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POSTER ABSTRACTS

503.CLONAL HEMATOPOIESIS, AGING AND INFLAMMATION

Impact of PARP Inhibitor and Platinum Therapy on Clonal Hematopoiesis

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Poly (ADP-ribose) polymerase inhibitors (PARPi) are a promising new class of targeted therapy used in a variety of solid tumors with homologous recombination deficiencies (HRD). Data from clinical trials and observational studies have linked PARPi and platinum-based agents to therapy-related myeloid neoplasia (tMN). However, interpretation of these findings is limited by confounding variables including germline mutation status and prior therapeutic exposure. We and others have shown that the oncologic therapies known to confer an elevated risk of leukemia also promote the expansion of clonal hematopoiesis (CH) due to mutations of genes in the DNA damage response (DDR) pathway, including *TP53, PPM1D* and *CHEK2*. However, the extent to which CH is associated with targeted therapies such as PARPi is not clear. We hypothesized that exposure to PARPi confers a competitive advantage to hematopoietic stem/progenitor cells (HSPCs) containing mutations in DDR pathway genes. Moreover, we hypothesized that in patients with germline mutations in HRD genes, such as *BRCA1/BRCA2*genotoxic stress induced by PARPi or cytotoxic agents is increased, further enhancing the fitness of HSPCs carrying DDR gene mutations
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To test these hypotheses, we performed longitudinal studies on 942 peripheral blood samples collected from 418 patients (ages 32 to 94) before and after treatment with PARPi (n = 100), carboplatin (n = 142), and untreated individuals (n = 176). Patients with lung, ovarian, uterine, prostate, and breast cancer who received PARPi or carboplatin on clinical trials or through standard of care were included. Patients were treated with a variety of PARPi including Olaparib (n=48), Talazoparib (n=33), Rucaparib (n = 13) and Niraparib (n = 6.) Of the 418 patients, 45 individuals harbored an HRD germline mutation. Samples were sequenced at a depth of 18,946x using a UMI-based panel including 9 common CH genes (*DNMT3A, TET2, ASXL1, TP53, PPM1D, SRSF2, SF3B1 and JAK2*). Both carboplatin and PARPi treatment significantly increased the growth rate of CH mutations, driven almost entirely by mutations in DDR genes (Figure 1). Patients undergoing carboplatin treatment had significantly higher rates of mutational growth compared to those undergoing PARPi therapy (p-value = $5e^{-17}$). The strongest PARP-trapping member, Talazoparib, had the largest effect on the growth rate of CH mutations in DDR genes (p-value = $3e^{-9}$) but still lower compared to carboplatin. Surprisingly, DDR CH expansion was largely abrogated in patients harboring a pathogenic HRD germline variant for both carboplatin (p-value = $3e^{-5}$) and PARPi (p-value = $7e^{-10}$).

To validate these findings, we developed a mouse model of *TP53*-mutatedCH by transplanting a limited number of *Trp53 R172H*bone marrow cells along with congenic wildtype bone marrow into irradiated recipients. The percentage of *Trp53 R172H*cells in the blood was measured by flow cytometry at baseline (6 weeks after transplantation) and after treatment with vehicle alone, Talazoparib or Olaparib daily, or cisplatin weekly, for 4 weeks. As expected, treatment with cisplatin resulted in a significant expansion of *TP53*-mutated cells (Figure 2). A non-significant trend to expansion of *TP53*-mutated cells also was observed after talazoparib, but not olaparib. We next modeled the effect of germline HRD mutations by generating bone

marrow chimeras containing heterozygous *Brca1*-mutated HSPCs competed with *Brca1*-mutated HSPCs also carrying *Trp53 R172H*. Consistent with the human CH data, no expansion of *TP53*-mutated cells was observed after treatment with either cisplatin or Talazoparib, indeed there was a small, but significant decrease (Figure 2).
Collectively, these data support the hypothesis that mutations in DDR genes provide a fitness advantage to HSPCs following PARP inhibitor and platinum therapy. However, compared to platinum therapy, PARPi shows less selective pressure on DDR CH. Importantly, these data strongly argue against our initial hypothesis that germline HRD variants enhance this fitness advantage. Indeed, our data suggest the opposite, with the fitness advantage of DDR gene-mutated HSPCs lost in cells with a heterozygous *Brca1*-mutations. These data suggest that PARPi therapy may have less of an impact on leukemia risk compared to carboplatin and in fact may show synergistic effects with HRD in blocking the competitive advantage of DDR CH during genotoxic stress.

