Genomic instability as a major mechanism for acquired resistance to EGFR tyrosine kinase inhibitors in cancer

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The mutation-mediated overexpression of epidermal growth factor receptor tyrosine kinase (EGFR TK) and its activation play an important role in the cellular proliferation and epithelial tumorigenesis. A series of inhibitors targeting the intracellular tyrosine kinase (TK) domain of EGFR have been developed and applied to clinical practice. Although these inhibitors safely and effectively restrain tumor cell proliferation and prolong survival in some patients, acquired resistance ultimately arises. DNA mutations contribute to drug-induced cancer-cell resistance. Genomic instability, especially DNA replication and repair error, provides the major source for DNA mutations. Identifying the central mechanisms underlying the generation and selection of resistance mutations may provide critical opportunities for novel regimens in combating drug resistance. In this review, we provide an overview of EGFR kinase inhibitors (TKIs) in non-small cell lung carcinoma (NSCLC) treatment and their challenges. We also discuss the major source of genomic instability in TKI resistance and hypothesize that the maintenance of DNA replication and repair machinery might be used to develop novel treatment regimens for patients with NSCLC.

EGFR is a member of the receptor tyrosine kinase (RTK) family (Lemmon et al., 2014). The activation of cytosol membrane EGFR via binding EGF-like ligands initiates receptor dimerization, phosphorylation of its own tyrosine residues, and activation of downstream signaling pathways. Aberrant EGFR activation, due to its single-nucleotide substitutions in exons 18–21, in-frame duplications/insertions in exon 20, or short in-frame deletions in exon 19, can amplify a series of downstream pro-oncogenic signaling pathways including JAK/STAT, PI3K/AKT/mTOR, PLC/PKC/NFκB and MEK/ERK. These pathways aim to support and benefit cancer cell survival, proliferation and tissue differentiation (El-Hashim et al., 2017) (Fig. 1). Three generations of EGFR TKIs have been developed to specifically target EGFR mutations to the kinase domain in NSCLC. However, an ever-increasing number of mutation-mediated resistances are inevitable (Zhang, 2016b).

Due to the mutation-mediated destabilization of the EGFR TK domain, abnormal activation of EGFR constitutively propagates EGFR TK activity and downstream pro-oncogenic signaling pathways to drive cancer cell survival and proliferation. Moreover, the expressions and interactions of a vast amount of genes and proteins are significantly changed during EGFR activation, suggesting the profound and extensive role of EGFRs involvement in the diverse signaling networks of cells (Waters et al., 2012). Although there are various pharmaceutical agents that target the proteins involved in the EGFR-mediated network of NSCLC, EGFR TKI remain the first line of treatment (Dong et al., 2021). Activated EGFR can promote protein nuclear translocation or redistribute to the nucleus via autophosphorylation, where it functions in DNA replication and repair which is an important process for genome fidelity (Wang et al., 2010, 2012). Reduced EGFR TK activity in response to TKIs might impair DNA replication and repair processes and boost the production of mutations for cancer progression. Both pre-existing and de novo generation of genome wide mutations have been observed in vivo and in vitro, suggesting the EGFR TKIs initiate genomic instability to generate and select for mutations that confer resistance to their inhibition of cancer cell growth and induction of apoptosis (Hata et al., 2016). Therefore, a better understanding of how TKIs initiate genomic instability is critical for developing novel strategies to control NSCLC progression.

