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Recur, Review and Recheck!

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Case Presentation

Miss Leung, a 62-year-old lady, was a nonsmoker and had diabetes well controlled with metformin. She presented with two weeks of productive cough, fever and weight loss of 2 kg in May 2017. Upon admission, she had fever of 38 degree Celsius, required 2 L of O2/min and right upper chest crepitations on auscultation. Blood tests found white blood cell 12 X 10^9/L, CRP 50mg/l and normal liver and renal function tests. Chest X ray noted a roundish mass with spiculated border and small central cavity at the centre in right upper zone and another smaller irregular mass in left upper zone. **(Figure 1)** Urgent contrast CT thorax found a 3 X 3 cm roundish lesion with necrotic centre, fluid density and gas pockets in right upper lobe posterior segment. **(Figure 2)** It had an irregular border, rim enhancement and adjacent ground glass opacities. There was also scattered consolidation at left lower lobe anterior segment. She was treated as lung abscess with empirical intravenous Augmentin. CT guided drainage of cavitary lesion yielded 50 ml heavily blood-stained fluid but culture showed coagulase negative staphylococcus only, suspected contamination. Other microbiological workup including blood and sputum cultures were negative. She improved clinically and radiologically with four weeks of Augmentin.

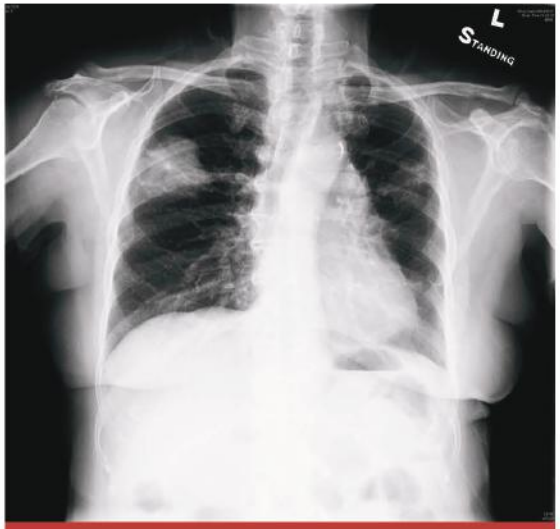
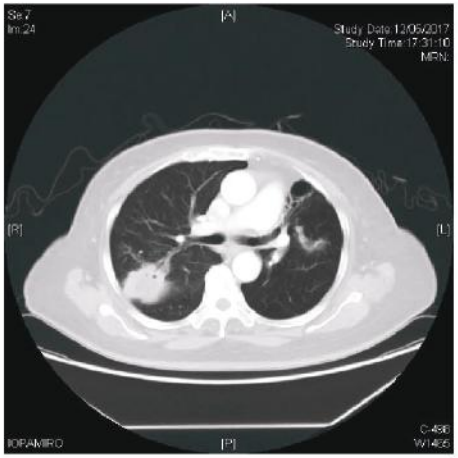


Figure 1: Admission CXR in the first hospitalization



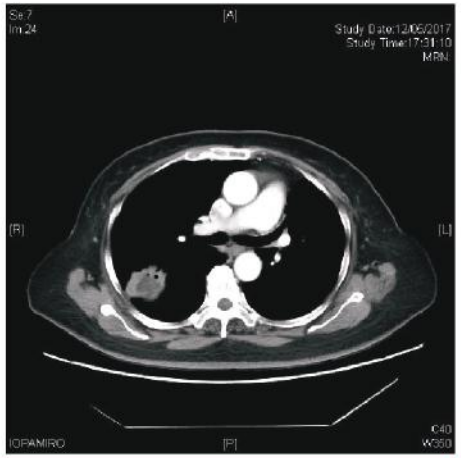


Figure 2: CT thorax in the first hospitalization

However, the patient complained of on and off fever, productive cough and blood-stained sputum for one month in December 2017 during her clinic follow-up. Chest X ray noted recurrent right upper zone consolidation and new right lower zone consolidation. Her symptoms didn't improve with empirical oral Augmentin so was advised for further inpatient workup. Serial CXR noted right lung consolidations enlarged and cavitated. **(Figure 3)** Sputum cultures grew oral commensals, acid fast bacilli and cytology were negative. Urgent contrast CT thorax showed two irregular lesions with central necrosis and rim enhancement in right upper lobe and right middle lobe without much fluid level.

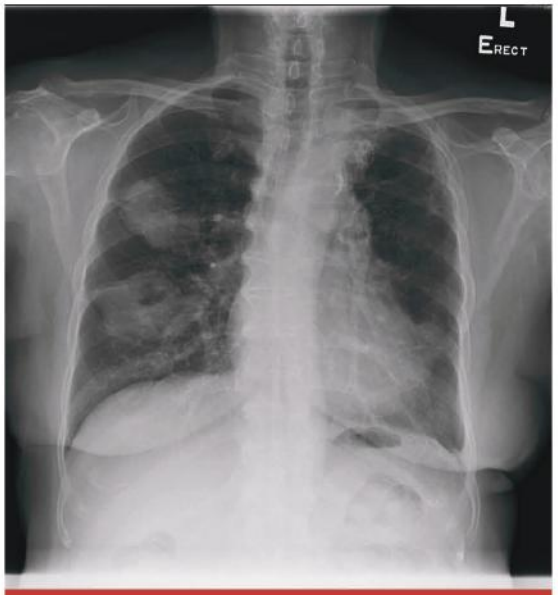


Figure 3: Admission CXR in the second hospitalization

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(Figure 4) CT guided drainage of the two abscesses yielded 50 ml of blood-stained fluid but fluid bacterial, tuberculosis and fungal cultures were all negative. Bronchoscopy showed no subglottic stenosis or other endobronchial lesions and bronchoalveolar lavage cultures were negative. Echocardiogram showed no vegetation. Blood tests for tumor markers, autoimmune markers and HIV were unremarkable. Dental assessment found no source of infection and swallowing assessment was normal. Despite negative extensive workup, the patient responded with intravenous ceftriaxone clinically and radiologically. She was discharged after four weeks of antibiotic.

