A randomized, double-blind, placebo-controlled, phase III study comparing the combination of PDR001, dabrafenib and trametinib versus placebo, dabrafenib and trametinib in previously untreated patients with unresectable or metastatic BRAF V600-mutant melanoma (COMBI-I)


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Background: Checkpoint inhibitor and targeted therapies are both important tools in the management of BRAF V600–mutated unresectable or metastatic melanoma. Although these therapies have improved responses and overall survival, many patients still progress and die from this disease. Thus, additional treatment strategies are needed to improve durability of responses and related long-term outcomes in these patients. Based on preclinical and preliminary clinical data, BRAF and MEK inhibitors can reverse the oncogenic BRAF-induced immune-suppressive phenotype through enhanced melanoma antigen expression and enhanced tumor antigen-specific T-lymphocyte recognition in vivo. These data suggest that there is potential clinical benefit in combining dabrafenib and trametinib with checkpoint inhibitor therapy.

Trial design: The 3-part COMBI-I phase 3 study (NCT02967692) will evaluate the safety and efficacy of PDR001, an investigational anti–programmed death 1 antibody, in combination with dabrafenib and trametinib in previously untreated patients with BRAF V600–mutated unresectable or metastatic melanoma. In part 1, a safety run-in will establish the recommended phase 3 regimen (RP3R) for use in part 3 using an adaptive Bayesian logistic regression model. In part 2, tissue and blood samples from the biomarker cohort will be used to characterize baseline immune markers and explore potential immune marker modulation by the triplet therapy. Part 3 is the randomized, double-blind, placebo-controlled portion that will open once the RP3R has been determined. Approximately 500 patients will be randomized 1:1:1 to receive either PDR001 in combination with dabrafenib and trametinib or placebo in combination with dabrafenib and trametinib, with randomization stratified based on Eastern Cooperative Oncology Group performance status and lactate dehydrogenase level. The primary endpoint will be progression-free survival per investigator’s assessment according to RECIST v1.1. Overall survival will be a key secondary endpoint.

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