JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Lung Cancer That Harbors a *HER2* Mutation: Epidemiologic Characteristics and Therapeutic Perspectives

Julien Mazières, Solange Peters, Benoit Lepage, Alexis B. Cortot, Fabrice Barlesi, Michéle Beau-Faller, Benjamin Besse, Hélène Blons, Audrey Mansuet-Lupo, Thierry Urban, Denis Moro-Sibilot, Eric Dansin, Christos Chouaid, Marie Wislez, Joachim Diebold, Enriqueta Felip, Isabelle Rouquette, Julie D. Milia, and Oliver Gautschi

A B S T R A C T

Purpose

HER2 mutations are identified in approximately 2% of non–small-cell lung cancers (NSCLC). There are few data available that describe the clinical course of patients with *HER2*-mutated NSCLC.

Patients and Methods

We retrospectively identified 65 NSCLC, diagnosed with a *HER2* in-frame insertion in exon 20. We collected clinicopathologic characteristics, patients' outcomes, and treatments.

Results

HER2 mutation was identified in 65 (1.7%) of 3,800 patients tested and was almost an exclusive driver, except for one single case with a concomitant *KRAS* mutation. Our population presented with a median age of 60 years (range, 31 to 86 years), a high proportion of women (45 women *v* 20 men; 69%), and a high proportion of never-smokers (n= 34; 52.3%). All tumors were adenocarcinomas and 50% were stage IV at diagnosis. For these latter cases, 22 anti–human epidermal growth factor receptor 2 (HER2) treatments were administered after conventional chemotherapy in 16 patients. Subsequently, four patients experienced progressive disease, seven experienced disease stabilizations, and 11 experienced partial responses (overall response rate, 50%; disease control rate [DCR], 82%). Specifically, we observed a DCR of 93% for trastuzumab-based therapies (n = 15) and a DCR of 100% for afatinib (n = 3) but no response to other HER2-targeted drugs (n = 3). Progression-free survival for patients with HER2 therapies was 5.1 months. Median survival was of 89.6 and 22.9 months for early-stage and stage IV patients, respectively.

Conclusion

This study, the largest to date dedicated to *HER2*-mutated NSCLC, reinforces the importance of screening for *HER2* mutations in lung adenocarcinomas and suggests the potential efficacy of HER2-targeted drugs in this population.

J Clin Oncol 31. © 2013 by American Society of Clinical Oncology

INTRODUCTION

Lung cancer remains the leading cause of cancerrelated death worldwide. Research into the molecular basis of lung cancer has revealed insights into various critical pathways that are deregulated in lung tumorigenesis and, in particular, the key driver genetic alterations that control cell survival and proliferation. The oncogene addiction model proposes that cancers harboring such gene amplifications, rearrangements, or mutations rely on the protein produced by the gene, which dictates their malignant phenotype and can be thus referred to as driver alterations.¹ Among them, epidermal growth factor receptor (*EGFR*) –activating mutations or rearrangement of the anaplastic lymphoma kinase (*ALK*) gene are associated with better outcomes when targeted by selective tyrosine kinase inhibitors. Other transforming genetic alterations have been identified, including *MET* and *FGFR1* amplification, *PIK3CA*, *AKT*, *KRAS*, *NRAS*, *BRAF*, *MEK1*, *AKT1*, *FGFR2*, *DDR2*, and *HER2* mutations, as well as *RET* and *ROS1* rearrangements found in rare subsets of non–small-cell lung cancer (NSCLC). Their frequency depends on the histologic subtype and some are associated with specific clinical characteristics, such as smoking history, gender, or ethnicity. However, the epidemiology of most of these biomarkers remains elusive and the natural history of diseases that carry such genetic changes remains unspecified.

