

**Photodynamic therapy for BCC  
with methyl aminolevulinate  
and CureLight 01**

NDA 21-576

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**Introduction and Rationale for  
development of photodynamic  
therapy with methyl  
aminolevulinate (MAL PDT)**

Vidar Hansson, MD PhD  
President and CEO  
PhotoCure ASA

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## AGENDA - Presentations by Sponsor PhotoCure ASA

Topic	Presenter
<b>Introduction and Rationale for development of photodynamic therapy with methyl aminolevulinate (MAL PDT)</b>	Vidar Hansson, MD, PhD
<b>Regulatory Overview</b>	William A. Clementi, Pharm D, FCP
<b>Overview of Clinical Development Program of MAL PDT in BCC</b>	Kjetil Hestdal, MD, PhD
<b>MAL PDT in low risk basal cell carcinoma; vehicle and active controlled studies</b>	David M. Pariser, MD, FACP
<b>Methyl Aminolevulinate Photodynamic Therapy in Patients with High Risk Basal Cell Carcinoma</b>	Dédée F Murrell, MD, FAAD
<b>Safety of MAL-PDT</b>	John Posner, MD, PhD, FRCP
<b>MAL PDT in BCC Benefit/risk</b>	Kjetil Hestdal, MD, PhD

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## PhotoCure ASA

- A pharmaceutical / biotech company established by Research Foundation at The Norwegian Radium Hospital in 1993
- Products are based on long experience in basic and clinical research in photobiology and development of novel Photodynamic Therapy (PDT) technologies

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## **Rationale for development of photodynamic therapy with methyl aminolevulinate (MAL PDT)**

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### **Properties of methyl aminolevulinate (MAL)**

- Methyl ester of 5-aminolevulinic acid (ALA)
- Unique biological properties for BCC treatment compared to ALA
  - Rapid and efficient induction of intracellular photoactive porphyrins (PAP) in cancer cells
  - Low induction of PAP in normal skin
  - Minimal systemic uptake due to low ability to cross the basal membrane
- Illumination with red light induces photoactivation of intracellular porphyrins and tumor cell death

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## Example of MAL penetration and PAP induction in a nodular BCC

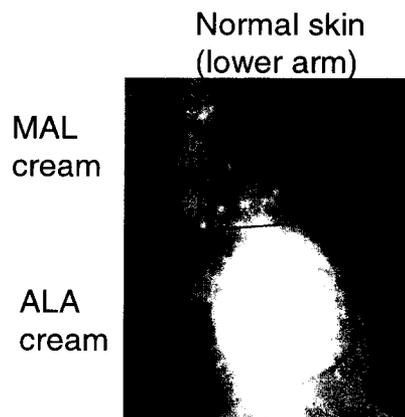
- ❑ MAL cream was applied to nodular BCC (2 mm deep) for 3 hours
- ❑ Fluorescence image shows that PAP is formed in all parts of the lesion and much less in peri-lesional tissue after 3 hours application



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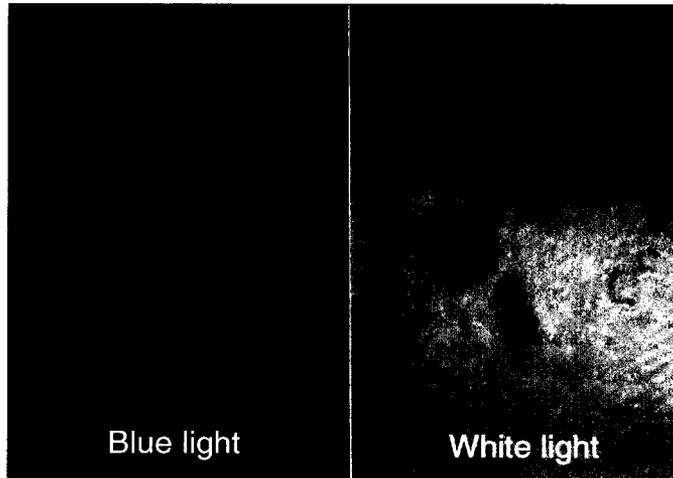
## Low PAP induction after MAL in normal skin

- ❑ Creams containing MAL or ALA were applied to normal skin for 3 hours
- ❑ Fluorescence (white) of PAP in the application area was imaged by fluorescence photography after blue light activation
- ❑ In contrast to ALA, MAL did not induce significant PAP fluorescence in normal skin



