Isabelle Ray-Coquard
Lyon France

Rare epithelial & non epithelial tumors – treatment & networks for research

Epidemiology, management, organisation

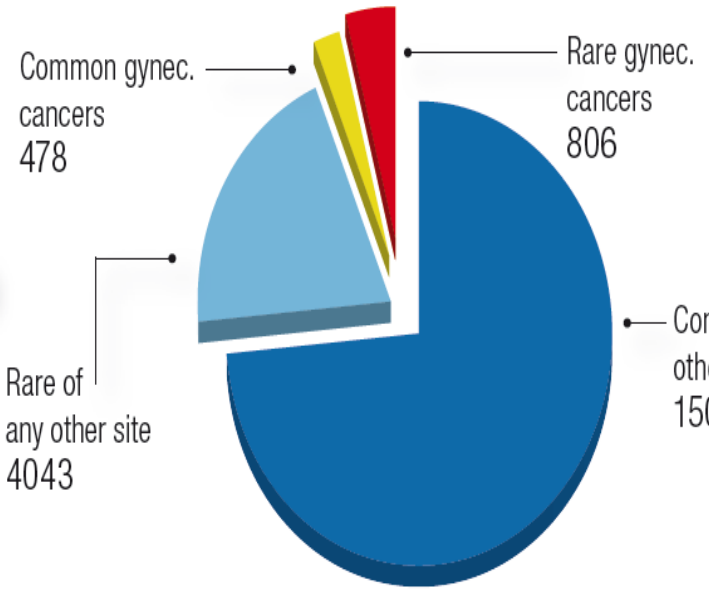
Rare gynaecological cancers (RGCs, defined as <6/100 000/year) represent 55% of all gynaecological cancers. This major proportion is highly specific to gynaecology (except sarcomas).

Rarity may be due to unusual histology (e.g. sex cord, trophoblastic), localisation (e.g. vaginal melanoma), or histological subtype (e.g. mucinous, clear cell carcinoma).

The histological definition is based on pathological classification and molecular biology subgroup, which may increase heterogeneity.

EPIDEMIOLOGY

Incidence of rare versus common cancers in Europe, 200



Focus on the most “frequent” rare ovarian tumors

- Rare ovarian non epithelial tumors:
  - ✓Germ cell tumors
  - – Sex cords stromal tumors
  - – Small cell carcinoma
- Rare epithelial carcinoma
  - – LGSC
  - – Mucinous carcinoma
  - – Carcinosarcoma
  - ✓Clear cell carcinoma

Sex Cord Stromal Tumors

- 7% of all ovarian cancer & Peak age 50 years
- Endocrine manifestations (oestrogen secretion 70%)
- Endometrial hyperplasia (25%) or endometrial carcinoma (5 – 10%)
- Recent findings on mutated genes : FOXL2 for adult Granulosa & DICER1 for Juvenile Granulosa & Sertoli Leydig

Sex Cords tumors
Histology (WHO classification 2014)

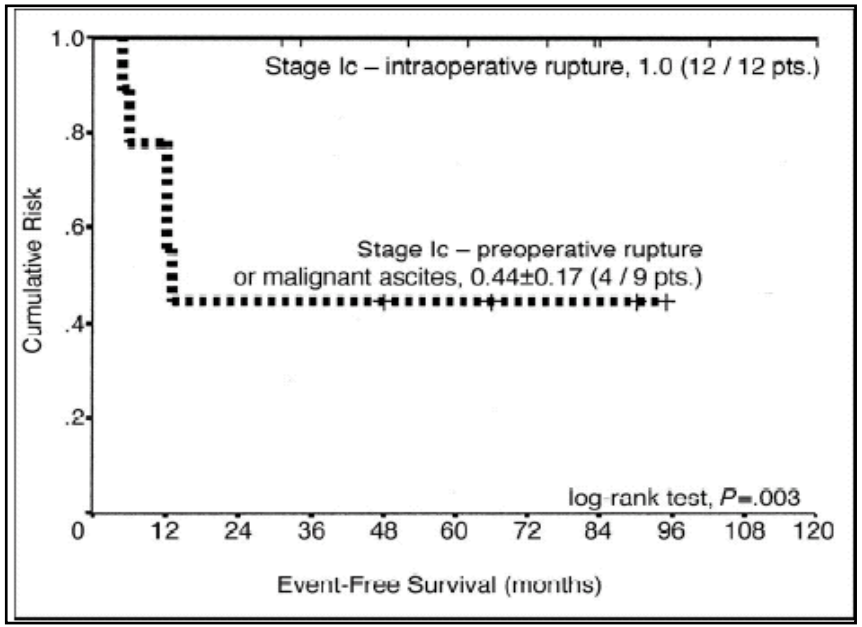
- Pure sex cord tumors
  - Adult Granulosa cell tumor
  - Juvenile granulosa cell tumor
  - Sertoli cell tumors (benign)
  - Sex Cord with anular tubules
- Mixed sex cord stromal tumors
  - Sertoli Leydig well diffrentiated (androgenic, secretory in 60% of the cases)
  - Sertoli Leydig Moderately differentiated with heterologous elements
  - Sertoli Leydig Poorly differentiated with heterologous elements
  - Sertoli Leydig Retiform with heterologous elements
  - Sex cord-stromal tumors NOS
- Pure stromal tumors
  - Fibrosarcoma
  - Steroid cell

GCT, Clinical prognostic factors

- FIGO Stage:
  - DFS at 5 years 95% (I-II) vs 59% (III-IV)
- Age (more than **50 years old**)
  - DFS at 5 years 93% (≤ 50y) vs 84% (> 50y)(Zhang M et al. Gynecol Oncol 2007)
- Tumor size (> 5-10 cm) (Chan JK, Gynecol Oncol 2005)
- Intra peritoneal tumor rupture (Schneider, JCO 2004)
- **Multivariate analysis**: age (HR 1.03) & stage (HR 1.79) (Zhang M et al. Gynecol Oncol 2007)

- For JGCT **stage** is the major pronostic factor

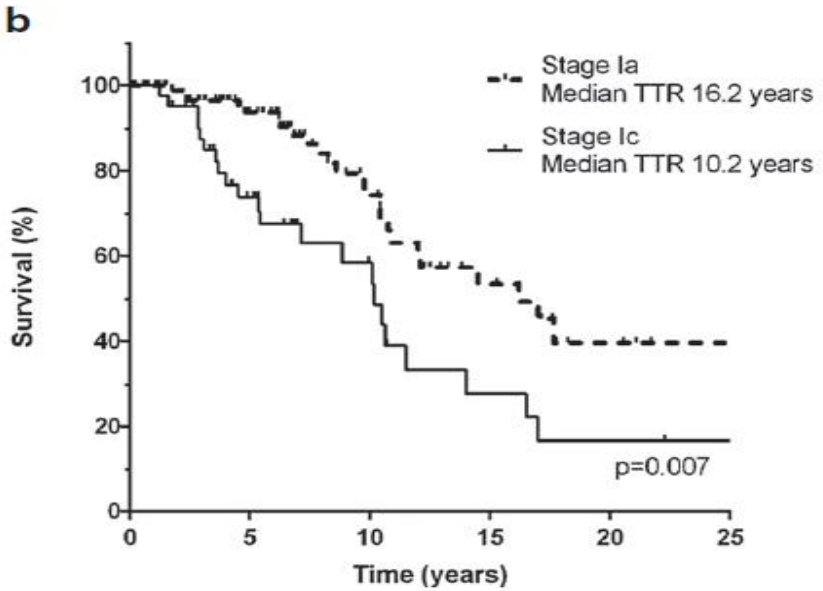
Intra peritoneal TUMOR RUPTURE



IC1: 3/12 pts received CT
IC2-3: 4/9 pts received CT

Schneider et al, JCO vol 22, n10, 2004

160 AGCT patients with stage I



IC2: 5/6 pts relapsed
IC1: 10/21 pts relapsed
Relapse stage Ia 24% vs IC 43%, p<0,01

Wilson et al, Gyn Oncol vol 138, 2015

Granulosa cell tumor : Molecular features & prognostic factors

- FOXL2 mutation (missense point mutation (402C -> G) in the FOXL2 gene (adult-type granulosa cell tumors) (Shah SP, NEJM 2009)
- Utility of FOXL2 immunostaining & FOXL2 mutation in all adult granulosa cell tumors but absent in other pure subtypes within the SCST category (Al-Agah OM, Am J Surg Pathol 2011).

Prognostic factor?

