Relative efficacies of EGFR-TKIs and immune checkpoint inhibitors for treatment of recurrent non-small cell lung cancer after surgery

Nozomu Motono (motono@kanazawa-med.ac.jp)
Kanazawa Medical University
Takaki Mizoguchi
Kanazawa Medical University
Masahito Ishikawa
Kanazawa Medical University
Shun Iwai
Kanazawa Medical University
Yoshihito Iijima
Kanazawa Medical University
Hidetaka Uramoto
Kanazawa Medical University

Research Article

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Abstract

Background

The relative efficacies of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) and immune checkpoint inhibitors (ICIs) for the treatment of recurrent non-small cell lung cancer (NSCLC) after surgery remain unclear.

Methods

Among 801 patients with NSCLC who underwent pulmonary resection at Kanazawa Medical University between 2017 and 2021, 64 patients had recurrence. We retrospectively compared the efficacies of EGFR-TKIs and ICIs in these patients with recurrent NSCLC who underwent pulmonary resection.

Results

The 3-year overall survival rates after recurrence were 79.3% in patients who received EGFR-TKIs, 69.5% in patients who received ICIs, and 43.7% in patients who received cytotoxic agents. There was no significant difference in overall survival between patients treated with EGFR-TKIs and ICIs ($p = 0.14$) or between patients treated with ICIs and cytotoxic agents ($p = 0.23$), but overall survival was significantly higher in patients treated with EGFR-TKIs compared with cytotoxic agents ($p < 0.01$) The probabilities of a 2-year response were 88.5%, 61.6%, and 25.9% in patients treated with EGFR-TKIs, ICIs, and cytotoxic agents, respectively. There was no significant difference in response periods between patients treated with EGFR-TKIs and ICIs ($p = 0.18$), but the response period was significantly better in patients treated with EGFR-TKIs ($p < 0.01$) or ICIs ($p = 0.03$) compared with cytotoxic agents. Percent-predicted vital capacity ($p = 0.03$) and epidermal growth factor receptor gene mutation ($p < 0.01$) were significant factors affecting the overall response to chemotherapy in multivariate analysis.

Conclusion

EGFR-TKIs and ICIs are effective for treating recurrent NSCLC after surgery. Although adjuvant chemotherapy for completely resected pathological stage II to IIIA NSCLC, atezolizumab or osimertinib, has also been recently approved as adjuvant chemotherapy, there is a risk that patients who relapse after adjuvant chemotherapy will have less choice.

1. Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for more than 80% of all cases [1]. Treatment strategies for advanced NSCLC have changed over the past decade, and tumors with epidermal growth factor receptor (EGFR) gene mutations

can be targeted therapeutically with tyrosine kinase inhibitors (TKIs). Several phase III studies in patients with advanced NSCLC harboring *EGFR* mutations have shown significant improvements in response rates and prognosis following treatment with EGFR-TKIs compared with platinum-based chemotherapy [2–5]. Furthermore, in addition to cytotoxic chemotherapy and targeted therapy for tumors harboring certain genetic aberrations, immunotherapy targeting immune checkpoints using antibodies to programmed cell death protein-1 (PD-1) and its ligand, PD-L1, has become an established treatment modality for NSCLC [6–9]. Immune checkpoint inhibitors (ICIs) have revealed greater efficacy than cytotoxic chemotherapy in patients with NSCLC whose tumors expressed PD-L1 on tumor cells and/or immune cells [6–9]. However, the relative efficacies of EGFR-TKIs and ICIs for the treatment of recurrent NSCLC after surgery remains unclear.

In this study, we retrospectively evaluated the efficacies of EGFR-TKIs and ICIs in patients with recurrent NSCLC who underwent pulmonary resection.

2. Patients and Methods

2.1 Patients

Among 801 patients with NSCLC who underwent pulmonary resection at Kanazawa Medical University between 2017 and 2021, 64 patients had recurrence and were enrolled in this retrospective study. This study was conducted in accordance with the principles of the Declaration of Helsinki and the protocol was approved by the institutional review committee of Kanazawa Medical University (approval number: I392). All patients provided written informed consent.

