Clinical utility of TP53 mutations (TP53m) dynamic monitoring in circulating tumor DNA (ctDNA) in patients (pts) with high-grade ovarian carcinomas (HGOC).

#4333

M. Kfoury[1], C.Bonnet[2], N.Delanoy[3], C. Brizais[4], A. Leformal[4], K. Howarth[5], C. Morris[5], E. Lecerf[1], A. Leary[1].

[1] Oncology Department, Gustave Roussy Cancer Center, Villejuif, [2] Oncology Department, Hôpital Saint-Louis, Paris, [3] Oncology Department, Hôpital Européen Georges Pompidou, Paris, [4] Inserm UMR 981, Gustave Roussy Cancer Center, Villejuif, [5] Inivata Ltd, Babraham, Cambridge, UK.

BACKGROUND

70% of pts with HGOC relapse within 3 years after optimal treatment with debulking surgery (DS) and platinum doublet chemotherapy. Current serum tumor markers (CA-125) and imaging studies (CT or MRI) lack the sensitivity and specificity to predict outcome following initial treatment and to detect early relapse[2]. ctDNA has been investigated as a potential non-invasive dynamic biomarker for several cancer types including gynaecological cancer[1]. TP53m are identified in most pts with HGOC[3] and its monitoring in ctDNA could be used as a tumor specific biomarker in the follow-up of patients with HGOC.

OBJECTIVE

Evaluate the clinical utility of TP53m in ctDNA for detecting minimal residual disease (MRD) and as a marker of early response to chemotherapy and early relapse.

PATIENTS AND METHODS

Patients with HGOC enrolled in a prospective academic biological study (OvBIOMark,NCT03010124) consented to analysis of ctDNA samples obtained throughout the disease course :

- at diagnosis,
- after DS,
- during chemotherapy or
- at relapse.

ctDNA was analysed using InVisionSeq™ to detect the presence of SNVs, indels and CNAs in 37 cancer-related genes, including TP53m to confirm presence of ctDNA.

Overall survival (OS) and Progression Free Surgical (PFS) were estimated using the Kaplan-Meier method in each group. Groups were compared using the log-rank test. Correlation tests were performed using the Spearman's test. All analyses were performed using PRISM.

VIRTUAL 2020 ESMO congress
SCIENCE: 19-21 SEPTEMBER 2020
EDUCATION: 16-18 OCTOBER 2020
THE LATEST ADVANCES IN ONCOLOGY 2020 now in a virtual format

RESULTS

A total of 37 patients with HGOC were included in the study. Median time of follow up was 42 months (range 27.7-101.9 months). At the time of analysis, 23 patients were still alive, 9 have never relapsed and are free of disease.

1. Mutated ctDNA was detected in 94% of blood samples

140 samples from 37 pts with HGOC were collected at various time points during the disease course (Figure 1). ctDNA was identified in 132 samples (94.3%) samples, in 32 patients (86.4%) overall at any time point. 5 patients had no mutation at any time point.

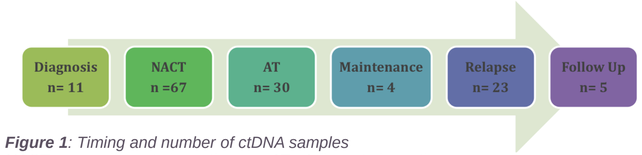

***Figure 1**: Timing and number of ctDNA samples*
NACT : neo-adjuvant chemotherapy, AT : Adjuvant chemotherapy

2. ctDNA is sensitive both at initial diagnosis and relapse

For 22 patients with a sample available, **ctDNA was detected in 100% of blood samples at diagnosis and in 87.5% at relapse**. The most frequent mutation in ctDNA was TP53m in 85,7% at diagnosis and in 87.5% at relapse.

3. ctDNA detects MRD and provides prognostic information

A sample was available immediately after DS for 13 pts. Patients with detectable ctDNA after DS had a median PFS of 17.5 months versus 26.4 months for those with undetectable ctDNA: HR 2.84 (95%CI, 0.6 -12.9), p= 0.18. Median OS was not reached in both groups (Figure 2).

