ORIGINAL ARTICLE

Afatinib in NSCLC With *HER2* Mutations: Results of the Prospective, Open-Label Phase II NICHE Trial of European Thoracic Oncology Platform (ETOP)

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ABSTRACT

Introduction: Mutations in erb-b2 receptor tyrosine kinase 2 (*HER2*) oncogene are observed in approximately 3% of lung adenocarcinomas or mixed tumors with adenocarcinoma component. Activity of various biologically distinct HER2 inhibitors, including the pan-HER inhibitor afatinib, has been reported in several retrospective trials or small series in advanced pretreated NSCLC with *HER2* mutations. We report the first prospective evaluation of afatinib for the treatment of this molecularly defined entity.

Methods: NICHE, a single-arm phase II trial using a two-stage Simon's design, explored the potential of afatinib to control disease in pretreated patients with advanced NSCLC harboring *HER2* exon 20 mutations. A total of 13 patients entered the trial and were treated with afatinib 40 mg/day until tumor progression or lack of tolerability.

Results: The first-stage stopping boundary was crossed when five of nine patients did not achieve disease control at 12 weeks. The accrual into the trial was stopped with total 13 patients enrolled, with 7 (53.8%) achieving disease control at 12 weeks. Except for 1 patient with early death, progression was documented for all patients, with median progression-free survival of 15.9 weeks (95% confidence

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interval: 6.0–35.4), and median overall survival of 56.0 weeks (95% confidence interval: 16.3– upper limit not estimable). The toxicity profile was in the expected range.

Conclusions: Afatinib did not show the expected potential for disease control in NSCLC. However, more than half of the patients in the full cohort achieved disease control at 12 weeks.

Keywords: NSCLC; erb-b2 receptor tyrosine kinase 2 (*HER2*) mutations; Afatinib

Introduction

Progress in molecular characterization of NSCLC led to identification of several oncogenic driving molecular aberrations, such as *EGFR*, erb-b2 receptor tyrosine kinase 2 (*HER2*), *KRAS*, *BRAF,* and Mesenchymal-epithelial transition factor gene (c*MET*) exon 14 skipping mutations or ALK receptor tyrosine kinase (*ALK*), *ROS1,* and ret proto-oncogene (*RET*) rearrangements. Mutations in *HER2* oncogene are well characterized in NSCLC; they are observed in approximately 3% of lung adenocarcinomas or mixed tumors with adenocarcinoma component, and typically constitute insertions in exon 20, encoding tyrosine kinase of the gene.[1] The most common 12 bp insertion, resulting in duplication of amino acids YVMA at codon 775, is observed in approximately 80% of *HER2*-mutant tumors, whereas single amino acid substitutions are found in the remaining cases.[2] These mutations have functional significance, leading to activation of the HER2 tyrosine kinase activity and subsequent downstream signaling, resulting in increased proliferation and tumor growth.[3] Patients presenting with *HER2*-mutant tumors are in majority women, moderately younger than the median age for patients with lung cancer, and more frequently never- or light-smokers.[4,5]

Given the rarity of this disease, the activity of various biologically distinct HER2 inhibitors in *HER2* mutant NSCLC is mostly characterized in cohort studies and phase II clinical trials only.[6-11]

Afatinib, an oral, irreversible pan-HER inhibitor commonly used in patients with tumors harboring *EGFR* mutations, has been associated with some activity in patients with *HER2*-mutant tumors,[10,12,13-15] although prospective clinical trials with this agent are lacking.

The aim of the NICHE trial, a single-arm, Simon's two-stage, phase II clinical trial, was to prospectively assess the activity of afatinib in a multicenter setting in NSCLC patients with *HER2*-mutant tumors.

Material and Methods

Study Participants

Adult patients with histologically confirmed predominantly nonsquamous cell lung cancer were eligible for the study after locally documented exon 20 *HER2*-activating mutations in the tumor samples. Small-cell histologic components were excluded. Other eligibility criteria included stage IIIB (not amenable to definitive treatment) or IV according to the seventh edition of the TNM classification, measurable disease according to Response Evaluation Criteria in Solid Tumors 1.1 criteria, platinum-refractory disease, Eastern Cooperative Oncology Group performance status 0–2, life expectancy more than 3 months, as well as adequate hematologic, renal, and hepatic function. Patients were excluded from the trial if they were previously treated with HER2 tyrosine kinase inhibitor (TKI) or HER2-directed monoclonal antibody or other concurrent anticancer therapies.

