Supplementary Submission No 5a

INQUIRY INTO OFF-PROTOCOL PRESCRIBING OF CHEMOTHERAPY IN NSW

Name: Dr Leong-Fook Ng

Date received: 6 February 2017

Supplementary Submission to # 5 – Dr Leong-Fook Ng (with independent commentaries on the commentary, not the content)

(Also submitted as "Correspondence" to the ongoing Senate Community Affairs Committee inquiring into "Medical Complaints in Australia")

Technical Version (citation errors corrected 10 Feb 2017)

1. First it must be stressed that human head and neck cancers are unique in oncology. This is the only group of tumours which are classed by location and not by cytopathological characterics. This is because they are rare and very hetrogenous (biologically different) by nature. Thus, a cancer of the tongue in the mouth is very different a cancer from a cancer of nasopharynx – but they are classed as "Head and Neck" cancers for the purposes of taxonomy and treatment (and clinical trials). All oncologists know this but yet follow the thinking whilst there are some North American colleagues who do classify them meticulously by site (e.g. the NCCN) but not by therapy – because of low numbers.

2. Having this in the background, a newly touted 2nd line "standard of care" of (difficult to manage) Head and Neck cancers had emerged in May 2016, published in the USA - away from the low utility palliative chemotherapy option - to a new group of drugs termed "check point inhibitors" used in combination with radiotherapy[1]. The study is called "Check mate 141" The agent is Nivolumab. The method of measuring tumour response was the conventional RECIST 1.1 and not the recommended the Immune-Related Response Criteria (irRC)[2]. Also, the first public abstract presentation was, strangely, in a science research (AACR) and not the clinical research meeting (ASCO) of a sister organisation. Bristol Myers Squibb (BMS) funded the 'landmark' study[3]

3. For example, the similarly costly Pembrolizumab is also said to be an important agent of equal footing (standing). This agent has been approved for use singly by the TGA for only Stage III and IV melanoma and non small cell lung cancer [4] and only in combination with (equally costly) ipilumumab (Yervoy, Pfizer) for Stage IV melanoma. The FDA approval documentation tells all [5] The approvals appear to be similar with another drug Nivolumab which has also been evaluated by the TGA[6]. The FDA approval documentation is exactly similar (refer to the statistical analysis) [7] These drugs are from the same family but are different as evaluated independently[8].

Comment by Dr Y Lucire on the comments in this document (not as an expert):

On the basis of a single clinical study (Check Mate 141) of a new drug, nivolumab, conducted and sponsored by its the manufacturers Bristol Myers Squibb (BMS) a newly recommended "standard of care" for head and neck cancers emerged in May 2016.

In the case of conditions are as hard to manage as head and neck cancers, the United States Food and Drug Administration takes the position that a single trial is sufficient to "approve" a drug for use. The Australian therapeutic goods administration followed suit.

However a single trial should not be considered sufficient to recommend an entirely new "standard of care," until further investigation has been undertaken.

4. In both the FDA analyses, clinical (imaging) methods of measurement of response RECIST 1.1 (not irRC criteria[9]) were used - without knowing the quaint implications then of immunotherapeutics. Approval was based on the application of this fundamental confusion/error. The time foibles of evaluation are explained in a 2015 publication.

5. The TGA report issued on 7 Sept 2016 continued to rely on RECIST 1.1 and not the irRC for evaluation of tumour response as argued and suggested a by ICLIO to be 'work in progress'. It also appears that the superior benefit of Nivolumab may have been premature and even inaccurate, thus generating much hope for both patients and the profession. For example, one could of course argue that the survival benefit demonstrated was dramatic, without realising that various biases[10] (including lead time bias) may be operating. Less obvious is that Australia is conforming to the US led TPP treaties. Now, President Trump has rescinded it.

6. For new agents, all (off protocol) use outside clinical trials are 'compassionate' on a case-to-case basis in negotiation with the company, written off or paid for privately. It remains unknown whether additional Pharma disbursements have occurred/are occurring during these circumstances.

7. These fairly similar new drugs are manufactured by two different competing companies. Pembrolizumab is by Merck Sharpe and Dohme (MSD) and Nivolumab by Bristol Meyers Squibb (BMS).

8. Classically, therapies with some Radiotherapy, have led to the hope of an 'abscopal' effect [11] which is very exciting hypothetical science (commonly called 'proof of principle' amongst research oncologists) – but till now, not fully proven clinically. Fundamental to the allegations of 'underdosing' (to us, a scientifically illogical term) is the notion that chemotherapy acts via its direct toxic effects. This is flawed and non inclusive. As have been shown in the laboratory for a long time, chemotherapy acts also in different ways.

