Editorial

Kinase inhibitor-responsive genotypes in *EGFR* mutated lung adenocarcinomas: moving past common point mutations or indels into uncommon kinase domain duplications and rearrangements

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Abstract: The most frequent *epidermal growth factor receptor* (*EGFR*) mutations found by traditional or comprehensive molecular profiling of lung adenocarcinomas include indels of exon 19 (the exon 19 deletion delE746_A750 being the most common) and the exon 21 L858R point mutation. The current approval labels for first line palliative gefitinib 250 mg/day, erlotinib 150 mg/day and afatinib 40 mg/day for advanced lung cancers require the presence of the aforementioned classical/sensitizing *EGFR* mutations. Other gefitinib, erlotinib and afatinib sensitizing mutations include exon 18 indels, G719X, exon 19 insertions, A763_Y764insFQEA, S768I and L861Q; for which off-label EGFR kinase inhibitor use is generally agreed upon by thoracic oncologists. The main biological mechanism of resistance to approved first line EGFR inhibitors is the selection/acquisition of *EGFR*-T790M that in itself can be inhibited by osimertinib 80 mg/day, a 3rd generation EGFR inhibitor that is bypassed by *EGFR*-C797X mutations. Another class of *de novo* inhibitor insensitive mutation includes *EGFR* exon 20 insertions. More recently, the dichotomy of only point mutations or indels explaining aberrant kinase activation of EGFR plus inhibitor response has been shattered by the discovery of uncommon (<0.5% of all *EGFR* mutations) genomic events involving exon 18–25 kinase domain duplications (KDD) and rearrangements (*EGFR-RAD51* or *EGFR-PURB*). The latter lead to oncogene addiction, enhanced sensitivity to kinase inhibitors *in vitro* and clinical responses to approved EGFR inhibitors. The enhanced landscape of EGFR inhibitor-responsive genotypes highlights that comprehensive molecular profiling may be necessary to maximize the identification of all cases that can benefit from precision oncology.

Keywords: Epidermal growth factor receptor (EGFR); exon 18–25 duplication; rearrangement; exon 19; L858R; L861Q; G719X; exon 18; exon 20; T790M; C797S

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Epidermal growth factor receptor (*EGFR*) mutations were first identified as driver oncogenes in non-small-cell lung cancers (NSCLCs) in 2004 by three separate independent groups (1-3), and originally thought to consistent of only in-frame deletions, insertions (i.e., indels) or point mutations within exons 18 to 21 of the kinase domain of *EGFR* (4). The most abundant *EGFR* mutations are deletions/indels (around amino-acid residues 747 to 752) of exon 19 (these account for ~45% of all *EGFR* mutations, with the most common delE746_A750) and the exon 21 point mutation L858R mutation (~35% of all *EGFR* mutations). Inhibition of mutant EGFR in preclinical models through tyrosine kinase inhibitors (TKIs) unsettles the intracellular signaling cascade, generating cell cycle arrest and apoptosis (5). In the clinic, the 1st generation EGFR TKIs gefitinib and erlotinib, both reversible ATP mimetics with a favorable therapeutic window in relation to the wild-type (WT) EGFR (4,6), induce overall response rate (ORR),

progression-free survival (PFS) and quality of life (QoL) improvements that exceed platinum-doublet cytotoxic chemotherapies in advanced *EGFR* mutated NSCLCs (7,8). The 2nd generation irreversible EGFR TKI afatinib, with a narrower therapeutic window due to its exceedingly potent inhibition of WT EGFR, also improves ORR, PFS and QoL when compared to cytotoxic agents (9). Exceedingly high ORRs of >70% have been observed for *EGFR*-exon 19 deletion mutated NSCLCs treated with gefitinib 250 mg/day, erlotinib 150 mg/day or afatinib 40 mg/day (7-9). The ORR of *EGFR*-L858R mutated tumors seems to be slightly lower than 70% with afatinib 40 mg/day, while only at around 50–60% with gefitinib 250 mg/day and intermediate with erlotinib 150 mg/day (7-9). Indeed, a head-to-head phase II trial (LUX-Lung7) of afatinib 40 mg/day versus gefitinib 250 mg/day showed that the ORRs were 66% *vs*. 42% and median PFSs of 10.9 *vs*. 10.8 months (HR 0.71), respectively, for the 133 *EGFR*-L858R mutated NSCLCs (10). The ORRs were 73% *vs*. 66% and median PFSs of 12.7 *vs*. 11.0 months (HR 0.71), respectively, for the 186 *EGFR*-exon 19 deletion mutated NSCLCs (10). The improved predictive and prognostic impact of tumor *EGFR*-exon 19 deletions versus *EGFR*-L858R in TKI-treated patients are well known since 2006 (11,12) and confirmed in all randomized clinical trials of EGFR TKI versus chemotherapy (13). All three—gefitinib, erlotinib and afatinib—Food and Drug Administration (FDA) approved EGFR TKIs continue to be prescribed worldwide without a clear "go-to" drug in view of their different biological doses, toxicities (afatinib with higher rates of mucositis and diarrhea, erlotinib of rash, and gefitinib of liver dysfunction) and provider-patient preferences. As afatinib is the more toxic of the approved first line EGFR TKIs, one must take into consideration its reported higher ORR and PFS rates together with the increased rates of adverse events plus dose reductions required with this agent (9,10).

