CASE REPORT

Lower dose pembrolizumab monotherapy in the treatment of brain metastases from non-small cell lung carcinoma: A report of two cases

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ABSTRACT

Introduction: Lung cancer is the leading malignancy metastatic to the central nervous system with approximately 20% to 44% of all cases developing brain metastasis. Immunotherapy using pembrolizumab, an anti-PD1monoclonal antibody, is a novel method in lung cancer treatment and has shown favorable results in patients with metastatic brain lesions from non-small cell lung carcinoma (NSCLC). However, the cost of the recommended treatment dose limits its use especially in developing countries like the Philippines.

Case Presentation: The authors report two patients with lung cancer with brain metastasis upon diagnosis. The first patient is a 65-year-old male, non-smoker with PD-L1 expression of 60%. He was started on pembrolizumab 100 mg IV every three (3) weeks and a repeat CT scan after 11 cycles revealed a reduction of the two brain metastatic lesions and no fluoro-D-glucose (FDG) uptake on positron emission tomography (PET) scan even after one year into treatment. The second patient is a 67-year-old female, a previous smoker with PD-L1 expression of 50% with a metastatic solitary solid nodule in the cortex of the right cerebellum. After five cycles of pembrolizumab 100 mg IV every three weeks, there was noted complete resolution of brain metastasis on PET scan even after one year of treatment.

Conclusion: A lower dose of pembrolizumab (100 mg given every 3 weeks) was found to be effective in the management of advanced NSCLC with brain metastasis in the two patients. Further studies are recommended to investigate lower dose pembrolizumab as monotherapy without radiation therapy or surgery in patients with NSCLC with brain metastasis especially in the setting of a resource-limited country like the Philippines.

Keywords: *immunotherapy, lower-dose pembrolizumab, NSCLC, lung cancer, brain metastasis, case report, developing country, Philippines*

Introduction

Lung cancer is the leading cause of cancer-related mortality and the second most common cancer worldwide [1]. In the Philippines, lung cancer is likewise the leading cause of mortality (18.4%) among all types of cancers [2]. Non-small cell type lung cancer (NSCLC) accounts for approximately 85% of all lung cancer patients with 20-44% of them having brain metastases at one point in their disease course [3-7]. In fact, studies report that at least 50% will have brain metastases on autopsy [8-11]. Metastatic brain lesions from NSCLC upon diagnosis of NSCLC are associated with poor prognosis with a median overall survival (OS) of only 1-2 months in untreated patients [12].

The standard treatment for NSCLC with solitary and multiple brain metastasis/es is surgical resection and/or radiation therapy or stereotactic radiosurgery (SRS) [13,14]. The role of systemic therapy has traditionally been used after performing surgery and/or radiation therapy. However, with the advent of more targeted treatments that may penetrate the blood-brain barrier more, the role of systemic therapy may take its place in the forefront, especially for smaller and less symptomatic brain metastasis/es.

The expression of immune checkpoint programmed death ligand-1 (PD-L1) is believed to allow cancer cells to

avoid detection of the innate immune response whereas the programmed cell death 1 (PD-1) receptor is expressed mainly on cell surfaces of activated cytotoxic (CD8+) T-cells [15]. (15) The activated T-cells have PD-1 receptors to which the PD-L1 binds resulting in the suppression of the immune system via inhibition of the regulatory T-cell apoptosis and induction of cytotoxic T-cell apoptosis [16-19]. The formation of the ligand-receptor complex causes inhibition of interleukin-2 (IL2) synthesis that is responsible for the activated T-cells proliferation, cell differentiation, and death which altogether regulates the immune response [18-20].

Immunotherapy using pembrolizumab, an anti-PD1 monoclonal antibody which is a novel method in lung cancer treatment, has shown favorable results in patients with metastatic brain cancer from NSCLC. However, the cost of the recommended treatment dose limits its use especially in developing countries like the Philippines [21,22]. Furthermore, patients with metastatic diseases sometimes refuse invasive procedures including surgical intervention and even SRS, hence, the use of other treatment options including pembrolizumab immunotherapy is being explored. However, literature using pembrolizumab as monotherapy for NSCLC with brain metastasis remains scarce [24]. This paper presented two cases of patients with NSCLC metastasis to the brain managed with lower dose pembrolizumab monotherapy.

