Supplementary Online Content

Arrieta O, Barrón F, Salinas Padilla M-A, et al. Effect of metformin plus tyrosine kinase inhibitors compared with tyrosine kinase inhibitors alone in patients with epidermal growth factor receptor–mutated lung adenocarcinoma: a phase 2 randomized clinical trial. *JAMA Oncol.* Published online September 5, 2019. doi:10.1001/jamaoncol.2019.2553

eTable 8. Overall survival among patients who received a second-line of therapy after intervention

eTable 9. Univariate and LKB1-stratified analysis of the clinic-pathological factors associated with progression-free survival

eTable 10. Univariate and LKB1-stratified analysis of the clinic-pathological factors associated with overall survival

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Possible mechanisms of action for metformin´s antitumor activity
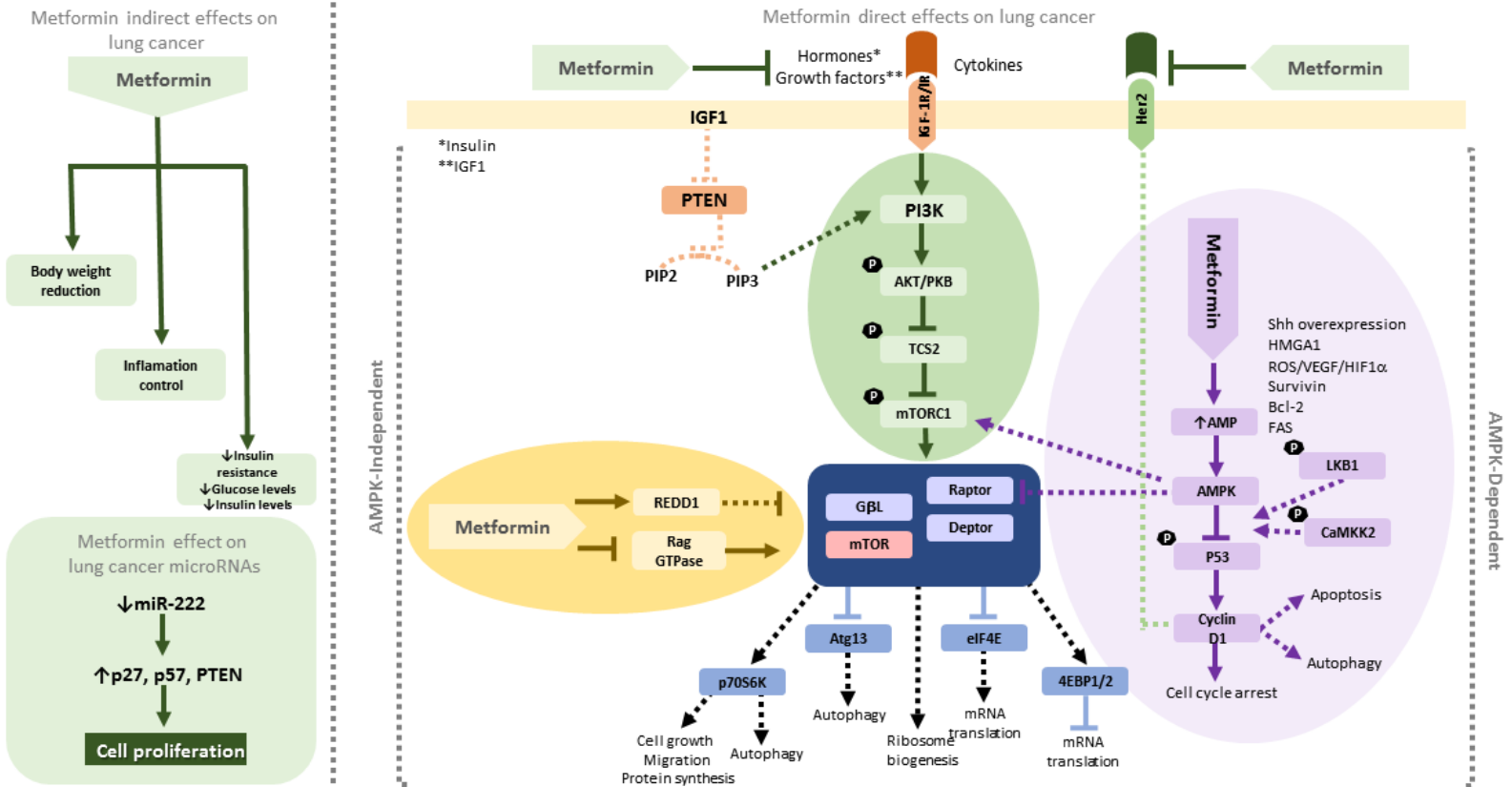
eFigure 2. Progression-free survival (radio-oncologist 2)

