by blocking 1 of 2 checkpoint pathways (Figure 3) that connect T-cell receptors to corresponding tumor-antigen ligands. The pathway where CTLA-4 binds to the B7 ligands (CD80, CD86) impedes immunity early in the process (eg, within the lymph nodes, lower right of Figure 3). The PD-1/PD-L1 checkpoint applies the brakes later in peripheral areas (eg, where solid tumor is located, lower left of Figure 3). At least 23 other inhibitory and stimulatory immune pathways are currently being investigated in approximately 95 early-phase trials.[28]

IMMUNE-RELATED ADVERSE EVENTS

Compared with the predictable and intense severity of chemotherapy toxicities, the generally reduced toxicity of ICI therapeutics is a welcome relief for many. The side effects of chemotherapy often interfere with the completion of adequate treatment for older patients, because of treatment discontinuation and reduced dosage to avoid the effects.[29] Nonetheless, ICIs can have unwelcome side effects and can occasionally be severe and even deadly (<1% across ICIs).[30,31] Immune-related adverse events (irAEs) are primarily inflammatory reactions triggered by immune stimulation but can affect any organ system. Manifestations involve the skin (eg, itching and rash), eyes, intestines (eg, diarrhea, colitis), lungs (eg, interstitial pneumonitis), endocrine systems (eg, thyroid, adrenal), and nerves (eg, peripheral neuropathy), among other organ systems.[32] Life-threatening toxicities have included pneumonitis, colitis, and pancreatitis.[33] A meta-analysis that included >11,000 patients in 73 ICI trials found irAEs of any grade to be considerably higher in patients receiving CTLA-4 treatment (53.8%) compared with PD-1 (26.5%) and PD-L1 treatments (17.1%) ($P < .001$).[28] Although patients with preexisting autoimmune disorders are predictably vulnerable to irAEs, even grade 3 and 4 irAEs prove to be manageable with immune-suppressive treatment (eg, corticosteroids).[34,35]

ICIs are generally considered to be as well tolerated in older patients as in younger patients.[12,35] Nonetheless, an understanding of pharmacodynamic effect and toxicity of ICIs in older patients is not yet solid, primarily because of the continued underrepresentation of that population in clinical trials and possibly because of suboptimal reporting.[28] For those >75 years of age, the literature conflicts on rates of toxicity.[34,36,37] Clinical care for older patients receiving ICIs will likely necessitate closer monitoring than standard procedures: for instance, watching for dehydration and renal insufficiency with an irAE of diarrhea and watching for an increased risk of bone fracture with extended corticosteroid use.

