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Haematology & Oncology

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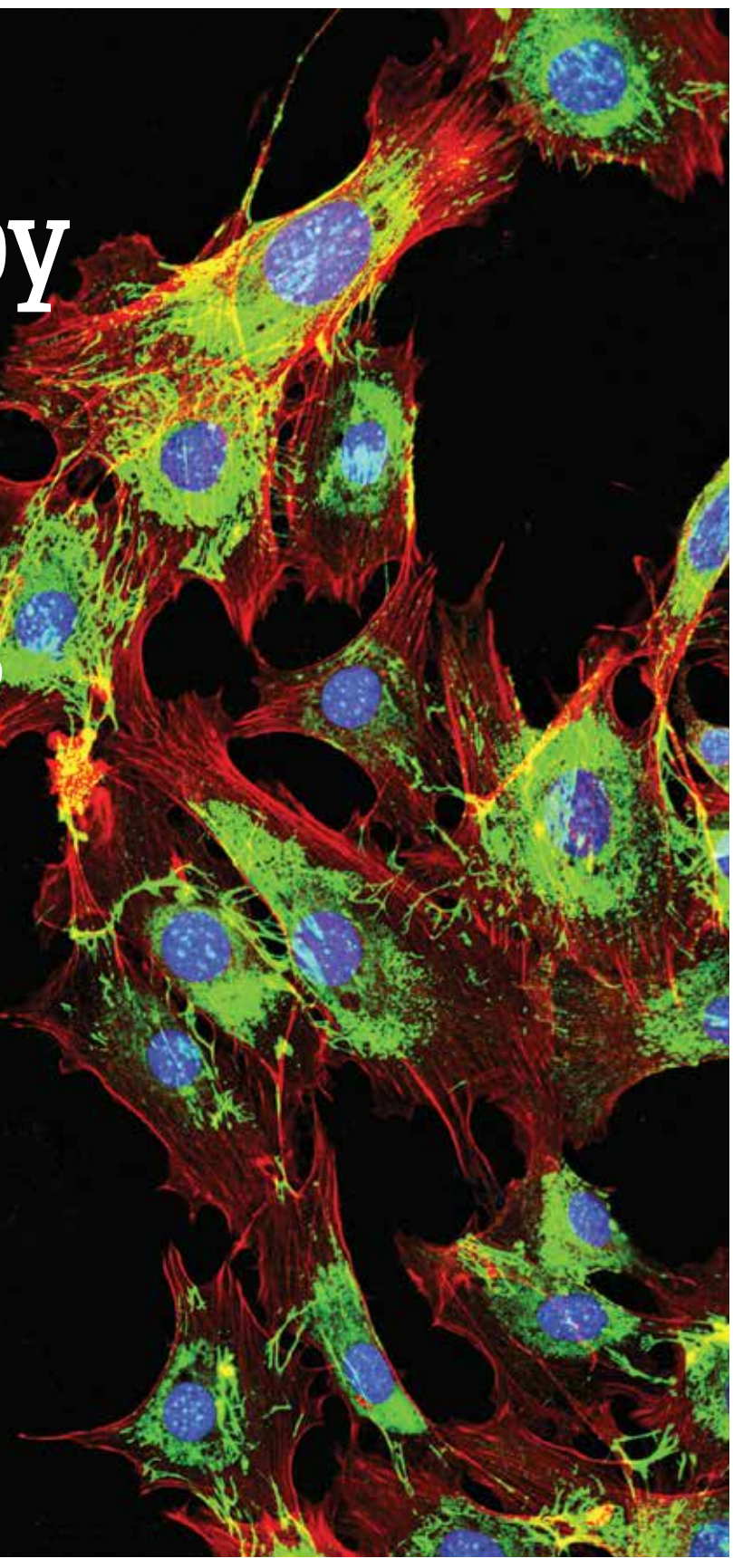
RESEARCH NEWS AND VIEWS FROM ELSEVIER

FORMERLY HAEMATOLOGY & ONCOLOGY NEWS

CD4 T cell immunotherapy targeting MAGE-A3 is safe and shows early response in metastatic cancer



An immunotherapy developed by genetically engineering CD4 T cells targeting the MAGE-A3 protein in cancer cells was found to be safe in patients with metastatic cancer, and some had clinical response. This outcome of a phase 1 clinical trial was reported at the 2016 Annual Meeting of the American Association for Cancer Research, from April 16–20. ▸3

Immune response in breast cancer brain metastases and their microenvironment

Breast Cancer Research

PD-1 expression has a favourable impact on prognosis and suggests a role for immune checkpoint inhibitors in the treatment of BCBM. ▸4

Cost implications of omission of breast radiotherapy in low-risk luminal A breast cancer

Clinical Oncology

Should omission of radiotherapy become recommended practice, there will be significant cost savings. ▸5

Response of recurrent GBM to immune checkpoint inhibition

Journal of Clinical Oncology

The authors suggest that the increasing availability of sequencing technologies may facilitate analysis of mutation burden and neoantigens in ways that may improve treatment of these patients. ▸7

Pembrolizumab for advanced Merkel cell carcinoma

The New England Journal of Medicine

Treatment of advanced Merkel cell carcinoma with first-line pembrolizumab resulted in an objective response rate of 56%. ▸14

OPINION

"...if you are really looking at the tumour tissue prior to your targeted approach, you will probably get more out of the treatment than if you take a one-size-fits-all type of approach

Dr Wolfgang Wick ▸7

BREAST

Almost 90% of women with early-stage breast cancer reported using complementary and alternative medicine ▸5

BRAIN

What is the future of neuro-oncology? ▸6

Could a drug such as bevacizumab be used in conjunction with immunotherapy to decrease oedema rather than using steroids? ▸6

CONFERENCE

AACR 2016

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Neoadjuvant combi therapy may improve HER2+ BRCA outcomes ▸11

CheckMate-141

Nivolumab improved survival in head and neck SCC ▸14

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MORE JOURNAL ARTICLE REVIEWS
MORE CONFERENCE COVERAGE NEWS

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CD4 T cell immunotherapy targeting MAGE-A3 is safe and shows early response in metastatic cancer

Continued from page 1.

"The majority of studies on T cell-based cancer immunotherapy focus on CD8 T cells due to their capability to kill tumour cells directly. Evidence from preclinical and clinical studies, however, indicates that another type of T cell, CD4 T cell, can also induce tumour regression. This was the first clinical trial evaluating an immunotherapy that uses gene-engineered CD4 T cells against metastatic cancer," explains Steven A. Rosenberg, MD, PhD, of the US National Cancer Institute, US National Institutes of Health, Bethesda, Maryland.

The main goal was to determine the maximum number of modified CD4 T cells that can be safely given to a patient.

To develop CD4 T cell immunotherapy for each individual patient, Dr Rosenberg's team first collects T cells from the circulating blood of a patient and isolates CD4 T cells. Next, they genetically modify these T cells using a retrovirus with the gene for the T cell receptor that recognises MAGE-A3. Last, they grow the modified T cells in the laboratory in large numbers, and transfer them back to the patient.

The team engineers the CD4 T cells to target MAGE-A3 protein in cancer cells. MAGE-A3 is a member of a class of proteins expressed during foetal development. MAGE-A3 expression is often lost in adult normal tissue but reexpressed in many cancers.

Through cell surface human leukocyte antigens (HLA), T cells distinguish between normal and tumour cells by checking whether a protein, such as MAGE-A3, is expressed in the cells. The T cell receptor has to match the patient's specific type of HLA. The investigators chose HLA-DPB1*0401 for this purpose. HLA-DPB1*0401 is the most common HLA among Caucasians (approximately 60% carry this HLA allele.

The investigators enrolled 14 patients in the trial who had the HLA allele DPB1*0401 and whose metastatic cancers carried the MAGE-A3 protein. All had received at least one unsuccessful first-line therapy. Eight patients received one of the many tested doses of modified CD4 T cells, ranging from 10 million to 30 billion cells, while six patients received the highest dose level of about 100 billion cells.

> "Based on the encouraging results in the phase 1 clinical trial, we hope to enrol more cancer patients with different malignancies for the phase 2 study

One patient with metastatic cervical cancer, one with metastatic oesophageal cancer, and one with metastatic urothelial cancer had objective partial responses. The cervical cancer patient's tumour response continues 15 months after treatment initiation. The urothelial cancer patient's tumour response continues 7 months after treatment.

The majority of patients experienced high fever, and high levels of the interleukin-6 were detected in all patients' serum after treatment. These effects were manageable.

Dr Rosenberg concluded, "Based on the encouraging results in the phase 1 clinical trial, we hope to enrol more cancer patients with different malignancies for the phase 2 study".

New drugs and devices listing

THERAPEUTIC GOODS ADMINISTRATION (TGA)
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Avanafil (Spedra), A Menarini
Erectile dysfunction

Cobimetinib (Cotellic), Roche
Unresectable or metastatic melanoma

Idarucizumab (rch) (Praxbind), Boehringer Ingelheim
Reversal agent for dabigatran

Evolocumab (rch) (Repatha), Amgen
Primary hypercholesterolaemia and homozygous familial hypercholesterolaemia

Eltrombopag (Revolade), Novartis
Severe aplastic anaemia (SAA)

Ibrutinib (Imbruvica), Janssen-Cilag
Small lymphocytic lymphoma (SLL), mantle cell lymphoma

Enzalutamide (Xtandi), Astellas Pharma
Metastatic castration-resistant prostate cancer

PHARMACEUTICAL BENEFITS SCHEME
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Buprenorphine (Norspan), Mundipharma

Oxycodone + naloxone (Targin), Mundipharma

Paritaprevir + Ritonavir + Ombitasvir & Dasabuvir & Ribavirin (Viekira Pak-RBV), AbbVie

Ustekinumab (Stelara), Janssen-Cilag

Nadroparin (Fraxiparine), Aspen

Rituximab (Mabthera SC), Roche

Sumatriptan (Imigran FDT), Aspen

Trastuzumab (Herceptin SC), Roche

Please consult the full Product Information before prescribing.

JOURNAL SCAN

The MAGE-A3 cancer immunotherapeutic as adjuvant therapy in resected MAGE-A3-positive NSCLC

The Lancet Oncology

Take-home message

- In this multicentre, randomised, double-blind, phase III clinical trial, the authors compared adjuvant immunotherapy (recMAGE-A3/AS15 immunostimulant) with placebo in 2312 patients with MAGE-A3-positive resected stage IB–IIIA non-small cell lung cancer (NSCLC). Median disease-free survival (DFS) was 60.5 months vs 57.9 months in the treatment and placebo groups, respectively (P = 0.74).
- Adjuvant MAGE-A3 immunotherapy did not improve DFS vs placebo in patients with early-stage, resected, MAGE-A3-positive NSCLC.

Brandt Esplin, MD, PhD

Abstract

BACKGROUND Fewer than half of the patients with completely resected non-small-cell lung cancer (NSCLC) are cured. Since the introduction of adjuvant chemotherapy in 2004, no substantial progress has been made in adjuvant treatment. We aimed to assess the efficacy of the MAGE-A3 cancer immunotherapeutic in surgically resected NSCLC.

METHODS In this randomised, double-blind, placebo-controlled trial, we recruited patients aged at least 18 years with completely resected stage IB, II, and IIIA MAGE-A3-positive NSCLC who did or did not receive adjuvant chemotherapy from 443 centres in 34 countries (Europe, the Americas, and Asia Pacific). Patients were randomly assigned (2:1) to receive 13 intramuscular injections of recMAGE-A3 with AS15 immunostimulant (MAGE-A3 immunotherapeutic) or placebo during 27 months. Randomisation and treatment allocation at the investigator site was done centrally via internet with stratification for chemotherapy versus no chemotherapy. Participants, investigators, and those assessing outcomes were masked to group assignment. A minimisation algorithm accounted for the number of chemotherapy cycles received, disease stage, lymph node sampling procedure, performance status score, and lifetime smoking status. The primary endpoint was broken up into three co-primary objectives: disease-free survival in the overall population, the no-chemotherapy population, and patients with a potentially predictive gene signature. The final analyses included the total treated population (all patients who had received at least one treatment dose).

