The Evolution of Ovarian Cancer

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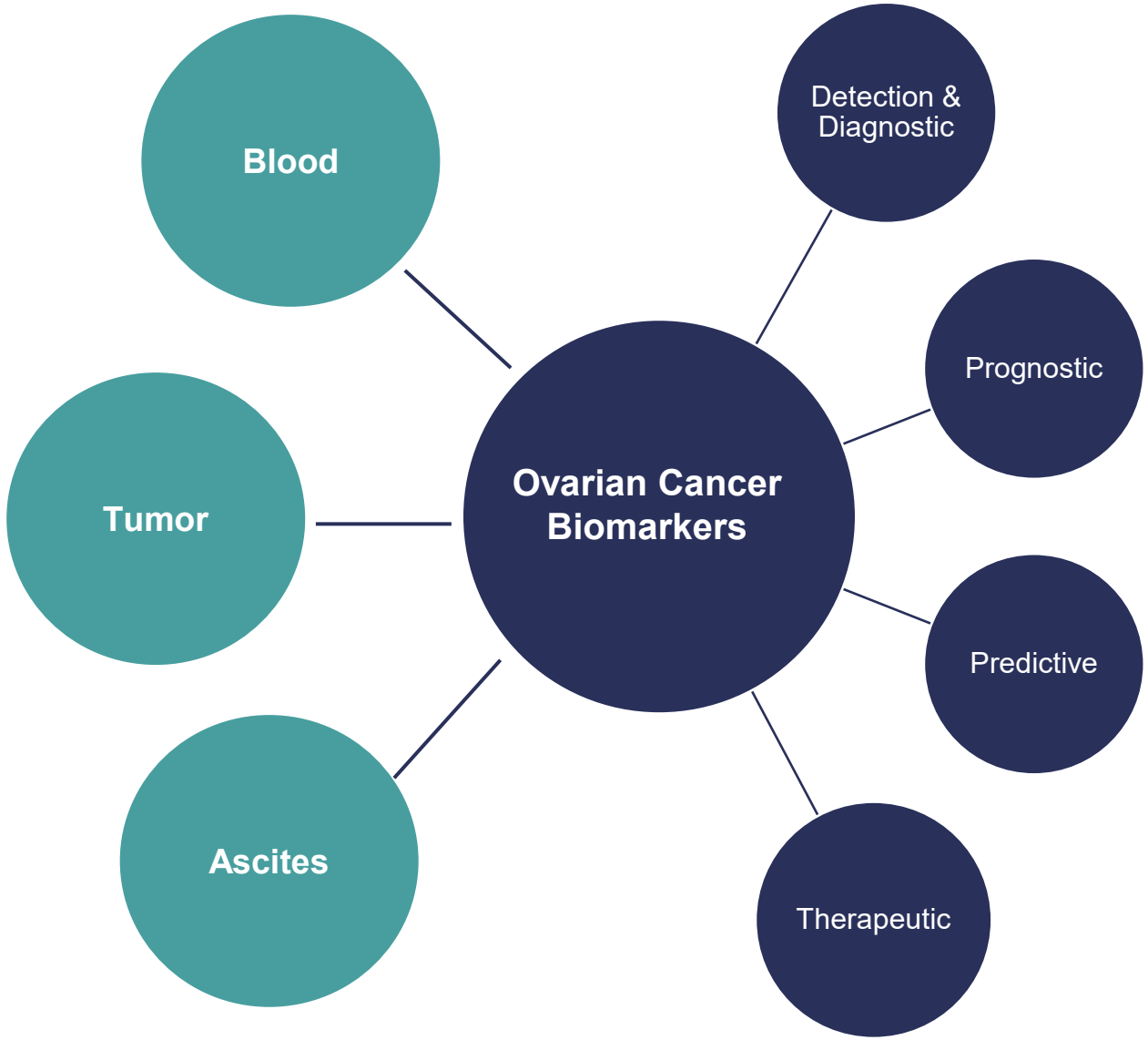
Evolution of Biomarkers

