

Optimising Topical Treatment for Skin Cancer



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Skinspots

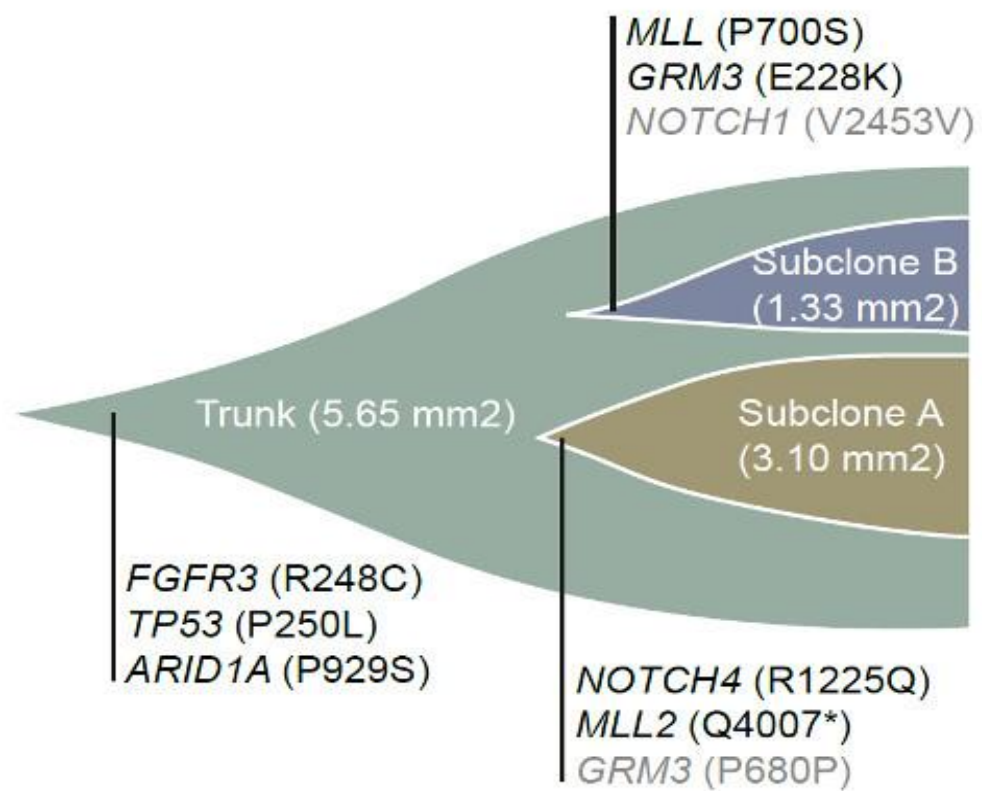
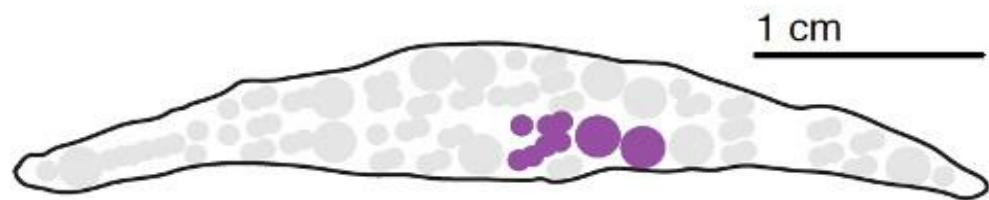
skin cancer clinic

SKIN CANCER
COLLEGE
AUSTRALASIA



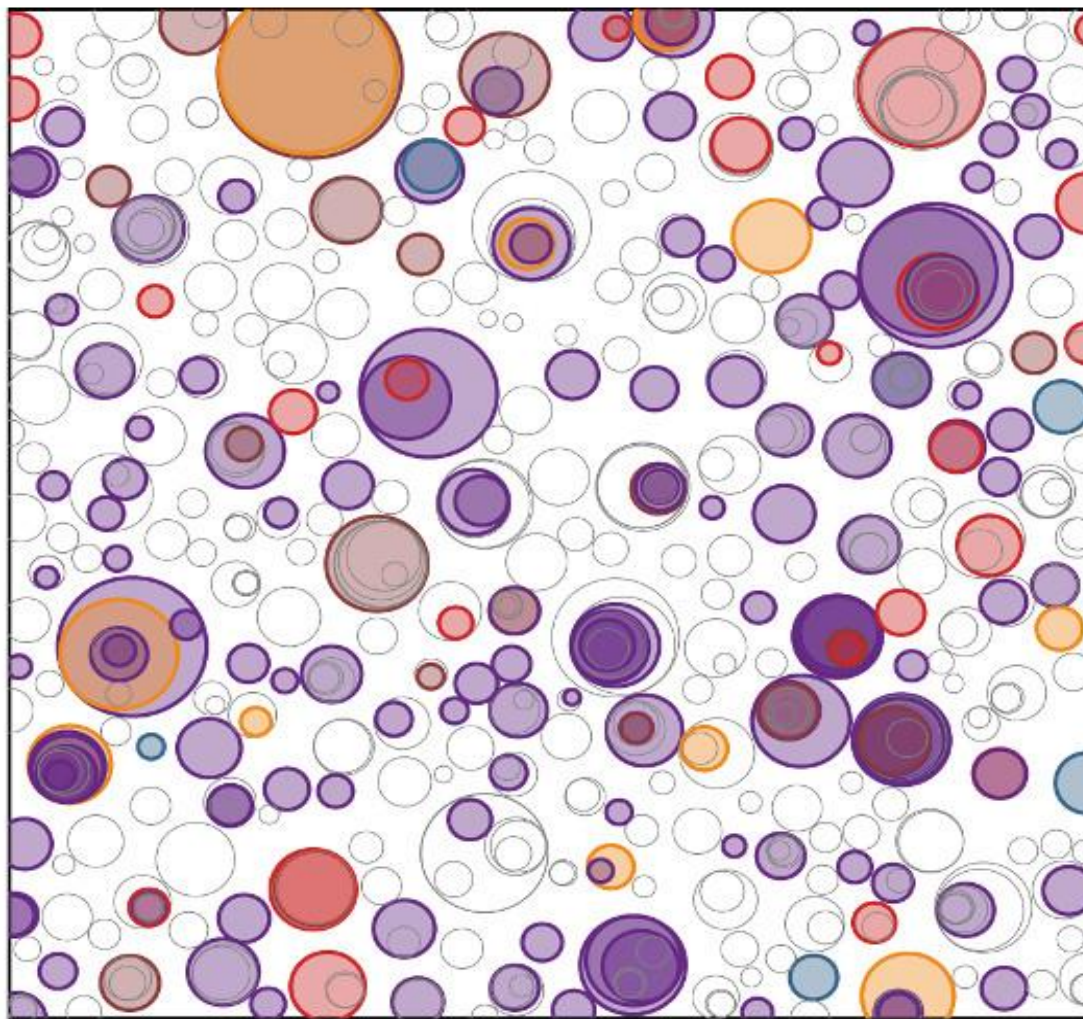






- | | | |
|------------|---------|---------|
| ■ NOTCH1-3 | ■ TP53 | ■ FGFR3 |
| ■ FAT1 | ■ RBM10 | □ Other |

1 mm



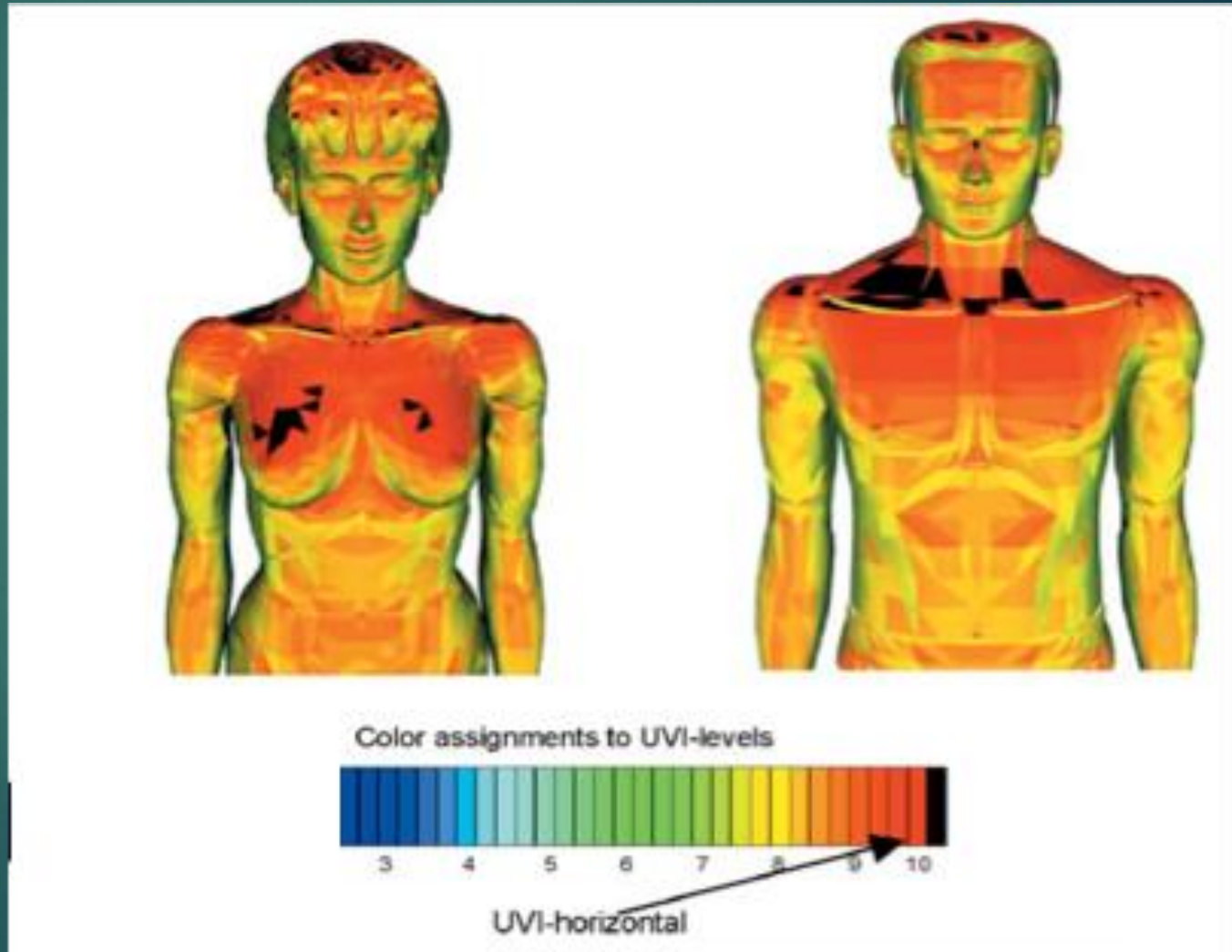
Skin what skin.....

