GCIG Translational Committee

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University of Glasgow | Institute of Cancer Sciences

the Beatson institute for cancer research

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Delia Mezzanzanica (MITO) - Update on MaNGO/MITO16 translational research

- Randomised trial of chemo +/- bev in platinum-sensitive relapse in patients with prior bev exposure
- Multiple blood samples for translational research
- Access to archival FFPE tumour material

- Multiple translational hypotheses, including CEC, CEP and CTCs

MITO-16/MaNGO Ov2: trials

1) First line observational study with traslational end points (only in Italy)

400 patients planned:
Chemo-naive
Stage III-IV
OC, PP or FT cancer

→

GOG 218 protocol: 6 cycles CBDCA+Paclitaxel + Bevacizumab followed by Bevacizumab for 15 months

→

END POINTS
- Biological markers
- Clinical prognostic factors

PHASE IV prospective study of first-line bevacizumab plus chemotherapy in advanced ovarian cancer patients (IIIB-IV) with translational objectives and conducted only in Italy

2) Second line randomized phase III trial in platinum sensitive patients

400 patients to be recruited with sensitive ovarian cancer progressing after first line carbo-tax+Bevacizumab

→

Carbo+PLD or Carbo+Gem or Carbo+ Pacl

Carbo+PLD or Carbo+Gem or Carbo+ Pacl + Bevacizumab until progression

→

END POINTS
- Primary: PFS
- Secondary: OS, translational

PHASE III randomised controlled trial on the efficacy of the addition of bevacizumab to second line chemotherapy following first-line treatment including bevacizumab in platinum-sensitive advanced ovarian cancer patients. To be conducted internationally.

***Bevacizumab will be provided by Roche ltd**

MaNGO
Mario Negri Gynecologic Oncology

Timing of the Samples

Sample type	Baseline	Chemotherapy Completion	PD
10 ml blood for plasma	X	X	X
5 ml blood for CEC/CEP	X	X	X
5 ml blood for DNA analyses	X		
Archival tissue	X*	at any subsequent surgical operation, if possible	

Archivial tissue: collection will be centralized at the NCI Pascale Naples with a continuous update of patient follow up.
FFPE tissues will be used forTMA preparation and nucleic acids extraction.

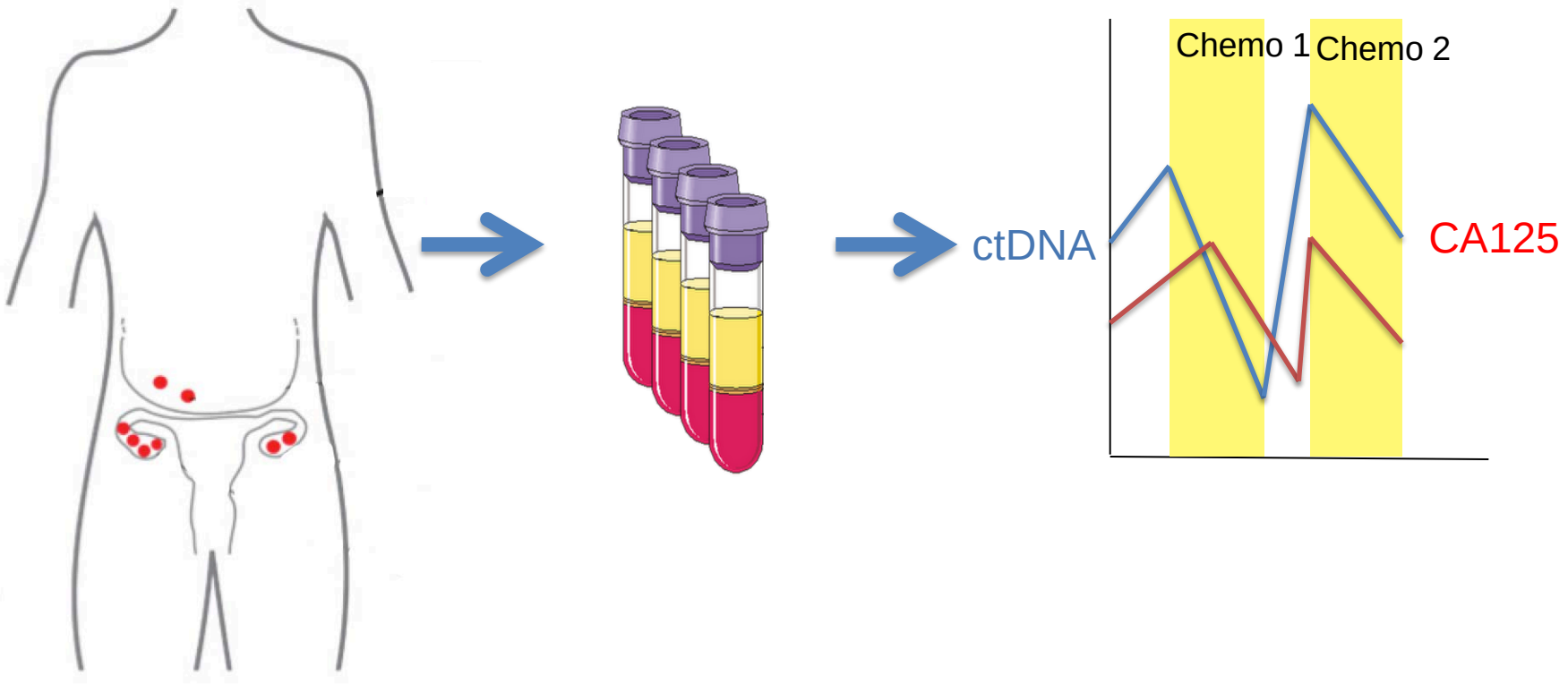
Blood and plasma: blood samples centralized at the IEO Milan, serum samples centralized at the Mario Negri Institute, Milan.

