When the first signals of modern immunotherapy began to emerge a little over a decade ago, many of us realised that oncology was about to change forever. I still remember the sense of astonishment when we saw the first durable responses with ipilimumab, the anti–CTLA-4 antibody that opened the door to a new therapeutic era. For the first time, we were not just treating cancer, we were engaging the immune system as an ally. And the goal was not merely to destroy cancer cells, but to turn an otherwise devastating disease into something that could be controlled, contained, and at times even made chronic.

But it was with the arrival of PD-1 inhibitors, such as nivolumab and pembrolizumab, that the field truly shifted. Suddenly, patients with advanced melanoma, people who previously had few options, were achieving long-lasting remissions. The survival curves flattened, something we had almost never seen in solid tumors. Those results quickly expanded beyond melanoma into lung cancer, renal cancer, head and neck cancers, and more.

For clinicians, it was a profound moment. For patients, transformational. And for immunotherapy, just the beginning.

Yet more than ten years later, we find ourselves at a crossroads. The PD-1 era has been revolutionary, but it has also reached a plateau. Not all patients respond. Many relapses. And in Europe, access remains uneven, where you live still too often determines the therapy you receive and the outcome you can hope for.

So, the question naturally arises: what comes after PD-1?

And equally important: how do we prepare for it?

The New Map of Immunotherapy

Innovation in immuno-oncology is vibrant, but it is moving away from the simplistic idea that adding more checkpoint inhibitors will solve resistance. The next phase will be defined by new immune targets, smarter cytokines, personalised vaccines, cellular therapies adapted to solid tumours, and, increasingly, T-cell engagers, which I believe may become one of the most important classes of the coming decade.

We should also remember the potential of oncolytic viruses, now being redesigned with enhanced tropism and immunogenicity.

The future will not rely on a single breakthrough, but on a toolbox of complementary strategies capable of reshaping the immune response in different clinical scenarios.

1. New Immune Targets: Beyond LAG-3, TIGIT, TIM-3

The emergence of additional checkpoints like LAG-3, TIGIT and TIM-3 sparked enthusiasm. If blocking CTLA-4 and PD-1 worked so well, perhaps blocking more checkpoints could push the field further.

Reality has been more modest. While the relatlimab–nivolumab combination showed benefit in melanoma, the activity is far from the dramatic impact seen with CTLA-4 plus PD-1 a decade ago. In other tumours, TIGIT and TIM-3 inhibitors have produced limited results.

These molecules tend to appear late in the exhaustion pathway; they fine-tune, rather than ignite, immune responses. In patients whose immune system has not been properly primed, they simply

have nothing to modulate.

However, the recent Relativity-048 triplet (anti-CTLA-4, anti-PD-1, anti-LAG-3) showed promising early activity, reminding us that some combinations may still find their place.

2. The Return of “Smart” Cytokines

Cytokines evoke memories of the early, difficult days of IL-2 therapy, but today’s versions are profoundly different, precision-engineered to empower immune cells while minimising toxicity.

Promising approaches include: IL-2 variants (e.g., MDNA11) that selectively expand effector T cells and NK cells without activating Tregs. IL-15 and IL-21 analogues, enhancing cytotoxicity and persistence.

Next-generation IL-18 engineered to escape its natural decoy receptor.

These “smart cytokines” may become powerful partners for PD-1 inhibitors, particularly in low-inflammation “cold” tumours.

3. Personalised mRNA Vaccines: The Neoantigen Wave

Among emerging strategies, personalised mRNA vaccines may be the most transformative. In melanoma, the V940 combined with pembrolizumab reduced the risk of recurrence or death by **44%** compared with pembrolizumab alone. But beyond the numbers, the mechanism is striking: mRNA vaccines rebuild immune priming, expand new T-cell clones, and dramatically diversify the adaptive response.

If PD-1 inhibitors remove the brakes, vaccines provide the fuel. This synergy could extend well beyond melanoma into lung and gastrointestinal cancers, marking the beginning of an entirely new chapter.

4. Cell Therapy for Solid Tumours: From Promise to Practice

Cell therapy is no longer the exclusive realm of haematology. TIL therapy (lifileucel) has demonstrated activity in heavily pretreated melanoma patients, even in those resistant to all approved immunotherapies.

New generations of cellular therapies are under development. Europe, however, faces infrastructure and cost challenges: specialised centres, complex logistics, and significant investments are required.