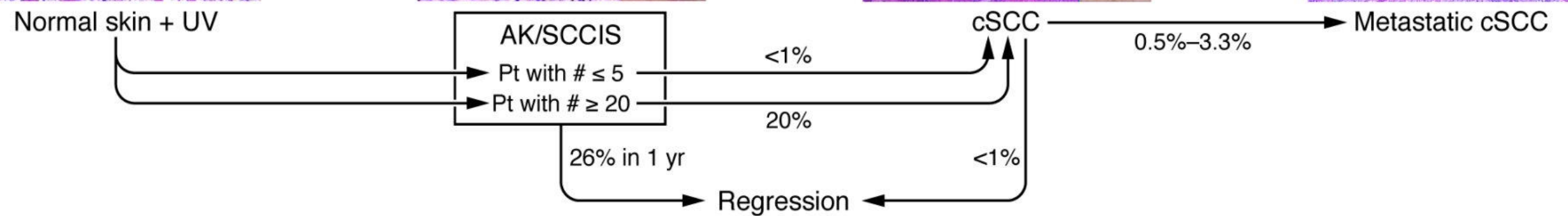
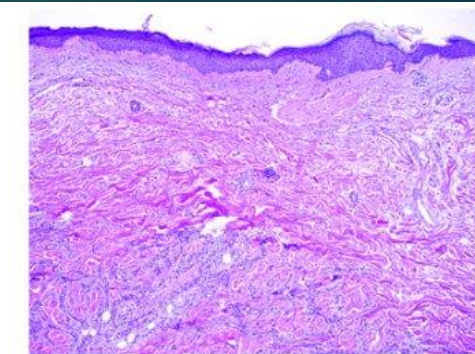
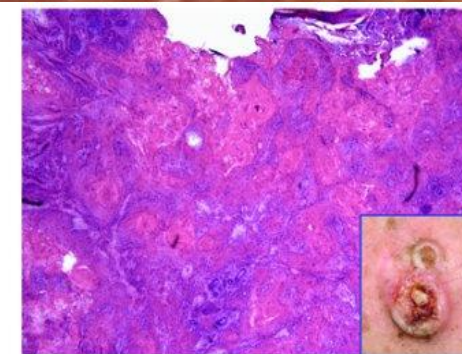
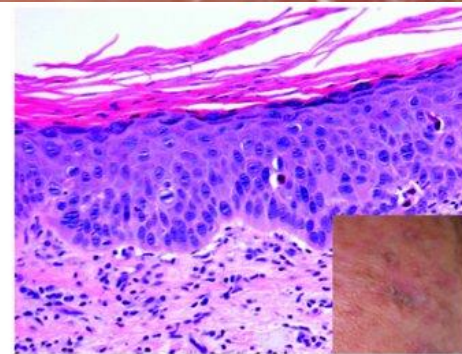
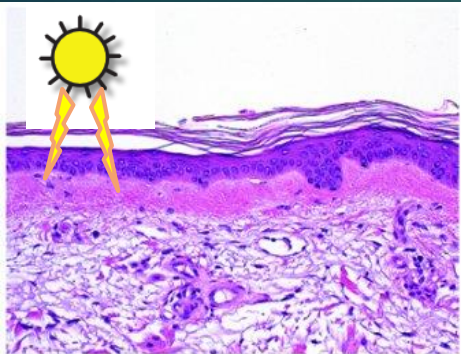
25 percent of clinically normal skin cells carried at least one mutation linked to cancer.

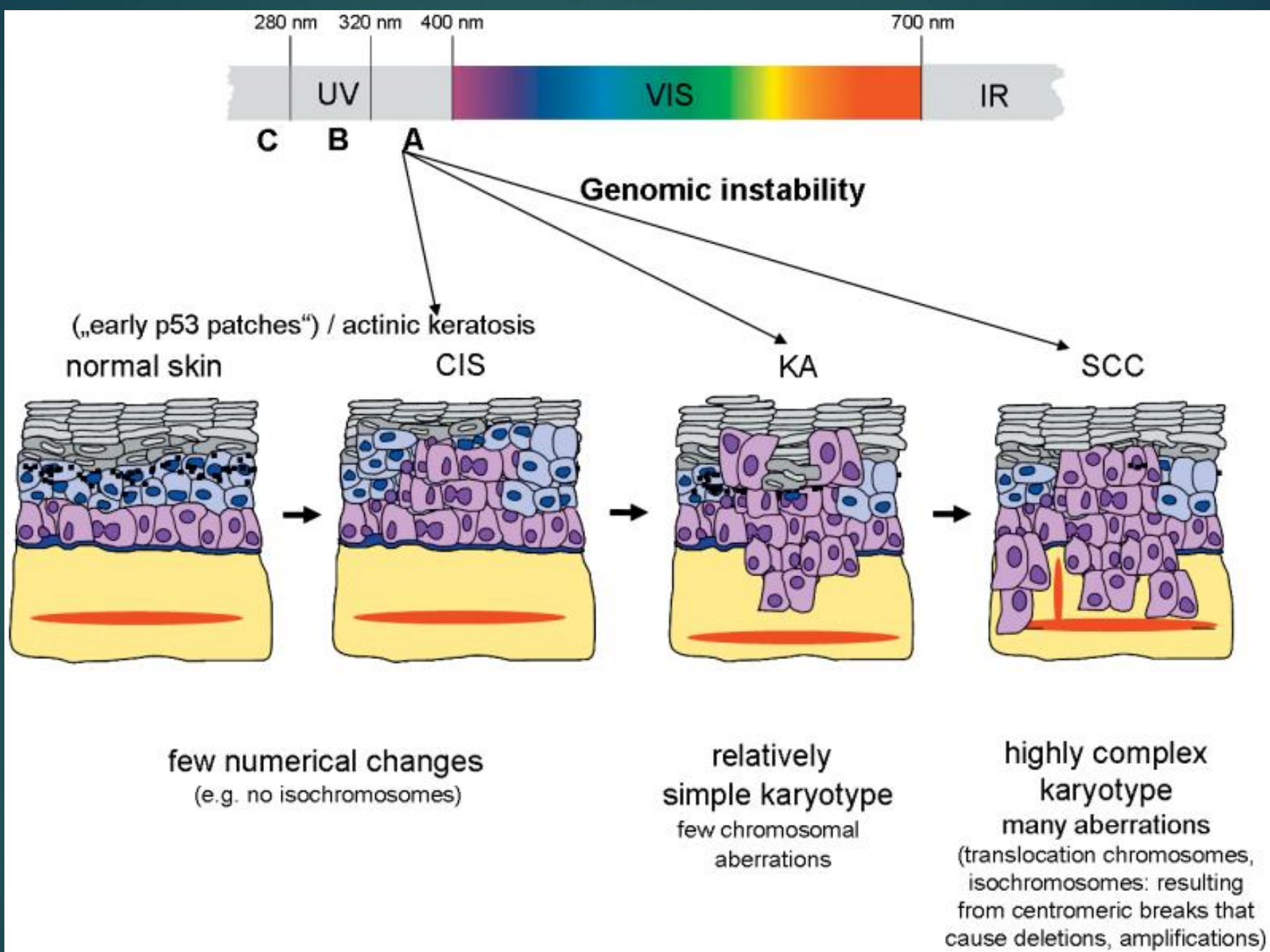
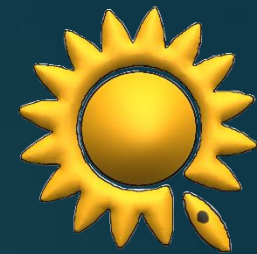
100 potentially cancer-causing DNA mutations in every 1 square cm

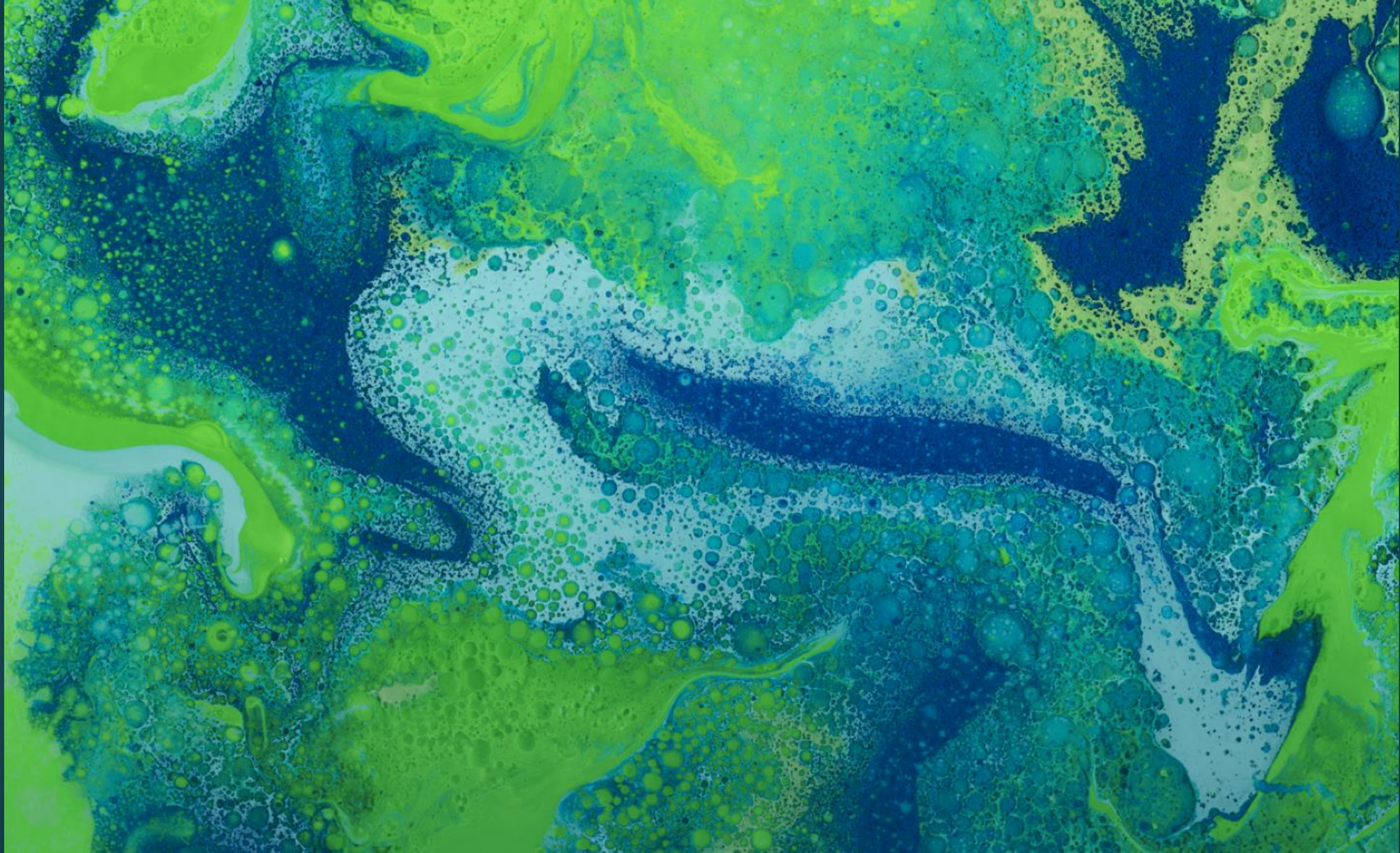
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Vol. 348 no. 6237 pp. 880-886

History of sun exposure is reflected on the skin for life.....











