# Durvalumab plus monalizumab, mFOLFOX6, and bevacizumab in patients with metastatic microsatellite-stable colorectal cancer

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## Background

- Immune checkpoint inhibitors have shown limited clinical benefits in metastatic microsatellite-stable colorectal cancer (MSS-CRC),[1,2] but dual targeting of nonredundant checkpoint pathways may enhance antitumour immune responses via innate and adaptive pathways.
- Checkpoint pathways in CRC include programmed cell death-1 (PD-1)/PD-1 ligand (PD-L1),[3] and NKG2A/major histocompatibility complex E (HLA-E).[4]
- Durvalumab is a monoclonal antibody (mAb) that blocks PD-L1 binding to PD-1 and CD80[5] (**Figure 1A**).
  - In Phase 2 trials, durvalumab showed promising antitumour activity and overall survival (OS) in patients with microsatellite-instability high cancers including advanced CRC,[6] and durvalumab plus the anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) agent tremelimumab prolonged OS over best supportive care in patients with refractory metastatic CRC (mostly MSS-CRC).[7]
- Monalizumab is an immunoglobulin G4 (IgG4) mAb that blocks NKG2A binding to HLA-E to reduce inhibition of natural killer (NK) and CD8+ T cells[8] (**Figure 1B**).
- In a first-in-human, Phase 1/2, multicentre, open-label study (NCT02671435), durvalumab was combined with monalizumab in patients with advanced solid tumours (**Figure 2**). The combination was well tolerated and showed encouraging clinical activity and pharmacodynamic effects in heavily pretreated patients with advanced MSS-CRC.[9,10]
- Randomised trials have shown that bevacizumab improves response rates, OS, and progression-free survival in patients with metastatic CRC when combined with various standard chemotherapy regimens.[11–13]
- Here we present data from a dose-exploration cohort in which durvalumab and monalizumab were added to standard of care (SoC) chemotherapy (modified [m] FOLFOX6; folinic acid, fluorouracil, and oxaliplatin) and bevacizumab as first-line therapy for advanced/metastatic MSS-CRC.

## Methods

- Eligible patients had histologically defined MSS-CRC, regardless of *RAS/BRAF* mutational status and location of colon primary tumour, at least one lesion measurable by Response Evaluation Criteria in Solid Tumours (RECIST) v1.1, Eastern Cooperative Oncology Group performance status of 0–1, adequate coagulation and organ function, and no prior systemic therapy.
- Patients received durvalumab 1500 mg intravenous (IV) every 4 weeks (Q4W), monalizumab 750 mg Q2W, mFOLFOX6 Q2W, and bevacizumab 5 mg/kg Q2W. Treatment continued until unacceptable toxicity, confirmed progressive disease, or withdrawal for other reasons.
- Chemotherapy dose modifications were allowed according to SoC practice except during the dose-limiting toxicity (DLT) evaluation period.
- The primary objective was assessment of safety and tolerability; secondary endpoints included antitumour activity.
- Median time to response, duration of response, and duration of disease control were assessed via Kaplan-Meier methods.

## Results

### Patients

- As of 29 July 2019, 18 patients were enrolled and treated in Cohort A1.
- Median duration of follow-up was 10.0 months (range, 1.6–14.2).
- Patient demographic and baseline disease characteristics are shown in **Table 1.**

**Figure 1. Mechanisms of action of (A) durvalumab and (B) monalizumab**

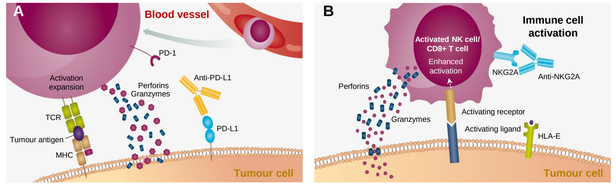
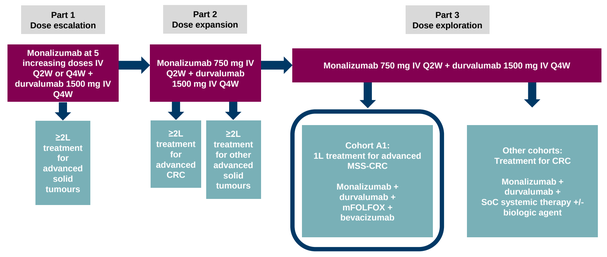



