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Review

Correlation of preclinical and clinical biomarkers with efficacy and toxicity of cancer immunotherapy

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***Abstract*:** Immune checkpoint inhibitors (ICIs) have revealed significant clinical values in different solid tumors and hematological malignancy, changing the landscape for the treatment of multiple types of cancer. However, only a subpopulation of patients has obvious tumor response and long-term survival after ICIs treatment, and many patients may experience other undesirable clinical features. Therefore, biomarkers are critical for patients to choose exact optimum therapy. Here, we reviewed existing preclinical and clinical biomarkers of immunotherapeutic efficacy and immune-related adverse events (irAEs). Based on efficacy prediction, pseudoprogression, hyperprogressive disease, or irAEs, these biomarkers were divided into cancer cell-derived biomarkers, tumor microenvironment-derived biomarkers, host-derived biomarkers, peripheral blood biomarkers, and multi-modal model and artificial intelligence assessment-based biomarkers. Furthermore, we describe the relation between ICIs efficacy and irAEs. This review provides the overall perspective of biomarkers of immunotherapeutic outcome and irAEs prediction during ICIs treatment.

Keywords: biomarker, hyperprogressive disease, immune checkpoint inhibitors, immune-related adverse events, pseudoprogression

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Introduction

Immune checkpoint inhibitors (ICIs), represented by cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed cell death ligand 1 (PD-L1) antibodies, have shown significant clinical benefits in different solid tumors and hematological malignancies, changing the landscape of the treatment of multiple cancer types. However, only one patient sub- population have obvious tumor response and long-term survival rate after ICIs treatment. A large number of patients may experience other undesirable clinical features, such as pseudoprogression (PsP), immune-related adverse events (irAEs), or even hyperprogressive disease (HPD). Therefore, biomarkers are critical for patients to receive optimum ICIs treatment and avoid irAEs. Here, we reviewed the research progress on the biomarkers including efficacy, HPD, PsP, and irAEs of ICIs (Figure 1).

Cancer cell-derived biomarkers

PD-L1

PD-L1 is the most widely studied and reported biomarker for ICIs efficacy. Theoretically, the more PD-L1 is expressed, the stronger the immunosuppressive effect will be generated, and the greater benefit will be achieved from ICIs treatment. Previous studies have supported this point. In the KEYNOTE-001 study, the objective response rate (ORR), median progression-free survival (PFS), and overall survival (OS) were significantly better in patients with PD-L1 expression greater than 50% than in those lower than 50%.[1] CheckMate 012 study revealed that

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ORR was higher in PD-L1-positive patients.[2] However, other studies showed that PD-L1-negative patients can also benefit from ICIs.[3] This may result from the lack of a consensus on PD-L1 detection, for example, different detection antibodies, detection platforms, tissue fixation, tissue sources, and scoring methods.[4–6] In addition to immunohistochemical detection of PD-L1 expression in tissues, enzyme-linked immunosorbent assay and fluorescence immunoassay can be used to detect PD-L1 in peripheral circulation.[7,8] Therefore, it is necessary to establish the standard process of PD-L1 detection and develop a reasonable scoring method in the future.

Tumor mutational burden

Tumor mutational burden (TMB) refers to the total number of mutations per megabase, that is, the total number of somatic mutations in the tumor genome after removing germline mutations. It can be assessed by computed tomography (CT) scan, fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT, circulating tumor cells, circulating tumor DNA (ctDNA), serum lactate dehydrogenase (LDH), and serum tumor markers.[9] A retrospective study of 27 cancers demonstrated that the higher TMB was, the better efficacy ICIs treatment would achieve and the higher ORR would be.[10] Subsequently, a prospective study showed that patients with TMB $\geqslant$ 10 achieved a significantly higher 1-year PFS rate (42.6% *versus* 13.2%) and a longer PFS (7.2 *versus* 5.0 months) than those with lower TMB.[11] CheckMate 568 study confirmed that the median PFS of patients with TMB $\geqslant$ 10 was significantly longer than those with TMB $<$ 10 (7.1 *versus* 2.6 months), and it was not related to the expression of PD-L1.[12] Recently, Jacob *et al.* reported that TMB $\geqslant$ 20 mut/MB were significantly associated with better clinical efficacy of ICIs. In the state of high TMB (TMB-H), specific oncogenic signaling pathway mutations are associated with poor response to ICIs in advanced non-small-cell lung cancer (NSCLC). Sands *et al.*[13] reported that among the TMB-H patients, TP53 ($p = 0.026$), PIK3CA ($p = 0.025$), and ROS1 ($p = 0.057$) gave worse response. When genetic pathways were assessed, mutations in the TP53 pathway were associated with poorer response ($p = 0.018$). Cao *et al.*[14] demonstrated that TMB is a promising biomarker for the prognosis of ICIs using meta-analysis and

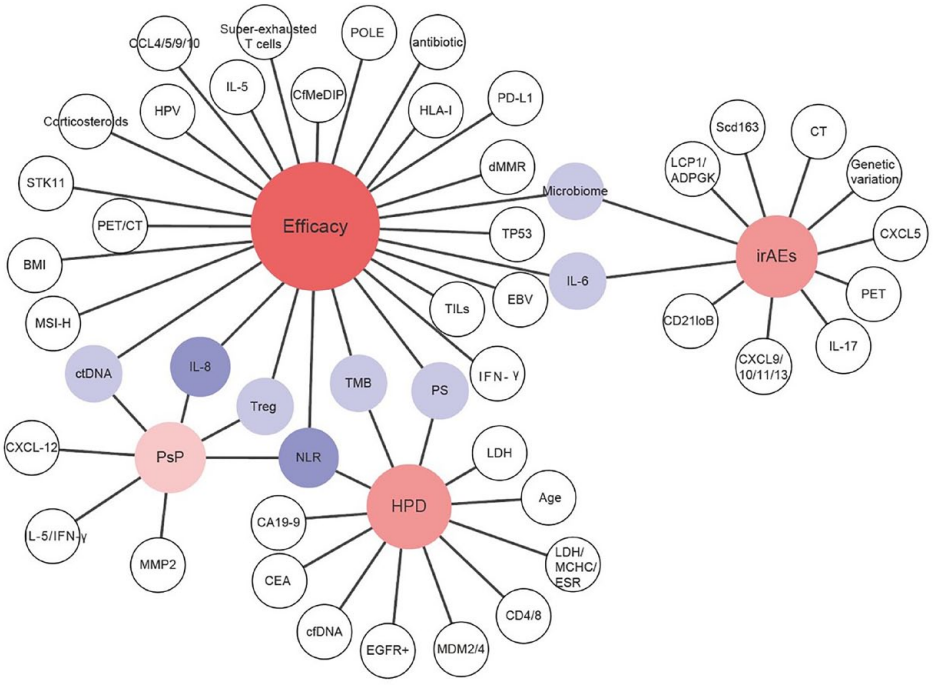

Figure 1. The biomarkers of ICIs efficacy, PsP, HPD, and irAEs.
HPD, hyperprogressive disease; ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events; PsP, pseudoprogression.

bioinformatic analysis, as it is positively correlated with ORR, PFS, and OS, but the evaluation method and cutoff value of TMB need to be further standardized.