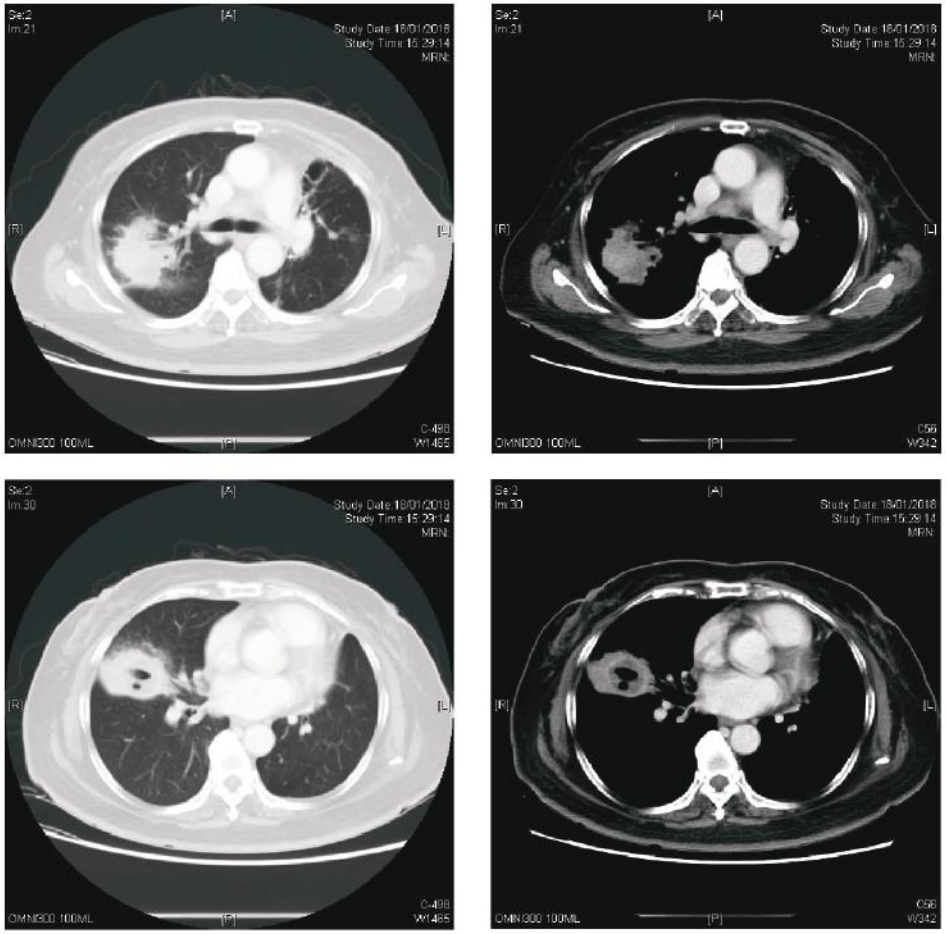

Figure 4: CT thorax in second hospitalization

Unfortunately, the patient admitted again in April 2018 for two weeks of fever and hemoptysis and one week of left painful red eye. Initially blood tests found raised inflammatory makers and acute renal failure with creatinine up to 180 ummol/l. CXR showed new bilateral upper zone consolidative changes. **(Figure 5)** Contrast CT thorax confirmed bilateral upper lobe lesions with necrotic centre and peripheral solid component. **(Figure 6)** CT guided drainage of both abscesses was done and fluid cultures were negative. CT guided FNAC of solid component of right upper lobe cavitary lesion showed organizing pneumonia with acute inflammation. There were no malignant cells noted and staining for micro-organisms was negative. Extensive workups were repeated including bronchoscopy, echocardiogram, dental assessment and blood tests for HbA1c, tumor markers and HIV and autoimmune markers. Results were unrevealing except positive cANCA and raised PR3 titre 196 RU/ml. Ophthalmologist confirmed left episcleritis accounting for painful red eye. Ultrasound kidney showed bilateral renal parenchymal disease only and fresh urine microscopy found no cast or dysmorphic blood cells. Twenty-four-hour urine noted 0.5gram proteinuria and renal biopsy confirmed crescentic glomerulonephritis, compatible with pauci-immune type glomerulonephritis.

