binds to membrane receptors (types I and II serine/threonine kinases) that signal via the Smad pathway. Smads are signalling molecules, acting as transcription factors for genes coding for procollagens and other matrix compounds, and fibrogenic growth factors. Alternative signalling routes from the TGFb1 receptor (TGFb1R) complex to the nucleus bypass cytoplasmic Smad proteins, using the so-called p38, JNK, ras/ERK MAP kinase and Rho/rho kinase (ROCK) pathways. Anti-TGF-b1 strategies including soluble RII have shown efficacy to prevent and halt radiation-induced fibrogenic process and recently Pirfenidone has shown some effectiveness in halting diabetic nephropathy and IPF in humans. No trial is scheduled on radiation fibrosis, however due to the pleiotropic role of TGF-b1 in tissue homeostasis serious side-effects can be anticipated.
TGFb1 is not the only fibrogenic cytokine, the products of Thy-2 lymphocytes can be mentioned including IL-4 and IL-13. Amongst the growth factors bFGF, PDGF, IGF; and several chemokines such as ET-1 and CTGF form a longer list of potent fibrogenic factors acting alone or in conjunction with TGFb1.
PDGF family mainly target mesenchymal cells. Their physiological and fibrogenic actions are achieved by homodimerisation of the growth factors (creating PDGF-AA, PDGF-BB etc dimers) that bind to specific plasma membrane receptors (PDGFR-a and PDGFR-betc). PDGFR-a is transactivated by TGF-b1 and is especially associated with fibrosis. PDGF signals through major transduction pathways including PI3K, Ras/MAPK and PLCg to stimulate myofibroblast proliferation and extracellular matrix synthesis. Targeting PDGF pathway using Glivec prevented radiation-induced pulmonary fibrogenesis. Clinical trials are ongoing in systemic sclerosis, nephropathy and IPF but no specific trial on radiation fibrosis is planed so far.
CTGF is a matricellular protein that promotes fibroblast proliferation and ECM production *via* a yet uncharacterized membrane receptor. CTGF inhibition using anti-CTGF monoclonal antibody and Pravastatin has shown very promising results in both preventing and reversing radiation fibrosis in experimental rodent model. Therefore the anti-fibrotic efficacy of Pravastatin is currently investigated in a phase II/III study at IGR.

Special Session (Sun, 25 Sep, 13:15−14:15)
Fertility Concerns

150 INVITED

Frozen Hope − Fertility Preservation for Women With Cancer

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Increasingly successful treatments for cancer and higher survival rates mean that considering future fertility is an important factor in the treatment of pre menopausal and nulliparous women and younger girls. The parallel scientific and clinical advances in reproductive technologies now present more options for the preservation of fertility at the time of treatment for cancer and assisted conception may be used for reduced fertility later in life.
The diagnosis of any type of cancer is usually devastating and confronting mortality and the other complex emotional, social and practical issues associated with preserving fertility is not easy for patients or practitioners when dealing simultaneously with all the other decisions.
Understandably the immediate emphasis is on the treatment for cancer and it may be difficult to think beyond to life later on. The psychological impact of the prospect of infertility may be mitigated by freezing embryos or oocytes (eggs). For women, the options for preserving their fertility depend on individual medical and social circumstances. Embryo freezing, first successful in 1983, is now a routine part of in vitro fertilisation cycles (IVF) but can only be used if the woman has a partner to create embryos or uses donated sperm. Cryopreservation of oocytes may be preferred by many women but it has proved more technically challenging. Although the first live birth from a cryopreserved oocyte was reported in 1986 the success rates remain low and it is much less widely available than embryo freezing. Research is ongoing into freezing ovarian tissue and this may be an option in the future. Most people would choose to have their own genetic children but using donated eggs may be considered by women who are infertile after the treatment for cancer if preservation of embryos or oocytes fails or are not chosen for medical or personal reasons. The window of opportunity for preserving embryos and oocytes is limited and a decision may have to be made about whether to delay starting treatment to take advantage of these options. However with the advances in fertility preservation and treatment, an integral part of cancer care should be discussing the implications for reproduction and counselling patients to help with their decisions. The legal and regulatory framework will also impact on what may be offered, for example embryo freezing is not allowed in some countries. Some cancer centres have established links with assisted conception units to provide fertility oncology services but this is not yet routine.