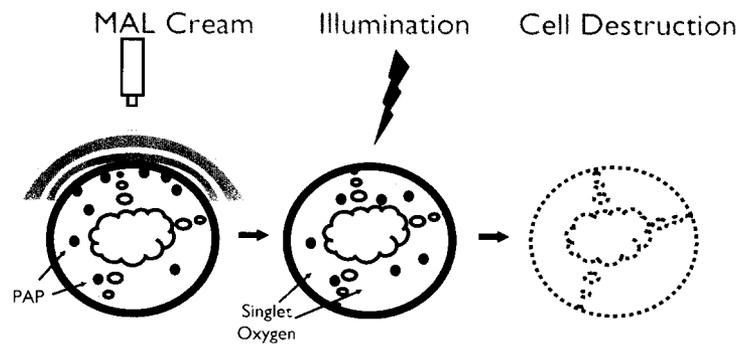
8

**High selectivity for BCC:  
Tumor demarcation is evident by  
fluorescence of PAP**



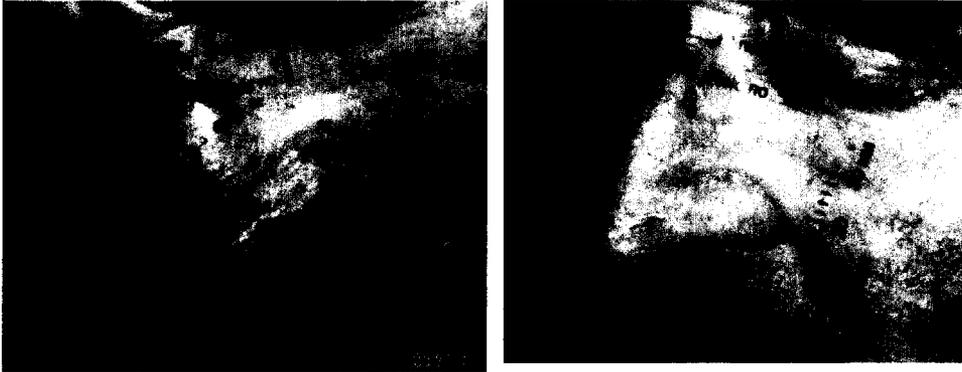
9

**MAL PDT Mechanism of Action**



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**Lesion selectivity and full depth penetration gives the possibility for tumor removal and tissue conservation**



Study PC T310/00: Patient 1004. Baseline and 3 months after treatment. Complete response, sustained response verified 24 months after treatment

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## Regulatory Overview

Methyl aminolevulinate cream 168 mg/g  
CureLight BroadBand model CureLight 01

William A. Clementi, Pharm. D., F.C.P  
President, Clementi & Associates  
US Regulatory Agent PhotoCure ASA

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## Submission Milestones

- AK
  - IND 03/2000
  - NDA 09/2001
  - Approvable Letters
    - MAL 09/2002
    - PDT 02/2002
  - Response To Filing Letter 07/2003
- BCC
  - IND 12/1999
  - NDA 02/2003

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## Division Sponsor Meetings

- |   |  |
|---|--|
| <ul style="list-style-type: none"> <li>• <b>AK</b> <ul style="list-style-type: none"> <li>– Pre-IND 08/1999</li> <li>– Phase II 06/2000</li> <li>– Pre-NDA 05/2001</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>• <b>BCC</b> <ul style="list-style-type: none"> <li>– Pre-IND 08/1999</li> <li>– Phase II 03/2000</li> <li>– Pre-NDA 06/2002</li> </ul> </li> </ul> |
|---|--|

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## **Overview of Clinical Development of MAL-PDT in BCC**

**Kjetil Hestdal, MD, PhD  
Vice President Research &  
Development, PhotoCure ASA**

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### **Clinical development program**

- Dosing parameters (cream concentration and cream application time, and illumination parameters) were established in phase I/II studies
- Efficacy was demonstrated in 2 adequate and well controlled studies in primary nodular BCC using the vehicle as the control
- Relative efficacy was also studied in primary nodular and superficial BCC using surgery and cryotherapy as comparators
- Supportive evidence of efficacy has been provided in nodular and superficial high risk BCC
- Safety profile has been established in patients with BCC and AK and special safety studies

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## Assessment of cream concentration, cream application time and light dose

- ❑ Cream concentration (study 101)
  - Lesion penetration: PAP fluorescence with 16 mg/g, 80 mg/g, 168 mg/g cream
- ❑ Cream application time (studies 101, 206, 203)
  - Lesion selectivity: PAP fluorescence over 28 h
  - Lesion penetration: PAP fluorescence at 3 and 18 h
  - Clinical efficacy and safety: 1 h, 3 h, 5 h, 18 h
- ❑ Light dose (study 206)
  - Photobleaching of PAP