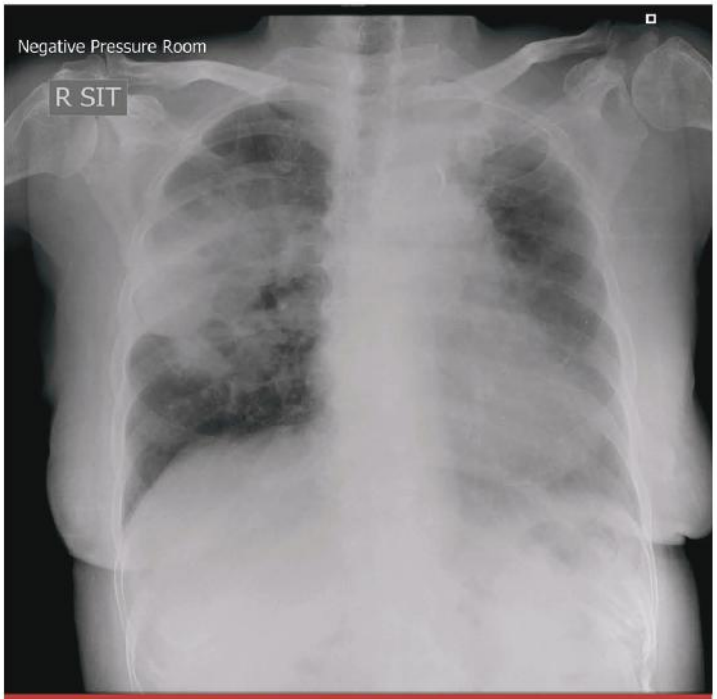

Figure 5: Admission CXR in the third hospitalization

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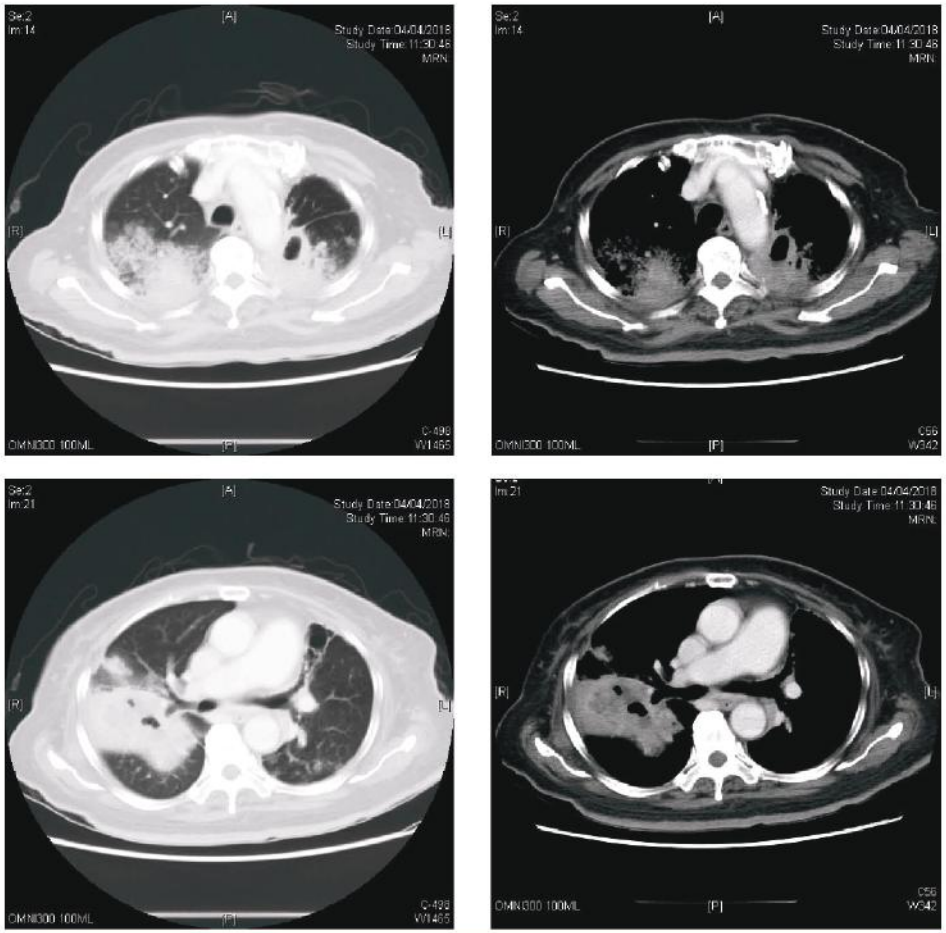

Figure 6: CT thorax in the third hospitalization

Finally, we arrived a diagnosis of granulomatosis with polyangiitis as suggested by recurrent lung abscess/cavitary lesions, pauci-immune type glomerulonephritis, episcleritis and a positive PR3-ANCA. Rheumatologists was consulted and the patient was treated with pulse methylprednisolone and pulse cyclophosphamide followed by maintenance azathioprine. Her chest symptoms, renal function and lung abscesses resolved. So far, she had no recurrence of lung abscess.

Discussion

There are many causes for recurrent pneumonia or lung abscesses, including infective and non-infective ones. Inadequate antibiotic coverage is the most common cause so antibiotic regimen should be adjusted according to sensitivity results. In patients who are immunocompromised or with structural lung diseases, mycobacterial, fungal and even parasitic infections should be excluded. Besides chest infection, extrapulmonary sources of infection, such as infective endocarditis and dental infection should be excluded. In cases of lung abscess, drainage should be considered for microbiological workup and enhancing effectiveness of antibiotics. Apart from infection, non-infectious diseases can mimic pneumonia. Malignancy especially squamous cell carcinoma sometimes presents as cavitary lesions. Pulmonary infarct can lead to peripheral wedge-shaped consolidation as a result of infected segmented infarcts. Inflammatory diseases, such as vasculitis, cryptogenic organizing pneumonia and eosinophilic pneumonia, can also cause recurrent and fleeting consolidation.

Granulomatosis with polyangiitis, previously known as Wegener's granulomatosis, was first described by Dr. Klinger in 1931 as variant of polyarteritis nodosa. Dr. Friedrich Wegener, a German pathologist, described it as a separate syndrome in 1936. It was renamed in 2011 as granulomatosis with polyangiitis, GPA in short, because Dr. Friedrich Wegener was a member of the Nazi party before and during World War II. In addition, the new terminology better describes the syndrome by pathological features and vasculitic involvement.

GPA, together with Microscopic polyangiitis (MPA) and Eosinophilic granulomatosis with polyangiitis (EGPA), are examples of ANCA-associated vasculitis, affecting small-medium sized vessels. It is a rare disease, accounting for 12.8 cases per 1 million person-years for adult onset diseases in the USA [1] and less than 2 per 1 million person-years in HK [2]. It has an unclear etiology but likely with an autoimmune element. It's has a classical triad of necrosing granulomatous inflammation of respiratory tract, necrotizing vasculitis of small-medium sized vessels and necrotizing glomerulonephritis. Females with a mean age of 50-60 are more commonly affected and have a 5-year survival between 75-90% [3].

GPA is a systemic disease and multiple organs can be involved. The most commonly affected organs are ENT and respiratory tract, followed by renal system and musculoskeletal system. Around 90% of cases will have a positive c-ANCA [4].

Rheumatologist are still using American College of Rheumatology (ACR) criteria [5] for diagnosis of GPA though it was proposed in 1990 before the recognition that MPA and GPA were different disease entities and ANCA was important in pathogenesis. A diagnosis of GPA can be established if at least two of four criteria are fulfilled: nasal or oral inflammation (such as painless or painful oral ulcers or purulent or bloody nasal discharge), abnormal chest radiograph (such as nodules, fixed infiltrates or cavities), urinary sediment (microhematuria or red cell casts in urine sediment) and granulomatous inflammation on biopsy of vessels. It is simple

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to use clinically, with sensitivity of 88% and specificity of 92% [6]. However, it may not be able to diagnose the disease at an early stage and it cannot differentiate GPA from MPA.

ANCA can be detected by two types of essays, indirect immunofluorescence assay (IF), using alcohol-fixed buffy coat leukocytes, and enzyme-linked immunosorbent assay (ELISA) [6]. In indirect immunofluorescence assay, ethanol is used to alter granule membranes, allowing positively charged contents to migrate to the negatively charged nuclear membrane, resulting in perinuclear membrane staining i.e. perinuclear ANCA (p-ANCA). On the other hand, the positively charged proteins like antibody against proteinase 3 (PR3) remain in the cytoplasm, causing diffuse cytoplasmic staining i.e. cytoplasmic ANCA (c-ANCA). Most antibody against myeloperoxidase (MPO) belong to p-ANCA but antinuclear antibody (ANA) can also lead a false positive p-ANCA. The two can be differentiated by formalin fixation by which anti-MPO will become cytoplasmic staining while ANA remained nuclear staining. ELIZA directly detects anti-PR3 and anti-MPO quantitatively. IF is more sensitive while ELIZA is more specific. Interpretation of staining pattern might have interobserver variation and it can be falsely positive in other autoimmune diseases, like connective tissue disorders, inflammatory bowel disease and autoimmune hepatitis, while it can be falsely negative if the disease is limited or at an early stage. The positive predictive values of GPA using c-ANCA is 45%, ati-PR3 is 75% and both is 88% respectively [6]. Therefore, it is recommended that a positive IF result is followed by ELIZA to detect and quantify the specific ANCA.