Clinical data including sex, age, smoking history, carcinoembryonic antigen, prognostic nutrition index (PNI), neutrophil-to-lymphocyte ratio (NLR), [18]F-fluorodeoxyglucose positron emission tomography/computed tomography maximum standardized uptake value (SUV_{max}), and lobe involvement were collected. Respiratory function parameters including percent-predicted vital capacity (%VC) and forced expiratory volume in 1 s as a percentage of forced vital capacity (FEV_1%) were also collected. Smoking history was assessed using the Brinkman index, which was calculated by multiplying the number of cigarettes smoked per day by the number of years that the patient had smoked [10]. Preoperative PNI, which has been reported as a prognostic factor in patients with NSCLC [11, 12], was calculated by combining serum albumin levels with the total peripheral lymphocyte count in peripheral blood. NLR is used as an indicator of systemic inflammation and stress in critically ill surgical and medical patients [13], and has also been reported to be a prognostic factor in patients with NSCLC who have undergone pulmonary resection [14, 15]. The most effective chemotherapy regimen in each patient was classified as EGFR-TKI, ICI monotherapy or combined with a cytotoxic agent, and cytotoxic agent.

2.2 Pathological factors

Data on histological type, lymphatic invasion, vascular invasion, differentiation, pathological stage, *EGFR* mutation, and PD-L1 expression were collected.

2.3 Statistical analyses

Frequencies of variables were compared using Pearson's χ^2 test of independence. Cumulative survival was calculated by the Kaplan–Meier method, and survival curves were compared using the log-rank test. Cut-off values for factors associated with recurrence were calculated by receiver operating characteristic (ROC) curve analysis, and prognostic analyses were performed using these cut-off values. Significant factors affecting overall response were analyzed by logistic regression. Risk factors for overall survival after recurrence were analyzed by Cox proportional hazards regression. All statistical analyses were two-sided and the statistical significance was set at $p < 0.05$. Statistical analyses were performed using JMP software v13.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1 Patient characteristics

The relationships between the clinicopathological characteristics of the 64 patients with recurrent NSCLC after surgery and their overall responses to chemotherapy are shown in Table 1. The proportion of males (55.5% vs 100%, $p < 0.01$) and the Brinkman index (300 vs 800, $p < 0.01$) were significantly lower among patients with a complete or partial response, compared with those with stable or progressive disease. The proportions of patients with adenocarcinoma (88.9% vs 42.8%, $p < 0.01$), lymphatic invasion (58.3% vs 32.1%, $p = 0.03$), and positive *EGFR* mutation (63.8% vs 3.5%, $p < 0.01$) were also higher among those with a complete or partial response, compared with those with stable or progressive disease. The objective response rates are shown in Table 2. The objective response rates were 100%, 38.7%, and 10.0% in patients receiving EGFR-TKIs (n = 23), ICIs (n = 31), and cytotoxic agents (n = 10), respectively. Of those patients, 95% of patients received EGFR-TKIs on the first line, 84% for ICI, and 60% for cytotoxic agent.

Table 1
Comparison of patient characteristic between complete response or partial response and stable disease or progressive disease.

	CR or PR (n = 36)	SD or PD (n = 28)	*p*-value
Gender (male / female)	20 / 16	28 / 0	< 0.01
Age, median, range (y)	67 (34–87)	71 (52–86)	0.34
Brinkman index, median, range	300 (0–2700)	800 (100–2250)	0.02
CEA, median, range (ng/ml)	3.4 (1.1–70.3)	6.5 (1.0–100.2)	0.15
%VC, median, range	100.2 (83.8-136.3)	93.9 (64.9-129.5)	0.05
FEV_1%, median, range	73.6 (44.8–88.8)	73.6 (36.8–92.2)	0.65
PNI, median, range	50.0 (41.2–61.3)	47.6 (336.6–60.4)	0.62
NLR, median, range	2.58 (1.12–7.55)	2.60 (0.53–13.71)	0.57
SUV_{max}, median, range	7.91 (1.32–23.35)	8.94 (1.50–22.59)	0.23
Histological type (Ad / Sq / LCNEC / AdSq / Large)	32 / 4 / 0 / 0 / 0	12 / 12 / 1 / 1 / 2	< 0.01
Ad	32 (88.9%)	12 (42.8%)	< 0.01
Lobe (RU / RM / RL / LU / LL)	10 / 4 / 11 / 6 / 5	4 / 1 / 8 / 8 / 7	0.08
Lower lobe	16 (44.4%)	15 (53.5%)	0.46
Ly (absent / present)	15 / 21	19 / 9	0.03
V (absent/present)	10 / 26	12 / 16	0.20
G (1 / 2 / 3 / 4)	6 / 23 / 7 / 0	2 / 18 / 6 / 2	0.29
G3-4	7 (19.4%)	8 (28.5%)	0.39

