ISSN 1751-4975

Oncology news

Volume 10 Issue 4 • September/October 2015 • www.oncologynews.biz

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ON THE COVER

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Reports from ESMO 17th World Congress on Gastrointestinal Cancer

Date: 1-4 July 2015; Barcelona, Spain.

PV-10 shows potential in hepatocellular carcinoma and metastatic liver disease

Two patients – one with hepatocellular carcinoma (HCC) and one with colorectal cancer (CRC) metastatic to the liver – had non-existent liver cancer at more than 40 months follow-up after a single liver injection of PV-10.

Treatment of HCC with chemotherapy, surgical resection, transplantation and other approaches (such as cryoablation, radiofrequency ablation, and chemo ablation) have increased overall survival, but remain suboptimal.


Eric Wachter

PV-10, a 10% solution of rose bengal originally used as a textile dye and later as an agent to stain necrotic tissue in the cornea, has demonstrated high rates of complete response and durable response in metastatic melanoma. In phase 2 data, presented at ESMO last October, 50% of a subgroup of 28 patients with stage III melanoma who had all their cutaneous lesions injected with PV-10 achieved a compete response and 71% achieved an overall response.

For the current study two cohorts of patients, one with non-resectable HCC (n=6 patients) and the second with other forms of cancer metastatic to the liver (n=7, 3 CRC tumours, 2 non-small cell lung, 2 melanoma and 1 ovarian) underwent a single percutaneous injection of PV-10 (dose 0.25 to 0.50 mL per cm^3 lesion volume) guided by CT to one liver target lesion. For the first analysis of five patients, two patients showed no evidence of disease at more than 40 months follow-up according to RECIST and EASL criteria. The first patient was a 68 year old male with HCC (hepatitis B + cirrhosis) alive at 54 months follow-up with no evidence of disease; while the second was a 61 year old male with metastatic CRC alive at 42 months follow-up with no evidence of disease.

Furthermore at up to 54 months follow-up, 10 out of the initial 13 patients were alive. Adverse events were generally limited to injection site reactions and photosensitivity and resolved without sequelae.

"Having liver cancer patients alive at up to 54 months of follow-up with no evidence of disease is remarkable. The study suggests that PV-10 has moved beyond just melanoma and may be agnostic to tumour type," says Eric Wachter (pictured), who co-developed PV-10, adding that the study represents the first report of a chemoablative effect for PV-10 outside melanoma

As with melanoma, the mechanism of PV-10 is believed to be due to local chemoablative effects where the agent enters lysosomes causing tumour necrosis that can stimulate immunological effects. In melanoma, patients injected with PV-10 have shown increased T cells in peripheral blood following injection including CD8+, CD4+, CD3+ and NKT.

Janet Fricker, Medical Journalist.

Reference

Poster Number: P-116. P Goldfarb, MD Russell Low, J Lyon, et al. Phase 1 Study of PV-10 for Chemoablation of Hepatocellular Cancer and Cancer Metastatic to the Liver.

Elderly HCC patients do better on sorafenib

Elderly hepatocellular carcinoma (HCC) patients treated with sorafenib demonstrate longer overall survivals than younger patients, reported the Italian cohort of the observational phase IV Gideon study.

Sorafenib is a multikinase inhibitor used for the treatment of unresectable HCC (uHCC). Two Phase III studies (SHARP and Asia-Pacific) demonstrated significant improvements in overall survival in uHCC patients, the majority of whom had Child-Pugh A with the result sorafenib is now suggested as first-line therapy in HCC patients with advanced-stage disease. The GIDEON study set out to evaluate the safety of sorafenib in uHCC patients under 'real-life' conditions and to gather more comprehensive data on use of sorafenib in patients with Child-Pugh B liver function who had been excluded from clinical trials. Since elderly patients are often underrepresented in clinical trials, the current analysis of the GIDEON study set out to evaluate the tolerability and efficacy of sorafenib in patients older than 70 years.

While the GIDEON study enrolled over 3200 patients to evaluate the safety and efficacy of sorafenib in real life clinical practice, the current analysis explored 278 patients in the Italian cohort, of whom 141 were older than 70 years and 133 younger than 70 years.

Results showed that the median overall survival was 10 months (8-18) months in the younger age subgroup versus 20 (12-23) months in older patients. Furthermore, elderly patients had a PFS of 6 months versus 4.1 months in younger patients; and elderly patients had a time to progression of 7.6 months versus 5 months for younger patients.

The type and incidence of adverse events (AE) serious and non-serious were similar in the younger and elderly subgroups and in line with the known safety profile of sorafenib. The most serious adverse events were gastrointestinal (diarrhea), dermatologic (hand-foot skin reaction/rash) and fatigue.

Elderly patients had longer overall survival, the authors suggest, due to more advanced disease in the younger subgroup.

Janet Fricker, Medical Journalist.

Reference

P-182 T Zolfino, V Lorusso, S D'Angelo, et al. Hepatocellular carcinoma in elderly patients: Final results of the Italian cohort of GIDEON study.

SIRFLOX: Longer PFS with First-Line SIRT in Patients with Liver-Only Metastases

BARCELONA—"First-line radioembolization in combination with bevacizumab and chemotherapy is able to retard progression in the liver, and it does seem to be safe," said Professor Chris Verslype, MD, a specialist in oncology and hepatology at University Hospital, Leuven, Belgium. Professor Verslype was commenting on results of the phase 3 SIRFLOX trial that valuated FOLFOX-based chemotherapy and bevacizumab with or without selective internal radiation therapy (SIRT) in metastatic colorectal cancer patients with liver-dominant metastases.


Guy van Hazel

SIRT is a minimally invasive technology approved for inoperable liver cancer in the European Union, the United States, Argentina, Brazil, Australia, and several countries in Asia. It delivers doses of radiation directly to the site of tumours through a hepatic artery catheter infusion of millions of radioactive (yttrium -90) resin microspheres (SIR-Spheres®). While sparing healthy tissue, the microsphere radiation selectively targets liver tumours with a dose of internal radiation up to 40 times higher than conventional radiotherapy.

At this meeting, Professor Guy van Hazel, University of Western Australia, Perth, updated and extended findings recently announced at the ASCO (American Society of Clinical Oncology) annual meeting, showing the addition of SIRT to have reduced disease progression in the liver by 31%. In the overall population receiving SIRT, the primary endpoint of progression-free survival (PFS) was not significantly longer in the SIRT plus bevacizumab and chemotherapy group (p=0.43).

The SIRT benefit in Professor van Hazel's new SIRFLOX data presentation was highly significant. The analysis pertained to 318 patients (159 FOLFOX + bevacizumab; 159 FOLFOX + bevacizumab + SIRT) who had metastases only in the liver. For them, PFS with SIRT added was 8.7 months longer (FOLFOX + bevacizumab 12.4 months; FOLFOX + bevacizumab + SIRT 21.1 months, hazard ratio 0.64, 95% confidence interval: 0.48-0.86, p=0.003). A further analysis of the impact of bevacizumab found that the cumulative incidence of disease progression in the liver was lower for patients receiving SIRT regardless of whether they had or had not received bevacizumab (p=0.018/p=0.028, respectively).

"Locoregional therapies like this," noted Professor Verslype, "are gaining interest due to the fact that the liver is the predominant site of disease for most of these [metastatic colorectal cancer] tumours."

Walter Alexander, Medical Journalist.

Meet the Editorial Team

Denys Wheatley
Editor

Profiles, signatures, patterns and motifs in screening for cancer

Life is complex, but when disorder and disease enter the fray, it becomes even more complex. Our bodies respond to change by adapting to achieve a reasonable level of homeostasis consistent with the prevailing conditions and circumstances. An infection changes our metabolic balance sharply and markedly, but after a time the body regains its composure; we regain our former healthy condition.

But the development of a cancer is not like the onset of an infectious disease. Many progress slowly, and even fast developing tumours can be relatively asymptomatic. The changes that occur in both cases might be subtle regarding the whole of our metabolome, although the possibility exists that metabolomics may help detect how the physiology of the body has been altered [1].

If we are suspicious that something is awry, the more concerned person will soon seek medical help, but many others will ignore changes and some even repudiate the possibility that they have a medical condition. Campaigns have helped to some extent to educate the general public about seeking early attention if they suspect a tumour might be developing [2]. A good example in the UK is the increase in awareness of prostate cancer ("Menunited"). Even so, many cancers can keep a low profile for weeks, months or years before progressing, and it might be difficult and too expensive to carry out many screening procedures in the hope of catching different types of cancer in their early stages. Detecting changes also means that these must be from a baseline. The medical profession knows that very many baselines (e.g. blood parameters) are averages over a broad range, and each needs to be determined first for the individual patient. If early detection is to be achieved on the basis of metabolic disturbances, one has to know what the situation was beforehand and follow up by sequential testing, along with a thorough knowledge of any symptomology. In a recent issue we learned about volatolomics, based on the findings of Hossam Haick [3], which might help in this respect because changes in volatile substances in the breath, urine or blood could aid detection of changes.

However, for many years since CEA was found, we have relied chiefly on biomarkers that might be directly associated with cancer, although this was misguidedly believed of PSA [4], emphasising the fact that "one swallow does not make a summer" – we need to get more markers and use associated tests in screening and early detection procedures. Can we find several biomarkers that are changed (usually increased) for each of the very many different types of cancers that arise? Undoubtedly so it would seem, which is why considerable media attention was given to the findings on one of the most aggressive types, pancreatic cancer, known to give only a short survival time [5]. In this case, three proteins could be found in the urine of early cases, Trefoil factor 1, lithostatine 1-α, and Regenerating Gene 1A. The results seem remarkable because the correlation was 95% accurate. This profile, signature, pattern or motif (call it what you will) indicates that there may be specific characteristics associated with a particular type of tumour. If this is the case for pancreatic cancer, it follows that the same could be true for many other types. Harping back to volatolomics, the hundreds of volatile compounds that can be detected do not have to be specifically identified; it is the pattern or profile that is more useful since they can be matched with different disease and hopefully cancers. The concern must be with false positive. On the biomarker side, while it is difficult to find a second that is well correlated with a particular type of tumour, finding 3 or more is even more arduous. It will require many exacting tests on the enormous number of permutations and combinations of proteins, factors, hormones, and even waste products needed to be analysed. This is where recognising changes in patterns or profiles come in since computerised analysis can reduce the number to a more manageable level. If the PSA situation could be followed up with several other substances that are found to be closely associated with prostate cancer to give a characteristic profile, this might greatly improve the early detection of a prevalent, and often unpredictable, cancer that is on the increase.

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Volume 10 Number 4 • September/October 2015

Oncology News is published by McDonnell Mackie, 88 Camderry Road, Dromore, Co Tyrone, BT78 3AT, N Ireland.

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Printed by: Warners Midlands PLC,
T: +44 (0)1778 391057

Are you organising an annual meeting or conference which you would like to tell our readers about?
Or would you like to write a report on a meeting or conference of particular interest?
If so, contact Patricia McDonnell at Oncology News on T/F: +44 (0)288 289 7023, E: patricia@oncologynews.biz

BNOS Annual Conference "Neuro-Oncology across the Ages"

Date: 1-3 July 2015. **Venue:** Nottingham, UK.

The British Neuro Oncology Society (BNOS) conference opened with the Education Day simulating the clinical challenges faced by Multi Disciplinary Teams (MDTs) in the young, adults, and elderly. After that there were all the usual plenary sessions, "Meet the Experts", proffered papers, posters and exhibitions by sponsors, plus a debate and role play.

We were delighted to welcome as invited speakers Mr Henry Marsh (St George's, London), Prof Jonathan Finlay (Columbus, Ohio), Prof Michael Weller (Zurich, EANO President), Dr Simona Parrinello (Imperial College, London), Dr Mathilde Chevignard (Hôpitaux de Saint Maurice, France), Dr Katherine Warren (National Cancer Institute, USA), Dr Helen Bulbeck (Brainstrust, UK), Glenis Wilmot (MEP, East Midlands) and Dr Ralf Herold (European Medicines Agency).

In addition to the invited speakers, there were several opportunities for those who had submitted abstracts (121 in total) to take part, with the added incentive of prizes for junior researchers.

- 13 abstracts were selected for rapid-fire 4-minute presentations on the Wednesday evening, giving mainly young researchers a chance to highlight their research. A prize was awarded to Miss Rebecca Lewis (Next Generation Sequencing informing diagnosis and prognosis).
- 28 abstracts were selected for 10-minute presentations across the themed sessions on Thursday and Friday. Prizes were awarded to Dr Matthew Baker (Stratified serum spectroscopic diagnostics) and Dr Ruhman Raham (Metabolomic and Phospho-proteomic heterogeneity).
- A further 8 rapid-fire 4-minute presentations were selected from the poster competition at lunchtime on Thursday for presentation later that afternoon. Miss Kate Hollinshead (IDH1 mutations and hypoxia) and Miss Durga Sabnis (Circumventing MGMT with new temozolomide analogues) gave winning presentations.

