

Tumor-informed circulating tumor DNA identifies high-grade serous ovarian cancer patients at highest risk for recurrence despite optimal first-line treatment with primary macroscopic complete resection

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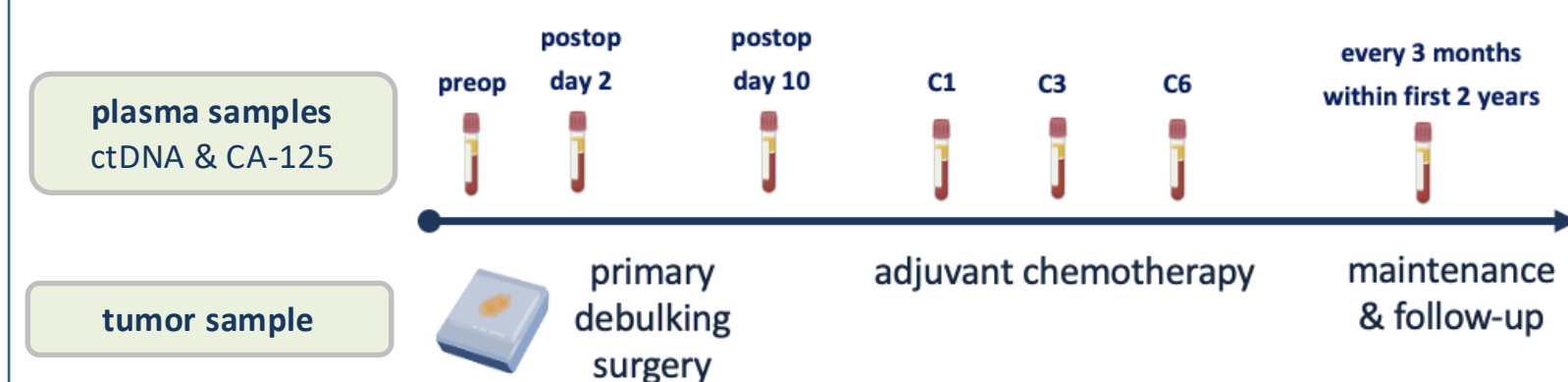
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Introduction

Objective measures of postoperative molecular residual disease (MRD) in high-grade serous ovarian cancer (HGSOC) surgery are lacking, including serologic and radiologic evaluation. Tumor-informed circulating tumor DNA (ctDNA) has shown promise as a new approach to identify patients at high risk for relapse.

Methods and Materials

- Prospective bicentric study
- Advanced HGSOC patients (pts)
- Primary debulking surgery followed by six cycles of chemotherapy and maintenance therapy
- Patient enrollment: 07/2021 – 09/2024
- Whole-genome sequencing of tumor tissue identified structural variants, used to design personalized multiplex dPCR assays to detect MRD.



Characteristics	Details	n=84 (%)
Age (years)		median 64 (33-86)
FIGO	IIIA/B	23 (27%)
	IIIC	43 (51%)
	IVA	1 (1%)
	IVB	17 (20%)
BRCA and HRD status	BRCA mutated	23 (27%)
	BRCA negative	54 (64%)
	HRD positive	11 (13%)
	BRCA unknown	7 (8%)
Postoperative residual disease	yes	22 (26%)
	no	62 (74%)
Targeted maintenance therapy	yes	71 (83%)
	Bevacizumab	35 (42%)
	Bevacizumab + PARPI	18 (21%)
	PARPI	18 (21%)
	no	8 (10%)
	unknown	5 (6%)
Outcome	Death	12 (14%)
	Relapse	36 (43%)
	PFS in months	17.5 (0.2-51.2)

Table 1. Patients' clinical characteristics.

Perioperative ctDNA detection

- ✓ ctDNA detection at baseline → 94% (77/82 pts)
- ✓ ctDNA postoperatively → 85% (63/74 pts)

At postop day 10, pts with complete tumor resection had significantly lower ctDNA levels than pts with postop residual disease ($p=0.0018$).

Median ctDNA level decreased by 94% between preop and postop day 10 in pts with complete tumor resection ($p=0.0247$), but not in pts with postop residual disease ($p=0.891$).

