large open-label phase III studies (LUX-Lung 3 [LL3] and LUX-Lung 6 [LL6]) comparing afatinib with chemotherapy (CT). J Clin Oncol 2014; 32: 5s.
6. Lindeman NI, Cagle PT, Beasley MB et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. Arch Pathol Lab Med 2013; 137: 828–860.
7. Leighl NB, Rekhtman N, Biermann WA et al. Molecular testing for selection of patients with lung cancer for epidermal growth factor receptor and anaplastic lymphoma kinase tyrosine kinase inhibitors: American Society of Clinical Oncology Endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology Guideline. J Clin Oncol 2014; 32: 3673–3679.
8. Reck M, Popat S, Reinmuth N et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25(Suppl 3): iii27–iii39.
9. Nowak F, Soria JC, Calvo F. Tumour molecular profiling for deciding therapy-the French initiative. Nat Rev Clin Oncol 2012; 9: 479–486.
10. Cutz J, Craddock K, Torlakovic E et al. Canadian Anaplastic Lymphoma Kinase Study: a model for multicenter standardization and optimization of ALK testing in lung cancer. J Thorac Oncol 2014; 9: 1255–1263.
11. Gridelli C, Ardizzoni A, Douillard JY et al. Recent issues in first-line treatment of advanced non-small-cell lung cancer: results of an International Expert Panel Meeting of the Italian Association of Thoracic Oncology. Lung Cancer 2010; 68: 319–331.
12. Ellis PM, Vandermeer R. Delays in the diagnosis of lung cancer. J Thorac Dis 2011; 3: 183–188.
13. Pirker R, Herth FJ, Kerr KM et al. Consensus for EGFR mutation testing in non-small cell lung cancer: results from a European workshop. J Thorac Oncol 2010; 5: 1706–1713.
14. Langer CJ. Individualized therapy for patients with non-small cell lung cancer: emerging trends and challenges. Crit Rev Oncol Hematol 2012; 83: 130–144.
15. Zer A, Cutz J, Sekhon HS et al. A targeted intervention to improve awareness to molecular testing in NSCLC. J Clin Oncol 2014; 32: abstr 6547.

Annals of Oncology 26: 1421–1427, 2015
doi:10.1093/annonc/mdv186
Published online 21 April 2015

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

M. G. Kris[1]*, D. R. Camidge[2], G. Giaccone[3], T. Hida[4], B. T. Li[1], J. O'Connell[5], I. Taylor[6], H. Zhang[7], M. E. Arcila[8], Z. Goldberg[9] & P. A. Jänne[10]

[1]Thoracic Oncology Service, Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York; [2]Department of Medical Oncology, University of Colorado Denver, Aurora; [3]Lombardi Cancer Center, Georgetown University, Washington, USA; [4]Department of Thoracic Oncology, Aichi Cancer Center, Chikusa-ku Nagoya, Japan; [5]Pfizer Oncology, Pfizer, Inc., New York; [6]Translational Oncology, Pfizer, Inc., Groton, USA; [7]Pfizer (China) Research & Development Co. Ltd, Pfizer, Inc., Shanghai, China; [8]Molecular Diagnostics Service, Department of Pathology, Memorial Sloan Kettering Cancer Center, New York; [9]Pfizer Oncology, Pfizer, Inc., San Diego; [10]Lowe Center for Thoracic Oncology and the Belfer Institute for Applied Cancer Science, Dana Farber Cancer Institute, Boston, USA

Received 23 February 2015; revised 6 April 2015; accepted 9 April 2015

Background: *HER2* mutations and amplifications have been identified as oncogenic drivers in lung cancers. Dacomitinib, an irreversible inhibitor of HER2, EGFR (HER1), and HER4 tyrosine kinases, has demonstrated activity in cell-line models with *HER2* exon 20 insertions or amplifications. Here, we studied dacomitinib in patients with *HER2*-mutant or amplified lung cancers.

Patients and methods: As a prespecified cohort of a phase II study, we included patients with stage IIIB/IV lung cancers with *HER2* mutations or amplification. We gave oral dacomitinib at 30–45 mg daily in 28-day cycles. End points included partial response rate, overall survival, and toxicity.

Results: We enrolled 30 patients with *HER2*-mutant ($n = 26$, all in exon 20 including 25 insertions and 1 missense mutation) or *HER2*-amplified lung cancers ($n = 4$). Three of 26 patients with tumors harboring *HER2* exon 20 mutations [12%; 95% confidence interval (CI) 2% to 30%] had partial responses lasting 3+, 11, and 14 months. No partial responses occurred in four patients with tumors with *HER2* amplifications. The median overall survival was 9 months from the start of

*Correspondence to: Dr Mark G. Kris, Memorial Sloan Kettering Cancer Center, 300 E 66th St, New York, NY 10065, USA. Tel: +1-11-646-888-4197; E-mail: krism@mskcc.org

dacomitinib (95% CI 7–21 months) for patients with *HER2* mutations and ranged from 5 to 22 months with amplifications. Treatment-related toxicities included diarrhea (90%; grade 3/4: 20%/3%), dermatitis (73%; grade 3/4: 3%/0%), and fatigue (57%; grade 3/4: 3%/0%). One patient died on study likely due to an interaction of dacomitinib with mirtazapine.

