ICR The Institute of Cancer Research

BREAST CANCER NOW The research & care charity

CANCER RESEARCH UK

in partnership with The ROYAL MARSDEN NHS Foundation Trust

Systemic therapies for Granulosa Cell Tumours

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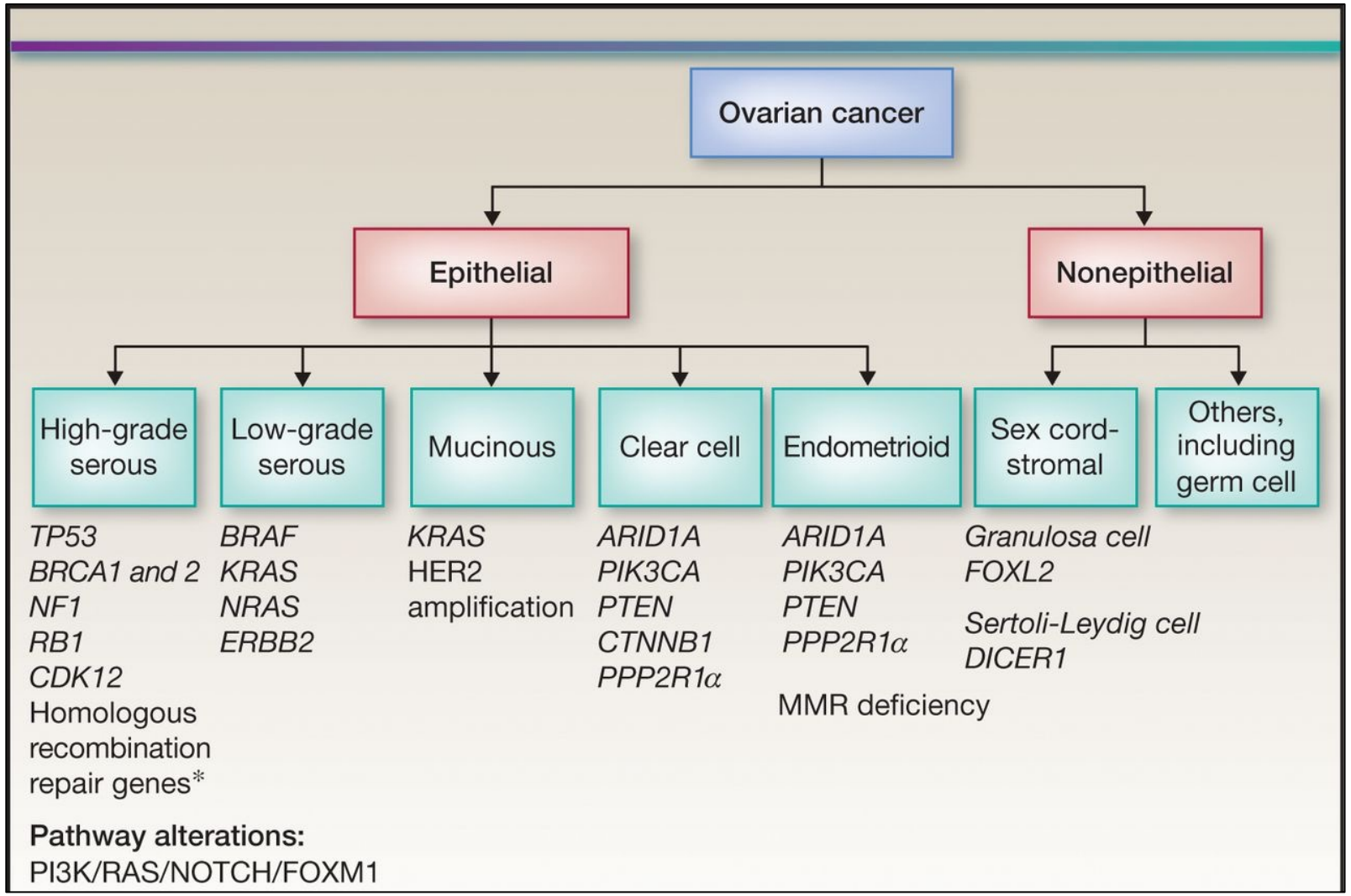
Objectives

