Beyond *EGFR* and *ALK*: targeting rare mutations in advanced non-small cell lung cancer

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Abstract: Lung cancer remains the leading cause of cancer-related death in men and women, despite its constantly declining rates in incidence and mortality in the developed world. The past decade has witnessed an unprecedented rise in the development of molecular targeted therapies in various types of tumors. In non-small cell lung cancer (NSCLC), the greatest paradigm shift is the implementation of *EGFR* and *ALK* tyrosine kinase inhibitors in the first line and subsequent lines of therapy, with impressive results. Though less frequent than the molecular alterations in the aforementioned genes, a number of aberrations in potential oncogenic drivers has been discovered, namely mutations in the genes *KRAS*, *BRAF*, *HER2*, *PI3KCA* and *DDR2*, *ROS1* and *RET* rearrangements and *MET*, *HER2* and *FGFR1* gene amplifications. A great number of clinical trials are currently underway, evaluating agents specifically designed to target these alterations, with mixed results so far. The greatest cumulative benefit offered by these trials is that, despite their success or failure in their objective goals, they have provided us with a better understanding of the complexity of the molecular intracellular processes, necessitating thus the accurate interpretation of the preclinical data in order to appropriately select the patients that may derive benefit from targeted treatment strategies.

Keywords: Non-small cell lung cancer (NSCLC); oncogenic drivers; *KRAS*; *BRAF*; *MET*; *HER2*; *PI3KCA*; *DDR2*; *RET*; *ROS1*; *FGFR1*

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Introduction

Lung cancer remains the leading cause of cancer-related death in both sexes, although its incidence and mortality rates, at least in the developed world, are steadily declining, mostly as a result of the anti-smoking campaign (1). The recent advances in molecular biology of cancer, made possible by the implementation of techniques such as next-generation sequencing, have deciphered the oncogenic processes in many types of malignant diseases, including lung cancer. Initiatives such as The Lung Cancer Mutation Consortium have elucidated the molecular heterogeneity of non-small cell lung cancer (NSCLC), discovering molecular alterations in key regulatory pathways that spearhead the malignant process, which in turn made possible their effective targeting and the subsequent impairment of the cancer growth (2). The clinical benefit from targeting the epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) translocations has already been established through pivotal clinical trials, and a number of effective targeted agents for these alterations comprise a vital part of our armamentarium against

NSCLC harboring the relevant aberrations. Although these two molecular alterations occur most frequently among oncogene-addicted NSCLC, others have been described as well and attempts to target them in clinical trials have already been taken, with varying levels of success. Herein, we present the most frequent genetic alterations that may function as oncogenic drivers in NSCLC, apart from *EGFR* and *ALK*, and we analyze some of the attempts that have been made so far in order to discover a specific and efficient targeted agent for each of them.

BRAF mutations

BRAF (B-Raf proto-oncogene, serine/threonine kinase) inhibition was recently officially added to the armamentarium of targeted therapies for oncogene-driven NSCLC, via the implementation of the combination of *BRAF* inhibitor, namely Dabrafenib, with a *MEK* inhibitor, namely Trametinib. A *BRAF* mutation, which in at least half the cases represents the V600E mutation, constitutes the driving force of oncogenesis in approximately 1–2% of NSCLC (3), and deregulates the mitogen-activated protein kinase (MAPK) pathway, thus affecting major cell processes such as cell proliferation, differentiation, angiogenesis, senescence and cell death.

In the two larger relevant studies, nearly all the tumors harboring a *BRAF* mutation were adenocarcinomas of poor differentiation and manifested with a more aggressive pattern. Also, in both studies, most of the patients carrying the mutation were current or former smokers (4,5).

Dabrafenib showed clinical activity as a single agent in this setting in a phase II, multicentre, non-randomised, open-label study in previously treated and untreated patients with stage IV metastatic $BRAF_{V600E}$-positive NSCLC (NCT01336634). The dual inhibition of *BRAF* and *MEK* via the combination of Dabrafenib-Trametinib has produced impressive results, both in first line and in subsequent lines of therapy. The combination was first compared to Dabrafenib monotherapy in previously treated patients in a phase II study, where it produced an impressive overall survival (OS) of 18 months over 12.7 months of single agent Dabrafenib (6). Similarly, in the phase II study in treatment-naïve patients, it showed an overall response rate (ORR) of 64%, progression-free survival (PFS) of 11 months and preliminary OS of 25 months (7). Based on these results, the regulatory authorities of USA and European Union granted approval to the combination for patients carrying the V600E mutation, irrespective of the line of therapy.

KRAS mutations

KRAS (*KRAS* proto-oncogene, GTPase) constitutes the most frequently mutated oncogene in NSCLC, at least in Caucasian populations, with reported frequencies reaching up to 26% (8), while its presence signals the absence of driver mutations in *EGFR* and *ALK* (9). The most common alteration is a missense mutation in codon 12, followed by mutations in codons 13 and 61 (10,11). These mutations result in a constitutively active, GTP-bound protein product, which constantly produces anti-apoptotic and pro-proliferation signals, mainly through the MAPK pathway, thus promoting the oncogenic process.

KRAS mutations mostly characterize non-squamous NSCLC, with varying levels of differentiation. Although initially believed that *KRAS* mutations were found predominately in smokers, recent reports provided evidence of the mutation appearing with a frequency of 15% in non-smokers (12). Among the different human races, it appears to be more prevalent in African-Americans as compared to Caucasians, with the lower prevalence found in Asians (13).

Ironically, although appearing in such a high frequency, *KRAS* mutated-NSCLC seems to be the hardest one to target effectively. The most promising novel agent was Selumetinib, a *MEK* 1/2 inhibitor, targeting a molecule downstream the constitutively active MAPK pathway. This small molecule demonstrated superior response rates and PFS in combination with Docetaxel over placebo, in a recent phase II trial, thus paving the way for the phase III SELECT-1 (14). This trial was set in the second line, in patients harboring a *KRAS* mutation, with the same drug combination (Selumetinib and Docetaxel *vs.* Placebo and Docetaxel), with PFS being the primary endpoint. Unfortunately, no improvement was noted either in PFS or in OS and ORR in the experimental arm (15).

