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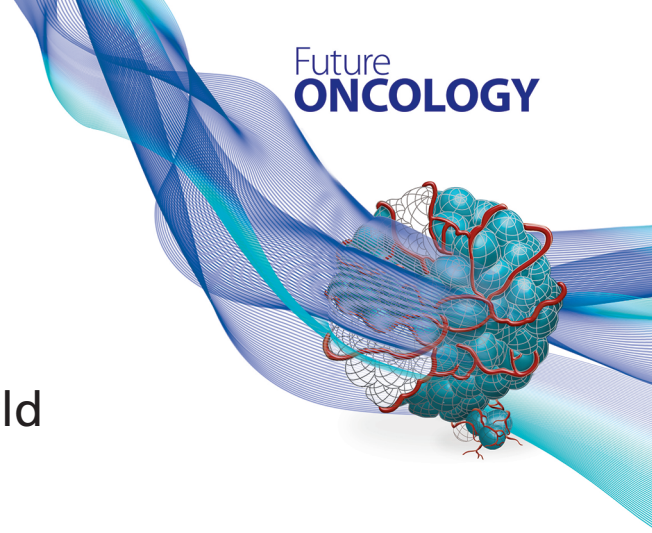
Foreword





# Treatment sequencing in oncology: balancing clinical trial and real-world evidence

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> "Over the last decade, the availability of new active agents that can significantly improve patients' life expectancy has changed the panorama of systemic anticancer treatments."

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Over the last decade, the availability of new active agents that can significantly improve patients' life expectancy has changed the panorama of systemic anticancer treatments. The most impressive improvements have been seen in the case of pathologies for which the efficacy of targeted treatments and immunotherapies has been demonstrated [1,2], and this enrichment of the therapeutic armamentarium has led to the possibility of sequentially using agents whose different mechanisms of action make it possible to prevent cross-resistance. However, this opportunity has also raised some still unanswered questions concerning the optimization of sequences that maximize cancer control and ensure the best cumulative survival.

When the introduction of new agents into everyday clinical practice was slow, it was considered that real-world data were less helpful in suggesting optimal therapeutic strategies than the clearly more robust data coming from randomized trials. However, today's more rapid drug development has led to a new scenario in which the patients attending everyday healthcare facilities may be very different from those enrolled in the pivotal trials used to obtain marketing authorization and, consequently, modern sequencing strategies are now frequently based on real-world data.

The complementary nature of randomized trial and real-world settings is underlined in the interview of Professor Angela Märten published in this Special Focus issue of *Future Oncology*, which explores the question of treatment sequencing in various fields of oncology [3]. In the same interview, Märten talks more about the paper recently published in *Future Oncology* (and updated in another article in this issue of the Journal [4]) that describes her real-world experience of sequentially using afatinib and osimertinib in EGFR-mutated patients with non-small-cell lung cancer (NSCLC). Her observational GioTag study demonstrated that sequencing tyrosine kinase inhibitors can significantly prolong the chemotherapy-free period, and this issue of *Future Oncology* also contains other papers describing further treatments for NSCLC patients [5].

Sukrithan *et al.* discusses sequencing in oncogene-addicted NSCLC patients in whom the availability of active second-generation agents can overcome EGFR mutation- and ALK translocation-related resistances: patients with a T790M mutation who are resistant to old-generation tyrosine kinase inhibitors can benefit from the administration of osimertinib, and patients with an ALK translocation and progressing during first-line crizotinib treatment should receive one of the new-generation ALK inhibitors (ceritinib, alectinib or brigatinib) [6]. The possibility of optimizing outcomes of EGFR positive NSCLC patients by sequencing TKIs is also largely addressed in the paper of Nicolas Girard which provides a large review on the argument [7]. However, there is still the question as to whether it is better to sequence old- and new-generation drugs or directly administer the latter as first-line treatment, and a need to overcome the mechanisms underlying resistance to new-generation drugs. Furthermore, the activity of immunotherapy in oncogene-addicted NSCLC patients remains an open question.

An additional issue in EGFR-mutated patients concerns the detection of a T790M mutation; Hochmair considers the role of liquid biopsy as a potentially easier and noninvasive method of mutation testing than tissue biopsies, thus overcoming the difficulties related to repeat biopsy procedures [8].

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The question of real-world strategies for nononcogene-addicted NSCLC patients with low PD-L1 levels who progress during or after first-line chemotherapy is discussed in the paper by Molife *et al.* [9]. The authors evaluated 4054 patients treated with ramucirumab, immune checkpoint inhibitors or both in everyday clinical practice, and provide an interesting description of survival estimates for such patients.

In the last paper concerning NSCLC published in this special issue, Ryan *et al.* provide a wide-ranging description of the therapeutic approaches usually adopted in the real-world treatment of patients with unresected stage III disease, and the subsequent treatments administered upon disease progression [10]. As the authors underline, the paper was not able to capture the impact of checkpoint inhibitors in the therapeutic sequence because the analysis did not evaluate patients diagnosed after March 2016. Nevertheless, looking at the introduction of durvalumab-based maintenance treatment for these patients with locally advanced NSCLC, this real-world report offers a benchmark for understanding the impact of new drugs on the changing treatment landscape of community oncology.

