Challenging subtypes in gynaecological cancer: stage 2 ovarian clear cell carcinoma progressing

Dr David SP Tan

BSc(Hons), MBBS(Hons), MRCP(UK)(Medical Oncology), PhD

Consultant Medical Oncologist, National University Cancer Institute, Singapore

Asst Prof Yong Loo Lin School of Medicine, National University of Singapore

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- **Other Remuneration:** None

Mrs K, 40yrs, Stage 2A Ovarian Clear Cell Carcinoma (OCCC)

- **Nov 2013:**
  - PV bleeding and pelvic discomfort, No other medical hx of note.
  - Family hx: Father died of colorectal cancer aged 60
  - Saw Gynaecologist who found 9cm Left ovary cyst.
  - Laparoscopic left salphingooopherectomy --> clear cell carcinoma of the ovary
  - Subsequent staging/debulking surgery – R oopherectomy, omentectomy, hysterectomy → OCCC on surface of fallopian tube → FIGO Stage 2A
- **Dec 2013:** Developed back pain post op
  - **PET CT:** L paraaortic node and L common iliac node metabolically active

- **Dec 2013-Feb 2014:** Carboplatin and paclitaxel x 3 cycles → worsening back pain
  - **PET CT:** 2 FDG avid lesions in left adnexa. Enlarged inguinal LN 1.6 x 1.8 and L paraaortic LN

- **Feb 2014 – April 2014:** Carboplatin/ paclitaxel + avastin x 3 cycles - with symptomatic progression - back pain and fatigue worsening

Mrs K continued

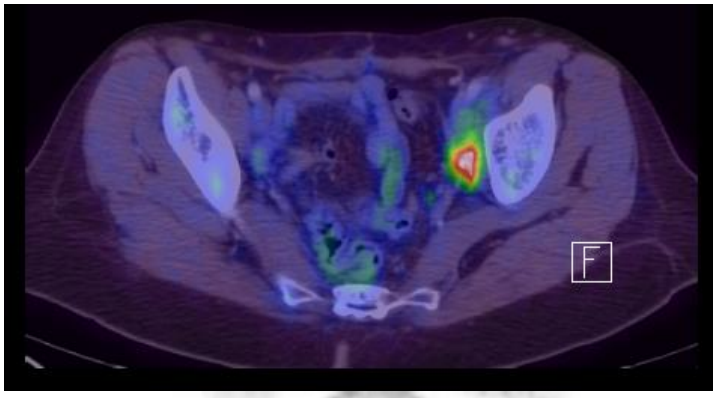
- **May 2014:** RT to Left Paraaortic LN mass due to worsening symptoms of back pain with improvement after RT

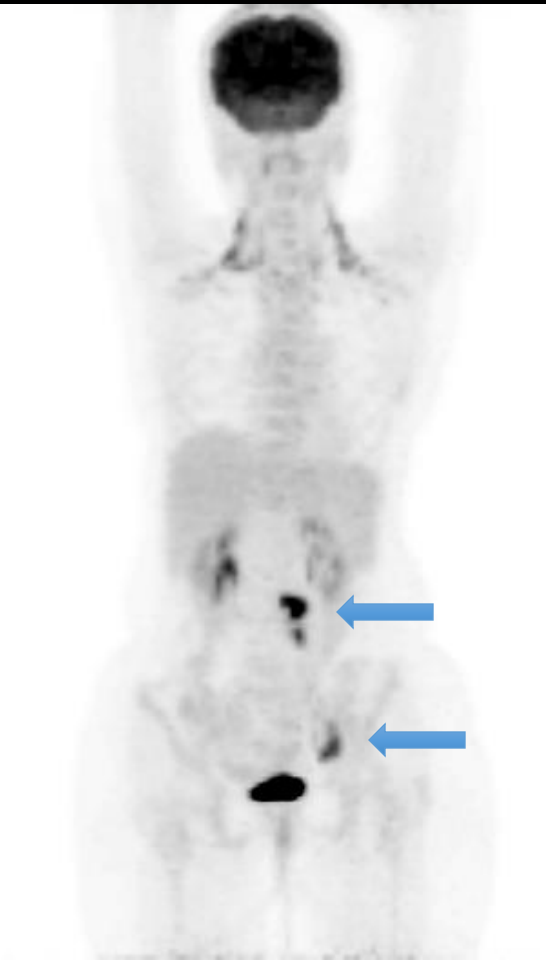
- **May- Nov 2014:** Started Cisplatin and gemcitabine weekly with avastin:

- **PET CT in Nov 2014:**
  - No change in size of Left paraaortic LN
  - Left lateral pelvic wall more FDG avid
  - Back pain started to get worse

- **Nov 2014: Referred to NUH for second opinion** → what are the options?

Nov 2014





Ovarian Clear Cell Carcinomas

- 10-25% of all epithelial ovarian cancers (EOC) – 25% in oriental population
- Associated with a poorer prognosis and resistance to conventional platinum-based chemotherapy
  - Pather et al – In the setting of recurrent OCCC, 0/11 patients had a complete or partial response
  - Takano et al – In Japanese patients with recurrent OCCC, results with second-line chemotherapy were poor
    - Platinum Sensitive: RR 8% (2/24); OS 16m
    - Platinum Resistant: RR 6% (3/51); OS 7m
- Current chemotherapy strategies in the management of recurrent OCCCs are suboptimal

Int J Gynecol Cancer 2005;15:432–437.
Int J Gynecol Cancer 2008, 18, 937–942

Response to Chemotherapy in Recurrent OCCC (Analysis of outcomes in 137 patients with recurrent ovarian clear cell carcinoma)