Another approach implemented Abemaciclib, a CDK4/6 inhibitor currently employed in the treatment of hormone receptor-positive metastatic breast cancer, which produced a disease control rate of 55.2% in heavily pretreated NSCLC patients, in an early trial (NCT01394016). The phase III JUPINER trial, that compared Abemaciclib with Erlotinib in a pretreated population harboring *KRAS* mutations, failed to show superiority in the experimental arm (16).

The reasons behind these failed attempts at targeting

KRAS-mutant NSCLC are still unclear. A possible explanation might be the reactive upregulation of other intracellular molecules or molecular pathways, as it has proven to happen with AKT, which function as an escape mechanism (17). If that is indeed the resistance mechanism, dual inhibition strategies may provide benefit in this difficult to approach therapeutically clinical setting.

MET deregulation

The *MET* (MET proto-oncogene, receptor tyrosine kinase) gene encodes for a transmembrane receptor that is normally activated by the binding of its ligand, the hepatocyte growth factor (HGF). Aberrant or excessive activation of the receptor, through gene amplification or mutation, has an established role in various oncogenic processes such as cell survival, proliferation and metastasis (18). *MET* overexpression in NSCLC has been found in frequencies between 25–75% and has been associated with inferior outcomes (19,20).

An important association between *EGFR* and *MET* has been established. Firstly, *MET* has been found to upregulate EGF, thus impairing the effect of *EGFR*-targeting TKIs (21). Furthermore, amplification of the *MET* gene is a mechanism of acquired resistance to first-generation EGFR-TKIs (22,23), while it has also been recently involved in resistance to the third generation *EGFR* inhibitor Osimertinib in *EGFR*-mutated NSCLC (24). Moreover, the exon 14 skip mutation, which is found in approximately 3% of NSCLC, is an established resistance mutation that confers inferior prognosis, and which may be targeted with TKIs (25).

Based on these data, numerous clinical trials have been designed, targeting the *MET* gene product or its ligand, which tested novel small molecules or monoclonal antibodies, alone or in combination with *EGFR*-TKIs. Unfortunately, the majority of the trials did not produce positive results.

One of the first novel molecules tested, Tivantinib, a novel MET-TKI inhibitor, was combined with Erlotinib in a randomized, phase II trial that, although not achieving statistical significance in PFS (median PFS was 3.8 and 2.3 months in the Tivantinib and placebo group, respectively, with HR 0.81; 95% CI, 0.57 to 1.16; P=0.24) (26), prompted the design of the phase III MARQUEE trial, that compared the combination Tivantinib-Erlotinib *vs.* Erlotinib-placebo in pretreated, non-squamous NSCLC patients. The study population included 1,048 patients, one third of whom were heavily pretreated. In the interim analysis no difference was shown between the two groups in the primary endpoint of OS, and the trial was terminated for futility, though a difference was noted in the secondary endpoints of PFS and RR (27).

Onartuzumab, a monoclonal antibody targeting the extracellular domain of the MET receptor, was also combined with Erlotinib in a phase II trial in previously treated NSCLC patients who were unselected for *MET* expression. Although in the intention to treat (ITT) population no difference in OS and PFS was noted, in the subgroup that expressed MET (as a score 2+ or 3+ as per the MET IHC scoring system) a longer PFS and OS was noted (PFS 2.9 *vs.* 1.5 months, HR 0.53; P=0.04 and OS 12.6 *vs* 3.8 months, HR 0.37; P=0.002) (28). These results prompted the evaluation of Onartuzumab with Erlotinib versus placebo and Erlotinib in a large, randomized phase III trial in a preselected for MET expression patient population with pretreated advanced NSCLC. Unfortunately, no difference was observed between the two arms in terms of OS, PFS and RR (29). A potential explanation for this may be that patients were selected on the basis of positivity as estimated by IHC and not by *MET* gene amplification.

Recently, another randomized phase II trial attempted to introduce emibetuzumab, a *MET*-targeting monoclonal antibody, in combination with Erlotinib in treatment-naïve, *EGFR*-mutated NSCLC patients. This trial also failed to produce positive results, though an exploratory analysis suggested a potential PFS benefit in the subgroup of high *MET* expressors (30).

Although targeting NSCLC patients with *MET* inhibitors based on gene amplification and/or overexpression of the protein product has failed to produce the required results so far, it seems that targeting the exon 14 skip mutation (*METdel14*) may prove much more promising. In a recent multicenter retrospective analysis of 148 patients with *METdel14* mutant NSCLC, a vast difference in survival was noted between those who were never treated with *MET* inhibition and those who did. More specifically, in the first subgroup the OS was 8.1 months, which is consistent with the dismal prognosis conferred by this specific mutation. However, in the patient subgroup that received at least one *MET* inhibitor (including Crizotinib, Glesatinib, Capmatinib, and ABBV-399), the OS reached 24.6 months. These encouraging

results may offer insight in the proper way to select patients for future clinical trials testing MET inhibitors in NSCLC patients (31).

PI3KCA mutations

Phosphatidylinositol-3 kinases (*PI3K*) belong to a family of heterodimeric kinases, whose physiologic role is the conversion of phosphatidylinositol-3,4-bisphosphate to phosphatidylinositol-3,4,5-trisphosphate, which subsequently activates its downstream pathway, namely AKT/mTOR, to regulate growth, survival, and motility of the cell. The *PI3K* family has been divided in three classes, of which *PI3KCA* (Class I) is mostly implicated in human carcinogenesis, through its constitutively active catalytic subunit (p110), that can be aberrantly activated either through mutation or through gene amplification (32).

PI3KCA gene amplification characterizes mostly the squamous subtype of NSCLC, where it has been reported in frequencies ranging between 33% and 37%, as compared to only 5% to 6% in adenocarcinoma (33,34). Mutations in the *PIK3CA* gene occur more rarely, in about 2–5%, being prevalent again in squamous NSCLC (33-35), while they seem to confer inferior prognosis in adenocarcinoma (36). Interestingly, these mutations have been reported to occur in parallel with other oncogenic driver mutations and they have also been discovered in *EGFR*-mutant NSCLC that has developed acquired resistance to *EGFR*-TKIs (37,38). This may provide a hind toward the function of these mutations, since they most probably develop later in the multistep oncogenic process, possibly representing escape mechanisms from the TKI inhibition.

