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Drug-resistant EGFR mutations in lung cancer

Since the clinical introduction of imatinib as a cancer therapeutic in 2001, the development of kinase inhibitors has focused on identification of first-in-class drugs for specific targets. Additionally, the search for next generation drugs targeting drug resistant kinase mutants has greatly expanded, initiating a focus on personalized medicine, particularly in oncology. Lung cancer is the most commonly diagnosed cancer worldwide and was the leading cause of cancer death in 2018[1]. EGFR active mutants have been identified in lung cancer, most notably in lung adenocarcinoma, which accounts for the majority of non-small cell lung cancer (NSCLC) cases. Furthermore, drug-resistant mutations of EGFR have frequently been observed in patients treated with EGFR inhibitors. Therefore, novel next generation inhibitors for EGFR mutations are eagerly awaited.

EGFR is a receptor tyrosine kinase. Specific ligands bind to the extracellular domain of EGFR, which leads to the formation of dimers. Dimerization stimulates intrinsic tyrosine kinase activity of the receptors and triggers autophosphorylation of specific tyrosine residues. Signal transducers initiate multiple downstream pathways such as MAPK, PI3K-AKT and STAT 3 and 5, which regulate proliferation and apoptosis[2].

Approximately 80% of EGFR mutations in EGFR mutation-positive lung cancer are either short in-frame deletions of approximately 5 amino acids in exon19 (del19) or a single missense mutation in exon 21 (L858R)[2], which cause ligand-independent EGFR activation. AstraZeneca reported that the EGFR mutation frequency range in patients with NSCLC of adenocarcinoma histology is 20-76% in the Asia-Pacific, 6-41% in Europe and 3-42% in North America[3].

With first, second or third generation EGFR inhibitor treatment, the objective clinical response rate is approximately 60-85% for lung cancer patients whose tumors harbor del19 or L858R EGFR mutations[4]. However, while tumor responses are accompanied by marked tumor shrinkage in patients, the response is typically not long lasting. The most prominent molecular resistance mechanism associated with disease progression in 50-70% of patients treated with first and second generation EGFR inhibitors is the acquisition of a secondary mutation in EGFR, namely the gatekeeper mutation T790M (Fig.1). This mutation is located in the ATP binding pocket, and it is believed that the mutation attenuates the binding affinity of EGFR inhibitors[5].

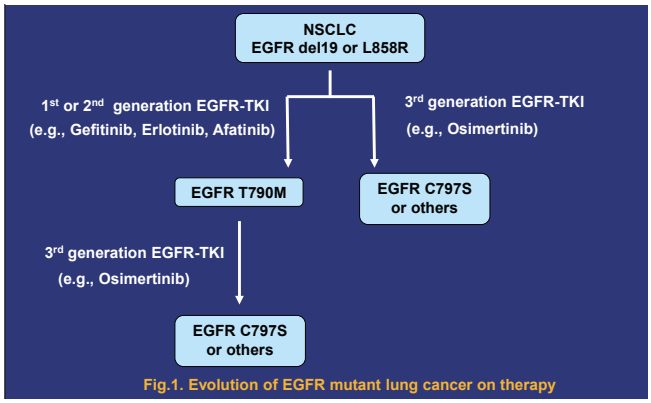

Fig.1. Evolution of EGFR mutant lung cancer on therapy

Osimertinib is a third generation EGFR inhibitor developed as a drug to effectively inhibit the primary EGFR mutations del19 and L858R, independent of the presence or absence of the secondary T790M resistance mutation. While osimertinib demonstrates clear clinical efficacy when used in second line treatment of T790M/(del19 or L858R)-positive NSCLC patients, disease progression still occurs after an average duration of 10 months. Recent data suggest that 20-40% of second line patients relapsing on osimertinib acquire a tertiary EGFR mutation at a cysteine residue (C797S) that is required for covalent inhibitor binding (Fig.1). EGFR (del19 or L858R)/T790M/C797S can no longer be inhibited by any of the approved first, second, or third generation EGFR inhibitors. Therefore, research and development of fourth generation EGFR inhibitors able to inhibit the EGFR (del19 or L858R)/T790M/C797S mutant is now advancing[4].