Three generations of EGFR TKIs, as the ATP mimetic inhibitors, have been developed so far to target the most common somatic EGFR mutations, including the exon 19

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which leads to the deamination of 5-methylcytosine to activation-induced cytidine deaminase (AICDA) expression, in vitro. Evaluations have been reported to harbor T790M mutations in pre-existing mutations, pre-treatment sample obtained from 50% of patients (Ma et al., 2011). Despite difficulties in the detection of pre-existing mutations, post-treatment sample evaluations have been reported to harbor T790M mutations (Watanabe et al., 2015). Furthermore, using a 790M-negative in vitro system, it was also demonstrated that EGFR TKI treatment can generate T790M mutations de novo (Kim et al., 2012). Specifically, a study conducted by Kadi and colleagues, found that NFκB activation by TKIs promotes activation-induced cytidine deaminase (AICDA) expression, which leads to the deamination of 5-methylcytosine to thymine and finally generates the T790M mutation (El Kadi et al., 2018). Second-generation TKIs, including afatinib and dacomitinib, irreversibly bind to the mutated and wild-type EGFR, as well as the receptors from bypass signaling pathways, such as HER2 (Genova et al., 2014; Baraibar et al., 2020), to provide a more sustained and potent EGFR inhibitory function. However, the acquired mutations including T790M still occur over the course of treatment. Recently, the mutant-selective third generation TKI osimertinib was designed to selectively and covalently bind to the C797 residue of EGFR at the ATP-binding pocket edge of its TK domain to repress EGFR-activating mutations while sparing wild-type receptors (Greig, 2016). Previously, osimertinib was used as second-line treatment in NSCLC patients who developed T790M-mediated resistance to first- and second-generation TKIs (Zhang, 2016a). Recent studies suggested that it was more effective to use osimertinib as first-line therapy (Aguilar-Serra et al., 2019). However, the most common mutation, C797S in exon 20, has been observed in around 10–26% of patients with resistance to second-line osimertinib treatment and around 7% of patients with resistance to first-line treatment (Mehlman et al., 2019).

In addition to EGFR-dependent mutations, an array of alternative EGFR-independent bypass signaling pathways may be concurrently activated to exacerbate tumor heterogeneity and therapeutic difficulty under EGFR-TKI treatment. Thus, the combination strategies which target both oncogenic mutations of EGFR and EGFR-independent bypass signaling pathways have been applied to delay the acquisition of resistance to some extent in many cases. The most common mechanism for bypass signaling-mediated acquired resistance, in 5%–50% of patients receiving second-line osimertinib treatment and 7%–15% of patients receiving first-line osimertinib treatment, occurs due to high levels of MET gene amplification (Ou et al., 2016). The MET gene amplification can induce constitutive activation of the EGFR downstream pro-oncogenic signaling pathways, such as JAK/STAT, PI3K/AKT/mTOR, PLC/PKC/NFκB and MEK/ERK pathways (Rotow et al., 2020; Yu et al., 2021). Thus, MET inhibitors have been used in combination with osimertinib to overcome acquired resistance (Awad et al., 2019). Another common bypass alteration is the overexpression of Anexelekto (AXL), a tyrosine kinase receptor, which can interact with EGFR and has been reported to be associated with poor osimertinib responses (Taniguchi et al., 2019). The combination of AXL inhibitor cabozantinib with osimertinib is a promising strategy to prolong osimertinib sensitivity (Reckamp et al., 2019). However, clinical trials are needed to confirm the long-term response for these strategies in patients. Beyond these EGFR-dependent and independent alterations to chromosomal DNA, there are yet other routes promoting drug resistance at the genomic level. For example, extrachromosomal DNA (ecDNA), which can be unevenly segregated into daughter cells due to the lack of a centromere, has been found in nearly half of human cancers (Turner et al., 2017). It has been reported that mutant EGFR

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**Figure 1. The EGFR protein structure and corresponding gene exons.** Exons 1–16 encode extracellular domains I–IV (orange) which can form the ligand interaction conformation. Exons 17–18 encode the transmembrane domain (blue) for connecting extracellular domains and intracellular domains. Exons 19–24 encode tyrosine kinase domain. Exon 19 deletion and exon 21 L858R mutation are original mutations that cause constant activation of tyrosine kinase activity in non-small cell lung carcinoma. Exon 20 T790M is the dominant secondary mutation acquired in response to the 1st and 2nd generation TKIs, while exon 20 C797S mutation is the secondary mutation acquired in response to the 3rd generation TKI osimertinib. Exon 25–28 encode C-terminal phosphorylation domain which mediates the interactions between the receptor and downstream substrates upon receptor activation. Abbreviations: EGF, epidermal growth factor; ECD, extracellular domain; TM, transmembrane; ICD, intracellular domain; TK, tyrosine kinase; RD, regulatory/phosphorylation domain.
ecDNA is eliminated in tumor cells during TKI treatment, inducing drug resistance, but restores after drug withdrawal (Nathanson et al., 2014).