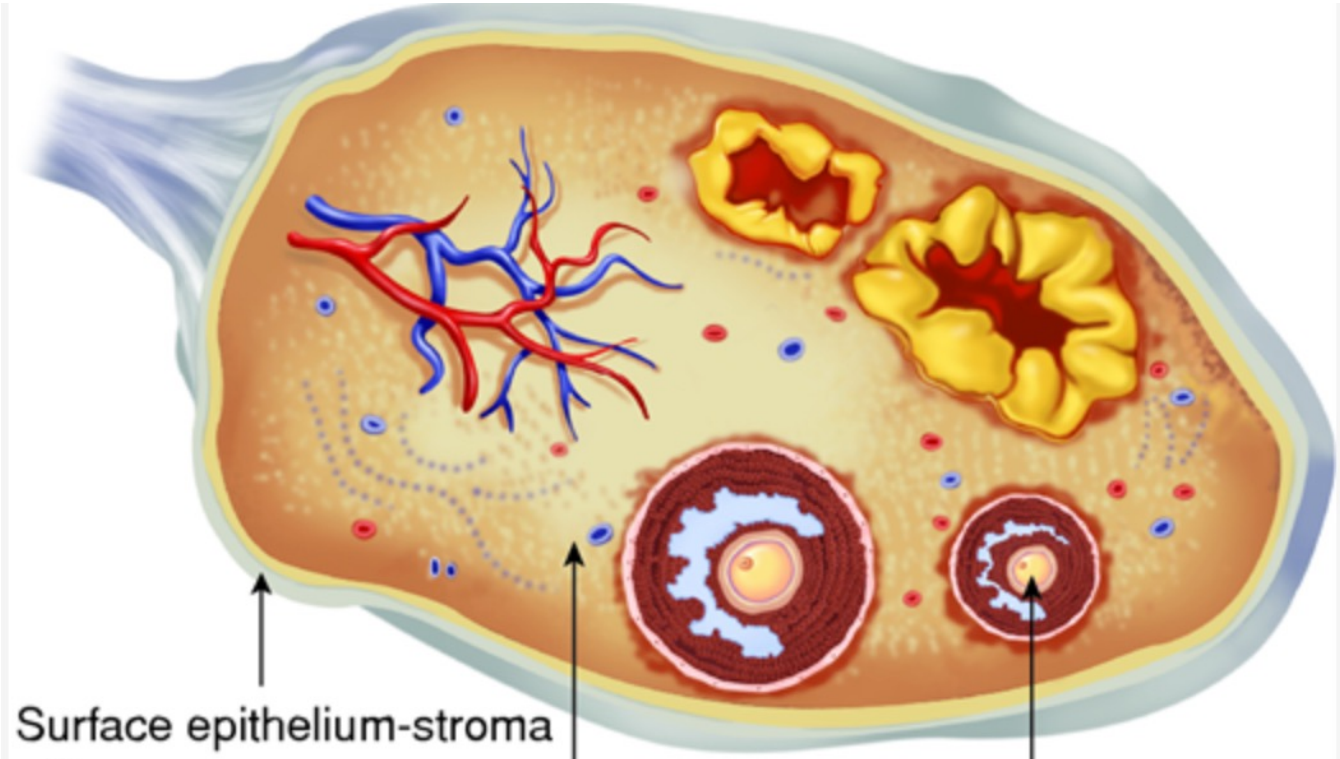
1. Overview of ovarian cancer
2. Introduction to GCTs
3. Histopathological features
4. Molecular features
5. Introduction to SACT
6. Chemotherapy for adult GCT
7. Endocrine therapy for adult GCT
8. Future perspectives

Ovarian cancer is not a singular disease



Banerjee. S. and Kaye. S. Clin Cancer Res (2013).

Ovarian cancer is not a singular disease



Surface epithelium-stroma
- Serous
- Mucinous
- Endometrioid
- Clear cell
- Transitional cell

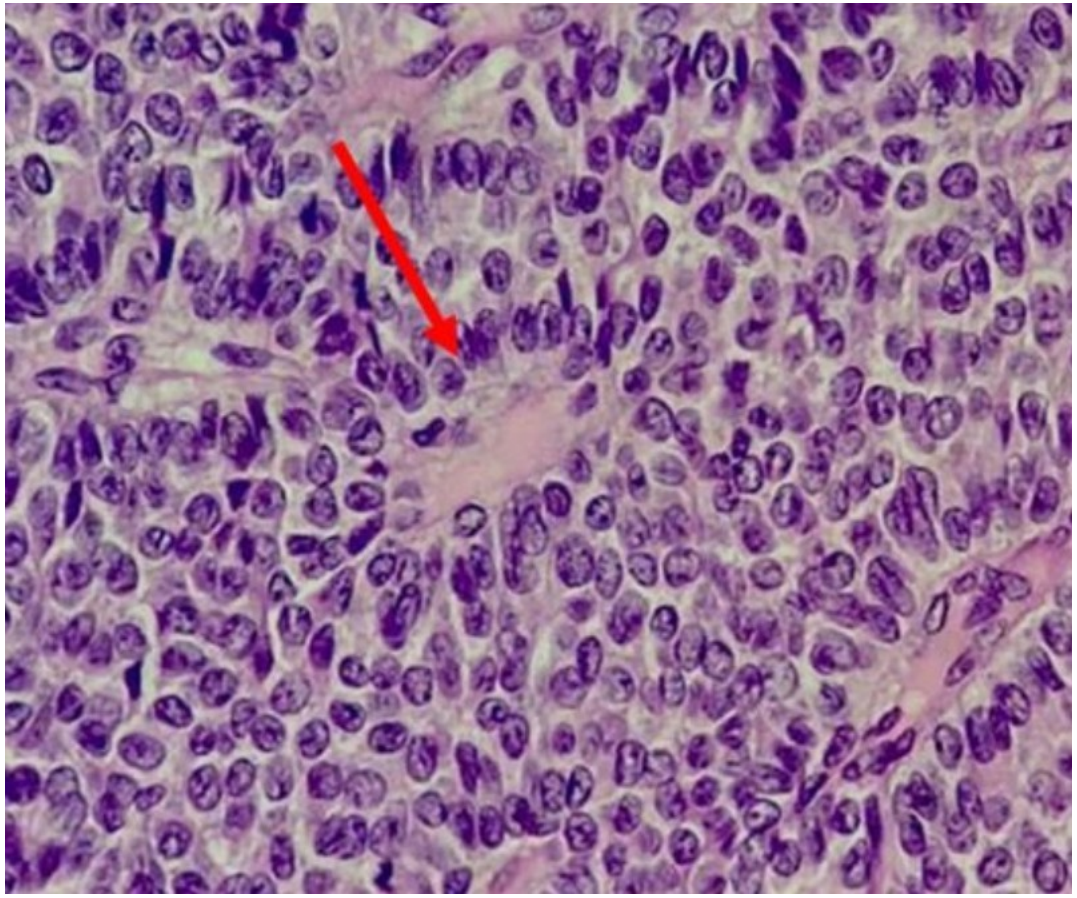
Sex cord-stroma
- Granulosa cell
- Thecoma
- Fibroma
- Sertoli cell
- Sertoli-Leydig
- Steroid

