Case Report

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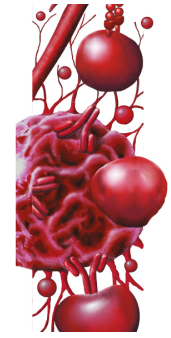
Immunotherapy



Investigative therapy for advanced esophageal cancer using the option for combined immunotherapy and chemotherapy

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Aim: Advanced esophageal cancer has limited therapeutic options and a poor outcome. The efficacy of immunotherapy, as the first-line treatment of advanced esophageal cancer, is uncertain. **Results:** A stage IV advanced esophageal cancer patient received the first-line treatment with a combination of pembrolizumab and chemotherapy. Partial response (PR) was achieved after three cycles, and the efficacy was evaluated as stable after six cycles of immunochemotherapy and two cycles of maintenance monotherapy. Immune-related adverse events (irAEs) were not obvious. The patient was followed up till November 2019 when he died of gastrointestinal hemorrhage. **Conclusion:** The combination of an immune checkpoint inhibitor and chemotherapy is effective and safe for the initial treatment of advanced esophageal cancer. To confirm the evidence from this case, larger clinical trials are required in the future.

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Keywords: chemotherapy • esophageal cancer • immune checkpoint inhibitor • partial response • pembrolizumab

Esophageal cancer is the eighth most common cancer, and the sixth leading cause of cancer-related mortality worldwide [1] and mortality continues to rise year by year, especially in low- and middle-income countries [2]. The incidence of the disease is three- to four-times higher in males than in females, and there are two main types, squamous cell carcinoma (SCC) and adenocarcinoma. The long-term prognosis remains poor due to postoperative recurrence and metastasis. Current guidelines for first-line treatment of advanced esophageal still recommend chemotherapy [3]. Less evidences are available for esophageal SCC (ESCC) than are for adenocarcinoma, and reduced efficacy can be achieved by chemotherapy in ESCC. At present, platinum-containing chemotherapy provides response rates of 20–50% and median overall survival (mOS) duration of 8–10 months [4,5].

In recent years, immune checkpoint inhibitors (ICIs) that targeting programmed cell death-1/programmed death-ligand 1 (PD-1/PD-L1) have made a breakthrough in the treatment of multiple solid tumors [6–8]. Compared with the OS of patients who are treated with conventional chemotherapeutics, PD-1/PD-L1 inhibitors-based therapies can lead to significant improvements in OS and progression-free survival (PFS) in some cancers [9,10].

Current guidelines recommend pembrolizumab for second-line or subsequent therapy for PD-L1-positive esophageal cancer [3]. While there are few reports of first-line immunotherapy for esophageal cancer. Here, we report a case of a patient who has been treated with a combination of pembrolizumab and chemotherapy as the first-line treatment. This patient achieved PR after treatment with pembrolizumab and chemotherapy, and there were no irAEs.

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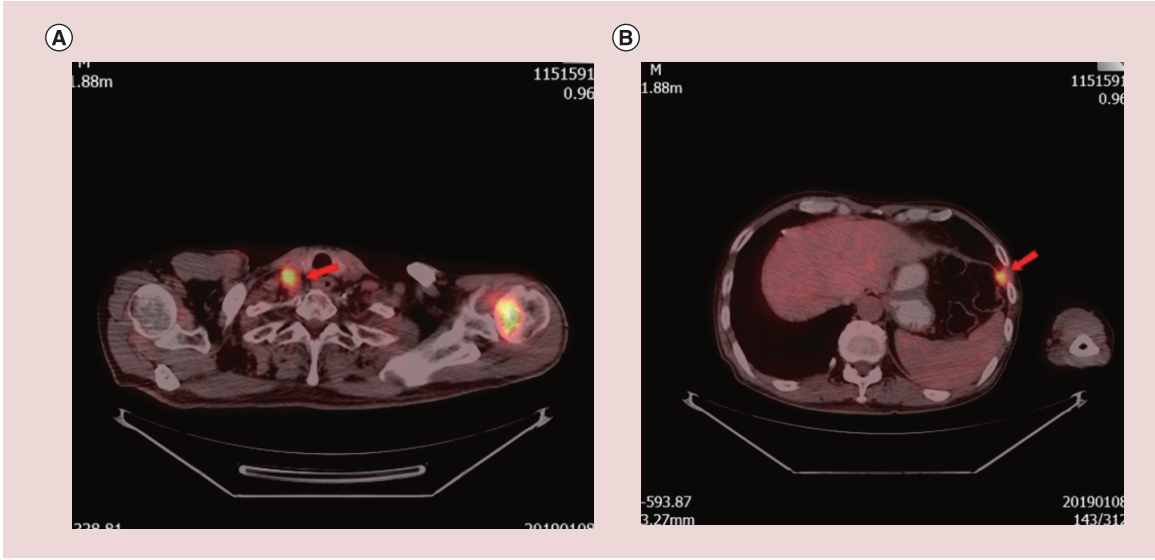

