NEWSROUND

Selected reports edited by Janet Fricker

Everolimus plus octreotide improves progression-free survival in advanced NET

→ The Lancet

The addition of everolimus to octreotide improved progression-free survival in patients with advanced neuroendocrine tumours (NETs) associated with carcinoid syndrome, the phase III RADIANT-2 study has concluded.

Advanced NET remains a clinical challenge due to the lack of effective treatment options. Generally, chemotherapeutic drugs are not active in advanced non-pancreatic NET patients, and they have furthermore been associated with substantial toxic effects. Currently there are no treatments for NET tumours outside the pancreas that are approved by the US regulator the FDA.

Everolimus, an oral inhibitor of the mammalian target of rapamycin (mTOR), has recently shown antitumour activity in patients with advanced pancreatic NETs. The role of everolimus in NETs of other primary sites or in combination with other drugs, however, has not been explored. In the current study, James Yao, from MD Anderson Cancer Center, Houston, Texas, and colleagues, set out to assess the combination of everolimus plus octreotide long-acting repeatable (LAR) in patients with low-grade or intermediate-grade NETs. The long-acting formulation of octreotide, a somatostatin analogue known to improve hormone-related symptoms associated with NETs, has been shown to prolong time to disease progression in patients with certain types of NETs.

Between January 2007 and April 2010, 429 patients with unresectable locally advanced or distant metastatic NETs were randomised in a 1:1 ratio to receive either everolimus plus octreotide (n=216) or placebo plus octreotide (n=213). Patients were recruited from Australia, Belgium, Canada, Czech Republic, Finland, France, Germany, Greece, Israel, Italy, Netherlands, Slovakia, Spain, Sweden, Turkey and the USA.

Results show that the median progression-free survival was 16.4 months in the everolimus plus octreotide LAR group (based on 103 events) versus 11.3 months in the placebo plus octreotide group (based on 120 events) (HR 0.77, 95%CI 0.59–1.00; P=0.026).

Adverse effects were higher but manageable in the combination arm, including stomatitis (62% vs 14%), fatigue (31% vs 23%), and diarrhoea (27% vs 16%).

"No approved antitumour drugs are available for treating progressive disease in patients with gastrointestinal or lung neuroendocrine tumours, consequently affecting the survival of patients. Therefore, our findings that show the efficacy of the mTOR inhibitor everolimus plus octreotide LAR in advanced neuroendocrine tumours are important," write the authors. "These data support the efficacy of everolimus for the treatment of patients with a broad spectrum of advanced neuroendocrine tumours," they conclude.

In an accompanying editorial, Guido Rindi, from the Università Cattolica-Policlinico A. Gemelli (Rome, Italy), and Martyn Caplin, from the Royal Free Hospital (London, UK), write that while everolimus is undoubtedly an important advance in the management of carcinoid tumours, the toxic effects are "not insignificant" and the survival benefit is unknown. Questions remain, they add, around whether everolimus should be used alone or in combination, before or after other drugs, and for how long. Additional issues include whether the agent has any role in the adjuvant setting and what effect it has on overall survival and quality of life.

■ M Pavel, J D Hainsworth, E Baudin et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet* 10 December 2011, 378:2005–12

■ G Rindi and M Caplin. mTOR inhibitor therapy for patients with carcinoid. *ibid* pp1978–80

Study supports dual blockade of HER2 growth factor

→ New England Journal of Medicine

The addition of pertuzumab to standard chemotherapy (trastuzumab plus docetaxel) results in an additional six months of progression-free survival in patients with HER2-positive metastatic breast cancer, the CLEOPATRA study has found. The study was presented at the 2011 San Antonio Breast Cancer Conference and simultaneously published online.

Pertuzumab is designed to work in combination with trastuzumab as a dual blockade of the HER2 growth factor, which fuels around one-third of all breast tumours. Both drugs are monoclonal antibodies that bind to the HER2 receptor protein in different locations. Pertuzumab plays an additional role as a 'dimerisation inhibitor' that prevents the HER2 receptor from linking to HER3 and thereby forming a dimer that further signals tumour growth.

In the Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) study, José Baselga and colleagues, from the Harvard Medical School and the Massachusetts General Hospital Cancer Center (Boston, Massachusetts), randomised 808 women with HER2-positive metastatic breast cancer in a 1:1 ratio to receive a placebo plus the standard therapy of trastuzumab plus docetaxel (*n*=406), or pertuzumab plus the standard therapy (*n*=402).

