NRG GI004

Report Based on Data Through 4/30/2019

Colorectal Cancer Metastatic dMMR Immuno-Therapy (COMMIT) Study: A Randomized Phase III Study of mFOLFOX6/Bevacizumab Combination Chemotherapy with or without Atezolizumab or Atezolizumab Monotherapy in the First-Line Treatment of Patients with Deficient DNA-Mismatch Repair (dMMR) Metastatic Colorectal Cancer

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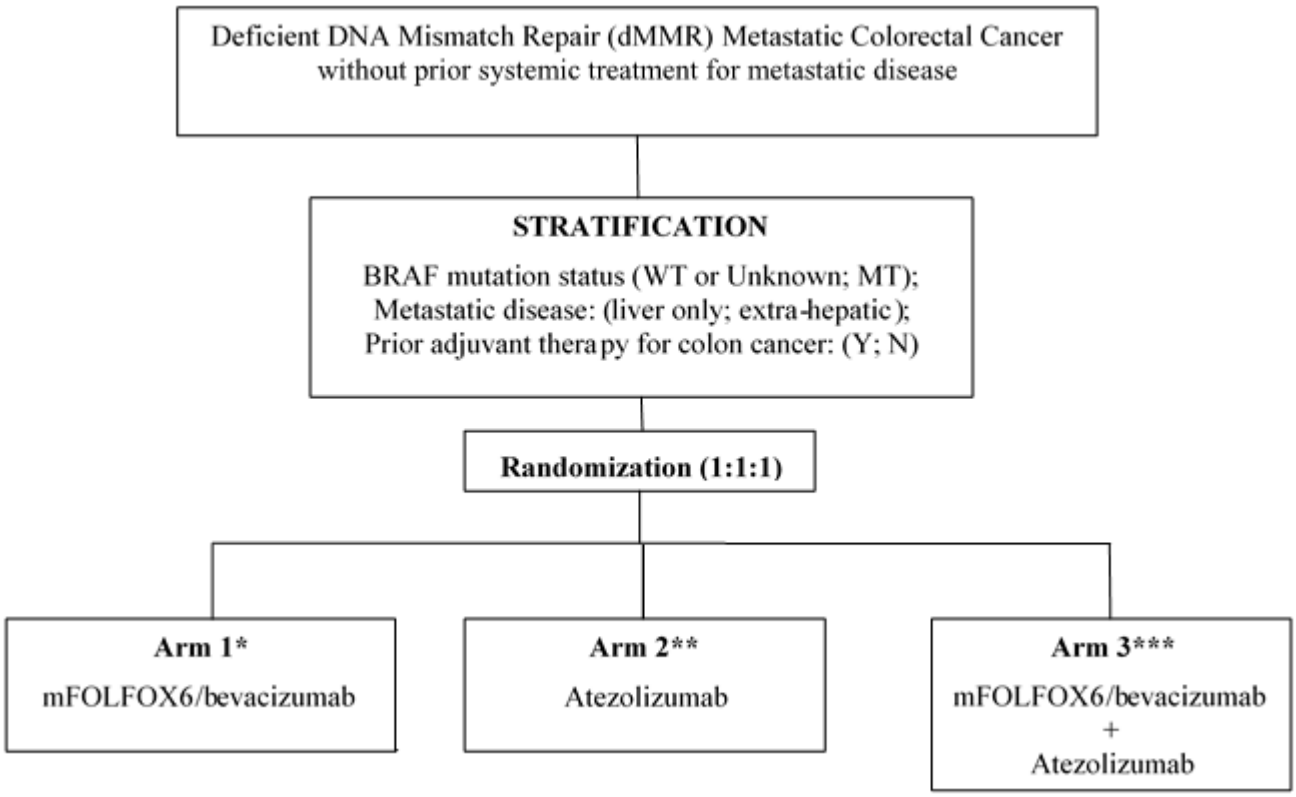
Activated:	November 7, 2017
Status:	Accruing

