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POSTER ABSTRACTS

503.CLONAL HEMATOPOIESIS, AGING AND INFLAMMATION

Clonal Hematopoiesis in Whole-Blood and Cell-Free DNA of Ovarian Cancer Patients Undergoing PARP-Inhibitor Treatment: An Exploratory Analysis of the ENGOT-ov48/Eudario Trial

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Clonal hematopoiesis (CH), characterized by the expansion of somatically mutated hematopoietic stem cells, is an age-related phenomenon associated with the development of hematologic malignancies, increased cardiovascular risk, and other age-related proinflammatory conditions. In patients with solid tumors, cytotoxic therapies differentially select for clones with mutations in the DNA damage response (DDR) pathway, i.e. *TP53* and *PPM1D*, leading to an elevated risk for therapy-related myeloid malignancies (t-MNs). Poly(ADP-ribose) polymerase inhibitors (PARPi) are frequently used to treat ovarian cancer with particularly high efficacy reported in tumors exhibiting homologous recombination (HR) deficiency caused by mutations in *BRCA1/2* or other HR pathway genes. However, recent data indicate that PARPi treatment is also associated with an elevated risk for t-MNs.

Here, we performed an in-depth analysis of CH in whole-blood (WB) and plasma of patients with relapsed high-grade ovarian cancer (HGOC) receiving platinum-based chemotherapy and PARPi treatment, elucidating the mutational landscape of CH, gene-specific dynamics, as well as the potential interference of CH with putative tumor-derived mutations in cell-free DNA (cfDNA). Serial specimen of 103 patients with relapsed, platinum-sensitive HGOC participating in the European Trial on Enhanced DNA Repair Inhibition in Ovarian Cancer (EUDARIO) study (ENGOT-ov48/NCT03783949) were analyzed using error-corrected targeted sequencing with a custom panel covering 45 myeloid and 27 HR-related genes. Study treatment consisted of six cycles of carboplatin-based chemotherapy followed by maintenance therapy with Niraparib ± the HSP90 inhibitor Ganetespib.

A total of 128 somatic mutations with variant allele frequencies (VAFs) ≥ 1% were identified in 58 patients (56%) with a high fraction of DDR mutations (51 *PPM1D* mutations in 27 patients, 7 *TP53* mutations in 7 patients). Age (median 62 years) and the number of previous therapy lines (median 1, range 1-5 lines) were significantly associated with the presence of CH. Specifically, prior exposure to PARPi treatment was strongly associated with both the presence of CH and the number of CH mutations. CH-positive patients had significantly shorter progression-free survival (median 7.9 months vs 10.6 months, p = 0.021 in log-

rank test), and a trend for shorter overall survival (median 21.1 months vs 27.7 months, $p = 0.16$) in univariate survival analysis. With respect to adverse events, CH-positive patients more frequently had infections during study treatment (49% vs 26%, $p = 0.025$).

All but 5 CH mutations with VAF $\geq$ 1% were also detectable in cfDNA with significant correlation of VAFs ($R = 0.84$, $p < 0.0001$). Mutations occurring solely in cfDNA (putatively tumor-derived) had a high fraction of *TP53* and HR-related mutations, while *DNMT3A* and *PPM1D*, were rarely mutated (Figure 1). However, 23/87 (26%) of *TP53* mutations and 31/98 (32%) of mutations in HR-related genes detected in cfDNA were of hematopoietic origin, underlining the importance of parallel sequencing of WB in liquid biopsies to avoid false positive results.

The dynamics of CH clones under carboplatin and PARPi treatment were assessed in paired WB samples at initiation/end of treatment, which were available for 62 patients. 96 clones that initially had a VAF < 1% emerged during the treatment, including 56 *PPM1D*- and 10 *TP53*-mutated clones. Gene-wise comparison revealed a significantly higher median clonal fitness in *PPM1D*- and *TP53*-mutated clones compared to *TET2*- or *DNMT3A*-mutated clones (Figure 2). *PPM1D*-mutated clones exhibited lower fitness during PARPi treatment compared to carboplatin treatment ($p = 0.0015$ in Wilcoxon rank sum test), which was not the case for *TP53*-mutated clones.