The protocol was approved by institutional review boards at each site and the trial was conducted in accordance with the Declaration of Helsinki, the Guideline for Good Clinical Practice, and the International Conference on Harmonization Tripartite Guideline. Safety was reviewed by the European Thoracic Oncology Platform (ETOP) Independent Data Monitoring Committee.

The trial is registered with ClinicalTrials.gov, number NCT02369484.

Study Treatment

Patients enrolled in the trial received oral afatinib at a dose of 40 mg once daily. Treatment continued until disease progression, intolerable toxicity, or the patient or investigator decided to discontinue treatment. Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 4. Treatment compliance was assessed with patient diaries.

Trial Design and Statistical Methods

The primary objective of the phase II NICHE study was to evaluate the efficacy of afatinib treatment to control disease in platinum-pretreated patients with advanced NSCLC harboring *HER2* exon 20 mutations. The primary endpoint evaluated at 12 weeks was disease control rate (DCR), where disease control (DC) was defined as complete (CR) or partial response (PR), or stable disease (SD) lasting at least 12 weeks.

For sample size determination, a Simon's two stage phase II design was adopted.[16] The null hypothesis of DCR less than or equal to 50% was tested versus the alternative of DCR greater than or equal to 75%. For a one-sided type I error of 10% and power of 80%, a total

of 22 patients were needed to enter the study, with 9 patients in the first stage. If 6 of 9 patients in the first stage achieved DC at 12 weeks, then the trial would proceed to the second stage and recruit an additional 13 patients for a total of 22 patients. If at least 14 of 22 patients achieved DC, then this finding would indicate that it would be reasonable to proceed to a phase III trial. The binomial exact one-sample test was used for evaluation of the primary endpoint (DCR).[16,17]

Secondary endpoints included objective response (OR), defined as best overall response (CR or PR, according to Response Evaluation Criteria in Solid Tumors 1.1 criteria)[18] across all assessment timepoints during the period from enrollment to termination of trial treatment; progression-free survival (PFS), defined as the time from the date of enrolment until documented progression or death; overall survival (OS), defined as time from the date of enrollment until death from any cause (censoring occurring at the last follow-up date) and toxicity as specified by the adverse events classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.

Interim safety analyses for the full cohort were conducted every 6 months, and reviewed by the ETOP's Independent Data Monitoring Committee (IDMC).

The final statistical analysis was implemented when the last enrolled patient completed 6 months of follow-up and was performed for all enrolled patients. DCR was calculated along with a 90% exact binomial confidence interval (CI). PFS and OS (medians and rates) were estimated based on the product-limit Kaplan-Meier method, whereas the complementary log-log transformation was used for the corresponding 95% CIs for the median values. A spider plot was also used to show for each patient the change over time in the sum of target lesions' diameters relative to baseline measurement.

In addition, sensitivity analyses exploring the robustness of the interim results were performed through simulations. All analyses were performed with the SAS 9.4 statistical package, whereas R was used for specific plots and the simulations performed for sensitivity analysis.

Translational Research

The presence of *HER2* mutation was assessed according to the standard assay used in the local laboratories. Tissue biopsy timing was not specified. Appropriate molecular tests to detect clinically relevant *HER2* mutations included direct sequencing of exon 20 of the *HER2* gene, validated polymerase chain reaction–based techniques, and clinically validated next-generation sequencing methods, according to the standards of each laboratory. Presence of *HER2* mutation was centrally confirmed by next-generation sequencing. No HER2-targeted agent was allowed before inclusion, excluding a specific selective pressure on that signaling pathway, which might have impacted the HER-2 mutational detection.

Archival formalin-fixed, paraffin-embedded tumor samples of patients participating in the trial were sent for central confirmation of *HER2* mutational status, assessment of other driving molecular aberrations, programmed death ligand 1 (PD-L1) expression by clone SP142 antibody (Ventana, Oro Valley, Arizona) and total mutational burden (TMB) to better characterize this rare cohort. The above assessments were performed through the Foundation Medicine service (www.foundationmedicine.com).