What to treat Treat

- ▶ Both local and field-directed treatments to reduce the subsequent emergence of AKs and squamous cell carcinomas from the treatment area by removing keratinocytes with malignant potential.

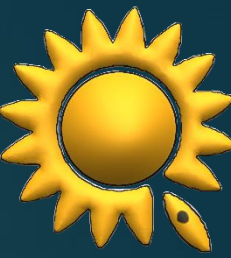
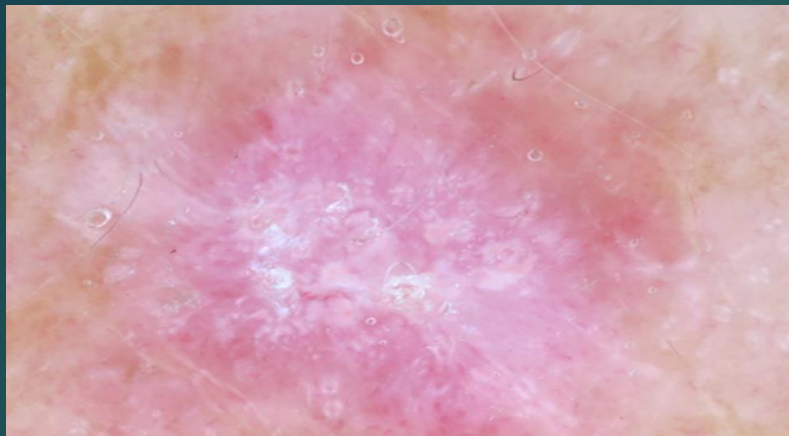
Lesion

or

Field treatment



Rx Spot



Rx
the problem





The Ideal treatment

- ▶ Selective destruction of malignant /abnormal cells
- ▶ Minimal destruction of normal cells (no scars)
- ▶ Minimal systemic effects
- ▶ Treatment of precursor cells
- ▶ Safe and easy to apply by patient
- ▶ CHEAP



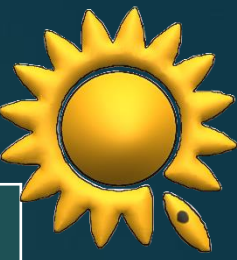
Topical treatment



- ▶ Compliance is poor
- ▶ Labour/time intensive
- ▶ Patients don't like it
- ▶ Doc's don't like it

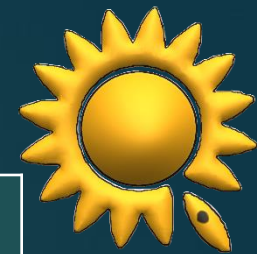


Lesion-directed treatment



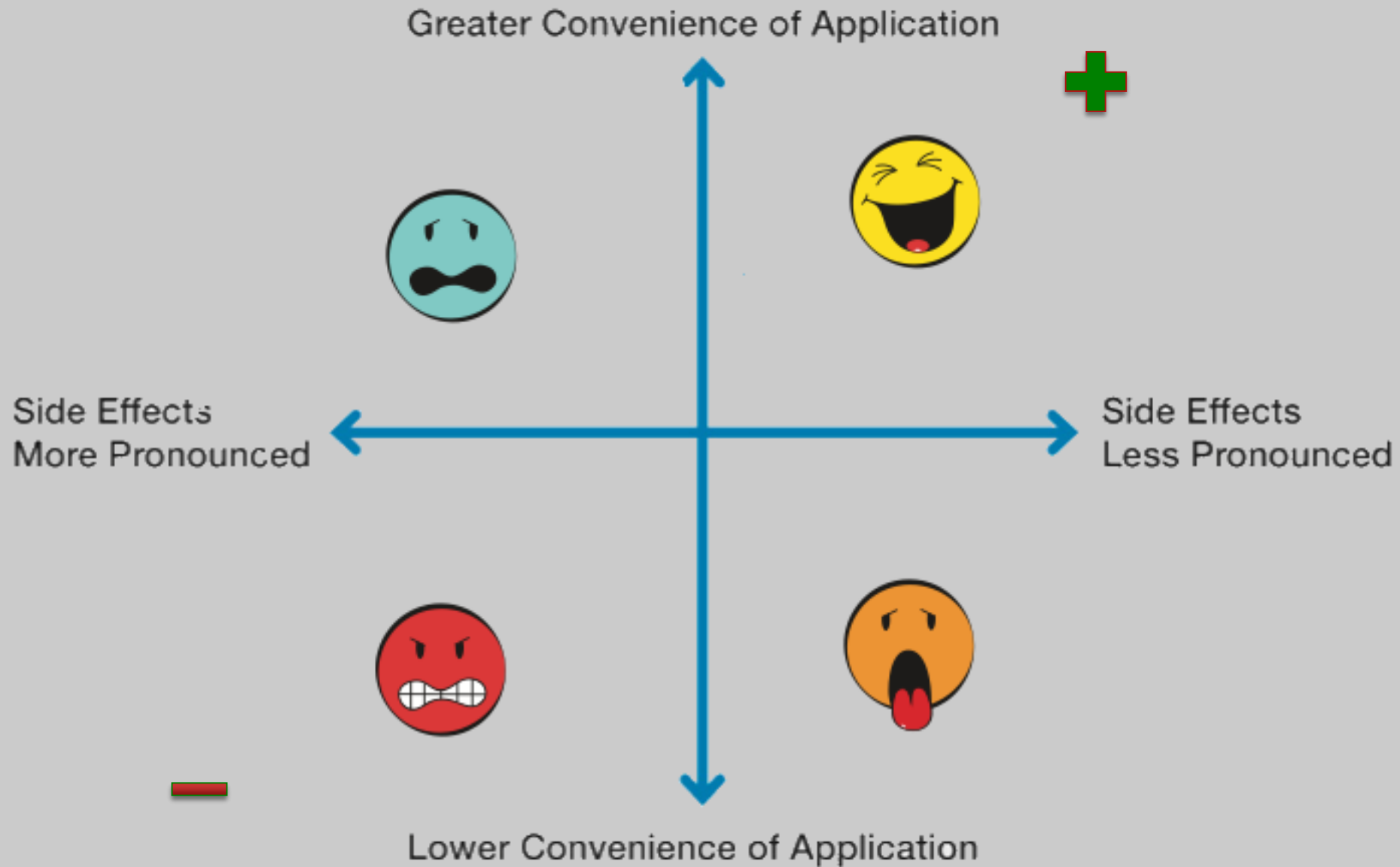
Treatment	Response	Recurrence
Cryosurgery (liquid nitrogen)	75–98%	1.2–50%
Laser therapy	*90%	10–15%
Curettage/excision/ shave biopsy	Margin taken?? Field damage	Margin taken?? Field damage

Field-directed therapy

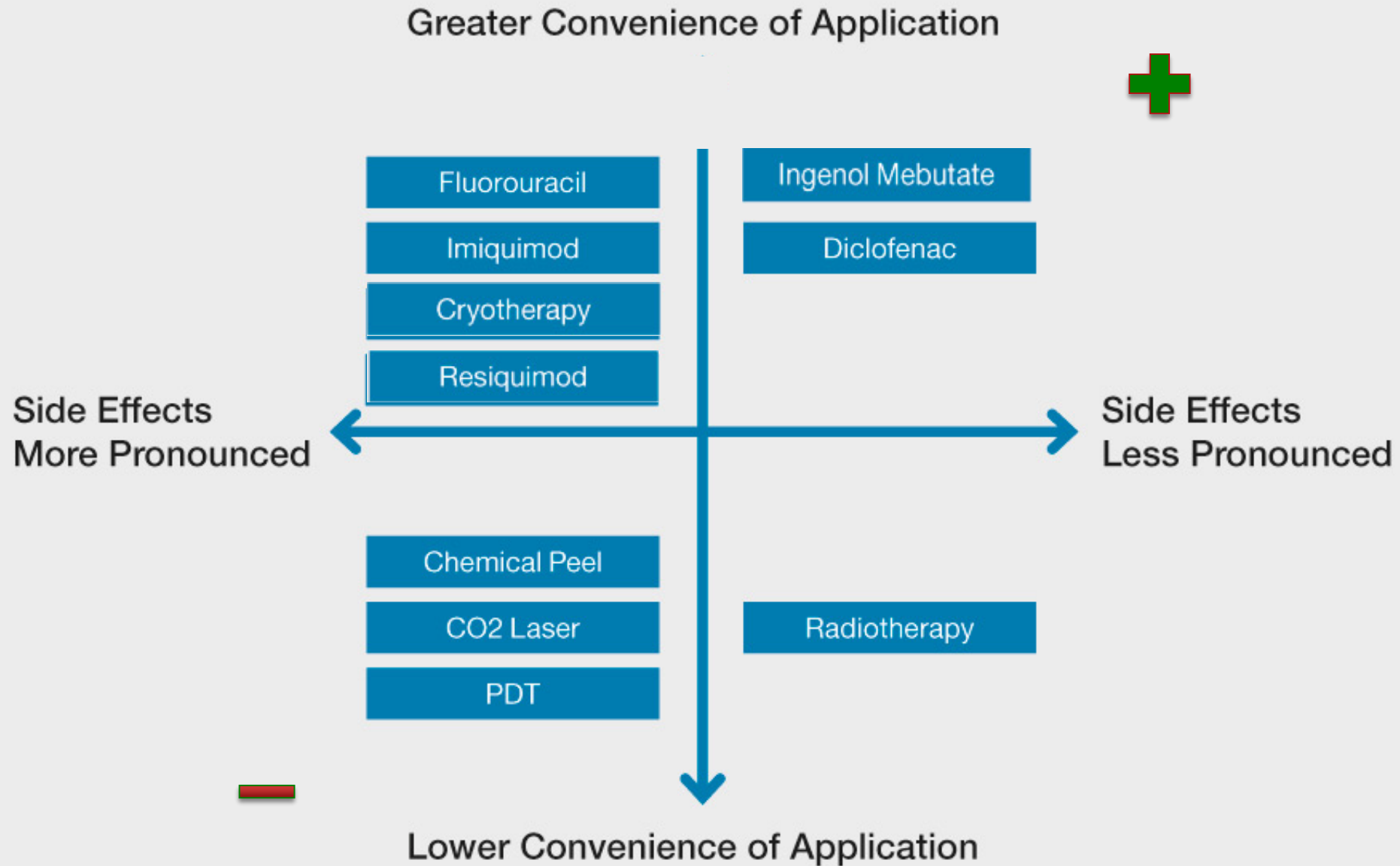


Treatment	Response	Recurrence
Ingenol mebutate	34.1–42.2% ^b	44.6–67.6%
Topical 5-FU	50%	55%
Imiquimod 5%	55–84%	10%
Diclofenac 3% gel	50–79%	?
Topical photodynamic therapy	70–90% ^c	

