Respiratory Medicine Case Reports 26 (2019) 310–314

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case report

Efficacy of immunotherapy in sarcomatoid lung cancer, a case report and literature review

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ARTICLE INFO

Keywords:
Sarcomatoid
Pleomorphic
Immunotherapy
Long survivor
Lung cancer

ABSTRACT

Sarcomatoid carcinoma is a subtype of non-small cell lung cancer (NSCLC) characterized by mesenchymal – epithelial transition component and awful prognosis. In this report, based on a case of stage IV lung sarcomatoid carcinoma with an extraordinary evolution and survival over 4 years, we address unresolved questions about the treatment of this cancer. We also make a literature review about the key factors that characterize this histology and that should be considered when treating those patients. Sarcomatoid carcinoma presents with mutations as KRAS, EGFR, ALK or MET in up to 70% of cases, and an important expression of PD-L1 (also called B7-H1), which can influence treatment of those patients with new drugs as immune checkpoint inhibitors. Immunotherapy has changed the horizon of patients with stage IV lung cancers without driver mutations, as their survival has improved extraordinary. Moreover, radical treatments are being considered in long survivors with oligometastatic disease. In this report, we review targeted and radical therapy, treatment duration and the mechanisms responsible of disease evolution of sarcomatoid tumors.

1. Introduction

NSCLC is the major cause of cancer death [1]. Before targeted therapies and immunotherapy emerged, benefit of chemotherapy treatment had reached a plateau of overall survival (OS) of less than 8% at 5 years for patients with advanced NSCLC [2].

Sarcomatoid carcinoma (SC) is a less frequent subtype of NSCLC characterized by mesenchymal – epithelial transition component and inflammatory infiltration, which worse prognosis is well known [3].

We present a case of a patient with an advanced sarcomatoid lung carcinoma with a special evolution witch checkpoint inhibitors treatment. This case brings up the unresolved questions about patient's management, immunotherapy and sarcomatoid histology.

2. Case exposure

2.1. Patient information and diagnosis

The patient is a 53 years old male, with personal history of insulin-dependent diabetes and former smoker of 33 packs-year.

In October 2013, he presented with cough and mild hemoptysis. After the work out, he was diagnosed of sarcomatoid lung carcinoma stage T3N2Mx (due to a PET finding in ileum without correlation in other imaging tests). The patient received 4 cycles of carboplatin AUC 5 plus paclitaxel 175 mg/m2 between December 2013 and February 2014. He achieved partial response and underwent radical radiotherapy. In May 2014, a PET scan showed progressive disease with peritoneal and small bowel masses, mesenteric nodes and liver metastasis and no new findings in the thoracic area. The pathological analysis confirmed metastasis of the lung tumor, and the patient came to our center for a clinical trial with a PD-1/PD-L1 checkpoint inhibitor. The treatment was well tolerated and the patient achieved abdominal complete response (CR) and stable lung findings (Fig. 1).

He continued treatment, until February 2015, when the pulmonary lesion started to grow slowly (Fig. 2) while maintaining abdominal CR. The patient was asymptomatic, but due to the progressive enlargement of the lesion, after a discussion in the multidisciplinary committee, he underwent a right superior lobectomy and lymphadenectomy.

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https://doi.org/10.1016/j.rmcr.2019.02.017
Received 24 August 2018; Received in revised form 18 February 2019; Accepted 19 February 2019

