

# Cases in Actinic Keratosis – What Would YOU Do?



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School of Medicine  
& Health Sciences



CLINICAL RESEARCH CENTER  
OF THE CAROLINAS

South Beach  
Symposium  
medical + aesthetic dermatology

# Learning Objectives

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**At the conclusion of this activity, participants should be better able to:**

- **Review the latest clinical and real-world data for current therapies for actinic keratosis (AK)**
- **Identify appropriate therapies for AK treatment considering patient preferences**

# Relevant Disclosures

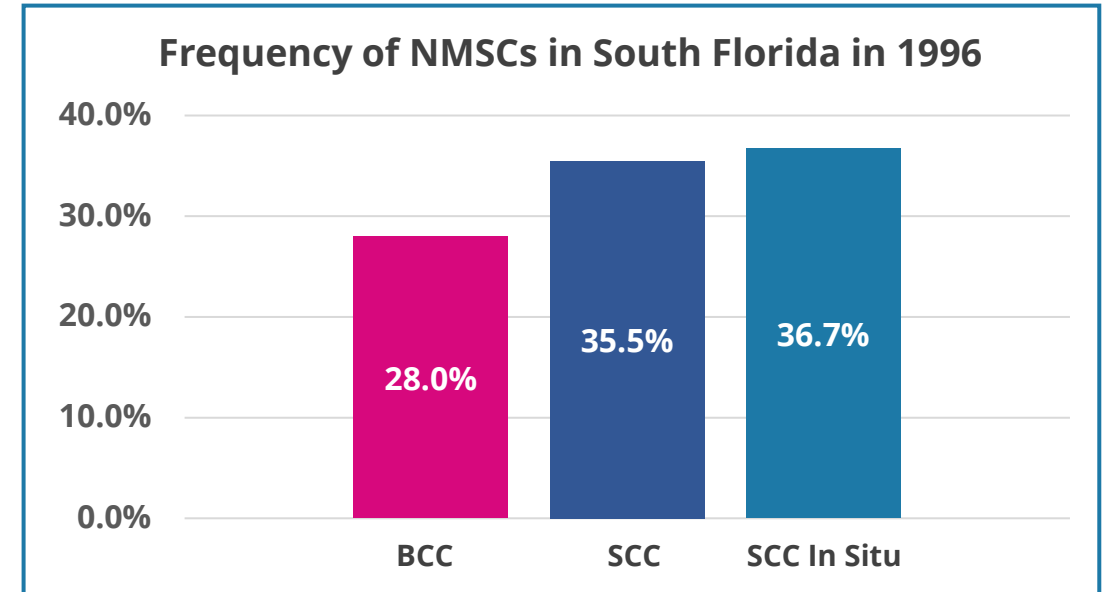
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## **Investigator/speaker and/or consultant:**

AbbVie, Almirall, Amgen, Apogee, Arcutis, Biofrontera, Boehringer-Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Castle Biosciences, Dermsquared, Eli Lilly and Company, Galderma, Incyte, Janssen, Novartis, Pfizer Inc., Regeneron, Sanofi, SiSaf, Sun Pharma, Takeda, RBC Consultants, Verrica and UCB.

# Nonmelanoma Skin Cancers in South Florida

- Incidence of nonmelanoma skin cancer (NMSC)<sup>1</sup>
  - 0-65 years: 466.5 per 100,000 people/year
  - > 65 years: **10,689.8** per 100,000 people/year
- Incidence of actinic keratosis (AK)<sup>1</sup>
  - 0-65 years: 4,464.6 per 100,000 people/year
  - > 65 years: **110,450.3** per 100,000 people/year
- **If we reduce AK burden, we could reduce future squamous cell carcinomas (SCCs)**
- Over 90% of patients report discomfort due to local site reactions associated with prior topical AK treatments, negatively impacting social interactions and work life<sup>2</sup>
- 3 main treatment approaches to AKs: cryosurgery, topicals, and photodynamic therapy



***“[I mind] duration of treatment time; the duration of recovery time; the photosensitivity...” “if something came along that might be more effective according to my dermatologist and at the same time, in less time than that, [and less] stinging, and I go for it...”***

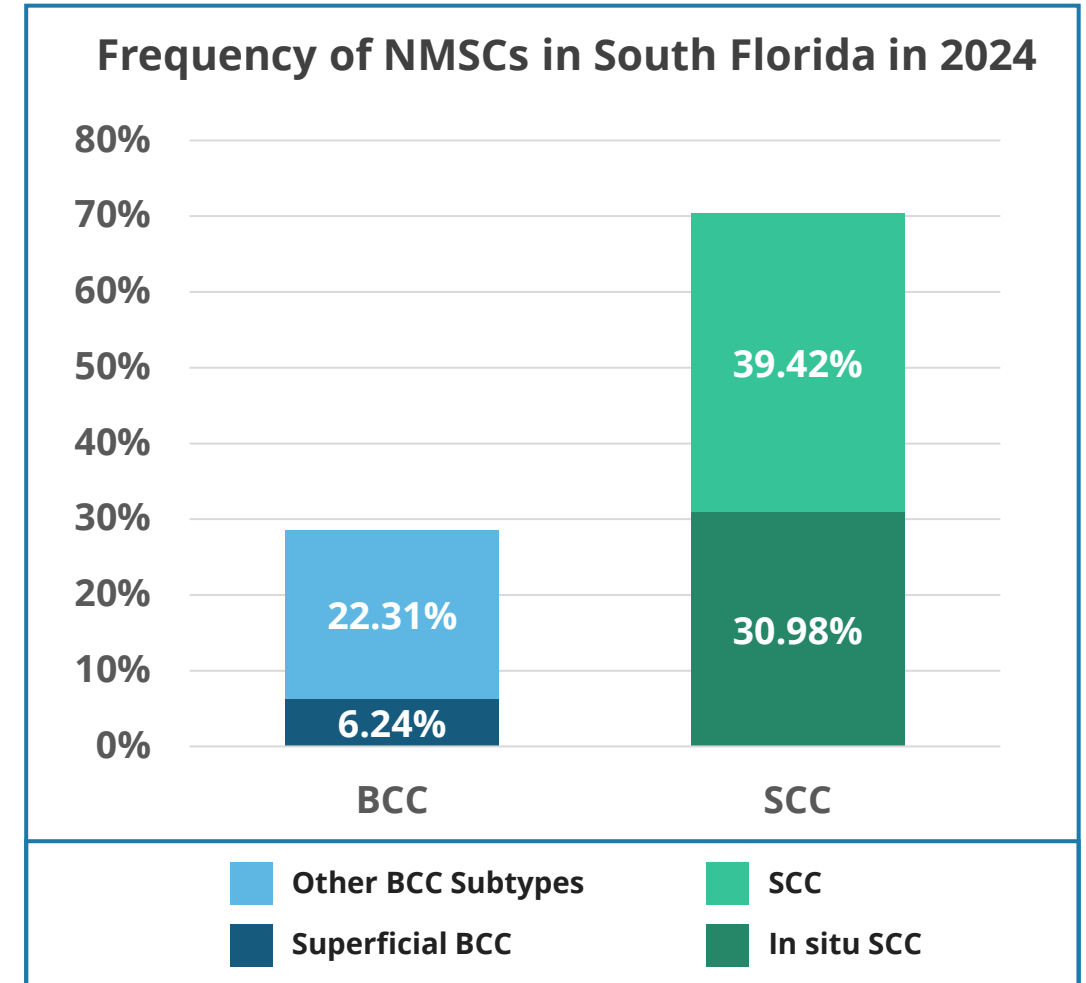
AK, actinic keratosis, BCC, basal cell carcinoma, NMSC, nonmelanoma skin cancer, SCC, squamous cell carcinoma

1. Nestor MS, Zarraga MB. *J Clin Aesthet Dermatol*. 2012;5(4):20-24.

2. Kasujee I, et al. ISPOR; May 15-18, 2022; Washington, DC

# 2024 Incidence of Squamous Cell Carcinoma Subtypes in South Florida

- Electronic histopathology database was searched for all confirmed NMSC results in 2024
- 856 NMSCs were assessed and categorized into basal cell carcinoma (BCC) and SCC subgroups
- SCC subtypes represented over 70% of all biopsy-confirmed NMSC
- High ratio of SCC to BCC is similar to that of 1996, suggesting an evolution in the incidence of UVA-associated NMSC, where many arise from AKs
- **Treating AKs and the overall actinic damage field is important for preventing future SCCs**



AK, actinic keratosis, BCC, basal cell carcinoma, NMSC, nonmelanoma skin cancer, SCC, squamous cell carcinoma  
1. Nestor MS, et al. Winter Clinical Dermatology Conference Miami 2025. Miami, FL. January 17-20, 2025.  
2. Nestor MS, Zarraga MB. *J Clin Aesthet Dermatol*. 2012;5(4):20-24.

# Case #1



What Would YOU Do?

Image courtesy of Todd Schlesinger, MD




## Case #2



What Would YOU Do?

Image courtesy of Todd Schlesinger, MD

# Topical Therapies and American Academy of Dermatology Guideline Efficacy



	Tirbanibulin (1%)	Imiquimod (3.75%)	5-Fluorouracil (5-FU, 5%)	Diclofenac
Efficacy	72% partial clearance 49% complete clearance	80% partial clearance 53.7% complete clearance	80% partial clearance 52.2% complete clearance	29% complete clearance
Treatment regimen	1X/day for 5 days	Varies from daily to 3-5X a week for 3-6 weeks as tolerated	Daily BID to 3-5X a week for 1-4 weeks	60-90-day course
Total # of Applications	5	28	14-28	120-180

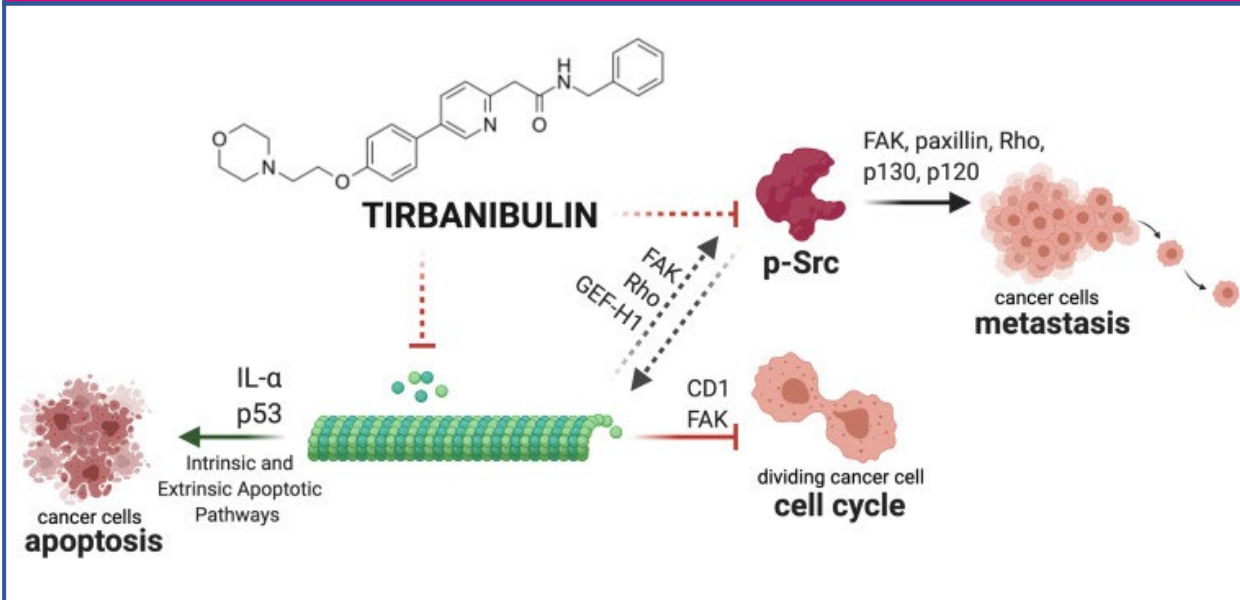
Partial clearance:  $\geq 75\%$  reduction of AK lesion; AK, actinic keratosis; BID, twice a day

Eisen DB et al. *J Am Acad Dermatol*. 2022;87(2):373-374.e5; Blauvelt A et al. *N Engl J Med*. 2021;384(6):512-520.; 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.; Thomas GJ et al. *Dermatol Ther*. 2019;32(3):e12800.; McEwan LE et al. *Australas J Dermatol*. 1997;38(4):187-189.

