DSSG Digest

The DSSG Digest has the most up to date news and listing of cancer trials and studies underway in Ireland.

The Add-Aspirin trial has opened in Ireland—see page 2.

cancer trials ireland

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Add-Aspirin trial seeks to find out if aspirin can help prevent cancer returning after treatment.

The first ever large-scale trial to investigate if aspirin, the inexpensive common drug, can prevent early stage cancer returning after treatment, has opened in Ireland.

The trial involves collaboration among experts from Ireland, UK and India. It will have 11,000 participants from all three countries.

The trial will recruit over 300 eligible volunteers in Ireland, from 10 participating hospitals (see list below), who have had, or have started, treatment for early stage cancer of the breast, stomach, oesophagus (food pipe) or prostate.

The trial is called Add-Aspirin and will investigate whether taking aspirin daily for 5 years after treatment can prevent a patient's cancer returning, and ultimately prolong life.

To date studies have looked primarily at the effect of aspirin on heart disease and its side effects, and found that fewer people taking aspirin appeared to developed cancer. Among those who developed cancer, the cancer appeared to be less likely to spread.

As these studies were not specifically designed to investigate the impact, if any, of aspirin on cancer, it is necessary therefore to compile and analyse data on its efficacy in relation to cancer in a large clinical trial.

The Add-Aspirin trial aims to achieve this and will look at both the benefits and the side effects of taking aspirin in a large group of people who have had early stage cancer.

University College London (UCL) is the overall sponsor of the trial and the Tata Memorial Centre (TMC) in Mumbai, India, is co-sponsor of the trial and sponsor the Indian component. Funding is provided by Cancer Research UK, the National Institute for Health Research Health Technology Assessment Programme, the Medical Research Council Clinical Trials Unit at UCL, all UK based, and the Sir Dorabji Tata Trust in India.

In Ireland the trial is co-ordinated by Cancer Trials Ireland and supported by funding from the Health Research Board and the Irish Cancer Society. Bayer is providing the aspirin that will be used during the trial.

Dr Gregory Leonard, Consultant Medical Oncologist, Galway University Hospital, is the trial's Chief Investigator for Ireland. The overall Chief Investigator for the study is Professor Ruth Langley, based at UCL in London.

Dr Leonard said that while aspirin has been in use for over 100 years for pain relief, and more recently to prevent heart attacks and strokes, there has been a growing body of evidence during the past decade of its potential as an anti-cancer agent.

"This is the first trial ever to investigate if aspirin could stop or prevent the return of cancer among such a significantly large group of patients with early stage cancer.

The team at Galway University Hospital recruited the first patient to the Add-Aspirin trial in October. Pictured (l to R) are Helen O'Reilly, Unit manager; Olive Forde. Clinical Trial Coordinator; Orlaith Cormican, Research Nurse; and Orla O' Toole. Clinical Trial Pharmacist.

Cover Photo: Announcing the opening of the Add-Aspirin trial (L to R) Prof Bryan Hennessy, Clinical Lead, Cancer Trials Ireland; Emma Corcoran, patient advocate; Dr Greg Leonard, Chief Investigator for the Add-Aspirin trial in Ireland, Consultant Medical Oncologist, Galway University Hospital; and Dr Janice Walshe, Consultant Medical Oncologist at St Vincent's University Hospital, Dublin.

"At a time when we are used to new cancer treatments being relatively costly, the possibility of repurposing an inexpensive, generic drug that is available worldwide to stop or slow cancer is potentially ground breaking," he said.

"The results of this trial could have a huge impact on the global cancer burden, particularly given the increasing cancer incidence in lower resource countries," he said.

Participants will be recruited over 3 to 6 years and will self-administer tablets daily for at least 5 years. Participants will be actively followed up for a further 10 years after treatment.

The Add-Aspirin trial is a phase III, double-blind, placebo-controlled, randomised trial. The trial will have three groups. Two groups will receive a different dose of aspirin. This is because it is not yet known how much aspirin may be needed to have an effect, if any, against cancer. The third group will receive a placebo. This is to avoid the potential for bias.

Participants for each group will be selected at random by a computer. Neither the participant nor the research team will know who receives aspirin and who does not.

If you are an individual who is interested in taking part in the Add-Aspirin trial, please talk to your oncologist, who will be able to consider whether you are suitable for the trial.

Hospitals participating in the Add-Aspirin trial

- Beaumont Hospital
- Tallaght University Hospital
- Mater Misericordiae University Hospital
- Mater Private Hospital
- St Vincent's University Hospital
- Bon Secours Hospital, Cork
- Cork University Hospital
- Sligo University Hospital
- University Hospital Galway
- University Hospital Limerick

Eight in ten living with cancer would take part in a trial to help others

The results of a nationwide survey of people living with cancer found that being able to advance research for future patients features prominently in peoples' decision to take part in a trial.

When asked to list the most important factors in deciding to take part in a cancer trial the top three most important factors were: (i) living longer/feeling better (82%), (ii) the chance to advance research (81%) and (iii) getting a recommendation by their cancer doctor (76%).

Led by Dr Catherine Kelly, Consultant Oncologist at the Mater Misericordiae University Hospital, Dublin, and Associate Professor at University College Dublin (UCD), Dublin, the research found that most people living with cancer are receptive to going on a trial, with most who were offered the opportunity to participate in a trial accepting it.

Commenting on the altruism of people taking part in cancer trials, Prof Bryan Hennessy, Clinical Lead with Cancer Trials Ireland, said, "This research clearly illustrates the generosity of people living with cancer.

"While cancer trials can give people access to promising new treatments not yet available through the mainstream health service, it's humbling to see that one of the most important factors for their participation is to advance cancer research to help future generations," he said.

Dr Kelly said, "We want to better understand how we can further support people living with cancer and this research will help us do that.

