Review Article

Targeted therapy in NSCLC driven by HER2 insertions

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Abstract: *HER2* mutations, largely exon 20 in-frame insertions, have been described as an oncogenic driver alteration in 1% to 4% of NSCLC, exclusively in adenocarcinoma histology. The prognostic implication of these alterations is not known. Phase I and II trial data suggest that afatinib, neratinib and dacomitinib have some activity in this molecular subgroup. No comparative data, or any data regarding the activity of pertuzumab or trastuzumab-emtansine is available. HER2 deregulation either by protein overexpression or gene amplification, has little clinical relevance to date, as trials investigating trastuzumab activity merely suggest a benefit in the very small minority of patients whose tumor highly overexpresses HER2, a subpopulation that amounts to 2% to 6% of mostly adenocarcinomas.

Keywords: HER2 mutations; lung cancer; afatinib; dacomitinib; irreversible pan HER-receptor inhibitor

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Introduction

Research into the molecular basis of lung cancer has revealed insights into various critical pathways that are deregulated, and among them, key driver genetic alterations that promote cell survival and proliferation. In the oncogene addiction model, cancer cells harbor gene amplification, rearrangement or mutations that dictate their malignant phenotype, and can thus be referred to as driver alterations (1). Among them, human epidermal growth factor 2 (HER2 erbB-2/neu) is a member of the erbB receptor tyrosine kinase family. The *ERBB2* gene which encodes for HER2 is a major proliferative driver that activates downstream signaling through PI3K-AKT and MEK-ERK pathways (2). Unlike HER1/epidermal growth factor receptor (EGFR), HER2 has no known ligand, and is activated by homo-dimerization or hetero-dimerization with other members of the erbB family. Under resting conditions, these cell-surface receptors are found as monomers folded in a so-called "closed" inactive conformation that prevents dimerization (3). Upon ligand binding to the extracellular domain, conformational rearrangements lead to an "open" state that exposes the dimerization interface. This extracellular dimeric structure results in the transactivation of the intracellular tyrosine kinase portion of each receptor. Three principal mechanisms of oncogenic activation of HER2 have been described: *HER2* gene amplification, gene mutation resulting in molecular alterations of the receptor or HER2 protein overexpression.

HER2 has been found to be amplified in approximately 30% of breast cancers, systematically resulting in protein overexpression. While historically HER2-positive breast cancer had been associated with a poorer prognosis, outcome shave improved significantly through the use of HER2-targeted agents like trastuzumab (4). *HER2* has also been found to be amplified and subsequently overexpressed in a subset of gastric carcinoma and carcinoma of the gastro-esophageal junction, in which it is associated with improved outcomes through the addition of trastuzumab to standard chemotherapy (5). Mutational activation of *HER2* can result from various somatic molecular alterations: small insertions and missense mutations on the kinase domain, missense mutations in the extracellular domain, or large deletions of the extracellular domain that results in a truncated form of HER2 (6).

HER2 alterations in NSCLC

HER2 was shown to be overexpressed in 13% to 20% of

NSCLC, although 3+ expression is found in only 2% to 6% (7-9) *HER2* gene amplification, as assessed by fluorescent in situ hybridization (FISH) is uncommon, found in 2% to 4% of predominantly adenocarcinoma-type NSCLCs. Similarly to breast cancer, despite the relative lack of large series, concordance between FISH and IHC 3+ has been evidenced (8).

HER2 amplifications have been described as a potential mechanism of resistance to EGFR tyrosine kinase inhibitor (TKI) therapy in mouse models of EGFR-mutant tumor cells, where FISH analysis revealed that HER2 was amplified in 12% of tumors with acquired resistance versus only 1% of untreated lung adenocarcinomas. Notably, HER2 amplification and *EGFR* T790M mutation, the most common mechanism of acquired resistance, were mutually exclusive (10). In a large series of 155 patients with acquired resistance to EGFR TKI that underwent rebiopsy, HER2 amplification was seen in 13%, and no ERBB2 mutation was detected (11).

