Circulating tumour DNA in patients with advanced ovarian cancer receiving neoadjuvant chemo-immunotherapy

Elin Gray
Edith Cowan University,
Perth, Western Australia

Conflict of interest disclosure

ESMO Congress 2022 attendance supported by Thermo Fisher Scientific

Recipient of a Thermo Fisher Scientific Oncomine Clinical Research Grant

Previous travel support from BioRad

Disclaimer

Thermo Fisher Scientific and its affiliates are not endorsing, recommending or promoting any use or application of Thermo.

Fisher Scientific products by third parties during this seminar.

Information and materials presented or provided by third parties as-is and without warranty of any kind, including.

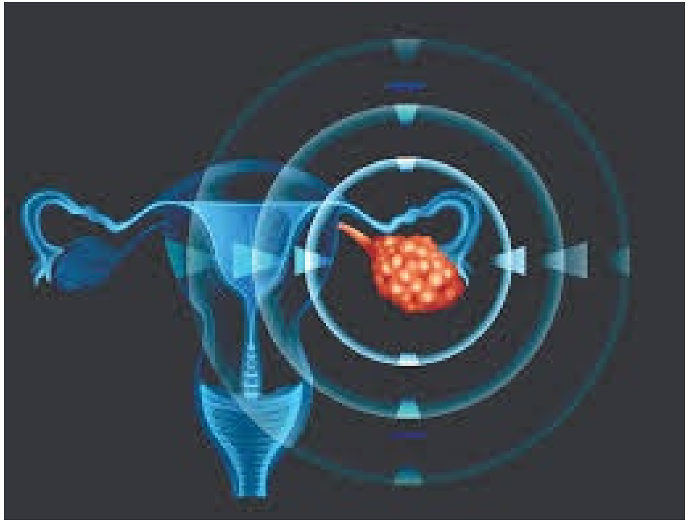
regarding intellectual property rights and reported results.

Parties presenting images, text and material represent they have the right to do so.

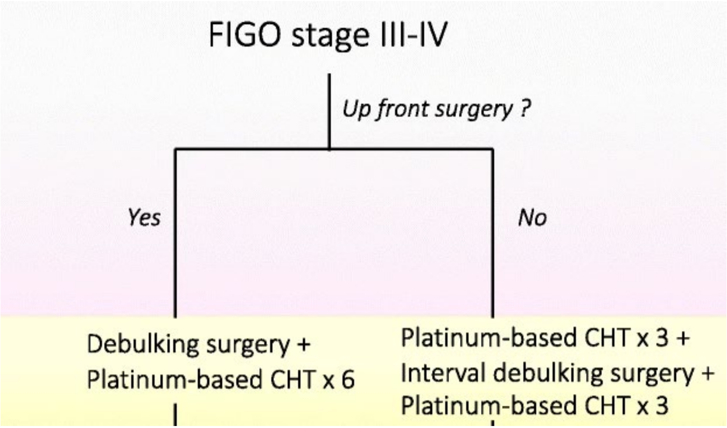
Speaker is provided travel and hotel support by Thermo Fisher Scientific for this presentation.

Speaker is provided honorarium for this presentation.

High-grade serous ovarian carcinoma



- High-grade serous ovarian carcinoma (HGSOC) is the most frequent type of ovarian cancer and has a poor outcome.
- The majority of HGSOC cases are usually treated with a combination of chemotherapy and surgery, targeting cancerous cells that make up the tumour.



FIGO stage III-IV

Up front surgery ?

Yes

No

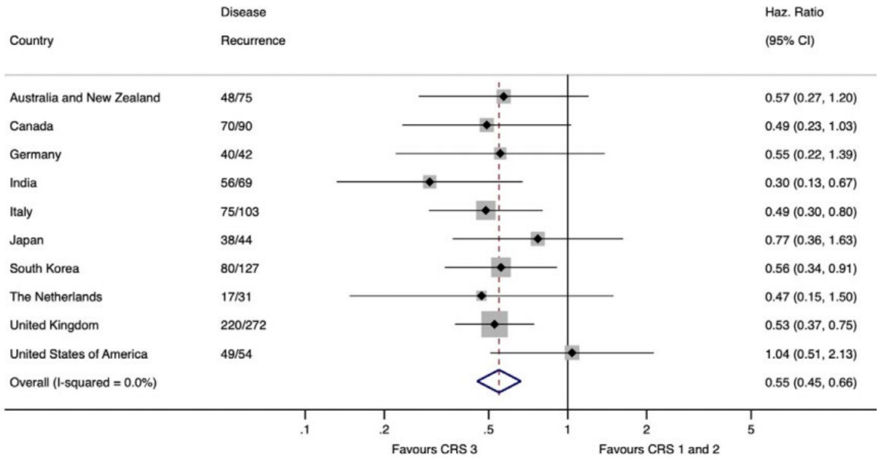
Debulking surgery +
Platinum-based CHT x 6

Platinum-based CHT x 3 +
Interval debulking surgery +
Platinum-based CHT x 3

Chemotherapy response score (CRS)

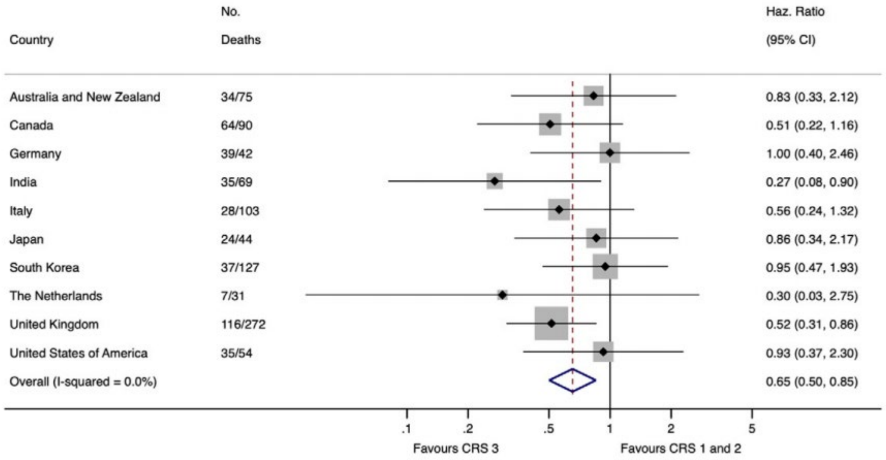
Complete/near-complete response - (CRS3)
is significantly associated with improved PFS and OS

a) PFS adjusted Forest plot.