FINDINGS Between Oct 18, 2007, and July 17, 2012, we screened 13 849 patients for MAGE-A3 expression; 12 820 had a valid sample and of these, 4210 (33%) had a MAGE-A3-positive tumour. 2312 of these patients met all eligibility criteria and were randomly assigned to treatment: 1515 received MAGE-A3 and 757 received placebo and 40 were randomly assigned but never started treatment. 784 patients in the MAGE-A3 group also received chemotherapy, as did 392 in the placebo group. Median follow-up was 38.1 months (IQR 27.9–48.4) in the MAGE-A3 group and 39.5 months (27.9–50·4) in the placebo group. In the overall population, median disease-free survival was 60.5 months (95% CI 57.2-not reached) for the MAGE-A3 immunotherapeutic group and 57·9 months (55.7-not reached) for the placebo group (hazard ratio [HR] 1.02, 95% CI 0.89–1.18; p=0.74). Of the patients who did not receive chemotherapy, median disease-free survival was 58·0 months (95% CI 56.6-not reached) in those in the MAGE-A3 group and 56.9 months (44.4–not reached) in the placebo group (HR 0.97, 95% CI 0.80–1.18; p=0.76). Because of the absence of treatment effect, we could not identify a gene signature predictive of clinical benefit to MAGE-A3 immunotherapeutic. The frequency of grade 3 or worse adverse events was similar between treatment groups (246 [16%] of 1515 patients in the MAGE-A3 group and 122 [16%] of 757 in the placebo group). The most frequently reported grade 3 or higher adverse events were infections and infestations (37 [2%] in the MAGE-A3 group and 19 [3%] in the placebo group), vascular disorders (30 [2%] vs 17 [3%]), and neoplasm (benign, malignant, and unspecified (29 [2%] vs 16 [2%]).

INTERPRETATION Adjuvant treatment with the MAGE-A3 immunotherapeutic did not increase disease-free survival compared with placebo in patients with MAGE-A3-positive surgically resected NSCLC. Based on our results, further development of the MAGE-A3 immunotherapeutic for use in NSCLC has been stopped.

Efficacy of the MAGE-A3 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive non-small-cell lung cancer (MAGRIT): a randomised, double-blind, placebo-controlled, phase 3 trial

Lancet Oncol 2016 Apr 27;[EPub Ahead of Print], JF Vansteenkiste, BC Cho, T Vanakesa, et al.

EXPERT OPINION

Breast cancer therapeutics: trastuzumab and aromatase inhibitors

By Dr Joerg Herrmann

Cardiovascular morbidity in cancer patients has generated and received mixed reactions, from concern to neglect, from being considered significant to meaningless. Here, we join the debate on two of the most commonly used therapeutics in breast cancer patients: trastuzumab and aromatase inhibitors (AIs).

Studies of women with hormone receptor-positive breast cancer comparing AIs and tamoxifen have concluded that AIs are associated with a higher risk of arterial ischaemic events. However, this might have been a biased view as tamoxifen improves the cardio-metabolic risk profile and thus might have a lower arterial ischaemic risk profile even in comparison with placebo (and not just AIs). Indeed, in randomised controlled trials comparing AIs and placebo, no such signal was noted. The current study of >13,000 postmenopausal breast cancer survivors further attests to this.[1] Even in time-dependent analyses, there was no increased risk of arterial events with AIs over time. On the contrary, the risk of arterial events, especially cardiac ischaemia, seemed to decline after 3 years in tamoxifen users. While based on claims data rather than detailed chart review and verification and adjudication of events, this study still provides reassurance for the use of AIs and the information needed when patients are inquiring about the cardiovascular risk of this therapy, especially considering its chronic treatment dimension.

With regard to the active treatment of breast cancer and women with HER2+ breast cancer, the Ontario Cancer Registry study provides very intriguing information, confirming and challenging some of the current viewpoints.[2] First of all, the rate of major cardiac events was highest in the first year after the start of therapy; in fact, it matched the non-cardiac mortality rate, and declined thereafter to the level of the age-matched general population. In conjunction with data on the therapy-related risk further outlined below, these findings support the view that the largest risk is largely confined to the period of adjuvant trastuzumab therapy. Secondly, these dynamics of a "vulnerable first year" were noted in women under 65 years of age. On the contrary, women 65 years of age or older had approximately a three times higher risk of major cardiac events than younger women and remained on a steeper cardiac event rate curve than the general population even after 1 year. In both age groups, non-cardiac death was the main cause of death after 1 year, significantly higher than the incidence of cardiac events combined – a constellation opposite the general population, especially among those 65 years of age and older. Thus, older patients have a higher baseline cardiovascular risk, higher cardiac risk during therapy, and a persistently higher cardiac risk after cancer therapy while the risk remains confined to 1 year in younger patients. Thirdly, over the observed follow-up period of up to 5 years, the hazard ratio of cardiac events roughly doubled from anthracycline therapy to trastuzumab therapy and from trastuzumab therapy to sequential anthracycline/trastuzumab therapy. The latter group also met the threshold for heart failure hospitalisation risk.

Thus, as expected, those with combined anthracycline/trastuzumab therapy were at highest cardiac risk; however, what might be surprising is the higher cardiac risk in those on trastuzumab therapy alone, a risk even higher than with anthracycline therapy alone. We do not have detailed information on how long the trastuzumab therapy-related risk persisted, any reversibility dynamics, and if this was noted in women with cardiovascular risk factors and/or disease, essentially unmasking a lower cardiovascular reserve. However, it can likely be extrapolated from the above that even younger patients undergoing trastuzumab need surveillance for at least 1 year, and those with an underlying disease burden even long term. With regard to the follow-up period in this study, it might have been too short to capture all anthracycline-related events. Accordingly, this study is more revealing for trastuzumab than it is for anthracyclines, and it comes at a time when the current recommendation of echocardiograms every 3 months while on trastuzumab therapy is being reconsidered, and details on how much such a monitoring strategy decreases events and at which cost-effectiveness level remain to be defined.

Mixed reactions, but seemingly no reassurance that we can simply forget about cardiotoxicity with trastuzumab therapy. ■

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1. Haque R, Shi J, Schottinger JE, et al. Cardiovascular Disease After Aromatase Inhibitor Use. *JAMA Oncol* 2016 Apr 21. DOI: 10. 1001/jamaoncol.2016.0429. [Epub ahead of print]
2. Thavendiranathan P, Abdel-Qadir H, Fischer HD, et al. Breast Cancer Therapy-Related Cardiac Dysfunction in Adult Women Treated in Routine Clinical Practice: A Population-Based Cohort Study. *J Clin Oncol* 2016 Apr 18. DOI: 10.1200/JCO.2015.65.1505. [Epub ahead of print]

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NEWS

Increased breastfeeding by African-American women could lower their incidence of triple-negative breast cancer

Increased breastfeeding by African-American women could decrease their incidence of triple-negative breast cancer. This conclusion, drawn from results of a retrospective, single-centre analysis of 289 patients diagnosed with breast cancer over a 9-year period, was presented at the Oncology Nursing Society 41st Annual Congress, from April 28–May 1.

> A few studies have suggested that a lack of breastfeeding may be associated with an increase in the aggressive type of triple-negative breast cancer in African-American women.

Julia Eggert, PhD, AGN-BC, AOCN, FAAN, of Clemson University, South Carolina, explained that for African American women, breastfeeding rates have been historically low, reported as 58.1% (vs 73–83% for four non-African American groups) from 2000–2007 in the US.

A few studies have suggested that a lack of breastfeeding may be associated with an increase in the aggressive type of triple-negative breast cancer (without receptors for oestrogen, progesterone, or human epidermal growth factor) in African-American women.

No studies have been performed in South Carolina. Such findings could affect the relationships of oncology nurses with their patients, solidify research results, and lead to the creation of a national education program targeting African-American women to increase their breastfeeding practice to potentially reduce their incidence of aggressive triple-negative breast cancer.

A total of 289 women with a diagnosis of breast cancer in an inherited breast cancer clinic were identified between 2006 and 2015. Self-reported data was collected about hormone-associated risk factors, including breastfeeding. Pathology reports were abstracted for breast cancer biomarkers. All data was double-checked for accuracy by three researchers

Data analysis suggested a relationship between a lack of breastfeeding and the incidence of triple-negative breast cancer in African-American women. The African-American Breast cancer Epidemiology and Risk (AMBER) Consortium study found similar results with a questionnaire. Other studies have found similar results, but with less statistical strength.

Dr Eggert concluded that the results suggested that increased breastfeeding by African-American women could decrease their incidence of triple-negative breast cancer. Since younger African American women tend to be diagnosed with triple-negative breast cancer, an educational intervention might affect their incidence.

Developing a simple educational program similar to that developed for breast self-examination, interdisciplinary teams from oncology nursing, public health, physician offices, and schools could implement programs directed to different age groups of African-American girls and women, and perhaps men and boys as well.

Further research could address long-term results on breastfeeding practice, changes in attitudes toward breastfeeding, and whether a reduction in the incidence of triple-negative breast cancer in African-American women resulted from the educational effort. ■

JOURNAL SCAN

Immune response in breast cancer brain metastases and their microenvironment

Breast Cancer Research

Take-home message

- The immune responses in 84 patients with breast cancer brain metastases (BCBM) were evaluated. PD-L1 expression was seen in 53% of cases and PD-L2 expression in 36%, regardless of BCBM phenotype. Both PD-1 expression and CD68+ were associated with CD4+ and CD8+ tumour-infiltrating lymphocytes. Following excision of BCBM, survival correlated positively with PD-1 expression on tumour-infiltrating lymphocytes, CD68+ infiltration, brain radiotherapy, and endocrine therapy. There was a negative correlation seen between survival and hormone receptor-negative/HER2-positive phenotype of the primary tumour and HER2 expression.
- Expression of both PD-L1 and PD-L2 is common in all phenotypes of BCBM. PD-1 expression has a favourable impact on prognosis and suggests a role for immune checkpoint inhibitors in the treatment of BCBM.

BACKGROUND A better understanding of immune response in breast cancer brain metastases (BCBM) may prompt new preventive and therapeutic strategies.

METHODS Immunohistochemical expression of stromal tumour-infiltrating lymphocytes (TILs: CD4, CD8, CTLA4), macrophage/microglial cells (CD68), programmed cell death protein 1 receptor (PD-1), programmed cell death protein 1 receptor ligand (PD-L)1, PD-L2 and glial fibrillary acid protein was assessed in 84 BCBM and their microenvironment.

RESULTS Median survival after BCBM excision was 18.3 months (range 0-99). Median number of CD4+, CD8+ TILs and CD68+ was 49, 69 and 76 per 1 mm(2), respectively. PD-L1 and PD-L2 expression in BCBM was present in 53 % and 36 % of cases, and was not related to BCBM phenotype. PD-1 expression on TILs correlated positively with CD4+ and CD8+ TILs (r = 0.26 and 0.33), and so did CD68+ (r = 0.23 and 0.27, respectively). In the multivariate analysis, survival after BCBM excision positively correlated with PD-1 expression on TILs (hazard ratio (HR) = 0.3, P = 0.003), CD68+ infiltration (HR = 0.2, P < 0.001), brain radiotherapy (HR = 0.1, P < 0.001), endocrine therapy (HR = 0.1, P < 0.001), and negatively with hormone-receptor-negative/human epidermal growth factor receptor 2 (HER2)-positive phenotype of primary tumour (HR = 2.6, P = 0.01), HER2 expression in BCBM (HR = 4.9, P = 0.01).

CONCLUSIONS PD-L1 and PD-L2 expression is a common occurrence in BCBM, irrespective of primary tumour and BCBM phenotype. Favourable prognostic impact of PD-1 expression on TILs suggests a beneficial effect of preexisting immunity and implies a potential therapeutic role of immune checkpoint inhibitors in BCBM.

Immune Response in Breast Cancer Brain Metastases and Their Microenvironment: The Role of the PD-1/PD-L Axis *Breast Cancer Res* 2016 May 01;18(1)43, R Duchnowska, R Pęksa, B Radecka, et al.

