

# Making Sense of Individualised Molecular Data in Gynaecological Cancer

Caris Symposium  
Palais De Congres  
February 4<sup>th</sup> 2014

*Hani Gabra*

*Ovarian Cancer Action Research Centre*

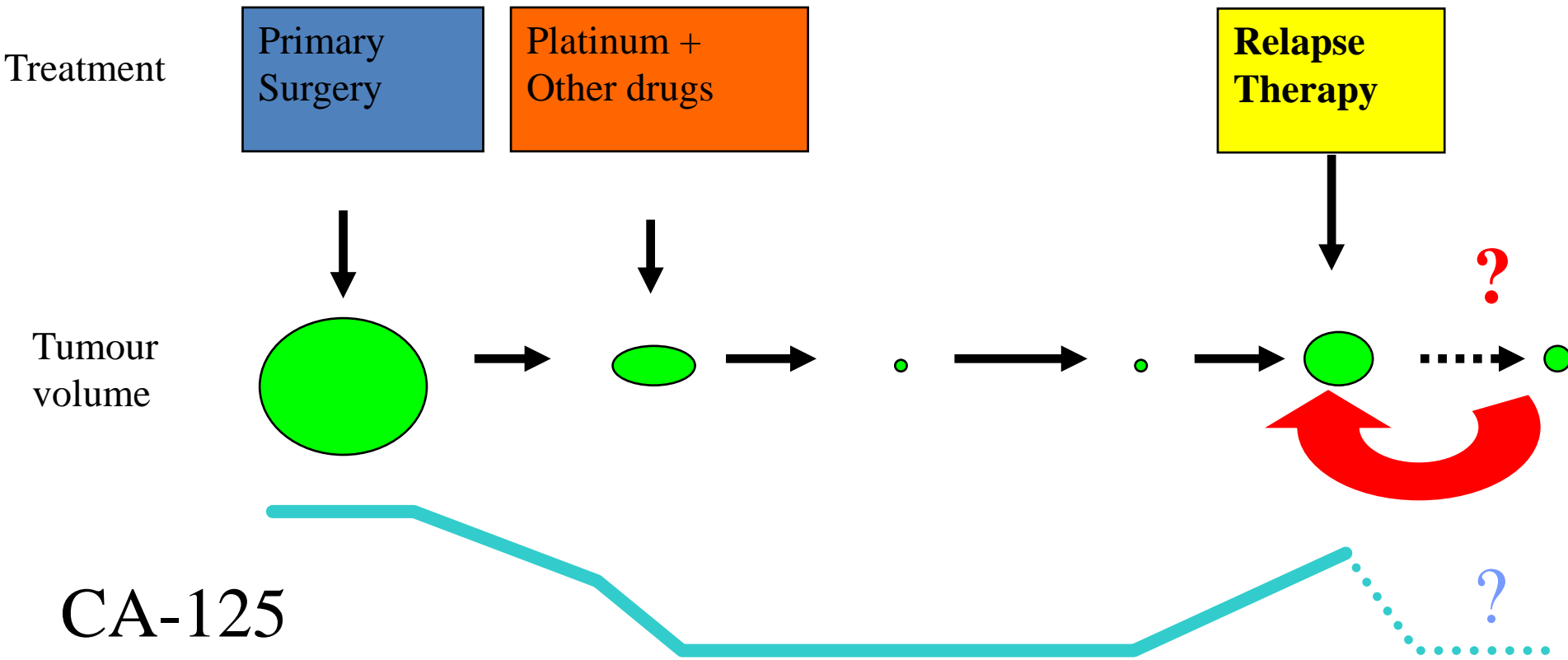
*Imperial College London*

- 45 year old Female, presented with abdominal distension
- CT Scan showed disseminated peritoneal disease
- CA125 of 2500
- Proceeded to Laparotomy

# Locoregional peritoneal dissemination



# Ovarian Cancer is typically a Chronic Disease



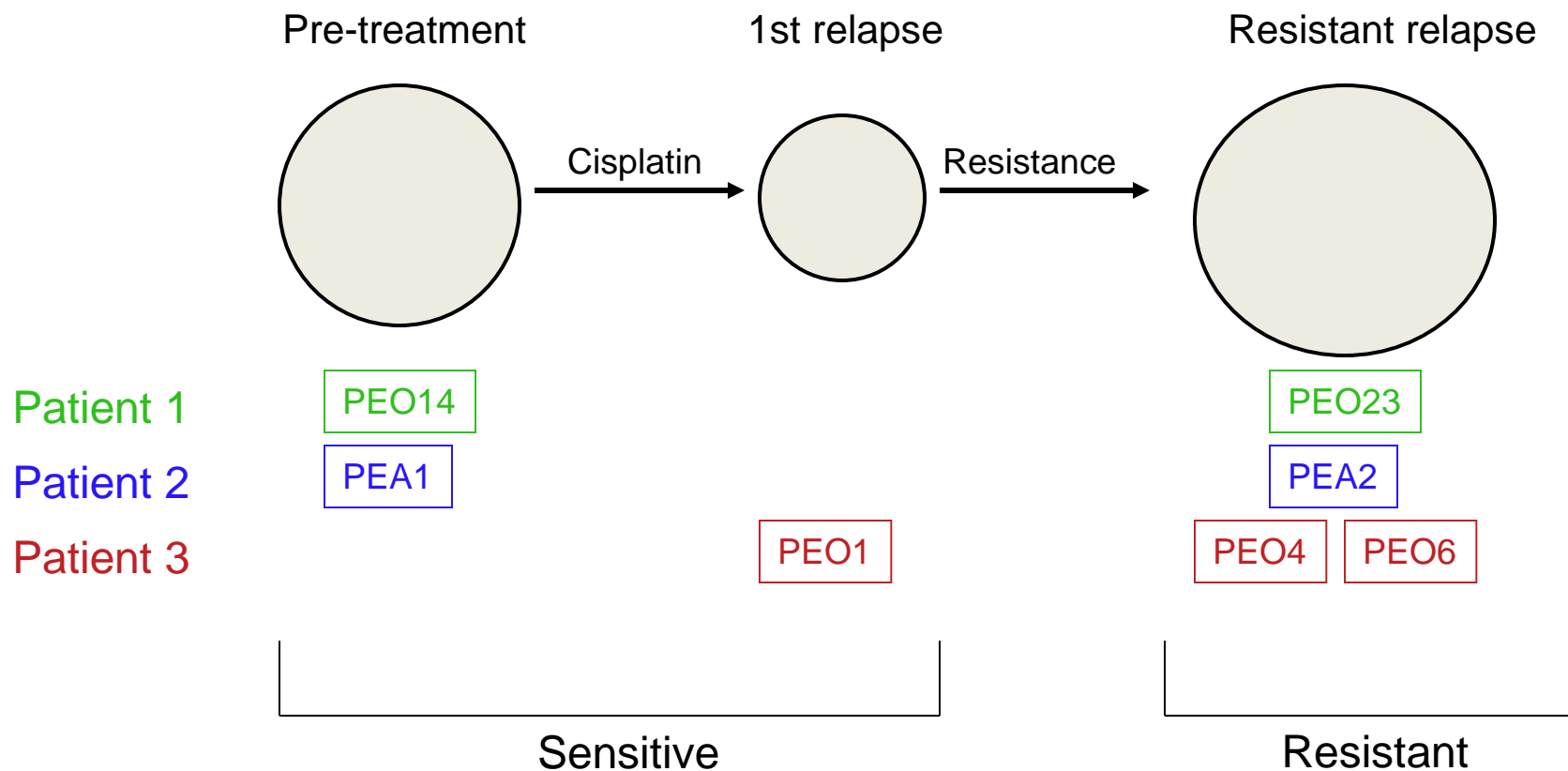
• Chronic survivability ends with drug resistance

# Definitions of Platinum Sensitivity/Resistance

(Friedlander 2011)

- **Platinum Refractory:** Progression while receiving last line of platinum-based therapy or within 4 weeks of last platinum dose
- **Platinum Resistant:** Progression free interval since last line of platinum greater than 1 month and less than 6 months
- **Partially Platinum Resistant (Intermediate Sensitivity):** Progression free interval since last line of platinum of 6-12 months
- **Platinum Sensitive:** progression free interval since last line of platinum greater than 12 months.

# Isogenic paired cell lines from women with ovarian cancer before and after resistance

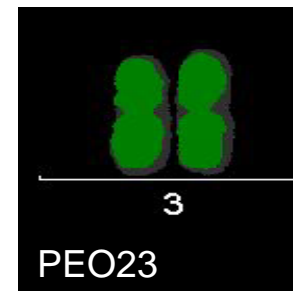
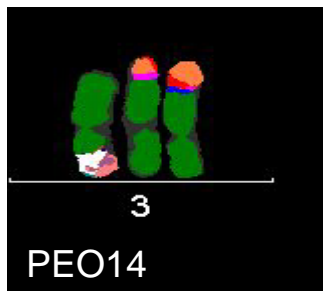
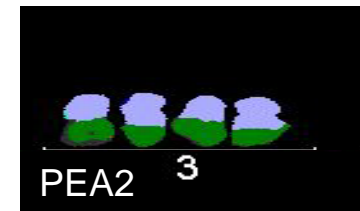
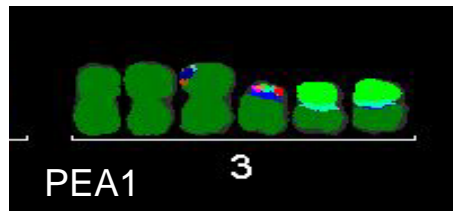
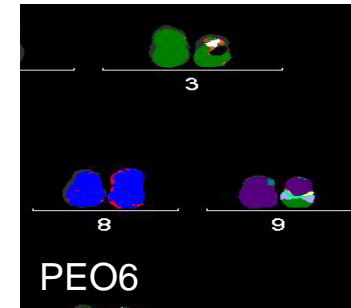
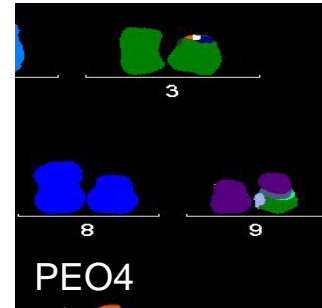
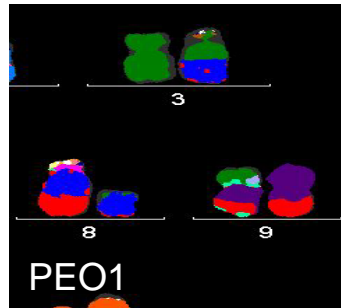