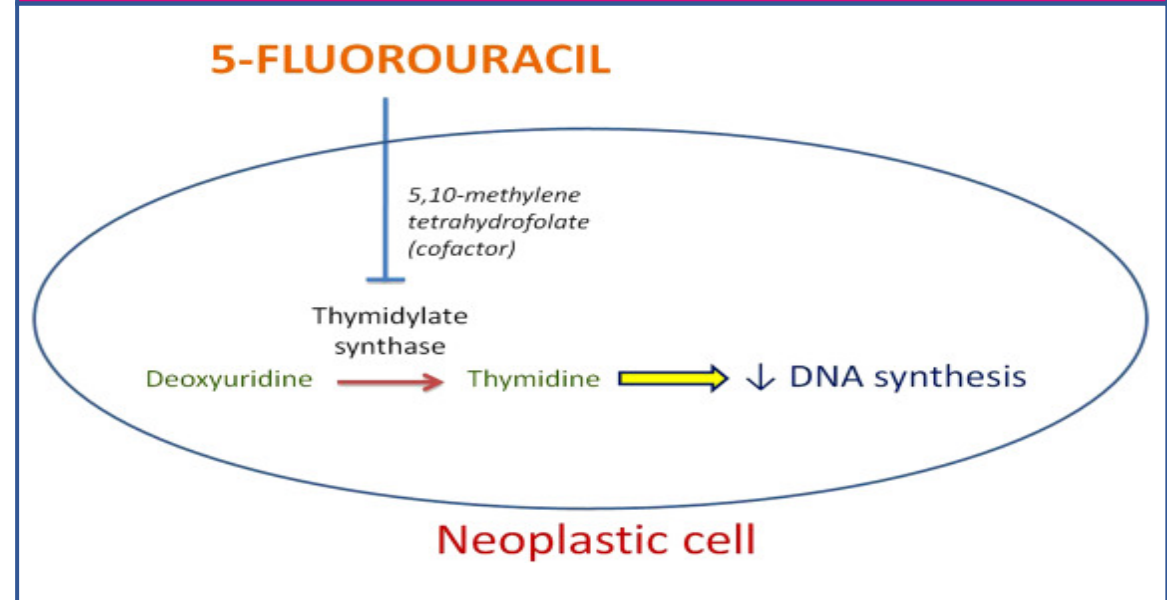


# Mechanisms of Action for Tirbanibulin and 5-Fluorouracil

## Tirbanibulin Mechanism of Action



## 5-Fluorouracil Mechanism of Action



# Efficacy of Tirbanibulin 1% for 100 cm<sup>2</sup> Field Therapy

- Studies of 25 cm<sup>2</sup> area: 49% and 72% treated with tirbanibulin had complete or partial response at day 57, (compared to 9% and 18% on vehicle)<sup>1</sup>

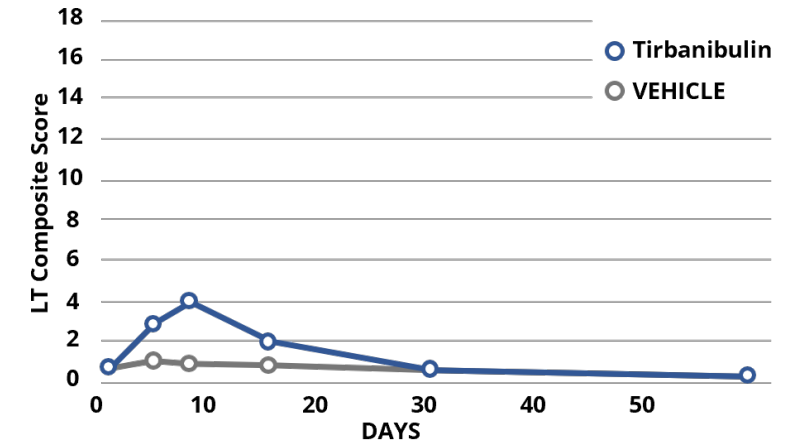
 **The FDA recently approved tirbanibulin 1% QD x 5 days for an up to 100 cm<sup>2</sup> treatment field<sup>2</sup>**

- Phase 3 study of 100 cm<sup>2</sup>: mean percent change from baseline in lesion count at Day 57 was 77.7%<sup>3</sup>
- Tolerability of tirbanibulin over a 100 cm<sup>2</sup> area is consistent with use over 25 cm<sup>2</sup>, and is not affected by number of AKs nor area of application<sup>4</sup>
  - Mean local tolerability scores peak at 4 (out of 18) before returning to near baseline levels

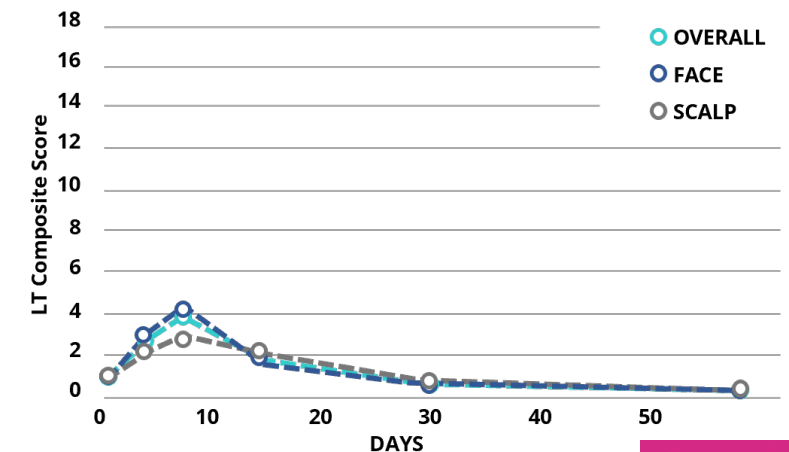
QD, once daily, AK, actinic keratosis

1. Blauvelt A et al. *N Engl J Med*. 2021;384(6):512-520.
2. Tirbanibulin ointment [package insert]. Published June, 2024
3. Bhatia N et al. *JAAD Int*. 2024;17:6-14.
4. Bhatia N et al. *SKIN The Journal of Cutaneous Medicine*. 2023;7(6),s264.