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## Conclusion – dosage regimen

- ❑ Cream concentration:
  - highest penetration in BCC lesions: **168 mg/g**
- ❑ Application time:
  - optimal penetration, highest selectivity and clinical efficacy: **3 hours**
- ❑ Light dose:
  - complete photobleaching: **red light of wavelength 570-670 nm and a total dose of 75 J/cm<sup>2</sup>**

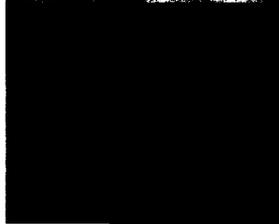
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## MAL-PDT Procedure

*Lesion preparation*



*MAL Cream application  
3 hours*



*Illumination  
about 10 minutes*



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## Treatment regimen used in Phase III program

- Cream concentration: 168 mg/g applied in a 1 mm thick layer on the lesion and 5 mm of surrounding skin after lesion preparation
- Application time: 3 hours under occlusive dressing
- Light dose: red light of wavelength 570-670 nm and a total dose of 75 J/cm<sup>2</sup>
- Generally, two treatment sessions one week apart (one treatment cycle), with a second treatment cycle 3 months later if non-complete response

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## CureLight BroadBand Model CureLight 01

- ❑ Halogen light bulb
- ❑ Lens system to provide focus and homogeneous light
- ❑ Filters remove blue, UV and infrared light
- ❑ Provides red light of wavelength 570 – 670 nm
- ❑ Light intensity 50–200 mW/cm<sup>2</sup> (dependent on distance)
- ❑ Circular treatment area of 30-55 mm diameter
- ❑ This lamp has been used in all clinical studies



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## Main efficacy and safety endpoints

- ❑ **Efficacy**
  - Patient response
  - Lesion response
    - Clinical
    - Histologic
  - Recurrence
- ❑ **Cosmetic outcome**
  - Investigator
  - Patient
- ❑ **Safety**
  - Local and non-local (systemic) AEs
  - Clinical hematology and biochemistry (5 Phase I/II studies)

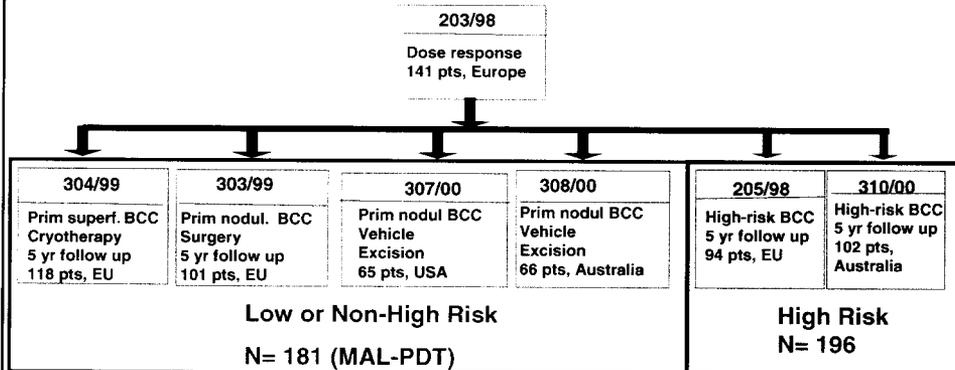
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## Study populations in Phase III

- ❑ Low risk superficial and nodular BCC (studies 303,304,307 and 308)
  
- ❑ High risk\* nodular and superficial BCC (studies 205 and 310):
  - Lesions in H-zone (310) or mid face and ear (205)
  - Large lesions (diameter of >20mm (>15 mm in 310) on extremities, >30 mm (>20 mm in 310) on trunk or >15 mm on face)
  - Recurrent lesions (205)
  - Lesions in severely sun-damaged skin (205)
  
- ❑ Morpheaform or infiltrative lesions were always excluded

\*Ref: HW Randle (Derm Surg,1996), J-C Martinez (Mayo Clin Proc,2001), NA Swanson (J Derm Surg Oncol, 1989)

## MAL PDT in superficial and nodular BCC Phase III



## Safety of MAL PDT

- Phase I/II and III studies
  - Clinical studies in AK: 383 patients
  - Clinical studies in BCC: 538 patients
- Compassionate use study with >1000 patients
- Special safety studies (3) in healthy subjects
- Post marketing data >35,000 AK and BCC patients

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## MAL PDT in low risk basal cell carcinoma; vehicle and active controlled studies

David Pariser, MD  
Professor, Dept of Dermatology,  
Eastern Virginia Medical School  
Norfolk, Virginia

