

Continuing Medical Education (CME) articles

Molecularly directed therapy of advanced/metastatic non-small cell lung cancer

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Lung cancer is the leading cause of cancer deaths in the United States and worldwide. Recent advances in molecularly directed therapy have expanded treatment options and improved outcomes for patients with advanced or metastatic disease. Subsequent generation inhibitors have been developed targeting EGFR and ALK alterations to guide current management. Novel treatment strategies have been developed for patients with additional alterations, including EGFR exon 20 insertion, ROS1 fusions, BRAF V600E mutations, KRAS G12C mutations, NTRK fusions, RET rearrangements, and MET exon 14 skipping. The increased rate of development and approval of these targeted agents provides hope for further discovery and refinement in our treatments for patients with metastatic NSCLC. New treatment options and combinations promise to push this field forward in coming years.

ARTICLE HIGHLIGHTS

- Targeted therapies are available for nine classes of mutations in NSCLC
- Herein we discuss the clinical trials laying the foundation for their use in first-line and subsequent settings
- Current and future studies will lead to the discovery of next-line therapies to address resistance mutations and novel targetable genes

INTRODUCTION

Lung cancer accounts for around 150,000 deaths annually and is the leading cause of cancer-related mortality while being the second most common cause of cancer in the United States.¹ Given its status as the leading cause of cancer death, there is an urgent need to identify new treatment options and improve our current therapies for this condition. The management of non-small cell lung cancer (NSCLC) has experienced a revolution thanks to the development of molecularly targeted therapies that have improved response rates and duration of response in many patients. It is estimated that approximately half of the patients with NSCLC harbor activating mutations, including alterations in *EGFR* in 15.6–22%, *KRAS* in 25%, *ALK* in 1.9–8.5%, *ERBB2* in 2.4%, and more, depending on the population studied.^{2–4} These changes provide attractive targets for our growing armamentarium of oncogene targeted therapy. Recent and ongoing studies have shown an amazing ability to improve our outcomes for patients with newer TKIs targeting *EGFR* mutations and *ALK* rearrangements, as well as open new avenues of therapy for patients with other alterations, such as *KRAS G12C* mutations, *MET* exon

14 skipping, and *RET* rearrangements, and more. In this review, we outline the key clinical trials that guide our current molecularly targeted management of NSCLC.

EGFR EXON 19 DELETIONS AND L858R MUTATIONS

There are several options for the treatment of NSCLC with *EGFR* exon 19 deletions or L858R mutations. The preferred agent in this class is osimertinib, which received this status based on results from the FLAURA study.^{5,6} This trial compared osimertinib 80 mg daily with standard *EGFR*-tyrosine kinase inhibitor (TKI) therapy, involving gefitinib at 250 mg daily or erlotinib at 150 mg daily, in the first-line setting. With 556 patients, median overall survival (OS) with osimertinib was 38.6 months (95% Confidence interval (CI), 34.5–41.8) compared to 31.8 months (95% CI 26.6–36.0). This comparison was found to be statistically significant, with a hazard ratio (HR) of 0.046 (95% CI, 0.64–1.00). The rates of grade 3 or higher adverse events were 32% in the osimertinib group and 41% in the *EGFR*-TKI group, as reported by Soria et al. In an update in 2020, Ramalingam et al. reported 42% and 47%, respectively, for grade 3 or higher adverse events. Of note, patients receiving osimertinib had a longer duration of exposure, at 20.7 versus 11.5 months, respectively.

Other potential options for first-line therapy of patients with NSCLC with *EGFR* exon 19 deletions or L858R mutations include erlotinib,^{7–9} afatinib,^{10–14} gefitinib,¹⁵ dacomitinib,^{16,17} erlotinib plus ramcicrumab,¹⁸ and erlotinib plus bevacizumab.¹⁹ Results from trials demonstrating the efficacy of these agents can be found in [Table 1](#). Notably, combination therapy appears to have a median progression-free survival (PFS) more comparable to what is found in

the FLAURA study, with erlotinib 150 mg daily plus ramucirumab showing a 19.4 month (95% CI, 15.4-21.6) median PFS compared to 12.4 months (95% CI, 0.46-0.76) for erlotinib.¹⁸ This was statistically significant, with a HR of 0.59 (95% CI, 0.46-0.76) and $p < 0.0001$. Serious adverse effects were more likely in the combination group, with 29% versus 21% experiencing these, respectively. Median overall survival data for this study has not yet been reported.

