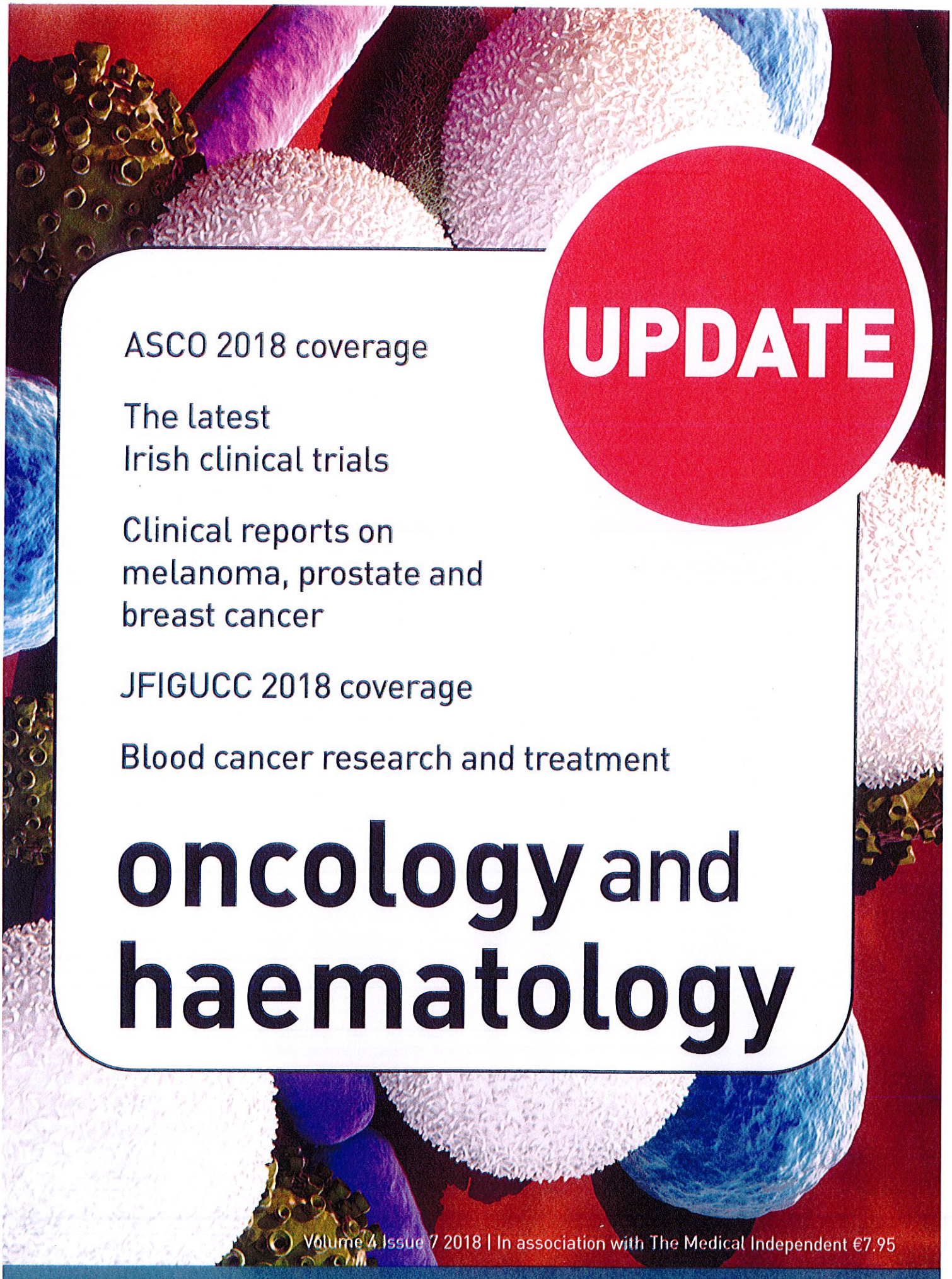

UPDATE

ASCO 2018 coverage

The latest Irish clinical trials

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JFIGUCC 2018 coverage

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# Ground-breaking TAILORx trial finds that most women with early breast cancer do not benefit from chemotherapy

New findings presented at ASCO 2018 from the ground-breaking Trial Assigning Individualised Options for Treatment (Rx), or TAILORx trial, show no benefit from chemotherapy for 70 per cent of women with the most common type of breast cancer.