PFS (95%CI)
--- EGFR-TKI: 9.7 (5.1-14.3)
---EGFR-TKI + M: 11.8 (7.3-20.6)
HR (95%CI): 0.64 (0.41-0.99), p=0.049

No. at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36
TKI	70	55	36	27	16	10	5	2	1	1	0	0	0
M+TKI	69	55	44	33	20	12	9	7	6	2	1	1	0
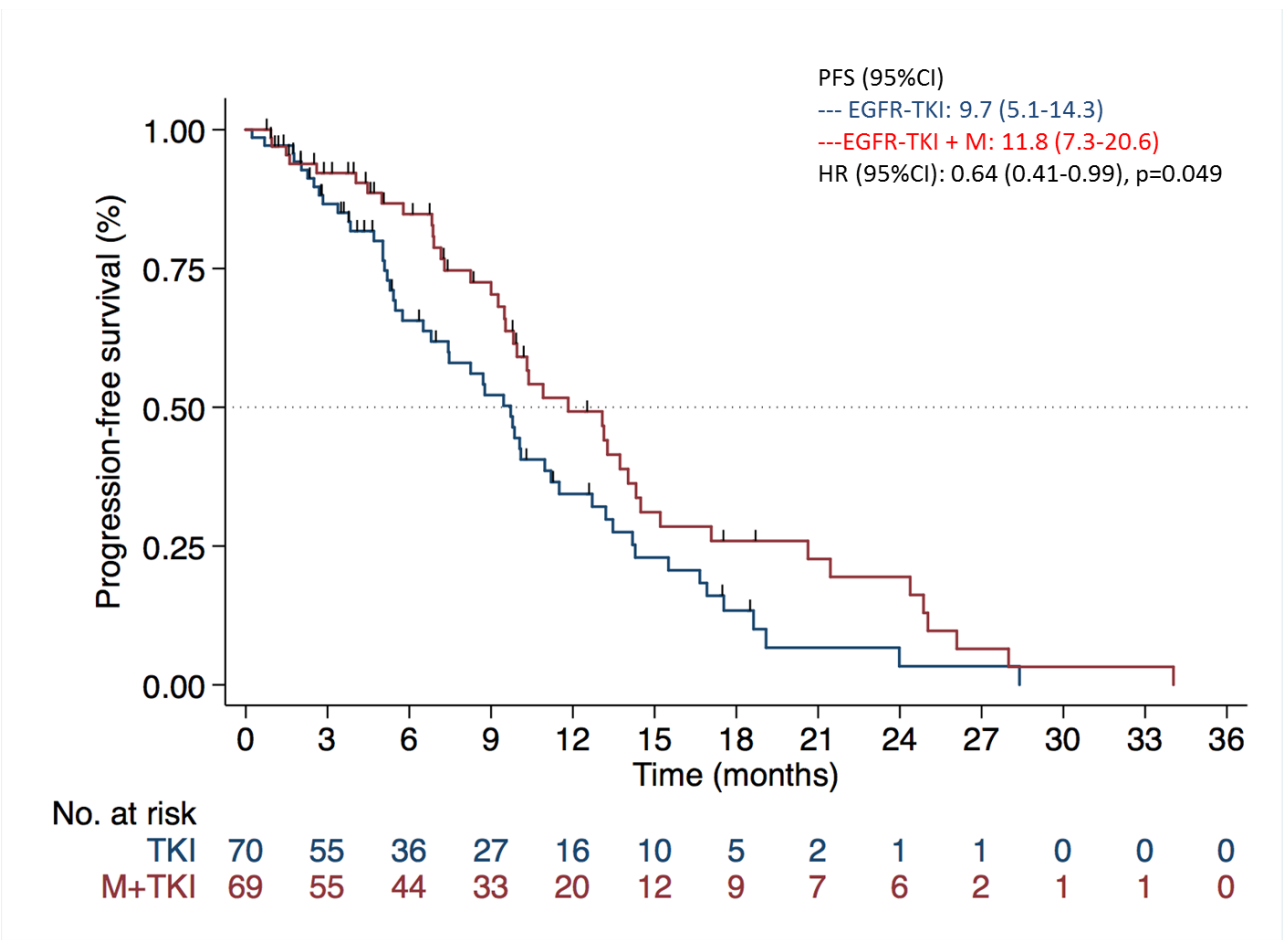
eFigure 3. (A) Kaplan-Meier curves for overall survival among patients who received second-line treatment and (B) patients who did not receive a second-line of treatment.
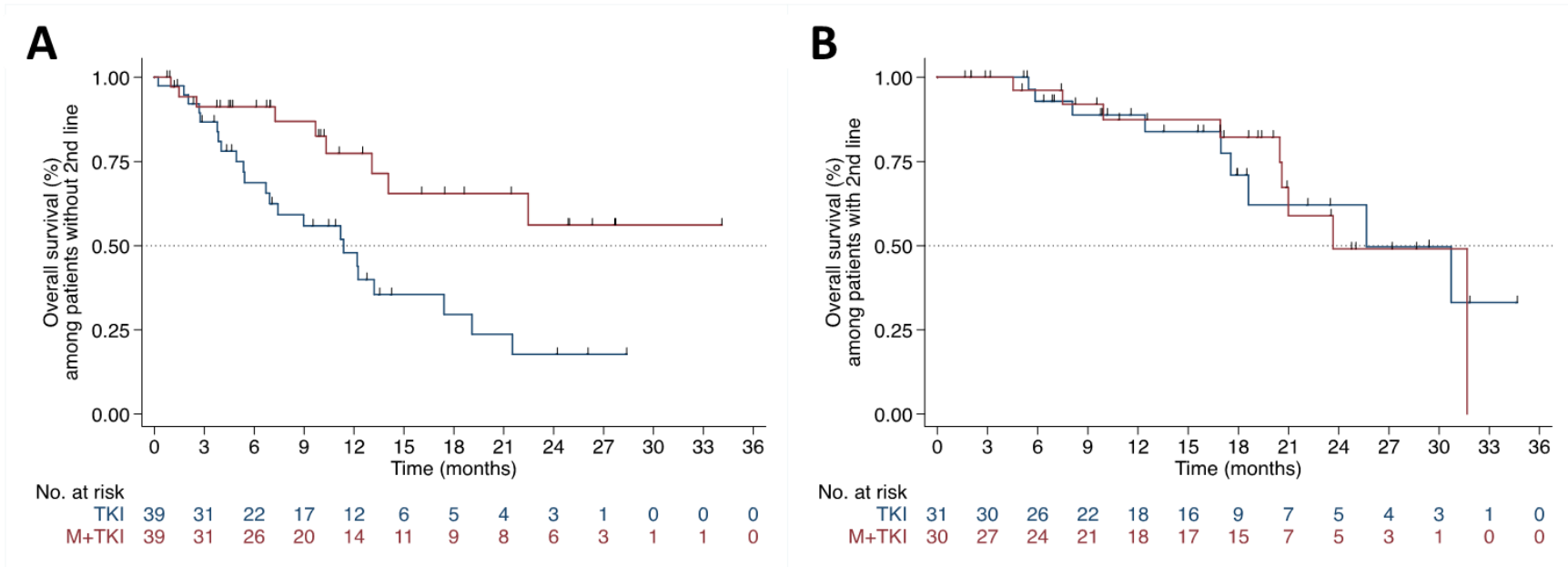
eFigure 4. Kaplan-Meier curves for (A) Progression-free survival comparison between patients with negative LKB1 expression according to the therapeutic arm. (B) Overall survival comparison between patients with negative LKB1 expression according to the received treatment. (C) Progression-free survival comparison between patients with positive LKB1 expression according to the received treatment. (D) Overall survival comparison between patients with positive LKB1 expression according to therapeutic arm.
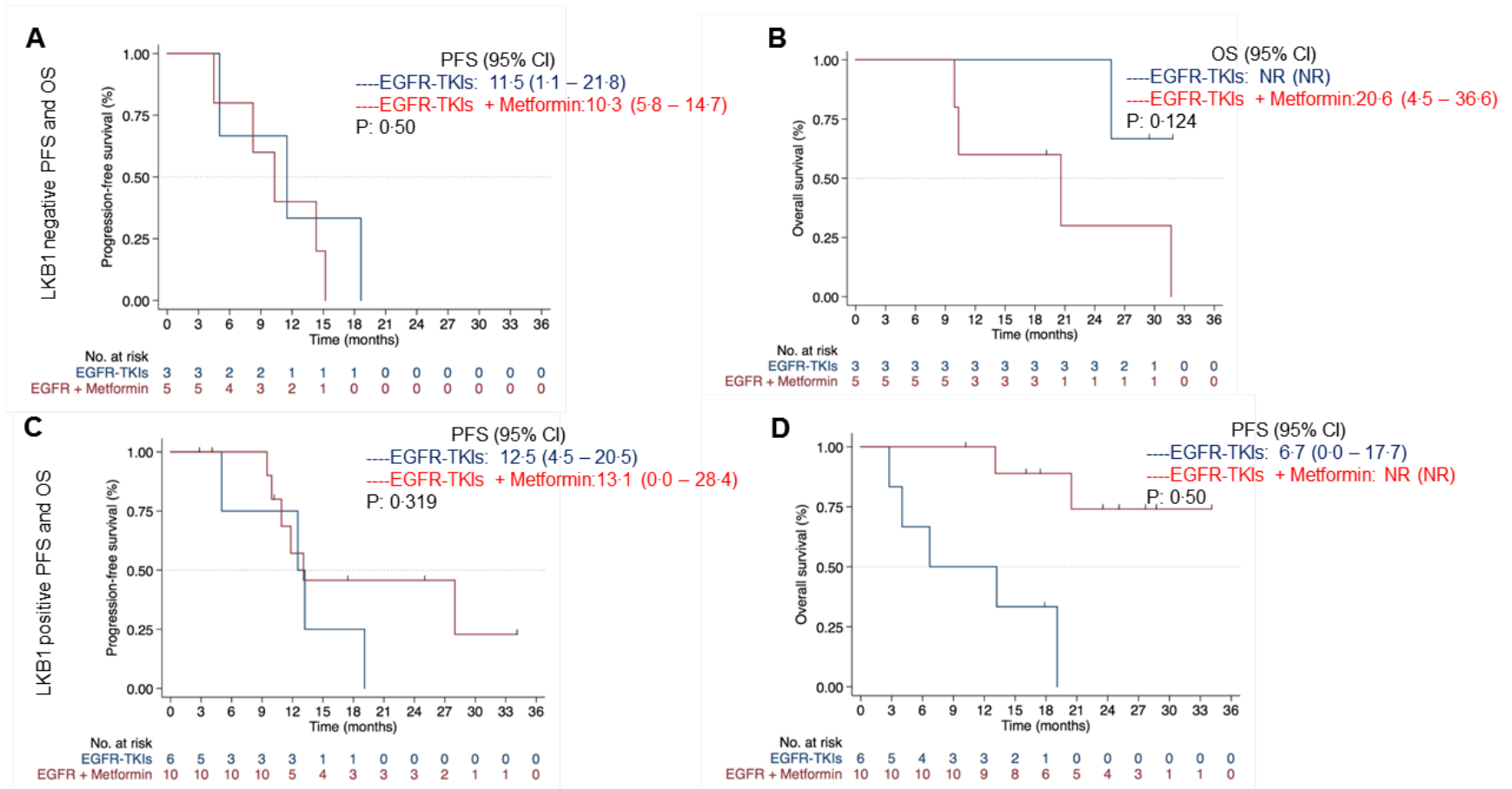
eFigure 5. Box-plots of the serum levels of Glucose (A), HbA1c (B), Interleukin-6 (C), and Insulin growth factor receptor (D) at baseline, the endo of 1st, and 2nd EGFR-TKIs cycle.
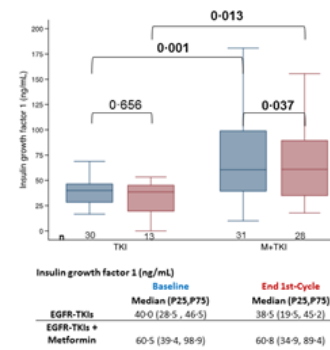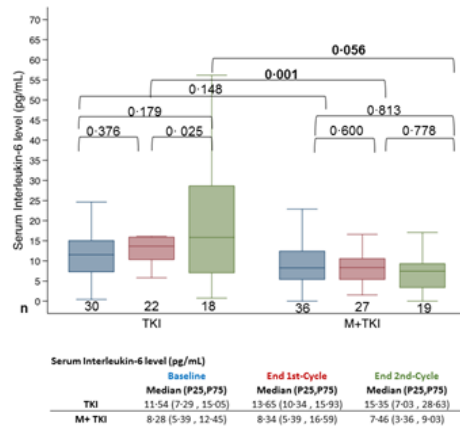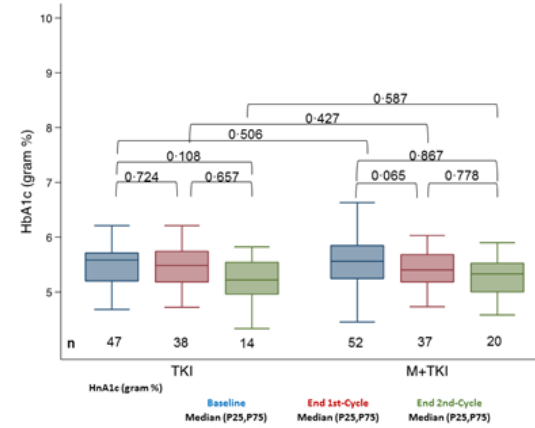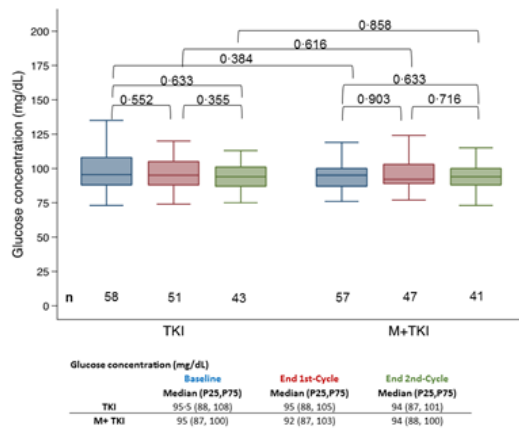
eMethods 1

