Nivolumab and cabozantinib show strong survival benefits in advanced RCC

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Nivolumab and cabozantinib show strong survival benefits in advanced RCC

JACKEY SUEN

Nivolumab and cabozantinib, used separately as monotherapy, offer a survival benefit over everolimus in patients with advanced renal cell carcinoma (RCC) after failure of first-line anti-VEGF therapy, according to the results of two late-breaking phase III trials presented at the European Cancer Congress (ECC) 2015 in Vienna, Austria.

The CheckMate 025 study randomized 821 patients with advanced RCC, who had failed one or two previous anti-VEGF therapies, to receive nivolumab or everolimus until disease progression or intolerable toxicity. [ECC 2015, abstract 3LBA; N Engl J Med 2015, doi:10.1056/NEJMoa1510665]

“This is the first phase III study to demonstrate a survival benefit with an immune checkpoint inhibitor vs current standard treatment in previously treated advanced RCC,” said lead investigator Professor Padmanee Sharma of the MD Anderson Cancer Center, Houston, Texas, US.

“The survival benefit with nivolumab was observed irrespective of programmed death-ligand 1 [PD-L1] expression,” added Sharma. “The median OS was 21.8 months with nivolumab vs 18.8 months with everolimus in patients with PD-L1 expression level ≥1 percent, and 27.4 vs 21.2 months among those with PD-L1 expression level <1 percent.”

The objective response rate (ORR) was also higher with nivolumab vs everolimus (25 vs 5 percent; p<0.0001), but the median progression-free survival (PFS) was similar between the two arms (4.6 months for nivolumab vs 4.4 months for everolimus; p=0.1135).
“Overall grade 3/4 adverse events [AEs] were less frequent in patients receiving nivolumab vs everolimus [19 vs 37 percent],” reported Sharma. “Quality of life of patients in the nivolumab group improved over time and differed significantly from those in the everolimus group at each assessment.”

Meanwhile, cabozantinib was compared with everolimus in the METEOR (Metastatic RCC Phase III Study Evaluating Cabozantinib vs Everolimus) trial of 658 advanced RCC patients who had progressed within 6 months after receiving VEGF receptor (VEGFR)-tyrosine kinase inhibitor (TKI) therapy. [ECC 2015, abstract 4LBA; N Engl J Med 2015, doi:10.1056/NEJMoa1510016]

After a minimum follow-up of 11 months, the primary endpoint of PFS nearly doubled in patients receiving cabozantinib vs everolimus (median, 7.4 vs 3.8 months; p<0.001).

“The PFS benefit offered by cabozantinib was even more prominent in patients who received sunitinib as their only prior VEGFR-TKI [9.1 months vs 3.7 months for everolimus],” reported lead investigator Professor Toni Choueiri of the Dana-Farber Cancer Institute, Boston, Massachusetts, US.

“Similarly, the ORR was significantly higher with cabozantinib than with everolimus [21 vs 5 percent; p<0.001],” he added. “The interim OS analysis demonstrated a strong trend favouring cabozantinib [HR, 0.67; p=0.005].”

The most frequent grade 3/4 AEs for cabozantinib were hypertension (15 percent), diarrhoea (11 percent), fatigue (9 percent) and hand-foot syndrome (8 percent), while those for everolimus were anaemia (16 percent), fatigue (7 percent) and hyperglycaemia (5 percent).

“The OS benefit of 25 months offered by nivolumab sets a new benchmark for advanced RCC patients previously treated with anti-VEGF therapy,” commented discussant Dr. Cora Sternberg of the San Camillo and Forlanini Hospitals, Rome, Italy. “The impressive efficacy of cabozantinib as shown in the METEOR trial makes it a potential new treatment option for these patients.”

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Regorafenib-induced partial response in metastatic rectal cancer

Over the past few decades, the incidence of colorectal cancer (CRC) has increased around the world. Today, nearly 1.35 million patients worldwide are diagnosed with and close to 700,000 patients die from CRC each year, making CRC the third most common cancer and the second leading cause of cancer death. [Globocan CRC Fact Sheet 2012] It is believed that at least 50% of patients develop metastases with unacceptable tumours. [Ann Oncol 2014;25 Suppl 3:i2i-i3i] Standard treatment for these patients involves chemotherapy based fluoropyrimidines, oxaplatin and irinotecan. However, in recent years, options for the treatment of metastatic CRC have evolved to include the more potent systemic therapies like monoclonal antibodies and an oral multikinase inhibitor.

Dr Lam Kai Seng discusses a case of aggressive metastatic CRC that had undergone extensive treatments with standard chemo-radiotherapy and monoclonal antibody before regorafenib, an oral multikinase inhibitor, was offered as a monotherapy option for this patient whose disease has progressed on standard treatments.

Presentation and management

A 55-year-old male was first diagnosed with an Astler-Coller Stage C2 (3/14) G2 rectal adenocarcinoma in 2006. He underwent an anterior resection and was then started on adjuvant chemo-radiotherapy. He completed six cycles of 5-flourouracil-olivic acid (SFU-FA) and remained in clinical remission for close to 4 years. However, in 2010, a recurrence was detected in the left para-aortic lymph nodes with continuous elevation in his carcinoembryonic antigen (CEA) level. With the hope to cure the patient from this radiotherapy, regorafenib was discussed and coupled with two cycles of SFU-FA. A marked reduction in his CEA level was subsequently seen. The response did not last long and disease progression was detected 3 months later on PET-CT scan following rising CEA level for which patient opted for radiotherapy. Subsequent follow-up showed gradual elevation of his CEA level with no change was detected in a repeat PET-CT scan. A trial of CyberKnife (CK) was offered and resulted in temporary reduction of his CEA level.

In October 2012, progressive disease (PD) was detected at L2 vertebra and oesophageal lymph node. The patient was diagnosed with a KRAS wild type tumour, he was offered XELOX-bevacizumab for six cycles and a complete response (CR) was achieved. He continued treatment for two additional cycles before opting for a break. When patient returned in September 2013, he was judged to have PD on thoracic oesophagus and L2 vertebra. He was counselled on the available standard therapies but opted against irinotecan-cetuximab due to concern of its adverse events (AEs) thus a reintroduction of XELOX-bevacizumab was given. Following four cycles, a repeat PET-CT scan showed partial response (PR) to previous CK treatment where his CEA level stabilized at 38.9 ng/mL. He was advised to continue the treatment but decided not to as he wanted a break from AEIs including rashes, nausea and vomiting. PD was still evident for intravenous drug administration. As a result of deferred treatment, his CEA rose to 55.2 ng/mL later that year.