The study, which included 690 women from Ireland, found that for women with hormone receptor (HR)-positive, HER2-negative, axillary lymph node-negative breast cancer, treatment with chemotherapy and hormone therapy after surgery is not more beneficial than treatment with hormone therapy alone.

The new data will help inform treatment decisions for many women with early-stage breast cancer.

TAILORx, a phase 3 clinical trial, opened in 2006 and was designed to provide an evidence-based answer to the question of whether hormone therapy alone is not inferior to hormone therapy plus chemotherapy. The trial used a molecular test (Oncotype DX Breast Recurrence Score) that assesses the expression of 21 genes associated with breast cancer recurrence to assign women with early-stage, HR-positive, HER2-negative, axillary lymph node-negative breast cancer to the most appropriate and effective post-operative treatment. The trial enrolled 10,273 women with this type of breast cancer at 1,182 sites in the US, Australia, Canada, Ireland, New Zealand and Peru.

Women in the trial who had a score in the intermediate range (11-to-25) were randomly assigned to receive hormone therapy alone or hormone therapy with adjuvant chemotherapy.

The rates of overall survival were very similar in the two groups. At five years, the overall survival rate was 98.0 per cent for those who received hormone therapy alone and 98.1 per cent for those who received both therapies, and at nine years, the respective overall survival rates were 93.9 per cent and 93.8 per cent.

The Irish arm of the trial was conducted by Cancer Trials Ireland and led by Prof Maccon Keane, Consultant Medical Oncologist, University Hospital Galway, as the Chief Investigator.

St Vincent's University Hospital in Dublin had the second-highest number of participating patients from the 1,182 research units involved in the trial.

"The TAILORx trial result is a major advance in precision medicine for women with hormone receptor-positive, node-negative breast cancer," Prof Keane said.

"Having the trial in Ireland has enabled more personalised treatment recommendations for women with this stage and type of breast cancer, as we have had access to the test through the HSE since 2011.

"Irish women contributed significantly to this trial and can be rightly proud of their input into improving care for future women who present with breast cancer."

Commenting on the results, Prof Bryan Hennessy, Clinical Lead, Cancer Trials Ireland, said: "This is a globally important breast cancer trial. These results will inform clinical decision-making and in future, many women with certain types of early-stage breast cancer can avoid chemotherapy, without impacting on the success of their treatment.

"We are delighted that with the support of these patients, our research teams, under the umbrella of Cancer Trials Ireland, were able to play a leading role in this research", he said. Findings from the study are published in the *New England Journal of Medicine*.

# Blood test shows potential as a detection tool for early-stage lung cancer — Cell-Free Genome Atlas study

An initial report from the large, ongoing Circulating Cell-Free Genome Atlas (CCGA) study, presented at ASCO 2018, provides preliminary evidence that a blood test may be able to detect early-stage lung cancer. This is one of the first studies to explore blood tests analysing free-floating or cell-free DNA as a tool for early detection of cancer.

"We're excited that initial results from the CCGA study show it is possible to detect early-stage lung cancer from blood samples using genome sequencing," said lead study author Dr Geoffrey R Oxnard, Associate Professor of Medicine at Dana-Farber Cancer Institute and Harvard Medical School in Boston, US. "There is an unmet need globally for early detection tests for lung cancer that can be easily implemented by healthcare systems."

# A US-Irish view on cancer research collaboration

**Prof Peter O'Dwyer**, co-Chair of the US ECOG-ACRIN Cancer Research Group, addressed a Cancer Trials Ireland DSSG scientific meeting earlier this year. **Priscilla Lynch** reports

The ECOG-ACRIN Cancer Research Group is one of the leading international cancer research groups and its research spans the cancer care pathway through studies of prevention, early detection, diagnosis, treatment, patient-centred outcomes and associated correlative science, including the development of cancer-related biomarkers

It has nearly 1,100 member institutions in the US and around the world, including Cancer Trials Ireland (CTI), with approximately 12,000 professionals involved in group research.

