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Impact of *CCNE1* Amplification on Molecular Signatures and Patient Outcomes in High Grade Serous Ovarian and Endometrial Cancer

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Financial Disclosure for:
Erin George

I have the following financial relationships with ACCME defined ineligible companies to report over the past 24 months:

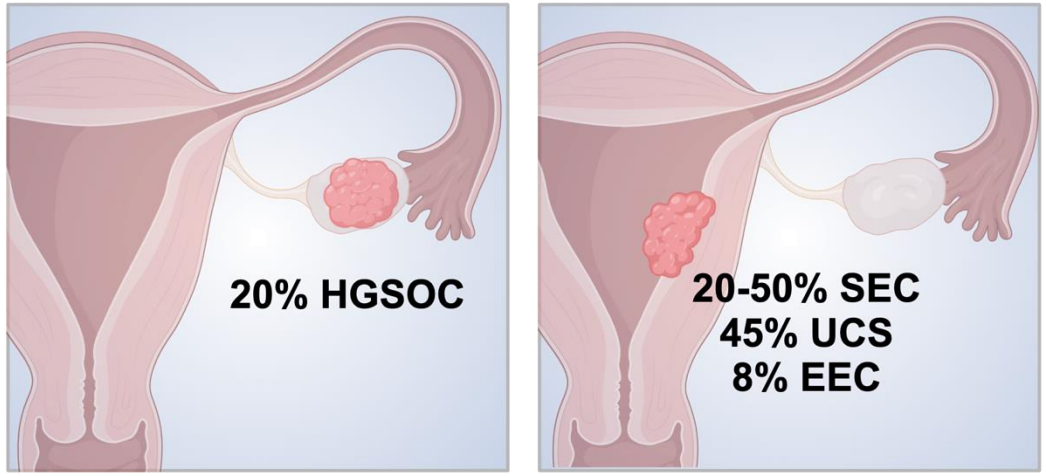
Incyclix Bio, LLC, Consultant, ongoing

Unlabeled/Investigational Uses

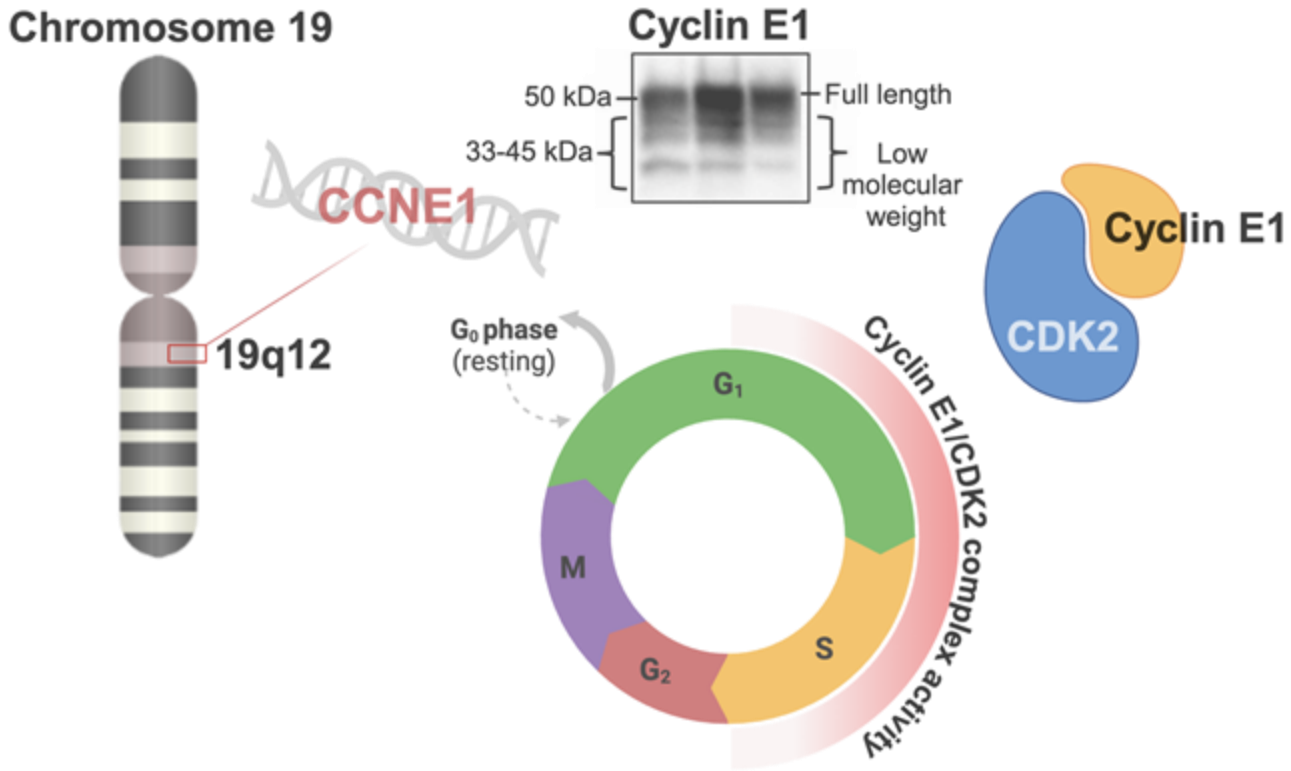
I will/will not be discussing any unlabeled or investigational uses of any pharmaceutical products or medical devices.

CCNE1 amplified gynecologic cancer: *Addressing an unmet need*

***CCNE1* amplification rates in ovarian and endometrial cancer**



HGSOC: high grade serous ovarian cancer
SEC: serous endometrial cancer
UCS: uterine carcinosarcoma
EEC: endometrioid endometrial cancer



CCNE1 amplification → Treatment resistance & worse outcomes

PMID: 25527175, 21720365, 24309323, 22923510, 28292439, 23359684, 26647729, 34622231

CCNE1 amplification rates are affected by different calling methods

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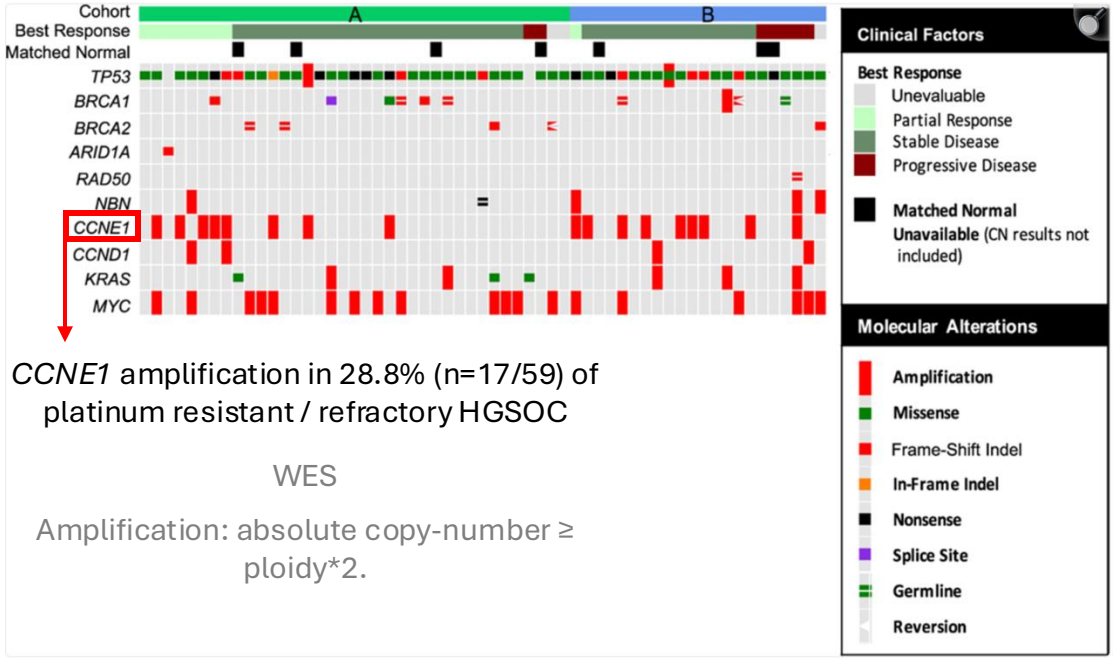
Gemcitabine plus adavosertib for platinum-resistant/refractory recurrent ovarian cancer: A randomized placebo-controlled trial