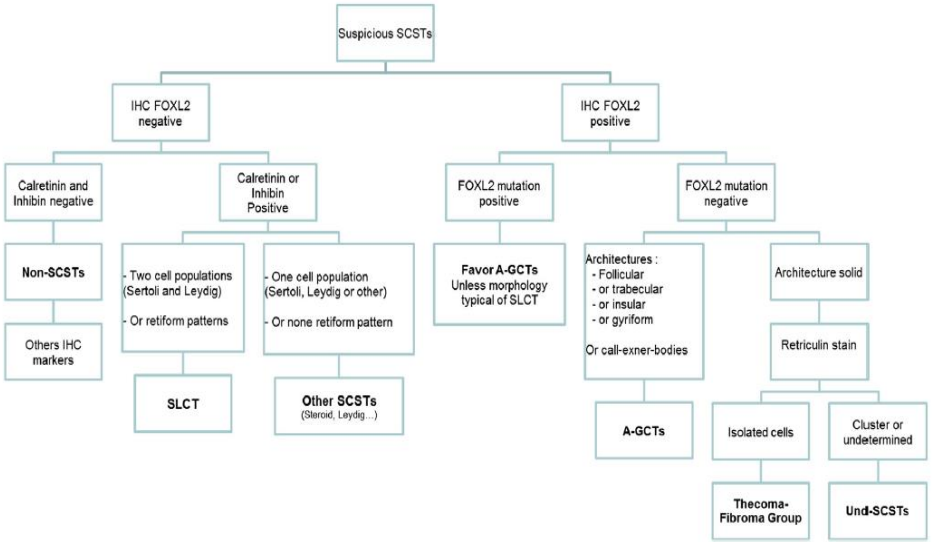
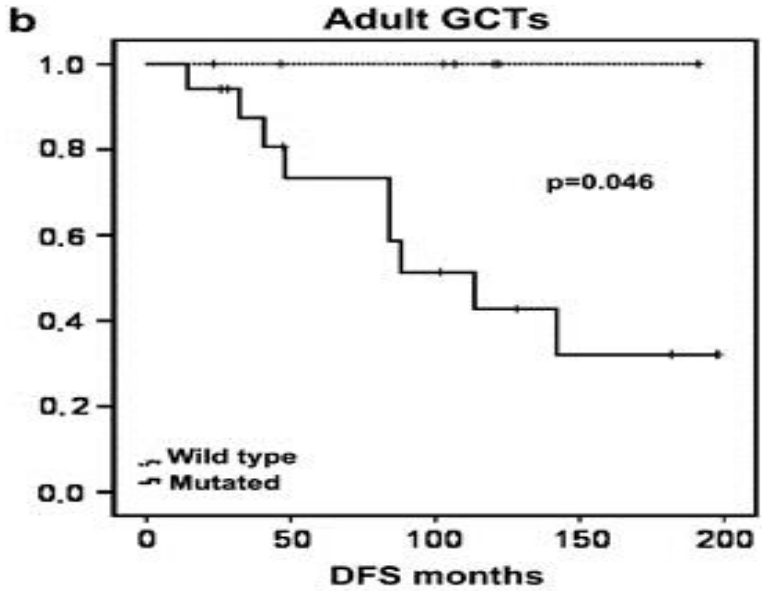


Fig. 2. Diagnosis algorithm for Ovarian-SCSTs. Abbreviations: A-GCT, Adult Granulosa Cell Tumor; SLST, Sertoli–Leydig Cell Tumor; Und SCSTs, Undifferentiated Sex Cord-Stromal Tumors; IHC, Immunohistochemistry.



Sertoli-Leydig cell tumors

- 0.5% ovarian neoplasm
- Median age at diagnosis: 25 yrs
- DICER-1 mutation younger (Rio FT, *Jama 2011*)
- 40 to 60% : hirsutism or virilization
- Occasionally oestrogen-related manifestation isosexual pseudoprecocity)

Sex cord tumor with annular tubules

- < 1% SCST
- Median age at diagnosis: 27 yrs
- Sporadic or association with Peutz Jeghers syndroma
- Germ-line STK11 mutation (no somatic mutation)

SLCT, Prognostic factors

Prognostic factors (Sigismondi C, Gynecol Oncol 2012):

- Stage : recurrence 12.7% st.I compared to 100% st. II-IV
- Grade : Well diff. OS = 100%, Poorly diff. OS= 41%
- Presence of mesenchymal heterologous elements or retiform component
- DICER1?

Histopathology

Histopathology 2016, 68, 279–285. DOI: 10.1111/his.12747

DICER1 and *FOXL2* mutations in ovarian sex cord–stromal tumours: a GINECO Group study

- n = 156 SCST from GINECO/TMRO
  - 101AGCT, 8JGCT, 19 SLST, 12 UndSC, other
  - mDICER1 31% SLST
  - mDICER1 25% JGCT

Table 3. Hormonal status of Sertoli–Leydig cell tumours (SLCTs)

SLCT	*DICER1*-mutated SLCTs/total cases studied (%)	*DICER1*-non-mutated SLCTs/total cases studied (%)
ER+	6/6 (100)	6/13 (46)
PR+	6/6 (100)	12/13 (92)

ER, oestrogen receptor; PR, progesterone receptor.

Table 6. Follow-up of Sertoli–Leydig cell tumours (SLCTs)

Age (years)	Follow-up (months)	Relapse
SLCTs with *DICER1* mutations		
43	14	Yes
17	37	No
49	29	No
66	7	Yes
27	26	No
SLCTs without *DICER1* mutations		
67	7	No
28	43	No
22	23	No
53	56	No
64	62	No
65	115	No
65	16	No
67	19	No

Surgical therapy for Sex Cord Stromal T

- **Surgery, key point treatment including**
  - Surgical staging:
    - infracolic omentectomy,
    - biopsy of the diaphragmatic peritoneum, paracolic gutters, pelvic peritoneum
    - peritoneal washings
  - Bilateral salpingo oophorectomy
  - Total hysterectomy
  - **Young age and early stage IA/IC1 : fertility sparing surgery + uterine curettage for GCT**

- controversial:
  - Restaging
  - Lymphadenectomy
  - laparoscopy

Conservative Surgery

- **SEER database of 339 pts (1992 to 2001)**
  - 265 young patients (<50 years) with stage I-II
    - 110 pts (54%) had conservative uterine-sparing surgery
  - No outcome difference between women undergoing standard vs. conservative surgery (95%)

- **Lauszus (Denmark) n = 181 (1962 to 2003)**
  - 153 stage I AGCT & 51 with less than 50 years old
    - 51 (33%) received conservative surgery (30 < 50 years old)
  - Adjuvant CT : n = 11 after standard Surgery (11%) vs 1 (5%) for cons. surgery
    - Recurrences rate: 20% Standard surg vs 31% conservative S (all age class)
    - Recurrences rate: 19% Standard surg vs 27% conservative S (< 50 y)
    - Death rate: 12% Standard surg vs 19% conservative S (all age class)
    - Death rate: 15% Standard surg vs 13% conservative S (< 50 y)

Zhang et al, Gynecol Oncol, 2007; Lauszus FF, et al, EJOG & Rep Bio 2014

Lymphadenectomy?

- MD Anderson retrospective serie
  - N = 257 pts with SCST; relapse 45%; 2% N+

Histology	N	No of relapse	Positive Nodes at recurrence
Adult GCT	178	85 (48%)	5
Juvenile GCT	27	14 (52%)	
Sertoli Leydig cell tumor	31	9 (28%)	0
SCTAT*	6	4 (67%)	0
Mixed SCST	13	4 (31%)	1
Undifferenciated SCST	2	1 (50%)	0

J Brown, Gynecol Oncol, March 2006, Thrall M, et al Gynecol Oncol 2011)

Adjuvant Therapy in Stage I

- Chemotherapy:
  - Stage I Granulosa cell tumor have a very low risk of recurrence (9%)
    - Range of adjuvant therapy in the literature 19%-57%
    - Effect on outcome not proved
    - After conservative surgery no data
    - **Option** : Adjuvant therapy for stage IC patients
  - Stage I SLCT
    - Adjuvant therapy for Poorly differentiated or with heterologous elements

- Radiotherapy:
  - In a retrospective series there was no observed benefit to adjuvant irradiation

(Schneider 2007 & ESMO CPG's 2011, GCIG guidelines 2014)

Adjuvant Therapy in Stage II to IV

- Platinum based chemotherapy should be proposed
- Response rate for chemotherapy in the literature 44%-83% (advanced and recurrent disease)
  - **Most frequent platinum based regimen** : BEP (3 to 4 cycles)
  - Options: carboplatine-paclitaxel X 6 (Brown J , JCO 2004), (ESMO guidelines 2012)

Amenorrhea and Fertility After BEP Chemotherapy

- Conservative surgery
  - 41/52 (79%)
- Amenorrhea after BEP
  - 12/15 (80%)
- Median duration to re-establish cycles
  - 5 months [1-8]
- Pregnancies
  - 12/16 (75%)
- French Guidelines :
  - Interest to explore oocytes reserve before treatment not clearly confirmed but need to be adjust on the individual profile of patient → **interest of oncofertility consultation**
  - Hormone replacement is recommended if needed after radical surgery

de La Motte Rouge T, et al. *Ann Oncol.* 2008;19(8)
Saint Paul de Vence Guidelines 2017

Surveillance (GCIG recommendations)

- Physical examination & tumor markers (inhibin B dosage could be considered) every 4- 6 months for the first 2 years, every 6 months during year 3rd, 4th and 5th or until progression.
- Pelvic ultrasound every 6 months after fertility sparing surgery
  - CT-scan of the abdomen and pelvis more frequently selected for recurrences suspected.
  - The use of PET-scan for follow up is **not** established yet.
- Due to very late relapse, experts recommend prolonged follow up until 10 or 15 years.