Leading US oncologist Prof Peter O'Dwyer, who was born in Ireland and educated in Trinity College Dublin, is the incoming co-Chair of ECOG-ACRIN. Addressing a recent CTI DSSG scientific meeting, entitled '21 years of cancer trials in Ireland – What's next?, he outlined the history, current research work and future priorities of the group.

Prof O'Dwyer explained that the history of cancer co-operative groups "actually parallel the history of cancer treatment right back to when Sidney Farber treated ALL [acute lymphoblastic leukaemia] patients with methotrexate" [US paediatric pathologist Farber became known as the father of chemotherapy and his landmark results were published in the *New England Journal of Medicine* (*NEJM*) in 1948].

"Shortly after that a chemotherapy service centre was set up by Congress and in 1955 the Eastern Solid Tumour Group, the precursor of ECOG, was formed. Three years later, in 1958 the first randomised co-operative trial was reported and in 1960 there were 11 co-operative groups. What is important here is the idea of the controlled trial, the importance of the statisticians in determining how these trials would evolve, was there from the very beginning."

Prof O'Dwyer said that the activities of the co-operative groups, "not just ECOG, but many of the other groups too, have been practice-changing".

"They have changed the practice of medicine, they have changed the care of patients with cancer," he told the meeting, citing the positive findings on the benefits of adjunct chemotherapy in node-negative breast cancer patients as an early example.

Prof O'Dwyer added, however, that "some of the most important contributions may not actually be positive trials, they may be negative trials", giving the example of a 1999 trial published in the *NEJM* that contradicted the then prevailing view that stem cell transplantation was essential for the management of metastatic breast cancer. He cited similar trial findings for prostate cancer, melanoma, and lymphoma, etc.

## Collaboration

Prof O'Dwyer praised the setting up of ICORG, now CTI and its collaboration with ECOG-ACRIN.

"The participation of Cancer Trials Ireland in ECOG studies has been associated with outstanding performance reviews. Every audit has been outstanding. The quality of the data is phenomenal."

Acknowledging the barriers to international collaboration, such as logistics and regulatory differences, he called on the pharmaceutical industry to ensure stable drug supply in multi-centre clinical trials.

Discussing the creation of ECOG-ACRIN in May of 2012, when two US National Cancer Institute-sponsored co-operatives came together, Prof O'Dwyer explained "biomarker-driven science lay at the heart of the merger".

"And that biomarker could be imaging, it could be genomic, it could be a multitude of current technologies, but that we would be able to find biomarkers as we went forward that would tell us who were the patients at risk, how to diagnose them early, and finally, how to treat them.... So what the addition of ACRIN added was screening and surveillance and the potential for cancer prevention in large populations."

Prof O'Dwyer added that increasing the involvement of cancer patients and advocates in cancer research, "and all aspects of the design and work of our clinical trials", has been a key task of the group.

Highlighting the organisation's current work, he gave updates on a number of ongoing trials, including a major one on breast cancer screening.

## Future

Future research priorities for ECOG-ACRIN include genomics, immuno-oncology therapies, and de-intensification of treatment; "if patients are going to be cured they want to be cured without side effects...".

Prof O'Dwyer said: "Novel biomarkers and matched novel therapies are clearly important [too]. The field evolves and we are involved in cancer treatment so we need to be bringing forward in a very measured and logical way some of these novel therapies and then applicability to different racial and ethnic populations. In a diverse country like the US and an increasingly diverse society as is present in the EU, it is clearly going to be important and is part of our future vision."

He noted that further exploration of existing ECOG-ACRIN data, such as genomics, "is really important. Exploring genomics in standard therapy is a key goal". He confirmed that the group has now secured funding to sequence all patients on five of its clinical trials.

"We are close to doing a deal on sequencing all of the patients who get on ECOG-ACRIN trials, and we are looking into the potential for germline sequencing and how that could be managed, obviously there are big issues there. So getting as much information on the tumours and the patients that we treat we think is really going to help refine treatment going forward," he told the meeting.