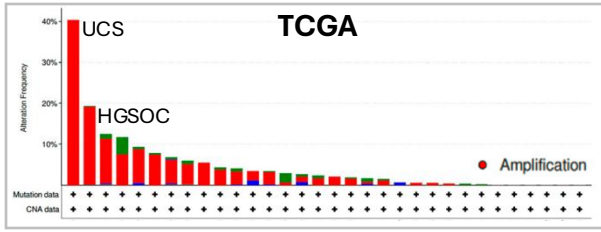
Lheurex et al., Lancet, 2021 (PMID: 33485453)



CCNE1 amplification in 28.8% (n=17/59) of platinum resistant / refractory HGSOC

WES

Amplification: absolute copy-number ≥ ploidy*2.



CCNE1 amplification in ~20% of HGSOC

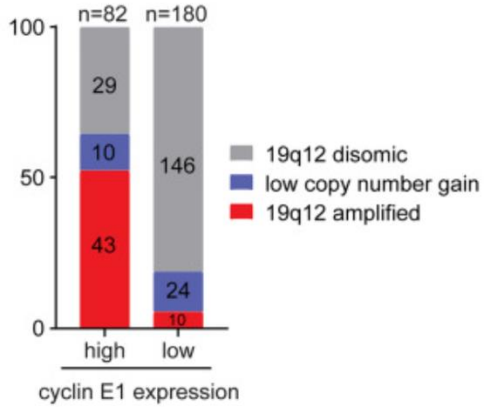
Microarray

Amplification: log 2 ratio ≥ 2 (CN ≥ 4)

(PMID: 32380689)

19q12 amplified and non-amplified subsets of high grade serous ovarian cancer with overexpression of cyclin E1 differ in their molecular drivers and clinical outcomes

Aziz et al., Gyn Onc, 2018 (PMID: 30209015)



CCNE1 amplification in 20.2% (n=53/262) HGSOC patients

ISH of 19q12 locus

Probes: *CCNE1* & *URI1* and insulin receptor (INSR) DIG ISH probe (ref for diploid CN)

Amplification: 19q12: INSR ratio ≥ 3 and/or 19q12 locus CN ≥ 6

Combined *CCNE1* high-level amplification and overexpression is associated with unfavourable outcome in tubo-ovarian high-grade serous carcinoma

Chan et al., J Pathol Clin Res, 2020 (PMID: 32391646)

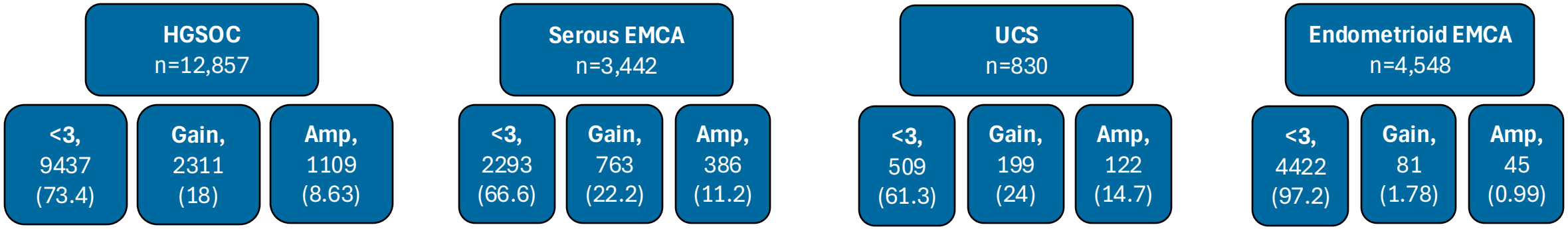
CCNE1 amplification in ~10% (n=53/262) HGSOC patients

ISH assay for detection of *CCNE1*

Amplification: >8 copies of *CCNE1*

Methods

- Tumor samples were analyzed by NGS (NextSeq, 592 genes or NovaSeq, WES) and RNA (NovaSeq, WTS) and IHC (Caris Life Sciences, Phoenix, AZ).
- Copy Number Alterations (CNA) of each exon were determined by normalizing the sequencing depth of each exon divided by the average sequencing depth of the sample, and comparing it to the pre-calibrated mean of normalized values in the training data (The mean values are re-calibrated every 60 days with up to 10,000 samples)
  - Here we determined Amplification (Amp, ≥6 copies), Gain (≥3 and <6 copies) and <3 copies (Heterozygous/Homozygous Loss/Copy Neutral)
  - If the gene is not reported as amplified and any exon (excluding the aforementioned low coverage regions) tested for the CNA call for a gene has average depth lower than 100x, then the CNA calling result for the gene becomes indeterminate. Ploidy is not corrected for.
- Real-world overall survival (OS) was obtained from insurance claims data and Kaplan-Meier estimates were calculated for molecularly defined patient cohorts



HGSOC: high grade serous ovarian cancer
EMCA: endometrial cancer
UCS: uterine carcinosarcoma