NRG GI004 Schema



Study Regimen:

* **Arm 1:** ***mFOLFOX6/bevacizumab until disease progression. Discontinue oxaliplatin after Cycle 10 (1 cycle = 2 weeks)***

- Oxaliplatin 85 mg/m^2 IV + leucovorin 400 mg/m^2 IV + bevacizumab 5 mg/kg IV+ 5-FU 400 mg/m^2 IV bolus on Day 1 followed by 5-FU 2400 mg/m^2 IV over 46 hours (Days 1 and 2)
- In the event of unacceptable toxicity without disease progression, including grade ≥ 3 neuropathy, individual components of mFOLFOX6/bevacizumab/atezolizumab may be discontinued at the physician's discretion. All other components of mFOFOX6/bevacizumab may be continued at their current dose and schedule.

** **Arm 2:** ***Atezolizumab monotherapy until disease progression or up to and including a maximum of 48 cycles (1 cycle = 2 weeks)***

- Atezolizumab 840 mg IV on Day 1 of every cycle

*****Arm 3:** ***mFOLFOX6/bevacizumab/atezolizumab until disease progression. Discontinue oxaliplatin after Cycle 10; discontinue atezolizumab after Cycle 48 (1 cycle = 2 weeks)***

- mFOLFOX6/bevacizumab same as Arm 1 + atezolizumab 840 mg IV on Day 1 of every cycle
- In the event of unacceptable toxicity without disease progression, including grade ≥ 3 neuropathy, individual components of mFOLFOX6/bevacizumab/atezolizumab may be discontinued at the physician's discretion. All other components of mFOFOX6/bevacizumab/ atezolizumab may be continued at their current dose and schedule.

Note: *At disease progression, study therapy will be discontinued. Further treatment is at the investigator's discretion; however, patients will continue to be followed for survival.*

Study description

This prospective randomized phase III open label trial studies how well combination chemotherapy, bevacizumab, and/or atezolizumab work in treating patients with deficient deoxyribonucleic acid (DNA) mismatch repair colorectal cancer that has spread to other places in the body. Drugs used in chemotherapy, such as fluorouracil, oxaliplatin, and leucovorin calcium, work in different ways to stop the growth of tumor cells, either by killing the cells, by stopping them from dividing, or by stopping them from spreading. Immunotherapy with monoclonal antibodies, such as bevacizumab and atezolizumab, may help the body's immune system attack the cancer, and may interfere with the ability of tumor cells to grow and spread. Giving combination chemotherapy, bevacizumab, and atezolizumab may work better in treating patients with colorectal cancer.

The main hypothesis of this study is that the addition of atezolizumab to standard mFOLFOX6/ bevacizumab as first line therapy will improve progression-free survival in patients with dMMR mCRC as compared to standard mFOLFOX6/bevacizumab combination chemotherapy.

This study will enroll 347 patients with dMMR metastatic colorectal cancer. Stratification factors include BRAF V600E mutation status (wild-type or unknown; mutant), metastatic disease: (liver-only; extra-hepatic), and prior adjuvant therapy for colon cancer (yes; no). Patients will be randomized with equal allocation (1:1:1) to the three trial arms: mFOLFOX6/Bevacizumab, Atezolizumab, or mFOLFOX6/Bevacizumab + Atezolizumab. Treatment will continue until progression. (Oxaliplatin will be discontinued after Cycle 10, and Atezolizumab will be discontinued after Cycle 48.)

Patient Accrual

This protocol was opened for accrual on November 7, 2017. The first patient was accrued to the study on January 19, 2018. Accrual has been slower than projected (Table 1, Figure 1). As of April 30, 2019, 29 patients have been accrued.

An interim analysis for efficacy and futility will be performed when approximately 60% of the required events (134 3 arms/92 pairwise) have been observed. This was anticipated to occur approximately 26 months into the study. However, based on the current accrual, we do not anticipate an interim analysis occurring until 2028.

