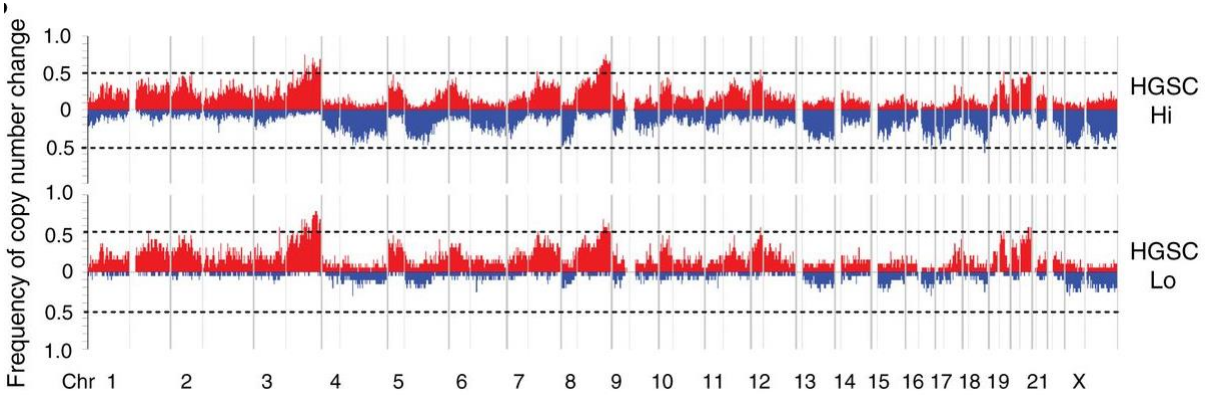
Primary surgery or neoadjuvant chemotherapy for ovarian cancer

Is there a molecular analysis that can help us define a subgroup of patients?

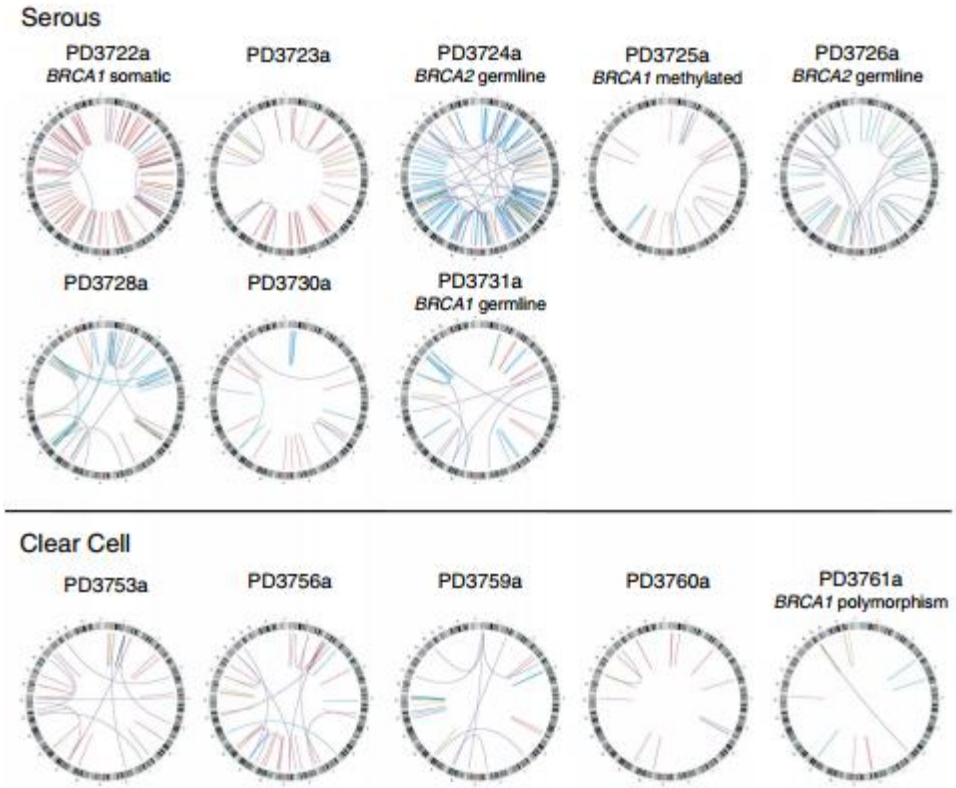
Prof Charlie Gourley, University of Edinburgh

Disclosures

- Research funding (commercially sponsored clinical trials): AstraZeneca, GlaxoSmithKline, Aprea
- Honoraria/lecture fees: Roche, GlaxoSmithKline, AstraZeneca