Results

Patients

A total of 13 patients from three European institutions were enrolled in the NICHE trial from September 2015 until August 2016.

The baseline characteristics are summarized in Table 1. The median age of the 13 enrolled patients was 59 years (range: 39 to 82 years). Nine (69.2%) patients were female, 8 (61.5%) patients were never-smokers, and only 2 patients (15.4%) had a performance status of 2. According to the trial's inclusion criteria, all patients had received platinum-based chemotherapy. During the trial, afatinib was administered as the second line of treatment in 6 patients (46.2%), third line in 4 patients (30.8%), and higher line in the remaining 3 patients (23.1%). After progression on afatinib, subsequent therapy was administered in 7 patients (53.8%).

Interim Efficacy Analysis: First Stage in Simon's Two-Stage Design

The interim analysis, evaluating the 12-week status of the first nine patients according to the first stage of Simon's two-stage optimal design, was presented to the ETOP IDMC in October 2016. Five patients (55.6%) had progressed by 12 weeks, and thus, the stopping threshold of at most three patients not achieving DC by 12 weeks was crossed. Based on these results, and following the recommendation of the ETOP IDMC, the trial Steering Committee decided to stop recruitment into the trial. Treatment and follow-up for the enrolled patients continued as per protocol.

Sensitivity Analysis

To evaluate how often a different ordering of the enrollment of patients could lead to a different interim analysis decision, sensitivity analysis was performed

Table 1. Patient and Tumor Characteristics

Characteristic	All patients (N = 13)
Age (y at enrollment)	
n (%)	13
Mean (95% CI)	58.8 (51.2, 66.4)
Median (min-max)	59 (39-82)
Sex, n (%)	
Female	9 (69.2)
Male	4 (30.8)
Smoking history, n (%)	
Current	1 (7.7)
Former	4 (30.8)
Never	8 (61.5)
ECOG performance status (at enrollment), n (%)	
0	7 (53.8)
1	4 (30.8)
2	2 (15.4)
Treatment information	
Type of prior platinum treatment	
Adjuvant	2 (15.4)
Advanced disease	11 (84.6)
Afatinib treatment line	
Second	6 (46.2)
Third	4 (30.8)
Fourth	1 (7.7)
Fifth	2 (15.4)
Further treatment	
Yes	7 (53.8)
No	3 (23.1)
Not applicable	3 (23.1)
Type of further treatment	
Carbo/gem/trastuzumab ×2 cycles with PD	1 (7.7)
Carboplatin/pemetrexed	1 (7.7)
Cisplatin/pemetrexed	1 (7.7)
Combination of RAF and ERK inhibitor	1 (7.7)
Trastuzumab − paclitaxel, pemetrexed monotherapy	1 (7.7)
WBRT 5 × 4 Gy, paclitaxel-trastuzumab 2×; PD nivolumab	1 (7.7)
Tremelimumab/durvalumab followed by durvalumab maintenance	1 (7.7)
No/not applicable	6 (46.2)

CI, confidence interval; min, minimum; max, maximum; ECOG, Eastern Cooperative Oncology Group; PD, progression of disease; ERK, extracellular signal-regulated kinase; WBRT, whole brain radiotherapy.

through simulations. For the 13 enrolled patients, there are 715 different sets of nine patients with the observed five cases of progression. A percentage of 78.3% of these sets would have led to stopping the trial at the first stage. Correspondingly, only 21.7% of them would have allowed continuation of the trial to completion.

Further, the conditional probability of study success, if it had continued to completion, was explored. Considering what was already observed (i.e., 7 of the first 13 patients reaching 12 weeks with DC), success would require that at least 7 of the next 9 patients entering the study, reached 12 weeks with DC. Based on the observed information and assuming that the probability of success for the next 9 patients is 0.538 (i.e., the same as the one observed for the 13 patients), the probability of success of the hypothetical full study would be only 13.3%.

In a further sensitivity analysis at the Simon's first stage 1 patient, for whom the central conformation of the *HER2* mutation failed, was excluded from the safety analysis. In this case, the conclusion would still have been the same; that is, the stopping threshold would have been crossed.