"While most people living with cancer said they fully understand the term cancer clinical trials, the research also highlighted a myth about what participating in a cancer trial really means.

"Many patients consider cancer trials to be a last resort treatment option, with 22% of people surveyed believing that cancer trials were only used when standard treatments had not worked.

"On the contrary, cancer trials can offer hope to all patients with cancer, not just those for whom standard treatment has not been successful.

"Cancer trials test new and potentially more effective ways to prevent, diagnose, and treat cancer. Most of our trials involve testing new drugs which show promise or new combinations of existing drugs which may offer better outcomes than treatments currently used," Dr Kelly said.

The survey also found that when making decisions about cancer trial participation nearly six in ten (56%) would consult their family as a frequent source of support, with two in ten (21%) frequently consulting the internet.

Cancer doctors and specialist nurses scored highest in terms of trust among people living with cancers; 70% and 50% of respondents gave them full scores respectively.

Dr Catherine Kelly, Consultant Oncologist, Mater Misericordiae University Hospital and UCD.

Need for more patient education.

Speaking at the launch of the ***Just Ask Your Doctor!*** campaign, during which Dr Kellly presented her findings, Eibhlín Mulroe, CEO of Cancer Trials Ireland said, "The findings of this research show us that less than one in ten (9%) patients living with cancer ask about participating in cancer trials and their knowledge of the workings of cancer trials needs to be developed.

"They point to the need to improve the community's understanding of cancer trials and their potential benefits.

"The Cancer Trials Ireland ***Just Ask Your Doctor!*** campaign aims to empower people with cancer to trigger information-rich conversations with their doctor and support teams.

Eibhlín Mulroe, CEO of Cancer Trials Ireland

"We're calling on all people living with cancer to just ask their doctor if there is a relevant cancer trial that they can join to enhance their treatment options. All cancer trials are listed on our website; www.cancertrials.ie.

The ***Just Ask Your Doctor!*** campaign is part-funded by unrestricted grants from the pharmaceutical companies MSD, Pfizer, AbbVie, Novartis and Roche.

First trial of its kind opens in Ireland to examine the next step in the multimodal treatment of head and neck cancer - combining immunotherapy with chemoradiotherapy (CRT).

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 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 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. It is 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 Human Papilloma Virus (HPV). Of newly diagnosed patients with SCCHN, approximately 60% present with locally or regionally advanced disease, for whom standard of care is combination CRT with cisplatin. In this group, locoregional failure rates can range between 35-65% (depending on tumour site, stage, and HPV status), with 10-30% of patients developing distant metastases. A 3-year progression free survival (PFS) rate of approximately 61.2% 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 treatment 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 by 6.5% at 5 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). There is also emerging clinical data suggesting the development of an immune anti-tumour memory after such combination therapy.

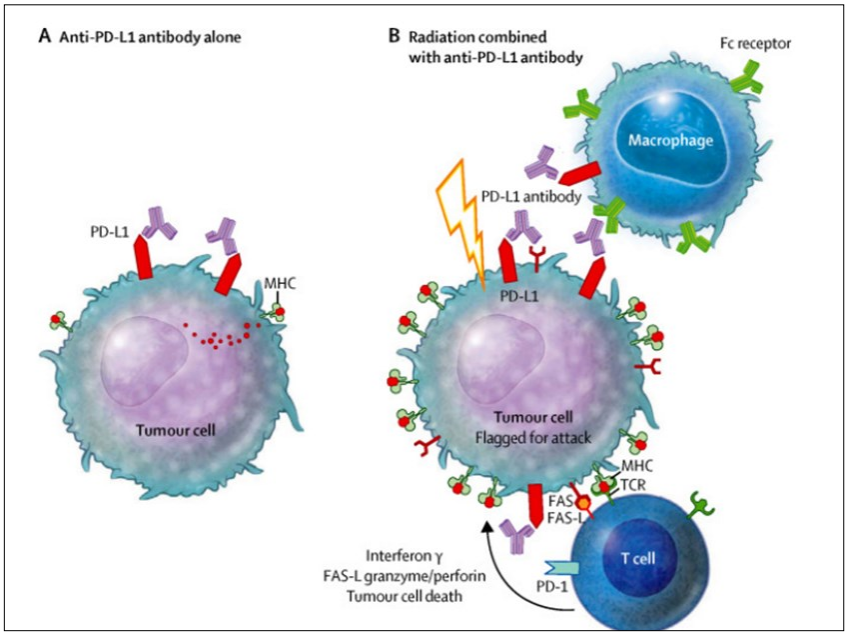

Figure: Synergistic therapeutic effect of Anti-PD-L1 antibody and radiotherapy

The primary hypothesis of this trial 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 overall survival, 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 (swallowing difficulties) optimised intensity modulated radiotherapy (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 coordinated (De-ESCALaTE HPV) in Ireland by Cancer Trials Ireland, and are now closed to accrual with follow up ongoing and early results awaited.

Six Irish radiation oncology departments to participate in study to reduce side effects for patients undergoing radiotherapy (RT) 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 Lydia O'Sullivan, Clinical Research Associate, Cancer Trials Ireland.

TRI LARC is a randomised Phase II 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 6 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% of cancers in women and 14% in men in Ireland and is the third leading cause of cancer death in women and the second in men (Source: NCRI).

