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Cetuximab fails to make the grade in patients with operable colorectal metastases

In probably the most shattering news from the meeting, data from the phase III EPOC study showed that not only did the addition of cetuximab fail to improve survival in k-RAS wild-type patients with operable metastases from colorectal cancer, it made matters so much worse that the trial had to be halted prematurely.

Professor John Primrose from Southampton General Hospital and colleagues from around the UK described the 9.2-month difference in terms of progression-free survival between cetuximab and chemotherapy and chemotherapy alone as 'surprising and totally unexpected'.

In 2008, EPOC data demonstrated a 7·3% improvement in 3-year progression-free survival, favouring surgery plus chemotherapy over surgery alone. An extension was designed to evaluate the benefit of cetuximab in addition to standard chemotherapy in patients with operable liver metastases.

A total of 272 k-RAS wild-type patients were randomized to receive a combination of fluoropyrimidine and oxaliplatin, plus or minus cetuximab for 12 weeks before then 12 weeks after surgery. Patients who had been treated with adjuvant oxaliplatin could receive irinotecan and 5-fluorouracil.

Following an independent data monitoring committee recommendation, the study was stopped when it met a predefined futility analysis. With only 45.3% (96 of 212) of the expected events observed, progression-free survival was significantly worse with cetuximab (14.8 months *vs* 24.2 months, hazard ratio 1.50037, $P<0.048$), and the result of a pre-planned analysis excluding the 23 patients treated with irinotecan-based chemotherapy was similar.

'The EPOC data represent a 50% worsening of progression-free survival with cetuximab. We are not sure quite how this happened,' said Professor Primrose, 'but we hope to find the answers within the next few months.'

Stephen Pinn

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First-line cetuximab gives longer survival than bevacizumab in metastatic colorectal cancer

Patients with metastatic colorectal cancer treated first-line with the EGFR inhibitor cetuximab (Erbitux) plus FOLFIRI show significantly longer overall survival (around 4 months) than those treated with bevacizumab (Avastin), which targets VEGF, plus FOLFIRI, according to results from a randomized phase III trial.

The investigator-led German FIRE-3 study randomized 592 patients with wild-type k-RAS metastatic colorectal cancer to first-line therapy with cetuximab plus FOLFIRI (folinic acid, fluorouracil, irinotecan) or to bevacizumab plus FOLFIRI.

Professor Volker Heinemann, Professor of Oncology, University of Munich, Germany

Results from FIRE-3 showed a higher overall response rate with cetuximab, reaching statistical significance in the 526 patients who underwent at least one imaging procedure after baseline. The median time to disease progression was similar with the two drug regimens (10.0 months with cetuximab *vs* 10.3 months with bevacizumab, $P=0.547$), but the overall survival was significantly longer in patients treated with cetuximab (28.7 months) than to those given bevacizumab (25.0 months, $P=0.017$). Sixty-day mortality was low in both arms (1.01% *vs* 2.71%).

Lead author, Volker Heinemann, Professor of Oncology at the University of Munich, Germany, concluded: 'We believe a substantial gain in survival can be achieved when doctors offer first-line treatment with FOLFIRI plus cetuximab.'

Susan Mayor

Bevacizumab extends survival in advanced cervical cancer

Adding bevacizumab to chemotherapy increased overall survival by an average of 4 months over chemotherapy alone in women with recurrent or metastatic cervical cancer, showed the first phase III study to show a benefit with targeted therapy in this type of cancer.

The study randomly assigned 452 women with recurrent or metastatic cervical cancer to treatment with chemotherapy alone or to chemotherapy plus bevacizumab (not currently approved in any gynaecological cancer). It tested two different regimens: cisplatin plus paclitaxel and topotecan plus paclitaxel to see whether topotecan was more beneficial than cisplatin.

There was no significant difference between the two regimens, but the median survival for patients treated with bevacizumab plus chemotherapy was longer (17.0 months) than those treated with chemotherapy alone (13.3 months, $P=0.035$). The percentage of patients responding to therapy increased from 36% to 48% with the combination ($P=0.0078$).

Tumour shrinkage rates were higher with the combination of bevacizumab and chemotherapy (48% *vs* 36%) and responses to treatment lasted longer.

Susan Mayor