The other papers in this special issue concern different forms of cancers. Caffo *et al.* addresses the question of the optimal sequence of medical treatments for patients with advanced prostate cancer [11]. The existence of various agents with different mechanism of action makes it possible to choose different sequencing strategies but, unfortunately, real-world experience can only provide data concerning potential cross-resistances and thus suggest not optimal but potentially less effective sequences. Furthermore, the possibility of administering drugs that are active in metastatic castration-resistant patients or offering new-generation hormonal agents to patients with early disease (such as those with nonmetastatic castration-resistant or *de novo* metastatic castration-sensitive disease) increases the difficulty of sequencing medical treatments.

In the case of patients with metastatic melanoma and a *BRAF* mutation, data concerning the efficacy of immune checkpoint inhibitors is raising the question as to whether the best first-line strategy is to use immunotherapy or the well-established approach of dual *BRAF* and MEK inhibition. In the absence of head-to-head prospective comparative trials, real-world data may help in selecting the best strategy. In the paper published in this journal, Luke *et al.* review the clinical records of 440 patients with metastatic *BRAF*-positive melanoma, and their findings suggest that first line targeted agents lead to higher response rate and longer treatment duration [12].

Finally, Gately *et al.* review the state-of-the-art of the neo-adjuvant approach to locally advanced rectal cancer [13]. As the authors underline, there is an unmet clinical need for individualized treatment when choosing the optimal approach, and they discuss the advantages and disadvantages of the currently proposed treatments, and possible future therapeutic strategies and biomarkers.

In conclusion, the medical management of advanced tumors has improved mainly as a result of the introduction of targeted agents and immunotherapies. This has made it possible to achieve unprecedented gains in patient survival expectancy but, at the same time, has raised a number of unsolved questions concerning optimal sequencing strategies. In the absence of prospective head-to-head trials, the only suggestions may come from the real-world experiences that are already playing a central role in defining optimal therapeutic algorithms for various pathological conditions [14]. This approach is likely to become increasingly valuable in a historical period characterized by reduced economic resources.

### Financial & competing interests disclosure

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## References

1. Keung EZ, Wargo JA. The current landscape of immune checkpoint inhibition for solid malignancies. *Surg. Oncol. Clin. N. Am.*28(3), 369–386 (2019).
2. Ke X, Shen L. Molecular targeted therapy of cancer: the progress and future prospect. *Front. Lab. Med.*1(2), 69–75 (2017).
3. Märten A. What could the future hold for treatment sequencing in cancer medicine? An interview with Angela Märten. *Future Oncol.* 15(25), 2891–2893 (2019).
4. Hochmair MJ, Morabito A, Hao D *et al.* Sequential afatinib and osimertinib in patients with EGFR mutation-positive non-small-cell lung cancer: updated analysis of the observational GioTag study. *Future Oncol.*15(25), 2905–2914 (2019).
5. Hochmair MJ, Morabito A, Hao D *et al.* Sequential treatment with afatinib and osimertinib in patients with EGFR mutation-positive non-small-cell lung cancer: an observational study. *Future Oncol.* 14(27), 2861–2874 (2018).

6. Sukrithan V, Snyder R, Cheng H, Halmos B. Sequencing therapies in oncogene-driven non-small cell lung cancer – how to get the best mileage? *Future Oncol.* 15(25), 2899–2904 (2019).
7. Girard N. Optimizing outcomes and treatment sequences in EGFR mutation-positive NSCLC: recent updates. *Future Oncol.* 15(25), 2983–2997 (2019).
8. Hochmair MJ. How can better identification of T790M help to inform treatment sequencing decisions in EGFR mutation-positive NSCLC? *Future Oncol.* 15(25), 2895–2898 (2019).
9. Molife C, Hess LM, Lin Cui Z *et al.* Sequential therapy with ramucirumab and/or checkpoint inhibitors for non-small cell lung cancer in routine practice. *Future Oncol.* 15(25), 2915–2931 (2019).
10. Ryan K, Skinner KE, Fernandes AW *et al.* Real-world treatment patterns among patients with unresected stage III non-small cell lung cancer (NSCLC). *Future Oncol.* 15(25), 2943–2953 (2019).
11. Caffo O, Maines F, Kinspergher S, Veccia A, Messina C. Sequencing strategies in the new treatment landscape of prostate cancer. *Future Oncol.* 15(25), 2967–2982 (2019).
12. Luke JJ, Ghate S, Kish J *et al.* Targeted agents or immuno-oncology therapies as first-line therapy for BRAF-mutated metastatic melanoma: a real-world study. *Future Oncol.* 15(25), 2933–2942 (2019).
13. Gately L, Wong HL, Tie J. Emerging strategies in the initial management of locally advanced rectal cancer. *Future Oncol.* 15(25), 2955–2965 (2019).
14. Khozin S, Blumenthal GM, Pazdur R. Real-world data for clinical evidence generation in oncology. *J. Natl. Cancer Inst.*109, 11 (2017).