Predictive value of ctDNA for PFS

Within the subgroup of pts with complete tumor resection, ctDNA clearance at C1 (20%) and C6 (70%) was associated with significantly lower recurrence risk compared to persistent ctDNA levels (C1: 80%, C6: 30%) with an even stronger association at C6 (C1: HR=3.78, $p=0.022$, C6: HR=33.44, $p<0.0001$). As shown in Figure 1, ctDNA dynamics appear to be associated with recurrence risk when stratified by postoperative residual disease. Median time to recurrence in the C6 ctDNA positive group was 10.7 months compared to 21.3 months in the C6 ctDNA negative group.

Conclusions

Structural variant-based tumor-informed ctDNA analysis can accurately stratify HGSOC patients at high risk of recurrence despite primary surgery with complete macroscopic tumor resection.

ctDNA assessment at C6 may provide an opportunity window for risk-stratified treatment adjustments directly after chemotherapy, enabling new personalized maintenance strategies.

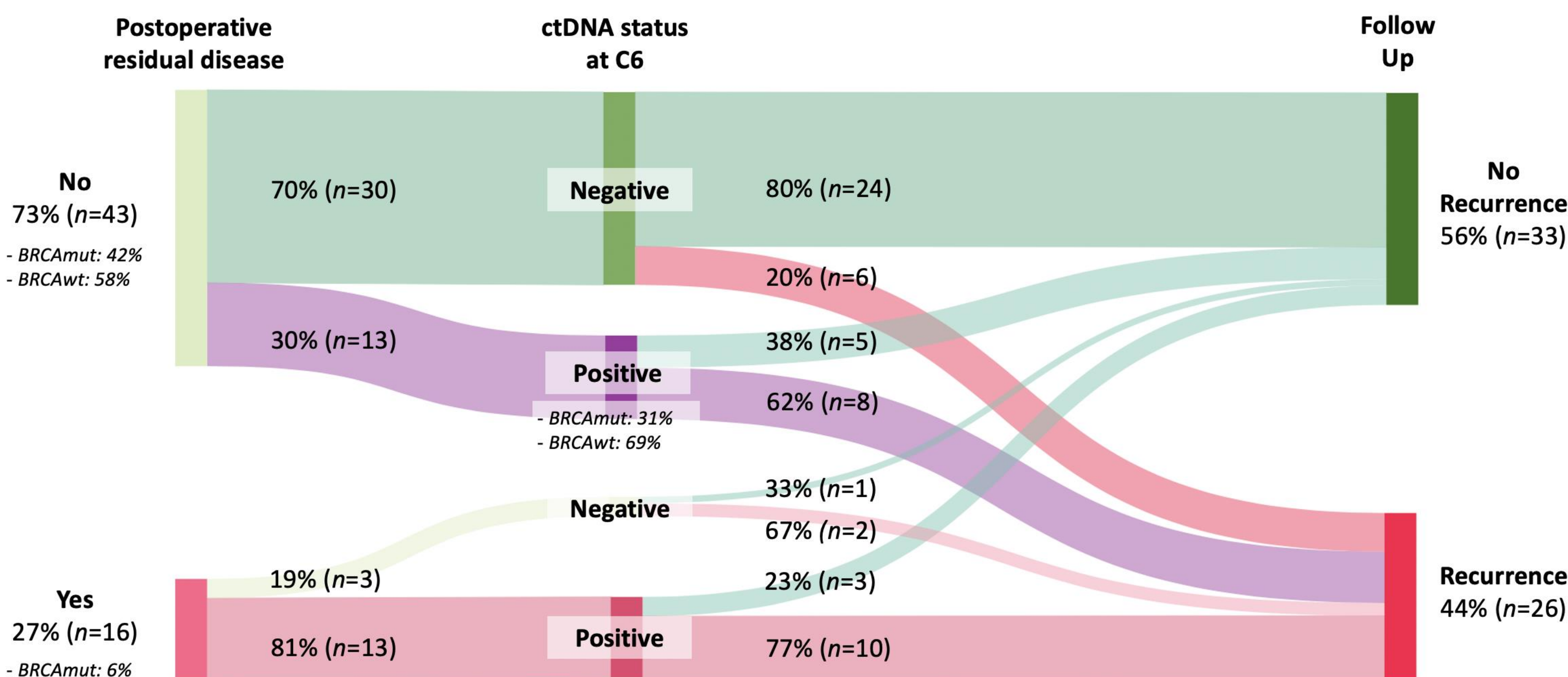


Figure 1. Association of ctDNA dynamics with recurrence risk, stratified by postoperative residual disease, in a cohort of 59 patients with available ctDNA status at C6 and a median follow-up of 18.8 months.

