First-line combination immunotherapy for metastatic non-small cell lung cancer

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ABSTRACT

Immunotherapy has recently become an important treatment modality, especially for non-small cell lung cancer (NSCLC) and melanoma patients. Several large-scale phase III trials of first-line treatments for metastatic NSCLC have documented prolonged patient survival, including progression-free survival and overall survival for immune checkpoint inhibitors (ICIs) used alone or in combination with chemotherapy. However, a significant proportion of patients experienced disease progression shortly after starting single-agent ICI treatment even after biomarker selection, such as programmed cell death-ligand 1 and tumor mutation burden. The present review was performed to identify ways to enhance ICI efficacy in the first-line treatment of metastatic NSCLC patients. At least four effective ways of combination treatment modalities are currently available, namely, immune therapy in combination with radiotherapy, chemotherapy, antiangiogenesis, or other immunotherapeutic agents.

Keywords: Check-point inhibitor; Chemotherapy; Immunotherapy; Non-small cell lung cancer

1. INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in the world, including Taiwan. The five-year survival rate between 2002 and 2008 in Taiwan was only 15.9%, with a median survival of 13.2 months.[1] Immunotherapy is a major advancement in oncology and a potential solution for lung cancer. Since 2013, immunotherapy has become an important treatment modality for non-small cell lung cancer (NSCLC).[1–4] The approval of nivolumab, pembrolizumab, and atezolizumab for second-line treatment of metastatic NSCLC firmly established pembrolizumab alone or in combination with chemotherapy, atezolizumab in combination with chemotherapy and antiangiogenesis for the first-line treatment of metastatic NSCLC, and the use of immune checkpoint inhibitor (ICI) treatment in NSCLC[5–14]; moreover, these have become the latest and novel treatment modalities in the decade following the introduction of the targeted therapy.

2. RELATIVELY LOW RESPONSE RATES AND HIGH PROPORTION OF PATIENTS WITH EARLY DISEASE PROGRESSION WITH USE OF ICIS ALONE

Although ICI treatment is a new standard of treatment for NSCLC, the overall objective response rate is usually only around 10% to 20% in second line-treatment and the progression-free survival (PFS) is also similar to or poorer than that for the conventional second-line chemotherapy (Table 1).[10–13] The objective response rate is below 45% in treatment-naïve and highly biomarker-selected NSCLC patients such as those with tumor programmed death-ligand 1 (PDL1) expression, when single-agent ICI treatment was administered (Table 2).[5,6,14,15] These results are far poorer than those reported for the efficacy of molecular-targeted therapy.[16–19] Furthermore, 30% to 40% and 40% to 60% of patients experienced disease progression within 3 or 6 months, respectively, of the first-line single agent ICI treatment (Fig. 1). This situation is even poorer in the second-line setting, with progressive disease as the best treatment response occurring in 44% of nivolumab-treated patients in the Checkmate 057 study of second-line nonsquamous NSCLC patients compared to 29% in docetaxel-treated patients.[5,6,15]

3. CANCER IMMUNITY CYCLE AND BARRIERS TO CYTOTOXIC T CELL ACTIVITY

The mechanisms by which the immunotherapeutic effect can be enhanced include enhancement of interactions between cancer and the immune cycle and conquering the barriers of cytotoxic T cell activity.[20,21] The cancer immunity cycle includes immune cell recognition and destruction of tumor cells. These processes involve the initial release of tumor cell antigens followed by their presentation to macrophages. Cytotoxic T cells are then primed and activated and trafficked to tumor sites where they recognize, infiltrate, and kill tumor cells.[20] The barriers to cytotoxic T cell effects include hostile tumor environments (hypoxia, acidic, nutrient-depleted, and toxic metabolites), immunosuppressive immune infiltrates in tumors (including T-regulatory cells, myeloid-derived stem cells, tumor-associated macrophages, and tumor-associated neutrophils), suppressive molecules in the tumor environment (including interleukin-10, transforming growth factor-β [TGF-β], adenosine, and prostaglandin E2), tumor-expressed suppressive receptors [including PDL1/

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Table 1.

Efficacy of immune check-point inhibitors in second line non-small cell lung cancer treatment

Study	Tumor PDL1	Response rate, %	Median PFS, mo	Median OS, mo
Keynote010	≥1%			
Pembrolizumab[a]		18	3.9	10.4
Docetaxel		9	4	8.5
(Hazard ratio)		$p = 0.0005$	(0.88)	(0.71)
Checkmate017[b]	All comer			
Nivolumab		20	3.5	9.2
Docetaxel		9	2.8	6
(Hazard ratio)		$p = 0.008$	(0.62)	(0.59)
Checkmate057[c]	All comer			
Nivolumab		19	2.3	12.2
Docetaxel		12	4.2	9.4
(Hazard ratio)		$p = 0.02$	(0.92)	(0.73)
OAK	All comer			
Atezolizumab		14	2.8	13.8
Docetaxel		13	4	9.6
(Hazard ratio)			(0.95)	(0.73)

OS=overall survival; NSCLC=non-small cell lung cancer; PDL=programmed cell death-ligand 1; PFS=progression-free survival.
[a]Only data of 2 mg/kg showed.
[b]Squamous NSCLC.
[c]Nonsquamous NSCLC.

Table 2.