The Debate Panel

British Neuro-Oncology Society

We mustn't forget, of course, another vital ingredient: plenty of opportunity for networking at the social functions (a reception at an Elizabethan mansion surrounded by a deer park – complete with lessons in how to shoot a long bow, an opera singer, and the conference dinner at which we were entertained by a band called "The Spinal Chords"). It is difficult to summarise all the topics covered but major discussion points were:

- How to reduce morbidity in child patients. A scoring system for identifying medulloblastoma patients at greatest risk of cerebellar mutism syndrome and possible altered surgical practice. Impact of using a centralised review panel on resection in ependymoma.
- How to provide optimum treatment in the elderly; the need for new national standards.
- How to encourage data submission to the English National Cancer Registration Service over and above what is mandatory.
- Reinstatement of non-human primate studies prior to Phase I trials in order to conduct pharmacological studies, particularly in Diffuse Pontine Glioma.
- A review of ongoing trials, focussing on bevacizumab in relapsed GBM and rindopepimut, ICT-107 and Novocure's TTF-100A.
- The details of the Clinical Trial Regulation, which will replace the European Clinical Trials Directive in 2016.
- The top 10 clinical research priorities identified by the James Lind Alliance.
- Some of the latest techniques being developed to better characterise the biology of tumours.
- Exciting data arising from preclinical models investigating invasion/metastasis and new therapeutics approaches
- Rehabilitation and the impressive long term in- and out-patient rehabilitation, education and treatment facilities available in Paris.
- Communicating treatment options and implications to patients.

The panel in the Debate answered questions posed by the audience on the topic: "Are brain tumour services in the UK comparable to the rest of Europe?" The UK was thought superior in use of MDTs, availability of specialist nurses, a well-developed charity sector and its impact on decision-makers, and the existence of mandatory data collection. However, the UK was thought to be lagging behind in terms of diagnostic procedures, surgical technologies, post-operative MRIs, and patient recruitment into clinical trials. BNOS 2016 will be held from 29 June to 1 July in Leeds, UK.

Maryanne Roach on behalf of the BNOS Council and BNOS 2015 organising committee, July 2015.

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Substance-specific side effects: *Uncommon:* Hypotension; nausea, photosensitivity reaction, photodermatosis.
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TYAC conference: Genes, genetics and TYA cancer...from the science to the MDT

Date: 28-29 September 2015. **Venue:** Leicester, UK. Preview

Teenagers and Young Adults with Cancer (TYAC) is a multi-disciplinary membership organisation that brings together professionals involved in the care of young people with cancer. The fundamental aim of TYAC is to help professionals work together through the sharing of good practice, learning and networking.

TYAC will hold its first two-day conference Genes, genetics and TYA cancer: from the science to the MDT on 28 and 29 September 2015 at College Court Conference Centre in Leicester. Cancer genetics is currently a hot subject and a carefully tailored programme has been designed to meet the needs of the whole multi-disciplinary team, with the option of attending on either one or both days.

The event aims to provide an introduction to genetics and its application to cancer, explore the medical and psychological impact of inherited and non-inherited cancers on young people and their families and enable professionals to apply this knowledge to clinical practice with TYAs. Delegates will hear from world class speakers and young people as they share their knowledge and experiences and have the opportunity to join a lively discussion around whether genetic testing is right for everyone.

TYAC is also thrilled to have secured Toby Peach to speak at the conference dinner on Monday evening. Toby, a TYA cancer survivor, is a theatre maker and BBC Performing Arts Fellow in Community Theatre at The Old Vic. Toby will attend the TYAC conference fresh from the Edinburgh Fringe where he received rave reviews for 'The Eulogy of Toby Peach' – a play that follows Toby's journey with Hodgkin's Lymphoma, from diagnosis aged 19 years.

TYAC conferences are open to all professionals involved in the care and support of teenagers and young adults with cancer and are seen as an important forum for sharing knowledge and for networking with professionals from across the UK.

Find out more and register at: www.tyac.org.uk/conference

30th Anniversary British Lymphology Society Conference 2015

Date: 4-6 October 2015. **Venue:** Birmingham, UK. Preview

In November 1985; the British Lymphology Interest Group (BLIG) was formed in Oxford by professionals in the field – who identified that this area of medicine was being neglected. Their aims were to:

- Promote interest and co-ordinate a strategy for improving the management of lymphatic conditions, particularly lymphostatic disorders – lymphoedema.
- Alert the medical profession to the extent of the problem and patient requirements.
- Develop a register of centres providing treatment.
- Encourage research programmes which improve investigative techniques and treatment schedules.

One year later, BLIG held its first annual conference and AGM, in Oxford. It was organised by Professor Peter Mortimer (BLS patron) and Dr TJ Ryan. The British Lymphology Society (BLS) has continued to grow and is now celebrating its 30th anniversary! The current BLS constitution has built upon the initial aims:

1. To advance education and knowledge in the field of lymphology and related subjects.
2. To foster interest in and co-ordinate a strategy for improving the management of chronic oedema, particularly lymphoedema.
3. To produce and maintain a register of specialist centres in the United Kingdom and Ireland.
4. To benefit patients by improving the knowledge, expertise and skills of health care professionals treating them.

Our strap line encompasses our objectives – "Actively promoting professional standards".

Our annual educational and fundraising conference has grown year on year to include internationally renowned speakers – topics including surgical advances and the use of technology to improve lymphatic conditions. We now have 500 members and 30 corporate exhibitors – some of whom have remained loyal to the society for many years. We now include three charitable stands at a substantially discounted rate; as well as honouring our long-standing arrangements with colleagues in the National Lymphoedema Partnership, a BLS initiative.

The educational conference now attracts at least 10 continuing professional development points awarded by the Royal College of Physicians. This formal application is entirely based on programme content. We now offer awards and prizes to incentivise new research by our members.

2015 is our 30th anniversary year and we have been jointly campaigning with the Lymphoedema Support Network for a national strategy for lymphoedema in England. In March; during Lymphoedema Awareness Week; BLS members appeared on BBC Midlands Today to promote the campaign and the work of the British Lymphology Society.

Jane Durston, BLS Operations Manager

For further information visit: www.thebls.com

Clinical strategies for chemoprevention of breast cancer (Part 1)

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This is the first of a two part article on chemoprevention of breast cancer which will address the biological rationale for this strategy and relevant clinical trials to date whilst the second part will focus on current guidelines and discussion thereof.

Figure 1: Professor Antoine Lacassagne first proposed a therapeutic antagonist to"prevent the congestion of oestrone" in 1936.

Long term exposure to oestrogen is a well-established risk factor for breast cancer development and most of the non-hereditary risk factors for this disease relate to the hormonal environment either directly or indirectly [1]. Oestrogens increase the rate of cell proliferation by stimulating oestrogen receptor (ER)-mediated transcription which in turn increases the chance of more frequent errors of DNA replication [2]. In addition to these direct effects of oestrogen, there is evidence that metabolites of oestrogen are genotoxic depurinators that can directly remove base pairs from DNA which then becomes susceptible to point mutations consequent to defective DNA repair mechanisms. Therefore metabolites of oestrogen act in conjunction with ER-mediated events to induce breast cancer. Approaches to treatment and prevention of hormone-dependent breast cancer are based either on interference with the action of oestrogen at the cellular level or preventing/reducing oestrogen production. As long ago as 1936, Lacassagne (Figure 1) first proposed that if development of breast cancer was linked to an aberrant increased sensitivity to oestrogen, then an antagonist should be an appropriate strategy to prevent "congestion of oestrogen in the breast" [3]. It is now recognised that ER alpha binds oestrogen which accumulates in target sites (including mammary tissue and some breast cancers). Tamoxifen is a pioneering non-steroidal drug whose primary action is effected by competitively antagonising the interaction between endogenous oestrogen and ER. It is an example of a selective oestrogen receptor modulator (SERM), which is a group of triphenylethylene compounds with mixed oestrogen agonist/antagonist effects [4] (Figure 2). This duality of action renders these agents attractive for chemoprevention by virtue of their antiestrogenic properties in breast tissue and oestrogenic effects in bone. Raloxifene is another SERM which is a candidate for use in chemoprevention of breast cancer but it has a slightly different risk:benefit profile compared to tamoxifen and has now been evaluated in clinical trials. Use of aromatase inhibitors as chemopreventive agents is an alternative strategy based on reduction of peripheral oestrogen synthesis in post-menopausal women. Following cessation of ovarian function at the menopause oestrogens in post-menopausal women are derived mainly from peripheral synthesis in adipose tissue and the adrenal glands. The enzyme oestrogen synthetase (or aromatase) is present not only within these tissues, but also skeletal muscle and two-thirds of breast tumours and functions to convert androgenic precursors (testosterone and androstenedione) to oestradiol and oestrone respectively. This process of

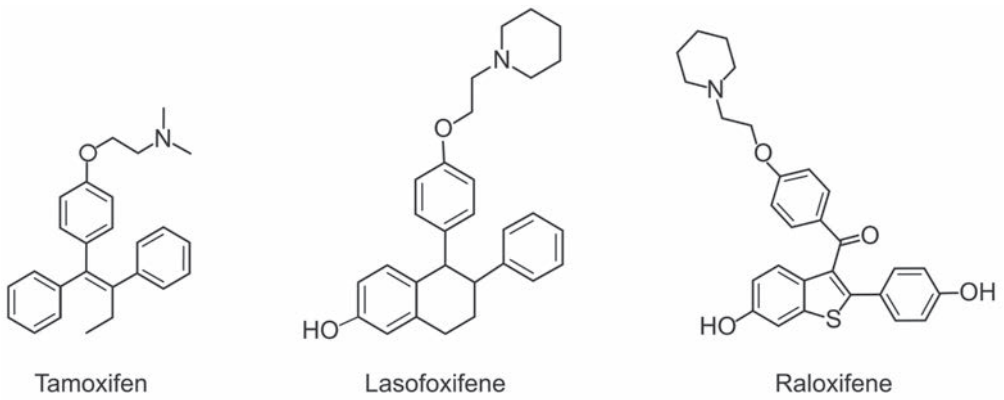

Figure 2: Selective oestrogen receptor modulators with potential chemopreventive action for reduction of breast cancer incidence

Table 1: Recommendations for chemoprevention in higher risk women		
	PRE-MENOPAUSAL WOMEN	POST-MENOPAUSAL WOMEN
USA	TAMOXIFEN * (20mg daily for 5 years)	TAMOXIFEN * (20mg daily for 5 years)
		RALOXIFENE** (60mg daily for 5 years)
		EXEMESTANE (25mg daily for 5 years)
UK	TAMOXIFEN* (20mg daily for 5 years)	TAMOXIFEN * (20mg daily for 5 years)
		RALOXIFENE** (60mg daily for 5 years)
* – no significantly increased risk of endometrial cancer or blood clots ** – no significantly increased risk of endometrial cancer [tamoxifen, raloxifene and exemestane taken as oral preparations]		

aromatisation in peripheral tissues releases relatively small amounts of oestrogen into the general circulation compared with ovarian sources in pre-menopausal women. However, local concentrations of oestrogen within the post-menopausal breast can reach levels comparable to the pre-menopausal state due to local production by breast adipose tissue supplemented by intra-tumoral aromatase activity.

Aromatase inhibitors block peripheral aromatisation of androgens and reduce both serum and intra-mammary tissue levels of oestrogen and have therapeutic efficacy in post-menopausal women only. Interestingly, SERMs only antagonise the action of oestrogens on ER positive cancer cells whilst (potentially carcinogenic) oestrogen metabolites remain unchallenged and can directly damage normal breast epithelial cells. An additional mechanistic benefit of aromatase inhibitors is blocking the formation of both oestrogen and its metabolites. This could render aromatase inhibitors true chemopreventive agents in the sense that they interfere with both the initiation (oestrogen metabolites) and promotion (parent oestrogen) of cancer [3]. These hormonal agents could potentially be employed either alone or combined with a SERM to maximise clinical benefits. Table 1 summarises the key studies to date on chemoprevention agents involving tamoxifen, raloxifene and aromatase inhibitors.

Selective oestrogen receptor modulators as chemopreventive agents

TAMOXIFEN

Tamoxifen has proven efficacy in treatment of breast cancer over the past 30 years, with significant increases in survivorship in ER positive patients receiving systemic adjuvant therapy [5]. Accrual of a vast clinical database underpinned by mechanistic evaluation from pre-clinical models and in vitro studies catalysed the exploration of tamoxifen as a chemopreventive in high risk women. The clinical rationale for this approach was further re-inforced by reduction in risk of contralateral breast cancer in adjuvant trials of tamoxifen [6]. Several placebo-controlled chemoprevention trials of tamoxifen in high risk pre- and post-menopausal women have revealed a reduction of about 50% (ranging from 31% to 67%) in the cumulative incidence of both invasive and non-invasive breast cancer at a median follow ranging from 96 to 158 months [7,8,9,10]. Primary effects are confined to ER positive disease with comparable benefits evident for white and black women in the NSABP P-1 trial but inconclusive data on the efficacy of tamoxifen for risk reduction in BRCA-1 and BRCA-2 gene mutation carriers [11]. Risk reductions in excess of 50% were noted for BRCA-2 but not BRCA-1 mutations carriers in the NSABP P-1 study which may relate to ER positivity of tumours in BRCA-2 carriers [7]. Moreover, recent data suggests that not only is tamoxifen effective during therapy, but chemoprevention is enhanced for many years following cessation of therapy with a carry-over effect. Longer-term follow up data is now available from the IBIS-1 trial which randomised high risk pre- and post-menopausal women to either tamoxifen (3579) or placebo (3575) [12]. Of note, some women had used hormone replacement therapy (oestrogen alone or combined) and about one-third had undergone hysterectomy. During the first 10 years of follow up, breast cancer incidence for tamoxifen and placebo arms was 4.6% and 6.3% respectively with a number needed to treat (NNT) of 59 women to prevent 1 breast cancer. At 20 years follow-up, these figures were 7.8% (95% CI 6.9 – 9.0) and 12.3% (95% CI 10.1 – 14.5) respectively with the NNT having fallen to 22 (95% CI 19 – 26). There is a sustained benefit from tamoxifen with incidence curves remaining divergent. This important observation demonstrates the continuing anti-tumour action of tamoxifen at a time when there are very few side effects (e.g. weight gain, hot flushes) from the drug and therefore a highly favourable therapeutic index. Increased risks of thromboembolism were seen only during treatment with tamoxifen in the IBIS-1 trial and no significant cardiac side-effects were reported from a 5 year pulse of tamoxifen. Indeed, the side effect profile of tamoxifen and other potential agents are crucial considerations in the chemopreventive setting when the risk:benefit ratio is shifted and healthy women receive a pharmacological intervention for which the benefits are less tangible in the absence of any validated biomarker of response. A modest increase in endometrial cancer in postmenopausal women has been well documented with relative increases of 2.53 and 1.45 in the NSABP P-1 and IBIS-1 trials respectively A total of 29/3579 and 20/3575 women in tamoxifen and placebo groups respectively developed endometrial cancer in the IBIS-1 trial and most of these cases occurred during the first 5 years [7,10]. Nonetheless, neither this problem nor any significantly elevated risk of thromboembolism has been noted in premenopausal women [13].