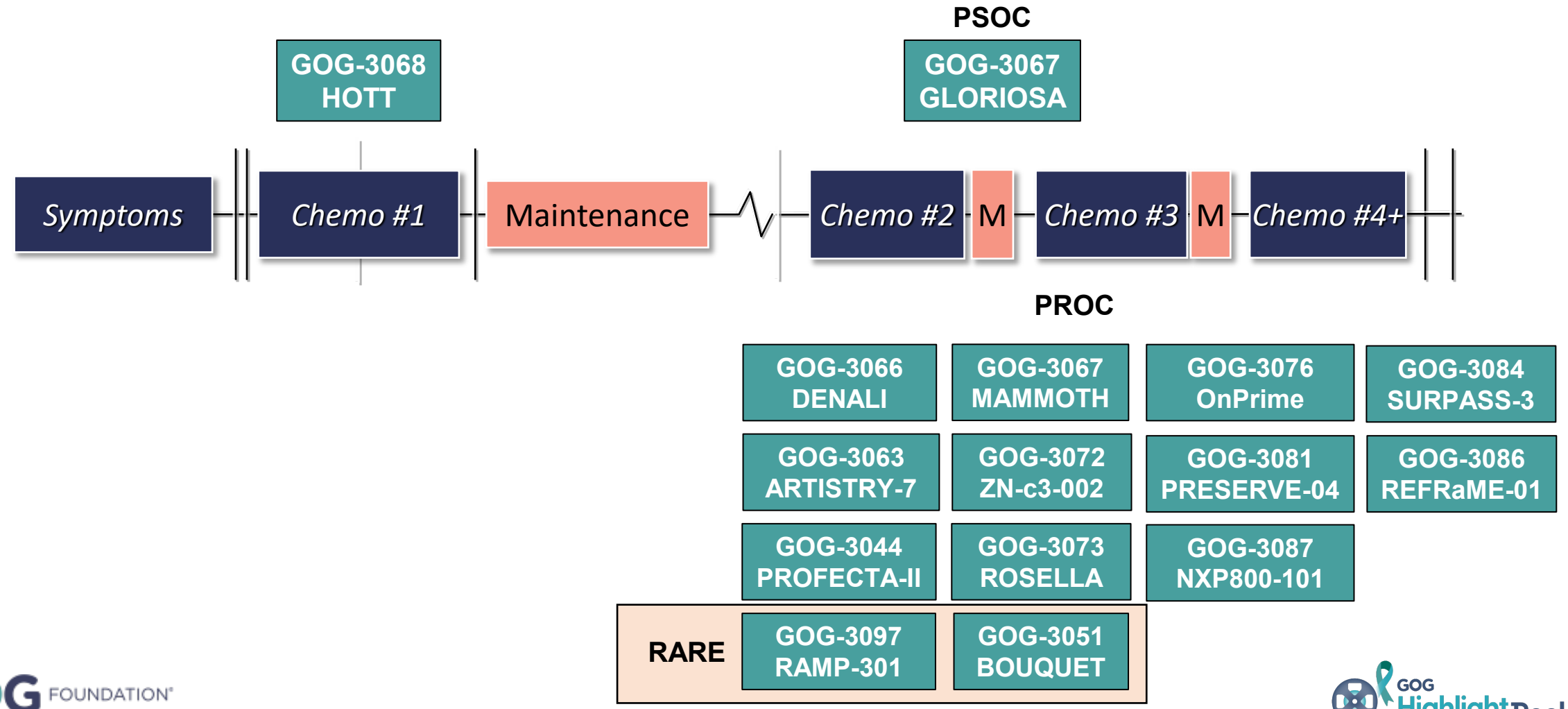


HGSOC	LGSOC
CA125 HE4	
BRCA1/2 HRD	
VEGF ARID1A	
FOLR1/FRα Her2 TROP2 CDH6 MAGE-A4 B7-H4	*PTEN/PIK3CA/AKT1* *BRAF/KRAS/NRAS* ER+ *ERBB2*

