#3056: A Plasma Proteomics-based Model for Predicting Response to Neoadjuvant Chemotherapy in Ovarian Cancer
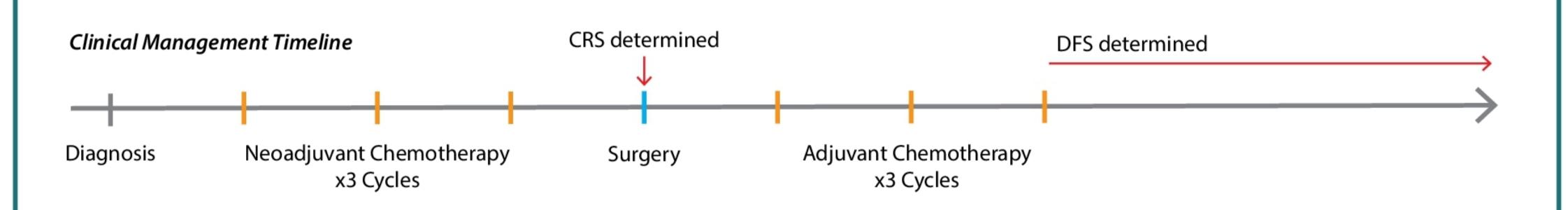
Coren Lahav[1], Stav Sapoznik[2], Michal Harel[1], Yehonatan Elon[1], Keren Levanon[3,4]

(1) OncoHost, Binyamina, Israel; (2) Sheba Cancer Research Center, Sheba Medical Center, Ramat Gan, Israel; (3) The Jusidman Cancer Center, Sheba Medical Center, Ramat Gan, Israel; (4) School of Medicine, Faculty of Medical and Health Sciences, Tel Aviv University, Ramat Aviv, Israel.

ONCOHOST GUIDED ONCOLOGY
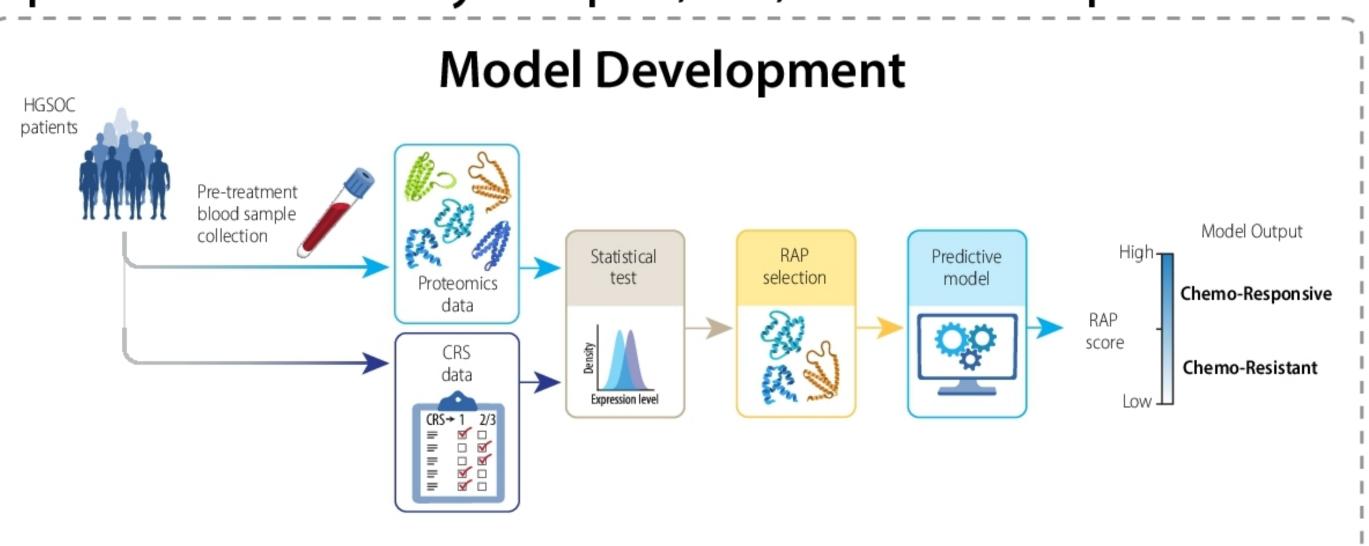
SHEBA Tel HaShomer | Cancer Center

BACKGROUND

Advanced stage high grade serous ovarian carcinoma (HGSOC) patients are commonly treated with 3 cycles of platinum-taxane chemotherapy, followed by interval cytoreductive surgery and 3 adjuvant cycles of identical chemotherapy. Pathological response is evaluated following surgery using a standardized chemotherapy response score (CRS), which corresponds with clinical outcomes. There are no predictors for benefit from neoadjuvant chemotherapy (NACT), nor biomarkers for personalization of adjuvant therapy. Here we describe a pre-treatment plasma proteomics-based model for predicting response to NACT.