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

Julien Mazières, Julie D. Milia, Hôpital Larrey, Centre Hospitalier Universitaire de Toulouse. Université de Toulouse III (Paul Sabatier): Benoit Lepage, Centre Hospitalier Universitaire Toulouse; Isabelle Rouquette, Hôpital Ranqueil, Centre Hospitalier Universitaire de Toulouse, Toulouse; Alexis B. Cortot, Centre Hospitalier Universitaire de Lille: Eric Dansin, Centre Oscar Lambret, Lille: Fabrice Barlesi, Hôpital Nord, Marseille: Michéle Beau-Falle, Hôpita de Hautepierre. Centre Hospitalier Universitaire de Strasbourg et EA 4438. Université de Strasbourg, Strasbourg Benjamin Besse, Institut Gustave Roussy: Hélène Blons, Hôpital Européen Georges Pompidou, Hôpitaux de Paris; Audrey Mansuet-Lupo, Hôtel Dieu; Christos Chouaid, Hôpital Saint Antoine; Marie Wislez, Hôpital Tenon; Thierry Urban, Centre Hospitalier Universitaire, Angers; Denis Moro-Sibilot, Hôpital A, Michallon, Centre Hospitalier Universitaire, Grenoble, France: Solange Peters, Centre Hospitalier Universitaire Vaudois, Lausanne; Joachim Diebold, Oliver Gautschi, Lucerne Cantonal Hospital, Lucerne Switzerland; Enriqueta Felip, Vall d'Hebron University Hospital, Barcelona, Spain

Published online ahead of print at www.jco.org on April 22, 2013.

J.M. and S.P. contributed equally to the work.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Professeur Julien Mazières, MD, PhD, Unité d'Oncologie Cervico-Thoracique, Clinique des Voies Respiratoires, Hôpital Larrey, CHU Toulouse, Chemin de Pouvourville, 31059 Toulouse Cedex, France; e-mail:

mazieres.j@chu-toulouse.fr.

© 2013 by American Society of Clinical Oncology

0732-183X/13/3199-1/\$20.00

DOI: 10.1200/JCO.2012.45.6095

© 2013 by American Society of Clinical Oncology 1

Downloaded from pdf.highwire.org on April 22, 2013. For personal use only. No other uses without permission. Copyright © 2013 American Society of Clinical Oncology. All rights reserved.

Copyright 2013 by American Society of Clinical Oncology

activates downstream signaling through PI3K-AKT and MEK-ERK pathways.² No ligand has been described for this receptor, which is activated by homodimerization or heterodimerization with other members of the erbB family.

HER2 mutations consist of in-frame insertions in exon 20, leading to constitutive activation of the receptor and downstream AKT and MEK pathways.³ *HER2* mutations respond to the genetic driver definition and preclinical models have proved the concept of transforming property of such a genetic alteration.⁴ Inducible expression of a HER2 mutant (HER2YVMA) in lung epithelium of mice results in the emergence of invasive adenosquamous carcinomas, with tumor maintenance requiring the continuous expression of the driver, as observed with EGFR-driven cancer.

HER2 protein overexpression and gene amplification are present in 6% to 35% and in 10% to 20%, respectively, of NSCLC.⁵⁻¹⁰ *HER2* mutations were identified in approximately 2% to 4% of NSCLC.¹¹⁻¹³ In the selected population of *EGFR/KRAS/ALK*-mutation–negative patients, *HER2* mutations can reach up to 6%.¹¹ This mutation is predominantly observed in female patients, nonsmokers, and patients with adenocarcinoma subtype, similar to *EGFR*-mutated NSCLC.¹¹⁻¹³

Among reported lung cancer biomarkers, HER2 as a target remains poorly described. HER2 overexpression or gene amplification is widely known to be associated with sensitivity to HER2-targeting drugs (trastuzumab, lapatinib, pertuzumab, and T-DM1) in breast cancer.¹⁴ Involvement of HER2 in lung carcinogenesis has been known for many years but clinical research was slowed down when the first clinical trials with trastuzumab were negative. Indeed, adding trastuzumab to gemcitabine-cisplatin or to docetaxel failed to show any survival benefits in patients with HER2-immunohistochemistry (IHC) –positive lung cancer.¹⁵⁻¹⁶ However, *HER2* mutations may be more relevant in lung carcinogenesis than HER2 amplification or overexpression. Single case reports suggest that *HER2* mutations may be predictive for HER2-targeting therapies in lung cancer^{13,17,18} Some ongoing clinical trials are enrolling patients with *HER2*-mutated, mixed together with *HER2*-amplified or *EGFR*-mutated NSCLC patients. Large biomarker screening programs such as the French National Program or the US Lung Cancer Mutation Consortium thus propose testing for *HER2* mutations.

