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REVIEW

MOLECULAR TARGETS OF NON-SMALL CELL LUNG CANCER OUTSIDE THE "TOP THREE"

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ABSTRACT

Lung cancer (LC) is the most frequent cancer and the leading cause of cancer death in men in Russia and other countries. The majority of new LC cases are diagnosed in patients over 65 years old, and the number is growing. LC is a heterogeneous group of malignant tumors with different genetic and biological characteristics. Although smoking is considered the leading cause of non-small cell lung cancer (NSCLC), genetic predisposition and environmental influences are responsible for 10–15 % of cases. The tactics of treating patients with NSCLC alone has long been developed and, as a rule, does not cause any difficulties. Surgery is the main treatment for the early NSCLC stages. However, as the disease progresses the risk of metastasis increases and the effectiveness of the surgical treatment decreases sharply. The development of new medical therapy regimens and the use of targeted drugs have improved the survival rate of LC patients with carcinogenic driver mutations. Personalized treatments are becoming more available as sequencing technology develops. Targeted therapy undoubtedly improves the outcomes of NSCLC patients with tumors carrying carcinogenic EGFR driver mutations, ALK fusion, and ROS1 rearrangement. However, in addition to the main molecular targets, other genetic alterations have been identified and studied, such as: KRAS, MET, RET, HER2 and NRG. Some of these mutations (BRAF and NTRK) are already available for targeted therapy. The list of genetic alterations is growing and the molecular profiling of patients with NSCLC is expanding, which is very important in the progression of the disease. Molecular genetic selection identifies specific groups of patients who benefit from targeted therapy and provides insight into the potential mechanisms of resistance. Despite the progress made, further studies are needed to clarify interactions with immune cells in the tumor microenvironment as factors affecting survival. In addition, it is becoming increasingly important to study targeted therapy in the context of multimodal treatment. This review is devoted to understanding genetic changes, searching for new genetic targets, problems and future directions of development of targeted therapy in the treatment of patients with lung tumors.

Keywords:
genetic alterations, KRAS, BRAF, HER2, NTRK, RET, MET, targeted therapy

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ОБЗОР

МОЛЕКУЛЯРНЫЕ МИШЕНИ НЕМЕЛКОКЛЕТОЧНОГО РАКА ЛЕГКОГО ВНЕ «ГЛАВНОЙ ТРОЙКИ»

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РЕЗЮМЕ

Рак легкого (РЛ) занимает первое место в структуре общей онкологической заболеваемости и смертности у мужчин как в России, так и в зарубежных странах. Большинство новых случаев РЛ диагностируется у пациентов старше 65 лет, и в последние годы наблюдается тенденция к увеличению данного показателя. РЛ представляет собой гетерогенную группу злокачественных опухолей с различными генетическими и биологическими характеристиками. Несмотря на то, что курение считается основной причиной немелкоклеточного рака легкого (НМРЛ), генетическая предрасположенность и воздействие окружающей являются причиной развития 10–15 % случаев заболевания. Тактика лечения пациентов с одним НМРЛ давно отработана и, как правило, не вызывает никаких трудностей. Хирургическое вмешательство является основным методом лечения ранних стадий НМРЛ. Однако, по мере прогрессирования заболевания возрастает риск метастазирования, и в этом случае эффективность хирургического метода лечения резко снижается. Разработка новых схем лекарственной терапии, использование таргетных препаратов улучшила выживаемость больных с РЛ, несущими онкогенные драйверные мутации. Персонифицированное лечение становится все более доступным по мере развития технологии секвенирования. Таргетная терапия несомненно улучшает исходы больных НМРЛ, опухоли которых несут онкогенные драйверные мутации EGFR, слияние ALK и реаранжировки ROS1. Однако, помимо основных молекулярных мишеней, выявлены и изучаются другие генетические альтерации, такие как: вирусный онкоген Kirsten RAS (KPAS), MET, RET, HER2 и NRG. Некоторые из таких мутаций (BRAF и NTRK) уже доступны для таргетной терапии. Перечень генетических альтераций растет и расширяется молекулярное профилирование больных НМРЛ, что имеет весьма важное значение при прогрессировании заболевания. Молекулярно-генетический отбор идентифицирует конкретные группы пациентов, которые получают пользу от таргетной терапии и дает представление о потенциальных механизмах резистентности. Несмотря на достигнутый прогресс, необходимы дальнейшие исследования для выяснения взаимодействий с иммунными клетками в микроокружении опухоли как факторов, влияющих на выживаемость. Кроме того, становится все более важным изучение таргетной терапии в контексте мультимодального лечения. Настоящий обзор посвящен пониманию генетических изменений, поиску новых генетических мишеней, проблемам и будущим направлениям развития таргетной терапии в лечении пациентов с опухолями легких.