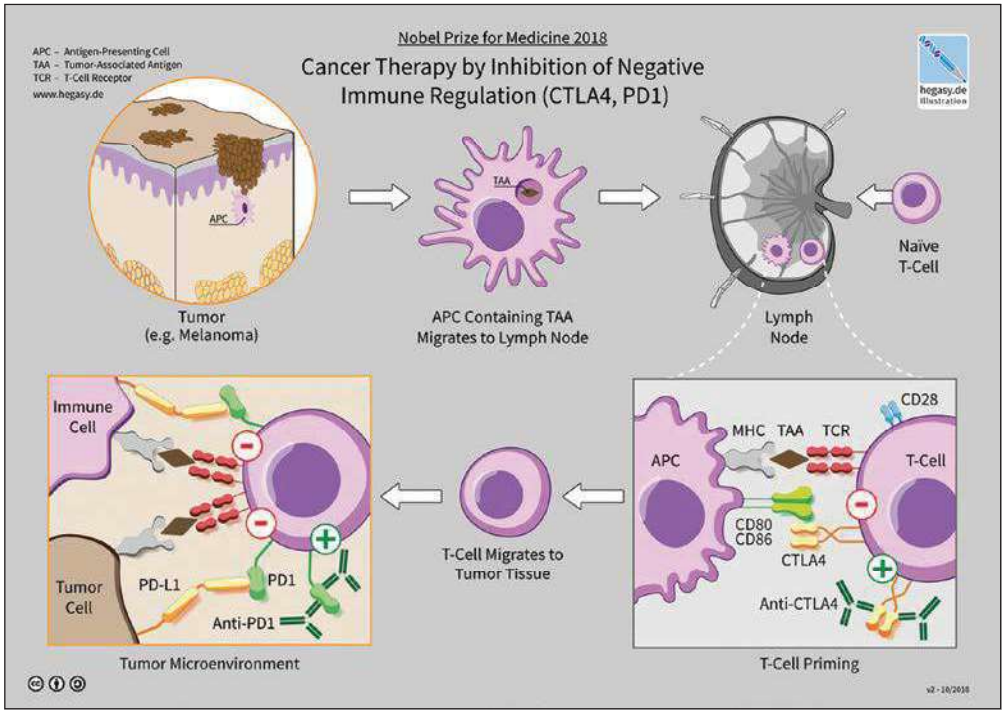


Figure 3. The CTLA-4/B7 and PD-1/PD-L1 checkpoints and blockers. Once a T cell with a matching receptor (TCR) receives the summons (shown here within a lymph node), the TCR binds to the major histocompatibility complex (MHC-1) expressed on the APC. This communication between T cell and APC (lower right) includes the binding of the CTLA-4 and B7 ligand complex (CD80 and CD86) checkpoint. Blocking these proteins from binding with anti–CTLA-4 therapy is effective against some solid tumors (eg, melanoma). When a T cell arrives at the peripheral tumor and the TCR links to MHC-1 on the tumor, the corresponding PD-1/PD-L1 checkpoint can be interrupted to prohibit tumor evasion (lower left). APC, antigen-presenting cell; CTLA-4, cytotoxic T lymphocyte–associated antigen 4; MHC-1, major histocompatibility complex 1; PD-1, programmed cell death protein type 1; PD-L1, programmed cell death ligand type 1; TAA, tumor-associated antigen; TCR, T-cell receptor. Image compliments of Dr Guido Hegasy, via Wikimedia Commons (https://commons.wikimedia.org/wiki/File:11_Hegasy_CTLA4_PD1_Immunotherapy.png). This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license. No changes were made to the image.

KNOWN EFFICACY FOR OLDER PATIENTS

In general, clinical trials of ICIs find comparable effects in older and younger populations. A 2016 meta-analysis compared ICI efficacy between younger (<65 years) and older patients (65 years to 75 years).[35] The subanalysis of overall survival (OS) that included 4,725 patients found the survival benefit with ICIs to be consistently superior to that of controls, regardless of age (hazard ratio [HR] = 0.75, 95% confidence interval [CI] = 0.68 to 0.82; $P < .001$ for younger patients and HR = 0.73, 95% CI = 0.62 to 0.87; $P < .001$ for the older group). In those >75 years of age, the OS benefit was not significant and in some studies was not superior to that of standard treatments.[37-39] Although many researchers agree that insufficient statistical power could be more responsible than age for the reduced benefit in the oldest group, most speculate that the influence of ICIs may weaken in older adults.[35,37] Nonetheless, although new cancer diagnoses in patients >75 years make up >25% of new cancer cases, this population is dramatically underrepresented in clinical trials.[40]

Investigational combinations of ICIs with radiation therapy, chemotherapy, tyrosine kinase inhibitors, and other immunotherapies are being studied. Combination ICI therapy, using nivolumab with low-dose ipilimumab, received FDA approval in July 2018 for the treatment of colorectal cancer with specific genetic markers. Although the combination proves superior to nivolumab alone for patients <65 years of age, the combination elicits more severe toxicities for all populations and provides mixed results in progression-free survival and OS for older-aged subgroups.[41]

WHAT'S OLD IS NEW

A recent translational study from the Wistar Institute in Philadelphia investigated responses to anti–PD-1 therapy associated with the aged tumor microenvironment of patients with melanoma.[42] Using regression analysis, the team estimated that patients >60 respond to anti–PD-1 more efficiently than younger patients, with a probability of progression decreasing 13% for each decade of life for patients treated with pembrolizumab. Their hypothesis pointed to the depletion of Tregs resulting from immune aging as the cause. Because Tregs suppress $CD8^+$ T-cell proliferation, a lower ratio of Tregs to $CD8^+$ T cells within tumor tissue, when combined with anti–PD-1 therapy, may allow the body to "step on the gas" against tumor, without having to counteract the brakes at the same time.[40,43] The authors propose that such results may inform future approaches to improve the efficacy of anti–PD-1 therapy in younger patients by depleting Tregs within the tumor microenvironment before the start of anti–PD-1 treatment. Further research is needed, and the full results from the Wistar study's long-term OS analysis are awaited.

GENOMIC BIOMARKERS GIVE INSIGHTS INTO PREDICTING EFFECT

Why some patients respond well with ICIs and others do not motivates researchers to investigate which proteins might indicate treatment effect. Predictive biomarkers represent a major advance toward precision or "personalized" therapies. Most anti–PD-1 monoclonal antibody approvals specify treatment for those with higher tumor expression of PD-L1 as determined by genetic profiling, with thresholds of both ≥1% and ≥50% (based on the statistical significance and current manual immunohistochemical methods). The summer of 2017 saw a radical change in oncology therapeutic approvals when the FDA approved pembrolizumab based not on the original location of the tumor but on the expression of a genetic biomarker (ie, microsatellite instability–high or mismatch repair deficiency [MMRd] genetic marker).[44] These are mutated proteins in some solid tumors picked up by immunohistochemical testing.