Conclusions: Dacomitinib produced objective responses in patients with lung cancers with specific *HER2* exon 20 insertions. This observation validates *HER2* exon 20 insertions as actionable targets and justifies further study of HER2-targeted agents in specific *HER2*-driven lung cancers.

ClinicalTrials.gov: NCT00818441.

Key words: dacomitinib, *HER2* mutations, *HER2* amplification, lung cancers, tyrosine kinase inhibitors

introduction

Aberrations in human epidermal growth factor receptor 2 (HER2, *ERBB2*) have emerged as oncogenic drivers and therapeutic targets in lung cancers, with *HER2* mutations occurring in ~1%–4% [1–5], and *HER2* amplifications occurring in 2%–5% [6–8] of lung adenocarcinomas. Preclinical studies have described the antitumor activity of HER2-targeted therapies, inhibiting both *HER2*-mutant and *HER2*-amplified lung cancer cell lines [9, 10], including mutations in the *HER2* extracellular domain [11]. The growing use of multiplexed genomic assays that can detect both mutations and amplifications has led to the identification of an increasing number of individuals with *HER2*-driven lung cancers [12]. The availability of HER2-targeted agents makes HER2 an 'actionable' target, further spurring the implementation of assays to detect it. Several reports have demonstrated the activity of HER2-directed therapies in patients with *HER2*-mutant [13–16] and *HER2*-amplified [15] lung cancers.

Dacomitinib (PF-00299804; Pfizer, New York, NY) is a pan-HER inhibitor that irreversibly binds to HER2, HER1 (EGFR), and HER4 tyrosine kinases [17, 18]. We have reported the results of the phase II trial of dacomitinib in patients with lung adenocarcinomas clinically and/or molecularly selected for the presence of epidermal growth factor receptor (*EGFR*) mutations [19]. As part of this larger effort, we studied a separate molecularly selected cohort of individuals with tumors harboring *HER2* mutations or amplification.

methods

patients and treatments

We conducted a multicenter, phase II study of adults with pathologically confirmed stage IIIB or IV lung adenocarcinomas, Eastern Cooperative Oncology Group performance status 0–2, and measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST version 1.0) [20]. Results in the group with *EGFR*-driven tumors have been reported [19]. Inclusion and exclusion criteria for this HER2 cohort were identical to the EGFR cohort with the exception of the target and including patients with any prior systemic therapy [19]. Molecular selection was carried out by fluorescence *in situ* hybridization (FISH) or sequencing by multiplexed testing of tumor samples in CLIA laboratories at individual study sites. *HER2* amplification was defined as a HER2/centromere of chromosome 17 signal ratio ≥2 [6, 21]. *HER2* mutations included exon 20 insertions, deletions, and point mutations in intra- or extracellular domains. The study was approved by an Institutional Review Board at each site. All patients provided written, informed consent. This trial was linked to the Lung Cancer Mutation Consortium (LCMC) project (National Cancer Institute, USA, 1RC2CA148394-010, NCT0114286) [4].

We gave dacomitinib 45 mg orally, once-a-day, in 28-day cycles. In five individuals who had received no prior systemic therapy, an initial dose of 30 mg was given. Treatment was continued until disease progression or unacceptable toxicity. Dacomitinib was not continued beyond disease progression.

Tumor assessments were done at baseline, 4 weeks, 8 weeks, and then every 8 weeks. Investigators determined response per RECIST version 1.0 [20]. Toxicities were assessed continuously, classified using the Medical Dictionary for Regulatory Activities (MeDRA; version 15.0) and graded by the National Cancer Institute (USA) Common Terminology Criteria for Adverse Events, version 3.0.1 (NCI CTCAE v3.0.1).

outcomes and assessments

Study end points reported included the proportions of patients with *HER2* mutations and amplifications achieving partial responses, duration of responses, progression-free survival at data analysis cutoff, overall survival at data analysis cutoff, and the frequencies of treatment-related toxicities. The duration of responses was measured from the time of the first documentation of response to the date of disease progression. Progression-free survival was defined as the interval from the date of the first dose of dacomitinib to the date of disease progression or death. Overall survival was defined as the interval from the date of the first dose of dacomitinib to the date of death. The information presented reflects information in the database as of 30 May 2014.