EGFR EXON 20 INSERTION

A couple recent studies have led to the accelerated approvals of amivantamab and mobocertinib for the treatment of NSCLC with *EGFR* exon 20 insertion. The phase I CHRYSALIS study treated patients who progressed following platinum chemotherapy with amivantamab 1400 mg weekly for the first four weeks, followed by the same dose every two weeks.²⁰ This study showed an ORR of 40% (95% CI, 29-51) and a median PFS of 8.3 months (95% CI, 6.5-10.9). Median OS was 22.8 months (95% CI, 14.6-NR). Grade 3 or higher adverse events were experienced by 35% of the safety population and 39% of those treated with the recommended phase 2 dose. Infusion-related reactions were common but generally isolated to the first two doses of treatment and can be managed with premedication and lowering of infusion rate.

Zhou et al. recently reported the results of a pooled phase I/II study evaluating the efficacy of mobocertinib 160 mg daily in patients with platinum-pretreated NSCLC and *EGFR* exon 20 insertion.²¹ These patients showed an ORR of 28% (95% CI, 20-37), and a median PFS of 7.3 months (95% CI, 5.5-9.2). The median OS for this group was 24.0 months (95% CI, 14.6-28.8). Grade 3 or higher adverse events were experienced in 69% of patients.

ALK FUSION

Several second- and further-generation TKIs have demonstrated efficacy in NSCLC with *ALK* fusions, leading to no defined preferred agent. The ALEX study evaluating alectinib 600 mg BID in the first-line setting in patients with *ALK* fusions has demonstrated an impressive overall survival on this therapy, with the median not reached, compared to 57.4 months (95% CI, 34.6-NR) with crizotinib 250 mg BID.^{22,23} The HR for this comparison was 0.67 (95% CI, 0.46-0.98). The ORR was 82.9% (95% CI, 76.0-88.5) in patients receiving alectinib compared to 75.5% (95% CI, 67.8-82.1), though this difference was not found to be statistically significant. The median PFS did show a statistically significantly improved median PFS at 34.8 months (95% CI, 17.7-NE) compared to 10.9 months (95% CI, 9.1-12.9). The HR for this comparison was 0.43 (95% CI, 0.32-0.58), with $p < 0.0001$. The frequency of grade 3 or higher adverse events were reported by Peters et al. as 41%

with alectinib and 50% with crizotinib in 2017. In a 2020 update, Mok et al. reported similar rates between the groups, at 52.0% for alectinib and 56.3% for crizotinib.

The ALTA-1L study compared brigatinib 180 mg daily to crizotinib 250 mg BID in first-line treatment with patients with *ALK* fusions.^{24,25} This study demonstrated an ORR of 74% (95% CI, 66-81) for brigatinib compared to 62% (95% CI, 53-70) for crizotinib. This was statistically significant, with a HR of 1.73 (95% CI, 1.04-2.88). Brigatinib had a median PFS of 24.0 months (95% CI, 18.5-NR) compared to 11 months (95% CI, 9.2-12.9) with crizotinib. Median OS has been reported as a HR of 0.92 (95% CI, 0.57-1.47), with a lack of statistical significance, given $p = 0.771$. Patients experienced grade 3 or higher adverse events at a rate of 73% in the brigatinib group and 61% in the crizotinib group.

Provocative findings have been reported from the CROWN study, in particular for patients with CNS metastasis.²⁶ Lorlatinib 100 mg daily was compared to crizotinib 250 mg BID. The ORR with lorlatinib was 76% (95% CI, 68-83) compared to 58% (95% CI, 49-66) for crizotinib. This comparison has an OR of 2.25 (95% CI, 1.35-3.89). The median PFS for lorlatinib was not reached and 9.3 months (95% CI, 7.6-11.1) for crizotinib. This difference was statistically significant, with a HR of 0.28 and $p < 0.001$. Median OS has not yet been reported, but the investigators did report a HR of 0.72 (95% CI, 0.41-1.25) for this metric. Grade 3 or higher adverse effects occurred in 72% of lorlatinib patients and 56% of crizotinib patients. [Table 2](#) serves to summarize these and subsequent studies discussed leading to the approval of targeted agents for molecularly altered NSCLC.