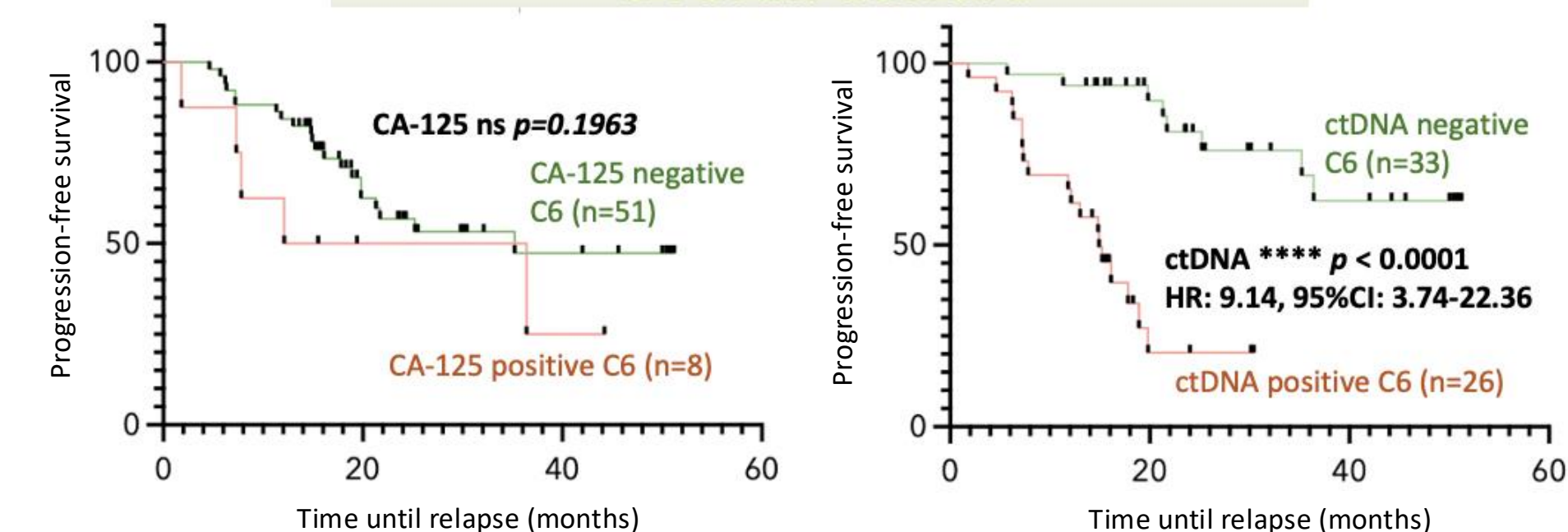
ctDNA is a better indicator for prognosis than CA-125

ctDNA outperformed CA-125 for prognosis, as CA-125 levels at C1 or C6 failed to predict recurrence (C1: $p=0.192$; C6: $p=0.196$). C6 analysis is shown in Figure 2 ($n=59$ with complete data for all C6 timepoints).

