RARE GYNECOLOGICAL TUMORS

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MaNGO
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Honoraria (self) from Agenus, Blueprint, BMS, PharmaMar, Genmab, Pfizer, AstraZeneca, Roche, GSK, MSD, Deciphera, Mersena, Merck Sereno, Novartis, Amgen, Macrogenics, Tesaro and Clovis;

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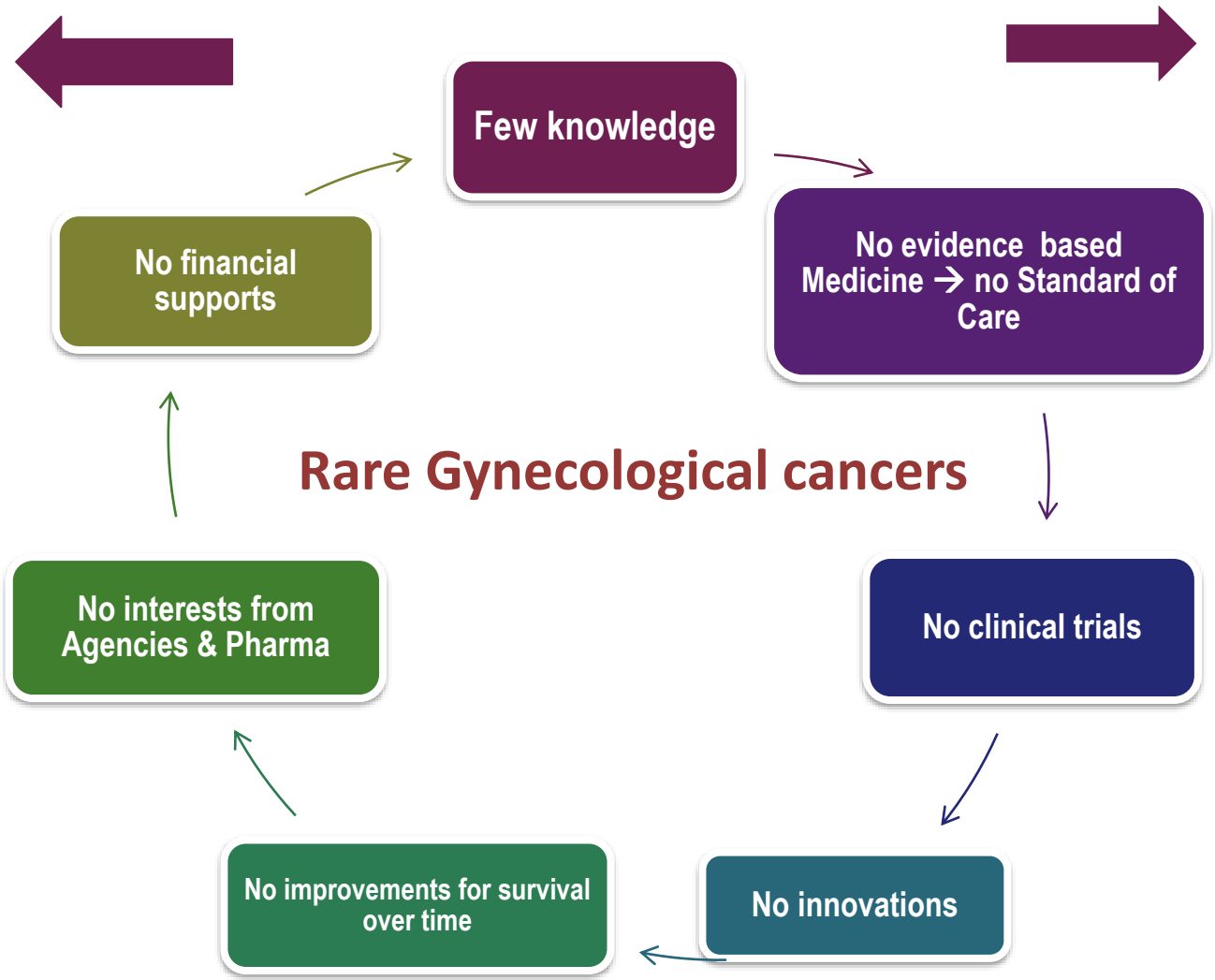
Travel support from Roche, MSD, AstraZeneca and GSK.

DECLARATION OF INTERESTS

NEGATIVE SPIRAL FOR RARE CANCERS

2. Potential options to upgrade our competences

1. Current evidence and unanswered questions



Why to focus on rare ovarian/Gyn tumors?

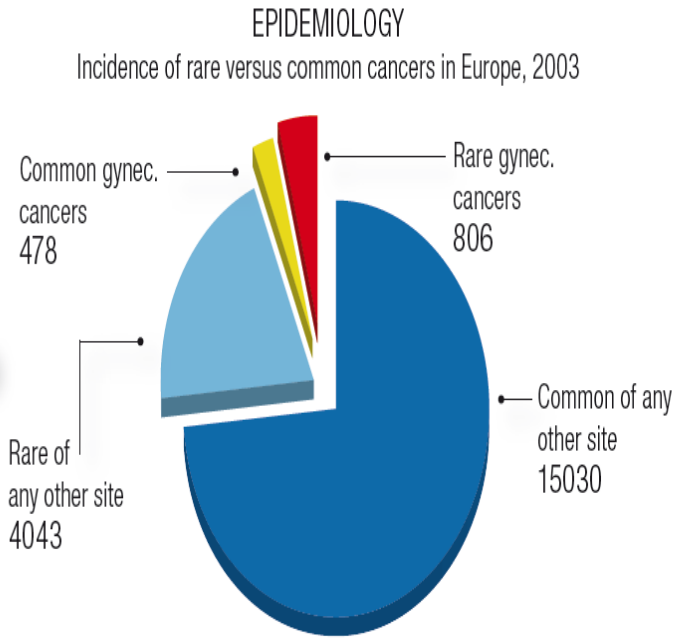
We have to address diversity and Rarety

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.



- Rare ovarian non epithelial tumors:
  - Germ cell tumors
  - Sex cords stromal tumors
  - Small cell carcinoma
- Rare epithelial carcinoma
  - Low grade serous carcinoma
  - Mucinous carcinoma
  - Clear cell carcinoma
  - Carcinosarcoma

RARE EPITHELIAL CARCINOMA

Often early stages …

2 questions :

Conservative surgery

Adjuvant CT

In relapse the best therapeutic options for these patients resistant to Platine

EARLY STAGE AND BORDERLINE

Decision making algorithm for adjuvant chemotherapy

Histologies	Grade/Form	Stage IA	Stage IB/C1	Stage IC2-3	Stage IIA
Serous	Low	No	Option	option	Yes
	high	Yes	Yes	Yes	Yes
Mucinous	Expansile Grade 1-2 / Infiltrative Grade 3	No	Option* / Yes	Option* / yes	Yes to all
Clear cell	NA	Option*	Option*	Yes	Yes
Endometrioid	Grade 1-2 / Grade 3	No / Yes	Option* / yes	Yes to all	Yes to all

*** Considered no adjuvant chemotherapy only for patients with complete surgical staging**

SYSTEMIC THERAPY IN RARE EPITHELIAL CARCINOMA

	Platinum based 1st line (advanced disease)	2 nd line and after
LGSOC	ORR n=145 **23.1%**[1] mOS (n=140) 88.2 mo[2]	Hormonal Tt: ORR **4-14%**[10,11] Paragon ph II : anastrozole ORR: 13.9% mPFS 11.1 mo
OCCC	ORR n=32: **37.5%**[3] mOS st III : 11-25 mo[4]	CT ORR **5-20%** Gemcitabine, irinotecan, platinum
MOC	ORR 38.5-60%[5-8]; n=54 : **60%**[5] mOS 12-33 mo; n=54: 21.6mo[5]	CT ORR **<10%**[8]
Carcinosarcoma	ORR (n=50) **62%**[9] mOS 24 mo	CT ORR **<20%**[4]
HGSOC	ORR: **90%**[1] mOS : 40,7 mo[2]	CT ORR **<20%** for ROC[12]

1:Grabowski JP, Obstet Gynecol 2017; 2: Gockley A, Gynecol Oncol 2016; 3: Sugiyama T J Clin Oncol 2016; 4: Del Carmen MG Gynecol Oncol 2012; 5: Alexandre J, Ann Oncol 2010; 6: Bamias A, Cancer 2010; 7: Pectasides D Gynecol Oncol 2002; 8: Pisano C, Anticancer Res 2005; 9: Rauh-Hain AJ, Gynecol oncol 2011; 7: Gershenson D, Gynecol Oncol 2020; 8: Tang M, Gynecol Oncol 2019; 9: Crotzer D Gynecol Oncol 2007; 10: Takano M, int J Gynecol Cancer; 11: Yoshino K, Int J Clin Oncol 2013; 12: Pujade-Lauraine E J Clin Oncol 2019

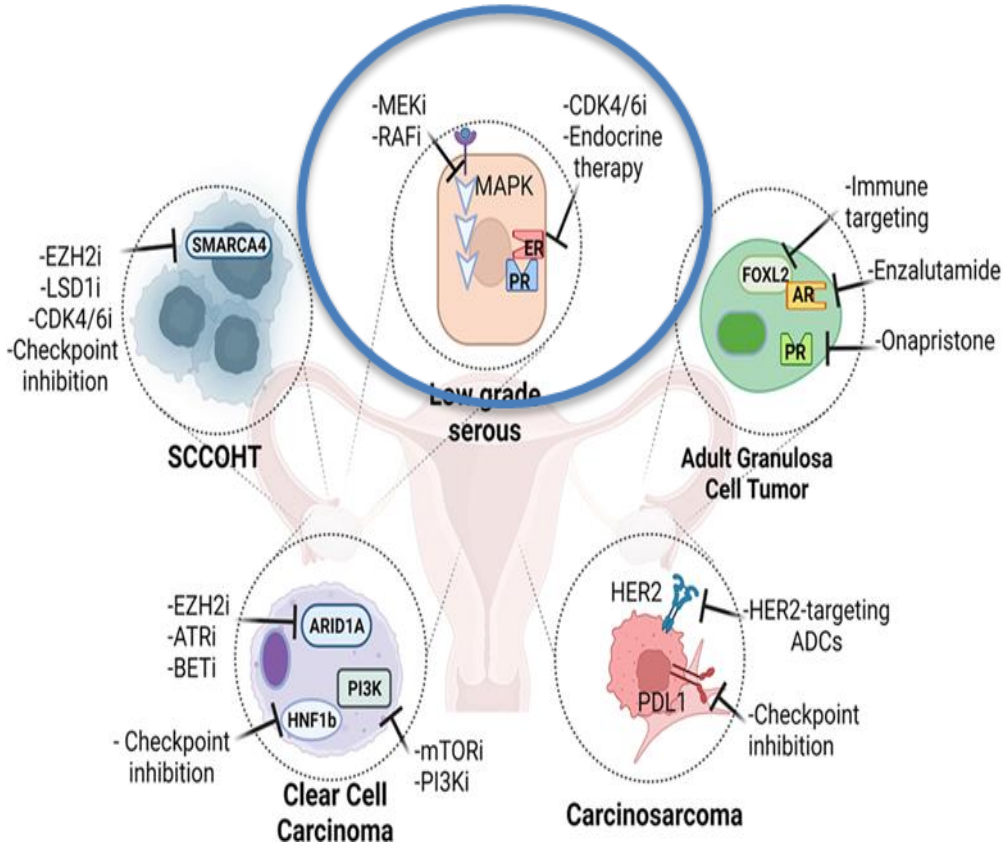
MOLECULAR CHANGES IN OVARIAN CARCINOMAS

	HGS	Endometrioid	Clear cell	Mucinous	LGS
Approximate proportion of OC cases	70%	10%	10%	<5%	<5%
Overall prognosis	Poor	Favourable	Intermediate	Intermediate	Intermediate
Tissue of origin / precursor lesion	Distal fallopian epithelium	Endometriosis	Endometriosis	Poorly defined	Serous borderline tumor
Intrinsic chemosensitivity	High	High	Low	Low	Low
Associated hereditary syndromes	Germline *BRCA1/2*	Lynch syndrome	Lynch syndrome		
Typical stage at diagnosis	80% advanced stage	50% early stage	60% early stage	80% early stage	Typically advanced stage
Frequent molecular abnormalities	Chromosome instability *BRCA1, BRCA2 TP53, NF1, RB1 CCNE1 amp.*	*PTEN, PIK3CA, ARID1A, CTNNB1*	*PTEN, PIK3CA, ARID1A,* chr20q13.2, *amp*	*KRAS, HER2 amp*	*KRAS, BRAF*

1: Matsuo K Gynecol Oncol 2020

LOW-GRADE SEROUS OVARIAN CARCINOMA

- 5% of serous carcinoma
- Most often stage I
- Young patients
- Should derived from borderline serous T
- Chemoresistant
- **ER + tumors**
- ***KRAS/BRAF* mutations (1/3 of patients)**
- mPFS st II-IV : 56 mo; mOS 130 mo[1]
- Pronostic factors[1]
  - No gross residual disease
  - Normal CA 125 at diagnosis
  - Primary peritoneal site
  - Presence of extensive psammamatous calcifications
  - BRAF expression



Gershenson D, Gynecol Oncol 2022; Bejar FG ASCO educational book 2022

Impact of mutational status on survival in low-grade serous carcinoma of the ovary or peritoneum

David M Gershenson*,[1], Charlotte C Sun[1] and Kwong-Kwok Wong

The presence of BRAF or KRAS mutation may predict an improved prognosis

OS= 107mo vs 67mo, p=0.018

Not attributable to differences in stage distribution (both 60% stage III)

BJC 2015

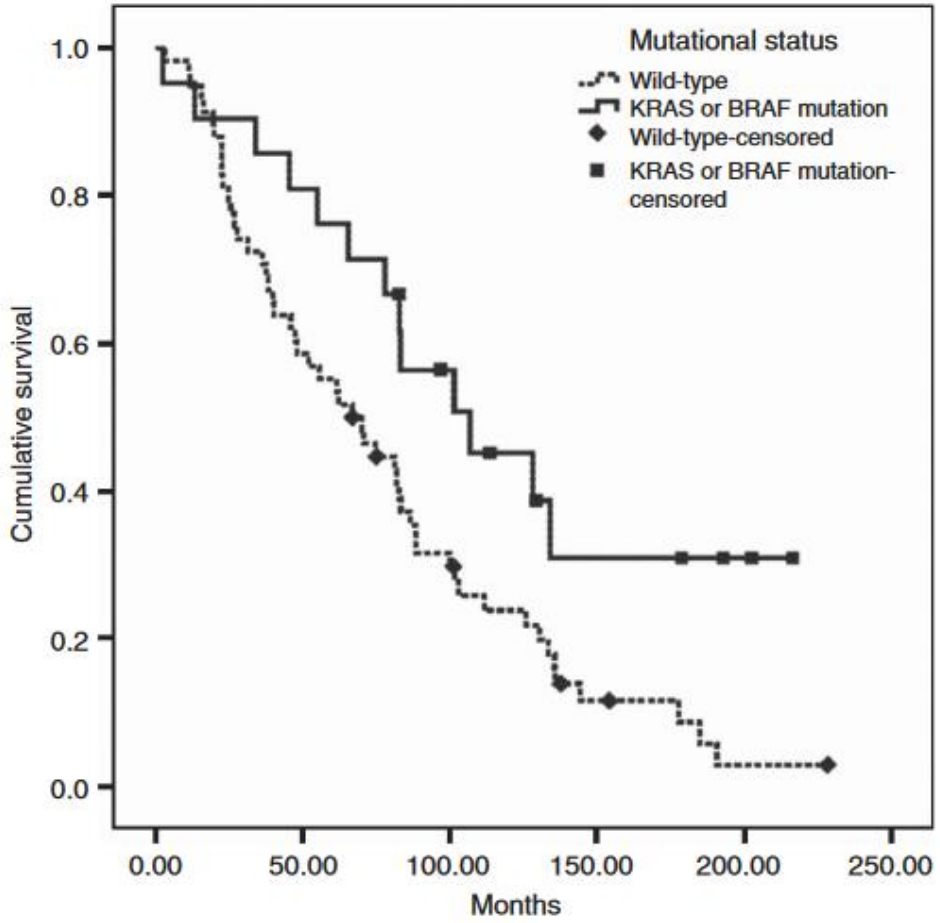


Figure 1. Overall survival. The median OS for women with KRAS or BRAF mutation was 106.8 months (95% CI, 50.6, 162.9) compared with 66.8 months (95% CI, 43.6, 90.0) for women whose tumours contained no KRAS or BRAF mutations ($P=0.018$).

LOW GRADE SEROUS CANCER (LGSC)

Initial treatment (Advanced stage)

- **Surgery remains the mainstay for initial treatment** with the goal of no residual disease
- **First Line systemic chemotherapy platinum/taxane-based for patients with FIGO Stage II–IV disease.**
- Few sensitivity to platine:
  - ✓ Only 52% had no evidence of disease at completion of first line chemotherapy
  - ✓ Only 23% RR compared to 90% for HGSC
- In the neoadjuvant series including 25 Advanced stage LGSC:
  - ✓ Only 1 out of 24 had an objective response
  - ✓ Most SD: 88%

Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial

	Clear cell tumours*		Low-stage high-grade tumours		Low-grade serous tumours	
	Standard therapy (n=77)	Bevacizumab (n=82)	Standard therapy (n=75)	Bevacizumab (n=67)	Standard therapy (n=49)	Bevacizumab (n=33)
Follow-up duration (months)	52·5 (29·0–57·5)	50·7 (28·2–57·9)	55·3 (49·1–60·6)	55·4 (51·2–61·6)	50·5 (28·2–55·1)	55·3 (47·9–62·0)
Deaths	20 (26%)	24 (29%)	6 (8%)	9 (13%)	13 (27%)	7 (23%)
Log-rank test p value	p=0·74		p=0·44		p=0·60	
HR (95% CI)	1·09 (0·64–1·88)		1·49 (0·53–4·20)		0·78 (0·31–1·97)	
Non-proportionality p value†	p=0·58		p=0·002		p=0·07	
(Restricted) mean survival time (months; 95% CI)‡	48·0 (43·9–52·2)	47·6 (43·6–51·6)	56·2 (51·5–60·9)	57·5 (55·7–59·4)	50·4 (45·6–55·2)	50·5 (43·9–57·0)
Restricted mean survival time difference (95% CI)	−0·4 (−6·1 to 5·3)		1·3 (−3·7 to 6·4)		0·1 (−7·9 to 8·0)	

Data are median (IQR) or n (%), unless otherwise indicated. HRs, p values, and survival time differences are for differences between the standard therapy and bevacizumab groups. *The clear cell tumour group includes some patients with mixed histology. †Grambsch-Therneau test. ‡Restricted at 5 years.

