

A PHASE II OPEN-LABEL STUDY WITH ATEZOLIZUMAB (ATEZO) IN COMBINATION WITH BEVACIZUMAB (BEV) IN PATIENTS (PTS) WITH ADVANCED CHEMOTHERAPY-RESISTANT COLORECTAL CANCER (CRC) AND MSI-LIKE MOLECULAR SIGNATURE: THE MOTRICOLOR CONSORTIUM CT₃ STUDY.



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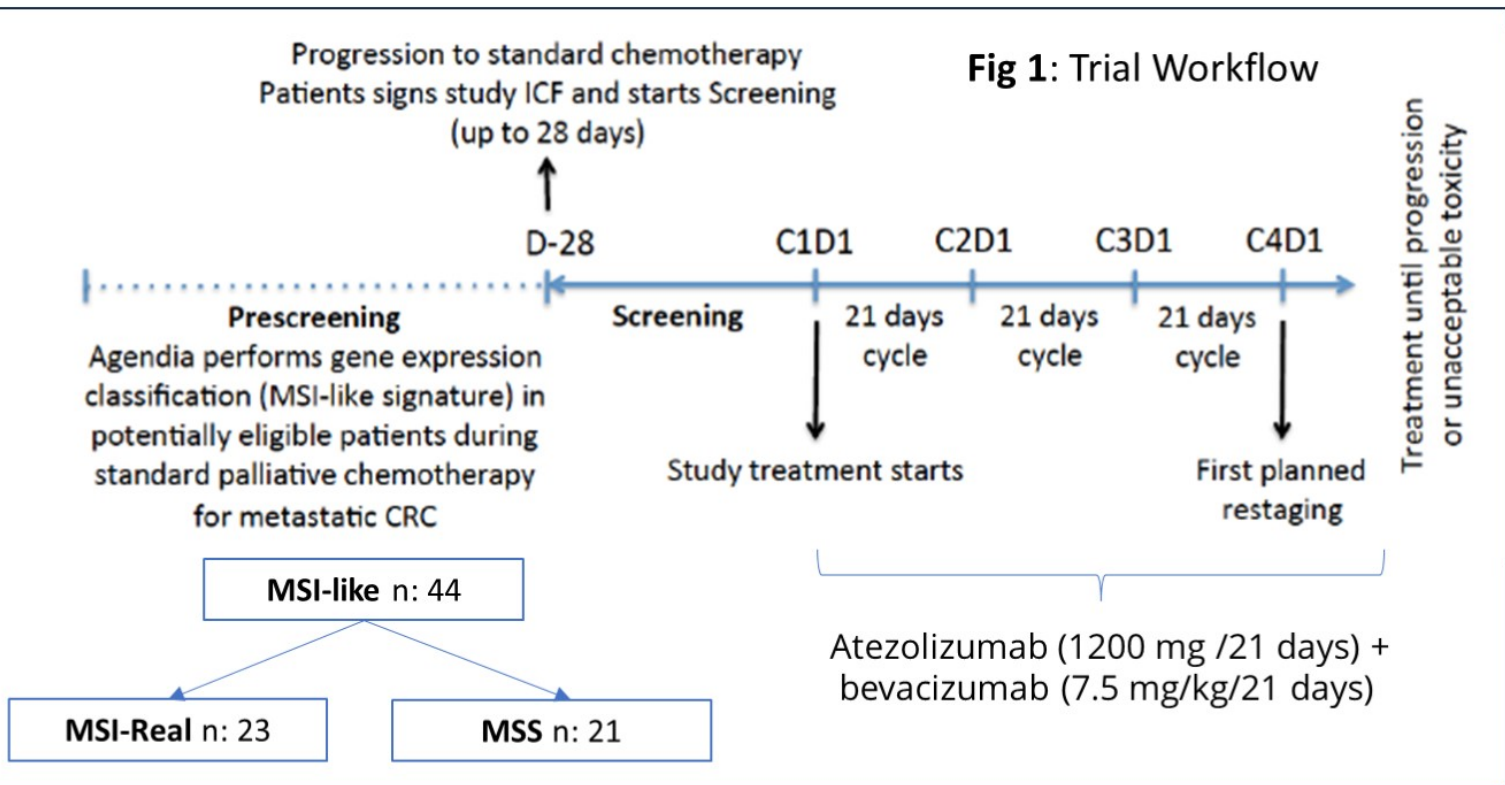
BACKGROUND

The **MOTRICOLOR** project aimed to test hypotheses generated in prospective clinical trials that stratified pts based on molecular genomic signatures matched to selected therapies.

