Review Article

Advances in clinical trials of targeted therapy and immunotherapy of lung cancer in 2018

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Abstract: There were many clinical studies on lung cancer in 2018. In particular, significant progress has been made in immunotherapy and targeted therapy. Whether in small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC), immune checkpoint inhibitors (ICIs) have shown good results. For patients with specific gene mutations, the new generation inhibitors also showed good results in clinical trials. In this review, we summarize the clinical trials in lung cancer in 2018 and describe the progress and prospects for lung cancer therapies.

Keywords: Non-small cell lung cancer (NSCLC); small cell lung cancer (SCLC); immunotherapy; targeted therapy; clinical trails

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Introduction

Among the new cases of malignant tumors and tumor deaths worldwide in 2018, the incidence (11.6%) and mortality (18.4%) of lung cancer ranked first (1). In China, the incidence and mortality of lung cancer has gradually increased over the past 30 years, and this trend is expected to continue (2). The malignant tumor incidence and mortality study in China in 2015 showed that the incidence and mortality of lung cancer were the highest of any cancers (3). Lung cancer has become one of the problems that threatens human health worldwide. But at the same time, there were many clinical trials that made significant progress in the treatment of lung cancer in 2018. Programmed cell death protein-1 (PD-1) inhibitors, programmed cell death ligand protein-1 (PD-L1) inhibitors, and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) inhibitors showed good results, both in small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). For inoperable patients with gene mutations, targeted therapy has shown superior efficacy compared to traditional chemotherapy. Targeted therapy and immunotherapy may therefore become the first-line treatments for inoperable NSCLC and SCLC.

Targeted therapy

Among all NSCLC patients, approximately 30–40% of Asian patients and 10–20% of Caucasian patients have epidermal growth factor receptor (EGFR) gene mutations, while approximately 10% of Asian patients and 30% of Caucasian patients have Kirsten rat sarcoma viral oncogene (KRAS) mutations, and 1–7% and 1.7% of patients have anaplastic lymphoma kinase (ALK) and ROS1 gene mutations, respectively. A small number of patients also have human epidermal growth factor receptor-2 (HER2) gene mutations (4).

The EGFR gene mutation

Compared with chemotherapy, EGFR tyrosine kinase inhibitors (TKIs) not only show better efficacy, but also have the advantages of oral administration, better compliance, and lower toxicity (5). Whether for local advanced or metastatic NSCLC patients, or for postoperative adjuvant therapy, using tissues or peripheral blood for molecular testing to determine EGFR mutations, and then using EGFR-TKIs as recommended by the NCCN guidelines as a first or second-line therapy is suggested (6). Since the first EGFR-TKI, gefitinib, was used at the beginning of this century, new generation EGFR-TKIs, including afatinib and osimertinib have been used successfully. Clinical trials for those drugs occurred in 2018 (*Table 1*).

First generation EGFR-TKIs

In a phase IV clinical study (NCT01609543) (7) of erlotinib as the first-line treatment, a total of 62 patients were treated with this drug. The objective response rate (ORR) was 66.1%, and the median progression-free survival (mPFS) was 12.8 months. Although determination of the overall survival (OS) was premature, the 1-year survival was 82.5%, which was a significant improvement compared with traditional chemotherapy having a remission rate of 20–35% and median survival time of 10–12 months (20). As for second-line treatment, the ORR of erlotinib was 25.5%, the mPFS was 4.8 months, and the OS was 10.4 months (8). Compared with vinorelbine and cisplatin as the postoperative adjuvant chemotherapy for stage IIIA NSCLC patients, the median disease-free survival was doubled in the erlotinib group (42.2 *vs.* 21.0 months, P=0.0054). The 2- and 3-year disease-free survival rate also increased significantly at the same time (81.4% *vs.* 44.6%, P=0.0054; 54.2% *vs.* 19.8%, P=0.0460, respectively) (9).

In another clinical study comparing the effects of EGFR-TKIs and chemotherapy as first-line therapies (NCT00997230) (10), 53% of all 334 patients chose gefitinib. Gefitinib's mPFS was longer than that of chemotherapy (10.0 *vs.* 7.0 months, P=0.022), and the mOS was also extended to 4.5 months (18.1 *vs.* 13.6 months, P=0.005). However, in a study by Yang *et al.* (11), gefitinib combined with platinum had no statistical difference in the mPFS and ORR compared with using platinum alone. The combination was superior only in the mOS (18.6 *vs.* 14.9 months). Uchibori *et al.* (12) studied the efficacy of gefitinib in combination with pemetrexed as the second-line treatment after using gefitinib. The results showed that the mPFS was 6.7 months and the mOS was 24.3 months, which meant a combination of the two drugs could be used for patients who could not be treated with platinum and did not have the T790M mutation after first-line gefitinib treatment.

Second generation EGFR-TKIs

The second-generation inhibitors represented by afatinib are characterized by irreversible binding to the EGFR mutant. In addition to competitively occupying the ATP binding site on EGFR, they can also alkylate or covalently bond with specific amino acid residues near the EGFR binding site, which can dramatically increase the drug concentration, to provide persistent blocking and enhancement of the tumor cell inhibition (21).

Some studies compared the effects of first-generation inhibitors, such as gefitinib and erlotinib, with the second-generation inhibitor, afatinib, as a first-line therapy. In a retrospective study, Fujiwara *et al.* (13) found no significant difference in the failure time (gefitinib: 9.2 months; erlotinib: 9.8 months; and afatinib: 13.1 months) and mPFS (gefitinib: 27.3 months; erlotinib: 29.3 months; and afatinib not reported) for these three drugs. However, in another study, Tu *et al.* (14) found that the mPFS of afatinib was longer than that of gefitinib (12.2 *vs.* 9.8 months, P=0.035), but similar to erlotinib (12.2 *vs.* 11.4 months, P=0.38). Afatinib had a longer mPFS in a subgroup of patients without brain metastasis (afatinib: 13.1 months; gefitinib: 9.8 months; and erlotinib: 11.7 months; P=0.010).

