Balancing act: improving safety while retaining efficacy in I-O

Lauren Coyle, Editor, Immuno-Oncology Insights, speaks with Paolo Ascierto, Director of the Unit of Melanoma, Cancer Immunotherapy and Innovative Therapy, National Tumor Institute ‘Fondazione G. Pascale’, to discuss development of I-O treatments and emerging strategies, specifically in melanomas, improving the balance safety profiles and treatment-related toxicities.

What progress has been made in balancing efficacy and safety in the I-O field?

PA: The immune checkpoint inhibitor marked the beginning of modern immunotherapy. Ipilimumab was the first approved immune checkpoint inhibitor in the field of melanoma, and produced impressive results. Previously, most metastatic melanoma patients did not survive; with ipilimumab, 20% of patients achieved a cure. However, the price to pay for this success was toxicity, in the form of immune-related adverse events (irAE). The powerful immune response following treatment with ipilimumab led to strong activity against the tumor but also triggered a potentially harmful autoimmune reaction. The percentage of severe irAEs from ipilimumab was relatively high, and mainly seen with high dosages.
Next, we saw the emergence of anti-PD-1 therapies, which brought significantly greater efficacy and fewer side effects. In melanoma, the overall survival (OS) rate increased from 20–40% and the incidence of grade III and IV adverse events dropped from 30% to 12–15% compared with ipilimumab. This represented a crucial advancement.

The introduction of combination therapies provided even more potency. Now, we see a remarkable 50% response rate in melanoma treatment; however, it results in more side effects and increased toxicity due to the inclusion of ipilimumab. This evolution primarily affected the field of melanoma and, in contrast with other cancers, a similar toxicity profile with anti-PD-1 monotherapy was found. However, when combined with chemotherapy, the side effects increased. Further, the combination of anti-CTLA-4 and anti-PD-1 therapies also led to a higher incidence of irAEs.

**Q** Are there any emerging strategies that could help moderate the risk of toxicities for I-O treatment?

**PA:** There is a common saying in the medical community, “No side effect, no efficacy.” If you don’t have side effects, it means that the drug is not efficacious. An example of this was epacadostat, an IDO1 inhibitor that, in phase I/II, showed no side effects, even when used in combination with pembrolizumab, but also had no efficacy. Naturally, we aim for treatment strategies with greater potency and fewer side effects.

An example was recently approved by the US FDA and EMA: the combination of nivolumab and relatlimab. Relatlimab is an anti-LAG-3 checkpoint, which follows CTLA-4 and PD-1 checkpoints. This combination provides increased efficacy compared to single-agent treatments, but it comes with a slight (10%) increase in side effects, especially in the field of melanoma. At this point, we cannot definitively say that this new combination matches the efficacy of ipilimumab and nivolumab, but it does promise fewer side effects. This is a promising development and likely the direction of travel in the future.

Combinational approaches will involve new targets that can enhance efficacy, although there may still be some additional toxicity. It is an idealistic notion to expect a combination strategy that significantly enhances efficacy without any side effects. The introduction of new targets, like LAG-3, exemplifies this trend of achieving increased efficacy with only slightly more toxicity.

Recently, we have been focusing more on biomarkers to predict why some patients respond better to I-O treatments, with limited attention to predicting side effects. Now, there are some interesting studies looking into genetic modification and genetic predisposition of patients toward adverse effects. Given the high rate of toxicity, this is an area where we must strive for improvement. While we are seeing some promising data in this field, there is still much more we could and should do.

**Q** Can you shed light on ongoing research focusing on improving safety profiles in melanoma?

**PA:** After obtaining important data in the field of metastatic disease, we shifted our focus to the adjuvant setting to prevent metastasis with the adjuvant treatment.
Anti-PD-1 therapy and BRAF/MEK inhibitors have now become a standard of care. However, even in this context, 50% of patients benefit from these treatments while the other 50% do not, highlighting the need for further research and new therapies.

We have recently seen some impressive data from a randomized phase II with an mRNA vaccination constructed of 38 new epitopes. Further, when this mRNA vaccine was combined with pembrolizumab, there was an absolute benefit at 2 years compared to pembrolizumab monotherapy, with a risk reduction of 44% for relapse. Additionally, at ASCO 2023, we saw significant data with this combination regarding distant metastasis-free survival, which is a surrogate for OS. Notably, the increase in toxicity was minimal, primarily limited to local injection reactions and fever.

This combination therapy aligns perfectly with what we’ve been discussing—more efficacy with only a slight increase in irAE. There is an ongoing randomized phase III trial with this vaccine which is showing great promise and could open a new avenue of research and not only for melanoma. This personalized vaccine works on the neoepitope in the tumor, which can be applied to other cancers. In my opinion, these developments represent the most significant news in the field right now.

A noteworthy topic here is adoptive cell therapy, which is an area of increasing interest in the I-O field. However, it still carries a degree of toxicity due to the use of IL-2, which can be particularly taxing in the short-term. I believe that we need to focus more on the long-term side effect as there is currently few data.

**Q** When patients show no response to I-O treatment but develop treatment-related toxicity, how this should be addressed?

**PA:** Generally, what we observe is that when there is toxicity, there is usually a response—but this isn’t true for all patients. Sometimes we see activation of the immune system but it falls short of effectively curing the tumor. It is important to note that when patients are treated with immunotherapy, they actually welcome some degree of toxicity. Naturally, they prefer mild toxicity, but they understand that it comes hand-in-hand with the activation of the immune system.

In cases of significant disease with no efficacy despite immune system activation, the patients naturally question the effectiveness of the treatment. It’s a challenging subject to explain because it seems that it should be straightforward. When situations like this arise, it’s a clear sign that the treatment is not delivering the expected results.

**Q** What challenges do you expect in ensuring long-term safety of these treatments, especially in combination, and how can these be tackled?

**PA:** The challenge, of course, is to find a treatment that can increase the number of patients experiencing long-term benefits. The Society of Immunotherapy of Cancer (SITC) is doing important work in the field of safety in the survival to immune checkpoint
inhibitors, particularly in patients with long-term benefit. We urgently need more data, especially from all the pivotal trials, particularly those that were started 7 or 8 years ago.

By gaining access to the long-term safety data with long survival in these patients who have an activated immune system, we can then further determine if there are late irAEs. Organizations like SITC and regulatory bodies should pull together all this data in order to gain a larger dataset that will consider the increase in the number of patients with the long-term survival.

BIOGRAPHY

**PAOLO ANTONIO ASCIERTO** is the Director of the Department of Skin Tumors, Experimental Oncological Immunotherapy and Innovative Therapies, as well as Director of the Unit of Experimental Oncology Melanoma, Immunotherapy and Innovative Therapies of the National Cancer Institute IRCCS ‘Fondazione G. Pascale’ of Naples. Ranking first in the Expertscape ranking of the University of North Carolina as the leading melanoma expert in the world for the decade 2013–2023, he is a pioneering oncologist of immuno-oncology, as well as author of over 650 publications in the field. Ascierto is a member of the working group responsible for drawing up the ASCO (American Society of Clinical Oncology) guidelines, coordinator of ESMO (European Society of Clinical Oncology) and the AIOM (Italian Association of Medical Oncology) on melanoma. Considered one of the best Italian researchers, Ascierto has made his clinical and research activity a true vocation, basing all his work on the prevention and treatment of cancer, in particular, the management of patients with melanoma and on the use of immunotherapy. To date, he is the promotor of numerous training and awareness events and initiatives, aimed at specialists and the general public.

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