# Non-linear evolution of karyotypes

Cooke et al Oncogene 2010

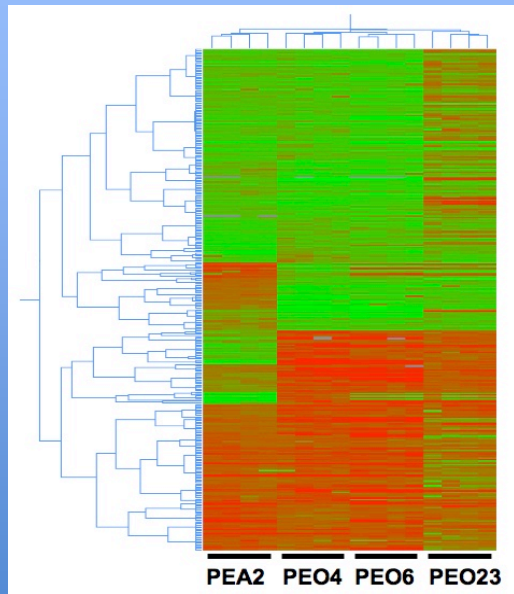
Sensitive

Resistant

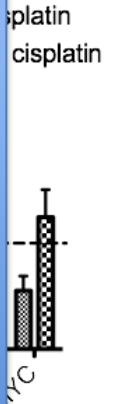


# Functional genomics of clinical platinum resistance- Expression Microarray

Stronach et al Cancer Res 2011



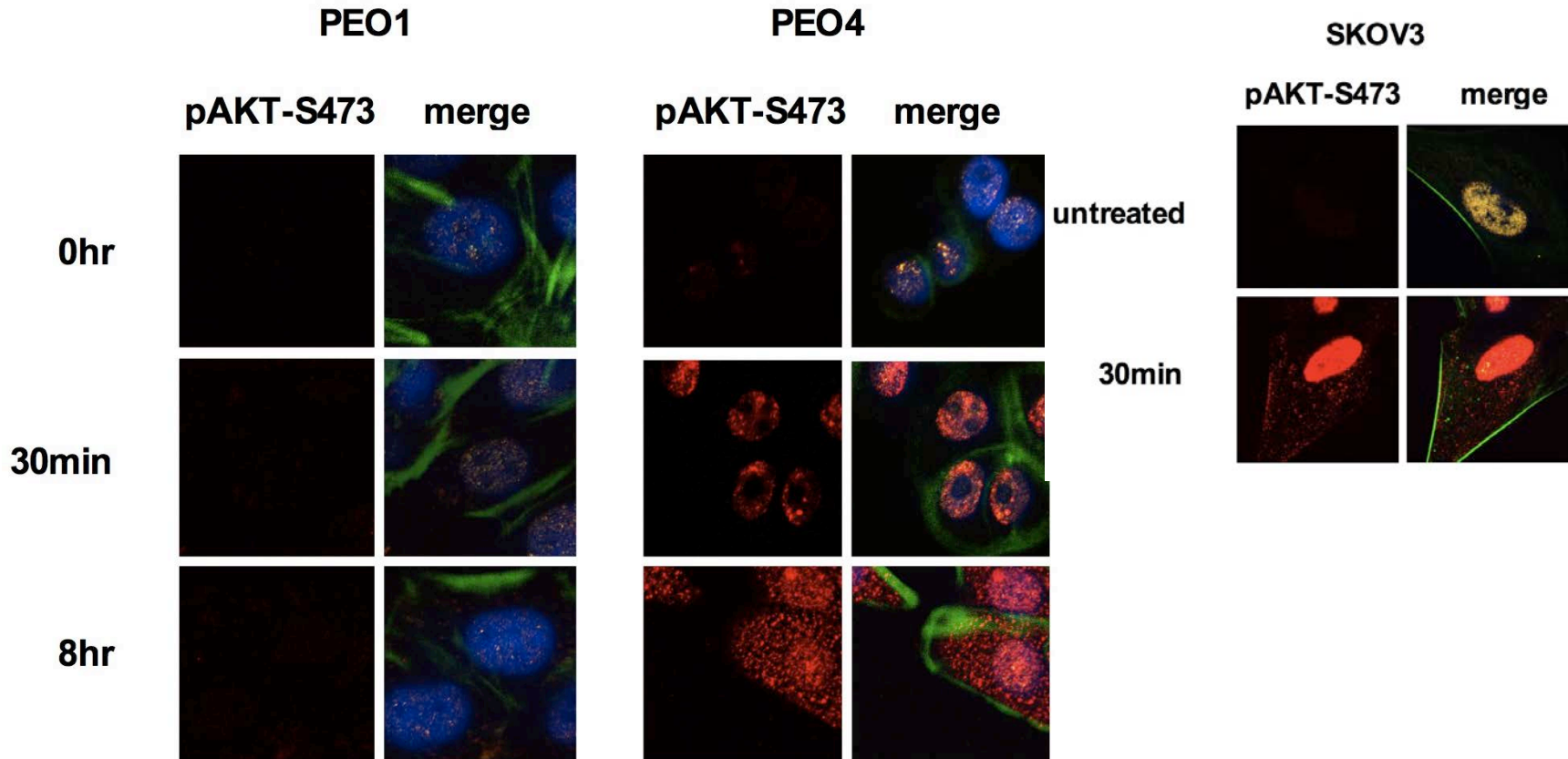
- STAT1
- HDAC4
- FOLR2
- PI3K/AKT





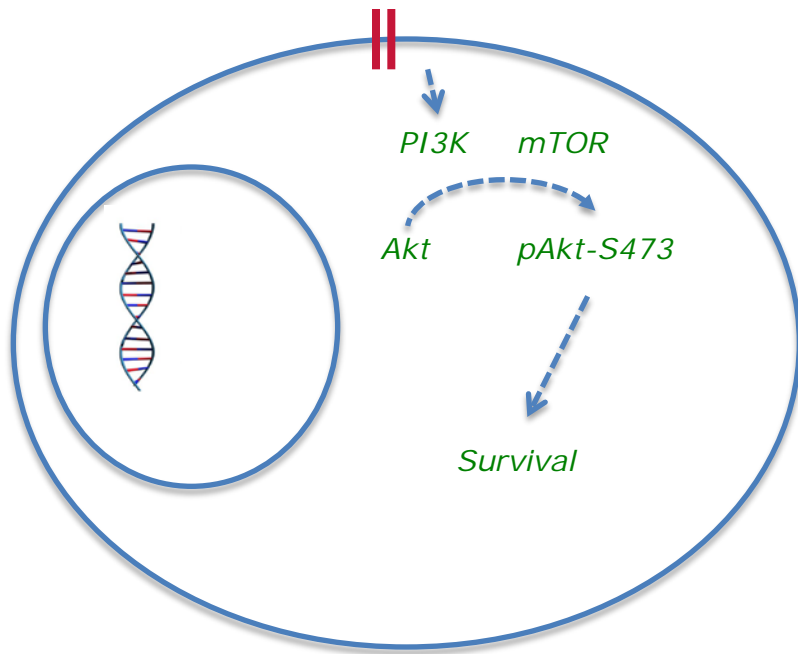
AKT

# Platinum induces nuclear pAKT in resistant cells

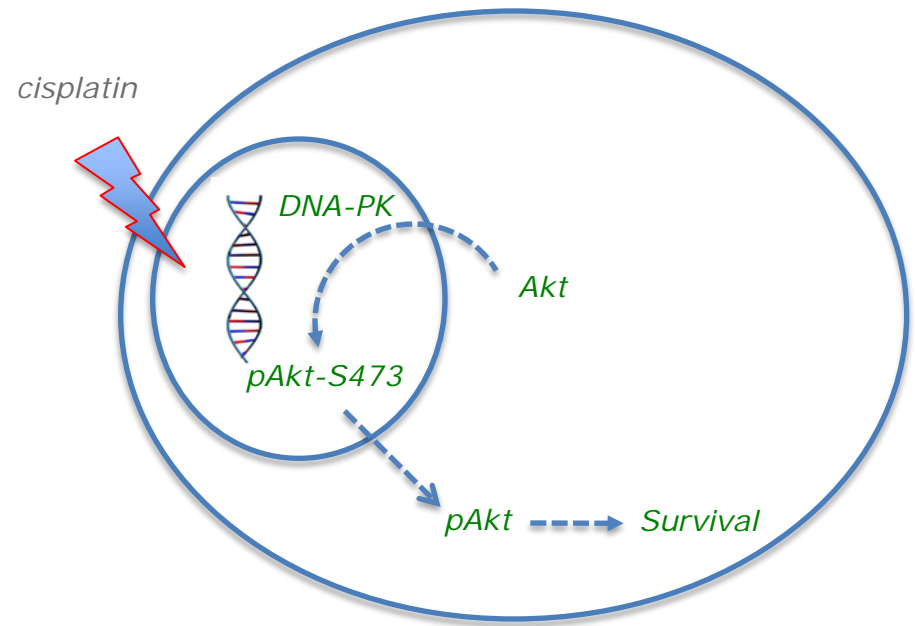


# A new model for Clinically Acquired Resistance- SPECIFIC AKT activation: *Stronach et al Neoplasia 2011*

## Outside-in activation

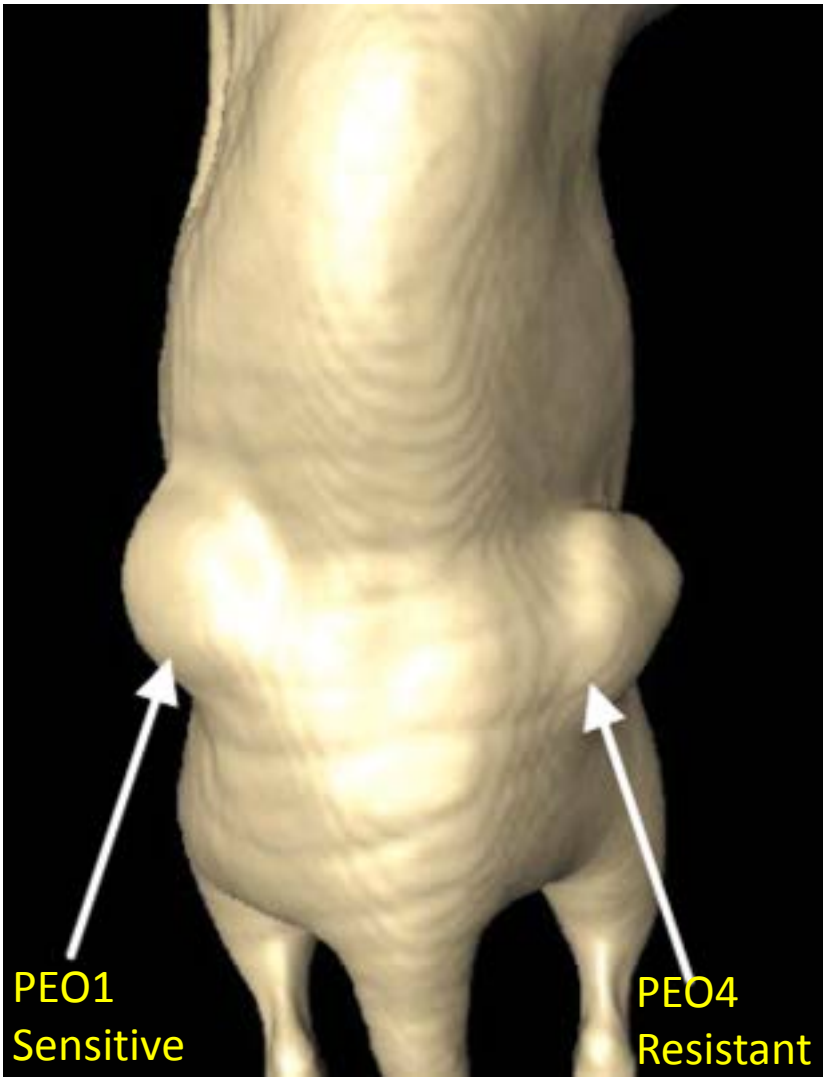


## DNA-damage activation



# FDG/FLT Imaging as Biomarkers of Therapy Response in Platinum-Resistant Ovarian Cancer

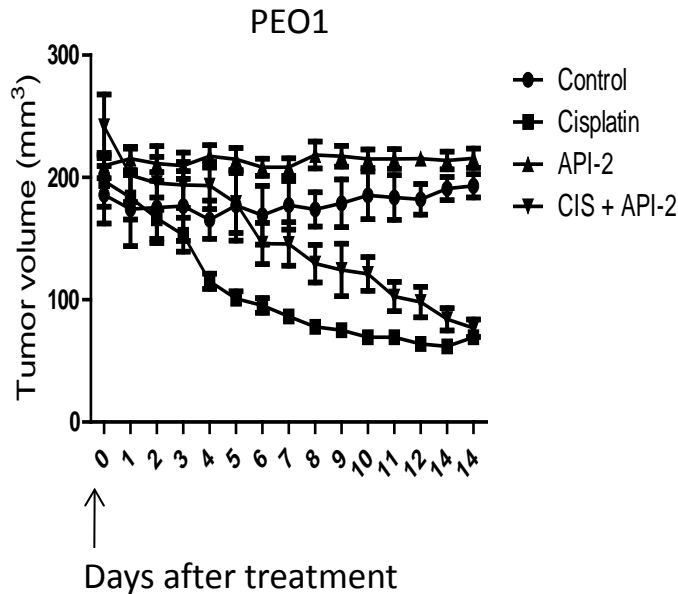
*Perumal et al Mol Imaging Biol 2012*



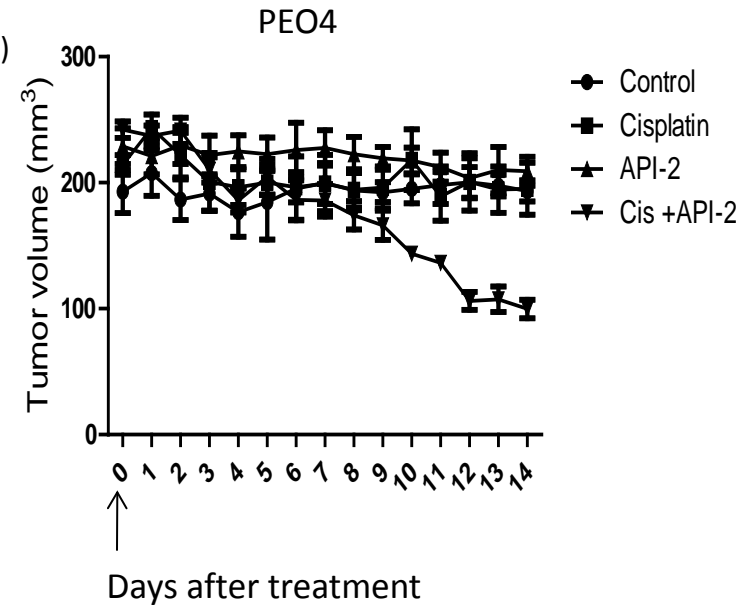
# AKTi resensitises clinically resistant cells to platinum in vivo

