

INTRODUCTION

- Mesothelioma (pleural MPM; peritoneal MPeM) is rare, aggressive, and has poor survival.
- Frontline choice among epithelioid mesothelioma: **chemotherapy (chem)**, **immune checkpoint inhibitors (ICI)**, or **combination treatment with bevacizumab (bev)** is made empirically.

THE GAP: no validated biomarker guides frontline therapy; PD-L1 and TMB are unreliable.

- Do **transcriptomic subtypes** predict which frontline therapy works best?

METHODS

- 386 MPM + MPeM tumors, Caris Life Sciences (bulk RNA-seq + WES).
- k-means clustering (k=3), top 1,000 variable genes; GSEA; genomic alterations, PD-L1 (q-corrected).
- Endpoints: OS from frontline start
- 3 subtypes: **C1 30%, C2 49%, C3 21%**; frontline 165 chemo / 118 ICI / 101 bev-based combinations.

DISCUSSION AND CONCLUSION

Conclusions & Take-Home

- 2/3 of patients (C1, C3): frontline **ICI had significantly shorter OS** than chemo/bev (C3: ICI 9.5 mo).
- ICI-resistant clusters = **9p21 loss + TGF- β immune exclusion**, despite high PD-L1.
- C2 (immune-engaged): no difference across therapies.

Future Directions

- Prospective validation: RNA profiling to guide frontline choice.

REFERENCES & ACKNOWLEDGEMENTS

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Artificial Intelligence (AI) Use Disclosure

AI tool: Anthropic Claude (Opus 4): poster layout/formatting and drafting/condensing text from the authors' abstract, figures, and results.
AI did not generate or analyze data, statistics, or figures; all scientific content was produced and verified by the authors (ACCME Standards for Integrity and Independence).