Germ cells
- Dysgerminoma
- Yolk sac
- Embryonal carcinoma
- Choriocarcinoma
- Teratoma

Adult-type GCTs

- 2-5 % of ovarian cancer cases
- Median age of presentation is 50 years
- Majority of patients diagnosed with stage I disease
- Symptoms associated with excessive oestradiol production
- Inhibin B and antimullerian hormone (AMH) levels are helpful in diagnosis

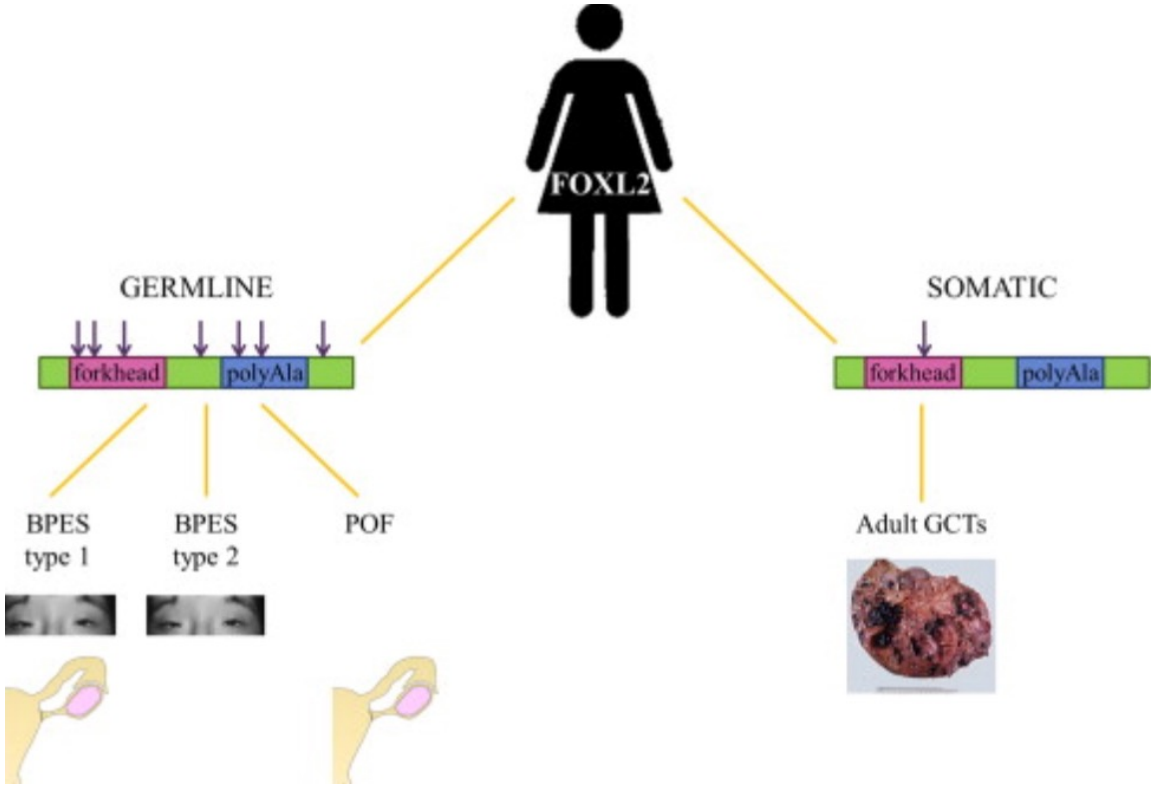
Histopathological features of adult GCT



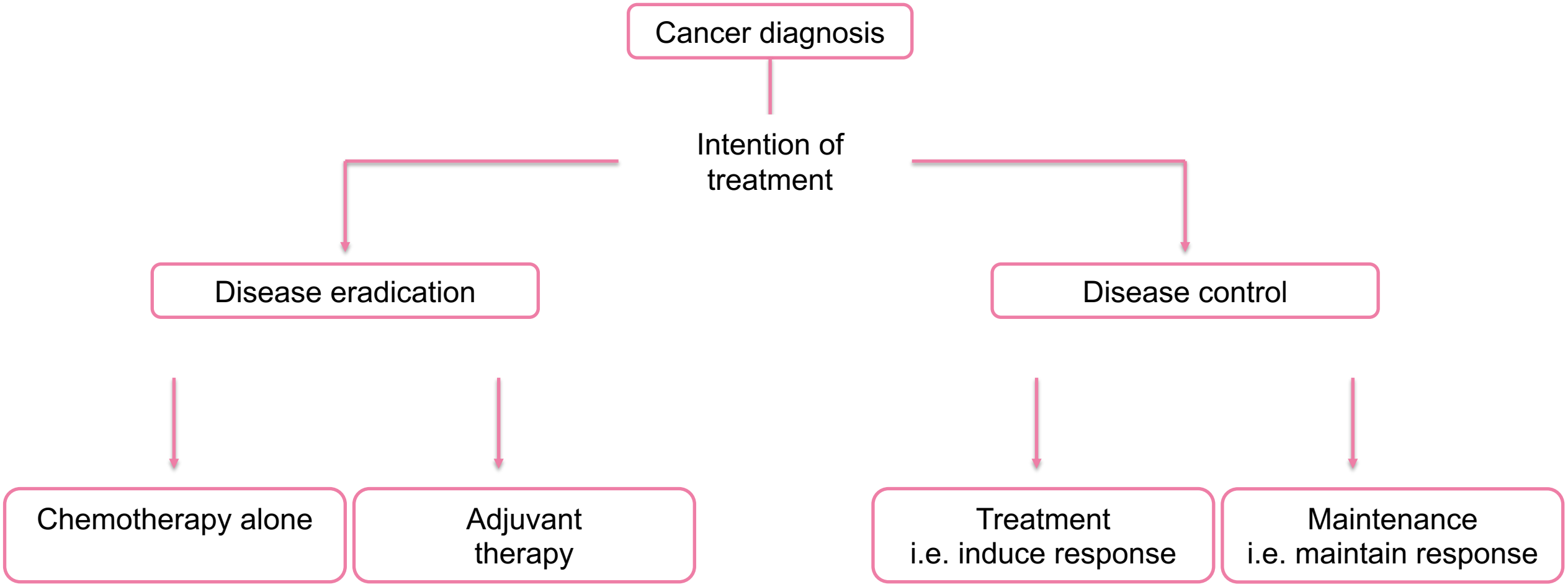
- Tumours composed of small cuboidal cells
- Call-Exner bodies (red arrow)
- Nuclear groove = coffee been cells

Molecular features of adult GCT

- Somatic mutations in FOLX2 identified in 97% of adult GCT cases
- Somatic therefore cannot be passed on to children
- FOXL2 mutations associated with disruption in steroid metabolism (oestrogen) and activation of pro-tumorigenic pathways



Systemic anticancer therapy (SACT) overview



This traditional treatment paradigm has been challenged by the introduction of targeted agents and IO drugs

Adjuvant SACT

Neoadjuvant

- Given before definitive treatment
- Reduce tumor size
- Increase likelihood of successful removal
- Reduce the risk of relapse
- Given prior to surgery if associated morbidity precludes delivery of postoperative chemotherapy

Adjuvant

- Given after definitive treatment
- Reduce the risk of relapse following procedure
- Magnitude of benefit often expressed as relative risk