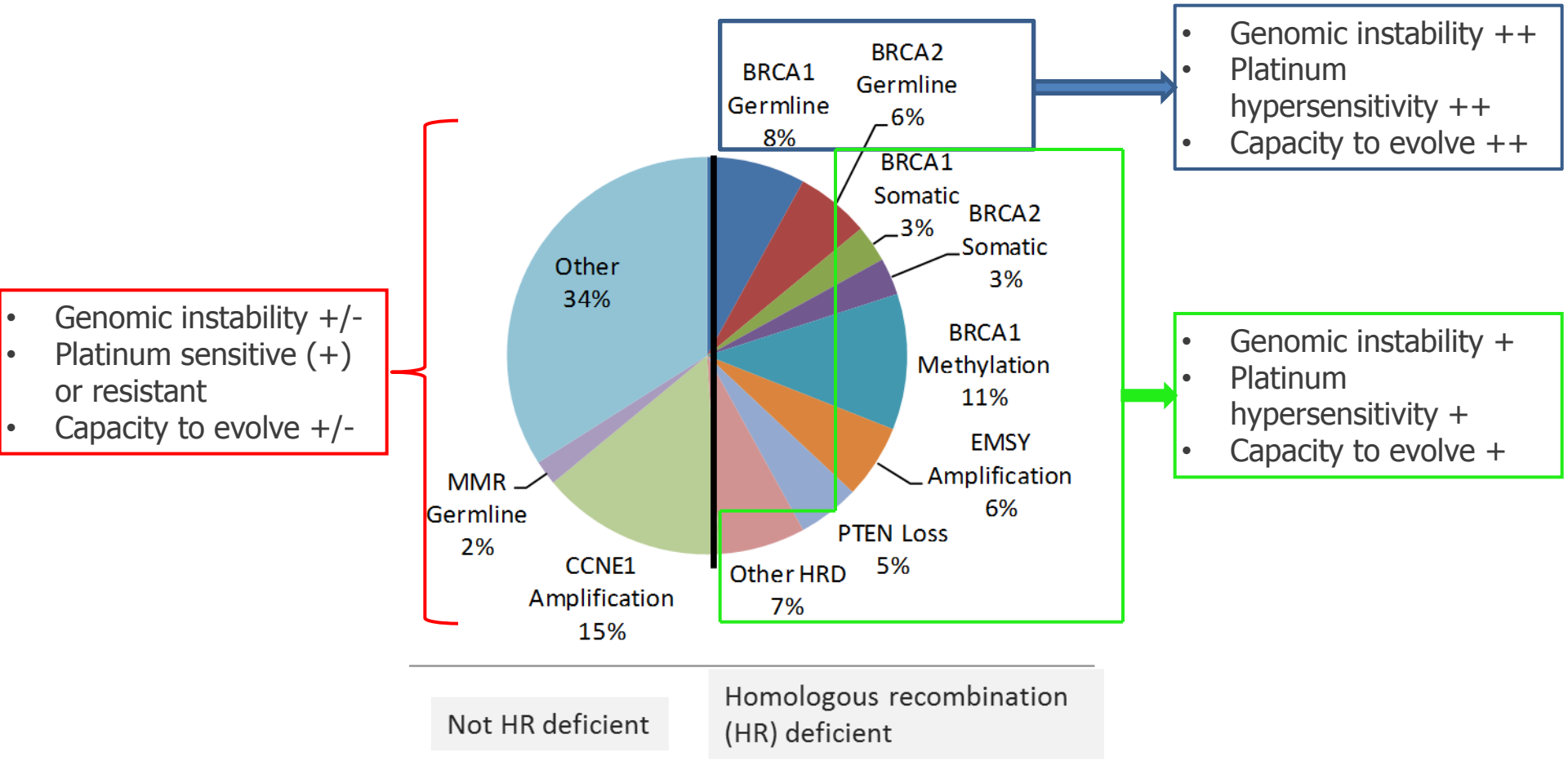


Wang et al CCR 2012



McBride et al J Pathol 2012

Link between HRD, platinum sensitivity and capacity to evolve

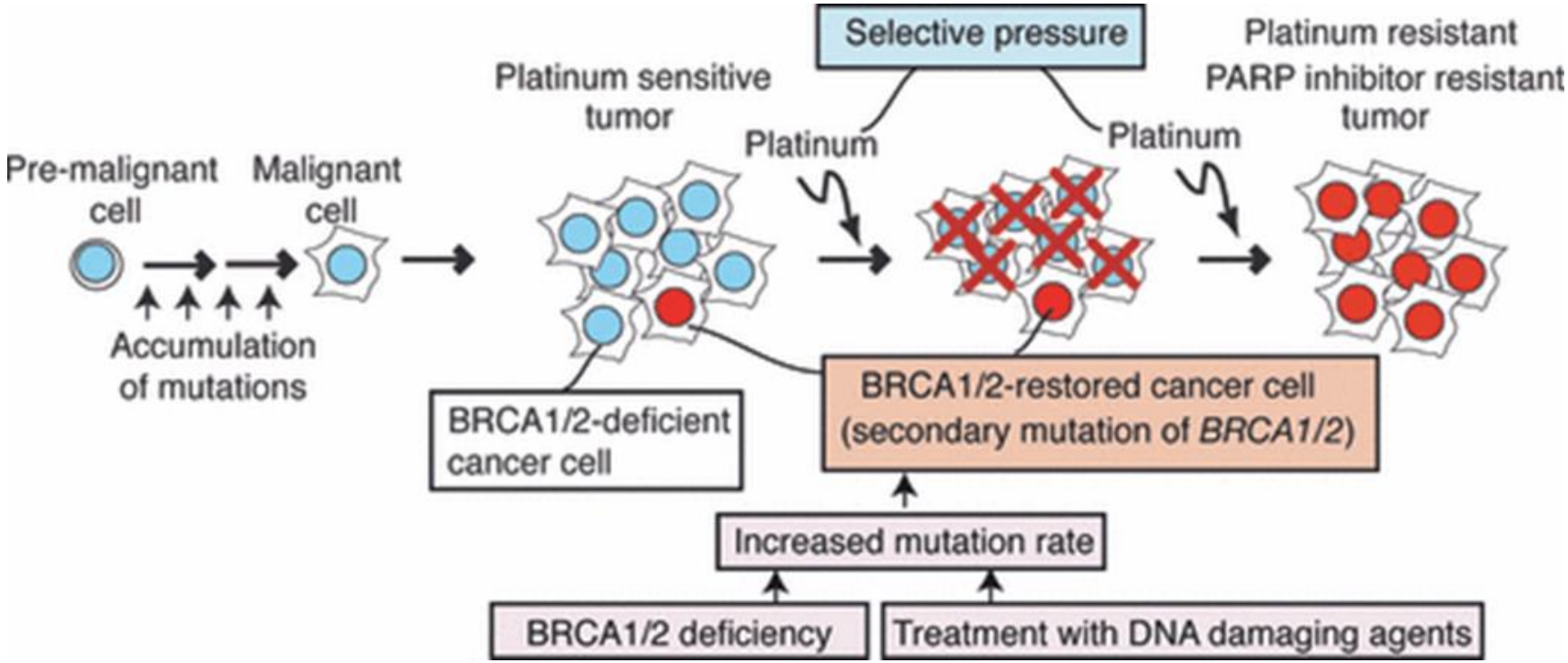


- Genomic instability ++
- Platinum hypersensitivity ++
- Capacity to evolve ++

- Genomic instability +
- Platinum hypersensitivity +
- Capacity to evolve +

- Genomic instability +/-
- Platinum sensitive (+) or resistant
- Capacity to evolve +/-

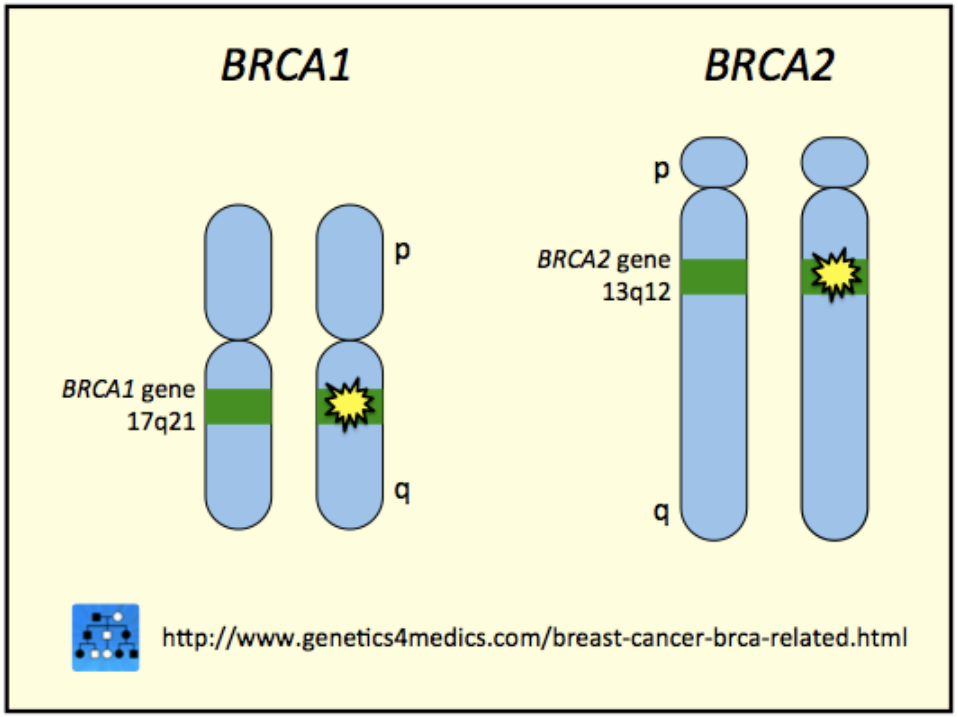
Adapted from TCGA, Nature 2011



Dhillon et al, Cancer Science 2011

Are there any truly validated biomarkers fit for purpose wrt guiding surgical effort/timing?

Are there any other current biomarkers with potential relevance wrt surgery?



