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2016 inc Research Clinical Research Site Award RECIPIENT

What is a rare tumor and its treatment options

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Disclosure

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Project of Surveillance of Rare Cancer In Europe (RARECARE, 2012-2015): data from 94 cancer registries in 27 European Countries covering 48% of cancer patients diagnosed from 1978 to 2007

More than 4.3 million people in the European Union are living with a rare cancer. *

Despite the rarity of each of the 198 rare cancers, they represent in total about 22% of all cancer cases, including all cancers in children, diagnosed in the EU each year. *

Rare cancer definition; incidence <6/100.000/year

* Rare Cancers Europe/RareCare

Incidence & prevalence by sites

Table 3. Incidence and prevalence of rare and common cancers by site in EU27

		Incidence rate per 100,000	Standard error	Estimated incident cases in EU27	Incidence distribution (%)	Prevalence per 100,000	Standard error	Estimated prevalent cases in EU27	Prevalence distribution (%)
Common	Digestive tract	76,1	0,1	380 565	67	400,3	1,2	2 001 514	84
Rare	Digestive tract	17,2	0,1	86 143	15	50,0	0,4	250 005	11
All	Digestive tract	114,1	0,1	570 236	100	474,6	1,4	2 373 151	100
Common	Respiratory tract	31,6	0,1	157 903	49	56,2	0,3	280 918	43
Rare	Respiratory tract	13,6	0,0	68 125	21	60,2	0,4	300 876	46
All	Respiratory tract	64,1	0,1	320 391	100	130,0	0,6	649 911	100
Common	Skin	61,3	0,1	306 427	96	744,6	1,5	3 722 876	95
Rare	Skin	1,5	0,0	7 487	2	14,8	0,3	74 116	2
All	Skin	63,7	0,1	318 615	100	779,7	1,5	3 898 655	100
Common	Breast	47,7	0,1	238 471	74	522,6	4,1	2 612 913	75
Rare	Breast	4,9	0,0	24 415	8	56,9	0,7	284 484	8
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Common	Female genital tract	9,6	0,0	47 779	32	126,7	0,6	633 546	38
Rare	Female genital tract	16,1	0,0	80 669	55	176,2	0,8	881 107	53
All	Female genital tract	29,5	0,1	147 597	100	331,7	1,1	1 658 589	100
[illegible]									
Rare	Male genital tract	4,3	0,0	21 673	8	93,0	0,8	465 225	23
All	Male genital tract	52,0	0,1	259 868	100	399,6	1,6	1 997 975	100
Common	Urinary system	25,9	0,1	129 253	78	202,2	0,7	1 011 037	85
Rare	Urinary system	2,5	0,0	12 693	8	18,5	0,4	92 689	8
All	Urinary system	33,1	0,1	165 457	100	238,7	0,8	1 193 504	100
Common	Haematopoietic system	11,1	0,0	55 273	50	59,0	0,5	295 022	48
Rare	Haematopoietic system	9,6	0,0	48 077	44	62,5	0,5	312 462	50
All	Haematopoietic system	21,9	0,1	109 721	100	123,9	0,7	619 550	100
Common	All sites	309,6	0,2	1 548 036	61	2428,2	4,9	12 141 163	68
Rare	All sites	97,1	0,1	485 697	19	797,3	2,0	3 986 679	22
All	All sites	503,6	0,3	2 518 108	100	3565,4	7,2	17 826 767	100

THE RARECAREnet DATABASE

Table 2 – RARECARE estimates of incidence, survival and prevalence of cancers for EU27, together with expected number of new cases per year and prevalent cases in EU27.

Rare (R) or common (C) (middle tier only)	Tier	Top tier (upper case) and middle tier (lower case) tumour categories	Crude incidence per 100,000 per year	Standard error incidence	Expected new cases per year	Observed 5-year survival (%)	Relative 5-year survival (%)	Standard error relative survival (%)	Complete prevalence per 100,000	Standard error complete prevalence	Prevalent Cases
	1	EPITHELIAL TUMOURS OF CORPUS UTERI	10.40	0.04	51,743	69.5	79.5	0.2	133.11	0.61	662,186
C	2	Adenocarcinoma with variants of corpus uteri	9.53	0.03	47,393	71.7	81.3	0.2	126.65	0.61	630,048
R	2	Squamous cell carcinoma with variants of corpus uteri	0.12	0.00	581	46.2	53.5	2.3	0.95	0.05	4721
R	2	Adenoid cystic carcinoma of corpus uteri	0.00	0.00	7	70.0	74.5	15.4	0.29	0.05	1445
R	2	Transitional cell carcinoma of corpus uteri	0.00	0.00	1	NE	NE	NE	0.01	0.00	31
	1	EPITHELIAL TUMOURS OF CERVIX UTERI	6.08	0.03	30,227	62.0	66.7	0.3	106.46	0.66	529,610
R	2	Squamous cell carcinoma with variants of cervix uteri	4.28	0.02	21,295	62.9	67.4	0.3	76.24	0.56	379,273
R	2	Adenocarcinoma with variants of cervix uteri	1.01	0.01	5023	62.3	66.8	0.7	15.59	0.24	77,548
R	2	Undifferentiated carcinoma of cervix uteri	0.03	0.00	125	30.2	34.4	4.6	0.32	0.03	1589
	1	MIXED EPITHELIAL AND MESENCHYMAL TUMOURS OF UTERUS	0.44	0.01	2213	31.4	37.3	1.2	2.59	0.08	12,888
R	2	Mixed epithelial and mesenchymal tumours of uterus	0.44	0.01	2213	31.4	37.3	1.2	2.59	0.08	0
	1	EPITHELIAL TUMOURS OF OVARY AND FALLOPIAN TUBE	9.39	0.03	46,735	33.0	37.7	0.3	59.78	0.44	297,397
R	2	Adenocarcinoma with variants of ovary	5.97	0.03	29,692	33.0	36.9	0.3	39.13	0.37	194,668
R	2	Mucinous adenocarcinoma of ovary	0.85	0.01	4206	52.5	58.1	0.8	9.55	0.18	47,536
R	2	Clear cell adenocarcinoma of ovary	0.32	0.01	1611	50.0	53.9	1.3	2.55	0.08	12,691
R	2	Adenocarcinoma with variants of fallopian tube	0.26	0.01	1316	42.5	47.8	1.5	1.99	0.07	9866
	1	NON-EPITHELIAL TUMOURS OF OVARY	0.43	0.01	2153	57.9	62.6	1.1	6.69	0.17	33,286
R	2	Mixed epithelial/mesenchymal tumours of ovary	0.16	0.00	775	15.9	18.2	1.5	0.49	0.03	2461
R	2	Sex cord tumours of ovary	0.13	0.00	670	76.1	82.7	1.7	1.85	0.08	9224
R	2	Malignant/Immature teratomas of ovary	0.07	0.00	337	80.5	83.3	2.1	1.50	0.09	7481
R	2	Germ cell tumour of ovary	0.07	0.00	371	83.5	84.3	1.8	2.23	0.16	11,128
	1	EPITHELIAL TUMOURS OF VULVA AND VAGINA	1.91	0.02	9517	47.0	60.9	0.7	15.34	0.18	76,299
R	2	Squamous cell carcinoma with variants of vulva and vagina	1.50	0.01	7480	46.4	59.6	0.7	12.42	0.17	61,791
R	2	Adenocarcinoma with variants of vulva and vagina	0.08	0.00	383	35.5	43.2	2.9	0.52	0.03	2610
R	2	Paget's disease of vulva and vagina	0.05	0.00	249	77.5	97.8	3.2	0.47	0.04	2338
R	2	Undifferentiated carcinoma of vulva and vagina	0.01	0.00	40	26.3	31.5	8.0	0.05	0.01	235
	1	TROPHOBLASTIC TUMOUR OF PLACENTA	0.02	0.00	119	89.6	90.0	2.7	0.86	0.12	4275
R	2	Choriocarcinoma of placenta	0.02	0.00	119	89.6	90.0	2.7	0.86	0.12	3886

CRUDE AND AGE-ADJUSTED INCIDENCE RATE (PER 100.000) OF RARE OVARIAN CANCER IN THE RARECAREnet DATABASE

		Crude IR	95% CI		Age adj IR	95% CI	
Rare epithelial tumours of ovary		**1.22**	**1.20**	**1.23**	**1.05**	**1.04**	**1.07**
Mucinous adenocarcinoma of ovary	(63%)	0.77	0.76	0.78	0.67	0.66	0.68
Clear cell adenocarcinoma of ovary	(25%)	0.30	0.29	0.31	0.27	0.26	0.28
Carcinosarcoma of ovary	(12%)	0.14	0.14	0.15	0.12	0.11	0.12
Non epithelial tumours of ovary		**0.25**	**0.24**	**0.26**	**0.24**	**0.23**	**0.25**
Sex cord tumours of ovary		**0.12**	**0.12**	**0.13**	**0.11**	**0.11**	**0.12**
Granulosa cell tumours malignant	(90%)	0.11	0.11	0.12	0.10	0.10	0.10
Sertoli Leidig cell tumours	(4%)	0.00	0.00	0.01	0.00	0.00	0.01
Other sex cord tumours of ovary		0.01	0.01	0.01	0.01	0.01	0.01
Germ cell tumour of ovary		**0.13**	**0.12**	**0.13**	**0.13**	**0.12**	**0.13**
Yolk sac tumours	(15%)	0.02	0.02	0.02	0.02	0.02	0.02
Dysgerminoma	(33%)	0.04	0.04	0.05	0.04	0.04	0.05
Mixed germ cell tumours	(4%)	0.01	0.00	0.01	0.01	0.00	0.01
Malignant/Immature teratomas of ovary	(42%)	0.05	0.05	0.06	0.05	0.05	0.06
Other germ cell tumours of ovary		0.01	0.00	0.01	0.01	0.00	0.01

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AGE SPECIFIC INCIDENCE RATE (PER 100.000) OF RARE OVARIAN CANCER IN THE RARECAREnet DATABASE