CEA; carcinoembryonic antigen, %VC; % vital capacity, FEV_1%; forced expiratory volume % in one second, PNI; prognostic nutrition index, NLR; neutrophil-to-lymphocyte ratio, SUV_{max}; maximum of standardized uptake value, Ad; adenocarcinoma, Sq; squamous cell carcinoma, LCNEC; large cell neuroendocrine carcinoma, AdSq; adenosquamous cell carcinoma, Large; large cell carcinoma, RU; right upper, RM; right middle, RL; right lower, LU; left upper, LL; left lower, Ly; lymphatic invasion, V; vascular invasion, G; grade of differentiation, pStage; pathological stage, PD-L1; programmed death-ligand 1, EGFR; epithelial growth factor receptor, ICI; immune checkpoint inhibitor, TKI; tyrosine kinase inhibitor, Cytotoxic; cytotoxic agent.

	CR or PR (n = 36)	SD or PD (n = 28)	*p*-value
pStage (IA / IB / IIA / IIB / IIIA / IIIB)	9 / 5 / 1 / 9 / 11 / 1	9 / 6 / 1 / 4 / 8 / 0	0.77
pStage ≧ II	22 (61.1%)	13 (46.4%)	0.24
PD-L1, median, range (%)	12.5 (0–95)	25 (0–95)	0.21
Positive of EGFR mutation	23 (63.8%)	1 (3.5%)	< 0.01
Effective regimen (ICI / EGFR-TKI / Cytotoxic)	12 / 23 / 1	19 / 0 / 9	< 0.01
Line of effective regimen (1st / 2nd / 3rd / 4th)	33 / 2 / 0 / 1	21 / 4 / 1/ 2	0.29
Relapse free survival of effective regimen, median, range (days)	731 (133–1847)	169 (21–1094)	< 0.01
Overall survival after recurrence, median, range (days)	861 (171–1935)	416 (43–1188)	< 0.01

CEA; carcinoembryonic antigen, %VC; % vital capacity, FEV_1%; forced expiratory volume % in one second, PNI; prognostic nutrition index, NLR; neutrophil-to-lymphocyte ratio, SUV_{max}; maximum of standardized uptake value, Ad; adenocarcinoma, Sq; squamous cell carcinoma, LCNEC; large cell neuroendocrine carcinoma, AdSq; adenosquamous cell carcinoma, Large; large cell carcinoma, RU; right upper, RM; right middle, RL; right lower, LU; left upper, LL; left lower, Ly; lymphatic invasion, V; vascular invasion, G; grade of differentiation, pStage; pathological stage, PD-L1; programmed death-ligand 1, EGFR; epithelial growth factor receptor, ICI; immune checkpoint inhibitor, TKI; tyrosine kinase inhibitor, Cytotoxic; cytotoxic agent.