Figure 1. Representative images of positron emission tomography-CT scan showing a strong cancer-related uptake of fluorodeoxyglucose. (A) The radioactive uptake by the right clavicle lymph node increased and dissolved the destruction of the left humeral head. **(B)** Increase of the radioactive uptake by pleural nodules in the left anterior inferior wall.

Case presentation

Clinical history

A 59-year-old man was admitted to our division with recurrent esophageal cancer, and who had received radical esophagectomy 11 years ago. He was diagnosed with systemic metastases before coming to our hospital. Physical examination revealed an obvious tenderness in the left shoulder. The routine laboratory parameters were found normal, except for a leukopenia and a white blood cell count of 3.15 × 109/l. The levels of tumor markers, such as the carcinoembryonic antigen and the carbohydrate antigen (CA 19-9), were 1.14 and 3.85 ng/ml, respectively (normal carcinoembryonic antigen <5 ng/ml, CA 19-9 <37 ng/ml). Blood screening for autoimmune and endocrine function, including thyroid function, before ICI therapy, showed no abnormal changes.

Further examination of the patient using CT scans, showed multiple lymphadenopathies around the right supraclavicular soft tissue, the right submaxillary and the mediastinum. Pleural nodules, in the left anterior inferior wall, and an osteolytic destruction of the left humeral head and right fifth rib, were also found. Examination with 18Ffluorodeoxyglucose positron emission tomography revealed an abnormal fluorodeoxyglucose uptake in the same lesions detected by computed tomography (Figure 1). Open right supraclavicular lymph node biopsy showed histological features that were identical to the ones observed in ESCC (Figure 2), indicating a right supraclavicular lymph node metastasis of esophageal cancer. Based on these clinical and pathological findings, the clinical stage was diagnosed as stage IV according to the Union for International Cancer Control (UICC 7th edition).

To determine potential therapeutic methods, with the patient's consent, the tissue samples from the right supraclavicular lymph node and whole blood as control were subjected to next-generation sequencing using a 757-genes panel (Yucebio, Shenzhen, China). The genomic testing showed mutations in *TP53* (R282W), and copy number (CN) variation gains in *KRAS*, *EGFR* and *CCND1*. Next-generation sequencing also showed microsatellite stability and moderate tumor mutational burden (4.03 Mut/Mb). Immunohistochemistry analysis showed that the PD-L1 tumor proportion score of tissue samples ranged from 6% to 10% and the combined positive score was 4.2 (Figure 3), indicating that the expression of PD-L1 was positive, but not high.