	00–14 years			15–24 years			25–64 years			65 + years		
	IR	95%CI		IR	95%CI		IR	95%CI		IR	95%CI	
Rare epithelial tumours of ovary	**0.001**	**0.000**	**0.003**	**0.118**	**0.104**	**0.134**	**1.312**	**1.288**	**1.337**	**3.055**	**2.986**	**3.124**
Mucinous adenocarcinoma of ovary	0.001	0.000	0.003	0.113	0.099	0.129	0.837	0.818	0.857	1.879	1.825	1.933
Clear cell adenocarcinoma of ovary	NA	NA	NA	0.004	0.002	0.008	0.369	0.356	0.382	0.640	0.609	0.672
Mullerian mixed tumour of ovary	NA	NA	NA	0.001	0.000	0.004	0.107	0.100	0.114	0.536	0.508	0.565
Non epithelial tumours of ovary	**0.114**	**0.101**	**0.128**	**0.331**	**0.306**	**0.357**	**0.257**	**0.246**	**0.268**	**0.302**	**0.281**	**0.324**
Sex cord tumours of ovary	**0.004**	**0.002**	**0.008**	**0.026**	**0.019**	**0.034**	**0.150**	**0.142**	**0.159**	**0.240**	**0.221**	**0.260**
Granulosa cell tumours malignant	0.003	0.001	0.006	0.017	0.012	0.024	0.137	0.129	0.145	0.214	0.197	0.233
Sertoli Leidig cell tumours	0.001	0.000	0.003	0.005	0.003	0.010	0.005	0.004	0.007	0.006	0.004	0.010
Other sex cord tumours of ovary	0.000	0.000	0.001	0.003	0.001	0.006	0.008	0.007	0.011	0.019	0.014	0.025
Germ cell tumour of ovary	**0.110**	**0.097**	**0.123**	**0.305**	**0.281**	**0.330**	**0.107**	**0.100**	**0.114**	**0.062**	**0.053**	**0.073**
Yolk sac tumours	0.019	0.014	0.026	0.050	0.041	0.061	0.017	0.014	0.020	0.004	0.002	0.007
Dysgerminoma	0.039	0.032	0.047	0.144	0.128	0.161	0.028	0.025	0.032	0.009	0.006	0.013
Mixed germ cell tumours	0.008	0.005	0.012	0.016	0.011	0.022	0.003	0.002	0.005	0.001	0.000	0.003
Malignant/Immature teratomas of ovary	0.039	0.032	0.047	0.087	0.074	0.101	0.051	0.047	0.056	0.047	0.039	0.056
Other germ cell tumours of ovary	0.005	0.002	0.008	0.008	0.005	0.013	0.007	0.005	0.009	0.002	0.001	0.005

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5-YEAR RELATIVE SURVIVAL (RS) OF RARE OVARIAN CANCER IN THE RARECAREnet DATABASE

	N	5-year RS (%)	95% CI	
Rare epithelial tumours of ovary	**19,009**	**54**	**53.59**	**55.25**
Mucinous adenocarcinoma of ovary	12,010	60	58.84	60.88
Clear cell adenocarcinoma of ovary	4761	55	53.78	57.17
Mullerian mixed tumour of ovary	2242	21	19.41	23.49
Non epithelial tumours of ovary	**3906**	**82**	**80.82**	**83.71**
Sex cord tumours of ovary	**1937**	**79**	**76.86**	**81.49**
Granulosa cell tumours malignant	1741	80	77.73	82.57
Sertoli Leidig cell tumours	74	68	54.55	78.96
Other sex cord tumours of ovary	122	72	60.12	80.38
Germ cell tumour of ovary	**1969**	**85**	**83.38**	**86.85**
Yolk sac tumours	302	86	81.30	89.78
Dysgerminoma	659	90	87.64	92.62
Mixed germ cell tumours	85	85	74.03	91.31
Malignant/Immature teratomas of ovary	829	83	80.35	86.02
Other germ cell tumours of ovary	94	63	50.77	72.53

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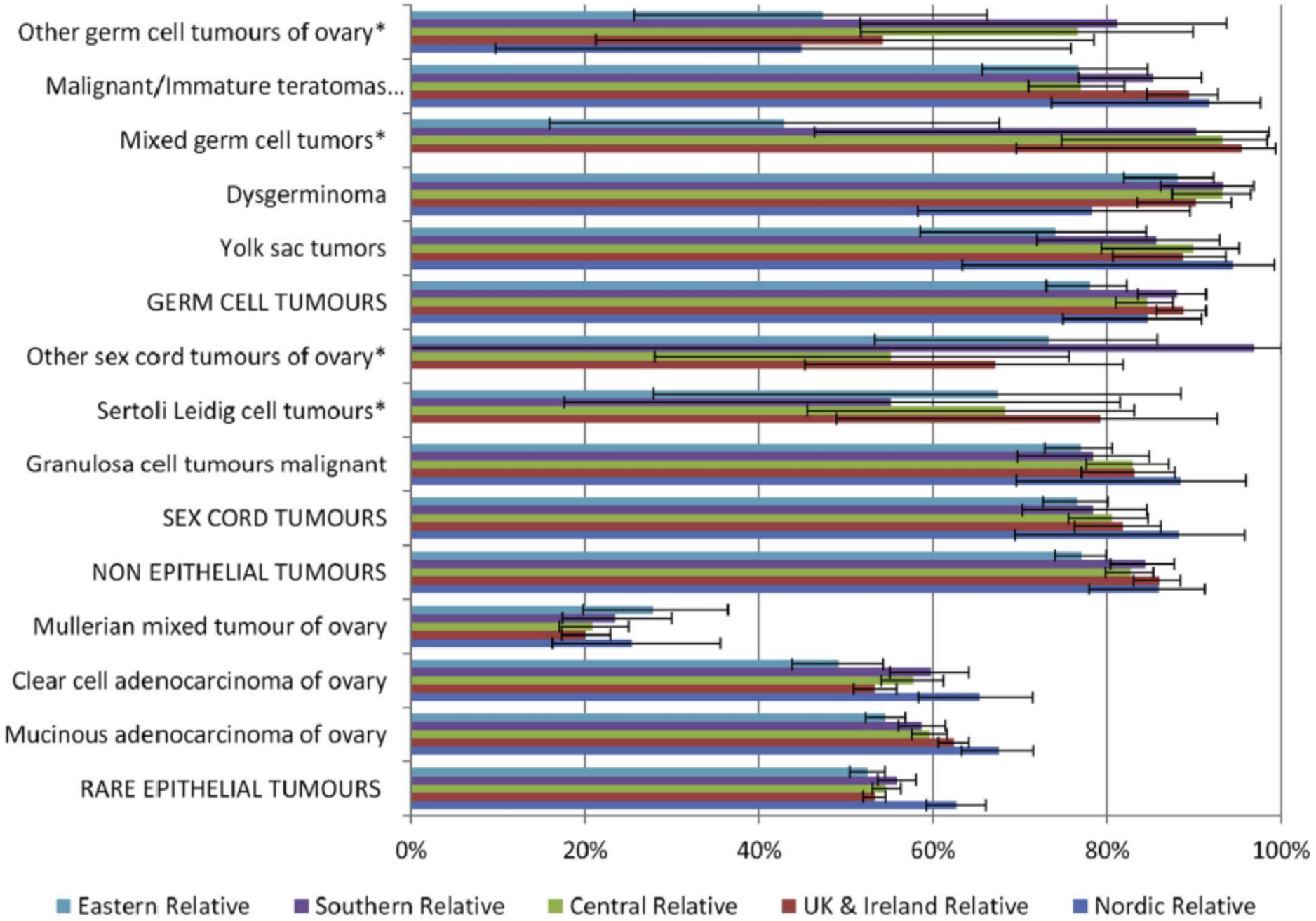
5-year Relative Survival or Rare Epithelial and Non Epithelian Ovarian cancer by European Area



5-year Relative Survival or Rare Epithelial and Non Epithelian Ovarian cancer by Age in the RARECAREnet DATABASE

Table 4
Number of cases on which the analyses are based, 5-year relative survival (RS%) of rare ovarian cancers by histology with 95% Confidence Intervals (95%CI) in the RARECAREnet database.

	00–14 years				15–24 years				25–64 years				65 + years			
	N	RS	95%CI		N	RS	95%CI		N	RS	95%CI		N	RS	95%CI	
Rare epithelial tumours of ovary	**2**	**50.04%**	**0.59%**	**91.07%**	**238**	**87.31%**	**82.15%**	**91.06%**	**11,166**	**61.75%**	**60.74%**	**62.74%**	**7603**	**41.98%**	**40.57%**	**43.39%**
Mucinous adenocarcinoma of ovary	2	50.04%	0.59%	91.07%	227	88.05%	82.83%	91.76%	7114	67.74%	66.53%	68.91%	4667	45.73%	43.89%	47.55%
Clear cell adenocarcinoma of ovary	0	NE	NE	NE	8	74.19%	29.61%	92.94%	3150	57.63%	55.62%	59.59%	1603	51.05%	47.80%	54.20%
Mullerian mixed tumour of ovary	0	NE	NE	NE	3	66.77%	5.35%	94.58%	904	26.93%	23.65%	30.32%	1335	17.45%	14.97%	20.08%
Non epithelial tumours of ovary	**298**	**94.95%**	**91.34%**	**97.08%**	**666**	**91.80%**	**89.23%**	**93.77%**	**2192**	**83.91%**	**82.06%**	**85.57%**	**750**	**63.28%**	**58.29%**	**67.85%**
Sex cord tumours of ovary	**11**	**78.03%**	**35.35%**	**94.25%**	**52**	**68.34%**	**52.73%**	**79.74%**	**1280**	**83.87%**	**81.32%**	**86.10%**	**594**	**70.14%**	**64.44%**	**75.11%**
Granulosa cell tumours malignant	8	71.71%	25.17%	92.30%	35	64.93%	45.26%	79.04%	1165	84.76%	82.12%	87.05%	533	71.29%	65.24%	76.48%
Sertoli Leidig cell tumours	3	NE	NE	NE	11	71.86%	35.46%	90.00%	44	73.96%	55.21%	85.80%	16	48.20%	20.55%	71.41%
Other sec cord tumours of ovary	0	NE	NE	NE	6	83.44%	27.06%	97.53%	71	75.12%	61.34%	84.58%	45	64.85%	41.14%	80.96%
Germ cell tumour of ovary	**287**	**95.60%**	**92.06%**	**97.58%**	**614**	**93.76%**	**91.30%**	**95.54%**	**912**	**83.92%**	**81.17%**	**86.31%**	**156**	**36.60%**	**26.87%**	**46.37%**
Yolk sac tumours	51	96.03%	84.49%	99.03%	101	91.80%	84.08%	95.87%	141	83.43%	75.83%	88.82%	9	NE	NE	NE
Dysgerminoma	101	100.08%	NE	NE	290	95.85%	92.43%	97.74%	244	85.56%	79.98%	89.68%	24	29.97%	10.09%	53.09%
Mixed germ cell tumours	21	90.15%	65.73%	97.47%	32	85.96%	65.83%	94.68%	30	81.69%	59.59%	92.40%	2	NE	NE	NE
Malignant/Immature teratomas of ovary	102	96.34%	88.63%	98.86%	175	94.70%	89.87%	97.26%	436	86.28%	82.40%	89.35%	116	41.99%	30.39%	53.14%
Other germ cell tumours of ovary	12	65.83%	32.40%	85.63%	16	78.22%	45.97%	92.53%	61	62.07%	47.02%	73.98%	5	25.66%	0.72%	68.74%

NE: not estimable because no cases were observed in the period (2000–2007).