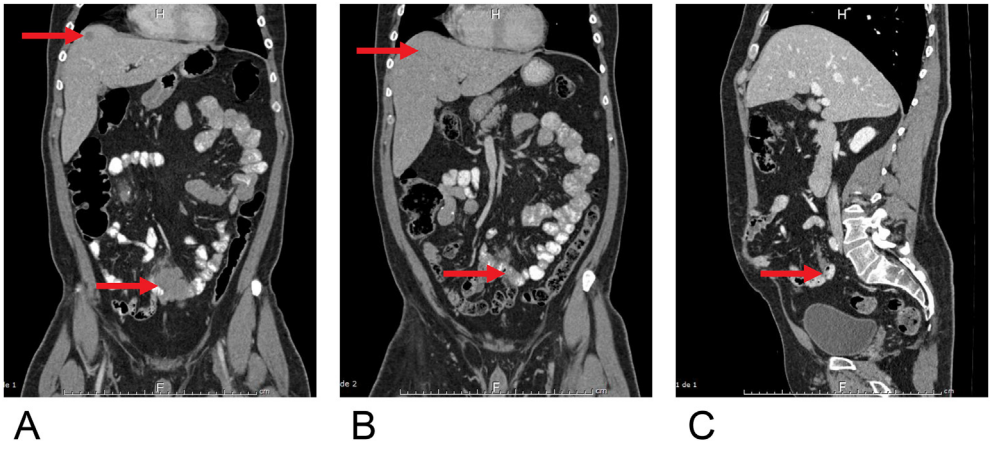

Fig. 1. Evolution of hepatic lesion and abdominal mass on the different CT scans.

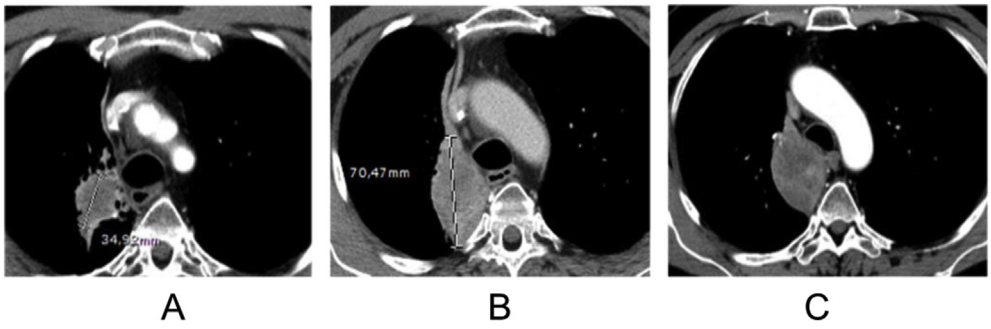

Fig. 2. Response of main lesion: right superior lobe mass on the different CT scans performed.

Pathological analysis confirmed a pulmonary undifferentiated lung sarcomatoid carcinoma, stage ypT2aN0. PD-L1 expression was over 95%, although it barely contained tumor-infiltrating lymphocytes (TILs). Molecular analysis revealed c-MET amplification with 6,9 copies and no mutation in exon 14, EGFR, BRAF and KRAS wild type, no ALK translocation and no ROS-1 rearrangement.

We performed a next generation sequencing on the surgical samples of lung and small bowel with Targets Oncomine Focus Panel, but only showed a mutation in exon 4 of isocitrate dehydrogenase 1 (IDH) gene on the bowel metastasis.

The patient decided to resume immunotherapy and finally stopped it in February 2018. So far, the patient is still in CR without any current treatment, highlighting that advanced sarcomatoid carcinoma of the lung also benefits from multidisciplinary strategies. Fig. 3 shows the timeline of the patient evolution.

3. Discussion

Lung sarcomatoid carcinoma is included in the World Health Organization (WHO) lung carcinomas classification. Its main subtypes are pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma or sarcomatoid carcinoma (SC) and pulmonary blastoma [4].

Its incidence is less than 1% of lung carcinomas [5], and it is related to tobacco smoking [6]. Its histological and clinical characteristics are different from other types of NSCLC. SC presents with a component of squamous carcinoma or adenocarcinoma, as well as heterologous elements of sarcoma, rhabdomyosarcoma, chondrosarcoma or osteosarcoma [7]. Metastases to central nervous system and adrenal glands, besides other rare locations such as small bowel, rectum or kidney are common. Extended disease and/or short time to relapse is common. Usually the prognosis is poor with a median overall survival in advanced stage patients of 6 months [1,8].

SC is a clonal tumor that may present mutations in up to 70% of cases. Fig. 4 shows the most frequent ones, and 39% of cases can share up to four simultaneous mutations [9]. Usually, the tumor is positive for cytokeratine 7 and TTF1, but not in the sarcoma component [10]. Recently, MET amplification and exon 14 mutation have been reported in 22% of cases [11], including some cases with MET exon 14 mutation plus anaplastic lymphoma kinase (ALK) translocation in the same tumor [12,13].