Country	Disease Recurrence	Haz. Ratio (95% CI)
Australia and New Zealand	48/75	0.57 (0.27, 1.20)
Canada	70/90	0.49 (0.23, 1.03)
Germany	40/42	0.55 (0.22, 1.39)
India	56/69	0.30 (0.13, 0.67)
Italy	75/103	0.49 (0.30, 0.80)
Japan	38/44	0.77 (0.36, 1.63)
South Korea	80/127	0.56 (0.34, 0.91)
The Netherlands	17/31	0.47 (0.15, 1.50)
United Kingdom	220/272	0.53 (0.37, 0.75)
United States of America	49/54	1.04 (0.51, 2.13)
Overall (I-squared = 0.0%)		0.55 (0.45, 0.66)

b) OS adjusted Forest plot.

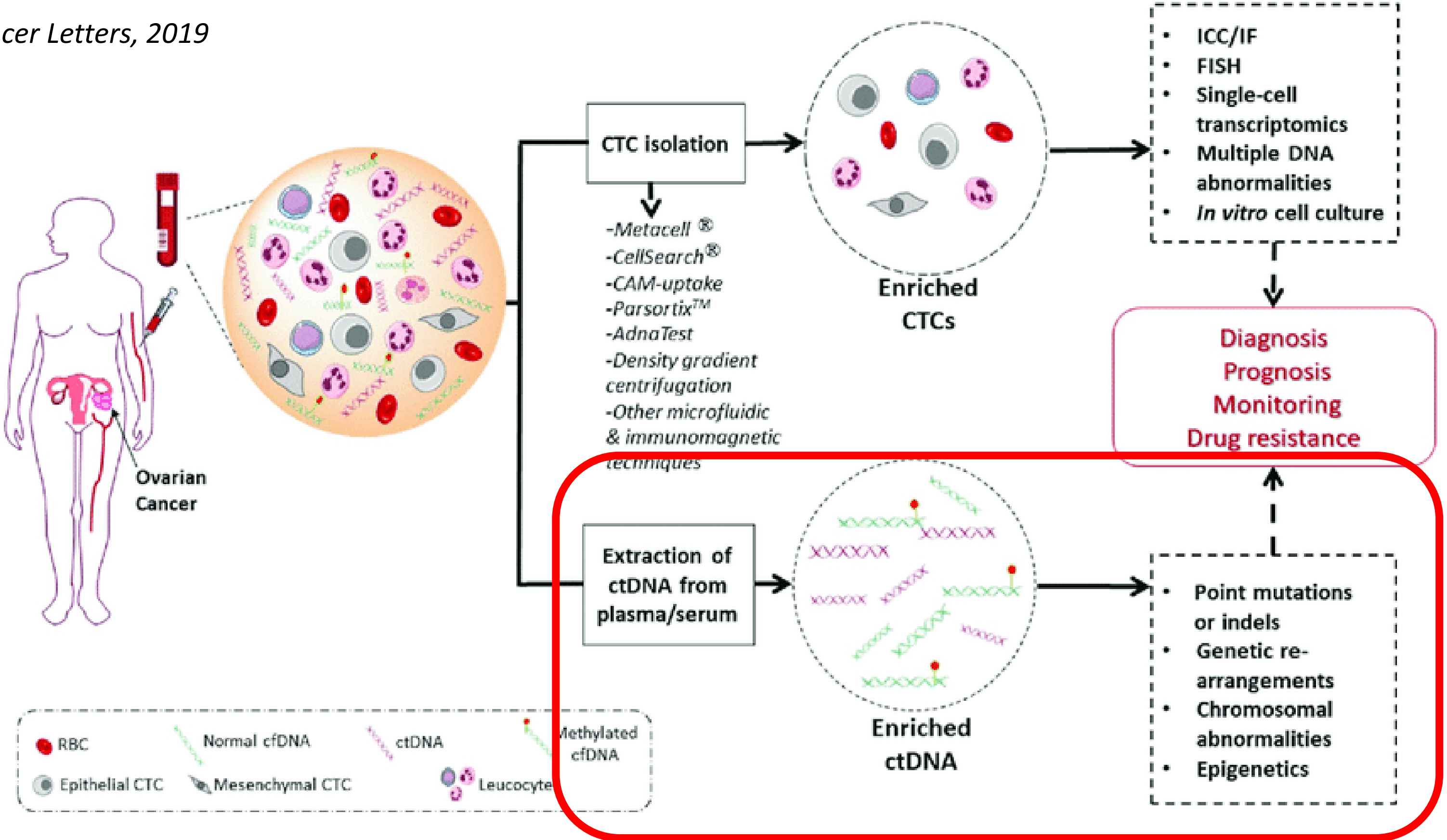


Country	No. Deaths	Haz. Ratio (95% CI)
Australia and New Zealand	34/75	0.83 (0.33, 2.12)
Canada	64/90	0.51 (0.22, 1.16)
Germany	39/42	1.00 (0.40, 2.46)
India	35/69	0.27 (0.08, 0.90)
Italy	28/103	0.56 (0.24, 1.32)
Japan	24/44	0.86 (0.34, 2.17)
South Korea	37/127	0.95 (0.47, 1.93)
The Netherlands	7/31	0.30 (0.03, 2.75)
United Kingdom	116/272	0.52 (0.31, 0.86)
United States of America	35/54	0.93 (0.37, 2.30)
Overall (I-squared = 0.0%)		0.65 (0.50, 0.85)

Cohen et al. Gynecologic Oncology 2019

Liquid Biopsy for OC

Asante et al. Cancer Letters, 2019



Ovarian Cancer

CTC isolation

- -*Metacell ®*
- -*CellSearch®*
- -*CAM-uptake*
- -*Parsortix™*
- -*AdnaTest*
- -*Density gradient centrifugation*
- -*Other microfluidic & immunomagnetic techniques*

Enriched CTCs

- ICC/IF
- FISH
- Single-cell transcriptomics
- Multiple DNA abnormalities
- *In vitro* cell culture