- ✓ Up to 10% of MSS/pMMR mCRC have (MSI)-like genomic expression signature (GES) characterized by higher cytotoxic microenvironment infiltration and mutational burden.
- ✓ Preclinical data suggest that the addition of bev to atezo may improve antitumor effect in both MSI-H/dMMR and MSS/pMMR-MSI-like tumors.
- ✓ The MoTriColor international phase II CT3 (NCT02982694) study was designed to assess this combination.

STUDY DESIGN

- ✓ Pts with mCRC on progression to ≥1 chemotherapy (CT) line whose tumors were classified as MSI-like by GES in primary tissue samples (Agendia microarray), either MSI-H/dMMR or MSS/pMMR by standard diagnostic assays,
- ✓ Pts received atezo (1200 mg /21 days) plus bev (7.5 mg/kg/21 days) until progression, unacceptable toxicity, or withdrawal of consent.
- ✓ The primary endpoint was objective response rate (ORR) in the MSI-like population, assuming minimum response rate of 25% and an overall efficacy of 45%.



CONCLUSION

The primary study endpoint was not met, but we found clinically meaningful ORR with atezo in combination with bev in pts with MSI-H/dMMR-MSI-like tumors. In MSS/pMMR-MSI-like tumors, anti-tumor activity was confined to pts without liver mets. These results open a new therapeutic option for mCRC pts with MSI-H/dMMR tumors.

RESULTS

Table 1: Population Characteristics

		MSI-LIKE n:46	MSI-REAL n:24	MSS n: 22
Age (median, years)		63,5	64	62,5
Sex	Male	24 (52%)	12 (50%)	12 (55%)
	Female	22 (48%)	12 (50%)	10 (45%)
Sideness	Right	11 (16%)	7 (29,5%)	4 (18,5%)
	Left	34 (73,9%)	16 (67,5%)	18 (81,7%)
	Transverse	1 (2,2%)	1 (4,2%)	0 (0%)
Liver M1		15 (33%)	6 (25%)	9 (41%)
Prior lines	0	3 (6,5%)	3 (13%)	0 (0%)
	1	21 (46%)	15 (63%)	6 (27%)
	2	11 (24%)	5 (21%)	6 (27%)
	>=3	11(24%)	1 (4,2%)	10 (46%)
Previous bevacizumab		31 (67%)	13 (54%)	18 (82%)
Number of cycles (median)		20,3 (1-81)	27,6 (1-81)	12 (2-55)
Atezolizumab Compliance (Median, IQR)		9 (4-34)	22 (6,5-37)	6 (3-11)
Bevacizumab Compliance (Median, IQR)		9 (4-34)	22 (6,5-37)	6 (3-11)

Table 2: Overall ORR

Best Response	MSI-LIKE n: 44	MSI-REAL n:23	MSS n:21	p value
Complete Response	6 (14%)	6 (26%)	0 (0%)	0,001
Partial Response	11 (25%)	9 (39%)	2 (9,5%)	
Stable disease	16 (36%)	5 (22%)	11 (52%)	
Progressive disease	11 (25%)	3 (13%)	8 (38%)	

Table 3: Overall ORR, patients without liver metastases

Best Response	MSI-LIKE n: 30	MSI-REAL n:17	MSS n:13	p value
Complete Response	5 (17%)	5 (29%)	0 (0%)	0,007
Partial Response	10 (33%)	8 (47%)	2 (15%)	
Stable disease	11 (37%)	3 (18%)	8 (62%)	
Progressive disease	4 (13%)	1 (5,9%)	3 (23%)	

