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Title: RET-rearranged Non-small-cell Lung Cancer and Therapeutic Implications

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ZL collated the data and wrote the paper, SA designed and critically revised the paper, TJ and PM reviewed the paper. All authors approved the final version.

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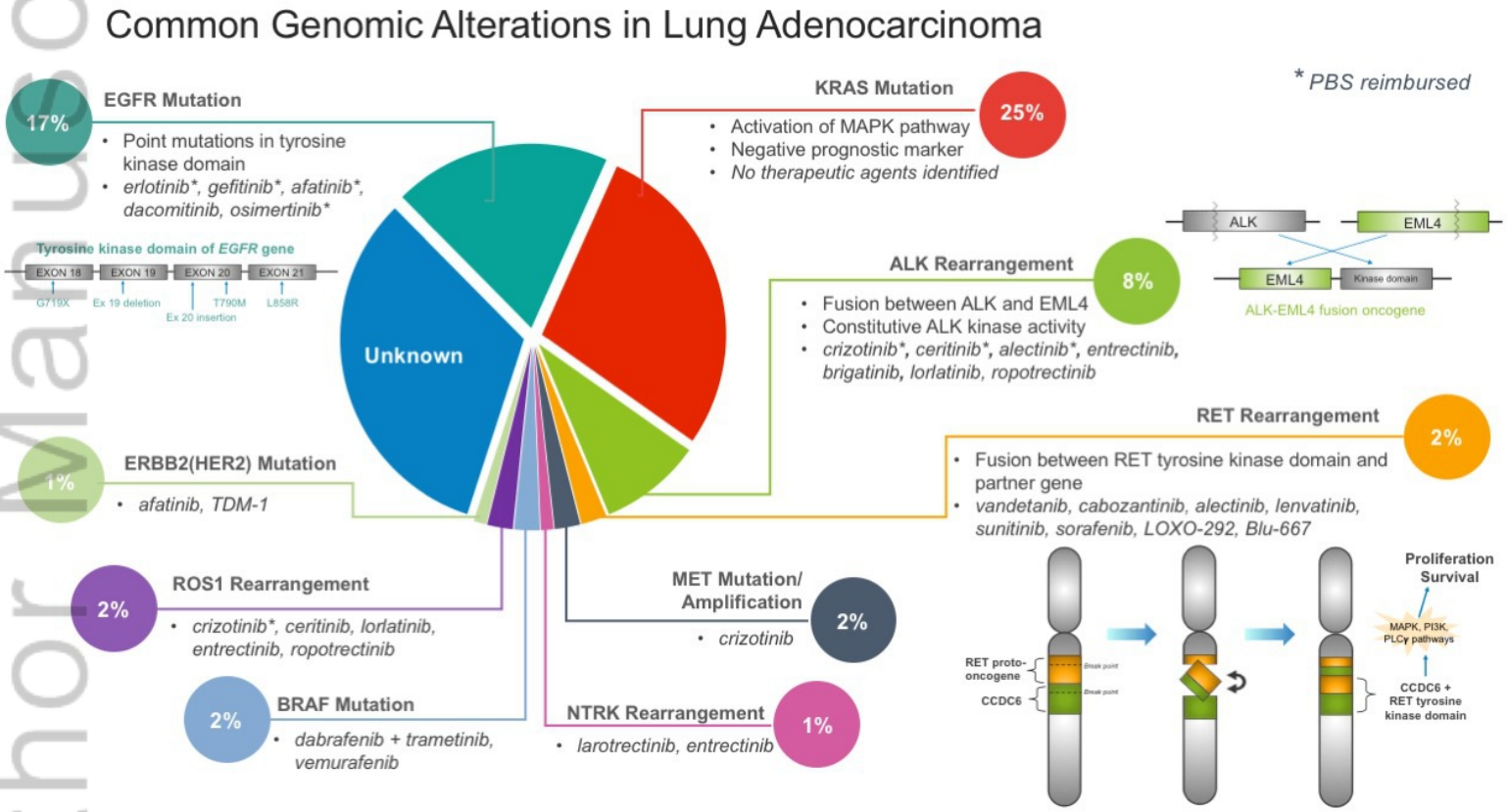
ABSTRACT

First line tyrosine kinase inhibitors are standard of care for non-small-cell lung cancers (NSCLC) harbouring an *EGFR* mutation, *ALK* fusion, or ROS1 rearrangement Other targetable oncogenic drivers have been identified but testing for these is neither funded nor commonly performed in Australia. Using a case example, we discuss the importance of considering several other genomic aberrations in our population, such as rearrangements in the RET proto-oncogene, which occur in 1-2% of lung adenocarcinoma. New oncogenic drivers and corresponding targeted agents are constantly being discovered; these will continue to refine the treatment of NSCLC in the era of precision medicine.



