HSD47

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Targeted Literature Review – Assessment of the Appropriateness of Readministering (retreatment/rechallenge) Immune Checkpoint Inhibitors in Oncology

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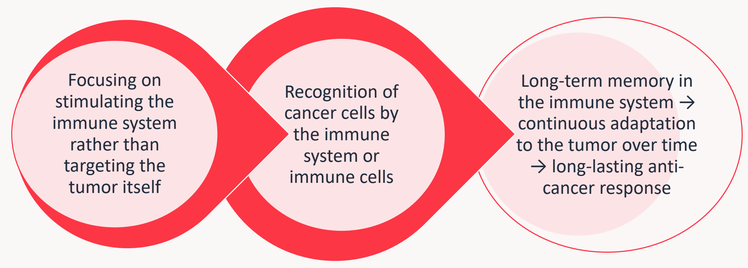
Background

- Immuno-oncology (IO) is an innovative cancer treatment approach that offers greater selectivity than traditional therapies, minimizing damage to healthy tissues and reducing toxicity [1, 2].
- The discovery of immune checkpoint inhibitors—targeting CTLA-4, PD-1, and PD-L1—marked a major breakthrough in cancer therapy [3].
- IO is increasingly being used earlier in the course of disease, not only for metastatic cancers but also in adjuvant (e.g., renal cell carcinoma) and neoadjuvant (e.g., non-small cell lung cancer) settings.
- Patients who have previously received IO may face limited access to other innovative treatments that could extend and improve their quality of life.

The mechanism of immunotherapy



Objectives

The overarching objective of this report was to answer key questions related to the retreatment/rechallenge of immune checkpoint inhibitors (ICIs) in patients with melanoma, non-small cell lung cancer (NSCLC), and renal cancer (RCC):

- MAIN GOAL To evaluate the appropriateness of retreatment (ReT) or rechallenge (ReC) with ICIs in patients previously treated with immunotherapy, by addressing the following critical questions:
  - Clinical Evidence: Is there robust scientific data supporting the efficacy and safety of ICI readministration?
  - Evidence Quality: How strong and reliable is the current body of evidence?
  - Paradigm Shift: Is the existing evidence compelling enough to influence or redefine current treatment strategies?
- DETAILED GOALS To answer additional questions
  - What is the definition of retreatment or rechallenge with ICIs?
  - What do clinical guidelines say about re-immunotherapy?
  - What does scientific evidence say about the clinical value of ICIs after ICIs in melanoma, NSCLC, and RCC?

Methods

- SEARCH STRATEGY
  - Targeted literature review was conducted in the PubMed database;
  - Search date was September 9, 2024;
  - Systematic literature reviews (SLR), targeted literature review (TLR), clinical guidelines and original studies analyzing the clinical effectiveness of ReT/ReC immunotherapy, particularly in patients with melanoma, NSCLC, and RCC were sought for inclusion and analysis
- DATA ANALYSIS COVERED:
  - Analysis of key evaluating the clinical effectiveness of reuse of ICIs in patients with melanoma, NSCLC and RCC
  - Review clinical guidelines to identify recommendations on ReT and ReC

Results

Main ReT/ReC definitions in the literature

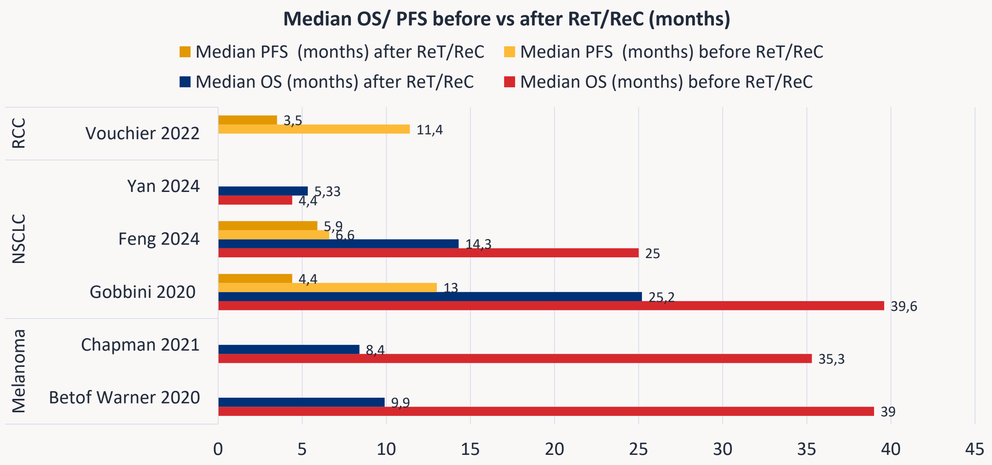
- RETREATMENT (ReT): ICIs → ICIs discontinuation (e.g., due to progression, response, adverse events) → ICIs [4–13];
- RECHALLENGE (ReC): ICIs → ICIs discontinuation → non-ICIs therapy → discontinuation → ICIs [14–17];
- RE-INTRODUCTION: Re-administration of a treatment regimen or a single drug from which the patient previously benefited, and which was discontinued due to toxicity (without disease progression), either as a preventive measure against toxicity or as part of a planned maintenance therapy. [20];

Clinical guidelines recommendations

- CLINICAL GUIDELINES: do not present consistent recommendations regarding the reuse of ICIs but devote increasing space to discussing the use of ICIs after ICIs, indicating groups of patients for whom the reuse of ICIs offers the possibility of clinical benefit. ReT/ReC of ICIs is most widely addressed in the guidelines for melanoma and most cautiously for NSCLC [21-34].