ADCs Under Evaluation in Ovarian Cancers

Generic Name	Conjugate	Indication	Target	Phase	NCT
Mirvetuximab soravtansine	Maytansinoid (DM4)	Ovary	Folate Receptor α	3: Gloriosa 3: MIRASOL 2: SORAYA 2: PICCOLO	NCT05445778 NCT04209855 NCT04296890 NCT05041257
STRO-002 Luveltamab tazevibulin	SC209 (tubulin targeting)	Ovary	Folate Receptor α	1	NCT03748186 NCT05200364
MORAb-202	Eribulin	Ovary	Folate Receptor α	2	NCT05613088
Sacituzumab Govitecan (IMMU-132)	SN-38 (metabolite of topo 1 inhibitor)	Ovary	TROP2	2	NCT006028932
Ado-trastuzumab emtansine	DM1	Solid tumor (endo & ovary)	HER2	2	NCT04439110
Trastuzumab deruxtecan	Deruxtecan	Solid tumor (endo, ovary, cervix)	HER2	2	NCT04482309
Raludotatug deruxtecan (DS6000a)	Deruxtecan	Solid tumor (ovary)	CDH6	1	NCT04707248
XB002	Auristatin	Solid tumor (endo, ovary, cervix)	TF	1	NCT04925284
XMT-1660	Auristatin F-Hydroxypropylamide	Solid tumor (endo, ovary)	B7-H4	1	NCT05377996
SGN-B7H4V	Monomethyl Auristatin E	Solid tumor (endo, ovary)	B7-H4	1	NCT05194072
AZD8205	Topoisomerase I inhibitor	Solid tumor (endo, ovary)	B7-H4	1	NCT05123482

GOG Ovarian Enrolling Portfolio



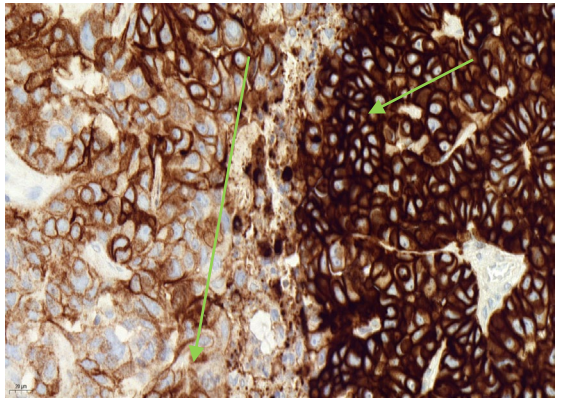
FRα Scoring

PS2+ Scoring

Determined by staining intensity and percentage of tumor cells staining at 0, 1+, 2+, or 3+

PS2+ Scoring Positive: ≥ 50% tumor cells with ≥ 2+ FRα membrane staining.

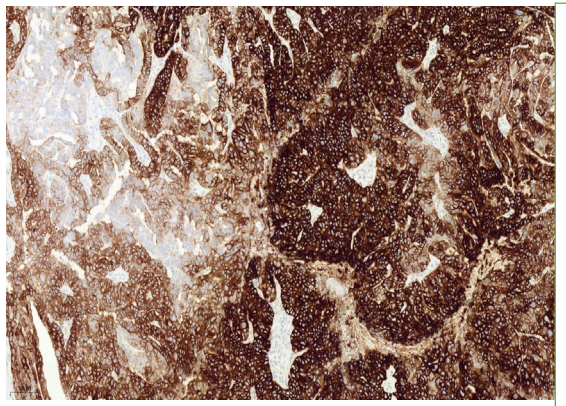
1+ 2+ 3+ intensity



10X Scoring

Simplified scoring method based on % cells with membrane staining by ≤10X magnification, without regard to intensity

10X Scoring Positive: ≥ 50% of tumor cells with FRα membrane staining visible at 10X microscope objective



TPS Scoring

A scoring paradigm based on the % of cells with any intensity expression.