Comment by Dr Y Lucire on the comments in this document (not as an oncologist):

The FDA approval documentation tells all. The approvals appear to be similar with another drug, nivolumab which has also been evaluated by the TGA. The FDA approval documentation is exactly similar (refer to the statistical analysis). These drugs are from the same family but are different as evaluated independently. For example, in both the FDA analyses RECIST 1.1 and not irRC criteria were used - without knowing the quaint implications then of immunotherapeutics.

Approval was based on this fundamental error. The foibles of evaluation are explained in a 2015 publication. The TGA report issued on 7 Sept 2016 continued to rely on RECIST 1.1 and not irRC for evaluation of tumour response as suggested and argued by ICLIO to be 'work in progress'. It also appears that the superior benefit of Nivolumab may have been premature and even inaccurate, thus generating much hope for both patients and the profession. For example, one would of course argue that the survival benefit demonstrated was dramatic, without realising that various biases (including lead time bias) may be operating.

9. This includes the inhibition of the formation of new blood vessels (which feed a growing tumour) etc. A decade old classic publication[12] of cetuximab (a monoclonal antibody) combined with radiotherapy has been found to be superior to RT alone but never ever compared head to head with a platinum-compound sensitising RT. Not every patient may tolerate to severe adverse effects. This was found in EviQ and supported by the PBS but was never ever mentioned in the external review as an option at St Vincent's. The article independently warns at the end of the first paragraph:

"The value of chemoradiotherapy is, however, counterbalanced by increased and often prohibitive toxicity, particularly among patients with coexisting medical conditions and decreased performance status"

10. That includes a treating clinician's "clinical judgment" off ***and*** on protocol - which were the various accused doctors' primary roles and duties to their patients. They had adhered to the ethical imperatives and are now falsely punished for – with the dysfunctional regulator playing along.

Comment by Dr Y Lucire on the comments in this document (not as an oncologist):

Chemotherapy delivered along with radiotherapy has resulted in a hypothesis called the "abscopal' effect but it has not as yet been confirmed by clinical trials .[5] Chemotherapy is known to be toxic to the tumour but, it may, for example also inhibit the formation of new blood vessels which feed a growing tumour. A close review of trials shows the inconsistent role of the dose hence of "dose dependency" for palliation. Nonetheless there is a popular notion that there is a correct dose, an algorithmic dose based on one size fits all, and failure to comply with such a recommendation created by the pharmaceutical industry is somehow the wrong thing to do. Parallel to this is the notion that if the dose delivered to a group of patients is lower than someone else's average it may be called, pejoratively and in loaded language "under dosing."

"Abscopal" refers to a hypothetical effect suggesting that radiation stimulates migratory killer cells and destroys metastases distant from the primary tumour. Two drugs, paclitaxel (BMS) and possibly oxaliplatin (Sanofi) are contenders for this mode of action, however evidence for clinical success remains unclear.

People respond differently to different medications, for genetic reasons, because of co-prescribed medications or because of their liver, iron and general health status. The notion that one size fits all, which the pharmaceutical industry wants us all to accept, is ridiculous because it obviously does not.

11. Distantly relevant, an “abscopal effect” essentially means immunological stimulation of migratory killer cells by radiation (also unproven clinically for any type of chemotherapy except possibly paclitaxel (another BMS product) and perhaps even oxaliplatin[13]) leading to secondary cancer (metastatic) cell destruction distant from the primary tumour. This notion is only gradually gaining clinical credence, again with no clear evidence available at this time. However there appears no evidence that the doctors were ‘experimenting’ with this hypothesis on their patients. They were just using their long established non-controversial “clinical judgements”, based on simple patient-doctor relationships. But this is not the key point - administratively speaking. We will show why this may be the case.

12. A new standard of care is not usually immediately accepted by practitioners globally. This standard must be tested independently, preferably with no Pharma industry or vested interest third party input or funding. So far, only one Pharma funded study has been peer reviewed and published in the Head and Neck scenario.

Comment by Dr Y Lucire on the comments in this document (not as an oncologist):

Pembrolizumab has been approved by the Therapeutic Goods Administration (TGA) for use as a single agent for non small cell lung cancer, Stage III melanoma and in combination with (equally costly) ipilumumab for Stage IV melanoma.

Another drug, costly and new, pembrolizumab (Merck Sharpe and Dohme (MSD), is said to be an important agent of equal standing.