Case Presentation

Case 1

A 65-year-old male, weighing 63 kg, with no history of smoking and no family history of malignancy, presented at the emergency department with an enlarging and tender right mandibular mass associated with left-sided body weakness. Plain cranial CT scan was done revealing two intracranial masses measuring 1.6 x 1.5 cm and 1.8 x 1.4 cm to which he was given dexamethasone. Positron emission tomography (PET) scan was done revealing the following findings: the primary lung mass measuring 6.0 x 6.5 x 6.0 cm at the superior segment of the right lower lobe, right mandibular mass measuring 3.3 x 2.5 x 2.7 cm, and the previously seen two areas of brain metastasis: right frontal lobe and left fronto-parietal lobe measuring 1.6 x 1.5 cm and 1.8 x 1.4 cm, respectively [Figure 1 – a, b]. Biopsy of the lung mass showed non-small cell lung carcinoma that is positive for PD-L1 with an expression of 60% and negative for EGFR mutation. The patient was referred for SRS but refused. Neurosurgical consultation was not done because the sizes and number of the cranial lesions were both acceptable for SRS and this is the least invasive procedure and will not delay systemic workup. However, the patient refused SRS and opted to be treated with immunotherapy due to its side effect profile. He was started on pembrolizumab 100 mg IV every three weeks and denosumab 120 mg subcutaneously every four (4) weeks. Before mid-cycle of the regimen, there was a noted resolution of the left-sided body weakness with the disappearance of the right mandibular mass. After 11 cycles of pembrolizumab, the primary lung lesion also decreased in size measuring 2.4 x 2.0 x 2.4 cm. The two brain metastatic lesions – right frontal lobe and left frontoparietal lobe – were reduced to 1.0 x 0.9 cm and 0.7 x 0.5 cm respectively [Figure 1 – c, d], and both had no fluoro-D-glucose (FDG) uptake. The patient had no significant toxicity during chemotherapy as the major toxicity observed was grade 1 transaminitis based on the Common Terminology Criteria for Adverse Events (CTCAE Version 5.0). After 1 year of lower dose pembrolizumab, the brain lesion remained stable with no new discrete enhancing mass or abnormal meningeal enhancement noted. The previously noted bone metastases had no FDG uptake and the lung metastases remained stable. The plan is to continue pembrolizumab and the patient willingly agreed to this.

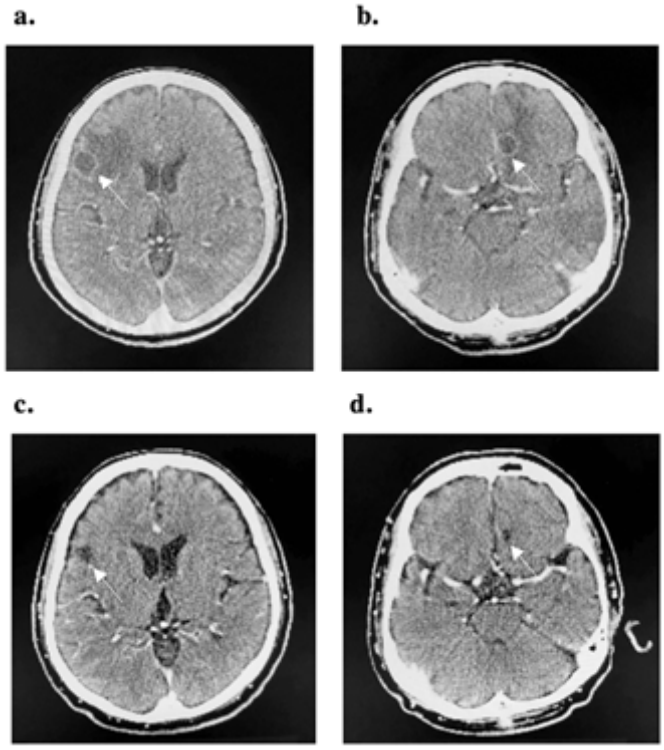

Figure 1. *Brain computed tomography image before pembrolizumab treatment showing metastases in the right frontal lobe (a) and left fronto-parietal lobe (b) measuring 1.6 x 1.5 cm and 1.8 x 1.4 cm, respectively, and repeat scan after 7 cycles showing a reduction in the size of the lesion to 1.0 x 0.9 cm (c) and 0.7 x 0.5 cm (d) with no FDG uptake.*