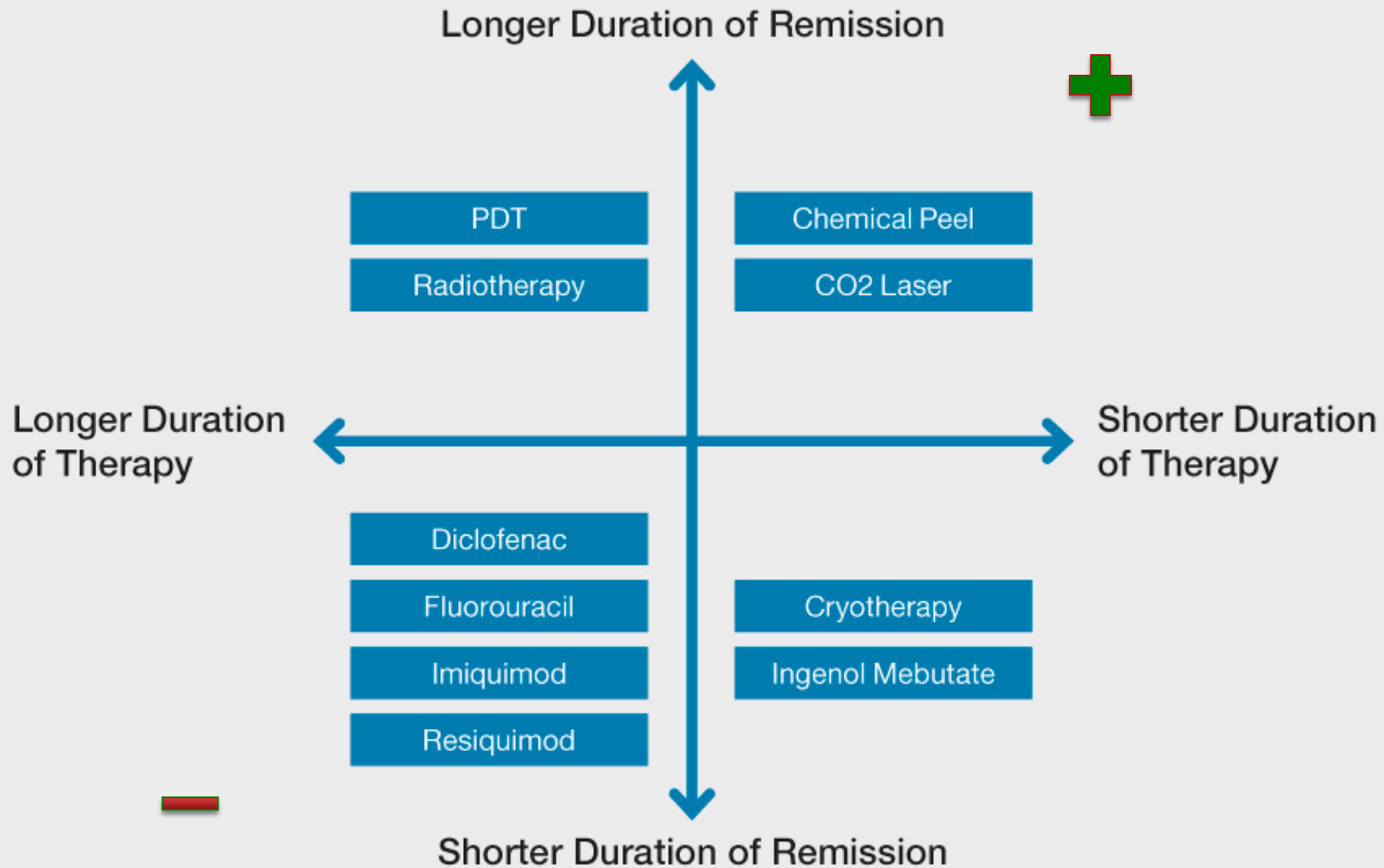
Side Effects and Convenience of Application



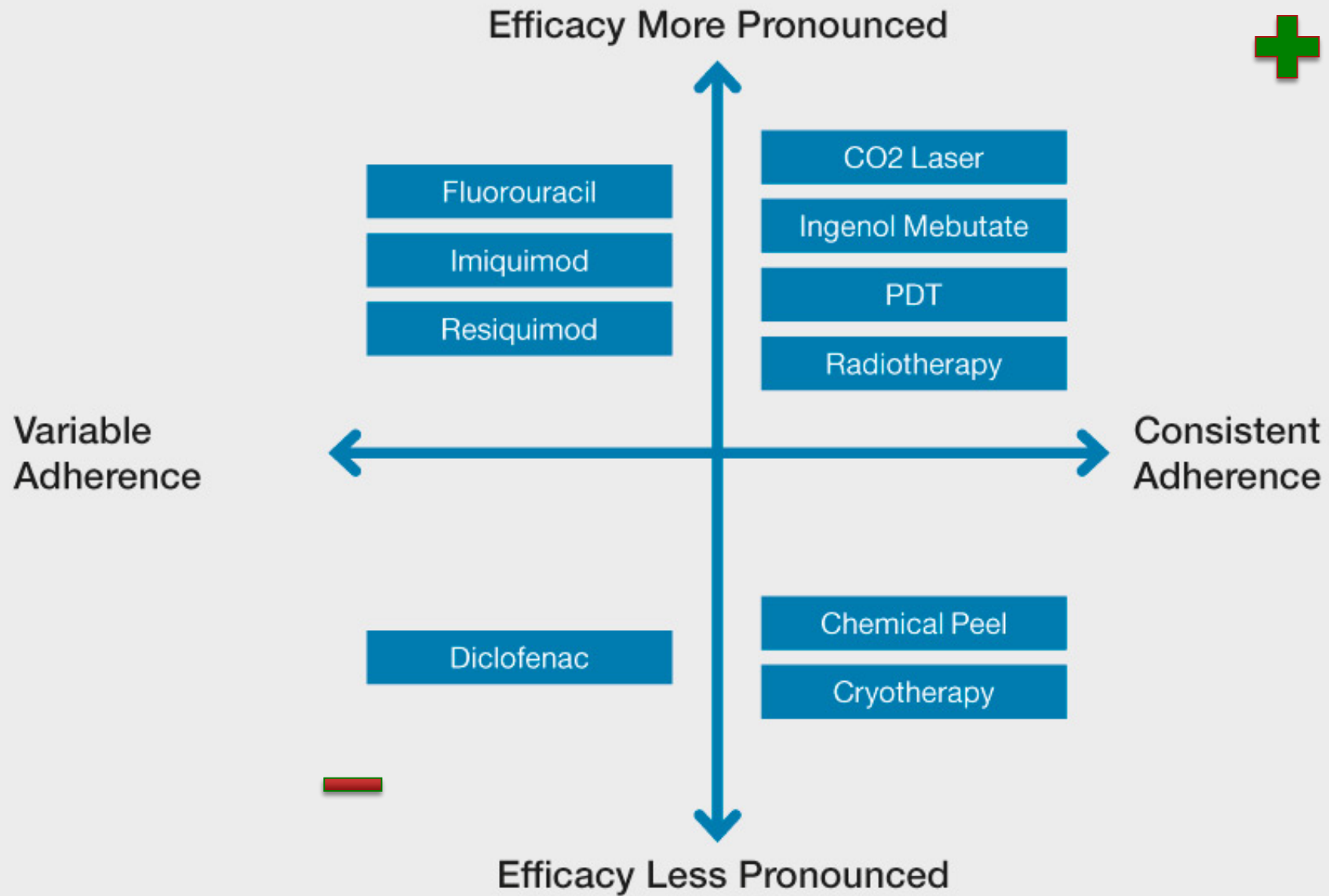
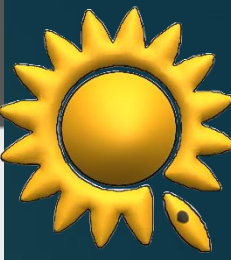
Side Effects and Convenience of Application