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## BCC – Treatment Goals

- Eradication of tumor**
- Maximum Normal Tissue Preservation**
- Optimal Cosmesis**
- Palliation and/or observation**

Ref: Martinez J-C, Otley CC. Mayo Clin Proc; 2001; 76; 1253

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## **BCC – Current Treatment Guidelines For High and Low Risk BCC**

### **Academy (AAD) Guidelines**

- Electrosurgery and curettage**
- Cryosurgery**
- Excision surgery**
- Mohs micrographic surgery**
- Laser Surgery**
- Radiation Therapy**

Ref. JAAD, 1992; Volume 26; 117

### **Major Reviews**

- Electrodesiccation and curettage**
- Cryotherapy/Cryosurgery**
- Excision surgery**
- Mohs micrographic surgery**
- Radiotherapy**
- Topical 5-FU**
- Experimental therapies: Intralesional interferon, topical imiquimod, and PDT**

Ref. NEJM; 1992; 327; 1650  
Mayo Clin Proc; 2001; 76; 1253

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## **Factors Important for Treatment Selection**

- Lesion Characteristics**
  - **Anatomic location**
  - **Histopathological type**
  - **Primary vs Recurrent**
  - **Size**
- Patient Factors**
  - **Cosmetic concern**
  - **Patient preference**
  - **Life expectancy/age**
  - **Comorbid conditions**
- Treatment factors**
  - **Physician's skill and preference**
  - **Cost**

Adapted from: NEJM; 1992; 327; 1650 and Mayo Clin Proc; 2001; 76; 1253

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## **BCC – No Uniformly Established Standard of Care**

- ❑ No randomized well-controlled trials of the treatment modalities currently in widespread use
- ❑ Heterogeneous population and lesions makes uniformity of treatment difficult
- ❑ No evidence based guidelines for treatment of different type of lesions exist
- ❑ Lack of uniformity in populations and lack of uniformity in reporting of treatment outcome confounds comparisons
- ❑ No studies compare cure rate, cosmesis, patient satisfaction and cost

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## **Controlled Studies with MAL-PDT**

- ❑ Double blind vehicle controlled (307 and 308)
- ❑ Active controlled
  - Surgery (303)
  - Cryotherapy (304)
- ❑ Prospective
- ❑ Multicenter
- ❑ Randomized
- ❑ Two parallel groups

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**MAL PDT in low risk basal cell carcinoma;  
vehicle controlled studies  
307 and 308**

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**Vehicle controlled efficacy study in  
primary nodular BCC (307)  
USA**

**INVESTIGATORS**

- Menter A**
- el-Azhary R A**
- Lowe NJ**
- Jarratt M**
- Pariser D M**
- Rich P**
- Oseroff A**
- Tope WD**

**SITES (8)**

- Dallas, TX**
- Rochester, MN**
- Santa Monica, CA**
- Austin, TX**
- Norfolk, VA**
- Portland OR**
- Buffalo, NY**
- Minneapolis, MN**

**HISTOPATHOLOGY: Gibson L; Rochester, MN**

36

**Vehicle controlled efficacy study in  
primary nodular BCC (308)  
AUSTRALIA**

**INVESTIGATORS**

- Foley P**
- Freeman M**
- Siller G**
- Gebauer K**
- Murrell D**
- Barnetson R**
- Anderson C**

**SITES (7)**

- Melbourne, VIC**
- Gold Coast, QLD**
- Brisbane, QLD**
- Fremantle, WA**
- Sydney, NSW**
- Sydney, NSW**
- Sydney, NSW**

**HISTOPATHOLOGY: Kossard, S; Sydney, NSW**

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**Study Population  
307 and 308**

- Inclusion criteria:**
  - **Primary nodular BCC, not previously treated**
  
- Exclusion criteria:**
  - **Large lesions (largest diameter >20mm on extremities, >30mm on trunk, >15mm on the face)**
  - **Lesions located in mid-face (nose, nasolabial or orbital areas) or ear**
  - **Morpheaform or infiltrating lesions**

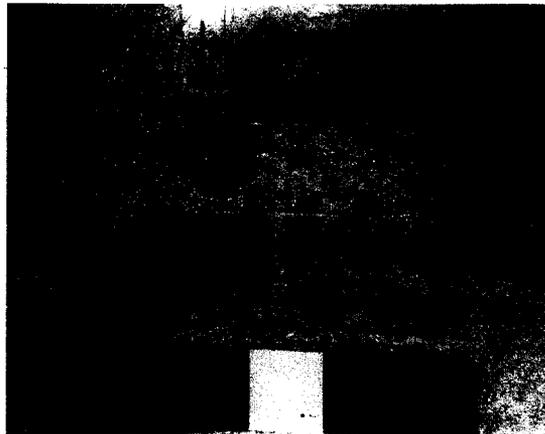
38

## **Lesion Identification 307 & 308**

- Tattoo was used to mark the lesions before treatment.**
- The tattoo was removed during surgical excision of the treated area.**
- "Before and after" photographs were taken.**
- Body charts were used to record lesion locations.**