How do spontaneous somatic mutations originate, particularly under the stresses such as drug administration? A series of repair processes coordinate with DNA replication to reduce spontaneous mutagenesis and maintain DNA fidelity. The key determinant of DNA fidelity depends on DNA polymerases selectivity and proof reading functions, which are important in organized incorporation of nucleotides into DNA during replication (Ludmann and Marx, 2016; Bębenek and Ziuzia-Graczyk, 2018; Xing et al., 2019). Moreover, during the DNA synthesis in lagging strand, the DNA polymerases, such as Pol α and primase, de novo synthesize the RNA primer and α-segment with high error rates. Elimination of those errors relies on the structure-specific nucleases, such as FEN1 and DNA2, which are involved in the accurate RNA primer removal and the editing of α-segment errors. Deficiency in these processes will not only leave in those errors, but also generate duplication mutations due to failure of RNA primer removal which then exacerbates the mutation burden (Zheng and Shen, 2011; Li et al., 2018; Zheng et al., 2020).

The mismatch repair (MMR) signaling is another determinant of DNA replication fidelity by correcting the remaining mismatches after DNA replication to promise DNA fidelity under homeostasis (Haradhvala et al., 2018). However, EGFR TKIs might hijack the key DNA replication/repair components and impair these processes for promoting single tumor cells to acquire multi-level molecular alterations at the genetic, transcriptional, post-translational, and epigenetic levels and ultimately boost intrinsic tumor heterogeneity for genome wide mutation generation (Majem and Remon, 2013).

It is established now that EGFR TK possesses more than 200 substrates (https://www.phosphosite.org/homeAction.action; https://string-db.org/network/9606.ENSP00000275493). These protein substrates are not only components of onco- genetic signaling pathways (JAK/STAT, PI3K/AKT/mTOR, PLC/PKC/NFκB and MEK/ERK) that promote cancer cell survival and proliferation, but are also involved in DNA replication machinery (Fig. 2). Although EGFR inhibition with TKIs may suppress pro-oncogenic pathways, it may also result in other unintended effects such as the impairment of DNA replication fidelity and promotion of somatic mutagenesis. Supporting evidence is available for such a hypothesis. Cao and colleagues have recently demonstrated that the expression of heat shock protein 70 (HSP70), an ATP-dependent molecular chaperone, is reduced by EGFR TKI treatment (Cao et al., 2018). They found that HSP70 physically interacts with multiple enzymes in base excision repair (BER) and DNA replication pathways. Thus, the down regulation of HSP70 in response to TKIs enhances the gene mutation rate and attenuates BER to facilitate acquired resistance. Activated EGFR from the cytosol membrane can redistribute to the nucleus via the Golgi and endoplasmic reticulum (ER) under the assistance of translocon (Wang and Hung, 2009). Nuclear EGFR plays an essential role in stabilization of DNA replication and repair proteins, such as proliferation cell nuclear antigen (PCNA). PCNA recruits and