I Ray-Coquard, et al, GCIG guidelines IJGC 2014

Relapse

- Relapse after initial treatment without CT:
  - Debulking surgery & repeated cytoreductive surgeries whenever possible
  - Platinum based chemotherapy
- Additional treatment after CT failure:
  - Debulking surgery
  - Chemotherapy (Paclitaxel, VAC, etoposide, bevacizumab, etc. …)
  - Hormonal therapy for AGCT (anti aromatase, LH-RH inh, tamoxifen, progestins)
  - Radiation therapy in selected cases
  - Considered clinical trial : randomized phase II trial with wPaclitaxel +/- bevacizumab on-going (ALIENOR trial) stop inclusion in november 2016
  - Future clinical trial GamaMABs including inh AMRH (ab) monotherapy (Sept – 2017)

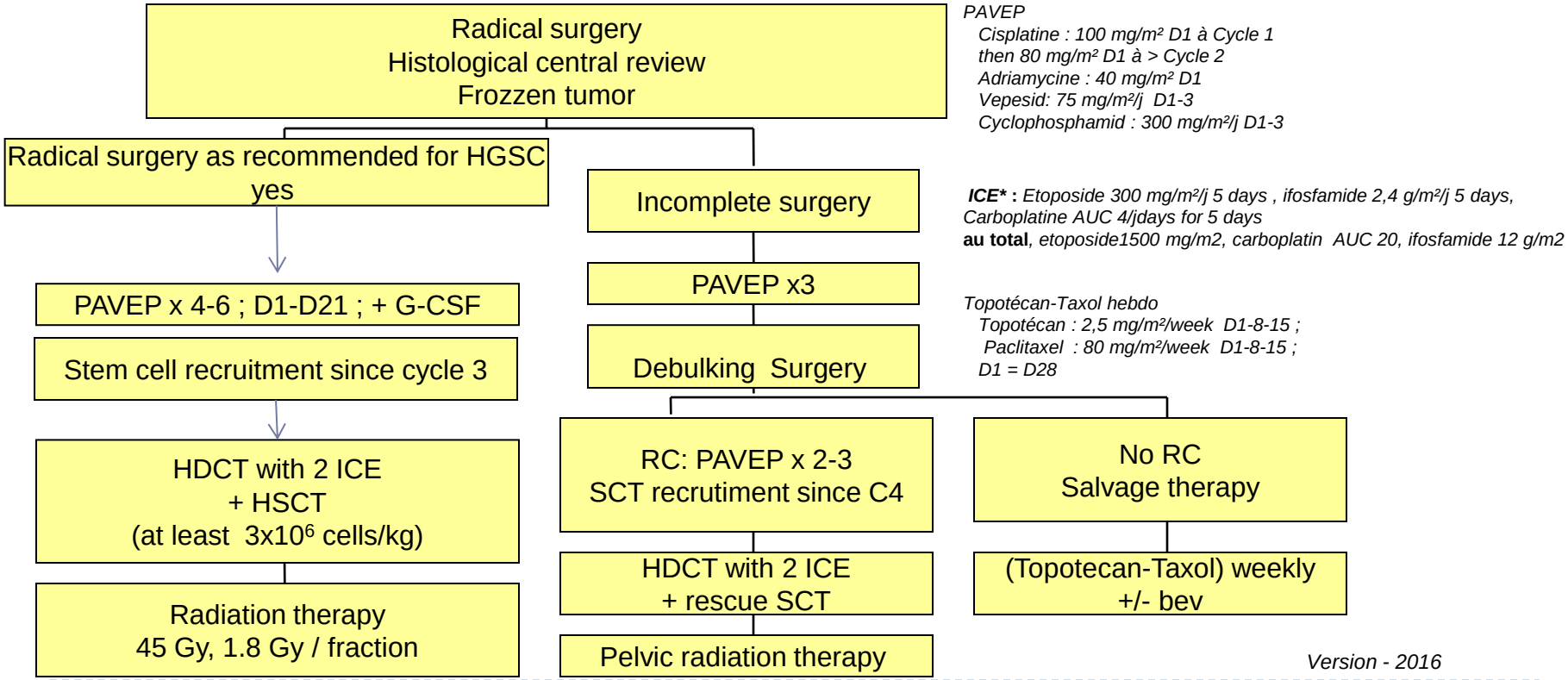
Summary Sex Cord Stromal tumors

- Initial diagnosis: molecular test & second opinion
- 1st line therapy
  - Radical surgery or conservative surgery in young pts for IA
  - Postoperative chemotherapy for
    - GCT st. II-IV , and for st. IC2/3; no consensus for IC1
    - Sertoli-Leydig tumor st. II-IV or stage I poorly differentiated, with mesenchymal heter. elem. and/or retiform component
- Relapse
  - Repeat surgical resections whenever feasible
  - Hormonal therapy in selected cases
  - Chemotherapy options: Carboplatine, paclitaxel, CAP, VAC…

SCCOHT
Standard of care & Questions

- Extremely rare
- Median age 24 years for HT
- Prognostic factors : age > 30 y, calcium level, size < 10 cm, only small cells
- Inactive mutation SMARCA4 (*Nat genetics* 2014): SCCO Hypercalcemic type = rhabdoid tumor family
- **Treatment**
  - Radical surgery, platinum based chemotherapy & pelvic radiation
- **Questions**
  - conservative surgery reasonable ?
  - HD CT impact?
  - New drugs to target SMARCA4 deficiency

SCCOHT management
French TMRO network



Version - 2016

Low grade serous carcinoma

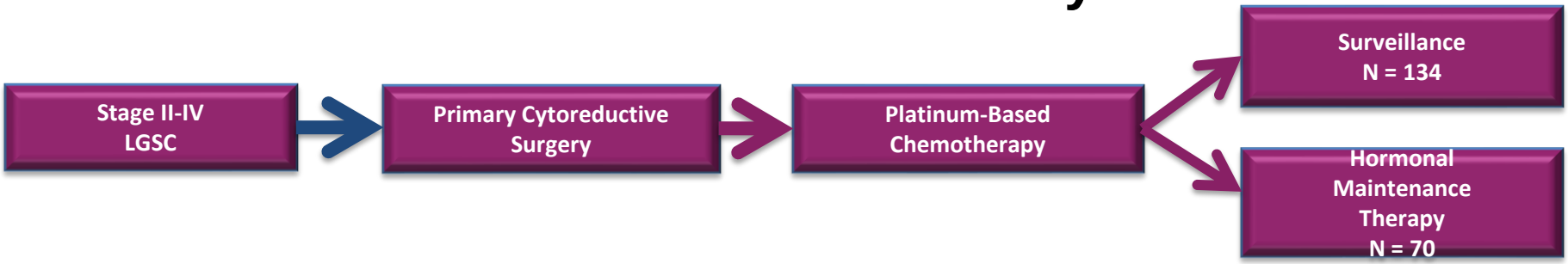
- **Low-grade serous carcinoma (LGSC) is rare subtype that accounts for ~ 10% of serous carcinomas of the ovary/peritoneum**
- **May arise *de novo* or following diagnosis of serous borderline tumor**
- **<u>Relative</u> to high-grade serous carcinoma, LGSC characterized by:**
  - **Young age at diagnosis**
  - **Chemo resistance**
  - **Prolonged overall survival**
  - **Aberrations within the MAP kinase signaling pathway**

Adjuvant therapy

- **Advanced disease**
  - **No prospective clinical trials in front-line setting**
  - **Data from MD Anderson Low-Grade Serous Tumor Database has suggested relative chemo resistance in multiple settings**
  - **Front-line chemotherapy setting:**
    - **> 40% frequency of persistent disease**
    - **NACT setting: < 5% ORR**
- **Early stage**
  - **IA grade I (confirmed by central review) & complete staging, no adjuvant therapy (*Young et al, NEJM 1990*)**
  - **Question for IC2 or IC3**

Gershenson et al. Gynecol Oncol 2006; Gershenson et al. J Clin Oncol 2015; Schmeler et al. Gynecol Oncol 2008;