Genomic DNA extractions were performed from tissue biopsies with >50% tumorous cells using a QIAamp DNA FFPE Tissue Kit (QIAGEN) according to the instructions of the manufacturer. Mutations within the *EGFR* gene exons 18, 19, 20, and 21 were detected by screening using the RGQ PCR Kit (QUIAGEN, Scorpions ARMS method).

In order to perform Immunohistochemistry testing for LKB1, biopsies and surgical resection specimens fixed in formalin and embedded in paraffin were analyzed. Tissue sections (5 µm) were deparaffinized in xylene, and hydrated in a graded ethanol series, endogenous peroxidase activity was quenched with hydrogen peroxidase for 10 minutes, followed by heat-induced epitope retrieval with immunoDNA Retriever 20X with citrate (Bio SB, Inc.CA, USA). Samples were washed with 1X Tris-buffered saline (TBS Automation Wash Buffer,40X), and the tissue sections were incubated with Anti-STK11 (1:50, HPA017254, SIGMA) at room temperature for 45 minutes. The reaction was visualized using MACH 4 universal HRP-polymer kit (BIOCARE. CA, USA) incubated with DAB for 3 minutes. Sections were then counterstained with hematoxylin and ammonium hydroxide. Isotype-matched IgG was used as a control for staining. A blinded and independent pathologist (AAS) examined all tissue samples. The intensity of LKB1 staining and the percentage of stained cells were assessed and recorded. A sample was considered positive for LKB1 when any intensity staining was registered.

Serum samples were collected before the start of treatment with EGFR-TKIs, after the end of the 1st and 2nd cycle of treatment. Il-6 and IGF serum levels were determined using using ELISA, which was performed according to Quantikine Il-6 and IGF ELISA Kit (R&D System, Minneapolis, MN, USA). All assays were performed in duplicate. Color intensity was measured at 450 nm with a spectrophotometric plate reader. Il-6 and IGF concentrations were determined by comparison with standard curves.

eMethods 2

Statistical analyses

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STATISTICAL ANALYSIS DOCUMENTATION.

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*sum id.

*set more off.

*describe.

*tab gender.

*hist age, normal.

*swilk age.

*sum age, det.

*tab age_groups.

*tab smk.

*tab wse.

*tab adeno_subtype.

*tab bone_mets.

*tab pleural_mets.

*tab cl_mets.

*tab adrenal_mets.

*tab brain_mets.

```
*tab liver_mets.

*tab mut.

*tab intervention.

*tab EGFR_TKI.

*tab best_gps.

*tab orr.

*tab dcr.

*tab recist_masao.

*tab orr_masao.

*tab dcr_masao.

*tab segunda_linea.

*tab tipo_segunda_linea.

*tab tercera_linea.

.

*tab gender intervention, col chi.

*bysort intervention: sum age, det.

*tab age_groups intervention, col chi.

*tab smk intervention, col chi.

*tab wse intervention, col chi.

*tab adeno_subtype intervention, col chi.

*tab bone_mets intervention, col chi.

*tab pleural_mets intervention, col chi.

*tab cl_mets intervention, col chi.

*tab adrenal_mets intervention, col chi.

*tab brain_mets intervention, col chi.

*tab liver_mets intervention, col chi.

*tab mut intervention, col chi.

*tab intervention intervention, col chi.

*tab EGFR_TKI intervention, col chi.

*tab intervention intervention, col chi.
```

*tab best_gps intervention, col chi.

*tab orr intervention, col chi.

*tab dcr intervention, col chi.

*tab recist_masao.

*tab orr_masao.

*tab dcr_masao.

*tab segunda_linea intervention, col chi.

*tab tipo_segunda_linea intervention, col chi.

