REVIEW

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Recent advances in primary resistance mechanisms against immune checkpoint inhibitors

Yi-Ze Li and Hong-Mei Zhang

Purpose of review
The resistance of immune checkpoint inhibitors (ICIs) has become an obstacle to further improve the survival of patients with advanced cancer. This review provides an overview of recent advances in primary resistance mechanisms of ICIs.

Recent findings
With the improvement of study approach, new characteristics and trends have emerged in the classification of tumor immune subtypes. The effects of germline genetic on tumor microenvironment and the efficacy of immunotherapy have been further studied. Exosomal programmed death-ligand 1 (PD-L1) is an increasing focus of research in primary resistance mechanisms of ICIs. In addition to antibiotics and steroids, the influence of other concomitant medications on the efficacy of ICIs has recently gained more attention.

Summary
Exploring the resistance mechanisms of ICIs is one of the great challenges in the field of tumor immunotherapy. Continued work to understand the resistance mechanism of ICIs is ongoing.

Keywords
exosomal programmed death-ligand 1, germline genetic, immune checkpoint inhibitors, immune subtype, medications, resistance

INTRODUCTION

The emergence of immune checkpoint inhibitors (ICIs) has greatly improved the survival of patients with advanced cancer. However, resistance of ICIs has created a bottleneck in the application of ICIs. According to the criterions of the American Society for Immunotherapy of Cancer [1▪▪], primary resistance for advanced patients receiving ICIs needs to meet the following three requirements: (1) drug exposure $\geq$6 weeks, (2) progressive disease (PD) or stable disease (SD) for $<$6 months as best response, (3) confirmatory scan for PD is required at least 4 weeks after initial disease progression. An important feature of the definition of primary resistance is to be able to reflect the population that does not benefit from initial immunotherapy, which is essential to distinguish patients who do not benefit from initial and longer exposure to monotherapy of programmed death receptor 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors. We only summarized the rate of 'PD as best response ', because it is difficult to distinguish the patients with the best response of SD $<$ 6months based on the current literature. It can be seen that the rate of 'PD as best response' of Hodgkin's lymphoma is the lowest, less than 15%, whereas the rates of other tumors, including melanoma, nonsmall cell lung cancer (NSCLC), urothelial carcinoma (UC) and hepatocellular carcinoma (HCC) and more, are generally high (Table 1). It appears to be a negative relationship between the rate of 'PD as best response' and median overall survival (OS) (Fig. 1). It is important to note that the actual proportion of patients with primary resistance of ICIs is higher than our data. However, the response and prognosis of the patients with PD in our statistics are much worse.

Exploring the mechanisms of ICIs resistance has become one of the significant challenges in the field of tumor immunotherapy. The known and putative mechanisms of primary resistance to ICIs include: lack of antigen mutations or tumor

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KEY POINTS

- The feature of primary resistance is essential to identify patients who do not benefit from initial and longer exposure to PD- (L) 1 inhibitors monotherapy.
- An in-depth understanding of the role of tumor immune subtype, germline genetic, exosomal PD-L1, concomitant medications in tumor immunity will serve to further clarify the mechanism of resistance to ICIs.
- The success of the combination therapy strategy is inseparable from the in-depth study of the resistance mechanism of ICIs.

antigen expression, loss of human leukocyte antigen expression, mitogen-activated protein kinase pathway activation, loss of phosphatase and tensin homolog (PTEN) expression leads to enhancement of phosphatidylinositide 3-kinases (PI3K) signaling pathway; WNT/β-catenin signaling pathway activation; lack of interferon-γ (INF-γ) signaling pathway, mutation or deletion of INF-γ signaling pathway-related receptor chains janus kinase 1 (JAK1), JAK2, signal transducer and activators of transcription (STAT) and INF regulatory factor 1, mutation of the epidermal growth factor receptor/anapastic lymphoma kinase, and constitutive PD-

Table 1. The rate of 'PD as best response' and the median overall survival of cancer patients treated with ICIs in clinical trials

