THE WALNUT

MARCH 2018

Newsletter of the Prostate Cancer Support Group—ACT Region

Affiliated with the Prostate Cancer Foundation of Australia (PCFA)
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Next monthly meeting

Our next monthly meeting will be on **Wednesday 21 March**.

On this occasion, we will be visiting the John Curtin School of Medical Research at the Australian National University. We will have a presentation from Professor Ross Hannan, Centenary Chair in Cancer Research and Head of the ACRF Department of Cancer Biology and Therapeutics. This will be followed by a tour of the research laboratories and our monthly meeting.

We will gather at **6:45 pm at the School, which is located at 131 Garran Road** at the ANU.

No notice is required. However, on this occasion, it would be helpful if you could advise John Hayhoe (email: treasurer@prostate-cancer-support-act.net) if you plan to attend. This will enable us to give the ANU an indication of the number of people who plan to attend and a list of people entering the building.

All are welcome to attend our regular monthly meetings and coffee mornings, including partners and carers.

Next coffee morning

10:00 am, Tuesday, 13 March, Canberra Southern Cross Club, Woden.

President's Message

What a wonderful presentation we had from Dr Grant Buchanan in February! It is clear that we will have to invite Grant to address us again soon, as he obviously only touched the surface of the many informative things he has to tell us. Thanks, Grant, for your great presentation.

This month we have a lot going on. Our meeting is being held at the John Curtin School of Medical Research, not at Pearce. We look forward to gaining a good insight into the research the School is doing into cancer, including prostate cancer. Hopefully we will also gain a better understanding of the direction of research into prostate cancer around the world.

On Thursday 15 March, we will be represented at the Seniors Week Expo at Exhibition Park and, a few days later on Sunday 18 March, we will be represented at the Royalla Country Fair. We see these as good opportunities to increase awareness in the community of the need for men to have regular checks of their prostate health and of the role of the Prostate Cancer Support Group in helping men who have been diagnosed with prostate cancer. If you are able to assist at either of these events, please email me on president@prostate-cancer-support-act.net.

If you haven't already attended one of our coffee mornings, why not join us? They are most enjoyable. These are held on the second Tuesday of each month and we alternate them between the Woden and Jamison venues of the Canberra Southern Cross Club so that people who live on both sides of Canberra are able to join us from time to time. The next coffee morning will held at Woden on Tuesday 13 March.

John McWilliam

Appreciation

The Group recognises and expresses its appreciation for the support provided by: the PCFA, SHOUT staff, the Canberra Southern Cross Club, Holy Family School Gowrie, ACT Veterans' Hockey Association Inc, Paddywack Promotional Products, the Naval Association of Australia, German Auto Day and the many individuals who have assisted in our fund-raising activities.

Personal support

For general information, please call SHOUT (Self Help Organisations United Together) during normal office hours on (02) 6290 1984, and their staff will arrange for someone to contact you. After hours, please call 0490 784 151.

If you would like immediate advice, support or assistance, please contact one of the following two people:

President: John McWilliam
Phone: 0416 008 299
Email: president@prostate-cancer-support-act.net

Secretary: David Hennessy
Phone: (02) 6154 4274
Email: secretary@prostate-cancer-support-act.net

Are you able to help?

We are looking for volunteers for our booths at:

- the Seniors Week Expo on Thursday, 15 March; and
- the Royal Country Fair on Sunday, 18 March.

If you can help, please email John McWilliam at: president@prostate-cancer-support-act.net

Our February Meeting

Five new members and some partners attended the February meeting. They included people who had recently been diagnosed with prostate cancer and were being treated or their condition was under active surveillance, and a man who had had a prostatectomy some years previously, but whose PSA was now rising again.

Our speaker for this meeting was Dr Grant Buchanan, Registrar, Radiation Oncology at the Canberra Hospital and Senior Research Fellow at the ANU School of Health and Medicine. Dr Buchanan answered questions during his talk, which was longer than normal because of intense interest by members. His talk would have been of great assistance to our new members because of the thoroughness and clarity of his presentation and his willingness to take many questions.

Dr Buchanan being thanked by President John McWilliam for his interesting presentation

Dr Buchanan explained that:

- The prostate gland gives fluidity to sperm in an ejaculate and prostate cancer disrupts this action. It has a glandular structure (similar to grapes) with each micro gland producing prostate specific antigen (PSA). When the structure is broken, PSA leaks into the blood where a rise is detected from blood sampling.

