BOLD-100-001 (TRIO039): A Phase 1b/2a Dose-Escalation Study of BOLD-100 in Combination with FOLFOX Chemotherapy in Patients with Pre-Treated Advanced Colorectal Cancer: Interim Efficacy, Safety and Tolerability Analysis

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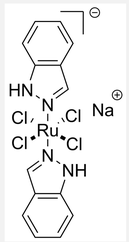
Introduction

- BOLD-100 is a first in class ruthenium-based anticancer agent in development for the treatment of gastrointestinal cancers.
- BOLD-100 is currently being tested in a Phase 2 clinical trial in combination with standard of care FOLFOX in patients with advanced GI cancers (NCT04421820) and has potential in a range of solid and liquid cancer indications.[1]
- BOLD-100 exerts its function via the modulation of the unfolded protein response via GRP78 downregulation, with secondary mechanistic pathways including generation of reactive oxygen species, DNA damage, modulation of lipid metabolism, and interactions with ribosomal proteins – *see BOLD-100 preclinical poster #2259*
- Here, we present interim efficacy, safety and tolerability data in patients with heavily pre-treated (3L+) metastatic colorectal cancer (mCRC).

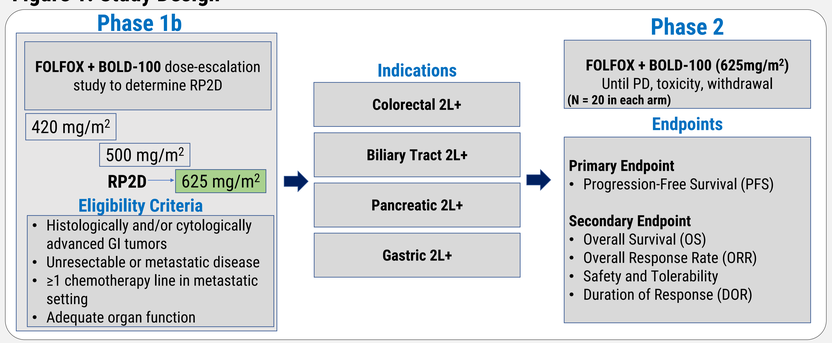


BOLD-100

Methods

STUDY DESIGN

Figure 1. Study Design



FOLFOX regimen: oxaliplatin 85 mg/m^2 IV Q2W; leucovorin 400 mg/m^2 IV Q2W; and 5-FU 2400 mg/m^2 (continuous 46 hour infusion). 5-FU, 5-fluorouracil; IV, intravenously; Q2W, once every 2 weeks; RP2D, Recommended phase 2 dose; 2L+. Second line and beyond.

STATISTICAL ANALYSIS

- Safety analyses included all 3L+ patients who received ≥1 dose of any study drug
- Efficacy analyses included all 3L+ patients who had a baseline and ≥1 post-baseline assessment or discontinued study treatment due to progressive disease or death
  - Clinical activity was assessed via RECIST v1.1 criteria
  - Disease control rate (DCR) was defined as the percentage of patients with a best overall response of complete response (CR), partial response (PR), or stable disease (SD)
  - A Bayesian approach was used to calculate the posterior probability that each endpoint is greater than the landmark historic value and 95% credible intervals were calculated.
  - It is recommended that the posterior probability of superiority to the landmark exceed at least 70% for at least one endpoint.

Results

PATIENT BASELINE CHARACTERISTICS

Table 1. Demographics and Disease Characteristics	**All Patients** (n = 17)		
Median age (range), years	62 (47-78)	**ECOG Performance Status, n (%)**	
Male sex, n (%)	8 (47)	0	5 (29)
Race		1	12 (71)
White	7 (41)	**Stage IV disease, n (%)**	16 (94)
Asian	9 (53)	**Median prior therapies**	4 (2, 8)
American Indian	1 (6)	Prior FOLFOX	14 (82)
		No FOLFOX	3 (18)

- 17 patients with mCRC were enrolled from 6 sites in Canada (n = 8), 6 sites in South Korea (n = 8), and two sites in the US (n = 1) between October 9 2020, and April 20, 2022
- The majority of patients had prior FOLFOX for metastatic disease

SAFETY

Table 2 summarizes the TEAEs related to BOLD-100 + FOLFOX; the most common TEAEs were neutrophil count decrease (53%), nausea (41%), fatigue (29%), and pyrexia, platelet count decrease, and decreased appetite (24% each).