The MITO 16/MANGO OV2 project: translational project

Tissue Biomarkers	
ALCAM[63,64]	ADAM17/TACE[64]
VEGFR1-2	EphA/EphAR[65]
EphB/EphBR[65]	HOXB3/HOXD3 [66,67]
TRAP1[68-70]	HSP90[70]
GRP78/Bip[69]	CHOP[69,70]
MCT1/MCT4	GLUT-1
LDH-4	LKB1
pACC	pAMK
CD31	Endothelin 1-3 (ET-1)
Endothelin Receptor A-B	ET converting Enzymes 1 e 2 (ECE1-2)
Plasma/Serum Biomarkers	
sALCAM[71]	IL-18[71]
VEGFA-B-C	Thymidine Phosphorylase (TP)
Thymidialte Synthase (TS)	Dihydropyrimidine dehydrogenase (DPD) [72]
PlGF	sVEGFR1-2-3
Thrombospondin-1 [73]	MMP-2/MMP-9 [74] [75]
TIMP-1/TMP-2 [74] [75]	PDGF
FGF	SDF-1
IL6-8	Circulating Endothelial Cells/Progenitors (CEC/CEP) [76]
Endostatin	PAI-1
Axl	miRNAs

Delia Mezzanzanica (MITO)

ctDNA in Advanced Ovarian Cancer – Study Design



N=41

324 plasma samples

54 episodes (‘lines’) of chemo

Christine Parkinson

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Christine Parkinson (SGCTG) - Circulating cell-free DNA as a biomarker in ovarian cancer

- 90% patients with relapsed HGSOC have circulating free tumour DNA
- Can be identified via *TP53* mutations
- Potential use as response marker – wider dynamic range than CA125
- ? Also use as marker of novel mutations/genetic heterogeneity