Case 2

A 67-year-old female, weighing 53 kg, previous smoker for 9 pack-years but stopped 10 years ago with an unremarkable family history, sought consult due to chronic coughing episodes. She was initially managed as a case of parapneumonic pleural effusion. Results of the pleural fluid cytology revealed adenocarcinoma with PD-L1 expression of 50% and negative for EGFR mutation. Metastatic work-up revealed a solitary solid nodule in the cortex of the right cerebellum measuring 0.6 x 0.7 x 0.5 cm (AP/T/CC). The patient had no neurologic deficits but presented only with dizziness. The patient was also referred for SRS but refused. She preferred to be treated with immunotherapy instead due to its side effect profile. She was started on pembrolizumab 100 mg IV every three weeks and zoledronic acid every three weeks. The plan was to do SRS but the patient did not consent. After 5 cycles of pembrolizumab, there was a noted disappearance of the cerebellar mass on PET-CT scan. One year into treatment with lower dose pembrolizumab, there was still no identifiable cranial mass on the PET-CT scan and the patient remains asymptomatic and has no adverse toxicity from the treatment based on the Common Terminology Criteria for Adverse Events (CTCAE Version 5.0). The right lung lesion is stable, has probable metabolic resolution based on the PET scan, and there was further regression of the right-sided pleural effusion. No FDG-avid disease in the liver and elsewhere. The plan is to continue pembrolizumab therapy and the patient willingly agreed to this.

Discussion

Metastatic brain tumor is the leading cause of malignancy in the central nervous system (CNS) [24]. Non-small cell lung cancer (NSCLC) accounts for 85% of patients with lung cancer and brain metastases from NSCLC account for approximately 20% to 44% of all cases of brain metastasis [3-7]. Traditional therapies for metastatic NSCLC such as chemotherapy, radiotherapy, and surgery are often employed in combination to be more effective in eliminating residual metastatic disease but this approach is still unsuccessful in completely eliminating residual cancer cells particularly in the CNS [25,26]. Traditional chemotherapeutic agents used in metastatic NSCLC to the brain include the use of platinum-based chemotherapy like cisplatin and carboplatin, and paclitaxel and docetaxel although the last two agents have poor brain penetration at sufficient concentration to cause substantial anti-tumor effect [27-32].

Immunotherapy using pembrolizumab, an anti-PD-1 monoclonal antibody, has shown favorable outcomes in patients dealing with advanced NSCLC. However, more robust studies regarding blood-brain barrier penetration have been limited but existing studies suggest that disruption of the blood-brain barrier as well as neovascularization may allow penetration into the CNS [23,33-35]. The use of pembrolizumab is the recommended standard of treatment for patients with metastatic NSCLC without driver mutations and the tumor expresses PD-L1 mutation of 50% [36]. Penetration of pembrolizumab in the central nervous system remains in question, although reports suggest possible activity and beneficial therapeutic response [7,23,37-39]. Aside from its possible effect and penetration to the CNS, the minimal optimal dose required to cause a substantial anti-tumor effect on the brain is still unknown.

The US Food and Drug Administration approved pembrolizumab as an adjunct treatment for NSCLC with brain metastasis with a dose of 200 mg every three weeks. Several studies showed that partial or complete CNS response can be achieved with the administration of this drug at this dose [22,40]. However, the cost of treatment using the recommended treatment dose limits its use especially in developing countries including the Philippines [21,22,40].

