

Gut Microbial Signatures Linked to Radio-Immunotherapy Response Reveal Opposite Alistipes–Host Crosstalk in Oligometastatic NSCLC

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Track: Oligometastatic disease management

No industry funding • Not a clinical trial • No medical writers

1 BACKGROUND

- Oligometastatic NSCLC: combining definitive radiotherapy with systemic immunotherapy can achieve durable control, yet resistance remains common and predictive biomarkers are lacking.
- The gut microbiome modulates systemic immunity and influences responses to both radiotherapy and ICIs.
- The genus *Alistipes* has context-dependent effects; TGF- β /SMAD3 signaling regulates radiosensitivity, EMT, and the immune microenvironment.
- Knowledge gap: no study has investigated whether and how the gut microbiome influences combined radio-immunotherapy outcomes in oligometastatic NSCLC.
- Hypothesis: pre-treatment gut microbial signatures, particularly *Alistipes* abundance, predict radio-immunotherapy resistance through microbiome-host crosstalk.

2 METHODS

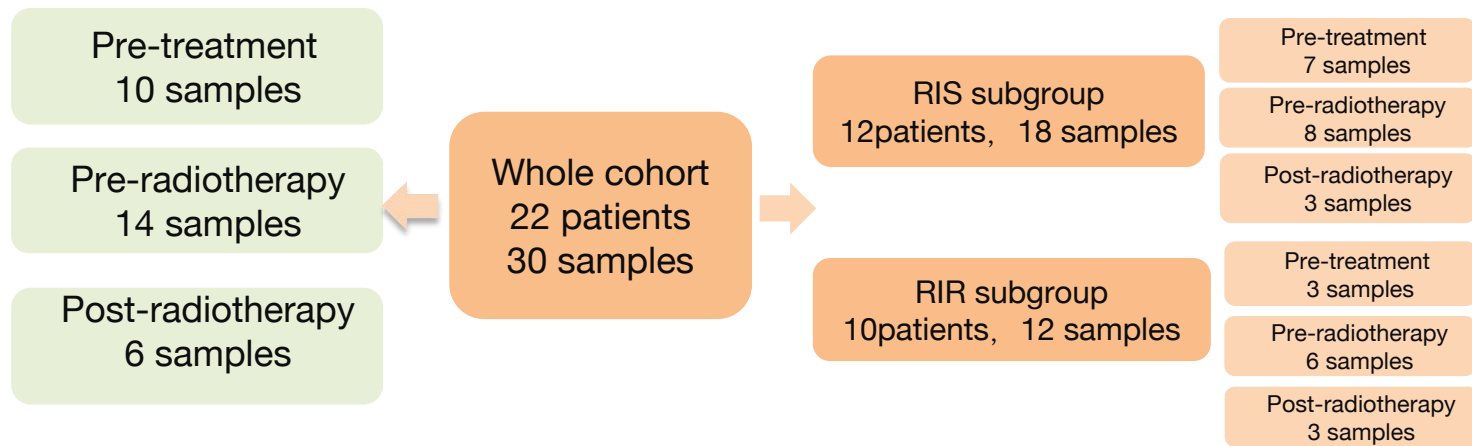
- Prospective cohort of 22 oligometastatic NSCLC patients.
- Treatment: induction chemo-immunotherapy $\rightarrow$ definitive radiotherapy.
- Serial fecal and blood samples at 3 timepoints: pre-treatment, pre-radiotherapy, post-radiotherapy.
- 16S rRNA sequencing + shotgun metagenomics (fecal); RNA-seq of PBMCs (host).
- Bioinformatics: Wilcoxon/Kruskal-Wallis, Cox regression, Spearman correlation, GO/KEGG, GSEA, VIPER, STRING.
- External validation: anti-PD-1 cohort (Routy et al., PRJEB22863) and TCGA-LUAD.