Prevalence: in 2008 in Europe 119,000 women were expected to be alive with a past diagnosis of rare ovarian cancer (86,000 rare epithelial OC, 31,369 non epithelial OC)

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Specific background for rare cancers

RARECARE Project

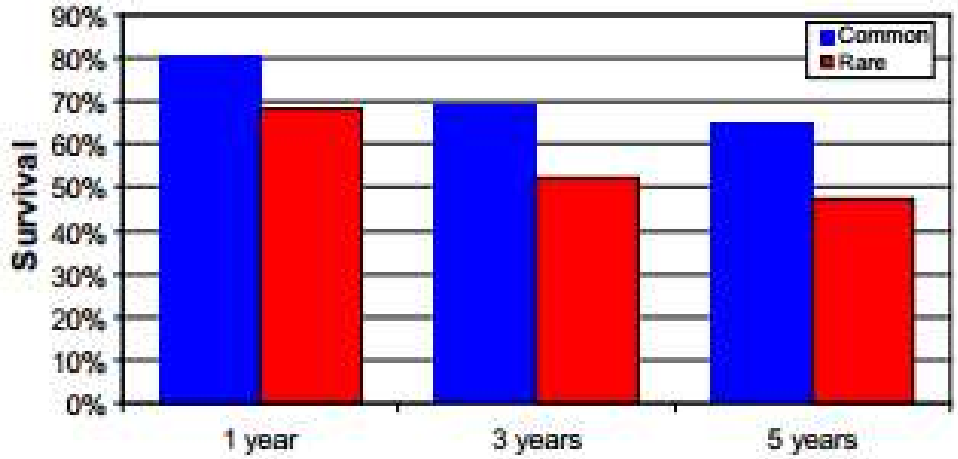


Fig. 3 – RARECARE estimates of relative survival for rare and common cancers in EU27 by year since diagnosis.

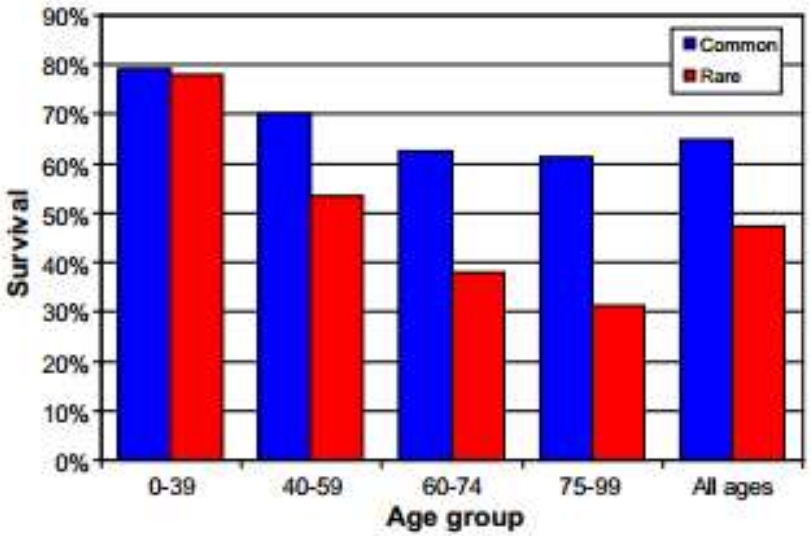


Fig. 4 – RARECARE estimates of relative survival for rare and common cancers in EU27 by age group.

Five-year relative survival was on average worse for rare cancers (47%) than common cancers (65%).

Gatta G Eur J Cancer 2011

Germ Cell Tumors
Presentation

- Dysgerminoma, non dysgerminoma (Yolk sac…), immature teratoma
- 2-3% of ovarian tumours & Peak age 15-19 years
- Before puberty, 90% ovarian tumors are germ cell tumors
- Rare tumors, often aggressive but curable
- 85% of patients are cured today! Big challenge
- Excellent prognosis for a majority of patients (with specific and rapid management)
- Prognostic factors are histologic subtype, age, and stage

Management/Questions

- Conservative surgery to preserve fertility & hormonal activity for majority
- Resection of residual disease post CT if need
- BEP for all stage Ic to IV – surveillance or CT for Stage I (intra ovarian)
- Second opinion and dedicated multidisciplinary staff (oncologists, pediatricians, surgeons…)
- Improvements:
  - Less toxic CT for LR & more intensive CT for HR (HDCT)
  - Alternative CT or new therapies in relapse
  - More biology research

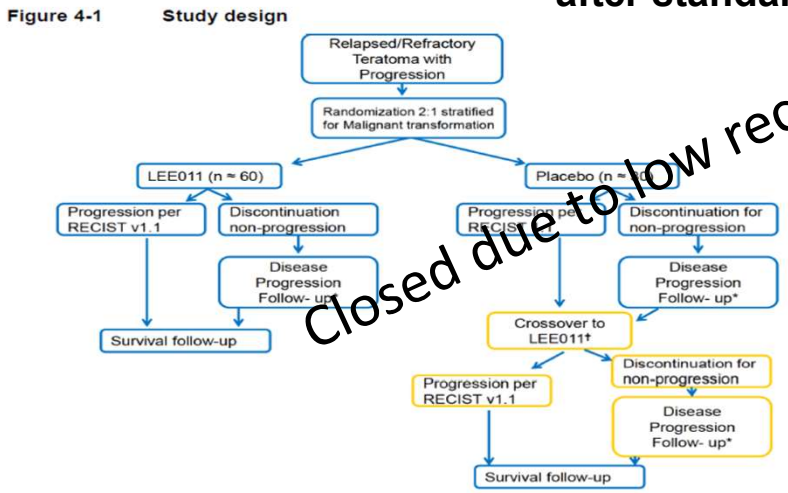
Novartis : ribociclib, CDK4/6 inh (pRb & cell cycle)

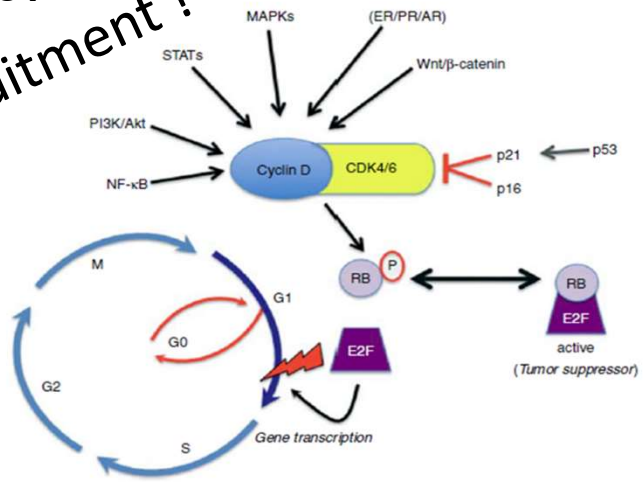
Background: CDK4 & CyclinD2 upregulated GCT

Clinical trials in GCT

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

Closed due to low recruitment !





Sex cord stromal Tumors Presentation

- 7% of all ovarian cancer & Peak age 50 years
- Granulosa cell tumors, Sertoli-Leydig cell tumors….
- Endocrine manifestations (oestrogen secretion 70%)
- Endometrial hyperplasia or endometrial carcinoma to be associated
- 20 to 30% of patients relapsed (late relapse)
- Stage & age: prognostic factors
- New findings: mutated genes : FOXL2 for adult Granulosa & DICER1 for Juvenile & Sertoli Leydig

Standard of care & Questions

- Surgery is the cornerstone of treatment: consider fertility-preserving surgery in young pts with stage I
- Postoperative chemotherapy (BEP/CP) for
  - GCT st. II-IV , Sertoli-Leydig tumor st. II-IV and stage I if aggressive disease
- Relapse:
    - Repeat surgical resections
    - Hormonal therapy in selected cases
    - Chemotherapy regimen options: Carboplatin, paclitaxel, …
- Improvements :
  - Specific & personalized targeted therapy for metastatic disease