JOURNAL SCAN

Complementary and alternative medicine use and breast cancer chemotherapy initiation

JAMA Oncology

Take-home message

- This was a multicentre, prospective cohort study designed to evaluate the association between use of complementary and alternative medicine (CAM) and breast cancer chemotherapy initiation in 685 women with early-stage breast cancer. Baseline CAM use was reported in the majority of patients (87%) prior to enrolment. Patients who reported higher use of CAM, particularly dietary and vitamin supplements, were more likely to forgo recommended chemotherapy.
- Almost 90% of women with early-stage breast cancer reported using CAM. The use of some CAM modalities may affect uptake of chemotherapy, and oncologists should include a discussion on CAM when formulating a management plan.

Jeremy Jones, MD

Abstract

IMPORTANCE Not all women initiate clinically indicated breast cancer adjuvant treatment. It is important for clinicians to identify women at risk for noninitiation.

OBJECTIVE To determine whether complementary and alternative medicine (CAM) use is associated with decreased breast cancer chemotherapy initiation.

DESIGN, SETTING, AND PARTICIPANTS In this multisite prospective cohort study (the Breast Cancer Quality of Care [BQUAL] study) designed to examine predictors of breast cancer treatment initiation and adherence, 685 women younger than 70 years with nonmetastatic invasive breast cancer were recruited from Columbia University Medical Center, Kaiser Permanente Northern California, and Henry Ford Health System and enrolled between May 2006 and July 31, 2010. Overall, 306 patients (45%) were clinically indicated to receive chemotherapy per National Comprehensive Cancer Network guidelines. Participants were followed for up to 12 months.

EXPOSURES Baseline interviews assessed current use of 5 CAM modalities (vitamins and/or minerals, herbs and/or botanicals, other natural products, mind-body self-practice, mind-body practitioner-based practice). CAM use definitions included any use, dietary supplement use, mind-body use, and a CAM index summing the 5 modalities.

Main Outcomes And Measures Chemotherapy initiation was assessed via self-report up to 12 months after baseline. Multivariable logistic regression models examined a priori hypotheses testing whether CAM use was associated with chemotherapy initiation, adjusting for demographic and clinical covariates, and delineating groups by age and chemotherapy indication.

RESULTS A cohort of 685 women younger than 70 years (mean age, 59 years; median age, 59 years) with nonmetastatic invasive breast cancer were recruited and followed for up to 12 months to examine predictors of breast cancer treatment initiation. Baseline CAM use was reported by 598 women (87%). Chemotherapy was initiated by 272 women (89%) for whom chemotherapy was indicated, compared with 135 women (36%) for whom chemotherapy was discretionary. Among women for whom chemotherapy was indicated, dietary supplement users and women with high CAM index scores were less likely than nonusers to initiate chemotherapy (odds ratio [OR], 0.16; 95% CI, 0.03–0.51; and OR per unit, 0.64; 95% CI, 0.46–0.87, respectively). Use of mind-body practices was not related to chemotherapy initiation (OR, 1.45; 95% CI, 0.57–3.59). There was no association between CAM use and chemotherapy initiation among women for whom chemotherapy was discretionary.

CONCLUSIONS AND RELEVANCE CAM use was high among patients with early-stage breast cancer enrolled in a multisite prospective cohort study. Current dietary supplement use and higher number of CAM modalities used but not mind-body practices were associated with decreased initiation of clinically indicated chemotherapy. Oncologists should consider discussing CAM with their patients during the chemotherapy decision-making process.

Association Between Complementary and Alternative Medicine Use and Breast Cancer Chemotherapy Initiation: The Breast Cancer Quality of Care (BQUAL) Study
JAMA Oncol 2016 May 12;[EPub Ahead of Print], H Greenlee, AI Neugut, L Falci, et al.

JOURNAL SCAN

Cost implications of omission of breast radiotherapy in low-risk luminal A breast cancer

Clinical Oncology

Take-home message

- The authors of this Canadian study estimated the potential cost savings to a publicly funded healthcare system with the omission of radiotherapy for women ≥ 60 years of age with grade I/II T1N0 luminal A breast cancer. Adjuvant radiotherapy was given to 539 women in the study period, and 329 of these women had grade I/II luminal A subtype disease. At a cost of $6135.85 per case, the potential cost savings across Canada totals over $5 million.
- Should omission of radiotherapy become recommended practice, there will be significant cost savings.

Abstract

AIMS The economic burden of cancer care is substantial, including steep increases in costs for breast cancer management. There is mounting evidence that women age ≥ 60 years with grade I/II T1N0 luminal A (ER/PR+, HER2- and Ki67 ≤ 13%) breast cancer have such low local recurrence rates that adjuvant breast radiotherapy might offer limited value. We aimed to determine the total savings to a publicly funded health care system should omission of radiotherapy become standard of care for these patients.

MATERIALS AND METHODS The number of women aged ≥ 60 years who received adjuvant radiotherapy for T1N0 ER+ HER2- breast cancer in Ontario was obtained from the provincial cancer agency. The cost of adjuvant breast radiotherapy was estimated through activity-based costing from a public payer perspective. The total saving was calculated by multiplying the estimated number of luminal A cases that received radiotherapy by the cost of radiotherapy minus Ki-67 testing.

RESULTS In 2010, 748 women age ≥ 60 years underwent surgery for pT1N0 ER+ HER2- breast cancer; 539 (72%) underwent adjuvant radiotherapy, of whom 329 were estimated to be grade I/II luminal A subtype. The cost of adjuvant breast radiotherapy per case was estimated at $6135.85; the cost of Ki-67 at $114.71. This translated into an annual saving of about $2.0 million if radiotherapy was omitted for all low-risk luminal A breast cancer patients in Ontario and $5.1 million across Canada.

CONCLUSIONS There will be significant savings to the health care system should omission of radiotherapy become standard practice for women with low-risk luminal A breast cancer.

Omission of Breast Radiotherapy in Low-Risk Luminal A Breast Cancer: Impact on Health Care Costs *Clin Oncol (R Coll Radiol)* 2016 Apr 29;[EPub Ahead of Print], K Han, ML Yap, JH Yong, et al.

EXPERT OPINION DR MINESH MEHTA

Personalised medicine in neuro-oncology: current status

By Dr Farzanna S Haffizulla

Dr Haffizulla: Let's talk about precision medicine and personalised advances, targeted treatment based on the individual rather than having a blanket standard of care treatment. What are your thoughts, and what are some of the advances to come?

Dr Mehta: Well, obviously, finding specific targets in each individual patient's tumour has become the Holy Grail of oncology, and this has been very successful, in, for example, non-small cell lung cancer. Unfortunately, in the neuro-oncology space, our successes have not been that great in finding individualised targetable mutations, for which specific drugs can be utilised.

This search continues, but there is another direction in which this personalisation of therapy is beginning to emerge, and that's the utilisation of immune checkpoint inhibitors.

Immune checkpoint inhibitors have become the darling child in the oncology world in the last 2 to 3 years, especially with all the dramatic advances in melanoma, and they're beginning to find application in neuro-oncology in new clinical trials and new concepts.

Dr Haffizulla: Matrix metalloproteinase, you mentioned melanoma – I think about that – and isocitrate dehydrogenase (IDH), co-deletions, 1p/19q, et cetera. Can you tell me what else is on the horizon?

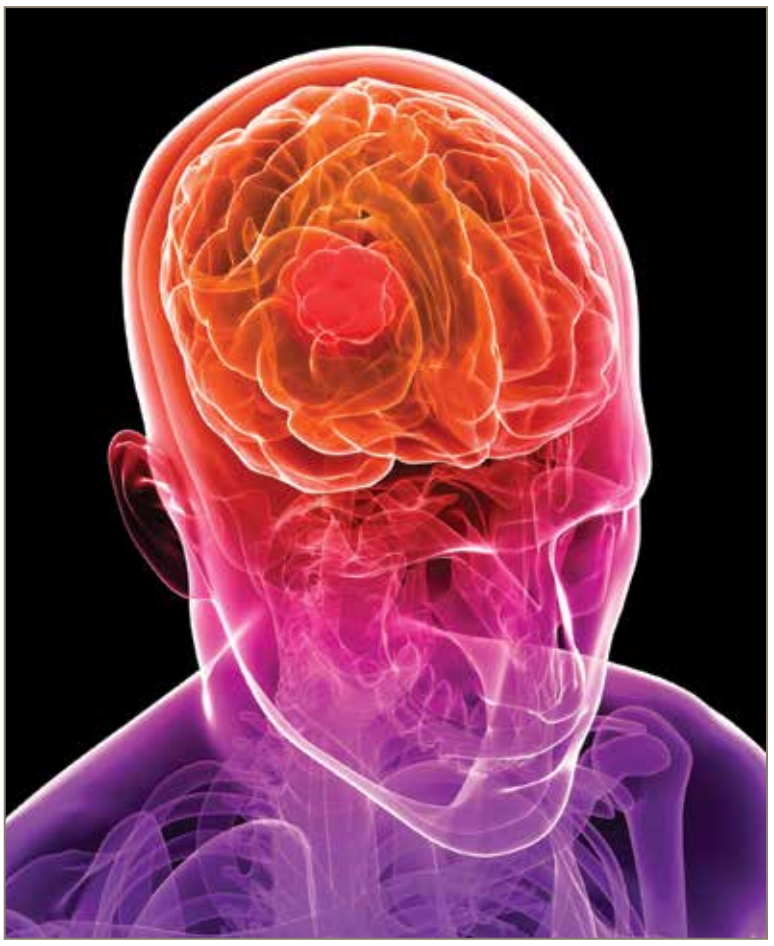
Dr Mehta: All of the molecular markers that you mentioned have now been shown to have significant prognostic implications in many brain tumours, and in some situations they're even predictive of therapeutic benefit.

It's quite likely that these molecular markers will become incorporated in the future classifications of brain tumours, moving from histology-based to molecular marker-based classification, and some of them like IDH might even provide us therapeutic avenues using IDH inhibitors in future practice.

> "So, collaboration is important. Making sure the different specialties, not just in neuro-oncology, oncology, radiation oncology, et cetera – imaging – all come together to really have that personalised approach.

Dr Haffizulla: Fantastic. I know the World Health Organisation classification scheme that you mentioned is based on the histology, and bringing in the molecular signature of the tumour itself, and using that to further classify these particular tumours, will help, as you said, gear treatment in the correct direction. What are your thoughts on when this is coming out?

Dr Mehta: In particular, for the lower-grade gliomas, the grade II and the grade III gliomas, there is such a confluence in terms of the clinical outcomes for patients with similar molecular patterns that it's very likely that the molecular pattern, rather than the grade, might become the future driver of the newer classification. And such a classification is being worked on as we speak.



Dr Haffizulla: So, collaboration is important. Making sure the different specialties, not just in neuro-oncology, oncology, radiation oncology, et cetera – imaging – all come together to really have that personalised approach.

Are there any other study designs that are being thought up now that might come to fruition a little bit later down the road? Maybe not just using a retrospective review of the clinical trial data that we have now, but taking a new lens, a new approach, to how we've approached some of the clinical trials for brain tumour research.

Dr Mehta: Well, let me give you two examples that I think are about to take off somewhat rapidly in the neuro-oncology space.

The first is really the example of combining immune checkpoint inhibitors with radiation. It turns out that radiation, especially high-dose radiation, can be quite immunogenic by causing tumour cell death, and combining that with an immune checkpoint inhibitor that allows a sustained anti-tumour response to be maintained, might be an innovative therapeutic avenue. Clinical trials based on this concept of combining radiation and immune checkpoint inhibitors are about to be launched, and these might be very intriguing to study.

Dr Haffizulla: I know it's always significantly challenging sometimes to recruit the right number of patients, especially with this disease type. How has it been to collaborate among different groups? With the different clinical trials and the designs that we have today, we need to have some good statistical power.