151 INVITED

Male Infertility and Cancer

A.A. Pacey[1]. [1]*University of Sheffield, Human Metabolism, Sheffield, United Kingdom*

Many cancer treatments increase the risk male infertility, particularly those involving irradiation of the pelvis and/or systemic treatment with chemotherapy drugs. Hence, the opportunity to bank sperm, before cancer treatment begins, is invaluable for many males as 'fertility insurance'.
Sperm banking has been technically possible since the 1950's, but the organisation of sperm banking services as part of oncology care only became developed in the 1970's. In spite of this long history, their remains considerable evidence today that many males are often not given the opportunity to bank sperm (or when it is offered they do not accept it). Consequently, the ability of some men to father children post-treatment will be compromised if their fertility does not recover.
The prospects of sperm production recommencing following cancer treatment among men who bank sperm is quite good with only a third of men remaining azoospermic in the long-term. However, data on the probability of male cancer survivors achieving paternity spontaneously (i.e. without assisted conception) is less clear with some studies providing conflicting estimates of how likely fatherhood may be.
If necessary, frozen-thawed sperm, or freshly ejaculated sperm (if some natural fertility returns), may be used in a variety of assisted conception procedures including Intra-Cytoplasmic Sperm Injection (ICSI). Even in men who are azoospermic after cancer treatment, current data suggests that sufficient numbers of sperm can sometimes be obtained from testicular biopsy to make fertilisation of oocytes using ICSI possible.
The long-term health outcome of children born to cancer-survivors is thought to be very good, although there are few studies that have looked at this cohort specifically. However, singleton babies born through assisted conception (using frozen or fresh sperm) are healthy as their naturally conceived counterparts. There is increasing recognition that the major adverse outcomes are associated with multiple births.
Unfortunately, for pre-pubertal males who could not bank sperm, or in post-pubertal males who were too ill or where banking was not offered, there are no known therapies to stimulate sperm production if it does not return naturally at the end of treatment. In such cases, the use of donor sperm or adoption remains the only known methods to allow such men to establish families.

152 INVITED

Same Sex Couples Fertility Issues

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I have made a Pub Med database search to see if there are differences concerning fertility issues between same sex couples and heterosexual couples.
The review did not find any publications concerning same sex couples fertility issues.
There are no differences in how to preserve fertility in heterosexual- or same sex couples.
The differences concern the attention on homosexual realities and psychosocial needs.
It has been shown that providers not inquire about sexual orientation. Same sex couples were afraid to reveal their sexual orientation out of fear of stigmatization and homophobia.
It is of great importance that the ambiance in healthcare is open concerning sexual orientation and that health givers ask about sexual orientation to make same sex couples feel at ease and then dare to disclose their sexual orientation.

Special Session (Sun, 25 Sep, 13:15−14:15)
Esophageal Cancer − Ways to Improve Outcome

153 INVITED

How Radical Should Surgery Be?

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Esophagectomy for carcinoma can be viewed as being comprised of two components: resection of the esophagus and resection of the enveloping lymphatics. Controversy exists regarding how radical, or extensive these two components should be. Non-radical (standard) resection of the esophagus involves simple extirpation of the organ,

leaving behind adjacent peritumoral tissues and organs. Radical resection, or en bloc esophagectomy, removes all peritumoral tissues in addition to the esophagus. The extent of lymphadenectomy performed during esophagectomy is also highly variable, ranging from minimal to radical. A radical esophagectomy refers to a procedure by which the esophagus and its enveloping tissues are removed as a single specimen (en bloc), combined with either two-field (abdominal and mediastinal), or three-field (abdominal, mediastinal, cervical) lymphadenectomy. Nonrandomized comparative studies evaluating radical lymphadenectomy have reported mixed findings, with a number that have failed to identify a survival benefit, whereas some others have reported a benefit. An indirect evidence supports radical lymphadenectomy with an independent association found between the number of surgically removed lymph nodes and overall survival. Despite these data, the answer to this controversy should ideally come from prospective, randomized trials, since the phenomenon of stage migration may occur in comparison with non-randomized series of patients. In this regard, the only published phase III trial till this date compared non-radical transhiatal esophagectomy with transthoracic esophagectomy with two-field lymphadenectomy for patients with adenocarcinoma of the esophagus. The overall 5-year survival with the radical approach was 39%, compared with 29% for the patients undergoing the non-radical resection. Although not statistically significant due to underpowered study, many esophageal cancer specialists would consider less of an increase in survival to be clinically relevant. For squamous cancer there have been two small randomized controlled trials published. The first one compared 2-field lymphadenectomy to 3-field lymphadenectomy without significant 5-year survival difference (48% vs. 66%, respectively). The second one compared 2-field lymphadenectomy to lymph node sampling with a survival benefit favoring radical resection (36% vs. 25%). To conclude, radical transthoracic esophagectomy with two-field lymphadenectomy appears to offer an optimal balance between benefits and risks to a majority of EC patients, especially in the growing area of neoadjuvant treatments. Non-radical resection should be probably reserved for patients with a poor general status whereas 3-field lymphadenectomy may be reserved to selected patients with loco-regional disease in experienced hands, surely for patients with upper esophageal tumours.