Cancer type	Trial Name	Group number	Treatment	Line of Therapy	Median OS (95% CI), mo	ORR (%)	PD as best response (%)	Reference
NSCLC	Keynote 001	101	Pembrolizumab (treatment-naïve)	1	22.3 (17.1–32.3)	41.6	9.9	[2,3]
	Keynote 001	449	Pembrolizumab (previously treated)	2+	10.5 (8.6–13.2)	22.9	27.6	[2,3]
	Keynote 042	637	Pembrolizumab	1	16.7 (13.9–19.7)	27	21	[4]
	OAK	425	Atezolizumab	2+	13 8 (11 8–15 7)	14	44	[5,6]
	CheckMate 057 (nonsquamous)	292	Nivolumab	2+	12.2 (9.7–15.0)	19	44	[7]
	CheckMate 017 (squamous)	135	Nivolumab	2+	9.2 (7.3–13.3)	20	41	[8]
	CheckMate 026	211	Nivolumab	1	14.4 (11.7–17.4)	26	27	[9]
	Javelin 200 Lung	264	Avelumab	2+	11 4 (9 4–13 9)	19	35	[10]
Melanoma	Keynote 002	180	Pembrolizumab (2mg/kg)	2+	13.4 (11.0–16.4)	21	47	[11,12]
	Keynote 002	181	Pembrolizumab (10mg/kg)	2+	14.7 (11.3–19.5)	26	48	[11,12]
	Keynote 006	277	Pembrolizumab (10mg/kg Q3W)	1+	32.7 (24 5–41.6)	36	42	[13,14]
	Keynote 006	279	Pembrolizumab (10mg/kg Q2W)	1+	32.7 (24 5–41.6)	37	38	[13,14]
	CheckMate 037	272	Nivolumab	2+	16.4 (12.9–20.3)	31.7	35	[15,16]
	CheckMate 066	210	Nivolumab	1	37.5 (25.5-NR)	42.9	33.3	[17,18]
	CheckMate 067	316	Nivolumab	1	36.9 (28.2–58.7)	45	38	[19–21]
UC	Keynote 052	370	Pembrolizumab	1	11.3 (9.7–13.1)	28.6	42.4	[22,23]
	Keynote 045	270	Pembrolizumab	2+	10.3 (8.0–11.8)	21.1	48.5	[24]
	IMvigor210	119	Atezolizumab	1	15.9 (10.4-NE)	23	36.1	[25]
	IMvigor210 Cohort2	310	Atezolizumab	2+	7.9 (6.6–9.3)	15	51	[26]
	IMvigor211	467	Atezolizumab	2+	8.6 (7.8–9.6)	13 4	52	[27]
	CheckMate 275	265	Nivolumab	2+	8.74 (6.05-NR)	19.6	39	[28]
	Study 1108	191	Durvalumab	2+	18.2 (8.1-NE)	17.8	63.4	[29]
	JAVELIN Solid Tumor	161	Avelumab	2+	6.5 (4.8–9.5)	17	42	[30]
HNSCC	Keynote 012	45	Pembrolizumab	2+	13 (5-NR)	18	56	[31]
	CheckMate 141	240	Nivolumab	2+	7 0.5 (5.5–9.1)	13.3	41.3	[32,33]
	CONDOR	65	Durvalumab	2+	6.0 (4.0–1.3)	9.2	64.6	[34]
	HAWK	111	Durvalumab	2+	7.1 (4.9–9.9)	16.2	52.3	[35]
	NCT01375842	32	Atezolizumab	1+	6.0 (0.5–51.6)	22	40.6	[36]

Table 1 (*Continued*)

Cancer type	Trial Name	Group number	Treatment	Line of Therapy	Median OS (95% CI), mo	ORR (%)	PD as best response (%)	Reference
dMMR	Keynote 158	233	Pembrolizumab	2+	23.5 (13.5-NR)	34.3	39.5	[37]
TNBC	Keynote 012	27	Pembrolizumab	1+	11.2 (5.3-NR)	18.5	48.1	[38]
	Keynote 086 cohort A	170	Pembrolizumab	2+	9.0 (7.7–11.2)	5.3	60.6	[39]
	Keynote 086 cohort B	84	Pembrolizumab	1	18 (12.9–23.0)	21.4	58.3	[40]
	JAVELIN Solid Tumor	58	Avelumab	1+	9.2 (4.3-NE)	5.2	65.5	[41]
ESCC	ATTRACTION-3	171	Nivolumab	2	10 9 (9 2–13 3)	19	55	[42]
	ONO-4538-07	64	Nivolumab	3+	10.8 (7.4–13.3)	17	45	[43]
ESCC/EAC/ GEJC	Keynote 181	314	Pembrolizumab	2	7.1 (6.2–8.1)	13.1	50.3	[44]
	Keynote 180	121	Pembrolizumab	3+	5.8 (4.5–7.2)	9.9	58.7	[45]
GC/GEJC	JAVELIN Gastric 300	185	Avelumab	3	4.6 (3.6–5.7)	2.2	50.8	[46]
	Keynote 059 cohort 3	31	Pembrolizumab	1	20.7 (9.2–20.7)	25.8	38.7	[47]
	ATTRACTION-2	330	Nivolumab	3+	5 26 (4 60–6 37)	11.2	46	[48]
	Keynote 059 cohort 1	259	Pembrolizumab	3	5.6 (4.3–6.9)	11.6	56	[49]
GC/ESCA/ GEJC	CheckMate 032	59	Nivolumab	2+	6.2 (3.4–12.4)	7	44	[50]
HCC	Keynote 224	104	Pembrolizumab	2	12 9 (9 7–15 5)	17	33	[51]
	Keynote 240	278	Pembrolizumab	2	13.9 (11.6–16.0)	18.3	32.4	[52]
CRC (dMMR/ MSI-H)	Keynote 177	153	Pembrolizumab	1	NR	43.8	29.4	[53]
	Keynote 164 cohort A	61	Pembrolizumab	3+	31.4 (21.4-NR)	33	46	[54]
	Keynote 164 cohort B	63	Pembrolizumab	2+	NR (19.2-NR)	33	40	[54]
	CheckMate 142	74	Nivolumab	2+	NR	32	28	[55]
RCC	CheckMate 025	410	Nivolumab	2+	25.8 (22.2–29.8)	22.9	34.6	[56,57]
SCLC	Keynote 028	24	Pembrolizumab	2+	9.7 (4.1-NR)	33.3	54.2	[58]
	CheckMate 032	98	Nivolumab	2+	4.4 (3.0–9.3)	10	53	[59]
	CheckMate 032	109	Nivolumab	3+	5.6 (3.1–6.8)	11.9	51.4	[60]
	IFCT-1603	43	Atezolizumab	2+	9.5 (3.2–14.4)	2.3	69.8	[61]
cHL	CheckMate 039	23	Nivolumab	3+	NR	87	0	[62]
	CheckMate 205	243	Nivolumab	2+	NR	69	9	[63]
	Keynote 013	31	Pembrolizumab	3+	NR	65	13	[64]
	Keynote 087	210	Pembrolizumab	4+	NR	69	14.3	[65]