In that context, several small molecules targeting *PI3KCA* are in development. Buparlisib (BKM120) is a pan-*PI3K* inhibitor that has demonstrated activity in NSCLC in preclinical models combined with the downstream mTOR inhibitor Everolimus (38). This was confirmed in a phase I dose-escalation trial (39), but a subsequent phase II basket trial (NCT01501604) that investigated efficacy of single-agent Buparlisib in a variety of cancers harboring *PIK3CA* mutations (lung, breast, colorectal, cholangiocarcinoma and other solid tumors), was prematurely terminated due to poor accrual. Another phase II study, BASALT-1 (NCT01820325), evaluating Buparlisib in patients with relapsed squamous or non-squamous NSCLC, molecularly selected for *PI3KCA* mutation, failed to demonstrate sufficient clinical activity of the drug (40). The investigators concluded that *PI3K* mutations may not be the main oncogenic driver in NSCLC, suggesting instead that combination strategies with other targeted agents may provide better results. Interestingly, this combination approach provided positive results in a phase II study of Buparlisib combined with Paclitaxel in pretreated Head-Neck squamous cell carcinoma patients (41).

Pictilisib (GDC-0941) is another P13K inhibitor that is being studied in a phase Ib trial in advanced NSCLC in unselected patients, in combination with cytotoxic chemotherapy, with the addition of Bevacizumab in non-squamous NSCLC (NCT00974584). The drug is also being studied in a large phase II, placebo-controlled trial in previously untreated advanced or recurrent NSCLC, where it is combined with Carboplatin/Paclitaxel, with the addition of Bevacizumab in non-squamous NSCLC (NCT01493843). The study has completed accrual and results are awaited.

Pilaralisib (SAR245408, XL147) is a pan-class I PI3K inhibitor that has shown dose-dependent activity in inhibiting growth in human cancer cell lines with constitutive *PI3K* activation (42) in combination with Erlotinib in patients with solid malignancies. In a phase I dose-escalation study in combination with Erlotinib in unselected patients with solid tumors, it produced limited antitumor activity, irrespective of the *PI3K* mutation status. In yet another phase Ib study including a subset of NSCLC, where it was combined with Carboplatin/Paclitaxel, it did not offer any further enhancement in the antitumor activity of cytotoxics (NCT00756847).

The information provided from these trials, which may be useful to incorporate in future efforts to implement *PI3K* inhibition in clinical practice, is that single-agent *PI3K* inhibitors offer limited, if any, activity, while combination with other targeted agents and/or cytotoxic chemotherapy, may prove to be more efficacious. On the other hand, we also need to establish the optimal setting in which *PI3K* inhibition will be incorporated, since it seems that *PI3K* is most active as an oncogenic force in advanced, pretreated cancer, where it functions as an escape mechanism to other targeted agents.

RET rearrangement

The *RET* fusion oncogene was initially discovered in thyroid carcinoma (43,44), and since then it has been implicated as an oncogenic driver in a variety of solid tumors. In NSCLC, at least 12 different gene partners of *RET* have been described (45-47), leading to various forms

of rearrangement, with perhaps the most frequent and best characterized of them occurring between the exons 1–15 of *KIF5B* and the exons 12–20 of *RET* proto-oncogene, which encodes the tyrosine kinase portion. The downstream pathways activated are the JAK/STAT3 and RAS/RAF/MEK/ERK, which promote cell proliferation and survival (48).

The frequency of the rearrangement in NSCLC is estimated between 1% and 2% (45), and the definitive standard for its detection is FISH, regardless of the fusion partner (49). A retrospective analysis revealed that *RET*-driven oncogenesis produces poorly differentiated tumors, featuring a solid, lepidic or papillary predominant morphologic pattern, often including signet-ring cells. In that same study, most of the patients were never-smokers and younger than 60 years (82% and 73%, respectively). Furthermore, although all patients had small primary tumors, even smaller than 3 cm, they were characterized by extensive lymph node involvement, (at least N2 at presentation) (49), a correlation also noted in another large retrospective study (50).

Several multitarget agents have exhibited activity against *RET*-rearranged tumors, such as Vandetanib, Cabozantinib, Lenvatinib, Alectinib, and Sunitinib, with response rates ranging between 16% and 47%, and median PFS from 2.3 to 7.3 months (51-54). Sunitinib and Sorafenib have failed in their respective clinical trials (55,56). A retrospective worldwide analysis (GLORY) including patients receiving a variety of TKIs (vandetanib, cabozantinib, lenvatinib, sunitinib, sorafenib, alectinib, ponatinib, and regorafenib) also produced disappointing results, with ORR, PFS and OS reaching 26%, 2.3 and 6.8 months, respectively (50). The most promising agent so far is Vandetanib, which was evaluated in 2 non-randomized phase II trials in 2017, in Japanese (LURET) and Korean populations. The ORR, PFS and OS in these trials were 53%, 5 and 11 months and 18%, 4.5 and 11.6 months, respectively. An interesting finding in both studies was the negative predictive role of the *KIF5B-RET* fusion variant as compared to other fusion types (51,52).

A possible explanation for the moderate success of targeting *RET* in NSCLC may be the early onset of acquired resistance, mainly as a result of the presence of concomitant molecular alterations in a clonally diverse cell population (57-59). In that regard, a dual or triple inhibition could prove to be an effective strategy. Indeed, a hint of the potential value of this approach has been offered by a recent phase I study, where the combination of Vandetanib with Everolimus produced a preliminary ORR of 83% in a *RET*-rearranged population with advanced NSCLC (60). Finally, the future may hold promise for a novel, selective *RET* inhibitor, potent against the *KIF5B-RET* fusion, currently designated LOXO-292 or BLU-667, that has demonstrated significant *in vitro* and *in vivo* activity (61).