statistical methods

The study proposed to enroll about 25 patients with *HER2*-mutant or amplified lung cancers to explore the activity of dacomitinib in this molecularly defined group. No statistical hypothesis was tested. Time-to-event end points were analyzed using the Kaplan–Meier method. All patients who received any study drug were included in both the response and toxicity analyses. We used SAS version 9.1.3 for all statistical analyses.

results

We enrolled and treated 30 individuals with pathologically confirmed recurrent or *de-novo* lung cancers between January 2011 and February 2013. Patient characteristics are detailed in supplementary Table S1, available at *Annals of Oncology* online. Half were women, 60% were never smokers, and all but two had stage IV disease. Dacomitinib was the first systemic therapy for 17% and 83% had received at least one prior i.v. cytotoxic chemotherapy. Two patients (7%) were previously treated with trastuzumab. Twenty-eight patients were enrolled from Lung Cancer Mutation Consortium sites.

The specific aberrations detected in the 26 patients with *HER2* mutations are detailed in Table 1. Thirteen tumors harbored identical 12-bp exon 20 insertions [A775_G776insYVMA, alternative nomenclature p.Y772_A775dup(c.2313_2324dup)]. There were four 9-bp insertions and three 3-bp insertions. Two patients

Table 1. Description of *HER2* mutations and clinical outcomes of patients treated with dacomitinib

HER2 mutation type Partial responses noted	*HER2* amplification status by FISH (HER2/CEP17 ratio)	Mutation Amino acid change (and nucleotide change)	Alternate nomenclature (based on HGVS guidelines)	Survival from start of dacomitinib (months)
Exon 20 insertion (12-bp duplication)	Not tested	p. A775_G776insYVMA (c. 2324_2325ins12)	p.Y772_A775dup (c.2313_2324dup)	23
Exon 20 insertion (12-bp duplication)	<2.0	p. A775_G776insYVMA (c. 2324_2325ins12)	p.Y772_A775dup (c.2313_2324dup)	10
Exon 20 insertion (12-bp duplication)	<2.0	p. A775_G776insYVMA (c. 2324_2325ins12)	p.Y772_A775dup (c.2313_2324dup)	16
Exon 20 insertion (12-bp duplication)	Not tested	p. A775_G776insYVMA (c. 2324_2325ins12)	p.Y772_A775dup (c.2313_2324dup)	3
Exon 20 insertion (12-bp duplication)	Not tested	p. A775_G776insYVMA (c. 2324_2325ins12)	p.Y772_A775dup (c.2313_2324dup)	2
Exon 20 insertion (12-bp duplication)	Not tested	p. A775_G776insYVMA (c. 2324_2325ins12)	p.Y772_A775dup (c.2313_2324dup)	9
Exon 20 insertion (12-bp duplication)	Not tested	p. A775_G776insYVMA (c. 2324_2325ins12)	p.Y772_A775dup (c.2313_2324dup)	9
Exon 20 insertion (12-bp duplication)	Not tested	p. A775_G776insYVMA (c. 2324_2325ins12)	p.Y772_A775dup (c.2313_2324dup)	29
Exon 20 insertion (12-bp duplication)	<2.0	p. A775_G776insYVMA (c. 2324_2325ins12)	p.Y772_A775dup (c.2313_2324dup)	5
Exon 20 insertion (12-bp duplication)	Not tested	p. A775_G776insYVMA (c. 2324_2325ins12)	p.Y772_A775dup (c.2313_2324dup)	2+
Exon 20 insertion (12-bp duplication)	Not tested	p. A775_G776insYVMA (c. 2324_2325ins12)	p.Y772_A775dup (c.2313_2324dup)	7
Exon 20 insertion (12-bp duplication)	Not tested	p. A775_G776insYVMA (c. 2324_2325ins12)	p.Y772_A775dup (c.2313_2324dup)	14
Exon 20 insertion (12-bp duplication)	<2.0	p. A775_G776insYVMA (c. 2324_2325ins12)	p.Y772_A775dup (c.2313_2324dup)	26+
Exon 20 insertion (9-bp duplication) Partial response Duration 14 months	<2.0	p. P780_Y781insGSP (c. 2339_2340ins GGCTCCCCA)	p.G778_P780dup (c.2331_2339dup)	27
Exon 20 insertion (9-bp duplication) Partial response Duration 11 months	<2.0	p. P780_Y781insGSP (c. 2339_2340ins GGCTCCCCA)	p.G778_P780dup (c.2331_2339dup)	25+
Exon 20 insertion (9 bp)	Not tested	Not specified	Nor specified	4
Exon 20 insertion (9 bp)	<2.0	Not specified	Not specified	8
Exon 20 insertion (3 bp)	<2.0	Not specified	Not specified	3
Exon 20 insertion (3 bp)	Not tested	p. G776 > VC (c.2326_2327insTGT)	p.G776delinsVC (c.2326_2327insTGT)	21
Exon 20 insertion (3 bp)	Not tested	p. G776 > VC (c.2326_2327insTGT)	p.G776delinsVC (c.2326_2327insTGT)	2
Exon 20 insertion	Not tested	Not specified	Not specified	7
Exon 20 insertion	<2.0	Not specified	Not specified	18+
Exon 20 insertion	Not tested	Not specified	Not specified	21+
Exon 20 indel Partial response Duration 3+ months	Not tested	p. M774delinsWLV (c.2320A > TGGCTGG)	p. M774delinsWLV (c.2320delins TGGCTGG)	23+
Exon 20 indel	<2.0	p. G776 > LC (c. 2326G > TTGT)	p.G776delinsLC (c.2326delinsTTGT)	9
Exon 20 missense mutation	Not tested	p. V777L (c.2329G > T)	p. V777L (c.2329G > T)	3