Approved by the Research Ethics Committees of Qilu Hospital (Qingdao) of Shandong University, and based on the compassionate use principle, the treatment using a combination of pembrolizumab and chemotherapy was carried on with the patient's fully informed and agreement. After treatment with pembrolizumab (200 mg, q3w), albumin-bound taxol and nedaplatin (albumin-bound taxol 260 mg/m^2, d1; nedaplatin 100 mg/m^2, d1) for three cycles, computed tomography showed that the metastatic lesions had significantly decreased in size, and the osteolytic bone destruction of the left iliac bone became osteogenic (Figure 4). The curative effect on the

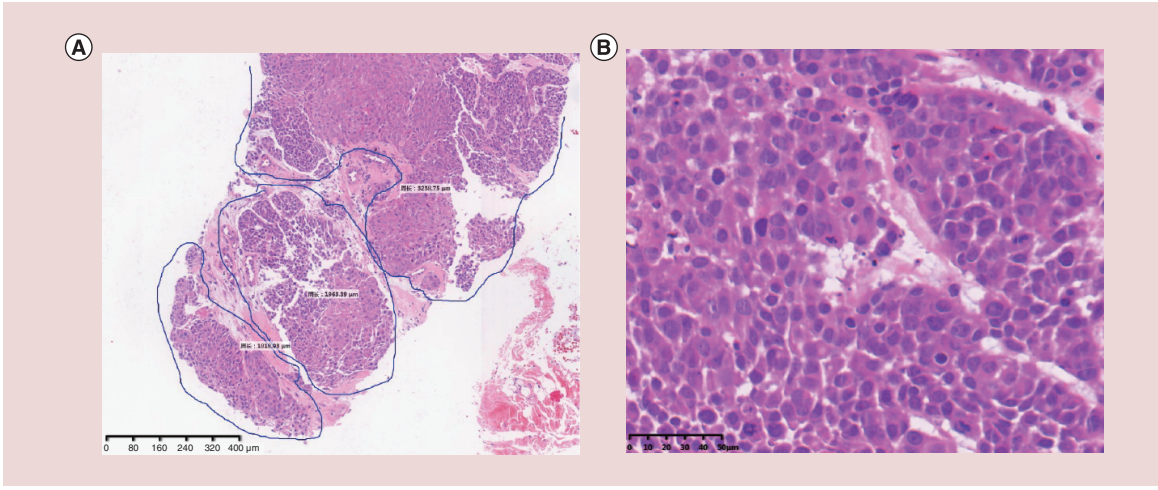

Figure 2. Representative images of hematoxylin & eosin-stained esophageal cancer tissues. (A & B) The tumor cells were characterized by the variation in the nucleus size and shape, the deep staining and the increased nucleoplasm index, which was marked by a closed curve. Also, hematoxylin & eosin staining shows that the tumor cells invaded the surrounding tissue. **(A)** 100× and **(B)** 400×.