Pre-operative RT or chemoradiotherapy (CRT) is internationally accepted as standard practice in the management of locally advanced rectal cancer (i.e. 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 pre-operative 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 3 or 4 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% acute grade III and IV toxicity (12% acute diarrhoea, 11% dermatologic effects), and 14% grade III and IV late toxicity (9% chronic diarrhoea and/or small bowel obstruction, 2% re-operation rate for small bowel obstruction, 4% anastomotic strictures, 2% 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). The advantages of this technique

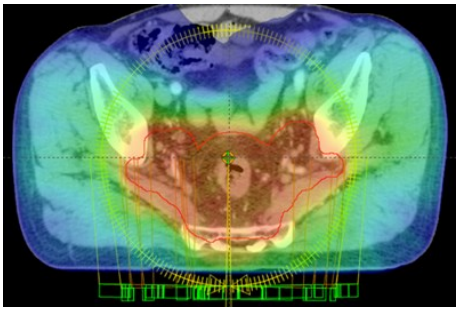

Figure: Volumetric Modulated Arc Therapy plan for patient with rectal cancer.

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 pre-operative 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 the Royal College of Surgeons in Ireland (RCSI) / Beaumont Hospital and the National Institute for Cellular Biotechnology / Dublin City University 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 its support of the translational sub-studies.

Celebrating at Farmleigh House

A huge thanks to our patient advocates who played a pivotal role in our 2018 International Clinical Trials Day celebrations and the launch of our 2018 ***Just Ask Your Doctor!*** public information campaign at Farmleigh House in Dublin. They gave their time generously and with great energy to spread the cancer trial message far and wide to encourage people with cancer to Just Ask!

We would like to thank our partners for supporting and being part of our ***Just Ask Your Doctor!*** campaign: MSD, Pfizer, AbbVie, Novartis and Roche. And we would like to thank the teams in research units around the country, our funders and our central office team for making this year's celebrations a great success.

Finally we would like to thank the Minister for Health and the team at Farmleigh House for making the facilities available to us.

(Above) The panel speakers at Farmleigh House included (L to R) Ashley Bazin, Team Leader, Clinical Trials Unit, Tallaght Hospital; Patrick Kivlehan, Advocate; Evelyn O'Rourke (Chair), Member of the Board of Cancer Trials Ireland; Dr Linda Coate, Vice Clinical Lead, Cancer Trials Ireland & Consultant Medical Oncologist, University Hospital Limerick; and Emma Corcoran, Advocate.

(Left) Pictured at the launch of this year's Just Ask Your Doctor! public information campaign were patient advocates (L to R): Loreto Gregory, Drogheda; Ruth Larkin, Dublin; Patrick Kivlehan, Kildare; Emma Corcoran, Dublin and Eddie MacEoin, Cork.

Pictured at the launch were (L to R) Ann Marie Cullen, Head of Oncology Medical Affairs, Novartis; Orlaith Gavan, Oncology Medical Lead, Pfizer; Paula Moyles and Mairead Henderson, both Country Study Managers at Roche; Prof Bryan Hennessy, Clinical Lead, Cancer Trials Ireland; Ashlin Dunne, Regional Project Management Lead – Oncology, MSD; Eibhlín Mulroe, CEO, Cancer Trials Ireland; Dr Linda Coate, Vice Clinical Lead, Cancer Trials Ireland; Dr Jonathan Westrup, Chair of Cancer Trials Ireland; Evelyn O'Rourke, Member of the Board of Cancer Trials Ireland; Dr Paul Kelly, Consultant Radiation Oncologist at Cork University Hospital and Dr Robert O'Connor, Head of Research, Irish Cancer Society, both members of the Board of Cancer Trials Ireland.

Members of the clinical trials team in Galway gearing up for the big day: (L to R) Dr Robert Henderson, Specialist Registrar in Haematology; Jessica Walsh, Research Nurse BCNI; Olive Forde, Cancer clinical trial coordinator; and Swapnil Gaware, Clinical Research Associate.

(L to R) Martina Smith, Unit Co-Ordinator; and Pauline Joseph, Research nurse, both from Mater Misericordiae University Hospital, Dublin.

Advocate Eddie MacEoin with his two grandchildren James and Laoise chasing the elusive ducks at Farmleigh House.

Above: Research Assistants Fausta Barizaite and Naoise Kelly spread trial awareness at St. Vincent's University Hospital, Dublin.

Left: From University Hospital Limerick (L to R) Ms Lorraine O'Connell CNM 2; Dr. Greg Korpanty Consultant Medical Oncologist; Maureen O'Grady CNM3 and Rachel Harnett, Administration.

Posters and Abstracts with Cancer Trials Ireland Members involved presented at ESMO2018 Congress which this year attracted 28,000 attendees. (Follow hyperlinks for more detail.)

Monitoring the effect of PI3K inhibition on HER2 therapy resistant breast cancer using serial analysis of PIK3CA mutant tumour DNA in plasma

N. Keegan[1], S. Toomey[2], A. Farrelly[2], A. Carr[2], G. Calzaferri[3], J. Walshe[4], G. Gullo[4], J.P. Crown[4], K. Egan[5], A. Hernando[6], A. Teiserskiene[6], L. Grogan[7], O.S. Breathnach[7], P.G. Morris[5], B. Hennessy[8]

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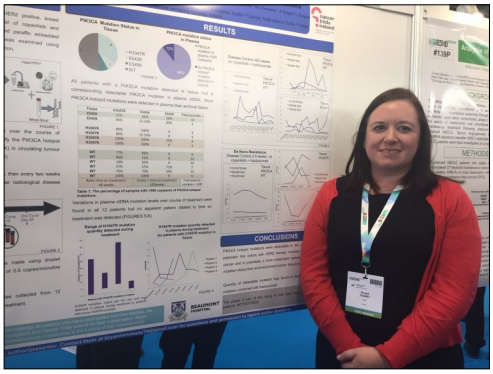

Pictured at the PantHER Poster at ESMO2018, Dr Sinead Toomey, lecturer and translational oncology research scientist at RCSI.

