NSCLC immunotherapy coming of age

**NEWS**
Vitamin D slows prostate tumour growth

**CONFERENCE COVERAGE**
Circulating tumour DNA helps detect EGFR mutations

**NEWS**
Breath test detects gastric cancer and precancerous gastric lesions

**RESEARCH REVIEWS**
Fasting enhances anticancer activity of TKIs
NSCLC immunotherapy coming of age

NAOMI RODRIG

Following the success of immune checkpoint inhibitors such as programmed cell death 1 (PD-1) and programmed death ligand 1 (PD-L1) inhibitors in advanced melanoma, these agents are now emerging as effective treatments for non-small-cell lung cancer (NSCLC).

“This year, nivolumab became the first PD-1 inhibitor to receive US FDA approval for advanced NSCLC that has progressed on platinum-based chemotherapy,” said Dr. Solange Peters of the Centre Hospitalier Universitaire Vaudois in Lausanne, Switzerland, at the European Lung Cancer Conference (ELCC) 2015 held recently in Geneva, Switzerland.

“In a phase III trial of 272 patients, nivolumab reduced mortality by 41 percent and prolonged survival by 3.2 months vs docetaxel,” she continued. [US FDA press release, 4 March 2015] “In an earlier phase II trial, single-agent nivolumab achieved a 15 percent response rate in heavily pretreated squamous cell NSCLC.”

Next in line is likely to be pembrolizumab, having shown an overall response rate of 45.2 percent in patients with ≥50 percent of tumour cells positive for PD-L1 expression. [N Engl J Med 2015, doi: 10.1056/NEJMoa1501824]

“These drugs as well as a number of other agents, such as ipilimumab and tremelimumab, and the PD-L1 inhibitors MPDL3280A, MEDI4736 and BMS936559, are also being evaluated in phase II/III trials with very encouraging results. Given the huge lung cancer market, the pharmaceutical companies are in a tight race,” she added.

Despite the early stage, some experts are now advocating immunotherapy as first-line treatment. “PD-1/PD-L1 inhibitors have demonstrated better clinical outcomes than chemotherapy, with a 15 percent increase in response rate and a 2-month longer progression-free survival. Importantly, immunotherapy elicits a fast and durable response and is less toxic,” argued Dr. Jean-Charles Soria of the Institut Gustav Roussy, Villejuif, France, at a debate session. “For these reasons, it’s a good first-line alternative for advanced non-oncogene-addicted NSCLC.”

The opponent, Dr. Kenneth O’Byrne of Queensland University of Technology in Brisbane, Australia, claimed, however, that the enthusiasm is premature and phase III data are needed to establish immunotherapy’s role in the first-line setting.

Despite the excitement, many challenges
remain with immunotherapy, including side effects (diarrhoea, colitis, fatigue and pneumonitis) and pseudo progression, which should be considered when assessing patient response.

Another drawback is the lack of a suitable biomarker. “PD-L1 expression in tumour cells is of limited value in predicting activity, as some patients with weak expression also respond, and could benefit from immunotherapy,” noted Peters. “The criteria for patient selection should be refined, as patient and tumour characteristics, including smoking status, previous therapy, histology and mutations, have been associated with responses to immunotherapy.”

The combination of immunotherapy with other treatment modalities such as chemotherapy, targeted therapy, radiotherapy or another immunotherapy is also being explored in many trials, according to Dr. Martin Reck of the Lung Clinic Grosshansdorf, Germany. “There are promising data but also conflicting results. Clinical development has somewhat overtaken the science behind. Proper translational research will be crucial and we should never forget safety when dealing with the powerful immune system,” he said.
MIMS rolls out new identity, purpose

Leading medical and drug information provider MIMS has rolled out a major rebrand initiative to better engage healthcare communities and provide healthcare professionals with unified multichannel information they can put into practice.

All MIMS publications – *Medical Tribune*, *Oncology Tribune*, *Pharmacy Today*, and *JPOG* – were renamed *MIMS Doctor*, *MIMS Oncology*, *MIMS Pharmacy* and *MIMS JPOG*, respectively. The publication titles now carry the new red logo to mirror the company’s renewed commitment to connect and engage people.

Mr Ben Yeo, managing director of MIMS Asia Pacific, recognized the importance of communicating the company’s new identity and purpose across a global platform.

“We see MIMS as the link that brings together healthcare communities, helping them to obtain and exchange knowledge to improve patient outcomes through better care,” he said.

To further support clinicians’ treatment decisions, MIMS introduced 12 disease specialty channels (Multispecialty, Pharmacy, Oncology, Cardiology, Respirology, Endocrinology, Hepatology, Gastroenterology, Neurology, Psychiatry and Obstetrics & Gynaecology and Paediatrics) on its website www.mims.com and MIMS mobile app.

“We’re going beyond just providing information,” said Ms Diana Edwards, managing director, MIMS Hong Kong and Singapore.

“To build and sustain thriving communities, we need to engage and connect people. We hope our news and insights, eLearning programs, congress coverage and other services will facilitate knowledge-sharing and build such communities.”

MIMS, a subsidiary of AXIO Data Group, with presence across 13 countries, has been the source of clinical news and drug information for health care professionals in Asia. With MIMS’ integrated multichannel content, information becomes even more accessible on print, online and mobile, said Ms Sherlynn Tan, deputy director, MIMS Marketing.

“This allows MIMS to grow its registered user base to over 2 million and to generate an average of 30,000 new users each month.”
NCDs and the need for policy solutions, effective interventions

Excerpted from a speech by Dr Margaret Chan, WHO director general, during a dialogue on non-communicable diseases held recently in Geneva, Switzerland.

Noncommunicable diseases (NCDs) have overtaken infectious diseases as the leading cause of mortality worldwide. WHO estimates that 80 percent of the burden from NCDs now falls on low- and middle-income countries, where people develop these diseases earlier, fall sicker, and unfortunately die sooner than their counterparts in wealthy nations. WHO estimates that NCDs are responsible for 14 million premature deaths in the developing world each year.

In some developing countries in Asia, the number of deaths from cardiovascular disease before the age of 55 is twice that in wealthy countries. The reference to type 2 diabetes as “adult onset diabetes” is no longer apt as so many children are now being diagnosed with this disease.

The responsibility for the rise in NCDs does not fall on individuals who choose to eat, smoke, and drink too much or opt for a sedentary lifestyle. The responsibility falls on the environments in which these choices are made. Can children be blamed for an addiction to nicotine when single cigarettes are sold at the gates of their schoolhouse? Can parents be blamed for their overweight children when cities have no green spaces or the crime rate is so high that children are not safe playing outdoors? For the millions of people living in so-called “urban food deserts”, healthy eating is simply not an option.

This is the first big challenge. The evidence, statistics, and arguments you put forward for international cooperation must stress the need for policy solutions that shape social environments. These solutions must be supported at the highest level of government, and they need to be put in place through a whole-of-government approach.

A second big challenge is competition. With 17 goals and 169 targets currently proposed for the post-2015 development agenda, this is competition for a sliver or some crumbs from the pie, not a piece.

You are being asked to sharpen the evidence showing the two-way links between NCDs and poverty. You are being asked to make a stronger case for viewing the prevention and control
of NCDs as an explicit poverty-reduction strategy.

You are being asked to provide an inventory of international agencies that have integrated NCDs into their development policies and extract the lessons learned. We want to hear your proposals about how official development assistance can be used to strengthen prevention and control, yet without compromising funding for other health priorities.

We ask you to do all of these things because of your expertise, knowledge, and experience.

A third big challenge is the opposition. This is opposition from powerful economic operators who strongly oppose any regulatory control or restrictions on their marketing of health-harming products.

This is a formidable obstacle to prevention. Economic power readily translates into political power. We rely on civil society for support in many areas, but most especially in this one.

