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COMMENTARY

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Multimodal "synergistic" treatment based on tumour immunological contexture for advanced non-driver non-small cell lung cancer: A myth or reality?

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Non-small cell lung cancer (NSCLC) is the predominant lung malignancy comprising approx. 85% of lung tumours. At diagnosis, about 40% of patients will present with metastatic disease and dismal 5-year relative survival rate of approximately 5% (Goldstraw et al., 2016; Noone et al., 2018; Siegel, Miller, & Jemal, 2020).

Integration of immune checkpoint inhibitors (ICIs) in the management of advanced "non-driver" non-small cell lung cancer (NSCLC) has revolutionised patient prognosis (Borghaei et al., 2015; Brahmer et al., 2015). A combination of acceptable toxicity with impressive treatment response and duration has led to rapid dissemination (Antonia et al., 2017; Antonia et al., 2019:; Käsmann et al., 2019; Reck et al., 2019). Further studies integrating chemotherapy with ICIs in metastatic disease demonstrated synergism of combined therapy versus chemotherapy alone regardless of tumour histology and PD-L1 status (Gandhi et al., 2018; Paz-Ares et al., 2018; Socinski et al., 2018). Parallel to these developments, there have been continuous advancements in the technical aspects of radiation treatment allowing radiation oncologists to deliver high-dose radiotherapy to multiple tumour sites while limiting toxicity. Simultaneous integrated boost techniques have permitted further customisation of the delivered dose.

Based on results of trials focused on locally advanced disease (stage III) and post hoc analyses for metastatic disease, sequential or concurrent application of chemo-, immuno- and radiotherapy demonstrated favourable results with acceptable toxicity (Antonia et al., 2017; Antonia et al., 2019; Shaverdian et al., 2017). However, the underlying synergistic effects of this combination remain unknown. Establishing the underlying mechanisms for these synergistic interactions may lead to novel potential treatment paradigms. So far, the pillars of modern cancer treatment in advanced NSCLC have developed mostly independently. Furthermore, identification of predictive markers and risk factors has taken place independently neglecting the effect of one treatment modality on the other. Subsequently, there is a paucity of data characterising these synergistic effects.

The goal is to change the status quo by including radiation oncology ab initio in the planning of multimodal studies. These opportunities should include comprehensive characterisation of initial tumour immunogenicity and escape as well as patient (host) immunological state. Comprehensive immune profiling should include an analysis of biopsy material of the primary tumour, involved lymph nodes and metastatic lesions as well as immunophenotyping of circulating tumour cells and patients' PBMCs. This analysis must be longitudinal, that is register dynamic changes of immune markers in the course of treatment and by application of different modalities.

Of interest, comprehensive characterisation of tumour immunogenicity, especially its cellular components may have an impact on radiation dose fractionation and timing. In addition, radiation delivery to the target volume may be further optimised based on individual tumour immunogenicity. Considering intrinsic radiation

sensitivity of the tumour cells, infiltrating lymphocytes and macrophages as well as cancer fibroblasts and endothelial cells, new opportunities for dose customisation within irradiated tumours can open new perspectives for improvement of local and "abscopal" systemic anti-tumour response.

In conclusion, future analyses should endeavour to characterise these synergistic mechanisms, which will lead to a better understanding of the underlying immunological phenomena. This will be a challenge, but it is in our hands to change the notion from myth to reality.

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REFERENCES

Antonia, S. J., Villegas, A., Daniel, D., Vicente, D., Murakami, S., Hui, R., … PACIFIC Investigators (2017). Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. *New England Journal of Medicine*, *377*, 1919–1929.

Antonia, S. J., Villegas, A., Daniel, D., Vicente, D., Murakami, S., Hui, R., … Özgüroğlu, M. (2018). Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. *New England Journal of Medicine*, *379*(24), 2342–2350.

Borghaei, H., Paz-Ares, L., Horn, L., Spigel, D. R., Steins, M., Ready, N. E., … Brahmer, J. R. (2015). Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *New England Journal of Medicine*, *373*(17), 1627–1639. https://doi.org/10.1056/NEJMoa1507643

Brahmer, J., Reckamp, K. L., Baas, P., Crinò, L., Eberhardt, W. E. E., Poddubskaya, E., … Spigel, D. R. (2015). Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer. *New England Journal of Medicine*, *373*(2), 123–135. https://doi.org/10.1056/NEJMoa1504627

Gandhi, L., Rodríguez-Abreu, D., Gadgeel, S., Esteban, E., Felip, E., De Angelis, F., … Garassino, M. C. (2018). Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. *New England Journal of Medicine*, *378*(22), 2078–2092. https://doi.org/10.1056/NEJMoa1801005

Goldstraw, P., Chansky, K., Crowley, J., Rami-Porta, R., Asamura, H., Eberhardt, W. E., … Bolejack, V. (2016). 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. *Journal of Thoracic Oncology*, *11*(1), 39–51. https://doi.org/10.1016/j.jtho.2015.09.009

Käsmann, L., Eze, C., Dantes, M., Roengvoraphoj, O., Niyazi, M., Belka, C., & Manapov, F. (2019). State of clinical research of radiotherapy/chemoradiotherapy and immune checkpoint inhibitor therapy combinations in solid tumours-a German radiation oncology survey. *European Journal of Cancer*, *108*, 50–54. https://doi.org/10.1016/j.ejca.2018.11.026

Noone, A. M., Howlader, N., Krapcho, M., Miller, D., Brest, A., Yu, M., … Feuer, E. J. (eds). (2018). *SEER Cancer Statistics Review, 1975–2015*. Bethesda, MD: National Cancer Institute.

Paz-Ares, L., Luft, A., Vicente, D., Tafreshi, A., Gümüş, M., Mazières, J., … Kowalski, D. M. (2018). Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer. *New England Journal of Medicine*, *379*(21), 2040–2051. https://doi.org/10.1056/NEJMoa1810865

Reck, M., Rodríguez–Abreu, D., Robinson, A. G., Hui, R., Csőszi, T., Fülöp, A., … Brahmer, J. R. (2019). Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. *Journal of Clinical Oncology*, *37*(7), 537–546.

Shaverdian, N., Lisberg, A. E., Bornazyan, K., Veruttipong, D., Goldman, J. W., Formenti, S. C., … Lee, P. (2017). 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. *The Lancet Oncology*, *18*, 895–903. https://doi.org/10.1016/S1470-2045(17)30380-7

Siegel, R. L., Miller, K. D., & Jemal, A. (2020). Cancer statistics, 2020. *CA: A Cancer Journal for Clinicians*, *70*(1), 7–30. https://doi.org/10.3322/caac.21590

Socinski, M. A., Jotte, R. M., Cappuzzo, F., Orlandi, F., Stroyakovskiy, D., Nogami, N., … Reck, M. (2018). Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. *New England Journal of Medicine*, *378*(24), 2288–2301. https://doi.org/10.1056/NEJMoa1716948