Original Article

Nivolumab plus ONC201 plus in microsatellite stable (MSS) metastatic colorectal cancer (mCRC) patients: a Brown University Oncology Research Group phase Ib/II study (BrUOG379)

Khaldoun Almhanna[1], Rimini Breakstone[1], Alexander Raufi[1], Roxanne Wood[1], Amy Webber[1], Sopha Dionson[1], Lindsay Cavanagh[1], Attila A. Seyhan[2], Howard Safran[1], Wafik El-Deiry[1,2,3]

[1]The Rhode Island Hospital/Lifespan Cancer Institute and The Brown University Oncology Research Group, Providence, RI, USA; [2]Legorreta Cancer Center at Brown University, The Warren Alpert Medical School, Brown University, Providence, RI, USA; [3]Department of Pathology and Laboratory Medicine, The Warren Alpert Medical School, Brown University, Providence, RI, USA

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Correspondence to: Khaldoun Almhanna, MD. Associate Professor, The Rhode Island Hospital/Lifespan Cancer Institute and The Brown University Oncology Research Group, 593 Eddy St., Providence, RI 02903, USA. Email: Kalmhanna@lifespan.org.

Background: Immune checkpoint inhibitors alone, or in combination with chemotherapy failed to provide meaningful clinical activity for patients with microsatellite stable (MSS) colorectal cancer (CRC). ONC201 is a small molecule that inactivates AKT and ERK signaling and actives the TRAIL pathway. Preclinical studies indicated potential benefits of combining ONC201 with checkpoint inhibitors. This is a phase Ib/II trial of ONC201 plus nivolumab for patient with MSS CRC who progressed on standard treatment.

Methods: Enrolled patients received ONC201 plus nivolumab in a dose de-escalation fashion to determine the maximum tolerated dose (MTD). Additional patients were enrolled in the dose-expansion cohort. ONC201 at a dose of 625 mg was given orally at day −7 of cycle 1, followed by weekly dosing. Nivolumab was given every 2 weeks at 240 mg IV starting on day 1 of every cycle (cycle =28 days). The primary end point was dose-limiting toxicity (DLT) during the observation window (run-in dose day −7, cycle 1 to assessment pre-dosing cycle 2). The plan was to enroll 28 additional patients at the MTD so that a total of 34 patients would be treated at the MTD. Pharmacokinetics (PKs) and tumor biopsies were collected at several time points per study protocol.

Results: A total of 13 patients (8 patients in the dose escalation *6 evaluable*) were enrolled between December 4, 2019 and March 2021. All patients had received ≥2 previous lines of chemotherapy and had confirmed microsatellite stability or mismatch repair-proficient tumors. No DLTs were observed with 625 mg ONC201 in the first three patients. Three additional patients were enrolled at the same dose to confirm safety. Two patients progressed during the DLT period and had to be replaced. During the dose-expansion part, five patients were enrolled and none required dose reduction or modification. No objective tumor response was observed in the 13 treated patients. Disease progression was confirmed at the time of the first imaging evaluation at 8 weeks following cycle 2. Post discussion at the Data and Safety Monitoring Board (DSMB) on May 25, 2021, the principal investigator (PI) and Committee voted to close the study to new patient enrollment prior to reaching accrual of 34 patients, secondary to lack of efficacy.

Conclusions: In this study of patients with advanced MSS CRC, combination ONC201/nivolumab was well-tolerated; objective responses to ONC201/nivolumab were not observed.

Keywords: Colon cancer; nivolumab; ONC201; microsatellite stable (MSS)