Seeing the active progression of his disease, coupled with the previous efficacy, he was advised to start treatment with regorafenib at 160 mg once daily in April 2014 (Figure 1). He was monitored weekly for any AEs for the first 2 weeks, subsequently once every 2 weeks, and then on a monthly basis. He reported mild hand-foot skin reactions (HFSR) but generally tolerated the treatment without requiring dose adjustment. He was advised to take it in the evening prior to treatment initiation and had his treatment-related hypertension and liver function test (LFT) well under control. Given his well-managed AEs, he remained on treatment at the same dose. Despite waning and waning CEA levels over 10 months on regorafenib (Figure 2), the patient continued the drug well with a PR achieved at L2 vertebra, with decreased intensity of staining at the para-vertebral node and L2, despite previous progression on standard treatments.

However, patient stopped treatment with regorafenib in late January 2015 after his PET-CT scan showed new lesions at T6 and L1 vertebra, despite the previously seen metabolic focus. The treatment was less active. Following treatment discontinuation due to PD, patient and his caregiver refused further treatment and this resulted in the decline of his ECOG PS from 0 to 2. He developed cord compression arising from L1 vertebra resulting in paraparesis. He still returns for follow up intermittently and is continuously monitored for symptoms with supportive care given if necessary.

Discussion

Patients with metastatic CRC who have progressed on standard therapies bear a dismal prognosis with no approved treatment options. However, this outcome has since changed based on the promising results seen in patients receiving regorafenib in Phase 3a and CONCUR trials where median OS of 8.8 months was reported in pre-treated Asian populations. [Lancet Oncol 2015;16:69-692] The recently presented Phase 3b CONSIGN trial further validates efficacy and safety of regorafenib in real-world setting in 2,872 patients, substantiating the role of regorafenib as an important treatment option for patients whose disease has progressed on standard treatments. [Ann Oncol 2015;26 Suppl 4]

The patient above represents a good example of the clinical benefits of regorafenib when it is offered early in the treatment algorithm once patient has failed standard treatments. Although most patients in the CORRECT and CONCUR trials had disease progression on standard treatments, this patient achieved a PR with reduced tumour mass at the para-vertebral node and L2 vertebra. The timing at which regorafenib was started for this patient concurs with the recommendation of the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO) guidelines after second disease progression on standard treatments thus yielding a significant extension of his PFS.

The ECOG PS of patient at the initiation of regorafenib could also influence how well patients fare during the course of treatment. At ECOG PS ≥ 2 prior to starting treatment with regorafenib, this patient fared considerably well without deterioration of his quality of life. This was confirmed by the results from a large cohort Regorafenib-Pancha Compassionate Program (REBECCA) which recruited more than 500 pre-treated metastatic CRC patients (Figure 4). [Lancet Oncol 2015;16:69-692] It is also worth noting that all patients enrolled in the CORRECT and CONCUR trials had ECOG PS ≤ 1 before treatment initiation with regorafenib. [Lancet 2013;383:103-112] [Lancet Oncol 2013;16:69-692]

Early and proactive prophylaxis, and management of AEs, especially hand-foot skin reaction (HFSR) and liver function test (LFT) abnormalities are important to ensure that patients are able to remain on treatment with regorafenib for as long as they can benefit from it. As the onset of HFSR typically occurs within the first 2 weeks of treatment, this patient was well advised on self-care and was diligently followed up for management of his grade 1 HFSR. Management strategies before the appearance of symptoms are focused on the 3Cs approach – callus, cream and cushion. Pre-existing calluses should be removed, skin moisturised with appropriate creams, and pressure points cushioned with cotton socks, comfortable shoes and insoles. Stepwise dose reduction or interruption of regorafenib should only be considered in the event of symptoms worsening. [The Oncologist 2014;19:669-680]

In summary, this case illustrates that extension of survival benefit is achievable with regorafenib in patients with metastatic CRC after failure of standard treatments, especially if they are offered this oral monotherapy early at second disease progression and if patients are initiated at good ECOG PS. With proactive monitoring, starting within 3 to 4 days of treatment initiation, and timely intervention, the AEs can be effectively managed. [The Oncologist 2014;19:669-680]

Figure 1. The patient’s treatment timeline from diagnosis to termination of treatment with regorafenib

Figure 2. Serum CEA levels of the patient from initiation to termination of treatment with regorafenib

Figure 3. Thoracic and lumbar PET-CT scans (a) before initiation of regorafenib, and (b) 3 months after treatment with regorafenib, showing partial response to the treatment

Figure 4. Patients with good ECOG PS prior to initiation of regorafenib in the REBECCA study had significantly prolonged OS than those with worse ECOG PS

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Strengthened by the treatment of patients with metastatic colorectal cancer (CRC) with regorafenib previously treated with fluoropyrimidines, irinotecan, oxaliplatin, and cetuximab. Regorafenib exhibited promising activity across multiple advanced CRC populations. 2015 MEDITECH. All rights reserved. No part of this publication may be reproduced by any process in any language without the written permission of the publisher. MEDITECH Asia Sdn Bhd (242016-U), Level 3A, Luther Centre, No. 6, Jalan Utara, 46200 Petaling Jaya, Malaysia. Tel: (603) 6209 3088, Fax: (603) 7955 1724, Website: www.bayer.com.
Everolimus and 177Lu-Dotatate extend PFS in lung and midgut NETs

CHRISTINA LAU

This year’s European Cancer Congress (ECC) featured impressive results from phase III neuroendocrine tumour (NET) trials, with everolimus being the first drug to show significant activity in lung NETs and 177Lu-Dotatate showing superiority to octreotide long-acting repeatable (LAR) in midgut NETs.

In the RADIANT-4 trial of 302 patients with grade 1/2, progressive, well-differentiated, non-functioning advanced NETs of lung or gastrointestinal origin, everolimus 10 mg/day reduced the risk of disease progression or death by 52 percent vs placebo. [ECC 2015, abstract 5LBA]

Progression-free survival (PFS), the primary endpoint, was 11 months in the everolimus arm (n=205) vs 3.9 months in the placebo arm (n=97) (hazard ratio [HR], 0.48; p<0.00001).

