




Wedding of Molecular Alterations and Immune Checkpoint Blockade: Genomics as a Matchmaker

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Abstract

The development of checkpoint blockade immunotherapy has transformed the medical oncology armamentarium. But despite its favorable impact on clinical outcomes, immunotherapy benefits only a subset of patients, and a substantial proportion of these individuals eventually manifest resistance. Serious immune-related adverse events and hyperprogression have also been reported. It is therefore essential to understand the molecular mechanisms and identify the drivers of therapeutic response and resistance. In this review, we provide an overview of the current and emerging clinically relevant genomic biomarkers implicated in checkpoint blockade outcome. US Food and Drug Administration–approved molecular biomarkers of immunotherapy response include mismatch repair deficiency and/or microsatellite instability and tumor mutational burden of at least 10 mutations/megabase. Investigational genomic-associated biomarkers for immunotherapy response include alterations of the following genes/associated pathways: chromatin remodeling (*ARID1A*, *PBRM1*, *SMARCA4*, *SMARCB1*, *BAP1*), major histocompatibility complex, specific (eg, ultraviolet, *APOBEC*) mutational signatures, T-cell receptor repertoire, *PDL1*, *POLE/POLD1*, and neo-antigens produced by the mutanome, those potentially associated with resistance include β 2-microglobulin, *EGFR*, *Keap1*, *JAK1/JAK2*/interferon-gamma signaling, *MDM2*, *PTEN*, *STK11*, and Wnt/Beta-catenin pathway alterations. Prospective clinical trials are needed to assess the role of a composite of these biomarkers to optimize the implementation of precision immunotherapy in patient care.

Immunotherapies such as checkpoint inhibitors have demonstrated durable responses in selected patients with diverse tumor types. However, only about 20% of patients respond to immune checkpoint blockade, and a clinically significant proportion of patients who derive benefit from this treatment eventually develop resistance (1). Additionally, serious immune-related adverse events have been reported in a clinically significant proportion of patients who receive checkpoint inhibitors, and others have experienced accelerated disease progression (known as hyperprogression) (2-4). It is therefore essential to identify robust biomarkers of immune checkpoint blockade efficacy to select the optimal treatment for each patient.

Programmed cell death-ligand 1 (PD-L1) expression on tumor or immune cells was the first US Food and Drug Administration (FDA)–approved immune-related biomarker, predicting

response to checkpoint blockade in diverse tumor types, including non-small cell lung cancer (NSCLC), melanoma, urothelial cancer, renal cell cancer, and triple-negative breast cancer (5). However, patients with PD-L1–negative tumors often respond to immunotherapy, and therefore PD-L1 expression as a solitary biomarker for checkpoint blockade benefit is suboptimal.

Deficient mismatch repair (dMMR)/microsatellite instability (MSI) (6,7) and intermediate-to-high tumor mutational burden (TMB) (>10 mutations/megabase [mut/mb]) (8,9) predict salutary effects from checkpoint inhibitors, regardless of tumor of origin. Recently, the FDA approved these genomic alterations as pan-solid cancer immunotherapy response predictors. Current efforts and this review (Table 1) (6,8,10,12-38,40-46,48-52) are focused on the rapidly evolving field evaluating novel genomic immunotherapy biomarkers in diverse tumor types.

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Table 1. Genomic biomarkers for response or resistance to checkpoint blockade^a

Genomic biomarker	Cancer type	Role	Predictive value and comments	Selected references
FDA-approved biomarkers associated with response				
Deficient mismatch repair/microsatellite instability	Across solid tumor types, adult and pediatric	MSH2, MSH5, MLH1, PMS2, and EPCAM Repairs mismatches in microsatellites	Predicts response FDA approved for pembrolizumab	Le, et al. 2020 (10) Marabelle, et al. 2019 (6) Overman, et al. 2018 (11) Lenz, et al. 2020 (12)
TMB (>10 mutations/mb) regardless of microsatellite status	Across solid tumor types, adult and pediatric	Increased mutations/neoantigens	Predicts response FDA-approved: pembrolizumab and TMB >10 mutations/mb	Goodman, et al. 2017 (8) Hellman, et al. 2018 (13) Gandara, et al. 2018 (14)
Reported/Investigational response alterations				
Chromatin remodeling (SWI/SNF complex)				
ARID1A	Across solid tumors (eg, ovarian clear cell, endometrial, and gastric)	SWI/SNF chromatin remodeling	ARID1A deficiency leads to impaired MMR function	Shen, et al. 2018 (15) Okamura, et al. 2020 (16) Kim, et al. 2019 (17)
PBRM1	Clear cell renal cancer	SWI/SNF chromatin remodeling	Contradictory data; some papers suggest that PBRM1 alterations predict response to immunotherapy, others do not	Miao, et al. 2018 (18) Braun, et al. 2019 (19) Liu, et al. 2020 (20)
SMARCA4	Driver in small cell ovarian cancer with hypercalcemia (found in uterine and thoracic sarcomas [undifferentiated], NSCLC, bladder, colorectal)	SWI/SNF chromatin remodeling	SMARCA4-deficient tumors have immunogenic microenvironment May predict immunotherapy response Requires validation	Jelinic, et al. 2018 (21) Naito, et al. 2019 (22) Iijima, et al. 2020 (23)
SMARCB1	Rhabdoid tumors	SWI/SNF chromatin remodeling	Preliminary: SMARCB1 loss in rhabdoid tumors may correlate with immunotherapy response	Bakouny, et al. 2020 (24)
Other alterations				
BAP1 alterations	Mesothelioma	Promotes immune inflammatory environment in mesothelioma	Predicts response Requires validation	Alley, et al. 2017 (25) Scherperel, et al. 2019 (26) Shrestha, et al. 2019 (27)
Major histocompatibility complex class-I (MHC-I) genotype	Across solid tumors	Efficient presentation of driver neoantigens to CD8+ T cells	Predicts response in patients with high TMB Requires validation	Goodman, et al. 2020 (28)
Mutational signatures APOBEC-related ultraviolet-related	Across solid tumors	Associated with high immunogenicity	Predicts response independently of TMB Requires validation	Boichard, et al. 2020 (29) Pham, et al. 2019 (30)
Mutational signatures ultraviolet-related	Across solid tumors	Associated with high immunogenicity	Predicts response in patients with low TMB Requires validation	Pham, et al. 2019 (30)
PD-L1 amplification	Across solid tumors (and in Hodgkin lymphoma)	PD-L1 ligand is important in the immune checkpoint machinery	Predicts response Requires validation	Goodman, et al. 2018 (31)
POLE/POLD1	Across solid tumors	High tumor mutational rates, high TIL rates,	Predicts response	Wang, et al. 2019 (32) Yao, et al. 2019 (33)

(continued)

Table 1. (continued)