The identification of *EGFR* mutations, another member of the ERBB-family kinases, in a distinct subset of non-squamous NSCLCs was followed by the identification of *HER2* mutations, which mainly consist of in-frame insertions in exon 20, leading to constitutive activation of the receptor and downstream AKT and MEK pathways. *HER2* mutations fit the definition of genetic driver, and preclinical models have proved the transforming property of this alteration. Transgenic mice expressing the *Her-2* Tyr-Val- Met-Ala mutation develop lung adenosquamous carcinomas. In these models, substantial tumor shrinkage was observed when BIBW2992, a tyrosine kinase inhibitor that inhibits EGFR and Her-2, was combined with temsirolimus, an inhibitor of the downstream effector protein mTOR (12,13). *HER2* mutations have been identified in approximately 1% to 4% of NSCLC. In the initial report, mutations in the HER2 kinase domain were identified in 4.2% of 120 primary NSCLC overall and 9.8% in adenocarcinomas (14). A subsequent study of 671 primary resected NSCLC, HER2 mutations were found in 1.6% of samples overall, but in 3.9% of adenocarcinoma samples, and more frequently in Asian ethnicity (15-17). The largest retrospective series published to date, comprising 65 patients with NSCLC and *HER2* mutations, provides important insights into the clinic-pathological features and correlates: mutations were found exclusively in patients with adenocarcinoma subtype, and predominantly in female patients and non-smokers, a population similar to the EGFR-mutated NSCLC (18). Nevertheless, mutations were found in some men and heavy smokers, suggesting that *HER2* testing could be guided by tumor subtype (adenocarcinoma), but should not be restricted to clinically defined subgroups. All mutations were in-frame insertions of exon 20 within the *HER2* gene coding sequence, with duplication of amino-acids YVMA at codon 775. All *HER2*-mutated tumors were found negative for EGFR-activating mutation in exon 18 to 21, as well as ALK rearrangement and *BRAF* and *PI3KCA* mutations. Of interest, a high frequency of patients with disseminated lung nodules and tumor excavation patterns was observed. Of note, using stringent definition of gene amplification (as opposed to gene copy number gain), *HER2* mutations were not found associated with concurrent *HER2* gene amplification in this series and a previous report (15).

Although oncogenic tyrosine kinase mutations most frequently alter the ATP-binding pocket, as *EGFR* exon 19 and 21 as well as in *HER2* exon 19 or 20 mutations, mutations affecting the extracellular domain have recently been described, resulting in constitutively dimerized and activated HER2 (19). Mutations in the transmembrane domain of HER2 have also been described in familial lung adenocarcinomas (20).

There is scarce data regarding the prognostic impact of *HER2* mutations. In a series of 504 Japanese patients with resected NSCLC, 2.6% were found to harbor a *HER2* mutation. There was no difference in overall survival of patients with *HER2* mutations compared with patients harboring *EGFR* mutations and patients harboring wild types for both *EGFR* and *HER2* (17).

HER2 as a target

In the landscape of lung cancer biomarkers-based precision medicine, HER2 as a target remains poorly described. While in breast cancer HER2 overexpression or gene amplification is widely known to be associated with sensitivity to HER2-targeting drugs like trastuzumab, lapatinib, pertuzumab, and trastuzumab-emtansine, clinical research in lung cancer has been slowed down after the first negative clinical trials of trastuzumab added to chemotherapy in advanced NSCLC. In a phase II trial performed by the Cancer and Leukemia Group B, single-agent trastuzumab did not exhibit significant clinical activity against HER2 2+ or 3+ non-small cell lung carcinoma (21). A randomized phase II trial investigated the addition of trastuzumab to gemcitabine and cisplatin, in 103 previously untreated HER2-positive NSCLC patients. Trastuzumab

