Clear cell carcinoma

Biology and therapy

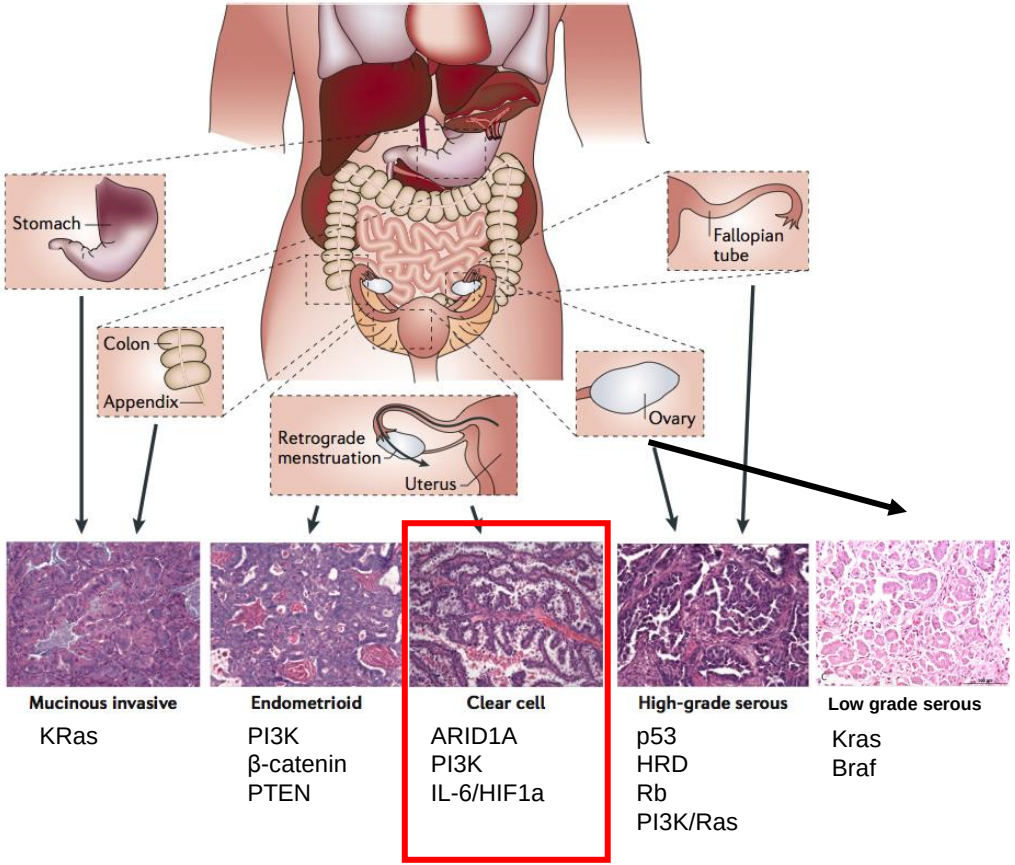
ESMO Preceptorship, Prague, 22nd April 2017

Iain McNeish
Professor of Gynaecological Oncology
Wolfson Wohl Cancer Research Centre
Institute of Cancer Sciences
University of Glasgow, UK

What I shall discuss

- Clinical behaviour
- Biology
- Future trials and treatments

Current view of ovarian cancer biology



Vaughan et al Nat Rev Cancer (2011) 11:719

Histologically Distinct

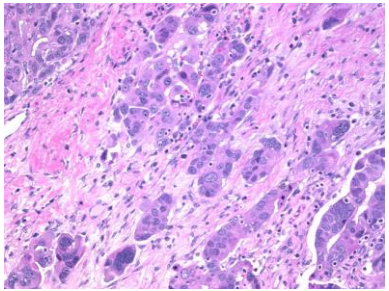
First described in 1939 as mesonephroma ovarii

Cells arranged in tubules, nests or cysts

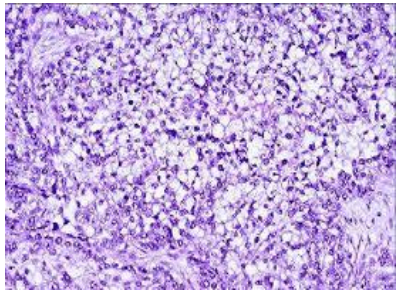
Clear, glycogen-rich cytoplasm

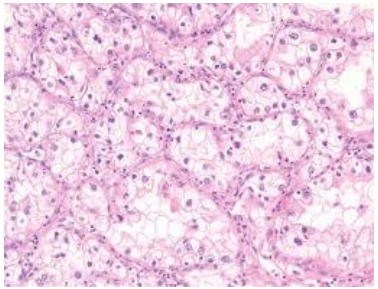
Immunophenotype: ER and WT1 –ve, HNF-1β +ve*

High Grade Serous



Clear Cell Carcinoma





*Kobel *et al* Am J Surg Pathol 2009

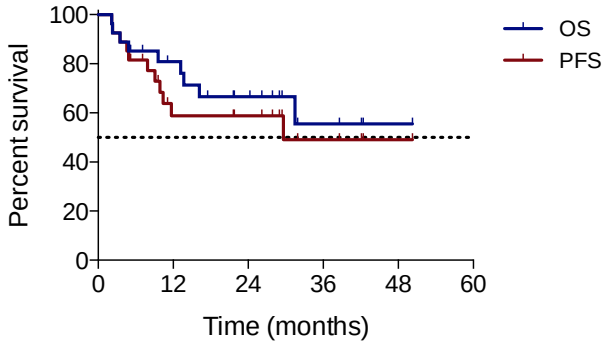
Clinical Behaviour

- Younger (median 55 v 64 yr)
- Endometriosis
- Venous thromboembolic complications
- Hypercalcaemia
- More likely to present at an early stage
  - (Stage 1: 50% v <20% in HGS)
  - EORTC-ACTION: 5Y DFS 71% in CCC v 61% in serous cancer

Real clinical experience (my own….)

Subtype	No.cases	%	No. deaths	%
High Grade Serous	294	74.1	99	79.8
Low Grade Serous	15	3.8	1	0.8
Endometrioid	33	8.3	2	1.6
Clear Cell	27	6.8	9	7.3
Mucinous	8	2.0	4	3.2
Carcinosarcoma	14	3.5	7	5.6
Squamous cell carcinoma	4	1.0	2	1.6
Adenocarcinoma NOS	2	0.5	0	0.0
Total	397		124	

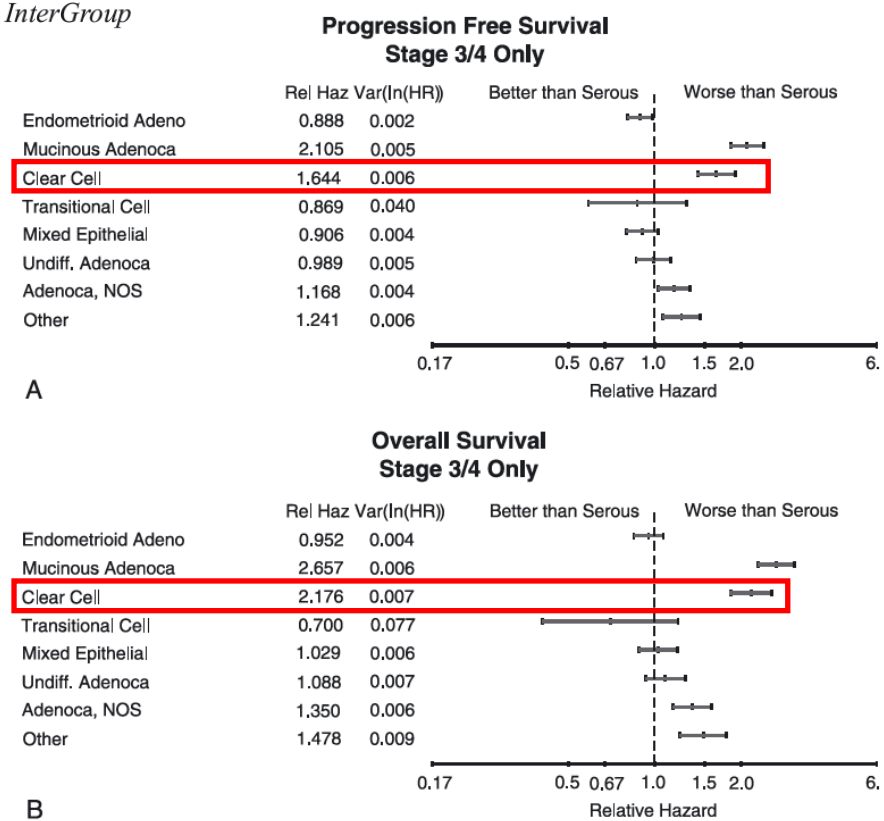
Stage	HGS	%	Clear cell	%
Stage 1A+1B	7	2.4	1	3.7
Stage 1C	9	3.1	14	51.9
Stage 2	18	6.1	0	0.0
Stage 3A+3B	12	4.1	4	14.8
Stage 3C	175	59.5	5	18.5
Stage 4	73	24.8	3	11.1
Total	294		27	



McNeish/Glasspool Beatson Cancer Centre newly diagnosed patients 2013 – 2017

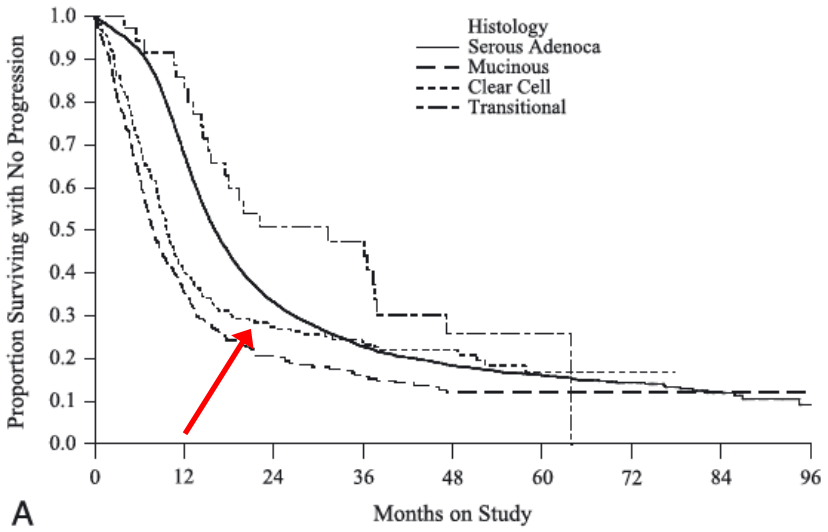
Prognostic Relevance of Uncommon Ovarian Histology in Women With Stage III/IV Epithelial Ovarian Cancer