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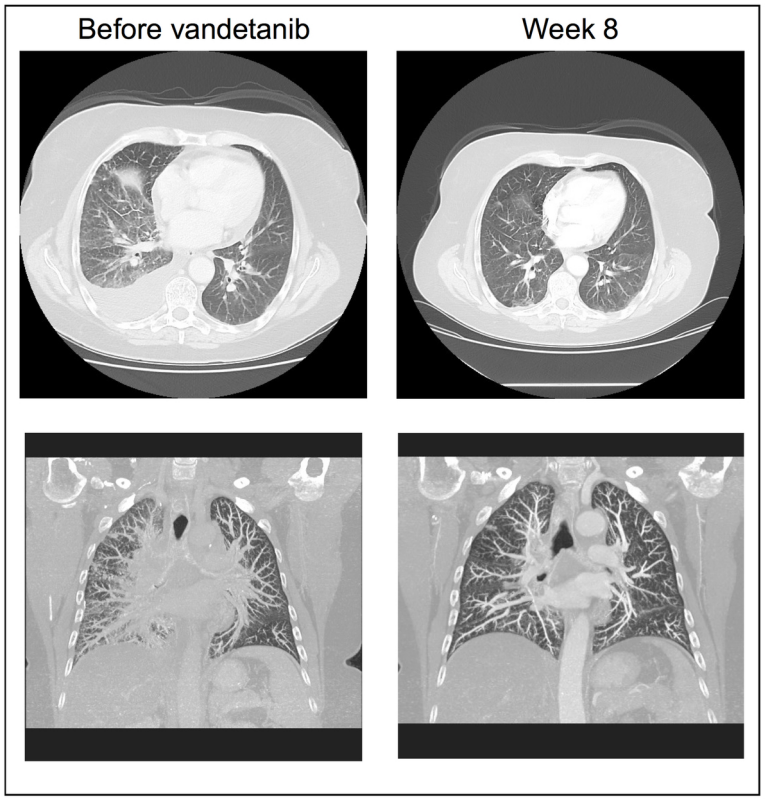

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INTRODUCTION

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related deaths in Australia, with a 5-year overall survival rate of 16.5%[1]. While tobacco exposure continues to be the main risk factor[2], a proportion of lung cancers result from molecular drivers and are not always associated with a smoking history. The Epidermal Growth Factor Receptor (*EGFR*) mutation, Anaplastic Lymphoma Kinase (*ALK*) translocation and c-ros oncogene 1 (*ROS-1*) rearrangement are the most common of these drivers, and since the discovery of effective targeted therapies for these subtypes, several newer generation agents have been developed, which continue to improve survival rates[3,4]. In recent years, other platforms including Fluorescent *In Situ* Hybridisation (FISH) and next generation sequencing have led to the identification of other oncogenic drivers such as *NTRK*, *BRAF*, *MET*, *HER-2* and *RET*.

RET *(rearranged during transfection*) is a tyrosine kinase receptor which activates downstream cell proliferation and differentiation pathways. Point mutations in the *RET* gene were originally found to be associated with medullary thyroid carcinoma[5]. In NSCLC, chromosomal rearrangements create a fusion gene between the *RET* gene and another domain, most commonly *kinesin family 5B* (KIF5B) and *coiled coil domain containing-6* (CCDC6), leading to overexpression of the RET protein[6].

The *RET* fusion oncogene occurs in 1-2% of NSCLC[7], particularly in younger, non-smoking patients with adenocarcinoma histology. RET rearrangements are thought to be exclusive of *EGFR*, *ALK*, *KRAS* and *BRAF* mutations, suggesting that it has its own oncogenic driver potential. However, one series reported that 8/11 (73%) of patients with the KIF5B-RET fusion gene also harboured an EGFR or KRAS mutation[8]. Importantly, RET-rearranged tumours have been shown to respond to tyrosine kinase inhibitors (TKIs) with anti-RET activity, such as cabozantinib[9], vandetanib[10,11] and lenvatinib.

