Tumor-informed ctDNA as an early predictive marker for relapse in advanced epithelial ovarian cancer

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Background

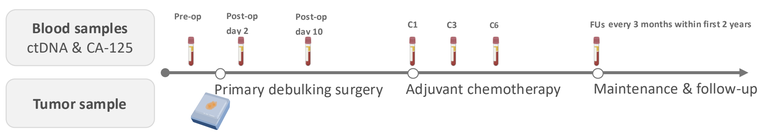
- Prediction of relapse following first-line treatment in patients with high-grade serous ovarian cancer (HGSOC) remains a major challenge despite recent advances in clinical management
- Reliable markers for assessment of relapse risk are urgently needed to tailor treatment strategies

How to predict risk for relapse in ovarian cancer after first-line treatment?

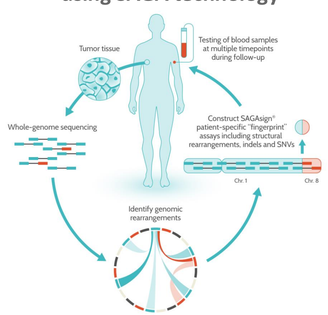
Circulating tumor DNA evaluation at end of chemotherapy reveals promising results

Study design

Prospective bi-centric study: *n*=100 patients with advanced HGSOC



Patient-specific ctDNA profiles using SAGA technology



- Whole genome sequencing was used to identify structural variants, single nucleotide variants, indels
- Detection of a high number of SVs ensuring a personalized fingerprint for every patient with a median of 8 biomarkers tracked
- Positive ctDNA detection rate
  - at baseline 98% (46/47)
  - post-surgery d10 88% (40/45)
  - C6 59% (30/51)

Characteristics	Details	*n*=51 (%)
Age (years)	median 61 (33-86)	
FIGO	IIIA/B	12 (24%)
	IIIC	27 (53%)
	IVA	3 (6%)
	IVB	9 (18%)
tBRCA status	mutated	14 (27%)
	wildtype	26 (51%)
	unknown	11 (22%)
Postoperative residual disease	macroscopic	17 (33%)
	none	34 (67%)
Targeted maintenance therapy	yes	47 (92%)
	no	3 (6%)
	unknown	1 (2%)
Relapse		21 (41%)
	PFS median (months)	11.8 (1.8-36.4)
	postoperative residual disease	
	macroscopic	11 (52%)
	microscopic	10 (48%)

Table 1. Patient characteristics. Data of *n*=51 pts with samples from preop through chemotherapy available

Results

Lower rates of recurrence in patients with ctDNA clearance compared to regular CA-125 serum levels at the end of chemotherapy (C6)

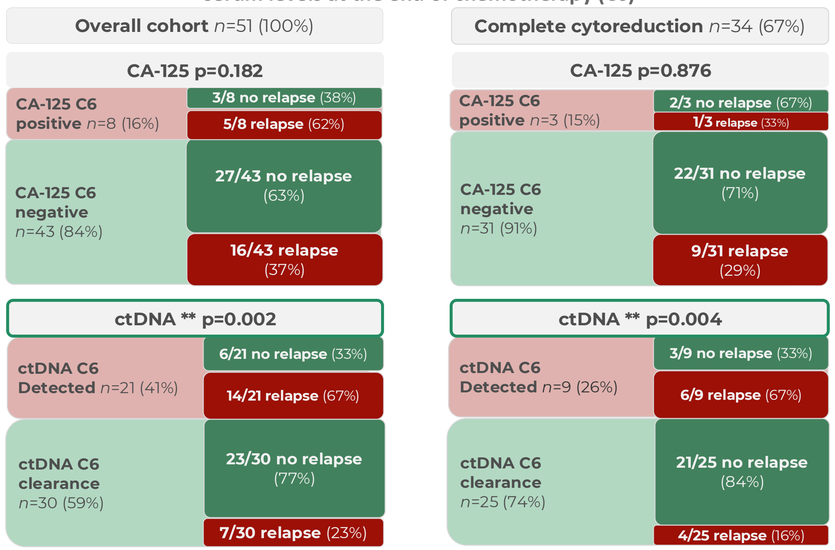


Figure 1. Recurrence rate according to method for detection. Contingency analysis performed with Chi-square test

