Abstract N°: 2680

Topical PI3K/mTOR inhibitor bimiralisib (PQR309) in Actinic Keratoses and Cutaneous Squamous Cell Carcinoma

Vladimir Cmiljanovic[1], Matthew Hedberg[2], juergen mestan[1], Xiaoping Yang[3], Christine Marshall[3], Paul Hebeisen[1], Anton Stuetz[4], Christopher Miller[3], Thuzar Shin[3], Joseph Sobanko[3], dominique vinet[5], Arnaud PILLON[5], laurent creancier[5], Katrin Tiffner[6], thomas birngruber[6], john seykora[3], Doriano Fabbro*[1]

[1]TORQUR AG , Research, Basel, Switzerland
[2]Department of Dermatology, Perelman School of Medicine, University of Pennsylvania,, Philadelphia, United States
[3]Perelman School of Medicine, University of Pennsylvania,, Department of Dermatology , Philadelphia, United States
[4]Akribes Biomedical GmbH , Wien, Austria
[5]Pierre Fabre Research Center, Research, Toulouse, France
[6]Joanneum Research Forschungsgesellschaft mbH, Graz, Austria

Introduction & Objectives:

Actinic keratoses (AKs) are prevalent precancerous skin lesions associated with increased risk of cutaneous squamous cell carcinoma (cSCC). Treatment options for AKs include topical drugs, destructive modalities and surgical removal. However, all of these agents induce skin inflammation of varying severity and their clinical efficacies are sub-optimal.

The PI3K/mTOR signaling is hyperactivated in cSCC, squamous cell carcinoma in situ (SCCIS) and AKs, making this pathway a potential therapeutic target. This study evaluated the application of topical bimiralisib (PQR309), a dual PI3K/mTOR inhibitor, as a potential therapy for AK/SCCIS/cSCCs in 2 preclinical *in vivo* models with the aim to develop a topical formulation for clinical use.

Materials & Methods:

We have tested *in vivo* a topical gel containing 1-3 % bimiralisib on K14-Fyn-Y528F transgenic mice, which produce spontaneous skin lesions that mimic human AK, SCCIS and cSCC as well as in the SKH-1 immune-competent hairless mice that developed AK/SCC like lesions after 14 weeks of daily UV-B-irradiation.

To develop a topical non-aqueous formulation 2% of bimiralisib (NA03-2% bimiralisib) for clinical use a range of formulations were tested on human and porcine skin ex-vivo or in-vivo. This allowed to develop the topical non-aqueous 2% bimiralisib formulation was developed for clinical use and tested in clinical studies to evaluate the efficacy and safety (Windt et al. 2022) as well as in patients suffering from AK (NCT06319794; 2024).

Results:

Experimental topical formulation of 1% showed marked regression of treated cSCCs in K14-Fyn-Y528F transgenic mice by 99% which correlated with inhibition of PI3K/mTOR signaling. In the SKH-1 immune-competent hairless mice that developed AK/SCC like lesions after 14 weeks of daily UV-B-irradiation application of topical bimiralisib gel for four weeks clearly prevented the progression of AK lesion as quantified by a global macroscopic score using three masks and relative weighting. Although no statistical significance could be assessed, these data demonstrate that the topical treatment of UVB-induced cutaneous lesions in SKH-1 mice with PQR309 was very

well tolerated with no weight loss or any detectable skin irritation compared to Zyclara. Topical PQR309 decreased the lesion progression from AK to SCC although the protective effects of PQR309 is lost when the treatment is ceased. Topical bimiralisib in both K14-Fyn-Y528F and UV-B-irradiated SKH-1 mice was well tolerated and did not induce skin erythema, crusting or ulceration.

A topical non-aqueous 2% bimiralisib formulation for clinical use showed that the concentrations of PQR309 achieved in the epidermis and dermis of pig skin following a single exposure was sufficient to significantly inhibit the PI3K/mTOR pathway, The excellent penetration of bimiralisib could be confirmed in by MALDI imaging into the epidermis of human patients (Windt et al. 2022).

Conclusion:

Overall, topical bimiralisib combines high efficacy in animal models with AK/SCCIS/cSCC lesions, with low detectable adverse effects and high skin penetration properties. A topical formulation of 2% bimiralisib for clinical use was developed and has been tested in healthy volunteers without significant safety issues (Windt et al. 2022) and is currently in a clinical trial to evaluate the efficacy and safety in patients suffering from AK (NCT06319794; 2024).