Berlin, Germany: Researchers have made significant advances in the treatment of metastatic malignant melanoma - one of the most difficult cancers to treat successfully once it has started to spread - according to a study to be presented at Europe's largest cancer congress, ECCO 15 - ESMO 34, in Berlin on Thursday.

In the phase I extension study, researchers have seen rapid and dramatic shrinking of metastatic tumours in patients treated with a new compound that blocks the activity of the cancer-causing mutation of the BRAF gene, which is implicated in about 50% melanomas and 5% of colorectal cancers. In new results from 31 melanoma patients with the BRAF mutation who were treated with 960mg of PLX4032 twice a day, 64% (14) of the 22 patients who could be evaluated so far met the official criteria for partial response (this involves the diameter of tumours shrinking by at least 30% for at least a month). A further six of the 22 patients also showed a response, but, at the time of the congress presentation, it was too early to say whether the tumours would shrink far enough to meet these criteria.

Dr Paul Chapman, an attending physician on the Melanoma/Sarcoma service at Memorial Sloan-Kettering Cancer Center (New York, USA) and who was one of the leaders of the trial, told a news briefing: "We are very excited about these results. Of the 22 patients we have been able to evaluate so far, 20 have had some objective tumour shrinkage. This is impressive as they all had metastatic disease and most of them had failed several prior therapies. A lot of these patients were pretty sick but many
of them had a significant and rapid improvement in the way they function. We've had patients come off oxygen and we've got several patients who have been able to come off narcotic pain medication soon after starting treatment."

The trial is investigating PLX4032 in patients with the BRAF mutation, and results from the first 55 patients were reported at a cancer meeting earlier this year (ASCO 2009). These data had been aimed at finding the best dose of PLX4032 to give to patients. However, the phase I extension data reported at ECCO 15 - ESMO 34 focuses on a subsequent group of an additional 31 patients who were all treated at the maximum tolerated dose of the drug (a 960 mg pill twice a day). All the patients had the BRAF mutation.

Dr Chapman said: "What makes this treatment different from standard chemotherapy is that standard chemotherapy attacks the machinery involved in cell division; so to stop the cancer cells dividing uncontrollably, most standard chemotherapy aims to block the mechanism of division by interfering directly with DNA replication or with microtubules in the dividing cells. PLX4302 is different because it attacks the genetic programme that is causing the cells to divide uncontrollably, and we think the BRAF mutation is driving that programme. The drug is blocking the genetics of the tumour, rather than trying to interfere with the proliferation of the cells and, as a result, there are fewer side effects, although there are some. We are seeing some pretty dramatic and rapid responses, and they are occurring in sites where we rarely see responses to chemotherapy, such as in the bone.

"There are some important caveats. All these patients had failed previous therapies, either chemotherapy or treatment with Interleukin 2, as well as surgery. However, we know that only 10-30% of patients will respond to standard chemotherapy, so it's not surprising that our patients had not responded, or have responded and then the cancer has recurred. In our
study 64% of patients have had a partial response, but because we are only treating patients with the BRAF mutation, we are cutting out about 40% of melanoma patients who do not have this mutation and whom we know will not respond to this treatment. That is one reason why we are seeing a much higher response than with conventional treatments.

"Also, we don't know yet how long these responses will last, and we have had patients whose cancer has progressed after initially responding; so we are putting a lot of effort in to studying the patients who do relapse, trying to understand how their tumours have become resistant.

"In addition, one of the main side effects we've seen is that some patients develop early, non-melanoma skin cancers such as squamous cell skin cancer. We are very vigilant about this and although they are very easy to cut out, it's something we are keeping a close eye on."

Dr Chapman and his colleagues are planning a phase II trial of 90 patients starting at the end of this year. In addition, a large phase III randomised controlled trial involving several hundred patients is planned to start either at the end of this year or beginning of next year involving centres in North America, Europe and Australia.

Dr Chapman said it was too early to be talking about a cure for advanced melanoma, but that this drug had potential. "Most of us think that a drug like this would ultimately be part of the regimen, but that we might need additional drugs with it to complete the cure. Right now we are seeing dramatic responses but it's too early to say whether we've actually cured people because most patients still have evidence of some level of tumour on their skin. I think this is a huge step forward; whether or not it will be sufficient by itself really remains to be seen."

Source: ECCO-the European CanCer Organisation