Ключевые слова:
генетические альтерации, KRAS, BRAF, HER2, NTRK, RET, MET, таргетная терапия

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INTRODUCTION

Lung cancer is a heterogeneous genomic disease [1]. Despite the fact that smoking is considered the main cause of non-small-cell lung cancer (NSCLC), genetic predisposition and environmental exposure are responsible for the development of 10–15 % of cases of the disease. Targeted therapy improved the survival of patients with tumors carrying oncogenic driver mutations [2]. There is an obvious need to deepen knowledge about genetic changes in NSCLC in order to create new targeted drugs. This review examines molecular genetic targets that are outside of the epidermal growth factor receptor (UPAC) gene mutation, ADC fusion and ROS1 rearrangement, new drugs, problems and future directions of targeted therapy development.

Viral oncogene KRAS

The viral oncogene Kirsten RAS (KRAS) is the most frequently mutating isoform of the RAS family and is found in 22 % of solid tumors, being one of the most common oncogenic driver mutations in cancer [3]. KRAS mutations are present in approximately 20–30 % of NSCLC patients. Despite the early discovery of the mutation, KRAS-mutant NSCLC is very heterogeneous, and therapy aimed at the KRAS mutation is just beginning to develop [4]. Most KRAS mutations were found in exons 12 and 13: 012C – 39 %, G12V –18–21 % and G12D – 17–18 % [5]. The presence of the KRAS mutation in the tumor is associated with a worse prognosis of NSCLC [6].

KRAS is one of the 4 proteins encoded by the RAS gene, guanosine triphosphate binds to KRAS in the active state, and guanosine diphosphate binds to KRAS in the inactive state. Activating point KRAS mutations initiate oncogenesis by losing the activity of GTPases (GTPase – guanosine triphosphate hydrolase enzymes), which leads to an active state and constantly activates the downstream signaling pathways of PI3K and MARK, causing resistance of NSCLC to existing drug therapy methods [7].

Early attempts to use the KRAS mutation as a target for targeted therapy failed due to the lack of known allosteric binding sites, alternative pathways, and the high affinity of the protein to the active guanosine triphosphate-bound state [8]. Combination therapy with (MEK1/MEK2) MARK kinase inhibitors formed the basis of a phase 2 clinical trial in patients with advanced KRAS-mutant NSCLC. The combination of selumetinib with docetaxel resulted in an increase in the overall response to treatment (ORR- Overall Tumor Responses Rate) to 37 % and the duration of median survival to progression (RFS) by 3.2 months. compared to patients who received only docetaxel. In the combination therapy group, there was an increase in the number of adverse toxic events of the 3rd degree by 15 %, among which neutropenia, febrile neutropenia and asthenia prevailed [9]. As a result, the study demonstrated sufficient effectiveness, but at the expense of increased toxicity. Another phase 1 study showed that in patients with KRAS-mutant NSCLC treated with trametinib with docetaxel, ORR reached 24 %, while in patients treated with trametinib with pemetrexed, this indicator was 17 % [10].

The first phase 1 clinical trial of the small molecule AMG 510, which specifically and irreversibly inhibits the KRAS G12C mutation by blocking it in the bound state, presented immediate results of treatment of 22 patients with progressive solid tumors carrying the KRAS G12C mutation. Of the 6 patients with NSCLC, 2 had a partial response after 6 weeks of treatment and 2 more had stabilization of the disease. The average duration of therapy, which was well tolerated, was 9.7 weeks [11]. Adverse toxic phenomena of the 1st degree were noted in 68 % of observations; two toxic reactions of the 3rd degree, namely anemia and diarrhea, have been reported.

A study examining KRAS co-mutations found lower response rates of KRAS-mutant lung adenocarcinomas with inactivation of KEAR1 (Kelch-like ECH-associated protein 1) [12]. A subset of tumors resistant to anti-PD1 antibodies was characterized by low expression of PD-L1 and inactivation of the tumor suppressor gene STK11/LKB1 (Serine – Threonine Kinase 11/Liver kinase B1), which led to the accumulation of tumor-associated neutrophils with a suppressive effect on T cells [13]. Somatic mutations of LCV1 are noted in about 30 % of lung adenocarcinomas. Preliminary studies have shown that NSCLC with KRAS/LKB1 co-mutations clearly responds to targeted therapy. A study on mice with KRAS/LKB1 or KRAS/p53 mutations revealed a selective apoptotic response of KRAS/LKB1 – mutant NSCLC to the metabolic drug phenformin, an analog of metfurmin. Apoptosis is observed in NSCLC cell lines with the LKB1 mutation, but not with wild-type KRAS [14]. Thus, KRAS – mutant NSCLC is once again becoming a rapidly developing area of research for

the development of new treatment options for patients with unrealized liver needs.

BRAF proto-oncogene

The BRAF proto-oncogene encodes serine/threonine kinase, which is located below RAS and leads to the transmission of signals via RAS-RAF (rapidly accelerated fibrosrcoma) – MARK (mitogen-activated protein kinase) – MARK/ERK (extracellular-signal-regulated kinase) MARK/ERK signaling pathway, which is a key molecular cascade regulating cell growth [15]. After the discovery of BRAF mutations in melanoma, mutant BRAF was found to mediate lung adenocarcinoma carcinogenesis. BRAF mutations are detected in 2–3 % of lung adenocarcinomas and in 50–75 % are represented by the BRAF V600E mutation, more often observed in smokers or quit smoking patients [16; 17].