Deficient mismatch repair and microsatellite instability-high

In a prospective study of patients with mismatch repair deficiency in 12 types of advanced solid tumors receiving PD-1 antibodies, objective radiographic responses were observed in 53% of patients, and complete disease remission was assessed in 21%, suggesting that a large proportion of deficient mismatch repair (dMMR) cancer tissues generate neoantigens to make the tissues sensitive to ICIs, regardless of the origin of the cancer tissue. The mutation rate is 10–100 times higher in dMMR tumors than in proficient mismatch repair tumors.[15] Moreover, it was reported that dMMR tumors were easy to mutate in repetitive DNA sequences, possibly leading to microsatellite instability-high (MSI-H).[16,17] Therefore, FDA-approved pembrolizumab treatment in patients with metastatic or unresectable solid tumors was characterized by MSI-H or dMMR. This is the first pan-cancer ICI drug based not on cancer type but on genetic alterations.[18]

DNA damage repair-related genes

DNA damage repair (DDR)-related genes, including *ERCC2*, *BRCA1*, *BRCA2*, *FANCA*, *RAD51C*, and *MSH2*, play an important role in DDR.[19] Studies have shown that DDR-related genes can also predict the efficacy of ICIs. BRCA2 mutations can predict the efficacy of PD-1 antibody therapy in patients with advanced melanoma.[20] POLE gene mutations can rapidly accumulate a large number of somatic mutations, which can promote the production of tumor-specific neoantigens, resulting in enhanced immunogenicity and high mutation load.[21,22] Recent studies have reported that POLE gene mutations can be used to predict the efficacy of ICIs for endometrial cancer and colorectal cancer.[23,24] TP53 is probably the most widely studied tumor suppressor gene, and patients with TP53 mutations always have a poor prognosis. Some studies have found that TP53 mutations reduce genomic stability and are associated with DDR defects, suggesting that tumors with TP53 mutations may have a higher TMB.[25–27] TP53/STK11 often occurs with KRAS mutations in NSCLC patients, and PD-L1 expression levels are high, which can be used to guide ICI usage.[27]

Genetic variation

Genetic variation can serve as a biomarker to predict ICIs efficacy, irAEs, and HPD. The CTLA-4 gene variant $-1661A>G$ predicts endocrine adverse events in patients with metastatic melanoma and treated with ipilimumab, and SNPPDCD1804C>T is associated with lower incidence of irAEs.[28,29] Kato *et al.* analyzed the genomic profile of 155 patients by next-generation sequencing (NGS) and found that MDM2/4 ($p=0.02$) and EGFR ($p=0.02$) were associated with poor efficacy and 67% of patients with MDM2/4 amplification developed HPD. The possible mechanism is that ICIs trigger MDM2 amplification by promoting the expression of interferon regulatory factor 8 (IRF-8), which binds to the MDM2 promoter *via* JAK-STAT signaling. Thus, the amplification of MDM2/4 may be a biomarker for HPD, and MDM2 inhibitors may be potential therapy for HPD. EGFR-sensitive mutations may also be biomarkers for the development of HPD. One study showed that 8 of 10 patients with EGFR mutations had time-to-treatment failure (TTF) less than 2 months, and 2 of them had HPD.[30] Another study showed HPD in 20% (2/10) of patients with EGFR changed. These findings can be possibly explained by EGFR activation leading to the upregulation of PD-1/PD-L1, which, in turn, drives immune escape and leads to HPD.[31]

Tumor microenvironment-derived biomarkers

Tumor-infiltrating lymphocytes

The phenotype, distribution, and infiltration of tumor-infiltrating lymphocytes (TILs) are the focus of many ongoing studies. It has been reported that higher score of $CD8^+$ TILs has better clinical benefit.[32,33] A recent study demonstrated that the model of TILs density calculated from digital H & E images can predict the objective response to PD-1 inhibitor in patients with advanced lung adenocarcinoma. But the area under the curve was not high (0.61). TILs need to combine with other biomarkers, such as PD-L1 and TMB.[34] However, $CD8^+$ TILs are highly heterogeneous. Only a small fraction of the population can recognize tumor mutation-associated antigens. $CD8^+$ TILs in the stromal and invasive

marginal compartments of the tumor have better clinical outcomes than those in the intra-tumoral compartment.[33,35]

Super-exhausted T cells

Super-exhausted T cells were characterized by co-expression of key immune checkpoints, including PD-1, LAG3, TIGIT, and TIM3. From 435 patients with solid tumors, tissue samples were collected prior to the initiation of ICIs therapy. Multiplex immunofluorescence using CD3/PD1/TIM3/LAG3/TIGIT/CTLA-4 panels and multispectral image analysis were employed for immune cell characterization. The association between co-expression of T-cell-associated exhausted markers and clinical response rate, PFS, and OS was investigated by the COX proportional hazards model. The results indicate that super-exhausted T-cell-positive tumor has higher ORR and better PFS and OS than the control.[36]

HLA-I

HLA molecules are expressed on the surface of different immune cells and play a crucial role in antigen presentation and immune signal transduction. Disruption of the HLA-I antigen processing and presentation mediates immune evasion, being one of the mechanisms of acquired resistance to ICIs. Several HLA genotypes have been reported as biomarkers for ICIs. For example, HLA-a * 03 allele is a predictor of lower ORR and shorter PFS and OS and loss of heterozygosity patients have shorter OS. HLA-B44 and HLA-A02 supertypes indicate longer OS in melanoma patients.[32,37,38]

Host-derived biomarkers

Microbiome and antibiotics

The dynamic balance of intestinal microbiota plays an active role in maintaining the homeostasis of the immune system. A study has shown that the intestinal microbiome can influence cancer immune reference point by inducing specific memory T cells through $CD4^+$ and $CD8^+$ T cells secreting Interferon gamma (IFN-γ), which is related to good prognosis after ICI treatment.[39] Another study showed that hepatocellular carcinoma patients who responded to ICIs had higher bacterial flora richness in their fecal samples than non-responders, and there was a significant difference in the dissimilarity of beta diversity at week 6 of treatment. Among non-responders, Proteobacteria predominated at week 12, while Ackermanella and Ruminococcaceae increased significantly among responders.[40] Similarly, a prospective study showed that abundant Ruminococcaceae UCG 13 and Agathobacter may predict better ORR and longer PFS. Enriched Ruminococcaceae UCG 13 was associated with longer OS. Moreover, microbiome was different between patients experiencing different grade of irAEs.[41,42]

A retrospective study evaluating the effect of antibiotics on OS and PFS in the subsequent treatment of NSCLC showed a significant reduction in OS in patients receiving antibiotics in the atezolizumab group, but no association between antibiotic usage and survival time in the docetaxel group.[43] However, antibiotics before ICIs treatment did not affect the OS of NSCLC patients treated with first-line ICIs combined with chemotherapy.[44] Studies have shown that intestinal flora and the effect of ICIs are related to the type of cancer and patient subpopulation. Further studies are needed to explore the mechanism of intestinal flora in affecting the immune microenvironment and thus the effect of ICIs.

Performance status

Recent studies have reported that first-line ICIs combination therapy in cancer patients with excellent Eastern Cooperative Oncology Group performance status (ECOG PS = 0) has a better prognosis, with improved PFS and OS.[45] PS can also predict HPD. It was reported that HPD is more likely to occur in patients with Royal Marsden Hospital score ≥ 2, ECOG performance status ≥ 2, more than two metastases, recurrent metastatic head and neck squamous cell carcinoma of the primary oral cavity, and PD-L1 positive combined score ≥ 10 in liver metastasis of gastric cancer.[46–49]

BMI

Higher body mass index (BMI) may be associated with better response to ICI therapy. ORR for patients with normal BMI and obesity treated with ICIs was 28% and 42%, respectively ($p = 0.03$). Obese patients had significantly improved median PFS (36.4 *versus* 23.5 months, $p < 0.0001$) and OS (HR: 0.64, 95% CI: 0.44–0.91, $p = 0.014$) compared with normal BMI patients.[50]

Age

Studies have shown that age is a biomarker for HPD, because immunosenescence is age related and characterized by a decline in cell-mediated immune function and a decline in humoral immune response.[51] Some studies have shown that in NSCLC and cervical squamous cell carcinoma, the HPD patients are younger.[52–54] Therefore, age cannot be used as an independent biomarker to predict HPD. As for irAEs, some studies reported that severe irAEs more frequently occur in younger patients, while others showed the opposite results.[55–57] Therefore, age could not be used as an independent biomarker, instead it needs to be combined with other biomarkers.