### Table 1. Summary of key EGFR-TK inhibitors

| EGFR-TKIs  | Trade name | Primary target | Mechanism of action | Dominant secondary mutation | Clinical trial number | Refs               |
|-----------|------------|----------------|---------------------|-----------------------------|-----------------------|-------------------|
| First generation | Gefitinib | Iressa | EGFR | Reversible | T790M | NCT02959749 | Muhsin et al. (2003) |
| Erlotinib | Tarceva | EGFR | Reversible | T790M | NCT00364351 | Bareschino et al. (2007) |
| Lapatinib | Tyverb | EGFR; ErbB2 | Reversible | T790M | NCT01125566 | Moy et al. (2007) |
| Icotinib | Conmana | EGFR | Reversible | T790M | NCT03231501 | Shi et al. (2013) |
| Second generation | Afatinib | Gilotrif | EGFR; ErbB2; ErbB4 | Irreversible | T790M | NCT02094573 | Dungo and Keating (2013) |
| Dacomitinib | Vizimpro | EGFR; ErbB2; ErbB4 | Irreversible | T790M | NCT01000025 | Wu et al. (2017) |
| Neratinib | Nerlynx | EGFR; ErbB2; ErbB4 | Irreversible | T790M | NCT01000025 | Sequist (2010) |
| Third generation | Osimertinib | Tagrisso | EGFR T790M | Irreversible | C797S | NCT01449461 | Greig (2016) |
coordinates DNA synthesis machinery to ensure accurate DNA replication and repair at the replication forks (Moldovan et al., 2007). Nuclear EGFR mediates the phosphorylation of PCNA in its chromatin-bound form, which is important for maintenance of PCNA stability and protection of chromatin-bound PCNA from proteasome-dependent degradation via lysine polyubiquitination (Wang et al., 2006; Lo et al., 2012). Blockage of its phosphorylation by EGFR TKIs may impair the assembly of the replication and repair machinery and lead to genome instability. The other important example is DNA-dependent protein kinase (DNA-PK) which is required for rejoining double-strand breaks to repair DNA. The nuclear EGFR can physically interact with DNA-PK and trigger DNA-PK phosphorylation (Bandyopadhyay et al. 1998; Dittmann et al., 2005a). Impaired DNA-PK phosphorylation due to the blockage of EGFR nuclear translocation reduces DNA-PK activity and promotes DNA damage (Dittmann et al., 2005b, 2008). These pieces of evidence suggest that EGFR TKIs may not cause DNA damage directly but can impair DNA replication and repair machinery due to degradation of the component proteins that missing phosphorylation protection and then lead to the acquired genome wide mutations.

Mimicking the therapeutic approach of the HIV "cocktail" regimens, the recently approved combination therapeutic regimen with the 3rd generation EGFR TKI osimertinib and MET inhibitor Tepotinib is based on the observation that MET gene amplification bypasses the EGFR TK activity and upregulates the EGFR downstream pro-oncogenic signaling pathway in EGFR TKI-treated patients (Markham, 2020). The combinations of EGFR-TKIs with immune checkpoint inhibitors are an emerging trend in NSCLC treatment (Jin et al., 2020). The immune checkpoint inhibitors include the ones for the programmed cell death-1 receptor and its ligand (PD-1/PD-L1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) (Johnson et al., 2014). However, these regimens do not include a strategy to minimize the mutations from its origin. Our proposal for a therapeutic avenue is to protect the integrity of the DNA replication machinery and to suppress the S-phase cell cycle checkpoint activation in order to avoid drug-induced mutations. To maintain DNA replication fidelity, the employment of a proteasome inhibitor coordinates DNA synthesis machinery to ensure accurate DNA replication and repair at the replication forks (Moldovan et al., 2007). Nuclear EGFR mediates the phosphorylation of PCNA in its chromatin-bound form, which is important for maintenance of PCNA stability and protection of chromatin-bound PCNA from proteasome-dependent degradation via lysine polyubiquitination (Wang et al., 2006; Lo et al., 2012). Blockage of its phosphorylation by EGFR TKIs may impair the assembly of the replication and repair machinery and lead to genome instability. The other important example is DNA-dependent protein kinase (DNA-PK) which is required for rejoining double-strand breaks to repair DNA. The nuclear EGFR can physically interact with DNA-PK and trigger DNA-PK phosphorylation (Bandyopadhyay et al. 1998; Dittmann et al., 2005a). Impaired DNA-PK phosphorylation due to the blockage of EGFR nuclear translocation reduces DNA-PK activity and promotes DNA damage (Dittmann et al., 2005b, 2008). These pieces of evidence suggest that EGFR TKIs may not cause DNA damage directly but can impair DNA replication and repair machinery due to degradation of the component proteins that missing phosphorylation protection and then lead to the acquired genome wide mutations.