Adjuvant therapy not restricted to cytotoxic chemotherapy e.g. endocrine therapy in breast cancer, IO in melanoma

SACT in the context of GCT

- Systemic anticancer therapy (SACT) indicated when local treatments (e.g. surgery, radiotherapy) are not deemed appropriate
  - Multi-focal disease
  - Anatomical location
  - Relapse after definitive treatment (short interval)

- Deciding when to initiate SACT dependent on number of factors
  - Symptoms
  - Pace of disease
  - Patient preference

- In GCT SACT mainly consists of
  - Cytotoxic chemotherapy
  - Endocrine therapy

Chemotherapy for advanced GCT…..an ongoing story

Year	Regime
1974	Cyclophosphamide
1976	Actinomycin, cyclophosphamide, 5-FU
1978	Doxorubicin
1982	Cisplatin, doxorubicin
1983	Cisplatin, cyclophosphamide, doxorubicin
1984	Altretamine, cisplatin
1986	Cisplatin, cyclophosphamide, doxorubicin
1986	Bleomycin, cisplatin, vinblastine
1987	Cisplatin, cyclophosphamide, doxorubicin
1996	Bleomycin, cisplatin, etoposide

Mostly anecdotal cases of response or small case series

BEP (Bleomycin, etoposide, cisplatin)

- Borrowed regime from treatment of germ cell tumours
- First regime to be trialed in relatively large number of patients
- 75 women with GCT
  - Incompletely resected
  - Relapsed following surgery
- Response assessed via second look laparotomy
- 37% of patients enrolled demonstrated no disease at second surgery
- Grade 4 myelotoxicity (blood counts) observed in 61% patients

Homesley et al. Gynaecol Oncol (1999)