Fig 2: MSI-like mPFS

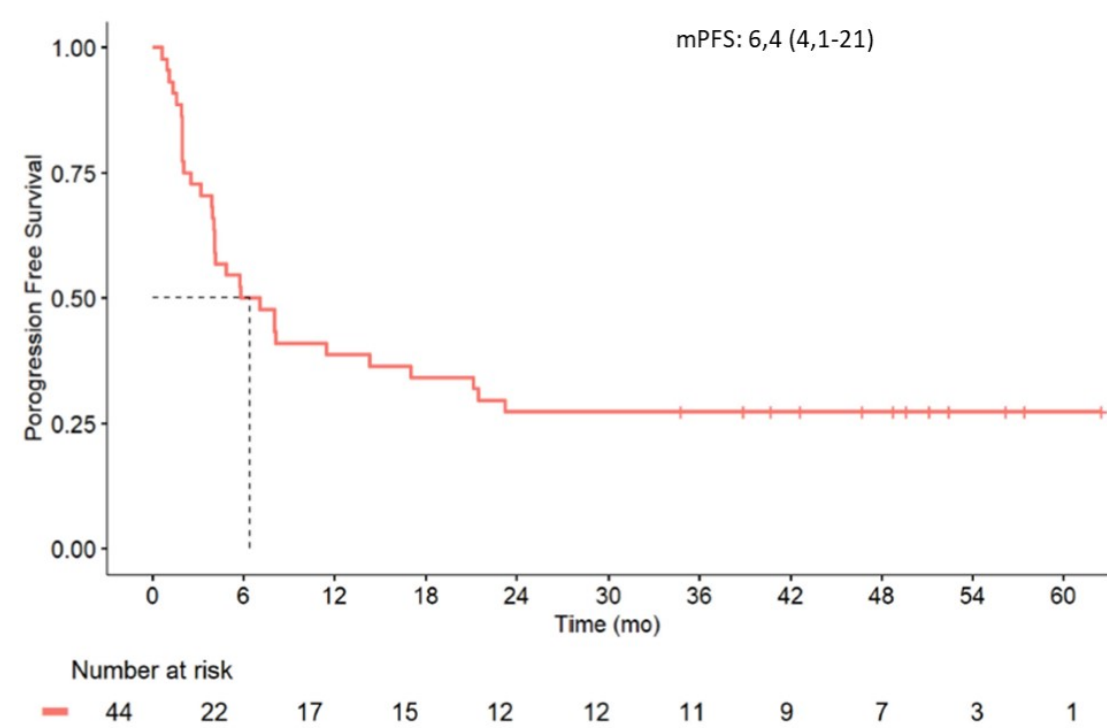


Fig 3: mPFS based on Agendia signature

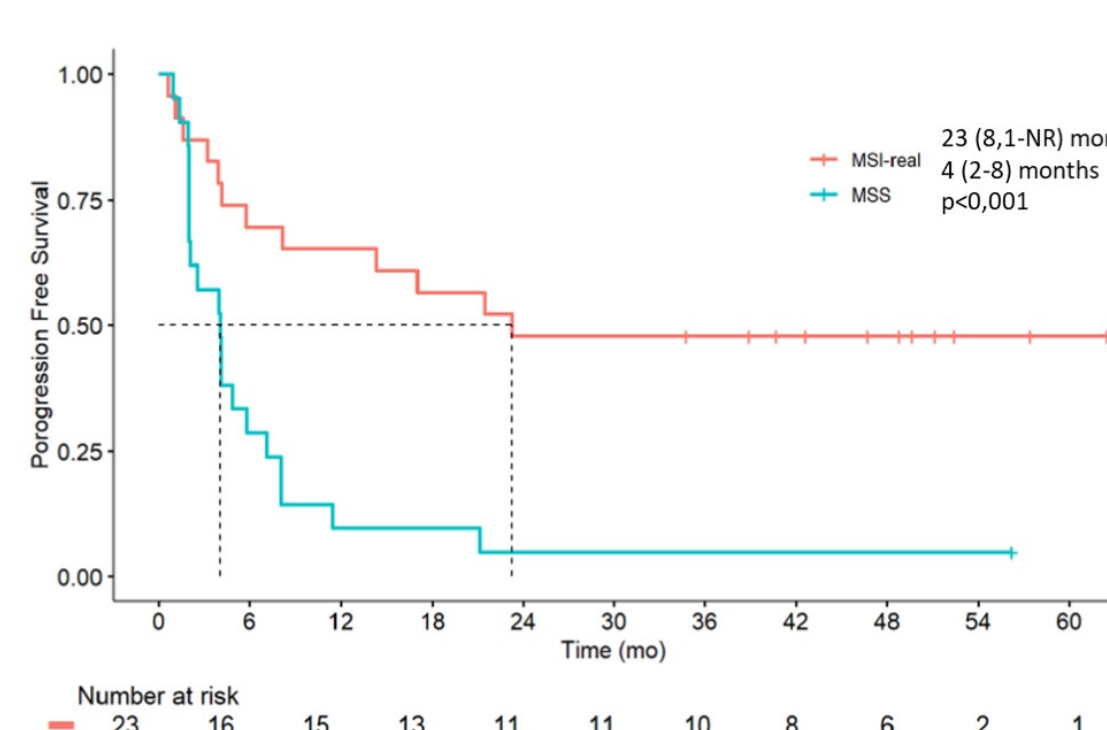


Fig 4: Overall mPFS without liver metastases based on Agendia signature

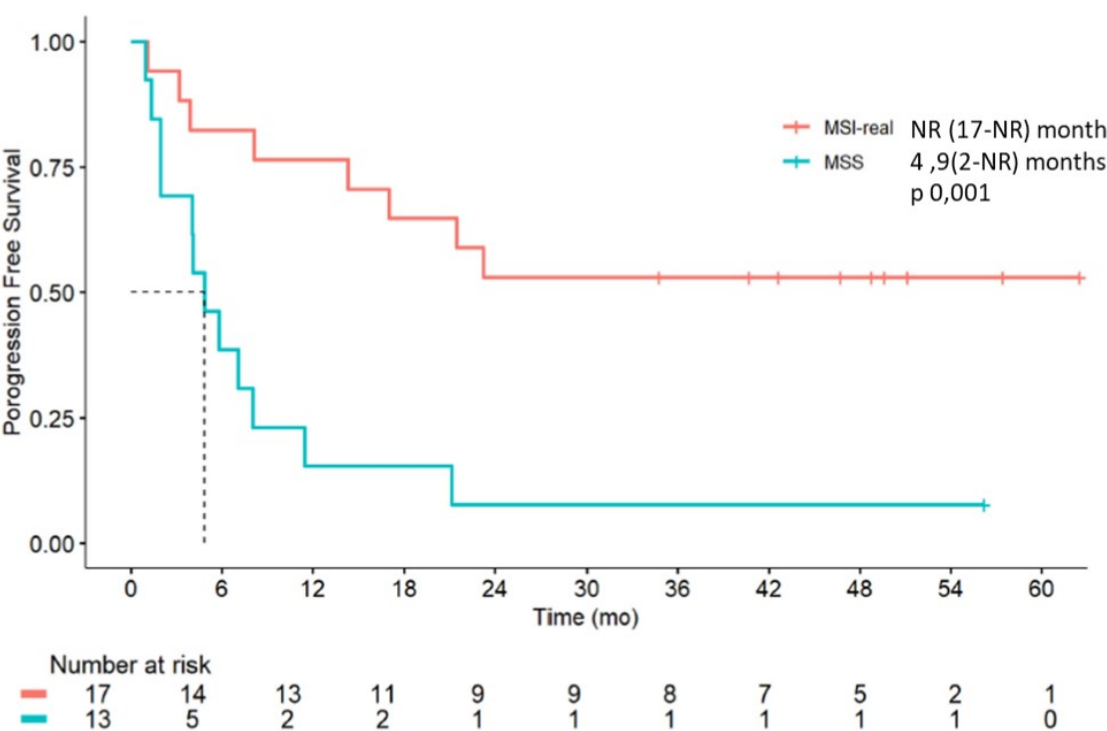


Fig 5: MSI-like Overall mOS

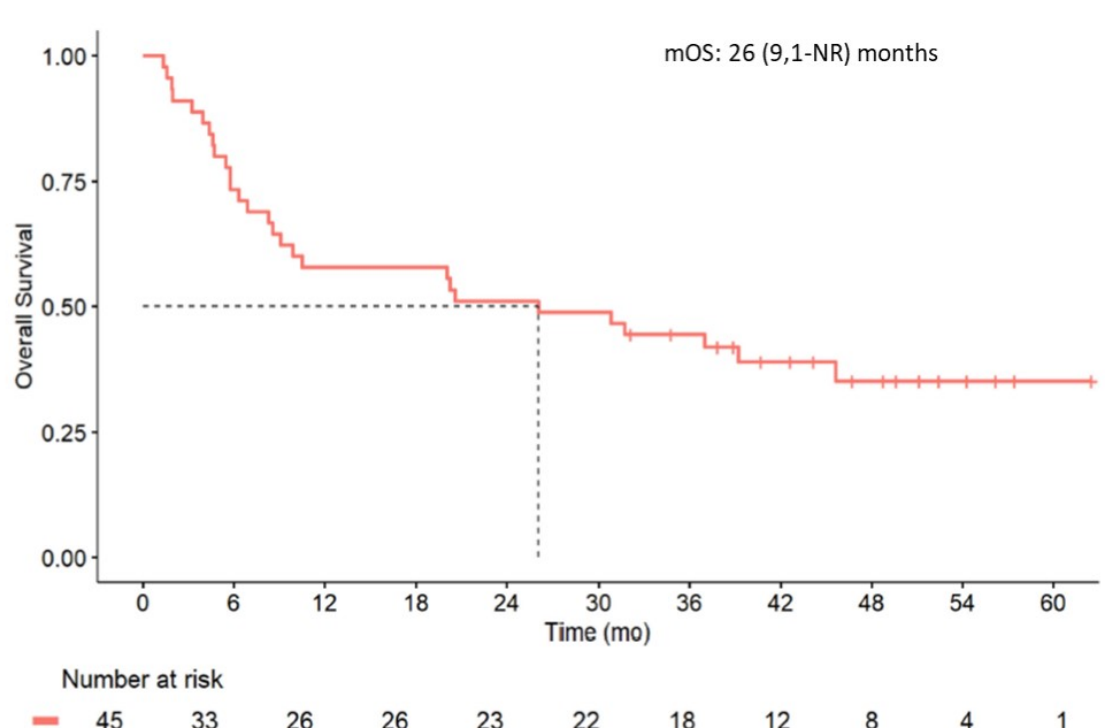


Fig 6: Overall mOS without liver metastases based on Agendia signature

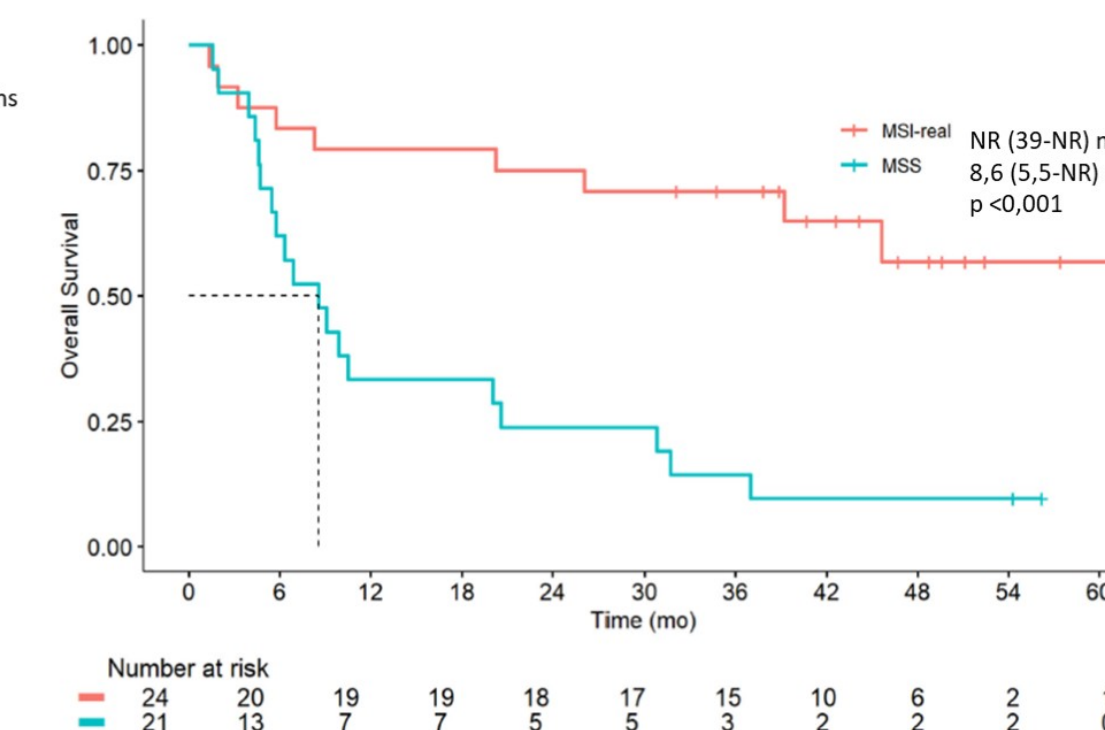


Fig 7: Overall mOS without liver metastases based on Agendia signature

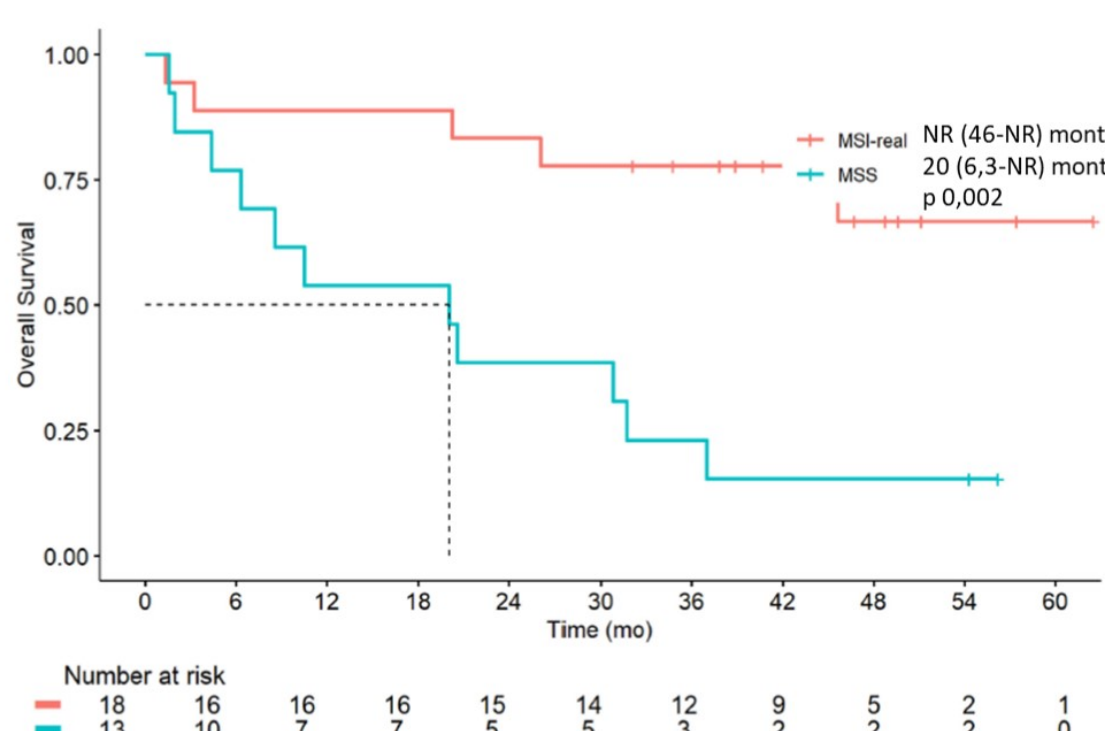


Fig 8: Median Duration of Response based on Agendia signature

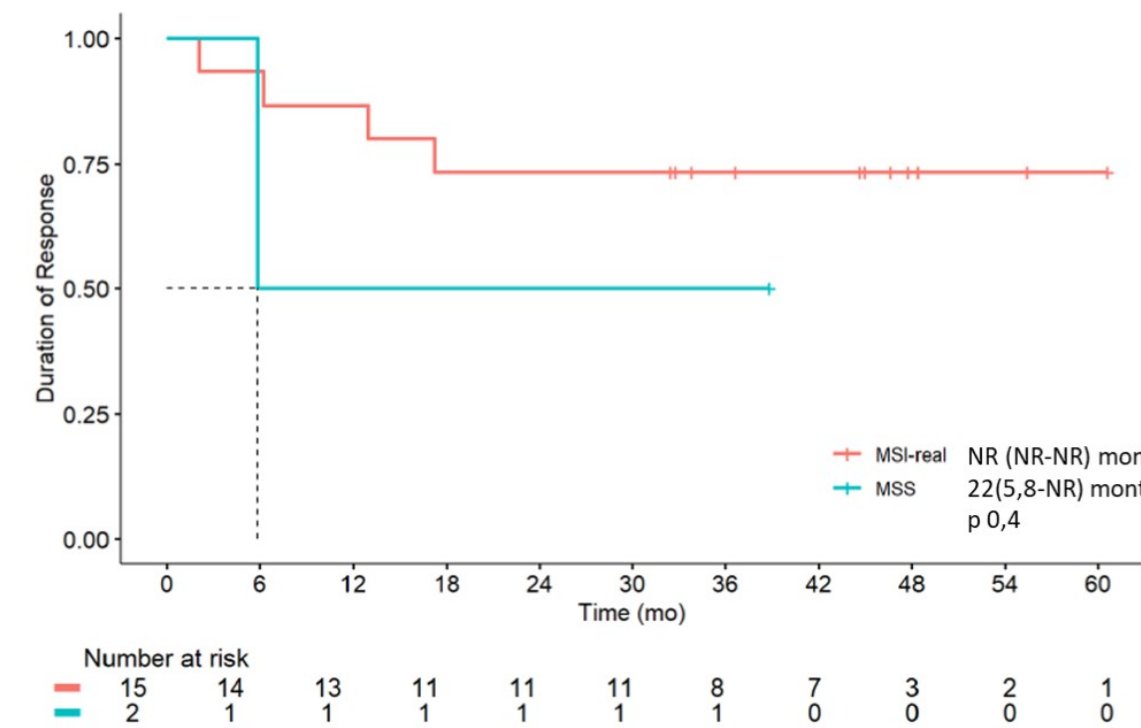


Table 4: Summary of toxicities

	MSI-like			MSI-real			MSS		