RALOXIFENE

Concerns over an increased incidence of endometrial cancer amongst post-menopausal women taking tamoxifen have led to re-assessment of other non-steroidal antioestrogens with attenuated uterotrophic activity in the rodent uterus. The recognition that tamoxifen and raloxifene were selective oestrogen receptor modulators (SERMs) with oestrogenic effects in bone created a new dimension in therapeutics which has been exploited in current chemoprevention strategies. If a SERM is oestrogenic in bone but antioestrogenic in breast tissue, then perhaps a SERM could be used to prevent osteoporosis with concomitant prophylaxis

of breast cancer in postmenopausal women. Raloxifene has been successfully tested for reduction of fractures in women at high risk for osteoporosis and has been confirmed to significantly reduce the incidence of ER positive breast cancer (58% risk reduction) in those patients receiving long term raloxifene for prevention of breast cancer [14,15]. These encouraging findings combined with the desire to minimise overall side effects sporned the Study of Tamoxifen and Raloxifene (STAR) trial, a head-to-head comparison of tamoxifen and raloxifene as chemopreventive agents in higher risk postmenopausal women [16]. Initial analysis performed at a median follow up of 4.6 years showed that raloxifene was equivalent to tamoxifen in reducing the incidence of ER positive breast cancer by 50%, but was less effective in prevention of non-invasive disease. Raloxifene may therefore interfere with progression of in situ to invasive disease, but have no impact on the pre-malignant to in situ transition. Raloxifene had a more favourable side effect profile with marginally yet statistically significant reductions of thromboembolic events (deep venous thrombosis only), cataracts, lens replacement, benign uterine hyperplasia and endometrial cancer (more than half the patients had undergone prior hysterectomy in the STAR trial) [16]. Interestingly, with slightly longer follow up (6 years) there is some attrition in the efficacy or raloxifene relative to tamoxifen with the former associated with significantly increased risk of invasive breast cancer (RR 1.24) and a non-significant increased risk of ductal carcinoma in situ (RR 1.22) [17,18]. A further update of the STAR trial was presented at the American Society of Clinical Oncology (ASCO) meeting earlier this year and confirmed that these results remain consistent [19].

LASOFOXIFENE

The Post-menopausal Evaluation and risk Reduction with Lasofoxifene (PEARL) trial assessed one of the newer SERMs (lasofoxifene) against placebo [20]. This trial specifically evaluated the benefits of lasofoxifene in terms of reduced fracture rates (vertebral/non-vertebral) together with the incidence of ER positive breast cancer and showed risk reductions for breast cancer (79%), vertebral fractures (42%), coronary events (32%) and stroke (36%) [21].

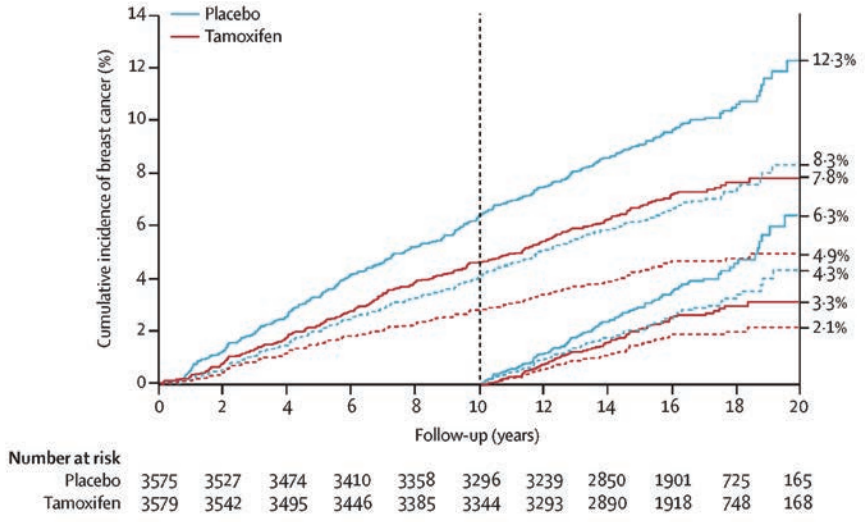

Figure 3: Cumulative incidence of breast cancers for tamoxifen and placebo groups (solid lines = all breast cancers; dashed lines = ER positive cancers) Cuzik J et al. Lancet Oncol 2015; 16: 67 – 75 Figure 1, page 70. Reproduced with permission of *The Lancet Oncology.*

Aromatase inhibitors as chemopreventive agents

Aromatase inhibitors (alone or sequenced before/after tamoxifen) have been shown in clinical trials to have marginally improved anti-tumour efficacy than tamoxifen alone and are associated with notably greater reductions in contralateral cancer (up to 70% compared with 50% for tamoxifen) [22]. Although aromatase inhibitors are associated with a lower risk of thromboembolism compared with tamoxifen, there is an increased risk of fractures, osteoporosis, arthritis, and arthralgias. Indeed, patients consistently report a higher incidence of musculoskeletal symptoms and these can be troublesome for older women. The potential side-effect profile of aromatase inhibitors has led to some caution in pursuance of chemopreventive strategies based on these agents. Use of aromatase inhibitors in this context may be premature in the absence of longer term data on side-effects including not only musculoskeletal symptoms but also elevated cholesterol and neurocognitive problems (memory loss, attention span, executive functioning and word finding). Nonetheless, two trials have specifically addressed the benefit of aromatase inhibitors in the chemopreventive setting and the most recent update of the ASCO guidelines on pharmacological interventions for breast cancer risk reduction lists an aromatase inhibitor as a chemopreventive option [23].

ANASTROZOLE

The International Breast Cancer Intervention (IBIS –II) study randomised 3,864 high risk (strong family history of breast/ovarian cancer, lobular carcinoma in situ, ductal carcinoma in situ and proliferative disease with atypia) postmenopausal women to receive either 5 years of anastrozole (1mg daily) (n=1,920) or placebo (n=1,944). Compliance rates were 72% and 68% for anastrozole and placebo respectively and at a median follow up of 5 years anastrozole was associated with halving of breast cancer risk (hazard ratio 0.47, 95% CI 0.32 – 0.68; p<0.0001) (Figure 3); 40 deaths were recorded in the anastrozole group compared with 85 for placebo. Moreover, only 10% of excess musculoskeletal side-effects in the anastrozole group were attributable to aromatase inhibitor therapy and there was a small non-significant increase in fracture rate (8.5% versus 7.7%). Both musculoskeletal symptoms and fracture rates were remarkably similar between the treatment and placebo groups – indicating that women reported relatively high levels of symptoms in the placebo group. Approximately half the women in both groups reported musculoskeletal and vasomotor symptoms with about one-fifth experiencing significant gynaecological problems [24].

EXEMESTANE

The other aromatase inhibitor chemoprevention trial (MAP3) examined the benefit of exemestane (25 mg daily for 5 years) versus placebo in a randomised comparison of 4,560 post-menopausal women at increased risk of breast cancer. With a limited median follow up of 3

years, there were 32 cases of invasive breast cancer in the placebo group compared with 11 amongst 2,285 women receiving exemestane, representing a 65% reduction in risk of breast cancer [25]. Interestingly, exemestane did not impact upon the incidence of non-invasive cancer thereby contrasting with IBIS-II but echoes results of the raloxifene arm in the STAR trial. Side effects of aromatase inhibitor therapy were generally reported as not severe with hot flushes and joint pains being relatively common but no increased incidence of osteoporosis, fractures or deaths from any cause. In particular, there were no significant increases in bone fractures, hypercholesterolaemia or cardiovascular events attributable to exemestane which has some bearing in terms of choice of aromatase inhibitor for any proposed chemoprevention trials. It should be noted that supplemental vitamin D and calcium did not prevent age-related bone loss in the MAP-3 trial [26]. This trial also demonstrated the benefit of exemestane in reducing risk of contralateral disease in women who undergo mastectomy for ductal carcinoma in situ (DCIS).

LETROZOLE

The non-steroidal aromatase inhibitor letrozole is currently being evaluated in a couple of smaller trials in the United States. The randomised double-blind LIBER trial is investigating use of this agent for prevention of breast cancer in post-menopausal women who are BRCA-1 or BRCA-2 mutation carriers whose cumulative lifetime risk is 56 – 80%. The intervention group will receive letrozole (2.5mg daily) for a total duration of 5 years (versus placebo) as a potential alternative strategy to either anastrozole or exemestane [27].

FENRETINIDE

Fenretinide is a vitamin A analogue shown to inhibit breast carcinogenesis in pre-clinical studies. Veronesi and colleagues conducted a randomised trial to assess the efficacy of this agent in prevention of second malignancies in women with early breast cancer. Almost 3,000 women who had undergone surgical resection for stage I breast cancer or DCIS were randomised to receive either 5 years of fenritinide orally (200 mg/day) or no treatment. There was no difference in the incidence of contralateral or ipsilateral breast cancer between the two groups, although a posthoc analysis revealed benefit amongst pre-menopausal women with a significant reduction of second breast cancers in this group which persisted for several years after cessation of treatment. These results have prompted arguments for a trial of fenretinide in young women at high-risk of developing breast cancer, although it is no longer under development as a chemopreventive agent [28,29].

Impact of chemoprevention on mortality

Despite almost 20 years of follow up within the IBIS-1 trial, it remains too early to conclude whether chemoprevention with tamoxifen will impact upon mortality as only 5 deaths from breast cancer have so far been reported (RR 1.19) [22]. Moreover, both this and other chemoprevention trials have limited power to detect potential reductions in mortality (primary endpoint was reduction of incidence rather mortality).

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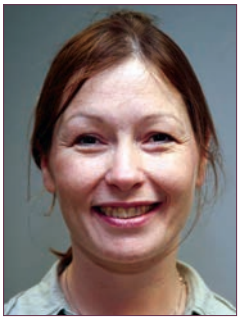
Diet and lifestyle after a breast cancer diagnosis



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Diet, lifestyle and breast cancer

Data from Cancer Registries attest to global variations in cancer incidence and mortality supporting the notion that the risk of developing breast cancer correlates with environment and, somewhat more controversially, the likelihood of developing recurrent disease. Studies of migrants have shown that when individuals move from an area of low incidence to an area of higher incidence and adopt Western modes of behaviour both in terms of diet and lifestyle, the incidence increases to approximately that of the host nation after few generations. Alongside this, improved survival rates after a breast cancer diagnosis is not only attributed to advances in multimodality treatment but also to the actions of patients seeking to change their behaviours in order to improve their likely long term outcomes. Our experience with the DietCompLyf cohort showed that significant dietary changes occur 12 ± 3 months after diagnosis [1]. It is important to note that the challenge for healthcare professionals is to make sense of evidence which is often heterogeneous; dietary effects may be both positive for some diseases but negative for others. Therefore it is difficult to interpret data, and to guide patients who are notable in their desire to adopt changes.

Any investigation concerning diet is multifactorial, and this gives rise to a particularly difficult area to research, fraught with methodological issues and difficulties in standardisation. The misinterpretation of scientific data as well as a desire to label foods as "bad" or "evil" means that "at risk" groups of individuals (as well as patients) can be subjected to mixed messages around diet and lifestyle.

Last year, the much awaited "Continuous Update Project – diet, nutrition, physical activity and breast cancer survivors" from the World Cancer Research Fund reported continued issues with the design of studies and the manner in which some research was undertaken and reported few relationships between diet and lifestyle and breast cancer survivorship. Recommendations include maintaining "a healthy body weight, being physically active, eating foods containing fibre, eating foods containing soy, a lower intake of total fat and, in particular, saturated fat" [2]. Put simply, advice to patients focus on behavioural traits associated with a healthy dietary and lifestyle habits, without labelling any components as taboo.

Weight gain and obesity

A recent analysis of data from GLOBOCAN, by Arnold et al in the *Lancet Oncology* [3] estimated the relative risk of developing cancer based on particular population attributes. In the period from 2002-2012 it was estimated that approximately 3.6% of all new cancers in adults >30 years of age were likely to be attributable to a high body mass index (BMI >25 kg/m^2). Alongside this, the World Health Organisation reported that in the Americas, European and Eastern Mediterranean regions over 50% of women are overweight and that approximately half of the overweight women are obese [4]. The association between increasing BMI, the risk of developing breast cancer and poorer breast cancer survival means that preventing weight gain and obesity are of particular importance in breast cancer prevention. Nevertheless, advice needs to be personalised in order for it to be adopted to good effect.