GOG 172

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intraperitoneal Cisplatin and Paclitaxel in Ovarian Cancer

Deborah K. Armstrong, M.D., Brian Bundy, Ph.D., Lari Wenzel, Ph.D., Helen Q. Huang, M.S., Rebecca Baergen, M.D., Shashikant Lele, M.D., Larry J. Copeland, M.D., Joan L. Walker, M.D., and Robert A. Burger, M.D., for the Gynecologic Oncology Group*

- Patients debulked to <1c.m. residual

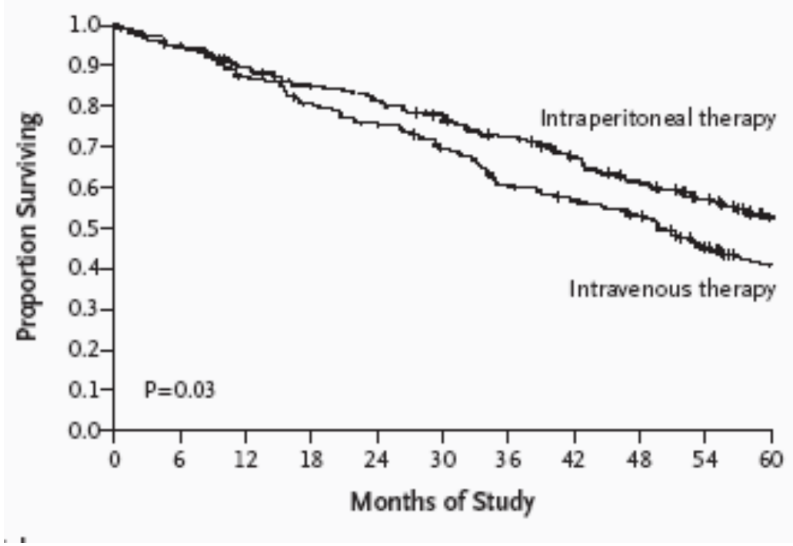
IV paclitaxel 135mg/m^2 over 24 hours then:

IV cisplatin 75mg/m^2 on day 2

or

IP cisplatin 100mg/m^2 day2 and IP paclitaxel 60mg/m^2 day 8

- Chemotherapy given 3-weekly x 6

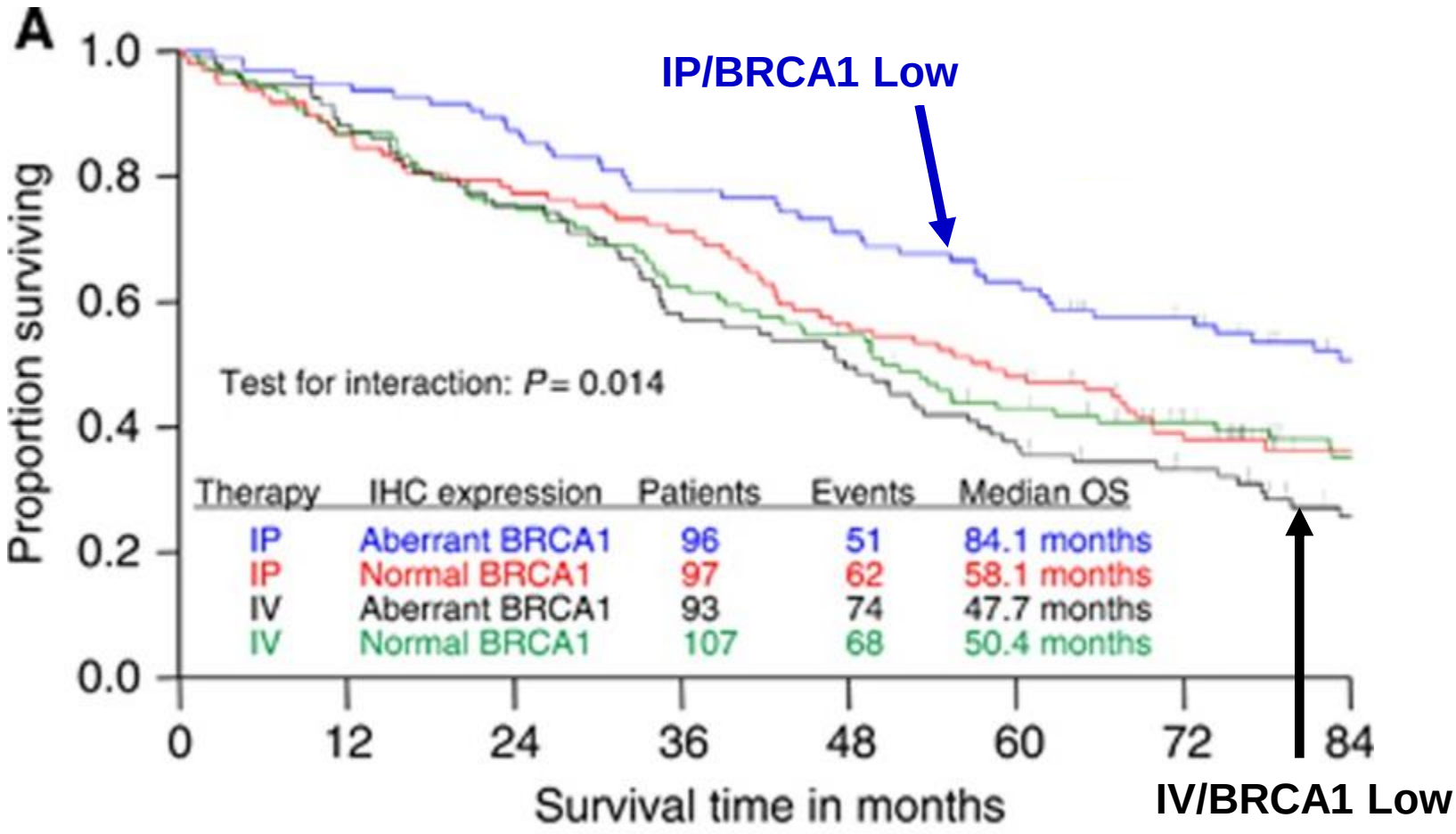


- PFS was 18 cf 24 months (p=0.05)
- OS was 66 cf 50 months (p=0.03)