Autoimmune disease history

irAEs are most common in the skin, endocrine glands, gastrointestinal system, and liver, and can affect almost any organ system, including the cardiovascular, pulmonary, musculoskeletal, ocular, and central nervous systems.[58] Compared with chemotherapy-related adverse reactions, irAEs have the characteristics of long duration and late onset. Therefore, it is important to recognize and manage irAEs early in clinical practice.[59] Studies have revealed that autoimmune disease history is associated with the development of irAEs.[60,61] Researchers had analyzed autoimmune diseases and irAEs at the molecular level, and found that the frequency of HLA-DRB1 shared epitope alleles was higher in patients with immune-mediated arthritis, and HLA-DR4 alleles were associated with ICIs-related type I diabetes.[62] In addition, some studies have shown that autoantibodies before ICI treatment are closely related to the occurrence of irAEs, such as antinuclear antibodies, anti-thyroglobulin, and anti-thyroid peroxidase.[63] To sum up, if patients have autoimmune diseases before treatment, they should be particularly alert to the occurrence of irAEs during ICIs.

Viral infection

Some tumors are related to viral infections, such as cervical cancer and HPV, gastric cancer, and EB virus. Studies have shown that viral infection can be also used as a potential biomarker for the efficacy of ICIs. A prospective study of advanced gastric cancer treated with pembrolizumab demonstrated that the ORR of EBV-positive patients was 100%, while another meta-analysis found that the ORR and survival time of HPV-positive patients with head and neck squamous cell carcinoma and being treated with PD-1 inhibitors were better than those HPV-negative patients.[64,65]

Corticosteroids

Corticosteroids are widely used due to their potent anti-inflammatory and immunosuppressive effects. Unfortunately, studies have shown that corticosteroid use is associated with poorer clinical outcomes. A retrospective study discovered that baseline corticosteroid use of $\geqslant$10 mg prednisone was associated with worse outcomes in patients with NSCLC and treated with PD-L1 inhibitors.[66]

Imaging examination

Studies have reported that PET/CT can predict the occurrence of thyroiditis in patients with lung cancer, which is manifested by increased uptake of FDG in the thyroid gland of patients on PET images, and this uptake increase occurs before the increase in serum TSH.[67] In addition, CT-based radiomics methods can accurately predict immune-associated pneumonia.[68] At present, it is difficult to find efficient biomarkers to predict the occurrence of irAEs in the early stage. Reported biomarkers for irAEs are often based on retrospective studies. Specific types of adverse reactions need to be clarified and expensive detection techniques uncommonly used in clinical practice are required. Therefore, more large-scale, and prospective studies should be conducted to validate the above biomarkers.

Peripheral blood biomarkers

Peripheral blood cell count

Peripheral blood detection is a hot field of biomarker study because of its strong feasibility, easy receptivity, and non-invasive characteristics. It was reported that neutrophil-to-lymphocyte ratio (NLR) was associated with poor immunotherapeutic outcomes.[69,70] A meta-analysis found that a higher level of NLR indicated poorer PFS and OS in melanoma, NSCLC, and genitourinary cancers.[71] In patients with stage III–IV melanoma treated with nivolumab, a high absolute lymphocyte count ($\geqslant$1000/μL) and a low absolute neutrophil count ($<$4000/μL) early in the course of therapy were significantly associated with better OS.[72] Other studies constructed risk blood

biomarkers by combining white blood cell count and NLR.[73] Meanwhile, high eosinophil count (⩾1.5%) and relative lymphocyte count (⩾17.5%) were proved to be independent baseline characteristics associated with longer OS in melanoma patients treated with pembrolizumab.[74] Kiriu *et al.*[75] found that patients with PsP have significantly lower NLR than patients with true tumor progression before and after treatment.

Derived NLR (dNLR) and platelet counts were higher in HPD patients with NSCLC or head and neck squamous cell carcinoma.[47,76,77] It was reported that ΔNLR > 75% indicates the occurrence of HPD in NSCLC at week 4 with an accuracy of 86.1%.[78]

In addition, baseline NLR was reported to be an independent predictor of irAEs in patients with NSCLC.[79] Also, baseline circulating eosinophils are associated with higher immune pneumonia.[80]

In conclusion, NLR is a promising biomarker that indicates efficacy, HPD, PsP, and irAEs. However, more prospective studies are needed to confirm the role of this biomarker.

CtDNA, cfDNA, and cfMeDIP

ctDNA helps to recognize tumor-specific abnormalities and can be used for diagnosis, follow-up therapy, and prognosis. Recently, a meta-analysis carried out 17 trials to explore the relationship between changes in ctDNA levels and prognosis in patients with advanced solid tumors treated with ICIs. ctDNA clearance was defined as a reduction in ctDNA greater than 50% or to an undetectable level. The results showed that in non-selected advanced solid tumors, a significant decrease in ctDNA after ICIs was associated with significant improvement in PFS and OS.[81] In a prospective study, 125 patients with advanced melanoma received single or dual ICIs, among whom 29 patients (23.2%) developed PsP, which occurred in patients with good ctDNA profile. ctDNA was not detectable at baseline, or decreased by 10 times or not detectable within 12 weeks of treatment.[82] Similar results were reported by Guibert *et al.*,[83] who used ddPCR to detect plasma ctDNA to monitor the response to anti PD-1 therapy in patients with KRAS-mutant lung adenocarcinoma. Methylated circulating tumor DNA (cfMeDIP) can be used as a predictive marker for the efficacy of pembrolizumab.[84] One study evaluated 56 patients for cfDNA sequencing, using the chromosome number instability score to quantify chromosomal instability, and showed that quantification of chromosomal instability can be used as an early indicator of response to ICIs.[85] When tumor tissue cannot be obtained, due to deep tumor location or complications, ctDNA is a good choice. However, the ideal time to evaluate the change in ctDNA level and the diagnostic criteria of PsP need further study.