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in combination with EGFR-TKI therapies may preserve DNA replication protein stability and should be considered. As previously mentioned, HSP70 is susceptible to proteasome degradation in response to EGFR TKIs. Recent experiments in our laboratory showed that when administering a protease inhibitor, Bortezomib, there is a clear reduction of HSP70 degradation. Furthermore, after conducting cellular based assays we observed a significant improvement to EGFR TKI sensitivity as well. A vast majority of the somatic mutations are generated through error prone DNA synthesis including aberrant Okazaki fragment maturation in the S-phase cells, which requires extended S-phase time and activation of the checkpoints. Combining the checkpoint inhibitors, such as ATR inhibitors, with TKIs, to reduce the acquired resistance is an alternative proposed strategy (Vendetti et al., 2015). In summary, EGFR serves a multifaceted role in cells and its inhibition can prove deleterious effects to genome stability. As we continue to face the persistent challenge of drug resistance in EGFR TKIs, we turn our focus to maintaining the integrity of DNA replication and repair pathways. By conserving the fidelity of the DNA replication and repair machinery we may increase drug sensitivity and impede tumor cell mutations that aid in the acquisition of drug resistance.

AUTHOR CONTRIBUTIONS

BL conceived and wrote the manuscript; DD, LZ, and KR contributed to the manuscript editing. BHS conceived and supervised the project and wrote the manuscript.

ABBREVIATIONS

AICDA, activation-induced cytidine deaminase; AXL, anexelekt; BER, base excision repair; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; DNA-PK, DNA-dependent protein kinase; ecDNA, extrachromosomal DNA; EGFR, epidermal growth factor receptor; ER, endoplasmic reticulum; HSP70, heat shock protein 70; MMR, mismatch repair; NSCLC, non-small cell lung carcinoma; RTK, receptor tyrosine kinase; TK, tyrosine kinase; TKIs, tyrosine kinase inhibitors; PD-1/PD-L1, programmed cell death-1 receptor and its ligand; PCNA, proliferating cell nuclear antigen.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