	Any Grade	G3-4	G5	Any Grade	G3-4	G5	Any Grade	G3-4	G5
Any Adverse Event	44 (97.8%)	20 (44.4%)	2 (4.4%)	24 (100%)	12 (50%)	1 (4.2%)	20 (95.2%)	8 (38.1%)	1 (4.8%)
Fatigue	22 (48.9%)	1 (2.2%)	0 (0%)	12 (50%)	1 (4.2%)	0 (0%)	10 (47.6%)	0 (0%)	0 (0%)
Hypertension	13 (28.9%)	3 (6.7%)	0 (0%)	5 (20.8%)	1 (4.2%)	0 (0%)	8 (38.1%)	2 (9.5%)	0 (0%)
Abdominal Pain	11 (24.4%)	1 (2.2%)	0 (0%)	4 (16.7%)	0 (0%)	0 (0%)	7 (33.3%)	1 (4.8%)	0 (0%)
Diarrhea	10 (22.2%)	0 (0%)	0 (0%)	4 (16.7%)	0 (0%)	0 (0%)	6 (28.6%)	0 (0%)	0 (0%)
Anemia	8 (17.8%)	2 (4.4%)	0 (0%)	3 (12.5%)	1 (4.2%)	0 (0%)	5 (23.8%)	1 (4.8%)	0 (0%)
Anorexia	8 (17.8%)	0 (0%)	0 (0%)	4 (16.7%)	0 (0%)	0 (0%)	4 (19%)	0 (0%)	0 (0%)
Fever	8 (17.8%)	1 (2.2%)	0 (0%)	4 (16.7%)	1 (4.2%)	0 (0%)	4 (19%)	0 (0%)	0 (0%)