Diagnosis
Prognosis
Monitoring
Drug resistance

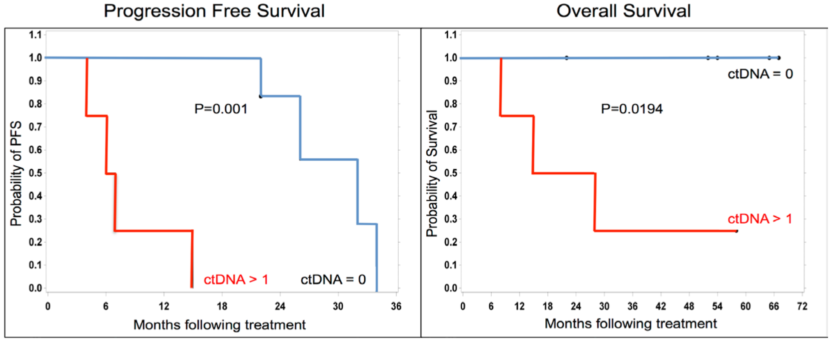
Extraction of ctDNA from plasma/serum

Enriched ctDNA

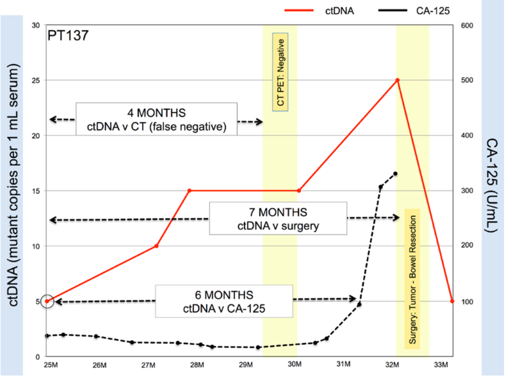
- Point mutations or indels
- Genetic re-arrangements
- Chromosomal abnormalities
- Epigenetics

Alterations in ctDNA as a Novel Biomarker for Patients with HGSOC

- ctDNA carries comprehensive information about tumour mutational profile
- Somatic mutations in *TP53* have been found in 80-100% in HGSOCs using next NGS (TCGA, 2011)
- Screening for *TP53* mutations allows ctDNA in most HGSOC patients (Park et al. 2018)
- ctDNA has been shown to be an independent predictor of survival in OC patients (Pereira et al. 2015, Parkinson et al. 2016)
- ctDNA have been shown to be a better biomarker than CA-125 in OC patients (Pereira et al. 2015 , Parkinson et al. 2016)



Pereira et al. 2015. Plos One, 10(12): e0145754

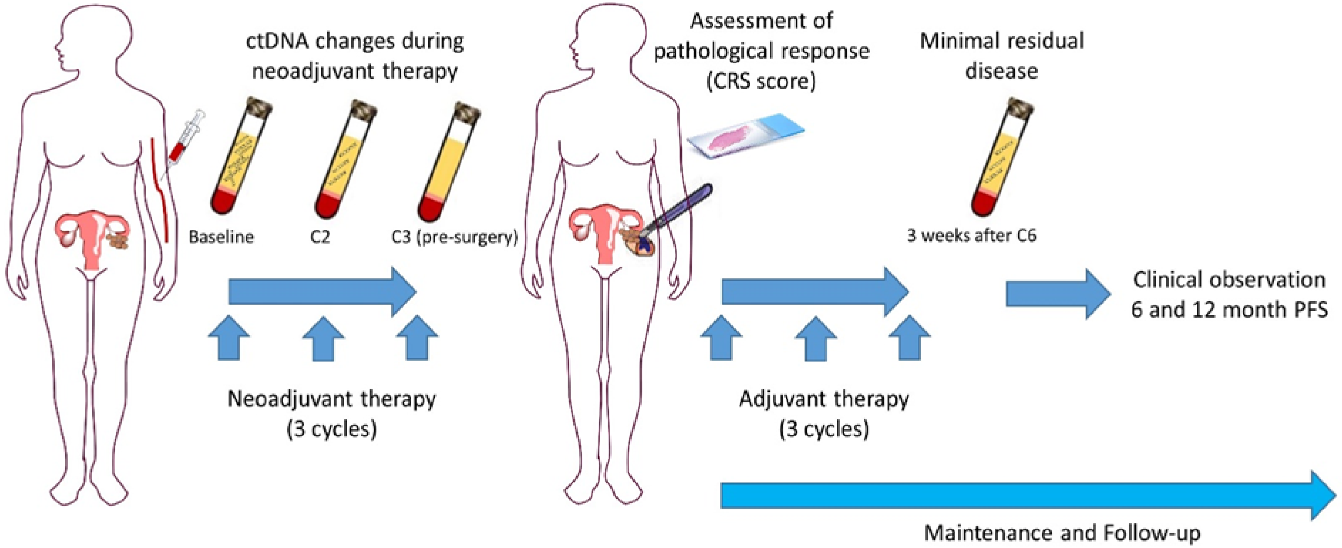


iPRIME - Immuno-chemotherapy as **PRIM**ary treatment for **E**pithelian ovarian cancer.

iPRIME : A Phase II Study of Durvalumab and Tremelimumab in combination with Neoadjuvant Carboplatin and Paclitaxel in newly diagnosed women with advanced high grade Serous Ovarian, Fallopian Tube and Peritoneal Cancers (ACTRN12618000109202).