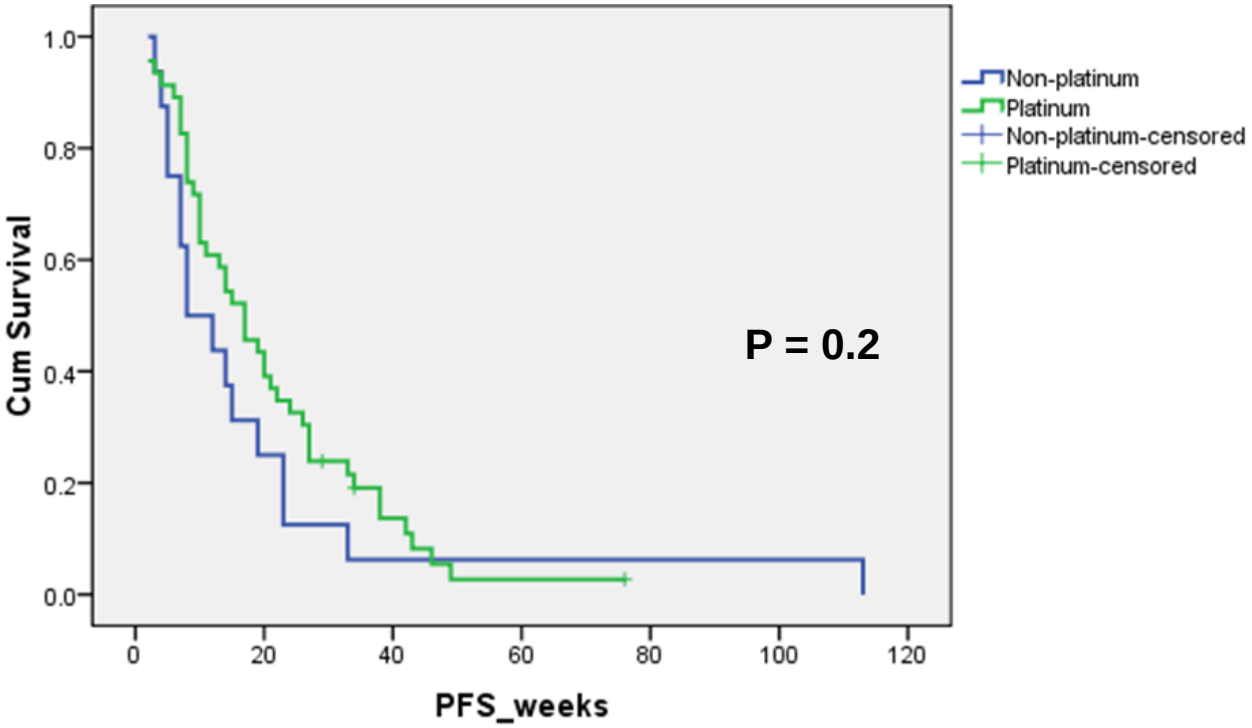
RECIST Response Rates to individual treatments						
Treatment	**N**	**No. Evaluable**	**Platinum-Sensitive**	**CR/PR (%)**	**CBR (%)**	**Median PFS (weeks)**
Plt-based	63	38	Yes (46)	18	39	17
		14	No (17)	14	36	11
Paclitaxel	8	7		0	14	8
Gemcitabine	7	7		14	14	4
Doxil/ Doxorubicin	29	25		4	16	10
Anti-angiogenic agents	15	13		8	46	14
Topoisomerase inhibitors	30	27		4	19	8
Hormonal therapy	8	6		0	17	12
Others	6	5		0	0	11

- **Response Rates (RR) and PFS in evaluable patients:**
  - **1st Relapse: 10/72 (14%); PFS 12weeks (No significant difference between platinum sensitive / resistant patients)**
  - **2nd Relapse: 3/36 (8%); PFS 11weeks**
- **Overall RR 9%; Median 6m PFS 19%; Median OS 10mths**

Tan et al ASCO 2014, abstract 5548

Does platinum free interval affect platinum response in relapsed OCCC?

Progression free survival (PFS) in platinum sensitive ROCCC treated with platinum vs non-platinum based chemotherapy at 1st relapse



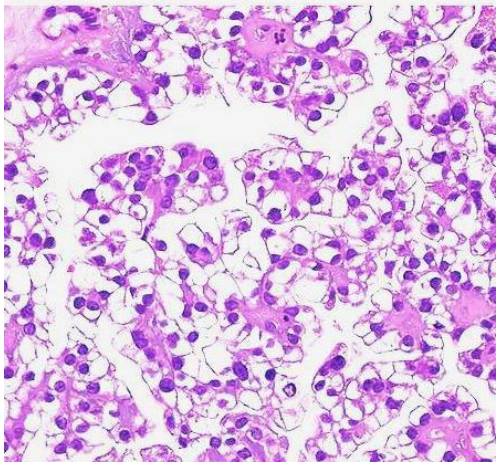
Platinum free interval does not appear to influence subsequent response to platinum-based chemotherapy in ROCCC