Genomic biomarker	Cancer type	Role	Predictive value and comments	Selected references
		and increased expression of cytotoxic T-cell markers		
Biomarkers associated with resistance/ Hyperprogression				
Beta-2 microglobulin mutations	Melanoma	Defects in antigen presentation, escape of immune recognition	Predicts resistance Requires validation	Zaretsky, et al. 2016 (34) Sade-Feldman, et al. 2017 (35) Rodig, et al. 2018 (36)
EGFR alterations	Across tumor types	Unclear	Predicts resistance and hyperprogression Requires validation	Kato, et al. 2017 (3) Ferrara, et al. 2018 (37)
KEAP1 mutations	NSCLC	Associated with "cold" tumor microenvironment	Not clear if KEAP1 alterations are predictive or prognostic	Chen, et al. 2020 (38) Arbour, et al. 2018 (39) Rizvi, et al. 2019 (40) Papillon-Cavanagh, et al. 2020 (41)
JAK1/2 loss	Across tumor types (melanoma, colorectal)	Defects in interferon-receptor signaling pathways	Predicts resistance Requires validation	Zaretsky, et al. 2016 (34) Shin, et al. 2017 (42) Horn, et al. 2018 (43)
MDM2 amplification	Melanoma	Unclear	Predicts hyperprogression Requires validation	Kato, et al. 2017 (3) Kato, et al. 2018 (44)
PTEN loss	Melanoma	Upregulation of immunosuppressive cytokines; may decrease CD8+ T cell infiltration	Predicts resistance Requires validation	Peng, et al. 2016 (45) Zhao, et al. 2019 (46)
STK11 mutations with KRAS alterations	Lung	Altered cytokines/chemokines, metabolic restriction of T cells, impaired antigenicity	Not clear if STK11 alterations are predictive or prognostic	Skoulidis, et al. 2018 (47) Papillon-Cavanagh, et al. 2020 (41)
Wnt/Beta-catenin pathway alterations	Melanoma, colon cancer	Decreases T-cell infiltration	Predicts resistance Requires validation	Spranger, et al. 2015 (48) Abril-Rodriguez, et al. 2020 (49)

^aBAP1 = BRCA1-associated protein 1; EGFR = epidermal growth factor receptor; FDA = US Food and Drug Administration; JAK = Janus kinase; KEAP1 = Kelch-like ECH associated protein 1; mb = megabase; MDM2 = murine double minute 2; MHC-I = major histocompatibility complex class-I; MMR = mismatch repair; NSCLC = non-small cell lung cancer; PBRM1 = polybromo-1; PD-1 = programmed cell death-1; PD-L1 = programmed cell death-ligand 1; POLE = DNA polymerase epsilon; PTEN = phosphatase and TENsin homolog deleted on chromosome 10; SMARCB1 = SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B; STK11 = serine/threonine kinase 11; TIL = tumor infiltrative lymphocyte; TMB = tumor mutational burden.

FDA-Approved Biomarkers

On May 23, 2017, the FDA granted accelerated approval to pembrolizumab for dMMR/MSI diverse solid cancers (Table 1). This was a landmark approval because, for the first time, a regulatory agency approved an immunotherapy drug based on a genomic marker and, importantly, that approval was tissue agnostic. On June 16, 2020, the FDA gave a second similar (histology-agnostic) approval to pembrolizumab. This time, the approval was for solid tumors harboring TMB of at least 10 mut/mb. It is important to note that the vast majority of tumors with dMMR/MSI have a high TMB, but most tumors with a high TMB are not MSI. Therefore, it is probable that high TMB mediates the responsiveness to checkpoint blockade, perhaps by resulting in a high number of mutanome-derived neoantigens, hence increasing the chances that one or more of these neo-antigens will be immunogenic and trigger T-cell activation, leading to eradication of the cancer cells bearing the immunogenic neo-antigens.

dMMR and Microsatellite Instability

MMR proteins control the excision of DNA mismatches introduced by DNA polymerase during cell division; these mismatches commonly occur in repetitive DNA sequences known as microsatellites. Impairment of the MMR system leads to MSI, which is characterized by the accumulation of mismatches in repeated sequences. Defects in the MMR system can be assessed using polymerase chain reaction-based assays that test for MSI or immunohistochemical (IHC) analyses of the expression of MMR proteins, including MLH1, MSH2, MSH6, and PMS2. Both tests are approved for selecting patients for treatment. MSI-high (MSI-H) or dMMR tumors can arise because of somatic or epigenetic MMR gene alterations (53,54) or to Lynch syndrome-associated germline MMR gene mutations (55-57).

The genomic analysis of more than 15 000 cancers (>50 types of malignancy) revealed MSI-H in 2.2% of specimens of which 16% had a germline mutation in an MMR gene, consistent with Lynch syndrome (58-60). MSI-H has been identified in 28% of

patients with endometrial cancer and in 19% of patients with colon cancer (58,59). It is also reported in diverse tumor types (not classically considered in Lynch syndrome), including gastric (22%), adrenal cortical (5%), and esophageal (3%) carcinomas (58).

Several trials have shown statistically significant responses to anti-programmed cell death-1 (PD-1) agents in heavily pretreated patients with MSI-H/dMMR in diverse tumor types, leading to FDA approval of MSI/dMMR as a predictive biomarker for immune checkpoint blockade. Notably, in May 2017, pembrolizumab received the first tissue and site-agnostic FDA approval for the treatment of adult and pediatric patients with unresectable or metastatic MSI-H or dMMR solid tumors that had progressed after prior treatment (7). Five single-arm trials evaluated the use of pembrolizumab in patients with dMMR or MSI-H tumors; the overall response rate (ORR) was 39.6% (complete response [CR] = 7%), with a large subgroup of responses being durable (6,10,61,62). Additionally, pembrolizumab was approved for the treatment of unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC) that had progressed after treatment with a fluoropyrimidine, oxaliplatin, and irinotecan (63). In June 2020, pembrolizumab was further approved for the first-line treatment of patients with advanced MSI-H or dMMR CRC, based on the results of a multicenter, open-label, randomized trial (KEYNOTE-177) (64). Patients who received treatment with pembrolizumab had longer median progression-free survival (PFS) compared with patients who received standard chemotherapy (16.5 vs 8.2 months; hazard ratio [HR] = 0.60, 95% confidence interval [CI] = 0.45 to 0.80, $P = .0002$). The ORR was 43.8% with pembrolizumab vs 33.1% with chemotherapy, whereas median duration of response was not reached with pembrolizumab vs 10.6 months with chemotherapy (64).