The impact of the 21 gene recurrence score (RS) on chemotherapy (CHemoRx) prescribing in hormone receptor (HR) positive, lymph node positive (LN1) early-stage breast cancer (BC) in Ireland: A national, multi-centre, prospective study (CTRIAL-IE 15-34)

Hassan[1], N. Keegan[1], C. O'Leary[1], L. McSorley[1], T. Mahgoub[1], S. O'Reilly[2], J. Walshe[3], M.J. Kennedy[4], L. Coate[5], M. O'Connor[6], M. Keane[7], C.M. Kelly[8], M. Milewski[1], S. Molloy[1], K. Eagan[1], V. Murphy[9], O.S. Breathnach[1], L. Grogan[1], B. Hennessy[1], P.G. Morris[1]

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Pictured at the 21 Recurrence Score poster at ESMO2018 018 were Dr Anees Hassan; the first author and consultant oncologist at Letterkenny University Hospital, Dr Verena Murphy; Translational Research Leader, Cancer Trials Ireland and Dr Kathleen Scott; Head of Operations and Clinical Programs, Cancer Trials Ireland.

Clinical outcomes in patients (pts) with estrogen receptor–positive (ER1)/human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC) with objective response (OR) or without objective response (non-OR) in PALOMA-2

H.S. Rugo[1], R.S. Finn[2], K.A. Gelmon[3], A.A. Joy[4], O.N. Lipatov[5], N. Harbeck6, A. Castrellon[7], H. Mukai[8], J.M. Walshe[9], A. Mori[10], E. Gauthier[11], D.R. Lu[12], E. Bananis[13], M. Martın[14], V. Dieras[15]

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Non-invasive genotyping and monitoring of tumor evolution in locally advanced rectal cancer (LARC) patients using circulating tumor DNA (ctDNA)

S. Toomey[1], A. Sartori[2], D. Irwin[3], S. Hummel[4], A. Carr[1], C.L. Lee[5], P. Armstrong[1], A. Farrelly[6], S. El-Masry[7], D. McNamara[8], P.G. Morris[9], L. Grogan[9], O.S. Breathnach[9], L. O'Sullivan[10], S. Bradshaw[11], A.N.A.M. Rashed[12], R. Smyth[1], J. Workman[1], B. O'Neill[13], B. Hennessy[9]

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Evolution and clinical impact of EGFR mutations in circulating free DNA in the BELIEF trial

A. Curioni[1], E. Felip[2], U. Dafni[3], M-A. Molina[4], O. Gautschi[5], S. Peters6, B. Massutı[7], R. Palmero[8], S. Ponce[9], E. Carcereny[10], M. Fruh[11], M. Pless[12], S. Popat[13], S. Cuffe[14], N. Karachaliou[15], R. Kammler[16], M. Kassapian[17], H. Roschitzki-Voser[16], R.A. Stahel[1], R. Rosell[15]

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Response to neoadjuvant chemotherapy in ICON8: A GCIG phase III randomised trial evaluating weekly dose-dense chemotherapy integration in first-line epithelial ovarian/ fallopian tube/ primary peritoneal carcinoma (EOC) treatment

A.R. Clamp[1], I.A. McNeish[2], A. Dean[3], D. Gallardo-Rincon[4], J-W. Kim[5], D.M. O'Donnell[6], J. Hook[7], S. Blagden[8], J.D. Brenton[9], R. Naik[10], T.J. Perren[7], S. Sundar[11], A.D. Cook[12], E.C. James[13], H. Gabra[14], R. Lord[15], M. Hall[16], G. Dark[17], R.S. Kaplan[13], J.A. Ledermann[18]

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A randomised phase III trial evaluating the addition of denosumab to standard first-line treatment in advanced NSCLC: The ETOP and EORTC SPLENDOUR trial

S. Peters[1], S.J. Danson[2], B. Hasan[3], N. Reinmuth[4], M. Majem[5], K.G. Tournoy[6], M.T. Mark[7], M. Pless[8], M. Cobo[9], D. Rodriguez-Abreu[10], L. Falchero[11], B. Massutı[12], L. Coate[13], R. von Moos[14], C.C. Zielinski[15], E. De Maio3, M. O'Brien[16], H. Roschitzki-Voser[17], U. Dafni[18], R.A. Stahel[19]

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Academic publications from Cancer Trials Ireland Investigators

Dr Orla Casey, Translational Project Manager, Cancer Trials Ireland

Here's a list of the 14 publications in academic peer reviewed journals since the last DSSG Digest (Spring) in which Cancer Trials Ireland investigators participated. If you would like your publications included in our next listing please contact orla.casey@cancertrials.ie

Breast

Cancer Trials Ireland Study Number: short name. 04-01: AZURE
Brown, J., E. Rathbone, S. Hinsley, W. Gregory, F. Gossiel, H. Marshall, R. Burkinshaw, H. Shulver, H. Thandar, G. Bertelli, K. Maccon, A. Bowman, A. Hanby, R. Bell, D. Cameron and R. Coleman (2018). "**Associations Between Serum Bone Biomarkers in Early Breast Cancer and Development of Bone Metastasis: Results From the AZURE (BIG01/04) Trial**." J Natl Cancer Inst 110(8): 871-879.

Cancer Trials Ireland Study Number: short name. 12-40: EORTC 10085
Cardoso, F., J. M. S. Bartlett, L. Slaets, C. H. M. van Deurzen, E. van Leeuwen-Stok, P. Porter, B. Linderholm, I. Hedenfalk, C. Schröder, J. Martens, J. Bayani, C. van Asperen, M. Murray, C. Hudis, L. Middleton, J. Vermeij, K. Punie, J. Fraser, M. Nowaczyk, I. T. Rubio, S. Aebi, C. Kelly, K. J. Ruddy, E. Winer, C. Nilsson, L. Dal Lago, L. Korde, K. Benstead, O. Bogler, T. Goulioti, A. Peric, S. Litière, K. C. Aalders, C. Poncet, K. Tryfonidis and S. H. Giordano (2018). "**Characterization of male breast cancer: results of the EORTC 10085/TBCRC/BIG/ NABCG International Male Breast Cancer Program**." Ann Oncol 29(2): 405-417.

