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Early indication of survival benefit from ERCC1 and RRM1 tailored chemotherapy in patients with advanced Non-Small Cell Lung Cancer (NSCLC). Evidence from an individual patient analysis

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Abstract

Background—ERCC1 and RRM1 are molecular determinants that predict sensitivity or resistance to platinum agents and gemcitabine, respectively. Tailored therapy using these molecular determinants suggests patient benefit in a previously reported phase II trial. Here we report an individual patient analysis of prospectively accrued patients treated with the ‘personalized therapy’ approach versus other ‘standard’ non-customized approaches.

Patients and Methods—NSCLC patients with extranodal metastatic disease and an ECOG PS of 0/1 were accrued to four phase II clinical trials conducted at the H Lee Moffitt Cancer Center (HLMCC): Trial A) carboplatin/gemcitabine first-line followed by docetaxel; Trial B) docetaxel and gefitinib therapy in patients aged 70 years or older; Trial C) combination therapy with carboplatin/paclitaxel/atrasentan; Trial D) personalized therapy (PT) based on ERCC1 and RRM1. Patients with low RRM1/low ERCC1 received gemcitabine/carboplatin; low RRM1/high ERCC1, gemcitabine/docetaxel; high RRM1/low ERCC1, docetaxel/carboplatin; high RRM1/high ERCC1, vinorelbine/docetaxel. Patients treated on trials A, B and C were pooled together and analyzed as the ‘standard therapy’ group. Patients accrued to trial D were called the ‘personalized therapy’ group. Individual patient data were updated as of 02/08/11. Overall Survival (OS) and progression free Survival (PFS) were estimated using the Kaplan-Meier method.

Results—There was a statistically significant improvement in responses (44% versus 22%; $p=0.002$), OS (median OS; 13.3 months vs. 8.9; $p=0.016$) and PFS (median PFS 7.0 vs. 4.3; $p=0.03$).

Conclusions—This individual patient analyses suggests that *ERCC1* and *RRM1* tailored selection of first-line therapy improves survival over standard treatment selection approaches.

Keywords

Personalized chemotherapy; Lung Cancer; ERCC1; RRM1; Gemcitabine; Carboplatin; Docetaxel; Gefitinib

Introduction

In the United States, there were 212, 500 cases of lung cancer diagnosed in the year 2010 and accounted for more than one fourth of all cancer-related deaths¹. Among lung cancers, Non-Small Cell Lung Cancer (NSCLC) comprises about 85% of all newly diagnosed cases. Approximately 40% of all incident cases of NSCLC present with extra-nodal metastatic disease where treatment with combination chemotherapy is considered to be palliative, with low measurable response rates (20–35%) with complete responses being rare, eventual progression being inevitable, and the disease proving to be fatal in the majority of instances^{2–4}.

In most patients, a doublet chemotherapy regimen is considered the standard of care for first-line treatment of patients with advanced NSCLC^{2, 4}. It produces median overall survival of 8–10 months and a 1-year survival rate of 31–36%. Recent clinical trials have shown that adding bevacizumab⁵ or cetuximab⁶ to specific chemotherapy doublets improves survival. No single doublet regimen has emerged as the best choice in terms of efficacy, though recent trials have shown that pemetrexed-cisplatin combinations may be better in

non-squamous NSCLC than gemcitabine-cisplatin. The reverse is true for squamous cell carcinoma³. Nevertheless, the selection of chemotherapy for the majority of patients remain arbitrary and is typically dictated by the oncologist's personal preference, convenience of delivery, and regimen-specific toxicity.

Excision repair cross complementing gene 1 (*ERCC1*) is a DNA damage repair gene that encodes the 5' endonuclease of the nuclear excision repair complex (NER) and plays an important role in DNA damage repair. Platinum compounds are heavy metal complexes that form adducts with, and cross-links between, DNA molecules and thus effectively block DNA replication and transcription. Repair of these adducts and cross-links are dependent on *ERCC1*. The NER complex recognizes and removes these adducts, and thus triggers resistance to platinum agents⁷. The *RRM1* gene is the regulatory subunit of ribonucleotide reductase (RR). *RRM1* is also the predominant cellular determinant of chemotherapeutic efficacy for gemcitabine⁸.

