EJC news
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New hope for patients with advanced prostate cancer

A first-in-class alpha-pharmaceutical, which could change practice in advanced prostate cancer, was one of several new agents for the disease highlighted at the 2011 European Multidisciplinary Cancer Congress (Stockholm, Sweden (23-27 September 2011). A phase III trial on radium-223 chloride (Alpharadin) was stopped early after a pre-planned interim analysis demonstrated an improvement in overall survival surpassing the pre-defined threshold.

The ALSYMPCA study examined the effects of radium-223 chloride in 922 patients with castration-resistant prostate cancer and symptomatic bone metastases. It was stopped early on the recommendation of the Independent Data Monitoring Committee (IDMC).

Chris Parker

Presenting the results (*EJC 2011. 47: Supp 2; LBA#1*), Chris Parker (Royal Marsden Hospital, Surrey, UK) said, “In my opinion, radium-223, subject to regulatory approval, is likely to become a new standard of treatment for men with advanced prostate cancer with bone metastases.”

Radium’s similarity to calcium means that it targets bone, in particular new bone formation such as cancer metastases, and it emits alpha particles. Two or three alpha particles can kill a cell, compared with the thousands of hits that would be needed from beta radiation: “Alpha particles are highly damaging – they’re lethal – but they’re also very short range,” said Parker. “The rational is that if you have radium in your bone mineral, then any adjacent cancer cells will be killed by the alpha particles, but the more distant bone marrow cells will be spared,” said Parker.

ALSYMPCA included men from 150 hospitals in 19 countries who had either previously received docetaxel, were ineligible for docetaxel or had refused it. They were randomised 2:1 to receive radium-223 or placebo.

The pre-planned analysis, based on 314 deaths, found that median survival in the radium-223 group was 14.0 months, compared to 11.2 months among controls. Safety and tolerability of the new agent were high; grade 3/4 neutropenia was seen in 1.8% patients receiving radium-223, compared to 0.8% among those receiving placebo.

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"This is an important result," Parker said. "This is the first drug targeted to bone metastases in prostate cancer to improve overall survival. There are other bone-targeted drugs that are used in prostate cancer but they help to minimise symptoms, they don't improve survival."

---- Abiraterone acetate and fatigue ----

Other new agents have different modes of action. Abiraterone acetate (Zytiga) is an oral drug that specifically blocks the production of androgens by the prostate tumour itself, as well as the testes and adrenal glands. These androgen sources can fuel the progression of prostate cancer.

Previously reported work has demonstrated a survival advantage with abiraterone acetate among men with castration-resistant prostate cancer (CRPC). The phase III COU-AA-301 study included 1195 men with metastatic CRPC who had previously received docetaxel. They were given prednisone with either abiraterone acetate (797 patients or placebo (398 patients). The survival advantage associated with the new drug (*N Engl J Med 2011 364 (21): 1995-2005*) led to its recent approval by the FDA, EMA and European Commission for the treatment of metastatic CRPC following failure of docetaxel.

'Abiraterone acetate can reduce fatigue in this patient population, in addition to the previously demonstrated survival benefit'

At the European Multidisciplinary Cancer Congress, Cora Sternberg (San Camilla and Forlanini Hospitals, Rome, Italy) presented a retrospective analysis assessing its effect on patient-reported fatigue. All those enrolled in COU-AA-301 completed a Brief Fatigue Inventory (BFI) questionnaire at various times during the study.

The data indicated that patients who received abiraterone acetate had significantly better patient-reported outcomes for fatigue than the placebo group. The progression of fatigue intensity and interference with general activity, mood, walking, work, relationships and enjoyment of life was significantly delayed in patients who received abiraterone acetate (*EJC 2011. 47: Suppl 1 #7015).*

"One of the most distressing issues these metastatic CRPC patients face during hormone treatment is extreme fatigue," Sternberg said: "Our results show that abiraterone acetate has the potential to reduce cancer-related fatigue in this patient population, in addition to the previously demonstrated survival benefit."