Conclusion

- ctDNA evaluation at the end of completed first-line chemotherapy might serve as a more reliable predictive marker for recurrence compared to CA-125
- Individualized ctDNA-informed treatment strategies might be established using serial ctDNA analysis especially for patients with complete macroscopic cytoreduction

Outlook

- Validation in final patient cohort (*n*=100)
- Assessment as biomarker for postoperative tumor residual disease
- Lead time to relapse of ctDNA versus conventional follow-up
- Identification and tracking of gene variants & clonal aberrations under therapeutic pressure

Detection of residual ctDNA at C6 is associated with a shorter PFS in the overall cohort and especially in pts with complete cytoreduction

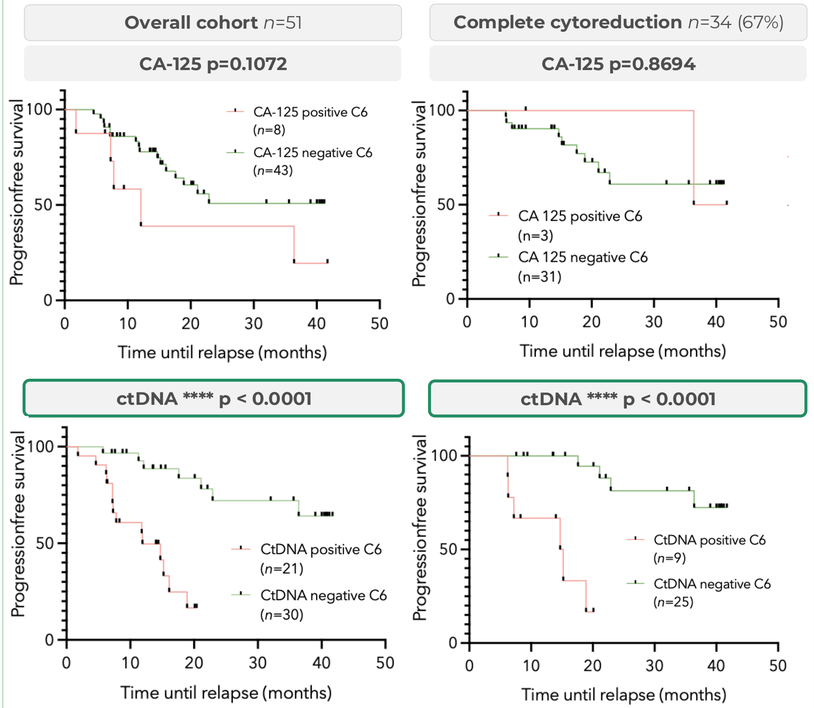
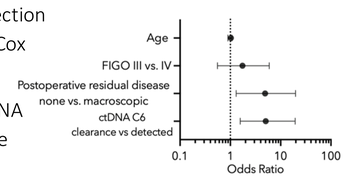


Figure 2. Survival analysis. Patients with detection of ctDNA at C6 showed a significantly shorter median PFS in the overall cohort (median 11.8 vs. 20.6 months, HR 10.09, p<0.0001) and in patients with complete cytoreduction (median 14.9 vs. 22.9 months, HR 119.5, p<0.0001). This effect was not seen in patients with residual tumor (data not shown). No effect on PFS was observed for CA-125 status at C6.

Multivariate analysis

- The independent prognostic value of ctDNA detection at C6 on PFS was evaluated using a multivariate Cox proportional hazards survival regression model
- Independent predictors of PFS were positive ctDNA status at C6 (HR=5.05, p=0.0096) & postoperative tumor residual (HR=4.92, p=0.0196)



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