The public health community has some tools in hand to respond to these challenges. The 2011 UN Political Declaration on NCDs sets out some compelling arguments. It positions these diseases as one of the major challenges for development in the 21st century. It points out their threat to economies and their contribution to inequalities. It gives the primary role and responsibility of responding to these challenges to governments. And it underscores how strongly prevention and control depend on the engagement of multiple non-health sectors.

To guide work, we have an action plan through 2020, a monitoring framework with nine global targets, and a set of effective and affordable interventions, known as “best buys,” that can make a difference in any resource setting.

As the root causes of NCDs lie beyond the direct purview and responsibility of the health sector, combatting these diseases is a complex task involving multiple sectors. Here, too, we have support from the Global Coordination Mechanism and a UN Interagency Task Force.

There are two points made in the discussion paper prepared for this meeting. First, the UN General Assembly’s 2014 progress review found no lack of high-level government commitment to NCDs. But it witnessed, in far too many countries, a lack of capacity to act, largely because of insufficient national expertise in low- and middle-income countries. International cooperation can provide this expertise. Second, efforts to prevent and control NCDs depend on a well-functioning health system, ideally one that aims to reach universal health coverage.

Any look at the interactions between NCDs and poverty must also look at ways to increase access to care and reduce the catastrophic medical bills that push so many millions of families below the poverty line each year.
Circulating tumour DNA helps detect EGFR mutations

NAOMI RODRIG

While biopsy remains the gold standard for EGFR mutation testing in advanced non-small-cell lung cancer (NSCLC), circulating tumour-derived DNA (ctDNA) may provide a more feasible methodology.

“We were looking for a valid test that can identify an EGFR mutation when the tumour is not accessible for bronchoscopy or CT-guided biopsy, and that’s in agreement with the gold standard tissue test,” said Dr. Martin Reck from the Lung Clinic Grosshansdorf, Germany.

Reck reported data from the real-world ASSESS study, which compared tumour biopsy with plasma ctDNA in 1,162 matching samples from European and Japanese patients. “Mutation status showed a high 89 percent concordance between the two methods,” he said. “The sensitivity of the plasma test was 46 percent, specificity was 97 percent, and positive predictive value [PPV] 78 percent.” [ELCC 2015, abstract 35O_PR]

Use of a highly sensitive DNA sequencing methodology and identical methods for tissue and plasma testing in a subset of patients further increased sensitivity to 72 percent, specificity to 99 percent and PPV to 94 percent.

“While improvements are still required in mutation analysis practices of both tissue/cytology and plasma samples, our data show that plasma ctDNA may be a feasible, suitable sample for EGFR mutation analysis,” he suggested. “It is important to use robust and sensitive methodologies to ensure patients receive appropriate treatment to address the molecular features of their disease.”

Another study reported the extraction of urine ctDNA to test for EGFR T790M mutation - a hallmark of disease progression in advanced NSCLC that is useful for patient monitoring. [ELCC 2015, abstract 36O]

The investigators obtained urine samples from patients who progressed on erlotinib and were confirmed to have EGFR T790M mutation by a tumour biopsy test. “EGFR T790M status was analyzed by a sensitive assay that had a lower limit of detection of 2 copies in a background of 20,000 copies of wild-type DNA,” ex-
explained Dr. Hatim Husain from the University of California, San Diego, CA, US.

Using this assay, they detected T790M mutation in 10 out of 10 confirmed EGFR T790M-positive patients (sensitivity, 100 percent). In addition, three patients with negative tissue testing results tested positive by urine analysis. EGFR T790M mutation was detected as early as 3.5 months prior to radiographic progression on first-line EGFR tyrosine kinase inhibitor (TKI) therapy, identifying five patients who may be eligible for second-line EGFR TKI treatment due to emergence of T790M mutation.

“This method, combining the extraction of urine ctDNA with an ultra-sensitive next-generation sequencing and mutation enrichment technology, has the advantage of urine as ctDNA source, potentially enabling dynamic monitoring of EGFR TKI therapy response from a completely noninvasive sample,” concluded Husain.

Survey: Targeted therapies for NSCLC underused

NAOMI RODRIG

Nearly a quarter of patients with advanced non-small-cell lung cancer (NSCLC) in Europe, Asia and North America are started on first-line therapy before their EGFR mutation testing results are available, which compromises their access to individualized treatment.

The data came from an international survey that looked at the treatment practices of 562 treating physicians from 10 countries (Canada, France, Germany, Italy, Japan, Korea, Spain, Taiwan, UK and USA). [ELCC 2015, abstract LBA2_PR]

Mutation testing rate was 82 percent in Asia, 77 percent in Europe and 76 percent in North America. “That’s suboptimal, as international guidelines recommend that all advanced NSCLC patients with non-squamous histology should be tested, so they can receive appropriate treatment according to their mutation status,” remarked Dr. James Spicer of Guy’s hospital, London, UK, who reported the results.

The main reasons for not testing all patients, aside from tumour histology, are insufficient tissue, poor performance status, smoking, and long turnaround time for test results.

“In Asia, more patients are being tested for EGFR mutations and getting the results in a time-
ly manner. Only 10 percent of Asian patients do not have the results before treatment decisions are made, vs 21 percent in North America and 26 percent in Europe,” noted Spicer.

The most important factor in the choice of first-line treatment across all regions was a clinically relevant increase in overall survival, but the survey showed that prescribing practices for EGFR-positive patients vary among regions.

“Physicians in North America and Asia offer significantly more first-line EGFR tyrosine kinase inhibitors [TKIs] than those in Europe [83, 81 and 76 percent, respectively]. Even when available, the use of mutation status to inform treatment decisions is variable, and a significant minority of EGFR-positive patients worldwide receive chemotherapy first, contrary to established guidelines,” he pointed out.

According to Spicer, the reasons why many patients with EGFR mutations receive chemotherapy first need to be understood. “Not being tested or being tested but not given a treatment associated with significant benefits affects patient outcomes,” he concluded.

The discussant, Professor Tony Mok of the Chinese University of Hong Kong, pointed out the survey’s limitations, including the small sample size, selection bias, and differences between types of physicians between continents.

“We don’t know whether the respondents were academic oncologists or private physicians, which may affect their access to EGFR analysis facilities,” he said. “Moreover, we don’t know whether testing or treatment selection had any financial implications for the patient or the physician. For example, were the respondents paid? Are testing and TKI therapy reimbursed?”

Mok also pointed out that a 2011 survey on EGFR mutation testing in Asia showed that overall, only 32 percent of Asian patients were tested, ranging from 18 percent in China to 65 percent in Japan. “The good news is that the proportion of those tested has been increasing steadily in the past few years,” he said. “As for the choice of first-line therapy, I don’t think Europe is that different from Asia and North America.”
BRAF inhibitors promising in lung adenocarcinoma

NAOMI RODRIG

The BRAF inhibitors vemurafenib and dabrafenib, currently approved for use in advanced melanoma, are also effective in a subset of lung adenocarcinoma patients with BRAF mutations, according to a retrospective European trial.

In the EURAF cohort study, researchers reviewed data of 35 patients with BRAF mutations who were treated with BRAF inhibitors (29 had BRAF V600E mutation; six had other BRAF mutations). Thirty-one patients received one BRAF inhibitor and four patients received two BRAF inhibitors. Altogether, 28 patients received vemurafenib, 10 received dabrafenib, and one received sorafenib. [ELCC 2015, abstract 980_PR]

“Best response by RECIST [Response Evaluation Criteria In Solid Tumours] was available for 36 of the 39 BRAF inhibitor therapies. Overall response rate was 53 percent, including 6 percent complete response and 47 percent partial response. Thirty-six percent of patients had stable disease, and 11 percent had disease progression. No unexpected toxicities were reported,” said Dr. Oliver Gautschi from Lucern Cantonal Hospital, Switzerland, who presented the results. “These data support BRAF testing in advanced lung adenocarcinoma, and BRAF inhibitor therapy in patients with V600E mutation.”

