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ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS

AstraZeneca

A phase IIIb-IV trial testing **Ol**aparib and bev**a**cizumab in the fro**n**tline **T**reatment of ovarian carcinoma with results analysed according to an academic **H**RD t**e**st (**iOlanTHe trial**).

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September 21st, 2020

EMA recommends the approval of Olaparib/Bevacizumab combo for frontline maintenance in HRD + advanced ovarian cancer on the basis of results of PAOLA-1 trial.

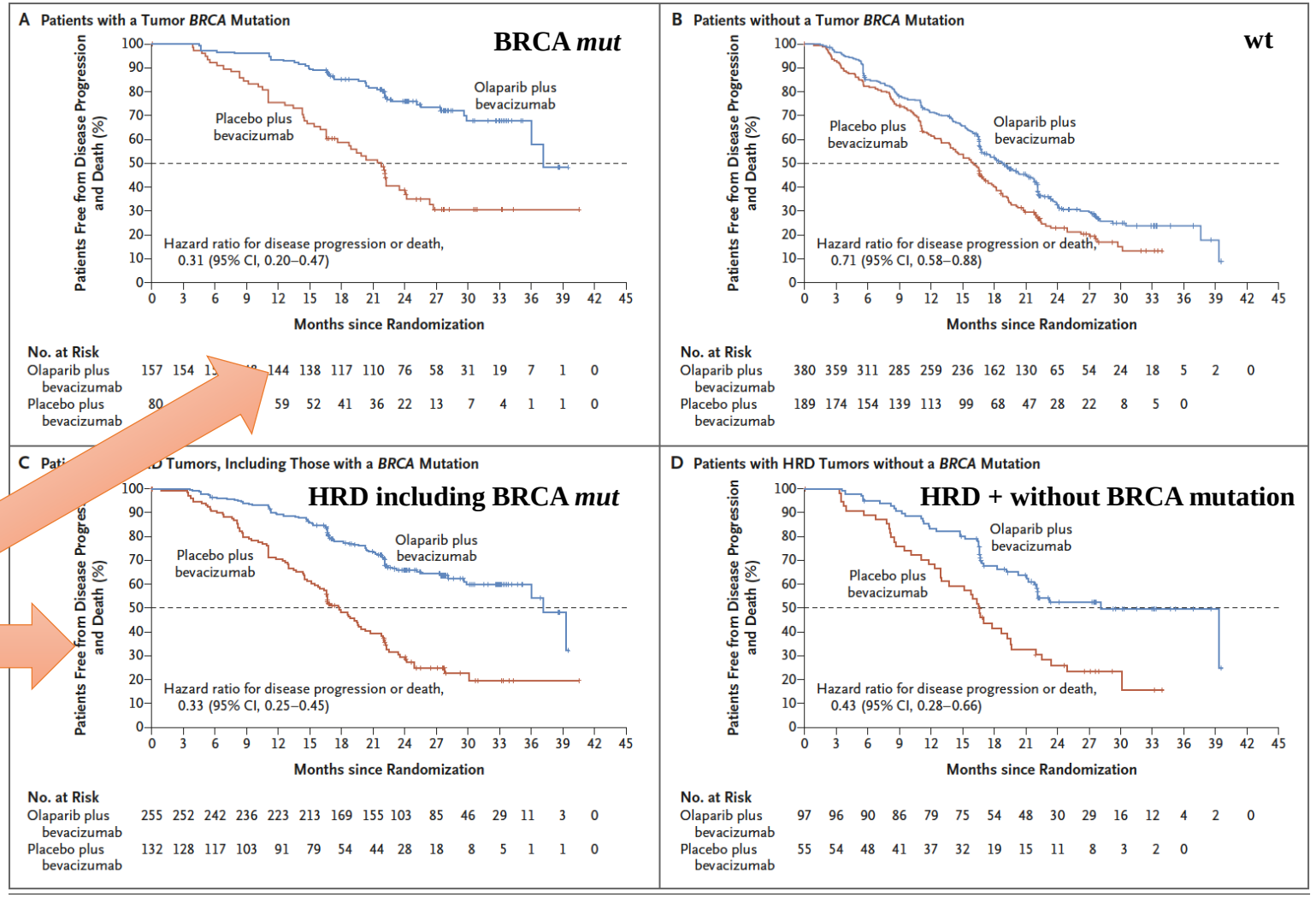
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer

