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Navigating the “No Man's Land” of TKI-Failed EGFR-Mutated Non-Small Cell Lung Cancer (NSCLC): A Review



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Abstract

As the leading cause of cancer-related mortality, lung cancer is a worldwide health issue that is overwhelmingly caused by smoking. However, a substantial minority (~25%) of patients with non-small cell lung cancer (NSCLC) has never smoked. In these patients, activating mutations of the epidermal growth factor receptor (EGFR) are more likely, which render their tumors susceptible for a finite period to treatment with EGFR tyrosine kinase inhibitors (TKIs) and confer a better prognosis than EGFR wild-type NSCLC. On progression, due to the inevitable insurgence of resistance, TKIs are generally followed by second- or third-line salvage chemotherapy until treatment failure, after which no standard treatment options are available, resulting in a poor prognosis and a high risk of death. With the focus of clinical attention on treatment with TKIs, few studies on optimal salvage therapies, including cytotoxic chemotherapy, after failure of EGFR TKIs have been reported. Despite a paucity of available data, the aim of this review is to summarize the “no-man's land” of TKI-failed EGFR-mutated NSCLC and expand on alternative strategies as well as potential future directions.

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Introduction

According to the GLOBOCAN 2012 database, the most recent year for which statistics are available, lung cancer is the most common cancer (1.8 million cases) and the leading cause of cancer-related death (1.59 million deaths) worldwide [1]. Tobacco smoking remains the dominant cause of all non-small cell lung cancers (NSCLCs) except in the case of adenocarcinomas with fusions or mutations of the kinase genes such as epidermal growth factor receptor (EGFR), which occur specifically in light or never-smokers [2]. These mutations, which have been identified in exons 18 to 21 of the TK domain and appear most commonly in exon 19 (*del19*) and in exon 21 (*L858R*), activate the receptor tyrosine kinase pathway (hence the term “activating mutations”), leading to overstimulation of downstream signaling prosurvival pathways including Ras-Raf-MAP-kinase and PI3K-Akt-mTOR that confer oncogenicity. Activating EGFR mutations, to which tumors are “addicted” for survival,

are primarily associated with adenocarcinoma histology; frequently mutually exclusive with other activating tumor mutations; and only rarely found in large cell carcinomas, small cell carcinomas, and squamous carcinomas [3]. While deletions in exon 19 and L8585R point mutation in exon 21 are considered activating, other EGFR mutations such as exon 20 insertions are not activating and, therefore, do not tend to respond to EGFR tyrosine kinase inhibitor (TKI) treatment.

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The frequency of EGFR driver mutations in lung adenocarcinomas differs according to ethnicity and sex, appearing at a rate of approximately 10% to 15% in North Americans and Europeans [4] and as high as 30% to 50% in East Asians [5], most commonly in East Asian women that have never smoked. Unlike SCLC, which is strongly linked to smoking behavior, a history of never or minimal smoking is the strongest predictor of harboring the EGFR mutation in NSCLC, which strongly suggests that EGFR mutagenesis arises from nontobacco carcinogens: in fact, the total number of pack-years smoked has been found in multiple studies to inversely correlate with the rate of EGFR TK mutations [6,7]. In addition, the high mutation burden typically induced by carcinogens in cigarette smoke, which putatively leads to a higher quantity of neoantigens [8], may underlie the generally poorer response to PD-1 inhibition in EGFR+ NSCLC. According to the Surveillance, Epidemiology, and End Results database of the National Institutes of Health [9], lung cancer accounts for approximately 6.4% of all malignancies, and since ~10% to 15% of these are EGFR mutated, the lifetime prevalence of EGFR-mutated tumors is between 88,300 and 132,400, making it an orphan disease in the United States from a prevalence count perspective (<200,000 prevalent cases).