ICIs, immune checkpoint inhibitors; OS, overall survival; ORR, objective response rate; PD, progressive disease; NSCLC, nonsmal cell lung cancer; UC, urothelial carcinoma; HNSCC, head and neck squamoucel carcinom; dMMR, deficient mismatch repair tumors; TNBC, triple-negative breast cancer; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; GEJC, gastroesophageal junction cancer; GC, gastric cancer; ESCA, esophageal carcinoma; HCC, hepatocellular carcinoma; CRC, colorectal cancer; dMMR, deficient mismatch repair; MSI-H, microsatellite instability-high; RCC, renal cell carcinoma, SCLC, smal cell lung cancer; cHL, classical Hodgkin lymphoma; NR, not rearch; NE, not estimable.

L1 expression. Tumor immune microenvironment components, such as myeloid-derived suppressor cells, regulatory T cells (Tregs), M2 type macrophages and immunosuppressive substances. In addition, many host factors have been identified to be associated with the efficacy of ICIs.

MECHANISMS OF PRIMARY RESISTANCE OF IMMUNE CHECKPOINT INHIBITORS

The underlying reason for primary resistance of ICIs is that immunotherapy cannot initiate an antitumor immune response, or tumor-induced immunosuppression cannot be relieved. In this review, we summarize the latest advances in mechanisms of primary resistance of ICIs and some other factors which are relatively easy to ignore (Fig. 2).

Tumor immune subtype

Since tumor immune response is a dynamic and complex process, it is difficult to rely on any single immune biomarker to accurately predict the prognosis of patients and chose suitable treatment plan. The nature of immune microenvironment is closely related to treatment response and prognosis, and

