

Radiomic Biomarkers on Baseline CT Scans for Predicting Response to Teliso-V in NSCLC: A Machine Learning Approach

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OBJECTIVE

Exploratory radiomic analysis of baseline CT scans to identify biomarkers associated with overall survival (OS) in patients with non-small cell lung cancer (NSCLC) treated with telisotuzumab vedotin (Teliso-V).

CONCLUSIONS

Machine learning-derived RRS was found to be associated with treatment efficacy in Teliso-V-treated advanced NSQ *EGFR* WT NSCLC patients with c-Met OE.

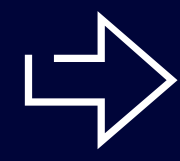
Within the c-Met OE population, ORR was higher in the low RRS group than in the high RRS group, indicating a more favorable treatment response to Teliso-V among patients with a lower radiomic risk profile.

Low RRS was also associated with longer OS and more favorable PFS among patients with c-Met OE, suggesting that RRS may further stratify survival outcomes within this biomarker-selected population.

Preliminary findings suggest radiomic features on baseline CT scans hold promise as potential non-invasive prognostic and/or predictive biomarkers to inform outcomes in patients with c-Met OE treated with Teliso-V.

These findings will be validated in an ongoing Phase 3 study (NCT04928846).

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AbbVie funded this study and participated in the study design, research, analysis, data collection, interpretation of data as well as review and approval of the abstract. All authors had access to relevant data and participated in the drafting, review, and approval of this abstract. No honoraria or payments were made for authorship. We thank Shilpi Patel and Abhishek Pandey for their contributions on collection and assembly of data, and interpretation. Financial arrangements of the authors with companies whose products may be related to the present report are listed as declared by the authors.

Disclosures and COI:

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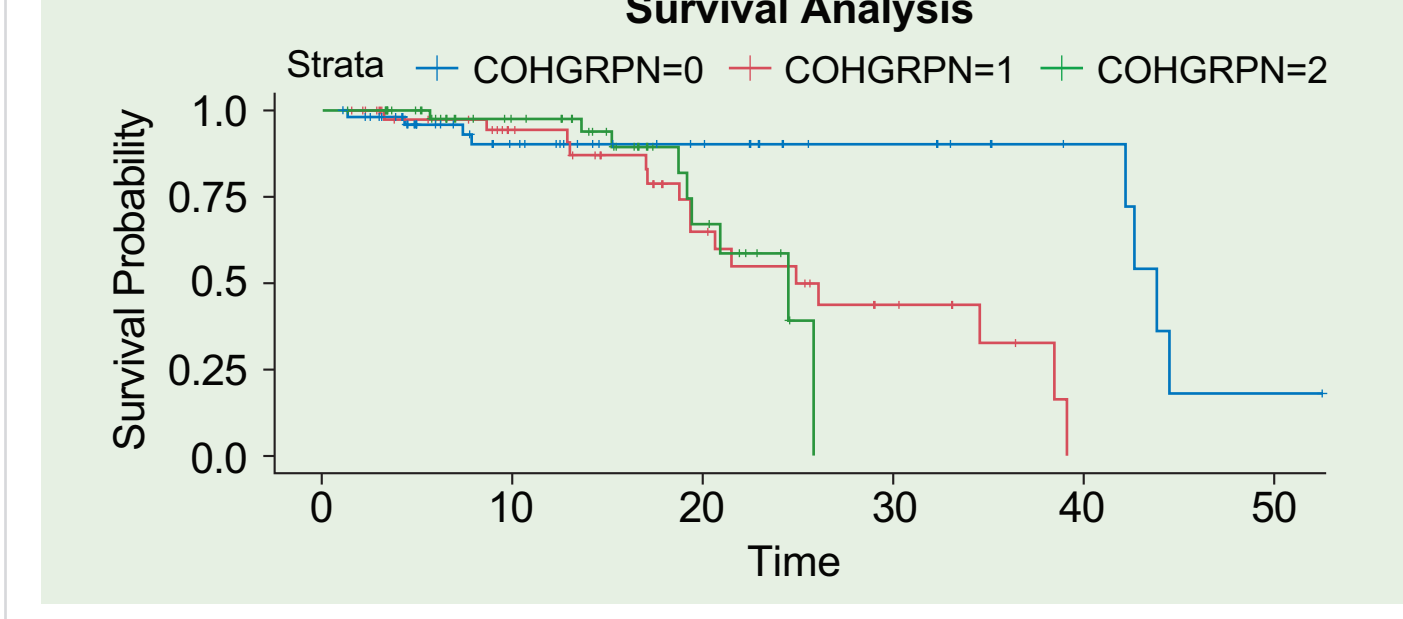
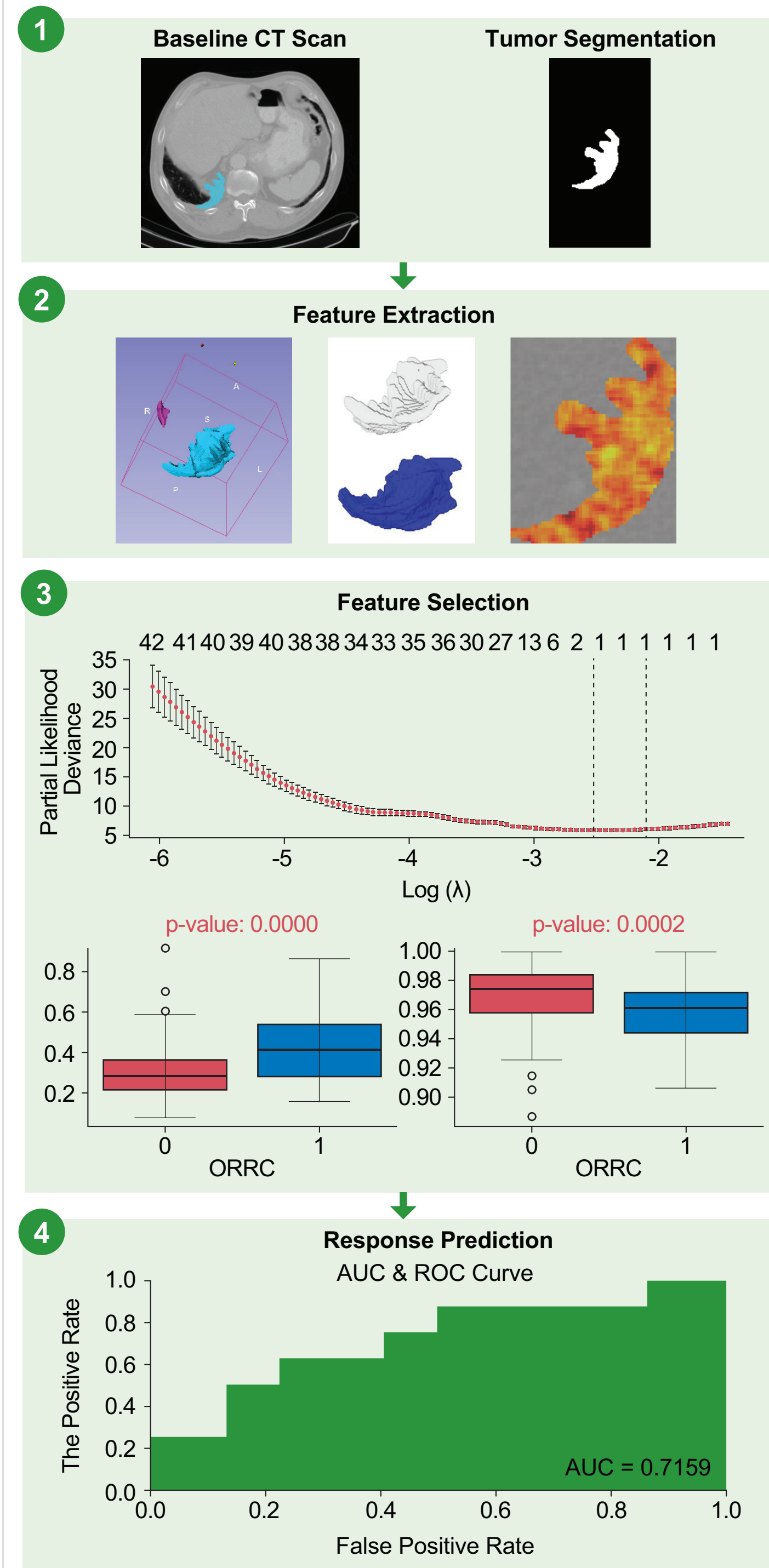
INTRODUCTION

- Teliso-V is a c-Met protein–targeted antibody drug conjugate (ADC) comprising the monoclonal antibody telisotuzumab linked to the microtubule polymerization inhibitor monomethyl auristatin E (MMAE) with a cleavable linker¹.
- In phase 2 LUMINOSITY study (NCT03539536), Teliso-V showed durable responses and manageable safety,² resulting in its accelerated approval by the US Food and Drug Administration (FDA) in adult patients with locally advanced/metastatic non-squamous (NSQ) NSCLC with high c-Met protein overexpression (OE) (3+, ≥50%), as determined by an FDA-approved test, who received a prior systemic therapy.