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## **CLINICAL TRIALS 307 & 308**

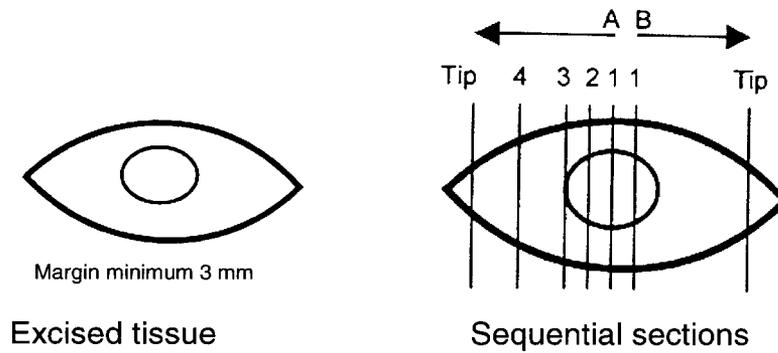


**Tattoo**

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## Processing of Excised Specimen

### Studies 307 & 308



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## Number of sections examined per mm of specimen

Study	N	Mean	Std Dev	Min	Max
307	78	0.97	0.54	0.14	2.58
308	66	1.45	1.03	0.4	5.0

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## **Investigator training for MAL PDT in studies 307 and 308**

- ❑ Training included on-site demonstration and practice for investigators before or at the time of first patient enrolment
- ❑ Instructional video supplied to all investigators and support personnel
- ❑ Written instructions were included in the protocol, in the case report forms and the investigator's brochure

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**Surface debridement**



**Cream application**

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## **Efficacy and safety evaluation**

### **Primary Efficacy Variable**

Histologic complete response by patient 6 months after last PDT cycle

### **Secondary Efficacy Variables**

Histologic complete response by lesion

Clinical complete response by patient and lesion

Cosmetic outcome (investigator and patient)

### **Safety Variables**

Adverse Events

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## **Efficacy evaluation (histology)**

### **Patient Histologic Response Assessment:**

- Complete Response (CR): All lesions within the patient have histologic complete response.

### **Lesion Histologic Response Assessment:**

- *Complete response (CR)*: Complete disappearance of all tumor cells.
- *Non-complete response (non-CR)*: Non-complete disappearance of tumor cells.

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## Efficacy evaluation (clinical)

### Clinical Response Assessment:

- *Complete response (CR)*: Complete disappearance of a lesion
- *Partial response (PR)*: The longest diameter of the lesion is reduced by 50% or more
- *No response (NR)*: The longest diameter of the lesion is less than 50% reduced
- *Progression (P)*: The longest diameter of the lesion is increased by 20% or more

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## Investigator assessment of cosmetic outcome

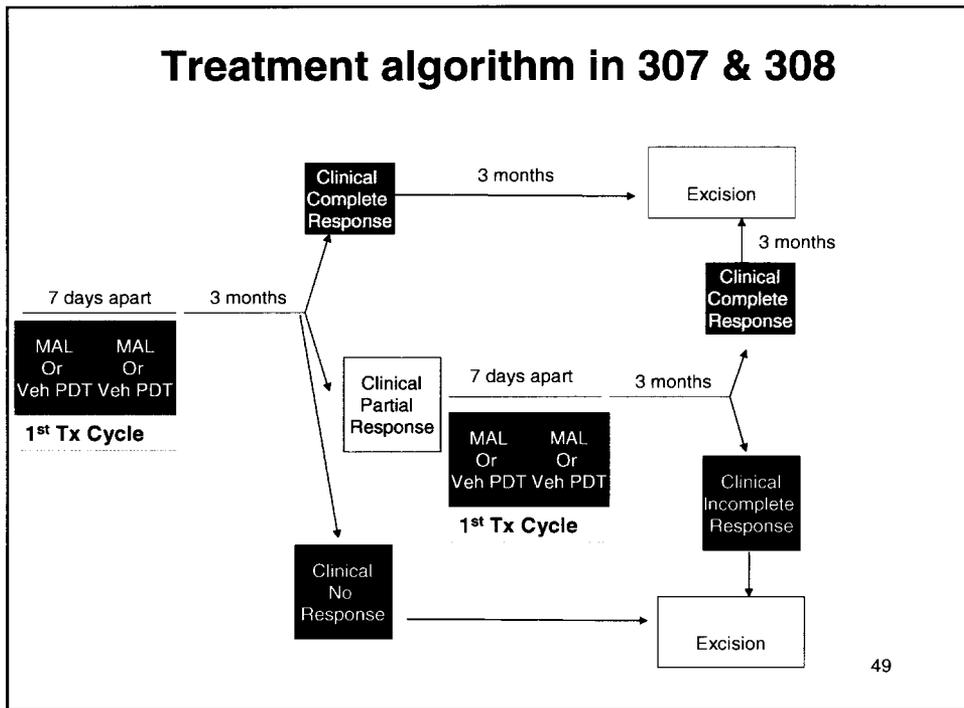
### Signs assessed:

- scarring
- change in pigmentation
- atrophy
- induration
- erythema

### Grading:

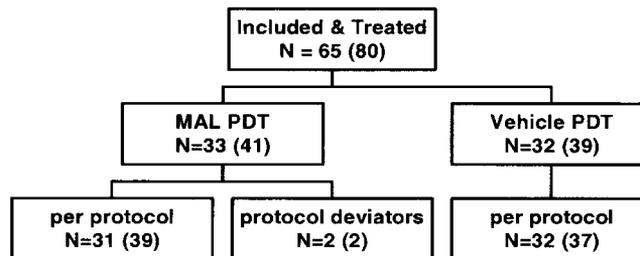
- Excellent:  
No scarring, atrophy or induration, no or slight erythema or change in pigmentation
- Good:  
No scarring, atrophy or induration, moderate erythema or change in pigmentation
- Fair:  
Moderate occurrence of any symptom
- Poor:  
Extensive occurrence of any symptom

## Treatment algorithm in 307 & 308



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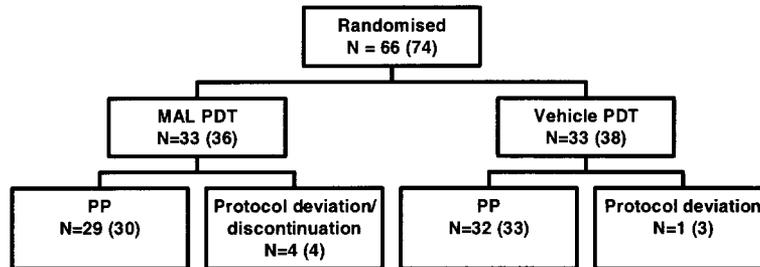
## Disposition of Patients (Lesions) Study 307



Deviations/discontinuations: 1 lesion only treated once, 1 lesion larger than inclusion criteria

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## Disposition of Patients (Lesions) Study 308



Deviations/discontinuations:

2 withdrawn consent before excision, 1 death, 1 time window deviation, 1 lesion not prepared before treatment

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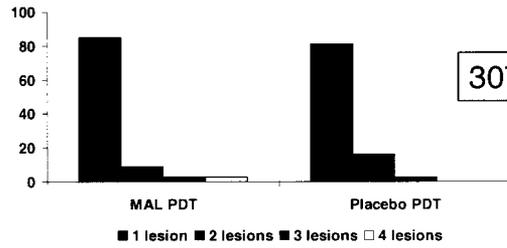
## CLINICAL TRIALS 307 & 308

### Demographics

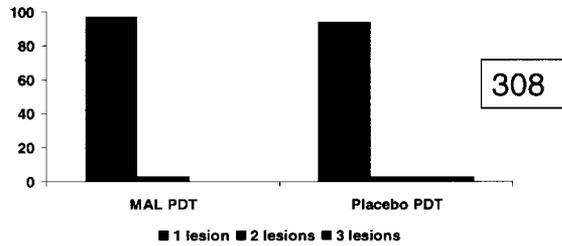
TREATMENT	Study	AGE			GENDER			
		n	Mean	Std	MALE		FEMALE	
					n	%	n	%
STUDY 307	MAL PDT	33	62	14	25	76	8	24
	Vehicle PDT	32	67	14	25	78	7	22
STUDY 308	MAL PDT	33	70	10	22	67	11	33
	Vehicle PDT	33	66	11	27	82	6	18

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## CLINICAL TRIALS 307 & 308