## Tumour size changes

i)



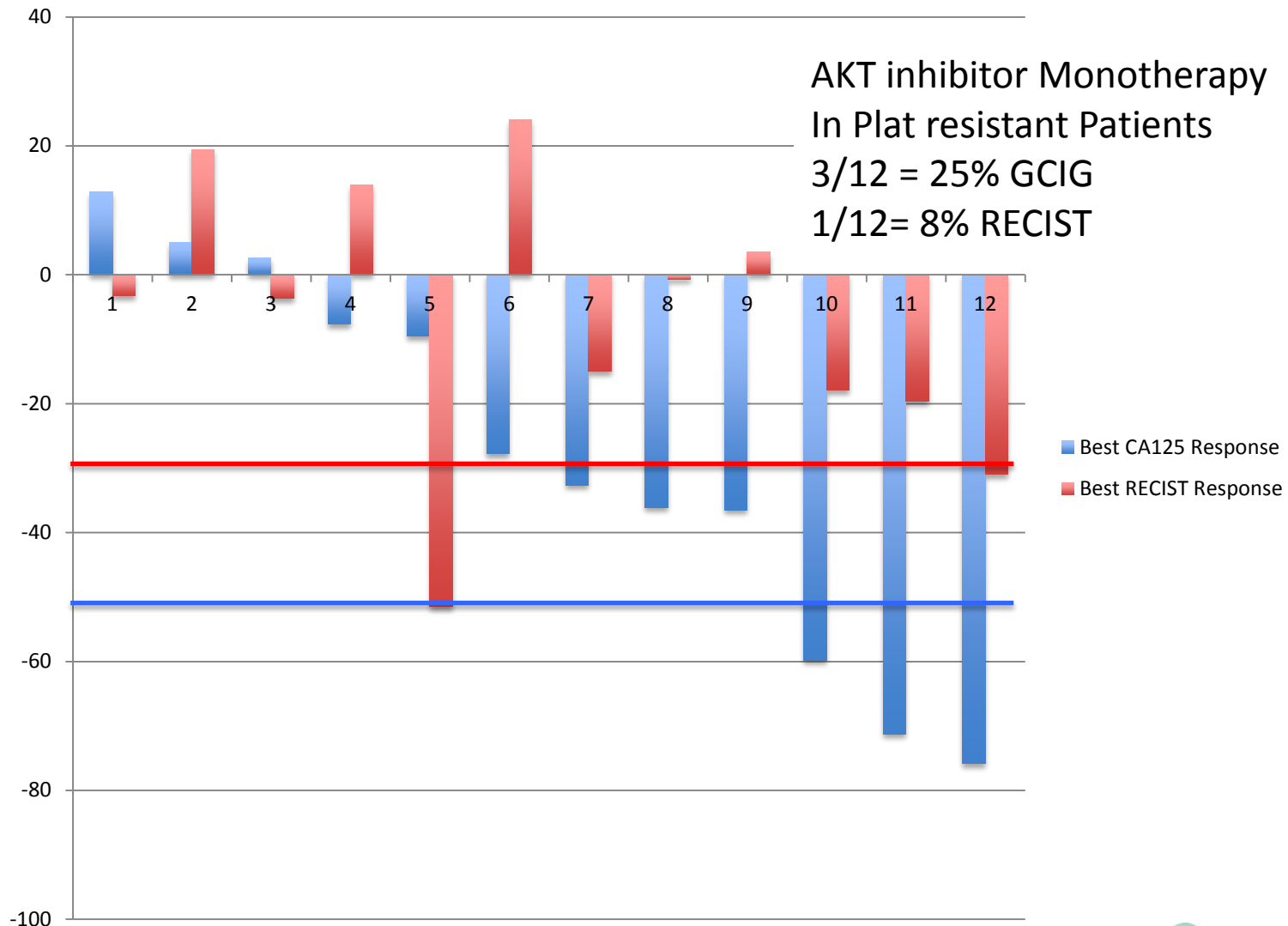
ii)



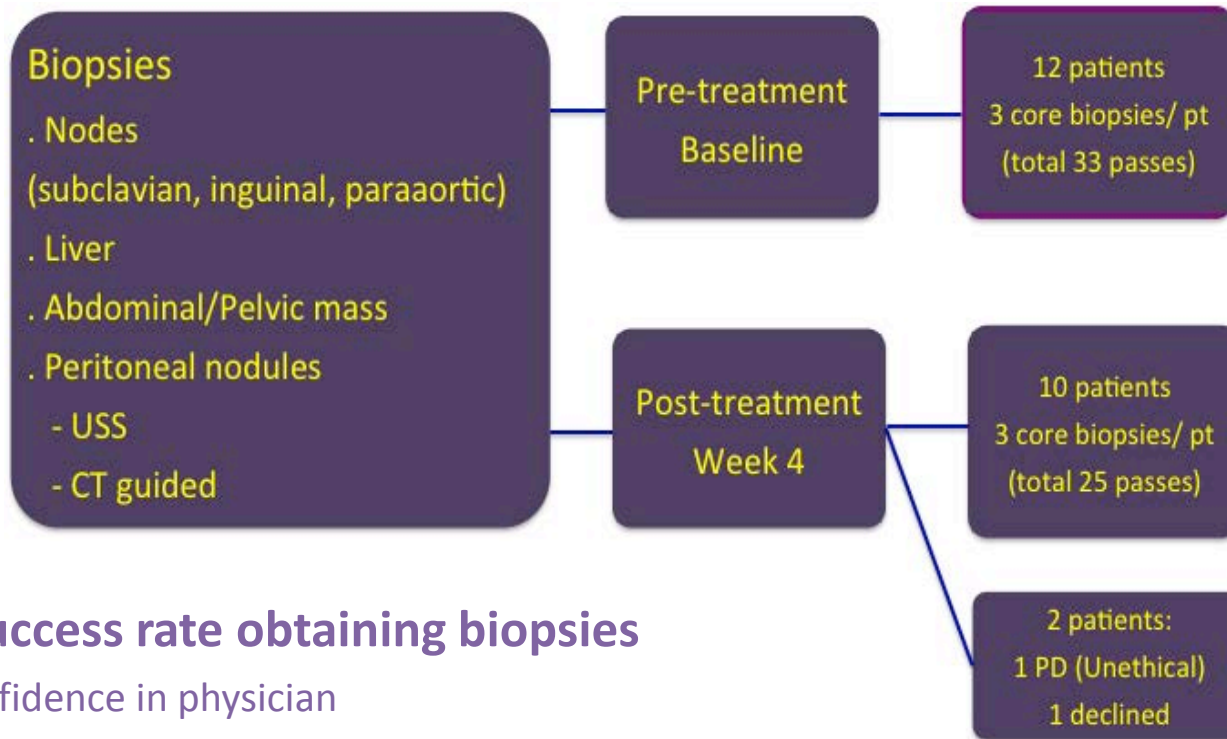
# Activity of GSK2141795

- RECIST responses = 1/12 (8%)
- GCIIG Responses = 3/11 (27%)
- Clinical Benefit Rate = 3/11 (27%)

# Ca-125 and Radiological responses



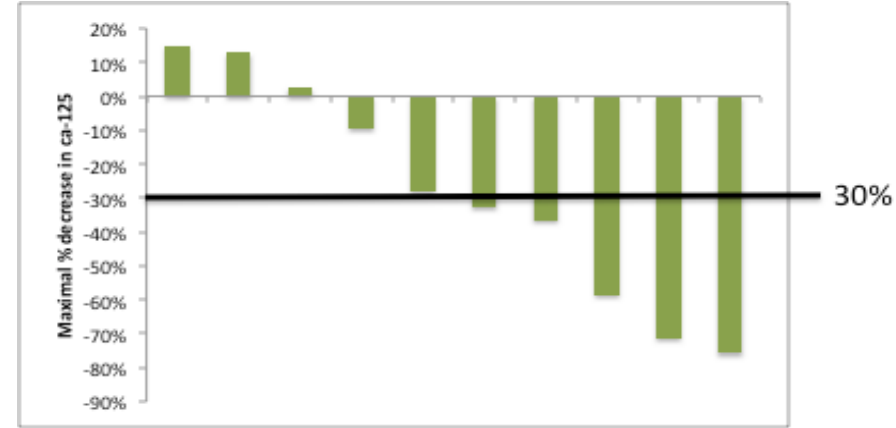
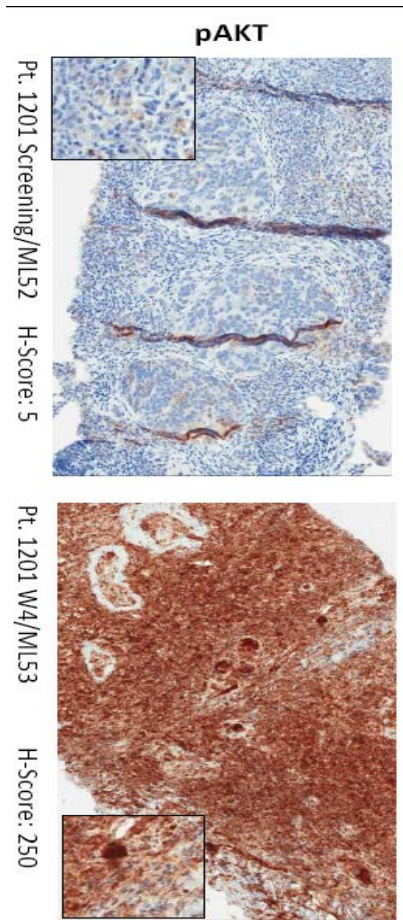
# Paired Tumour Biopsies (n=58)



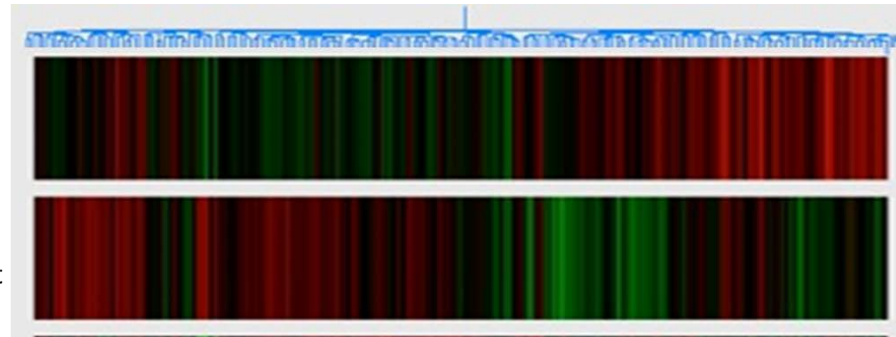
- **High success rate obtaining biopsies**
  - Confidence in physician
  - Education both pre- and post biopsy
  - A dedicated team of interventional radiologists
- **Complication rate: 1.72%**
  - hematoma



