Supplementary Table 1: Summary of the various combination strategies.

Combination strategy	Advantage/synergy	Target	Drugs and main trials	Main results	References
ICIs + radiotherapy	*In situ* vaccine release, improved antigen presentation, removal of inhibitory immune microenvironment, and promotion of PD-L1 expression on tumor cells	–	Pooled analysis of PEMBRO-RT (phase 2) and MDACC (phase 1/2) trials	PFS: 9.0 months *vs.* 4.4 months (HR 0.67, 95% CI 0.45–0.99; $P = 0.0450$); OS: 8.7 months *vs.* 19.2 months (HR 0.67, 95% CI 0.54–0.84; $P = 0.0004$)	[10]
ICIs + chemotherapy	Directly and indirectly stimulate immune responses and increase tumor immunogenicity	–	Pooled analysis of Keynote-021 Cohort G, Keynote-189, and Keynote-407	PFS (HR 0.68, 95% CI 0.56–0.83); OS (HR 0.63, 95% CI 0.50–0.79)	[11]
Next-generation IRs	Improve the function of $CD8^+$ T cells and NK cells, reduce Treg-mediated suppressive effects,[22] and overcome immunotherapeutic resistance mediated by different IRs.	LAG-3	Anti-PD-1+BMS-986016 (CA224-020); relatlimab (BMS-986916) + nivolumab or ipilimumab; LAG525 (IMP701) + spartalizumab; TSR-033 + TSR-042 (anti-PD-1) or TSR-022 (anti-TIM-3); pembrolizumab + MK-4280 (KEYNOTE-495 [NCT03516981 and NCT02720068]); eftilagimod alpha (IMP321) + pembrolizumab (TACTI-002	Many are in preliminary exploration. Preliminary results published from the ongoing trial: ORR: 27%; ORR: 47%; ongoing	[13]

			[NCT03625323])		
		TIM-3	Anti-PD-1 + TIM-3 inhibitor (NCT03099109); simultaneous blockade of LGA-3 and TIM-3 or MHC-II and LAG-3, or quadruple blockade	Response: more than 20%; some anti-PD-1-resistant patients experienced PR; ongoing	[16]
		TIGIT	Anti-TIGIT (MK-7684) + pembrolizumab; anti-TIGIT (ongoing): MK-7684; tiragolumab (MTIG7192A); etigilimab (OMP-313M32)	In preliminary exploration	[13]
Next-generation immune agonists	Achieve pleiotropic immune activation through the IL-2 pathway, preferentially activating specific anti-tumor T cells and NK cells in the TIME, and increasing the expression of PD-1 on the surface of these immune cells	CD122	NTRK-214 + nivolumab (PIVOT-02); NKTR-214 + pembrolizumab/atezolizumab (2018 ASCO TPS3115)	Achieved a good efficacy regardless of baseline PD-L1 status and TILs	[18, 19]
		CD27, CD40, OX40, GITR, ICOS, etc.		Related studies have entered clinical trials	[20]
bsAb	Binds two different epitopes or antigens at the same time to achieve a variety of functions with synergistic effect; reduces the complexity of clinical development and drug side effects	PD-L1 /TGF-β	Drug: M7824 (bintrafusp alfa) (MSB0011359C). Trials: INTREPID LUNG 037 (NCT03631706, NCT02517398)	Preliminary good clinical efficacy; ongoing	[18, 21]
		KN046 and AK104 targeting PD-L1/CTLA-4; A-337 and M307 targeting CD3/EpCAM; SHR-1701 targeting PD-L1/TGF-β;		Have entered clinical trials in China	–

