

New ESMO framework to resolve uncertainties about the de-intensification of cancer treatments

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ESMO, a professional organization for medical oncology, has developed a new evidence-based classification to guide research and interpretation of data on treatment de-escalation in oncology. The ESMO framework for the risk-adapted modulation through de-intensification of cancer treatments, published today in *Annals of Oncology*, offers oncologists, research bodies and regulatory decision-makers a set of common definitions and criteria for driving progress in this important field of treatment personalization.

Since the first risk-modulated treatment strategy in oncology was proposed for children with acute lymphoblastic leukemia based on their response to initial therapy, de-escalation approaches using prognostic or predictive biomarkers to risk-stratify [patients](#) have been increasingly explored in other tumor settings and created a heterogeneous research landscape marked by variability in methodology, studied endpoints and non-inferiority thresholds. Having recognized the need to resolve uncertainties about how to translate data from novel trial designs to the approval and implementation of biomarkers for the wider patient population, an expert subgroup within the ESMO Translational Research and Precision Medicine Working Group built on the methodology of the ESMO-MCBS and ESCAT to propose a three-tiered classification of evidence for treatment de-intensification.

Senior author Prof. Fabrice André, Gustave Roussy Cancer Campus, France, explained the rationale behind this approach: "Randomized controlled non-inferiority trials are the gold standard when it comes to testing de-escalated treatments, but they take many years, very large sample sizes and heavy financial investments to run. To drive progress in this field of research, led more often by academic groups than by the pharma industry, we need to be able to design high-quality studies with fewer patients and shorter running times, which may be used to assess de-intensification in very low-risk populations. This framework therefore aims to help investigators better match trial design to the type of

biomarker and clinical situation they want to address, as well as define the conditions necessary for results to be considered valid at different levels of evidence."

Among other things, the group agreed on expedient surrogate endpoints for overall survival that are acceptable within the framework. In addition to survival, safety and quality of life were also deemed to be crucial endpoints for de-escalation studies and have, according to André, too rarely been reported in the past. "We should not assume that achieving equivalent efficacy with less treatment is intrinsically better: quantifying the improvement in terms of quality of life, decreased toxicity or cost-effectiveness is crucial to confirm that the residual risk of incurring a small loss in survival—which is inherent to the confidence intervals used to show non-inferiority—is offset by an important benefit," he explained.

A further recommendation concerns the need to communicate this trade-off effectively to patients, who have expressed reluctance to participate in de-escalation research due to fears of being undertreated. Co-first author Dr. Dario Trapani, European Institute of Oncology, Italy, and Dana Farber Cancer Institute, USA, highlighted the importance of using the right language to help patients understand the risk-benefit ratio of therapy: "Patient advocates report that the term 'de-escalated' is commonly perceived to mean substandard, which is why our framework proposes 'modulated' or 'tailored' as alternative phrasing. We must make it clear to patients, especially when the evidence for de-intensification is strong, that their outcomes are not being compromised for the sake of avoiding side-effects. Rather, the particular biology of their tumor makes it highly unlikely that they will benefit from further treatment, so much so that exposing them to its toxicities would be unreasonable."

While transparency about the degree of uncertainty associated with de-escalated treatment strategies is recognized as integral to shared decision-

making at all levels of evidence, Trapani emphasized that the definition of what constitutes a desirable trade-off can also vary according to patient values and priorities, and called for future efforts to collect input from patients and collaborate with the field of social science to better define the risk acceptance threshold for treatment modulation.

"We ultimately designed the ESMO framework to give a clear structure to the de-intensification research landscape: we hope it will make assessing the risks and benefits of modulated approaches more straightforward for all parties involved—including physicians in [clinical practice](#), clinical trialists, and regulators seeking to prioritize their approval and reimbursement decisions," co-first author Dr. Maria Alice Franzoi, Gustave Roussy Cancer Campus, France, concluded.

More information: D. Trapani et al, Risk-adapted modulation through de-intensification of cancer treatments: an ESMO classification, *Annals of Oncology* (2022). [DOI: 10.1016/j.annonc.2022.03.273](https://doi.org/10.1016/j.annonc.2022.03.273)

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