

# Dramatic improvement shown for patients with melanoma skin cancer through a new targeted treatment

## Introduction

One adverse outcome of our increasing love affair with recreational sun-exposure is an increasing incidence of a particular type of skin cancer (melanoma), particularly among fair-skinned populations and sun-bed users. Unfortunately, when the melanoma spreads this leads to a poor prognosis. The response rate with current licensed therapies is poor, with no more than one in five patients responding and little impact on overall survival.

However, there is considerable cause for optimism for treatment of patients who have a specific change (V600E BRAF) in the DNA of the melanoma cells. A majority of these patients showed a response in a recent trial of a new targeted agent PLX4032 (<http://www.nejm.org/doi/full/10.1056/NEJMoa1002011>).

## What the latest results mean for patients

Because PLX4032 is not yet licensed for general prescription, the only way to obtain this drug today is through participation in a formal trial of the drug. Such clinical trials are an essential step to the validation of any new drug to ensure that the balance between harm and benefit is acceptable. The dramatic success observed in this early trial, despite concerns that resistance to treatment might occur, makes it likely that the drug regulators will assess it under their accelerated schemes. If the drug performs to expectation, the drug could then be licensed rapidly, particularly for patients who do not respond to existing treatments.

## The importance of mutations in the BRAF gene in melanoma

One of the major pathways for regulating growth, survival and differentiation of cells is the MAPK pathway (see Fig. 1).

One of the enzymes in this pathway is B-RAF (or BRAF) a serine-threonine protein kinase which is encoded by the gene BRAF. BRAF mutations were reported to be present in the majority of cutaneous melanoma in 2002 and so BRAF took centre-stage in translating research findings into treatment.

## Treatment was based on understanding the effects of the mutation

About 90% of mutations found in BRAF in patients with melanoma reported to date are due to one particular tumour-causing mutation. This change in one copy of the gene leads to its being activated constantly, and not responsive to the usual control before that stage in the MAPK pathway.

In technical terms, the mutated gene causes one amino acid in the enzyme protein it produces to be changed for another – the substitution of valine with glutamic acid (V600E) due to a single letter of the DNA sequence of the gene being changed (1799T>A).

Molecular modelling experiments, which took into account the shape of the enzyme, led to the design of a compound (PLX4032) which is a highly specific inhibitor of the mutated enzyme. PLX4032 was evaluated in the latest trial.

Stimulation of the many receptors which activate the MAPK pathway leads firstly to activation of RAS and then phosphorylation of the Raf kinases (which include ARAF and CRAF as well as BRAF) followed by the cascade activation of two other downstream kinases MEK and ERK. ERK then phosphorylates transcription factor proteins either in the cytoplasm or after translocation into the nucleus, to regulate genes involved in cell proliferation, differentiation and survival.

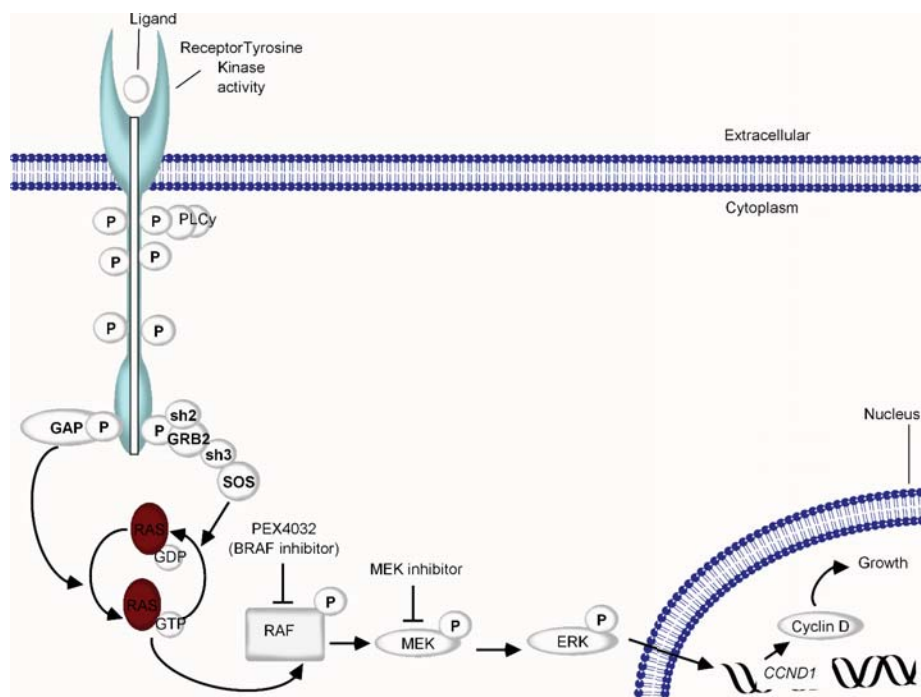


Fig.1 The MAPK pathway showing the site of action for PLX4032

## Clinical implications

The results of a recent trial of PLX4032 are clinically exciting. Of 32 patients, 26 had a response, a dramatic improvement relative to existing therapies, although only two had a complete response. There are concerns that resistance to agents specifically targeted against the enzyme occurs, but through understanding the molecular pathways and developing new agents, the prospect of better treatment, or treatment combinations, for melanoma is improving. With time it is likely that melanoma too will be as successfully treated as chronic myelogenous leukaemia, the current flag-bearer for stratified medicine.

## More detailed information about the trial

The trial was a complicated Phase I study <sup>(1)</sup>, aimed to obtain maximum information, including dose-response and drug-formulation effects, on relatively few patients (55 in the first part). Therefore it recruited subjects with and without the V600E BRAF mutation and in fact included 6 subjects with solid tumours other than melanoma.

However, the study was augmented by an extension phase, more akin to a Phase II study. In this extension phase, 32 patients with melanoma, all with the V600E mutation were given 960 mg twice daily; 26 had a response. The median survival without the melanoma progressing was estimated to be more than 7 months and the estimated median overall survival had not been reached by the time of the study report.

The study also highlights the problems ahead. In addition to non-responders (subjects showing intrinsic resistance despite presence of the V600E mutation in the melanoma), acquired resistance developed even within the short time-scale of the study with duration of response as low as 2 months in some patients. The underlying mechanisms of resistance are still unclear but the tumour switching between genetic pathways and mutation of tumour suppressor genes may well contribute. Secondary resistance is a feature with all targeted agents in clinical use so far.

## Further Reading

(1) Flaherty KT, Puzanov I, Kim KB, Ribas A, McArthur GA, Sosman JA, et al. Inhibition of Mutated, Activated BRAF in Metastatic Melanoma. *N Engl J Med* 2010;363(9):809-819.