It has been approved by the for use in non small cell carcinoma of the lung, stage III melanoma and in combination with ipilumumab for stage IV melanoma. The Therapeutic Goods Administration approval was based on that of the United States Food and Drug Administration (FDA) and a similar statistical analysis. These drugs are from the same family but about independent evaluation showed up their differences. For example, in both the FDA analyses, RECIST 1.1 and not irRC criteria was used, by clinical trial evaluators, unaware of the quaint implications of immunotherapeutics.

According to a 2015 publication, this approval was based on this fundamental error. The report of the Therapeutic Goods Administration appears similar.

13. In Australia, the long accepted concept of a doctor-patient relationship is that of the common law tradition founded on a contractual model. What is new and emerging but not generally and widely accepted is the 'Trust model', which has been written about[14]. Good medical practice does not compel a practitioner to follow this model, the 'trust model' but to be only aware of it – which may be evolving in the minds of the team of complainants, who by nature of a mob effect, claim they are correct. They may not be. Clearly this is not permissible in any civilised society – it is tantamount to bullying. Also one does really need to be reminded of rogue oncologists[15] and what they may be capable of propagating as a team with no checks and balances.

14. Hot off the press is a paper on the ethics of Pharma funding of patient groups and their effects on these[16] .

15. Returning to the Inquiry, one does know the following:

i. that a certain doctor was accused (internally) around March 2016 (according to the NSW Health reports).
ii. that his patients were not entered into any clinical trial.

What one does not know are the following:

i. that where there was whether another member of the MDT was enthusiastic about inviting more Head and Neck patients into clinical trials (despite such patient comorbidities)
ii. whether BMS (the manufacturer of the agent used in the 'new standard of care" had approached some person(s)
iii. whether entities for paid "consultancies" existed.
iv. This may have 'conflicted' with the accused doctors' non-clinical trial entry approach and put indirect pressure on the accused to enter patients.

However, the exercise may not have been successful. A pertinent question may be:

What clinical trials (including Pharma funded ones) on Head and Neck tumours were being conducted and what was/were being considered at these hospitals within the time line, and if so, with what Pharma company funding it?

14. Usually clinical investigators will know about the intended developmental pathway of a new drug many months before the publication of clinical research data and also whom they may wish to silence. All these accused doctors may have rightly applied the ethical principle of *equipoise* in clinical trials consideration and chose not to participate – something not taught in Australian medical school or structured post-graduate education till recently.

15. Indeed, on a related subtle issue, one does not know whether the NSW Government receives "special funding", concessions or "fees" from Pharma companies, the monies of which could then be used to fund the NSW Cancer Institute (which publishes EviQ). Further, the signatories of the corporate governance document are the Chief Cancer Officer himself (who led the external investigation of at least one doctor) with another ex premier of NSW who had an interesting past track record[17].

16. The safeguards for alleged fraud, which appear to be in place, cannot be seriously addressed if the funding is to the NSW Government which polices its own agencies - including the ICAC. There are thus, no real safeguards for poor ethical conduct.

17. A forward thinking, wise and accurate article on the judicious use of chemotherapy appeared recently in the British Medical Journal [18].

18. The notion of sham peer reviews[19] of any undesired oncologist to pave the way for unusual (including vested interests) activities by third parties will always need to be in the minds of independent investigators in this type of possible diversionary activity. This hypothesis is now becoming increasingly attractive. Instruments used included the Regulators of practitioners and more and more have surfaced in other parts of NSW and of the nation. Cross bench MLCs must be drawn into active participation of this inquiry.

19. Medicine in the 21st century can easily fall into the trap of "popular science" and "pharmaceutical politics". We are afraid one may be seeing elements of these here, tainted with legal 'distractions' – the alleged application of *subtle bullying* to serve its purpose. We will be happy to assist in giving clarifications *in camera*

20. *"Only then will cancer care serve patients rather than governments and industry."* [20]

Final Comments by Dr Y Lucire on the comments in this document (not as an oncologist):

As a result, nivolumab's approval has possibly been premature, even improper, and may be inducing false hope in the patients and in those who treat them.

For example, one would of course argue that the survival benefit demonstrated was dramatic, without realising that various biases [4] (including lead time bias) may be operating.

We suggest that before a drug is accepted and promoted as a new "standard of care," the raw data in the clinical trials used for its approval, needs to be critically evaluated.

This data is published on the website of the United States Food and Drug Administration. The evaluator should demand access to all clinical trials as some may have been withheld from public scrutiny by the pharmaceutical industry.