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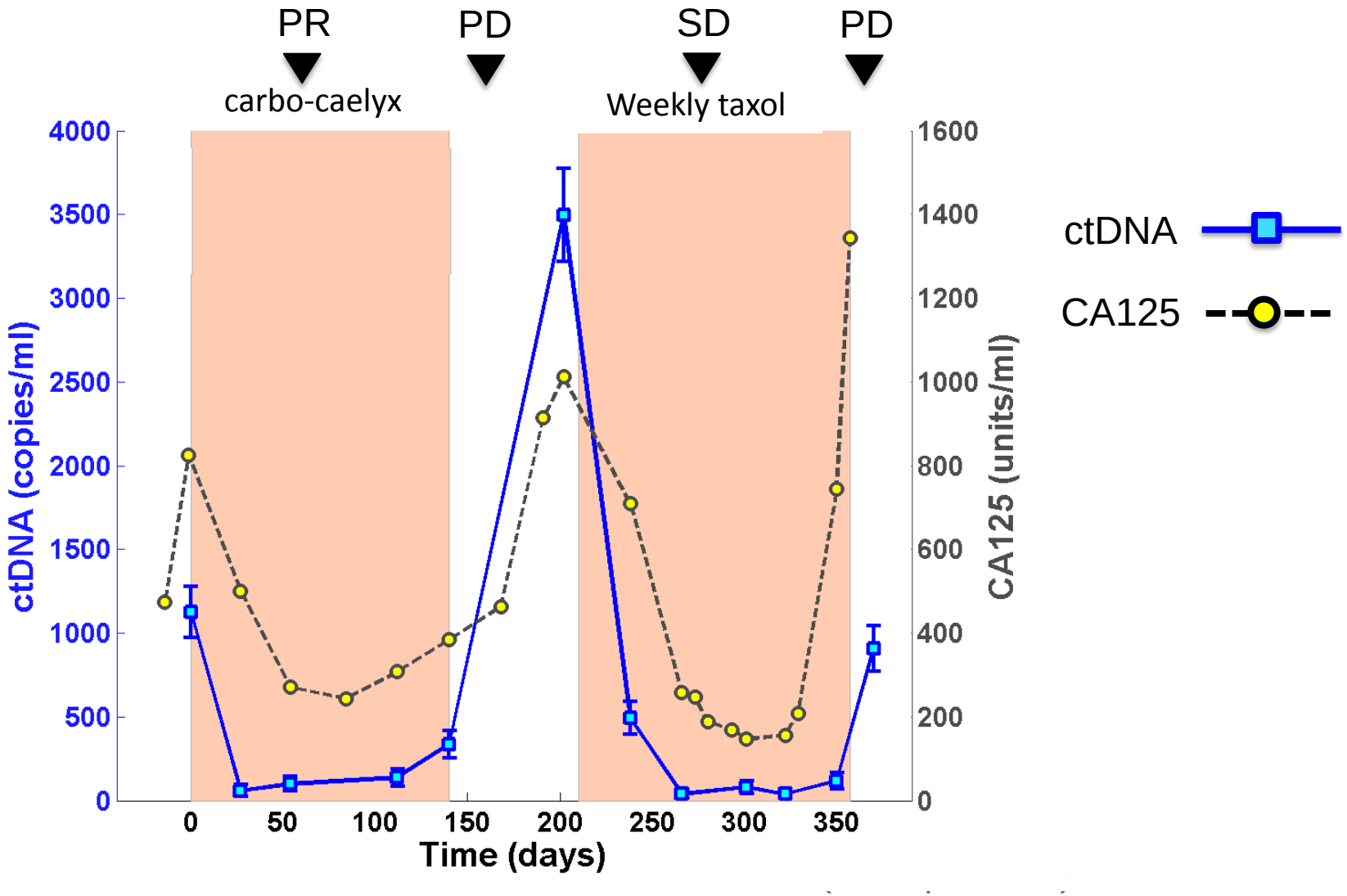
Kinetic patterns of ctDNA levels have the same trends as clinical progression and CA125 levels



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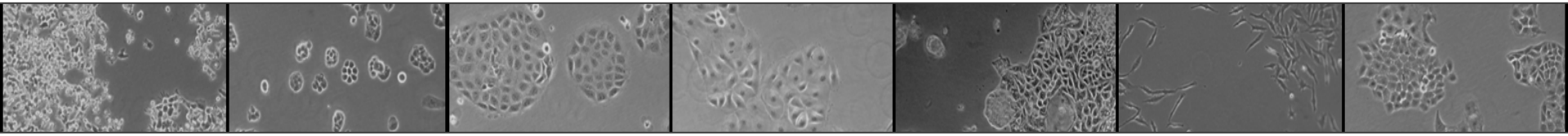
Jozien Helleman (DGOG) - Characterising ovarian cancer cell lines – are they fit for purpose for translational research?

- Multiple analyses on established ovarian cancer cells – morphology, gene expression profiling, miRNA expression, exon sequencing, MSI analysis, chemotherapy sensitivity
- Little correlation between established cell lines and ovarian subtype morphology
- Care to be taken when alloting subtypes to individual cell types

Ovarian cancer cell line panel

- Morphological and growth properties
- mRNA expression (Affymetrix Human Exon 1.0 ST)
- MicroRNA expression (Appl.Biosystems, TaqMan microRNA ArraySet)
- Mutation analysis (SNAPshot analysis, PI3K/Ras genes / Exon sequencing)
- Microsatellite instability status (Promega, MSI Analysis system)
- Membrane expression of proteins (FACS analysis)
- Response curves for eight chemotherapeutics used in first- and second-line treatment (MTT assay)



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Ros Glasspool (SGCTG) - NiCCC – Nindetanib in Clear Cell Carcinoma: proposals for translational research

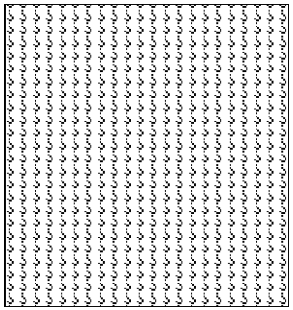
- Clear cell is obviously different from HGSOC
- Need for translational CCC-specific trials
- Randomised European trial of BIBF1120 vs chemo in relapsed CCC
- Discussion of potential therapeutic targets and biomarkers.