Nivolumab, another anti-PD-1 agent, was also granted FDA approval as a monotherapy and in combination with ipilimumab for the treatment of patients 12 years of age or older with MSI-H or dMMR metastatic CRC after prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan (65,66). Both approvals were based on the results of CHECKMATE-142, a nonrandomized phase II trial evaluating nivolumab with or without other anti-cancer drugs. Patients with MSI-H/dMMR CRC after 1 or more lines of treatment received nivolumab until disease progression, death, or unacceptable toxicity (50). Among the 74 patients studied, the ORR was 31%, and the median depth of response was not reached. In the combination arm, patients received nivolumab every 2 weeks in combination with low-dose ipilimumab (1 mg/kg) every 6 weeks. The ORR was 55%, and the median duration of response was not reached; the 12-month PFS rate was 71% (11). In an updated analysis, the ORR was 60% (95% CI = 44.3 to 74.3); median PFS and overall survival (OS) were not reached (12). These data demonstrate that MSI-H/dMMR is a powerful marker for response to pembrolizumab and nivolumab in diverse tumor types.

TMB of at Least 10 Mut/mb

TMB is defined as the number of somatic synonymous and non-synonymous mutations (base substitutions and indels) per megabase of analyzed DNA. Nonsynonymous molecular alterations lead to transcription of abnormal proteins, which are recognized by the immune system as neoantigens and render the tumor highly immunogenic. In June 2020, the FDA granted accelerated approval to pembrolizumab for the treatment of patients with advanced solid tumors with intermediate to high TMB (ie, ≥ 10 mut/mb) whose disease had progressed on prior

treatment and who had no satisfactory alternative treatment options (9). Additionally, the FoundationOneCDx assay was also approved by the FDA as a companion diagnostic test for pembrolizumab. This approval was based on the results of KEYNOTE-158, a nonrandomized clinical trial of patients with diverse solid tumor types who received treatment with pembrolizumab until disease progression or unacceptable toxicity (67). The trial aimed to evaluate predictive biomarkers through a prospectively planned retrospective analysis of 10 cohorts of patients. Among 102 patients with tumors with TMB of at least 10 mut/mb, the ORR (primary endpoint) was 29% (CR = 4%), and about half of the responses were durable at 2 years (67).

An analysis of 104 814 tumor tissue samples from the Foundation Medicine database showed that TMB of at least 10 mut/mb was identified in about 13% of all solid tumors (68-70). Other investigators retrospectively reviewed data on 1638 patients with diverse tumor types who had undergone comprehensive genomic profiling and reported that TMB-high (TMB-H) tumor status, which was defined as at least 20 mut/mb, was more commonly noted in patients with melanoma (34%) and NSCLC (24%) (8). In that study, among patients who received immunotherapy, TMB-H was independently associated with a higher ORR (58% vs 20%; $P = .0001$) and longer median PFS (12.8 vs 3.3 months; $P < .0001$) and OS (not reached vs 16.3 months; $P = .0036$). Several additional studies have shown a statistically significant clinical benefit of checkpoint inhibitor treatment in patients with higher TMB (13,14). In patients with NSCLC and TMB of at least 10 mut/mb, frontline nivolumab plus ipilimumab was associated with longer PFS compared with chemotherapy, irrespective of the PD-L1 expression level (13). Next-generation sequencing (NGS) of 148 803 samples from the University of California San Diego and Foundation Medicine databases further revealed that 9762 (6.6%) were TMB of at least 20 mut/mb, and 2179 (1.5%) were MSI-H (69). Among 60 patients who received immunotherapy, the median PFS was longer in patients with low MSI and TMB of at least 20 mut/mb compared with those with low MSI and TMB of less than 20 mut/mb (26.8 vs 4.3 months; $P = .0173$). Additionally, higher TMB was linearly correlated with better outcomes after immune checkpoint blockade (8), and the impact of TMB was independent of microsatellite status (69).

Despite robust data demonstrating the association of higher TMB with response to immunotherapy, several challenges remain. First, harmonization of TMB assays is critical. Some investigators suggest that TMB response thresholds might differ across tumor types (70). Additionally, neoantigen immunostimulation differs on the basis of the corresponding molecular alteration, with certain mutations likely inducing a strong immune response (71). Further, not all studies show a survival benefit for higher TMB, even when there are robust and durable responses. Importantly, current TMB evaluation algorithms do not take into consideration neoantigens that might be generated from posttranslational modifications or gene fusions. Furthermore, TMB calculation using circulating tumor DNA analysis is being assessed. In patients with advanced NSCLC treated with pembrolizumab, plasma analysis using a 500-gene panel demonstrated that TMB of at least 16 mut/mb was associated with longer PFS (72). Other biologic considerations such as major histocompatibility complex (MHC) presentation and T-cell receptor (TCR) repertoire may also be important.

PD-L1 Immunohistochemistry

PD-L1 expression is being evaluated in numerous clinical trials as a biomarker predicting response to immunotherapy agents.

High PD-L1 membrane expression is assessed by immunohistochemistry and defined using various scoring methods and cutoff points ranging from more than 1% to more than 50%. PD-L1 expression has been approved by the FDA as a companion diagnostic for the administration of immune checkpoint inhibitors in various indications, including first-line treatment for advanced NSCLC, head and neck squamous cell carcinoma, urothelial carcinoma, and triple-negative breast cancer and second-line therapy and beyond for advanced NSCLC, esophageal squamous cell carcinoma, cervical cancer, and gastric-esophagogastric junction adenocarcinoma. High PD-L1 expression has been associated with clinical benefit in patients with selected tumor types (73-76). This variability in the predictive value of PD-L1 expression and in the cutoff used to determine PD-L1 expression positivity is attributed to differences in tumor type, disease stage, types of checkpoint inhibition (PD-1 vs PD-L1), and methodology. Methodological differences are associated with technical issues regarding assessment of PD-L1 expression in tumor cells and immune cells; the use of scoring systems combining expression in tumor cells, lymphocytes, and macrophages; and the antibodies used for biomarker evaluation. Examples of monoclonal antibodies used to assess PD-L1 expression include SP142 and SP263 (Ventana Medical Systems, Oro Valley, Arizona, USA) and 22C3 pharmDx (Agilent, Santa Clara, California, USA). Scoring methods include the combined positive score, defined as the number of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of cells (tumor cells, lymphocytes, and macrophages) and multiplied by 100, and the tumor proportion score (TPS), defined as the number of PD-L1-positive tumor cells divided by the total number of tumor cells and multiplied by 100. To overcome the variability in PD-L1 assessment, standardization of methodology is warranted.

Investigational Biomarkers Conferring Sensitivity to Immunotherapy

Beyond MSI-H (which results in high TMB) and TMB of at least 10 mut/mb, there are several biomarkers that may confer sensitivity to immune checkpoint blockade. These genomic biomarkers include, but are not limited to, alterations in chromatin remodeling genes, PD-L1 amplification, specific MHC types that permit neo-antigen presentation, and specific mutational signatures that are associated with increased TMB and/or increased immunogenicity of neo-antigens (Table 1 and Figure 1).