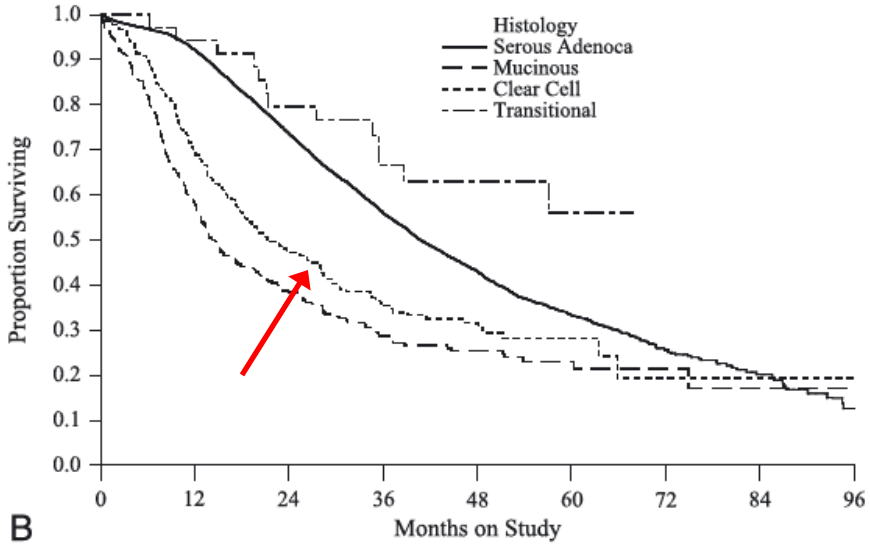
Helen J. Mackay, MD, Mark F. Brady,† Amit M. Oza,* Alexander Reuss,‡ Eric Pujade-Lauraine,§ Ann M. Swart,|| Nadeem Siddiqui,¶ Nicoletta Colombo,** Michael A. Bookman,† Jacobus Pfisterer,‡ and Andreas du Bois,‡ and on behalf of the Gynecologic Cancer InterGroup*



McKay et al (2010) Int J. Gynecol Cancer 20:945

PFS and OS in GCIG trials





McKay et al (2010) Int J. Gynecol Cancer 20:945

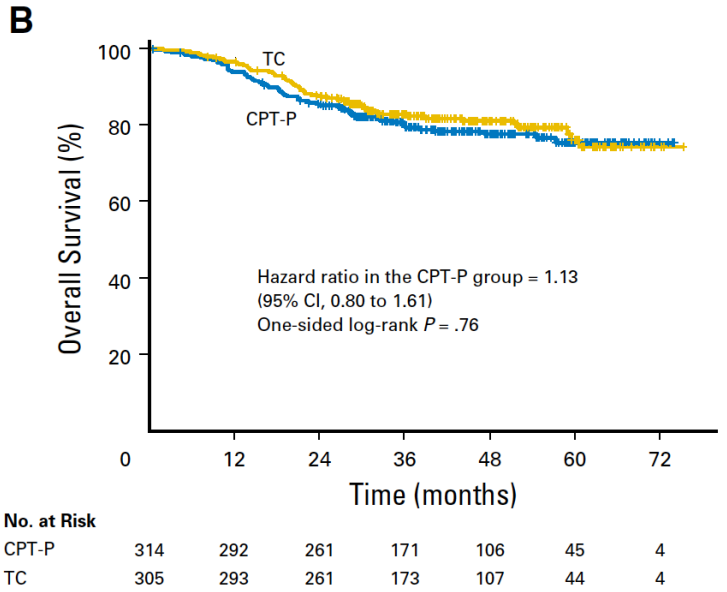
Only phase III trial specifically in clear cell carcinoma

VOLUME 34 · NUMBER 24 · AUGUST 20, 2016
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized Phase III Trial of Irinotecan Plus Cisplatin Compared With Paclitaxel Plus Carboplatin As First-Line Chemotherapy for Ovarian Clear Cell Carcinoma: JGOG3017/GCIG Trial

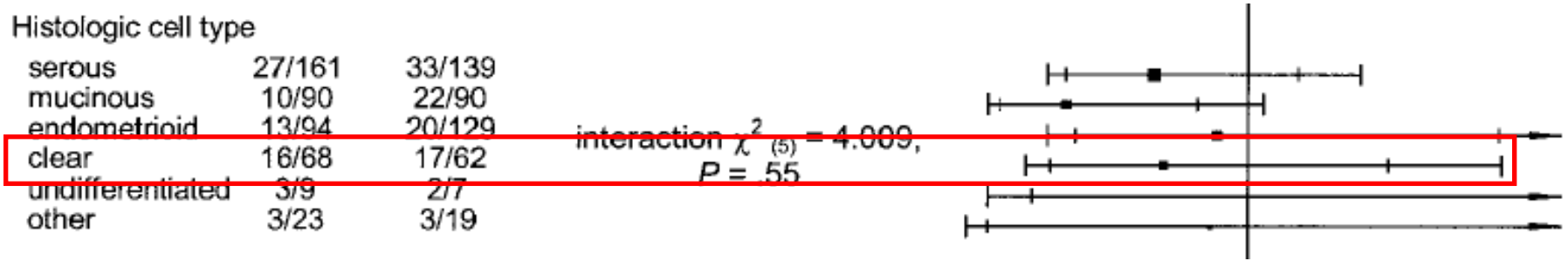
Toru Sugiyama, Aikou Okamoto, Takayuki Enomoto, Tetsutaro Hamano, Eriko Aotani, Yasuhisa Terao, Nao Suzuki, Mikio Mikami, Nobuo Yaegashi, Kiyoko Kato, Hiroyuki Yoshikawa, Yoshihito Yokoyama, Hiroshi Tanabe, Koji Nishino, Hiroyuki Nomura, Jae-Weon Kim, Byoung-Gie Kim, Sandro Pignata, Jerome Alexandre, John Green, Seiji Isonishi, Fumitoshi Terauchi, Keiichi Fujiwara, and Daisuke Aoki

- N = 677
- Stage I – IV
- Carboplatin (AUC6) + paclitaxel (175mg/m^2) q3/52 vs.
- Irinotecan (60mg/m^2 weekly) + cisplatin (60mg/m^2) q3/52
- Primary endpoint = PFS
- Central pathology review following registration: 43/667(6.4%) ineligible
- 32 (5.2%) had measureable disease – overall response rate 37.5%

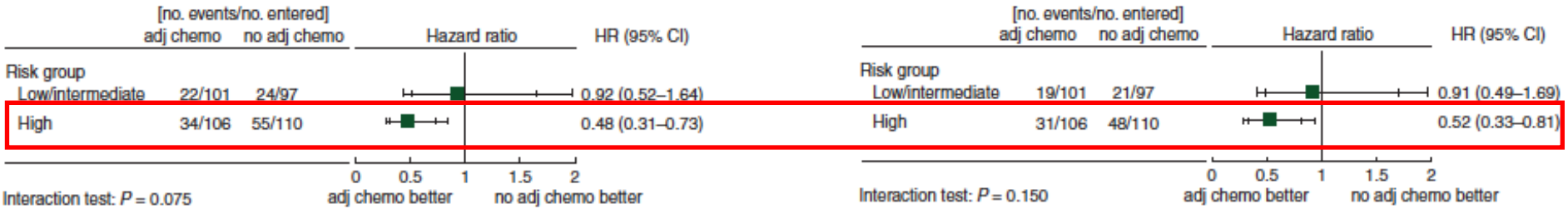


Sugiyama et al (2016) J Clin Oncol 34:2881

Chemotherapy in early stage clear cell

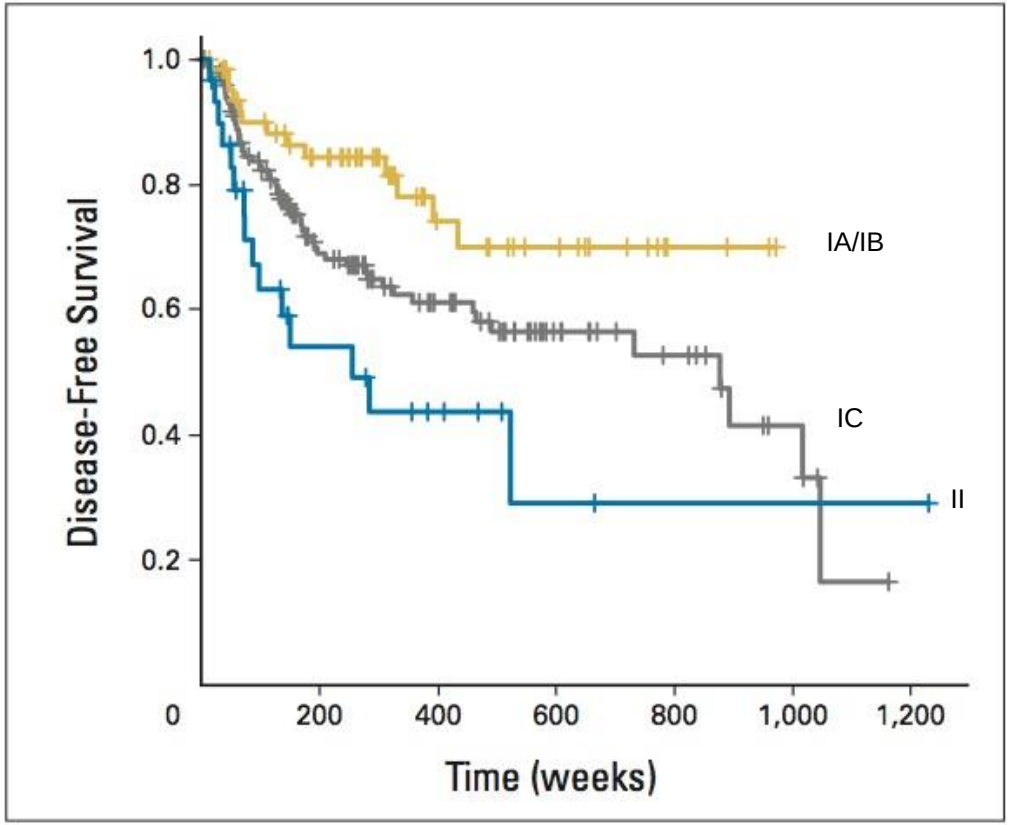


Trimbos et al (2003) JNCI 95:105



Collinson et al (2014) Ann. Oncol. 25:1165

Does stage IA clear cell need chemotherapy?