Tumor mutational burden (TMB), which measures the number of somatic (acquired) mutations present within tumor tissue, may not only be a more accurate biomarker than PD-L1 but could also shed light on the efficacy of ICIs in older patients. Many common solid tumors express a high TMB (eg, melanoma, squamous cell NSCLC, small-cell lung cancer, urothelial cancers, and MMRd-positive cancers).[45,46] Researchers believe that high-TMB tumors harbor neoantigens that can be readily targeted by activated T cells.[47] A 2017 meta-analysis evaluating 27 cancer types showed a clear and significant correlation between TMB and objective response rate for anti–PD-1/PD-L1 therapeutics, regardless of PD-L1 expression ($P < .001$, Figure 4).[43] Another systematic review highlighted 150 patients treated with ICI monotherapies whose tumors expressed various somatic mutations on next-generation sequencing.[48] Patients with high-TMB tumors (≥20 mutations per megabase) had nearly 3-times-higher response rates than those with low to intermediate TMB levels (58% compared with 20%, $P = .0001$), corresponding to progression-free survival (HR = 0.34; 95% CI = 0.23 to 0.50) and OS (HR = 0.33, 95% CI = 0.19 to 0.58). These results correlated to genomic profiling of >100,000 patient tumors from >500 distinct cancer types, revealing significantly increased TMB levels associated with advanced age ($P < 1 \times 10^{-16}$).[45]

CONCLUSION

Researchers agree that immune-oncology is still in its infancy, yet the advent of ICIs has woken science to the vital role of the immune system in eradicating tumors. Many discoveries in the nuances of lymphocytic signaling, prognostic and predictive biomarkers, and the workings of tumor microenvironment sprang from the last decade of research in ICIs and other dawning immunotherapies such as adoptive T cell