Most patients were treatment naïve

A. Demographics															
Characteristics	**HGSOC**			**Endometrial Cancer**											
				All EMCA			**Serous EMCA**			**UCS**			**Endometrioid EMCA**		
	<3	**Gain**	**Amp**	**<3**	**Gain**	**Amp**	**<3**	**Gain**	**Amp**	**<3**	**Gain**	**Amp**	**<3**	**Gain**	**Amp**
N (%)	9437 (73.4)	2311 (18)	1109 (8.63)	13795 (84.7)	1708 (10.5)	790 (4.85)	2293 (66.6)	763 (22.2)	386 (11.2)	509 (61.3)	199 (24)	122 (14.7)	4422 (97.2)	81 (1.78)	45 (0.99)
Age, median (range)	64 (15->89)	67 (31->89)	69 (29->89)	64 (0->89)	68 (37->89)	68 (29-89)	67 (31->89)	68 (39->89)	68 (47-88)	66 (25-89)	68 (45-89)	67 (49-89)	64 (22-89)	67 (41-89)	66 (49-89)
Site, N (%)															
Primary	4326 (45.8)	1094 (47.3)	546 (49.2)	9284 (67.3)	1163 (68.1)	584 (73.9)	1771 (77.2)	598 (78.4)	310 (80.3)	416 (81.7)	163 (81.9)	96 (78.7)	3772 (85.3)	69 (85.2)	41 (91.1)
Metastatic	4975 (52.7)	1190 (51.5)	555 (50)	4370 (31.7)	535 (31.3)	197 (24.9)	495 (21.6)	160 (21)	71 (18.4)	85 (16.7)	35 (17.6)	23 (18.9)	611 (13.8)	12 (14.8)	4 (8.9)
Unclear	136 (1.44)	27 (1.17)	8 (0.72)	141 (1.02)	10 (0.59)	9 (1.14)	27 (1.18)	5 (0.66)	5 (1.3)	8 (1.57)	1 (0.5)	3 (2.46)	39 (0.88)	0 (0)	0 (0)
Prior Treatment, *N (%)*															
Doxorubicin	2648 (28.3)	698 (30.5)	331 (30.2)	241 (1.82)	38 (2.34)	8 (1.06)	35 (1.58)	15 (2.06)	4 (1.07)	4 (0.81)	0 (0)	0 (0)	24 (0.56)	0 (0)	0 (0)
Gemcitabine	1844 (19.7)	473 (20.6)	229 (20.9)	196 (1.48)	15 (0.92)	4 (0.53)	9 (0.41)	1 (0.14)	2 (0.53)	3 (0.61)	2 (1.04)	2 (1.72)	8 (0.19)	0 (0)	0 (0)
Hormone Therapy	2022 (21.6)	417 (18.2)	227 (20.7)	1846 (14)	178 (11)	71 (9.39)	216 (9.75)	74 (10.2)	35 (9.36)	58 (11.7)	19 (9.9)	11 (9.48)	592 (13.8)	7 (8.97)	4 (8.89)
PARPi	2348 (25.1)	415 (18.1)	196 (17.9)												
Pembrolizumab	469 (5.01)	145 (3)	54 (4.93)	64 (0.48)	10 (0.62)	3 (0.4)	8 (0.36)	2 (0.28)	3 (0.8)	0 (0)	0 (0)	0 (0)	8 (0.19)	0 (0)	0 (0)
Bevacizumab	3370 (36)	852 (37.2)	381 (34.8)	311 (2.35)	48 (2.96)	19 (2.51)	55 (2.48)	22 (3.03)	11 (2.94)	7 (1.42)	2 (1.04)	2 (1.72)	60 (1.4)	1 (1.28)	2 (4.44)
Carbo/Taxol	3672 (39.2)	926 (40.4)	485 (44.3)	1387 (10.5)	269 (16.6)	99 (13.1)	325 (14.7)	114 (15.7)	42 (11.2)	53 (10.7)	26 (13.5)	13 (11.2)	249 (5.79)	6 (7.69)	2 (4.44)

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UCS: uterine carcinosarcoma

CCNE1 amplification (≥6) is much higher in HGSOC, serous and carcinosarcoma histologies compared to endometrioid EMCA

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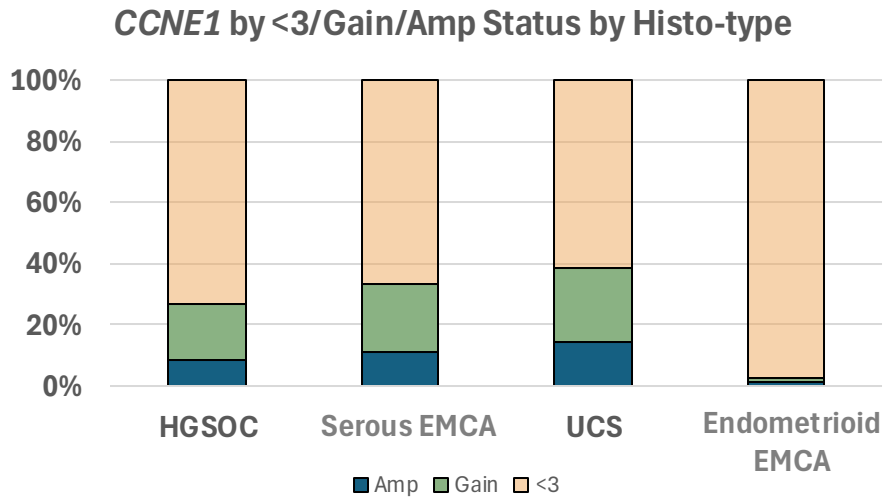
CCNE1 CNA			HGSOC	EMCA			
				All	*Serous EMCA*	*UCS*	*Endometrioid EMCA*
Amplified	**≥6**	*N, (%)*	1109 (8.63)	790 (4.85)	386 (11.2)	122 (14.7)	45 (0.99)
		CN median (range)	9.18 (6-62.2)	9.01 (6-105.4)	9.14 (6-105.4)	9.56 (6-51.9)	8.74 (6.41-59.2)
Gain	**≥3, <6**	*N, (%)*	2311 (18)	1708 (10.5)	763 (22.2)	199 (24)	81 (1.78)
		CN median (range)	3.80 (3-5.99)	3.8 (3-5.99)	3.83 (3-5.99)	3.94 (3.01-5.96)	3.80 (3.02-5.93)
Copy Neutral, HZ/HM Loss	**<3**	*N, (%)*	9437 (73.4)	13795 (84.7)	2293 (66.6)	509 (61.3)	4422 (97.2)
		CN median (range)	2.11 (0.68-2.99)	1.99 (0.8-2.99)	2.19 (1.12-2.99)	2.10 (1.17-2.99)	1.93 (1.1-2.98)



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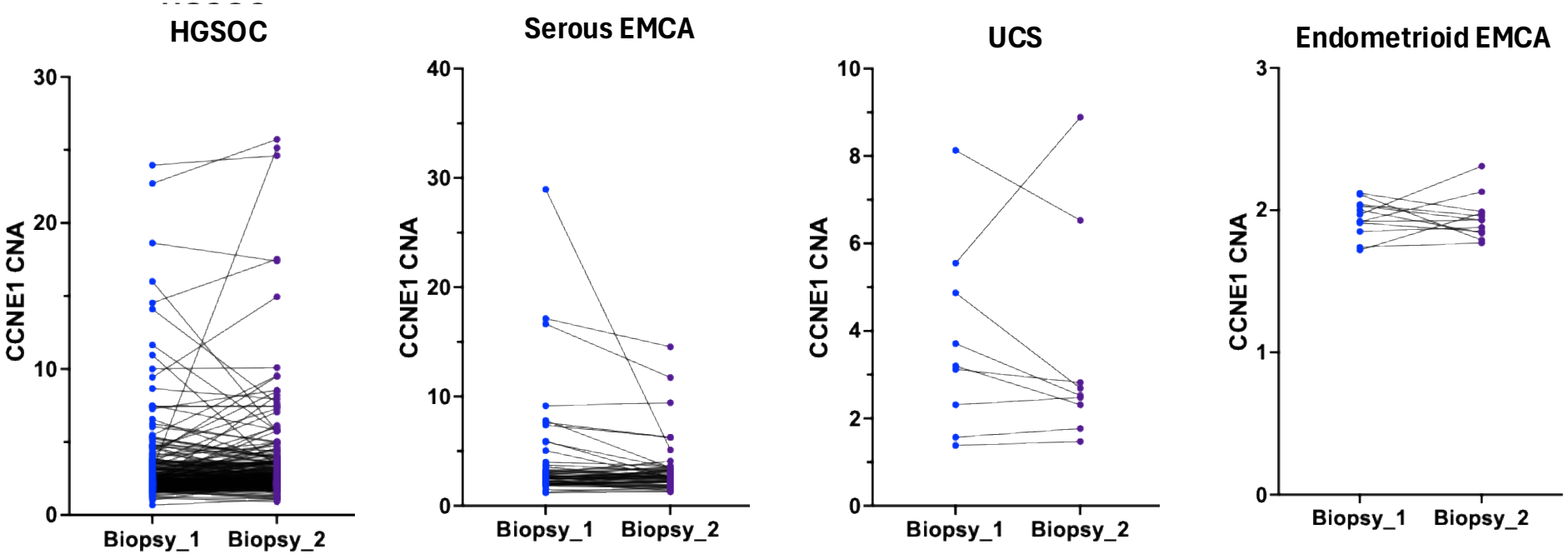
CCNE1 was amplified in 1,109/12,857 (8.6%) of HGSOC, 386/3,442 (11.2%) of serous EMCA, 122/830 (14.7%) of UCS, 45/4,548 (0.99%) of endometrioid EMCA.