PD-L1 is expressed in these tumors in 70–90% of cases [14–18] and until now, no correlation was found between PD-L1 expression and the mutation of EGFR, APC, PTEN, PIK3CA, TP53 and STK11 genes [19].

Immune check point inhibitors (anti PD-1 and anti PD-L1) have demonstrated its efficacy in NSCLC treatment. Pembrolizumab, an anti PD-1 humanized monoclonal antibody, demonstrated improvement of overall survival versus docetaxel in pretreated NSCLC patients with PD-L1 expression of at least 1% of tumor cells (HR of 0·61, 95% CI 0·49–0·75; $p < 0·0001$) [20]. In the same setting, Nivolumab, a human anti PD-1 IgG4 immunoglobuline, demonstrated similar efficacy in NSCLC patients. In non-squamous lung cancer, it reduced risk of death (HR, 0.73; 95% CI, 0.59 to 0.89; $P = 0.002$) and prolonged overall survival from 9.4 to 12.2 months [21]. In squamous NSCLC, It also improved overall survival from 6 to 9.2 months (HR 0.59; 95% CI, 0.44 to 0.79; $P < 0.001$) [22]. However, none of the trials evaluated efficacy in sarcomatoid lung cancer.

In this case, the right upper lobe mass progressed during immunotherapy treatment in spite of achieving complete abdominal response. Surprisingly, both lesions had a similar genetic profile, high PD-L1 expression and similar pathological findings. .

Density of $CD8^+$ TILs may be an emerging prognostic biomarker in SC as found in the study of Chen [23]. For all stages, the median overall survival was 92.3 month for patients with a high density of $CD8^+$ versus 31.2 months for those patients with lower density of $CD8^+$ TILs. ($HR = 0.455$, $P < 0.05$). The degree of infiltration of $CD8^+$ TILs was

