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Immune checkpoint inhibitors have antitumour activity in gastric, oesophageal cancers

BY SUSAN LONDON
Frontline Medical News
At the Gastrointestinal Cancers Symposium, San Francisco

Two immune checkpoint inhibitors that help restore the antitumour response are active and well tolerated in patients with advanced, generally heavily pretreated gastric and oesophageal cancers, according to a pair of early-phase trials reported at the Gastrointestinal Cancers Symposium.

Results from CheckMate-032 showed that nivolumab, an antibody that targets the cell surface receptor programmed death-1 (PD-1), yielded a response rate of 14% in patients with advanced gastric and related cancers. And updated results from KEYNOTE-028 showed that pembrolizumab, another antibody targeting PD-1, led to a response rate of 30% in patients with advanced oesophageal and related cancers that expressed the ligand programmed death ligand 1 (PD-L1).

"Checkpoint inhibitors are clearly promising new agents ... All compounds are still in development, but we already have at least phase 1 data that they are effective," commented invited discussant Dr Markus H. Möhler of the University Medical Center Mainz (Germany). "Combination treatment strategies are clearly under investigation, and it is our task as a scientific community to look into interesting modern combinations, like combinations with antiangiogenic agents or maybe even with stem cell inhibition."

He commended the KEYNOTE-028 investigators, in particular, for their development of a tumour gene signature that appeared to predict benefit from pembrolizumab.

"Molecular and immunological characterisation of the patients is key, and we have seen now in the pembrolizumab study with the six-gene signature the first step in the right direction," Dr Möhler said, recommending that it be correlated with data from The Cancer Genome Atlas project, which has identified four distinct molecular subtypes of oesophagogastric cancer.

"It is now clear that some of these subtypes express higher PD-L1 compared to the others, particularly inflamed subtypes," he elaborated. "Therefore, it is clear that all the studies in the future really should try to look into the correlation with these four gene subgroups characterised."

CHECKMATE-032 TRIAL

Patients with a variety of solid tumours were eligible for CheckMate-032, a phase I/II trial. First author Dr Dung T. Le reported results for 59 patients with locoregionally advanced or metastatic gastric cancer, oesophageal, or gastro-oesophageal junction cancer who had received at least one prior therapy.

The patients were treated with nivolumab every 2 weeks. (Nivolumab is currently TGA approved for the treatment of melanoma, non-small cell lung cancer, and in combination with ipilimumab for metastatic (stage IV) melanoma.)

With a median follow-up of 4.6 months, the response rate was 14%, reported Dr Le of Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins, Baltimore, at the symposium, which was sponsored by ASCO, ASTRO, the American

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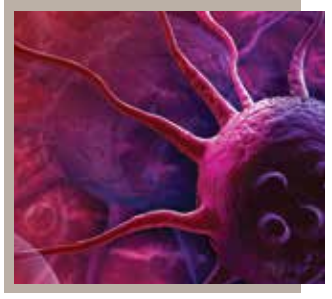

Nanoparticles deliver Aurora kinase inhibitor with increased safety and efficacy

BY JENNIFER SHEPPHIRD
Frontline Medical News
From Science Translational Medicine

Using nanoparticles to encapsulate an Aurora B kinase inhibitor improved the efficacy and tolerability of the drug and allowed less frequent dosing in preclinical models, according to researchers (*Sci Transl Med* 2016 Feb 10. doi: 10.1126/scitranslmed.aad2355).

"The AZD2811 nanoparticles identified in this study have the potential to increase efficacy at tolerable doses using a more convenient dosing regimen, which may in turn extend the utility of Aurora B kinase inhibition to a broader range of haematological and solid tumour cancer indications," wrote Susan Ashton of AstraZeneca, and her colleagues.

"The improved bone marrow profile observed with slow-releasing nanoparticles may enable efficacious combination treatments" with chemotherapy, radiotherapy, or poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors.

The study was undertaken because a free-drug version of the agent, known as AZD1152, had led to a significant improvement in the complete response rate of acute myeloid leukaemia compared to standard of care in a phase II trial. Efficacy, however, was associated with major toxicities, including myelosuppression. Further, AZD1152 had to be administered as a 7-day continuous intravenous infusion.

By using the Accurin nanoparticle platform to vary drug release kinetics, the researchers devised a formulation to maximise the therapeutic effect of the kinase inhibitor while sparing healthy tissue. AZD1152 is a water-soluble prodrug of AZD2811, which the researchers used to develop their the nanoparticle formulation.

AZD2811 was encapsulated in polymeric nanoparticles termed Accurins, which are composed of block co-polymers of poly-D,L-lactide (PLA) and poly(ethylene glycol) (PEG). Accurins accumulate in tumours, increasing the drug's concentration and duration of exposure to the cancer cells. Organic acid counterions were used to increase encapsulation efficiency and decrease the release rate of AZD2811.

"We identified a formulation profile that could deliver active drug for more than 1 week, resulting in prolonged target inhibition in tumour tissue together with improved preclinical efficacy and therapeutic index over the AZD1152 prodrug in several animal models," they wrote.

In nude rats bearing human colorectal adenocarcinoma SW620 xenografts, the nanoparticles inhibited kinase over a 96-hour time course, while the free drug resulted in complete enzyme recovery at 24 hours. Nanoparticles inhibited tumour growth by over 90%, compared with 58% for the free drug at twice the dose, and showed little toxicity as evidenced by stable body weight. Nanoparticles were retained in the tumour xenografts for up to 6 days, while the free drug was undetected in tumours 24 hours after administration.

"Although we selected a lead formulation using a tumour model (SW620) that supported the AZD1152 program – and, as such, we had extensive comparator data from which to benchmark the tolerability, PD, and efficacy of candidate nanoparticles – the model is subject to the known limitations of xenografted human tumour cell lines in assessing therapeutic candidates in oncology. Moreover, although rat bone marrow is commonly used to model myelotoxicity in humans, interrogation of the nanoparticle dose and schedule in patients may be required to achieve optimal clinical results," they concluded.

AstraZeneca funded the study. Dr Ashton and several coauthors are current or former employees and shareholders of AstraZeneca or BIND. The companies are developing the drug and technologies.

NEWS

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Immune checkpoint inhibitors have antitumour activity in gastric, oesophageal cancers

Gastroenterological Association, and the Society of Surgical Oncology.

However, "PD-L1 expression appears to be numerically associated with a higher objective response rate," she noted. Specifically, the response rate was 27% among patients whose tumour cells showed 1% or greater PD-L1 staining, and an even higher 33% among those whose tumour cells showed 5% or greater PD-L1 staining.

Median overall survival was 5 months. The 6-month overall survival rate was 49%, and the 12-month rate was 36%.

"The adverse event profile was similar to that seen in patients with other tumour types," Dr Le commented.

In all, 17% of patients experienced grade 3 or 4 treatment-related adverse events, and 5% experienced grade 3 or 4 treatment-related serious adverse events. These events included elevation of liver enzymes, pneumonitis, fatigue, diarrhoea, and vomiting. There were no treatment-related deaths.

KEYNOTE-028 TRIAL

Patients with various types of advanced solid tumours were eligible for KEYNOTE-028, a phase Ib trial, if at least 1% of their tumour or inflammatory cells expressed PD-L1. First author Dr Toshihiko Doi reported results for 23 patients with oesophageal or gastro-oesophageal junction cancer who had experienced failure of standard therapy or were unable to tolerate it.

The patients were treated with pembrolizumab every 2 weeks. (Pembrolizumab is TGA approved for the treatment of melanoma and non-small cell lung cancer.)

With a median follow-up of 7.1 months, the overall response rate was 30%, reported Dr Doi of the National Cancer Center Hospital East in Chiba, Japan. By tumour histology, it was 29% for squamous cell carcinomas and 40% for adenocarcinomas.

He and his colleagues performed gene expression profiling of tumour tissue, identifying a six-gene interferon gamma signature that appeared predictive.

Specifically, patients with high signature scores, indicating more inflamed tumours, tended to have a better response rate than those with low scores (43% vs 11%) as well as longer progression-free survival.

> PD-L1 expression appears to be numerically associated with a higher objective response rate.

In all, 17% of patients experienced grade 3 treatment-related adverse events (reduced appetite, lymphopenia, liver disorder, and pruritic rash). There were no treatment-related deaths or discontinuations. With respect to adverse events of special interest because of their immune aetiology, 9% of patients experienced hypothyroidism, 4% adrenal insufficiency, and 4% pruritic rash.

"Further evaluation of pembrolizumab in oesophageal cancer is ongoing," Dr Doi concluded, pointing to the KEYNOTE-180 trial, which is testing the agent as third-line therapy, and the KEYNOTE-181 trial, which is pitting it against treatment of physician's choice as second-line therapy.

Study finds lower-than-expected rate of occult uterine sarcoma

BY MARY ANN MOON
Frontline Medical News
From Obstetrics & Gynecology

The risk of finding occult uterine sarcoma during hysterectomy for benign indications was lower than expected in a single-centre retrospective cohort study, at 0.089%, or 1 in 1124 hysterectomies, according to a recent analysis.

This is markedly lower than the estimated risks in previous studies, which ranged from 1 in 204 to 1 in 667 procedures for women with presumed myomas. The American College of Obstetricians and Gynecologists estimated the risk to be 1 in 500 hysterectomies, and the US Food and Drug Administration pegged it at 1 in 352 based on a pooled analysis of nine studies of women undergoing hysterectomy or myomectomy for presumed myomas. The last estimate in particular has been criticised as inaccurate because of concerns about the quality of data and methodologic flaws of the nine studies, reported Dr Kimberly A. Kho of the University of Texas Southwestern Medical Center, Dallas, and her associates (*Obstet Gynecol* 2016;127:468–73.).

The investigators analysed information in a database for all 10,119 hysterectomies performed for benign indications at their medical centre during a 14-year period, and correlated it with data concerning all cases of uterine sarcoma in their centre's tumour registry. A total of 59.4% of these procedures used an abdominal approach, 21.6% were laparoscopic or robot assisted, and 18.9% used a vaginal approach. The most common indications were leiomyomata (37%), abnormal uterine bleeding (28%), and pelvic organ prolapse (11%).

Nine women were found to have an occult uterine sarcoma, including five leiomyosarcomas, two endometrial stromal sarcomas, and two uterine adenocarcinomas.

"All patients had received up-to-date cervical cancer screening and, in the majority of cases, women had received preoperative evaluation with either endometrial sampling or imaging, which did not suggest malignancy. Of the suggested risk factors for sarcoma, it is notable that none of the women we identified were postmenopausal, exposed to pelvic radiation or tamoxifen, nor had a family history of cancer," the researchers wrote.

Only one patient underwent manual morcellation of a large, bulky uterus before her sarcoma was discovered during total abdominal hysterectomy. The abdominal cavity was then thoroughly explored, and no suspicious lesions were found. This patient later received chemotherapy and had no evidence of disease 3 years later.

The study findings may be helpful for surgical planning and for counseling patients about management options. "It is important to stress that although low, the risk of encountering an occult sarcoma exists. Hence, ongoing efforts to identify potentially safer methods for tissue extraction are essential, as are efforts to improve preoperative identification of malignancies," the researchers noted.