# Single agent GSK '795 trial: RPPA analysis (n=170 antibodies)



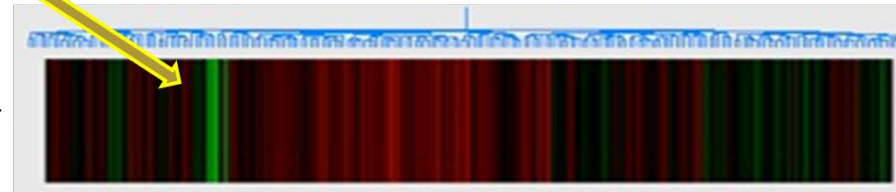
Responder  
Pre-treatment



Responder  
Post-treatment

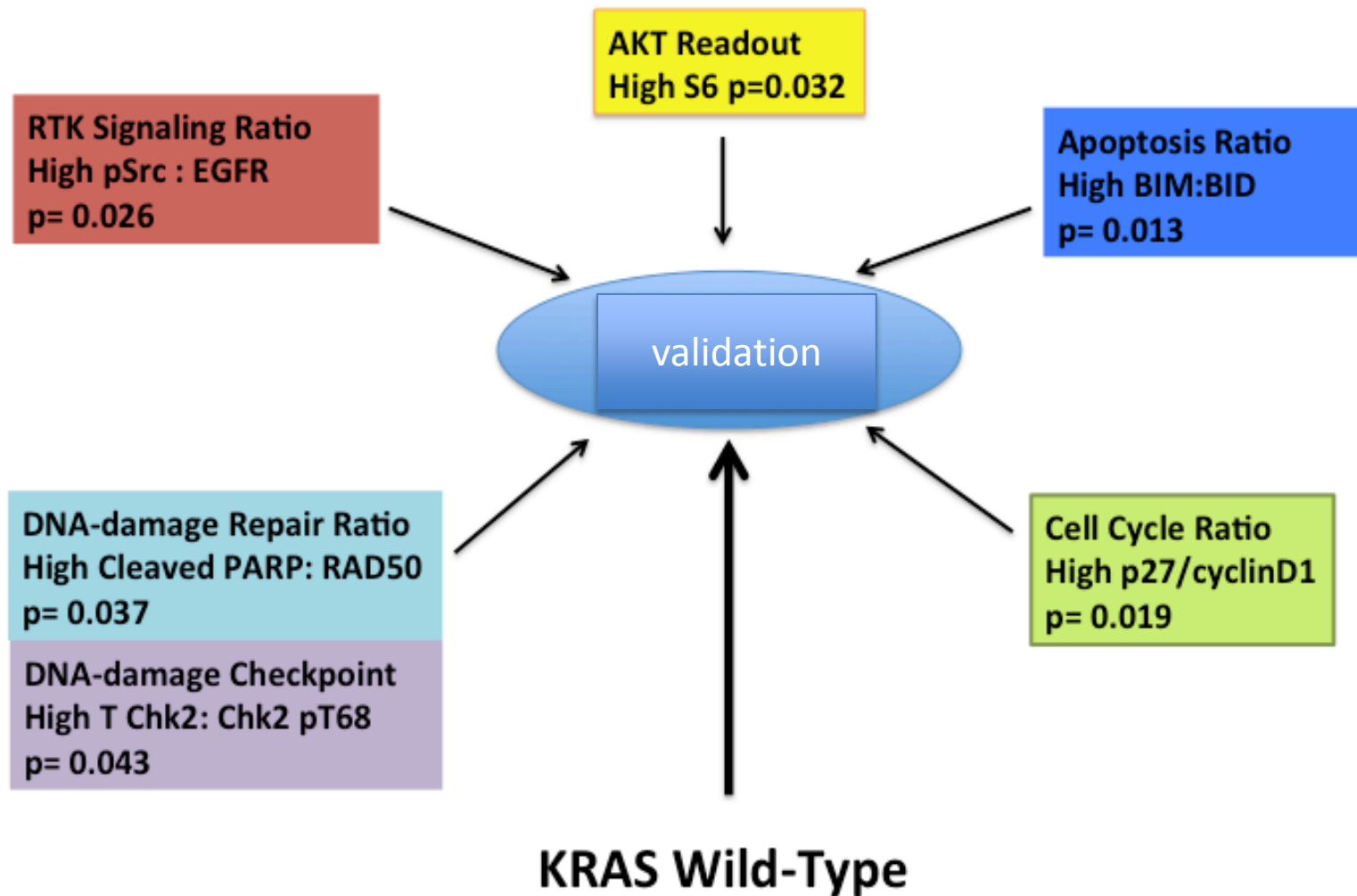
**pAKT**

Non-responder  
Pre-treatment



Non-responder  
Post-treatment

# Biomarkers associated with clinical activity



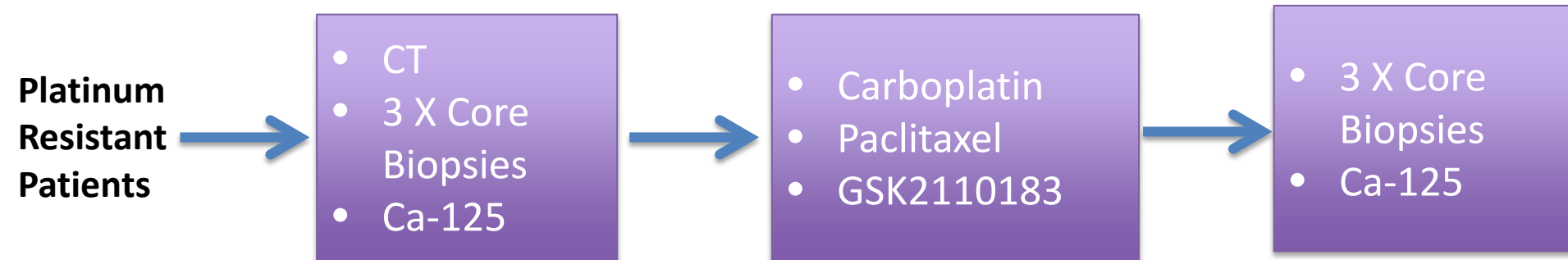
# AKTRES Phase Ib

(AKT inhibition in Platinum RESistant ovarian cancer)

Carbo-Taxol + GSK2110183:  
Oral Pan kinase AKT inhibitor

Dr Sarah Blagden EUTROC Clinical CI

Dr Euan Stronach EUTROC Translational CI



- Feasibility
- Activity
- Safety



# Drivers for change in Cancer Care

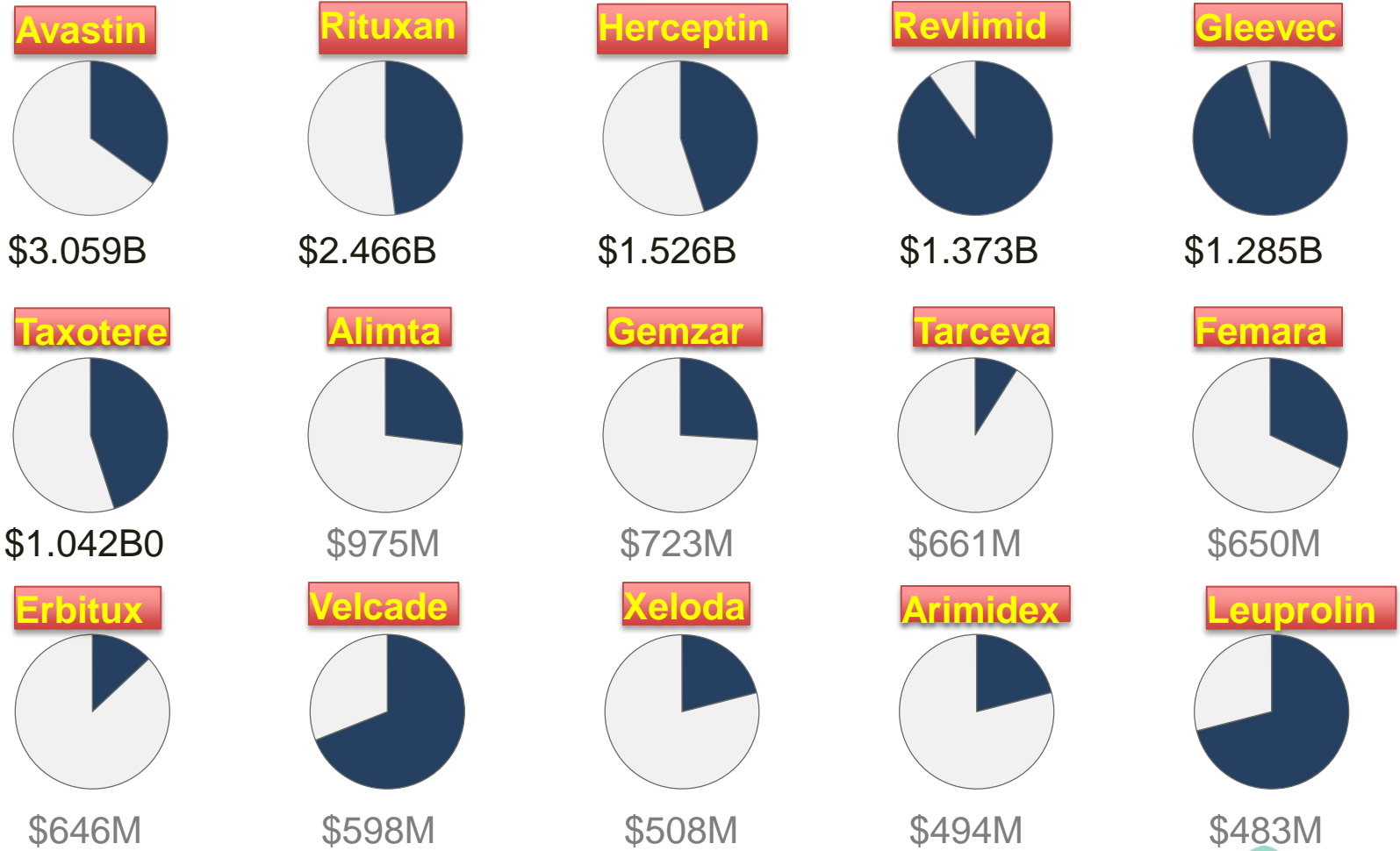
- Prevalence is rising
- Costs are rising
- Conventional use of anticancer medicines =waste due to poor selection
- Patients have a tough enough time with chemotherapy: failure is bad for us and very bad for patients
- Our scientific understanding of individual cancer types has dramatically increased
- Molecular profiling the answer?