CCNE1 copy number increases after treatment with chemotherapy



Histology	Statistic	Changes in Copy Number			Change in CN Categorical Call		
		Increase	Decrease	No Change	Increase	Decrease	No Change
HGSOC	N (%)	127 (51)*	86 (34.5)	36 (14.5)	22 (8.84)	17 (6.83)	210 (84.3)
	Median (range)	0.28 [0.11-22.1]	-0.34 [-10.3 - -0.11]				
Serous EMCA	N (%)	18 (36)	26 (52)	6 (12)	1 (2)	4 (8)	45 (90)
	Median (range)	0.48 [0.17-1.25]	-0.59 [-0.21 - -23.8]				
UCS	N (%)	3 (33.3)	5 (55.6)	1 (11.1)	2 (22.2)	0 (0)	7 (77.8)
	Median (range)	0.2 [0.17-3.34]	-1.19 [-0.3 - -2.18]				
Endometrioid EMCA	N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Median (range)	0.26 [0.21-0.34]	-0.15 [-0.1 - -0.32]				

*$p<0.05$ biopsy 1 to biopsy 2

HGSOC: high grade serous ovarian cancer
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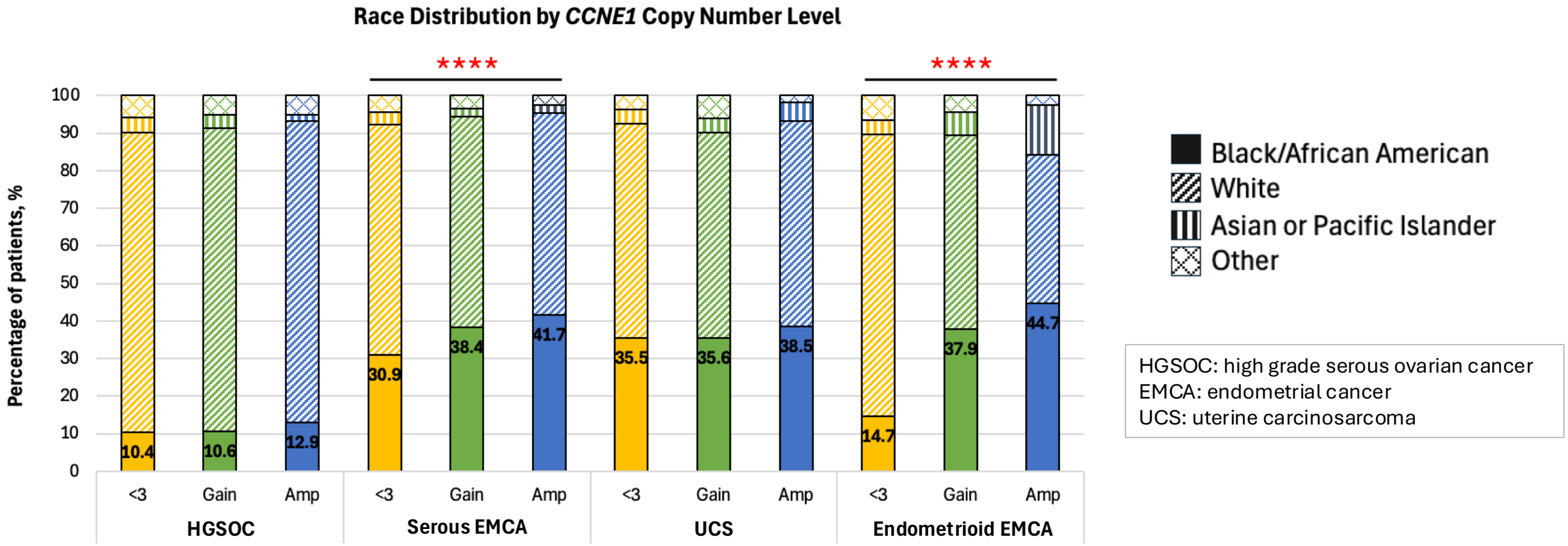
Increased rates of *CCNE1* amplification in Black/African American compared to white patients



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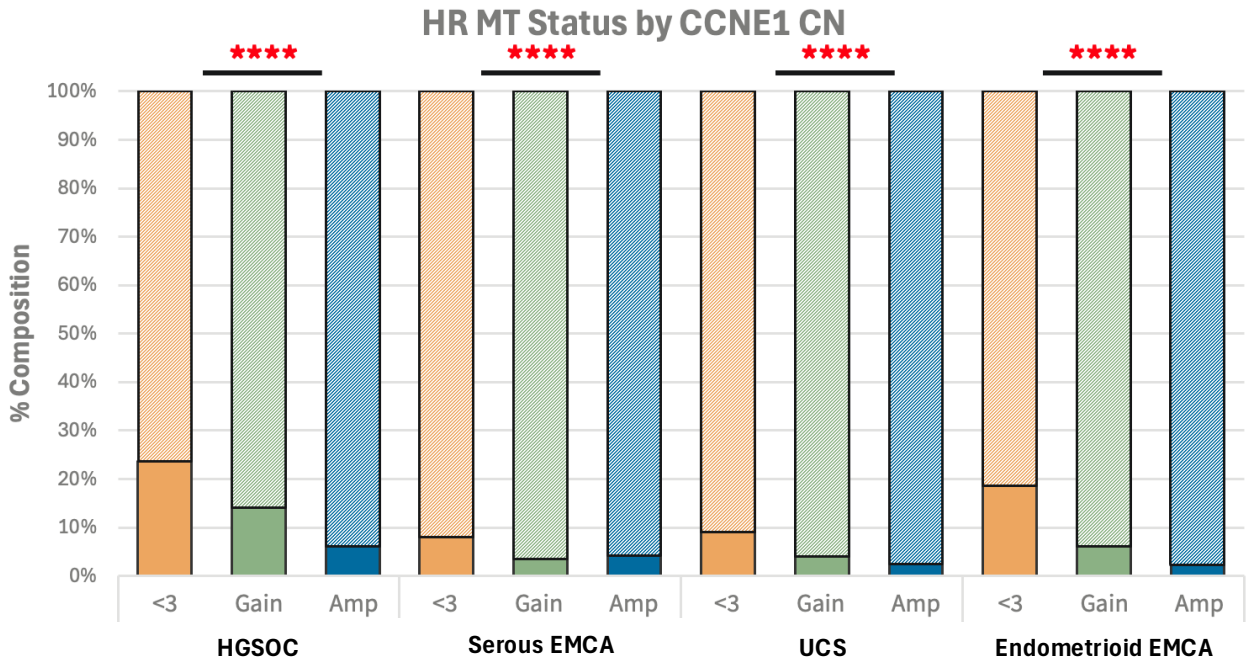
There was an increase in the proportion of Black/African American patients with *CCNE1* amplification compared to CCNE1$^{<3}$ in serous EMCA and endometrioid (Serous EMCA: 41.7% vs 30.9%, Endometrioid EMCA: 44.7% vs 14.7, $p<0.05$).