Hormonal Maintenance Therapy for Women with Low-Grade Serous Carcinoma of the Ovary or Peritoneum



Of 204 women:

- **Women who received HMT > median PFS vs. SURV (64.9 vs 27.3 mo; P < .001)**

Of 148 women NED following primary chemo:

- **Women who received HMT > median OS vs. SURV (191.3 vs 106.8 mo; P = .04)**

Multivariable analysis: HT (HR = 0.23; 95% CI 0.11, 0.51), NED, No gross tumor, peritoneal loc., reduced risk of relapse compared to SURV

Metastatic treatment

	Chemotherapy n = 58	Hormono therapy n= 64	GOG 239 (Selumetinib) n = 52
Remission complete	1%	7%	2%
Remission partial	2.8%	2%	13.5%
SD	64%	71%	80%
Median PFS	7.3 m	7.4 m	11 m

Farley JH, et al. *AACR Meeting Abstracts.* 2012;2012: Abstract CT-05

Low grade serous carcinoma
Standard of care

- Prognostic factor: stage & complete surgery
- Less sensitive to chemotherapy
- 1st line treatment included front line maximum debulking surgery
- Early stage: surgery alone can be curative
- Adjuvant CT +/- bev for advanced disease
- In relapse:
  - Consider surgery
  - platinum sensitive/platinum resistant
  - CT +/- bev & HT same PFS better RR for HT!

Mucinous ovarian carcinoma
Standard of care / Questions

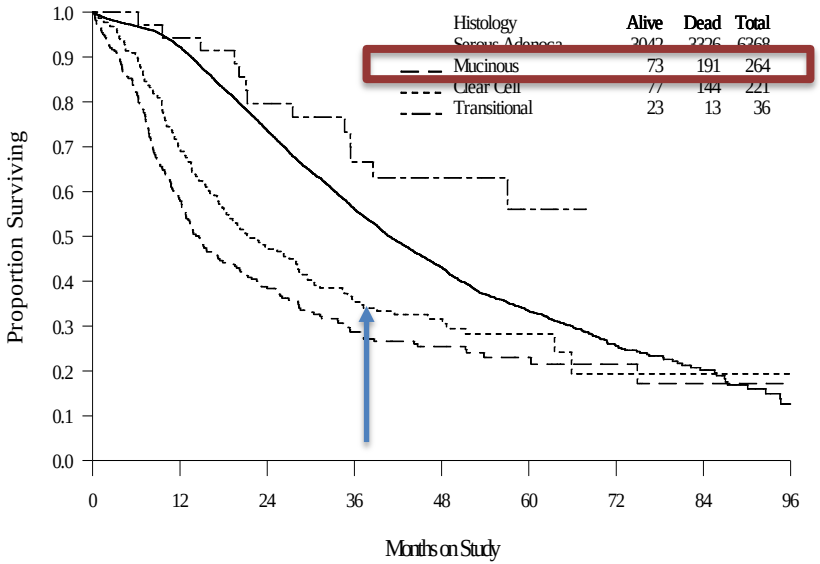
- < 10% of all epithelial carcinoma
- Localized stage good prognosis
  - Expansive no caps rupture (fertility sparing surgery)
  - Infiltrative or IC (radical surgery)
- Advanced disease: worse survival
- Management = HGSC but low response to standard CT with Carboplatine & paclitaxel (XelOx no diff vs. CP; M Gore, ASCO15)
  - **Early stage: surgery**
  - **Advanced stage as HGSC**
- **Improvement**
  - Initial pathological diagnosis : systematic review by experts
  - Drivers
  - Active CT & adjuvant CT
  - New drugs
  - .....

Survival analysis by histology

Advanced vs Early stage

Clear Cell, Transitional, Mucinous, Serous

Overall survival in stage=(3,4) patients



AGO-GINECO, GOG-ANZGOG, MRC- MANGO

Disease specific Survival in early stage I/II, n = 8572 pts

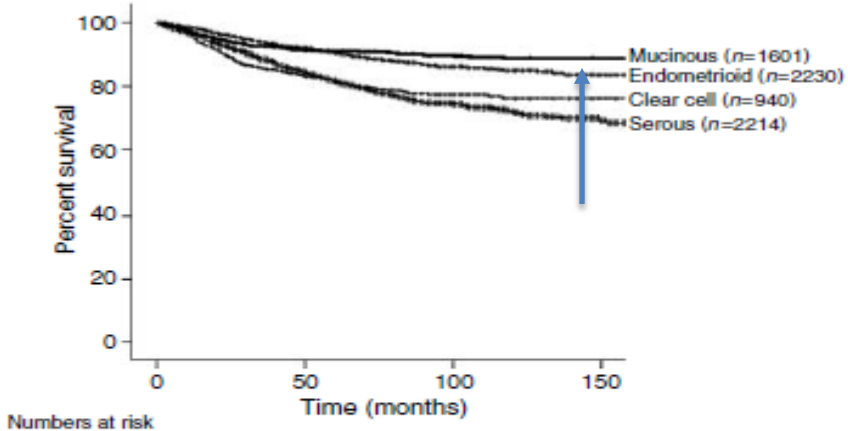


Figure 2 Kaplan–Meier disease-specific survival by histology ($P < 0.001$).

SEER database, Chan et al, BJC 2008

International multicentre trial of carboplatin/paclitaxel versus oxaliplatin/capecitabine, each with/without bevacizumab, as first line chemotherapy for patients with mucinous Epithelial Ovarian Cancer (mEOC)

Martin Gore[1] (Royal Marsden Hospital, London, UK), Allan Hackshaw[1], William Brady[2], Richard Penson[2], Richard Zaino[2], W Glenn McCluggage[1], Raji Ganesan[1], Nafisa Wilkinson[1], Timothy Perren[1], Ana Montes[1], Jeffrey Summers[1], Rosemary Lord[1], Graham Dark[1], Gordon Rustin[1], Melanie Mackean[1], Nicholas Reed[1], Sean Kehoe[1], Amanda Feeney[1], Helen Christensen[1], Jonathan Ledermann[1], David Gershenson[2]

Background:

- Mucinous epithelial ovarian cancers (mEOC) account for approximately 9% of epithelial ovarian cancers, and 5% of all advanced epithelial ovarian cancers
- Their biology, natural history and response to treatment differs from other histological subtypes.
- Advanced mEOC responds poorly to standard therapy
- Because it comprises only <8% pts in ovarian cancer trials, it is difficult to examine treatment effects in this subgroup

Methods:

The Gynecologic Cancer InterGroup (mEOC(UK) & GOG 241 (USA) set up the first ever randomised trial specifically for mEOC patients (2x2 factorial)

Aims:

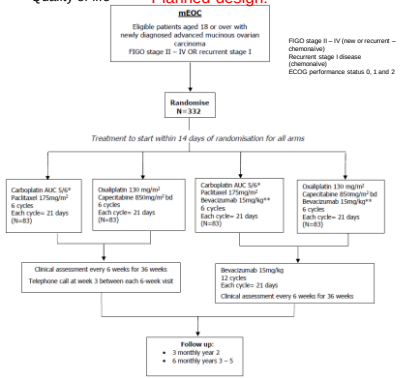
1. Whether oxaliplatin/capecitabine, a treatment in mucinous gastrointestinal cancer, improves survival compared to standard therapy using carboplatin/paclitaxel
2. Whether bevacizumab improves survival

Target overall survival hazard ratio for each aim: 0.71 (80% power)

Outcomes:

- Overall and progression-free survival
- Tumour response
- Adverse events
- Quality of life

Planned design:



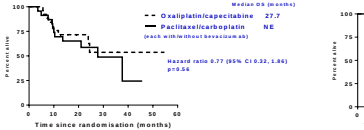
Trial stopped early (in 2013) due to poor accrual (N=50)

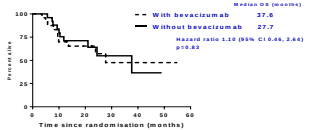
	Carboplatin paclitaxel	Oxaliplatin capecitabine	Carboplatin paclitaxel bevacizumab	Oxaliplatin capecitabine bevacizumab
No. patients	13	13	11	13
Median age (yrs)	55	56	47	51
FIGO stage				
II	4	3	4	4
III	6	6	5	8
IV	1	1	1	1
recurrent	2	3	1	0
ECOG				
0	8	10	5	11
1	5	3	5	2
2			1	

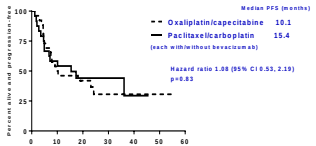
	Carboplatin paclitaxel	Oxaliplatin capecitabine	Carboplatin paclitaxel bevacizumab	Oxaliplatin capecitabine bevacizumab
No. patients	13	13	11	13
Completed 6 cycles combination therapy	62% (8)	85% (11)	82% (9)	69% (9)
Completed 12 cycles maintenance	-	-	36% (4)	46% (6)
Complete or partial response (/evaluable); best response	N=2/7	N=2/10	N=4/7	N=2/7