Cytokines and chemokines

Cytokines activate immunity and chemokines attract $CD8^+$ T cells, which are prerequisites for ICIs. IFN-γ is a cytokine that plays a role in innate and adaptive immunity. A study showed that patients with highly expressed IFN-γ before ICIs had higher ORR, PFS, and OS. POPLAR and other studies found that higher IFN-γ expression indicated better OS.[86–88] Interleukin (IL)-8 is a member of the CXC chemokine family and was originally identified as a chemokine for neutrophils. Retrospective studies on advanced melanoma or NSCLC have revealed that early elevation of serum IL-8 level is a predictor for poor outcome, while higher IL-6 at baseline is associated with better clinical outcome.[89,90] However, in a recent prospective real-world study of 78 patients with advanced melanoma and NSCLC treated with ICIs, a higher median relative increase of IL-6, IL-8, and IL-8 at T2 was associated with a significantly lower rate of disease control.[91] A study of melanoma and NSCLC demonstrated that target lesion volume increased but serum IL-8 decreased during imaging assessment of PsP. Target lesion volumes subsequently remained below baseline and serum IL-8 steadily increased with disease progression. This suggests that serum IL-8 can accurately reflect true tumor response and can be used to distinguish PsP from true progression.[89] Khan *et al.*[92] found that baseline cytokine levels were low in patients with irAEs and increased after treatment, suggesting that immune dysregulation may be associated with a higher risk of irAEs, and that the pattern of inducible CXCL9, 10, 11, and 13 levels are most strongly associated with irAEs. Low baseline IL-6 serum levels are associated with high incidence of colitis and psoriasis.[42,90,93] Serum IL-17 levels before treatment are associated with grade 3 or

higher colitis.[94] Fujimura *et al.*[95] reported that soluble CD163 and CXCL5 can predict the occurrence of irAEs. A prospective study found that patients with a decrease in circulating B cells (70% of baseline) and a greater than twofold increase in CD21loB cells and plasmablasts are more likely to develop irAEs, and that the severity of the early decline in B cell numbers after treatment is directly related to the time of toxicity onset.[96] It has also been reported that T cell-activated lymphocyte cytosolic protein 1 combined with ADP-dependent glucokinase can accurately predict the occurrence of immune pneumonia in lung cancer patients.[97] For chemokines, a recent study showed that cancer patients with high expression of four chemokines (CCL4, CCL5, CXCL9, and CXLC10) had a longer median progression time (104 days *versus* 71 days, $p = 0.013$) and longer OS (391 days *versus* 195 days, $p = 0.016$).[98] Matsuo *et al.*[99] revealed that decreased plasma CXCL12 levels and increased MMP2 levels after anti-PD-1 treatment are significantly associated with an improvement in PFS. Furthermore, CXCL12 levels in patients with PsP are consistently lower than baseline levels after pretreatment, and MMP2 levels are consistently higher than baseline levels.

Peripheral blood biochemical index

LDH, one of the key enzymes in the glycolytic pathway, has been considered a negative biomarker of ICI therapy.[100] A high LDH level may predict poorer response and worse PFS and OS after nivolumab treatment in patients with advanced NSCLC.[101] Similarly, normal baseline LDH level may indicate longer OS in melanoma received nivolumab.[102] Furthermore, baseline serum LDH has also been reported to be the most crucially factor associated with OS in patients with melanoma and treated with nivolumab plus ipilimumab. Patients with higher baseline serum LDH had a median OS of 17.4 months compared with 60 months in patients with normal serum LDH.[103] In a large retrospective study of ICIs for advanced melanoma, high baseline serum LDH in patients with HPD suggested aggressive tumor biology.[104] It has also been reported that rapid elevation of carcinoembryonic antigen in colorectal cancer and carbohydrate antigen 19-9 in pancreatic and cholangiocarcinoma during the first month of ICIs indicates the development of HPD.[105]

Multi-modal models and artificial intelligence assessment

Multi-modal models based on expert-guided learning machines can predict the immune response of NSCLC patients more accurately.[106] A study demonstrated that numerical quantification of TILs in HE images by machine learning models may be used to analyze NSCLC responses to ICIs.[107] Another study showed that deep network machine learning analysis (AE-SDN) can screen out the main genes related to immunity, carcinogenesis, and tumor suppression. This model improved the prediction quality of OS by 20% compared with using the immune score.[108] Furthermore, a study revealed that automated tumor immunophenotyping and spatial statistics based on metric learning can successfully link spatial features to manual immunophenotyping and link patient response to treatment.[109] A recently published retrospective study established a nomogram model based on LDH/MCHC/ESR for predicting the occurrence of HPD with a concordance index of 0.899.[110] Using big data and databases to construct various prediction models is the future trend in HPD biomarkers research.

Relationship between efficacy and irAEs

A systematic review has shown a positive association between the development of irAEs and ORR, PFS, and OS in patients receiving ICIs, regardless of tumor site, type of ICIs, and type of irAEs. Moreover, irAEs at grade 3 or higher level have better ORR but poorer OS.[111] Zhou *et al.*[112] demonstrated that the occurrence of irAEs is positively correlated with the efficacy of ICIs, especially endocrine, skin, and low-grade irAEs. The results of these studies are based on systematic reviews and meta-analyses, therefore requiring further confirmation by large-scale prospective trials.

Conclusion and prospect

At present, there are many biomarkers for efficiency of immunotherapeutic outcome, HPD, PsP, and irAEs, but most of them still need to be confirmed by large-scale prospective clinical trials (Table 1). How to convert non-targeted population into targeted population and how to make ICIs more accurate, controllable, and have lower toxicity and longer-term benefits will be the focus of future research on biomarkers of efficacy and adverse reactions of ICIs.

Table 1. Significance of biomarkers of ICIs efficacy, PsP, HPD, and irAEs.

Biomarkers		Significance	Reference
Efficacy	PD-L1	Higher PD-L1 expression may be associated with better prognosis	Garon *et al.*,[1] Hellmann *et al.*[2]
	TMB	Higher TMB may be associated with better prognosis	Dall'Olio *et al.*,[9] Yarchoan *et al.*,[10] Hellmann *et al.*,[11] Ready*et al.*,[12] Sands *et al.*,[13] Cao *et al.*[14]
	dMMR/MSI-H	dMMR/MSI-H response better to ICIs	Dudley *et al.*,[15] Timmermann *et al.*,[16] The Cancer Genome Atlas Network,[17] Le *et al.*[18]
	HLA-I	HLA-a * 03 allele predict lower ORR and worse PFS and OS; LOH predicts shorter OS. HLA-B44 and HLA-A02 supertypes mean longer OS	Chen and Mellman,[32] Naranbhai *et al.*,[37] Chowell *et al.*[38]
	TIL	CD8 + TILs may be associated with better prognosis	Chen *et al.*,[32] Geng *et al.*,[33] Corredor *et al.*,[34] Tumeh *et al.*[35]
	Super-exhausted T cells	Super-exhausted T-cell-positive tumor had higher ORR and better PFS and OS	Peyraud *et al.*[36]
	Cytokines and chemokines	IL-8 predicts poor outcome, higher IL-6 at baseline, four chemokines (CCL4, CCL5, CXCL9, and CXLC10), IFN-γ are associated with better clinical prognosis	Fehrenbacher *et al.*,[86] Sharma *et al.*,[87] Socinski *et al.*,[88] Sanmamed et al.,[89] Valpione *et al.*,[90] Pasello *et al.*[91]
	Microbiome and antibiotic	Proteobacteria, Ackermanella, and ruminococcaceae increased significantly among responders	Fluckiger *et al.*,[39] Chalabi *et al.*,[43] Cortellini *et al.*[44]
	DDR-related genes	POLE gene mutations in endometrial cancer and colorectal cancer, TP53/STK11 in KRAS mutant NSCLC patients predict better efficacy	Mouw *et al.*,[19] Hugo *et al.*,[20] Shlien *et al.*,[21] Andrianova *et al.*,[22] Howitt *et al.*,[23] Hwang *et al.*,[24] Cortez *et al.*,[25] Ji *et al.*,[26] Jeanson *et al.*[27]
	Viral infection	EBV positive predicts better ORR in advanced gastric cancer, HPV positive predicts better ORR and survival time in head and neck squamous cell carcinoma	Wang *et al.*,[64] Kim *et al.*[65]
	Corticosteroids	More than 10 mg prednisone is associated with worse outcomes	Arbour *et al.*[66]
	Personal factor	PS scored 0, BMI high predicts better prognosis	Grohe *et al.*,[45] Wang *et al.*[50]
	Multimodal models and AI assessment	Positive/negative	Rakaee *et al.*,[107] Ghasemi Saghand *et al.*,[108] Orlova *et al.*,[109] Cao *et al.*[110]
PsP	ctDNA	Good ctDNA profile develop PsP	Lee *et al.*,[82] Guibert *et al.*[83]
	IL-8	IL-8 can accurately reflect true tumor response	Sanmamed *et al.*,[89] Valpione *et al.*,[90] Pasello *et al.*[91]
	NLR	Lower NLR before and after ICIs treatment	Kiriu *et al.*[75]
	CXCL-12 and MMP2	Lower CXCL12 and higher MMP2 levels after anti-PD-1 treatment predicts PsP	Mezquita *et al.*[100]