Hypothyroidism	8 (17.8%)	0 (0%)	0 (0%)	4 (16.7%)	0 (0%)	0 (0%)	4 (19%)	0 (0%)	0 (0%)
Proteinuria	7 (15.6%)	0 (0%)	0 (0%)	5 (20.8%)	0 (0%)	0 (0%)	2 (9.5%)	0 (0%)	0 (0%)
Weight Loss	7 (15.6%)	0 (0%)	0 (0%)	4 (16.7%)	0 (0%)	0 (0%)	3 (14.3%)	0 (0%)	0 (0%)
Colonic Hemorrhage	2 (4.4%)	0 (0%)	1 (2.2%)	2 (8.3%)	0 (0%)	1 (4.2%)	0 (0%)	0 (0%)	0 (0%)
Progressive Clinical Deterioration	1 (2.2%)	0 (0%)	1 (2.2%)	1 (4.2%)	0 (0%)	1 (4.2%)	0 (0%)	0 (0%)	0 (0%)
Respiratory Distress Syndrome	1 (2.2%)	0 (0%)	1 (2.2%)	0 (0%)	0 (0%)	0 (0%)	1 (4.8%)	0 (0%)	1 (4.8%)
Reasonable possibility of association with Atezolizumab									
Any Adverse Event	33 (73.3%)	5 (11.1%)	0 (0%)	18 (75%)	5 (20.8%)	0 (0%)	15 (71.4%)	0 (0%)	0 (0%)
