

**Table 1. Major randomized trials with first-line EGFR inhibitors in metastatic non-small cell lung cancer**

Study	Target	Design	ORR (%)	PFS (months)
<b><i>First-generation TKI vs chemotherapy</i></b>				
NEJ002 [27]	EGFR	Geftinib vs carboplatin plus paclitaxel	73.7 vs 30.7	10.8 vs 5.4
IPASS [28]	EGFR	Geftinib vs Carboplatin plus paclitaxel	72.1 vs 47.3	9.5 vs 6.3
WJTOG- 3405 [29]	EGFR	Geftinib vs cisplatin plus docetaxel	62.1 vs 32.2	9.2 vs 6.3
OPTIMAL [30]	EGFR	Erlotinib vs carboplatin plus gemcitabine	83 vs 36	13.1 vs 4.6
EURTAC-3405 [31]	EGFR	Erlotinib vs platinum doublet	58 vs 15	9.7 vs 5.2
<b><i>Second- versus first-generation TKI</i></b>				
LUX-Lung-7 [33]	EGFR	Afatinib vs gefitinib	72.5 vs 56	11 vs 10.9
ARCHER-1050 [34]	EGFR	Dacomitinib vs gefitinib	75 vs 72	14.7 vs 9.2
<b><i>Third- vs first-generation TKI</i></b>				
FLAURA[39]	EGFR	Osimertinib vs gefitinib or erlotinib	80 vs 76	18.9 vs 10.2

Abbreviations: EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ORR, objective response rate; PFS, progression-free survival

**Table 2. Major randomized trials with first line ALK inhibitors in metastatic non-small cell lung cancer**

Study	Target	Design	ORR(%)	PFS (months)
PROFILE-1014 [51]	ALK	Crizotinib vs cisplatin plus pemetrexed	74 vs 45	10.9 vs 7
ASCEND-4 [57]	ALK	Ceritinib vs platinum plus pemetrexed	72.5 vs 26.7	16.6 vs 8.1
J-ALEX [58]	ALK	Alectinib vs crizotinib	92 vs 79	NR vs 10.2
ALEX [59]	ALK	Alectinib vs crizotinib	82.9 vs 75.5	NR vs 11.2
ALTA-1L [61]	ALK	Brigatinib vs Crizotinib	71 vs 60	67 vs 43

Abbreviations: ALK, anaplastic lymphoma kinase; ORR, objective response rate; PFS, progression-free survival

**Table 3. Summary of major randomized trials evaluating the benefit of immunotherapy with or without chemotherapy in non-small cell lung cancer**

Study name	Testing agent vs comparator	Sample size	PFS (months)	OS (months)
<b><i>First-line treatment</i></b>				
Keynote-024 (PD-L1>50%) [82]	Pembrolizumab vs platinum based chemotherapy	305	10.3 vs 6	Median OS not reached in either group. OS at 6 months: 80.2% vs 72.4%
Keynote-024 Update [83]	Pembrolizumab vs platinum based chemotherapy at 3 years	305		30.0 vs 14.2
Keynote -021 [85]	Pembrolizumab with carboplatin and pemetrexed vs carboplatin and pemetrexed alone	123	24.0 vs 9.3	Not reached vs 21.1
Keynote-189 [86]	Pemetrexed and platinum-based chemotherapy with or without pembrolizumab	616	8.8 vs 4.9	Not reached vs 11.3
Keynote- 407 [87]	Chemotherapy with or without pembrolizumab	559	6.4 vs 4.8	15.9 vs 11.3
IMpower 150 [88]	Bevacizumab plus carboplatin plus paclitaxel (ABCP) or atezolizumab plus carboplatin plus paclitaxel (ACP) versus standard-of-care bevacizumab plus carboplatin plus paclitaxel (BCP)	1202	ABCP vs BCP: 10.2 vs 6.9 ACP vs BCP: 6.9 vs 6.9	ABCP vs BCP: not estimable vs 18.7 with BCP ACP vs BCP: 21.4 vs 18.7
IMpower 130 [89]	Atezolizumab plus chemotherapy plus nab-paclitaxel versus chemotherapy alone	723	18.6 vs 13.9	7.0 vs 5.5
IMpower 132 [90]	Atezolizumab plus pemetrexed-based chemotherapy or pemetrexed-based chemotherapy alone	578	7.6 vs 5.2	OS benefit of 4.5 in atezolizumab group
IMpower131 [91]	Atezolizumab plus chemotherapy versus chemotherapy alone	1021	6.3 vs 5.6	14.2 vs 13.5
Checkmate- 026 [93]	Nivolumab vs platinum-based chemotherapy	423	4.2 vs 5.9	14.4 vs 13.2
Checkmate- 227 [94]	Nivolumab plus ipilimumab vs chemotherapy	1739	10.5% vs. 4.6% at 2 years	17.1 vs 14.9
Checkmate9LA [95]	Nivolumab plus ipilimumab combined with limited course chemotherapy vs chemotherapy	719	6.7 vs 5.0	15.6 vs 10.9