*tab tercera_linea intervention, col chi.

.

*preserve.

*parmby "prop orr, over (intervention)", norestore.

*restore.

*preserve.

*parmby "prop dcr, over (intervention)", norestore.

*restore.

*preserve.

*parmby "prop orr_masao, over (intervention)", norestore.

*restore.

*preserve.

*parmby "prop dcr_masao, over (intervention)", norestore.

*restore.

.

*kappa best_gps recist_masao, tab.

*kappa orr orr_masao, tab.

*kappa dcr dcr_masao, tab.

.

*twoway (bar BEST_tumor_response_percentage id2 if intervention==0, sort)//>/,>

*(bar BEST_tumor_response_percentage id2 if intervention==1).

*twoway (bar A id2 if intervention==0, sort) ///, >

*(bar A id2 if intervention==1).

.

*0 Overall.

*preserve.

*set more off.

*stset slp_139, failure (progres1=1).

*stsum.

*stci.

*sts graph, risktable censored(single).

*restore.

* 1 Sex.

*preserve.

*set more off.

*stset slp_139, failure (progres1=1).

*stsum, by(gender).

*stci, by(gender).

*stcox i.gender.

*sts test gender.

*sts graph, by(gender) risktable censored(single).

*restore.

* 2 Age.

*preserve.

*set more off.

*stset slp_139, failure (progres1=1).

*stsum, by(age_groups).

*stci, by(age_groups).

*stcox c.age.

*streg age, dist(exponential) tr.

*sts test age.

*sts graph, by(age_groups) risktable censored(single).

*restore.

* 3 Smoking status.

*preserve.

*set more off.

*stset slp_139, failure (progres1=1).

*stsum, by(smk).

*stci, by(smk).

*stcox i.smk.

*sts test smk.

*sts graph, by(smk) risktable censored(single).

*restore.

* 4 Wood---smoke exposure.

*preserve.

*set more off.

*stset slp_139, failure (progres1=1).

*stsum, by(wse).

*stci, by(wse).

*stcox i.wse.

*sts test wse.

*sts graph, by(wse) risktable censored(single).

*restore.

* 5 Adenocarcinoma Subtype.

*preserve.

*set more off.

*stset slp_139, failure (progres1=1).

*stsum, by(adeno_gp).

*stci, by(adeno_gp).

*stcox i.adeno_gp.

*sts test adeno_gp.

*sts graph, by(adeno_gp) risktable censored(single).

*restore.

* 6 Bone metastases.

*preserve.

*set more off.

*stset slp_139, failure (progres1=1).

*stsum, by(bone_mets).

*stci, by(bone_mets).

*stcox i.bone_mets.

*sts test bone_mets.

*sts graph, by(bone_mets) risktable censored(single).

*restore.

* 7 Pleural metastases.

*preserve.

*set more off.

*stset slp_139, failure (progres1=1).

*stsum, by(pleural_mets).

*stci, by(pleural_mets).

*stcox i.pleural_mets.

*sts test pleural_mets.

*sts graph, by(pleural_mets) risktable censored(single).

*restore.

* 8 Contralateral metastases.

*preserve.

*set more off.

*stset slp_139, failure (progres1=1).

*stsum, by(cl_mets).

*stci,by(cl_mets).

*stcox i.cl_mets.

*sts test cl_mets.

*sts graph, by(cl_mets) risktable censored(single).

*restore.

* 9 Adrenal metastases.

*preserve.

*set more off.

*stset slp_139, failure (progres1=1).

*stsum, by(adrenal_mets).

*stci, by(adrenal_mets).

*stcox i.adrenal_mets.

*sts test adrenal_mets.

*sts graph, by(adrenal_mets) risktable censored(single).

*restore.

* 10 Brain metastases.

*preserve.

*set more off.

*stset slp_139, failure (progres1=1).

*stsum, by(brain_mets).

*stci, by(brain_mets).

*stcox i.brain_mets.

*sts test brain_mets.

*sts graph, by(brain_mets) risktable censored(single).

*restore.

* 11 Liver metastases.

*preserve.

*set more off.

*stset slp_139, failure (progres1=1).

*stsum, by(liver_mets).

*stci, by(liver_mets).

*stcox i.liver_mets.

*sts test liver_mets.

*sts graph, by(liver_mets) risktable censored(single).

*restore.

* 12 Mutation status.

*preserve.

*set more off.

*stset slp_139, failure (progres1=1).

*stsum, by(mut) . *stci, by(mut).

*stcox i.mut.

*sts test mut.

*sts graph, by(mut) risktable censored(single).

*restore.

* 13 EGFR TKIs.

*preserve.

*set more off.

*stset slp_139, failure (progres1=1).

*stsum, by(EGFR_TKI).

*stci, by(EGFR_TKI).

*stcox ib3.EGFR_TKI.

*sts test EGFR_TKI.

*sts graph, by(EGFR_TKI) risktable censored(single).

*restore.

* 14 Objective Response Rate (ORR).

*preserve.

*set more off.

*stset slp_139, failure (progres1=1).

*stsum, by(orr).

*stci, by(orr).

*stcox i.orr.

*sts test orr.

*sts graph, by(orr) risktable censored(single).

*restore.

* 15 Disease control rate (DCR).

*preserve.

*set more off.

*stset slp_139, failure (progres1=1).

*stsum, by(dcr).

*stci, by(dcr).

*stcox i.dcr.

*sts test dcr.

*sts graph, by(dcr) risktable censored(single).

*restore.

* 16 Intervention (Therapeutic arm).

*preserve.

*set more off.

*stset slp_139, failure (progres1=1).

*stsum, by(intervention).

*stci, by(intervention).

*stcox i.intervention.

*sts test intervention.

*sts graph, by(intervention) risktable censored(single).

*restore.

* 17 LKB---1.

*preserve.

*set more off.

*stset slp_139, failure (progres1=1).

*stsum, by(lkb1).

*stci, by(lkb1).

*stcox i.lkb1.

*sts test lkb1.

*sts graph, by(lkb1) risktable censored(single).

*restore.

* 18 Previous treatment.

*preserve.

*set more off.

*stset slp_139, failure (progres1==1).

*stsum, by(tto_previo).

*stci, by(tto_previo).

*stcox i.tto_previo.

*sts test tto_previo.

*sts graph, by(tto_previo) risktable censored(single).

*restore.

* 19 2nd Line.

*preserve.

*set more off.

*stset slp_139, failure (progres1=1).

*stsum, by(segunda_linea).

*stci, by(segunda_linea).

*stcox i.segunda_linea.

*sts test segunda_linea.

*sts graph, by(segunda_linea) risktable censored(single).

*restore.

* 20 3rd Line.

*preserve.

*set more off.

*stset slp_139, failure (progres1=1).

*stsum, by(tercera_linea).

*stci, by(tercera_linea).

*stcox i.tercera_linea.

*sts test tercera_linea.

*sts graph, by(tercera_linea) risktable censored(single).

*restore.

.

*preserve.

*set more off.

*stset slp_139, failure (progres1==1).

*sw, pe (0.10)lockterm1:stcox intervention gender age ///, >

*smk wse adeno_gp bone_mets pleural_mets cl_mets ///, >

*adrenal_mets brain_mets liver_mets mut ///, >

*EGFR_TKI orr dcr segunda_linea tercera_linea.

*estat phtest.

*estat ic.

*restore.

*preserve.

*set more off.

*stset slp_139, failure (progres1==1).

*sw, pe (0.05)lockterm1:stcox intervention gender age ///, >

*smk wse adeno_gp bone_mets pleural_mets cl_mets ///, >

*adrenal_mets brain_mets liver_mets mut ///, >

*EGFR_TKI orr dcr segunda_linea tercera_linea.

