Actinic Keratosis: An Update

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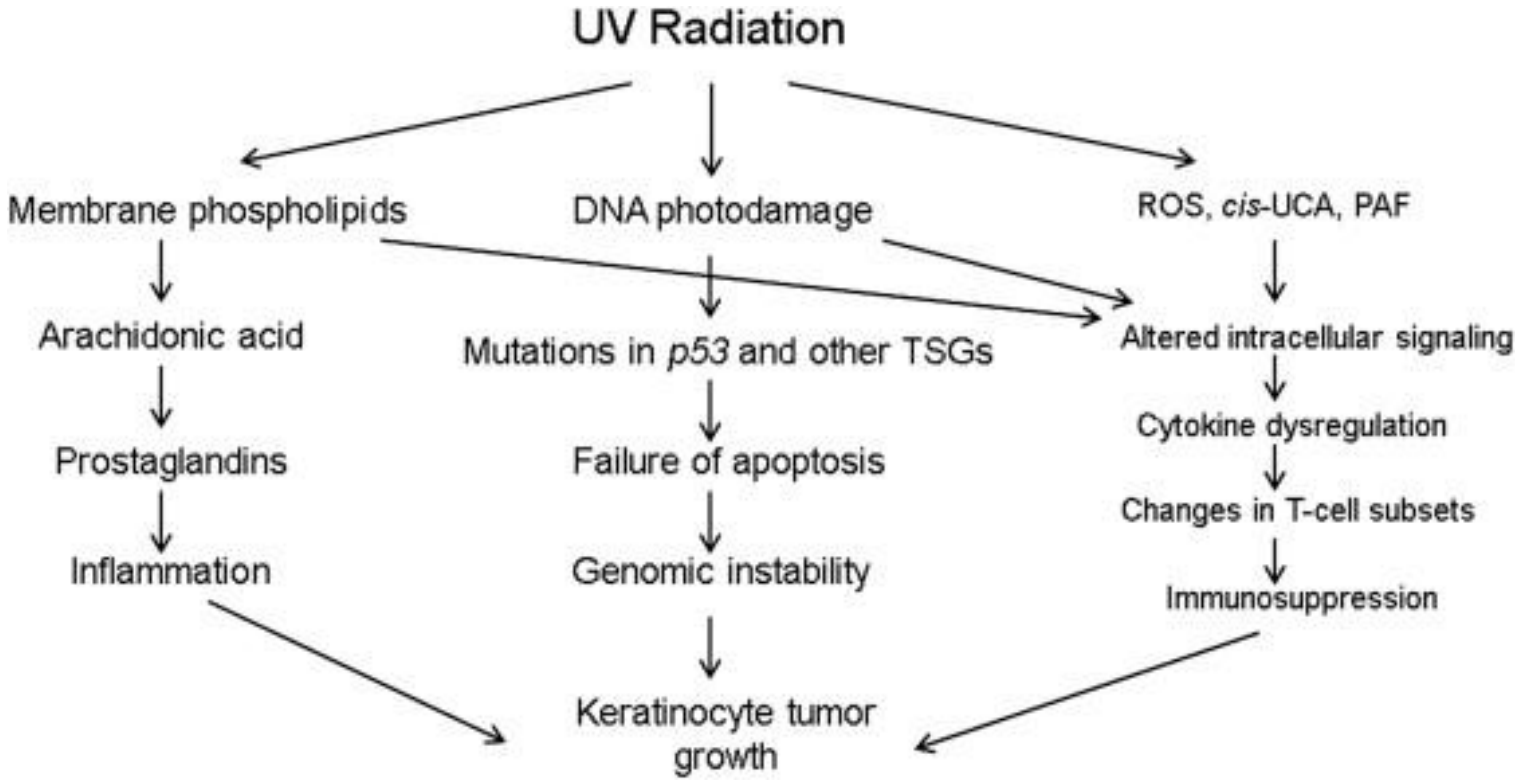
Disclosures

- I serve/have served as a consultant, advisor, principal investigator, and/or speaker for:
  - Verrica
  - LEO
  - Almirall
  - Athenex
  - Sanofi
  - Regeron
  - Castle
  - Mindera
  - Novartis

Pathogenesis Mechanism

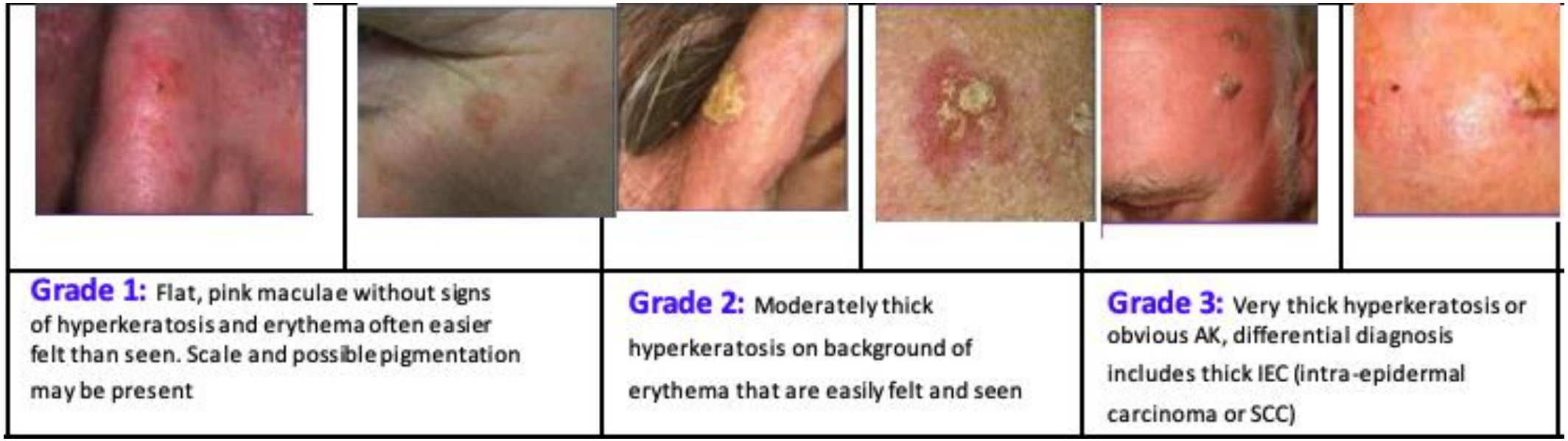


•UV = ultraviolet.

Berman B, et al. *J Am Acad Dermatol*. 2013;68(1 Suppl 1):S10-S19.

Clinical Classification

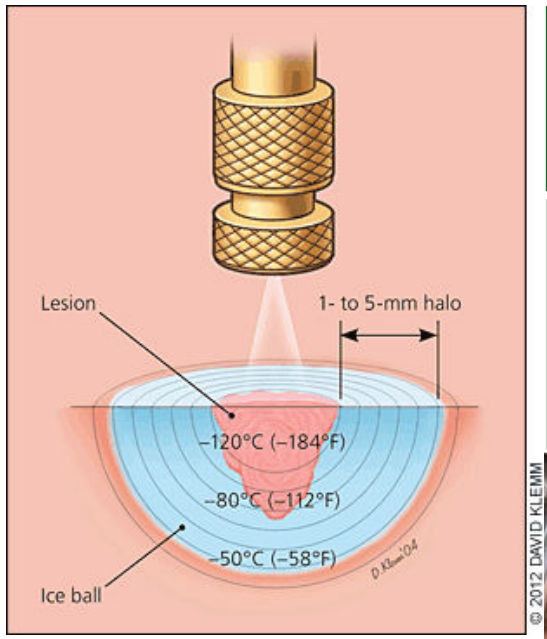
The Olsen Scale



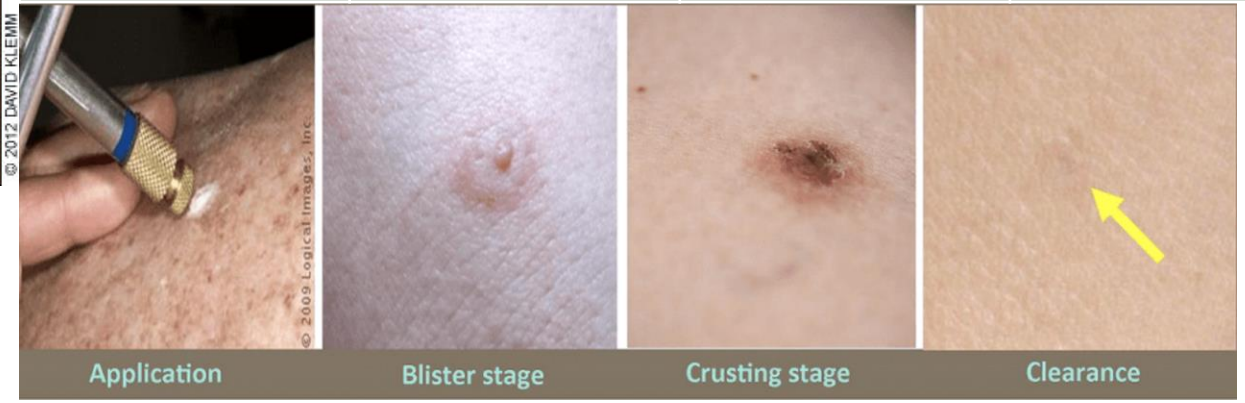
SCC = squamous cell carcinoma.