In the landmark study KEYNOTE-001, study on the ex vivo pharmacokinetics (PK) of PD-1 receptor saturation demonstrated that at 1 mg/kg, there was complete peripheral target engagement. In the initial dose escalation cohort, there was durable anti-tumor activity across all patient cohorts at 1-10 mg/kg given every three weeks. Succeeding studies demonstrated the efficacy of 2 mg/kg given every three weeks and 10 mg/kg dose given every two weeks were both similar, but no study was done to examine a dose of <2 mg/kg or a lower fixed-dose [41-44]. Despite the PK profile of

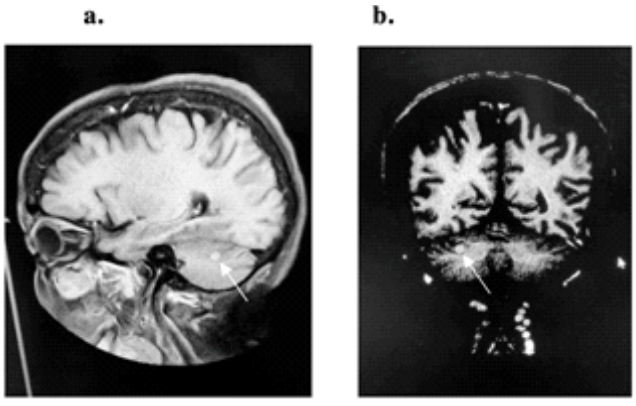

Figure 2. *Brain magnetic resonance image before pembrolizumab treatment. Sagittal view measuring 0.6 x 0.7 x 0.5 cm (a) and coronal view (b).*

pembrolizumab at the PDL1 receptor with saturation and clinical efficacy at 1 mg/kg and 2 mg/kg, respectively, the standard fixed-dose of 200 mg given every three weeks was used in a Phase III clinical trial that later on led to its FDA approval [45].

Limited studies using a lower dose of pembrolizumab at 100 mg given every three weeks are being explored. In a retrospective, an observational study done in Singapore by Li Low *et al.* (Table 1) involving 114 patients who received pembrolizumab, the efficacy, progression, and survival outcomes of adult patients weighing between 31-103 kg diagnosed with advanced NSCLC without prior chemotherapy were observed and compared using the lower dose of pembrolizumab at 100 mg (n= 65), and the standard dosing of 200 mg (n=49) given every three weeks in a single center from 2016 to 2020 has shown no significant difference in the progression-free survival and overall survival outcomes between the two doses. Patients who were given a lower dose of pembrolizumab 100 mg when combined with chemotherapy also responded well to the treatment with noted significant cost savings [22]. However, this study did not specify the effect of pembrolizumab in CNS metastasis.

In a case report by Marvin and colleagues (2020), monotherapy using pembrolizumab 200 mg given every three weeks for three months is effective and showed resolution of brain metastasis from NSCLC based on radiographic findings [23].

In a case report by Di and Zhang (2019), a 51-year-old man, heavy smoker, with stage IV NSCLC who underwent surgical removal of lung tumor and had adjuvant chemotherapy using cisplatin and etoposide had subsequent metastasis to the brain. He was treated with pembrolizumab 100 mg every two weeks and after 18 cycles of pembrolizumab, the cranial CT scan and MRI revealed obvious reduction of brain metastasis and the patient remains completely asymptomatic [39].

In this case report, the two patients with NSCLC with brain metastasis responded well to treatment using monotherapy with a lower dose of pembrolizumab 100 mg every two weeks. The follow-up scan of the second case showed complete resolution of the intracranial lesion and loss of FDG uptake suggesting blood-brain barrier permeability even with the low dose of pembrolizumab. In both patients, the edema associated with active brain lesions was also resolved.