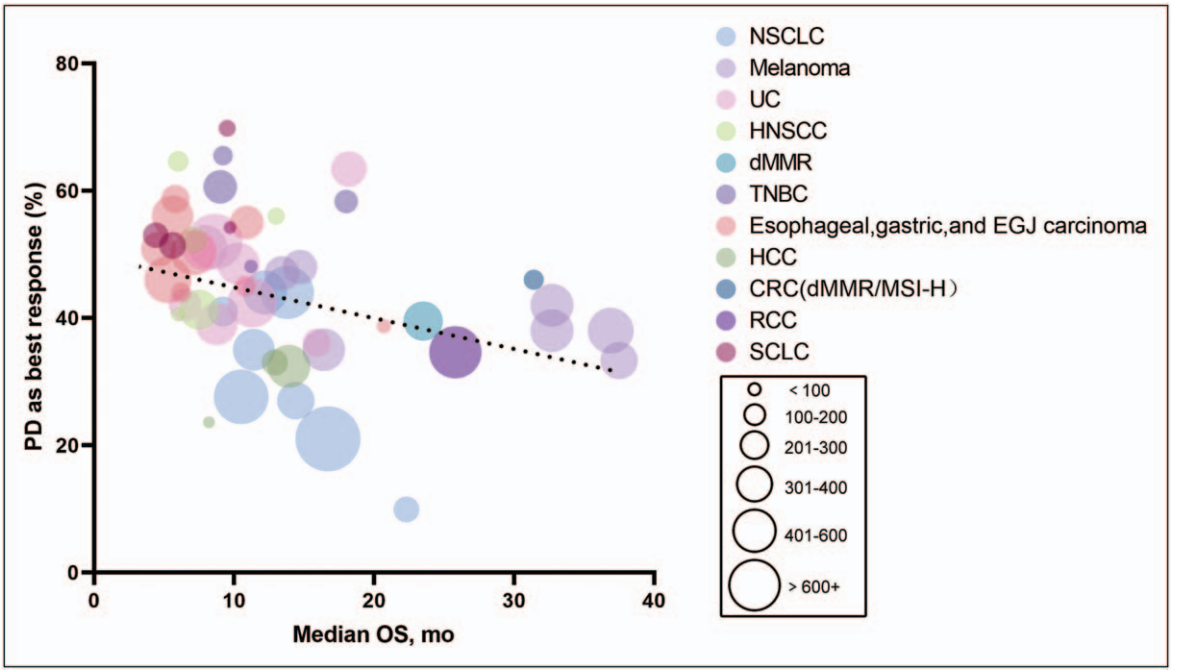

FIGURE 1. The rate of 'PD as best response' and the median overall survival of cancer patients treated with immune checkpoint inhibitors (ICIs). The colored circles represent different tumor types, and the size of the circles represents the number of cancer patients. Trials that did not reach the median overall survival in Table 1 are not included in the figure.

immunosuppressive microenvironment is currently recognized as a major factor that mediates the primary resistance of tumor to ICIs. Researchers have divided tumor immune subtypes from different perspective, such as tumor immunogenicity or PD-L1 expression and tumor infiltrating lymphocytes (TILs) or characteristics of tumor tissue sections [66–68]. In 2018, based on immunogenomic analysis, researchers divided the tumor microenvironment (TME) into six immune subtypes [69]. Recently, by integrating transcriptomic and genomic data, researchers have described tumor structure, mutation burden, immune composition, antitumor immunity, immune suppression or escape mechanisms, and divided tumors into four different microenvironments [70▪▪]. The characteristic of immune-enriched, fibrotic (IE/F) melanomas subtype is that the high expression of functional gene expression signatures (FGES) related to angiogenesis and activation of cancer-associated fibroblasts (CAFs). The immune-enriched, nonfibrotic (IE) subtype is characterized by high degree of immune infiltration and significantly elevated cytolysis scores, the highest mutation burden, CD8+ T cell/Tregs ratio and M1/M2 macrophage ratio, JAK/STAT pathway activation increased. Fibrotic (F) and depletion (D) subtype have little or no leukocyte/lymphocyte infiltration, and D subtype contains the highest percentage of malignant cells. In contrast, melanoma classified as subtype F shows increased expression of FGES and increased CAF associated with angiogenesis. Fibroblasts become powerful immunosuppressive agents by secreting transforming growth factor-β (TGF-β). Patients with subtype IE melanoma have significantly longer OS and progress free survival (PFS) than subtype F and D, and patients with subtype F have the worst OS. Interestingly, the researchers dynamically observed the evolution of TME during treatment and found that people who responded to anti-PD-1 treatment mainly had IE/F and IE subtypes which remained unchanged during treatment or became immune enriched environment. In contrast, the TME of most patients who did not respond to PD-1 treatment seemed to maintain or tend to be immune-unfavorable TME, with weaker immune function and increasing fibrosis [70▪▪]. With the improvement of analysis methods and continuous increase of integrated factors, tumor immune subtypes have been further refined and the accuracy of prediction of therapeutic response and prognosis has been improved. What is more, the characteristics of tumor immune subtypes with poor prognosis can enable us to understand the resistance mechanism of ICIs more deeply, and it may be a breakthrough for researchers to find more efficient strategies to overcome resistance of ICIs.

Different tumors may have their own characteristics in the tumor immune microenvironment, which is of great importance for elucidating the