Testing for RET rearrangements is uncommonly performed in Australia due to lack of reimbursement. Here we describe a remarkable response to TKI treatment in a case of *RET*-rearranged NSCLC in Australia to illustrate the importance of considering these novel oncogenic mutations in our population.

CASE

A 54-year-old Australian-born Caucasian woman, a former smoker of 25 pack-years, was referred to the lung oncology service at the Olivia Newton-John Cancer and Wellness Centre in December 2015 with stage IIIB NSCLC. Computed tomography (CT) of the chest demonstrated a 36mm right hilar mass and extensive bilateral mediastinal lymphadenopathy. Transbronchial fine needle aspiration of a subcarinal node revealed lung adenocarcinoma. Next generation sequencing using the TruSight panel did not show any mutations in *EGFR*, *KRAS* or *BRAF* and her *ALK* and *ROS1* immunohistochemistry (IHC) staining was negative.

Her case was discussed at our thoracic multidisciplinary meeting and the volume of disease was considered too extensive for radical-intent chemo-radiotherapy. Therefore, she was enrolled onto a clinical trial and received treatment with carboplatin and paclitaxel chemotherapy, in addition to bevacizumab, an anti-vascular growth factor agent. A partial response was achieved after four cycles of induction chemotherapy, and she received four further cycles of maintenance bevacizumab until disease progression, at six months from commencing therapy. An increase in pulmonary lymphadenopathy was demonstrated on a restaging CT.

Thereafter, the patient received nivolumab, an anti-programmed cell death 1 receptor antibody, however after six cycles was found to have extensive disease progression with development of vertebral and liver metastases, right-sided pleural effusion and lymphangitis carcinomatosis. Clinically, she developed dyspnoea, cough and weight loss with a rapid decline in her performance status.

Her archival tumour sample was sent overseas for further mutational profiling beyond the standard oncogenic alterations and a RET-CCDC6 rearrangement was discovered. She was commenced on vandetanib, an oral TKI with broad activity against several mutations including RET, at 300mg daily.

Within three days, she reported dramatic improvement in energy levels, with complete resolution of her cough and exertional dyspnoea. A restaging CT scan 2 months later showed a near complete response to therapy. (Figure 1). Importantly, the treatment was well tolerated; the only side effect was hypertension, which was medically managed.

After four months, she developed signs of early resistance to vandetanib, with evidence of increasing right hilar lymphadenopathy. Treatment was changed to carboplatin and pemetrexed chemotherapy which was poorly tolerated and ceased after two cycles due to disease progression. She was subsequently commenced on alectinib, another TKI with documented anti-RET activity[12]. She did not experience any side effects, however a repeat CT scan six weeks later showed re-emergence of the right sided pleural effusion and progressive mediastinal disease. She was also experiencing haemoptysis and severe back pain. She received two cycles of oral vinorelbine chemotherapy without benefit, followed by lenvatinib, an oral TKI with anti-RET activity (24mg daily) for three weeks before dying from her disease, 21.6 months after the initial diagnosis of NSCLC.

DISCUSSION

Upfront tumour molecular profiling is the standard of care for all patients with advanced NSCLC. Joint guidelines from the College of American Pathologists, International Association for the Study of Lung Cancer (IASLC), and Association for Molecular Pathology[13] recommend testing for eight genomic alterations in advanced lung adenocarcinoma (Figure 2) - *EGFR, ALK* and *ROS1* as a minimum, and if negative, multiplex genetic sequencing for the remaining genes (*RET, MET, ERBB2, BRAF* and *KRAS*) in an expanded panel. Alternatively, a comprehensive cancer panel can be performed upfront to analyse all 8 genes.

In Australia, only *EGFR,ALK* and ROS1 testing is funded and routinely performed, predominantly via next generation sequencing (NGS) for *EGFR*, IHC or FISH for *ALK*, and FISH for *ROS1*. Broad genomic profiling has the ability to identify the full range of genomic alterations with higher

specificity and sensitivity, without the need to perform multiple individual tests. If performed upfront, it may be more cost and time efficient than sequential testing, and has been shown to identify additional patients who would benefit from targeted therapy[14]. It is strongly recommended by the NCCN for advanced lung adenocarcinoma. However, is it not publicly reimbursed in Australia and local options include participation in a clinical trial which involves genomic testing or privately funded testing in laboratories with validated assays.