# How can molecular analysis help?

- Can enhance understanding of likely operating pathways for an individual tumour (Not just single biomarkers)
- Can add value to a physician's intuition (eg which endocrine agent?)
- Can help a tumour board/MDT achieve rational decisions
- May avoid toxicity of useless drugs
- Can direct patients to clinical trials / help to enrich clinical trials rationally
- Can assist with temporal analysis of sequential changes in tumours: Darwinotherapy

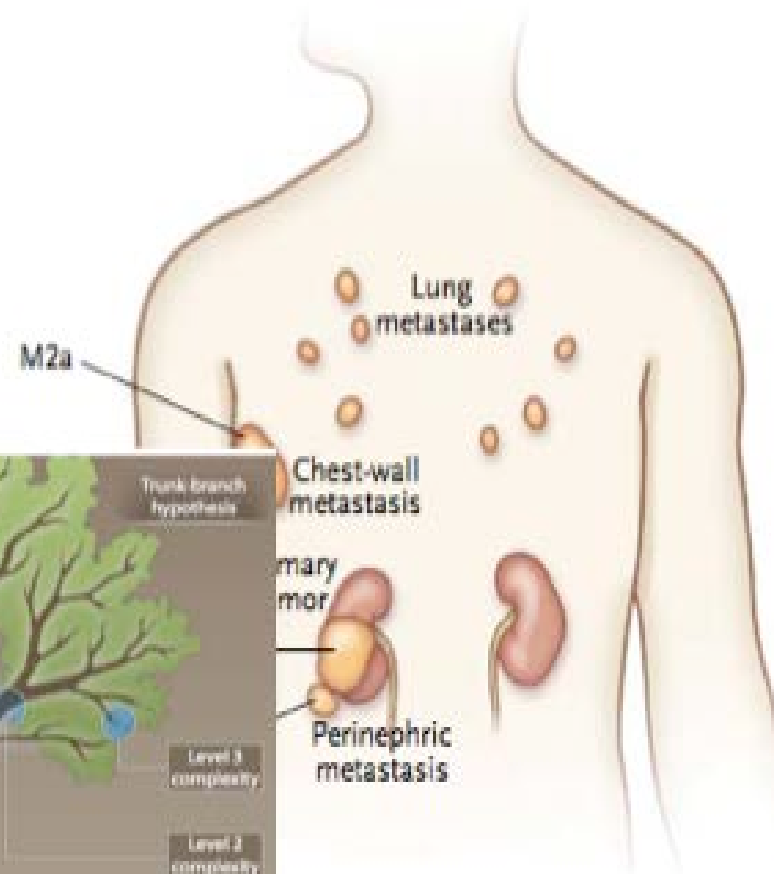
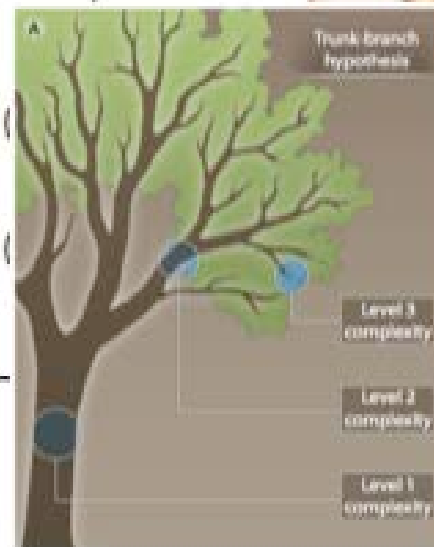
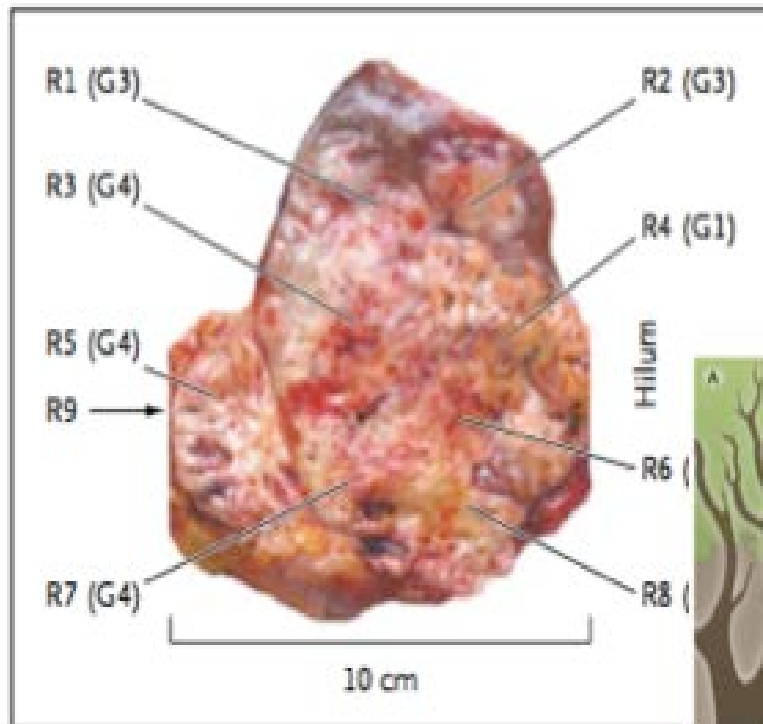
# High Cost Burden due to Non-responders

Responder  
 Non-responder



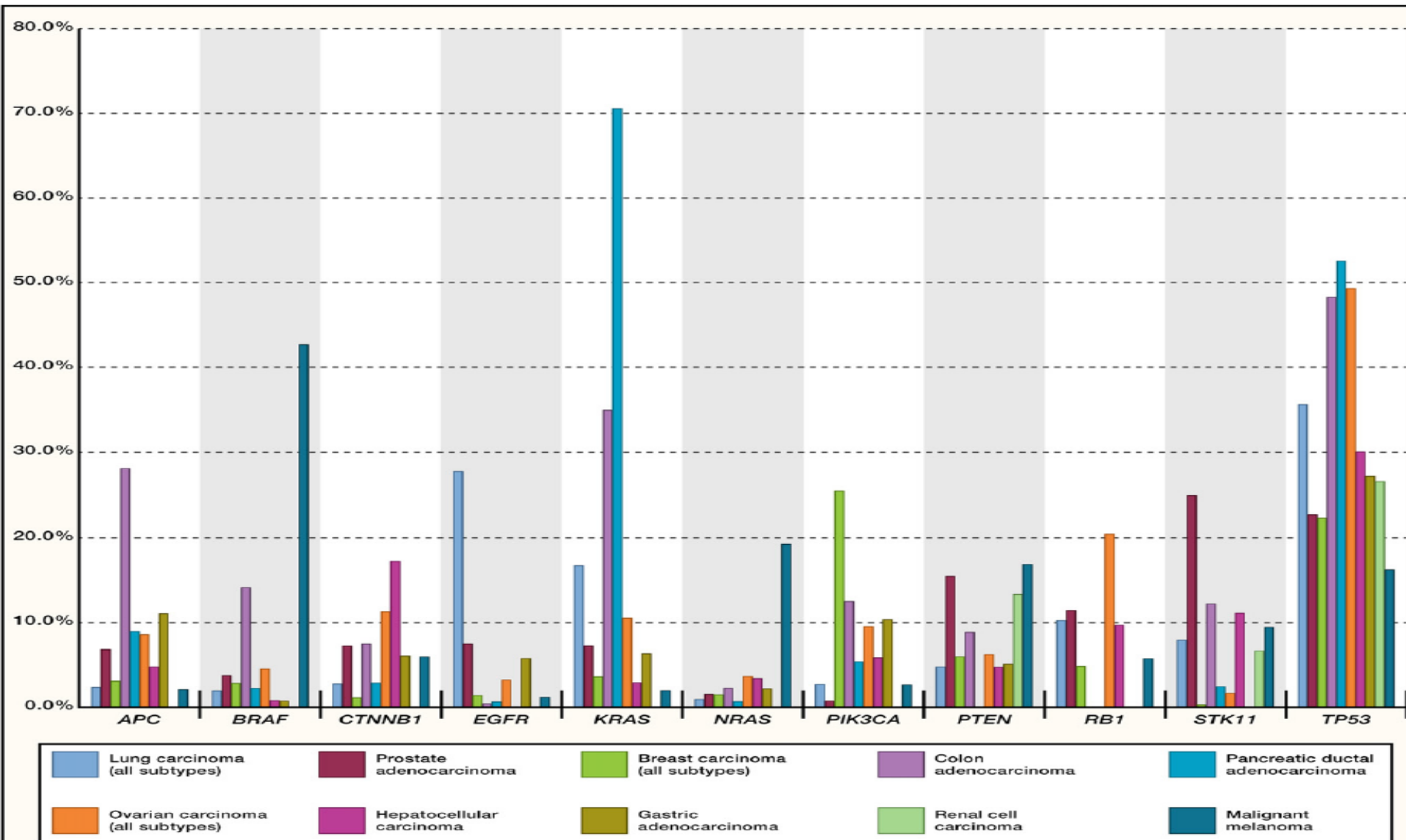
# Heterogeneity in clinical cancers

## A Biopsy Sites



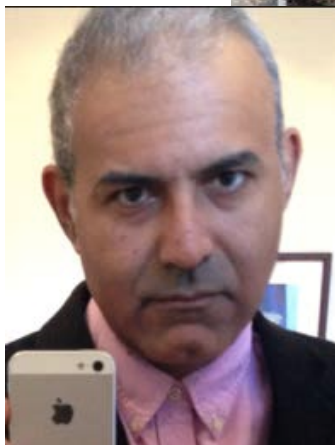
Gerlinger et al  
NEJM 2012

# Mutation Frequencies in Common Cancers





# Imperial College Molecular Tumour Board



"Selfie"



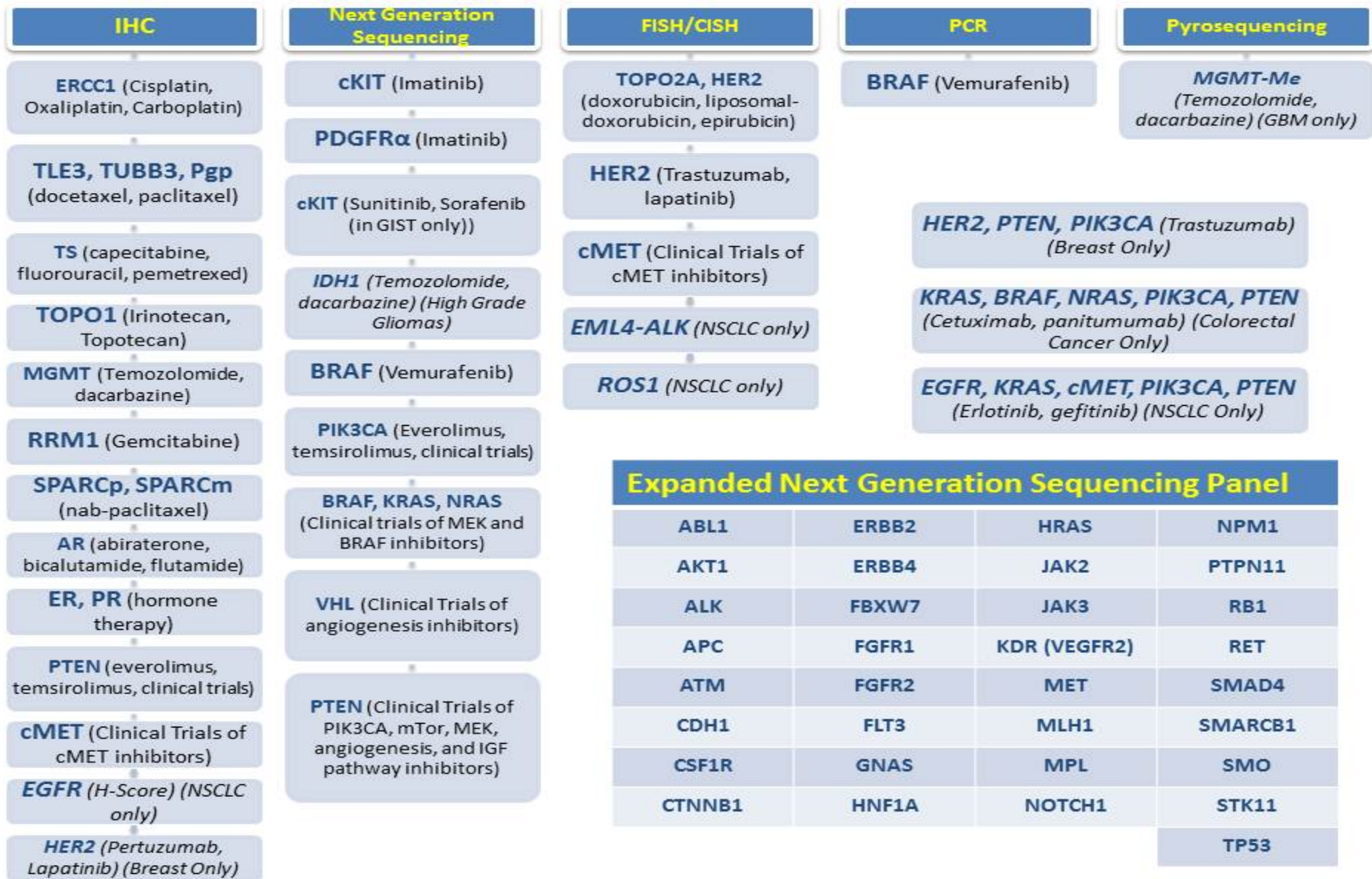
- Prof Gordon Stamp: Pathologist
- Prof Hani Gabra: Oncologist
- Dr Steven Moser: Radiologist
- Prof Bob Leonard: Oncologist
- Prof Christina Fotopoulou: Surgeon