Vemurafenib has demonstrated its effectiveness in patients with generalized NSCLC carrying the BRAF V600E mutation [18; 19]. Dabrafenib was studied in a phase 2 clinical trial in patients with BRAF V600E mutant metastatic NSCLC [20]. ORR reached 33 %, and the median overall survival(s) was 12.7 months. The combination of dabrafenib and trametinib was studied in another phase 2 study in patients with BRAF V600E mutant NSCLC. Combination therapy led to an increase in ORR to 63.2 % and was approved by the European Medicines Agency and the US FDA (Food and Drug Administration) for the treatment of patients with stage IV BRAF V600E mutant NSCLC [7].

Neurotrophin tyrosine kinase receptor

The tropomyosin receptor kinase (TRK) gene encodes tyrosine kinase receptors for neurotrophins found in many tissues and associated with the nerve growth factor family. Three members of the family are proto-oncogenes encoded by NTRK1, NTRK2 and NTAK3, which respectively produce TrkA, TrkB and THC proteins, activation of which leads to the transmission of signals along the signaling pathways of MARK and ACT, leading to cell proliferation, differentiation and survival [21]. NTRK rearrangements occurring in all 3 genes have been identified in various malignancies, including lung cancer [22]. Less than 1 % of cases of NSCLC carry NTRK mergers and occur in men and women of different ages with different smoking history [23].

Numerous tyrosine kinase inhibitors (TRK) are being investigated in the treatment of malignant tumors with altered NTRK. The US FDA approved the appointment of larotrectinib and entrectinib for the treatment of solid tumors with NTRK mutations in adults and children [21]. The first report of a patient with a regression of the tumor carrier NTRK fusion, achieved as a result of the appointment of a selective tyrosine kinase inhibitor larotrectinib, dates back to 2015 [24]. Subsequently, the inhibition of tumor growth was confirmed experimentally. In a phase 1 clinical trial, larotrectinib was studied in adults and children with different tumors carrying NTRK mergers. In 55 patients with 13 types of tumors included in the study, the most common were NTRK3 mergers (n = 29), followed by NTRK1 (n = 25) and NTRK2 (n = 1). As a result, the study demonstrated an overall response rate of 75 % to therapy [25].

The results of the phase 1 study of entrectinib indicated the antitumor activity of the drug in a patient with NTRK 1 positive NSCLC [26].

Analysis of the results of 3 studies of entrectinib, which included 54 patients with NTRK or ROS1 positive tumors, demonstrated an ORR equal to 57 % with a median progression-free survival of 11.2 months and a median of 20.9 months [27]. Additional clinical trials of TRK inhibitors are currently underway.

Epidermal growth factor receptor 2

The human epidermal growth factor receptor 2 (NR2), a member of the ErbB receptor tyrosine kinase family, activates signaling via the RISC–ACT and MEK–EAK signaling pathways. NONR2 is activated by homo- and heterodimerization with other members of the ErbB family, but has no established ligand [28]. Overexpression of NR2 is observed in 13–20 % of cases of NSCLC and is more common in women who have never smoked with adenocarcinoma [29]. HER2 mutations are oncogenic and lead to constitutive HER2 phosphorylation and activation of EGFR stimulating signaling pathways. Amplification and mutations of NONR2 are rare, accounting for 9 % and 3 % of cases of NSCLC, respectively [30]. NONR2 mutations usually occur in exons 18–21, usually in exon 20 in codon 776 with a 12-pair duplication/insertion of the YVMA amino acid sequence. It remains unclear whether patients with NONR2 mutant NSCLC have a worse outcome compared to other patients.

A prospective study of the pan-HER tyrosine kinase inhibitor dacomitinib, irreversibly binding NONR2, NONR1(EGFR) and HER4, included 26 patients with NONR2-mutated and 4 with NONR2-amplified NS-

CLC [31]. The overall response rate to therapy was 12 % in patients with NONR2 – mutant NSCLC; in patients with NONR2-amplified NSCLC, no tumor response was registered in any observation. Median RES was 3 months for all patients. In the group of NONR2 mutant tumors, the median progression-free survival was also 3 months. with a one-year OV equal to 44 %. Pan-HER tyrosine kinase inhibitor afatinib, has shown limited action in NONR2-mutant NSCLC. The study of afatinib activity showed a median progression-free survival of 15.9 weeks, and a median of 56 weeks [32].

Other low-molecular-weight TCS are also being tested. Thus, with monotherapy with the irreversible pan-HER inhibitor neratinib, the median PFS was 2.9 months. Median PFS increased to 4 months. with the combined appointment of neratinirb and temsirolimus [33].

It was found that the response to neratinib varied depending on co-mutations and parallel activation of signaling pathways. Patients with NONR2-mutant NSCLC were characterized by a very low response rate and often had co-mutations in TP53 and NONR3. Activation of the RAS/RAF signaling pathway coinciding with aberrations of cell cycle control points was associated with worse results and generally with a lack of clinical efficacy [34].

Antibody-based drugs have shown efficacy against NONR2-mutant NSCLC. In a phase 2 study, 18 patients with NONR2 mutant lung adenocarcinomas were treated with T-DM1 with a 44 % partial response rate and a median PFS of 5 months [35].

