

Treatment Outcome and Clinical Characteristics of HER2 Mutated Advanced Non-Small Cell Lung Cancer Patients in China

Fei Xu

National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College

Guangjian Yang

National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College

Haiyan Xu

National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College

Lu Yang

National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College

Weini Qiu

Haalthy

Junling Li

National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College

Yan Wang (✉ wangyanyifu@163.com)

National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College <https://orcid.org/0000-0002-1743-6383>

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Abstract

Background: HER2 mutation is found in 1-2% of lung cancer patients. Chemotherapy remains the standard of care for patients harboring HER2 mutations, while many HER2 targeted tyrosine kinase inhibitors (TKIs) have been applied to them in practice in recent years. Studies comparing chemotherapy to HER2-TKIs were limited. This study was aimed to investigate the molecular and clinical patterns of HER2 mutations in advanced non-small cell lung cancer, and compare the different outcomes between chemotherapy and HER2-TKIs. Methods: Advanced or recurrent non-small cell lung cancer patients with de novo HER2 mutations (N=75) were included in this study. Molecular information, clinical features, and treatment outcomes were retrospectively collected from a web-based patient registry and hospital chart review. Results: Between October 2012 and December 2018, 65 patients with in-frame insertion mutations, 8 with point mutations and 2 with gene amplification were found. The most common subtypes of insertion mutations were A775_G776insYVMA, G776delinsVC, and V777_G778insGSP. HER2 mutated patients were mostly young-aged, females, never or light smokers, and adenocarcinoma. For HER2 mutated advanced NSCLC, chemotherapy achieved better outcomes than HER2-TKIs (median PFS: 5.5 vs 3.7 months in the first line setting and 4.2 vs 2.0 months in the second line setting, $P=0.001$ and 0.031 , respectively). Especially for the most common subtype, YVMA insertions, PFS was significantly longer in chemotherapy than HER2-TKIs both in the first line (6.0 vs 2.6 months, $P=0.008$) and the second line (4.2 vs 2.6 months $P<0.001$). Conclusions: HER2 mutated lung cancer patients were younger, mostly females, never or light smokers, histologically adenocarcinomas dominated. Compared to existed HER-TKIs, chemotherapy might bring more benefit to HER2 mutated advanced lung cancer patients, especially the most common type of HER2 exon 20 insertions, A775_G776insYVMA subtype. Trial registration: ChiCTR1800017709. Registered 10 August 2018.

Background

Say cancer is the emperor of all maladies, lung cancer may be the king of all cancers, with the highest mortality rate and a rather high incidence in both sex. 5-year survival rate of lung cancer was only 19%. In 2019, there will be an estimated 228150 new patients with lung and bronchus tumor in the United States, as estimated deaths of 142670[1]. Non-small cell lung cancer(NSCLC) makes up the major part in lung carcinoma. The battle against NSCLC was a long, tough one until the discovery of small-molecule tyrosine kinase inhibitors (TKIs) in 2000s, regarded as "targeted therapy". Two decades later, TKIs targeting epidermal growth factor receptors (EGFR), anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 receptor tyrosine kinase (ROS1) and B-Raf proto-oncogene serine/threonine kinase (BRAF) have now been developed and put into practice[2-5], while those who do not harbor these mutations have a choice between traditional chemotherapy and immunotherapy as standard of care. However, a minority in lung cancer patients are drawing more attention, who have driver mutations other than the forgoing ones, such as RET, HER2 and so on. These patients pitifully cannot benefit from targeted therapies and still struggling with side effects of chemo agents.

HER2 mutations was identified as a unique mutation in NSCLC. Unlike HER2 gene amplification commonly seen in breast cancer and gastric cancer, HER2 mutations possess a different molecular pattern in lung cancer samples, that is, in-frame insertions in exon 20. According to information from COSMIC websites and published papers, HER2 exon 20 in-frame insertions mainly have four patterns, A775_G776insYVMA, E770_A771insAYVM, P780_Y781insGSP and G776_V777insVGC[6].