Dr Mehta: In neuro-oncology where we deal with tumours that are relatively uncommon, compared with many of the other tumours that we see in the oncology space, collaboration is crucial; so, we have mounted transatlantic collaborations among cooperative groups in the US, as well as in Europe, and we're even looking at collaborations across the world to complete some of these trials. ■

Dr Minesh Mehta is professor of radiation oncology; associate director of clinical research, radiation oncology, University of Maryland School of Medicine; medical director, Maryland Proton Treatment Center, Baltimore, Maryland.

Dr Farzanna Haffizulla is national president of the American Medical Women's Association (AMWA) 2014–2015; private practice, Internal Medicine, Davie, Florida.

JOURNAL SCAN

Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma

The New England Journal of Medicine

Take-home message

- This was a multicentre, randomised phase III trial including 251 patients with newly diagnosed low-grade gliomas designed to compare postoperative radiation therapy (RT) alone vs radiation therapy followed by combination chemotherapy with procarbazine, lomustine, and vincristine (RT+PCV).
- At a median follow-up of 11.9 years, the median overall survival was substantially longer in the RT+PCV group compared with those who received only radiation (OS, 13.3 vs 7.8 years). Grade 3 or 4 haematologic adverse events occurred in nearly 50% of patients treated with RT+PCV.

Jeremy Jones, MD

BACKGROUND Grade 2 gliomas occur most commonly in young adults and cause progressive neurologic deterioration and premature death. Early results of this trial showed that treatment with procarbazine, lomustine (also called CCNU), and vincristine after radiation therapy at the time of initial diagnosis resulted in longer progression-free survival, but not overall survival, than radiation therapy alone. We now report the long-term results.

METHODS We included patients with grade 2 astrocytoma, oligoastrocytoma, or oligodendroglioma who were younger than 40 years of age and had undergone subtotal resection or biopsy or who were 40 years of age or older and had undergone biopsy or resection of any of the tumour. Patients were stratified according to age, histologic findings, Karnofsky performance-status score, and presence or absence of contrast enhancement on preoperative images. Patients were randomly assigned to radiation therapy alone or to radiation therapy followed by six cycles of combination chemotherapy.

RESULTS A total of 251 eligible patients were enrolled from 1998 through 2002. The median follow-up was 11.9 years; 55% of the patients died. Patients who received radiation therapy plus chemotherapy had longer median overall survival than did those who received radiation therapy alone (13.3 vs 7.8 years; hazard ratio for death, 0.59; P=0.003). The rate of progression-free survival at 10 years was 51% in the group that received radiation therapy plus chemotherapy versus 21% in the group that received radiation therapy alone; the corresponding rates of overall survival at 10 years were 60% and 40%. A Cox model identified receipt of radiation therapy plus chemotherapy and histologic findings of oligodendroglioma as favourable prognostic variables for both progression-free and overall survival.

CONCLUSIONS In a cohort of patients with grade 2 glioma who were younger than 40 years of age and had undergone subtotal tumour resection or who were 40 years of age or older, progression-free survival and overall survival were longer among those who received combination chemotherapy in addition to radiation therapy than among those who received radiation therapy alone.

Radiation Plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma *N Engl J Med* 2016 Apr 07;374(14)1344-1355, JC Buckner, EG Shaw, SL Pugh, et al.

Future directions for targeted therapies in neuro-oncology

INTERVIEW WITH DR PATRICK Y. WEN

What is the future of neuro-oncology? Dr Wen, director of the Center for Neuro-Oncology at Dana-Farber Cancer Institute and professor of neurology at Harvard Medical School shares his perspective.

Generalised inflammation and brain tumours: is the brain an 'immunosanctuary'?

INTERVIEW WITH DR JEFFREY J RAIZER

Could a drug such as bevacizumab be used in conjunction with immunotherapy to decrease oedema rather than using steroids? Dr Jeffrey Raizer, Director of Medical Neuro-Oncology at Northwestern University, Chicago, explains.

EXPERT OPINION DR WOLFGANG WICK

Clinical implications of new molecular understanding in glioblastoma

By Dr Farzanna S Haffizulla

Dr Haffizulla: Let's talk more of the personalised approach – looking at molecular targets, understanding the tumours themselves and the antigens that they express, and how we can best direct targeted therapies in different patient populations.

Dr Wick: I think it's a very important. It is already an important aspect for radiotherapy; so, we have different responses to radiotherapy. It's an important aspect for all sorts of chemotherapy. It's an important aspect for so-called targeted agents because, if you are really looking at the tumour tissue prior to your targeted approach, you will probably get more out of the treatment than if you take a one-size-fits-all type of approach. Of course, the same assay and the same approach, the same kind of molecular workup could also be used to then identify neoantigens, mutated antigens, which then could be used for targeted and molecularly driven immune therapies. You have an active immunotherapy with a peptide, or with an mRNA, or whatever, and then you have that in combination with a checkpoint inhibitor or something, but you should use that active part in a personalised way and not in a one-size-fits-all approach.

> "If you are really looking at the tumour tissue prior to your targeted approach, you will probably get more out of the treatment than if you take a one-size-fits-all type of approach.

Dr Haffizulla: Absolutely. You maximise benefit to the patient, and minimise risk and side effects and adverse events. You know, we could probably even use some of the antigens that are expressed to create vaccines to prevent some of these tumour types.

Dr Wick: It would be great. IDH is a good example. We've actually had our own trial, and we had a very nice publication last year on mutated IDH being used as a peptide vaccine to treat low-grade tumours. This is not quite prevention, but this is – outside the disease of glioblastoma – really in the early stages with the primary treatments, trying to have a maintenance treatment that prevents a low-grade tumour from getting more malignant and recurring.

Dr Haffizulla: Absolutely, because what percentage of the low-grade gliomas convert to glioblastoma? It's about 30% or…?

Dr Wick: Yes. I think it's about that range, but 90% are expressing IDH. I think for those tumours, since it is uniquely expressed, IDH is really an interesting and very smart target to tackle, especially in that disease because it's not directly dividing. There is enough time for an immunotherapeutic response.

Dr Haffizulla: Right. What are your thoughts on the matrix metalloproteinase?

Dr Wick: You mean as a target or as a biomarker?

Dr Haffizulla: As a biomarker.

Dr Wick: It could be a nice biomarker for anti-angiogenic treatments. There will be patients who will benefit from those treatments, but we probably have not been smart enough to identify them, and matrix metalloproteinases in the serum could be one aspect, and one possibility to discover.

Dr Haffizulla: I'm just thinking about us getting signalling prior to the tumour forming. The possible release of other markers that might be out there that we haven't explored yet. Any that you might be working on in your lab, or within research?

Dr Wick: You mean markers prior to the formation of the tumour?

Dr Haffizulla: Prior to the…or the detection, we should say, because a marker could be there, but we may not be able to see it with some of the imaging techniques we have.

Dr Wick: What we are doing is really looking at the serum for non-coding RNAs; so, this is something we are really interested in.

Dr Haffizulla: MicroRNA.

Dr Wick: Yes, microRNA and long non-coding RNA. All the non-coding parts of the genome, which are probably more stably expressed at some stages, and, on the one hand, difficult to detect, but if you have the measures to do the detection, I think it could be something which is really specific for tumour development versus normal brain or other diseases.

Dr Haffizulla: Well, we're looking forward to seeing more to come from you. Thank you so much for joining us today.

Scan the QR code with your smartphoe to see the video interview

Dr Wolfgang Wick is division head, neuro-oncology, German Cancer Research Center (DKFZ); program chair, neuro-oncology, National Center for Tumor Diseases; Hertie Professor of Neuro-Oncology and director, National Tumor Center, University of Heidelberg, Heidelberg, Germany.

Dr Farzanna Haffizulla is national president of the American Medical Women's Association (AMWA) 2014–2015; private practice, Internal Medicine, Davie, Florida.

JOURNAL SCAN

Response of recurrent GBM to immune checkpoint inhibition

Journal of Clinical Oncology

Take-home message

- In this study, exome sequencing and neoantigen prediction of 37 biallelic mismatch repair deficiency (bMMRD) cancers were performed to make comparisons with brain neoplasms. The 32 malignant tumours identified were all hypermutant. The mutational load was significantly higher in bMMRD glioblastomas (GBMs) than in other tumours. Additionally, bMMRD GBMs showed neoantigen loads that were 7 to 16 times higher than found in several immunoresponsive tumour types (including melanomas, lung cancers, and microsatellite-unstable gastrointestinal cancers). A pair of siblings with bMMRD GBM experienced clinically significant responses after treatment with nivolumab.
- This study suggests that recurrent GBM may be responsive to immune checkpoint inhibition. The authors suggest that the increasing availability of sequencing technologies may facilitate analysis of mutation burden and neoantigens in ways that may improve treatment of these patients.

Patrick Y. Wen MD

While there is significant interest in immune checkpoint inhibitors in glioblastomas, the activity of these agents and predictors of response are unknown. There is increasing evidence in other cancers that hypermutated tumours may have a better response. Biallelic mismatch repair deficiency (bMMRD) is a childhood cancer syndrome that often results in glioblastomas characterised by a high mutational burden. In this study, 2 children with bMMRD with recurrent glioblastomas were treated with the anti-PD1 antibody nivolumab and experienced durable and significant responses. This represents one of the first reports of responses of recurrent glioblastoma to immune checkpoint inhibition.

Immune Checkpoint Inhibition for Hypermutant Glioblastoma Multiforme Resulting From Germline Biallelic Mismatch Repair Deficiency *J Clin Oncol* 2016 Mar 21;[EPub Ahead of Print], E Bouffet, V Larouche, BB Campbell, et al.

JOURNAL SCAN

Stereotactic radiosurgery vs whole-brain radiation for brain metastases from breast or non-small cell lung cancer

Cancer

Take-home message

- Patients treated with radiation therapy for brain metastases from NSCLC or breast cancer were evaluated to compare outcomes between treatment with stereotactic radiosurgery (SRS) alone and whole-brain radiation therapy (WBRT). SRS alone was performed in 27.8% of patients with NSCLC and 13.4% of patients with breast cancer. SRS was usually selected for patients with ≤3 metastases and lesions ≤4 cm in size, and these patients achieved longer survival times than those treated with WBRT.
- SRS alone is effective for patients with <4 brain metastases secondary to NSCLC or breast cancer.

Abstract

BACKGROUND The optimal treatment for patients with brain metastases remains controversial as the use of stereotactic radiosurgery (SRS) alone, replacing whole-brain radiation therapy (WBRT), has increased. This study determined the patterns of care at multiple institutions before 2010 and examined whether or not survival was different between patients treated with SRS and patients treated with WBRT.

METHODS This study examined the overall survival of patients treated with radiation therapy for brain metastases from non-small cell lung cancer (NSCLC; initially diagnosed in 2007-2009) or breast cancer (initially diagnosed in 1997–2009) at 5 centres. Propensity score analyses were performed to adjust for confounding factors such as the number of metastases, the extent of extracranial metastases, and the treatment centre.

RESULTS Overall, 27.8% of 400 NSCLC patients and 13.4% of 387 breast cancer patients underwent SRS alone for the treatment of brain metastases. Few patients with more than 3 brain metastases or lesions ≥ 4 cm in size underwent SRS. Patients with fewer than 4 brain metastases less than 4 cm in size (n = 189 for NSCLC and n = 117 for breast cancer) who were treated with SRS had longer survival (adjusted hazard ratio [HR] for NSCLC, 0.58; 95% confidence Interval [CI], 0.38–0.87; P = 0.01; adjusted HR for breast cancer, 0.54; 95% CI, 0.33–0.91; P = 0.02) than those treated with WBRT.

CONCLUSIONS Patients treated for fewer than 4 brain metastases from NSCLC or breast cancer with SRS alone had longer survival than those treated with WBRT in this multi-institutional, retrospective study, even after adjustments for the propensity to undergo SRS.

Comparative effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for patients with brain metastases from breast or non-small cell lung cancer. *Cancer* 18 Apr 2016 [online]; L Halasz, H Uno, M Hughes, et al.