was given both concomitantly to chemotherapy and as a maintenance. Although the combination was well tolerated, it failed to show a survival benefit in all HER2 IHC-positive lung cancer overall. However, 80% of patients with IHC 3+ disease on study treatment were still alive after a follow up of 6months, compared with 64% of the overall population, and a response rate of 83% and median progression free survival (PFS) of 8.5 months was observed in the six trastuzumab-treated patients with HER2 3+ or FISH-positive NSCLC (22). In a phase II trial comprising only 13 patients with HER2-positive tumors (2+ or 3+), the addition of trastuzumab to weekly docetaxel after failure of platinum based-chemotherapy showed limited clinical activity, with a PR rate of 8% (23). The Eastern Cooperative Oncology Group launched a phase II study evaluating the combination of carboplatin, paclitaxel and trastuzumab in patients with HER2-positive (1+ to 3+) NSCLC. Of 139 screened patients, 36% were indeterminate, 5% inconclusive, 27% scored 1+, 22% score 2+, and 13% were 3+. Overall survival was found to be similar to historical data using carboplatin and paclitaxel alone, while patients with 3+ HER2 expression did well in contrast to historical data (24).

These trials are a reminder of the definition of an oncogenic driver alteration, as HER2 overexpression and probably amplification per se are probably only modulators of cancer biology. In addition, as in breast cancer, the need to define-specifically for every cancer type-a threshold of significance for HER2 overexpression becomes obvious. In particular, the biological role of HER2 expression in the absence of gene amplification remains to be defined, potentially explaining the negative results of clinical trials relying on an inaccurate selection of patients.

HER2 mutations may be much more relevant in lung cancer carcinogenesis than HER2 amplification or overexpression, and several kinase inhibitors are being evaluated for the treatment of HER2-dependant lung adenocarcinoma. Lapatinib, an oral reversible dual TKI of EGFR and HER2, has been tested in a phase II trial that included 75 patients with recurrent or metastatic NSCLC; no responses were seen in the 3 patients with *EGFR* mutations. No mutations in *HER2* were found in this population, leaving the question of lapatinib activity in HER2-mutant tumors unanswered (25). In the European retrospective study (18), 2 patients were treated with lapatinib, all experiencing progressive disease. The most promising data to date have been obtained using irreversible TKIs targeting HER2/3 and EGFR, such as afatinib, neratinib, and dacomitinib. Afatinib is a potent irreversible ErbB receptor family blocker. In an exploratory phase II study, 5 patients with *HER2* mutated advanced adenocarcinoma were treated with afatinib, 3 out of which were evaluable for response. Objective response was observed in all three, even after failure of other EGFR- and/or HER2-targeted treatments (26). This series was completed with the treatment of 7 additional *HER2* mutated patients, all 5 evaluable with a stable disease (27).

Neratinib, another irreversible pan ErbB-receptor family blocker, has been evaluated in a phase I trial in combination with temsirolimus on the basis of preclinical data suggesting synergy of HER2 inhibition and mTOR inhibition on lung cancer models. Partial response was observed in 2 out of 6 patients with *HER2*-mutant NSCLC (28). Dacomitinib is an irreversible pan-HER TKI. Tested in a phase II cohort of patients with *HER2*-mutant or amplified lung cancers, dacomitinib demonstrated an overall 13% response rate in the 26 *HER2*-mutant patients, and no response in the 4 patients with *HER2* amplification or the 2 with *HER2* point mutations (29).

Pertuzumab, a first-in-class HER2 dimerization inhibitor, is a humanized monoclonal anti-HER2 antibody that prevents HER2 dimerization and inhibits HER2 signaling. A phase II trial of pertuzumab monotherapy in patients with recurrent NSCLC showed no response in 43 patients, but information on the mutational status of HER2 in these patients is lacking (30).

Ongoing trials

Surprisingly, neither pertuzumab nor trastuzumab-emtansine is presently being studied in *HER2*-mutant lung cancer. A phase II exploratory trial is evaluating neratinib monotherapy and in combination with temsirolimus in patients with *HER2*-mutant NSCLC (NCT1827267). Dacomitinib is being tested in a variety of settings, but its present development remained to date mainly focused on *EGFR*-mutant NSCLC. Its phase I trials in combination with pemetrexed (NCT01918761), or c-MET inhibitor PF-02341066 (NCT01121575) will not improve our understanding of its activity in *HER2*-mutant NSCLC. No late-phase trial targeting this particular subgroup of patients in presently ongoing.