ANCA can be used clinically to assist diagnosis of ANCA-associated vasculitis, predict organ involvement and monitor disease progress but not flare prediction. The reliability of disease diagnosis depends on the subtypes of vasculitis and disease activity. ANCA can be positive in 90% of GPA and MPA cases and only 50% of EGPA cases [5]. Around 90% of GPA cases have a positive anti-PR3 while most MPA and EGPA cases have a positive anti-MPO [5]. A negative ANCA cannot rule out ANCA associated vasculitis especially when the disease is in an early stage or controlled with treatment [7]. This is well illustrated in our case that ANCA was negative upon presentation when there was only pulmonary abnormality and it turned positive when there were ENT and renal involvement. Clinical manifestation can overlap in GPA and MPA while specific ANCA can provide a hint on the possible organ involvement. In both diseases, a positive anti-PR3 might predict nasal and oral inflammation, and respiratory tract involvement while skin, renal and pulmonary manifestation will be more likely with a positive anti-MPO [8]. However, ANCA is less useful in predicting future relapse because those who have disease relapse show no difference in trends of ANCA levels compared those who don't [9].

According to European League Against Rheumatism (EULAR) recommendations in 2015 [10], the management of ANCA-associated vasculitis depends on the severity of the disease. **(Figure 7)** For non-organ threatening disease, a combination of glucocorticoid with either methotrexate or mycophenolate mofetil are recommended in remission-induction followed by azathioprine as maintenance therapy. For remission-induction of new-onset organ or life-threatening disease, a combination of glucocorticoids with either cyclophosphamide or rituximab should be used. After disease remission, methotrexate or rituximab should be followed with glucocorticoid tapering. If the disease is well controlled, azathioprine or methotrexate should taper off gradually and rituximab should be stopped. If rapidly progressive renal failure or life-threatening pulmonary hemorrhage occurs, plasma exchange can be considered as it may prevent end-stage renal failure or death at 3 months [11] although long-term follow-up data revealed no benefit in 5-year mortality [12].

The choice between cyclophosphamide and rituximab for severe GPA depends on disease status, patient factors, like patient preference, financial status and comorbidities, as well as treatment factors, including treatment efficacy and side effect profiles.

Cyclophosphamide is a precursor of an alkylating nitrogen mustard that works by suppressing B cell activity. It has been used with corticosteroid as induction therapy since 1970s at a dose of 2mg/kg/day [13]. It can cause serious neutropenic sepsis and bladder complications, including hemorrhagic cystitis in the short term and bladder carcinoma in the long term because its metabolites are toxic to urothelium [13]. Prophylaxis against infection with Pneumocystis jirovecii with trimethoprim/sulfamethoxazole is recommended unless contraindicated. Cyclophosphamide is also

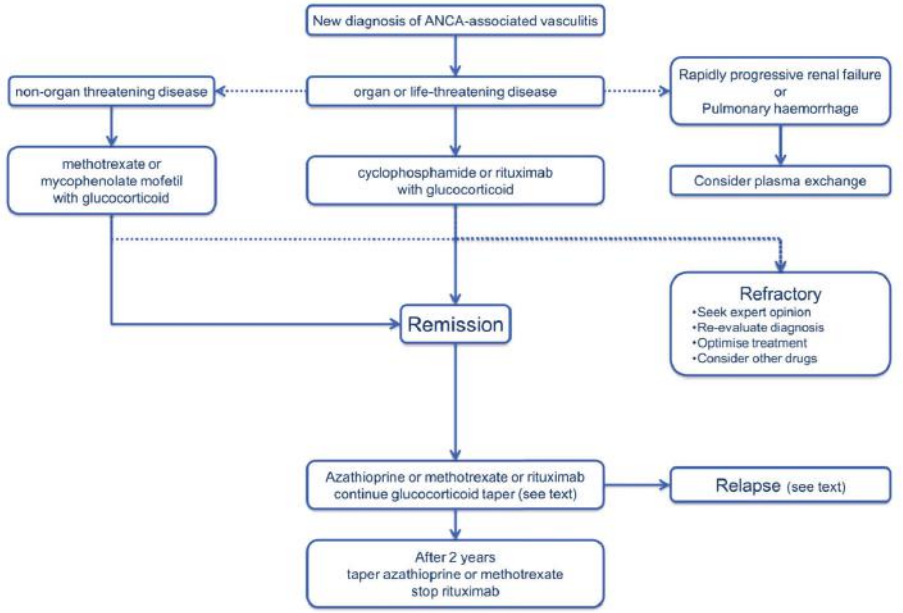

Figure 7: EULAR recommendations for the management of newly diagnosed ANCA-associated vasculitis

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associated with reduced ovarian reserve, ovarian failure and male infertility [15,16] as well as a 11-fold increase in risk of lymphoma [17]. The toxicity of cyclophosphamide is dose dependent, therefore pulsed intravenous regimens were preferred after the CYCLOPS trial [18]. It was a randomized controlled trial involving 149 patients with newly diagnosed generalized ANCA-associated vasculitis with renal involvement, receiving either pulse cyclophosphamide (15 mg/kg every 2 to 3 weeks) or daily oral cyclophosphamide (2 mg/kg/day) plus corticosteroid. The two regimens had no significant difference in disease remission rate and renal function preservation. However, the pulse regimen had a smaller cumulative dose of cyclophosphamide, leading to few side effects, such as leukopenia and bladder complications. Long-term follow-up of the CYCLOPS cohort revealed that although the proportion of participants with relapses was higher in those individuals treated with pulsed cyclophosphamide (40% versus 21%), there were no differences in mortality and renal function between the two arms [19].

Rituximab, a B-cell–depleting anti-CD20 monoclonal antibody, has been tested in two randomized controlled trials for treatment of ANCA-associated vasculitis- RAVE (Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis) and RITUXVAS (Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis) trials [20,21]. In the RAVE trial, rituximab-based regimen was noninferior to oral cyclophosphamide-corticosteroid regimen in disease remission in new-onset cases and was even superior in relapsing disease. **(Figure 8)** However, RITUXVAS trial failed to demonstrate superiority of rituximab over intravenous pulse cyclophosphamide-corticosteroid in disease remission and mortality. **(Figure 9)** The rituximab dose in both studies was 375 mg/m2 of body surface area, once a week for four infusions. Common side effects include infusion reaction and reactivation of occult infection like hepatitis B. Infusion reaction can occur in over half of patients, usually within 30-120 min of the first infusion. This is likely due to reaction between Rituximab and CD20 on lymphocytes, releasing cytokines into circulation. Presentation varies from mild fever, headache and rash to hypotension, bronchospasm and myocardial infarct or even death. Management depends on the reaction severity and symptoms usually resolve after stopping infusion and symptomatic treatment. Infusion can be resumed later at a slower rate. Prophylactic antihistamine and panadol with gradual increase in infusion rate can help reduce the chance of infusion reaction.