Image courtesy of NHS Camden Clinical Commissioning Group. De Berker D, et al. *Br J Dermatol*. 2017;176(1):20-43.

Current Treatment Approaches – Cryosurgery for Single Lesion



Freeze Time	<5 Seconds	>5 Seconds	>20 Seconds
Complete clearance rate	39%	69%	83%



•Thai KE, et al. *Int J Dermatol*. 2004;43(9):687-692. Skin M.D. and Beyond. Accessed July 20, 2021. https://www.skinmdandbeyond.com/liquid-nitrogen-cryotherapy/. Zimmerman EE, et al. *Am Fam Physician*. 2012;86(12):1118-1124.

Risk of Squamous Cell Carcinoma After Actinic Keratosis Diagnosis (a Marker of Sun Damage)

- Included 220,236 patients with a diagnosis AK and 220,236 matched control patients (mean age, 64.1, years; 52.5% female)
- At 10 years, the cumulative incidence of cSCC reached **17.1%** in patients with AK and **5.7%** in control patients

Madani, et al. JAMA Dermatol. doi:10.1001/jamadermatol.2021.0372 Published online March 24, 2021

U.S. Clinical Prevalence

Clinical Prevalence 1995-1997	Clinical Prevalence 2015-2017
4.9 million office visits per year	5.2 million office visits per year

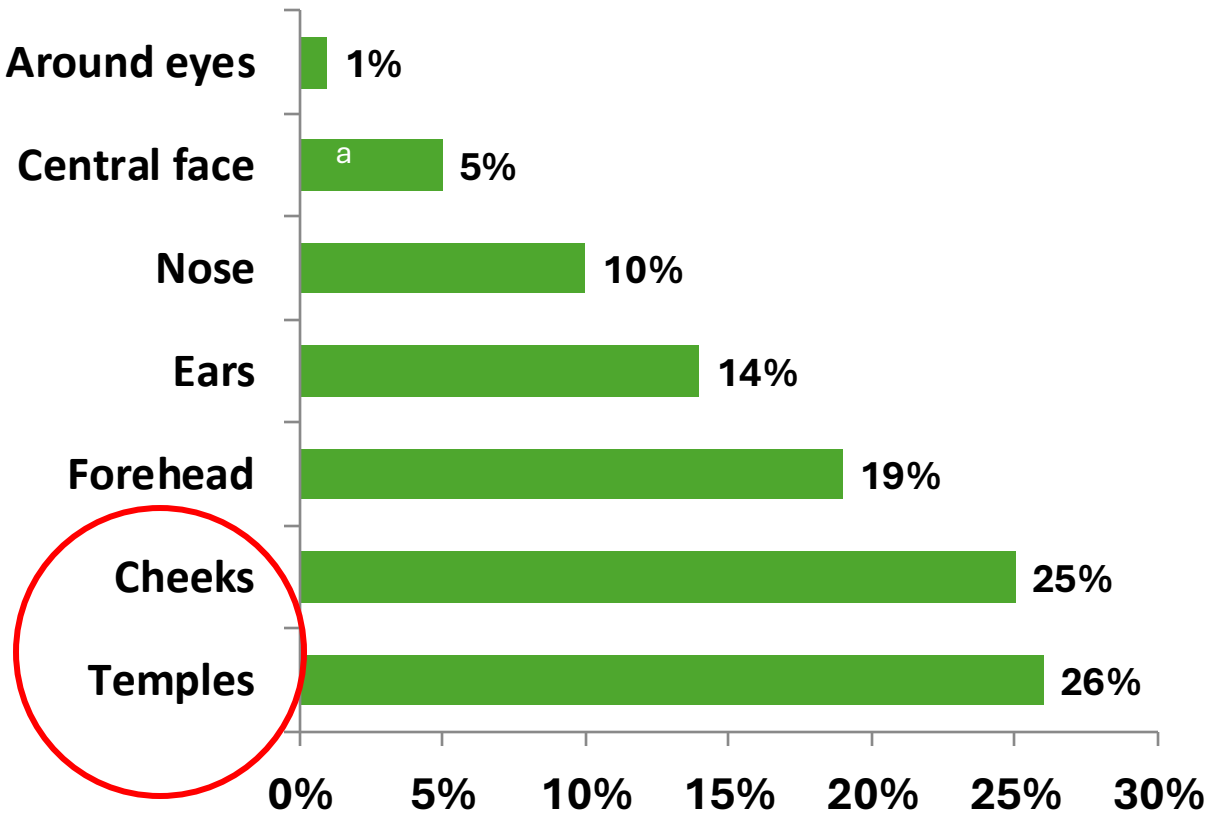
Transformation of AK to SCC

Anywhere between 0.025 and 16% of AKs can progress to invasive SCC

Extrapolation studies suggesting the risk of progression at approximately 8%

	Risk of Progression (%)	
	1 y (95% CI, %)	4 y (95% CI, %)
AK to Primary SCC	0.60 (0.44-0.82)	**2.57** (2.12-3.12)
AK to Primary Invasive SCC	0.39 (0.26-0.57)	**1.97** (1.58-2.47)
AK to Primary BCC	0.48 (0.34-0.68)	1.56 (1.21-2.02)
AK to Any KC (SCC or BCC)	1.08 (0.85-1.36)	4.10 (3.52-4.77)

Fuchs A,, Marmur E, "The kinetics of skin cancer: progression of actinic keratosis to squamous cell carcinoma," *Dermatol Surg*.,2007 Sep;33(9):1099-101.
Glogau RG. "The risk of progression to invasive disease, *J Am Acad Dermatol* 2000;42(1 Pt 2):23–4.



[a]Below the nose.

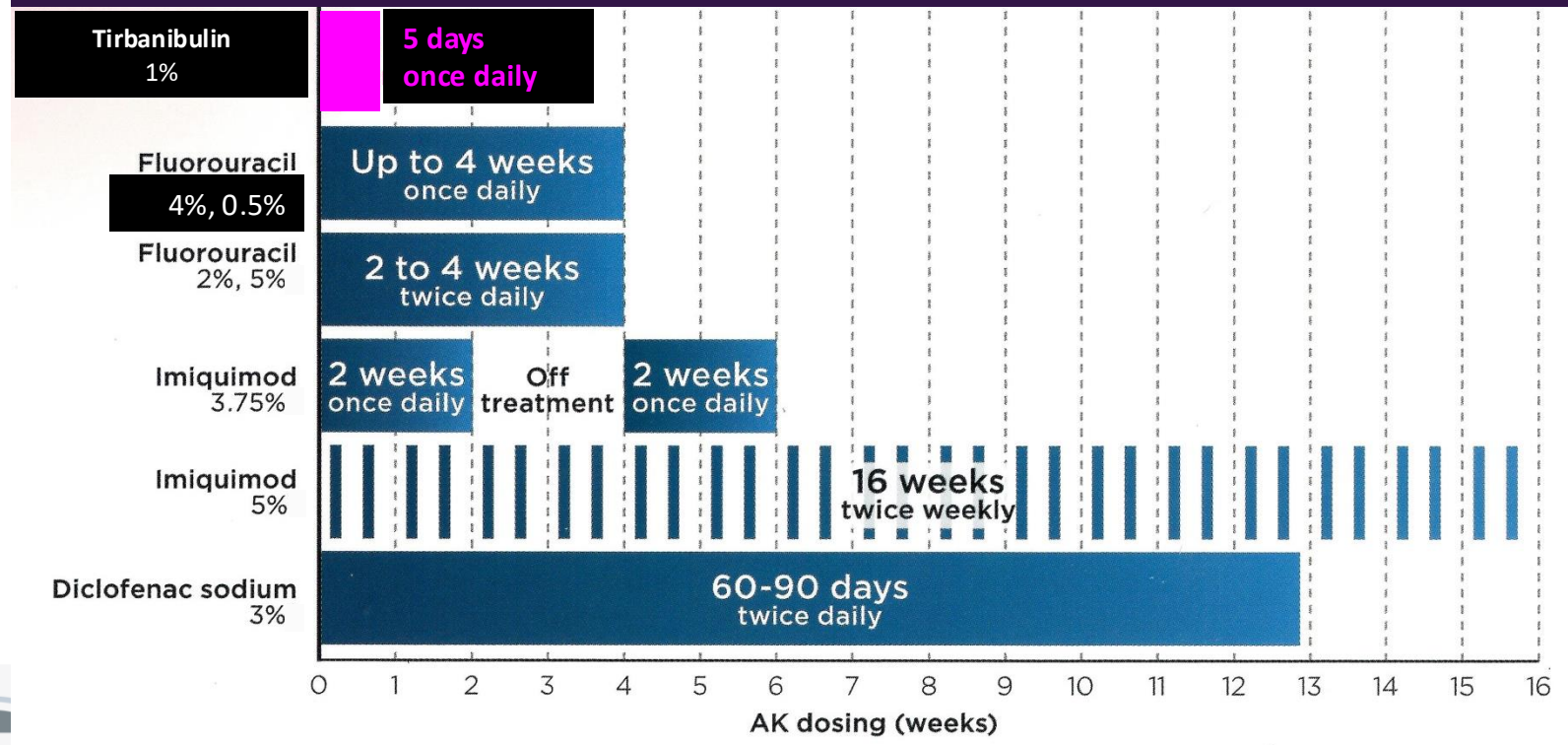
Criscione VD et al. *Cancer*. 2009;115:2523–2530.