- Around 20,000 new cases of prostate cancer are diagnosed each year in Australia, with a death rate of 3,600 annually from the cancer. However, great strides have been made in increasing survival rates in Australian men. In 1982 the 5–year survival rate was 58% – by 2016 it was 90%.

- There is a strong hereditary factor. If one, first-degree relative has prostate cancer, the risk of that man getting prostate cancer is 2.5 times greater. If two, first-degree relatives have prostate cancer the risk is 3.5 times greater.

- Dr Buchanan listed the risk factor of developing prostate cancer from PSA levels (µg/L) as follows:
  - <10 low risk
  - 10-20 Intermediate
  - 20-100 High
  - >100 poor survival diagnosis.

- In PCA diagnoses, a Clinical Status Model is set–up, based on TNMR, as follows:
  - **Tumour**, (T1- T4) with T3 still in the Pg but T3b indicates invasion into the seminal vesicles, and T4 into other tissues.
  - **Nodes**, Nx no detection, N0 some presence, N1 metastasised.
  - **Metastases**, M0 none, M1a in lymph, M1b in bones and M1c in other tissues.
  - **Reaction**, R0 no metastatic cells, R1, micro-metastatic cells.

- Disease prognosis is also based on a grouping according to the Gleason Score, viz Gp1 is a Gleason < 6, Gp 2 is a 3+4, Gp 3 is a 4+3, Gp 4 is 8 and Gp 5 is 10.

- In general there are four treatment strategies for those diagnosed with prostate cancer:
  - active surveillance;
  - hormone (ADT) treatment;
  - surgery; and
  - radiotherapy.

- Active surveillance is recommended for those with Gleason < 6.
  - ADT (hormone) is initially effective in lowering prostate cancer but is not curative.
  - Surgery depends on whether or not the prostate cancer has metastasised (PSMA-PET scans are increasingly been used to help detect any spread of the cancer); and
  - radiotherapy can be considered before or after metastasising has been detected.

- Radiotherapy has different forms – low (or high) density brachytherapy or external beam radiotherapy (ERBT). For Intermediate risk patients (Gleason 3+4), the choices are: surgery, EBRT or androgen deprivation therapy (ADT). For high risk (Gleason 8-10) patients the choices are Surgery, high dose rate brachytherapy, or EBRT and proximal salvage radiotherapy.

- Surgery is generally not possible after radiotherapy (because the radiotherapy damages the tissue). However, the radiotherapy would have killed off the prostate cancer in the prostate gland and so surgery would not be a viable option anyway in these circumstances.

February and March Executive Committee Meetings

The Executive Committee met on 7 February and 7 March. At these meetings, the Committee, among other things:

- reaffirmed its decision to commence discussions with SHOUT on administrative support for outreach activities;

- agreed to have an exhibit at this year's Seniors Week Expo on Thursday, 15 March at Exhibition Park and to trial some new approaches on this occasion to make the exhibit more

appealing.This was in addition to the exhibit at the Royalla Country Fair, which had previously been endorsed;

- agreed to advertise meetings in the Canberra Times/Chronicle where meetings are being held at Pearce;
- agreed to ask PCFA for support in producing display materials about prostate cancer that can be used in exhibits. We did this, and the PCFA have agreed to develop suitable materials for the use of all support groups;
- trial the provision of iced water for a gold coin donation and lollies (e.g. mints) at outreach displays to help encourage men to approach or displays;
- discussed arrangements for the visit to the John Curtin School of Medical Research and other future meetings; and
- noted that the Treasurer has submitted documentation to the Australian Taxation Officer for a change of name and Australian Business Number.

Stay up-to-date

Stay up-to-date by joining the PCFA Online Community. The PCFA Online Community is open to everyone who has been impacted by prostate cancer to share their experiences and connect with others. Through the Research Blog, PCFA Online Community members can also learn more about the latest prostate cancer research developments and findings.

It is free and easy to become a member of the PCFA Online Community. You can sign up at: http://onlinecommunity.pcfa.org.au .

The March PCFA *Community Digest* includes articles on:

- prostate cancer in women (there are at least ten documented cases of prostate cancer in women);
- the challenges of biomarker development;
- new treatments for men with non-metastatic castration resistant prostate cancer; and
- new progress in the development of liquid biopsies for prostate cancer.