Cancer Trials Ireland Study Number: short name. 12-45: SNAP
Gennari, A., Z. Sun, U. Hasler-Strub, M. Colleoni, M. J. Kennedy, R. Von Moos, J. Cortés, M. J. Vidal, B. Hennessy, J. Walshe, K. A. Parraga, K. Ribi, J. Bernhard, S. M. Murillo, O. Pagani, A. Barbeaux, S. Borstnar, M. Rabaglio-Poretti, R. Maibach, M. M. Regan, G. Jerusalem and C. n. T. I. a. S. G. International Breast Cancer Study Group (2018). "**A randomized phase II study evaluating different maintenance schedules of nab-paclitaxel in the first-line treatment of metastatic breast cancer: final results of the IBCSG 42-12/BIG 2-12 SNAP trial**." Ann Oncol 29 (3): 661-668.

Cancer Trials Ireland Study Number: short name. 06-31: TAILORx
Sparano, J. A., R. J. Gray, D. F. Makower, K. I. Pritchard, K. S. Albain, D. F. Hayes, C. E. Geyer, E. C. Dees, M. P. Goetz, J. A. Olson, T. Lively, S. S. Badve, T. J. Saphner, L. I. Wagner, T. J. Whelan, M. J. Ellis, S. Paik, W. C. Wood, P. M. Ravdin, M. M. Keane, H. L. Gomez Moreno, P. S. Reddy, T. F. Goggins, I. A. Mayer, A. M. Brufsky, D. L. Toppmeyer, V. G. Kaklamani, J. L. Berenberg, J. Abrams and G. W. Sledge (2018). "**Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer**." N Engl J Med 379(2): 111-121.

Gastrointestinal

Cancer Trials Ireland Study Number: short name. 12-07: LCCC 1029 (Regorafenib)
Sanoff, H. K., R. M. Goldberg, A. Ivanova, S. O'Reilly, S. S. Kasbari, R. D. Kim, R. McDermott, D. T. Moore, W. Zamboni, W. Grogan, A. L. Cohn, T. S. Bekaii-Saab, G. Leonard, T. Ryan, O. O. Olowokure, N. H. Fernando, J. McCaffrey, B. F. El-Rayes, A. M. Horgan, G. B. Sherrill, G. H. Yacoub and B. H. O'Neil (2018). "**Multicenter, randomized, double-blind phase 2 trial of FOLFIRI with regorafenib or placebo as second-line therapy for metastatic colorectal cancer**." Cancer 124 (15): 3118-3126.

Cancer Trials Ireland Study Number: short name. 14-19: BMS CA209-142/CheckMate 142
Overman, M. J., S. Lonardi, K. Y. M. Wong, H. J. Lenz, F. Gelsomino, M. Aglietta, M. A. Morse, E. Van Cutsem, R. McDermott, A. Hill, M. B. Sawyer, A. Hendlisz, B. Neyns, M. Svrcek, R. A. Moss, J. M. Ledeine, Z. A. Cao, S. Kamble, S. Kopetz and T. André (2018). "**Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer**." J Clin Oncol 36(8): 773-779.

Cancer Trials Ireland Study Number: short name. 12-16: AC-ANGIOPREDICT
Smeets, D., I. S. Miller, D. P. O'Connor, S. Das, B. Moran, B. Boeckx, T. Gaiser, J. Betge, A. Barat, R. Klinger, N. C. T. van Grieken, C. Cremolini, H. Prenen, M. Mazzone, J. Depreeuw, O. Bacon, B. Fender, J. Brady, B. T. Hennessy, D. A. McNamara, E. Kay, H. M. Verheul, N. Maarten, W. M. Gallagher, V. Murphy, J. H. M. Prehn, M. Koopman, C. J. A. Punt, F. Loupakis, M. P. A. Ebert, B. Ylstra, D. Lambrechts and A. T. Byrne (2018). "**Copy number load predicts outcome of metastatic colorectal cancer patients receiving bevacizumab combination therapy**." Nat Commun 9(1): 4112.

Cancer Trials Ireland Study Number: short name. 12-16: AC-ANGIOPREDICT
van Dijk, E., H. D. Biesma, M. Cordes, D. Smeets, M. Neerincx, S. Das, P. P. Eijk, V. Murphy, A. Barat, O. Bacon, J. H. M. Prehn, J. Betge, T. Gaiser, B. Fender, G. A. Meijer, D. A. McNamara, R. Klinger, M. Koopman, M. P. A. Ebert, E. W. Kay, B. T. Hennessey, H. M. W. Verheul, W. M. Gallagher, D. P. O'Connor, C. J. A. Punt, F. Loupakis, D. Lambrechts, A. T. Byrne, N. C. T. van Grieken and B. Ylstra (2018). "**Loss of Chromosome 18q11.2-q12.1 Is Predictive for Survival in Patients With Metastatic Colorectal Cancer Treated With Bevacizumab**." J Clin Oncol 36(20): 2052-2060.

Genitourinary

Cancer Trials Ireland Study Number: short name. 15-20: P3BEP
Lawrence, N. J., H. Chan, G. Toner, M. R. Stockler, A. Martin, S. Yip, N. Wong, A. Yeung, D. Mazhar, F. Pashankar, L. Frazier, R. McDermott, R. Walker, H. Tan, I. D. Davis, P. Grimison and ANZUP (2018). "**Protocol for the P3BEP trial (ANZUP 1302): an international randomised phase 3 trial of accelerated versus standard BEP chemotherapy for adult and paediatric male and female patients with intermediate and poor-risk metastatic germ cell tumours**." BMC Cancer 18(1): 854.