Results showed median progression-free survival was 12.4 months in the control group versus 18.5 months in the pertuzumab group (HR for progression or death = 0.62, 95%CI 0.51–0.75; *P*<0.001).

The interim analysis of overall survival, performed after 165 events (43% of the prespecified total number for the final analysis) showed a strong trend in favour of the combination of pertuzumab plus trastuzumab plus docetaxel. No increased rates of symptomatic or asymptomatic cardiac dysfunction were observed in the pertuzumab group compared with the control group. Diarrhoea, rash, mucosal inflammation, febrile neutropenia, and dry skin, however, were reported more frequently in the pertuzumab group, although most of these effects were grade 1 or 2 and occurred during the period of concomitant docetaxel administration.

"Our findings suggest that targeting HER2-positive tumors with two anti-HER2 monoclonal antibodies that have complementary mechanisms of action results in a more comprehensive blockade of HER2," write the authors.

Enrolment is already underway in a new double-blind, randomised clinical trial (APHINITY), they add, testing use of pertuzumab and trastuzumab as adjuvant therapy in patients with newly diagnosed HER2-positive breast cancer.

In an accompanying commentary, William Gradishar, from the Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, writes, "For patients with metastatic breast cancer who have progressive disease, there may be numerous anti-HER2 agents available that could be used in combination or in sequence. In patients with early-stage breast cancer, more effective anti-HER2 agents as adjuvant therapies may translate into metastatic disease developing in fewer patients."

■ J Baselga, J Cortés, S Kim et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *NEJM* 12 January 2012, 366:109–119

■ WJ Gradishar. HER2 therapy – an abundance of riches. *ibid* pp 176–178

Androgen deprivation alone inadequate for high-risk prostate cancer

→ The Lancet

Combining radiation therapy (RT) with androgen deprivation therapy (ADT) reduced overall mortality and disease-specific mortality in men with locally advanced prostate cancer compared to ADT treatment alone, a joint UK, US and Canadian study has found. The study, which was funded by the American NCI, the Canadian Cancer Society Research Institute, and the UK Medical Research Council, reported an interim analysis, planned for publication when two-thirds of final analysis events had taken place.

Until now the question of whether the addition of radiation therapy improved overall survival in men with locally advanced prostate cancer managed with ADT has been unclear.

Between March 1995 and August 2005, investigators from the Princess Margaret Hospital in Toronto, Ontario, Canada, the MRC Clinical Trials Unit in London, UK, and Cardiff University School of Medicine in Wales, randomly assigned 1205 prostate cancer patients to receive either a combination of ADT and radiotherapy (*n*=603) , or ADT alone (*n*=602). Of all patients in the study, 1057 had locally advanced T3 or T4 prostate cancer, while 119 had a T2 tumour with PSA concentrations >40 ng/ml and 25 had T2 with Gleason scores of 8 or higher.

After a follow-up period of six years, 320 of the patients had died. Of these, 175 were in the ADT-only group and 145 were in the combined ADT and radiotherapy group. Altogether at seven years, 74% of patients in the combined ADT and radiotherapy group were alive compared with only 66% in the ADT group (HR 0.77, 95%CI 0.61–0.98; *P*=0.033).

The addition of radiation therapy slightly increased toxicity and reduced health-related quality of life, the investigators found, but few patients suffered serious side-effects as a result of either treatment strategy.

"Our findings suggest that the benefits of the combination of ADT and RT should be discussed with all patients considering a curative treatment approach," write the authors.

The 65–69 Gy dose of radiation therapy used in the trial, they add, while low by modern standards, represented the standard of care when the trial was initiated in the 1990s. "The improvement in survival with the addition of RT to ADT recorded in this trial could be increased again with modern RT dose fractionation," they write.

In an accompanying commentary, Matthew Cooperberg, from the University of California in San Francisco, writes, "This study has provided the strongest evidence to date that androgen deprivation therapy alone for men with high-risk prostate cancer is not adequate. These

patients require an aggressive, multimodal approach incorporating prostate-directed local therapy. However, the crucial question – whether the optimum initial strategy should include radiation combined with androgen deprivation therapy, or surgery followed by selective radiation on the basis of pathological findings and early biochemical outcomes – is still open." The definitive answer, he adds, will come through trials randomising men with high-risk disease to receive surgery or radiation as an initial treatment.

