



NEWS RELEASE

20th EORTC-NCI-AACR SYMPOSIUM on “Molecular Targets and Cancer Therapeutics” Geneva, Switzerland, 20-24 October 2008

Embargoed: 12.15 hrs CEST, Thursday 23 October 2008

NB: this will be the subject of a news briefing by Dr Federica Di Nicolantonio at 12.15 hrs CEST on Thursday 23 October in the press conference room (Room F in Hall 2)

Study finds BRAF mutations in colorectal cancer cause resistance to anti-EGFR therapy

Geneva, Switzerland: European researchers have found that metastatic colorectal cancer patients with a mutation in the BRAF gene do not respond to anti-EGFR therapy with cetuximab and panitumumab. The finding could help doctors better identify which patients are likely to benefit from such treatment, which is commonly used as last-effort therapy but only works in a fraction of patients. The research was presented at the 20th EORTC-NCI-AACR [1] Symposium on Molecular Targets and Cancer Therapeutics in Geneva today (Thursday 23 October).

Colorectal cancer is one of the most common cancers worldwide and a leading cause of cancer death. Once the disease has spread, the five-year survival rate is less than 10%. The targeted drugs cetuximab (Erbix) and panitumumab (Vectibix) - monoclonal antibodies that inhibit EGFR - are used to treat patients with chemotherapy-resistant metastatic colorectal cancer. However, they are effective in only 10-20% of such patients. Mutations in the KRAS gene explain about 30-40% of the non-responsive cases, but the reason for the rest of the failures is unknown.

The results of a study presented by Dr Federica Di Nicolantonio of the Institute for Cancer Research and Treatment at the University of Turin School of Medicine in Italy suggest that BRAF mutations may account for another 12% of resistant cases.

In the study, Dr Di Nicolantonio and colleagues conducted a genetic analysis of 113 tumours taken from patients with advanced colorectal cancer who had been treated with cetuximab or panitumumab at Ospedale Niguarda Ca' Granda (Milan, Italy) or at the Oncology Institute of Southern Switzerland (Bellinzona, Switzerland). They found that KRAS mutations were present in 30% of the patients, and that this mutation was associated with resistance to the drugs. A BRAF V600E mutation was detected in 11 of the remaining 79 patients who did not have KRAS mutations, representing 10% of the total number of patients. Mutations in the two genes are mutually exclusive.

“None of the patients with tumours containing BRAF mutations had responded to the treatment, and in cases where the treatment did work, none of those patients had BRAF mutations. This shows that for anti-EGFR therapy to work, the BRAF gene must be the wild type and suggests that BRAF status could be a useful biomarker for selecting patients suitable for anti-EGFR treatment,” Dr Di Nicolantonio said, adding that progression-free survival and overall survival was significantly shorter in patients who had the BRAF mutation than in patients without the mutation.

The researchers also tested the influence of BRAF mutation on the success of anti-EGFR treatment prospectively by conducting a laboratory study that involved adding the drugs to colorectal cells altered to contain the mutated version of the BRAF gene. They found that introducing the mutated gene dramatically impaired the ability of cetuximab and panitumumab to work. They then added the BRAF inhibitor sorafenib. That restored the sensitivity of the cells to the anti-EGFR treatment, with the combination of the cetuximab and sorafenib resulting in massive cell death in the cells carrying the mutated BRAF gene.

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“These findings suggest that combination therapy that simultaneously blocks EGFR and BRAF in patients with BRAF-mutated tumours may be a useful approach to increase the number of patients who could benefit from anti-EGFR therapy, but that remains to be assessed in a clinical trial,” Dr Di Nicolantonio said.

“This research does not complete the picture of resistance to EGFR inhibitors. In spite of the predictive value of both KRAS and BRAF mutations, in our cohort 52 per cent of non-responsive patients did not have mutations in either gene. This means further molecular markers are needed to better define patients who are unlikely to benefit from EGFR-targeted treatment,” she added.

(ends)

Abstract no: 247, oral presentation in plenary session 6, Room ABC, 14.30-16.00 hrs Thursday 23 October.

Notes:

[1] EORTC [European Organisation for Research and Treatment of Cancer, NCI [National Cancer Institute], AACR [American Association for Cancer Research].

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From 09.00 hrs CEST Tuesday 21 October to 14.30 hrs CEST Friday 24 October

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