Table 2: Overall survival in predefined subgroups

Oza A. et al ; Lancet Oncol 2015; 16: 928–36

ESMO

Grabowski J.P et al. Gynecologic Oncology 140 (2016) 457–462
Gershenson DM et al;Obstet Gynecol 2006; 108(2): 361–368; Schmeler KM et al. Gynecol Oncol 2008; 108(3): 510–514.

Low grade serous cancer (LGSC)

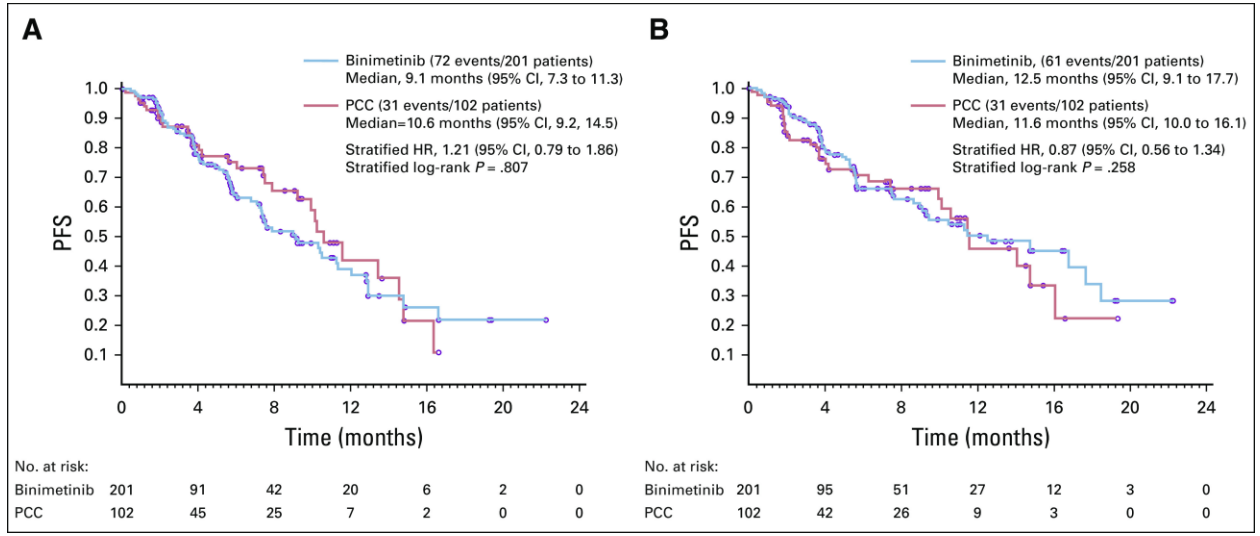
Treatment: Metastatic phase

	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

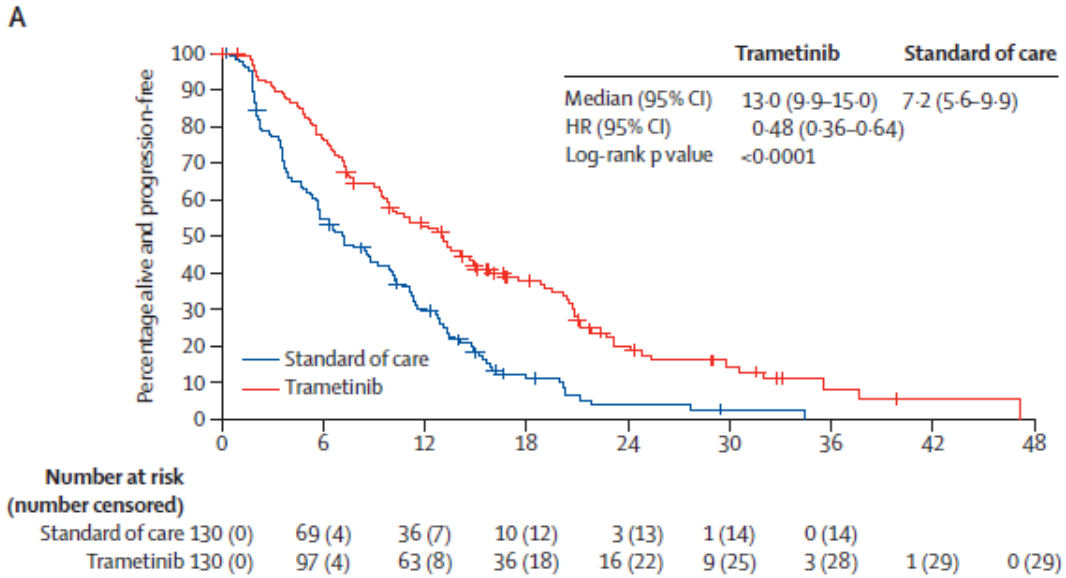
Farley JH, et al. *AACR Meeting Abstracts.* 2012;2012: Abstract CT-05

MEK INHIBITORS AND LGSOC PH 3 IN RELAPSE

MILO study[1]: **binimetinib** *vs* CT n=303
ORR 16% (*vs* 13%), 44% in KRAS m



GOG0281[2]: **trametinib** *vs* SOC (CT or HT) n=260; 34% mMAPK pathway alterations KRAS,BRAF,NRAS
ORR 26% vs 6%



1: Monk B, J Clin Oncol 2020; 2: Gershenson D, Lancet 2022

RAMP201 trial Efficacy

- Confirmed ORRs of 45% (13/29; 95% CI: 26%, 64%) and 10% (3/30; 95% CI: 2%, 24%) were observed on the combination and monotherapy arms, respectively.
  - *KRAS* mt responses: 60% (9/15) for avutometinib + defactinib, 13% (2/15) for avutometinib.
  - *KRAS* wt responses: 29% (4/14) for avutometinib + defactinib, 6% (1/16) for avutometinib.
- Tumor shrinkage was observed in the vast majority of patients on the combination and monotherapy arms, 86% (25/29) and 90% (28/31), respectively.
- Responses observed in 3/4 patients who received prior MEK inhibition therapy in combination arm (1/10 in monotherapy arm).
- Median time to response in combination arm: 5.5 months (range: 1.6-14.7 months) and monotherapy arm: 7.3 months (range 2.1-11 months).
- Median duration of response and progression-free survival have not been reached.

RAMP 201 Part A Efficacy Results per BICR (Efficacy Evaluable Patient Population[a])

	Avutometinib			Avutometinib + Defactinib		
	KRAS mt (n=15)	*KRAS* wt (n=16)	Total (n=31)	*KRAS* mt (n=15)	*KRAS* wt (n=14)	Total (n=29)
Confirmed ORR, n (%)	2 (13)	1 (6)	3 (10)	9 (60)	4 (29)	13 (45)
CR, n (%)	1 (7)	0	1 (3)	0	0	0
PR, n (%)	1 (7)	1 (6)	2 (7)	9[b] (60)	4 (29)	13 (45)
SD, n (%)	12 (80)	13 (81)	25 (83)	6 (40)	7 (50)	13 (45)
Disease control rate[c], n (%)	14 (93)	14 (88)	28 (93)	15 (100)	11 (79)	26 (90)
PD, n (%)	1 (7)	2 (13)	3 (10)	0	3 (21)	3 (10)
Confirmed + unconfirmed ORR, n (%)	2 (13)	1 (6)	3 (10)	11 (73)	4 (29)	15 (52)

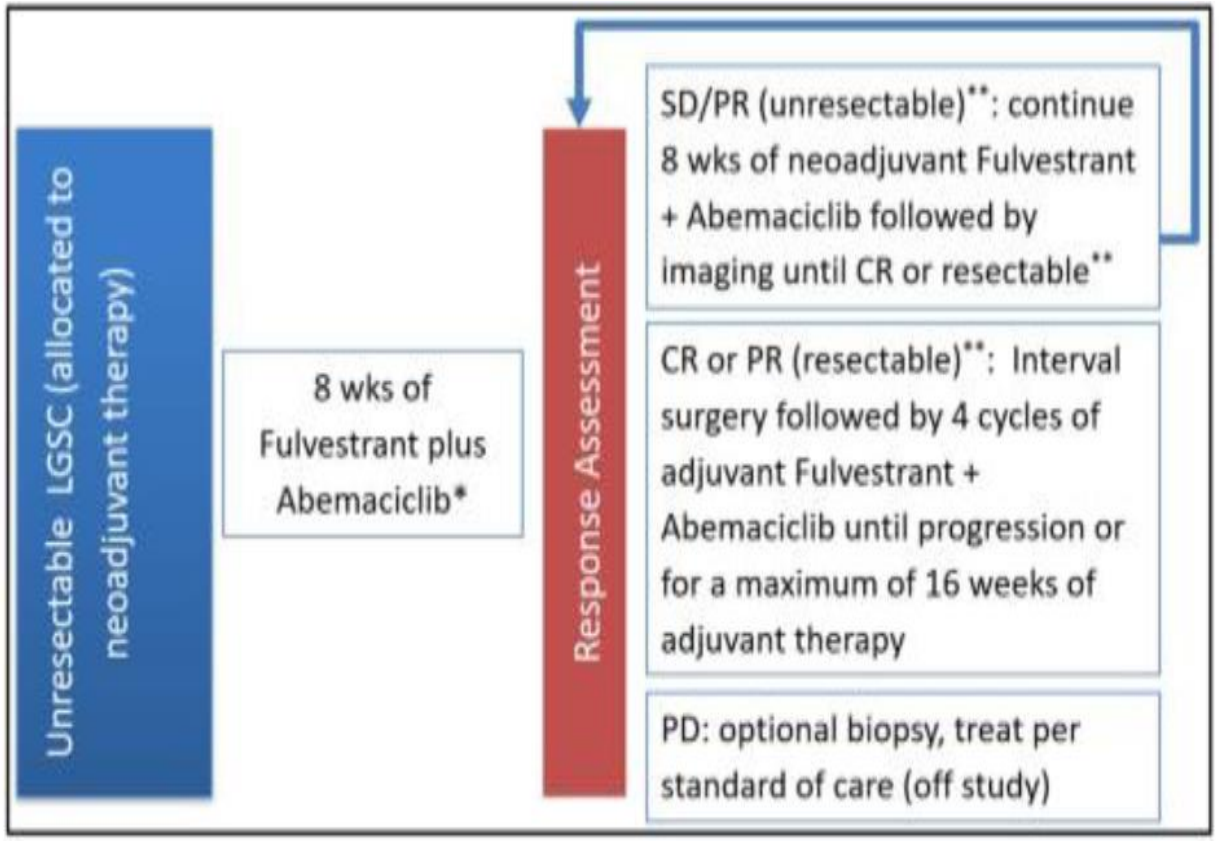
Data cutoff: April 6, 2023

[a]Evaluable for efficacy: At least one blinded imaging assessment in 31 of 33 and 29 of 31 patients enrolled in monotherapy and combination arms, respectively. [b]One patient deepened to CR at last assessment; CR not yet confirmed.
[c]Disease control rate (SD + PR + CR) at 8 weeks.

BICR, blinded independent central review; mt, mutant; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; wt, wild type.

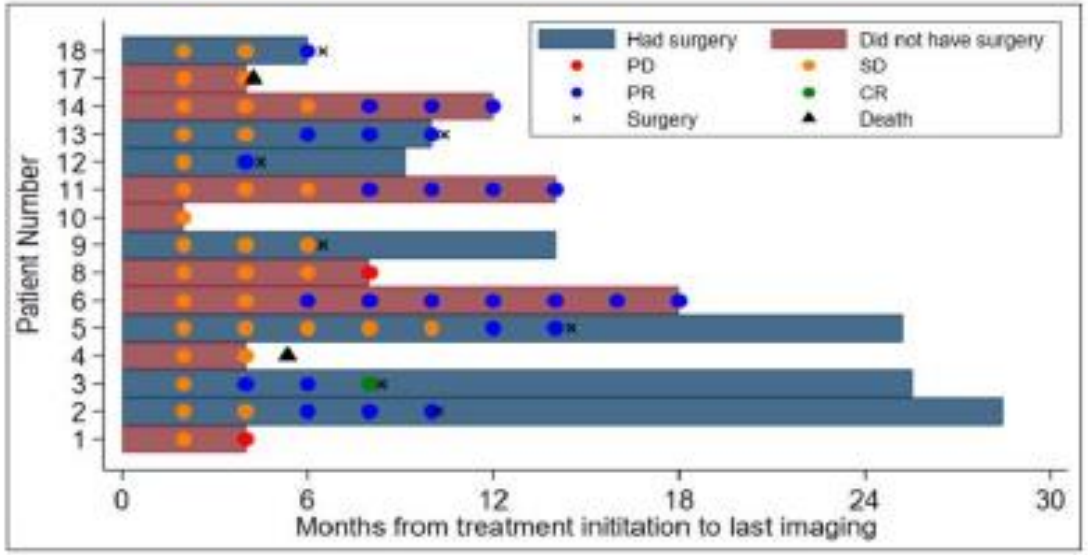
Banerjee et al ASCO 2023

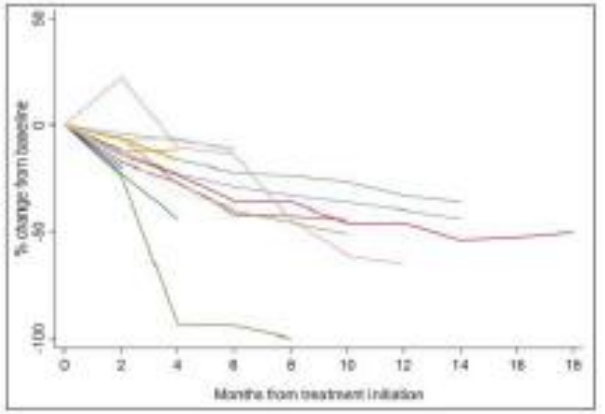
NEO- ADJUVANT HORMONAL THERAPY IN WOMEN WITH ADVANCED LGSC
FULVESTRANT PLUS ABEMACICLIB (ASCO 2022, L COBB)



Results:

47% were operated (71% CCO)





BORR	# of Subjects	%
Complete Response	1	6.7%
Partial Response	8	53.3%
SD	6	40%
BORR	9	60%
PD	0	20%
Total with at least one scan	15	100%

LGOC ONGOING TRIALS

- **IO**: Pembrolizumab + CT in PS Recurrent LGSOC (PERCEPTION) ph 2: NCT04575961

- **Hormonal therapy**
  - Maintenance Therapy With Aromatase Inhibitor in EOC (MATAO) ph 3 vs placebo NCT04111978
  - Letrozole +/- Paclitaxel + Carboplatin Stage II-IV ph 3 LGSOC; NCT04095364

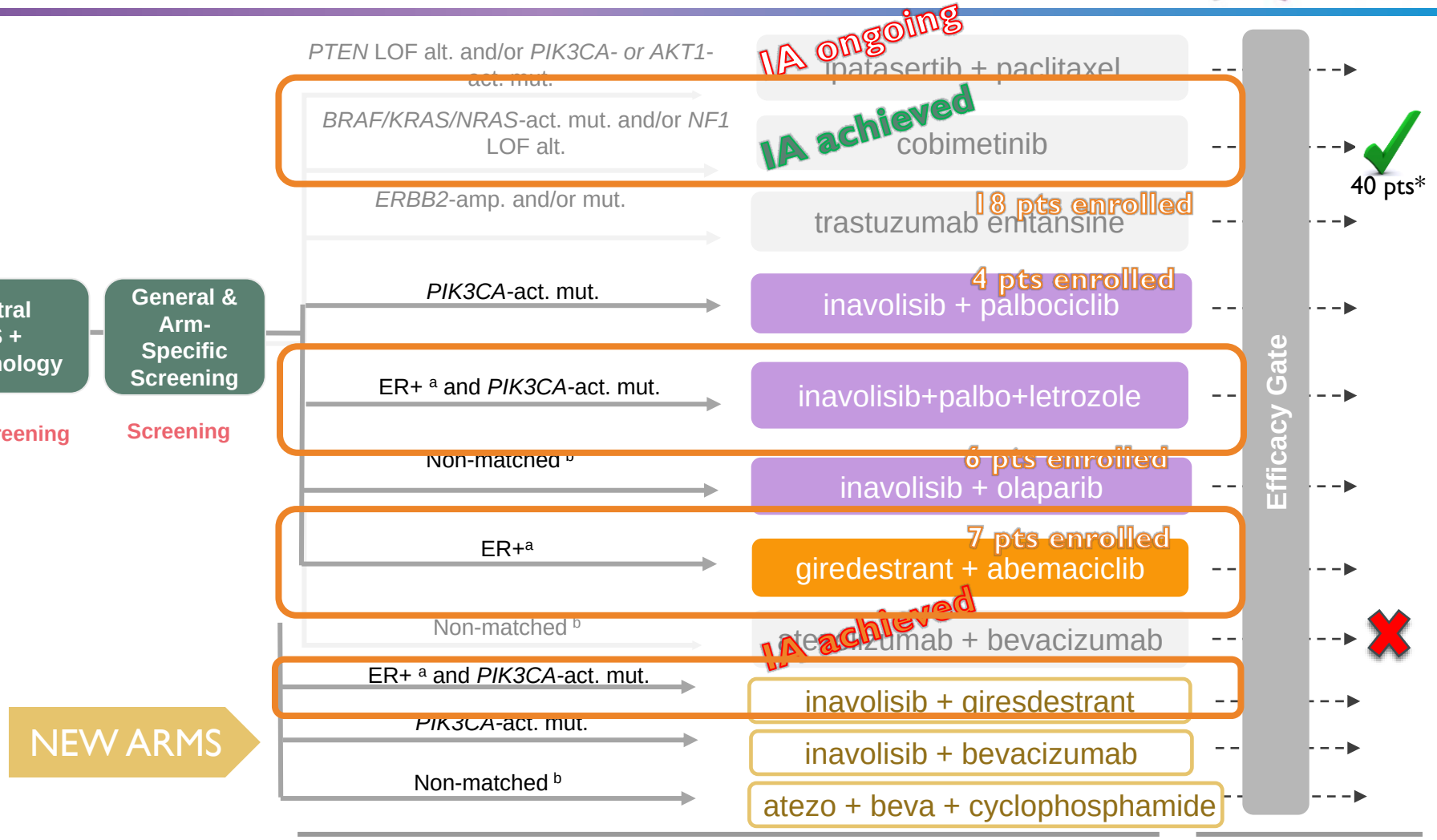
- **BASKET trial BOUQUET molecular driven**

BOUQUET Study

- Persistent or recurrent rare EOC, FTC, PPC
- 1–4 priors
  - ≥1 prior platinum
- ECOG 0 or 1
- Measurable disease
- Submission of tumor specimen

Central NGS + Pathology — Prescreening

General & Arm-Specific Screening — Screening



LOF=loss of function.

