

111P mTOR inhibitors in combination regimens guided by encyclopedic tumour analysis show superior outcomes compared to monotherapy in refractory cancers

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Background: Though mTOR inhibition is considered an attractive strategy for cancer management, anti-mTOR monotherapies have not shown meaningful benefits. We hypothesized that an Encyclopedic Tumor Analysis (ETA) can identify vulnerabilities in the tumor in addition to mTOR activation. We further hypothesized that tandem synergistic targeting of these vulnerabilities using combination of mTOR inhibitors and other systemic anticancer agents in a label- and organ-agnostic manner can improve outcomes in refractory solid organ cancers as compared to mTOR inhibition monotherapy alone.

Methods: Molecular Profiling (MP) of patients' fresh tumor tissue interrogated gene alterations and differentially regulated metabolic pathways to identify druggable molecular targets in a label-agnostic manner. Immunohistochemistry (IHC) identified targetable hormone receptors (HR). Chemoresistance and response (CRR) profiling of viable tumor derived cells (TDCs) identified vulnerabilities of the tumor against a panel of systemic anticancer agents. Molecular indications linked to PIK3CA, mTOR, PTEN or TP53 genes were used for selection of mTOR inhibitors. Synergistic integration of MP, IHC and CRR datasets (i.e., ETA) generated patient-specific drug priority lists with projected efficacy and safety. Patients who received such ETA-guided treatments were evaluated by PET-CT scan to determine treatment response.

Results: Among 41 patients who received combination treatments, 23 patients showed PR (ORR = 56.1%), 16 showed SD (DCR = 95.1%) and progression was observed in 2 patients. One patient who received monotherapy progressed at 27 days. Median PFS was 110 days (range 27 to 592). In the SHIVA trial where patients with mTOR activation (n = 46) received monotherapy with mTOR inhibitor, median PFS of 72 days (range 57 to 100) was reported. No significant therapy-related adverse events were reported in any patient. Most patients reported stable to improved Quality of Life (QoL).

Conclusions: ETA-guided combination regimens with mTOR inhibitors offer a viable and efficient strategy in advanced refractory malignancies and outperform mTOR inhibitor monotherapy.

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