In this article, our aim was to improve our understanding of the clinicopathologic characteristics of patients with NSCLC who carry the *HER2* mutation, by performing a retrospective study of patients with *HER2*-positive NSCLC from three European countries, constituting a large group of this rare NSCLC subset. We also analyzed the outcome of patients treated with conventional chemotherapy and/or HER2-targeted drugs.

PATIENTS AND METHODS

Patients

This study was conducted in France, Switzerland, and Spain and represents a consecutive series of all identified patients carrying a HER2 mutation in exon 20 in the participating centers. Informed consent from patients and institutional review board approval for genetic analysis and data collection were obtained by all participating institutions. Clinical and biologic data were collected from each patient by pathologists and physicians, respectively. The data were made anonymous at the local centers and then were centralized and analyzed in Toulouse, France. Histology was assessed by a specialist lungcancer pathologist using the WHO criteria, and adenocarcinoma described according to the new International Association for the Study of Lung Cancer classification.¹⁹ Patients who were diagnosed before the new classification were reclassified specifically for the obsolete bronchiolo-alveolar subtype. Histologic review was performed for every patient included in this study to exclude breast cancer. Specific markers such as TTF1, hormonal receptors, cytokeratins, and mammaglobin (if needed) were used to ensure the diagnosis of primary lung tumor. Clinicopathologic stage was assigned according to the seventh tumor-node-metastasis classification.²⁰ We collected clinical data (age at diagnosis, date of diagnosis, tobacco consumption [never, current, former smoker, and packs per year], and tumor stage), outcome variables (recurrence and survival events), and therapeutics parameters (including chemotherapy and HER2-targeted treatment) for all patients. We ensured that the follow-up



Fig 1. Diagnostic of *HER2* mutation (patient No. 32). (A) Sanger sequencing read with heterozygous *HER2* exon 20 insertion (p.G776_777insVC). (B) Human epidermal growth factor receptor 2 (HER2) immunohistochemistry with score 2+ (antibody 4B5). (C) Fluorescent in situ hybridization with *HER2* amplification (*HER2* in red; centromer 17 in green). (D) Tricolor visualization of HER2 protein (in brown), *HER2* gene (in black), and centromer 17 (in red).

2 © 2013 by American Society of Clinical Oncology

JOURNAL OF CLINICAL ONCOLOGY

Downloaded from pdf.highwire.org on April 22, 2013. For personal use only. No other uses without permission. Copyright © 2013 American Society of Clinical Oncology. All rights reserved.

Table 1. Clinical and Biologic Characteristics of Patients With $HER2$ -Mutated Disease (n = 65)						
Characteristic	No. of Patients	%				
Age at diagnosis, years	65	100				
Mean	61.1					
SD	11.6					
Median	60.4					
Sex						
Women	45	69				
Men	20	31				
lobacco	0.4	50.0				
Never	34	52.3				
Former	11	16.9				
Current	12	18.5				
	8	12.3				
i umor stage	11	10.0				
		10.9				
	3	4.0				
	22	Z3.1 50.9				
Unknown	3	1.6				
Metastasis sites for stage IV	33	4.0				
	8	24.2				
Brain	3	9.1				
Bone	2	6.1				
Multiples organs	13	39.4				
Other or unknown	7	21.3				
Abbreviation: SD, standard deviation.						

was performed by a computed tomography scan of the thorax and abdomen once every 6 to 8 weeks in all participating centers, concomitantly with a clinical follow-up every 2 to 3 weeks. Responses were defined as the best response from the start of treatment until disease progression according to response evaluation criteria in solid tumor (RECIST v1.1) guidelines. If needed, a strict reassessment using these criteria was repeated for every case and locally undetermined responses were discussed and solved by a minimum of three investigators involved in this article.