**Mean Local Tolerability Score for 25cm<sup>2</sup> area**

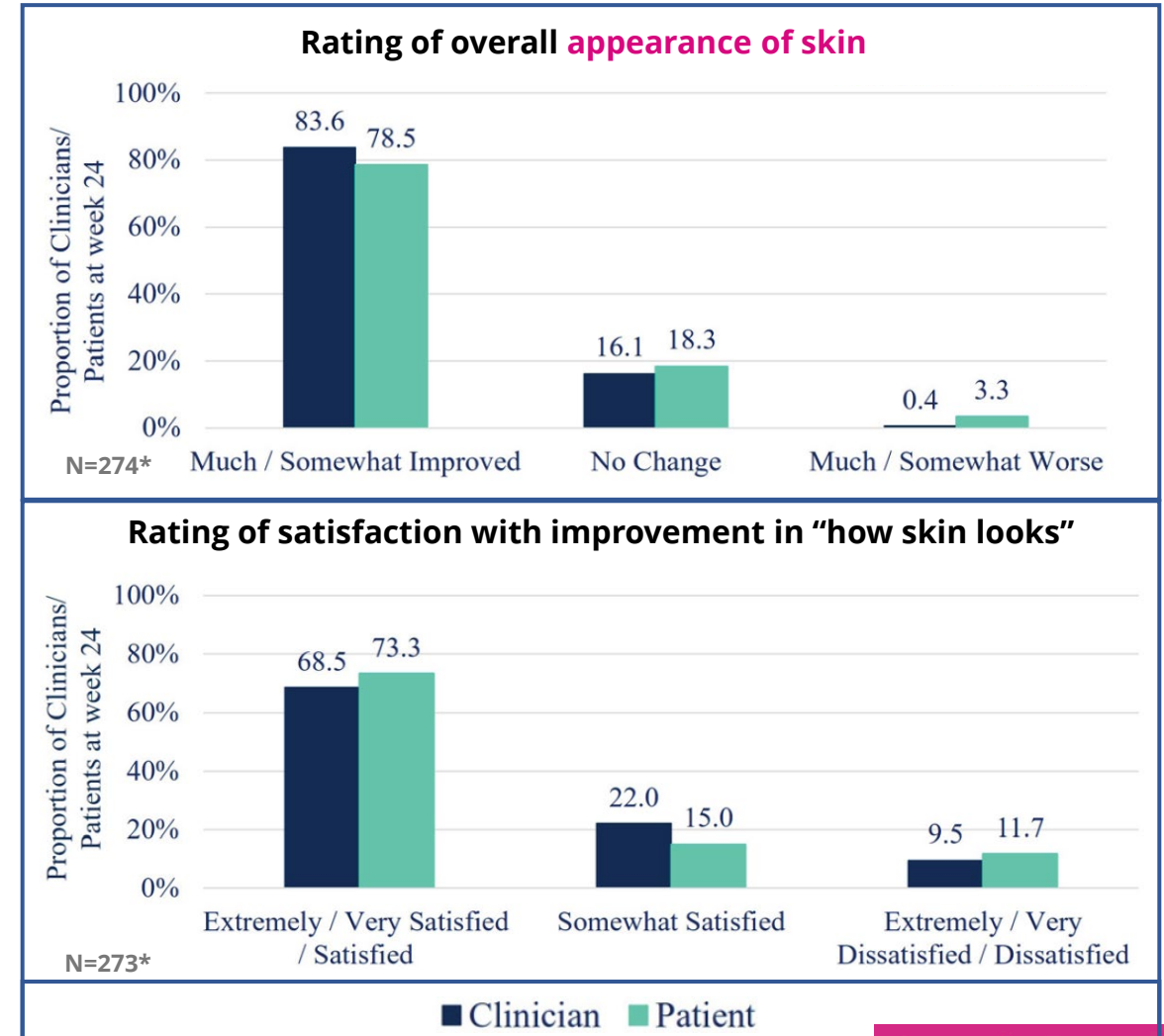


**Mean Local Tolerability Score for 100cm<sup>2</sup> area**

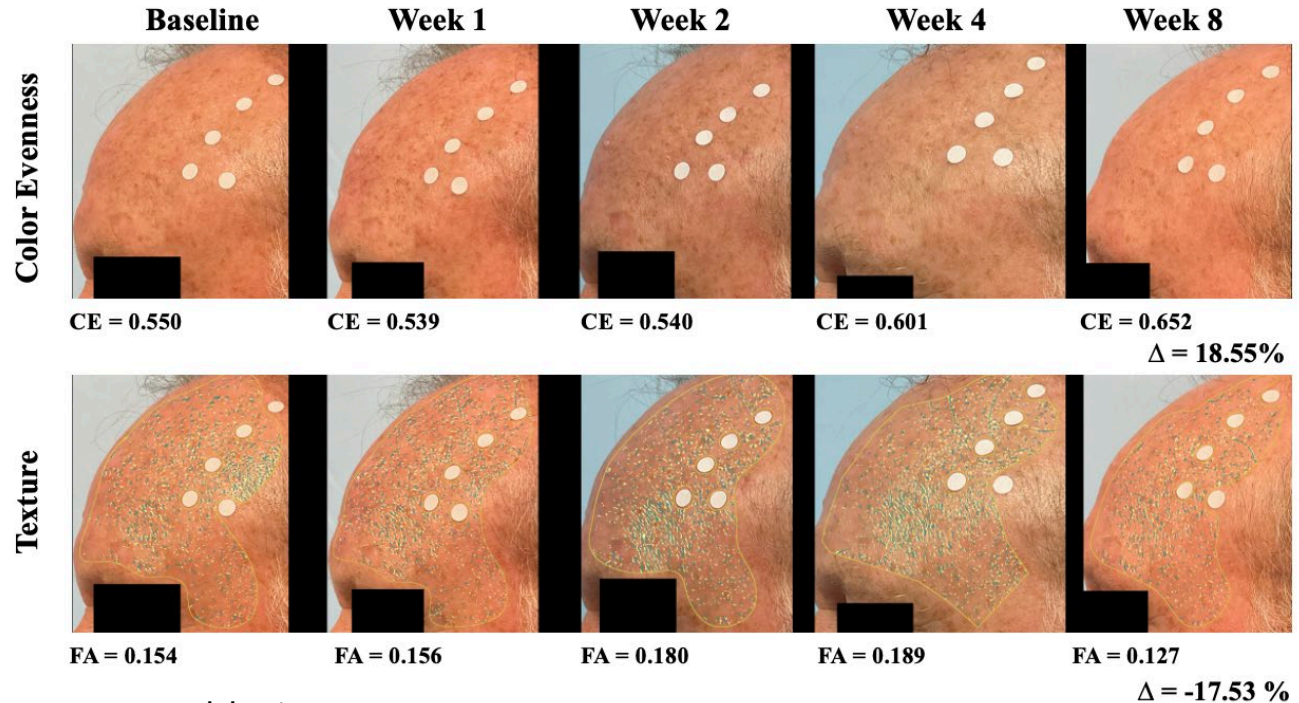
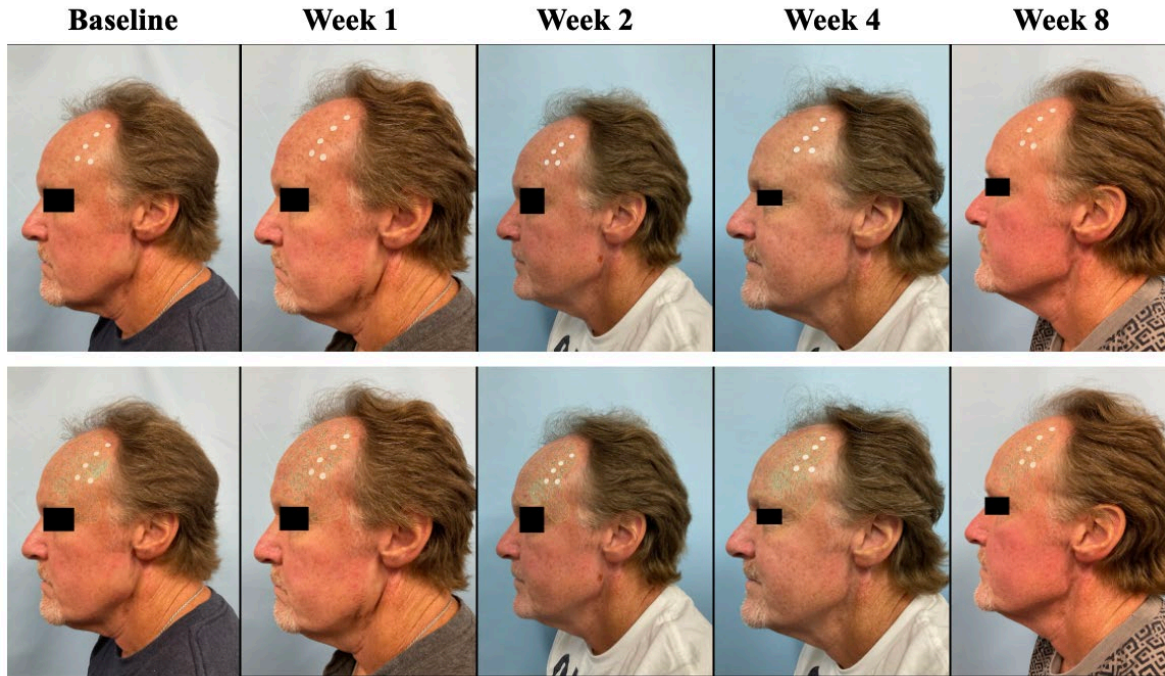


# PROAK Study: Clinician and Patient Treatment Satisfaction With Tirbanibulin

- At Week 8, a statistically significant difference was observed for Skindex-16 domains in all assessed subgroups
- Clinicians and patients reported high global satisfaction (mean scores of 74.9 and 72.0, respectively) at Week 24
- Overall skin appearance improved from baseline to Week 24 (83.6% clinicians; 78.5% patients)
- IGA success (IGA score of 0-1) was achieved by 71.9% of patients at Week 24 with a similar % at Week 8 (73.8%) suggesting a stable effectiveness over time



# Case Example #3 – 63-Year-Old Patient From the PROAK Trial



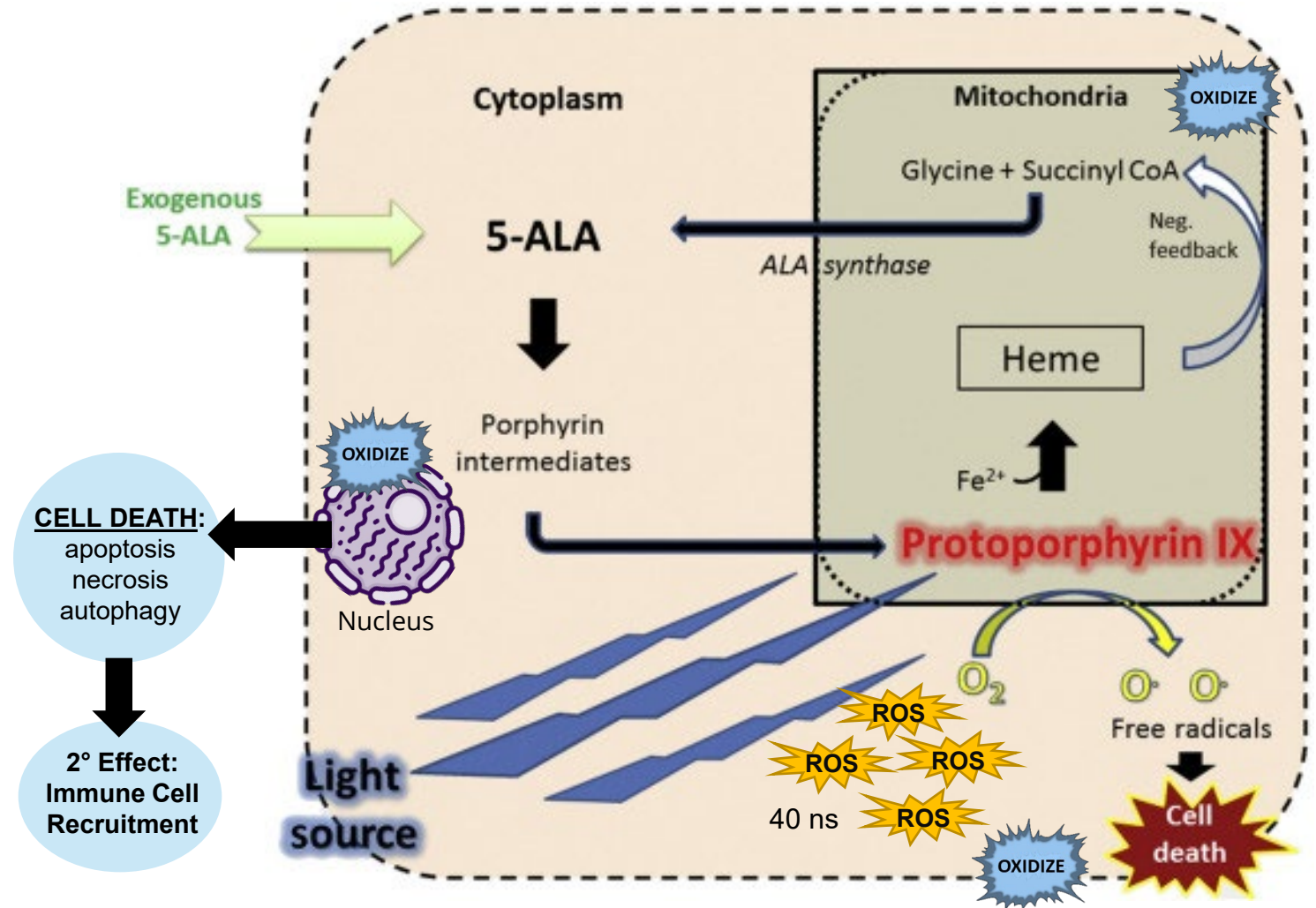
Images courtesy Dr. Schlesinger

- At entry into PROAK study: 8 AKs on the hands, arms, and scalp treated with cryosurgery
- Treatment: tirbanibulin 1% ointment for 5 days
- At 3 months: 5 AKs on the face and scalp treated with cryosurgery
- Results: cosmetic improvement in color evenness (CE) (18.55%), decreased unevenness in skin texture (-17.53%)



# Photodynamic Therapy Mechanism of Action

- Topical 5 aminolevulinic acid (ALA) is taken up by cells and converted to protoporphyrin IX (PpIX), a potent photosensitizer
- Precancerous, malignant, or fast-growing cells (sebaceous) selectively take up & converts ALA
- Light of appropriate wavelength activates PpIX ( $O_2$ ) leading to specific cell death
- Selective therapeutic benefit is due to selective application followed by the accumulation of PpIX in target cells