Therefore, cyclophosphamide is used in most of the cases while rituximab is preferred in severe relapsing cases, fertility preservation and prevention of bladder complications. However, it is still a self-financed item in public hospitals requiring financial assessment. It costs around HK $75,000 per course (weekly for four doses).

In conclusion, it is important to rule out non-infectious causes for recurrent pneumonia. The clinical, radiological and biochemical findings should be reviewed in each episode of the disease. ANCA needs to be rechecked if there is high clinical suspicion of ANCA associated vasculitis despite prior negative results. Both rituximab and intravenous cyclophosphamide are effective induction therapies for GPA and treatment choice depends on the patient, disease and treatment factors.

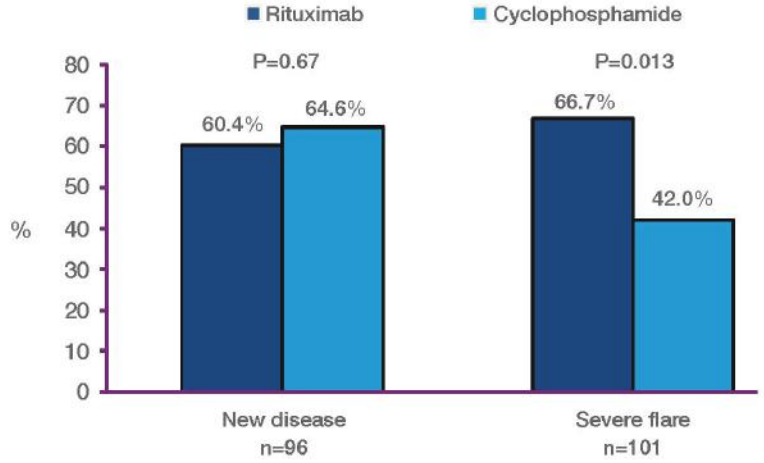

Figure 8: RAVE trial: Rituximab was noninferior to cyclophosphamide in disease remission in new cases but inferior in relapsing cases.

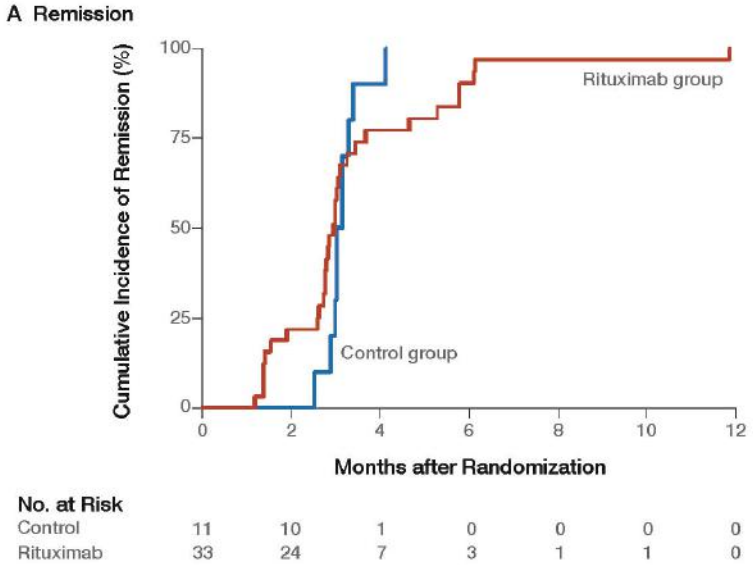

Figure 9: RITUXVAS trial: Rituximab was not superior to pulse cyclophosphamide in disease remission.

References:

1. Panupattanapong, S, et al. Epidemiology and Outcomes of Granulomatosis With Polyangiitis in Pediatric and Working-Age Adult Populations In the United States: Analysis of a Large National Claims Database. *Arthritis & Rheumatology*, 2018, 70.12: 2067-2076.
2. Lee, SH, and John WM Lawton. Heterogeneity of anti-PR3 associated disease in Hong Kong. *Postgraduate medical journal*, 2000, 76.895: 287-288.
3. Mukhtyar, C, et al. Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force. *Annals of the rheumatic diseases*, 2008, 67.7: 1004-1010.
4. Jennette, JC, et al. Small-vessel vasculitis. *New England Journal of Medicine*, 1997, 337.21: 1512-1523.
5. Hoffman, GS, et al. Arthritis Rheum 1998.
6. Stone, JH., et al. Test characteristics of immunofluorescence and ELISA tests in 856 consecutive patients with possible ANCA-associated conditions. *Arthritis Care & Research*, 2000, 13.6: 424-434.
7. Hoffman, GS, et al. Wegener granulomatosis: an analysis of 158 patients. *Annals of internal medicine*, 1992, 116.6: 488-498.
8. Lionaki, S, et al. Classification of antineutrophil cytoplasmic autoantibody vasculitides: the role of antineutrophil cytoplasmic autoantibody specificity for myeloperoxidase or proteinase 3 in disease recognition and prognosis. *Arthritis & Rheumatism*, 2012, 64.10: 3452-3462.
9. Finkielman, JD, et al. Antiproteinase 3 antineutrophil cytoplasmic antibodies and disease activity in Wegener granulomatosis. *Annals of Internal Medicine*, 2007, 147.9: 611-619.
10. Yates, M, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Annals of the rheumatic diseases*, 2016, 75.9: 1583-1594.
11. Jayne, David RW, et al. Prednisolone as adjunctive therapy for severe renal vasculitis. *Journal of the American Society of Nephrology*, 2007, 18.7: 2180-2188.
12. Szpirt, WM, et al. Plasma exchange for induction and cyclosporine A for maintenance of remission in Wegener's granulomatosis—a clinical randomized controlled trial. *Nephrol Dial Transplant* 2011;26:206–13.
13. Novack SN, et al. Cyclophosphamide therapy in Wegener's granulomatosis. *New England Journal of Medicine*, 1971, 284.17: 938-942.
14. Talar-Williams C, et al. Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. *Ann Intern Med* 1996;124:477–84.
15. Schrader M, et al. Impact of chemotherapy on male fertility. *Oncology Research and Treatment*, 2001, 24.4: 326-330.
16. Clowse ME, et al. Ovarian reserve diminished by oral cyclophosphamide therapy for granulomatosis with polyangiitis (Wegener's). *Arthritis Care Res (Hoboken)* 2011;63:1777–81.
17. Knight A, AJ, et al. Cancer incidence in a population based cohort of patients with Wegener's granulomatosis. *Int. J. Cancer.* 2002;100:82–85.
18. de Groot, K, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med* 2009;150:670–80.
19. Harper, L, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. *Ann Rheum Dis* 2012;71:955–60.
20. Jones RB, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *New England Journal of Medicine* 2010;363:211–20.
21. Stone, JH., et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *New England Journal of Medicine* 2010;363:221–32.