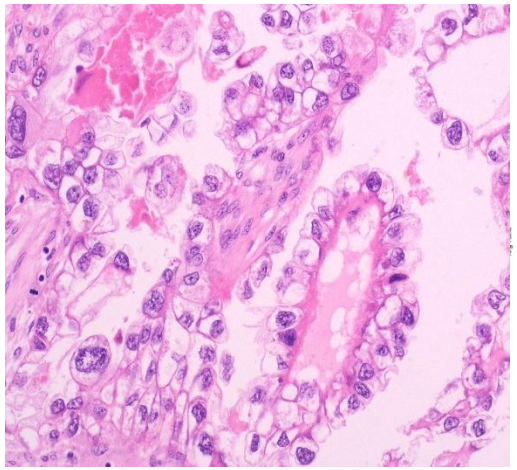
Tan et al ASCO 2014, abstract 5548

Current Perspectives on Precision Therapy in recurrent OCCC

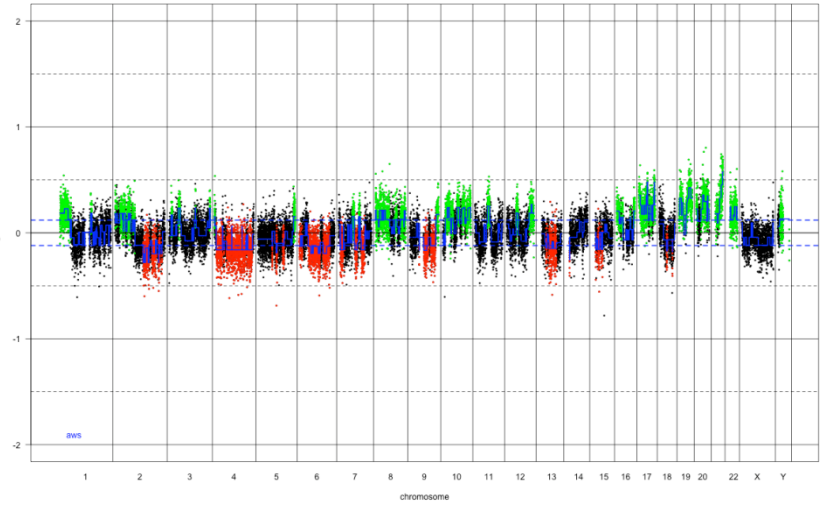
Molecular Heterogeneity in OCCCs

Ovarian clear cell carcinomas

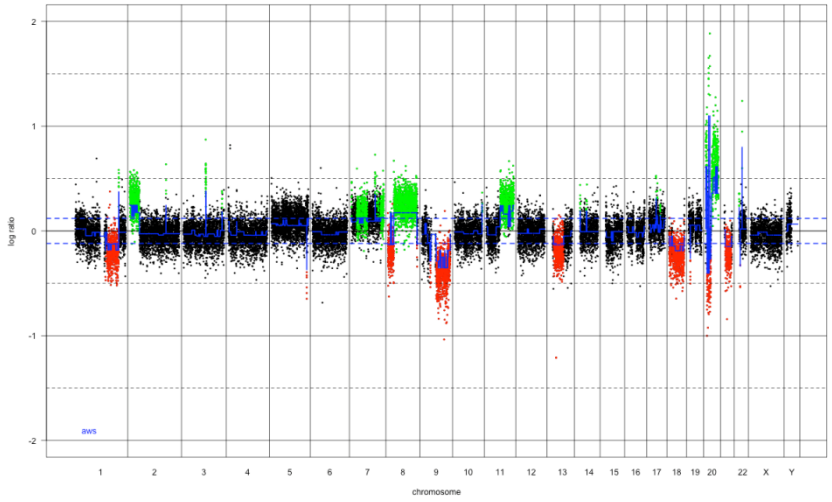




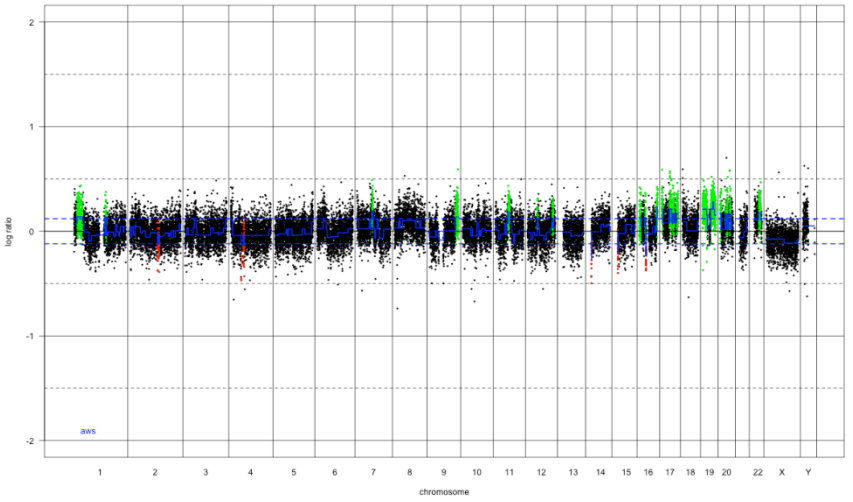
Complex sawtooth 22% (11/50)



Complex firestorm 40% (20/50)

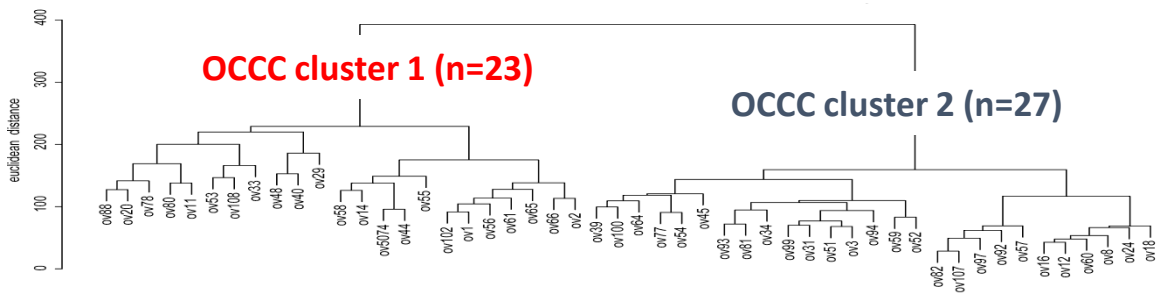


Simplex 38% (19/50)

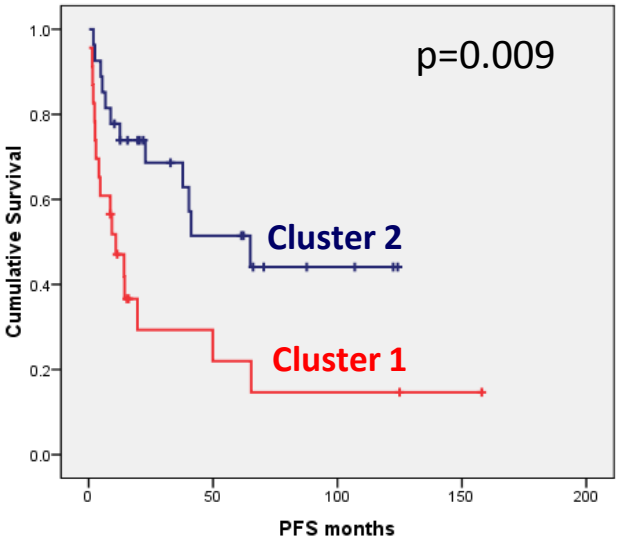


Tan et al Clin Cancer Res 2011

Cluster 1 vs Cluster 2 OCCCs and Survival



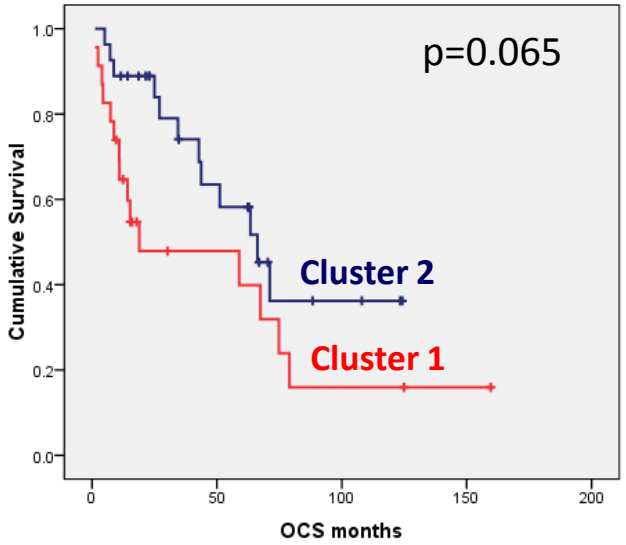
Progression free survival (PFS)



Cluster-1 vs Cluster-2 patients

(median survival 11 vs 65 months, p=0.009)

Ovarian cancer specific survival (OCS)