Hoskins et al J Clin Oncol (2012) 30:1656-62

Does stage IA clear cell need chemotherapy?

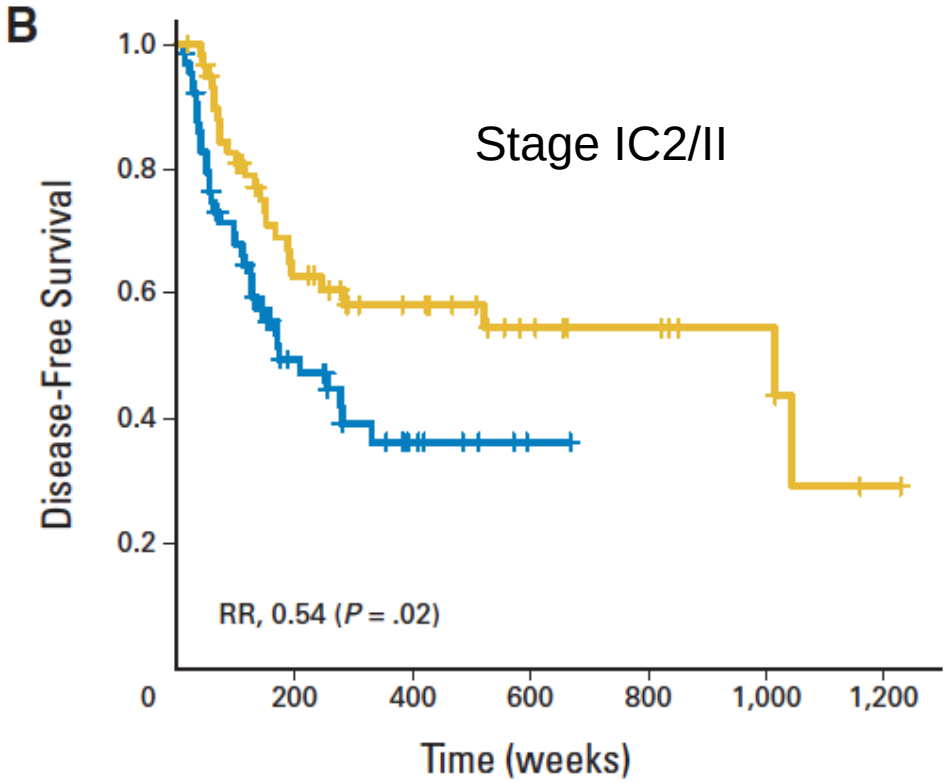
Table 2. Five-Year DFS in the Modern Era

Study Characteristic and DFS	Study					
	Chan et al[4]	Takano et al[16]	Suzuki et al[25]	Sugiyama et al[10]	Mizuno et al[19]	Current Study
No. of patients	1,411	254	143	49	82	241
Country	United States	Japan	Japan	Japan	Japan	Canada
Study period	1988-2001	1992-2003	1986-2006	1998-1998	1988-1996	2000-2008
Disease-free survival by stage, %						
IA	92	96		100	96	84
IC	77		77	63	76	64
IC (rupture alone)		89			86	88
IC (other)*		66			59	41
II	66	57			62	44

Abbreviation: DFS, disease-free survival.
*Stage IC (other): cytologic positivity and/or surface involvement.

Hoskins et al J Clin Oncol (2012) 30:1656-62

Does radiotherapy play a role?

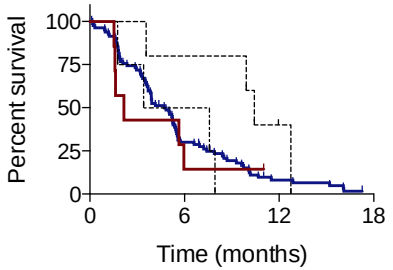


Hoskins et al J Clin Oncol (2012) 30:1656-62

Relapsed ovarian clear cell carcinoma

Trial	Total	% clear cell	% clear cell
CALYPSO	973	27	2.8
OCEANS	484	13	2.7
AURELIA	361	16	4.4
TOTAL	**1818**	**56**	**3.1**

SaPPROC



	RR, N (%)
HGS/G3 endometrioid	25/76 (37.3%)
LGS	
G1/2 Endometrioid	
Clear cell	2/6 (33.3%)

McNeish et al (2014) Ann. Oncol. 25:1988

Low response rate of second-line chemotherapy for recurrent or refractory clear cell carcinoma of the ovary: a retrospective Japan Clear Cell Carcinoma Study

M. TAKANO*, T. SUGIYAMA†, N. YAEGASHI‡, M. SAKUMA‡, M. SUZUKI§, Y. SAGA§, K. KUZUYA||, J. KIGAWA¶, M. SHIMADA¶, H. TSUDA#, T. MORIYA**, A. YOSHIZAKI†, T. KITA* & Y. KIKUCHI*

*Department of Obstetrics and Gynecology, National Defense Medical College, Tokorozawa, Saitama, Japan; †Department of Obstetrics and Gynecology, Iwate Medical University, Morioka, Iwate, Japan; ‡Department of Obstetrics and Gynecology, Tohoku University, Sendai, Miyagi, Japan; §Department of Obstetrics and Gynecology, Jichi Medical College, Kawachi-gun, Tochigi, Japan; ||Department of Gynecology, Aichi Cancer Center Hospital, Nagoya, Aichi, Japan; ¶Department of Obstetrics and Gynecology, Tottori University, Yonago, Tottori, Japan; #Department of Pathology II, National Defense Medical College, Tokorozawa, Saitama, Japan; and **Pathology Laboratory of Central Clinical Facilities, Tohoku University, Sendai, Miyagi, Japan

	PR, N (%)	SD, N (%)	PD, N (%)	ORR (%)	Non-PD rate (%)
>6 months PFI	2 (8%)	5 (21%)	17 (71%)	8	29
<6 months PFI	3 (6%)	6 (12%)	42 (82%)	6	1
TOTAL	**5 (7%)**	**11 (15%)**	**59 (79%)**	**7**	**21**

Takano et al (2008) Int. J. Gynecol. Cancer 18:937

What I shall discuss

- Clinical behaviour
- Biology
- Future trials and treatments

Different Biology

- *TP53* wild type and *BRCA* mutations rare
- Some genomic instability but far less than HGSC
- Gene expression – angiogenesis and IL-6
- *ARID1A* (c.50%) mutation
- *PIK3CA* (c.33%) mutation
- MET amplification

Endometriosis

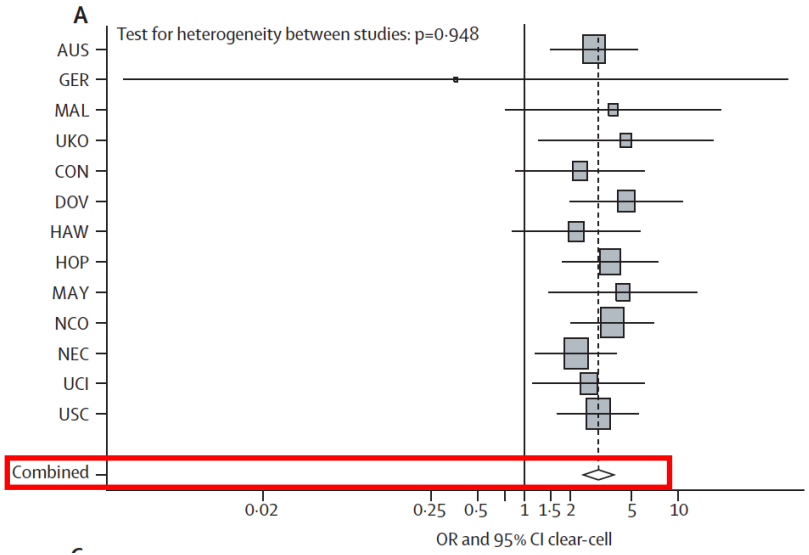
Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case–control studies

Celeste Leigh Pearce, Claire Templeman, Mary Anne Rossing, Alice Lee, Aimee M Near, Penelope M Webb, Christina M Nagle, Jennifer A Doherty, Kara L Cushing-Haugen, Kristine G Wicklund, Jenny Chang-Claude, Rebecca Hein, Galina Lurie, Lynne R Wilkens, Michael E Carney, Marc T Goodman, Kirsten Moysich, Susanne K Kjaer, Estrid Hogdall, Allan Jensen, Ellen L Goode, Brooke L Fridley, Melissa C Larson, Joellen M Schildkraut, Rachel T Palmieri, Daniel W Cramer, Kathryn L Terry, Allison F Vitonis, Linda J Titus, Argyrios Ziogas, Wendy Brewster, Hoda Anton-Culver, Alexandra Gentry-Maharaj, Susan J Ramus, A Rebecca Anderson, Doerthe Brueggmann, Peter A Fasching, Simon A Gayther, David G Huntsman, Usha Menon, Roberta B Ness, Malcolm C Pike, Harvey Risch, Anna H Wu, Andrew Berchuck, on behalf of the Ovarian Cancer Association Consortium