Chromatin Remodeling (SWI/SNF Complex)

Cells have developed several mechanisms to manipulate DNA and package it into chromatin. The building block of chromatin is the nucleosome. ATP-dependent chromatin remodeling complexes such as switch/sucrose non-fermentable (SWI/SNF) complexes are specialized protein machinery complexes able to restructure the nucleosome to make its DNA accessible during transcription, DNA repair, and replication. Several genes that make up these complexes, including those in the ARID and SMARC families and PBRM1, have been associated with responsiveness to immune checkpoint blockade (15,16,19,24,77). Mechanistically, reexpression of endogenous retroviruses resulting from deficiency of the SWI/SNF complex chromatin remodeling complex may contribute to activation of the immune response in these malignancies (78).

ARID1A alterations. The AT-rich interaction domain 1A (ARID1A) gene encodes a subunit of the ATP-dependent chromatin remodeling SWI/SNF complex (79,80). Inactivating mutations in ARID1A are frequently identified in many tumor types: ovarian clear cell (45%), endometrial (45%), gastric (19%), and hepatocellular (14%) carcinomas (81-85). ARID1A functional loss has been clinically and experimentally correlated with immunotherapy response (15,16,86).

ARID1A deficiency interferes with MMR system regulation, leading to increased tumor mutational load and higher PD-L1 expression and more immune infiltrates (15,17,86,87). During DNA replication, ARID1A binds and recruits MSH2, a key MMR protein, to chromatin (15). ARID1A-deficient ovarian tumors in syngeneic mice were characterized by increased mutation load, tumor-infiltrating lymphocytes, and PD-L1 expression (15). Anti-PD-L1 antibody administration led to improved survival rates of mice with ARID1A-deficient vs ARID1A-wild-type ovarian tumors. Further, in 3304 patients with diverse tumor types, ARID1A molecular alterations correlated with MSI-H and TMB-H, but immunotherapy response in ARID1A-altered tumors was independent of these factors (16). In patients treated with immunotherapeutic agents, those with ARID1A-altered vs wild-type tumors had improved PFS (11 vs 4 months; $P = .006$) (16). These data indicate that ARID1A alterations should be further validated as a pan-cancer predictive biomarker for immune checkpoint blockade response.

PBRM1 molecular alterations. Polybromo-1 (PBRM1) is a tumor suppressor gene that encodes a subunit of the SWI/SNF complex and participates in regulation of the cell cycle, apoptosis, and centromeric cohesion. The data regarding PBRM1 alterations and response to checkpoint blockade are mixed, with some studies suggesting that aberrant PBRM1 is predictive and others indicating that it is not.

Molecular alterations in PBRM1 are commonly identified in clear cell renal cell carcinoma (RCC) (approximately 40%) (77,88) and are considered a biomarker predicting response to immunotherapy (18,19). Additionally, PBRM1 mutations have been identified in cholangiocarcinoma (17%) (89), mesothelioma (15%) (90), pancreatic cancer (8%) (91), and lung cancer (3%) (77). In patients with clear cell RCC treated with nivolumab, those harboring PBRM1 mutations had higher rates of clinical benefit (odds ratio [OR] = 2.14, 95% CI = 1.00 to ∞ , $P = .0497$) and longer PFS (HR = 0.67, 95% CI = 0.47 to 0.96, $P = .03$) and OS (HR = 0.65, 95% CI = 0.44 to 0.96, $P = .03$) compared with patients without such mutations (19). Other investigators, using whole-exome sequencing in 35 patients with clear cell RCC, also demonstrated that loss-of-function mutations in PBRM1 were associated with improved clinical benefit from immune checkpoint inhibitors (OR = 12.93, 95% CI = 1.54 to 190.8, $P = .012$) (18). Their findings were independently validated in 63 patients with clear cell RCC who had been treated with PD-1 or PD-L1 inhibitors (OR for clinical benefit = 6.10, 95% CI = 1.42 to 32.64, $P = .0071$).

Contrary to these data, investigators recently showed that PBRM1 knockout (assessed by mRNA and protein levels) resulted in reduced interferon-gamma (IFN- γ)-STAT1 signaling in murine and human RCC cell lines (20). A retrospective analysis of approximately 700 patients with renal cancer from 3 independent clinical cohorts (IMmotion150 dataset, MSK-IMPACT cohort, and The Cancer Genome Atlas cohort) demonstrated that PBRM1 mutations were associated with fewer immune infiltrates and lower response rates to immunotherapy (20). Finally, in a retrospective analysis of 441 patients with NSCLC from 2 independent cohorts (385 patients from Memorial Sloan Kettering Cancer Center and 56 from Dana Farber Cancer