ROS rearrangement

The *ROS* gene rearrangement promotes carcinogenesis in a unique yet still unclear way, since most of the fusion partners of the *ROS1* proto-oncogene lack dimerization domains. Nevertheless, the receptor encoded by the rearranged *ROS* gene regulates downstream pro-survival and antiapoptotic signalling pathways, such as the MAPK, PI3K/AKT, and STAT3. Nine different *ROS1* fusion partners have been identified so far, with *CD74* being the most common (62).

In NSCLC, *ROS* rearrangements are found in approximately 1%, with FISH being the definitive diagnostic method, irrespective of the fusion partner (63). Similarly to other driver oncogenes, *ROS1* rearrangements are mutually exclusive with other mutations, such as *ALK*, *EGFR* or *KRAS*. Clinically, the patients harboring that specific rearrangement have the same characteristics as those with the *ALK* one: they are diagnosed at a younger age, they have a light or no smoking history, and their tumors are usually adenocarcinomas (64).

Since the ATP-binding sites of *ROS* and *ALK* share a 77% homology, molecules initially developed against *ALK* have been found to demonstrate activity, both *in vitro* and *in vivo*, against *ROS* as well (65,66). Based on this fact and on data from preclinical models that demonstrated activity of Crizotinib against *ROS*-rearranged NSCLC (62), an expansion cohort of *ROS1*-positive patients, previously TKI-untreated, was included in a phase I trial evaluating the activity of Crizotinib in *ALK*-rearranged NSCLC patients. The results indicated a clinically meaningful benefit of this drug to this subset of patients, which showed a 72% ORR and a median PFS of 19.2 months, thus establishing Crizotinib as the standard of care for *ROS1*-rearranged NSCLC (63). Other *ALK*-targeting agents have been tested in this setting: Ceritinib has produced similar results in a TKI-naïve population, producing an ORR of 62% a median PFS of 19 months (67), while Entrectinib, a *ROS*- and *NTRK*-TKI, showed an ORR of 78%, intracranial responses of 83% and a PFS of 29.6 months in a similar patient population (68).

An important issue with *ROS* inhibition, as is with

ALK- and *EGFR*-inhibition, is that after a certain time of treatment, most of the patients will eventually develop resistance, which, in a considerable number, is attributed to novel mutations within the targeted molecule. Second-line TKIs are being developed: Lorlatinib, an *ALK*-inhibitor developed to target Crizotinib-resistant *ALK*-rearranged NSCLC, has demonstrated activity in this setting; In a phase II trial of *ROS1*-positive patients, 70% of which were Crizotinib-resistant, Lorlatinib produced a 36% ORR, an intracranial ORR of 56% and a median PFS of 9.6 months (69). Another problem with *ROS1* targeting is the presence of *de novo* resistance to currently employed agents, conferred by mutations such as *CD74-ROS1G2032R*, for which Ceritinib, Lorlatinib and Entrectinib have performed poorly in preclinical models (70-72). Cabozantinib, however, has produced more encouraging results in preclinical studies, and a phase II trial is currently ongoing (73).

HER2 alterations

HER2 is a unique member of the *ErbB* family of transmembrane receptors, that lacks an activating ligand. Instead, activation results from either homodimerization of the molecule, or the heterodimerization with other members of the family, namely *EGFR* and *HER3*. Heterodimerization leads to activation of transduction pathways including PI3K, MAPK and JAK/STAT, which augment proliferation and survival (74). *HER2* has been found altered in a variety of solid neoplasms, and specific anti-*HER2* agents have been incorporated in breast and gastric cancers where the HER2 protein product is amplified. In NSCLC, HER2 protein expression and gene amplification are present in 2–6% and in 1–5% of NSCLC respectively (75,76). *HER2* is also mutated in approximately 2–4% of NSCLC, with the most frequent mutation being the YVMA 776–779 insertion in exon 20, which results in a constantly active Kinase domain that phosphorylates downstream signals such as *AKT* and *MEK* (77).

HER2 mutations in NSCLC have been correlated with adenocarcinoma histology, they are mutually exclusive with *EGFR* and *KRAS* mutations, while in certain reports they have been associated with female gender, Asian ethnicity and never-smoking status (77). The prognostic significance of these alterations has yet to be elucidated, with some reports attributing poor prognosis in cases where the protein product has been found amplified by IHC, while the amplification of the gene itself, as detected by FISH, is of indeterminate significance (76).

Although the current armamentarium of anti-*HER2* agents features various drugs with different mechanisms of action that have a proven efficacy in a similar setting in breast and gastric cancer, and despite the encouraging preclinical and early clinical results, the targeting of *HER2* in NSCLC has so far failed to provide positive results in larger trials. To begin with, Dacomitinib, an irreversible pan-*HER* inhibitor, has demonstrated a poor ORR of only 12% in a phase II clinical trial of patients with advanced (stage III or IV) NSCLC with *HER2* mutations or amplifications (78). Similarly low ORR, in an equivalent setting, was produced by Neratinib, another irreversible pan-*HER* inhibitor, either as a single agent or in combination with the mTOR inhibitor Temsirolimus [Neratinib (0%), and Neratinib plus Temsirolimus (19%)] (79). Furthermore, Afatinib, a dual *HER2* and *EGFR* inhibitor with first-line approval for EGFR-mutant NSCLC, when employed for the treatment of HER2-mutant NSCLC patients in a phase II clinical trial, produced no responses at all (80), while in a multicentric, retrospective study, it showed an ORR of only 15% (81). Finally, TDM-1 also failed to show adequate benefit in NSCLC patients with *HER2* overexpressing tumors, producing responses of 0% and 20% in *HER2* IHC2+ or 3+, respectively (82).

No clear explanation has been offered yet for these negative results that, up to some extent, reflect the negative results produced in gastric cancer trials where the incorporation of *HER2* agents, other than trastuzumab, in various lines of therapy, failed to show any clinical benefit. A potential explanation and a hint for future trials may be derived from a basket TDM-1 trial, where, in a subset of *HER2*-mutant NSCLC patients, the ORR was 44% and the median PFS was 5 months and did not correlate with IHC positivity. Instead, IHC positivity differed widely in responders and was not predictive of clinical benefit (83). These data may point to the need of implementing a scoring system for evaluating *HER2* positivity consisting of more than 3 (ICH) or 2 (FISH) values.

