Reclassification and variant distribution in the GINECO GREAT study of ovarian cancer patients: insights into HRD status

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BACKGROUND

In advanced ovarian cancer (AOC), a better understanding of specific genomic/proteomic alterations beyond tumor BRCA mutation (tBRCAm) and homologous recombination repair deficiency (HRD) is of critical importance for the next generation drug development and patient outcome improvement. **The main objective of GREAT was to develop a large AOC clinico-biological database** thanks to a tight collaborative network between clinicians, pathologists, biologists and researchers to correlate the real-life clinical and evolutionary characteristics of AOC patients (pts) with future innovative genomic and molecular tumor abnormalities.

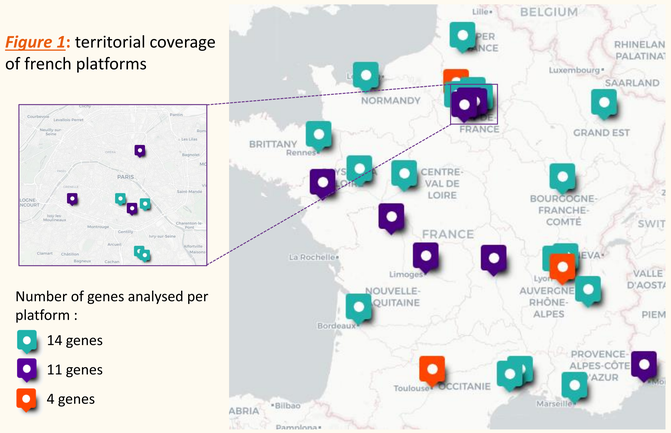
MAIN ENDPOINTS

- **Primary endpoint:**
  Evaluate the clinical and evolutive characteristics of patients according to the presence of a BRCA1 or BRCA2 mutation or biological tumor anomalies beyond BRCA that are likely to have a therapeutic impact.
- **Secondary endpoints:**
  - **To contribute to the development of future therapies for ovarian cancer by setting up a bank of tumor samples that will enable the subsequent implementation of cross-sectional exploratory research.**
  - To assess the real-life management of patients included in the study and, particularly, the type of BRCA test performed (tumor and/or germline).

METHODOLOGY

- From 2019 to 2022, **1507 patients with advanced (FIGO stage 3 or 4) non-mucinous epithelial OC** , were included in GREAT study **by 94 French centers** to better describe the molecular background of this cancer.
- **The HRD test was implemented subsequently in February 2021** following the Myriad test's availability (Myriad myChoice test for 95% and 5% patients analysed with other HRD tests).
- Genomic analyses were performed by 29 biological platforms coordinated at the national level ***(figure1)*** with evaluation of a gene tumor panel comprising **BRCA1/2, RAD51C/D, FANCA, CDK12, NBN, ATM, CHEK2, BRIP1, PALB2, PIK3CA, ARID1A**. The reference transcript, nomenclature of protein/nucleotide and class of genetic variants (VUS and pathogen) were collected.

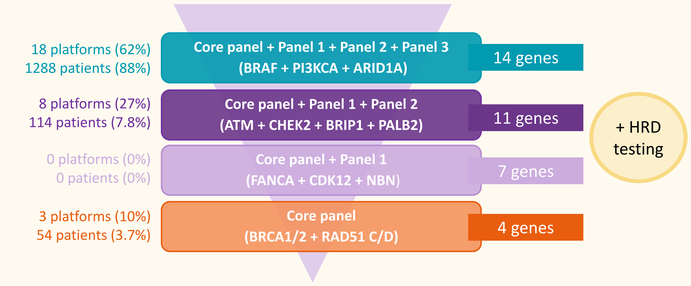
Figure 1: territorial coverage of french platforms



GENE PANEL TESTING AND REVIEW

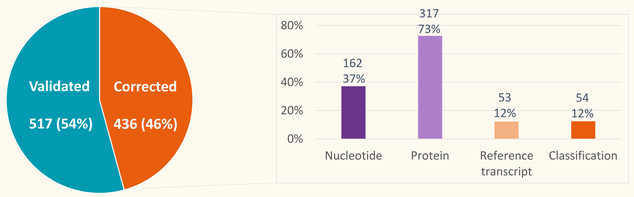
- **1456 patients** were tested by a panel of genes that varied according to the development of the platforms. **1288 (88%)** patients were tested by the **18 platforms** which screened a panel with at least **14 genes ;** 8 platforms screened a panel with at least 11 genes and tested 114 patients (7.8%) ; and the 4 genes of the mandatory core panel were performed by 3 platforms for 54 patients (3.7%) ***(figure 1 and 2).***