METHODS

- In the LUMINOSITY study, there were 168 efficacy-evaluable patients⁴ with NSQ epidermal growth factor receptor (*EGFR*) wildtype (WT) NSCLC and c-Met protein OE who received Teliso-V at 1.9 mg/kg Q2W.
- c-Met protein OE was assessed using an immunohistochemistry assay for MET (SP44; Roche Diagnostics). Total c-Met OE was defined as ≥25% of tumor cells showing 3+ staining intensity.
 - Intermediate c-Met protein OE: 25% to 49% of tumor cells with 3+ staining intensity
 - High c-Met protein OE: ≥50% of tumor cells with 3+ staining intensity
- The analysis included baseline scans from 92 efficacy-evaluable 2L+ NSQ WT NSCLC patients with c-Met OE treated with Teliso-V from LUMINOSITY with adequate imaging for the analysis.

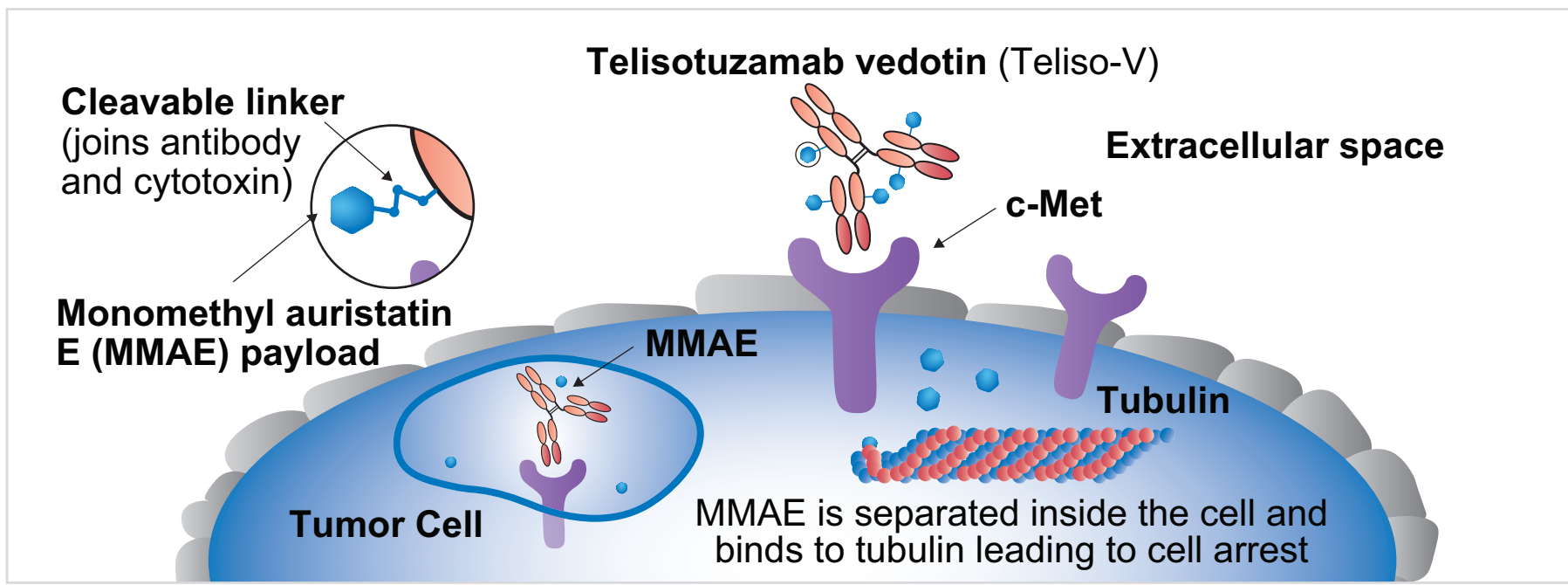
Figure 2. Schematic of the Analytical Approach.



Disclaimer: Figure 2 is for illustrative purposes only and does not represent actual results or patient data.

