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ASCO: 46th Annual Meeting
June 4–8, 2010; Chicago, Illinois, USA

Helen Saul reports

Clinical trials system in crisis

The opening session of ASCO's 46th Annual Meeting (June 4–8, 2010; Chicago, Illinois, USA) was dominated by discussion about the state of National Cancer Institute (NCI)-funded clinical trials in the US.

Both Dr. James Doroshaw (Director of the NCI Division of Cancer Treatment and Diagnosis) and Dr. Douglas Blayney (President of ASCO) used their talks to highlight the need for reform.

The talks follow the recent publication of the US' Institute of Medicine (IoM) report, *A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program.*

"Improved treatments for cancer will be delayed and patient lives will be lost unnecessarily unless the efficiency of the clinical trials system improves," the report concludes. Changes across the board are urgently needed, it states, and all stakeholders – physicians, patients, insurers, federal agencies including NCI, academia, foundations and industry – "must re-evaluate their roles and responsibilities in cancer clinical trials and work together to develop an improved, efficient multidisciplinary trials system."

The report, which was produced at the behest of NCI, outlined four overarching goals:

- Improving the speed and efficiency of the design, launch, and conduct of clinical trials
- Making optimal use of scientific innovations
- Improving selection, prioritisation, support, and completion of clinical trials
- Fostering expanded participation of both patients and physicians

At the Opening Ceremony, Dr. Doroshaw said that, since 2005, efforts to improve the system had involved hundreds of clinical triallists, scientists, advocates and patients. This effort "has been based on the fundamental premise that our clinical trials system must substantively change to reflect the dramatic alterations in cancer biology that have occurred over the past 20 years."

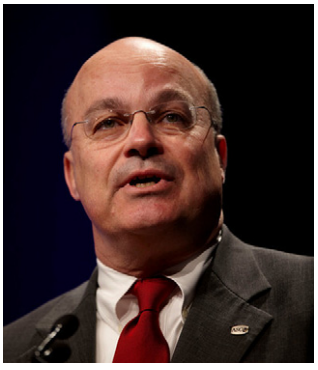

Photo by © ASCO/Todd Buchanan 2010

Dr. Douglas Blayney, ASCO President

But he said there is still a long way to go. "It will take more time than we want it to, but we cannot fail to develop a national clinical trials system since, in my opinion, it is of fundamental importance to the future of cancer research."

Dr. Douglas Blayney called for greater investment in the NCI's cooperative group program. "Sustaining momentum in clinical research requires commitment at the federal level to preserve a jewel of our national research enterprise."

The cooperative group program is comprised of more than 3100 institutions, 14,000 investigators and contributes more than 25,000 patients to clinical trials each year. It complements the multiple systems of industry sponsored trials, which are mainly directed towards FDA approval of new treatments. It is the only mechanism for conducting large scale adjuvant trials, to study rare diseases including childhood cancers and the attendant long term side effects; and for developing studies which define and limit the use of already-marketed agents. "Support for such trials, I believe, is a legitimate function of government," he said.

The cooperative group programme receives 5% of the NCI's budget, and ASCO has already called for a doubling of funds over the next 5 years. "This will sustain the cooperative system and stop the erosion in participation we have observed in the last 5 years. The system is in crisis and must be preserved," he said.

The IoM report is available at http://www.iom.edu/Reports/2010/A-National-Cancer-Clinical-Trials-System-for-the-21st-Century-Reinvigorating-the-NCI-Cooperative.aspx

See also PODIUM, this issue, for further comment

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ASCO 2010

Helen Saul reports

PARP inhibition in ovarian cancer

The poly(ADP-ribose) polymerase (PARP) inhibitor olaparib showed "quite remarkable" activity in women with high grade serous ovarian cancer, discussant Dr. James Doroshaw (Director of the NCI Division of Cancer Treatment and Diagnosis) told a clinical sciences session on *PARP Inhibition: DNA Repair as the Target*.

Describing the Canadian research as "one of the most important abstracts you will hear at this meeting," he said the study was based on solid pre-clinical information and "demonstrated that serous ovarian cancer is a disease – or at least it may be a disease – of inability to repair DNA."

The drug was active, not only in women with germline BRCA mutations but also in women with mutations in their tumours themselves. "The extent of activity of this single agent in platinum-refractory patients, as observed in this study, is quite remarkable," he said.