Finally, 8 samples with multiple mutations were subjected to single-cell genotyping on the Mission Bio Tapestri platform to investigate their clonal architecture. Preliminary data indicate clonal exclusiveness of co-occurring DDR mutations.

In summary, our data reveals a high prevalence of CH in patients with relapsed HGOC and provides novel insights into the clonal architecture and dynamics of CH under carboplatin and PARPi treatment with a differential selection of DDR-driven clones. Moreover, we report a relevant interference of CH-derived mutations with tumor-derived mutations in cfDNA.

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Figure 1

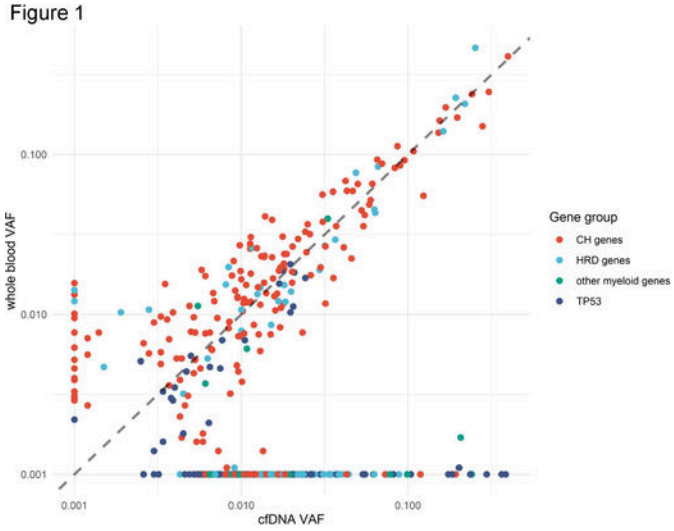

Figure 1. Variant allele frequencies (VAFs) of somatic mutations detected in cfDNA and/or WB DNA of 102 paired samples at initiation of treatment. For reasons of graphical illustration, VAFs of mutations detected in only one DNA source were set to the detection limit of 0.1% in the other. Color depicts mutated gene group. CH genes include *ASXL1, BCOR, BCORL1, CBL, DNMT3A, GNB1, GNAS, IDH1, IDH2, JAK2, PPM1D, PTPN11, RUNX1, SF3B1, SRSF2, STAG2, STAT3, TET2, U2AF1*; HRD genes include *ATM, ATR, BARD1, BRCA1, BRCA2, BRCC3, BRIP1, CDK12, CHEK1, CHEK2, EMSY, FAM175A, FANCA, FANCC, FANCI, FANCL, MLH1, MRE11, MSH2, MSH6, NBN, PALB2, PMS2, RAD21, RAD50, RAD51, RAD51C, RAD51D, RAD52, RAD54L, PTEN*; other myeloid genes include *CEBPA, KIT, KRAS, NRAS, ETV6, CSF3R, WT1, SETBP1, MYD88, FLT3, NF1, EZH2, GATA1, GATA2, CALR, MPL, NPM1, PHF6, BRAF, NOTCH1, XPO1*.

Figure 2

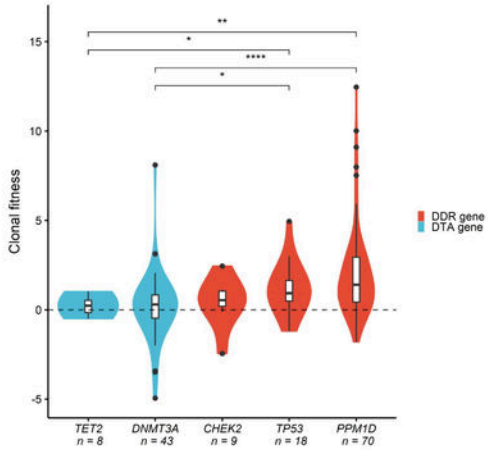

Figure 2. Gene-specific clonal fitness estimates obtained from analysis of 62 paired WB samples at the initiation and end of study treatment. Clonal fitness s was estimated by modeling clonal growth over time as a sigmoid function $\mathrm{VAF}(t) = \frac{1}{2}\frac{1}{1+Ae^{-st}}$, where t is the time in years and A is a numeric constant. Median values of s were compared using the Wilcoxon rank sum test. * p < 0.05, ** p < 0.01, *** p < 0.001, **** p < 0.0001

Figure 1

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