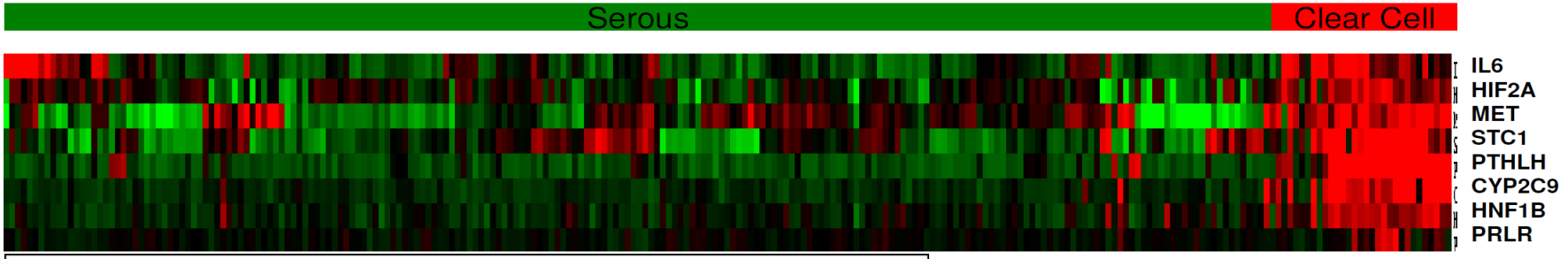


Cluster-1 vs Cluster-2 patients

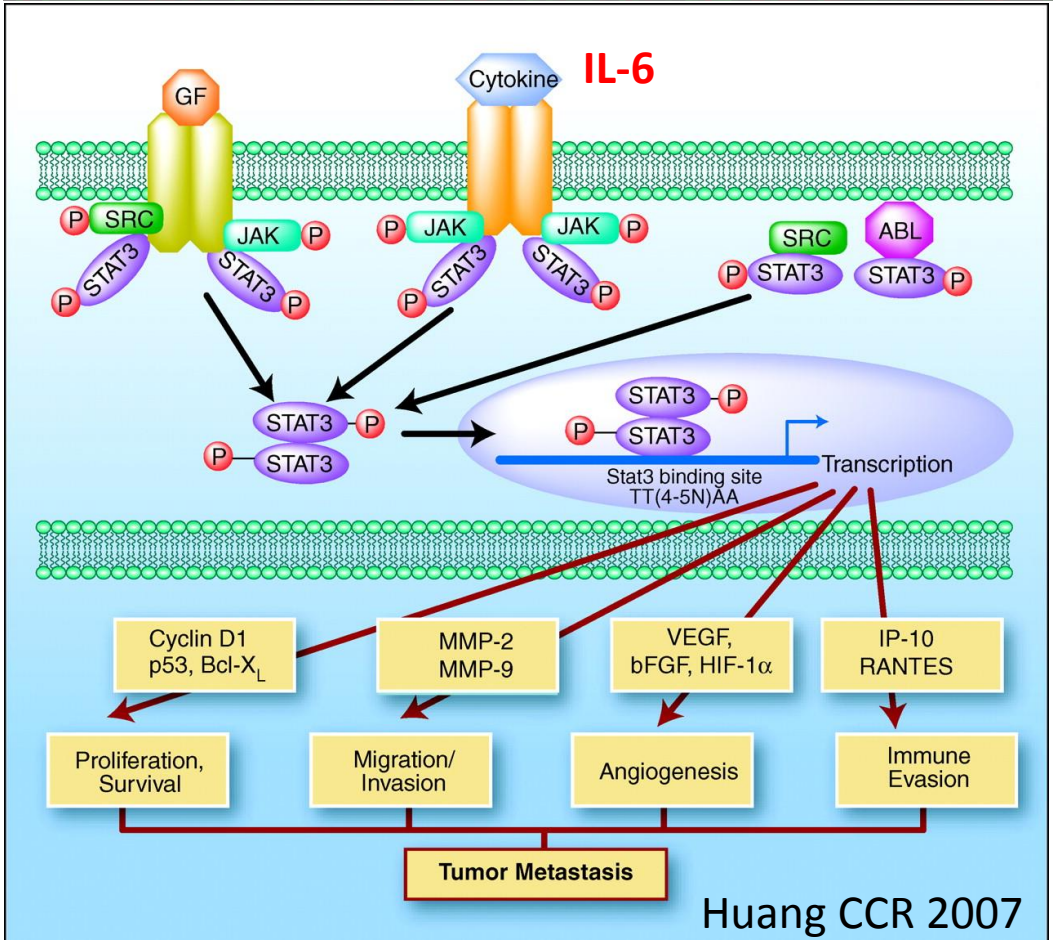
(median survival 19 vs 66 months, p=0.065)

Tan et al Clin Cancer Res 2011

Angiogenesis and OCCC: Upregulation of IL6-STAT3-HIF1α Pathway



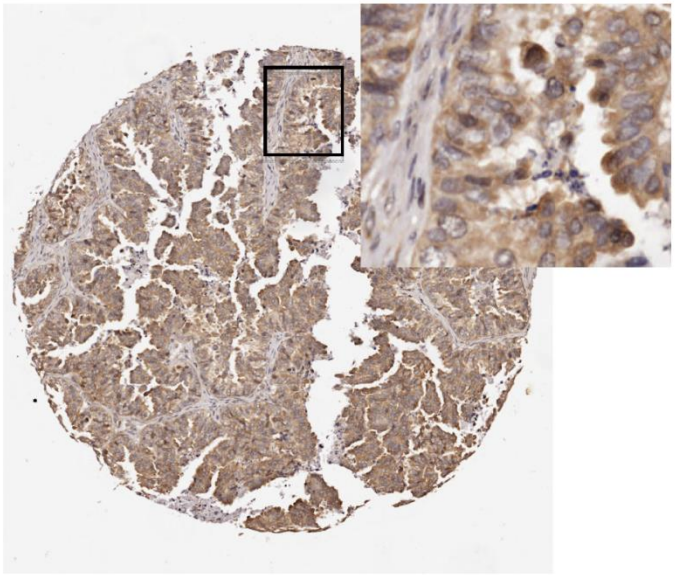
Anglesio et al CCR 2011

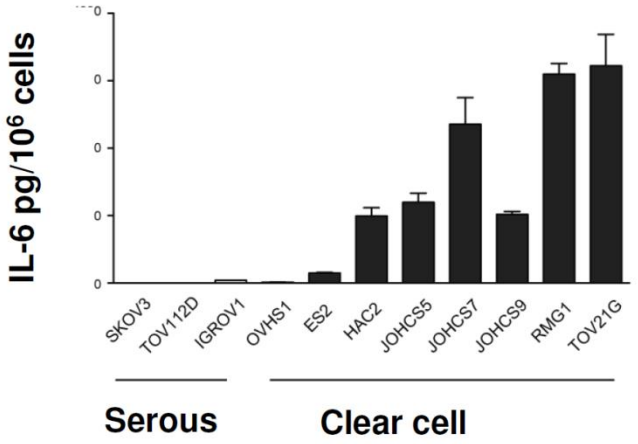


- **Increased IL-6 associated with thrombocytosis (increased DVT risk)**
- **IL-6 signals via STAT3 and activates expression of downstream genes including *PTHLH* (hypercalcaemia) and *HIF1A* (angiogenesis)**
- **Anti-IL-6 antibody (siltuximab), Coward et al CCR 2011**
- **Anti-angiogenic approaches e.g. Bevacizumab, Sunitinib, ENMD2076**
- **STAT3 inhibitor?**

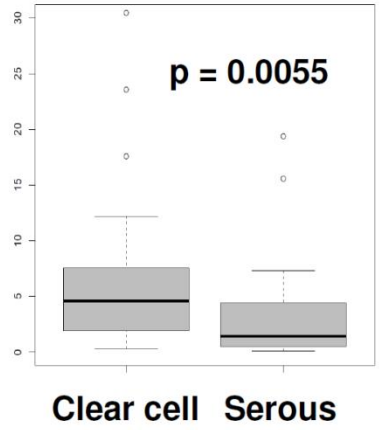
Increased expression of IL-6 in OCCCs

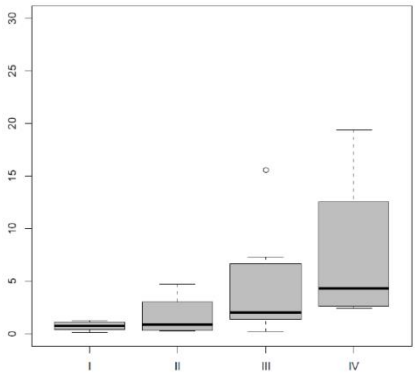
IL-6 expression in OCCC tumours and cell lines

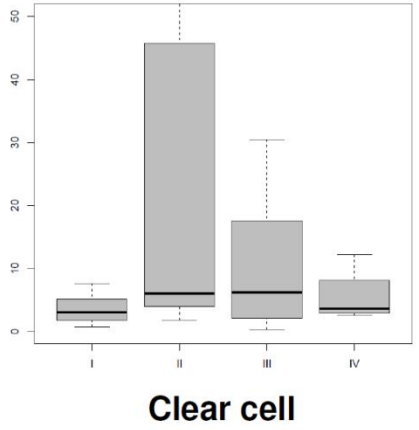




IL-6 levels in serum of pre-surgical patients







Anglesio et al CCR 2011

Antiangiogenic therapy in recurrent OCCC:

A phase II evaluation of sunitinib (SU11248) in the treatment of persistent or recurrent clear cell ovarian carcinoma

(Chan et al – presented at SGO 2015, Gyn Onc May 2015 Vol. 138, Supp 1, Pg 3)

Primary endpoints: to determine if the drug had a response rate of at least 20% or PFS at 6 months of 25%.