The data was presented by Dr. Karen Gelmon (British Columbian Cancer Agency, Vancouver, Canada). The open label, non-randomised, phase II trial included women with advanced breast or ovarian cancer. All had recurrent, locally-advanced or metastatic disease and at least one lesion of 10 mm or greater, as observed on CT scan, to enable assessment of response. The reference cohort was comprised of patients with known BRCA mutations.

All patients received 400 mg bid of olaparib as monotherapy. They had tumour biopsies prior to treatment, after 2 cycles, and at progression, to assess PARPi activity, loss of heterozygosity, mutational changes, BRCA1/2 expression, and markers of response.

In all, 64 women with ovarian cancer were included in the study. The primary endpoint – an objective RECIST response – was seen in 40 percent (4 of 10 women) who were BRCA carriers; and in 26.4% (14 of 53 women) of those with unknown BRCA status. Neither breast cohort (known or unknown BRCA status) met the criteria for a RECIST response.

Incorporating the women's actual BRCA mutation status in analysis led to some with unknown status joining the BRCA positive group. Even then, the overall response rate in the BRCA positive group was 41.2% (7 of 17 women); in the BRCA negative group it was 23.9% (11 of 46 women).

"This is the first single agent trial to have demonstrated very encouraging activity of olaparib in high grade, non-BRCA, serous ovarian cancer," Dr. Gelmon told the session.

Almost as important, Dr. Doroshaw said, was the investigators' ability, in this multi-centre study, to obtain pre- and post-treatment biopsies in a population of ovarian cancer patients. It is a difficult disease to access, he said, "to obtain the critical information necessary in terms of sequencing these tumours to find out whether or not the impact that we see was related to intrinsic mutations in the tumours themselves."

He said that the abstract "is likely over time, to make a major impact on the treatment of advanced ovarian cancer, especially ovarian cancer not of the BRCA1/2 mutation phenotype."

In the same session, first-in-human data was presented on the PARP inhibitor MK-4827. In patients with advanced ovarian BRCA-deficient and sporadic cancers, the agent showed "promising anti-tumour activity". Dr. Doroshaw praised the large, well-conducted study but said the critical question with this molecule – as with so many other PARP inhibitors – will be how they differ, one to another, and where its place will be compared to the other agents being actively evaluated.

Professor Hilary Calvert (University College, London, UK) outlined potential problems with PARP inhibitors in further development. In some but not all trials of their use in combination with cytotoxic agents, the mild toxicity of the cytotoxic agents has been enhanced by the combination, making it difficult to maintain the dose. Resistance can develop, he said, and there's a theoretical possibility of genotoxicity in long term use of drugs which block DNA repair.

The necessary extent and duration of PARP inhibition is still unknown, meaning that doses and schedules have yet to be determined. The patient population most likely to benefit has not been identified, and a test for homologous recombination repair deficiency is needed. Work is ongoing but there is not, so far, a single accepted predictive test.

But he said that in four to five years' time, he anticipated seeing many of the PARP inhibitors in use in combination therapy for many of the common tumours. "There's quite a lot of data showing that responses to cisplatin and so on are more common in patients who have low expression of BRCA1, with fairly simple tests. I think we may find that up to one third of patients with the common tumours will benefit by the addition of a PARP inhibitor to their treatment."

2010 ASCO Annual Meeting Proceedings, #3002; #3001

Bevacizumab 'prolongs progression-free survival'

Adding bevacizumab (Avastin) to initial chemotherapy – and then continuing it as maintenance therapy – significantly slowed disease progression in women with advanced epithelial ovarian, primary peritoneal or fallopian tube cancer, Dr. Robert Burger (Fox Chase Cancer Center, Philadelphia, Pennsylvania) told the meeting.

He led a phase III Gynecologic Oncology Group (GOG) trial, including 1873 women with newly diagnosed stage III or IV disease who had undergone surgery. Women who received standard chemotherapy (paclitaxel plus carboplatin) plus bevacizumab, followed by up to 10 months of bevacizumab maintenance had a median progression-free survival (PFS) of 14.1 months. Those who received standard chemotherapy alone had a median PFS of 10.3 months, and the difference was statistically significant.

"This is the first time a phase III trial has demonstrated that an anti-angiogenic agent improved PFS in women with this very hard-to-treat disease," Dr. Burger said.

2010 ASCO Annual Meeting Proceedings, LBA #1

ASCO 2010

Helen Saul reports

A new era in melanoma?

A monoclonal antibody looks set to end the "decades of disappointment" in research into the treatment of melanoma, Dr. Steven O'Day (The Angeles Clinic and Research Institute, Santa Monica, California, USA), told the meeting.