What's wrong with the "Immune Booster"?

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Case History

A 67-year-old lady was diagnosed with adenocarcinoma of lung with liver metastases in late 2017. She was given pembrolizumab by a private oncologist after poor response to chemotherapy, and was complicated by pulmonary embolism in December 2017 and given NOAC thereafter. She was admitted in our hospital on 6/8/2018 for progressive dyspnoea. She, however, had no cough, sputum, chest pain, fever, or travel history. On physical examination, she was found to have cyanosis on 15 LO2 mask and bilateral basal crackles on chest examination. Her arterial blood gases showed type I respiratory failure. She had mild neutrophilia but unremarkable liver and renal functions. The CXR was shown in **(Figure 1)**. She was empirically given piperacillin-tazobactam and doxycycline and high flow nasal cannula with FiO2 0.8 on the same day of admission. An urgent plain CT thorax was arranged on that evening **(Figure 2)**.

The ESR and CRP levels were mildly elevated but the procalcitonin level was low. Her nasopharyngeal swab, blood

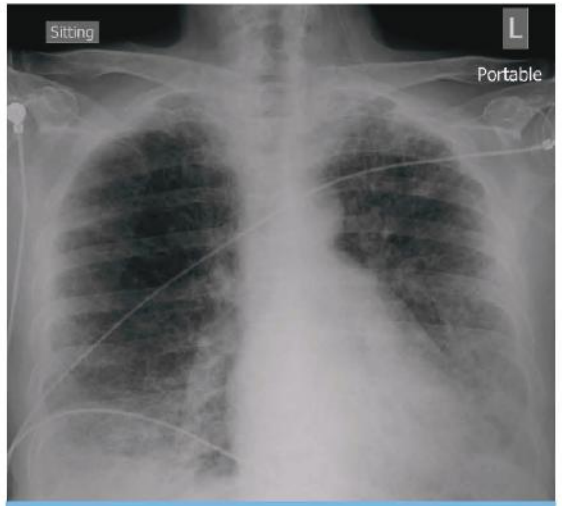

Figure 1

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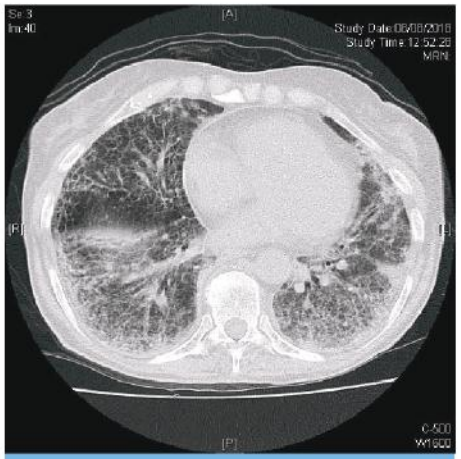
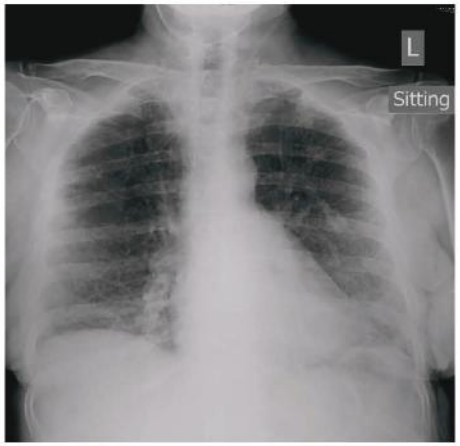


Figure 2

culture and sputum culture were negative, and so were the blood CMV DNA, 1,3-beta-D-glucan and aspergillus antigen tests. Autoimmune markers were negative and she did not have any rash, myalgia or arthralgia.

She has been dependent on high flow nasal cannula for the following days. In view of respiratory failure and high oxygen supply, bronchoscopy would be too risky. We consulted the oncology team for suspected pembrolizumab-related lung toxicity. The oncologist suggested to stop pembrolizumab permanently and suggested corticosteroid. She was given pulse steroid of methylprednisolone 200mg per day for 6 days. She had subjective improvement thereafter and we could decrease the FIO2 of the high flow nasal cannula. She was finally able to wean off high flow nasal cannula and transferred to a private hospital about 2 weeks after admission. She was transferred back to our hospital about 2 months later, when she was stabilised, requiring oxygen through nasal cannula at 4-6L/min. The CXR and the CT thorax were shown in **(Figure 3)**. She is currently followed up in both private and public outpatient settings.



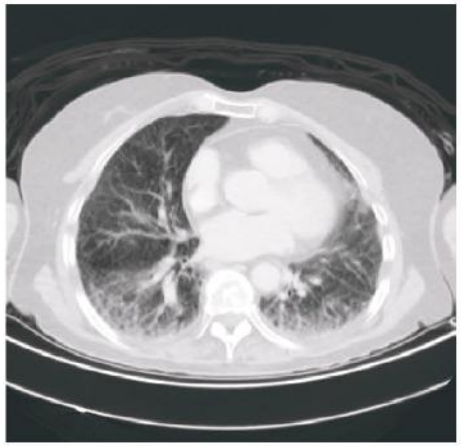


Figure 3

Discussion

The management of Non-Small Cell Lung Cancer (NSCLC) has changed dramatically in the last decade with an increase in the understanding of the biology and with the development of new and multiple treatments. There is emerging evidence of immunotherapy in treating NSCLC.

The immunosurveillance theory proposes that our immune system can identify and eliminate tumour cells when antigens expressed by the tumour cells (neo-antigen) are recognised by the immune system as foreign, eliciting an immune response. Antigens are internalised, processed and displayed by antigen-presenting cells, particularly dendritic cells (DC). The DCs then migrate to the lymph nodes, where they activate T lymphocytes via interaction of specific T-cell receptor with antigen presented by the MHC protein on the dendritic cells' surface. It is now realised that besides the antigen-MHC-TCP interaction, other co-stimulatory signals like T cells' CD28 with APC CD80/86 interaction are important [1].

Tumour cells can however escape the immunosurveillance by several mechanisms. They can manipulate the antigens, cytokines, or upregulate the expression of immune checkpoint molecules. Immunoediting is a dynamic process between the tumor cells and the immune system. It is made up of three phases: elimination, equilibrium, and escape [2].

In order to prevent autoimmunity phenomena, immune checkpoints are set in place. Two very important immune checkpoint molecules are cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1), and in fact Tasuku Honjo and Jim Alison were granted the Nobel Prize in 2018 for the discovery of the two important immune checkpoint molecules which made a great impact on the development of immunotherapy in malignancy.