National network and clinical research: an example

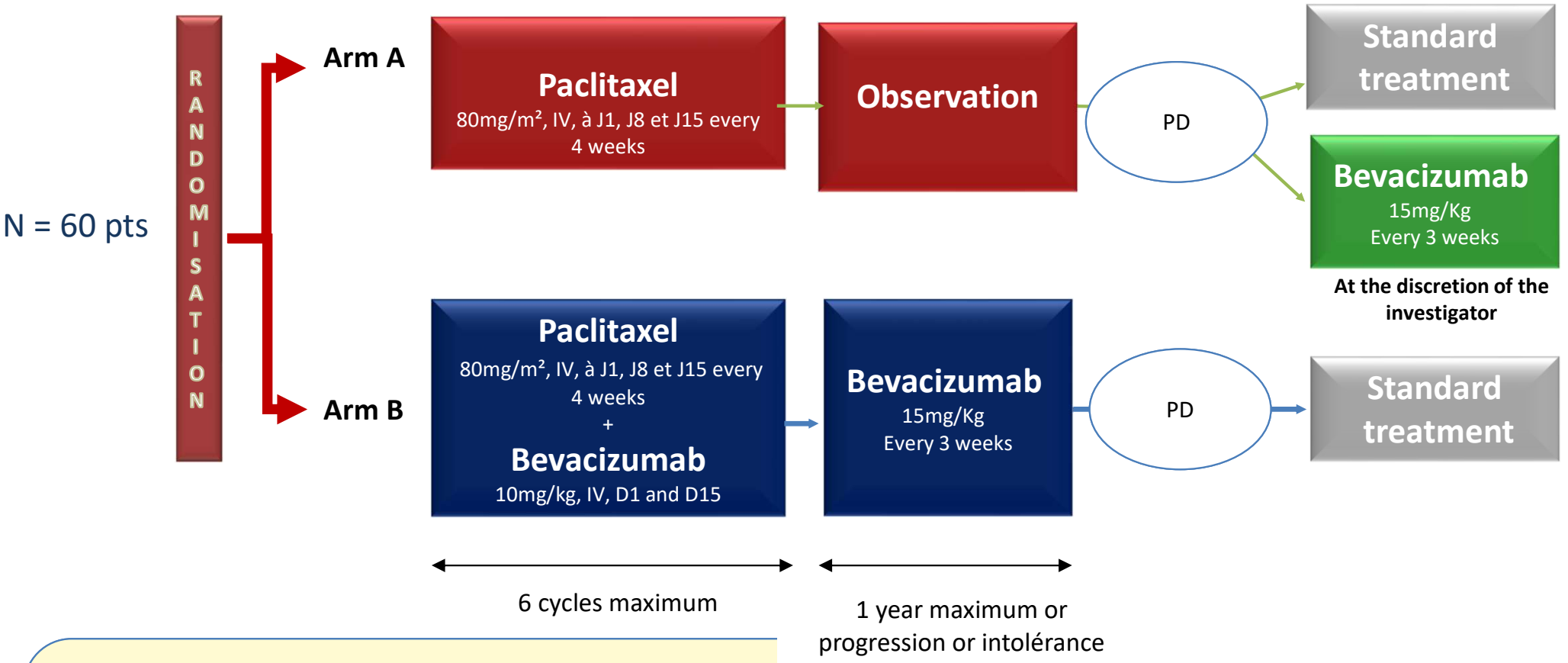
ALIENOR

ENGOT- OV7

Avastin and weekly pac**LI**taxel use in s**E**x cord-stromal ovaria**N** tum**OR**s

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

Study design



Population

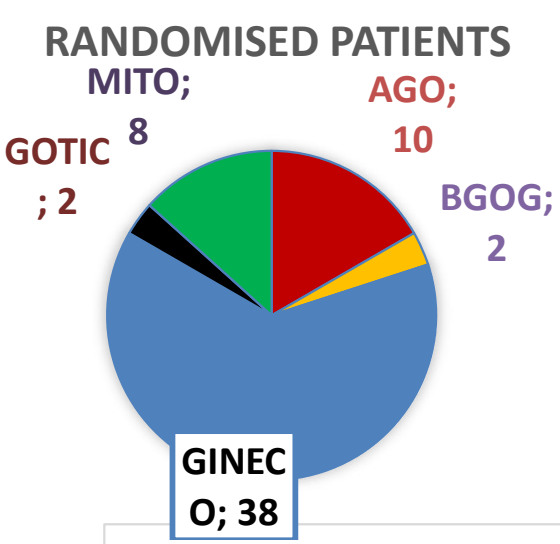
Patients in **relapse with ovarian sex-cord tumor and/or stroma,** histologically confirmed, previously treated by platinum-based chemotherapy.

Main Objective

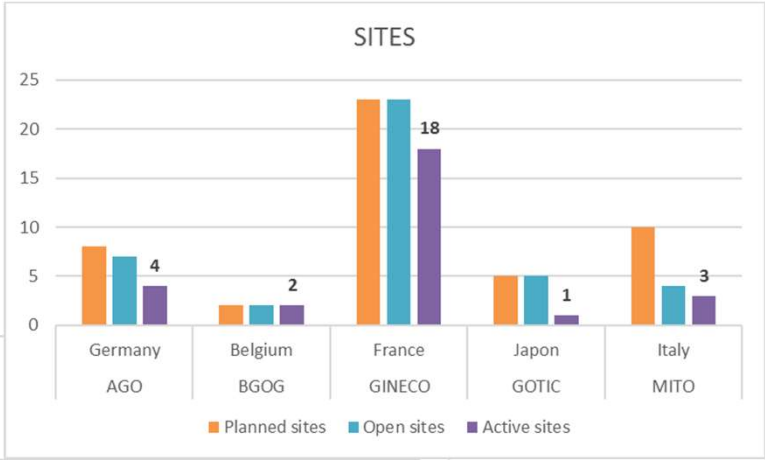
Clinical benefit
(non progression after 6 months)

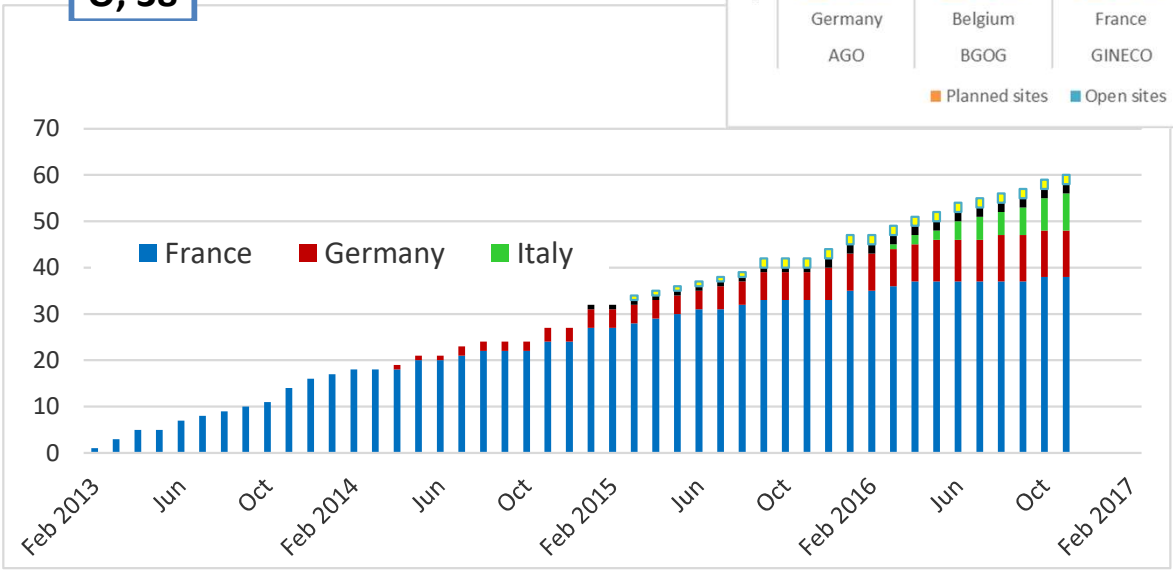
20 open centres / 22 ; 10 active centres; 22 pts included in France

International Collaboration



ALIENOR





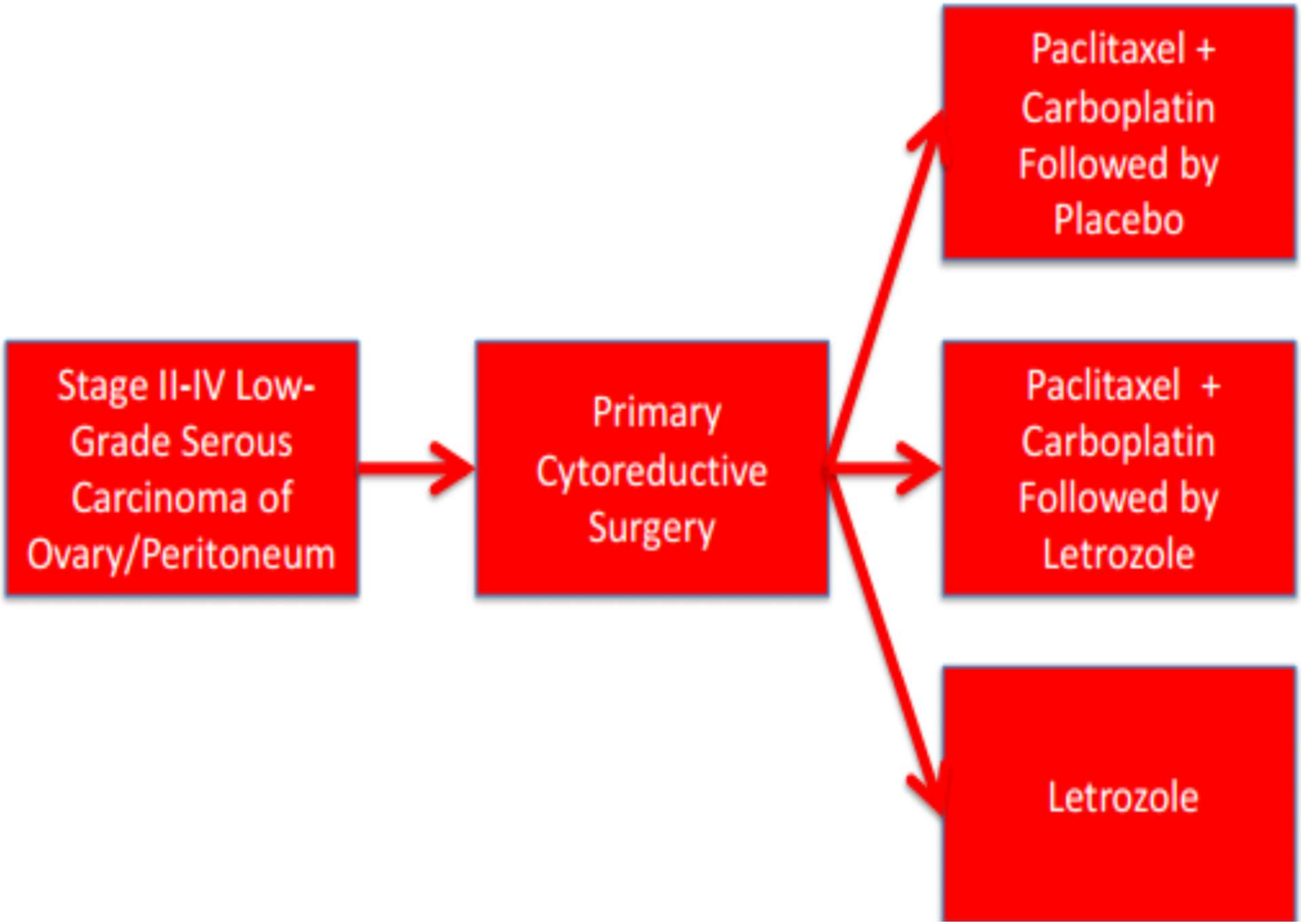
ALIENOR - GCIG
June 1st 2017

Faculté de Médecine Lyon Est

Low grade serous carcinoma
Standard of care/ Questions

- 6 to 10% of all ovarian **carcinoma** & Peak age 50 years
- HR positive & KRAS/ BRAF mutation in 70%, no p53 mutation
- Prognostic factor (stage)
- Less sensitive to chemotherapy
- 1st line treatment included front line maximum debulking surgery & adjuvant CT +/- bev for advanced disease
- In relapse:
  - Consider surgery
- Improvements:
  - Better adjuvant therapy (hormonal?)