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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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- OPDIVO, as monotherapy is indicated for the treatment of locally advanced or metastatic non-squamous NSCLC with progression on or after prior chemotherapy. In patients with tumour EGFR or ALK genomic aberrations, OPDIVO should be used after progression on or after targeted therapy[1]

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Bristol-Myers Squibb | Immuno-Oncology

American Association for Cancer Research annual meeting

16–20 APRIL 2016 • NEW ORLEANS, LOUISIANA, USA

A record 20,000 cancer community stakeholders from research, healthcare, academia, industry, government, and advocacy attended the American Association for Cancer Research Annual Meeting in New Orleans, last month, committed to finding a cure for cancer, to hear breaking research on precision medicine, immunotherapy and risk prediction models.

New technology can potentially overcome CAR T cell immunotherapy limitations

An engineered organic bispecific adaptor molecule that functions as a bridge between a chimeric antigen receptor (CAR) T cell and a cancer cell can potentially overcome some of the limitations posed by CAR T cell immunotherapy.

Yong Gu Lee, BS, of Purdue University, West Lafayette, Indiana, explained, "T cells constitute the main weapon the immune system employs to kill cancer cells. A number of laboratories have developed genetically engineered T cells that can recognise and kill cancer cells more efficiently. These CAR T cell technologies, however, have many limitations."

Existing technology allows for developing CAR T cells to target only one protein present in tumour cells. New CAR T cells need to be genetically engineered for each different cancer cell that expresses a different target protein. Engineered T cells are highly cytotoxic, and using current technology they cannot be deactivated once tumour cells are eliminated. Target proteins present on cancer cells are often present on normal cells as well, so CAR T cells can cause off-target toxicity leading to serious side effects.

To overcome these limitations, Mr Lee and colleagues engineered an adaptor using small organic molecules, and attached a yellow dye, fluorescein isothiocyanate (FITC), on one end. They attached a ligand on the other end that can bind to a specific tumour protein. The ligand can be designed to target various tumour proteins, such as the folate receptor, present on about a third of human cancers; and prostate-specific membrane antigen, present in prostate tumours.

Mr Lee and the team engineered second-generation CAR T cells based on existing technology and incorporated an anti-FITC antibody fragment into the intracellular domain of CD137 and CD3 zeta chain so it could bind to the FITC end of the adaptor molecule.

When a patient receives CAR T cells and adaptor molecules, the adaptor molecule will bind to the CAR T cell at the FITC end and to the tumour cell at the ligand-binding end.

The tumour cell is recognised by the adaptor and not by the CAR T cell itself, so the same CAR T cell can be targeted to multiple distinct tumour cells expressing nonoverlapping (orthogonal) tumour-specific antigens, simply by administering a cocktail of the correct antigen- matched adaptor molecules. The adaptors survive for no more than 20 minutes in the blood circulation, so it is possible to control the rate and extent of tumour cell killing and cytokine release in order to avoid serious adverse effects such as tumour lysis syndrome and/or cytokine storm.

Mr Lee concluded, "Our new CAR T cell design allows for more sensitive control the tumour lysis and cytokine release rate, enabling the physician to permanently terminate the cell-killing process as soon as the cancer has been eliminated from the body and avoid sustained off-target toxicity to healthy cells."

Further, by adjusting the binding affinity of the tumour-binding end of the adaptor molecule, it is possible to force the CAR T cell to bind only to cells that express high levels of a protein, as in the case of tumour cells, and not to cells that express low levels of the protein, as with normal cells.

Philip S. Low, PhD, director of the Center for Drug Discovery at Purdue University, said "The technology provides a universal platform that incorporates a cell-based immunotherapeutic 'living drug' and an organically synthesised inert small-molecule adaptor. This technology has the potential to extend CAR T cell immunotherapy beyond its current reach."

The technology has currently only been tested in animals and not in humans.

"We tested our technology in animal models and learned that our CAR T cells are only able to eradicate tumour cells when the correct antigen-matched adaptor molecules are administered," Lee said. "Moreover, we have demonstrated that we can eliminate two different tumour cell types in the same animal by administering a mixture of the desired adaptor molecules."

Low and team are in the process of patenting their technology.

Adding multiple biological risk markers improves breast cancer risk prediction models

Adding biological markers of risk to breast cancer risk prediction appears to improve risk prediction, especially for postmenopausal women not taking hormone therapy.

Xuehong Zhang, MD, ScD, of Harvard Medical School, Boston, Massachusetts, explained that an improved ability to identify a woman's breast cancer risk could help to tailor chemopreventives and screening recommendations more precisely.

Dr Zhang continued, "Risk prediction models are a type of statistical model that can provide insight into whether an individual is at low, medium, or high risk of a specific disease given the person's individual risk factor profile," Breast cancer risk prediction models, such as the Gail and Rosner-Colditz models, have been used to estimate women's breast cancer risk in order to tailor chemoprevention and screening recommendations.

Dr Zhang said, "These models generally have included only traditional breast cancer risk factors such as age, family history of breast cancer, reproductive factors, body mass index, and alcohol intake. Their ability to discriminate women with vs without breast cancer has been limited. Neither model, however, as initially developed includes multiple biological markers of risk."

Dr Zhang added, "We conducted the first comprehensive evaluation of the independent and joint contribution of several biological markers of risk in the two validated breast cancer risk prediction models (Gail and Rosner-Colditz models) using data from up to 10,052 breast cancer cases and 12,575 controls of European ancestry from the Nurses' Health Study and Nurses Health Study II."

Assessed biological risk markers were genetic risk score, mammographic density, and

> Our new CAR T cell design allows for more sensitive control the tumour lysis and cytokine release rate, enabling the physician to permanently terminate the cell-killing process as soon as the cancer has been eliminated from the body and avoid sustained off-target toxicity to healthy cells. >10

> The therapy can not only shrink the breast tumour effectively, but potentially reduce the risk of metastasis. This also shows that by replacing older, non targeted therapies with more effective, less toxic ones, we have the potential to both improve outcomes and decrease side effects. >11

> Ipsilateral breast tumour risk was **26%** higher for women who had delayed radiation and **35%** higher for women who did not receive radiation therapy during the first course of treatment. >15

levels of the endogenous hormones testosterone, oestrone sulfate, and prolactin. Each of these markers has been associated with breast cancer risk in multiple studies.

Dr Zhang asserted, "A genetic risk score can summarise in a single number an individual's genetic predisposition to a certain disease outcome (for example, breast cancer in this study) based on multiple risk alleles." He and colleagues calculated a breast cancer genetic risk score based on 67 single-nucleotide polymorphisms identified from a recently published meta-analysis of nine genome-wide association studies.

After stratifying the data by menopausal status, the researchers assessed how the newly added biological factors improved risk prediction for developing invasive breast cancer and oestrogen and progesterone receptor-positive disease (ER+ PR+) over a 5-year period. They measured improvement by calculating area under the curve (AUC), adjusting for age.

The units of AUC span from 50, meaning that a model's ability to predict risk is no better than a coin toss, to 100, meaning that the model's ability to predict risk is perfect.

Of the women whose data were used in the study, about 45% were premenopausal, 25% postmenopausal and not using hormone therapy, and 30% postmenopausal, using hormone therapy.

For postmenopausal women not using hormone therapy, adding genetic risk score, percent mammographic density, and hormone levels to the Gail model improved the AUC by 10.8 units, from 55.2 to 66; for the Rosner-Colditz model, corresponding AUC improved by six units, from 60.2 to 66.2.

To predict the risk of developing ER+ PR+ breast cancer in postmenopausal women not using hormone therapy, adding the biological factors improved the AUC by 11.7 units and 9.4 units for Gail and Rosner-Colditz models, respectively.

Dr Zhang concluded, "Based on 1999–2010 data from the US National Health and Nutrition Examination Survey (NHANES), over 90% of postmenopausal women are not using hormone therapy, thus the larger improvements we saw for this subgroup would apply to the majority of postmenopausal women in the US. An important next step in this research will be to validate these initial findings in other study populations." ■

A neoadjuvant combination therapy may improve outcomes of HER2-positive breast cancer

Results from the I-SPY 2 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And moLecular Analysis) have shown that a neoadjuvant therapy combination of the antibody-drug conjugate trastuzumab emtansine (T-DM1) + pertuzumab was more beneficial than paclitaxel + trastuzumab for women with HER2-positive invasive breast cancer.

Angela DeMichele, MD, MSCE, of the Perelman School of Medicine at the University of Pennsylvania, Philadelphia, explained that in this portion of the I-SPY2 TRIAL, she and her colleagues set out to determine whether T-DM1 + pertuzumab could bring a substantially greater proportion of patients to the primary endpoint of pathological complete response vs paclitaxel + trastuzumab. They also determined whether this combination could meet that goal without the need for paclitaxel.

Dr DeMichele said, "The combination of T-DM1 + pertuzumab graduated from I-SPY 2 in all biomarker signatures tested. Pathological complete response improved substantially for all subgroups of HER2-positive breast cancers compared with those in the control group, and would be likely to succeed in a confirmatory 300-patient, neoadjuvant, phase 3, randomised trial testing this combination against paclitaxel + trastuzumab. "This could, in turn, result in fewer women developing recurrent, metastatic breast cancer without the short- and long-term toxicity of taxane therapy," she added.

Traditional trials have simply added new drugs to the existing regimens, but paclitaxel carries very bothersome and disabling symptoms, including neuropathy, lowered blood counts, and hair loss. "Being able to offer patients a more effective and less toxic regimen would be extremely beneficial to patients' overall prognosis, and their quality of life," noted Dr DeMichele.

"Cancer drug development costs over $2.5 billion, a 12- to 15-year commitment, and the involvement of 1000 to 6000 patient-volunteers to bring one drug to market. Despite this high cost, 60% to 70% of drugs fail or do not complete phase 3 trials," said senior author Laura Esserman, MD, MBA, of the University of California, San Francisco. "The I-SPY approach to clinical trials is designed to reduce the cost, time, and number of patients required, in order to identify active drugs and tumour types most likely to respond and get such drugs to market sooner, as well as to identify inactive drugs that should not be further developed."

Coprincipal I-SPY 2 investigator Donald Berry, PhD, of the University of Texas MD Anderson Cancer Center, Houston, said, "The I-SPY2 TRIAL is a standing platform trial, in which drugs can be evaluated on an ongoing basis, without designing a new trial for each new drug.

This trial platform allows drugs to enter and leave the trial quickly and seamlessly. We use adaptive randomisation to learn faster about better-performing drugs and to treat trial participants more effectively, depending on their tumours' molecular characteristics."

Studies have shown that a combination of T-DM1 and pertuzumab was safe and effective against advanced, metastatic HER2-positive breast cancer. In this trial, the investigators determined whether this combination would also be effective if given earlier in the course of treatment, before surgery.

Using Bayesian probability of superiority vs control, patients whose HER2-positive invasive breast cancers were 2.5 cm or larger were adaptively randomly assigned to 12 weekly cycles of paclitaxel + trastuzumab (control) or T- DM1 + pertuzumab (test). Then they received four cycles of doxorubicin and cyclophosphamide, and surgery.

Tumours were determined to have one of three biomarker signatures: HER2-positive, HER2-positive and hormone receptor (HR)-positive, and HER2-positive and HR-negative.

At the time of assessment, 52 patients remained in the test arm and 31 in the control arm.

The unique statistical method confirmed that, based on pathological complete response data, there is a 90% to 94% chance that T-DM1 + pertuzumab will deliver positive results in a 300- patient phase 3 trial in women with HER2-positive breast cancers with any of the three aforementioned biomarker signatures.

Dr DeMichele concluded, "The data provide a possible new treatment option for patients with newly diagnosed breast cancer. The therapy can not only shrink the breast tumour effectively, but potentially reduce the risk of metastasis. This also shows that by replacing older, nontargeted therapies with more effective, less toxic ones, we have the potential to both improve outcomes and decrease side effects."

She continued, "While these results are promising, a phase 3 confirmatory study is necessary. In addition, since pertuzumab received accelerated approval in the neoadjuvant setting, many patients now receive a taxane with both trastuzumab and pertuzumab [THP]. The THP regimen was also tested in I- SPY2, and was also superior to standard paclitaxel and trastuzumab.