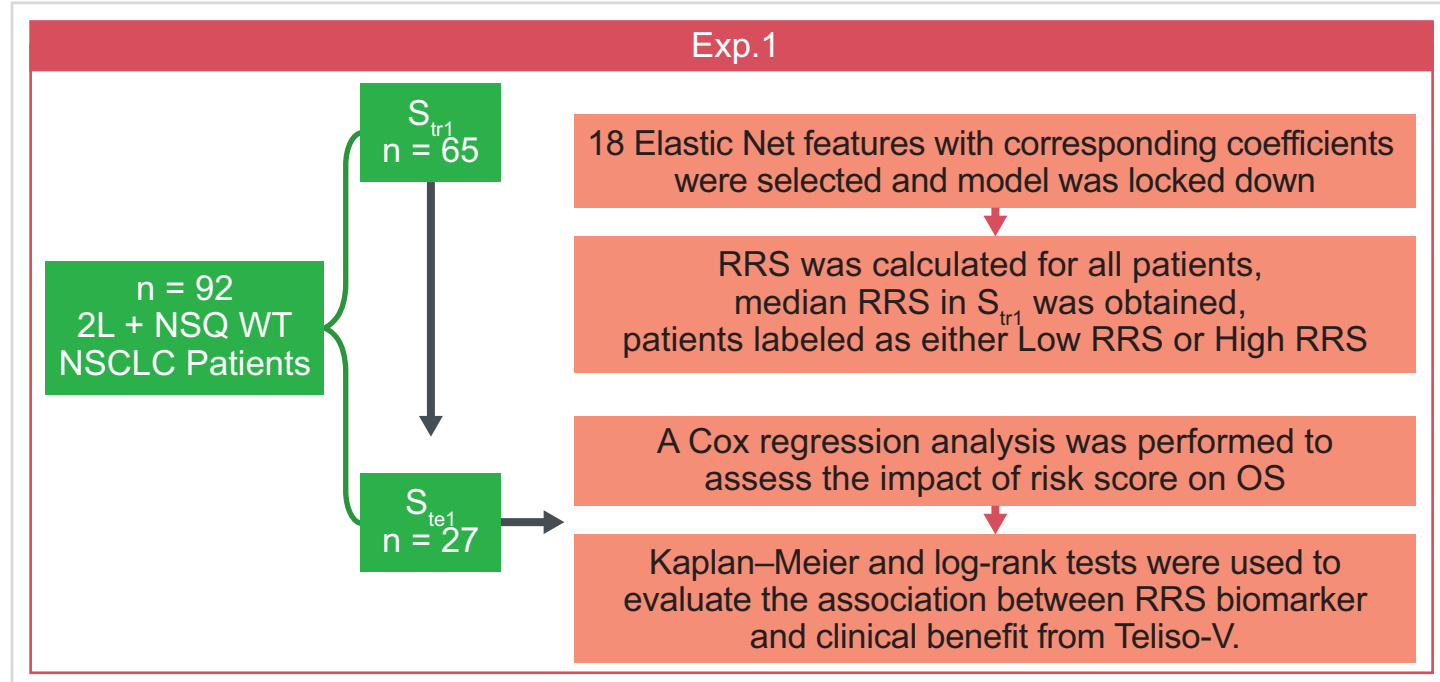
- Baseline contrast-enhanced CT images (slice thickness 3 mm) were processed using a nnUnet-based 3D model for NSCLC lesion detection, capturing all detectable lesions per patient; Baseline contrast-enhanced CT images (slice thickness 3 mm) were processed using a nnUnet-based 3D model for NSCLC lesion detection, capturing all detectable lesions per patient. All segmentations were reviewed and approved by a radiologist.
- Radiomic features were extracted from all CT-identified lesions to characterize tumor heterogeneity. These features included intensity, shape, texture complexity, gray-level distribution, and entropy-based metrics⁵, each capturing different aspects of lesion morphology and intratumoral organization.

Figure 1. Teliso-V Mechanism of Action.



MMAE, monomethyl auristatin E.

