Research Article

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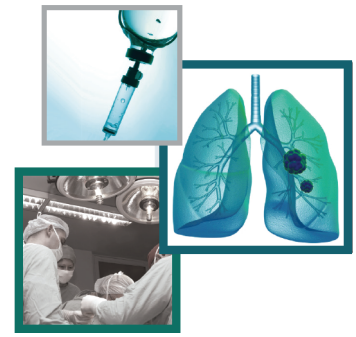
Lung Cancer Management



Treatment effect and safety profile of salvage chemotherapy following immune checkpoint inhibitors in lung cancer

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Aim: To assess the relationship of treatment effects between immune checkpoint inhibitor (ICI) and salvage chemotherapy, with the safety profile of salvage chemotherapy. **Patients & methods:** 18 patients with advanced NSCLC treated using salvage chemotherapy following ICI treatment were retrospectively included. We assessed the overall response rate to and adverse events of salvage chemotherapy. **Results:** The overall response rate to salvage chemotherapy was 33.3% and that of ICI responders was significantly higher than that of ICI nonresponders (66.7 vs 16.7%, respectively, p = 0.03). The incidence rate of adverse events to salvage chemotherapy was 55.6%. **Conclusion:** The efficacy of salvage chemotherapy was similar to that preceding ICI. Moreover, the safety of salvage chemotherapy was good.

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Keywords: immune checkpoint inhibitor • NSCLC • salvage chemotherapy

Immune checkpoint inhibitors (ICI) are prevalent and are often used to treat advanced NSCLC, not only as a second-line or later treatment but also as a first-line treatment. The duration of the disease control is long for high responders to ICI treatment; however, most patients do not achieve a satisfactory benefit from the treatment because the overall response rate (ORR) to ICI is 18.0–22.0% [1–3]. Thus, salvage chemotherapy is commonly administered to patients resistant to ICI. The most common type of chemotherapy after ICI and its efficacy were previously unknown, although several recent studies have showed improvements in ORR to salvage chemotherapy following ICI, platinum-based doublet or single agent. Conversely, the ORR to conventional chemotherapy alone as a second-line or later treatment not following ICI treatment is lower than the ORR to its use as a first-line treatment; the ORRs to carboplatin + pemetrexed (CBDCA + PEM), docetaxel and PEM are 12.6%, 15.0–22.0% and 9.1% [4–6], respectively, although the ORR to salvage chemotherapy following ICI is higher (ORR: 39.0–46.9%) [7,8]. However, the conditions of good responders to salvage chemotherapy and the safety profile of salvage chemotherapy remain unclear. Herein, we report the relationship of treatment effects between ICI and salvage chemotherapy, and the safety profile of salvage chemotherapy following ICI.

Patients & methods

Patient selection & data collection

This was a retrospective cohort study. We obtained information about the patients from their medical charts. This study included patients with stage IV or unresectable stage III or postoperative recurrent NSCLC treated with ICI and following chemotherapy at the Japanese Red Cross Medical Center between January 2016 and August 2018. To allow comparison with the treatment effects of conventional chemotherapy as a second-line or later treatment that were previously reported, patients were excluded if ICI was administered as a first-line treatment. Additionally, patients who received salvage chemotherapy after ICI and who were diagnosed with progressive disease (PD) despite preceding efficacy of tumor reduction were selected and classified into two groups – responders (best overall response of ICI was partial response [PR]) and nonresponders (best overall response of ICI was stable disease [SD]

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Table 1. Patient baseline characteristics.

Variables	N = 18
Age (years)	69 (46–84)
Gender:	
– Male	12 (66.7)
– Female	6 (33.3)
– Smoking	12 (66.7)
ECOG performance status, 0/1/2–4	5/13/0
Histology:	
– Adenocarcinoma	13 (72.2)
– Squamous cell carcinoma	5 (27.8)
– EGFR mutation positive	2 (11.1)
– ALK mutation positive	1 (5.6)
– PD-L1 expression-positive	8 (44.4)
– Pre-ICI treatment line	1 (1–3)

Data are presented as median (range) or n (%).
ALK: Activin receptor-like kinase; ECOG: Eastern Cooperative Oncology Group; ICI: Immune checkpoint inhibitor.

or PD) – to investigate the factors influencing the efficacy of salvage chemotherapy. PD-L1 testing was performed by the companion diagnostic antibodies '22-C3'.