[a] ER-positive, defined as detection of ERα in ≥10% of tumor cells as assessed by central ER IHC (CellCarta; Ventana SP1 IHC assay).

[b] The Atezo+Bev and Inavo+Ola arms are for eligible patients who do not have a biomarker profile matching them to an open and enrolling biomarker-driven treatment arm, or do not meet the arm-specific eligibility criteria for an arm they are matched to based on their biomarker profile, or withdraw from another arm.

* Rare EOC other than Clear cell, mucinous carcinoma or carcinosarcoma

MUCINOUS OVARIAN CARCINOMA
PROBLEMATIC

3% of all epithelial carcinoma

80% are Mets!

1. Localized stage good prognosis

2. Second Opinion:
- 52% change in MEOC trial
- More than 29% in French network

Expansive no caps rupture (fertility sparing surgery)

Infiltrative or IC (radical surgery)

Advanced disease: worse survival

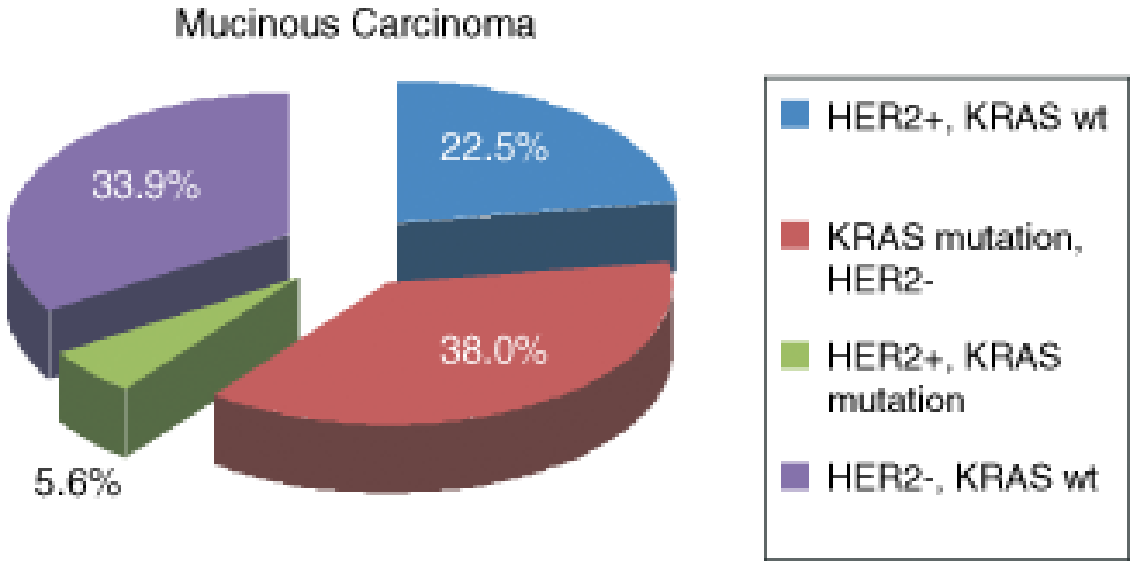
Management = HGSC but low response (38%) to standard CT with carboplatine & paclitaxel

Improvement

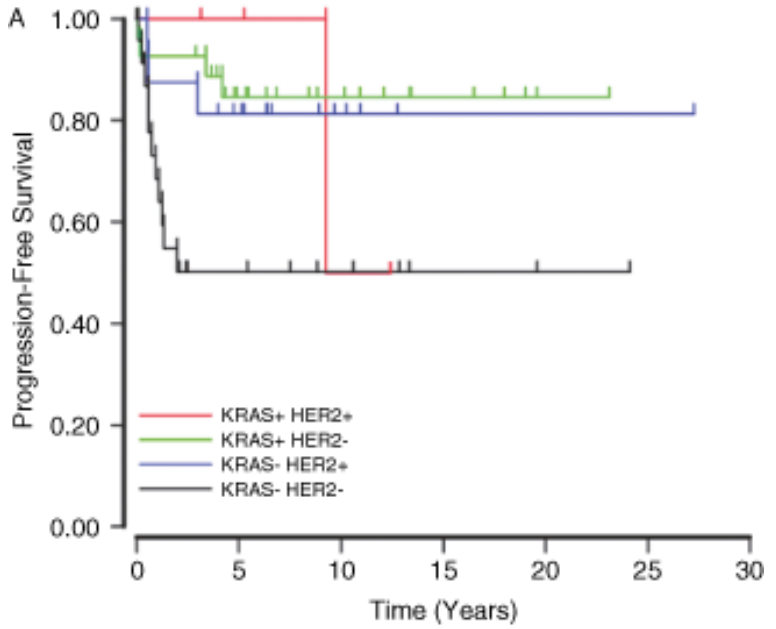
- Initial pathological diagnosis : systematic review by experts
- Oncogenic Drivers
- Active CT & adjuvant CT for advanced stage → MeOC trial XELOX = Carboplatin paclitaxel , interest of bev?
- Role of HIPEC?
- New drugs → Bouquet trial

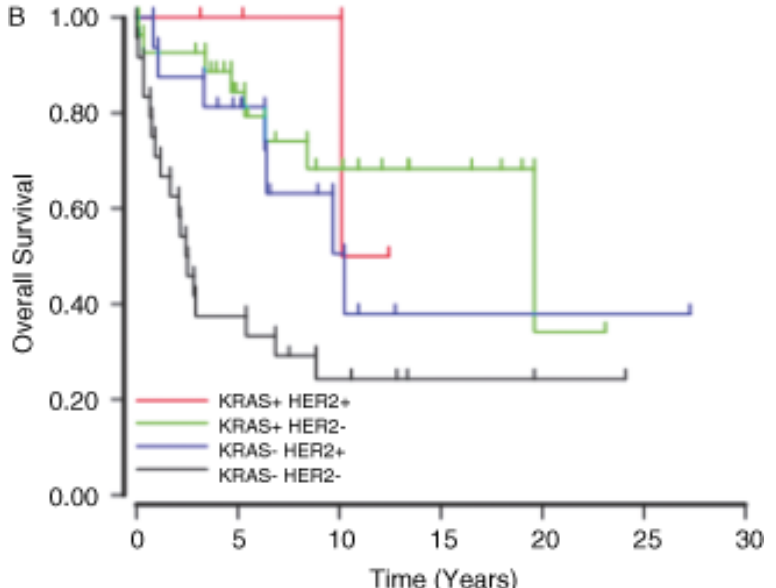
M Gore, ASCO 2015; N Chen, Annals Oncol 2017

MOLECULAR CHARACTERIZATION OF MUCINOUS OVARIAN TUMOURS: KRAS MUTATIONS AND HER2 AMPLIFICATION FREQUENT AND MUTUALLY EXCLUSIVE



The Journal of Pathology, Anglesio, 2012





ONGOING TRIALS IN MOC

- **No specific Drug MOC dedicated study**

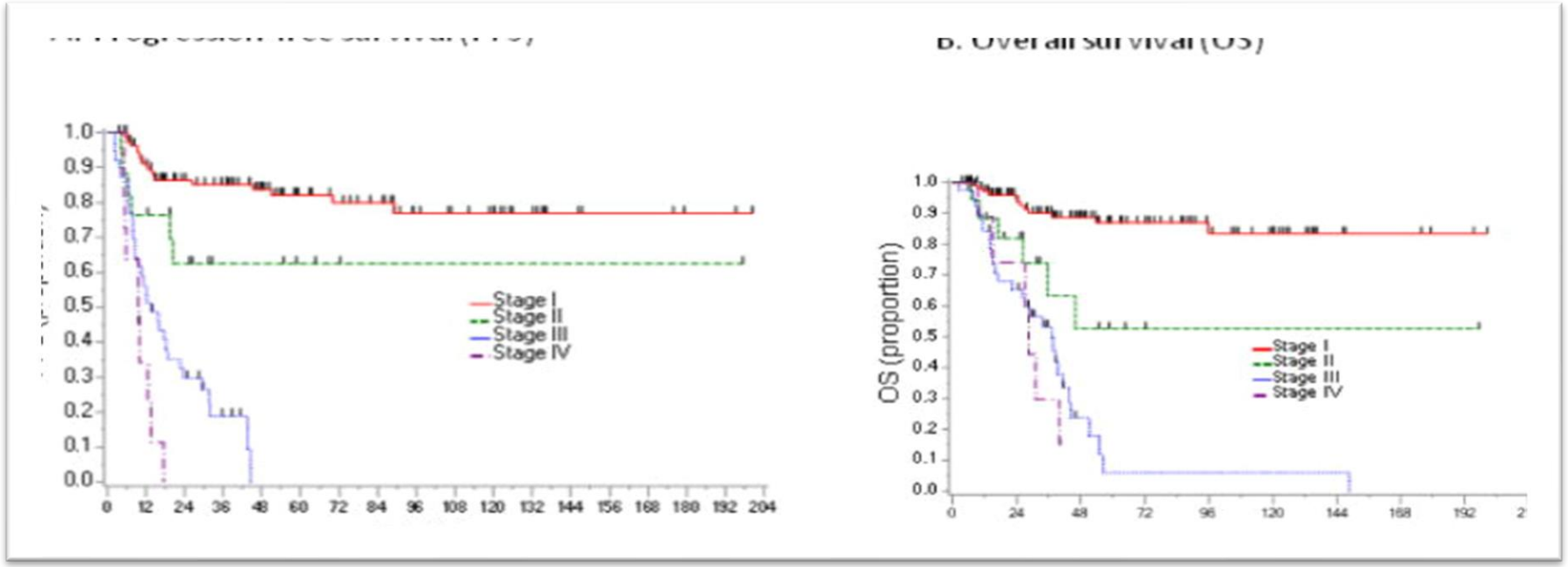
- **Surgery and HIPEC for Recurrent MOC (HI-MOC Study) Ph 2;** NCT05123807

- **Very fee studies where MOC should be included:**
  - **Cediranib +/- Durvalumab +/- Olaparib vs CT (4 arms) Ph 2R; all ROC: N**CT04739800
  - **Oncolytic virus** (MV-NIS) **ph 1/2 OC;** NCT02068794

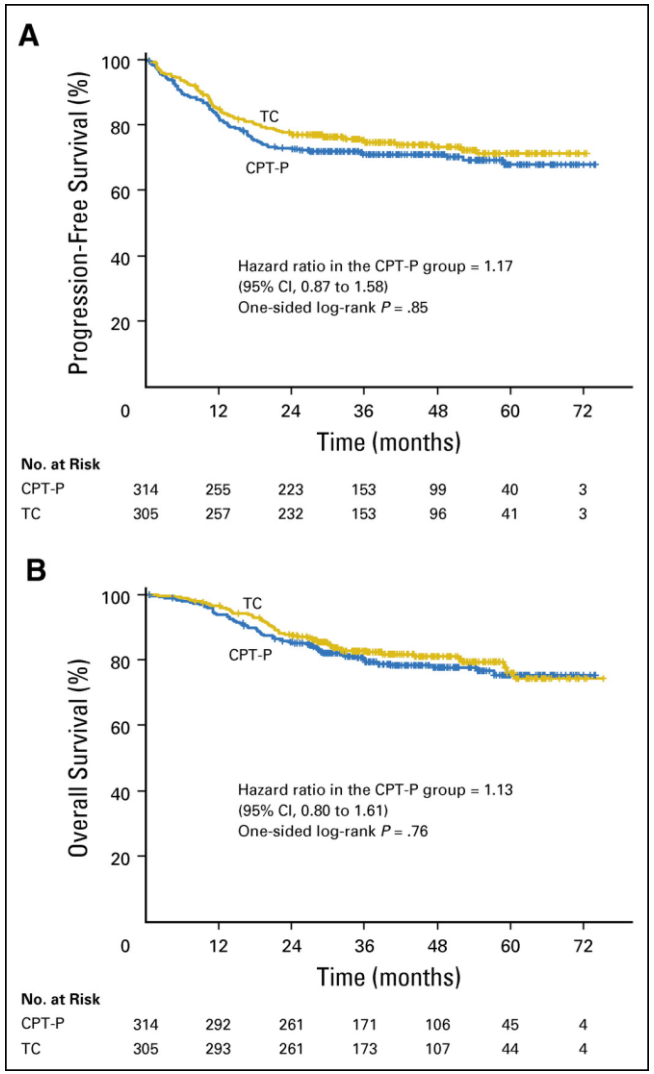
- **Studies dedicated to molecular alterations : BOUQUET**
  - Trastuzumab emtansine when HER2 amplification or mutation
  - Ipatasertib + paclitaxel when PI3KC or PTEN mutation

GENERAL CHARACTERISTICS OCCC

- Rare disease, 2nd most commun sub-type EC (5-11%) [1]
- More frequent in Asia (20%)
- Associated with endometriosis (20%) [2]
- More often localized 60% ≈[3]
- Worse prognosis when advanced[3]
- CT : carbopaltine paclitaxel

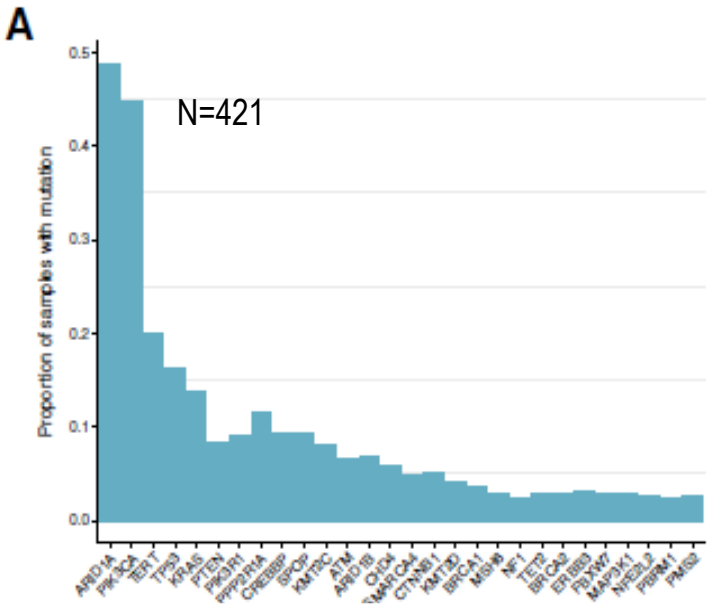


Ph III : cisplatin irinotecan vs carbo-taxol



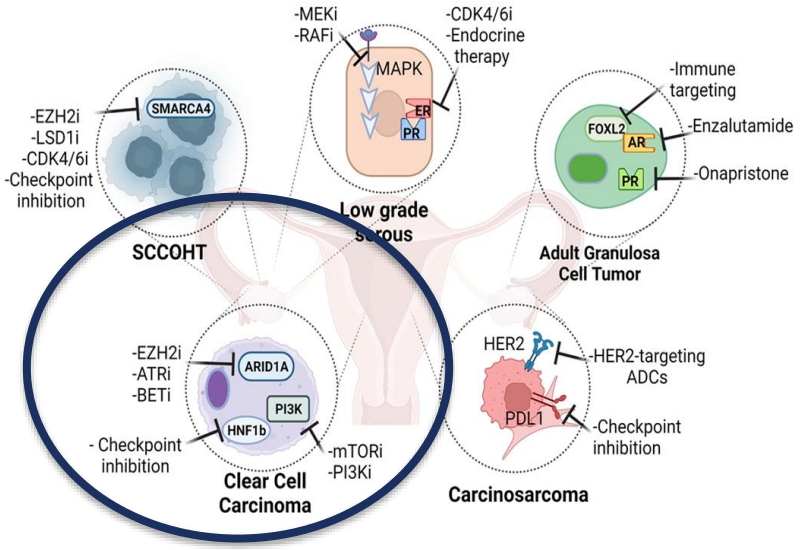
*1 del Carmen MG, Gynecol Oncol 2012; **2** Munksgaard PS, Gynecol Oncol 2012; 3 Shu C, Gynecol Oncol 2015; Suguiyama T JCO 2016*

MOLECULAR CHARACTERISTICS OCCC



Putative driver somatic mutation in 95% of the cases:

- ARID1A : 49%
- PIK3CA : 49%
- TERT : 20%
- TP 53 : 16%

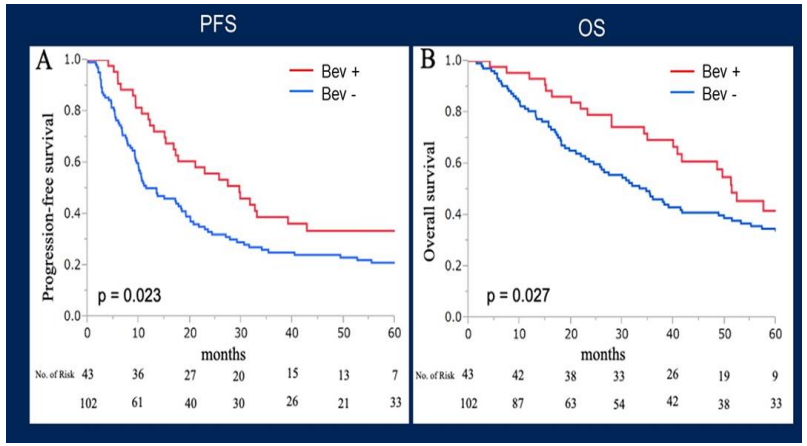


Tumor origin	Epithelial ovarian cancer	
Histology subtype	Clear cell ovarian cancer	
Molecular classification	*ARID1A*-mutated tumors	*TP53* mutations
Genome Transcriptome	Enriched expression of canonical CCOC, genes involved in metabolic pathways	Enriched expression of genes involved in extracellular matrix organization, mesenchymal differentiation, and immune-related pathways
Clinical presentation	Early stage at diagnosis Associated with endometriosis Poor response to platinum	Advanced-stage disease Aggressive pattern Poorer survival
Experimental approaches	Targeting SWI/SNF ARID1A and P13K	Targeting high genomic instability

Bolton et al Clin Cancer Res 2022; Bejar FG ASCO educational book 2022

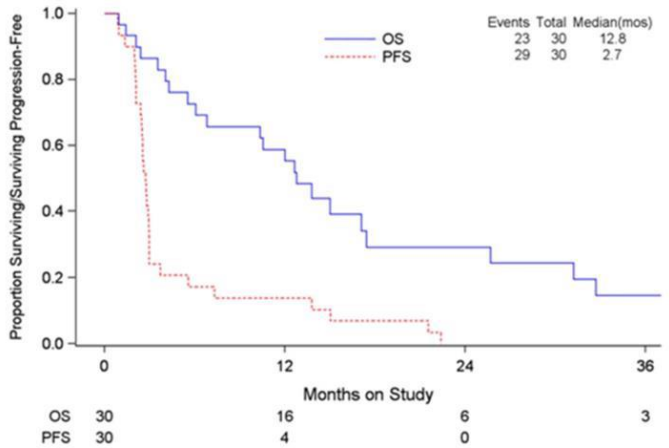
ANTIANGIOGENIC THERAPY AND OCCC

CT +/- Bevacizumab 1rst line
Retrospective analysis: before Bev approval n=102
vs after bev approval n = 43



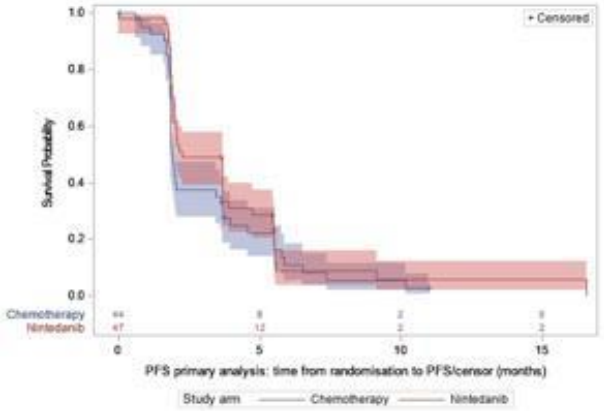
Toshiyuki S ASCO 2022

Sunitinib alone ph II R-OCCC
ORR: 2/30 (6.7%)
mPFS : 2.7 mo, mOS 12.8 mo



Chan Gynecol Oncol 2018

Nintedanib *vs* CT R-OCCC
R PhII, n=90
mPFS: 2.3 vs 1.9 mo

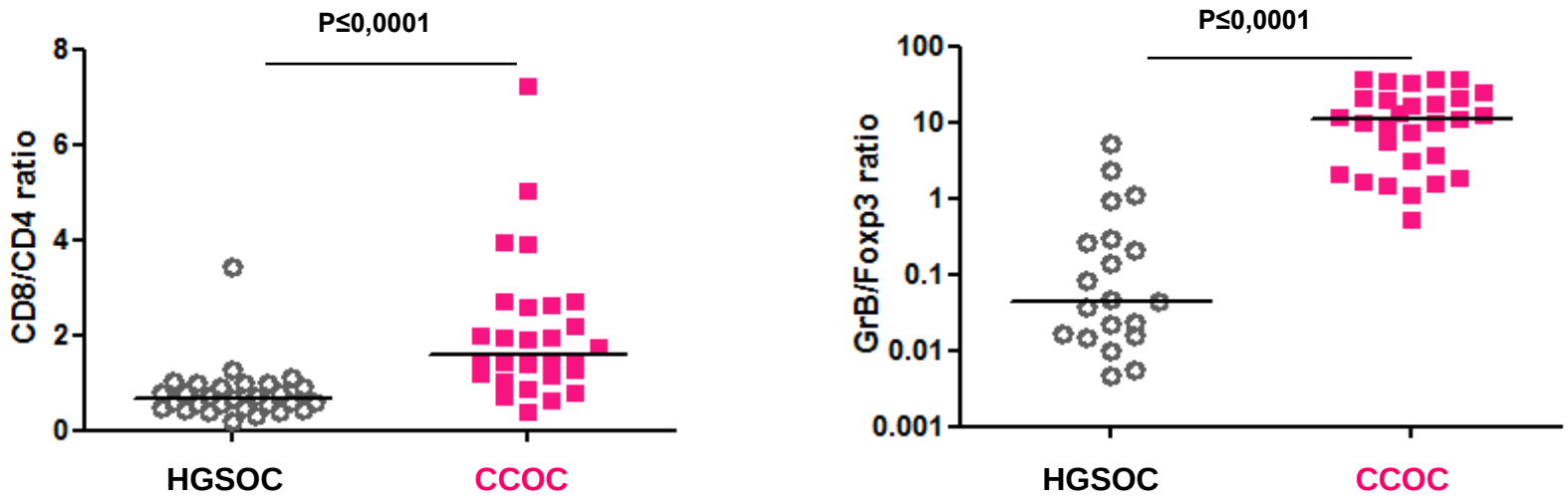


Glaspool R ESGO 2020, A 127

Questions
TKI versus Bevacizumab
1st line versus Relapse

IMMUNE MICROENVIRONMENT OF CLEAR CELL OC

Compared 30 CCOC to 30 HGSOC



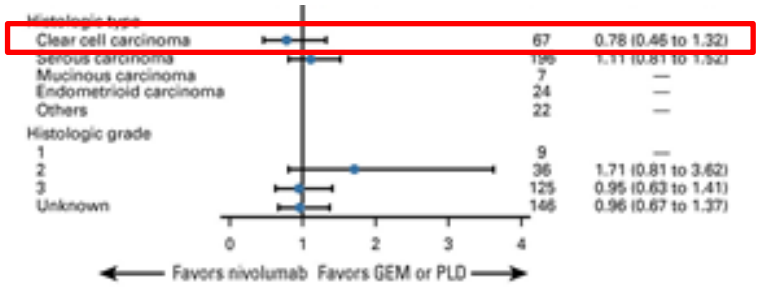
- The CD8/CD4 ratio was significantly higher in CCOCs (p≤0,0001).
- The ratio of GrB (marker of T cell cytotoxicity)/FOXP3 (suppressor Tregs) significantly higher.
- In favor of an anti-tumor immune response: good candidates for immunotherapies?

Genestie et al USCAP 2020

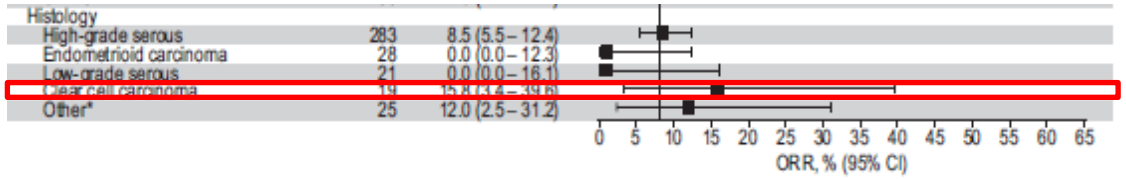
IMMUNE CHECKPOINT INHIBITORS IN OCCC

ALONE

Nivo: 20 pts 1 PR + 2CR (1OCCC) (ORR15%)[1]



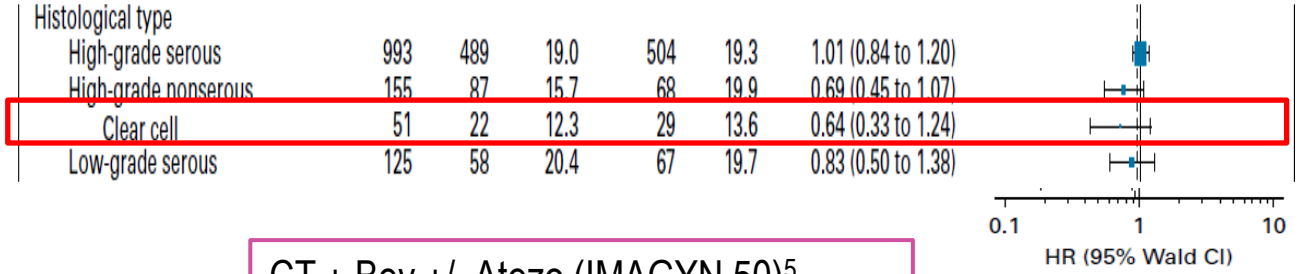
Nivo vs Gemcitabine (NINJA trial)[2]



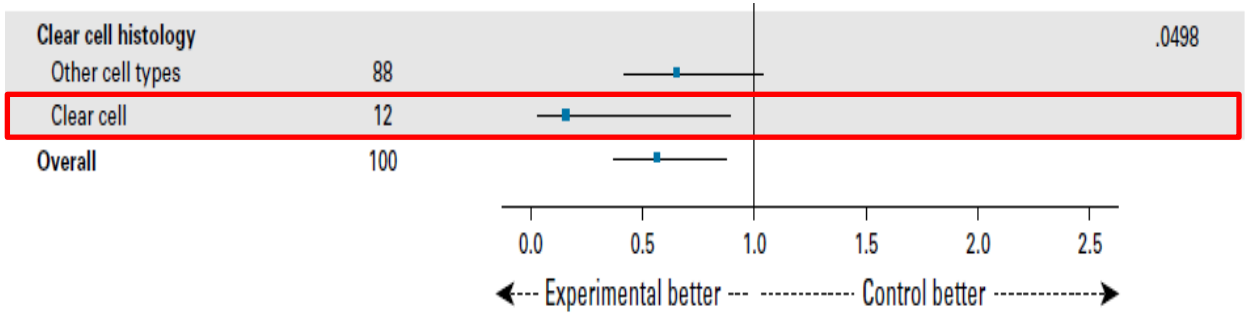
Pembrolizumab (Keynote 100)[3]

IN COMBINATION

Nivo + beva; 2 OCCC PS relapse : 1 SD + 1durable PR[4]



CT + Bev +/- Atezo (IMAGYN 50)[5]



Nivo +/- Ipi (12 OCC/100 pts) NRG trial[6]

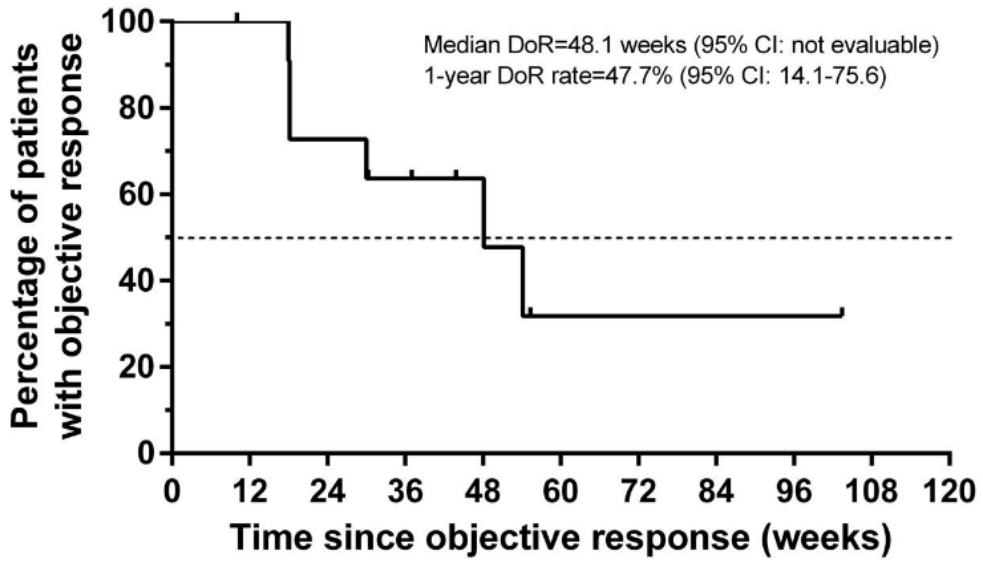
1: Hamanishi J, J Clin Oncol 2015; 2: Hamanishi J, J Clin Oncol 2021; 3: Matulonis U Ann Oncol 2019; 4: Liu JF, Jama Oncol 2019; 5: Moore K, J Clin Oncol 2021; 6: Zamarin D, J Clin Oncol 2020

DEDICATED IO STUDIES IN OCCC

PEACOCC: pembrolizumab in OCCC

N=48
TR=25%

DOR



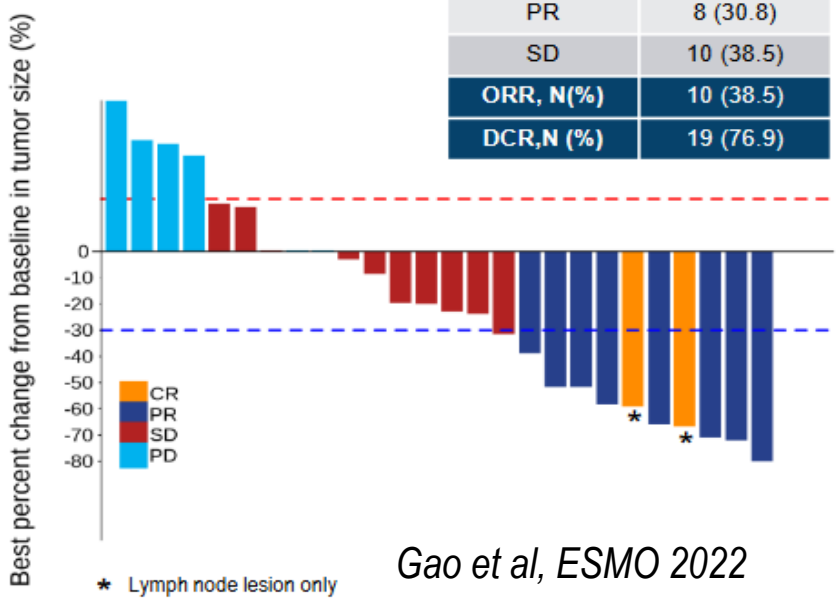
Kristeleit et al, ESMO 2022

INOVA: Sintilimab + Beva in OCCC

DOR= 12 mo

N=26
TR=38%

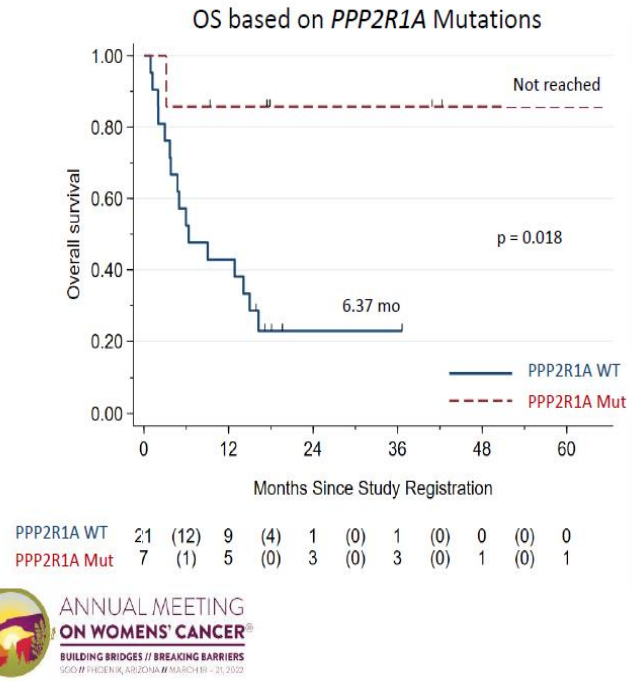
	N=26(%)
CR	2 (7.7)
PR	8 (30.8)
SD	10 (38.5)
ORR, N(%)	10 (38.5)
DCR,N (%)	19 (76.9)



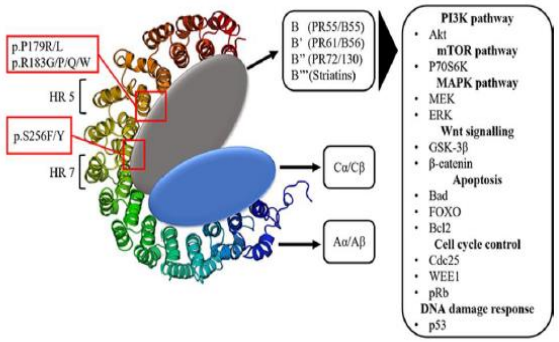
Gao et al, ESMO 2022

COMBINATION BUT FOR SOME OVARIAN CLEAR CELL SUBGROUP?
DURVALUMAB TREMELIMUMAB (NTC03026062) IN RESISTANT OVARIAN CANCER

PPP2R1A mutations associated with prolonged overall survival



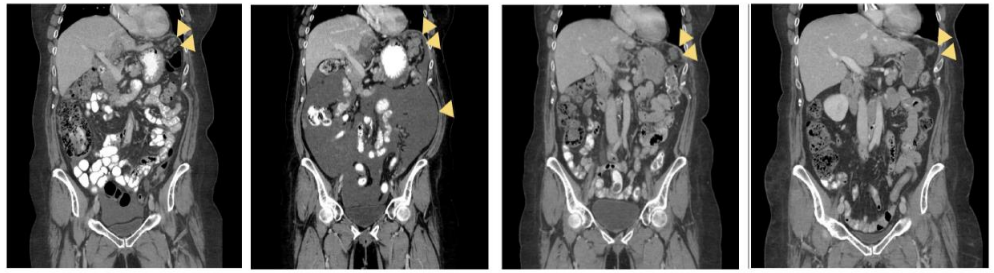
- Survival:
  - Median follow up 11.06 mo
  - Median OS: Not reached vs 6.37mo
- Scaffold subunit of protein phosphatase IIA