“The PFS benefit appeared early and was durable,” reported lead investigator Dr. James Yao of the University of Texas MD Anderson Cancer Centre in Houston, TX, US. “The benefit was consistent in subgroups stratified by prior somatostatin analogue [SSA] treatment, tumour origin and performance status. Benefit was seen across the spectrum of primary liver tumour burden, but those with tumour burden over 25 percent had the lowest risk of disease progression or death with everolimus vs placebo [HR, 0.18].”

In the subgroup of patients with lung NETs, the PFS HR was 0.50.

“Everolimus is the first drug shown to have significant activity in lung NETs in a randomized trial,” said discussant Dr. Enrique Grande of the Hospital Ramón y Cajal in Madrid, Spain. “The results of RADIANT-1, -2, -3 and -4 are all consistent and support the use of everolimus in grade 1 and 2 disseminated, progressive NETs regardless of primary tumour origin.”

In RADIANT-4, the first interim analysis of overall survival (OS) showed a non-significant trend favouring everolimus vs placebo (HR, 0.64; p=0.037 [p-value boundary for significance=0.002]). Tumour shrinkage was observed in 64 percent of everolimus-treated patients vs 26 percent of those receiving placebo. Adverse events (AEs) associated with everolimus were consistent with the known safety profile of the drug.
“In patients with progressive metastatic midgut NETs, $^{177}$Lu-Dotatate, a peptide receptor radionuclide therapy [PRRT], was superior to octreotide LAR in terms of PFS and objective response rate [ORR],” reported Dr. Philippe Ruszniewski of the Hospital Beaujon in Clichy, France, lead investigator of the NETTER-1 trial. [ECC 2015, abstract 6LBA]

In the trial, 230 patients who progressed under SSA treatment with octreotide LAR 30 mg were randomized to receive $^{177}$Lu-Dotatate 7.4 GBq every 8 weeks plus octreotide LAR 30 mg, or octreotide LAR 60 mg alone.

Median PFS was not yet reached in the $^{177}$Lu-Dotatate arm vs 8.4 months in the octreotide LAR arm (HR, 0.209; p<0.0001). ORR was 19 vs 3 percent, while interim OS analysis showed fewer deaths in the $^{177}$Lu-Dotatate arm (13 vs 22 events).

“Currently available safety data confirms the results of phase I and II studies of $^{177}$Lu-Dotatate and shows a favourable safety profile,” said Ruszniewski.

“The PFS finding of NETTER-1 is the most impressive we have seen in NET trials, and is especially important as the comparator is a really active treatment,” commented Grande. “PRRTs are here to stay.”

Gene assay IDs those who can skip chemo

CHRISTINA LAU

A 21-gene expression assay can identify patients with early-stage breast cancer who can skip adjuvant chemotherapy without facing an increased risk of recurrence at 5 years.

The findings are from the TAILORx trial (Trial Assigning Individualized Options for Treatment) (n=10,273) designed to validate and refine the clinical usefulness of the Oncotype DX Recurrence Score in guiding treatment in patients with ER-positive, HER2-negative, axillary node-negative breast cancer. [ECC 2015, abstract 5LBA; N Engl J Med 2015, doi: 10.1056/NEJMoa1510764]

“Among 1,626 low-risk patients with recurrence scores of 0 to 10 who were treated with endocrine therapy alone, clinical outcomes were excellent at 5 years, with a low risk of distant recurrence of 1 percent,” reported lead investigator Dr. Joseph Sparano of the Albert Einstein College of Medicine, New York, NY, US.

In this low-risk cohort, the rate of 5-year invasive disease-free survival, recurrence-free survival (RFS), distant RFS and overall survival was 93.8 percent, 98.7 percent, 99.3 percent and 98.0 percent, respectively.

“Patient age and tumour grade had no significant impact on recurrence risk. The rates of
recurrence were low irrespective of histologic grade,” said Sparano. “Since adjuvant chemotherapy prevents mostly early recurrences within 5 years, our results suggest that chemotherapy may be spared in this patient population.”

“The prospective TAILORx trial provides the highest level of evidence supporting the clinical utility of the 21-gene assay in patients with ER-positive, HER2-negative, axillary node-negative breast cancer,” he continued. “The findings confirm expert opinion-based clinical guidelines that recommend using the recurrence score to risk-stratify patients for adjuvant chemotherapy.”

The trial also included 6,897 patients with mid-range recurrence scores of 11-25, who were randomized to receive chemotherapy plus endocrine therapy or endocrine therapy alone. Continued follow-up will address the question of whether chemotherapy improves outcomes in these intermediate-risk patients.

The recurrence score ranges used in TAILORx were different from those originally used to define low (0-10 vs <18) and intermediate risk (11-25 vs 18-30). According to the investigators, this was to minimize the potential for undertreatment of the study participants.

“Previous studies showed that 7.3 percent of patients with a recurrence score of 11 experienced distant recurrence at 10 years. For those with a recurrence score of 25, the 10-year rate of distant recurrence was 16.1 percent,” Sparano noted. “While chemotherapy has demonstrated clear benefits in patients with high recurrence scores of ≥31, the benefit in patients with intermediate or low recurrence scores has been uncertain.”
More than three quarters of those who require cancer surgery have no access to the essential treatment, according to a recent report on the global state of cancer surgery.

“For the majority of patients in whatever income setting, surgery is absolutely necessary for good outcomes, be that either curative or in the palliative setting,” said lead author Professor Richard Sullivan of the Institute of Cancer Policy at King’s Health Partners Comprehensive Cancer Centre, King’s College London, London, England, UK, in an interview with The Lancet.

In 2015, 15.2 million new cancer cases were diagnosed and more than 80 percent could need one or more surgeries, most of which would be impossible with the current state of access. The number of new cancer cases is expected to balloon to almost 22 million by 2030, 17 million of whom will need surgery, a majority in low- and middle-income countries (LMICs) [Lancet Oncol 2015;16:1193-224]

As a result, only one in 20 patients have access to basic cancer surgery resources in low income countries while the figure in middle income countries is about one in five.

But improving cancer surgery services doesn’t seem to be part of most countries’ national cancer plans, Sullivan said, largely because of competing priorities and financial constraints.

However, the authors estimated economic losses from potentially surgically treatable cancers could reach US$12 trillion – a projected 0.5-1.5 percent in lost GDP per country annually until 2030.