Severe AKs Increased Risk of SCC

- Multicenter study in Netherlands, n=624, 90% males, 5 AKs
  - Randomly assigned to treatment with 5% FU, 5% imiquimod, MAL-PDT, or 0.015% ingenol mebutate
- 26 pts developed SCC in treatment area
- Grade III AKs: 20.9% higher risk of subsequent invasive SCC
- 33.5% who need additional treatment for AK develop SCC
- 3.7% 4-year risk of SCC in a previously treated area
  - 2.2% in patients using 5-FU, 5.8% in patients using imiquimod

Ahmady S, Jansen MHE, Nelemans PJ, *et al*. Risk of Invasive Cutaneous Squamous Cell Carcinoma After Different Treatments for Actinic Keratosis: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Dermatol*. Published online April 27, 2022. doi:10.1001/jamadermatol.2022.1034

FDA-Approved Dosing Regimens for Topical Field Therapies for AKs



Total Number Applications
5
7-28
14-28
28
32
120-180

Field Therapy for Actinic Keratoses: Efficacy

TABLE 1. Comparison of Short-Term Efficacy for Field-Directed Treatments of AK

Therapy	% Patients With Complete Clearance (No. of Studies)
5-FU 0.5% cream	32–58 ($n = 4$)[29–32]
5-FU 4% cream	54–80 ($n = 2$)[38]
5-FU 5% cream	58–75 ($n = 2$)[38]
Imiquimod 5% cream	24–64 ($n = 4$)[37,39–41]
Imiquimod 3.75% cream	36 ($n = 1$)[34]
Diclofenac sodium 3% gel	19–41 ($n = 3$)[35–37,43]
BF-200 ALA 10% gel	62–91 ($n = 2$)[42,44]
Tirbanibulin 1% ointment	44–54 ($n = 2$)[33]

Lampley III, N., Rigo, R, Schlesinger, T., & Rossi, A. M. (2022). Review of Efficacy, Cost, and Adherence of Field Therapies for Actinic Keratosis . SKIN The Journal of Cutaneous Medicine, 6(6), s91. https://doi.org/10.25251/skin.6.supp.91

Field Therapy for Actinic Keratoses: Adherence

TABLE 3. Adherence to Field Therapy for AK	
Therapy	**% Patients Completing Entire Regimen (No. of Studies)**
5-FU 5%	89 ($n = 1$)[21]
Imiquimod 5%	91 ($n = 1$)[41]
Diclofenac 3%	70 ($n = 1$)[46]
MAL-PDT	97 ($n = 1$)[21]

Lampley III, N., Rigo, R, Schlesinger, T., & Rossi, A. M. (2022). Review of Efficacy, Cost, and Adherence of Field Therapies for Actinic Keratosis . SKIN The Journal of Cutaneous Medicine, 6(6), s91. https://doi.org/10.25251/skin.6.supp.91

Randomized Trial Assessing 4 Treatment Approaches

ORIGINAL ARTICLE

Randomized Trial of Four Treatment Approaches for Actinic Keratosis

Maud H.E. Jansen, M.D., Janneke P.H.M. Kessels, M.D., Ph.D., Patty J. Nelemans, M.D., Ph.D., Nina Kouloubis, M.D., Aimee H.M.M. Arits, M.D., Ph.D., Han P.A. van Pelt, M.D., Ph.D., Patricia J.F. Quaedvlieg, M.D., Ph.D., Brigitte A.B. Essers, Ph.D., Peter M. Steijlen, M.D., Ph.D., Nicole W.J. Kelleners-Smeets, M.D., Ph.D., and Klara Mosterd, M.D., Ph.D.

- Inclusion criteria (N=624): 5+ AKs in 1 continuous area on head or neck
- Primary measure: Partial clearance rate at 3 and 12 months post-treatment
- Treatment groups
    1. 5% fluorouracil cream
    2. 5% imiquimod
    3. MAL-PDT
    4. 0.0015% ingenol mebutate

*Partial Clearance: ≥75% reduction of AK lesion

•Jansen MHE, et al. *N Engl J Med*. 2019;380(10):935-946.

I/E Criteria

INCLUSION CRITERIA:

1. Five or more actinic keratosis lesions in one continuous area of skin measuring 25 to 100 cm2 in the head and neck area
2. All grades of actinic keratosis lesions (Olsen grades I to III, a three-point grading system based on thickness of hyperkeratosis, with higher grades indicating more severe lesions) were included.

EXCLUSION CRITERIA:

1. Patients were not eligible to participate if they had received any treatment for actinic keratosis (including cryotherapy) in the target area or had used systemic retinoids or systemic immunosuppressant drugs within 3 months before inclusion.

BASELINE VISIT - In all patients, superficial curettage of all actinic keratosis lesions was performed manually before every treatment or retreatment, and patients did not receive anesthesia.

I/E Criteria

PDT- Three Hour Occlusion using MAL-PDT

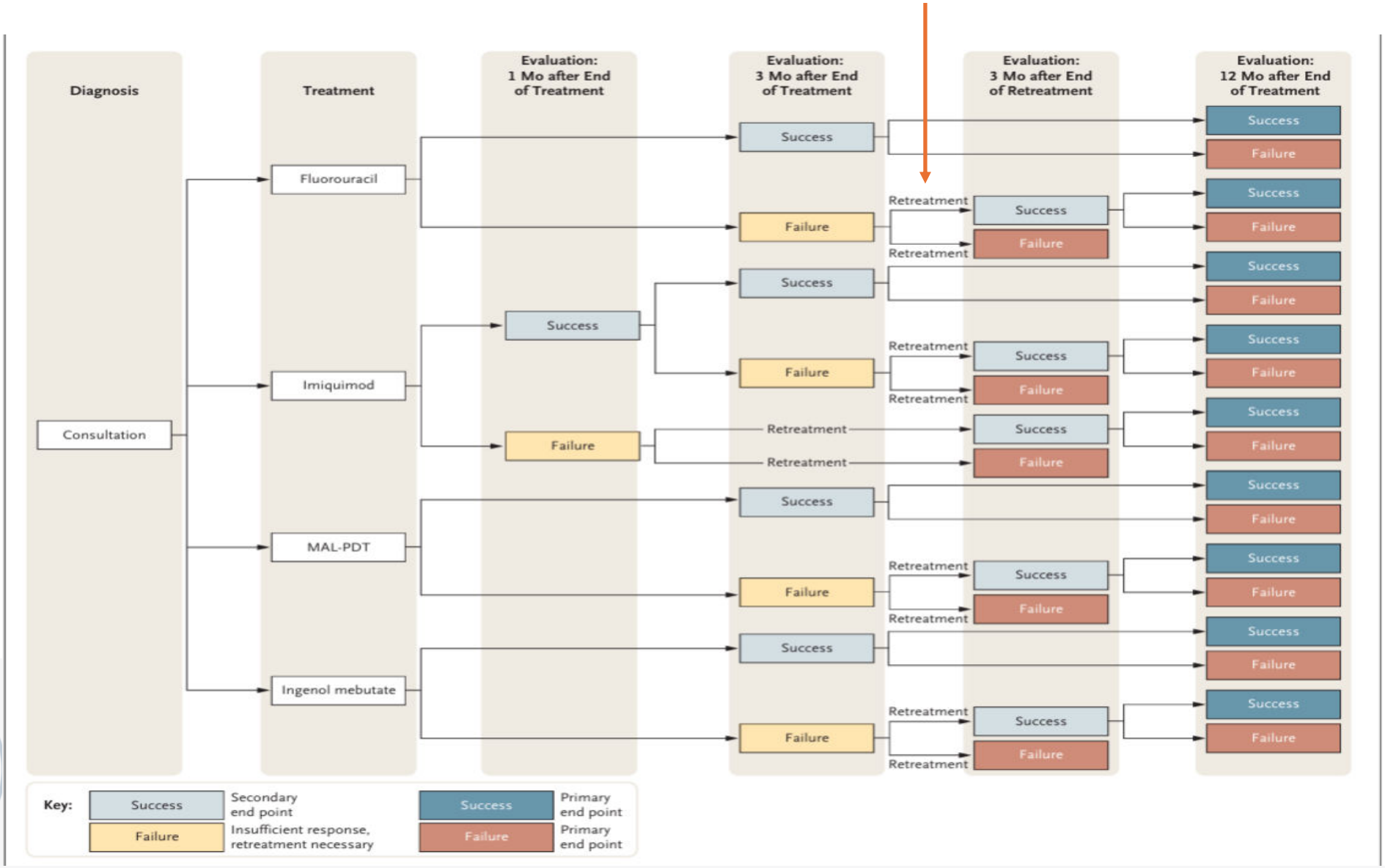
Imiquimod 5% - Three times per week for 4 weeks