HR mutations are less likely to occur with *CCNE1* CN ≥6



HR Pathway: BAP1, BARD1, BLM, BRCA1, BRCA2, BRIP1, CDK12, MRE11, NBN, PALB2, RAD50, RAD51B, RAD51C, RAD51D, WRN, EXO1, STAG2, PARP1

Legend:

Cohorts
Amplified (CCNE1 CN≥6)
Copy Gain (CCNE1 CN≥3, <6)
<3 (CCNE1 CN<3)
Copy Number
HR MT or LOH-High
HR WT or LOH-low

*	q<0.05
**	q<0.01
***	q<0.001
****	q<0.0001

HGSOC: high grade serous ovarian cancer
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HR mutation status decreases with *CCNE1*^{Amp}

Co-mutations and co-amplifications with *CCNE1* differ between HGSOC and EMCA

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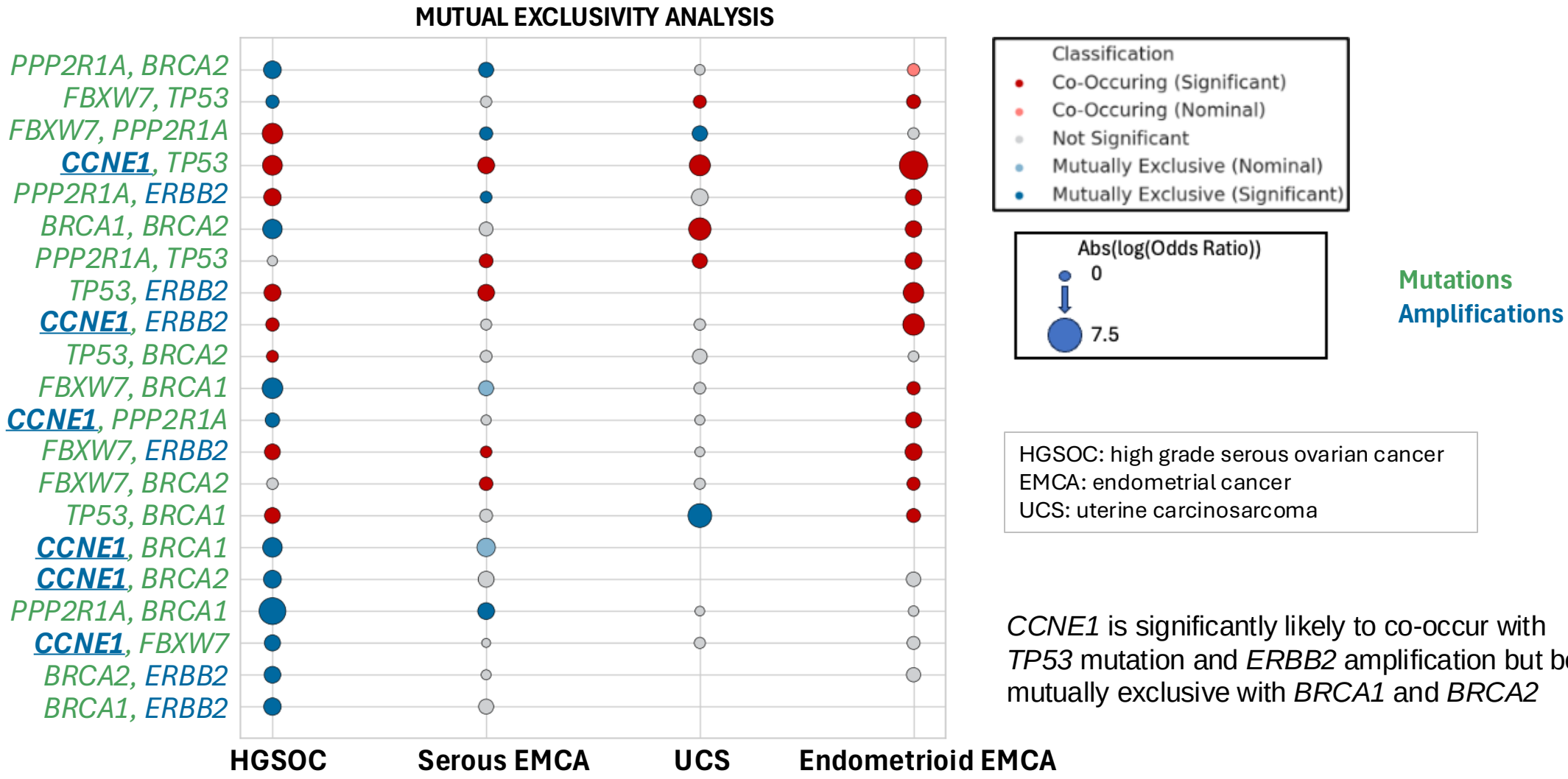

Mutations
Amplifications

HGSOC: high grade serous ovarian cancer
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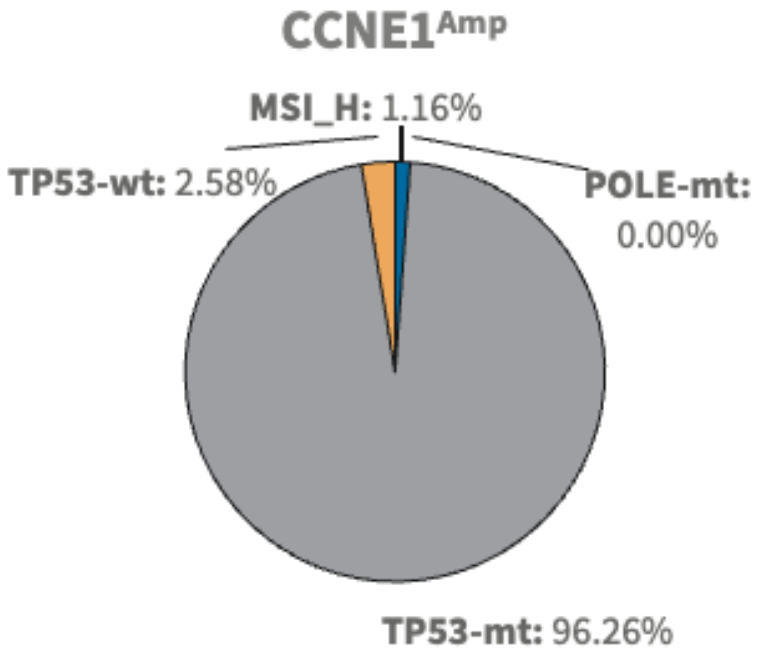
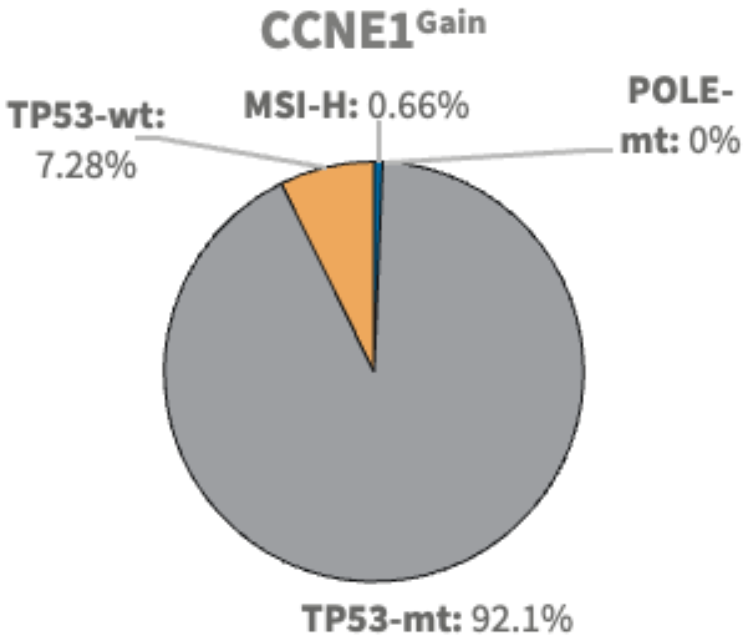
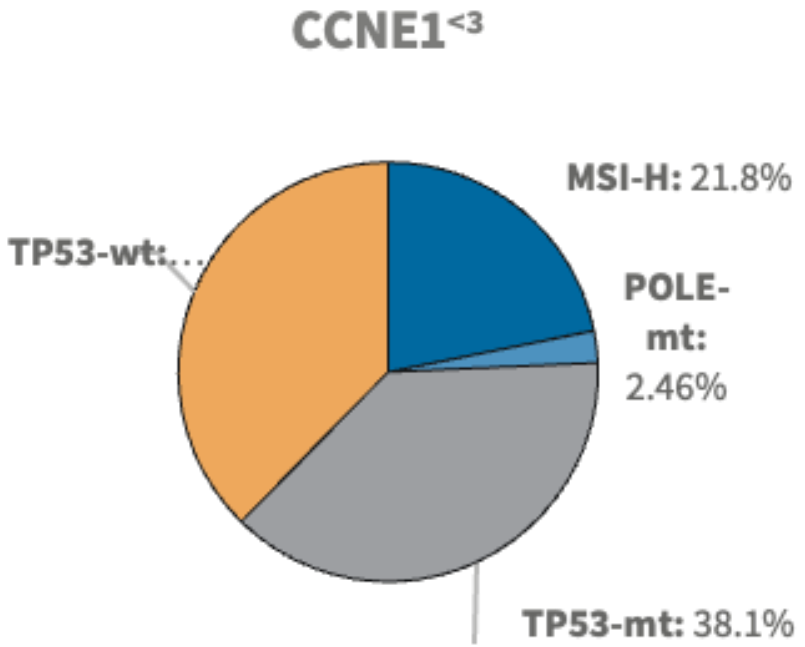
UCS: uterine carcinosarcoma