ANNUAL MEETING ON WOMENS' CANCER
BUILDING BRIDGES // BREAKING BARRIERS

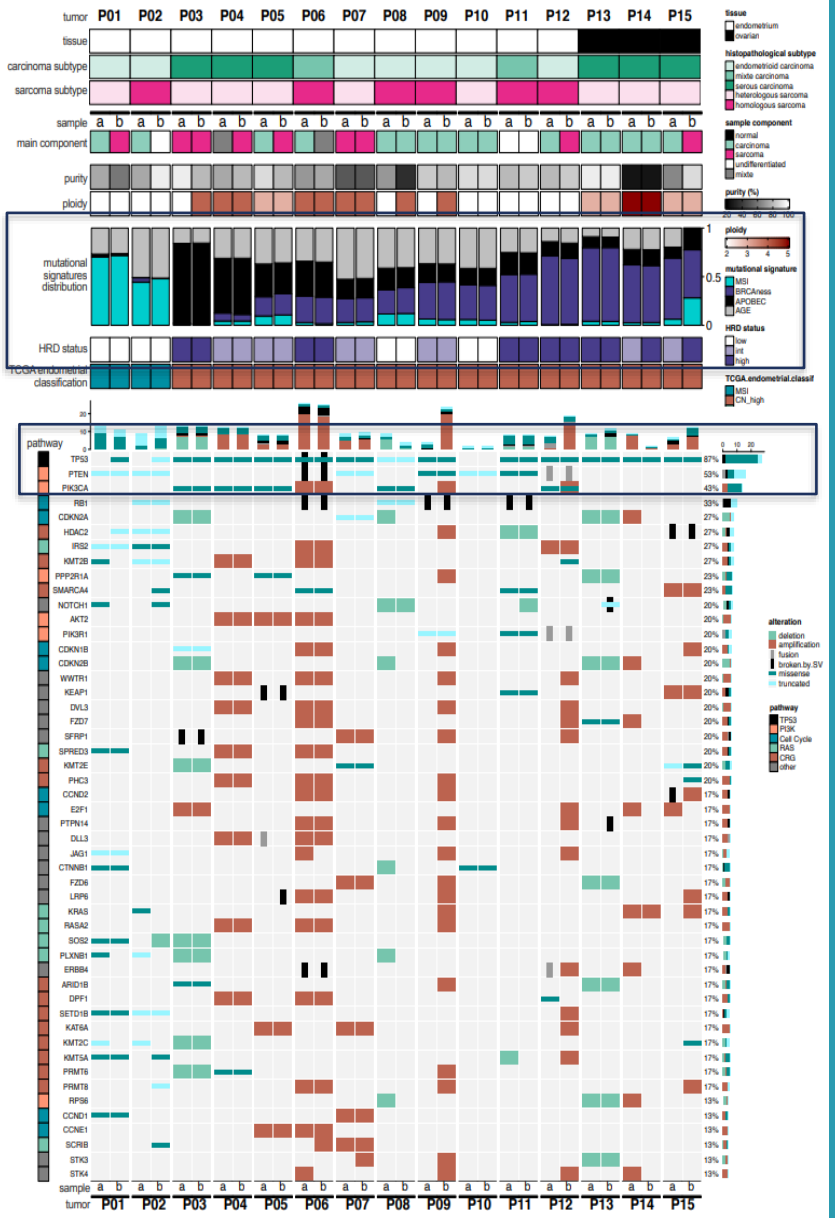
N = 28 patients
No correlation with ARIDA1 mutation or PDL1 expression
Large correlation with AE's G3 (71% vs 9%)
On going trial
MD Anderson sponsor - Amir Jazaeir

Survival benefit associated with delayed responses post-initial progression



CARCINOSARCOMA (OV & UT)
Disease context and current management

- Epithelial tumor < 5% & Elderly patients (median 65 y)
- High grade, advanced disease (75%) poor prognosis compared to HGSC
- P53 mutation (65%); HRD, PTEN; PI3K, HER2; ….
- **Specificities**
  - 1st line Standard chemotherapy Carboplatin paclitaxel disappointing
  - **2nd line CT monotherapy OR 16%, PFS 2-3 months, OS 7 months**
  - Most Recent data:
    - Pazopanib ORR 0% (n = 19 pts) (Gynecol Oncol. 2014)
    - Cabozantinib + Nivolumab ORR 10% (n = 10) (J Immunother Cancer. 2022)
    - Lenvatinib + Pembrolizumab:
      - 7 pts 0% ORR, 1SD, median PFS 2.3 months OS 2.6 months (Gynecol. Oncol. 2021)
      - 13 pts 20% ORR & 53% CB (Gynecol Oncol Rep. 2021)
    - PI3K inh (selective or not) 0% ORR (n = 5) - ENDOPIK GINECO study
    - HER2 (amplified 3+) TdXD ORR 54% (n = 34)
    - RUBY trial CP + Dostarlimab in 1st line
- **Questions**
  - Molecular characteristics— to overcome the EMT hypothesis ?
  - New options in relapse



A Puisieux,I Ray-coquard et al, Cancer Research 2023

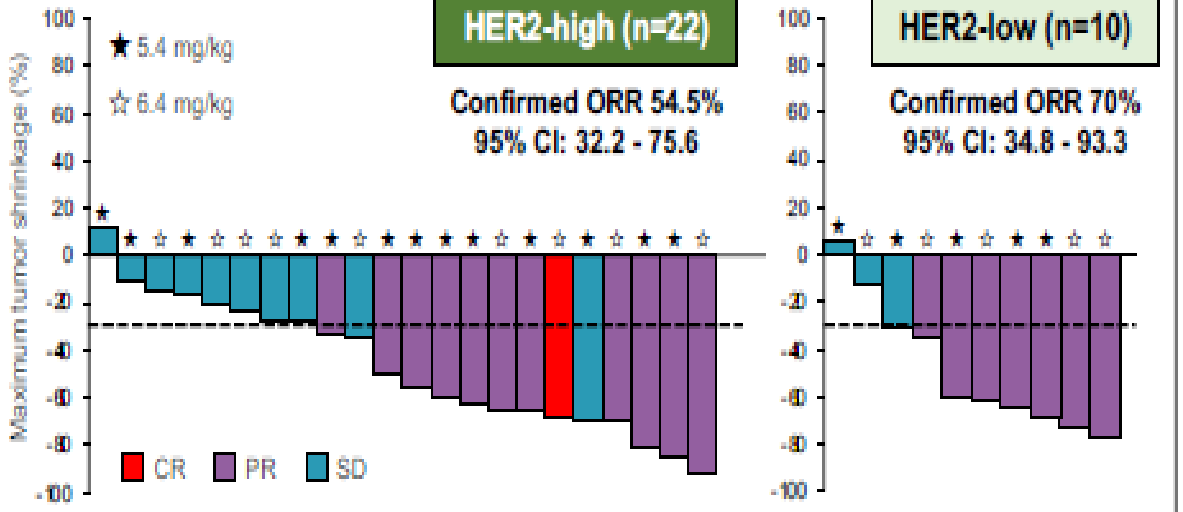
HER2 AMPLIFICATION AND CARCINOSARCOMA

STATICE trial (K Hasegara, SGO 2021)

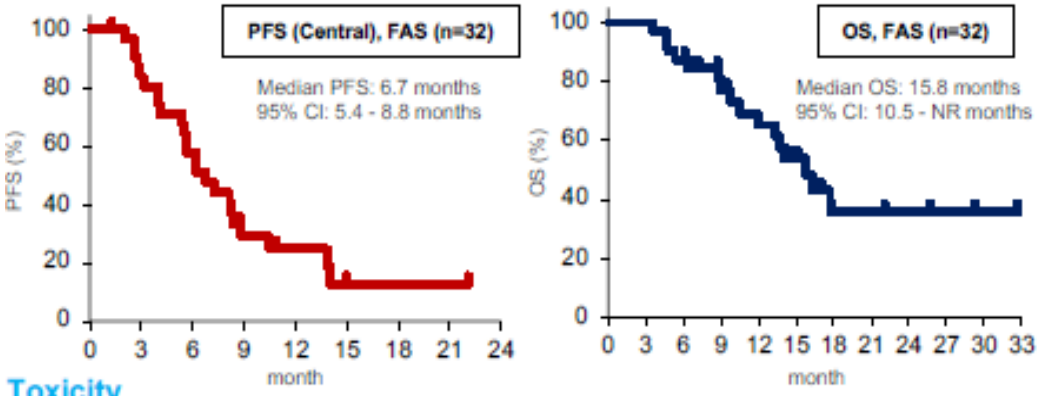
Efficacy and safety of trastuzumab deruxtecan in HER2-expressing uterine carcinosarcoma (STATICE TRIAL, NCCH1615): A MULTICENTER, PHASE 2 CLINICAL TRIAL

K. Hasegawa[1], T. Nishikawa[2], A. Hirakawa[3], M. Kawasaki[4], S. Tomatsuri[4], Y. Nagasaka[4], K. Nakamura[4], K. Matsumoto[5], M. Mori[6], Y. Hirashima[7], K. Takehara[8], K. Ariyoshi[9], T. Kato[10], S. Yagishita[11] A. Hamada[11], H. Yoshida[12], K. Yonemori[2]

Efficacy (Central review)



Confirmed Response Rate	CR (n, %)		PR (n, %)		SD (n, %)		PD (n, %)		ORR (%)
HER2-high (n=22)	1	(4.5)	11	(50)	10	(45.5)	0	(0)	54.5
HER2-low (n=10)	0	(0)	7	(70)	3	(30)	0	(0)	70



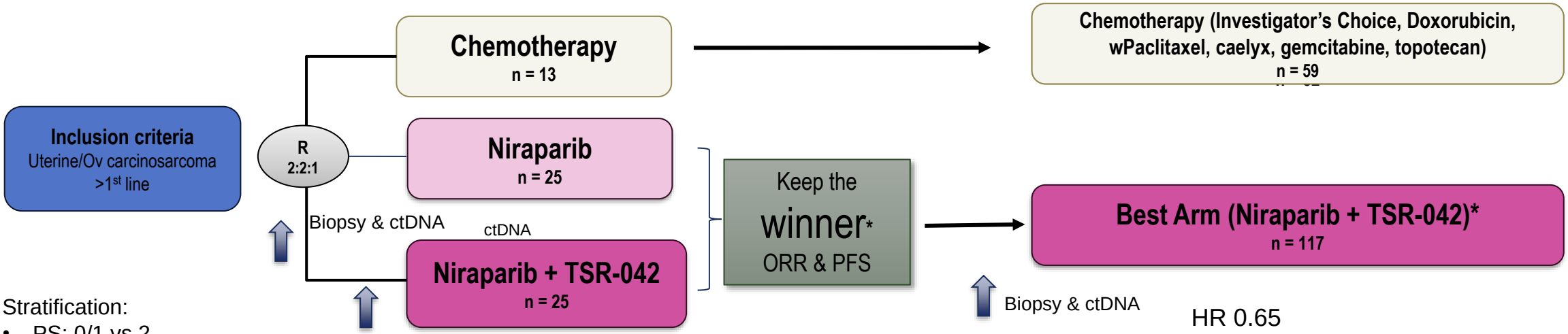
Toxicity

Adverse Event	Grade	SAS (n=33)	(%)
Any	3 - 4	20	(60.6)
Anemia	3 - 4	8	(24.2)
Neutropenia	3 - 4	9	(27.3)
Fatigue	3 - 4	2	(6.1)
Pneumonitis	1 2 3	4 4 1	(12.1) (12.1) (3.0)
Leading to drug withdrawal (permanent)		11	(33.3)

ROCSAN TRIAL - ROCSANBIO

Multicentric Randomized Phase II/III Study

ROCSAN (Recurrent Ovarian-Uterus CarcinoSarcoma Anti-PD 1 Niraparib)



Stratification:

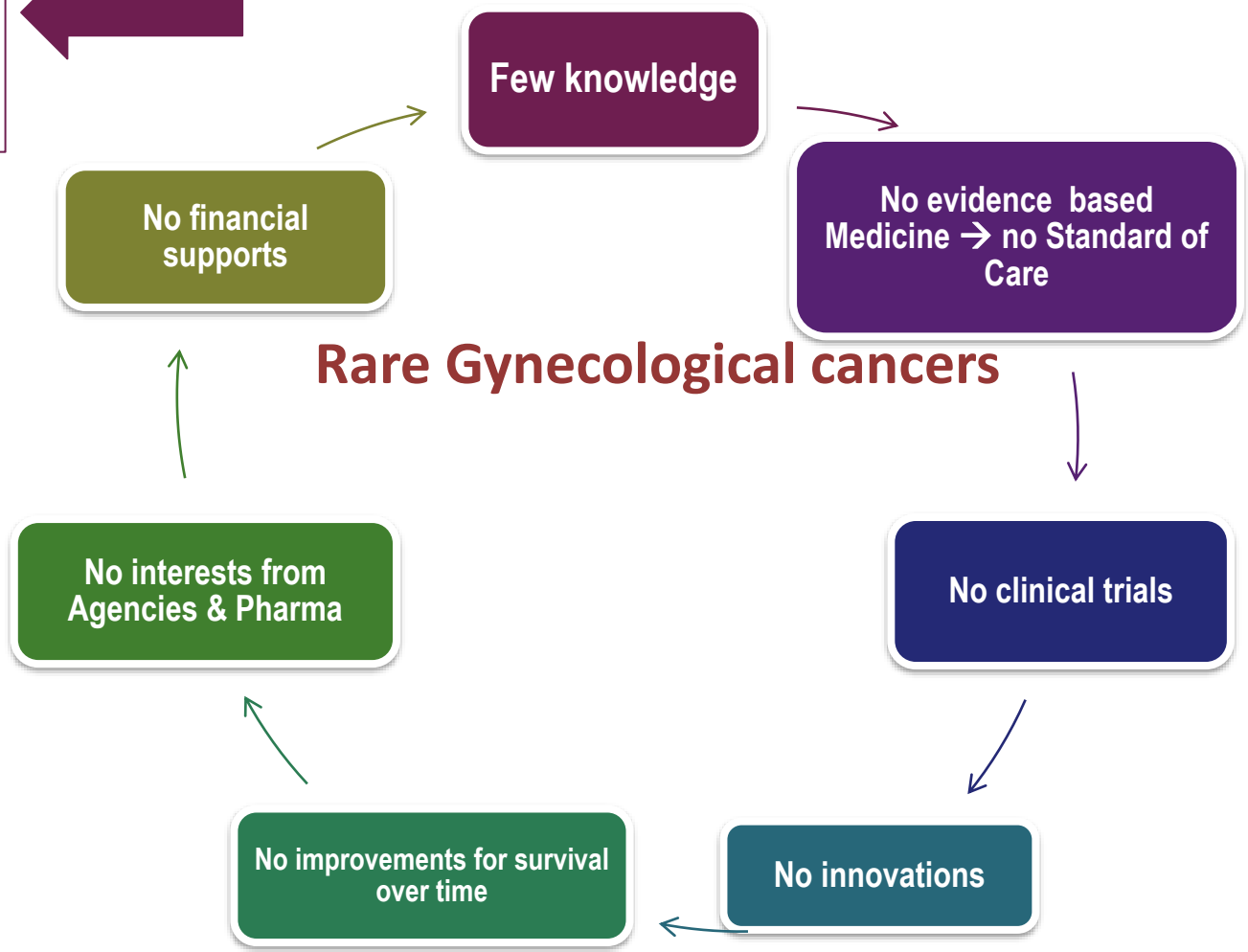
- PS: 0/1 vs 2
- Number of previous lines: 1 or > +
- Initial FIGO stage: I/II vs III/IV
- (Ov vs Ut)

HR 0.65
Median OS from 7 to 11 months

- Endometrial & Ovarian Carcinosarcoma
- Endpoints RR/PFS for 1st step, then OS, PFS, safety & translational
- Predictive markers (WGS, MultiIF & ctDNA) for efficacy and resistance

NEGATIVE SPIRAL FOR RARE CANCERS

2. Potential challenges to resolve & potential options to upgrade our competences



Most important challenges

For patients

- To identify the right diagnosis
- To define the prognosis
- To define the best “standard” of care
  - Radical surgery versus FSS
  - Adjuvant therapies “which one and for who”
  - The best option in relapse
- To follow sequelae and late toxicities including psychological aspects

For stakeholders and scientists

- Routine management and quality of care
- Develop regional and national networks
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- Clinical trials
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French TMRG network, Ann Oncol 2017

Rate of 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					28/355) (**8%**)
2013					40/445) (**9%**)
2014					61/658) (**9%**)
2015					70/784) (**10**%)
Total					**6/2601) (10%)**

1. Large heterogeneity between diagnosis
2. Between 10 to 20% major changes for medical decision
3. Concern all histologies

Henno et al 2022 : ovarian cases from 2018

Discordances minor : 114/937 (12,2%)
Discordances major : 209/937 (22,3%)

N Chiannilkulchai, Annals Oncol 2017
Henno S, Gynecol Oncol. 2022 Jun;165(3):637-641.