Simple and straight forward interpretation. Does not require differentiation between staining intensity. TPS >25% was selected for further analysis in STRO-002 studies.

Mirvetuximab FDA approved treatment for platinum-resistant ovarian cancer patients whose tumors express ≥75% viable cells show 2+ and/or 3+ staining.

Moore KN et al. ESMO. 2019; Oaknin A et al. ASCO 2023; www.fda.gov

Trials in Focus: Targeting FRa

REFRaME-01

Part 1

- Recurrent disease
  - Platinum resistant 1–3 prior regimens or platinum-sensitive 2–3 prior regimens
- Fresh or archival tissue required
- No mandate for FolRα expression
- At least 1 target lesion

N=44

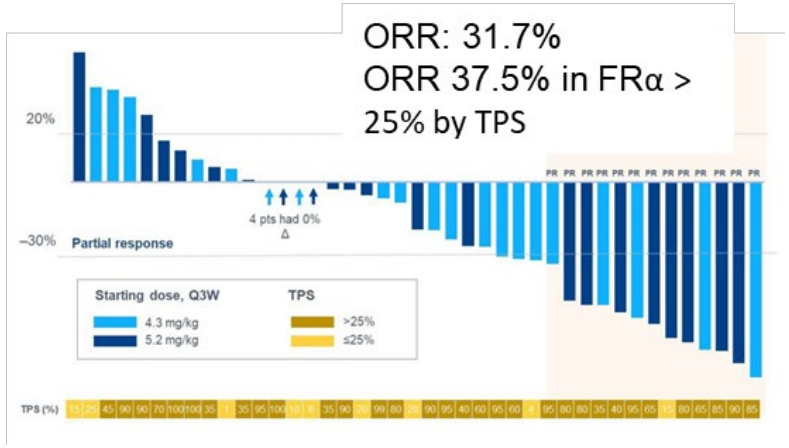
R 1:1

- Luveltamab 4.3 mg/kg Q3W n=23
- Luveltamab 5.2 mg/kg Q3W n=21

Part 2

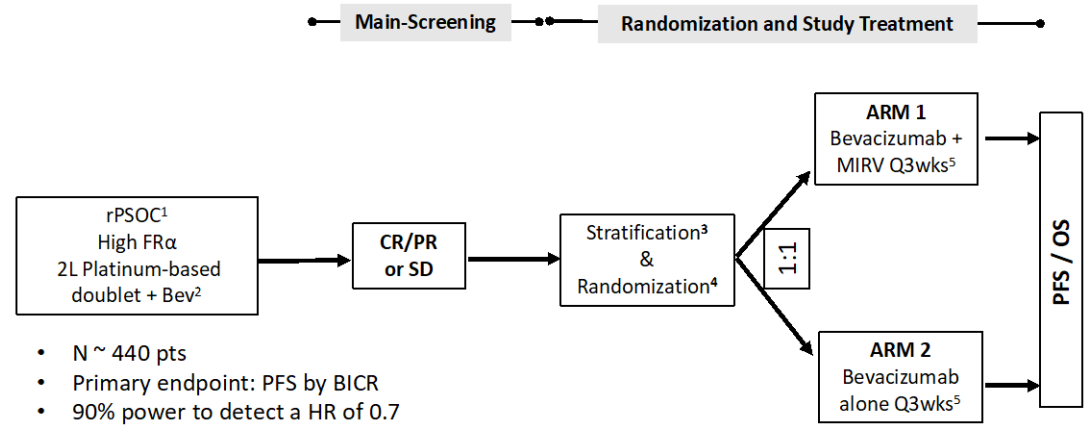
ORR

N ~100



Oaknin et al. ASCO 2023 Abstract 5508

GLORIOSA



- N ~ 440 pts
- Primary endpoint: PFS by BICR
- 90% power to detect a HR of 0.7
- Assumes a mPFS of 10 months on the control arm
- Final PFS analysis @ 330 PFS events