ROS1 FUSION

Results from several phase I and II studies have guided the management of NSCLC with *ROS1* fusion. Dziadziuszko et al. summarized three such studies which explored the response of patients who were *ROS1*-inhibitor naive to entrectinib ≥ 600 mg daily.²⁷ Patients who received this treatment had an ORR of 67.1% (95% CI, 59.3-74.3). Median PFS was 15.7 months (95% CI, 11.0-21.1). Median OS was immature at the time of publication.

The PROFILE 1001 study evaluated the use of crizotinib 250 mg BID in *ROS1*-inhibitor naive patients.^{28,29} The ORR in this population was 72% (95% CI, 58-83). The patients had a 19.3 month (95% CI, 15.2-39.1) median PFS and median OS of 51.4 months (29.3-NR). Grade 3 adverse effects were experienced by 36% of these patients.

Lim et al. evaluated ceritinib 750 mg daily in *ROS1*-inhibitor naive patients with *ROS1*-rearranged NSCLC.³⁰ The ORR in this cohort was 62% (95% CI, 45-77). The median PFS in this group was 9.3 months (95% CI, 0-22). The median OS was 24 months (95% CI, 5-43). Grade 3 or higher adverse events affected 37% of patients in this study.

Table 1. Summary of select clinical trials of targeted agents for EGFR alterations

	Study or studies	Phase	Line	Treatment	# of patients	ORR (95% CI)	PFS (months) (95% CI)	OS (months) (95% CI)
EGFR exon 19 deletion, L858R	FLAURA ^{5,6}	III	First	Osimertinib 80 mg daily vs. standard EGFR-TKI	556	80% (75-85) vs. 76% (70-81), OR 1.27 (0.85-1.90), p=0.24	18.9 (15.2-21.4) vs. 10.2 (9.6-11.1), HR 0.46 (0.37-0.57), p<0.001	38.6 (34.5-41.8) vs. 31.8 (26.6-36.0), HR 0.80 (0.64-1.00), p=0.046
	OPTIMAL ^{7,8}	III	First	Erlotinib 150 mg daily vs. carboplatin AUC 5 D1 and gemcitabine 1000 mg/m ² D1, D8 of 21 day cycle	165	83% vs. 36%, p<0.0001	13.1 (10.58-16.53) vs. 4.6 (4.21-5.42), HR 0.16 (0.10-0.26), p<0.0001	22.8 vs. 27.2, HR 1.19, p=0.2663
	EURTAC ⁹	III	First	Erlotinib 150 mg daily vs. chemotherapy	173	64% vs. 18%	9.7 (8.4-12.3) vs. 5.2 (4.5-5.8), HR 0.37 (0.25-0.54), p<0.0001	19.3 (14.7-26.8) vs. 19.5 (16.1-not assessable), HR 1.04 (0.64-1.68), p=0.87
	LUX-Lung 3 ^{10,12}	III	First	Afatinib 40 mg daily vs. cisplatin plus pemetrexed	345	56% vs. 23%	11.1 vs. 6.9, HR 0.58 (0.43-0.78), p=0.001	28.2 (24.6-33.6) vs. 28.2 (20.7-33.2), HR 0.88 (0.66-1.17), p=0.39
	LUX-Lung 6 ^{11,12}	III	First	Afatinib 40 mg daily vs. cisplatin plus gemcitabine	364	66.9% vs. 23.0%, p<0.001	11.0 (9.7-13.7) vs. 5.6 (5.1-6.7), HR 0.28 (0.20-0.39), p<0.0001	23.1 (20.4-27.3) vs. 23.5 (18.0-25.6), HR 0.93 (0.72-1.22), p=0.61
	LUX-Lung 7 ^{13,14}	II	First	Afatinib 40 mg daily vs. gefitinib 250 mg daily	319	70% vs. 56%, OR 1.873 (1.176-2.985), p=0.0083	11.0 (0.6-12.9) vs. 10.9 (9.1-11.5), HR 0.73 (0.57-0.95), p=0.017	27.9 vs. 24.5, HR 0.86 (0.66-1.12), p=0.2580
	Patil et al. ¹⁵	III	First	Gefitinib 250 mg daily vs. pemetrexed 500 mg/m ² and carboplatin AUC5 followed by pemetrexed maintenance	290	63.5% vs. 45.3%, p=0.003	8.4 (6.3-10.5) vs. 5.6 (4.2-7.0), HR 0.66 (0.513-0.851), p=0.001	18 (15.2-20.8) vs. 22.6 (18.6-26.6), HR 0.78 (0.56-1.09), p=0.133
	ARCHER 1050 ^{16,17}	III	First	Dacomitinib 45 mg daily vs. gefitinib 250 mg daily	452	75% (69-80) vs. 72% (65-77), p=0.4234	14.7 (11.1-16.6) vs. 9.2 (9.1-11.0), HR 0.59 (0.47-0.74), p<0.0001	34.1 (29.5-39.8) vs. 27.0 (24.4-31.6), HR 0.748 (0.591-0.947), p=0.0155
	RELAY ¹⁸	III	First	Erlotinib 150 mg daily plus ramucirumab 10 mg/kg every 2 weeks vs. placebo plus erlotinib 150 mg daily	449	76% (71-82) vs. 75% (69-80), p=0.741	19.4 (15.4-21.6) vs. 12.4 (11.0-13.5), HR 0.59 (0.46-0.76), p<0.0001	
	NEJ026 ¹⁹	III	First	Erlotinib 150 mg daily plus bevacizumab 15 mg/kg every 3 weeks vs. erlotinib 150 mg daily	228	72% (63.1-80.4) vs. 66% (56.5-74.7), p=0.31	16.9 (14.2-21.0) vs. 13.3 (11.1-15.3), HR 0.605 (0.417-0.877), p=0.016	
EGFR exon 20 insertion	CHRYSALIS ²⁰	I	Second	Amivantamab 1400 mg weekly for the first four weeks, then every two weeks	81	40% (29-51)	8.3 (6.5-10.9)	22.8 (14.6-NR)
	PPP plus EXCLAIM ²¹	I/II	Platinum pretreated	Mobocertinib 160 mg daily	114	28% (95% CI, 20-37)	7.3 (5.5-9.2)	24.0 (14.6-28.8)