Tumours at least 50% clear cell histomorphology and negative for WT-1 and ER by IHC

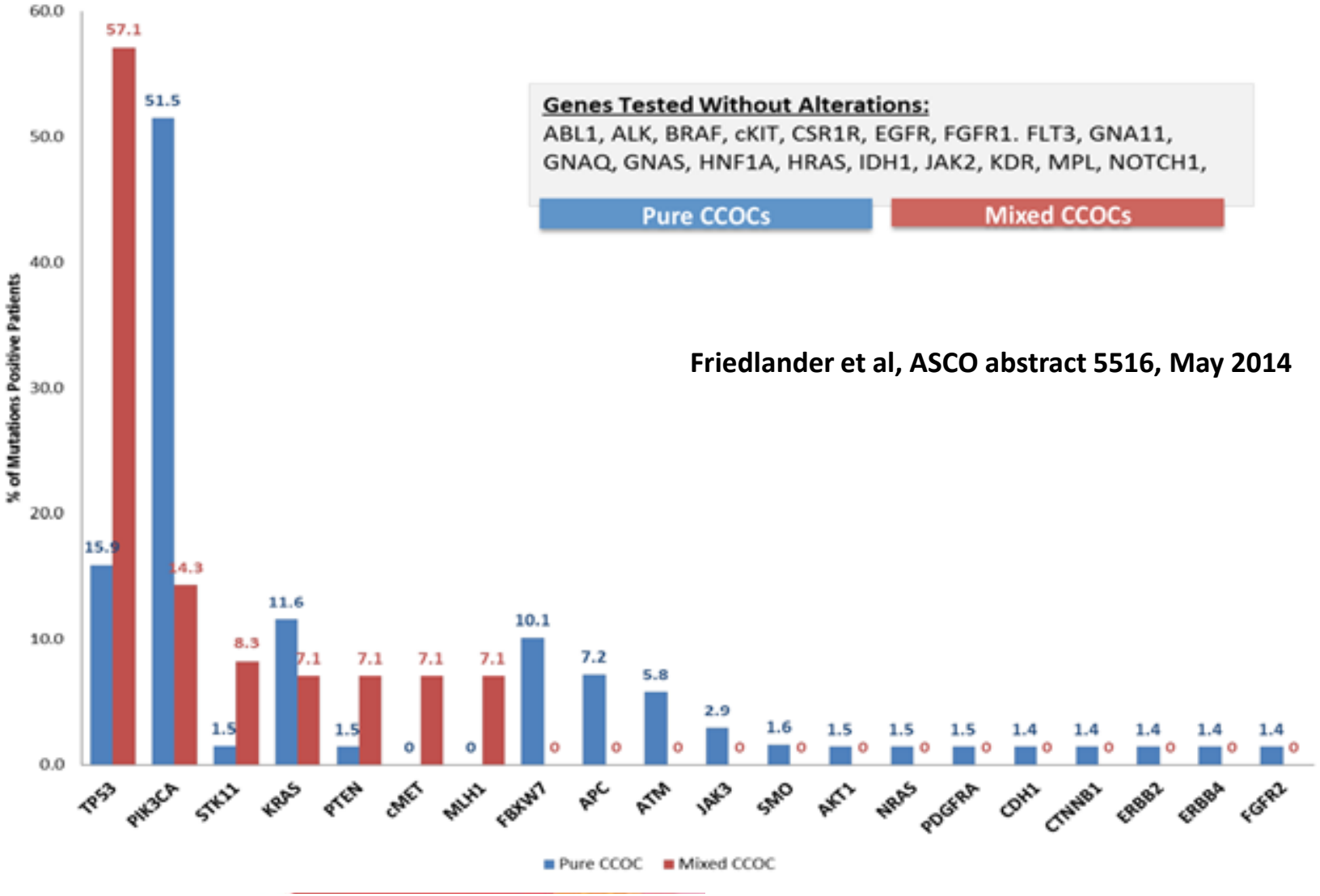
Sunitinib 50 mg per day for 4 out of 6 weeks until PD or prohibitive toxicity.

Out of 30 patients: 25 (83%) were Whites, 4 (13%) Asians, and 1 (3%) unknown.
All had received 1-2 prior lines of treatment. Performance status of 0-2.

Results:
PFS ≥ 6 months = 5/30 (16.7%)
Response rate (PR/CR) = 2/20 (6.7%) patients
Median PFS = 2.7 months.
Median OS = 12.8 months.
→ Conclusion: sunitinib demonstrated minimal activity in the second- and third-line treatment of persistent or recurrent clear cell ovarian carcinoma

OCCCs Harbour Actionable Mutations

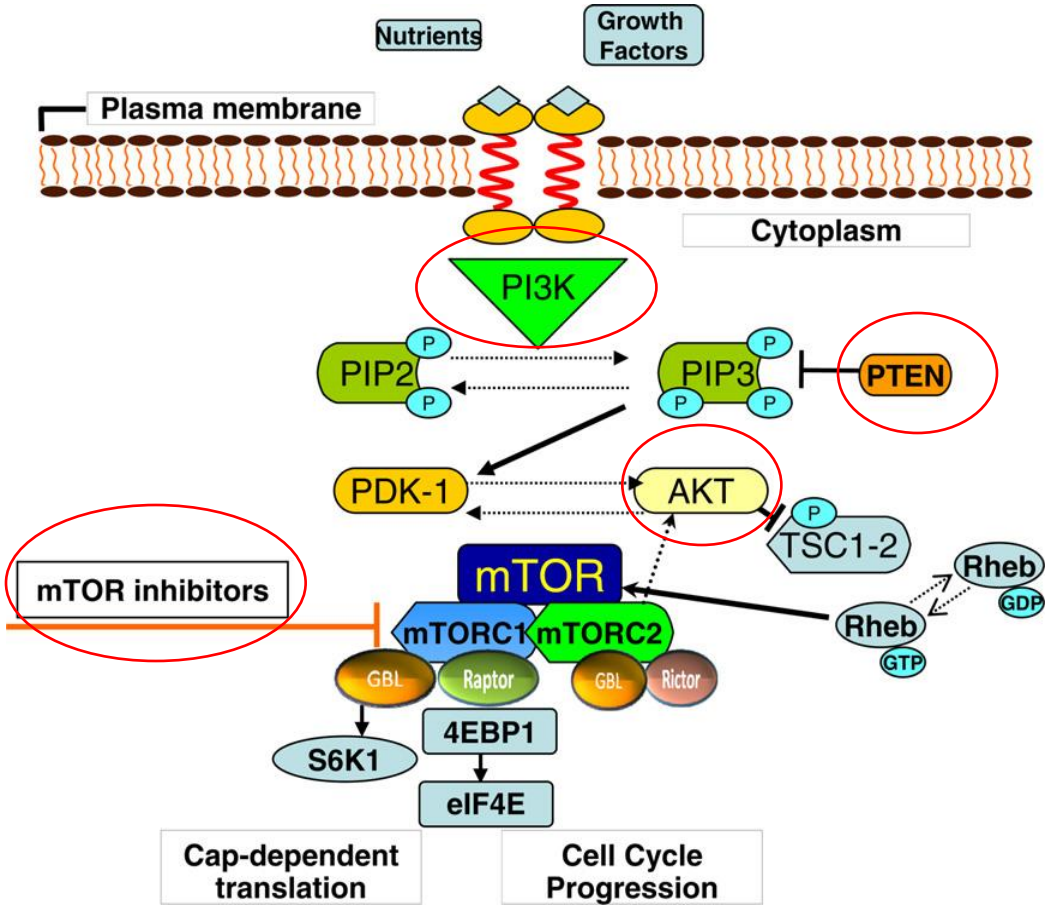
Figure 3: Mutation prevalence in patients with pure CCOC (n=69) and mixed CCOC (n=14) tested with NGS