Commenting on the findings, Dr. David Planchard of the Institut Gustave Roussy in Villejuif, France, noted that only about 2 percent of lung adenocarcinomas harbour BRAF mutations. “Because of the low frequency of BRAF mutations in lung cancer, it is unlikely we will have randomized phase III trials in this population. The results of this study add to growing support for the approval of BRAF inhibitors for use in lung cancer.”

Ongoing studies are evaluating BRAF inhibitors in combination with other therapies and potential drug resistance mechanisms in this population.
PD-1 inhibitors surpass ipilimumab in advanced melanoma

CHRISTINA LAU

Programmed cell death 1 (PD-1) inhibitors such as pembrolizumab and nivolumab, as monotherapy or in combination with ipilimumab, are better first-line therapies than ipilimumab alone in patients with advanced melanoma.

In the phase III KEYNOTE-006 trial (n=834; 65.8 percent previously untreated), pembrolizumab significantly improved progression-free survival (PFS), overall survival (OS) and response rates (RRs) vs ipilimumab, a cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) inhibitor that is currently a standard first-line therapy for advanced melanoma. [N Engl J Med 2015, doi: 10.1056/NEJMoa1503093]

At 6 months, estimated PFS rates were 47.3 percent for pembrolizumab 10 mg/kg every 2 weeks and 46.4 percent for pembrolizumab 10 mg/kg every 3 weeks, compared with 26.5 percent for ipilimumab (3 mg/kg, 4 doses every 3 weeks) (hazard ratio [HR], 0.58; p<0.001 for both pembrolizumab regimens).

“At 12 months, estimated OS rates were 74.1 percent for pembrolizumab every 2 weeks [HR, 0.63; p=0.0005] and 68.4 percent for pembrolizumab every 3 weeks [HR, 0.69; p=0.0036], vs 58.2 percent for ipilimumab,” reported lead author Dr. Antoni Ribas of the University of California, Los Angeles, CA, US.

RRs were also higher with pembrolizumab (33.7 percent for 2-weekly dosing, 32.9 percent for 3-weekly dosing) vs ipilimumab (11.9 percent; p<0.001 for both).

Treatment-related grade 3-5 adverse events (AEs) were less common with pembrolizumab (13.3 and 10.1 percent for 2-weekly and 3-weekly dosing, respectively) than ipilimumab (19.9 percent).

“These results exceeded our expectations of the benefit of pembrolizumab over ipilimumab,” said Ribas. “The data will change the paradigm of treatment of advanced melanoma.”

Nivolumab, when used in combination with ipilimumab, also showed significant benefits over ipilimumab in patients with previously untreated advanced melanoma.

In a phase II trial of 142 patients, PFS and objective response rate (ORR) were significantly improved with the nivolumab/ipilimumab combination vs ipilimumab alone. [N Engl J Med}
2015, doi: 10.1056/NEJMoa1414428]

“Among 109 patients with BRAF wild-type tumours, median PFS was not reached in the combination therapy arm vs 4.4 months in the ipilimumab monotherapy arm [HR, 0.40; p<0.001],” reported lead investigator Dr. Stephen Hodi of the Dana-Farber Cancer Institute in Boston, MA, US.

ORR was 61 percent with combination therapy vs 11 percent with ipilimumab monotherapy (p<0.001). “Importantly, 22 percent of patients achieved complete response with the combination regimen,” said Hodi. “There were no complete responses with ipilimumab monotherapy.”

The investigators reported similar results for PFS and ORR in the 33 patients with BRAF V600 mutation-positive tumours. Again, 22 percent of patients achieved complete response with combination therapy.

However, the combination regimen was associated with higher rates of grade 3/4 drug-related AEs (54 percent vs 24 percent for ipilimumab monotherapy).

Pembrolizumab and nivolumab are currently approved by the US FDA for treatment of unresectable or metastatic melanoma that progressed after treatment with ipilimumab or a BRAF inhibitor.

Biomarkers may predict olaparib efficacy in advanced prostate cancer

CHRISTINA LAU

Genomic defects in DNA repair genes may predict response to olaparib in patients with metastatic castration-resistant prostate cancer (mCRPC), a phase II study has shown.

Among 49 patients with mCRPC who received olaparib in the TOPARP-A study, 16 responded, giving an overall response rate of 32.7 percent. [AACR 2015, abstract CT322]

“Patients with homozygous deletions and/or putatively deleterious mutations in DNA repair genes were more likely to respond to olaparib,” reported Dr. Joaquin Mateo of the Institute for Cancer Research and Royal Marsden NHS Foundation Trust, London, UK. “The majority of these genomic defects occurred in BRCA2 and ATM, but biallelic loss of other relevant genes, including members of the Fanconi Anaemia complementation group and CHEK2, were also found.”
Of 15 patients with these genomic defects, 13 (86.7 percent) responded to olaparib, including all seven patients with BRCA2 loss and four of five patients with ATM truncating mutations.

“The specificity of the biomarker suite was 94 percent,” said Mateo. “Our findings offer a possibility for the very first molecular treatment stratification of advanced prostate cancer.”

“Olaparib showed durable anti-tumour activity in our heavily-pretreated population of mCRPC patients,” he added. “All study patients had received prior docetaxel therapy, 96 percent had received prior abiraterone, and 58 percent had received prior cabazitaxel. Of the 16 patients who responded to olaparib, 11 and four had been on olaparib therapy for >6 and >12 months, respectively.”
MIMS Mobile app - your all-in-one clinical reference tool.

**Drugs**
Search the MIMS database of concise and full prescribing information

**Calculators**
Instant access to clinical calculator and scoring tools

**News & CME**
Stay up-to-date with the latest medical news & CME updates

**Disease Resources**
At-a-glance disease management guidelines for quick referencing on-the-go

**Special Reports**
Medical congress highlights and updates on drugs, diseases and clinical management trends

**Multimedia**
Gain quick clinical insights through 5-minute expert opinion videos

Download MIMS from the app store today!

Join over a million MIMS members who have incorporated MIMS into their daily workflow. Connect with MIMS today.

www.mims.com  MIMS mobile/tablet app  facebook.com/mimscom
American Society of Clinical Oncology (ASCO) 2015 Genitourinary Cancers Symposium, 26-28 February, Orlando, FL, US

**No benefit with adjuvant sunitinib, sorafenib in RCC**

**JENNY NG**

Adjuvant therapy with sunitinib or sorafenib does not benefit patients with locally advanced renal cell carcinoma (RCC), interim results from the phase III ASSURE (Adjuvant Sorafenib or Sunitinib for Unfavourable Renal Carcinoma) trial have shown.

The results showed that giving either VEGF tyrosine kinase inhibitor to RCC patients who had complete resection of their primary tumour led to similar rates of disease-free survival (DFS) and overall survival (OS) vs treatment with standard of care plus placebo. [ASCO GU 2015, abstract 403]

Patients randomized to receive daily sunitinib (for 4 weeks of a 6-week cycle) or sorafenib for 1 year had a median DFS time of 5.6 years (in both arms) vs 5.7 years for placebo. OS rates ranged from 77 to 81 percent and rates of recurrence were around 40 percent, with no difference between the three arms.

“No one is more disappointed than I am, except perhaps the patients who participated in this trial,” said lead investigator Dr. Naomi Haas of the Abramson Cancer Centre, University of Pennsylvania, Philadelphia, US.

“As we analyze smaller subsets of patients, hopefully we will learn more about who might benefit from these kinds of approaches and who they may be detrimental to, but overall, we certainly did not see any difference in median DFS in the larger group of patients,” she said.

The trial included 1,943 patients enrolled in the US and Canada with intermediate-high to very-high risk RCC (high-grade pT1B to any grade pT4) without metastasis. Risk factors for recurrence, including disease stage and grade, overall patient health, histology and type of surgery, were similar between the three arms.