Flourouracil 5% - BID for 4 weeks

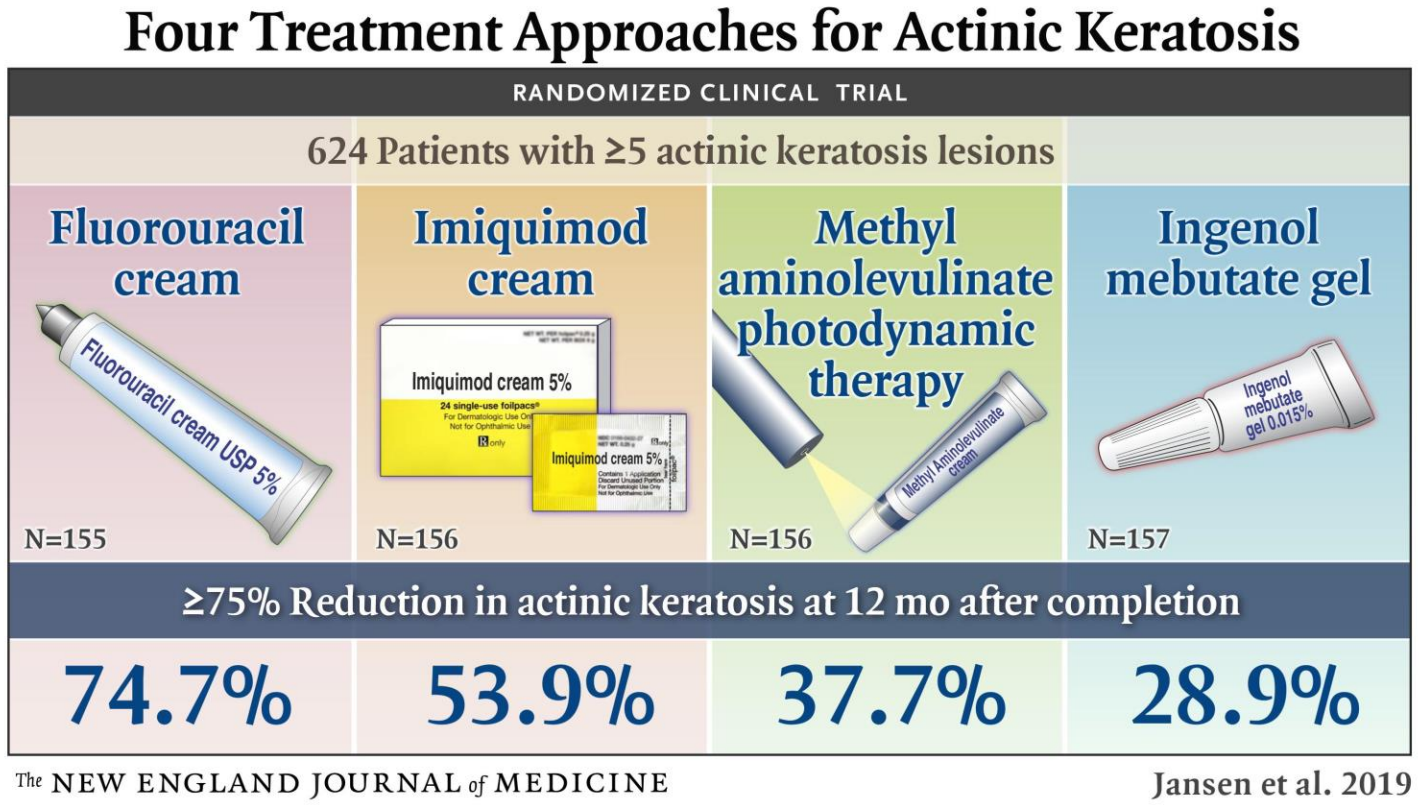
Patient Satisfaction – asked 12 months after RX

	Willing to Retreat?	Recommend to another?
5-FU	86%	93%
Imiquimod	75%	81%
PDT	60%	70%

Treatment Protocol – Retreatment Was Allowed



Randomized Trial Assessing 4 Treatment Approaches



AE Incidence:

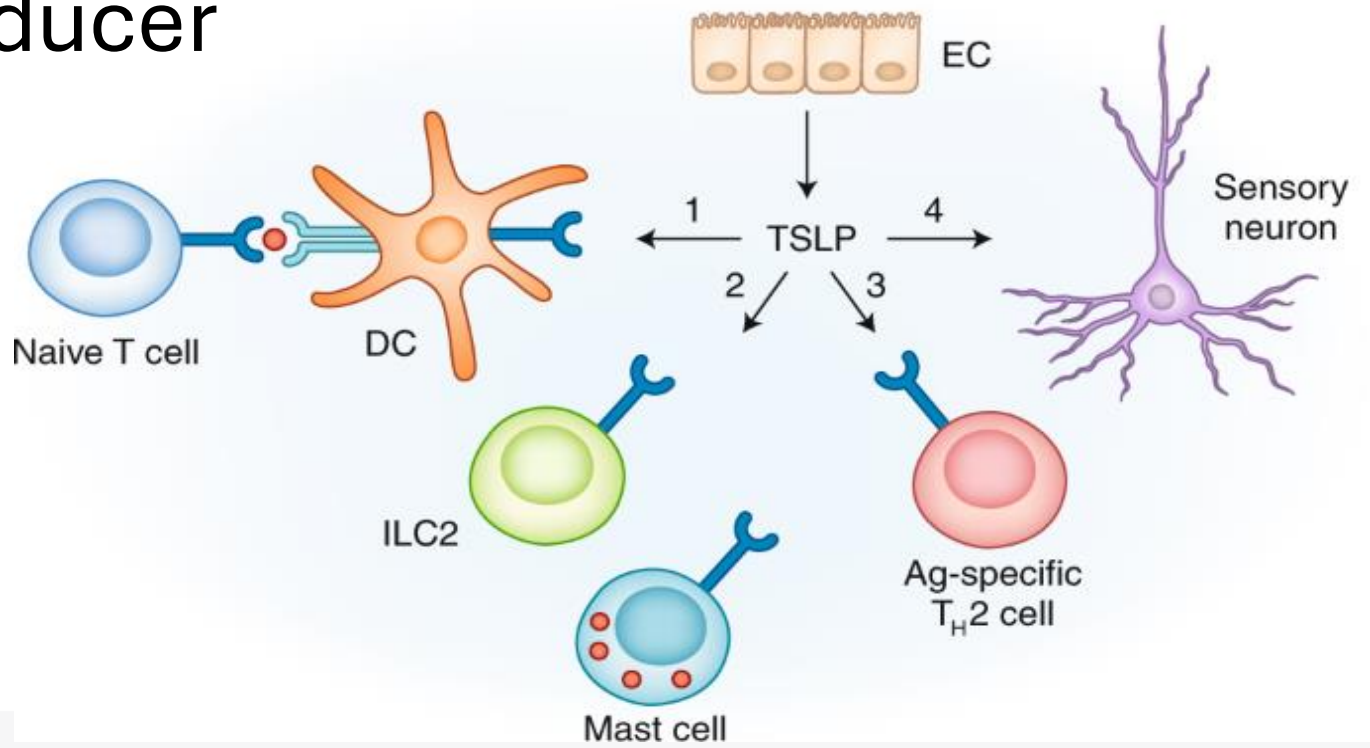
5FU:	92.6%
5% Imiquimod:	85.1%
MAL-PDT:	96.6%

Jansen MHE, et al. *N Engl J Med*. 2019;380(10):935-946.

5-FU + Calcipotriol

What is calcipotriol?

