A-213 - Efficacy and safety of tirbanibulin 1% ointment in elderly patients with actinic keratosis: a pooled analysis of phase 3 clinical trials [Abstract]

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Results: The L. casei–derived postbiotic solution showed clear antimicrobial activity, supporting its role in microbial load control and guiding dose selection. The postbiotics exhibited low to moderate inhibition zones against B. subtilis, E. faecalis, P.s aeruginosa, and Candida spp. in the agar diffusion assay, indicating a broad-spectrum antimicrobial activity. MIC results demonstrated that the postbiotics exerted inhibitory effects particularly against Gram-positive bacteria and yeast species, with MIC values ranging between 2500 and 5000 µg/mL. At a concentration of 10 mg/mL, L. casei–derived postbiotics inhibited biofilm formation by 51.94% in Staphylococcus aureus and 42.35% in Pseudomonas aeruginosa. Both spray formulations showed skin-compatible pH values for oncology-related compromised skin, and incorporation of the postbiotic solution did not affect formulation homogeneity or spray performance; antimicrobial testing of the final formulations is ongoing.

Conclusions: This study reports the development of postbiotic-based topical sprays for supportive skin care in oncology-associated cutaneous complications. Antimicrobial and antibiofilm activities of the L. casei–derived postbiotic solution supported dose selection, while chitosan and carbopol provided suitable functions for compromised skin. The cell-free nature of the formulation may offer a safety advantage for immunocompromised patients and supports further in vitro microbial and pharmaceutical evaluation for oncology-related dermal care. This study was supported by Anadolu University Scientific Research Projects Commission under the grant no: YTT-2024-2606.

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A-422

Dissecting the shift in YAP/TAZ signalling modalities with disease progression in cancer-associated fibroblasts of cutaneous squamous cell carcinoma

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Background: Cancer-associated fibroblasts (CAFs) can promote or supress tumour growth. YAP/TAZ signalling is often dysregulated in cancers, including cutaneous squamous cell carcinoma (cSCC), and YAP-TEAD inhibitors are already in clinical trials for cancers. Little is known about YAP/TAZ signalling in CAFs during cancer progression and how inhibition affects CAF phenotype. Using isogenic fibroblast lines isolated in our lab from normal skin tissue, primary tumour, and recurrent tumour, we aim to dissect the distinct YAP/TAZ signalling modalities in CAFs. We hypothesise that YAP/TAZ signals through different co-factors in cancer cells and CAFs and targeted inhibition will affect these cell types differently during cSCC progression.

Methods: Changes in YAP/TAZ signalling with disease progression were assessed using ATAC/RNAseq datasets, 2D and 3D skin co-culture models, YAP/TAZ transient knockdowns, and YAP-TEAD inhibitor treatment as a discovery tool.

Results: Immunofluorescent staining of cSCC tissue shows increased stromal YAP/TAZ expression, and RNAseq and RT-qPCR data confirmed YAP/TAZ signalling in CAFs increases with disease progression. While YAP/TAZ signal through TEADs in cSCC keratinocytes, analysis of ATAC/RNAseq data indicates a shift in association of YAP/TAZ between TEAD and AP-1 in our CAF progression series. Accessibility of AP-1 binding motifs peaks in primary CAFs, and TEAD motif accessibility peaks in recurrent CAFs. While normal fibroblasts respond strongly to TEAD-specific inhibition, impacting proliferation, contraction, and ECM remodelling, CAFs become less responsive with disease progression, providing further evidence of a signalling switch. We are currently investigating how this switch influences CAF-cancer cell crosstalk by modulating YAP-TEAD and AP-1 signalling in 3D organotypic co-cultures.

Conclusions: These results suggest YAP/TAZ signalling is altered in CAFs and evolves with disease progression. A switch in association of YAP/TAZ with downstream transcription factors could affect efficacy of TEAD inhibitors in clinical development at different stages of cSCC.

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A-213

Efficacy and safety of tirbanibulin 1% ointment in elderly patients with actinic keratosis: a pooled analysis of Phase 3 clinical trials

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Background: Actinic keratosis (AK) is more common in patients with cumulative sun exposure, and therefore elderly patients are at a higher risk of developing the disease. These patients often present multiple comorbidities and polypharmacy, which must be considered when selecting a treatment. This post-hoc analysis aims to evaluate the efficacy and safety of tirbanibulin in very elderly patients (≥80 years), an immunosenescent higher risk population [1].

Methods: Data were pooled from 2 Phase 3 studies (NCT03285477 and NCT03285490) with treatment field (TF) of 25 cm2, and 2 Phase 3 trials (1 US Phase 3 study [NCT05279131] and 1 EU Phase 3 study [NCT06135415]) in patients with TF up to 100 cm2. Patients with skin diseases other than AK that could interfere with study results or with unstable medical conditions that could pose an unacceptable risk were excluded. Efficacy and safety were assessed after 1 treatment cycle of tirbanibulin (once daily 5 days). Efficacy assessment includes percent change from baseline in lesion count. Safety assessment includes treatment-emergent adverse events (TEAEs) and local tolerability signs (LTS) severity (0-4) for

erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation and erosion/ulceration. Post-hoc analyses were performed by age group (≥80 years vs <80 years).