**Figure 2. Study design**




CRC, colorectal cancer; mFOLFOX, modified FOLFOX; MSS, microsatellite-stable; MTD, maximum tolerated dose

**Table 1. Demographic and baseline disease characteristics**

| Characteristic | MSS-CRC (N=18) |
|---|---|
| Median age (range), years | 62.0 (36, 75) |
| Sex, n (%) | |
| Male | 10 (55.6) |
| Female | 8 (44.4) |
| Race, n (%) | |
| White | 13 (72.2) |
| Black or African American | 2 (11.1) |
| Asian | 1 (5.6) |
| Other | 2 (11.1) |
| *KRAS* mutation, n (%) | 11 (61.1) |
| *BRAF* (V600E) mutation, n (%) | 1 (5.6%)* |
| ECOG PS, n (%) | |
| 0 | 9 (50) |
| 1 | 9 (50) |

ECOG PS, Eastern Cooperative Oncology Group performance status
*The BRAF mutation status of 4 patients was unknown and 13 had no mutation.

**Table 2. Safety summary**

| Safety parameter | MSS-CRC (N=18) n (%) |
|---|---|
| Any AEs | 18 (100) |
| Grade 3/4 AEs | 14 (77.8) |
| SAEs | 7 (38.9) |
| Monalizumab-related AEs | 14 (77.8) |
| Monalizumab-related SAEs | 1 (5.6) |
| Durvalumab-related AEs | 15 (88.3) |
| Durvalumab-related SAEs | 0 |
| Chemotherapy-related AEs | 18 (100) |
| Chemotherapy-related SAEs | 2 (11.1) |
| Bevacizumab-related AEs | 10 (55.6) |
| Bevacizumab-related SAEs | 2 (11.1) |

AE, adverse event; SAE, serious adverse event

### Safety

- The safety profile of combination treatment is summarised in **Table 2**.
- Monalizumab-related adverse events (AEs) occurred in 14 patients (77.8%), most commonly fatigue (27.8%) and increased aspartate aminotransferase (16.7%) (**Table 3**).
  - One patient (5.6%) had a serious monalizumab-related AE (SAE): Grade 3 embolism, which was also considered to be related to chemotherapy and bevacizumab.
- Durvalumab-related AEs occurred in 15 patients (83.3%), most commonly fatigue (27.8%), increased amylase (22.2%), and increased lipase (22.2%) (**Table 3**). None had SAEs.
- All patients had chemotherapy-related AEs, most commonly fatigue (55.6%), nausea (55.6%), and peripheral neuropathy (50.0%) (**Table 3**).
  - Two patients (11.1%) had chemotherapy-related SAEs: Grade 3 embolism (the patient described above) and Grade 3 febrile neutropenia, which was also considered to be related to bevacizumab.
- Bevacizumab-related AEs occurred in 10 patients (55.6%), most commonly epistaxis (16.7%), fatigue (16.7%), increased lipase (11.1%), and rash (11.1%) (**Table 3**).
  - Two patients (11.1%) had bevacizumab-related SAEs: Grade 3 embolism and Grade 3 febrile neutropenia (the patients described above).
- AEs leading to discontinuation are summarized in **Table 4**.
- There were no Grade 5 AEs or DLTs.

**Table 3. Treatment-related AEs: any-grade events occurring in ≥20% of patients and all grade 3/4 events**

| Monalizumab-related AEs, n (%) | | |
|---|---|---|
| | Any grade | Grade 3/4 |
| Any TRAE | 14 (77.8) | 6 (33.3) |
| Fatigue | 5 (27.8) | 0 |
| Increased AST | 3 (16.7) | 1 (5.6) |
| Increased lipase | 2 (11.1) | 2 (11.1) |
| Increased bilirubin | 2 (11.1) | 1 (5.6) |
| Decreased lymphocytes | 2 (11.1) | 1 (5.6) |
| Neutropenia | 2 (11.1) | 1 (5.6) |
| Rash | 2 (11.1) | 1 (5.6) |
| Embolism* | 1 (5.6) | 1 (5.6) |
| Increased ALT | 1 (5.6) | 1 (5.6) |
| Hyponatraemia | 1 (5.6) | 1 (5.6) |