As such, it is likely that RET rearrangements are underreported in our Australian population. There have been very few identified cases in Australia, yet in previous studies, the prevalence of RET fusions has been as high as 16% in tumours negative for *ALK*, *EGFR* and *KRAS*[15] .

Our case highlights several important reasons to consider testing for RET and relatively uncommon oncogenic drivers in all advanced lung adenocarcinoma patients. Firstly, appropriate targeted agents such as vandetanib can produce substantial clinical benefit in rapidly progressive disease. Our patient reported almost immediate resolution of her symptoms and achieved several more months of markedly improved quality of life. Similarly impressive responses to other TKIs such as alectinib, cabozantinib, sorafenib and sunitinib in pre-treated *RET*-rearranged tumours have been reported[12,16].

Due to the rarity of *RET*-rearranged NSCLC, the best evidence for vandetanib currently comes from two phase II multicentre clinical trials in the Asian population [10,11]. These reported a median progression-free survival (PFS) of 4.7 months and 4.5 months, and response rates of 53% and 18%.

Admittedly, these response rates and duration of response are lower than that seen with selective TKIs for *EGFR* mutations and *ALK* fusions. The TKIs with RET activity are not specific for RET and may not achieve sufficient RET inhibition levels, as dosing is limited by toxicities associated with other targets. However, exciting novel therapies are on the horizon. Blu-667 [17] and LOXO-292 [18] are highly selective RET inhibitors with considerably greater RET potency in vitro; Phase I trials of these agents are currently ongoing, with impressive interim results from the LOXO-292 trial (LIBRETTO-001)

presented at the ASCO Annual Conference in May 2018. At the April 2018 cut off, 90% of NSCLC patients remain on treatment, 77% had confirmed objective response, and none had developed progressive disease. Importantly, two-thirds of patients enrolled had received prior treatment with at least one TKI, and most adverse events were mild (Grade 1), with tumour lysis syndrome the only dose-limiting toxicity observed. The maximum tolerated dose has not yet been reached.

Secondly, these agents may have a more favourable toxicity profile. In the first phase III trial of vandetanib in 331 patients with advanced medullary thyroid carcinoma[19], the most common adverse events were diarrhoea, rash, nausea and hypertension, occurring in over 30% of participants. However, dose discontinuation was uncommon (12%), even with a median treatment duration of 90 weeks. In most cases, an early, proactive approach to management of these side effects enables prolonged use of kinase inhibitors[20]. In contrast, platinum doublet chemotherapy is associated with myelosuppression, nausea, vomiting and neuropathy, and increasing toxicity with further lines of chemotherapy. This is often challenging in patients with poor baseline performance status.

Furthermore, while there is gaining momentum for use of immunotherapy in lung cancer, this subset of oncogene-driven tumours may not derive the same benefit from these treatments. Patients with *EGFR mutations* and *ALK* rearrangements appear to be less responsive to immune checkpoint blockade[21], presumably due to a lower tumour mutational burden. This has been demonstrated in pooled subgroup analyses of several large randomized trials for immune checkpoint inhibitors (ICI) versus docetaxel chemotherapy in NSCLC; no survival benefit was found in patients with EGFR mutations[22]. Subsequent studies have explored various combinations of TKI therapy and ICI, however high rates of severe hepatotoxicity [23,24] and interstitial pneumonitis[25], as well as lack of improvement in response rates, have led to premature termination of several trials and uncertainty regarding the clinical feasibility of these combinations. While there is no specific data for ICI in RET-rearranged NSCLC, RET-targeted therapy alone is likely to be the preferred upfront strategy.

Finally, as recommended in guidelines[13], testing for these mutations should not be performed on the basis of clinical characteristics. Indeed, we have described a case of a Caucasian, middle-aged ex-smoker, whose driver mutation was only detected by chance after completing two lines of treatment.

At present, neither testing for RET rearrangement nor RET inhibitor treatment is currently funded in Australia. FISH and NGS are the preferred tests and these may be accessed either at certain academic centres with established FISH testing, via self-funded expanded sequencing panels, or through clinical trials with sequencing panels. Access to RET-targeted drugs is either through clinical trial participation or application to respective pharmaceutical industry partners.