The third most common type of *EGFR* mutations (>7% of all *EGFR* mutations) consist of in-frame insertions and indels following/encompassing the regulatory C-helix amino-acids of exon 20 (14,15). In preclinical models, these mutations lead to auto-phosphorylation of EGFR and engagement of the mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-kinases (PI3K) cascades; concurrent with oncogene addiction (15). However, these mutant EGFRs at the structural and biological level do not have a favorable therapeutic window in relation to WT EGFR. The later realization explains why gefitinib (16), erlotinib (15) and afatinib (17) have limited activity (near 0% ORRs and short PFSs) in *EGFR* exon 20 insertion mutated NSCLCs (14). Grippingly, near identical exon 20 insertion mutations can be found on the *erb-b2 receptor tyrosine kinase 2* (*ERBB2*) gene and the resulting encoded proteins are also not particularly sensitive to standard dosing schemes of dual EGFR/ERBB2 TKIs (18). The development of TKIs for these recalcitrant variants in EGFR and ERBB2 continues to be an unmet medical need for the management of NSCLC.

Certain other clinically-relevant kinase domain *EGFR* mutations, named by others as uncommon or atypical mutations, seem to be EGFR TKI sensitive in preclinical models (where they are transforming and activate the MAPK/PI3K signaling cascades) and in available published clinical reports (4,16,17). These mutations encompass *EGFR*-exon 18 indels/E709X (<0.5% of *EGFR* mutations), exon 18 G719X (~3% of *EGFR* mutations), exon 19 insertions (<0.5% of *EGFR* mutations), exon 20 A763_Y764insFQEA (<0.5% of *EGFR* mutations), exon 20 S768I (<1.5% of *EGFR* mutations) and the exon 21 L861Q (~3% of *EGFR* mutations); either alone or compound with other *EGFR* mutations (19). It is interesting to note that in preclinical models, the inhibitory concentrations of 1st generations EGFR TKIs are usually 10–200 times higher for *EGFR*-exon 18 indels/E709X (20,21), exon 18 G719X (20), exon 19 insertions (22), exon 20 A763_Y764insFQEA (15), exon 20 S768I (23) and the exon 21 L861Q (23) when compared to EGFR-exon 19 deletion mutants. These observations may explain why the ORRs in the clinic seldom exceed 55% for tumors that harbor these mutations types in patients treated with gefitinib or erlotinib (15,16). The same preclinical models show slightly higher relative potency for the 2nd generation EGFR TKI afatinib, specifically for *EGFR* exon 18 mutations (20). Indeed, the ORRs to afatinib 40 mg/day seem to be higher than 55% for tumors harboring *EGFR*-G719X, L861Q or S768I mutations (17).

Despite initial rapid and sometimes prolonged responses to gefitinib, erlotinib and afatinib for lung cancers with the aforementioned EGFR TKI-sensitizing mutations, acquired resistance to EGFR TKIs is inevitable for most tumors due to biological (on-target mutations, bypass tracks or histological transformation) and pharmacokinetic mechanisms (24). The most common abnormality identified on rebiopsy specimens is the *EGFR*-T790M (within the gatekeeper position of exon 20) mutation in >50–60% of progressing lesions (6,25). *EGFR*-T790M is most commonly identified in *EGFR*-exon 19 deletion

Table 1 Types, frequency and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor sensitivity of *EGFR* kinase domain mutations in lung cancer