| Durvalumab-related AEs, n (%) | | |
|---|---|---|
| | Any grade | Grade 3/4 |
| Any TRAE | 15 (88.3) | 8 (44.4) |
| Fatigue | 5 (27.8) | 0 |
| Increased amylase | 4 (22.2) | 1 (5.6) |
| Increased lipase | 4 (22.2) | 4 (22.2) |
| Increased AST | 3 (16.7) | 1 (5.6) |
| Increased bilirubin | 2 (11.1) | 1 (5.6) |
| Decreased lymphocytes | 2 (11.1) | 1 (5.6) |
| Neutropenia | 2 (11.1) | 1 (5.6) |
| Rash | 2 (11.1) | 1 (5.6) |
| Increased ALT | 1 (5.6) | 1 (5.6) |
| Hyponatraemia | 1 (5.6) | 1 (5.6) |

| Chemotherapy-related AEs, n (%) | | |
|---|---|---|
| | Any grade | Grade 3/4 |
| Any TRAE | 18 (100) | 11 (61.1) |
| Fatigue | 10 (55.6) | 0 |
| Nausea | 10 (55.6) | 0 |
| Peripheral neuropathy | 9 (50.0) | 2 (11.1) |
| Diarrhoea | 7 (38.9) | 0 |
| Neutropenia | 7 (38.9) | 4 (22.2) |
| Temperature intolerance | 7 (38.9) | 0 |
| Decreased appetite | 5 (27.8) | 0 |
| Dysgeusia | 5 (27.8) | 0 |
| Alopecia | 4 (22.2) | 0 |
| Oral pain | 4 (22.2) | 0 |
| Increased bilirubin | 3 (16.7) | 2 (11.1) |
| Increased AST | 3 (16.7) | 1 (5.6) |
| Paraesthesia | 3 (16.7) | 1 (5.6) |
| Increased lipase | 2 (11.1) | 2 (11.1) |
| Decreased lymphocytes | 2 (11.1) | 2 (11.1) |
| Decreased white blood cells | 2 (11.1) | 1 (5.6) |
| Decreased neutrophils | 1 (5.6) | 1 (5.6) |
| Increased ALT | 1 (5.6) | 1 (5.6) |
| Drug hypersensitivity | 1 (5.6) | 1 (5.6) |
| Embolism* | 1 (5.6) | 1 (5.6) |
| Febrile neutropenia† | 1 (5.6) | 1 (5.6) |
| Hyponatraemia | 1 (5.6) | 1 (5.6) |
| Infusion-related reaction | 1 (5.6) | 1 (5.6) |

| Bevacizumab-related AEs, n (%) | | |
|---|---|---|
| | Any grade | Grade 3/4 |
| Any TRAE | 10 (55.6) | 4 (22.2) |
| Epistaxis | 3 (16.7) | 0 |
| Fatigue | 3 (16.7) | 0 |
| Increased lipase | 2 (11.1) | 2 (11.1) |
| Rash | 2 (11.1) | 1 (5.6) |
| Increased ALT | 1 (5.6) | 1 (5.6) |
| Embolism* | 1 (5.6) | 1 (5.6) |
| Febrile neutropenia† | 1 (5.6) | 1 (5.6) |
| Decreased lymphocytes | 1 (5.6) | 1 (5.6) |
| Decreased neutrophils | 1 (5.6) | 1 (5.6) |

*Represents 1 patient: AE was Grade 3, serious, and related to monalizumab, chemotherapy, and bevacizumab
†Represents 1 patient: AE was Grade 3, serious, and related to chemotherapy and bevacizumab