Disclosures Patel: *Isabl Inc:* Current Employment. **Li:** *Amgen, Genentech, AstraZeneca, Daiichi Sankyo, Lilly, Illumina, GRAIL, Guardant Health, Hengrui Therapeutics, MORE Health and Bolt Biotherapeutics:* Research Funding. **Levine:** *Novartis:* Consultancy; *AstraZeneca:* Consultancy, Honoraria; *Janssen:* Consultancy; *Qiagen:* Membership on an entity's Board of Directors or advisory committees; *Incyte:* Consultancy; *Isoplexis:* Membership on an entity's Board of Directors or advisory committees; *C4 Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Prelude:* Membership on an entity's Board of Directors or advisory committees; *Auron:* Membership on an entity's Board of Directors or advisory committees; *Zentalis:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Mission Bio:* Membership on an entity's Board of Directors or advisory committees; *Ajax:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Roche:* Honoraria; *Lilly:* Honoraria; *Amgen:* Honoraria. **Link:** *Roche:* Other: Roche provided Idasanutlin free of charge. No compensation was provided, and Roche was not involved in design, conduction, or analysis of experiments.. **Bolton:** *GoodCell:* Membership on an entity's Board of Directors or advisory committees; *Servier:* Research Funding.

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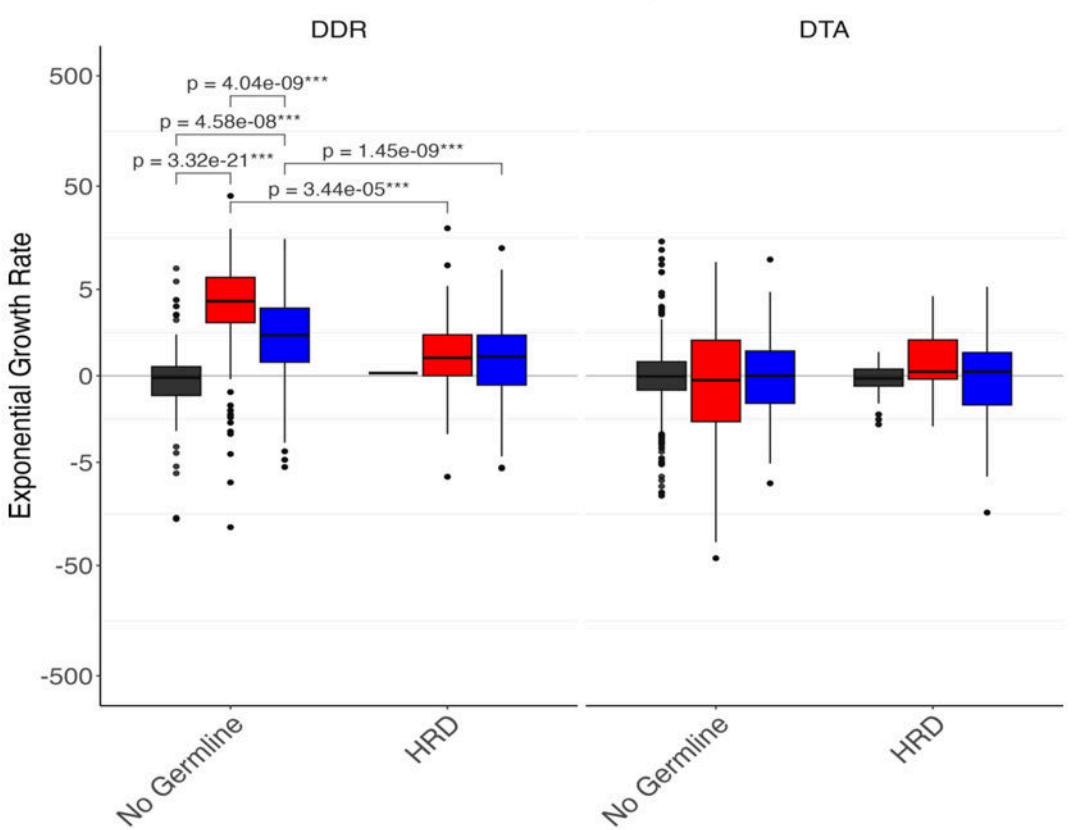