Steroid hormone production by adipose tissue

The production of oestrogens by adipose cells and their role in post-menopausal breast cancer has been recognised for many years. Less well-studied is the importance of androgens produced by adipose cells. Approximately 85% of breast cancers are reported to express androgen receptor (AR) the intracellular receptor responsible for the downstream action of androgens. Activated AR has been implicated in cell signalling via FOXA1, PI3K/AKT/MAPK, PTEN, p53 pathways which have all been shown to be altered in breast cancer [5]. Adipose tissue of the breast has been shown to contain testosterone and oestrogen hormone levels supporting the concept of an "obesity-inflammation-aromatase axis" within the breast with the potential to promote breast cancer development [6]. Many overweight and obese individuals are also type-2 diabetics. The chronic inflammatory phenotype associated with type-2 diabetes alters circulating steroid hormone levels (both oestrogens and androgens) and increases insulin and insulin-like growth factor (IGF) levels [7]. In terms of breast cancer development, insulin receptor phosphorylation has been shown to promote mammary tumourigenesis [8] but the role of insulin-like growth factor receptors (IGF-1R/IGF-2R) is less clear.

The potential for a biological effect resulting from hyperinsulinemia acting in a synergistic

Images by Martha Slater

manner with steroid hormones shows the difficulties in studying this area of biology as well as the importance of considering the interplay between hormones and growth factors on individuals at the systemic level. Nevertheless, dietary advice for breast cancer needs to be consistent with advice for other co-morbidities such as diabetes or cardiovascular disease.

Alcohol and breast cancer

In the UK approximately 70% of women between 45-64 years of age and >60% of those aged 65 years or more consume alcohol. There is a dose-dependent relationship between alcohol consumption and breast cancer risk with 25g/day consumption associated with a relative risk of 1.25; 50g/day consumption a relative risk of 1.55 and so on [9, 10]. This has led to an interest in the mechanism(s) underlying the associations between alcohol consumption and breast cancer. Plausible explanations include free radical production during the metabolism of ethanol, increased concentrations of circulating sex-hormone levels and impaired removal of androgens by the liver [11] following alcohol usage.

A significant association between breast cancer mortality and frequent heavy-drinking has been reported [12] but the effect on recurrence rates of low/moderate alcohol consumption is less clear [13-16]. Accordingly, it may be beneficial to focus on patterns of drinking (for example the relevance of binge drinking) as well as the alcohol type consumed rather than on the sole amount of ethanol ingested. The observation that even light/moderate alcohol consumption can lead to an increase in breast cancer recurrence in post-menopausal women with an increased BMI suggests that applying the precautionary principle in this group of patients is warranted [17].

Phytoestrogens and breast cancer

The importance of oestrogen in the development and progression of breast cancer is also well recognised. Phytoestrogens are naturally occurring dietary compounds with structural similarities to 17β-oestradiol, they fall into two main categories: isoflavones (conventionally found in Eastern diets) and lignans (conventionally found in Western diets). Phytoestrogens bind to ERα/ERβ and increased dietary consumption is associated with a reduced risk of developing breast cancer.

The relationship between phytoestrogen consumption and breast cancer prognosis is not; however, entirely clear [18]. The multi-centre UK based DietCompLyf study has been established to determine the role of phytoestrogen consumption on breast cancer recurrence rates [19] and takes into account the consumption of both isoflavones: mostly found in soy based products, legumes, coffee and nuts; as well as lignans: mostly found in berries, nuts, seed, whole grains and some alcoholic beverages. Five-year follow up has been completed for the 3,159 patients on the DietCompLyf study and the findings will be reported soon.

Dietary advice for breast cancer patients

When advising breast cancer patients about diet it is important to remain aware that all nutrients have functionality and their inclusion must be considered within the confines of an energy balanced diet. The importance of providing information to patients around diet and lifestyle was our motivation in developing the "Breast Cancer Cookbook" (see opposite page) which is due to be published in October of this year [20].

Dietary recommendations need to be made according to the groups of nutrients consumed. For example, advice around "reduction of intake of saturated fat" will relate to more than 12 different fatty acids, each with different functionality, the basis being to prevent excessive energy intake. Similarly, promotion of exercise mitigates cancer risk through both weight reduction as well as by lowering the levels of circulating oestrogens. It is imperative to be aware that no single foodstuff is known to cause (or prevent) cancer from developing or recurring but evidence has identified some foods (and nutrients) which should be eaten in small proportions, or completely avoided, to minimise risks.

Although minimal evidence links intakes of trans fatty acids to cancer outcomes, the use of artificial sources of fats increases the total cholesterol and lower high density

lipoprotein "good" cholesterol. Similarly, whilst intake of red meat can have positive impacts on iron (and therefore energy) levels, over-cooking is linked to increased levels of heterocyclic amines and polycyclic aromatic hydrocarbons, accordingly, boiling, steaming or stewing methods should be recommended. Preservatives used in the production of processed meats including bacon and ham are thought (but not proven) to be carcinogenic [21, 22]. More typically, guidelines suggest a reduction in intakes due to the high saturated fat, energy or salt levels. It is pragmatic to recommend restricted intakes of processed meats therefore, to perhaps a maximum of 20 g/day. Similarly, dietary choices should avoid intakes of refined processed carbohydrates as these can be associated with high blood glucose levels and consequently elevated insulin concentrations, a known risk factor for breast cancer development (described above).

Since the central premise of any sustainable diet is balance – patients are advised to comply with the consumption of five portions a day (400g) from as diverse a range of fresh fruit and vegetable products as possible including tomatoes: a powerful source of the antioxidant lycopene; cruciferous vegetables, an excellent source of phytonutrients; dark green leafy vegetables rich in folate; wholegrain, nutrient-rich starchy staples and sufficient protein to enable repair of damage imposed by cancer treatments.

It is recommended that milk and dairy products are also consumed on a daily basis to promote bone health, and omega-3 rich oily fish (selected from sustainable sources see http://www.sustainweb.org/sustainablefood/plenty_more_fish_in_the_sea/) is recommended weekly to decrease inflammation and contribute a dietary source of vitamin D (promoting calcium absorption). Olive oils are recommended due to the higher than typical monounsaturated fat content which can prevent oxidative processes. The elevated risks from osteoporosis after breast cancer treatment and the need for exercise to keep inflammatory responses down means that carefully constructed fitness regimens (taking into account any risk of fractures) may be warranted.

Recognising that many patients seek to make changes in their diet and lifestyle after a breast cancer diagnosis, clear nutritional guidance is required. Comprehensive elucidation of the effects of single foods and nutrients for cancer outcomes is unlikely given the complexities of diet and eating patterns. The advice outlined here is evidence-based and scientifically justified, following the premise that all foods and nutrients can add benefits to our diet. Patients are urged to reflect on the need for balance in their food choices; mindful that diet and lifestyle choices will influence their health and enjoyment of what they eat.

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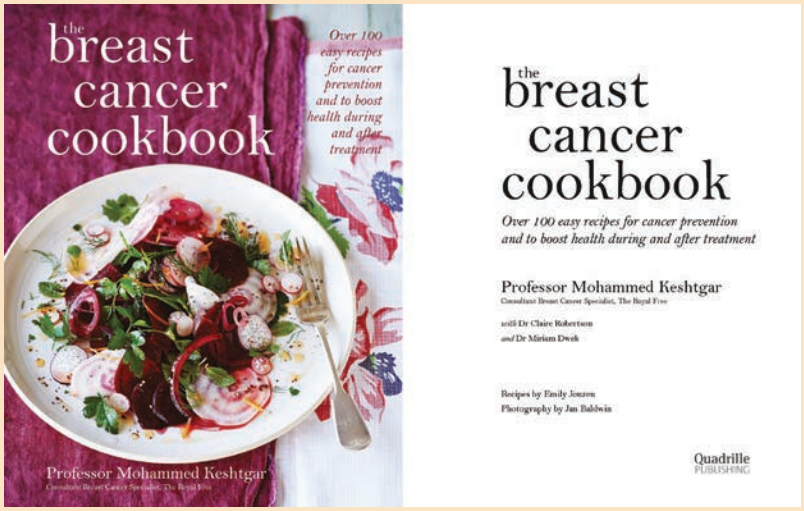
The Breast Cancer Cook Book



This Cookbook by Keshtgar, Robertson and Dwek is based on the latest scientific evidence and the authors' extensive experience, which takes you through the lifestyle influences and foods that can play a positive role in the prevention and treatment of breast cancer, encouraging readers towards a healthier diet.

There is an introductory chapter describing breast cancer in an easy to understand way and explaining the evidence on the effects different diet and food products. Over 100 inviting, simple recipes to help cancer prevention and to boost health during and after treatment follow this.

These are especially created to take in all the dietary considerations linked to breast cancer and possible side effects of treatment. Covering breakfasts, soups, salads, fish and shellfish, poultry and meat, vegetarian dishes, desserts, treats and drinks, they make for a healthy, satisfying way of eating.

Publisher: Quadrille. Price £20. www.quadrille.co.uk

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What the new NICE guidelines would mean for the early diagnosis of carcinoma of the penis

Women have overcome the embarrassing factors when talking about intimate cancers, in favour of the high levels of awareness and many support networks now associated with them.

Breast cancer and cervical cancer are two such cancers, which are now openly discussed amongst the public and in the media, and have significant charity backing and provisions for patients and their families. Sadly, men and some male-specific cancers are lagging behind. Whilst prostate cancer ,and to a lesser extent testicular cancer, have increasing levels of awareness, there is one male cancer which remains taboo, penile cancer. Whilst some may say that the levels of awareness reflect the incidence rates, I believe that awareness is key for patient outcome, particularly with penile cancer, which is one of the last unspoken cancers.

If the NHS follows up on the NICE guidance released in June 2015 to help early diagnosis of cancer, this could be a major breakthrough for the early diagnosis of carcinoma of the penis, but with one major caveat. Men must be more willing to talk about the signs and symptoms, and present themselves earlier, if the new symptoms-based approach to diagnosis is to be most effective.

Why are the new guidelines so important for penile cancer?

NICE has stated [1] that 5,000 lives in England alone could be saved if the NHS follows up on its new guidelines for early diagnosis of cancer, targeting patients who present at primary care level with symptoms that seem to be non-specific. It has listed guidelines for 37 cancers, including penile cancer, recommending appropriate treatments and considering cancer as a possible cause of the symptoms earlier on in diagnosis.

Whilst this is a positive step for all of the 37 cancers listed in the guidelines, this is particularly encouraging for penile cancer patients due to common misdiagnosis of the disease. According to recent findings [2], cases of penile cancer have soared by 20% in the past 30 years, one reason being frequent misdiagnosis of an STI. A review of referrals to the penile cancer clinic at Clatterbridge has shown that hold-ups in diagnosis can be due to referrals to dermatology or plastic surgery. These factors, along with the embarrassment factor and lack of awareness amongst men, lead to an average delay in presentation of symptoms of about six months. Anything that can be done amongst GPs to reduce this delay could drastically improve outcomes for patients.

Research shows that there are more challenges than most when presenting with penile cancer symptoms

In 2009, studies were carried out into public awareness of cancer in Britain [3] that could provide a baseline for government policy initiatives regarding campaigns on cancer awareness and early diagnosis. Some of the findings show why penile cancer awareness and presentation is starting from such a low starting-point.

First, it was recognised that men were more likely to delay presenting with symptoms than women, but awareness of risk factors was also a cause for concern. Recognition of HPV infection as a risk factor of cancer was the lowest recalled in both surveys used to compile the report. In the study, unprompted recall of HPV as a risk factor was as low as 1%, whilst prompted recognition was 26%, the lowest of all the presented risk factors.

HPV is a common infection passed by sexual contact, of which there over

100 types. For most people, the virus is harmless and will vanish without treatment, but men with HPV have an increased risk of developing cancer of the penis. Studies found that approximately 47% of men with penile cancer showed evidence of HPV infection [4]. Circumcision seems to reduce the risk of HPV infection of the penis.

HPV vaccine could be a possible solution, but this is not being considered for adolescent boys until 2017 according to a recent ruling by the Joint Committee of Vaccination and Immunisation (JCVI), which has since outraged GPs. Giving boys the same vaccination as girls now receive for cervical cancer could be another preventive measure for penile cancer. However, at present, male HPV vaccination solely for the purpose of preventing penile cancer cannot be recommended due to a lack of clear data that shows its benefit. In terms of cost efficacy, male vaccination solely for the prevention of penile cancer would be untenable, given the rarity of the disease.

Clinical trials for penile cancer

Along with other centres in the UK, The Clatterbridge Cancer Centre is currently taking part in two multi-centre clinical trials for penile cancer. VinCaP is currently investigating the chemotherapy drug, vinfluinne, for cancer that has spread beyond the penis to other parts of the body. The second, soon to open at Clatterbridge, is JAVA-P, which is investigating the chemotherapy drug, cabazitaxel, in relapsed or locally advanced cancer of the penis.

Conclusion

The new NICE guidelines recommend a suspected cancer pathway referral (for an appointment within two weeks) when an STI has been ruled out or treatment has been completed, or for any unexplained or persistent symptoms affecting the foreskin or glans.

It is hoped that these guidelines, if pursued, will uncover earlier cases of penile cancer, with swift diagnosis being key to treatment. But men will first need to overcome the embarrassment associated with penile cancer if the available help is to be most effective.

About penile cancer

Penile cancer is a relatively rare form of the disease. In the UK, around 550 men are diagnosed with it every year, mostly in the over 60's age-group. Despite it being much less common than prostate or testicular cancer, its incidence is increasing, for unknown reasons; however one reason could be down to changing sexual practises and involvement of the same HPV virus that relates to cervical cancer in women.

References

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2. http://www.nhs.uk/news/2014/02February/Pages/penis-cancer-cases-up-20-percent-between-1979-and-2009.aspx
3. http://www.cancerresearchuk.org/sites/default/files/public_awareness_of_cancer_in_britain_dh_report.pdf
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ESMO launches Women for Oncology Award

The European Society for Medical Oncology (ESMO) has launched the ESMO Women for Oncology Award to recognise an ESMO member who has significantly contributed to supporting the career development of women in oncology. Every year this important accolade will acknowledge someone who has actively worked to sensitise organisations to perceive the female oncology workforce as a valuable resource.