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Introduction

Background

In recent years, immune checkpoint inhibitors, such as anti-programmed cell death 1 (PD-1) or programmed cell death ligand 1 (PD-L1) monoclonal antibodies (mAbs), have improved outcome of patients with various types or cancer including several gastrointestinal malignancies. In colorectal cancer (CRC), the first Food and Drug Administration (FDA) approved checkpoint inhibitors for the treatment of microsatellite instable (MSI) metastatic CRC (mCRC) were pembrolizumab (1) and nivolumab (2). MSI CRC represents approximately 4% of mCRC, they could be associated with Lynch syndrome or caused by sporadic, acquired hypermethylation of the promoter of the *MLH1* gene. This subset of tumors has a slightly better prognosis than microsatellite stable (MSS) colorectal but are chemotherapy resistant. Following the pembrolizumab, nivolumab approval, a phase II CheckMate-142 trial evaluated the combination of nivolumab plus ipilimumab for the treatment in this patient population; the combination provided meaningful clinical benefit in previously treated MSI mCRC providing durable clinical benefits with good response and a manageable toxicity profile (3). On the other hand, checkpoint inhibitors, as a single agent or in combination, have not demonstrated meaningful clinical activity for patients with MSS CRC. For example, the addition of atezolizumab to first line treatment with FOLFOXIRI plus bevacizumab in the first line treatment of metastatic MSS CRC showed promising improvement in progression free survival (PFS), the overall survival (OS) benefits are yet to be confirmed in a phase III trial (4). One of the possible explanations of failure with PD-1 blockade for MSS CRC is immune suppression through other immune checkpoints or pathways that regulate lymphocyte activation (5). Extensive efforts are ongoing to identify the optimal PD-1 blockade combinations needed for activity in the MSS CRC disease.

ONC201 is a first-in-class small molecule that activates the integrated stress response (ISR) in tumor cells leading to downstream anticancer effects through inactivation of pro-survival Akt and ERK signaling along with induction of the TRAIL pathway (6). The efficacy of ONC201 has been consistently demonstrated in numerous *in vitro* and *in vivo* experiments. The profile of ONC201 is well suited for an oncology product: preclinical efficacy with infrequent administration, orally active, compelling safety profile, highly stable, water soluble, and can penetrate the blood-brain barrier (7).

Rationale and knowledge gap

ONC201 has demonstrated single agent anti-tumor effects in several solid tumor models including subcutaneous and orthotopic colon cancer. The clinical safety of single agent ONC201 has been evaluated in an open-label, dose-escalation phase I trial in patients with advanced refractory solid tumors. The drug was well tolerated, no grade >1 drug-related toxicities were observed. The drug achieves micromolar plasma concentrations, and was biologically active when orally administered at 625 mg every 3 weeks. Radiographic regression of several individual metastatic lesions was observed along with prolonged stable disease (SD) (8). With ONC201 dose intensification, it was noted a potent anti-metastasis effect and inhibition of cancer cell migration and invasion leading to a change in ONC201 dosing in all open clinical trials.

Preclinical results indicate the potential utility for ONC201 plus anti-PD-1 therapy. The combination of anti-PD-1 therapy with ONC201 *in vitro* showed increased efficacy in comparison to anti-PD-1 monotherapy in tumors treated with high doses of ONC201, indicating that alleviating T cells of PD-1 expression may enhance ONC201's potency *in vivo* (9). We present this article in accordance with the TREND reporting checklist (available at https://tgh.amegroups.com/article/view/10.21037/tgh-23-69/rc).

Highlight box

Key findings

- ONC201/nivolumab is well-tolerated; objective responses to ONC201/nivolumab were not observed.

What is known and what is new?

- Checkpoint inhibitors have not shown meaningful clinical activity in patients with microsatellite stable colorectal cancer (CRC). Several new agents are being evaluated to identify the best combination to reverse resistance.
- To our knowledge, this is the first trial testing the combination of nivolumab and ONC201 in this patient population.

What is the implication, and what should change now?

- The combination of ONC201 plus nivolumab demonstrated manageable safety profiles without antitumor activity in patients with CRC. Further testing is needed.

Objective

We conducted a phase Ib/II, open-label, dose de-escalation, dose-expansion study to assess the safety and efficacy of ONC201 plus nivolumab for patients with MSS mCRC.

Methods

Study design

For the phase Ib part of the study, the primary objective was to determine the maximum tolerated dose (MTD) and/or the recommended phase 2 dose (RP2D) of ONC201 when administered orally in combination with nivolumab in patients with MSS metastatic colon cancer who progressed after at least 2 lines of therapy.

Secondary objectives included safety profile, evaluate the pharmacokinetic (PK) profile, and the pharmacodynamic effects and efficacy of the combination. For the phase II portion, the primary objective was to determine PFS, response rate as assessed using the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 (10), and the secondary objectives was to confirm safety, assess preliminary OS and correlate clinical outcome with tumor & blood biomarkers including cancer stem cells, signaling intermediates and inhibitors, natural killer (NK) cells, TRAIL, granzyme, perforin, and M30. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and Good Clinical Practice Guidelines after approval by the Lifespan Institutional Review Board (Providence, RI, USA; Registration No. 209419).