PARPi treatment increase the growth rate of mutations in DDR genes, but not within patients harboring germline HRD mutations. Exponential growth rate calculated as the linear regression coefficient of the log change in VAF as a function of the change in age before and after treatment. CH in patients driven by existing mutations in the DDR pathway as compared to more commonly CH associated genes like DNMT3A, TET2, and ASXL1 (DTA). Significance determined by linear regression model. N=416 total patients

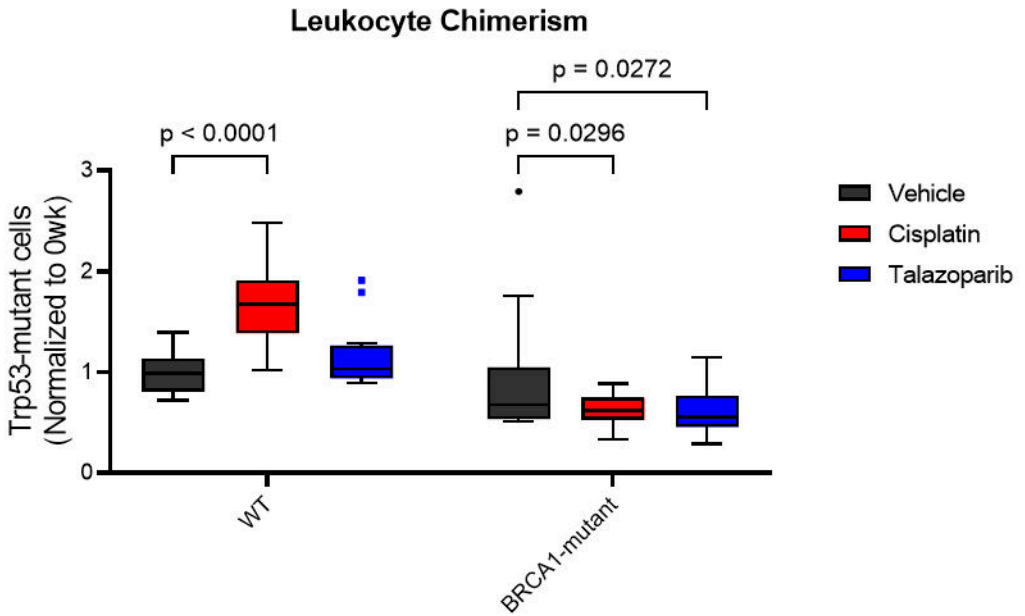

Figure 2. Treatment with cisplatin confers a fitness advantage to Trp53-mutated leukocytes on a wildtype background, but a disadvantage on a *Brca1*-mutated background. Shown is the ratio of $Trp53^{R172H/+}$ cells to wildtype competitor cells in the peripheral blood 12 weeks post-treatment with the indicated agent; data are normalized to the vehicle-only control. "BRCA1 mutant": both Trp53-mutated and wildtype competitor cells carry a germline mutation of *Brca1* ($Brca1^{F22\text{-}24/+}$). Significance determined by 2-way ANOVA (n=11-21).