Immunotherapy in Non-small Cell Lung Cancer: Current and Future Use

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Citation: EMJ Oncol. 2022;10[1]:20-23. DOI/10.33590/emjoncol/10128767. https://doi.org/10.33590/emjoncol/10128767.

ESMO 2022

EXPLORING the current state of use of immunotherapies in the treatment of non-small cell lung cancer (NSCLC) and looking to future immunotherapeutic pathways, three expert speakers presented a session at European Society for Medical Oncology (ESMO) Congress 2022, on the 12th of September. The speakers shared insights on personalising current uses of immunotherapeutics in NSCLC, the use of immunotherapies in patient populations traditionally excluded from clinical trials, and the immune pathways and strategies that could be utilised in future immunotherapeutic management of lung cancer.

PERSONALISING CURRENT IMMUNOTHERAPEUTIC TREATMENT

Personalised medicine is regularly practised in the management of NSCLC; however, this is mostly related to the approximately one-third of patients with specific tumour mutations. For the remaining two-thirds of patients, treatment is "dominated" by immunotherapy, outlined the first speaker, Luis Paz-Ares, Hospital Universitario 12 de Octubre, Madrid, Spain. Paz-Ares discussed data from various studies and analyses to highlight that there are many different genomic biomarkers and aberrations under investigation for use in personalising treatment of NSCLC, but in most cases these biomarkers are not yet ready for clinical use.

Paz-Ares particularly considered programmed death-ligand 1 (PD-L1) expression and the use of programmed cell death protein 1 (PD-1) inhibitor immunotherapies where, for the most part, "benefit is proportionate to the expression in magnitude and in frequency," although they cautioned that this is not "the whole truth," as other factors such as gender and tumour mutational burden (TMB) may have an impact. In immunotherapy monotherapy approaches, PD-1 inhibitors improve survival and progression-free survival where PD-L1 expression is >50%;[1] this is now part of standard practice in these patients. However, this treatment choice is less reliable in patients with <50% PD-L1 expression, as Paz-Ares stated that disease progression is observed in 30–40% of these patients within the first 3 months. To further clarify which patients may benefit from immunotherapy monotherapy, Paz-Ares suggested that TMB may be a valuable marker, as data suggest that tumours with low TMB and high PD-L1 expression may have the best response to immunotherapeutics. In those patients with <50% PD-L1 expression, Paz-Ares noted that the

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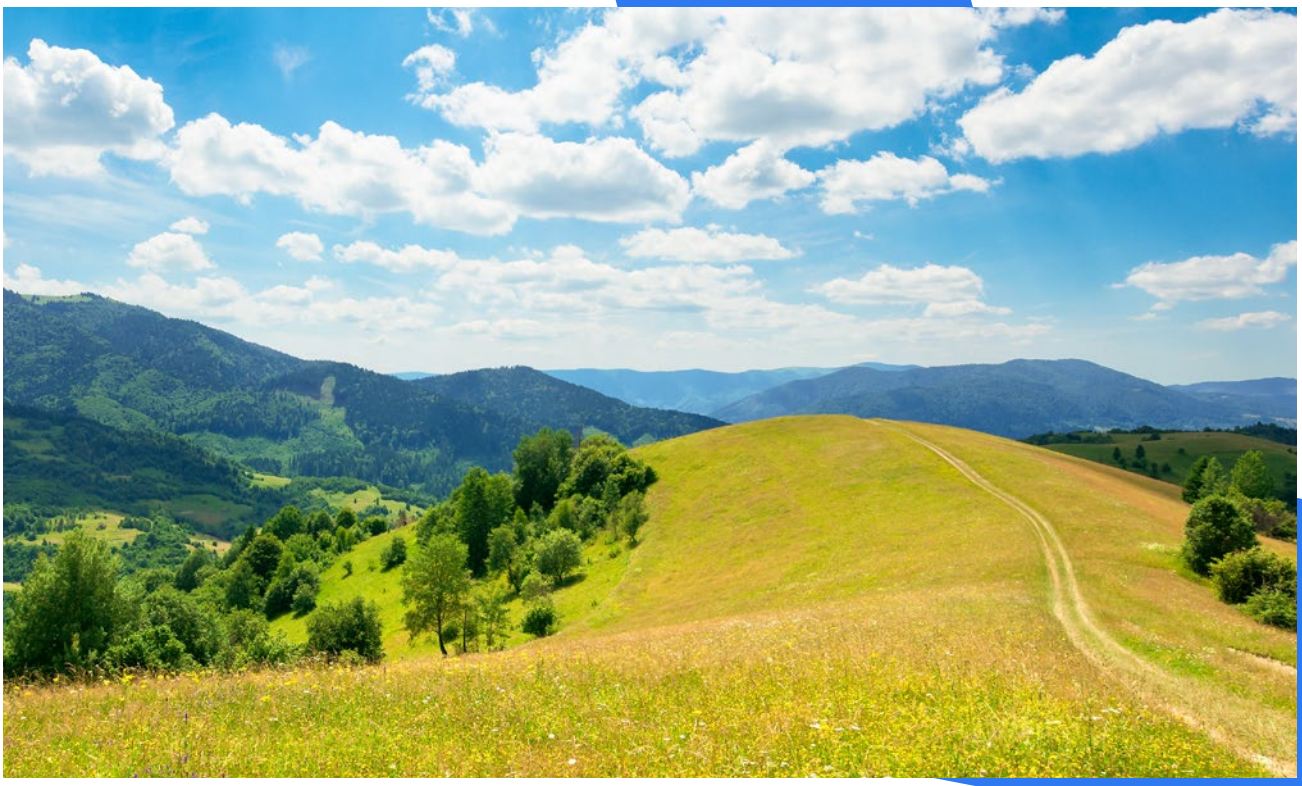