ORR: Objective response rate CI: Confidence interval PFS: Progression-free survival OS: Overall survival TKI: Tyrosine kinase inhibitor OR: Odds ratio HR: Hazard ratio AUC: Area under the curve NR: Not reached

Table 2. Summary of select clinical trials of targeted agents with approved molecularly targeted indications in NSCLC

	Study or studies	Phase	Line	Treatment	# of patients	ORR (95% CI)	PFS (months) (95% CI)	OS (months) (95% CI)
ALK fusion	ALEX ^{22,23}	III	ALK inhibitor naïve	Alectinib 600 mg BID vs. crizotinib 250 mg BID	303	82.9% (76.0–88.5) vs. 75.5% (67.8–82.1), p=0.09	34.8 (17.7-NE) vs. 10.9 (9.1–12.9), HR 0.43 (0.32–0.58), p < 0.0001	NR vs. 57.4 (34.6-NR), HR 0.67 (0.46–0.98)
	ALTA-1L ^{24,25}	III	ALK inhibitor naïve	Brigatinib 180 mg daily vs. crizotinib 250 mg BID	275	74% (66-81) vs. 62% (53-70), OR 1.73 (1.04-2.88), p=0.0342	24.0 (18.5-NR) vs. 11 (9.2–12.9), HR 0.49 (0.35–0.68), p < 0.0001	HR 0.92 (0.57–1.47), p = 0.771
	CROWN ²⁶	III	First	Lorlatinib 100 mg daily vs. crizotinib 250 mg BID	296	76% (68–83) vs. 58% (49–66), OR 2.25 (1.35-3.89)	NR (NR-NR) vs. 9.3 (7.6–11.1), HR 0.28 (0.19–0.41), p < 0.001	HR 0.72 (0.41–1.25)
ROS1 fusion	ALKA-372-001, STARTRK-1, STARTRK-2 ²⁷	I/II	ROS1 inhibitor naïve	Entrectinib ≥600 mg daily	161	67.1% (59.3-74.3)	15.7 (11.0-21.1)	
	PROFILE 1001 ^{28,29}	I	ROS1 inhibitor naïve	Crizotinib 250 mg BID	53	72% (58-83)	19.3 (15.2-39.1)	51.4 (29.3-NR)
	Lim et al. ³⁰	II	ROS1 inhibitor naïve (except 2)	Ceritinib 750 mg daily	32	62% (45-77)	9.3 (0-22)	24 (5-43)
BRAF V600E	Planchard et al. ³¹	II	First	Dabrafenib 150 mg BID and trametinib 2 mg daily	36	64% (46-79)	14.6 (7.0-22.1)	24.6 (12.3-NE)
KRAS G12C	CodeBreak100 ^{32,33}	II	Patients progressed following immunotherapy and/or platinum-based therapy	Sotorasib 960 mg daily	126	37.1% (28.6-46.2)	6.8 (5.1-8.2)	12.5 (10.0-NE)
NTRK1/2/3 fusion	NAVIGATE and NCT02122913 ^{34,35}	I/II	Heavily pretreated	Larotrectinib 100 mg BID	20	73% (45-92)		40.7 (17.2-NE)
	ALKA-372-001, STARTRK-1, STARTRK-2 ^{34,36}	I/II	TRK-inhibitor naïve	Entrectinib, varying doses	10 with NSCLC	70% (35-93)		21 (14.9-NE) for all 54 patients
RET fusion	LIBRETTO ³⁷	I/II	First and post-platinum treatment	Selpercatinib 160 mg BID	39 treatment naïve and 105 platinum-treated	85% (70-94) in treatment naïve and 64% (54-73) in platinum-treated	16.5 (13.7-NE) in platinum-treated patients	