Clinical Management Timeline: Diagnosis → Neoadjuvant Chemotherapy x3 Cycles → Surgery (CRS determined) → Adjuvant Chemotherapy x3 Cycles → DFS determined
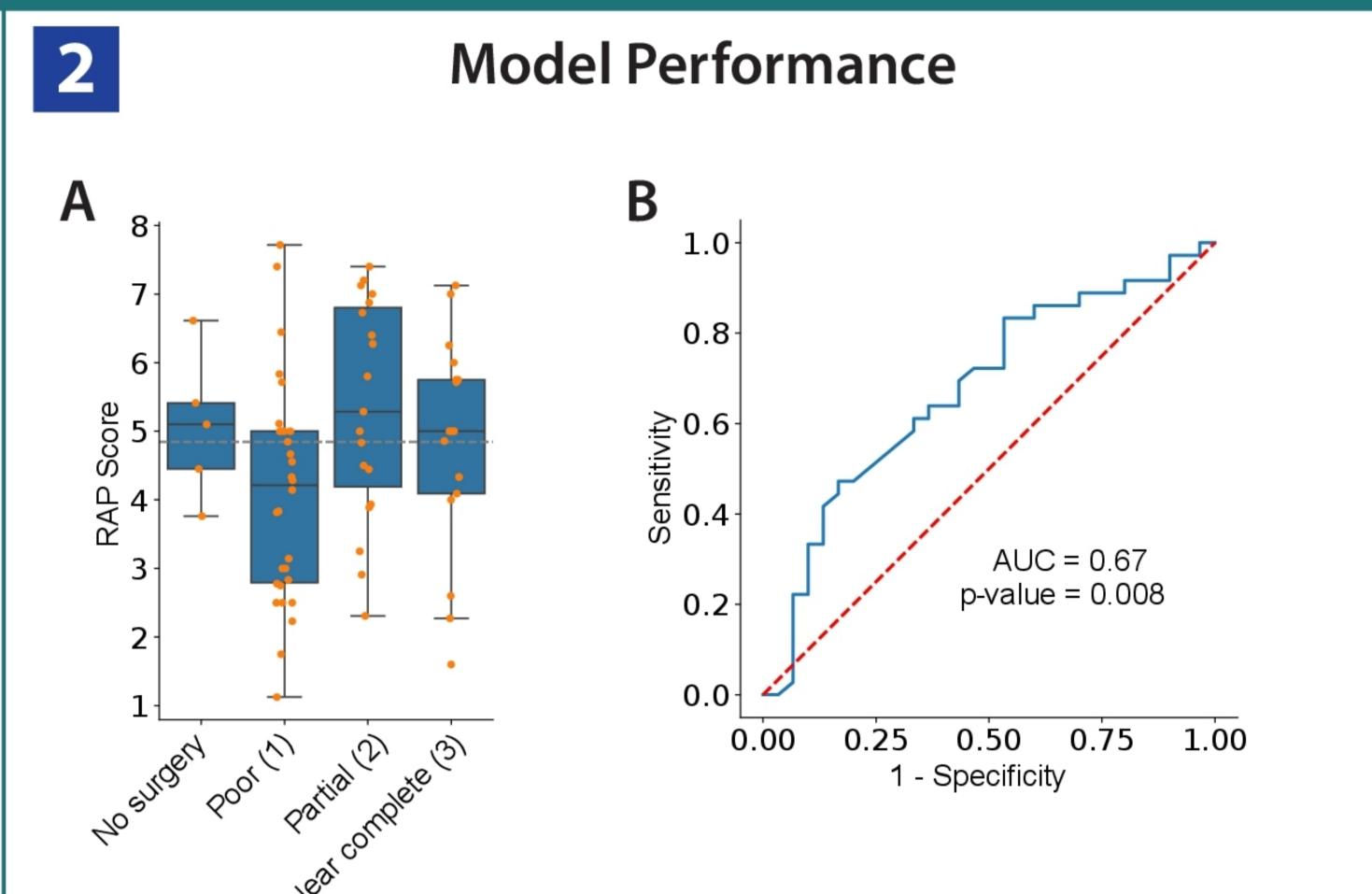
METHODS