- Most TEAEs were Grade 1-2. 11 Grade 3 AEs were reported, most common was neutrophil count decrease (n = 8).
- The combination of BOLD-100 + FOLFOX is well tolerated with no new safety signals in patients that are heavily pre-treated (median 4 prior therapies).
- Reasons for discontinuation: disease progression (n = 8); adverse event (n = 3), physician decision (n = 2); clinical progression (n = 2) and other (n = 2)

Table 2. Summary of Treatment Emergent Adverse Events (TEAEs) Related to BOLD-100 + FOLFOX ≥20%	**Any Grade**	**Grade ≥ 3**
Any TEAE[a]	16 (94)	11 (65)
Neutrophil count decreased	9 (53)	8 (48)
Nausea	7 (41)	0 (0)
Fatigue	5 (29)	0 (0)
Stomatitis	4 (24)	0 (0)
Vomiting	4 (24)	0 (0)
Platelet count decreased	4 (24)	0 (0)

Data are reported as number of patients, n (%). **a.** All AEs were recorded using the Medical Dictionary for Regulatory Activities (MedDRA) with severity graded by investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

EFFICACY

- Median Bayesian PFS was 4.7 [2.9, 8.6] months with a median Bayesian OS of 9.8 [5.2, 22.0] months (**Table 3**, **Figure 2)**, which compares favourably with current SOC in late-line mCRC (median PFS 2.0 months; median OS 7.1 months for trifluridine/tipiracil.[2]
- Median number of cycles was 7 (range 1-12)

Figure 2. Median Bayesian Progression Free Survival (A) and Overall Survival (B)

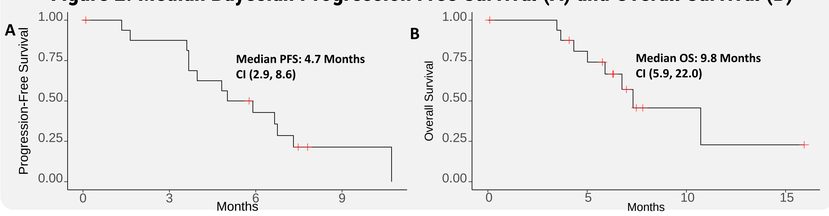
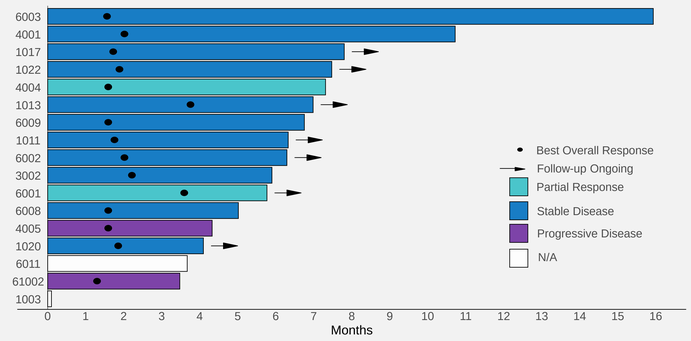


Table 3. Summary of Efficacy Data	**BOLD-100 + FOLFOX**	**Landmark**	**Posterior Probability Median > Benchmark**
Progression-Free Survival (PFS), months	4.7 [2.9, 8.6]	2.0	100%
Overall Survival (OS), months	9.8 [5.2, 22]	7.1	83%
Overall Response Rate (ORR)	13%	2%	NA
Disease Control Rate (DCR)	87%	44%	NA

A priori determination that posterior probability of superiority to the landmark of ≥70% for at least one endpoint would be significant

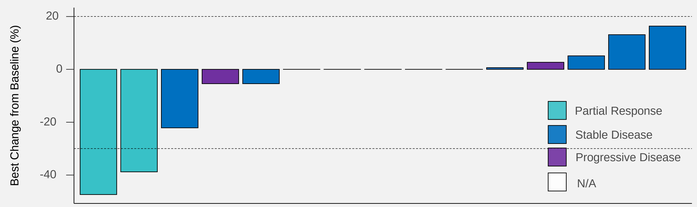
Figure 3. Overall Survival and Time of Best Clinical Response



BEST OVERALL RESPONSE

- In the 3L+ setting, PR's were observed in 2/15 patients (ORR: 13%) and 11 patients had SD as best overall response (**Figure 4**)
- For all 3L+ patients, investigator-assessed disease control rate was 87%, 2 patients were ineligible for assessment of tumour response.

Figure 4. Waterfall Plot of Best Change from Baseline in Sum of Target Lesions



2 patients who discontinued the study prior to the first disease assessment are not included in this analysis.

Conclusions

- In 3L+ patients (median 4 prior therapies), median PFS of **4.7 months** and OS of **9.8 months**, an ORR of **13%** and DCR of **87%** compares favourably to SOC (median PFS: 2.0 months; median OS: 7.1 months, ORR: 1.5% and DCR: 44%).
- The combination of BOLD-100 + FOLFOX is well tolerated with no new safety signals in patients that are heavily pre-treated.

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References: 1. DOI: 10.1200/JCO.2021.39.3_suppl.TPS145.*Journal of Clinical Oncology* 39, no. 3_suppl. 2. 1.. Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer. *N Engl J Med*. 2015;372(20):1909-1919. doi:10.1056/NEJMoa1414325

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