

Method: HCC surgical and biopsy tissues were processed and cultured to generate PDOs. Established PDOs were characterized with hepatocytic and biliocytic markers. Those positive to hepatocytic markers were considered true HCC-PDOs and used for a massive drug screening with 270 compounds. Drug efficacy was established by cell viability assay, and Z-scores were used for ranking. Top ten drugs were further analyzed with various doses. We also tested the same HCC-PDOs with standard 1st and 2nd lines systemic therapy agents for aHCC.

Results: True HCC-PDOs were generated in 4/52 HCC samples (8%). Biopsies yielded a higher success rate 2/9 (22%) than surgical samples 2/43 (5%). In 7/52 (13%) cases, the organoids expressed biliocytic markers. The massive drug screening showed, in all HCC-PDOs, consistent results for nine compounds. Among them, dinaciclib, homoharringtonine, volasertib, mocetinostat, and daunorubicin, have been already reported as effective on HCC. Three compounds, osimertinib, D1, and D2, are already used for EGFR-mutant lung cancers. Finally, one compound, D3, inhibits replication. Among standard treatments, only sorafenib inhibited HCC-PDOs.

Conclusion: The identification of dinaciclib and homoharringtonine as potent agents aligns with recent literature on novel HCC drugs, and validates the robustness of our approach and the potential of our results. Moreover, our results disclosed a significant potential for some drug repurposing. A recent study showed that ceritinib, a drug targeting ALK mutation in advanced non-small cell lung cancer, inhibits β -catenin mutated HCC via non-canonical WNT pathway independent of ALK (J Hep Reports, 2025). Our data disclosed two compounds, D1 and D2, effective in EGFR-mutant lung cancers, which promise to be effective, off label, also on HCC. In keeping with this, osimertinib, another drug highlighted by the screening on HCC-PDO and currently used for EGFR-mutant lung cancer, has been reported as effective also in HCC (J. Cancer Res. Clin. Oncol., 2023; Plos One, 2023).

WED-235

Involvement of the hERG1 potassium channel in cholangiocarcinoma cell biology

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Background and aims: hERG1 is a voltage-gated potassium channel normally found in excitable cells, but it is often overexpressed in tumors, where it interacts with β 1 integrin and activates cancer-related pathways. Intrahepatic cholangiocarcinoma (iCCA) is an aggressive liver malignancy with limited treatment options. This study aimed to investigate the role of hERG1 and its downstream signaling in iCCA biology.

Method: hERG1 expression was assessed in three iCCA cell lines, and functional studies were performed using siRNA-mediated silencing (siHERG1) and pharmacological inhibition (E4031). Cellular behavior was evaluated through standard assays, and molecular and structural changes were analyzed using qRT-PCR, Western blotting, electron microscopy, and transcriptomics.

Results: hERG1 silencing led to a 75–80% reduction in mRNA and protein expression but did not impact proliferation or viability. In contrast, both genetic silencing and pharmacological inhibition significantly reduced cell motility and impaired angiogenesis, as shown by reduced tube formation in HUVECs exposed to si hERG CCA conditioned media. Gene expression analyses revealed downregulation of epithelial mesenchymal transition (EMT) and angiogenesis

markers. Key oncogenic pathways, including FAK, PI3K, and AKT, were notably suppressed. Ultrastructural analysis showed endoplasmic reticulum swelling and increased vesicular trafficking, indicating cellular stress and altered membrane turnover. Transcriptomic analysis revealed a common profile of gene alteration, mainly in vesicular trafficking, transmembrane ion regulation, and extracellular matrix reorganization, highlighting a broader impact of hERG1 on intracellular dynamics.

Conclusion: hERG1 plays a critical role in supporting motility and angiogenic potential in iCCA cells without affecting proliferation. Its inhibition alters key oncogenic and cellular processes, positioning hERG1 as a promising therapeutic target in iCCA.

WED-236

Baseline tumor and circulating gamma/delta T-Cell signatures and early on-treatment CD8⁺PD-1⁺ T-Cell expansion predict response to Atezolizumab–Bevacizumab in hepatocellular carcinoma

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Background and aims: Atezolizumab–bevacizumab (AtezoBev) is the standard first-line therapy for unresectable hepatocellular carcinoma (HCC), but predictive biomarkers of response are lacking. We aimed to identify baseline and early immune features associated with treatment outcomes.

Method: We conducted a prospective study of patients receiving first-line AtezoBev, integrating longitudinal immune profiling at baseline and 3 weeks after treatment initiation, including peripheral blood mononuclear cell (PBMC) immunophenotyping (17 markers), serum cytokine profiling (31 proteins), and paired whole-blood RNA sequencing. Tumor RNA-sequencing data from the GO30140 and IMbrave150 trials were analyzed (209 patients treated with AtezoBev and 58 with sorafenib), with external validation in an independent cohort of metastatic MSI-H colorectal cancer (n = 163).

Results: Longitudinal blood samples were available for 31 patients (median age 65 years; 87% male); 29% experienced radiological progression at 6 months. Patients with disease control had higher baseline circulating $\gamma\delta$ T-cell levels (2.2% vs. 0.7%, p = 0.008), which were associated with longer progression-free survival (PFS; HR 0.71, 95% CI 0.55–0.92; p = 0.009), as well as higher baseline IL-18 plasma levels (p = 0.01). At the tumor level, a high $\gamma\delta$ T-cell transcriptional signature was associated with higher response rates (p < 0.01), longer PFS (p < 0.001), and longer overall survival (OS; p = 0.003) in AtezoBev-treated patients, but not in those receiving sorafenib. This $\gamma\delta$ T-cell signature outperformed the AtezoBev Response Score (ABRS) for OS and PFS prediction. Consistently, in an independent