KRAS Mutant Epithelial Ovarian Carcinomas (EOC) Represent Distinct Genomic Genotypes

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ABSTRACT

Background: Inhibitors of *KRAS* mutant disease have shown efficacy in non-small cell lung, pancreas and colon cancers. *KRAS* mutations (mts) in ovarian cancer may be therapeutic targets and population *KRAS* data in ovarian cancer are needed.

Methods: The Caris Database of 7325 EOC (all histologies) were queried for presence of actionable mutations and subtypes. Next-generation sequencing (NGS) results of 592 genes were available. Comparison was done using Fisher-Exact/ChiSquare (*p*-values) and adjusted for multiple tests by Benjamini-Hochberg (q).

Results: A. *KRAS mts in EOC:* KRAS mts were seen in 8.2% (606/7325) EOC analyzed. Of 606 KRAS mts, subtypes G12D = 221 (36.5%) and G12V = 217 (35.8%) were most common; G12C = 51 (8.4%), other G12 mts (A, F, I, L, R, S) = 55 (9%). Pathogenic mts at codons 13, 61, and others were seen in 62 tumors (10.2%). Remaining EOCs were wt = 6719 (91.7%). **B.** *KRAS mts infrequently co-occur with BRCA1/2 mutations: BRCA* mts are significantly less prevalent in KRAS mt EOC compared to wt (*BRCA1*: 0.9% vs 9.2%; *BRCA2*: 1.3% vs 6.1% wt, q<0.05), and G12C-mt tumors show the highest co-occurrence with *BRCA1* (4.6%) and *BRCA2* (2.3%) among all *KRAS* mts. **C.** *KRAS mts infrequently overlap with other oncogenic drivers*: Mts in HRAS with KRAS vs wt were (0.3% vs 0.1% wt, *p*>0.05) and MEK1 with KRAS vs wt (0.3% vs 0.1% wt, *p*>0.05). GNASmt is higher in KRAS mt tumors (1.2% vs 0.1% wt, q<0.05). Enhancer mutations of the PI3K pathway are significantly higher in KRAS mt tumors. In *KRAS* mt vs wt, PTEN were 7.3% vs 3.4%, PIK3CA 17.2% vs 7.8% (both q<0.05) and PIK3R1 2.1% vs 1.0% *(p*<0.05). **D.** *Known biomarkers of immunotherapy response occur at low frequency in both KRAS mt and wt:* MSI-H and TMB-H (>17 mt/MB) were seen 1.6% and 3.1% in the KRAS mt and 1% and 2.2% in wt, respectively (p>0.05). STK11 mts were 0.5% *KRAS* mt and 0.1% wt (*p*<0.05). **E.** *Differences in markers of genomic integrity:* Tumors with *KRAS* mts had lower rates of p53 mts than *KRAS* wt (29.6% vs 80% of wt, q<0.05), but higher rates of ARID1A mts (49.7% vs 29.1%, q<0.05). ATM mts were more frequent in *KRAS* mt disease (3.7% vs 1.6%, q<0.05).

Conclusions: *KRAS* mt disease represents a genomically distinct group of EOC with minimal overlap to other targeted therapy or immunotherapy options. *BRCA1/2* mts were mutually exclusive from *KRAS* mt suggesting a separate treatment opportunity for recurrent disease or maintenance therapy.

INTRODUCTION

- Kirsten rat sarcoma 2 (*KRAS*) viral oncogene is the most commonly mutated oncogene in human cancer. *KRAS* G12C and G12D mutations are present in ovarian carcinoma and are clinically actionable targets for targeted therapy approaches with novel therapeutic agents *(Panyavaranant et al, 2019).*
- *KRAS* has long been regarded as non-druggable given the absence of an ATP binding pocket and “smooth surface” polymer conformation (*Kim et al, 2020).*
- Novel inhibitors of *KRAS* activity hydrolysis, AMG510 and MTRX849, have been tested in phase 1 clinical trials focusing on non-small cell lung cancer (NSCLC), pancreatic carcinoma and colorectal carcinoma, suggesting clinical efficacy and feasible tolerability of this targeting approach (*Lee et al, 2016)*. These drugs are genotype specific and limited to G12C subtypes. Additional genotype targeting is explored via interaction of *KRAS* with the *SOS1* protein.
- *KRAS* mutations have previously reported in endometrial and ovarian carcinoma, although these studies were limited with regards to size and genomic correlation (*Nagasawa et al, 2020).*
- To date, *KRAS* mutations has no significant clinical relevance in gynecological carcinomas *(Xu et al, 2017*). To identify potential new rationally designed treatment approaches, we interrogated the Caris database for presence of *KRAS* and associated genetic alterations.

OBJECTIVES

- *KRAS* inhibitors have shown efficacy in NSCLC, pancreas and colon cancers. Data about *KRAS* mutations in ovarian cancer for targeted therapy are lacking.
- This preclinical data will assess the potential clinical feasibility of targeting *KRAS* mutants in ovarian carcinoma.

METHODS

- The Caris Database of 7325 epithelial ovarian cancers were queried for presence of actionable mutations. NGS results of 592 genes were available.

Comparison was done using Fisher-Exact / Chi Square (*p*-values) and adjusted for multiple tests by Benjamini-Hochberg (q).

Table 1. *KRAS* Mutations by Subtype.