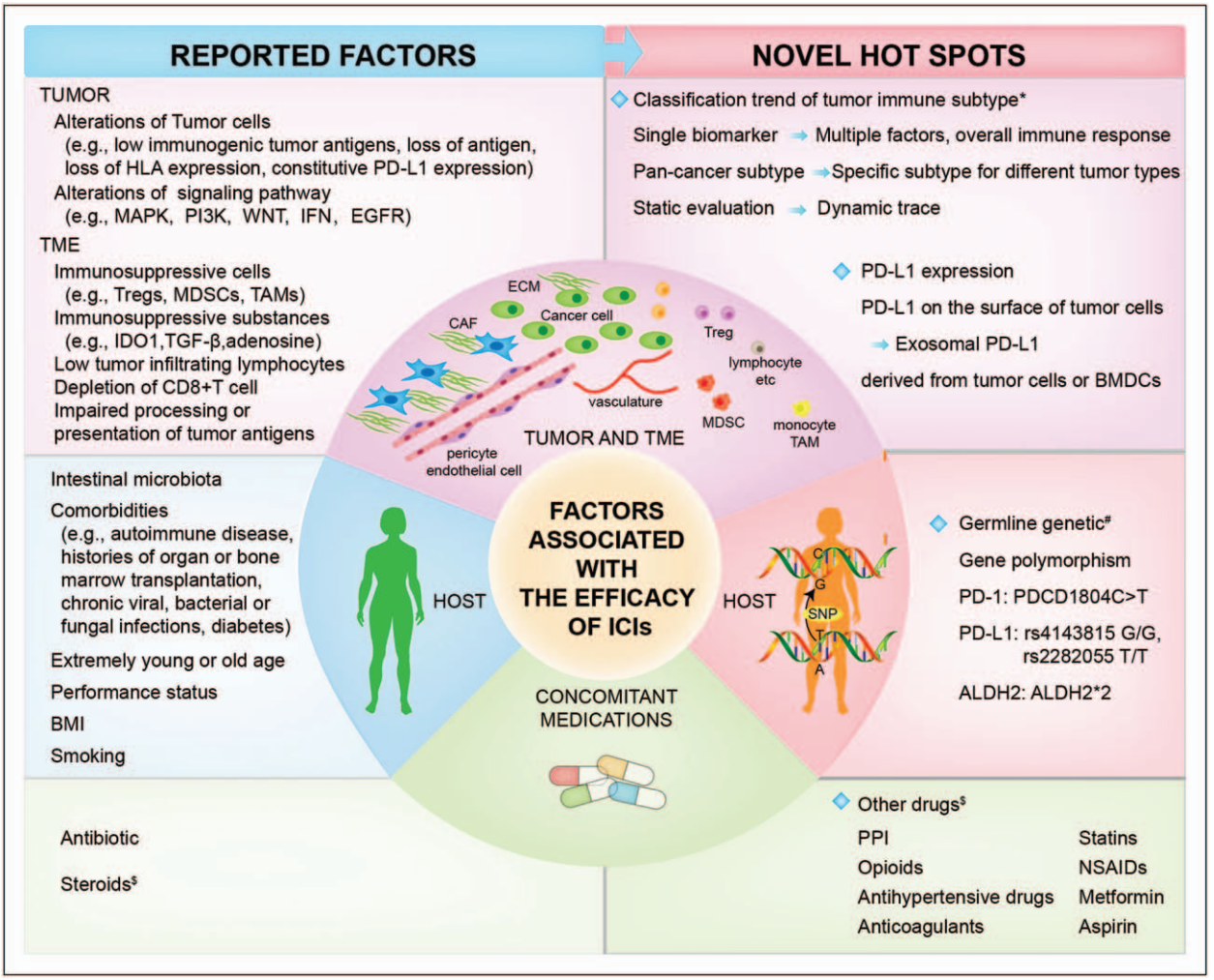

FIGURE 2. Novel hot spots in tumor and TME, host, concomitant medications related to the efficacy and resistance of ICIs. *The current classification methods are no longer limited to traditional methods, such as tumor immunogenicity or PD-L1 expression and tumor infiltrating lymphocytes (TILs) or characteristics of tumor tissue sections. Multiple omics analysis has also become a very promising method. # Germline genetic has recently become a research hotspot that affects the efficacy of immunotherapy, we only list a few gene polymorphisms directly related to ICIs resistance. $ There is controversy about the effects of the above-mentioned drugs on the efficacy of ICIs. ICIs, immune checkpoint inhibitors; PD, progressive disease; TME, tumor microenvironment.

distinction in the effects of different tumor types of ICIs. Many studies are trying to classify different immune subtypes for specific tumors to reveal the reasons for the differences in efficacy. Some researchers have classified lung adenocarcinoma into two distinct subtypes which were characterized by significant differences in survival outcomes. High-risk subtype is more likely to respond to ICIs treatment which is characterized by lower tumor immune dysfunction and exclusion score, up-regulated expression of PD-L1, higher tumor mutation burden, and significantly increased mutations in cell cycle regulatory factors CDK4/CDK6 and TP53 [71]. In gastroesophageal adenocarcinoma (GEA), the subtypes of severely inflammatory microsatellite instability (MSI) or Epstein–Barr virus positive respond well to treatment with ICIs, whereas chromosomal instable (CIN) and diffuse/genome-stable (GS) have a significantly lower response to ICIs. Further studies have found that CIN-GEAs not only have a lower density of CD8+ T cell, but they are mainly present at the invasive edge, whereas CD68+ macrophages were more evenly distributed within the tumor, indicating that T cell exclusion is the main mechanism of immunosuppression but not T cell suppression. In addition, the immunological 'cold' CIN GEAs was characterized by the enrichment of MYC and cell cycle pathways including CCNE1 amplification. The GS subtype showed enrichment of CD4+ T cells, macrophages and B cells, and tertiary lymphoid structure was seen

