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Title

Encyclopedic Tumor Analysis Guided Personalized Treatments in Advanced Refractory Malignancies: A Paradigm Shift in Cancer Management.

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ABSTRACT

Background : Standard of Care (SoC) systemic regimens have limited efficacy in advanced refractory solid organ malignancies. Though patients in such settings of cancer may be referred for treatments with checkpoint inhibitors, their benefit is restricted to populations with PD-L1 expression or mismatch repair deficiency (dMMR). We hypothesized that integrative molecular and cellular investigations (Encyclopedic Tumor Analysis, ETA) can reveal unexplored vulnerabilities in advanced refractory malignancies which can be targeted using conventional agents in a label-free and organ-agnostic combinations to yield treatment benefit. In the RESILIENT trial, patients with advanced refractory malignancies were treated with ETA-guided personalized treatments.

Methods : Fresh tumor tissue was obtained from 200 patients and used for ETA, which included gene alterations and differential gene expression as well as *in vitro* chemoresistance and response (CRR) profiling of viable tumor derived cells (TDCs) against a panel of approved anti-tumor agents. Patient-specific combination regimens included agents selected on the basis of molecular indications and *in vitro* drug efficacy against TDCs. In patients who received ETA-guided treatments, treatment response was evaluated radiologically to determine Objective Response Rate (ORR), Disease Control Rate (DCR) and Progression Free Survival (PFS).

Results : Among the 143 patients who received ETA-recommendations, 126 were evaluable for response *per protocol*. PR was observed in 54 patients (ORR = 42.9%) and 114 patients continued to exhibit PR or SD at study termination (DCR = 90.5%). Median PFS was 134 days. Median PFS rate at 90 day was 93.9%. There were no grade IV therapy related adverse events (AEs), nor any treatment related mortalities. Most patients reported stable to improved Quality of Life (QoL) in terms of disease-related symptoms and functional status.

Conclusion : ETA-guided treatments can offer pan-cancer ORR and PFS benefits in heavily pretreated populations. The clinical benefits reported in RESILIENT outperformed those reported for other systemic treatment options such as checkpoint inhibitors.