Fatigue	18 (40%)	1 (2.2%)	0 (0%)	12 (50%)	1 (4.2%)	0 (0%)	6 (28.6%)	0 (0%)	0 (0%)
Anorexia	6 (13.3%)	0 (0%)	0 (0%)	4 (16.7%)	0 (0%)	0 (0%)	2 (9.5%)	0 (0%)	0 (0%)
Diarrhea	6 (13.3%)	0 (0%)	0 (0%)	4 (16.7%)	0 (0%)	0 (0%)	2 (9.5%)	0 (0%)	0 (0%)
Hypothyroidism	6 (13.3%)	0 (0%)	0 (0%)	4 (16.7%)	0 (0%)	0 (0%)	2 (9.5%)	0 (0%)	0 (0%)
Hyperthyroidism	5 (11.1%)	0 (0%)	0 (0%)	2 (8.3%)	0 (0%)	0 (0%)	3 (14.3%)	0 (0%)	0 (0%)
Fever	3 (6.7%)	1 (2.2%)	0 (0%)	3 (12.5%)	1 (4.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Arthralgia	2 (4.4%)	0 (0%)	0 (0%)	2 (8.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Arthritis	2 (4.4%)	0 (0%)	0 (0%)	2 (8.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hypertension	2 (4.4%)	0 (0%)	0 (0%)	1 (4.2%)	0 (0%)	0 (0%)	1 (4.8%)	0 (0%)	0 (0%)