He presented phase III data on ipilimumab, a fully human monoclonal antibody against cytotoxic T-lymphocyte antigen-4 (anti-CTLA4). It was tested alongside the gp100 peptide vaccine, which had previously shown immunological and clinical responses in combination with other immunotherapy. Efficacy and safety of the two agents, as monotherapy and in combination, were studied in 676 adults with unresectable stage III/IV melanoma. All had been previously treated.

Ipilimumab, either alone or in combination, significantly improved overall survival; there was a risk reduction of 32–34% compared to the vaccine. Patients receiving the antibody also had significantly better disease control rates, and progression-free survival.

The antibody represents a new class of T cell potentiators, Dr. O'Day said, and is "an important advance for the field of immuno-oncology." While the dose and schedule of ipilimumab are still being refined – and alterative combinations considered – it is "very exciting" to see the drug applied to other diseases, in particular, non-small cell lung cancer (NSCLC), and prostate cancer.

Speaking later to *EJC*, Professor Alexander Eggermont (Erasmus University, Rotterdam, the Netherlands) said the excitement over the results was justified: "The survival curves at 24 and 36 months months suggest that a number of patients may have been cured. It's a realistic possibility because studies into high dose Interleukin-2 have shown that patients in complete response beyond two and a half years don't relapse; they seem to be cured. The same phenomenon seems to happen with ipilimumab, but seemingly in a higher percentage of patients.

"The other important thing about ipilimumab is that it is not specific to the tumour cell, which is ironic in this age of targeted therapies. Ipilimumab re-activates a silenced immune response inside tumour lesions. So there's an initial immune response to the tumour, but then the T cells are suppressed by T regulatory cell function. It's truly amazing that just by giving a monoclonal antibody you can reactivate – and maintain the reactivation of – an immune response. It can lead to partial or complete responses, and slower or stable disease.

"This is going to be true not just for melanoma, but for a whole range of tumours. It's already been shown in renal cell cancer, there's a positive randomised phase II report on NSCLC, and there are ongoing trials in prostate and pancreatic cancer."

The antibody had an unusual side-effect profile in that adverse effects were immune related. "It can make silenced immune responses clinically overt, and lead to colitis, thyroiditis or dermatitis," Professor Eggermont said. But corticosteroids were used to treat the side effects without altering the antibody's efficacy. "It seems the damage at the tumour site has already been done. We sometimes see initial progression of the disease before the response starts. It may be that infiltration and expansion of the T cell population inside the tumours makes them bigger at first CT scan, before they go into regression. If that process in already set in motion at the tumour site, corticosteroids given later don't seem to reduce the anti-tumour response because it's already established."

Combination with the peptide vaccine was not beneficial; all endpoints were slightly worse in combination: survival, response rate, the percentage of durable responses. Professor Eggermont: "We have a poor understanding of the difference between different vaccines. But laboratory models have found a whole range of vaccines that interact synergistically with ipilimumab. It's more complex in humans – and vaccination alone has not moved forward significantly in melanoma over the last 35 years – but further understanding of this and other monoclonal antibodies could dramatically relaunch attempts to find an interesting vaccine/antibody combination."

Already, work is ongoing into chemotherapeutics which lead to the kind of tumour death that enhances the immune response and antigen presentation. "We're witnessing the discovery of a drug which is going to be much more important than many think at the moment. We're getting a foretaste of what is to come," Professor Eggermont said.

Professor Eggermont is coordinating the first adjuvant trial of ipilimumab in patients with lymph node positive, stage III B and C melanoma (EORTC 18071). Accrual is ongoing and expected to be complete in a little over a year; it will take a further 3 years or so for full analysis.

2010 ASCO Annual Meeting Proceedings #8505

End of the line for ganglioside vaccine

The final results of phase III study EORTC 18961 concluded that adjuvant ganglioside GM2-KLH/QS-21 vaccination "is ineffective and could even be detrimental in stage II melanoma patients."

The trial recruited 1314 patients between 2002 and 2005, but was stopped after the second interim analysis when the EORTC's Independent Data Monitoring Committee (IDMC) concluded that the vaccine could never have a positive effect. Patients received no further vaccinations, but follow up continued.

The final per protocol analysis showed a significant detrimental effect on overall survival (Hazard ratio = 1.43; $p = 0.02$). Overall survival in the intention-to-treat analysis did not show a significantly detrimental effect of the vaccine, but Professor Eggermont said this was difficult to interpret because the analysis includes some 150 patients who were actively stopped from having the vaccine (by the IDMC). "It does not exclude the potential for the vaccine having a negative effect," he said.