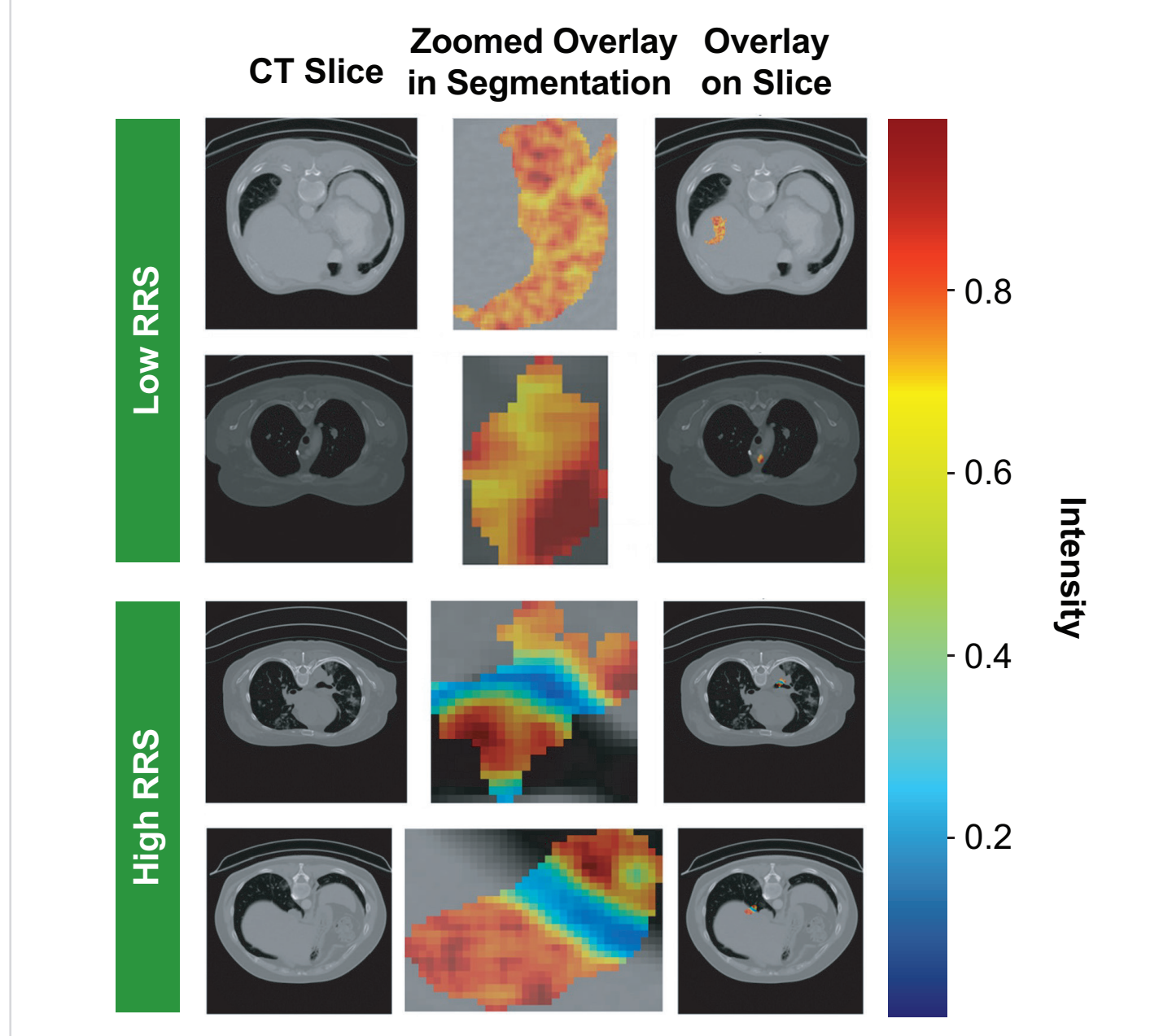
Figure 3. Schematic overview of Experiment 1, study design and analytical workflow.



Goal: finding the radiomic biomarker to predict outcome. Patients were randomly divided into a training set (S_{tr} , n=65) and a testing set (S_{te} , n=27). Feature selection was performed using an Elastic Net, which identified 18 potential prognostic features for overall survival in S_{tr} . A radiomic risk score (RRS) was computed as a linear combination of the selected features and their corresponding coefficients. High and low RRS groups were determined based on the median RRS in S_{tr} . High RRS is defined as above median whereas low RRS to be below median. Exp. experiment, NSQ, non-squamous; WT, wildtype; NSCLC, non-small cell lung cancer; S_{tr} , training set; S_{te} , testing set.

- In this framework, the radiomic risk score (RRS) reflects the overall imaging phenotype of each patient rather than any single radiomic descriptor.