Table 1. *Summary Table of Lower Fixed-dose Pembrolizumab Studies*

Author	Study objective	Study design	Participants	Conclusion	Intervention
Li Low *et al.* (2021) [22]	To assess the efficacy of a lower fixed-dose of 100mg, which is closer to 2 mg/kg weight-based dose in the average-size Asian patient.	Retrospective observational study	A total of 114 patients received pembrolizumab for advanced NSCLC. Sixty-five (57%) and 49 (43%) received fixed-dose pembrolizumab 100 mg and 200, respectively. Weight of patient ranges from 31 kg to 103 kg with no significant differences between the two groups	Pembrolizumab had efficacy at a dose of 100 mg every three weeks. No significant differences between the two groups in terms of progression-free survival (PFS) and overall survival (OS). A randomized prospective trial is required for further investigation	Pembrolizumab 100mg vs pembrolizumab 200mg.
Li Low et al. (2020) [37]	To determine the efficacy of pembrolizumab at a low fixed-dose (100mg) compared to the standard dosing (200mg).	Retrospective observational study	A total of 92 ECOG 0-2 patients with advanced stage NSCLC were treated with pembrolizumab 100mg (46 patients, 50%) and 200mg (46 patients, 50%).	A lower fixed-dose (100mg) showed no difference in the progression-free survival and response rate in an Asian cohort. Further randomized trial in Asian population is recommended.	Pembrolizumab 100mg vs pembrolizumab 200mg.
Di and Zhang (2019) [39]	To present two cases of NSCLC with brain metastasis treated with pembrolizumab and to discuss the safety and efficacy in these patients.	Case report	Two patients with NSCLC with CNS metastasis previously treated with combination therapy (surgery, chemotherapy, and RT) treated with pembrolizumab (100 mg/ 2 weeks and 120 mg/ 3 weeks).	Pembrolizumab showed activity in brain metastasis of the 2 patients with NSCLC and with an acceptable safety profile.	Pembrolizumab 100 mg and 120 mg

Given no significant difference between the 2 mg/kg and the fixed-dose of 200 mg given every three weeks, the lower weight of Asian patients, and the economic benefit of a lower dose, a lower fixed-dose of 100 mg pembrolizumab given every three weeks requires further evaluation [22,46].

As of the present, there are no cost-effectiveness with efficacy studies directly comparing the standard dose to lower dose pembrolizumab. In the Philippines, one vial of pembrolizumab 100 mg costs approximately Php 75,000-85,000 [47]. This is not within reach of most patients, especially since our healthcare system is mostly out-of-pocket. Giving it at the recommended dose of 200 mg will cost Php 150,000 - 170,000 every three weeks until the resolution of all active lesions. Studies to assess the efficacy of low-dose pembrolizumab monotherapy among patients with NSCLC with metastatic brain lesions also remain scarce but the limited studies and case reports have shown promising results. The use of a lower than recommended dose of pembrolizumab (100 mg every 3 weeks) should be explored in resource-limited areas such as the Philippines, especially since patients in this study responded well to it. The authors suggest that patients with brain metastasis from NSCLC who are not amenable to the standard therapy (surgical resection of brain tumor or radiotherapy) and with minimal symptoms from brain metastases, good functional capacity, and high PD-L1 expression (>/= 50%) may be given a trial of systemic treatment alone with pembrolizumab.

This study has limitations; despite the beneficial effects seen in the patients and the beneficial economic impact, it should be interpreted with caution, especially in a much larger patient population and those with brain metastasis since most studies dealing with NSCLC with brain metastasis used the fixed-dose of pembrolizumab 200 mg given every three weeks and not the lower fixed-dose of 100 mg. Moreover, since this is a case report, the power of the study to show a statistically significant difference is not possible, thus, a larger study using a lower fixed-dose pembrolizumab at 100 mg for patients with advanced NSCLC who already have brain metastasis is recommended especially in the Asian population.

Conclusion

Two cases of brain metastases from NSCLC who were treated with a lower dose of pembrolizumab 100 mg given every three weeks as monotherapy, without surgery or radiation therapy was presented. This treatment was found to be effective in treating the primary lesion as well as other metastatic foci including the brain metastases, with one of the patients reported to have complete resolution of the intracranial lesion and loss of FDG uptake even after 1 year into treatment. However, foregoing the recommended initial treatment such as surgery and/or radiation therapy in the hope that the lower dose immunotherapy (100 mg every 3 weeks) will successfully treat the primary lung lesion and/or the brain metastasis/es may be a point of discussion that needs further investigation. There is still limited data regarding the use of the lower dose pembrolizumab in the treatment of advanced NSCLC, especially those with brain metastases. A larger–scale, cost–effectiveness, and efficacy study comparing standard dose to lower dose pembrolizumab in lung cancer with brain metastasis will benefit patients immensely in third-world countries like the Philippines.