***KRAS* in EOC**	***N***	**(%)**
All pathogenic *KRAS* mutations	606	8.3
G12C	51	8.4
G12D	221	36.4
G12V	217	35.8
G12 other (A, F, I, L, R, S)	55	9.1
G13 all	62	10.2
Q61		
None 12,13, 61		
Wild type	6719	

Chart 1. Differences in Markers of Genomic Integrity

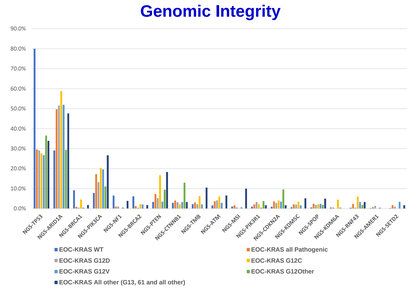


Chart 2. Differences in Markers of Genomic Integrity

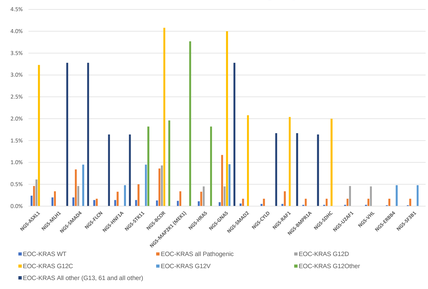
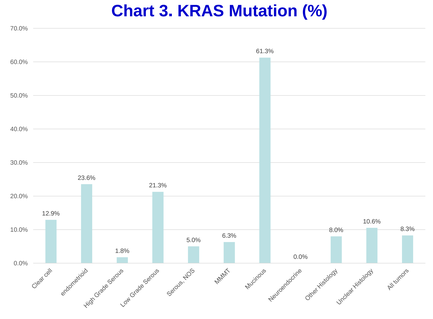


Table 2. *KRAS* Mutant Ovarian Cancers by Histology.

Histology	*KRAS* MT (N)	*KRAS* WT (N)	*KRAS* Mutation (%)
Clear Cell	45	303	12.9%
Endometrioid	66	214	23.6%
High Grade Serous	17	938	1.8%
Low Grade Serous	20	74	21.3%
Serous, NOS	166	3138	5.0%
MMMT	16	238	6.3%
Mucinous	68	43	61.3%
Neuroendocrine		2	0.0%
Other Histology	2	23	8.0%
Unclear Histology	206	1746	10.6%
All tumors	606	6719	8.3%

Abbreviations: MT = Mutant; WT = Wild Type; NOS = Not Otherwise Specified; MMMT = Malignant Mixed Mullerian Tumor

Chart 3. KRAS Mutation (%)



RESULTS SUMMARY

- Of 606 *KRAS* mts, subtypes G12D = 221 (36.5%) and G12V = 217 (35.8%) were most common. G12C = 51 (8.4%) and other G12 mutants (A, F, I, L, R, S = 55, 9%) were found. Pathogenic mutations at codons 13, 61, and others were identified in 62 (10.2%). The remaining EOCs were wildtype = 6719 (91.7%) **(Table 1).**
- *BRCA* mutations are significantly less prevalent in *KRAS* mutant EOC compared to wildtype (*BRCA1*: 0.9% vs 9.2%, *BRCA2*: 1.3% vs 6.1% wt, q<0.05), and G12C-mt tumors show the highest co-occurrence with *BRCA1* (4.6%) and *BRCA2* (2.3%) among all *KRAS* mutations.
- Mutations in *HRAS* (0.3% vs 0.1% wt, *p*>0.05), *MEK1* (0.3% vs 0.1% wt, *p*>0.05) do not overlap with *KRAS* mt while *GNAS* is higher in *KRAS* mutant tumors (1.2% vs 0.1% wt, q<0.05). Enhancer mutations of the PI3K pathway are significantly higher in *KRAS* mutant tumors. In *KRAS* mutant vs wildtype, *PTEN* were 7.3% vs 3.4%, *PIK3CA* 17.2% vs 7.8% (both q<0.05) and *PIK3R1* 2.1% vs 1.0% (*p*<0.05). **(Charts 1 and 2).**
- MSI-H and TMB-H (>17 mt/MB) were seen 1.6% and 3.1% in the *KRAS* mutants and 1% and 2.2% in wildtype, respectively (*p*>0.05). *STK11* mts were 0.5% *KRAS* mt and 0.1% wt (*p*<0.05).
- Tumors with *KRAS* mutants had lower rates of *p53* mts than *KRAS* wt (29.6% vs 80% of wt, q<0.05), but higher rates of *ARID1A* mts (49.7% vs 29.1%, q<0.05). *ATM* mts were more frequent in *KRAS* mt disease (3.7% vs 1.6%, q<0.05).

CONCLUSIONS

- *KRAS* mutant disease represents a frequent and genetically distinct group of epithelial ovarian cancers with minimal overlap to predictive markers of immunotherapy (MSI-H, TMB-H) and targeted therapy.
- *KRAS* mutations infrequently overlap with other oncogenic drivers.
- *BRCA1/2* mutations were mutually exclusive from *KRAS* mutations suggesting a separate treatment opportunity for recurrent disease or maintenance therapy.
- Clinical trials evaluating subtype-specific KRAS inhibitors in ovarian tumors are warranted.

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Conflict of Interest
Dr. Karolina A. Kilowski has nothing to disclose.

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