EGFR, a transmembrane glycoprotein, is part of the ErbB/HER family of receptor tyrosine kinases, which includes three other members: HER2 (ErbB2), HER3 (ErbB3), and HER4 (ErbB4) [10]. The presence of activating EGFR mutations in advanced NSCLC confers sensitivity to standard-of-care TKIs such as afatinib, gefitinib, erlotinib [11], dacomitinib, and osimertinib and predicts a better prognosis as compared to EGFR wild-type NSCLC. While the use of TKIs, which are superior to chemotherapy, has resulted in substantial benefits including an initial response rate of approximately 70% and an overall survival from 1 to nearly 3 years [12], the universality of treatment resistance limits the duration of their use.

Clinical management of TKI-failed patients constitutes an uncertain “no man’s land” since, to date, there are no clear guidelines, and new accepted strategies to improve outcomes are lacking [13,14]. A retrospective analysis of 521 EGFR TKI-failed patients by Song et al. [15] highlights the poor prognosis in this population since of the 223 patients who previously received long-term TKI therapy (>6 months), overall survival was a dismal 5 months. In the absence of satisfactory therapeutic options and treatment guidelines after failure of subsequent salvage second- and third-line chemotherapy EGFR-positive NSCLC is an area of high unmet medical need. A systematic review of the available literature highlights a wealth of data from high-quality clinical trials on clinical outcomes with TKIs and a corresponding paucity of information and evidence pertaining to treatment of tumors that have exhausted TKI options. With the focus of attention on treatment with TKIs, a hotspot of clinical research, the question of how to manage patients that exhaust TKI and chemotherapy options is an open one. Despite the relative paucity of available data on this subject, this review aims to summarize current and alternative treatment strategies as well as potential future directions in advanced TKI-failed EGFR-mutated NSCLC.

Current treatment strategies

First-line TKIs

Several randomized trials including EURTAC [16] and OPTIMAL [17] for erlotinib; NEJGSG_002 [18], WJTOG 3405 [19], and IPASS [20] for gefitinib; and LUX LUNG 3 [21] and LUX LUNG 6 [22] for afatinib have demonstrated the superiority of EGFR TKIs to chemotherapy in terms of overall response rates and progression-free survival (PFS) for first-line therapy (see Figure 1).

Erlotinib and gefitinib are first-generation reversible TKIs, while afatinib and lapatinib are second-generation irreversible pan-HER