Informed Consent

Both patients have authorized the use of this material for publication in print and/or via internet dissemination for others to read. Informed consent was obtained after detailed explanation of the nature and purpose of this case report. Strict anonymity of the persons involved was maintained.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. (2021) Global cancer statistics (2020): GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 71: 209- 249. https://doi.org/10.3322/caac.21660
2. Globocan 2020 via file:///Users/admin/Downloads/Globocan%20philippines.pdf
3. Duma, Narjust *et al.* (2019) Non–Small Cell Lung Cancer: Epidemiology, Screening, Diagnosis, and Treatment Mayo Clinic Proceedings, 94(8)1623 – 1640
4. Dela Cruz CS, Tanoue LT, Matthay RA. (2011) Lung cancer: epidemiology, etiology, and prevention. Clin Chest Med. 32(4):605-644. doi:10.1016/j.ccm.2011.09.001
5. Lim JH, Um SW. (2018) The risk factors for brain metastases in patients with non-small cell lung cancer. Ann Transl Med. 6(Suppl 1):S66. doi:10.21037/atm.2018.10.27
6. Tsakonas G. *et al.* (2017) Management of brain metastasized non-small cell lung cancer (NSCLC) – From local treatment to new systemic therapies. Cancer Treatment Reviews, 54:122 – 131
7. Wang S, Hu C, Xie F, Liu Y. (2020) Use of Programmed

Death Receptor-1 and/or Programmed Death Ligand 1 Inhibitors for the Treatment of Brain Metastasis of Lung Cancer. Onco Targets Ther. 13:667-683. doi:10.2147/OTT.S235714