- Obtained pre-treatment plasma samples from 71 women with International Federation of Gynecology and Obstetrics (FIGO) stage 3C-4 HGSOC who were treated with neoadjuvant platinum-taxane NACT.
- Collected clinical data including CRS, disease-free survival (DFS), and overall survival (OS).
- Performed deep proteomic profiling of plasma samples using an aptamer-based assay measuring ~7000 proteins.
- Developed a computational model to predict CRS, focusing on differentiating between poor CRS (CRS1) versus partial or near-complete CRS (CRS2/3).
- Proteins displaying differential pretreatment expression in patients with CRS1 versus CRS2/3 were defined as **Response-Associated Proteins (RAPs)**. The RAPs (n=62) were incorporated into a machine learning-based model that computes a RAP score and provides a binary output, i.e., chemo-responsive or chemo-resistant.
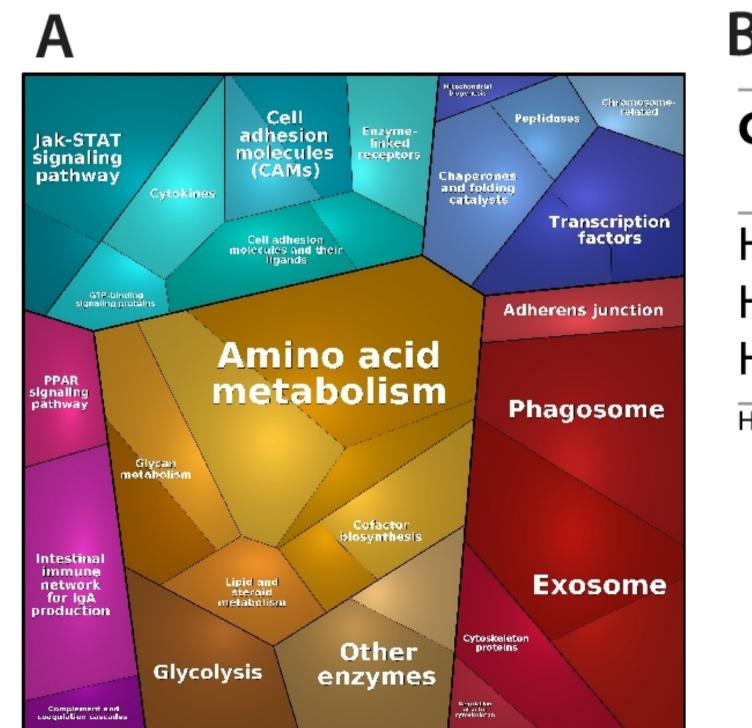- Bioinformatic analysis of the RAPs was performed to gain mechanistic insights into NACT response.

Model Development

RESULTS

1 Patient Characteristics

Characteristic	Number (%)
Sex	
• Female	71 (100)
Treatment	
• Platinum-taxane chemotherapy	71 (100)
Stage	
• 3	40 (56.3)
• 4	31 (43.7)
BRCA germline mutation	
• WT	59 (83.1)
• BRCA 1	7 (9.9)
• BRCA2	3 (4.2)
• Unknown	2 (2.8)
CRS	
• Complete/near complete (3)	17 (23.9)
• Partial (2)	19 (26.8)
• Poor (1)	30 (42.3)
• Did not undergo surgery	5 (7.0)