Before any drug can be recommended as a new "standard of care" or placed on the Pharmaceutical Benefits List, it needs to have demonstrated safety and efficacy and be an improvement on drugs that are known to be effective, or more effective than other less expensive drugs in use (not simply more effective than placebo in two trials out of any number done termed "evidence of efficacy" which is the criterion for approval at the United States Food and Drug Administration.

The process is such that the public (and physicians and patients) should not rely on the fact of FDA approval as an indication that medicines, including new and very highly priced ones, possess efficacy that is meaningfully greater than no efficacy at all.

That is not to say that new oncology drugs should not be released but until there is proof of efficacy, the recommendation of calling it, with fanfare, a new standard of care should be withheld with appropriate reservations.

Clinical trials need to be conducted independently of the pharmaceutical industry. A drug should not be recommended as a "standard of care "on the basis of the drug companies own report of a trial or trials that the drug company itself conducted and was willing to disclose to the FDA.

There will always be doctors who, for reasons of their own, attack their peers or superiors. Such doctors should not rely on pharmaceutical industry information and should remain aware that clinical trials are selectively reported in promotional material, in journals and published those different tumours and patients have different responses to the same drug.

They need to remember that medicine is also an art. When that art is misinformed by less than scientific studies promoted by the pharmaceutical industry it is the patients ultimately who suffer.

We need to be aware that the pharmaceutical industry has conflicting interests and values, basically a desire to make a profit, that are inconsistent with desires of doctors and patients who want their health restored, above all else.

REFERENCES

1. American Society for Clinical Oncology 2016 http://www.ascopost.com/issues/may-10-2016/nivolumab-new-standard-of-care-for-progressive-head-and-neck-cancer-after-platinum-therapy/

2. Immune Related Reponse Criteria (a simplified Wikipaedia definition) https://en.wikipedia.org/wiki/Immune-Related_Response_Criteria

3. Gillison ML et al 2016 American Association for Cancer Research

Annual Meeting “Nivolumab (nivo) vs investigator’s choice (IC) for recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): CheckMate-141” http://www.abstractsonline.com/Plan/ViewAbstract.aspx?mID=4017&sKey=b01a929a-449c-4fd7-89e5-7dc10238925f&cKey=7bbfb029-c64c-4ed8-97e9-515de57892d3&mKey=1d10d749-4b6a-4ab3-bcd4-f80fb1922267

4. Therapeutic Goods Administration 2016 AusPar https://www.tga.gov.au/auspar/auspar-pembrolizumab-rch

5. FDA Approval Reviews 2014 (Pembrolizumab) http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125514Orig1s000TOC.cfm

6. Therapeutic Goods Administration 2016 AusPar https://www.tga.gov.au/auspar/auspar-nivolumab

7. FDA Approval Reviews 2014 (Nivolumab) http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125554Orig1s000TOC.cfm

8. Carbogin L et al 2015 Differential Activity of Nivolumab, Pembrolizumab and MPDL3280A according to the Tumor Expression of Programmed Death-Ligand-1 (PD-L1): Sensitivity Analysis of Trials in Melanoma, Lung and Genitourinary Cancers https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4472786/

9. ICLIO 2015 “Assessing immunotherapy response – why irRC matters” http://accc-iclio.org/resources/assessing-immunotherapy-response-why-irrc-matters/ & Schwartzberg L 2015 ICLIO 01 Webinar *accc-iclio.org/wp-content/uploads/2015/07/ICLIO-01-Webinar-irRC-Slides.pdf*

10. Penn State University Stat 506 2016 “Screening biases” https://onlinecourses.science.psu.edu/stat507/node/74

11. Carson AH 2016 Medscape “Immunotherapy 'Plus': Adding Radiation and Chemo to Immune Therapies” http://www.medscape.com/viewarticle/865242_2

12. Bonner JA et al 2006 NEJM 354: 567 et seq Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck http://www.nejm.org/doi/full/10.1056/NEJMoa053422#t=article

13. Kershaw MH et al 2013 Onco Immunology “Enhancing immunotherapy using chemotherapy and radiation to modify the tumor microenvironment “https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3850060/

14. Benging, ZJ 2014 Reconceptualising the Doctor–Patient Relationship: Recognising the Role of Trust in Contemporary Health Care http://link.springer.com/article/10.1007/s11673-014-9570-z

15. Christina Sterbenz 2015 Business Insider "Cancer doctor who prescribed $35 million worth of unnecessary chemotherapy gets 45 years in prison" http://www.businessinsider.com.au/michigan-oncologist-farid-fata-charged-with-fraud-sentenced-to-45-years-in-prison-2015-7