■ P Warde, M Mason, K Ding et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised phase 3 trial. *Lancet* 17 December 2011, 378:2104–11

■ MR Cooperberg. High-risk prostate cancer: treat the prostate [commentary]. *ibid* pp 2056–57

Uncertainty over denosumab's effects on bone metastasis in prostate cancer

➜ The Lancet

Targeting the bone microenvironment with denosumab delays bone metastasis by 4.2 months in men with non-metastatic castration-resistant prostate cancer, the authors of a phase III study have concluded. The author of the accompanying editorial, however, took issue over this interpretation.

Bone metastases are a major cause of morbidity and mortality in men with prostate cancer. Preclinical studies have suggested that osteoclast inhibition might prevent bone metastases, and that one approach might be via a molecular pathway involving the signalling molecule RANKL. Denosumab is a fully human monoclonal antibody that specifically targets, binds and inactivates RANKL.

In the current study, Matthew Smith, from the Massachusetts General Hospital Cancer Center, Boston, and colleagues, set out to evaluate the effects of denosumab on bone-metastasis-free survival in men with castration-resistant prostate cancer with no evidence of bone metastases at baseline, but a high risk of progression based on raised PSA or short PSA doubling times.

Between February 2006 and July 2008, 1432 men, enrolled at 319 centres in 30 countries, were randomly assigned in a 1:1 ratio to receive subcutaneous denosumab 120 mg (n=716) or subcutaneous placebo (n=716) every four weeks until a study event, defined as bone metastasis or death, occurred. Participants underwent bone scans every four months to detect bone metastases.

Results showed that the time to development of bone metastases was 29.5 months for men receiving denosumab versus 25.2 months for men receiving placebo (HR 0.85; P=0.028). However, overall survival was not found to differ between the two groups (HR 1.01; P=0.91).

Rates of adverse events and serious adverse events were similar in both groups, except for osteonecrosis of the jaw, which developed in 5% of patients taking denosumab versus none taking placebo.

"Our finding that denosumab increases bone-metastasis-free survival provides clinical evidence for the important role of the bone microenvironment and RANKL signalling in development of bone metastases in men with prostate cancer," conclude the authors.

In an accompanying commentary, Christopher Logothetis from the MD Anderson Cancer Center, in Houston, Texas, pointed out that the delay in the time to metastases found with denosumab in the study of 4.2 months, was similar to the delay in time to skeletal-related events reported in earlier studies comparing denosumab and zoledronic acid in men with metastatic castration-resistant prostate cancer. It is possible, he adds, that Smith and colleagues might have included patients with undetected metastases in their study.

"If clinically undetected metastases were present at study entry, the investigators did not study the so-called metastasis prevention properties of denosumab, but rather explored the drug's effect on the biological continuum of metastases," he writes.

While the study supports the use of denosumab as an alternative to zoledronic acid, argues Logothetis, it fails to support its broad use as a preventive agent for bone metastases.

■ MR Smith, F Saad, R Coleman et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet* 7 January 2012, 379:39–46

■ CJ Logothetis. Treatment of prostate cancer metastases: more than semantics. *ibid* pp 4–6

Hodgkin's lymphoma: chemotherapy alone delivers greater long-term survival

➜ New England Journal of Medicine

Standard chemotherapy alone is more effective than radiation in keeping patients with limited-stage nonbulky Hodgkin's lymphoma alive long-term, the latest results of the Hodgkin's Disease 6 (HD6) trial has found.

In 1994, Ralph Meyer and colleagues from the NCIC Clinical Trials Group and Eastern Cooperative Oncology Group initiated the HD6 trial to investigate whether ABVD chemotherapy alone (doxorubicin [Adriamycin], bleomycin [Blenoxane], vinblastine [Velbe], and dacarbazine) in patients with nonbulky stage IA or IIA Hodgkin's lymphoma resulted in similar disease control to that achieved with radiation-based therapy, but with fewer deaths from late treatment effects.

Altogether in the study 405 patients were randomly assigned to receive ABVD chemotherapy alone or subtotal nodal radiation at a dose of 35 Gy in 20 daily fractions. Patients in the radiation group with favourable risk profiles received radiation alone, while those with unfavourable risks received two cycles of ABVD followed by radiation therapy.

In an earlier publication, after a median follow-up of 4.2 years the investigators

reported that the rate of freedom from disease progression was higher among patients assigned to radiation therapy than ABVD therapy alone, and that no differences in survival were detected.

In the current publication, investigators report that the latest results show that, at 12 years, 94% of patients who had received ABVD chemotherapy were alive, compared with 87% of patients who were given subtotal nodal radiation with or without chemotherapy (HR for death = 0.50; *P*=0.04).