Friedlander et al, ASCO abstract 5516, May 2014

PI3-kinase-AKT-mTOR pathway in OCCCs

- Key growth factor-mediated signal transduction pathway
- In OCCCs
  - PTEN loss (40%)
  - *PIK3CA* mutation (33%)
  - *AKT2* amplification (14%)
- No significant association between *PIK3CA* mutations and pAKT or p-mTOR IHC in OCCC
- *PIK3CA* mutations associated with a more favorable prognosis, but may not predict the sensitivity of OCCCs to PI3K/AKT/mTOR inhibitors



Tan et al BJC 2013
Rahman et al Int J Mol Sci 2013
Rahman et al Hum Pathol 2013

Targeting the PI3-kinase-AKT-mTOR pathway in OCCCs: clinical evidence?

- Weekly Temsirolimus (mTOR inhibitor) 10mg/m2 in 6 cases of OCCC

  → 1 PR (PFS 14mths) and 1 SD

  (Takano et al Int J Clin Oncol. 2011)

- CH5132799 48 mg BID (novel PI3K inhibitor, selective inhibitor of class I PI3Ks α, β, δ and γ) in 1 case of OCCC with *PIK3CA* mutation

  →>50% decrease in SUV on a PET scan at C1D8 and a 75% decrease in CA-125 at C2D1

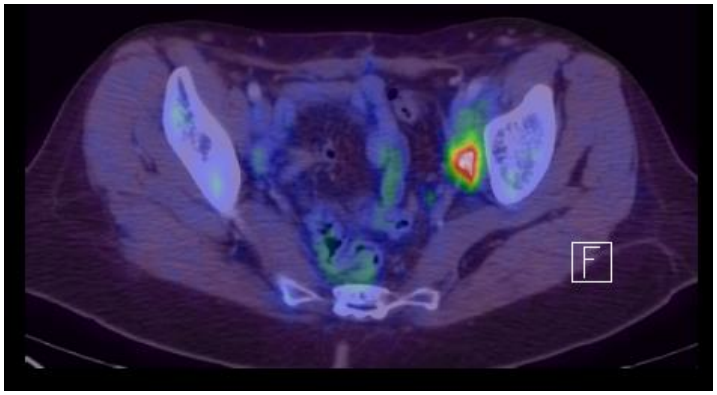
  (Omlin et al 2012 ASCO abstract 3022)

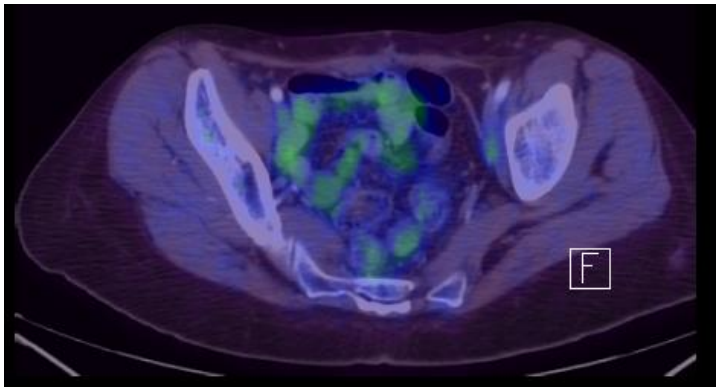
The Emerging Molecular Landscape of OCCCs

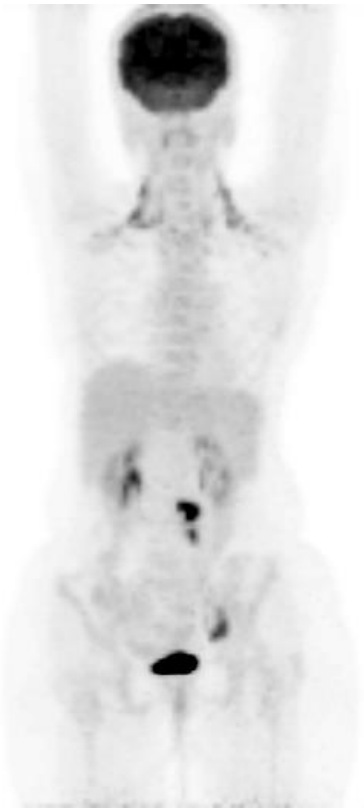
Table 1. Molecular characteristics of ovarian clear cell carcinomas and their cellular effectsAbbreviations: ARID1A = AT-rich interactive domain 1A; ATM = ataxia-telangiectasia mutated; MSI = microsatellite instability; mTOR = mammalian target of rapamycin; PI3K = phosphatidylinositol 3-kinase; PPP2R1A = protein phosphatase 2 regulatory subunit A.

Molecular characteristic	Frequency	Cellular effect
ARID1A mutation (Jones *et al*, 2010; Wiegand *et al*, 2010)	40–57%	• Loss of BAF250a, a key component of the SWI–SNF chromatin remodelling complex
IL6-STAT3-HIF upregulation (Anglesio *et al*, 2011b)	IL-6 expression in 49%	• Angiogenesis
HNF-1β upregulation (Kato *et al*, 2006; Yamaguchi *et al*, 2010)	Almost 100%	• Apoptotic escape
TMS/1/ASC methylation (Terasawa *et al*, 2004)	69%	• Apoptotic escape
PI3K/AKT/mTOR pathway activation by PTEN loss (Hashiguchi *et al*, 2006)/*PIK3CA* mutation (Kuo *et al*, 2009)/*AKT2* amplification (Tan *et al*, 2011)	PTEN loss in 40% *PIK3CA* mutation in 33% *AKT2* amplification 14%	• Activation of cell cycle progression • Inhibition of apoptosis • Increased cell motility • Impaired homologous recombination
HER2 amplification and overexpression (Tan *et al*, 2011)	14%	• Activation of PI3K, MAPK, STAT signalling pathways • Promotes cellular proliferation • Inhibition of apoptosis
PPM1D amplification (Tan *et al*, 2009)	10%	• Negative regulation of p53, Chk2 and ATM
Loss of mismatch repair genes (*hMLH1* and *hMSH2;* Cai *et al*, 2004; Pal *et al*, 2008; Ketabi *et al*, 2011)	7–18%	• MSI
PPP2R1A mutations (Jones *et al*, 2010)	7%	Impaired PP2A function leading to uncontrolled cell growth
KRAS mutations (Jones *et al*, 2010)	4.7%	Activation of RAS/RAF/MEK/ERK and PI3K/AKT/mTOR pathways

