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# A phase 1/2 multi-center study of ABI-009 (*nab*-sirolimus) combined with FOLFOX and bevacizumab as first-line (1L) therapy in patients (pts) with metastatic colorectal cancer (mCRC) with or without PTEN loss


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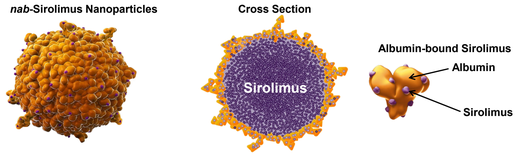
## INTRODUCTION

- Colorectal cancer is the 3rd most common cancer, with a 5-year survival of 14% for pts with mCRC.[1]
- FOLFOX + bevacizumab is a standard of care (SOC) for the 1st-line treatment of pts with mCRC.[2] The median PFS is 9-11 months, and ORR is ~50% in most studies. [3-5]
  - Improvement in reducing tumor burden and time to progression in the 1st-line setting is still needed.
- The mTOR oncogenic pathways (PI3K/AKT/mTOR) are frequently dysregulated in human cancers, including colorectal cancer. [6]
- A recent phase 1/2 study with everolimus, an mTOR inhibitor, plus mFOLFOX6 + bevacizumab for the 1st-line treatment of mCRC showed promising results (NCT01047293): [7]
  - 6-month PFS rate was 96% at the maximum-tolerated dose (MTD)
  - ORR: 53% for all pts and 86% in pts with PTEN loss
- ABI-009 is a novel injectable albumin-bound sirolimus nanoparticle (*nab*®-sirolimus, *nab*®-rapamycin) with a mean particle size of ~100 nm and that has demonstrated both a favorable safety profile and evidence of efficacy in patients with metastatic solid tumors (NCT00635284). [8]




- ABI-009 IV produced significantly greater antitumor activity and prolonged survival vs with equal weekly dosing of oral rapamycin and oral everolimus in a tumor xenograft model. [9]
- This phase 1/2 study investigates ABI-009 given IV with mFOLFOX6 + bevacizumab (an SOC) as 1st-line treatment for mCRC with respect to PTEN status.

## References


1. Siegel, Cancer Statistics, 2017
2. NCCN, CRC v4 2018
3. Bendell et al., Oncologist, 2012
4. Saltz et al., J Clin Oncol, 2008
5. Rivera et al., Int J Colorectal Dis, 2012
6. Laes et al., Oncotarget, 2017
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8. Gonzalez-Angulo et al., Clin Cancer Res, 2013
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## METHODS

- **The goal of this phase 1/2 multi-center study is to evaluate if ABI-009 + a standard of care A) is safe and efficacious and B) may have improved benefit in patients with PTEN loss.**

### Study Design

**Key Eligibility**

- Confirmed measurable mCRC
- No prior chemo for adv disease
- ≥18 years old
- ECOG PS 0-2
- No prior mTORs

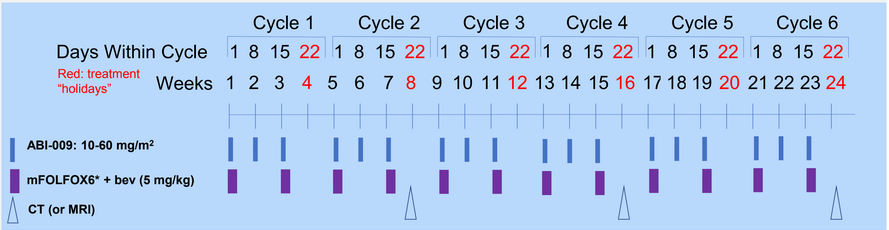
**For Full Eligibility Criteria, please visit: ClinicalTrials.gov: NCT03439462**

**Phase 1**
ABI-009 + mFOLFOX6 + bev
N= up to 18 pts
3+3 Dose-finding

| Dose Levels | ABI-009, mg/m² |
|---|---|
| 3 | 60 IV |
| 2 | 45 IV |
| **1** | **30 IV** |
| -1 | 20 IV |
| -2 | 10 IV |

RP2D identified

**Phase 2**
ABI-009 at RP2D + mFOLFOX6 + bev
N = up to 40, incl ph 1 at RP2D




* Oxaliplatin 85 mg/m² IV, 5FU bolus 400 mg/m² IV + LV 400 mg/m² IV over 2 hrs, 5FU 2400 mg/m² infusion over 46 hrs.
Note: **Treatment until disease progression or unacceptable toxicities.** Patients treated for more than 6 months may be switched to mFOLFOX and bevacizumab every 3 weeks.

### Primary Endpoints

- **Phase 1**: MTD and dose-limiting toxicities of ABI-009 in combination with mFOLFOX6 and bevacizumab
- **Phase 2:** Progression-free rate at 6 months

### Secondary Endpoints

- **Phase 1:**
  - Safety profile of dose cohorts analyzed separately and together
  - Disease control rate assessed by investigators, all pts and per dose cohorts
- **Phase 2:** data both from phase 1 and 2
  - Median progression-free survival, overall response rate, duration of response, and disease control rate in all pts and based on PTEN status
  - Progression-free rate at 6 months based on PTEN status
  - Safety at the recommended phase 2 dose (RP2D)

### Exploratory Endpoints

- **Biomarkers:**
  - **Pre-treatment metastatic tumor biopsy:** baseline biomarker and mutational analysis for PTEN loss, PIK3CA and Ras mutational status, and mTOR pathway markers.
  - **Blood samples:** cell-free plasma DNA collection (pretreatment, C3 D1, C6 D1, and end treatment) to assess changes over time as response to therapy.

### Dose Modifications

- ABI-009: max 2 dose level reductions are allowed based on a predefined guideline.
- Modified FOLFOX6: Dose modifications of each agent in FOLFOX may be made independently based on specific toxicities observed and should follow the package insert.
- Bevacizumab (5 mg /kg) may be skipped or discontinued for toxicities, but not reduced.

### Key Safety and Efficacy Assessments

- All AEs will be collected throughout the study until 28 days after the last dose of ABI-009. AEs will be graded by NCI CTCAE v5.0.
- Tumor response assessed by CT per RECIST v1.1 until disease progression or unacceptable toxicity at:
  - baseline
  - every 8 weeks for the first year
  - every 12 weeks thereafter.
- Post-treatment follow-up every 12 weeks until death, withdrawal of consent, or the study closes.

## ANTICIPATED CONCLUSIONS

- This trial may help determine whether ABI-009 IV plus a standard of care mFOLFOX6 + bevacizumab is an effective and safe treatment option for pts with mCRC with respect to PTEN status.
- The trial is currently enrolling patients to cohort 1 in the phase 1 dose-finding portion of the study.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