The difference, say the authors, was due to the number of deaths from causes other than Hodgkin's lymphoma, including second cancers and cardiovascular events. Among the patients randomly assigned to ABVD, six died from Hodgkin's lymphoma or an early treatment complication, while 12 died from other causes; whereas among patients who underwent radiation therapy, four died from Hodgkin's lymphoma or early treatment complications, while 20 died from other causes. Event-free survival was similar – 80% with radiation therapy and 85% with ABVD (HR 0.88; *P*=0.60).

"Our results show that improving long-term survival is less dependent than previously assumed on further reducing deaths due to progressive Hodgkin's lymphoma and instead emphasize a need for treatments that will not lead to deaths from late treatment effects," write the authors. Trial endpoints, the add, should be redefined so that the importance of deaths from causes other than Hodgkin's lymphoma is captured.

In an accompanying commentary David Straus, from Memorial Sloan-Kettering Cancer Center, New York, writes, "Although radiation therapy remains a useful tool for the treatment of some patients with Hodgkin's lymphoma, the challenge is to define the subgroup of patients for whom the benefits outweigh the increased risk of late complications."

Limiting the use of radiation therapy to the fraction of patients who require it, he adds, would make an important contribution to the ultimate goal of maximising the long-term cure rate while minimising late morbidity and mortality.

■ RM Meyer, MK Gospodarowicz, JM Connors et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. *NEJM* published online 11 December 2011, doi:10.1056/NEJMoa1111961.

■ DJ Straus. Chemotherapy alone for early-stage Hodgkin's lymphoma. *ibid* published online 11 December 2011, doi:10.1056/NEJMe1113291

Serial FDG-PET/CT predicts chemotherapy outcomes in mCRC

➜ Annals of Oncology

Metabolic response measured by FDG–PET/CT can be used to identify patients with metastatic colorectal cancer (mCRC) who will not benefit from chemotherapy after a single course of treatment, a study has shown.

The fact that tumour shrinkage is known to be the final step in a complex cascade of chemotherapy-induced alterations, suggests that earlier changes in cellular metabolism might be used to predict treatment response. Alain Hendlisz and colleagues, from the Institut Jules Bordet (Brussels, Belgium), reasoned that FDG-PET/CT might be used as a surrogate marker of tumour glycolytic activity, allowing the assessment of tumour response to treatment after just one or two cycles. "The aim of identifying patients with non-responding metastatic disease early is to quickly stop ineffective treatments. This can avoid unnecessary toxic effects and possibly allow alternative more effective therapies," write the authors.

Between November 2005 and October 2009, FDG–PET/CT scans were undertaken on 41 patients with unresectable metastatic colorectal cancer undergoing treatment with a biweekly regimen of chemotherapy (29 patients received chemotherapy as first-line therapy and 11 as second line) both at baseline and on day 14. For the study, metabolic non-response was defined by <15% decrease in FDG uptake in the patient's lesions, or if a lesion was found to be metabolically progressive. The PET-based response was then correlated with the primary endpoint of radiological Response Evaluation Criteria in Solid Tumours (RECIST) and the secondary endpoints of progression-free survival and overall survival.

Results show that the RECIST response rate in metabolically responding patients was 43% (10 of 23) compared with 0% (0 of 17) in non-responding patients (*P*=0.002). Comparing metabolically responding versus non-responding patients, the HR for overall survival was 0.28 (95%CI 0.10–0.76) and for progression-free survival it was 0.57 (95%CI 0.27–1.21).

The authors add that 68% of participants displayed a mixed metabolic response, i.e. both responsive and non-responsive PET lesions coexisted within the same patient, and sometimes even within the same organ.

Patients with exclusively metabolic non-responding lesions or at least one metabolically progressive lesion showed the worst outcomes, with the overall survival of these 10 patients being significantly worse than the remaining 30 patients (HR 4.78; *P*=0.001), as was progression-free survival (HR 2.30; *P*=0.043).

The target sample size of 45 patients was not achieved, write the authors, due to slow study accrual and replacement of the FDG-PET/CT scanner used for the study.

"Early FDG-PET/CT metabolic reassessment after one chemotherapy cycle in patients with nonresectable mCRC is able to discriminate, with a high NPV [negative predictive value], tumors unlikely to respond to treatment," write the authors. If independently validated, they add, the results could have a significant impact on future treatment strategies and design of clinical trials.

■ A Hendlisz, V.Golfinopoulos,C. Garcia, et al. Serial FDG–PET/CT for early outcome prediction in patients with metastatic colorectal cancer undergoing chemotherapy. Published online 23 November 2011, *Ann Oncol* doi:10.1093/annonc/mdr554