Molecular and immune profiling of *TP53*-mutated ovarian cancers with non-*BRCA1/2* homologous recombination gene alterations
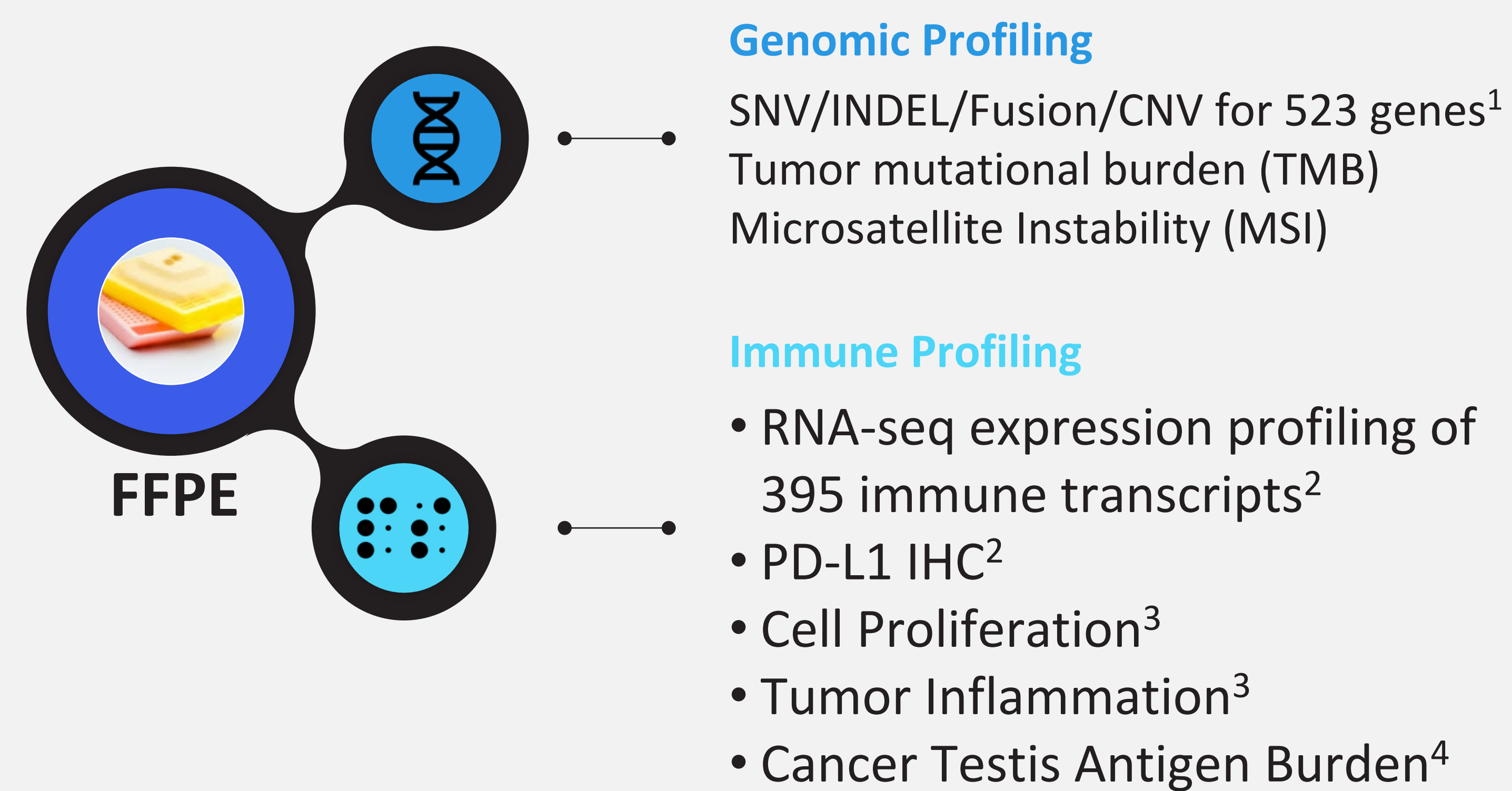
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Introduction