Table 2. The impact of concomitant medications on the efficacy of ICIs

Reference (year)	Cancer type	ICIs	Concomitant medications		Effect of concomitant medications on ICIs
[96▪▪] (2020)	NSCLC	Atezolizumab	PPIs (234/757)		PPI use was associated with shorter OS (9.6 vs. 14.5 months, HR 1.45, 95% CI 1.20–1.75, $P=0.0001$) and PFS (1.9 vs. 2.8 months, HR 1.30, 95% CI 1.10–1.53, $P=0.001$).
[97] (2020)	NSCLC Kidney Bladder Melanoma Head and neck Others	Nivolumab Pembrolizumab Atezolizumab Nivolumab + Ipilimumab	PPIs (78/102) Opioids (55/102)		PPIs use did not affect clinical outcome of ICIs. Opioids use was significantly associated with shorter PFS (4.5 vs. 8.1 months, $P=0.010$) and OS (8.6 vs. 26.3 months, $P<0.001$).
[98▪] (2021)	NSCLC Melanoma Head and neck Renal and urothelial Others	Nivolumab Pembrolizumab Ipilimumab Nivolumab+ipilimumab	PPIs(149/372) Opioids(173/372) Metformin(17/372) NSAIDs(23/372) Statins(83/372)	AVKs (16/372) Levothyrox (40/372) Cholecalciferol(59/372/) Phloroglucinol(19/372) Antiarrhythmics(20/372)	PPIs use did not affect OS, but tumor response is lower (18.8% vs. 30.1%, $P=0.036$). opioids use was significantly associated with shorter OS (36.6 vs. 126.4 months, $P<0.001$) and lower ORR (16.2% vs. 33.7%, $P<0.001$). Metformin use did not affect OS, but tumor response is higher (47.1% vs. 24.5%, $P=0.020$). The use of NSAIDs, statins, AVK anticoagulants, levothyroxine, cholecalciferol, phloroglucinol, or antiarrhythmics did not affect OS.
[100▪] (2020)	NSCLC Melanoma Renal cell carcinoma Others	Pembrolizumab Nivolumab Atezolizumab Others	H2 antagonists(56/1012) PPIs(491/1012) Statins(196/1012) Aspirin(189/1012) Other lipid lowerings(48/1012) Anticoagulants(145/1012)	NSAIDs (59/1012) ACEI/ARBs(313/1012) Calcium antagonist(140/1012) Beta blockers (114/1012) Metformin (114/943) Opioids(68/921)	Baseline statins (HR 1.60, 95% CI 1.14–2.25, $P=0.0064$), aspirin (HR 1.47, 95% CI 1.04–2.08, $P=0.0267$) and β-blockers (HR 1.76, 95% CI 1.16–2.69, $P=0.0080$) were associated with an increased ORR. Prophylactic gastric acid suppressants (HR 1.29, 95% CI 1.09–1.53, $P=0.0021$), PPIs (HR 1.26, 95% CI 1.07–1.48, $P=0.0050$), anticoagulants (HR 1.43, 95% CI 1.16–1.77, $P=0.0007$) and opioids (HR 1.71, 95% CI 1.28–2.28, $P=0.0002$) were associated with a significantly higher risk of disease progression. Prophylactic gastric acid suppressants (HR 1.29, 95% CI 1.06–1.57, $P=0.0091$), PPI (HR 1.26, 95% CI 1.04–1.52, $P=0.0172$), anticoagulants (HR 1.45,95% CI 1.14–1.84, $P=0.0024$) and opioids (HR 1.53, 95% CI 1.11–2.11, $P=0.0098$) were confirmed to have a significantly higher risk of death.
[116] (2020)	NSCLC	Nivolumab	PPIs(64/224) NSAIDs(45/224)	Statin(31/224) Metformin(18/224)	The risk of progression in patients who are not taking NSAIDs is 1.596 times that of patients taking NSAIDs.A possible positive effect of the concomitant use of NSAIDs at the initiation of nivolumab treatment was revealed.

Table 2 (*Continued*)

Reference (year)	Cancer type	ICIs	Concomitant medications	Effect of concomitant medications on ICIs
[123] (2021)	NSCLC Renal cell carcinoma Urothelial cancers	Atezolizumab	Renin–angiotensin system inhibitor(604/2539) Other classes of antihypertensives	No statistically significant difference in OS (HR 0.92, 95% CI 0.79–1.07, $P=0.29$), PFS (HR 0.95, 95% CI 0.84–1.08, $P=0.42$) between renin–angiotensin system inhibitor users and nonusers. Other classes of antihypertensives were also not associated with survival.
[124] (2021)	NSCLC	Anti-PD-1/PD-L1 Antibodies monotherapy	Renin–angiotensin system inhibitors(37/256)	The median PFS of patients treated with renin–angiotensin system inhibitors was significantly longer than that of patients treated without (HR = 0.59, 95% CI = 0.40–0.88). The median OS of patients treated with Renin–angiotensin system inhibitors tended to be longer than that of patients treated without (HR = 0.71, 95% CI = 0.45–1.11).
[125▪] (2020)	NSCLC	Pembrolizumab Nivolumab Durvalumab	ACEI (22/178)	ACEI use was associated with shorter median PFS (1.97 vs. 2.56 months, HR = 1.8, 95% CI 1.1–2.8, $P=0.01$).
[126▪] (2020)	Advanced melanoma	Anti-PD-1 therapy	NSAIDs (122/330) Metformin(34/330) Beta blocker(65/330)	The use of NSAIDs has a tendency to improve PFS (median PFS 8.5 vs. 5.2 months; $P=0.054$). Multivariate analysis did not reveal an association with NSAID, metformin or beta blockers with ORR, PFS, or OS.
[127▪] (2021)	MPM NSCLC	PD-1 inhibitors	Statin(67/261)	statin use was associated with increased ORR (32% vs. 18%, $P=0.02$), PFS (median 6.7 vs. 2.9 months, HR 0.57, 95% CI 0.39–0.83, $P<0.01$), and OS (median 13.1 vs. 8.7 months, HR 0.67, 95% CI 0.45–1.00, $P=0.05$) in an intensity-dependent manner.