3 STUDY DESIGN

Patients stratified by 12-month PFS threshold:

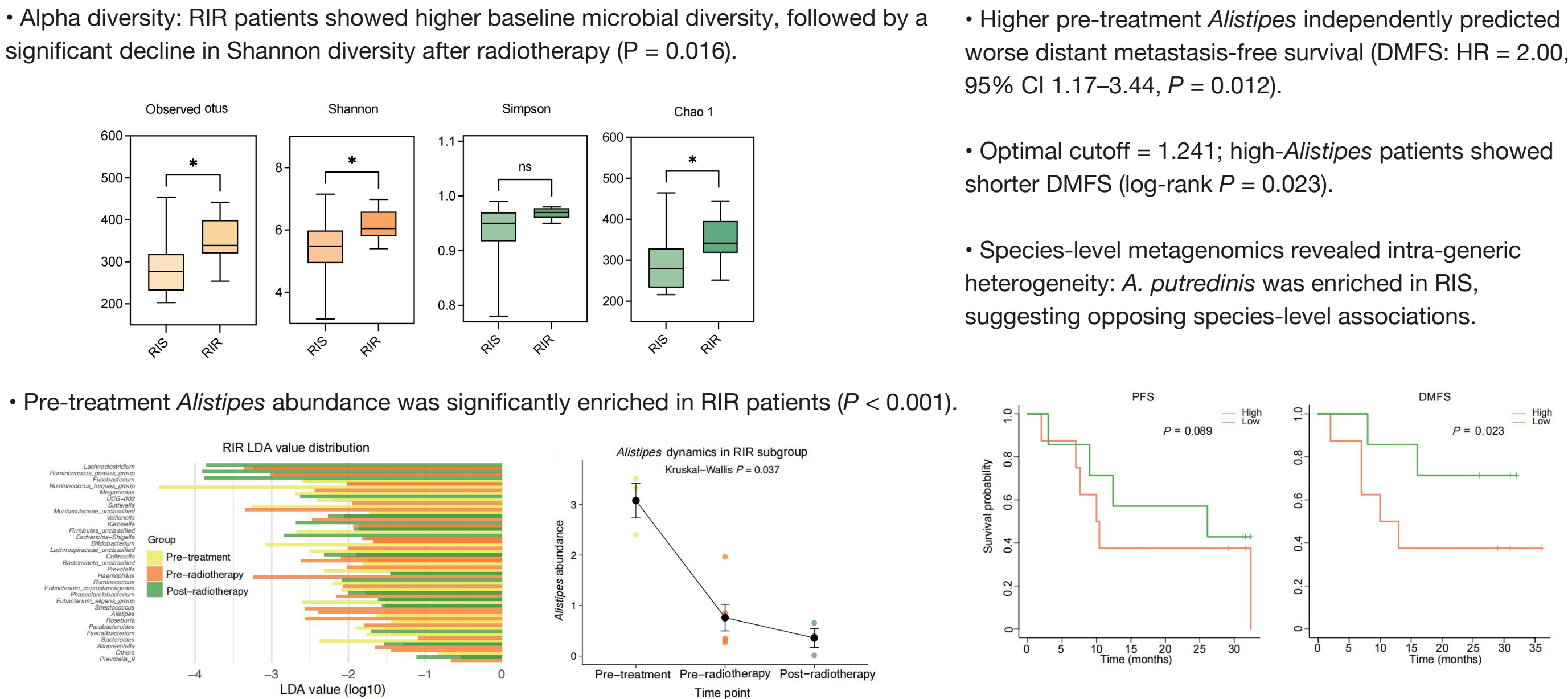
• Radio-Immunotherapy Sensitive (RIS):
n = 12 PFS $\geq$ 12 months