Compared with traditional chemotherapy, the first- and second-generation EGFR-TKIs have significant effects in patients with EGFR gene mutations, thus they are considered as first-line treatment. However, the effects between them still need to be further compared.

Third generation EGFR-TKIs

A meta-analysis showed that the mPFS using gefitinib or erlotinib as first-line treatments was 11 months (22). The main cause of tumor progression (≥50%) occurred when the threonine790 of the EGFR gene was replaced by methionine (T790M) (23). The T790M mutation weakened the binding ability of gefitinib or erlotinib to EGFR-TKI and increased the affinity of EGFR for ATP by altering the EGFR spatial conformation (24).

Osimertinib is a selective, irreversible combination third generation inhibitor. It is sensitive not only to EGFR mutations, but also to T790M mutations (24,25). Previous AURA series studies (26,27) and other trials (28,29) showed

Table 1 Clinical trials in *EGFR*-mutated NSCLC performed or published in 2018

Authors	Trail	Phase	Pathology	Treatment	Line	Patients (N)	ORR (%)	PFS (months)	OS (months)
Markóczy *et al.* (7)	NCT01609543	IV	EGFRm LUAD	Erlotinib	I	62	66.1	12.8	82.5%†
Faehling *et al.* (8)	NCT01194050	III	Stage IIIB or IV NSCLC	Erlotinib	II	272	25.5	4.8	10.4
Yue *et al.* (9)	NCT01683175	II	IIIA EGFRm NSCLC	Erlotinib *vs.* vinorelbine + cis-platin	Adjuvant chemotherapy	51 *vs.* 51	81.4 *vs.* 44.6‡	42.4 *vs.* 21.0§	54.2% *vs.* 19.8%¶
Schuette *et al.* (10)	NCT00997230	–	EGFRm stage III/IV NSCLC	TKI/gefitinib *vs.* no TKIs	I	188/176 100	53.2/53.4 45.0	9.7/9.6 *vs.* 8.7	17.4/17.4 *vs.* 18.1
Yang *et al.* (11)	Not mentioned	–	IIIB/IV EGFRm LUAD	Gefitinib + platinum-based chemotherapy *vs.* platinum-based chemotherapy	I	40 *vs.* 40	P>0.05	P>0.05	18.56 *vs.* 14.87
Uchibori *et al.* (12)	UMIN000010709	II	EGFRm NSCLC	Gefitinib + pemetrexed	II	35	22.9	6.7	24.3
Fujiwara *et al.* (13)	No. 150401-1	III	EGFRm NSCLC	Gefitinib *vs.* erlotinib *vs.* afatinib	I	83 *vs.* 36 *vs.* 28	NA	27.3 *vs.* 29.3 *vs.* NA	9.2 *vs.* 9.8 *vs.* 13.1
Tu *et al.* (14)	Not mentioned	No brain metastasis	EGFRm NSCLC	Gefitinib *vs.* afatinib	I	195 *vs.* 104	NA	9.8 *vs.* 12.2 (P=0.035)	NA
				Afatinib *vs.* erlotinib		104 *vs.* 123		12.2 *vs.* 11.4 (P=0.38)	
		Brain metastasis		Gefitinib *vs.* erlotinib *vs.* afatinib		34 *vs.* 17 *vs.* 22		9.8 *vs.* 11.7 *vs.* 13.1	
Soria *et al.* (15)	NCT02296125	III	EGFRm advanced NSCLC	Osimertinib *vs.* gefitinib or erlotinib	I	279 *vs.* 277	80 *vs.* 76	18.9 *vs.* 10.2	NR, 83% *vs.* 71% (18months)
Kiura *et al.* (16)	NCT01802632	II/III	EGFRm T790M NSCLC	Osimertinib	II	28	75	8.3	NR
Mann *et al.* (17)	NCT01802632, NCT02094261, NCT01544179	III	EGFRm T790M NSCLC	Osimertinib *vs.* platinum-based chemotherapy	II	405 *vs.* 61	64.3 *vs.* 34.3	10.9 *vs.* 5.3	NR *vs.* 14.1
Akamatsu *et al.* (18)	AURA3 (NCT02151981)	III	EGFR T790M advanced NSCLC	Osimertinib *vs.* platinum + pemetrexed	II	41 *vs.* 22	70.7 *vs.* 36.4	12.5 *vs.* 4.3	NR
Murakami *et al.* (19)	NCT02192697	II	EGFRm T790M NSCLC	ASP8273	II	76	42	8.1	NA

†, 1-year survival OS rate; ‡, 2-year disease-free survival; §, median disease-free survival; ¶, 3-year disease-free survival. ORR, overall response rate; OS, overall survival; PFS, progression-free survival; NA, not available; NR, not reached.

that it was an effective first- or second-line treatment for EGFR mutant NSCLC, even when compared with first generation EGFR-TKIs. However, osimertinib had a better ability to penetrate the blood-brain barrier (30). Thus, osimertinib is the first choice for disease progression with the T790M mutation after treatment with EGFR-TKIs.

In a clinical trial (NCT02296125) (15), 279 patients received osimertinib and 277 received the standard EGFR-TKIs (gefitinib or erlotinib). The mPFS in the osimertinib group was prolonged by nearly 8.7 months (18.9 *vs.* 10.7 months, P<0.001), and fewer brain metastases were observed (6% *vs.* 15%). In terms of disease control rate (DCR), both groups reached 90% (97% *vs.* 92%) or more and the ORR of osimertinib was slightly higher, but had no statistical significance (80% *vs.* 76%, P=0.24). Before the end of the trial, OS was not yet determined, but osimertinib treatment was much safer. Therefore, in patients with EGFR mutations, osimertinib can be considered as a first-line therapy.