Borrowing items from the library

You can borrow items from the Group's library. There is a wide range of materials, from books to videos. Those who are interested in borrowing items from the library or finding out more about our collection can contact U.N. Bhati, email: librarian@prostate-cancer-support-act.net

Articles and reports of interest

The following articles which have appeared recently on web sites or other sources may be of interest to some members. Any opinions or conclusions expressed are those of the authors. See Disclaimer below. With thanks to Don Bradfield and Mike Boesen for their assistance with this segment.

Low PSA on ADT remains prognostic in new treatment era

Authors:	Lauren C. Harshman and Christopher J. Sweeney, et al
Original article title:	Seven-month Prostate-Specific Antigen Is prognostic in metastatic hormone-sensitive prostate cancer treated with androgen deprivation with or without Docetaxel
Journal:	Journal of Clinical Oncology, 36, No. 4
Date:	February 2018
View article at:	https://tinyurl.com/yd8lxfvv

Medscape (Nick Mulcahy, 23 January 2018, http://tinyurl.com/y97tsl9w) reports on the above article.

A low prostate specific antigen (PSA) value continues to be a helpful prognostic marker in the setting of hormone sensitive metastatic prostate cancer, even as standard treatment evolves, according to a retrospective analysis undertaken by the research authors mentioned above.

Among oncologists and urologists, it is well known that a PSA level of 0.2 ng/mL or less in these men at 7 months after the initiation of androgen deprivation therapy (ADT) portends a significantly longer survival than seen in men with PSA values above this cutoff point. But that insight comes from a study published more than 10 years ago, the Southwest Oncology Group 9346 trial (J ClinOncol, 2006;24: 39843990). At that time, ADT alone was the mainstay of treatment. But times and treatments change.

Now, thanks to findings from the more recent CHAARTED and STAMPEDE trials, many of these patients receive chemotherapy with docetaxel in addition to ADT, especially if they have high volume metastatic disease. Both of these major trials showed significantly improved overall survival when chemotherapy was added to androgen blockade in advanced prostate cancer. But it has not been known, in the current treatment era, whether the PSA biomarker remained prognostic when docetaxel was added to ADT. So the CHAARTED investigators performed a retrospective "landmark survival analysis" at seven months using the database from their trial.

They conclude that "PSA ≤ 0.2 ng/dL at 7 months is prognostic for longer overall survival with ADT for metastatic hormone sensitive prostate cancer irrespective of docetaxel administration."

The addition of docetaxel increased the likelihood of achieving a PSA level of 0.2 ng/dL or less at 7 months (45.3% vs 28.8% of patients receiving ADT alone). However, the patients who had the best median overall survival in the study (72.8 months) were those receiving ADT alone who achieved a 7-month PSA level of 0.2 ng/dL or less. (These men were also more likely to have low-volume disease, at 56.7%).

Dr Harshman and Dr Sweeney pointed out that the timing of receipt of docetaxel was variable in the study. Notably, they also observed that "getting docetaxel around the time of ADT initiation increased the chances of achieving this good prognostic feature, and there was evidence patients may have been more likely to achieve this endpoint, the closer the docetaxel was given to the ADT start."

However, the pair cautioned clinicians not to make too much of the new findings in terms of making upfront treatment decisions. "While intriguing, given the study's retrospective nature, clinicians should not make treatment decisions based on the PSA level at 7 months (eg, defer adding docetaxel based on the 7 month PSA level)," they said.

They also said that: "Our results are prompting many questions about whether these patients would benefit from therapy intensification prior to PSA or radiologic progression with the newer androgen-receptor targeted agents. These newer agents include abiraterone acetate (Zytiga, Janssen) and enzalutamide (Xtandi, Astellas).

New approaches to drug therapy in prostate cancer

(a) The Spartan study

Authors:	M R Smith, F Saad, S Chowhury, et al for the SPARTAN investigators
Original article title:	Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer
Journal:	New England Journal of Medicine
Date:	8 February 2018
View article at:	https://tinyurl.com/yd8lxfvv

Fred Mulcahy in Medscape provides a report on the findings of the SPARTAN study (https://tinyurl.com/ybjeenpd).

Long-needed change appears to be coming to the management of a group of prostate cancer patients for whom there is no apparent standard of care – men with early-stage disease whose prostate-specific antigen (PSA) score is rapidly rising after surgery or radiotherapy despite androgen-deprivation therapy (ADT).

There are currently no approved treatments for these men, who are destined to develop metastatic disease and are at increased risk of death. Now, two phase 3, placebo-controlled clinical trials have shown that there are drugs that significantly delay the onset of metastasis in these patients.