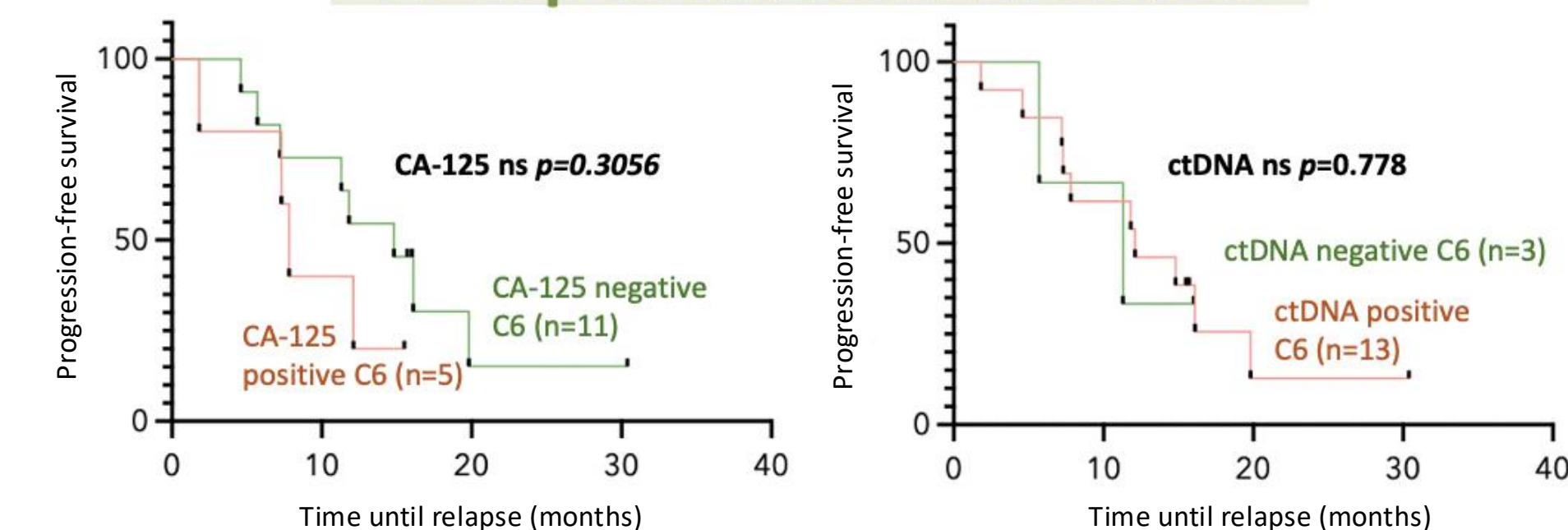
Multivariate analysis

In a multivariate analysis, ctDNA persistence at C1 ($p=0.025$), at C6 ($p<0.0001$) and postoperative residual disease ($p=0.004$) were confirmed as independent prognostic markers.

Overall cohort



Postoperative residual disease



Complete tumor resection

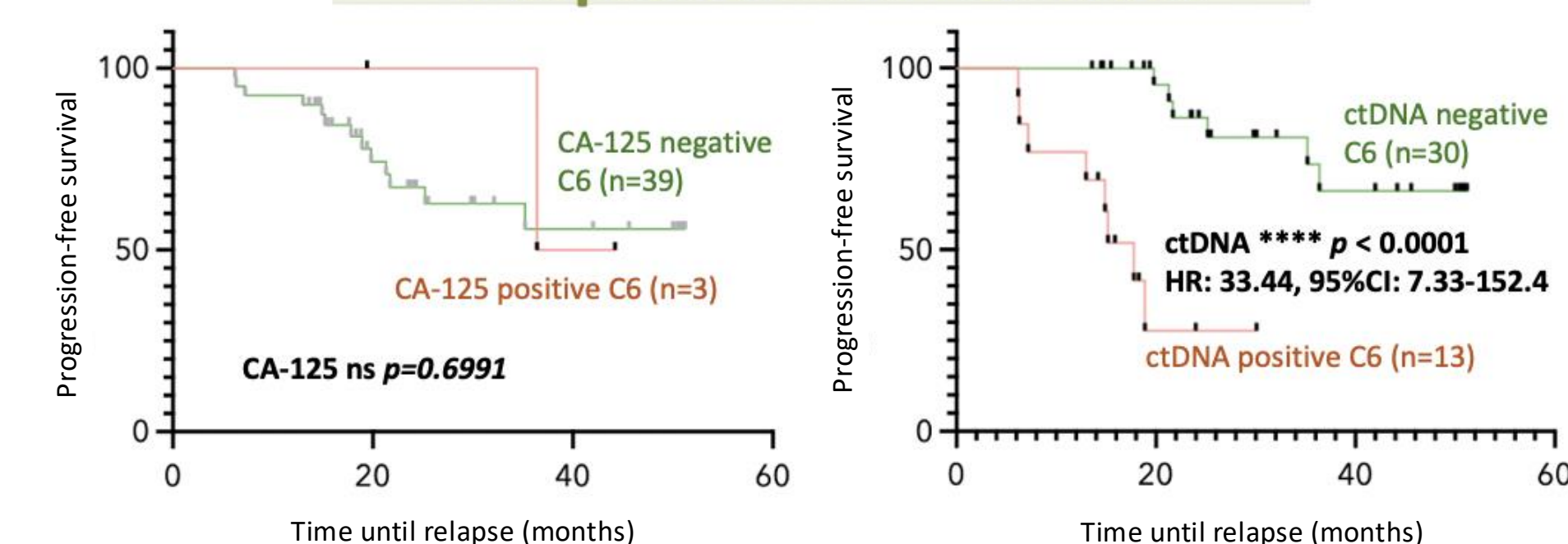


Figure 2. Progression-free survival according to levels for CA-125 (left) and ctDNA (right) at C6.