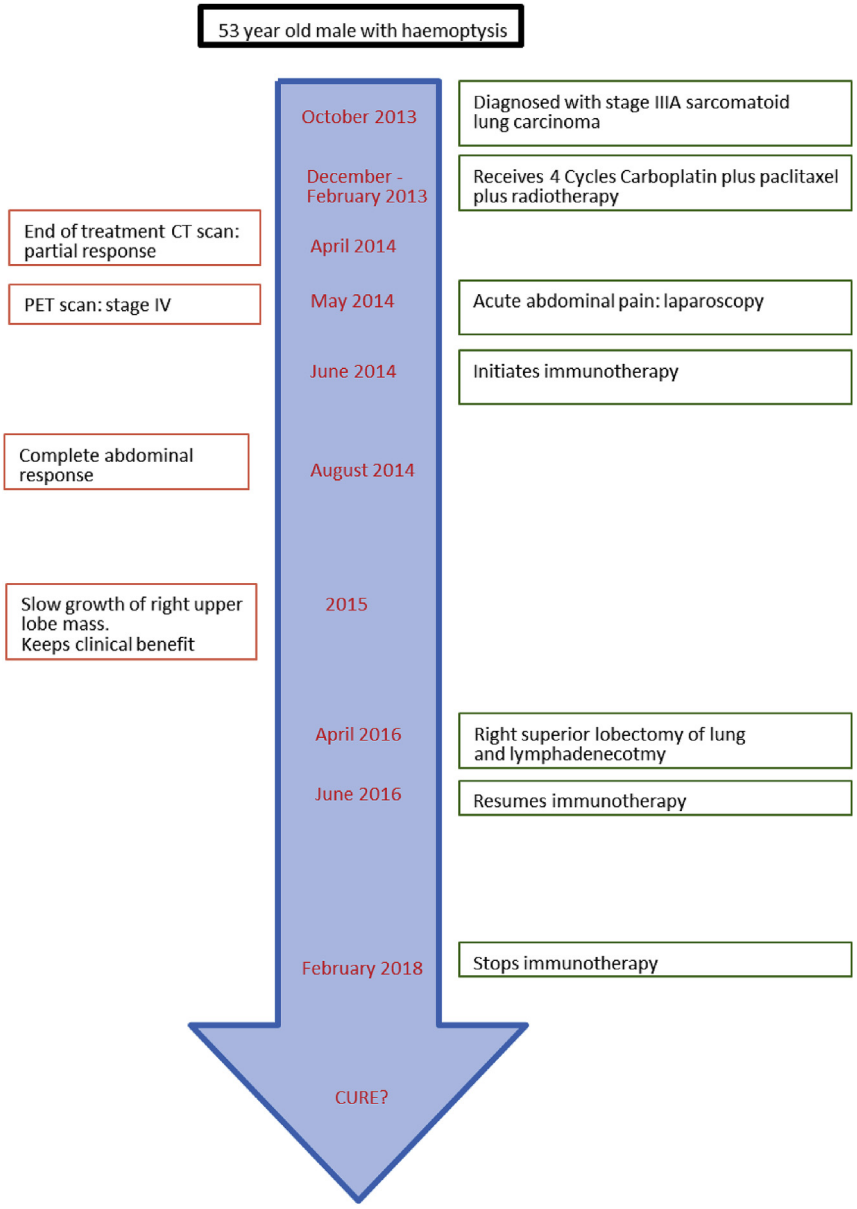

Fig. 3. Timeline of patient evolution.

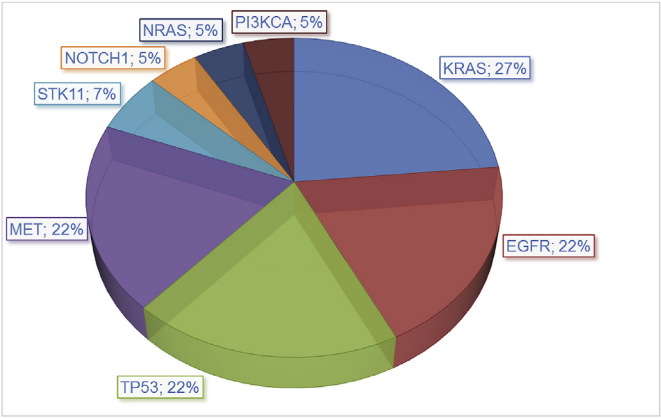

Fig. 4. Most frequent mutations in lung sarcomatoid carcinoma.

also significantly correlated with clinicopathological stage of lung SC ($P < 0.05$).

The analysis of PD-L1 Expression has some issues in NSCLC. It may be constitutively expressed by B and T cells, dendritic cells, macrophages, tumor cells, mesenchymal stem cells and a variety of non-hematopoietic cells. In each site, it is up or down regulated depending on the inflammatory response [24]. The expression also varies between TILs versus tumor cells. Taube et al. found that surface expression of PD-L1 varied among different types of tumor cells and TILs, and tumor cell PD-L1 expression correlated with objective response to anti-PD-1 drugs because of immune active microenvironment [25].

Primary lesion or metastasis also can have different expression of PD-L1. Hye et al. compared PD-L1 expression in primary tumor and after metastatic relapse, finding that it was double in metastatic sites [26].

The antibody clone used to analyze PD-L1 expression by immunohistochemistry has also differences that should be taken into account. Dako (Pfizer, Bristol and Merk) and Ventana clones (Astra Zeneca and Roche) are the most used. The cutoffs for positivity were different in each trial for each drug, making it difficult to compare

results and sometimes compromising the efficacy of the clinical data [27,28].

The pathologist making the observation can also allocate a different value for PD-L1 expression. This occurs especially when the staining is positive in less than 10% of cells, so the interpretation of the stain is more difficult [29].

In this case, the pathologic key-differentiating element between surgical pieces was the scarce TILs observed in the thoracic sample. From the clinical point of view, the only difference was the thoracic radiotherapy administered to the lung tumor before starting immunotherapy. However, the expected effect would be the opposite taking into consideration preclinical data. These data suggest that previous chemotherapy and radiotherapy can increase expression of PD-L1 [30,31] and tumor response. Dovedi et al. [32] showed that fractionated radiotherapy administered with anti PD-1 or anti PD-L1 antibodies generated efficacious $CD8^+$ T-cell responses that improved local tumor control. $CD8^+$ T cells produced IFNγ that was responsible for PD-L1 up regulation on tumor cells after delivery of concomitant but not sequential radiotherapy.