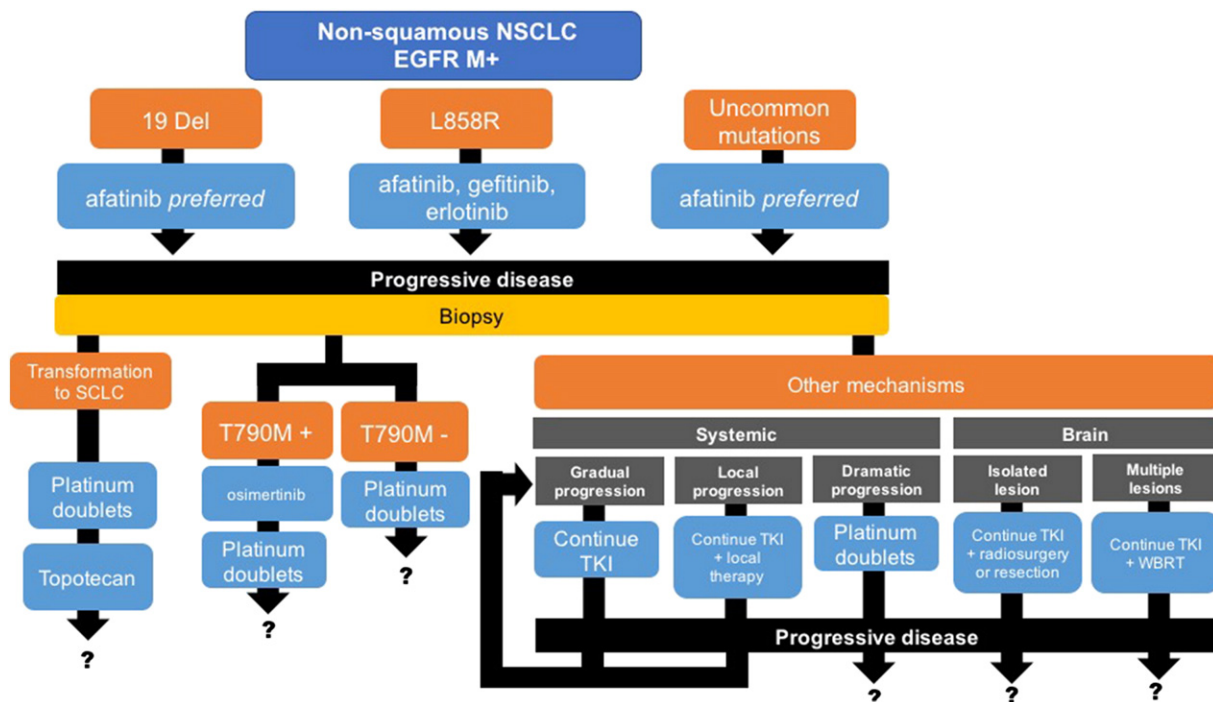


Figure 1. Patterns of clinical relapse and algorithm for EGFR mutation–positive NSCLC. Abbreviations: WBRT, whole brain radiotherapy; M+, mutation positive.

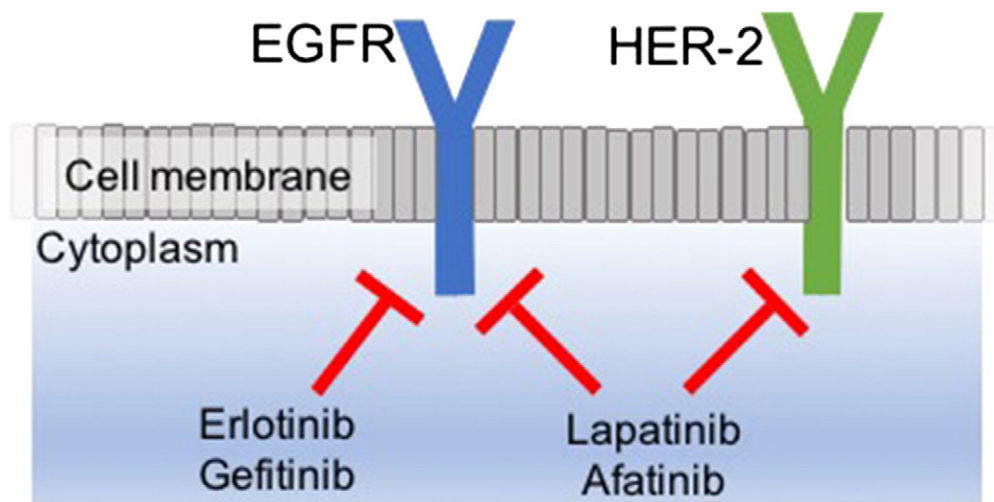


Figure 2. Mechanism of different EGFR TKIs. Abbreviations: HER-2, human epidermal growth factor receptor 2.

TKIs [23] that are reported to be superior to gefitinib in EGFR exon 19 deleted tumors and other less common mutations (see Figure 2).

