**A PHASE 1, DOSE ESCALATION STUDY OF PACLITAXEL WITH GSK1120212 (TRAMETINIB) FOR THE TREATMENT OF ADVANCED MELANOMA**

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**Aim:** Limited treatment options are available for patients with BRAF wildtype and NRAS mutant metastatic melanoma. Paclitaxel has modest activity as monotherapy in melanoma. ERK is constitutively activated in melanoma regardless of BRAF mutational status and this leads to degradation of pro-apoptotic proteins, hypothesized to result in resistance to paclitaxel. Trametinib is a highly selective allosteric MEK inhibitor that effectively suppresses ERK. The combination of trametinib and paclitaxel is therefore potentially synergistic and explored in this phase 1 trial.

**Methods:** Eligible patients had advanced melanoma, known BRAF (wildtype and mutant both eligible) and NRAS status, a maximum of two prior lines of systemic therapy and a performance status of 0 or 1. Patients received trametinib daily in escalating doses with a fixed dose of weekly paclitaxel (80mg/m2, given three weeks of four). The trametinib dose was capped at 2.0mg daily (the maximum tolerated dose (MTD) from earlier monotherapy studies).

**Results:** Fifteen patients were enrolled. Trametinib dosing was escalated via three cohorts (cohort 1 = 1.0mg, cohort 2 = 1.5mg, cohort 3 = 2.0mg) in combination with paclitaxel. Eight (53%) patients had NRAS mutations, and one (7%), a BRAF mutation. Two dose limiting toxicities (DLTs) were observed; one event in cohort 1 (visual disturbance) and another in cohort 3 (elevated liver function tests). The MTD of trametinib was 2.0mg. Toxicity was mostly manageable and reversible. Significant toxicity included central serous retinopathy (one patient), pneumonitis (one patient) and grade 4 liver enzyme elevations (one patient). A suspected drug related fatality was reported, secondary to renal failure and considered possibly related to trametinib. Patients remained on study for a median of 111 days. 12 patients (80%) achieved a radiological response. Six partial responses were reported. Four partial responses were in patients with NRAS mutations (50% of patients with this mutation). Progression free survival was 5.5 months (95% CI 1.8 - 7.8 months). Overall survival was 14.1 months (95% CI 4.6 months – not reached).

**Conclusions:** Trametinib can be given safely with paclitaxel. The combination shows early evidence of activity in BRAF wildtype, and in particular NRAS mutant, advanced melanoma.

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