In clinical practice, we found HER2 mutated lung cancer patients had dilemmas when choosing their treatment plans: they do harbor driver mutations but cannot take targeted drugs approved by food and drug administration; their counterparts in breast cancer can benefit from HER2 mono-antibodies like trastuzumab while they themselves cannot[7]; guideline-directed suggestions to their treatment were barely written. In real clinical scenario, the treatment varied from chemotherapy to targeted therapy, even immunotherapy. Patients' compliance to the prescription was depressed because of intolerable side effects or minimal tumor responses. They usually jump from one kind of treatment to another, urging for any hope as a cure, adding on to the already heavy burden of the patient's family. We clearly recognize that there is a need for investigating which therapy might benefit more for HER2 mutated advanced lung cancer patients.

Data on HER2 mutations in NSCLC is limited. Previous articles focused more on mutation patterns, while lacking information on treatment choice or the relation between therapy and prognosis. We retrospectively summarized information of HER2 mutated advanced NSCLC patients from China and analyzed their molecular patterns, clinical characteristics and treatment outcome.

Methods

Study design

A retrospectively collected, nation-wide study was designed to figure out the clinical features of HER2 mutated advanced non-small cell lung cancer patients, as well as the difference in between two main treatment regimens, chemotherapy and HER2 targeted therapy.

Patients

Between October 2012 and December 2018, information of 75 advanced NSCLC patients with HER2 mutations were collected from a web-based patient registry and hospital chart review, including patients from National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (information of patients' frequently visited hospitals was presented in Supplementary Table1 S1). Clinicopathological characteristics were collected for analysis including gender, age at diagnosis, smoking history, histologic subtypes, clinical TNM stage, and variables of insertion mutations. Therapeutic outcomes were documented and retrospectively collected. Disease recurrence and survival outcomes were recorded according to follow-up clinic visits or telephone calls. This study was approved by Ethics Committee of National Cancer Center /National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College. Written informed consent was obtained from all patients.

HER2 Mutant Identifications

HER2 mutant identifications (exon17-26) were performed by next-generation sequencing. Either peripheral blood or tumor samples were used.

Statistical Analysis

The Kaplan-Meier method was used to calculate the curves for PFS. The Cox proportional hazards regression model was used to evaluate the impact of collected clinical variables on PFS. Significant differences were determined by the log-rank test. P value less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS® software, version 22.0 software (IBM Corp., Armonk, NY, USA).

Results

Seventy-five cases were diagnosed with de novo HER2 mutated advanced lung cancer, including 65 with in-frame insertion mutations, 8 with point mutations and 2 with gene amplifications. Among them, one squamous cell lung carcinoma with HER2 amplification were found. There were mainly 3 common subtypes of insertions detected in HER2 exon 20: c.2326_2327insTGT, p.Gly776delinsValCys, simplified as G776VC; c.2313_2324dupATACGTGATGGC, p.Ala775_Gly776insTyrValMetAla, simplified as YVMA; c.2330_2331insGGGCTCCCC, p.Val777_Gly778insGlySerPro, simplified as GSP. Patient number in each subgroup was 13, 38 and 7, respectively. HER2 mutation was mutually exclusive with other driver mutations of lung cancer in most cases, except for two patients harboring EGFR exon20 co-mutations. As Table 1 showed, forty HER2 mutated lung cancer patients also harbored other mutations in next-generation sequencing (NGS) results, of which 31 patients had TP53 co-mutations.

Among 75 patients, females were the majority with only 23 patients were male. Median age was 57 (range from 31 to 78). 21 patients had smoking history, and only 5 of them were heavy smokers. In thirty patients with documentary histological subtype information, half were poorly differentiated, another half were moderately or well differentiated. All patients were advanced or recurrent cancers, with 9 of them were unresectable stage IIIB (locally advanced) patients. Metastasis were also investigated. For 66 stage IV patients, 34 of them had oligometastasis, and metastasis to brain, liver, bone, lung was 12, 5, 22, 25, respectively. All these pre-treatment clinical characteristics were listed in Table2.

For univariate analysis of PFS1 (PFS of first-line treatment), all clinical characters mentioned above were analyzed. None had significant effect on the duration of response to drugs used in the first line setting. Table 3 showed the detailed results.