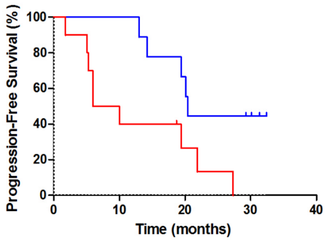

***Figure 2:** PFS of pts with detectable vs. undetectable ctDNA immediately after debulking surgery.*

4. Unfavorable ctDNA response during chemotherapy predicts surgical failure and poor PFS

Longitudinal ctDNA samples were available for 19 patients during chemotherapy: 14 in the neoadjuvant setting and 5 at relapse

In 10/19 patients, TP53m ctDNA increased, or a new TP53m appeared. For pts with increasing ctDNA during NACT, half (3/6) failed to have a debulking surgery.

In 9/19 patients, ctDNA concentration decreased considerably or became and remained undetectable after only 2 cycles of chemotherapy, and predicted CC0 interval debulking in 100% of pts undergoing NACT.

The detection of a new TP53m or an increase in TP53m ctDNA was **significantly** associated with worse survival : PFS 8.01 versus 20.4 months, HR 3.71 (CI 95% 1.2-11.42) (p= 0.02) (Figure 3).

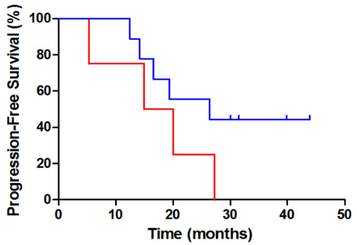

***Figure 3:** PFS of patients with ctDNA collected during chemotherapy*

5. ctDNA predicts early relapse

The detection of a new TP53m or an increase in ctDNA concentration preceded first CA-125 elevation by a median of 6.07 months (-0.4-22.2) and 7.9 months (1.1-21.2) (Figure 3).

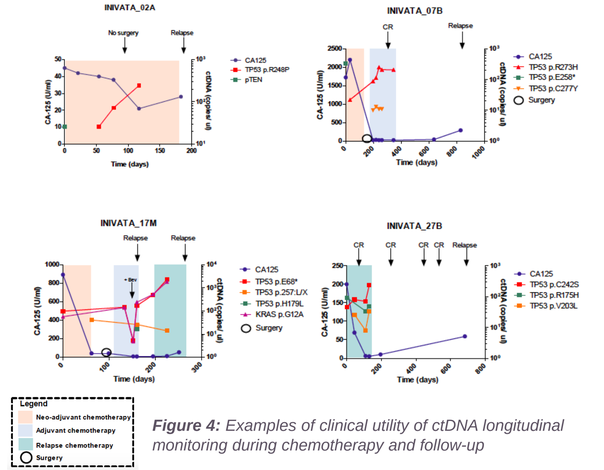

***Figure 4:** Examples of clinical utility of ctDNA longitudinal monitoring during chemotherapy and follow-up*

CONCLUSION

Our pilot study confirms the sensitivity and clinical utility of ctDNA monitoring in HGSOC patients in several areas. The detection of TP53m in ctDNA after DS seems to be associated with poor outcome and its increase or appearance during neoadjuvant chemotherapy may predict failure to achieve complete DS. ctDNA can detect occult disease and preceded biological or radiological relapse by at least 6 months. In HGOC pts, TP53m in ctDNA could be used as an early surrogate marker of response to treatment, can help identify those who should benefit from maintenance treatment or therapy escalation to eliminate minimal residual disease.

REFERENCES

1. Pereira E, et al. *PLoS ONE*. 2015;10(12):e0145754.2.
2. Meyer T, et al. *Br J Cancer*. 2000;82(9):1535-1538.
3. CGA Research Network. *Nature* 2011;474(7353):609-615

CONTACT

Maria KFOURY, MD.
maria.kfoury@gustaveroussy.fr
Has no conflict of interest

ACKNOWLEDGMENTS

This academic study is sponsored by Gustave Roussy Cancer Center
Funding from Inivata Ltd