2010 ASCO Annual Meeting Proceedings, LBA #4

ASCO 2010

Helen Saul reports

ALK inhibitor shows 'impressive activity'

An expanded phase I trial of a novel ALK inhibitor showed such a dramatic effect in patients with non-small cell lung cancer (NSCLC), that it led directly to a phase III trial of the agent, the meeting heard.

Presenting the data, Dr. Yung-Jue Bang (Soeul National University College of Medicine, Seoul, Korea), said that the oral agent, crizotinib (PF-02341066) "resulted in impressive clinical activity."

The agent was given to 82 patients with advanced, pre-treated NSCLC. An objective response was seen in 57%, and the responses were durable, lasting up to 15 months in three patients at the time of the presentation. Almost three-quarters (72%) were progression free at 6 months. Overall, more than 90% of patients had tumour shrinkage. Furthermore, the drug was well-tolerated.

Fusion between the ALK (anaplastic lymphoma kinase) gene and the EML4 gene was determined to be an oncogenic driver of NSCLC as recently as 2007 (*Soda et al., Nature, 2007*). Dr. Bang said that 3–5% of patients with NSCLC have the EML4-ALK fusion gene; they tend to be younger than most NSCLC patients, and either non-smokers or former smokers.

Commenting on the study, Dr. Mark Kris (Memorial Sloan Kettering, New York, USA) said, "In just 3 short years, we have gone from a description of an oncogene to a therapy, and I think that's an amazing example of the power of understanding the workings of a cancer cell." People with the fusion gene "can expect dramatic benefit" from this treatment, he said.

A phase III study (PROFILE 1007) and a phase II study (PROFILE 1005) on-going (*details at www.pfizercancertrials.com*).

2010 ASCO Annual Meeting Proceedings #3

Axillary node dissection unnecessary?

Axillary node dissection may be safely avoided in many women with breast cancer, even where the sentinel node is positive, the meeting heard.

Dr. Armando Giuliano (John Wayne Cancer Institute, Santa Monica, California) presented data which found that axillary node dissection made no significant difference to survival in some sentinel node positive women.

The study (ACOSOG Z0011) included women who were clinically node-negative, and had one or 2 sentinel nodes with metastases detected by hematoxylin and eosin. They were randomised to receive axillary node dissection ($n = 445$) or no further axillary specific treatment ($n = 446$). Those in the former group had a median of 17 nodes removed, compared with 2 in the latter group.

At a median follow up of 6.2 years, 5 year survival was 91.9% among those who had the axillary node dissection, compared with 92.5% among those who did not. Recurrence was 3.7% compared with 2.1% at 5 years, and disease-free survival 82.2% compared with 83.8%.

Multivariant analysis showed that only older age, ER-negative status and a lack of adjuvant systemic therapy were associated with worse overall survival.

The study closed early because of a low accrual/event rate but Dr. Giuliano said it remains the largest phase III study of axillary node dissection for node-positive women. He acknowledged the widely-held belief that axillary dissection improves survival, but said this study "demonstrates no trend toward clinical benefit of axillary node dissection for patients with limited nodal disease.

"The role of this operation should be reconsidered, especially in light of targeted therapy and new means of determining the need for adjuvant systemic therapy," he concluded.

Discussing the study, Professor William Wood (Emory University School of Medicine, Atlanta, Georgia) drew attention to the study's caveats: patients had to have less than 3 positive sentinel nodes, which were not matted. They received radiation to the whole breast, covering much of the axilla, and systemic therapy as appropriate.

- In the same session, Dr. David Krag (Vermont Cancer Center, Burlington, Vermont) presented phase III data comparing sentinel node resection to axillary dissection in clinically node-negative patients.

The study (NSABP B-32) included 3986 sentinel-node negative patients who were randomised to receive either sentinel node resection or axillary dissection. With a follow-up of almost 8 years, the researchers found no differences in overall survival, disease-free survival or regional control.

He concluded: "When the sentinel node is negative, sentinel node surgery with no further axillary dissection is appropriate, safe and an effective therapy for breast cancer patients with clinically negative lymph nodes.

2010 ASCO Annual Meeting Proceedings #CRA506, #LBA505

Selenium 'doesn't help'

Selenium was not effective in preventing a second primary lung cancer in patients treated for early-stage, non-small cell lung cancer (NSCLC), Professor Daniel Karp (MD Anderson Cancer Center, Houston, Texas) told the meeting.