HGVS, Human Genome Variation Society.

doi:10.1093/annonc/mdv186 | 1423

had *HER2* exon 20 indels and one a missense mutation. Mutation details were not specified in three cases with exon 20 insertions. Data on the four *HER2*-amplified cases is detailed in supplementary Table S2, available at *Annals of Oncology* online. Only one case had high-level amplification. Of the 10 patients with *HER2* mutations that were also tested for *HER2* amplification, none were amplified.

Confirmed partial responses were seen in three patients, two with tumors harboring a 9-bp exon 20 insertion, lasting 11 and 14 months and one with a tumor harboring an exon 20 indel lasting 3+ months. The two patients with the exon 20 insertions that had the longest responses had identical amino acid changes (p. P780_Y781insGSP, Table 1). The overall response for the patients with *HER2*-mutant disease was 12% (95% CI 2% to 30%) and 0% (95% CI 0% to 60%) for the four patients with *HER2*-amplified tumors. Figure 1 is a waterfall plot depicting the greatest change in target lesion size for each patient.

For the *HER2*-mutant cohort, the median progression-free survival was 3 months (95% CI 2–4 months). The four individuals with *HER2*-amplified tumors remained progression free for 1, 1, 5, and 5 months. The median overall survival was 9 months from the start of dacomitinib (95% CI 7–21 months) for patients with *HER2*-mutant cancers and their 1-year survival was 44% (95% CI 25–62). Overall survivals were 5, 7, 15, and 22 months for the individuals with *HER2*-amplified tumors. The patient with the highest degree of amplification (*HER2*/CEP17 ratio 17) had the longest survival. Kaplan–Meier survival curves from the start of dacomitinib for the *HER*-mutant and *HER2*-amplified groups are shown in supplementary Figure S1, available at *Annals of Oncology* online.

Treatment-related toxicities are listed in supplementary Table S3, available at *Annals of Oncology* online, reporting the maximum toxicity seen at any time while on study for all 30 patients. Some diarrhea was seen in 90% and skin rash in 73%. There was one case of grade 4 diarrhea and no grade 4 rash. Rash and diarrhea resolved with either supportive measures or dacomitinib cessation. Due to treatment-related toxicity, the dose of dacomitinib was reduced in 17% and in 13%, dacomitinib was stopped. There was one drug-related death. This individual developed hepatic failure likely due to an interaction of mirtazapine and dacomitinib. Mirtazapine is metabolized by CYP2D6 and dacomitinib is a strong inhibitor of the same cytochrome. Mirtazapine was started 6 days after the initiation of dacomitinib. Pharmacokinetic evaluations after development of liver failure revealed plasma mirtazapine levels increased 26-fold over expected. The patient died 13 days after starting mirtazapine.

discussion

This is the first phase II trial of a HER2-targeted agent in patients with lung cancers molecularly selected for study based on the presence of *HER2* mutations or amplification in their tumors. Durable partial responses were documented in 12% of individuals with *HER2* mutations using dacomitinib, an inhibitor of the HER2 tyrosine kinase.

Stephens et al. [1] and Shigematsu et al. [2] independently identified mutations in *HER2* in lung cancers that were mutually exclusive with *EGFR* and *KRAS*. Reports exploring the association between *HER2* amplification and *HER2* mutation in lung cancers have yielded divergent results [3, 22]. Kinase domain mutations, mainly exon 20 insertions and point mutations [3]