Despite strikingly high initial response rates with these TKIs, the development after 11 to 14 months of acquired resistance, as defined by the Jackman criteria [24] (disease progression after objective response or durable stable disease for >6 months on a TKI), is a virtual *fait accompli* [25]. In over 60% of patients that have progressed on first- and second-generation TKIs, the mechanism of resistance is an acquired threonine-to-methionine amino acid substitution at the gatekeeper position 790 of EGFR in exon 20 or T790M [26], which increases the affinity of the EGFR kinase domain for ATP and thereby outcompetes the binding of EGFR TKIs; the T790M-resistant tumor cells may arise from the selective pressure of a TKI or present *de novo*. Based on data from the Phase II AURA 2 trial and the AURA extension cohort, T790M-positive tumors are responsive to treatment with the third-generation TKI osimertinib [27]. However, secondary mutations have also been described as a mechanism of acquired resistance to osimertinib. In addition to T790M, the occurrence of other resistance mechanisms including activation of the MET pathway, HER2 amplification, mutations in Pi3kinase and BRAF, and transformation to small cell lung cancer supports rebiopsy at clinical progression to determine the molecular/morphologic changes and to personalize the therapy accordingly.

Chemotherapy

After progression on osimertinib, despite a lack of strong supporting evidence (no prospective trials comparing the efficacy of chemotherapy regimens have been conducted), platinum doublets, e.g., cisplatin/carboplatin plus paclitaxel, nab-paclitaxel or pemetrexed \times 4 to 6 cycles \pm bevacizumab, are routinely recommended for patients without any targetable mutations followed by the option of single-agent pemetrexed, docetaxel, or erlotinib. For so-called T790M-negative tumors, second-line therapy is a chemotherapy doublet. Options for patients with T790M mutation-negative tumors that progress on chemotherapy are limited.

EGFR Inhibition Beyond Progression

Based on the concept of “oncogene addiction” in which tumors, dependent on oncogenes such as EGFR for their continued proliferation and survival, experience accelerated regrowth or “flare” after stopping TKI therapy, progressive disease on a TKI does not necessarily equate with

exhausted benefit. Accordingly, one option is to continue TKIs beyond progression in asymptomatic patients. In a 2013 study, Yang et al. [28], having stratified TKI-failed patients according to three types of progression (dramatic, gradual, and local), demonstrated that the continuation of EGFR TKI is feasible for gradual and local progression (+ local modalities such as surgical resection, stereotactic radiotherapy, and cryotherapy); continued sensitivity to therapy is suggested. For dramatic progression, chemotherapy, not EGFR TKI continuation, is indicated as well as a biopsy to rule out histologic transformation from NSCLC to small cell lung cancer, which constitutes an additional resistance mechanism to TKI therapy [29].

The effect of TKI continuation past true progression in EGFR⁺ NSCLC was also explored in the ASPIRATION “Asian Pacific Trial of Tarceva as First-Line in EGFR Mutation” and IMPRESS “IRESSA Mutation-Positive Multicenter Treatment Beyond Progression Study.” In the nonrandomized ASPIRATION (Asian Pacific trial of Tarceva as first-line in EGFR mutation) study, patients with indolent, small-volume asymptomatic growth, i.e., gradual progressors and oligometastatic progressors, selected at investigators’ discretion, that were continued on single-agent erlotinib beyond RECIST progression showed an improvement in PFS by 3.1 months [30] from 11.0 to 14.1.

However, in the randomized Phase 3 IMPRESS (IRESSA Mutation-Positive Multicenter Treatment Beyond Progression Study), patients that remained on gefitinib during doublet chemotherapy did not experience improved response rates or PFS, which established doublet chemotherapy as the standard of care after progression on EGFR TKIs [31]. Nevertheless, the overall consensus is that while dramatic progression mandates a change in treatment strategy, EGFR TKI continuation in the setting of oligometastatic disease is a feasible option [32] to delay the time to progression and the need for subsequent platinum-based treatments, eventually with the addition of local therapy.