In the remaining studies on osimertinib as a second-line treatment, Kiura *et al*. (16) found that the ORR of osimertinib was 75%, and the mPFS was 8.3 months. Mann *et al*. (17) compared the effects of osimertinib in the AURA and AURA2 trials and the effects of platinum in the IMPRESS trial. In these trials, patients had the T790M mutation. Osimertinib had a longer PFS (mPFS: 10.9 *vs.* 5.3 months, P<0.0001), better ORR (64.3% *vs.* 34.3%), and better DCR (92.1% *vs.* 75.0%). Although the OS of the osimertinib group has not been reached, it was significantly improved compared to platinum (HR =0.412, P<0.0001). Akamatsu *et al*. (18) studied the efficacy of Japanese patients in the AURA3 trial, where osimertinib also showed better results than platinum (ORR 70.7% *vs.* 36.4%; mPFS 12.5 *vs.* 4.3 months).

Although osimertinib showed good results as a first- or second-line therapy, with the widespread use of osimertinib, the problem of drug resistance has gradually emerged. Studies including FLAURA indicated that the most common resistance mechanisms for osimertinib was MET amplification (15%) and EGFR C797S mutation (7%). Others resistance mechanisms included HER2 amplification (2%), PIK3CA, (7%) and RAS mutations, while no T790M mutations were found (31,32). The new drug, EAI045, has been successful in mice against osimertinib resistance (33).

Whether as first- or second-line treatment, osimertinib has shown good potential. Thus, using osimertinib as first-line treatment or the sequential therapy after the drug resistant of the first-generation TKIs, is the focus of the further studies.

Regarding another T790M mutation inhibitor, ASP8273, in a phase I and II trial (NCT02192697) (19) involving Asian patients the drug provided an ORR of 42% and a PFS of 8.1 months. Although ASP8273 showed some effect, there was still a gap compared with osimertinib.

ALK rearrangement

The *ALK* gene mutation is caused by inversion of the short arm of the second chromosome, making the *EML4* gene and the *ALK* gene form the EML4-ALK fusion gene, which results in a key tumorigenic driver (34). Compared with chemotherapy, ALK inhibitors, including crizotinib can significantly prolong the survival of patients with *ALK* gene mutations (35) (*Table 2*).

First generation ALK rearrangement inhibitors

Crizotinib, the first ALK-TKI approved by the FDA for the treatment of local advanced or metastatic NSCLC with *ALK* gene mutations, is effective not only for ALK mutants, but also for ROS1 and cMET kinases. Since 2011, Crizotinib has always been used as the first line of treatment for *ALK*-mutation NSCLC.

In a retrospective cohort study of US patients with *ALK* mutations, Davies *et al*. (36) reported that the total OS of patients using crizotinib or ceritinib reached 29.4 months, while it reached 27.1 months in patients with central nervous system (CNS) metastasis, and 36.9 months in patients without CNS metastasis. Nishio *et al*. (37) reviewed two Phase III clinical trials: PROFILE 1007 (NCT00932893) and PROFILE 1014 (NCT01154140). They found that compared with chemotherapy, if Asian patients were treated with crizotinib as a first-line treatment, the mPFS nearly doubled (13.6 *vs.* 7.0 months, P<0.001) and the ORR was 70% *vs.* 54%. In non-Asian patients, the mPFS prolongation was not significant when compared with the Asian group (9.6 *vs.* 7.2 months, P<0.001), with an ORR of 78% *vs.* 37%, respectively. As for the second-line treatments, the mPFS was also significantly prolonged in Asian patients (8.1 *vs.* 2.8 months, P<0.001); the effect was equally pronounced in non-Asian patients (7.1 *vs.* 3.2 months, P<0.001). The trial also showed that Crizotinib had a faster onset time, longer duration, and less side effects.

Although the effects of crizotinib are significant, the problem of drug resistance is inevitable. In a retrospective study of 199 patients, the average time to failure with crizotinib as a first-line treatment was 10.4 months and

Table 2 Clinical trials in ALK-rearranged NSCLC performed or published in 2018

Authors	Trail	Phase	Treatment	Line	Patients (N)	ORR (%)	PFS (months)	OS (months)
Davies *et al*. (36)	Retrospective study	–	ALK-targeted treatment	I/II	2011	NA	NA	29.4
Nishio *et al*. (37)	PROFILE 1007/ PROFILE 1014	III	Crizotinib *vs.* chemotherapy	–	–	–	–	–
			Previously treated Asian patients	II	79/78	75/22	8.1/2.8	NA
			Previously treated non-Asian patients	II	94/96	57/18	7.1/3.2	
			Previously untreated Asian patients	I	77/80	70/54	13.6/7.0	
			Previously untreated non-Asian patients	I	95/91	78/37	9.6/7.2	
Reynolds *et al*. (38)	Retrospective study	/	Crizotinib	I	199	NA	10.4	33.8
Metro *et al*. (39)	Not mentioned	III	Ceritinib	II	70	40.6	8.2	15.5
Hida *et al*. (40)	ASCEND-9 (NCT02450903)	II	ceritinib	II	20	25	3.7	75.6%†
Kiura *et al*. (41)	ASCEND-5 (NCT01828112)	III	Ceritinib *vs.* chemotherapy	II	11 vs. 18	54.5 *vs.* 0	9.8 *vs.* 1.6	23.9 *vs.* 22.8 (HR=0.88)
Gadgeel *et al*. (42)	NCT02075840	III	Alectinib *vs.* crizotinib	CNS metastases	64 *vs.* 58	78.6 *vs.* 40.0	NR *vs.* 7.4	NR
				None CNS metastases	93 *vs.* 88	85.7 *vs.* 75.4	NR *vs.* 14.8	NR
Camidge *et al*. (43)	NCT02737501	III	Brigatinib *vs.* crizotinib	I	137 *vs.* 138	71 *vs.* 60	67% *vs.* 43%‡	NR
Horn *et al*. (44)		II	Ensartinib (X-396)	ALK+	NA	60.0	9.2	NA
				ALK-	NA	80.0	26.2	NA
				Prior crizotinib	NA	69.0	9.0	NA
Solomon *et al*. (45)	NCT01970865	III	Lorlatinib	I	30	90.0	NA	NA
				II or more	198	47.0	NA	NA
			Brain metastases		81	63.0	NA	NA

†, 12-month OS rate; ‡, 12-month PFS rate. NA, not available; NR, not reached.

the OS was 33.8 months (38). The main cause of drug resistance was the production of secondary mutations or amplification of *ALK* genes (38). Therefore, after the first generation of ALK inhibitors, second generation inhibitors such as alectinib, ceritinib, and rigatinib began to be used.