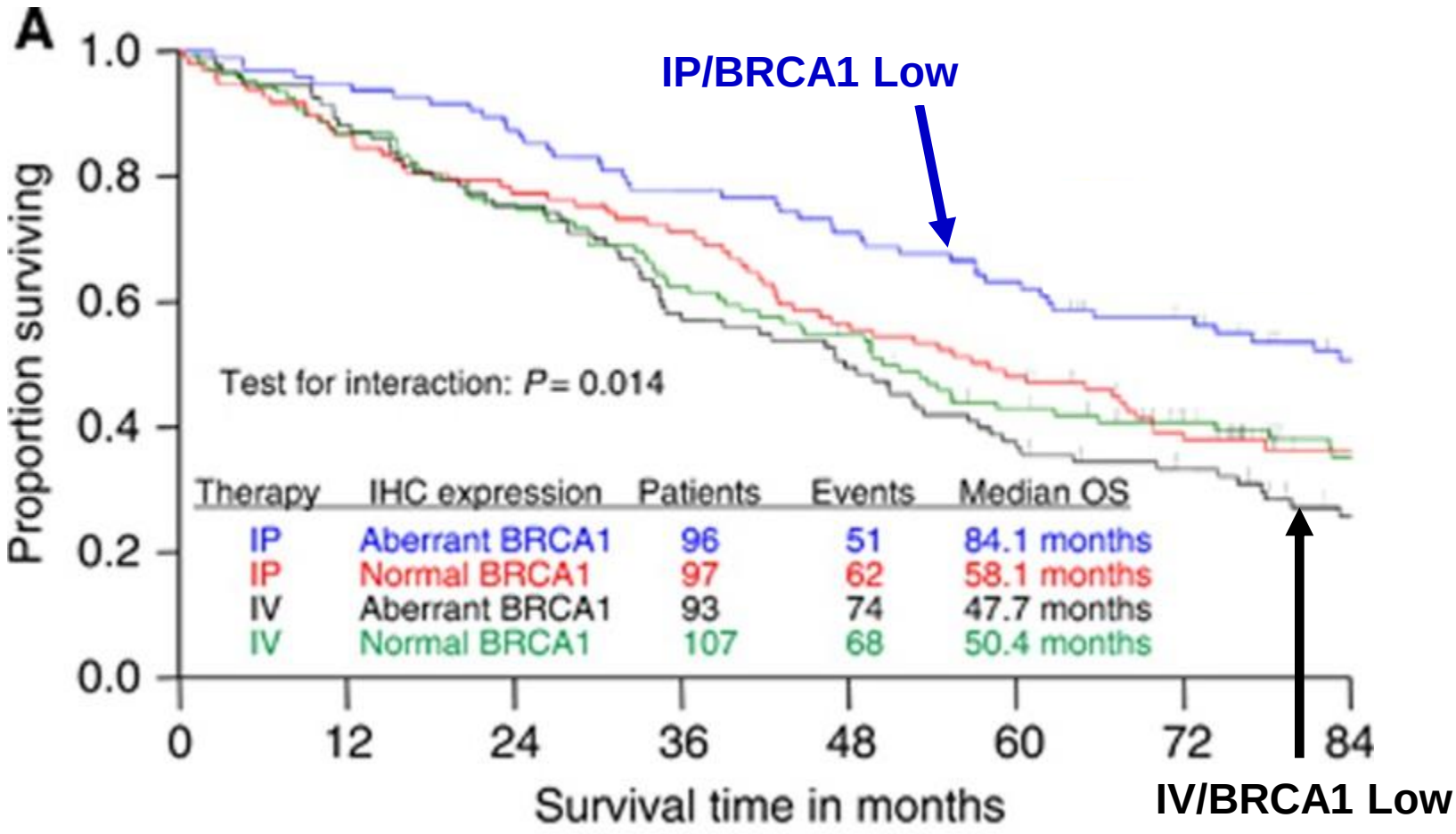
Updated GOG114 and 172 survival analysis

- Patients with microscopic disease had median OS of 110 months following IP chemo cf 82 months following IV chemo
- In GOG172 stage III patients with no residual disease post primary debulking the median OS is 128 months (10.7 years)

Tewari et al, SGO 2013 (abstr)
Landrum et al, Gyne Oncol 2013



Lesnock et al, BJC 2013



Dose-response relationship aberrant *BRCA1* tumours?

IP benefit confined to BRCA1? BRCA2? HRD?

- This is the most impressive survival (+survival benefit) in any first line phase III ovarian cancer study to date.
- More translational work is required to clarify the subgroup that particularly benefits from intraperitoneal therapy
- **No suggestion that this benefit extends to IP chemo following NACT and DPS**

Exploratory biomarkers

- Gene expression signatures

Supervised versus unsupervised analysis

Supervised

- Choose a factor (e.g. survival, chemosensitivity, debulking status)
- Identify genes that pull out your patient group of choice
- Validate
- ‘Loading the dice’

Unsupervised

- Cluster tumours together according to how similar their gene expression is
- ‘Let the biology do the talking’

Supervised analyses

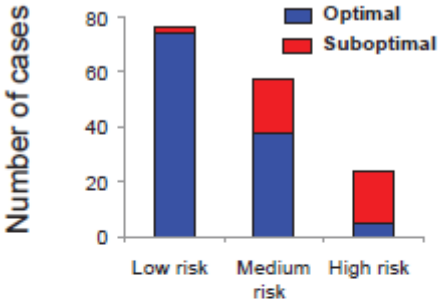
Risk Prediction for Late-Stage Ovarian Cancer by Meta-analysis of 1525 Patient Samples

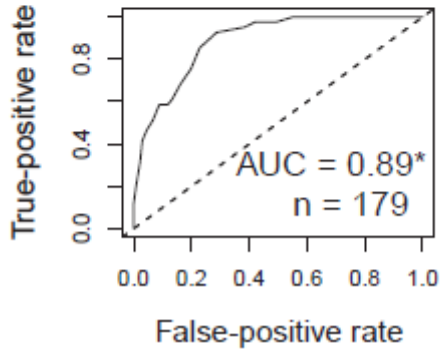
Markus Riester, Wei Wei, Levi Waldron, Aedin C. Culhane, Lorenzo Trippa, Esther Oliva, Sung-hoon Kim, Franziska Michor, Curtis Huttenhower, Giovanni Parmigiani, Michael J. Birrer

Manuscript received October 10, 2013; revised January 23, 2014; accepted January 29, 2014.

Correspondence to: Michael J. Birrer, MD, PhD, Massachusetts General Hospital Cancer Center, Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114 (e-mail: mbirrer@partners.org).

- 1061 patients from 8 public datasets
- Developed a gene expression signature for debulking (supervised analysis)
- Accurate prediction in validation dataset was poor for the signature (AUC=0.59)
- Selected seven highly differentially expressed geneswith known roles in ovarian tumorigenesis and validated their predictive power by qRT-PCR and IHC
- The sum of IHC intensities for 3 proteins (POSTN, CXCL14 and phospho SMAD2/3) correctly classified 93% of patients (AUC=0.89)