CTLA-4 is an inhibitory molecule in naïve T cells. It binds to CD80/86 with a high affinity and the action is de-activate T cells. PD-1 is primarily expressed in mature T cells in peripheral tissues. The PD1 signaling is mediated through interaction its ligands PD-L1 and PD-L2. PD-L1 molecules are present in peripheral tissue and some tumour cells, while PDL2 molecules are present mainly on the surface of hematopoietic cells. The PD-1 signaling serves as an inhibitory pathway to inhibit apoptosis of tumour cells, to promote T effector cells exhaustion and to convert T effector cells to inhibitory regulatory T cells [3].

Immune check point inhibitors gain popularity in treating malignancy in recent few years. Anti-PD-1/anti-PD-L1 antibodies are the only immunotherapy approved for NSCLC by the FDA, and meanwhile they are also approved for other malignancies, including melanoma, renal cell carcinoma and head and neck tumours.

The results of major trials in immunotherapy in NSCLC are summarized in table 1 [4-12]. In the randomised controlled trials, patients on anti-PD-1/anti-PD-L1 were found to have improved overall survival and progression free survival, regardless the immune checkpoint inhibitors were used as the 2nd line treatment for metastatic

NSCLC, as the adjuvant therapy to chemotherapy in stage 3 NSCLC, as the 1st line monotherapy treatment for metastatic NSLCL with PD-L1 expression > 50%, or as a constituent of the combination therapy with chemotherapy for untreated metastatic NSCLC.

Immune-related Adverse Events (IrAEs)

As immune checkpoints are important molecules to maintain self-tolerance, the immune checkpoint inhibitors may lead to autoimmunity. In fact, the inhibitory function of PD1 was discovered when PD1-null mice developed autoimmunity. The precise mechanism is however unknown but translational studies showed T cells, antibodies and cytokines may be involved.

The common symptoms are fatigue, rash, dermatitis, myalgia and arthralgia and thyroid dysfunction, but severe IrAEs can manifest as colitis, hepatitis, hypophysitis, pneumonitis, neurological system involvement, pancreatitis and myocarditis. Anti-CTLA-4 immunotherapy related IrAEs are usually more severe and more common when compared with anti-PD-1/anti-PD-L1 therapy, and anti-CTLA-4 therapy is associated with a higher incidence of colitis and hypophysitis, while anti-PD1/anti-PDL1 antibodies are more associated with pneumonitis and thyroiditis [13].

IrAEs usually start to develop within the first few weeks to months, but the onset time can be variable and the adverse events can occur as long as 1 year after treatment discontinuation. The onset is more predictable in CTLA4 inhibitors, usually within 8-12 weeks but the onset can be more variable in anti-PD-1/PD-L1 antibodies with a median onset varies in range of 6 months [14].

The risk factors of irAEs are multi-factorial, including genetic make-up and previous history of autoimmune diseases, although the sensitivity of auto-antibodies is low in irAEs. A combination of immune checkpoint inhibitors and a history of irAEs are also risk factors for irAEs. A Dose-dependent relationship has been observed in anti-CLTA-4 therapy but not anti-PD1/anti-PDL1 antibodies [14].

The National Cancer Institute recommends a standard Common Terminology Criteria for Adverse Events (CTCAE) grading system [15].It ranged from grade 1 to 5 in which grade 1 as asymptomatic or mildly symptomatic, grade 2 as moderate symptoms without hospitalisation, grade 3 as severe symptoms requiring hospitalization, grade 4 as life-threatening disease, and grade 5 as death.

When comparing with traditional chemotherapy, immune checkpoint inhibitor has relatively less side effects. A meta-analysis showed that immunotherapy has significantly less leucopenia, neutropenia and ≥ grade 3 adverse events. The incidence of ≥ grade 3 adverse events is estimated to be 10 -42%, 11-20% and 1-9% respectively in patients on ant-CTLA-4, anti-PD-1 and anti-PD-L1, but the incidence can increase up to 60% in combination immunotherapy of anti-CTLA-4 and anti-PD1/anti-PDL1 [16].

Immune-related Pneumonitis

Respiratory events like cough and dyspnea have been documented in up to 20-40% of patients on immunotherapy, though the incidence of documented pneumonitis is much lower with a reported incidence of 2-4%. The incidence of ≥ grade 3 adverse events and fatal pneumonitis was reported to be 1-2% and 0.2% respectively. There are no symptomatic, pathological or radiographic features pathognomonic of immune-related pneumonitis, and the onset time can be variable [13].

A meta-analysis showed that anti-PD-1 has a higher risk of pulmonary toxicity when compared with conventional chemotherapy, unless the chemotherapy regimens include everolimus which is well-known to result in lung toxicity [17]. The incidence of pneumonitis is higher in anti-PD-1 or anti-PD-L1, when compared with anti-CTLA-4, and it is even higher in combination immunotherapy.

In a cohort of 900 patients on antiPD1 or antiPDL1 for melanoma or NSCLC, the time of onset of pneumonitis ranged from 9 days to 19 months. The incidence was higher in combination therapy compared with monotherapy, i.e. 10% vs 3%. The incidence was similar in patients with melanoma and NSCLC. There was higher proportion of ≥ grade 3 adverse events in combination therapy. The radiological patterns are variable, which can be organizing pneumonia like, ground glass opacities, interstitial thickening, nodular ground glass, or not otherwise specified [18].

A meta-analysis published found NSCLC more likely to be associated with pneumonitis, about three times more common than other malignancies [19], and another meta-analysis found that anti-PD-1 had a higher incidence of pneumonitis compared with antiPD-L1, and treatment naïve patients were also at a higher risk [20].

Both guidelines by American College of Clinical Oncology [21] and European Society of Medical Oncology [13] suggest lung biopsy would be unnecessary unless there are radiological or clinical doubts. Acute interstitial pneumonia/ diffuse alveolar damage is the histology finding for most acute and life-threatening pneumonitis, but immune-related pneumonitis can manifest as non-specific interstitial pneumonia, hypersensitivity pneumonitis like changes or organizing pneumonia in histological findings. Both guidelines recommend bronchoscopy for cases with ≥ grade 2 lung toxicity in order to rule out infection and to safely introduce immunosuppressive agents.

The ESMO guideline [13] suggests to introduce immunosuppressant and to prescribe empirical antibiotics immediately once immune-related pneumonitis is diagnosis. The treatment for grade 1 and grade 2 is similar: to prescribe oral steroid and consider withhold immune check point inhibitors. For grade 3 and 4, ESMO suggests to give pulse steroid and to consider other immunosuppressants.