The trials feature two different androgen-receptor inhibitors that are orally administered.

The SPARTAN trial employed the next-generation investigational agent apalutamide (Janssen Biotech). The PROSPER trial employed the earlier-generation enzalutamide (Xtandi, Astellas/Pfizer), which is already approved for men who have metastatic prostate cancer.

Both trials showed that in the treatment of men with non-metastatic castrate-resistant prostate cancer, daily administration of the respective agents reduced the relative risk for metastasis or death by more than 70% and prolonged metastasis-free survival (MFS) by more than 20 months compared to placebo. All patients, in both the treatment and placebo arms, also received ADT.

Both trials enrolled men who had undergone definitive treatment, either surgery or radiotherapy, for prostate cancer but whose PSA scores subsequently double within 10 months or less, despite ADT. For each trial, MFS was the primary endpoint. Each trial showed a trend toward improved overall survival in an early interim analysis.

In the 1207-patient SPARTAN trial, apalutamide decreased the risk for distant metastasis or death by 72% (hazard ratio [HR] = 0.28; 95% confidence interval [CI], 0.23 - 0.35; P < .0001), with a median MFS of 40.5 vs 16.2 months in the placebo group (an improvement of 24.3 months). Median follow-up was 20.3 months.

"These data suggest that apalutamide should be considered as a new standard of care for men with high-risk non-metastatic castrate-resistant prostate cancer," lead study author Eric J. Small, MD, professor of medicine at the University of California, San Francisco, was reported as saying.

Another report on the SPARTAN trial (by Brian Furlow) can be found in the *Cancer Network* – home of the Journal Oncology (see http://tinyurl.com/ycdlbj56).

(b) Use of abiraterone

A report on a separate study published in the *Lancet* on 8 January 2018 was published by Pam Harrison – *QOL Data Reassuring for Abiraterone in Prostate Cancer* - Medscape - Jan 24, 2018.

Results from the previous LATITUDE trial have shown that adding abiraterone (Zytiga, Janssen) and prednisone to androgen deprivation therapy (ADT) improves overall survival when compared with ADT alone in men with newly diagnosed, high-risk metastatic, castration-naive prostate cancer.

Now this new analysis shows that the combination treatment also consistently improves pain, fatigue, and overall quality of life.

The study authors, led by Kim Chi, MD, associate director, clinical research, Vancouver Prostate Centre, British Columbia, Canada, comment that: "The improvements in both survival and HRQOL shown in the LATITUDE trial suggest that treatment with ADT plus abiraterone acetate and prednisone could be considered a new standard-of-care option for patients with metastatic castration-naive prostate cancer."

(c) Advanced prostate cancer in 2018 — a look ahead

The following is taken from an article by Gautam Jayram MD and David S Morris MD on the treatment of advanced prostate cancer in *Practice*

Update on 13 February 2018 (http://tinyurl.com/ycvnx9rh).

In 2015, data from two large trials, CHAARTED and STAMPEDE, changed the treatment of newly diagnosed metastatic prostate cancer to include concomitant docetaxel. Urologists and medical oncologists alike have begun to embrace this new regimen, especially in men with higher-volume metastatic disease, as that was the subset that seemed to garner the greatest benefit.

In 2017, two more studies were released that challenged that new, albeit short-lived, standard. LATITUDE and an update of STAMPEDE explored the alternative combination of abiraterone with standard ADT. LATITUDE was limited to men with metastatic disease and included a truly a high-risk cohort of patients having either Gleason >8 and/or more than three bone/visceral metastases. STAMPEDE, on the other hand, had 48% of its cohort comprised of nonmetastatic patients—locally advanced disease (PSA >40, and/or T3/4 or Gleason 8–10) or node-positive men.

The results were overwhelming – in both men with metastatic and men with non-metastatic disease, there was significant benefit to adding abiraterone. Specifically, abiraterone with standard ADT in metastatic men improved overall survival, time to pain progression, time to chemotherapy and PSA progression compared with ADT alone. The men with localised disease also had an improvement in failure-free survival, but overall survival data were not mature or significant, likely given the prolonged timeline for nonmetastatic patients.

In terms of where do to go from here, Dr Jayram and Dr Morris said that the abiraterone trials did not have a docetaxel control arm, so direct comparison of the two agents is difficult. Based on almost identical hazard ratios across studies, the magnitude of benefit appears to be very similar between abiraterone and docetaxel in this patient population.