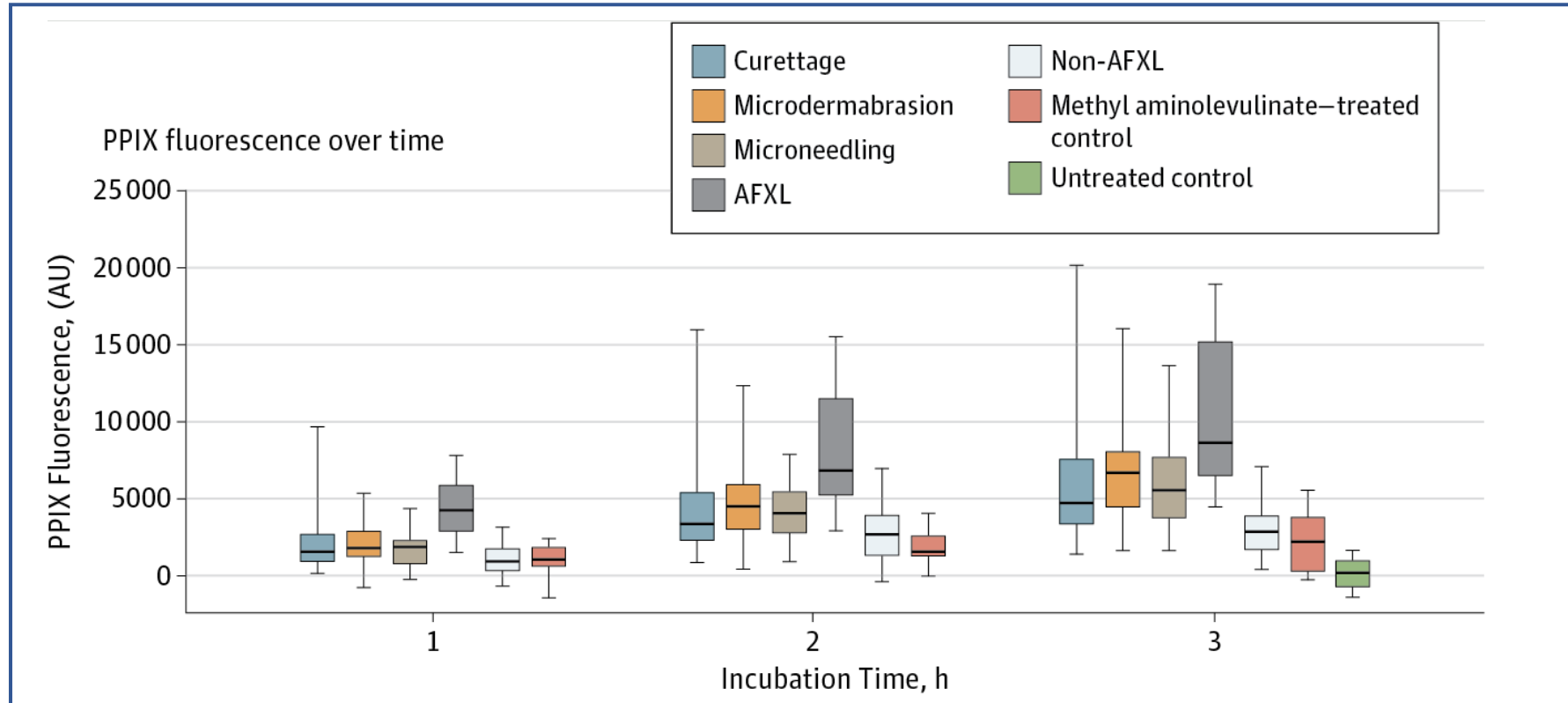
AK, actinic keratosis; ALA, aminolevulinic acid; PDT, photodynamic therapy; PpIX, Protoporphyrin IX, ROS, reactive oxygen species  
Sharma D et al. *Nanomaterials for Photodynamic Therapy*. Woodhead Publishing; 2023:41-54.

# Photodynamic Therapy Variables in Treatment

- Specific photosensitizer (Drug)
  - 20% ALA solution with blue light illumination
  - 10% ALA gel with red light illumination
- Skin Preparation
  - Microdermabrasion
  - Warming
- Incubation time
- Light source
  - Red vs. Blue
  - Laser
  - Daylight
- Indication
  - Actinic Keratosis
  - Off Label: Chemoprevention, NMSC, Acne, Aesthetic, Other



# Skin Preparation With Microdermabrasion



**Results:** PpIX fluorescence AFXL (8661 AU) > microdermabrasion (6731 AU), microneedling (5609 AU) > curettage (4765 AU) ( $P < .001$  among which similar enhancement was shown) >> non-AFXL (2898 AU), methyl ALA controls (2254 AU), and untreated (239 AU) ( $P < .03$ ).

# Skin Preparation With Warming

- **Study Design:**

- Upper or lower extremities treated with 20% ALA under occlusion. One extremity was heated during the 1-hour incubation.
- The median temperatures of the heated and control sides were 38.8°C and 29.4°C, respectively.

- **Results:**

- Median clearance for heated side was significantly greater than control side at 2 and 6 months ( $p < .0001$ ).
- Typical PDT side effects were greater on the heated side compared with control.

- **Conclusion:** Warming the skin during incubation of ALA improves efficacy of PDT and is well tolerated.

# Shortened Incubation Protocols

- **Study design:** Split-face study comparing 15-min incubation and 60-min versus conventional PDT (20% solution, 75 min, 100 sec Blue). Separate pain assessment study.
- **Results:**
  - 52% vs 44% reduction, maximum VAS was 0 vs 7.
  - Results from the pain assessment study were VAS of 0-2.
- **Conclusion:** In-office “painless” ALA-PDT with shortened incubation appears to be effective for removing actinic keratoses and is associated with little or no pain.

# No-Incubation Protocols With 20% ALA

- **Study design:**

- 20% ALA applied to face and/or scalp; on one side blue light started immediately and continued for 30, 45, or 60 min ("simultaneous PDT") vs. contralateral at 1-hour post-ALA for 1000 sec ("conventional PDT").

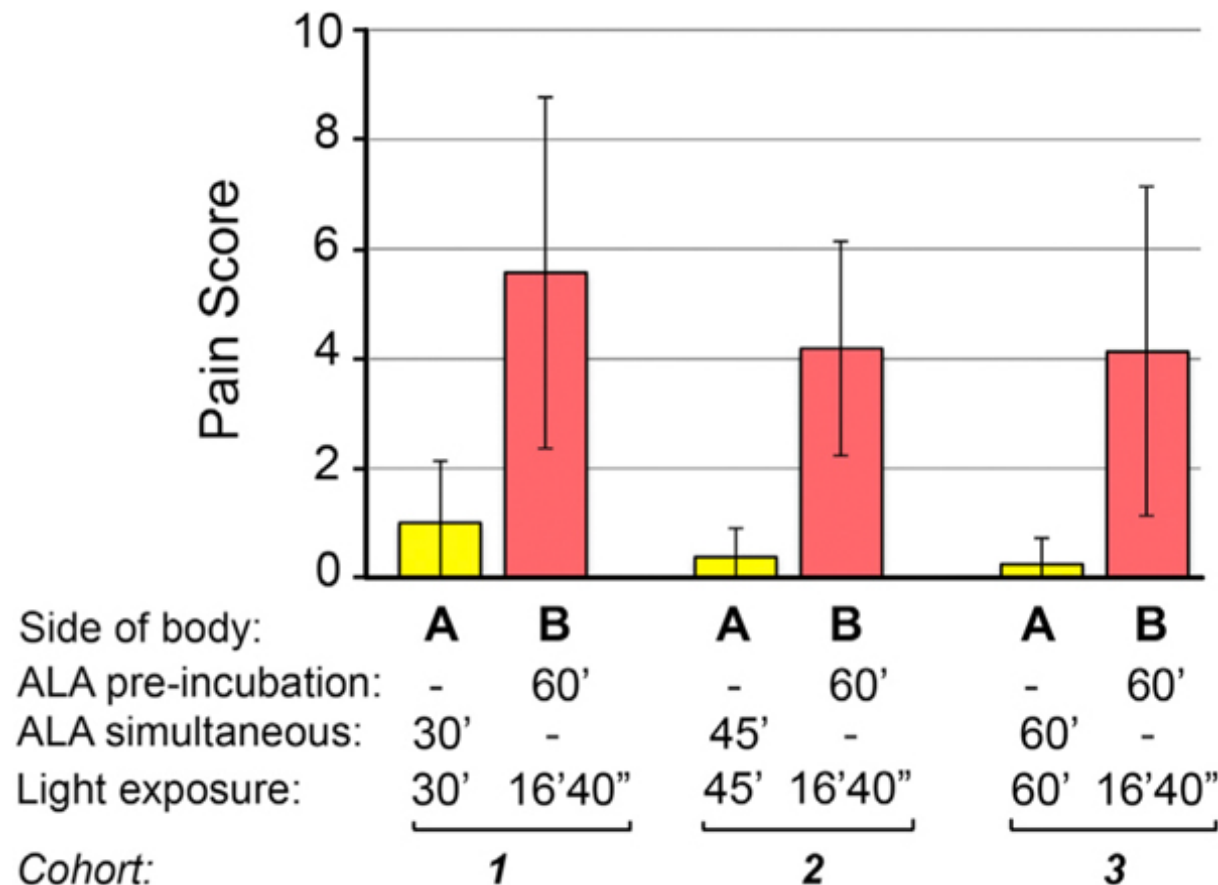
- **Results:**

- All patients experienced significantly less pain during simultaneous PDT (VAS = 0.52, vs. 3.57  $p < 0.001$ ).
- At 3 months, lesion clearance nearly identical on both sides, (57.7% vs 59.1%, face; 43.8% vs. 41.9%, scalp).

- **Conclusion:** The no-incubation PDT regimen is essentially painless yet provides treatment efficacy similar to a conventional regimen.

## Patient-Reported Maximum Pain Scores

Side A: simultaneous PDT; Side B: conventional PDT



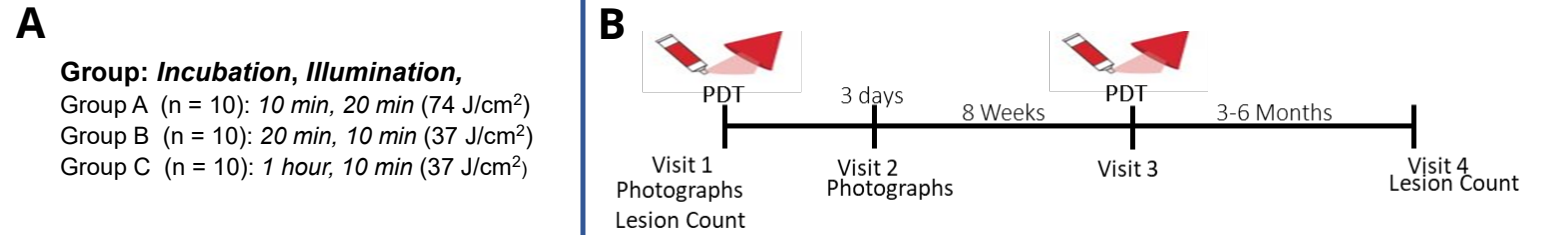
AK, actinic keratosis; ALA, aminolevulinic acid; PDT, photodynamic therapy; VAS, 10-point visual analog scale

Kaw U et al. *J Am Acad Dermatol*. 2020;82(4):862-868.