A European retrospective study analyzed data from 101 patients with NONR2-mutant NSCLC who received chemotherapy and/or NONR2-targeted therapy. The median OV was 24 months for all patients, despite whether or not targeted therapy was performed. The overall response to treatment was highest in patients who received trastuzumab with or without chemotherapy, or in those who received T-DM1 with a median PFS of 4.8 months [36].

Mesenchymal-epithelial junction (MET) is a protooncogene encoding transmembrane METH. Binding of the hepatocyte growth factor ligand by it activates the signaling pathways PI3K/ACT, MARK, NF-KB, as well as a signal transductor and activator of transcription proteins that promote proliferation, increase cell mobility and invasion, block apoptosis. METH alterations are found in many cancers, including NSCLC. They induce tumor progression through gene amplification, mutations, rearrangements, overexpression and phosphorylation of proteins [37].

MET-positive NSCLC is most often manifested by overexpression of proteins, while MET amplification is relatively rare and is observed in about 2.2 % of newly diagnosed cases of adenocarcinoma and up to 7 % of cases of all NSCLC. The amplification of the MET gene is a negative prognostic factor in the surgical treatment of NSCLC with an OV equal to 25.5 months in patients with 5 or more copies per cell versus 47.5 months for patients with less than 5 copies per cell, respectively. KIF5B MergerMETH was registered in lung adenocarcinoma, other METH rearrangements are rare [38].

Alterations of the MET gene in exon 14, observed in 4 % of lung adenocarcinomas, are diverse and lead to carcinogenesis; changes are associated with age and a long history of smoking [39]. Substitutions of bases or deletions in MET that violate the 3' or 5' sites of the intron 14 junction lead to the omission of the 14 exon of MET. The omission of exon 14 causes a decrease in ubiquitination and degradation of METH, which leads to an increase in the level of METH and the downward transmission of a signal stimulating carcinogenesis. Alterations of the 14 exon of MET vary widely. 126 different variants were identified in 223 different aberrations of 14 exons [40].

Multi-purpose TKI and TKI with increased sensitivity to METH are used against METH alterations. In addition, monoclonal antibodies are being studied in patients with METH-driver tumors. The dual MET/ALK inhibitor crizotinib demonstrated objective responses of MET-amplified and MET-mutant NSCLC [40]. Additionally, the combination of crizotinib with cabozantinib causes an antitumor response in patients with lung adenocarcinoma carrying a MET mutation in exon 14. A phase 1 clinical study showed that in patients with NSCLC with a high level of METH amplification, crizotinib has antitumor activity with a median PFS of 6.7 months [41].

A phase 2 study considered a specific MET inhibitor for the MET mutant in exon 14 of NSCLC-tepotinib. In patients with MET mutation identification by liquid biopsy, preliminary results showed a 50 % level of objective response with a median PSF of 9.5 months; in patients with mutation detection in tumor tissue during biopsy, the level of objective response was 45.1 % with a median PSF of 10.8 months [42].

In another phase 2 study, a specific MET inhibitor capmatinib was studied in progressive NSCLC

carrying a MET mutation in exon 14. According to preliminary data, the level of objective response was 40.6 %, and the median PFS was 5.42 months. Previously untreated patients had an objective response rate of 67.9 % and a median PFS of 9.69 months [43]. Kapmatinib has demonstrated action against brain metastases and good tolerability.

A specific biomarker for the selection of patients remains unidentified, therefore, at present, the detection of mutation is a predictor of an effective response to NONR2-targeted therapy. Molecular aberrations in NONR2 mutant NSCLC are heterogeneous, which determines the different effectiveness of NONR2 kinase inhibitors. It is necessary to take into account important characteristics such as the type of mutation, the presence of NONR2 amplification, expression and parallel activation of signaling pathways.

Proto-oncogene (RET)

RET – receptor tyrosine kinase mediating the development of the neural crest, the activation of which causes cell proliferation, migration and differentiation of cells [44]. Alterations of RET genes are most common in thyroid and lung cancers [45]. With NSCLC, fusion with KIF5B is most common. RET mergers lead to ligand-independent dimerization and activation of the downstream signaling pathway.

RET mergers occur in approximately 1.4 % of cases of NSCLC and in 1.7 % of lung adenocarcinomas and are found mainly in non-smoking patients older than 60 years. An NGS study of more than 4,800 patients with various malignancies showed that the altered status of the RET gene occurs in 1.8 % of cases, most of which had concomitant genomic changes, suggesting that successful treatment should include individual combined approaches [46].

Various multikinase TKIs have been studied with NSCLC carrying RET rearrangements. A prospective phase II study to evaluate the efficacy of cabozantinib in 25 patients with RET-positive lung adenocarcinoma revealed a 28 % response rate to therapy with a median PFS of 5.5 months and median S = 9.9 months [47]. A similar clinical study of vandetanib in 19 patients with PFS-positive NSCLC showed a 53 % overall response rate with a median RET of 4.7 months [48]. The global multicenter registry contains data on the results of treatment of 165 patients with RET-positive NSCLC, of which 53 were prescribed at least one RET inhibitor therapy [49]. The use of cabozantinib, sunitinib and vandetanib gave an overall response rate of 37 %, 22 % and 18 %, respectively, in addition, lenvatinib and nantedanib also caused a tumor response. In all patients, the median PFS was 2.3 months, and the median S reached 6.8 months. Despite the fact that studies have confirmed the inhibitory activity of multikinase TKI in RET-positive NSCLC, the reaction to them was modest and short-lived.

