The anti-rheumatic drug, leflunomide, synergizes with MEK inhibition to suppress melanoma growth

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ABSTRACT

Cutaneous melanoma, which develops from the pigment producing cells called melanocytes, is the most deadly form of skin cancer. Unlike the majority of other cancers, the incidence rates of melanoma are still on the rise and the treatment options currently available are being hindered by resistance, limited response rates and adverse toxicity. We have previously shown that an FDA approved drug leflunomide, used for rheumatoid arthritis (RA), also holds potential therapeutic value in treating melanoma especially if used in combination with the mutant BRAF inhibitor, vemurafenib. We have further characterized the function of leflunomide and show that the drug reduces the number of viable cells in both wild-type and *BRAF*^{V600E} mutant melanoma cell lines. Further experiments have revealed leflunomide reduces cell proliferation and causes cells to arrest in G1 of the cell cycle. Cell death assays show leflunomide causes apoptosis at treatment concentrations of 25 and 50 μM. To determine if leflunomide could be used combinatorialy with other anti-melanoma drugs, it was tested in combination with the MEK inhibitor, selumetinib. This combination showed a synergistic effect in the cell lines tested. This drug combination led to an enhanced decrease in tumour size when tested *in vivo* compared to either drug alone, demonstrating its potential as a novel combinatorial therapy for melanoma.

INTRODUCTION

Melanoma is the most deadly form of skin cancer, causing the majority of skin cancer deaths despite only accounting for 5% of reported skin cancer cases (Skin Cancer Foundation, 2017; [1]) and unlike most other cancers, incidence rates are still on the rise. The cause of melanoma is a combination of exogenous (environmental) and endogenous (genetic) factors [2]. If detected early cutaneous melanomas are easily curable through resection, as unlike many other cancers, they are externally visible and it is only once they have metastasized in later stages that the disease becomes difficult to treat (Skin Cancer Foundation, 2017). Until recently treatment for metastatic melanoma was limited. However, in recent years, a number of new therapies have been developed that provide a better prognosis for patients. These include immunotherapies, in particular immune checkpoint inhibitors such as ipilimumab, pembrolizumab and nivolumab that show remarkable clinical responses in some melanoma patients [3–5]. These therapies however are not without their drawbacks, including immune-related