Imaging, Diagnosis, Prognosis

Clinical Cancer Research

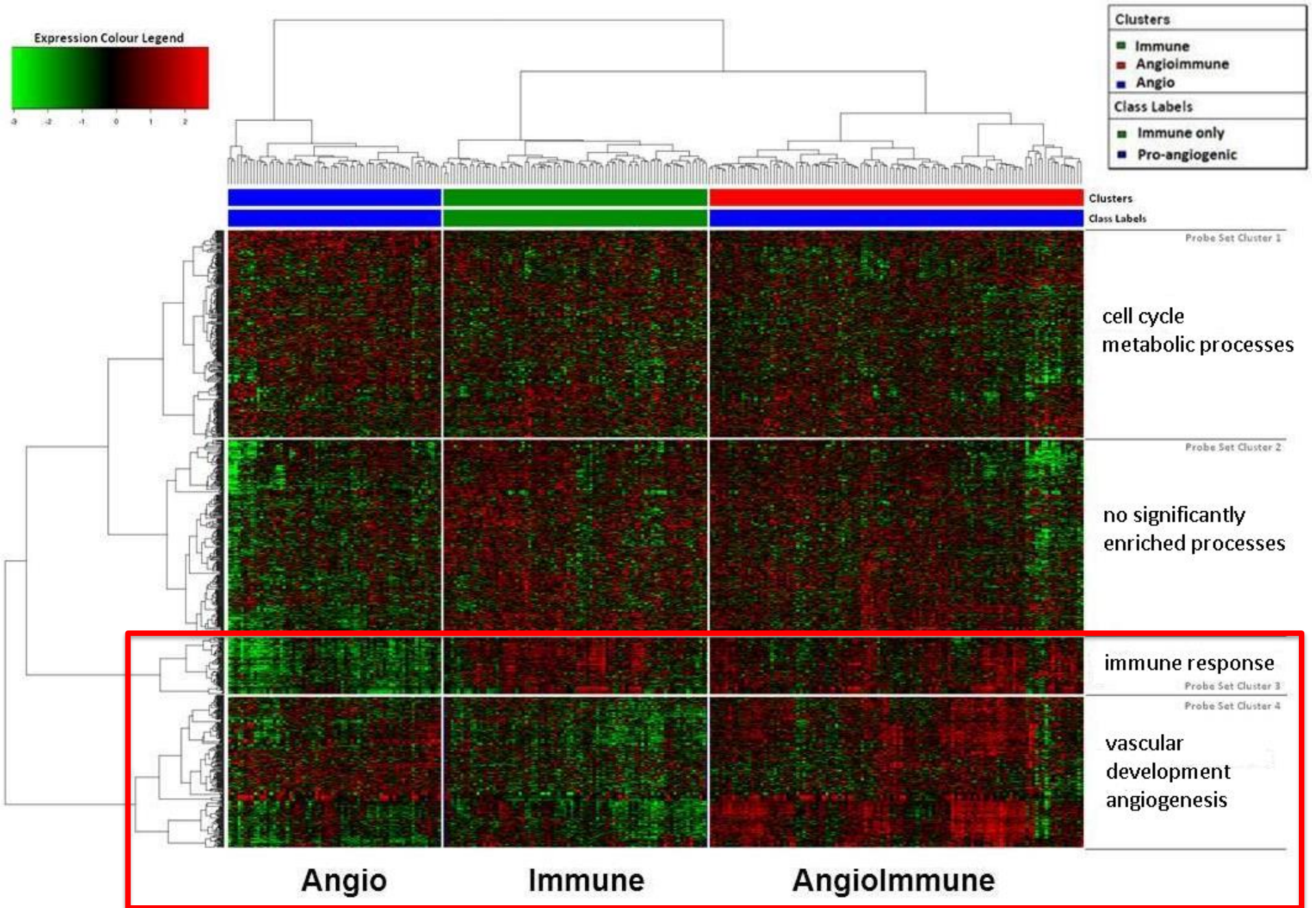
Molecular Biomarkers of Residual Disease after Surgical Debulking of High-Grade Serous Ovarian Cancer

Susan L. Tucker[1], Kshipra Gharpure[2], Shelley M. Herbrich[1], Anna K. Unruh[1], Alpa M. Nick[2], Erin K. Crane[2], Robert L. Coleman[2], Jamie Guenthoer[6], Heather J. Dalton[2], Sherry Y. Wu[2], Rajesha Rupaimoole[2], Gabriel Lopez-Berestein[3,5], Bulent Ozpolat[3], Cristina Ivan[2], Wei Hu[2], Keith A. Baggerly[1], and Anil K. Sood[2,4,5]

- Supervised gene expression analysis of 680 patients from two publicly available datasets (Tothill and TCGA)
- 47 probes met the required level of statistical significance in both datasets
- In the validation cohort high expression of FABP4 and ADH1B were both assoc with significantly increased risk of residual disease
- Unusually the most predictive result was that from a single gene (FABP4):
  - Upper quartile predicted 30 out of 35 suboptimally debulked (PPV=86%)
  - Rest of patients (i.e other ¾): 54 out of 104 suboptimally debulked

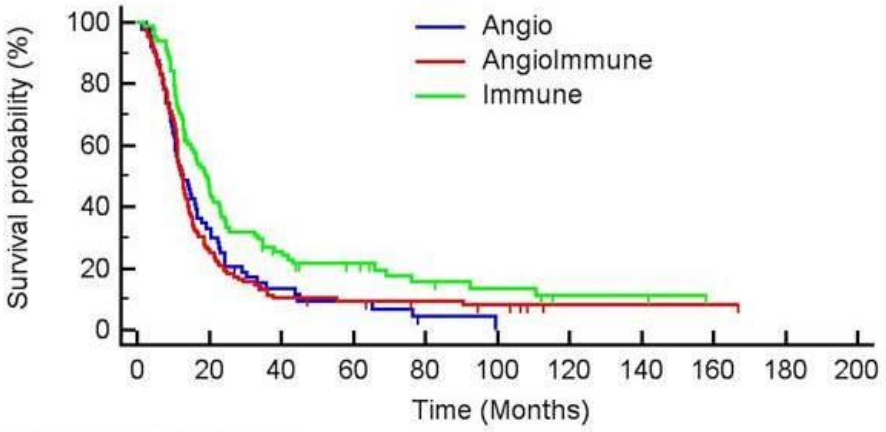
Unsupervised analysis

Edinburgh dataset; unsupervised hierarchical clustering



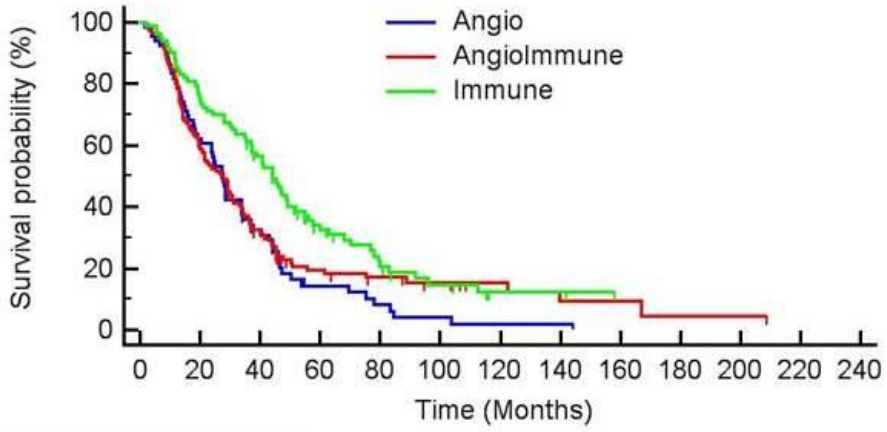
Edinburgh dataset; survival analysis

Progression free survival



	HR	95% C.I.	p-value
Immune vs Angioimmune	0.60	0.44-0.82	0.002
Immune vs Angio	0.64	0.45-0.92	0.02

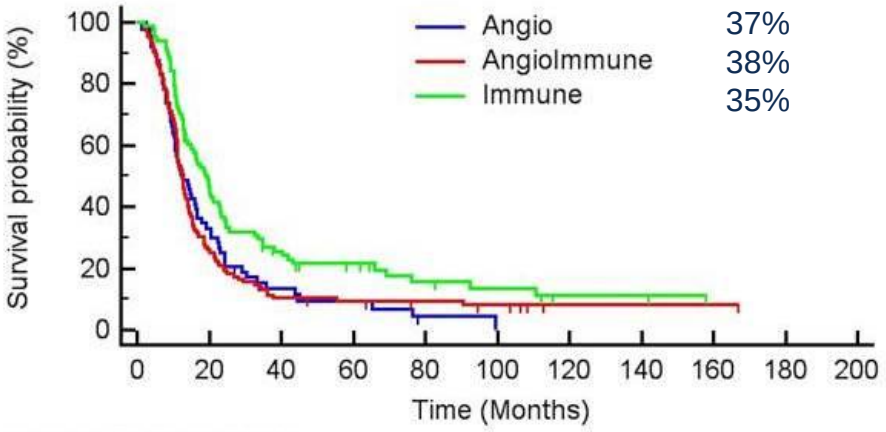
Overall survival



	HR	95% C.I.	p-value
Immune vs Angioimmune	0.58	0.41-0.82	0.001
Immune vs Angio	0.55	0.37-0.80	0.001