*estat phtest.

*estat ic.

*restore.

*preserve.

*set more off.

*stset slp_139, failure (progres1==1).

*sw, pe (0.05):stcox intervention gender age ///, >

*smk wse adeno_gp bone_mets pleural_mets cl_mets ///, >

*adrenal_mets brain_mets liver_mets mut ///, >

*EGFR_TKI orr dcr segunda_linea tercera_linea.

*estat phtest.

*estat ic.

*restore.

* Note: LKB1 was excluded a priori from multivariable model.

* due to the low frequency of available data (n=24).

.

*0 Overall.

*preserve.

*set more off.

*stset sg_139, failure (status=1).

*stsum.

*stci.

*sts graph, risktable censored(single).

*restore.

* 1 Sex.

*preserve.

*set more off.

*stset sg_139, failure (status=1).

*stsum, by(gender).

*stci, by(gender).

*stcox i.gender.

*sts test gender.

*sts graph, by(gender) risktable censored(single).

*restore.

* 2 Age.

*preserve.

*set more off.

*stset sg_139, failure (status=1).

*stsum, by(age_groups).

*stci, by(age_groups).

*stcox c.age.

*streg age, dist(exponential) tr.

```
*sts test age.

*sts graph, by(age_groups) risktable censored(single).

*restore.

* 3 Smoking status.

*preserve.

*set more off.

*stset sg_139, failure (status=1).

*stsum, by(smk).

*stci, by(smk).

*stcox i.smk.

*sts test smk.

*sts graph, by(smk) risktable censored(single).

*restore.

* 4 Wood---smoke exposure.

*preserve.

*set more off.

*stset sg_139, failure (status=1).

*stsum, by(wse).

*stci, by(wse).

*stcox i.wse.

*sts test wse.

*sts graph, by(wse) risktable censored(single).

*restore.

* 5 Adenocarcinoma Subtype.

*preserve.

*set more off.

*stset sg_139, failure (status=1).

*stsum, by(adeno_gp).

*stci, by(adeno_gp).

*stcox i.adeno_gp.
```

*sts test adeno_gp.

*sts graph, by(adeno_gp) risktable censored(single).

*restore.

* 6 Bone metastases.

*preserve.

*set more off.

*stset sg_139, failure (status=1).

*stsum, by(bone_mets).

*stci, by(bone_mets).

*stcox i.bone_mets.

*sts test bone_mets.

*sts graph, by(bone_mets) risktable censored(single).

*restore.

* 7 Pleural metastases.

*preserve.

*set more off.

*stset sg_139, failure (status=1).

*stsum, by(pleural_mets).

*stci, by(pleural_mets).

*stcox i.pleural_mets.

*sts test pleural_mets.

*sts graph, by(pleural_mets) risktable censored(single).

*restore.

* 8 Contralateral metastases.

*preserve.

*set more off.

*stset sg_139, failure (status=1).

*stsum, by(cl_mets).

*stci,by(cl_mets).

*stcox i.cl_mets.

*sts test cl_mets.

*sts graph, by(cl_mets) risktable censored(single).

*restore.

* 9 Adrenal metastases.

*preserve.

*set more off.

*stset sg_139, failure (status=1).

*stsum, by(adrenal_mets).

*stci, by(adrenal_mets).

*stcox i.adrenal_mets.

*sts test adrenal_mets.

*sts graph, by(adrenal_mets) risktable censored(single).

*restore.

* 10 Brain metastases.

*preserve.

*set more off.

*stset sg_139, failure (status=1).

*stsum, by(brain_mets).

*stci, by(brain_mets).

*stcox i.brain_mets.

*sts test brain_mets.

*sts graph, by(brain_mets) risktable censored(single).

*restore.

* 11 Liver metastases.

*preserve.

*set more off.

*stset sg_139, failure (status=1).

*stsum, by(liver_mets).

*stci, by(liver_mets).

*stcox i.liver_mets.

*sts test liver_mets.

*sts graph, by(liver_mets) risktable censored(single).

*restore.

* 12 Mutation status.

*preserve.

*set more off.

*stset sg_139, failure (status=1).

*stsum, by(mut).

*stci, by(mut).

*stcox i.mut.

*sts test mut.

*sts graph, by(mut) risktable censored(single).

*restore.

* 13 EGFR TKIs.

*preserve.

*set more off.

*stset sg_139, failure (status=1).

*stsum, by(EGFR_TKI).

*stci, by(EGFR_TKI).

*stcox ib3.EGFR_TKI.

*sts test EGFR_TKI.

*sts graph, by(EGFR_TKI) risktable censored(single).

*restore.

* 14 Objective Response Rate (ORR).

*preserve.

*set more off.

*stset sg_139, failure (status=1).

*stsum, by(orr).

*stci, by(orr).

*stcox i.orr.

*sts test orr.

*sts graph, by(orr) risktable censored(single).

*restore.

* 15 Disease control rate (DCR).

*preserve.

*set more off.

*stset sg_139, failure (status=1).

*stsum, by(dcr).

*stci, by(dcr).

*stcox i.dcr.

*sts test dcr.

*sts graph, by(dcr) risktable censored(single).

*restore.

* 16 Intervention (Therapeutic arm).

*preserve.

*set more off.

*stset sg_139, failure (status=1).

*stsum, by(intervention).

*stci, by(intervention).

*stcox i.intervention.

*sts test intervention.

*sts graph, by(intervention) risktable censored(single).

*restore.

* 17 LKB---1.

*preserve.

*set more off.

*stset sg_139, failure (status=1).

*stsum, by(lkb1).

*stci, by(lkb1).

*stcox i.lkb1.

*sts test lkb1.

*sts graph, by(lkb1) risktable censored(single).

*restore.

* 18 Previous treatment.

*preserve.

*set more off.

*stset sg_139, failure (status=1).

*stsum, by(tto_previo).

*stci, by(tto_previo).

*stcox i.tto_previo.

*sts test tto_previo.

*sts graph, by(tto_previo) risktable censored(single).

*restore.

* 19 2nd Line.

*preserve.

*set more off.

*stset sg_139, failure (status=1).

*stsum, by(segunda_linea).

*stci, by(segunda_linea).

*stcox i.segunda_linea.

*sts test segunda_linea.

*sts graph, by(segunda_linea) risktable censored(single).

*restore.

* 20 3rd Line.

*preserve.

*set more off.

*stset sg_139, failure (status=1).

*stsum, by(tercera_linea).

*stci, by(tercera_linea).

*stcox i.tercera_linea.

*sts test tercera_linea.

*sts graph, by(tercera_linea) risktable censored(single).

*restore.

*preserve.

*set more off.

*stset sg_139, failure (status=1).

*sw, pe (0.10):stcox intervention gender age ///, >

*smk wse adeno_gp bone_mets pleural_mets cl_mets ///, >

*adrenal_mets brain_mets liver_mets mut ///, >

*EGFR_TKI orr dcr segunda_linea tercera_linea.

*estat phtest.

*estat ic.

*restore.

*preserve.

*set more off.

*stset sg_139, failure (status=1).

*sw, pe (0.05)lockterm1:stcox intervention gender age ///, >

*smk wse adeno_gp bone_mets pleural_mets cl_mets ///, >

*adrenal_mets brain_mets liver_mets mut ///, >

*EGFR_TKI orr dcr segunda_linea tercera_linea.

*estat phtest.

*estat ic.

*restore.

*preserve.

*set more off.

*stset sg_139, failure (status=1).