- Molecular alterations in homologous recombination (HR) pathway genes lead to homologous recombination deficiency (HRD) in ~50% of high grade serous ovarian carcinomas (HGSOC)
- The immune microenvironment of BRCA1/2-mutated (BRCAm) HGSOC has been well-characterized, but there is limited understanding of tumors with genomic alterations in other HR genes (NBHRD).
- The objective of the current study is to compare the molecular and immune signatures of BRCAm vs. NBHRD tumors

Figure 1. Summary of comprehensive genomic and immune profiling assay

FFPE

Genomic Profiling
SNV/INDEL/Fusion/CNV for 523 genes[1]
Tumor mutational burden (TMB)
Microsatellite Instability (MSI)

Immune Profiling
- RNA-seq expression profiling of 395 immune transcripts[2]
- PD-L1 IHC[2]
- Cell Proliferation[3]
- Tumor Inflammation[3]
- Cancer Testis Antigen Burden[4]

Methods

- We identified 173 epithelial ovarian carcinomas (EOC) characterized by comprehensive genomic and immune profiling (Omniseq INSIGHT, Labcorp, Buffalo, NY)[1,2] from June 2021 to November 2022 (Figure 1).
- The BRCAm cohort was defined as tumors with known pathogenic alterations in BRCA1 and BRCA2 (Table 1). Tumors were classified as NBHRD if BRCA1 and BRCA2 lacked alterations and tumors harbored pathogenic alterations in any of the following genes: *ARID1A, ATM, ATRX, BARD1, BLM, BRIP1, CHEK1/2, FANCA, FANCE, FANCL, FANCD2, FANCF, FANCC, MRE11A, NBN, PALB2, RAD50, RAD51* (Table 2).

Table 1. BRCAm cohort mutations

BRCAm Case	Gene(s)	Mutation(s)
1	BRCA2	6837delA (V2280fs)
2	BRCA2	5609dupT (S1871fs)
3	BRCA1	2126_2127delTT (F709fs)
4	BRCA1	181T>G (C61G)
5	BRCA2	7617+1G>A ()
6	BRCA1	5266dupC (Q1756fs)
7	BRCA1	1263_1265dupATA (E421_Y422ins*)
8	BRCA1	886A>T (R296*)
9	BRCA1	3627dupA (E1210fs)
10	BRCA1	5266dupC (Q1756fs)
11	BRCA1	4679delG (G1560fs)

Table 2. NBHRD cohort mutations

| NBHRD Case	Gene(s)	Mutation(s)
1	ATM	3085dupA (T1029fs)
1	BRIP1	517C>T (R173C)
2	FANCA	3494T>G (L1165*)
3	BRIP1	1871C>A (S624*)
4	BRIP1	2010dupT (E671*)
5	FANCF	388dupC (Q130fs)
6	BRIP1	1489delG (V497fs)
7	CHEK2	1100delC (T367fs)

Non-BRCA1/2 HR-deficient high grade ovarian tumors have enhanced immunogenicity compared to BRCA1/2-mutated tumors, which may be independent of neoantigen load.