Edinburgh dataset; % optimal debulking

Progression free survival



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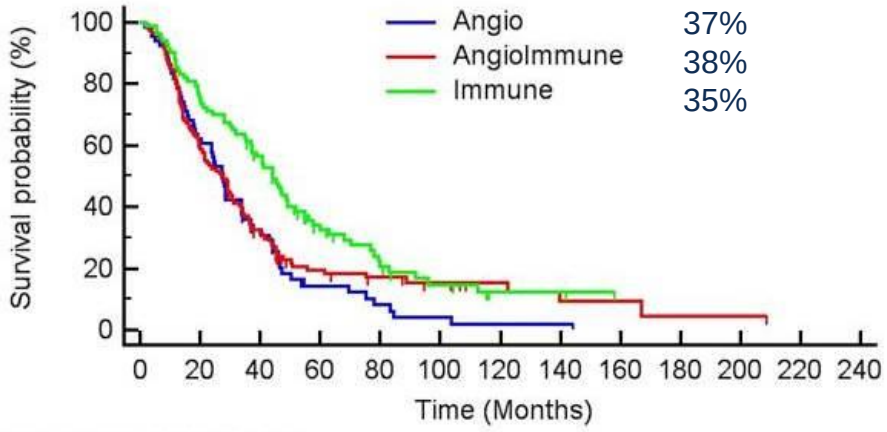

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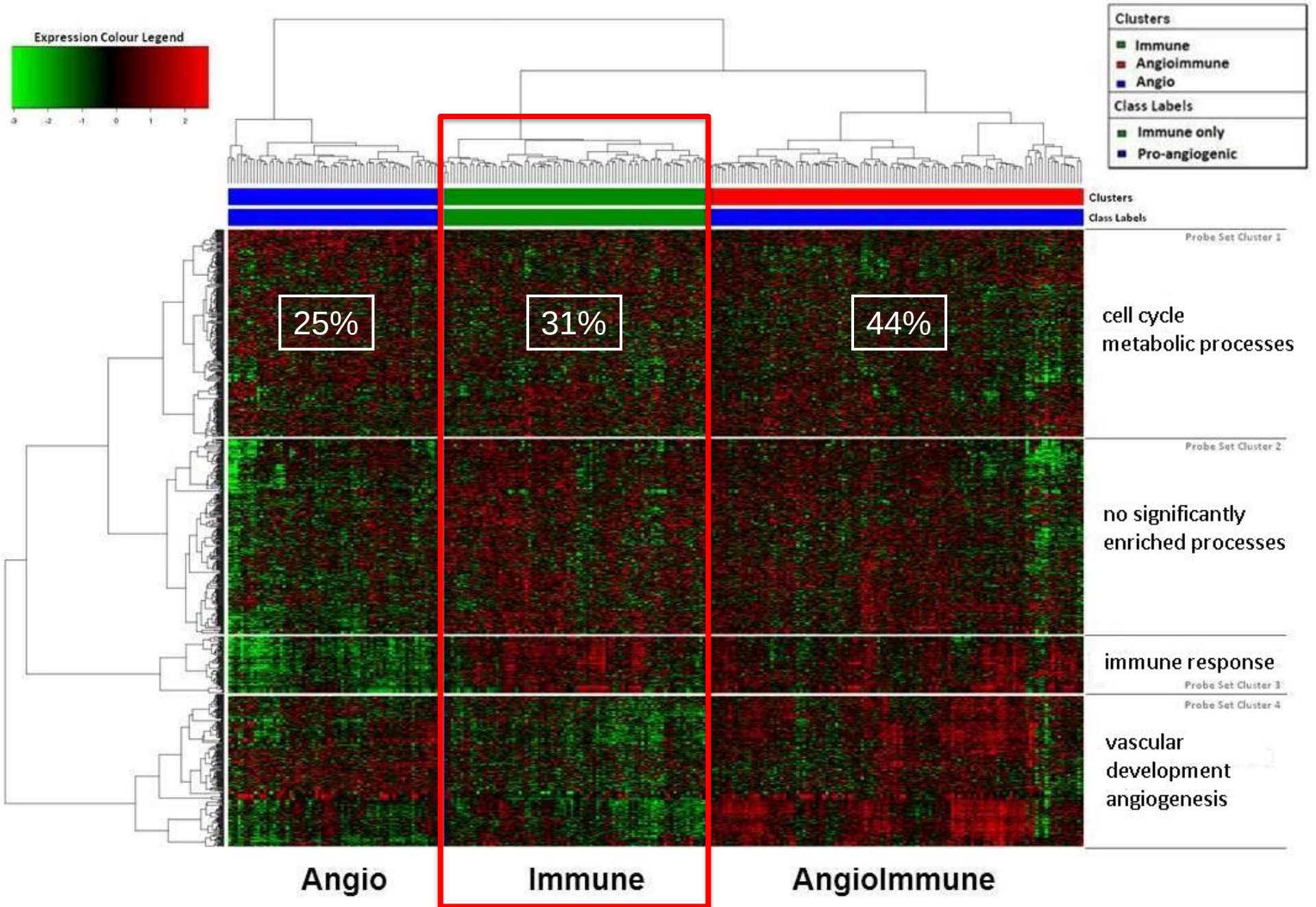
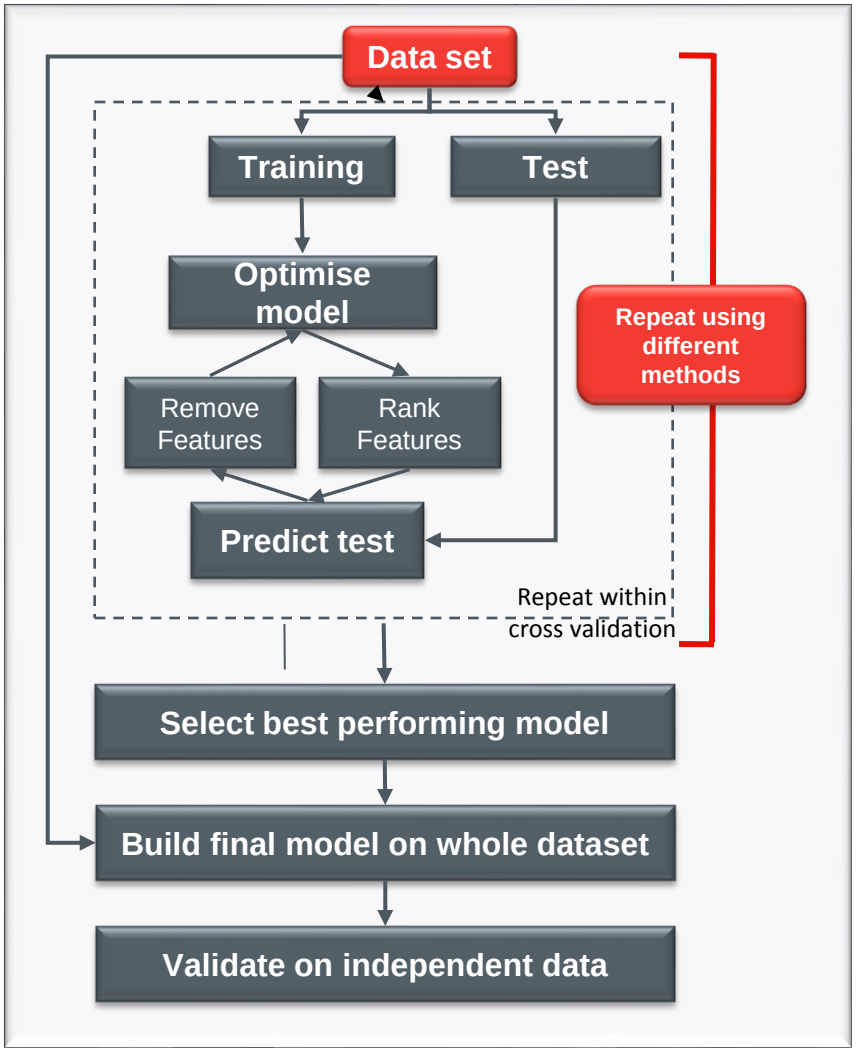
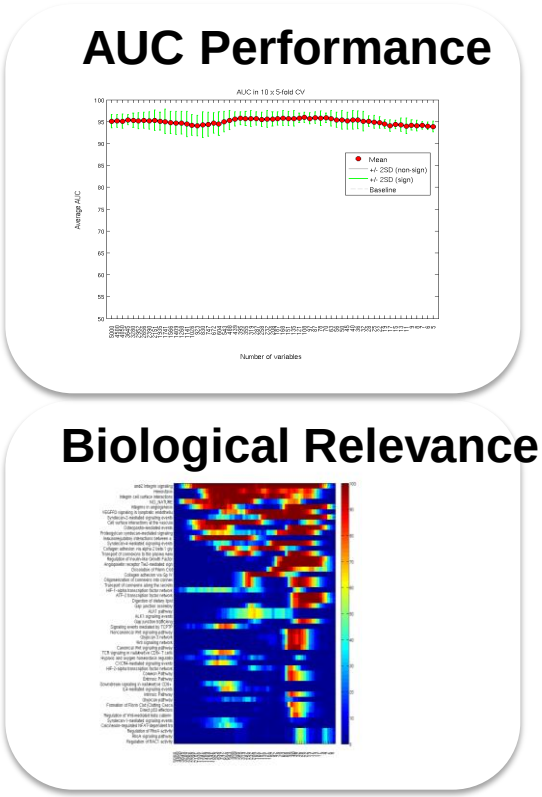
Edinburgh dataset; unsupervised hierarchical clustering