Patient eligibility

To be enrolled in the study, patients at Lifespan Cancer Center in Providence, Rhode Island had a histologically confirmed MSS primary colorectal adenocarcinoma with radiographic or clinical evidence of metastatic disease that has progressed after at least two prior regimens. Patients had measurable disease by RECIST criteria located in an area that can be biopsied. All previous therapies for cancer were discontinued for ≥14 days before the first dose with all adverse events (AEs) resolved to grade ≤1. Patient had an Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2 and Adequate organ and marrow function. Women of childbearing potential (WOCBP) agreed to follow instructions for method(s) of contraception from time of consent and for the duration of the study. Main exclusion criteria included: patients with symptomatic brain metastases, patients with prior treatment with ONC201 or who have had prior therapy with any other antibody or drug specifically targeting T-cell co-stimulation or immune check point pathways, patients with active inflammatory gastrointestinal disease, pregnant or breast feeding, or have an uncontrolled intercurrent illness. Participants with an active, known or suspected autoimmune disease were excluded as well as participants with a condition requiring systemic treatment with corticosteroids >10 mg daily of prednisone equivalent. Participants who have received a live/attenuated vaccine within 30 days of first treatment were excluded as well. All patients provided written informed consent for participation in the study.

Study treatments

Biopsy and tissue collection

There were three specimens anticipated for collection, a pre-treatment biopsy and a mid-treatment biopsy—both of which were required. If the patient did not progress at time of 2nd biopsy, a 3rd biopsy would be required at time of progression. Archival tissue was provided when available.

Drug administration and dose-escalation procedure

Eligible patients received a single dose of ONC201 7 days prior to cycle 1 day 1 (day –7) then weekly. Each cycle was 4 weeks long (28 days). Nivolumab was given on day 1 then every 2 weeks at a dose of 240 mg. The treatment was administered on an outpatient basis. No dose reduction or escalation of nivolumab was allowed. ONC201 dosing was done according to a standard 3+3 design. Dosing was given day 1 of each week. On days when ONC201 and nivolumab were administered on the same day, ONC201 was administered within 30 minutes after completion of nivolumab. All patients ingested ONC201 capsules in front of research clinical staff during cycle 1. Dose-limiting toxicity (DLT) was assessed in the phase Ib portion of the trial. DLTs were collected during the run-in (dose 1 of ONC201), cycle 1 and prior to dosing cycle 2 day 1. All patients in a cohort were assessed for DLTs prior to opening the next cohort. DLT was defined as hematological and non-hematological toxicities; Hematological toxicities included: grade 4 neutropenia that persists for >7 consecutive days, febrile neutropenia, grade ≥3 neutropenic infection, grade 4 thrombocytopenia or grade ≥3 thrombocytopenia with bleeding. Non-hematological toxicities included any other treatment related, clinically significant grade ≥3 toxicity not classified under CTCAE

blood or bone marrow with the exception of grade 3 nausea, vomiting, or diarrhea in patients who have received optimal treatment with antiemetics or anti-diarrheals and did not downgrade to a grade 1 within 72 hours; grade 4 (life threatening) diarrhea or vomiting was considered DLTs irrespective of the duration of the event. Treatment delay of >2 weeks secondary to a treatment related AEs that is deemed possibly or probably related to treatment was considered a DLT.

New cycle requirement included platelets >75,000/mcl and granulocytes >1,000/mcl and recovery from any clinically significant, treatment related non-hematologic toxicities. The plan was to enroll three additional patients at any dose level if 0 of 3 patients experienced a DLT to confirm safety. If 1 of 3 patients experienced a DLT, three additional patients would be enrolled at that same dose cohort. If two or more of the 3–6 subjects within a cohort encountered a DLT, then the MTD has been exceeded and de-escalation would proceed to the next dose level (dose level 2, etc.). Only two-dose reductions of ONC201 were allowed.

The Brown University Oncology Group (BrUOG) confirmed patient eligibility and the dose level was then assigned. Data collection, analysis, and interpretation were performed by the BrUOG group and the investigators.