Table 2
Objective response rate of chemotherapy

	Objective response rate (%)	*p*-value
Epithelial growth factor receptor-tyrosine kinase inhibitor (n = 23)	100	< 0.01
Immune checkpoint inhibitor (n = 31)	38.7	
Cytotoxic agent (n = 10)	10.0	

3.2 Univariate and multivariate analyses

The relationships between the clinicopathological characteristics and overall response to chemotherapy are shown in Table 3. The following cut-off values for factors associated with recurrence were calculated using ROC curve analysis: age, 72 years; %VC, 90; FEV_1%, 70; PNI, 47.55; NLR, 4.04; SUV_{max}, 13.36; and PD-L1, 50. Univariate analysis identified Brinkman index (p = 0.01), %VC (p = 0.01), NLR (p = 0.02), SUV_{max} (p = 0.04), adenocarcinoma (p < 0.01), lymphatic invasion (p = 0.03), *EGFR* mutation (p < 0.01), and ICIs (p < 0.01) as significant factors affecting the overall response to chemotherapy. However, only %VC (odds ratio [OR]: 0.03, 95% confidence interval [CI]: 0.003–0.78, p = 0.03) and *EGFR* mutation (OR: 681.40, 95%

CI: 15.75–29471.21, p < 0.01) were significant factors in multivariate analysis, and ICI was not a significant factor (OR: 6.41, 95%CI: 0.48–85.80, p = 0.16). The relationships between the clinicopathological characteristics and overall survival after recurrence are shown in Table 4. Univariate analysis identified adenocarcinoma (p = 0.04) and *EGFR* mutation (p = 0.01) as risk factors for overall survival after recurrence; however, neither adenocarcinoma (HR: 0.54, 95%CI: 0.28–1.66, p = 0.28) nor *EGFR* mutation (HR: 0.24, 95% CI: 0.05–1.21, p = 0.08) were risk factors in multivariate analysis.

Table 3
Univariate analysis and multivariate analysis of significant factors for complete response or partial response.

	Univariate analysis			Multivariate analysis		
	OR	95%CI	*p*-value	OR	95%CI	*p*-value
Male	NA		NA			
Age > 72	0.50	0.18–1.41	0.19			
BI ≧ 600	0.26	0.09–0.78	0.01	3.44	0.37–31.34	0.27
CEA > 5	0.39	0.14–1.09	0.07			
%VC < 90	0.19	0.05–0.69	0.01	0.05	0.003–0.78	0.03
FEV_1% < 70	0.51	0.17–1.54	0.23			
PNI < 47.55	0.50	0.18–1.37	0.18			
NLR > 4.04	0.19	0.04–0.79	0.02	0.11	0.006-2.10	0.14
SUV_{max} > 13.36	0.29	0.08–0.98	0.04	0.45	0.05–4.08	0.48
Ad	10.66	2.96–38.39	< 0.01	5.70	0.63–50.96	0.11
Lower lobe	0.69	0.25–1.86	0.46			
Ly (+)	2.95	1.05–8.30	0.03	0.29	0.02–3.31	0.32
V (+)	1.95	0.68–5.54	0.21			
G3-4	0.60	0.18–1.93	0.39			
pStag ≧ II	1.81	0.66–4.93	0.24			
PD-L1 ≧ 50	0.51	0.18–1.45	0.21			
mEGFR (+)	47.76	5.79-393.46	< 0.01	681.40	15.75-29471.21	< 0.01
ICI	0.23	0.08–0.67	< 0.01	6.41	0.48–85.80	0.16
1st line	5.20	1.15–23.38	0.03	4.51	0.37–53.98	0.23

OR; odds ratio, CI; confidence interval, BI; Brinkman index, CEA; carcinoembryonic antigen, %VC; % vital capacity, FEV_1%; forced expiratory volume % in one second, PNI; prognostic nutrition index, NLR; neutrophil-to-lymphocyte ratio, SUV_{max}; maximum of standardized uptake value, Ad; adenocarcinoma, Ly; lymphatic invasion, V; vascular invasion, G; grade of differentiation, pStage; pathological stage, PD-L1; programmed death-ligand 1, EGFR; epithelial growth factor receptor, ICI; immune checkpoint inhibitor.

Table 4
Univariate analysis and multivariate analysis of risk factors for overall survival after recurrence.

