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Smooth sailing for immunotherapy for unresectable stage III non-small cell lung cancer: the PACIFIC study

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The tumor microenvironment, the soil in which tumors grow in the body, has become a rich source of potential therapeutic intervention. Tumor cells, endothelial cells, fibroblasts, dendritic cells, macrophages, T cells, and numerous other cell types collaborate to create a pro-tumorigenic environment. Initial attempts to alter the microenvironment focused on endothelial cells and angiogenesis, but there is now a growing appreciation of the complex contributions of each cell type to tumor growth. Most recently, the dramatic success of immunotherapy in metastatic melanoma (1), non-small cell lung cancer (NSCLC) (2,3), as well as multiple other cancer types has shown that modulation of the immune microenvironment can be an effective therapeutic strategy. It is now clear that the tumor microenvironment is a hypoxic milieu that promotes immunosuppression via T-cell exhaustion, anergy, accumulation of immunosuppressive cell types, among numerous other mechanisms (4).

The availability of drugs that block the programmed death (PD)-1 receptor and its ligand PD-L1 have shown that that these pathways are critical for tumor immune evasion. PD-1 is expressed on multiple immune cell types upon activation, including T-cells, B-cells and natural killer (NK) cells (5). PD-L1 is expressed on antigen presenting cells, as well as multiple non-hematopoietic cells. Ligation of PD-1 to PD-L1 inhibits T cell function and increases T-cell apoptosis, functioning as a brake on T-cell mediated immunity (5). Tumor cells have co-opted this pathway by expressing PD-L1, and thus blocking antibodies to PD-1 and PD-L1 (immune checkpoint inhibitors) have transformed our treatment of many malignancies.

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NSCLC is the most common cancer worldwide, and is the most common cause of cancer related death, accounting for approximately 1.7 million deaths per year. Patients diagnosed in earlier stages, when tumor involves only a primary site in the lung (stage I) or the hilar lymph nodes (stage II), can be treated surgically, with or without adjuvant chemotherapy. The 5-year survival rates for these early stages is 40–50%. For stage III lung cancer, usually involving the mediastinal lymph nodes, chemoradiotherapy is the standard of care for patients with unresectable disease. The median survival of patients in modern chemoradiation trials with FDG-PET staging is about 29 months from diagnosis, with a 5-year survival of only 30%. Furthermore, attempts to improve outcomes with higher radiation doses (6), or adding adjuvant chemotherapy (7) have not shown any clear improvement in survival. Thus, it was clear that new modalities were sorely needed to improve patient outcomes.

In NSCLC, the use of immunotherapy has quickly risen from an afterthought to become the standard of care. Randomized phase III trials done in the setting of metastatic disease have shown a survival benefit of immune checkpoint blockade compared to chemotherapy in both the second-line (2,3) and first-line setting (8). The pioneering advances of immunotherapy for stage IV disease have raised the question of the potential role for immunotherapy in earlier stages of disease. For example, adjuvant ipilimumab has been shown to improve outcomes for stage III resected melanoma (9), suggesting that immune checkpoint blockade may be beneficial in delaying or preventing disease recurrence after definitive therapy.

The PACIFIC trial represents the first major attempt to move immune checkpoint blockade into the treatment of stage III lung cancer (10). A total of 713 patients with unresectable stage III NSCLC who completed chemoradiation were randomized 2:1 to durvalumab (10 mg/kg every 2 weeks for 1 year) *vs.* placebo. The vast majority (91%) were current or former smokers, and 46% of patients had a squamous histology. Assessment of PD-L1 expression was not used to select patients for enrollment, although these data were collected for analysis.

The co-primary endpoint of progression-free survival (PFS) was 16.8 months (95% CI, 13.0–18.1 months) for patients receiving durvalumab compared to 5.6 months with placebo (95% CI, 4.6–7.8 months), with a hazard ratio of 0.52 ($P<0.001$). This PFS difference was seen across all prespecified and demographic subgroups evaluated, including non-smokers. Even the subgroup of patients with PD-L1 expression <25% showed a significant benefit. The only subset of patients where there may not have been a benefit were the relatively small number of patients with EGFR mutations. Significantly fewer new lesions, including brain metastases, were identified in the patients receiving durvalumab.

Importantly, this improvement in outcomes was not accompanied by a significant increase in toxicity. Although there were slightly more cases of pneumonitis in the durvalumab arm compared to placebo (33.9% *vs.* 24.8%), there was no significant increase in grade ≥3 events. Overall grade ≥3 toxicity was quite rare.

These results, while exciting, come with a few caveats. First, the PFS in the control arm is relatively short. As noted above, in the RTOG 0617 study, the median PFS is 11.8 months,

double that seen in this study. Although the randomization occurred up to 42 days after completion of chemoradiotherapy, this would only account for approximately 3 months (6 weeks for chemoradiation and 6 weeks for recovery) of the difference in PFS. This discrepancy raises the question of whether these patients all had stage III disease. For example, if patients were not routinely staged with FDG-PET, occult metastatic disease could explain the poor median PFS, and could also explain the benefit of immune checkpoint blockade, which is known to be beneficial in the stage IV setting.