The study was supported by the University of Texas Southwestern Medical Center. Dr Kho reported ties to Actamax Surgical Materials and Applied Medical; one of her associates reported ties to AstraZeneca and Genentech.

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Dabigatran etexilate *Pradaxa*, Boehringer Ingelheim	Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and for the prevention of recurrent DVT and PE in adults.
Lenalidomide *Revlimid*, Celgene	For the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation.
Lenvatinib *Lenvima*, Eisai	For the treatment of patients with progressive, locally advanced or metastatic, radioactive iodine refractory differentiated thyroid cancer.
Nintedanib esilate *Ofev/Vargatef*, Boehringer Ingelheim	Indicated in combination with docetaxel for the treatment of patients with locally advanced, metastatic or recurrent non-small cell lung cancer of adenocarcinoma tumour histology after failure of first line chemotherapy. It is also indicated for the treatment of idiopathic pulmonary fibrosis.
Nivolumab *Opdivo*, Bristol-Myers Squibb	As monotherapy for the treatment of patients with unresectable (stage III) or metastatic (stage IV) melanoma, or locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy. In combination with ipilimumab for the treatment of patients with metastatic (stage IV) melanoma with M1c disease or elevated lactic dehydrogenase.
Olaparib *Lynparza*, AstraZeneca	Monotherapy for the maintenance treatment of patients with platinum-sensitive relapsed BRCA-mutated (germline or somatic) high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) after platinum-based chemotherapy.

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Acupressure improves persistent fatigue in breast cancer survivors

BY BRUCE JANCIN
Frontline Medical News
At SABCS 2015

Self-administered acupressure focused on enhancing relaxation significantly reduced persistent fatigue symptoms in breast cancer survivors, according to a randomised clinical trial presented at the San Antonio Breast Cancer Symposium.

"Self-administered relaxation acupressure offers an inexpensive, easy-to-learn method to manage fatigue and co-occurring poor sleep quality and overall quality of life in breast cancer survivors with persistent fatigue," said Suzanna M. Zick, ND, MPH, of the department of family medicine, and the complementary and alternative medicine research centre at the University of Michigan, Ann Arbor.

She conducted the study because persistent fatigue is arguably the most common and debilitating symptom experienced by breast cancer survivors, affecting 30% of women for up to 10 years after they've completed their breast cancer therapy. Yet treatment options remain limited, she said.

Acupressure is a form of traditional Chinese medicine in which pressure is applied to a few specific acupoints on the body using the fingers, thumbs, or a device. Two forms were evaluated in the three-arm, single-blind clinical trial: relaxation acupressure, traditionally used to improve sleep, and stimulation acupressure, which targets pressure points that boost energy.

> Even though both forms of acupressure reduce fatigue to a similar extent, relaxation acupressure is the one we should think about as being more effective.

Dr Zick presented a 10-week study in which 288 breast cancer survivors who had completed cancer therapy other than hormone treatment at least 12 months before and who still experienced persistent fatigue as defined by a score of 4 or more on the validated Brief Fatigue Inventory. Participants were randomised single-blind to usual care as directed by their physician or to 6 weeks of relaxation or stimulation acupressure, which they administered on their own after receiving instruction. After 6 weeks, women were instructed to stop the acupressure. They were reassessed at week 10 to determine whether acupressure had a sustained carryover effect.

At 6 weeks, 66% of the relaxation acupressure group and 61% of the stimulation acupressure cohort had achieved a normal Brief Fatigue Inventory score of less than 4, as did only 31% of the usual-care controls. Both acupressure groups showed maintenance of benefit at week 10, after 4 weeks of no acupressure, indicating the self-treatment isn't something patients need to do continuously in order to derive the desired effect.

While both forms of acupressure were similarly effective at reducing complaints of fatigue, there was an important difference between the two. Only relaxation acupressure resulted in significant improvement in sleep quality as measured on the Pittsburgh Sleep Quality Index. Moreover, relaxation acupressure but not stimulation acupressure resulted in quality-of-life improvements on the somatic, fitness, and social support subscales of the Long-Term Quality of Life scale. However, neither form of acupressure had a significant on the spiritual subscale, the quality-of-life instrument's fourth subscale.

"We really have to conclude that even though both forms of acupressure reduce fatigue to a similar extent, relaxation acupressure is the one we should think about as being more effective," Dr Zick said.

One might have predicted, incorrectly as it turns out, that breast cancer survivors complaining of persistent fatigue would find stimulation acupressure to be more beneficial than relaxation acupressure. Dr Zick suspects the two techniques might reduce chronic fatigue via different mechanisms. She and her coinvestigators have conducted brain imaging studies that show patients with persistent cancer-related fatigue have three neurochemical markers: elevated brain levels of insular glutamate, which causes excitation, as well as high brain levels of creatine phosphokinase and proinflammatory cytokines. In their next round of imaging studies, the investigators plan to see whether the two forms of acupressure have differing effects on these markers.

Session moderator Dr Norah Lynn Henry liked the concept of self-administered acupressure.

"The great thing about this is you don't have to make appointments with an acupuncturist. You can do it at home. But is acupressure ready for prime time in clinical practice?" asked Dr Henry, a medical oncologist at the University of Michigan.

"My answer is yes," Dr Zick replied, "because it's got pretty much zero side effects, it's inexpensive, and it's easy to learn. If it doesn't work for a person then they can just stop, but if it works, great."

As the next step in this research, Dr Zick and her coinvestigators hope to develop a smartphone app to deliver instruction in self-administered relaxation acupressure in a readily accessible way.

The clinical trial was funded by the US National Cancer Institute. Dr Zick reported having no financial conflicts.

Novel test detects low levels of residual CML

BY MARY JO DALES
Frontline Medical News
From the Journal of Molecular Diagnostics

A novel DNA-based test may prove useful for identifying which chronic myeloid leukaemia patients with undetectable BCR-ABL1 transcripts can safely discontinue tyrosine kinase inhibitor (TKI) therapy, according to Mary Alikian, PhD, of Hammersmith Hospital, London, and her colleagues.

The test can quantify very low levels of residual disease in peripheral blood samples from patients with CML in whom BCR-ABL1 transcripts were undetectable using reverse transcription quantitative polymerase chain reaction (RT-qPCR), the researchers reported in a study published online in the *Journal of Molecular Diagnostics*.

Their personalised DNA-based digital PCR method rapidly identifies t(9;22) fusion junctions using targeted next-generation sequencing and generates high-performance DNA-based hydrolysis probe assays that are specific to the unique molecular footprint of each patient's CML clone. The researchers further enhanced the sensitivity of the DNA-based approach by optimising the technique for use on a digital PCR (dPCR) platform, which provides absolute molecular quantification without the need for a standard curve. This approach avoids laborious breakpoint mapping and improves sensitivity.

The researchers successfully mapped genomic breakpoints in all samples from 32 patients with early-stage disease. Using DNA-based dPCR, disease was quantified in 46 follow-up samples from 6 of the 32 patients, including 36 samples that were in deep molecular remission.

Digital PCR for BCR-ABL1 DNA detected persistent disease in 81% of the molecular-remission samples, outperforming both RT-dPCR (25%) and DNA-based quantitative PCR (19%), the researchers reported (*J Mol Diagn* 2016;18:176e189).

Of CML patients who achieve sustained undetectable BCR-ABL1 transcripts on TKI therapy, about 60% experience the return of detectable disease after stopping TKIs and have to restart treatment. An improved method of identifying patients with the lowest likelihood of relapse would allow safe withdrawal of TKI therapy for the 40% of patients who would remain disease free.

The researchers are currently investigating the impact of residual-disease level as assessed by dPCR at the time of treatment withdrawal on outcome within the UK-based DESTINY clinical trial (Deescalation and Stopping Treatment of Imatinib, Nilotinib or Sprycel in Chronic Myeloid Leukaemia). "If validated in clinical trials of stopping TKI, the technique will permit a more personalised approach to recommendations for dose reduction or drug cessation in individual patients, ensuring that therapy is withdrawn only from patients with the highest likelihood of long-term remission," they wrote.

Identifying genomic breakpoints as soon as CML is diagnosed would allow for the design and optimisation of a patient-specific assay. Patients' response to therapy would then be monitored via standard RT-qPCR until they have reached molecular response. Thereafter, routine monitoring would be augmented with DNA quantification by dPCR and would benefit from the publication of standardised guidelines, as with RT-qPCR.

In the future, it will therefore be important to explore not only whether the risk of relapse after withdrawal is a feature of the number of residual CML cells but also whether it relates to the degree of transcriptional activity in those cells, the researchers wrote. "We observed that 8% (3 of 36) of the samples were positive by RNA-based but negative by DNA-based methods. Conversely, in samples with detectable BCR-ABL1 DNA, there was heterogeneity in the detectability of transcript by RT-dPCR that appeared to be unrelated to the amount of BCR-ABL1 DNA detected. It should be borne in mind that RT and cDNA synthesis steps remain a potential source of variation affecting cDNA concentration, and therefore these results should be interpreted with caution."

The researchers had no relevant disclosures. The study was supported by Leading Leukaemia Research (LEUKA) charity grant 06/Q0406/47, the National Institute for Health Research Biomedical Research Centre Funding Scheme, and the Imperial College High Performance Computing Service.

Clinical Trials in Australia

Health conditions/problems studied	Trial identification	Title	Recruitment
Relapsing remitting multiple sclerosis	ACTRN12616000151437	A phase II study: haematopoietic stem cell transplantation for highly active treatment resistant multiple sclerosis.	VIC
Squamous cell carcinoma of the anus	ACTRN12616000061437	An international multicentre open label randomised phase II advanced anal cancer trial comparing cisplatin plus 5-fluorouracil versus carboplatin plus weekly paclitaxel in patients with inoperable locally recurrent or metastatic disease.	NSW, QLD, SA, VIC, TAS Not yet recruiting
Advanced or metastatic solid tumours	ACTRN12616000008426	A phase I, open-label, dose-escalation study of the safety and pharmacokinetics of RX108 in patients with advanced or metastatic solid tumours.	NSW
Non-small cell lung cancer	ACTRN12615001265561	Pentixafor positron emission tomography scan: a new imaging test for staging in non-small cell lung cancer.	WA

Source: Australian and New Zealand Clinical Trials Registry, *www.anzctr.org.au*

NEWS

High-dose interferon offered no survival benefit in patients with melanoma and a single tumour-positive sentinel lymph node

BY JENNIFER SHEPPHIRD
Frontline Medical News
From the Journal of Clinical Oncology

Patients with melanoma and a single tumour-positive sentinel lymph node (SLN) had no improvement in overall (OS) or disease-free survival (DFS) with adjuvant high-dose interferon alfa-2b (HDI), and patients with histologically negative, RT-PCR-positive SLNs had no improvement with completion lymph node dissection (CLND) or CLND plus interferon, according to researchers.

