INTRODUCTION

• Multikinase chemotherapy remains the cornerstone of treatment for metastatic colorectal cancer (mCRC), with most patients receiving some combination of capecitabine, fluorouracil, or irinotecan in the first-line setting, often in combination with a monoclonal antibody targeting the epidermal growth factor receptor (EGFR) or vascular endothelial growth factor (VEGF) pathway.

• Improvements in overall survival (OS) and progression-free survival (PFS) gained from combining bevacizumab, fluorouracil, oxaliplatin, and irinotecan (FOLFOXIRI) with bevacizumab-induced myelosuppression and use of this regimen at the standard-of-care dose and schedule.

STUDY OBJECTIVES

1. PRIMARY OBJECTIVE

To evaluate the effects of trilaciclib versus placebo on the neutrophil/nadir in patients receiving FOLFOXIRI bevacizumab for pMMR/MSS mCRC

2. KEY SECONDARY OBJECTIVES

• To assess the effects of trilaciclib versus placebo on chemotherapy-induced fatigue, measured using the Functional Assessment of Chronic Illness Therapy—Fatigue (FACT-F) scale.

• To assess the effect of trilaciclib versus placebo on OS and PFS, and per Response Evaluation Criteria in Solid Tumours version 1.1

PHASE 1: RANDOMIZED, DOUBLE-BLIND TRIAL OF TRILACLIB VS PLACEBO IN PATIENTS RECEIVING FOLFOXIRI/BEVACIZUMAB FOR METASTATIC COLORECTAL CANCER

JOLENE M. HUBBARD, MD; MATTHEW PROCTOR, MD; SATISH SHARMA, BS; ASHRAF EL GABAYAT, MD; RICHARD SEGEL, MD; YI LI, MD; PRITCHETT, MD; JOHN YI, MD; JENNET HORTON, MD; AND FORTUNATO CARIDIOLI

Saudi Clinic, Richmond, VA, USA; Genentech Cancer Center, Genentech, South San Francisco, CA, USA; Beverly Hills Cancer Center, Beverly Hills, CA, USA; Luochrome Cancer Specialists, Arlington Heights, IL, USA; GS Therapeutics, Inc, Research Triangle Park, NC, USA; University of Cambridge Languar, Naples, Italy

STUDY DESIGN

Phase 1, multi-center, randomized, double-blind, placebo-controlled study evaluating myeloprotection and antitumor efficacy of trilaciclib administered prior to FOLFOXIRI/bevacizumab for patients receiving first-line treatment for proficient mismatch repair/microsatellite stable (pMMR/MSS) mCRC.

• FOLFOXIRI is more efficacious and more myelosuppressive than other fluorouracil-based regimens used in the treatment of mCRC. Therefore, patients should benefit from a reduction in the incidence of chemotherapy-related toxicity, including myelosuppression, diarrhea, and mucositis.

• As a result, the use of FOLFOXIRI is limited to younger patients with fewer comorbidities.

• Chemotherapy-induced myelosuppression, which commonly manifests as neutropenia, anemia, and/or thrombocytopenia, is a dose-limiting and potentially fatal complication of treatment that can result in hospitalization and the need for supportive care interventions.

• Symptoms of fatigue, and the development of infections and bleeding can seriously affect quality of life, and dose reductions and treatment delays may affect treatment response and long-term survival.

• Trilaciclib is an intravenous cyclo-pregnynolone-48-glutathione inhibitor indicated to decrease the incidence of chemotherapy-induced myelosuppression in adult patients administered prior to a platinum/etoposide- or topotecan-containing chemotherapy regimen for extensive-stage small-cell lung cancer.

• Data from 3 randomized, placebo-controlled, phase 2 clinical trials showed that administering trilaciclib prior to chemotherapy reduced the incidence of chemotherapy-induced myelosuppression, and reduced the need for supportive care interventions and chemotherapy dose reductions/alterations.

• Additionally, in a randomized phase 2 trial in patients with metastatic triple-negative breast cancer, administering trilaciclib prior to gemcitabine plus carboplatin significantly improved OS compared with chemotherapy alone, potentially through protection and activation of immune function.

TRILACLIB MECHANISM OF ACTION

• Trilaciclib (CNK010487666) is a phase 2, multi-center, randomized, double-blind, placebo-controlled study evaluating myeloprotection and antitumor efficacy of trilaciclib administered prior to FOLFOXIRI/bevacizumab for patients receiving first-line treatment for proficient mismatch repair/microsatellite stable (pMMR/MSS) mCRC.

• The phase 1 study enrolled 296 patients (148 per group) will be required for the study.

• The sample size is determined to support the primary efficacy analysis for the 2 primary efficacy endpoints.

• 252 patients will be needed to detect treatment effect on OS using a Mann-Whitney-Wilcoxon test, and on occurrence of SAE using a chi-square test, with 90% power at the 2-sided 0.05 level.

• Assuming 5% of randomized patients will not have any postbaseline data, a total of 296 patients (148 per group) will be required for the study.

CONCLUSIONS

• FOLFOXIRI/bevacizumab for proficient mismatch repair/microsatellite stable (pMMR/MSS) colorectal cancer improves OS, progression-free survival and overall survival.

• Total study sites: 120

• Estimated date last patient randomized: May 2022

• Estimated date myeloprotection analysis: Q1 2023

• Estimated date PFS/OS analysis: Q3 2025

DISCLAIMER:

• To ensure strong control of family-wise type I error rate at the level of 2-sided 0.05, the following statistical considerations are specified.

• Overall alpha (α) will be split for analyses between 2 groups:

  1. Group 1: analyses of the 2 primary myeloprotection endpoints and time to first confirmed deterioration in fatigue (TTCD-fatigue) using α = 0.0125

  2. Group 2: analyses of PFS and OS using α = 0.005

• Heuristic procedures are specified to test treatment effects within each group:

  • As corrrompitive endpoints, duration of severe grade 4 neutropenia (DSN) in cycle 1, and occurrence of severe neutropenia (SN) during induction will each be tested at 2-sided 0.04 level. Both of which are positive, i.e., will be passed to test treatment effect on PFS.

  • Treatment effect for OS will be tested after the treatment effect for PFS is established at the α level.

  • Results from Group 1 to Group 2:

    • If the treatment effects are established for all 3 endpoints in Group 1, PFS and OS will be tested at the 2-sided 0.05 level, otherwise, they will be tested at the PFS level.

• The overall α is 0.04, with the following type I error rate at the level of 2-sided 0.05, the following statistical considerations are specified.

• Overall alpha (α) will be split for analyses between 2 groups:

  1. Group 1: analyses of the 2 primary myeloprotection endpoints and time to first confirmed deterioration in fatigue (TTCD-fatigue) using α = 0.0125

  2. Group 2: analyses of PFS and OS using α = 0.005

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  • Treatment effect for OS will be tested after the treatment effect for PFS is established at the α level.

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