Patient and Tumor Characteristics

Seven patients (24.1%, 1 mFOLFOX6/BEV, 2 Atezolizumab, 4 mFOLFOX6/BEV + Atezolizumab) have been declared ineligible as of April 30, 2019 (Table 2), due to no prothrombin time received (1 mFOLFOX6/BEV + Atezolizumab patient) and improper screening for proteinuria (n=6). These six patients were screened for proteinuria, but not in a manner consistent with the protocol language. There is an amendment in progress that would relax the language related to proteinuria screening and alleviate this issue in the future.

There are no consent withdrawals. Patient and tumor characteristics are presented in Table 3. There does not appear to be any obvious treatment imbalances at this early stage of accrual.

Atezolizumab Compliance in Group 2 and 3

As of April 30, 2019, seven patients (5 Atezolizumab, 2 mFOLFOX6/BEV + Atezolizumab) discontinued Atezolizumab due to the following reasons: 2 deaths, 1 withdrawl/refusal, 1 symptomatic deterioration, 3 disease progression. Only the single withdrawal/refusal would constitute an early withdrawal.

Adverse Events

As of April 30, 2019, adverse event information is available for all 29 patients (7 in the mFOLFOX6/BEV group, 12 in the Atezolizumab group, and 10 in the mFOLFOX6/BEV + Atezolizumab group). The distribution of patients by the highest grade experienced within each system organ class is summarized in Table 4. There were no toxicities with a treatment difference of three or more in the number of grade 3-5 toxicities. Seven patients experienced a grade 3 toxicity as their highest (2 mFOLFOX6/BEV, 4 Atezolizumab, 1 mFOLFOX6/BEV + Atezolizumab). There were three patients who experienced a grade 4 adverse event as their highest (one in the mFOLFOX6/BEV group, and two in the mFOLFOX6/BEV + Atezolizumab group). Two patients died (1 in the Atezolizumab group, 1 in the mFOLFOX6/BEV + Atezolizumab group), and the reason given was death (NOS).

Table 1

NRG GI004 Accrual Summary - Data as of 4/30/2019

Date activated to accrual:	11/7/2017
Targeted Sample Size:	347
Projected monthly accrual: *	10
Average monthly accrual over last 3 months:	2
Projected accrual as of 4/30/2019:	137
Total accrual as of 4/30/2019:	29
Percent of projected accrual achieved as of 4/30/2019:	21%
Percent of total targeted accrual as of 4/30/2019:	8%
Projected completion date based on last 3 months accrual:	1/31/2028

*After a 4-month startup phase assuming no accrual

Table 2

NRG GI004 Consent Withdrawals and Ineligibility - Data as of 4/30/2019

	mFOLFOX6/BEV	**Atezolizumab**	**mFOLFOX6/BEV + Atezolizumab**	**Total**
Randomized	7	12	10	29
Withdrew consent	0	0	0	0
Eligible	6	10	6	22
Ineligible	1	2	4	7

Table 3

Patient and Tumor Characteristics for All Randomized Patients in GI004 - Data as of 04/30/2019

Patient or Tumor Characteristic	mFOLFOX6/BEV n	mFOLFOX6/BEV %	Atezolizumab n	Atezolizumab %	mFOLFOX6/BEV + Atezolizumab n	mFOLFOX6/BEV + Atezolizumab %	Total n	Total %
Gender								
Female	5	71.4	6	50.0	4	40.0	15	51.7
Male	2	28.6	6	50.0	6	60.0	14	48.3
Age (years)								
<50	3	42.9	2	16.7	3	30.0	8	27.6
50-59	0	0.0	2	16.7	4	40.0	6	20.7
60-69	1	14.3	1	8.3	2	20.0	4	13.8
70+	3	42.9	7	58.3	1	10.0	11	37.9
Race								
Black or African American	0	0.0	3	25.0	2	20.0	5	17.2
Not Reported	2	28.6	1	8.3	1	10.0	4	13.8
White	5	71.4	8	66.7	7	70.0	20	69.0
Ethnicity								
Hispanic or Latino	1	14.3	0	0.0	0	0.0	1	3.4
Not Hispanic or Latino	6	85.7	12	100.0	9	90.0	27	93.1
Not Reported	0	0.0	0	0.0	1	10.0	1	3.4
BRAF Status								
V600E Mutation	1	14.3	3	25.0	2	20.0	6	20.7
non-V600E mutation, WT, or Unknown	6	85.7	9	75.0	8	80.0	23	79.3