Efficacy of single agent immune check-point inhibitors in first-line non-small cell lung cancer treatment

Study	Tumor PDL1	Response rate, %	Median PFS, mo	Median OS, mo
Keynote042	≥1%			
Pembrolizumab		27	5.4	16.7
Doublet chemotherapy		27	6.5	12.1
(Hazard ratio)			(1.07)	(0.81)
Pembrolizumab	≥50%			
Chemotherapy		39	7.1	20
(Hazard ratio)		32	6.4	12.2
			(0.81)	(0.69)
Keynote024	≥50%			
Pembrolizumab		44.8	10.3	30
Chemotherapy		27.8	6	14.2
(Hazard ratio)			(0.5)	(0.63)
Checkmate026[a]	≥5%			
Nivolumab		26	4.2	14.4
Chemotherapy		33	5.9	13.2
(Hazard ratio)			(1.15)	(1.02)

OS=overall survival; PDL1=programmed cell death-ligand 1; PFS=progression-free survival.
[a]Primary end-point of better PFS of Nivolumab treatment was not met.

L2 and V-domain Ig suppressor of T cell activation] or inhibitory enzymes (including arginase and indoleamine 2,3-dioxygenase-1 [IDO-1]), tumor major histocompatibility complex (MHC) downregulation (genetic or epigenetic), aberrant tumor vasculature, and lack of cytotoxic T cell costimulation [intrinsic T cell dysfunction, upregulation of suppressive signaling such as PD1, lymphocyte-activation gene 3 protein, and T cell immunoglobulin domain and mucin domain-3].[21] Augmentation of the cancer immunity cycle or removing barriers to cytotoxic T cell activity will enhance immunotherapy efficacy; these mechanisms comprise the basis of combination immunotherapies.[22,23]

Although there are several possible combinations, those most frequently used for NSCLC treatment include immunotherapy (mainly ICIs) in combination with radiotherapy, chemotherapy, antiangiogenesis, or another immunotherapy. The following sections focus on these relatively well-documented treatment modalities.

4. IMMUNOTHERAPY COMBINED WITH RADIOTHERAPY

The possible modalities for locoregional control include radiotherapy, surgery, and local ablation. When combined with systemic ICI therapy, local radiotherapy can improve overall response or control rates and even has survival effects through an abscopal effect.[24,25] "Abscopal" is defined as a position away from a shooting target. The abscopal effect in this context refers to phenomena in cancer treatment, whereby shrinkage of untreated tumors occurs concurrently with shrinkage of tumors within the scope of the localized treatment. The underlying mechanism by which local radiotherapy enhanced the effects of ICI is that radiation induces tumor cell DNA and cell membrane damage; the cytoplasmic reactive oxygen species activate transcription factors and signaling pathways that modulate the immune-phenotyping and immunogenicity of tumor cells.