We have previously reported a single institution phase II trial in patients with advanced NSCLC, where the selection of a chemotherapy doublet was based on tumoral *RRM1* expression (determining whether or not gemcitabine was used) and *ERCC1* expression (determining whether or not platinum was used). The outcome of patients on the trial was encouraging, with improved responses (44%; 95% CI, 31% to 59), median overall (13.3 months; 95% CI, 11.5 months to < 24) and progression free 6.6 months; 95% CI, 4.7 to 8.8 months) survivals⁹.

Here we show that response and survival of patients treated with this personalized therapy approach compared favorably with patients treated with non-customized (for the purposes of this report called 'standard') treatments in a prospectively accrued cohort of patients.

Patients and Methods

The patients were prospectively accrued to four phase II clinical trials conducted at the H. Lee Moffitt Cancer Center and Research Institute, Tampa FL (ClinicalTrials.gov identifiers NCT00226590, NCT00231465, NCT00215930 and one study identified as MCC-13303). Patients were eligible for inclusion in these trials if they had NSCLC, and had stage IV or stage IIIB disease with malignant pleural effusion. Patients with brain metastases were allowed if the patient had treatment for brain metastases and was deemed to be stable. Only patients with Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1 were eligible.

Staging studies had to include a physical examination and computed tomography of the chest and upper abdomen and computed tomography or magnetic resonance imaging of the brain, if clinically indicated. Patients underwent ¹⁸F-fluorodeoxyglucose positron-emission tomography for staging per the investigator's discretion and were previously untreated for advanced disease. The University of South Florida Institutional Review Board (IRB) approved all the trials included in this report and all patients signed an IRB approved informed consent.

In the first trial (Trial A), enrolling patients between March 2001 and February 2003, (NCT00226590) patients were treated with second-line therapy (docetaxel) soon after first-line therapy (carboplatin and gemcitabine) was concluded¹⁰. In the second-trial (Trial B) enrolling only patients aged 70 years or older, between March 2003 and May 2005 (NCT00231465), a novel combination of a chemotherapeutic drug (docetaxel) and an oral epidermal growth factor tyrosine kinase inhibitor (gefitinib) was tested as first-line therapy¹¹. Thirdly, between July 2003 and August 2005, (Trial C) patients were enrolled in a phase I/II trial combining chemotherapy (carboplatin and paclitaxel) with a novel anti-

angiogenesis agent (aflibercept) (MCC 13303) ¹². In these three trials, patients were considered eligible for analyses if they received at least one cycle of treatment. For purposes of this analysis, patients enrolled in these studies were considered to have had '*non-personalized*' therapy and are grouped together as the '*standard therapy*' group.

Finally, a single-institution phase II trial (NCT00215930) (Trial D) accrued patients between February 2004 and December 2005, which evaluated the feasibility and efficacy of selecting double-agent chemotherapy based on tumoral *RRM1* and *ERCC1* expression in previously untreated patients with advanced NSCLC ⁷. This study required a pre-treatment biopsy. Tumoral *ERCC1* and *RRM1* were measured by real-time quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) as previously reported and chemotherapy was assigned based on the expression of these molecular determinants¹³⁸. *ERCC1* and *RRM1* are known to be predictors of platinum and gemcitabine resistance, respectively. In this study, patients were included for analyses if they had a biopsy for gene measurements. Predetermined values for *RRM1* and *ERCC1* were used to dichotomize between high versus low. If *RRM1* was equal to or below the value of 16.5, gemcitabine was used in the treatment doublet; if *ERCC1* was equal to or below the value of 8.7, carboplatin was used in the treatment doublet. Docetaxel was used if the *ERCC1* or *RRM1* levels were high in lieu of carboplatin or gemcitabine, respectively. These levels were selected based on our previously published experience¹³⁸. This strategy resulted in four possible gene expression strata with the following doublet therapies: the low *RRM1* and low *ERCC1* group was treated with gemcitabine, 1,250 mg/m² on days 1 and 8, and carboplatin, AUC 5 on day 1, every 21 days (GC group); the low *RRM1* and high *ERCC1* group was treated with gemcitabine, 1,250 mg/m² on days 1 and 8, and docetaxel, 40 mg/m² on days 1 and 8, every 21 days (GD group); the high *RRM1* and low *ERCC1* group was treated with docetaxel, 75 mg/m² on day 1, and carboplatin, AUC 5 on day 1, every 21 days (DC group); and the high *RRM1* and high *ERCC1* group was treated with vinorelbine, 45 mg/m² on days 1 and 15, and docetaxel, 60 mg/m² on days 1 and 15, every 28 days (DV group). Patients enrolled in this study are considered to have had '*personalized therapy*' and referred to as the '*personalized therapy*' group.