The potential abscopal effect [33,34] and the recent experience in stage III NSCLC patients treated with Durvalumab maintenance after chemoradiotherapy [35] would make us expect better responses with radiotherapy combination. Those findings suggest that previous radiation of a lesion should not have a negative impact on the probability of response to checkpoint inhibitors, although time lapse from radiotherapy is significant. In fact, Dovedi and cols [18] pointed out that increased levels of PD-L1 fall 7 days after finishing radiotherapy because of generation of CD8 lymphocytes with specific memory against tumor antigens.

In our case, the irradiated progressed slowly. As mentioned above, the only pathological difference were TILs and radiotherapy administered until February 2013. It is important to explore the changes tumor microenvironment after radiotherapy.

The potential influence of driver mutations and co-mutations as biomarkers for immunotherapy has been addressed recently. In his study, Jiang pointed out that, PD-L1 positivity overlapped with known alterations in NSCLC oncogenic tumor drivers in 26% of squamous cell carcinoma and 76% of adenocarcinoma samples. [36], although in our case, the analysis with 40 gene sequencing panel did not differ in both tumor samples with exception of IDH mutation finding in the abdominal metastasis.

Gounant [37] and Salati [38] described other two cases of sarcomatoid lung cancer with optimal response to immune check point inhibitor, in similar circumstances to our case, but with shorter evolution.

In summary, molecular analysis of driver mutations and immune markers are opening new treatment possibilities for patients with extremely poor prognosis. Besides, if systemic treatment achieves good response, it is reasonable consider radical treatment despite of stage IV tumor.

The long survival of this patient with an adverse histology, and the different disease evolution of two sites pathologically similar point out that immunotherapy combined with radical treatments in some patients may be an option while keeping on finding the clues to better patient's selection.

Conflicts of interest

The authors declare no competing interests.

Author contributions

Magda Palka and Pilar Garrido researched data for the article, made substantial contributions to discussions of the content and wrote the article.

Ana Gomez Rueda and Maria Eugenia Olmedo made substantial contributions to discussions of the content and reviewed and edited the manuscript before submission.

Amparo Benito, Almudena Santon, Luis Gorospe, Jose Palacios and Maria Angeles Fernandez researched data for the article and reviewed and edited the manuscript before submission.

Ethical adherence

This work respects the ethical rules as detailed in the Publishing Ethics for Authors detailed in Elsevier Publishing Ethics.