Continuation of EGFR TKI with Brain Metastases

The incidence of brain metastases in NSCLC is 25% to 30%, and that incidence is increased in EGFR-mutated NSCLC to 44% to 63% [33], possibly because patients live longer on TKIs and the risk of brain metastases increases with lifespan or possibly because the propensity to metastasize is greater in EGFR-mutated cancers. For patients with oligometastatic progression in the brain after EGFR TKI therapy, the consensus is to continue EGFR TKI with local

therapies such as radiotherapy, surgery, and stereotactic ablative radiotherapy on the suspicion that poor blood brain barrier penetration of the TKI rather than cellular resistance [34] is to blame; in this case, EGFR TKI continuation may serve to maintain systemic remission. Jackman et al. [24]. demonstrated that high-dose gefitinib penetrates the blood-brain barrier more effectively, and likewise, pulsatile high-dose erlotinib was found to overcome acquired resistance to standard-dose erlotinib [35].

Treatment-Free Interval (Drug Holiday)

Despite the potential for disease flare during an EGFR TKI-free period, restoration of TKI sensitivity, which may be epigenetically mediated, has been documented after a drug holiday. In a study of 23 patients who were rechallenged with gefitinib after a median 7-month break, during which time they received cytotoxic anticancer therapy, Tomizawa et al. [36] reported a partial response rate of 22% and a disease control rate of 65%. In a retrospective study of 14 patients [37], reintroduction of erlotinib after a median 9.5-month holiday resulted in 36% ($n = 5$) partial response, 50% stable disease ($n = 7$), and 14% progressive disease ($n = 2$). However, these were small-scale studies, and further investigation from larger prospective trials is required to confirm these outcomes.

Alternative Treatment Strategies/Future Directions

Immunotherapy + TKI

Four randomized phase III trials have reported a statistically significant improvement in response rate (RR) and overall survival (OS) with immune checkpoint inhibitors such as nivolumab and pembrolizumab over standard second-line docetaxel chemotherapy in platinum-refractory NSCLC [38]. By contrast, EGFR-mutant advanced NSCLC patients gained no overall survival (OS) benefit from immune checkpoint inhibitors over docetaxel [39], which may be related to the general lack of tobacco use in this population since smoking is associated with a higher mutational burden, a biomarker of response to immunotherapy [40].

Nonetheless, PD-L1 expression has been associated with EGFR mutation [41], which has been reported to correlate with a higher likelihood of response to PD-1 blockade, suggesting that immunotherapy in EGFR-mutant NSCLC may still hold promise. However, despite evidence of clinical activity, combinations of nivolumab plus erlotinib, gefitinib plus durvalumab, and osimertinib plus durvalumab (anti-PD-L1 monoclonal antibody) resulted in a relatively high incidence of treatment-related grade 3 to 4 toxicities [42], and in fact, two trials with the osimertinib plus durvalumab combination were halted due to an excess of pulmonary toxicity. However, many new immunotherapy agents are under development including the inhibitory molecules TIM-3, LAG-3, IDO (indoleamine-pyrrole 2,3-dioxygenase), BTLA (B- and T-lymphocyte attenuator), adenosine, and VISTA (V-domain immunoglobulin containing suppressor of T cell activation) and the stimulatory molecules 4-1BB, OX40, CD40, and CD27. Therefore, the “jury is still out” on the clinical feasibility of immunotherapy in this population.

Mesenchymal-Epidermal Transition (MET) Inhibition

Amplification (but probably not mutation) of MET, a receptor tyrosine kinase, occurs in up to 20% of tumors [43] with acquired resistance to EGFR TKIs, which suggests the potential for synergistic benefit from combination treatment with an EGFR and MET inhibitor [44]. MET amplification and T790M mutation are not