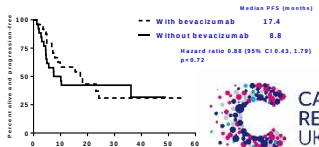
median follow up 23 months

- 20 deaths
- 31 PFS events









1. UK_mEOC_Trial
2. US_GOG-241_Trial

	Carboplatin paclitaxel	Oxaliplatin capecitabine	Carboplatin paclitaxel bevacizumab	Oxaliplatin capecitabine bevacizumab
No. patients	13	13	11	13
Any grade 3-4 toxicity	62% (8)	62% (8)	55% (6)	92% (12)
Neutropenia	n=5	n=1	n=1	-
Hypertension	-	n=4	n=3	n=6

Specialist pathology review

- A diagnosis of primary ovarian mucinous carcinoma was confirmed in only 17 of 36 (47%) cases which have already undergone specialist pathology review.
- Misdiagnosed cases were predominantly considered to represent secondary mucinous carcinomas, primary ovarian mucinous borderline tumours and primary ovarian carcinomas of other morphological types.
- The process of specialist pathology review confirmed well known problems in the diagnosis of primary ovarian mucinous carcinomas.

Conclusions:

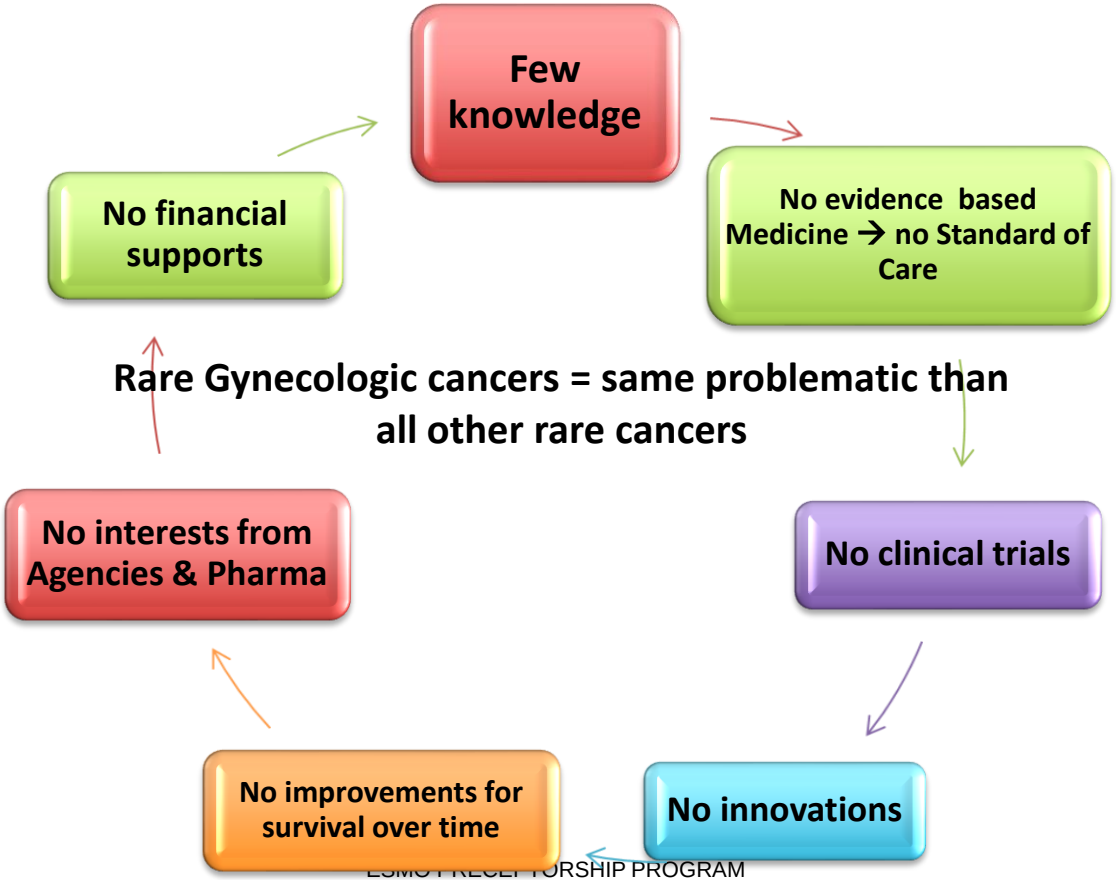
•Although the trial stopped early, we now have some randomised trial data specifically for mEOC patients
•There was a hint that bevacizumab delayed progression (ITT analyses), but no conclusions can be made due to small study size
•Primary mEOC is rarer than previously thought so different approaches are needed to evaluate new therapies
•A major problem with this particular trial was due to the difficulties in the histopathological diagnosis

General comments about rare cancer trials:

•Funding streams for trials in rare cancers are difficult because such trials are not 'cost effective': the same effort and cost is required to set up a trial whether the investigator plans to enter 2 patients as 20
•Funders could consider financial support as incentives for recruiting sites
•Some institutions and trial groups have the same rules and guidance on the funding of an experimental therapy for rare cancers as common ones. This results in prolonged discussions about the cost of the treatment in a rare tumour trial that are disproportionate to the total cost for an institution because only 1-2 patients per institution are entered.
•International studies of rare cancers could work more effectively, but only if the extent of clinical trial regulatory bureaucracy reduces; allowing streamlined processes for institutional/local approvals, and minimising work spent on contracts/agreements between institutions

Funding:
UK (Cancer Research UK C1569/A9620)
US (NRG Oncology/Gynecologic Oncology Group study, mEOC/GOG-241)

Negative spiral for rare cancers



How to change the future?

- 5th OCCC GCIG in Tokyo 2015
  - Have fixed standard of care in 1st line & relapse
  - Have highlighted the need for investigational treatments
  - New prognostic factors including molecular factors

- New organizations for management & clinical research
  - Dedicated cancer network (eg French model)
  - European network for rare cancer
  - Education for physicians, care givers and public
  - Motivate Patients advocacy group

Gynecologic Cancer InterGroup (GCIG) Consensus Review for Ovarian and Primary Peritoneal Low-Grade Serous Carcinomas

Charlie Gourley, MD, PhD, FRCP,* John Farley, MD,† Diane M. Provencher, MD,‡
...nata, MD, PhD,§ Linda Mileshkin, MD,|| Philipp Harter, MD,¶
...D. PhD.# Jae-Weon Kim. MD. PhD.** Eric Puiaide-Lauraine. MD. PhD.††

...ic Cancer InterGroup (GCIG) Consensus ...iew for Vulvovaginal Melanomas

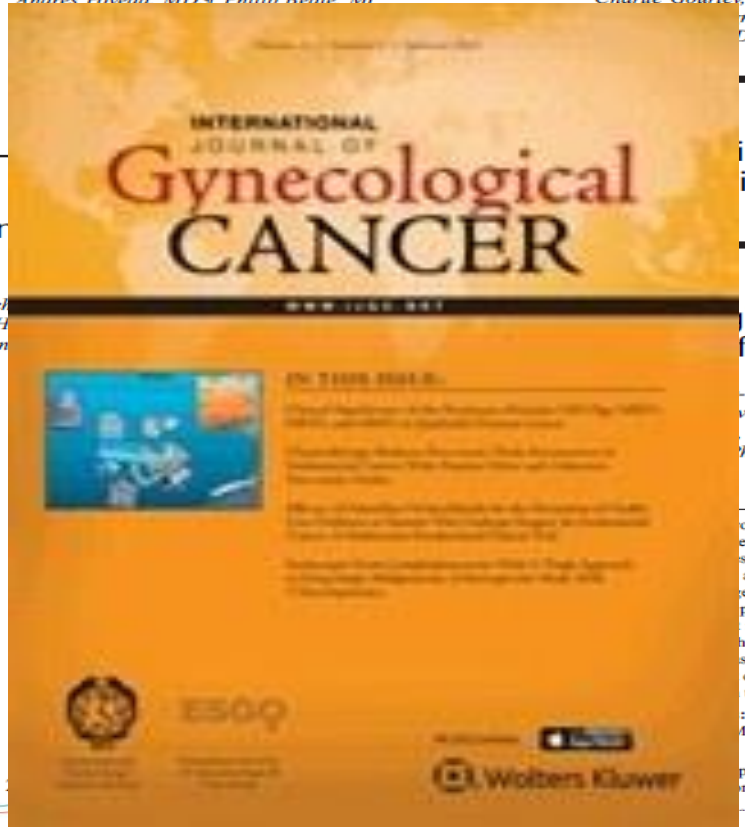
...ic Cancer InterGroup (GCIG) Consensus ...for Ovarian Sex Cord Stromal Tumors

