Background

Immune checkpoint inhibitors have shown limited clinical benefits in metastatic microsatellite-stable colorectal cancer (MSSCRC). PD-1/PD-L1 dual targeting of nonobstructive checkpoint pathways may enhance antitumour immune responses via immune and adaptive pathways. Checkpoint pathways in CRC include programmed cell death 1 (PD-1)/PD-L1 and NG2/ligand homotypic complex 3 (HLA-2).

Duraluzimab is a monoclonal antibody (mAb) that blocks PD-L1 leading to PD-1 and CD8B (Figure 1A).

• In Phase 2 trials, duraluzimab showed promising antitumour activity and overall survival (OS) in patients with metastatic MSI CRC. Clinical activity and duraluzimab plus the anti-CTLA-4 agent tremelimumab produced OS over best supportive care in patients with refractory metastatic CRC (medically MSSCRC).

• Duraluzimab is an immunoglobulin G4 (IgG4) mAb that blocks NG2 binding to HLA-E to reduce inhibition of natural killer (NK) and CD8+ T-cell activity (Figure 1B).

• Randomised trials have shown that bevacizumab improves response rates, OS, and progression-free survival in patients with metastatic CRC when combined with various standard or investigational agents.

• Here we present data from a dose-escalation cohort in which duraluzimab and durvalumab were added to standard-of-care (SoC) therapy for MSSCRC (dual mAb therapy), and bevacizumab as first-line therapy for advanced metastatic MSSCRC.

Methods

• Eighty patients had historically defined MSS-CRC, regardless of RAS/BRCA mutation status and location of colonic primary tumour, at least one lesion irresectable by Resection Evaluation Criteria in Solid Tumours (RECIST) v1.1, Eastern Cooperative Oncology Group performance status 0–1, adequate coagulation and organ function, and no prior systematic therapy.

• Patients received duraluzimab 155 mg/m2 Q2W, durvalumab 750 mg every 4-weeks (Q4W), monalizumab 750 mg Q4W, and bevacizumab 5 mg/kg Q2W. Treatment continued until unacceptable toxicity, confirmed progressive disease, or withdrew for other reasons.

• Chemotherapy dose modifications were allowed according to SoC practice except during the dose-escalation study phase.

• 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 26 July 2019, 18 patients were enrolled and treated in Cohort A.

• Median duration of follow-up was 24 weeks (range 0–80 weeks).

• Patient demographic and baseline disease characteristics are shown in Table 1.

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

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 appetite/oncogenic anorexia (16.7%).

• One patient (5.6%) had a serious monalizumab-related AE (SAE); Grade 3 embolism, which was managed by desaturation to be treated for chemotherapy and bevacizumab.

• Duraluzimab-related AEs occurred in 15 patients (83.3%), most commonly fatigue (27.8%), increased appetite (22.2%), and increased lipase (22.2%) (Table 2); fatal SAEs. All patients had chemotherapy-related AEs, most commonly fatigue (55.5%), nausea (55.5%), and periarterial neuropathy (55.5%) (Table 2).

Clinical activity

• 17 patients were evaluable for response. 9 (52.9%) had partial responses (7 confirmed, 2 unconfirmed); 6 (41.2%) had stable disease, and 2 (11.1%) had progressive disease. There were no complete responses (Table 3).

• Tumour size change and duration of treatment are shown in Figure 3.

• Median time to response was 15.4 weeks.

• Responses were durable (median not reached), ranging from 16 to 33.1 weeks. All but one of the responses were ongoing at the time of data analysis.

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.

References


Acknowledgments

The study was supported by AstraZeneca. AstraZeneca may provide support for Future Medicine Online and Digital Communications (Chester, UK) and was involved in study design.

Disclaimer

No author has disclosed any potential conflicts of interest.

Conflicts of interest

Presenting author: S. O. S. has Receiving Research Funding from AstraZeneca. No other author has declared a conflict of interest.

Table 1. Demographic and baseline disease characteristics

Table 2. Safety summary

Table 3. Treatment-related AEs: any-grade events occurring in ≥20% of patients and at grade ≥3 events

Table 4. AEs leading to discontinuation

Table 5. Clinical activity

Figures 1, 2, 3, 4, and 5 are shown for additional information. Table 1 is shown in the online version only.