FGFR1 amplification

FGFR1 (fibroblast growth factor receptor 1) belongs to a family of transmembrane tyrosine kinases consisting of four

members (*FGFR1-4*), that are active mainly in squamous epithelia, where they regulate proliferation via the *RAS/RAF/MAPK* and the *PI3K/AKT* signaling pathways (84). In NSCLC, especially in the squamous subtype, *FGFR1*, and possibly *FGFR2* and *FGFR3*, have been found to promote carcinogenesis in a variety of ways (85,86). An interaction has been discovered between *FGFR1* and *EGFR* in the progression of the malignant phenotype (87), and overexpression of the receptor has been associated with inferior survival. More specifically, the *FGFR1* gene is amplified in about 20% of squamous-NSCLC, and 3.5-fold amplification has been recognized as the cut-off point for distributing patients in different survival groups. That cut-off limit may function as a stratification factor for clinical trials (88-90).

Several small molecules have been tested in this setting. Brivanib, or BMS-540215, a multitargeted TKI that also targets *FGFR1*, has failed to produce responses in a randomized discontinuation study in previously treated, unselected NSCLC patients (91). Dovitinib (TKI258) inhibits *FGFR1-3* and is being tested in an ongoing phase II trial in a population of pretreated patients with squamous NSCLC, selected for *FGFR1* amplification (NCT01861197). Another phase II trial of Nintedanib in the same setting, in patients with *FGFR1*-amplified squamous-NSCLC, has been completed and results are awaited (NCT01948141).

DDR2 mutations

Discoidin domain receptor 2 (*DDR2*) is a receptor tyrosine kinase which, along with *DDR1*, is implicated in cell processes crucial for tissue homeostasis and repair, such as cell adhesion, migration and proliferation (92,93). Gain-of-function mutations in *DDR2* have been discovered mainly in squamous NSCLC in a frequency of around 4%, where they appear to promote carcinogenesis via cell migration and proliferation, thus rendering this receptor a promising targetable molecule (94,95). Dasatinib initially appeared effective for targeting *DDR2*, since it had demonstrated activity in preclinical models of SCC cell-lines that harbored activating *DDR2* mutations, while a rapid response has also been noted in a patient carrying a relevant mutation, when received treatment with the combination of Dasatinib plus Erlotinib (94).

Based on these positive early results, a phase II trial was developed, in which patients with advanced squamous NSCLC that harbored *DDR2* mutation or inactivating *BRAF* mutation and have failed standard chemotherapy, received daily 140 mg of Dasatinib. Unfortunately, this trial was terminated prematurely, after the enrollment of only five patients, due to the development of extreme toxicity in the test subjects. More specifically, 3 of 5 (60%) patients experienced ≥ grade 3 toxicities (dyspnea, fatigue, AST elevation, anorexia, nausea), while intolerable grade 2 pleural effusions were noted in 2 of 5 patients (96). Another phase II trial in a similar setting also terminated prematurely due to lack of efficacy and slow accrual (NCT01514864). The negative outcome of these trials can be primarily attributed to excessive toxicity, which appears to hinder the potential benefit of this drug in a specific, molecularly selected patient population. Consequently, a phase II trial is currently active, attempting to discover the highest tolerated dose of the combination of Dasatinib and Crizotinib that can be safely administered to patients with advanced cancer (NCT01744652).

Conclusions

Even though the majority of the clinical trials investigating targeted agents for NSCLC have not produced the desired results so far, their failures might be attributed mostly to poor patient selection. Indeed, as manifested better in the various trials targeting *MET*, strict selection criteria need to be applied when evaluating positivity for a specific genetic alteration. In that last case, it has been made evident that gene amplification rather than simple protein expression characterize true positivity and reflect an active role in the oncogenic process of a specific gene. Furthermore, while learning more about the molecular cellular biology, we realize the vast complexity of intracellular pathways and the importance of their interaction. In many of the above mentioned trials there have been hinds about the importance of implementing dual inhibition, combining two agents that inhibit different pathways, or even the combination of cytotoxics with targeted agents. Also, it is of paramount importance to decide the time frame where we offer targeted therapy, taking into account the potential escape mechanisms and the unavoidable clonal selection our treatment is bound to eventually produce in the diverse tumor cell population.

To conclude, it is clear that NSCLC is a heterogeneous disease driven by a spectrum of molecular alterations. Consequently, it is necessary to carefully translate the

results of basic science into clinical trials, not only by using the right set of biomarkers, but also by learning how to best interpret them. In this way we may achieve rationalization in our decisions when managing patients with this specific tumor type, tailoring and individualizing our treatment approach in order to provide optimal care to our patients.