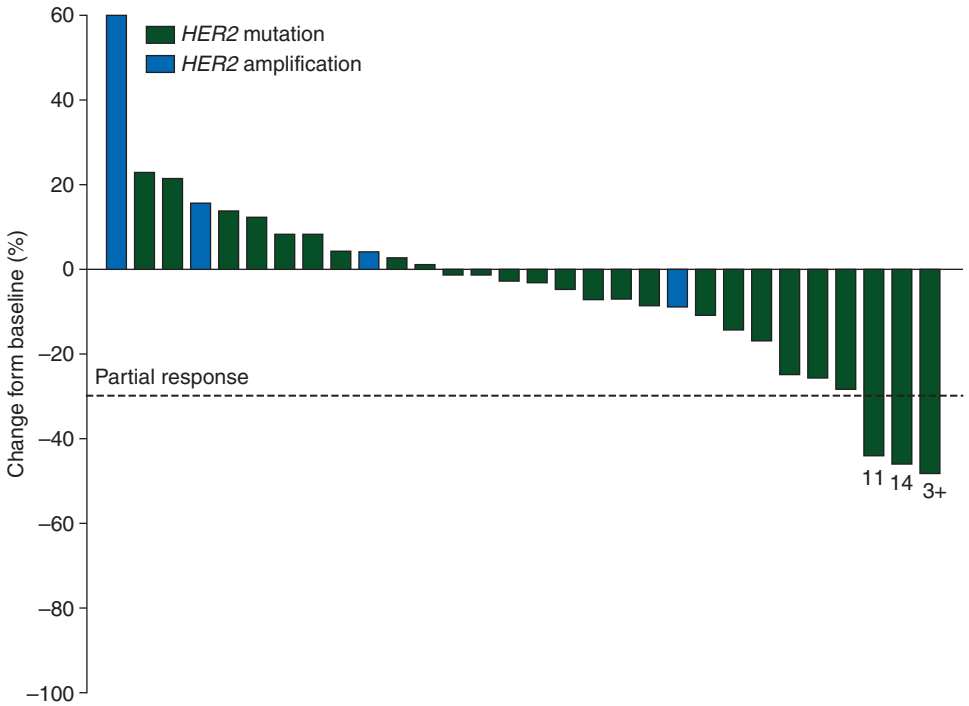

Figure 1. Best change from baseline for each patient ($n = 30$): waterfall. The duration of responses are noted below the bar for each of the three patients with partial responses (RECIST 1.0). Numbers below the bars note the duration of the partial responses in months.

lead to constitutive HER2 kinase activation which is felt to underlie the sensitivity of cancers driven by these mutations to kinase inhibitors [9]. Subsequently, there have been several reports that HER2 kinase inhibitors, including afatinib [13, 14], lapatinib [23], neratinib [24], and neratinib plus temsirolimus [16, 24], can lead to regressions in patients with tumors harboring these mutations. Cappuzzo et al. [15] also reported a partial response in a patient with lung cancer harboring both a *HER2* exon 20 (G776 > LC) mutation and *HER2* amplification, following treatment with the combination of trastuzumab and paclitaxel. The clinical series by Mazieres et al. [13] reported 10 of 16 patients with tumors with YMVA *HER2* exon 20 insertions experienced partial responses to HER2-targeted therapies, 9 of them with concurrent chemotherapy and 8 with trastuzumab. One partial response with trastuzumab alone was reported. Tomizawa reported a response with trastuzumab plus vinorelbine in a similar patient [25]. While a randomized phase II trial by Gatzemeier et al. [21] concluded that the addition of trastuzumab to chemotherapy produced no added activity in HER2 protein overexpressed lung cancers, the six patients with either 3 + HER2 overexpression or *HER2* amplification had a response rate of 83%. A trial of ado-trastuzumab emtansine (TDM-1) in patients with lung cancers with HER2 protein overexpression is underway (ClinicalTrials.gov, NCT02289833). Reviews of this topic have recently been published [26, 27]. But despite these reviews and series, no prospective trials have explored single-agent HER2-targeted agents in patients molecularly selected by the presence of *HER2* mutations or amplifications. The majority of the responses reported were using a HER2-targeted agent with chemotherapy.

The activity of dacomitinib in patients with *HER2* mutations in this trial confirms the earlier reports of benefit with HER2 kinase inhibitors in similar patients. While the responses all provided clinical benefit, they were few in number and were seen only in two of four patients with 9-bp *HER2* exon 20 insertions and one of two patients with indels in *HER2* exon 20. Preclinical studies demonstrate that a number of *HER2* mutations are oncogenic both *in vitro* and *in vivo*, similar to *EGFR* mutations [9, 28]. The sensitivity to dacomitinib among the *HER2* mutations may vary, in part explaining the clinical findings. The most common *HER2* mutation is located in the analogous position as *EGFR* exon 20 insertion mutations and some but not all of these are also dacomitinib sensitive. No partial responses were documented here in patients with the most common *HER2* mutation, a 12-bp insertion in exon 20 (p. A775_G776insYVMA (c. 2324_2325ins12). In contrast, the responses reported with afatinib were described in patients with tumors with the YVMA exon 20 insertion found in 13/26 of the patients in this trial [13, 14]. These observations suggest that the benefits of an individual agent may be confined to specific aberrations and the term 'HER2-positive lung cancers' does not adequately define these illnesses. The specific type of *HER2* mutation, presence and degree of *HER2* amplification, and HER2 protein expression should be precisely defined for each patient in future studies of HER2-targeted agents.