Secondly, the overall survival (OS) data are not mature, and longer follow-up is needed to ensure the benefit of this therapy. It remains possible that despite the impressive benefit in PFS, early salvage treatment with immune checkpoint inhibitors may result in similar survival. However, the PFS of 17.8 months is certainly quite impressive, and in many immunotherapy trials the OS benefit ends up being greater than the impact on PFS. These results are likely to be practice changing in the United States, pending FDA approval of durvalumab for this indication.

This trial raises several interesting questions from a translational standpoint. First, there are a number of exploratory translational objectives that are likely to be examined as the data matures. This includes data on the correlation of PD-L1 expression, both within the tumor and within other cell types within the tumor microenvironment, with outcomes such as PFS and OS. Secondly, analysis of the biomarkers in both blood and tissue may yield interesting insights for both responders and non-responders. Evaluation of the changes in the immune cell populations or gene expression analysis of cytokines and other signaling molecules may help refine the population most likely to benefit from immune checkpoint blockade. Recent mass cytometry data coupled with single cell gene expression analysis have shown that specific populations of macrophages accumulate in human tumors compared to the normal lung parenchyma (11), and evaluation of these subsets of immune cells in patients who responded to adjuvant durvalumab may prove insightful.

On a more fundamental level, the design of the trial raises a number of questions regarding the role of immune checkpoint blockade in NSCLC. In the KEYNOTE-001 study of NSCLC, the response rate to pembrolizumab was significantly influenced by the expression of PD-L1 in the tumor (12). While the overall response rate was approximately 20% for the entire group, patients whose tumors had a >50% expression of PD-L1 had a response rate of 45%. In this study, no difference was seen among patients based on pre-treatment PD-L1 status. One intriguing hypothesis is that the initial chemoradiotherapy may enhance the response to immunotherapy. It is possible that chemoradiation can alter the immunosuppressive microenvironment in these tumors (13) or result in the creation of neoantigens that prime an immune response (14).

One interesting analysis found that in patients treated on KEYNOTE-001, the patients who had previously received radiotherapy showed a significantly longer median PFS and OS compared to those who had not received radiotherapy (15). Similarly, data from KEYNOTE-021 testing the combination of pemetrexed based chemotherapy with pembrolizumab showed that patients with PD-L1 staining in <1% of tumor cells receiving the combination still had a response rate of 57% compared to 13% with chemotherapy alone

(16). These data hint that treatment with chemotherapy or radiotherapy may impact the tumor or infiltrating immune cells in a way that promotes response to immune checkpoint inhibitors. The question of whether treatment prior to initiation of immune checkpoint blockade influences activity is a key one, as the next frontier of immunotherapy in lung cancer is likely to be trials in the preoperative setting (e.g., NCT02259621) for earlier stages of disease.

Another question raised by this study is whether these results may be improved by further manipulation of the tumor microenvironment. Although the results of this trial were quite impressive, by 18 months about half the patients had either progressed or died despite durvalumab therapy. Thus, there is room to try to improve both the likelihood of response as well as the duration of benefit. While there are many potential therapies to test, it is reasonable to consider strategies to promote an immunologically active tumor microenvironment. For example, tumors are quite hypoxic due to leaky vessel formation (17), vessel compression (18), and mechanical stress resulting from desmoplastic tumor stroma (19). This tumor hypoxia promotes an immunosuppressive environment (4), which may impede response to immune checkpoint blockade. Thus, strategies to normalize the vasculature in tumors during or after chemoradiotherapy may improve the likelihood of response to immune checkpoint inhibition.

One candidate, bevacizumab, has been shown to improve vascular permeability and has been studied as maintenance therapy in metastatic NSCLC (20). While probably not appropriate as concurrent therapy with chemoradiation (21), it may be that lower doses can be used safely to normalize the vasculature (17). Although there is no published data regarding this combination yet, the phase III Empower 150 study tested the addition of atezolizumab (a PDL-1 inhibitor) to a chemotherapy regimen containing bevacizumab. A press release from Roche (22) has noted that the combination is safe, and that the addition of atezolizumab increased PFS compared to chemotherapy alone. Additional published analysis of this trial may shed some light on the potential synergy between vascular normalization and immunotherapy.

Another pathway that may prove to be worth modulating is the renin-angiotensin system (RAS), which is known to play a key role in the immunosuppressive tumor microenvironment (23). The RAS is a major regulator of TGF-β signaling, which influences many different aspects of immunosuppression. Retrospective data has shown that use of drugs modulating the RAS are associated with improved survival in NSCLC patients receiving chemotherapy (24). In pancreatic tumors, which have a very desmoplastic stroma and have been resistant to immunotherapy, treatment with drugs that modulate the RAS has been shown to dramatically alter the immunological microenvironment, promoting an anti-tumor immune response (25). These data raise the possibility that modulation of the RAS may improve the response of patients to immune checkpoint blockade in the adjuvant setting.