- Thymic stromal lymphopoietin (TSLP) inducer → antitumor immunity in barrier-defective skin



Rationale for Inducing TSLP

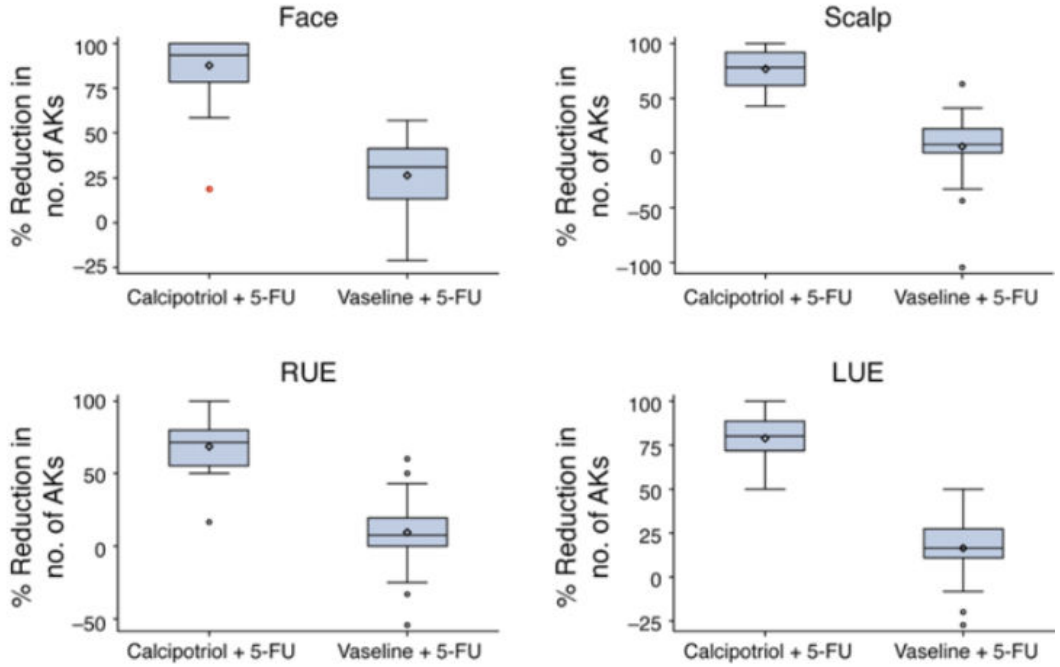
- Cytokine produced by keratinocytes released in barrier-defective skin T cell immunity and memory cell induction
- Calcipotriol induces expression of TSLP and recruits CD4+ T cells to generate antitumor immunity
  - Calcipotriol produces a significant increase in TSLP expression when compared to controls and reduces tumor burden in mice
- Impact on SCC
  - 5-FU+ calcipotriol reduces SCC risk within 3 years of treatment
  - *3-year follow-up: 7% combo group vs 28% 5-FU alone developed SCC on the face and scalp*

Rosenberg AR, Tabacchi M, Ngo KH, Wallendorf M, Rosman IS, Cornelius LA, Demehri S. Skin cancer precursor immunotherapy for squamous cell carcinoma prevention. *JCI Insight*. 2019 Mar 21;4(6):e125476. doi: 10.1172/jci.insight.125476. PMID: 30895944; PMCID: PMC6483001.

	Calcipotriol + 5-FU	Vaseline + 5-FU
	(*n* = 64)	(*n* = 67)
Age, mean (SD), yr	69 (7)	70 (9)
Range	(51–88)	(52–89)
Sex, *n* (%)		
Male	51 (80)	55 (82)
Female	13 (20)	12 (18)
Drug amount used, mean (SD), g (per anatomical site)	7.06 (3.38)	7.72 (3.05)
Anatomical sites treated, *n* (%)		
Face	45 (70)	50 (75)
Scalp	34 (53)	34 (51)
RUE	23 (36)	26 (39)
LUE	32 (50)	31 (46)

Combining Calcipotriol and 5-FU

- Combination cream of both superior to 5-FU alone
- 131 pts applied combo or 5-FU alone bid for 4 days
- 8 weeks after: combo 87% mean AK reduction vs. 26% 5-FU
  - Face, scalp, and upper arms also tested
- Higher incidence burning and erythema in combo group
  - 39% combo group vs. 13% 5-FU alone
- Concerns: stability of combo, treatment time, AEs

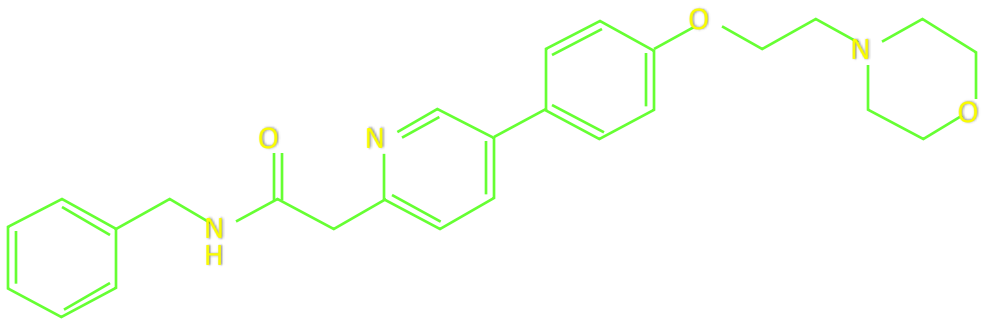


Cunningham TJ, Tabacchi M, Eliane JP, Tuchayi SM, Manivasagam S, Mirzaalian H, Turkoz A, Kopan R, Schaffer A, Saavedra AP, Wallendorf M, Cornelius LA, Demehri S, "Randomized trial of calcipotriol combined with 5-fluorouracil for skin cancer precursor immunotherapy," *J Clin Invest*. 2017 Jan 3;127(1):106-116. doi: 10.1172/JCI89820. Epub 2016 Nov 21.

Tirbanibulin – Mechanisms of Action

Synthetic, new chemical entity which:

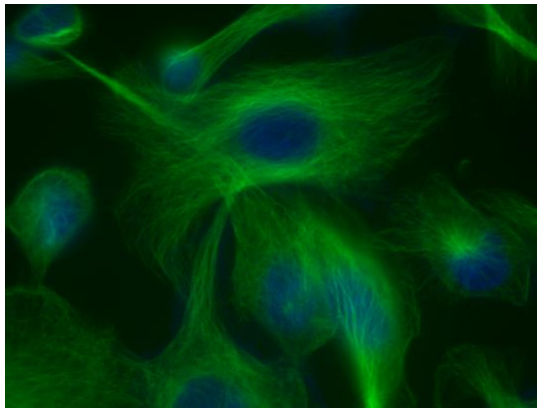
- **Inhibits tubulin polymerization & microtubule formation**
- **Disrupts Src kinase signaling**



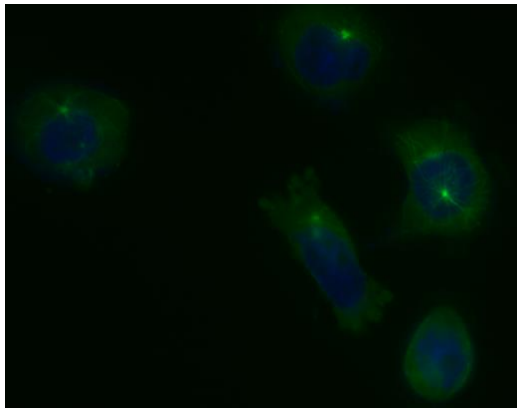
Molecular weight: 431.53 g/mole

Potent anti-proliferative and pro-apoptotic activies

Vehicle



Tirbanibulin (200 nmol/L)



Tirbanibulin inhibits tubulin polymerisation by binding to a novel binding site on alpha-beta tubulin heterodimers in MDA-MB-231 breast cancer cells *in vitro*

Berman B, Berman DK. Actinic keratoses: The latest in therapy. Dermatological Reviews. 2021; 1-4. doi:10.1002/der2.96
Blauvelt, et al. N Engl J Med 2021;384:512-20

AAD Focused Update (April 12, 2022) - Guidelines of Care Management of AK

Unlike other topical agents, Tirbanibulin 1% ointment received both a STRONG recommendation with a HIGH certainty of evidence for the field treatment of AKs

AK Topical Recommendations from the Updated Guidelines of Care[1]

Topical Field Treatment	Strength of Recommendation	Certainty of Evidence
Tirbanibulin	**Strong**	**High**
5-Fluorouracil	Strong	Moderate
Imiquimod	Strong	Moderate
Diclofenac*	Conditional	Low

Guidelines, AAD; Frazer-Green, Lindsy (2022), "AAD Focused update- Guidelines of Care for the Management of Actinic Keratosis Supplement", Mendeley Data, V1, doi: 10.17632/8b9k4mzsgx.1

Tirbanibulin 1% Ointment QD x 5d Critical Clinical Outcomes [1]

