

Phase I Results of PLX4032 a BRAF-inhibitor in melanoma patients

Results of a phase I clinical trial of PLX4032, a highly selective BRAF-inhibitor, in cancer patients have been presented at the American Society of Clinical Oncology meeting in Orlando on the 1st of June. This agent is being developed by Plexxikon, a California-based biotechnology company, in partnership with Roche Pharmaceuticals.

This treatment is in the very early stages of development and although early results are promising more trials are needed to confirm results to see if the treatment should be used routinely for patients with advanced melanoma. There is no evidence that this treatment can cure people with advanced melanoma. There is also no role for this treatment at this point in melanoma that has been fully removed by surgery. Surgery remains the treatment of choice of early melanoma and can cure the majority of patients.

Detailed Summary of the trial:

In the first part of the trial that aimed to find the safe dose, 55 cancer patients have been treated, including 24 mutation-positive melanoma patients (23 with the most common V600E BRAF mutation(see below)) and 3 mutation-positive thyroid patients, as well as 28 melanoma, rectal and ovarian cancer patients who did not have the mutation or whose mutation status was not known.

In 16 *BRAF* mutation-positive melanoma patients treated with PLX4032 doses at or above 240 mg twice daily data show:

- PLX4032 is well tolerated at very high doses, with 960 mg twice a day under evaluation as the maximum tolerated dose
- Partial responses in 9 patients showing greater than 30% tumor regression
- Regression of melanoma lesions in sites to which melanoma commonly spreads, including liver, lung and bone
- Minor responses in 4 patients showing tumor regression greater than 10% but less than 30%
- Disease control lasting up to 14 months with continuous therapy, with some patients still receiving treatment
- Preliminary median progression-free survival of at least six months, with many responding patients still receiving treatment

By contrast, no treatment response was observed in a small group of patients without the V600E mutation.

Most significant side effects, primarily rash, fatigue and joint pains, were seen at 1120 mg twice a day. Drug-related side effects have been predominantly mild in severity and transient, including rash and photosensitivity (increased sensitivity to the sun) Serious adverse events (possible side effects that are medically important) were observed in some patients after chronic treatment, including possibly drug-related cutaneous squamous cell carcinoma. A risk management plan has been implemented for baseline evaluation of the skin and monitoring of all patients by dermatologists while on study.

Oncologists find these results very encouraging but further clinical trials are essential and required by regulatory authorities.

Future Studies in Australia:

At this point in time it is planned to open Australian sites for a phase 2 study for patients with V600E positive melanoma and advanced disease (melanoma that has spread and cannot be removed by surgery) in the second half of 2009. A larger global multicentred randomised study is also likely to open in Australia later in 2009/early 2010. Australian oncologists are working with Roche and Plexxikon to open these trials as fast as possible. Update on the status of the trials can be found on the Roche Clinical Trials Registry (<http://www.roche-trials.com/>), Plexxikon's website (www.plexxikon.com) as well as www.clinicaltrials.gov

About BRAF

What is BRAF and why is it important in cancer?

The *BRAF*^{V600E} gene mutation has been associated with malignant tumors and is a common cancer-causing gene. It is found in approximately 50% of malignant melanomas. It has been reported in 8% of all solid tumors, including approximately 10% of colorectal cancers and 35% of thyroid cancers. However activity of the drug is unknown for any cancer other than melanoma.

Are there any other cancers besides melanoma, colorectal and thyroid cancer that may have the *BRAF*^{V600E} gene mutation?

Scientific literature indicates that 8% of all solid tumors carry the *BRAF*^{V600E} mutation. In addition to melanoma, colorectal, and thyroid cancers, this also includes a smaller percentage of serous low-grade ovarian cancer and smaller numbers of breast cancer, prostate cancer, etc.

What is PLX4032 (R7204)?

PLX4032 (R7204) is a selective drug that targets tumor cells that have the *BRAF*^{V600E} mutation. Because PLX4032 (R7204) is highly selective for the mutated *BRAF*^{kinase}, it should work specifically on cancer cells carrying this mutation, leaving healthy cells relatively untouched in contrast to many other anti-cancer agents.

Current Clinical Trials

What is the status of the clinical trials with PLX4032 (R7204)?

Roche, Plexxikon and the Peter MacCallum Cancer Centre are collaborating to develop PLX4032 (R7204) for treatment of cancers that are positive for the *BRAF*^{V600E} mutation. The clinical trial is currently in Phase 1, the earliest phase for evaluating the safety and efficacy of PLX4032 (R7204). The clinical trial has reached its enrolment, meaning there are no further patients able to be treated on this trial. Drug development regulations prevent over-enrolment on clinical trials.