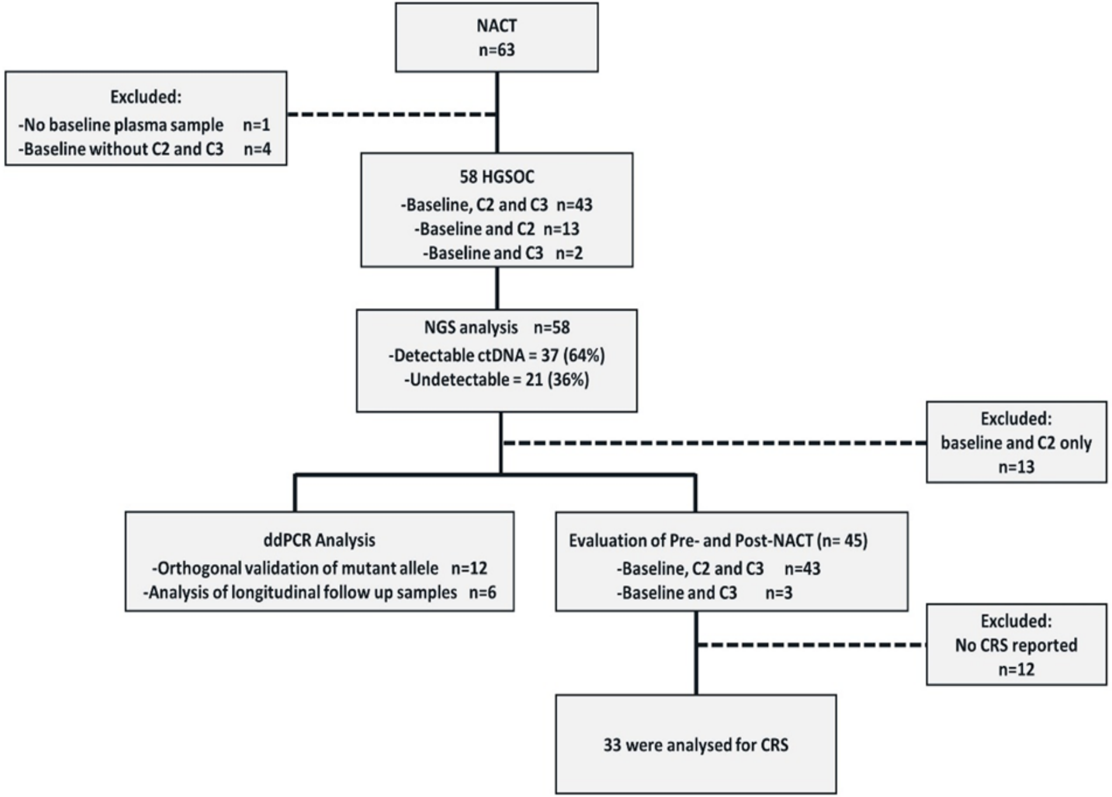
N=75

FIGO stage IIIC
or IV disease
ECOG 0-1



Hypothesis:
Decreasing ctDNA concentrations during NACT is predictive of complete response (CRS 3)

Study Cohort



NACT
n=63

Excluded:
-No baseline plasma sample n=1
-Baseline without C2 and C3 n=4

58 HGSOC
-Baseline, C2 and C3 n=43
-Baseline and C2 n=13
-Baseline and C3 n=2

NGS analysis n=58
-Detectable ctDNA = 37 (64%)
-Undetectable = 21 (36%)

Excluded:
baseline and C2 only
n=13

ddPCR Analysis
-Orthogonal validation of mutant allele n=12
-Analysis of longitudinal follow up samples n=6

Evaluation of Pre- and Post-NACT (n= 45)
-Baseline, C2 and C3 n=43
-Baseline and C3 n=3

Excluded:
No CRS reported
n=12

33 were analysed for CRS

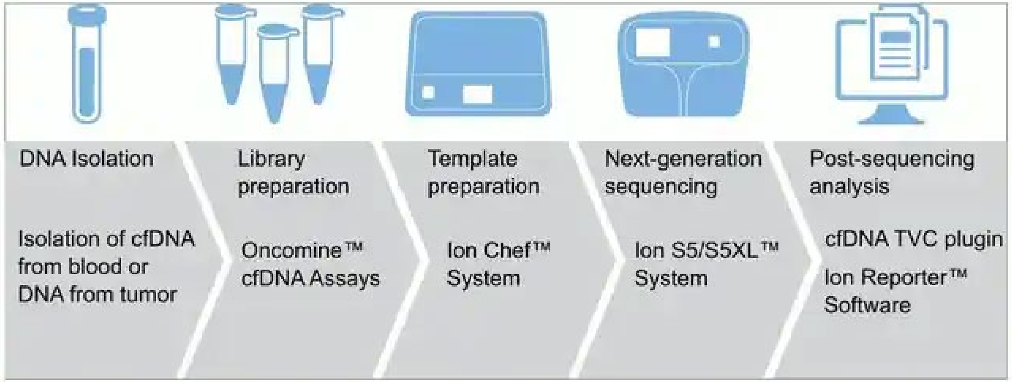
Parameter	No. of patients (%)
Number of patients	58
Median age (years)	64
Age range (years)	36 - 78
Histological subtype	
High grade serous	58 (100)
FIGO classification (stage)	
IIIC	27 (46.6)
IV	31 (53.4)
CRS grouping	
CRS1	14 (24.1)
CRS2	14 (24.1)
CRS3	5 (8.7)
NA	25 (43.1)
BRCA status	
BRCA 1/2 mutation	4 (6.9)
BRCA wild type	41 (70.7)
NA	13 (22.4)

ctDNA analysis

Oncomine™ Breast cfDNA Assay

80% TP53 exonic regions

Plasma



DNA Isolation

Isolation of cfDNA from blood or DNA from tumor

Library preparation

Oncomine™ cfDNA Assays

Template preparation

Ion Chef™ System

Next-generation sequencing

Ion S5/S5XL™ System

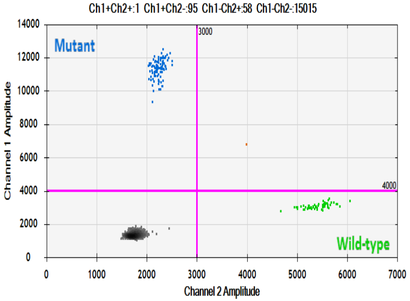
Post-sequencing analysis

cfDNA TVC plugin

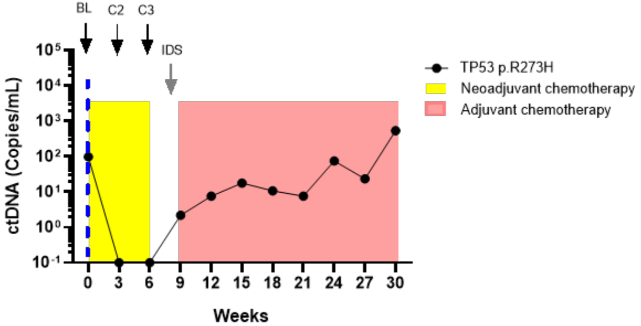
Ion Reporter™ Software

Comparison to clinical outcomes (CRS)