On treatment analysis, apart from 8 patients without available treatment information and 1 squamous cell lung cancer patient, 66 patients with treatment outcomes were analyzed. The median line of treatment for advanced patients was three. Afatinib, pyrotinib and poziotinib were regarded as one class of treatment named as HER2-TKI therapy. Chemotherapy included pemetrexed and platinum with or without anti-VEGF agents. Others included mono anti-vascular agents such as anlotinib and immune checkpoint inhibitors. Only first and second line treatment outcome were included in analysis. In the first line setting, patients received chemotherapy had longer progression free survival (PFS) than those accepted HER2-TKIs. The median PFS1 of HER2-TKIs and chemotherapy was 3.7 months (95% CI 2.3 to 5.0 months) and 5.5 months (95% CI 4.5 to 6.5 months), $p=0.001$. Similar difference was seen in the second line treatment as shown in Figure 1a; b. The median PFS2 of chemotherapy and HER2-TKIs was 4.2 months (95% CI 2.2 to 6.3 months) and 2.0 months (95% CI 0.8 to 3.3

months), $p=0.031$. In subgroup analysis, YVMA, the most common subtype of HER2 exon 20 insertions, possessed similar treatment response patterns compared to the population as a whole. As shown in Figure 2a; b, the median PFS1 for chemotherapy and HER-TKIs was 6.0 months (95% CI 5.3 to 6.8 months) and 2.6 months (95% CI 2.2 to 3.0 months) in YVMA subgroup, $p=0.008$. And the median PFS2 for chemotherapy and HER-TKIs was 4.2 months (95% CI 2.4 to 6.1 months) and 2.6 months (95% CI 0.1 to 5.1 months) in this subgroup, $p<0.001$. While for non-YVMA insertions, chemotherapy brought 0.8 month longer PFS than HER2-TKIs, but there was no significant difference seen between the two groups ($p=0.084$). When taken together, survival (PFS1+PFS2) of HER2-TKIs plus chemotherapy were not affected by the sequential of the two agents ($p=0.263$), but shorter than two lines of chemotherapy as illustrated in Figure 3.

Discussion

HER2 mutations in our cohort included point mutations, in-frame insertions, which counted the most, and gene amplification seen in one patient with squamous cell lung cancer. Mutation in squamous cell lung cancer is rather rare, and HER2 mutation was not publicly reported before. Among HER2 exon 20 insertions, there were A775_G776insYVMA, G776delinsVC, V777_G778insGSP and so on, with the most common type being YVMA, in accordance with previous findings. We also paid attention to the co-mutations of HER2, for patients harboring exon 20 insertions, TP53 was the most common co-mutation. However, limited by various NGS platforms from different gene companies, we could not summarize the relevance between mutation abundance and clinical characteristics of those patients.

Consistent with former studies, HER2 mutated patients in our cohort were mainly females, never or light smokers, poorly or moderately differentiated adenocarcinoma[8]. They were younger, with more than three quarters aged less than 65 years old.

In terms of treatment outcome, only first and second lines of treatment were analyzed. In the first line settings, our data showed that HER2 targeted therapy had inferior outcome than standard of care chemotherapy. This was in contrary with previous studies. One study including 24 HER2 exon 20 insertion lung cancer patients revealed that the overall survival of targeted therapy was longer than non-targeted agents, with 2.1 years and 1.4 years, respectively[9]. Another article involved 38 cases of HER2 mutated patients, the PFS of HER2-TKIs was 2.2 months, with 5.2 months in first line treatment and 1.8 months in latter lines. And the overall median PFS of chemotherapy was 4.3 months, with pemetrexed plus platinum or bevacizumab possessing the longest of 6.2 months[10]. The PFS of first line HER2-TKIs in our study was longer than previously reported, and chemotherapy was longer as well. Maybe this was because a majority of patients used pemetrexed plus platinum as their chemotherapy regimen.