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	Study or studies	Phase	Line	Treatment	# of patients	ORR (95% CI)	PFS (months) (95% CI)	OS (months) (95% CI)
	ARROW ³⁸	I/II	First and post-platinum treatment	Pralsetinib 400 mg daily	27 treatment naïve and 87 platinum-treated	70% (50-86) in treatment naïve and 61% (50-71) in platinum-treated	9.1 (6.1-13.0) in treatment naïve and 17.1 (12.7-18.4) in platinum-treated	
<i>MET</i> exon 14 skipping	GEOMETRY ³⁹	II	Various	Capmatinib 400 mg BID	28 treatment naïve and 69 who had received one or two lines of prior therapy	68% (48-84) in treatment naïve and 41% (29-53) in patients with one or two prior lines of therapy	12.4 (8.2-NE) in treatment naïve and 5.4 (4.2-7.0) in patients with prior treatment	
	VISION ⁴⁰	II	Previous treatment with up to two courses	Tepotinib 500 mg daily	99	46% (36-57)	8.5 (6.7-11.0)	17.1 (12.0-26.8)

ORR: Objective response rate CI: Confidence interval PFS: Progression-free survival OS: Overall survival OR: Odds ratio HR: Hazard ratio NE: Not estimable NR: Not reached

BRAF V600E MUTATION

A combination of dabrafenib and trametinib has been evaluated for NSCLC with *BRAF* V600E mutation in the first-line setting.³¹ In this phase II study, patients were treated with dabrafenib 150 mg BID and trametinib 2 mg daily. The ORR in this study was 64% (95% CI, 46-79). The patients receiving this combination had a median OS of 24.6 months (95% CI, 12.3-NE) and median PFS of 14.6 months (7.0-22.1). Grade 3 or higher adverse effects were experienced in 69% of patients.

KRAS G12C MUTATION

Sotorasib has recently gained accelerated approval for the treatment of *KRAS* G12C-mutated NSCLC in the post-chemotherapy, and optimally post chemoimmunotherapy, setting. The CodeBreaK100 study provided the data to support its use in this indication.^{32,33} In this study, patients received sotorasib 960 mg daily in patients who had progressed on immunotherapy and/or platinum-based chemotherapy. The ORR was 37.1% (95% CI, 28.6-46.2). Patients showed a median PFS of 6.8 months (95% CI, 5.1-8.2). The median OS was 12.5 months (95% CI, 10.0-NE). Grade 3 treatment-related adverse events affected 19.8% of patients, and one had a grade 4 adverse event. Of note, the use of proton pump inhibitors with sotorasib may substantially reduce drug levels and should be avoided.