ddPCR

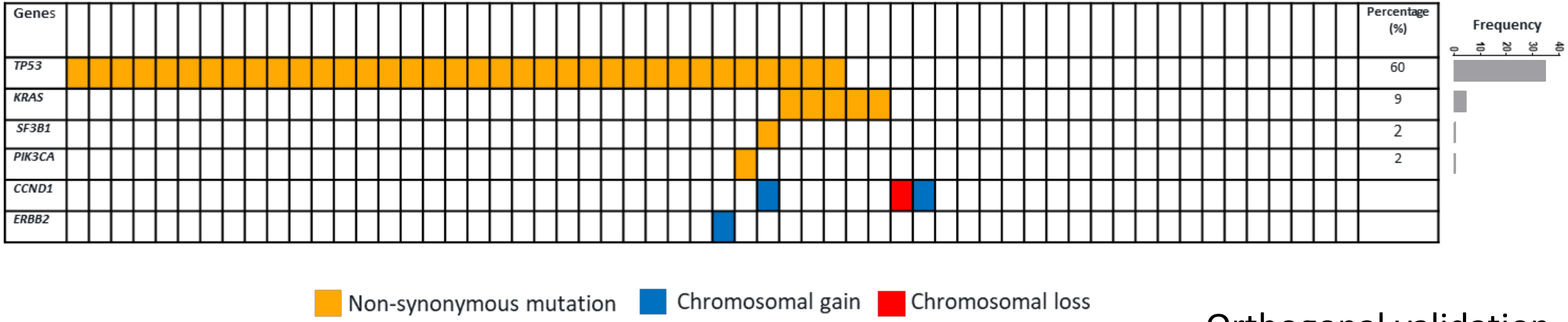


Analysis of ddPCR results

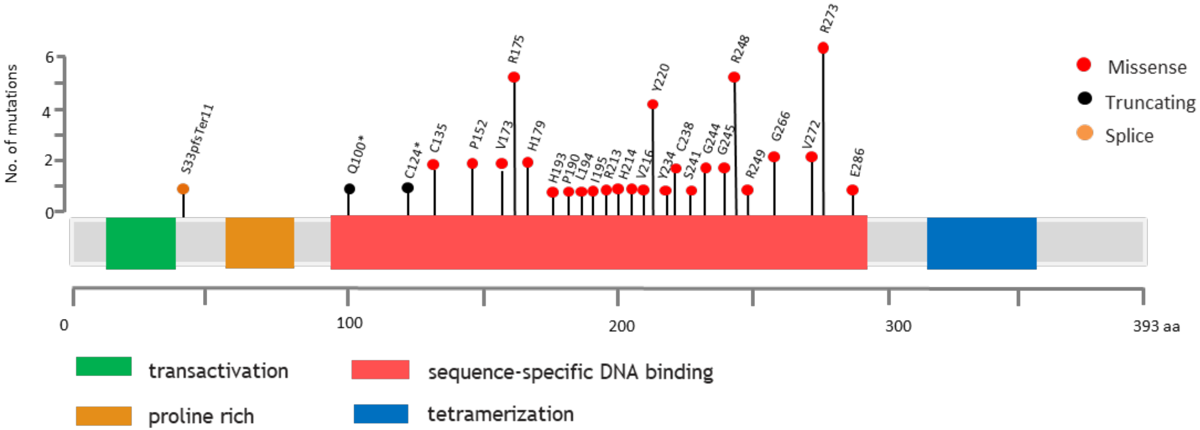


Mutations identified

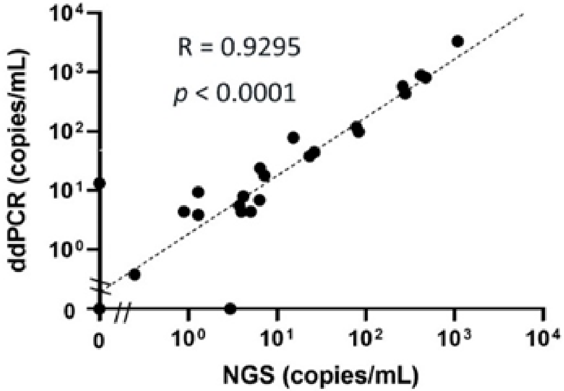
39 (65%) of patients had detectable somatic alterations