[1] High-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers
[2] Platinum + chemo + bevacizumab for planned 6 cycles (minimum of 4 and maximum or 8 cycles) including at least 3 cycles of bevacizumab
[3] Stratification factors: prior PARP inhibitor: Yes vs No; CR or PR or SD; prior bevacizumab: Yes vs. No.
[4] Enrollment into Trial for Randomization will require documented radiographic confirmed CR, PR or SD
[5] Maintenance treatment must begin 12 weeks or less from last dose of triplet therapy and w/in 30 days of randomization. Treatment continued until progressive disease, unacceptable toxicity, withdrawal of consent, death, or Sponsor terminates the study

Abbreviations:
CR complete response
PR partial response
SD stable disease
MIRV mirvetuximab soravtansine every 3 weeks
PFS progression free survival
OS overall survival

Targeting HER2 in Ovarian Cancers

Ovarian cancer

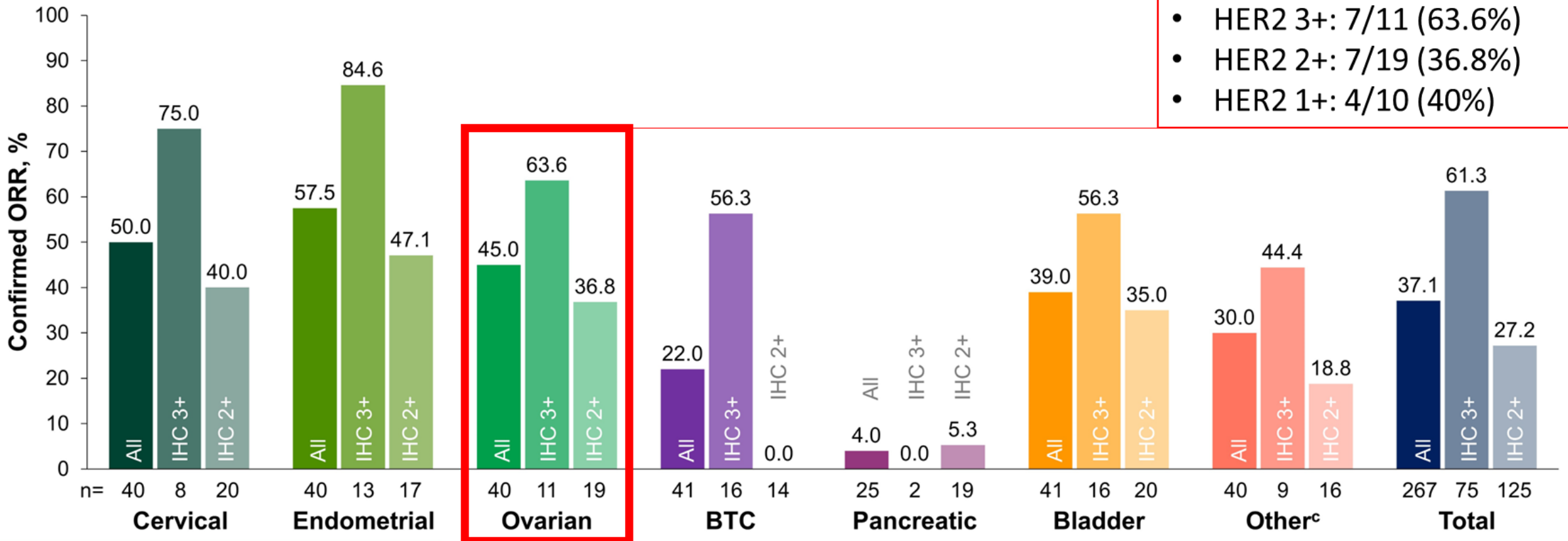
- Amplification: 14%.
- Highest in mucinous carcinomas (25%); mixed-type carcinomas (11.9%), clear cell carcinomas (4%), serous papillary carcinomas (3%), and endometrioid carcinomas (2.1%)
- HER2 expression was associated with worse PFS and OS
- In GOG160, a phase II trial evaluating trastuzumab in patients with recurrent or refractory ovarian cancer had ORR of 7.3 % in patients with HER2 overexpression (n=41)

