Progression-Free Survival and Overall Survival in Patients with Mismatch Repair Deficient Tumours Treated with Dostarlimab in the GARNET Study

**Background**

- Precision cancer medicine has led to biomarker-driven tumour-agnostic therapies.
- In mismatch repair deficient (dMMR) tumours, DNA mismatch repair genes fail to function properly, with many mutations in microsatellite regions, leading to microsatellite instability (MSI).
- dMMR tumours demonstrate increased mutational load and neoantigenic repertoire, making these tumours attractive candidates to respond to anti-programmed death 1 (anti-PD-1) therapy.
- dMMR tumours can be found across solid tumour types, but the frequency varies by tumour type:
  - Endometrial cancer (EC) and colorectal cancer (CRC) have been reported to have a high prevalence of dMMR (70%–80%), at 25%–30% and 10%–15%, respectively.
  - Patients with advanced dMMR tumours who experience disease progression despite standard systemic therapy have limited treatment options.
- Dostarlimab is an anti-PD-1 monoclonal antibody that blocks interaction with the ligand PD-L1 and PD-L2 and is being investigated in multiple tumour types.

**Objectives**

- To report the secondary endpoints of progression-free survival (PFS) and OS in a phase 1 study of dMMR EC patients with dMMR solid tumours.
- To report on safety and tolerability of dMMR EC patients with dMMR solid tumours.
- To report on in-depth analysis of key secondary endpoints in the overall population and key subgroups.

**Methods**

- GARNET is phase 1/2, multi-centre, open-label, investigator-study of dMMR-based therapy in patients with advanced or recurrent solid tumours with defined dMMR/MSI backgrounds.
- Patients with dMMR tumours were included if they had received at least one prior systemic therapy for advanced disease and had pretreatment dMMR testing performed.
- The primary endpoint was PFS for patients with dMMR EC.
- Median PFS for patients with dMMR EC was 5.6 months and for patients with non-EC was 7.0 months for patients with dMMR solid tumours.
- Median OS for patients with EC was 50.5 months and for patients with non-EC was 58.4 months for patients with dMMR solid tumours.
- Patients with dMMR solid tumours (EC, CRC, and others) treated with dostarlimab had a 61% (95% CI: 44%–77%) overall response rate (ORR) at 16 weeks.
- Patients with dMMR tumours had a 63% (95% CI: 56%–69%) objective response rate (ORR) at 16 weeks.

**Results**

- For this third interim analysis, 341 patients with dMMR solid tumours were evaluable for PFS and 327 patients with dMMR solid tumours were evaluable for OS.
- The median PFS for all patients was 6.6 months; the probability of PFS at 12 months, 2 years, and 3 years was 68.1%, 45.1%, and 30.8%, respectively (Table 1, Figure 1).
- Median PFS for patients with EC was 5.4 months for patients with non-EC was 7.3 months (Table 2).
- For patients with EC, OS was not reached (data not yet matured for non-EC solid tumours).
- For patients with dMMR solid tumours, at 3 years, the estimated OS was 95.9% (95% CI: 92.4%–98.6%).
- Overall, adverse events were generally similar across both dMMR cohorts (EC and non-EC solid tumours).
- The most common study-drug–related adverse events (AEs) in patients with EC were gastrointestinal (GI) disorders, including anorexia, nausea, vomiting, and diarrhoea (Table 3).
- Grade ≥3 (concurrent with death) AEs in patients with dMMR solid tumours included colitis (5.2%), lipase increased (2.1%), and hyperglycaemia (1.2%).
- Grade ≥3 AEs leading to death in patients with dMMR solid tumours included colitis (5.2%), lipase increased (2.1%), and hyperglycaemia (1.2%).

**Conclusions**

- In 341 patients with dMMR solid tumours, dMMR-demonstrated multiple antitumour activity and 44% overall objective response rate (ORR) across 16 tumour types.
- The landmark estimates of 32, 34, and 36 months (45.4%, 46.6%, and 38.7%, respectively) demonstrated the stability of PFS benefits for responders in this dMMR-selected patient population.
- Adverse events were generally similar across both dMMR cohorts (EC and non-EC solid tumours).
- For patients with dMMR solid tumours (EC, CRC, and others) treated with dostarlimab, the overall response rate (ORR) at 16 weeks was 61% (95% CI: 44%–77%).
- In-depth analysis of key secondary endpoints in the overall population and key subgroups showed a median PFS of 5.6 months and median OS of 50.5 months for patients with EC with dMMR solid tumours.
- Patients with dMMR solid tumours (EC, CRC, and others) treated with dostarlimab had a 63% (95% CI: 56%–69%) objective response rate (ORR) at 16 weeks.
- Patients with dMMR solid tumours had a 61% (95% CI: 44%–77%) overall response rate (ORR) at 16 weeks.