...-Coquard, MD, PhD,* Jubilee Brown, MD,† Philipp Harter, MD,‡
...vencher, MD,§ Peter C. Fong, MD,|| Johanna Maenpaa, MD, PhD,¶
... MD, FRCP,# Gunter Emons, MD, PhD,** Dominique Berton Rigaud, MD,††
...hD, MBBS, FRCP,‡‡ Delia Mezzanzanica, PhD,§§ and Nicoletta Colombo, MD||||

...omal tumors (SCST) are rare cancers of the ovarian area in adults. They con-
...erogeneous group of tumors that develop from the sex cords and the ovarian
...se tumors are detected typically at an early stage, and they may recur as late
... after the initial treatment. Because 70% of the patients present with stage I
...tery represents the most important therapeutic arm. There are no data to support
... postoperative adjuvant treatment for patients with stage IA or IB SCSTs, given
... nature of these neoplasms and the overall good prognosis. The long natural
...he disease may lead to repeated surgical procedure should a relapse occurs.
...sed chemotherapy is currently used for patients with advanced stage SCSTs
... disease, with an overall response rate of 63% to 80%. The indolent nature of
... the tendency for late recurrence requires long-term follow-up.

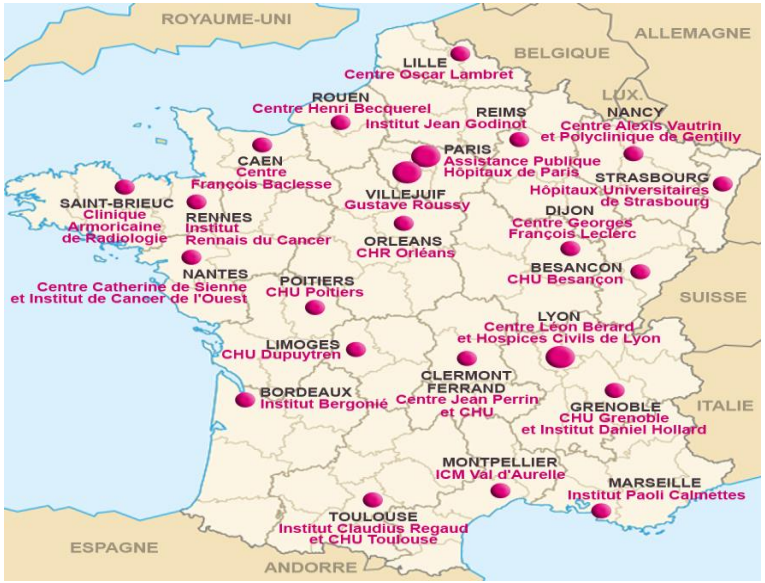
: Rare tumor, Sex cord stromal tumors, Molecular analysis, First-line
Metastatic disease

...pril 22, 2014, and in revised form July 23, 2014.
...r publication July 27, 2014.



The French National Network dedicated to Rare gynecologic Malignant Tumors

National Network including
3 national + 22 regional expert centers



- **Objectives**
  - **Management** : medical strategy decided in **dedicated regional multidisciplinary tumor boards**
  - **Diagnosis**:
  - **systematic second review**
  - molecular diagnosis for all patients (eg FOXL2, SMARCA4, DICER1….).
  - **Education**:
  - workshops & continuing medical education.
  - information for patients, families and advocacy groups.
  - To elaborate CPG's

INSTITUT NATIONAL DU CANCER

GINECO

Dedicated website – http:// www.ovaire-rare.org

ARCAGY GINECO

Observatoire des Tumeurs Malignes Rares Gynécologiques
LE SITE DES CENTRES EXPERTS

- espace public
  - → En savoir plus sur les pathologies
  - → Les Centres experts
- espace médecin

accès membres

Login

Mot de passe

ENTRER

Mot de passe oublié
Créer un compte

Tumeurs des cordons sexuels - Tumeurs de la Granulosa - Tumeurs à cellules de Sertoli-Leydig - Tumeurs germinales - Dysgerminomes - Tumeurs vitellines - Carcinomes embryonnaires - Tératomes - Adénocarcinome à cellules claires - Adénocarcinome mucineux invasif - Tumeurs borderline ou à malignité atténuée - Carcinome à petites cellules - Carcinosarcomes - Adénocarcinome séreux de bas grade

Les tumeurs malignes rares gynécologiques (TMRG) sont un ensemble de tumeurs qui surviennent en majorité chez des jeunes femmes. **Leur prise en charge est très différente de celles des tumeurs gynécologiques habituelles.** Une problématique importante dans ces tumeurs est souvent la conservation de la fertilité.
Pour en savoir +

La prise en charge thérapeutique est aujourd'hui facilitée en France par l'existence **des Centres Experts Nationaux et Régionaux**
Pour en savoir +

Informations sur les Tumeurs Malignes Rares Gynécologiques et accès aux référentiels →

Réservé aux membres

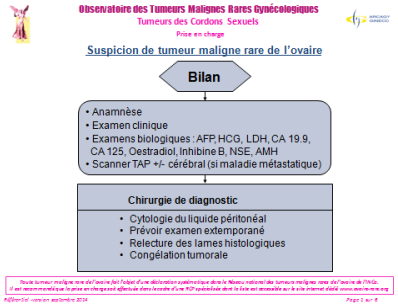
→ **DEMANDE D'AVIS AU CENTRE EXPERT** **Relecture** histologique diagnostique et/ou proposition de prise en charge par une **réunion de concertation pluridisciplinaire** spécialisée.

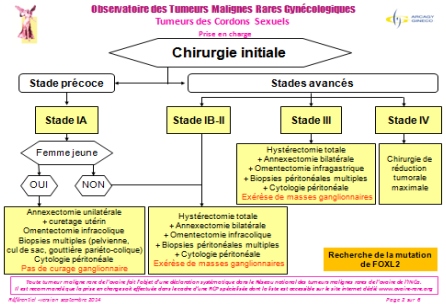
→ **Etudes cliniques en cours** sur les tumeurs malignes rares gynécologiques

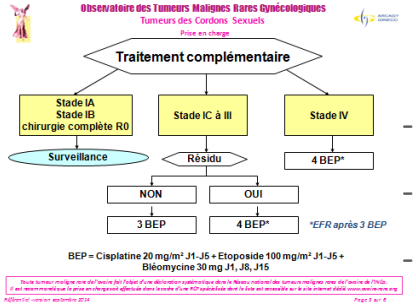
→ **Présentations et documents à télécharger**

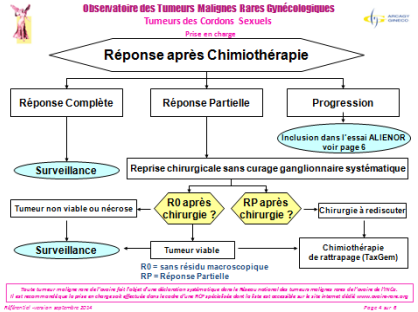
Contact | Qui sommes nous | Mentions légales | Liens

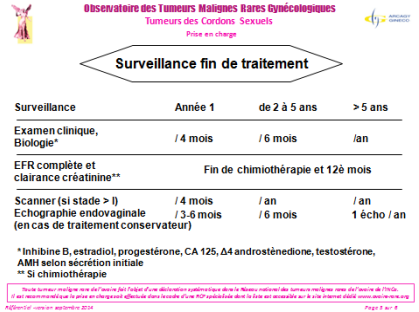
Decision-making algorythmes are available on web site for 8 types of tumors

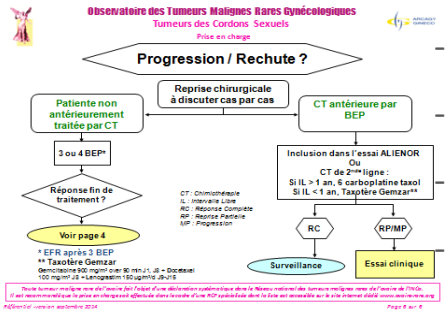












- Stromal and sex-cord T
- Germ-cell T
- Serous & mucinous borderline
- Clear-cell adenocarcinoma
- Mucinous adenocarcinoma
- Low grade serous carcinoma
- Small cell carcinoma
- Carcinosarcoma