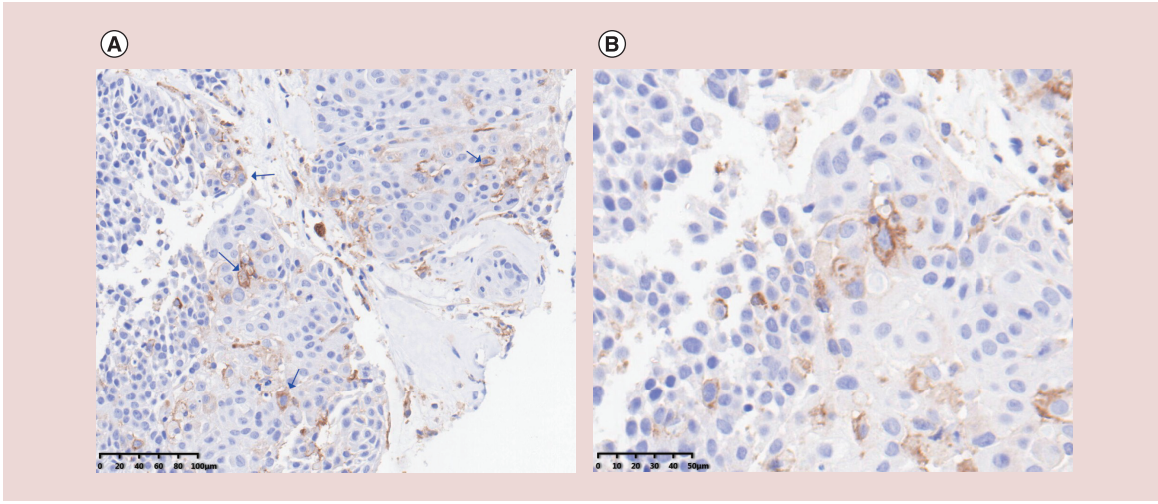

Figure 3. PD-L1 expression determined by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit. The positive tumor cells are indicated with blue arrows. The positive tumor cells are characterized by plasma membranes stain. PD-L1 protein expression is determined using tumor proportion score, which is the percentage of viable tumor cells showing partial or complete membrane staining. PD-L1 protein expression in the gastric or gastroesophageal junction adenocarcinoma is determined by combined positive score (CPS). The number of PD-L1 staining cells (tumor cells, lymphocytes and macrophages) are divided by the total number of viable tumor cells and multiplied by 100. The specimen is considered to have PD-L1 expression if CPS ≥1. **(A)** 200× and **(B)** 400×.

patient was evaluated as PR. After the first cycle of treatment, an IV-degree bone marrow depression appeared, and the condition improved after G-CSF treatment. Following the second cycle of chemotherapy, a longer G-CSF treatment was used. A Degree III of thrombocytopenia occurred after the fourth cycle of chemotherapy, which improved after treatment with recombinant human thrombopoietin. Then, chemotherapy was adjusted using a treatment regimen with pembrolizumab and albumin-bound taxol for two cycles, resulting in the stabilization of the metastatic lesions assessed by CT scans after six cycles. Following this step, the patient was given a monotherapy as maintenance therapy. The patient received a total of six cycles of pembrolizumab and chemotherapy and then received a pembrolizumab maintenance monotherapy for two cycles, from January 2019 to July 2019. Immune-

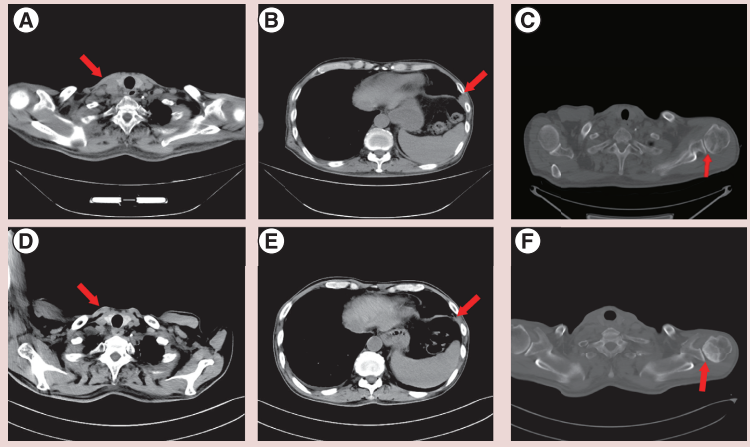

Figure 4. Response of the main lesion estimated by computed tomography. (A–C) CT scan shows multiple lymphadenopathies around the right supraclavicular soft tissue, pleural mass in the left anterior inferior wall and an osteolytic destruction of the left humeral head. Arrows in figures indicate the position of lesions. **(D–F)** The supraclavicular lymph node and pleural mass in the left anterior inferior were significantly reduced after three cycles. The osteolytic bone destruction of the left iliac bone became osteogenic.

related adverse reactions were not observed. The patient was followed up till November 2019 when he died of gastrointestinal hemorrhage.

Discussion

Esophageal cancer is a clinically challenging malignancy with poor prognosis. Oncology guidelines recommend monotherapy as first-line therapy in patients with SCC, however this therapy provided patients limited survival benefits. Although chemotherapy can achieve tumor regression in the acute stage of a disease, chemotherapy alone may not be able to completely control cancer progression due to drug resistance or the presence of chemo-resistant cancer stem cells. On these conditions, other treatments, such as immunotherapy, should be combined with chemotherapy to eliminate troublesome cancer cells. At present, the strategy of immune chemotherapy has been used in other solid tumors [11]. According to the current data, adding chemotherapeutic agents to immunotherapy can stimulate host production of long-term and effective tumor antigen-specific T lymphocytes and synergistically optimize the antitumor effects [12,13]. Different drugs have different regulatory mechanisms on tumor immune microenvironment [14]. In addition, the discovery of immunogenic cell death and damage associated molecular patterns has promoted the combination of chemotherapy and immunotherapy [15], which has achieved a better and more sustained therapeutic effect than single immunotherapy.