ICIs, immune checkpoint inhibitors; CI, confidence interval; HR, hazard ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; AVKs, antivitamin K; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; MPM, malignant pleural mesothelioma.

in about 50% of cases [72▪▪]. These may provide new directions for overcoming resistance of ICIs. Gastric cancer is classified into immune-activation, immunosuppressive and nonimmune subtypes. Immunosuppressive subtype has high immune infiltration, stromal enrichment and activation of TGF-β signaling pathway, which is related to the nonresponse of checkpoint blocking therapy, and may be suitable for anti-PD-L1 and anti-TGF-β combined therapy [73]. The above results not only illustrate the heterogeneity of the immune environment of different tumors, but also provide opportunities for more personalized targeted or combined immunotherapy.

GERMLINE GENETIC

There is growing evidence that host immunity is affected by inherited factors. Genetic germline factors may affect cancer immune responsiveness (CIR) in many ways, such as mutations in gene involved in life style habits or DNA repair genes, polymorphisms of genes related to INF signaling, T and B cell differentiation, variants in genes controlling antigen presentation and related to the function of macrophages, natural killer (NK) cells and granulocyte [74]. Recently, the question of whether PD-(L)1 gene polymorphism affects the efficacy of ICIs has received much attention. It has been reported that the OS of patients with the germline variant *PDCD1*804C>T (rs2227981) deteriorated significantly, and the 3-year survival rate was 51.8%, whereas that of wild-type patients was 71.0% (OR 2.366; 95% CI 1.111–5.036; $P = 0.026$). Initial studies on mechanism have shown that this single nucleotide polymorphism may affect the clinical efficacy of ICIs by reducing the transcription initiation and expression of PD-1 in T cells [75]. Compared with A/G genotype, patients with PD1.3 (rs11568821) G/G genotype have a higher complete response (16.5% vs. 2.6%) [76]. PD-L1 rs4143815 G/G and rs2282055 T/T are associated with worse objective response rate (ORR) and PFS in NSCLC patients receiving nivolumab [77–79]. Aldehyde dehydrogenase 2 (ALDH2) serves a key role in the detoxification of endogenous acetaldehyde. ALDH2∗2 is a variant allele of ALDH2 polymorphism rs671, which provoked reduced enzyme activity. ALDH2∗2 can enhance the presentation of tumor antigens caused by acetaldehyde-induced DNA damage, whereas inhibiting peripheral blood T cell count and T cell activation. ALDH2∗2 may be a negative predictor of the short-term prognosis of ICIs in thoracic malignancies. The best response rate of rs671(−) patients to ICIs (PR/SD/PD) was 36%/50%/14%, whereas that of rs671(+) patients was relatively lower (27%/29%/45%) ($P = 0.002$), the hazard ratio of disease progression within 6 months of rs671(+) patients was much higher than rs671(−). Researchers speculated that ALDH2∗2 inhibited the PI3K-Akt pathway in T cells through the accumulation of endogenous aldehydes, which negatively affected the initial efficacy of ICIs [80]. Recent studies have shown that germline gene variations impact the richness of immune cells and infiltration in tumor, which significantly affect the composition and functional localization of tumor immune microenvironment. Some loci of immune traits with significant heritability are related to leukocytes subset enrichment and IFN signal, which may affect the effect of immunotherapy [81▪▪]. The above-mentioned initial research results aroused our keen interest to explore the key molecular mechanisms of germline genetic variation that may regulate antitumor immunity. In the future, combining germline data with somatic alterations, epigenetics and other information may improve the accuracy of CIR prediction and provide new targets for immunotherapy.

EXOSOMAL PROGRAMMED DEATH-LIGAND 1

Many studies have shown that exosomal PD-L1 derived from tumor cells can also inhibit the activation of CD8+ T cells. In addition, the exosomal PD-L1 acquired more characteristics than PD-L1 on the surface of tumor cells and may play a role in tumor lymphatic metastasis [82–85]. Some studies have suggested that the exosomal expression of PD-L1 is one of the mechanisms of primary resistance of ICIs. On one hand, PD-L1 inhibitors can bind to exosomal PD-L1, resulting in inability to inhibit PD-L1 on the surface of tumor cells or weakening of the inhibitory effect, and on the other hand, exosomal PD-L1 can directly bind to PD-1 on effector T cells. Both of the above conditions will affect the blocking effect of the antibody, leading to the persistence of PD-L1-mediated immunosuppression [86▪▪]. A recent study revealed that in addition to tumor cells, exosome of bone marrow-derived cells (BMDCs) can also carry PD-L1 in tumor-bearing mice, which has biological functions and can inhibit the proliferation and activation of CD8+ T cells both *in vivo* and *in vitro*, playing a major role in tumor immunosuppression. This may be useful to understand that some patients whose tumor cells do not express PD-L1 can also respond to anti-PD-1 treatment. Anti-PD-L1 therapy can abolish immunosuppression caused by exosomal PD-L1 of BMDCs, thereby activating antitumor immunity [87▪]. However, the PD-L1 expressed by exosomes derived from tumor cells has not always been the same as the PD-L1