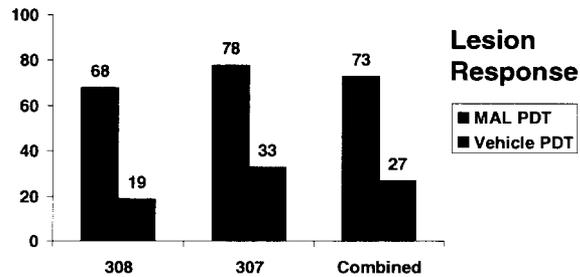
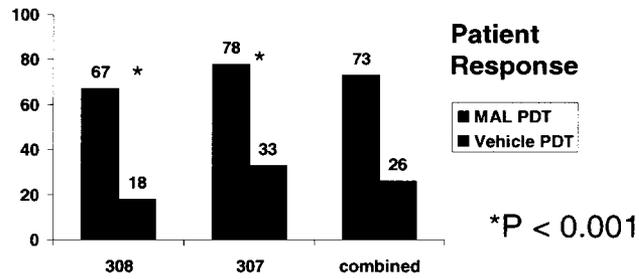


Number of lesions per patient (% of patients)



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## Response Rates 3-6 months post-treatment, ITT



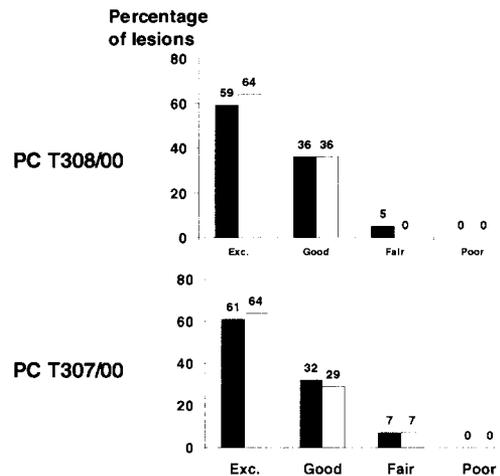
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## Treatment effects across centers

- ❑ No significant treatment by center interaction in the primary efficacy variable (Breslow-Day test  $p=0.27$  in 307 and  $p=0.49$  in 308 )
- ❑ Higher response rates for MAL PDT compared to vehicle PDT at all sites in both studies
- ❑ The two sites with extreme values in study 307 only contribute 20% of the data in the primary efficacy analysis

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## Cosmetic outcome 307 & 308



Cosmetic outcome of MAL PDT assessed by  
Investigators (■) and Patients (□)

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## **Efficacy conclusions from vehicle controlled studies 307 and 308**

- The beneficial treatment effect of MAL PDT was demonstrated in two identical adequate and well controlled studies
- MAL PDT was shown to be clinically and statistically superior to vehicle PDT on the basis of histologic endpoints (the predefined primary endpoint)

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## **MAL PDT in non-high risk basal cell carcinoma – Active controlled studies**

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## **MAL PDT vs. simple excision surgery in primary nodular BCC (303)**

### **INVESTIGATORS**

- Wolf P
- Rhodes L
- de Rie M
- Enström Y
- Groves R
- Morken T
- Goulden V
- Grob JJ
- Varma S
- Bedane C
- Basset-Seguín N
- Thomas P
- Delaunay M

### **SITES (13)**

- Graz, Austria
- Liverpool, UK
- Amsterdam, Netherlands
- Trollhättan, Sweden
- London, UK
- Bergen, Norway
- Leeds, UK
- Marseille, France
- Cardiff, UK
- Limoges, France
- Paris, France
- Lille, France
- Bordeaux, France

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## **MAL PDT vs. cryotherapy in primary superficial BCC (304)**

### **INVESTIGATORS**

- Basset-Seguín N
- Ibbotson S
- Emtestam L
- Tarstedt M
- Morton C
- Maroti M
- Calzavara-Pinton P
- Varma S
- Roelandts R
- Wolf P
- Saksela O
- Rosdahl I

### **SITES (12)**

- Paris, France
- Dundee, UK
- Stockholm, Sweden
- Örebro, Sweden
- Falkirk, UK
- Jönköping, Sweden
- Brescia, Italy
- Cardiff, UK
- Leuven, Belgium
- Graz, Austria
- Helsinki, Finland
- Linköping, Sweden

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## **MAL PDT in Non-High Risk BCC Studies 303 & 304**

### **Main Objective:**

To compare the response rates in the two groups 3 months after last treatment (MAL PDT and cryotherapy or surgery)

The protocol defined a clinically relevant difference as a difference of 15% or more.

In order to show non-inferiority of MAL PDT compared to the active comparators, the lower confidence limit for the difference had to be above -15%.