In subtype analysis, the conclusion remained. Within YVMA subtype, afatinib was inferior than chemotherapy. This finding was again in contrary with some of the previous studies. One article argued that the time to treatment failure(TTF) was 9.6 months in YVMA subtype, much longer than the 2.9 months of all patients[11]. Another study compared the different responses to first-line chemotherapy, finding that YVMA had a PSF of 0.9 month shorter

than the overall[12]. Our result indicated that for YVMA patients, chemotherapy would be a better choice in first line treatment. Since patients with YVMA in our cohort had been exposed to both treatment, our result might represent a more direct conclusion. In subtypes other than YVMA, there was no significant difference seen between chemotherapy and HER2-TKIs.

The HER2-TKIs used as first or second lines in our patient cohort were mainly afatinib. This is partly because of the availability of legal drugs in China. Orally taken HER2-TKIs such as poziotinib, dacomitinib and pyrotinib were rarely used. So was trastuzumab and T-DM1 which were used as intravenous agents in health care centers. But that does not mean that these drugs were invalid for HER2 mutated lung cancer patients. For HER2 amplification positive lung cancer patients, adding trastuzumab to chemotherapy seemed not to bring more clinical benefit to them[7]. However, it was reported that trastuzumab or T-DM1 had an objective response rate (ORR) of 50.9% and PFS of 4.8 months in HER2 exon 20 mutated patients[13]. In another cohort involving 7 HER2 exon 20 insertion patients, 5 patients reached partial response or stable disease on T-DM1 treatment[14]. That could mean that trastuzumab or T-DM1 might be beneficial to these minority. Among small molecule TKIs, afatinib was most widely used in China in recent years, with PFS ranging from 2.9 to 6 months[11, 15-18]. Poziotinib, neratinib and pyrotinib had similar PFS, with 4.5-5.5 months, 5.5 months and 6.4 months, respectively[6, 19, 20]. Dacomitinib and Osimertinib was inferior in this population, either with a short PFS or invalid in cell lines experiments[21, 22].

Our study collected information from wide-spread geographical parts of China, discussing the different outcomes of treatment among HER2 mutated advanced lung cancer patients. We drew the conclusion that for HER2 mutated advanced non-small cell lung cancer patients, chemotherapy would bring more benefit than available tyrosine kinase inhibitors, especially in the most common subtype of exon 20 insertions. Nevertheless, limited by the retrospective information collection, some important parameters were missed out. In patients lacking tumor tissue samples, we accepted NGS outcomes from peripheral blood samples. Treatment was rich in their variety, so it was no easy task to categorize them appropriately. Patients' samples were sent to different centers for analysis, so we could not summarize the relevance between mutation abundance and the response to treatment. A prospective study is warranted to explore the efficacy of chemotherapy and different TKIs in HER2 mutated lung cancer patients, and a standardized platform to test the mutant alleles should be more convincing.

Conclusions

In conclusion, our study revealed that the most common HER2 mutations in advanced lung cancer were exon 20 insertions. HER2 mutated lung cancer patients were younger, mostly females, never or light smokers, histologically adenocarcinomas dominated. Compared to existed HER2-TKIs, chemotherapy might bring more benefit to HER2 mutated advanced lung cancer, especially the most common type of HER2 exon 20 insertions, A775_G776insYVMA.

Abbreviations

ALK: anaplastic lymphoma kinase; BRAF: B-Raf proto-oncogene serine/threonine kinase; EGFR: epidermal growth factor receptors; HER2: Human epidermal growth factor receptor2; NGS: next-generation sequencing; NSCLC: Non-

small cell lung cancers; ORR: Objective response rate; PFS: Progression free survival; RET: Ret Proto-Oncogene; ROS1: ROS proto-oncogene 1 receptor tyrosine kinase; TKIs: tyrosine kinase inhibitors; TNM: Tumor Node Metastasis; TP53: Tumor protein P53; T-DM1: Ado-trastuzumab emtansine; VEGF: vascular endothelial growth factor

Declarations

Ethics, consent and permissions

The study protocol was approved by the Ethics Committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (18-070/1648) and informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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The funding body had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Authors' contributions

FX and GY contributed equally in preparing and conducting this research. HX, LY followed the patient survival data. WQ collected part of patient information. JL and YW designed and coordinated the research in the whole process. All authors read and approved the final manuscript.