The initial dosing was altered after accrual of 1,322 patients to mitigate the effect of patient discontinuation from treatment intolerance. Patients received a reduced starting dose and individualized dose titration, which reduced the discontinuation rate in the experimental arms from 26 percent to 14 percent.

However, patients receiving sunitinib or sorafenib showed greater rates of grade ≥3 hy-
pertension (16 percent vs 4 percent with placebo), hand-foot syndrome (15 and 33 percent vs 1 percent), rash (2 and 15 percent vs <1 percent) and fatigue (17 and 7 percent vs 3 percent).

According to the researchers, this is the first and largest trial to report the efficacy of sunitinib or sorafenib as adjuvant therapy in patients with locally advanced RCC and a high risk of recurrence.

The trial was designed and led by the Eastern Cooperative Oncology Group (ECOG) and the American College of Radiology Imaging Network (ACRIN) Cancer Research Group, along with support from the National Cancer Institute.

---

“Extreme caution” needed with surveillance in intermediate-risk prostate cancer

CHRISTINA LAU

Extreme caution is needed when using active surveillance in patients with intermediate-risk prostate cancer as new data show a substantially increased risk of long-term mortality with this approach compared with patients with low-risk disease.

In the first study to examine the long-term outcomes of patients with intermediate- vs low-risk prostate cancer managed with active surveillance, the 15-year risk of dying from the disease was 3.75 times higher in the intermediate-risk group (11.5 vs 3.7 percent; p=0.01). [ASCO GU 2015, abstract 163]

The study included 237 intermediate-risk patients (prostate-specific antigen [PSA] >10 ng/mL or Gleason score of 7 or clinical stage T2b/2c) and 708 low-risk patients managed with active surveillance between 1995 and 2013 at the Sunnybrook Health Sciences Centre, Toronto, Canada. Median follow-up was 6.9 years in the intermediate-risk group and 6.4 years in the low-risk group.

At 10 and 15 years, the rate of cause-specific survival (CSS) was 95.5 vs 98.2 percent and 88.5 vs 96.3 percent, respectively, favouring those with low-risk disease (hazard ratio [HR], 3.75; p=0.01).

Overall survival (OS) rates at 10 and 15 years
were also significantly lower in the intermediate-risk group, being 68.4 and 50.3 percent, respectively, compared with 83.6 and 68.8 percent in the low-risk group (HR, 2.08; p<0.0001).

“In the intermediate-risk group, 86 patients [36.3 percent] received treatment, mainly with radiation, due to PSA doubling within 3 years or Gleason score or clinical progression. The median treatment-free interval was 12.3 years,” reported investigator Dr. Andrew Loblaw of the Sunnybrook Health Sciences Centre, Toronto, Canada.

“Our findings suggest that active surveillance should be implemented with extreme caution in patients with intermediate-risk prostate cancer,” he concluded. “More research is needed to better characterize those patients with intermediate risk who can be safely managed with this approach.”

One direction the researchers are pursuing is to further analyze data from patients with favourable and unfavourable intermediate risk.

In a recent study of 5,580 men with localized prostate cancer, researchers found similarly low risks of mortality between men with favourable intermediate-risk disease and those with low-risk disease following brachytherapy. Eight-year estimates for prostate cancer-specific mortality and all-cause mortality were 0.48 and 10.45 percent for those with favourable intermediate-risk disease, vs 0.33 and 8.68 percent for those with low-risk disease. [JAMA Oncol 2015, doi: 10.1001/jamaoncol.2014.284]
The rate of intermediate- and high-risk prostate cancer, defined as a prostate-specific antigen (PSA) level greater than 10 ng/mL, has increased in the US between 2011 and 2013.

This increase follows the US Preventive Services Task Force’s draft recommendation in 2011 against the use of PSA in prostate cancer screening.

To investigate the potential consequences of the Task Force’s recommendation, researchers analyzed data from 87,562 men diagnosed with prostate cancer between 2005 and 2013. The patient data were extracted from the proprietary National Oncology Data Alliance (NODA) database, which captures newly diagnosed cancer cases at more than 150 US hospitals. [ASCO GU 2015, abstract 143]

“The NODA database includes data from 2011 to 2013, which were not available on the National Cancer Institute’s Surveillance, Epidemiology and End Results [SEER] database at the time of our analysis,” said lead study author, Professor Timothy Schultheiss of the City of Hope Cancer Centre, Duarte, CA, US. “The NODA data are identical to the data sent to state tumour registries and SEER in regions that participate in SEER.”

The retrospective analysis showed a gradual decrease in the proportion of prostate cancer patients with PSA levels >10 ng/mL between 2005 and 2011.

“However, the proportion of men diagnosed with intermediate- and high-risk prostate cancer increased significantly by 3 percent per year between 2011 and 2013, for a total of 6 percent, without evidence of a plateau,” Schultheiss reported.

“The proportion of men aged 75 years or above who presented with PSA levels greater than 10 ng/mL nearly doubled from 2011 to 2013, compared with the rate for men of all ages,” he added.

Based on the estimated 233,000 new prostate cancer cases in the US in 2014, the researchers said approximately 14,000 men per year will shift from a low-risk to a higher-risk disease group.

“This apparent trend could produce 1,400 additional prostate cancer deaths per year,” said Schultheiss. “Men at increased risk for prostate cancer should consider talking to their doctor about PSA screening.”

CHRISTINA LAU

American Society of Clinical Oncology (ASCO) 2015 Genitourinary Cancers Symposium, 26-28 February, Orlando, FL, US

Higher-risk prostate cancer increased in the US
Health officials highlight challenges in cancer care in Asia, call for coordinated efforts

JENNY NG

The WHO’s 2014 World Cancer Report predicts a crisis in cancer over the next 20 years, with a 75 percent surge in cases worldwide from 2008 and a projected economic cost totalling USD 1 trillion.

Half of the global burden of cancer lies in Asia, where the incidence is expected to increase from 6.1 million in 2008 to 10.6 million by 2030, in part as a consequence of ageing societies and socioeconomic development. [GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10. International Agency for Research on Cancer: Lyon, France; 2010]

At the recent Healthcare in Asia Summit 2015 organized by The Economist, more than 180 health ministers and officials across Asia, along with industry leaders, policymakers, private-sector healthcare providers and medical professionals, gathered in Hong Kong to discuss points of action amidst the looming cancer crisis in Asia.

At the event, Dr. Rengaswamy Sankaranarayanan, Special Adviser on Cancer Control and Head of Early Detection and Prevention at the International Agency for Research on Cancer, WHO, stated, “Planned and timely investments in prevention, early detection and cancer management in public health services, and development of resource-appropriate healthcare financing schemes are key to cancer control in Asia.”

Government officials from across Asia spoke on the challenges they face in cancer control policies to which Charles Goddard, Editorial Director of The Economist Intelligence Unit, described as very heterogeneous across the region. Cancer control, he said, was still very much a work in progress in Asia.

“Cancer control plans in Asia are often scattered across various policies with no single unified model. But this can be a positive tool, helping us to identify the valuable strategies from both low- and high-income countries,” said Goddard.

High-quality data and the development of cancer registries are fundamental aspects of cancer control that are lacking in many Asian countries, Goddard explained. GLOBOCAN rankings for
cancer data quality show high rankings for Korea and Taiwan, while substantial investments are being made in countries such as China. “It is not just about money. The ranking represents the commitment put forth by countries. For example, Thailand is ranked as high as Japan on data,” he added.

Calls for improving early detection and prevention resonated with summit attendees due to the overwhelming burden of cancer care on healthcare systems. “Cancer care is expensive, so we need to think about how to get people to go in for early detection,” said Indonesia Minister of Health, Dr. Nila Moeloek. “Primary healthcare is the gatekeeper for the people,” she added.

“With proper [cancer] prevention measures, we could expect healthcare expenditures [in the Philippines] to reduce by 45 to 50 percent,” said Philippines Secretary of Health, Dr. Janette Loreto-Garin.