Proposed Clinical Trial



Mucinuous ovarian carcinoma
Standard of care / Questions

- 2% of all epithelial carcinoma
- Localized stage good prognosis
- Advanced disease: worse survival
- Management = low response to standard CT with Carboplatine & paclitaxel

- **Improvement**
  - Initial pathological diagnosis : systematic review by experts
  - Active CT & adjuvant CT
  - New drugs

Mucinous

mEOC

Randomise

(332 patients – 83 patients in each arm)

- Carboplatin & Paclitaxel 6 x 21-day cycles
- Oxaliplatin & Capecitabine 6 x 21-day cycles
- Carboplatin & Paclitaxel 6 x 21-day cycles; Bevacizumab given every 3 weeks for 5 or 6* cycles
- Oxaliplatin & Capecitabine 6 x 21-day cycles; Bevacizumab given every 3 weeks for 5 or 6* cycles

Clinical assessment every 6 weeks for 36 weeks

Bevacizumab given every 3 weeks for 12 cycles
Clinical assessment every 6 weeks for 36 weeks

Follow-up

*Bevacizumab can be omitted from the first cycle if chemotherapy must be started within 4 weeks of surgery

Faculté de Médecine

2010-2013: 50/333 pts in 198 centres (UK+US)

Clear cell carcinoma (Ov & Ut)
Standard of care / Questions

- 10% epithelial tumors; + frequent in Japanese pop (frequent story of endometriosis)
- More frequently localized disease (less better prognosis if capsule rupture or peritoneal cytology +)
- New finding : Mutation ARID1A (46% des CC)
- **Management**
  - Radical surgical staging
  - Adjuvant CT including CP or C-CPT11 (JGOG)
- **Questions**
  - Role of adjuvant RT for early stage disease
  - New targeted therapies

(ENGOT-GYN1)
A Randomised Phase II study Of Nintedanib (BIBF1120) Compared To Chemotherapy in Patients With Recurrent Clear Cell Carcinoma Of The Ovary Or Endometrium

Patients with resistant relapse (<6 mois)

Ovarian Clear cell carcinoma (90 pts) or uterus CCC (30 pts)

↓

Registration

↓

Central review of histology

↓

Randomization

Control arm

Chemotherapy investigator choice

Ovarian carcinoma

- Paclitaxel (80mg/m²) IV d1, 8, 15 4w x6 cycles.
- PLD (40mg/m²) IV D1D28 x6 cycles,
- Topotecan (4mg/m²) IV D1, 8, 15 4w x6 cycles

Endometrial carcinoma

-Carboplatin (AUC 5) + paclitaxel (175mg/m²) IV 3W, x6 cycles
- Doxorubicin IV (60mg/m²) 3w x6 cycles

Expérimental arm

Nintedanib (1 cp 200 mg) TWD, continuous until progression

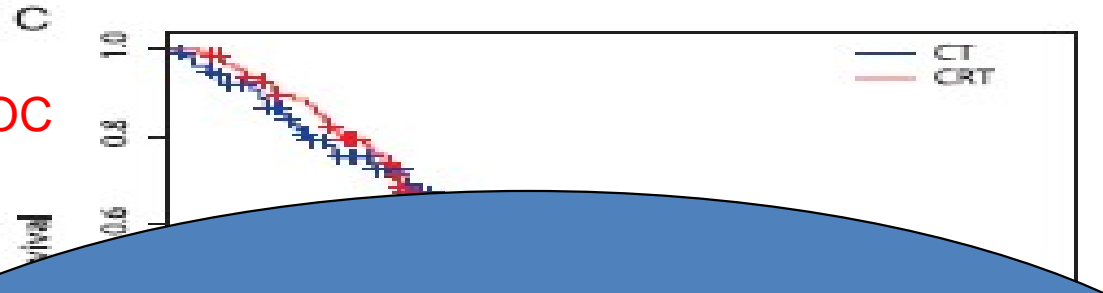
Primary Endpoint: PFS

Secondary Endpoints: OS, QoL, QTWIST, ORR, & DCR at 12 weeks

Revisiting the Role of Radiation Treatment for Non-serous Subtypes of Epithelial Ovarian Cancer

G. Thomas, BSc, MD, FRCC

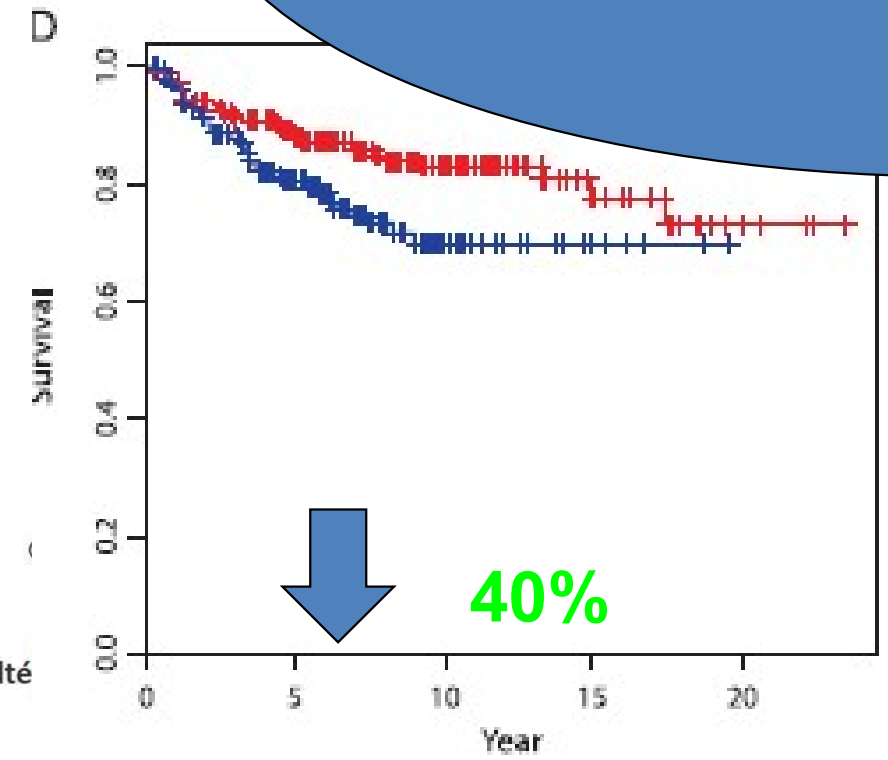
STAGE I-II SEROUS OC

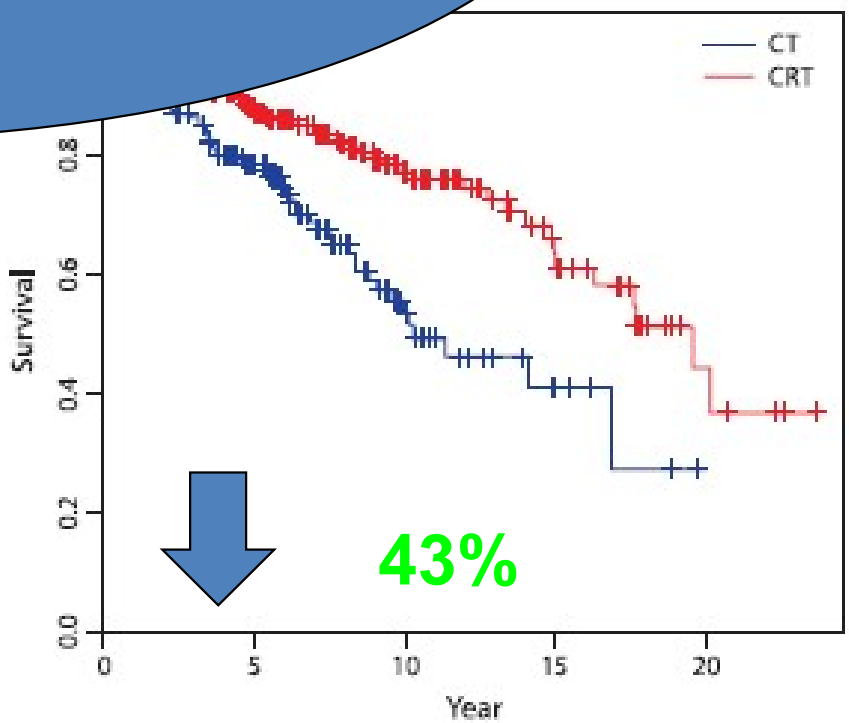


703 pts
351 RT+CHT

BREAKING NEWS!