RESULTS

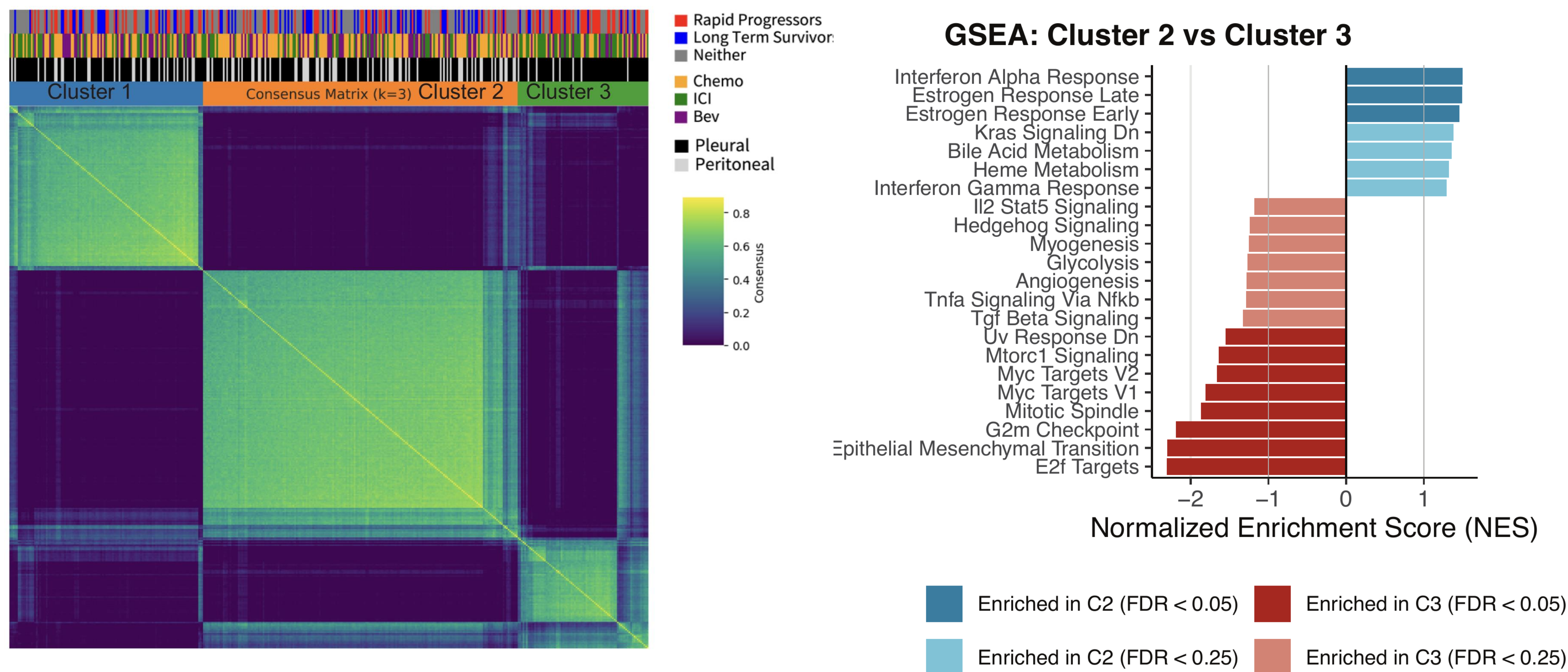


Figure 1. Consensus k-means clustering (k=3) defines three transcriptomic subtypes across pleural and peritoneal mesothelioma.

Figure 3. GSEA (C2 vs C3): C3 enriched for E2F, G2M and TGF- β (immune exclusion); C2 for IFN- α/γ

Table 1. Molecular alterations by cluster (%; q = FDR-corrected).

Alteration	C1	C2	C3	Enriched (q)
delCDKN2A (9p21)	53.8	40.9	69.6	C3 (0.004)
delCDKN2B (9p21)	42.3	33.9	66.1	C3 (<0.001)
delMTAP (9p21)	34.6	28.3	53.6	C3 (0.006)
PD-L1 positive	27.6	17.5	37.7	C3 (0.006)
TP53	9.3	8.3	28.8	C3 (<0.001)
KRAS	0.9	0.0	5.4	C3 (0.026)
SETD2	14.8	11.5	2.7	C1 (0.026)
BAP1	38.1	39.4	24.3	ns

q: FDR-corrected (Benjamini-Hochberg) pairwise p-value for the contrast isolating the enriched cluster (C2 vs C3; SETD2: C1 vs C3). ns: not significant across clusters.

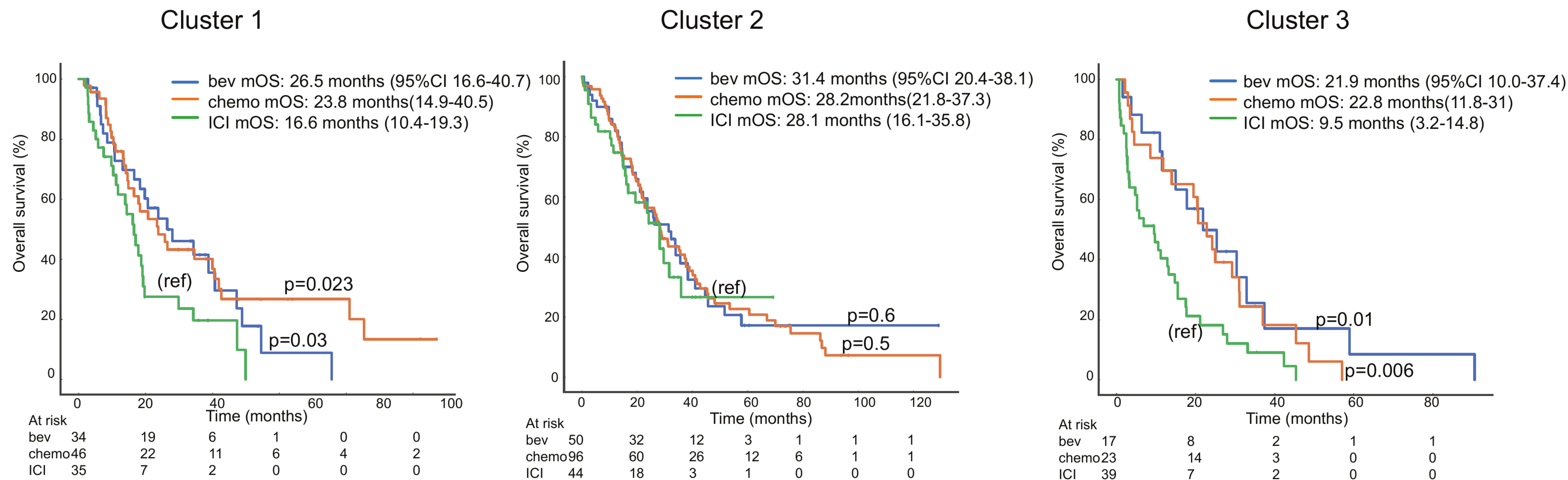


Figure 2. Overall survival by frontline therapy within each cluster (reference = ICI). C1 and C3: patients treated with bevacizumab and chemotherapy have significantly better survival compared to ICI, most pronounced in C3 (ICI 9.5 mo). C2: no difference (all p>0.5).