

Basel, 23 September 2009

Roche announces results from two early studies which show promise for patients with malignant melanoma

New data from phase II Avastin study and a phase I extension study of highly selective BRAF inhibitor

- Results from the phase II BEAM study investigating use of Avastin plus chemotherapy in patients with malignant melanoma demonstrate that Avastin may have the potential to improve progression-free survival (PFS) and overall survival (OS) in this deadly disease.
- The primary endpoint of progression free survival showed a 22% risk reduction for progression in Avastin treated patients in this Phase II study. Overall survival, a secondary endpoint, showed an improvement in median overall survival of three months, a 21% risk reduction of death. These data are encouraging and warrant further investigation.
- In a phase I extension study of previously treated melanoma patients who harbour the BRAF mutation, 70% experienced shrinkage of their tumours when treated with PLX4032, a BRAF selective inhibitor.
- Results from both studies were presented today at the joint ECCO 15¹ and ESMO 34² congress.
- Malignant melanoma is a highly aggressive cancer that is incurable and can be rapidly fatal once it spreads. There are currently few treatment options so these developments are encouraging.

“The results from the BEAM study are very encouraging and warrant continued investigation,” said Dr Steven O’Day, Chief of Research and Director of the Melanoma program at The Angeles Clinic and Research Institute, California, USA. “Malignant melanoma currently has so few treatment options with less than 5% of patients living beyond 5 years so I am very pleased that we are seeing evidence that an improvement in outcomes may soon be possible for this devastating disease.”

In the phase II BEAM study with Avastin, which included 214 patients with previously untreated advanced malignant melanoma, patients received Avastin in combination with chemotherapy (carboplatin and paclitaxel) or chemotherapy alone. The study had a primary endpoint of progression-free survival (PFS), and secondary endpoint of overall survival (OS), response rate and safety. The BEAM study demonstrated:

- A trending benefit in PFS in patients that received Avastin (median 5.6 months vs. 4.2 months) with a hazard ratio (HR) of 0.78, p=0.14 [95% confidence interval (CI) and range 0.56-1.09].

- Encouraging results were also seen in overall survival, with a median survival of 12.3 months in the Avastin arm and 9.2 months in the control arm, with a hazard ratio of 0.79 (95% CI, 0.55, 1.13); $p = 0.19$.
- The combination of Avastin and chemotherapy was well tolerated in advanced malignant melanoma patients and no new safety events were observed.

Separately, data from a phase I extension study of PLX4032 confirmed earlier findings that this highly selective treatment led to both significant tumour shrinkage and delay in tumour progression in patients whose tumours harbour a cancer-causing mutation of the BRAF gene. More than fifty percent of melanomas and about eight percent of all solid tumours carry this mutation. PLX4032 is being co-developed by Roche and its partner, Plexxikon. A companion diagnostic also is being co-developed along side of PLX4032 to determine the BRAF mutation status of patients.

In the extension study which included 31 patients with advanced metastatic melanoma, patients with the *BRAF*^{V600E} mutation, most of whom had the worst stage of metastatic disease (M1c), were treated with PLX4032 at 960 mg twice daily. Among the 27 evaluable patients to date, results confirmed the preliminary safety and efficacy seen in the previous phase I dose escalation study:

- PLX4032 was well tolerated at 960 mg twice daily, now confirmed as the maximum tolerated dose.
- Complete response in 1 patient treated for 3 cycles.
- Partial responses of greater than 30% tumour regression* criteria were observed in 18 patients, with 15 patients showing responses of greater than 50%.
- Minor responses in 6 patients showed tumour regression between 10% and 30%.

PFS has not yet been reported for the extension study since it is too early. However, the earlier reported interim median PFS for the phase I dose escalation study has now increased to seven months as patients continue on treatment. Drug-related adverse events were predominantly mild in severity.

“There is a real need to identify treatments for this terrible disease and we are committed to bringing forward new drugs that will make a genuine difference” said William M. Burns, CEO of Roche’s Pharmaceuticals Division. “We are greatly encouraged by the BEAM data and the additional results for PLX4032, which if proven through later stage studies, will be available with a companion diagnostic test being developed to test for the BRAF gene mutation”.

Malignant melanoma is the most serious type of skin cancer, with about 160,000 new cases diagnosed

worldwide each year. Melanoma is treatable if caught early but patients who develop metastatic disease are rarely cured with available treatments. Historically, median progression-free survival for a patient with metastatic melanoma is less than 60 days, and the median overall survival for these patients is less than 12 months.

About the BEAM (AVF4096g) study

BEAM is a phase II randomised, placebo-controlled study designed to estimate the clinical benefit and characterise the safety of Avastin when added to carboplatin and paclitaxel chemotherapy in patients with previously untreated advanced malignant melanoma. Avastin was administered at a dose of 15mg/kg every 3 weeks. Patients were randomised 2:1 into the following arms:

- Carboplatin + paclitaxel + Avastin
- Carboplatin + paclitaxel

BEAM included 214 patients at disease stage M1a/b and M1c (73% of patients had M1c disease – the most advanced stage of malignant melanoma).

About the PLX4032 (RG7204) phase I extension study

To date, 31 patients who tested positive for the *BRAF*^{V600E} mutation have been enrolled in the open-label, single-arm extension cohort. All patients have been treated with PLX4032 at 960mg twice daily (BID), with anti-tumour effects measured by RECIST* every eight weeks.

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* Response Evaluation Criteria in Solid Tumours
1 European CanCer Organisation
2 European Society for Medical Oncology