Second generation ALK rearrangement inhibitors

Ceritinib, as a new generation ALK rearrangement inhibitor, has shown good results as the first-line treatment compared with chemotherapy in a previous ASCEND-4 study (46) (mPFS: 16.6 *vs.* 8.1 months; ORR: 74% *vs.* 45%). In a study by Metro *et al.* (39) who used ceritinib as a second-line treatment for progression after the use of crizotinib, patients had an ORR of 40.6%, mPFS of 8.2 months, and mOS of 15.5 months. In the phase II ASCEND-9 study (NCT02450903) (40), ceritinib was used

as a second-line treatment for progression after treatment with alectinib. The patient ORR was 20%, mPFS was 3.7 months, and one-year survival was 75.6%. In the phase III ASCEND-5 (NCT01828112) trial (41), 29 Japanese patients had previously undergone crizotinib or platinum treatment, 11 of which subsequently received ceritinib therapy, and 18 received chemotherapy (pemetrexed or docetaxel). Compared with chemotherapy, the ceritinib group had a better ORR (54.5% *vs.* 0%) and mPFS (9.8 *vs.* 1.6 months), but there was no significant difference in the OS (23.9 *vs.* 22.8 months, HR =0.88). Although ceritinib has shown good results in first-line treatment, further researches are still needed as second-line therapy.

Alectinib was originally used in advanced NSCLC patients with *ALK* mutations who had progression after treatment with crizotinib or were resistant to crizotinib. However, in a comparison study in 2017, alectinib showed better results than crizotinib as the first-line treatment (47). In addition, patients with *ALK* mutations were more likely to have CNS metastases (48). Compared to crizotinib, alectinib has a better ability to cross the blood-brain barrier, and thus, alectinib is more effective in patients with CNS metastases (49). The phase III ALEX trial including 303 patients (42). Investigator-assessed PFS with alectinib was consistent between patients with baseline CNS metastases (HR: 0.40, 95% CI: 0.25–0.64) and those without (HR: 0.51, 95% CI: 0.33–0.80) compared with crizotinib, regardless of prior radiotherapy. The results demonstrated superior CNS activity and significantly delayed CNS progression versus crizotinib in patients with previously untreated, advanced ALK+ NSCLC, irrespective of prior CNS disease or radiotherapy (42).

As a result, alectinib can be used as a first-line treatment to achieve better results, rather than waiting until the disease progresses to the CNS before deciding whether to use it.

Brigatinib is a second-generation inhibitor that was approved in 2017 for treatment of crizotinib resistance or progression after crizotinib treatment. In the phase III ALTA-1L trial (43), the effects of brigatinib and crizotinib were compared as first-line treatments in advanced *ALK*-mutation NSCLC patients. The results showed that the mPFS of the brigatinib group was higher; the 12-month survival rate was 67% *vs.* 43% (P<0.001), the ORR was 71% *vs.* 60%, and the OS was premature. A study also found that brigatinib was not only effective against *ALK* mutation NSCLCs, but also effective for EGFR mutation NSCLCs, especially for C797S and T790M mutations produced by EGFR-TKIs (50). Therefor brigatinib not only has the significant effects in progression after crizotinib treatment, but also has the potential to become a targeted drug as a fourth generation EGFR-TKI.

In the phase I/II clinical trial of another new ALK inhibitor, ensartinib (X-396), Horn *et al.* (44) reported that in patients who had not previously received ALK-TKI, the RR was 80% and the mPFS was 26.2 months. Ensartinib also showed effects in patients who had previously received treatment with crizotinib (RR: 69%; mPFS: 9.0 months). However, the effects of ensartinib require phase III trials to confirm the results of the initial trial.

Third generation ALK rearrangement inhibitors

Lorlatinib is a potential third-generation ALK, ROS1 mutation inhibitor that can easily cross the blood-brain barrier. Solomon *et al.* studied the effect of lorlatinib in a clinical trial (NCT01970865) (45). Of the 30 patients who had not previously received treatment, 27 achieved an objective response, and two of three who had brain metastases had an objective response. The ORR was 47.0% in 198 patients who had previously received at least one ALK inhibitor, of which 81 patients with brain metastases had an ORR of 63.0%. In each subgroup, 53 patients who had previously received only crizotinib had an ORR of 69.5%, and in 111 of those who had received more than two ALK-TKIs, the ORR was 38.7%. The trial showed that lorlatinib has great potential in I/II/III treatments or in patients with brain metastases. Lorlatinib was not only effective against ALK mutations, but was also useful for ROS1 mutations. In a trial of Asian patients, 12 patients with ALK or ROS1 mutations who had previously progressed after ALK-TKI treatment had an ORR of 64% and a mPFS of 6.5 months. Of the three patients with intracranial metastases, one patient achieved a complete response and the remaining two had partial responses (51).

Lapatinib has shown good results in patients with brain metastases. However, similar to osimertinib, we still need further researches to prove whether using it as first-line treatment or second-line treatment after disease progression.

Vascular endothelial growth factor receptor (VEGFR) inhibitors

Apatinib is a VEGFR-2 targeting drug that has had great success in the treatment of advanced gastric cancer. In a phase II trial (NCT02515435) (52,53), Wu *et al.* determined the efficacy of apatinib in patients with advanced NSCLC

Table 3 Clinical trials of VEGFR inhibitors in NSCLC performed or published in 2018

Authors	Trail	Phase	Treatment	Line	Patients (N)	ORR (%)	PFS (months)	OS (months)
Wu *et al.* (52)	NCT02515435	II	Apatinib	II/III	40	13.2	3.06	7.69
Han *et al.* (53)	NCT02388919	III	Anlotinib *vs.* placebo	III	296 *vs.* 143	9.2 *vs.* 0.7	5.4 *vs.* 1.4	9.6 *vs.* 6.3

who had received chemotherapy, but failed or could not tolerate it. The results showed that in 40 patients, the ORR and DCR were 13.2% and 63.2%, respectively, the mPFS was 3.06 months, and the mOS was 7.69 months. In another phase III clinical study, ALTER 0303 (NCT02388919), 52 of the multi-target-TKI, anlotinib, showed good effects as a third-line treatment of NSCLC. A total of 296 Chinese patients received anlotinib and 143 patients received an equal dose of placebo. Compared with the placebo group, patients treated with anlotinib had a prolonged mOS of more than 3 months (9.6 *vs.* 6.3 months, P=0.002), the mPFS was also extended for 4 months (5.4 *vs.* 1.4 months, P<0.001), and the ORR was increased (9.2% *vs.* 0.7%) (*Table 3*).