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Footnote

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References

1. Siegel R, Ma J, Zou Z, et al. Cancer statistics 2014. CA Cancer J Clin 2014;64:9-29.
2. Johnson BE, Kris MG, Berry LD, et al. A multicenter effort to identify driver mutations and employ targeted therapy in patients with lung adenocarcinomas: the lung cancer mutation consortium (LCMC). J Clin Oncol 2013;31:abstr 8019.
3. Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. JAMA 2014;311:1998-2006.
4. Marchetti A, Felicioni L, Malatesta S, et al. Clinical features and outcome of patients with non-small-cell lung cancer harboring BRAF mutations. J Clin Oncol 2011;29:3574-9.
5. Paik PK, Arcila ME, Fara M, et al. Clinical characteristics of patients with lung adenocarcinomas harboring BRAF mutations. J Clin Oncol 2011;29:2046-51.
6. Planchard D, Besse B, Kim TM et al. Updated survival of patients (pts) with previously treated BRAF V600E-mutant advanced non-small cell lung cancer (NSCLC) who received dabrafenib (D) or D + trametinib (T) in the phase II BRF113928 study. J Clin Oncol 2017;35:abstr 9075.
7. Planchard D, Smit EF, Groen HJM et al. Phase 2 Trial (BRF113928) of Dabrafenib (D) Plus Trametinib (T) in Patients (pts) With Previously Untreated BRAF V600E-Mutant Metastatic Non- Small Cell Lung Cancer. Ann Oncol 2017;28:v605-v649.
8. Dearden S, Stevens J, Wu YL, et al. Mutation incidence and coincidence in non small-cell lung cancer: meta-analyses by ethnicity and histology (mutMap). Ann Oncol 2013;24:2371-6.
9. Gainor JF, Varghese AM, Ou SH, et al. ALK rearrangements are mutually exclusive with mutations in EGFR or KRAS: an analysis of 1683 patients with non-small cell lung cancer. Clin Cancer Res 2013;19:4273-81.
10. Roberts PJ, Stinchcombe TE. KRAS mutation: should we test for it, and does it matter? J Clin Oncol 2013;31:1112-21.
11. Dogan S, Shen R, Ang DC, 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;18:6169-77.
12. Riely GJ, Kris MG, Rosenbaum D, et al. Frequency and distinctive spectrum of KRAS mutations in never smokers with lung adenocarcinoma. Clin Cancer Res 2008;14:5731-4.
13. Reinersman JM, Johnson ML, Riely GJ, et al. Frequency of EGFR and KRAS Mutations in Lung Adenocarcinomas in African-Americans. J Thorac Oncol 2011; 6: 28-31.
14. Jänne PA, Shaw AT, Pereira JR, 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;14:38-47.
15. Jänne PA, van den Heuvel MM, Barlesi F, et al. Selumetinib Plus Docetaxel Compared With Docetaxel Alone and Progression-Free Survival in Patients With KRAS-Mutant Advanced Non-Small Cell Lung Cancer: The SELECT-1 Randomized Clinical Trial. JAMA 2017;317:1844-53.
16. A Study of Abemaciclib (LY2835219) in Participants With Previously Treated KRAS Mutated Lung Cancer. Available online: https://clinicaltrials.gov/ct2/show/NCT02152631
17. Tolcher AW, Khan K, Ong M, et al. Antitumor activity in RAS-driven tumors by blocking AKT and MEK. Clin Cancer Res 2015;21:739-48.
18. Yi S, Tsao MS. Activation of hepatocyte growth factor-met autocrine loop enhances tumorigenicity in a human lung adenocarcinoma cell line. Neoplasia 2000;2:226-34.
19. Ichimura E, Maeshima A, Nakajima T, et al. Expression of c-met/HGF receptor in human non-small cell lung carcinomas in vitro and in vivo and its prognostic significance. Jpn J Cancer Res 1996;87:1063-9.
20. Nakamura Y, Niki T, Goto A, et al. C-Met activation in lung adenocarcinoma tissues: an immunohistochemical analysis. Cancer Sci 2007;98:1006-13.
21. Matsubara D, Ishikawa S, Sachiko O, et al. Co-activation of epidermal growth factor receptor and c-MET defines

a distinct subset of lung adenocarcinomas. Am J Pathol 2010;177:2191-204.
22. Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science 2007;316:1039-43.
23. Bean J, Brennan C, Shih JY, et al. MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. Proc Natl Acad Sci U S A 2007;104:20932-7.
24. Piotrowska Z, Thress KS, Mooradian M, et al. MET amplification (amp) as a resistance mechanism to osimertinib. J Clin Oncol 2017;35:abstr 9020.
25. Tong JH, Yeung SF, Chan AWH, et al. MET Amplification and Exon 14 Splice Site Mutation Define Unique Molecular Subgroups of Non-Small Cell Lung Carcinoma with Poor Prognosis. Clin Cancer Res 2016;22:3048-56.
26. Sequist LV, von Pawel J, Garmey EG, et al. Randomized phase II study of erlotinib plus tivantinib versus erlotinib plus placebo in previously treated non-small-cell lung cancer. J Clin Oncol 2011;29:3307-15.
27. Scagliotti G, von Pawel J, Novello S, et al. Phase III Multinational, Randomized, Double-Blind, Placebo-Controlled Study of Tivantinib (ARQ 197) Plus Erlotinib Versus Erlotinib Alone in Previously Treated Patients With Locally Advanced or Metastatic Nonsquamous Non-Small-Cell Lung Cancer. J Clin Oncol 2015;33:2667-74.
28. Spigel DR, Ervin TJ, Ramlau RA, et al. Randomized phase II trial of Onartuzumab in combination with erlotinib in patients with advanced non-small-cell lung cancer. J Clin Oncol 2013;31:4105-14.
29. Spigel DR, Edelman MJ, O'Byrne K, et al. Onartuzumab plus erlotinib versus erlotinib in previously treated stage IIIb or IV NSCLC: Results from the pivotal phase III randomized, ulticentre, placebo-controlled METLung (OAM4971g) global trial. J Clin Oncol 2014;32:abstr 8000.
30. Scagliotti GV, Moro-Sibilot D, Kollmeier J, et al. A randomized, controlled, open label phase II study of erlotinib (E) with or without the MET antibody emibetuzumab (Emi) as first-line treatment for EGFRmt non-small cell lung cancer (NSCLC) patients who have disease control after an 8-week lead-in treatment with erlotinib. J Clin Oncol 2017;35:abstr 9019.
31. Awad MM, Leonardi GC, Kravetz S, et al. Impact of MET inhibitors on survival among patients (pts) with MET exon 14 mutant (METdel14) non-small cell lung cancer (NSCLC). J Clin Oncol 2017;35:abstr 8511.
32. Ji M, Guan H, Gao C, et al. Highly frequent promoter methylation and PI3KCA amplification in non-small cell lung cancer (NSCLC). BMC Cancer 2011;11:147.
33. Kawano O, Sasaki H, Endo K, et al. PIK3CA mutation status in Japanese lung cancer patients. Lung Cancer 2006;54:209-15.
34. Yamamoto H, Shigematsu H, Nomura M, et al. PI3KCA mutations and copy number gains in human lung cancers. Cancer Res 2008;68:6913-21.
35. Spoerke JM, O'Brien C, Huw L, et al. Phosphoinositide (PI3K) pathway alterations are associated with histologic subtypes and are predictive of sensitivity to PI3K inhibitors in lung cancer preclinical models. Clin Cancer Res 2012;18:6771-83.
36. Zhang L, Shi L, Zhao X, et al. PI3KCA gene mutation associated with poor prognosis of lung adenocarcinoma. Onco Targets Ther 2013;6:497-502.
37. Chaft JE, Arcila ME, Paik PK, et al. Coexistence of PI3KCA and other oncogene mutations in lung adenocarcinoma rationale for comprehensive mutation profiling. Mol Cancer Ther 2012;11:485-91.
38. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med 2011;3:75ra26.
39. Ren H, Chen M, Yue P, et al. The combination of RAD001 and NVP-BKM120 synergistically inhibits the growth of lung cancer in vitro and in vivo. Cancer Lett 2012;325:139-46.
40. Bendell JC, Rodon J, Burris HA, et al. Phase I, dose-escalation study of BKM120, an oral pan-Class I PI3K inhibitor, in patients with advanced solid tumors. J Clin Oncol 2012;30:282-90.
41. Vansteenkiste JF, Canon JL, De Braud F, et al. Safety and Efficacy of Buparlisib (BKM120) in Patients with PI3K Pathway-Activated Non-Small Cell Lung Cancer: Results from the Phase II BASALT-1 Study. J Thorac Oncol 2015;10:1319-27.
42. Soulières D, Faivre S, Mesía R, et al. Buparlisib and paclitaxel in patients with platinum-pretreated recurrent or metastatic squamous cell carcinoma of the head and neck (BERIL-1): a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Oncol 2017;18:323-35.
43. Chakrabarty A, Sánchez V, Kuba MG, et al. Feedback upregulation of HER3 (ErbB3) expression and activity attenuates antitumor effect of PI3K inhibitors. Proc Natl Acad Sci U S A 2012;109:2718-23.