Efficacy

In the full cohort of 13 patients, 7 patients (53.8%; 90% CI: 28.7%–77.6%) achieved DC by week 12. There was no CR, only 1 patient (7.7%) achieved confirmed PR, and 6 patients (46.2%) achieved SD. There was 1 early death at 7 days after enrollment (non-evaluable for response), and 5 patients were classified as having progression of disease (38.5%) by week 12.

The retrospective central analysis of tumor samples allowed for identification of the type of *HER2* mutation. The spider plot in Figure 1 shows the change over time in tumor size (sum of target lesions' diameters) relative to the baseline measurement for each patient according to the *HER2* mutation (A775_G776insYVMA versus others) type. It includes the 12 patients with at least 1 post-treatment tumor assessment.

At a median follow-up of 76.9 weeks, all 13 patients enrolled in the study had progressed, with median PFS of 15.9 weeks (95% CI: 6.0–35.4), and a 12-week PFS rate of 53.8% (95% CI: 24.8%–76.0%) (Fig. 2). In OS analysis, 8 deaths had been recorded, with median OS of 56 weeks (95% CI: 16.3–not estimable), and 36-week OS rate of 69.2% (95% CI: 37.3%–87.2%) (Fig. 2).

Safety

Adverse events were reported for all 13 patients and were generally consistent with current data on afatinib toxicity. Most frequent grade 1–2 events included diarrhea, vomiting, abdominal pain, skin rash, paronychia, fatigue, mucositis, and dyspnea. Grade 3–4 toxicities were uncommon (<10% of patients for each event except dyspnea, which occurred in 2 of 13 patients) and included oral mucositis, dyspnea, epistaxis, pleural effusion, gamma-glutamyl transferase increase, electrolyte abnormalities, urinary tract obstruction, paraplegia, anemia, and febrile neutropenia. There was 1 patient with fatal acute renal injury, possibly related to afatinib, who died 7 days after enrollment into the trial.