ESMO President Rolf A Stahel announced the new award at ESMO 2014: "The ESMO Executive Board has decided to promote women for leadership in a new way and I am very proud to announce for next year [2015] the launch of the ESMO Women for Oncology Award, aimed to recognise contributors who support the development of women in oncology."

All ESMO W4O activities are led by the newly established ESMO Women for Oncology Task Force, chaired by Solange Peters, ESMO Executive Board member: "ESMO Women for Oncology is a dynamic network of women oncology professionals, united by common challenges and common objectives: pursue a successful scientific professional career and be placed to be part of the leaders of tomorrow, by sharing experiences, collaborate on new projects and exchanging ideas."

The W4O Award will be presented for the first time this year during the ESMO Women for Oncology Session on 27 September 2015 during ECC 2015 [1].It will be bestowed on Enriqueta Felip (pictured right), a medical oncologist who kick-started awareness of the dearth of women oncologists in leadership roles. Dr Felip collected information about the lack of women leaders to give a lecture at ASCO 2013 on the challenges and keys to success for women in academic oncology, which triggered the at that time ESMO President Martine Piccart to create the ESMO Women for Oncology initiative.

"I feel this is not an award specifically for me but for all women professionals working day to day in oncology," said Felip. "I have been fortunate in having the opportunity to work on several ESMO initiatives in which I have always felt I was a relevant part of the team. This award is a way to highlight the importance of the role of women in academic oncology."

[1] The first ESMO Women for Oncology Award will be presented to Enriqueta Felip during the ESMO Women for Oncology Session on Sunday, 27 September 2015, 13:00-14:30, Stolz 2, during ECC2015.

Journal of Clinical Oncology

Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach – the ALBI grade

Johnson PJ, Berhane S, Kagebayashi C, et al. Journal of Clinical Oncology 2015; 20 Feb; 33(6):550-8.

Purpose: Most patients with hepatocellular carcinoma (HCC) have associated chronic liver disease, the severity of which is currently assessed by the Child-Pugh (C-P) grade. In this international collaboration, we identify objective measures of liver function/dysfunction that independently influence survival in patients with HCC and combine these into a model that can be compared with the conventional C-P grade.

Patients and Methods: We developed a simple model to assess liver function that involved only serum bilirubin and albumin levels, based on 1,313 patients from Japan with HCC of all stages. We tested the model using similar cohorts from other geographical regions (n=5,097) and clinical situations (patients undergoing resection [n=525] or sorafenib treatment for advanced HCC [n=1,132]). The specificity of the model for liver (dys)function was tested in patients with chronic liver disease but without HCC (n=501).

Results: The model, the Albumin-Bilirubin (ALBI) grade, performed at least as well as the C-P grade in all geographic regions. The majority of patients with HCC had C-P grade A disease at presentation, and within this C-P grade, ALBI revealed two classes with clearly different prognoses. Its utility in patients with chronic liver disease alone supported the contention that the ALBI grade was indeed an index of liver (dys)function.

Conclusion: The ALBI grade offers a simple, evidence-based, objective and discriminatory method of assessing liver function in HCC that has been extensively tested in an international setting. This new model eliminates the need for subjective variables, such as ascites and encephalopathy, a requirement in the conventional C-P grade.

Reviewer's opinion: The majority of cases of HCC arise on a background of chronic liver disease, most often hepatic cirrhosis. HCC has become one of the leading causes of mortality in cirrhotic patients in recent times. Even though the multi-targeted tyrosine kinase inhibitor, sorafenib, has proved to be modestly effective in advanced (Stage C) HCC, several subsequent Phase III studies of other targeted therapies (such as brivanib) have been negative and progress has been slow. The rationale for this very interesting study was that the Child-Pugh-Turcott classification of chronic liver disease was developed to stratify risk in patients undergoing surgery for bleeding oesophageal varices over three decades ago and therefore might not be the most appropriate tool in patients with advanced HCC not undergoing surgery. Also, in the CPT classification, two variables are inter-related (ascites and low albumin), and assessment of mild encephalopathy and severity of ascites can be subjective. This study showed that the ALBI grade (calculated solely using serum albumin and bilirubin levels) performed at least as well as the Child-Pugh grade in predicting survival in European, Japanese and Chinese patients with cirrhosis with or without HCC. Of particular relevance to clinical trials of systemic treatment in HCC, in patients with CP grade A cirrhosis and HCC, the ALBI grade delineated two distinct groups in terms of survival with ALBI grade 1 patients having a median overall survival of 86 and 25 months in the Japanese and European cohorts compared with 55 and 15 months in ALBI grade 2 patients. Similar findings were validated in patients treated with sorafenib for advanced HCC in clinical trials. The implications of these data are that with use of the ALBI score rather than Child-Pugh grade, selection of patients for trials of systemic therapy in HCC may be refined and lead to more positive studies in this difficult-to-treat cancer. – AR

Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor

Kochenderfer JN, Dudley ME, Kassim SH, et al. Journal of Clinical Oncology 2015; 20 Feb; 33(6):540-9.

Purpose: T cells can be genetically modified to express an anti-CD19 chimeric antigen receptor (CAR). We assessed the safety and efficacy of administering autologous anti-CD19 CAR T cells to patients with advanced CD19+ B-cell malignancies.

Patients and Methods: We treated 15 patients with advanced B-cell malignancies. Nine patients had diffuse large B-cell lymphoma (DLBCL), two had indolent lymphomas, and four had chronic lymphocytic leukemia. Patients received a conditioning chemotherapy regimen of cyclophosphamide and fludarabine followed by a single infusion of anti-CD19 CAR T cells.

Results: Of 15 patients, eight achieved complete remissions (CRs), four achieved partial remissions, one had stable lymphoma, and two were not evaluable for response. CRs were obtained by four of seven evaluable patients with chemotherapy-refractory DLBCL; three of these four CRs are ongoing, with durations ranging from 9 to 22 months. Acute toxicities including fever, hypotension, delirium, and other neurologic toxicities occurred in some patients after infusion of anti-CD19 CAR T cells, but these toxicities resolved within three weeks after cell infusion. One patient died suddenly of an unknown cause 16 days after cell infusion. CAR T cells were detected in the blood of patients at peak levels, ranging from 9 to 777 CAR-positive T cells/μ L.

Conclusion: This is the first report to our knowledge of successful treatment of DLBCL with anti-CD19 CAR T cells. The results demonstrate the feasibility and effectiveness of treating chemotherapy-refractory B-cell malignancies with anti-CD19 CAR T cells. The numerous remissions obtained provide strong support for development of this approach.

Reviewer's opinion: The corner-stone of treatment of B-cell malignancies has been multi-agent cytotoxic chemotherapy (sometimes including stem cell transplantation), supplemented by the anti-CD20 monoclonal antibody rituximab since 1997. Survival remains poor for disease refractory to two lines of chemotherapy or recurs after stem cell transplantation, so that many alternative treatment strategies are being sought. A recently approved therapy is blinatumomab, a bispecific T-cell engager that binds to CD19 on the target tumour cell and activates T-lymphocytes via CD3. This study clinically evaluated the adoptive transfer of transgenic autologous T-lymphocytes expressing a CD19-specific

single-chain variable fragment and the intracellular signaling domains of CD3 (ζ chain) and the co-stimulatory molecule CD28 after gamma-retroviral transduction in patients with heavily pretreated (range: 1-12 regimens) B-cell malignancies, including diffuse large B-cell lymphoma, chronic lymphocytic leukaemia, primary mediastinal B-cell lymphoma and splenic marginal-zone lymphoma. Patients also received lymphodepleting chemotherapy prior to the cellular product to generate a homeostatic 'drive' to expansion of the infused cells, but did not receive exogenous IL-2. There are several interesting points in this study. The ability to generate sufficient peripheral blood mononuclear cells for viral transduction after apharesis in patients who had received so much chemotherapy and who generally had lymphopenia is noteworthy. The efficiency of transduction was also high, with a mean of 70% of T-cells expressing the chimeric construct. About a third of the chimeric-antigen-receptor (CAR) expressing T-cells showed a central memory phenotype. Thirteen out of 15 patients were evaluable for response and 12 of these showed complete or partial responses. Nine patients have ongoing responses, many already lasting over 12 months. Toxicity was manageable and transient, and included features of the cytokine-release syndrome, such as fever and hypotension in most patients, although some patients developed a variety of neurological deficits, including aphasia, myoclonus, facial nerve palsy, tremor, confusion and apraxia. CSF analysis of these patients demonstrated T-cells expressing the chimeric antigen receptor gene despite lack of CD19 expression in multiple brain regions. The ability of the infused T-cells to reach their targets was demonstrated in one patient with a large cervical nodal mass due to chronic lymphocytic leukaemia where 30% of tumour-infiltrating T-cells expressed the transgene. The levels of CAR-positive T-cells in peripheral blood peaked at 7-17 days and CAR-positive T-cells developed a more differentiated phenotype with time. It will be of great interest to see if CAR transduced T-cells can be used to treat other malignancies with targets other than CD19, such as Her2Neu. – AR

New England Journal of Medicine

Pembrolizumab for the treatment of non–small-cell lung cancer

Garon EB, Rizvi NA, Hui R, et al for the KEYNOTE-001 Investigators; N Engl J Med 2015; 372:2018-28; May 21, 2015; DOI: 10.1056/NEJMoa1501824.

Background: We assessed the efficacy and safety of programmed cell death 1 (PD-1) inhibition with pembrolizumab in patients with advanced non–small-cell lung cancer enrolled in a phase 1 study. We also sought to define and validate an expression level of the PD-1 ligand 1 (PD-L1) that is associated with the likelihood of clinical benefit.

Methods: We assigned 495 patients receiving pembrolizumab (at a dose of either 2mg or 10mg per kilogram body weight every three weeks or 10mg per kilogram every two weeks) to either a training group (182 patients) or a validation group (313 patients). We assessed PD-L1 expression in tumour samples using immunohistochemical analysis, with results reported as the percentage of neoplastic cells with staining for membranous PD-L1 (proportion score). Response was assessed every nine weeks by central review.

RESULTS: Common side effects attributed to pembrolizumab were fatigue, pruritus, and decreased appetite, with no clear difference according to dose or schedule. Among all the patients, the objective response rate was 19.4%, and the median duration of response was 12.5 months. The median duration of progression-free survival was 3.7 months, and the median duration of overall survival was 12.0 months. PD-L1 expression in at least 50% of tumour cells was selected as the cut-off from the training group. Among patients with a proportion score of at least 50% in the validation group, the response rate was 45.2%. Among all the patients with a proportion score of at least 50%, ➤

What If?

Still from Terry Burke's film for What if? 2012

What if? is a Gallery Exhibition of nine films made by nine women diagnosed with breast cancer. The films form part of a three-year research project at the University of Westminster that questioned the ethics of representing and making visible the lives of those with illness.

Breast cancer is a highly visible disease within the population, but much knowledge of individual experience is often either lost or generalised, concealed by conventional research and filmmaking practices that are rarely challenged. A heavy reliance on predetermined themes, questionnaires and even scripts, and a tendency to submit to persuasive narratives to appeal to audiences and broadcasters, often characterise established production processes. Individual testimonies are frequently compressed to easily consumed sound bites, bolstered using 'expert' voices, and subjugated to director's views and/or broadcast agendas.

The women were diagnosed with breast cancer nine to 36 months prior to commencement of the research. They were invited to take part from support and community groups, and were self selecting. Each was given a camera and asked to film whatever was important to them. They kept the cameras for an average of 10 months. All were invited to take part in the editing process.

Contrasting experiences, lifestyles and attitudes led to the production of nine highly personal films, and a vast body of experiential knowledge. The film-making process demonstrated that approaches using traditional investigative practices may fail to give true insight into the lived experience of breast cancer. Most women found taking part in the project a highly therapeutic process.

What if? brings together all nine films as a Gallery Exhibition. It ran at London Gallery West, University of Westminster, for three weeks from 26th June – 19th July attracting large audiences. The Exhibition is set to tour other UK cities.

Christine Douglass, Centre for Research and Education in Arts and Media, University of Westminster.

Professor Joram ten Brink, Centre for Research and Education in Arts and Media, University of Westminster.

Dr Miriam Dwek, Reader in Biochemistry, Cancer Research Group Leader, Department of Biomedical Sciences, University of Westminster.

median progression-free survival was 6.3 months; median overall survival was not reached.

Conclusion: Pembrolizumab had an acceptable side-effect profile and showed antitumour activity in patients with advanced non–small-cell lung cancer. PD-L1 expression in at least 50% of tumour cells correlated with improved efficacy of pembrolizumab.

Reviewer's opinion: The role of immune system in the development and progress of cancer is complex. Similarly, the ability of our immune system to recognise tumour cells and tumour associated antigens is poorly understood. However, due to recent advances in genomic profiling leading to better understanding of the importance of driver mutations in the development of cancer and advances in the understanding of cellular mechanisms, the therapeutic options for cancer patients is dramatically improving. Development of targeted therapy along with significant progress in the understanding and development of immunotherapeutic agents in hematological malignancies, prostate cancer and malignant melanoma has markedly changed the management outcome for many individuals. Recent developments in tumour immunotherapy have resulted in the identification of several effective agents for the control of non-small cell lung cancer. Some of these agents have been already approved and Pembrolizumab (anti-PD1/PDL-1) is a new addition. The above data not only confirms its activity in NSCLC, but provides support for the importance of identification of markers and patient selection. A response rate of 45% in tumours expressing PDL-1 in 50% or more cells with acceptable side effects is encouraging. Tumour immunotherapy due to availability of T-cell checkpoint inhibitors like Pembrolizumab, Nivolumab and MPDL3280A is here to stay. These breakthroughs are going to bring exciting time for patients, clinicians and pharmaceutical industry alike in the near future. – SU

To have your event listed in the Oncology News diary, E: patricia@oncologynews.biz by October 5th 2015.