HER2 Sequencing and Fluorescent In Situ Hybridization

Direct sequencing was performed after polymerase chain reaction amplification of *HER2* exon 20 in most participating centers. Purified DNA was sequenced using a BigDye Terminator Cycle Sequencing Kit (Applied Biosystems, Foster City, CA). Sequencing reactions were analyzed on a 16-capillary ABI3130 or on a 48-capillary 3730 DNA Analyzer in both sense and antisense directions from at least two independent amplifications. Sequences reading and alignment were performed with SeqScape software (Applied Biosystems). Other procedures were used in some centers: insertions in exon 20 were identified using fragment analysis, run on a 96 capillaries ABI3730. Primers are available on request.

Fluorescent in situ hybridization (FISH) testing was performed on selected patients with available tissue by dedicated and experienced pathologists. Assessment of *HER2* gene copy number and amplification was performed on the same formalin-fixed paraffin-embedded specimens used for DNA extraction. The Vysis PathVysion *HER2* DNA Probe Kit (Abbott Laboratories, Abbott Park, IL) was used following standard manufacturer's protocol. Tumors were classified as disomy or polysomy (> two copies of HER2 in > 40% of cells), or amplified (HER2/CEP17 ratio per cell > 2 or homogeneously staining regions with > 15 copies in > 10% of the cells).

Statistics

We used percentages for qualitative variables; mean and standard deviation for quantitative variables. We estimated and compared survival curves using Kaplan-Meier method and log-rank tests. Overall survival was calculated from the date of diagnosis to date of death or last follow-up. We compared the overall survival by stage (stage I, II, or III *v* stage IV). Progression-free survival (PFS) is defined as the time elapsed between diagnosis and the first among the following events: tumor progression, ending of the first anti-*HER2*–targeted treatment, or death from any cause; patients who were lost to follow-up without progression were censored. Follow-up was updated as of July 2012. We estimated and compared PFS in the subpopulation of stage IV patients, according to the administration of anti-HER2–targeted drugs. Statistical analyses were performed using STATA SE v11.2 (STATA, College Station, TX).

RESULTS

Genetic Characteristics of Lung Cancer With HER2 Mutations

We identified 65 patients carrying a *HER2* mutation. *HER2* mutation testing was performed in 3,800 patients, leading to an incidence of 1.7%. All tumors displayed an exon-20 mutation within the *HER2* gene coding sequence, as analyzed by validated procedures (see Patients and Methods for details and Fig 1 for examples). All mutations were in-frame insertions of exon 20 (Fig 1A), with duplication of amino acids YVMA at codon 775 (mainly three or 12 amino acids).



Fig 2. Survival curves of patients carrying HER2 mutations. (A) Overall survival in the whole population (n = 65). (B) Overall survival of stage IV patients (n = 33) versus early-stage patients (stages I to III; n = 32).

Patient	First-Line Treatment		Second-Line Treatment		Third-Line Treatment		Fourth-Line Treatment	
	Treatment	Best Disease Response	Treatment	Best Disease Response	Treatment	Best Disease Response	Treatment	Best Disease Response
11	VIN-HER	PR						
15	CAR-PAC-TRAS	SD						
19	TXT-MASA	PD						
24	VIN-TRAS	PR						
26	CAR-PAC-TRAS	PR						
27	VIN-TRAS	PR						
28	VIN-TRAS	SD						
30	LAP	PD						
31	NVB-HER	PR						
32	LAP	PD	TRAS-VIN	PR	AFA	SD	CAR-TRAS	SD
37	VIN-TRAS	PD						
41	DOC-TRAS	PR						
43	VIN-TRAS	PR	AFA	PR				
44	VIN-TRAS	PR	AFA	SD				
45	VIN-TRAS	SD	PAC-TRAS	SD				
47	TRAS	PR						

NOTE. Conventional treatment: CAR, PAC, VIN, and DOC. HER2-specific treatments: TRAS, LAP, AFA, and MASA.

Abbreviations: AFA, afatinib; CAR, carboplatin; DOC, docetaxel; HER2, human epidermal growth factor receptor 2; LAP, lapatinib; MASA, masatinib; NE, not evaluated; NVB, Navelbine (VIN; Pierre Fabre, Castres, France); PAC, paclitaxel; PD, progressive disease; PR, partial response; SD, stable disease; TRAS, trastuzumab; TXT, Taxotere (DOC; sanofi-aventis, Paris, France); VIN, vinorelbine.