For patients with a single positive SLN who received HDI, compared with the observation-only group, 5-year OS was 71.4% and 74.8% and 5-year DFS was 70.9% and 67.1%, respectively. For patients with reverse transcription polymerase chain reaction (RT-PCR)-positive but histologically negative SLNs who received CLND plus interferon, or CLND only, compared with the observation-only group, 5-year OS was 86.9%, 85.9%, and 85.5%, and 5-year DFS was 83.9%, 84.0%, and 79.4%, respectively.

The finding that HDI offers no survival benefit contradicts an earlier study (ECOG E1694) that compared HDI with ganglioside vaccine treatment.

"The results of this study refute the conclusion that improved DFS and OS in ECOG E1694 was due to a beneficial effect of HDI because HDI treatment in ECOG E1694 was not compared with observation or placebo, but to a vaccine that is now known to be associated with a greater risk of recurrence and mortality," wrote Dr Kelly M. McMasters, surgical oncologist at the University of Louisville, Kentucky, and his colleagues (*J Clin Oncol* 2016 Feb 8. doi: 10.1200/JCO.205.63.3776).

The prospective, randomised Sunbelt Melanoma Trial included patients with melanoma of thickness 1 mm or greater without evidence of metastasis. Protocol A, with 218 patients with histologically positive SLNs, did not meet its accrual goal of 150 patients each for arms 1 and 2. Protocol B had 556 patients with RT-PCR-positive but histologically negative SLNs. The median follow-up was 71 months.

The trial found that HDI therapy after CLND did not improve DFS or OS for patients with minimal nodal tumour burden. For patients randomly assigned to HDI versus observation after CLND, hazard ratios for DFS and OS were 0.82 (95% confidence interval, 0.50–1.36; P = 0.45) and 1.10 (0.69–1.76; P = 0.68).

In patients with stage I or II melanoma who have tumour-negative SLNs by hematoxylin and eosin histopathology and immunohistochemistry, but have molecular evidence of melanoma by RT-PCR analysis, no significant differences were observed among patients randomly assigned to CLND or CLND plus interferon treatment. Compared with observation, CLND alone showed a slight DFS improvement (hazard ratio, 0.58; 95% CI, 0.35–0.94; P = 0.0277), but no OS improvement (HR, 1.00; 95% CI, 0.634–1.59; P = 0.99). Patients who received CLND plus interferon had no significant improvement in DFS or OS, compared with observation.

Subgroup analysis showed that in patients with a single positive SLN, HDI was associated with improved DFS only in patients with ulceration (HR, 0.43; 95% CI, 0.21–0.87; P = 0.0183; n = 75) and with Breslow thickness more than 4 mm (HR, 0.35; 95% CI, 0.14–0.88; P = 0.0259; n = 42). No OS improvement was observed.

"Taken together, these data support the conclusion that the benefit of HDI is small, perhaps because only a fraction of the patient population responds to therapy," the investigators wrote.

Smoking after breast cancer diagnosis a risk factor in cancer death

BY NEIL OSTERWEIL
Frontline Medical News
From the Journal of Clinical Oncology

Women who smoke before or after a diagnosis of breast cancer have a significantly higher risk for death from breast cancer, respiratory tract cancers, and other causes than never smokers or quitters, follow-up results of a population-based prospective observation study show.

Among a subcohort of 4562 women from the ages of 20 to 70, those who were active smokers within 1 year of a breast cancer diagnosis had a 25% greater risk for death from breast cancer, 14-fold higher risk for death from respiratory cancer, 6-fold risk for death from other respiratory diseases, and 2-fold higher risk for death from cardiovascular disease, found Dr Michael N. Passarelli of the University of California, San Francisco, and his colleagues.

"Our study reinforces the importance of cigarette smoking cessation in women with breast cancer. For the minority of breast cancer survivors who continue to smoke after their diagnoses, these results should provide additional motivation to quit," they write (*J Clin Oncol* 2016 Jan 25. doi: 10.1200/JCO.2015.63.9328).

The investigators studied a cohort of 4562 women who had taken part in the Collaborative Breast Cancer and Women's Longevity Study, conducted in Massachusetts, New Hampshire, and Wisconsin. The study enrolled 20,691 women diagnosed from 1988 through 2008 with incident localised or regional invasive breast cancer.

The investigators re-contacted 4562 participants a median of 6 years after their diagnosis. For women who reported smoking after breast cancer diagnosis, they calculated survival from the date of return of the questionnaire to the date of death or the end of follow-up.

The authors also created pre- and post-diagnosis proportional hazard regression models controlling for body mass index, education, parous status, age at first birth, menopausal status, family history of breast cancer, use of post-menopausal hormones, alcohol consumption, and the number of years between date of diagnosis and return of the study questionnaire.

For women who reported being active smokers within 1 year before a breast cancer diagnosis, hazard ratios (HR) for death from various causes were as follows (all statistically significant as shown by confidence intervals): breast cancer, HR 1.25; respiratory cancer, HR 14.48; other respiratory disease, HR 6.02; cardiovascular disease, HR 2.08.

For the 434 women (10%) who reported active smoking after diagnosis, the HR for breast-cancer death vs never smokers was 1.72. Compared with women who continued to smoke, women who quit smoking after diagnosis had a lower risk for both breast-cancer death (a non-significant trend) and respiratory-cancer deaths (HR 0.39).

Defibrotide offers benefit for severe veno-occlusive disease and multiorgan failure

BY JENNIFER SHEPPHIRD
Frontline Medical News
From the Journal of Clinical Oncology

Defibrotide improved survival at 100 days after haematopoietic stem cell transplantation (HSCT) in patients with hepatic veno-occlusive disease, based on an open-label trial that compared trial participants with historical controls.

Of the 102 patients in the defibrotide group, 39 were alive 100 days after HSCT (38.2%), compared with 8 of 32 (25.0%) in the historical control group. The propensity-adjusted, between-group difference was 23.0% (95.1% confidence interval, 5.2–40.8%; P = 0.0109). At 180 days post-HSCT, the difference in survival between the groups was not significant.

Defibrotide has Fast Track designation from the US FDA and the new drug application is currently under Priority Review with a decision expected by March 31, 2016. A potentially fatal complication of HSCT, hepatic veno-occlusive disease is characterised by hepatomegaly, jaundice, rapid weight gain, fluid retention, and ascites. There are no approved therapies.

"In this context, defibrotide provides a promising treatment option for patients with a high unmet medical need," wrote Dr Paul G. Richardson of Dana-Farber Cancer Institute in Boston and his colleagues.

At day 100 post-HSCT, complete response was seen in 25.5% of the defibrotide group and in 12.5% of the historical control group. The propensity-adjusted, between-group difference was 19% (95.1% CI, 3.5–34.6%; P = 0.0160). The complete response was durable in 22 of the 26 patients. In the control group, complete response was limited in two patients, impossible to assess in one patient, and durable in one patient.

The multicentre, open-label, phase III trial prospectively enrolled 102 patients with hepatic veno-occlusive disease from 2006 to 2008. Defibrotide was administered intravenously at 25 mg/kg/day in 4 divided doses for a minimum of 21 days. Treatment continued beyond 21 days until resolution of veno-occlusive disease or until the patient was discharged from the hospital.

To identify the historical controls, 6867 medical charts of HSCT patients hospitalised from 1995 to 2007 were reviewed, and 32 historical control patients were selected. Most (21 of 32) were diagnosed with during 2000–2006, and 11 were diagnosed before 2000. The historical controls were selected by an independent medical review committee, and met the same entry criteria as the defibrotide group.

Because recruiting for the defibrotide group and screening for historical controls occurred at the same institutions during similar time periods, patient management and supportive care were likely similar for the two groups. Propensity scores were included in the analysis to adjust for prognostic factors that were unbalanced between treatment and control groups, including ventilator and dialysis dependency at study entry, age greater or less than 16 years, prior HSCT (0 vs 1), and allogeneic or autologous transplant.

> Defibrotide provides a promising treatment option for patients with a high unmet medical need.

Hypotension was the most common adverse event reported in the defibrotide and control groups (39% and 50%, respectively), followed by diarrhoea (23.5% and 37.5%, respectively). The defibrotide and control groups had similar incidences of common haemorrhagic adverse events (64% and 75%, respectively). Fatal adverse events occurred in 64% of the defibrotide group and 69% of the control group, and fatal haemorrhagic events occurred in 14.7% of the defibrotide group and 6.3% of the control group.

Approved by the European Union, defibrotide is a single-stranded, deoxyribonucleic acid derivative that stabilises damaged endothelial cells and prevents further endothelial cell damage.

Dr Richardson reported consulting or advisory roles with Gentium/Jazz Pharmaceuticals, the maker of defibrotide.

Minimal residual disease a powerful prognostic factor in AML

BY PATRICE WENDLING
Frontline Medical News
From the New England Journal of Medicine

The presence of minimal residual disease predicts relapse in patients with NMP1-mutated acute myeloid leukaemia and is superior to currently used molecular genetic markers in determining whether these patients should be considered for stem cell transplantation, a new study has found.

At 3 years, patients with minimal residual disease (MRD) had a significantly greater risk of relapse than those with no MRD (82% vs 30%; univariate hazard ratio, 4.80; $P < 0.001$) and a lower rate of survival (24% vs 75%; univariate HR, 4.38; $P < 0.001$), Adam Ivey of King's College London reported.

In an editorial that accompanied the study Dr Michael J. Burke from the Children's Hospital of Wisconsin in Milwaukee wrote, "Time will tell, but this moment may prove to be a pivotal one in the assessment of minimal residual disease to assign treatment in patients with AML".

In adult AML, assessment of MRD has taken a back seat to analyses of cytogenetic and molecular lesions in determining a patient's risk and treatment strategy. Typically, allogeneic stem cell transplantation is used for patients with high-risk features such as chromosome 3, 5, or 7 abnormalities or the FLT3-internal tandem duplication (ITD) mutation, while chemotherapy alone is used for low-risk disease.

The role of transplantation is unclear, however, for cytogenetically standard-risk patients, which includes those with a mutation in the gene encoding nucleophosmin (NPM1).

To address this issue, the investigators used a reverse-transcriptase quantitative polymerase chain reaction assay to evaluate 2569 bone marrow and peripheral-blood samples from 346 patients with NPM1 mutations who had completed two cycles of induction chemotherapy in the UK National Cancer Research Institute AML17 trial.

MRD, defined as persistence of NPM1-mutated transcripts in peripheral blood, was present in 15% of patients after the second chemotherapy cycle.

Patients with MRD were significantly more likely than those without MRD to have a high UK Medical Research Council clinical risk score and to carry the FLT3-ITD mutation.

On univariate analysis, the risk of relapse was significantly higher with the presence of MRD in peripheral blood, an increased white cell count, and with the DNMT3A and FLT3-ITD mutations.

Only the presence of MRD and an elevated white cell count significantly predicted survival, Mr Ivey reported.

"We could find no specific molecular subgroup consisting of 10 patients or more that had a rate of survival less than 52%; in contrast, the rate in the group with the presence of minimal residual disease was 24%," he observed.

In multivariate analysis, the presence of MRD was the only significant prognostic factor for relapse (HR, 5.09; $P < 0.001$) or death (HR, 4.84; $P < 0.001$).