Failure to train surgeons – of which there is a significant shortage in over 82 percent of countries – and improve systems would cost an additional US$6 trillion, according to co-author Professor John Meara, director of the Program in Global Surgery and Social Change at Harvard Medical School in Boston, Massachusetts, US.

In addition, the authors note less than 5 percent of cancer research pertains to surgery, most of it done in just a few countries, even
though LMICs need their own localized research programmes.

“Really what we’re trying to achieve across all settings is the recognition that developing cancer surgery really is essential to improving outcomes and that without this the idea that we can achieve a 25 percent reduction of premature cancer mortality by 2025 is simply not going to happen,” Sullivan said, referring to the World Health Organization’s Global Action Plan’s global mortality targets for non-communicable disease.

“There is no magic bullet or single path to improving cancer surgery. For some it’s a question about the evolution of the most advanced robotics and imaging in the world. For many others it’s simply about having a surgeon trained to perform basic cancer procedures.”

Experts call for nearly US$100 billion for accessible radiotherapy

RADHA CHITALE

Major investments in access to quality radiotherapy in low- and middle-income countries (LMICs) now could save millions of lives and have significant economic benefits, according to a new report, which detailed a plan to improve low worldwide access to radiotherapy through 2035.

The cancer burden is growing worldwide, particularly with the transition from communicable to non-communicable disease, and many nations lack the infrastructure and capacity to treat the estimated 12 million cancer patients who might benefit from radiotherapy in 2035, according to the report. [Lancet Oncol 2015;16:1153-1186]

Although up to 60 percent of cancers, including lung, breast, cervical, and head and neck cancers, require radiotherapy, access stands at about 40-60 percent worldwide.

The problem is most acute in LMICs, but even high-income countries such as the US and Australia fall short in equitable access to quality facilities and staff.

“We see the train wreck happening in slow motion,” said Dr. David Jaffray, co-author and head of the International Secretariat of the Global Task Force on Radiotherapy for Cancer Control (GTFRCC), in an interview with The Lancet.

“The moral obligation is to help society. [Is
there] a financial argument that could motivate the investment to assure that radiotherapy is there as this burden emerges over the next 20 years?"

The report authors suggested a model that allocated US$96.8 billion for improvements to radiotherapy in LMICs, which would span research, planning, implementation, and operations, and would scale up over time.

The authors noted the high upfront costs but said the operational costs per patient would be low and the economic returns – up to an estimated US$365.4 billion – exceed the investment figure.

The model predicted 27 million life years saved, among other health benefits.

The Commission gave three key targets to be met by 2020:
1) 80 percent of countries to have comprehensive cancer plans that include radiotherapy.
2) Each LMIC to create one new centre for treatment and training.
3) 80 percent of LMICs to include radiotherapy services in their universal health coverage plans.

And three more to be met by 2025:
1) A 25 percent increase in radiotherapy treatment capacity.
2) LMICs to train 7,500 radiation oncologists, 20,000 radiotherapy radiographers, and 6,000 medical physicists.
3) US$46 billion of upfront investment to be raised to establish radiotherapy infrastruc-

ture and training in LMICs (with help from international banks and the private sector).

In an accompanying comment, Dr. Fong Kam Weng of the National Cancer Centre Singapore noted the diverse countries of southeast Asia presented a variety of challenges for improving cancer services. [Lancet Oncol 2015;16:1149-1150]

Large rural populations or geographically isolated populations, most obvious among those populating the Indonesian archipelago, can suffer from poor access to basic cancer facilities, exacerbated by poor infrastructure and the difficulty in retaining a significant number of capable staff from small pools of local talent. Fong noted the region is deficient an estimated 2,230 machines.

"Governments need to spend their health budgets in such a way that this deficit is reduced by investing in the most suitable equipment that gives the best outcomes at a population level," he said.

"The priority must be to treat patients who would otherwise die because of inaccessibility to treatments that are too expensive either because of physical distance to a centre or because the high costs of buying unnecessarily advanced machines are transferred to the patient. In this regard, world bodies… could issue guidance for a set of optimum specifications for equipment with the aim of helping governments in the region to set up cost-effective centres that address the particular issues of those countries."
A paradigm shift in how early clinical trials are conducted is having profound implications for accelerating drug development and improving treatment response.

“Altogether, early clinical trials now have real registration value, with the ability to achieve breakthrough designation or conditional approval without a phase III trial,” said Professor Jean-Charles Soria of the Gustave Roussy Cancer Centre in Paris, France.

These early trials are no longer small, single-arm studies looking to assess safety and toxicity, he said, but trials looking to provide key information on drug activity, response and even preliminary survival.

The key reason for the shift is the advent of precision medicine and molecular targeted agents that are leading to increased response rates. In a study looking at phase I cancer trials across Europe between 2005 and 2007, one in two patients enrolled achieved some benefit (50 percent showing complete response, partial response or stable disease). In comparison, phase I clinical trials conducted between 1970 and 1993 demonstrated a 6 percent overall response rate (ORR) and 5 percent stable disease rate. [J Clin Oncol 2012;30:996-1004; Invest New Drugs 1991;9:115-122]

The approval and registration of crizotinib by the US FDA was an example of this shift. Crizotinib was registered in less than 5 years on the basis of phase I and II single-arm studies that included an enriched population of 119 and 136 patients, respectively. “The median duration for a drug to be approved is typically 8-10 years with the classical clinical trial paradigm,” Soria noted. “With precision medicine, phase I studies designed with enriched molecularly selected [matched] patient populations can increase the ORR from <10 percent to >30 or even >50 percent.”

Similarly, holistic molecular screening technologies are accelerating drug development by identifying target populations defined by specific biomarkers. Researchers can then develop drugs against these biomarkers. “This is the direction we are heading in. Enrolment for clinical trials is above expectations and we are seeing a clear enthusiasm for molecular screening in both patients and doctors,” said Soria.

Soria describes the developments in non-invasive liquid biopsy and immune-stimulatory antibodies as game changers in clinical tri-
als. “We are on the verge of having liquid biopsies that can detect not only mutations, but also translocations and amplifications,” he explained.

The reality of this shift can already be observed with immune checkpoint inhibitors, where breakthrough designations and early approvals have been given based on phase I/II trials that have uniquely included multiple parallel expansion cohorts and long-term follow-ups.