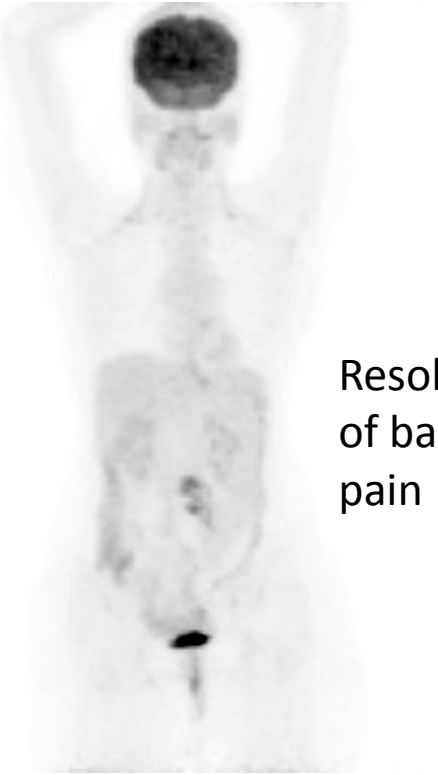
Tan et al BJC 2013







Sunitinib 50mg: 2 weeks on 1 week off 3-weekly schedule



Resolution of back pain

Nov 2014

March 2015

June 2015

June 2015:
Increased back pain and repeat PET scan shows increased FDG avidity in PA nodes

PFS 8mths on Sunitinib

What next??

Gene	Alteration	Type	Variant Frequency (%)	Quality	Depth
GNAS	R844H	SNP	11	70	181
MLH1	Q391*	SNP	8	164	922
TP53	P190L	SNP	49	5783	1148

Known family hx of colorectal cancer – father

Germline genetic testing for Lynch syndrome discussed – patient declined

OCCC: a genetically inherited disease?

Contents lists available at ScienceDirect

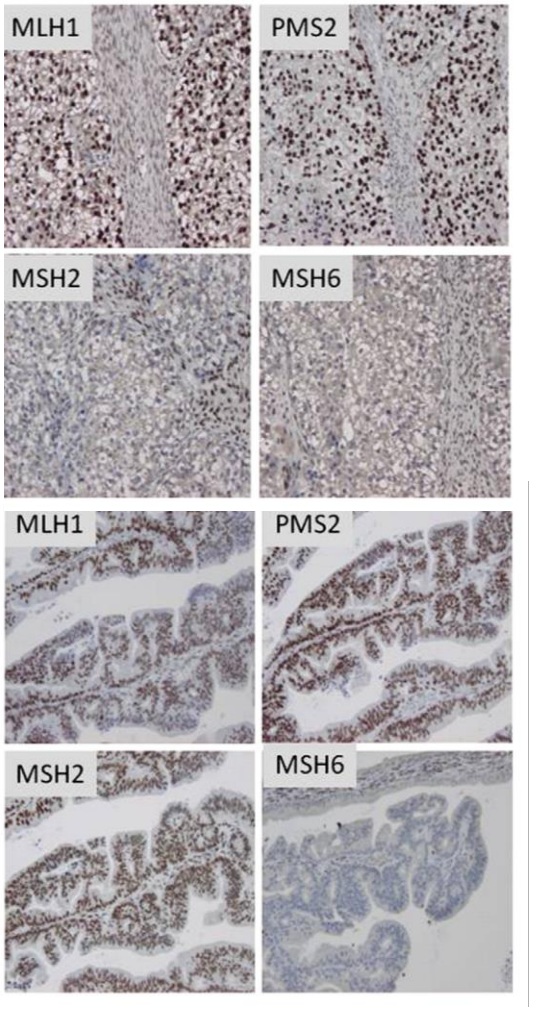
Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Ovarian cancer linked to lynch syndrome typically presents as early-onset, non-serous epithelial tumors

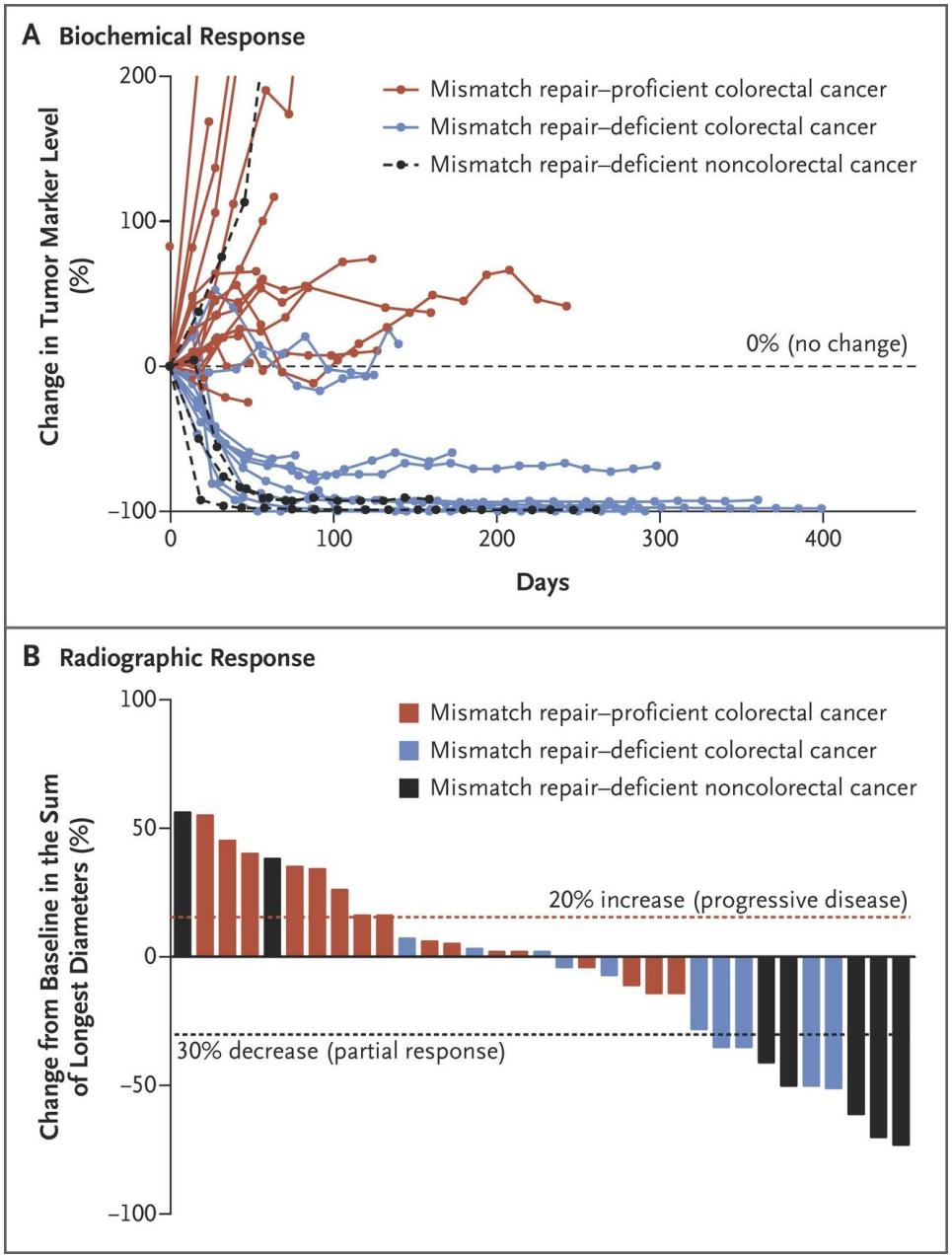
Zohreh Ketabi [a], Katarina Bartuma [b], Inge Bernstein [a], Susanne Malander [b], Henrik Grönberg [c], Erik Björck [d], Susanne Holck [e], Mef Nilbert [a,b,*]