All patients were previously tested for *EGFR*, and a vast majority were tested for *KRAS* mutations (93%) and *ALK* rearrangement (91%). If tumor material was still available, *BRAF* and *PI3KCA* mutation tests were also performed. All *HER2*-mutated tumors were found negative for *EGFR*-activating mutation in exon 18 to 21 and *ALK* rearrangement, as well as for *BRAF* and *PI3KCA* mutations. Most of the mutations were exclusive, except for one patient with a tumor carrying a *HER2* mutation plus a classical *KRAS* exon 2 mutation.

Only *HER2* mutations were tested in the vast majority of centers. Nevertheless, some platforms added *HER2* FISH testing on request on *HER2*-mutated NSCLC (Fig 1C). We collected 34 tests. Among them, we found eight samples with *HER2* increased gene copy number in the context of polysomy (23%) and only three with *HER2* amplification (9%).

Clinicopathologic Characteristics of Lung Cancer With HER2 *Mutations*

Clinical features of patients carrying *HER2* mutations were analyzed (Table 1). Patients were diagnosed with *HER2* mutation at a median age of 60.4 years (range, 31 to 86 years; standard deviation, 11.6). Higher proportions of women (45 women v 20 men; 69%) and of never-smokers (34 never-smokers v 11 former-smokers and 12 current-smokers; 52.3%) were observed, with a median of 20 packyears for the smokers. All tumors were adenocarcinomas, including two with a lepidic component. All stages were represented: 11 patients with stage I, three patients with stage II, 15 patients with stage III, and 33 patients with stage IV disease. Sites of metastases were lungs (n = 8), brain (n = 3), and bone (n = 2), and most patients had metastases in several organs concomitantly (n = 13). Of interest, we observed a high frequency of patients with disseminated lung nodules and tumor excavation patterns (Appendix Fig A1, online only). Median overall survival was 40 months for all stages. More specifically, overall survival was 89.6 months and 22.9 months for patients with stages I to III disease and stage IV disease, respectively (P = .01; Fig 2).

Treatment Response to HER2-Targeted Drugs in Patients With NSCLC Who Carried a HER2 Mutation

Thirty-three patients with stage IV or recurrent NSCLC received conventional chemotherapy (platinum-based doublet with or without bevacizumab). Of these, 16 patients also received HER2-targeted therapies in additional lines of treatment (Table 2). Because some patients received two (n = 3) or four (n = 1) different HER2-targeting drugs, a total of 22 individual anti-HER2 treatments were evaluable. Overall, we observed four patients with progressive disease, seven with disease stabilization, and 11 with partial responses according to RE-CIST v1.1 (overall response rate, 50%; disease control rate, 82%).



Fig 3. Progression-free survival of stage IV patients treated with anti–human epidermal growth factor receptor 2 (HER2) targeted drugs (n = 15). Only first-line HER2-targeted treatments were analyzed.

JOURNAL OF CLINICAL ONCOLOGY

Downloaded from pdf.highwire.org on April 22, 2013. For personal use only. No other uses without permission. Copyright © 2013 American Society of Clinical Oncology. All rights reserved. Specifically, we observed a disease control rate of 96% for trastuzumab-based therapies (n = 15) and 100% for afatinib (n = 4), but no response to lapatinib (n = 2) or to masatinib (n = 1). It should be noticed that trastuzumab was always used in combination with chemotherapy (vinorelbine, docetaxel, or carboplatin-paclitaxel). In contrast, afatinib and lapatinib were used as monotherapy. We also analyzed PFS from the start of the first HER2-specific treatment until documented disease progression by RECIST v1.1 (n = 15). Median PFS was 5.1 months in patients treated with HER2-targeting drugs (Fig 3). The clinical course of a patient receiving several HER2-targeting drugs is shown in Figure 4, including lapatinib as the first drug, trastuzumab as the second, and afatinib as the third.