HER2	Breast (ASCO/CAP 2007)	Breast (ASCO/CAP 2013; 2018*)	Gastric (ASCO/CAP 2016)	Colorectal (HERACLES trial)	UPSC (Fader et al.) Endometrial
IHC 3+	>30% strong, uniform, complete	>10% circumferential, strong, complete	≥10%, strong complete or basolateral/lateral	≥50% strong, complete or basolateral/lateral	>30% strong complete or basolateral/lateral
FISH amplification	HER2/CEPT17 ratio >2.2 Patients with HER2/CEPT17 ratio 2-2.2 eligible	HER2/CEPT17 ratio ≥2.0 OR ratio <2.0 and HER2 signal ≥6.0/nucleus *(if IHC 2+ or 3+)	HER2/CEPT17 ratio ≥2.0 OR ratio <2.0 and HER2 signal ≥6.0/nucleus	HER2/CEPT17 ratio ≥2.0 in ≥50% of cells	HER2/CEPT17 ratio ≥2.0

Lassus H et al Gynecol Onc 2004; McCaughan H et al J Clin Pathol 2012; Hale RJ et al In J Gynecol Pathol 2013; Bellone S et al J Clin Pathol 2003; Ersoy E et al Gyn Path 2022

Objective Response Rate by HER2 status

Ovarian – 18 responders
- HER2 3+: 7/11 (63.6%)
- HER2 2+: 7/19 (36.8%)



	All patients (N=99)	IHC 3+ (n=46)	IHC 2+ (n=34)
Median DOR, months (95% CI)	11.8 (9.8–NE)	22.1 (9.3–NE)	9.8 (4.2–12.6)

Analysis of ORR was performed in patients who received ≥1 dose of T-DXd; all patients (n=267; including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=75) or IHC 2+ (n=125) status. Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd; all patients (n=99; including 19 patients with IHC 1+ [n=6], IHC 0 [n=9], or unknown IHC status [n=4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=46) or IHC 2+ (n=34) status. [a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.
BTC, biliary tract cancer; CI, confidence interval; DOR, duration of response; IHC, immunohistochemistry; NE, non-estimable; ORR, objective response rate.

ADC, antibody-drug conjugate; DAR, drug-to-antibody ratio; ERBB2, erb-b2 receptor tyrosine kinase 2; GYN, gynecologic; HER2, human epidermal growth factor receptor 2; OC, ovarian cancer; q3w, every 3 weeks.

1. Meric-Bernstam F et al. ASCO 2022. Abstract TPS623. 2. ClinicalTrials.gov. NCT04482309. Accessed March 1, 2023.

Unmet needs in recurrent OC[1,2]

- Identification of new molecular targets and corresponding therapies to improve outcomes for more patients
- Identify new therapeutic options for patients with HRP cancers
- New treatment options for patients who progress after PARP inhibitor treatment
- New treatment options for patients with recurrent platinum-resistant disease

Select novel emerging investigational agents in recurrent OC

ADCs (target)

- DS-6000a (CDH6)[13]
- Farletuzumab ecteribulin (FRα)[14]
- Luveltamab tazevibulin (FRα)[15]
- Tisotumab vedotin (tissue factor)[16]
- XMT-1660 (B7-H4)[17]

Immunotherapy

- Nemvaleukin alfa[3]
- Olvimulogene nanivacirepvec[4]
- Gemogenovatucel-T (Vigil)[5]
- Immune checkpoint inhibitors combinations (eg, pembro + pac + bev[6])
- Oncolytic viruses[7]
- Cellular therapy[8]

Targeting cell cycle regulation and DNA repair

- PI3K inhibitors (eg, alpelisib[9])
- CHK1 inhibitor (eg, afuresertib[10])
- WEE1 inhibitor (eg, adavosertib,[11] ZN-c3[12])

Other

- Batiraxcept[19]
- Relacorilant[20]

ADC, antibody-drug conjugate; bev, bevacizumab; BRCA, BRCA DNA repair associated gene; CDH6, cadherin 6; CHK1, checkpoint kinase 1; EOC, epithelial ovarian cancer; FRα, folate receptor alpha; HRP, homologous recombination proficient; NaPi2b, sodium-dependent phosphate transport protein 2B; pac, paclitaxel; pembro, pembrolizumab; PARP, poly (ADP-ribose) polymerase; PI3K, phosphatidylinositol-3 kinase.