RET-specific inhibitors are being developed in the hope of overcoming the limitations inherent in multikinase inhibitors. A report on patients with RET-positive malignancies showed that the powerful KW inhibitor LOXO-292 caused a general response to treatment in 65 % of 26 patients with NSCLC. BLU-667, another selective RET inhibitor, has demonstrated activity in preclinical studies and objective tumor responses in patients with RET-positive NSCLC [50]. A study of 48 patients showed a 58 % overall response rate for the entire group, in addition, BLU-667 is effective in patients with various KW mergers and metastases [51; 52].

Neuroregulin 1

The neuregulin 1 gene (NRG1) encodes the neuregulin protein. Unlike other mergers in NSCLC, NRG1 encodes the tyrosine kinase receptor ligand HERZ and HER4. In these mergers, NRG1 is a 3' partner, other genes such as CD74, RBPMS, WRN and SDC4 are 5' partners. The EGF domain NRG1, located in the carboxy-terminal region, is necessary for the interaction of receptors. NRG1 mergers in NSCLC samples are detected in isolation from other known driver mutations [53; 54]. CD74-NRG1 mergers account for 1.7 % of lung adenocarcinomas and are most often found in invasive mucinous adenocarcinoma subtype of NSCLC, which accounts for 2 % to 10 % of all cases of lung adenocarcinoma [55]. CD74-NRG1 fusion causes activation of the PI3K ACT signaling pathway, which induces carcinogenesis.

Despite the small amount of data available, an in vitro study showed that lapatinib and afatinib inhibit the phosphorylation of HER2, HER3 and ERK produced by CD74-NERG1 fusion. In two cases of NSCLC carrying NRG1 fusion, a response to therapy with afatinib, an inhibitor of HER2, was noted. Median PFS with NSCLC carrying the fusion of SLC3A2-NRG1 and CD74-NRG1 was 12 months and 10 months, respectively. Recently, it was reported that a patient with CD74-NRG1-positive NSCLC reacted to the introduction of a monoclonal antibody against HER3 for 19 months [56].

CONCLUSION

Lung cancer is a heterogeneous group of malignant tumors with different genetic and biological characteristics. Molecular genetic studies determine the appropriate therapy for many patients with NSCLC by precision drug exposure to specific alterations. The list of genetic alterations is growing and expanding molecular profiling of patients with NSCLC is very important in the progression of the disease. Molecular genetic selection identifies specific groups of patients who benefit from targeted therapy and provides insight into the potential mechanisms of resistance. Despite the progress made, further studies are needed to clarify interactions with immune cells in the tumor microenvironment as factors affecting survival. In addition, it is becoming increasingly important to study targeted therapy in the context of multimodal treatment.