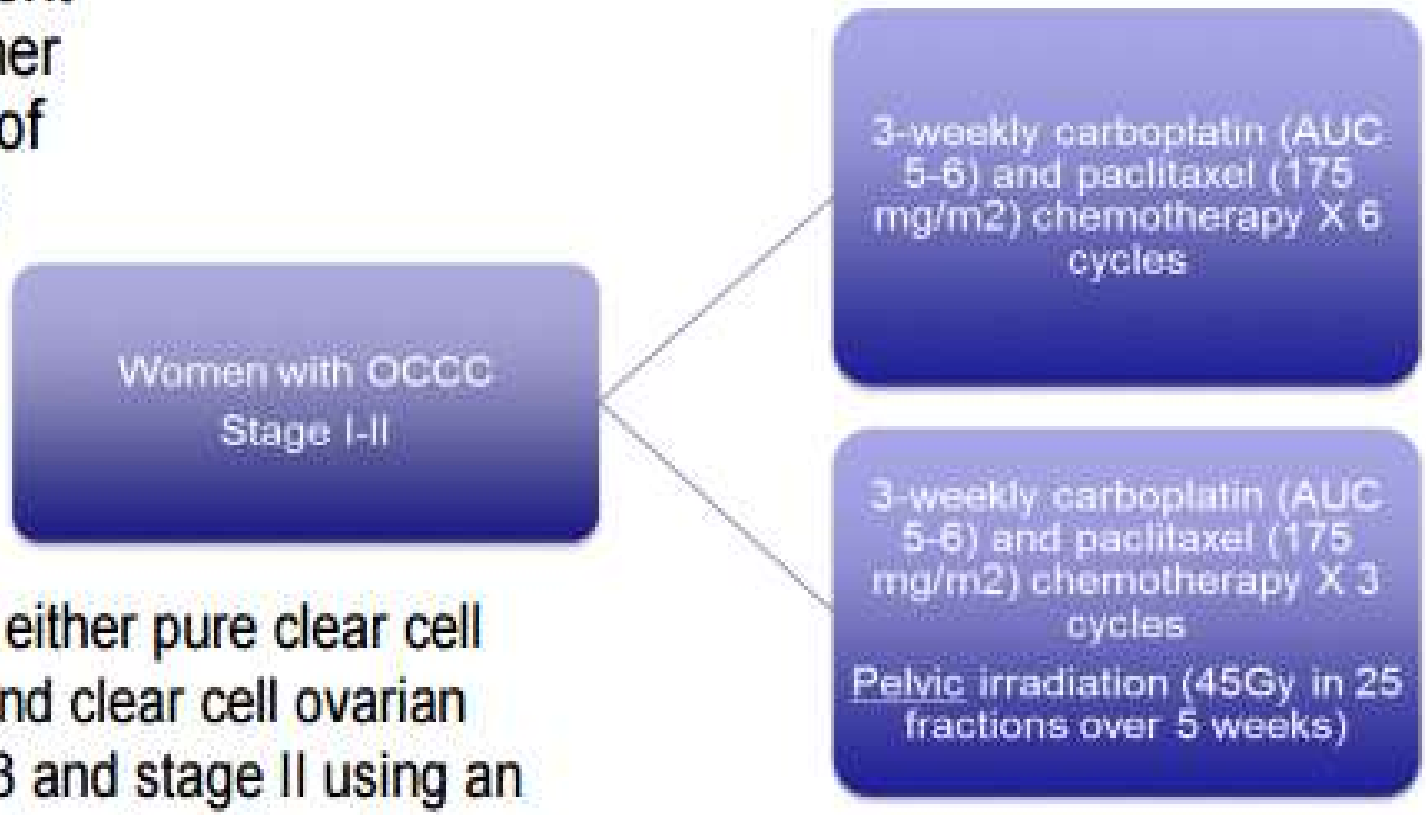
STAGE I-II M





ROCC Agreed Trial Design

Preference for upfront randomisation (rather than after 3 cycles of chemo) and Phase II/III design



- Women diagnosed with either pure clear cell or mixed endometriod and clear cell ovarian cancer FIGO stage Ic2/3 and stage II using an agreed pathology manual and confirmed on retrospective central pathology review
- Full surgical staging to include pelvic and para-aortic lymph nodes

Uterine sarcoma : prognostic strata & stratified analysis

Age 40-60 y
5-10 % of uterine corpus malignancies

Histology	Prognosis
Endometrial Stromal Sarcoma low grade Adenosarcoma of low grade	Good
Leiomyosarcoma	Bad
High grade undifferentiated sarcoma Endometrial Stromal Sarcoma high grade Adenosarcoma with Sarcomatous Overgrowth	Very bad

Low grade ESS
Standard of care / Questions

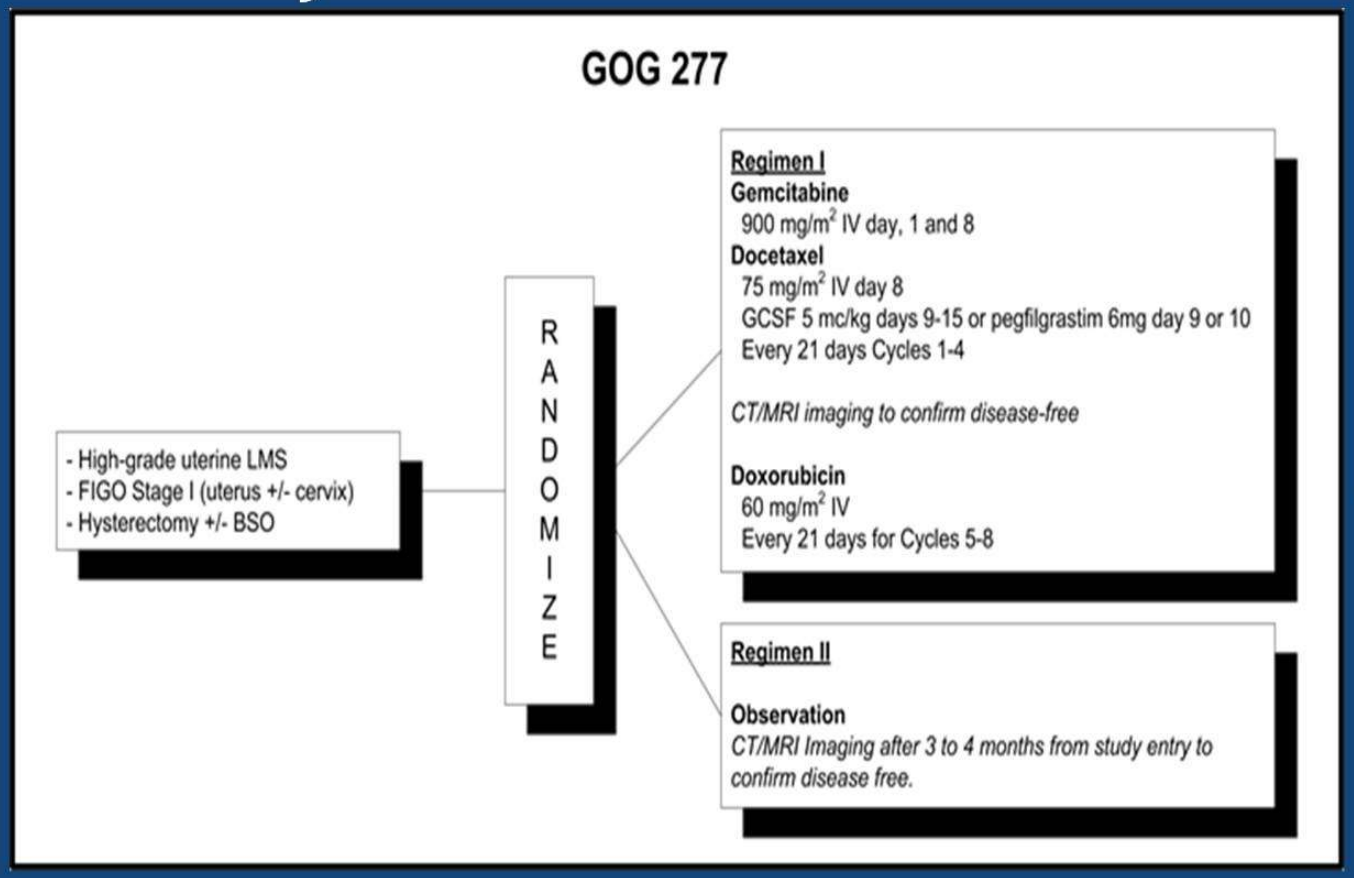
- Indolent tumor , t(7;17)(p15;q21) present in 60%, HR positive (all)
- Median age 48 years
- 15-20% have metastatic disease at diagnosis
- Prognosis and treatment vary greatly by histology— REVIEW the PATH
- No adjuvant treatment until today for localized completely resected tumor
- Low grade ESS are hormone-sensitive, indolent tumors— DON'T GIVE CHEMO, use hormone blockade for advanced disease with residual tumor after surgery

- **Questions**
  - Benefit of systematic ovarian asportation
  - Interest to consider HT after surgery for adj & met phase
  - More specified treatment taking into account translocation

Uterine LMS
Standard of care / Questions

- Median age 56 years, high risk for recurrence for uterus-limited disease
- Complete surgical excision is the only established curative treatment modality for localized disease.
- No specific symptoms/signs or diagnostic imaging can reliably differentiate ULMS from leiomyoma preoperatively. Because of this, inadvertent morcellation of ULMS is increasingly seen in clinical practice.
- RT & CT need to be used for residual disease
- Active agents for LMS: doxorubicin +/- ifosfamide, trabectedin, gem+docetaxel, gemcitabine, pazopanib
- **Problems - Questions**
  - Big challenge : morcellation alters the natural course of ULMS leading to an increased incidence and earlier recurrences!
  - Role of CHT in adjuvant setting

Study Schema



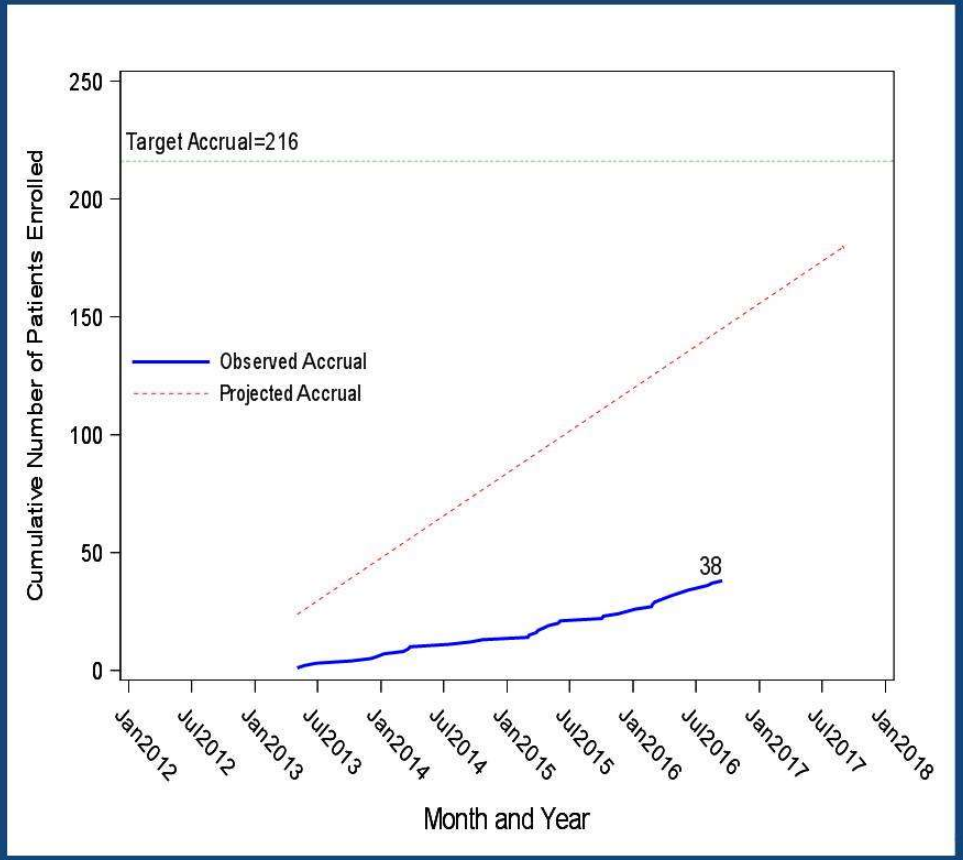
- CT CAP or CT chest + MR a/p prior to randomization to confirm NED
- CT CAP or CT chest + MR a/p every 4 months for 3 years, then every 6 months for 2 years