• Radio-Immunotherapy Resistant (RIR):
n = 10 PFS < 12 months

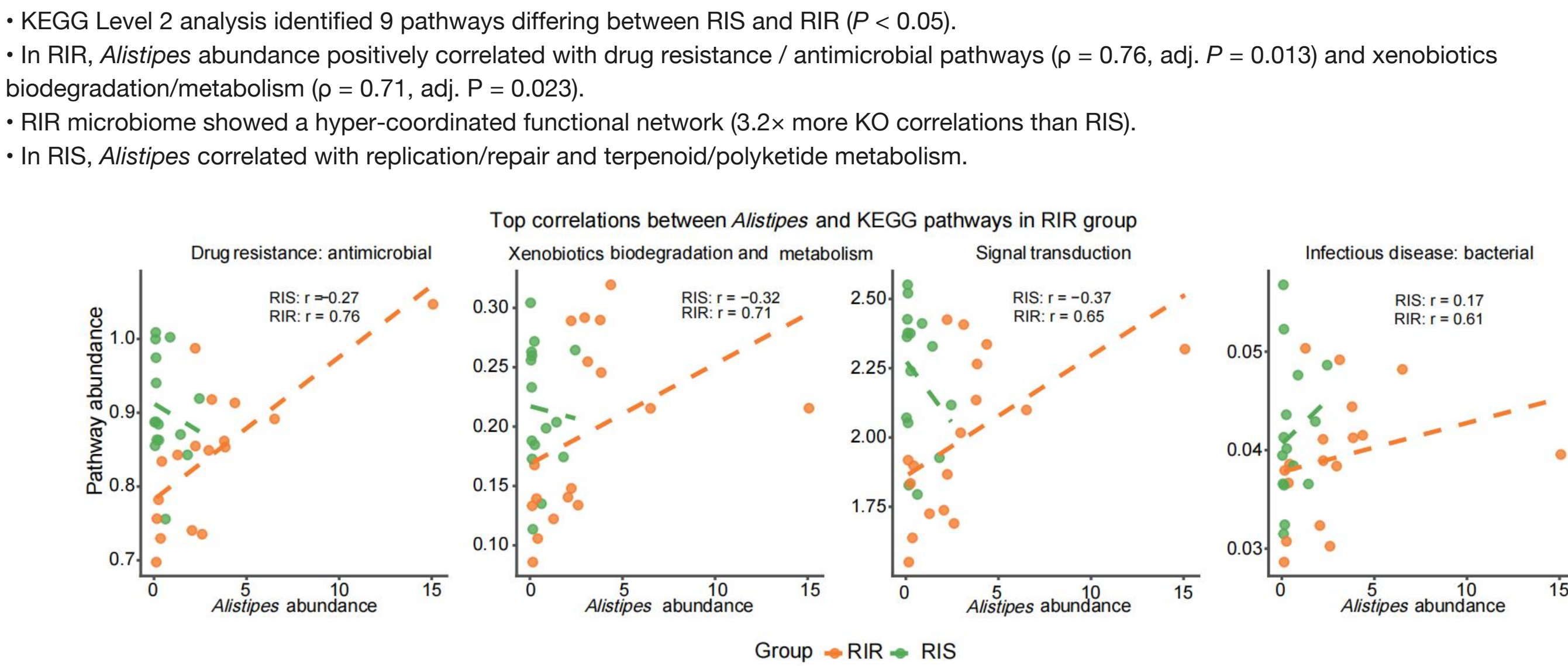


- Groups were balanced for age, sex, BMI, stage, and histology (all $P > 0.05$).
- Prospective longitudinal cohort at SYSUCC (2022–2024).
- Patients with oligometastatic NSCLC received induction systemic therapy followed by radiotherapy.
- Serial matched samples enabled longitudinal and between-group comparisons.
- Molecular changes were correlated with PFS, DMFS, LRFS, and OS.