Introduction of taxanes – a less toxic approach

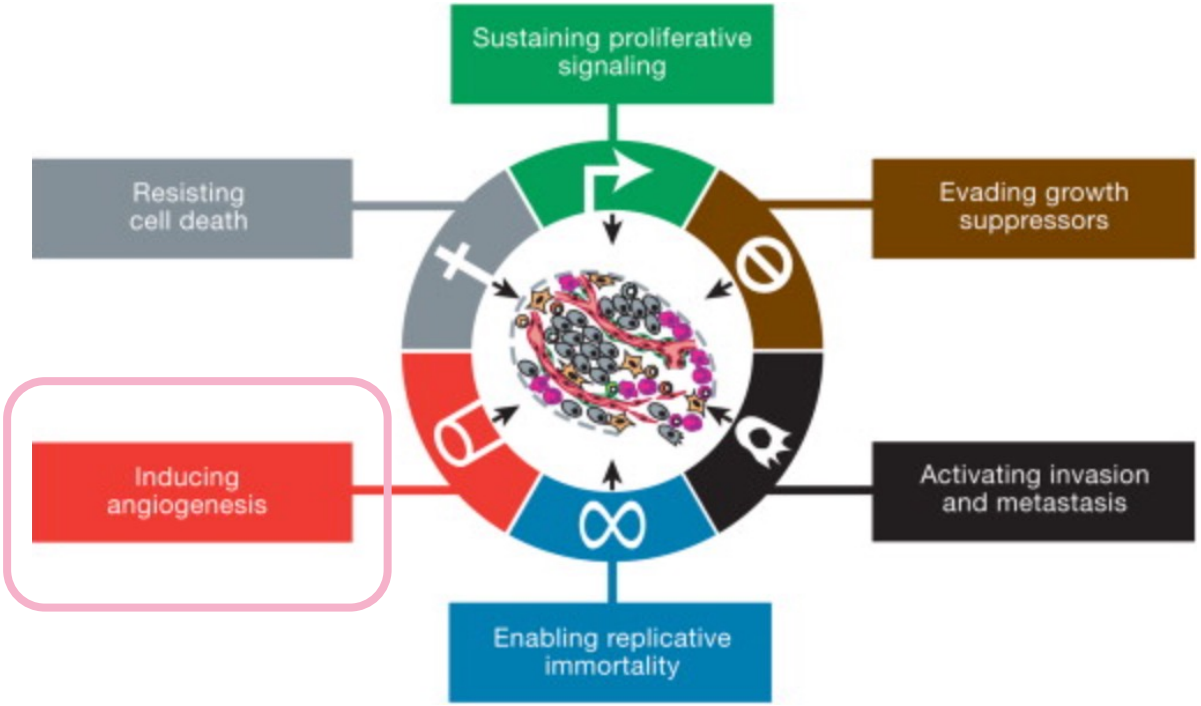
The activity of taxanes compared with bleomycin, etoposide, and cisplatin in the treatment of sex cord-stromal ovarian tumors☆

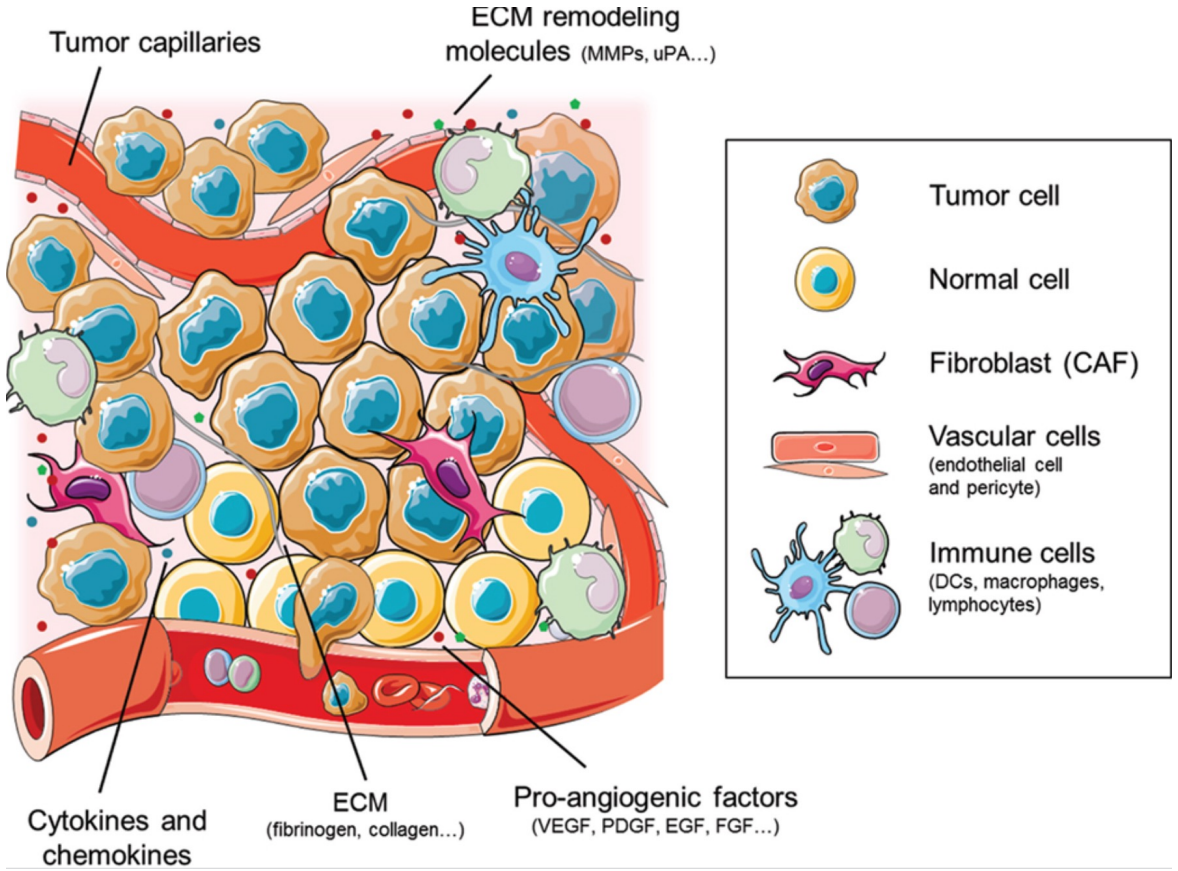
Jubilee Brown[a,*], Hyun S. Shvartsman[a,1], Michael T. Deavers[b], Lois M. Ramondetta[a], Thomas W. Burke[a], Mark F. Munsell[c], David M. Gershenson[a]