Advances in technology have made it possible to routinely identify oncogenic drivers in patients with lung cancers using multiplex panels [29] which are today recommended for use in all patients with adenocarcinomas in treatment guidelines [30]. The Lung Cancer Mutation Consortium in the United States and the French Cooperative Thoracic Intergroup have detected mutually exclusive *HER2* mutations in 3% (95% CI 2% to 4%) and 1% (95% CI 1% to 2%) of tumors from patients with lung cancers respectively [4, 5]. Next-generation sequencing (NGS) is quickly replacing current multiplex panels. With regard to *HER2*, in addition to identifying mutations in exon 20, NGS panels can assess extracellular domain mutations and the presence of amplifications [12]. These expanding capabilities are increasing the number of patients with *HER2* aberrations that can treated by both approved and investigational agents.

The data reported here have limitations. This was an exploratory study with no predefined primary end point, study outcome, or sample size specific to this HER2 cohort. The end points chosen for this report were the same as for the EGFR cohort previously reported [19]. Because we were uncertain about the frequency of *HER2* mutations and amplifications, no sample sizes were prespecified for either group. Central confirmation of molecular abnormalities was not mandated since *HER2* amplification testing was a standard test for breast cancer specimens and multiplex testing for oncologic drivers carried out within CLIA standards were in place at all study sites. Tissue was not collected to determine HER2 protein expression.

These results with dacomitinib emphasize both the promise and pitfalls of testing drugs in patients with tumors harboring *HER2* aberrations. While durable responses are documented, their frequency is a fraction of what we have observed with kinase inhibitors targeting *EGFR* and *ALK* in mutation-positive cases where response rates in excess of 50% are seen, including a 76% partial response rate and 18 months progression-free survival with dacomitinib in patients with sensitizing *EGFR* mutations [19]. Beyond the diversity of the specific molecular aberrations in *HER2* in lung cancers, the variable effectiveness of HER2 kinase inhibitors may also reflect the inherent activity of the drugs themselves. Although we demonstrated partial responses here with dacomitinib in *HER2*-mutant lung cancers, no responses were reported with the HER2 kinase inhibitor neratinib in similar patients [24]. Care must be taken before concluding that the results for any one agent define the overall effectiveness of 'HER2-targeted therapies' in lung cancers. Future trials must assess adequate numbers of cases with precise molecular alterations for each agent under study. The relationships among *HER2* amplification, HER2 protein expression, and *HER2* mutation are largely unknown. The impact of these abnormalities on therapeutic efficacy of HER2-targeted agents either alone or in the context of *HER2* mutations is equally unclear. Activation of other pathways, particularly PI3KCA/mTOR, may also play a role as suggested by the observation that the combination of the mTOR inhibitor temsirolimus plus neratinib (a HER2 kinase inhibitor) produced a higher response rate in patients with *HER2*-mutant lung cancers than with neratinib alone [24]. Further complicating the picture is the fact that in other cancers, HER2-targeted antibodies show greater clinical benefit than tyrosine kinase inhibitors in *HER2*-amplified cancers despite being far weaker inhibitors of oncogenic HER2 signaling [31]. These knowledge gaps for an important target in a rapidly growing patient group make further research and comprehensive assessment of *HER2* mutation,

HER2 copy number, and HER2 protein expression in all cases enrolled on trials of HER2-targeted agents.

This study also emphasizes the complexity of determining the existence of 'actionable' mutations in lung cancers. Precise molecular targets for 'actionability' require that they are of sufficient frequency to make their study in prospective clinical trials feasible. If the activating mutations of *EGFR* had represented only 15% of all *EGFR* mutations, rather than the 80+ percent that have been found, could clinical trials detect a 'signal' of sufficient clarity to justify drug development? The challenges and resources to identify a drug and prove that it has meaningful clinical activity are substantial. Tracking an activity 'signal' in a 'segment of a segment' of a molecularly defined patient population could prove to be challenging in today's drug development and testing environment. A commitment to sharing precise molecular profiles of tumors using a standardized nomenclature and a searchable database that bridges institutional and pharmaceutical company efforts could go a long way in unraveling these complexities.