I. Ray-Coquard, P. Pautier, S. Pignata, D. Pérol, A. González-Martín, R. Berger, K. Fujiwara, I. Vergote, N. Colombo, J. Mäenpää, F. Selle, J. Sehouli, D. Lorusso, E.M. Guerra Alía, A. Reinthaller, S. Nagao, C. Lefeuvre-Plesse, U. Canzler, G. Scambia, A. Lortholary, F. Marmé, P. Combe, N. de Gregorio, M. Rodrigues, P. Buderath, C. Dubot, A. Burges, B. You, E. Pujade-Lauraine, and P. Harter, for the PAOLA-1 Investigators*

Whole population: PFS = 22.1 months with combo vs 16.6 months with Beva + placebo (HR 0.59 P<0.001)



In patients with advanced ovarian cancer receiving first-line standard therapy including bevacizumab, the addition of maintenance olaparib provided a significant progression-free survival benefit, which was substantial in patients with HRD-positive tumors, including those without a BRCA mutation.

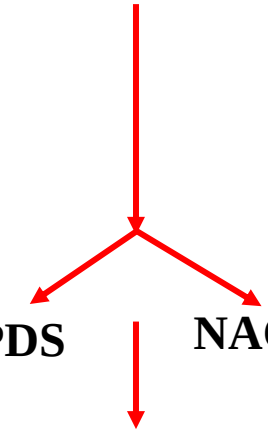
the «real life» protocol

The primary aims of this study are:

1) to confirm **the efficacy of the combination** of bevacizumab and olaparib maintenance after first line, in terms of progression free-survival (PFS). PFS will be defined as the time from start of Olaparib therapy until disease progression or death whichever comes first.
2) 2) **to describe demographical and clinical characteristics of patients who will be treated with Bevacizumab and Olaparib as maintenance at first line in a real life setting**.

Secondary objectives will be: 1) **to validate the in house-developed HRD-score** (Homologous Recombination Deficiency score) considering the Myriad Mychoice as gold standard. 2) **to describe the compliance to the combination** of Olaparib and Bevacizumab in terms of treatment modifications and number of cycle received, 3) **to describe the safety profile of the combination** and 4) **efficacy in terms of progression free survival 2** (defined as the time from starting Olaparib to the second progression or death whichever comes first).

~ 400 patients with histologically confirmed OC



PDS

NACT + IDS

HRD test

Chemiotherapy (+/- bevacizumab)

~ 170 pts eligible* for Olaparib/Bevacizumab combined regimen regardless BRCA1-2/HRD mutational status

Translational study I on liquid biopsy in the subgroup HGSOC: ~100 pts

Translational study II in the subgroup treated with the combination on organotypic models:

30 pts with NACT

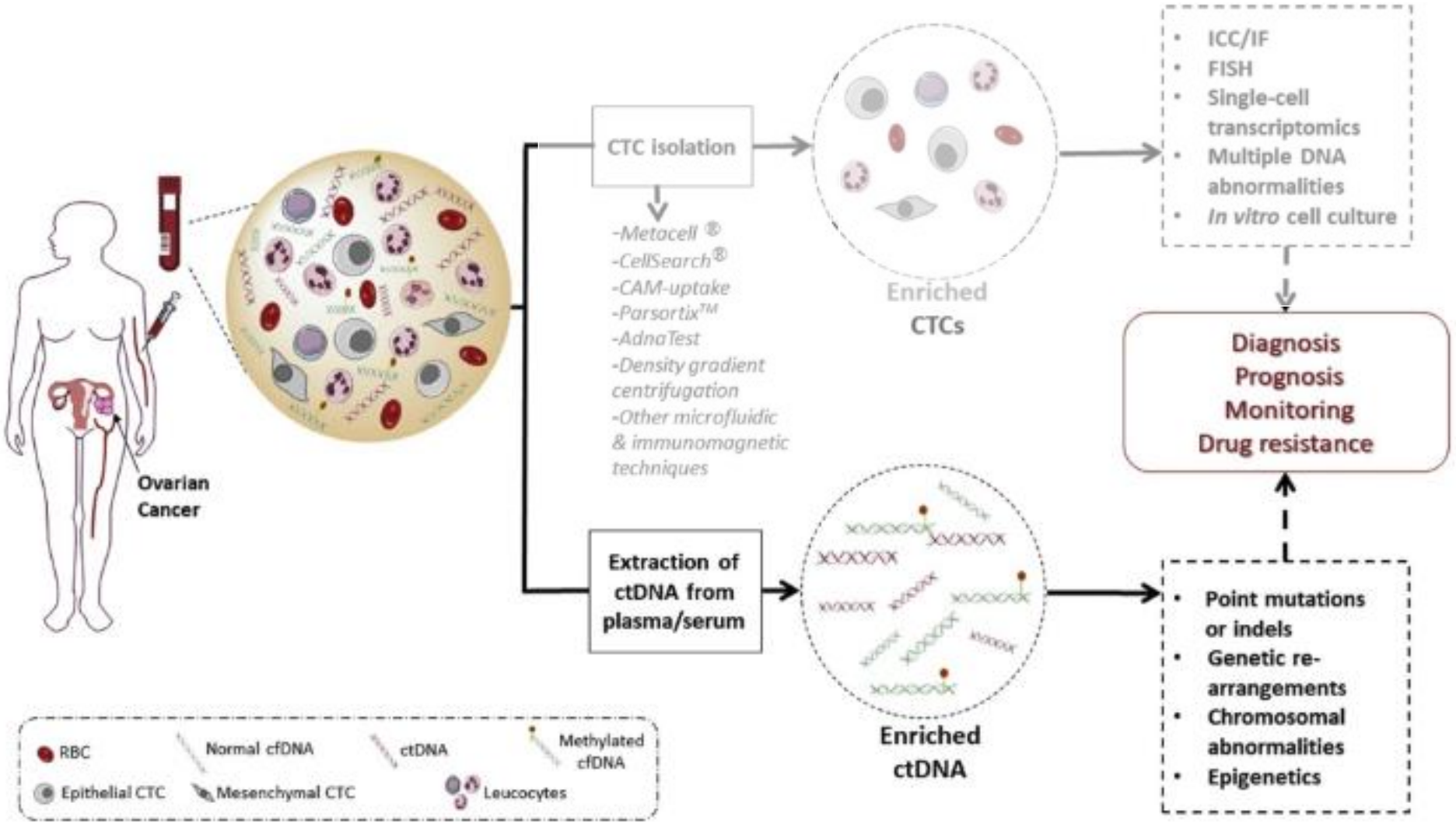
Olaparib tablets at 300 mg twice daily and Bevacizumab at a dose of 15 mg per kilogram of body weight every 3 weeks.

Study duration: 12 months of accrual and 24 of follow-up

***Eligibility criteria for Ola+beva**

- Patient with newly diagnosed ovarian cancer, primary peritoneal cancer and/or fallopian-tube cancer
- Histologically confirmed high grade serous or high grade endometrioid or other epithelial non mucinous ovarian cancer at an advanced stage **regardless the BRCA1-2 mutational status**
- **minimum of 3 cycles of bevacizumab in combination with the 3 last cycles of platinum-based chemotherapy**. Only in case of IDS it is allowed to realize only 2 cycles of bevacizumab in combination with the last 3 cycles of platinium-based chemotherapy.