Key study design features

- International collaboration (IRCI) with EORTC and CR-UK
- Consensus regarding-
  - Critical clinical research question
  - Study design
  - Standard arm = observation
- Primary Endpoint: OS
- Secondary Endpoints:
  - Recurrence-free survival (RFS)
  - Frequency of adverse events

Study Accrual

- Opened 4 June 2012
- 701 international sites
- Target accrual = 216
- Actual accrual = 38
- All sites closed per NCI CTEP *Early Stopping Guidelines* on 20 Sep 2016



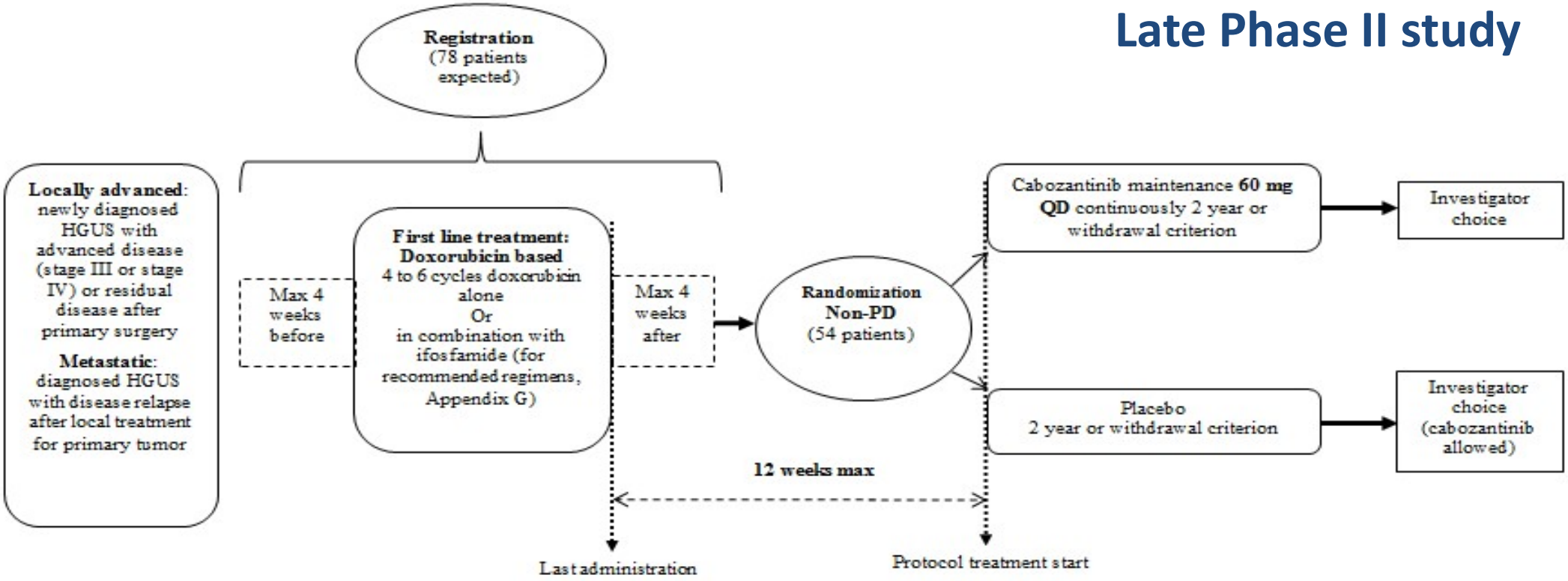
(HG) Undifferentiated Uterine Sarcoma
Standard of care / Questions

- Median age 58 y
- Occult LN metastases are common (75%) & 50% stage IV
- Median PFS & OS worse
- No standard except radical surgery when possible & adjuvant therapy if acceptable
- **Questions a lot!!!**
  - Active CT & adjuvant treatment or all
  - New drugs

EORTC 62113-55115

A randomized double-blind phase II study evaluating the role of maintenance therapy with cabozantinib in High Grade Undifferentiated Uterine Sarcoma (HGUS) after stabilization or response to doxorubicin +/- ifosfamide following surgery or in metastatic first line treatment

Late Phase II study



1° endpoint: PFS rate at 4 months from randomization

2° endpoints: PFS, OS, RR and duration of response (RECIST 1.1), QoL (QLQ-C30 + QLQ-EN24), Toxicity (CTCAE 4.0)

Accrual 14 pts since 03/2015

Summary

- **Rare Gynecologic cancers = same problematic than all other rare cancers:**
  - **Absence of knowledge, curability, few therapeutic options, no very *few* dedicated clinical trials….**
  - **New trials design in rare tumors**
  - **Organization of care pathway at all levels**
    - **Regional, national European & international**

REVIEW ARTICLE

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 Pujaide-Lauraine, MD, PhD,††*

REVIEW ARTICLE

ic Cancer InterGroup (GCIG) Consensus iew for Vulvovaginal Melanomas

REVIEW ARTICLE

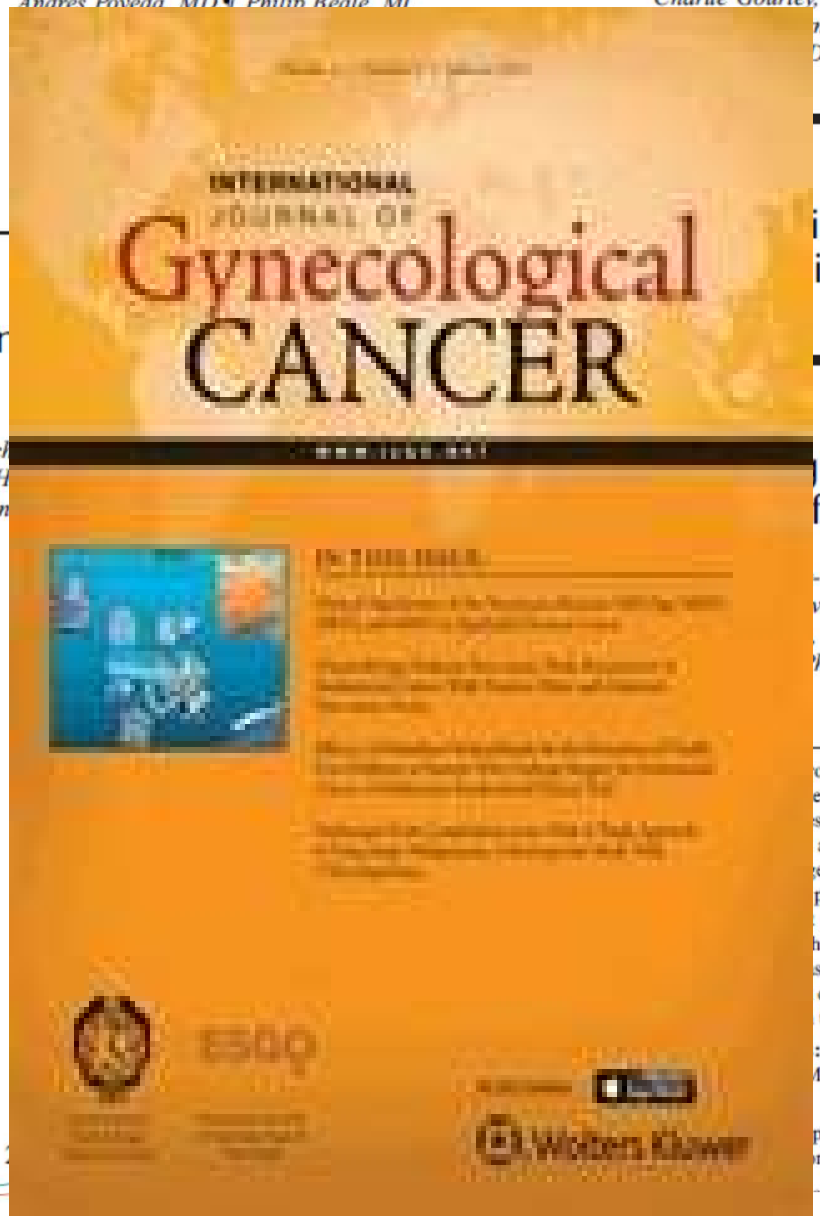
ic Cancer InterGroup (GCIG) Consensus for Ovarian Sex Cord Stromal Tumors

-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
ery 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.



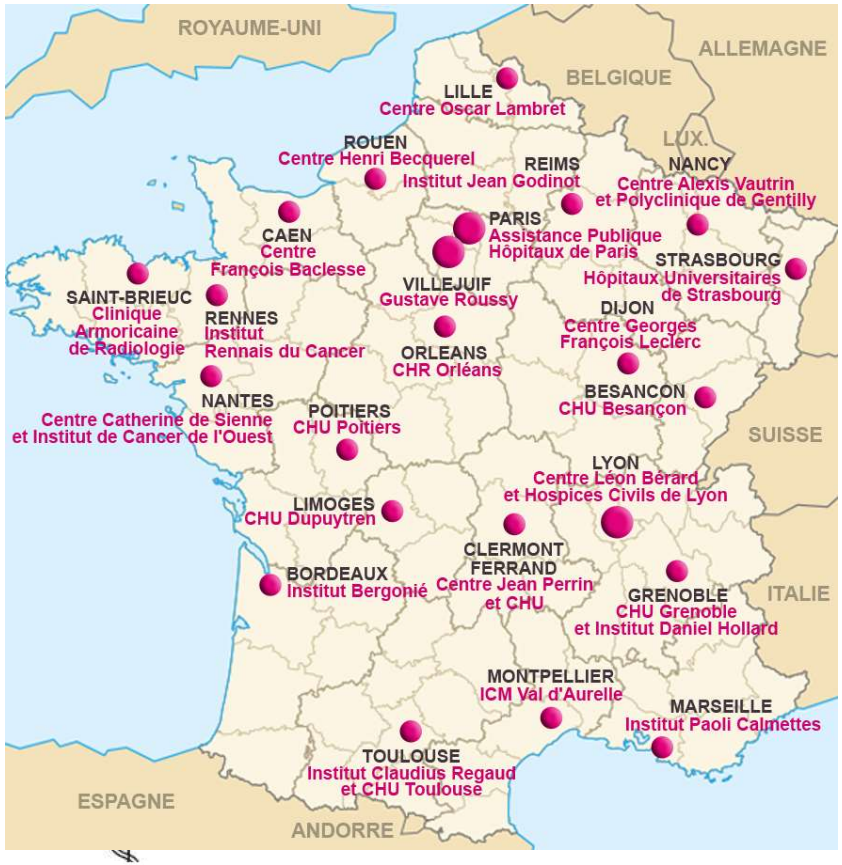
How to change the future?