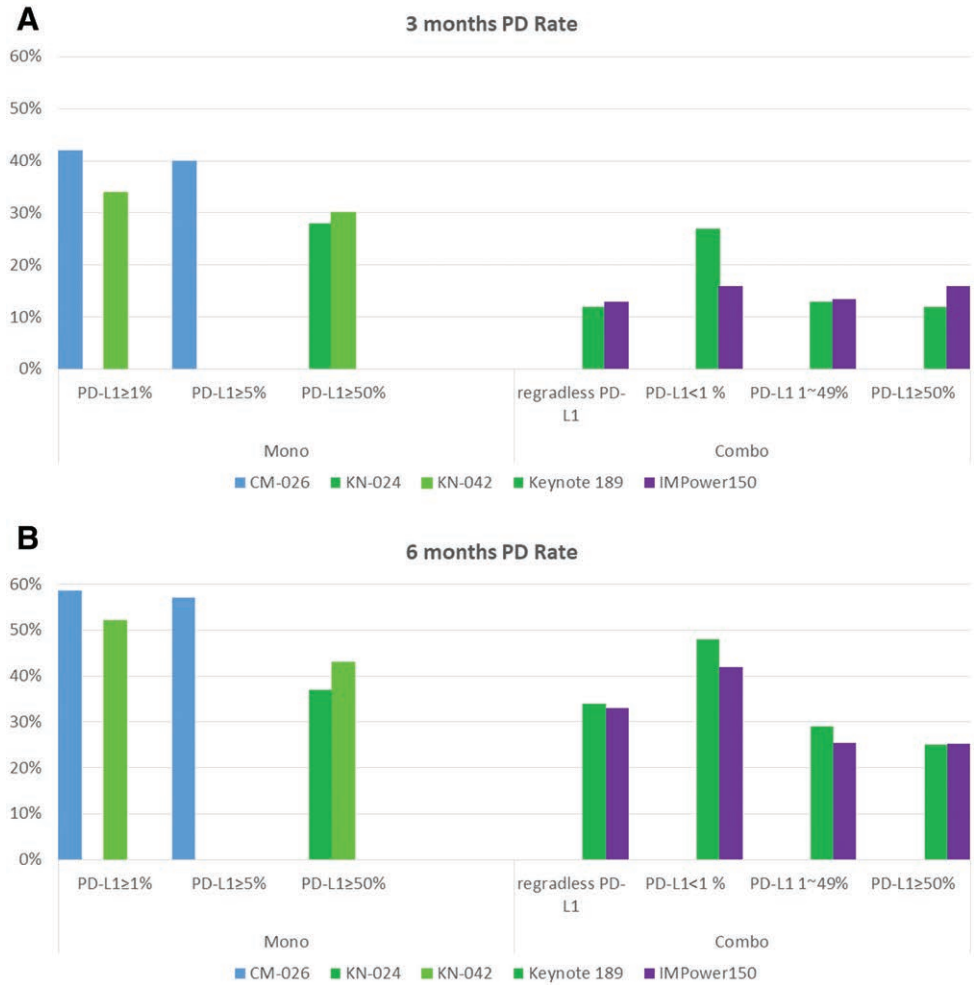

Fig. 1 Three- and 6-month disease progression rates for first-line immune check-point inhibitor single-agent or combination treatments. A, Three-month progressive disease rate. B, Six-month progressive disease rate.

The radiation-induced danger signals from tumor cells enhance dendritic cell-mediated antigen presentation, resulting in tumor-specific $CD8^+$ T cell activation and proliferation. The combination of anti-PD(L)1 with radiotherapy upregulates MHC and FAS on tumor cells to increase tumor cell susceptibility to T cell–mediated cytotoxicity.[26] Ongoing clinical trials are evaluating stereotactic body radiation therapy and immunotherapy in patients with metastatic NSCLC.[27] However, more large-scale prospective clinical trial data are needed before we can conclude that the effects of ICI are in combination with radiotherapy.

5. IMMUNOTHERAPY COMBINED WITH CHEMOTHERAPY

Chemotherapy was previously considered an immune suppressive therapy; however, certain chemotherapies can augment tumor immunity by inducing immunogenic cell death and disrupting strategies used by tumors to evade immune recognition. The effects of chemotherapy on immunotherapy depend on the chemotherapeutic drug used, dose applied, and the schedule of chemotherapy administration in relation to tumor antigen exposure or release.[28,29] Chemotherapy may boost the anticancer immune response through chemotherapy-induced immunogenic cell death; enhancing tumor antigen presentation by upregulating the expression of tumor antigens themselves or of the MHC class I molecules to which the antigens bind; upregulating costimulatory molecules or downregulating coinhibitory molecules expressed on tumor cell surface; depleting myeloid cells and T regulatory cells; and inducing inflammation and influx of tumor-infiltrating lymphocytes.[28,30,31] Chemotherapy-induced immunogenic tumor cell death involves the concomitant release of tumor antigens and the release of danger-associated molecular patterns in the tumor microenvironment during cell death.[28,30] Immunotherapy could also modify the microenvironment of the tumor to increase its sensitivity to chemotherapy by reducing cancer cell support and reprogramming tumor vasculature. These findings have resulted in renewed interests in combining immunotherapy with chemotherapy to achieve additive or synergistic clinical activity.

Potential deleterious effects of cytotoxic agents are also possible. For instance, frequently used taxanes (paclitaxel or docetaxel) could inhibit T cell and NK cell proliferation and activation and steroid premedication for pemetrexed and taxanes could upregulate TGF-β production, impair NK cell function, suppress proinflammatory cytokines and chemokines, induce Th2-cell bias, and impair dendritic cell differentiation or activation.[32] Ironically, a phase III study testing GVAX prostate [a cellular vaccine consisting of irradiated cells from PC-3 and prostate cancer cell lines modified to constitutively express granulocyte-macrophage colony-stimulating factor (GM-CSF)] combined with standard-dose docetaxel chemotherapy, randomized patients to receive GVAX every 3 weeks without prednisolone

(due to concern of inhibition of T cell response), or docetaxel with prednisolone (10 mg) daily was closed after 408 patients were randomized due to imbalanced deaths in the vaccine arm relative to the control arm, most likely due to severe adverse events induced by inadequate docetaxel steroid premedication.[33]

Several randomized phase III clinical trials assessing immunotherapy + chemotherapy vs chemotherapy alone for treatment-naïve metastatic NSCLC were published as full articles or abstracts in 2018. Tables 3 and 4 summarize the findings of ICIs in combination with chemotherapies for nonsquamous and squamous NSCLC, respectively. Among them, the Keynote 189 and IMpower 150 studies are the two most important for nonsquamous NSCLC, while the Keynote 407 and IMpower 131 studies are two most important for squamous cell lung cancer.

The Keynote 189 study randomly assigned 616 patients with metastatic nonsquamous NSCLC without sensitizing epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations who had received no previous treatment for metastatic disease in a 2:1 ratio to receive pemetrexed and a platinum-based drug + either a fixed dose of pembrolizumab or placebo every 3 weeks for four cycles, followed by pembrolizumab or placebo for up to a total of 35 cycles + pemetrexed maintenance therapy.[7] Crossover to pembrolizumab monotherapy was permitted among patients in the placebo-combination group with verified disease progression. The primary end points were OS and PFS as assessed by a blinded, independent central radiologic review. After a median follow-up of 10.5 months, the estimated OS rate at 12 months was 69.2% in the combination arm vs 49.4% in chemotherapy arm [hazard ratio (HR) for death 0.49; 95% CI, 0.38-0.64; $p < 0.001$]. Improved OS was observed across all evaluated PDL1 categories (<1%, 1%-49%, and ≥50%) and higher PDL1 expression showed better survival in subgroup analysis. The median PFS were 8.8 and 4.9 months in the combination and chemotherapy arms, respectively (HR for disease progression or death 0.52; 95% CI, 0.43-0.64; $p < 0.001$). The response rates were 47.6% and 18.9% in the combination and chemotherapy arms, respectively ($p < 0.001$). The addition of pembrolizumab to the standard chemotherapy of pemetrexed and a platinum-based drug resulted in significantly longer OS and PFS than those for chemotherapy alone.[7] Survival data were updated at the 2019 American Society of Clinical Oncology (ASCO) annual meeting, with median OS of 22 months in the combination arm and 10.7 months in the chemotherapy arm (HR, 0.56; 95% CI, 0.45-0.7). OS and PFS were significantly better in the combination arm regardless of the PDL1 expression level.[34]