	Univariate analysis			Multivariate analysis		
	HR	95%CI	*p*-value	HR	95%CI	*p*-value
Male	2.33	0.74–10.23	0.15			
Age > 72	1.44	0.51–3.81	0.46			
BI ≧ 600	1.60	0.60–4.66	0.34			
CEA > 5	1.31	0.49–3.54	0.57			
%VC < 90	2.51	0.85–6.70	0.09			
FEV_1% < 70	1.62	0.58–4.28	0.34			
PNI < 47.55	0.89	0.32–2.33	0.81			
NLR > 4.04	2.36	0.74–6.52	0.13			
SUV_{max} > 13.36	1.66	0.52–4.51	0.35			
Ad	0.36	0.13–0.99	0.04	0.60	0.18–1.84	0.38
Lower lobe	1.44	0.55–3.87	0.44			
Ly (+)	0.45	0.14–1.23	0.12			
V (+)	0.58	0.21–1.62	0.28			
G3-4	1.24	0.39–3.37	0.68			
pStag ≧ II	0.81	0.30–2.18	0.67			
PD-L1 ≧ 50	0.83	0.26–2.26	0.73			
mEGFR	0.28	0.07–0.84	0.02	0.37	0.09–1.44	0.15
ICI	1.28	0.47–3.41	0.60			
1st line	0.57	0.25–2.54	0.71			

HR; hazard ratio, CI; confidence interval, BI; Brinkman index, CEA; carcinoembryonic antigen, %VC; % vital capacity, FEV_1%; forced expiratory volume % in one second, PNI; prognostic nutrition index, NLR; neutrophil-to-lymphocyte ratio, SUV_{max}; maximum of standardized uptake value, Ad; adenocarcinoma, Ly; lymphatic invasion, V; vascular invasion, G; grade of differentiation, pStage; pathological stage, PD-L1; programmed death-ligand 1, mEGFR; mutation of epithelial growth factor receptor, ICI; immune checkpoint inhibitor.

3.3 Survival curves

The overall survival curves after recurrence according to chemotherapy regimen are shown in Fig. 1. The 3-year overall survival rates after recurrence were 79.3% 69.5%, and 43.7% in patients receiving EGFR-TKIs, ICIs, and cytotoxic agents. There was no significant difference in overall survival between patients receiving EGFR-TKIs and ICIs ($p = 0.14$) or between patients receiving ICIs and cytotoxic agents ($p = 0.23$); however, overall survival was significantly higher in patients treated with EGFR-TKIs compared with those treated with cytotoxic agents ($p < 0.01$). The response periods according to the chemotherapy regimens are shown in Fig. 2. The median response periods were 821, 232, and 250 days in patients receiving EGFR-TKIs, ICIs, and cytotoxic agents, respectively, and the respective probabilities of a 2-year response were 88.5%, 61.6%, and 25.9%. There was no significant difference in response periods between patients receiving EGFR-TKIs and ICIs ($p = 0.18$), but the response periods were significantly higher in patients receiving EGFR-TKIs ($p < 0.01$) or ICIs ($p = 0.03$) compared with those receiving cytotoxic agents. The results of a sub-analysis of the response periods in relation to PD-L1 expression in patients receiving ICIs are shown in Fig. 3. There was no significant difference in the probability of a 2-year response between patients with and without high expression levels of PD-L1 ($p = 0.91$), or between patients with and without PD-L1 expression ($p = 0.57$).

4. Discussion

In this study, we evaluated and compared the efficacies of EGFR-TKIs and ICIs for the treatment of recurrent NSCLC in patients who underwent pulmonary resection. Although EGFR-TKIs have demonstrated significant improvements in response rates and prognosis in patients with advanced NSCLC harboring *EGFR* mutations in several studies [2–5], EGFR-TKIs were also associated with significantly higher complete or partial response rates and a longer response period compared with cytotoxic agents in patients with recurrent NSCLC after surgery in this study. Although the overall survival curves suggested that EGFR-TKIs were significantly more effective than cytotoxic agents in patients with recurrent NSCLC after surgery, there was no significant difference between EGFR-TKIs and ICIs. ICIs have demonstrated efficacy in patients with advanced NSCLC [16–19]. In the current study, the response period was significantly longer in patients treated with ICIs compared with cytotoxic agents, suggesting that ICIs may be an effective treatment for recurrent NSCLC after surgery. However, although the efficacy of ICIs has been reported to depend on PD-L1 expression [16, 17, 19], the response periods in the current study did not differ between patients with and without PD-L1 expression, suggesting that PD-L1 expression might not be a useful predictor of ICI response in patients with postoperative recurrence.