			IBI-318 targeting PD-1/PD-L1		
ICIs + antiangiogenic agents	The mutual regulation between the tumor vasculature and immunity can form a reinforcement loop to reorganize the TIME, thereby inducing long-lasting anti-tumor immunity; proangiogenic factors can modulate immune responses by reducing T cell infiltration into the TME and by systemic effects on the function of immunoregulatory cells	VEGF/ VEGF R-2, FGFR	Ramucirumab + pembrolizumab (JVDF study); lenvatinib (a type V kinase inhibitor) + pembrolizumab; bevacizumab (anti-VEGF) + atezolizumab; pembrolizumab + pemetrexed + platinum-based chemotherapy ± lenvatinib (LEAP-006 [NCT03829319]); pembrolizumab ± lenvatinib (LEAP-007[NCT03829332])	DCR: 85%; PFS: 9.7 months (95% CI 4.6–27.6), 1-year PFS rate: 43%, OS: 26.2 months (95% CI 11.8–NR), 1-year OS rate: 68%; good tolerance; has good anti-tumor therapeutic effect; ongoing	[23–26]
Immunomodulatory drugs	Inhibit adenosine pathway-mediated immunosuppression at multiple levels and modulate the resistance to PD-L1 inhibitors	Adenosine pathway: CD73 nucleotidase/ ADORA2A	CPI-444 (anti-ADORA2A) ± anti-PD-L1; oleclumab targeting CD73 (NCT02503774); CPI-444 (NCT02655822) and PBF-509 (NCT02403193) targeting ADORA2A	Favorable antitumor effects in preclinical models; ongoing	[27]
	Decrease Tregs and increase TILs.	IDO	Epacadostat (IDO inhibitor) + pembrolizumab ECHO-301 (KEYNOTE-252)	Failure	[29]

	Reduce the infiltration of immunosuppressive cells into the TME	IL-1β	CANTOS (NCT01327846): canakinumab; phase III clinical studies of canakinumab: CANOPY-1 (NCT03631199); CANOPY-2 (NCT03631199); CANOPY-N (NCT03968419); CANOPY-A (NCT03447769)	Reduced morbidity and mortality of patients with lung cancer; ongoing	–
ICIs + individualized tumor vaccines	Neoantigen-based individualized cancer vaccine: exert stronger anti-tumor effects, which is also an effective means of conquering "cold tumors"	NEO-PV-01 + nivolumab (NT-001 trial); NEO-PV-01 + pembrolizumab (NT-002 trial); CIMAvax-EGF + PD-1 inhibitor (NCT02955290 and NCT02955290); personalized neoantigen/cancer testis antigen nanovaccine (ChiCTR1900022986); RO7198457 (a personalized cancer vaccine) + atezolizumab		Had good tolerance and anti-tumor activity; has promising application prospects; ongoing;	[30, 31]
ICIs + cellular immunotherapy	Adoptive transfer of tumor-targeted T cells may fill the immunotherapy gap in patients with less immunogenic or "non-inflammatory" tumors	CAR-mediated co-stimulation + PD-1 DNR		Counteracts PD-1-mediated inhibition in the presence of tumor PD-L1 expression to enhance T cell function, resulting in long-term DFS after low-dose infusion of CAR-T cells	[33]
	NK cells are involved in the clinical benefit of anti-PD-1/PD-L1 antibody therapy by directly killing tumor cells and/or recruiting T cells	PM21-NK cells + anti-PD-L1 therapy; allogeneic NK cell therapy + pembrolizumab		ICIs combined with NK cell therapy has good efficacy and safety	[34, 35]

bsAb: Bispecific antibody; CAR: Chimeric antigen receptor; CI: Confidence interval; CTLA-4: Cytotoxic T-lymphocyte-associated protein-4; DFS: Disease-free survival; DNR: Dominant negative receptor; EpCAM: Epithelial cell adhesion molecule; FGFRs: Fibroblast growth factor receptors; GITR: Glucocorticoid-induced tumor necrosis factor receptor; HR: Hazard ratio; ICIs: Immune checkpoint inhibitors; ICOS: Inducible T cell co-stimulator; IRs: Inhibitory receptors; IL-1β: Interleukin-1β; LAG-3: Lymphocyte-activation gene 3; MHC: Major histocompatibility complex; NK cells: Natural killer cells; ORR: Objective response rate; OS: Overall survival; PD-L1: Programmed cell death 1 ligand 1; PFS: Progression-free survival; Treg: Regulatory T cell; TGF-β: Transforming growth factor-β; TIGIT: T cell immunoreceptor with Ig and ITIM domains; TIM-3: T-cell immunoglobulin and mucin molecule 3; TIME: Tumor immune microenvironment; TME: Tumor microenvironment; VEGFR-2: Vascular endothelial growth factor receptor 2.