Background: The MAPK pathway is constitutively activated in uveal melanoma (UM), a disease for which there remains no standard of care for metastatic disease. In a randomised phase II clinical trial, selumetinib (AZD6244, ARRY-142886), a MEKi, showed superiority vs dacarbazine (DTIC). A phase III study of the combination of selumetinib (SEL) + DTIC however failed to show superiority over DTIC alone. Pre-clinical data support synergistic cytotoxic activity for MEK + taxane combinations in a number of cancer cell line models and suggest that interrupting selumetinib before taxane exposure may be beneficial.

Methods: Following ethical approval, 77 patients with metastatic UM who had not received previous chemotherapy were randomised to either A: SEL 75mg bd po B: SEL 75mg bd po + PT 80mg/m² weeks 1, 2 and 3 (g28) or C: SEL 75mg bd po interrupted for 2 days before exposure to PT 80mg/m² weeks 1, 2, 3 (g28) at 13 UK sites. Primary endpoint was PFS; OS, ORR and toxicity were secondary endpoints. After an amendment, arms B & C were combined and compared to arm A for PFS, OS and ORR using intention to treat analyses. Reflecting the pooled comparison, the sample size was re-adjusted to detect hazard ratios: 0.55, 80% power at 1-sided significance level. Sensitivity analysis was performed to explore whether there were detectable differences in outcome between patients receiving continuous or interrupted SEL in combination with PT (arms B & C).

Results: Primary analysis was triggered after 68 events. The median PFS in the combination arms B & C was 4.8 months (95% CI: 3.8 - 5.6) compared with 2.0 months (95% CI: 2.0 - 3.9) in the SEL alone arm A (hazard ratio 0.61 [90% CI 0.41 - 0.92], 1-sided p-value = 0.022). ORR was 14% and 4% in arms B & C and A respectively. Median OS in arms B & C was 9 months and was not significantly different from arm A at 10 months (hazard ratio 0.98 [90% CI 0.83 - 1.66], 1-sided p-value = 0.469). SAEs and grade 3+ toxicities were similar between treatment arms.

Conclusions: SelPac met its primary endpoint, demonstrating a statistically significant improvement in PFS for SEL + PT without a significant increase in toxicity. No trend for a prolongation of OS was observed.

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Cutaneous squamous cell carcinoma (CSCC) harbors a high tumor mutation burden (TMB) due to ultraviolet light-mediated DNA damage, and are highly immune-responsive. Cemiplimab, a monoclonal antibody directed against programmed death 1 (PD-1), is approved by the FDA and EMA as treatment for advanced melanoma. Here we explore the efficacy of neoadjuvant cemiplimab in patients with advanced CSCC who are not candidates for curative surgery. A single-institution phase II study was conducted at the University of Texas MD Anderson Cancer Center. Patients with stage III/IV (M0) CSCC were enrolled if they had at least one bidimensionally measurable tumor and were not candidates for curative surgery. Patients received 2 cycles of neoadjuvant cemiplimab (350 mg intravenously every 3 weeks). The primary endpoint was overall response rate (ORR) per RECIST v1.1. Secondary endpoints included pathologic complete response (pCR) and duration of response. Eleven (55%) patients achieved pCR and 10% achieved a major pathologic response. High TMB and high PD-L1 expression were observed in 11 (55%) patients and 10% viable tumor respectively. Eleven (55%) patients received two cycles of neoadjuvant cemiplimab followed by surgery. Relapses were observed in 1/64 (2%) pathological responders versus 1/38 (2%) patients with a major pathologic response. High TMB and high PD-L1 expression were associated with durable relapse-free survival (RFS). Cytokine and PD-1 levels in plasma increased post-treatment irrespective of response. High TMB and high PD-L1 expression were associated with improved RFS and durable responses. Cemiplimab has the potential to be an effective treatment for advanced CSCC.