The KRAS gene mutation

Until 2018, almost all clinical studies using first-generation EGFR-TKIs to treat *KRAS* mutations ended in failure (54,55). However, in 2018, an *in vitro* study by Moll *et al.* (56) reported that the second-generation EGFR-TKI, afatinib inhibited the growth of lung adenocarcinoma tissues that expressed the KRAS gene. This may have been related to the ability of afatinib to more broadly inhibit the activity of the ERBB family than the first generation EGFR-TKIs (57). If afatinib still maintains this effect in subsequent clinical studies, it may be effective in the targeted therapy of *KRAS* mutations.

Immunotherapy

PD-1 monoclonal antibodies

Before the advent of immunosuppressants, the treatment of advanced NSCLC lacking targeted genes such as *EGFR* and *ALK* was mainly based on platinum combination chemotherapy (58). With the development of tumor immunology research, ICIs, including PD-1 and PD-L1, have become a popular research topic. In the process of tumor cells escaping from immunity, tumors can inhibit the activation of the PD-1 signal, resulting in reduced T cell activity, so that they can avoid being eliminated by the immune system (59). Investigators therefore developed anti-PD-1 mAb (nivolumab and pembrolizumab) and anti-PD-L1 monoclonal antibodies (mAbs) (atezolizumab and durvalumab) to target the immune escape of tumor cells (*Table 4*).

Nivolumab

In the Phase III CheckMate 227 (NCT02477826) trial (60), Hellmann *et al.* studied the relationship between the effects of combining nivolumab (PD-1 mAb) with ipilimumab (CTLA-4 mAb) and the PD-L1 expression levels in NSCLC patients with high tumor mutation burdens (TMBs). Compared to the use of Nivolumab alone, the safety and effectiveness of the combination was confirmed in previous phase I trials (68). Patients who had not received chemotherapy were divided into two groups according to their level of PD-L1 expression, and the two groups were randomly assigned 1:1:1 to the three subgroups of nivolumab + ipilimumab, nivolumab, and chemotherapy. The results showed that the mPFS was significantly higher in patients receiving nivolumab + ipilimumab than in the chemotherapy group (7.2 *vs.* 5.5 months; P<0.001), and the 1-year progression-free survival was 42.6% *vs.* 13.2%. The ORR of the combination group was 45.3%, while the chemotherapy group was only 26.9%. The validity of these results was confirmed in both subgroups with PD-L1 expression levels above 1% or below 1%. In patients with a low TMB, the combination group did not prolong the mPFS compared with the chemotherapy group.

Data on using nivolumab alone has not been published. However, the study showed that high TMB patients using nivolumab + ipilimumab as a first-line therapy had better results than chemotherapy, regardless of PD-L1 expression levels, and TMB could also be used as a biomarker to assess possible outcomes. This result was also confirmed in another phase II trial, CheckMate 568, in which nivolumab + ipilimumab were used in combination (69). Another retrospective study of nivolumab confirmed that it was equally useful as a second-line treatment (61). A total of 77 patients in that study had an ORR of 19%, a DCR of 60%, and a mPFS and mOS of 4.0 and 8.0 months, respectively.

Table 4 Clinical trials of PD-1/PD-L1 in SCLC and NSCLC performed or published in 2018

Authors	Trail	Phase	Treatment	Line	Patients (N)	ORR (%)	PFS (months)	OS (months)
Hellmann *et al.* (60)	CheckMate 227 (NCT02477826), NSCLC	III	Nivolumab + ipilimumab *vs.* nivolumab *vs.* chemotherapy[†]	I	396 *vs.* 396 *vs.* 397	45.3% *vs.* NA *vs.* 26.9%	7.2 *vs.* NA *vs.* 5.5	NA
			Nivolumab + ipilimumab *vs.* nivolumab + chemotherapy *vs.* chemotherapy[‡]		187 *vs.* 177 *vs.* 186	NA	3.2 *vs.* NA *vs.* 5.5	NA
Shamai and Merimsky (61)	Retrospective analysis		Nivolumab	II	77	19.0%	4.0	8.0
Hellmann *et al.* (62)	CheckMate 032, SCLC	III	Nivolumab + ipilimumab *vs.* nivolumab	Low TMB	27 *vs.* 45	22.2% *vs.* 4.8%	6.2%[§] *vs.* NR	23.4%[¶] *vs.* 22.1%
			Nivolumab + ipilimumab *vs.* nivolumab	Medium TMB	25 *vs.* 44	16.0% *vs.* 6.8%	8.0% *vs.* 3.1%	26.0% *vs.* 19.6%
			Nivolumab + ipilimumab *vs.* nivolumab	High TMB	26 *vs.* 47	46.2% *vs.* 21.3%	30.0% *vs.* 21.2%	62.4% *vs.* 35.2%
Gandhi *et al.* (63)	KEYNOTE-189 (NCT02578680), NSCLC	III	Pembrolizumab + chemotherapy *vs.* placebo + chemotherapy	I	410 *vs.* 206	47.6% *vs.* 18.9%	8.8 *vs.* 4.9	NR *vs.* 11.3
Paz-Ares *et al.* (64)	KEYNOTE-407 (NCT02578680), SCLC	III	Pembrolizumab + chemotherapy *vs.* placebo + chemotherapy	I	278 *vs.* 281	58.4% *vs.* 35.0%	6.4 *vs.* 4.8	15.9 *vs.* 11.3
Socinski *et al.* (65)	IMpower150 (NCT02366143) NSCLC	III	Atezolizumab + carboplatin + paclitaxel *vs.* bevacizumab + carboplatin + paclitaxel *vs.* Atezolizumab + bevacizumab + carboplatin + paclitaxel	I	348 *vs.* 336 *vs.* 356	NA	NA *vs.* 6.8 *vs.* 8.3	NA *vs.* 14.7 *vs.* 19.2
Horn *et al.* (66)	IMpower 133 (NCT02763579), SCLC	III	Atezolizumab + Chemotherapy *vs.* placebo + Chemotherapy	I	201 *vs.* 202	NA	5.2 *vs.* 4.3	12.3 *vs.* 10.3
Antonia *et al.* (67)	PACIFIC trial (NCT02125461)	III	After CRT *vs.* durvalumab *vs.* placebo	II	473 *vs.* 236	30.0% *vs.* 17.8%	17.2 *vs.* 5.6	66.3%[+] *vs.* 55.6%