Edinburgh dataset; Immune subgroup signature generation

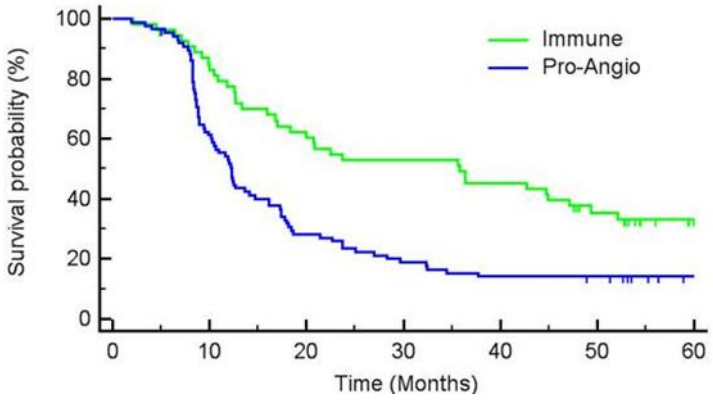




63-gene signature developed to distinguish Immune subgroup patients from those in the Angio and Angioimmune subgroups.

Immune signature prognostic within the control arm of ICON7

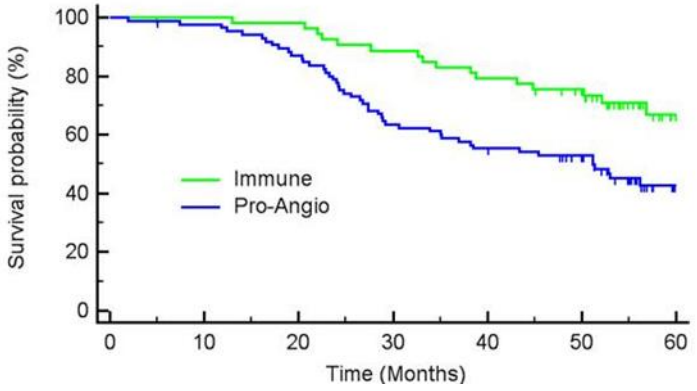
PFS



Univariate: **HR = 0.47 [0.32-0.71], p < 0.001**

Multivariable: **HR = 0.52 [0.33-0.81], p = 0.004**

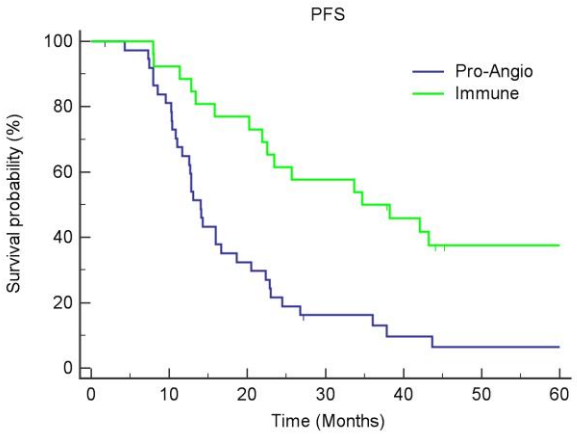
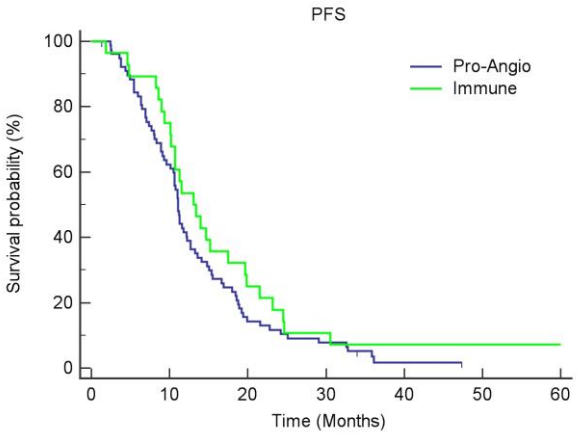
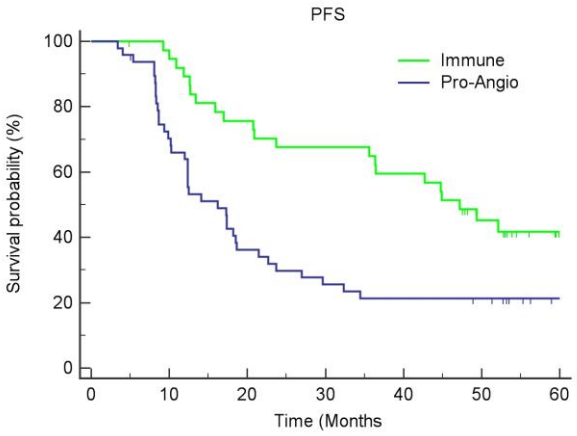
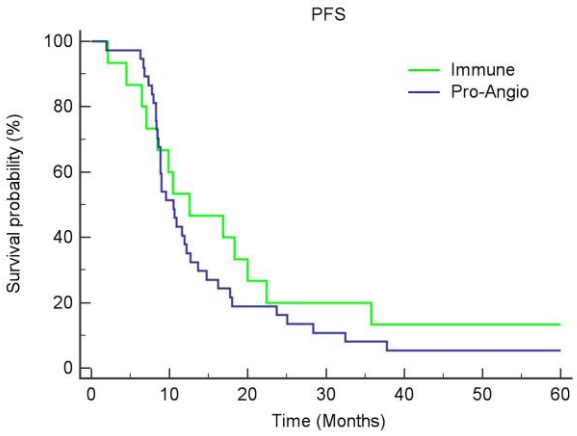
OS



