SO-17 The global POLAR program: Top-line results of placebo-controlled studies of calmangafodipir on top of modified FOLFOX6 to prevent chemotherapy-induced peripheral neuropathy

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Background: Results from the PLIANT study in Caucasian, metastatic, colorectal cancer (CRC) patients with the superoxide dismutase mimetic and iron chelator calmangafodipir (CaM) suggested its potential to prevent chemotherapy-induced peripheral neuropathy (CIPN) in patients treated with oxaliplatin (Glimelius et al. 2018).

Methods: The POLAR program consisted of two phase 3, global, multicenter, placebo (PLC)-controlled trials with CaM (5µmol/kg) to prevent CIPN: POLAR-A in CRC patients with Stage III or high-risk Stage II who were treated with adjuvant modified FOLFOX6 (mFOLFOX6) for up to 6 months and; POLAR-M in patients with metastatic colorectal cancer, who were eligible for first-line mFOLFOX6 chemotherapy for at least 3 months. The primary endpoint was patient-reported symptoms as a proportion of patients scoring 3 or 4 (i.e. moderate or severe) in at least 1 of the first 4 items of the FACT/GOG-NTX-13 questionnaire targeting numbness, tingling or discomfort in hands or feet, assessed 9 months after the first dose of IMP (CaM or PLC). In Q2 2020, the POLAR program was prematurely stopped based on the Data Safety Monitoring Board's recommendation due to a number of severe allergic reactions observed after repeated dosing. Patients enrolled in the POLAR program continued with their scheduled study procedures, while not receiving IMP until all patients in the modified Intention To Treat (mITT) population (patients eligible for 6 cycles of treatment with IMP, n=434) had completed data collection of the primary endpoint 9 months after the first dose of IMP.

Results: In the primary analysis of Moderate to Severe CIPN 9 months after first dose of IMP in the pooled (POLAR-A and POLAR-M) mITT population (n=351), patients receiving CaM had an increased relative risk of CIPN vs PLC; 54.8% vs 40.0%; RR=1.37 [95% CI: 1.01; 1.86]; p=0.0445. There were no clinically significant differences between the treatment arms on secondary endpoints related to CIPN. Furthermore, the proportion of AEs in the safety analysis set (n=486), related to CIPN was similar between the treatments. The number (%) of patients with treatment-emergent serious adverse events (TESAE) was 41 (17.1%) vs 44 (17.9%) on CaM 5µmol/kg vs PLC. There was a total of 14 SAEs on CaM vs 2 SAEs on PLC related to allergic-hypersensitivity reactions. In a post hoc analysis of the primary endpoint in Caucasian patients in POLAR-M (a patient population similar to the population in the previous PLIANT study with CaM) the observed RR of CaM 5µmol/kg vs PLC was 0.72, albeit based on a limited number of patients (n=47).

Conclusions: The global POLAR program did not meet the primary objective. The etiology of increased CIPN symptoms is unclear.

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