mutually exclusive; both may coexist, or MET amplification may occur on its own. Therefore, concomitant inhibition of MET and EGFR is likely required. Several published case reports with a TKI + crizotinib, a known MET and ALK inhibitor that has demonstrated activity in MET-amplified patients, and other clinical data [26] support this assumption [45,46]. In a Phase 2 study with erlotinib + tivantinib, a selective c-MET inhibitor, in a TKI-failed EGFR-positive population, a subgroup of patients with high MET expression responded to the combination therapy, although the study as a whole did not meet its endpoint [47]. In a Phase 1b/2 study (NCT01610336), the combination of capmatinib (INC280), another MET inhibitor, and gefitinib in 65 high-MET EGFR TKI-resistant NSCLC patients yielded a disease control rate of 80% (overall response rate 18%; stable disease 62%) [48]. In a Phase 1 study of tepotinib (MSC2156119J) plus gefitinib, 18 patients were treated, and 5 had a partial response [49]. While the combination of MET inhibitors and EGFR TKIs seems promising, the potential for overlapping or additive toxicities based on the mechanisms of action of these agents is an important consideration, which requires testing in large clinical trials.

Oncolytic Virotherapy

Since nonsmoking EGFR-mutated NSCLC patients may resist checkpoint therapy due to a low mutational load, treatments like radiotherapy or virotherapy that induce the release of tumor antigens may augment the activity of PD-1/L1 inhibitors. As cancer-specific lytic agents, with or without therapeutic transgenes to augment the immune response, locally injected replicating oncolytic viruses that liberate nonself neoantigens for T-cell priming may elicit abscopal effects at distant metastatic sites; however, unlike radiotherapy, which also is associated with abscopal effects but may induce pneumonitis and scarring in the lungs, oncolytic viruses have been genetically engineered for attenuation and nonpathogenicity in normal cells and are, hence, in general, minimally host toxic.

The mechanism by which oncolytic viruses even in the absence of therapeutic transgenes kill tumor cells and elicit a systemic immune effect involves direct lysis of tumor cells and cell death via synthesis of new viral particles with subsequent spread of tumor-associated antigens and epitopes after the cell lysis [50]. When the virus is armed with therapeutic immunomodulatory transgenes, which theoretically enhance the immune response, the infected tumor cell serves as a “factory” for protein synthesis such that the beneficial transgene is overproduced and may spread to distant tumor sites via the circulation.

Talimogene laherparepvec (Imlygic), commonly referred to as T-VEC, an attenuated herpes simplex virus type 1 virus armed with a GM-CSF transgene that is approved for the treatment of melanoma [51], has the potential to overcome tumor-induced T-cell anergy and thereby enhance the activity of anti-CTLA and PD-1 antibodies in EGFR-mutated NSCLC. Several oncolytic adenoviruses carrying different immunomodulatory [52] transgenes and theoretically safer than herpes virus appear poised to enter the clinic in early 2018 as potential treatments for multiple tumor types including EGFR⁺ NSCLC.

Epigenetic Resensitization

The term “epigenetics” refers to reversible modifications that influence gene expression without directly changing or affecting the DNA coding sequence [53]. Epigenetic alterations, which include DNA methylation, microRNA regulation, and histone/nucleosome modifications, influence multiple cellular processes such as transcription, replication, and repair and are implicated in tumorigenesis and chemotherapy resistance [54,55]. Epigenetic mechanisms have been proposed to explain the

reversion to TKI sensitivity after a drug holiday. Epigenetic inhibitors such as histone deacetylators and DNA methyltransferases, which dynamically reprogram the epigenome, the collective name for chromatin and DNA modification patterns, have been associated with resensitization of several refractory tumor types including EGFR+ NSCLC to conventional therapies such as cisplatin and carboplatin. One such agent is the experimental tumor-associated macrophage and neutrophil-repolarizing agent RRx-001, which in Phase 2 clinical trials has been shown to resensitize refractory TKI- and chemotherapy-failed EGFR-positive NSCLC patients [27] to subsequently administered platinum doublets. If successful, the potential to reverse resistance to chemotherapy and possibly TKIs as well might significantly improve overall survival in this last-line population.