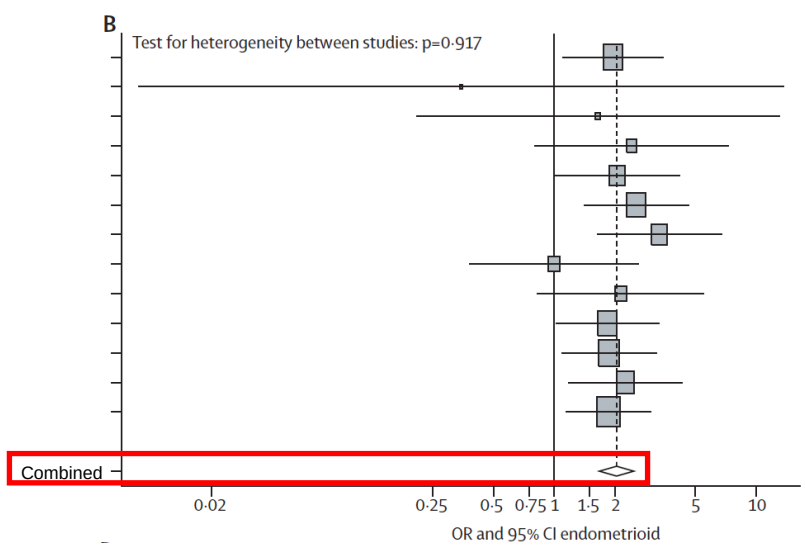
Pearce et al (2012) Lancet Oncol. 13:385

Endometriosis

Clear cell



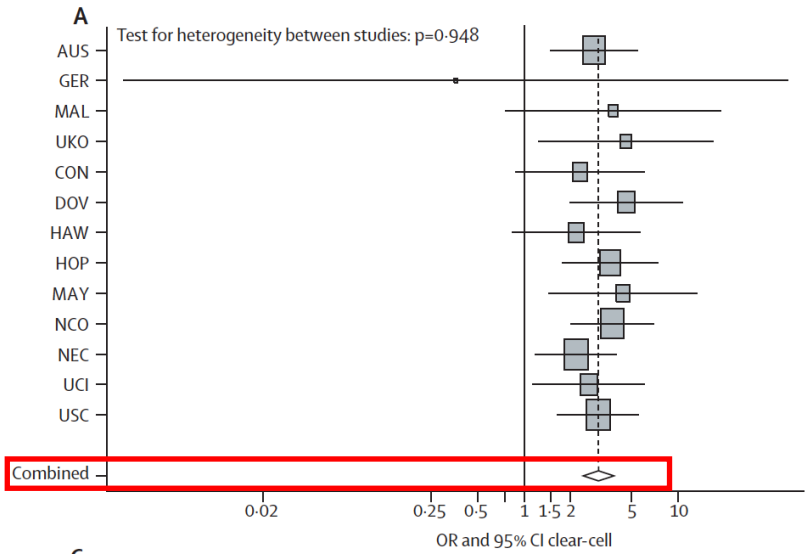
Endometrioid



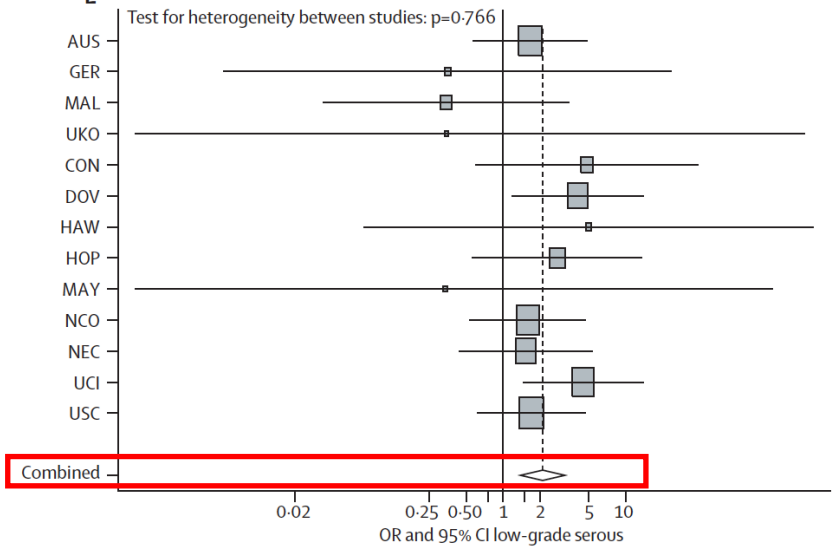
Pearce et al (2012) Lancet Oncol. 13:385

Endometriosis

Clear cell



Low grade serous



Pearce et al (2012) Lancet Oncol. 13:385

Endometriosis

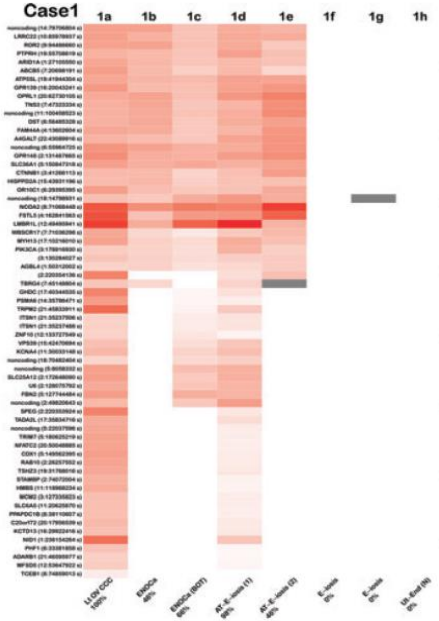
Journal of Pathology
J Pathol 2015; **236:** 201–209
Published online 23 March 2015 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/path.4516

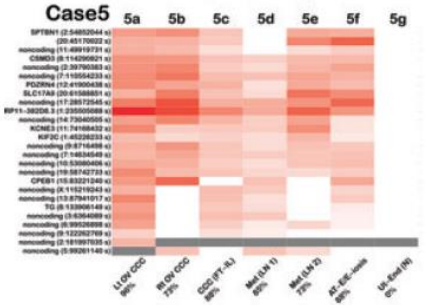
ORIGINAL PAPER

Multifocal endometriotic lesions associated with cancer are clonal and carry a high mutation burden

Michael S Anglesio,[1,†] Ali Bashashati,[2,†] Yi Kan Wang,[2,†] Janine Senz,[1] Gavin Ha,[2] Winnie Yang,[2] Mohamed R Aniba,[2] Leah M Prentice,[2] Hossein Farahani,[2] Hector Li Chang,[1] Anthony N Karnezis,[1] Marco A Marra,[3] Paul J Yong,[4] Martin Hirst,[3,5] Blake Gilks,[1,6] Sohrab P Shah[1,2] and David G Huntsman[1,2,4*]

- Sequenced CCC, endometriosis (atypical and typical)
- Up to 98% CCC mutations seen in endometriosis
- No unique mutations in CCC
- Atypical endometriosis ‘borderline CCC’





IL-6 in endometriosis

FERTILITY AND STERILITY®
VOL. 75, NO. 3, MARCH 2001

Published by Elsevier Science Inc.
Printed on acid-free paper in U.S.A.

Interleukin 1β, interleukin-6, and tumor necrosis factor-α in endometriotic tissue and in endometrium

Agneta Bergqvist, M.D., Ph.D., Christine Bruse, M.D., Magdalena Carlberg, Ph.D., and Kjell Carlström, Ph.D.

REPRODUCTION
RESEARCH

Nuclear factor κB pathway and interleukin-6 are affected in eutopic endometrium of women with endometriosis

Carlos Ponce[1], Marisa Torres[1], Carolina Galleguillos[1], Hugo Sovino[1,2], M Angélica Boric[1], Ariel Fuentes[1,2] and M Cecilia Johnson[1]

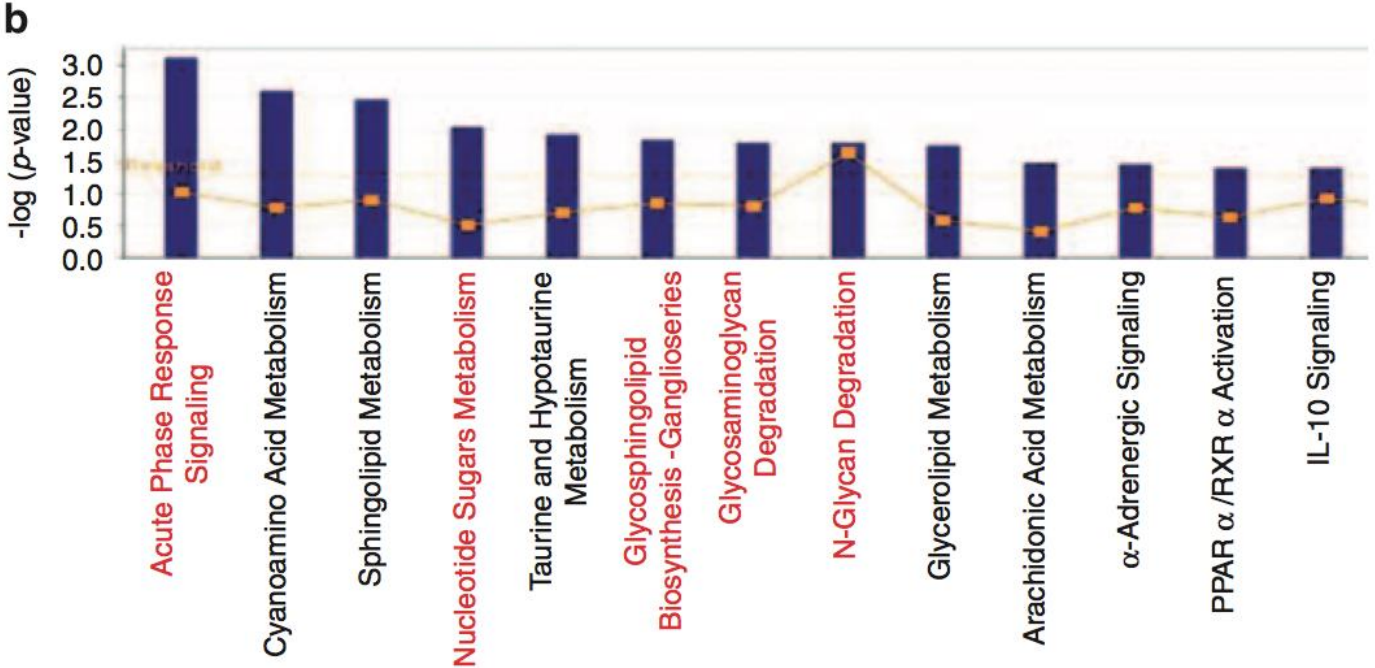
[1]School of Medicine, Institute of Maternal and Child Research and [2]San Borja Arriarán Clinical Hospital, University of Chile, PO Box 226-3, Santiago, Chile