DISCUSSION

In this article, we report on the largest series to date (n = 65) of patients with NSCLC and *HER2* mutations. Despite the limitations of this retrospective study, it provides important insights into HER2-driven NSCLC.

Data about the real incidence of *HER2* mutations occurring in patients with lung cancer are heterogeneous, ranging from 1% to 6% in highly selected patients. In this article, we reported an incidence of 1.7%, which is consistent with recent publications.^{9,11-12} Nevertheless, we cannot conclude the real incidence of *HER2* mutations, because we cannot exclude a selection bias in some participating centers.

First, we confirm the suggested profile of patients presenting with *HER2*-mutated NSCLC, as suggested in smaller series.^{11,21} Our NSCLC patients with mutated *HER2* were mainly female, nonsmokers, and exclusively suffering from adenocarcinoma subtype disease. Nevertheless, we identified some men and heavy smokers (up to 60 packs-year) suggesting that *HER2* testing could be guided by tumor subtype (adenocarcinoma), but should not be restricted to clinically defined subgroups. Looking at the natural history of *HER2*-mutated NSCLC, irrespective of the treatment delivered, which was highly variable in our study, we found that overall survival (89 months for early-stage disease and 23 months for stage IV disease) seemed to be better than reported in large, unselected NSCLC cohorts. In a recent series, Arcila et al¹¹ reported a median overall survival of 19 months for patients with *HER2*-mutated NSCLC in advanced stages (stages IIIb



Fig 4. Example of tumor response (patient No. 32). (A) Positron emission tomography-computed tomography scan at initial diagnosis. (B) No response to chemotherapy (platinum, gemcitabine, and bevacizumab, followed by pemetrexed). (C) No response to lapatinib. (D and E) Good partial remission with trastuzumab and vinorelbine. (F) Local progression with trastuzumab maintenance therapy. (G) No response to afatinib. (H) Mixed response to trastuzumab and carboplatin. (I) Disseminated progression, switch to nab (nanoparticle albumin-bound) –paclitaxel and trastuzumab.

5

or IV), compared with a survival rate of 30 months for patients with *EGFR* mutation.

In a meta analysis of 40 published studies, HER2 overexpression assessed by IHC was associated with poor prognosis in NSCLC, specifically in adenocarcinomas, with no prognostic value in squamous cell carcinomas.²² Other reports confirmed the prognostic impact of HER2 overexpression, which has been found in up to 35% of patients with NSCLC.¹⁰ Conversely, *HER2* amplification determined by FISH was not prognostic.²² In our series, because only a subset of patients received HER2-targeted agents in variable lines of treatment, sometimes in the final course of the disease, survival is reported from the time of diagnosis for the whole *HER2*-mutated population. Obviously, the retrospective nature of the report precludes a definitive statement on whether *HER2* mutations in patients with NSCLC are prognostic or predictive. Based on the encouraging responses and the long median survival of our patients, we can speculate that *HER2* mutations are equally predictive and prognostic but this warrants prospective validation.

Most *HER2* mutations described to date are insertions within a small stretch of exon 20 with A775_G776insYVMA insertion/duplication on the COOH-terminal side of the α C-helix. In our series, although many centers sequenced exons 18 to 20 of the *HER2* gene, all patients presented with an exon 20 insertion and no mutation in exons 18 and 19 were found. *HER2* amplification (or polysomy) by FISH was not tested routinely. Nevertheless, we asked some platforms to perform additional FISH on available tissues. As already published,¹¹ we found only a minority of patients with mutated gene with *HER2* real amplification, suggesting that the two molecular alterations are not associated. In addition, until this point, data are lacking to address the possible interest of FISH testing in a general NSCLC population.