EGFR mutation		EGFR TKI [*in vitro* sensitivity and expected overall response rate (ORR)]		
EGFR TKI sensitivity type	Approximate frequency (%)	1st generation	2nd generation	3rd generation
		Gefitinib 250 mg Erlotinib 150 mg	Afatinib 40 mg	Osimertinib 80 mg
Sensitizing				
Exon 19 deletion	45.0	++++ (ORR >70%)	++++ (ORR >75%)	++++ (ORR >70%)
L858R	35.0	++++ (ORR >60%)	++++ (ORR >70%)	++++ (ORR >60%)
G719X	3.0	++ (ORR >55%)	+++ (ORR >65%)	++ (ORR ?)
L861Q	3.0	++ (ORR >55%)	++ (ORR >55%)	++ (ORR ?)
S768I	<1.5	+ (ORR >45%)	++ (ORR >55%)	? (ORR ?)
Exon 18 indel/E709X	<0.5	++ (ORR >55%)	+++ (ORR >65%)	++ (ORR ?)
Exon 19 insertion	<0.5	++ (ORR >55%)	++ (ORR ?)	++ (ORR ?)
A763_Y764insFQEA	<0.5	++ (ORR >55%)	++ (ORR ?)	++ (ORR ?)
Exon 18–25 duplication (*EGFR*-KDD)	<0.5	++ (ORR >55%)	+++ (ORR >65%)	++ (ORR ?)
Rearrangement (*EGFR-RAD51)*	<0.5	++ (ORR >55%)	+++ (ORR ?)	++ (ORR ?)
Insensitizing				
Exon 20 insertion	>7.0	– (ORR <5%)	– (ORR <10%)	– (ORR ?)
T790M inherited	<1.0	– (ORR ~0%)	– (ORR ~0%)	++++ (ORR >60%)
Others	>2.0	? (ORR ?)	? (ORR ?)	? (ORR ?)
Acquired resistance				
T790M + sens.	>50.0 (1st/2nd gen. TKI)	– (ORR ~0%)	– (ORR <5%)	++++ (ORR >60%)
C797X + T790M + sens.	<50.0 (osimertinib)	– (ORR ~0%)	– (ORR ~0%)	– (ORR ~0%)

++++, maximum inhibition; +++, moderate inhibition; ++, adequate inhibition; +, minimal inhibition; –, no significant inhibition beyond the therapeutic window of wild-type EGFR; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ?, unknown; sens, sensitizing mutation; gen., generation.

mutated tumors but has also been reported in conjunction with L858R, L861Q, and S768I among others (26). Germline *EGFR*-T790M has also been described as a rare (<1%) high relative risk susceptibility allele in families with lung cancers independent of smoking risk (27,28). Eloquent structural and biochemical experiments have irrefutably defined that the addition of *EGFR*-T790M to a sensitizing mutant alters the kinetics of inhibitor binding of gefitinib, erlotinib and afatinib (29,30); leading to resistance to achievable clinical doses of these EGFR TKIs. However, 3rd generation EGFR TKIs that were selected on the basis of their covalent binding to *EGFR*-C797, plus their mutation over WT EGFR sensitivity, can inhibit *EGFR*-T790M bearing cancers (6,31). The most advanced of the clinical candidate 3rd generation EGFR TKIs is osimertinib given at 80 mg/day (32). The drug is exceedingly active against tumors with acquired resistance to gefitinib, erlotinib or afatinib when *EGFR*-T790M is present, with reported ORRs of >55% (26). Osimertinib was FDA-approved in 2015. Unfortunately, resistance to osimertinib monotherapy seems again to be inevitable with a predominance of on-target mutation events (including *EGFR*-C797S) in progressing tumors or circulating tumor DNA (33). The Thoracic Oncology community awaits a new generation of EGFR TKIs and of anti-cancer therapy combinations with EGFR TKIs to prevent and/or treat resistance to 3rd generation EGFR TKIs.

Just as the field of *EGFR* mutated NSCLC seemed to restricted to point mutations and indels that congregated in the kinase domain (as reviewed above and summarized in *Table 1*), two new reports led by investigators of the commercial comprehensive genomic profiling company Foundation Medicine and of Vanderbilt University School of Medicine have broadened our horizon to rare genomic events that also activate the kinase domain of EGFR: *EGFR*-exon 18–25 kinase domain duplication (*EGFR*-KDD)

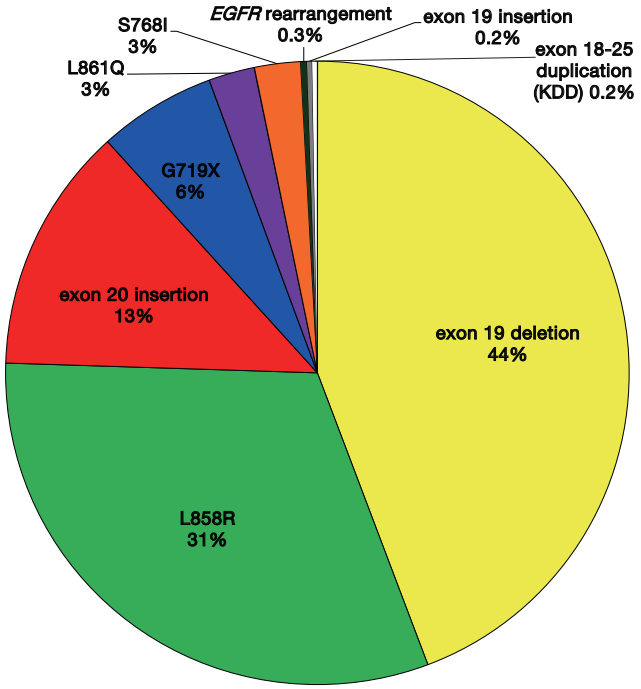

Figure 1 Pie chart display of epidermal growth factor receptor (*EGFR*) genomic aberrations identified by a single commercial vendor (Foundation Medicine) using the FoundationOne comprehensive genomic profiling that can be identify indels, point mutations, copy number changes, kinase domain duplications (KDD) and rearrangements. The data was obtained from (35).