- Ovarian cancers developed at mean 48 years of age
- FIGO stage I in 47% of cases
- Histologically, endometrioid (35%) and clear cell (17%) tumors were overrepresented.
- The underlying MMR gene mutations in these families affected MSH2 in 49%, MSH6 in 33% and MLH1 in 17%.
- IHC loss of the corresponding MMR protein in 92% of tumors



Gynecologic Oncology 121 (2011) 462–465

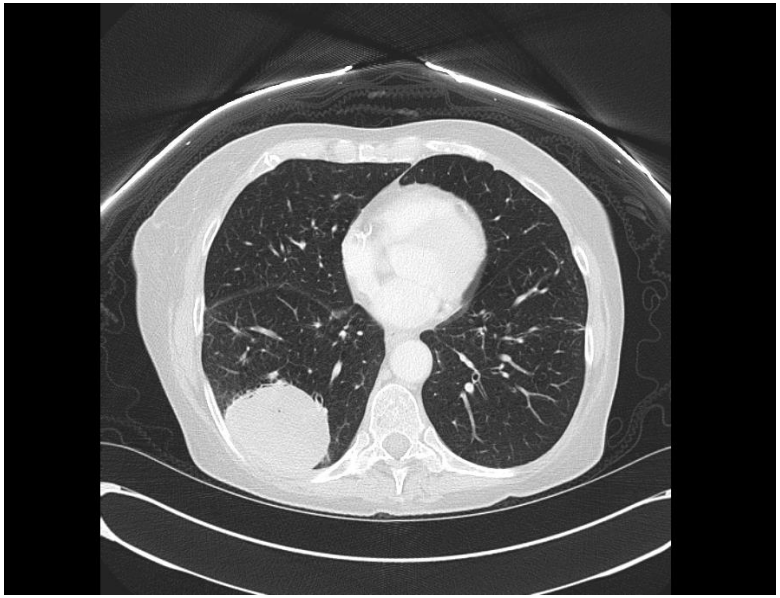
Clinical Responses to PD-1 inhibitor pembrolizumab in MMR deficient vs proficient cancers



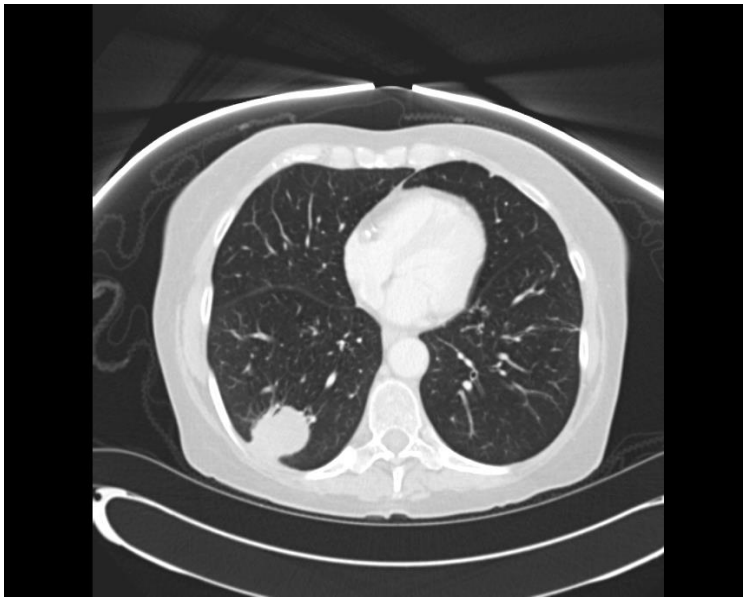
Le DT et al. N Engl J Med 2015;372:2509-2520

Partial response to PDL1 inhibitor Avelumab in metastatic clear cell ovarian cancer

Baseline: 69 mm RLL lesion

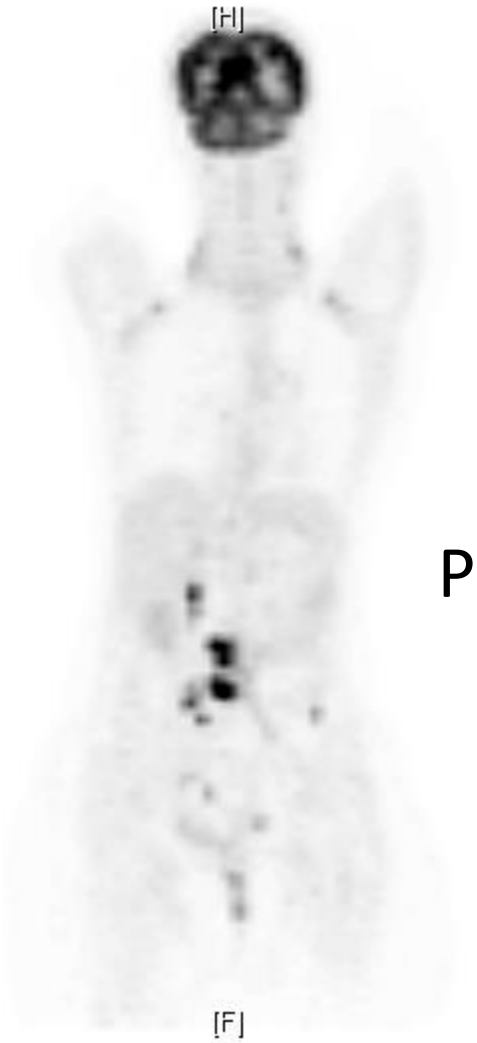


Week 25: 41 mm (-40.6%)



- 65 years old; 6 prior lines for metastatic disease
- 4th assessment cycle, still on treatment

Disis et al ASCO 2015



PFS 8mths on Sunitinib

PD-1/ PDL-1 inhibitor?

June 2015

Conclusions

- OCCC is a clinically and molecularly heterogeneous disease
- Largely chemoresistant disease with poor OS from 1st relapse → "watch and wait for symptoms" approach to management may not be appropriate
- Current optimal management in recurrent disease is unclear but should include early molecular stratification for consideration of clinical trials.
- More OCCC specific studies required and the ability to identify molecular subtypes of OCCC reliably and early on in treatment will be crucial to expedite recruitment into trials.
- Antiangiogenic and immunotherapeutic approaches (either sequentially or in combination) may be effective in particular subgroups of OCCC but will require further confirmatory clinical studies