Faculté de Médecine Lyon Est

Observatoire des Tumeurs Malignes Rares Gynécologiques

LE SITE DES CENTRES EXPERTS

Bienvenue Dr RAY-COQUARD Isabelle - Lyon

Déconnexion

- espace public
- espace médecin
  - → Information sur les TMRG et référentiels
  - → Les patientes de mon centre
  - → Nouvelle Patiente - Demande d'avis au Centre expert
  - → Nouvel avis de RCP pour une patiente existante
  - → Voir tous les résultats de relecture
  - → Voir tous les avis de RCP
  - → Liste des médecins référents
  - → Les études cliniques
  - → Activités du groupe
  - → Annuaire
  - → Bibliographie
- Centre Expert
  - → Voir les demandes de RCP
- gérer mon compte →

Liste des centres :

001 - Centre Léon Bérard

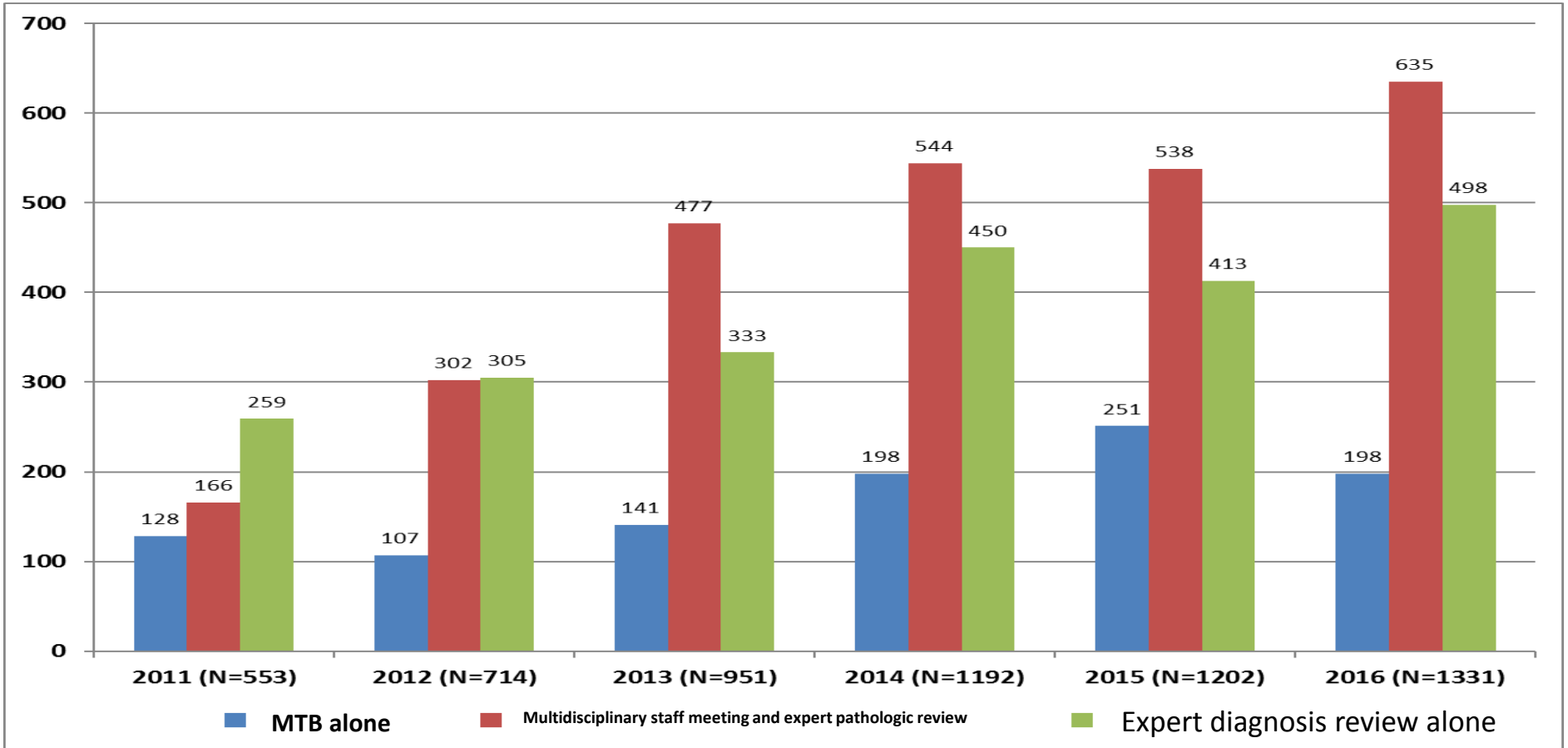
Nouvelle patiente | Nouvel avis de RCP pour une patiente existante

Pat. N°	Init.	Date de naissance	Date inclus.	Médecin	Type d'histologie	Relecture lame	Etat de la RCP	Cons. bio.	Dernières nouvelles
0252	FP	20/02/1968	11/01/2011	CA	Tumeur de la granulosa forme adulte	Non demandé	Non demandé	✗	perdue
0246	BW	10/02/1973	29/10/2010	CA	Tumeur de la granulosa forme adulte	Non demandé	Non demandé	✗	perdue
0247	RL	16/07/1942	27/10/2010	CA	Tumeur de la granulosa forme adulte	Non demandé	Non demandé	✗	perdue
0243	PL	25/06/1989	12/10/2010	CA	Tumeur à cellules de Sertoli-Leydig	Non demandé	Non demandé	✓	perdue
0200	CA	13/03/1945	20/09/2010	CA	Tumeurs des cordons sexuels	Non demandé	Non demandé	✓	en vie
0199	MM	01/04/1950	20/09/2010	CA	Tumeur de la granulosa forme adulte	Non demandé	Non demandé	✓	en vie
0197	NA	11/07/1948	06/08/2010	CA	Tumeur à cellules de Sertoli-Leydig	Non demandé	Non demandé	✓	rechute
0196	RV	30/10/1954	26/07/2010	CA	Tumeur de la granulosa forme adulte	Non demandé	Non demandé	✗	en vie
0190	ST	20/09/1944	02/06/2010	NC	Tumeur de la	Non	Non	✓	

Yearly new cases of rare ovarian tumors

Ovarian Tumor types	2011	2012	2013	2014	2015	2016	Cumulated
Sex cord-stromal tumor	128	202	191	235	216	298	1270
Germ cell tumor	95	93	102	113	125	127	655
Small cell carcinoma	6	8	8	12	7	12	53
Carcinosarcoma	30	42	50	42	36	67	267
Low-grade serous carcinoma	2	13	14	36	70	85	220
Clear cell carcinoma	42	77	83	105	123	100	530
Mucinous carcinoma	41	83	117	109	125	135	610
Borderline Tumors	172	182	355	450	472	429	2060
Malignant Brenner tumor	9	3	5	6	9	13	45
Other rare tumor	28	11	26	84	19	27	185
Total Ovary	553	714	951	1192	1202	1331	5943

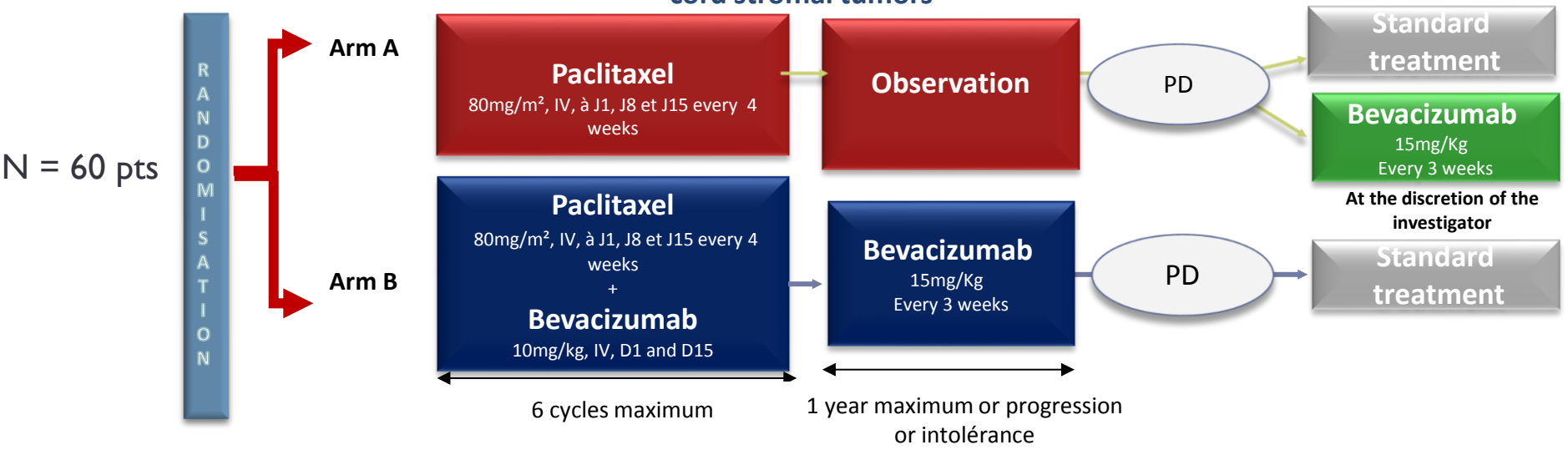
Progression of clinical and diagnosis review