CCNE1 is significantly likely to co-occur with *TP53* mutation and *ERBB2* amplification but be mutually exclusive with *BRCA1* and *BRCA2*

TCGA molecular classification in EMCA by *CCNE1* amplification status







All EC	Amp	Gain	<3
POLE-mt	0 (0)	0 (0)	327 (2.46)
MSI-H (POLE-wt)	9 (1.16)	11 (0.66)	2909 (21.8)
TP53_mt (POLE-wt/MSS)	747 (96.3)	1530 (92.1)	5067 (38.1)
TP53_wt (POLE-wt/MSS)	20 (2.58)	121 (7.28)	5014 (37.7)

CCNE1 amplified tumors appear non-immunogenic

Immune Tumor Microenvironment between *CCNE1*-amp/gain vs CCNE1 <3 tumors.					
Biomarker		HGSOC	Serous EMCA	UCS	Endometrioid EMCA
IO Biomarkers (Δ%)	dMMR/MSI-H	-0.279	-1.323	**-9.344**	**-37.469**
	TMB High	-0.325	**-3.236**	**-9.556**	**-37.133**
	PD-L1 (SP142)	-0.258	0.057	1.078	0.499
Immune Checkpoint Genes (FC)	CD80	1.045	1.088	0.882	0.938
	CD86	0.980	1.018	0.831	0.983
	CD274	**1.059**	0.951	0.748	0.885
	CD276	**0.920**	0.974	0.854	0.896
	PDCD1	*0.939*	1.036	0.797	0.813
	PDCD1LG2	0.986	*0.944*	0.735	0.935
	IFNG	1.010	0.945	0.815	0.633
	IDO1	**0.881**	0.938	0.805	0.832
	HAVCR2/TIM3	*0.935*	1.017	0.863	0.998
	LAG3	**1.127**	0.936	0.735	1.147
	CTLA4	0.965	0.903	0.666	0.729
Immune Cell Infiltration (FC)	B cell	1.073	1.081	1.926	1.077
	Cytotoxicity Score	**0.916**	0.873	0.922	*0.787*
	Macrophage/Monocyte	**0.946**	0.984	0.852	0.840
	Monocyte	**0.946**	0.984	0.852	0.840
	Myeloid dendritic cell	**0.929**	**0.861**	0.792	**0.786**
	Neutrophil	0.963	1.021	0.773	**0.754**
	NK cell	1.035	1.037	0.922	0.819
	T cell	1.036	1.016	0.825	0.957
	T cell CD8+	0.938	1.005	1.485	0.951
	Endothelial cell	0.975	0.954	0.934	**0.775**
	Cancer associated fibroblast	**0.811**	**0.799**	0.858	**0.807**
Immune Signature (Δ%)	T-Cell Inflamed Score	-3.8	-4.0	-3.0	-3.6

**bolded indicates (q<0.05)*

- There was no difference in immuno-oncology biomarkers (TMB-H, dMMR/MSI, PD-L1) in HGSOC
- dMMR/MSI-H and TMB-H were decreased in *CCNE1*^{Amp} EMCA (q<0.05)
- *CCNE1*^{Amp} was also associated with decreased fibroblasts in HGSOC (1.25-fc) and serous EMCA (1.39-fc) (q<0.05)

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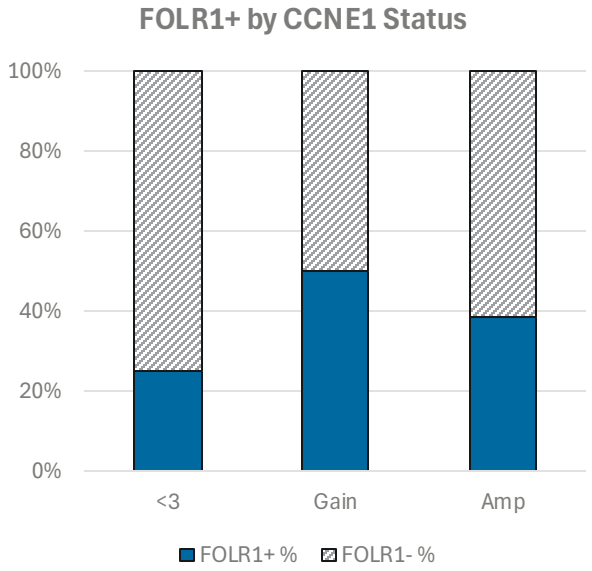
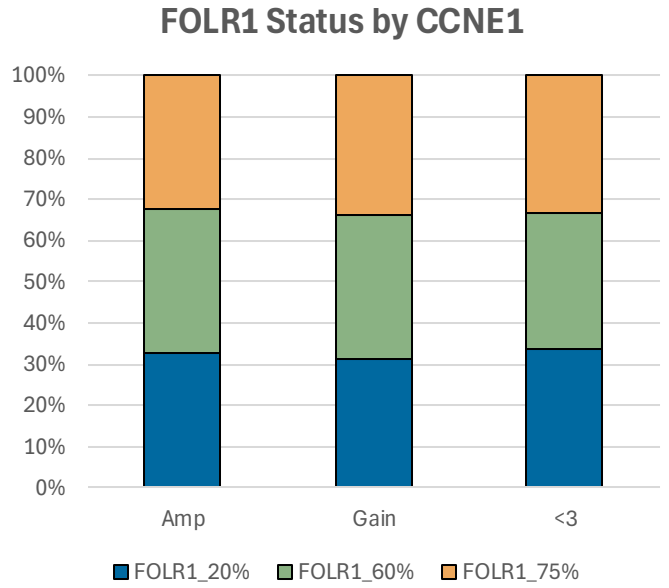
UCS: uterine carcinosarcoma