*sw, pe (0.05):stcox intervention gender age ///, >

*smk wse adeno_gp bone_mets pleural_mets cl_mets ///, >

*adrenal_mets brain_mets liver_mets mut ///, >

*EGFR_TKI orr dcr segunda_linea tercera_linea.

*estat phtest.

*estat ic.

*restore.

* Note: LKB1 was excluded a priori from multivariable model.

* due to the low frequency of available data (n=24).

*.

*END.

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eTable 1. Concordance agreement assessment among radiooncologists (n=2) for the radiographic evaluation of the best response rate through RECIST v1.1

		Radiologist 2				
Radiologist 1	Best response rate	Complete response	Partial Response	Stable disease	Disease progression	Total
	Complete response	11	0	0	0	11
	Partial Response	2	69	5	0	76
	Stable disease	0	6	38	2	46
	Disease progression	0	1	0	5	6
	Total	13	76	43	7	139
Agreement scores						
Agreement		Expected agreement	Kappa	Std. Err	Z	Prob>Z
88.49%		41.09%	0.8046	0.0621	12.96	0

		Radiologist 2			
Radiologist 1		Responders	Not responders	Total	
	Responders	82	5	87	
	Not responders	7	45	52	
	Total	89	50	139	
Agreement scores					
Agreement	Expected agreement	Kappa	Std. error	Z	Prob>Z
91.37%	53.53%	0.8142	0.0848	9.6	0

eTable 2. Univariate and multivariate analysis of the clinic-pathological factors associated with progression-free survival according to Radiooncologist 2

	Overall	Number of events	Median months (95% CI)	*p*-Value	HR (95% CI)	*p*-value
Global	139	92	10.0 (5.8 – 15.5)			
Gender						
Female	91	63	9.9 (5.5 – 15.5)			
Male	48	29	10.3 (6.8 – 14.3)	0.7789		
Age						
<60	76	53	10.1 (6.8 – 17.5)			
≥60	63	29	10.9 (5.5 – 14.3)	0.4562		
Tobacco exposure						
Absent	101	65	10.1 (5.8 – 15.5)			
Present	38	27	10.3 (6.9 – 17.5)	0. 8061		
Wood-smoke exposure						
Absent	87	57	10.1 (6.5 – 16.9)			
Present	52	35	10.4 (5.4 – 14.2)	0.7972		
Predominant histological pattern						
Well/Moderately differentiated	56	42	11.2 (6.8 – 18.6)			
Poorly/Non differentiated	83	50	9.8 (5.8 – 14.0)	0. 1538	1.21 (0.77 - 1.89)	0.4
Metastases						
Bone						
Absent	82	54	10.4 (5.5 – 16.9)			
Present	57	38	9.9 (6.8 – 14.0)	0.3849		
Pleura						
Absent	92	57	10.4 (5.5 – 16.9)			

	Overall (continued)	Number of events	Median months (95% CI)	*p*-Value	HR (95% CI)	*p*-value
Present	47	35	10.1 (6.9 – 14.2)	0.7434		
Contralateral lung						
Absent	92	59	10.1 (6.5 – 16.7)			
Present	47	33	10.3 (5.8 – 14.3)	0.9507		
Adrenal glands						
Absent	130	87	10.1 (5.8 – 15.5)			
Present	9	5	11.2 (9.9 – 13.5)	0.8108		
Central Nervous System						
Absent	86	52	11.8 (6.8 – 16.9)			
Present	53	40	9.5 (5.2 – 13.2)	0.0778	1.55 (1.01 - 2.38)	**0.043**
Liver						
Absent	130	84	10.4 (6.9 – 16.7)			
Present	9	8	5.8 (4.7 – 7.3)	0.0116	2.83 (1.28 - 6.27)	**0.010**
EGFR mutational profile						
Exon 18 (G719X)	5	5	9.9 (7.2 – 24.9)			
Exon 19 (Deletion)	89	56	10.1 (5.8 – 16.7)	0.6075		
Exon 21 (L858R)	45	33	10.3 (5.8 – 13.7)			
EGFR-TKIs treatment characteristics						
Gefitinib	50	31	9.8 (5.8 – 17.1)			
Afatinib	63	40	11.2 (5.3 – 15.2)	0.8064		
Erlotinib	26	21	10.1 (6.83 – 18.6)			
Overall response rate						
Present	89	59	13.1 (7.4 – 17.5)			
Absent	50	33	9.0 (4.7 – 10.9)	**0.0011**		
Disease control rate						

	Overall (continued)	Number of events	Median months (95% CI)	*p*-Value	HR (95% CI)	*p*-value
Present	132	85	10.9 (6.9 – 16.7)			
Absent	7	7	2.8 (1.8 – 5.2)	**<0.0001**	4.54 (1.70 - 12.11)	**0.003**
Therapeutic arm						
EGFR-TKIs	70	50	9.7 (5.1 – 14.3)			
EGFR-TKIs + metformin	69	42	11.8 (7.3 – 20.6)	**0.0391**	0.64 (0.41 - 0.99)	**0.049**
LKB1 expression						
Negative	8	8	25.7 (13.2 - 38.1)			
Positive	16	11	20.5 (NR)	0.054		
Second line						
Absent	78	43	11.8 (5.8 – 19.1)			
Present	61	49	9.7 (6.8 – 14.3)	**0.1817**		
Third line						
Present	114	71	10.9 (5.8 – 16.9)			
Absent	17	17	9.8 (7.3 – 13.2)	0.1629		

eTable 3. Crude and adjusted Hazard Ratios for PFS by Radio-oncologists 1 and 2.

Variables and Comparisons		Radio-oncologist 1				Radio-oncologist 2			
		Crude		Adjusted		Crude		Adjusted	
Variable	Comparison	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Sex	M vs. F	0.97 (0.62 - 1.54)	0.918			0.93 (0.60 - 1.46)	0.779		
Age	For each year	1.00 (0.99 - 1.02)	0.302			0.99 (0.98 - 1.01)	0.847		
Smoke	Ever vs. Never	0.86 (0.53 - 1.39)	0.554			0.94 (0.60 - 1.48)	0.806		
WSE	Present vs. Absent	1.13 (0.73 - 1.75)	0.586			1.05 (0.69 - 1.62)	0.797		
Adenocarcinoma subtype	Poor vs. Well/Moderate	1.39 (0.89 - 2.17)	0.144	0.82 (0.5 - 1.3)	0.423	1.36 (0.88 - 2.09)	0.155	1.21 (0.77 - 1.89)	0.4
Bone metastases	Present vs. Absent	1.13 (0.73 - 1.75)	0.592			1.20 (0.79 - 1.83)	0.386		
Pleural metastases	Present vs. Absent	1.12 (0.72 - 1.74)	0.602			1.07 (0.70 - 1.63)	0.744		
Contralateral	Present vs. Absent	1.05 (0.67 - 1.64)	0.827			1.01 (0.65 - 1.56)	0.951		
Adrenal	Present vs. Absent	0.94 (0.38 - 2.33)	0.898			0.89 (0.36 - 2.21)	0.811		
Brain	Present vs. Absent	1.43 (0.93 - 2.21)	0.105	1.54 (0.9 - 2.4)	0.058	1.45 (0.95 - 2.21)	0.080	1.55 (1.01 - 2.38)	**0.043**
Liver	Present vs. Absent	2.29 (1.04 - 5.05)	**0.039**	2.71 (1.2 - 6.3)	**0.021**	2.52 (1.19 - 5.29)	0.015	2.83 (1.28 - 6.27)	**0.010**
EGFR mutation status	E18(G719X)	1.00 (Reference)	…			1.00 (Reference)	…		
	E 19 (del)	2.31 (0.56 - 9.55)	0.244			1.77 (0.55 - 5.71)	0.333		
	E 21 (L858R)	2.30 (0.54 - 9.67)	0.254			1.65 (0.50 - 5.43)	0.408		
EGFR TKI	Gefitinib	1.00 (Reference)	…			1.00 (Reference)	…		
	Afatinib	0.98 (0.59 - 1.62)	0.941			1.10 (0.68 - 1.78)	0.683		
	Erlotinib	1.05 (0.59 - 1.83)	0.866			0.92 (0.53 - 1.62)	0.799		
ORR	Not responders vs. Responders	1.92 (1.20 - 3.05)	0.006			2.08 (1.32 - 3.25)	**0.001**		