“Early detection of cancer is one of the most important strategies for cancer care,” said Hong Kong Secretary for Food and Health, Dr. Wing-Man Ko. “Many cancers are preventable simply with changes in lifestyle and diet.”

“However, the success of policies will be totally dependent on the actions and the participation of priority stakeholders,” said Loreto-Garin.

The issue of access to care also emerged out of discussions of government intent as opposed to meaningful action.

“There is a tremendous gap between the intent of governments and their actual implementation of strategies,” said Raman Singh, President of Emerging Markets at Mundipharma.

“The difficulty in translating plans into action often lies in access to care, and it is not just about pricing, but also about infrastructure, having trained healthcare providers, as well as education and awareness,” said Singh.

Taiwan, often mentioned as a model for Asian healthcare systems, adopted its National Health Insurance programme in 1995. The programme now sees more than 96 percent coverage of Taiwan’s population. Dr. Shu-Ti Chiou, Director-General of Health Promotion Administration, Taiwan, explained, however, that health insurance for all does not equate to health for all.

“Screening may help with early detection, but this doesn’t always lead patients to the necessary care. Just a few years ago, 16 percent of our cancer patients did not receive treatment within 3 months of their diagnosis. Today, we’ve been able to reduce this by almost half, to just 9 percent,” said Chiou.

“Currently, only 47 percent of our cancer patients receive palliative care before they die. We still see 28 percent of deaths due to cancer,” she added.

Challenges with financing the system in Taiwan and a shortage of physicians remain, highlighting the need for a strong infrastructure for an effective cancer control plan.

“This year, we have declared war on cancer, a disease that is rapidly becoming a major cause of death in the region, and a complex and costly challenge to health systems. Coordinated efforts and shared experiences across developed and emerging Asian countries can help tackle the cancer burden more effectively,” said Goddard.
Sentiments on the private healthcare industry’s role in cancer care are at times contentious, but experts from both the public and private sectors agree on the need for improving public-private partnerships.

The private sector has a unique role that is critical to the challenge of improving access to cancer care in Asia, experts noted. By offering innovative strategies for improving infrastructure, regulatory lags, reimbursement, prevention, and the discovery and delivery of new treatments, the private sector and industries including pharmaceutical and insurance agencies have a shared responsibility to help stem the war on cancer.

For example, lag times in drug approval and limitations of reimbursement systems are preventing cancer patients in Asia from receiving more effective treatments. Much fewer cancer drugs were approved in Asia than in Europe in 2009-2013, with lag times in approvals of 10-17 months in some Asian countries compared with Europe.

Similarly, reimbursement schemes in Asia are slow and cover few innovative cancer drugs. Although some oncology medications were added to China’s Essential Drug List in 2012-2013, no initial reimbursements are offered for innovative drugs. In India, there is currently no national reimbursement system.

While governments are working to address these issues, pharmaceutical companies will need to consider them in the development and marketing of new drugs.

“Part of the challenge is also the requirement of local clinical data prior to final marketing approval,” said Masum Hossain, Regional President of Pfizer Oncology in the Asia-Pacific region. Most randomized clinical trials leading to drug approvals are done in Western countries with Western populations. Working with governments to find solutions to these challenges is just one way improving public-private partnerships will overcome the delays in access to cancer care.

“Fundamentally, what we’re trying to do is to improve patients’ quality of life through the discovery and delivery of new medicines, but we have to do this in partnership,” said Hossain. “It is absolutely critical that we form partnerships across a broad range of government and non-government organizations.”

Healthcare in Asia Summit 2015, 20 March 2015, Hong Kong
Fasting enhances anticancer activity of TKIs

Administering tyrosine kinase inhibitors (TKIs) under fasting conditions enhances their anticancer activity, according to a recent report.

In a preclinical trial, researchers evaluated the effect of fasting conditions on the anticancer activity of common TKIs, namely erlotinib, gefitinib, lapatinib, crizotinib and regorafenib. In particular, they evaluated the ability of each TKI to block cancer cell growth, inhibit the mitogen-activated protein kinase (MAPK) signalling pathway, and strengthen E2F-dependent transcription inhibition. Anticancer effects of TKIs were also evaluated under fed and fasting conditions in murine xenograft models. [Onco-target 2015, e-pub 30 Mar]

Starvation conditions were shown to have a synergistic anticancer effect with TKIs, as cancer cell growth was significantly slowed when each of the TKIs was administered under starvation conditions for 4 to 6 days. Further in vitro testing under varying conditions revealed that this potentiation was due to increased blocking of cell signalling via the MAPK cascade. Subsequent tests in xenograft mice revealed that although both TKIs and fasting slowed tumour growth, significantly greater reductions were observed when fasting and TKI therapy were combined.

The researchers commented that although their results are promising, clinical trials are needed to evaluate the effects of cycles of fasting or specially designed diets that mimic fasting on TKI efficacy.
A novel molecular method for predicting response to decitabine among patients with chronic myelomonocytic leukaemia (CMML) has been developed based on differential DNA methylation and gene expression.

Researchers studied DNA isolated from bone marrow mononuclear cells collected from 40 patients with de novo CMML who had received six cycles of decitabine 20 mg/m²/day for 5 days; 20 patients had responded to therapy. Using genome-wide next-generation sequencing assays and transcriptional analysis, the researchers examined baseline differences in mutations, DNA methylation, and gene expression in the patients. [J Clin Invest 2015, doi:10.1172/JCI78752]

No somatic mutation was significantly correlated with decitabine response, but 167 differentially methylated regions of DNA distinguished responders and non-responders. An epigenetic classifier based on these methylation profiles was found to accurately predict decitabine response.

Furthermore, transcriptional analysis revealed the upregulation of a number of genes associated with cell cycle regulation among decitabine responders. Although fewer genes were upregulated in decitabine non-responders, further analysis of two, CXCL4 and CXCL7, revealed that they blocked the effects of decitabine on normal CD34+ cells and primary CMML cells, suggesting that the upregulation of these two genes is linked to decitabine resistance.
Adjuvant chemoradiation improves prognosis in node-positive vulvar cancer

Adjuvant chemoradiation appears to improve the prognosis of women with lymph node-positive vulvar cancer.

In a recent retrospective, multicentre, cohort study, researchers analyzed data from 1,249 patients with primary or recurrent squamous cell vulvar cancer who received treatment at 29 gynaecological centres in Germany between 1998 and 2009. A total of 447 women were lymph node-positive (the majority with one or two positive nodes), and 802 were lymph node-negative. [J Natl Cancer Inst 2015;107:dju426]

Among the node-positive patients, the 3-year progression-free survival (PFS) rate was 39.6 percent in the 244 women who underwent adjuvant therapy vs 25.9 percent in those who did not (hazard ratio [HR], 0.67; p=0.004). The overall survival (OS) rate was also improved with adjuvant therapy (57.7 vs 51.4 percent; HR=0.79; p=0.17).

After adjusting for age, Eastern Cooperative Oncology Group performance status, Union Internationale Contre le Cancer stage, cancer grade, tumour invasion depth, and number of positive nodes, adjuvant therapy was found to be significantly associated with improvements in the rates of both PFS (HR, 0.58; p<0.001) and OS (HR, 0.63; p=0.01). However, outcomes among node-positive patients were still poor compared with node-negative patients (3-year PFS, 35.2 vs 75.2 percent; OS, 56.2 vs 90.2 percent).
Vitamin D supplements reduced inflammation in the prostate gland and kept early stage tumours from progressing, according to preliminary study results of men diagnosed with prostate cancer presented at the recent meeting of the American Chemical Society in Denver, Colorado, US.

Some studies associate high-dose vitamin D supplementation with a reduced risk of colorectal cancer but similar associations for other types of cancer is still unclear. Therefore, vitamin D supplementation is neither recommended nor advised against, according to the US National Cancer Institute.