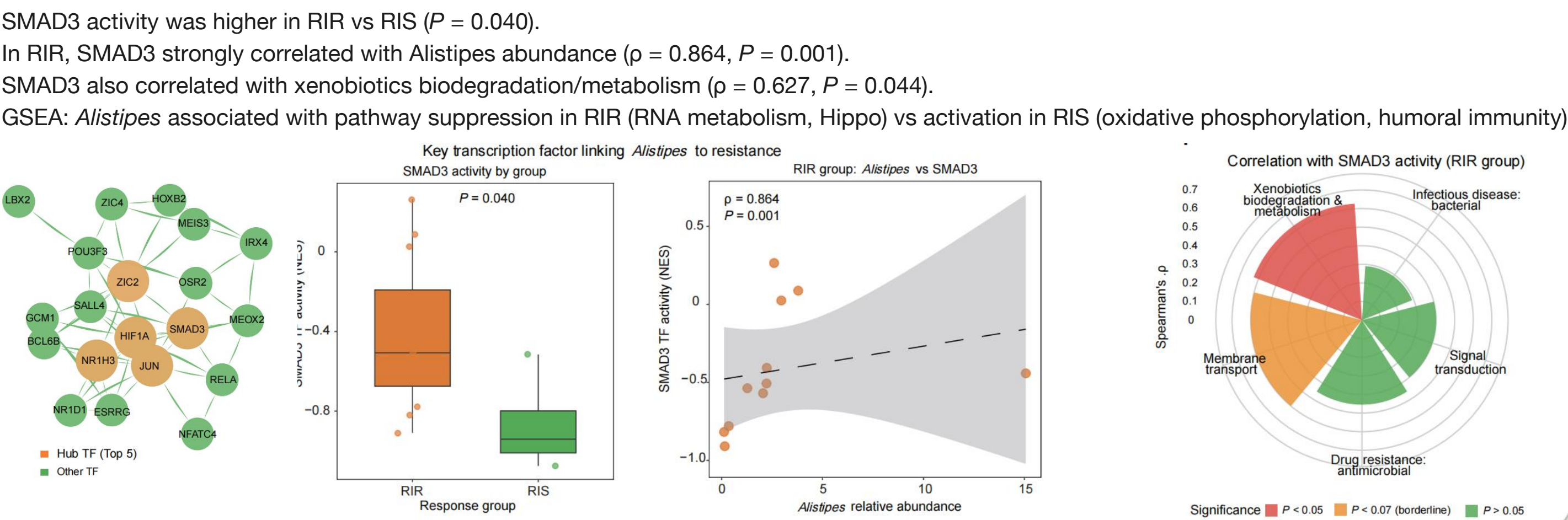
4 RESULTS 1: *Alistipes* is a Biomarker of Resistance



5 RESULTS 2: *Alistipes* Links to Resistance Functions



6 RESULTS 3: Host SMAD3 Axis in RIR



★ KEY FINDINGS

- Pre-treatment *Alistipes* abundance independently predicts worse DMFS (HR = 2.00).
- Alistipes* is enriched in RIR and associated with microbial drug-resistance pathways.
- Host SMAD3 activation correlates with *Alistipes* abundance specifically in RIR ($\rho = 0.864$).
- Alistipes* shows opposite functional associations in RIS vs RIR, revealing context-dependent crosstalk.
- External cohorts support *Alistipes* as a member of an immunotherapy-relevant microbial module.

7 CONCLUSIONS

- Pre-treatment gut *Alistipes* abundance is an independent prognostic biomarker of radio-immunotherapy resistance in oligometastatic NSCLC.
- Alistipes* enrichment is linked to microbial xenobiotic metabolism, antimicrobial resistance, and host SMAD3 activation.
- Alistipes* represents a potential biomarker for patient stratification and a therapeutic target to overcome radio-immunotherapy resistance.
- These findings reveal context-dependent microbiome–host crosstalk that distinguishes radiosensitivity from resistance.

8 EXTERNAL VALIDATION

- Anti-PD-1 cohort (Routy et al., n=127): *Alistipes* co-occurred with Akkermansia (FDR = 0.002), a known immunotherapy-response taxon.
- TCGA-LUAD (n=358): higher SMAD3 expression showed a trend toward worse OS (HR = 1.22, $P = 0.082$), strongest in current smokers.

9 ACKNOWLEDGMENTS & REFERENCES

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Key references:

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