DCR	Uncontrolled vs. Controlled diseases	5.85 (2.25 - 15.3)	**<0.001**	4.81 (0.8 - 12.9)	**0.002**	7.96 (3.44 - 18.40)	**<0.001**	4.54 (1.70 - 12.11)	**0.003**
Intervention	M+TKI vs. TKI alone	0.59 (0.38 - 0.92)	**0.019**	0.60 (0.4 - 0.94)	**0.028**	0.64 (0.42 - 0.98)	0.041	0.64 (0.41 - 0.99)	**0.049**
LKB1	Positive vs. Negative	0.43 (0.16 - 1.16)	0.096			0.38 (0.14 - 1.05)	0.064		
Second line	Present vs. Absent	1.45 (0.95 - 2.24)	0.090			1.32 (0.87 - 2.00)	0.182		
Third line	Present vs. Absent	1.41 (0.81 - 2.45)	0.218			1.46 (0.85 - 2.50)	0.165		

eTable 4. Adverse events

Adverse event	EGFR-TKI			EGFR-TKIs + Metformin			p-Value for comparisons	
	Any grade n (%)	G 1/2 n (%)	G ≥3 n (%)	Any grade n (%)	G 1/2 n (%)	G ≥3 n (%)	Absent vs. Present	G1/2 vs. G ≥3
Diarrhea	59 (84.3)	55 (93.2)	4 (6.8)	54 (78.3)	48 (88.9)	11.1 (6)	0.362	0.418
Rash	47 (67.1)	44 (93.6)	3 (6.4)	48 (69.6)	47 (97.9)	2.1 (1)	0.759	0.362
Nausea	31 (44.3)	30 (96.8)	1 (3.2)	31 (44.9)	30 (96.8)	1 (3.2)	0.939	1.000
Mucositis	28 (40.0)	27 (96.4)	1 (3.6)	26 (37.7)	100.0 (26)	0 (0)	0.779	1.000
Paronichya	21 (30.0)	100.0 (21)	0 (0)	21 (30.4)	100.0 (21)	0 (0)	0.955	1.000
Asthenia	24 (34.3)	23 (95.8)	4.2 (1)	19 (27.5)	100.0 (19)	0 (0)	0.389	1.000
Xerostomia	19 (27.1)	100.0 (19)	0 (0)	15 (21.7)	100.0 (15)	0 (0)	0.459	NA
Vomit	12 (17.1)	10 (83.3)	2 (16.7)	16 (23.2)	100.0 (16)	0 (0)	0.374	0.175
Xerophtalmia	11 (15.7)	100.0 (11)	0 (0)	7 (10.1)	100.0 (7)	0 (0)	0.328	NA
Anorexia	14 (20.0)	100.0 (14)	0 (0)	12 (17.4)	100.0 (12)	0 (0)	0.693	NA
Constipation	8 (11.4)	100.0 (8)	0 (0)	9 (13.0)	100.0 (9)	0 (0)	0.771	NA
Neuropathy	7 (10.0)	100.0 (7)	0 (0)	9 (13.0)	100.0 (9)	0 (0)	0.574	NA

eTable 5. Details of metformin treatment

Details of metformin treatment	n=69
	n (%)
Metformin dose reduction	24(34.8)
Definitive metformin discontinuation	16(23.2)
Continue with metformin after progression	33(47.8)

eTable 6. Further lines of treatment

Treatment	TKI % (n) (n=70)	TKI + M % (n) n=69	p-Value
Second line			
Absent	55.7 (39)	56.5 (39)	
Present	44.3 (31)	43.5 (30)	0.924
Second line regiment			
Carboplatin + Pemetrexed	80.6 (25)	60.0 (18)	
Carboplatin + Paclitaxel	19.4 (6)	40.0 (12)	0.077
Progression to 2nd line			
No	25.8 (8)	33.3 (10)	
Yes	74.2 (23)	66.7 (20)	0.653
Third line			
Absent	85.7 (60)	89.9 (62)	
Present	14.3 (10)	10.1 (7)	0.309
Third line regimen			
Treatment (continued)	**TKI % (n) (n=70)**	**TKI + M % (n) n=69**	**p-Value**
Docetaxel	50.0 (5)	28.6 (2)	
Docetaxel + Pembrolizumab	30.0 (3)	14.3 (1)	
Pemetrexed	10.0 (1)	28.6 (2)	
Nivolumab	10.0 (1)	14.3 (1)	
Gemcitabine	0.0 (0)	14.3 (1)	0.527
Progression to 3rd line			
No	0.0 (0)	28.6 (2)	
Yes	100.0 (10)	71.4 (5)	0.086

eTable 7. Overall survival among patients who did not receive a second-line of therapy after intervention

Variable	Comparison	Crude		Adjusted	
		HR (95% CI)	p-Value	HR (95% CI)	p-Value
Sex	M vs. F	0.79 (0.37 - 1.68)	0.547		
Age	For each year	1.00 (0.97 - 1.03)	0.640		
Smoke	Ever vs. Never	0.61 (0.23 - 1.57)	0.303		
WSE	Present vs. Absent	1.13 (0.55 - 2.27)	0.739		
Adenocarcinoma subtype	Poor vs. Well/Moderate	1.36 (0.65 - 2.82)	0.405		
Bone metastases	Present vs. Absent	1.07 (0.52 - 2.21)	0.837		
Pleural metastases	Present vs. Absent	0.73 (0.35 - 1.55)	0.424		
Contralateral	Present vs. Absent	0.51 (0.23 - 1.13)	0.097		
Adrenal	Present vs. Absent	1.34 (0.32 - 5.64)	0.694		
Brain	Present vs. Absent	1.42 (0.70 - 2.87)	0.332		
Liver	Present vs. Absent	2.53 (0.74 - 8.75)	0.140		
EGFR mutation status	E18(G719X)	NA*	…		
	E 21 (L858R) vs. E 19 (Del)	0.79 (0.38 - 1.62)	0.522		
EGFR TKI	Gefitinib	1.00 (Reference)	…		
	Afatinib	0.72 (0.33 - 1.59)	0.425		
	Erlotinib	0.62 (0.25 - 1.55)	0.313		

Variable (continued)	Comparison	Crude		Adjusted	
		HR (95% CI)	p-Value	HR (95% CI)	p-Value
DCR	Uncontrolled vs. Controlled diseases	21.4 (3.85 - 118.47)	**<0.001**	26.13 (4.47 - 152.58)	**<0.001**
Intervention	M+TKI vs. TKI alone	0.33 (0.15 - 0.73)	**0.006**	0.32 (0.14 - 0.70)	**0.005**
LKB1	Positive vs. Negative	0.33 (0.03 - 3.20)	0.340		
* NA: Not available; there were any event (death) among this group					

eTable 8. Overall survival among patients who received a second-line of therapy after intervention.