(Continued)

Table 1. (Continued)

Biomarkers		Significance	Reference
HPD	Clinicopathological features	Younger, PS scored more than 2, more than 2 metastases, primary oral cavity with recurrent mHNSCC, gastric cancer liver metastasis with positive combined PD-L1 score more than 10	Lin *et al.*,[46] Castello *et al.*,[47] Hagi *et al.*,[48] Han *et al.*,[49] Park *et al.*,[52] Choi *et al.*,[53] Economopoulou *et al.*[54]
	Biochemical indexes	High LDH, dNLR, and platelet count; rapid elevation of CEA, CA19-9 may predict HPD	Cortellini *et al.*,[44] Sanchez-Gastaldo *et al.*,[73] Weide *et al.*,[74] Kiriu et al.,[75] Mezquita *et al.*,[100] Agullo-Ortuno *et al.*[101]
	cfDNA	CNI score	Weiss *et al.*[85]
	MDM2/4 amplification	Negative	Wang *et al.*[31]
	EGFR mutation	Negative	Queirolo *et al.*,[28] Bins *et al.*[29]
	nomogram model	LDH/MCHC/ESR nomogram model	Cao *et al.*[110]
irAEs	Autoimmune disease history	Negative	Postow *et al.*,[58] Puzanov *et al.*,[59] Abdel-Wahab *et al.*,[60] Michailidou *et al.*,[61] Stamatouli *et al.*,[62] Toi *et al.*[63]
	Circulating cytokines and immune cells	Inducible CXCL9, 10, 11, and 13 levels; twofold increase in CD21loB cells and plasmablasts; low baseline IL-6 predicts colitis and psoriasis; serum IL-17 predicts colitis; LCP1 and ADPGK predict immune pneumonia	Chaput et al.,[42] Tanaka *et al.*,[93] Tarhini *et al.*,[94] Fujimura *et al.*,[95] Das *et al.*,[96] Jing *et al.*,[97] Romero *et al.*,[98] Matsuo *et al.*[99]
	Genetic variation	CTLA-4 gene variant −1661A > G predict higher incidence of irAEs, while SNPPDCD1804C > T predicts lower incidence	Queirolo *et al.*,[28] Bins *et al.*[29]
	Microbiome	Fecal bacilli and other Firmicutes predict high incidence rate of colitis, while Bacteroides predict lower incidence rate	Hakozaki *et al.*,[41] Chaput *et al.*[42]
	Imaging examination	PET-CT to predict thyroiditis, CT to immune-associated pneumonia	Eshghi *et al.*,[67] Colen *et al.*[68]

ADPGK, ADP-dependent glucokinase; AI, artificial intelligence; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; cfDNA, cell-free DNA; CNI, chromosome number instability; CT, computed tomography; ctDNA, circulating tumor DNA; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; DDR, DNA damage repair; dMMR, deficient mismatch repair; dNLR, derived neutrophil-to-lymphocyte ratio; ESR, erythrocyte sedimentation rate; ICIs, immune checkpoint inhibitors; IFN-γ, interferon gamma; IL, interleukin; LCP1, lymphocyte cytosolic protein 1; LDH, lactate dehydrogenase; LOH, loss of heterozygosity; MSI-H, microsatellite instability-high; NLR, neutrophil-to-lymphocyte ratio; NSCLC, non-small-cell lung cancer; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PET, positron emission tomography; PFS, progression-free survival; TILs, tumor-infiltrating lymphocytes; TMB, tumor mutational burden.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contribution(s)

Lin-Peng Zheng: Conceptualization; Writing – original draft; Writing – review & editing.

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Xie-Wan Chen: Writing – review & editing.

Ling-Chen Li: Data curation; Visualization.

Jian-Guo Sun: Conceptualization; Supervision; Validation; Writing – review & editing.

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Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
Main data are shown in this article and additional data about this study could be obtained from the corresponding author on reasonable request.

References

1. Garon EB, Rizvi NA, Hui R, *et al*. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* 2015; 372: 2018–2028.
2. Hellmann MD, Rizvi NA, Goldman JW, *et al*. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. *Lancet Oncol* 2017; 18: 31–41.
3. Planchard D, Yokoi T, McCleod MJ, *et al*. A phase III study of durvalumab (MEDI4736) with or without tremelimumab for previously treated patients with advanced NSCLC: rationale and protocol design of the ARCTIC study. *Clin Lung Cancer* 2016; 17: 232–236.
4. Adam J, Le Stang N, Rouquette I, *et al*. Multicenter harmonization study for PD-L1 IHC testing in non-small-cell lung cancer. *Ann Oncol* 2018; 29: 953–958.
5. Rimm DL, Han G, Taube JM, *et al*. A prospective, multi-institutional, pathologist-based assessment of 4 immunohistochemistry assays for PD-L1 expression in non-small cell lung cancer. *JAMA Oncol* 2017; 3: 1051–1058.
6. Uruga H, Bozkurtlar E, Huynh TG, *et al*. Programmed cell death ligand (PD-L1) expression in stage II and III lung adenocarcinomas and nodal metastases. *J Thorac Oncol* 2017; 12: 458–466.
7. Yang Q, Chen M, Gu J, *et al*. Novel biomarkers of dynamic blood PD-L1 expression for immune checkpoint inhibitors in advanced non-small-cell lung cancer patients. *Front Immunol* 2021; 12: 665133.
8. Schott DS, Pizon M, Pachmann U, *et al*. Sensitive detection of PD-L1 expression on circulating epithelial tumor cells (CETCs) could be a potential biomarker to select patients for treatment with PD-1/PD-L1 inhibitors in early and metastatic solid tumors. *Oncotarget* 2017; 8: 72755–72772.
9. Dall'Olio FG, Marabelle A, Caramella C, *et al*. Tumour burden and efficacy of immune-checkpoint inhibitors. *Nat Rev Clin Oncol* 2022; 19: 75–90.
10. Yarchoan M, Hopkins A and Jaffee EM. Tumor mutational burden and response rate to PD-1 inhibition. *N Engl J Med* 2017; 377: 2500–2501.
11. Hellmann MD, Ciuleanu TE, Pluzanski A, *et al*. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med* 2018; 378: 2093–2104.
12. Ready N, Hellmann MD, Awad MM, *et al*. First-line nivolumab plus ipilimumab in advanced non-small-cell lung cancer (CheckMate 568): outcomes by programmed death ligand 1 and tumor mutational burden as biomarkers. *J Clin Oncol* 2019; 37: 992–1000.
13. Sands J, Zhang L, Schrock AB, *et al*. *Clinical and genomic characteristics of pts with durable benefit from immune checkpoint inhibitors (ICI) in advanced non-small cell lung cancer (aNSCLC)*. *2022 ASCO Annual Meeting I*, Chicago, 2022.
14. Cao J, Yang X, Chen S, *et al*. The predictive efficacy of tumor mutation burden in immunotherapy across multiple cancer types: a meta-analysis and bioinformatics analysis. *Transl Oncol* 2022; 20: 101375.
15. Dudley JC, Lin MT, Le DT, *et al*. Microsatellite instability as a biomarker for PD-1 blockade. *Clin Cancer Res* 2016; 22: 813–820.