In all the four above-mentioned trials, disease response was sequentially assessed after every two cycles by computed tomography (CT) of the chest and upper abdomen, and other areas as indicated. Other imaging modalities used for disease response assessment included magnetic resonance imaging (MRI) of the brain and soft tissues. Patients without disease progression were continued on therapy for at least four cycles. Patients enrolled on the docetaxel and gefitinib trial were treated with the combination of docetaxel and gefitinib for four cycles if there was no progression and then maintained with gefitinib alone until progression ¹¹. Subsequent clinical management in all studies was at the discretion of the treating physician.

Follow-up data for overall survival, disease-free survival, and sites of tumor recurrence were obtained at regular intervals and updated. We recommended that patients have follow-up visits every three months until progression. All patients not being routinely followed at the H Lee Moffitt Cancer Center were contacted and current status ascertained as of February 8th, 2011.

Statistical methods

Overall Survival (OS) was defined as the time from date of first chemotherapy to the date of death. Progression-free survival (PFS) denoted the time from date of first chemotherapy to recurrence or death whichever came first. For patients still alive or progression free, data were censored at the time of the last follow-up visit.

Baseline characteristics were reported as counts and percentages dichotomized by the two study groups (personalized or standard therapy groups). The Mantel-Haenszel Chi-square for 2-by-2 table and Fisher's exact test for 2-by-3 table were utilized to explore the association of study groups with baseline characteristics. All outcome analyses were performed according to the intent-to-treat principle. Overall Survival and PFS were estimated using the Kaplan-Meier method and differences in OS and PFS between study groups were assessed by a two-sided log-rank test. Cox proportional hazard (PH) model was employed to assess the effect of baseline characteristics including study groups on survival. Variables with p-value of 0.25 or less in univariable analysis were selected for construction of the multivariable model. The backward elimination procedure was utilized and a variable with p-value of 0.15 or less stayed in the model. All statistical analyses were performed using SAS, version 9.2 (SAS Institute Inc, Cary, NC).

Results

Between March 2001 and December 2005, 181 patients were accrued to these four clinical trials. A summary of the four clinical trials is outlined in Table 1. The salient patient and disease characteristics of the *standard therapy* and *personalized therapy* groups are summarized in Table 2. There were no statistically significant differences between the two groups except for age. More patients older than 70 were enrolled in the *standard therapy group* secondary to the fact that one of the studies (ClinicalTrials.gov identifier, NCT00231465), enrolled only elderly patients (i.e. age ≥ 70). Patients were treated for two cycles beyond maximal response. Treatment was then stopped and patients were then observed until progression. The median number of cycles delivered in both arms was four.

Response

There was a statistically significant improvement in response (complete or partial response) in the *personalized therapy* group compared to the *standard therapy* group 44% versus 22% ($p=0.002$). Achieving a response had an unambiguous effect on survival; hazard ratios (HRs) for non-response in OS and PFS were 1.63 (95% confidence intervals (CI): 1.15 – 2.29) and 1.82 (95% CI: 1.30 – 2.54), respectively.

Overall Survival

There was a statistically significant improvement in OS ($p=0.01$) in the *personalized therapy* group over the *standard therapy* group; median survival was 13.3 months (95% CI; 10.3 – 19.3) vs. 8.9 (95% CI; 6.4 – 11.2) (Fig. 1A). The effect of age on survival was evaluated carefully given the fact that the *standard therapy* group had more patients who were 70 years of age and older when compared to the *personalized therapy* group and this difference was statistically significant ($p < 0.0001$). The median OS for the patients 70 yrs of age or older of the entire study population was 12.1 months (95% CI; 5.6 – 16.1) compared to 10.3 months for patient younger than 70 yrs of age (95% CI; 8.5 – 12.0) ($p=0.897$). The median PFS was 5.1 months for the older age group (95% CI; 2.8 – 7.0) compared to 4.8 months for the younger age group (95% CI; 3.8 – 6.0) ($p = 0.398$). Thus the survival of older patients in this analysis was not inferior to the survival of younger patients.

Progression Free Survival

The median PFS was 7.0 (95%CI; 4.7 – 9.0) months in the *personalized therapy* group vs. 4.3 (95% CI; 3.0 – 5.3) months in the *standard therapy* group ($p=0.030$) (Fig. 1B), although nearly all patients have eventually progressed or died.