2 Model Performance

A. Association between RAP score and CRS.
B. Receiver operating characteristics (ROC) curve demonstrating the ability of the model to distinguish between CRS1 vs CRS2/3. Area under the curve (AUC) of 0.67 indicates good predictive performance.
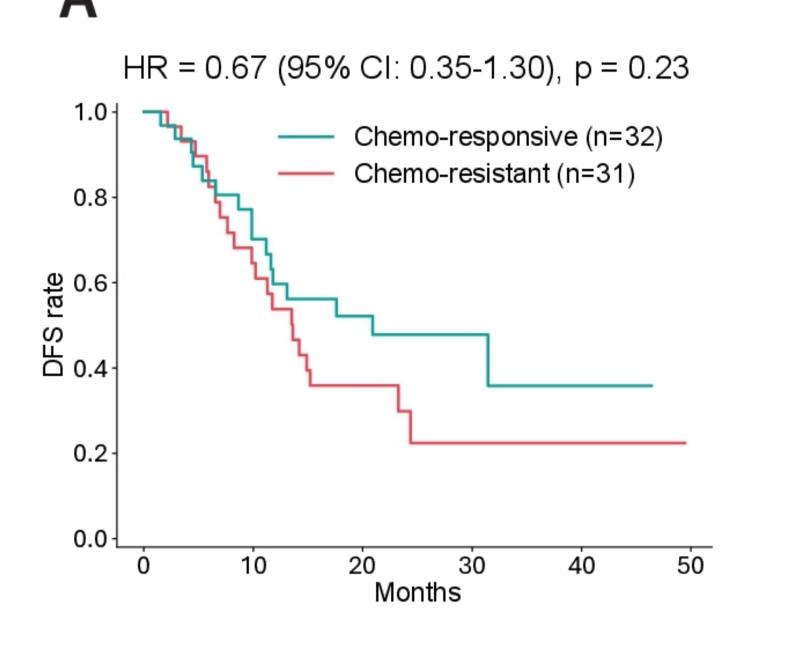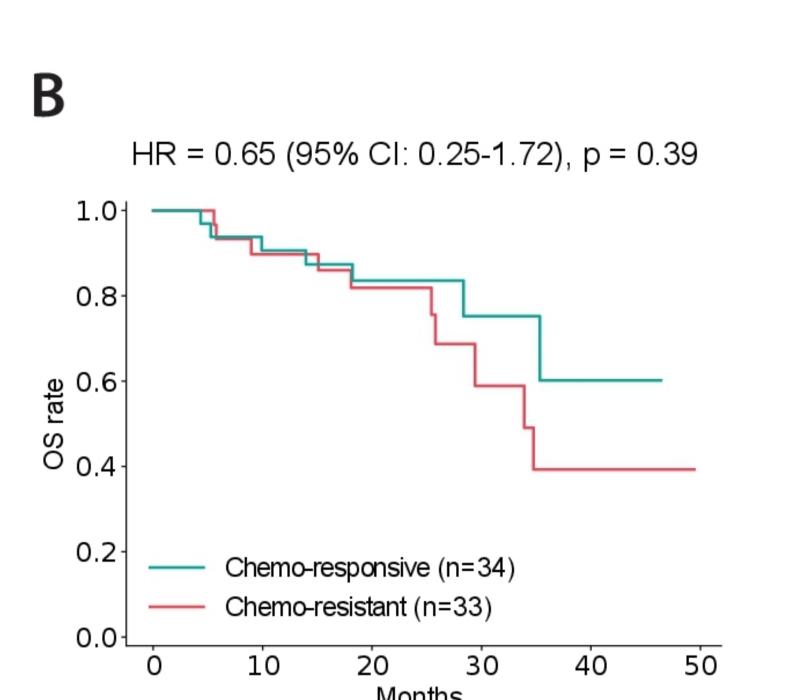
AUC = 0.67
p-value = 0.008

3 Association with Survival Outcomes

A. HR = 0.67 (95% CI: 0.35-1.30), p = 0.23; Chemo-responsive (n=32); Chemo-resistant (n=31)

B. HR = 0.65 (95% CI: 0.25-1.72), p = 0.39; Chemo-responsive (n=34); Chemo-resistant (n=33)

The binary output of the model stratifies patients according to survival outcomes. Patients classified as chemo-responsive had longer disease-free survival (DFS; A) and overall survival (OS; B) than those classified as chemo-resistant, although not reaching statistical significance.

C. HR = 0.62 (95% CI: 0.27-1.42), p = 0.25; Near complete (3) (n=15); Partial/Poor (1-2) (n=46)

D. HR = 0.67 (95% CI: 0.21-2.09), p = 0.48; Near complete (3) (n=17); Partial/Poor (1-2) (n=48)

In our cohort, CRS is associated with DFS (C) and OS (D), however not reaching statistical significance. Our findings are consistent with a previous meta-analysis (Cohen et al. Gynecologic Oncology 2019).