and *EGFR* rearrangements (34,35). It seems the frequency of these changes does not exceed individually 0.5% of all *EGFR* mutation events (*Table 1*). In the 1,510 *EGFR* mutated tumor cohort described from 10,097 analyzed cases using FoundationOne's comprehensive genomic profiling (35), the frequency of *EGFR*-KDD was 0.2% and of *EGFR* rearrangements was 0.3% (*Figure 1*). These changes had not been reported previously because most traditional *EGFR* sequencing strategies used in day-to-day clinical care (Sanger sequencing, allele-specific PCR-based or focused next generation sequencing panels) are unable to identify these rare genomic variants.

The *EGFR*-KDD alteration consists of an intragenic alteration in *EGFR*, resulting in the tandem duplication of exons 18 to 25 (34). As these exons encompass the tyrosine kinase domain, this duplication generates an in-frame kinase domain duplication at the protein level. This type of *EGFR*-KDD had only been previously reported in rare cases of glioma (36) and was additionally found to occur in sarcomas, peritoneal carcinomas and Wilms' tumors (34). In preclinical and computational models, the resulting EGFR-KDD protein is transforming, may generate EGFR intramolecular asymmetric activated dimers, and is hypersensitive to 1st, 2nd and 3rd generation EGFR TKIs (34). The same report also describes a case of advanced chemotherapy-progressive *EGFR*-KDD mutated lung adenocarcinoma with a 7-month partial response to afatinib (doses not provided) and subsequent progression due to amplification of the *EGFR*-KDD allele (34). Another case report of a prolonged multi-year response to gefitinib and then erlotinib has been described for advanced *EGFR*-KDD mutated lung adenocarcinoma (37). Therefore, it seems these variants are responsive to 1st and 2nd generation EGFR TKIs in the clinic.

EGFR rearrangements were for the first time described in 2016, with rearrangements following the kinase domain of *EGFR* (at exon 25) with other partners. The two reported partners include the C-terminal portion of the *RAD51 recombinase* (RAD51) or *purine-rich element binding protein B* (*PURB*) genes (35). The resulting N-terminal EGFR-RAD51 C-terminal fusion protein retains an important regulatory auto-phosphorylation site (Y845) of EGFR (35). In preclinical models, EGFR-RAD51 is transforming, activates downstream signaling pathways, may form activation dimers, and is hypersensitive to 1st, 2nd and 3rd generation EGFR TKIs (35). Of most interest, three patients with *EGFR-RAD51* and one patient with *EGFR-PURB* rearranged NSCLCs had between 5- to 20-month periods of partial response to standard clinical doses of erlotinib (35); confirming that EGFR fusion proteins are TKI-sensitive variants. Other type of *EGFR* genomic aberrations outside the kinase domain of EGFR—including extracellular domain in-frame deletions (such as the truncated EGFR-vIII deletion), extracellular domain point mutations and C-terminal activating exon 25-26 deletions—have also been described in whole genome sequencing cohorts of lung adenocarcinoma (38). The prevalence and clinical significance of the latter genomic changes remains to be elucidated in the clinical care of NSCLC with off-label use of FDA-approved EGFR TKIs.

In summary, the enhanced landscape of EGFR TKI-responsive genotypes (including exon 19 deletions, L858R, exon 18 indels, G719X, exon 19 insertions, A763_Y764insFQEA, S768I, L861Q, KDD and rearrangements to gefitinib, erlotinib or afatinib; and T790M to osimertinib) highlights that comprehensive molecular profiling may be necessary to maximize the identification of all cases that can benefit from precision oncology when dealing with *EGFR*

mutated NSCLC. It also demonstrates that we have not yet identified all genomic variants that are actionable and/or clinically-relevant in NSCLC (39-50).

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Footnote

Conflicts of Interest: The author has received consulting fees from Pfizer Inc., Boehringer Ingelheim and Ariad. The author also conducts unremunerated clinical trials using afatinib (Boehringer Ingelheim), erlotinib (Astellas), osimertinib (AstraZeneca) and rociletinib (Clovis Oncology).

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