Chemotherapy after ICI included cytotoxic anticancer agents (platinum-based and single agents) that immediately followed immunotherapy but not molecular-targeted drugs. We computed the ORR to ICI and salvage chemotherapy, and the patients' response to treatment was assessed based on the Response Evaluation Criteria in Solid Tumors Version 1.1 (RESIST v1.1) by the attending physician. Adverse events that occurred during the observation period were assessed based on the National Cancer Institute Common Terminology Criteria for Adverse Events (Version 4.0).

Ethical considerations

This retrospective study was approved by the institutional review board of the Japanese Red Cross Medical Center (No. 911) and was registered with the University Hospital Medical Information Network (UMIN000033594).

Statistical analysis

To evaluate the factors associated with a high response to salvage chemotherapy following ICI, we used Fisher's exact test for categorical data and the Mann–Whitney U test for numeric data. The ORR to salvage chemotherapy was compared using the chi-square test. The descriptive statistics presented in this study includes mean, frequency and percentage. The correlation between the best percentage changes of ICI and salvage chemotherapy was analyzed using Spearman's rank correlation. All reported p-values are two sided with a p-value of <0.05 being considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (the R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient baseline characteristics

Fifty-nine patients were treated with ICI for advanced NSCLC; however, 15 patients were excluded because ICI was administered as a first-line treatment (N = 11) or ICI was being administered without PD (N = 4) till 30 September 2018. One patient received a molecular-targeted drug immediately after ICI. Of the remaining 43 patients, 18 received salvage chemotherapy and were included in this study. All patients received platinum doublets preceding ICI, and their baseline characteristics at the time of receiving ICI are described in Table 1.

Treatment data & efficacy

All 18 patients who received salvage chemotherapy following ICI were treated with nivolumab. The median number of ICI treatment courses was seven courses (range: 2–26 courses). The ORR to ICI was 33.3% (PR: N = 6, SD: N = 6, PD: N = 6). Of the 18 patients, 6 received platinum doublet chemotherapy (CBDCA + nab-paclitaxel

Table 2. The factors by response to salvage chemotherapy following immune checkpoint inhibitors treatment.

Variables	Salvage chemotherapy responder (N = 6)	Salvage chemotherapy nonresponder (N = 12)	p-value
Age (years)	70 (46–84)	68 (51–78)	1.0
Gender:			1.0
– Male	4 (66.7)	8 (66.7)	
– Female	2 (33.3)	4 (33.3)	
– Smoking	4 (66.7)	8 (66.7)	1.0
ECOG performance status, 0/1/2–4	2/4/0	3/9/0	1.0
Histology:			1.0
– Adenocarcinoma	4 (66.7)	9 (75.0)	
– Squamous cell carcinoma	2 (33.3)	3 (25.0)	
– EGFR mutation positive	1 (16.7)	1 (8.3)	1.0
– ALK mutation positive	0 (0)	1 (8.3)	1.0
– PD-L1 expression positive	4 (66.7)	4 (33.3)	0.32
Response to ICI:			
– ICI responder	4 (66.7)	2 (16.7)	0.03
– ICI nonresponder	2 (33.3)	10 (83.3)	

Data are presented as n (%); n = 18.
ALK: Activin receptor-like kinase; ECOG: Eastern Cooperative Oncology Group; ICI: Immune checkpoint inhibitor.