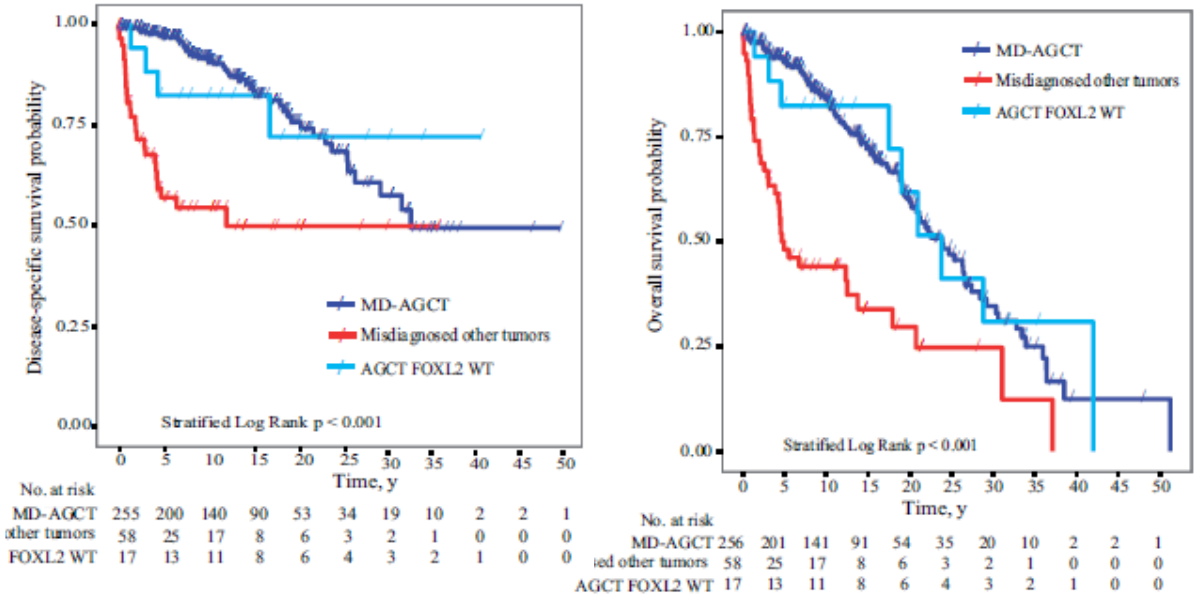
Molecular tools

Adult Granulosa cell tumor→ FOXL2 as molecular marker integrated within current guidelines

FOXL2 mutation (402C -> G) in the FOXL2 gene (Adult form Granulosa cell tumors) (Shah SP, NEJM 2009)

Utility of *FOXL2* immunostaining & mutation in all adult granulosa cell tumors but absent in other pure subtypes (D Maillet et al, 2013, McCluggage 2014, McConechy JNCI 2016)

More a diagnosis tool than a prognostic factor



M Mc Conechy, et al JNCI 2016

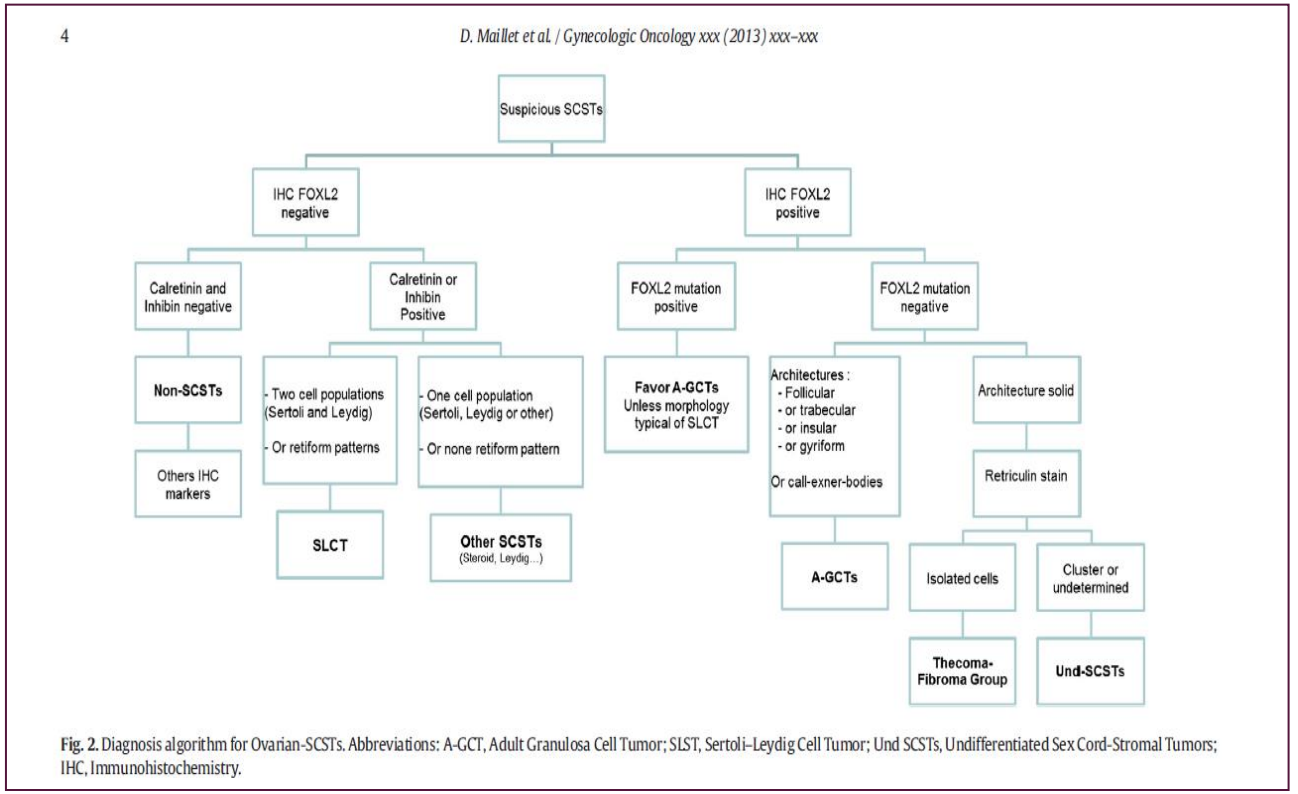


Fig. 2. Diagnosis algorithm for Ovarian-SCSTs. Abbreviations: A-GCT, Adult Granulosa Cell Tumor; SLST, Sertoli–Leydig Cell Tumor; Und SCSTs, Undifferentiated Sex Cord-Stromal Tumors; IHC, Immunohistochemistry.

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EXAMPLE OF OVARIAN GERM CELL TUMORS

How to select relevant candidate for chemotherapy?

5% of all ovarian malignancies

Usually in adolescents or young adults

60-70% FIGO STAGE I at diagnosis, despite very aggressive

Highly chemo-responsive and curable if properly treated

No randomized trials in OGCT, extrapolation from randomized trials in testis cancer

1. Data bases analyses from different groups

Ovarian germ cell tumors and need for CT in early stage (FIGO stage I)

- **Charing Cross** FIGO Stage IA series: 22% **dysgerminomas** and 36% of **non-dysgerminomas** relapsed. 10/11 cured with chemotherapy
- **COG** (0-16 yr: poor prognosis histologies) 12/25 relapsed and 11/12 were salvaged
- **MITO** 9 **IT** (gr1-3, Stage 1): 4/19 relapsed all salvaged in surveillance vs 2/9 in CT group
- **MaGIC IT** (98 ped vs 81 adult) PFS & OS ≈ but diff pop (1DOD vs 6 DOD)
- Barts **NHS**, CT reduced relapse rate in **DYs** (n = 37, CT 0% vs. no CT 20%), **YST** (n = 23, 26.3% vs.75%) and MGCT(n = 32, 40%vs.70%) **but not in IT (n = 42, 33% vs.15%)**. 25 stage I, 10 relapsed, all salvaged by CT
- **TMRG** (GINECO) (n= 257) Relapses YST 3/3 no CT vs 2/22 if adj CT,

  IT 3/15 no CT vs 1/24 if adj CT

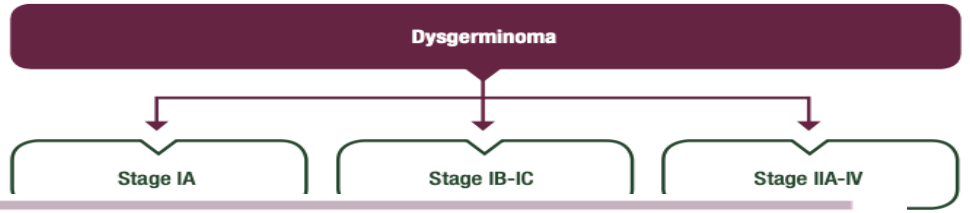
→ **No difference for OS (96,3 versus 97,8%)**

Billmire et al, JCO 2014, De La Motte Rouge, Ann Oncol 2018 & 2020, Derkin, et al Ann Oncol 2018, Mangili et al Gyn Oncol 2010, Pashankar & MaGIC coll Cancer 2016, C Newton EJC 2019),

2. Changing Guidelines: Management of early stage GCT

From the European level to international level

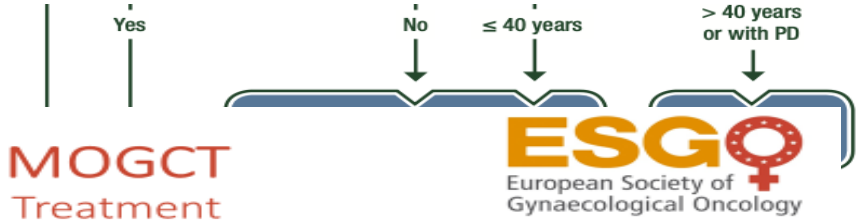
- 2017

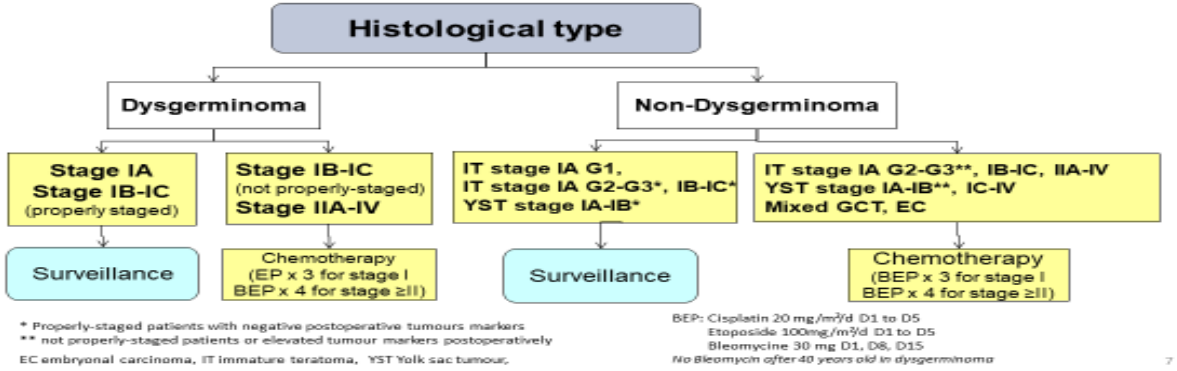


Non-epithelial ovarian cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

I. Ray-Coquard[1], P. Morice[2], D. Lorusso[3], J. Prat[4], A. Oaknin[5], P. Pautier[2] & N. Colombo[6], on behalf of the ESMO Guidelines Committee*

- 2019 ESGO GCIG collaboration





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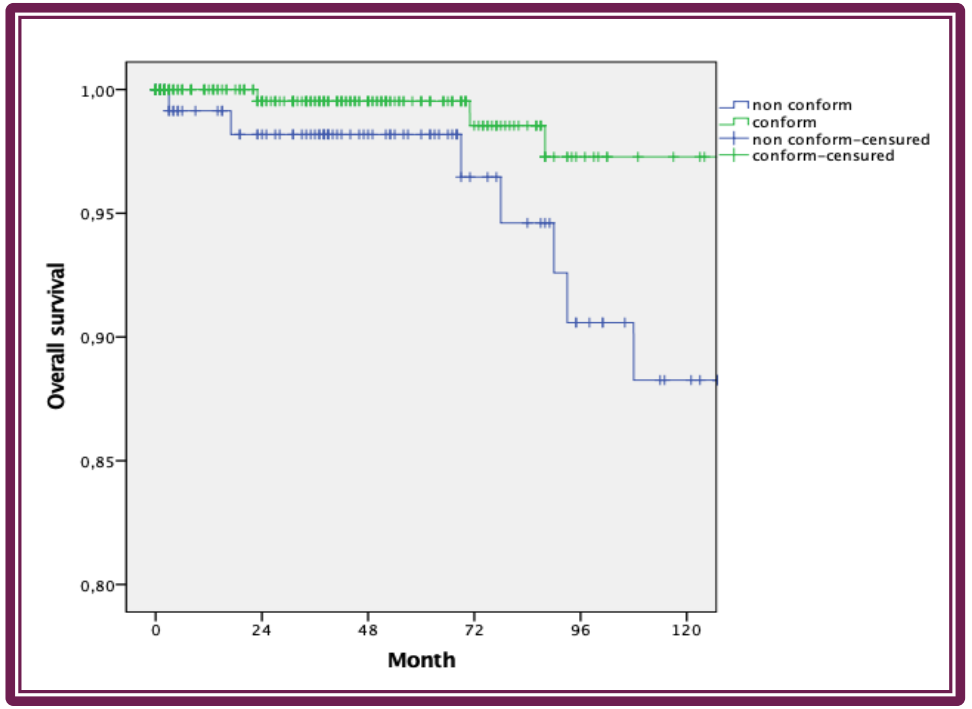
Retrospective analysis from prospective registries

How the conformity of surgical practice with the national guidelines improved the quality of management of ovarian Granulosa cell tumors (GCT)

463 patients		BEFORE 2012	AFTER 2012	
SURGICAL CONFORMITY	Total	13 (6.9%)	52 (23%)	P < 0.001
	Partial	103 (54.8%)	109 (48.2%)	
	Non conformed	72 (38.3%)	65 (28.8%)	



- Statistically significant improvement in the surgical management with this network organisation
  - increased endometrial evaluation (p=0,026)
  - lower per operative tumor rupture rates (p=0,010)
  - better global compliance of the surgery to guidelines (p<0,001)

Celine Lenck, et al, Gyn Oncol 2020

CENTRES EXPERTS TMRG
TUMEURS MALIGNES RARES GYNÉCOLOGIQUES
ARCAGY - GINECO

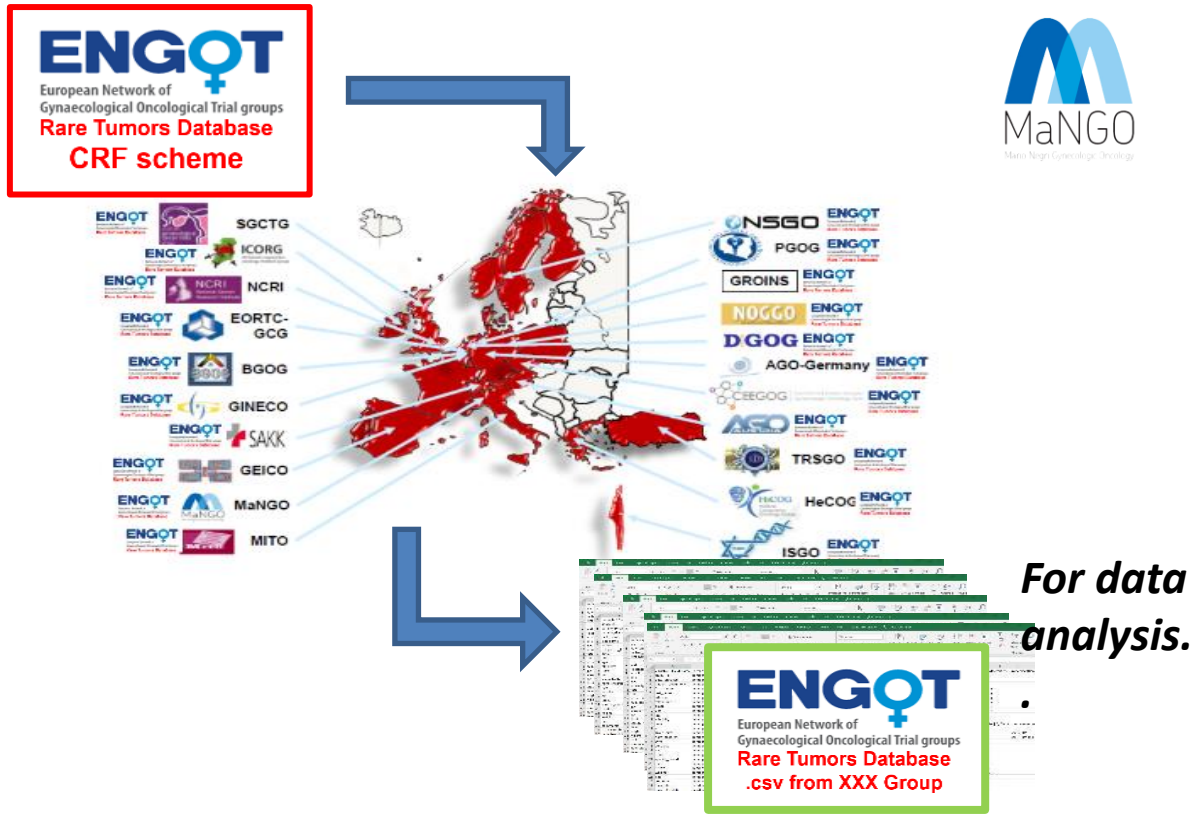
Rare Cancers in Gynecologic Oncology, ENGOT initiative for a European Registry

L. CEPPI[1], A. BERGAMINI[2], E.BIAGIOLI[3], O.SELHEIM[4], A. GONZALEZ-MARTIN[5], N. OTTEVANGER[6], E. VAN NIEUWENHUYSEN[7], A. HASENBURG[8], K.CADOO[9], E.BRAICU[10], M.HALL[11], D.BAUSERSCHLAG[12], S.AUST[13], R.GLASSPOOL[14], C.LOK[15], J.KORACH[16], D.CIBULA[17], S.PIGNATA[18], I.RAY-COQUARD[19] on behalf of ENGOT Rare Tumors Group.