The results were validated in an independent cohort of 91 AML17 study patients. It confirmed that MRD in peripheral blood predicts worse outcome at 2 years than the absence of MRD, with a cumulative incidence of relapse of 70% vs 31% ($P = 0.001$) and overall survival rates of 40% vs 87% ($P = 0.001$), reported the investigators, including senior author Professor David Grimwade, also from King's College London.

The clinical implications of these results "are substantive" because NPM-1 mutated AML is the most common subtype of AML and because of the uncertainty over the best treatment strategy for patients typically classified as standard risk, editorialist Dr Burke observed.

"Now with the ability to reclassify standard-risk or low-risk patients as high-risk on the basis of the persistent expression of mutant NPM1 transcripts, it may be possible that stem-cell transplantation is a better approach in patients who otherwise would be treated with chemotherapy alone and that transplantation may be avoidable in high-risk patients who have no evidence of minimal residual disease," he wrote. "Such predictions will need to be tested prospectively."

The presence of MRD is also known to be an important independent prognostic factor in acute lymphoblastic leukaemia, but since AML has a greater molecular heterogeneity, routine MRD assessment has not been as quickly adopted in AML, Dr Burke noted.

The Children's Oncology Group, however, recently adopted MRD assessment by flow cytometry to further stratify children with newly diagnosed AML after first induction therapy into low-risk or high-risk groups.

The study was supported by grants from Bloodwise and the National Institute for Health Research. Mr Ivey and Dr Burke reported having no disclosures.

Venetoclax shows promise for relapsed CLL, SLL

BY SHARON WORCESTER
Frontline Medical News
From the New England Journal of Medicine

This first trial of venetoclax showed the potential of BCL2 antagonism as an additional therapeutic avenue for patients with relapsed CLL. The 79% overall response rate in this study provides support for further development of venetoclax as a treatment option for patients with heavily pretreated relapsed or refractory CLL or SLL.

Daily oral treatment with venetoclax induced substantial responses with manageable adverse effects in patients with relapsed chronic lymphocytic leukaemia or small lymphocytic lymphoma in a first-in-human phase I dose-escalation study.

The promising effects of the highly selective investigational inhibitor of BCL2 – a protein central to the survival of CLL cells – were noted even in patients with poor prognostic features, who comprised 89% of the cohort, reported Dr Andrew W. Roberts of Royal Melbourne Hospital, Australia, and his colleagues. The study was published online Jan. 28 in *The New England Journal of Medicine*.

In the dose escalation phase of the study, 56 patients received active treatment at doses ranging from 150 to 1200 mg daily, and 60 additional patients received weekly stepwise ramp-up with doses beginning at 20 mg daily with weekly increases to 50 mg, 100 mg, and 200 mg daily up to the target dose of 400 mg daily. The patients had received a median of 3 previous therapies (range, 1–11).

Of 116 treated patients, 92 (79%) had a response, and 20% achieved complete remission, including 5% with no minimal residual disease on flow cytometry, the investigators said.

Venetoclax was active at all doses used in the study, and no maximum tolerated dose was identified.

Tumour lysis syndrome occurred in 10 patients, but clinically important sequelae occurred in only 3 of those patients, 2 of whom had severe sequelae. After adjustments were made to dosing schedule, no further cases occurred.

Other side effects included mild diarrhoea, upper respiratory tract infection, nausea, and grade 3 or 4 neutropenia, which occurred in 41–52% of patients. Serious adverse events included febrile neutropenia in 6% of patients, pneumonia in 4%, upper respiratory tract infection in 3%, and immune thrombocytopenia in 3%.

Among the patients with an adverse prognosis, treatment response rates ranged from 71% to 79%, depending on the subgroup. For example, the response rate was 79% in 70 patients with resistance to fludarabine, and 71% in 31 patients with chromosome 17p deletions.

New treatments, including ibrutinib monotherapy and idelalisib in combination with rituximab, have improved outcomes for patients with relapsed CLL, but despite these advances, complete remissions remain uncommon, the authors said.

"This first trial of venetoclax showed the potential of BCL2 antagonism as an additional therapeutic avenue for patients with relapsed CLL," they wrote, adding that the 79% overall response rate in this study – including deep responses and complete responses without minimal residual disease in patients up to age 86 years and patients with poor prognostic factors – "provides support for further development of venetoclax as a treatment option for patients with heavily pretreated relapsed or refractory CLL or SLL."

Of note, the US Food and Drug Administration on Jan. 28 – the date this study was released – granted venetoclax Breakthrough Therapy Designation for use in combination with hypomethylating agents for the treatment of acute myeloid leukaemia patients who aren't eligible for standard induction chemotherapy. The designation – the third for the agent – is supported by data from a single study of untreated patients aged 65 years or older with AML. Prior venetoclax Breakthrough Therapy Designations were granted in April 2015 for its use as monotherapy in patients with refractory CLL who have the 17p deletion genetic mutation, and in January for its use with rituximab for the treatment of relapsed/refractory CLL.

AbbVie and Genentech supported the study. Dr Roberts reported receiving grant support and study drugs form AbbVie, serving as an investigator in trials sponsored by Genentech, AbbVie, Janssen, and Beigene, and receiving institutional research funding from Genentech for the development of venetoclax. His coauthors reported ties to various pharmaceutical companies.

Venetoclax is not approved for use in Australia.

Research refining radiomic features for lung cancer screening

BY PATRICE WENDLING
Frontline Medical News
At an AACR/IASLC joint conference

A series of radiomics-derived imaging features may improve the diagnostic accuracy of low-dose CT lung cancer screening and help predict which nodules are at risk of becoming cancers.

"We are providing pretty compelling evidence that there is some utility in this science," Matthew Schabath, PhD, said at a conference on lung cancer translational science sponsored by the American Association for Cancer Research and the International Association for the Study of Lung Cancer.

Radiomics is an emerging field that uses high-throughput extraction to identify hundreds of quantitative features from standard computed tomography (CT) images and mines that data to develop diagnostic, predictive, or prognostic models.

Radiologists first identify a region of interest (ROI) on the CT scan containing either the whole tumour or spatially explicit regions of the tumour called "habitats." These ROIs are then segmented via computer software before being rendered in three dimensions. Quantitative features are extracted from the rendered volumes and entered into the models, along with other clinical and patient data.

"Right now our tool box is about 219, but by the end of the year we are hoping to have close to 1000 radiomic features we can extract from a 3-D rendered nodule or tumour," said Dr Schabath, of the Moffitt Cancer Centre in Tampa, Florida.

Although not without its own challenges, radiomics is a far cry from the current practice that relies on a single CT feature, nodule size, and clinical guidelines to evaluate and follow-up pulmonary nodules, none of which provides clinicians tools to accurately predict the risk or probability of lung cancer development.

CT images are typically thought of as pictures, but in radiomics, "the images are data. That's really the underlying principle," he said.

Led by Dr Robert Gillies, often referred to as the father of radiomics, the researchers extracted and analysed the 219 radiomic features from nodules in 196 lung cancer cases and in 392 controls who had a positive but benign nodule at the baseline scan and were matched for age, sex, smoking status, and race.

The post hoc, nested case-control study used images and data from the pivotal National Lung Screening Trial, which identified a 20% reduction in lung cancer mortality for low-dose CT screening compared with chest x-rays, but with a 96% false-positive rate, which also highlighted the challenges of LDCT as a screening tool.

Two classes of features were extracted from the images: semantic features, which are commonly used in radiology to describe ROIs, and agnostic features, which are mathematically extracted quantitative descriptors that capture lesion heterogeneity.

Univariable analyses were used to identify statistically significant features (threshold $P < 0.05$) and a backward elimination process (threshold $P < 0.1$) performed to generate the final set of features, Dr Schabath said.

Separate analyses were performed for predictive and diagnostic features.

In the risk prediction model, eight "highly informative features" were identified, Dr Schabath said. Five were agnostic and three were semantic – circularity of the nodule, volume, and distance from or pleural attachment.

The receiver operating characteristic (ROC) area under the curve for the model was 0.92, with 75% sensitivity and 89% specificity. When the model included only patient demographics, it was no better than flipping a coin for predicting nodules at risk of becoming cancerous (ROC 0.58), he said.

Six highly informative features were identified in the agnostic model, which extracted features from the nodules found at the first and second follow-up interval, Dr Schabath said. Three were agnostic and three semantic – longest diametre, volume, and distance from or pleural attachment.

The ROC for the diagnostic model was 0.89, with 74% sensitivity and 89% specificity.

When an additional analysis was performed using a nodule threshold of less than 15 mm to account for nodule growth over time and smaller nodule size at baseline in controls, the ROC and specificity held steady, but sensitivity dropped off to 59%, he said.

"I think we're showing a rigorous [statistical] approach by identifying really unique, highly informative features," Dr Schabath concluded.

The overlap of volume and distance from or pleural attachment in both the diagnostic and predictive models suggests "there might be something very important about these two features," he added.

Dr Schabath stressed that the findings are preliminary and said additional analyses will be run before the results are ready for prime time. Long-term goals are to implement radiomic-based decision support tools and models into radiology reading rooms.

"In the future, we envision that all medical images will be converted to mineable data with the process of radiomics as part of standard of care," Dr Gillies said in an interview. "Such data have already shown promise to increase the precision and accuracy of diagnostic images, and hence, will increasingly be used in therapy decision support."

Among the many challenges that first need to be resolved are that images are often captured with settings and filters that can be different even within a single institution. The inconsistency adds noise to the data that are extracted by computers.

"Hence, the most robust data we have today are generated by radiologists themselves, although this has its own challenges of being time-consuming with inter-reader variability," Dr Gillies noted.

Another major challenge is sharing of the image data. Right now, radiomics is practiced at only a few research hospitals and thus, building large cohort studies requires that the images be moved across site. In the future, the researchers anticipate that software can be deployed across sites to enable radiomic feature extraction, which would mean that only the extracted data will have to be shared, he said.

Intense tumour lymphocytic infiltration indicates favourable prognosis in NSCLC

BY JENNIFER SHEPPHIRD
Frontline Medical News
From the Journal of Clinical Oncology

Tumour lymphocytic infiltration (TLI), categorised as intense or nonintense, was an independent prognostic indicator for survival in non-small cell lung cancer (NSCLC).

John Hayman/Wikimedia Commons/Public Domain

Patients with intense TLI had significantly longer overall survival (OS) and disease-free survival (DFS), compared with patients who had nonintense TLI. In the validation data set, 5-year OS for patients with intense TLI was 85% (95% confidence interval, 70-92), compared with 58% (95% CI, 54–62) for patients with nonintense TLI ($P = 0.002$). Five-year DFS was 79% (95% CI, 65–88) for intense and 50% (95% CI, 47–54) for nonintense TLI ($P = 0.001$).

The retrospective study evaluated data from four randomised clinical trials, separated into a discovery set of 783 patient samples and a validation set of 763 patient samples. The LACE-Bio (Lung Adjuvant Cisplatin Evaluation Biomarker) collaborative group trials examined the benefit of platinum-based adjuvant chemotherapy in NSCLC. The median follow-up for the discovery and validation sets were 4.8 and 6.0 years, respectively.