The ASCO guideline [21] suggests a stepwise approach: to withhold immune checkpoint inhibitor in grade 1, to consider empirical antibiotics and oral steroid in grade 2 disease, and to give pulse steroid in ≥ grade 3 diseases. It also suggests co-trimoxazole and proton pump inhibitors for patients with prolonged steroid use.

In conclusion, immune checkpoint inhibitors are evidence-based therapy for certain types of tumours, including metastatic NSCLC. They can

cause immune-related adverse events, though the incidence of adverse effects is lower compared with traditional chemotherapy. Immune-related pneumonitis is uncommon but life-threatening.

Table 1

Name of Trial	Histology	Line of Treatment	Randomisation	Size	First End-point Results
Checkmate 017	Metastatic squamous NSCLC	2	nivolumab vs docetaxel	272	Significant improvement in OS for patients receiving nivolumab compared with docetaxel (median, 9.2 vs. 6.0 mo; HR, 0.59; p < .001).
Checkmate 057	Metastatic non-squamous NSLCL	2	nivolumab vs docetaxel	582	Significant improvement in OS for patients receiving nivolumab compared with docetaxel (median 12.2 vs. 9.4 mo; HR, 0.73; p = .002).
Keynote 010	Metastatic NSCLC PDL1 +ve tumour > 1%	2	pembrolizumab vs docetaxel	1034	Significant improvement in OS for pembrolizumab at 2 mg/kg (median 10.4 vs. 8.5 mo; HR, 0.71; p = .0008) and pembrolizumab at 10 mg/kg (median, 12.7 vs. 8.5 mo; HR, 0.61; p < .001) compared with docetaxel.
POPULAR	Metastatic NSCLC	2	atezolizumab vs docetaxel	287	Significant improvement in OS for patients receiving atezolizumab compared with docetaxel (median, 12.6 vs. 9.7 mo; HR, 0.73; P = .04).
OAK	Metastatic NSCLC	2	atezolizumab vs docetaxel	850	Significant improvement in OS for patients receiving atezolizumab compared with docetaxel (median 13.8 vs. 9.6 mo; HR, 0.73; P = .0003).
PACIFIC	stage III NSCLC with no disease progresion after > 2 cycles of chemoradiotherapy	Adjuvant to chemo	durvalumab vs placebo	709	Significant improvement in PFS and OS for patients with durvalumab vs. with placebo (PFS median 17.2 vs. 5.6 mo; HR, 0.51, P < 0.001; HR for OS =0.68, P = 0,0025);
Keynote 024	Metastatic NSCLC PDL1 +ve > 50%, no EGFR/ ALK	1	pembrolizumab vs plantinum based chemo	305	Significant improvement in PFS for patients receiving pembrolizumab compared with chemotherapy (median 10.3 vs. 6.0 mo; HR, 0.5; p < .00001).
Keynote 407	untreated metastatic, squamous NSCLC	1	Pembrolizumab + chemo vs chemo (carboplatin and either paclitaxel or nanoparticle)	559	Significant improvement in overall survival was 15.9 months in the pembrolizumab-combination group and 11.3 months (95% CI, 9.5 to 14.8) in the placebo-combination group (hazard ratio for death, 0.64; 95% CI, 0.49 to 0.85; P<0.001).
Keynote 189	Untreated metastatic non-squamous NSCLC with no EGFR/ ALK	1	Pembrolizumab + chemo vs chemo (pemetrexed and a platinum-based drug)	616	Rate of overall survival at 12 months was 69.2% (95% confidence interval [CI], 64.1 to 73.8) in the pembrolizumab-combination group versus 49.4% (95% CI, 42.1 to 56.2) in the placebo-combination group Median progression-free survival was 8.8 months (95% CI, 7.6 to 9.2) in the pembrolizumab-combination group and 4.9 months (95% CI, 4.7 to 5.5).

References:

1. Domingues D, Turner A, Silva MD, et al. Immunotherapy and lung cancer: current developments and novel targeted therapies. *Immunotherapy* 2014; 6:1221–123.
2. Mittal D, Gublinn MM, Schreiber RD, et al. New insights into cancer immunoediting and its three component phases – elimination, equilibrium and escape. Curr Opin Immunol. 2014; 27:16-25 .
3. Shine R, Ranjit J, Sameep S. Review of checkpoint inhibitor immunotherapy for the management of non-small cell lung cancer. ImmunoTargets and Therapy 2018:7 63–75.
4. Paz-Ares L, Luft A, Vicente D, et al Pembrolizumab plus chemotherapy for squamous non-small cell lung cancer. NEJM 2018; 379(21): 2040-51.**5.** Borghaei H, Luis PA, Leora H, et al. Nivolumab versus docetaxel in Advanced nonsquamous non-small-cell lung cancer. N Eng J Med 2015; 373: 1627-39.
6. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small cell lung cancer (KEYNOTE-010): a randomized controlled trial. Lancet 2016; 387: 1540-50.
7. Fehbrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPULAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2018; 391: 748-57.
8. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomized controlled trial. Lancet 2017; 389: 255-65.
9. Antonia SJ, Villegas A, Daniel D, et al: Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med 377:1919-1929, 2017.
10. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Eng J Med 2016; 375(19):1823-33.
11. Brahmer J, Reckamp KL, Baas P. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Eng J Med 2015; 373(2): 123-35 .
12. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab pluse chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med. 2018 May 31;378(22):2078-2092.
13. Postow MA, Sidlow R, Hellmann MD, et al. Immune-related adverse events associated with immune checkpoint blockade. N Eng J Med 2018; 378:158-68.
14. Haanen JBAG, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice guidelines for diagnosis, treatment and follow-up Ann Oncol 2017; 28(suppl 4): iv 119-42.
15. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf (Accessed on March 09, 2018).
16. Larkin J, Chiarion Sileni V, Gonzalez R et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Eng J Med 2015; 373: 23–34.
17. Baxi S, Yang A, Gennarelli RL, et al. Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis. BMJ 2018;360:k793.
18. Naidoo J, Wang X, Woo KM, et al. Pneumonitis in patients treated with anti-programmed death 1/ programmed death ligand 1 therapy. Journal of Clinical oncology. 2017:35; 707-17.
19. Nishino M, Giobbie-Hurder A, Hatabu H, et al. Incidence of Programmed Cell Death 1 Inhibitor–Related Pneumonitis in Patients with Advanced Cancer A Systematic Review and Meta-analysis. JAMA oncology 2016;2(12):1607-16.
20. Khunger M, Rakshit S, Pasupuleti V, et al. Incidence of Pneumonitis With Use of Programmed Death 1 and Programmed Death-Ligand 1 Inhibitors in Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis of Trials. Chest. 2017 Aug;152(2):271-281.
21. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American society of clinical oncology clinical practice guideline. Journal of Clinical Oncology; 36: 1714-68.