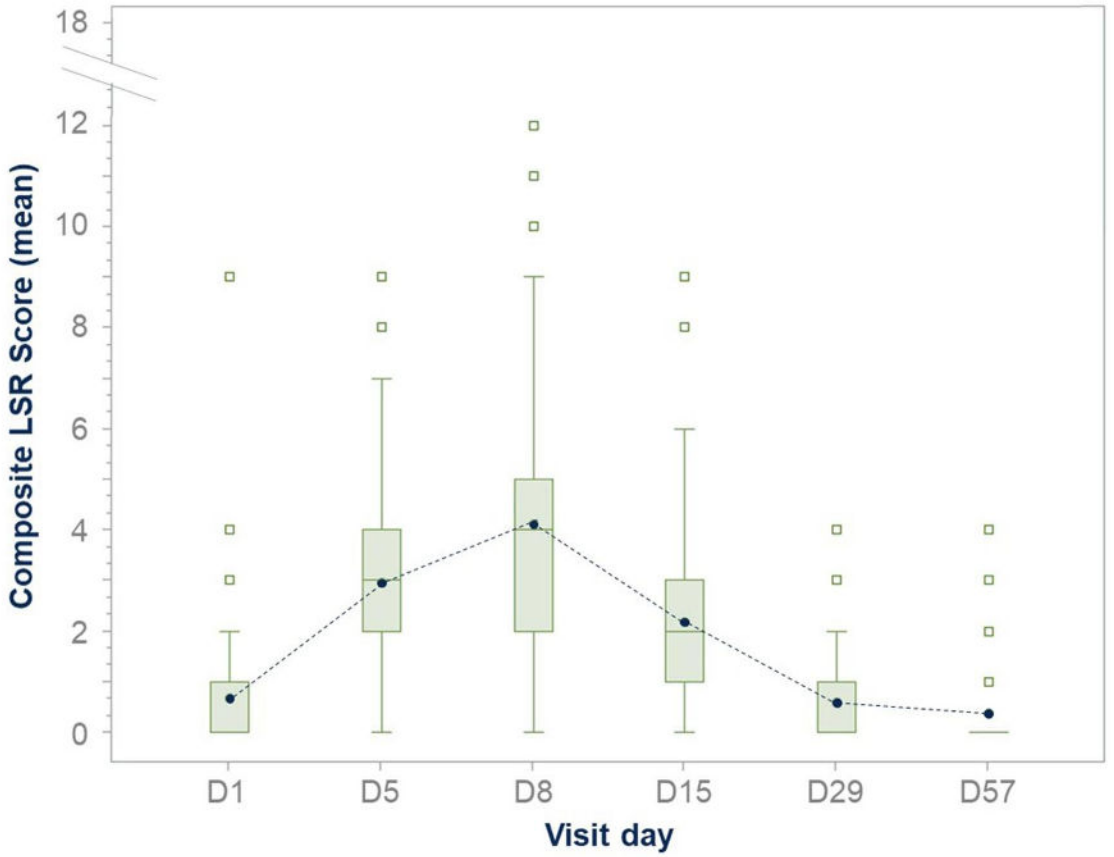
Primary Outcome	Importance Ranking	KLISYRI® Clinical Results
Mean reduction in AK counts (%)*	CRITICAL	**79% for Tirbanibulin[2]** 31% for vehicle at Day 57 (pooled analysis set)
Complete clearance of lesions (% of patients)†	CRITICAL	**49% for Tirbanibulin[3]** 9% for vehicle at Day 57
Partial clearance of lesions (% patients)‡	CRITICAL	**72% for Tirbanibulin[3]** 18% for vehicle at Day 57
Withdrawal due to Adverse Events (# of patients)	CRITICAL	**None[3]**

Chart adapted from Focused update to the Guidelines of Care for the Management of Actinic Keratosis: *Journal of the American Academy of Dermatology* (2022).
*From baseline to assessment.
†Complete clearance of all AKs within a defined field.
‡At least a 75% reduction in AKs in a predefined field.
Additional outcomes: Investigator global improvement index (participants rated as "completely improved" by the investigator); Participant global improvement index (participants self-assessed as "completely improved"); and Adverse Events.

1. Eisen DB, Dellavalle RP, Frazer-Green L, Schlesinger TE, Shive M, Wu PA. Focused Update: Guidelines of care for the management of actinic keratosis. *JAAD*. 2022. doi: https://doi.org/10.1016/j.jaad.2022.04.013
2. Blauvelt A, Kempers S, Schlesinger T, et al. Tirbanibulin ointment 1% for actinic keratosis (AK): pooled data from two phase 3 studies. Presented at: 40th Annual Fall Clinical Dermatology Conference (Fall CDC 2020); Virtual Congress; October 29-November 1, 2020.
3. Blauvelt A, et al. *N Engl J Med*. 2021;384(suppl):1-6.

Secondary Endpoint: Mean Local Skin Reaction (LSR) Composite Scores over Time for Tirbanibulin

PHASE III



Composite score is the sum of all 6 LSR grades with a possible range 0-18

Todd Schlesinger [1], Eggert Stockfleth[2], Ayman Grada [3], Brian Berman [4]
Clinical, Cosmetic and Investigational Dermatology 2022:15

5-Fluorouracil – Topical

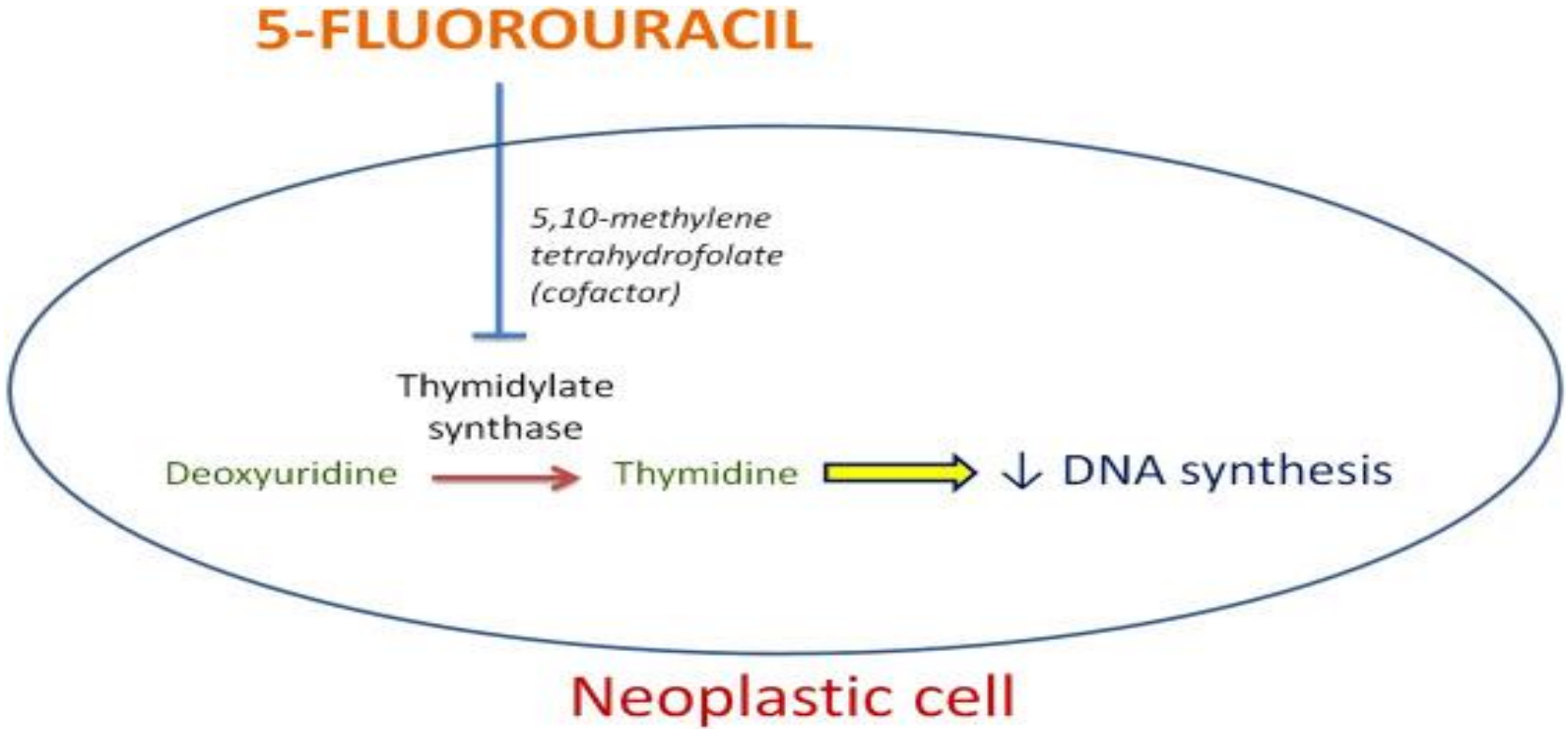
Efficacy

- 80% partial clearance*
- 52.2% complete clearance

Common adverse events

- Local skin reactions: >90%

*Partial clearance: ≥75% reduction of AK lesion



•Micali G, et al. *J Am Acad Dermatol*. 2014;70(6):965.e1-12; quiz 977-978. Eisen DB...Schlesinger T, et al. *J Am Acad Dermatol*. 2021 [Epub ahead of print].