Nintedanib in **C**lear **C**ell **C**ancer

A Randomised Phase II Study of Nintedanib versus Chemotherapy in Recurrent Clear Cell Carcinoma of the Ovary or Endometrium

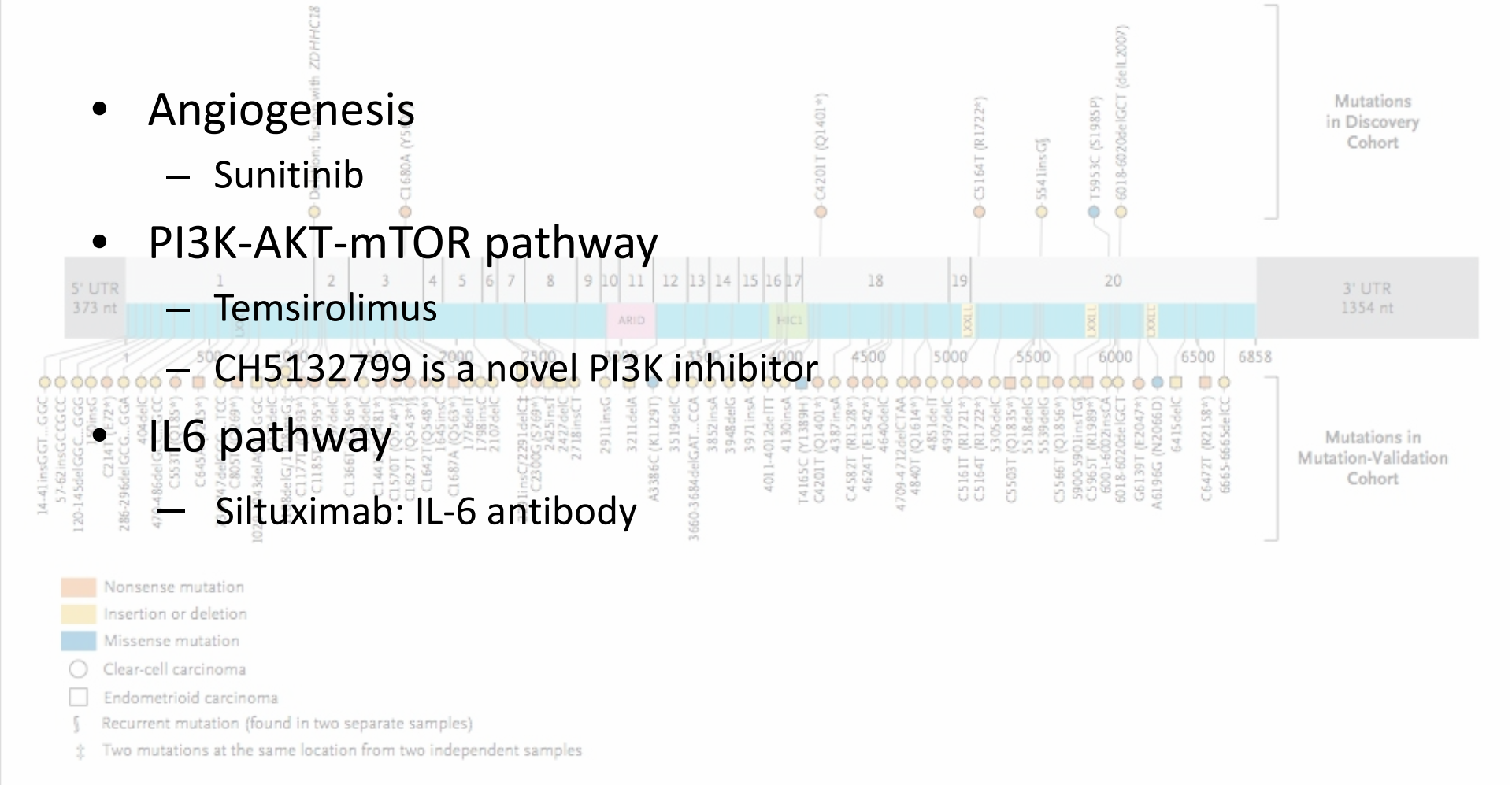
SGCTG/NCRI/NSGO

EORTC/GINECO



Potential CCC targets and biomarkers

- Angiogenesis
  - Sunitinib
- PI3K-AKT-mTOR pathway
  - Temsirolimus
  - CH5132799 is a novel PI3K inhibitor
- IL6 pathway
  - Siltuximab: IL-6 antibody



Ros Glasspool (SGCTG)