“While this allows patients to access innovative drugs quicker, we are still faced with challenges and will need to conduct randomized trials to fully define the real medical value of these drugs,” added Soria.

Hypofractionated radiotherapy safe and effective in prostate cancer

NAOMI RODRIG

Giving fewer but higher doses of radiotherapy to men with localized prostate cancer (PC) is as effective as the standard low-dose treatment in terms of disease control and side effects, according to 5-year data from a large phase III noninferiority trial.

In the CHHiP (Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer) trial, patients were randomized to receive standard radiotherapy of 2 Gy per day (74 Gy over 37 days; n=1,065) or hypofractionated therapy of 3 Gy per day (either 60 Gy over 20 days [n=1,074] or 57 Gy over 19 days [n=1,077]). Baseline patient characteristics were well matched across the three treatment arms. [ECC 2015, abstract 8LBA]

The primary endpoint was prostate cancer recurrence or biochemical (prostate-specific antigen) failure. Secondary endpoints included acute and late radiation-induced side effects, quality of life and prostate cancer-related and overall mortality.

“At a median follow-up of 62 months, intent-to-treat analysis showed that the 60 Gy/20 day schedule was noninferior to standard radiotherapy [hazard ratio, (HR), 0.83; p=0.003], while the result for the 57 Gy/19 day schedule was inconclusive [HR, 1.19; p=0.91],” reported lead investigator Professor David Dearnaley of the Institute of Cancer Research in London, UK. “An
HR of <1 favours hypofractionation.”

Bowel and bladder side effects were more common with the higher daily radiotherapy doses than with standard treatment during and immediately after radiotherapy, but were not long lasting. “There was no difference in toxicity or quality of life after 6 months or during the next 5 years,” he noted. “The rates of prostate cancer-related and total deaths were also similar between the groups.”

“The excellent control rates and mild side-effect profile are encouraging news for men. Giving patients larger doses of radiotherapy over a shorter time will mean fewer hospital trips and less radiation needed overall, and we recommend it as a new standard of care,” said Dearnaly.

He added that the advanced methods used in the study – intensity-modulated radiation therapy (IMRT) with integrated boost technique to include the prostate and seminal vesicles and mandatory normal tissue dose constraints – are necessary to deliver short, high-dose treatments safely.

“Hypofractionation offers an attractive option for prostate cancer patients, but special attention should be paid to radiotherapy planning, including appropriate image guidance for patient positioning and limiting the fraction size to 3 Gy for now,” said the discussant, Professor Philip Poortmans, President of the European Society for Radiotherapy & Oncology (ESTRO). “Further trials are needed to evaluate whether higher fraction sizes are feasible.”

EGFR/VEGF dual inhibition works in T7T90M-positive NSCLC

JACKEY SUEN

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hhibition of the EGFR and VEGF pathways with erlotinib plus bevacizumab is effective in patients with non-small-cell lung cancer (NSCLC) harbouring EGFR T790M mutation, the phase II BELIEF trial shows. [ECC 2015, abstract 3BA]

In this study, 102 patients with advanced, non-squamous, EGFR-positive NSCLC were treated with the EGFR-tyrosine kinase inhibitor erlotinib 150 mg daily plus the VEGF inhibitor bevacizumab 15 mg/kg every 3 weeks. Only a few of these patients had previously received
adjuvant chemotherapy (8.3 percent) or post-operative radiotherapy (22.0 percent).

Pretreatment T790M mutation was detected in 34 percent of the patients (n=35). Their treatment outcomes were compared with those without the T790M mutation (n=67).

“At a median follow-up of 17.5 months, the primary endpoint of progression-free survival [PFS] was longer in patients with T790M-positive NSCLC than those with T790M-negative NSCLC [median PFS, 16.0 vs 10.5 months; 12-month PFS rate, 72.4 vs 49.4 percent],” reported principal investigator Professor Rolf Stahel of the University Hospital Zurich, Zurich, Switzerland. “There was a trend in PFS favouring T790M-positive patients in all subgroups.”

The median duration of response was not reached in the T790M-positive group vs 12.0 months in the T790M-negative group.

The toxicity profile of the combination regimen was consistent with previous experience. The most common grade 3 adverse events were hypertension (34.9 percent), maculopapular rash (18.9 percent) and diarrhoea (7.5 percent).

“Treatment was discontinued in 52.8 percent of patients in the T790M-positive group and 72.9 percent of those with T790M-negative tumours, mainly because of disease progression,” added Stahel.
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Late-stage cancer patients who responded to the opioid-induced constipation treatment methylnaltrexone lived twice as long, on average, as similar patients who did not respond or were on a placebo and experienced slower tumour growth.

This retrospective survival analysis is the first to show the association between an opioid blockade and improved survival in humans and raises the possibility of opioid pathways as therapeutic targets in cancer patients, according to the researchers, who presented their findings during the recent annual meeting of the American Society of Anesthesiologists in San Diego, California, US.

The analysis included 229 patients from two studies that used methylnaltrexone to relieve constipation as a result of palliative cancer care. Constipation is a common side effect of opioid therapy. [ASA 2015, abstract A4032]

Of the 117 patients randomized to methylnaltrexone, 57 percent experienced constipation relief and 43 percent did not.

Patients who responded to methylnaltrexone lived longer than non-responders or patients who got a placebo (118 vs 58 days; p=0.001). Patients also reported tumour progression less in the methylnaltrexone responder group (7.6 percent) compared with the non-responders (22 percent) or the placebo group (25.4 percent, p=0.003).

The researchers, who said they had long suspected methylnaltrexone’s role in inhibiting cancer growth, had proceeded to human analyses after lab results showed some human cancer cells have an overabundance of opioid receptors and that morphine increases tumour cell proliferation, migration, and invasion.

The two studies from which the researchers pulled their patient pool also included patients with terminal illness other than cancer, including congestive heart failure and chronic obstructive pulmonary disease, but an analysis of methylnaltrexone in 135 of those patients showed constipation relief but no improved survival among responders.

“This makes it far less likely that improved bowel function is the only explanation for...
our finding of improved survival in cancer patients,” said co-author Dr. Filip Janku, assistant professor of investigational cancer therapeutics at the University of Texas MD Anderson Cancer Center in Houston, Texas, US.