Genes	Percentage (%)
TP53	60
KRAS	9
SF3B1	2
PIK3CA	2
CCND1	
ERBB2	

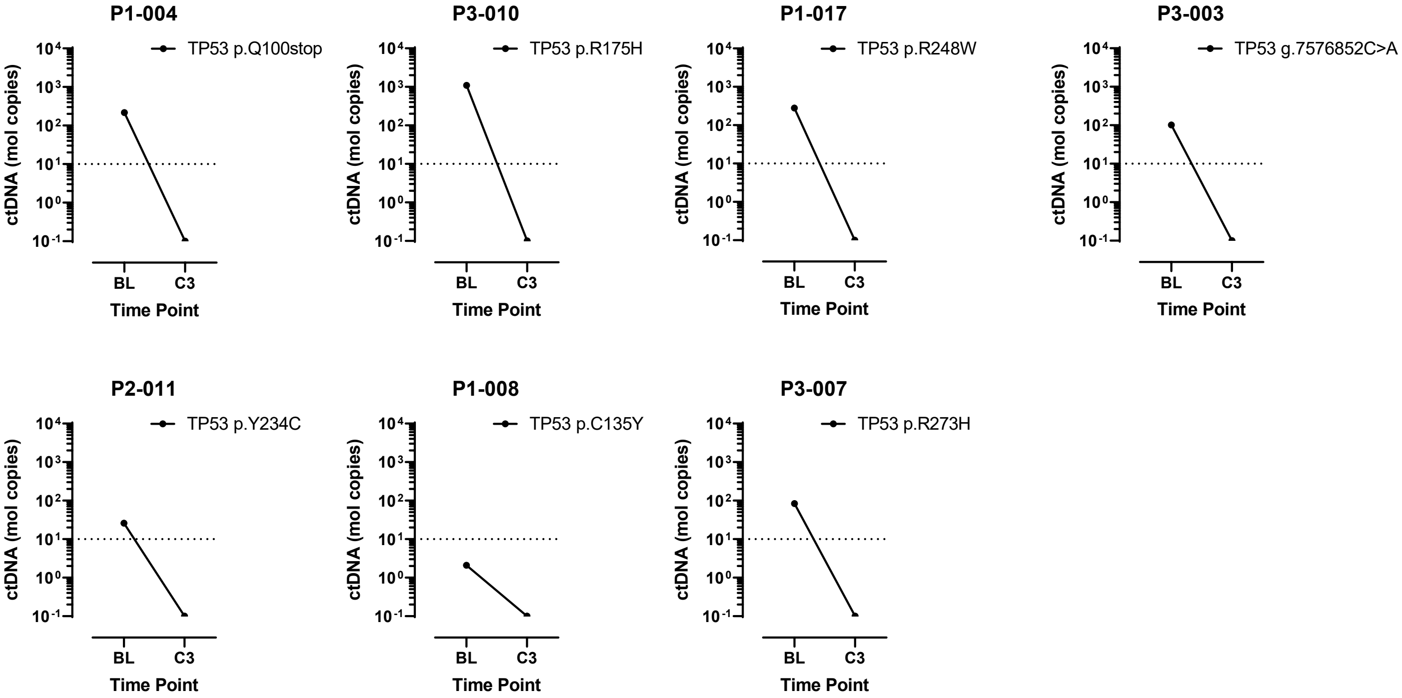


Orthogonal validation



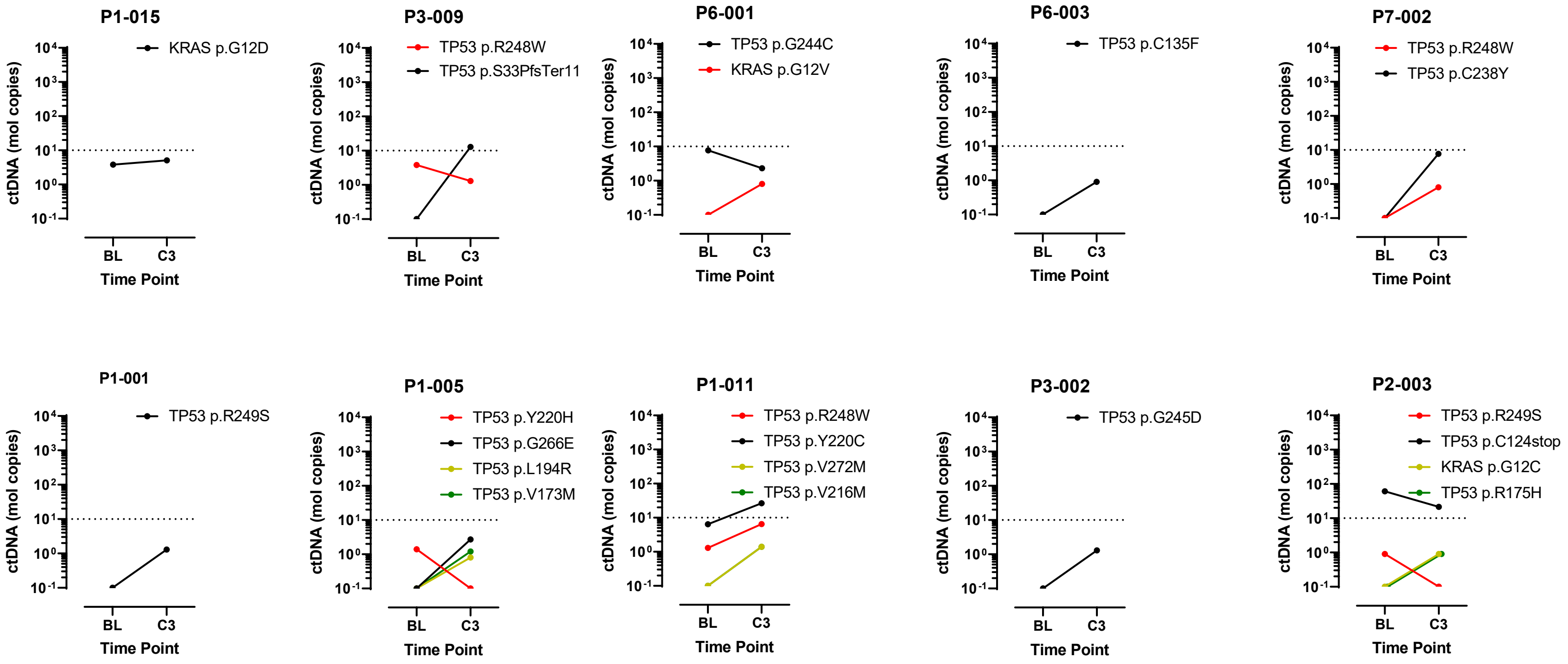
Cases with complete ctDNA response

A. Complete ctDNA response (ctCR)



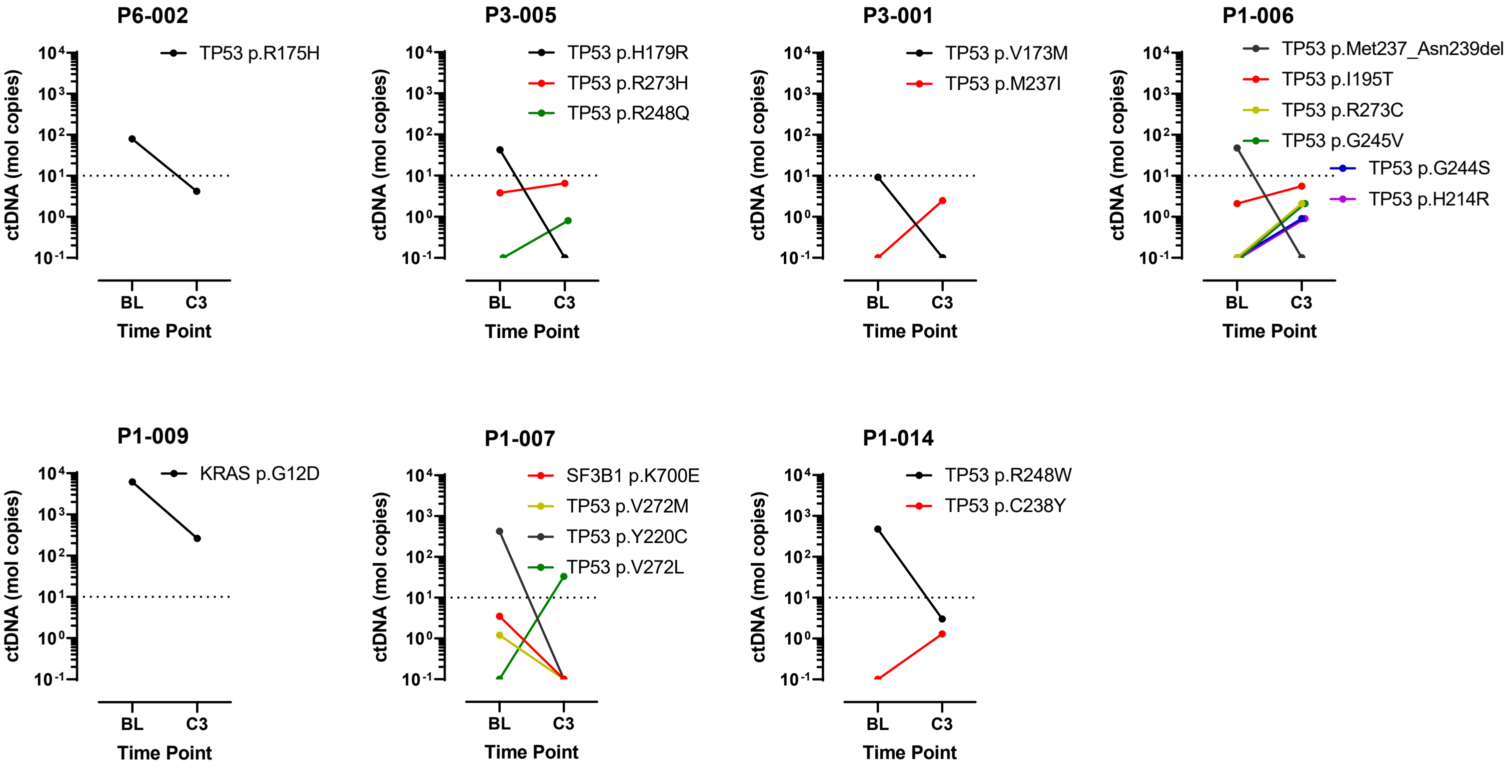
Cases with no ctDNA response

C. No ctDNA response (ctNR)

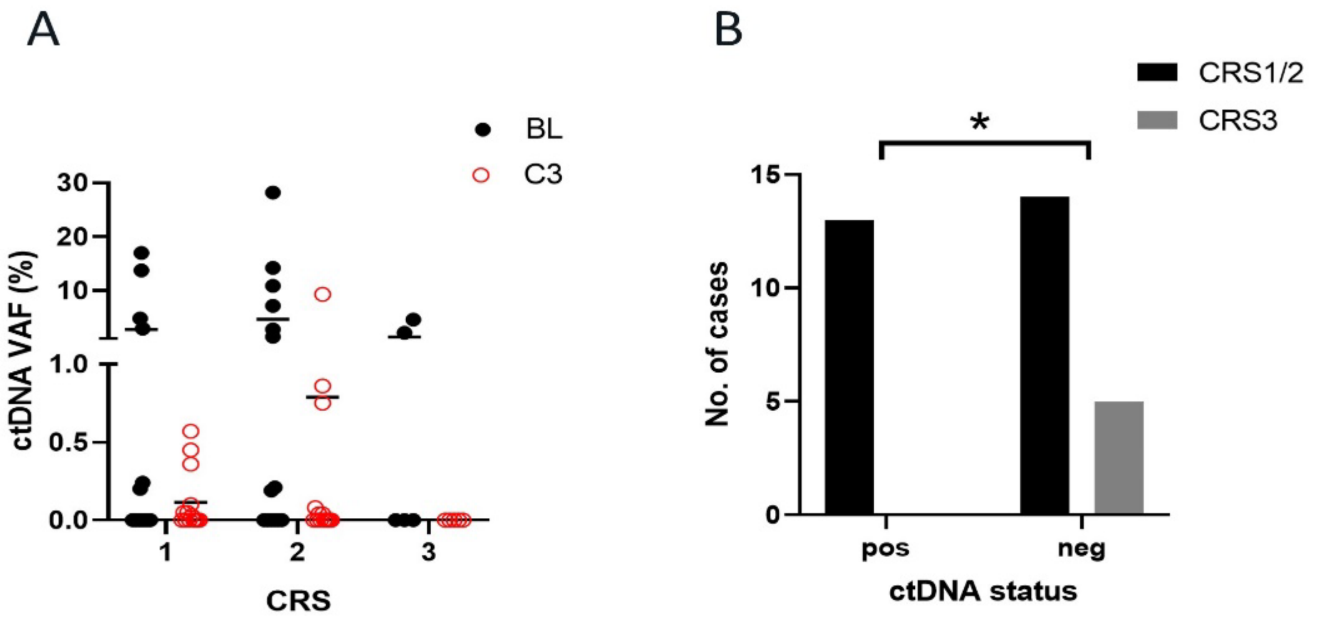


