Stomach cancer is the fourth leading cause of cancer-related deaths worldwide [1]. There are approximately one million new cases of gastric cancer worldwide each year, with about 45% occurring in China [1]. In China, the number of deaths from gastric cancer ranks second among all tumors each year [2], the majority of patients are diagnosed at an advanced or late stage, making them ineligible for surgical treatment. Some of these patients can regain the opportunity for surgery through conversion therapy, while more patients can only receive comprehensive treatment with cytotoxic drugs, anti-metabolite drugs, DNA-targeting drugs, and targeted drugs [3]. The efficacy of traditional comprehensive treatment methods is limited, and the incidence of adverse reactions is relatively high, with a median survival period of less than 12 months in patients. HER-2 positive gastric cancer patients show better response to HER-2 targeted therapy and have a better prognosis compared to HER-2 negative gastric cancer [4]. However, the majority of gastric cancers are HER-2 negative. Therefore, there is an urgent need to develop new treatment methods to further improve the efficacy of advanced gastric cancer patients. Inflammation is a double-edged sword in the occurrence and development of tumors, as it can both promote tumor growth and enhance immune responses [5, 6]. In recent years, how to target the tumor immune microenvironment, enhance the anti-tumor ability of the body’s immune cells, and improve the efficacy of tumor treatment has become a research hotspot. Immunotherapy is the focus of research in this field. Immunotherapy has shown significant efficacy in various types of cancers [7–11]. In recent years, there have been promising breakthroughs in immunotherapy for advanced gastric cancer, with immune checkpoint inhibitors demonstrating anti-tumor effects in first-line, second-line, and later-line treatments, particularly in the context of first-line therapy.

Immunotherapy is not effective for all gastric cancer patients, and accurately identifying the population that will respond to immune checkpoint inhibitor therapy is currently a challenge in the field of tumor immunology research. Currently, there are still limited molecular markers available for predicting the efficacy of immunotherapy. Programmed death ligand 1 (PD-L1), combined positive score (CPS), microsatellite instability (MSI), tumor mutational burden (TMB), and deficient mismatch repair (dMMR) are molecular markers that are widely recognized by most peers [12–14]. Tumors with high CPS scores often rely on PD-L1-mediated immune escape, while tumors with MSI, TMB-H, and dMMR have increased tumor-specific antigens due to genetic mismatch repair defects and increased tumor mutation burden, which enhances the recognition of tumor antigens by the immune system. Therefore, CPS score, MSI, TMB, and dMMR have become indicators for predicting the efficacy of immunotherapy, among which CPS score is the most commonly used indicator. The threshold for CPS score varies in different tumors, mainly because CPS not only counts PD-L1-positive tumor cells but also counts PD-L1-positive tumor-associated immune cells, and the proportion of the latter varies in different types of cancer. In gastric cancer, the CPS score is generally divided by 1, 5, and 10 points as cutoffs. However, there are still differences in the predictive value of CPS for treatment response in different patients, which may be influenced by factors such as heterogeneity of gastric cancer tissue and other factors like MSI and TMB. Similarly, there is currently controversy surrounding the specific cutoff values for MSI, TMB, and dMMR, and more clinical research is still needed to determine the optimal cutoff values. The integrated analysis model based on genomics and radiomics has certain value in predicting the efficacy of immunotherapy and chemotherapy in gastric cancer. However, more large-scale clinical trials are still needed to validate its effectiveness. In addition, some new molecular markers have also been gradually discovered, such as tertiary lymphoid structures, BRCA2 mutations, obesity, immune cell infiltration levels, and immune-related adverse events [15–18]. Common immune-related adverse events with potential immunological etiology include adverse reactions in the endocrine, gastrointestinal, hepatic, pulmonary, renal, and cutaneous systems. On the other hand, chemotherapy-related adverse reactions mainly manifest in the gastrointestinal and cutaneous systems. Research in ATTRACTION-2 found that patients who experienced immune-related adverse events had better prognosis. The gut microbiota also has a certain predictive role in immunotherapy efficacy. It has been found that the increase in certain gut bacterial populations indicates greater sensitivity to immunotherapy. However, there is significant heterogeneity in results among different study populations, and no bacterial population has been found to be universally applicable in all populations. Molecular subtyping of gastric cancer is a concept proposed in recent years, and currently there are mainly two classifications: The Cancer Genome Atlas classification and the Asian Cancer Research Group classification, which is based on Asian populations. The The Cancer Genome Atlas classification includes four types: chromosomal instability, Epstein-Barr virus (EBV), genomically stable, and MSI [19]. The Asian Cancer Research Group classification includes four types: MSI, microsatellite stable (MSI)/TP53+, MSS/TP53+, and MSS/epithelial-mesenchymal transition [20]. Some EBV-positive gastric cancer patients can benefit from immunotherapy [21]. However, further clinical research is needed to uncover the role of EBV in immunotherapy for advanced gastric cancer. In addition, certain treatment modalities can also induce changes in the expression levels of immune checkpoint, such as the monoclonal antibody trastuzumab, which can regulate interferon-gamma-mediated PD-L1 upregulation through interaction with natural killer cells in peripheral blood mononuclear cells [22]. Therefore, dynamic monitoring of PD-L1 can serve as a potential predictive biomarker for treatment efficacy.

In recent years, significant progress has been made in the exploration of molecular biomarkers for immunotherapy. We anticipate that extensive translational research, preclinical studies, and multi-omics analysis are the optimal approaches to identify molecular biomarkers and achieve precision immunotherapy. We hope to achieve new breakthroughs in immunotherapy in the near future.

References