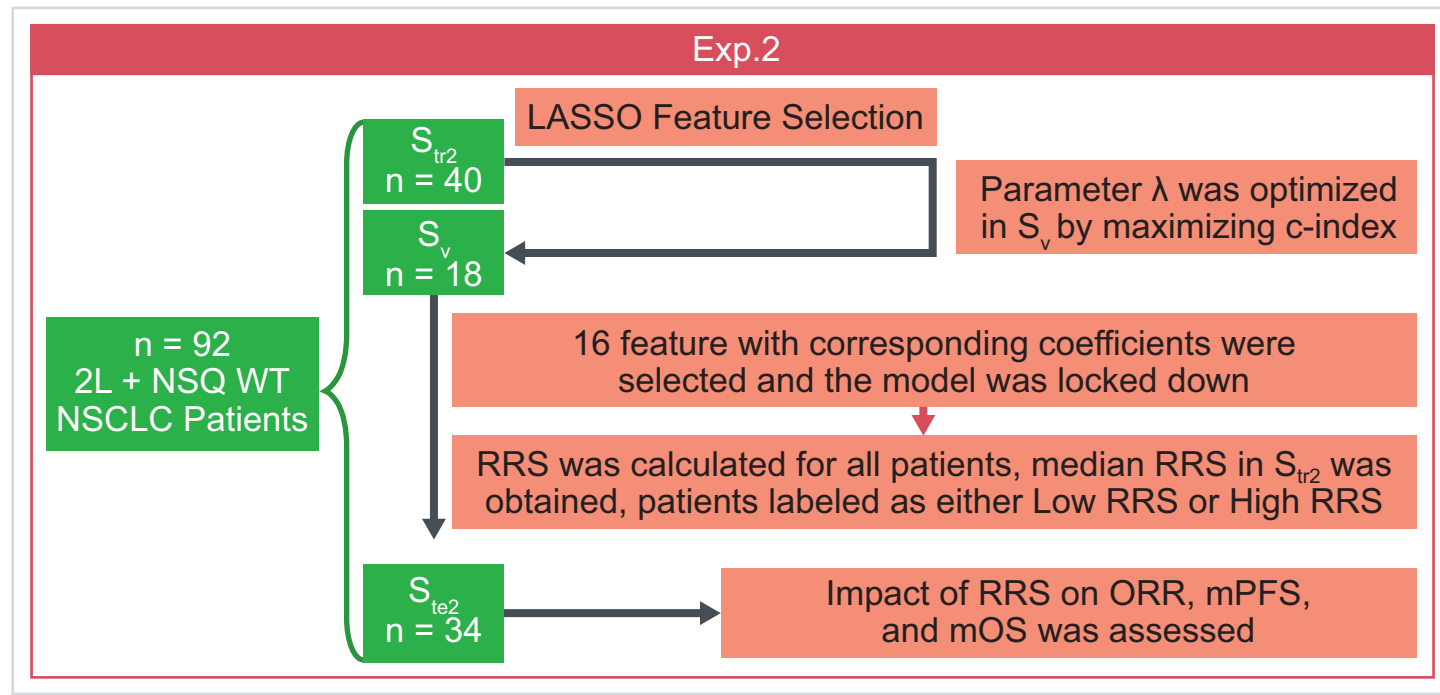
Figure 4. Representative CT slices and corresponding radiomic intensity overlays for patients in the low RRS and high RRS groups.



RRS, radiomic risk score; IDM, Inverse Difference Moment.

- On average, low RRS tumors showed predominantly warm, uniform intensity patterns and were generally flatter, more homogeneous, and more geometrically consistent, whereas high RRS tumors exhibited a broader and more variable intensity range with greater intratumoral heterogeneity and morphological irregularity across shape and intensity distribution features.
- In experiment 1 (Exp. 1), a Cox regression analysis was performed to assess the impact of RRS on OS. Kaplan-Meier and log-rank tests were used to assess the predictive value of the RRS biomarker to Teliso-V.

Figure 5. Schematic overview of Experiment 2, study design and analytical workflow.



Goal: hyperparameter tuning to strengthen model robustness. The cohort of 92 patients was randomly partitioned into three non-overlapping sets: a training set (S_{tr} , n=40), a validation set (S_{v} , n=18), and an independent test set (S_{te} , n=34). The S_{tr} and S_{v} sets were balanced for c-Met expression levels. Feature selection was performed in S_{tr} using LASSO. The regularization parameter (λ) was optimized in S_{v} by maximizing the concordance index (c-index), yielding a final model comprising 16 selected features. Following model lock-down, RRS was computed for each patient in S_{te} . The median RRS derived from S_{tr} served as the threshold to stratify patients into low RRS and high RRS groups. Exp. experiment, NSQ, non-squamous; WT, wildtype; NSCLC, non-small cell lung cancer; S_{tr} , training set; S_{v} , validation set; LASSO, least Absolute shrinkage and selection operator; RRS, radiomic risk score.

- In experiment 2 (Exp.2), the impact of RRS grouping was evaluated within the independent test set (S_{te}), across three clinical endpoints: Objective Response Rate (ORR), median progression-free survival (mPFS), and median OS (mOS).