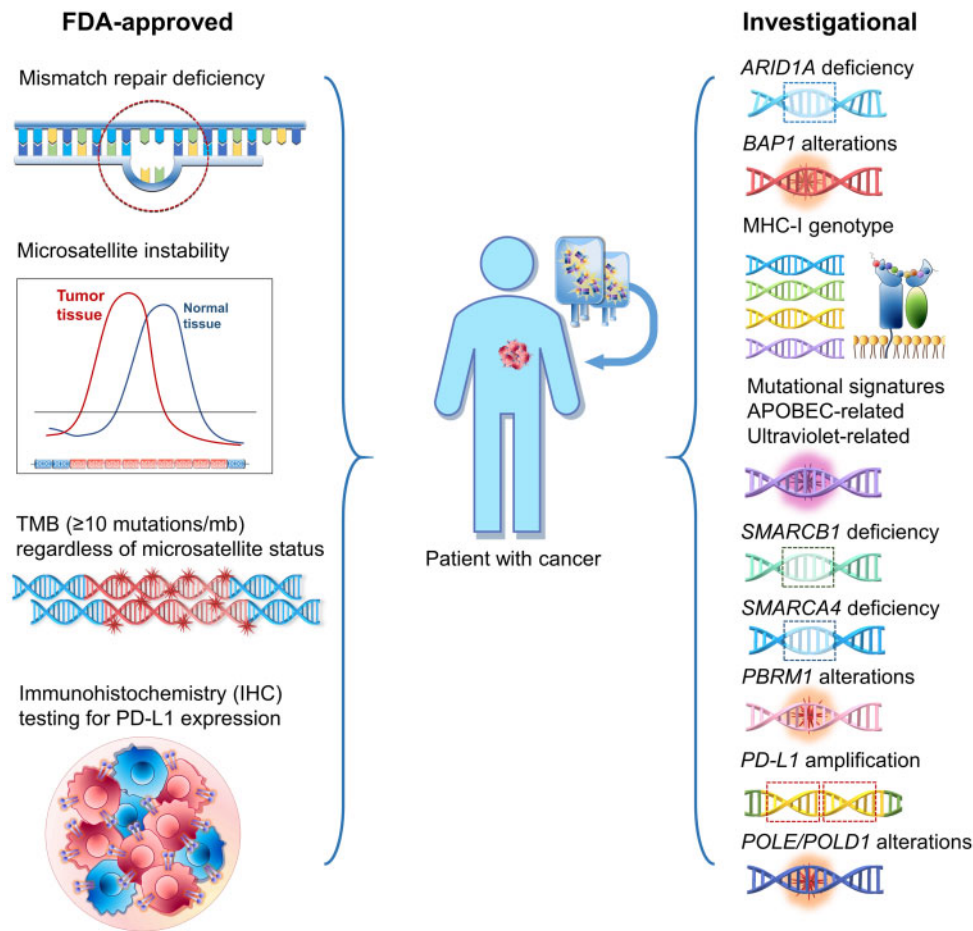


Figure 1. US Food and Drug Administration–approved and investigational biomarkers associated with response to immuno-oncology therapy. APOBEC = apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like; *ARID1A* = AT-rich interaction domain 1A; *BAP1* = BRCA1-associated protein 1; MHC-I = major histocompatibility complex class-I; *PBRM1* = polybromo-1; *PD-L1* = programmed cell death-ligand 1; *POLD1* = DNA polymerase delta 1; *POLE* = DNA polymerase epsilon; *SMARCA4* = SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A, member 4; *SMARCB1* = SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B, member 1; TMB = tumor mutational burden.

Institute) who received immunotherapy, the presence of *PBRM1* mutations correlated with shorter OS (6 months in *PBRM1*-mutated vs 13 months in *PBRM1*-wild-type patients; $P = .03$), including in multivariate analysis (77). These data collectively indicate that the predictive role of altered *PBRM1* for immunotherapy is inconclusive.

SMARCA4. *SMARCA4* encodes another subunit of the chromatin remodeling SWI/SNF complex. *SMARCA4* molecular alterations have been identified in 4% of cancers, including lung (10%), bladder (7%), colorectal (5%), and breast (2%) cancers (92,93). *SMARCA4* alterations seem to be the “driver” molecular change in almost all small cell carcinomas of the ovary, hypercalcemic type (94,95); loss of *SMARCA4* per IHC has been reported in up to 10% of patient with NSCLC (96).

Recently, *SMARCA4* loss was used to define groups of undifferentiated carcinomas, including *SMARCA4*-deficient undifferentiated uterine sarcomas that share morphologic, IHC, and genetic similarities to small cell carcinoma of the ovary, hypercalcemic type (97), and undifferentiated thoracic carcinomas (98). Durable responses have been noted in anecdotal reports of patients with small cell carcinoma of the ovary, hypercalcemic type (21), NSCLC (22), and thoracic sarcoma (23,99). Preliminary data suggest that, although *SMARCA4*-deficient tumors have low

TMB, they have high *PD-L1* expression and T-cell infiltration, suggestive of an immunogenic microenvironment (21).

SMARCB1. *SMARCB1*, another component of the chromatin remodeling SWI/SNF complex, functions as a tumor suppressor gene. Complete *SMARCB1* and/or *SMARCA4* inactivation has been associated with aggressive tumor behavior in malignant rhabdoid and atypical teratoid rhabdoid tumors (100), and it has been suggested that *SMARCB1*-altered rhabdoid tumors respond to immunotherapy (101). In a recent study, the analysis of genomic, transcriptomic, and immune microenvironment data from sarcomatoid and rhabdoid RCC demonstrated the upregulation of immune pathways and greater CD8+ T-cell infiltration and *PD-L1* expression on tumor cells in these subtypes compared with other RCC subtypes (24). Patients with sarcomatoid and rhabdoid tumors who received immunotherapy had improved outcomes compared with patients who did not (24).

Other Alterations Possibly Associated With Immunotherapy Response

BAP1. BRCA1-associated protein 1 (*BAP1*) is a tumor suppressor gene involved in the regulation of chromatin remodeling and

DNA damage repair (102,103). BAP1 copy number loss or inactivating mutations are frequently noted in mesothelioma (40%-64%) and result in the accumulation of DNA-damaged cells (104-106). BAP1 loss promotes an immune inflammatory environment in mesothelioma (27). Integrative genomic, proteomic, and transcriptomic analyses of 19 peritoneal mesotheliomas showed that, in tumors with BAP1 loss (vs wild type), there were higher rates of infiltrated immune cells (27). Clinical trials demonstrated that PD-1 inhibitors are active in patients with malignant pleural mesothelioma, and these mesotheliomas frequently harbor BAP1 alterations (25,26,106).

MHC genotype. In addition to the quality of the neo-antigens, the host immune system's ability to efficiently present driver neo-antigens to T cells plays a critical role in immune response. The MHC class-I (MHC-I) genotype is predictive of response to immunotherapy in combination with TMB (28). The ability to present neo-antigens, defined by the Patient Harmonic-mean Best Rank (PHBR) score, was calculated in 83 patients with diverse malignancies who received immune checkpoint inhibitors. The PHBR score represents the ability of a specific human leukocyte antigen (HLA) class I genotype to bind and present a missense mutation; a lower PHBR score is suggestive of more efficient antigen presentation (107). Among patients with higher TMB (>20 mut/mb), those whose tumors had low PHBR scores had higher ORRs (78% vs 43%; $P = .049$) and longer PFS (26.8 vs 5.8 months; $P = .03$) compared with patients with PHBR-high tumors (28). The PHBR score did not predict response in patients with TMB-low tumors. Other investigators have also demonstrated that HLA-corrected TMB can reconcile the observed disparity in relationships between TMB and checkpoint blockade responses (108). Furthermore, MHC class II-restricted neo-antigens also play a crucial role in the antitumor response that is nonoverlapping with that of MHC class I-restricted neo-antigens and, therefore, needs to be considered when identifying patients who will most benefit from immunotherapy (109,110).

Mutational signatures. Neo-antigens are mutated peptides that enable the immune cells to recognize the tumor cell as foreign. The specific types of neo-antigens that stimulate a strong immune reaction remain unclear, but certain mutational signatures appear to be predictive of high immunogenicity and immunotherapy response. For instance, APOBEC (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like, a family of evolutionarily conserved cytidine deaminases involved in viral infections) hyperactivity has been implicated in localized hypermutagenesis (also designated as *kataegis*) in patients with breast cancer (111). In a study of 99 patients with diverse tumor types who received immunotherapy, APOBEC-related mutagenesis was associated with higher response rates (OR = 9.69, $P = .0106$) and longer PFS (3.1 vs 2.1 months; $P = .0239$), independent of TMB (29). APOBEC-related neo-antigens tend to be more hydrophobic, and therefore more immunogenic, because they are better presented by the MHC and more easily recognized by T cells. Similarly, neo-antigens produced from an ultraviolet (UV)-mutated genome had increased hydrophobicity and immunogenicity (30). A high UV signature correlated with longer PFS and OS in patients with low or intermediate TMB tumors after checkpoint inhibitor treatment, but there was no association in patients with TMB-H (>20 mut/mb) tumors.