BLU-945, developed by Blueprint Medicines Corporation, is a fourth generation EGFR inhibitor capable of inhibiting EGFR (del19 or L858R)/T790M/C797S. The company has announced its plan to initiate an international phase 1 dose-escalation trial of BLU-945 in patients with treatment-resistant EGFR-mutated NSCLC in the first half of 2021[6]. Chugai Pharmaceutical (Roche group) is also among companies developing a similarly focused drug candidate with their inhibitor, CH7233163, which is in preclinical development[7].

Additionally, patients with EGFR Exon20 insertion mutations, which globally account for about 2% of all NSCLC cases, have no approved targeted therapy options.

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Production of promising new drug candidates targeting this mutation is also underway. Takeda Pharmaceutical has developed TAK-788 (mobocertinib), a small-molecule tyrosine kinase inhibitor targeting EGFR Exon20 insertion mutations. This compound is currently advancing to phase 3 trials, as noted by Takeda's CEO at the recent 39th annual J.P. Morgan HEALTH CARE CONFERENCE[8].

Carna Biosciences' commitment to expand its portfolio of products and services for the development of EGFR inhibitors targeting clinically relevant kinase mutations has given rise to the expansive portfolio of reagents shown below (Table 1). Our products can be utilized not only in biochemical activity assays, but also for biacore based SPR data acquisition, binding assays using TR-FRET or AlphaScreen/AlphaLISA, and other applications.

If you are interested in any EGFR mutant that is not included in the table below, please feel welcome to contact us.

Kinase targets other than EGFR have reportedly been associated with drug resistance to osimertinib, namely amplification of MET, HER2 and PIK3CA, acquisition of BRAF[V600E] and PIK3CA[E545K] mutations, and oncogenic fusion mutations of FGFR3, RET and NTRK,etc.[9][10]. Thus, inhibitors for these related kinases may serve as viable therapeutic options for osimertinib resistant cancers. Carna Biosciences also offers an extensive array of products and services for these and many other kinases to assist you with your kinase inhibitor drug discovery, as listed below:

- Kinase Proteins
- Biotinylated Kinases
- Profiling Services
- NanoBRET™ TE Intracellular Kinase Cell-Based Assay Services

Please contact us today with any questions or if you'd like additional details.

References：

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5) N Engl J Med. 2005; 352(8): 786-92. Kobayashi S.
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8) Takeda's website, IR Events FY2020, 39th J.P.Morgan Healthcare Conference Presentation.
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Table 1. EGFR product list

Product Name	Catalog No.	Catalog No.
	GST-tagged	Biotinylated (BTN-)
EGFR	08-115	08-415-20N
EGFR [L858R]	08-502	08-402-20N
EGFR [d746-750]	08-527	08-427-20N
EGFR [T790M]	08-194	08-494-20N
EGFR [L792H]	Not available	Under development
EGFR [C797S]	Under development	Under development
EGFR [L861Q]	08-513	Not available
EGFR [T790M / L858R]	08-510	08-410-20N
EGFR [C797S / L858R]	08-563	08-763-20N
EGFR [d746-750 / T790M]	08-528	Under development
EGFR [d746-750 / C797S]	08-564	08-764-20N
EGFR [T790M / C797S / L858R]	08-559	Under development
EGFR [d746-750 / T790M / C797S]	08-565	Under development
EGFR [D770_N771insNPG]	08-553	Under development
EGFR [D770_N771insNPG / T790M]	Under development	Under development
EGFR [D770_N771insSVD]	Not available	Under development
EGFR [V769_D770insASV]	Not available	Under development

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