Prof O'Dwyer also spoke about the potential of artificial intelligence in cancer detection through imaging analysis and other "multiple areas".

Concluding, Prof O'Dwyer said that ECON-ACRIN is keen to "create opportunities for early career investigators and scientists to participate in these studies and to interrogate these big datasets that will be available and to propose clinical trials...".

A video of his full presentation and the other meeting speakers can be viewed at *www.cancertrials.ie.*

# Multimodal treatment of head and neck cancer – combining immunotherapy with chemoradiotherapy

**Dr Siobhra O'Sullivan**, Specialist Registrar in Radiation Oncology, Saint Luke's Radiation Oncology Network (SLRON); **Dr Sinéad Brennan**, Consultant Radiation Oncologist, SLRON – Irish Chief Investigator for the JAVELIN Head and Neck 100, DARS and De-ESCALaTE Studies; and **Ms Lydia O'Sullivan**, Clinical Research Associate, Cancer Trials Ireland

The JAVELIN Head and Neck 100 trial is a phase III double-blind randomised controlled trial (RCT) studying the effect of avelumab, versus placebo, in combination with standard of care chemoradiotherapy (CRT) in the frontline treatment of patients with high-risk locally advanced squamous cell carcinoma of the head and neck (SCCHN).

The trial has opened in St Luke's Radiation Oncology Network in Rathgar and St James's Hospital, Dublin, funded by Pfizer and with the support of St Luke's Institute of Cancer Research and Cancer Trials Ireland.

The trial strengthens Cancer Trials Ireland's collaborative international links and increases opportunities for Irish patients with head and neck cancer to avail of the most up to date treatment approaches. It increases future opportunities for further collaboration and the ongoing recruitment of Irish patients to high quality international studies.

In 2012, there were almost 140,000 new cases of head and neck cancer diagnosed in Europe, the majority of which are squamous cell carcinoma. In Ireland, almost 500 people are diagnosed with cancer of the mouth or pharynx annually. Risk factors include smoking, alcohol, and infection with humanpapilloma virus (HPV). Of newly diagnosed patients with SCCHN, approximately 60 per cent present with locally or regionally advanced disease, for whom standard of care is combination chemoradiotherapy with cisplatin. In this group, locoregional failure rates can range between 35-65 per cent (depending on tumour site, stage, and HPV status), with 10-30 per cent of patients developing distant metastases. A three-year progression-free survival (PFS) rate of approximately 61.2 per cent is reported. Outcomes for both locoregional and distant recurrences are poor, with limited effective treatment options, and high morbidity and mortality. Thus, there is a push to explore avenues to optimise multimodal treatment and improve PFS in the upfront setting.

Ionising radiation causes cell death through the generation of free oxygen radicals and double strand DNA breaks, resulting in mitotic catastrophe. The tumour is targeted with normal tissue relatively spared with the use of modern techniques including intensity modulated radiotherapy (IMRT). Cisplatin added to radiation therapy in the treatment of SCCHN has been shown to improve overall survival (OS) by 6.5 per cent at five years.

A key step in the development and progression of cancer is the ability to evade and inhibit the body's normal immune response to tumour cells. Avelumab is a fully human IgG1 monoclonal antibody (mAb), which selectively binds to PD-L1 (present on some cancer cells) and competitively blocks its interaction with PD-1 (on cytotoxic T-cells), thereby reactivating the immune system's response to cancer. Radiation increases PD-L1 expression, and so adding avelumab results in a synergistic therapeutic effect (see *Figure 1*). There is also emerging clinical data suggesting the development of an immune anti-tumour memory after such combination therapy.

The primary hypothesis of this study is that the addition of avelumab to standard of care cisplatin-based CRT will improve PFS in the upfront treatment of locally advanced SCCHN. Secondary endpoints include OS, and evaluation of safety and tolerability of the combined treatment. Both patients and physicians are blinded to the treatment allocation.