'A combination of abiraterone acetate and radium-223 looks very attractive. Both prolong survival, are extremely well-tolerated, and work in completely different ways'

Parker said that radium-223 has not been tested in combination with other drugs but that this is an avenue for future research. "It's not at all clear where radium-223 will fit in with the new drugs. If I could speculate about the long term future, I'd say that a combination of abiraterone acetate and radium-223 looks very attractive. We have two drugs, both of which prolong survival, both of which are extremely well-tolerated, which work in completely different ways. To me, it's logical to think about using them in combination."

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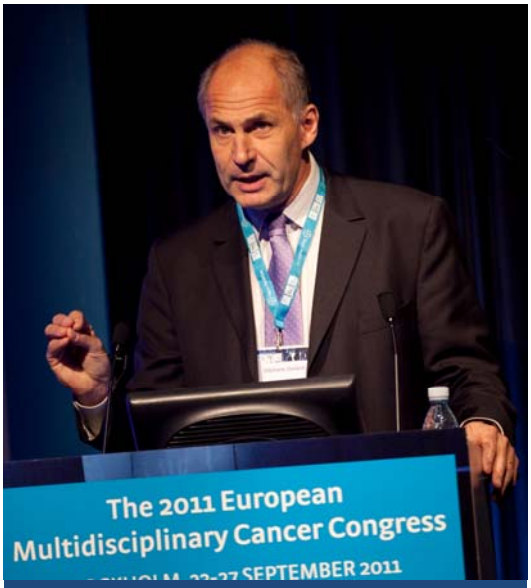
---- Denosumab and bone health ----

Another drug appears to be effective at an earlier stage of the disease. Data presented at the meeting demonstrated the effect of the monoclonal antibody, denosumab (Xgeva), in men with CRPC before they have developed bony metastases.

Denosumab inhibits the RANKL protein, which plays a key role in the formation of osteoclasts. Osteoclasts normally destroy bone, so a drug such as denosumab, which impedes osteoclasts, may strengthen bone in advanced prostate disease, and, potentially, reduce the formation of bony metastases.

Stéphane Oudard (Georges Pompidou Hospital, Paris, France) presented data which suggests that denosumab may indeed significantly prolong bone metastasis-free survival (*EJC 2011. 47: Suppl 1 #7003*).



Stéphane Oudard

An international, double-blind, phase III trial included 1432 men with non-metastatic CRPC who were at high risk of developing bone metastases (PSA value ≥ 8.0ng/mL and/or PSA doubling time ≤ 10.0 months). They were randomised to receive either denosumab or placebo and calcium and vitamin D supplements were encouraged.

The primary analysis took place when more than 660 men had either died or developed bone metastases. It found that median bone metastasis-free survival was 29.5 months in the denosumab group, compared with 25.2 months among controls (hazard ratio = 0.85; p = 0.03). The results were consistent among different sub-groups of the disease and demographic variables such as age, ethnicity, and geographical location. Denosumab can delay the appearance of bone metastasis, said Oudard: “In a condition where there is currently no effective treatment, this is a highly significant finding,” he said.

Commenting on the results, ECCO President Professor Michael Baumann said, “This is the first large clinical trial to demonstrate that targeting of the bone micro-environment significantly delays onset of bone metastases in hormone resistant prostate cancer patients with high risk for development of bone metastases.

“This offers new options for a considerable group of patients and also will stimulate important further research this field.”

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---- Reducing the pain caused by bone metastases ----

The bisphosphonate ibandronate (IB) binds to calcium and thus also inhibits the activity of osteoclasts and prevents bone loss. Peter Hoskin (University College London, UK) presented a study which examined its efficacy in reducing pain in men with prostate cancer and bone metastases.

"We found that using IB was as good as single dose radiotherapy in controlling pain," said Hoskin, presenting the data at the Congress: "We believe that the findings will also be applicable to other primary cancers that can lead to bone metastases, for example breast cancer, where they are very common," he said.