Cancer immunotherapy aims to release the inhibition of immune surveillance to activate tumor recognition, which may result in antitumor cytotoxic activity [16]. Immunotherapy may provide cancers with an immune surveillance mechanism, regardless of drug resistance or the presence of cancer stem cells, and which would be indispensable for long-term antitumor efficacy [17,18]. So far, these inhibitors have been applied to a variety of anticancer regimens, including melanoma, non-small-cell lung cancer, renal cell carcinoma, bladder cancer and Hodgkin lymphoma [19–23]. The results of a Phase III study evaluating second-line pembrolizumab in advanced or metastatic ESCC, EAC or adenocarcinoma of gastroesophageal junction (KEYNOTE-181, NCT02564263) showed that pembrolizumab resulted in superior OS compared with second-line chemotherapy (9.3 vs 6.7 mOS; hazard ratio: 0.69; 95% CI: 0.52–0.93), and mOS for ESCC with combined positive score $\leq$10 was 10.3 months compared with 6.7 months [24]. In addition, ATTRACTION-3 study, a Phase III study evaluating second-line nivolumab versus chemotherapy in patients with advanced ESCC supports the use of nivolumab monotherapy. OS was significantly improved in the nivolumab group compared with the chemotherapy group (median 10.9 months, 95% CI: 9.2–13.3 vs 8.4 months, 7.2–9.9; hazard ratio for death 0.77; 95% CI: 0.62–0.96; p = 0.019) [25]. As a result of the findings of KEYNOTE-181 and ATTRACTION-3, pembrolizumab and nivolumab were granted US FDA approval as monotherapy in second-line treatment for ESCC. Several studies have shown that the

efficacy of a combination immunotherapy is better than that of a single immunotherapy [26,27]. KEYNOTE-059 (NCT02335411) evaluates pembrolizumab usage in combination with chemotherapy, or as monotherapy, in the first line for advanced gastric/gastroesophageal junction cancers. The pembrolizumab demonstrates well tolerated, manageable safety and induced antitumor activity for monotherapy as well as in combination with chemotherapy. The combination of pembrolizumab and chemotherapy (cisplatin plus 5-FU) resulted in a 60% objective response rate (ORR) with 4% complete response (CR) and median PFS of 6.6 months while ORR for patients receiving pembrolizumab monotherapy was 25.8% with CR of 6.5% and median PFS of 3.3 months [28]. It is therefore imperative to explore effective therapies for ESCC. However, data from the ongoing Phase III KEYNOTE-590 study using pembrolizumab as a first-line immune chemotherapeutic treatment for advanced esophageal carcinoma have not been available and additional information is needed. This study is being conducted to investigate the safety and efficacy of pembrolizumab as the first-line treatment for advanced esophageal carcinoma [29]. Our patient repeatedly expressed his desire to improve the therapeutic effect before the start of the treatment. With the patient's consent, we gave the patient a combination of an ICI and chemotherapy. We hope that the strategy of the ICI combined with chemotherapy in advanced esophagus will be as effective as that for other cancers, and could be added into first-line treatment. A PR was achieved and the patient did not experience irAEs, after treatments with pembrolizumab and chemotherapy.