CCNE1 amplification overlap with FOLR1+ is modest in HGSOC



CCNE1	FOLR1+	FOLR1-
<3	3 (25)	9 (75)
Gain	10 (50)	10 (50)
Amp	38 (38.4)	61 (61.6)



CCNE1	FOLR1 20%	FOLR1 60%	FOLR1 75%
<3	68 (74.7)	44 (72.1)	39 (73.6)
Gain	16 (17.6)	12 (19.7)	10 (18.9)
Amp	7 (7.69)	5 (8.2)	4 (7.55)

Some overlap of *CCNE1* amplification with HER2+ in HGSOC

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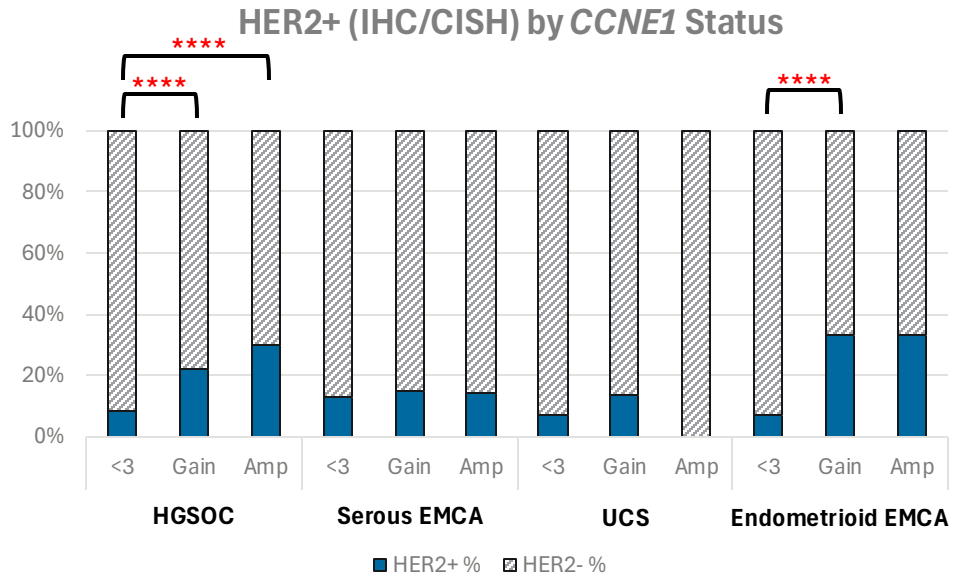

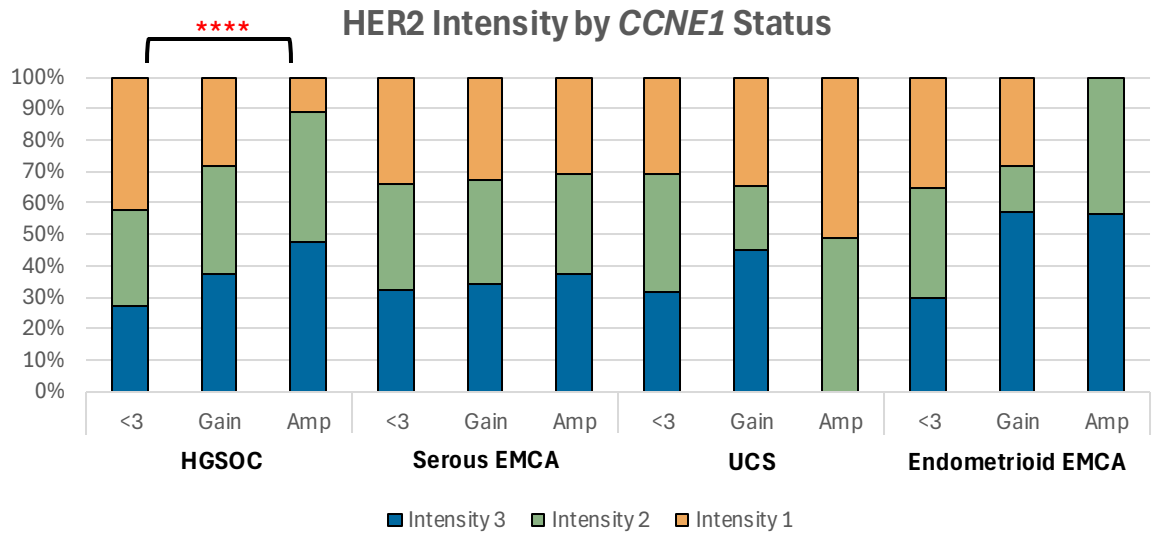

HGSOC: high grade serous ovarian cancer

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Histology	CCNE1	HER2+	HER2-
HGSOC	*<3*	31 (8.33)	341 (91.7)
	Gain	22 (22.2)	77 (77.8)
	Amp	16 (30.2)	37 (69.8)
Serous EMCA	*<3*	214 (12.8)	1459 (87.2)
	Gain	86 (15)	487 (85)
	Amp	41 (14.2)	248 (85.8)
UCS	*<3*	5 (7.25)	64 (92.8)
	Gain	4 (13.3)	26 (86.7)
	Amp	0 (0)	16 (100)
Endometrioid EMCA	*<3*	12 (6.63)	169 (93.4)
	Gain	3 (33.3)	6 (66.7)
	Amp	1 (33.3)	2 (66.7)

HER2_Intensity		Intensity 3	Intensity 2	Intensity 1
HGSOC	<3	68 (70.1)	36 (50.7)	32 (45.1)
	Gain	24 (24.7)	21 (29.6)	23 (32.4)
	Amp	5 (5.15)	14 (19.7)	16 (22.5)
Serous EMCA	<3	342 (66.8)	501 (65.7)	255 (63.1)
	Gain	116 (22.7)	177 (23.2)	97 (24)
	Amp	54 (10.5)	84 (11)	52 (12.9)
UCS	<3	14 (56)	18 (69.2)	7 (58.3)
	Gain	8 (32)	5 (19.2)	5 (41.7)
	Amp	3 (12)	3 (11.5)	0 (0)
Endometrioid EMCA	<3	31 (91.2)	20 (90.9)	13 (76.5)
	Gain	3 (8.82)	1 (4.55)	3 (17.6)
	Amp	0 (0)	1 (4.55)	1 (5.88)