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Figure 2. Volcano plot of gene expression changes in BRCAm (BRCA1/2+) and NBHRD (BRCA1/2-, HR+) cohorts.
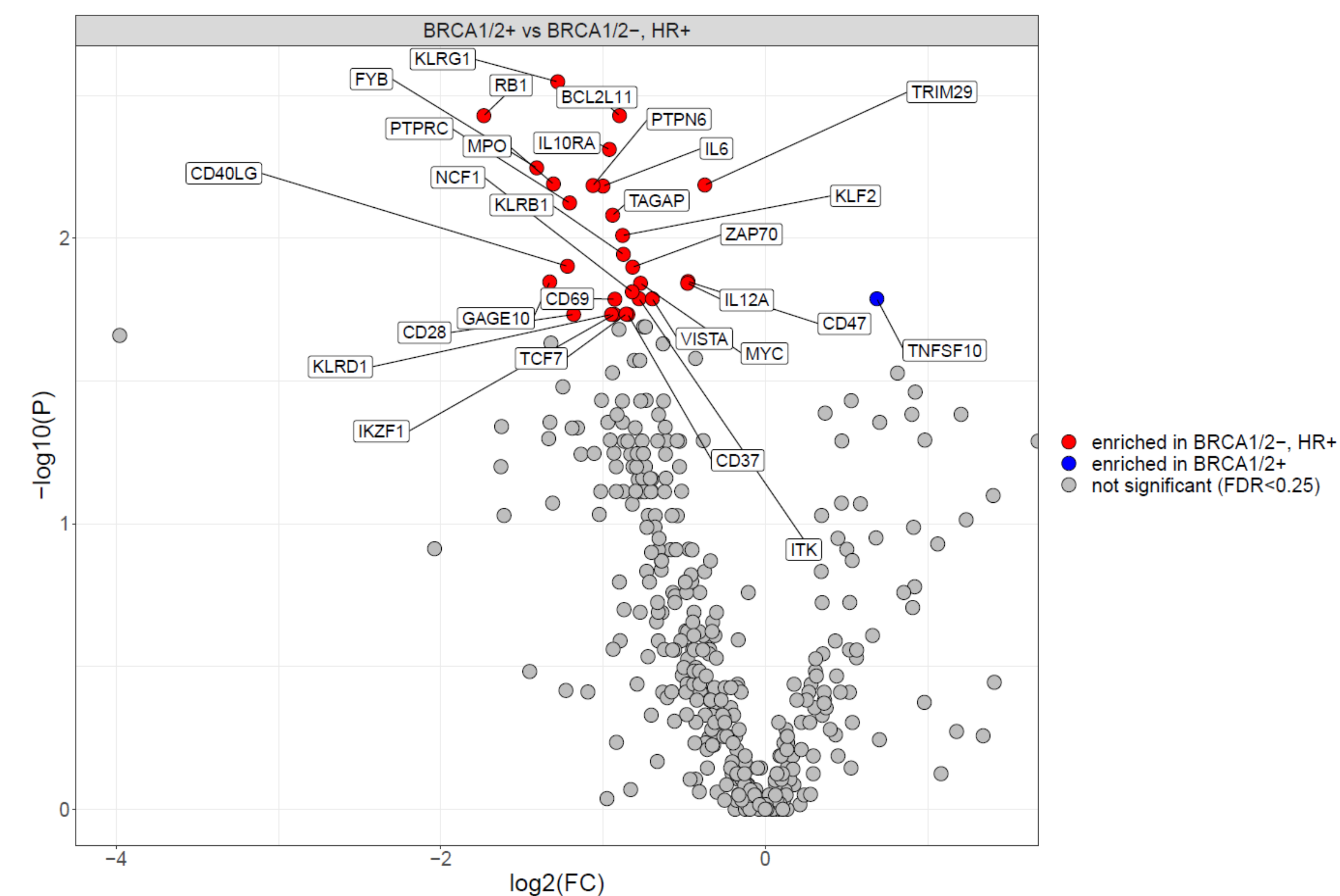

Results

84 cases had complete CGIP, including 11 BRCAm, 7 NBHRD, and 67 without HR gene alterations (HR-proficient, HRP). The histology of BRCAm and NBHRD tumors was consistent with high grade serous ovarian carcinoma (Figure 3).

