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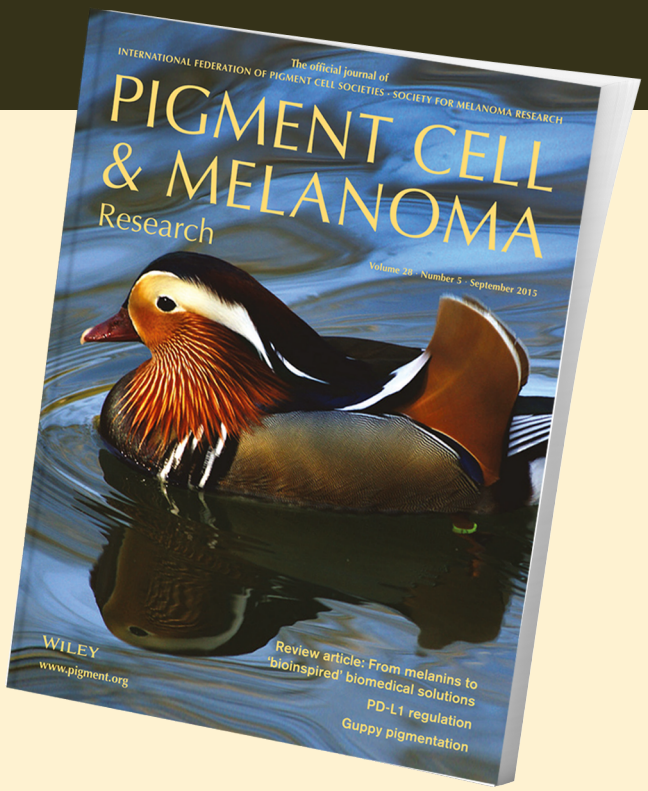

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Severe gastrointestinal toxicity with administration of trametinib in combination with dabrafenib and ipilimumab

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Dear Editor,

Advances in treating metastatic melanoma with immunotherapy (Hodi et al., 2010), and with the targeted *BRAF* inhibitor, dabrafenib, and *MEK* inhibitor, trametinib, have produced important improvements in clinical outcomes (Flaherty et al., 2012a,b; Long et al., 2014; and Robert et al., 2015). Differences in the mechanisms of action suggest that combinations may lead to further improvements. We are conducting a Phase 1/2 study investigating the safety of doublet therapy with dabrafenib and ipilimumab and of triplet therapy with dabrafenib, trametinib, and ipilimumab in metastatic *BRAF* V600E/K-mutated melanoma. We report two cases of colitis followed by intestinal perforation out of seven patients who received dabrafenib and ipilimumab with trametinib (NCT01767454). In accord with the Declaration of Helsinki, the trial was conducted with the approval of appropriately constituted institutional review boards for the protection of human subjects. All patients gave written informed consent at the time of study entry. Each patient completed a 14-day run-in of dabrafenib 100 mg BID and trametinib 1 mg QD without toxicity prior to dosing ipilimumab at 3 mg/kg.

Case 1: A 67-year-old woman with metastatic melanoma received triple-drug therapy. Two weeks after the first dose of ipilimumab, she developed diffuse colitis with a CT scan showing an extramural air and fluid collection consistent with a recto-sigmoid perforation in the setting of acute diverticulitis. Study medications were discontinued and the patient was hospitalized. Methylprednisolone 2 mg/kg and intravenous antibiotics were administered, leading to improvement. Her perforation healed without surgery, and methylprednisolone was tapered over 2 months.

Case 2: A 45-year-old woman with metastatic melanoma received triple-drug therapy. She tolerated dabrafenib, trametinib, and the first dose of ipilimumab well, but 2 weeks after the second dose of ipilimumab, she presented with grade 2 diarrhea. Colonoscopy confirmed pancolitis. Study medications were discontinued and the patient was hospitalized. Methylprednisolone and then prednisone were given at 2 mg/kg/day for 3 days, with prompt clinical improvement, followed by prednisone 1 mg/kg/day for 3 days. Diarrhea improved to grade 1 and prednisone was reduced to 0.65 mg/kg daily. Ten days later, symptoms worsened and the patient was re-hospitalized. Sigmoidoscopy with biopsy confirmed colitis. Despite increasing methylprednisolone to 2 mg/kg, the patient's condition worsened, and CT confirmed diffuse colitis with bowel perforation. Emergent right ileo-colectomy was performed 41 days after the last dose of ipilimumab. Pathological examination of the resected colon was consistent with ipilimumab-induced colitis. The patient recovered to baseline and subsequently received dabrafenib 150 mg BID with control of her melanoma. Infectious disease testing was negative in both patients, and neither had bowel metastases.

Following these two cases, the triplet combination cohort of the study was closed. While patient numbers are small, this experience of two intestinal perforations in seven patients after one or two doses of ipilimumab, administered with dabrafenib and trametinib therapies, raises the possibility of added toxicity with the triplet combination over ipilimumab as a single agent, where grade 3–5 colitis occurs in 5% and intestinal perforations in 1.1% of patients (Ipilimumab package insert, 2014). In support of this interpretation, the clinical combination of dabrafenib and trametinib has rarely been associated with colitis, and no cases of colitis leading to colonic perforation have been reported (Hu-Lieskovan et al., 2014; Long et al., 2014; and Robert et al., 2015). The study cohort evaluating dabrafenib 150 mg BID and ipilimumab 3 mg/kg continues enrollment with only one resolved case of grade 3 colitis in 25 patients to date. These observations suggest that the addition of 1 mg daily trametinib, which is 50% of the recommended dose, to dabrafenib and ipilimumab

may have increased the risk of perforation. In turn, the speed of tapering steroid therapy in the second case may have contributed to the re-emergence of colitis.

How trametinib, or perhaps MEK inhibitors in general, may add to the toxicity of ipilimumab is unclear. Diarrhea was seen in 43% of patients in the initial clinical trials of trametinib, but cases were predominantly grade 1 or 2 (Flaherty et al., 2012b) Conceivably, trametinib increases the immune-mediated toxicity of ipilimumab, or perhaps MEK has an important role in normal colon tight junction formation (Kinugasa et al., 2000). Recent experimental evidence suggests that BRAF inhibitors may promote T-cell activation mediated by paradoxical activation of the MAP kinase pathway, leading investigators to postulate a risk of increased toxicity in patients receiving concurrent ipilimumab (Callahan et al., 2014). An alternative hypothesis is that the potential for an increased infiltration of activated T cells is due to a decrease in immunosuppressive cytokines such as CCL2 and VEGF mediated by inhibition of the MAPK pathway in BRAF V600E/K-mutated melanoma metastases (Sumimoto et al., 2006).

Our findings reinforce the need for the evaluation of novel combination therapies in carefully conducted Phase I clinical trials. Toxicities may be unpredictable as evidenced by the severe colon toxicity in two of seven patients with the addition of trametinib to dabrafenib and ipilimumab. Physicians should be aware of the potential risk of administering unapproved drug combinations such as MEK inhibitors with immune-checkpoint inhibitors and should limit these combinations to clinical trials with appropriate immune-related adverse event monitoring and management guidelines.

Disclosure

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