References

1. Govindan R, Ding L, Griffith M, Subramanian J, Dees ND, Kanchi KL, et al. Genomic landscape of non-small cell lung cancer in smokers and never-smokers. Cell. 2012 Sep 14;150(6):1121–1134. https://doi.org/10.1016/j.cell.2012.08.024
2. Kris MG, Johnson BE, Berry LD, Kwiatkowski DJ, Iafrate AJ, Wistuba II, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. JAMA. 2014 May 21;311(19):1998–2006. https://doi.org/10.1001/jama.2014.3741
3. Prior IA, Lewis PD, Mattos C. A comprehensive survey of Ras mutations in cancer. Cancer Res. 2012 May 15;72(10):2457–2467. https://doi.org/10.1158/0008-5472.CAN-11-2612
4. Horn L, Cass AS. Current Landscape of Personalized Therapy. Thorac Surg Clin. 2020 May;30(2):121–125. https://doi.org/10.1016/j.thorsurg.2020.01.011
5. Dogan S, Shen R, Ang DC, Johnson ML, D'Angelo SP, Paik PK, et al. Molecular epidemiology of EGFR and KRAS mutations in 3,026 lung adenocarcinomas: higher susceptibility of women to smoking-related KRAS-mutant cancers. Clin Cancer Res. 2012 Nov 15;18(22):6169–6177. https://doi.org/10.1158/1078-0432.CCR-11-3265
6. Johnson ML, Sima CS, Chaft J, Paik PK, Pao W, Kris MG, et al. Association of KRAS and EGFR mutations with survival in patients with advanced lung adenocarcinomas. Cancer. 2013 Jan 15;119(2):356–362. https://doi.org/10.1002/cncr.27730
7. Karen KL. Molecular Targets Beyond the Big 3. Thorac Surg Clin. 2020 May;30(2):157–164 https://doi.org/10.1016/j.thorsurg.2020.01.004
8. Ostrem JM, Peters U, Sos ML, Wells JA, Shokat KM. K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. Nature. 2013 Nov 28;503(7477):548–551. https://doi.org/10.1038/nature12796
9. Jänne PA, Shaw AT, Pereira JR, Jeannin G, Vansteenkiste J, Barrios C, et al. Selumetinib plus docetaxel for KRAS-mutant advanced non-small-cell lung cancer: a randomised, multicentre, placebo-controlled, phase 2 study. Lancet Oncol. 2013 Jan;14(1):38–47. https://doi.org/10.1016/S1470-2045(12)70489-8
10. Gandara DR, Leighl N, Delord J-P, Barlesi F, Bennouna J, Zalcman G, et al. A Phase 1/1b Study Evaluating Trametinib Plus Docetaxel or Pemetrexed in Patients With Advanced Non-Small Cell Lung Cancer. J Thorac Oncol. 2017 Mar;12(3):556–566. https://doi.org/10.1016/j.jtho.2016.11.2218
11. Fakih M, O'Neil B, Price T, Falchook G, Desai J, Kuo J, et al. Phase 1 study evaluating the safety, tolerability, pharmacokinetics (PK), and efficacy of AMG 510, a novel small molecule KRAS G12C inhibitor, in advanced solid tumors. Journal of Clinical Oncology. 2019 May 20;37:3003–3003. https://doi.org/10.1200/JCO.2019.37.15_suppl.3003
12. Jeanson A, Tomasini P, Souquet-Bressand M, Brandone N, Boucekine M, Grangeon M, et al. Efficacy of Immune Checkpoint Inhibitors in KRAS-Mutant Non-Small Cell Lung Cancer (NSCLC). J Thorac Oncol. 2019 Jun;14(6):1095–1101. https://doi.org/10.1016/j.jtho.2019.01.011
13. Skoulidis F, Goldberg ME, Greenawalt DM, Hellmann MD, Awad MM, Gainor JF, et al. STK11/LKB1 Mutations and PD-1 Inhibitor Resistance in KRAS-Mutant Lung Adenocarcinoma. Cancer Discov. 2018 Jul;8(7):822–835. https://doi.org/10.1158/2159-8290.CD-18-0099
14. Shackelford DB, Abt E, Gerken L, Vasquez DS, Seki A, Leblanc M, et al. LKB1 inactivation dictates therapeutic response of non-small cell lung cancer to the metabolism drug phenformin. Cancer Cell. 2013 Feb 11;23(2):143–1¬58. https://doi.org/10.1016/j.ccr.2012.12.008
15. Cardarella S, Ogino A, Nishino M, Butaney M, Shen J, Lydon C, et al. Clinical, pathologic, and biologic features associated