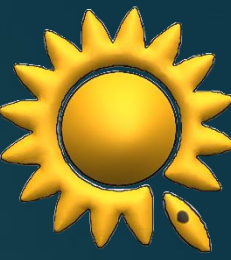


Duration of Therapy and Remission



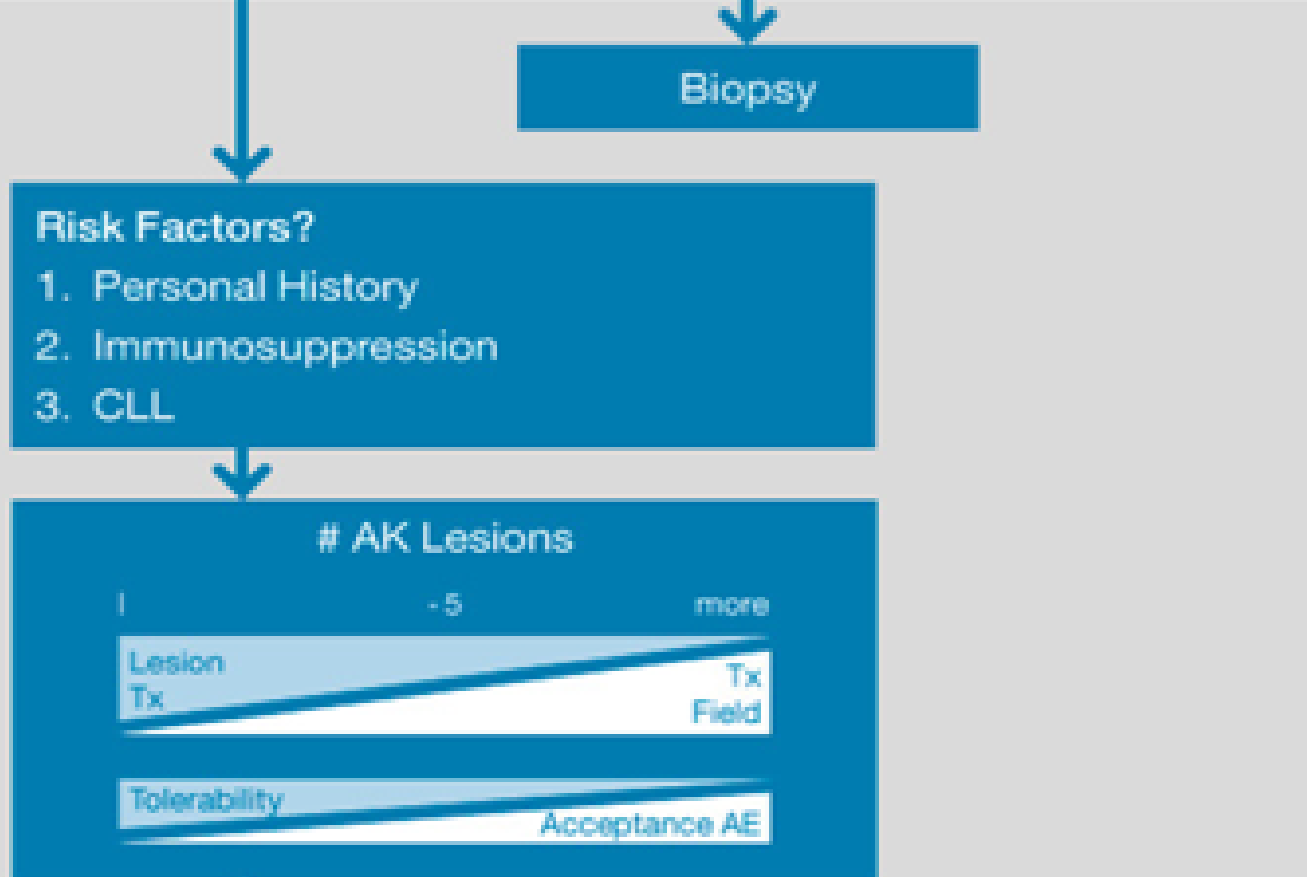
Treatment Adherence and Efficacy





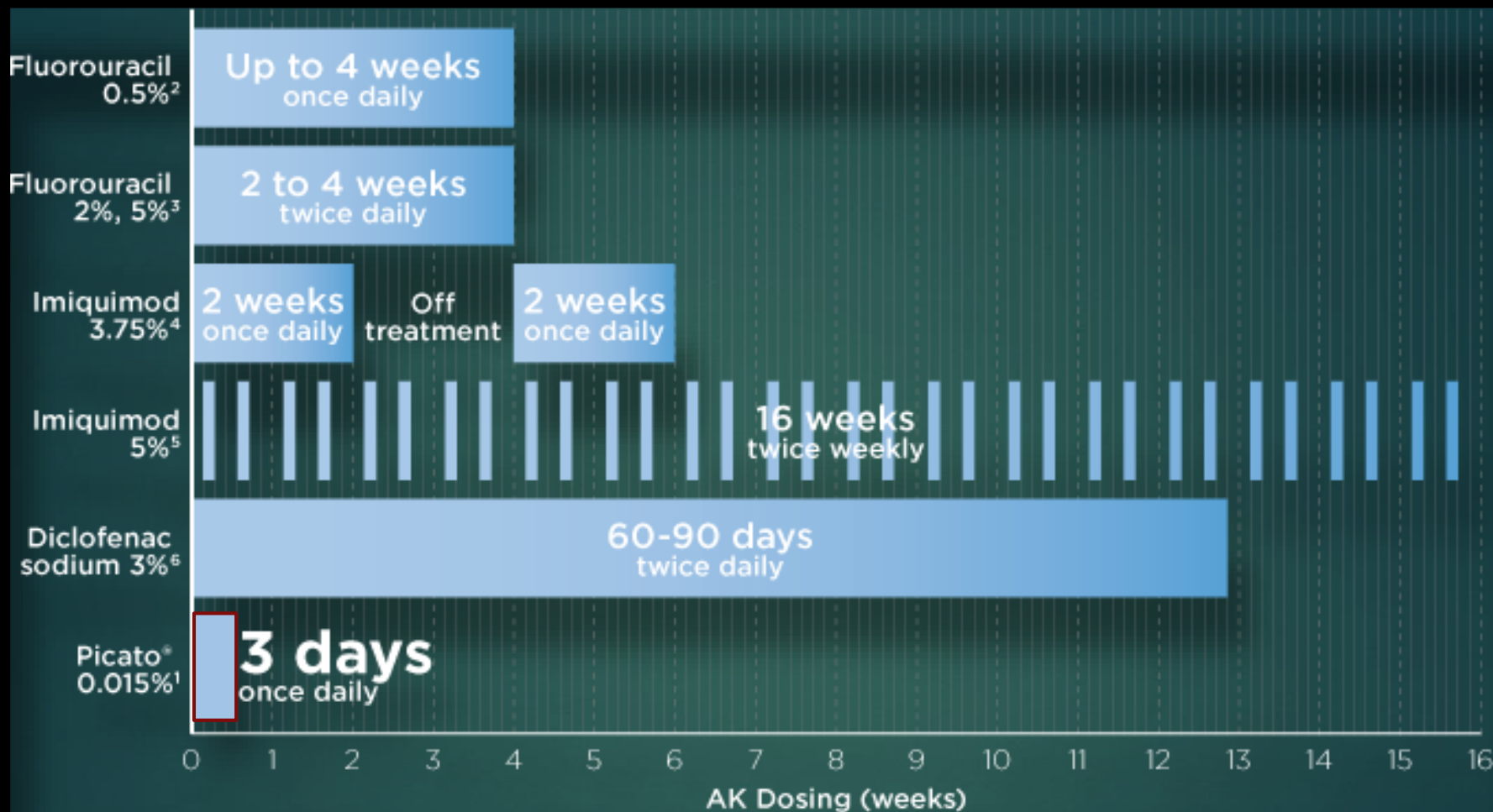
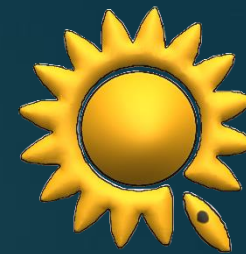
Actinic keratosis and field cancerization treatment algorithm

Evaluate



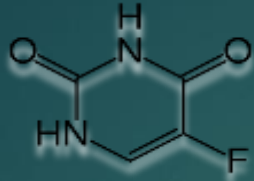
Treat





*Fluorouracil 0.5% + 2% and Imiquimod 3.75% not available in Australia.

References: 1. Australian Picato® gel Product Information. 9 November 2012. 3. Australian Efidix® Product Information. 01 May 2013. 6. Australian Solaraze® Gel Product Information. 16 December 2013. 5. Australian Aldara™ Product Information. 24 June 2014.



5-Fluorouracil



	Advantages	Disadvantages
Topical		
5-fluorouracil	<ul style="list-style-type: none">• Effective• Can treat clinically apparent and inapparent lesions• Can treat multiple lesions• Minimal scarring risk	<ul style="list-style-type: none">• Potential skin irritation• Requires high patient compliance• Risk for potentially severe inflammatory reaction• Skin may require 1 to 2 months to heal

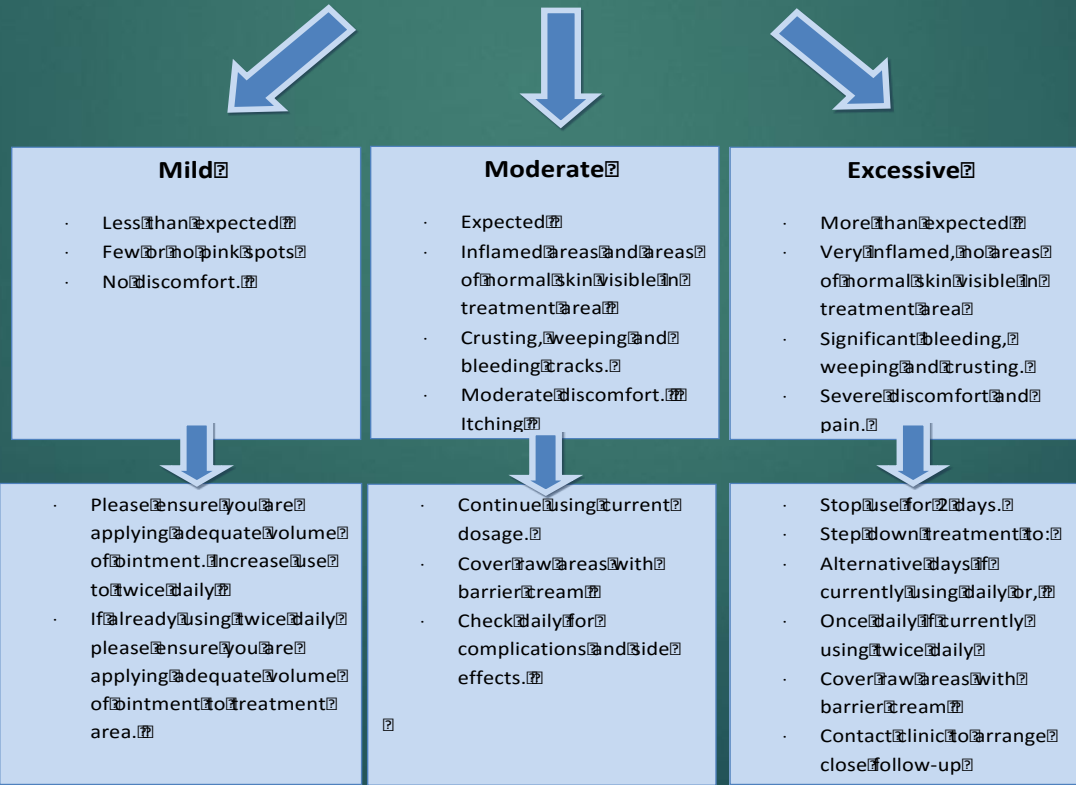


Topical Skin Cancer Daily Treatment and

Start treatment and continue for 4 weeks or as directed.
Check daily for complications and side effects.

- Complications:**
- Infection
 - Excessive reaction
 - Swelling
 - Eye irritation

Adjust dosage as per diagram.
Decide which level best describes your treatment and then follow the action below.





5 FU field treatment Legs

Cling-wrap
cover

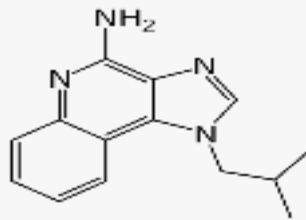




ALDARA™



Imiquimod



- Effective
- Can be used on multiple lesions
- Minimal scarring risk
- Induces an individual's own immune system
- Can treat clinically apparent and inapparent lesions
- Potential skin irritation
- Dispensed in small packets
- Requires high patient compliance
- May rarely cause systemic symptoms





Milk weed plant (*Euphorbia peplus*)



Apply to the affected area once daily for 3 consecutive days.¹

Tubes not actual size.

What to expect from treating with Picato

Before treatment



Day 3 of treatment



2 weeks after



BEFORE TREATMENT 4 DAYS AFTER START 8 DAYS AFTER START 15 DAYS AFTER START 57 DAYS AFTER START

Mild
Severe

Patient 1



Patient 2



Patient 3





PICATO



1. Picato® should be applied to a defined treatment area. A treatment area is defined as one contiguous area of approximately 25 cm² (e.g., 5 cm x 5 cm). Each tube contains enough gel to treat a 25 cm² treatment area.