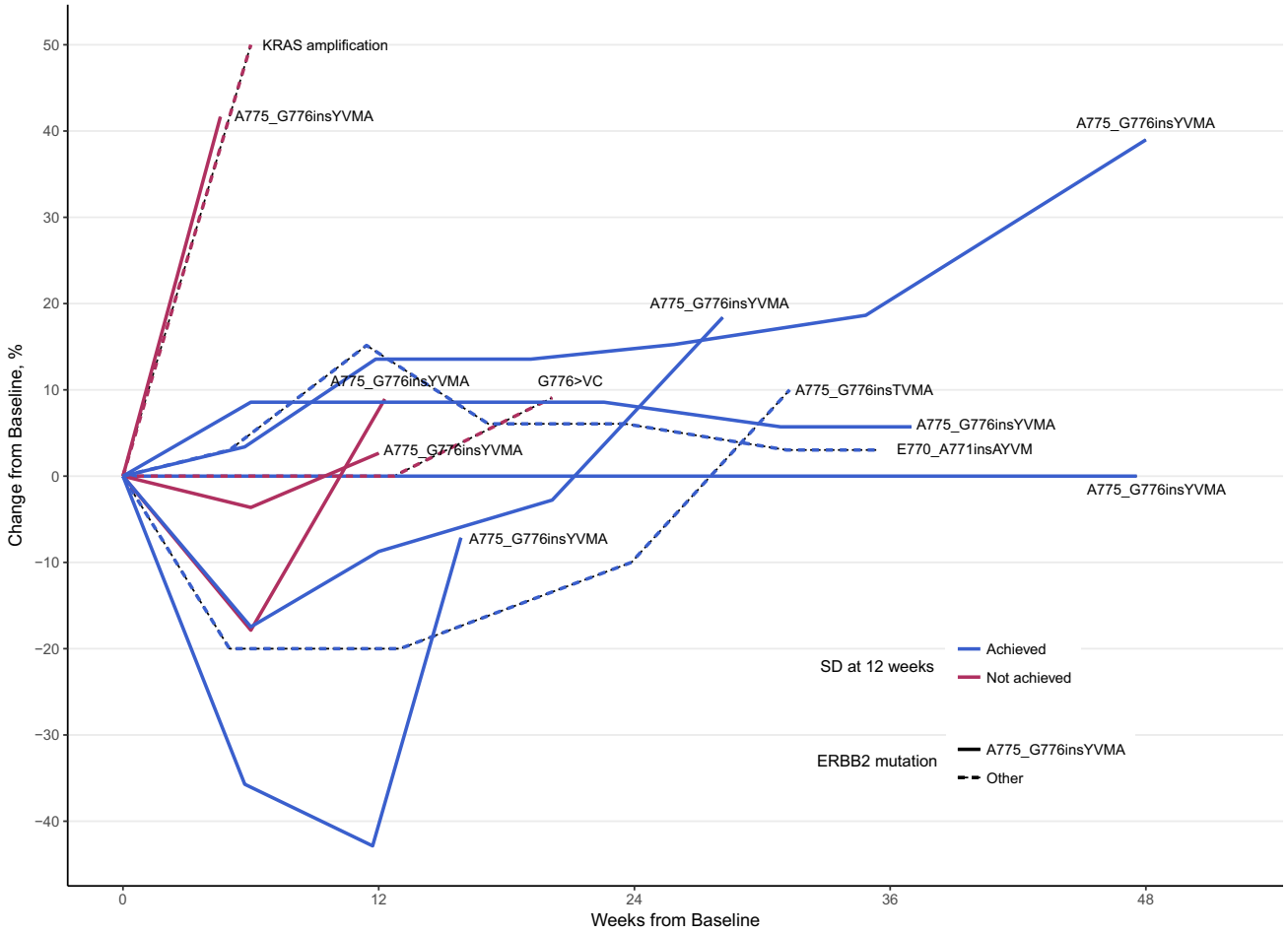


Figure 1. Plot of tumor response by week (spider plot) for all patients evaluable for tumor-response (n = 12, excluding 1 patient with early death [8 days]). SD, stable disease.

Translational Research

The ETOP 7–14 NICHE trial provided an excellent opportunity to extensively characterize the rare group of NSCLC patients with *HER2*-activating mutations. In retrospective central assessment, one tumor sample was not confirmed as having activating exon 20 *HER2* mutation. In the tumor of one patient who did not respond to afatinib, *KRAS* amplification was found as a possible driving abnormality.[19] This tumor showed the highest TMB (19 mut/Mb) in the entire cohort. All other samples had confirmed *HER2* mutations, with frequency in accordance with literature data.[20] PFS time along with important clinical and molecular characteristics of each study participant is shown in Figure 3. In 12 patients with confirmed *HER2* mutations, we found no other known oncogenic drivers, such as *EGFR*, *KRAS*, *BRAF*, *MET*, or *MEK* mutations or known driving gene rearrangements, such as *ALK*, *ROS1* or *RET*. PD-L1 expression was evaluable in six tumor samples and was negative in all cases. Two of those samples showed weakly or moderately PD-L1-positive tumor immune-infiltrate score, whereas the remaining four samples were negative. TMB was evaluable in 11 samples, showing low levels (2 to 7 mut/Mb), except for the one sample with centrally unconfirmed *HER2* mutation, where TMB was high (19 mut/Mb).[21-23] All available results from translational research for the NICHE patients are presented in the supplement (Table S1).

Discussion

In the NICHE trial, afatinib therapy in pretreated patients with advanced NSCLC harboring *HER2* exon 20 mutations resulted in a lower DCR than expected based on the Simon's two-stage design and failed to meet the set criteria for further clinical testing. Beyond the boundaries of these trial results, signs of activity were seen in the full analysis set with 13 patients, with a total of 7 patients (53.8%) achieving DC at 12-weeks.

HER2 is a known oncogenic driver. In NSCLC, activation of HER2 can occur through various mechanisms including protein overexpression, gene copy number