Cases with mixed or partial ctDNA response

B. Partial ctDNA response (ctPR)

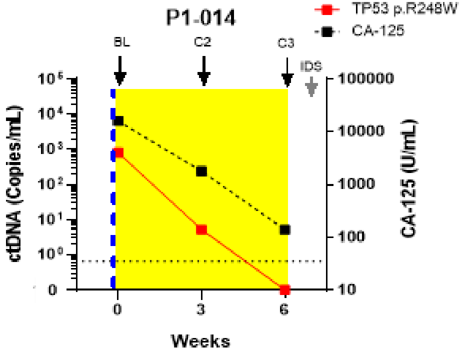


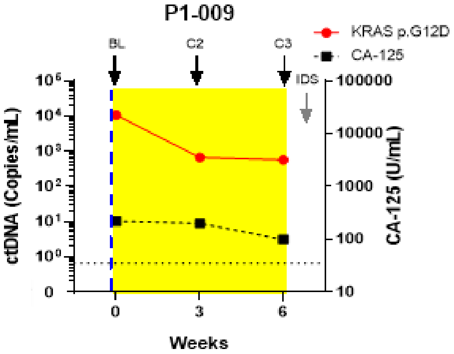
Comparison of change in ctDNA VAF and CRS (N=33)

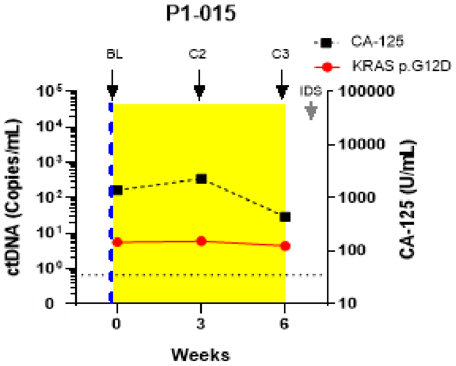


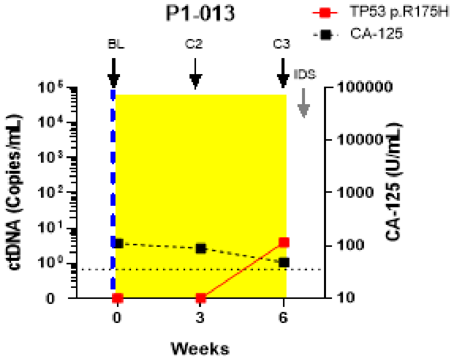
All cases with CRS3 were ctDNA negative at last time point prior surgery (CRS3)