Conclusion and discussion

While EGFR TKI inhibitors yield impressive and durable responses, prolonged PFS, and improved quality of life when compared to chemotherapy, inevitable resistance to them as well as to subsequent platinum doublets is a “no man’s land” of unmet medical need, as patients at this terminal stage have exhausted all available lines of treatment. Careful analysis of resistance mechanisms and mutation status at the time of clinically significant disease progression may guide the selection of subsequent treatment, if one exists; but if not, the only options that remain to patients are local ablative therapies, clinical trials, or hospice with poor quality of life and death at the end of their palliative care. New strategies to prevent or reverse the development of resistance are therefore urgently needed and include immunotherapy, concomitant EGFR + MET inhibition, oncolytic virotherapy, epigenetic resensitization with subsequent administra-

tion of previously failed chemotherapies, and potentially the discovery of currently unknown driver mutations that synergize with all of the above especially immunotherapy.

The key advantage of immunotherapy in NSCLC is the durability of responses. Where resistance development is a near-universal feature of chemotherapy and targeted agents, the tumor-specific memory function of the immune system has the potential to confer lasting remission/regression of metastatic disease. However, as stated earlier in this review, EGFR-mutated tumors seem not to benefit from checkpoint inhibitors possibly due to a relatively low mutation burden despite higher levels of PD-L1 expression, which has been shown to correlate with response. Since it is infeasible to increase the mutational load in EGFR+ cancers, one strategy to refocus the immune response is to selectively increase the exposure/release of tumor neoantigens, inflammatory cytokines, and particular damage-associated molecular patterns that can stimulate the immune system and potentiate the efficacy of formerly inactive checkpoint inhibitors. If successful, targeted therapies such as dual EGFR + MET inhibition and particularly oncolytic virotherapy will mediate release of tumor neoantigens from lysed cells along with cytotoxics in epigenetically resensitized tumors.

On this basis, potentially optimal sequential immunotherapeutic priming strategies to trigger the release of immunogenic antigens from dying cancer cells in TKI- and chemotherapy-failed tumors might include 1) pretreatment of a non-MET-amplified tumor for several weeks with an epigenetic inhibitor before starting a cytotoxic like cisplatin or carboplatin for four to six cycles followed by checkpoint inhibition and 2) administration of oncolytic viruses in combination with EGFR TKI + MET targeted therapy in MET-amplified tumors followed by checkpoint inhibition (see Figure 3).