with BRAF mutations in non-small cell lung cancer. Clin Cancer Res. 2013 Aug 15;19(16):4532–4540. https://doi.org/10.1158/1078-0432.CCR-13-0657
16. Paik PK, Arcila ME, Fara M, Sima CS, Miller VA, Kris MG, et al. Clinical characteristics of patients with lung adenocarcinomas harboring BRAF mutations. J Clin Oncol. 2011 May 20;29(15):2046–2051. https://doi.org/10.1200/JCO.2010.33.1280
17. Litvak AM, Paik PK, Woo KM, Sima CS, Hellmann MD, Arcila ME, et al. Clinical characteristics and course of 63 patients with BRAF mutant lung cancers. J Thorac Oncol. 2014 Nov;9(11):1669–1674. https://doi.org/10.1097/JTO.0000000000000344
18. Gautschi O, Pauli C, Strobel K, Hirschmann A, Printzen G, Aebi S, et al. A patient with BRAF V600E lung adenocarcinoma responding to vemurafenib. J Thorac Oncol. 2012 Oct;7(10):e23–24. https://doi.org/10.1097/JTO.0b013e3182629903
19. Hyman DM, Puzanov I, Subbiah V, Faris JE, Chau I, Blay J-Y, et al. Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. N Engl J Med. 2015 Aug 20;373(8):726–736. https://doi.org/10.1056/NEJMoa1502309
20. Planchard D, Kim TM, Mazieres J, Quoix E, Riely G, Barlesi F, et al. Dabrafenib in patients with BRAF(V600E)-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial. Lancet Oncol. 2016 May;17(5):642–650. https://doi.org/10.1016/S1470-2045(16)00077-2
21. Vaishnavi A, Le AT, Doebele RC. TRKing down an old oncogene in a new era of targeted therapy. Cancer Discov. 2015 Jan;5(1):25–34. https://doi.org/10.1158/2159-8290.CD-14-0765
22. Vaishnavi A, Capelletti M, Le AT, Kako S, Butaney M, Ercan D, et al. Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer. Nat Med. 2013 Nov;19(11):1469–1472. https://doi.org/10.1038/nm.3352
23. Farago AF, Taylor MS, Doebele RC, Zhu VW, Kummar S, Spira AI, et al. Clinicopathologic Features of Non-Small-Cell Lung Cancer Harboring an NTRK Gene Fusion. JCO Precis Oncol. 2018;2018. https://doi.org/10.1200/PO.18.00037
24. Doebele RC, Davis LE, Vaishnavi A, Le AT, Estrada-Bernal A, Keysar S, et al. An Oncogenic NTRK Fusion in a Patient with Soft-Tissue Sarcoma with Response to the Tropomyosin-Related Kinase Inhibitor LOXO-101. Cancer Discov. 2015 Oct;5(10):1049–1057. https://doi.org/10.1158/2159-8290.CD-15-0443
25. Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. N Engl J Med. 2018 Feb 22;378(8):731–739. https://doi.org/10.1056/NEJMoa1714448
26. Farago AF, Le LP, Zheng Z, Muzikansky A, Drilon A, Patel M, et al. Durable Clinical Response to Entrectinib in NTRK1-Rearranged Non-Small Cell Lung Cancer. J Thorac Oncol. 2015 Dec;10(12):1670–1674. https://doi.org/10.1097/01.JTO.0000473485.38553.f0
27. Siena S, Doebele R, Shaw A, Karapetis C, Tan D, Cho B, et al. Efficacy of entrectinib in patients (pts) with solid tumors and central nervous system (CNS) metastases: Integrated analysis from three clinical trials. Journal of Clinical Oncology. 2019 May 20;37:3017–3017. https://doi.org/10.1016/S1470-2045(19)30691-6
28. Peters S, Zimmermann S. Targeted therapy in NSCLC driven by HER2 insertions. Transl Lung Cancer Res. 2014 Apr;3(2):84–88. https://doi.org/10.3978/j.issn.2218-6751.2014.02.06
29. Mazieres J, Peters S, Lepage B, Cortot AB, Barlesi F, Beau-Faller M, et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. J Clin Oncol. 2013 Jun 1;31(16):1997–2003. https://doi.org/10.1200/JCO.2012.45.6095
30. Landi L, Cappuzzo F. HER2 and lung cancer. Expert Rev Anticancer Ther. 2013 Oct;13(10):1219–12¬28. https://doi.org/10.1586/14737140.2013.846830
31. Kris MG, Camidge DR, Giaccone G, Hida T, Li BT, O'Connell J, et al. Targeting HER2 aberrations as actionable drivers in lung cancers: phase II trial of the pan-HER tyrosine kinase inhibitor dacomitinib in patients with HER2-mutant or amplified tumors. Ann Oncol. 2015 Jul;26(7):1421–1427. https://doi.org/10.1093/annonc/mdv186
32. Dziadziuszko R, Smit EF, Dafni U, Wolf J, Wasąg B, Biernat W, et al. Afatinib in NSCLC With HER2 Mutations: Results of the Prospective, Open-Label Phase II NICHE Trial of European Thoracic Oncology Platform (ETOP). J Thorac Oncol. 2019 Jun;14(6):1086–1094. https://doi.org/10.1016/j.jtho.2019.02.017
33. Gandhi L, Bahleda R, Tolaney SM, Kwak EL, Cleary JM, Pandya SS, et al. Phase I study of neratinib in combination with temsirolimus in patients with human epidermal growth factor receptor 2-dependent and other solid tumors. J Clin Oncol. 2014 Jan 10;32(2):68–75. https://doi.org/10.1200/JCO.2012.47.2787
34. Hyman DM, Piha-Paul SA, Won H, Rodon J, Saura C, Shapiro GI, et al. HER kinase inhibition in patients with HER2- and HER3-mutant cancers. Nature. 2018 Feb 8;554(7691):189–194. https://doi.org/10.1038/nature25475
35. Li BT, Shen R, Buonocore D, Olah ZT, Ni A, Ginsberg MS, et al. Ado-Trastuzumab Emtansine for Patients with HER2-Mutant Lung Cancers: Results From a Phase II Basket Trial. J Clin Oncol. 2018 Aug 20;36(24):2532–2537. https://doi.org/10.1200/JCO.2018.77.9777
36. Mazieres J, Barlesi F, Filleron T, Besse B, Monnet I, Beau-Faller M, et al. Lung cancer patients with HER2 mutations treated