16. Timmermann B, Kerick M, Roehr C, *et al.* Somatic mutation profiles of MSI and MSS colorectal cancer identified by whole exome next generation sequencing and bioinformatics analysis. *PLoS One* 2010; 5: e15661.

17. The Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. *Nature* 2012; 487: 330–337.

18. Le DT, Durham JN, Smith KN, *et al.* Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017; 357: 409–413.

19. Mouw KW, Goldberg MS, Konstantinopoulos PA, *et al.* DNA damage and repair biomarkers of immunotherapy response. *Cancer Discov* 2017; 7: 675–693.

20. Hugo W, Zaretsky JM, Sun L, *et al.* Genomic and transcriptomic features of response to anti-PD-1 therapy in metastatic melanoma. *Cell* 2016; 165: 35–44.

21. Shlien A, Campbell BB, de Borja R, *et al.* Combined hereditary and somatic mutations of replication error repair genes result in rapid onset of ultra-hypermutated cancers. *Nat Genet* 2015; 47: 257–262.

22. Andrianova MA, Bazykin GA, Nikolaev SI, *et al.* Human mismatch repair system balances mutation rates between strands by removing more mismatches from the lagging strand. *Genome Res* 2017; 27: 1336–1343.

23. Howitt BE, Shukla SA, Sholl LM, *et al.* Association of polymerase e-mutated and microsatellite-instable endometrial cancers with neoantigen load, number of tumor-infiltrating lymphocytes, and expression of PD-1 and PD-L1. *JAMA Oncol* 2015; 1: 1319–1323.

24. Hwang HS, Kim D and Choi J. Distinct mutational profile and immune microenvironment in microsatellite-unstable and POLE-mutated tumors. *J Immunother Cancer* 2021; 9: e002797.

25. Cortez MA, Ivan C, Valdecanas D, *et al.* PDL1 regulation by p53 via miR-34. *J Natl Cancer Inst* 2016; 108: djv303.

26. Ji M, Liu Y, Li Q, *et al.* PD-1/PD-L1 expression in non-small-cell lung cancer and its correlation with EGFR/KRAS mutations. *Cancer Biol Ther* 2016; 17: 407–413.

27. Jeanson A, Tomasini P, Souquet-Bressand M, *et al.* Efficacy of immune checkpoint inhibitors in KRAS-mutant non-small cell lung cancer (NSCLC). *J Thorac Oncol* 2019; 14: 1095–1101.

28. Queirolo P, Dozin B, Morabito A, *et al.* CTLA-4 gene variant -1661A>G may predict the onset of endocrine adverse events in metastatic melanoma patients treated with ipilimumab. *Eur J Cancer* 2018; 97: 59–61.

29. Bins S, Basak EA, El BS, *et al.* Association between single-nucleotide polymorphisms and adverse events in nivolumab-treated non-small cell lung cancer patients. *Br J Cancer* 2018; 118: 1296–1301.

30. Kato S, Goodman A, Walavalkar V, *et al.* Hyperprogressors after immunotherapy: analysis of genomic alterations associated with accelerated growth rate. *Clin Cancer Res* 2017; 23: 4242–4250.

31. Wang X, Wang F, Zhong M, *et al.* The biomarkers of hyperprogressive disease in PD-1/PD-L1 blockage therapy. *Mol Cancer* 2020; 19: 81.

32. Chen DS and Mellman I. Elements of cancer immunity and the cancer-immune set point. *Nature* 2017; 541: 321–330.

33. Geng Y, Shao Y, He W, *et al.* Prognostic role of tumor-infiltrating lymphocytes in lung cancer: a meta-analysis. *Cell Physiol Biochem* 2015; 37: 1560–1571.

34. Corredor G, Ding R, Prasanna P, *et al. Density patterns of tumor-infiltrating lymphocytes and association with objective response to nivolumab in patients with lung adenocarcinoma from CheckMate 057. 2022 ASCO Annual Meeting I*, Chicago, 2022.

35. Tumeh PC, Harview CL, Yearley JH, *et al.* PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature* 2014; 515: 568–571.

36. Peyraud F, Guegan J-P, Rey C, *et al. Identification of super-exhausted T cells: a novel population predictive of response to immunotherapy. 2022 ASCO Annual Meeting I*, Chicago, 2022.

37. Naranbhai V, Viard M, Dean M, *et al.* HLA-A*03 and response to immune checkpoint blockade in cancer: an epidemiological biomarker study. *Lancet Oncol* 2022; 23: 172–184.

38. Chowell D, Morris L, Grigg CM, *et al.* Patient HLA class I genotype influences cancer response to checkpoint blockade immunotherapy. *Science* 2018; 359: 582–587.

39. Fluckiger A, Daillere R, Sassi M, *et al.* Cross-reactivity between tumor MHC class I-restricted antigens and an enterococcal bacteriophage. *Science* 2020; 369: 936–942.

40. Zheng Y, Wang T, Tu X, *et al.* Gut microbiome affects the response to anti-PD-1 immunotherapy

in patients with hepatocellular carcinoma. *J Immunother Cancer* 2019; 7: 193.