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Not Applicable.

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Tables

Table 1 co-mutation patterns of HER2 mutated lung cancer

Patient No	HER2	TP53	KRAS	STK11	PIK3CA	RET	TERT	BRAF	MET	RB1	JAK2	EGFR	NTRK1	MYC
1	a								Q					
2	a	Q		Q										
3	a	Q												
4	a	Q			Q									
5	a		Q			Q								
6	a	Q												
7	e						Q							
8	e	Q						Q						
9	e	Q												
10	e								Q					
11	b	Q							Q					
12	b	Q												
13	b	Q												
14	b	Q												
15	b	Q								Q	Q			
16	b											Q		
17	b	Q												
18	b	Q											Q	
19	b							Q						
20	b	Q	Q											
21	b	Q												
22	b	Q												
23	d											Q		
24	b	Q												
25	b	Q												
26	b				Q									
27	d	Q												
28	d	Q												
29	d	Q												Q

30	b	Q												
31	b	Q												
32	c	Q												
33	c	Q												
34	c	Q				Q								
35	e	Q												
36	c	Q					Q							
37	c	Q												
38	c											Q		
39	c	Q												
40	e	Q												

Table 1. Forty advanced lung cancer patients who harbored more than one mutation were included in this table (HER2 mutations: a: point mutation; b: YVMA; c: G776VC; d: GSP; e: others). “Q” represented mutations found in that gene. The most frequently mutated gene was TP53 mutation, with 77.5% patients harboring.

Table 2 Clinical characteristics of HER2 mutated advanced lung cancer patients

Parameters	Groups	N (%)
Age	<65	57(76.0)
	≥65	18(24.0)
Sex	Male	23(30.7)
	Female	52(69.3)
Smoking history	Never	54(72.0)
	Light smoker	16(21.3)
	Heavy smoker	5(6.7)
Stage	IIIB	9(12.0)
	IV	66(88.0)
Histology	Poorly differentiated adenocarcinoma	15 of 30 (50.0)
	Moderately or well differentiated adenocarcinoma	15 of 30 (50.0)
	Squamous cell carcinoma	1 of 75 (1.3)
Metastasis number	Oligometastasis	34 of 66 (51.5)
	Multi-organ metastasis	32 of 66 (48.5)
Metastasis sites	Brain	12 of 66 (18.1)
	Lung	25 of 66 (37.9)
	Liver	5 of 66 (7.6)
	Bone	22 of 66 (33.3)

Table 2. Clinical characteristics of HER2 mutated advanced and recurrent non-small cell lung cancer patients. If not specifically written, the percentage was calculated by the number of patients in the subgroup divided by the whole.

Table 3 Univariate analysis on clinical features on treatment responses (Cox regression model)

Clinical parameters	B	HR(CI)	P value
Age	0.576	1.778(0.973-3.249)	0.061
Sex	0.367	1.443(0.803-2.593)	0.220
Smoking history	-0.295	0.744(0.491-1.127)	0.163
Metastasis number	0.038	1.038(0.619-1.740)	0.886
Brain metastasis	0.459	1.582(0.815-3.069)	0.175
Stage	-0.352	0.703(0.217-2.273)	0.556
Histology	0.208	1.231(0.550-2.755)	0.613
TP53 co-mutation	-0.173	0.841(0.497-1.423)	0.841

Table 3. Univariate analysis showed no significant impact of all clinical parameters on first-line treatment outcome.