Univariable and multivariable Cox proportional hazard models for OS and PFS

Female sex, PS of 0 (vs. 1) and *personalized therapy* group were predictors of improved survival by both univariable and multivariable Cox proportional hazards model analyses for OS (Table 3) and PFS (Table 4).

Discussion

This individual patient analysis suggests that *ERCC1* and *RRM1* tailored chemotherapy improves survival in patients with advanced NSCLC. Several phase III randomized trials are currently underway testing the efficacy of customized chemotherapy versus standard treatment selection approaches both in the adjuvant and advanced settings¹⁴. Cobo et al¹⁵ conducted a randomized trial to test the hypothesis that *ERCC1*-tailored therapy would improve objective responses. Patients were randomly assigned in a 1:2 ratio to either the control arm or genotypic arm. Patients in the control arm received docetaxel plus cisplatin. In the genotypic arm, patients with low *ERCC1* levels received docetaxel plus cisplatin, and those with high levels received docetaxel plus gemcitabine. Of the 346 patients assessable for response, objective responses were noted in 53 patients (39.3%) in the control arm and 107 patients (50.7%) in the genotypic arm ($p = .02$). There were, however, no survival differences in the two study arms, which this study was not designed to show. A phase III randomized trial is currently underway that will test the hypothesis that *ERCC1* and *RRM1* tailored therapy will improve survival over the standard chemotherapy regimen of carboplatin and gemcitabine (Clinicaltrials.gov identifier NCT00499109).

Another interesting observation is that the OS curves for personalized and standard therapy separate out early and stay separate for the entire duration of the follow up period (nine years) (Figure 1A), despite the fact that the PFS curves essentially re-join together at the end of two years (Figure 1B). This leads us to speculate that the benefits of the four cycles of personalized chemotherapy, usually concluded in the first four months after diagnosis, may continue even after the initial therapy has been concluded. We and others have previously shown that higher expression of *ERCC1* and *RRM1* predicts for a more indolent phenotype¹³¹⁶¹⁷. Treatment with cisplatin in low *ERCC1* patients will induce the increased expression of *ERCC1* that in turn will bestow the surviving tumor with an indolent phenotype. Treatment with gemcitabine will have a similar effect on patients with low *RRM1* expression. Indeed, in this stage IV population of patients, we had 11.3% of patients still alive after seven years in the personalized therapy arm compared to 4.5% in the control arm. To confirm this hypothesis, serial biopsies will need to be performed in future studies to better understand how the expression of these and other genes change in response to treatment.

In conclusion, our data suggest that *ERCC1* and *RRM1* tailored selection of first-line therapy improves survival over standard treatment selection approaches. The limitations of our analyses are that this is a pooled analyses of patients accrued to four different phase II trials. There was significant overlap between the accrual periods of these four trials with patients being accrued between the years 2001 and 2005. Though there was parity between the performance status and other eligibility criteria across all four studies (outlined in Table 2), patients in the personalized therapy group required a second biopsy to enable molecular analyses. This could have led to a cohort of 'more motivated' patients enrolling in the personalized therapy group potentially introducing a bias in favor of the personalized therapy group. Hence the results of this analysis can only be considered corroboratory but not confirmatory. Confirmation of these data must come from the currently ongoing randomized phase III trials.

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Glossary

ECOG	Eastern Cooperative Oncology Group
<i>ERCC1</i>	Excision repair cross complementing gene 1
IRB	Institutional Review Board
MRI	Magnetic Resonance Imaging
NSCLC	Non-Small Cell Lung Cancer
NER	nuclear excision repair complex
OS	Overall Survival
PS	Performance Status
PH	Proportional Hazard
PFS	Progression-free Survival
<i>RRM1</i>	gene is the regulatory subunit of ribonucleotide reductase
RR	ribonucleotide reductase