NTRK 1/2/3 FUSION

Larotrectinib and entrectinib are options for therapy in NSCLC patients with *NTRK* 1/2/3 fusions. Lin et al. pooled results from the NAVIGATE and NCT02122913 studies and showed that 20 patients with NSCLC and *NTRK* fusions treated with Larotrectinib 100 mg BID had an ORR of 73% (95% CI, 45-92).^{34,35} These patients had a median OS of 40.7 months (95% CI, 17.2-NE). Two patients (10%) experienced treatment-related grade 3 adverse events.

Doebele et al. evaluated the use of entrectinib in patients with advanced or metastatic *NTRK* fusions in a combination of phase I and II trials.³⁶ Of the 54 patients, 10 had *NTRK* fusion NSCLC. These patients showed an ORR of 70% (95% CI, 35-93). Median OS for the entire cohort, not just the NSCLC patients, was 21 months (95% CI, 14.9-NE). Serious treatment-related adverse events affected 10% of the *NTRK* fusion-positive patients and 9% of the overall safety population.

RET FUSION

Selpercatinib and pralsetinib have recently gained accelerated approval for the management of *RET* fusion NSCLC. Selpercatinib was evaluated in patients with prior platinum-based chemotherapy or without prior treatment in the LIBRETTO phase I/II study.³⁷ The phase II dose was selpercatinib 160 mg BID. The patients with prior platinum-based chemotherapy had an ORR of 64% (95% CI, 54-73). This cohort had a median PFS of 16.5 months (95% CI,

13.7-NE). In the treatment naïve cohort, the ORR was 85% (95% CI, 70-94). Median OS was not reached in this group, and neither group reached median OS. Grade 3 or higher treatment-related adverse events were experienced by 28% of patients.

The use of pralsetinib in patients with *RET* rearrangements was tested in the ARROW study.³⁸ Similar to LIBRETTO, this study was a phase I/II evaluation of patients treated with pralsetinib, with the phase II dose of 400 mg daily. Patients were separated into prior platinum-based chemotherapy and treatment naïve groups. The ORR for these groups were 61% (95% CI, 50-71) and 70% (50-86), respectively. Median PFS was 17.1 months (95% CI, 12.7-18.4) for the platinum-treated group and 9.1 months (95% CI, 6.1-13.0) in the treatment naïve group. Grade 3 or worse treatment-related adverse events affected 48% of patients in the NSCLC safety population.

MET EXON 14 SKIPPING MUTATION

Capmatinib and tepotinib have been approved by the FDA for the treatment of advanced NSCLC with *MET* exon 14 skipping mutations. The GEOMETRY trial provided support for capmatinib's approval for this indication.³⁹ In this phase II study, patients with this mutation were binned into cohorts based on prior treatment regimens and received capmatinib at a dose of 400 mg BID. The ORR for treatment naïve patients receiving this therapy was 68% (95% CI, 48-84). The ORR for patients with one or two prior lines of therapy was 41% (95% CI, 29-53). Median PFS for these groups were 12.4 months (95% CI, 8.2-NE) and 5.4 months (95% CI, 4.2-7.0), respectively. Grade 3 or higher adverse effects were experienced by 67% of patients.

Tepotinib was studied for NSCLC with *MET* exon 14 skipping mutations in the phase II VISION study.⁴⁰ Enrolled patients were allowed to have up to two prior lines of therapy. The ORR for the treated population was 46% (95% CI, 36-57). The median PFS was 8.5 months (95% CI, 6.7-11.0). The median overall survival data was not mature, but it was reported as 17.1 months (95% CI, 12.0-26.8). Topotinib-related grade 3 or higher adverse events occurred at a frequency of 28%.

CONCLUSION

The impressive studies above have provided exciting improvements for the management of patients with molecularly-altered NSCLC. Importantly, they have provided hope for our patients with new and effective first- and subsequent-line options for their cancer. Notably, the pace of approvals of these agents seems to be quickening, with several gaining accelerated approval over the past couple of years. Future studies will attempt to refine and expand on these options to continue pushing to improve outcomes for patients with NSCLC.