# Setting up a molecular profiling MDT

- Can discuss individual case management in context of molecular readout
- Major input from pathology and radiology drives intervention, and review of old and new data
- Collect outcome data to validate efficacy of approach: the crucial empirical approach in audit loop format
- Potential to explore heterogeneity in metastatic cancers: Temporal and Spatial
- Allows building of a whole clinical pathway for integration of molecular information

# Caris Molecular Intelligence Services

## Comprehensive for Solid Tumors

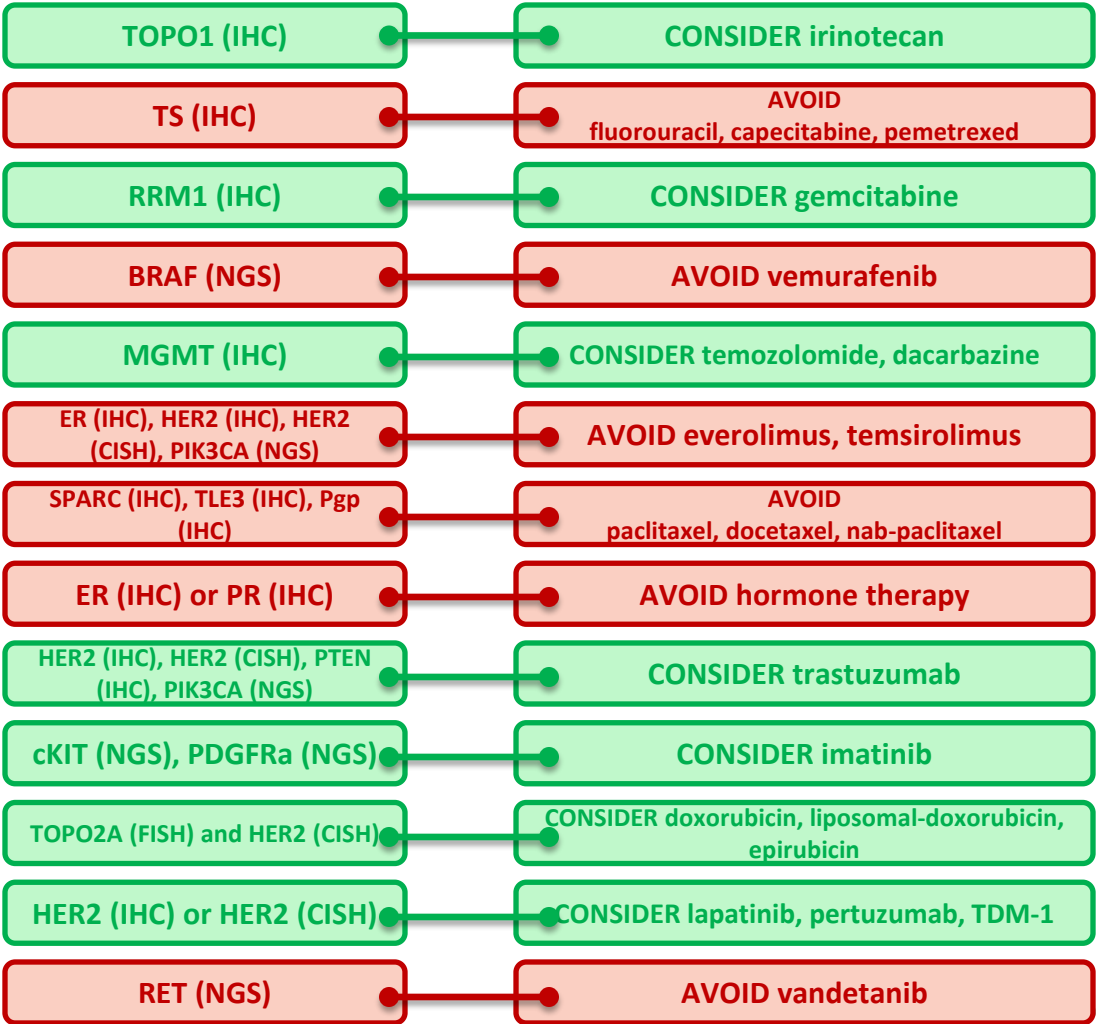


# Each Biomarker Result May Help You Select Therapeutic Options

How do I treat a patient with ovarian cancer where standard treatment options have failed?

Biomarker associated with potential benefit

Biomarker associated with potential lack of benefit



# Currently

- Increasing information using FFPE material-forget about frozen tissue
- Can get answers back in 7-10 working days
- Results of profiles with accompanying evidence level
- We have 'molecular MDT' meetings to discuss problem patients
- Ideally get re-biopsy for CURRENT disease profile
- How much better than guessing?
- **Audit of results is essential**

# 25 CASES ASSESSED BY PROFILING

CANCER TYPE			POSITIVE TARGETS FOUND, EXCLUDING ER
OVARY	10	2/2 ASSESSABLE RESPONDED	
BREAST	7	5/6 ASSESSABLE RESPONDED	TS;SPARC[ <u>TOPO2A</u> ;TOPO1;RRM1; PGP; <u>TLE3</u>
CERVIX	1	N/A	
ENDOMETRIUM	2	N/A	
COLON	2	1/1 ASSESSABLE RESPONDED	TOPO1; <u>MGMT</u> ;SPARC;ERCC1;HIF1A;VEGFR2
KIDNEY	1	0/1	TS; <u>TOPO1A</u> ;RRM1;AR
GALL BLADDER	1	NR TO INITIAL	[ <u>GP</u> ;SPARC;TOPO2A[TOPO1;HER2
CUP	1	N/A	



# Be Critical: CARIS are trying to be, but you have to be too!!

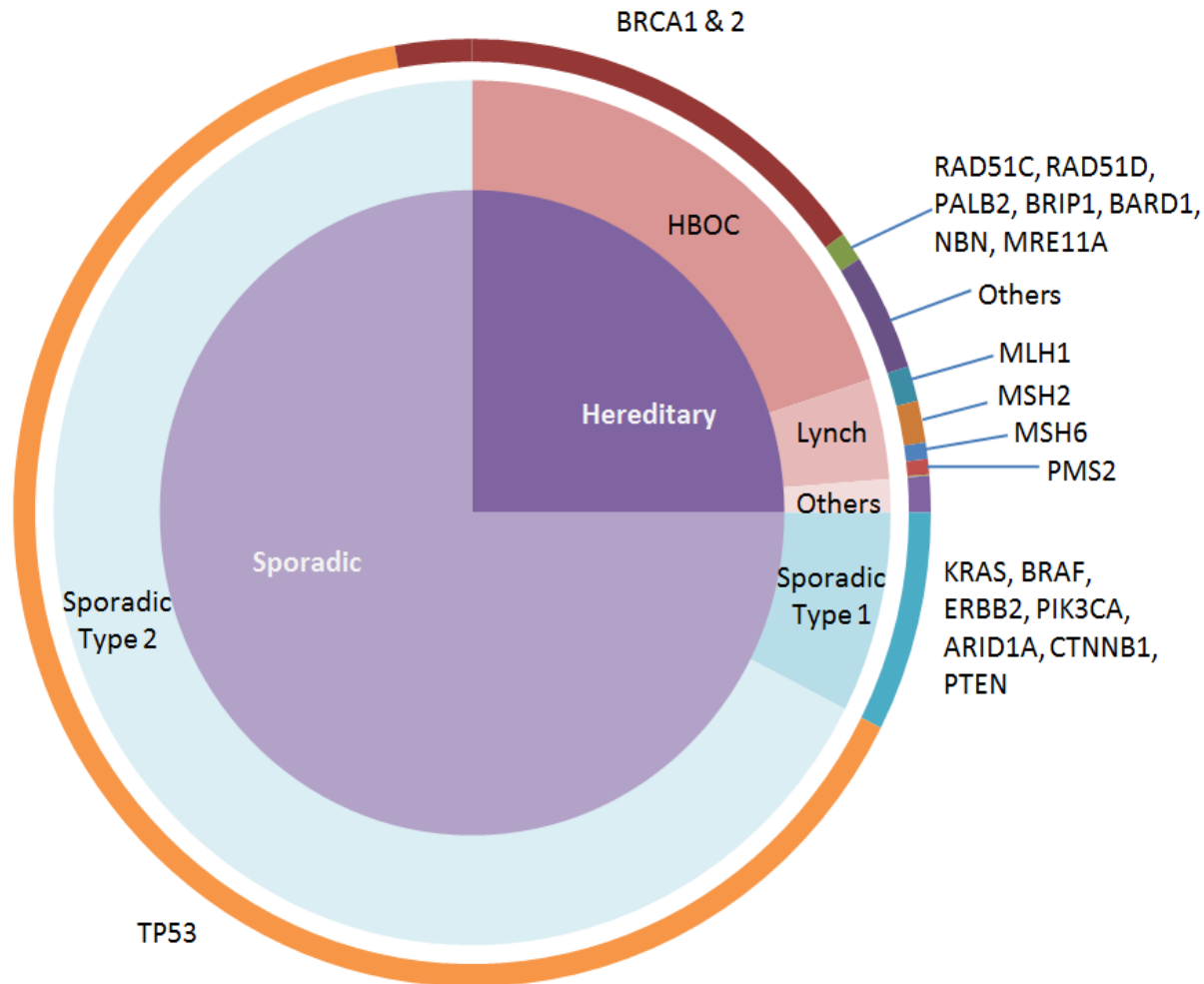
## LITERATURE LEVEL OF EVIDENCE ASSESSMENT FRAMEWORK\*

Study Design	
Hierarchy of Design	Criteria
I	Evidence obtained from at least one properly designed <b>randomized controlled trial</b> .
II-1	Evidence obtained from well-designed controlled trials <b>without randomization</b> .
II-2	Evidence obtained from well-designed <b>cohort or case-control</b> analytic studies, preferably from more than one center or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Study Validity	
Grade	Criteria
Good	The study is judged to be valid and relevant as regards results, statistical analysis, and conclusions and shows no significant flaws.
Fair	The study is judged to be valid and relevant as regards results, statistical analysis, and conclusions, but contains at least one significant but not fatal flaw.
Poor	The study is judged to have a fatal flaw such that the conclusions are not valid for the purposes of this test.