The IMpower 150 study also added an antiangiogenesis drug (bevacizumab) to ICI and chemotherapy combination treatment (arm B) in addition to ICI and chemotherapy combination treatment (arm A).[8] The standard control treatment arm was administered antiangiogenesis drug + doublet chemotherapy treatment (arm C). Patients were randomly assigned to receive atezolizumab + paclitaxel + carboplatin (arm A), bevacizumab + atezolizumab + paclitaxel + carboplatin (arm B), or bevacizumab + paclitaxel + and carboplatin (arm C) every 3 weeks for four or six cycles, followed by maintenance therapy with atezolizumab (arm A), bevacizumab (arm C), or both (arm B). Patients with *EGFR* or *ALK* mutations were also allowed to enter the study if they had previously received tyrosine kinase inhibitor treatment. The two primary endpoints were investigator-assessed PFS both among patients in the intention-to-treat (ITT) group with wild-type genotypes (WT population; patients with *EGFR* or *ALK* genetic alterations were excluded) and among patients in the WT population with high expression of an effector T cell (Teff) gene signature in the tumor (Teff-high WT population) and OS in the WT population. Arm B was compared with arm C before arm A was compared with arm C. Among the ITT patients, 400 each were assigned to arms B and C, including 44 and 64 patients with *EGFR* or *ALK* mutations and s356 and 336 patients with WT genotypes, respectively. The median PFS was longer in arm B than that in arm C (8.3 vs 6.8 months; HR for disease progression or death, 0.62; 95% CI, 0.52-0.74; $p < 0.001$); the corresponding values in the Teff-high WT population were 11.3 and 6.8 months (HR, 0.51; 95% CI, 0.38-0.68; $p < 0.001$). PFS was also longer in arm B than that in arm C in the entire ITT population (including those with *EGFR* or *ALK* genetic alterations) and among patients with low or negative PDL1 expression, low Teff gene-signature expression, and with liver metastases. The median OS among patients with WT genotypes was longer in arm B than that in arm C (19.2 vs 14.7 months; HR for death, 0.78; 95% CI, 0.64-0.96; $p = 0.02$). The investigator-assessed unconfirmed objective response rates (data cutoff, September 15, 2017) among patient with WT genotypes were 63.5% in arm B and 48.0% in arm C. Secondary and exploratory analyses among patients with *EGFR* mutations or *ALK* translocations showed longer PFS in arm B than in arm C (median 9.7 vs 6.1 months; unstratified HR, 0.59; 95% CI, 0.37-0.94). PFS was also longer in arm B than that in arm C for the entire ITT population, including patients with *EGFR* mutations or *ALK* translocations (median, 8.3 vs 6.8 months; stratified HR, 0.61; 95% CI, 0.52-0.72). Subgroup analysis including patients without PDL1 expression showed a positive association between PDL1 expression and PFS. A benefit with respect to PFS was also observed in arm B patients with liver metastases (median 7.4 vs 4.9 months in arm C) and patients with *KRAS* mutations (median, 8.1 vs 5.8 months in arm C). Therefore, the addition of atezolizumab to bevacizumab + chemotherapy significantly improved PFS and OS among patients with metastatic nonsquamous NSCLC, regardless of PDL1 expression and *EGFR* or *ALK* genetic alteration status. Whether this kind of regimen can improve survival in patients with *EGFR/ALK* mutations requires further study because these patients were not included in the primary endpoint analysis. Updated subgroup analysis reported at the 2019 ASCO annual meeting showed a 48% reduced risk of death in patients in arm B with liver metastases compared with those in arm C (HR, 0.52; 95% CI, 0.33-0.82), while no difference in the risk of death in patients with liver metastases was observed between arms A and C (HR, 0.87; 95% CI, 0.57-1.32).[35]

The IMpower 132 phase III randomized study evaluated first-line pemetrexed + carboplatin or cisplatin with or without atezolizumab in patients with stage IV nonsquamous NSCLC without *EGFR* or *ALK* driver mutations.[36] The patients were randomized to receive four or six cycles of carboplatin or cisplatin + pemetrexed alone (arm B) or in combination with atezolizumab (arm A), followed by pemetrexed (arm B) or atezolizumab + pemetrexed (arm A) maintenance therapy. PFS and OS were the coprimary endpoints. Investigator-assessed PFS per response evaluation criteria in solid tumors (RECIST) v1.1 (final analysis), OS (interim analysis), and safety data were reported at the 2018 WCLC meeting. Arms A and B included 292 and 286 patients, respectively. PFS analysis showed a significant improvement in arm A (median PFS 7.6 vs 5.2 months; HR, 0.60, 95% CI, 0.49-0.72, $p < 0.0001$). The objective response rates were 47% and 32% in arms A and B, respectively. Interim analysis showed median OS of 18.1 months in arm A and 13.6 months in arm B (HR, 0.81; 95% CI, 0.64-1.03; $p = 0.0797$). Thus, PFS met the primary endpoint while the interim OS showed numerical improvement without statistical significance.