Dr DeMichele added, "Though we found both T-DM1 + pertuzumab and the THP regimen to superior to paclitaxel + trastuzumab, our trial was not designed to compare THP to T-DM1 + pertuzumab directly. The toxicity seen in the TDM-1 + pertuzumab arm, however, was clearly less than with paclitaxel + trastuzumab or THP." ■

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References: 1. Flebogamma® 5% DIF Product Information. January 2012. **2.** Flebogamma® 10% DIF Product Information. 12 February 2013. **3.** National Blood Authority. Criteria for the clinical use of intravenous immunoglobulin in Australia. 2nd Edition, July 2012. **4.** Data on file. **Sponsored by: Grifols Australia Pty Ltd.** Unit 5/80 Fairbank Road, Clayton South VIC 3169, Australia. Tel: +61 3 9535 9333. Fax: +61 3 9535 9300. Email: Australia_info@grifols.com. Date of preparation: March 2016. GRI0004/HON

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MINIMUM PRODUCT INFORMATION

Flebogamma® 5% DIF Human normal immunoglobulin (IVIg)
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INDICATIONS Flebogamma 5% DIF is indicated for: Replacement therapy in: Primary immunodeficiency syndromes such as:- congenital agammaglobulinaemia and hypogammaglobulinaemia - common variable immunodeficiency – severe combined immunodeficiency - Wiskott Aldrich syndrome; myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections; children with congenital AIDS and recurrent infections; Immunomodulation; Idiopathic thrombocytopenic purpura (ITP), in children or adults at high risk of bleeding or prior to surgery to correct the platelet count; Guillain Barré syndrome; allogeneic bone marrow transplantation. **CONTRAINDICATIONS** Hypersensitivity to any of the components. Hypersensitivity to homologous immunoglobulins, especially in very rare cases of IgA deficiency, when the patient has antibodies against IgA. Fructose intolerance. **PRECAUTIONS** Flebogamma® 5% DIF is made from human plasma. As with all plasma derived products, the risk of transmission of infectious agents, including viruses and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated. Special warnings about excipients: This medicinal product contains 50 mg of sorbitol per ml as excipient. Patients with rare hereditary problems of fructose intolerance should not take this medicine. Special precautions should be taken with babies and young children because this fructose intolerance may not yet be diagnosed and may be fatal. Interferences with determination of blood glucose levels are not expected. Certain severe adverse drug reactions may be related to the rate of infusion. The recommended infusion rate given in the Product Information must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period. Certain adverse reactions may occur more frequently: - in case of high rate of infusion - in patients with hypo- or agammaglobulinaemia with or without IgA deficiency - in patients who receive human normal immunoglobulin for the first time, or in rare cases, when the human normal immunoglobulin product is switched or when there has been a long interval since the previous infusion. Caution should be exercised in prescribing and infusing IVIg in obese patients and in patients with pre-existing risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilisation, severely hypovolemic patients, and patients with diseases which increase blood viscosity). Cases of acute renal failure have been reported in patients receiving IVIg therapy. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, concomitant nephrotoxic medicinal products or age over 65. In all patients, IVIg administration requires: - adequate hydration prior to the initiation of the infusion of IVIg - monitoring of urine output - monitoring of serum creatinine levels - avoidance of concomitant use of loop diuretics. In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. Immunoglobulin administration may impair the efficacy of live attenuated virus vaccines and may result in transient misleading positive results in serological testing. Use with caution in pregnant women and breastfeeding mothers. Overdose may lead to fluid overload and hyper viscosity, particularly in patients at risk, including elderly patients or patients with renal impairment. **ADVERSE EFFECTS** Adverse reactions such as chills, headache, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur occasionally. Rarely human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration. Cases of reversible aseptic meningitis, isolated cases of reversible haemolytic anaemia/haemolysis and rare cases of transient cutaneous reactions, have been observed with human normal immunoglobulin. Increase in serum creatinine level and/or acute renal failure have been observed. Very rarely: Thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses. For safety with respect to transmissible agents, see the Product Information. **DOSAGE AND ADMINISTRATION Dosage** In replacement therapy the dosage may need to be individualised for each patient dependent on the pharmacokinetic and clinical response. The following dosage regimens are given as a guideline. *Replacement therapy in primary immunodeficiency syndromes:* The dosage regimen should achieve a trough level of IgG (measured before the next infusion) of at least 4 – 6 g/l. Three to six months are required after the initiation of therapy for equilibration to occur. The recommended starting dose is 0.4 - 0.8 g/kg followed by at least 0.2 g/kg every three weeks. The dose required to achieve a trough level of 6 g/l is of the order of 0.2-0.8 g/kg/month. The dosage interval when steady state has been reached varies from 2 - 4 weeks. Trough levels should be measured in order to adjust the dose and dosage interval. *Replacement therapy in myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections; replacement therapy in children with AIDS and recurrent infections:* The recommended dose is 0.2-0.4 g/kg every three to four weeks. *Idiopathic thrombocytopenic purpura:* For the treatment of an acute episode, 0.8 - 1g/kg on day one, which may be repeated once within 3 days, or 0.4 g/kg daily for two to five days. The treatment can be repeated if relapse occurs. *Guillain Barré syndrome:* 0.4 g/kg/day for 3 to 7 days. *Allogeneic bone marrow transplantation:* Human normal immunoglobulin treatment can be used as part of the conditioning regimen and after the transplant. For the treatment of infections and prophylaxis of graft versus host disease, dosage is individually tailored. The starting dose is normally 0.5 g/kg/week, starting seven days before transplantation and for up to 3 months after transplantation. In case of persistent lack of antibody production, dosage of 0.5 g/kg/month is recommended until antibody level returns to normal. **Method of administration** The product should be brought to room or body temperature before use. The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Flebogamma 5% DIF should be infused intravenously at an initial rate of 0.01-0.02 ml/kg/min for the first thirty minutes. If well tolerated, the rate of administration may gradually be increased to a maximum of 0.1 ml/kg/min. This medicinal product must not be mixed with other medicinal products or intravenous fluids. It should be administered by a separate intravenous line. Product is for single use in one patient only. Discard any residue. Any unused product or waste material should be disposed of in accordance with local requirements. **DATE OF PREPARATION** January 2016, based on Product Information approved January 2012.

MINIMUM PRODUCT INFORMATION

Flebogamma® 10% DIF Human normal immunoglobulin (IVIg)
100 mg/ml – Solution for infusion.

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INDICATIONS Replacement therapy indications: - Primary Immunodeficiency (PI) Diseases - Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment. **Immunomodulation indications:** - Idiopathic Thrombocytopaenic Purpura (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count - Guillain Barré syndrome - Kawasaki disease. **CONTRAINDICATIONS** Hypersensitivity to the active substance or to any of the excipients. Hypersensitivity wto human immunoglobulins, especially in very rare cases of IgA deficiency, when the patient has antibodies against IgA. Hereditary fructose intolerance. **In babies and young children hereditary fructose intolerance may not yet be diagnosed and may be fatal, thus, they should not receive this medicinal product**. **PRECAUTIONS** An apparent increase in the rate of adverse events was observed in clinical trials with Flebogamma 10% DIF compared to Flebogamma 5% DIF. Flebogamma 10% DIF should be infused intravenously at an initial rate of 0.01 ml/kg/min (1 mg/kg/min) for the first thirty minutes. If tolerated, advance to 0.02 ml/kg/min (2 mg/kg/min) for the second 30 minutes. Again, if tolerated, advance to 0.04 ml/kg/min (4 mg/kg/min) for the third 30 minutes. If the patient tolerates the infusion well, additional increments of 0.02 ml/kg/min may be made at 30-minute intervals up to a maximum of 0.08 ml/kg/min (8 mg/kg/min). Special warnings about excipients: This medicinal product contains 50 mg of sorbitol per ml as excipient. Patients with rare hereditary problems of fructose intolerance should not take this medicine. Special precautions should be taken with babies and young children because this fructose intolerance may not yet be diagnosed and may be fatal. Interferences with determination of blood glucose levels are not expected. Infusion/adminstration Certain severe adverse reactions to the medicinal product may be related to the rate of infusion. The recommended infusion rate given in the Product Information must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period. Certain adverse reactions may occur more frequently: - in case of high rate of infusion – in patients with hypo- or agammaglobulinaemia with or without IgA deficiency - in patients who receive human normal immunoglobulin for the first time, or in rare cases, when the human normal immunoglobulin product is switched or when there has been a long interval since the previous infusion. In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. In all patients, IVIg administration requires: - adequate hydration prior to the initiation of the infusion of IVIg - monitoring of urine output - monitoring of serum creatinine levels - avoidance of concomitant use of loop diuretics. Caution should be exercised in prescribing and infusing IVIg in obese patients and in patients with pre-existing risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilisation, severely hypovolemic patients, and patients with diseases which increase blood viscosity). In patients at risk for thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable. In case of renal impairment, IVIg discontinuation should be considered. Haemolytic anaemia. IVIg recipients should be monitored for clinical signs and symptoms of haemolysis. Monitor patients for pulmonary adverse reactions. After injection of immunoglobulin the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing. Flebogamma 10% DIF is made from human plasma. As with all plasma derived products, the risk of transmission of infectious agents, including viruses and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated. Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. Use with caution in pregnant women and breastfeeding mothers. **ADVERSE EFFECTS** Adverse reactions such as chills, headache, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain have been observed. Human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration. Cases of reversible aseptic meningitis, isolated cases of reversible haemolytic anaemia/haemolysis and rare cases of transient cutaneous reactions, have been observed with human normal immunoglobulin. Increase in serum creatinine level and/or acute renal failure have been observed. Very rarely, thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses have been observed with human normal immunoglobulin. For safety with respect to transmissible agents, see Product Information. **DOSAGE AND ADMINISTRATION Dosage** In replacement therapy the dosage may need to be individualised for each patient dependent on the pharmacokinetic and clinical response. The following dosage regimens are given as a guideline. **Replacement therapy indications:** Primary Immunodeficiency (PI) Diseases: The dosage regimen should achieve a trough level of IgG (measured before the next infusion) of at least 4-6 g/l. Three to six months are required after the initiation of therapy for equilibration to occur. The recommended starting dose is 0.4-0.8 g/kg followed by at least 0.2 g/kg every three weeks. The dose required to achieve a trough level of 6 g/l is of the order of 0.2 - 0.8 g/kg/month. The dosage interval when steady state has been reached varies from 2 - 4 weeks. Trough levels should be measured in order to adjust the dose and dosage interval. Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment: The recommended dose is 0.2 - 0.4 g/kg every three to four weeks. **Immunomodulation indications:** Idiopathic thrombocytopenic purpura: For the treatment of an acute episode, 0.8 - 1 g/kg on day one, which may be repeated once within 3 days, or 0.4 g/kg daily for two to five days. The treatment can be repeated if relapse occurs. The product has not been studied in patients diagnosed of acute idiopathic thrombocytopenic purpura. Guillain Barré syndrome: 0.4 g/kg/day for 3 to 7 days. Experience in children is limited. Kawasaki disease: 1.6 - 2.0 g/kg should be administered in divided doses over two to five days or 2.0 g/kg as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid. **Method of administration** The product should be brought to room or body temperature before use. This medicinal product must not be mixed with other medicinal products or intravenous fluids. It should be administered by a separate intravenous line. Product is for single use in one patient only. Discard any residue. Any unused product or waste material should be disposed of in accordance with local requirements. **DATE OF PREPARATION** January 2016, based on Product Information approved January 2013.

Pembrolizumab shown to yield durable responses in advanced Merkel cell carcinoma

Many patients with advanced Merkel cell carcinoma, an aggressive type of skin cancer, who received pembrolizumab as first-line therapy, achieved a durable response.