We aimed to analyze the potential interest of HER2-targeted drugs. To our knowledge, our report is the largest series to date reporting on HER2-mutated NSCLC treated with HER2-targeted drugs. In our study, 17 patients with advanced NSCLC did not receive any HER2-targeting drugs, owing to the absence of standard at the time of diagnosis, the lack of dedicated clinical trials, and the difficulties to access some unregistered drugs. Some patients were therefore treated following conventional guidelines without taking into account their HER2 mutation status. Available data from the literature concerning HER2-targeted agents in NSCLC are still scarce and are somewhat anecdotal. The addition of trastuzumab to chemotherapy has clearly improved survival in breast cancer patients with HER2 protein expression or gene amplification.14 Trastuzumab in combination with cisplatin and gemcitabine in advanced NSCLC patients failed to show a benefit, although a trend toward better outcome with trastuzumab was observed in patients with strongly positive (3+) HER2-IHC or positive HER2-FISH.¹⁵ In HER2-amplified NSCLC, there seems to be no clear benefit from lapatinib.²³ A single-arm trial with afatinib used as a monotherapy showed a response in three of three evaluable patients with HER2-mutated adenocarcinoma, even in the context of resistance to other EGFR- or HER2-targeted compounds.¹⁷ In addition, there are single reports of patients with HER2-mutated NSCLC who responded to trastuzumab in combination with paclitaxel or vinorelbine.13,18 Trastuzumab is currently being tested as a singleagent in patients with HER2-IHC-positive, HER2-mutated, or HER2amplified NSCLC (trials NCT00004883 and NCT00758134), as well as in combination with carboplatin and paclitaxel. Pertuzumab is currently being tested in a phase II trial in patients with advanced, pretreated NSCLC (trial NCT00063154). Our study indicates that anti-HER2 therapies are associated with encouraging response rates (50%), disease control rates (80%), and PFS (5.1 months) in patients with heavily pretreated HER2-mutated NSCLC. Three different HER2-targeting drugs were used in our study. Trastuzumab and afatinib seemed to be associated with satisfactory disease control, whereas lapatinib was not, which is consistent with a prior case report.¹⁸ In our study, trastuzumab was mostly used in combination with chemotherapy as the first anti-HER2 therapy, whereas lapatinib and afatinib were mostly used at later stages, except in one patient. The relative efficacy of these molecules clearly deserves prospective evaluation in larger international clinical trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors. Employment or Leadership Position: None Consultant or Advisory Role: Denis Moro-Sibilot, Pfizer (C), Roche (C), Boerhinger Ingelheim (C); Eric Dansin, Roche (C); Christos Chouaid, Amgen (C), Eli Lilly (C), GlaxoSmithKline (C) Stock Ownership: None Honoraria: Alexis B. Cortot, Boehringer Ingelheim; Thierry Urban, Roche; Eric Dansin, AstraZeneca, Boehringer Ingelheim, Eli Lilly; Joachim Diebold, Roche Research Funding: Christos Chouaid, Eli Lilly, Roche Expert Testimony: None Other Remuneration: None

AUTHOR CONTRIBUTIONS

Conception and design: Julien Mazières, Solange Peters, Fabrice Barlesi, Oliver Gautschi

Administrative support: Julie D. Milia

Provision of study materials or patients: All authors Collection and assembly of data: Julien Mazières, Solange Peters, Alexis B. Cortot, Fabrice Barlesi, Michéle Beau-Faller, Benjamin Besse, Thierry Urban, Denis Moro-Sibilot, Eric Dansin, Christos Chouaid, Marie Wislez, Joachim Diebold, Julie D. Milia, Oliver Gautschi Data analysis and interpretation: Julien Mazières, Solange Peters, Benoit Lepage, Fabrice Barlesi, Isabelle Rouquette, Julie D. Milia, Oliver Gautschi Manuscript writing: All authors

Final approval of manuscript: All authors

REFERENCES

1. Pao W, Hutchinson KE: Chipping away at the lung cancer genome. Nat Med 18:349-351, 2012

2. Spector NL, Blackwell KL: Understanding the mechanisms behind trastuzumab therapy for

human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol 27:5838-5847, 2009

3. 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 106:474-479, 2009

4. Shimamura T, Ji H, Minami Y, et al: Nonsmall-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 66:6487-6491, 2006

6 © 2013 by American Society of Clinical Oncology

JOURNAL OF CLINICAL ONCOLOGY

5. Rouquette I, Lauwers-Cances V, Allera C, et al: Characteristics of lung cancer in women: Importance of hormonal and growth factors. Lung Cancer 76:280-285, 2012