\* Adapted from Harris, T., D. Atkins, et al. (2001). "Current Methods of the U.S. Preventive Services Task Force." Am J Prev Med 20(3S)<sup>9</sup>

# Distribution of Mutation in Ovarian Cancer





# Case 1

- 48 yr woman second opinion from Egypt
- NOVEMBER 2009: TAH/BSO total macroscopic clearance
- STAGE IIIC GRADE 3 ENDOMETRIOID CARCINOMA OF OVARY
- CA125 at presentation was 2400
- Patient lost to follow up no chemotherapy
- Marker progression noted march 2010 to 175
- commenced on carboplatin and taxol (first line, first recurrence) with good marker regression to end of therapy, July 2010

# Case 1

- August 2011 CA125 started to climb to 134.
- Weekly Taxol and Carboplatin
- Due to PD at midway scan, avastin was added but had marker PD after 3 months, when CA125 was 152
- marker rise and PET-CT lesions with gemcitabine carboplatin starting July 2012 and CA125 responded initially but PD in December 2012
- 2 cycles Caelyx - PD

# Case 1

- Came to Imperial Molecular MDT for second opinion
- CT Review showed further progression with new hepatic metastases
- Surgical Review ruled out surgery
- Vault biopsy of tumour done
- Pathology review indicated Squamous Carcinoma of Cervix !!
- HPV high risk subtypes confirmed by PCR in-situ, p53 wildtype!
- CARIS analysis undertaken

# CARIS Associations

## Agents Associated with Potential BENEFIT

[irinotecan, topotecan](#)

[gemcitabine](#)

[doxorubicin, liposomal-doxorubicin, epirubicin](#)

[fluorouracil, capecitabine, pemetrexed](#)

[nab-paclitaxel](#)

[trastuzumab](#)

## Agents Associated With Potential LACK OF BENEFIT

[docetaxel, paclitaxel](#)

[tamoxifen, fulvestrant, letrozole, anastrozole](#)

[leuprolide, megestrol acetate](#)

[everolimus, temsirolimus](#)

[temozolomide, dacarbazine](#)

[imatinib](#)

[sunitinib](#)

[vemurafenib](#)

# Molecular basis for potential benefit

Agents	Test	Method	Result	Value <sup>†</sup>	Clinic
					Potential Benefit
<a href="#">irinotecan</a> , <a href="#">topotecan</a>	<a href="#">TOPO1</a>	IHC	Positive	2+ 90%	✓
<a href="#">gemcitabine</a>	<a href="#">RRM1</a>	IHC	Negative	2+ 20%	✓
<a href="#">doxorubicin</a> , <a href="#">liposomal-doxorubicin</a> , <a href="#">epirubicin</a>	<a href="#">Her2/Neu</a>	CISH	Not Amplified	1.74	
	<a href="#">PGP</a>	IHC	Negative	0+ 100%	✓
	<a href="#">TOP2A</a>	IHC	Positive	2+ 25%	✓
<a href="#">fluorouracil</a> , <a href="#">capecitabine</a> , <a href="#">pemetrexed</a>	<a href="#">TS</a>	IHC	Negative	1+ 1%	✓
<a href="#">nab-paclitaxel</a>	<a href="#">SPARC Monoclonal</a>	IHC	Negative	2+ 5%	
	<a href="#">SPARC Polyclonal</a>	IHC	Positive	2+ 60%	✓
<a href="#">trastuzumab</a>	<a href="#">Her2/Neu</a>	CISH	Not Amplified	1.74	
	<a href="#">Her2/Neu</a>	IHC	Positive	3+ 15%	✓

# Expanded Mutational Analysis by Next Generation Sequencing

## Genes Tested Without Alterations

ABL1	AKT1	ALK	APC	ATM	BRAF
c-KIT	CDH1	cMET	CSF1R	CTNNB1	EGFR
ERBB2	ERBB4	FBXW7	FGFR1	FGFR2	FLT3
GNA11	GNAS	HNF1A	IDH1	JAK2	JAK3
KDR	KRAS	MLH1	MPL	NOTCH1	NPM1
NRAS	PDGFRA	PIK3CA	PTEN	PTPN11	RB1
RET	SMAD4	SMARCB1	SMO	STK11	TP53
VHL					

## Genes Tested with Indeterminate Results

HRAS

# Outcome

- Cisplatin Topotecan recommended
- Patient underwent good partial response after 3 cycles
- Returned to Egypt to continue chemotherapy
- MDT recommended capecitabine and Herceptin at PD

# Case 2

- 70 year old Engineer from China
- Presented 2005 CA125 388
- Laparotomy total macroscopic clearance
- Serous borderline tumour
- 3 cycles taxol only
- CT Scan 2010 showed pleural disease, spleen and stomach peritoneal disease
- Attended Imperial Molecular MDT for 2<sup>nd</sup> Opinion



# Case 2

- Repeat CT showed extensive dissemination of disease including left supraclavicular fossa
- Progressive abdominal massive peritoneal disease and new left hydronephrosis
- Surgical clearance ruled out due to widely disseminated disease
- Fresh biopsy by interventional radiologist Dr Moser, and stenting of Left Hydronephrosis as a one stage procedure
- Patient went home same day

# Case 2

- Pathology Review showed METASTATIC BORDERLINE TUMOUR
- No evidence of invasive elements even in metastatic disease
- Question about heterogeneity!!
- Biopsy sent to CARIS for analysis

# CARIS Associations

## Agents Associated with Potential BENEFIT

[paclitaxel](#), [docetaxel](#), [nab-paclitaxel](#)

[irinotecan](#), [topotecan](#)

[gemcitabine](#)

[tamoxifen](#), [toremifene](#), [fulvestrant](#), [letrozole](#),  
[anastrozole](#), [exemestane](#), [megestrol acetate](#),  
[leuprolide](#), [goserelin](#)

[fluorouracil](#), [capecitabine](#), [pemetrexed](#)

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## Agents Associated With Potential LACK OF BENEFIT

[doxorubicin](#), [liposomal-doxorubicin](#), [epirubicin](#)

[trastuzumab](#), [pertuzumab](#), [ado-trastuzumab](#)  
[emtansine \(T-DM1\)](#)

[temozolomide](#), [dacarbazine](#)

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# Molecular basis for potential benefit

Agents	Test	Method	Result	Value <sup>†</sup>	Clinical Association			Data Level*	Reference
					Potential Benefit	Decreased Potential Benefit	Lack of Potential Benefit		
<a href="#">paclitaxel</a> , <a href="#">docetaxel</a> , <a href="#">nab-paclitaxel</a>	<a href="#">PGP</a>	IHC	Negative	0+ 100%	✓			○	6, 7
	<a href="#">SPARC Monoclonal</a>	IHC	Negative	1+ 90%		✓		◐	1, 2
	<a href="#">SPARC Polyclonal</a>	IHC	Negative	1+ 100%		✓		◐	1, 2
	<a href="#">TUBB3</a>	IHC	Negative	2+ 10%	✓			◐	3, 4, 5
<a href="#">irinotecan</a> , <a href="#">topotecan</a>	<a href="#">TOPO1</a>	IHC	Positive	2+ 100%	✓			◐	8, 9, 10
<a href="#">gemcitabine</a>	<a href="#">RRM1</a>	IHC	Negative	1+ 90%	✓			◐	11
<a href="#">tamoxifen</a> , <a href="#">toremifene</a> , <a href="#">fulvestrant</a> , <a href="#">letrozole</a> , <a href="#">anastrozole</a> , <a href="#">exemestane</a> , <a href="#">megestrol acetate</a> , <a href="#">leuprolide</a> , <a href="#">goserelin</a>	<a href="#">ER</a>	IHC	Positive	2+ 100%	✓			●	18, 19, 20, 21, 22, 23, 24, 25, 26
	<a href="#">PR</a>	IHC	Negative	0+ 100%		✓		●	19, 20, 21, 22, 23, 24, 25, 27, 28
<a href="#">fluorouracil</a> , <a href="#">capecitabine</a> , <a href="#">pemetrexed</a>	<a href="#">TS</a>	IHC	Negative	0+ 100%	✓			◐	29, 30, 31

# NGS Alterations

## Genes Tested With Alterations

Gene	Alteration	Frequency (%)	Exon	Result
KRAS	G12V	40	2	Pathogenic

**Interpretation:** A pathogenic mutation was detected in KRAS

KRAS or V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog encodes a signaling intermediate involved in many signaling cascades including the EGFR pathway. KRAS somatic mutations have been found in pancreatic (57%), colon (35%), lung (16%), biliary tract (28%), and endometrial (15%) cancers. Mutations at activating hotspots are associated with resistance to EGFR tyrosine kinase inhibitors (erlotinib, gefitinib) in NSCLC and monoclonal antibodies (cetuximab, panitumumab) in CRC patients. Patients with KRAS G13D mutation have been shown to derive benefit from anti-EGFR monoclonal antibody therapy in CRC patients. Various clinical trials (on [www.clinicaltrials.gov](http://www.clinicaltrials.gov)) investigating agents which target this gene may be available, which include the following: NCT01248247.

Several germline mutations of KRAS (V14I, T58I, and D153V amino acid substitutions) are associated with Noonan syndrome.

## Genes Tested Without Alterations

ABL1	AKT1	ALK	APC	ATM	BRAF
c-KIT	CDH1	cMET	CSF1R	CTNNB1	EGFR
ERBB2	ERBB4	FBXW7	FGFR1	FGFR2	FLT3
GNA11	GNAQ	GNAS	HNF1A	HRAS	IDH1
JAK2	JAK3	KDR	MLH1	MPL	NOTCH1
NPM1	NRAS	PDGFRA	PIK3CA	PTEN	PTPN11
RB1	RET	SMAD4	SMARCB1	SMO	STK11
TP53	VHL				

# Outcome

- Commenced Letrozole
- Good pain control with tramadol and paracetamol
- PS 0/1
- Good appetite
- Patient well after 2 months
- Will return from China for CT Scan and CA125 formal evaluation in 1 month

**CONTINUOUS LOW-FLOW ASCITES-DRAINAGE AND SEQUENTIAL  
NON-INVASIVE TUMOR-CELL SAMPLING THROUGH THE URINARY  
BLADDER VIA THE ALFA-PUMP CLOSED SYSTEM IN PLATINUM-  
RESISTANT-OVARIAN-CANCER**



# Alfapump AMAZE randomised trial:

A new translational and therapeutic platform for noninvasive temporal precision oncology



**EUTROC**

European Network for Translational Research in Ovarian Cancer

**Ovarian**  
cancer action



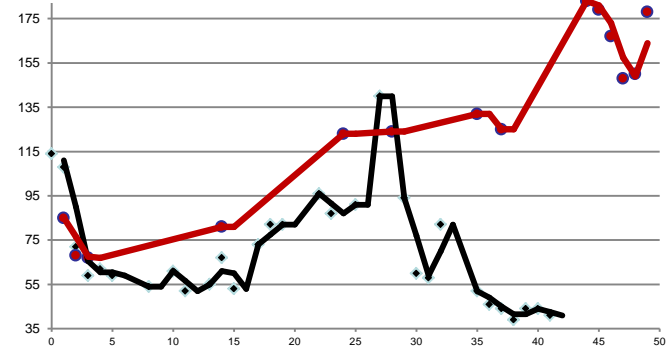
# Treatment related patients characteristics

	Patient 1	Patient 2
<i>Days of implant</i>	81	58
<i>Total amount of fluid removed [L]</i>	28.2	12
<i>Average daily volume [L] (range)</i>	<b>370</b> (121-2343)	<b>200</b> (0.25-1582)
<i>Mean successful pump cycles (range)</i>	50 (7-163)	25 (0-145)
<i>Days shake mode was active</i>	0	52

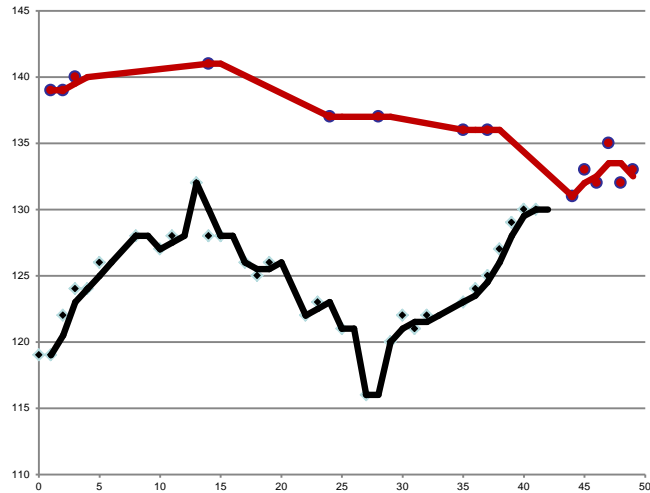
# Biochemical Follow up during treatment