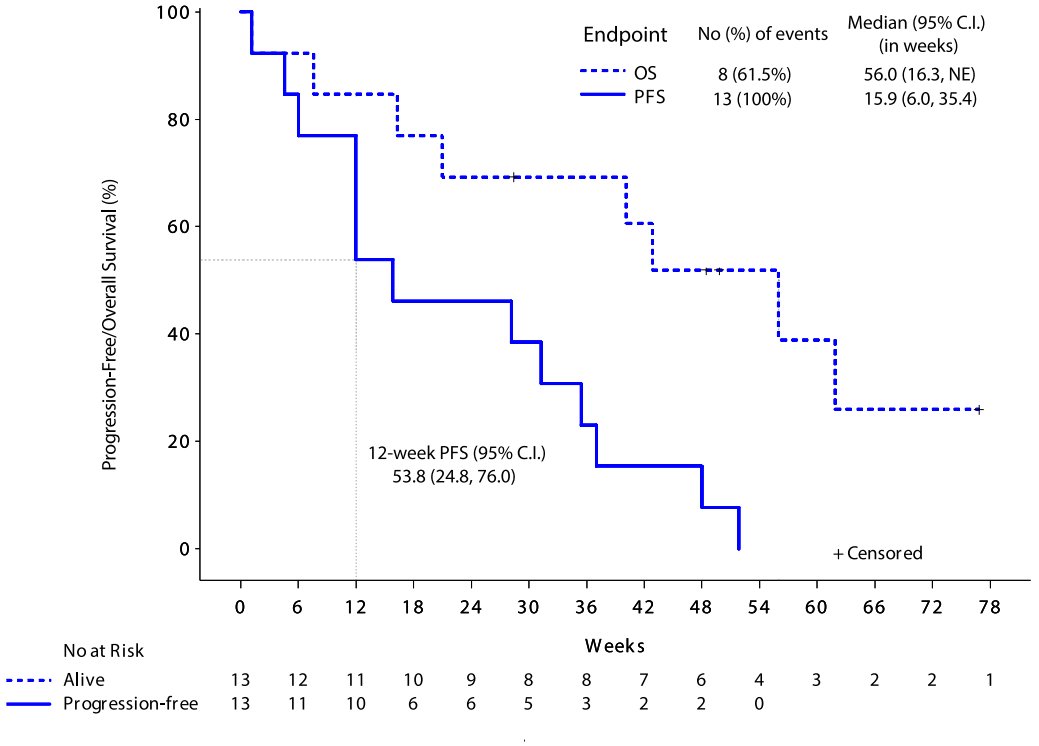


Figure 2. PFS and OS for all enrolled patients (n = 13). PFS, progression-free survival; OS, overall survival; CI, confidence interval; NE, not estimable.

gain (due to gene amplification or chromosome 17 polysomy), gene amplification, or mutation.

HER2 exon 20 mutations are considered the most important driving aberrations with functional significance in NSCLC.

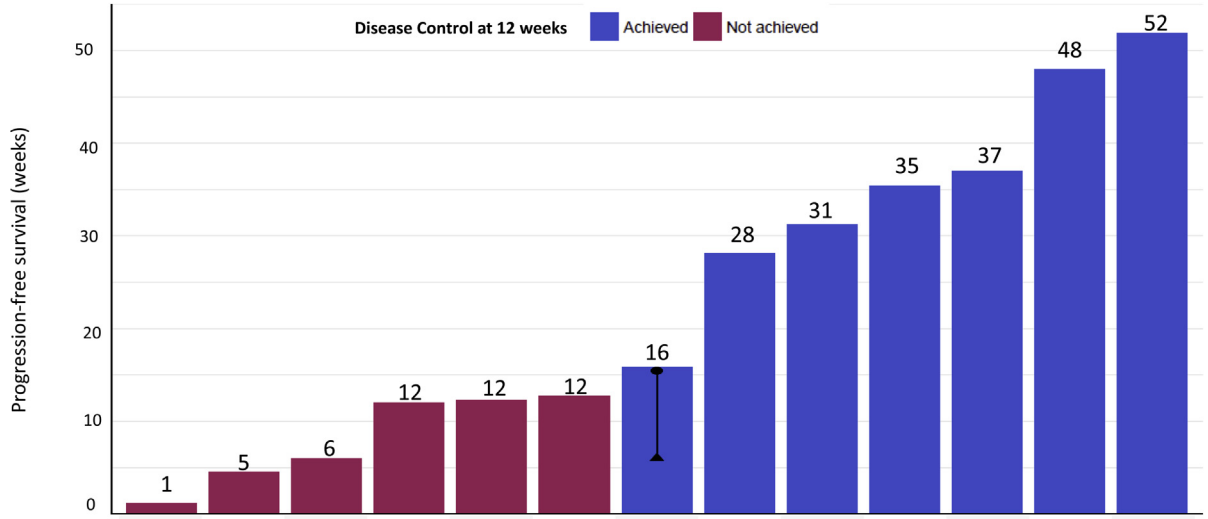
A limited number of retrospective series or small prospective trials have established the existence of several anti-HER2 therapies. These therapies are associated with modest activity as compared to other personalized strategies for oncogenes such as EGFR- and ALK-activating alterations in NSCLC.