Cancer Trials Ireland Study Number: short name. 05-03: Spinal Cord Compression
Lee, K. A., M. Dunne, C. Small, P. J. Kelly, O. McArdle, J. O'Sullivan, D. Hacking, M. Pomeroy, J. Armstrong, M. Moriarty, A. Clayton-Lea, I. Parker, C. D. Collins and P. Thirion (2018). "**(ICORG 05-03): prospective randomized non-inferiority phase III trial comparing two radiation schedules in malignant spinal cord compression (not proceeding with surgical decompression); the quality of life analysis**." Acta Oncol 57(7): 965-972.

Cancer Trials Ireland Study Number: short name. 15-35: INTERVAL-GAP4
Newton, R. U., S. A. Kenfield, N. H. Hart, J. M. Chan, K. S. Courneya, J. Catto, S. P. Finn, R. Greenwood, D. C. Hughes, L. Mucci, S. R. Plymate, S. F. E. Praet, E. M. Guinan, E. L. Van Blarigan, O. Casey, M. Buzza, S. Gledhill, L. Zhang, D. A. Galvão, C. J. Ryan and F. Saad (2018). "**Intense Exercise for Survival among Men with Metastatic Castrate-Resistant Prostate Cancer (INTERVAL-GAP4): a multicentre, randomised, controlled phase III study protocol**." BMJ Open 8(5): e022899.

Gynaecological

Cancer Trials Ireland Study Number: short name. 09-03: AGO-OVA 16 (GSK: VEG110655)
Friedlander, M., J. Rau, C. K. Lee, W. Meier, A. Lesoin, J. W. Kim, A. Poveda, M. Buck, G. Scambia, M. Shimada, F. Hilpert, M. T. King, P. Debruyne, A. Bologna, S. Malander, B. J. Monk, E. Petru, P. Calvert, T. J. Herzog, C. Barrett and A. du Bois (2018). "**Quality of life in patients with advanced epithelial ovarian cancer (EOC) randomized to maintenance pazopanib or placebo after first-line chemotherapy in the AGO-OVAR 16 trial. Measuring what matters-patient-centered end points in trials of maintenance therapy**." Ann Oncol 29(3): 737-743.

Lymphoma and Haematology

Cancer Trials Ireland Study Number: short name. 07-01: CLL-IRL
Appleby, N., D. O'Brien, F. M. Quinn, L. Smyth, J. Kelly, I. Parker, K. Scott, M. R. Cahill, G. Crotty, H. Enright, B. Hennessy, A. Hodgson, M. Leahy, H. O'Leary, M. O'Dwyer, A. Hayat and E. A. Vandenberghe (2018). "**Risk adjusted therapy in chronic lymphocytic leukemia: a phase II cancer trials Ireland (CTRIAL-IE [ICORG 07-01]) study of fludarabine, cyclophosphamide, and rituximab therapy evaluating response adapted, abbreviated frontline therapy with FCR in non-del(17p) CLL**." Leuk Lymphoma 59(6): 1338-1347.

Lung

Cancer Trials Ireland Study Number: short name. 06-34: Palliative Lung
McDermott, R. L., J. G. Armstrong, P. Thirion, M. Dunne, M. Finn, C. Small, M. Byrne, C. O'Shea, L. O'Sullivan, A. Shannon, E. Kelly and D. J. Hacking (2018). "**Cancer Trials Ireland (ICORG) 06-34: A multi-centre clinical trial using three-dimensional conformal radiation therapy to reduce the toxicity of palliative radiation for lung cancer**." Radiother Oncol 127(2): 253-258.

Practice-changing radiation therapy trials for the treatment of cancer: where are we 150 years after the birth of Marie Curie?

Compiled by Aoife Shannon, Clinical Project Manager, Cancer Trials Ireland, and Dr Pierre Thirion, Consultant Radiation Oncologist, St Luke's Radiation Oncology Network.

Marie Curie discovered radium and polonium, and made a huge contribution to cancer research.

To mark the 150th birthday of Marie Curie, the 'Godmother of Radiotherapy', National Cancer Research Institute (NCRI)'s Radiotherapy Research Group (CTRad) reviewed key practice changing trials in radiotherapy that have been performed in the UK and across the world over the last two decades. The review, recently published in the *British Journal of Cancer*, identified 47 practice changing trials, involving around 50000 patients. https://www.nature.com/articles/s41416-018-0201-z

Cancer Trials Ireland radiotherapy centres joined two of the studies referenced in the review article, which begins as follows:

'As we mark 150 years since the birth of Marie Curie, we reflect on the global advances made in radiation oncology and the current status of radiation therapy (RT) research. Large-scale international RT clinical trials have been fundamental in driving evidence-based change and have served to improve cancer management and to reduce side effects. Radiation therapy trials have also improved practice by increasing quality assurance and consistency in treatment protocols across multiple centres. This review summarises some of the key RT practice-changing clinical trials over the last two decades, in four common cancer sites for which RT is a crucial component of curative treatment: breast, lung, urological and lower gastro-intestinal cancer. We highlight the global inequality in access to RT, and the work of international organisations, such as the International Atomic Energy Agency (IAEA), the European SocieTy for Radiotherapy and Oncology (ESTRO), and the United Kingdom National Cancer Research Institute Clinical and Translational Radiotherapy Research Working Group (CTRad), that aim to improve access to RT and facilitate radiation research h. We discuss some emerging RT technologies including proton beam therapy and magnetic resonance linear accelerators and predict likely future directions in clinical RT research.'

