A single-agent trial assessed the single-agent efficacy and safety of the PARP inhibitor olaparib in patients with metastatic colorectal cancer (mCRC) stratified by microsatellite status (MSs).

II. Hypotheses

1. Olaparib administered to patients with disseminated CRC leading during or after standard systemic therapy will result in clinical benefit (partial or complete) remission and stable disease (progression free survival).

2. Patients who exhibit germ line mutations in mismatch repair genes (MMR) or those patients with high grade endometrial cancer will have higher response rates and longer progression free survival (PFS) than those patients whose tumors are non-MSH.

Exploratory Translational Objectives

1. To determine whether PARP-1 levels found in archival tissue prior to treatment have a relationship to response and/or toxicity for patients treated with olaparib.

2. In patients who continue to experience fatigue on therapy, to measure and explain drug activity levels after 7 to 10 days of therapy with olaparib.

3. To determine if pharmacogenomic parameters as determined from pre-therapy blood samples affect response or toxicity to olaparib.

III. Clinical Methodology - Trial OCR01

- All patients with mCRC failing standard tx and ECOG PS 0-1 were eligible regardless of MS status.
- Patients receive olaparib 400 mg po bid; one cycle was 28 days.
- CT scan evaluations q 8 wks.
- MS status was performed centrally in a CLIA certified lab by RT-PCR under the direction of Dr. Stanley Hamilton at the M.D. Anderson Cancer Center.
- Exploratory Translational Objectives

- Response data for MSI-H patients are not available.
- MSI-H patients with mCRC represent a small fraction of the total mCRC population enrolled.
- Patients treated with olaparib.
- At least 30% of all patients eligible for this protocol

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IV. Current Results

- 20 non-MSH patients were enrolled in 3 sites.
- Median age 56 (range 39-62).
- Median PS: 0.
- 4 patients had grade 3 or 4 non-heme toxicities, fatigue most common.
- 2 patients had grade 3 or 4 non-heme toxicities.
- 10 MSI-H patients have been enrolled.
- Response data for MSI-H patients are not available.

V. Conclusions

- Olaparib was well tolerated in both non-MSH and MSI-H patients.
- Rapid accrual of non-MSH mCRC patients to 3rd line therapy attempts to move for new agents in CRC.
- MSI-H patient accrual continues.
- MSI-H patients with disseminated CRC who fail to standard therapy represent less than 30% of all patients eligible for this protocol.

Although it may not be feasible to develop agents targeting MSH-H patients with disseminated CRC (15% or less), a positive outcome could have greater meaning in the adjacent setting where 20% of patients are MSI-H.

Even in the 3rd line setting, highly motivated patients are willing to undergo treatments with this severity of side effects, in an attempt to achieve improvement in clinical outcomes for patients with advanced colorectal cancer. Relevant biomarkers for the biopsies are explained by highly recruited investigators. Efficacy results and the biopsies for patients on this trial will be subjected to a separate report.

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