Biomarkers of primary resistance to sacituzumab govitecan in metastatic triple negative breast cancer

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Introduction

Sacituzumab govitecan (SG) is a third-generation ADC composed of a humanized monoclonal anti-Trop2 (sacituzumab) conjugated via a hydrolysable linker to the topoisomerase 1 inhibitor SN-38 as the cytotoxic payload[1]. It is approved in mTNBC based on the ASCENT trial, a phase 3 clinical trial, in which SG improved survival outcomes in patients with pretreated metastatic triple negative breast cancer (mTNBC). Nevertheless 24% had progressive disease as best response and patients eventually progressed after a median of 6.3 months (95% CI, 5.5 to 9.0)[2]. The observed primary and acquired resistance to SG could arise through interference with the action of the monoclonal antibody and/or payload. Little is known about the resistance mechanisms to SG among patients with metastatic TNBC [3-6].

We conducted TRICS study to explore the resistance patterns to SG among patients with mTNBC by evaluating comprehensively genomic and transcriptomic biomarkers potentially associated with the loss of antibody mediated activity and impairment of payload-mediated cytotoxicity as well as the interaction with the immune microenvironment.

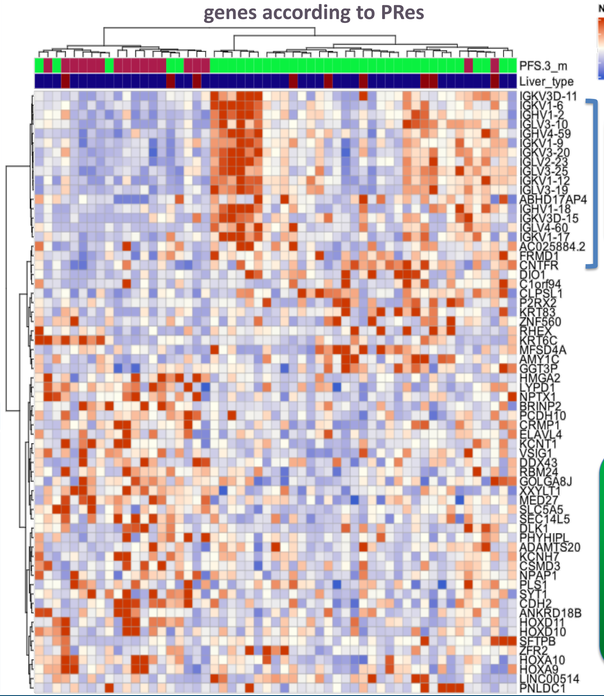
Methods and Materials

This retrospective study analyzed data from women with histologically confirmed mTNBC treated with SG at Gustave Roussy, France, between 2021 and 2024, as per standard practice. Inclusion required a formalin-fixed, paraffin-embedded tissue sample collected before treatment. FFPE blocks with sufficient tumor cell content of at least 50% underwent further processing for TROP2 IHC analysis, multiplex immunofluorescence (using SignalStar Multiplex IHC platform), targeted genomic panel and whole transcriptomic analysis using next-generation sequencing. **Herein, we report the results of multiplex immunofluorescence and bulk RNA seq**. The study was approved by the Institutional Board Review at Gustave Roussy under the registration number 2023-300.

Results

The study included 55 patients. 12 (21.8%) had *de novo* metastatic disease, and 13 (23.6%) were pretreated with immune checkpoint inhibitors in earlier lines. Germline *BRCA 1/2* mutations were reported in 8 patients (14.5%); 43 patients (78.2%) had wild-type status and 4 (7.3%) did not have a reported *BRCA* status.

Figure 1. Heatmap of the gene expression present in 64 top genes according to PRes



In responders, the genes with the highest log fold change involved immunoglobulins

Figure 2. GESA dotplot comparing gene expression patterns between patients with PRes to SG vs non PRes

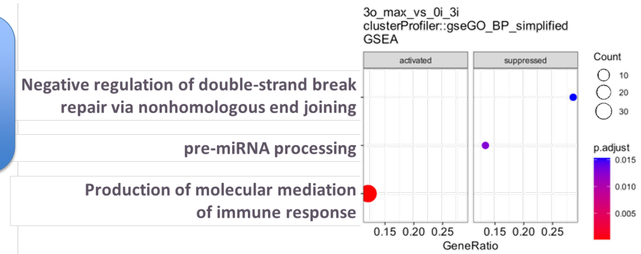
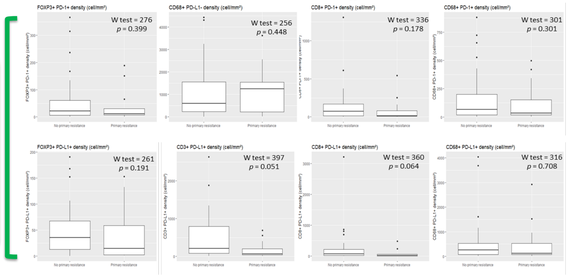


Figure 4. Immune phenotypes densities in tumor microenvironment according to PRes to SG

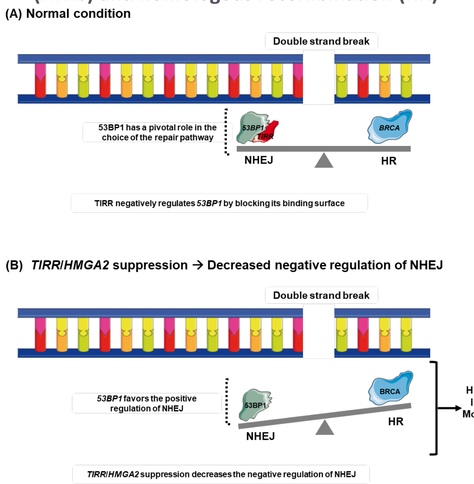


Trend toward decreased CD3+PD-L1+ (62.6 cells/mm² versus 209.7 cells/mm², p = 0.051) and CD8+PD-L1+ (20.4 cells/mm² versus 69.7 cells/mm², p = 0.064) cell densities.

Results

The median interval between tissue biopsy acquisition and treatment initiation was 6.8 months.17 patients had primary resistance (PRes) to SG, defined by PFS ≤ 3 months. Our findings are reported in figure 1 to 4.

Figure 3. The balance between nonhomologous end joining (NHEJ) and homologous recombination (HR)



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Conclusions

This study did not identify any mechanisms of PRes to SG associated with alterations in TROP2 or topoisomerase 1. PRes seemed to be driven by a complex interplay between the tumor and the immune microenvironment, as well as mechanisms related to DNA damage repair.

Acknowledgments

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