Still, cell therapy is coming to solid tumours, and we must be ready to integrate it.

5. The Rise of T-Cell Engagers: A New Frontier

If I look at the future of immunotherapy, T-cell engagers (TCEs) emerge as one of the most compelling and disruptive classes ahead.

Unlike checkpoint inhibitors, which modulate existing immune responses, TCEs physically bridge T cells to tumour cells, forcing an immune synapse where none existed. The next generations, with improved half-life, reduced cytokine-release risk, and tumour-specific targets, may profoundly reshape treatment across multiple tumour types.

In a way, T-cell engagers bring together the strengths of immunotherapy and targeted therapy:

specificity, potency, and the ability to bypass the need for pre-existing immune priming.

They may become central tools in overcoming resistance to PD-1 inhibitors, especially in tumours with low T-cell infiltration, where traditional immunotherapy has struggled.

I believe T-cell engagers are emerging as one of the most promising modalities of the next immunotherapy era.

The Crucial Point: Immune Priming

Perhaps the most important lesson of recent years is that the future of immunotherapy does not lie in “more checkpoint inhibitors” but in rebuilding immune priming.

This is especially evident in the adjuvant setting. Minimal residual disease is immunologically different: fewer neoantigens, weaker inflammatory signals, and limited spontaneous activation.

That’s why many dual-checkpoint strategies effective in metastatic disease fail in earlier stages.

In early melanoma and other solid tumours, PD-1 inhibitors do not work by releasing exhausted T cells; they work by educating the immune system before exhaustion even occurs.

This “immune education” framework may define the next decade: mRNA vaccines to teach the immune system, what to target, engineered cytokines to amplify early activation, T-cell engagers to force direct tumour targeting, cellular therapies to broaden the repertoire, and PD-1 inhibitors to maintain long-term memory.

It is not a competition; it is a sequence.

European Challenges: Access, Regulation and Sustainability

Europe has produced many pioneers of immunotherapy, yet access to innovation remains profoundly uneven. Regulatory timelines lag behind the US, and disparities persist between northern and southern regions, urban and rural areas. For example, Germany and the Netherlands routinely adopt new immunotherapies within months of EMA approval, whereas delays of **12–24 months** remain common in some lower-income countries such as Cyprus, Latvia and Lithuania. These differences directly affect survival outcomes.

Next-generation therapies, especially personalised vaccines and cellular treatments, will intensify these gaps unless we act proactively.

Europe now faces three urgent challenges:

- Infrastructure
- Biobanks, sequencing hubs, and manufacturing sites are all essential and currently insufficient.
- Sustainable reimbursement models.

These therapies will come at a high cost and may not be sustainable if left to individual health systems.

Governments, industry, and academia must cooperate to ensure access for as many patients as possible.

Stronger Cross-Border Collaboration

Through EORTC, European cooperative groups, and ERNs.

Innovation cannot stop at national borders. Without coordinated investment, the next wave of immunotherapy risks becoming a privilege rather than a standard.

Preparing for the Next Wave: Five Messages for the Oncology Community

Personalisation is the future.

Neoantigen-based vaccines and biomarker-driven combinations will require sophisticated diagnostics and integrated molecular platforms.

Clinical Trials Must Evolve.

Adaptive designs, rational combinations, and strong translational endpoints will be essential.

Biological Infrastructure is Essential.

Advanced immunomonitoring and curated biobanks must become standard components of cancer centres.

Reimbursement Must Keep Pace with Innovation.

New economic frameworks are required to support personalised therapies.

Avoid Repeating Past Mistakes.

Combinations without a biological rationale rarely succeed.

In a priming-focused era, combinations must be designed with intention.

Conclusion: Beyond the Checkpoint

We are standing at the beginning of the second phase of immunotherapy.

The next breakthroughs will not emerge from multiplying checkpoints, but from integrating intelligent strategies that activate, shape, and sustain anti-tumour immunity.

The future belongs to therapies that educate the immune system, not merely release it.

Melanoma will continue to serve as the natural testbed for innovation, but the implications will reach far beyond it. “Beyond the checkpoint” is not just a theme.

It is the work ahead of us.

And that work must start **NOW.**

About the Author

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He is the Director of the Melanoma Cancer Immunotherapy and Development Therapeutics Unit at Istituto Nazionale Tumori IRCCS Fondazione G. Pascale.nd equally important: how do we prepare for it?