# Short Contact Protocols With 10% ALA-PDT

- In a prospective study of short contact (30-minute incubation) redlight PDT vs. indoor daylight PDT, Ruiz et al. found:
  - No difference in AK clearance or pain
  - Statistically significant difference in change in erythema (Red light = 0.6, indoor daylight = 1.1; change in erythema scale 0-4).<sup>1</sup>
- A randomized trial of short contact protocols by Johnson et al. found:
  - Reduction in AK lesions was non-inferior between Group A and C. Group B did not meet non-inferiority.
  - Pain in Groups A and B was significantly lower than for Group C.<sup>2</sup>

## Short Contact Protocol Treatment Groups (A) and Visit Schedule (B) <sup>2</sup>



## Short Contact Protocol Patient Photos from Group A and Group C <sup>2</sup>



AK, actinic keratosis; ADR, Adverse Drug Reaction; ALA, aminolevulinic acid; PDT, photodynamic therapy

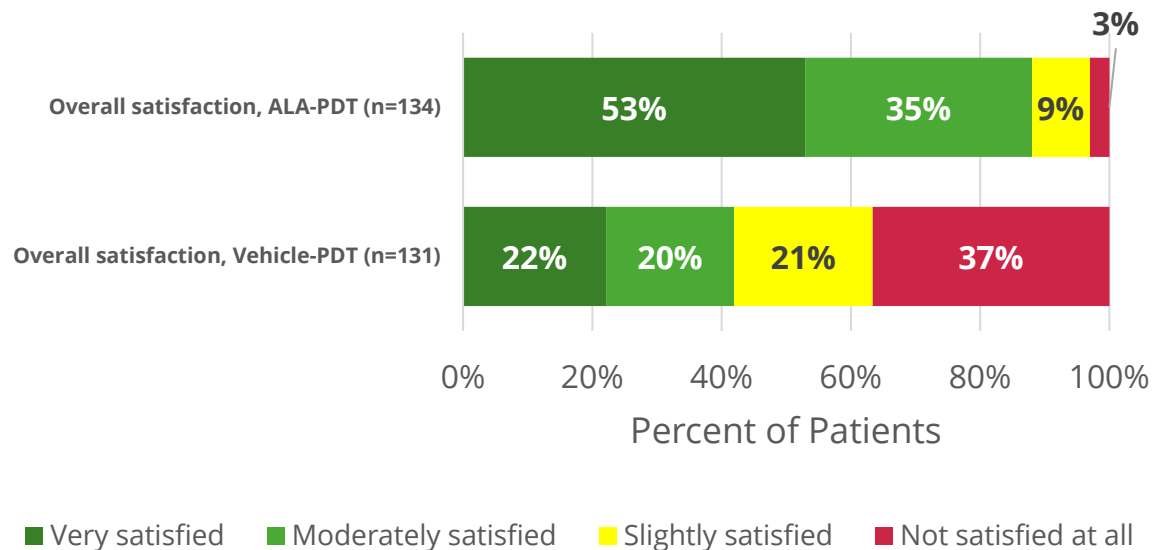
1. Ruiz AJ et al. *Skin Health Dis.* 2023;3(4):e226.

2. Johnson J et al. Fall Clinical Dermatology Conference 2024. Las Vegas, NV. October 24-27, 2024.

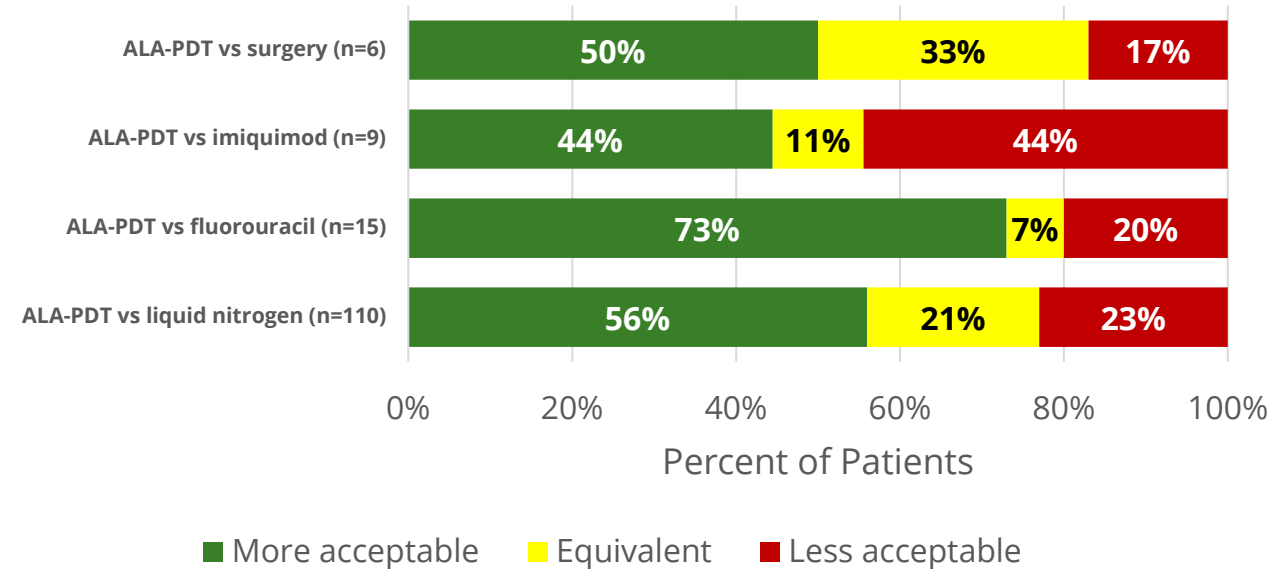
# Treatment Satisfaction With 20% ALA PDT

**Patients were satisfied with 20% ALA-PDT for the treatment of AKs of the face, scalp, and upper extremities and considered this to be equal to or more acceptable than prior treatments**

**Overall Patient Satisfaction  
With ALA-PDT at Week 12**



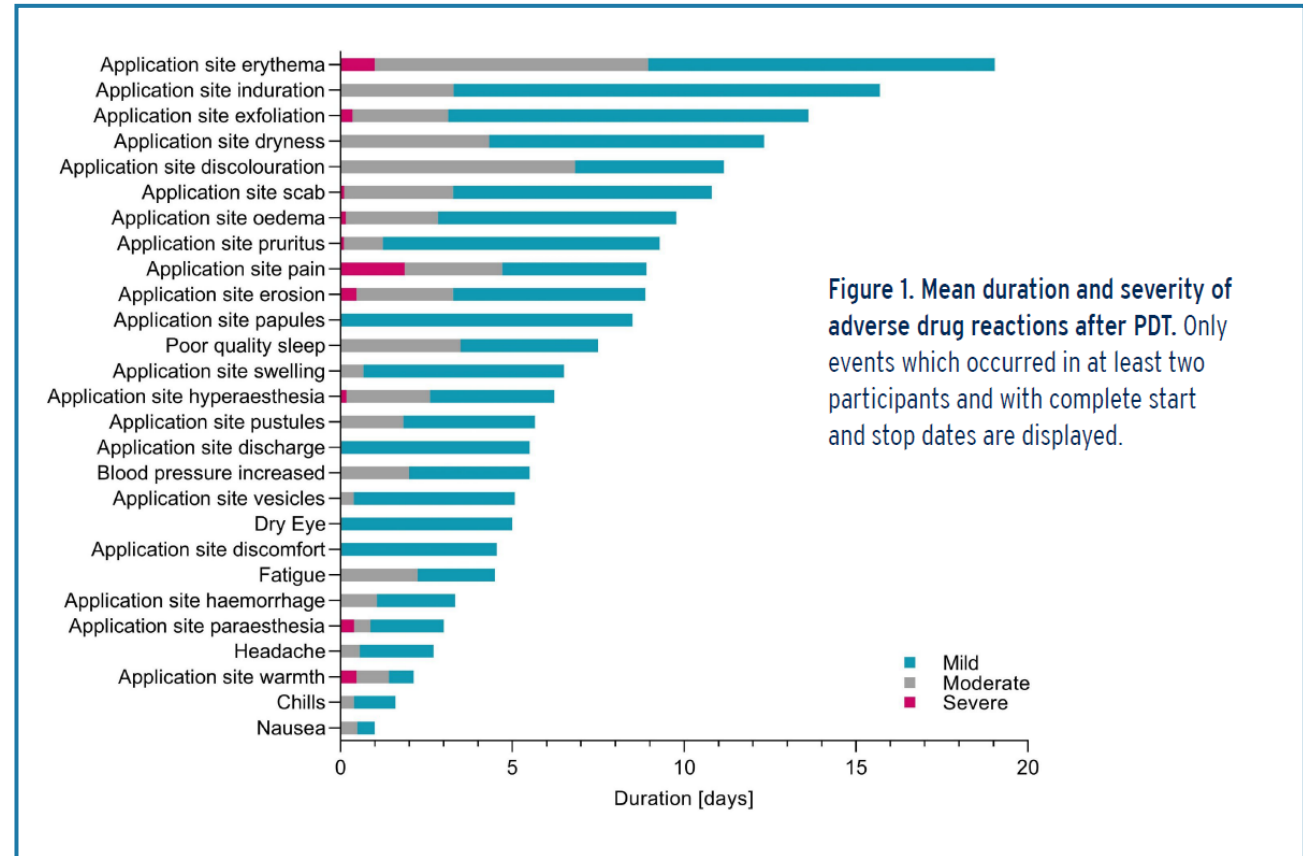
**Patient Satisfaction With ALA-PDT  
Compared to Prior Treatments**





# Large Field Actinic Keratosis Clearance With 10% ALA-PDT

- Recent FDA approval for use of up to 3 tubes of topical 10% ALA gel, allowing for large field treatment **which will also treat subclinical AK**
- ADRs at application site comparable to those of 20cm<sup>2</sup> treatment field
  - Mean duration of ADRs slightly prolonged (larger areas may need longer to recover)
- PDT procedure:
  - Did not affect body temperature or heart rate
  - Had no clinically significant effect on mean blood pressure
- Large field PDT with 10% ALA gel and red light was generally well tolerated



# Case #1



Image courtesy of Todd Schlesinger, MD

## Recommended treatment:

- 1<sup>st</sup> - Cryosurgery for higher grade Aks
- 2<sup>nd</sup> – Short contact PDT with aggressive skin preparation x 2
- 3<sup>rd</sup> – topical treatment with 5-FU 5% cream vs Imiquimod 5% cream vs. Tirbanibulin

## Case #2



Image courtesy of Todd Schlesinger, MD

### Recommended treatment:

- 1<sup>st</sup> – PDT – consider enhancing ALA activation with warming, occlusion and aggressive skin preparation – 2 treatments
- 2<sup>nd</sup> – topical treatment with 5-FU 5% cream or Imiquimod 5% cream