Participation in this trial follows the successful enrolment of patients within the St Luke's Radiation Oncology Network to earlier head and neck studies. The Cancer Research UK DARS trial is a phase III, multicentre randomised radiotherapy trial examining whether dysphagia optimised IMRT (Do-IMRT) compared to standard IMRT (S-IMRT) improves post radiotherapy dysphagia in patients with head and neck cancer. A second trial, De-ESCALaTE HPV, is a phase III randomised trial in patients with HPV-positive oropharyngeal carcinoma to compare the acute and late effects using cetuximab with radiotherapy versus cisplatin with radiotherapy. These trials were sponsored (DARS) or co-ordinated (De-ESCALaTE HPV) in Ireland by Cancer Trials Ireland, and are now closed to accrual with follow up ongoing and early results awaited.

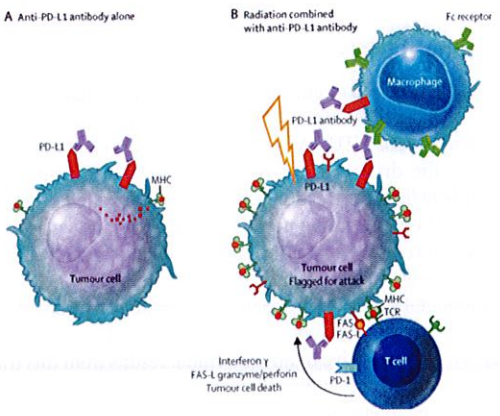


Figure 1: Synergistic therapeutic effect of anti-PD-L1 antibody and radiotherapy

# New studies investigate overcoming HER2-therapy resistance in breast cancer

**Dr Anees Hassan**, Beaumont Hospital, Dublin; **Dr Niamh M Keegan**, RCSI Molecular Medicine; **Andrés Hernando**, MSc, Senior Clinical Project Manager, Cancer Trials Ireland; and **Prof Bryan T Hennessy**, Clinical Lead, Cancer Trials Ireland, RCSI Molecular Medicine and Consultant Medical Oncologist, Beaumont Hospital, Dublin

Sponsored by Cancer Trials Ireland, the PantHER (CTRIAL-IE 15-02) and Panthera (CTRIAL-IE 17-13) trials will assess the addition of copanlisib to HER2-targeted agents to overcome HER2-therapy resistance in breast cancer (BC).

BC is the second most common cancer and the fifth cause of cancer mortality worldwide[1]. Approximately 20 per cent of cases of BC overexpress the human epidermal growth factor receptor (HER2), and HER2-positivity is associated with a significantly worse prognosis. HER2 was first targeted by trastuzumab, which significantly improved outcomes, but the efficacy of trastuzumab is limited by acquired and *de novo* resistance[2].

The phosphoinositide 3 kinase (PI3K) pathway is important in the oncogenic function of HER2 (**Figure 1**)[3]. Aberrant activation of PI3K is implicated in resistance to trastuzumab and other HER2-targeted therapies[4] and is frequent, with up to 22 per cent of HER2-positive BC having a PIK3CA mutation[5]. Copanlisib is a pan-class 1 PI3K inhibitor administered intravenously, with low nanomolar activity against both PI3Kα and PI3Kβ. Copanlisib has been shown to re-sensitise trastuzumab resistant cell lines to trastuzumab with synergism seen in some cell lines between copanlisib and HER2 targeted therapy[6].

PantHER is a phase Ib/II trial that assesses the addition of copanlisib to trastuzumab in patients with histologically confirmed HER2-positive BC that are metastatic or incurable recurrent, following disease progression during, or after, treatment with at least one trastuzumab-based or trastuzumab emtansine (T-DM1)-based treatment regimen in the metastatic or recurrent setting. The phase 1b part of this clinical trial assessed two dose levels of copanlisib (45mg and 60mg on days one, eight, and 15) to determine the maximum tolerated dose (MTD) based on the occurrence of dose limiting toxicity (DLT) and therefore the recommended phase II dose (RP2D). There were no DLT at either dose level and 60mg of copanlisib was then determined as the RP2D for the combination of copanlisib and trastuzumab. The copanlisib-trastuzumab combination was safe and well tolerated. This part of the trial ran in cancer trials research units in three hospitals around Ireland. The phase II part is currently running in cancer trials research units in five hospitals around Ireland and will evaluate the anti-tumour efficacy of the combination in terms of clinical benefit rate (CBR) that is defined as complete response (CR) or partial response (PR) at any time-point on the study; or stable disease (SD) lasting at least 24 weeks based on radiological assessment. Other efficacy measures (such as progression-free survival (PFS), time to treatment failure (TTF), duration of response (DR) and overall survival (OS)) will be evaluated as well as the incidence of cardiotoxicity. We plan to enrol 16 patients with PI3KCA hot spot mutations in the phase II part of PantHER.