The IMpower130 randomized phase 3 first-line study evaluated carboplatin + nab-paclitaxel with or without atezolizumab in patients with stage IV nonsquamous NSCLC.[37] Patients received atezolizumab + carboplatin + nabpaclitaxel (arm A) or carboplatin + nab-paclitaxel (arm B) in a 2:1 ratio for four

Table 3.

Efficacy of immunotherapy (immune check point inhibitor) combined with chemotherapy vs chemotherapy alone in first-line nonsquamous non-small cell lung cancer treatment

Study	Tumor PDL1	Response rate, %	Median PFS, mo	Median OS, mo
Keynote189	All comer			
Pembrolizumab+platinum+pemetrexd		47.6	8.8	NR
Platinum+pemetrexed		18.9	4.9	11.3
(Hazard ratio)			(0.52)	(0.49)
	≥50%			
		61.4	9.4	NR
		22.9	4.7	10
			(0.36)	(0.42)
	1%–49%			
		48.4	9	NR
		20.7	4.9	12.9
			(0.55)	(0.55)
	<1%			
		32.3	6.1	15.2
		14.3	5.1	12
			(0.75)	(0.59)
IMpower150	All comer			
Atezolizumab+bevacizumab+paclitaxel+carboplatin		56	8.3	19.2
Bevacizumab+paclitaxel+carboplatin		41	6.8	14.7
(Hazard ratio)			(0.59)	(0.76)
	TC3 or IC3			
		69	11.1	25.2
		49	6.9	15
			(0.49)	(0.7)
	TC1/2 or IC1/2			
		58	8.3	20.3
		41	6.1	16.4
			(0.53)	(0.8)
	TC0 and IC0			
		51	8.2	17.1
		36	7	14.1
			(0.77)	(0.82)
IMpower130	All comer			
Atezolizumab+nab-paclitaxel+carboplatin		49	7	18.6
Nab-paclitaxel+carboplatin		32	5.5	13.9
(Hazard ratio)			(0.64)	(0.79)
	TC3 or IC3			
		NR	6.4	17.3
		NR	4.6	16.9
			(0.51)	(0.84)
	TC1/2 or IC1/2			
		NR	8.3	23.7
		NR	6	15.9
			(0.61)	(0.7)
	TC0 and IC0			
		NR	6.2	15.2
		NR	7.4	12
			(0.72)	(0.81)
IMpower132	All comer			
Atezolizumab+pemetrexed+platinum		47	7.6	18.1
Pemetrexed+platinum		32	5.2	13.6
(Hazard ratio)			(0.6)	(0.81)
	TC3 or IC3			
		72	10.8	NR
		55	6.5	NR
			(0.51)	NR
	TC1/2 or IC1/2			
		38	6.2	NR
		38	5.7	NR
			(0.8)	NR
	TC0 and IC0			
		44	8.5	NR
		27	4.9	NR
			(0.45)	NR

NR=no reported; OS=overall survival; PDL1=programmed cell death-ligand 1; PFS=progression-free survival.

Table 4.

Efficacy of Immunotherapy (immune checkpoint inhibitor) combined with chemotherapy vs chemotherapy alone in first-line squamous non-small cell lung cancer treatment

Study	Tumor PDL1	Response rate, %	Median PFS, mo	Median OS, mo
Keynote407	All comer			
Pembrolizumab+carboplatin+ (paclitaxel/nabpaclitaxel)		57.9	6.4	15.9
Carboplatin+(paclitaxel/nabpaclitaxel)		38.4	4.8	11.3
(Hazard ratio)			(0.56)	(0.64)
	≥50%			
		NR	8	Not reached
		NR	4.2	Not reached
			(0.37)	(0.64)
	1%–49%			
		NR	7.2	14
		NR	5.2	11.6
			(0.56)	(0.57)
	<1%			
		NR	6.3	15.9
		NR	5.3	10.2
			(0.68)	(0.61)
IMpower131	All comer			
Atezolizumab+carboplatin+nab-paclitaxel		49	6.5	14.6
Carboplatin+nab-paclitaxel		41	5.6	14.3
(Hazard ratio)			(0.74)	(0.92)
	TC3 or IC3			
		60	10.1	23.6
		33	5.5	14.1
			(0.44)	(0.56)
	TC1/2 or IC1/2			
		52	6	12.4
		44	5.6	16.6
			(0.7)	(1.34)
	TC0 and IC0			
		44	5.7	13.8
		42	5.6	12.5
			(0.81)	(0.86)

NR=no reported; OS=overall survival; PDL1=programmed cell death-ligand 1; PFS=progression-free survival.