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event

**Table 4. AEs leading to discontinuation**

| AEs leading to discontinuation | MSS-CRC (N=18) n (%) |
|---|---|
| **AEs leading to discontinuation of monalizumab and durvalumab** | |
| Grade 3 increased ALT and AST | 1 (5.6) |
| **AEs leading to discontinuation of chemotherapy** | |
| Neutropenia<br>Grade 1<br>Grade 2<br>Grade 3 | 4 (22.2)<br>1 (5.6)<br>2 (11.1)<br>1 (5.6) |
| Grade 1 paraesthesia | 2 (11.1) |
| Grade 1 peripheral neuropathy | 1 (5.6) |
| Grade 2 fatigue | 1 (5.6) |
| Grade 3 drug hypersensitivity | 1 (5.6) |
| Grade 3 infusion-related reaction | 1 (5.6) |
| Grade 1 decreased platelets | 1 (5.6) |
| **AEs leading to discontinuation of bevacizumab** | |
| Grade 3 colonic fistula | 1 (5.6) |
| Grade 3 failure to thrive | 1 (5.6) |

### Clinical activity

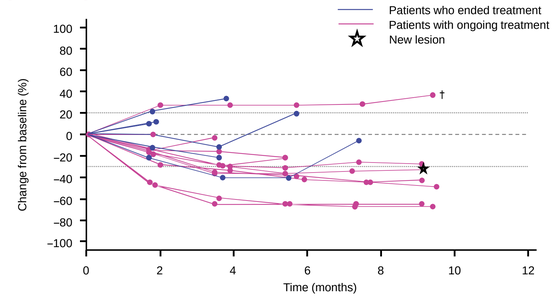
- 17 patients were evaluable for response; 9 (52.9%) had partial responses (7 confirmed, 2 unconfirmed), 8 (47.1%) had stable disease, and 2 (11.8%) had progressive disease. There were no complete responses (**Table 5**).
- Tumour size change and duration of treatment are shown in **Figures 3** and **4**.
- Median time to response was 15.4 weeks.
- Responses were durable (median not reached), ranging from 16.1 to 33.1 weeks. All but one of the responses were ongoing at the time of data analysis.

**Table 5. Clinical activity**

| Disease response | Response-evaluable population* (N=17) |
|---|---|
| Best overall response, n (%) | |
| CR | 0 |
| PR | 7 (41.2) |
| SD | 8 (47.1) |
| Unconfirmed PR | 2 (11.8) |
| PD | 2 (11.8) |
| CR + PR, confirmed and unconfirmed, n (%)<br>95% CI | 9 (52.9)<br>27.8–77.0 |
| CR + PR (ORR), n (%)<br>95% CI | 7 (41.2)<br>18.4–67.1 |
| CR + PR + SD ≥24 weeks, n (%)<br>95% CI | 11 (64.7)<br>38.3–85.8 |
| Median time to response (95% CI), weeks | 15.4 (7.4–17.0) |
| Median duration of response (95% CI), weeks | NR (16.1–NE) |

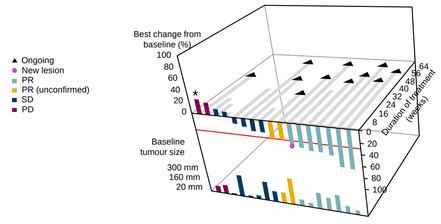
*Response-evaluable population includes patients in the as-treated population who have at least 1 post-baseline disease assessment or discontinued due to death or disease progression prior to the first post-baseline disease assessment
CR, complete response; NE, not estimable; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

**Figure 3. Change in tumour size on treatment**




†Patient remained on treatment due to unconfirmed progressive disease, and discontinued treatment after 10 months

**Figure 4. Best change from baseline in tumour size and duration of treatment**




*Patient had a PR but developed a new lesion at Disease Assessment 5. New disease assessment is pending

## Conclusions

- The combination of monalizumab, durvalumab, SoC chemotherapy, and bevacizumab had a manageable safety profile as first-line therapy for advanced/metastatic MSS-CRC, with no DLTs, similar to SoC alone.
- Preliminary efficacy data show encouraging antitumour activity with durable responses.
- Combination treatment has the potential for additional and deeper responses.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### Acknowledgements

This study was funded by AstraZeneca. Medical writing support was provided by Fiona Chaplin, DPhil, of Cirrus Communications (Macclesfield, UK) and was funded by AstraZeneca.




### Conflicts of interest

Presenting author – Dr Cho has no conflicts of interest to declare.
Co-authors – for co-author disclosure, please kindly refer to the Abstract.

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*Presented at the European Society for Medical Oncology Congress, Barcelona, Spain, 27 September–1 October 2019*