The results of the PACIFIC trial have opened a new paradigm for the use of immunotherapy in lung cancer. Given the benefits of adding immune checkpoint blockade in stage IV and stage III NSCLC, it is tempting to speculate that it may have a benefit in both stage I and

stage II lung cancer, which have traditionally been managed primarily with surgical resection. For patients who are not fit for surgery, radiation therapy with stereotactic body radiotherapy (SBRT) is a standard of care. It will be interesting to see if there are differences in the response rates and outcomes for patients with early-stage disease treated with immunotherapy based on the definitive modality used for treatment (surgery *vs.* radiotherapy). Given the speculation that radiation may alter the tumor microenvironment in a favorable way, it is tempting to hypothesize that adjuvant immunotherapy may be uniquely beneficial for early-stage patients receiving SBRT.

In summary, the PACIFIC trial is a practice-changing study that opens a lot of doors for investigation and improvement of immunotherapy in lung cancer. It is an exciting time for clinicians and scientists interested in the study of lung cancer and the tumor microenvironment. Most importantly, this study offers hope to a large number of patients who have historically had poor outcomes despite aggressive therapy, and we are eagerly awaiting the final mature results.

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References

1. Kaufman HL, Kirkwood JM, Hodi FS, et al. The Society for Immunotherapy of Cancer consensus statement on tumour immunotherapy for the treatment of cutaneous melanoma. Nat Rev Clin Oncol 2013;10:588–98. [PubMed: 23982524]
2. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:1627–39. [PubMed: 26412456]
3. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:123–35. [PubMed: 26028407]
4. Martin JD, Fukumura D, Duda DG, et al. Reengineering the Tumor Microenvironment to Alleviate Hypoxia and Overcome Cancer Heterogeneity. Cold Spring Harb Perspect Med 2016;6 pii: a027094.
5. Sharpe AH, Pauken KE. The diverse functions of the PD1 inhibitory pathway. Nat Rev Immunol 2017 [Epub ahead of print].
6. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-smallcell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol 2015;16:187–99. [PubMed: 25601342]
7. Hanna N, Neubauer M, Yiannoutsos C, et al. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. J Clin Oncol 2008;26:5755–60. [PubMed: 19001323]
8. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375:1823–33. [PubMed: 27718847]
9. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy. N Engl J Med 2016;375:1845–55. [PubMed: 27717298]

10. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med 2017;377:1919–29. [PubMed: 28885881]
11. Lavin Y, Kobayashi S, Leader A, et al. Innate Immune Landscape in Early Lung Adenocarcinoma by Paired Single-Cell Analyses. Cell 2017;169:750–65.e17. [PubMed: 28475900]
12. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372:2018–28. [PubMed: 25891174]
13. Weichselbaum RR, Liang H, Deng L, et al. Radiotherapy and immunotherapy: a beneficial liaison? Nat Rev Clin Oncol 2017;14:365–79. [PubMed: 28094262]
14. Formenti SC, Demaria S. Combining radiotherapy and cancer immunotherapy: a paradigm shift. J Natl Cancer Inst 2013;105:256–65. [PubMed: 23291374]
15. Shaverdian N, Lisberg AE, Bornazyan K, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. Lancet Oncol 2017;18:895–903. [PubMed: 28551359]
16. Langer CJ, Gadgeel SM, Borghaei H, et al. 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;17:1497–508. [PubMed: 27745820]
17. Jain RK. Antiangiogenesis strategies revisited: from starving tumors to alleviating hypoxia. Cancer Cell 2014;26:605–22. [PubMed: 25517747]
18. Padera TP, Stoll BR, Tooredman JB, et al. Pathology: cancer cells compress intratumour vessels. Nature 2004;427:695. [PubMed: 14973470]
19. Chauhan VP, Boucher Y, Ferrone CR, et al. Compression of pancreatic tumor blood vessels by hyaluronan is caused by solid stress and not interstitial fluid pressure. Cancer Cell 2014;26:14–5. [PubMed: 25026209]
20. Patel JD, Socinski MA, Garon EB, et al. PointBreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer. J Clin Oncol 2013;31:4349–57. [PubMed: 24145346]
21. Socinski MA, Stinchcombe TE, Moore DT, et al. Incorporating bevacizumab and erlotinib in the combinedmodality treatment of stage III non-small-cell lung cancer: results of a phase I/II trial. J Clin Oncol 2012;30:3953–9. [PubMed: 23045594]
22. Media Release. Basel, 20 11 2017 Available online: https://www.roche.com/media/store/releases/medcor-2017-11-20.htm
23. Pinter M, Jain RK. Targeting the renin-angiotensin system to improve cancer treatment: Implications for immunotherapy. Sci Transl Med 2017;9. pii: eaan5616.
24. Menter AR, Carroll NM, Sakoda LC, et al. Effect of Angiotensin System Inhibitors on Survival in Patients Receiving Chemotherapy for Advanced Non-Small-Cell Lung Cancer. Clin Lung Cancer 2017;18:189–97.e3. [PubMed: 27637408]
25. Liu H, Naxerova K, Pinter M, et al. Use of Angiotensin System Inhibitors Is Associated with Immune Activation and Longer Survival in Nonmetastatic Pancreatic Ductal Adenocarcinoma. Clin Cancer Res 2017;23:5959–69. [PubMed: 28600474]