154 INVITED

Neoadjuvant Treatment – Better Than Surgery Alone?

Abstract not received

155 INVITED

Will Centralization Improve Outcome?

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Oesophageal cancer particularly adenocarcinoma is increasing in incidence in the west. Resection of such tumours has been associated with significant morbidity and mortality and poor long term survival. In recent studies from the UK, Europe and USA improved outcomes for surgical resection have been achieved by centralisation of services to specialist centres. It appears that both surgeon and institution volume are equally important. This has achieved in hospital mortality figures of well under 5%. This may well be a combination of better staging and selection as well as improved technique and postoperative care.

Whether this improvement in short term outcome can be reflected in improvement in long term survival is not clear and there are conflicting results. Such an improvement will undoubtably be the result of better selection and staging, and the recruitment of patients into trials of multimodality treatment. It is suggested that radical surgery with extensive resection and lymphadenectomy will improve long term survival. There is little evidence to support this in oesophageal resection in contrast to radical gastrectomy.

The most important factors for improvement in outcome are a multidiciplinary approach with accurate staging, selection and multimodal therapy of a high standard.

Taking this approach over the last 20 years we have reduced inhospital mortality from 3.5% to 0.9% and 5 year survival from 28% to 48% with no significant change in stage of presentation but an increased use of preoperative chemotherapy from <10% to >90%.

Special Session (Sun, 25 Sep, 13:15–14:15)
Cross-Over in Trials

156 INVITED

Early Approval Versus Late Approval

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"Early approval" strategies include the "Conditional Marketing Authorisation" in the E.U. and "Accelerated Approval" in the U.S.A. Both mechanisms aim to license new drugs as early as possible in the development, while ensuring that confirmatory efficacy and safety data are duly submitted post-marketing. Regardless of the approval mechanism, sufficient data need to be available in terms of clinically relevant endpoints, to allow a benefit-risk assessment before an approval can be granted.

Acceptable primary endpoints for phase III studies for licensing include overall survival (OS) and progression-free survival (PFS) [1,2]. From the perspective of drug developers, the interest in PFS is because of the expectation that treatment effect will be numerically larger and quicker to observe compared to OS, making PFS an ideal candidate for "early approval" strategies. However, the general acceptance of PFS as a primary endpoint from a regulatory perspective is frequently debated. This is often due to difficulties in quantifying the clinical benefit of this radiological endpoint in the context of the benefit-risk balance assessment for regulatory decision. Furthermore, EMA guidelines recommend that when PFS is the chosen primary endpoint, sufficient data on OS have to be available at the time of assessment in order to at least rule out a negative effect. The analysis of OS can be done on the basis of planned secondary analyses or planned co-primary analyses.

Where one-way cross-over to the experimental arm after progression is considered appropriate (e.g. studies *v.* best supportive care with the possibility to switch to experimental treatment at time of progression), non-compliance with the randomized treatment is likely to hamper any subsequent comparisons in terms of OS. Currently, there is no general agreement on acceptable methods or modelling assumptions to correct for non-compliance for subjects who cross-over after progression. Thus, when PFS is the primary endpoint, there is a need to define situations and timing when cross-over is appropriate, to ensure adequately powered treatment comparisons, in accordance with the objectives of the study. The lack of well-powered OS analyses may be less of a concern when the treatment in terms of PFS is large or the expected OS after progression is short.

When the clinical relevance of PFS in its own right is questioned, this endpoint may still be used for "early approval" if it is considered to be a reasonably likely surrogate endpoint for OS. However, in these situations, conclusive results to confirm a benefit in terms of OS would be expected from relevant trials to be submitted post-approval. In this case, the timing of the post-marketing studies is critical, since "early approval" may again hamper the conduct of ongoing or subsequent randomized studies in the same indication.

Although at times relevant post-marketing studies can be conducted in related indications or combinations, there needs to be sufficient biological and pharmacological rationale to allow meaningful extrapolation of results across different settings.

In conclusion, when considering "early approval" strategies it is critical to consider the clinical relevance of the primary endpoint to allow a benefit-risk assessment at the time of approval, the appropriateness and timing of cross-over, and the feasibility of completing further studies post-marketing.

Publication disclaimer: The views presented here are personal and should not be understood or quoted as those of the European Medicines Agency.

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157 INVITED

Cross-over in Oncology Clinical Trials – Statistical Issues

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Background: Cross-over randomized clinical trials, where patients in one arm are allowed (or required) after some predefined time event to receive