1. Bejar FG et al. *Am Soc Clin Oncol Educ Book*. 2022;42:1–17. 2. Moore K. *OncLive*. Published July 17, 2020. Accessed December 5, 2020. https://www.onclive.com/view/dr-moore-on-unmet-clinical-needs-in-platinum-resistant-ovarian-cancer 3. ClinicalTrials.gov. NCT05092360. Accessed January 30, 2023. 4. ClinicalTrials.gov. NCT05281471. Accessed January 30, 2023. 5. ClinicalTrials.gov. NCT02346747. Accessed February 2, 2023. 6. ClinicalTrials.gov. NCT05116189. Accessed January 30, 2023. 7. Lauer UM, Beil J. *Future Oncol*. 2022. doi: 10.2217/fon-2022-0440. 8. Sarivalasis A et al. *Ther Adv Med Oncol*. 2021;13:17588359211008399. 9. ClinicalTrials.gov. NCT04729387. Accessed January 30, 2023. 10. ClinicalTrials.gov. NCT04374630. Accessed January 30, 2023. 11. ClinicalTrials.gov. NCT03579316. Accessed February 22, 2023. 12. ClinicalTrials.gov. NCT05198804, NCT04516447. Accessed January 30, 2023. 13. ClinicalTrials.gov. NCT04707248. Accessed January 30, 2023. 14. ClinicalTrials.gov. NCT04300556, NCT05613088. Accessed February 23, 2023. 15. ClinicalTrials.gov. NCT05200364, NCT03748186. Accessed February 22, 2023. 16. ClinicalTrials.gov. NCT03657043. Accessed February 2, 2023. 17. ClinicalTrials.gov. NCT05377996. Accessed January 30, 2023. 19. ClinicalTrials.gov. NCT04729608. Accessed January 30, 2023. 21. ClinicalTrials.gov. NCT05257408. Accessed January 30, 2023.