# Efficacy of 10% ALA and 20% ALA With Blue Light

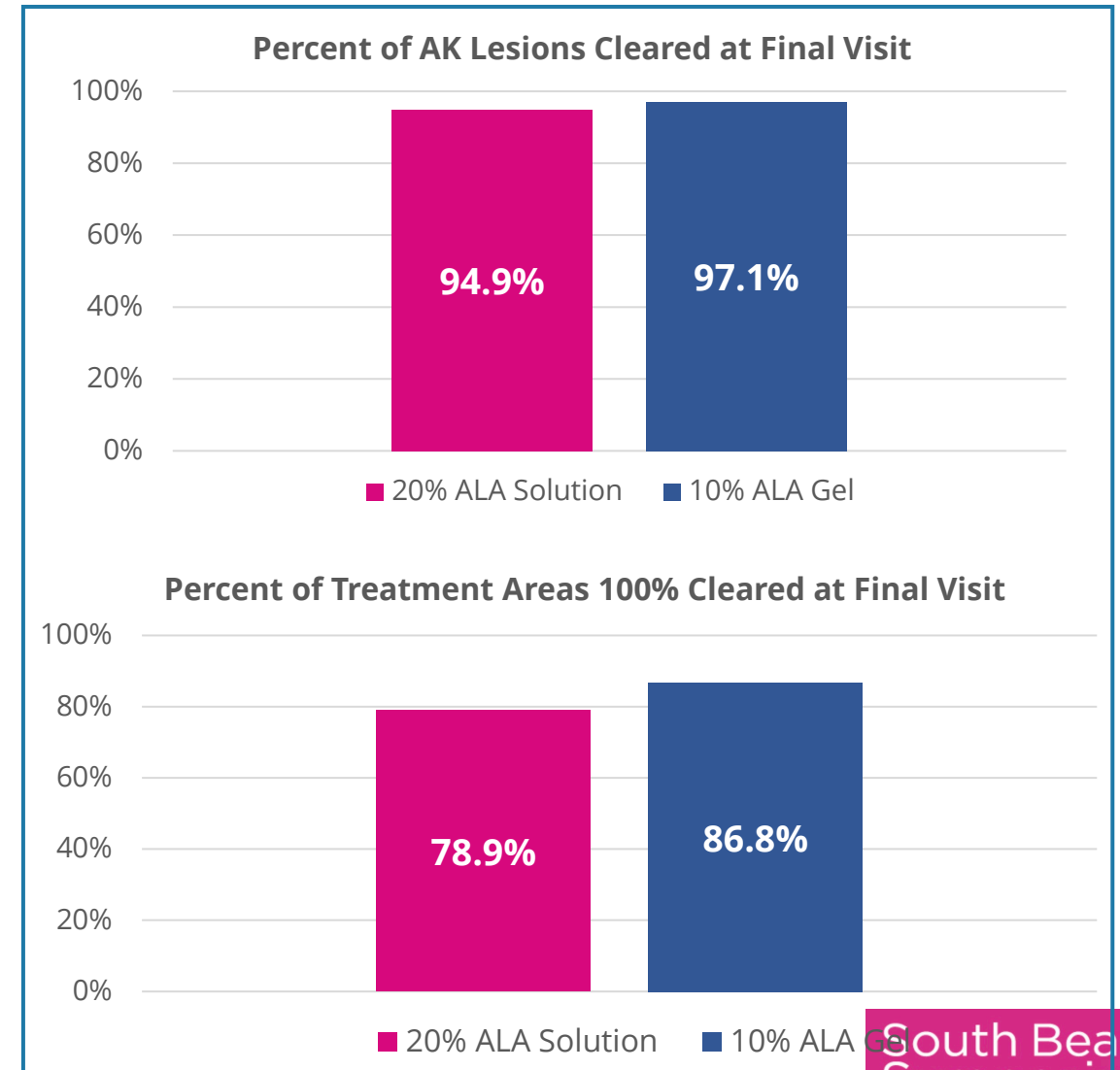
- **Study design:**

- Single-center double-blind trial; 4 – 8 AK 25-cm<sup>2</sup> contiguous field on each side of the face or scalp
- Contralateral of 10% ALA topical gel, and 20% ALA solution, (no curettage, 1hr incubation) with blue light for 1,000 seconds on Day 0 and Day 28.

- **Results:**

- In subject areas treated with 20% ALA solution , 57.7% of AKs were cleared by Day 28, increasing to 94.9% by Day 84 ( $p < 0.00001$ ).
- In subject areas treated with 10% ALA gel , 52.3% AKs were cleared at Day 28 increasing to 97.1% by Day 84 ( $p < 0.00001$ ).
- 78.9% of solution vs. 86.8% of gel subject areas showed 100% clearance at Day 84 ( $p < 0.0001$  Both groups)

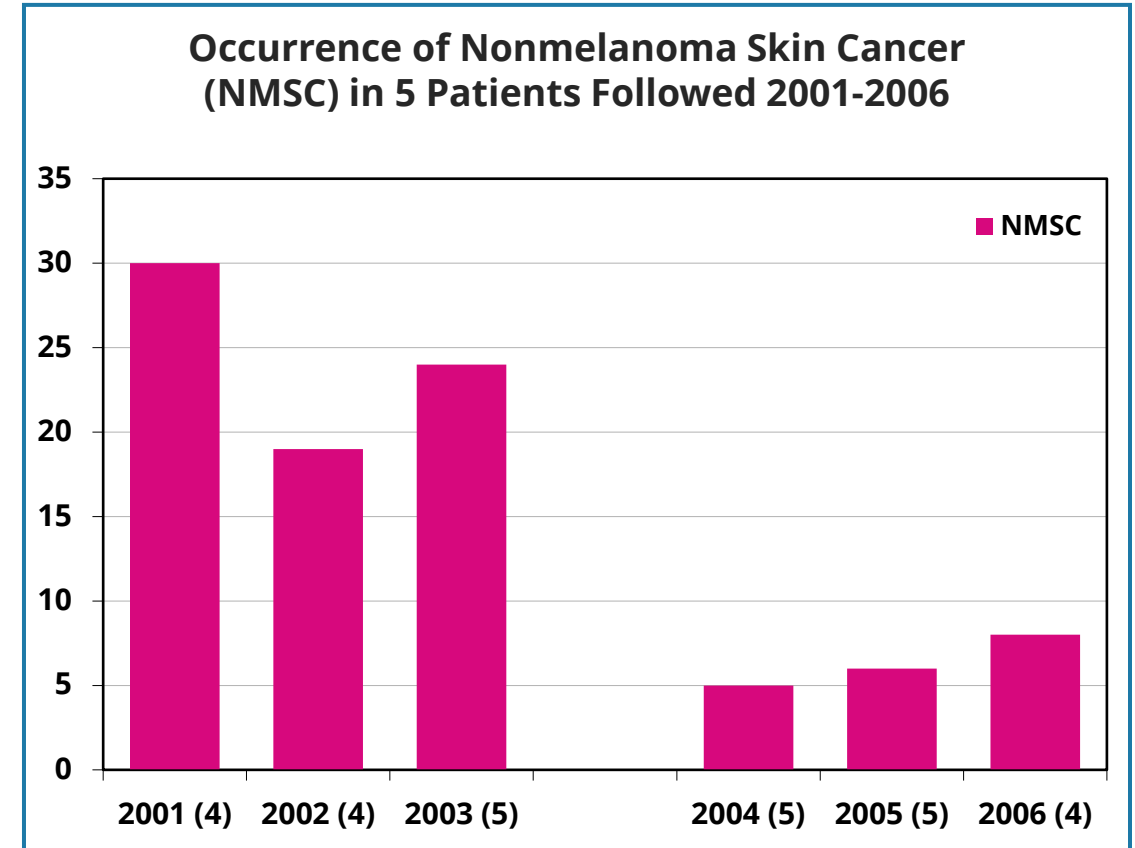
AK, actinic keratosis; ALA, aminolevulinic acid; PDT, photodynamic therapy  
Nestor MS, Berman B, Patel J, Lawson A. *J Clin Aesthet Dermatol*. 2019;12(3):32-38.



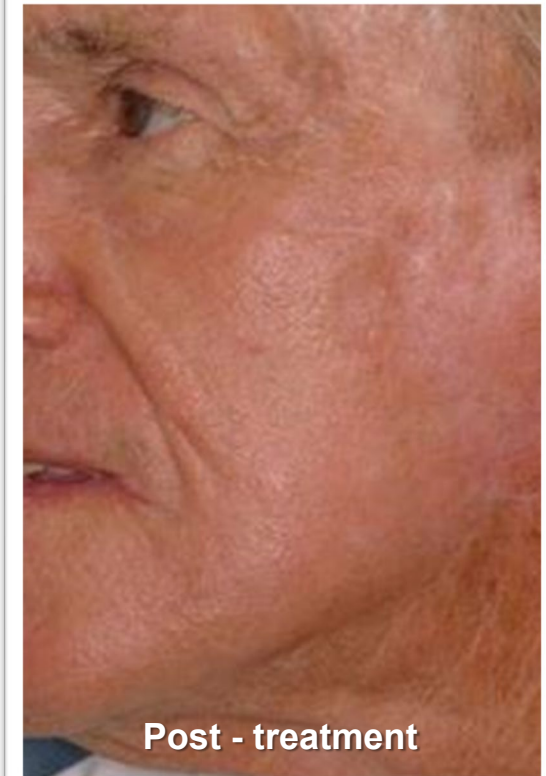
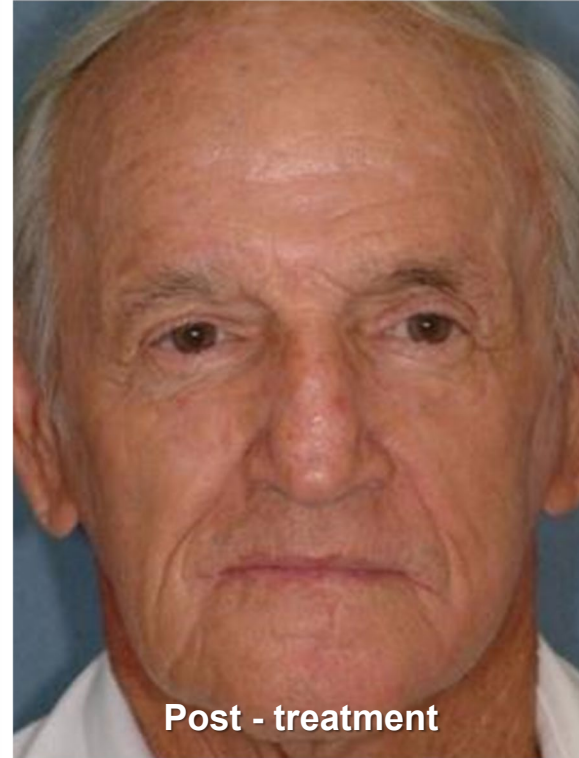
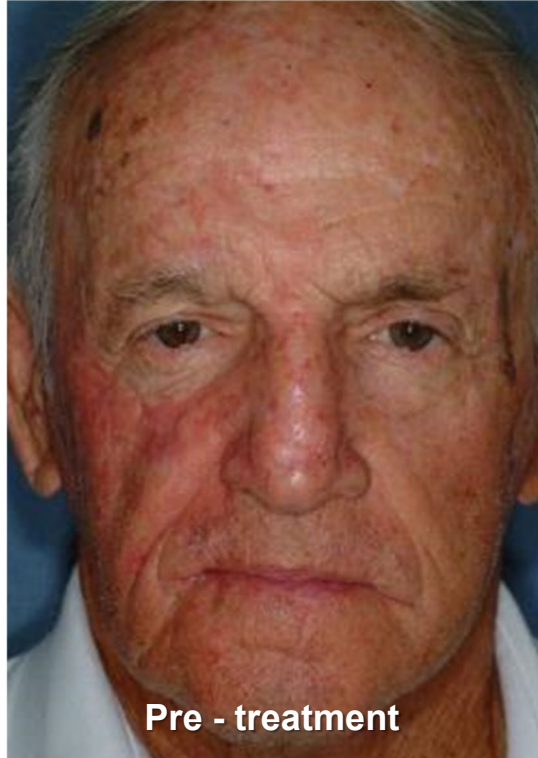