expressed on tumor cells [83,88–92]. Whether the factors that regulate the expression of PD-L1 on the surface of tumor cells will regulate the level of exosomal PD-L1, and how to regulate it also need more research to clarify.

CONCOMITANT MEDICATIONS

Antibiotics and steroids are the most investigated concomitant medications during ICIs therapy. It is currently accepted that antibiotics use is an independent risk factor for primary resistance of ICIs [93], which leads to worse OS and PFS [94,95,96▪▪, 97,98▪], lower ORR [99▪▪]and higher risk of progression and death [100▪]. The time window [101▪,102–111] and course [112] of antibiotics use may have varying degrees of impact on the efficacy of ICIs. Previous studies have shown that baseline or early use of steroids (equivalent to>10 mg of prednisone/d) was associated with worse ORR, OS and PFS [113–116,117▪]. However, recent studies suggest that only patients treated with steroids for tumor-related symptoms have deleterious effects on OS and PFS in NSCLC [118], intercurrent introduction of steroids for the treatment of cancer unrelated symptoms or immune-related adverse events (irAE) has no harmful effect on clinical outcomes [119–121,122▪].

Many other nononcological medications have been speculated to influnce the TME, and then affect the depth, duration of response, and survival of patients receiving ICIs (Table 2). Proton pump inhibitors (PPI) may cause immunosuppression by reducing the expression of adhesion molecules of inflammatory cell or changing the secretion of pro-inflammatory cytokines. On the other hand, PPI use can affect the intestinal microbiota composition, reduce the diversity of intestinal microbiota and induce positive and negative selection of specific bacterial species. For example, the use of PPI is related to the greater species abundance of bifidobacteria, which may increase the effectiveness of ICIs, but it also leads to the decrease of the alpha diversity of the gut microbiota, which seems to be related to the higher response rate of melanoma patients treated with ICIs [96▪▪,97,98▪,100▪,128, 129]. The analgesic effect of opioids is achieved by targeting μ receptors in the central nervous system, but opioid receptors are also expressed on intestinal epithelial cells and immune cells, which means that opioids may cause changes in the intestinal microflora and alter immune response. Therefore, it is not surprising that the exposure of opioids during ICIs treatment will impact the effect of immunotherapy. However, it is also necessary to consider that patients taking opioids may have lower body mass index, higher prevalence of alcohol consumption and, and worse Eastern Cooperative Oncology Group performance [97]. The impact of antihypertensive drugs on the efficacy of ICIs is not consistent in the literature [123,124,125▪]. One of the papers reported that patients using angiotensin-converting enzyme inhibitors (ACEI) were in an immunosuppressive state with decrease of M1 macrophages, activated mast cells, NK cells and memory activated T cells. Captopril induced the expression of M2 marker CD206, when monocytes were involved in the differentiation of M1 macrophages *in vitro*. Animal experiments showed the same results that the therapeutic effect of anti-PD-1 monoclonal antibody was inhibited when used in combination with captopril [125▪]. Current research is mainly focused on observing the effect of concomitant medications on the efficacy of ICIs. However, there are few studies describing the biological mechanism of these drugs affecting the effect of ICIs. It is urgent to clarify the possible mechanisms of the interaction between ICIs and concomitant medications.

Additionally, inter- and intra-class differences between PD-1 inhibitors and PD-L1 inhibitors, including molecular, pharmacodynamics and pharmacokinetics characteristics, will affect their efficacy [130–138]. For example, pembrolizumab seems to have the best affinity and engagement among PD-1 inhibitors. Avelumab seems to have the best affinity, and atezolizumab has the longest half-life among the PD-L1 inhibitors [130]. In some cases, antidrug antibody will neutralize the activity of the antibody, which is also a reason for resistance of ICIs in some patients [137].

CONCLUSION

The huge advantages of immunotherapy over traditional treatment have made it an effective treatment for various malignant tumors. However, drug resistance has created a bottleneck in the application of immunotherapy. At present, there are endless combination treatment strategies for drug resistance, but the successful clinical application is quite limited. In the future, it will be necessary to deeply understand the mechanism of resistance and adopt appropriate methods to avoid resistance in order to achieve better treatment effects.

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Conflicts of interest

There are no conflicts of interest.

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