Background

- The efficacy of Olaparib in BRCA-associated cancers with germline or somatic mutations has been well demonstrated. The benefit of Olaparib in other homologous recombination (HR) genes has been poorly assessed.
- The MOST-Plus trial (NCT02029001) is a prospective study, designed to assess the clinical activity of targeted therapy, including olaparib, in advanced or metastatic solid tumors based on molecular tumor board recommendations.

Aim: To determine which sets of HR mutations and tumor types are associated with Olaparib sensitivity (tumor response or stable disease)

Methods

- Ongoing multicenter, prospective, randomized trial
- Conducted in six French university hospitals
- Patients known to have germline or somatic alterations in one of the HR genes
- Treated with Olaparib (300mg, BID) outside EMA approval, until disease progression, unacceptable toxicity, patient or investigator decision.
- Disease response was evaluated at 12 weeks of treatment per RECIST V1.1.

Results

1. Molecular alterations based on cancer type 30 different cancer types, 23 HR gene alterations

2. Tumor response at Week 12 for the main molecular alterations

   - BRCA1
   - BRCA2
   - PALB2
   - ATM
   - BAP1
   - Others

   - Baseline Characteristics (No. 213 patients)

   - Age – year, median (range)
   - Sex – No. (%)
   - Race – No. (%)
   - ECOG-performance-status score – no. (%)
   - Prior – No. (%)

3. Treatment discontinuation and adverse events

   - Interruption of intervention
   - Interruption of intervention due to adverse event
   - Dose reduction due to adverse event
   - Discontinuation of intervention due to adverse event
   - Death due to adverse event

4. Characteristics of CR/PR patients (N=14)

   - Tumor type
   - Gene alteration
   - Type of alteration
   - Clinical response
   - Radiological response
   - Graduation

   - BRCA1
   - BRCA2
   - PALB2
   - ATM
   - BAP1
   - Others

Histology:
- Breast cancer accounted for 57% of objective responses, and 26% of the overall population

Germline mutation:
- Information available for 39 patients (18%), 32 with germline mutations
- For germline mutated patients: disease control rate of 42%, compared to 19% in the population with somatic mutation and unknown germline status.

BRCA-associated tumor-types:
- Breast, ovary, prostate and pancreas cancers
- 50% of all patients
- 86% of partial responses
- 60% of non-progressing patients.

Conclusion

After 12 weeks of treatment, disease-control rate with Olaparib was 23% (48/213) across all tumor types and HR gene alterations. MOST Olaparib has allowed the specific evaluation of Olaparib as part of a molecular-matched strategy, much like what is routinely done by molecular tumor boards. These results led us to limit inclusions to BRCA2, BRCA1, RADS1, RADS1D, PALB2, and in case of double hit, BAP1, ATM, BRIP1 mutations.

Adverse events of any grade were reported in 88% of patients. Eight deaths occurred during this induction phase. These were due to cancer progression, ileus, pericardial effusion, pulmonary embolism and asystolic complications, none of which were directly related to Olaparib treatment.