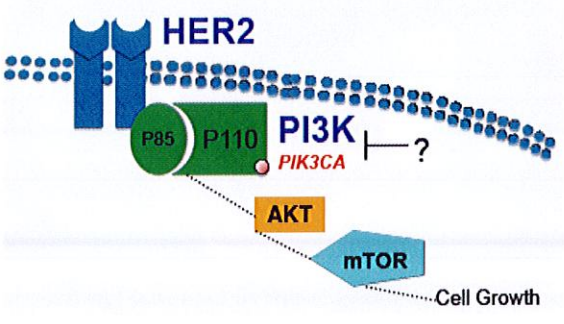


Figure 1: PI3K pathway and HER2 signalling

Panthera is a phase Ib trial that will assess the addition of copanlisib to T-DM1 in patients with unresectable locally advanced or metastatic HER2-positive BC who previously received trastuzumab and a taxane, separately or in combination. There will be three different dose levels of copanlisib according to the dose escalation scheme (dose level 1: 45mg on days one and eight, dose level 2: 60mg on days one and eight, dose level 3: 60mg on days one, eight, and 15) to determine the MTD based on the occurrence of DLT. There will be a dose level -1 (45mg on day one only) in case dose de-escalation is needed. Although the main endpoint of this trial is safety, efficacy measures (such as PFS, TTF, DR and OS) will also be evaluated. This trial is a binational study that will run in Ireland (three sites) and Spain (one site) and it is planned to enrol the first patient in October 2018. A maximum of 24 patients with either wild or mutant PI3KCA will be enrolled in this trial.

Both trials have translational sub-studies to examine predictive biomarkers in tumour tissue and blood as well as molecular tumour adaptation to clinical trial therapy.

Addition of a PI3K inhibitor to anti-HER2 therapy is a potential hope to improve outcomes in HER2-positive advanced BC.

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# Study to reduce side effects for patients undergoing radiotherapy treatment for rectal cancer

**Dr Brian O'Neill**, Consultant Radiation Oncologist, St Luke's Radiation Oncology Network – Chief Investigator of the TRI LARC study; and **Ms Lydia O'Sullivan**, Clinical Research Associate, Cancer Trials Ireland

TRI LARC is a randomised phase 2 study of pre-operative 3-D conformal radiotherapy (3-DCRT) versus intensity modulated radiotherapy (IMRT) for locally advanced rectal cancer. It is sponsored by Cancer Trials Ireland and will involve 268 patients across six Irish radiation oncology departments. The study aims to reduce side effects, and hence improve quality-of-life, for patients undergoing radiotherapy (RT) treatment for rectal cancer. The trial is already open in the St Luke's Radiation Oncology Network centres in Beaumont Hospital, St James's Hospital and St Luke's Hospital, Dublin, with over 60 patients enrolled.

Colorectal cancer accounts for 11 per cent of cancers in women and 14 per cent in men in Ireland and is the third leading cause of cancer death in women and the second in men (National Cancer Registry Ireland).

Pre-operative RT or chemo-radiotherapy (CRT) is internationally accepted as standard practice in the management of locally advanced rectal cancer (ie, cT3N0-2, cT4N0-2, cT(any)N1-2). Multiple randomised trials have proven pre-operative CRT and RT, compared to surgery alone, reduces local recurrence (even prior to optimal surgery) and may improve survival for T3 circumferential resection margin (CRM) negative patients. Pre-operative treatment is theoretically superior to post-operative treatment due to well oxygenated preoperative tissue, better treatment compliance, and the potential for tumour downsizing/downstaging, and increasing CRM clearance rates.