44. Jhiang SM. The RET proto-oncogene in human cancers. Oncogene 2000;19:5590-7.
45. Nikiforov YE. Thyroid carcinoma: molecular pathways and therapeutic targets. Mod Pathol 2008;21:S37-S43.
46. Lipson D, Capelletti M, Yelensky R, et al. Identification of new ALK and RET gene fusions from colorectal and lung cancer biopsies. Nat Med 2012;18:382-4.
47. Takeuchi K, Soda M, Togashi Y, et al. RET, ROS1 and ALK fusions in lung cancer. Nat Med 2012;18:378-81.
48. Kohno T, Ichikawa H, Totoki Y, et al. KIF5B-RET fusions in lung adenocarcinoma. Nat Med 2012;18:375-7.
49. Qian Y, Chai S, Liang Z, et al. KIF5B-RET fusion kinase promotes cell growth by multilevel activation of STAT3 in lung cancer. Mol Cancer 2014;13:176.
50. Wang R, Hu H, Pan Y, et al. RET fusions define a unique molecular and clinicopathologic subtype of non-small cell lung cancer. J Clin Oncol 2012;30:4352-9.
51. Gautschi O, Milia J, Filleron T, et al. Targeting RET in patients with RET-rearranged lung cancers: results from the global, multicenter RET Registry. J Clin Oncol 2017;35:1403-10.
52. Yoh K, Seto T, Satouchi M, 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;5:42-50.
53. Lee SH, Lee JK, Ahn MJ, et al. Vandetanib in pretreated patients with advanced non-small cell lung cancer-harboring RET rearrangement: a phase II clinical trial. Ann Oncol 2017;28:292-7.
54. Drilon A, Rekhtman N, Arcila 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;17:1653-60.
55. Velcheti V, Hida T, Reckamp KL, et al. Phase 2 study of lenvatinib (LN) in patients (Pts) with RET fusion-positive adenocarcinoma of the lung. Ann Oncol 2016;27.
56. Scagliotti GV, Krzakowski M, Szczesna A, et al. Sunitinib plus erlotinib versus placebo plus erlotinib in patients with previously treated advanced non-small-cell lung cancer: a phase III trial. J Clin Oncol 2012;30:2070-8.
57. Paz-Ares LG, Biesma B, Heigener D, et al. Phase III, randomized, double-blind, placebo-controlled trial of gemcitabine/cisplatin alone or with sorafenib for the first-line treatment of advanced, nonsquamous non-small-cell lung cancer. J Clin Oncol 2012;30:3084-92.
58. Kim JO, Lee J, Shin JY, et al. The clinical characteristics of RET rearranged lung adenocarcinoma patients. J Clin Oncol 2015;33:abstr e18528.
59. Klempner SJ, Bazhenova LA, Braiteh FS, et al. Emergence of RET rearrangement co-existing with activated EGFR mutation in EGFR-mutated NSCLC patients who had progressed on first- or second generation EGFR TKI. Lung Cancer 2015;89:357-9.
60. Michels S, Scheel AH, Scheffler M, et al. Clinicopathological Characteristics of RET Rearranged Lung Cancer in European Patients. J Thorac Oncol 2016;11:122-7.
61. Cascone T, Subbiah V, Hess KR, et al. Significant systemic and CNS activity of RET inhibitor vandetanib combined with mTOR inhibitor everolimus in patients with advanced NSCLC with RET fusion. J Clin Oncol 2016;34:abstr 9069.
62. Velcheti V, Bauer T, Subbiah V et al. OA 12.07 - LOXO-292, a Potent, Highly Selective RET Inhibitor, in MKI-Resistant RET Fusion-Positive Lung Cancer Patients with and without Brain Metastases. J Thorac Oncol 2017;12:1778.
63. Gainor JF, Shaw AT. Novel targets in non-small cell lung cancer: ROS1 and RET fusions. Oncologist 2013;18:865-75.
64. Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med 2014;371:1963-71.
65. Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol 2012;30:863-70.
66. Shen L, Ji HF. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med 2014;370:2537.
67. Awad MM, Shaw AT. ALK inhibitors in non-small cell lung cancer: crizotinib and beyond. Clin Adv Hematol Oncol 2014;12:429-39.
68. Lim SM, Kim HR, Lee J-S, et al. Open-Label, Multicenter, Phase II Study of Ceritinib in Patients With Non-Small-Cell Lung Cancer Harboring ROS1 Rearrangement. J Clin Oncol 2017;35:2613-8.
69. Ahn M, Cho BC, Siena S, et al. OA 14.06 - Entrectinib in Patients with Locally Advanced or Metastatic ROS1 Fusion-Positive Non-Small Cell Lung Cancer (NSCLC). J Thorac Oncol 2017;12:1783.
70. Solomon BJ, Shaw A, Ou SH, et al. OA 05.06 - Phase 2 Study of Lorlatinib in Patients with Advanced ALK+/ROS1+ Non-Small-Cell Lung Cancer. J Thorac Oncol 2017;12:1756.
71. Awad MM, Katayama R, McTigue M, et al. Acquired resistance to crizotinib from a mutation in CD74-ROS1.