Adjuvant chemotherapy is currently preformed in patients with completely resected pathological stage II to IIIA NSCLC. Atezolizumab and osimertinib have also recently been approved as adjuvant chemotherapeutic agents, and were shown to significantly improve disease-free survival in patients receiving postoperative adjuvant chemotherapy [20, 21]. However, it cannot deny the possibility of administering unnecessary adjuvant chemotherapy even for cases that do not recurrence, and there is a risk that patients who relapse after adjuvant chemotherapy will have less choice.

This study had several limitations. First, it was a retrospective study and may have included unobserved confounding and/or selection biases. Second, the study was performed at a single institution, and the study population was relatively small.

In summary, our findings revealed that EGFR-TKIs and ICIs could provide effective treatment for patients with recurrent NSCLC after surgery. Although adjuvant chemotherapy for completely resected pathological stage II to IIIA NSCLC, atezolizumab or osimertinib, has also been recently approved as adjuvant chemotherapy, there is a risk that patients who relapse after adjuvant chemotherapy will have less choice.

Declarations

Acknowledgment:

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Ethics approval and consent to participate

The present study was conducted in accordance with the amended Declaration of Helsinki. The Institutional Review Boards of Kanazawa Medical University approved the protocol (approval number: I392), and written informed consent was obtained from all of the patients.

Consent to publish

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to [our institutional restrictions e.g., them containing information that could compromise research participant privacy/consent], but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author’s contributions

N. M. performed the research, collected and analyzed the data and wrote the paper. T.M., M.I., S. I., and Y.I. contributed to sample collection. H. U. contributed to supervision of this study and revision of the

manuscript. All authors have read and approved the manuscript, and ensure that this is the case.