Figures

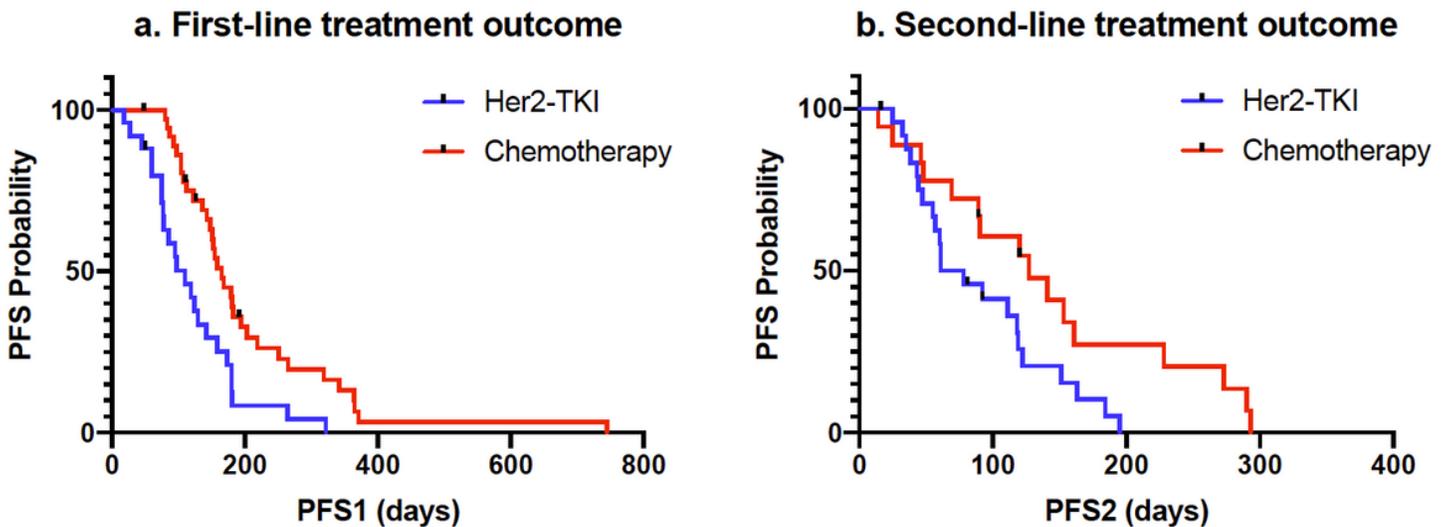


Figure 1

Treatment response among HER2 mutated lung cancer patients as a whole. Treatment response was different between HER2-targeted TKIs and chemotherapy, both in first-line (a) and second-line settings (b).