- Retrospective analysis of patients diagnosed with SCSTs recruited at MD Anderson Cancer Centre
  - Predominantly adult GCT
  - some juvenile GCT and unclassified SCSTs
- Compared outcomes for patients treated with BEP vs taxanes +/- platinum agent
  - 21 received BEP for new (n = 11) or recurrent disease (n = 10);
  - 44 received a taxane for new (n = 11) or recurrent disease (n = 37)
- Taxanes (alone or with platinum agent) non-inferior to BEP
- Taxane containing regime associated with lower levels of toxicity

Brown et al. JCO (2004)

Targeting angiogenesis – a potential approach in GCT

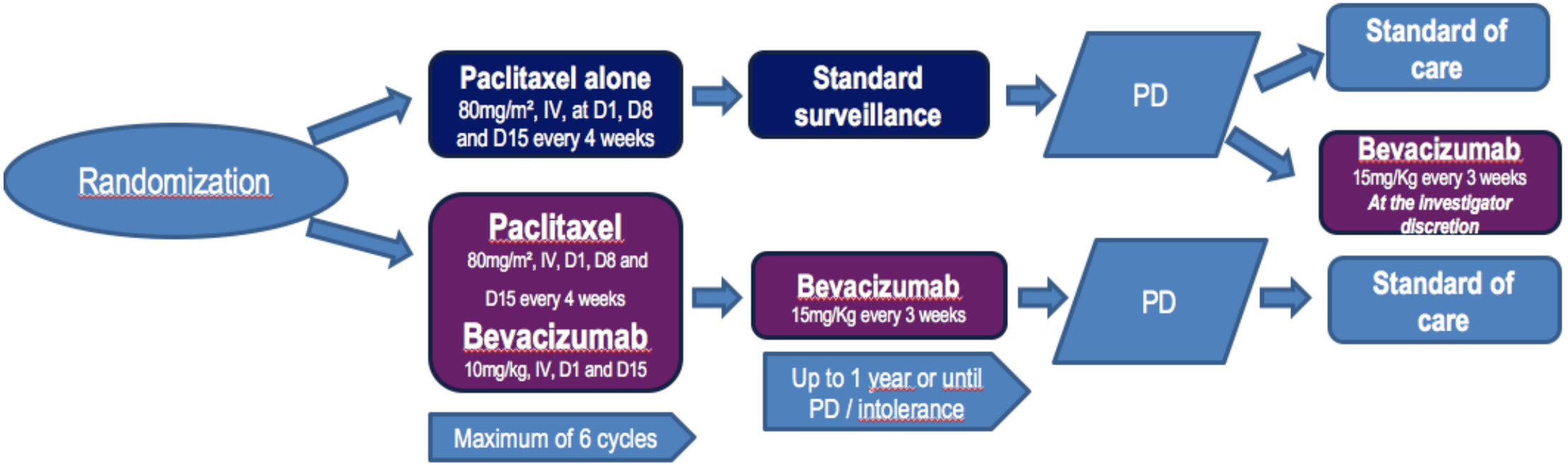




Hanahan and Weinberg. Cell. 2011

ALIENOR/ENGOT-OV7

- First randomised trial in GCTs
- Multi-centre, International
- Example of Collaborative research and engagement in Rare Cancers



ALIENOR/ENGOT-OV7

Patients

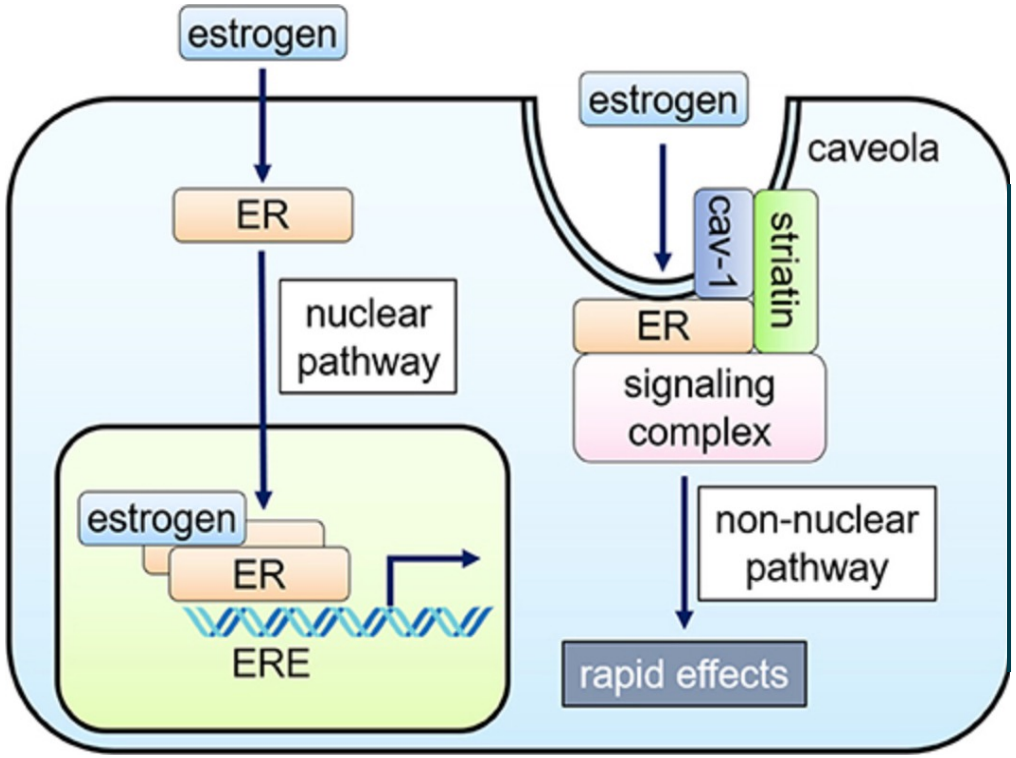
- 60 patients
  - 87% adult GCTs
- 28% <12 month platinum-free interval
- 22% >2 chemotherapy lines
- 28% prior hormonal therapy