8. Wakuda, Kazushige *et al.* (2021) Efficacy of pembrolizumab in patients with brain metastasis caused by previously untreated non-small cell lung cancer with high tumor PD-L1 expression Lung Cancer, 151:60 – 68
9. Yuzhalin AE, Yu D. (2020) Brain Metastasis Organotropism. Cold Spring Harb Perspect Med. 10(5):a037242. doi: 10.1101/cshperspect.a037242. PMID: 31548224; PMCID: PMC7197417.
10. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. (2004) Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. J Clin Oncol. 22(14):2865-72. doi: 10.1200/JCO.2004.12.149. PMID: 15254054.
11. Waqar SN. Samson PP. Robinson CG. *et al.* (2018) Non-small-cell lung cancer with brain metastasis at presentation. Clin. Lung Cancer. 19: e373-e379
12. Hubbs JL, Boyd JA, Hollis D, Chino JP, Saynak M, Kelsey CR. (2010) Factors associated with the development of brain metastases: analysis of 975 patients with early stage non small cell lung cancer. Cancer. 116(21):5038-46. doi: 10.1002/cncr.25254. PMID: 20629035.
13. Shinde A, Akhavan D, Sedrak M, Glaser S, Amini A. (2019) Shifting paradigms: whole brain radiation therapy versus stereotactic radiosurgery for brain metastases. CNS Oncol. 8(1):CNS27. doi:10.2217/cns-2018-0016
14. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, Arbuckle RB, Swint JM, Shiu AS, Maor MH, Meyers CA. (2009) Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol. 10(11):1037-44. doi: 10.1016/S1470-2045(09)70263-3. Epub 2009 Oct 2. PMID: 19801201.
15. Parra ER, Villalobos P, Mino B, Rodriguez-Canales J. (2018) Comparison of Different Antibody Clones for Immunohistochemistry Detection of Programmed Cell Death Ligand 1 (PD-L1) on Non-Small Cell Lung Carcinoma. Appl Immunohistochem Mol Morphol. 26(2):83-93. doi: 10.1097/PAI.0000000000000531. PMID: 28719380; PMCID: PMC5815635.
16. Lin G, Fan X, Zhu W, Huang C, Zhuang W, Xu H, Lin X, Hu D, Huang Y, Jiang K, Miao Q, Li C. (2017) Prognostic significance of PD-L1 expression and tumor infiltrating lymphocyte in surgically resectable non-small cell lung cancer. Oncotarget. 8(48):83986-83994. doi: 10.18632/oncotarget.20233. PMID: 29137398; PMCID: PMC5663570.
17. Shimoji M, Shimizu S, Sato K, Suda K, Kobayashi Y, Tomizawa K, Takemoto T, Mitsudomi T. (2016) Clinical and pathologic features of lung cancer expressing programmed cell death ligand 1 (PD-L1). Lung Cancer. 98:69-75. doi: 10.1016/j.lungcan.2016.04.021. Epub 2016 May 25. PMID: 27393509.
18. Asao H. (2014) Interleukin-2, Reference Module in Biomedical Sciences, Elsevier, ISBN 9780128012383, https://doi.org/10.1016/B978-0-12-801238-3.04058-7.
19. Francisco LM, Sage PT, Sharpe AH. (2010) The PD-1 pathway in tolerance and autoimmunity. Immunol Rev. 236:219-42. doi: 10.1111/j.1600-065X.2010.00923.x. PMID: 20636820; PMCID: PMC2919275.
20. Sheppard KA, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, Qiu Y, Jussif JM, Carter LL, Wood CR, Chaudhary D. (2004) PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 574(1-3):37-41. doi:10.1016/j.febslet.2004.07.083. PMID: 15358536.
21. Pawelczyk K, Piotrowska A, Ciesielska U, *et al.* (2019) Role of PD-L1 Expression in Non-Small Cell Lung Cancer and Their Prognostic Significance according to Clinicopathological Factors and Diagnostic Markers. Int J Mol Sci. 20(4):824. doi:10.3390/ijms20040824
22. Low, JL, Huang, Y, Sooi, K, *et al.* (2021) Low-dose pembrolizumab in the treatment of advanced non-small cell lung cancer. Int. J. Cancer. 149: 169–176. https://doi.org/10.1002/ijc.33534
23. Marvin EA, Furrow KL, Kar A, Cuoco JA. (2020) Response of Pembrolizumab Alone for Non-small Cell Lung Cancer With Brain Metastasis: A Case Report and Literature Review. Front. Oncol., https://doi.org/10.3389/fonc.2020.577159
24. Fox BD, Cheung VJ, Patel AJ, Suki D, Rao G. (2011) Epidemiology of metastatic brain tumors. Neurosurg Clin N Am. 22:1–6. doi: 10.1016/j.nec.2010.08.007
25. Abid H, Watthanasuntorn K, Shah O, *et al.* (2019) Efficacy of Pembrolizumab and Nivolumab in Crossing the Blood Brain Barrier. Cureus 11(4): e4446. doi:10.7759/cureus.4446 2.
26. Dang TO, Ogunniyi A, Barbee MS, Drilon A. (2016) Pembrolizumab for the treatment of PD-L1 positive advanced or metastatic non-small cell lung cancer. Expert Rev Anticancer Ther. 16:13-20. 10.1586/14737140.2016.1123626
27. Fellner S, Bauer B, Miller DS, Schaffrik M, Fankhanel M, Spruss T, *et al.* (2002) Transport of paclitaxel (Taxol)

across the blood-brain barrier in vitro and in vivo. J Clin Invest. 110:1309–18. doi: 10.1172/JCI0215451