Results: Of 644 patients in the pooled safety population, 16.8% were ≥80 years (n=108), referred to as very elderly population. Mean baseline lesion count was similar across age groups (6.5 and 6.4, respectively). TF was predominantly the face (≥80 years: 71.3% face and 28.7% scalp; <80 years: 66.4% face and 33.6% scalp). At Day 57, very elderly patients achieved a mean 72.8% (95% CI: 66.4, 79.3) reduction in AK lesions (placebo: 26.9% [95% CI: 18.3, 35.5]), comparable to 77.5% (95% CI: 74.9, 80.0) for <80 years (placebo: 32.1% [95% CI: 28.3, 35.9]). TEAEs were also similar (38.9% and 36.4%, respectively). 6.5% of very elderly patients experienced severe TEAEs (vs 1.5% <80 years). LTS at Day 8 were consistent across groups, with mostly mild-to-moderate reactions; severe reactions were infrequent and similar: erythema (≥80 years: 9.3% vs <80 years: 7.4%), flaking/scaling (9.3% vs 7.2%), crusting (2.8% vs 1.7%), swelling (0.9% vs 0.4%), and vesiculation (0% vs 0.2%).

Conclusions: Tirbanibulin has shown efficacy and favorable safety/tolerability in very elderly patients. These outcomes support 5-day tirbanibulin treatment as a suitable field-directed therapy for AK in these high-risk patients.

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A-358

Efficacy, safety and willingness to be retreated with tirbanibulin 1% ointment in patients with actinic keratosis over a field treatment up to 100 cm²

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Background: Actinic keratosis (AK) is a pre-cancerous skin disease resulting from the atypical proliferation of keratinocytes that may progress to invasive squamous cell carcinoma (SCC). Tirbanibulin 1% ointment is approved for treating AK on the face or scalp in Europe over a field up to 25 cm2, and in the United States over a field up to 100 cm2.[1] This study aimed to evaluate tirbanibulin's efficacy and safety when applied to fields larger than 25 cm² and up to 100 cm², including up to two 5-day treatment courses, and to assess patients' and investigators' reported outcomes such as willingness to retreat with tirbanibulin.

Methods: This is a phase 3, multicenter, randomized, double-blind, vehicle-controlled study (NCT06135415). Patients with ≥4 to ≤12 AK lesions in a field of between 25 and 100 cm2 were randomized 2:1 to tirbanibulin or vehicle. All received a 5-day course; those not achieving complete clearance (CC) at Day (D) 57 received a second course. Primary endpoint was percent change from baseline in AK lesion count at D57. Key secondary endpoints were CC, defined as 100% clearance of AK lesions and partial clearance (PC), defined as ≥75% clearance of AK lesions, assessed at D57 and D113. Willingness to be retreated was evaluated at D113 by patient and investigator using a 5-point Likert scale (from very unlikely to very likely). For this subanalysis we merged "somewhat" and "very likely" categories.

Results: 187 patients were randomized to tirbanibulin and 93 to vehicle (mean age: 73.4 years; male: 83.9%). Tirbanibulin demonstrated a statistically significantly greater percent reduction in AK lesions from baseline to D57 versus vehicle (least-square mean: 64.2% vs 25.2%; p<0.001; median: 84.5% vs 20.0%; nominal p<0.001). At D57, a higher percentage of patients achieved CC and PC with tirbanibulin (41.2% and 58.8%, respectively) compared to vehicle (15.1% and 20.4%), and the improvement was further increased at D113 (CC and PC with tirbanibulin: 56.1% and 65.2% vs CC and PC with vehicle: 23.7% and 25.8%), the differences being statistically significant between groups both at D57 and D113 (p<0.001). Most treatment emergent adverse events (TEAEs) were mostly mild/moderate local skin reactions. Basal cell carcinoma occurred in 1.1% of both groups; and SCC occurred in 1.1% in the vehicle group. No SCC was reported in the tirbanibulin group. Willingness to be retreated (somewhat/very likely) was high in the tirbanibulin arm, both in patients (83.8%) and investigators (85.2%).

Conclusions: Tirbanibulin showed significantly greater efficacy and favorable safety/tolerability for AK treatment fields up to 100 cm² compared to vehicle, and was associated with high willingness to retreat, among both patients and investigators.

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A-355

Gene Signatures as Predictive Biomarkers for PD-1 Blockade in Cutaneous Squamous Cell Carcinoma

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Background: Anti-PD-1 therapy has substantially improved clinical outcomes in patients with advanced cutaneous squamous cell carcinoma (cSCC). However, approximately 50% of patients do not respond to PD-1 inhibition.

Methods: To explore the molecular mechanisms underlying treatment response and to find potential biomarkers, we performed whole-transcriptome profiling using the HTG EdgeSeq technology on 26 tumor samples of advanced cSCC who subsequently received anti-PD-1 therapy. Baseline clinical characteristics and treatment outcomes were collected, and differentially expressed genes (DEGs)