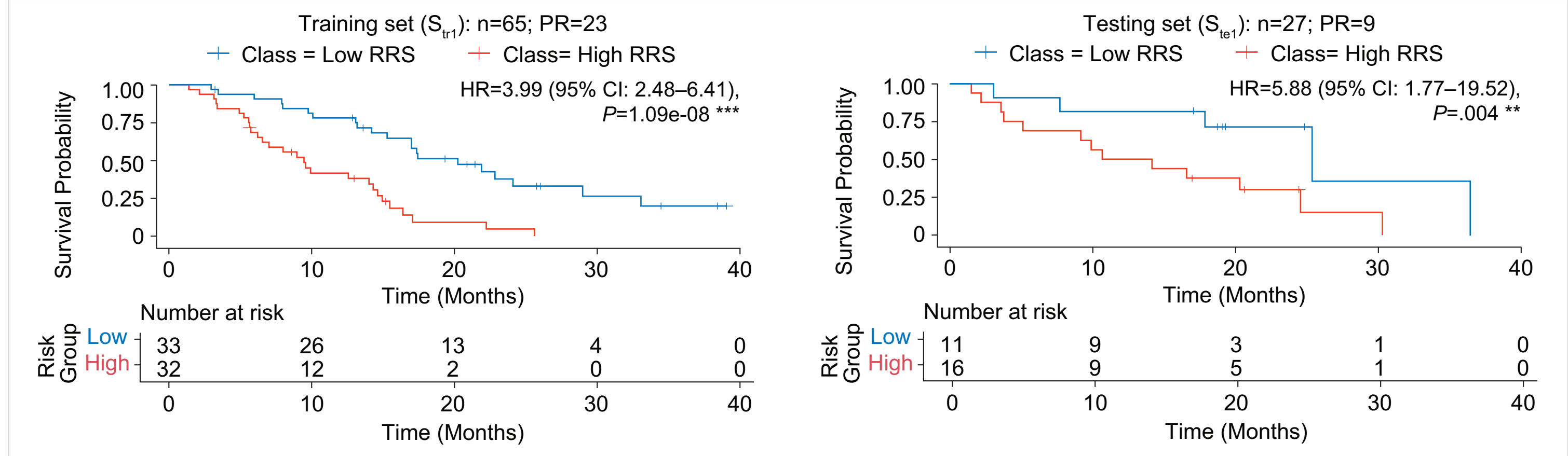
RESULTS

Table 1. Baseline demographics and disease characteristics of 2L+ NSQ *EGFR* WT NSCLC patients included in the radiomics biomarker subgroup analysis.

Characteristic	S_{tr} (n=65)	S_{te1} (n=27)	S_{te2} (n=40)	S_{te3} (n=34)	S_v (n=18)
Median age, years (range)	65 (33–83)	64 (45–78)	64 (33–83)	67 (45–79)	62 (38–75)
Sex, n (%)					
Male	44 (68)	22 (81)	34 (85)	23 (68)	9 (50)
Female	21 (32)	5 (19)	6 (15)	11 (32)	9 (50)
Race, n (%)					
White	41 (63)	18 (67)	23 (58)	26 (76)	10 (56)
Asian	23 (35)	8 (30)	16 (40)	8 (24)	7 (39)
Black or African American	1 (2)	1 (4)	1 (2)	0 (0)	1 (6)
Ethnicity, n (%)					
Hispanic or Latino	1 (1)	0 (0)	1 (2)	0 (0)	0 (0)
Not Hispanic or Latino	64 (98)	27 (100)	39 (98)	34 (100)	18 (100)
Geographic region, n (%)					
US/Canada	19 (29)	2 (7)	8 (20)	7 (21)	6 (33)
Europe	15 (23)	8 (30)	8 (20)	10 (29)	5 (28)
Pan-Asia	19 (29)	8 (30)	15 (38)	7 (21)	5 (28)
Rest of the World	12 (18)	9 (33)	9 (22)	10 (29)	2 (11)
Tobacco use, n (%)					
Current	5 (8)	3 (11)	4 (10)	2 (6)	2 (11)
Former	42 (65)	21 (78)	26 (65)	25 (74)	12 (67)
Never	18 (28)	3 (11)	10 (25)	7 (21)	4 (22)
c-Met OE status, n (%)					
High (3+, ≥50%)	27 (42)	16 (59)	19 (48)	16 (47)	8 (44)
Intermediate (3+, 25% to 49%)	38 (58)	11 (41)	21 (52)	18 (53)	10 (56)
Risk Group, n (%)					
High RRS	32 (49)	16 (59)	20 (50)	9 (26)	6 (33)
Low RRS	33 (51)	11 (41)	20 (50)	25 (74)	12 (67)

OE, Overexpression; Str1, training set in Exp.1; S_{tr1} , testing set in Exp.1; S_{te1} , training set in Exp.2; S_{te2} , testing set in Exp.2; S_v , validation set in Exp.2; Exp, experiment.

Figure 6. Results from Exp.1: Kaplan-Meier curves of the high RRS (red) and low RRS groups (blue) show that radiomic features capturing texture and shape differences in NSCLC lesions were nominally associated with OS in S_{tr1} and S_{te1} .



NSCLC, non-small cell lung cancer; OS, overall survival; S_{tr1} , training set in Exp.1; S_{te1} , testing set in Exp.1; PR, partial responders; RRS, radiomic risk score; HR, hazard ratio; CI, confidence interval; Exp.1, experiment 1.

- The RRS showed a potential relationship with OS in both S_{tr1} : HR 3.99 (95% CI, 2.48 – 6.41; $P=1.09\text{e-}8$); S_{te1} : HR 5.88 (1.77–19.52; $P=.004$). Kaplan-Meier analyses revealed shorter survival in the high RRS group compared to the low RRS group in both S_{tr1} ($P=1.09\text{e-}8$) and S_{te1} ($P=.004$). This result is exploratory and requires confirmation in larger cohorts.