Localised Prostate Cancer (CHHiP: CTRIAL-IE (ICORG) 08-18) – 20 Irish patients enrolled in SLRON and GUH:

'Based on the principle that prostate cancer may be more sensitive to increases in daily dose per fraction than previously thought, the CHHiP trial compared two hypofractionated regimens (60 Gy in 20 fractions vs. 57 Gy in 19 fractions) to the standard UK *[and Ireland]* regimen at the time (74 Gy in 37 fractions), in men with T1b–T3aN0M0 prostate cancer. The 5 year results demonstrated that 60 Gy in 20 fractions was non-inferior to the standard regimen in terms of biochemical or clinical failure, and was associated with similar toxicity. As a result, this trial has already changed practice in the majority of UK *[and Irish]* centres. The RTOG 0415, HYPRO and PROFIT trials have also recently published data supporting the use of moderate hypofractionation; it seems likely that these trials together will lead to wider international use of hypofractionation in low-intermediate-risk prostate cancer'.

Small Cell lung cancer (CONVERT: CTRIAL-IE (ICORG) 11-28)) – opened in SLRON.

'Very little progress was made for several decades in the systemic treatment of both limited- and extensive-stage small cell lung cancer (SCLC). Recently, advances in RT techniques, use of prophylactic cranial irradiation for all stages of SCLC, and improved combination of chemotherapy with RT have led to major improvements in survival. The current standard of care for patients with limited-stage SCLC is based on an RCT that compared once daily with twice-daily RT delivered concurrently with chemotherapy, which demonstrated superiority of twice-daily RT in terms of survival. However, since the publication of this study in 1999, there has been a lack of consensus regarding routine use of twice-daily RT, despite its superiority, due to logistical issues and concerns regarding toxicity (for example, one-third of the patients developed ≥grade 3 radiation oesophagitis). To help resolve this, the CONVERT trial compared twice-daily RT (45 Gy in 30 fractions) to a higher RT dose delivered once daily (66 Gy in 33 fractions), both given concurrently with chemotherapy. Overall survival outcomes did not differ between the two groups; however, the survival achieved in both groups was higher and toxicity much lower (>50% reduction) than previously reported. As this trial was designed to show superiority of once-daily RT and was not powered to show equivalence, the implication is that twice-daily RT should be considered the standard of care'. *[It is the present standard of care at Irish centres].*

'What is the future of RT research?

Future RT research will focus on reducing treatment toxicity and on further improving survival rates and management of locoregional relapse. This is likely to be increasingly driven by biomarkers to assist in individualising RT treatment. There now exist validated biomarkers for some cancer types, for example p16 positivity predicts better prognosis and response to chemoRT treatment in head and neck cancer. However, for most cancer types, biomarkers for response to RT treatment and toxicity are not yet established, and this will be an important area of future translational RT research.'

Cancer Trials Ireland studies open to accrual

Purple = Industry studies Green = Cancer Trials Ireland studies Orange = Collaborative Group studies

DSSG	General Group	Cancer Trials Ireland No:	Study Name:
Breast	Trans	09-07	Breast Cancer Proteomics and Molecular Heterogeneity
Breast	Trans	10-11	Circulating miRNA
Breast	Trans	10-15	Exosomal HER2
Breast	Trans	10-16	Ovarian Reserve
Breast	Trans	12-09	CharactHer
Breast	Trans	15-34	Recurrence Score
Breast	Clinical	15-17	PALLAS
Breast	Clinical	15-49	NeoTRIP
Breast	Clinical	15-02	PantHER
Breast	Radio	15-03	NSABP B-51
Breast	Clinical	15-16	FLIPPER
Breast	Clinical	16-20	POSITIVE
Breast	Clinical	17-08	KEYNOTE-522
Breast	Clinical	17-33	VIOLETTE
CNS	Trans	08-13	Serum Protein Markers for Glioma
CNS	Clinical	15-29	M13-813 INTELLANCE 1
CNS	Radio	15-41	ROAM
GI	Clinical	10-14	Neo-AEGIS
GI	Trans	12-27	CRAC Plasma Biomarkers
GI	Trans	12-31	PDAC Plasma Biomarkers
GI	Radio	12-38	TRI-LARC
GI	Clinical	14-19	BMS CA209-142 (CheckMate 142)
GI	Clinical	14-20	GERCOR STRATEGIC-1
GI	Clinical	16-73	BMS CA209-577
GI	Clinical	16-77	ARMO Artist
GI	Clinical	16-58	MErCuRIC
GI	Trans	17-26	COLOSSUS
GU	Clinical	11-34	TIGER
GU	Clinical	13-09	PEACE-1
GU	Clinical	13-23	Neo-adjuvant Abiraterone prostate
GU	Trans	14-04	iPROSPECT
GU	Clinical	14-07	ENZARAD (closed to recruitment 30-Jun-2018)
GU	Clinical	15-19	CARD
GU	Trans	16-07	IPCOR
GU	Clinical	16-21	PEACE III
GU	Clinical	16-63	Roche IMmotion010
GU	Clinical	16-69	Eisai E7080-G000-307
GU	Clinical	16-70	BMS CA209-274
GU	Clinical	17-03	Roche CO39303
GU	Clinical	17-04	Bayer 17403/ FORT-1
GU	Clinical	17-05	MSD KEYNOTE-361 (closed to recruitment 31-May-2018)
Gynae	Radio	09-06	Endometrial - IMRT v 3D RT
Gynae	Clinical	11-29	ICON8B
Gynae	Clinical	14-02	SHAPE
Gynae	Clinical	16-04	PRIMA
Gynae	Clinical	16-68	FORWARD 1
H & L	Clinical	15-38	CHRONOS-3
H & L	Clinical	15-36	Protocol 04-30 (INSPIRE)
H & L	Clinical	16-02	CyBorD-DARA (closed to recruitment since last DSSG)

Cancer Trials Ireland studies open to accrual

Purple = Industry studies Green = Cancer Trials Ireland studies Orange = Collaborative Group studies