N Engl J Med 2013;368:2395-401.
72. Facchinetti F, Loriot Y, Kuo M-S, et al. Crizotinib-Resistant ROS1 Mutations Reveal a Predictive Kinase Inhibitor Sensitivity Model for ROS1- and ALK-Rearranged Lung Cancers. Clin Cancer Res 2016;22:5983-91.
73. Chong CR, Bahcall M, Capelletti M, et al. Identification of Existing Drugs That Effectively Target NTRK1 and ROS1 Rearrangements in Lung Cancer. Clin Cancer Res 2017;23:204-13.
74. Cabozantinib in Patients With RET Fusion-Positive Advanced Non-Small Cell Lung Cancer and Those With Other Genotypes: ROS1 or NTRK Fusions or Increased MET or AXL Activity. Available online: https://clinicaltrials.gov/ct2/show/NCT01639508
75. Tzahar E, Waterman H, Chen X, et al. A hierarchical network of inter receptor interactions determines signal transduction by Neu differentiation factor/neuregulin and epidermal growth factor. Mol Cell Biol 1996;16:5276-87.
76. Heinmöller P, Gross C, Beyser K, et al. HER2 status in non-small cell lung cancer: results from patient for enrollment to a phase II study of herceptin. Clin Cancer Res 2003;9:5238-43.
77. Liu L, Shao X, Gao W, et al. The Role of Human Epidermal Growth Factor Receptor 2 as a Prognostic Factor in Lung Cancer: A Meta-Analysis of Published Data. J Thorac Oncol 2010;5:1922-32.
78. Shigematsu H, Takahashi T, Nomura M, et al. Somatic mutations of the HER2 kinase domain in lung adenocarcinomas. Cancer Res 2005;65:1642-6.
79. Kris MG, Camidge DR, Giaccone G, 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;26:1421-7.
80. Gandhi L, Besse B, Mazieres J, et al. Neratinib ± Temsirolimus in HER2-Mutant Lung Cancers: An International, Randomized Phase II Study. J Thorac Oncol 2017;12:358-9.
81. Smit E, Peters S, Dziadziuszko R, et al. A single-arm phase II trial of afatinib in pretreated patients with advanced NSCLC harboring a HER2 mutation: The ETOP NICHE trial. J Clin Oncol 2017;35:abstr 9070.
82. Lai V, Lebas L, Milia J, et al. Afatinib in patients with metastatic HER2-mutant lung cancers: An international multicenter study. J Clin Oncol 2017;35:abstr 9071.
83. Stinchcombe T, Stahel R, Bubendorf L, et al. Efficacy, safety, and biomarker results of trastuzumab emtansine (T-DM1) in patients (pts) with previously treated HER2-overexpressing locally advanced or metastatic non-small cell lung cancer (mNSCLC). J Clin Oncol 2017;35:abstr 8509.
84. Li B, Shen R, Buonocore D, et al. OA 14.05 - Phase 2 Basket Trial of Ado-Trastuzumab Emtansine in Patients with HER2 Mutant or Amplified Lung Cancers. J Thorac Oncol 2017;12:1783.
85. Drilon A, Rekhtman N, Ladanyi M, et al. Squamous-cell carcinomas of the lung: emerging biology, controversies, and the promise of targeted therapy. Lancet Oncol 2012;13:e418-26.
86. Behrens C, Lin HY, Lee JJ, et al. Immunohistochemical expression of basic fibroblast growth factor and fibroblast growth factor receptors 1 and 2 in the pathogenesis of lung cancer. Clin Cancer Res 2008;14:6014-22.
87. Liao RG, Jung J, Tchaicha J, et al. Inhibitor-sensitive FGFR2 and FGFR3 mutations in lung squamous cell carcinoma. Cancer Res 2013;73:5195-205.
88. Fischer H, Taylor N, Allerstorfer S, et al. Fibroblast growth factor receptor-mediated signals contribute to the malignant phenotype of non-small cell lung cancer cells: therapeutic implications and synergism with epidermal growth factor receptor inhibition. Mol Cancer Ther 2008;7:3408-19.
89. Weiss J, Sos ML, Seidel D, et al. Frequent and focal FGFR1 amplification associates with therapeutically tractable FGFR1 dependency in squamous cell lung cancer. Sci Transl Med 2010;2:62ra93.
90. Dutt A, Ramos AH, Hammerman PS, et al. Inhibitor-sensitive FGFR1 amplification in human non-small cell lung cancer. PLoS One 2011;6:e20351.
91. Gadgeel SM, Chen W, Cote ML, et al. Fibroblast growth factor receptor 1 amplification in non-small cell lung cancer by quantitative real-time PCR. PLoS One 2013;8:e79820.
92. Ratain MJ, Schwartz HGK, Oza AM, et al. Brivanib (BMS-582664) in advanced solid tumors (AST): results of a phase II randomized discontinuation trial (RDT). J Clin Oncol 2011;29:abstr 3079.
93. Vogel W. Discoidin domain receptors: structural relations and functional implications. FASEB J 1999;13:S77-S82.
94. Miao L, Wang Y, Zhu S, et al. Identification of novel driver mutations of the discoidin domain receptor 2 (DDR2) gene in squamous cell lung cancer of Chinese patients. BMC Cancer 2014;14:369.

95. Hammerman PS, Sos ML, Ramos AH, et al. Mutations in the DDR2 kinase gene identify a novel therapeutic target in squamous cell lung cancer. Cancer Discovery 2011;1:78-89.

96. Brunner AM, Costa DB, Heist RS. Treatment-related Toxicities in a Phase II Trial of Dasatinib in Patients with Squamous Cell Carcinoma of the Lung: A Brief Report. J Thorac Oncol 2013;8:1434-7.

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