Genomic mutation profiles of paired ovarian cancers across time

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BACKGROUND

- Ovarian cancers are known to have clonal heterogeneity, but variation due to treatment selection is not well described.
- Genomic testing is increasingly used to characterize ovarian cancer tumors to inform therapeutic decision-making and is now recommended by the NCCN for all patients with recurrent disease.

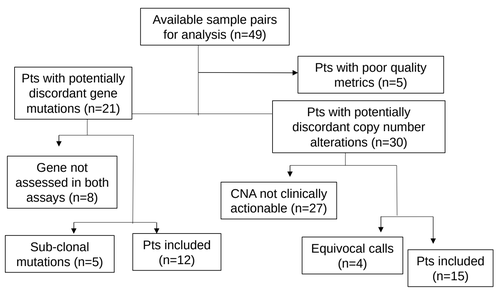
OBJECTIVE

To analyze comprehensive genomic profiles from paired ovarian cancer tumor samples and identify changes in somatic mutations and copy number alterations (CNA) over time.

METHODS

- Ovarian cancer patients in the Clearity Foundation Data Repository with multiple tumor profiles and clinical history were identified
- DNA from ≥2 FFPE samples analyzed with hybrid-capture, next-generation sequencing of up to 315 genes (Foundation Medicine, Cambridge, MA)
- Genomic profiles were compared between samples from the same patient
- Discordant mutations were excluded if:
  - Mutation was subclonal (<10% mutant allele fraction, MAF)
  - Gene/biomarker not assessed across both assays
  - Mutation was reclassified as benign or variant of unknown significance (VUS)
- We included genes with copy number amplification or deletions being used as enrollment criteria for clinical trials: amplifications of *AKT3, CCND1-3*, *CDK4*, *CDK6*, *MYC*, *CCNE1*, *FGFR1-4*, *EGFR*, *ERBB2*, *KRAS*, *PIK3CA*, *PIK3C2B*, *MET* and deletions of *ATM*, *CDKN2A*, *PTEN*, *RB1*. Discordant CNA were excluded if the interpretation was reported as equivocal in one sample.
- We compared clinical and treatment characteristics between patients with discordant mutations and CNA in relevant genes using standard two-sided statistical tests.

Figure 1. Selection of patients with eligible mutation/CNA events*



* Numbers may not sum to the total due to patients with discordant mutations/CNA that were excluded for more than one reason or with both reported and excluded discordant mutations/CNA

Table 1: Clinical, pathologic, and treatment characteristics*

	Patients, n (%)
Median age at diagnosis, years (range)	57 (35-77)
Stage	
I	3 (7%)
II	5 (11%)
III	27 (61%)
IV	7 (16%)
Primary disease site	
Ovary	35 (79%)
Fallopian tube	6 (14%)
Peritoneum	3 (7%)
Tumor histology	
Serous	31 (70%)
Clear cell	5 (11%)
Adenocarcinoma, NOS	2 (5%)
Mixed	2 (5%)
Carcinosarcoma	1 (2%)
Endometrioid	3 (7%)
Not otherwise specified	1 (2%)
Tumor grade	
1	1 (2%)
2	3 (7%)
3	37 (84%)
4	1 (2%)
Primary platinum response	
Sensitive	32 (72%)
Resistant	10 (23%)
Refractory	2 (5%)
Pair type	
Primary-recurrent	22 (50%)
Recurrent-recurrent	22 (50%)
Median survival after diagnosis, months (range)	61 (26-199)
Median number of treatment regimens between samples (range)	2 (1-13)
Median time between sample collections, months (range)	26 (8-76)

* Numbers may not sum to the total due to missing values

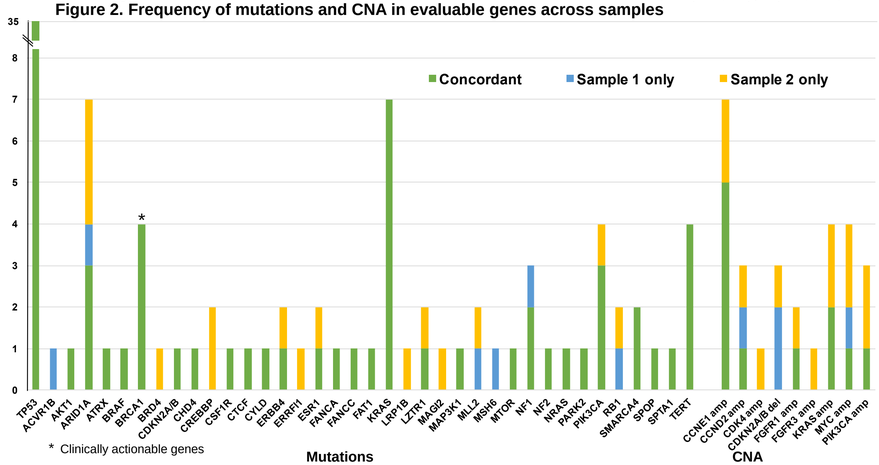
- Paired specimens from 44 patients analyzed
- Median of 2 mutations per specimen
- No difference in number of mutations between sample pairs (range 0-5)
- No difference in number of CNA between sample pairs (range 0-3)
- No samples with microsatellite instability or high tumor mutational burden

Table 2: Discordant mutations and CNA in evaluable genes from a commercially available gene panel across sample pairs