1. Australian Picato® gel Product Information, 9 November 2012.



23.05.2014







Before



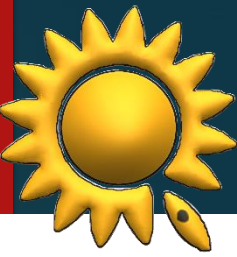
During



After

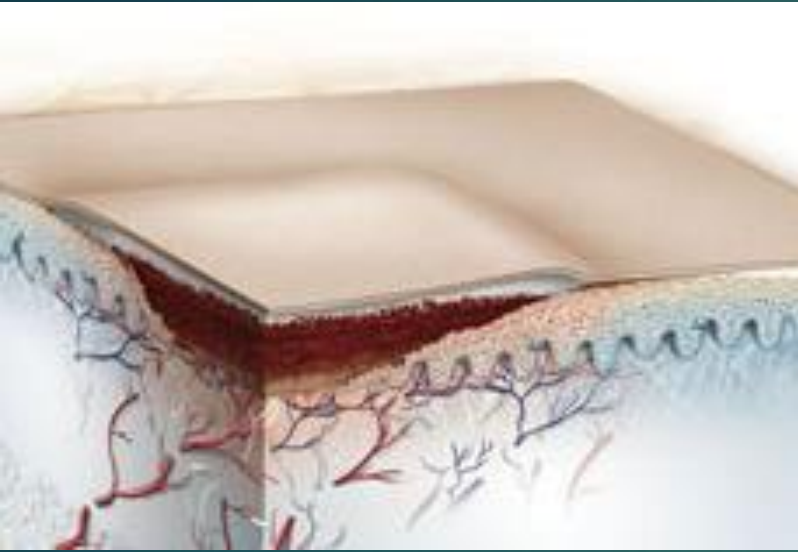


Wound management

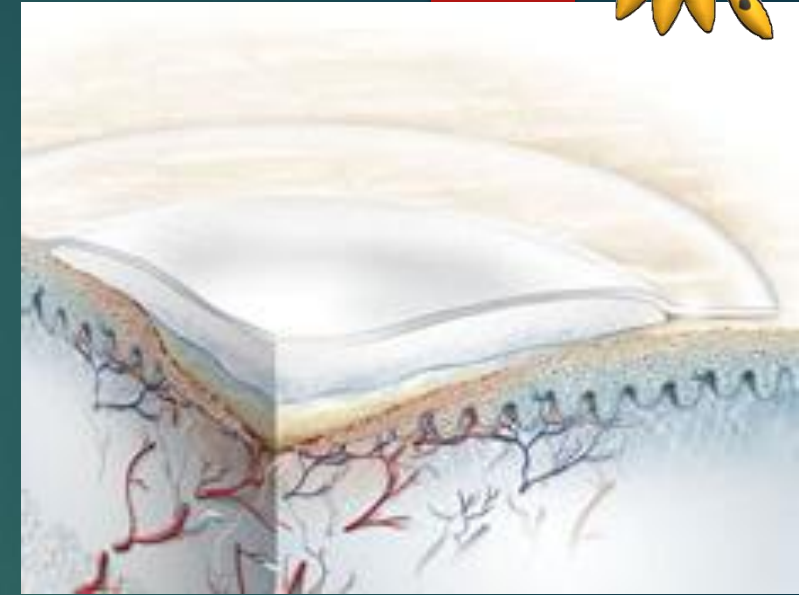


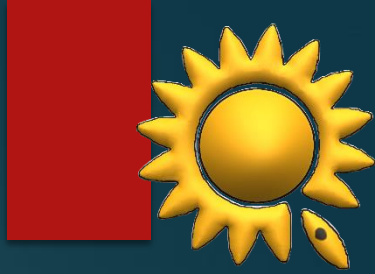
Dry

Wet



- Up to 50% faster wound healing (epithelisation and dermal repair).
- Lower rate of infection.
- Less Pain.
- Less scarring and better cosmetic results.

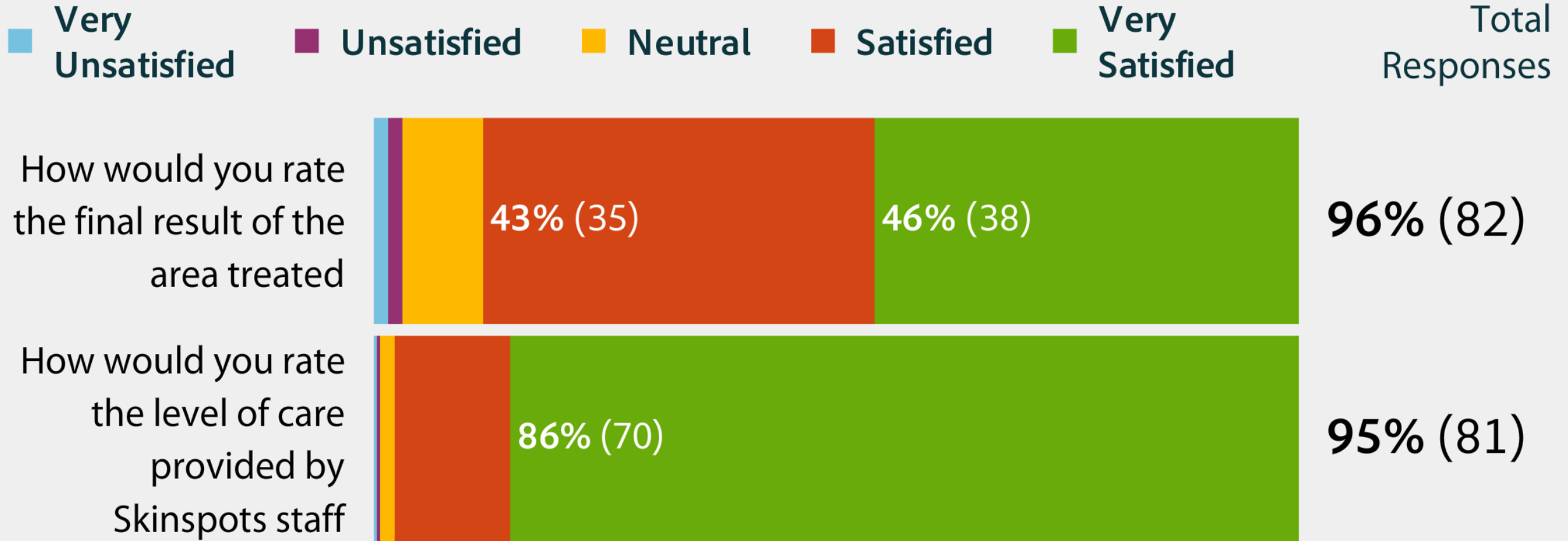


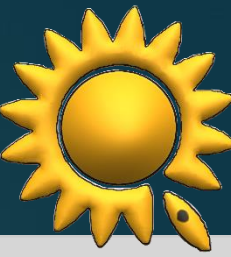


Audit of patient perceptions



satisfied





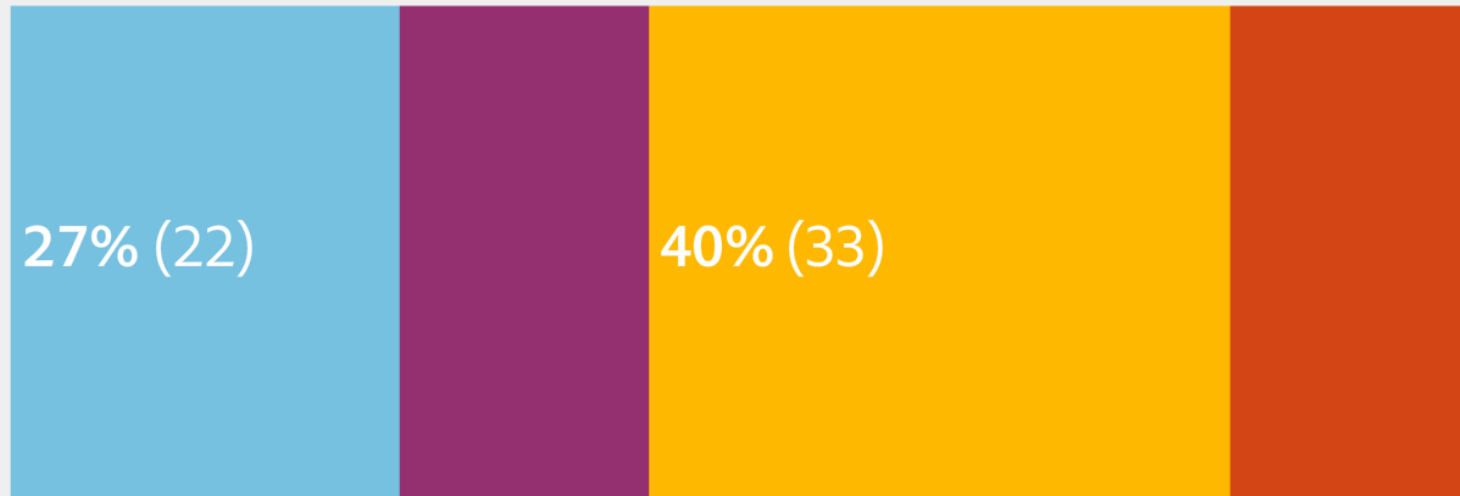
pain

Audit of patient perceptions



Total Responses

During the use of this drug all experienced some discomfort. Please rate your experience of this.



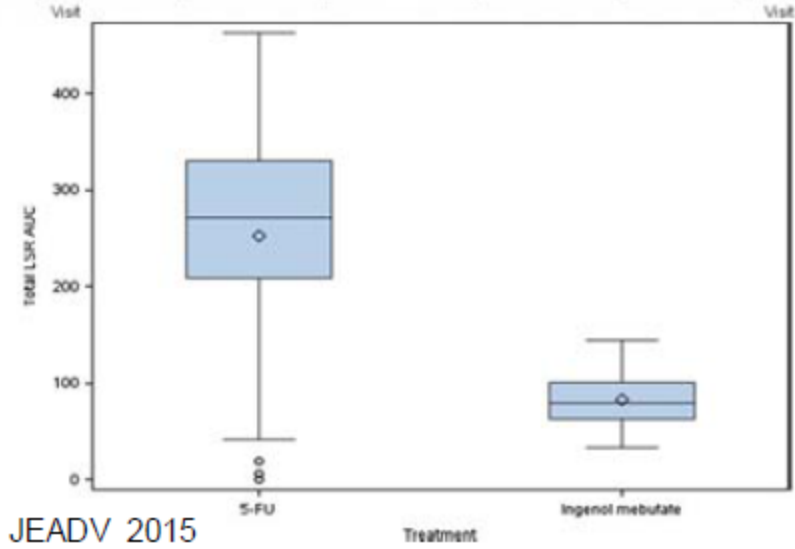
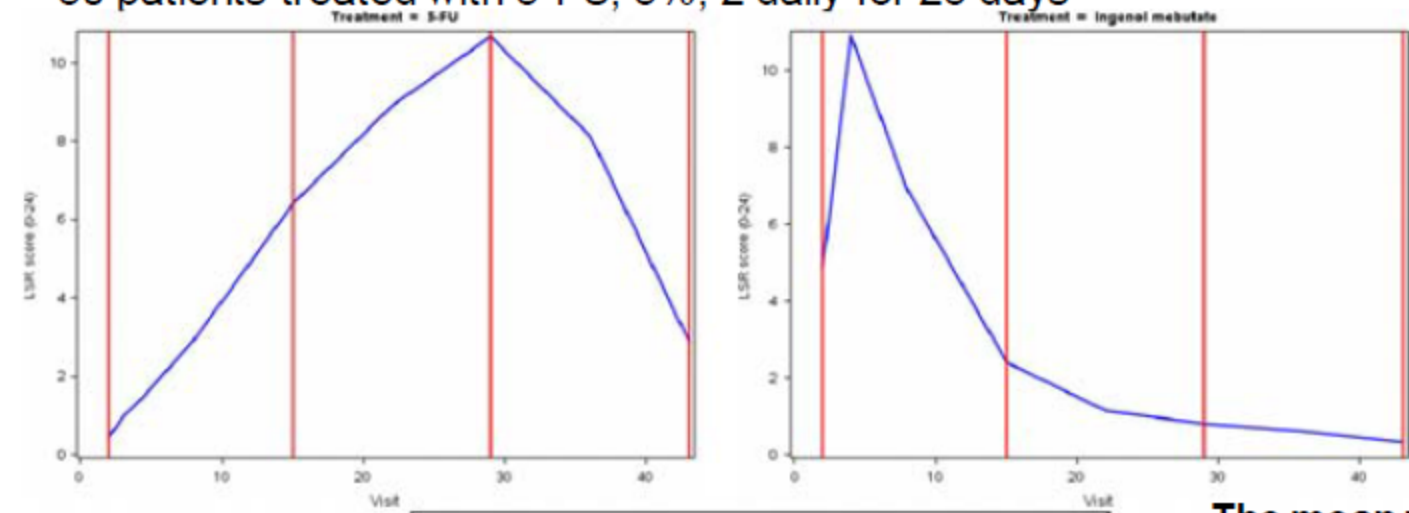
96% (82)