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin.* 2010; 60(5):277–300. [PubMed: 20610543]
2. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med.* 2002; 346(2):92–8. [PubMed: 11784875]
3. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol.* 2008; 26(21):3543–51. [PubMed: 18506025]
4. Treat JA, Gonin R, Socinski MA, et al. A randomized, phase III multicenter trial of gemcitabine in combination with carboplatin or paclitaxel versus paclitaxel plus carboplatin in patients with advanced or metastatic non-small-cell lung cancer. *Ann Oncol.* 2010; 21(3):540–7. [PubMed: 19833819]
5. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med.* 2006; 355(24):2542–50. [PubMed: 17167137]
6. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. *Lancet.* 2009; 373(9674):1525–31. [PubMed: 19410716]
7. Simon GR, Ismail-Khan R, Bepler G. Nuclear excision repair-based personalized therapy for non-small cell lung cancer: from hypothesis to reality. *Int J Biochem Cell Biol.* 2007; 39(7–8):1318–28. [PubMed: 17600754]
8. Bepler G, Kusmartseva I, Sharma S, et al. RRM1 modulated in vitro and in vivo efficacy of gemcitabine and platinum in non-small-cell lung cancer. *J Clin Oncol.* 2006; 24(29):4731–7. [PubMed: 16966686]
9. Simon G, Sharma A, Li X, et al. Feasibility and efficacy of molecular analysis-directed individualized therapy in advanced non-small-cell lung cancer. *J Clin Oncol.* 2007; 25(19):2741–6. [PubMed: 17602079]
10. Chiappori A, Simon G, Williams C, et al. Phase II study of first-line sequential chemotherapy with gemcitabine-carboplatin followed by docetaxel in patients with advanced non-small cell lung cancer. *Oncology.* 2005; 68(4–6):382–90. [PubMed: 16020967]

11. Simon GR, Extermann M, Chiappori A, et al. Phase 2 trial of docetaxel and gefitinib in the first-line treatment of patients with advanced nonsmall-cell lung cancer (NSCLC) who are 70 years of age or older. *Cancer*. 2008; 112(9):2021–9. [PubMed: 18300255]
12. Chiappori AA, Haura E, Rodriguez FA, et al. Phase I/II study of atrasentan, an endothelin A receptor antagonist, in combination with paclitaxel and carboplatin as first-line therapy in advanced non-small cell lung cancer. *Clin Cancer Res*. 2008; 14(5):1464–9. [PubMed: 18316570]
13. Simon GR, Sharma S, Cantor A, Smith P, Bepler G. ERCC1 expression is a predictor of survival in resected patients with non-small cell lung cancer. *Chest*. 2005; 127(3):978–83. [PubMed: 15764785]
14. Aggarwal C, Somaiah N, Simon GR. Biomarkers with predictive and prognostic function in non-small cell lung cancer: ready for prime time? *J Natl Compr Canc Netw*. 2010; 8(7):822–32. [PubMed: 20679541]
15. Cobo M, Isla D, Massuti B, et al. Customizing cisplatin based on quantitative excision repair cross-complementing 1 mRNA expression: a phase III trial in non-small-cell lung cancer. *J Clin Oncol*. 2007; 25(19):2747–54. [PubMed: 17602080]
16. Bepler G, Sharma S, Cantor A, et al. RRM1 and PTEN as prognostic parameters for overall and disease-free survival in patients with non-small-cell lung cancer. *J Clin Oncol*. 2004; 22(10):1878–85. [PubMed: 15143080]
17. Olaussen KA, Dunant A, Fouret P, et al. DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. *N Engl J Med*. 2006; 355(10):983–91. [PubMed: 16957145]

Figure 1.

Table 1

Summary of the Evaluated Clinical Trials

Study Group	Personalized Therapy Group	Standard	Therapy	Group
Reference	Simon et al, 2007 ⁹	Chiappori et al, 2005 ¹⁰	Chiappori et al, 2008 ¹²	Simon et al, 2008 ¹¹
Treatment Regimen	Gemcitabine/Carboplatin or Docetaxel/Carboplatin or Docetaxel/Gemcitabine or Docetaxel/Vinorelbine (First Line)	Gemcitabine/Carboplatin First Line followed by Docetaxel Second Line	Paclitaxel/Carboplatin/Atrasentan (First Line)	Docetaxel/Gefitinib First Line followed by Gefitinib maintenance
Phase of Trial	II	II	I/II	II
Number of Patients Accrued	53	40	44	44
Stage IIIB/IV- %	IIIB-2%, IV-98%	IIIB-5%, IV-95%	IIIB-13.6%, IV-86.4%	IIIB-11.4%, IV-88.6%
Median number of cycles	4.2	NR	4	4
Age (years), median (range)	63 (38–78)	62 (38–75)	61.5 (23–78)	75(70–84)
Female, %	42	42.5	40.9	41
Response Rate, %	44	15.8	18.2	40
Stable Disease, %	44	42.1	31.8	48
Median Progression Free Survival (months)	6.6	4.9	4.2	6.9
Median Overall Survival (months)	13.3	6.7	10.6	9.6
1 year Survival (%)	59	37.5	43	48

NR = Not Reported.