Early HER2-dedicated trials evaluated trastuzumab combined with chemotherapy in immunohistochemistry (IHC) tested, HER2-positive advanced NSCLC. Clinical benefit was not observed, although the results suggested some activity in a small subgroup of HER2-positive (IHC 3+/fluorescent in situ hybridization–positive) patients. The number of patients was, however, too small to provide definitive information.[24] Another subsequent phase II trial evaluating trastuzumab and docetaxel in HER2-positive (IHC 2+/3+) NSCLC was closed due to the low activity of this combination.[25]

After the failure of these poorly selected trials, refinement of biomarker-selected therapies for HER2-driven NSCLC has led to more promising treatment benefits in molecularly defined patient populations. Limitations in interpreting and applying these data rely on the multiplicity of available HER2-directed drugs, the distinct HER2-activating mechanisms requiring a focus on homogenous biomarker-defined small subgroups of NSCLC patients, and finally the need to biologically define and confirm an active match between specific oncogenic mechanisms and targeted agents. Conceptually, the lack of prospective data evaluating these new customized treatment strategies represents a major limitation to date, accentuated by the risk of bias inherent to retrospective series reporting on a rare alteration, not systematically screened for, and treated in very different clinical settings.

In an international retrospective registry of 16 patients with NSCLC harboring *HER2* mutations who received 22 individual anti-HER2 treatments, overall DCR with trastuzumab-based therapies was 93% (n = 15), and 100% with afatinib (n = 3).[10] However, such a small number of patients treated with afatinib cannot provide reliable results.

Trastuzumab emtansine (TDM-1) was recently assessed for HER2-overexpressing NSCLC in a phase II study with a limited clinical activity and ORs observed only in IHC level 3+ patients (objective response rate [ORR]: 20%).[11] In another phase II study, T-DM1 was assessed in patients with *HER2*-mutant NSCLC in the context of a basket trial, resulting in ORR of 44% (8 of 18 patients) using a Simon's two-stage optimal design.



Gender	F	F	M	F	F	F	M	M	F	F	F	F	M
Age	71	39	65	66	57	48	62	82	44	45	55	72	59
Smoking status	Never	Never	Former	Never	Former	Never	Former	Former	Current	Never	Never	Never	Never
Objective Response	NE	PD	PD	PD	PD	PD	PR	SD	SD	SD	SD	SD	SD
Overall Survival in weeks	1	21	8	43	56	40	16	28(+)	100(+)	48(+)	50(+)	77(+)	62
Treatment line:													
- Afatinib	2	3	5	5	3	2	4	2	2	2	2	3	3
- Further	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	No	No	Yes
Molecular:													
HER2 exon 20	A775 G776 insYVMA	A775 G776 insYVMA	-	A775 G776 insYVMA	A775 G776 insYVMA	G776 >VC	A775 G776 insYVMA	A775 G776 insYVMA	A775 G776 insTVMA	E770 A771 insAYVM	A775 G776 insYVMA	A775 G776 insYVMA	A775 G776 insYVMA
Other driver mutations			KRAS amplific										
Tumor mutation burder (Muts/Mb)	6	4	19	Unkn.	6	5	2	2	2	NA	6	7	5
PD-L1 (IHC) result	NA	NA	NA	NA				NA		NA	NA		
- TPS (%)					0%	0%	0%		0%			0%	0%
- TIIS (%)					0%	0%	0%		30%			10%	0%

Figure 3. Plot of PFS (in weeks) by patient, according to primary endpoint (DC achieved at 12-weeks).F, female; M, male; PFS, progression-free survival; NE, not estimable; PD, progression of disease; SD, stable disease; PR, partial response; +, censored observation; -, alteration not identified; Unkn, unknown; NA, not analyzed; TPS, tumor proportion score (%); TIIS, tumor-infiltrating immunocyte score (%); ▲, partial response start; ●, response episode end.