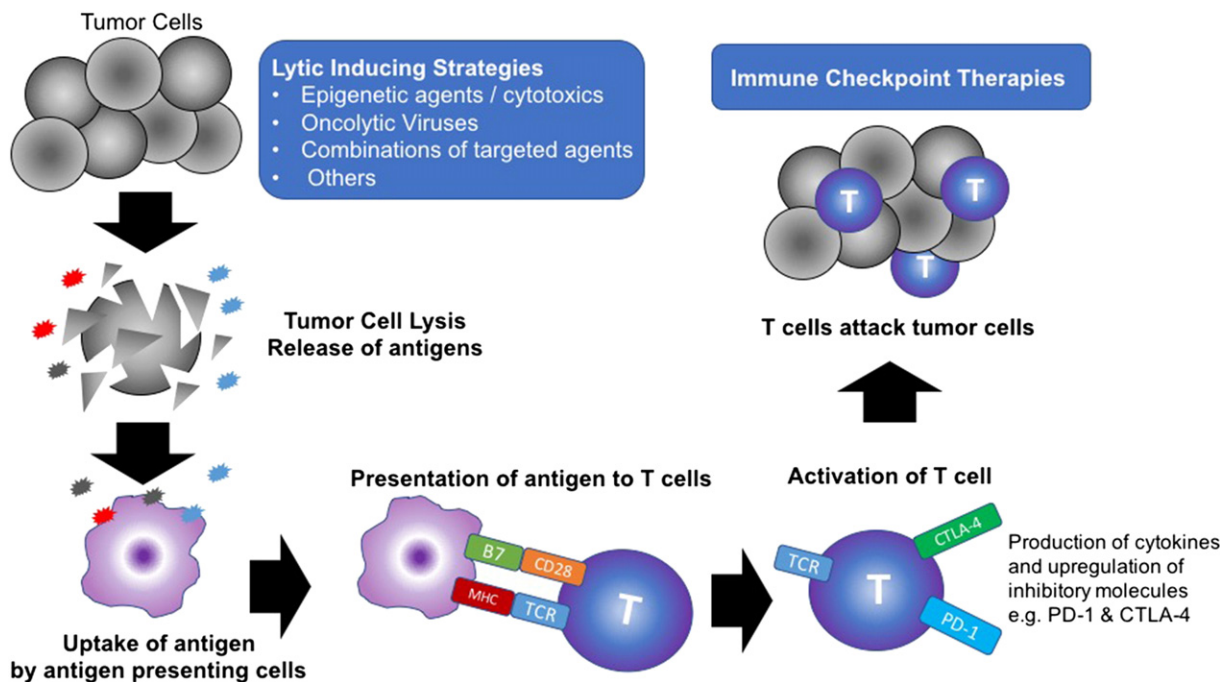


Figure 3. Lytic-inducing strategies in EGFR+ NSCLC are anticipated to result in the release of multiple tumor neoantigens. Tumor neoantigens are engulfed by antigen-presenting cells and processed and presented to T cells in the context of B7 costimulatory molecules and major histocompatibility complex. T cells express checkpoint inhibitory molecules such as PD-1 and CTLA-4, which prevent full activation. Immune checkpoint blockade relieves immune suppression, effectively taking the brakes off the T cells and restoring their effector function to effectively attack the tumor. Abbreviations: CTLA-4, cytotoxic T lymphocyte-associated protein 4; MCH, major histocompatibility complex; PD1, programmed cell death protein 1; PD-L1, PD1 ligand; TCR, T-cell receptor. Adapted from Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. *Cell* 2015;161:205-14.

The cancer-immunity cycle proposed by Chen and Mellman consists of seven steps [56]: 1) release of cancer antigens, 2) cancer antigen presentation, 3) priming and activation, 4) T-cell trafficking to tumors, 5) T-cell tumor infiltration, 6) recognition of cancer cells by T cells, and 7) killing of cancer cells.

In this cycle, the induction of an immune response begins when professional APCs, such as dendritic cells, engulf apoptotic or necrotic tumor cells and present tumor-associated antigens on their surface to their cognate T cells. A prerequisite for immune cell-mediated tumor cell destruction is interaction of the antigen-specific T cells with MHC-I-peptide complexes. Since NSCLC, like melanoma, kidney, and urothelial cancers, typically (although not always) presents as inflamed or T-cell rich, steps 1, 2, and 3 (i.e., release of cancer antigens, cancer antigen presentation, and priming and activation) arguably play the most important role in EGFR-mutated NSCLC.

In summary, while possibly an oversimplification of complex oncoimmunology, the overall low mutation load in EGFR+ NSCLC may render these tumors preferentially susceptible to lytic-inducing strategies that amplify intratumoral T cells against undefined antigens prior to administration of checkpoint inhibitors. Besides viruses, targeted therapies, epigenetic inhibitors, and cytotoxic chemotherapies other potentially lytic-inducing agents may include adoptive cell transfer therapies such as CAR-T, cytokines such as IL-2 and IL-15, bacteria and yeast vectors, and personalized polypeptide DNA vaccines that are selected on the basis of mutation status and MHC binding affinity.

The opposite of no man's land is a fertile plain. It is hoped that, in the near future, new, innovative strategies will be available to overcome resistance mechanisms, especially immunologically based resistance mechanisms, and thereby transform the no man's land of TKI- and chemotherapy-failed EGFR+ NSCLC into a vast fertile plain, rich with promising therapeutic options that result in meaningful improvements to quality of life and survival.

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Ethical Approval

This review article does not contain any studies with human participants or animals.

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