— Patient 1  
— Patient 2

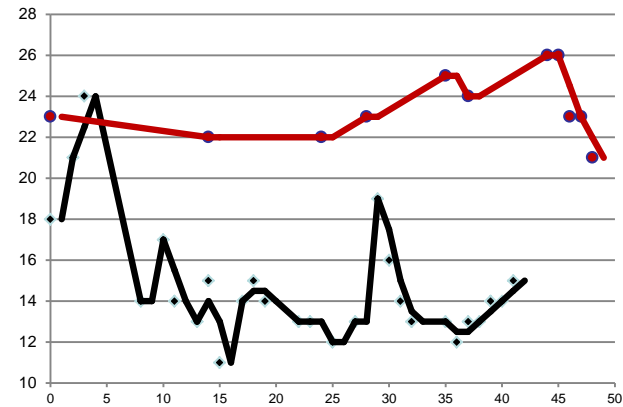
*Creatinine level, blood*



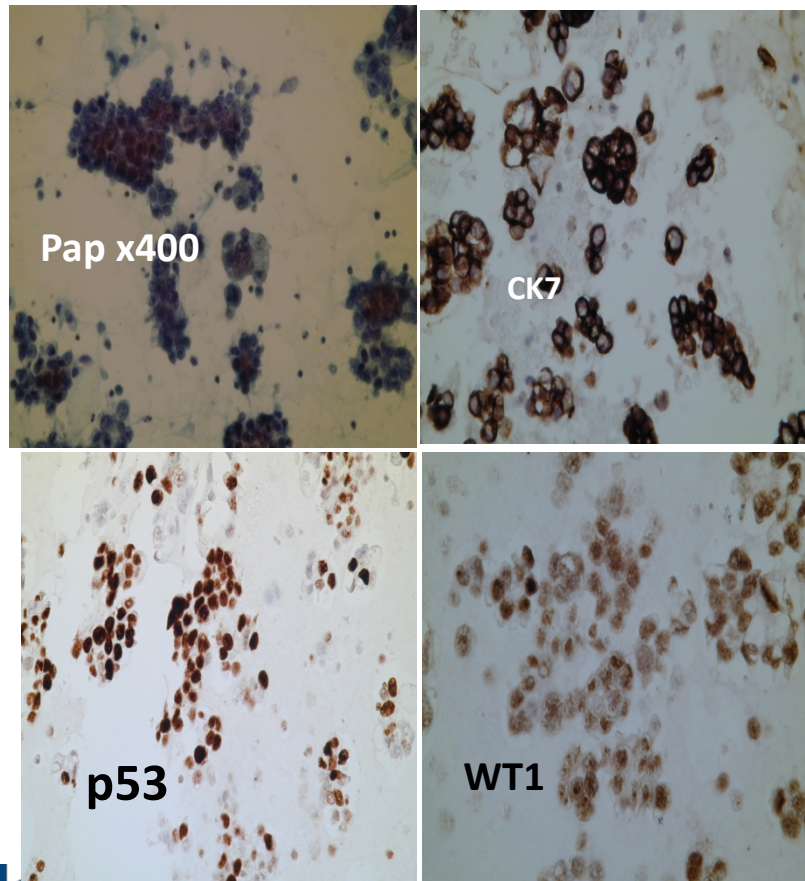
*Sodium level, blood*



*Albumin level, blood*



Histopathological analysis of the urine revealed rich malignant cell content; this was used to create FFPE-cell-blocks for molecular- pathological profiling with sequential Caris-Target-Now-analysis and full exome-sequencing.



**p53 mutation  
(R273L) frequency**



**Primary  
block**

**Urine at  
relapse**

**72%**


**96%**

# Blood markers- exosomes



**Exosomes Detection  
and Speciation by  
Nanoparticle Tracking  
Analysis (NTA) –  
Potential Biomarkers for a broad  
range of diseases.**

Jeremy Warren, CEO Nanosight Ltd  
Molecular Diagnostics World Conference  
29-30 Sept 2011



# Case 3

- 65 year old woman
- 10 year history of initially stage Ic grade 1 serous ovarian cancer
- Multiple recurrences
- 8 lines of chemotherapy
- Carboplatin, Taxol, Caelyx, Topotecan, gemcitabine, combinations
- Only one stabilisation : Gemcitabine, which slowed ascites formation

# CARIS Associations

## Agents Associated with Potential BENEFIT

[irinotecan](#), [topotecan](#)

[gemcitabine](#)

[tamoxifen](#), [fulvestrant](#), [letrozole](#), [anastrozole](#)

[leuprolide](#), [megestrol acetate](#)

[fluorouracil](#), [capecitabine](#), [pemetrexed](#)

## Agents Associated With Potential LACK OF BENEFIT

[paclitaxel](#), [docetaxel](#), [nab-paclitaxel](#)

[doxorubicin](#), [liposomal-doxorubicin](#), [epirubicin](#)

[trastuzumab](#), [pertuzumab](#), [ado-trastuzumab](#)  
[emtansine \(T-DM1\)](#)

[temozolomide](#), [dacarbazine](#)

# Molecular basis for potential benefit

## Agents Associated with Potential BENEFIT

Agents	Test	Method	Result	Value <sup>†</sup>	Clinical Association	
					Potential Benefit	Decreased Potential Benefit
<a href="#">irinotecan</a> , <a href="#">topotecan</a>	<a href="#">TOPO1</a>	IHC	Positive	2+ 30%	✓	
<a href="#">gemcitabine</a>	<a href="#">RRM1</a>	IHC	Negative	2+ 5%	✓	
<a href="#">tamoxifen</a> , <a href="#">fulvestrant</a> , <a href="#">letrozole</a> , <a href="#">anastrozole</a>	<a href="#">ER</a>	IHC	Positive	3+ 70%	✓	
<a href="#">leuprolide</a> , <a href="#">megestrol acetate</a>	<a href="#">ER</a>	IHC	Positive	3+ 70%	✓	
	<a href="#">PR</a>	IHC	Negative	0+ 100%		✓
<a href="#">fluorouracil</a> , <a href="#">capecitabine</a> , <a href="#">pemetrexed</a>	<a href="#">TS</a>	IHC	Negative	0+ 100%	✓	

# Outcome

- Marker fell from 400 to 125 after 1 month of Megestrol Acetate 160mg daily
- Appetite improved
- PS improved to 0/1
- Postural hypotension stopped, peripheral oedema disappeared!
- Ascites dried up
- Alfapump Pump went into “sleep” mode
- Patient will be formally assessed at 3 months



# Summary

- We have had a favourable experience of Molecular Profiling in the context of molecular tumour board decision making
- More information about the tumour in context of the patient allows us to make more sophisticated decisions when no other options exist
- This is increasingly the future, except that the future is now, and is integrated with new technologies

# Ovarian Cancer TSGs

Gene	Chromosome	Percentage of cancers in which downregulated or inactivated	Mechanisms of downregulation	Function
ARHI (DIRAS3)	1p31	60%	Imprinting; LOH; promoter methylation; transcription downregulated by E2F1 and E2F4	26 kDa GTPase; inhibits proliferation and motility; induces autophagy and dormancy; upregulates p21; inhibits cyclin D1, PI3K, Ras–Mapk signalling and STAT3
RASSF1A	3p21	60%	Hypermethylation	Inhibits proliferation and tumorigenicity in many different cancers; interacts with Ras inhibiting and downregulating cyclin D and signalling through JNK; stabilizes microtubules; regulates spindle checkpoint; regulates CD95- and TNF $\alpha$ -induced apoptosis
DLEC1	3p22.3	73%	Promoter hypermethylation and histone hypoacetylation	166 kDa cytoplasmic protein that inhibits anchorage-dependent growth
SPARC	5q31	70–90% decreased expression; 9% lost expression	Transcription	32 kDa Ca <sup>2+</sup> -binding protein; prevents adhesion
DAB2 (DOC2)	5q13	58–85% lost expression	Transcription	105 kDa protein binds GRB2, preventing Ras and Mapk activation; prevents FOS induction and decreases ILK activity; contributes to anoikis; inhibits proliferation; inhibits anchorage-independent growth and tumorigenicity
PLAGL1 (LOT1)	6q25	39%	Imprinting; LOH; transcription downregulated by EGF and TPA	55 kDa nuclear zinc-finger protein; inhibits proliferation and tumorigenicity
RPS6KA2	6q27	64%	Monoallelic expression in ovary; LOH	90 kDa ribosomal S6 serine threonine kinase; inhibits growth; induces apoptosis; decreases Erk phosphorylation and cyclin D1; increases p21 and p27
PTEN	10q23	3–8% mutated; expression lost in 27%, particularly in endometrioid and clear-cell histotypes	Promoter methylation; LOH; mutation	PI3 phosphatase; decreases proliferation, migration and survival; decreases cyclin D; increases p27
OPCML	11q25	56–83%	Promoter methylation; LOH; mutation	GPI-anchored IgLON family member; induces aggregation; inhibits proliferation and tumorigenicity
BRCA2	13q12–13	3–6%	Mutation; LOH	Binds RAD51 during repair of DNA DSBs
ARL11	13q14	62%	Promoter methylation	ADP ribosylation factor; induces apoptosis
WWOX	16q23	30–49%, particularly in mucinous and clear-cell histotypes	LOH; mutation	Decreases anchorage-independent growth and tumorigenicity; mouse homologue required for apoptosis
TP53	17p13.1	50–70%	Mutation	53 kDa nuclear protein; induces p21 leading to cell cycle arrest and promotion of DNA stability; induces apoptosis
DPH1	17p13.3	37%	LOH	50 kDa protein; decreases proliferation and clonogenicity; decreases cyclin D1
BRCA1	17q21	6–8%	Mutation; LOH	E3 ubiquitin ligase that participates directly in repair of DNA DSBs through homologous recombination; regulates ABL1; induces p53, androgen receptor, oestrogen receptor and MYC
PEG3	19q13	75%	Imprinting; LOH; promoter methylation; transcription	Induces p53-dependent apoptosis

# Ovarian Cancer Oncogenes

Gene	Chromosome	Percentage of cancers in which amplified	Percentage of cancers in which overexpressed	Percentage of cancers in which mutated	Function
<i>RAB25</i>	1q22	54%	80–89%	ND	Cytoplasmic GTPase and apical vessel trafficking
<i>EVI1</i>	3q26	ND	ND	ND	Transcription factor
<i>EIF5A2</i>	3q26	ND	ND	ND	Elongation factor
<i>PRKCI</i>	3q26	44%	78%	ND	Cytoplasmic serine–threonine protein kinase
<i>PIK3CA</i>	3q26	9–11%	32%	8–12%	Cytoplasmic lipid kinase
<i>FGF1</i>	5q31	ND	51%	ND	Growth factor for cancer and angiogenesis
<i>MYC</i>	8q24	20%	41–66%	ND	Transcription factor
<i>EGFR</i>	7p12	11–20%	9–28%	<1%	Protein tyrosine kinase growth factor receptor
<i>NOTCH3</i>	9p13	20–21%	62%	ND	Cell surface growth factor receptor
<i>KRAS</i>	12p11–12	5%	30–52%	2–24%	Cytoplasmic GTPase
<i>ERBB2</i>	17q12–21	6–11%	4–12%	ND	Protein tyrosine kinase growth factor receptor
<i>PIK3R1</i>	19q	ND	ND	ND	Cytoplasmic lipid kinase
<i>CCNE1</i>	19q12	12–36%	42–63%	ND	Cyclin
<i>AKT2</i>	19q13.2	12–27%	12%	ND	Cytoplasmic serine–threonine protein kinase
<i>AURKA</i>	20q13	10–15%	48%	ND	Nuclear serine–threonine protein kinase

# Other promising target pathways

Signalling pathway	Percentage of cancers in which activation is observed
PI3K	70%
Src	>50%
IL-6-IL-6R; Jak-STAT3	70%
LPA	90%
MEKK3-IKK-NF- $\kappa$ B	>50%
Mullerian inhibitory substance receptor	>50%
PKC $\alpha$	78%
Ras-Mek-Mapk*	<50% (activated in most low-grade type I cancers)