Results

- Did not meet primary endpoint- 6 month PFS rate (70.6% vs 72.4%)
- Median PFS 14.7 (paclitaxel) vs 14.9 months (paclitaxel + bevacizumab)
- Response rate higher with addition of bevacizumab 25% vs 44%

Endocrine therapies

- Pathognomonic FOXL2 mutations results in deregulation of steroid metabolism and excessive oestrogen production
- Endocrine therapies were initially introduced with the rationale of interrupting hormone receptor signaling to achieve antitumor effect
- Initial regimens included
  - Tamoxifen
  - Progestogins (e.g. Megestrol acetate)
  - Gonadotropin-releasing hormone agonists (e.g. gosarelin)
- No clinical trials of these agents
- Pooled analysis of 50 case reports (mostly prior to introduction of aromatase inhibitors) suggest
  - Disease control rate = 66%
  - Response rate = 34%



Aromatase inhibitors (AI)

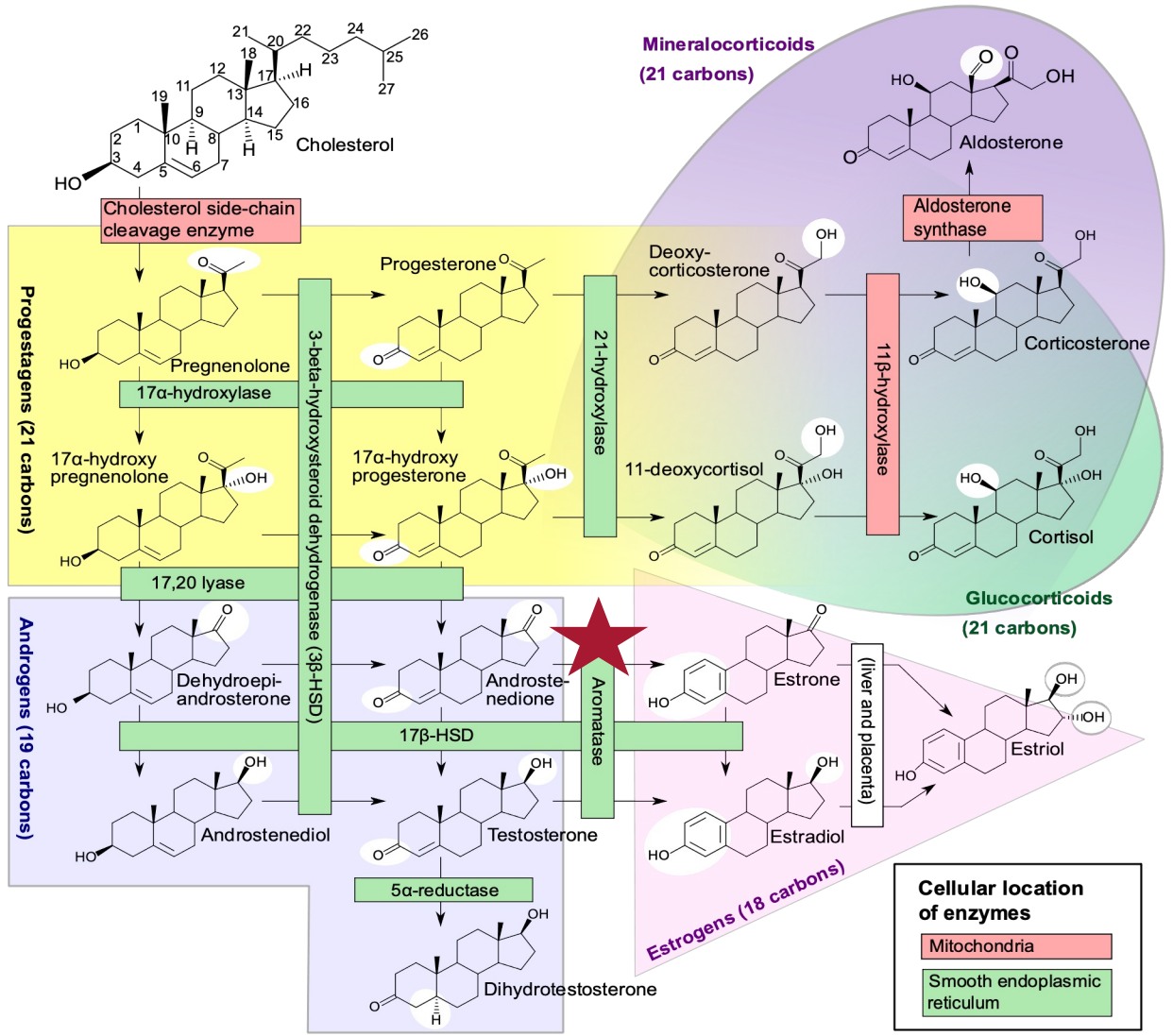
- Examples include
  - Letrozole
  - Anastrozole
  - Exemestane