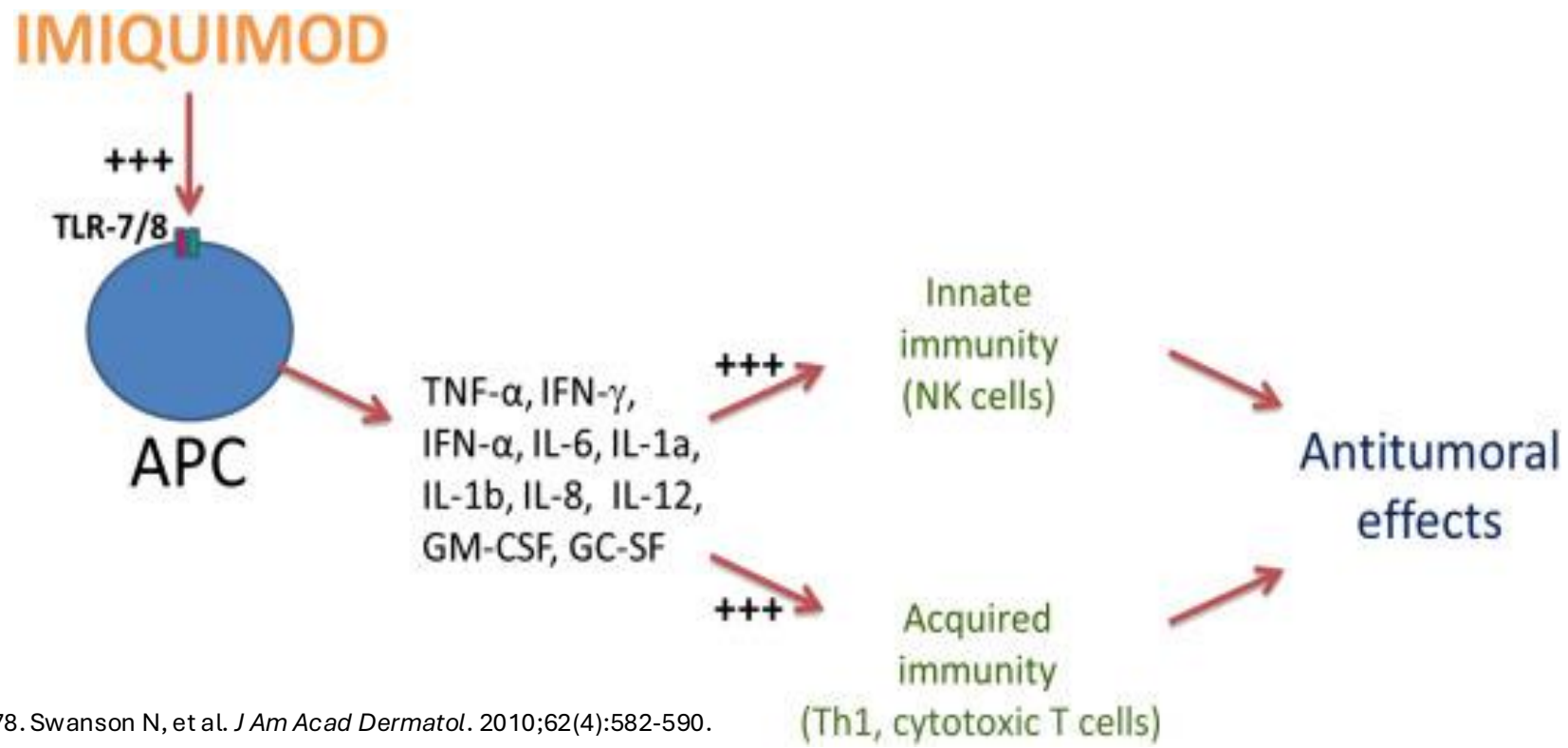
Imiquimod – Topical

Efficacy (3.75% imiquimod)

- 80% partial clearance
- 53.7% complete clearance

Common adverse events

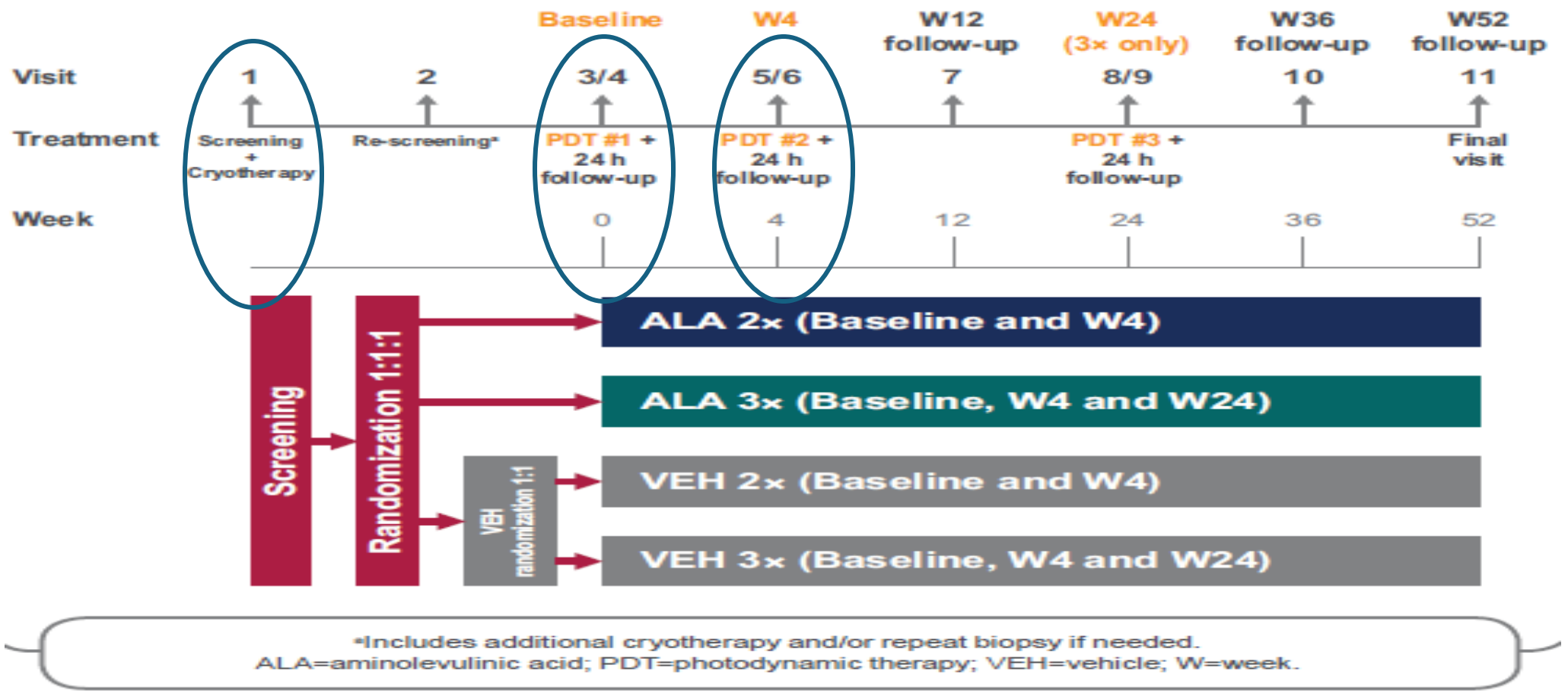
- Local skin reactions: 54.9%



•Micali G, et al. *J Am Acad Dermatol*. 2014;70(6):965.e1-12; quiz 977-978. Swanson N, et al. *J Am Acad Dermatol*. 2010;62(4):582-590.