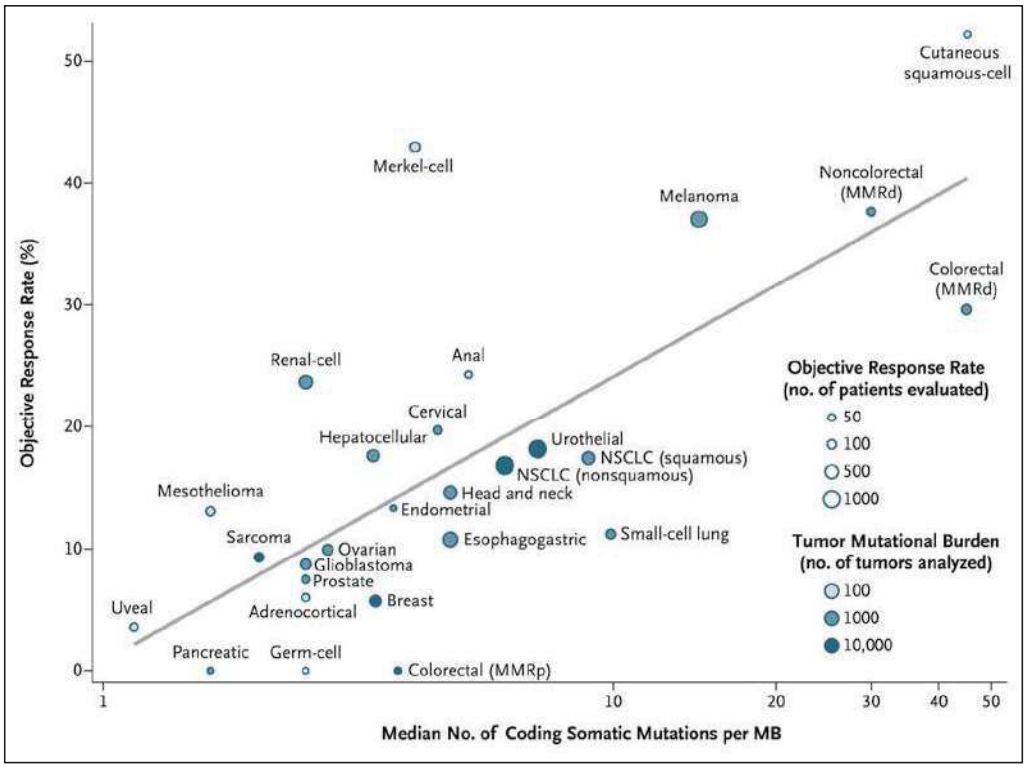


Figure 4. Tumor mutational burden across tumor types measuring responsiveness to anti–PD-1/PD-L1 therapies. Median number of coding somatic mutations per MB of DNA in 27 tumor types or subtypes among patients who received inhibitors of PD-1 protein or its ligand (PD-L1). Data on the x axis are shown on a logarithmic scale. MB, megabase; MMRd, mismatch repair deficiency; MMRp, mismatch repair proficiency; NSCLC, non–small cell lung cancer; PD-1, programmed cell death protein type 1; PD-L1, programmed cell death ligand type 1. From the *New England Journal of Medicine*, Yarchoan M, Hopkins A, Jaffee EM, Tumor Mutational Burden and Response Rate to PD-1 Inhibition, 377, 2500–2501. ©2017 Massachusetts Medical Society.[45] Reprinted with permission.

transfers and cancer vaccines. Moreover, endeavors in immunotherapies have shed new light on the importance of a healthy and diverse gut biome, the awareness of which could spur better public health. However, these signals of progress do come with high financial costs, as the development of ICIs has garnered tremendous resources, prompting concerns that commercial competition for the ICI market has driven costs irresponsibly skyward. Reuters reported in 2017 that anti–PD-1 therapy, the medicine alone, cost on average $13,000 per month.[49] Surely this equates to a burden on seniors, Medicare, and resources for other critical research.

As the population ages, health care professionals must increasingly address the distinct needs of older cancer patients. Dr Harvey Cohen from the Center for Aging and Human Development at Duke University commented, "Given the demographic trends, one might say that all oncologists need to become geriatric oncologists."[50] Although evidence regarding the effect of ICIs on older patients is still limited, efforts to mirror real-world demographics within clinical trial populations are improving the gap. Moreover, there are hopes that enhanced collection and analysis of real-world data and the trend to integrate real-world evidence into product labeling and postmarketing activities of novel therapeutics may fortify our understanding of the efficacy and safety of ICIs for older patients. Nonetheless, advocates agree, much more work is needed.[15]

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Glossary

Adaptive immune system— Portion of the immune system that produces a calculated, long-lasting, and exacting complex defense specific to a presenting antigen (whether an exogenous virus or an endogenous tumor cell).

Antigen-presenting cells (APCs)— On their own, T cells cannot detect pathogens. Immune cells that first attack a pathogen—for instance, phagocytes ("cell devourers")—carry antigen fragments with major histocompatibility complex (MHC) proteins (defined below) back to the T cells within the lymphatic system. T cells are then activated to find the corresponding target, and adaptive immunosuppression begins.

Cytotoxic T lymphocyte–associated antigen 4 (CTLA-4)— This protein receptor binds to CD80 and CD86 (2 of the manifold clusters of distribution, also B7-1 and B7-2), and the resulting checkpoint downregulates (ie, sends an inhibitory signal to T cells).

Cytotoxic T cell (also $CD8^+$ T cell or killer T cell)— This white blood cell kills tumor cells when activated.

Dendritic cell— This immune cell operates at the intersection of the innate and adaptive arms of the immune system; an APC that induces T-cell activation and differentiation.

Mismatch repair deficiency (MMRd) and microsatellite instability–high (MSI-H)—These are 2 genetic markers associated with various solid tumors (eg, colorectal and endometrial).

Immune checkpoint inhibitors (ICIs)— These monoclonal antibodies (mABs) are designed to disrupt the regulatory intersection where cancer can prevent its own elimination by manipulating the adaptive immune system.

Immune-editing— This describes the interaction between tumor and the immune system as a 3-phase process of elimination, equilibrium, and evasion.

Innate immune system— A portion of the immune system that prompts an immediate, short-lived, and blunt attack, characterized primarily by inflammation.

Class 1 major histocompatibility complex (MHC-1)— This is a protein molecule that carries antigen-specific information and unites with corresponding T-cell receptors (TCRs) to activate the adaptive immune system.

Neutrophil— This short-lived, highly active white blood cell acts as a first-responder at a site of inflammation.

Phagocyte— This white blood cell engulfs an antigen when cleaning up after the innate immune system's initial attack

Programmed cell death protein type 1 (PD-1)— When bound to its ligand (PD-L1), this receptor protein on cytotoxic T cells applies the "brakes," keeping the immune system from destroying healthy cells.

T cells— Functioning primarily within the adaptive immune system, T cells originate as progenitor cells in bone marrow and mature in the thymus (thus the T).

Tumor mutational burden (TMB)— This is a predictive biomarker that measures the number of mutations expressed by a specific tumor.

Regulatory T cells (Tregs; also called suppressor T cells)— These T cells moderate the function of other types of lymphocytes to maintain homeostasis.

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