Vemurafenib in metastatic melanoma: Phase II trials in action

Background

The prognosis for melanoma (a type of skin cancer) that spreads throughout the body (metastasizes) is very poor. Only about 10% of patients treated with the standard treatment, dacarbazine, will have a response (shrinkage of their tumours), and the median survival is only 6-8 months.

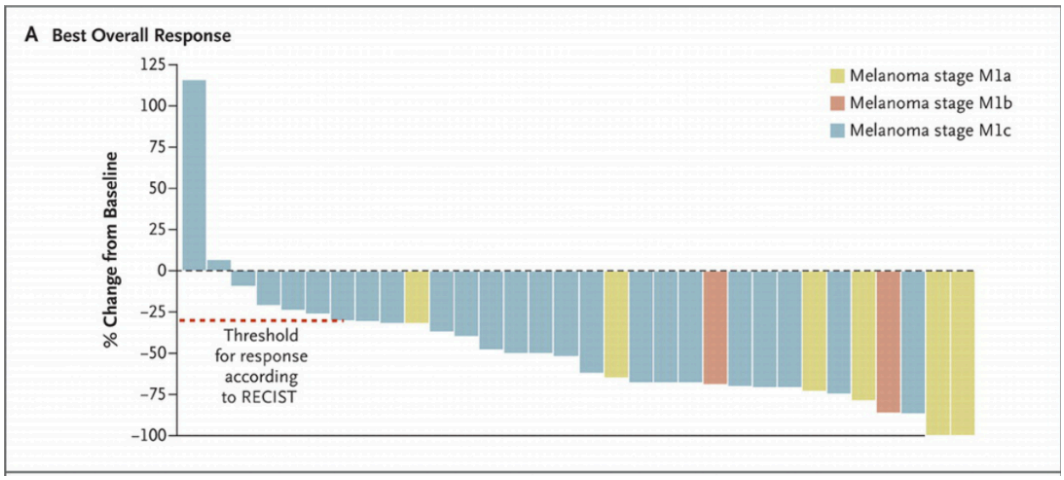
In the last several years, investigators discovered that about 60% of patients with metastatic melanoma have a specific genetic mutation – a B-RAF mutation that activates the cancer cells. If we could develop a drug that 'targets' this specific mutation and 'switch off' the activated growth pathway, then in theory we could stop the cancer cells from growing, at least for a period of time.

Vemurafenib

Vemurafenib is such a drug – a 'targeted therapy' - that was designed to block the effects of B-RAF mutations on tumor growth. In Week 2, you learned about a phase 1 study of vemurafenib that helped to define the dose of the drug to be used in clinical studies (1).

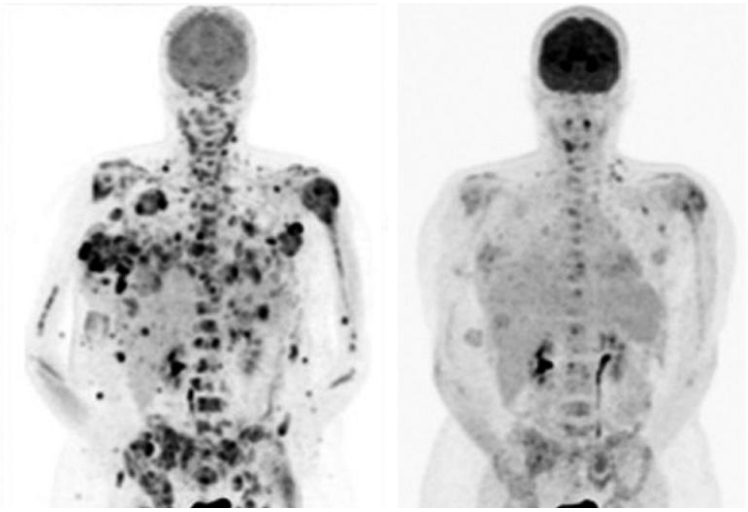
An uncontrolled phase 2 trial was performed to evaluate vemurafenib's effect on 32 patients with B-RAF mutant metastatic melanoma. (This was referred to as the 'extension cohort' in the published paper.) The patients received vemurafenib at the recommended phase 2 dose of 960 mg twice a day. Response to the drug was defined as a complete (if there was a 100% shrinkage of the tumor) or partial (at least 30% shrinkage) response. The investigators decided that an observed response rate of 40% or more would be an indication of success and justify further study.

Of the 32 patients who were studied, 26 achieved a partial or complete response; two of these were complete responses. To the right is a waterfall plot showing the 32 individual changes in tumor size.



Reference: http://www.nejm.org/doi/full/10.1056/NEJMoa1002011#t=articleBackground

Two positive emission tomography (PET) scans are shown from a single patient. Other than the brain or bladder, each black spot represents a tumor cluster. The scan on the left shows the patient before treatment with vemurafenib. The scan on the right is the same patient two weeks after treatment with vemurafenib.



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Questions and themes for discussion

a) Are you persuaded that vemurafenib would be a better drug than dacarbazine? Is response rate an adequate measure of success? What other information would help you make this determination?

b) There was controversy at the time about whether, and how, a phase 3 trial should be conducted given the extremely promising phase 2 results. Discuss the pros and cons of moving on to a phase 3 study. Discuss whether you think that clinical equipoise can be maintained.