[CBDCA + nab-PTX]: N = 4, CBDCA + PTX + bevacizumab [CBDCA + PTX + BEV]: N = 1, CBDCA + PEM: N = 1) and 12 received nonplatinum therapy immediately after ICI (docetaxel ± ramucirumab: N = 6, tegafur–gimestat–ostat potassium (TS-1): N = 5, PTX + BEV: N = 1). The median number of chemotherapy treatment courses was four (range: 1–12 courses) and the median length of time from the last ICI administration to the start of chemotherapy was 1 month (range: 0.5–11 months). The ORR to chemotherapy following ICI was 33.3% (PR: N = 6, SD: N = 7, PD: N = 5). The results of factors by response to salvage chemotherapy following ICI treatment are described in Table 2. The efficacy of salvage chemotherapy did not significantly depend on the time from the end of ICI treatment to the start of salvage chemotherapy (p = 0.547). The kind of salvage chemotherapy was also not significantly correlated with its efficacy (p = 0.245). However, the ORR to platinum doublet treatment tended to be higher than that to nonplatinum doublet treatment (ORR: 50.0 vs 25.0%, respectively). Remarkably, the efficacy of ICI was associated with the response to salvage chemotherapy. The ORR to salvage chemotherapy of ICI responders was significantly higher than that of ICI nonresponders (66.7 vs 16.7%, respectively, p = 0.03, Table 2). Moreover, the efficacies of ICI and salvage chemotherapy were similar. There was a significant correlation between the effects of ICI and salvage chemotherapy (rs: Spearman's rank correlation coefficient = 0.596; p = 0.021; Figure 1). As shown in Figure 1, three patients were excluded because they did not have any valuable target region wherein we could measure the best percentage changes of salvage chemotherapy. However, they had new lesions of lung cancer after receiving salvage chemotherapy and had efficacies of PD in response to salvage chemotherapy based on the RESIST v1.1, as noted by the attending physician. The incidence of grade 3 or worse adverse events in response to salvage chemotherapy was 55.6% (N = 10) and the most common adverse event was neutropenia (27.8%, N = 5); other events included anemia, thrombocytopenia, gastrointestinal disorder, neuropathy, pneumonitis, skin disorder and sepsis (5.6%, N = 1, each; Table 3). The incidence of immune-related adverse events in response to ICI and the response to salvage chemotherapy were not significantly associated with the adverse events to salvage chemotherapy (p = 0.294, p = 0.620, respectively). However, none of the ICI responders experienced grade 3 or worse adverse events in response to salvage chemotherapy (p = 0.001).

Discussion

In this study, the ORR to salvage chemotherapy following ICI tended to be higher than that to second-line or later chemotherapy not following ICI, as previously reported [7,8]. Additionally, the efficacy outcomes to ICI were significantly associated with the response to salvage chemotherapy, and the response to salvage chemotherapy was similar to that preceding ICI. The safety of salvage chemotherapy was comparable to that of chemotherapy not following ICI, given prior to ICI, as previously reported [4–6,9].