The checkpoint inhibitors based immunotherapy brings solid tumor treatment into a new era. However, this approach also brings new clinical challenges, such as predicting the efficacy, adverse reactions, hyperprogressive disease associated with immunotherapy and irAEs. The antitumor immune response is a complex process, involving several types of immune cells and molecules. Seeking predictive biomarkers for the efficacy of an immunotherapy is more challenging. In clinical practices and researches, PD-L1 is used as a biomarker for efficacy predicting. Overexpression of PD-L1 in tumor cells may cause immune escape, by inhibiting the function of cytotoxic T cells [30–32]. Therefore, the expression of PD-L1 is considered as a biomarker for predicting the efficacy of ICIs. Researchers found that patients with low or no expression of PD-L1 in non-small-cell lung cancer tumors, could also be benefit from anti-PD-L1 therapy [33].

The overexpression rate of EGFR in ESCC patients is as high as 60–70%, and EGFR CN variation can be detected in 28% of patients. However, because EGFR may not be the dominant upstream driving gene, it can be effectively intervened with some targeted drugs, its clinical effect is not very satisfactory, so immunotherapy is very necessary [34]. But in one hyperprogression study, five patients with immunotherapy hyperprogression, two of whom were esophageal cancer patients, were found to have *MDM2/MDM4* gene amplification, EGFR gene amplification and *CCND1/FGF3/FGF4/FGF19* gene amplification [35]. In another study of patients with head and neck SCC, authors explored the potential genetic markers associated with hyperprogressive disease following immunotherapy and the results showed that the changes of EGFR were related to the 'hyperprogressive disease' of PD-1/PD-L1 inhibitors after treatment [36]. Furthermore, *EGFR* and *CCND1* copy number were amplified in this patient, but the efficacy of PR was still achieved. Therefore, it may be one of the directions for future research to explore whose markers that can predict validly immunotherapy 'hyperprogressive disease'.

Conclusion

The development of immunotherapy improves the prognosis of several cancers. However, the benefits of ICIs for primary advanced esophageal cancer are still unclear. We report results obtained in one patient who was diagnosed with primary advanced esophageal cancer and was treated with a combination of an ICI and chemotherapy. We believe that a larger clinical trials investigating checkpoint inhibitor based immunotherapy as a first-line treatment for advanced esophageal cancer will be promising and help the people who succumbed to this disease.

Future perspective

At present, monotherapy is recommended by oncology guidelines as first-line therapy in patients with SCC, however this therapy provided patients limited survival benefits, and pembrolizumab for second-line or subsequent therapy for PD-L1-positive esophageal cancer. At present, many studies have shown that immunotherapy and chemotherapy have synergistic interaction, and some clinical trials have verified it. Phase III KEYNOTE-590 study, which was used as a first-line treatment of advanced esophageal carcinoma with immune chemotherapy, has been still ongoing. The treatment effect of the case we reported is very good and with no irAEs. We believe the large-scale clinical trials will be successful and improve the first-line treatment for esophageal cancer patients in the future.

Summary points

- The efficacy of immunotherapy, as a first-line treatment of advanced esophageal cancer, is uncertain.
- Current guidelines recommend pembrolizumab for second-line or subsequent therapy for PD-L1-positive esophageal cancer. While, there are few reports of first-line immunotherapy for esophageal cancer.
- We present a case of advanced esophageal treated with pembrolizumab and chemotherapy in the first line and PR was achieved without irAEs.
- Large prospective studies are needed to determine the safety and efficacy of this promising combination therapy.

Author contributions

All authors contributed to the study conception and design. H Wang wrote the case report. F-L Cao and T-T Xuan treated the patient. G Zhou made pathological interpretation. H Yu and T-T Gu modified the manuscripts. All authors read and approved the final manuscript.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