[1]Obstetrics and Gynecology, Grande Ospedale Metropolitano Niguarda, MaNGO, Milan, Italy; [2]San Raffaele Hospital, MITO, Milan, Italy; [3]Mario Negri Institute, MaNGO, Milan, Italy; [4]Department of gynecological oncology, Norwegian Radiumhospital, Oslo University Hospital, NSGO, Oslo, Norway; [5]Clinica Universidad de Navarra, GEICO, Madrid, Spain; [6]EORTC Gynaecological Cancer Group, Netherlands; [7]Gynaecologic Oncology, BGOG, Leuven, Belgium; [8]Clinic for Women's Health, Department of Gynecology and Obstetrics, Medical Center Johannes Gutenberg University, AGO, Mainz, Germany; [9]St. James's Hospital Dublin, Trinity St. James's Cancer Institute, Cancer Trials Ireland, Dublin, Ireland; 10Charité Universitätsmedizin Berlin, Berlin, NOGGO, Germany; [11]East and North hertfordshire NHS TRUST, NCRI, Northwood, United Kingdom; [12]University Medical Center Schleswig-Holstein, AGO, Kiel, Germany; [13]Medical University of Vienna, Department of Obstetrics and Gynecology, Comprehensive Cancer Center, A-AGO, Vien, Austria; [14]Beatson West of Scotland Cancer Centre and Institute of Cancer Sciences, University of Glasgow, SGCTG, Glasgow, United Kingdom; [15]Department of gynecological oncology The Netherlands Cancer Institute, Antoni van Leeuwenhoek hospital, DGOG, Amsterdam, Netherlands; [16]Sheba Medical Center, Sackler School of Medicine, ISGO, Tel Aviv, Israel; [17]Department of Obstetrics and Gynecology, General University Hospital in Prague, First Faculty of Medicine, Charles University, CEEGOG, Prague, Czech Republic; [18]Department of Urology and Gynecology, Istituto Nazionale Tumori IRCCS Fondazione Pascale, MITO, Naples, Italy; [19]Centre Leon Bérard, Laboratoire RESHAPE UI 290, Université Claude Bernard, GINECO, Lyon, France

* Survey results (n = 18 groups) **Sept. 2021**

- Many groups have scattered databases on rare tumors both retrospective and prospective, not all active and enrolling patients;
- Lack of manpower in database adoption/organization
- Lack of financial support



2, Meta analysis on SCT (MITO and GINECO involved other groups coming soon)

- One project dedicated to surgical question:
- Peritoneal staging as prognostic factor

(MITO/GINECO) working on

  - Alice Bergamini working on contract between to share the database from GINECO/CLB with MITO
  - 1st merging data set was done IN December, Stat on going !

- Next steps
  - Publication or presentation of the 1st step: 558 cases adult granulosa cancer
  - Several groups have mentioned to be interested to be part (MaNGO, CEEGOG, NSGO, ISGO, SCTGC, BGOG, DGOG)
- Issues: Contract and GDPR issues, Necessity to work on site.

ENGOT
European Network of Gynaecological Oncological Trial groups

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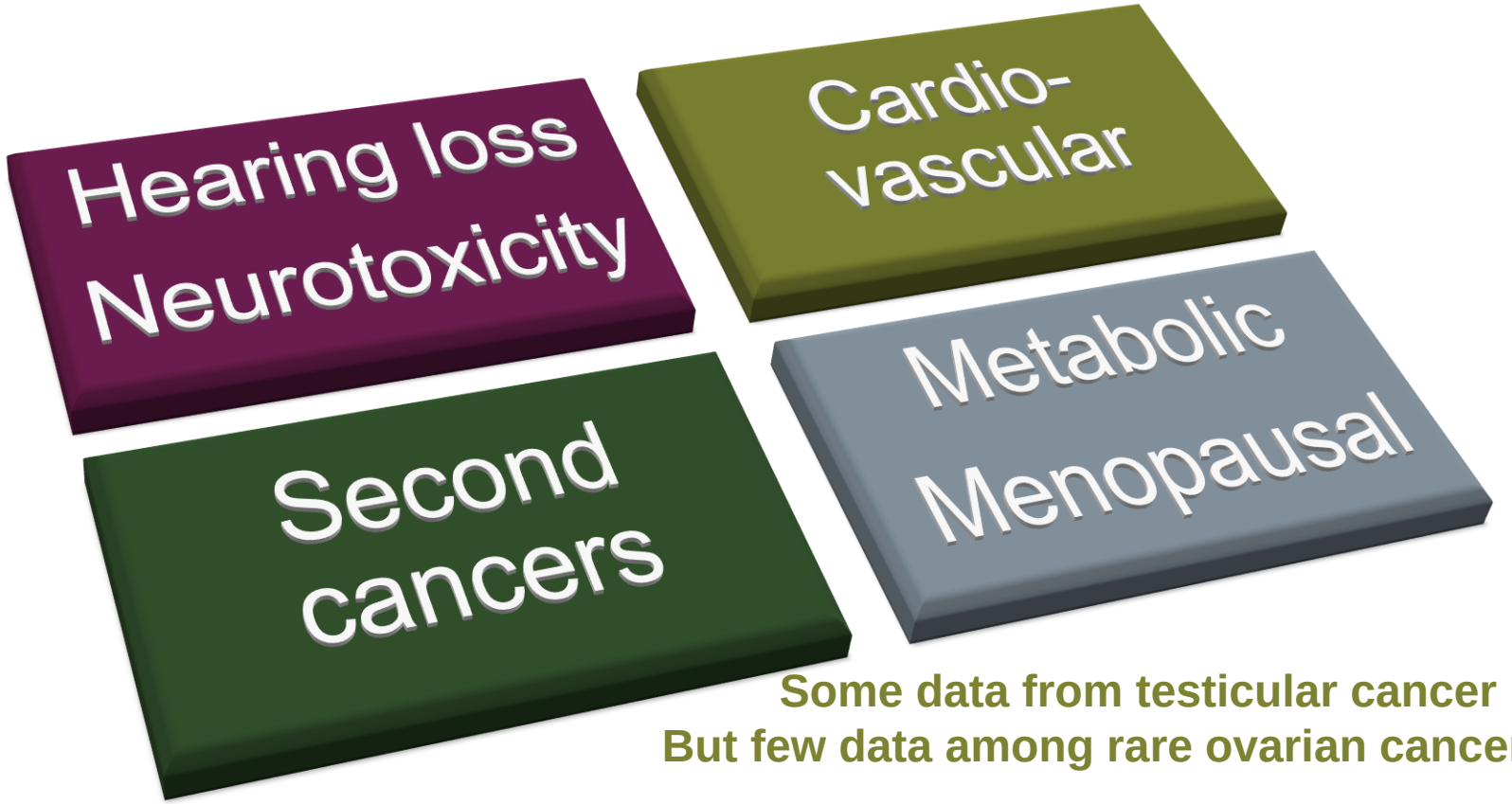
Long term toxicities among women treated with Chemotherapy for GCT/SCT



Some data from testicular cancer pts
But few data among rare ovarian cancer women

VIVROVAIRE STUDY RARE TUMORS

VIVROVAIRE TR study:

The French Rare Malignant Gynecological Tumors (TMRG)/GINECO case-control VIVROVAIRE Rare Tumors study assessed **Chronic fatigue**, **QoL** and **long-term side-effects**

of CT among GCT and SCST survivors treated with BEP, as compared to age-matched healthy women (controls)

⇒ **Group of interest: 144** GCTS & SCST **≥ 2 years after treatment** with surgery & **chemotherapy** (identified from the INCa French Network for TMRG)

⇒ **Healthy CONTROL group: 144** women without cancer age-matched to patients (± 2 years) issued from the 'Seintinelles' research platform

Self-administered questionnaires

- ✓ Fatigue (MFI-20[1])
- ✓ Quality of life (FACT-G[2]/FACT-O[3])
- ✓ Neurotoxicity (FACT/GOG-NTX[4])
- ✓ Cognition (FACT-Cog[5])
- ✓ Day to day life (Living condition questionnaire)
- ✓ Anxiety /Depression (HADS[6])
- ✓ Insomnia (ISI[7])

6 years after BEP chemotherapy:

- **Similar fatigue, global quality of life** between survivors and controls
- However, **more cognitive complaints & neuropathy** in survivors vs controls
- Higher risk of **premature menopause**
- Negative **impact on sexual health**
- More interference of health conditions in daily life among survivors than controls

Survival care plan with long term follow-up should be proposed to patients to **anticipate these long term effects.**

Most important challenges

For patients

- To identify the right diagnosis
- To define the prognosis
- To define the best “standard” of care
  - Radical surgery versus FSS
  - Adjuvant therapies “which one and for who”
  - The best option in relapse
- To follow sequelae and late toxicities including psychological aspects

For stakeholders and scientists

- Routine management and quality of care
- Develop regional and national networks
- National databases
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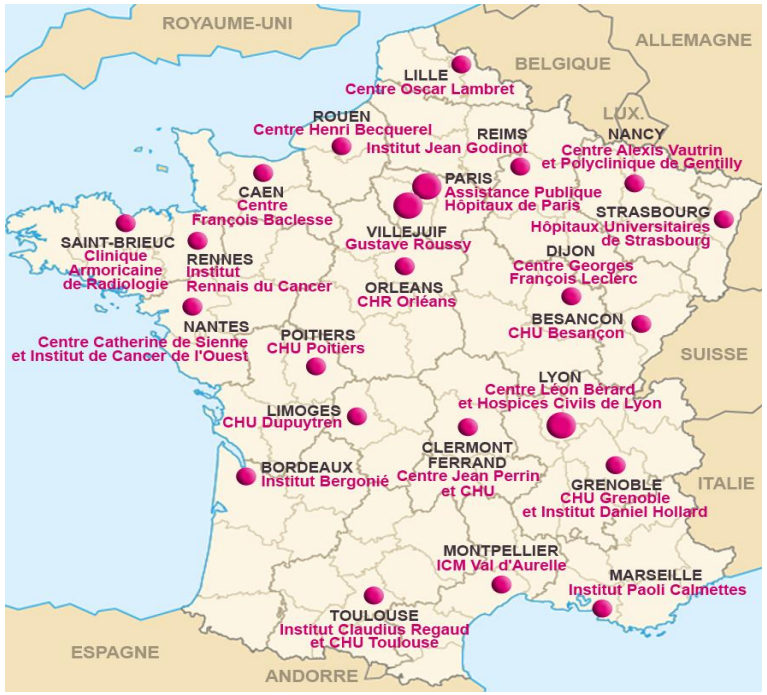
- To organize national management

ALIENOR IS THE FIRST INTERNATIONAL MULTICENTRIC PROSPECTIVE RANDOMIZED TRIAL ACHIEVED IN SCTS



The French National Network dedicated to Rare gynecologic Malignant Tumors (www.ovaire-rare.org)

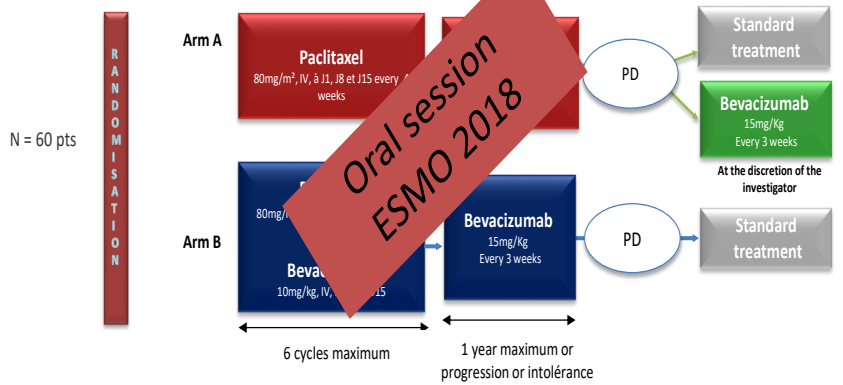
GYNECOLOGIC CANCER INTERGROUP

An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

Make it possible !

Rare Tumor committee engagement
Executive Commitee support
Annual satellite meetings

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



Ray-Coquard, JAMA Oncol 2020

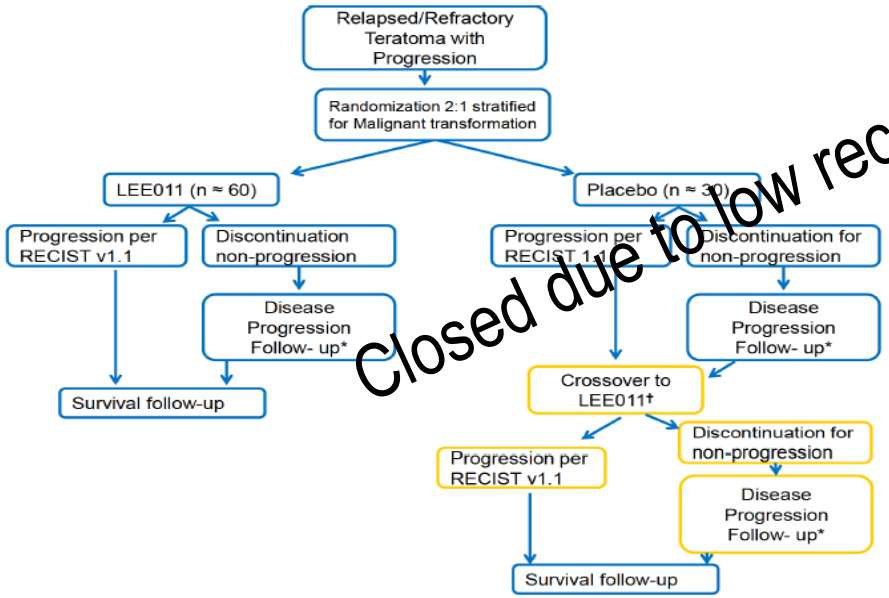
Other example without international and/or national network

Innovative targeted therapy for Germ cell tumors

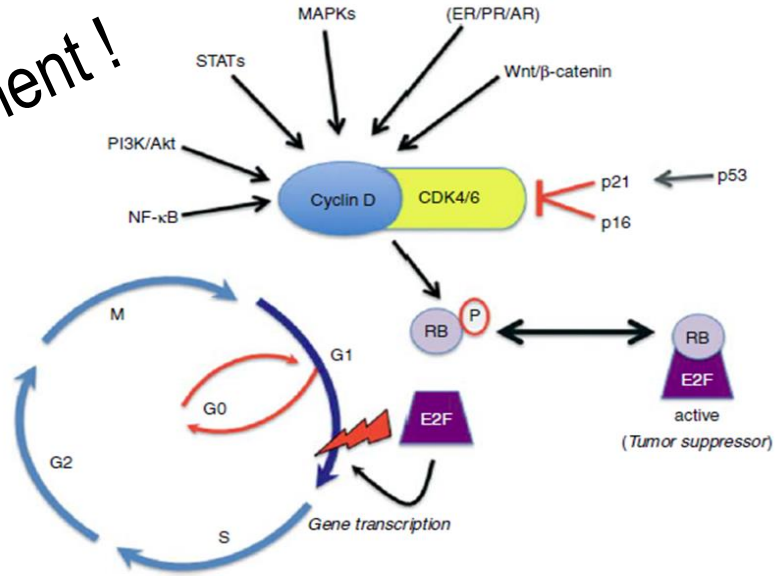
Ribociclib (Novartis), CDK4/6 inh (pRb & cell cycle)
CDK4 & CyclinD2 upregulated GCT

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 !