The phase III trial randomised 470 patients with primary prostate cancer and painful bone metastases to receive either a single dose of radiation (the standard therapy for these patients) or a single intravenous infusion of IB. Patients reported their primary site of pain at entry into the trial, and then at 4, 8, 12, 26 and 52 weeks after treatment.

> *'IB was as good as single dose radiotherapy in controlling pain. These findings will be applicable to other primary cancers that can lead to bone metastases, such as breast cancer'*

Those who had not responded to the first treatment at 4 weeks, crossed over to the alternative therapy. Pain levels were measured at 4 and 12 weeks by examining analgesic use (*EJC 2011. 47: Supp 2; LBA#7*).

There was no difference in pain relief between the two groups at 6 and 12 months. Median survival was 11.8 months (radiotherapy only), 11.4 months (IB only), 12.7 months (radiotherapy then IB), and 16.8 months (IB then radiotherapy).

> *'The future looks brighter for men with this disease. We have more hope for our patients, because they are not only living longer, they are also living better'*

"Currently we are unsure about the optimal timing and scheduling of treatment for these patients," Hoskin said. "We hope to analyse these survival differences further in the hope that it can give us further pointers as to how and whether we should use a combination of treatments."

Follow up work will examine biomarkers for bone resorption. "If we can correlate these markers with response to both radiotherapy and IB we will be able to see whether they can predict which patients would respond best to which treatment," said Hoskin.

Sternberg said that, overall, good progress has been made in the treatment of CRPC: "The future looks brighter for men with this disease and with several new therapies recently approved for advanced prostate cancer, we have more hope for our patients, because they are not only living longer, they are also living better. I think this is a huge step forward in the treatment of metastatic CRPC."

Helen Saul

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EUROFILE

European Academy gets to work

The European Academy of Cancer Sciences was launched in September 2009 to provide evidence to policymakers. While it has been slow to start work, releasing its first advice in 2011, policymakers see a niche for its specialist evidence on cancer policy.

Initiated under the auspices of ECCO, the European Academy of Cancer Sciences (EACS) is an independent body that has set itself the task of becoming a reference point for advice on decisions regarding cancer in Europe. It is well qualified, having amassed 164 experts, including Nobel prize-winners Professor Harald zur Hausen and Sir Paul Nurse; leading epidemiologist Sir Richard Peto; and the eminent Italian cancer surgeon Professor Umberto Veronesi.

> ***'You need hard evidence: epidemiology, demographic studies, cultural and social studies, and economic analysis. This is missing in cancer policy'***

This range of experience is necessary according to Richard Sullivan, Director of the King's Health Partners Centre for Global OncoPolicy. "Because of the breadth the depth and the complexity of cancer you need a separate disease-orientated approach to policymaking. Oncopolicy is a huge area to cover, from the fundamental sciences in terms of things like stem cells to regulation surrounding imaging, all the way to macroeconomic policy at national and supranational level to do with drug pricing," he says.

"A lot of it is opinion-based and to a certain extent that's acceptable - making policy is a political process. However, the days of getting a load of experts pontificating about what they think needs to be done have gone. You need hard evidence, comprising epidemiology studies, demographic studies, cultural and social studies, and economic analysis. Cancer policy is an area in which this is missing. Good evidence-based policy-making requires experts in all areas, to deal with it."

The Academy has outlined three initial ways of working: participating in Commission consultations on EU legislation affecting cancer; identifying a number of priority areas to investigate foresight studies; and, most importantly, providing evidence-based answers to questions posed by European or national policymakers or organisations.

The Academy's initial piece of work was a response to the Commission's open consultation on the future of EU funded research, in the spring of 2011. Shortly afterwards, in the summer of 2011, it was called upon by the Commission to provide advice for the European Partnership on Action Against Cancer, set up in 2009 by the Commission to tackle inequalities in cancer prevention and control.

According to Ulrik Ringborg of the ECCO Policy Committee, and an Academy fellow, "The Partnership has a remit to explore and investigate what sort of research should be co-ordinated at European level, and which at national level. It wanted the Academy to respond to a number of questions – like, what type of basic research could be improved with or benefit from EU co-ordination, what type of translational research, and clinical research."