Differences in outcomes according to TLI were significant in both discovery and validation data sets. In the discovery set, hazard ratios for OS and DFS were 0.56 (95% CI, 0.39–0.81; $P = 0.002$) and 0.59 (95% CI, 0.42–0.83; $P = 0.002$), respectively. In the validation set, OS and DFS hazard ratios were 0.45 (95% CI, 0.23–0.85; $P = 0.01$) and 0.44 (95% CI, 0.24–0.78; $P = 0.005$), respectively. Differences in risk reductions between the two data sets may be a result of differences in trial populations.

"The results raise the question about whether lymphocytic infiltration should be considered a stratification factor in trials that test immunotherapy or immunomodulation. Therefore, as suggested recently for CD8 density level in NSCLC, which predicted survival independently of all other variables and within each pathologic stage, intense lymphocytic infiltration could be a good candidate marker for establishing a TNM immunoscore," wrote Dr Elisabeth Brambilla of Institut Albert Bonniot–Institut National de la Santé et de la Recherche Médicale, La Tronche, France, and her colleagues (*J Clin Onc* 2016 Feb. 1. doi: 10.1200/JCO.2015.63.0970).

In contrast to results from breast cancer studies, TLI did not predict differential survival benefit from adjuvant chemotherapy in NSCLC.

The intensity of TLI on hematoxylin- and eosin-stained representative sections was first assigned into one of four categories (minimal, mild, moderate, and intense). The first three categories subsequently were collapsed into one to form a binary scoring system of intense and nonintense infiltration.

Cola enhances absorption of erlotinib in NSCLC

BY JENNIFER SHEPPHIRD
Frontline Medical News
From the Journal of Clinical Oncology

Drinking cola significantly improved bioavailability of the orally administered tyrosine kinase inhibitor (TKI) erlotinib in patients with lung cancer who were concomitantly taking the acid-reducing agent esomeprazole, investigators reported online in the *Journal of Clinical Oncology*.

Mean exposure of erlotinib was significantly higher after drinking cola, compared with water in patients treated concomitantly with esomeprazole (area under the plasma concentration curve, AUC0-12h was 39% higher; range, –12% to +136%; $P = 0.004$ and C_{max} was 42% higher; range, –4% to +199%; $P = 0.019$), probably due to increased solubility and absorption. In patients treated with erlotinib only (without esomeprazole), exposure was moderately increased with cola intake (AUC0-12h was 9% higher; range, –10% to +30%; $P = 0.03$ and C_{max} was comparable; range, –19% to +18%; $P = 0.75$).

Use of proton pump inhibitors (PPIs) is often indicated during erlotinib therapy for patients with gastroesophageal reflux disease, or for patients treated with corticosteroids and nonsteroidal anti-inflammatory drugs.

"When erlotinib and a PPI are given concomitantly, the AUC of erlotinib steeply decreases, which suggests that lower bioavailability due to PPI use (up to 46% for erlotinib) may deprive patients from optimal therapy. Thus, in the case that the combination of a PPI and erlotinib is inevitable, the pH-lowering effects of cola may help physicians to optimise erlotinib therapy," wrote Dr Roelof van Leeuwen of Erasmus MC Cancer Institute, Rotterdam, the Netherlands (*J Clin Oncol* 2016 Feb 7. doi: 10.1200/JCO.205.65.1158).

The researchers noted that Coca-Cola Classic has a substantially lower pH (about 2.5) than other acidic drinks, such as orange juice (pH about 4), 7-Up (pH about 3.5), and diet colas (pH about 3–4), making it well suited for use with erlotinib, since drinks with higher pH may not enhance absorption as well. Patients had 250 mL of cola, a volume that was well tolerated.

Previous studies have shown that erlotinib has significant intrasubject and intersubject variability, and intragastric pH is an important determinant. The drug's pKa, at 5.4, is near the stomach pH range of 1 to 4, and intragastric pH changes lead to shifts toward the nonionised (less soluble) form and subsequent lower bioavailability than TKIs with higher pKa values.

The results with erlotinib might extrapolate to other TKIs with pH-dependent solubility, such as dasatinib, gefitinib, nilotinib, the authors suggested, which should be tested in future studies.

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ALK = Anaplastic lymphoma receptor tyrosine kinase; EGFR = Epidermal growth factor receptor; NSCLC = Non-small cell lung cancer.

Reference: 1. OPDIVO (nivolumab) Approved Product Information, February 2016.

 BMS Medical Information: 1800 067 567. Bristol-Myers Squibb Australia Pty Ltd, ABN 33 004 333 322, 4 Nexus Court, Mulgrave, VIC 3170. NIV/0111/02-16. Date of preparation: February 2016. BMSA0070.

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ASCO Gastrointestinal Cancers Symposium

21–23 January 2016 • San Francisco, California

More than 3500 delegates gathered in San Francisco for presentations on the state-of-the-art advances in the prevention and management of GI cancers at the ASCO GI Cancers Symposium. Frontline Medical News reporter, **Susan London** shares the highlights.

Everolimus is effective across diverse patients with GI neuroendocrine tumours

Everolimus improves outcomes in patients with advanced, progressive neuroendocrine tumours of gastrointestinal (GI) or unknown origin regardless of primary location and prior therapy, according to new subgroup analyses of the RADIANT-4 trial.

The phase III trial is the largest of its type in patients with nonfunctioning GI tract or lung neuroendocrine tumours. The subgroup findings for those whose tumours originated in the GI tract or an unknown site (but suspected to be GI) were presented in a presscast held in advance of the Gastrointestinal Cancers Symposium.

Compared with placebo, everolimus prolonged progression-free survival by 6-9 months, corresponding to a 46–48% relative reduction in the risk of progression or death, reported lead study author Dr Simron Singh of Sunnybrook's Odette Cancer Centre in Toronto. Benefit was similar regardless of whether patients had midgut or non-midgut tumours, and whether they had previously received a somatostatin analog or not.

"In my opinion, this study in advanced, progressive neuroendocrine patients [shows] an effective, new and exciting treatment option in a disease where we've had very few treatments to date," Dr Singh said ahead of the symposium, which was sponsored by ASCO, ASTRO, the American Gastroenterological Association, and the Society of Surgical Oncology.

ASCO expert and presscast moderator Dr Smitha Krishnamurthi of Case Western Reserve University, Cleveland, agreed, saying that everolimus could help address an unmet need in this disease.

"Patients with GI neuroendocrine tumours have had very few treatment options. Once they have progressed on somatostatin analogues, there really are no good systemic treatments," she said. "So this finding is very important, that the mTOR inhibitor everolimus has demonstrated an improvement in risk of progression by over 40% and with very little severe toxicity. This is a welcome finding for these patients who have limited systemic treatment options."

Patients enrolled in RADIANT-4 had lung, GI, or unknown-origin neuroendocrine tumours that had progressed on other therapies, including somatostatin analogs, surgery, or chemotherapy. They were randomly assigned in 2:1 ratio to receive everolimus or placebo, each in addition to best supportive care. Everolimus is currently approved by the Food and Drug Administration for the treatment of pancreatic neuroendocrine tumours, as well as breast and kidney cancer, and subependymal giant cell astrocytoma.

Results for the entire trial population have been previously reported and showed that everolimus prolonged progression-free survival by 7.1 months, reducing the risk of events by 52% (*Lancet* 2015 Dec 15. doi.org/10.1016/S0140-6736[15]01234-9).

The new subgroup analyses were restricted to the patients with tumours originating in the GI tract (n =175) or an unknown site generally thought to be the GI tract (n = 36).

Among the group with GI tumours, median progression-free survival was 13.1 months with everolimus versus 5.4 months with placebo, Dr Singh reported. Among the group with tumours of unknown origin, it was 13.6 and 7.5 months, respectively.

Relative to placebo, everolimus prolonged progression-free survival by 6.41 months, reducing the risk of events by 29%, in patients whose tumours originated in the midgut (duodenum, ileum, jejunum, cecum, or appendix). The relative benefit was 6.17 months, with a reduction in the risk of events of 73%, in patients whose tumours originated in non-midgut sites (stomach, colon, and rectum).

In addition, everolimus prolonged progression-free survival by 6.73 months, reducing the risk of events by 46%, in patients who had previously received somatostatin analogues, and by 9.07 months, reducing the risk by 48%, in patients who had not received these agents.

The safety profile of everolimus was consistent with that expected based on the use of this agent in other patient populations, according to Dr Singh. The most common adverse events were stomatitis, infections, diarrhoea, peripheral oedema, and fatigue. No new safety signals were seen.

Dr Singh disclosed that he receives honoraria from, has a consulting or advisory role with, and receives research funding (institutional) and travel, accommodations, and expenses from Novartis. The study received funding from Novartis Pharmaceuticals.

Wide disparity in radiology reads without RECIST

Tumour response assessments differ widely, in ways that may affect treatment decisions, depending on whether Response Evaluation Criteria in Solid Tumours (RECIST) are used, suggests a study reported at the ASCO Gastrointestinal Cancers Symposium.

Researchers at Jefferson Medical College, Philadelphia undertook a study using 292 scans performed in patients with solid tumours who were treated in clinical trials during 2013–2014.

Results presented in a poster session showed that the RECIST report of tumour status agreed with the oncologist's interpretation of the standard radiology report, generated without these criteria, only about half the time.

"This study basically came about when I saw all of these [standard] reports calling it progression, and I would get the RECIST report back saying it was stable. And we are actually making treatment decisions" based on that, senior author Dr Ashwin R. Sama of Jefferson Medical College, Philadelphia, said in an interview. "This has never been studied, although everybody knew that there probably is a difference between regular reads and RECIST reads."

"The correlation was about 50% – that's like the flip of a coin. And that really has a big impact on treatment," he added. "You don't want to take patients off treatment too soon if they have stable disease; and vice versa, if they have progression, you don't want to keep them on chemo that is not working."

In the study, a single radiologist read the scans using RECIST criteria and generated a report. Multiple radiologists then read the same scans without using these criteria and generated a standard report. An oncologist and a resident separately interpreted the standard reports to classify patients as having a complete response, a partial response, stable disease, or progressive disease.

Overall agreement between the RECIST report and the oncologist-interpreted standard report was just 56%. In 29% of cases of RECIST-classified progressive disease, the oncologist interpreted the standard report as showing stable disease. On the other hand, in 19% of cases of RECIST-classified stable disease, the oncologist interpreted the standard report as showing progressive disease.

Findings were similar when the resident interpreted the standard report. Overall agreement with the RECIST report was just 54%. In 24% of cases of RECIST-classified progressive disease, the resident interpreted the standard report as showing stable disease. In 26% of cases of RECIST-classified stable disease, the resident interpreted the standard report as showing progressive disease.

"Clinical trials commonly use RECIST as a way to interpret tumour response. However, outside of clinical trial settings, RECIST criteria are less commonly used, especially if you are in a nonacademic institution," commented first author Dr Aileen Deng of the Thomas Jefferson University Hospital, Philadelphia.

Variability in standard reports likely contributes to considerable variability in practice, she speculated. "There need to be better ways to standardise how we interpret serial images that are done for our patients with solid tumours," she concluded.