“Whether our findings in advanced cancers can be extended to the treatment of earlier cancers, or whether the medication can help physician anaesthesiologists improve care during cancer surgery (where opioids are often given) will need to be tested directly,” said lead author Dr. Jonathan Moss, professor of anaesthesia and critical care at the University of Chicago, Chicago, Illinois, US.

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**Home-based CCT improved memory, cognition in childhood cancer survivors**

**KAVITHA G. SHEKAR**

A home-based computerized cognitive training (CCT) programme restored memory and mental function in childhood cancer survivors (CCSs) with brain tumour (BT) or acute lymphoblastic leukaemia (ALL) who had lost part of those functions because of disease and subsequent treatment, US researchers said.

Cognitive decline in CCSs, which can occur after cranial irradiation and/or intrathecal chemotherapy, injected directly into the cerebrospinal fluid surrounding the brain and spinal cord, can impede their academic, social, and work-related capabilities.

“Our findings are the first to demonstrate that CCSs who participated in [the programme] had significantly greater improvements than control participants,” said lead author Professor Heather M. Conklin, department of Psychology, St. Jude Children’s Hospital, Memphis, Tennessee, US.

“The scores that [CCSs] attained post-intervention, were consistent with normative data for their age, suggesting that performance was age-typical or normalized after training.” The randomized, single-blind, waitlist-controlled study, recruited 8- to 16-year-old English-speak-
ing BT and ALL CCSs who presented between December 2010 and 2013 (n=68). Those with a history of pre-morbid central nervous system injury or disease, pre-existing attention deficit hyperactivity disorder, consuming psychotropic medications within 2 weeks of enrollment, motor or sensory deficit, or psychological conditions, were excluded from the study. [J Clin Oncol 2015;12:pii JCO.2015.61.6672]

Patients were randomized to either the intervention programme, called Cogmed (n=34), or control (n=34) group. The intervention group completed 25 home-based sessions lasting 30-45 minutes consisting of visual-spatial and verbal games and received weekly telephone-based coaching and performance feedback. The control group received no cognitive, psychological or social intervention. Participants were assessed at study onset, 10 weeks and 6 months post-waitlist period.

The intervention group demonstrated greater short-term improvement in memory compared to the control group (p=0.002). The targeted secondary outcomes of working memory (p=0.017), attention (p=0.012) and processing speed (p=0.02) were also greater in the intervention group. Parents of CCS in the intervention group reported a greater reduction in executive dysfunction (p=0.002) compared to controls.

The study was also the first to measure cognitive changes with functional magnetic resonance imaging (fMRI) in CCSs.

“fMRI findings revealed brain-based changes that indicate training-related neuroplasticity.” Conklin said. “These findings are exciting as they point us to an underlying mechanism and suggest that changes might persist over time.”

Standard of care for CCSs include targeted cognitive rehabilitation services such as stimulant medications or therapist-delivered cognitive medication.

“Stimulant use is limited by medical contraindication and parental preference, and therapist-delivered interventions are associated with low participation rates as a result of high time investment and logistic challenges,” said Conklin.

Since Cogmed can be done at home, more users are likely to use and complete it, Conklin said.

The study was limited to short-term cognitive gains and the benefits did not translate to improved academic performance. However, the investigators did follow and assess the patients 6 months later, and Conklin said that those findings were encouraging and would be the subject of an upcoming manuscript.
Parabens may be more potent in tumour cell proliferation pathways than previously thought

RADHA CHITALE

Parabens may be much more potently linked to breast cancer than previously thought, according to a new study showing that these xenoestrogens, or synthetic oestrogen-like molecules, can encourage tumour cell proliferation even in small concentrations when a parallel tumour cell-proliferation pathway is activated.

“Parabens are among the most widely used xenoestrogens in cosmetics and personal care products, and generally considered safe,” said the authors of the US-based study. “However, previous cell based studies with parabens do not take into account the signalling cross-talk between oestrogen receptor (ERα) and the human epidermal growth factor receptor (HER) family.”

The researchers prepared breast cancer cells with receptors for both oestrogen and HER2, which is over-expressed in about a quarter of breast cancer cells, only oestrogen, or only HER2. They used heregulin to activate the HER2 receptors and exposed the cells to paraben solutions. [Environ Health Perspect 2015. doi:10.1289/ehp.1409200]

In cells with both types of receptors activated, the parabens – butylparaben in particular – stimulated cell proliferation at concentrations 100 times lower than cells treated with parabens alone.

The researchers did not observe a similarly low proliferation threshold in cells expressing only one type of receptor or in cells where the HER2 pathway was not activated with heregulin.

Parabens are actually weak estrogen binders, the researchers noted, and have not been definitively linked to cancer, though studies have confirmed that co-activated ERα and HER pathways are more potent at stimulating cell proliferation than either activated alone.

Parabens are used as a preservative and antimicrobial agent in a wide variety of products, from plastic containers to cosmetics and body care and are considered safe, though the researchers suggest this conclusion is the result of studies conducted outside of real-life settings where multiple signalling pathways cannot “cross talk.”

“While this study focused on parabens, it’s also possible that the potency of other estrogen
mimics have been underestimated by current testing approaches,” said co-author Dr. Chris Vulpe, a toxicologist at the Center for Environmental and Human Toxicology at the University of Florida College of Veterinary Medicine in Gainesville, Florida, US.

“Further work is needed to assess if indeed HER ligands enhance the potency of parabens in the normal human breast cells and breast tumours,” the researchers said. “We suggest that reevaluation of the potency of other xenoestrogens in the presence of HER ligands is warranted in the light of our findings.”
New data cast doubt over current DCIS treatment

CHRISTINA LAU

Experts are calling for a reassessment of the standard of care for women with ductal carcinoma in situ (DCIS) after a large study has shown no reduction in breast cancer-specific mortality in patients treated aggressively with radiotherapy (RT) following lumpectomy or with unilateral mastectomy.

In patients with DCIS who underwent RT after lumpectomy (n=42,250), the rate of breast cancer-specific mortality at 10 years was 0.8 percent – a nonsignificant difference compared with 0.9 percent for those who underwent lumpectomy alone (n=19,762) (adjusted hazard ratio [HR], 0.81; p=0.10). [JAMA Oncol 2015, doi: 10.1001/jamaoncol.2015.2510]

In patients who underwent unilateral mastectomy for DCIS (n=19,515), the 10-year rate of breast cancer-specific mortality was 1.3 percent – a nonsignificant difference compared with lumpectomy (adjusted HR, 1.20; p=0.11).