28. Lilenbaum RC, Herndon JE 2nd, List MA, Desch C, Watson DM, Miller AA, *et al.* (2005) Single-agent versus combination chemotherapy in advanced non-small-cell lung cancer: the cancer and leukemia group B (study 9730). J Clin Oncol.23(1):190–6.
29. Tije AJ, Loos WJ, Zhao M, Baker SD, Enting RH, van der Meulen H, *et al.* (2004) Limited cerebrospinal fluid penetration of docetaxel. Anticancer Drugs. 15:715–8. doi: 10.1097/01.cad.0000136882.19552.8f
30. Jacobs S, McCully CL, Murphy RF, Bacher J, Balis FM, Fox E. (2010) Extracellular fluid concentrations of cisplatin, carboplatin, and oxaliplatin in brain, muscle, and blood measured using microdialysis in nonhuman primates. Cancer Chemother Pharmacol. 65:817–24. doi: 10.1007/s00280-009-1085-7
31. Jacus MO, Daryani VM, Harstead KE, Patel YT, Throm SL, Stewart CF. (2016) Pharmacokinetic properties of anticancer agents for the treatment of central nervous system tumors: update of the literature. Clin Pharmacokinet. 55:297–311. doi: 10.1007/s40262-015-0319-6
32. Kerr JZ, Berg SL, Dauser R, Nuchtern J, Egorin MJ, McGuffey L, *et al.* (2001) Plasma and cerebrospinal fluid pharmacokinetics of gemcitabine after intravenous administration in nonhuman primates. Cancer Chemother Pharmacol. 47:411–4. doi: 10.1007/s002800000253
33. Ernani V and Thomas E (2019) Management of Brain Metastases in Non–Small-Cell Lung Cancer Stinchcombe Journal of Oncology Practice 2019 15:11, 563-570
34. Powell SF, *et al.* (2021) Outcomes With Pembrolizumab Plus Platinum-Based Chemotherapy for Patients With NSCLC and Stable Brain Metastases: Pooled Analysis of KEYNOTE-021, -189, and -407, Journal of Thoracic Oncology, 16(11).
35. Sun L, *et al*. (2021) Outcomes in Patients With Non–small-cell Lung Cancer With Brain Metastases Treated With Pembrolizumab-based Therapy. Clinical Lung Cancer. 22(1):P58-66.E3. DOI:https://doi.org/10.1016/j.cllc.2020.10.017
36. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. (2016) Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. New Engl J Med. 375(19):1823–33.
37. Goldberg SB, Gettinger SN, Mahajan A, Chiang AC, Herbst RS, Sznol M, *et al.* (2016) Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. Lancet Oncol. 17:976–83. doi: 10.1016/S1470-2045(16)30053-5
38. Goldberg SB, Schalper KA, Gettinger SN, Mahajan A, Herbst RS, Chiang AC, *et al.* (2020) Pembrolizumab for management of patients with NSCLC and brain metastases: long-term results and biomarker analysis from a non-randomised, open-label, phase 2 trial. Lancel Oncol. 21:655–3. doi: 10.1016/S1470-2045(20)30111-X
39. Di M, Zhang L. (2019) Pembrolizumab for non-small cell lung cancer with central nervous system metastases: A two-case report. Thorac Cancer. 10(2):381-385. doi:10.1111/1759-7714.12963
40. Low JL, Sooi K, Huang Y, *et al.* (2020) Cost and efficacy of low-dose pembrolizumab in the treatment of non-small cell lung cancer patients in Asia. Journal of Clinical Oncology 38:15_suppl, e19385-e19385
41. Garon EB, Rizvi NA, Hui R, *et al.* (2015) Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 372:2018-2028
42. Kang SP, Gergich K, Lubiniecki GM, *et al.* (2017) Pembrolizumab KEYNOTE-001: an adaptive study leading to accelerated approval for two indications and a companion diagnostic. Ann Oncol. 28:1388-1398.
43. Reck M, Rodríguez-Abreu D, Robinson AG, *et al.* (2019) Updated analysis of KEYNOTE-024: Pembrolizumab versus platinum-based chemotherapy for advanced non–small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. J Clin Oncol. 37:537-546.
44. Hui R, Garon EB, Goldman JW, *et al.* (2017) Pembrolizumab as first-line therapy for patients with PD-L1-positive advanced non-small cell lung cancer: a phase 1 trial. Ann Oncol. 2017;28:874-881.
45. Langer CJ, Gadgeel SM, Borghaei H, *et al.* (2016) Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol. 2016;17:1497-1508.
46. Freshwater T, Kondic A, Ahamadi M. *et al.* (2017) Evaluation of dosing strategy for pembrolizumab for oncology indications. j. immunotherapy cancer 5, 43 https://doi.org/10.1186/s40425-017-0242-5
47. Pembrolizumab (Keytruda). via https://www.drugs.com/price-guide/keytruda