Melanoma patients progressing after immune checkpoint inhibitors (ICI) and BRAF targeting therapy have a poor prognosis. We hypothesize that the addition of tinostamustine will improve clinical efficacy of melanoma treatment.

**Background**
- Melanoma patients (pts) progressing after immune checkpoint inhibitors (ICI) and BRAF targeting therapy have a poor prognosis.
- Tinostamustine is a multi-action therapy (first-in-class alkylating-deacetylase inhibitor) that facilitates access to the DNA within cancer cells, damages it, thereby repairing the system that is normally triggered once DNA is damaged.
- Preclinical experiments have revealed immunomodulatory characteristics of tinostamustine including induction of HLA class II and PD-L1 at a sub-myelosuppressive dose.
- We hypothesize that the addition of tinostamustine to nivolumab improves clinical efficacy of melanoma treatment.

**Study design**
- ENIGMA is an open-label, multi-center Phase 1b study (NCT03939458, S6CTP00000243) in pts with advanced melanoma.
- The primary objective is to evaluate the safety, tolerability, potential dose-limiting toxicity (DLT) and the recommended phase-2 dose (RP2D) of sub-myelosuppressive tinostamustine and nivolumab.

**Efficacy**
- Mean treatment duration was 22 weeks.
- 3 patients received ≤4 weeks of study treatment due to early progression.
- 6 out of 12 (46%) evaluable pts had at least stable disease (SD) as best treatment response, including 3 pts with PD-L1 with a confirmed partial response (PR).
- 7 out of 12 (54%) evaluable pts had progressive disease (PD) as best treatment response.
- Median progression-free survival was 8.3 weeks (95% CI 2.4 to 15.4 weeks).
- Median overall survival 19.1 weeks (95% CI 2.4 to 41 weeks).

**Conclusions**
- Tinostamustine at an immune-modulatory dose of 30 mg/m² over 60 min is safe when co-administered with nivolumab 3mg/kg.
- The combination resulted in 46% disease stabilization and 23% confirmed partial responses in pts with advanced melanoma failing standard ICI treatment.
- Tinostamustine / Nivolumab should be tested in melanoma patients in future controlled clinical trials.

**References:**

This study was funded by Mundipharma Research Ltd, Purdue Pharma LP, and Bristol-Myers Squibb.

Acknowledgements: Thank you to the patients, families, and sites for participating in the ENIGMA study.