Liquid biopsy in OC



D.B Asantes, Cancer Lett 2020

Objectives of «translational» sub-studies

Translational study I aims

the analysis of circulating free DNA (cfDNA) by Next Generation Sequencing (NGS) is aimed at:

1) investigating the mutational status of HR-related genes at time of diagnosis on primary lesions,
2) investigating the association between residual tumour and circulating-tumour DNA (ctDNA) levels,
3) monitoring the recurrence of disease analysing the presence of clonal events associated to disease, i.e. TP53 mutation or 8q24 and 3q26 amplifications (20)
4) monitor the mutational status of HR-related genes and other genes (Tp53BP1, POLQ, REV7)- known to contribute to resistance to PARP inhibitors- during the treatment.

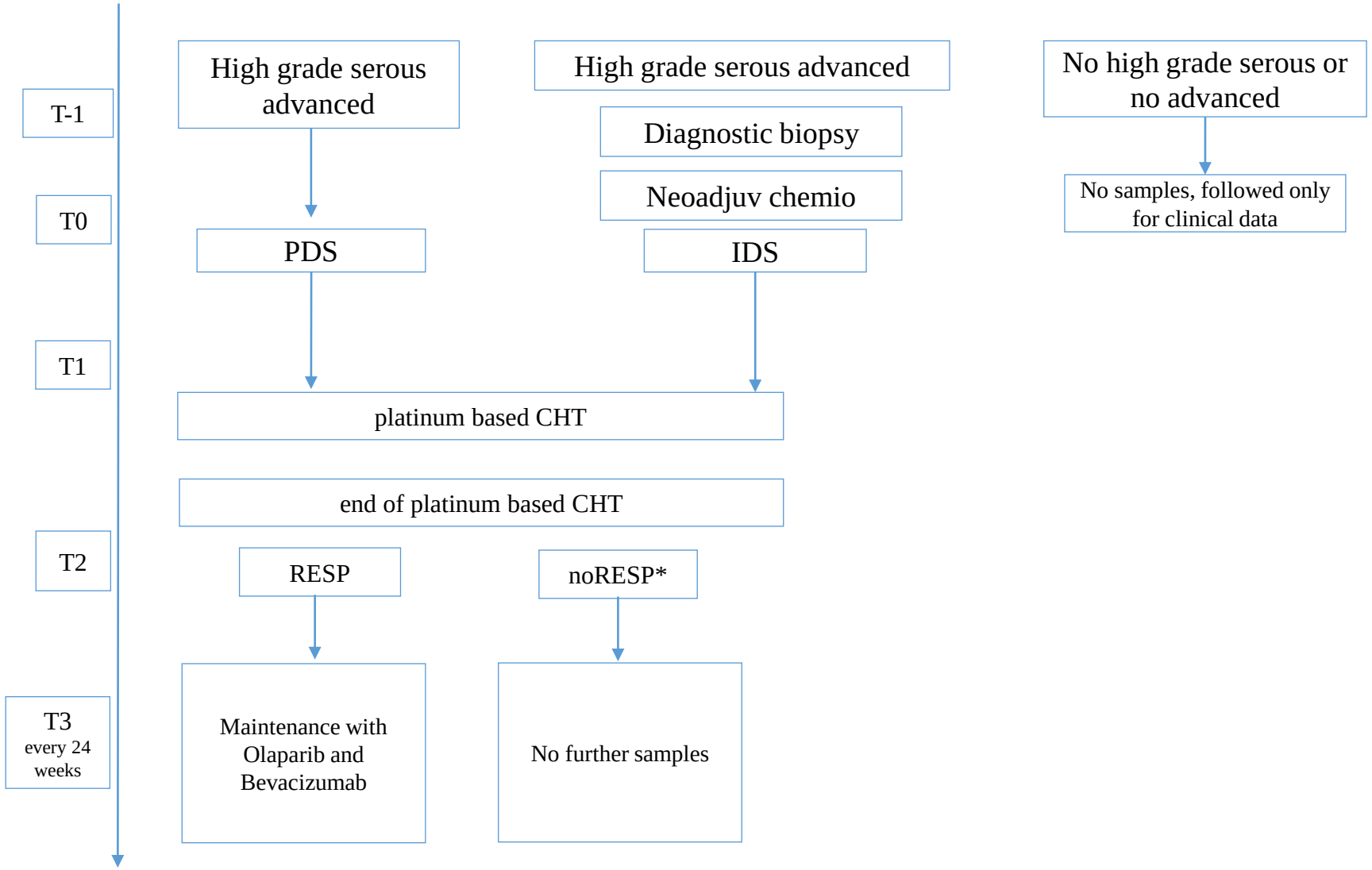
Translational study I design

DNA will be extracted and purified from blood cells (gDNA), biopsies (tumor DNA, tDNA) and plasma (cfDNA), and sequenced by low-pass whole-genome sequencing (KAPA Hyper plus, Roche) with Nextseq-500 Ilumina.
This in order to
-calculate the copy number burden (CNB) of the cfDNA and of tDNA
-calculate the tumor fraction in cfDNA and
-evaluate the presence of clonal 8q24 and 3q26 amplifications.

cfDNA whole-genome libraries generated, will be exploited to perform a targeted sequencing (Capture Seq, Roche) using a custom capture sequencing panel composed by 65 genes including TP53 and HR-related genes.

tDNA will be also exploited to perform whole exome sequencing experiments, to calculate the HRD-score based on the evaluation of three main genomic scars related to HR deficiency, i.e. Loss Of Heterozygosity (LOH), Telomeric Allelic Imbalance (TAI) and the Large Scale Transitions (LSTs).

