Puig et al_Eryfotona Supplementary Table 1. Summary of the most commonly used treatment approaches for AK in clinical practice.

Type of treatment	Short description	Type of treated lesions	Adverse events/disadvantages
I. Physical treatment methods			
Cryotherapy	Widely used mainly for isolated AK lesions. Represents a destruction of the tissue surface by vaporization of liquid nitrogen on the lesion.	Applied on visible lesions, not treating subclinical lesions.	The protocol is not standardized, and different outcomes are observed. Can destroy healthy cells, as well. Is associated with pain during and immediately after treatment.
Curettage	Physical ablation of lesions with a curette.	Isolated, non-suspicious and well-defined AK lesions.	
Surgical excision	Physical ablation of the lesion with a minimum margin. Not a first line treatment.	Typically used for suspicious isolated AK lesions that could progress to SCC.	
PDT	Based on the application of a photosensitizing substance, leading to a selective destruction of atypical cells.	Suitable as both lesion- and field-directed therapy.	Local burning sensation, pain, crusting or erythema reported by up to 80% of patients. Expensive and time-consuming.
Laser therapies	Ablation with an Er:Yag and CO2 laser ultrapulse.	Indicated for isolated or small lesions.	Efficiency has not been evaluated in double blind randomized controlled trials. Causes erythema, pain, irritation, oedema.
II. Topical treatment methods			
5-Fluorouracil (5-FU)	5-FU is a pyrimidine analog which interferes with DNA synthesis and inhibits its replication. Suitable for a field-directed treatment. It is applied once or twice daily for an average period of 3-4 weeks.	Suitable for both single and multiple lesions.	Local side effects such as pain, burning sensation, pruritus and hyperpigmentation. Clearance rate varies from 43% to 96% and appearance of new lesions has been reported in 65% of patients one year after treatment.
3% Diclofenac in 2.5% hyaluronic acid	A non-selective cyclooxygenase inhibitor, which inhibits cell proliferation and angiogenesis. Applied twice daily for 2-3 months. A clearance rate of 31% and 47% after 2 and 3 months respectively has been reported. The rate of appearance of new lesions at one year is 21%.	Suitable for a field-directed treatment.	Local side effects such as contact eczema, dryness, oedema, pruritus or ulcerations.
Ingenol mebutate (available as 150 µg/g and 500 µg/g)	A biological compound that causes cytotoxicity and delayed immunomodulation of innate immunity. The 150 µg/g gel is applied on the face and scalp once daily for 3 days, and the 500 µg/g format is applied on the trunk and extremities once daily for 2 days. Complete clearance observed in up to 42% of cases after a 2-month treatment. Appearance of new lesions has been reported in up to 56% of cases.	Suitable for a field-directed treatment.	Local side effect such as erythema, scaling, crusting or oedema
Imiquimod cream (available as 5% and 3.75% cream)	An imidazoquinoline-derivative which stimulates the cutaneous innate immunity, applied 3 times per week for 4 weeks (this cycle could be repeated once). A clearance rate of 26.8% and 55% after one and two cycles respectively has been reported. Appearance of new lesions has been reported in up to 39% of cases.	Suitable for a field-directed treatment.	Local side effects such as pruritus, burning, erythema, pain, oedema, dryness, crusting, erosions or ulcerations

Puig et al_Eryfotona Supplementary Table 2. Summary of available clinical studies evaluating the effect of Eryfotona AK-NMSC treatment on AK lesions

Study	Study design	Arms	Nº of patients	Duration	Main outcomes
Moscarella E, 2017	Pilot randomised, controlled, double-blind parallel-group study	Eryfotona AK-NMSC vs marketed very high protection sunscreen	50 overall (36 completed the study)	6 months	Significant reduction in the number of AK lesions after 6 months in both groups (up to 31%). According to a sub-analysis of patients with ≤10 lesions, only 14% of Eryfotona AK-NMSC treated patients presented new lesions (vs 54% of the patients using sunscreen).
Eibenschutz L et al., 2016	Randomised, assessor-blinded parallel-group study	Eryfotona AK-NMSC after PDT vs Sunscreen after PDT	30 AK patients who had previously undergone a successful PDT treatment (15 per arm)	9 months	Significant decrease in the number of new lesions in the Eryfotona AK-NMSC group in comparison to the sunscreen group in which there was a progressive increase in AK lesions.
Puig A et al., 2014	Pilot, prospective, controlled interventional clinical study	Eryfotona AK-NMSC vs sunscreen	12 (with multiple AK lesions) – 9 treated with Eryfotona AK-NMSC and 3 with Sunscreen	2 months	Significant improvement in erythema, scaling, pigmentation, thickness of the stratum corneum and degree of atypia in keratinocytes in the Eryfotona AK-NMSC group, as evaluated by clinical and dermoscopic assessment of AK lesions.
Puviani M et al., 2015	Pilot, prospective, open label, 1 arm study	Eryfotona AK-NMSC	11 with single or multiple AK lesions	3 months	The number of AK lesions in the CF was reduced by 60% at 1 month and by 75% at 3 months.
Puviani M et al., 2013	Case report series	Eryfotona AK-NMSC as single therapy (only in 1 case Eryfotona AK-NMSC was applied after surgery)	6 with single or multiple lesions	1-2 months	>50% reduction in the number of existing lesions in all patients. >75% reduction in the number of existing lesions in half of the cases.
Navarrete-Dechent et al., 2017	Prospective, single-arm, case-series	Eryfotona AK-NMSC	9 patients with CF/multiple AK	3 months	An overall reduction of 76,6% in the number of AK lesions. The majority of patients had an almost complete resolution of AK lesions.
Giustini S et al., 2014	Case series retrospective analysis	Eryfotona AK-NMSC	8 with multiple AK lesions	12 months	65% decrease in the manifestation of new AK lesions.
Laino L et al.,2015	Clinical and thermographic, single arm study	Eryfotona AK-NMSC	30 AK patients with CF (27 completed the study)	9 months	Reduction in the area hyperthermic halo at 9 months.
Puig-Butillé JA et al., 2013	1 arm study	Eryfotona AK-NMSC	7 AK patients with CF		Skin improvement in all patients confirmed by histopathological and molecular analysis. Complete histological clearance in 3/7 patients; >80% histological clearance in 1 patient, partial histological clearance in 3 patients.
Arroyo-Rstom et al., 2014	Observational longitudinal study	Eryfotona AK-NMSC	14 patients with single lesions (17 lesion evaluated)	4 months	Out of the 17 lesions, 13 were Grade I, the rest were Grade II. After a 4-month treatment, Grade I lesions presented less desquamation and an improvement of the epidermis pattern, while Grade II lesions showed no changes.
Vaño-Galvan S et al., 2014	Observational study	Eryfotona AK-NMSC in conjunction with cryotherapy	41 patients with at least 4 lesions	6 months	Decrease in the number of existing lesions at 6 months (9,56 mean lesion number at baseline and 1,51 at 6 months). A very small number of new lesions: 0,27 lesions at the end of the first month and 0,76 at the end of the study.