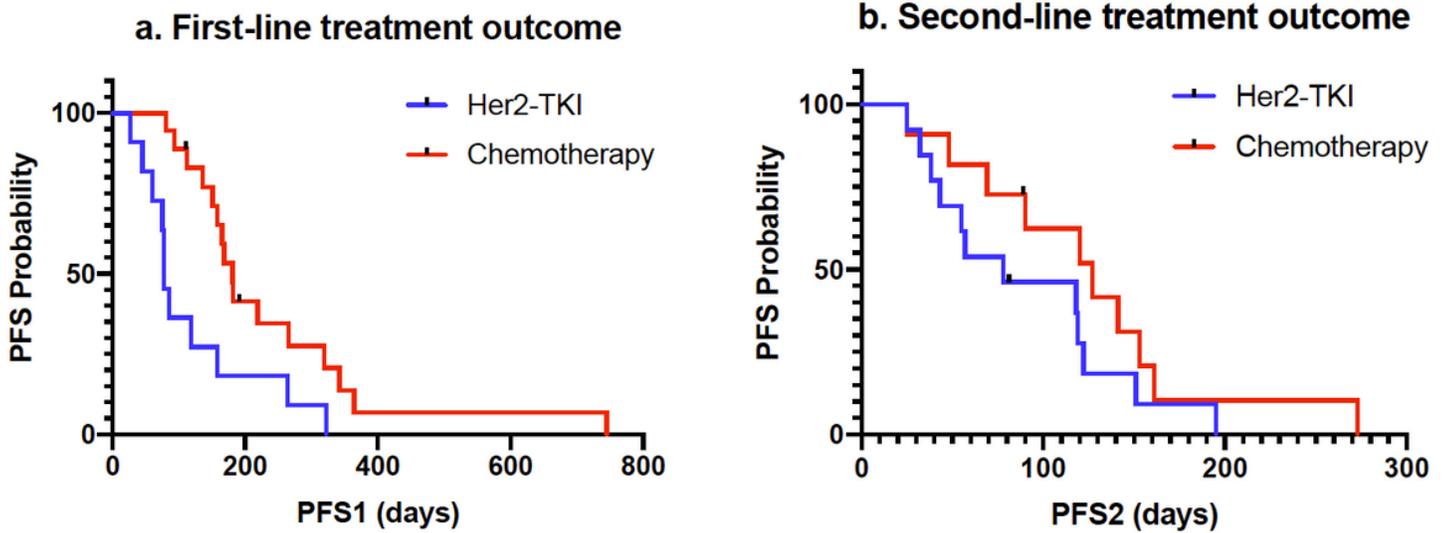
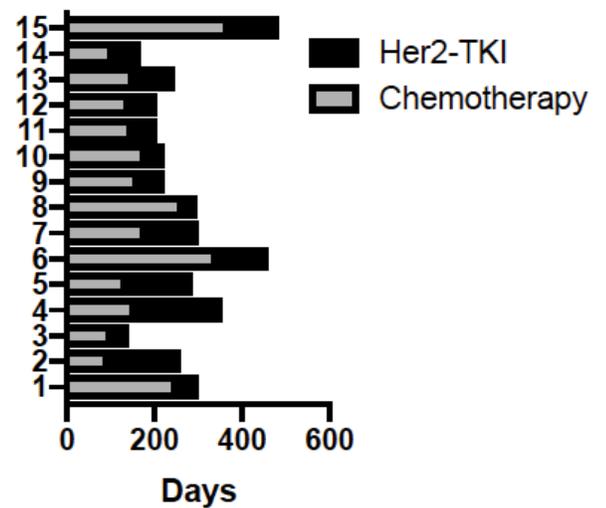
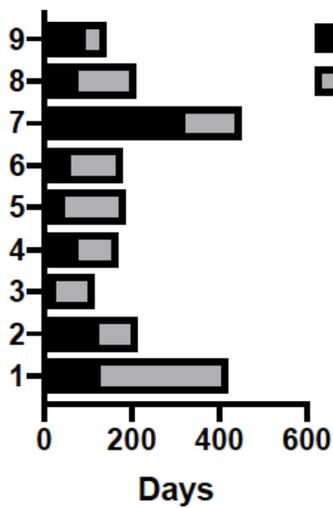


Figure 2

Treatment response difference in YVMA subtype of HER2 exon 20 insertion mutated lung cancer patients. Treatment response was different between HER2-targeted TKIs and chemotherapy in first-line settings in YVMA subtype of HER2 exon 20 insertion mutated lung cancer patients.

a. Chemotherapy following Her2-TKIs

b. Afatinib following chemotherapy



c. Two lines of chemotherapy

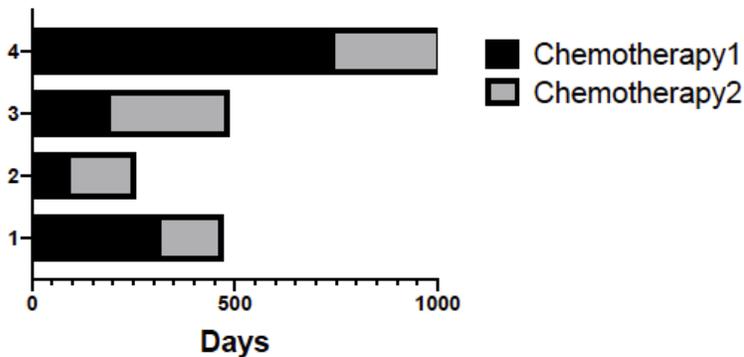


Figure 3

Progression-free survival of different first and second line treatment sequential. When taken together, whether applying HER2 targeted TKIs or chemotherapy as first line treatment, the overall progression free survival (PFS1+PFS2) was similar, while patients using two lines of chemotherapy benefit more. Nevertheless, only 4 patients chose two-line chemotherapy regimen.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementtable1Informationofpatients.docx](#)