Future Clinical Trials

What additional clinical trials with PLX4032 (R7204) are planned?

Larger trials are planned to be initiated in metastatic melanoma patients in the second half of 2009. Another trial in previously untreated mutation-positive melanoma patients is also planned for later in 2009.

Where will future trials with PLX4032 (R7204) be conducted?

Currently, trials are ongoing in the US and Australia. Future trials at additional sites in the US, Australia and other countries as multi-center, global clinical trials.

How many patients will be enrolled in the planned trials with PLX4032 (R7204)?

The protocols will be discussed with US and European regulatory authorities and, once final, information will be posted on the Roche Clinical Trials Registry (<http://www.roche-trials.com/>), Plexxikon's website (www.plexxikon.com) as well as www.clinicaltrials.gov.

How can I find out if I carry the *BRAF* mutation?

There is a test available to determine if a patient carries the *BRAF* mutation. Those patients who participate in the clinical trials for PLX4032 (R7204) will be screened for the *BRAF* mutation prior to enrollment.

Would you expect PLX4032 (R7204) to be efficacious in mutation-negative patients?

Our current hypothesis is that PLX4032 (R7204) would most likely be efficacious only in patients whose tumors have the *BRAF* mutation. Formal evaluation of PLX4032 mutation negative patients is likely to occur in the future.

Are you planning to study PLX4032 in combination with other cancer drugs?

Preclinical studies suggest that the activity of PLX4032 may be additive with other drugs used in the treatment of melanoma or colorectal cancer, and therefore, potential combinations may be evaluated clinically at a later time. The emphasis for now is on monotherapy based on the Phase 1 data to date in *BRAF* mutation-positive patients.

Since you are not seeing complete regressions yet, shouldn't you be testing combinations now?

The emphasis for now is on monotherapy based on the Phase 1 data in *BRAF* mutation-positive patients.

Will Roche develop PLX4032 in colorectal cancer? If so, when?

A Phase 1 extension cohort in mutation-positive colorectal cancer patients is currently ongoing.

Will Roche develop PLX4032 in thyroid cancer? If so, when?

Further development of PLX4032 for the treatment of thyroid cancer is under consideration.

Who manufactures PLX4032 (R7204)?

Roche is manufacturing all supplies of PLX4032 .

If the clinical trials go well, when would you anticipate launching PLX4032 into the marketplace allowing routine access for patients?

Roche and Plexxikon are in the early stages of development and cannot speculate on a potential approval or launch date.

Where can I learn more about the proposed trials? How can I enroll?

New clinical trials with PLX4032 will be posted on the Roche Clinical Trials Registry (<http://www.roche-trials.com/>), Plexxikon's web site (www.plexxikon.com) as well as www.clinicaltrials.gov. These are USA websites but will include information on ex-USA sites.

When do you expect the sites for the next trials to be posted?

Roche and Plexxikon are currently evaluating potential institutions for the upcoming trials. They will post these sites as soon as they become available.

Side Effects

What side effects of PLX4032 treatment have been observed?

PLX4032 (R7204) has been generally well tolerated to date at doses up to 960 mg twice daily. Drug-related adverse events, including rash and photosensitivity, have been mild in grade and transient. Serious adverse events, including diagnosis of cutaneous squamous cell carcinoma and basal cell carcinoma, have been reported in the Phase 1 study and are considered by the investigators to be possibly related to PLX4032. The benefit-risk assessment with regards to the cutaneous squamous cell carcinoma and basal cell carcinoma is considered by clinical investigators to be favourable for this patient population with appropriate dermatologic monitoring and treatment due to the high unmet medical need. A risk management plan has been implemented for baseline evaluation of the skin and monitoring of all patients while on study to evaluate the possible connection to therapy of these highly curable skin lesions.

What was the incidence of cutaneous squamous cell carcinoma (SCC) in patients treated with PLX4032 (R7204)? Do you have additional information on SCC?

To date, cutaneous squamous cell carcinoma and basal cell carcinoma have been reported in the Phase 1 study and are considered by study investigators to be possibly related to study drug. A risk management plan has been implemented for all ongoing and planned trials.

Expanded Access/ Drug Supply

Will patients who cannot enroll in the trials be able to obtain drug (e.g., compassionate use)?

No, there is no expanded access (compassionate use). Since Roche and Plexxikon are in the early stages of development and still assessing safety and efficacy of PLX4032, they are only providing drug to patients enrolled in the clinical trials.

Further Questions

How do I know if PLX4032 can help me? You should discuss this with your doctor or oncologist.

It is best that any questions related to your individual case be discussed with your doctor. *We are not able to provide advice on individual cases*

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