EDITORIAL

First-Line Lung Cancer Combinations: Are We Treating Better, or Simply Adding Drugs?

Combinações em Primeira Linha no Cancro do Pulmão: Estamos a Tratar Melhor, ou Apenas a Acrescentar Fármacos?

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Over the past two years, first-line systemic therapy for metastatic non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) has followed a recognisable pattern: to an already effective chemotherapy-immunotherapy backbone, a third agent is added. LAG-3 blockade, TROP2-directed antibody-drug conjugates (ADCs), dual PD-1/VEGF bispecifics, DLL3-targeted T-cell engagers — the list of molecules entering first-line development has never been longer, and it spans nearly every major sponsor in thoracic oncology. This editorial does not question whether these molecules are active. It asks whether we are developing and adopting them with the selection rigour their own pharmacology demands.

It is worth separating two phenomena often blurred together. The first is genuine biomarker-driven development: trials restricted to patients carrying a defined molecular alteration, with a drug mechanism that corresponds directly to it. This model continues to deliver reproducible results — the KRAS G12C-directed combinations are a clear example of a field that sequenced its logic correctly: identify the driver, then test the drug against it.

The second phenomenon is different, and should concern a specialty that prides itself on precision. Across several recent first-line programmes, a new agent is layered onto an active regimen, with patient selection based on criteria unrelated to the mechanism of the drug being added. In LAG-3 blockade trials, patients have been stratified by PD-L1 expression, histology, and performance status — not by any biomarker specific to the LAG-3 pathway, because none yet exists. In at least one first-line trial combining a TROP2-directed ADC with a checkpoint inhibitor, enrolment was based on PD-L1 status rather than TROP2 expression, the very target being delivered — and data from other treatment lines with the same drug have shown activity largely independent of that expression level. A dual PD-1/VEGF bispecific was compared with pembrolizumab in a PD-L1-selected population, with benefit reported as consistent across low, intermediate, and high PD-L1 subgroups, without any biomarker yet proposed for its VEGF-blocking component. In extensive-stage SCLC, a DLL3-targeted bispecific is being added to the standard backbone without an enrichment strategy, reflecting DLL3's near-universal expression in this histology rather than a deliberate selection hypothesis.

To be fair to the field, this is not a uniform failure of imagination. At least one TROP2-ADC programme has recently launched what its sponsor describes as its first genuinely biomarker-directed phase III trial, selecting patients by quantitative target expression rather than by PD-L1 or histology alone. That shift matters: it suggests the pressure described here is already being felt within industry, even if it is not yet the default.

The common denominator in the less encouraging examples is clear: we are largely testing whether "one more drug" improves an outcome at the population level, rather than identifying which patients truly need the additional agent. This carries two consequences our specialty discusses too rarely. Clinically, every added agent brings its own toxicity, and the cumulative burden on the patient is not neutral, even when each component is individually "manageable". Financially, each addition represents an incremental cost that health systems will eventually have to absorb or ration, often without an objective criterion to restrict that expense to patients who truly benefit.

This is not an argument against innovation. It is an argument for trial designs that treat biological stratification as central to the research question, not as a post hoc subgroup analysis. As a study group, we can engage critically with the design of ongoing trials and advocate, in the appropriate forums, for biological stratification to become a non-negotiable part of first-line combination development. The alternative is to keep treating "more drugs" as synonymous with "better treatment" — an equation neither our patients nor our health systems can sustain indefinitely.

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