Phase IB Study to Evaluate the Safety of Selinexor (KPT-330) in Combination with Pembrolizumab in Patients with Advanced Malignancies- the Melanoma Experience

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Background

The introduction of checkpoint inhibitors (CPI) into the clinic has revolutionized the treatment options for cancer patients among different tumor types. In melanoma, single agent anti-PD1 therapy leads to response rates of up to 40% in treatment naïve melanoma patients with unresectable stage III or IV disease. Combining anti-PD1 with anti-CTLA4 leads to upfront response rates of 58%, however, at a price of significant toxicities, with 59% of patients experiencing grade 3 or 4 toxicities, which is in stark contrast to the ~10% of grade 3 or 4 toxicities observed with single agent anti-PD1.

Despite these success, multiple areas of unmet need exist. For treatment naïve patients, combination of anti-PD1 with a different agent that leads to similar response rates like the combo of anti-PD1/CTLA4, but with significant grade 3 or 4 toxicities would represent a attractive options for patients, potentially especially for patients who would not be able to tolerate this combination. Furthermore, it is currently unclear how to best salvage patients who progress on either single PD-1 or anti-PD1/CTLA4 combo. Finally, patients with uveal melanoma (UM) have very limited treatment options, as prior trials have not shown encouraging overall outcomes.

Selinexor is a selective inhibitor of nuclear export used as anti-cancer drug. It works by binding to exportin 1 and thus blocking the mechanism of action. The hypothesis that using the combination of Selinexor with pembrolizumab (an anti CPI) is well tolerated by patients and will induce overall response rates that are comparable to the combination observed with anti-PD1/CTLA4, and to be able to salvage patients who progressed on prior CPI, and to induce response in patients with UM.

Results

Here, we describe the result for 25 patients with metastatic melanoma that were treated with the combination of selinexor at a starting dose of 60mg PO twice weekly and pembrolizumab at 240mg I.V. every 3 weeks in ARM L. Seventeen patients were treatment naïve.

Adverse Events

There were 248 adverse events from 25 patients reported after the first treatment date, which were either possibly, probably or definitely related to treatment. If a patient experienced the same AE at different period of time or reason for treatment or active or off treatment then the adverse events were counted as one event.

Conclusion

The median PFS of the entire cohort has not been reached.
• 6-month PFS rate was 0.65 (95% CI: 0.475, 0.91).
• 9-month PFS rate was 0.57 (95% CI: 0.37, 0.87).
• The median overall survival (OS) has not been reached.

Survival

Treatment with selinexor in combination with pembrolizumab is well-tolerated and shows significant clinical activity in tin pts compared to historic single agent pembrolizumab. The combination warrants further evaluation.