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The Academy was given three weeks to respond. Questions went out to all fellows and a consensus has been returned.

The fact that the Commission has solicited the Academy's advice is an implicit endorsement of its work. Yet Commission officials are reserved about the role the Academy could play in shaping policy when asked directly.

Stefan Schreck, head of the information unit at DG Sanco, the Commission's directorate for health and consumers says, "I believe it would not be appropriate for me or my colleagues to comment on this initiative which is created independently of the European Commission and is part of the civil society. Having said that, I do not wish to undermine the importance of a strong evidence base on which to take policy decisions."

> ***'My gut instinct is that if the medical and scientific world can put together a sufficiently authoritative, well-run structure which the political and legislative world can accept as a reference point, that's got to be better than a body created by the institutions'***

However, ECCO is seen as a trusted interlocutor. "ECCO is an important partner in the Partnership and as such we trust that it will find the best ways through which to contribute to its success by providing support and input from different mechanisms or initiatives under the ECCO auspices," says Schreck.

Schreck's predecessor, Nick Fahy, responsible for facilitating the evolution of the European Partnership on Action Against Cancer, and now an independent consultant, can speak more freely. "There used to be a European advisory committee on cancer but there isn't any more. At the moment the Commission and Europe as a whole does not have a one-stop shop for such an advisory process. Of course, the European institutions can create such an advisory structure if they want to, but then it's an advisory structure created by and with an agenda set by government of whatever form. Whereas here we already have an independent body. My gut instinct is that if the medical and scientific world can actually put together a sufficiently authoritative, well-run structure which the political and legislative world can accept as being a reference point, that's got to be better than a body created by the institutions," he says.

> ***'Smaller countries could find the Academy extremely useful in developing national cancer plans. It is exactly the sort of body that could bring best practices to the table'***

"I would hope DG Sanco takes it up, but whether or not the Commission does use it in that way will depend a lot on the authority of what it produces and whether it meets the needs of the Commission and other institutions. That's a whole other process of engagement," he adds.

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Former MEP Adamos Adamou, key in championing cancer policy through the European Parliament thinks the assembly could benefit from the Academy's advice, but there is even more potential to help at the national level. "Smaller countries in particular could find the Academy an extremely useful tool in developing their national cancer plans," he says. "This is exactly the sort of body that could bring best practices to the table."

Adamou was responsible for developing and implementing the national cancer plan in Cyprus and says he would have used such a body.

Fahy agrees this could be an important role for the Academy. "For a lot of countries, if the advice is European, it sidesteps domestic political interest, and is accepted as being more authoritative," he says.

But although the current composition of the Academy encompasses 164 fellows from around 20 countries, the UK and Germany could be perceived as over-represented.

"If it's going to play a European role, the Academy is going to have to make a really active effort to improve the European balance," says Fahy. "We might say cancer is the same wherever it is, but cancer treatment, cancer public health and cancer systems organisation - those things are not the same everywhere, and if you have an Academy which is very skewed towards one corner of Europe then I think that would affect how credible its recommendations are in another corner of Europe."

Saffina Rana
Brussels

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INTERVIEW

Positive results from BOLERO-2

Results from BOLERO-2, a phase III trial in postmenopausal women with advanced breast cancer who are refractory to letrozole or anastrozole, were widely discussed at the European Multidisciplinary Cancer Congress (Stockholm, Sweden; 23-27 September, 2011). A pre-planned interim analysis revealed that women who received exemestane plus everolimus had a progression-free survival (PFS) of 6.9 months, compared to 2.8 months among those who received exemestane plus placebo. The trial was stopped early (EJC 2011. 47: Supp 2; LBA#1). Discussant Fabrice André (Institut Gustave Roussy, Villejuif, France) described the finding as "the most important advance in breast cancer since trastuzumab".

***José Baselga** (Massachusetts General Hospital, Boston, USA**)** led the study.*

How does everolimus work?