Acknowledgements

This work was not supported by any funding.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2017, Cancer J. Clin. 67 (2017) 7–30.
[2] P. Goldstraw, K. Chansky, J. Crowley, et al., The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer, J. Thorac. Oncol. 11 (1) (2016 Jan) 39–51.
[3] T. Vieira, N. Girard, M. Ung, I. Monnet, A. Cazes, P. Bonnette, M. Duruisseaux, J. Mazieres, M. Antoine, J. Cadranel, M. Wislez, Efficacy of first-line chemotherapy in patients with advanced lung sarcomatoid carcinoma, J. Thorac. Oncol. 8 (12) (2013 Dec) 1574–1577.
[4] W.D. Travis, E. Brambilla, A.G. Nicholson, et al., WHO panel members. The 2015 World Health organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification, J. Thorac. Oncol. 10 (9) (2015 Sep) 1243–1260.
[5] Y.L. Chang, Y.C. Lee, J.Y. Shih, et al., Pulmonary pleomorphic (spindle) cell carcinoma: peculiar clinicopathologic manifestations different from ordinary non-small cell carcinoma, Lung Cancer 34 (2001) 91–97.
[6] N.F. Fishback, W.D. Travis, C.A. Moran, et al., Pleomorphic (spindle/giant cell) carcinoma of the lung. A clinicopathologic correlation of 78 cases, Cancer 73 (1994) 2936–2945.
[7] W.D. Travis, E. Brambilla, H.K. Muller-Hermelink, et al. (Eds.), World Health Organization Classification of Tumors: Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart, IARC Press, Lyon, 2004, pp. 53–58.
[8] H.M. Bae, H.S. Min, S.H. Lee, et al., Palliative chemotherapy for pulmonary pleomorphic carcinoma, Lung Cancer 58 (2007) 112–115.
[9] V. Fallet, R. Saffroy, N. Girard, et al., High-throughput somatic mutation profiling in pulmonary sarcomatoid carcinomas using the LungCarta™ Panel: exploring therapeutic targets, Ann. Oncol. 26 (8) (2015 Aug) 1748–1753, https://doi.org/10.1093/annonc/mdv232. Epub 2015 May 12.
[10] G.C.A. Rossi, N. Sturn, M. Migaldi, et al., Pulmonary carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements: a clinicopathologic and immunohistochemical study of 75 cases, Am. J. Surg. Pathol. 27 (2003) 11–24.
[11] X.1 Liu, Y.1 Jia, M.B.1 Stoopler, Y.1 Shen, H.1 Cheng, J.1 Chen, Mansukhani M1, S.1 Koul, B.2 Halmos, A.C.1 Borczuk, Next-generation sequencing of pulmonary sarcomatoid carcinoma reveals high frequency of actionable MET gene mutations, J. Clin. Oncol. 34 (8) (2016 Mar 10) 794–802.
[12] J.H. Tong, S.F. Yeung, A.W. Chan, et al., MET amplification and exon 14 splice site mutation define unique molecular subgroups of non-small cell lung carcinoma with poor prognosis, Clin. Cancer Res. 22 (12) (2016 Jun 15) 3048–3056, https://doi.org/10.1158/1078-0432.CCR-15-2061. Epub 2016 Feb 4.
[13] G. Pelosi, P. Gasparini, A. Cavazza, et al., Multiparametric molecular characterization of pulmonary sarcomatoid carcinoma reveals a nonrandom amplification of anaplastic lymphoma kinase (ALK) gene, Lung Cancer 77 (2012) 507–514.
[14] Velcheti, D.L. Rimm, K.A. Schalper, Sarcomatoid lung carcinomas show high levels of programmed death ligand-1 (PD-L1), J. Thorac. Oncol. 8 (2013) 803–805.
[15] S. Kim, M.-Y. Kim, J. Koh, H. Go, D.S. Lee, Y.K. Jeon, et al., Programmed death-1 ligand 1 and 2 are highly expressed in pleomorphic carcinomas of the lung: comparison of sarcomatous and carcinomatous areas, Eur. J. Cancer 51 (2015) 2698 ± 707.
[16] Y.-L. Chang, C.-Y. Yang, M.-W. Lin, C.T. Wu, P.C. Yang, High co-expression of PD-L1 and HIF-1α correlates with tumour necrosis in pulmonary pleomorphic carcinoma, Eur. J. Cancer 60 (2016) 125 ± 35.
[17] T. Vieira, M. Antoine, C. Hamard, V. Fallet, M. Duruisseaux, N. Rabbe, et al., Sarcomatoid lung carcinomas show high levels of programmed death ligand-1 (PD-L1) and strong immune-cell infiltration by TCD3 cells and macrophages, Lung Cancer 98 (2016) 51 ± 8.
[18] F. Lococo, F. Torricelli, G. Rossi, et al., Inter-relationship between PD-L1 expression and clinic-pathological features and driver gene mutations in pulmonary sarcomatoid carcinomas, Lung Cancer 113 (2017 Nov) 93–101.
[19] F. Lococo, G. Gandolfi, G. Rossi, et al., Deep sequencing analysis reveals that KRAS mutation is a marker of poor prognosis in patients with pulmonary sarcomatoid carcinoma, J. Thorac. Oncol. 11 (8) (2016 Aug) 1282–1292.
[20] R.S. Herbst, P. Baas, D.-W. Kim, E. Felip, et al., Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial, Lancet 387 (2015) 1540–1550.