Expert diagnosis review inducing medical decision change

Year	#Yearly new cases	# Cases diagnosed by pathologist referees	# Cases benefiting from both local and central review	# Minor diagnosis discrepancy	# Cases for which diagnosis modified therapeutic strategy
2011	553	425	359	28	17 (17/359) (**5%**)
2012	714	607	355	52	28 (28/355) (**8%**)
2013	951	810	445	93	40 (40/445) (**9%**)
2014	1192	994	658	155	61 (61/658) (**9%**)
2015	1202	897	784	118	40 (40/784) 5%
Total	4612	3280	2601	**446 (18%)**	**186 (186/2601) (7%)**

ALIENOR trial A randomized, open label, phase II trial of bevacizumab plus weekly paclitaxel followed by maintenance with bevacizumab monotherapy versus weekly paclitaxel followed by observation in patients with relapsed ovarian sex-cord stromal tumors



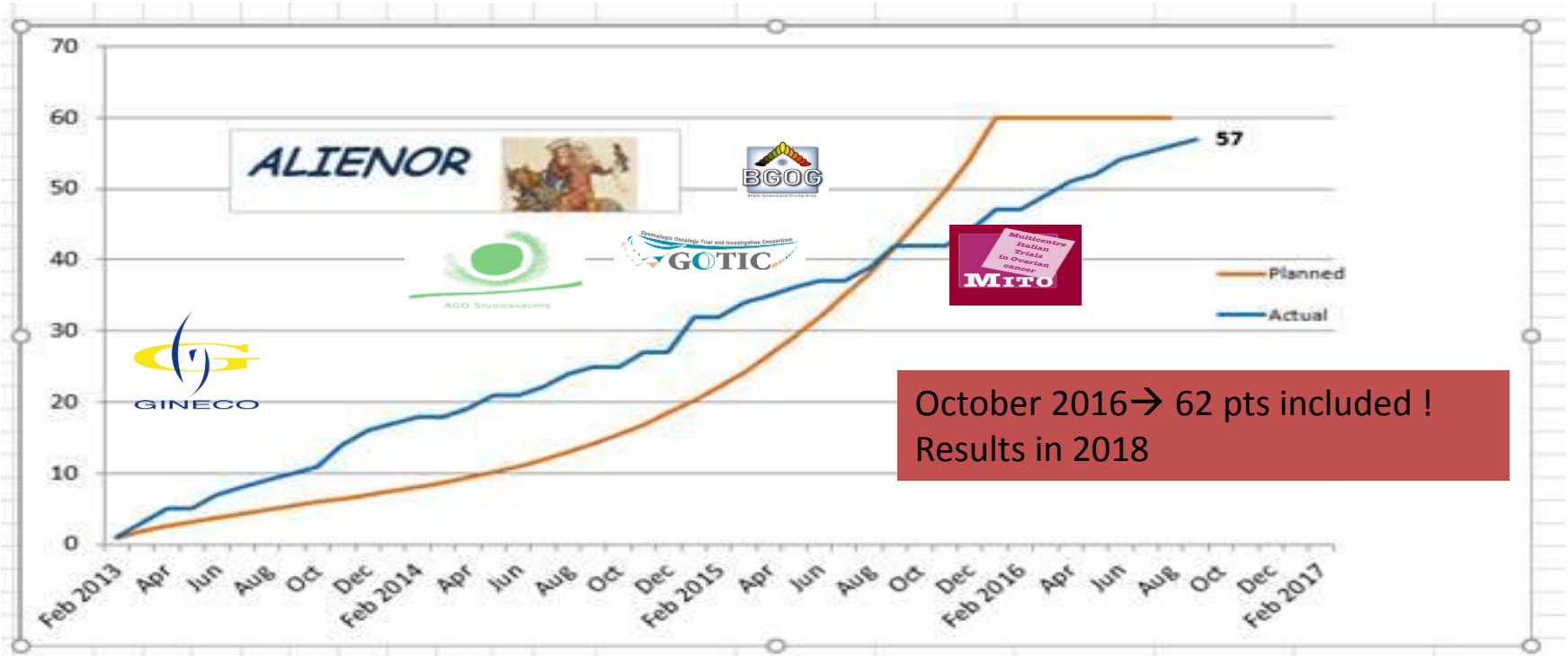
Population

Patients in **relapse with an ovarian sex-cord stromal tumor,** histologically confirmed, previously treated by platinum-based chemotherapy.

Main Objective

Clinical benefit
(non progression after 6 months)

ALIENOR Status (20/09/2016)



October 2016→ 62 pts included !
Results in 2018

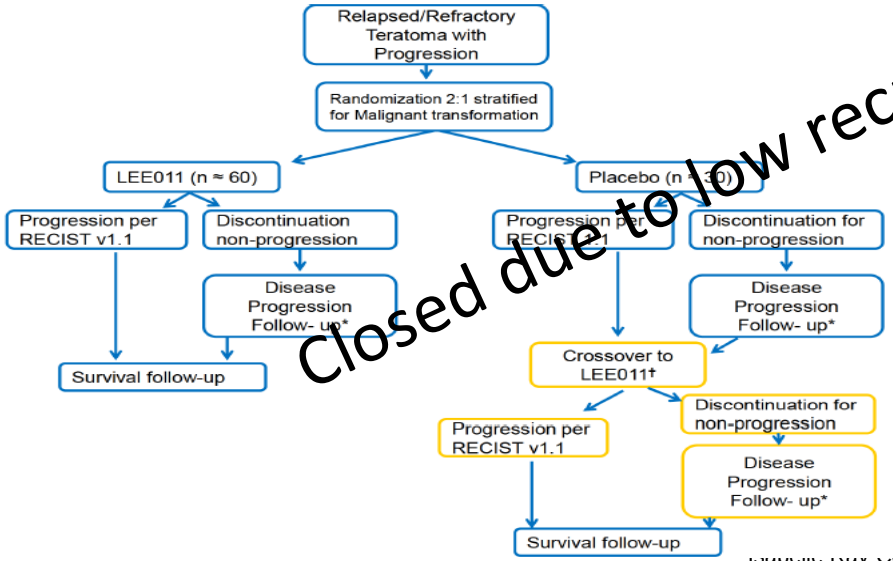
Clinical trials in GCT

Novartis : ribociclib, CDK4/6 inh (pRb & cell cycle)

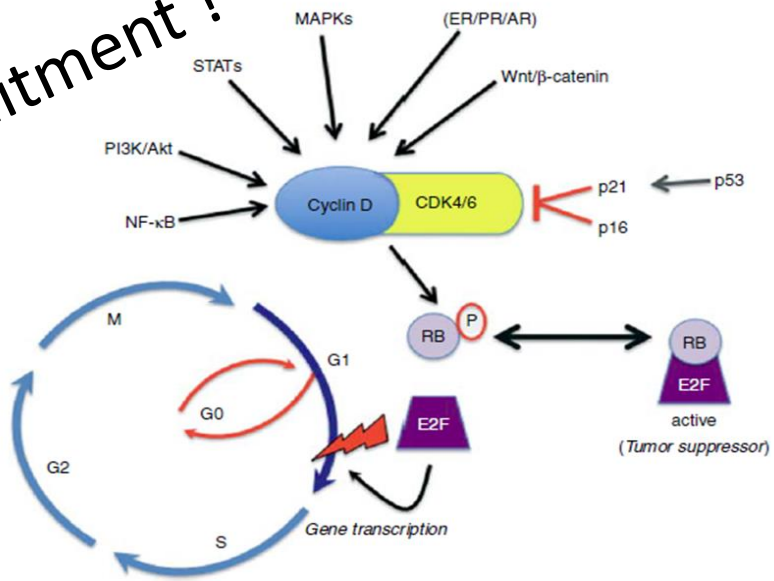
Background: CDK4 & CyclinD2 upregulated GCT

Randomized phase II with LEE011 for patients with immature teratoma in relapse after standard CT

Figure 4-1 Study design



Closed due to low recruitment !



Take home message

- Rare ovarian tumors are frequent!
  - Prognosis & clinical presentation really different
  - Fertility & of adjuvant treatment
  - Thinking to rarity before surgery!
- Management decision making:
  - Expert Pathologists
  - Expert Multidisciplinary Tumor Board
  - Dedicated Rare Cancer Network→ French experience
- Education for physicians & patients

- Tumoral minority is the future of the oncology
- European/International Cooperation (ESMO, ESO, ESGO, GCIG)
- European networks of reference for rare diseases: Euracan

http://ec.europa.eu