This work was approved by the Research Ethics Committees (REC) of Qilu Hospital (Qingdao) of Shandong University. The patient has consented to the submission of the case report for submission to the journal.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Ferlay J, Soerjomataram I, Dikshit R *et al.* Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int. J. Cancer* 136(5), E359–E386 (2015).
2. Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends: an update. *Cancer Epidemiol. Biomarkers Prev.* 25(1), 16–27 (2016).
3. Ajani JA, D'amico TA, Bentrem DJ *et al.* Esophageal and esophagogastric junction cancers, version 2.2019, NCCN clinical practice guidelines in Oncology. *J. Natl Compr. Canc. Netw.* 17(7), 855–883 (2019).
4. Kato K, Muro K, Minashi K *et al.* Phase II study of chemoradiotherapy with 5-fluorouracil and cisplatin for Stage II–III esophageal squamous cell carcinoma: JCOG trial (JCOG 9906). *Int. J. Radiat. Oncol. Biol. Phys.* 81(3), 684–690 (2011).
5. Adenis A, Bennouna J, Etienne PL *et al.* Continuation versus discontinuation of first-line chemotherapy in patients with metastatic squamous cell oesophageal cancer: a randomised Phase II trial (E-DIS). *Eur. J. Cancer* 111, 12–20 (2019).
6. Rijnders M, De Wit R, Boormans JL, Lolkema MPJ, Van Der Veldt AaM. Systematic review of immune checkpoint inhibition in urological cancers. *Eur. Urol.* 72(3), 411–423 (2017).
7. Emens LA, Ascierto PA, Darcy PK *et al.* Cancer immunotherapy: opportunities and challenges in the rapidly evolving clinical landscape. *Eur. J. Cancer* 81, 116–129 (2017).
8. Fiala O, Sorejs O, Pesek M, Finek J. [Immunotherapy in the treatment of lung cancer]. *Klin. Onkol.* 30(Suppl. 3), 22–31 (2017).
9. Ribas A, Hamid O, Daud A *et al.* Association of pembrolizumab with tumor response and survival among patients with advanced melanoma. *JAMA* 315(15), 1600–1609 (2016).
10. Hendriks LEL, Bootsma G, Mourlanette J *et al.* Survival of patients with non-small-cell lung cancer having leptomeningeal metastases treated with immune checkpoint inhibitors. *Eur. J. Cancer* 116, 182–189 (2019).
11. Gandhi L, Rodriguez-Abreu D, Gadgeel S *et al.* Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N. Engl. J. Med.* 378(22), 2078–2092 (2018).
12. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. *Nature* 480(7378), 480–489 (2011).
13. Emens LA, Middleton G. The interplay of immunotherapy and chemotherapy: harnessing potential synergies. *Cancer Immunol. Res.* 3(5), 436–443 (2015).

14. Chen YL, Chang MC, Cheng WF. Metronomic chemotherapy and immunotherapy in cancer treatment. *Cancer Lett.* 400, 282–292 (2017).
15. Garg AD, Galluzzi L, Apetoh L *et al.* Molecular and translational classifications of DAMPs in immunogenic cell death. *Front. Immunol.* 6, 588 (2015).
16. Smyth MJ, Dunn GP, Schreiber RD. Cancer immunosurveillance and immunoediting: the roles of immunity in suppressing tumor development and shaping tumor immunogenicity. *Adv. Immunol.* 90, 1–50 (2006).
17. Pan Q, Li Q, Liu S *et al.* Concise review: targeting cancer stem cells using immunologic approaches. *Stem Cells* 33(7), 2085–2092 (2015).
18. Curiel TJ. Immunotherapy: a useful strategy to help combat multidrug resistance. *Drug Resist. Updat.* 15(1–2), 106–113 (2012).
19. Klemen ND, Wang M, Feingold PL *et al.* Patterns of failure after immunotherapy with checkpoint inhibitors predict durable progression-free survival after local therapy for metastatic melanoma. *J. Immunother. Cancer* 7(1), 196 (2019).
20. Gettinger SN, Horn L, Gandhi L *et al.* Overall survival and long-term safety of nivolumab (anti-programmed death 1 antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-small-cell lung cancer. *J. Clin. Oncol.* 33(18), 2004–2012 (2015).
21. Alsharedi M, Katz H. Check point inhibitors a new era in renal cell carcinoma treatment. *Med. Oncol.* 35(6), 85 (2018).
22. Konala VM, Adapa S, Aronow WS. Immunotherapy in bladder cancer. *Am. J. Ther.* doi:10.1097/MJT.0000000000000934 (2019) (Epub ahead of print).
23. Postow MA, Chesney J, Pavlick AC *et al.* Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N. Engl. J. Med.* 372(21), 2006–2017 (2015).
24. Kojima T, Muro K, Francois E *et al.* Pembrolizumab versus chemotherapy as second-line therapy for advanced esophageal cancer: Phase III KEYNOTE-181 study. *J. Clin. Oncol.* 37(Suppl. 4), 2–2 (2019).