However, in the current study of 37 men diagnosed with less aggressive prostate cancer (Gleason scores of ≥6), more than 60 percent of those randomized to 4,000 units of vitamin D per day showed improvement in their tumours compared with men randomized to a placebo. Prostate tumours in the placebo group remained the same or worsened. [American Chemical Society National Meeting 2015. Abstract AGFD 11]

“We had a reluctant urology division that cooperated in this [study],” said lead researcher Dr. Bruce Hollis of the Medical University of South Carolina in Charleston, South Carolina, US. “By the end, it was standard of care in our urology division.”

Hollis said the results underscored an earlier study he did in which 55 percent of men with low-grade prostate cancer had improvement in Gleason scores or no evidence of tumours after a year of vitamin D supplements (4,000 units/day), based on baseline and 1-year follow-up biopsies. [J Clin Endocrinol Metab, 2012;doi:10.1210/jc.2012-1451]

The typical management strategy for low-grade prostate cancer is ‘active surveillance’ and a follow-up biopsy after a year, Hollis said, but this waiting game can cause stress and anxiety for patients, who may opt for a prophylactic prostatectomy.

Hollis and colleagues conducted their study during the 60-day waiting period between biopsy and prostatectomy, which is necessary to let the inflammation go down. The biopsied glands were re-examined following removal.

“If we look at age-matched controls within the same practice, historically, 90 percent of tumours get worse or stay the same,” he said.

The key driver of tumour improvement as a result of vitamin D may be its inflammation-
lowering effects, since inflammation is known to drive carcinogenesis.

“We don’t know yet whether vitamin D treats or prevents prostate cancer,” Hollis said. “At the minimum, what it may do is keep lower-grade prostate cancers from going ballistic.”

Hollis said a larger study on the effects of vitamin D on prostate cancer as well as future studies on different types of cancers and higher levels of vitamin D – he would go up to 12,000 units – might be appropriate.

“We’re treating these guys with normal body levels of vitamin D,” he said. The body can make 10,000-20,000 units of vitamin D per day depending on sun exposure. “We haven’t even moved into the pharmacological levels yet.”

Axillary evaluation still frequent in breast DCIS

JACKEY SUEN

Axillary lymph node evaluation is performed frequently in patients with ductal carcinoma in situ (DCIS) undergoing breast-conserving surgery (BCS) despite international guidelines recommending against its use, a recent study reveals.

Although axillary lymph node evaluation is the standard of care in the surgical management of invasive breast cancer, a benefit has not been shown in DCIS. Therefore, the American Society of Clinical Oncology and the National Comprehensive Cancer Network guidelines recommend against axillary lymph node evaluation in women with DCIS undergoing BCS. [J Clin Oncol 2005;23:7703-7720; NCCN Clinical Practice Guidelines in Oncology, Breast Cancer: Version 1, 2015: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf]

Despite the recommendations, researchers found that almost one-fifth of women in the US who had BCS between 2006 and 2012 underwent an axillary lymph node evaluation. [JAMA Oncol 2015, doi: 10.1001/jamaoncol.2015.0389]

In their analysis of 35,591 US women with DCIS, 17.7 percent of those undergoing BCS and 63.0 percent of those undergoing mastectomy were found to have undergone an axillary evaluation. The rate of axillary evaluation increased from 56.6 percent in 2006 to 67.4 percent in 2012 with mastectomy, but remained relatively stable with BCS (18.5 percent in 2006 and 16.2 percent in 2012).

In patients undergoing mastectomy, those treated at non-teaching hospitals in urban ar-
eas had a higher rate of axillary evaluation. In patients undergoing BCS, a higher rate of axillary evaluation was observed in those treated at non-teaching hospitals by low-volume surgeons (defined as having one DCIS operation per year).

While the researchers suggested a need for prospective evaluation of the clinical benefit of axillary evaluation in women with DCIS, Dr. Kimberly Van Zee of the Evelyn Lauder Breast Centre, New York, NY, US, attributed the unexpectedly high rate of axillary evaluation in BCS-treated patients to hospital and surgeon factors. “Only low-volume surgeons and non-teaching hospitals were associated with the greater use of nodal assessment, suggesting that such surgeons are less aware of or less able to adopt current recommendations,” she pointed out in an accompanying editorial. [JAMA Oncol 2015, doi: 10.1001/jamaoncol.2015.0390]

Brentuximab vedotin doubles PFS in unfavourable-risk Hodgkin’s lymphoma after ASCT

CHRISTINA LAU

Brentuximab vedotin, the first new drug for Hodgkin’s lymphoma in more than 30 years, doubles progression-free survival (PFS) in patients with unfavourable-risk disease when used as early consolidation therapy after autologous stem cell transplantation (ASCT), the phase III AETHERA study has shown.

In patients randomized to receive brentuximab vedotin (1.8 mg/kg intravenously every 3 weeks for 16 cycles) starting 30 to 45 days after ASCT, median PFS by independent review was 42.9 months compared with 24.1 months in patients receiving placebo (hazard ratio [HR], 0.57; p=0.0013). [Lancet 2015, doi:10.1016/S0140-6736(15)60165-9]

“At 2 years, 63 percent of patients in the brentuximab vedotin group were progression free, compared with 51 percent in the placebo group,” said lead study author Professor Craig Moskowitz of the Memorial Sloan Kettering Cancer Centre, New York, NY, US.

“Nearly all patients who are progression free at 2 years are likely to be cured, since relapse 2 years after a transplant is unlikely,” he ex-
A consistent PFS benefit of brentuximab vedotin was observed across different subgroups of patients.

“The study met its primary endpoint. No medication available today has had such dramatic results in patients with difficult-to-treat Hodgkin’s lymphoma,” said Moskowitz.

Brentuximab vedotin is an antibody-drug conjugate comprising an anti-CD30 monoclonal antibody attached by a protease-cleavable linker to a microtubule-disrupting agent, monomethyl auristatin E. The therapy is approved for relapsed or refractory CD30+ Hodgkin’s lymphoma in 50 countries, including Hong Kong, Japan and Singapore.

The antibody-drug conjugate was generally well tolerated in the AETHERA study of 329 patients with unfavourable-risk, relapsed or primary refractory classic Hodgkin’s lymphoma who had been treated with high-dose chemotherapy and ASCT. The most common side effects were peripheral sensory neuropathy (56 vs 16 percent with placebo) and neutropenia (35 vs 12 percent).

“AETHERA is a positive study establishing a promising new treatment approach for patients with Hodgkin’s lymphoma at high risk for relapse. However, with a PFS [rate] of about 50 percent at 24 months in the placebo group, whether this patient population is indeed high risk could be debated,” wrote Professor Andreas Engert of the University Hospital of Cologne, Germany, in a linked comment. [Lancet 2015, doi:10.1016/S0140-6736(15)60583-9]

“An international consortium is reassessing the effect of risk factors in patients with relapsed Hodgkin’s lymphoma to define a high-risk patient population in need of consolidation treatment,” he added.

**Personalized vaccine promising in advanced ovarian cancer**

CHRISTINA LAU

An experimental vaccine made from autologous tumour cells has shown promise in advanced ovarian cancer and will be tested in a phase III clinical trial.

In a small, open-label phase II study (n=31), patients with stage III/IV ovarian cancer who received the personalized FANG vaccine (n=21) had substantial improvements in recurrence-free survival vs those who did not (n=11). [Oh J, et al, American Society of Gynaecologic Oncology Annual Meeting on Women’s Cancer]
“In the FANG group, the median time to recurrence is not yet reached. The majority of patients have now been followed for well beyond 14.5 months,” reported Dr. Jonathan Oh of Texas Oncology, Dallas, TX, US. “In the control group, ovarian cancer recurred after a median of 14.5 months.”