Aguilar-Serra J, Gimeno-Ballestre V, Pastor-Clerigues A, Milara J, Martí-Bonmatí E, Trigo-Vicente C Alós-Almiñana M, Cortijo J (2019) Osimertinib in first-line treatment of advanced EGFR-mutated non-small-cell lung cancer: a cost-effectiveness analysis. J Comp Eff Res 8(11):853–863
Awad MM, Leonardi GC, Kravets S, Dahlberg SE, Drilon A, Noonan SA, Camidge DR, Ou SI, Costa DB, Gadgeel SM et al (2019) Impact of MET inhibitors on survival among patients with non-small cell lung cancer harboring MET exon 14 mutations: a retrospective analysis. Lung Cancer 133:96–102
Bandyopadhyay D, Mandal M, Adam L, Mendelsohn J, Kumar R (1998) Physical interaction between epidermal growth factor receptor and DNA-dependent protein kinase in mammalian cells. J Biol Chem 273(3):1568–1573
Baraibar I, Mezquita L, Gil-Bazo I, Planchard D (2020) Novel drugs targeting EGFR and HER2 exon 20 mutations in metastatic NSCLC. Crit Rev Oncol Hematol 148:102906
Bareschino MA, Schettino C, Troiani T, Martinelli E, Morgillo F, Ciardiello F (2007) Erlotinib in cancer treatment. Ann Oncol 18 (Suppl 6):vi35–vi41
Bębenek A, Zluzia-Graczyk I (2018) Fidelity of DNA replication-a matter of proofreading. Curr Genet 64(8):985–996
Cao X, Zhou Y, Sun H, Xu M, Bi X, Zhao Z, Shen B, Wan F, Hong Z, Lan L et al (2018) EGFR-TKI-induced HSP70 degradation and BER suppression facilitate the occurrence of the EGFR T790 M resistant mutation in lung cancer cells. Cancer Lett 424:161–167
Dittmann K, Mayer C, Fehrenbacher B, Schaller M, Raju U, Milas L, Chen DJ, Kehlbach R, Rodemann HP (2005a) Radiation-induced epidermal growth factor receptor nuclear import is linked to activation of DNA-dependent protein kinase. J Biol Chem 280(35):31182–31189
Dittmann K, Mayer C, Rodemann HP (2005b) Inhibition of radiation-induced EGFR nuclear import by C225 (Cetuximab) suppresses DNA-PK activity. Radiother Oncol 76(2):157–161
Dittmann K, Mayer C, Kehlbach R, Rodemann HP (2008) Radiation-induced caveolin-1 associated EGFR internalization is linked with nuclear EGFR transport and activation of DNA-PK. Mol Cancer 7:69
Dong RF, Zhu ML, Liu MM, Xu YT, Yuan LL, Bian J, Xia YZ, Kong LY (2021) EGFR mutation mediates resistance to EGFR tyrosine kinase inhibitors in NSCLC: from molecular mechanisms to clinical research. Pharmacol Res 167:105583
Dungo RT, Keating GM (2013) Afatinib: first global approval. Drugs 73(13):1503–1515
El Kadi N, Wang L, Davis A, Korkaya H, Cooke A, Vadnala V, Brown NA, Betz BL, Cascalho M, Kalenkerian GP et al (2018) The EGFR T790M mutation is acquired through AIDC-mediated deamination of 5-methylcytosine following TKI treatment in lung cancer. Cancer Res 78(24):6728–6735
El-Hashim AZ, Khajah MA, Renno WM, Babynson RS, Uddin M, Benter IF, Ezeamuzie C, Akhtar S (2017) Src-dependent EGFR transactivation regulates lung inflammation via downstream signaling involving ERK1/2, PI3K/Akt and NFκB induction in a murine asthma model. Sci Rep 7(1):9919
Genova C, Rijavec E, Barletta G, Burrafato G, Biello F, Dal Bello MG, Coco S, Truini A, Alama A, Boccoaro F et al (2014) Afatinib for the treatment of advanced non-small-cell lung cancer. Expert Opin Pharmacother 15(6):889–903
Greig SL (2016) Osimertinib: first global approval. Drugs 76(2):263–273
Haradhvala NJ, Kim J, Maruvka YE, Polak P, Rosebrock D, Livitz D, Hess JM, Leshchiner I, Kamburov A, Mouw KW et al (2018) Distinct mutational signatures characterize concurrent loss of polymerase proofreading and mismatch repair. Nat Commun 9(1):1746