or six cycles and maintenance (arm A: atezolizumab until loss of clinical benefit; arm B: best supportive care or pemetrexed every 3 weeks until disease progression). Crossover to atezolizumab at disease progression was permitted in Arm B. The coprimary endpoints were investigator-assessed PFS and OS in the ITT–WT population (*EGFR*-wild type/*ALK* translocation negative). Of 723 enrolled ITT patients, 679 were *EGFR*/*ALK* WT (ITT–WT). Statistically significant improvements in OS and PFS for ITT–WT patients were observed in arm A vs arm B (OS: 18.6 vs 13.9 months, HR = 0.79, 95% CI, 0.64-0.98, $p = 0.033$; PFS: 7.0 vs 5.5 months, HR = 0.64, 95% CI, 0.54-0.77, $p < 0.0001$). PFS and OS were also significantly improved in the ITT group. PFS and OS benefits were observed in all PDL1 subgroups [PDL1-high (TC3 or IC3), PDL1 low (TC1/2 or IC 1/2), and PDL1-negative (TC0 and IC0)]. The PFS and OS of patients with liver metastases and *EGFR*/*ALK* genomic alterations did not improve between arms A and B. Therefore, the IMpower130 study showed statistically significant and clinically meaningful improvements in OS and statistically significant improvements in PFS for chemoimmunotherapy in first-line, stage IV *EGFR*/*ALK* WT nonsquamous NSCLC treatment. However, chemotherapy is a less often used regimen, making this study less useful as a reference for clinical practice. Nevertheless, atezolizumab in combination with chemotherapy has better efficacy than chemotherapy alone, especially when antiangiogenesis drugs are not combined with chemotherapy when the results of the IMpower130, IMpower132, and IMpower150 studies are considered together. The results of ICI combined with chemotherapy in nonsquamous NSCLC are shown in Table 3.

The Keynote 407 study randomly assigned 559 treatment-naive stage IV squamous NSCLC patients to receive pembrolizumab (arm A) or saline placebo (arm B) for up to 35 cycles.[9] All patients also received carboplatin and either paclitaxel or nanoparticle albumin-bound [nab]-paclitaxel for the first four cycles. The primary endpoints were OS and PFS. After a median follow-up of 7.8 months, the median OS was 15.9 months in arm A and 11.3 months in arm B (HR, 0.64; 95% CI, 0.49-0.85; $p < 0.001$). The OS benefit was consistent regardless of the PDL1 expression level. The median PFS was 6.4 months in arm A and 4.8 months in arm B (HR for disease progression or death, 0.56; 95% CI, 0.45-0.70; $p < 0.001$). Therefore, the addition of pembrolizumab to chemotherapy with carboplatin + paclitaxel or nab-paclitaxel resulted in significantly longer OS and PFS than those for chemotherapy alone in previously untreated patients with stage IV squamous NSCLC.

The IMpower131 study evaluated atezolizumab + carboplatin + paclitaxel or nab-paclitaxel as first-line treatment for stage IV squamous NSCLC.[38] Patients were randomized to receive atezolizumab + carboplatin + paclitaxel (arm A), atezolizumab + carboplatin + nab-paclitaxel (arm B), or carboplatin + nab-paclitaxel (arm C). The patients received four or six cycles of chemotherapy and atezolizumab until loss of clinical benefit. The primary analysis of investigator-assessed efficacy in the ITT population for arm B vs arm C was presented at the

2018 ASCO annual meeting.[38] The study enrolled 338, 343, and 340 patients in arms A, B, and C, respectively. The median PFS was 6.3 months in arm B vs 5.6 months in arm C (HR, 0.71; 95% CI, 0.60-0.85; p = 0.0001). The PFS benefit was enriched in all PDL1-positive subgroups and was most pronounced for TC3 or IC3. The objective response rates of the ITT populations were 49% in arm B and 41% in arm C. The objective response rates in arm B were 60%, 52%, and 44% for TC3 or IC3, TC1/2 or IC 1/2, and TC0 and IC 0, respectively. The first interim OS analysis in the ITT population showed median OS of 14 and 13.9 months in arms B and C, respectively (HR, 0.96; 95% CI, 0.78-1.18; p = 0.6931). Thus, the IMpower13 study met its coprimary endpoint of investigator-assessed PFS in the ITT population in arm B vs arm C, while the first interim OS analysis showed no survival benefit. The results of ICI combined with chemotherapy in squamous NSCLC are shown in Table 4.

6. IMMUNOTHERAPY COMBINED WITH ANTIANGIOGENESIS DRUG

For patient treatment, cancer and anticancer immunity can be categorized into three main phenotypes; immune-desert, immune-excluded, and inflamed phenotypes. Each phenotype is associated with specific underlying biological mechanisms that may prevent the host's immune response from eradicating cancer.[23] Immune-excluded tumors may reflect particular vascular factors or barriers [including vascular endothelial growth factor (VEGF) and Fas ligand], extravascular matrix (such as collagen and fibronectin), or specific chemokine state [including chemokine ligand 12 (CXCL12) and chemokine proteases]. The use of anti-VEGF for immune-excluded tumors is frequently studied.[8] VEGF inhibits cytotoxic T-lymphocytes, restrains dendritic cell maturation and antigen presentation, promotes immunosuppressive cells, and results in abnormal tumor vasculature with low pH and hypoxic environments.[39] In addition to facilitating tumor infiltration by T cells, anti-VEGF also primes and activates T cells through dendritic cell maturation and establishes an immune-permissive tumor microenvironment by decreasing myeloid-derived stem cell and Treg populations.[8,23,39]

Although these underlying mechanisms by which antiangiogenesis agents augment anticancer immunity are well documented in in-vitro and in-vivo studies, only some phase I and II trials of pure ICI + antiangiogenesis agents have been performed, which have reported modest activity[40] and phase III study are rarely planned. More acceptable treatment strategies include ICIs combined with antiangiogenesis agents and doublet chemotherapy[41] such as the regimen evaluated in the IMpower150 study.[8] Other similarly designed phase III studies of chemoimmunotherapy + antiangiogenesis are also planned or are on-going.