2015

September

NEW
Managing Oral Complications in the Cancer and Palliative Care Setting
7 September 2015; London, UK
E: conferenceteam@rmh.nhs.uk
T: +44 (0)20 7808 2921
W: www.royalmarsden.nhs.uk/studydays

The Royal College of Radiologists Annual Scientific Meeting
7-9 September 2015; London, UK
E: conf@rcr.ac.uk
W: www.rcr.ac.uk/asm

NEW
1st Turkish-Azerbaijani Oncology Conference
10-13 September 2015; Baku, Azerbaijan-Baku
W: http://1atoc.org/

NEW
BTOG Bone Disease Study Day 2015
11 September 2015; London, UK
British Thoracic Oncology Group
T: +44 (0)116 2502811
E: dawn.mckinley@uhl-tr.nhs.uk
W: www.BTOG.org

NEW
Paediatric Oncology Solid Tumours Study Day
14 September 2015; London, UK
E: conferenceteam@rmh.nhs.uk
T: +44 (0)20 7808 2921
W: www.royalmarsden.nhs.uk/studydays

NEW
Lung Cancer Study Day
14 September 2015; Manchester, UK
E: education.events@christie.nhs.uk
W: www.christie.nhs.uk/school-of-oncology/education-and-training.aspx

NEW
Cancer Vaccines
16-17 September 2015; London, UK
W: www.smi-online.co.uk/pharmaceuticals/uk/conference/cancer-vaccines

NEW
The International Cancer Careers Conference
19 September 2015; Manchester, UK
E: education.events@christie.nhs.uk
W: www.christie.nhs.uk/school-of-oncology/education-and-training.aspx

NEW
Introduction to lymphoma
21 September 2015; Belfast, UK
E: healthprofessionals@lymphomas.org.uk
W: www.lymphomas.org.uk/health-professionals

ORBS International Scientific Meeting 2015
21–23 September 2015; Nottingham, UK
W: www.orbsmeetings.com

Head and neck
23 September 2015; Manchester, UK
E: conf@rcr.ac.uk
W: www.rcr.ac.uk/oncologyevents

European Cancer Congress 2015
25-29 September 2015, Vienna, Austria
W: esmo.org

NEW
Targeted Treatment for Cancers of the Digestive System: A Bird's Eye View
28 September 2015; London, UK
T: +44 (0)20 7808 2921
E: conferenceteam@rmh.nhs.uk
W: www.royalmarsden.nhs.uk/studydays

Trainee in Difficulty
29 September 2015; London, UK
E: conf@rcr.ac.uk
W: www.rcr.ac.uk/radiologyevents

European Cancer Congress 2015
25-29 September 2015; Vienna, Austria
W: esmo.org

NEW
Challenges in Palliative Care: Building from a new foundation
30 September 2015; Glasgow, UK
T: +44 (0)1489 565475
E: vanessa@compleatconference.co.uk
W: www.apmonline.org

October

NEW
Manchester Melanoma Surgical Meeting
1 October 2015; Manchester, UK
E: education.events@christie.nhs.uk
W: www.christie.nhs.uk/school-of-oncology/education-and-training.aspx

NEW
The choice to die at home – a reality or an aspiration? Does hospice at home hold the key? – NAHH Annual Conference
1-2 October 2015; Leeds, UK
T: +44 (0)1489 565475
E: kate@compleatconference.co.uk
W: http://nahh.org.uk/about-us/conferences/

NEW
The Eighth Annual Royal Marsden Breast Cancer Meeting: Hot Topics in Breast Cancer
2 October 2015; London, UK
E: conferenceteam@rmh.nhs.uk
T: +44 (0)20 7808 2921
W: www.royalmarsden.nhs.uk/conferences

NEW
BLS 30th Annual Conference 2015
4-6 October 2015; Solihull, UK
W: www.thebls.com

NEW
Introduction to Paediatric Cytotoxic Medication Study Day
6 October 2015; London, UK
E: conferenceteam@rmh.nhs.uk
T: +44 (0)20 7808 2921
W: www.royalmarsden.nhs.uk/studydays

NEW
Advanced Clinical Practice Endocrinology Masterclass
7 October 2015; Manchester, UK
E: education.events@christie.nhs.uk
W: www.christie.nhs.uk/school-of-oncology/education-and-training.aspx

BACR Breast Cancer Meeting
7-9 October 2015; Gateshead, UK
E: bacr@leeds.ac.uk

NEW
ESSO Course on Peritoneal Surface Malignancy
8-9 October 2015; Manchester, UK
E: education.events@christie.nhs.uk
W: www.christie.nhs.uk/school-of-oncology/education-and-training.aspx

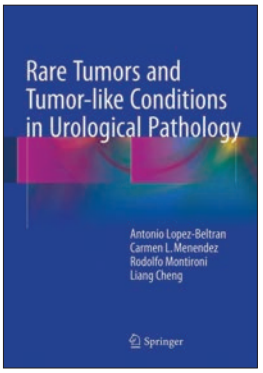
NEW
SIOP 2015 Congress
8-11 October 2015;
Cape Town, South Africa
W: www.siop-online.org

20th World Congress on Advances in Oncology & 18th International Symposium on Molecular Medicine
8-10 October 2015; Athens, Greece
E: conference@spandidos-publications.com
W: www.spandidos-publications.com

NEW
2nd Ovarian Cancer Forum of Ireland
9 October 2015; Enniskillen, UK
Lisa Gill E: lisa.gill@roche.com

Rare Tumors and Tumor-like Conditions in Urological Pathology

Lopez-Beltran A, Menendez CL, Montironi R, Cheng L. Published: Springer International Publishing. ISBN (Hardcover): 978-3319102528. Price: £126.00 ISBN (eBook): 978-331910253-5. Price: £119.70.



This is the first edition of *Rare Tumors and Tumor-like Conditions in Urological Pathology* from Springer International Publishing. The authors are Antonio Lopez-Beltran, Carmen L. Menendez, Rodolfo Montironi and Liang Cheng. The preface states that this book '..is a comprehensive guide to rare tumors and tumor-like conditions of the urinary system and male genital organs'.

The book is divided into five main chapters (kidney, bladder, prostate, testis and penis). Each chapter leads off with a basic overview and looks at the more common tumour types. However the bulk of each chapter focuses on the rarer tumour types and tumour-like conditions. For example less than half a page is dedicated to 'conventional renal cell carcinoma', but one and a half pages concentrate on 'MiT family translocation renal cell carcinoma'. The text describing each disease entity is very easy to read and understand as it is bulleted, so there is no 'waffle' to wade through before getting to the pertinent points. This really does save time! The text is also very up-to-date, with the inclusion of recent immunohistochemical stains and details on molecular genetics where appropriate. The text is also well referenced. The images are plentiful and well displayed. There are also numerous helpful tables summarising current staging and grading systems and immunohistochemistry panels.

This book is relatively comprehensive and the layout means it is fantastic as a reference source. However, there are occasions where a little more detail is required and a more substantial text would have to be referred to. The only other drawback that I have found is the fact that there is no index at the back of the book. Each chapter has a detailed contents section, but it would be much quicker and easier to be able to find a particular disease entity within an index section.

Overall I feel that the book achieves its stated goal of being an 'ideal source of core information and practical guidance for residents, fellows, pathologists, urologists, and oncologists'. This book is priced at £126 through Amazon and I feel that this represents value for money.

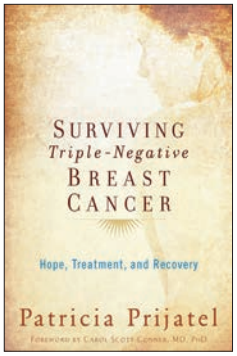
Dr Charlie Tilley, MB BS BSc MRCS FRCPath,
Consultant Histopathologist,
University Hospital Southampton.

Surviving Triple-Negative Breast Cancer: Hope, Treatment, and Recovery

Patricia Prijatel. Published by: Oxford University Press. ISBN: 978-0-19-939385-5. Price: £12.99.

This 223 page book is written by Patricia Prijatel, a journalist who developed triple negative breast cancer. Prijatel's experience of the cancer spurred her to research the disease and present the information in the form of a book; dedicated to patients, carers and family. It is written in a chatty, non-medical style, part memoir of her experiences as a patient in the USA where healthcare provision is vastly different to that of the UK.

Remarkably Prijatel has researched an enormous amount of medical information about breast cancer; in particular aetiological, biological and pathological information. Chapter 5, Treatment: Your Options discusses surgery, chemotherapy, radiation and biological therapies. I feel that this chapter highlighted the differences between oncological treatments in the USA and that of the UK where treatment is standardised within cancer networks, is protocol driven and is decided at a multidisciplinary level. However the morbidity of particular chemotherapy regimens was not discussed, nor mention of supportive therapies to reduce the side effects of chemotherapy. From an oncologists viewpoint there was no mention of performance status or past medical history which are crucial considerations when deciding on which chemotherapy regieme to employ. Overall I feel that one may derive an over simplistic view of the management of chemotherapy.



Prijatel also focuses on the holistic aspect of well being; diet, exercise and relaxation. The chapter is well referenced with examples of level 1 evidence.

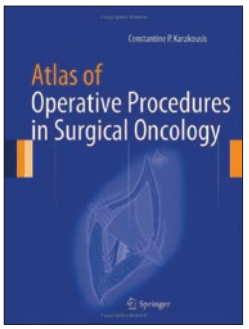
Chapter 6: The Positives of Healthy Living examines the role of exercise, physical activity, weight control and diet in maintaining a healthy lifestyle. I felt that much of the advice was sensible however undue emphasis was placed in certain areas; caffeine and vitamin D for instance, where the findings were not clear cut and conflicting evidence presented may appear confusing to the lay person. Chapter 7: My Life Right Now explores how the author has come to terms with the diagnosis and the uncertainties of the future and the dreaded possibility of disease recurrence.

On the whole this book is a remarkable achievement for a patient with no prior medical knowledge, who has undergone the ordeal of diagnosis and treatment whilst making the most of living in the present. It is very informative and will help to supplement information provided to the patient and carers by the medical professional.

Dr Karin Baria,
Retired Consultant Clinical Oncologist.

Atlas of Operative Procedures in Surgical Oncology

Constantine P Karakousis. Published by: Springer. Cost: 124.79. ISBN: 978-1-4939-1633-7.



Written by Contantine Karakousis, an experienced cancer surgeon from New York, USA, this 397-page hardback book is based on the *Atlas of Operations for Soft Tissue Tumors* published 30 years ago. This publication has added to the original book and new chapters added.

The book is aimed at the surgeon who manages patients with malignancies of the abdomen, retroperitoneum, pelvis and the extremities. It is also useful as a reference text to the Clinical Oncologist as it demonstrates the operative field, and enables one to appreciate the area or volume of tissue to be encompassed by the post-operative radiation field, if required.

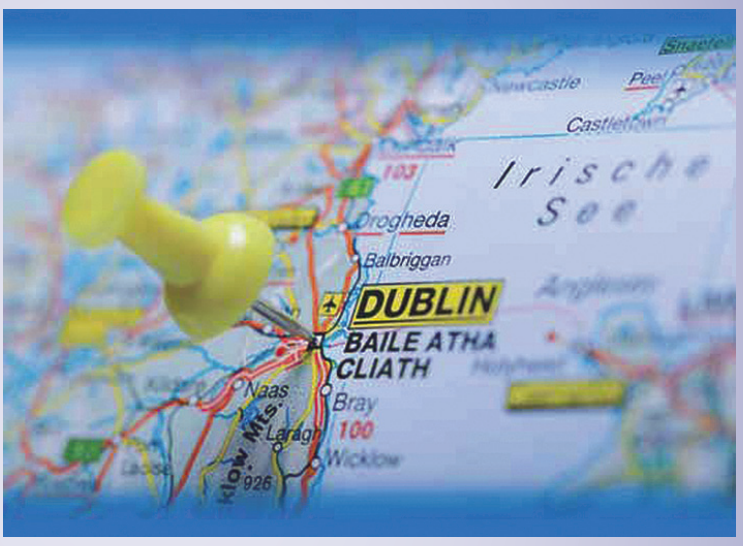
There are 57 chapters the majority of which are anatomy based. The book is illustrated with hundreds of beautiful, clear diagrams as well as many photographs of the operative field and clinical specimens, X-rays and other imaging. The reader is taken through the operation by the text, and illustrations of each stage of the procedure are shown. Patient positioning on the operating table, the choice of incisions, the dissection, post-operative care and complications are discussed in detail for each tumour site. I found the text to be well written and easy to read. The author demonstrates his vast surgical experience as he discusses the relevant surgical points. Karakousis also reports on rates of success and morbidity for each procedure. This book provides information on the important general surgical principles for approaching tumours in many locations and gives necessary the details for the safe and oncologically sound resection of these tumours. In essence it offers a practical "hands on" guide to dealing with soft tissue tumours and resections of demanding procedures such as hind quarter amputations which will be dealt with in specialist centres and this book provides an insight into how these operations are to be performed. A list of references or suggested reading is given for each chapter. Other chapters include Intraoperative Lymphatic Mapping/ Sentinel Lymphadenectomy, Regional Chemotherapy Infusion Via the Hepatic Artery, and Central Venous Access. My impression is that this is a useful book for the surgical oncologist and a good resource for the library.