Flow-chart on tissue and blood/plasma samples for translational study 1

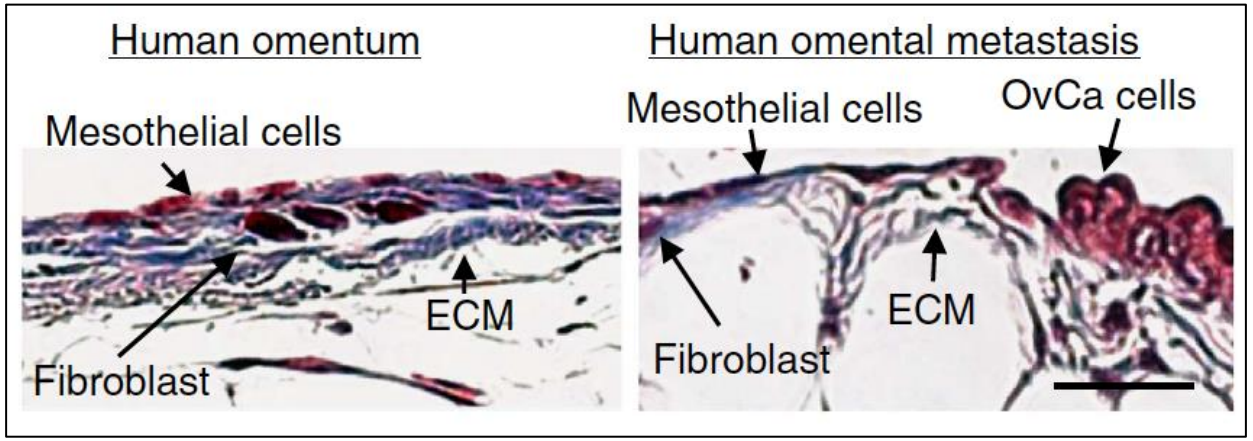


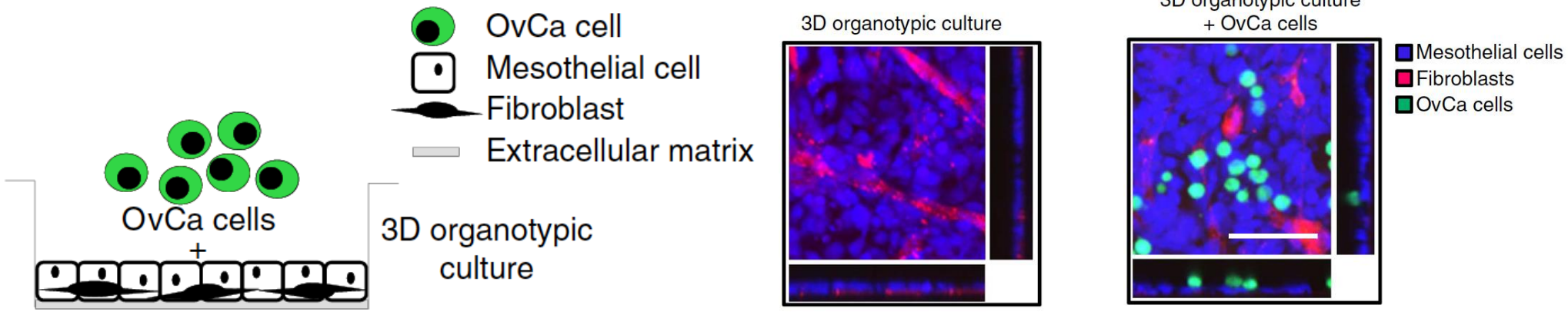
T -1 (only for IDS patients, before neo-chemo): tissue, blood and plasma;
T0 (before surgery): tissue, blood and plasma;
T1(after surgery-before chemo): plasma;
T2 (end of chemo): plasma;
T3 (until PD - max 5 years from last Pt): plasma;

Targeted custom capture panel	
ARID1A	RAD51D
ATM	RAD54L
ATR	SHFM1
BARD1	TP53
BRCA1	XRCC2
BRCA2	XRCC3
BRIP1	IL-12
CHEK1	BABAM1
CHEK2	BLM
FANCA	BRCC3
FANCB	EME1
FANCC	EME2
FANCD2	EXO1
FANCE	FAM175A
FANCF	GEN1
FANCG	H2AFX
FANCI	MDC1
MLH1	MRE11A
MLH3	NBN
MSH2	RAD51AP1
MSH3	RAD51B
MSH6	RAD52
MUS81	RAD544
NBN	RBBP8
PALB2	REV1
PMS1	RPA1
PMS2	RPA2
POLD1	RTEL1
POLE	SLX1A
RAD50	SLX1B
RAD51	SLX4
RAD51C	TP53BP1
UIMCI	POLQ
CDK12	REV7

Primary human 3D organotypic culture

(*avatar*)





Rebuild ovarian cancer TME architecture *in vitro*

Objectives of «translational» sub-studies

Translational study II aims

The organotypic models are aiming to:

- to compare patients' response to therapy (measured as best response during Olaparib or Olaparib plus Bevacizumab treatment) with that of cancer cells (either stem or bulk), derived from the same patient, and treated with the combination in the matched organotypic model (measured as percentage of dead cells respect to the total number of cells).

Translational study II design

The following samples will be archived at the time of surgery (T0) for the organotypic model generation:

1. Fresh tumor tissue for the isolation of primary tumor cells.
2. Ascitic fluid for the isolation of primary tumour cells.
3. Macroscopically healthy omentum for the isolation of primary mesothelial cells and fibroblasts

Due to the proof-of-concept nature of the translational study 2, the organotypic model will be reconstructed for a subgroup of patients enrolled by the coordinating centre, who has underwent Interval Debulking Surgery (IDS) upon NACT and treated with experimental strategy.