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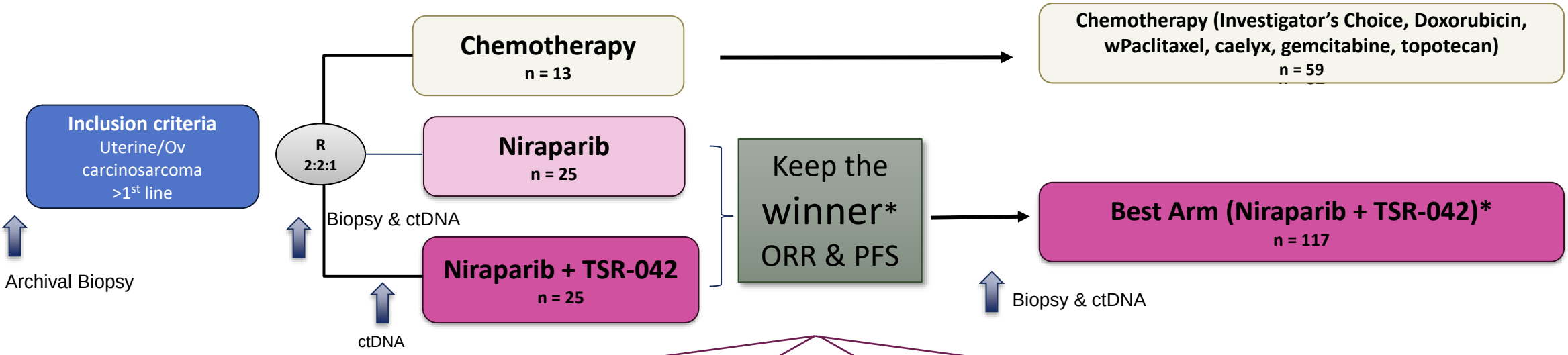
Adding large translational research program to Large Phase III trial dedicated to carcinosarcoma

ROCSAN trial is an academic sponsored trial



WP1: Predict response to PARPi/anti-PD1 therapy – Tumoral biomarkers

→ Tumor samples
- Immune system
- EMT score
- DNA mutations and genomic instability
- Tumor mutation load and neo-epitopes specific T cells

→ Multi-IF, RNAseq, sWGS, targeted seq, WES

WP2: Predict response to PARPi/anti-PD1 – Blood biomarkers

→ Blood samples
- ctDNA mutations
- Immune system
- T cell response to neo-epitopes

→ Flow cytometry and sequencing

WP3: Resistance biomarkers and new targets

→ Tumor samples
- Gene mutations
- EMT score, markers, transcription factors
- Immune system

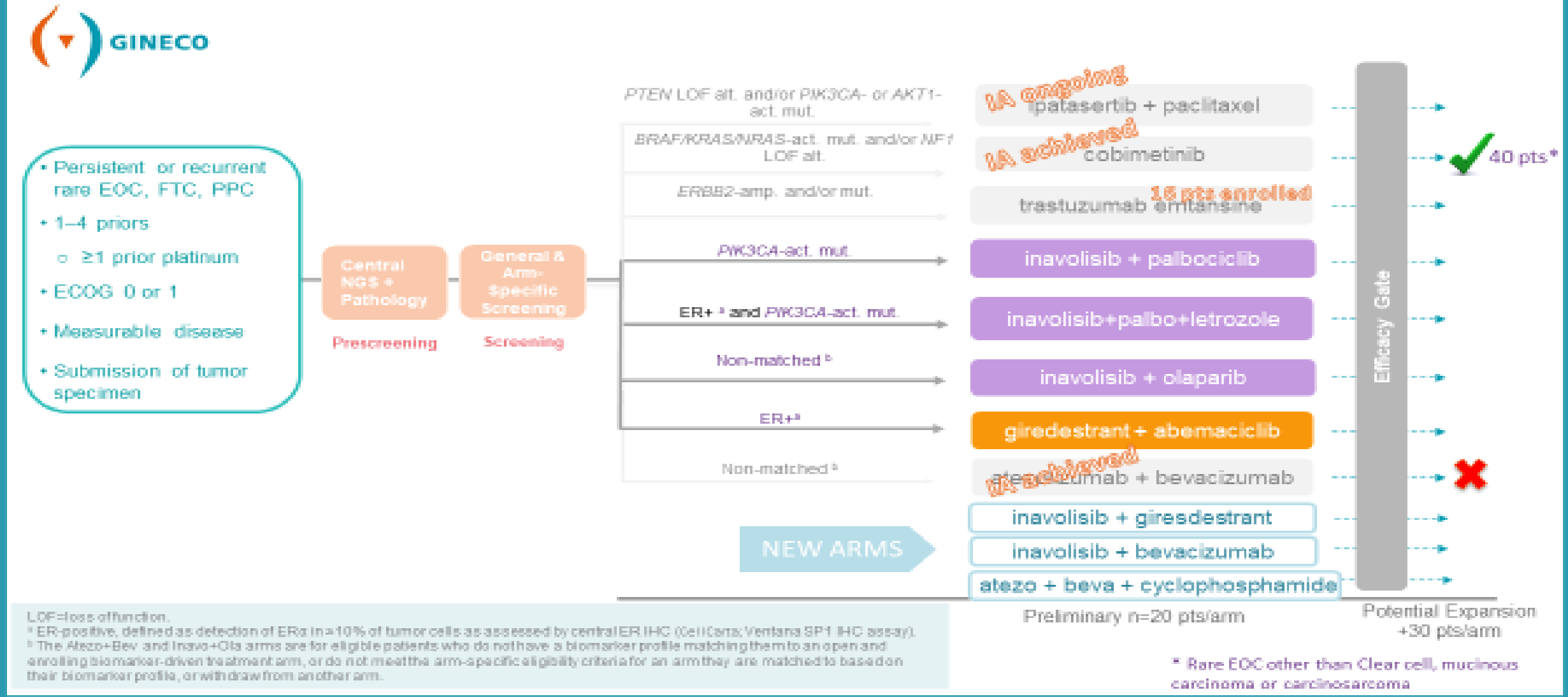
→ Multi-IF, flow cytometry, WES, RNAseq

WP4: Evaluation of patient's QOL

→ Patients questionnaires
- Effect of the therapy on patient's life and disease
- Analysis of anxiety, depression, toxicity

Molecular driven clinical trial si feasible for rare tumors ?

BOUQUET trial exists but need Pharma Sponsor to be at the world wide level



REVIEW ARTICLE

Gynecologic Cancer InterGroup (GCIG) Consensus Review for Carcinoid Tumors of the Ovary

*Eva Gomez-Garcia, MD,† Dolores Gallardo-Rincon, MD,‡ Michael Friedlander, MBChB, FRACP, PhD,¶ Jae-Weon Kim, MD,** Domenica Lorusso, MD,†† and Isabelle Ray-Coquard, MD, PhD§§*

ine tumors (NETs) are a heterogeneous group of neoplasms most the gastrointestinal tract or the lungs. More frequent are gastro- er the past 30 years, there have been a number of small series or ovarian NETs. Neuroendocrine tumors in the gynecologic tract are t for about 2% of all gynecologic malignancies but may also be es. They require a multimodality therapeutic approach determined and the primary organ of involvement. Pathological diagnosis is Surgery is the cornerstone of treatment for localized disease. There velopments for treatment of advanced NETs including somatostatin embolization, chemotherapy, interferons, mammalian target of d radiolabeled somatostatin analogs. Given the rarity and lack of y nature more of a guidance and recommendation for management il we can mount international studies.

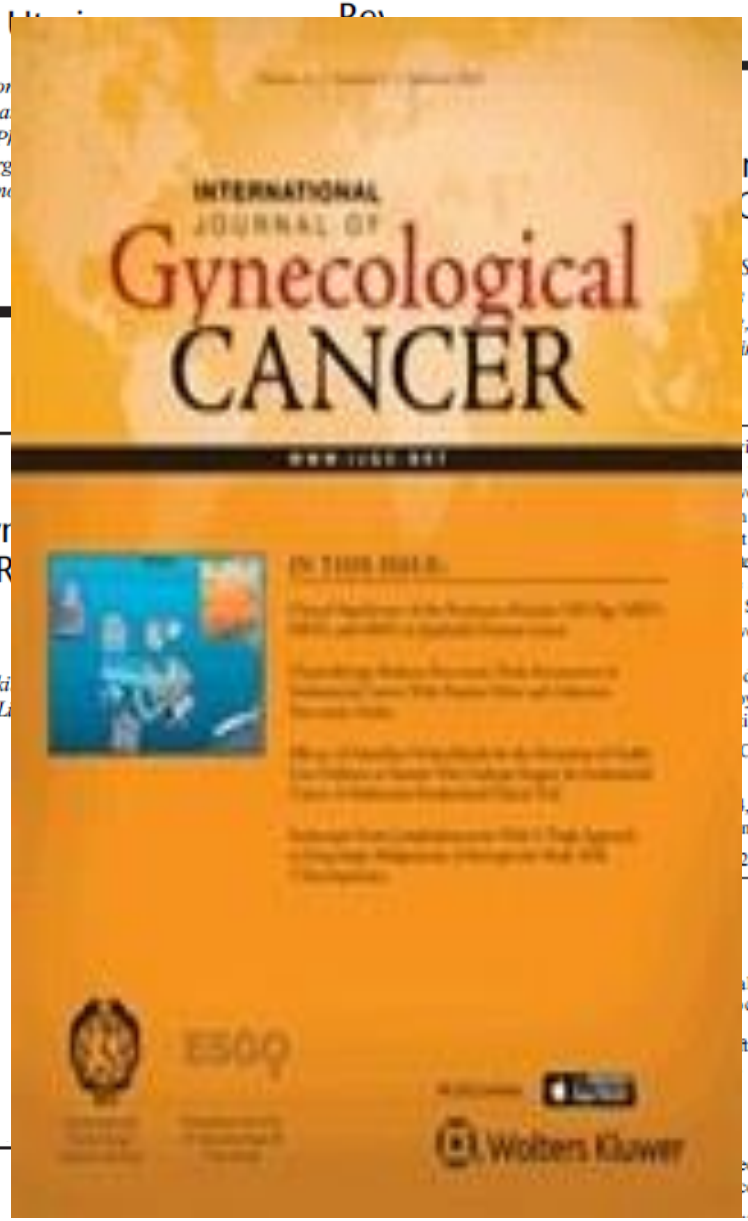
Carcinoid, Neuroendocrine, Somatostatin analogs

, and in revised form August 10, 2014.
n August 12, 2014.
2014;24: S35–S41)

- It is important to exclude a primary NET cancer from another site causing metastasis to the ovary; these are more usually bilateral.
- Most ovarian carcinoids are in the early stage and are usually curable with surgery alone.
- Somatostatin analogs are prescribed for patients with carcinoid syndrome; streptozocin-based regimens offer the best conventional chemotherapy approach. Mammalian target of rapamycin (mTOR) pathways inhibitors are showing

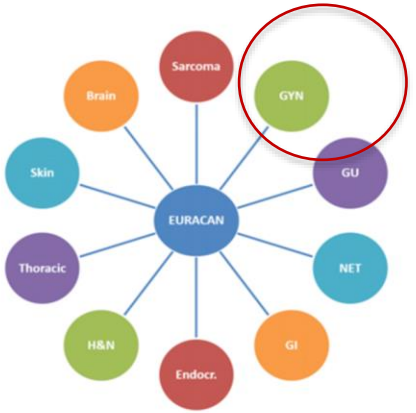
ll ovarian cancers.
ccur in perimeno-
ten combined with

ceived April 22, 2014, and in revised form July 23, 2014.
cepted for publication July 27, 2014.



European multi-disciplinary tumour boards support cross-border networking and increase treatment options for patients with rare tumours

- **European Reference Networks ERN**
  - 24 virtual networks across Europe launched 2017
  - Discussions on rare or complex diseases



EURACAN

European network for Rare adult solid Cancer

- **EURACAN**
  - ERN for rare adult solid tumours
  - Coordinated by the French Comprehensive Cancer Centre Léon Bérard in Lyon, France
  - **Virtual MDTs initiated for clinical management of patients with rare gynaecological tumours**

BENEFICE FOR PATIENTS?

EURCAN MTD (2017-2020) cases were monthly discussed (n = 91) ESGO 2021

1. Modification of the medical decision: 22% received surveillance and not adjuvant CT and 17% access to off label therapies
2. Examples:
3. Recommendation for diagnosis and management
   - 22-year old woman with low persisting levels of hCG
   - Extensive investigation with no findings, plan to start chemotherapy for GTN
   - Recommendation for further investigation, diagnosis of ovarian dysgerminoma successfully removed
4. Off-label treatment
   - 30-year old woman with relapsing GTN
   - Primary treatment of post-molar GTN with 3 lines of chemotherapy to CR
   - First relapse: multi-agent chemotherapy and hysterectomy
   - Second relapse: thoracic wedge resection followed by Pembrolizumab x10
   - One year later radiological and biochemical CR

Most important challenges

For patients

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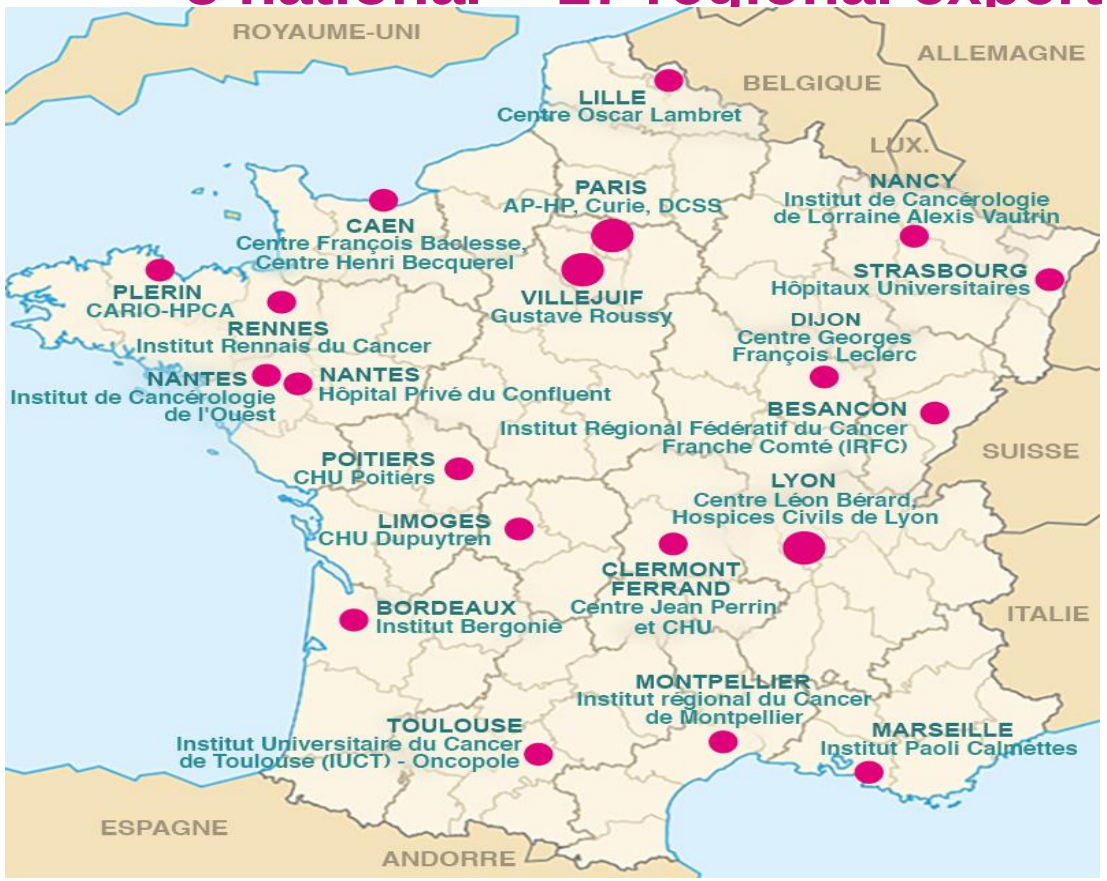
CENTRES EXPERTS TMRG
TUMEURS MALIGNES RARES GYNÉCOLOGIQUES

FRENCH MODEL -

National Network including 3 national + 17 regional expert



Start in 2011

Qualification since 2014 by INSTITUT NATIONAL DU CANCER

➢Management :

- Medical strategy decided in **dedicated Regional multidisciplinary tumor board (MTB)**
- **National MTB for more complex cases**

➢Diagnosis:

- **systematic double reading**
- molecular diagnosis for all patients (eg FOXL2, SMARCA4, DICER1….)

➢Education:

- workshops & continuing medical education.
- information for patients, families and advocacy groups.
- To elaborate & to diffuse Guidelines

➢Research

- clinical, fundamental & translational

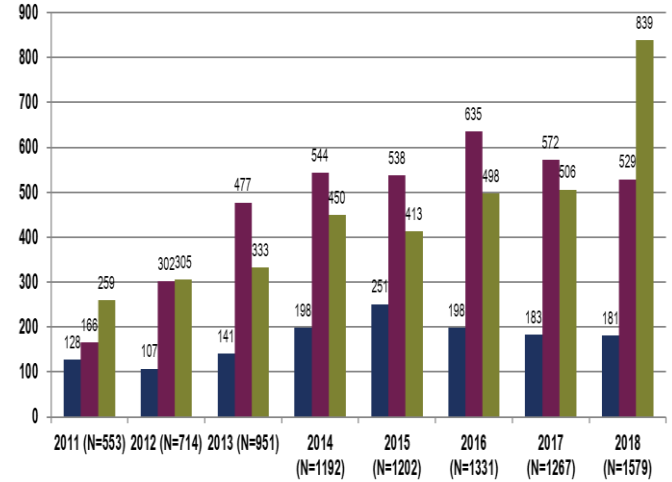
DEDICATED WEBSITE
HTTP:// WWW.OVAIRE-RARE.ORG

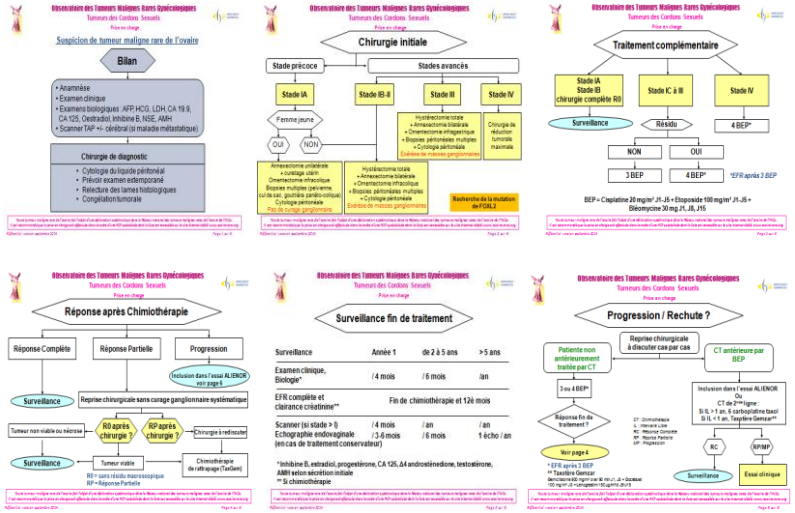
CENTRES EXPERTS TMRG
TUMEURS MALIGNES RARES GYNÉCOLOGIQUES

Which tools are mandatory?

CENTRES EXPERTS TMRG
TUMEURS MALIGNES RARES GYNÉCOLOGIQUES

- Dedicated prospective database
- Multidisciplinary expert tumor boards
- Dedicated Gyn Expert pathologists for systematic second opinion
- Adapted clinical guidelines
- Patient advocacy group





HOW TO CHANGE THE FUTURE?

- New drugs/innovations for rare ovarian patients (1st line or relapse) → identify the “K” questions & the molecular drivers
- New organizations for ‘routine’ management at the national level
  - Dedicated national rare cancer network (eg French model)
    - Education for physicians, care givers and public
    - Motivate Patients advocacy group
- International collaboration
  - European network for rare cancer (ESMO, ESGO, ESO, EURACAN) & more (GCIG)
    - To fix standard of care in 1st line & relapse
    - To develop international guidelines for clinical practice
    - To lobby on the need for investigational treatments

TAKE HOME MESSAGE

Rare Gyn tumors are frequent!

1. Management decision making:
   - Expert Pathologists
   - Expert Multidisciplinary Tumor Board
   - Dedicated Rare Cancer Network→ adding national support
2. Education for physicians & patients
3. European/International Cooperation (ESMO, ESGO, ESO, GCIG) is the must
4. Clinical trials also randomized are feasible !
5. Improvement will come soon
6. Tumoral minority is the future of the oncology