Conclusions

The identification of oncogenic driver mutations in NSCLC has triggered the development of multiple drugs interfering

with intracellular signaling pathways. HER2 deregulation by overexpression or amplification has been demonstrated to represent an important therapeutic target in breast and gastric cancer, but has to date little clinical relevance in NSCLC, potentially because due to the lack of definition of HER2 positivity in that particular disease. Phase II trial data merely suggests a benefit of trastuzumab therapy in patients with 3+ HER2-positive NSCLC. On the other hand, *HER2* mutations, largely exon 20 in-frame insertions, have been described as an oncogenic driver alteration in 1% to 4% of NSCLC, exclusively in adenocarcinoma histology. The prognostic implication of these alterations is not known. Phase I and II trial data suggest that afatinib, neratinib and dacomitinib have some activity in this molecular subgroup. No comparative data, or any data regarding the activity of pertuzumab or trastuzumab-emtansine is available. In order to improve our understanding of such alterations and aiming at offering new treatment options to our patients, given the high prevalence of lung cancer worldwide and the availability of investigational therapies targeting HER2, routine genotyping of lung adenocarcinoma should include HER2. Patient selection should be based on histology but should not discriminate for other clinic-pathologic features. The few currently ongoing trials are unlikely to foster our understanding of the role of HER2 TKIs in the treatment of this particular subgroup of patients. The sharp contrast between the wealth of investigational activity in other subgroups of NSCLC like *ALK*-rearranged NSCLC, which shares a similar prevalence, and the dearth of clinical research ongoing in *HER2*-mutant NSCLC is striking. Further development of afatinib and possibly of dacomitinib in this setting will be pursued. In addition, assessing the activity of pertuzumab in combination with trastuzumab, as well as trastuzumab-emtansine in patients presenting with NSCLC with 3+ HER2-overexpression would be of great interest.

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References

1. Pao W, Hutchinson KE. Chipping away at the lung cancer genome. Nat Med 2012;18:349-51.
2. Spector NL, Blackwell KL. Understanding the mechanisms behind trastuzumab therapy for human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol 2009;27:5838-47.
3. Ferguson KM, Berger MB, Mendrola JM, et al. EGF activates its receptor by removing interactions that autoinhibit ectodomain dimerization. Mol Cell 2003;11:507-17.
4. Ross JS, Slodkowska EA, Symmans WF, et al. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist 2009;14:320-68.
5. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376:687-97.
6. Herter-Sprie GS, Greulich H, Wong KK. Activating mutations in ERBB2 and their impact on diagnostics and treatment. Front Oncol 2013;3:86.
7. Hirsch FR, Varella-Garcia M, Franklin WA, et al. Evaluation of HER-2/neu gene amplification and protein expression in non-small cell lung carcinomas. Br J Cancer 2002;86:1449-56.
8. Heinmöller P, Gross C, Beyser K, et al. HER2 status in non-small cell lung cancer: results from patient screening for enrollment to a phase II study of herceptin. Clin Cancer Res 2003;9:5238-43.
9. Zinner RG, Glisson BS, Fossella FV, et al. Trastuzumab in combination with cisplatin and gemcitabine in patients with Her2-overexpressing, untreated, advanced non-small cell lung cancer: report of a phase II trial and findings regarding optimal identification of patients with Her2-overexpressing disease. Lung Cancer 2004;44:99-110.
10. Takezawa K, Pirazzoli V, Arcila ME, et al. HER2 amplification: a potential mechanism of acquired resistance to EGFR inhibition in EGFR-mutant lung cancers that lack the second-site EGFRT790M mutation. Cancer Discov 2012;2:922-33.
11. Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res 2013;19:2240-7.
12. Perera SA, Li D, Shimamura T, et al. HER2YVMA drives rapid development of adenosquamous lung tumors in mice that are sensitive to BIBW2992 and rapamycin combination therapy. Proc Natl Acad Sci U S A 2009;106:474-9.
13. Shimamura T, Ji H, Minami Y, et al. Non-small-cell lung cancer and Ba/F3 transformed cells harboring the ERBB2