[†], PD-L1 expression at least 1%; [‡], PD-L1 expression less than 1%; [§], 1-year PFS rate; [¶], 1-year OS rate; [+], 24-month OS rate. NA, not available; NR, not reached; TMB, tumor mutation burden.

For SCLC, the CheckMate 032 trial (62) also demonstrated that nivolumab and ipilimumab were effective in combination and associated with the patient's TMB. In that trial, 156 patients received a combination of nivolumab + ipilimumab and 245 received nivolumab alone. The ORR of the combination group was significantly higher than patients receiving nivolumab alone, and this result was confirmed in three subgroups of TMB that were high (46.2% *vs.* 21.3%), medium (16.0% *vs.* 6.8%), and low (22.2% *vs.* 4.8%). At the same time, whether the high TMB group was treated with monotherapy or combination therapy, the 1-year progression-free survival rate and 1-year survival rate were better than that of the medium or low TMB group. The study also reported that TMB was not directly related to survival in patients who did not receive immunotherapy.

Combined with the CheckMate 227 and CheckMate 032 trials, we found that the combination of nivolumab and ipilimumab achieved good results in both NSCLC and SCLC patients, and at the same time, the higher the TMB, the better the effects of ICIs. We hope that additional studies will confirm the effects of other ICIs in combination to facilitate immunotherapy as a dual ICI modality.

Pembrolizumab

In the previous phase II KEYNOTE-021 trial comparing pembrolizumab with chemotherapy and using chemotherapy alone, it was shown that pembrolizumab had superior efficacy in combination with chemotherapy (70). In the later phase III KEYNOTE-189 trial (63), the effects of pembrolizumab in combination with pemetrexed or platinum and placebo in combination with chemotherapy in patients with advanced, untreated, metastatic, non-squamous NSCLC were compared. When compared with the placebo, pembrolizumab prolonged the mPFS by nearly 4 months (8.8 *vs.* 4.9 months; P<0.001), the 1-year progression-free survival was 34.1% *vs.* 17.3%, the 1-year overall survival rate was 73.0% *vs.* 48.1%, and the ORR was 47.6% *vs.* 18.9%. At the main study end point (PFS, OS), pembrolizumab combined with pemetrexed or platinum reduced the risk of death by more than 50%. It was observed to have a better benefit in all subgroups of trials, including those with a PD-L1 expression ratio <1%.

The KEYNOTE-407 trial (64) focused on the performance of pembrolizumab in combination with chemotherapy in metastatic squamous cell carcinoma. A total of 278 patients received a combination of pembrolizumab, carboplatin and paclitaxel, and 281 patients received an equal amount of placebo, carboplatin and paclitaxel. In a similar manner, the mOS was significantly prolonged in the pembrolizumab group compared with the placebo group (15.9 *vs.* 11.3 months; P<0.001). The ORR of the pembrolizumab group was 57.9%, and the chemotherapy group was 38.4%. The mean remission time was 7.7 *vs.* 4.8 months, and the mPFS also increased (6.4 *vs.* 4.8 months; P<0.001). However, there was no significant difference in 1-year survival rate between the high, medium, and low PD-L1 expression ratio subgroups. Although the adverse effect of the pembrolizumab group was slightly higher than that of the chemotherapy group (69.8% *vs.* 68.2%), the overall risk was still greater than the benefit. Overall, the KEYNOTE-189 and KEYNOTE-407 trials showed that the combination of pembrolizumab and chemotherapy can be considered as first-line treatments in patients with advanced metastatic and non-targeted NSCLC without regard to the expression level of PD-L1.

PD-L1 mAbs

Atezolizumab

In the IMpower150 trial (65), Socinski *et al*. studied the effect of atezolizumab in combination with the VEGF antibody bevacizumab for advanced non-squamous NSCLC patients who had not previously received chemotherapy. A total of 356 patients were treated with atezolizumab + bevacizumab + carboplatin + paclitaxel (ABCP), 336 patients received bevacizumab + carboplatin + paclitaxel (BCP), and another 348 patients received atezolizumab + carboplatin + paclitaxel (ACP). The mPFS was 8.3 months in the ABCP group and 6.8 months in the BCP group (P<0.001). Subgroups with low PD-L1 expression levels or no PD-L1 expression confirmed the above results. However, in the subgroup with high expression of PD-L1, the efficacy of the ABCP was more significant (12.6 *vs.* 6.8 months). In the subgroup with liver metastasis or having *KRAS*, *EGFR*, or *ALK* mutations, the efficacy of ABCP was also better. Patients receiving ABCP had a prolongation of the mOS for nearly 4.5 months (19.2 *vs.* 14.7 months; P=0.02; the ORR was 63.5% *vs.* 48.0%). The data for the ACP group has not been published.