Dr Sama and Dr Deng disclosed that they had no relevant conflicts of interest.

Bipolar androgen therapy may be new option for hormone-sensitive prostate cancer

BY SUSAN LONDON
Frontline Medical News
At the Genitourinary Cancers Symposium

Depriving hormone-sensitive prostate cancer of testosterone and then hitting it with a supraphysiologic dose keeps the disease under control and nets good quality of life, results of a phase II trial suggest.

With this alternating strategy, called bipolar androgen therapy, nearly 60% of men in the trial achieved a prostate-specific antigen level of less than 4 ng/mL after two rounds of therapy, first author Dr Michael T. Schweizer reported at the Genitourinary Cancers Symposium. Moreover, men had improvements in quality of life after receiving the testosterone.

Many view androgen deprivation therapy (ADT) as the standard of care for such metastatic or biochemically recurrent disease, he explained in an interview. "In a sense, this is kind of analogous to forced intermittent androgen deprivation therapy, whereas instead of allowing testosterone levels to slowly recover, like is done in clinical practice, we administer high doses of testosterone."

The prostate-specific antigen results achieved "are relatively comparable to what you see with prior intermittent androgen deprivation therapy studies. So this looks like it may be as good as intermittent therapy, and it has the added benefit of improved quality of life," said Dr Schweizer of the University of Washington and Fred Hutchinson Cancer Research Centre, both in Seattle.

"This data is preliminary, and I don't think it should be used to guide treatment. But we think that it's promising enough as a justification for a future prospective study, ideally a randomised trial," he added. "Additional studies should probably include additional biomarker assessments to see if we can discover predictors for response to this type of therapy."

In a previous trial, Dr Schweizer and his colleagues tested bipolar androgen therapy in men with castration-resistant disease, finding a paradoxical antitumour effect, with a high response rate and some patients staying on the therapy for more than a year.

The new trial was conducted among 33 men who had a biochemical recurrence only, or had metastatic disease with a low tumour burden, and had not received therapy for advanced disease with a second-line hormonal agent or ADT. Most had previously undergone radical prostatectomy, radiation therapy, or both.

During a 6-month lead-in phase, they received ADT. "The idea behind that was that would allow for the androgen receptor to adaptively up-regulate, one of the molecular events we think sensitises cells to this form of therapy," he explained at the symposium, sponsored by the American Society of Clinical Oncology, ASTRO, and the Society of Urologic Oncology.

Overall, 29 men achieved a prostate-specific antigen suppression to less than 4 ng/mL or a value at least 50% below their baseline value, and therefore went on to receive two rounds of bipolar androgen therapy: monthly injections of testosterone cypionate or testosterone enanthate for 3 months, followed by ADT for 3 months.

At the end of the study, 59% had a prostate-specific antigen level of less than 4 ng/mL, exceeding the trial's prespecified value for success of 40% based on previous trials.

"It seemed like this therapy did quickly approximate the results of what you would expect from men with biochemical disease receiving intermittent androgen deprivation therapy," Dr Schweizer said. Among the 10 men who had RECIST-evaluable disease, 8 had a response to the therapy.

The patients also experienced an improvement in quality of life, going from the end of the lead-in phase to the end of the first round of testosterone. Specifically, they had median improvements in the Functional Assessment of Cancer Therapy-Prostate (FACT-P) (3.5 points, $P = 0.04$) and in the International Index of Erectile Function (IIEF) (10 points, $P < 0.001$).

Among all 29 men receiving at least one dose of testosterone, 79% had an adverse event thought to be at least possibly related to the hormone, most commonly hot flushes (52%), oedema (38%), and weight gain (14%), according to Dr Schweizer, who disclosed that he had no relevant conflicts of interest. However, all events were grade 1 or 2 in severity.

Statins don't appear to compromise effectiveness of abiraterone

BY SUSAN LONDON
Frontline Medical News
At the Genitourinary Cancers Symposium

Statins do not reduce the effectiveness of abiraterone acetate in men with castration-resistant prostate cancer, and they may even prove to add to therapy, according to data reported at the Genitourinary Cancers Symposium.

In a retrospective cohort study of 224 patients treated with abiraterone, duration of abiraterone acetate therapy, used as a surrogate for time to disease progression, was 5 months longer for men taking statins.

Prior work in patients with hormone-sensitive disease has suggested that statins compete with the androgen dehydroepiandrosterone sulfate – a precursor of more potent androgens – for cellular uptake via the SLCO2B1 transporter (*JAMA Oncol* 2015 Jul;1:495–504). But "contrary to our initial hypothesis and the preclinical data that drove our initial hypothesis, there was a trend toward longer abiraterone duration in statin users," commented Dr Lauren C. Harshman of the Lank Centre for Genitourinary Oncology at Dana-Farber Cancer Institute, and Harvard Medical School, both in Boston. "(A statin) may be additive with abiraterone's effect on androgen biosynthesis. Alternatively, statins could be inhibiting abiraterone's uptake by the liver and might be prolonging the drug exposure," she said at the 2016 Genitourinary Cancers Symposium sponsored by the American Society of Clinical Oncology, ASTRO, and the Society of Urologic Oncology.

> (A statin) may be additive with abiraterone's effect on androgen biosynthesis. Alternatively, statins could be inhibiting abiraterone's uptake by the liver and might be prolonging the drug exposure.

While the findings are "intriguing," they are not yet ready for clinical application, according to Dr Harshman, and "need to be validated before you would ever start a statin purely for prostate cancer treatment."

Based on preclinical data, the researchers had hypothesised that statins would compete with abiraterone for cellular influx by SLCO2B1, thereby reducing abiraterone's inhibition of androgen biosynthesis and its clinical efficacy.

They analysed data from men treated for predominantly metastatic castration-resistant prostate cancer with abiraterone at Dana-Farber between 2008 and 2015. In about three-fourths of cases, abiraterone was being given as the first treatment for castration-resistant disease. Overall, 41% of men were taking statins when they began abiraterone.

With a median follow-up of 27.8 months, the median duration of abiraterone therapy was 14.2 months for statin users and 9.2 months for nonusers, according to data reported in a poster session. In a multivariate analysis, statin use continued to predict a longer duration of abiraterone therapy, although the prolongation was not statistically significant.

Findings were much the same, with a trend toward greater benefit for statin users, among the subset of patients who had not previously received enzalutamide or docetaxel chemotherapy (21.3 vs 14.8 months).

"We are working with another centre to add numbers to see if we see a similar trend," concluded Dr Harshman, who disclosed that she receives research funding from Janssen, the maker of abiraterone. "We are thinking about how to test this prospectively, whether in a randomised trial or some sort of trial where you might add abiraterone plus statins."

The investigators are also analysing the impact of single-nucleotide polymorphisms in the SLCO transporter on abiraterone's efficacy in patients with castration-resistant prostate cancer, she said.

ADT resistance signature predicts failure of hormone therapy for prostate cancer

BY SUSAN LONDON
Frontline Medical News
At the Genitourinary Cancers Symposium

A new gene signature may take some of the guesswork out of selecting men with localised prostate cancer for adjuvant androgen deprivation therapy (ADT), according to a study reported at the 2016 Genitourinary Cancers Symposium.

The signature captures expression of 12 genes involved in neuroendocrine differentiation, which is known to be a marker of resistance to hormone therapy, according to first author Dr R. Jeffrey Karnes of the Mayo Clinic, Minnesota.

Results of the study of 785 men treated with radical prostatectomy for high-risk disease indicated that among the group given adjuvant ADT, those with a high signature were 71% more likely to experience failure of this therapy, as evidenced by the development of metastases, than did their peers with a low signature.

"If you were considering treatment with androgen deprivation therapy in an adjuvant fashion for disease that meets certain criteria, such as lymph node invasion, and some people will treat patients with seminal vesicle invasion, and you profile their tumour and they have a high score, a high androgen-resistance signature, you might want to consider something else," Dr Karnes said in an interview. "This is hypothesis generating, but the next steps are maybe looking at the signature in a randomised trial."

In addition, it will be helpful to evaluate the predictive value of the signature when assessed in biopsy tissue and, at the other extreme, when assessed in metastases that are already present at the time of diagnosis, he said.

In the latter setting, "if a patient has a high signature, maybe that's somebody you definitely – irrespective of the volume of [his] disease – want to treat [him] with chemohormonal therapy if [he] had a high signature, because this is sort of a marker of an innate or inherent resistance to castration."

For the study, Dr Karnes and his colleagues used the Decipher Genomics Resource Information Database (GRID) to analyse gene expression profiles of primary tumours from men treated with radical prostatectomy, with or without radiation therapy, for high-risk prostate adenocarcinoma.

They developed the gene signature in 360 men and validated it in 425 men. Overall, about a third of the cohort received ADT.

During follow-up, 35% of the men developed metastases (49% of those given ADT and 29% of those not given ADT), according to data reported in a poster session at the symposium, sponsored by the American Society of Clinical Oncology, ASTRO, and the Society of Urologic Oncology.

In Kaplan-Meier analysis among men treated with ADT, those with a high ADT resistance signature were more likely to develop metastases ($P = 0.03$). In contrast, among men not treated with ADT, the signature did not predict this outcome.

In a multivariate analysis, a high ADT resistance signature was associated with an elevated risk of metastases for men given ADT even after taking into account a variety of clinicopathologic features, surgical margin status, and receipt of various treatments (hazard ratio, 1.71; $P = 0.02$).

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References: 1. Tafinlar. Product Information. 2. Mekinist. Product Information. 3. Long G et al. Dabrafenib and Trametinib vs dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase-3 randomised controlled trial. *Lancet* 2015; 386:444-451. 4. Robert C et al. Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib. *N Engl J Med* 2015; 372:30-39. 5. Daud A et al. Updated Overall Survival for BRF113220:A Phase 1-2 Study of Dabrafenib Alone vs Combined Dabrafenib and Trametinib in Patients With BRAF V600 Mutation–Positive Metastatic Melanoma. Poster Presentation at the 51st ASCO Annual Meeting; May 29 - June 2, 2015; Chicago Illinois.

NOVARTIS

Anorectal melanoma rates rose significantly in 20-year analysis

BY AMY KARON
Frontline Medical News
From Dermatologic Surgery

Rates of anorectal melanoma rose substantially in the US from 1992 to 2011, according to a study published in *Dermatologic Surgery.*

The increases affected men and women, said Dr Adrienne Callahan of the department of dermatology, University Hospitals Case Medical Centre, Cleveland, and her associates. Anorectal carcinoma was significantly more common among Hispanic whites than non-Hispanic whites (P = 0.02), "suggesting that this population may be targeted for screening interventions," they added.. The highest rates were in Hispanic white elderly women.

Anorectal melanoma accounts for 1.3% of all melanomas and 16.5% of mucosal melanomas, and is most common among older women. The prognosis is often poor because the cancer tends to be asymptomatic until its late stages. To study the epidemiology of anorectal melanoma, the researchers analysed data from the Surveillance, Epidemiology, and End Results 13 (SEER 13) Registries Database for 1992 through 2011.