# Chemoprevention and PhotoDynamic Skin Rejuvenation

- 5 Severe CAD Patients (Immunocompetent)
- Followed 2000 – 2003
  - 72 facial NMSC (5.2/patient/year)
- Treated end of 2003: ALA 30–60 minutes – IPL/blue light
- Followed 2004 - 2005
  - 11 facial NMSC (1.3/patient/year)
  - Clinical improvement
- Conclusions: Effective chemoprevention short term
- Treatment of Actinic Keratosis with PDT has aesthetic benefit
  - Photodynamic skin rejuvenation combines the benefit of IPL (lentigines, telangiectasis, collagen remodeling) with the benefits of ALA (AK and sebaceous hyperplasia)
  - Supercharged Photorejuvenation



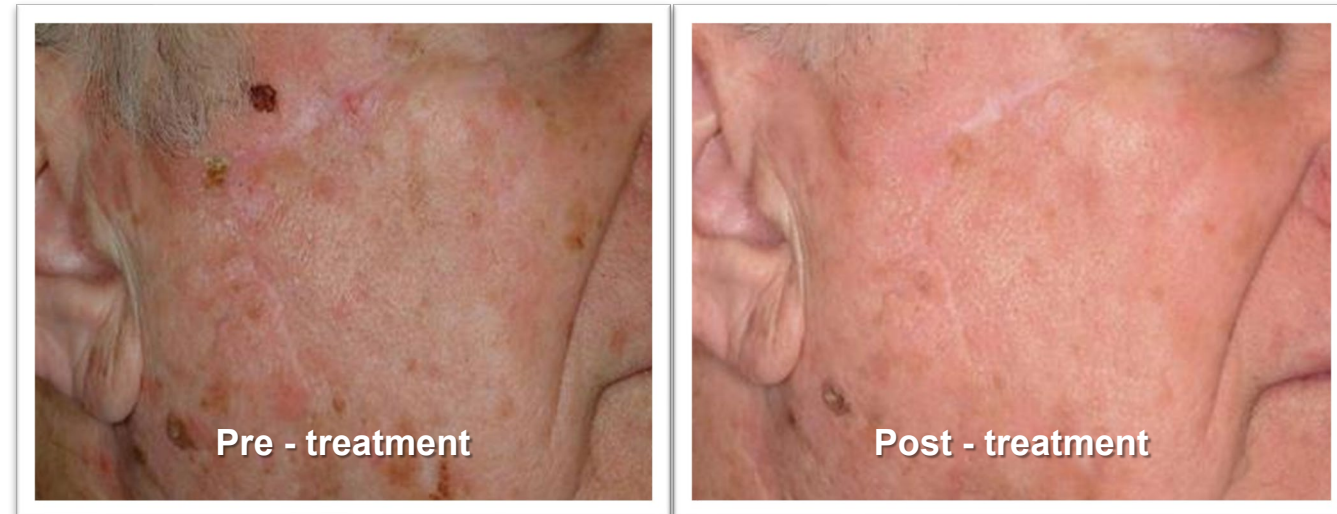
# PhotoDynamic Skin Rejuvenation



Images courtesy Dr. Nestor



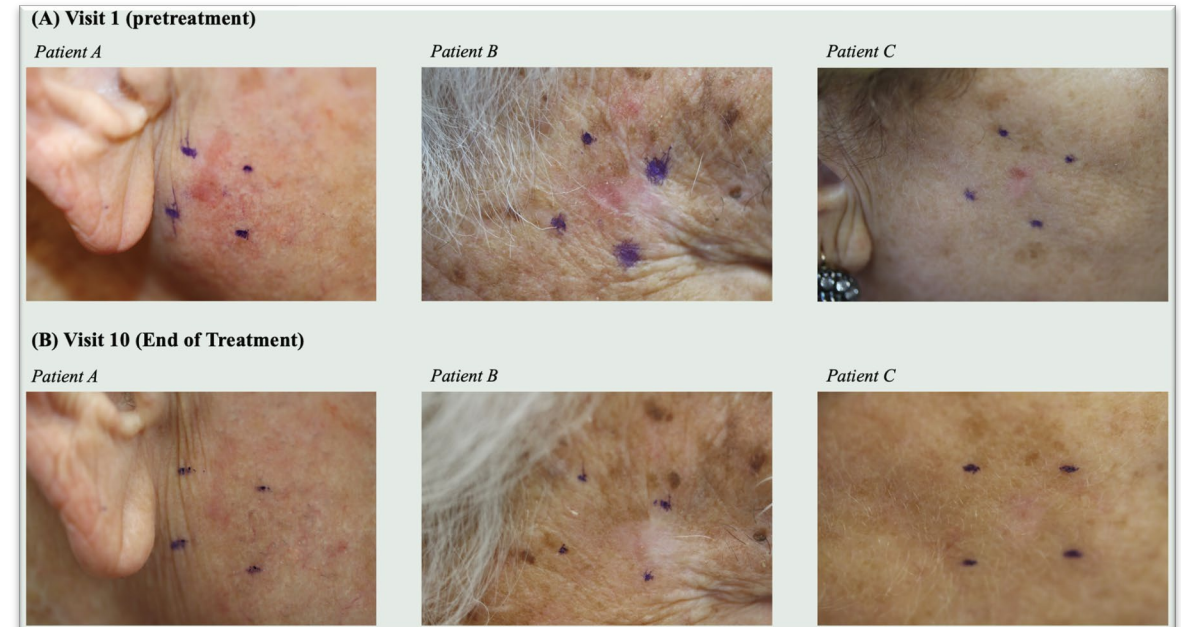
# PhotoDynamic Skin Rejuvenation



Images courtesy Dr. Nestor

# Aminolevulinic Acid 20% Solution PDT For Facial Squamous Cell Carcinoma *in situ* (isSCC)

- 30/32 patients with biopsy-confirmed, 0.4–1.3 cm, facial *isSCC* completed the study
- Lesion debrided with 4x4 gauze, ALA 20% topical solution applied & covered 18–24 hours, then blue light activation for 16 mins 40 secs at 10 J/cm<sup>2</sup>
- PDT repeated after 28 +/- 3 days and area excised 8 weeks later for histopathology
- Primary efficacy endpoint: 30/30 complete absence histologically of *isSCC* - **100%**
- Secondary efficacy endpoint: 30/30 clinical cure evaluation before excision - **100%**
- Local skin reactions – well tolerated, erythema, erosion/scaling, flaking/scaling peaking 1 day and 2 weeks after treatment, respectively. Greater after treatment 1.
- VAS (0–10) Mean Pain score was 2.71 +SD 2.77, 15 minutes after light treatment



# Phase 3 Efficacy of 10% ALA PDT in sBCC

	10% ALA gel	Placebo
<b>Complete clinical clearance (patients)</b>	83.4% (121/145)	21.4% (8/42)
<b>Complete histological clearance (lesions)</b>	75.9% (110/145)	19.0% (8/42)
<b>Patients achieving total clearance of all sBCC lesions</b>	64.1%	4.8%

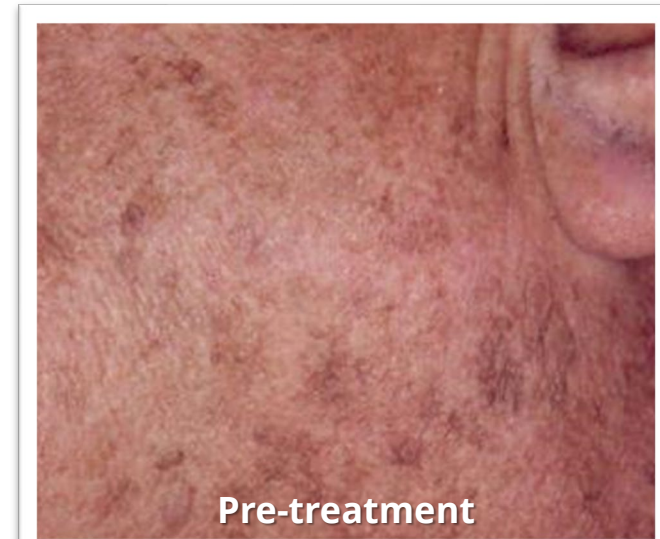
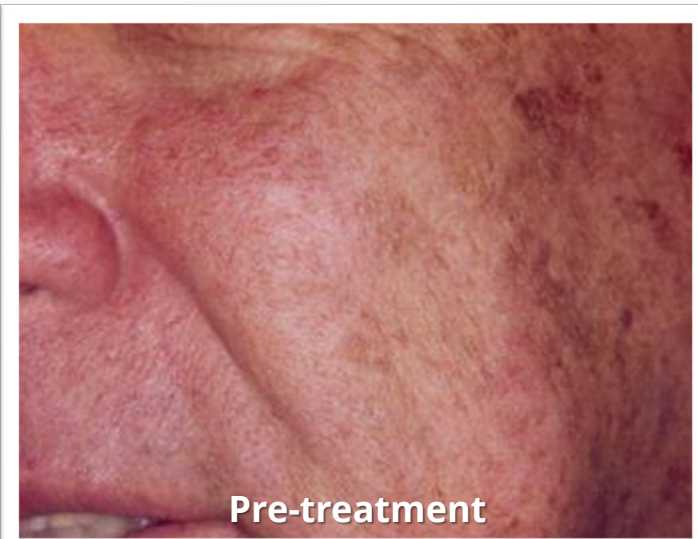
- 65.5% success with 10% ALA gel-PDT vs. 4.8% with placebo-PDT ( $p < 0.0001$ )
- Patients who received 10% ALA gel-PDT rated overall treatment satisfaction and aesthetic outcome as very good (64.3%) or good (22.2%)
- Correlates with European data- sBCC incorporated in the Summary of Product Characteristics

ALA, aminolevulinic acid; PDT, photodynamic therapy; sBCC, superficial basal cell carcinoma

<https://clinicaltrials.gov/study/NCT03573401>; GlobeNewswire. 2024. <https://www.globenewswire.com/news-release/2024/10/31/2972788/0/en/Biofrontera-Inc-Announces-Highly-Significant-Results-In-Phase-3-Study-Of-Ameluz-Photodynamic-Therapy-PDT-Regarding-The-Treatment-Of-Superficial-Basal-Cell-Carcinoma-sBCC.html>