- 5th OCCC GCIG in Tokyo 2015 and 1st European CC in Milan 2018
  - 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 and Italian model)
  - European network for rare cancer
  - Education for physicians, care givers and public
  - Motivate Patients advocacy group

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 (ex: FOXL2, SMARCA4….).
- ➢**Education**:
- ➢workshops & continuing medical education.
- ➢information for patients, families and advocacy groups.
- ➢To elaborate CPG’s

INSTITUT NATIONAL DU CANCER

GINECO

1st French Patient Advocacy group

IMAGYN

Published in the Official Journal of 31st May 2014

In Italy, every year there are 60,000 new diagnoses of rare cancers corresponding to 15% of all new cancer diagnoses.
A total of 770,000 patients were living in Italy in 2008 with a diagnosis of a rare cancer, 22% of the total cancer prevalence.
Five-year relative survival was on the average worse for rare cancers (53%) than for common cancers (73%).

- ~ 100 active institutions
- ~ 5000 patients in the DB
- ~ 800 clinically shared cases /yr
- ~ 1000 pathologic consultations /yr

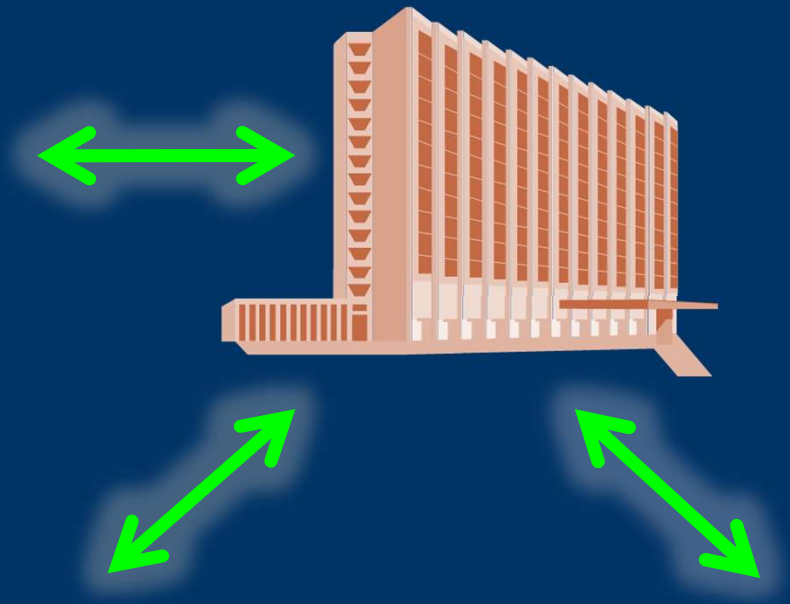
rete tumori rari

RARE
ADULT SOLID CANCERS

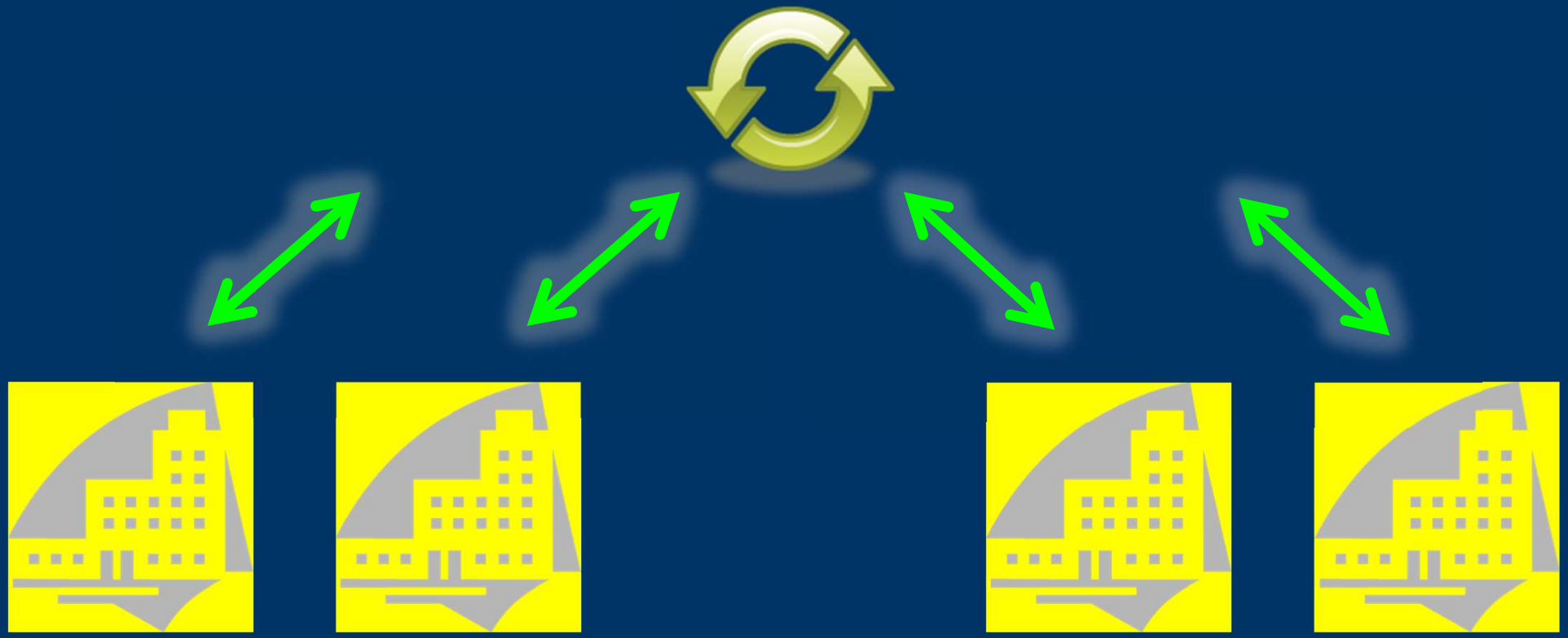
- ✓ Pediatric cancers
- ✓ Haematologic rare neoplasms

1. Sarcomas
2. Rare thoracic cancers
3. Neuroendocrine tumours
4. Head & neck cancers
5. Central nervous system tumours
6. Rare female genital cancers
7. Rare urological and male genital tumours
8. Endocrine gland tumours
9. Digestive rare cancers
10. Rare skin cancers & non-cutaneous melanoma

The centre of reference...



The health network...



Centralized referral

- expertise
- multidisciplinarity
- research

- health migration
- implicit rationing
- failures in routine care

European Reference Networks

Supported by the

European Reference Networks (ERNs) are networks connecting health care providers and centers of expertise of highly specialised healthcare, for the purpose of improving access to diagnosis, treatment and the provision of high-quality healthcare for patients with conditions requiring a particular concentration of resources or expertise in Europe.

24 Networks

The first ERNs were launched in March 2017, involving more than 900 highly specialised healthcare units from over 300 hospitals in 26 Member States. **24 ERNs are working on a range of thematic issues** including bone disorders, childhood cancer and immunodeficiency.

ERN-Rare Cancers

3 ERN candidates in the domain of **rare cancers** have been created:

- ERN for adult rare solid cancers: **EURACAN**
- ERN for adult rare hematological cancers: **EuroBloodNet**
- ERN for pediatric cancers: **ERN PaedCan**

What are European Reference Networks (ERNs)?

ERNS are networks of networks
Involving specialist healthcare providers across Europe.

The knowledge travels,
not the patients

(1) e

(2) to i ...European Union, es... ...s that require highly specialised healthcare and a concentration of knowledge and resources.

(3) securely facilitate patients' data travelling across borders

ERNS have been established under the 2011 EU Directive on patients' rights in cross-border healthcare. This Directive makes it easier for patients to access information on healthcare and thus increase their treatment options.

THE TEN DOMAINS OF EURACAN

Rare adult solid cancers are grouped in 10 domains corresponding to the RARECARE classification and the ICD10.

These domains are also based on pre-existing successful collaborations, in particular for clinical research and expert networks active in the last 10-20 years

ePAG REPRESENTATIVES' ROLES IN ERNs

Key roles (Governance)	Key objectives (Care)
• **Present and represent the patient voice**, providing patient experience • **Communicate and connect with our community**	• **Ensure transparency in quality of care, safety standards, clinical outcomes and treatment options.** • **Promote a patient-centric approach** in both delivery of clinical care, service improvement and strategic development and decision-making.
Key roles (Monitoring & Evaluation)	**Key objectives (research)**
• Review effectiveness of network **empowering patients, evaluate how network acts on feedback received**	• **Contribute to the definition of research priority areas** based on what is important to patients and their families. • **Ensure that patients are embedded in the research activities** performed within the ERN, including involvement in the assessment of clinical trials and in ethics committees.

Take home message

- Rare gynecologic tumors are not so rare
  - 87,000 new annual cases, more than 50% of all gynecological malignancies

- Management decision making:
  - Expert Pathologists
  - Multidisciplinary expert clinical staff

  - Dedicated Rare Cancer Network→ French and Italian experience
  - European and International Cooperation mandatory
  - European networks of reference for rare diseases: EURACAN

- Involvement of patients advocacy group of outmost importance
- Academic leadership to leverage of academic funding and to engage with industry is the key
- Commitment with the clinical and scientific community and local Institutions

- Tumoral minority is the future of the oncology