He presented phase III data from a randomised, double-blind intergroup study led by the Eastern Cooperative Oncology Group. Between 2000 and 2009, 1522 patients with resected stage IA and IB NSCLC were randomised to receive a daily selenium supplement or a placebo for 4 years.

The study was halted early, after a median 4 year follow up. About 1.9 percent of those taking selenium developed a second primary lung tumour after a year, compared to 1.4 percent taking placebo. However, overall, 4.1 percent of patients taking the supplement developed a second primary tumour of any type in that time frame, compared to 3.66 percent in the placebo group.

Professor Karp said, "Based on the data, we cannot recommend that patients with lung cancer take selenium to prevent a second primary tumour."

2010 ASCO Annual Meeting Proceedings #CRA7004

PODIUM

International collaboration in clinical trials

Dr. Denis Lacombe, Scientific Director of EORTC, presented the 'European Perspective on International Collaborative Clinical Trials' at ASCO's 46th Annual Meeting. Here, he discusses the subject with EJC.

How important is transatlantic cooperation?

Large, phase III trials are the ones best placed to change practice. The environment is changing and our focus on rare tumours, along with the fractionation of tumours, means we need this type of cooperation in order to perform large trials quickly. We collaborate not only with the US but also with Canada and Australia, and we're in discussion with colleagues in Asia.

You focused on the glioma trial in your talk

This trial (RTOG 0525/EORTC 26052-20053) resuscitated our co-operation with US' National Cancer Institute (NCI) after a long gap between 2000 and 2006. Initially, stricter requirements in the US, notably the recommendations from US' Office for Human Research Protections, made cooperation difficult, and then came the European Clinical Trials Directive (CTD). Our efforts to cooperate failed during that period; the glioma trial was the first after the gap.

How successful was the trial?

It happened and that was an achievement! One of the stumbling blocks was in adverse event reporting; we work according the ICH GCP (Good Clinical Practice) guidelines but the NCI's pharmacovigilance data base does not strictly work to the ICH GCP definition of serious adverse events. The problem is due to be solved when the NCI's current data base is replaced, but it's one of the remaining bottlenecks in cooperative trials and should be a priority now.

Amendments to the protocol also caused problems?

Yes; the NCI has a central Institutional Review Board (IRB) – along with local ethics committees – and can make amendments to protocols and implement them across the country almost overnight. They therefore make amendments on a regular basis. In Europe, every amendment has to go through each country's competent authority and ethics committees and it can take up to 6 months before an amendment is implemented everywhere. So in a cooperative trial, it's an issue if we're receiving an amendment every month. But there may not be a good way out; we are bound to the European system.

Talks at ASCO highlighted the Institute of Medicine (IoM) report into problems with the NCI clinical trials system. What impact will the impending overhaul have on European collaborators?

It's not clear yet what the overall effect will be. There may be a reduction in the number of 10 NCI-supported cooperative groups, and there will be new aggressive timelines; they want to speed up the review and activation of protocols. They're looking to activate a protocol within a year or so, as opposed to current practice, which is over 2 years. It's ambitious. At EORTC, our processes now ensure that a trial that doesn't meet any obstacles can be activated within 12 to 15 months from trial concept approval. But there are always trials with features that cause delays – having to wait for data maturity, or for a partner company to take a decision – and it doesn't mean the trial isn't worth doing.

Some measures – such as only conducting potentially practice-changing trials – are reminiscent of measures taken by EORTC some years ago. Will these similarities make cooperation easier?

The more our strategies overlap, the more we can cooperate. But there will always be trials that are only feasible in either Europe, or US. We don't have to collaborate on everything, and we have to be critical because intercontinental trials are difficult to set up. We have to select those that deserve such effort.

If we talk sooner and on a regular basis, we should be able to avoid duplication. It's a shame if two trials run side by side. You can merge the data base but it is better to do a large prospective clinical trial.

Are there aspects of the IoM report which could be addressed here?

As diseases become fractionated, we should question in Europe how we can further facilitate trial activation so that patients do not have to come to trials but rather that the trial can be activated wherever a potential patient – with the specific feature we're looking at – is. That is going to be a challenge.

What is the future for the large intercontinental trials?

These large academic trials are one of the ways forward, a unique opportunity not only for patients but also for regulators and industry. We need new models of cooperation to enable us, for example, to generate data that can readily benefit the community and industry. The international academic platform can deliver high quality science and deliver the basis for registration of new products but also conduct trials which a priori are not necessarily in the interest of industry but change practice. We need to work with EMA and FDA, and move standards of care forward together.

Helen Saul