PD-L1 amplification. PD-L1 expression, assessed by IHC, is currently approved as a biomarker for treatment with anti-PD-1 or anti-PD-L1 agents, albeit one with technical limitations (5). PD-L1 gene amplification, as assessed by next-generation sequencing, is the hallmark of Hodgkin disease, which is highly

responsive to checkpoint blockade (112), and also correlates with solid tumor immunotherapy responsiveness, although studied in only a small number of patients (31). In a retrospective analysis of comprehensive tumor molecular profiling data from 118 187 patients with diverse cancers, the prevalence of PD-L1 amplification was 0.7% (843 of 118 187 patients) (31). Solid tumors with the highest proportions of PD-L1 amplification (PD-L1 amplified/cases analyzed) were undifferentiated soft-tissue sarcoma (3.9%), head and neck squamous cell carcinoma (3.1%), breast carcinoma (1.9%), and lung squamous cell carcinoma (1.7%). Of 13 patients with solid tumors with PD-L1 amplification, 9 had received treatment with checkpoint blockade; the ORR was 66.7%, and the median PFS was 15.2 months (31). Interestingly, PD-L1 amplification did not always correlate with PD-L1 overexpression by IHC, even in responders, perhaps because of the technical limitations of IHC.

POLE/POLD1 mutations. DNA polymerase epsilon (POLE) and DNA polymerase delta 1 (POLD1) alterations correlate with immunotherapy response. These proteins play a critical role in DNA replication and repair regulation. In 47 721 patients (pan-cancer), POLE and POLD1 mutations were identified in 2.79% and 1.37%, respectively (32). Patients with POLE- or POLD1-mutated tumors had longer OS compared with patients with wild-type tumors after immunotherapy (32). Alterations in POLE or POLD1 have been associated with statistically significantly higher tumor mutational burden (33), higher CD8+ lymphocyte infiltration levels, and increased expression of cytotoxic T-cell markers compared with POLE or POLD1 wild-type tumors (113). In ongoing clinical trials (NCT02693535, NCT02912572, NCT03810339), patients with POLE or POLD1 mutations are selected for treatment with immunotherapy. For instance, in the Targeted Agent and Profiling Utilization Registry study (NCT02693535), a non-randomized clinical trial, patients with POLE or POLD1 mutations (or high mutational load) are selected for treatment with pembrolizumab or nivolumab and ipilimumab.

Investigational Biomarkers Conferring Resistance to Immunotherapy

Several genomic markers, such as loss of beta-2 (β 2)-microglobulin and JAK1/2, interfere with the immune response and hence correlate with resistance to immune checkpoint blockade. In addition, loss of Phosphatase and TENSin homolog deleted on chromosome 10 (PTEN) and alterations in EGFR, KEAP1, STK11/KRAS, and the B-catenin pathway have been associated with immunotherapy resistance, although the mechanisms are unclear. EGFR alterations and murine double minute 2 (MDM2) amplification have been correlated with accelerated progression (also known as hyperprogression) after checkpoint blockade, but the underlying biology has not been elucidated (Table 1, Figure 2) (44,114).

β 2-Microglobulin Mutations

β 2-microglobulin is a low-molecular-weight protein that forms MHC-I molecules in combination with the heavy chain. Proper functioning of β 2-microglobulin is critical for antigen presentation and assembly of HLA class I complexes. Loss of β 2-microglobulin facilitates tumor escape from immune recognition (115-117) and is implicated in resistance to immunotherapy. In one study, a truncated mutation in β 2-microglobulin was identified in tissue obtained from a patient with melanoma who progressed on anti-PD-1 therapy (34). IHC revealed loss of surface

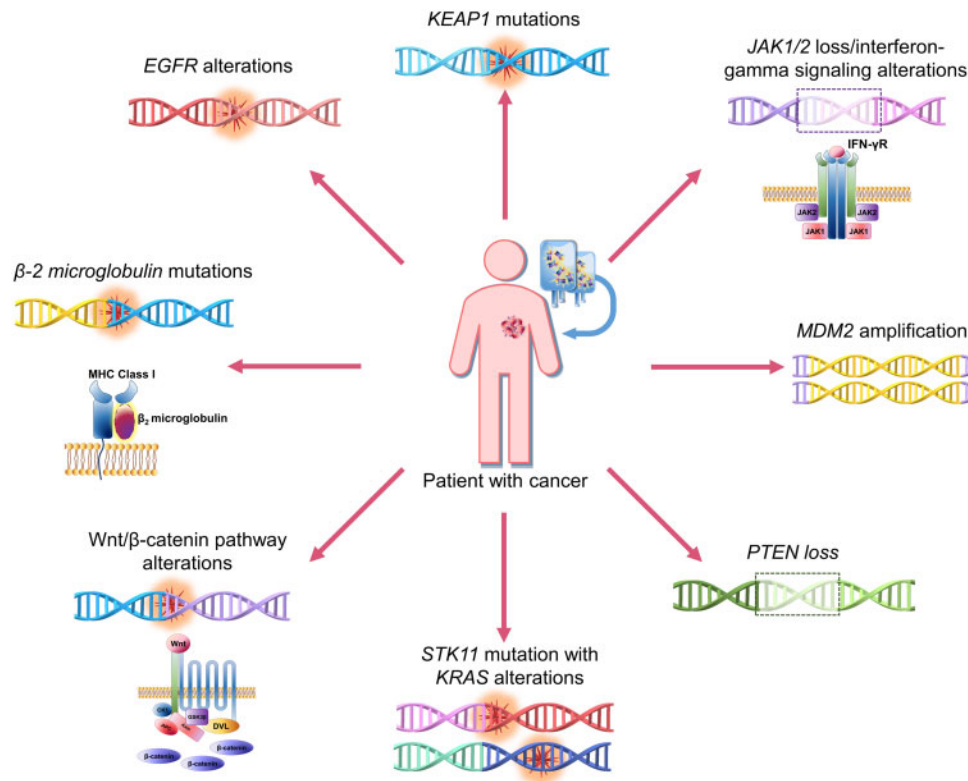


Figure 2. Investigational biomarkers associated with resistance to immuno-oncology therapy. It is not yet clear if some of these markers, such as KEAP1 and STK11 alterations, are prognostic or predictive. EGFR = epidermal growth factor receptor; JAK = Janus kinase; KEAP1 = Kelch-like ECH associated protein 1; KRAS = v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; MDM2 = murine double minute 2; PTEN = phosphatase and TENsin homolog deleted on chromosome 10; STK11 = serine/threonine kinase 11.

expression of MHC-I. In another study, analysis of longitudinal tumor biopsies demonstrated molecular alterations in β 2-microglobulin in 5 (29.4%) of 17 patients with advanced melanoma who progressed on immunotherapy (35). Loss of heterozygosity was noted only in nonresponders, whereas there was no molecular alteration in β 2-microglobulin detected in responders.