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Figures

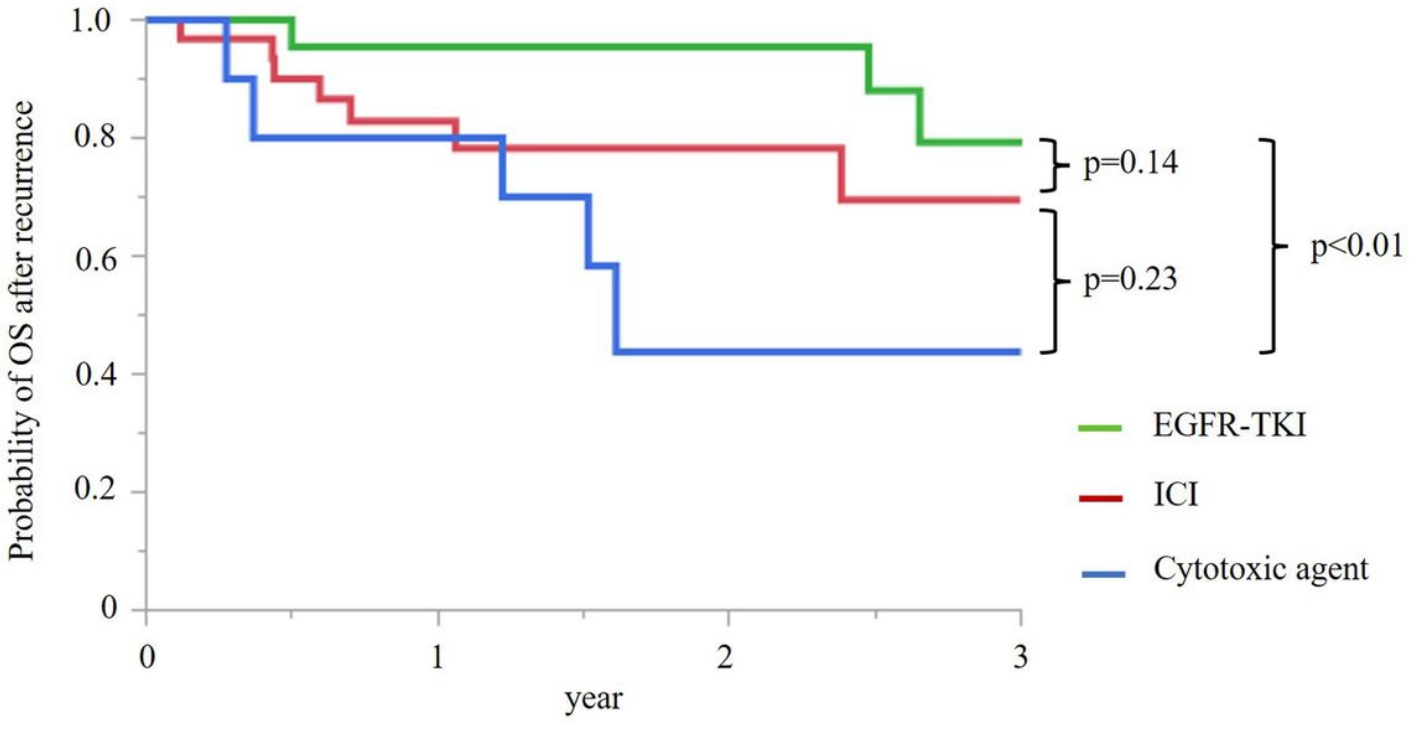

Figure 1

Overall survival after recurrence by chemotherapy regimens

There was not significant difference of OS between EGFR-TKI and ICI (p=0.14) or ICI and cytotoxic agent (p=0.23). There was significant difference between EGFR-TKI and cytotoxic agent (p<0.01).