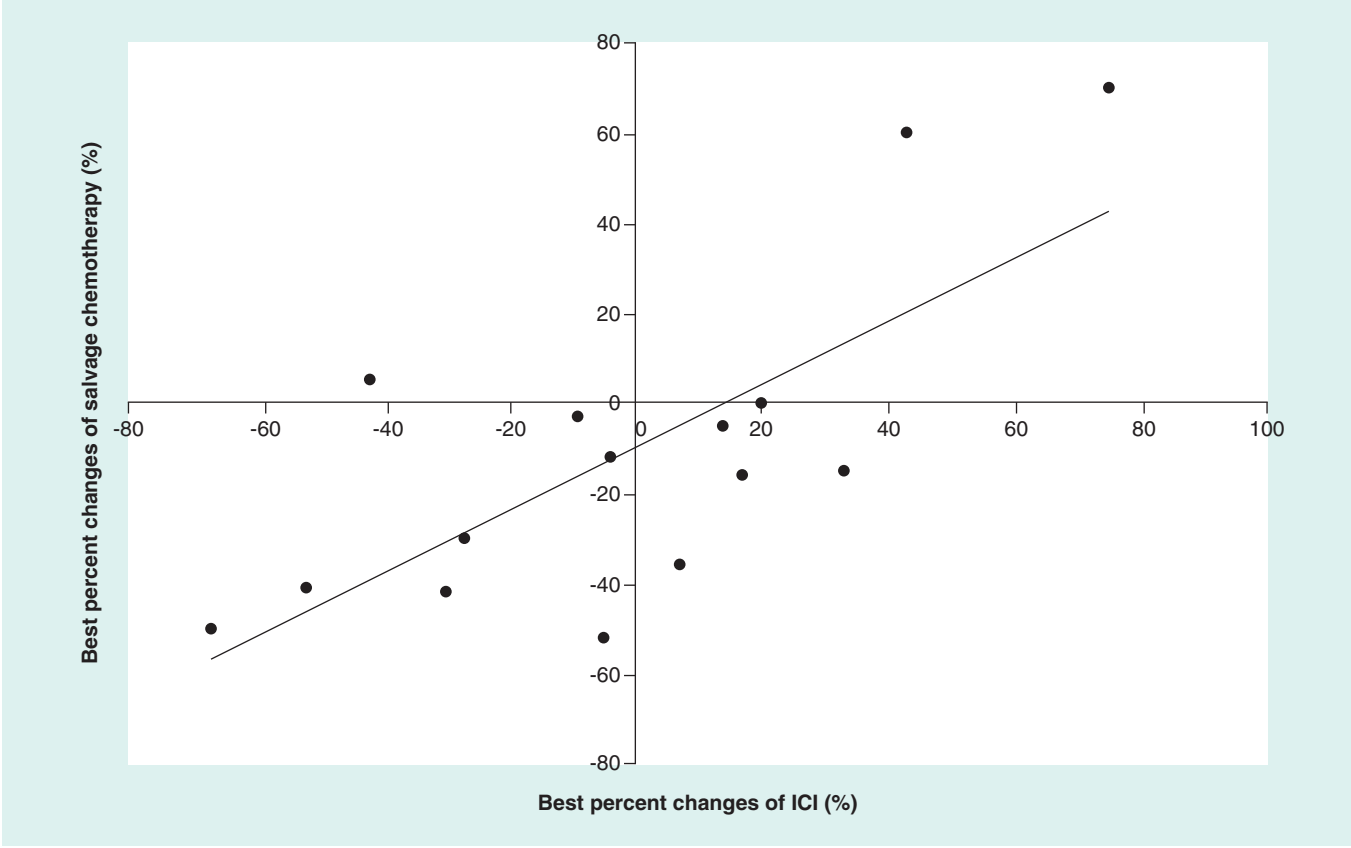

Figure 1. The correlation between the effects of immune checkpoint inhibitor and salvage chemotherapy.
The x-axis represents the best percentage changes in the target legions from baseline by ICI, and the y-axis represents those by salvage chemotherapy. There was a significant correlation between the effects of ICI and salvage chemotherapy (rs = 0.596; p = 0.021).
ICI: Immune checkpoint inhibitor; rs: Spearman's rank correlation coefficient.

Table 3. Adverse events of salvage chemotherapy following immune checkpoint inhibitor treatment.

Variables	Grades 3–5 (%)
Neutropenia	5 (27.8)
Anemia	1 (5.6)
Thrombocytopenia	1 (5.6)
Gastrointestinal disorder	1 (5.6)
Neuropathy	1 (5.6)
Pneumonitis	1 (5.6)
Skin disorder	1 (5.6)
Sepsis	1 (5.6)

Data are presented as n (%); n = 18.

Our results showed that the ORR to salvage chemotherapy following ICI tended to be higher (33.3%) than that to conventional chemotherapy not following ICI (9.1–22.0%) [6–8], which is in agreement with the results of the previous studies [7,8]. No correlation was found between the ORR and the type of cytotoxic agent used; however, the ORR to platinum doublet treatment tended to be higher than that to nonplatinum doublet treatment. A previous study also reported that the treatment effects of platinum doublets were significantly higher than those of nonplatinum doublets [8]; thus, to increase treatment efficacy, it is preferable to use platinum-based agents when possible for advanced NSCLC patients who have good performance status and organ function after failure of ICI treatment.

The mechanism for the effectiveness of salvage chemotherapy is thought to be due to the synergistic effect between ICI and salvage chemotherapy. Several studies have suggested immunological effects of chemotherapy, including reduced T-regulatory cell activity and increased neoantigen expression, antigen cross presentation and regulation of PD-L1 expression in tumor cells [10–14]. As for clinical trials, combined platinum-based doublet and ICI treatment as a first-line treatment was reported to be effective in both the KEYNOTE-189 and IMpower150 studies [15,16]. Additionally, the KEYNOTE-024 study compared the combined progression-free survival (PFS) for first-line and PFS for second-line (PFS2) treatment and found that PFS2 was longer in patients who received salvage chemotherapy following pembrolizumab than in patients who received pembrolizumab after chemotherapy [17]. The results suggest a synergistic effect between ICI and salvage chemotherapy in patients who received preceding pembrolizumab.

Moreover, the efficacy of ICI was significantly associated with the efficacy of salvage chemotherapy in our study. In a previous study, the response to anti-PD-1 was reportedly not significantly associated with the response to salvage chemotherapy; however, this result was thought to be caused by bias of the efficacy outcomes according to ICI (no PR; SD 50% and PD 50%) [7]. Similar to our study, in another previous report, the ORR to salvage chemotherapy of responders to ICI was higher than that of nonresponders to ICI. This should be further investigated in a large-scale prospective study as all previous studies were retrospective studies, each including a relatively small sample size. However, our study results suggest that the synergistic effect between ICI and salvage chemotherapy is stronger when the treatment effect of ICI is higher. It is possible that this outcome may be useful for predicting the prognosis of patients who have experienced treatment failure with ICI.