Responses were seen in patients with *HER2* exon 20 insertions and point mutations in the kinase, transmembrane, and extracellular domains. In these patients, HER2 expression did not predict the outcome.[26]

A phase II trial of T-DM1 monotherapy in relapsed NSCLC with documented HER2-positivity (IHC 3+, both an IHC score of 2+ and fluorescent in situ hybridization positivity, or exon 20 mutation) was terminated early because of limited efficacy. One patient of 15 with NSCLC harboring a *HER2* mutation achieved a PR with an ORR of 6.7%.[7]

Another multicenter, nonrandomized, phase IIa multiple basket study of a dual HER2 inhibition with pertuzumab plus trastuzumab enrolled patients with HER2-overexpressing (IHC3+), HER2-amplified, or *HER2*-mutant tumors, including lung cancer. Fourteen patients with *HER2*-mutant tumors had NSCLC with response reported in 3 patients (21%) and SD for more than 120 days in another 3 patients (21%). Early results show an ORR of 13% (2 of 16) in the HER2-amplified cohort.[27]

Real-world data on the use of afatinib are available from an international NPU program.[15] Afatinib was delivered in 28 heavily pretreated patients with documented *HER2*-mutant NSCLC. Of the 16 patients evaluable for response, 19% had an OR and 69% achieved DC, with a median overall time to treatment failure of 2.9 months.[15] In this small retrospective analysis, patients with *HER2*-mutant NSCLC harboring the most common *HER2* mutation, A775-G776insYVMA in exon 20, derived also the largest benefit.

In a recent analysis of data from 27 patients with metastatic *HER2*-mutant lung cancer who participated in an international, multicenter clinical trial between 2009 and 2016, the ORR to afatinib was 15% with YVMA insertion in exon 20 being the most common *HER2* mutation type in the clinical trial population (59%), and a signal for a larger benefit in this subgroup, too.[28]

In the NICHE trial, seven patients (54%) achieved DC at 12 weeks. Although the lack of activity in five among the first nine patients meant that the prespecified criteria for proceeding to further clinical testing were not met, descriptive molecular analysis suggested that prolonged disease stabilization occurred in some patients with YVMA-insertions. Therefore, despite the challenges of evaluating larger cohorts of patients with rarer *HER2* mutations, there is accumulating evidence that the presence of YVMA insertions in exon 20 identifies a subgroup of patients with *HER2*-mutant NSCLC for whom targeted therapies might be interesting treatment options.

When interpreting the modest results of our NICHE trial, also the relatively high exposure to preceding chemotherapies should be considered (54% of patients were treated in the third or higher line of therapy). All patients achieving SD received afatinib as second- or third-line therapy, whereas for two patients with early progression, afatinib was already the fifth line of therapy (Fig. 3).

New HER2 inhibitors are currently in early development phase. Poziotinib is an oral quinazoline-based irreversible TKI that has shown activity on *EGFR* and *HER2* exon 20 mutated NSLC in vitro.[29] In an open-label, single-center phase II study, confirmed ORR was 42% with a PFS of 5.1 months in 13 patients.[30]

TAK-788 is an investigational TKI. Preclinical data showed selective activity against activating *EGFR* and *HER2* mutations, including exon 20 insertions. An initial report from a phase I/II, first-in-human, single-arm study in 34 patients showed antitumor activity (responses in 3 of 14) with an adverse event profile consistent with that of other EGFR TKIs.[31]

Trastuzumab deruxtecan (DS-8201) is an antibody-drug conjugate composed of an anti HER2 humanized antibody and a topoisomerase I.[32] It has shown an acceptable safety profile in patients with HER2-expressing (IHC 2+ or 3+) or mutant NSCLC, and a confirmed ORR of 38.7% (12 of 31) and a PFS of 12.1 months.[33]

Applying the concept of precision medicine to HER2-positive tumors appears challenging. However, significant activity is observed across trials in a restricted number of patients, and several new targeted drugs with promising signals of activity are currently in development. Additional investigations are needed to define the potential predictive value of HER2 alterations (overexpression, amplification, and mutations) to more accurately select patient for the optimal treatment with novel agents.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2019.02.017.

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