Paul Nghiem, MD, PhD, of the University of Washington School of Medicine, Seattle, explained that Merkel cell carcinoma is rare, and Merkel polyomavirus (MCPyV) is its driving factor in about 80% of cases. About 2000 new cases are diagnosed in the US annually. Merkel cell carcinoma is 35-fold less common than melanoma, but on average, about three times more likely to kill a patient than melanoma. Response to chemotherapy is typically brief and half of patients develop progressive disease within 3 months of initiating treatment, he added.

> "Patients with metastatic Merkel cell carcinoma who received pembrolizumab had an objective response rate of 56%, which is similar to chemotherapy outcomes, but the duration of response to pembrolizumab appears to be significantly longer than that for chemotherapy.

Dr Nghiem and colleagues enrolled 26 patients with advanced/metastatic Merkel cell carcinoma who had received no prior systemic therapy, Seventeen had MCPyV-positive disease. All received 2 mg per kilogram body weight of pembrolizumab every 3 weeks and responses were assessed every 9 to 12 weeks. At the time of data analysis, patients had received 4 to 49 weeks of therapy.

The overall response rate was 63% in patients with virus-positive and 44% in those with virus-negative (ultraviolet-induced) Merkel cell carcinoma. Four patients, three with virus-positive disease, had complete responses, and 10 patients, seven with virus-positive disease, had partial responses.

Dr Nghiem said, "Patients with metastatic Merkel cell carcinoma who received pembrolizumab had an objective response rate of 56%, which is similar to chemotherapy outcomes, but the duration of response to pembrolizumab appears to be significantly longer than that for chemotherapy. While the study is still ongoing, the vast majority of patients (86%) who responded to pembrolizumab are still experiencing excellent disease control more than 6 months after starting therapy."

Adverse events were similar to other anti-programmed death (PD)-1 trials and were largely managed with steroid treatment and stopping the study drug. Two patients who developed severe drug-related toxicities improved with corticosteroid treatment and discontinuation of pembrolizumab. Dr Nghiem noted, "Importantly, both these patients have ongoing antitumour responses many months after discontinuation of pembrolizumab. We believe the immune system is likely 'seeing' different targets in virus-positive and virus-negative patients."

He explained that the virus-positive tumours produce viral proteins needed for tumours to grow. These viral proteins may be readily seen by the immune system. In contrast, virus-negative Merkel cell carcinoma harbours extremely high numbers of mutations caused by sunlight. These mutations can alter normal cellular proteins such that they no longer appear as "self." The immune system can then recognise and attack these tumours.

He added, "There are no FDA-approved drugs for Merkel cell carcinoma. We are expanding this trial to recruit additional patients and hope these data will contribute to meaningful new therapeutic options for these patients." ■

JOURNAL SCAN

Pembrolizumab for advanced Merkel cell carcinoma

The New England Journal of Medicine

Take-home message

- This was a multicentre, phase II, non-controlled study including 26 patients with advanced Merkel cell carcinoma designed to assess the safety and efficacy of pembrolizumab. In total, 4 patients had a complete response, and 10 had a partial response, making the objective response rate 56%. The rate of progression-free survival at 6 months was 67%. Drug-related grade 3 or 4 adverse events were reported in 15% of the patients.
- Treatment of advanced Merkel cell carcinoma with first-line pembrolizumab resulted in an objective response rate of 56%.

Jeremy Jones, MD

BACKGROUND Merkel-cell carcinoma is an aggressive skin cancer that is linked to exposure to ultraviolet light and the Merkel-cell polyomavirus (MCPyV). Advanced Merkel-cell carcinoma often responds to chemotherapy, but responses are transient. Blocking the programmed death 1 (PD-1) immune inhibitory pathway is of interest, because these tumours often express PD-L1, and MCPyV-specific T cells express PD-1.

METHODS In this multicenter, phase 2, noncontrolled study, we assigned adults with advanced Merkel-cell carcinoma who had received no previous systemic therapy to receive pembrolizumab (anti–PD-1) at a dose of 2 mg per kilogram of body weight every 3 weeks. The primary end point was the objective response rate according to Response Evaluation Criteria in Solid Tumours, version 1.1. Efficacy was correlated with tumour viral status, as assessed by serologic and immunohistochemical testing.

RESULTS A total of 26 patients received at least one dose of pembrolizumab. The objective response rate among the 25 patients with at least one evaluation during treatment was 56% (95% confidence interval [CI], 35 to 76); 4 patients had a complete response, and 10 had a partial response. With a median follow-up of 33 weeks (range, 7 to 53), relapses occurred in 2 of the 14 patients who had had a response (14%). The response duration ranged from at least 2.2 months to at least 9.7 months. The rate of progression-free survival at 6 months was 67% (95% CI, 49 to 86). A total of 17 of the 26 patients (65%) had virus-positive tumours. The response rate was 62% among patients with MCPyV-positive tumours (10 of 16 patients) and 44% among those with virus-negative tumours (4 of 9 patients). Drug-related grade 3 or 4 adverse events occurred in 15% of the patients.

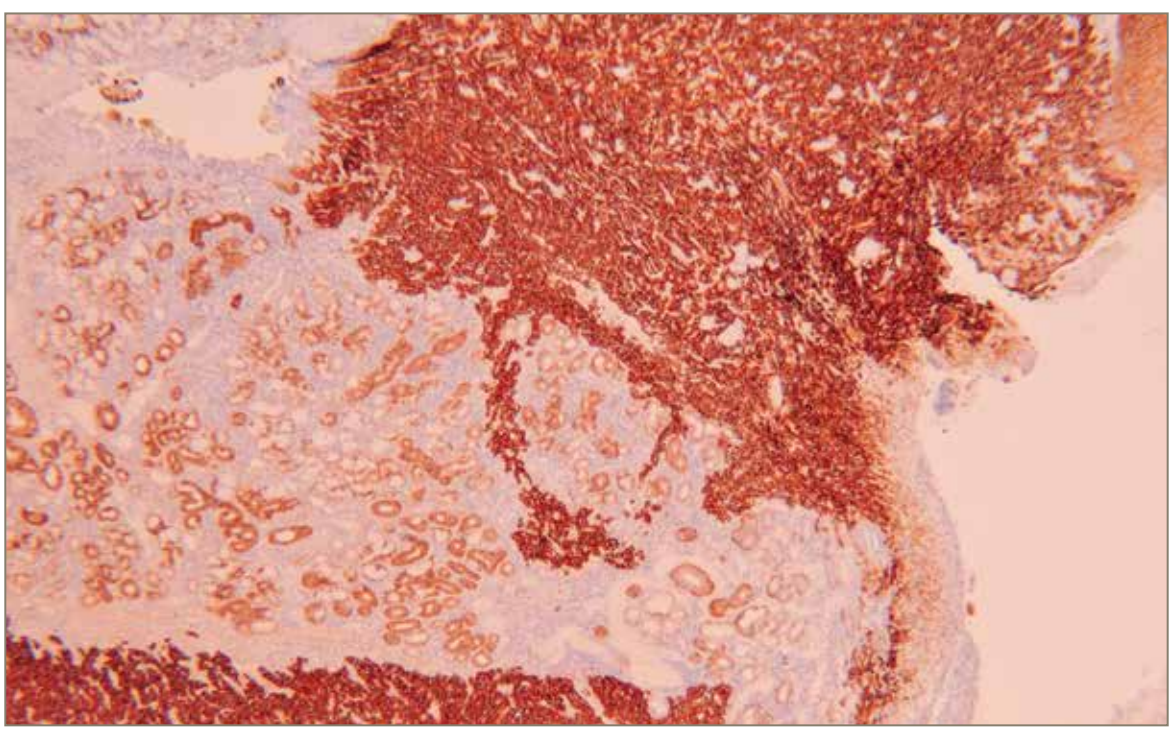
CONCLUSIONS In this study, first-line therapy with pembrolizumab in patients with advanced Merkel-cell carcinoma was associated with an objective response rate of 56%. Responses were observed in patients with virus-positive tumours and those with virus-negative tumours.

PD-1 Blockade With Pembrolizumab in Advanced Merkel-Cell Carcinoma
N Engl J Med 2016 Apr 19;[EPub Ahead of Print], PT Nghiem, S Bhatia, EJ Lipson, et al.

Nivolumab shown to improve survival in head and neck squamous cell carcinoma

Treatment with the immunotherapeutic nivolumab improved survival in recurrent or metastatic head and neck squamous cell carcinoma that progressed after platinum-based chemotherapy vs single-agent chemotherapy.

Maura L. Gillison, MD, PhD, of the Ohio State University Comprehensive Cancer Center, Columbus, explained, "Recurrent or metastatic head and neck squamous cell carcinoma that is not responsive to platinum-based chemotherapy progresses very rapidly, and patients have a very poor prognosis. Treatment usually involves single-agent chemotherapy. Yet no therapy has been shown to improve survival in this patient population. New treatment options are desperately needed."



She continued, "This study was the first randomised clinical trial to clearly demonstrate improved overall survival for patients with platinum-refractory recurrent or metastatic head and neck squamous cell carcinoma. We hope the results will establish nivolumab as a new standard-of-care option for this patient population and thereby fulfil a huge unmet need."

CheckMate-141 was designed to determine whether the programmed death (PD) – 1 inhibitor nivolumab could extend overall survival in patients with platinum-refractory recurrent or metastatic head and neck squamous cell carcinoma vs treatment of the investigator's choice, which was docetaxel, methotrexate, or cetuximab.

Of the 361 enrolled patients, 240 were randomised to nivolumab and 121 to single-agent chemotherapy of investigator's choice.

At the interim analysis, which was conducted after 218 events, patients assigned to nivolumab were found to have a 30% reduced risk of death vs those assigned therapy of investigator's choice. Median overall survival was 7.5 months for those assigned nivolumab vs 5.1 months for those assigned therapy of investigator's choice. At 12 months, 36% of patients treated with nivolumab were alive vs 17% of those assigned therapy of investigator's choice.

For patients assigned to nivolumab, the overall response rate as defined by Response Evaluation Criteria in Solid Tumours 1.1 criteria was 11.7%, with six complete responses and 22 partial responses, and for those assigned therapy of investigator's choice, the overall response rate was 7.4%, with one complete and eight partial responses.

Certain types of head and neck squamous cell carcinoma, particularly those arising in the oropharynx (back of the throat, including the base of the tongue and tonsils), have been linked with human papillomavirus (HPV) infection, so Dr Gillison and her team evaluated the data based on tumour HPV status.

The effect of nivolumab on overall survival was seen in both patients with HPV-positive and -negative disease. Among patients with HPV-positive disease, median overall survival was 9.1 months for those assigned to nivolumab vs 4.4 months for those assigned to therapy of investigator's choice. Among patients with HPV-negative disease, median overall survival was 7.5 months for those assigned to nivolumab vs 5.8 months for those assigned to therapy of investigator's choice.

A survival benefit for nivolumab was observed for the overall study population. Exploratory analysis suggested that the benefit was greater for patients treated with nivolumab whose tumours had PD-ligand 1 expression of ≥1% or were HPV-positive.

Dr Gillison concluded, "Overall, our data are extremely exciting. This clinical trial has established that head and neck squamous cell carcinoma responds to immunotherapy. We hope this represents the tip of the iceberg with regard to the benefit of immunotherapy in patients with head and neck squamous cell carcinoma." ■

Physical activity may improve prostate cancer prognosis

Prostate cancer patients and survivors who maintain a moderate to high level of physical activity may improve their survival prognosis.

Ying Wang, PhD, of the American Cancer Society, Atlanta, Georgia, explained, "Our results support evidence that prostate cancer survivors should adhere to physical activity guidelines, and suggest that physicians should consider promoting a physically active lifestyle to their prostate cancer patients."

Research has indicated that vigorous physical exercise could reduce the risk of prostate cancer-specific mortality. Dr Wang said her group's study showed that the reduced risk of prostate cancer-specific mortality is associated with moderate to vigorous activity both before and after prostate cancer diagnosis.

Additionally, the study evaluated the impact of "sitting time," which includes sedentary activities such as sitting or driving in vehicles, watching TV, and reading, and found that it was not associated with prostate cancer-specific mortality.