• **The PD-L1 pembrolizumab was approved as a second-line treatment by the US FDA based on this research.**

25. Kato K, Cho BC, Takahashi M *et al.* Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, Phase III trial. *Lancet Oncol.* 20(11), 1506–1517 (2019).

• **Nivolumab was approved as a second-line treatment by the FDA based on this research.**

26. Valsecchi ME. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N. Engl. J. Med.* 373(13), 1270 (2015).

• **Shows that the efficacy of a combination immunotherapy is better than that of a single immunotherapy in other cancer as first-line chemotherapy with pembrolizumab.**

27. Mayor S. Combined immunotherapy improves survival in metastatic melanoma. *BMJ* 350, h2993 (2015).
28. Bang Y-J, Kang Y-K, Catenacci DV *et al.* Pembrolizumab alone or in combination with chemotherapy as first-line therapy for patients with advanced gastric or gastroesophageal junction adenocarcinoma: results from the Phase II nonrandomized KEYNOTE-059 study. *Gastric Cancer* 22(4), 828–837 (2019).

•• **Demonstrates that pembrolizumab alone or in combination with chemotherapy as first-line therapy showed promising activity and manageable safety. It is, therefore, imperative to explore effective therapies for esophageal squamous cell carcinoma as a first-line treatment of advanced esophageal carcinoma with immune chemotherapy from the ongoing Phase III study.**

29. Kato K, Shah MA, Enzinger P *et al.* KEYNOTE-590: Phase III study of first-line chemotherapy with or without pembrolizumab for advanced esophageal cancer. *Future Oncol.* 15(10), 1057–1066 (2019).

•• **Investigates pembrolizumab in combination with chemotherapy as first-line treatment in patients with advanced esophageal or esophagogastric junction (EGJ) cancer. This research results may change current guidelines for first-line treatment.**

30. Patel SP, Kurzrock R. PD-L1 expression as a predictive biomarker in cancer immunotherapy. *Mol. Cancer Ther.* 14(4), 847–856 (2015).
31. Blank C, Gajewski TF, Mackensen A. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy. *Cancer Immunol. Immunother.* 54(4), 307–314 (2005).
32. Meng X, Huang Z, Teng F, Xing L, Yu J. Predictive biomarkers in PD-1/PD-L1 checkpoint blockade immunotherapy. *Cancer Treat. Rev.* 41(10), 868–876 (2015).
33. Chae YK, Pan A, Davis AA *et al.* Biomarkers for PD-1/PD-L1 blockade therapy in non-small-cell lung cancer: is PD-L1 expression a good marker for patient selection? *Clin. Lung Cancer* 17(5), 350–361 (2016).

• **Shows that patients with low or no expression of PD-L1 in non-small-cell lung cancer tumors, could also benefit from anti-PD-L1 therapy.**

34. Petty RD, Dahle-Smith A, Stevenson DaJ *et al.* Gefitinib and EGFR gene copy number aberrations in esophageal cancer. *J. Clin. Oncol.* 35(20), 2279–2287 (2017).
35. Singavi AK, Menon S, Kilari D *et al.* Predictive biomarkers for hyper-progression (HP) in response to immune checkpoint inhibitors (ICI):analysis of somatic alterations (SAs). *Ann. Oncol.* 28(Suppl.5), v403–v427 (2017).
36. Kato S, Goodman A, Walavalkar V, Barkauskas DA, Sharabi A, Kurzrock R. Hyperprogressors after immunotherapy: analysis of genomic alterations associated with accelerated growth rate. *Clin. Cancer Res.* 23(15), 4242–4250 (2017).