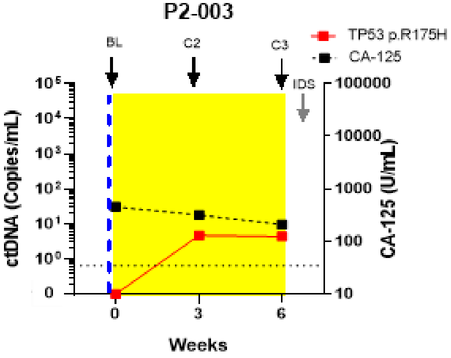
ctDNA and CA-125 during NACT

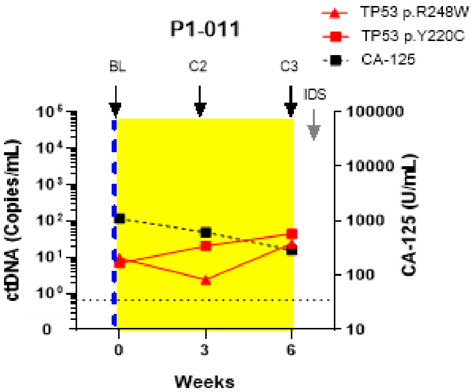




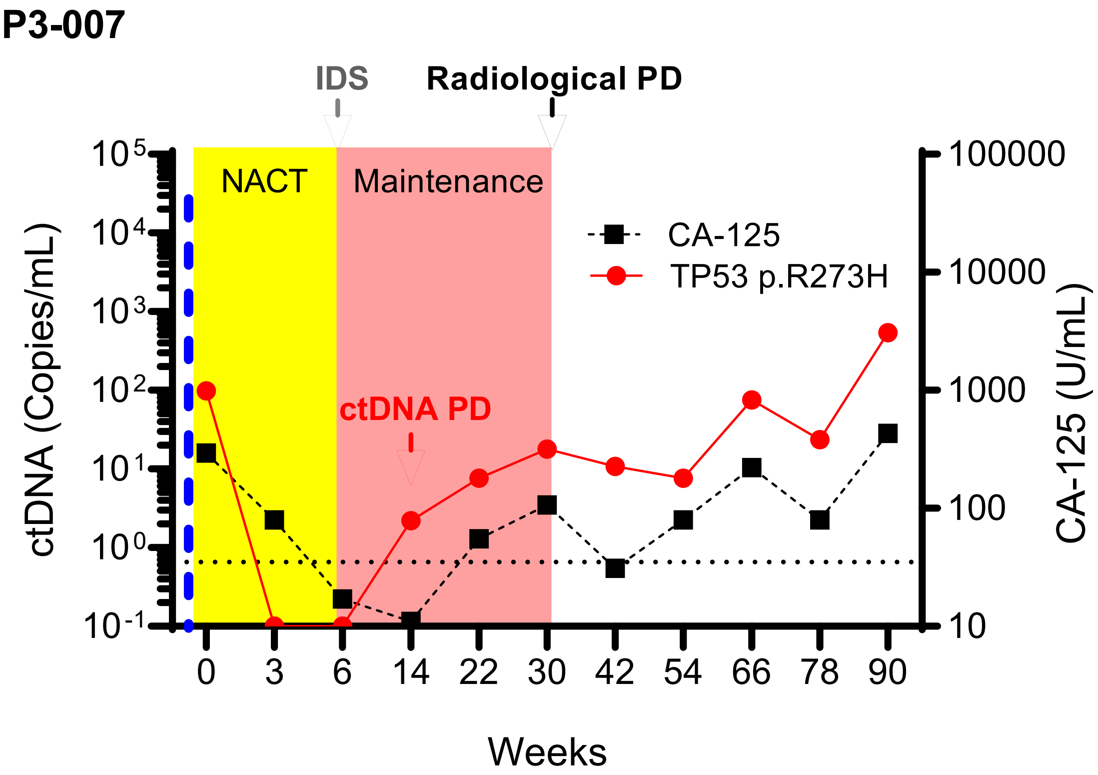




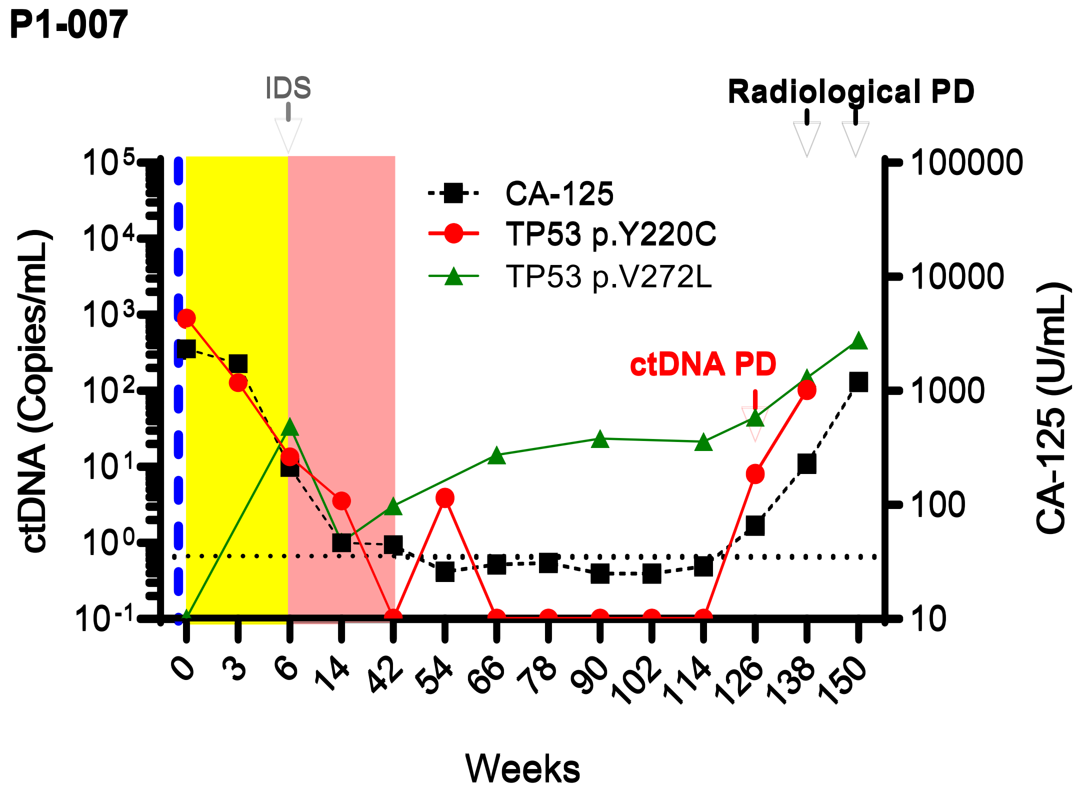




Longitudinal follow up (Case study 1)



Longitudinal follow up (Case study 2)



Conclusions

- 88% of patients with positive ctDNA harbored *TP53* mutations
- NGS enabled detection of evolving genomic alterations
- ctDNA clearance may be a predictor of response to NACT, defined as CRS3
- ctDNA increase preceded CA-125 and predicted disease progression
- Personalized monitoring of ctDNA in HGSOC may aid real-time assessment of treatment response.

Acknowledgements

ECU team

Dubois Asante
Aaron Beasley
Leslie Calapre

ANZ GOG

Cancer Council Western Australia

ThermoFisher SCIENTIFIC

iPRIME study team

PI: Dr Tarek Meniawy

Study Participants

THANK YOU!