Compared to the BRCAm cohort, NBHRD tumors were associated with (NBHRD vs BRCAm, p-value):

- Advanced age at diagnosis (mean 80y vs 63y, p=0.002)
- Lower TMB (3.9 vs 6.6, p=0.011)
- Higher Tumor Immunogenicity Score (mean 59.1 vs 41.7, p = 0.044)
- 32 immune genes with expression changes, 31 (97%) up-regulated (1.3-3.3 fold) in NBHRD compared to BRCAm tumors (Figure 2), including RB1
- No differences observed in PD-L1 TPS, Cellular Proliferation Score, or Cancer Testis Antigen Burden (p>0.05)

Figure 3. Representative images of H&E-stained BRCAm and NBHRD tumors
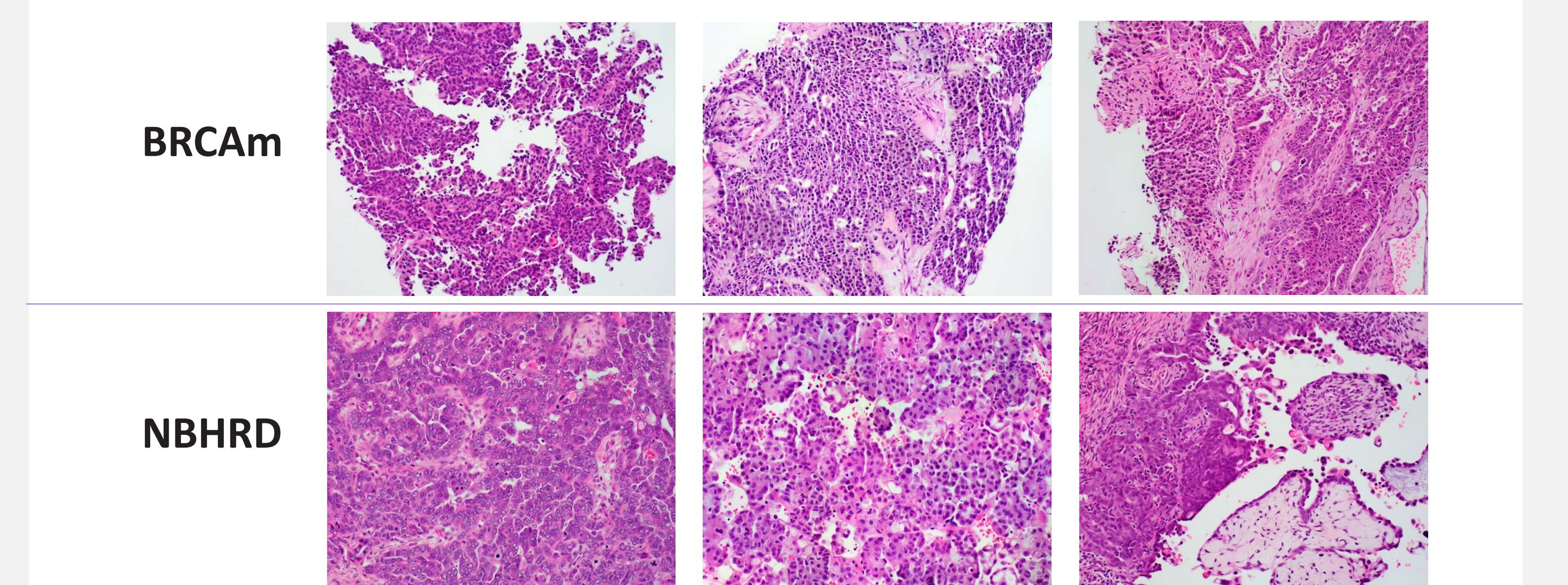
Conclusions

In this limited dataset, NBHRD tumors had a higher TIGS but harbored less mutational burden compared to BRCAm tumors

The findings suggest that:

- NBHRD tumors have enhanced immunogenicity that may be unrelated to neoantigen load
- NBHRD tumors may have distinct immune escape mechanisms versus BRCAm tumors.

Future Directions for Research:

- Establish whether the findings hold true for larger datasets
- Determine if NBHRD is associated with distinct clinico-pathologic features

References

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