Correspondence should be addressed to M C Johnson; Email: cjohnson@med.uchile.cl

Ponce et al (2009) Reproduct. 137:727

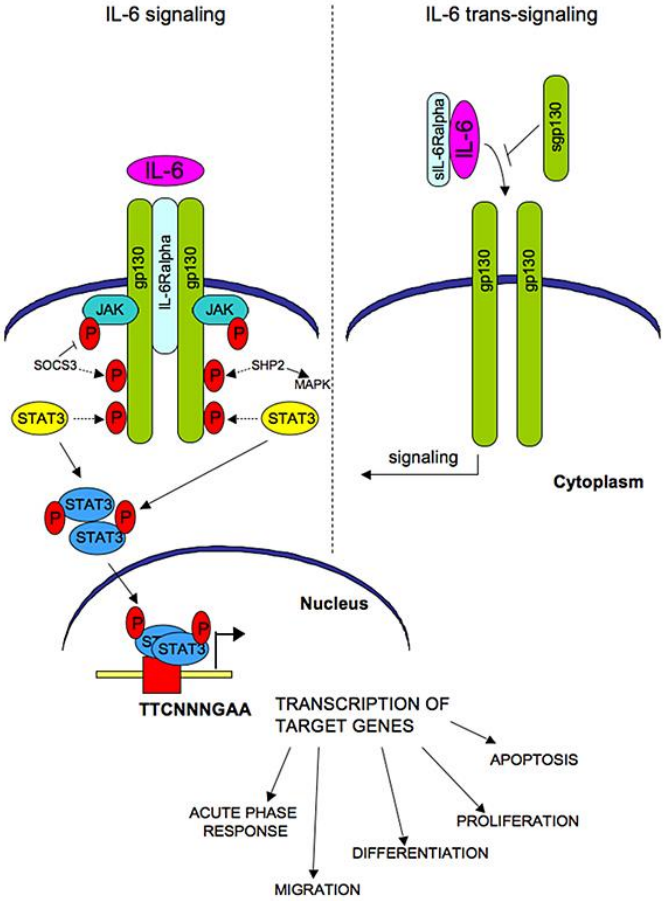
Bergqvist et al (2001) Fertil. Steril. 75:489

Gene expression



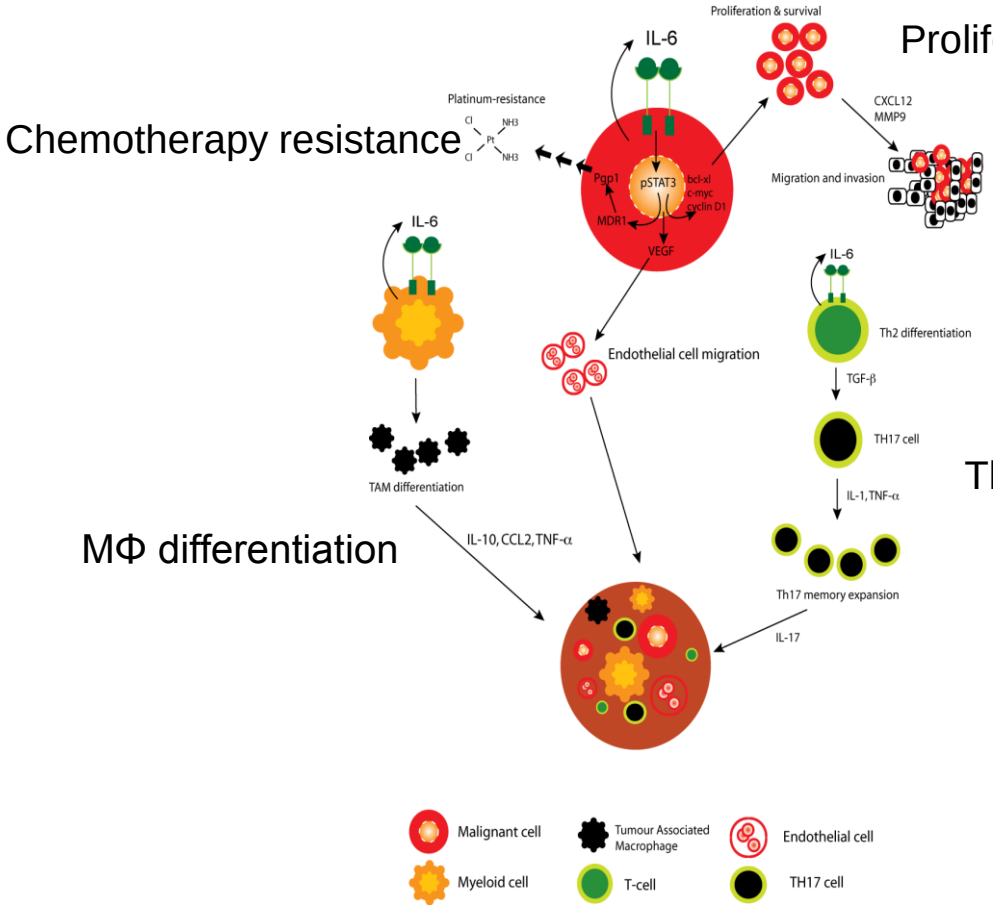
Yamaguchi et al (2010) Oncogene 29:1741

Interleukin-6 signalling



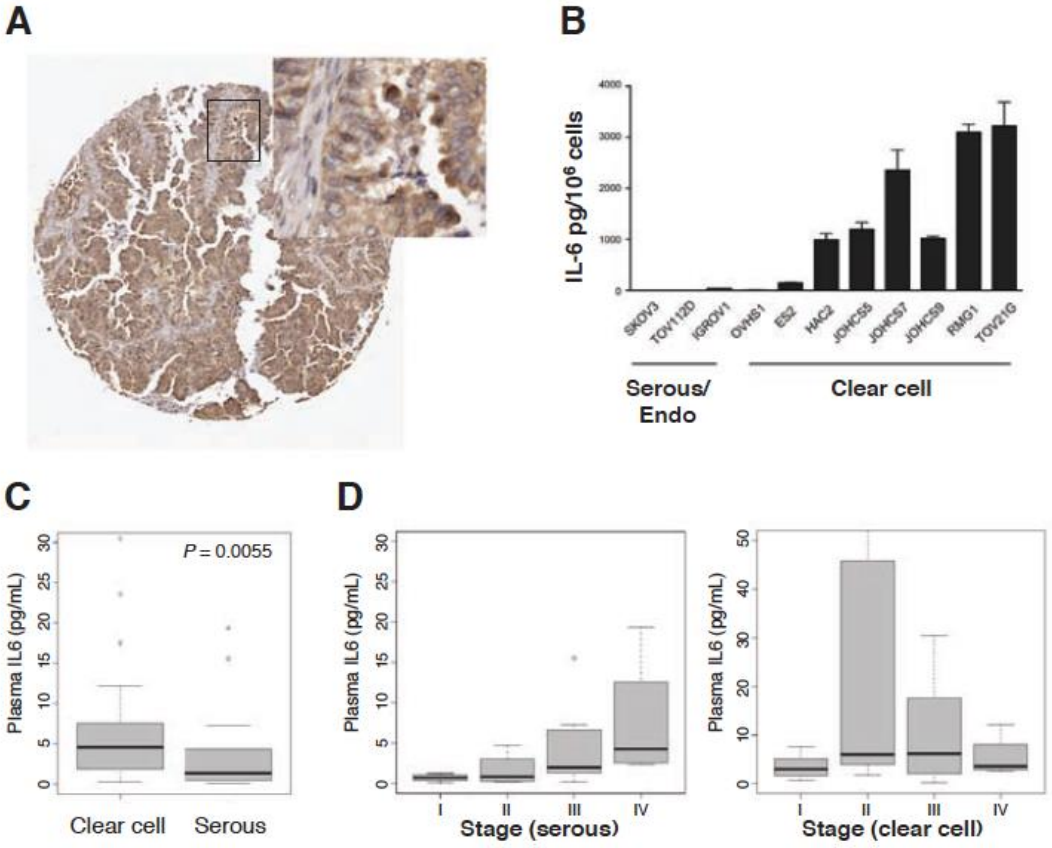
Camporeale et al Front. Bioscience (2012) 17:2306

Consequences of interleukin-6 signalling



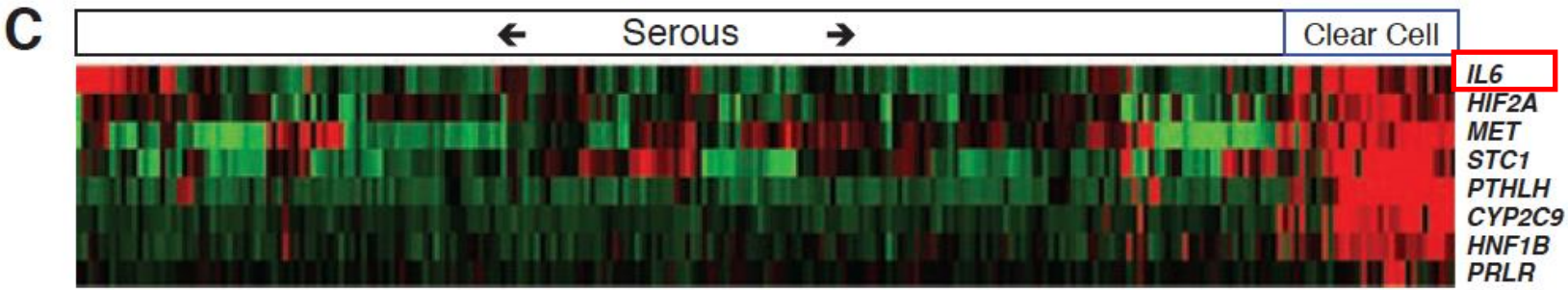
Jim Coward – PhD thesis, Barts Cancer Institute