data support combination therapy with chemotherapy and immunotherapy.[2] This may be attributable to the impact of chemotherapy "preventing early progression in some patients that would have happened with immunotherapy alone," Paz-Ares explained, although survival benefit still map to PD-L1 expression, and cautioned that patient expectations should be set clearly as for those patients with low PD-L1 expression, 3-year survival with chemotherapy plus immunotherapy is <5%.[3]

To further hone a personalised medicine approach in NSCLC, Paz-Ares suggested that some tumour factors could be incorporated into current management guidelines, particularly PD-L1 expression, and potentially tumour aggressiveness, tumour burden, and TMB. As always, treatment choice should be individualised to consider patient characteristics such as smoking status, gender, and comorbidities, as well as patient preferences and expectations around both side effects and survival. More data are needed that compare one treatment strategy to another, rather than across-trial comparisons, to make the most data-informed treatment guidelines.

IMMUNOTHERAPY IN SPECIAL PATIENT POPULATIONS

Martin Reck, LungenClinic, Airway Research Centre North, German Centre for Lung Research, Grosshansdorf, Germany, continued the discussion by considering the evidence available for the use of immunotherapies in patients from populations normally excluded from clinical trials, including those with chronic infections, autoimmune comorbidities, older age, or reduced performance status. "Immunotherapy has completely changed our opportunities to treat patients with advanced NSCLC," Reck highlighted, noting that immunotherapy in NSCLC has progressed from use in patients pre-treated with chemotherapy to integration into first-line treatment regimens. "We see, for the first time, 5-year survival rates exceeding 25% in patients that we do treat with checkpoint inhibitors."[4] However, a major issue with the real-world value of these findings is that promising data on new and developing use of immunotherapy are often via clinical trials, while <5% of adult patients with cancer are recruited into clinical trials.[5] To further compound the issue, exclusion criteria for clinical trials often reflect

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many characteristics of patients with lung cancer, such as age >65 years, chronic infections, autoimmune diseases, use of high-dose steroids, and poor performance status. There are data available for several of these exclusion characteristics that suggest the safe and successful use of immunotherapies in NSCLC treatment, but further dedicated studies are needed to inform formal treatment guidelines.