Everolimus is an mTOR inhibitor. Basically, MTOR activates ER; and there's a large body of experimental data showing that hyperactivation of the mTOR pathway is responsible for a proportion of tumours that are resistant to hormone therapy. So there's a strong rationale for using an mTOR inhibitor together with hormone therapy. In a way, this study represents confirmation of a strong scientific hypothesis.

How convincing are the BOLERO-2 results?

It was a large, registration study, including 724 postmenopausal women with advanced breast cancer. They were ER positive; they had received and were refractory to aromatase inhibitors, either letrozole or anastrozole. The primary endpoint of PFS is the most common measure of clinical efficacy we have in advanced breast cancer.

Local investigators found a significant improvement in PFS, going from 2.8 months in the control arm to 6.9 months in the everolimus arm. It was highly statistically significant and the hazard ratio is 0.43. This is a very uncommon result in patients with metastatic disease; it is very seldom you see a hazard ratio of this nature.

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Central assessment by an independent body also found in favour of the everolimus arm: 4.1 months' PFS compared to 10.6 months in the experimental arm and again it was highly statistically significant. Everolimus is the first agent to increase the clinical benefit of hormonal therapy in refractory disease. We saw in improvement in bone metabolism: aromatase inhibitors interfere with bone resorption and this was reversed, almost in full, by everolimus.

Why did you choose PFS rather than overall survival as the primary endpoint?

PFS is the primary endpoint that is most reliable on the benefit to the patient. Many of these patients are likely to receive additional therapy when they progress so there would be confounding elements that could interfere with survival data. If the extent of therapy after progression is asymmetric between the groups in the study, it could interfere with survival data. So although trials like this one that have a large PFS improvement frequently also have improved overall survival outcomes, it is hard to control.

What about the safety profile of everolimus?

We observed in the everolimus-containing arm the well-known and well-described side effects of mTOR inhibition, namely, increased stomatitis (ulcers and inflammation of oral mucosa); hyperglycaemia, (mTOR inhibitors interfere with glucose metabolism), fatigue, and a small proportion of patients with pneumonitis. The frequency of the more serious grade III events was low.
Patients who remain on study do not have a worse quality of life than those on aromatase inhibitors alone and that's an important measurement because it means that this therapy does not interfere with quality of life.

Do you have data on overall survival?

Yes, but the data is not mature yet, because the number of events is minimal. There was an excess of deaths in placebo group – 13% versus 10% in the group receiving everolimus. But it is too early to consider survival at this time; this is an interim analysis and we will have to wait for later updates.

Could this be a class effect?

It could be. A small, randomised phase II study called TAMRAD used tamoxifen instead of an aromatase inhibitor and came up with similar results (*Presented at 33rd Annual San Antonio Breast Cancer Symposium; December 8-12, 2010; #S1-6).* On top of that, we have data from a study using everolimus plus letrozole, in the primary adjuvant setting. Patients had ER positive tumours and had not received any prior therapy – they were very different from those in BOLERO-2 – and we also saw an effect (*JCO 2009. 27:16; 2630-37*). I believe that we may be seeing a class effect that indicates that mTOR has an important effect on oestrogen receptor transcription.

How expensive will the treatment be?

I have no idea what the pricing structure will be. Cost is an issue, no question, but cost per se is one parameter that only has meaning when it is analysed in context of the benefit derived. In this case, there is a huge improvement in PFS which will put clear pressure on cost/benefit analyses. Also the therapy is given orally, it's a pill a day,

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mostly given in outpatients. It's not like chemotherapy where you have to build in the cost of nursing, the cost of using facilities, cost of using the hospital, cost of being admitted with fever. These are not factors here; in a way it is like hormonal therapy in that the total cost is the cost of the therapy.

Are the data sufficient to change practice?

This trial is very positive and we are hopeful but we have to be respectful of the review process. The pharmaceutical company have started the filing process and I cannot see how it will not be successful. This is the most positive trial ever in ER positive breast disease.

Helen Saul

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