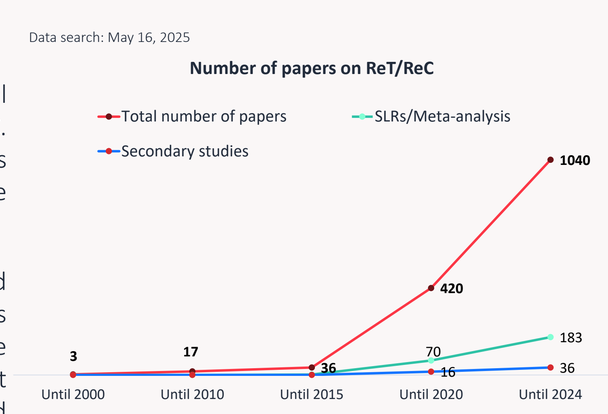
Identified literature

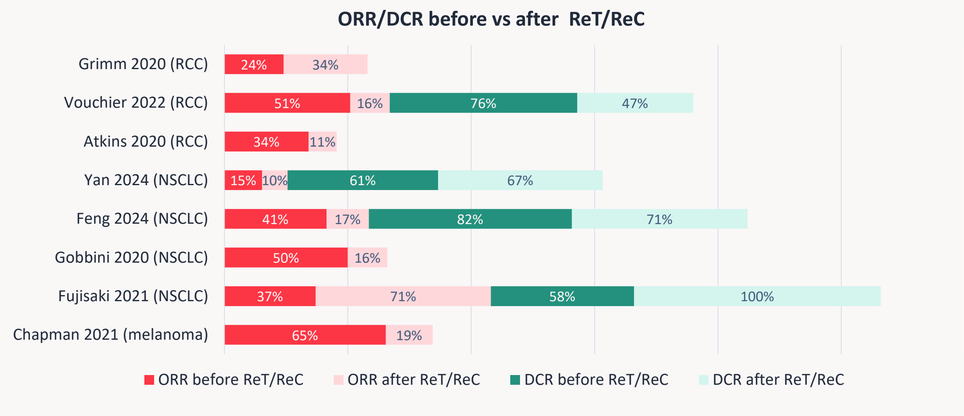
- Search results: 47 studies were identified [35-84]
  - 6 SLR/TLR
  - 10 RCTs
  - 31 other types of studies
- NSCLC: 15 studies, 2372 pts.
- Melanoma: 18 studies, 2317 pts.
- RCC: 8 studies, 1297 pts.



Key takeaways from the targeted review

1. Scientific evidence highlights a growing medical need for reusing ICIs, especially in RCC and NSCLC. An increasing number of studies and publications show that ICI reuse is becoming part of routine clinical practice.
2. Clinical guidelines support ICI reuse in selected patient groups, though they lack formal definitions of ReT/ReC. They suggest retreatment may be most effective within 6 to 12 months after the last immunotherapy, based on receptor saturation and molecule kinetics.
3. There is a need to standardize definitions for the reuse of immunotherapy. The most common definitions are: retreatment (ReT) and rechallenge (ReC). These terms are not unambiguous, but they all refer to situations in which patients previously treated with ICIs reuse ICIs.
4. The rationale for ICI reuse is supported by 41 high-quality studies, including 10 RCTs. As data continues to grow, evidence for this approach is expected to strengthen further.
5. The efficacy of immunotherapy used in the ReT/ReC strategy is usually lower than that observed during previous exposure. In patients with long-term remission (e.g., in NSCLC), retreatment with ICIs may bring clinical benefits.





Conclusions

Growing evidence from clinical and retrospective studies shows that re-treatment with IO is becoming more common and can yield meaningful clinical benefits. Reusing ICIs in treating melanoma, NSCLC, and RCC is supported by theoretical, molecular, and clinical evidence. Decisions should be individualized, considering patient health and the risk of serious adverse events. Further RCTs would be needed to confirm value of ICI ReT/ReC in strictly defined settings.

Abbreviations:
CTLA-4 – cytotoxic T lymphocyte-associated antigen 4; ICIs – immune checkpoint inhibitors; LAG3 – lymphocyte-Activation Gene-3; NSCLC – non-small cell lung cancer; PD-1 – programmed death receptor 1; PD-L1 – programmed-death ligand; RCC – renal cell carcinoma; ReC – rechallenge; ReT – retreatment; TKI – tyrosine Kinase Inhibitor

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