Head and neck squamous cell carcinoma (HNSCC) is a common and lethal cancer for which better therapy is needed.

Although immune checkpoint therapy (ICT) has a striking effect in some HNSCC patients, the majority have intrinsic or acquired resistance.

Human papilloma virus (HPV) is a common cause of HNSCC that leads to the development of the Retinoblastoma (Rb), RNF protein.

Rb-deficient cancers are hyper dependent upon Aurora kinases for survival (2, 6).

Alisertib (MNB237, TAK9527) is a selective small molecule inhibitor of Aurora A kinase.

Alisertib leads to immuneogenic cell death (ICD) in HPV-negative cancer cells (6).

This trial tested the hypothesis that Aurora A inhibition will lead to apoptotic and ICD in HPV- HNSCC leading to host T cell engagement and increased sensivity to ICT.

Study Objectives

Primary objectives:

• Phase I: To determine the recommended phase II dose of the combination of alisertib and pembrolizumab.

• Phase II: To determine the overall response rate and progression free survival (PFS) of patients with recurrent or metastatic Rb-deficient HNSCC treated with the combination.

Secondary objectives:

• To evaluate safety of the combination.

• To determine the overall survival (OS) in treated patients.

• To determine the relationship between response and pharmacokinetics (PK), biomarkers, and the effect of the therapy on HPV-reactive T cells.

Statistical Design

Phase I: Bayesian optimal interval design with a target toxicity rate for the maximum tolerated dose (MTD) at 0.3. Patients enrolled in cohorts of size 2. If the observed dose-limiting toxicity (DLT) rate at the current dose is ≤ 0.236, the next cohort of patients will be treated at the next higher dose level; if it is ≥ 0.359, the next cohort of patients will be treated at the next lower dose level; otherwise, the next cohort of patients will be treated at the same dose.

Phase II: Bayesian Optimal Phase 2 (BOP2) design. The assumptions are that the null response rate is 5% and the target response rate is 20%. Fourteen patients were enrolled initially. Per design, because there were no responses, the trial was terminated due to lack of efficacy.

Study Design and Eligibility

Phase I Eligibility

• Solid tumor without prior standard therapy-prolonging therapy.

• No requirement for Rb deficiency.

Phase II Eligibility

• Rb deficient HNSCC (HPV+ or Rb immunohistochemistry negative)

• Progressed on prior anti-PD1 without severe immune-related adverse events

Design

Pembrolizumab 200 mg IV Q 3 weeks

Alisertib 30-50 mg po BID on days 1-7 every 21 days

Imaging baseline and every 2 cycles

PK: Cmax and AUC on phase II

Blood for HPV mRNA, cytokines, E6/E7 transcripts, flow cytometry in phase II.

Response and Survival

Adverse Events – Total number of events regardless of attribution (r=1 or grade 2)

Alisertib pharmacokinetic (PK) parameters are similar to prior published studies

Levels HPV cell free DNA (cfDNA) increased when patients progressed

Baseline plasma TH2 cytokine response predicts outcome

Changes in the circulating levels of immune cells correlate with outcome

Biomarkers of Response – Phase II

• No prospective tumor biomarkers correlated with PFS or OS

• PD-L1 CPS score (p = 0.59 and 0.96)

• Mutations were heterogeneous precluding formal analysis

• TMB and MSI were not routinely collected

• Drug exposure did not correlate with PFS. Cmax – p = 0.67 and AUC – p = 0.58

Summary

• Alisertib (40 mg) combined with pembrolizumab was well-tolerated in patients with HNSCC.

• Toxicity was similar to known and expected.

• Dose reductions only required with prolonged treatment.

• One patient with CASTLE remained on therapy for over 2 years.

• Three HPV+ HNSCC patients remained on therapy for over 6 months.

• HPV cfDNA levels increased at the time of PD.

• PD-L1 did not predict PFS.

• PK results suggest that pembrolizumab does not affect alisertib PK.

• Baseline cytokines and changes in circulating immune cells correlated with response.

Conclusions and Future Directions

• This combination was well tolerated with expected toxicity.

• Several patients who had previously progressed on immunotherapy had prolonged SD, supporting our hypothesis that Aurora A inhibition can reverse immunotherapy resistance in Rb-deficient HNSCC.

• However, overall clinical activity was modest, and the trial closed for futility.

• Studies with HPV+ HNSCC T cells are on going.

• Future research will focus on mechanisms to increase ICD and apoptosis in Rb-deficient cancer cells treated with alisertib.

References


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