LSRs with IngMeb vs. 5FU

11 June 2015

p. 015

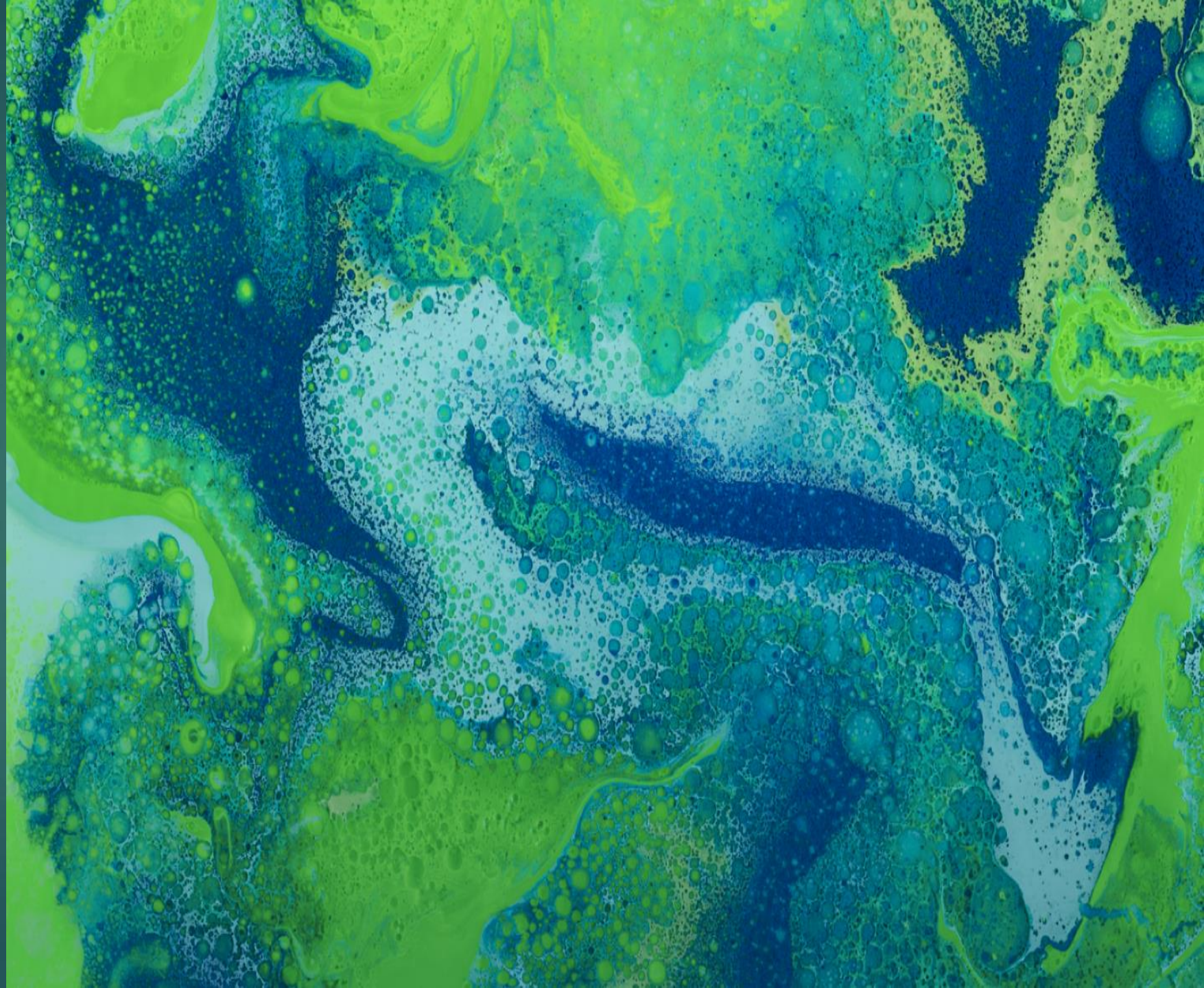
- AKs within a 25-cm² contiguous field on the face, evaluation on on days 2, 3, 4, 8, 15, 22, 29, 36 and 43
- 50 patients treated with IngMeb, 0.015%; 1 daily for 3 days
- 50 patients treated with 5-FU, 5%, 2 daily for 28 days



The mean reported pain intensity per visit was:
- IngMeb 1.3/10 peaked on day 4;
- 5-FU 6.9/10 peaked on day 29

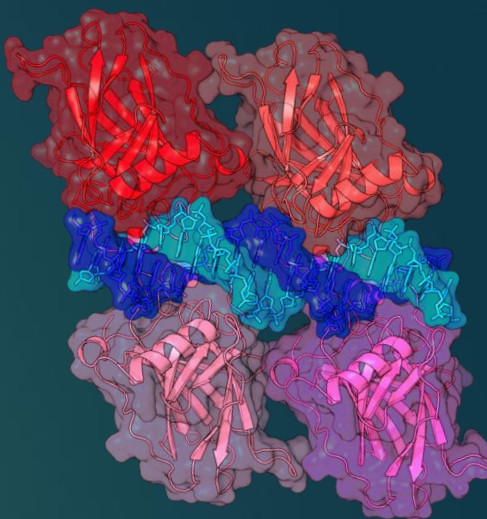


Does
It
Work
?

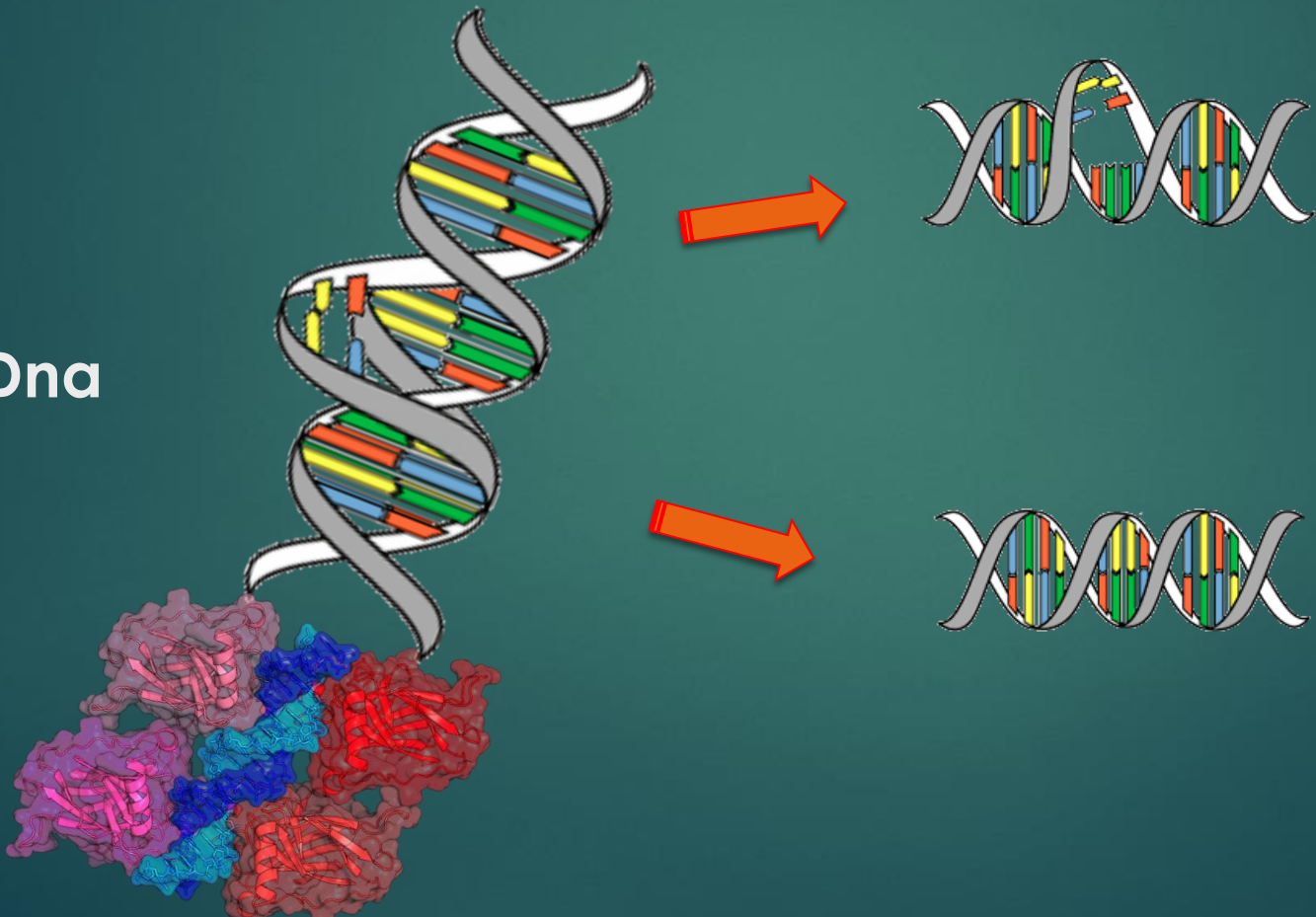




P53 Guardian of the genome or photo-oncogene



Uv induced Dna
mutation



Abnormal P53

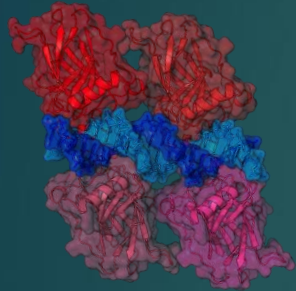
- No gene repair
- Cumulative genetic mutations
- Increasing Genetic instability