Table 2

Patient and Disease Characteristics.

Variables	Study Group		Total N (%)	p-value
	Personalized Therapy Group N (%)	Standard Therapy Group N (%)		
Age Group				<0.0001
Age at diagnosis $\geq$ 70	6 (11.3)	56 (43.7)	62 (34.3)	
Age at diagnosis < 70	47 (88.7)	72 (56.3)	119 (65.7)	
Gender				0.990
Female	22 (41.5)	53 (41.4)	75 (41.4)	
Male	31 (58.5)	75 (58.6)	106 (58.6)	
Performance Status (PS) *				0.206
0	25 (47.2)	47 (37.0)	72 (40.0)	
1	28 (52.8)	80 (63.0)	108 (60.0)	
Smoking Group				0.644
Current (Active or Quit years < 1)	16 (30.2)	46 (35.9)	62 (34.3)	
Former (Quit years $\geq$ 1)	31 (58.5)	65 (50.8)	96 (53.0)	
Never	6 (11.3)	17 (13.3)	23 (12.7)	
Histology				0.792
Adenocarcinoma	33 (62.3)	77 (60.2)	110 (60.8)	
All Other NSCLCs	20 (37.7)	51 (39.8)	71 (39.2)	
Stage				0.059
IIIB with Malignant Pleural Effusion	1 (1.9)	13 (10.2)	14 (7.7)	
IV	52 (98.1)	115 (89.8)	167 (92.3)	
Total	53 (29.3)	128 (70.7)	181 (100)	

* Performance status datum was not available in one patient.

Table 3

Univariable and multivariable Cox proportional hazard (PH) models for overall survival: female gender, performance status of 0 and *personalized therapy* study group were selected as significant factors for improved survival by both models.

Predictors	Univariable Analysis			Multivariable analysis		
	p-value	HR	95% CI of HR lower upper	p-value	HR	95% CI of HR lower upper
Age Group	< 70		reference			
	>= 70	0.8967	0.979 0.713 1.344			Not selected
Gender	Female		reference			
	Male	<.0001	1.898 1.385 2.602		reference	reference
PS	0		reference			
	1	0.0009	1.707 1.244 2.342		reference	reference
Smoking Status	Never		reference			
	Ever	0.0528	1.590 0.994 2.541			Eliminated from the final model (p=0.310)
Histology Group	Adenocarcinoma		reference			
	Others	0.1096	1.290 0.944 1.761			Eliminated from the final model (p=0.843)
Clinical Stage	IIIB		reference			
	IV	0.7485	0.912 0.517 1.606			Not selected
Study Group	Standard therapy		reference			
	Personalized therapy	0.0168	0.662 0.472 0.928		reference	reference
					0.0164	0.468 0.926

Note: 1) In the multivariable model, significant risk factors were selected by backward elimination method with factors eliminated when the p-value exceeded 0.15. 2) p-values in multivariable model were calculated at the final model.

Table 4

Univariable and multivariable Cox proportional hazard (PH) models for progression free survival: female gender, performance status of 0 and *personalized therapy* study group were selected as significant factors for improved progression free survival by both models.

Predictors		Univariable Analysis				Multivariable analysis			
		p-value	HR	95% CI of HR		p-value	HR	95% CI of HR	
Age Group	< 70		reference						
	>= 70	0.4017	0.875	0.640	1.196		Not selected		
Gender	Female		reference				reference		
	Male	0.0007	1.698	1.252	2.303	0.0002	1.801	1.319	2.458
PS	0		reference				reference		
	1	0.0020	1.620	1.193	2.199	0.0057	1.548	1.136	2.109
Smoking Status	Never		reference				Not selected		
	Ever	0.4181	1.203	0.769	1.884				
Histology Group	Adenocarcinoma		reference				Eliminated from the final model (p=0.787)		
	Others	0.1635	1.243	0.915	1.689				
Clinical Stage	IIIB		reference				Not selected		
	IV	0.7028	1.113	0.643	1.926				
Study Group	Standard therapy		reference				reference		
	Personalized therapy	0.0311	0.700	0.506	0.968	0.0278	0.690	0.496	0.960

Note: 1) In the multivariable model, significant risk factors were selected by backward elimination method with factors eliminated when the p-value exceeded 0.15. 2) p-values in multivariable model were calculated at the final model.