Figure 2: Description of the genes analysed



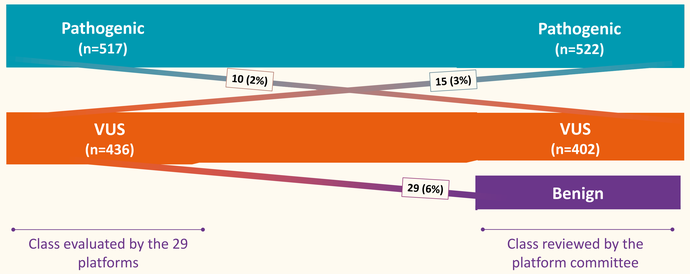
- Over a series of 15 meetings from 2020 to 2024, a **4-member expert committee** (Dr Etienne Rouleau, Dr Isabelle Soubeyran, Dr Veronique Haddad and Dr Dominique Vaur) **reviewed 953 variants**. The aim was to confirm variant nomenclature and classification.
- Of the **436 variants corrected**, variable errors were identified: 162 in nucleotide and 317 in protein nomenclature, 53 in reference transcript ***(figure 3).***

Figure 3: Description of the corrected type variants



- **54 classification errors detected for all the genes analysed** : 10 variants were reclassified from pathogenic to uncertain significance (VUS), 15 from VUS to pathogenic and 29 from VUS to benign ***(figure 4)***.
- **One patient BRCAm was reclassified in BRCAwt** while **3 patients BRCAwt were reclassified in BRCAm**, modifying their treatment.

Figure 4: Description of the corrected class variants



GENE VARIANT DISTRIBUTION

- Among the **1456 patients with molecular data**, 616 had at least one tumor variant (42%) and 388 had at least 1 pathogenic or likely pathogenic variant of which 140 (9.6%) in BRCA1 and 121 (8.3%) in BRCA2. There were **313 pathogenic variants in** Homologous Recombination Repair (HRR) core genes (mainly BRCA1/2-BRIP1-RAD51C/D) and 44 pathogenic variants in associated DNA repair genes (CDK12-ATM-CHEK2). For High Grade Serous Ovarian Cancer (HGSOC), primary pathogenic variants were 136 BRCA1 and 117 BRCA2 (including 13 large rearrangements) ; and 18 RAD51C/D. To note, 34 pathogenic variants in oncogenes uncommonly observed in HGSOC (PIK3CA-ARID1A-BRAF), were identified.
- **HRD status** was available for **1031 tumors** (68%) and 39% of HGSOC exhibit HRD. **98% of BRCA1 pathogenic variants were associated with HRD**, against **93% for BRCA2** and **100% for RAD51C and RAD51D**. At the opposite, pathogenic variants in associated DNA repair genes showed HRD in less than 26% of the cases ***(figure 5)***.

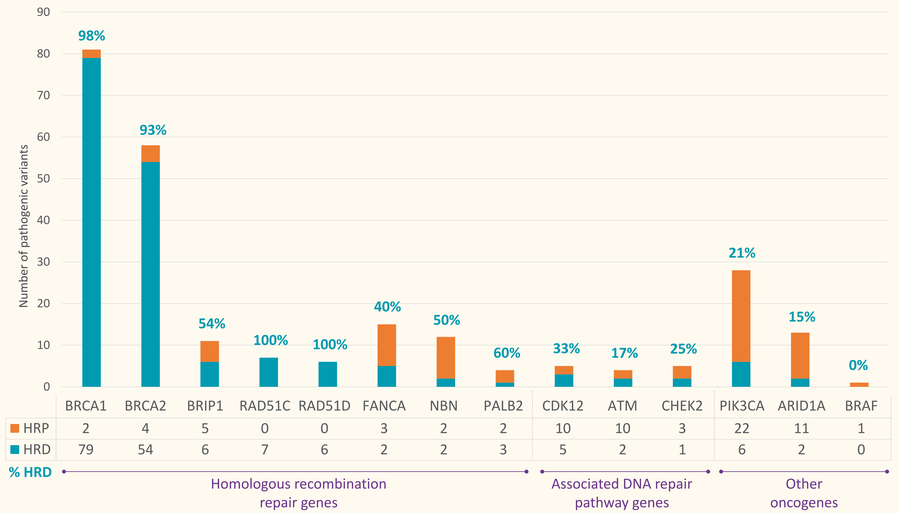


Figure 5: Gene mutation and HRD status (1031 tumors)

CONCLUSION

- Reclassification expert committee **plays a crucial role in accurately describing GREAT cohort** based on genomic data and confirms the significance of BRCA1/2-RAD51C/D in determining HR deficiency.
- The centralization of biological sample such as **DNA for 1370 patients** (among them, 539 have more than 500ng) and **FFPE blocks for 1353 patients** (947 patients with blocks that have tumoral surface >20mm² and cellularity > 20%) **will enable us to carry out large-scale translational research.**
- **TMAs is in progress, and we hope to be able to carry out projects aimed linked to therapeutic innovation.**

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