Longitudinal plasma evRNA reveals distinct biological states in MSS BRAFV600E mCRC

Response-associated molecular states emerge from plasma RNA without outcome supervision; resistance converges on TGF-β/ROCK/S6K biology.

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Disclosures

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BACKGROUND & STUDY DESIGN

- Patients with MSS BRAF V600E mCRC treated with encorafenib + cetuximab + nivolumab show heterogeneous benefit (ORR 50%, mPFS 7.4 months)
- Predefined signatures are limited to the genes they were built from; we asked whether label-free AI analysis of serial plasma evRNA could reveal response biology and resistance programs they miss.
- Analyses included supervised response comparison, unsupervised clustering, and regulatory manifold dynamics.

STUDY COHORT & SAMPLING



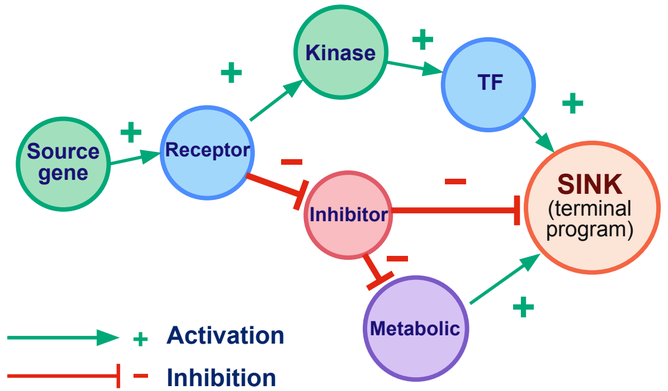
n = 21 patients

- **MSS BRAF V600E mCRC**
- **11 responders / 10 non-responders**
- **Treatment: encorafenib + cetuximab + nivolumab**



PATHWAY SIGNAL FLOW (PSF)

Pathway-level signal propagation to topology-defined endpoints



Acknowledgments

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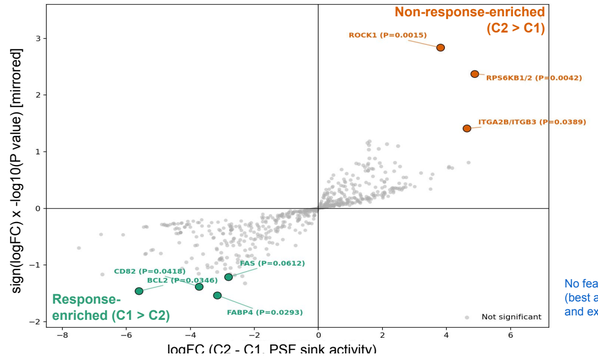
RESULTS

81% post-hoc concordance with RECIST outcomes

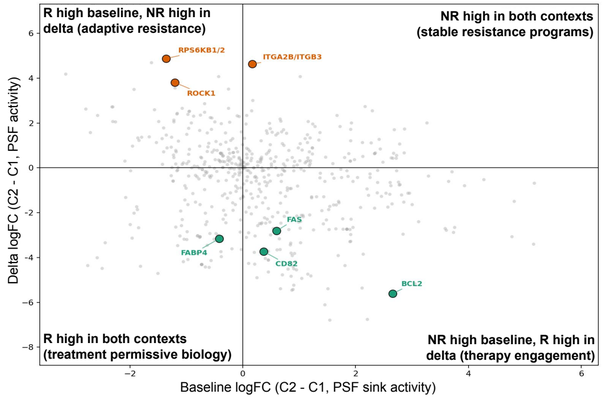
Differential PSF sink activity distinguishes response-enriched and non-response-enriched states

Miami plot (mirrored significance by direction)



No feature reaches adj. P < 0.05 at n=21 (best adj. P = 0.93); findings are nominal and exploratory.

Cross-context comparison separates stable baseline programs from treatment-associated shifts



Cross-cohort check

IFN/chemokine-associated biology was also observed in independent tumour epithelial scRNA-seq (Tian et al. 2023; n=13 MSS BRAFV600E). Rank-order preserved across shared genes (Spearman r=0.84); absolute magnitudes differ (Pearson r=0.36) — supportive, not confirmatory.

BIOLOGICAL INTERPRETATION

WORKING MODEL OF RESPONSE AND RESISTANCE

Response-enriched state (Cluster 1)

Cell death / tumor suppression
BCL2 apoptosis network
FAS death-receptor signaling

Metabolic & immune context
FABP4 (PPAR/FAO)
ANGPTL4
Immune-reactive environment

Metastasis suppression
CD82 and related p53 program

Apoptosis-competent + less invasive → treatment-permissive state

Non-response-enriched state (Cluster 2)

TGF-β resistance program
TGF-β (upstream driver)
ROCK1 (EMT / stromal barrier / immune exclusion)

mTORC1 / S6K
RPS6KB1/2 — putative mTORC1/S6K bypass signaling

Platelet / adhesion axis
ITGA2B / ITGB3
Platelet–tumor interactions
Metastatic niche / CTC protection

Adaptive resistance (encorafenib + cetuximab + nivolumab)

KEY TAKEAWAYS

1. Plasma evRNA recovers clinically meaningful molecular states in MSS BRAF V600E mCRC.
2. Independent analytical approaches converge on distinct response-associated and resistance-associated programs.
3. TGF-β/ROCK/S6K is newly uncovered in this novel AI-based approach, and constitutes a testable resistance-associated axis.

LIMITATIONS

- Small, single-center cohort (n = 21); exploratory analysis.
- Findings are nominal and hypothesis-generating (no features reach adj. P < 0.05).
- Causal relationships and clinical utility require further validation in larger, independent cohorts.

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