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Summary

Targeting cancer in the era of next-generation agents

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Mechanisms & Personalised Medicine | Digestive Oncology

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The speaker presented evidence that RAS inhibitors in pancreatic cancer face pre-existing and acquired resistance driven by KRAS amplification and tumor microenvironment dynamics, with a narrow therapeutic window for combining immunotherapy before immunosuppression re-establishes.

KEY POINTS

- The speaker reported that an FDA and EMA-approved RAS inhibitor doubled survival in previously treated metastatic pancreatic cancer patients, but resistance develops rapidly in about 50% of patients through RAS pathway reactivation and KRAS amplification.
- Analysis of barcoded tumors and over 1.3 million single cells from mouse models showed pre-existing resistant clones and a 1000-fold difference in RAS inhibitor sensitivity across more than 180 cell lines.
- The speaker stated that higher RAS levels correlate with greater T cell exhaustion and immunosuppression, while RAS inactivation leads to rapid macrophage changes within two days and T cell activation by seven days.
- Tumor cells resume proliferation after seven days of RAS inhibition and type one interferon response diminishes by day seven and disappears by day 14, creating a proposed ten-day therapeutic window before immunosuppression re-establishes.
- The speaker described a histology-based AI tool trained on millions of cells that can predict whether a tumor was treated with RAS inhibitor and may eventually predict resistance before treatment to guide combination therapy selection.
- In Q&A discussion, the speaker suggested that combining RAS inhibitors with degraders, sequential therapies targeting post-treatment vulnerabilities, and overcoming immunosuppression are key strategies, noting that some mice were cured with RAS inhibition plus immunotherapy in a referenced study.

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