HR = 0.45, [0.26-0.79], p =0.005

HR = 0.53 [0.29-0.96], p = 0.04

Immune subgroup patients only have improved outcome if they get good surgery

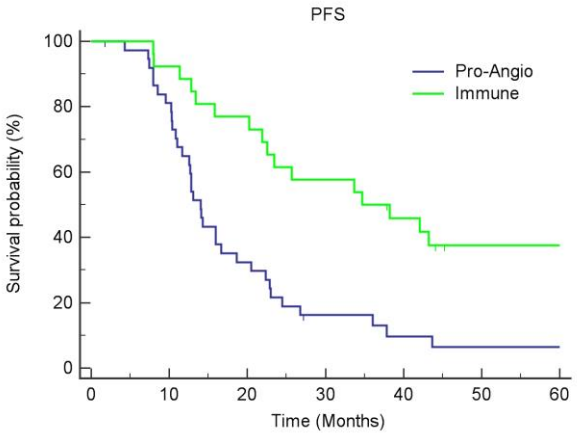
	Optimal surgery	Suboptimal surgery
Edinburgh patients		
	HR=0.34, p<0.001	HR=0.71, p=0.13
ICON7 patients (control arm)		
	HR=0.44, p=0.003	HR=0.64, p=0.12

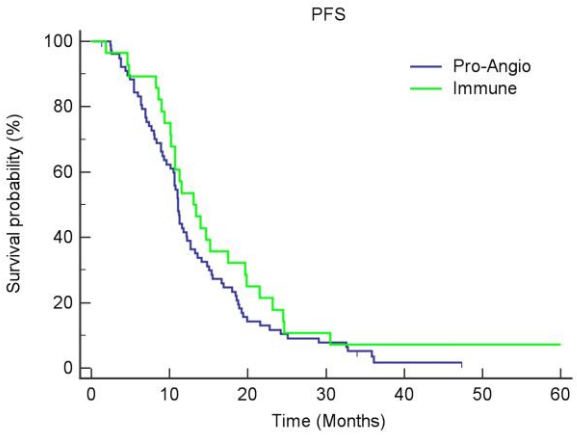
Immune subgroup patients only have improved outcome if they get good surgery

Optimal surgery

Suboptimal surgery

Edinburgh patients



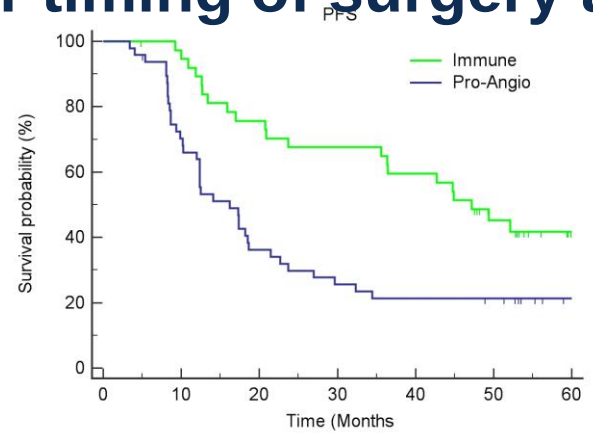


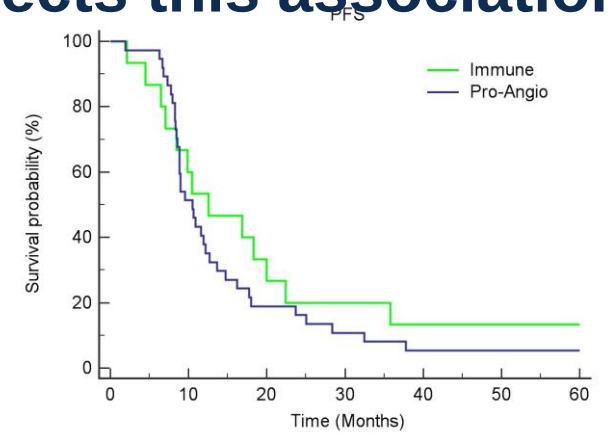
HR=0.34, p<0.001

HR=0.71, p=0.13

Not clear whether timing of surgery affects this association

ICON7 patients (control arm)





HR=0.44, p=0.003

HR=0.64, p=0.12

Case

- 36 year old lady; para 1+0 (2 year old boy)
- Identified as germ line *BRCA1* mutation carrier through genetics clinic
- 2012: Prophylactic bilateral mastectomies
  CA125 monitoring
- 2013: CA125 ↑ to 600 from 25 (asymptomatic)
  CT scan: ascites, omental and peritoneal disease; upper abdomen +++ para-aortic lymphadenopathy

What surgery do you advise?

- Laparoscopy +/- proceed?
- Upfront debulking?
- Neoadjuvant chemo+ delayed primary surgery?

Surgery received

Laparoscopy: disseminated disease; difficult but possible to optimally resect

Primary laparotomy: Total abdominal hysterectomy, bilateral salpingo-oophorectomy, appendicectomy, lymph node dissection and peritoneal stripping.

Resected to zero macroscopic residual

What systemic treatment do you advise?

- IV carboplatin and paclitaxel?
- IP carboplatin and paclitaxel?
- IP cisplatin and paclitaxel?

- Do you also advise bevacizumab?

Systemic treatment received

- IP cisplatin and paclitaxel (Armstrong regime)
- Randomisation to olaparib or placebo (SOLO1 study)

Summary

- High grade serous ovarian cancer has massive genomic instability and capacity to evolve
- Timing of surgery may be important in minimising residual cancer cells and this may only be apparent on analysing subgroups (BRCA1/2 status/HRD etc)
- There are no validated biomarkers to guide surgical timing but some can identify patients for whom complete primary debulking unlikely
- There are molecular subgroups whose prognostic benefit is dependent on extent of debulking but effect of surgical timing is unclear
- **More translational analyses required in surgical studies**

Acknowledgements

- **The patients and their families**

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  – Caroline Michie, Michael Churchman, Alistair Williams, David Harrison, Fiona Campbell, Tammy Piper and John Bartlett

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  – Tim Perren, investigators from all UK recruiting sites

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  – James Paul, Mahesh Parmar, Richard Kaplan

- Scientists from Queens University, Belfast
  – Glenn McCluggage, Patrick Johnston

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