The safety of salvage chemotherapy was similar to that of chemotherapy not following ICI, as previously reported [4–6,9]. In the present study, none of the ICI responders experienced grade 3 or worse adverse events in response to salvage chemotherapy. This is thought to be related to the good performance status of ICI responders and is a potential factor influencing the good effects of salvage chemotherapy in ICI responders.

The limitations of our study include the small sample size and the strict selection criteria for patients. In this study, 11 patients who were administered ICI as a first-line treatment were excluded; however, it is important to note that the number of patients who are administered ICI as a first-line treatment is increasing. Further investigation with a larger sample size including those who were administered ICI as a first-line treatment is needed. Additionally, the ORR to nivolumab in our study was higher than that in the previous studies despite the high percentage of nonsmokers [18,19]. As we compared the patient characteristics of our study with those previous studies, there seems to be significant difference, not in age or performance status but in race. Almost all patients in our study were Asians, while almost all patients in the previous studies were whites. We guess it may have made a little difference; however, the other previous study reported that the ORR to nivolumab in Japanese with advanced NSCLC was similar to whites with advanced NSCLC [20], and the factor most influencing to our results was the limitations of our study including the small sample size and the highly selected cohort of patients.

Conclusion

The response to chemotherapy after failure of ICI treatment was high and the efficacy outcomes of salvage chemotherapy were similar to those preceding ICI. Further, the safety of salvage chemotherapy following ICI treatment was good. These findings are valuable for prognostic prediction in patients who experience disease progression with ICI treatment.

Future perspective

ICI are prevalent and are often used to treat advanced NSCLC, not only as a second-line or later treatment but also as a first-line treatment. Our outcomes are valuable for the prognostic prediction in patients who have experienced disease progression after ICI treatment.

Authors' contributions

M Tone and T Izumo were responsible for study conception and design; M Tone, N Awano and M Inomata were responsible for literature search; M Tone, T Jo and H Yoshimura were responsible for acquisition of data; M Tone and N Kuse were responsible for data analysis; H Kunitoh, S Miyamoto and M Tone were drafting and did revision of the manuscript.

Financial & competing interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report. This retrospective study was approved by the institutional review board of the Japanese Red Cross Medical Center (No. 911) and was registered with the University Hospital Medical Information Network (UMIN000033594).

Data sharing statement

The authors certify that this manuscript reports original clinical trial data. Individual, deidentified participant data that underlie the results reported in this article (text, tables, figures and appendices) are available from the corresponding author following publication, including the clinical study report and study protocol.

Executive summary

- The efficacy of salvage chemotherapy following immune checkpoint inhibitor (ICI) is reportedly better than that of conventional chemotherapy as a second-line or later treatment not following ICI in patients with NSCLC.
- However, the characteristics of good responders to salvage chemotherapy and the safety profile of salvage chemotherapy remain unclear.
- Therefore, we report on the relationship of treatment effects between ICI and salvage chemotherapy, with the safety profile of salvage chemotherapy following ICI treatment.
- The overall response rate to salvage chemotherapy of ICI responders was significantly higher than that of ICI nonresponders (66.7 vs 16.7%, respectively; $p = 0.03$) and the efficacies of ICI and salvage chemotherapy were similar.
- The incidence rate of grade 3 or worse adverse events to salvage chemotherapy was 55.6% ($N = 10$) with no ICI responders experiencing such events to salvage chemotherapy ($p = 0.001$).
- The efficacy of ICI was significantly associated with a patients' response to salvage chemotherapy and the efficacy of salvage chemotherapy was similar to that preceding ICI. Moreover, the safety of salvage chemotherapy was good.
- Our outcomes are valuable for the prognostic prediction in patients who have experienced disease progression after ICI treatment.