IL-6 in Clear Cell Carcinoma



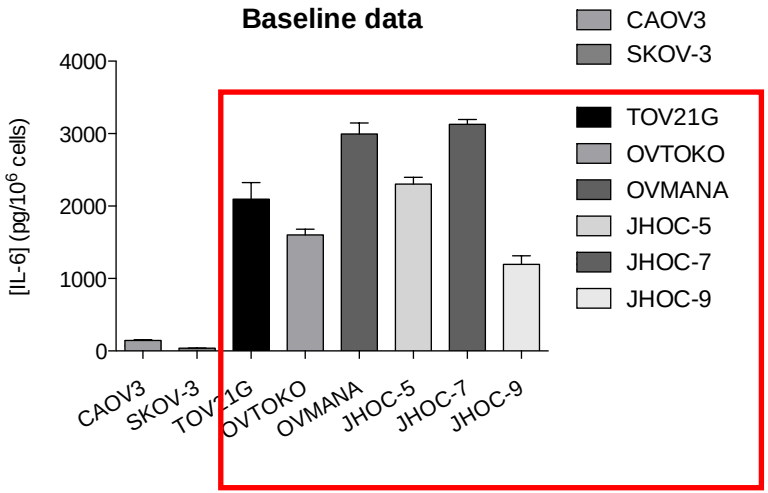
Anglesio et al (2011) Clin Cancer Res. 17:2538

Gene expression and inflammatory cytokines



Anglesio et al (2011) Clin Cancer Res. 17:2538

IL-6 in Clear Cell Carcinoma

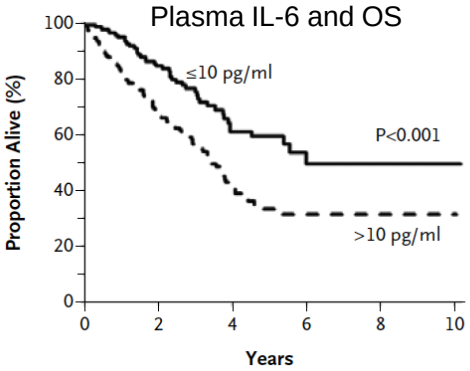


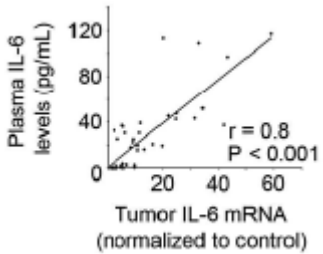
Suzanne Dowson

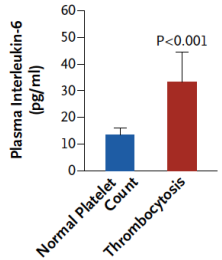
Interleukin-6, platelets and ovarian cancer

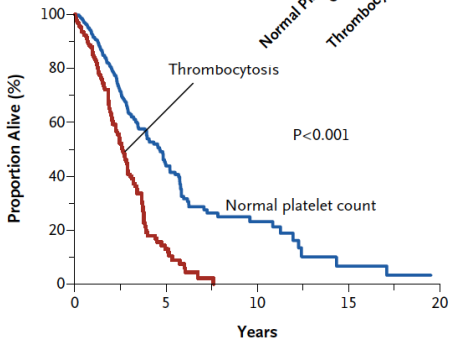
ORIGINAL ARTICLE

Paraneoplastic Thrombocytosis in Ovarian Cancer







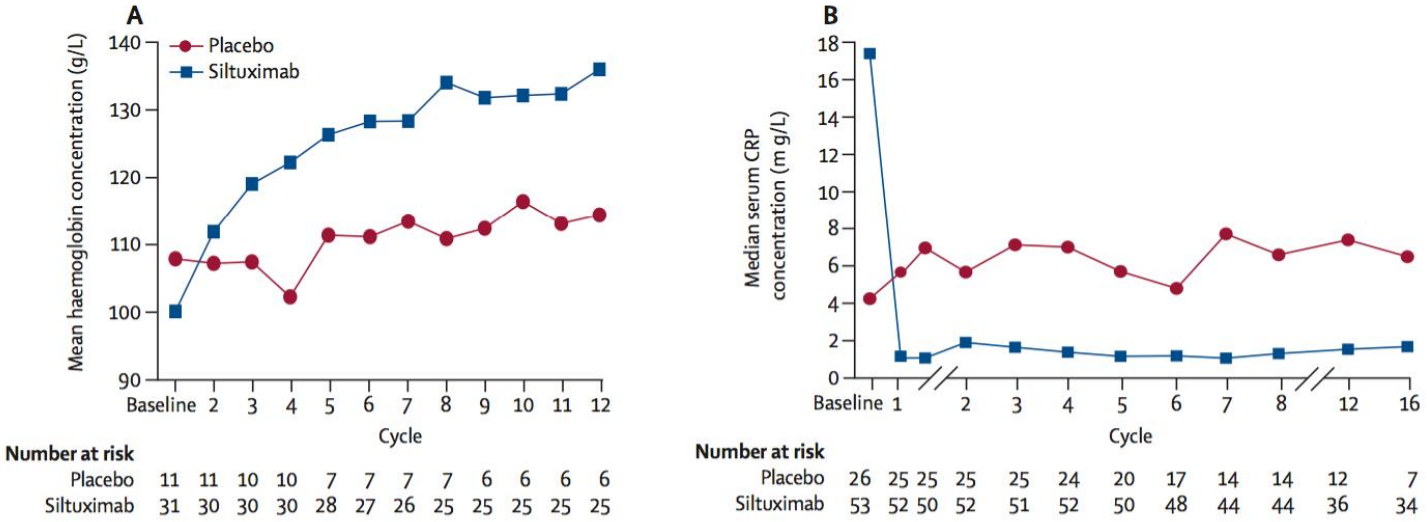


Stone et al (2012) NEJM 366:610

IL-6 in Castleman's Disease

Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial

Frits van Rhee, Raymond S Wong, Nikhil Munshi, Jean-Francois Rossi, Xiao-Yan Ke, Alexander Fosså, David Simpson, Marcelo Capra, Ting Liu, Ruey Kuen Hsieh, Yeow Tee Goh, Jun Zhu, Seok-Goo Cho, Hanyun Ren, James Cavet, Rajesh Bandekar, Margaret Rothman, Thomas A Puchalski, Manjula Reddy, Helgi van de Velde, Jessica Vermeulen, Corey Casper



Van Rhee et al. Lancet Oncol. (2014) 15:966

Copy number

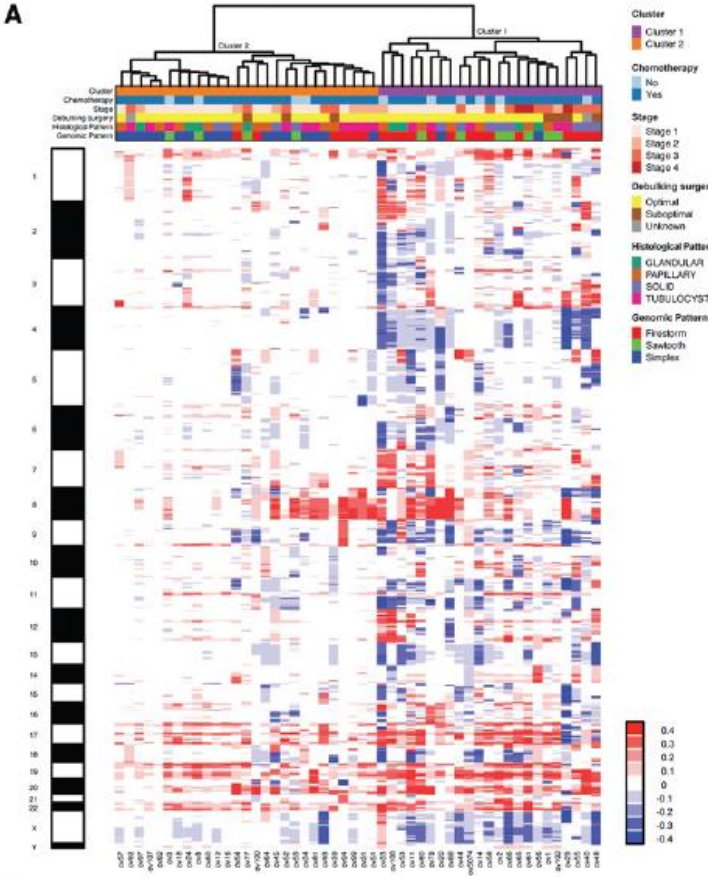
Clinical Cancer Research

Imaging, Diagnosis, Prognosis

Genomic Analysis Reveals the Molecular Heterogeneity of Ovarian Clear Cell Carcinomas

David S.P. Tan[1,2], Marjan Iravani[1], W. Glenn McCluggage[8], Maryou B.K. Lambros[1], Fernanda Milanezi[1], Alan Mackay[1], Charles Gourley[7], Felipe C. Geyer[1], Radost Vatcheva[1], Joanne Millar[9], Karen Thomas[3], Rachael Natrajan[1], Kay Savage[1], Kerry Fenwick[1], Alistair Williams[7], Charles Jameson[4], Mona El-Bahrawy[5], Martin E. Gore[2], Hani Gabra[6], Stanley B. Kaye[2], Alan Ashworth[1], and Jorge S. Reis-Filho[1]

- aCGH on 50 CCC samples
- Two copy number clusters
- Common amplicons 20q13, 17q23.2
- *HER2* amplified in 14% cases



Tan et al (2011) Clin. Cancer Res. 17:1521

ARID1A mutations

Frequent Mutations of Chromatin Remodeling Gene *ARID1A* in Ovarian Clear Cell Carcinoma

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Jones et al (2010) Science 330:228