Hata AN, Niederst MJ, Archibald HL, Gomez-Caraballo M, Siddiqui FM, Mulvey HE, Maruvka YE, Ji F, Bhang HE, Krishnamurthy Radhakrishna V et al (2016) Tumor cells can follow distinct evolutionary paths to become resistant to epidermal growth factor receptor inhibition. Nat Med 22(3):262–269
Jin R, Zhao J, Xia L, Li Q, Li W, Peng L, Xia Y (2020) Application of immune checkpoint inhibitors in EGFR-mutant non-small-cell lung cancer: from bed to bench. Ther Adv Med Oncol 12:1758835920930333
Johnson DB, Rioth MJ, Horn L (2014) Immune checkpoint inhibitors in EGFR-mutant non-small-cell lung cancer. Curr Treat Options Oncol 15(4):658–669
Kim Y, Ko J, Cui Z, Abohoda A, Ahn JS, Ou SH, Ahn MJ, Park K (2012) The EGFR T790M mutation in acquired resistance to an irreversible second-generation EGFR inhibitor. Mol Cancer Ther 11(3):784–791
Lemmon MA, Schlessinger J, Ferguson KM (2014) The EGFR family: not so prototypical receptor tyrosine kinases. Cold Spring Harb Perspect Biol 6(4):a020768
Li Z, Liu B, Jin W, Wu X, Zhou M, Liu VZ, Goel A, Shen Z, Zheng L, Shen B (2018) hDNA2 Nuclease/helicase promotes centromeric DNA replication and genome stability. EMBO J 37(14)
Lo YH, Ho PC, Wang SC (2012) Epidermal growth factor receptor protects proliferating cell nuclear antigen from cullin 4A protein-mediated proteolysis. J Biol Chem 287(32):27148–27157
Ludmann S, Marx A (2016) Getting it right: how DNA polymerases select the right nucleotide. Chimia (Aarau) 70(3):203–206
Ma C, Wei S, Song Y (2011) T790M and acquired resistance of EGFR TKI: a literature review of clinical reports. J Thorac Dis 3(1):10–18
Majem M, Remon J (2013) Tumor heterogeneity: evolution through space and time in EGFR mutant non small cell lung cancer patients. Transl Lung Cancer Res 2(3):226–237
Markham A (2020) Tepotinib: first approval. Drugs 80(8):829–833
Mehman C, Cadranel J, Rousseau-Bussac G, Lacave R, Pujals A, Girard N, Callens C, Gounant V, Théou-Anton N, Friard S et al (2019) Resistance mechanisms to osimertinib in EGFR-mutated advanced non-small-cell lung cancer: a multicentric retrospective French study. Lung Cancer 137:149–156
Moldovan GL, Pfander B, Jentsch S (2007) PCNA, the maestro of the replication fork. Cell 129(4):665–679
Molina-Vila MA, Bertran-Alamillo J, Mayo C, Rosell R (2009) Screening for EGFR mutations in lung cancer. Discov Med 8(43):181–184
Moy B, Kirkpatrick P, Kar S, Goss P (2007) Lapatinib. Nat Rev Drug Discov 6(6):431–432
Muhsin M, Graham J, Kirkpatrick P (2003) Gefitinib. Nat Rev Drug Discov 2(7):515–516
Nathanson DA, Gini B, Mottahedeh J, Visnyei K, Koga T, Gomez G, Eskin A, Hwang K, Wang J, Masui K et al (2014) Targeted therapy resistance mediated by dynamic regulation of extrachromosomal mutant EGFR DNA. Science 343(6166):72–76
Ou SI, Agarwal N, Ali SM (2016) High MET amplification level as a resistance mechanism to osimertinib (AZD9291) in a patient that symptomatically responded to crizotinib treatment post-osimertinib progression. Lung Cancer 98:59–61
Reckamp KL, Frankel PH, Ruel N, Mack PC, Giltiz BJ, Li T, Koczysw M, Gadgeel SM, Cristea MC, Belani CP et al (2019) Phase II trial of caboctinib plus erlotinib in patients with advanced epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer with progressive disease on epidermal growth factor tyrosine kinase inhibitor therapy: a california cancer consortium phase II trial (NCI 9303). Front Oncol 9:132
Rotow JK, Gui P, Wu W, Raymond VM, Lanman RB, Kaye FJ, Peled N, Fece de la Cruz F, Nadres B, Corcoran RB et al (2020) Co-occurring alterations in the RAS-MAPK pathway limit response to MET inhibitor treatment in MET exon 14 skipping mutation-positive lung cancer. Clin Cancer Res 26(2):439–449