Patient and Tumor Characteristics for All Randomized Patients in GI004 - Data as of 04/30/2019

	mFOLFOX6/BEV		Atezolizumab		mFOLFOX6/BEV + Atezolizumab		Total	
Patient or Tumor Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Metastatic Disease Site								
Liver only	0	0.0	2	16.7	2	20.0	4	13.8
Not confined to the liver	7	100.0	10	83.3	8	80.0	25	86.2
Prior Adjuvant Therapy for Colon Cancer								
No	7	100.0	9	75.0	8	80.0	24	82.8
Yes	0	0.0	3	25.0	2	20.0	5	17.2
Total	7	100.0	12	100.0	10	100.0	29	100.0

Table 4

Distribution of GI004 Patients by Highest Grade Adverse Event
by System Organ Class - Data as of 4/30/2019
For All Reported Adverse Events Including AERS without Regard to Attribution

System Organ Class	mFOLFOX6/BEV (n=7) n and (%) of Patients by Grade				Atezolizumab (n=12) n and (%) of Patients by Grade				mFOLFOX6/BEV > + Atezolizumab (n=10) n and (%) of Patients by Grade			
	2	3	4	5	2	3	4	5	2	3	4	5
Overall Highest Grade	2 (28.6)	2 (28.6)	1 (14.3)	0 (0.0)	4 (33.3)	4 (33.3)	0 (0.0)	1 (8.3)	4 (40.0)	1 (10.0)	2 (20.0)	1 (10.0)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	2 (16.7)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	1 (14.3)	1 (14.3)	0 (0.0)	0 (0.0)	4 (33.3)	1 (8.3)	0 (0.0)	0 (0.0)	3 (30.0)	1 (10.0)	1 (10.0)	0 (0.0)
General disorders and administration site conditions	2 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	0 (0.0)	0 (0.0)	1 (8.3)	1 (10.0)	2 (20.0)	0 (0.0)	1 (10.0)
Infections and infestations	0 (0.0)	1 (14.3)	1 (14.3)	0 (0.0)	1 (8.3)	1 (8.3)	0 (0.0)	0 (0.0)	1 (10.0)	1 (10.0)	1 (10.0)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	0 (0.0)	1 (14.3)	1 (14.3)	0 (0.0)	1 (8.3)	1 (8.3)	0 (0.0)	0 (0.0)	1 (10.0)	1 (10.0)	1 (10.0)	0 (0.0)
Metabolism and nutrition disorders	1 (14.3)	1 (14.3)	0 (0.0)	0 (0.0)	1 (8.3)	1 (8.3)	0 (0.0)	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)

Distribution of GI004 Patients by Highest Grade Adverse Event
by System Organ Class - Data as of 4/30/2019
For All Reported Adverse Events Including AERS without Regard to Attribution

System Organ Class	mFOLFOX6/BEV (n=7)				Atezolizumab (n=12)				mFOLFOX6/BEV > + Atezolizumab (n=10)			
	n and (%) of Patients by Grade				n and (%) of Patients by Grade				n and (%) of Patients by Grade			
	2	3	4	5	2	3	4	5	2	3	4	5
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (20.0)	1 (10.0)	0 (0.0)	0 (0.0)

Adverse events were graded with CTCAE version 5.

Figure 1

Cumulative Accrual for NRG GI004 – Data as of 4/30/2019