41. Hakozaki T, Richard C, Elkrief A, *et al.* The gut microbiome associates with immune checkpoint inhibition outcomes in patients with advanced non-small cell lung cancer. *Cancer Immunol Res* 2020; 8: 1243–1250.
42. Chaput N, Lepage P, Coutzac C, *et al.* Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. *Ann Oncol* 2017; 28: 1368–1379.
43. Chalabi M, Cardona A, Nagarkar DR, *et al.* Efficacy of chemotherapy and atezolizumab in patients with non-small-cell lung cancer receiving antibiotics and proton pump inhibitors: pooled post hoc analyses of the OAK and POPLAR trials. *Ann Oncol* 2020; 31: 525–531.
44. Cortellini A, Ricciuti B, Facchinetti F, *et al.* Antibiotic-exposed patients with non-small-cell lung cancer preserve efficacy outcomes following first-line chemo-immunotherapy. *Ann Oncol* 2021; 32: 1391–1399.
45. Grohe C, Wehler TC, Henschke S, *et al. Poster session effect of performance status (ECOG PS) on treatment outcome with second-line (2L) nintedanib (NIN) + docetaxel (DOC) for patients (pts) with lung adenocarcinoma after first-line (1L) immune checkpoint inhibitor (ICI) combination therapy. 2022 ASCO Annual Meeting I*, Chicago, 2022.
46. Lin M, Vanneste B, Yu Q, *et al.* Hyperprogression under immunotherapy: a new form of immunotherapy response?-a narrative literature review. *Transl Lung Cancer Res* 2021; 10: 3276–3291.
47. Castello A, Rossi S, Mazziotti E, *et al.* Hyperprogressive disease in patients with non-small cell lung cancer treated with checkpoint inhibitors: the role of (18)F-FDG PET/CT. *J Nucl Med* 2020; 61: 821–826.
48. Hagi T, Kurokawa Y, Kawabata R, *et al.* Multicentre biomarker cohort study on the efficacy of nivolumab treatment for gastric cancer. *Br J Cancer* 2020; 123: 965–972.
49. Han XJ, Alu A, Xiao YN, *et al.* Hyperprogression: a novel response pattern under immunotherapy. *Clin Transl Med* 2020; 10: e167.
50. Wang H, Ali A, Prather LL, *et al. Association between body mass index and treatment efficacy with immune checkpoint inhibitor therapy: a retrospective study. 2022 ASCO Annual Meeting I*, Chicago, 2022.
51. Zhao LP, Hu JH, Hu D, *et al.* Hyperprogression, a challenge of PD-1/PD-L1 inhibitors treatments: potential mechanisms and coping strategies. *Biomed Pharmacother* 2022; 150: 112949.
52. Park JH, Chun SH, Lee YG, *et al.* Hyperprogressive disease and its clinical impact in patients with recurrent and/or metastatic head and neck squamous cell carcinoma treated with immune-checkpoint inhibitors: Korean cancer study group HN 18-12. *J Cancer Res Clin Oncol* 2020; 146: 3359–3369.
53. Choi YJ, Kim T, Kim EY, *et al.* Prediction model for hyperprogressive disease in non-small cell lung cancer treated with immune checkpoint inhibitors. *Thorac Cancer* 2020; 11: 2793–2803.
54. Economopoulou P, Anastasiou M, Papaxoinis G, *et al.* Patterns of response to immune checkpoint inhibitors in association with genomic and clinical features in patients with head and neck squamous cell carcinoma (HNSCC). *Cancers (Basel)* 2021; 13: 286.
55. Kalinich M, Murphy W, Wongvibulsin S, *et al.* Prediction of severe immune-related adverse events requiring hospital admission in patients on immune checkpoint inhibitors: study of a population level insurance claims database from the USA. *J Immunother Cancer* 2021; 9: e001935.
56. Asada M, Mikami T, Niimura T, *et al.* The risk factors associated with immune checkpoint inhibitor-related pneumonitis. *Oncology* 2021; 99: 256–259.
57. Wong SK, Nebhan CA and Johnson DB. Impact of patient age on clinical efficacy and toxicity of checkpoint inhibitor therapy. *Front Immunol* 2021; 12: 786046.
58. Postow MA, Sidlow R and Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med* 2018; 378: 158–168.
59. Puzanov I, Diab A, Abdallah K, *et al.* Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer* 2017; 5: 95.
60. Abdel-Wahab N, Shah M, Lopez-Olivo MA, *et al.* Use of immune checkpoint inhibitors in the treatment of patients with cancer and preexisting autoimmune disease: a systematic review. *Ann Intern Med* 2018; 168: 121–130.
61. Michailidou D, Khaki AR, Morelli MP, *et al.* Association of blood biomarkers and autoimmunity with immune related adverse events in patients with cancer treated with immune checkpoint inhibitors. *Sci Rep* 2021; 11: 9029.

62. Stamatouli AM, Quandt Z, Perdigoto AL, *et al*. Collateral damage: insulin-dependent diabetes induced with checkpoint inhibitors. *Diabetes* 2018; 67: 1471–1480.

63. Toi Y, Sugawara S, Sugisaka J, *et al*. Profiling preexisting antibodies in patients treated with anti-PD-1 therapy for advanced non-small cell lung cancer. *JAMA Oncol* 2019; 5: 376–383.

64. Wang J, Sun H, Zeng Q, *et al*. HPV-positive status associated with inflamed immune microenvironment and improved response to anti-PD-1 therapy in head and neck squamous cell carcinoma. *Sci Rep* 2019; 9: 13404.

65. Kim ST, Cristescu R, Bass AJ, *et al*. Comprehensive molecular characterization of clinical responses to PD-1 inhibition in metastatic gastric cancer. *Nat Med* 2018; 24: 1449–1458.

66. Arbour KC, Mezquita L, Long N, *et al*. Impact of baseline steroids on efficacy of programmed cell death-1 and programmed death-ligand 1 blockade in patients with non-small-cell lung cancer. *J Clin Oncol* 2018; 36: 2872–2878.

67. Eshghi N, Garland LL, Nia E, *et al*. (18)F-FDG PET/CT can predict development of thyroiditis due to immunotherapy for lung cancer. *J Nucl Med Technol* 2018; 46: 260–264.

68. Colen RR, Fujii T, Bilen MA, *et al*. Radiomics to predict immunotherapy-induced pneumonitis: proof of concept. *Invest New Drugs* 2018; 36: 601–607.

69. Jiang T, Bai Y, Zhou F, *et al*. Clinical value of neutrophil-to-lymphocyte ratio in patients with non-small-cell lung cancer treated with PD-1/PD-L1 inhibitors. *Lung Cancer* 2019; 130: 76–83.

70. Salem JE, Manouchehri A, Moey M, *et al*. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. *Lancet Oncol* 2018; 19: 1579–1589.

71. Sacdalan DB, Lucero JA and Sacdalan DL. Prognostic utility of baseline neutrophil-to-lymphocyte ratio in patients receiving immune checkpoint inhibitors: a review and meta-analysis. *Onco Targets Ther* 2018; 11: 955–965.

72. Nakamura Y, Kitano S, Takahashi A, *et al*. Nivolumab for advanced melanoma: pretreatment prognostic factors and early outcome markers during therapy. *Oncotarget* 2016; 7: 77404–77415.

73. Sanchez-Gastaldo A, Munoz-Fuentes MA, Molina-Pinelo S, *et al*. Correlation of peripheral blood biomarkers with clinical outcomes in NSCLC patients with high PD-L1 expression treated with pembrolizumab. *Transl Lung Cancer Res* 2021; 10: 2509–2522.

74. Weide B, Martens A, Hassel JC, *et al*. Baseline biomarkers for outcome of melanoma patients treated with pembrolizumab. *Clin Cancer Res* 2016; 22: 5487–5496.

75. Kiriu T, Yamamoto M, Nagano T, *et al*. Pseudo-progression and the neutrophil-to-lymphocyte ratio in non-small cell lung cancer treated with immune checkpoint inhibitors: a case-control study. *Onco Targets Ther* 2019; 12: 10559–10568.

76. Petrova MP, Donev IS, Radanova MA, *et al*. Sarcopenia and high NLR are associated with the development of hyperprogressive disease after second-line pembrolizumab in patients with non-small-cell lung cancer. *Clin Exp Immunol* 2020; 202: 353–362.

77. Karabajakian A, Garrivier T, Crozes C, *et al*. Hyperprogression and impact of tumor growth kinetics after PD1/PDL1 inhibition in head and neck squamous cell carcinoma. *Oncotarget* 2020; 11: 1618–1628.

78. Kim SR, Chun SH, Kim JR, *et al*. The implications of clinical risk factors, CAR index, and compositional changes of immune cells on hyperprogressive disease in non-small cell lung cancer patients receiving immunotherapy. *BMC Cancer* 2021; 21: 19.

79. Eun Y, Kim IY, Sun JM, *et al*. Risk factors for immune-related adverse events associated with anti-PD-1 pembrolizumab. *Sci Rep* 2019; 9: 14039.

80. Chu X, Zhao J, Zhou J, *et al*. Association of baseline peripheral-blood eosinophil count with immune checkpoint inhibitor-related pneumonitis and clinical outcomes in patients with non-small cell lung cancer receiving immune checkpoint inhibitors. *Lung Cancer* 2020; 150: 76–82.