CONCLUSION

In the absence of *EGFR* mutations and *ALK/ROS1* rearrangements, clinicians should consider testing for these less common oncogenic drivers, especially given the increasing availability of well tolerated, rapidly-effective oral treatment options for a significant proportion of patients with metastatic lung adenocarcinoma. Due to the relative rarity of mutations such as *RET*, large phase III studies are challenging to conduct. Instead, large international collaborations, such as the Thoracic Alliance for Cancer Trials, are focusing their efforts on matching patients with rare oncogenic driver mutations to Phase I and II clinical trials to ensure that patients gain access to novel therapies.

REFERENCES

1 Cancer compendium: information and trends by cancer type, Lung cancer. Australian Institute of Health and Welfare. https://www.aihw.gov.au/reports/cancer/cancer-compendium-information-trends-by-cancer/report-contents/lung-cancer (accessed 1 Oct2018).

2 Malhotra J, Malvezzi M, Negri E, La Vecchia C, Boffetta P. Risk factors for lung cancer worldwide. *European Respiratory Journal* 2016; **48**: 889–902.

3 Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim D-W *et al.* Alectinib versus Crizotinib in Untreated *ALK* -Positive Non–Small-Cell Lung Cancer. *New England Journal of Medicine* 2017; **377**: 829–838.

4 Soria J-C, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH *et al.* Osimertinib in Untreated EGFR-Mutated Advanced Non–Small-Cell Lung Cancer. *N Engl J Med* 2017; **378**: 113–125.

5 Drosten M, Pützer BM. Mechanisms of Disease: cancer targeting and the impact of oncogenic RET for medullary thyroid carcinoma therapy. *Nature Clinical Practice Oncology* 2006; **3**: 564.

6 Santoro M, Melillo R, Carlomagno F, Fusco A, Vecchio G. Molecular Mechanisms of RET Activation in Human Cancer. *Annals of the New York Academy of Sciences* 2006; **963**: 116–121.

7 Takeuchi K, Soda M, Togashi Y, Suzuki R, Sakata S, Hatano S *et al.* RET, ROS1 and ALK fusions in lung cancer. *Nature Medicine* 2012; **18**: 378–381.

8 Kang JH, Kim J-O, Lee J, Shin J-Y, Oh J-E, Jung C-K *et al.* KIF5B-RET fusion gene and oncogenic mutations of EGFR or KRAS gene in lung adenocarcinomas. *JCO* 2014; **32**: 7537–7537.

9 Drilon A, Rekhtman N, Arcila M, Wang L, Ni A, Albano M *et al.* Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. *The Lancet Oncology* 2016; **17**: 1653–1660.

10 Lee S-H, Lee J-K, Ahn M-J, Kim D-W, Sun J-M, Keam B *et al.* Vandetanib in pretreated patients with advanced non-small cell lung cancer-harboring *RET* rearrangement: a phase II clinical trial. *Annals of Oncology* 2016; : mdw559.

11 Yoh K, Seto T, Satouchi M, Nishio M, Yamamoto N, Murakami H *et al.* Vandetanib in patients with previously treated RET-rearranged advanced non-small-cell lung cancer (LURET): an open-label, multicentre phase 2 trial. *The Lancet Respiratory Medicine* 2017; **5**: 42–50.

12 Lin JJ, Kennedy E, Sequist LV, Brastianos PK, Goodwin KE, Stevens S *et al.* Clinical Activity of Alectinib in Advanced RET -Rearranged Non–Small Cell Lung Cancer. *Journal of Thoracic Oncology* 2016; **11**: 2027–2032.