The findings are surprising because early treatment of DCIS has been presumed to reduce cancer incidence and mortality.

In the observational study on 108,196 women diagnosed with DCIS between 1988 and 2011, aggressive treatment was found to reduce the 10-year risk of ipsilateral invasive recurrence.

“For patients who had a lumpectomy, RT reduced the risk of ipsilateral invasive recurrence at 10 years from 4.9 percent to 2.5 percent [adjusted HR, 0.47; p<0.001],” the investigators reported. “Similarly, patients who underwent unilateral mastectomy had a lower risk of ipsilateral invasive recurrence at 10 years than patients who underwent lumpectomy [1.3 vs 3.3 percent; adjusted HR, 0.81; p<0.001].”

“Surprisingly, the majority of women with DCIS in the cohort who died of breast cancer did not experience an invasive ipsilateral or contralateral recurrence prior to death,” they pointed out.

Overall, the rate of breast cancer-specific mortality was low – 3.3 percent at 20 years. However, patients diagnosed with DCIS before 35 years of age had a higher risk of death from breast cancer at 20 years compared with those diagnosed at an older age (7.8 vs 3.2 percent; HR, 2.58; p<0.001).

“The current analysis fuels a growing concern that we should rethink our strategy for the
detection and treatment of DCIS,” wrote editorialists Dr. Laura Esserman and Dr. Christina Yau of the University of California, San Francisco, CA, US. “RT should not be routinely offered after lumpectomy for DCIS lesions that are not high risk because it does not affect mortality.” [JAMA Oncol 2015, doi:10.1001/jamaoncol.2015.2607]

High-risk cases, including women <40 years of age with symptomatic DCIS and women with hormone receptor-negative or HER2-positive DCIS, should continue to be treated according to today’s aggressive standards, they noted.

IMRT reduces lung toxicity, improves chemo tolerance in unresectable NSCLC

ELVIRA MANZANO

Treatment with intensity-modulated radiation therapy (IMRT) in patients with locally advanced or unresectable non-small cell lung cancer (NSCLC) reduces toxicity and improves tolerance of follow-up chemotherapy compared with three-dimensional conformal radiotherapy (3D-CMRT) in a secondary analysis of the phase III *RTOG-0617 study. [American Society for Radiation Oncology 2015, abstract 2]

“There was a significant reduction in severe pneumonitis, which we defined in the trial as lung toxicity requiring high-dose steroids, supplemental oxygen, hospital admission, ventilator support, or causing death, of about two-fold with IMRT versus 3D-CMRT [3.8 vs 8 percent; p=0.046] that was statistically significant,” said lead author Dr. Stephen Chun from the University of Texas MD Anderson Cancer Center in Houston, Texas, US. “Another key finding in the trial was that patients treated with IMRT were 8 percent more likely to complete full doses of consolidative chemotherapy which is deemed to be standard for locally advanced lung cancer.”

The standard of care for locally-advanced NSCLC is concurrent chemotherapy with radiotherapy (RT). The researchers compared the more advanced IMRT with 3D-CMRT in patients with locally advanced or unresectable NSCLC. Two-year overall survival (OS) was 53.2 percent with IMRT and 49.4 percent with 3D-CMRT.

In a multivariate analysis, IMRT remained associated with less severe pneumonitis (HR, 0.44; p=0.0653) and was particularly pronounced in large tumours. Across the board, IMRT was also associated with significantly lower doses of radiation delivered to the heart compared with 3D-CRT (V20: 19.3 vs 23.5 percent; p=0.049; V40:6.8 vs 11.4 percent; p=0.003; V60:1.4 vs 2.4 percent; p=0.045).
Progression-free survival, disease control and distant metastasis-free survival were no different between the two radiation techniques despite that patients on IMRT had more advanced disease and greater planning target volume. “Based on these findings, IMRT should be routinely considered for locally advanced lung cancer,” said Chun. “We believe the results of this study have the potential to dramatically change the patterns of use of IMRT for this population.”

The original study, published this year, compared overall survival (OS) in patients with inoperable stage III NSCLC treated with high dose and low dose (74 and 60 Gy, respectively) RT with concurrent chemotherapy (carboplatin and paclitaxel) with or without cetuximab, followed by consolidation chemotherapy, results of which showed poorer survival outcomes with the high dose RT. [Lancet Oncol 2015;16:187-199]

Nicotinamide helps prevent new nonmelanoma skin cancers in high-risk individuals

ROSHINI C.

Daily oral supplements of nicotinamide reduced the incidence of new nonmelanoma skin cancers among high-risk patients, according to the Oral Nicotinamide to Reduce Actinic Cancer (ONTRAC) study.

New nonmelanoma skin cancers (basal cell carcinoma and squamous cell carcinoma) occurred approximately 23 percent less frequently in the intervention group compared to the placebo group (95 percent CI, 4 to 38, p=0.02) during the 12-month study period. [N Engl J Med 2015;373:1618-1626]

The incidence of new squamous-cell carcinomas (SCCs) was lower by 30 percent (-6 to 39, p=0.12). Incidence of actinic keratoses was significantly reduced throughout the study period, from 11 percent lower (p=0.01) at 3 months to 20 percent lower (p<0.001) at 9 months. The number and types of adverse events were similar between the nicotinamide and placebo groups.

Nicotinamide supplements demonstrated no effect on nonmelanoma skin cancers in the 6 months after the study ended (relative difference [RD] -17 percent, 95 percent CI, -59 to 14, p=0.33). Researchers suggested that the potential ability of nicotinamide to suppress the progression of pre-existing cancers was lost upon discontinuation.

Researchers also ruled out potential bias due to sunscreen use – a preventive measure
against nonmelanoma skin cancers – as use of sunscreen was lower among participants in the nicotinamide arm.

In the ONTRAC study, 386 participants (193 in each group) with up to 5 years prior history of nonmelanoma cancers were randomized to receive either 500 mg of nicotinamide twice daily or placebo. Skin assessments were done at baseline and every 3 months for 18 months.