Sequist LV, Besse B, Lynch TJ, Miller VA, Wong KK, Giltiz B, Eaton K, Zacharchuk C, Freyman A, Powell C et al (2010) Neratinib, an irinotecan-like pan-erBb receptor tyrosine kinase inhibitor: results of a phase II trial in patients with advanced non-small-cell lung cancer. J Clin Oncol 28(18):3076–3083
Shi Y, Zhang L, Liu X, Zhou C, Zhang S, Wang D, Li Q, Qin S, Hu C, Zhang Y et al (2013) Icotinib versus gefitinib in previously treated advanced non-small-cell lung cancer (ICOGEN): a randomised, double-blind phase 3 non-inferiority trial. Lancet Oncol 14(10):953–961
Taniguchi H, Yamada T, Wang R, Tanimura K, Adachi Y, Nishiyama A, Tanimoto A, Takeuchi S, Araiho LH, Borroni M et al (2019) AXL confers intrinsic resistance to osimertinib and advances the emergence of tolerant cells. Nat Commun 10(1):259
Turner KM, Deshpande V, Beyer D, Koga T, Rusert J, Lee C, Li B, Arden K, Ren B, Nathanson DA et al (2017) Extrachromosomal oncogene amplification drives tumour evolution and genetic heterogeneity. Nature 543(7643):122–125
Vendetti FP, Lau A, Schamus S, Conrads TP, O’Connor MJ, Bakkenist CJ (2015) The orally active and bioavailable ATR kinase inhibitor AZD6738 potentiates the anti-tumor effects of
Wang SC, Hung MC (2009) Nuclear translocation of the epidermal growth factor receptor family membrane tyrosine kinase receptors. Clin Cancer Res 15(21):6484–6489
Wang SC, Nakajima Y, Yu YL, Xia W, Chen CT, Yang CC, McIntush EW, Li LY, Hawke DH, Kobayashi R et al (2006) Tyrosine phosphorylation controls PCNA function through protein stability. Nat Cell Biol 8(12):1359–1368
Wang YN, Lee HH, Lee HJ, Du Y, Yamaguchi H, Hung MC (2012) Membrane-bound trafficking regulates nuclear transport of integral epidermal growth factor receptor (EGFR) and ErbB-2. J Biol Chem 287(20):16869–16879
Wang YN, Wang H, Yamaguchi H, Lee HJ, Lee HH, Hung MC (2010) COPI-mediated retrograde trafficking from the Golgi to the ER regulates EGFR nuclear transport. Biochem Biophys Res Commun 399(4):498–504
Watanabe M, Kawaguchi T, Isa S, Ando M, Tamiya A, Kubo A, Saka H, Takeo S, Adachi H, Tagawa T et al (2015) Ultra-sensitive detection of the pretreatment EGFR T790M mutation in non-small cell lung cancer patients with an EGFR-activating mutation using droplet digital PCR. Clin Cancer Res 21(15):3552–3560
Waters KM, Liu T, Quesenberry RD, Willse AR, Bandyopadhyay S, Kathmann LE, Weber TJ, Smith RD, Wiley HS, Thrall BD (2012) Network analysis of epidermal growth factor signaling using integrated genomic, proteomic and phosphorylation data. PLoS ONE 7(3):e34515
Wu YL, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, Tsuji F, Linke R, Rosell R, Corral J et al (2017) Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol 18(11):1454–1466
Xing X, Kane DP, Bulock CR, Moore EA, Sharma S, Chabes A, Shcherbakova PV (2019) A recurrent cancer-associated substitution in DNA polymerase ε produces a hyperactive enzyme. Nat Commun 10(1):374
Yu D, Zhao W, Vallega KA, Sun SY (2021) Managing acquired resistance to third-generation EGFR tyrosine kinase inhibitors through co-targeting MEK/ERK signaling. Lung Cancer (Auckl) 12:1–10
Zhang H (2016a) Osimertinib making a breakthrough in lung cancer targeted therapy. Onco Targets Ther 9:5489–5493
Zhang H (2016b) Three generations of epidermal growth factor receptor tyrosine kinase inhibitors developed to revolutionize the therapy of lung cancer. Drug Des Devel Ther 10:3867–3872
Zheng L, Shen B (2011) Okazaki fragment maturation: nucleases take centre stage. J Mol Cell Biol 3(1):23–30
Zheng L, Meng Y, Campbell JL, Shen B (2020) Multiple roles of DNA2 nuclease/helicase in DNA metabolism, genome stability and human diseases. Nucleic Acids Res 48(1):16–35