Phase 2 Study of Intratumoral Vildotomid With Intravenous Cemiplimab in Patients With Locally Advanced or Metastatic Merkel Cell Carcinoma (PMP-001-009)


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Background and aims: Prior clinical trials of vildotomid, a Gq-coupled receptor-8 antagonist, failed in a non-small cell lung cancer (NSCLC) phase II study. The most common adverse event was injection-site reaction, and the trial was halted after fewer than 20% of patients enrolled. In this phase II study, we examined the clinical activity and safety of vildotomid alone and in combination with cemiplimab in patients with locally advanced or metastatic Merkel cell carcinoma (MCC).

Methods: Patients were eligible if they had measurable MCC after one or more prior systemic therapies and had not received prior pembrolizumab. Patients were randomized 2:1 to receive vildotomid alone or in combination with cemiplimab. The primary endpoint was confirmed objective response rate (ORR) per the Response Evaluation Criteria in Solid Tumors (RECIT) v1.1 at 12 weeks. Secondary endpoints included safety, duration of response, progression-free survival (PFS), and overall survival (OS).

Results: 41 patients were enrolled with 27 patients randomized to vildotomid alone and 14 patients randomized to vildotomid + cemiplimab. The median age was 71 years (range 45-81) and 81% of patients were male. The most common MCC sites included the skin, subcutaneous, and lymph nodes. Baseline characteristics were similar between the two groups.

The ORR was 15.1% (95% CI 3.4-36.4) in the vildotomid monotherapy group and 13.3% (95% CI 0.7-43.8) in the combination group. The median duration of response was not reached in either group. The median PFS was 2.2 months in the vildotomid monotherapy group and 3.0 months in the combination group. The median OS was not reached in either group. The most common adverse events were injection site reactions, fatigue, and pruritus.

Conclusions: This study did not meet its primary endpoint of 33% ORR with vildotomid monotherapy or combination therapy. Further evaluation of vildotomid in combination with immune checkpoint inhibitors is warranted.

Inhibition potentiates immunoegenicity in Merkel cell carcinoma: a promising approach to overcome resistance to PD-1/PD-L1 immunotherapy

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Background: Recent studies in various tumor types have demonstrated that inhibition of the Chk1 checkpoint pathway potentiates the anti-tumor effects of immune checkpoint blockade. However, little is known about the potential of Chk1 inhibition to improve immunotherapy in MCC.

Methods: MCC cell lines were treated with a Chk1 inhibitor and/or anti-PD-L1 antibody. A priori immunogenic cells were defined as those that expressed high levels of PD-L1 and shed the major histocompatibility complex (MHC) class I molecule. The expression of PD-L1 was assessed by flow cytometry and immunofluorescence microscopy.

Results: Treatment with the Chk1 inhibitor resulted in increased expression of PD-L1 and a reduction in the number of T-cell recognition epitopes. In addition, the Chk1 inhibitor enhanced the ability of MCC cell lines to generate an immune response in a xenograft model.

Conclusions: These results suggest that inhibition of Chk1 potentiates the immunogenicity of MCC cell lines and may be a promising approach to overcome resistance to PD-1/PD-L1 immunotherapy.

Merkel cell carcinoma

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Clinical and molecular studies of Merkel cell carcinoma (MCC) have led to the development of targeted therapies. The mitogen-activated protein kinase (MAPK) pathway is frequently activated in MCC, and inhibitors of this pathway have shown promise in preclinical studies. However, clinical trials of MAPK inhibitors have been largely unsuccessful.

Methods: We developed a patient-level risk model to predict the likelihood of response to MAPK inhibition in MCC patients. The model included demographic, clinical, and molecular variables. We then tested the model in an independent cohort of MCC patients.

Results: The model accurately predicted response to MAPK inhibition in an external cohort of MCC patients. Patients with high-risk scores were more likely to respond to MAPK inhibition than those with low-risk scores.

Conclusions: Our model provides a tool for risk-stratifying MCC patients and identifying those who are most likely to benefit from MAPK inhibition. This could inform clinical trial design and patient management.