FUTURE DIRECTIONS

The continued success and growth of molecularly directed therapy will rely on refining treatments for current targets,

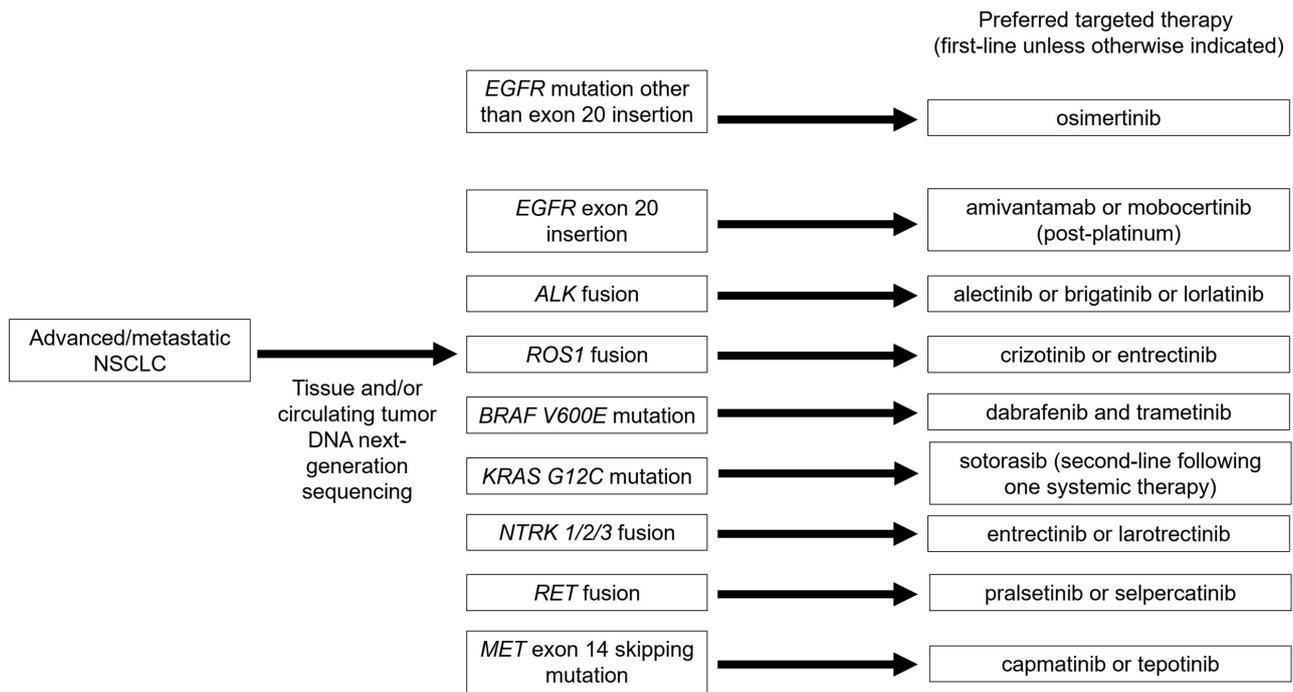


Figure 1. Preferred molecularly targeted agents are shown for each actionable mutation in NSCLC

developing effective treatments for known targets without currently approved treatments, and identifying new molecular targets for patients with advanced or metastatic NSCLC.

Agents targeting HER2 are likely to be added as the next wave of targeted therapies available to clinicians to treat their advanced NSCLC patients. Trastuzumab Deruxtecan has been granted breakthrough FDA designation based on results from the currently active DESTINY-Lung01 trial.⁴¹ This trial showed a 55% ORR (95% CI, 44-65), median PFS of 8.2 months (95% CI, 6.0-11.9), and median OS of 17.8 months (95% CI, 13.8-22.1) in patients refractory to stan-

dard treatment. Similarly, poziotinib has been granted FDA fast track designation for patients harboring HER2 exon 20 mutations based on findings from a phase II trial demonstrating an ORR of 58% (95% CI, 40.9-73.0).⁴²

The promising progress of recent years of molecularly targeted therapy in the NSCLC field will hopefully serve as a harbinger for continued discovery that will improve quality and duration of life for our patients.

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