Lymphocyte Count Decreased	2 (4.4%)	0 (0%)	0 (0%)	2 (8.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Reasonable possibility of association with Bevacizumab									
Any Adverse Event	34 (75.6%)	9 (20%)	1 (2.2%)	19 (79.2%)	5 (20.8%)	1 (4.2%)	15 (71.4%)	4 (19%)	0 (0%)
Fatigue	16 (35.6%)	1 (2.2%)	0 (0%)	12 (50%)	1 (4.2%)	0 (0%)	4 (19%)	0 (0%)	0 (0%)
Hypertension	12 (26.7%)	3 (6.7%)	0 (0%)	5 (20.8%)	1 (4.2%)	0 (0%)	7 (33.3%)	2 (9.5%)	0 (0%)
Proteinuria	7 (15.6%)	0 (0%)	0 (0%)	5 (20.8%)	0 (0%)	0 (0%)	2 (9.5%)	0 (0%)	0 (0%)
Diarrhea	6 (13.3%)	0 (0%)	0 (0%)	3 (12.5%)	0 (0%)	0 (0%)	3 (14.3%)	0 (0%)	0 (0%)
Anorexia	5 (11.1%)	0 (0%)	0 (0%)	4 (16.7%)	0 (0%)	0 (0%)	1 (4.8%)	0 (0%)	0 (0%)
Arthralgia	2 (4.4%)	0 (0%)	0 (0%)	2 (8.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Epistaxis	2 (4.4%)	0 (0%)	0 (0%)	1 (4.2%)	0 (0%)	0 (0%)	1 (4.8%)	0 (0%)	0 (0%)
Fever	2 (4.4%)	1 (2.2%)	0 (0%)	2 (8.3%)	1 (4.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Platelet Count Decreased	2 (4.4%)	0 (0%)	0 (0%)	2 (8.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Thromboembolic Event	2 (4.4%)	0 (0%)	0 (0%)	1 (4.2%)	0 (0%)	0 (0%)	1 (4.8%)	0 (0%)	0 (0%)
Colonic Hemorrhage	1 (2.2%)	0 (0%)	1 (2.2%)	1 (4.2%)	0 (0%)	1 (4.2%)	0 (0%)	0 (0%)	0 (0%)
Progressive Clinical Deterioration	1 (2.2%)	0 (0%)	1 (2.2%)	1 (4.2%)	0 (0%)	1 (4.2%)	0 (0%)	0 (0%)	0 (0%)

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