Activity of Olaparib in Metastatic Triple Negative Breast Cancer with BRCA-1 Mutation Variant of Undetermined Significance

Aurelio Castrellon*

Sylvester Comprehensive Cancer Center, University of Miami, Miller School of Medicine, Miami, USA

Corresponding Author*

Aurelio Castrellon
Sylvester Comprehensive Cancer
Center, University of Miami,
Miller School of Medicine,
Miami, USA
E-mail: acastrellon@mhs.net

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About the Study

The addition of targeted agents to the armamentarium of therapies for Triple-Negative Breast Cancer (TNBC), like in other types of breast cancer, has improved the overall survival of patients affected with advanced disease [1]. Inhibitors of the poly adenosine diphosphate-ribose polymerase (PARP inhibitors) block an important enzyme involved in the repair mechanism of DNA damage in cells. Following the findings of the olympiad phase 3 clinical trial, Olaparib was the first targeted therapy to be approved in the treatment of metastatic TNBC [2].

We present the case of a patient with widely metastatic TNBC who underwent several lines of chemotherapy, including Yttrium-90 therapy to metastatic disease in the liver. Following a tumor molecular profiling, patient was found to be a carrier of mutated BRCA1 Next-Generation Sequencing (NGS) Variant of Unknown Significance (VUS). The patient experienced a significance response to the use of Olaparib, which is ongoing for over 70 months at the time of this report.

In November 2014, a 62-year-old female presented with a palpable left breast mass, leading to a diagnosis of stage IV TNBC with liver metastases. Despite initial palliative therapy with Capecitabine, the disease progressed, necessitating a switch to Nab-paclitaxel. Unfortunately, this treatment also failed, and Gemcitabine was attempted but discontinued due to uncontrolled liver metastases (Figure 1).

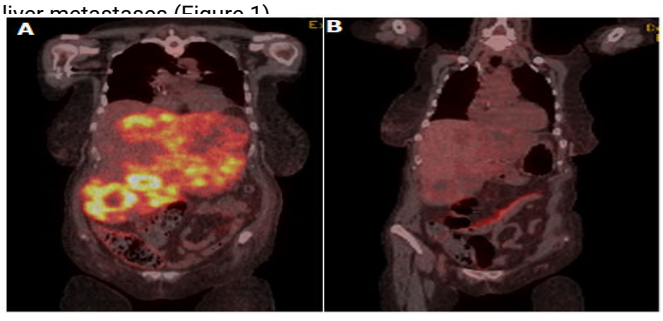

Figure 1. A) 2014, uncontrolled liver metastasis following capecitabine, nab-paclitaxel, gemcitabine; B) 2016, significant improvement following Yttrium-90 Selective Internal Radiation Therapy (SIRT) and weekly paclitaxel and carboplatin.

With a grim prognosis and worsening condition, the patient was considered for Yttrium-90 Selective Internal Radiation Therapy (SIRT), which was administered via the hepatic artery in April 2016. This intervention led to clinical improvement and to enhance its effects, weekly paclitaxel with carboplatin was introduced. The patient responded well, showing a marked decrease in hepatomegaly, and a second Y-90 SIRT procedure was performed in May 2016. She continued chemotherapy until September 2016 when it was stopped due to an allergic reaction to carboplatin. FDG-PET/CT scans demonstrated an impressive response to Y-90 SIRT which has been reported previously [3].

Patient was followed clinically and with serial FDG-PET/CT. In anticipation for future required therapy, molecular profiling using (CARIS Life Science®) was done to detect actionable mutations. The test demonstrated a mutated BRCA1 NGS VUS (Exon 2 I 15 deletion). In September 2017, the patient was found to have progressive disease with FDG-PET/CT revealing innumerable pulmonary metastases, new bilateral pleural metastases and interval development of bone metastases (Figure 2).

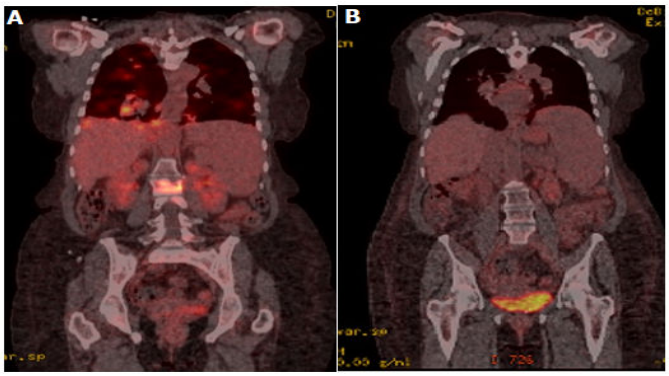

Figure 2. A) 2017, FDG-PET/CT revealing innumerable pulmonary metastases, new bilateral pleural metastases, and bone metastase; B) 2020, FDG-PET/CT showing no evidence of active metastases while being treated with Olaparib.

Olaparib was initiated in November 2017, and the patient responded well with minimal toxicity. Serial FDG-PET/CT scans showed continued response and by September 2020, no detectable evidence of active metastases was observed.

In June 2021, the patient was diagnosed with brain metastases, leading to surgical resection followed by cyber knife therapy. Subsequent MRIs did not reveal a recurrence of CNS disease, and molecular profiling once again detected the BRCA1 NGS mutated VUS (Exon 2 I 15 deletion).

As of August 2023, the patient remains without evidence of disease both systemically and in the CNS, experiencing minimal side effects and enjoying a good quality of life.

This case highlights a remarkable and enduring response with Olaparib in a heavily treated patient with metastatic TNBC harboring a somatic *BRCA-1* gene mutation (Exon 2 I 15 deletion). The patient showed a significant response to a platinum agent, which prompted the off-label use of Olaparib. Given the patient's lack of progression on platinum therapy, this approach appears promising. Studies suggest that introducing PARP inhibitors before platinum resistance develops can yield better outcomes [4]. In metastatic breast cancer, where standard treatments often lead to resistance and side effects, targeted agents like PARP inhibitors

offer hope for improved response rates and progression-free survival. The patient's unique response to Olaparib, with a VUS mutation in the *BRCA1* gene, underscores the potential of this therapy. We advocate that clinical trials should evaluate patients with VUS somatic mutations in order to identify additional patients that could benefit from PARP inhibitors.

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