Universal use of abiraterone in men with advanced disease can be problematic. Cost, long-term endocrine side effects, and the potential of changing the hormonal milieu of castration-resistant prostate cancer such that it may become resistant to other therapies upon progression are all valid concerns. Tissue typing and androgen receptor characterisation (eg, AR V-7 status) will likely be important biological classifiers to determine therapy and sequencing.

The next year will bring more answers – direct comparisons via further STAMPEDE analyses and androgen receptor antagonist trials (enzalutamide and apalutamide) will provide some clarity and elucidate biological mechanisms of action.

Trying to personalise treatment based on disease and performance status appears to be the best strategy at this point. Younger men with higher-volume disease may still be great candidates for upfront chemotherapy, whereas frailer patients may be ideal for abiraterone therapy.

Ovarian cancer may be passed down through Dad's X chromosome

Authors:	Eng KH, Szender JB, Etter JL, Kaur J, Poblete S, Huang R-Y, et al
Original article title:	Paternal lineage early onset hereditary ovarian cancers: a familial ovarian cancer registry study
Journal:	PLOS Genetics
Date:	15 February 2018
View article at:	http://tinyurl.com/y773ob3x

ABC News reported on the above article (see article by Genelle Weulle at http://tinyurl.com/yd7az43x). This useful commentary explains that there is some evidence that a gene for prostate cancer may be passed through the X chromosome and thus increase the risk of ovarian cancer in paternal granddaughters of a woman affected by ovarian cancer. The same gene also appears to be associated with prostate cancer risk in males.

Ovarian cancer is the eighth most commonly diagnosed cancer in Australian women. It is well known that women who have inherited the BRCA

1 and 2 gene mutations from their mother or father are at a high risk of developing ovarian or breast cancer.

"We know that BRCA are major risk genes, but we also know it doesn't explain everything," the study principal author, Dr Eng said.

One of the enduring puzzles in cancer research is why the sisters of a woman with ovarian cancer – even those without these mutations – are more likely to get ovarian cancer than their mother or their daughters. "That paradox got us thinking about going up a couple of generations to see if we could really explain this thing genetically," Dr Eng said.

Women have two X chromosomes. One is inherited from their mum, the other is inherited from their dad.

BRCA mutations are on non-X chromosomes, meaning a daughter has a 50/50 chance of inheriting the mutation. But all daughters in a family would inherit an X-linked mutation if it existed.

"The chance the granddaughter has ovarian cancer doubles if the disease pattern transmits through dad's side of the family," Dr Eng said.

The researchers also observed that fathers were more likely to have prostate cancer if their mother and daughters had ovarian cancer.

In addition, we found evidence that other cancers affect fathers and sons in these families.

In the grandmother-granddaughter trios with affected granddaughters, the intermediate father was more likely to report a prostate cancer diagnosis if his mother had had ovarian cancer (OR = 2.34, 95%CI: 1.07–5.06, Fisher's exact test p = 0.0336) implying that the three generation pattern—ovary, prostate, ovary—was unusually common.

To look at this pattern further, the researchers sequenced the X chromosome of 157 BRCA-negative women with ovarian cancer.

The sequencing identified a gene called MACEC3. Women who had inherited this gene were diagnosed on average more than six years earlier than those without it.

From the editor

If you are aware of news, products, publications, web sites, services or events that may be of interest to members of the group I'd like to be informed of them.

If you have received this newsletter indirectly and would like to be emailed a copy direct, or if you would like to add any of your friends or carers, or if you no longer wish to receive copies of the newsletter, please send us an email through the form here:

http://tinyurl.com/ybkxnlg4.

Disclaimer

From time to time in our newsletters we provide information about developments in the diagnosis and treatment of prostate cancer, research articles, documents, audiovisual products, presentations and other interesting materials. However, the Group's Executive and the editor of this newsletter do not have the medical expertise required to make an informed evaluation of the conclusions and recommendations presented in such materials, and we have not verified such conclusions and recommendations through appropriately qualified medical professionals. The information presented in this newsletter must not be interpreted as being endorsed or recommended by the Executive or the editor. Any recommendations made in such materials may not be applicable in your case. Before implementing any recommendations made in the materials that are reported, it is essential that you obtain advice from appropriately qualified medical professionals. The view of the Group's Executive is that no two prostate cancer cases are alike and that no single treatment option is better than any other in all cases. While the information in this newsletter should be of interest, there is no substitute for getting informed medical advice from your own GP, specialists and other medical professionals.