The SEER database listed 260 cases for the study period. Most involved the rectum, 58% affected adults aged 65 years and older, and almost two-thirds occurred in women – a finding that dovetails with other studies, the researchers said. Notably, the estimated annual change in age-standardised incidence rates increased in both men (5.08%) and women (3.02%), which were statistically significant increases (P < 0.05 for both trends).

Anorectal melanoma rates were significantly higher among Hispanic whites, compared with non-Hispanic whites. "Other studies have indicated that Hispanics are underscreened for skin cancer compared to other ethnic groups despite the increasing incidence of melanoma in this population," said the researchers. "Although this may suggest a role for improved screening among those with Hispanic ethnicity, additional studies must be done to corroborate these results and further elucidate the association of Hispanic ethnicity with anorectal melanoma."

As far as they know, this is the first study that has analysed anorectal melanoma incidence in Hispanic whites and non-Hispanic whites, they added.

Ethnicity did not affect survival, which was generally poor. Anorectal melanoma is very rare, so the number of cases was relatively small and rates might have been unstable, the investigators noted. They added that it was not known whether the increases they found were related to improved detection.

The study was funded by the Char and Chuck Fowler Family Foundation, the Dermatology Foundation, and the US National Cancer Institute. The researchers had no disclosures.

Immune-related events with checkpoint inhibitors are manageable

BY NEIL OSTERWEIL
Frontline Medical News
AT AACR–NCI–EORTC

Immune-related adverse events associated with checkpoint inhibitor therapy are generally mild to moderate and transient, but some less common side effects can be serious or even fatal, according to an immunotherapy researcher.

"Rapid identification of these side effects and initiation of systemic immunosuppression can improve outcomes without compromising the efficacy of immune-checkpoint inhibition," said Dr Antoine Italiano from the Institut Bergonié in Bordeaux, France.

There is also evidence to suggest that immune-related adverse events (irAEs) associated with the programmed-death 1 (PD-1) inhibitors pembrolizumab and nivolumab may be predictive of favourable outcomes. In contrast, although there was early clinical evidence to suggest that adverse reactions to immune checkpoint inhibition with cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) antibodies such as ipilimumab correlate with outcomes, more recent evidence suggests that toxicity with this class of agents is not predictive of efficacy, Dr Italiano said at the AACR–NCI–EORTC International Conference on Molecular Targets and Cancer Therapeutics.

"Correlation between safety profile and outcome must be confirmed by further studies," he said, adding that "further studies are also needed to identify patients at high risk of poor tolerability."

Immune-related adverse events associated with anti-CTLA-4 therapy generally involve organ systems such as the skin, digestive tract, and endocrine system. Rare adverse events reported with these agents include renal injury, sarcoidosis, uveitis, and myelitis, among others.

The events tend to arise around 10 weeks of therapy, following three cycles with either ipilimumab or the investigational agent tremelimumab. Late-occurring events, defined as those that arise more than 70 days after the last infusion, are uncommon, occurring in less than 7% of patients.

Most irAEs seen with anti-CTLA-4 therapy are reversible within about 6 weeks, although some events, such as hypophysitis (autoimmune inflammation of the pituitary gland), can take significantly longer to resolve, Dr Italiano said.

He cited a recent systematic review and meta-analysis showing that among patients treated with any anti-CTLA-4, the overall incidence of all-grade irAEs was 72%, and the overall incidence of high-grade irAEs was 24%. This study also showed that there was a dose-dependent risk of developing irAEs with ipilimumab, with the incidence of all grades of events at 61% for the 3 mg/kg dose, and 79% for the 10 mg/kg dose.

Two potential biomarkers for gastrointestinal irAEs, the neutrophil-activation markers CD177 and CEACAM1, were identified in a 2013 study. This finding suggests a possible role of neutrophils in ipilimumab-associated GI irAEs, Dr Italiano noted.

Evidence from early clinical studies of ipilimumab in metastatic melanoma suggested that irAEs correlated with outcomes, but a study published in October 2015 seems to debunk this notion, showing that among 298 patients treated with ipilimumab, neither time to treatment failure nor overall survival were affected by the occurrence of irAEs, he added.

As to whether therapy with anti-CTLA-4 antibodies is safe for treatment of cancer for patients with autoimmune diseases or immunodeficient states, the jury is still out, because these patients were typically excluded from clinical trials.

"But there are a few recent case reports suggesting that treating patients with autoimmune disease with ipilimumab is safe and does not induce exacerbation of the symptoms of the underlying autoimmune disease," Dr Italiano said.

PD-1 inhibitors

Adverse events common to the PD-1 inhibitors pembrolizumab and nivolumab and occurring in more than 5% of patients with each include fatigue/asthenia, decreased appetite, diarrhoea, rash, pruritus, nausea, and arthralgia.

In clinical trials of the agents for treatment of melanoma, vitiligo was the most common irAE, occurring in 7–8% of patients. Other events, occurring in similar frequency across the various trials, included hypo- or hyperthyroidism, pneumonitis, colitis, hepatitis, renal failure/nephritis, uveitis/iritis, and hypophysitis.

The time to first occurrence and resolution of irAEs with the PD-1 inhibitors varies by organ system, with skin toxicity occurring within the few weeks of therapy, peaking at about 15 weeks, and resolving by about 25 weeks. Gastrointestinal toxicities crop up at about 10 weeks, but quickly resolve.

Among the less common (less than 10%) irAEs, hepatic and pulmonary events seen to occur around week 8 or 9 and resolve within 2–4 weeks, whereas endocrine events start showing up around week 10, peak at about 25 weeks, and resolve around 40 weeks.

Among patients treated with PD-1 inhibitors for non-small cell lung cancer, the adverse-event profile is similar to that seen in treatment of patients with melanoma, except for the absence of vitiligo, Dr Italiano noted.

In contrast to the CTLA-4 inhibitors, irAEs seen with the PD-1 inhibitors, especially cutaneous events, appear to be associated with favourable outcomes.

For example, in a prospective, single-centre observational study of pembrolizumab in 67 patients with metastatic melanoma, 17 developed vitiligo, and 12 of these patients had an objective response (18% complete and 53% partial responses). The objective response rate in this group was 71%, compared with 28% (14 of 50 patients) for those who did not develop vitiligo.

In a second, retrospective study of 83 patients enrolled in clinical trials of pembrolizumab for melanoma, non-small cell lung cancer, prostate cancer, and Merkel cell carcinoma, patients in each of three pembrolizumab dosing groups who developed cutaneous AEs had significantly longer progression-free intervals than patients who did not develop cutaneous AEs.

A similar correlation between cutaneous events with nivolumab and favourable outcomes was seen in a study of pooled data on 148 patients with resected or unresectable metastatic melanoma. The investigators found that both rash and vitiligo correlated significantly with better overall survival.

Dabrafenib may be useful in patients who discontinue vemurafenib

BY SHARON WORCESTER
Frontline Medical News
From Journal of the European Academy of Dermatology and Venereology

Treatment with vemurafenib may result in severe skin toxicity, and dabrafenib appears to be useful in patients who discontinue vemurafenib due to such toxicity, according to a retrospective analysis of the cohort.

About a quarter (26%) of 131 melanoma patients treated in real life conditions with the BRAF inhibitor vemurafenib developed grade 3–4 skin toxicity, and 44% (34) of those patients permanently discontinued treatment, corresponding to 11% of the overall cohort, Dr Lucie Peuvrel of Nantes (France) University Hospital and colleagues reported in Journal of the European Academy of Dermatology and Venereology.

Discontinuations were mainly due to rash and classic adverse skin reactions, including Stevens-Johnson syndrome, drug reaction with eosinophilia, and systemic symptoms, whereas reactions involving only photosensitivity or cutaneous carcinomas rarely resulted in treatment adjustment; 14 of the remaining 19 patients with grade 3–4 toxicity who continued treatment had no dose adjustment, and 5 had a dose reduction.

Clinical or biological abnormalities occurred in 94% of those with grade 3–4 rashes, the investigators noted.

Study subjects were patients with a mean age of 60 years who were treated with vemurafenib for melanoma between November 2010 and December 2014. Grade 3–4 skin toxicity that emerged within the first 4–8 weeks of treatment was significantly associated with prolonged overall survival; severe skin rashes also were associated with prolonged median overall survival. Of seven patients who switched to dabrafenib due to their skin reaction, only one experienced recurrence of the reaction.

Vemurafenib, which is approved for the treatment of unresectable stage III-IV BRAF mutant melanoma, is commonly associated with skin toxicity, with severe cases occurring only rarely; the impact of severe forms of toxicity on treatment and patient outcomes was unknown, the investigators said.

The current findings reaffirm that vemurafenib is commonly associated with skin toxicity, but rarely with severe cases. Severe skin adverse reactions permanently preclude use of vemurafenib, but dabrafenib – the only other BRAF inhibitor with market authorisation for unresectable stage III-IV BRAF mutant melanoma – "seems to be beneficial in case of vemurafenib-induced skin intolerance," they noted, adding that for other skin toxicities, including photosensitivity and cutaneous carcinoma, treatment adjustment is generally not required, and that treatment resumption at a reduced dose should be considered after skin improvement in patients with rashes.

The finding of increased survival in cases involving severe skin toxicity that emerges within 4–8 weeks of treatment initiation should be confirmed in other studies, Dr Peuvrel and associates said.

The authors reported having no conflicts of interest.

ASCO GU 2016: Dr Fred Saad's Prostate cancer – year in review

BY DR MOSHE C ORNSTEIN

Dr Fred Saad, professor and chief of urology and director of G-U Oncology at the University of Montreal Hospital Centres, delivered the highlights of the past year's prostate cancer research at the ASCO GU symposium in San Francisco in January. Dr Saad began by pointing out that "although there were no new drugs approved in 2015, we learned a lot about what we have available – some good and some not so good." Here is Dr Saad's review of the latest progress in prostate cancer research.

Screening and active surveillance

PSA screening for prostate cancer remains a controversial subject. In 2012, the US Preventative Services Task Force (USPSTF) assigned a grade D recommendation to PSA screening, thus discouraging its use. However, a significant number of patients are still screened with the PSA test. A report by Drazer et al in August 2015 noted that, since the 2012 USPSTF recommendations, there has been a general decline in PSA screening (*J Clin Oncol* 2015;33[22]:2416–2423). Nevertheless, one-third of men over 75 years old and one-third of men over 65 years with a high probability of death within 9 years continue to be screened, against the formal recommendations. This equates to approximately 1.4 million men who are inappropriately screened.

Given the continued over-screening with PSA alone (albeit with an overall decline in its use), the question remains whether there is a better screening test to identify patients likely to have higher-risk prostate cancer. In other words, can we figure out a method of intelligent screening? This has been addressed well in a study published by Grönberg and the Swedish group in December (*Lancet Oncol* 2015;16[16]:1667–1676). They developed a Stockholm 3 (STHLM3) model, incorporating plasma protein biomarkers, genetic polymorphisms, and clinical variables. This screening method was investigated in a prospective population-based study to determine whether it could increase sensitivity of diagnosing high-risk prostate cancer compared with the current PSA model. The authors demonstrated that the STHLM3 model was indeed superior to PSA screening alone in its ability to detect prostate cancer with a Gleason score greater than 6. Use of this model could thus significantly reduce the number of biopsies done. Although not yet a standard of care, it suggests that the prostate cancer community is moving into an era of intelligent screening to minimise invasive procedures in patients unlikely to have higher-risk prostate cancer.