Patient	Mutations and CNA			Change in clinical trial eligibility	Low tumor % in one sample	Pair type	Age at diagnosis	Stage	Histology	Grade	Primary platinum response	Months between sample collection	Treatment history in between samples
	Discordant		Concordant										
	Sample one	Sample two											
1	*MSH6*	*ESR1*	*BRCA1, TP53*		X	R	40	IIC	S	3	Sens	36	C-G, V, P, D, B, C-B, T-B
2	*MLL2*	*RB1*	*ATRX, TP53*	X		P	69	IIIC	S	3	Sens	25	C-P, C-D-B, C
3	*RB1*		*NRAS, TP53*			R	55	IIIC	SE	3	Sens	53	C-P-Cis-Dt, G, Dt
4		*ERFFI1*	*TP53*			R	54	IV	S	3	Sens	56	T-Cy, Cy, Vino-Cap, Cy-NYESO, ONT, ABT,Def-Avel
5		*BRD4, ARID1A S138**	*ARID1A, TERT, TP53*			R	40	IC	CC	3	Sens	18	C-G, D-B
6	*ACVR1B*		*TERT, TP53, CCNE1, PIK3CA*			P	60	IIIC	S	3	Sens	25	C-P-B
7	*NF1*	*KRAS*	*ERBB4, TP53, CCNE1*	X		P	62	IIIC	S	3	Sens	33	C-Cis-P-B, C-G-B, Nivo-Cabi, C-D-B, Olap-Adav
8	*ARID1A, AKT3*	*CREBBP, PIK3CA*	*NF1, TP53*	X		P	77	IIC	S	3	Sens	24	C-P
9	*CCND2*	*ARID1A*	*TP53*	X		R	57	IIIC	S	3	Sens	16	C-D
10		*ARID1A, MAGI2, CDKN2A/B*	*KRAS, PIK3CA, TERT*	X	X	P	60	IIC	CC	3	Sens	21	C-P-B
11		*CREBBP, CCND2, CDK4, KRAS*	*KRAS*	X		R	65	IA	E	2	Sens	16	Pem, nabP, Tr, Tr-E
12		*LRP1B, MYC*	*TP53*	X		P	46	IIIC	S	3	Res	35	C-P, G, Pem, Pem-B, D, E
13		*CCNE1*	*TP53, MYC*	X		R	35	IIIC	S	3	Sens	26	C-P, C-G
14		*FGFR1*	*TP53, FANCA, CCNE1*	X		P	60	IV	S	3	Res	21	C-P, D, B
15		*CDKN2A/B*	*BRCA1, TP53*	X	X	P	61	IV	S	3	Sens	32	C-Dt-B, C-D-B, Olap
16		*MYC*	*TP53*	X		P	61	IIC	S	3	Sens	30	C-P, C-D
17		*CCND2*	*TP53*	X		R	58	IIIC	C	3	Sens	8	P-B, Cet-C
18		*CCNE1*	*TP53*	X		P	54	IIIC	S	3	Res	28	C-P, D
19		*FGFR3*	*TP53*	X	X	P	61	IIIC	S	3	Res	22	C, G
20		*MYC*	*TP53*	X		R	53	IIIC	NS	4	Sens	26	B, O, C-G-B
21	*CDKN2A/B*			X	x	R	43	IIIC	S	2	Sens	15	L

Mutations denoted in black; CN amplifications denoted in red; CN deletions denoted in blue Samples with 20% tumor content/purity considered to have low tumor %
P: Primary-recurrent R: Recurrent-recurrent S: Serous, CC: Clear cell E: Endometrioid SE: Serous endometrioid, C: Carcinosarcoma; NS: Not specified
ABT, ABT165; Avel, avelumab; Adav, adavosertib; B, bevacizumab; C, carboplatin; Cabi, cabiralizumab; Cap, capecitabine; Cet, cetuximab; Cis, cisplatin; Cy, cyclophosphamide; D, liposomal doxorubicin; Def, defactinib; Dt, docetaxel; E, erlotinib; G, gemcitabine; L, letrozole; nabP, nab-paclitaxel; Nivo, nivolumab; NYESO, NY-ESO-1c259 T cells; O, oxaliplatin; Olap, olaparib; ONT; ONT-10; P, paclitaxel; Pem, pemetrexate; V, veliparib; Vino, vinorelbine; T, topotecan; Tr, trametinib

Figure 2. Frequency of mutations and CNA in evaluable genes across samples



- *TP53* mutations were conserved across 35 samples
- The majority of mutations, including *BRCA1* (4) and *KRAS* (7) were conserved

- Discordant mutations or CNA were found in 21 (48%) pts
- Discordant mutations were found in 12 (27%) pts, with 4 in *ARID1A*
- Discordant CNA were found in 15 (31%) pts, with 3 each in *CCND2, MYC,* and *CDKN2A/B*
- No statistically significant associations between discordant alterations and clinical characteristics, pair type, months between sample collections, or survival

CONCLUSIONS

- The majority of mutations and CNA events were conserved across paired samples despite 1-7 rounds of intervening therapy.
- Low tumor purity accounts for some of the discordance between samples.
- None of the discordant mutations or CNA are currently clinically actionable, but many are inclusion criteria for enrollment in clinical trials.
- These data suggest that obtaining a new tissue sample for genomic testing for ovarian cancer patients at the time of recurrence may assist with clinical trial selection.