References

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

1. Zhao B, Zhang W, Yu D, Xu J, Wei Y. The benefit and risk of nivolumab in non-small-cell lung cancer: a single-arm meta-analysis of noncomparative clinical studies and randomized controlled trials. *Cancer Med.* 7(5), 1642–1659 (2018).
2. Lim SH, Sun JM, Lee SH, Ahn JS, Park K, Ahn MJ. Pembrolizumab for the treatment of non-small cell lung cancer. *Expert Opin. Biol. Ther.* 16(3), 397–406 (2016).
3. Ilie M, Hofman PJ. Atezolizumab in advanced non-small-cell lung cancer. *Thorac. Dis.* 9(10), 3603–3606 (2017).
4. Ardizzoni A, Tiseo M, Boni L *et al.* Pemetrexed versus pemetrexed and carboplatin as second-line chemotherapy in advanced non-small-cell lung cancer: results of the GOIRC 02-2006 randomized Phase II study and pooled analysis with the NVALT7 trial. *J. Clin. Oncol.* 30(36), 4501–4507 (2012).
5. Fossella FV, DeVore R, Kerr RN *et al.* Randomized Phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J. Clin. Oncol.* 18(12), 2354–2362 (2000).

6. Hanna N, Shepherd FA, Fossella FV *et al.* Randomized Phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J. Clin. Oncol.* 22(9), 1589–1597 (2004).
7. Schvartsman G, Peng SA, Bis G *et al.* Response rates to single-agent chemotherapy after exposure to immune checkpoint inhibitors in advanced non-small-cell lung cancer. *Lung Cancer* 112, 90–95 (2017).

• **Because these recent studies show improvements in overall response rate to salvage chemotherapy following immune checkpoint inhibitors (ICI), and our outcomes are in agreement with the results of these studies.**

8. Park SE, Lee SH, Ahn JS, Ahn MJ, Park K, Sun JM. Increased response rates to salvage chemotherapy administered after PD-1/PD-L1 inhibitors in patients with non-small-cell lung cancer. *J. Thorac. Oncol.* 13(1), 106–111 (2018).

• **Because these recent studies show improvements in overall response rate to salvage chemotherapy following ICI, and our outcomes are in agreement with the results of these studies.**

9. Ohe Y, Ohashi Y, Kubota K *et al.* Randomized Phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann. Oncol.* 18(2), 317–323 (2007).
10. Antony PA, Piccirillo CA, Akpinarli A *et al.* $CD8^+$ T cell immunity against a tumor/self-antigen is augmented by $CD4^+$ T helper cells and hindered by naturally occurring T regulatory cells. *J. Immunol.* 174(5), 2591–2601 (2005).
11. Srivastava RK, Sasaki CY, Hardwick JM, Longo DL. Bcl-2-mediated drug resistance: inhibition of apoptosis by blocking nuclear factor of activated T lymphocytes (NFAT)-induced Fas ligand transcription. *J. Exp. Med.* 190(2), 253–265 (1999).
12. Zhang B, Bowerman NA, Salama JK *et al.* Induced sensitization of tumor stroma leads to eradication of established cancer by T cells. *J. Exp. Med.* 204(1), 49–55 (2007).
13. Apetoh L, Ghiringhelli F, Tesniere A *et al.* Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. *Nat. Med.* 13(9), 1050–1059 (2007).
14. Tong Y, Song W, Crystal RG. Combined intratumoral injection of bone marrow-derived dendritic cells and systemic chemotherapy to treat pre-existing murine tumors. *Cancer Res.* 61(20), 7530–7535 (2001).
15. Gandhi L, Rodríguez-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).

•• **Because the results of these studies suggest that patients who receive preceding ICI show a synergistic effect between ICI and salvage chemotherapy, our outcomes are in agreement with the results.**

16. Socinski MA, Jotte RM, Cappuzzo F *et al.* IMpower150 Study Group. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N. Engl. J. Med.* 378(24), 2288–2301 (2018).

•• **Because the results of these studies suggest that patients who receive preceding ICI show a synergistic effect between ICI and salvage chemotherapy, our outcomes are in agreement with the results.**

17. Reck M, Rodríguez-Abreu D, Robinson AG *et al.* KEYNOTE-024 investigators: pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N. Engl. J. Med.* 375(19), 1823–1833 (2016).

•• **Because the results of these studies suggest that patients who receive preceding ICI show a synergistic effect between ICI and salvage chemotherapy, our outcomes are in agreement with the results.**

18. Brahmer J, Reckamp KL, Baas P *et al.* Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N. Engl. J. Med.* 373(2), 123–135 (2015).
19. Borghaei H, Paz-Ares L, Horn L *et al.* Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N. Engl. J. Med.* 373(17), 1627–1639 (2015).
20. Hida T, Nishio M, Nogami N *et al.* Efficacy and safety of nivolumab in Japanese patients with advanced or recurrent squamous non-small-cell lung cancer. *Cancer Sci.* 108(5), 1000–1006 (2017).