6. Menard S, Casalini P, Campiglio M, et al: HER2 overexpression in various tumor types, focusing on its relationship to the development of invasive breast cancer. Ann Oncol 12:S15–S19, 2001 (suppl 1)

7. Heinmoller 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 9:5238-5243, 2003

8. Stephens P, Hunter C, Bignell G, et al: Lung cancer: Intragenic ERBB2 kinase mutations in tumours. Nature 431:525-526, 2004

9. Buttitta F, Barassi F, Fresu G, et al: Mutational analysis of the HER2 gene in lung tumors from Caucasian patients: Mutations are mainly present in adenocarcinomas with bronchioloalveolar features. Int J Cancer 119:2586-2591, 2006

10. Pellegrini C, Falleni M, Marchetti A, et al: HER-2/Neu alterations in non-small cell lung cancer: A comprehensive evaluation by real time reverse transcription-PCR, fluorescence in situ hybridization, and immunohistochemistry. Clin Cancer Res 9:3645-3652, 2003

11. Arcila ME, Chaft JE, Nafa K, et al: Prevalence, clinicopathologic associations and molecular spec-

trum of ERBB2 (HER2) tyrosine kinase mutations in lung adenocarcinomas. Clin Cancer Res 18:4910-4918, 2012

12. Shigematsu H, Takahashi T, Nomura M, et al: Somatic mutations of the HER2 kinase domain in lung adenocarcinomas. Cancer Res 65:1642-1646, 2005

13. Tomizawa K, Suda K, Onozato R, et al: Prognostic and predictive implications of HER2/ERBB2/ neu gene mutations in lung cancers. Lung Cancer 74:139-144, 2011

14. Arteaga CL, Sliwkowski MX, Osborne CK, et al: Treatment of HER2-positive breast cancer: Current status and future perspectives. Nat Rev Clin Oncol 9:16-32, 2012

15. Gatzemeier U, Groth G, Butts C, et al: Randomized phase II trial of gemcitabine-cisplatin with or without trastuzumab in HER2-positive non-smallcell lung cancer. Ann Oncol 15:19-27, 2004

16. 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 5:231-236, 2004

17. De Greve 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 76:123-127, 2012

18. Cappuzzo F, Bemis L, Varella-Garcia M: HER2 mutation and response to trastuzumab therapy in non-small-cell lung cancer. N Engl J Med 354:2619-2621, 2006

19. Travis WD, Brambilla E, Noguchi M, et al: International association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of lung adenocarcinoma. J Thorac Oncol 6:244-285, 2011

20. Goldstraw P, Crowley J, Chansky K, et al: The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant turnours. J Thorac Oncol 2:706-714, 2007

21. Li C, Sun Y, Fang R, et al: Lung adenocarcinomas with HER2-activating mutations are associated with distinct clinical features and HER2/EGFR copy number gains. J Thorac Oncol 7:85-89, 2012

22. 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 5:1922-1932, 2010

23. 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 16:1938-1949, 2010

Support

Supported in part by Roche, Boehringer Ingelheim, and GlaxoSmithKline, which provided trastuzumab, afatinib, and lapatinib for some patients.

Mazières et al

Acknowledgment

We thank Klaus Strobel, MD, and Astrid Hirschmann (both from the Cantonal Hospital in Luzern, Switzerland) for the images. We thank all the investigators, including Xavier D'Halluin, MD; Pierre-Laurent Puig, PhD; Raphael Borie, MD; Arslane Rahal, MD; Jacques Cadranel, PhD; Franck Morin; Jeanne Chapron, MD; Dominique Spaeth, MD; Marie Therese Henzi, MD; Alain Ducoloné, MD; Isabelle Honoré, MD; Olivier Mir, MD; Frédéric Beuvon, MD; Jean-Pierre Laaban, MD; Jean-François Regnard, PhD; Maurice Perol, MD; Gérard Oliviero, MD; and Marie-Therese Henzi, MD.

Appendix



Fig A1. Tumor presentation with a high frequency of disseminated nodules and excavation (computed tomography scan for three patients).

8