In the IMpower 133 (NCT02763579) trial (66), Horn *et al*. studied the effect of atezolizumab in combination with platinum and etoposide as a first-line treatment for metastatic SCLC. A total of 201 patients received atezolizumab and chemotherapy, and 202 patients were treated with placebo and chemotherapy. The mOS of the atezolizumab group was 12.3 months, the placebo group was 10.3 months, and the risk of death was reduced by 30% (P=0.007). The 1-year survival was 51.7% *vs.* 38.2%. In a similar manner, the mPFSs were 5.2 and 4.3 months (HR: 0.77; 95% CI: 0.62–0.96; P=0.02) in the atezolizumab and placebo groups, respectively. However, the ORR did not show a significant difference between the two groups (2.5% *vs.* 1.0%). Analysis of each subgroup found that atezolizumab showed good efficacy, regardless of the TMB level.

Combined with the IMpower150 and IMpower133 trials, we found that the combination of atezolizumab and chemotherapy achieved good results in both NSCLC and SCLC patients. Thus, pembrolizumab and chemotherapy can be considered as first-line treatments in both NSCLC and SCLC patients.

Durvalumab

In the PACIFIC trial (67) of patients with stage III inoperable NSCLC who had previously received chemoradiotherapy and progressed, 473 patients received durvalumab and 236 patients received a placebo. The 2-year survival of the durvalumab group was 66.3%, and the placebo group was 55.6%. The mOS was significantly

Table 5 Clinical trials of monoclonal antibody in lung cancer performed or published in 2018

Authors	Trail	Phase	Treatment	Line	Patients (N)	ORR (%)	PFS (months)	OS (months)
Ikeda *et al.* (71)	UMIN000004368	III	Bevacizumab + cisplatin + docetaxel	I	47	74.5	9.0	27.5
Kato *et al.* (72)	JapicCTI-111390	II	Erlotinib + bevacizumab *vs.* erlotinib	I	75 *vs.* 77	NA	16.0 *vs.* 9.7	Not mature
Zhao *et al.* (73)	meta-analysis	–	Taxane-platinum *vs.* gemcitabine-platinum *vs.* pemetrexed-platinum *vs.* taxane-platinum + bevacizumab	I	2,000 *vs.* 2,735 *vs.* 1,555 *vs.* 1,471	OR=2.7, 2.5, 1.8	HR=0.54, 0.59, 0.69	HR=0.79, 0.81, 0.92
			Taxane-platinum *vs.* gemcitabine-platinum *vs.* pemetrexed-platinum *vs.* gemcitabine-platinum + bevacizumab		2,000 *vs.* 2,735 *vs.* 1,555 *vs.* 351	Insignificant improvements	Insignificant improvements	Insignificant improvements
			Taxane-platinum *vs.* gemcitabine-platinum *vs.* pemetrexed-platinum *vs.* pemetrexed-platinum + bevacizumab		2,000 *vs.* 2,735 *vs.* 1,555 *vs.* 472	OR=2.8, 2.6, 1.9	HR=0.45, 0.49, 0.58	HR=0.79, 0.81, 0.92
Liang *et al.* (74)	NCT02845856	II	Cetuximab + NK cells therapy *vs.* cetuximab	II/III	27 *vs.* 27	14.8% *vs.* 7.4%	6.0 *vs.* 4.5	9.5 *vs.* 7.5
Ciuleanu *et al.* (75)	NCT00981058 (SQUIRE study)	III	Necitumumab *vs.* gemcitabine-cisplatin	I	261 *vs.* 215	NA	7.4 *vs.* 6.9	16.1 *vs.* 14.9
Kim *et al.* (76)	NCT02079636	I	Abemaciclib + pemetrexed	II or more	23	57%†	5.55	NA
			Abemaciclib + gemcitabine		24	25%†	1.58	
			Abemaciclib + ramucirumab		39	54%†	4.83	
Gerber *et al.* (77)	SUNRISE (NCT01999673)	III	Docetaxel + bavituximab *vs.* docetaxel	II	297 300	14% *vs.* 11% (P=0.18)	No difference (HR =1.00)	10.5 *vs.* 10.9 (HR=1.06)

†, disease control rate. NA, not available; NR, not reached.

prolonged (HR: 0.68, P=0.0025). These conclusions were observed in each subgroup. In terms of the PFS, durvalumab also showed better results, reaching 17.2 months, compared with 5.6 months in the placebo group (HR: 0.51; 95% CI: 0.41–0.63). The ORR of the durvalumab group was 30.0%, and that of the placebo group was 17.8%. The proportion of brain metastases was also lower than that of the placebo group (6.3% *vs.* 11.8%). Although durvalumab showed good results compared to the placebo, the efficacy of durvalumab is yet to be proven compared to chemotherapy or other ICIs.

Other monoclonal antibodies

In addition to PD-1 mAb and PD-L1 mAb, other monoclonal antibodies like bevacizumab have also shown good results in immunotherapy of lung cancer (*Table 5*).

Bevacizumab

Bevacizumab, a monoclonal antibody against VEGFR, has achieved good results in the treatment of various advanced tumors such as colorectal cancer and breast cancer. In the phase II study by Ikeda *et al*. (71), 41 advanced, non-squamous NSCLC patients received three cycles of bevacizumab in combination with docetaxel and carboplatin, followed by consolidation with bevacizumab. In these patients, the ORR, mPFS, and mOS were 74.5%, 9.0 months, and 27.5 months, respectively. Although bevacizumab showed good results in the trial, 95.7% of the patients had neutropenia and 59.6% had leucopenia.

The high incidence of adverse effects makes it necessary to weigh the pros and cons and early intervention when using this drug in clinical use. Kato *et al*. (72) studied the efficacy of bevacizumab combined with erlotinib in patients with EGFR mutations (JapicCTI-111390). Compared to erlotinib alone, the combination prolonged the patient PFS (16.0 *vs*. 9.7 months). A large meta-analysis by Zhao *et al*. (73) studied the effect of bevacizumab combined with chemotherapy as a first-line therapy. Compared with using paclitaxel-platinum, gemcitabine-platinum, and pemetrexed-platinum, bevacizumab in combination with paclitaxel-platinum or pemetrexed-platinum showed a higher ORR and longer PFS and OS. However, when used in combination with gemcitabine-platinum, it did not show any significant differences.