Dr Wang and colleagues evaluated data from 10,067 men who were part of the Cancer Prevention Study II Nutrition Cohort. All the men had been diagnosed with nonmetastatic prostate cancer between the time they were enrolled (1992 or 1993) and 2011. Ages at the time of diagnosis ranged from 50 to 93 years. During the study period, 600 men died of prostate cancer.

The men reported the amount of time they spent sitting and engaged in recreational physical activity. Physical activity included walking, dancing, bicycling, aerobics, jogging or running, lap swimming, tennis, and racquetball. The researchers calculated metabolic equivalent hours per week of activity based on the men's reporting.

Researchers evaluated the men's activity both before and after receiving a diagnosis of prostate cancer, and found similar benefits. After controlling for multiple factors including age at diagnosis, those who exercised ≥17.0 metabolic equivalent hours weekly (equivalent to twice the minimum physical activity recommendations) before receiving their diagnosis had a 30% lower risk of prostate cancer-specific mortality than those who exercised < 3.5 metabolic equivalent hours weekly (equivalent to <1 h of moderately paced walking weekly).

When evaluating post-diagnostic recreational physical activity, researchers found that the men who exercised the most had a 34% lower risk of dying of the disease than those who exercised the least. Additionally, patients benefited whether they were maintaining physical activity or increasing their prediagnosis activity level after receiving a diagnosis of prostate cancer.

> "When evaluating post-diagnostic recreational physical activity, researchers found that the men who exercised the most had a 34% lower risk of dying of the disease than those who exercised the least.

Dr Wang said, "The American Cancer Society recommends adults engage in a minimum of 150 minutes of moderate or 75 minutes of vigorous physical activity weekly. These results indicate that following these guidelines might be associated with better prognosis." She added that further research could determine whether the results differ by age at diagnosis, body mass index, and smoking.

Dr Wang and colleagues also looked at the benefit of walking as the only form of physical activity, since about 40% of patients in the study said walking was their only form of recreational physical activity. Walking for 4 to 6 hours weekly before diagnosis was associated with a 33% lower risk of prostate cancer-specific mortality. Walking for ≥7 hours weekly was associated with a 37% lower risk. No statistically significant association was observed with walking after diagnosis.

Dr Wang said a limitation of the study is that subjects reported their own physical activity and sitting time data. Self-reported data is subject to errors in reporting and recall. Also, the study did not investigate the impact of vigorous exercise separately, though other research has suggested that vigorous exercise is associated with lower risk of prostate cancer-specific mortality. ■

Certain oral bacteria are associated with increased pancreatic cancer risk

The presence of two species of bacteria linked to periodontal disease in the mouths of healthy individuals was associated with an increased risk of subsequently developing pancreatic cancer.

Jiyoung Ahn, PhD, of New York University Langone Medical Center, explained, "Studies have shown that indicators of poor oral health, including a history of periodontal disease and numerous missing teeth, are associated with an increased risk of pancreatic cancer. To test the idea that this association is driven by species of oral bacteria linked to periodontal disease, we first needed to determine whether these bacteria are even associated with pancreatic cancer risk."

Dr Ahn continued, "We found that *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*, two species of bacteria linked to periodontal disease, were associated with >50% higher risk of pancreatic cancer. The data do not show a causal relationship, but they are the first steps in understanding a potential new risk factor for pancreatic cancer, which is vital if we are to develop new approaches for pancreatic cancer prevention and early detection."

Dr Ahn and Xiaozhou Fan, BS, and colleagues used samples and data from the Cancer Prevention Study II and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial cohorts. Both these cohorts enrolled healthy people and followed them over a long period for a variety of outcomes, including development of cancer.

The researchers analysed oral wash samples collected at study enrolment from 361 people who later developed pancreatic cancer and 371 matched controls. They used genomic technologies to generate a profile of the bacterial species present in each sample and performed logistic regression analysis to calculate the association between individual bacterial species and pancreatic cancer risk, controlling for other risk factors, including age, smoking status, and body mass index.

The presence of *P. gingivalis* in oral wash samples was associated with a 59% increased risk of pancreatic cancer. The presence of *A. actinomycetemcomitans* was associated with a 119% increased risk. Risks remained even after excluding samples from people who developed pancreatic cancer within 2 years of collection of their oral wash samples, which increased confidence in the identified associations.

Dr Ahn said, "About 1.5% of US men and women will be diagnosed with pancreatic cancer. Only 5%, however, survive 5 years or more after diagnosis. New approaches to pancreatic cancer prevention and early detection are urgently needed. Though our new findings cannot be directly translated into such approaches, if confirmed in additional studies, they could point to new ways to screen for the disease. If the associations are found to be causal, they could point to potential prevention approaches."

Dr Ahn noted that a major limitation of the study was that the population studied was predominantly non-Hispanic white and healthy – not diverse. The results might not be generalisable to the population at large. ■

Delays in radiation therapy for DCIS raise risk of tumour development

Women who underwent treatment for ductal carcinoma in situ (DCIS) were at higher risk of developing malignant breast tumours if they did not receive timely radiation therapy as part of their treatment.

Ying Liu, MD, PhD, of Washington University School of Medicine, St. Louis, Missouri, explained that DCIS is the most common premalignant breast lesion, with over 60,000 women diagnosed each year. Not all DCIS will develop into invasive cancer, but it is difficult to predict which cases will become cancerous, so most women diagnosed with DCIS opt to treat it.

"According to the National Comprehensive Cancer Network guidelines, primary treatment options for DCIS include breast-conserving surgery plus radiation, total mastectomy, and breast- conserving surgery alone. Our study showed that it is important for women to understand the benefits of timely radiation therapy after breast-conserving surgery."

Dr Liu and colleagues identified 5916 women in the Missouri Cancer Registry who were diagnosed with first primary DCIS between 1996 and 2011 and treated with breast-conserving surgery.

> "...primary treatment options for DCIS include breast-conserving surgery plus radiation, total mastectomy, and breast- conserving surgery alone. Our study showed that it is important for women to understand the benefits of timely radiation therapy after breast-conserving surgery.

Of those women, 1053 (17.8%) received radiation therapy 8 or more weeks after surgery, defined as a delay. Also, 1702 (28.8%) did not receive radiation therapy during the first course of treatment. The remaining 53.4% received radiation within 8 weeks of surgery.

During the 72-month follow-up period, 3.1% of women developed an ipsilateral breast tumour. After adjustment for propensity scores based on factors such as age, race, tumour size, and tumour grade, ipsilateral breast tumour risk was 26% higher for women who had delayed radiation and 35% higher for women who did not receive radiation therapy during the first course of treatment. Delays were more likely for certain groups

Dr Liu and the investigators identified several groups who were significantly affected by delays in radiation therapy. African-American women, single women, those covered by Medicaid, those whose DCIS tumours were larger, and those who were diagnosed more recently were all more likely to have received delayed treatment.

Dr Liu said, "Among these groups, African-American women, those covered by Medicaid, and those with a large DCIS were at higher risk of recurrence. Timeliness of radiation therapy should be improved."

Study data did not fully explain reasons for delay among certain groups, but Dr Liu said the quality and accessibility of healthcare providers and facilities could have been a possible cause. She added that further research could provide insight into factors influencing delays and help identify ways to encourage women to receive radiation therapy soon after DCIS surgery.

Dr Liu said a limitation of the study was that during the average 72 months of follow-up time, only a small number of subjects developed ipsilateral breast tumours.

She said, "Our preliminary finding needs to be confirmed in a large cohort of DCIS patients with a longer follow-up. Future studies should also address the contributions of patient choice, healthcare providers, facilities, and neighbourhoods to therapy delay." ■

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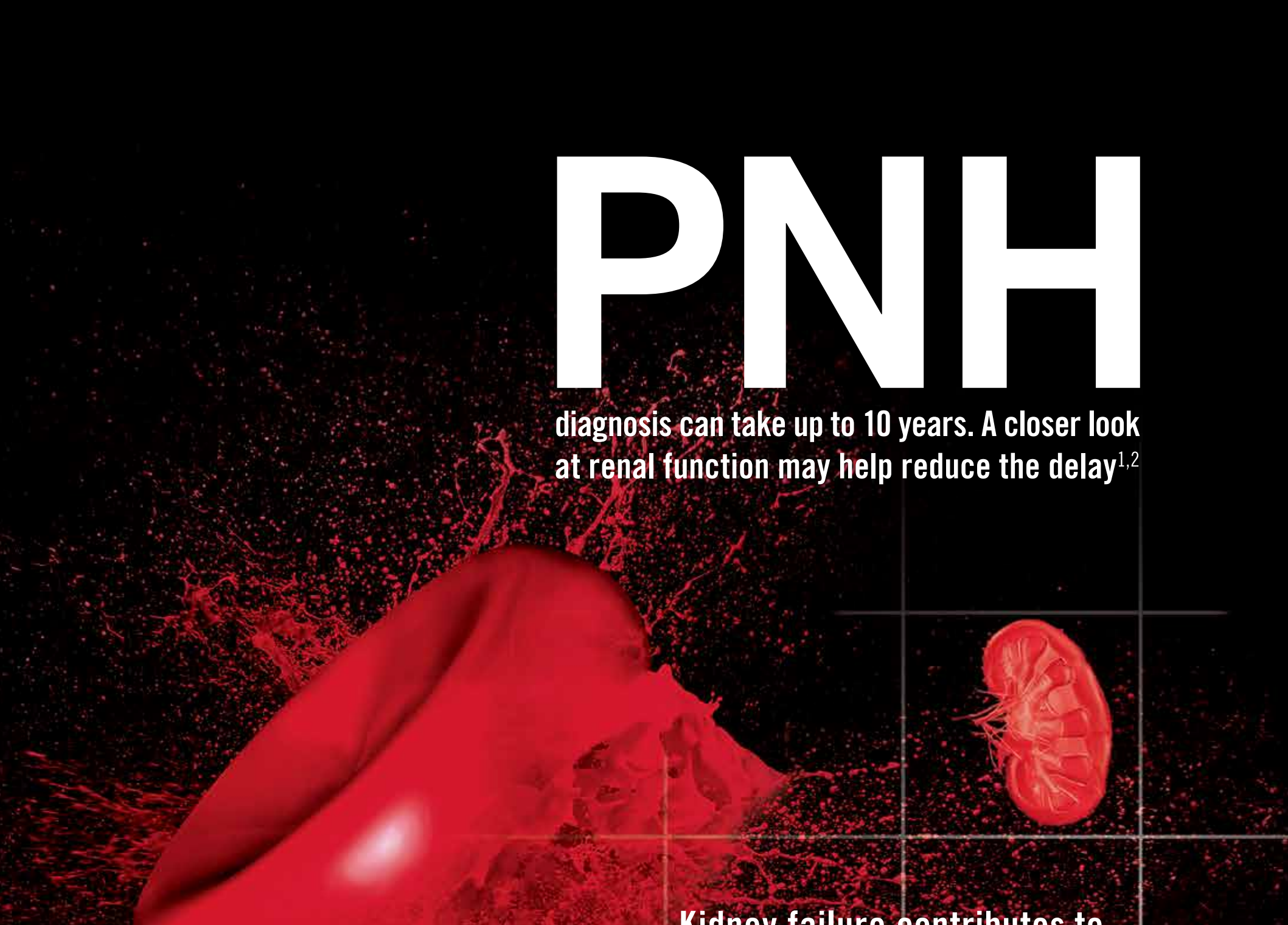
diagnosis can take up to 10 years. A closer look at renal function may help reduce the delay[1,2]



Kidney failure contributes to 8-18% of PNH related deaths [2,3]

- The complement-mediated haemolysis characteristic of PNH leads to cell-free plasma haemoglobin and, as a result, damage to patients' kidneys [2,4,5]
- Kidney failure is the cause of 8-18% of PNH-related deaths [2,3]

With early treatment, renal function improvement or stabilisation was achieved in 93.1% of PNH patients [5]

The early diagnosis and treatment of PNH helps save lives [2,5]

To find out more phone 1800 788 189 or visit identifyingpnh.com.au

PNH = Paroxysmal Nocturnal Haemoglobinuria.

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ALEXION