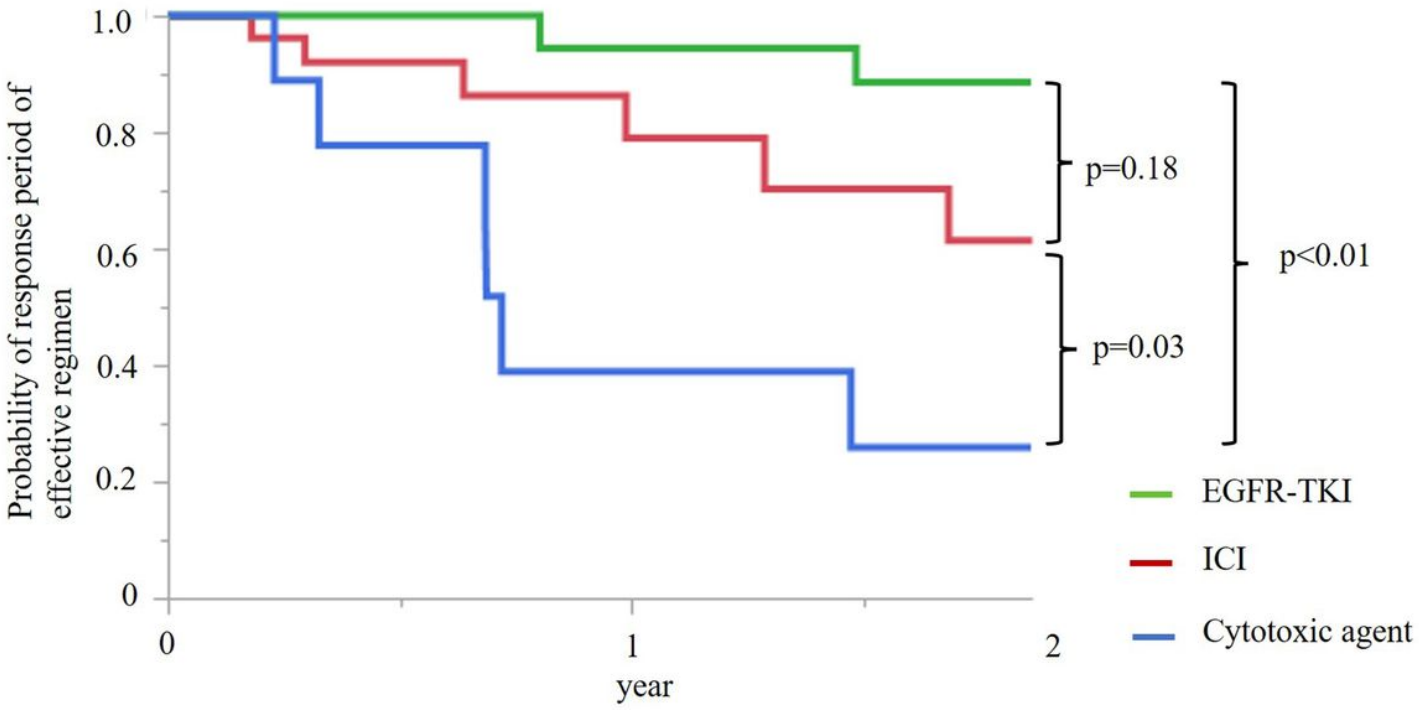

Figure 2

Response period by chemotherapy regimens

There was not significant difference of response period between EGFR-TKI and ICI (p=0.18). There was significant difference between EGFR-TKI and cytotoxic agent (p<0.01) or ICI and cytotoxic agent (p=0.03).

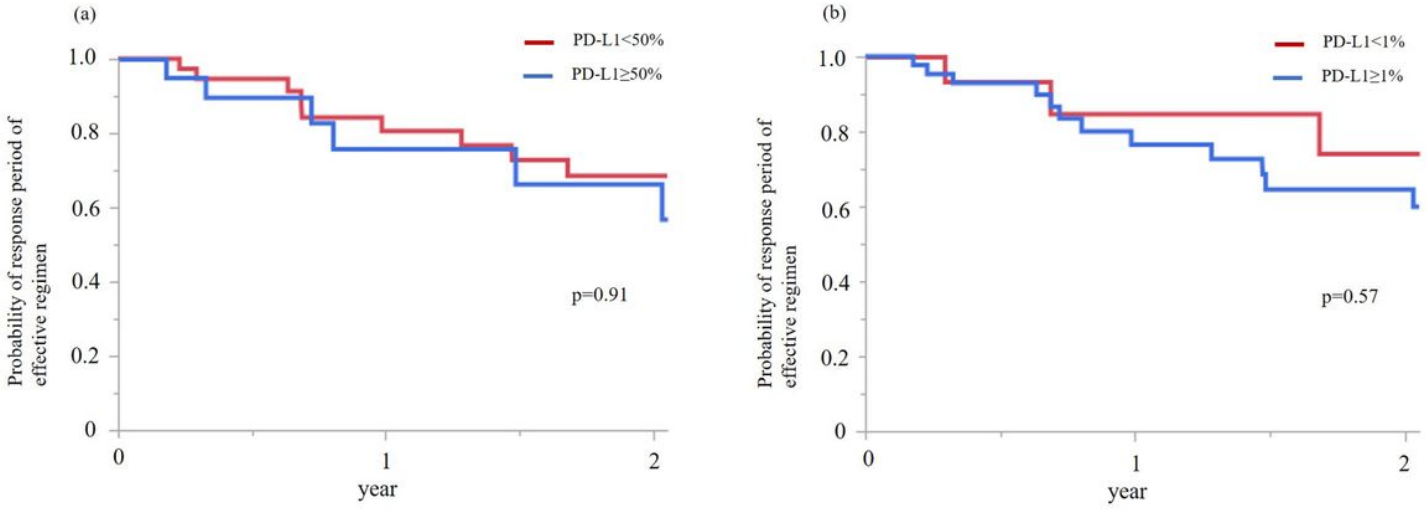

Figure 3

Response period of ICI

(a) There was not significantly different between with or without high expression of PD-L1 (p=0.91). (b) There was not significant difference between with or without expression of PD-L1 (p=0.57).