DSSG	General Group	Cancer Trials Ireland No:	Study Name:
H & L	Clinical	16-09	Astellas 2215 CL 0301 (closed to recruitment since last DSSG)
H & L	Clinical	16-60	CLL13
H & L	Clinical	17-06	CHRONOS 4
H & L	Clinical	17-07	CheckMate 744
H & L	Clinical	17-24	M16-043 (opened and closed since last DSSG)
H & L	Clinical	18-04	SMM-IMWG (opened and closed since last DSSG)
Head & Neck	Clinical	17-20	BMS CA209-615
Head & Neck	Radio + IMP	17-22	JAVELIN 100 Head and Neck
Lung	Radio	15-05	Oligo-Recurrent Metastatic Disease (closed to accrual May18)
Lung	Radio	15-47	INTENSE (on hold)
Lung	Clinical	17-Oct	MK3475-604
Lung	Clinical	16-61	ETOP BOOSTER
Lung	Clinical	15-40	MK3475-091 (PEARLS)
Lung	Clinical	17-36	MK3475-654
Lung	Clinical	16-25	Roche MO29872
Lung	Clinical	17-35	MK3475-715
Lung	Clinical	16-80	Abbvie Meru M16-298
Lung	Clinical	17-23	BMS CA209-9LA
Lung	Clinical	16-59	ALERT-Lung
Lung	Clinical	17-09	MK3475-598
Lung	Clinical	18-14	EMPOWER 16113
Melanoma	Trans	13-22	SYS-ACT
Melanoma	Trans	17-25	DESCRIBE III
Melanoma	Clinical	17-39	BMS CA017-055
Basket	Trans	08-40	SNP Study
Basket	Clinical	15-42	LOXO-101
Paeds	Trans	16-30	AALL08B1
Paeds	Clinical	16-31	AALL0932
Paeds	Clinical	16-32	AALL1131
Paeds	Clinical	16-33	UKALL 2011
Paeds	Trans	16-34	LLR Leukaemia Cell bank
Paeds	Clinical	16-36	EuroNet PHL-C1 (HD 2007 10)/ HD Interim Study
Paeds	Clinical	16-37	EWOG-MDS-2006
Paeds	Clinical	16-38	SIOP Europe
Paeds	Clinical	16-39	LTI Study
Paeds	Clinical	16-40	NBL BEACON
Paeds	Clinical	16-41	LINES
Paeds	Trans	16-42	IMPORT
Paeds	Trans	16-43	Tumour Banking Study
Paeds	Registry	16-44	EU-Rhabdoid Registry
Paeds	Trans	16-45	FACT
Paeds	Trans	16-46	EWOG-SAA 2010
Paeds	Clinical	16-47	STS 2006 04 - RMS 2005
Paeds	Clinical	16-50	AZA-JMML-001
Paeds	Clinical	16-51	MESRAT Study
Paeds	Clinical	16-52	EURO EWING 2012
Paeds	Clinical	16-53	Interfant 06
Paeds	Clinical	16-82	My Child
Paeds	Clinical	18-16	ITCC 059

Patient Consultants Committee established as Board committee

The Board of Cancer Trials Ireland has established a new sub-committee of the Board, the Patient Consultants Committee (PCC), which brings together people who have experience of clinical trials and are interested in becoming involved in the work of Cancer Trials Ireland.

The PCC held its inaugural meeting on Friday 12th October 2018. Participants included Diane Hanly (Chair), Eddie and Teresa MacEoin, Kay Curtin, Patrick Kivlehan and Seamus Cotter. Diane Hanly will represent the PCC on the main Board of Cancer Trials Ireland.

Members of the PCC have been inspired by the work of the Northern Ireland Cancer Research Consumer Forum and took the opportunity to visit Belfast over the summer (see photo). Margaret Grayson and Ruth Boyd met with members of the PCC and staff from Cancer Trials Ireland and shared their experiences over the past 10 years of involving patients in research.

There is a very clear distinction between engaging with patients on research and involving patients in research decisions. The Forum is very much a leader in this area where their members are reviewing protocols, patient information leaflets and questionnaires.

The PCC recognises that it has someway to go in this context but there are willing members who would like be more involved in our research and the PCC will give them the opportunity to do this.

Members of the newly established PCC and staff from Cancer Trials Ireland met with the Northern Ireland Cancer Research Consumer Forum in Belfast over the summer.

With this in mind there will be new faces from the PCC attending some of our closed DSSG meetings during the Autumn DSSG meeting.

Kay Curtin and Diane Hanly have been involved in the Melanoma and Breast DSSGs over the last number of years and this has been well received and appreciated by our members. We aim to have patient consultants in each DSSG by January 2019. Look out for Eddie, Teresa, Patrick and more in the next DSSG; say hello and welcome them aboard our Cancer Trials Ireland team!

BREAST-PREDICT celebrates

We were delighted to join our great partner the Irish Cancer Society at its family-friendly day out to celebrate one of its greatest research achievements, BREAST-PREDICT, the country's first collaborative cancer research centre.

Through the public's generous donations, €7.5 million was invested in this centre, which funds the work of 50 breast cancer researchers across the country.

Joining the celebrations (4th from left) is Dr Verena Murphy, Translational Research Leader, Cancer Trials Ireland.

Ministerial Meeting

A delegation from Cancer Trials Ireland met recently with Simon Harris TD, Minister for Health, and Dr Jerome Coffey, Director of the National Cancer Control Programme (NCCP), to discuss implementing the National Cancer Strategy, the opportunities to develop further Ireland's expertise in cancer trials and financial challenges.

Pictured (L to R) Dr Jerome Coffey, Director of the NCCP; Simon Harris TD, Minister for Health; Prof Bryan Hennessy, Clinical Lead; Dr Linda Coate, Vice Clinical Lead; and Eibhlin Mulroe, CEO.