Reck discussed the frequently excluded population of those with chronic infections, particularly highlighting HIV chronic infection in concurrent NSCLC. They noted that HIV infection is associated with chronic inflammation, which increases risk of cancer. Reck outlined study data that show comparable safety and efficacy of immunotherapy in patients with HIV infection compared to those without, specifically noting that immunotherapy treatment did not show a detrimental impact on viral load or cluster of differentiation (CD)4/CD8 counts.[6] For patients with COVID-19 infection and cancer, Reck shared a French study that showed "no deleterious effect of chemotherapy or cytotoxic treatment on outcome of patients who are affected with COVID-19 and cancer."[7] In a meta-analysis comparing the effect of different cancer treatments on both incidence of COVID-19 infection and mortality of COVID-19 infection, immunotherapy was associated with no increased incidence or mortality of COVID-19 compared with other cancer therapies.[8] Chronic infection, therefore, does not seem to be the significant barrier to immunotherapy treatment that clinical trial exclusion criteria suggest.

Currently, 50% of patients with metastatic NSCLC are diagnosed aged >70 years;[9] however, clinical trials frequently exclude patients >65 years. Reck commented on the "theoretical problem" of immunosenescence in older patients, highlighting that patients receiving immunotherapy as second-line treatment have been found to have a similar survival benefit compared to younger populations, without a noted increase in immune-related adverse events,[9] suggesting that immunosenescence does not have a significant impact on treatment effect.

Reck concluded by stating: "We are in the process of removing some of the traditional contraindications [to immunotherapy treatment]," and treatment of lung cancers in these patients should be determined with collaboration of multidisciplinary teams. Reck advocated that comorbidities, age, or reduced performance status should not be hurdles to immunotherapy, but that treatments should be determined within patients' contexts. Further dedicated studies are needed to improve our understanding of treatment performance across different patient populations.

FUTURE AVENUES FOR TREATMENT

While immunotherapies have been a game-changing treatment option in oncology, including in treatment of NSCLC, there are several pathways and mechanisms by which tumours can develop or demonstrate resistance to immunotherapies. Natasha Leighl, Princess Margaret Hospital, Toronto, Canada, outlined several of these resistance mechanisms, and explored the strategies by which immunotherapies could evade tumour resistance. Resistance mechanisms include tumours with 'immune desert' phenotypes, where no T cells can infiltrate; tumour differences in organ

location, which affects metabolomics and T cell infiltration; neoantigen loss, such that T cells do not recognise the tumour cells; defects of antigen presentation; abnormal inflammatory signalling; upregulation of co-inhibitory checkpoints (e.g., cytotoxic T-lymphocyte-associated protein 4); and immunosuppression in the tumour immune microenvironment.[10]

Combinations of therapies, as well as novel therapies, could overcome several of these resistance mechanisms. Leighl described pathophysiological pathways by which various treatment approaches could address resistance, as well as highlighted several ongoing trials investigating these treatment options. Using driving metaphors to illustrate these pathways, Leighl first outlined immunotherapy options that aim to "release the brakes," including treatments targeting inhibitory receptors such as PD-1 and cytotoxic T-lymphocyte-associated protein 4. This strategy could be considered in combination with therapies aiming to "step on the accelerator;" i.e., therapies that act to support receptor activation, including CD137, CD40, IL-2, IL-12, or IL-15. Leighl continued by highlighting treatment approaches that help to "steer the car," in which they noted treatment paths that help modulate the "against-self" adverse effects of immunotherapies, including vaccines, *in situ* vaccination, and adoptive T cell therapy. Finally, Leighl discussed treatment considerations that may "pave the road or smooth the way" by remodelling the tumour microenvironment and relieving immunosuppression, such as therapies targeting regulatory T cells, TNF, tumour-associated macrophages, and vascular endothelial growth factor, among others.

CONCLUSION

Immunotherapy in NSCLC has improved survival for many patients and become a cornerstone of usual management. However, the breadth of patients for whom immunotherapy may be a valuable option can be further understood through more dedicated studies that compare treatment approaches head-to-head, and that specifically include and consider patient populations that reflect the common comorbidities and characteristics of patients with NSCLC. There are also many exciting avenues for other immuno-oncological approaches to treatment under consideration or active study, that are awaited with great anticipation in the road ahead in the management of NSCLC.

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