G776insV_G/C mutation are sensitive to the dual-specific epidermal growth factor receptor and ERBB2 inhibitor HKI-272. Cancer Res 2006;66:6487-91.
14. Stephens P, Hunter C, Bignell G, et al. Lung cancer: intragenic ERBB2 kinase mutations in tumours. Nature 2004;431:525-6.
15. Arcila ME, Chaft JE, Nafa K, et al. Prevalence, clinicopathologic associations, and molecular spectrum of ERBB2 (HER2) tyrosine kinase mutations in lung adenocarcinomas. Clin Cancer Res 2012;18:4910-8.
16. Shigematsu H, Takahashi T, Nomura M, et al. Somatic mutations of the HER2 kinase domain in lung adenocarcinomas. Cancer Res 2005;65:1642-6.
17. Tomizawa K, Suda K, Onozato R, et al. Prognostic and predictive implications of HER2/ERBB2/neu gene mutations in lung cancers. Lung Cancer 2011;74:139-44.
18. Mazières J, Peters S, Lepage B, et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. J Clin Oncol 2013;31:1997-2003.
19. Greulich H, Kaplan B, Mertins P, et al. Functional analysis of receptor tyrosine kinase mutations in lung cancer identifies oncogenic extracellular domain mutations of ERBB2. Proc Natl Acad Sci U S A 2012;109:14476-81.
20. Yamamoto H, Higasa K, Sakaguchi M, et al. Novel germline mutation in the transmembrane domain of HER2 in familial lung adenocarcinomas. J Natl Cancer Inst 2014;106:djt338.
21. Clamon G, Herndon J, Kern J, et al. Lack of trastuzumab activity in nonsmall cell lung carcinoma with overexpression of erb-B2: 39810: a phase II trial of Cancer and Leukemia Group B. Cancer 2005;103:1670-5.
22. Gatzemeier U, Groth G, Butts C, et al. Randomized phase II trial of gemcitabine-cisplatin with or without trastuzumab in HER2-positive non-small-cell lung cancer. Ann Oncol 2004;15:19-27.
23. Lara PN Jr, Laptalo L, Longmate J, et al. Trastuzumab plus docetaxel in HER2/neu-positive non-small-cell lung cancer: a California Cancer Consortium screening and phase II trial. Clin Lung Cancer 2004;5:231-6.
24. Langer CJ, Stephenson P, Thor A, et al. Trastuzumab in the treatment of advanced non-small-cell lung cancer: is there a role? Focus on Eastern Cooperative Oncology Group study 2598. J Clin Oncol 2004;22:1180-7.
25. Ross HJ, Blumenschein GR Jr, Aisner J, et al. Randomized phase II multicenter trial of two schedules of lapatinib as first- or second-line monotherapy in patients with advanced or metastatic non-small cell lung cancer. Clin Cancer Res 2010;16:1938-49.
26. De Grève J, Teugels E, Geers C, et al. Clinical activity of afatinib (BIBW 2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2/neu. Lung Cancer 2012;76:123-7.
27. De Greve J, Moran T, Graas MP, et al. Phase II study of afatinib, an irreversible ErbB family blocker, in demographically and genotypically defined non-small cell lung cancer (NSCLC) patients. J Clin Oncol 2013;31:abstr 8063.
28. Gandhi L, Bahleda R, Tolaney SM, 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;32:68-75.
29. Kris MG, Camidge DR, Giacone G, et al. Results with dacomitinib (PF-00299804), an irreversible pan-her tyrosine kinase inhibitor, in a phase II cohort of patients with her2- mutant or amplified lung cancers. J Thorac Oncol 2013;8:S609. Available online: http://journals.lww.com/jto/Citation/2013/11001/15th_World_Conference_on_Lung_Cancer.1.aspx
30. Herbst RS, Davies AM, Natale RB, et al. Efficacy and safety of single-agent pertuzumab, a human epidermal receptor dimerization inhibitor, in patients with non small cell lung cancer. Clin Cancer Res 2007;13:6175-81.

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