16. Furlow, Bryant 2016 Cancer Therapy Advisor "Is drug maker funding for patient groups a hidden culprit in rising drug prices?" http://www.cancertherapyadvisor.com/general-oncology/cancer-drugmaker-funding-patient-groups-hidden-culprit-higher-drug-prices/article/575777/

17. NSW Cancer Institute 2016 Corporate Governance Attestation Governance Statement in https://www.cancerinstitute.org.au/Data-research/Research-ethics-committee

18. Wise P 2016 BMJ *Cancer drugs, survival, and ethics* http://www.bmj.com/content/355/bmj.i5792/rapid-responses

19. Ng, Leong; Broadbent, Russell; Teper, Yaroslav JPANDS 2016, 21: 104 - 109 "A Perspective on the emergence of Healthcare Sham Peer Reviews in Australia – past, present and the future" http://www.jpands.org/vol21no4/ng.pdf

20. Fiona Godlee 2016, Final line comment as Editor in Chief, British Medical Journal 2016 http://www.bmj.com/content/355/bmj.i6027.short?trendmd-shared=0

Comments from a Consumer's Perspective

Dr Anthony Pun*, OAM, Chair, Multicultural Communities Council of NSW Inc. and National President of Chinese Communities Council of Australia Inc.

Public confidence in the research and management & treatment of cancer should be maintained at all costs if the public is expected to "trust" their Oncologist and put their life in their hands. This trust must not be breached. The layperson does not have sufficient expert knowledge about the frontiers of cancer research and they put their "faith" in the Oncologist who act for their wellbeing.

In the US, the FDA plays an important role as a "Medical Policeman " in ensuring that Medicines used in the treatment of cancer and other diseases are safe and reviewing medical and scientific data in the testing and clinical trials of such substances. In Australia, the TGA plays a similar role. There is no room for complacency in this task and the TGA must ensure its decisions have integrity, honesty and are rigorously examined in order to maintain public faith and trust.

Ideally, independent research in the medical and scientific fields should be funded by the government in order to avoid "conflict" of interests
We are not against funding of clinical trials by the pharmaceutical companies if such work is done on a high moral and ethical basis, with no perception of bias introduced by the pharmaceutical companies, the clinical researcher and a "clean" clinical trial based on proper statistical procedures. When such standards are lacking, it could lead to chaos and the examples provided by Dr LF Ng in submission 5 and the controversial St Vincent's episode are glaring examples of possible "bias" by interested parties (whether pharmaceutical companies or medical oncologists).

The public airing of such controversial issues does not reflect well on TGA or Medical Oncologist. However, there is a good side of this revelation+ (better than sweeping it under the carpet). That is, a comprehensive review of the issues by a parliamentary committee would correct any misconceptions and restore the public confidence in the TGA and the Medical profession.

As a consumer representing a part of the public opinion, it is imperative that the government of the day should fine tune the TGA and Medical colleges. To strengthen public confidence and restore public faith in this noble and respectable profession.

Healthcare related experience

1996/1999	Expert Advisory Group - Optimum Cancer Management - Committee NSW Health Department.
2003-2007	Australian Pharmaceutical Advisory Council (APAC) – Member

Relevant Publications:

1. Atkinson K, Biggs JC, Ting A, Concannon AJ. Dodds AJ. **Pun A**. Cyclosporin A is associated with faster engraftment and less mucositis than methothrexate after allogenic bone marrow transplantation. Br. Jr. Haematol. 1983; 54:265-270.

2. Biggs JC, Atkinson K, Concannon AT, Dodds AJ, Harkness J, Yuile P, Causer P, Bashir H, Penny R, Nicholls M, Ting A, **Pun A**, Honeyman M, and St. Vincent's Bone Marrow Transplant Team. Bone Marrow Transplantation in 33 patients with malignant blood diseases and severe Aplastic Anaemia. Medical Journal of Australia 1983; 2:120-168.

3. Ting A, **Pun A**, Atkinson K, Dodds A, Biggs JC. The association of cytotoxic antidonor HLA antibodies and mismatched marrow graft rejection. Transplantation Proceedings. 1986:XVIII:264-266.

4. Ting A, **Pun A**, Dodds AJ, Atkinson K, Biggs JC. Red cell alloantibodies produced after bone marrow transplantation. Transfusion 1987; 27:145-147.

Comments on the technical comments are crafted voluntarily by Dr Y Lucire, who is a non-oncology specialist in her field, pharmacogenetics in psychiatry