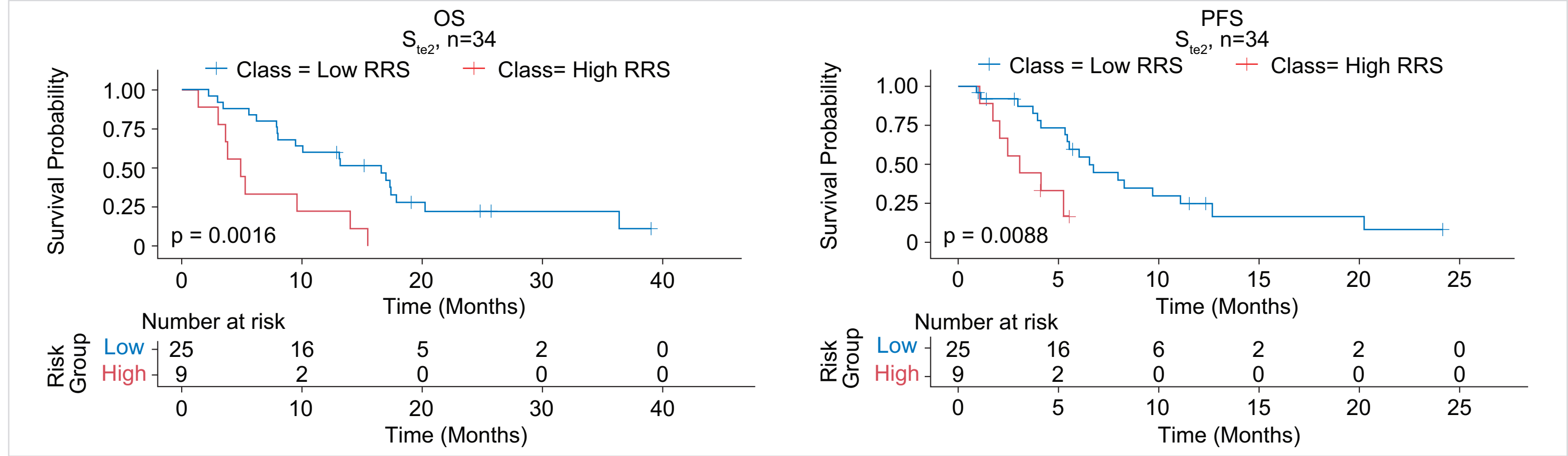
Table 2. Results from Exp. 2: Assessment of treatment efficacy in 2L+ NSQ *EGFR* WT NSCLC with c-Met OE defined by radiomic risk scores, in S_{te2} .

c-Met OE	Total c-Met OE (3+, ≥25%) (N=92)		
Tumor Response	Luminosity ^{2,4} (n=168)	Low RRS (n=25)	High RRS (n=9)
ORR, % (95% CI)	29.2 (22.4–36.7) ⁴	36.0 (18.0–57.5)	11.1 (0.3–48.2)
mPFS, mo (95% CI)	5.7 (4.6–6.9) ²	6.54 (5.32–9.69)	3.06 (1.05–5.26)
mOS, mo (95% CI)	14.5 (9.9–16.6) ²	16.59 (7.98–17.87)	4.93 (1.38–14.03)

ORR, objective response rate; mOS, median overall survival; mPFS, median progression-free survival; RRS, radiomic risk score; CI, confidence interval; Exp.2, experiment 2.

- Low RRS identified patients with better clinical outcome to Teliso-V compared to high RRS. Patients with low RRS had higher ORR (36%) longer mOS (16.59 mo) and mPFS (6.54 mo) compared to those with high RRS (11.1% ORR, 4.93 mo mOS and 3.06 mo mPFS, respectively).

Figure 7. Results from Exp. 2: Median OS and PFS were longer in the low RRS group of 2L *EGFR* WT NSCLC patients with c-Met OE (3+, ≥25%) treated with Teliso-V in S_{te2} .



PFS, progression-free survival; OS, overall survival; OE, overexpression; RRS, radiomic risk score, S_{te2} , testing set in Exp.2; Exp.2, experiment 2.

- Kaplan-Meier curves showed separation between the two risk groups of patients with c-Met OE (3+, ≥25%) for both OS and PFS. In both analyses, the low RRS group had a consistently higher survival probability over time, whereas the high RRS group experienced earlier and steeper declines in survival. This pattern suggests that the low RRS profile is associated with more favorable clinical outcomes, while the high RRS profile is associated with shorter OS and PFS.

Limitation:

- The limitation of this study includes the absence of a control arm, which limits assessment of whether the association between RRS and OS is specific to Teliso-V or in generalizable across other treatments, as well as the relatively small sample size, particularly the testing cohorts in both experiments, which may limit the statistical power and generalizability of the radiomic model.