Normal P53

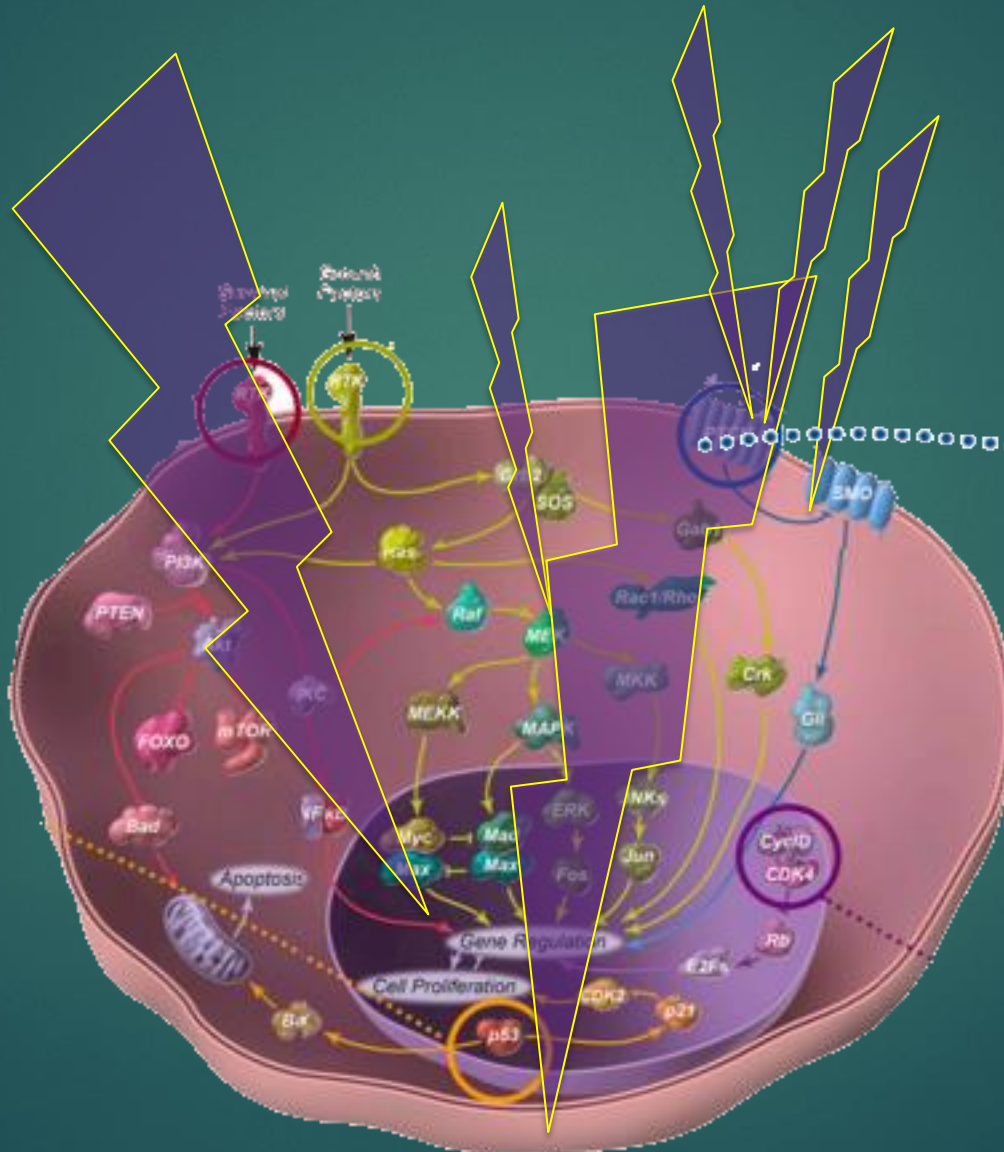
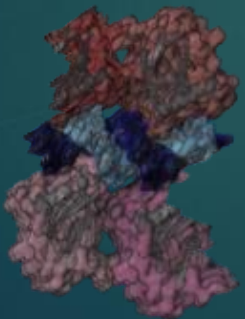
- Gene repair or apoptosis
- Normal gene function

Normal P53

Mutation's repaired

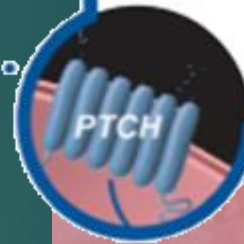


Mutant P53



HEDGEHOG PATHWAY

The Hedgehog (Hh) signaling pathway plays an important role in the embryonic development of organs. Its activity is reduced or absent in healthy adults. When dysregulated, Hh pathway activity is initiated, which can be associated with mechanisms that underlie tumor development. Mutated Hh pathways have been implicated in more than 90% of BCCs.²⁹⁻³¹





PI3K/Akt PATHWAY

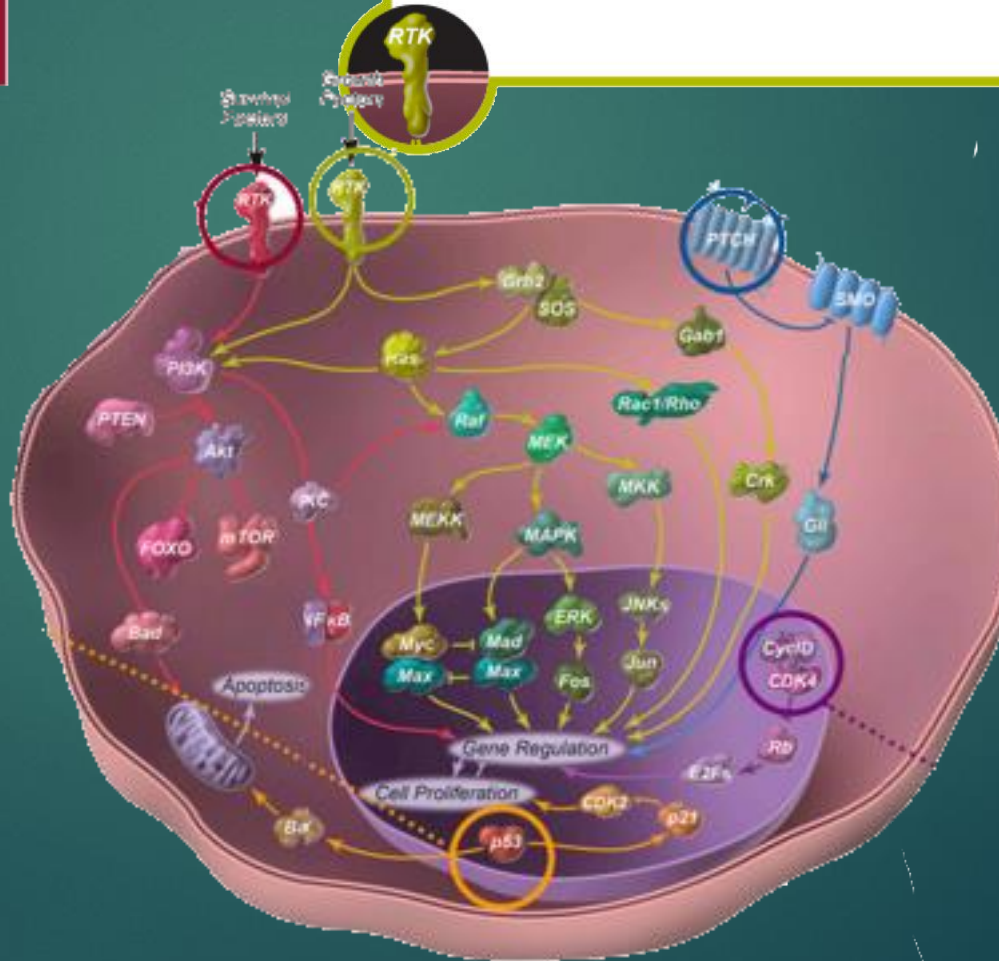
Similar to the MAPK pathway, the PI3K/Akt pathway can also be activated by Ras. Once activated, downstream effectors of Akt block apoptosis and promote cell proliferation and invasion. Although PI3K mutations are believed to be rare, downstream components of the PI3K/Akt pathway steadily increase during melanoma progression, and are altered in 50% to 60% of melanomas.²²



MAPK PATHWAY

The MAPK (mitogen-activated protein kinase) pathway, also called the Ras/Raf/MEK/ERK pathway, relays extracellular signals from the cell membrane to the nucleus via a series of consecutive phosphorylation events. In healthy individuals, this cascade of events is tightly regulated. However, when certain components of the MAPK pathway mutate, uncontrolled cellular proliferation may occur.^{23,26}

A BRAF mutation is present in the majority of melanomas, and an NRas isoform is present in 15% to 30% of melanomas. Two isoforms of Ras are present in approximately 10% of SCCs. SCC has also been correlated to epidermal growth factor (EGFR), an inducer of MAPK activity.^{9,26,27,28}



CDK4/CYCLIN D PATHWAY

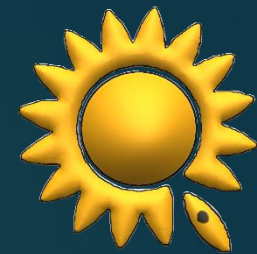
Approximately 10% of all melanomas are hereditary, and genetic analyses have linked the susceptibility of melanoma to the *CDKN2A* gene. Genetic *CDKN2A* mutations have been demonstrated in 25% to 50% of families with heritable melanoma and in at least 10% of patients with multiple primary melanomas. Somatic *CDKN2A* mutations have been reported in 30% to 70% of sporadic melanomas.²²



Does it work ??



- ▶ Application of 0.05% ingenol mebutate gel to photo-damaged skin resulted in a **≈70% reduction in the number of (P53)** skin lesions that subsequently emerged compared with placebo treatment.
- ▶ **topical sunscreen** (SPF 15) has the ability, at least in part, to block DNA damage in keratinocytes as well as **reduce p53 and proliferative responses.**
- ▶ Response rates to two cycles of **PDT** mainly on the scalp and face reduce **p53 from 69% to 91% in three randomized trials.**
- ▶ After **Imiquimod** therapy, staining for p53, p63, and PCNA was **decreased within the epidermis 60 – 80 %**



KEEP
CALM
AND
WEAR
SUNSCREEN



- ▶ 1) Clin. Cancer Res. 2003;9:228–234 Bolshakov S., et al. p53 mutations in human aggressive and nonaggressive basal and squamous cell carcinomas. .
- ▶ 2) J Invest Dermatol. 2012 Apr;132(4):1263-71. doi: 10.1038/jid.2011.418. Epub 2011 Dec 22. Ingenol mebutate field-directed treatment of UVB-damaged skin reduces lesion formation and removes mutant p53 patches. Cozzi SJ¹, Ogbourne SM, James C, Rebel HG, de Gruijl FR, Ferguson B, Gardner J, Lee TT, Larcher T, Suhrbier A.
- ▶ 3) Acta Derm Venereol 2001; 81: 81–86 Epidermal p53 Response and Repair of Thymine Dimers in Human Skin after a Single Dose of Ultraviolet Radiation: Effects of Photoprotection GAO LING¹, CAROLINE A. CHADWICK², BERIT BERNE³, CHRISTOPHER S. POTTEN², JAN PONTE¹ N† and FREDRIK PONTE¹
- ▶ 4) Warino L, Tusa M, Camacho F et al. Frequency and cost of actinic keratosis treatment. Dermatol Surg. 2006 Aug;32(8): 1045-9.
- ▶ 5) SF Zerp, British Journal of Cancer (1999) 79(5/6), 921–926
- ▶ 6) Dermatologic Surgery Volume 33, Issue 12, pages 1419–1429, December 2007

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