13 Lindeman NI, Cagle PT, Aisner DL, Arcila ME, Beasley MB, Bernicker EH *et al.* Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. *Archives of Pathology & Laboratory Medicine* 2018; **142**: 321–346.
14 Rozenblum AB, Ilouze M, Dudnik E, Dvir A, Soussan-Gutman L, Geva S *et al.* Clinical Impact of Hybrid Capture–Based Next-Generation Sequencing on Changes in Treatment Decisions in Lung Cancer. *Journal of Thoracic Oncology* 2017; **12**: 258–268.
15 Lee SE, Lee B, Hong M, Song J-Y, Jung K, Lira ME *et al.* Comprehensive analysis of RET and ROS1 rearrangement in lung adenocarcinoma. *Modern Pathology* 2015; **28**: 468–479.
16 Drilon A, Wang L, Hasanovic A, Suehara Y, Lipson D, Stephens P *et al.* Response to Cabozantinib in Patients with *RET* Fusion-Positive Lung Adenocarcinomas. *Cancer Discovery* 2013; **3**: 630–635.
17 Subbiah V, Gainor JF, Rahal R, Brubaker JD, Kim JL, Maynard M *et al.* Precision Targeted Therapy with BLU-667 for *RET* -Driven Cancers. *Cancer Discovery* 2018; **8**: 836–849.
18 Velcheti V, Bauer T, Subbiah V, Cabanillas M, Lakhani N, Wirth L *et al.* OA 12.07 LOXO-292, a Potent, Highly Selective RET Inhibitor, in MKI-Resistant RET Fusion-Positive Lung Cancer Patients with and without Brain Metastases. *Journal of Thoracic Oncology* 2017; **12**: S1778.
19 Wells SA, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M *et al.* Vandetanib in Patients With Locally Advanced or Metastatic Medullary Thyroid Cancer: A Randomized, Double-Blind Phase III Trial. *Journal of Clinical Oncology* 2012; **30**: 134–141.
20 Hirsh V. Managing treatment-related adverse events associated with egfr tyrosine kinase inhibitors in advanced non-small-cell lung cancer. *Current Oncology; Vol 18, No 3 (2011)* 2011. doi:10.3747/co.v18i3.877.
21 Gainor JF, Shaw AT, Sequist LV, Fu X, Azzoli CG, Piotrowska Z *et al.* EGFR Mutations and ALK Rearrangements Are Associated with Low Response Rates to PD-1 Pathway Blockade in Non–Small Cell Lung Cancer: A Retrospective Analysis. *Clin Cancer Res* 2016; **22**: 4585.
22 Lee CK, Man J, Lord S, Cooper W, Links M, Gebski V *et al.* Clinical and Molecular Characteristics Associated With Survival Among Patients Treated With Checkpoint Inhibitors for Advanced Non–Small Cell Lung Carcinoma: A Systematic Review and Meta-analysisAssociation of Checkpoint Inhibitors With Survival in Advanced Non–Small Cell Lung CarcinomaAssociation of Checkpoint Inhibitors With Survival in Advanced Non–Small Cell Lung Carcinoma. *JAMA Oncology* 2018; **4**: 210–216.
23 Lin JJ, Chin E, Yeap BY, Ferris LA, Kamesan V, Lennes IT *et al.* Increased Hepatotoxicity Associated with Sequential Immune Checkpoint Inhibitor and Crizotinib Therapy in Patients with Non–Small Cell Lung Cancer. *Journal of Thoracic Oncology* 2019; **14**: 135–140.
24 Yang JC-H, Gadgeel SM, Sequist LVD, Wu C-L, Papadimitrakopoulou VA, Su W-C *et al.* Brief Report: Pembrolizumab in Combination With Erlotinib or Gefitinib as First-Line Therapy for Advanced Non–Small-Cell Lung Cancer With Sensitizing EGFR Mutation. *Journal of Thoracic Oncology* doi:10.1016/j.jtho.2018.11.028.
25 Ahn M-J, Yang J, Yu H, Saka H, Ramalingam S, Goto K. Osimertinib combined with durvalumab in EGFR-mutant non-small cell lung cancer: results from the TATTON phase Ib trial. *J Thorac Oncol* 2016; **11**: S115.

FIGURE LEGENDS

Figure 1: Post contrast computed tomography (CT) images of the patient's chest A) at progression after 2nd line nivolumab - demonstrating confluent right hilar and mediastinal lymphadenopathy, moderate right-sided pleural effusion, and lymphangitis carcinomatosis and B) Marked treatment response at 8 weeks after commencing vandetanib

Figure 2: Common genomic alterations recommended for inclusion in a comprehensive cancer panel for advanced lung adenocarcinoma, and examples of targeted therapies. In *RET*-rearranged tumours, an inversion on chromosome 10 creates a fusion between the RET tyrosine kinase domain and a partner gene, leading to overexpression of RET tyrosine kinase. This activates downstream pathways involved in cell proliferation, differentiation, migration and survival.
PBS = Pharmaceutical Benefits Scheme