ORIGINAL ARTICLE

ARID1A Mutations in Endometriosis-Associated Ovarian Carcinomas

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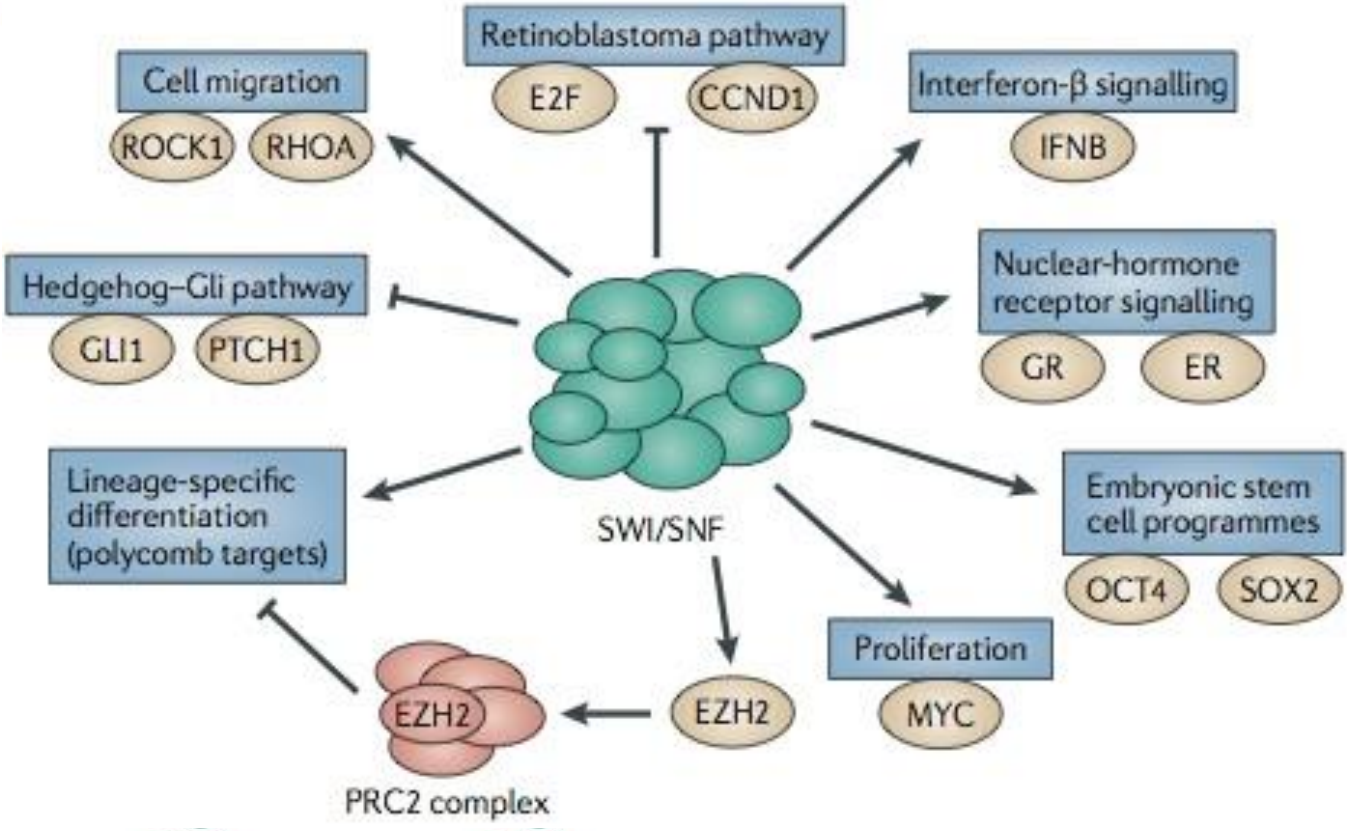
Wiegand et al (2010) N. Engl. J. Med. 363:1532

SWI/SNF complex

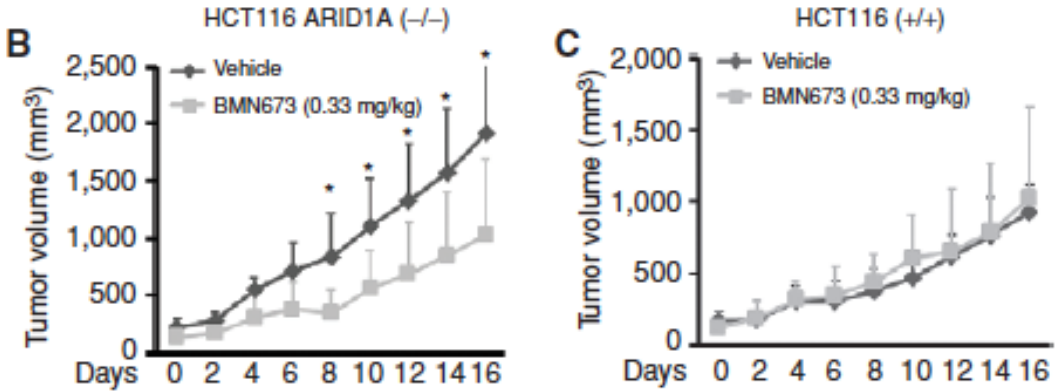


Wilson and Roberts (2011) Nat Rev Cancer 11:481

ARID1A mutations and DNA damage

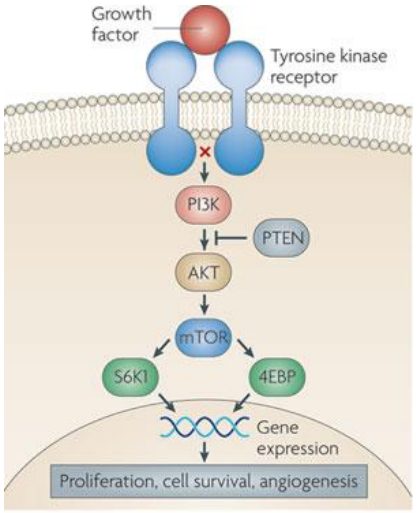
ARID1A Deficiency Impairs the DNA Damage Checkpoint and Sensitizes Cells to PARP Inhibitors

Jianfeng Shen[1], Yang Peng[2], Leizhen Wei[3,4], Wei Zhang[1], Lin Yang[1,5], Li Lan[3,4], Prabodh Kapoor[6], Zhenlin Ju[7], Qianxing Mo[8], Ie-Ming Shih[9], Ivan P. Uray[1], Xiangwei Wu[1], Powel H. Brown[1], Xuetong Shen[6], Gordon B. Mills[2], and Guang Peng[1,5]



Shen et al (2015) Cancer Discov. 5:752

PIK3CA



Nature Reviews | Drug Discovery

Holmes et al (2011) Nature Rev. Drug Disc. 10:563

Short Communication

Frequent Activating Mutations of *PIK3CA* in Ovarian Clear Cell Carcinoma

Table 2. Sequence Mutation Rates in Ovarian Clear Cell Carcinomas

Sample (*n*)	*KRAS*	*BRAF*	*TP53*	*PIK3CA*	*CTNNB1*	*PTEN*
JH (10)	20%	0%	10%	50%	0%	0%
TW (8)	0%	0%	ND	50%	0%	0%
Cell line (10)	10%	10%	20%	40%	0%	10%
TW-paraffin (44)	9%	0%	ND	25%	2%	ND
JP-paraffin (25)	0%	0%	ND	32%	8%	ND
Overall: non-paraffin (JH + TW + Cell line)	11%	3%	15%	46%	0%	5%
Overall (97)	7%	1%	15%	33%	1%	5%

Kuo et al (2009) Am. J. Pathol. 174:1597

Mouse model of ovarian CCC

ARTICLE

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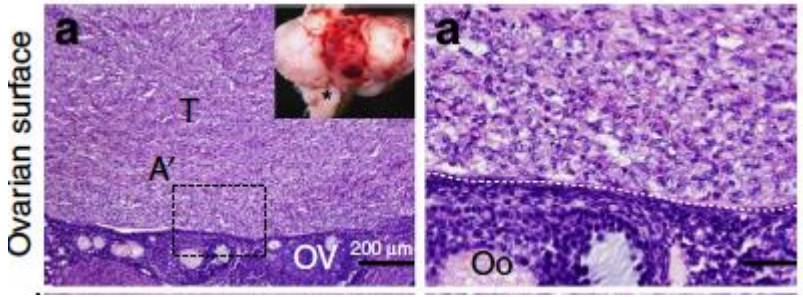
Coexistent ARID1A–PIK3CA mutations promote ovarian clear-cell tumorigenesis through pro-tumorigenic inflammatory cytokine signalling

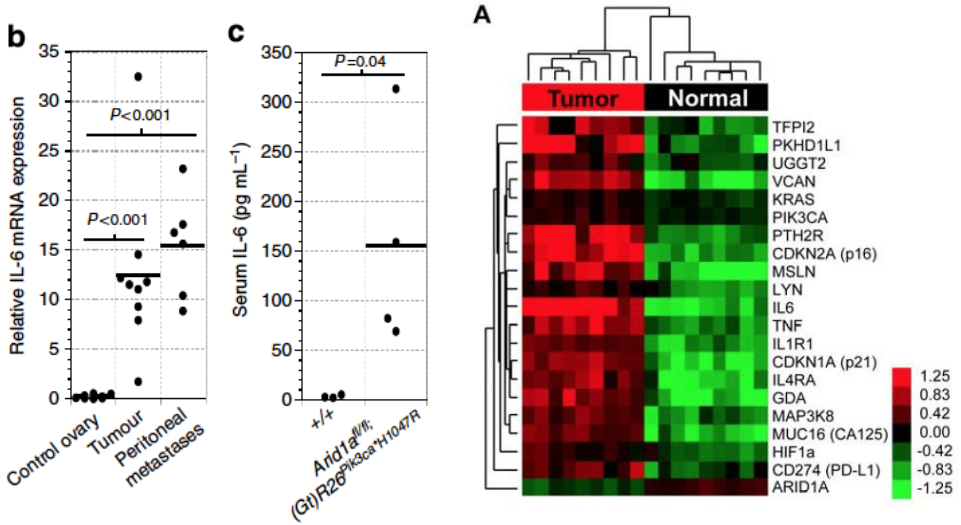
Ronald L. Chandler[1,2,*], Jeffrey S. Damrauer[1,2,*], Jesse R. Raab[1,2], Jonathan C. Schisler[3,4], Matthew D. Wilkerson[1,2], John P. Didion[1,2], Joshua Starmer[1,2], Daniel Serber[1,2], Della Yee[1,2], Jessie Xiong[2], David B. Darr[2], Fernando Pardo-Manuel de Villena[1,2], William Y. Kim[1,2,5] & Terry Magnuson[1,2]