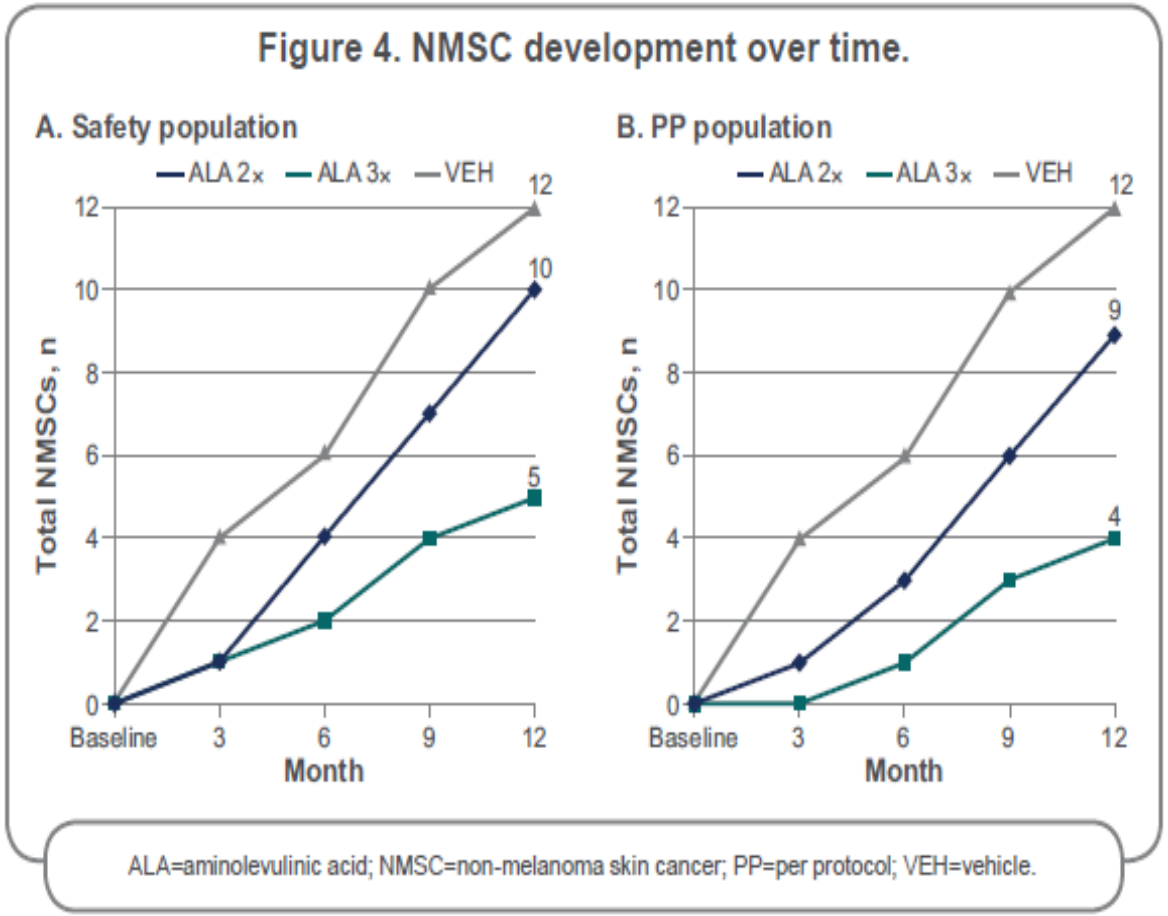
What about PDT

N=166



Piacquadio D, Houlihan A, Ferdon MB, Berg JE, Marcus SL, "A Randomized Trial of Broad Area ALA-PDT for Field Cancerization Mitigation in High-Risk Patients," *J Drugs Dermatol.* 2020;19(5):452-458.

PDT Reduces Cancer Formation



- In high-risk patients with facial AKs, significant improvements in reducing occurrence of AKs were seen with ALA-PDT treatment vs vehicle-PDT following cryotherapy

- *ALA-PDT subsequent to cryotherapy significantly reduced de novo development of NMSCs.*

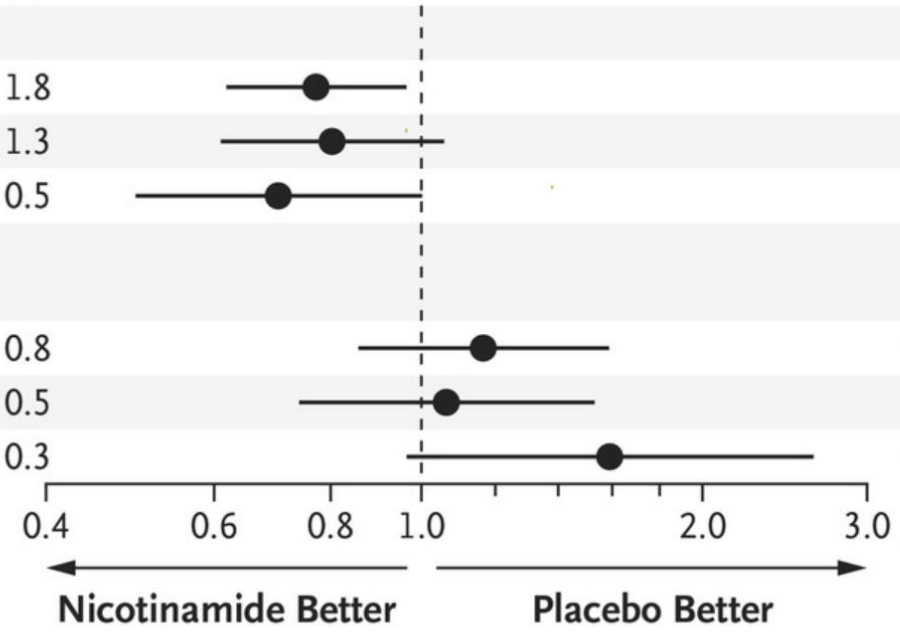
Piacquadio D, Houlihan A, Ferdon MB, Berg JE, Marcus SL, "A Randomized Trial of Broad Area ALA-PDT for Field Cancerization Mitigation in High-Risk Patients," *J Drugs Dermatol.* 2020;19(5):452-458.

A Phase 3 Randomized Trial of Nicotinamide for Skin-Cancer Chemoprevention

-All Subjects had at least 2 NMSC within previous 5 years

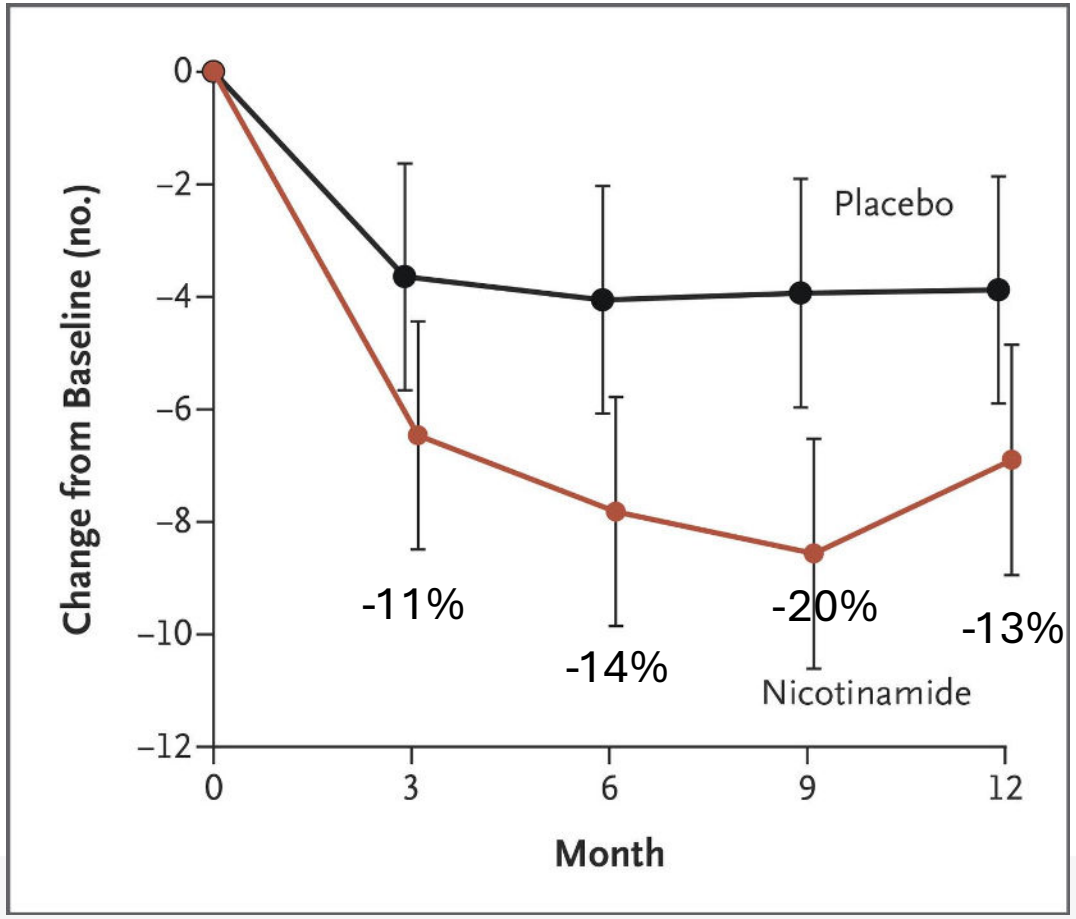
-500mg bid

Subgroup	Placebo (mean no. of lesions/person)	Nicotinamide (mean no. of lesions/person)	Relative Difference, % (95% CI)	P Value
12-mo intervention period				
NMSCs	2.4	1.8	23 (4 to 38)	0.02
BCCs	1.7	1.3	20 (–6 to 39)	0.12
SCCs	0.7	0.5	30 (0 to 51)	0.05
6-mo postintervention period				
NMSCs	0.8	0.8	–17 (–59 to 14)	0.33
BCCs	0.6	0.5	–6 (–53 to 26)	0.73
SCCs	0.3	0.3	–59 (–163 to 4)	0.07



Chen AC, Martin AJ, Choy B, Fernández-Peñas P, Dalziell RA, McKenzie CA, Scolyer RA, Dhillon HM, Vardy JL, Kricker A, St George G, Chinniah N, Halliday GM, Damian DL. A Phase 3 Randomized Trial of Nicotinamide for Skin-Cancer Chemoprevention. N Engl J Med. 2015 Oct 22;373(17):1618-26. doi: 10.1056/NEJMoa1506197. PMID: 26488693.

AK Reduction with Nicotinamide



THANK YOU!!