Dr Karin Baria,
Retired Consultant Clinical Oncologist.

BTOG 2016

14th Annual BTOG Conference 2016

Wednesday 27th January to Friday 29th January – Dublin



BTOG Chair, Dr Sanjay Popat

Feedback from BTOG 2015

"I like the multidisciplinary aspect and opportunity to learn from other specialties."

"Excellent conference with a good range of speakers from all the different disciplines and audience members."

"Fantastic mix of all aspects of Thoracic Cancer management – BTOG feels like all the good bits of a massive MDT meeting with added social aspects."

"An excellent learning forum, with pertinent and up-to-date presentations which were evidence based topics and news on current studies and trials."

IMPORTANT DATES

Poster submission: Opens 1st August 2015 • Closes 1st October 2015

Registration and hotel booking opens 1st September 2015

BTOG is a multi-disciplinary group for professionals involved with thoracic malignancies.
BTOG aims to improve the care of patients with thoracic malignancies through multidisciplinary education, developing and advising on guidelines for patient care and facilitating and nurturing clinical trial ideas into full protocols.
BTOG Chair: Dr Sanjay Popat

BTOG Secretariat

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Latest developments on products and services from the industry. To have your news included contact Patricia McDonnell at Oncology News on T/F: +44 (0)288 289 7023, E: patricia@oncologynews.biz

Provectus taking novel path to treat cancer

Rather than taking a biochemistry approach to develop drugs that kill cancer cells, Provectus Biopharmaceuticals is using physical chemistry by harnessing the unique properties of Rose Bengal, a first-in-class halogenated xanthene.

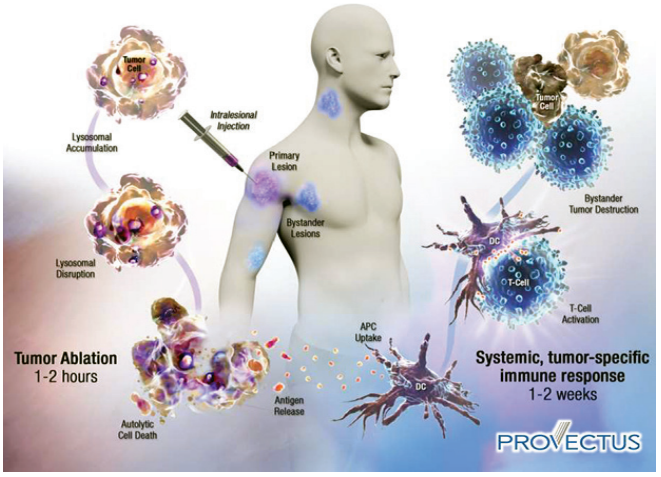
"We are taking a different type of molecule and a different basis for the mechanism of action than has been used in the industry," Peter Culpepper, CFO and COO, said in an interview with BioTuesdays.com.

"Our PV-10 drug candidate has the potential to be employed in the treatment of all solid tumour cancers like melanoma, liver and breast, without the typical safety issues, as demonstrated thus far in clinical testing," he contended. "Those are the cancers we're focusing on."

In addition, he said PV-10, which recently entered Phase 3 testing for the treatment of melanoma, has the potential to be used before, during and after surgery, and in combination with other therapeutic agents and therapies, and after all else fails. The technology is protected by some 60 US and international patents.

PV-10 is a new category of ablative immunotherapy made from an active ingredient, Rose Bengal, which has a long history of clinical use and an established FDA safety profile in liver and ophthalmic diagnostics, Mr Culpepper pointed out. "We are the first company to use Rose Bengal as a therapeutic."

For further information visit www.pvct.com



Provectus Biopharmaceuticals' poster presentation on PV-10 clinical data from phase 1 study for cancers of the liver presented at 17th World Congress on Gastrointestinal Cancer

Provectus Biopharmaceuticals, Inc have announced that the abstract titled, "Phase 1 Study of PV-10 for Chemoablation of Hepatocellular Cancer and Cancer Metastatic to the Liver," was presented at the European Society for Medical Oncology's 17th World Congress on Gastrointestinal Cancer. Sanjiv S Agarwala, MD, of St Luke's University Hospital and Health Network, Bethlehem, PA, was the presenter.

Dr Craig Dees, PhD, CEO of Provectus, said, "We are very pleased that Dr Agarwala presented this important information to the World Congress on Gastrointestinal Cancer. While our research into PV-10 as a treatment for melanoma continues, we are equally committed to determining its safety and efficacy in the treatment of other types of cancer. We are optimistic that PV-10 will prove to be a useful weapon against a wide variety of cancers."

PV-10, a 10% solution of Rose Bengal that is currently being investigated as a potential cancer therapeutic, is designed for injection into solid tumours (intralesional administration).

For further information visit www.pvct.com

PROVECTUS BIOPHARMACEUTICALS, INC.

Almac Group announce companion diagnostic partnerships with OncoMed

Almac Diagnostics announced recently that it has enteed into an agreement with OncoMed Pharmaceuticals, Inc to develop a companion diagnostic test to help predict a patient's likelihood of responding to OncoMed's novel therapeutic which targets R-Spondin 3 (RSPO3). Anti-RSPO3 (OMP-13R10) has demonstrated activity in preclinical models against a variety of major tumour types, including colon, lung and ovarian cancers.

Almac and OncoMed are currently developing a gene expression RSPO3 CLIA assay that can be used to prospectively select patients in the clinical development of anti-RSPO3. OncoMed has filed an Investigational New Drug (IND) application for anti-RSPO3 with the US Food and Drug Administration and a Phase 1a clinical trial is due to commence in summer 2015.

"We are very pleased to announce this partnership with OncoMed who we have worked with for many years. This companion diagnostic development program is a significant milestone in our work together and helps Almac achieve its goal of advancing human health globally," said Professor Paul Harkin, President of Almac's Diagnostic business unit.

For more information visit www.almacgroup.com or E: media@almacgroup.com.

ALMAC
Partnering to Advance Human Health

Devon Oncology Consortium leads the way with ChemoCare V6, the future of Chemotherapy ePrescribing

CIS Oncology is delighted to announce that the Devon Oncology Consortium is upgrading to its web-based ChemoCare V6 solution. The Consortium, comprising of South Devon Healthcare NHS Foundation Trust, Royal Devon and Exeter NHS Foundation Trust and Northern Devon Healthcare NHS Trust has chosen to deploy the latest version of CIS Oncology's ChemoCare product to help work towards a paperless NHS and further enhance patient safety.

ChemoCare is the system of choice for chemotherapy prescribing in over 70 per cent of UK hospitals. ChemoCare V6 provides a multi-device, web-based platform to ensure clinical service flexibility and technology compliance, enabling chemotherapy services to develop in line with the national requirements set out in the commissioning service framework.

A wide range of new features include an enhanced Drug Administration Module (including dual signature functionality) and full support for use on tablets, including touch screen functionality. In addition, ChemoCare V6 allows further integration with clinical portals to encourage joined-up healthcare - including textual laboratory results, real-time treatment summaries and A&E notifications. The solution also incorporates interaction checking and allergy registration via a link to Multilex, provided by First Databank (FDB).

Martyn Blundell of South Devon Healthcare NHS Foundation Trust says: "We have worked with CIS Oncology for many years and enjoy an excellent relationship with them. We are really excited about deploying ChemoCare V6, which we see as a vital step towards a paperless environment – a key driver for our Trust. ChemoCare V6 meets all our requirements and our prescribers are really looking forward to starting out on the road to a paper free setting."

Other exciting developments within ChemoCare V6 include the new Personalised Medicine Module (PMM) which simplifies the process of ordering & receiving genomics testing for adult and paediatric oncology & haematology, available as stand alone product or integrated into the ChemoCare pathway. PMM has been developed in conjunction with CIS Oncology's partner laboratory, a major NHS Genomics test laboratory. When integrated with ChemoCare, the PMM provides interpreted results at the point of prescribing, thus enabling the seamless review of genomic test results with the prescribing system.

For further information, please contact Nick Walker, Sales Director of CIS Oncology on +44 (0)7717 794340 or nick.walker@cis-healthcare.com

Abstract on Provectus Biopharmaceuticals' PV-10 in colon cancer models published by Society of Surgical Oncology

Provectus Biopharmaceuticals, Inc have announced that the Society of Surgical Oncology (SSO) has published an abstract describing preliminary research into use of the Company's investigational agent, PV-10, in murine models of colon cancer. A poster based on the published abstract was presented at the SSO's 68th Annual Cancer Symposium.

Titled, "Intralesional Injection of Rose Bengal Induces an Anti-tumor Immune Response and Potent Tumor Regressions in a Murine Model of Colon Cancer," the abstract detailed research by K Pardiwala, G Qiao, J Sundararajan, B Prabhakar, and AV Maker at the University of Illinois at Chicago, Chicago, IL.

Based on their findings, the researchers concluded, "Rose Bengal induced potent cell death in human and murine colon cancer cells in vitro. Intralesional injection in established tumours induced an anti-tumour immune response and significant tumour regressions in vivo. These studies establish that intralesional PV-10 therapy warrants further study as a potential immunotherapeutic agent in colorectal cancer and metastases."

The SSO has made available all the abstracts from the Symposium in an electronic supplement to *Annals of Surgical Oncology*, its house journal. The abstract on PV-10 can be found on page S86 of the book, http://expo.jspargo.com/exhibitor/web/SSO15Abstracts.pdf.

For further information visit www.pvct.com

Provectus Biopharmaceuticals announces abstract available on PV-10 for chemoablation of liver cancers

Provectus Biopharmaceuticals, Inc. have announced that the abstract titled, "Phase 1 Study of PV-10 for Chemoablation of Hepatocellular Cancer and Cancer Metastatic to the Liver" was presented at the ESMO 17th World Congress on Gastrointestinal Cancer is now available online at:

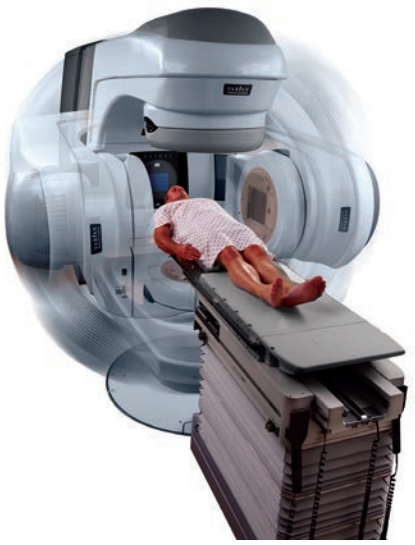
http://annonc.oxfordjournals.org/content/26/suppl_4/iv33.1.full?sid=82267ebd-da5c-4a1a-9320-a795571b6085

The abstract concludes "Preliminary efficacy in treatment of liver tumours with PV-10 was observed. Toxicity was transient, and treatment had acceptable tolerability. The study is continuing at three study centers with two expansion cohorts to assess response in hepatocellular carcinoma and other cancers metastatic to the liver."

Eric Wachter, PhD, Chief Technology Officer of Provectus, presented the abstract on July 2, 2015. Full details of the poster contents is now available from Provectus.

For further information visit www.pvct.com

Pioneering Indian hospital treats 10,000th patient with Varian's RapidArc



A three-year-old baby girl with a brain tumour has become the 10,000th patient at Yashoda Hospital in Hyderabad, India to be treated using RapidArc® radiotherapy technology from Varian Medical Systems.

The treatment comes just six years after RapidArc was first introduced clinically at the private hospital, which treats more than 4,000 patients a year from the states of Telangana and Andhra Pradesh in the south-east of India. "The patient responded well to the treatment," said Dr G S Rao, director of the Yashoda group of hospitals.

Yashoda was the first hospital in India to introduce RapidArc treatments and over the past six years it has phased out the use of 'static-field' intensity modulated radiotherapy (IMRT) treatments and replaced them with RapidArc. In so doing, it has become the first hospital to reach the landmark of 10,000 RapidArc treatments.

Over half the RapidArc treatments carried out at Yashoda over the past six years have involved tumours of the brain, head and neck. Three Varian linear accelerators at the hospital are equipped with RapidArc technology, which was introduced by Varian to speed up treatments and make advanced IMRT approaches more widely available to cancer patients globally.

For further information contact: Neil Madle, T: +44 7786 526068, E: neil.madle@varian.com W: www.varian.com

Provectus Biopharmaceuticals Signs Letter of Intent with Boehringer Ingelheim to Collaborate in Bringing PV-10 to Market in China

Provectus Biopharmaceuticals, Inc have announced that it has signed a Letter of Intent (the "LOI") with Boehringer Ingelheim (China) Investment Co Ltd. The purpose of the LOI is to lay a foundation for the two parties to collaborate in bringing PV-10, Provectus' novel investigational drug for cancer ("PV-10"), to market in mainland China, Hong Kong and Taiwan. Maxim Group LLC acted as strategic advisor to Provectus in structuring and negotiating the LOI.

Under the terms of the LOI, Boehringer will provide certain commercially reasonable support in the aspects of product registration with the China Food and Drug Administration ("CFDA"), communication preparation, market intelligence and other assistance to Provectus in China to the extent that is within Boehringer's approved business scope and permissible by Chinese laws.

In return, Provectus will grant Boehringer the first priority to be the exclusive collaborator of Provectus in China for PV-10 in the event that PV-10 is successfully registered and approved by the CFDA. At the appropriate time, Provectus and Boehringer will enter into a definitive agreement, including a non-compete provision, for PV-10 to be exclusively developed, distributed and promoted through the collaboration within China, although there can be no assurance that the parties will enter into a definitive agreement.