Patients in the study achieved clinical complete response following surgical debulking and chemotherapy. Tumours harvested at the time of surgical debulking were used to create a personalized vaccine for each patient.

“The FANG vaccine is composed of granulocyte macrophage colony-stimulating factor and bi-shRNAi furin vector transfected autologous tumour cells,” explained Oh. “In the study, the FANG vaccine was used as maintenance treatment following surgical debulking and chemotherapy. Patients in the FANG group received 1.0 x 10^7 cells/intradermal injection once monthly for up to 12 doses. Those in the control group were followed as per standard of care.”

“The vaccine was very well tolerated,” said Oh. “Based on the safety, the high rate of T-cell activation, and the marked delay in time to recurrence, we are now pursuing a phase III trial of the FANG vaccine involving 382 patients.”

Recruitment of the phase III trial is ongoing. The investigators will assess recurrence-free survival as the primary endpoint and overall survival as the secondary endpoint. The study is expected to be completed in 2019. [https://clinicaltrials.gov/ct2/show/NCT02346747]

“The majority of patients with stage III/IV ovarian cancer relapse within 2 years after achieving clinical complete response with surgical debulking and chemotherapy. The results of our phase II study are very promising,” said Oh.

Fish oil consumption may induce chemoresistance

JENNY NG

Consuming fish oil has been shown to induce chemo-resistance in mice, leading experts to advise avoiding fish and fish oil supplements when undergoing chemotherapy.

Patients with cancer often adopt lifestyle changes such as taking dietary supplements...
with the intention to influence and improve their health. However, mice studies showed that adding the fatty acid fish oil component 16:4(n-3) to cisplatin chemotherapy substantially reduced the drug’s effect on tumour suppression.

A 95.5 mm³ difference in tumour volume was seen in mice treated with 16:4(n-3) plus cisplatin vs cisplatin alone (p=0.04), while cisplatin alone effectively reduced tumour volume by 142.4 mm³. [JAMA 2015, doi:10.1001/jamaoncol.2015.0388]

Similar chemoresistant effects of 16:4(n-3) were seen with irinotecan and oxaliplatin (p<0.05 for both).

“Our results add to the growing awareness that not all dietary supplements are beneficial or harmless – some may interfere with treatment outcomes,” the researchers wrote.

In a survey of 118 patients undergoing cancer treatment, the researchers identified regular supplement use in 30 percent, and regular use of omega-3 fatty acids in 11 percent of patients.

Consuming the recommended daily amount of fish oil (10 mL) was shown to rapidly increase plasma levels of 16:4(n-3), up to 20 times baseline levels, in healthy volunteers. Different commercially available fish oils containing varied amounts of 16:4(n-3) were found to induce similar spikes in plasma 16:4(n-3).

16:4(n-3) levels peaked around 4 hours and normalized after 8 hours of intake. However, ingesting a high dose of fish oil (50 mL) led to a prolonged elevation of plasma 16:4(n-3).

Healthy volunteers who ate 100 g of herring and mackerel also showed increased plasma levels of 16:4(n-3). However, the level of plasma 16:4(n-3) was highly dependent upon the levels of 16:4(n-3) in the fish. Tuna, which contained the smallest amount of 16:4(n-3), had no effect on plasma 16:4(n-3) while salmon led to a small and short-lived spike.

In dose-response analyses, as little as 1 µL of 16:4(n-3) added to cisplatin was enough to induce chemoresistance in tumours. According to the researchers, the equivalent intake of 3 mL of fish oil in an average-sized adult is much lower than the recommended daily intake.

All six commercially available fish oils tested were found to contain substantial levels of 16:4(n-3), ranging from 0.2 to 5.7 µM. Moreover, the data suggest that other fatty acids in fish oil may be metabolized in the body to form 16:4(n-3), with the potential to interfere with chemotherapy.

“Based on our findings, until further data become available, we advise patients to temporarily avoid fish and fish oil from the day before chemotherapy until the day thereafter,” the researchers concluded.
Study unveils molecular mechanism of metastasis in stiff breast tumours

JACKY SUEN

In patients with stiff breast tumours, the increased risk of metastasis is shown to be driven by translocation of the TWIST1 protein – a finding that may pave the way for therapeutic strategies to slow tumour progression. [Nat Cell Biol 2015;17:678-688]

“In breast tumours, the presence of dense clusters of collagen fibrils indicates increased matrix stiffness and correlates with tumour progression and metastasis, as well as poor survival. However, it remains unclear how tumour stiffness is translated to transcriptional outputs that drive tumour progression,” wrote researchers from the University of California, San Diego School of Medicine and Moores Cancer Centre, CA, US. “Our present study demonstrated that cancer cell behaviour is not only driven by its own biochemical signals, but also by biomechanical signals from the tumour’s physical environment.”

“The cytoplasm-resident TWIST1 protein is an essential mechanomediator that promotes epithelial-mesenchymal transition in response to increasing matrix stiffness,” reported the researchers. “From our cultures of breast cells with varying degrees of matrix stiffness, we found that high stiffness promoted the entry of the cytoplasm-resident TWIST1 protein into the cell nucleus, activating genes that promote tumour invasion and metastasis.”

“In addition, loss of G3BP2 protein, the cytoplasmic binding partner of TWIST1, leads to constitutive TWIST1 nuclear localization and synergizes with increasing matrix stiffness to promote tumour invasion and metastasis,” noted the researchers. “This is shown in our mouse models of human breast tumours, in which tumours without G3BP2 protein were more invasive and developed more lung metastases than those with G3BP2.”

The above findings were confirmed in an analysis of tumour samples obtained from breast cancer patients. In the analysis, survival was shorter in patients with stiffer tumours (ie, more organized collagen structure) vs those with less stiff tumours (ie, disorganized collagen structure), and even shorter in patients with stiffer tumours which expressed low levels of G3BP2. “The correlation was so clear that we could use G3BP2 levels and matrix stiffness to predict patient outcome,” the researchers pointed out.

“Our findings reveal a TWIST1-G3BP2 mechanotransduction pathway that responds to bio-
mechanical signals from the tumour microenvironment to drive invasion and metastasis,” they concluded. “Next, we want to understand exactly how cells interpret mechanical cues and translate them into biological responses. This cross-talk between a tumour’s biomechanical microenvironment and the inter-workings of cancer cells may inspire new strategies for predicting patient outcomes and slowing down tumour progression.”

Breath test detects gastric cancer and precancerous gastric lesions

CHRISTINA LAU

A breath test developed by researchers in Israel and Latvia can identify patients with gastric cancer and precancerous gastric lesions with high accuracy, potentially offering a noninvasive tool for screening and surveillance.

The test, which analyzes patterns of volatile organic compounds (VOCs) in exhaled breath, is shown to discriminate between patients with gastric cancer (n=99) and controls (n=385) with 73 percent sensitivity, 98 percent specificity and 92 percent accuracy. [Gut 2015, doi: 10.1136/gutjnl-2014-308536]

“Importantly, the breath test provided excellent discrimination between patients with gastric cancer and those with high-risk precancerous gastric lesions,” noted lead investigator Professor Hossam Haick of the Technion–Israel Institute of Technology in Haifa, Israel.

The researchers stratified patients in the control group by the presence/absence and stage of precancerous gastric lesions using the Operative Link on Gastric Intestinal Metaplasia (OLGIM) staging system. Patients with OLGIM stages III-IV were considered to be at high risk of gastric cancer.

“The nanoarray analysis provided 93 percent sensitivity, 80 percent specificity and 90 percent accuracy in discriminating between patients with gastric cancer and those with OLGIM stages III-IV,” said Haick. “The classification sensitivity, specificity and accuracy for gastric cancer vs OLGIM stages 0-II were 97 percent, 84 percent and 87 percent, respectively.”