EGFR Alterations

Immunotherapy provides limited clinical benefit in patients with NSCLC harboring EGFR mutations (118). EGFR alterations are also associated with hyperprogression after treatment with immunotherapy in some studies, but not in others (3,37,114,119). In vivo investigation of tumor growth in T-cell-deficient mice, which were injected with EGFR-mutated patient-derived xenografts, showed that nivolumab triggered the accrual of macrophages and led to increased tumor growth and lung dissemination (120). Investigators have proposed upregulation of PD-1 and PD-L1 through EGFR activation as a mechanism of resistance (121).

KEAP1 Mutations

KEAP1 regulates cytoprotective responses to oxidative and electrophilic stress by binding the transcription factor NRF2 (122,123). Loss-of-function mutations in KEAP1 result in dissociation and constitutive activation of NRF2, cellular resistance to oxidative stress, and increased tumor cell growth (124,125).

Additionally, NRF2 activates drug efflux pump genes that confer resistance to cytotoxic drugs (126). KEAP1 mutations occur in 2.7% of patients with cancer, most commonly in patients with NSCLC (15.8%) (38). Studies suggest that KEAP1 mutations confer resistance to immunotherapy because they are associated with a “cold” tumor microenvironment (38,39). In 1 study, among 1661 patients who received immunotherapy, those with KEAP1 mutations had shorter OS compared with those with wild-type tumors (10 vs 20 months; $P = .0029$) (38). Other investigators showed that co-mutation of KRAS and KEAP1 (27% of KRAS-mutated tumors) in patients with NSCLC is an independent prognostic factor associated with shorter OS and duration of response to first-line platinum-based chemotherapy in patients who received immunotherapy (39). In the phase III MYSTIC NSCLC study, KEAP1 mutations correlated with poor outcome across arms (durvalumab alone, durvalumab plus tremelimumab or chemotherapy). Other studies have, however, reported that KEAP1 mutations may be associated with poor prognosis regardless of therapy and are not specifically predictive for checkpoint blockade outcome (40,41).

Janus Kinase 1 and 2 Loss

Janus kinase (JAK) is a family of intracellular, nonreceptor tyrosine kinases that transduce cytokine signals via the JAK-STAT pathway. Importantly, IFN- γ , critical to immune response, binds to its receptor and recruits and activates JAK1 and JAK2, and subsequently STAT1, thus resulting in immune cell activation

(127-129). Loss of IFN- γ signaling pathway genes has been implicated in immunotherapy resistance (34,42,43,130,131).

Whole-exome sequencing of paired melanoma tumors (primary tumor at diagnosis and metastatic tumor at the time of recurrence) after disease progression on anti-PD-1 therapy revealed acquired loss-of-function mutations in *JAK1* or *JAK2*, with deletion of the wild-type allele (34). Functionally, these mutations resulted in lack of response to IFN- γ . In another study, investigators showed that patients with *JAK1/2* inactivating mutations did not respond to immunotherapy (42). Additionally, *in vitro* exposure to IFN- γ failed to mediate downstream signaling. Finally, in another report, patients with *JAK2*-mutated advanced melanoma did not respond to anti-CTLA4 treatment, and melanoma cell lines with molecular alterations in IFN- γ pathway genes were refractory to immunotherapy (130). Together, these data indicate that loss-of-function *JAK1/2* mutations can mediate primary or acquired resistance to immunotherapy.

MDM2 Amplification

MDM2 encodes a nuclear-localized E3 ubiquitin ligase, which functions as a negative regulator of the *TP53* gene. *MDM2* amplification occurred in approximately 4% of more than 100 000 cancers analyzed (44,93,132) and was most commonly noted in patients with liposarcoma (64% of cases), gallbladder adenocarcinoma (11%), sarcoma (11%), and urothelial carcinoma (10%) (44). Most patients (99%) had additional molecular alterations (44). *MDM2* amplification has been linked to hyperprogression after treatment with immunotherapeutic agents (3,44,133,134). The biologic mechanism by which *MDM2* amplification mediates hyperprogression after treatment with immunotherapy is unknown, and it is possible that another gene on the *MDM2* amplicon is culpable. One study reported that *MDM2* mediates resistance to immunotherapy through degradation of transcription factor NFATc2, leading to reduced T-cell activation (135).

PTEN Loss

PTEN is the second most commonly mutated tumor suppressor gene. *PTEN* loss has been described in diverse tumor types, including hepatocellular (57% of patients), prostate (52%), endometrial (49%), and colorectal (48%) cancers (136). *PTEN* inhibits PI-3 kinase and AKT signaling by converting phosphoinositol-(3-5)-trisphosphate to phosphoinositol-(4, 5)-bisphosphate. *PTEN* loss, through mutations, epigenetic mechanisms, and gene silencing, disrupts its regulatory control of cell proliferation, energy metabolism, angiogenesis, and survival.

PTEN loss has been implicated in immunotherapy resistance in preclinical models, in an immune-suppressive microenvironment in prostate cancer and glioblastoma, and in acquired resistance in the clinic in a patient with metastatic uterine leiomyosarcoma, as well as to poor outcome from checkpoint blockade in melanoma (45,137-139).

STK11 Mutations With KRAS Alterations

Serine/threonine kinase 11 (*STK11*) is a tumor suppressor gene that regulates cell proliferation and energy metabolism. Patients with *STK11/KRAS*-mutated (compared with *KRAS*-only mutated) tumors have statistically significantly worse clinical outcomes after treatment with immunotherapy (47). In another study, the presence of *STK11* alterations was associated with

shorter PFS and OS and lower ORR in patients with NSCLC who received treatment with an anti-PD-1 agent combined with doublet chemotherapy (52). However, recently published real-world data (Flatiron Health Network) suggest that *STK11* mutations confer poor prognosis to patients with NSCLC regardless of treatment and show no specific prediction for immunotherapy outcomes (41).

TCR Repertoire

The TCR repertoire refers to the multiple possible combinations of TCR sequences and represents a “footprint” for T cells’ recognition of tumor neo-antigens. Higher TCR clonality has been associated with response to anti-PD-1 therapy in patients with melanoma (140,141). In patients with pancreatic cancer, low baseline clonality and higher rates of expanded clones after treatment with ipilimumab were associated with longer OS (142). Finally, neo-adjuvant treatment with nivolumab in patients with NSCLC induced expansion of neo-antigen-specific T-cell clones (143). Patients who achieved a major pathological response had higher rates of T-cell clonality.

