

Clinical Research Spotlight for *EGFR*-Mutated NSCLC



Combination Therapies in *EGFR*-Mutated NSCLC

- Combining *EGFR* tyrosine kinase inhibitors (TKIs) with other agents in the first-line setting may delay development of *EGFR* TKI resistance and ensuing progression¹
- Combination therapies represent an area of active clinical research (**Tables 1 and 2**)
 - EGFR* inhibition plus cytotoxic chemotherapy
 - Preclinical data suggest this combination acts synergistically to induce apoptosis and delay development of *EGFR* TKI resistance by suppressing Akt and extracellular signal-regulated kinase phosphorylation²
 - EGFR* inhibition plus MET inhibition
 - Because *EGFR* TKI resistance can develop via MET amplification, blocking both *EGFR* and MET signaling pathways may overcome resistance to osimertinib³
 - EGFR* inhibition plus VEGF(R) inhibition
 - Increased *EGFR* signaling in *EGFR*-mutated disease upregulates VEGF, a key mediator of angiogenesis that supports tumorigenesis and contributes toward the development of *EGFR* TKI resistance, suggesting that combining *EGFR* TKIs with antiangiogenic agents in the first-line setting may delay or prevent the development of *EGFR* TKI resistance⁴

Table 1. Select Ongoing Trials Evaluating Combination Therapies in the First-line Setting for *EGFR*-Mutated Advanced NSCLC (May 2022)

Trial	Phase	Study Population	Treatment Arm(s)	Primary Endpoint(s)	Country/ Countries
WJOG9717L (UMIN000030206)	II	Advanced, nonsquamous, <i>EGFR</i> -mutated NSCLC; no symptomatic brain metastases	Osimertinib ± bevacizumab	PFS	Japan
NCT02971501	II	<i>EGFR</i> -mutated NSCLC; ≥1 measurable, asymptomatic, untreated CNS lesion	Osimertinib ± bevacizumab	PFS	United States
SPIRAL II (UMIN000028071)	II	Advanced <i>EGFR</i> -mutated NSCLC	Osimertinib + bevacizumab	1-yr PFS rate	Japan
JapicCTI-184146	II	Advanced, nonsquamous, <i>EGFR</i> -mutated NSCLC; no symptomatic brain metastases	Osimertinib ± ramucirumab	PFS	Japan
RAMOSE/HCRN LUN18-355 (NCT03909334)	II	Locally advanced or metastatic NSCLC with <i>EGFR</i> L858R or exon 19 deletion; asymptomatic, treated, or neurologically stable brain metastases permitted	Osimertinib ± ramucirumab	PFS	United States
NORTHSTAR (NCT03410043)	II	Advanced NSCLC with <i>EGFR</i> L858R or exon 19 deletion; no unstable, symptomatic CNS metastases*	Osimertinib + surgery and/or radiation therapy	PFS	United States
EA5182 (NCT04181060)	III	Advanced, nonsquamous, <i>EGFR</i> -mutant NSCLC; treated, stable brain metastases permitted; untreated, stable brain metastases or leptomeningeal disease permitted if immediate therapy not required	Osimertinib ± bevacizumab	PFS	United States
FLAURA2 (NCT04035486)	III	Advanced, nonsquamous NSCLC with <i>EGFR</i> L858R or exon 19 deletion; T790M permitted; asymptomatic brain metastases permitted	Osimertinib ± chemotherapy	PFS	Argentina, Australia, Brazil, Canada, Chile, China, Czechia, France, India, Japan, Korea, Peru, The Philippines, Russia, Slovakia, South Africa, Taiwan, Thailand, United Kingdom, United States, Vietnam
RELAY (NCT02411448)	III	Metastatic NSCLC with <i>EGFR</i> L858R or exon 19 deletion; no brain metastases or leptomeningeal carcinomatosis	Erlotinib ± ramucirumab	PFS, safety	Canada, France, Germany, Greece, Hong Kong, Italy, Japan, Korea, Romania, Spain, Taiwan, Turkey, United Kingdom, United States
BEVERLY (NCT02633189)	III	Advanced, nonsquamous, <i>EGFR</i> -mutated NSCLC; no brain metastases	Erlotinib ± bevacizumab	PFS	Italy
MARIPOSA (NCT04487080)	III	Advanced NSCLC with <i>EGFR</i> L858R or exon 19 deletion; no symptomatic brain metastases or leptomeningeal disease	Lazertinib + amivantamab vs osimertinib	PFS	Argentina, Australia, Belgium, Brazil, Canada, China, France, Germany, Hungary, India, Israel, Italy, Japan, Korea, Malaysia, Mexico, The Netherlands, Poland, Portugal, Russia, Spain, Taiwan, Thailand, Turkey, Ukraine, United Kingdom, United States
PAPILLON (NCT04538664)	III	Advanced, nonsquamous NSCLC with <i>EGFR</i> exon 20 insertion mutations; no untreated brain metastases	Carboplatin/pemetrexed ± amivantamab	PFS	Australia, Belgium, Brazil, Canada, China, France, Germany, Hungary, India, Israel, Italy, Japan, Korea, Malaysia, Mexico, Poland, Portugal, Russia, Spain, Taiwan, Thailand, Turkey, Ukraine, United Kingdom, United States