7. IMMUNOTHERAPY COMBINED WITH OTHER IMMUNOTHERAPY

While the PD1/PDL1 pathway is the major checkpoint pathway for adoptive T cell function, other natural negative or positive feedback mechanisms also fine-tune immune response by activating or inhibiting T cell or NK cell function. These pathways also provide opportunities for tumors to escape the immune system. However, it also offers multiple opportunities for the combination of immunotherapeutic agents.[2,22,42]

Among combination immunotherapy regimens, the most frequent is anticytotoxic T-lymphocyte protein 4 (CTLA4) + anti-PD1 or anti-PDL1.[43,44] The CheckMate 227 open-label, multipart, phase 3 trial reported increased PFS with nivolumab (anti-PD1) + ipilimumab (anti-CTLA4) vs chemotherapy among patients with high (≥10 mutations per megabase) tumor mutational burden (TMB) in 2018.[43] Treatment-naïve metastatic or recurrent NSCLC patients with tumor PDL1 expression ≥1% were randomly assigned to receive nivolumab + ipilimumab, nivolumab monotherapy, or chemotherapy. Patients with tumor PDL1 expression <1% were also randomly assigned. TMB was determined using the FoundationOne CDx assay. PFS among patients with a high TMB was significantly longer for nivolumab + ipilimumab than for chemotherapy. The one-year PFS rate was 42.6% for nivolumab + ipilimumab vs 13.2% for chemotherapy, with median PFS of 7.2 vs 5.5 months (HR for disease progression or death 0.58; 97.5% CI, 0.41-0.81; p < 0.001). The objective response rates were 45.3% and 26.9% for nivolumab + ipilimumab and chemotherapy, respectively. Although the PFS and objective response rate were better for patients with high TMB who received combination immunotherapy than for patients who received chemotherapy, OS was not significantly improved in patients receiving combination immunotherapy between high TMB and low TMB or those with high TMB receiving combination immunotherapy vs chemotherapy.[45]

The MYSTIC open-label, phase 3 trial evaluated the first-line treatment with durvalumab (anti-PDL1) vs platinum-based doublet chemotherapy and durvalumab + tremelimumab (anti-CTLA4) vs platinum-based doublet chemotherapy in immunotherapy/chemotherapy-naïve metastatic NSCLC patients without *EGFR*-sensitizing mutations or *ALK* rearrangement.[44] The primary endpoints were OS for durvalumab vs chemotherapy and OS and PFS for durvalumab + tremelimumab vs chemotherapy in patients with tumor cell PDL1 expression ≥25% as determined by the VENTANA PDL1 (SP263) assay. The efficacy findings of 488 patients with PDL1 ≥25% among the 1118 randomized patients were presented at the 2018 ESMO-IO meeting. The median OS was 16.3 vs 12.9 months for durvalumab vs chemotherapy (HR, 0.76; 97.54% CI, 0.564-1.019; p = 0.036) and 11.9 vs 12.9 months for durvalumab + tremelimumab vs chemotherapy (HR, 0.85; 98.77% CI, 0.611-1.173; p = 0.202). Neither met the primary endpoint. The median PFS was 3.9 vs 5.4 months for durvalumab + tremelimumab vs chemotherapy (HR, 1.05; 99.5% CI, 0.722-1.534; p = 0.705). Therefore, the first-line immunotherapy with durvalumab or the combination of durvalumab and tremelimumab did not improve OS in unselected NSCLC patients. However, an exploratory analysis of OS according to high (≥16 mutations per megabase) or low (<16 mutations per megabase) blood TMB showed an OS of 16.5 months for durvalumab + tremelimumab vs 10.5 months for chemotherapy (HR, 0.64). The results of the exploratory analysis require validation in a future trial.

Other combination immunotherapies such as pembrolizumab with epacadostat (and IDO-1 inhibitor) showed promising antitumor activity in multiple advanced solid tumors, including NSCLC.[46] However, a negative result of phase III randomized trial in melanoma stopped consideration for a phase III trial in NSCLC.[47]

8. DISCUSSION

Combinations of immunotherapy (ICIs) with chemotherapy (platinum-based with/without antiangiogenesis agents) have improved treatment efficacy (response rate, PFS, OS, or all items) than chemotherapy, while combination immunotherapies such as anti-CTLA4 and anti-PD(L)1 have improved only response rate and PFS in highly selected patients, with OS results still pending. Both the CheckMate227 and MYSTIC trials randomized patients to receive anti-PD(L)1 alone, anti-CTLA4 + anti-PD(L)1, or chemotherapy alone. However, the primary endpoints of both studies did not compare anti-PD(L)1 alone to anti-CTLA4 + anti-PD(L)1. Moreover, no studies have compared

anti-PD(L)1 + chemotherapy vs anti-PD(L)1 alone. Thus, we can only conclude that immunotherapy combined with chemotherapy showed better efficacy than that for chemotherapy alone. However, indirect retrospective review of data from different clinical trials of the first-line single anti-PD1 treatment and anti-PD(L)1 + chemotherapy treatment studies showed a trend of better response rate and PFS (Tables 2–4). The OS of anti-PD(L)1 + chemotherapy treatment studies are too immature to compare with that for anti-PD1 treatment alone.