According to researchers, the rise in incidence of nonmelanoma skin cancers, potentially due to increasing sun exposure and better registration procedures, increases the need for preventive measures. [Br J Dermatol 2012;166:1069-1080] One placebo-controlled trial showed that retinol supplementation reduced the incidence of SCC but not BCC. [Cancer Epidemiol Biomarkers Prev 1997;6:949-956]. Another study demonstrated the significant efficacy of acitretin on SCCs but it had severe adverse effects. [Australas J Dermatol 2002;43:269-273]

The availability and cost-effectiveness of nicotinamide coupled with its efficacy and safety profile highlight its potential as a chemopreventive measure against nonmelanoma skin cancers, said researchers.
Surgical resection provides longer survival than immunotherapies in abdominal metastatic melanoma

Patients with abdominal metastatic melanoma who undergo surgical resection live twice as long as those who receive medical therapy only, according to a study presented at the Clinical Congress 2015 of the American College of Surgeons.

Researchers analyzed data from 1,623 patients treated in the US over a 45-year period. All of the patients had abdominal metastases and were referred for surgical evaluation. A total of 392 patients underwent metastasectomy (surgical resection of the metastases). Some of the patients also received medical therapy, radiofrequency ablation, or heat probe treatment. [J Am Coll Surg 2015, doi: org/10.1016/j.jamcollsurg.2015.07.325]

Median overall survival (defined as survival after the diagnosis of stage IV melanoma) was 18 months among surgically treated patients, compared with 7 months among patients who did not undergo surgery.

The researchers subsequently divided patients into groups based on whether they had received treatment before (1969-2003) or after (2003-2014) the advent of new systemic immunotherapies, to determine whether treatment era had an effect on survival. Results showed that the new therapies did not significantly affect overall survival compared with the earlier agents, and that surgical resection remained the best option.

According to the researchers, patients are good candidates for curative surgical resection if they have a long disease-free interval, a slow tumour doubling time, and if they are otherwise healthy.
Protein that helps tumours detect food supplies a potential new target for therapy

Researchers have identified a protein that is used by tumours to detect food supplies. The findings suggest the protein could be a potential new target for combination therapy.

The protein, PAT4, is overexpressed in colorectal cancer cells, but initial experiments have shown that reducing PAT4 levels can restrict colorectal tumour growth. [Oncogene 2015, doi: 10.1038/onc.2015.363]

The researchers developed a monoclonal antibody against PAT4 and used this antibody to study tumour samples taken from patients with colorectal cancer. They found that patients with higher levels of PAT4 in their tumours were more likely to experience a relapse. However, further experiments revealed that reducing PAT4 levels could slow the growth of colorectal cancer cells.
New method for chemo delivery for neuroblastoma patients

A new method for chemotherapy delivery may help reduce toxicity for patients with neuroblastoma, according to a study presented at the Clinical Congress 2015 of the American College of Surgeons.

Most neuroblastoma patients are 1-2 years old. While current chemotherapy protocols have improved survival rates (>90 percent of children with low- or intermediate-risk neuroblastoma survive ≥5 years), they are still associated with significant adverse effects such as cardiomyopathy, neuropathy, infertility and growth problems.

The new targeted method currently under development aims to deliver chemotherapy directly into the centre of the tumour using a device that contains a chemotherapy-loaded silk sponge. The amount of silk present in the device determines the amount of drug that is released. [J Am Coll Surg 2015, doi: org/10.1016/j.jamcollsurg.2015.07.240]

The novel device has been trialled in murine models of neuroblastoma. Vincristine and doxorubicin were delivered to the mice either intravenously or via the new device. Tumour growth was then measured using ultrasound.

Although there was no difference in efficacy between the two delivery methods for doxorubicin, sustained release of vincristine via the silk sponge was found to be more effective than intravenous delivery for slowing tumour growth.

More preclinical experiments are currently underway as the researchers are attempting to refine the delivery method, dosage, and drug combinations.
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http://www.sitcancer.org/sitc-meetings/aci2015/la

2015 San Antonio Breast Cancer Symposium
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Fax: +1 210 450 1560
E-mail: sabcs@uthscsa.edu
http://www.sabcs.org/

ESMO Asia 2015 Congress
18/12/2015 to 21/12/2015
Singapore
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JANUARY

2016 Gastrointestinal Cancers Symposium
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E-mail: meetings@asco.org
http://gicasym.org/

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E-mail: esmo@esmo.org
http://www.esmo.org/Conferences/Sarcoma-GIST-2016

2016 Multidisciplinary Head and Neck Cancers Symposium
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Scottsdale, AZ, US
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E-mail: headandneckreg@spargo.com
http://www.headandnecksymposium.org/Home/

25th Conference of the Asian Pacific Association for the Study of the Liver
20/2/2016 to 24/2/2016
Tokyo, Japan
Tel: +81 3 5796 5445
E-mail: registration-travel@apasl2016.org
http://www.apasl2016.org/

2016 Cancer Centre Business Summit
24/2/2016 to 25/2/2016
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http://cancerbusinesssummit.com/

ASCO Quality Care Symposium
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Cancer Immunotherapy: Emerging Biology, Targets and Strategies
San Francisco, CA, US
http://www.triconference.com/Cancer-Immunotherapy/

10th European Breast Cancer Conference (EBCC10)
Amsterdam, The Netherlands
Tel: +32 2 775 02 01
Fax: +32 2 775 02 00
E-mail: EBCC10@ecco-org.eu
http://www.ecco-org.eu/Events/EBCC10

International Conference on Ageing and Haematological Malignancies: Biology and Therapy
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3rd Immunotherapy of Cancer Conference (ITOC3)
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26th Annual Interdisciplinary Breast Cancer Center Conference
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http://www2.breastcare.org/welcome-to-the-24th-annual-national-interdisciplinary-breast-center-conference/

European Lung Cancer Conference (ELCC) 2016
13/4/2016 to 16/4/2016
Geneva, Switzerland
http://www.esmo.org/Conferences/ELCC-2016-European-Lung-Cancer-Conference

5th International Conference on Myelodysplastic Syndromes
14/4/2016 to 16/4/2016
Estoril, Portugal
Tel: +3301 57 27 68 33
E-mail: Nicolas.jaillard@univ-paris-diderot.fr
http://www.esh.org/conference/international-conference-on-myelodysplastic-syndromes/

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IMPAKT 2016 Breast Cancer Conference
12/5/2016 to 14/5/2016
Brussels, Belgium
http://www.esmo.org/Conferences/IMPAKT-2016-Breast-Cancer