For further information visit www.pvct.com

PROVECTUS BIOPHARMACEUTICALS, INC.

Leading Danish cancer center first in Europe to use Varian's Calypso Transponders for liver cancer patients

Aarhus University Hospital in Denmark has treated two liver cancer patients with stereotactic body radiotherapy (SBRT) using Calypso® 'GPS for the Body' transponders from Varian Medical Systems for real-time monitoring during the treatment. A 77-year-old man and a woman, aged 76, both with metastases in the liver, were treated in three sessions over six days, making them the first liver cancer patients in Europe, and only the second and third in the world, to be treated in this way.

"Our experience so far is that tracking tumours with Calypso transponders may help make a significant difference in liver SBRT treatments," says Morten Høyer, professor of clinical oncology at Aarhus. "In the past, we would have to apply a more generous treatment margin around the tumour because of uncertainties regarding the precise tumour position from day to day. Calypso allows us to monitor the treatment real-time and reduce the treatment margin, meaning less healthy tissue is treated."

Per Poulsen, associate professor responsible for motion management tools, adds, "Calypso is a real-time monitoring device that provides additional evidence that the dose is being delivered where it should be, which is even more important in higher dose treatments like radiosurgery. These implanted markers are a very good representation of what is happening real-time."

For further information contact: Neil Madle, T: +44 7786 526068, E: neil.madle@varian.com W: www.varian.com

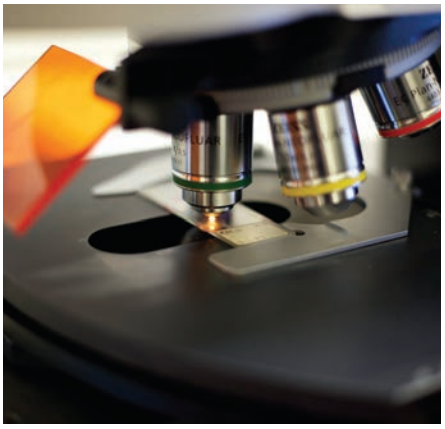
Brain Tumour Research is one of the fastest growing national charities in the UK

Our vision is to find a cure for brain tumours. Our mission is to build a network of experts in sustainable brain tumour research.

We are calling for an experienced research-aware professional to fill a dynamic new role within the charity – **Head of Research**.

Reporting to the Chief Executive, this position will be responsible for developing our unique Research Centre of Excellence strategy; programme governance; grant awards; contracts and research communications. You'll also be tasked with managing our annual scientific workshop.

The suitable candidate will have high-level understanding of research and its translation,



and may come from any one of a variety of backgrounds including research, science or industry. They will be credible with a range of audiences from senior academics to politicians, industry representatives, patients and supporters, and will have excellent communications skills to translate complex scientific medical research into engaging and meaningful content for our supporters and corporate partners.

Salary £35k to £45k depending on experience. Closing date: Friday 25th September. For info on this and other vacancies, visit www.braintumourresearch.org/work-for-us

Siemens syngo solutions ensure ease of compliance for new BTS pulmonary guidelines

Following a recent focus on research of the management of pulmonary nodules for lung cancer screening, the British Thoracic Society (BTS) [1] has developed evidence-based algorithms and recommendations for the investigation of nodules when using imaging techniques. These are expected to lead to a more efficient use of resources and consistent outcomes for lung cancer patients. Siemens Healthcare is also pleased to announce its syngo®.via MM Oncology software solution has been fully future-proofed to ensure ease of compliance with key areas of the BTS guidelines.

"Lung cancer is the second most common cancer in the UK and accounts for 13% of all new cases, according to Cancer Research UK. Pulmonary nodules are a common case presented within hospitals and a systematic and logical approach is key to their effective investigation and management. Determining the size and growth rate is a vital part of understanding whether a nodule may be cancerous and the impact on the patient," explains Ben Reed, syngo Business Manager GB & Ireland at Siemens Healthcare.

For further information visit www.siemens.co.uk/healthcare.

[1] https://www.brit-thoracic.org.uk/document-library/clinical-information/pulmonary-nodules/bts-guidelines-for-pulmonary-nodules/

Provectus Biopharmaceuticals, Sinopharm-China State Institute of Pharmaceutical Industry and Sinopharm A-Think Pharmaceutical Co, Ltd continue search for agreement on PV-10 use in China

Provectus Biopharmaceuticals, Inc have announced that it continues to work with Sinopharm-China State Institute of Pharmaceutical Industry and Sinopharm A-Think Pharmaceutical Co, Ltd to reach an agreement on PV-10 use in China.

Discussions continue with the frame of reference established in the original Memorandum of Understanding (MOU), signed last year and extended since the passing of the original deadline. The original MOU was signed in August 2014, and, since then, the parties have sought to enter into a definitive licensing agreement, subject to additional negotiation, due diligence, and any required regulatory and corporate approvals.

Since the signing of the MOU, management of Provectus and senior personnel at Sinopharm-CSIPI and Sinopharm A-THINK have held numerous conference calls, have met face-to-face in both China and the US, and Chinese scientists on staff at Sinopharm have discussed in person PV-10 and its clinical results with the lead investigators at St Luke's University Hospital and Health Network and Moffitt Cancer Center.

Dr Zhidan Jia, Chief Executive Officer of Sinopharm A-THINK, stated, "We continue to work closely with Provectus to arrive at an agreement which defines the terms of our collaboration in bringing PV-10 to the Chinese Market. We hope to come to terms in the near future."

For further information visit www.pvct.com

PROVECTUS
BIOPHARMACEUTICALS, INC.

New radiotherapy room

Cancer patients at Queen Elizabeth Hospital Birmingham are benefitting from a £1.5 million refurbishment project to dramatically improve their treatment environment.

Treatment room seven in the radiotherapy department has been re-opened after a nine-month refit including the installation of one of the first Elekta Versa HD linear accelerator machines in the region.

The Elekta Versa HD Linac can deliver a dose of radiation in a much shorter time than a conventional radiotherapy machine, increasing the number of patients that can be treated each day.

It also has the most advanced imaging system available which allows tracking of a tumour's motion during treatment by

performing a daily CT scan.

Any movement can then be taken into account as this image guided radiotherapy (IGRT) helps to reduce the amount of radiation given to normal tissues, which in turn reduces some of the long-term side effects for patients.

"This equipment offers the most advanced technology available, designed to improve patient care and treat a broader spectrum of cancers with high-precision beam shaping and tumour targeting abilities," said radiotherapy deputy manager Caroline Williams.

"Around 40 percent of cancer patients have radiotherapy and University Hospitals Birmingham is committed to having state-of-the-art technology for our patients."

Wall art is also a prominent feature of the new treatment room as the radiotherapy team seek to make the environment as comfortable as possible for patients.

For further information
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Provectus Biopharmaceuticals' Phase 1 PV-10 data on liver cancer presented at 6th Asia-Pacific Primary Liver Cancer Expert Meeting

Provectus Biopharmaceuticals, Inc have announced that data from its phase 1 study of PV-10 for chemoablation of hepatocellular carcinoma (HCC) and cancer metastatic to the liver was presented on July 3, 2015 at the 6th Asia-Pacific Primary Liver Cancer Expert Meeting in Osaka, Japan.

The presenter was Dr Sanjiv Agarwala, chief of medical oncology and hematology at St Luke's Cancer Center in Bethlehem, Pennsylvania, and professor of medicine at Temple University School of Medicine in Philadelphia, Pennsylvania. He serves as a principal investigator of the phase 1 clinical trial that produced the data presented, and is the lead investigator for the phase 3 clinical trial of PV-10 as an investigational treatment for melanoma which recently began. The poster presentation was titled "Phase 1 Study of PV-10 for Chemoablation of Hepatocellular Cancer and Cancer Metastatic to the Liver."

Based on the data presented, the researchers concluded that preliminary efficacy in treatment of liver tumours with PV-10, a 10% solution of rose Bengal, was observed with acceptable tolerability. The study is continuing at three study centers with two expansion cohorts to further assess safety and response in HCC and other cancers metastatic to the liver.

For further information visit www.pvct.com

PROVECTUS
BIOPHARMACEUTICALS, INC.

Varian Medical Systems Awarded Major Tender to Equip Network of Hospitals in North-West Spain

Varian Medical Systems has been awarded an eight-year tender to supply advanced radiotherapy equipment and software to a network of hospitals in Galicia, in the north west of Spain. Varian booked the order, worth an estimated 21m ($23m), in its fiscal third quarter.

Under the terms of the agreement Varian will supply 10 linear accelerators, including three advanced TrueBeam™ systems, to five hospitals in the SERGAS network of hospitals in the Galicia region. Varian will also be installing its full suite of treatment planning software and oncology information management systems across the network.

"This is the largest single order that Varian has been awarded in Spain and we are excited to work closely with the SERGAS group to make the most advanced radiation therapy available to cancer patients in the region," said Jaime Calderon, Varian's Iberia region managing director.

Under this investment project, the five public hospitals – Centro Oncológico de Galicia, Hospital Lucus Augusti de Lugo, Complejo Hospitalario Universitario de Santiago, Complejo Hospitalario Universitario de Vigo and Complejo Hospitalario Universitario de Ourense – will also be connected within Varian's ARIA™ network, enabling greater integration and knowledge-sharing between the five departments. This will be the first time the five centers have been connected in this way.

For further information contact: Neil Madle, T: +44 7786 526068,
E: neil.madle@varian.com W: www.varian.com

Varian Signs Contracts to Equip Two National Proton Therapy Centers in England

Varian Medical Systems UK Ltd announced recently that it had signed contracts with the National Health Service to equip and service two new national NHS proton therapy centers in England with the Varian ProBeam® proton therapy system. Earlier this year, Varian announced that it was selected as the preferred supplier for two three-room NHS centers to be constructed in London and Manchester. Varian expects to book the equipment portion of the order in its fiscal fourth quarter with the remainder of the order to be booked in accordance with the company's policies over the term of the agreements.

The UK government is investing £250m in building and equipping the two NHS centres at UCLH (University College London Hospitals NHS Foundation Trust) in London and The Christie NHS Foundation Trust in Manchester. Varian is contracted for up to £80 million for equipment supply and service. Equipment installation is expected to take place from August 2017, with patient treatments expected to begin from 2018.

"Varian is proud to have been contracted to equip and service the national NHS proton therapy centers at UCLH and The Christie," said Dow Wilson, Varian's chief executive officer. "ProBeam was selected after an extremely rigorous and thorough tender process that identified Varian's technology as the most suitable for the country's future proton therapy needs."

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Celebrating 40 years of Macmillan professionals

Forty years ago Macmillan built, equipped and opened the first Macmillan unit, at Christchurch Hospital (now Macmillan Caring Locally). They also funded the first Macmillan nurse.

Ann Nash was one of the first Macmillan professionals [1] and one of the first nurses to take her palliative care skills into the community. She represents how Douglas Macmillan's vision of a 'panel of voluntary nurses, who can be detailed off to attend to necessitous patients in their own homes,' became a reality.

Ann worked for Macmillan for eight years as a nurse consultant and helped to set up the first hospice in the former Soviet Union. She then went on to hold director roles at a number of NHS trusts and Clinical Commissioning Groups.

As cancer treatment and support has changed over the last 40 years, so has the range of Macmillan professionals and the type of support they provide to people throughout the cancer journey – from the moment of diagnosis, through treatment, and increasingly on the way back to health.

To find out more about our services or sign up to our quarterly newsletter, visit macmillan.org.uk/patientsupport

[1] Paul Rossi, Fighting Cancer with More Than Medicine: A History of Macmillan Cancer Support.

Provectus Biopharmaceuticals' Abstract on Liver Cancer for Poster Presentation at 6th Asia-Pacific Primary Liver Cancer Expert Meeting

Provectus Biopharmaceuticals, Inc have announced that the organising committee of the 6th Asia-Pacific Primary Liver Cancer Expert Meeting accepted the Company's abstract "Phase 1 Study of PV-10 for Chemoablation of Hepatocellular Cancer and Cancer Metastatic to the Liver", for a poster presentation.

The presentation happened on July 3, 2015. The presentation was made by Dr Sanjiv Agarwala, chief of medical oncology and hematology at St Luke's Cancer Center in Bethlehem, PA, and professor of medicine at Temple University School of Medicine in Philadelphia. He served as the principal investigator of the Phase I clinical trial that produced the data being presented, as well as the principal investigator in the Phase III clinical trial of PV-10 as a treatment for melanoma which has just begun.

The conference took place July 3-5, 2015, and was held at The Hyatt Regency Osaka, in Osaka, Japan. The Company posted the presentation on its website at www.pvct.com at the time of the presentation. For more information on the conference, please visit http://www2.convention.co.jp/apple2015/greeting/index.html

For further information visit www.pvct.com

PROVECTUS BIOPHARMACEUTICALS, INC.

Introducing the system that knows no boundaries.

Meet Leksell Gamma Knife® Icon™, the most advanced solution for cranial radiosurgery. Icon enables you to treat any cranial target with confidence – with significantly lower dose to normal tissue than other systems.

Frame-based or frameless immobilization, single session or hypofractionation, radiosurgery or ultra-precise microradiosurgery – the choice is yours. The introduction of Icon brings a number of new innovations. The unique High-Definition Motion Management system enables frameless treatments with industry-leading accuracy. With true stereotactic Cone Beam CT, Online Adaptive DoseControl™ technology and virtual 6D couch, the dose is always delivered exactly where planned.

Born of a profound care for patients with cranial disorders, every detail of Icon has been designed with the patient in mind, and those who treat them.

Leksell Gamma Knife® Icon™ is not for sale in all markets

Leksell Gamma Knife Icon® Care for the brain.

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ELEKTA