“Potential confounding factors, such as Helicobacter pylori infection, smoking, alcohol use and intake of proton-pump inhibitors 1 month before sampling, had no significant influence on the results,” he added.
In the study, the researchers collected two breath samples from each of the 484 patients for two different analyses. The first breath sample was analyzed by gas chromatography linked to mass spectrometry (GCMS), and the second by cross-reactive nanoarrays combined with pattern recognition.

GCMS revealed 130 different VOCs in the breath samples. Eight of these VOCs differed in statistically significant manners between patients with gastric cancer and different subgroups of those with OLGIM 0-IV.

“No single VOC could discriminate between the groups of patients, but the breath print, meaning the combination of the eight statistically validated VOCs, demonstrated clear differences between the control group of patients with OLGIM 0-IV and the gastric cancer group,” the researchers noted.

Given these promising results, the researchers have started a large-scale study, involving thousands of patients in multiple European centres, to validate the breath test in real screening settings.

“The breath test can potentially be used as a screening tool for gastric cancer and a surveillance tool for patients with precancerous gastric lesions,” they noted. “Its attractiveness lies in its noninvasiveness, ease of use [therefore high compliance would be expected], rapid predictiveness, insensitivity to confounding factors and potentially low cost.”

---

**NSCLC vaccines prolong patient survival**

KAVITHA G. SHEKAR

Vaccines for the treatment of advanced non-small-cell lung cancer (NSCLC) prolong overall survival (OS) and have fewer side effects compared to controls, a systematic review and meta-analysis reveals.

To evaluate the therapeutic efficacy and safety of tumour vaccines in NSCLC, researchers extracted randomized controlled trial (RCT) data published on PubMed, the Cochrane Central Register of Controlled Trials, ScienceDirect and EMBASE during January 1980 to

January 2015. [BMJ Open 2015;5:e006321]

Eleven multicentre RCTs assessing 3,986 patients with stage III-IV NSCLC were included.
In the trials, tumour vaccines, used alone or in combination with chemotherapy, were compared with placebo, chemotherapy or best supportive care.

The meta-analysis showed extended OS with the vaccines vs controls (hazard ratio [HR] 0.760; p=0.001). Time to progression (TTP), median progression-free survival (PFS) and objective response rate also improved after treatment with tumour vaccines (p=0.001, 0.005 and 0.05, respectively).

Patients in the vaccine arm had fewer treatment-related adverse effects, such as nausea and vomiting, thrombocytopenia and injection reaction (p≤0.05), compared to those in the control arm.

“Our meta-analysis suggests tumour vaccines improve the efficacy of treatment, and also provide superior treatment of patients with advanced NSCLC among a variety of immunotherapy strategies,” said lead author Dr. Min Wang from the Biotherapy Centre, General Hospital of Beijing Military Command, Beijing, China.
You can now enjoy MIMS Journal of Paediatrics, Obstetrics & Gynaecology (JPOG) through MIMS.com and the MIMS tablet and mobile applications. Log on to www.mims.com today for instant access to news and CME articles covering the latest trends and developments in paediatrics, obstetrics and gynaecology.

Join over a million MIMS members who have incorporated MIMS into their daily workflow. Connect with MIMS today.

Stay up-to-date on the latest medical trends and developments, wherever you may be.
WCPT Congress 2015
1/5/2015 to 4/5/2015
Location: Singapore
Info: World Confederation for Pain Therapy
Tel: (44) 0 20 7931 6465
Email: info@wcpt.org
Website: http://www.wcpt.org

Royal Australasian College of Surgeons Annual Scientific Congress 2015
4/5/2015 to 8/5/2015
Location: Perth, Australia
Info: World Confederation for Pain Therapy
Tel: (613) 9249 1219
Email: college.sec@surgeons.org
Website: http://www.surgeons.org

European Congress on Obesity 2015
6/5/2015 to 9/5/2015
Location: Prague, Czech Republic
Info: European Association for the Study of Obesity
Tel: (44) 20 3751 7967
Email: eco2015@guarant.cz
Website: http://eco2015.easo.org

48th Annual Meeting of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)
6/5/2015 to 9/5/2015
Location: Amsterdam, Netherlands
Info: ESPGHAN Secretariat
Tel: (44) 845 1800 360
Email: AnnualMeeting2015@espghan.org
Website: www.espghan2015.org

21st World Congress on Controversies in Obstetrics, Gynaecology & Infertility (COGI)
7/5/2015 to 10/5/2015
Location: Guilin, China
Info: COGI Secretariat
Tel: (972) 73 706 695
Fax: (972) 3 725 6266
Email: cogi@congressmed.com
Website: www.congress med.com/cogichina/index.php/en

14th World Congress of EAPC
8/5/2015 to 10/5/2015
Location: Copenhagen, Denmark
Info: European Association for Palliative Care
Tel: (44) 20 3751 7967
Email: eco2015@guarant.cz
Website: http://eapcnet.wordpress.com

33rd Annual Meeting of the European Society for Paediatric Infectious Disease (ESPID) 2015
12/5/2015 to 16/5/2015
Location: Leipzig, Germany
Info: Kenes International
Tel: (41) 22 908 0488
Fax: (41) 22 906 9140
Email: espid-meeting@kenes.com
Website: http://espid2015.kenes.com/

2015 International Conference of the American Thoracic Society
15/5/2015 to 20/5/2015
Location: Denver, Colorado, US
Info: The American Thoracic Society
Tel: (1) 212 315 8600
Email: ATSThInfo@Thoracic.org
Website: http://conference.thoracic.org

2015 American Society of Hypertension (ASH) Scientific Meeting & Exposition
16/5/2015 to 19/5/2015
Location: New York, US
Info: American Society of Hypertension
Tel: (212) 696 9099
Fax: (347) 916 0267
Email: ash@ash-us.org
Website: http://www.ash-us.org/

Inaugural Malaysian Conference on Clinical Hypnotherapy (IMCCH) 2015
22/5/2015 to 23/5/2015
Location: Kuala Lumpur, Malaysia
Info: Secretariat
Tel: (03) 7960 6439/6449
Fax: (03) 7960 6419
Email: info@hypnosis-malaysia.com
Website: http://www.conference.hypnosis-malaysia.com

American Society of Clinical Oncology (ASCO) 2015 Annual Meeting
29/5/2015 to 2/6/2015
Location: Chicago, Illinois, US
Info: ASCO Secretariat
Tel: (571) 4831300
Email: ascoregistration@jspargo.com
Website: http://am.asco.org/

UPCOMING

11th Asia Pacific Congress of Hypertension
4/6/2015 to 7/6/2015
Location: Bali, Indonesia
Info: APCH Secretariat
Tel: (62) 21 573 4978
Email: apch2015@inash.or.id
Website: http://www.apch2015.org/

75th Scientific Sessions of the American Diabetes Association (ADA)
5/5/2015 to 9/5/2015
Location: Boston, Massachusetts, US
Info: American Diabetes Association
Tel: (415) 268 2086
Fax: (415) 293 4073
Email: membership@diabetes.org
Website: http://professional.diabetes.org/
New diagnostics lab to improve infectious disease detection

Obese patients with type 2 diabetes (T2D), for example, should be started on -
morbidities, a move experts described as a -tension, rather than treating the comorbidities caused by the excess weight."

EGFR mutations and ALK gene rearrangements are mutually exclusive in most cases. EGFR mutations will be tested first because they are more common in NSCLC,” explained Dr. Kwok-Chi Lam of CUHK’s Department of Clinical Oncology. ALK gene rearrangement is present in 3 to 5 percent of NSCLC patients -niversity of Hong Kong in -l have not been successful with lifestyle therapy and psychological counseling to -ut with chemotherapy. The median -ating, nutrition and diet support, sup- and caregivers, and advice for employ-

These patients commonly present with -nition and mutations of IBD will help us to identify biological pathways causing the disease and to discover better drugs for patients. More studies are warranted to -nclusion in either arm.

Connect with MIMS Today

www.mims.com | MIMS mobile/tablet app | facebook.com/mimscom