Once we have determined a more sensitive and specific screening method for prostate cancer, the next question is whether active surveillance for those patients diagnosed with lower-risk disease is safe. A study published by Tosoian and colleagues in October 2015 reported the long-term follow-up from an active surveillance program for patients with favourable-risk disease (*J Clin Oncol* 2015;33[30]:3379–3385). Approximately one-third of patients were reclassified to higher-risk disease during active surveillance and were treated with curative intent, while the majority of the patients remained on active surveillance with lower-risk disease. Most reclassification went from GS 3+3 to 3+4. The results from this study demonstrated a treatment-free survival of 8.5 years, with cancer-specific survival of 99% at 15 years, indicating a high degree of safety for patients with lower-risk prostate cancer on active surveillance.

These data confirmed a report from January 2015 by Klotz et al of almost 1000 patients with favourable-risk prostate cancer on an active surveillance program (*J Clin Oncol* 2015;33[3]272–277). After 15 years of follow-up, only 2.8% of patients developed metastatic disease and 1.5% died from prostate cancer. These numbers are similar to those found in the same patient population treated upfront with definitive therapy. Indeed, a study by Cooperberg and Carroll published in July 2015 demonstrated that the rates of active surveillance in low-risk prostate cancer patients is rising (*JAMA* 2015;314[1]:80–82).

Importance of local therapy

After discussing the importance of appropriate screening and active surveillance for lower-risk patients, Dr Saad shifted the focus to local control for locally advanced prostate cancer. A publication in July 2015 by Mason and colleagues demonstrated that local control with radiation in patients getting lifelong androgen deprivation therapy (ADT) delays onset to castration-resistant disease that translated to cancer-specific and overall survival (*J Clin Oncol* 2015;33[19]:2143–2150).

The next question on this topic is whether there is a role for local control with radiation therapy for patients with advanced disease? This was answered with data published by James et al of the STAMPEDE trial (*JAMA Oncol* Published online November 25, 2015). They looked at radiation therapy for patients with negative nodes and positive nodes. There was a failure-free survival benefit associated with using radiation therapy in patients with node-positive disease. The role of radiation is thus more clearly defined for high-risk prostate cancer and locally advanced disease, with mounting evidence for its role in metastatic prostate cancer. However, the question of surgery in the metastatic setting lacks definitive data with randomised control trials.

The above data cover the role of radiation in locally advanced disease. What about hormonal therapy after salvage radiation therapy? To answer this question, Dr Saad reviewed the updated results of RTOG 9601 presented at this meeting by Dr William Shipley (*J Clin Oncol* 34, 2016 [suppl 2S; abstr 3]). In this study, patients with elevated PSA following radical prostatectomy for pT2–3, N0 prostate cancer were randomised to receive salvage radiation therapy with placebo or salvage radiation therapy plus bicalutamide during and after radiation for a total of 24 months. With a median follow-up of over 12 years, the authors demonstrated a benefit in terms of overall survival, reduced metastatic prostate cancer, and reduced death from prostate cancer in patients in the bicalutamide arm.

The question remains, however, how much ADT is truly needed in this setting? Results from RTOG 9601 as presented by Dr Shipley indicate that 24 months of ADT during and after radiation results in superior outcomes. The DART01/05 GICOR study published in March of 2015 by Zapatero et al randomised participants to 4 months of ADT vs 24 months of ADT in the setting of high-risk prostate cancer in patients receiving radiation therapy (*Lancet Oncol* 2015;16[3]:320–327). Patients receiving ADT for 24 months had improved 5-year biochemical-free survival, metastatic-free survival, and overall survival.

Taken together, these data demonstrate that patients with high-risk, locally advanced prostate cancer benefit from longer durations of ADT in addition to radiation therapy.

Androgen deprivation therapy and side effects

Despite the well-established data about the benefits of ADT, Dr Saad cautioned that in 2015 a number of studies were published about the "dark side of ADT." Gonzalez et al reported that after 6 and 12 months on ADT, patients were more likely to demonstrate cognitive decline compared with matched controls not on ADT (*J Clin Oncol* 2015;33[18]:2021–2027). This was confirmed by a similar study just recently published by Nead et al in which an increased risk for Alzheimer's disease was noted in patients on ADT within a general population cohort (*J Clin Oncol* Published online December 7, 2015). So, although the use of ADT is integral to the treatment of prostate cancer, it is not without potential long-term adverse events, and these issues cannot simply be brushed aside.

Benefits of chemotherapy in hormone-sensitive prostate cancer

The major update in 2015 regarding the use of chemotherapy in hormone-sensitive prostate cancer (HSPC) was the presentation made at the ASCO annual meeting in 2015 concerning the chemotherapy plus hormone therapy arm of the STAMPEDE trial. In the presentation by James et al, patients with metastatic HSPC receiving docetaxel in addition to ADT had an improved overall survival of 77 months compared with those patients receiving ADT alone of 67 months (*J Clin Oncol* 33, 2015 [suppl; abstr 5001]). These data confirmed the CHAARTED/ECOG 3805 data formally published in 2015 by Sweeney et al (*N Engl J Med* 2015;373[8]:737–746) but initially presented at ASCO 2014 (*J Clin Oncol* 32:5s, 2014 [suppl; abstr LBA2]).

STAMPEDE and CHAARTED address the role of chemotherapy in metastatic HSPC, but what about the use of chemotherapy in nonmetastatic HSPC? Fizazi et al addressed this question in a July 2015 publication of the GETUG 12 trial (*Lancet Oncol* 2015;16[7]:787–794). This study looked at high risk (defined as T3–4, GS≥8, PSA>20ng/mL, or pathological nodal disease) patients randomised to ADT alone for 3 years or ADT plus four cycles of docetaxel and estramustine. Relapse-free survival at the 8-year time point was statistically higher in the ADT and chemotherapy arm versus the ADT-alone arm (62% vs 50%; P = 0.017). Further follow-up is still needed to determine role of the addition of chemotherapy on metastasis-free and overall survival.

New options for metastatic prostate cancer

Highlighting the progress in metastatic castration-resistant prostate cancer (mCRPC), Dr Saad noted how the median overall survival for patients in this setting has most recently been reported as close to 3 years in the updated analysis from the PREVAIL trial, which compared enzalutamide with placebo in mCRPC (EAU Congress 2015, Madrid). Dr Saad also noted that final overall survival analysis of COU-AA-302 comparing abiraterone with placebo in the pre-chemotherapy setting, which was published by Ryan et al in February 2015, also indicates that earlier treatment in this setting results in improved outcome (*Lancet Oncol* 2015;16(2):152–160).

The other important topic from 2015 in the setting of mCRPC is whether there is a role for bone-targeted therapy in the era of the oral agents enzalutamide and abiraterone, which have bone-protective elements as well. A study published by Saad et al in October 2015 demonstrated that, in patients receiving abiraterone, the combination with zoledronic acid improved overall survival, delayed time to opiate use, and delayed decline in performance status (*Eur Urol* 201;68[4]:570–577).

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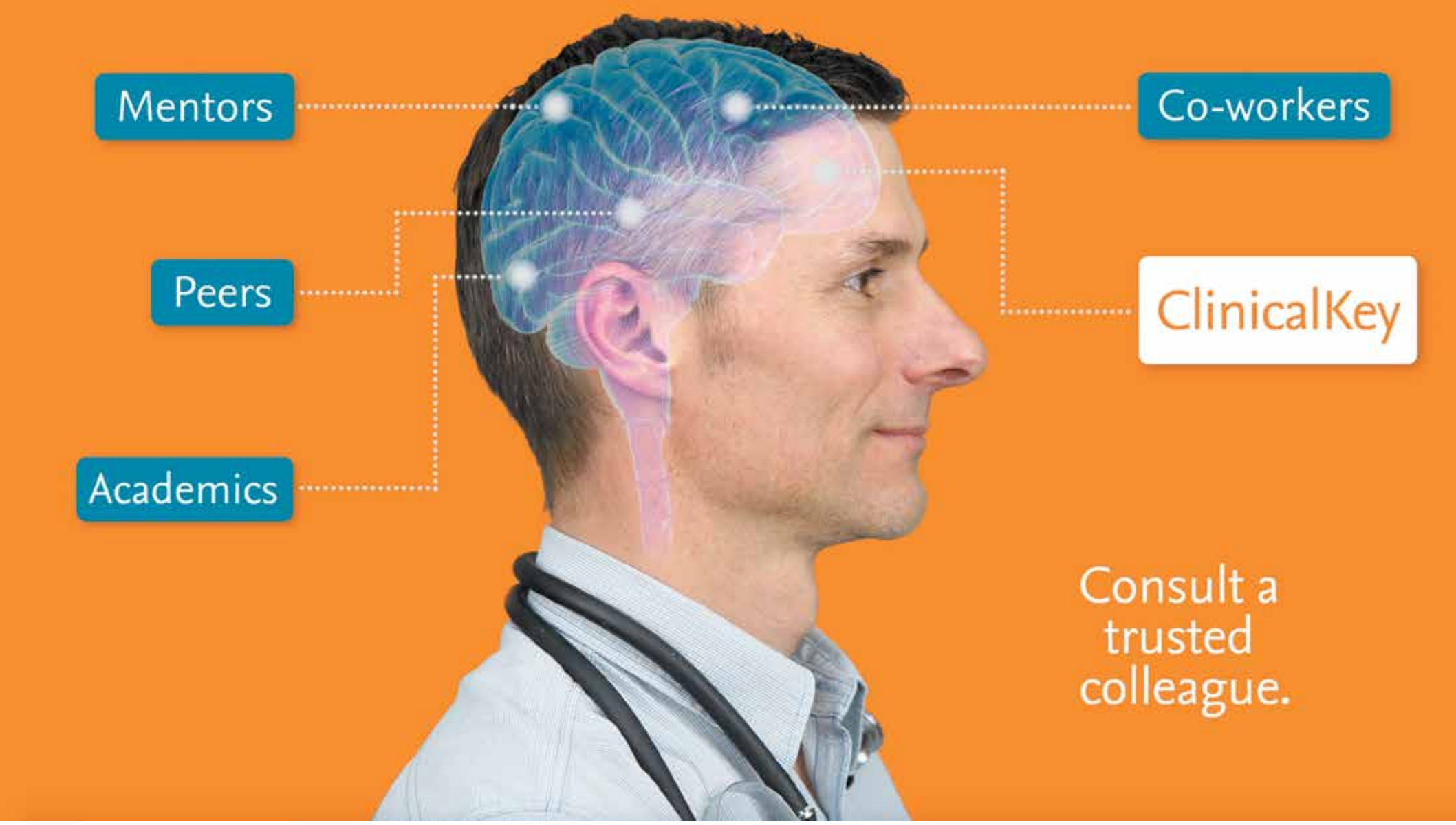

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