Cetuximab

Liang *et al*. (74) studied the combination of cetuximab and natural killer (NK) cell therapy in the treatment of advanced NSCLC. They found that compared with cetuximab alone, the combination increased the ORR, PFS, and OS (14.8% *vs*. 7.4%; 6.0 *vs*. 4.5 months; 9.5 *vs*. 7.5 months, respectively), showing that the combination can be an option besides chemoradiotherapy.

Necitumumab

Necitumumab is an EGFR monoclonal antibody. The effect of necitumumab on stage IV squamous cell carcinoma was reviewed in the SQUIRE study (NCT00981058) (75). Necitumumab in combination with chemotherapy was more effective in patients with EGFR mutations than chemotherapy alone (mOS: 16.1 *vs*. 14.9 months; HR: 0.76; 95% CI: 0.61–0.96, P<0.05). However, the effect on patients without EGFR gene mutation was not significant.

Other immunotherapies

Abemaciclib, a selective CDK4/6 cell inhibitor, had extensive anti-tumor activity in preclinical trials. It shows better results especially in tumor models with *KRAS* gene mutations (78). In a trial of stage IV NSCLC (NCT02079636) (76), abemaciclib was used in combination with pemetrexed (AP), gemcitabine (AG), and the VEGFR inhibitor, ramucirumab (AR). The DCR reached 57% and 54% in the AP and AR groups, respectively, and only 25% in the AG group. The mPFS of the AP group and the AR group were 5.55 and 4.83 months, respectively, while the AG group was only 1.58 months, which showed that abemaciclib might be better used with pemetrexed or ramucirumab. However, the trial failed to prove the relationship between abemaciclib and *KRAS* gene mutations.

Immunotherapy failure cases

In the CheckMate 026 (NCT02041533) (79) study of nivolumab, compared with chemotherapy, using nivolumab as a first-line treatment in advanced NSCLC patients who had PD-L1 expression levels above 5% did not improve the PFS (4.2 *vs*. 5.9 months; P=0.25), OS (14.4 *vs*. 13.2 months, HR: 1.02; 95% CI: 0.80–1.30) and ORR (26% *vs*. 33%). Not only nivolumab, but also the PD-L1 monoclonal antibody, duravulumab, were ineffective. In the phase III MYSTIC study, compared with chemotherapy, durvalumab combined with or without CTLA-4 mAb, tremelimumab, did not improve the OS or PFS in patients with stage IV NSCLC. For the phosphatidylserine (PS) mAb, bavituximab, in previous preclinical studies, it was found to inhibit tumor growth, prolong survival, and have a synergistic effect with chemotherapy or radiotherapy (80). The previous phase I and II studies also found that it had a tendency to prolong the survival time of patients (77,81). However, in the SUNRISE (NCT01999673) (82) trial, bavituximab combined with docetaxel had no significant advantage compared with docetaxel alone (ORR: 14% *vs*. 11%; P=0.18; PFS HR: 1.00; OS HR: 1.06). The potential advantages shown by bavituximab in preclinical trials therefore still needs further research.

The failure of the above clinical trials shows that immunotherapy as a new approach still needs further development, so we must learn from the failures and further explore the best indications for immunotherapy, with a view to giving cancer patients the maximum benefit.

Hyperprogressive disease

In 2017, Champiat *et al*. (83) found that in patients who received PD-1/PD-L1 inhibitors as immunotherapy for 2 months, approximately 9% (12/131) of the patient tumors paradoxically increased by more than 50% and the rate of progression doubled. This phenomenon is called hyperprogressive disease (HPD). In 2018, Ferrara *et al*. (84) found in a retrospective study that the probability of HPD in advanced NSCLC patients treated with ICIs was significantly higher than with chemotherapy. Of the 406 patients who received PD-1/PD-L1 inhibitor therapy, 56 (13.8%) developed HPD and of the 59 patients receiving

chemotherapy, only three (5.1%) developed HPD. Among patients receiving ICIs, the mOS in patients with HPD was significantly lower than in patients without HPD (3.4 *vs.* 6.2 months; HR: 2.18; P=0.003). The reason for the emergence of HPD is not clear, and may be related to blocking of the PD-1/PD-L1 pathway (85). The high incidence of HPD means that this may be a common pattern of cancer progression, requiring more vigilance in clinical use of ICIs, together with an early assessment of treatment outcomes.

Conclusions

In 2018, clinical trials of lung cancer yielded impressive results. In terms of targeted therapy, first generation inhibitors are still powerful, but new inhibitors are emerging, challenging the status of such first-generation inhibitors. Brigatinib is effective not only for ALK rearrangement tumor treatment, but also for osimertinib resistance. Lorlatinib is also effective for *ALK* or *ROS1* gene mutations and intracranial transfers.

As for immunotherapy, the CheckMate trial, IMpower trial, and KEYNOTE trial have confirmed that ICIs are effective for both NSCLC and SCLC. In particular, the CheckMate trial indicated that the combination of two ICIs was superior to the use of a single ICI or chemotherapy. The above trials also showed that the effect of immunotherapy had little relationship to the level of PD-L1 expression; however, TMB could be used to predict the effect of immunotherapy.

Despite all such positive results, the failure of the CheckMate 026 and MYSTIC trials, and the HDP after immunotherapy has questioned the efficacy of immunotherapy. For patients with mutations, the sequence of targeted therapy and chemotherapy still needs further clinical trials. We expect that with the development of new technologies, more high-level clinical trials will be conducted for lung cancer in the following year, making the treatment of lung cancer more standardized and accurate, and thus, benefiting more patients.

Search strategy and selection criteria

Data for this Review were identified by searches of PubMed, and references from relevant articles using the search terms "lung cancer", "immune checkpoint inhibitors", "PD-1/PD-L1 inhibitors", "chemotherapy", "EGFR mutation", "ALK Rearrangement" and other articles. Abstracts and reports from meetings were included only when they related directly to previously published work. Only articles published in English between 2018.1.1 and 2018.12.31 were included.

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Footnote

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