Wnt/ β -Catenin Pathway Alterations

Wnt/ β -catenin signaling plays a critical role in proliferation, migration, and division (144,145). Deregulation of this pathway is a strong “driver” in diverse tumors, mainly CRC, where it occurs in 93% of cases (146). Many investigators suggest that the Wnt/ β -catenin pathway—as a candidate immune-related modulator—correlates with impaired immune cell recruitment in melanoma and other tumor types (48,137,147-149). An integrative The Cancer Genome Atlas data analysis, based on genomic, transcriptomic, or proteomic approaches, showed that non-T-cell-inflamed tumors (3137 of 9244 tumors, 33.9%) were enriched for WNT/ β -catenin pathway activation (150). Preclinical and clinical models demonstrate that WNT/ β -catenin activation leads to suppression of CD8+ T-cell tumor infiltration and evasion of immune elimination (48,147-149). T-cell suppression through activation of the Wnt/ β -catenin pathway has been linked to decreased chemokine levels (151). In preclinical trials, RNAi-mediated inhibition of the Wnt/ β -catenin pathway combined with anti-PD-1/CTLA-4 agents led to T-cell infiltration and tumor growth inhibition (152).

Other Immune-Related Biomarkers

Biomarkers beyond genomics predicting response and resistance to immune checkpoint inhibitors are included in Table 2. High PD-L1 expression, defined using various cutoff points ranging from more than 1% to more than 50%, is associated with clinical benefit in patients with various tumor types, but not in all clinical settings. Other emerging predictive biomarkers include gene expression signatures (153,154), oral and gut microbiome (155,156), neo-antigen load (157,158), PD-1 expression on immune cells (159), and TCR repertoire (140,142). Biomarkers predicting susceptibility to immune-related adverse events include circulating pro-inflammatory cytokines (160) and gut microbiota (155).

Tumor microenvironment typically comprises infiltrating immune cells, such as cytotoxic T cells, helper T-cell subsets, regulatory T cells, tumor-associated macrophages, and dendritic cells. The clinical relevance of the density and location of tumor-infiltrating lymphocytes (TILs) in patients with cancer is

Table 2. Biomarkers beyond genomics for response and resistance to immune checkpoint inhibitors^a

Biomarker	Cancer type	Role	Predictive value and comments	Selected references
FDA-approved biomarkers				
PD-L1 expression	Bladder cancer, NSCLC, TNBC, cervical cancer, and gastric/GEJ cancer	Inhibits peripheral T-cell activation and suppresses immune surveillance	Predicts response to immune checkpoint inhibitors	Patel, et al. 2015 (5)
Reported/Investigational biomarkers				
Gene expression signatures	Melanoma, NSCLC	Immune-related signatures	Predicts response Requires validation	Ayers, et al. 2017 (153) Fehrenbacher, et al. 2016 (154)
Gut microbiome	Melanoma	Modulate immune-mediated colitis	Predicts response or resistance Predicts toxicity	Chaput, et al. 2017 (155) Gopalakrishnan, et al. 2018 (156)
Neoantigen load	Across tumor types (melanoma, NSCLC)	Increased mutations/neoantigens	Predicts response to adoptive T-cell therapy and checkpoint inhibitors	Lauss, et al. 2017 (157) Rizvi, et al. 2015 (158)
PD-1 expression	Across tumor types (melanoma, gastric cancer, NSCLC)	PD-1 expression on CD8+ T cells negatively influences effector functions	Predicts response	Kumagai, et al. 2020 (159)
TCR diversity	Melanoma, NSCLC	Associated with immune expansion of T-cell clone that recognizes a specific tumor neoantigen	Predicts response	Tumeh, et al. 2014 (140) Hopkins, et al. 2018 (142) Forde, et al. 2018 (143)
Proinflammatory cytokines	Melanoma	Increase proinflammatory activities	Predicts toxicity	Lim, et al. 2019 (160) Fujimura, et al. 2018 (161)

^aFDA = US Food and Drug Administration; GEJ = gastro-esophageal junction; NSCLC = non-small cell lung cancer; PD-1 = programmed cell death-1; PD-L1 = programmed cell death-ligand 1; TCR = T-cell receptor; TNBC = triple-negative breast cancer.

currently being investigated. Previous studies have demonstrated that increased TIL concentration is associated with improved prognosis in patients with various tumor types (162). Whether high TIL concentration is predictive of response to immune checkpoint inhibitors is currently under extensive evaluation (163). Investigators have shown that higher TIL concentrations are associated with higher response rates and improved clinical outcomes in patients who receive immunotherapy in different clinical settings (140,164). The presence of a high number of TILs has also been associated with high PD-L1 expression (165,166) and/or MSI-H and dMMR (167,168). Ongoing and future investigations will address the limitations involving the methodology, interpretation (invasive margin or central infiltration), and cutoff values for TILs and will optimize the standardization of TIL assessment to enable comparisons of various clinical trials (169).

Discussion

Tumor microenvironment complexity, intratumoral heterogeneity, and distinct host immunity complicate the identification of immune checkpoint blockade predictive biomarkers. Tumors and their surrounding ecosystem have individually distinct and complex immune profiles. Biomarkers such as PD-L1, assessed by IHC, may be imprecise predictors of immune checkpoint blockade response for technical reasons or because of the complexity of the immune response (5). In addition, overexpression of specific biomarkers, such as alternate checkpoints TIM-3 and VISTA, was also statistically significantly associated with shorter PFS after anti-PD-1- and PD-L1-based therapies in

patients with diverse malignancies (170). Therefore, patients may need customized combinations of immunotherapy. Ultimately, composite biomarkers that incorporate genomic and immune profiles, host pharmacogenome as reflected by MHC and the TCR repertoire, and other factors may be needed. Based on current data, it seems unlikely that a single biomarker will be predictive for all patients or all types of immunotherapeutic agents. Machine learning algorithms that can combine genomic, transcriptomic, epigenomic, and immune-related markers and consider their interactions may be exploitable to overcome the complexity of the immune system. Ideally, all patients with cancer should be screened for all available immuno-oncology markers and receive the corresponding best treatment. Prospective trials should focus on the systematic analysis of genomic and immune profiles of patients who are treated on immuno-oncology trials and the correlation of these profiles with response or resistance and toxicity. Given the plethora of biomarkers that have been correlated with resistance to immunotherapy, particularly hyperprogressive disease, caution is warranted when patients with these biomarkers are considered for immuno-oncology treatments. The identification of novel biomarkers and consensus regarding “molecular resistance” to immunotherapy would help optimize the deployment of these potentially curative treatments.

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