This phase II trial of dacomitinib demonstrated that trials of agents targeting HER2 in patients with lung cancers molecularly selected for tumors with *HER2* aberrations are possible and can lead to meaningful responses, but only for selected genotypes. We advocate that single-agent activity for HER2-targeted therapies be documented before proceeding to combination trials and that study of trastuzumab, pertuzumab, and TDM-1 be pursued in patients with *HER2*-amplified tumors. The results presented here can help guide future studies and further raise the hope that the significance of HER2 as a target in lung cancers will continue to grow, both in the numbers of individuals treated and the magnitude of the benefits achieved.

funding

This work was supported by Pfizer, Inc. No grant applied.

disclosure

MGK has received consultancy fees from AstraZeneca, Clovis Oncology, Daiichi Sankyo, and Genentech/Roche; BTL has received consultancy fees from Roche and Biosceptre International. JO, IT, HZ, and ZG are employees and stockholders of Pfizer. MEA has received consultancy fees from AstraZeneca. PAJ has received consultancy fees from Pfizer, AstraZeneca, Boehringer Ingelheim, Clovis Oncology, Chugai, and Genentech; DRC, GG, and TH declare no competing interests.

references

1. Stephens P, Hunter C, Bignell G et al. Lung cancer: intragenic ERBB2 kinase mutations in tumours. Nature 2004; 431: 525–526.
2. Shigematsu H, Takahashi T, Nomura M et al. Somatic mutations of the HER2 kinase domain in lung adenocarcinomas. Cancer Res 2005; 65: 1642–1646.
3. 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: 4910–4918.
4. 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.
5. Nowak F, Calvo F, Soria J. Europe does it better: molecular testing across a national health care system-the French example. Am Soc Clin Oncol Educ Book 2013: 332–337.
6. 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 2003; 9: 5238–5243.
7. Cappuzzo F, Cho YG, Sacconi A et al. p95HER2 truncated form in resected non-small cell lung cancer. J Thorac Oncol 2012; 7: 520–527.
8. The Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. Nature 2014; 511: 543–550.
9. Wang SE, Narasanna A, Perez-Torres M et al. HER2 kinase domain mutation results in constitutive phosphorylation and activation of HER2 and EGFR and resistance to EGFR tyrosine kinase inhibitors. Cancer Cell 2006; 10: 25–38.
10. Bunn PA, Jr, Helfrich B, Soriano AF et al. Expression of Her-2/neu in human lung cancer cell lines by immunohistochemistry and fluorescence in situ hybridization and its relationship to in vitro cytotoxicity by trastuzumab and chemotherapeutic agents. Clin Cancer Res 2001; 7: 3239–3250.
11. 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 USA 2012; 109: 14476–14481.
12. Frampton GM, Fichtenholtz A, Otto GA et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. Nat Biotechnol 2013; 31: 1023–1031.
13. Mazieres 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.
14. 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 2012; 76: 123–127.
15. Cappuzzo F, Bemis L, Varella-Garcia M. HER2 mutation and response to trastuzumab therapy in non-small-cell lung cancer. N Engl J Med 2006; 354: 2619–2621.
16. 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.
17. Engelman JA, Zejnullahu K, Gale CM et al. PF00299804, an irreversible pan-ERBB inhibitor, is effective in lung cancer models with EGFR and ERBB2 mutations that are resistant to gefitinib. Cancer Res 2007; 67: 11924–11932.
18. Janne PA, Boss DS, Camidge DR et al. Phase I dose-escalation study of the pan-HER inhibitor, PF299804, in patients with advanced malignant solid tumors. Clin Cancer Res 2011; 17: 1131–1139.
19. Janne PA, Ou SI, Kim D et al. Phase 2 trial of dacomitinib as initial treatment in patients with clinically and/or molecularly selected advanced non-small cell lung cancer. Lancet Oncol 2014; 15: 1433–1441.
20. Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92: 205–216.
21. 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.
22. 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 2012; 7: 85–89.
23. Kelly RJ, Carter CA, Giaccone G. HER2 mutations in non-small-cell lung cancer can be continually targeted. J Clin Oncol 2012; 30: 3318–3319.
24. Besse B, Soria J-C, Yao B et al. Neratinib (N) with or without Temsirolimus (TEM) in patiens (PTS) with non-small cell lung cancer (NSCLC) carrying HER2 somatic mutations: an international randomized phase II study. Ann Oncol 2014; 25(suppl 4): v1–v41.
25. 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: 139–144.
26. Landi L, Cappuzzo F. HER2 and lung cancer. Expert Rev Anticancer Ther 2013; 13: 1219–1228.

27. Ricciardi GR, Russo A, Franchina T et al. NSCLC and HER2: between lights and shadows. J Thorac Oncol 2014; 9: 1750–1762.
28. 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 USA 2009; 106: 474–479.
29. Pao W, Kris MG, Iafrate AJ et al. Integration of molecular profiling into the lung cancer clinic. Clin Cancer Res 2009; 15: 5317–5322.
30. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. http://wwwnccnorg/professionals/physician_gls/pdf/nsclpdf 2014; Version 2.2015 (13 February 2015, date last accessed).
31. Moasser MM. Two dimensions in targeting HER2. J Clin Oncol 2014; 32: 2074–2077.