81. Al-Showbaki L, Iafolla M, Tamimi F, *et al*. *Changes in circulating tumor DNA (ctDNA) and outcomes in solid tumors treated with immune checkpoint inhibitors (ICIs). 2022 ASCO Annual Meeting I*, Chicago, 2022.

82. Lee JH, Long GV, Menzies AM, *et al*. Association between circulating tumor DNA and pseudoprogression in patients with metastatic melanoma treated with anti-programmed cell death 1 antibodies. *JAMA Oncol* 2018; 4: 717–721.

83. Guibert N, Mazieres J, Delaunay M, *et al*. Monitoring of KRAS-mutated ctDNA to discriminate pseudo-progression from true progression during anti-PD-1 treatment of lung

adenocarcinoma. *Oncotarget* 2017; 8: 38056–38060.

84. Sanz-Garcia E, Zhao EY, Liu ZA, *et al.* *Methylated circulating tumor DNA (cfMeDIP) as a predictive biomarker of clinical outcome in pan-cancer patients (pts) treated with pembrolizumab (P). 2022 ASCO Annual Meeting I*, Chicago, 2022.

85. Weiss GJ, Beck J, Braun DP, *et al.* Tumor cell-free DNA copy number instability predicts therapeutic response to immunotherapy. *Clin Cancer Res* 2017; 23: 5074–5081.

86. Fehrenbacher L, Spira A, Ballinger M, *et al.* Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet* 2016; 387: 1837–1846.

87. Sharma P, Retz M, Siefker-Radtke A, *et al.* Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2017; 18: 312–322.

88. Socinski MA, Nishio M, Jotte RM, *et al.* IMpower150 final overall survival analyses for atezolizumab plus bevacizumab and chemotherapy in first-line metastatic nonsquamous NSCLC. *J Thorac Oncol* 2021; 16: 1909–1924.

89. Sanmamed MF, Perez-Gracia JL, Schalper KA, *et al.* Changes in serum interleukin-8 (IL-8) levels reflect and predict response to anti-PD-1 treatment in melanoma and non-small-cell lung cancer patients. *Ann Oncol* 2017; 28: 1988–1995.

90. Valpione S, Pasquali S, Campana LG, *et al.* Sex and interleukin-6 are prognostic factors for autoimmune toxicity following treatment with anti-CTLA4 blockade. *J Transl Med* 2018; 16: 94.

91. Pasello G, Fabricio ASC, Del Bianco P, *et al.* *Circulating cytokines as predictors of response to immune checkpoint inhibitors (ICIs) in patients (pts) with melanoma (Mel) and non–small cell lung cancer (NSCLC). 2022 ASCO Annual Meeting I, Chicago,* 2022.

92. Khan S, Khan SA, Luo X, *et al.* Immune dysregulation in cancer patients developing immune-related adverse events. *Br J Cancer* 2019; 120: 63–68.

93. Tanaka R, Okiyama N, Okune M, *et al.* Serum level of interleukin-6 is increased in nivolumab-associated psoriasiform dermatitis and tumor necrosis factor-alpha is a biomarker of nivolumab reactivity. *J Dermatol Sci* 2017; 86: 71–73.

94. Tarhini AA, Zahoor H, Lin Y, *et al.* Baseline circulating IL-17 predicts toxicity while TGF-beta1 and IL-10 are prognostic of relapse in ipilimumab neoadjuvant therapy of melanoma. *J Immunother Cancer* 2015; 3: 39.

95. Fujimura T, Sato Y, Tanita K, *et al.* Serum levels of soluble CD163 and CXCL5 may be predictive markers for immune-related adverse events in patients with advanced melanoma treated with nivolumab: a pilot study. *Oncotarget* 2018; 9: 15542–15551.

96. Das R, Bar N, Ferreira M, *et al.* Early B cell changes predict autoimmunity following combination immune checkpoint blockade. *J Clin Invest* 2018; 128: 715–720.

97. Jing Y, Liu J, Ye Y, *et al.* Multi-omics prediction of immune-related adverse events during checkpoint immunotherapy. *Nat Commun* 2020; 11: 4946.

98. Romero JM, Titmuss E, Wang Y, *et al.* *Assessment of a 4-chemokine signature in prediction of T-cell inflammation and response to immune checkpoint inhibition across tumor types. 2022 ASCO Annual Meeting I*, Chicago, 2022.

99. Matsuo N, Azuma K, Hattori S, *et al.* Association between soluble immune mediators and tumor responses in patients with nonsmall cell lung cancer treated with anti-PD-1 inhibitor. *Int J Cancer* 2019; 144: 1170–1179.

100. Mezquita L, Auclin E, Ferrara R, *et al.* Association of the lung immune prognostic index with immune checkpoint inhibitor outcomes in patients with advanced non-small cell lung cancer. *JAMA Oncol* 2018; 4: 351–357.

101. Agullo-Ortuno MT, Gomez-Martin O, Ponce S, *et al.* Blood predictive biomarkers for patients with non-small-cell lung cancer associated with clinical response to nivolumab. *Clin Lung Cancer* 2020; 21: 75–85.

102. Robert C, Long GV, Brady B, *et al.* Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015; 372: 320–330.

103. Rosner S, Kwong E, Shoushtari AN, *et al.* Peripheral blood clinical laboratory variables associated with outcomes following combination nivolumab and ipilimumab immunotherapy in melanoma. *Cancer Med* 2018; 7: 690–697.

104. Schuiveling M, Tonk E, Verheijden RJ, *et al.* Hyperprogressive disease rarely occurs during checkpoint inhibitor treatment for advanced melanoma. *Cancer Immunol Immunother* 2021; 70: 1491–1496.

105. Chen S, Gou M, Yan H, *et al*. Hyperprogressive disease caused by PD-1 inhibitors for the treatment of pan-cancer. *Dis Markers* 2021; 2021: 6639366.

106. Luo J, Vanguri RS, Aukerman AT, *et al*. *Multimodal integration of radiology, pathology, and genomics for prediction of response to PD-1 blockade in patients with non–small cell lung cancer. 2022 ASCO Annual Meeting I*, Chicago, 2022.

107. Rakaee M, Adib E, Ricciuti B, *et al*. *Digital quantification of lymphocytic infiltration on routine H&E images and immunotherapy response in non–small cell lung cancer. 2022 ASCO Annual Meeting I*, Chicago, 2022.

108. Ghasemi Saghand P, El Naqa I, Tan AC, *et al*. *Poster session a deep learning approach utilizing clinical and molecular data for identifying prognostic biomarkers in patients treated with immune checkpoint inhibitors: an ORIEN pan-cancer study. 2022 ASCO Annual Meeting I*, Chicago, 2022.

109. Orlova D, Li X, Eastham-Anderson J, *et al*. *Automated tumor immunophenotyping and response to immunotherapy in non-small cell lung cancer using a spatial statistics approach. 2022 ASCO Annual Meeting I*, Chicago, 2022.

110. Cao S, Zhang Y, Zhou Y, *et al*. A nomogram for predicting hyperprogressive disease after immune checkpoint inhibitor treatment in lung cancer. *Transl Lung Cancer Res* 2022; 11: 607–616.

111. Hussaini S, Chehade R, Boldt RG, *et al*. Association between immune-related side effects and efficacy and benefit of immune checkpoint inhibitors–a systematic review and meta-analysis. *Cancer Treat Rev* 2021; 92: 102134.

112. Zhou X, Yao Z, Yang H, *et al*. Are immune-related adverse events associated with the efficacy of immune checkpoint inhibitors in patients with cancer? A systematic review and meta-analysis. *BMC Med* 2020; 18: 87.