[21] H. Borghaei, L. Paz-Ares, L. Horn, et al., Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer, N. Engl. J. Med. 373 (2015) 1627–1639.
[22] J. Brahmer, K.L. Reckamp, P. Baas, et al., Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer, N. Engl. J. Med. 373 (2015) 123–135.
[23] J. Chen, Q. He, J. Liu, Y. Xiao, C. Xiao, K. Chen, D. Xie, X. Zhang, CD8+ tumor-infiltrating lymphocytes as a novel prognostic biomarker in lung sarcomatoid carcinoma, a rare subtype of lung cancer, Cancer Manag. Res. 10 (2018 Sep 13) 3505–3511, https://doi.org/10.2147/CMAR.S169074. eCollection 2018.
[24] A.H. Sharpe, E.J. Wherry, R. Ahmed, G.J. Freeman, The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection, Nat. Immunol. 8 (2007) 239–245.
[25] J.M. Taube, A. Klein, J.R. Brahmer, H. Xu, X. Pan, J.H. Kim, et al., Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy, Clin. Cancer Res. 20 (2014) 5064–5074.
[26] Hye Ryun Kim, Yoon Jin Cha, Min Hee Hong, et al., Concordance of programmed death-ligand 1 expression between primary and metastatic non-small cell lung cancer by immunohistochemistry and RNA in situ hybridization, Oncotarget 8 (50) (2017 Oct 20) 87234–87243.
[27] M.J. Ratcliffe, A. Sharpe, A. Midha, C. Barker, M. Scott, P. Scorer, H. Al-Masri, M. Rebelatto, J. Walker, Agreement between programmed cell death ligand-1 diagnostic assays across multiple protein expression cut-offs in non-small cell lung cancer, Clin. Cancer Res. 23 (2017) 3585-359.
[28] S. Hendry, D.J. Byrne, G.M. Wright, R.J. Young, S. Sturrock, W.A. Cooper, S.B. Fox, Comparison of four PD-L1 immunohistochemical assays in lung cancer, J. Thorac. Oncol. 13 (3) (2018 Mar) 367–376.
[29] K.M. Kerr, The PD- L1 immunohistochemistry biomarker: two steps forward, one step back? J. Thorac. Oncol. 13 (3) (2018 Mar) 291–294.
[30] L. Deng, H. Liang, B. Burnette, et al., Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice, J. Clin. Invest. 124 (2014) 687–695.
[31] P. Zhang, D.M. Su, M. Liang, J. Fu, Chemopreventive agents induce programmed death-1-ligand 1 (PD-L1) surface expression in breast cancer cells and promote PD-L1-mediated T cell apoptosis, Mol. Immunol. 45 (2008) 1470–1476.
[32] S.J. Dovedi, A.L. Adlard, G. Lipowska-Bhalla, et al., Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade, Cancer Res. 74 (2014) 5458–5468.
[33] W. Ngwa, O.C. Irabor, J.D. Schoenfeld, J. Hesser, S. Demaria, S.C. Formenti, Using immunotherapy to boost the abscopal effect, Nat. Rev. Cancer (2018 Feb 16), https://doi.org/10.1038/nrc.2018.6.
[34] R. Marconi, et al., A meta-analysis of the abscopal effect in preclinical models: is the biologically effective dose a relevant physical trigger? PLoS One 12 (2017) e0171559.
[35] S.J. Antonia, A. Villegas, D. Daniel, et al., Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer, N. Engl. J. Med. 377 (20) (2017 Nov 16) 1919–1929.
[36] L. Jiang, X. Su, T. Zhang, X. Yin, et al., PD-L1 expression and its relationship with oncogenic drivers in non-small cell lung cancer(NSCLC), Oncotarget 8 (16) (2017 Apr 18) 26845–26857, https://doi.org/10.18632/oncotarget.15839.
[37] V. Gounant, S. Brosseau, C. Naltet, M.A. Opsomer, M. Antoine, C. Danel, et al., Nivolumab-induced organizing pneumonitis in a patient with lung sarcomatoid carcinoma, Lung Cancer 99 (2016 Sep) 162–165.
[38] M. Salati, C. Baldessari, F. Calabrese, G. Rossi, E. Pettorelli, G. Grizzi, M. Dominici, F. Barbieri, Nivolumab-Induced impressive response of refractory pulmonary sarcomatoid carcinoma with brain metastasis, Case Rep. Oncol. 11 (3) (2018 Sep 7) 615–621, https://doi.org/10.1159/000492666. eCollection 2018 Sep-Dec.