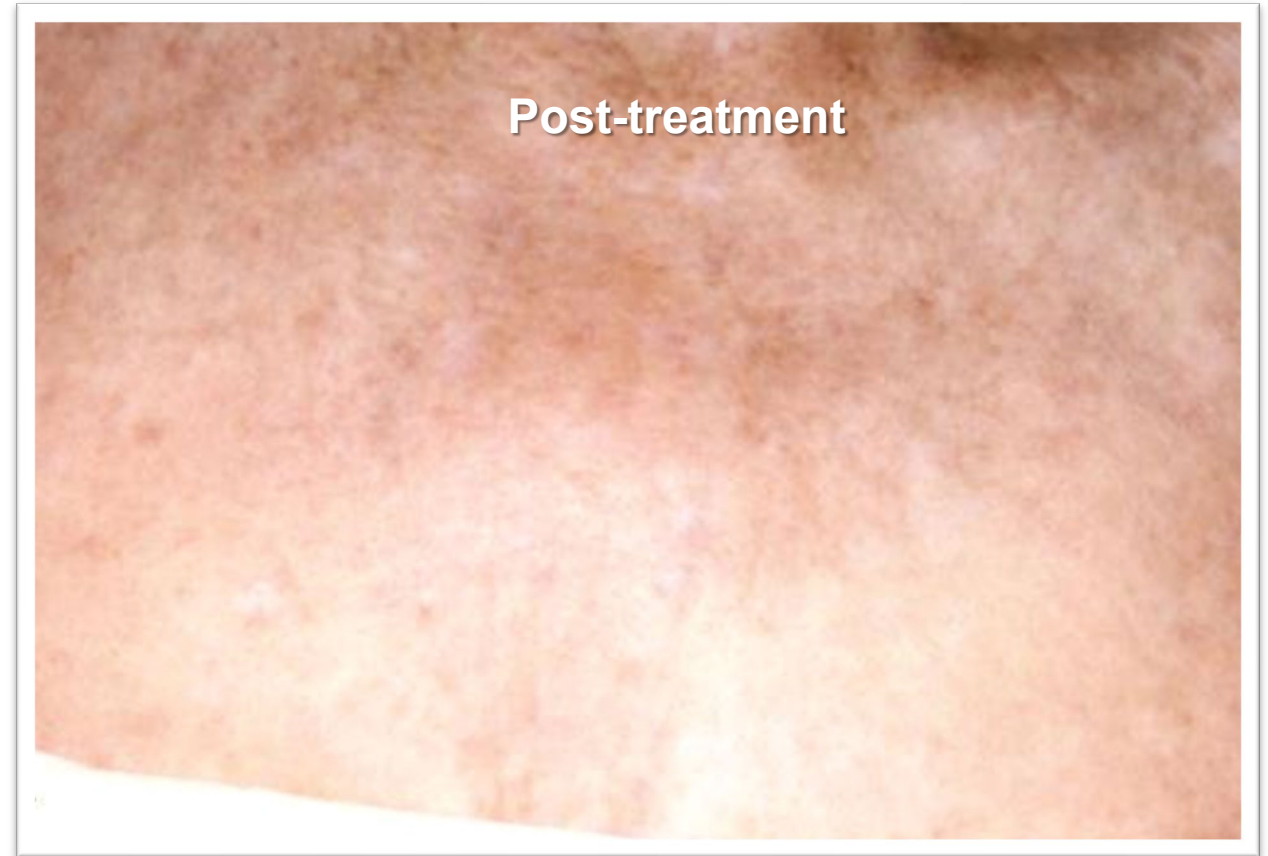
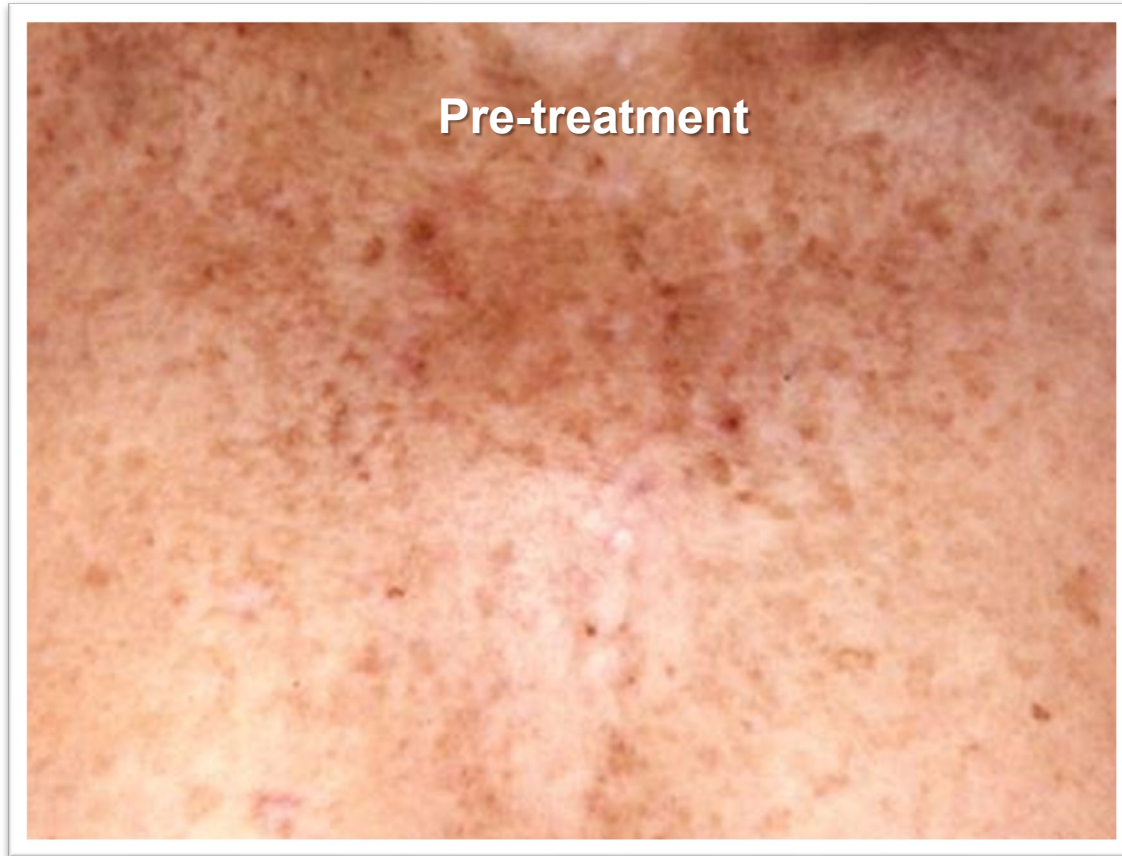


# Aesthetic – PhotoDynamic Skin Rejuvenation of the Face



Images courtesy Dr. Nestor

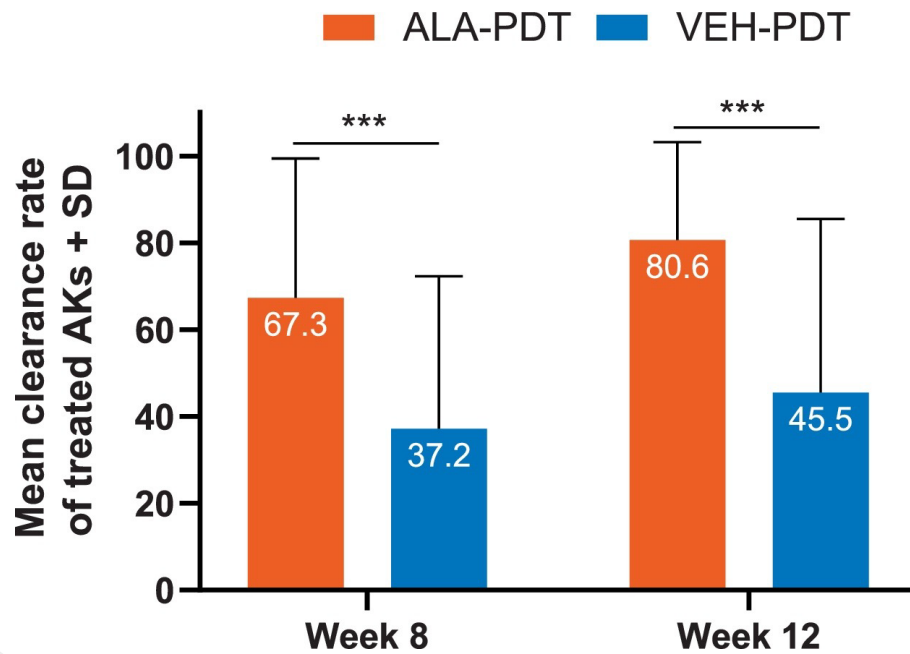
# Aesthetic – PhotoDynamic Skin Rejuvenation of the Chest



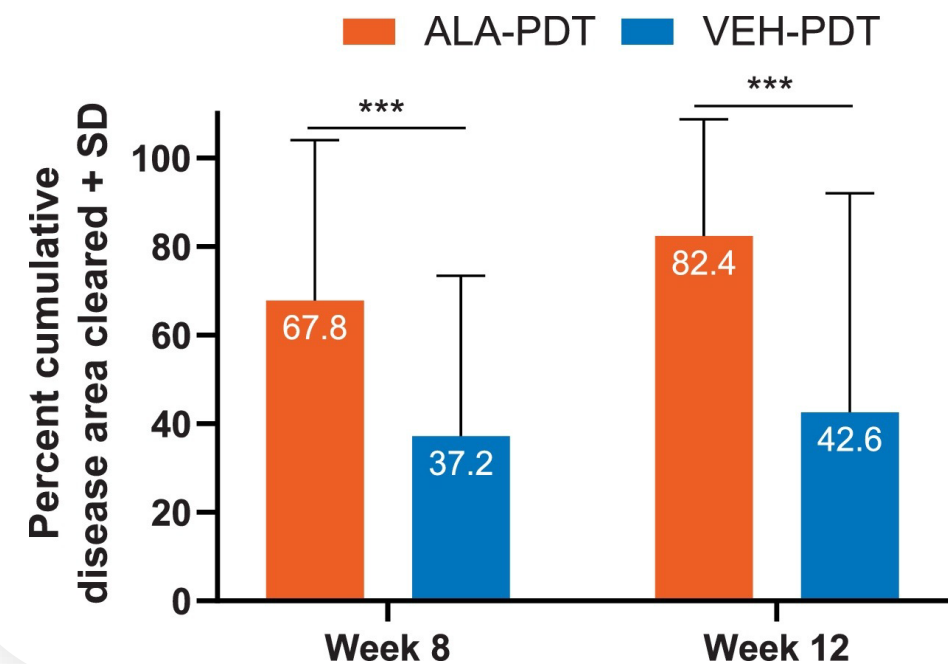
Images courtesy Dr. Nestor

# Upper Extremity Actinic Keratosis Clearance With 20% ALA-PDT

Significantly greater clearance of AK lesions (all sizes) and percent of cumulative disease area cleared at both weeks 8 and 12 following treatment with 20% ALA-PDT



\*\*\* $P < 0.0001$



\*\*\* $P < 0.0001$

AK, actinic keratosis; ALA, aminolevulinic acid; PDT, photodynamic therapy; VEH, vehicle; SD, standard deviation  
Berman B et al. *Photodiagnosis Photodyn Ther.* 2020;32:102013.



# Summary

- **AK is more prevalent, and is a chronic disease that requires ongoing therapy**
- **Field therapy is a better option and best used in combination (best practice)**
- **Topical therapy seems to indicate promising results**
- **PDT has come a long way from 10% gel or 20% solution**
  - **Treatment associated with low or no pain**
- **Future – treating superficial skin cancer**