alone				
<i>Second-line treatment</i>				
CheckMate017 [96]	Nivolumab vs docetaxel	272	3.5 vs 2.8	9.2 vs 6.0
CheckMate057 [97]	Nivolumab vs docetaxel	582	Overall: 2.3 vs 4.2 PFS at one year: 19% vs 8%	12.2 vs 9.4
Keynote 010 [98]	Pembrolizumab 2 mg/kg vs pembrolizumab 10 mg/kg vs docetaxel	1034	3.9 vs 4.0 vs 4.0	10.4 vs 12.7 vs 8.5
OAK [99]	Atezolizumab vs docetaxel	1225	Not reported	13.8 vs 9.6
IMpower110 [100]	Atezolizumab vs platinum-based chemotherapy	572	Not reported	Atezolizumab improved OS by 7.1
Abbreviations: ORR, objective response rate; PFS, progression-free survival				

**Table 4. Ongoing clinical trials of immunotherapy in advanced-stage non-small cell lung cancer**

NCT number	Clinical Setting	Intervention	Phase	Outcome Measures
NCT04163432	Metastatic NSCLC	Chemo-Immunotherapy With durvalumab, MEDI4736 pemetrexed & carboplatin	II	Rate of clinical benefit, Incidence of adverse events, ORR, PFS, OS
NCT03976375	Metastatic NSCLC and progressive disease after platinum doublet chemotherapy and immunotherapy (MK-7902-008/E7080-G000-316/LEAP-008)	Pembrolizumab (MK-3475) + lenvatinib (E7080/MK-7902) versus docetaxel	III	ORR, PFS, OS, DOR
NCT03581487	Recurrent or stage IV NSCLC	Selumetinib + durvalumab + tremelimumab	I/II	MTD, ORR, DCR, OS, DOR
NCT03573947	Untreated metastatic NSCLC	Nivolumab + ipilimumab + taxane	II	PFS, Safety and adverse events, ORR
NCT03786692	Stage IV NSCLC patients who have never smoked, irrespective of driver mutation status, and subjects with tumors that possess a driver mutation	Carboplatin + pemetrexed + bevacizumab +/- atezolizumab	II	PFS, Safety, ORR, DOR
NCT03377023	Advanced/metastatic NSCLC with no curative treatment options	Nivolumab + ipilimumab + nintedanib	I/II	MTD, DCR, ORR, PFS, OS,
NCT03178552	Unresectable, advanced or metastatic NSCLC with oncogenic somatic mutations or positive by tumor mutational burden (TMB) assay as identified by two blood-based next-generation sequencing (NGS) circulating tumor DNA (ctDNA) assays.	Multiple targeted therapies (atezolizumab, pemetrexed, cisplatin, carboplatin, gemcitabine, entrectinib, cobimetinib, vemurafenib, alectinib)	II/III	Confirmed Objective Response, DOR, PFS, OS
NCT02477826	Metastatic NSCLC	Nivolumab, or nivolumab + ipilimumab, or nivolumab + platinum-	III	ORR, PFS, OS

		doublet chemotherapy, versus platinum-doublet chemotherapy		
NCT04340882	Metastatic or recurrent NSCLC patients who progressed on platinum-doublet and PD-1/PD-L1 blockade	Docetaxel+ Pembrolizumab+ ramicirumab	II	PFS , Adverse events, ORR, OS
NCT02031458	Programmed death-ligand 1 (PD-L1)-positive locally advanced or metastatic NSCLC	Atezolizumab	II	ORR, DOR, PFS, OS
NCT03600701	Metastatic, recurrent, or refractory NSCLC	Atezolizumab + cobimetinib	II	Durable Response Rate, ORR, DOR, PFS, OS
NCT03965689	NSCLC previously treated with immunotherapy	MLN4924 (Pevonedistat), carboplatin, and paclitaxel	II	ORR, PFS, OS, Incidence of adverse events
NCT01138163	Locally advanced or metastatic non- squamous NSCLC	Bavituximab+ docetaxel	II	ORR
NCT01160601	Previously untreated NSCLC	Paclitaxel/carboplatin with or without bavituximab	II	ORR
NCT04310007	Previously treated non- squamous NSCLC	Cabozantinib+ nivolumab versus standard chemotherapy	II	PFS, OS, toxicity profile, best objective response

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Abbreviations: NSCLC: non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; DOR, duration of response; MTD, maximum tolerated dose; DCR, disease control rate

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