Assessment

AEs were evaluated throughout the treatment period using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5) (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf). Tumor measurements were obtained using computed tomography at baseline and every 8 weeks until disease progression or at the beginning of subsequent treatment. Tumor response was evaluated per RECIST version 1.1, and PFS of each patient was assessed. Overall response rate (ORR) was defined as the proportion of patients with the best overall response of complete response (CR) or partial response (PR). Disease control rate (DCR) was defined as the proportion of patients with the best overall response of CR, PR, or SD. PFS was defined as the time from the date of registration until the date of disease progression or the date of death as a result of any cause, whichever occurred first. OS was defined as the time from the date of registration until the date of death as a result of any cause. Tumor biopsies were collected prior to starting treatment and 8 weeks after initiation and at progression (if different than week 8).

Statistical analysis

The primary population for the assessment of the MTD is defined as all patients experiencing a DLT during DLT observation window (run-in dose day –7, cycle 1 to assessment pre-dosing cycle 2) following the first administration of the combination of ONC201 and nivolumab.

Patients receiving less than 80% of the ONC201 planned dose during the first cycle will not be evaluable for the assessment of the MTD provided that the dose reduction is not related to any-grade drug toxicity.

Formal early stopping rules was not be utilized. Safety in this trial was governed by the DLT rules and oversight provided by the BrUOG Data and Safety Monitoring Board (DSMB). It was anticipated that severe toxicity will not exceed 30%.

In the phase II cohort, an additional 28 patients were supposed to be accrued, so that a total of 34 patients would be treated at the RP2D (including six patients treated at the RP2D on the phase IB portion of the trial).

Accrual was to be suspended for excess toxicity if over 9 of the initial 12 phase II patients experienced an event that was defined as a DLT in the phase I portion. The chance of early study suspension (i.e., ≤17 subjects accrued) was 50% if the true toxicity is 50% and 4.0% if it is 30%. Similarly, accrual was to be suspended if, at any point among the 34 patients, 15 or more subjects was observed with an event that was defined as a DLT in the phase I portion.

A patient experiencing a toxicity defined as a DLT, post cycle 2 (phase I) or in the phase II portion, was required to have treatment (both drugs) held, once the toxicity reduced to a grade 1 or less, ONC201 would have been resumed at a lower dose.

Results

Patient characteristics

Patients were enrolled in the study between December 4, 2019 and March 2021 (*Table 1*). ECOG PS was 0 in 4 (31%) patients. All patients had received ≥2 previous lines of chemotherapy, including anti-angiogenetic inhibitors. None of the patients previously received anti-PD-1/PD-L1 inhibitors, and all of them experienced disease progression before study entry. All patients had MSS tumors, 6 (46%)

Table 1 Baseline characteristics

Characteristic	Value
No. of patients	13
Median age (years)	58
Sex (male)	5 [38]
ECOG PS	
0	4 [31]
1	9 [69]
Site of metastasis	
Lymph node	3 [23]
Liver	9 [69]
Lung	7 [54]
Others	2 [15]
Prior regimen	
Fluoropyrimidines	13 [100]
Oxaliplatin	13 [100]
Irinotecan	13 [100]
Angiogenesis inhibitors	13 [100]
EGFR targeted therapy	6 [46]
RAS mutation	7 [54]
B-Raf mutation	
Positive	2 [15]
Negative	4 [31]
Unknown	7 [54]
PD-L1 CPS =0	2

Data are presented as number or No. [%]. ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; RAS, rat-sarcoma; PD-L1, programmed cell death ligand 1; CPS, combined positive score.

had *RAS* wild type disease and 7 (54%) had *RAS* mutations. All *RAS* wild type patients received epidermal growth factor receptor (EGFR) targeted therapy (mainly cetuximab). Two patients had B-Raf mutant tumors. PD-1 expression was available in only two patients and they both had combined positive score (CPS) of zero.

Tolerability and AEs

During dose-escalation, treatment with nivolumab and weekly ONC201at 625 mg combination was not associated with any DLTs. Therefore, MTD of weekly ONC201 was determined as 625 mg when combined with nivolumab. Two patients failed to complete the first 4 weeks of treatment secondary to disease progression and were taken off study. These patients were replaced per study protocol. Outside the DLT period and during the dose-expansion part, no dose reduction was required. The plan was to enroll at least 28 patients followed by safety and efficacy evaluation, however, given the lack of efficacy, the DSMB recommended closing the study to enrollment prior to reaching the interim analysis.