CCNE1 amplification is associated with worse overall survival

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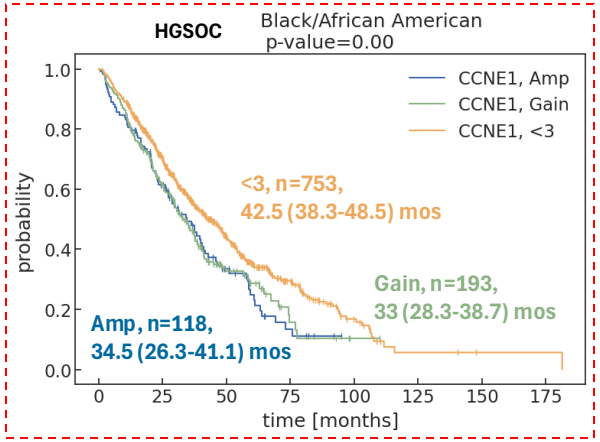
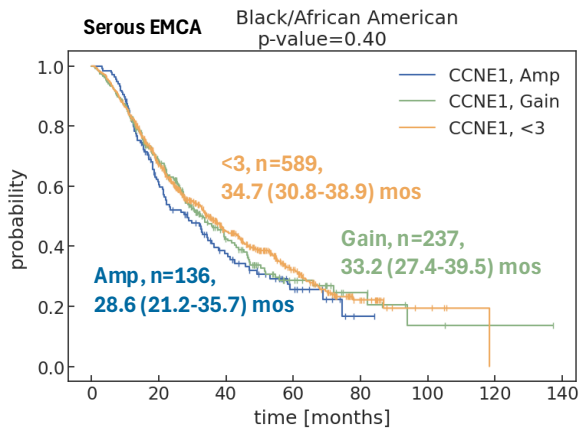
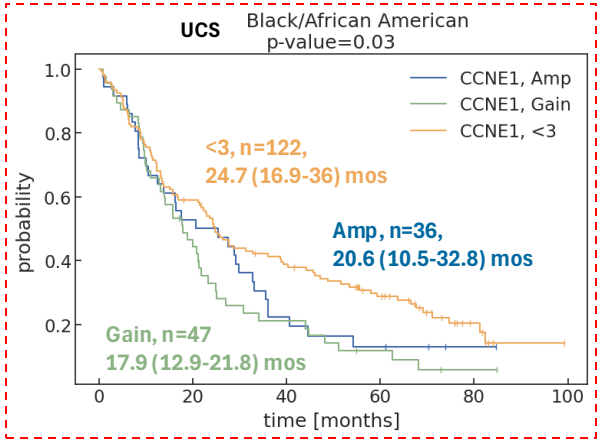
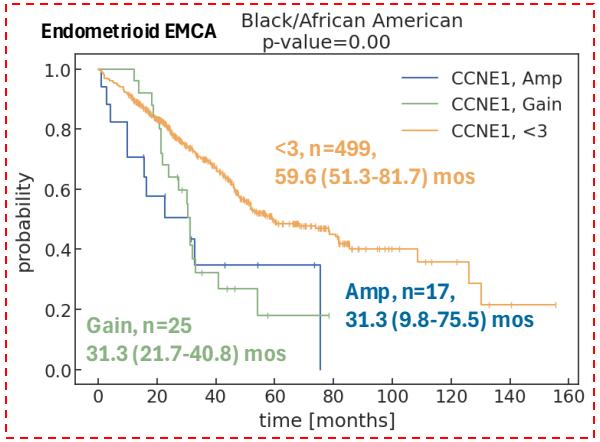
Black/AA

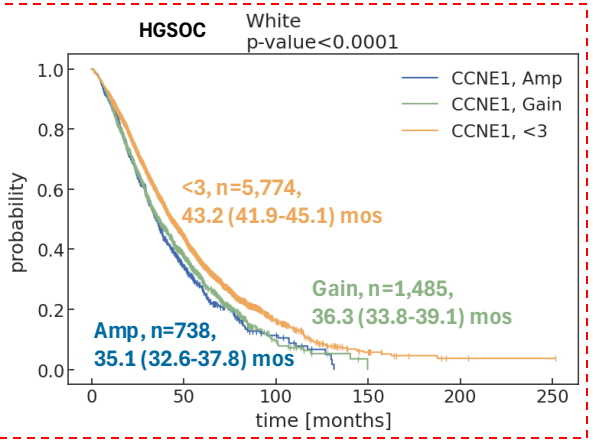


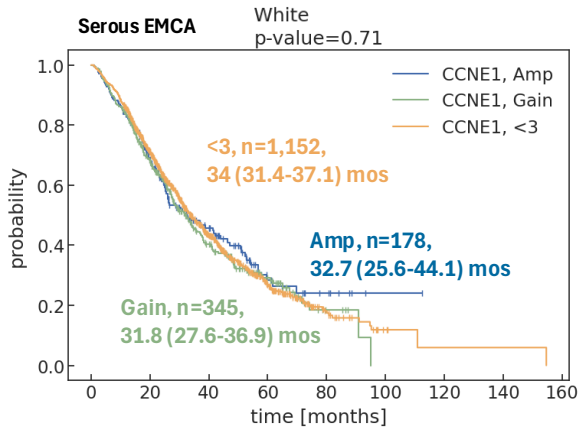


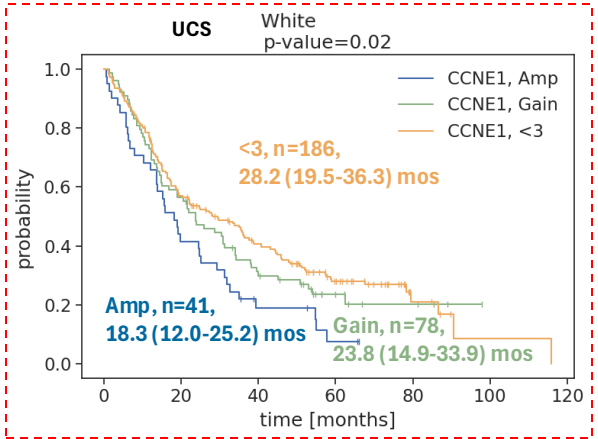


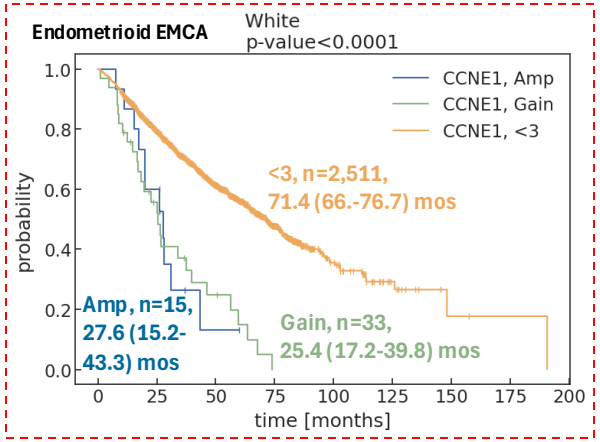


White









CCNE1^{Amp} was associated with worse OS in HGSOC as well as endometrioid EMCA with a trend in UCS in B/AA and White patients but not AAPI (not shown)

Conclusion

- *CCNE1* amplification rates in HGSOC and EMCA depend on calling method
- *CCNE1* CN may increase with emergence of treatment resistance suggesting re-biopsy at time of progression may be warranted to guide therapy options
- There are increased rates of *CCNE1* amplification in Black/African American compared to white women for all tumor types but statistically significant in serous EMCA and endometrioid EMCA
- *PIK3CA*, *ARID1A*, *PTEN*, *KRAS*, *NF1*, and *RB1* mutations were inversely associated with *CCNE1* amplification
- *CCNE1* is significantly likely to co-occur with *ERBB2* amplification, especially in endometrioid EMCA
- *CCNE1* amplified tumors appear overall non-immunogenic
- While there is some overlap with FOLR1+ and HER2+ other targeted agents will be needed to exploit *CCNE1* amplification

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