Variable	Comparison	Crude		Adjusted	
		HR (95% CI)	p-Value	HR (95% CI)	p-Value
Sex	M vs. F	0.63 (0.22 - 1.79)	0.379		
Age	For each year	0.99 (0.95 - 1.03)	0.754		
Smoke	Ever vs. Never	0.82 (0.31 - 2.28)	0.737		
WSE	Present vs. Absent	0.92 (0.34 - 2.45)	0.868		
Adenocarcinoma subtype	Poor vs. Well/Moderate	1.32 (0.52 - 3.39)	0.561		
Bone metastases	Present vs. Absent	0.63 (0.24 - 1.69)	0.360		
Pleural metastases	Present vs. Absent	1.39 (0.52 - 3.71)	0.501		
Contralateral	Present vs. Absent	1.99 (0.76 - 5.21)	0.160		
Adrenal	Present vs. Absent	1.42 (0.18 - 11.23)	0.738		
Brain	Present vs. Absent	1.23 (0.46 - 3.30)	0.675		
Liver	Present vs. Absent	1.12 (0.25 - 5.00)	0.883		
EGFR mutation status	E18(G719X)	NA			
	E 21 (L858R) vs. E 19 (Del)	0.91 (0.32 - 2.57)	0.863		
EGFR TKI	Gefitinib	1.00 (Reference)			
	Afatinib	0.71 (0.25 - 2.01)	0.525		
	Erlotinib	0.39 (0.09 - 1.54)	0.180		
ORR	Not responders vs. Responders	3.86 (1.41 - 10.50)	**0.008**	3.25 (0.78 - 13.57)	**0.104**

Variable (continued)	Comparison	Crude		Adjusted	
		HR (95% CI)	p-Value	HR (95% CI)	p-Value
DCR	Uncontrolled vs. Controlled diseases	2.79 (0.76 - 10.05)	0.116		
Intervention	M+TKI vs. TKI alone	1.02 (0.39 - 2.61)	0.967	1.31 (0.46 - 3.75)	0.605
LKB1	Positive vs. Negative	0.58 (0.05 - 5.80)	0.647		
* NA: Not available; there were any event (death) among this group					

eTable 9. Univariate and LKB1-stratified analysis of the clinic-pathological factors associated with progression-free survival

Variable	LKB1 Negative			LKB1 Positive		
	Number events	Median months (95% CI)	p-Value	Number events	Median months (95% CI)	p-Value
Gender						
Female	4 (4)	8.2 (0 - 18.8)	0.410	11 (8)	11.8 (9.3 - 14.3)	0.260
Male	4 (4)	10.3 (3.9 - 16.7)		5 (2)	27.9 (NR)	
Age						
<60	6 (6)	10.3 (6.4 - 14.2)	0.515	7 (3)	27.9 (8.9 - 47.0) 13.1 (11.4 - 14.7)	0. 520
≥60	2(2)	4.5 (NR)		9 (7)		
Tobacco exposure						
Absent	4 (4)	5.0 (1.3 - 8.7)	0. 085	12 (8)	12.5 (8.9 - 16.1)	0.702
Present	4 (4)	11.5 (6.7 -16.3)		4 (2)	13.1 (11.1 - 14.3)	
Absent	5 (5)	14.3 (5.7 - 22.9)	0.073	6 (3)	27.9 (NR)	0.402
Present	3 (3)	5.0 (4.1 - 5.9)		10 (7)	13.1 (10.2 - 15.9)	
Predominant histological pattern						
Well/Moderately differentiated	4 (4)	10.3 (3.4 - 17.2)	0. 346	7 (5)	13.1 (11.9 - 14.3)	0.431
Poorly/Non differentiated	4 (4)	8.2 (0.0 - 18.2)		9 (5)	11.8 (0.0 - 28.5)	
Metastases						
Bone						
Absent	4 (4)	10.3 (0.7 - 19.9)	0.595	11 (5)	19.1 (11.2 - 26.9)	0.153
Present	4 (4)	8.2 (1.9 - 14.6)		5 (5)	10.9 (8.9 - 12.9)	
Pleura						
Absent	5 (5)	14.3 (0.0 - 34.3)	0.331	11 (6)	19.1 (9.6 - 28.6)	0.403
Present	3(3)	10.3 (7.0 - 13.6)		5 (4)	13.1 (8.4 - 17.7)	
Contralateral lung						
Absent	5 (5)	11.5 (0.0 - 25.4)	0.554	9 (5)	19.1 (7.4 - 30.8)	0.469
Present	3 (3)	10.3 (7.0 - 13.6)		7 (5)	11.8 (9.9 - 13.8)	
Adrenal glands						
Absent	8 (8)	10.3 (5.0 -14.3)	N.E.	15 (10)	13.1 (10.9 - 27.9)	N.E.
Present	0 (0)	N.E.		1 (0)	N.E.	
Central Nervous System						
Absent	6 (6)	10.3 (6.4 - 14.2)	N.R.	8 (2)	NR (NR)	0.068
Present	2 (2)	4.5 (N.R.)		8 (8)	10.9 (6.6 - 15.2)	

Variable (continued)	LKB1 Negative			LKB1 Positive		
	Number events	Median months (95% CI)	*p*-Value	Number events	Median months (95% CI)	*p*-Value
Liver						
Absent	8 (8)	10.3 (5.8 - 14.3)	N.E.	16 (10)	13.1 (11.9 - 14.3)	N.E.
Present	0 (0)	N.E.		0 (0)	N.E.	
EGFR mutational profile						
Exon 18 (G719X)	0 (0)	NE	0.945	2 (1)	9.9 (NR)	
Exon 19 (Deletion)	4 (4)	11.5 (2.4 - 20.6)		8 (5)	19.1 (9.9 - 28.2)	0.989
Exon 21 (L858R)	4 (4)	8.2 (2.5 - 13.9)		6 (4)	13.1 (10.4 - 15.7)	
EGFR-TKIs treatment characteristics						
Gefitinib	1 (1)	8.2 (NR)	0.528	5 (3)	13.2 (0.0 - 27.8)	
Afatinib	5 (5)	11.5 (8.9 - 14.0)		5 (2)	10.9 (1.5 - 20.3)	0.369
Erlotinib	2 (2)	4.5 (NR)		6 (5)	11.8 (8.7 - 14.9)	
Disease control rate						
Present	8 (8)	10.3 (5.8 - 14.3)	N.E.	16 (10)	13.1 (11.9 - 14.3)	N.E.
Absent	0 (0)	N.E.		0 (0)	N.E.	
Treatment arm						
EGFR-TKIs	3 (3)	11.5 (1.1 - 21.8)	0.500	6 (4)	12.5 (4.5 - 20.5)	0.319
EGFR-TKIs + metformin	5 (5)	10.3 (5.8 - 14.7)		10 (6)	13.1 (0.0 - 28.4)	

eTable 10. Univariate and LKB1-stratified analysis of the clinic-pathological factors associated with overall survival

Variable	LKB1 Negative			LKB1 Positive		
	Number of events	Median months (95% CI)	*p*-Value	Number of events	Median months (95% CI)	*p*-Value
Gender						
Female	4 (2)	20.6 (4.6 - 36.5)	0.661	11 (5)	20.4 (17.1 - 23.7)	0.988
Male	4 (3)	25.6 (4.7 - 46.5)		5 (2)	29.1 (NR)	
Age						
<60	6 (3)	25.6 (0.0 - 57.7)	0.761	7 (3)	NR (NR)	0. 591
≥60	2 (2)	20.6 (NR)		9 (4)	20.5 (NR)	
Arm treatment						
EGFR-TKIs	3 (1)	NR (NR)	0.124	6 (5)	6.7 (0.0 - 17.7)	**0.002**
EGFR-TKIs + metformin	5 (4)	20.6 (4.5 - 36.6)		10 (2)	NR (NR)	