Annals of Oncology 26: 1427–1433, 2015
doi:10.1093/annonc/mdv197
Published online 23 April 2015

FOLFIRI plus bevacizumab as second-line therapy in patients with metastatic colorectal cancer after first-line bevacizumab plus oxaliplatin-based therapy: the randomized phase III EAGLE study†

S. Iwamoto[1,‡*], T. Takahashi[2,‡], H. Tamagawa[3], M. Nakamura[4], Y. Munemoto[5], T. Kato[6], T. Hata[7], T. Denda[8], Y. Morita[9], M. Inukai[10], K. Kunieda[11], N. Nagata[12], K. Kurachi[13], K. Ina[14], M. Ooshiro[15], T. Shimoyama[16], H. Baba[17], K. Oba[18], J. Sakamoto[19] & H. Mishima[20]

[1]Department of Surgery, Kansai Medical University Hirakata Hospital, Hirakata; [2]Department of Surgical Oncology, Gifu University Graduate School of Medicine, Gifu; [3]Department of Gastroenterological Surgery, Osaka General Medical Center, Osaka; [4]Aizawa Comprehensive Cancer Center, Aizawa Hospital, Matsumoto; [5]Department of Surgery, Fukuiken Saiseikai Hospital, Fukui; [6]Department of Surgery, Kansai Rosai Hospital, Amagasaki; [7]Department of Surgery, Osaka University, Suita; [8]Department of Gastroenterology, Chiba Cancer Center, Chiba; [9]Department of Radiology, Kobe Medical Center, Kobe; [10]Department of Integrated Medicine, Kagawa University, Kita; [11]Department of Surgery, Gifu Prefectural General Medical Center, Gifu; [12]Department of Surgery, Kitakyushu General Hospital, Kitakyusyu; [13]Second Department of Surgery, Hamamatsu University School of Medicine, Shizuoka; [14]Department of Medical Oncology, Nagoya Memorial Hospital, Nagoya; [15]Department of Surgery, Toho University Medical Center Sakura Hospital, Sakura; [16]Department of Chemotherapy, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo; [17]Department of Gastroenterological Surgery, Kumamoto University, Kumamoto; [18]Department of Biostatistics, School of Public Health, Graduate School of Medicine and Interfaculty Initiative in Information Studies, The University of Tokyo, Tokyo; [19]Tokai Central Hospital, Kagamihara; [20]Cancer Center, Aichi Medical University, Nagakute, Japan

Received 18 February 2015; revised 14 April 2015; accepted 15 April 2015

Background: A targeted agent combined with chemotherapy is the standard treatment in patients with metastatic colorectal cancer (mCRC). The present phase III study was conducted to compare two doses of bevacizumab combined with irinotecan, 5-fluorouracil/leucovorin (FOLFIRI) in the second-line setting after first-line therapy with bevacizumab plus oxaliplatin-based therapy.

Patients and methods: Patients were randomly assigned to receive FOLFIRI plus bevacizumab 5 or 10 mg/kg in 2-week cycles until disease progression. The primary end point was progression-free survival (PFS), and secondary end points included overall survival (OS), time to treatment failure (TTF), and safety.

Results: Three hundred and eighty-seven patients were randomized between September 2009 and January 2012 from 100 institutions in Japan. Baseline patient characteristics were well balanced between the two groups. Efficacy was evaluated in 369 patients (5 mg/kg, $n = 181$ and 10 mg/kg, $n = 188$). Safety was evaluated in 365 patients (5 mg/kg, $n = 180$ and 10 mg/kg, $n = 185$). The median PFS was 6.1 versus 6.4 months (hazard ratio, 0.95; 95% confidence interval [CI] 0.75–1.21; $P = 0.676$), and median TTF was 5.2 versus 5.2 months (hazard ratio, 1.01; 95% CI 0.81–1.25; $P = 0.967$), respectively, for the bevacizumab 5 and 10 mg/kg groups. Follow-up of OS is currently ongoing. Adverse events, including hypertension and hemorrhage, occurred at similar rates in both groups.

*Correspondence to: Dr Shigeyoshi Iwamoto, Department of Surgery, Kansai Medical University Hirakata Hospital, Shinnmachi 2-3-1, Hirakata, Osaka 573-1010, Japan. Tel: +81-72-804-0101; E-mail: iwamoto@hirakata.kmu.ac.jp

†Previously presented in part at the 2013 American Society of Clinical Oncology Annual Meeting, May 31–June 4, 2013, Chicago, IL.
‡Both authors contributed equally to this study.