4 Bioinformatic Analysis of RAPs

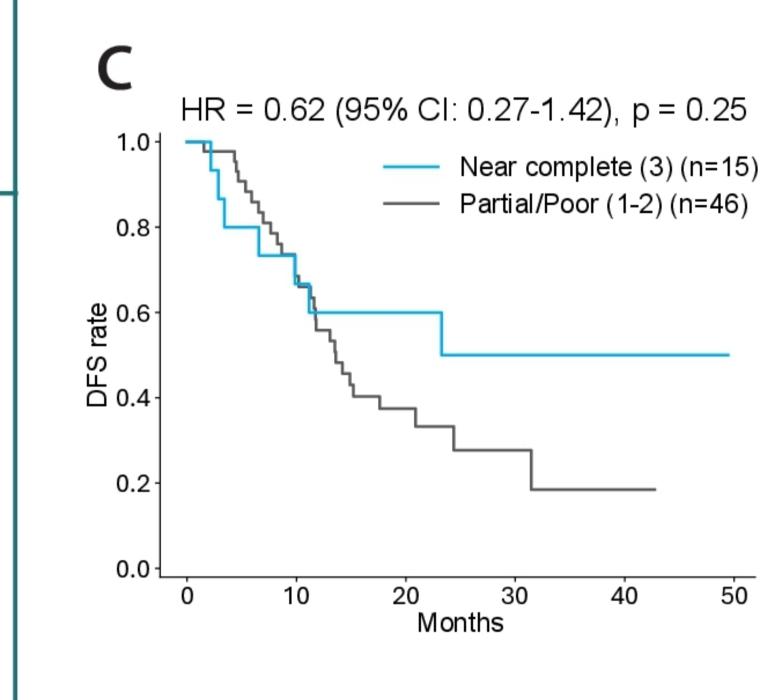| Group	Category	Enrichment Factor	Category Size	Intersection Size
Higher in CRS1	HoC - Resisting cell death	3.5	77	5
Higher in CRS2/3	HoC - Genome instability	1.6	186	7
Higher in CRS1	HoC - Genome instability	0.3	186	1

HoC, Hallmarks of cancer

A. Voronoi plot displaying the main biological processes in which RAPs may be involved.
B. Of the 62 RAPs, 27 were elevated in plasma of patients with CRS1 compared to CRS2/3. The table shows enrichment analysis per RAP subset, Fisher Exact test FDR < 0.1.
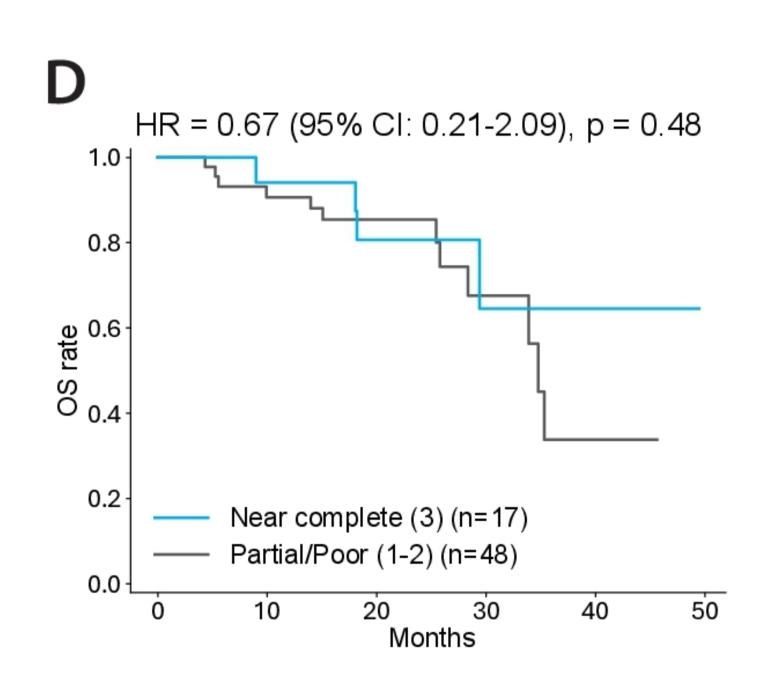
SUMMARY

- Plasma proteomics at baseline can predict CRS for patients with advanced-stage HGSOC receiving standard platinum-based neoadjuvant treatment.
- Validation in a larger cohort is needed to explore the association between model output and survival outcomes.

ACKNOWLEDGEMENTS