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EDITORIAL

Immune check points in cancer treatment: current challenges and perspectives

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After initial successes as single agents in paradigmatic settings such as melanoma or lung cancer, immune checkpoint inhibitors (CPIs) have rapidly reached a glass ceiling. This has led researchers and oncologists to turn to combinations as a means to further improve response rates and prolong survival in cancer patients, and to attempt to extend the use of immunotherapy to once-refractory tumours. These combinations are, of course, based on standard medical treatments such as chemotherapy, targeted therapy and other immunotherapies. The main aim of this special issue of the *British Journal of Cancer* is to describe and critically comment on the most important combinations between CPIs and canonical therapies.

Despite the therapeutic success of combinations of chemotherapy and CPIs, more mechanistically based studies are needed to provide a rational basis to better support such combinations and achieve sustained efficacy. In particular, the possible combinations to be tested should be further explored at both preclinical and clinical levels, with a focus on scheduling and sequencing issues. Efforts will also be made to identify the molecular/cellular factors associated with response or resistance to combination therapy. On the other hand, the combination of CPIs and anti-angiogenic agents has recently achieved undeniable success in liver and kidney cancer, benefiting from a strong preclinical background that supports the rationale of the combination, as highlighted in the paper by Brest et al. [1]. As underlined by most experts in the field, the preclinical data essentially point to the effects of anti-angiogenic agents on the activity of CPIs, i.e. impact on vascular structure and diffusion of cytotoxic T cells in the tumour bed. However, the reverse sequence is largely neglected and more data are needed to provide convincing evidence of the potential benefit of this combination. In addition, unravelling the dynamics of harnessing tumour immunity with cytotoxic drugs is a critical step in better understanding the correct sequencing of a combination. To date, most associations are based on concurrent dosing, whereas the study by Sicard et al. [2] suggests that timing is important and that sequencing treatments could help to optimise combinations.

In addition, the concept of dynamic biomarkers of overall survival, as presented by Bruno et al. [3], may be a valuable approach to develop new combination treatments with immunotherapy.

In order to ensure the widest possible access to CPIs, especially as part of combination therapy, cost-effectiveness must be taken into account, as illustrated by the paper from the Ratain group [4]. Recent reports on ultra-low dose immunotherapy with CPIs in combination with cytotoxic and targeted therapies have shown that this strategy can be cost-saving without adverse effects on patients [5], suggesting that de-escalation of CPI doses may be realistic.

New technologies may offer real opportunities to optimise the design of initial combinations with CPIs. For example, approaches have been developed to identify predictive markers, such as the quantitative multiplex technologies for single cell analysis. On the other hand, gene signatures may be complementary tools in the expanding field of predictive medicine with immune checkpoint inhibitors. The article by Yang et al. [6] is based on long non-coding RNAs associated with immune genes. Interestingly, the authors show that a nine-gene signature can predict low- and high-risk groups in lung cancer patients treated with immunotherapy. This allows the identification of different immune and non-immune clusters associated with outcome in different tumour types, and the identification of novel targets for combinatorial strategies with CPIs. Finally, the article by Domini et al. [7] highlights the need for a comprehensive understanding of the lymphocyte-independent functions of PD1. Their findings suggest that anti-PD1 therapies may open up new avenues and opportunities for clinical research.

Overall, after an initial phase of progress followed by a slowdown in the pace of clinical breakthroughs, the era of immunotherapy has entered an age in which it must reinvent itself using the latest advances in pharmacology. By integrating multi-tools (i.e. predictive biomarkers, model-based dosing, mechanistically based combinations, to name a few), immunotherapy will be able to further extend its potency and provide maximum benefit to cancer patients.

Joseph Ciccolini[1]✉ and Gerard Milano[2]
[1]*SMARTc COMPO, Inria Inserm U1068 Centre de Recherche en Cancérologie de Marseille, Marseille, France.* [2]*Centre Antoine Lacassagne, Nice, France.* ✉*email: ciccolini.joseph@gmail.com*

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ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Joseph Ciccolini.