CNS, central nervous system; NSCLC, non-small-cell lung cancer; PFS, progression-free survival.

*Also enrolling patients in later-line settings if not previously treated with third-generation *EGFR* TKI.

Table 2. Select Ongoing Trials Evaluating Combination Therapies in the Later-Line Setting for *EGFR*-Mutated Advanced NSCLC (May 2022)

Trial	Phase	Study Population	Treatment Arm(s)	Primary Endpoint(s)	Country/Countries
NCT02789345	I	Advanced, T790M-positive, <i>EGFR</i> -mutated NSCLC; no prior third-generation <i>EGFR</i> TKI or <i>EGFR</i> -directed monoclonal antibody; no symptomatic or growing brain metastases	Osimertinib + ramucirumab or necitumumab	DLT	France, Korea, Spain, Taiwan, United States
OWBLM (NCT04425681)	II	<i>EGFR</i> -mutated NSCLC with leptomeningeal metastasis	Osimertinib + bevacizumab	LM PFS, ORR	China
BOOSER (NCT03133546)	II	Advanced T790M-positive NSCLC with <i>EGFR</i> L858R or exon 19 deletion after progression following prior <i>EGFR</i> TKI as most recent treatment; no symptomatic or active CNS metastases	Osimertinib ± bevacizumab	PFS	Ireland, Korea, The Netherlands, Singapore, Spain, Switzerland
MARIPOSA-2 (NCT04988295)	III	Locally advanced or metastatic NSCLC with <i>EGFR</i> L858R or exon 19 deletion after osimertinib failure; no symptomatic brain metastases or leptomeningeal disease	Lazertinib + amivantamab ± platinum-based chemotherapy	PFS	Argentina, Belgium, Brazil, Bulgaria, Canada, China, Czechia, Denmark, France, Germany, Hong Kong, India, Israel, Italy, Japan, Korea, Malaysia, Mexico, The Netherlands, Poland, Portugal, Puerto Rico, Russia, Spain, Sweden, Taiwan, Turkey, United Kingdom, United States

DLT, dose-limiting toxicity; LM, leptomeningeal metastases; ORR, overall response rate.

Ongoing Unmet Clinical Needs

- Unmet need for treatments active against CNS disease in patients with *EGFR*-mutated NSCLC
 - o CNS disease—particularly leptomeningeal metastases—imparts a poor prognosis^{5,6}
 - o Approximately 20% of patients have CNS disease at diagnosis
 - With longer survival on current treatments, incidence increases to 40% to 50% over treatment course^{5,7}
 - o Phase III data from the FLAURA trial showed that first-line osimertinib more effective than older-generation *EGFR* TKIs at controlling CNS disease in *EGFR*-mutated NSCLC^{8,9}
 - Osimertinib improved CNS ORR and prolonged both PFS and CNS PFS vs a standard *EGFR* TKI in patients with CNS metastases
- Unmet need for treating and/or delaying the development of *EGFR* TKI resistance^{10,11}
 - o Resistance to *EGFR* TKIs occurs in both first-line and later-line settings
 - Limits treatment options and is associated with worse patient outcomes
 - o *EGFR* TKI resistance mediated via multiple mechanisms such as on-target *EGFR* mutations, off-target alterations, and transformation
 - On-target, *EGFR*-mediated resistance involves alterations to *EGFR* TKI binding sites (eg, T790M for first-generation and second-generation *EGFR* TKIs, C797S for osimertinib)
 - Off-target alterations include activation of bypass pathways and/or aberrant downstream signaling (eg, *MET* amplification, RAS-MAPK or PI3K pathway activation)
 - Histologic transformation to small-cell or squamous cell lung cancer imparts resistance to *EGFR* TKIs, including osimertinib

References

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