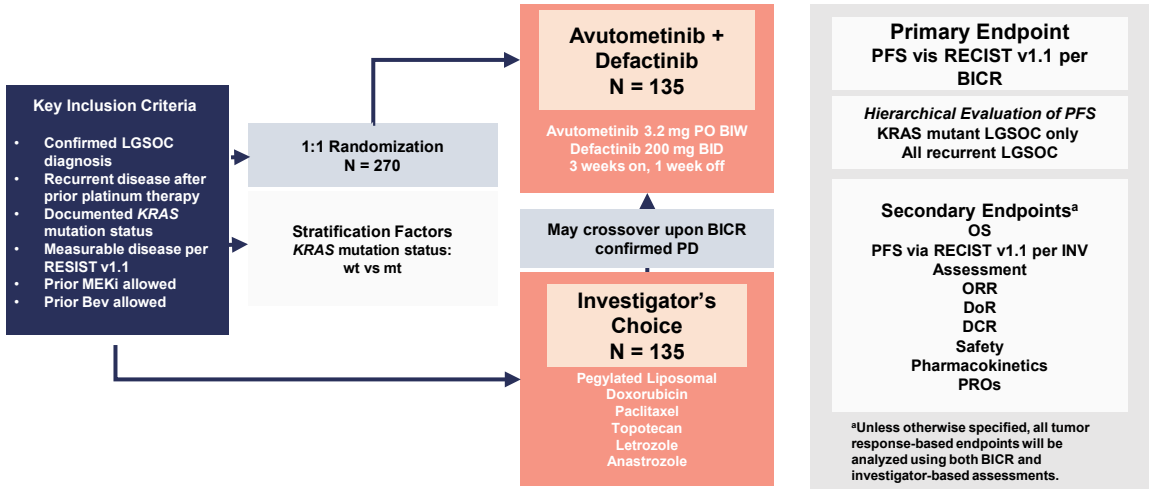
Trials in Focus

Study	Biomarker	Endpoints	Strategy/opportunity
GOG-3066 Zentalis	None (previous CCNE1 amp)	ORR, DOR	Trial in PROC, not restricted amendment being operationalized
GOG-3076 Genelux	None	PFS	Induction IP administration of oncolytic virus; platinum-doublet/bev retreatment in PROC
GOG-3087 Nuvectis	ARID1A	ORR, DOR	Targeting clear cell, endometrioid
GOG-3084 Adaptimmune	HLA 2:01, MAGE-A4	ORR, DOR	Screening can take place during other therapy; ± nivolumab

Trials in Focus: Rare Tumors

RAMP-201 ASCO/ESGO 2023: confirmed dosing and ORR 45%
Activity best in KRAS-mt (60%) but responses seen in KRAS-wt (29%)

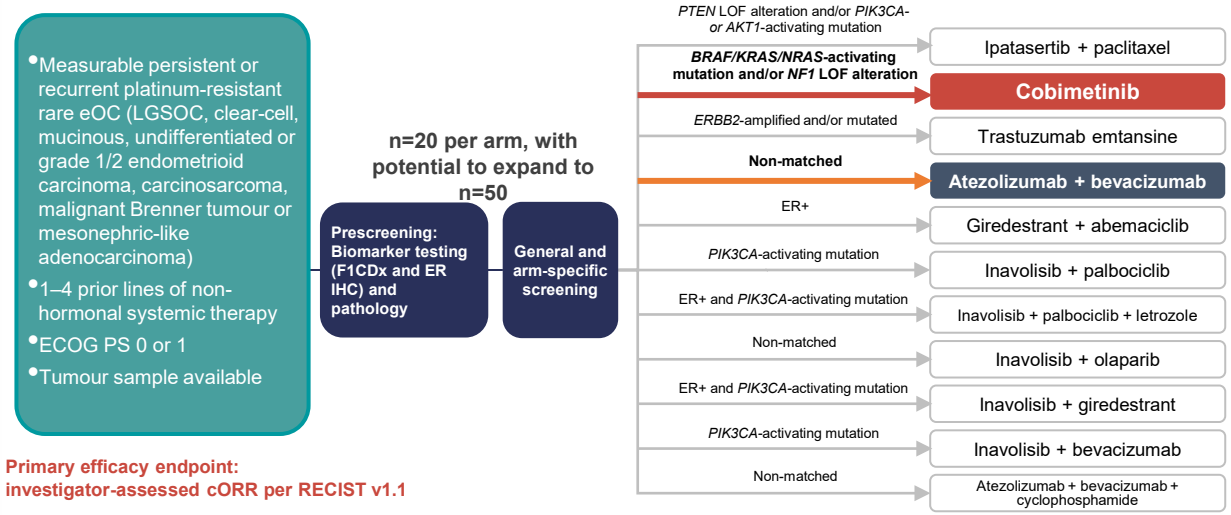
GOG-3097/ENGOT-ov81/RAMP 301



Coming Soon

ESMO 2023: Cobimetinib: ORR: 16% in ITT – 33% in LGSOC – to expand
Atezo/bev: 14% = will advance with metronomic CTX in Arm K

BOUQUET – GOG-3051



ASCO 2023 Abstract 5508, 5515, ESGO 2023

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Conclusions

- Clinical trial pipeline is robust and evolving especially with biomarker development providing prognostic and predictive inference to trial development and participation
- Opportunities to leverage expression and sequencing data in the GOG Partners portfolio are robust
- Screen frequently; expression portfolio may change with time and age of sample