The main purpose of combination immunotherapy is to enhance ICI treatment efficacy in consideration of the high initial 3- to 6-month disease progression rate for ICI use alone (Figure 1). The percentage of patients with initial rapid disease progression was markedly reduced for ICIs combined with chemotherapy with/without antiangiogenesis agents (Figure 1). Three months after starting treatment, combination immunotherapy showed a significantly lower percentage of patients with disease progression than immunotherapy alone, from approximately 35% to 15%. This reduction was also noted at 6 months after starting treatment (from approximately 50% for ICI monotherapy to approximately 35% for combination therapy). The median PFS of combination treatments are also improved (Tables 2–4). This enhancement of treatment effects is noted regardless of tumor PDL1 levels higher or lower than 50%. Thus, although single-agent ICI treatment could be used in patients with tumor PDL1 of 50% or higher, combination immunotherapy may be better to reduce the proportion of patients with initial rapid disease progression regardless of tumor PDL1 expression. The effects of combination immunotherapy on long-term survival require longer follow-ups in phase III clinical trials.

The efficacy and the optimal place of ICIs in the treatment strategy algorithm for oncogenic-addicted lung cancers, such those with *EGFR* or *ALK* mutation, remain controversial because only a minority of ICI trials enrolled oncogenic-addicted NSCLC patients previously treated with targeted therapy. A retrospective review of 551 advanced NSCLC patients with at least one oncogenic driver alteration treated in 24 centers from 10 countries included eight types of driver oncogenes.[48] The treatment efficacy was not good, with objective response rates of 12% in *EGFR* and 0% in *ALK*, and median PFS of 2.1 and 2.5 months, respectively. The authors concluded that patients with actionable tumor alterations should receive targeted therapies and chemotherapy before considering immunotherapy.[48] There are still open questions about ICIs in oncogenic-driven NSCLC, including their efficacies and toxicities, which need to be addressed before considering ICI treatment a standard approach in this population.[49] Regarding ICIs combined with targeted therapy, pembrolizumab in combination with erlotinib or gefitinib as a first-line treatment for advanced NSCLC patients with sensitizing *EGFR* mutation was reported in the phase 1/2 Keynote cohort F study.[50] Twelve patients received pembrolizumab + erlotinib and seven received pembrolizumab + gefitinib. Pembrolizumab + erlotinib was feasible, with adverse events similar to those expected for monotherapy. However, pembrolizumab + gefitinib was not feasible due to grade 3/4 liver toxicity in five of the seven patients (71.4%), leading to permanent treatment discontinuation in four patients. The objective response rate in this study was low (41.7%). The authors concluded that the combination of pembrolizumab and gefitinib was toxic and the combination of pembrolizumab + erlotinib did not improve the objective response rate compared to that for previous single-agent tyrosine kinase inhibitor treatment.[50] Another trial of osimertinib in combination with durvalumab in *EGFR*-mutated NSCLC was terminated early due to a high rate of interstitial pneumonitis.[51,52] We await an improved study design with a good rationale for combined targeted therapy and immunotherapy in NSCLC.

There remain many unresolved issues on treatment, including combination therapy for selected or all patients. The development of appropriate predictive biomarkers is urgently needed. Also outstanding are questions on the need for more aggressive combinations or if concurrent, sequential, or intercalating immunotherapy should be combined with chemotherapy.

The current clinical practice in Taiwan is still mainly platinum-based doublet chemotherapy for driver oncogene-negative metastatic NSCLC patients. Immunotherapy alone is used only in a few patients with high tumor PDL1 expression, and national health insurance rarely pays for the first-line NSCLC treatment. As for combination immunotherapy, the current clinical practice guidelines recommend atezolizumab or pembrolizumab + platinum-based chemotherapy with/without bevacizumab.[53] However, only the minority of NSCLC patients receive this treatment because the national insurance program does not currently provide reimbursement for combination immunotherapy.

In conclusion, combinations of immunotherapy and chemotherapy have shown improved efficacy compared with chemotherapy alone. In addition to tumor PDL1 expression, additional appropriate predictive biomarkers are needed. Combined immunotherapy with chemotherapy + antiangiogenesis agents also plays a role in NSCLC treatment, especially in patients with liver metastases and possibly patients with *EGFR*/*ALK* mutations. Whether the efficacy of antiangiogenesis agents combined with immunotherapy without chemotherapy could be better than that for platinum-based chemotherapy remains unknown due to limited phase I/II studies and lack of phase III study. Immunotherapy combinations such as anti-CTLA4 and anti-PD(L)1 improved the treatment response rate and PFS in selected patients with high TMB, while the OS effects are still pending and unlikely to show positive results. Thus, there currently is no clear winner for combination immunotherapy.

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