The therapeutic aim in the delivery of RT is optimal radiation dose delivery to the planning target volume (PTV), while minimising radiation dose to surrounding normal structures. Three-dimensional conformal radiotherapy (3-DCRT) is the current RT technique of choice in Ireland for the treatment of rectal cancer. Using this technique, the gross tumour volume, clinical target volume and PTV are contoured on a CT dataset. A three or four field beam arrangement is typically used to target the pelvis in order to treat those areas at risk of recurrence: The rectum, the mesorectum and the draining pelvic lymph nodes. However, when using such a technique relatively large volumes of normal tissues such as bowel and bladder are needlessly irradiated. Rates of 27 per cent acute grade III and IV toxicity (12 per cent acute diarrhoea, 11 per cent dermatologic effects), and 14 per cent grade III and IV late toxicity (9 per cent chronic diarrhoea and/or small bowel obstruction, 2 per cent re-operation rate for small bowel obstruction, 4 per cent anastomotic strictures, 2 per cent bladder) have been reported (Sauer *et al*, 2004).

Intensity modulated radiation therapy (IMRT) is a newer, but established RT technique which subdivides radiation beams into smaller beamlets, and varies the individual intensities of these beamlets, in order to achieve highly conformal dose distributions (see *Figure 1*). The advantages of this technique are improved target volume conformity, particularly for complex volumes (especially concave, such as pelvic volumes for rectal cancer), with improved sparing of organs at risk (OARs).

Disadvantages of IMRT are the more complex and time-consuming planning and quality assurance processes and a larger number of monitor units (MU) compared with conventional RT leading to an increase in the amount of low dose radiation, though this depends on the specific IMRT technique.

There are no randomised studies comparing 3-DCRT pelvic irradiation with IMRT in preoperative patients who have had surgery for rectal cancer. However, there are several small studies that report considerable sparing of normal tissues using IMRT and when compared retrospectively with conventionally treated patients demonstrate marked reductions in acute gastrointestinal (GI) and genitourinary (GU) toxicity.

It is clear from the available data that IMRT spares small bowel and bladder compared to 3-DCRT with acceptable PTV coverage in planning studies; and that IMRT has been introduced into clinical practice in many centres and is feasible and appears to clinically reduce GI and GU toxicity. The aim of the TRI LARC study is to determine in the context of a randomised clinical trial whether delivering pre-operative CRT to the pelvis using IMRT (as opposed to 3-DCRT) will reduce acute and late toxicity, while maintaining local control and survival.

There are also two exciting translational components to this trial, led by RCSI/Beaumont Hospital and the NICB/DCU respectively. RCSI/Beaumont Hospital are investigating somatic mutations and their proteomic and transcriptomic effects and associations and are aiming to validate known and identify new gene mutations in blood (circulating DNA (ctDNA) and circulating tumour cells (CTCs)) and tissue. They are also exploring the effect of RT on these mutations and the mismatch repair system, and investigating the utility of an RNA degradation assay in on-treatment biopsies as a pharmacodynamic biomarker of responsiveness of chemoradiotherapy. The team at NICB/DCU are working to identify blood biomarkers as indicators for responders/non-responders to treatment and to develop a panel of predictive/prognostic biomarkers.

**Acknowledgement:** *Saint Luke's Institute of Cancer Research for their support of the translational sub-studies.*

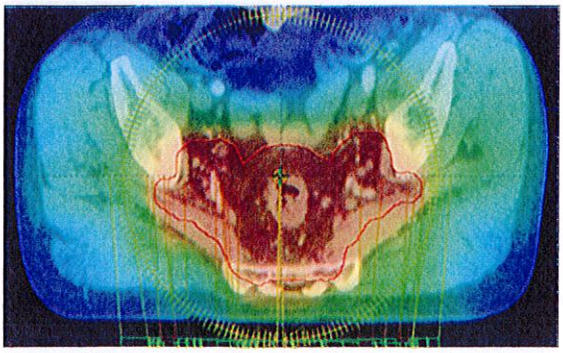

Figure 1: Volumetric modulated arc therapy plan for patient with rectal cancer