with chemotherapy and HER2-targeted drugs: results from the European EUHER2 cohort. Ann Oncol. 2016 Feb;27(2):281–286. https://doi.org/10.1093/annonc/mdv573
37. Sadiq AA, Salgia R. MET as a possible target for non-small-cell lung cancer. J Clin Oncol. 2013 Mar 10;31(8):1089–1096. https://doi.org/10.1200/JCO.2012.43.9422
38. Stransky N, Cerami E, Schalm S, Kim JL, Lengauer C. The landscape of kinase fusions in cancer. Nat Commun. 2014 Sep 10;5:4846. https://doi.org/10.1038/ncomms5846
39. Awad MM, Oxnard GR, Jackman DM, Savukoski DO, Hall D, Shivdasani P, et al. MET Exon 14 Mutations in Non-Small-Cell Lung Cancer Are Associated With Advanced Age and Stage-Dependent MET Genomic Amplification and c-Met Overexpression. J Clin Oncol. 2016 Mar 1;34(7):721–730. https://doi.org/10.1200/JCO.2015.63.4600
40. Frampton GM, Ali SM, Rosenzweig M, Chmielecki J, Lu X, Bauer TM, et al. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. Cancer Discov. 2015 Aug;5(8):850–859. https://doi.org/10.1158/2159-8290.CD-15-0285
41. Camidge R, Otterson G, Clark J, Ou S-H, Weiss J, Ades S, et al. Crizotinib in patients (pts) with MET-amplified non-small cell lung cancer (NSCLC): Updated safety and efficacy findings from a phase 1 trial. Journal of Clinical Oncology. 2018 May 20;36:9062–9062. https://doi.org/10.1200/JCO.2018.36.15_suppl.9062
42. Paik P, Veillon R, Cortot A, Felip E, Sakai H, Mazieres J, et al. Phase II study of tepotinib in NSCLC patients with MET ex14 mutations. Journal of Clinical Oncology. 2019 May 20;37:9005–9005. https://doi.org/10.1200/JCO.2019.37.15_suppl.9005
43. Wolf J, Seto T, Han J-Y, Reguart N, Garon EB, Groen HJM, et al. Capmatinib in MET Exon 14-Mutated or MET-Amplified Non-Small-Cell Lung Cancer. N Engl J Med. 2020 Sep 3;383(10):944–957. https://doi.org/10.1056/NEJMoa2002787
44. Wang R, Hu H, Pan Y, Li Y, Ye T, Li C, et al. RET fusions define a unique molecular and clinicopathologic subtype of non-small-cell lung cancer. J Clin Oncol. 2012 Dec 10;30(35):4352–4359. https://doi.org/10.1200/JCO.2012.44.1477
45. Drilon A, Hu ZI, Lai GGY, Tan DSW. Targeting RET-driven cancers: lessons from evolving preclinical and clinical landscapes. Nat Rev Clin Oncol. 2018 Mar;15(3):151–167. https://doi.org/10.1038/nrclinonc.2017.175
46. Kato S, Subbiah V, Marchlik E, Elkin SK, Carter JL, Kurzrock R. RET Aberrations in Diverse Cancers: Next-Generation Sequencing of 4,871 Patients. Clin Cancer Res. 2017 Apr 15;23(8):1988–1997. https://doi.org/10.1158/1078-0432.CCR-16-1679
47. Drilon A, Rekhtman N, Arcila M, Wang L, Ni A, Albano M, et al. Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. Lancet Oncol. 2016 Dec;17(12):1653–1660. https://doi.org/10.1016/S1470-2045(16)30562-9
48. Yoh K, Seto T, Satouchi M, Nishio M, Yamamoto N, Murakami H, et al. Vandetanib in patients with previously treated RET-rearranged advanced non-small-cell lung cancer (LURET): an open-label, multicentre phase 2 trial. Lancet Respir Med. 2017 Jan;5(1):42–50. https://doi.org/10.1016/S2213-2600(16)30322-8
49. Gautschi O, Milia J, Filleron T, Wolf J, Carbone DP, Owen D, et al. Targeting RET in Patients With RET-Rearranged Lung Cancers: Results From the Global, Multicenter RET Registry. J Clin Oncol. 2017 May 1;35(13):1403–1410. https://doi.org/10.1200/JCO.2016.70.9352
50. Gainor J, Lee D, Curigliano G, Doebele R, Kim D-S, Baik C, et al. Clinical activity and tolerability of BLU-667, a highly potent and selective RET inhibitor, in patients (pts) with advanced RET-fusion+ non-small cell lung cancer (NSCLC). Journal of Clinical Oncology. 2019 May 20;37(15):9008–9008. https://doi.org/10.1200/jco.2019.37.15_suppl.9008
51. Piotrowska Z, Thress K, Mooradian M, Heist R, Azzoli C, Temel J, et al. MET amplification (amp) as a resistance mechanism to osimertinib. Journal of Clinical Oncology. 2017 May 20;35:9020–9020.
52. Jonna S, Feldman RA, Swensen J, Gatalica Z, Korn WM, Borghaei H, et al. Detection of NRG1 Gene Fusions in Solid Tumors. Clin Cancer Res. 2019 Aug 15;25(16):4966–4972. https://doi.org/10.1158/1078-0432.CCR-19-0160
53. Fernandez-Cuesta L, Plenker D, Osada H, Sun R, Menon R, Leenders F, et al. CD74-NRG1 fusions in lung adenocarcinoma. Cancer Discov. 2014 Apr;4(4):415–422. https://doi.org/10.1158/2159-8290.CD-13-0633
54. Gay ND, Wang Y, Beadling C, Warrick A, Neff T, Corless CL, et al. Durable Response to Afatinib in Lung Adenocarcinoma Harboring NRG1 Gene Fusions. J Thorac Oncol. 2017 Aug;12(8):e107–e110. https://doi.org/10.1016/j.jtho.2017.04.025
55. Drilon A, Somwar R, Mangatt BP, Edgren H, Desmeules P, Ruusulehto A, et al. Response to ERBB3-Directed Targeted Therapy in NRG1-Rearranged Cancers. Cancer Discov. 2018 Jun;8(6):686–695. https://doi.org/10.1158/2159-8290.CD-17-1004

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