Transgenic mice (*Arid1a*$^{fl/fl}$*;(Gt)Rosa26Pik3ca*^{*H1047R})

- Ovarian surface epithelium
  - Bi-allelic loss of *Arid1a*
  - Knock-in of mutant *Pik3ca*

- CCC-like tumours
  - IL-6
  - HIF1a



Angiogenesis

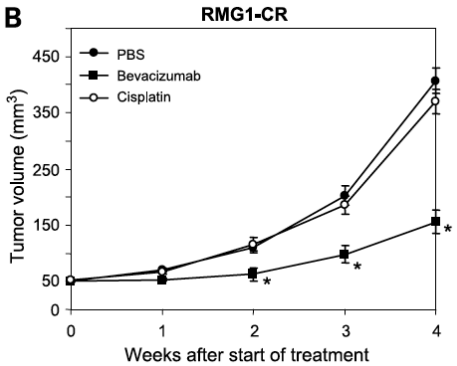
Molecular Medicine in Practice

Vascular Endothelial Growth Factor Is a Promising Therapeutic Target for the Treatment of Clear Cell Carcinoma of the Ovary

Seiji Mabuchi[1], Chiaki Kawase[1], Deborah A. Altomare[4], Kenichirou Morishige[1], Masami Hayashi[1], Kenjiro Sawada[1], Kimihiko Ito[7], Yoshito Terai[3], Yukihiro Nishio[2], Andres J. Klein-Szanto[5], Robert A. Burger[4,6], Masahide Ohmichi[3], Joseph R. Testa[5], and Tadashi Kimura[1]

Table 1. VEGF immunoreactivity by histology and clinical stage

	No. of patients	Immunoreactivity			
		Zero, *n* (%)	Weak (+0.5 or 1), *n* (%)	Moderate (+2), *n* (%)	Strong (+3), *n* (%)
CCCs					
Stage I-II	27	0	7 (26.9)	14 (51.9)	6 (22.2)
Stage III-IV	25	0	0	15 (60)	10 (40)



Mabuchi et al (2010) Mol. Cancer Ther. 9:2

But, ICON7 data…

	Clear cell tumours*	
	Standard therapy (n=77)	Bevacizumab (n=82)
Follow-up duration (months)	52·5 (29·0–57·5)	50·7 (28·2–57·9)
Deaths	20 (26%)	24 (29%)
Log-rank test p value	p=0·74	
HR (95% CI)	1·09 (0·64–1·88)	
Non-proportionality p value†	p=0·58	
(Restricted) mean survival time (months; 95% CI)‡	48·0 (43·9–52·2)	47·6 (43·6–51·6)
Restricted mean survival time difference (95% CI)	−0·4 (−6·1 to 5·3)	

Oza et al (2015) Lancet Oncol. 16:928

NICCC: Nintedanib in Clear Cell Cancer

CI: Ros Glasspool, Glasgow
Translational lead: Iain McNeish

NICCC

SGCTG/NCRI/NSGO

EORTC/GINECO

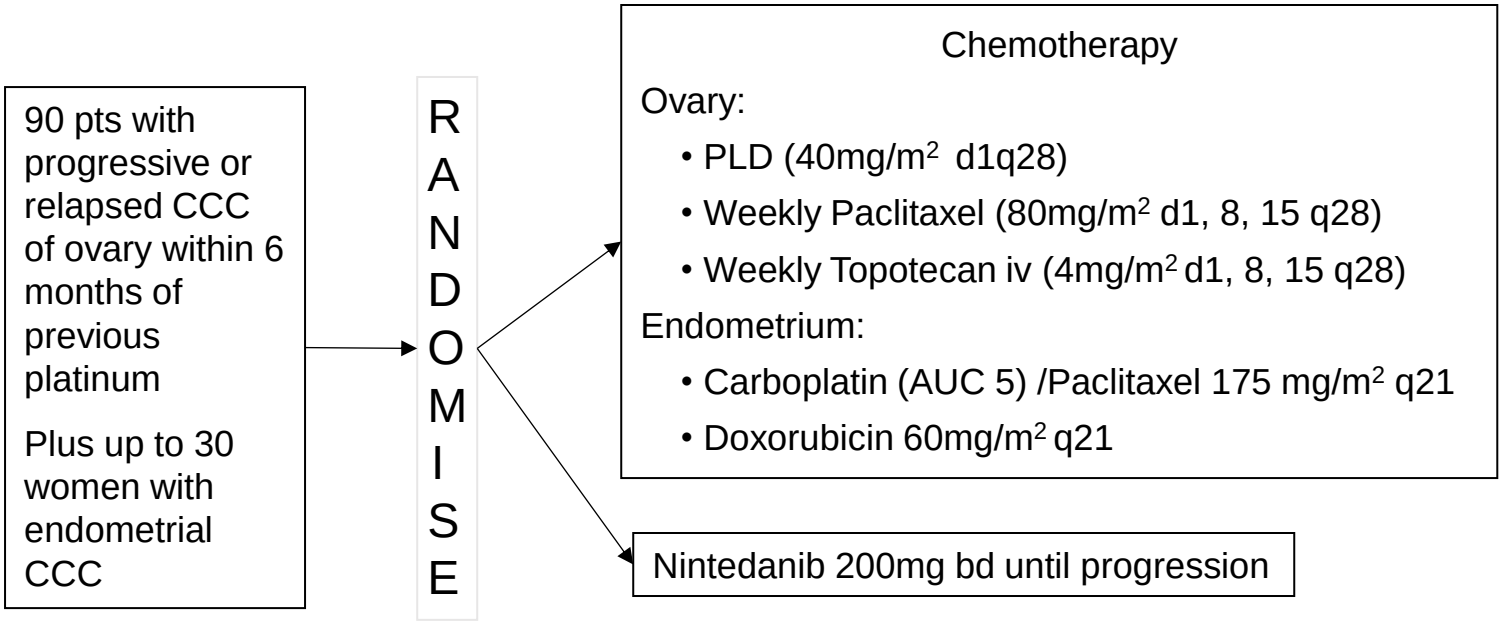
CANCER RESEARCH UK

scottish gynaecological cancer trials group

NCRI National Cancer Research Institute

NSGO

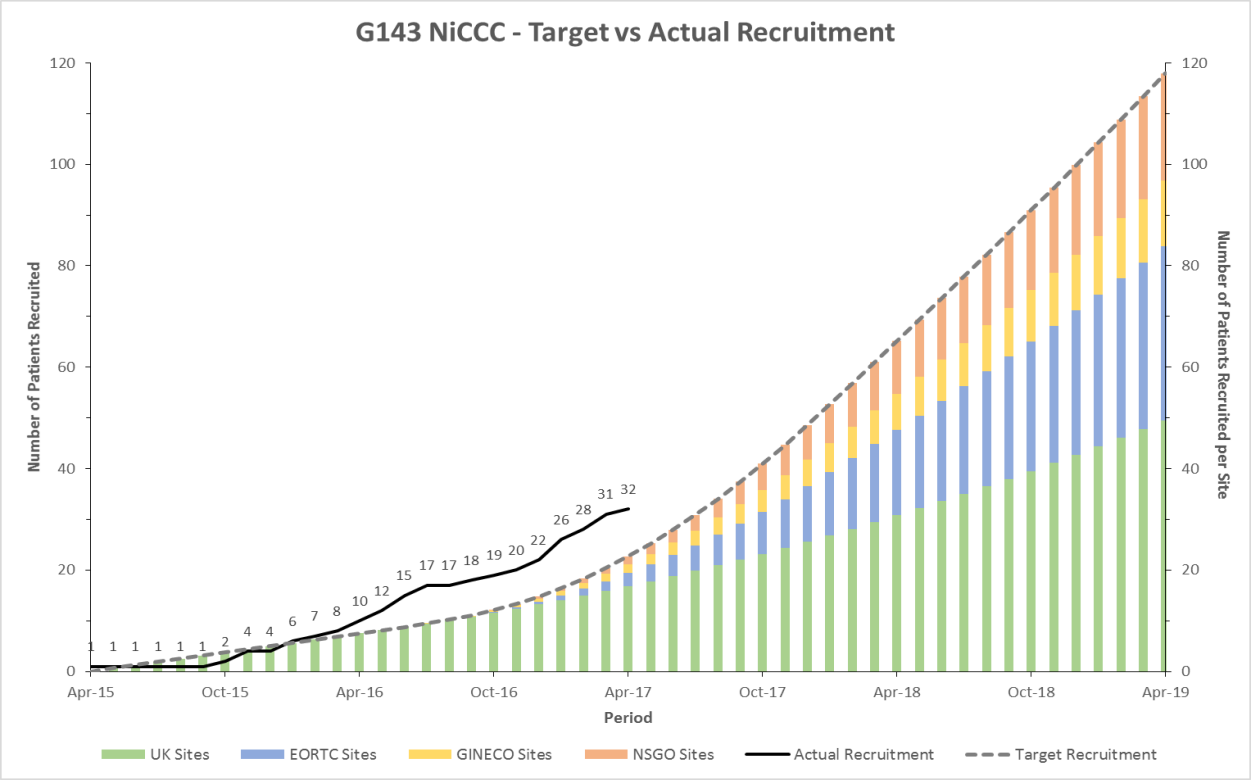
NICCC: Nintedanib in Clear Cell Cancer



Primary Endpoint: PFS

Secondary Endpoints: OS, Toxicity, RR, QoL, Q-Twist

NICCC: Nintedanib in Clear Cell Cancer



Other potential therapeutic targets

- MET
- HNF1β
- ?HER2

Other clear cell-specific trials from clinicaltrials.gov

- A Study of ENMD-2076 in Ovarian Clear Cell Cancers (recruiting)
- Sunitinib Malate in Treating Patients With Persistent or Recurrent Clear Cell Ovarian Cancer (active not recruiting)

Summary and future directions

- Stage IA/B (and possibly) stage IC1 patients may not need chemotherapy
- Carboplatin and paclitaxel remains standard first-line therapy
- Radiotherapy may play a role in early stage disease
- In relapsed disease, platinum-free interval may not matter
- Current phase II trials target angiogenesis
- Future trials must target IL-6, MET [alone or combined with angiogenesis inhibitors]