Table 2 Treatment-related adverse events (≥10% or any toxicities with grade ≥3)

Adverse event	All	Grade ≥3
Pain	9 [69]	7 [54]
Fatigue	6 [46]	1 [8]
Rash	2 [15]	1 [8]
Constipation	4 [31]	0
Decreased appetite	3 [23]	1 [8]
Liver dysfunction	10 [77]	2 [15]
Hypothyroidism	1 [8]	0
Hypertension	5 [38]	2 [15]
Anemia	10 [77]	1 [8]
Nausea/vomiting	4 [31]	1 [8]
Small bowel obstruction	4 [31]	4 [31]

Data are presented as No. [%].

All subjects were followed per study protocol, with final visit occurring 6 months post end of treatment (EOT). PFS and OS results were updated in November 2021, for which we updated the date with regard to the presence of disease progression, date of disease progression, occurrence of death, and date of death or last follow-up visit. The median number of treatment cycles was 2 cycles in the entire patient population. Two patients were taken of the study because of clinical deterioration prior to cycle 2. All remaining patients discontinued the protocol treatment secondary to disease progression (n=11). There was no discontinuation secondary to treatment-related AE or treatment-related death.

The most common AEs of any grade are summarized in *Table 2*. Pain, fatigue, hypertension, abnormal liver function and anemia were the most commonly reported AEs. The majority of AEs were thought to be related to disease progression, other than rash and fatigue which were

thought to be possibly related to treatment. Severe AEs were observed in 10 patients, and no severe events were related to study treatment. There were four cases of bowel obstruction, all thought to be disease related. No immune-related AEs were observed.

Antitumor activity and tumor biomarkers

Objective response was not observed. One patient had a transient decrease in his carcinoembryonic antigen (CEA). Median PFS was two months. At the data cutoff, 6 months post end of study treatment, two patients were alive. Median OS was 3.7 months. Given the lack of response, PK and PD samples were not processed.

Discussion

In this study, we evaluated the safety and efficacy of ONC201 plus nivolumab for MSS mCRC patients who progressed on standard of care. To our knowledge, this study is the first study to evaluate the combination activity of ONC201 with an immune checkpoint inhibitor. We did not observe any DLTs and no patients experienced treatment discontinuation as a result of toxicities. The benign toxicity profiles are consistent with those of ONC201 or nivolumab monotherapy in previous reports. Efficacy was evaluated as the secondary end point. Unfortunately, none of the patients had a response or SD.

In this study, and given the lack of clinical benefits, no exploratory analysis is currently planned. Meanwhile, no clear relationship between PD-L1 or tumor mutational burden (TMB) and efficacy outcomes was suggested in the limited number of patients, and therefore, additional analysis is necessary to clarify the optimal patient population for this combination. Additional biomarker analysis using the pre- and post-treatment biopsy samples might be considered in the future for elucidating the immunologic effect of this combination. The major limitation of the current study was the small sample size as it was stopped early for lack of efficacy.

It is disappointing that ONC201 combined with PD-1 antibody did not show an advantage in the treatment of MSS mCRC in this study. Potential reasons are several: firstly, the combination of anti-PD-1 therapy with ONC201 showed some increased efficacy in certain tumor cells *in vitro* and *in vivo* but not all cells. This could be due to the inability of the T-cell receptors to recognize the MSS tumors. Secondly, data on CPS and TMB are lacking which could predict response to PD-1 antibodies in solid tumors. Thirdly, patients enrolled in our study have progressed on several lines of treatment and more than half of them had a mutation in RAS predisposing to poor prognosis.

Conclusions

The combination of ONC201 at 625 mg plus nivolumab demonstrated manageable safety profiles without antitumor activity in patients with CRC.

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Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at https://tgh.amegroups.com/article/view/10.21037/tgh-23-69/rc

Data Sharing Statement: Available at https://tgh.amegroups.com/article/view/10.21037/tgh-23-69/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tgh.amegroups.com/article/view/10.21037/tgh-23-69/coif). K.A. reports grants from BMS and Chimerix to conduct the trial. W.E.D. is a co-founder of Oncoceutics, Inc., a subsidiary of Chimerix. W.E.D. has disclosed his relationship with Oncoceutics/Chimerix and potential conflict of interest to his academic institution/employer and is fully compliant with NIH and institutional policy that is managing this potential conflict of interest. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and Good Clinical Practice Guidelines after approval by the Lifespan Institutional Review Board (Providence, RI, USA; Registration No. 209419). All patients provided written informed consent for participation

in the study.

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