**Objectives**: The aim of our study was to investigate the *in vitro* activity and *in vivo* efficacy of rezafungin, anidulafungin, caspofungin and micafungin against *C. auris* isolates belonging to Iranian lineage.

**Materials & Methods:** Five clinical isolates evaluated (IFRC 2087, IFRC 4050, MRL40, TMML616 and TMML617) were derived from a previous study (Emerg. Microbes Infect. 2022;11:2405-2411). MICs in RPMI-1640 were determined using the standard broth microdilution .method (CLSI M27 ed4.). Time-kill assays with the four echinocandins were performed from 0.25 to 32 mg/L in RPMI-1640. In the survival (ten mice/group) and fungal tissue burden experiments (nine mice/group), cyclophosphamide treated BALB/c male mice were infected intravenously (107 CFU/mouse, respectively). Treatment was initiated 24 hours post-infection with intraperitoneal dosing of 20 mg/kg of rezafungin (Rezzayo®) on days 1, 3 and 6 or once-daily dosing for 6 days with 3 mg/kg of caspofungin (Cancidas®), 5 mg/kg of micafungin (Mycamine®) or 5 mg/kg of anidulafungin (Eraxis®). After 21 days, survival rates were compared using the Kaplan-Meier log-rank test. Fungal tissue burden (kidneys, hearts and brains) on day 7 were analysed with the Kruskal-Wallis test with Dunn’s post-test. Histopathological examination on day 7 with Periodic Acid Schiff was also performed (two mice/group).

**Results**: MIC ranges of rezafungin, anidulafungin, caspofungin, and micafungin were 0.06-0.25, ≤0.03-0.12, 0.12-0.5 and ≤0.03-0.12 mg/L, respectively. The four echinocandins at ≥1 mg/L were fungicidal against isolate MRL40. Against the remaining four isolates the echinocandins were fungistatic. All echinocandin regimens improved the survival in mice infected with isolates MRL40 and IFRC 4050 (P-values were ≤0.0002 and 0.0006, respectively). In contrast, against mice infected with isolate TML617, only rezafungin improved the survival (P = 0.0049) (Fig. 1). All four echinocandins induced more than 5 and 4 logs mean CFU/gram decreases in the kidneys (P<0.001) and hearts (P<0.001 for all echinocandins), respectively in mice infected with isolate MRL40 compared to control mice (day 7). In mice infected with isolate TML617 and IFRC 4050 the four echinocandins produced <3-log CFU mean fungal kidney and heart burden decreases some of which were not statistically significant (Fig. 1). Fungal growth regardless of the isolate tested in mice was poorly inhibited by echinocandins in the brain (Fig. 1). Histopathology showed large aggregates of blastoconidia, budding yeast cells and pseudohyphae in the hearts, kidneys and brains in control mice (Fig. 2). Echinocandins, especially rezafungin treated mice showed sporadic fungal cells in their hearts and kidneys, but fungal cells were always visible in cerebrum or cerebellum. Peudohyphae were found infrequently in echinocandin treated mice (Fig. 2).

**Conclusions**: *In vitro* activity and *in vivo* efficacy of the four echinocandins against the fifth clade of *C. auris* was echinocandin- and isolate-specific. Pseudohyphal production is common in control, but not in echinocandin treated mice. Rezafungin activity was comparable to or better than the three previously approved echinocandins.