- Inhibit oestrogen biosynthesis from andostrendione and testosterone both in the ovary and other tissues (e.g. fat)

- The use and benefit of AI in context of GCT was observed prior to identification of pathognomonic FOXL2 mutation

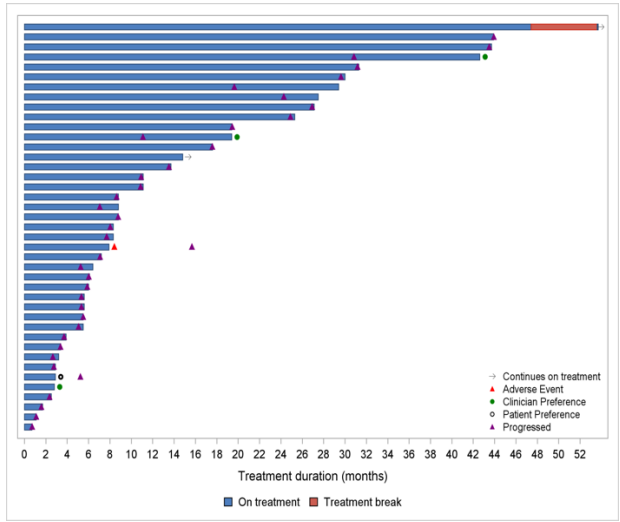
- Several proposed mechanisms of action
  - Alterations of the hormone-saturated cellular environment
  - Direct dampening effect on the tumor aromatase activation

- Retrospective pooled analysis suggests response rate of 48%



PARAGON – A phase 2 study of Anastrozole (An) in patients with oestrogen receptor (ER) and/ progesterone receptor (PR) positive recurrent/metastatic granulosa cell tumors/sex-cord stromal tumors (GCT) of the ovary - ANZGOG 0903

Endpoint	Response	n (%)	95% CI
Clinical benefit at 3 months (RECIST)	Clinical benefit	30 (78.9%)	(63.7–88.9%)
	Progressive disease	6 (15.8%)	
	Clinical progression	2 (5.3%)	
Response at 3 months (RECIST)	Partial Response	1 (2.6%)	(0.5–13.5%)
	Stable Disease	29 (76.3%)	
	Progressive disease	8 (21.1%)	



- 41 evaluable patients
- Response rate at 3 months = 2.6%
- Delayed response rate = 10.5%

Median PFS = 8.6 months
(95% CI 5.5–13.5 m).

This is the first prospective trial of an AI in recurrent GCTs
Although there was a high CBR, the objective response rate was much lower than in retrospective series

Banerjee et al. Gynecol Oncol. 2021

AIs are not without toxicity

Toxicity	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)
Arthralgia	19 (47.5%)	1 (2.5%)	1 (2.5%)
Headaches	12 (30.0%)	2 (5.0%)	
Anorexia	2 (5.0%)		
Nausea	11 (27.5%)	1 (2.5%)	
Fatigue	20 (50.0%)	4 (10.0%)	
Vomiting	3 (7.5%)	1 (2.5%)	
Abnormal lipids	1 (2.5%)	2 (5.0%)	
Alopecia	7 (17.5%)		
Hot flashes	20 (50.0%)	3 (7.5%)	
Rash	4 (10.0%)	1 (2.5%)	
Vaginal dryness	7 (17.5%)	2 (5.0%)	

Endocrine therapy future: Future directions

- To date PARAGON is the only clinical trial of endocrine therapy in GCT to report
- Trials of ketoconazole, orteronel and enzalutamide have all been discontinued
- We have anecdotal of activity of other endocrine therapies used alone or in combination but lack the clinical trial data to support their use
- Can we learn the lessons from oestrogen receptor positive breast cancer
  - Selective oestrogen receptor degraders (e.g. fulvestrant)
  - CDK4/6 inhibitors (Palbociclib, ribociclib, abemociclib)
  - mTOR inhibitors (everolimus)

GCT remains an area of great unmet need

Hospitals

NHS

Academic institutions

Clinical Trials

Patient advocacy groups

LADY GARDEN

CANCER RESEARCH UK

Charities and funders

Lessons from ovarian clear cell carcinoma…clinical trials in rare cancers are possible

521MO - Efficacy of pembrolizumab monotherapy (PM) for advanced clear cell gynaecological cancer (CCGC): Phase II PEACOCC trial

Pembrolizumab

Sintilimab + bevacizumab

522MO - Preliminary results of sintilimab (Sin)+bevacizumab (Bev) in recurrent/persistent ovarian clear cell carcinoma (INOVA): A multicenter, single-arm, phase II trial

Clinical trial

ATARI trial: ATR inhibitor in combination with olaparib in gynecological cancers with ARID1A loss or no loss (ENGOT/GYN1/NCRI)

ATR inhibitor

Thankyou.

Questions?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