### **Secondary Objectives:**

- Cosmetic outcome
- Adverse events
- 5 year follow-up

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## **Study Population, studies 303 & 304**

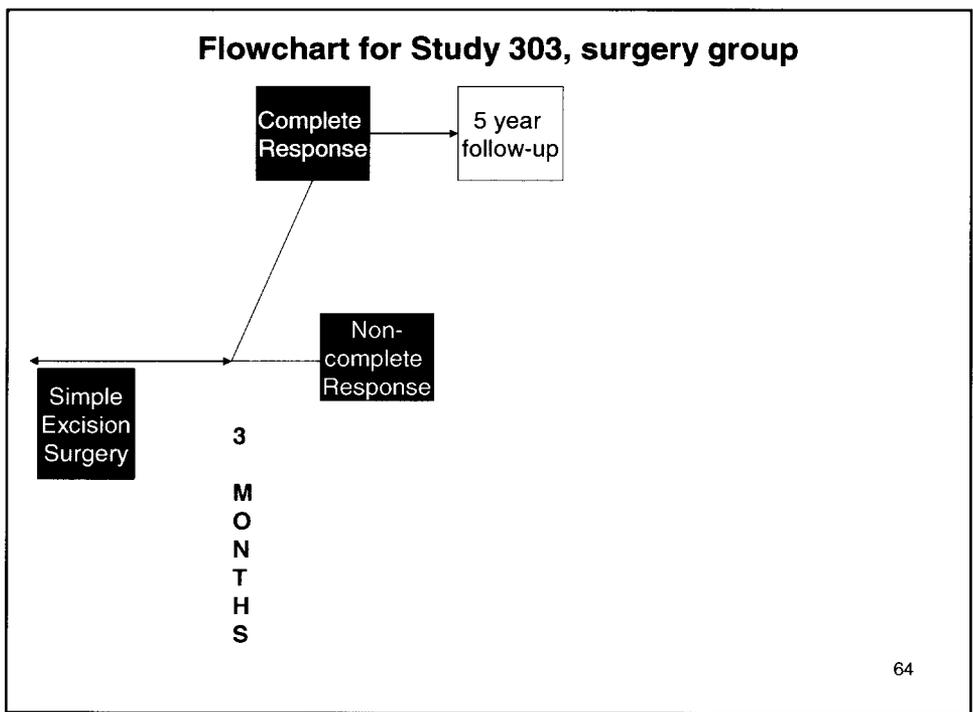
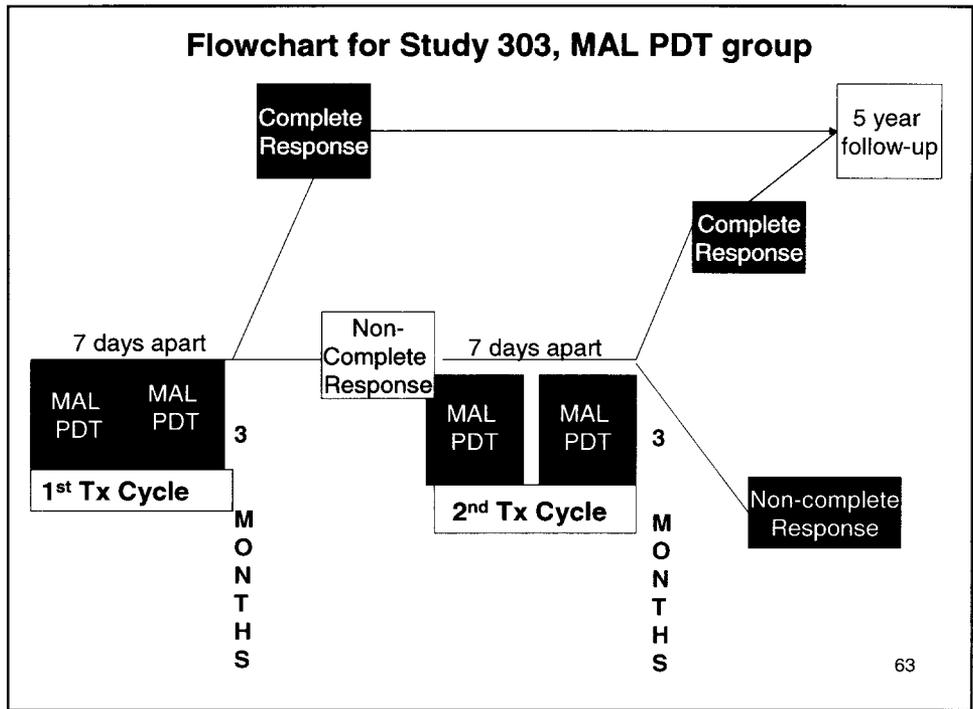
### **Inclusion Criteria:**

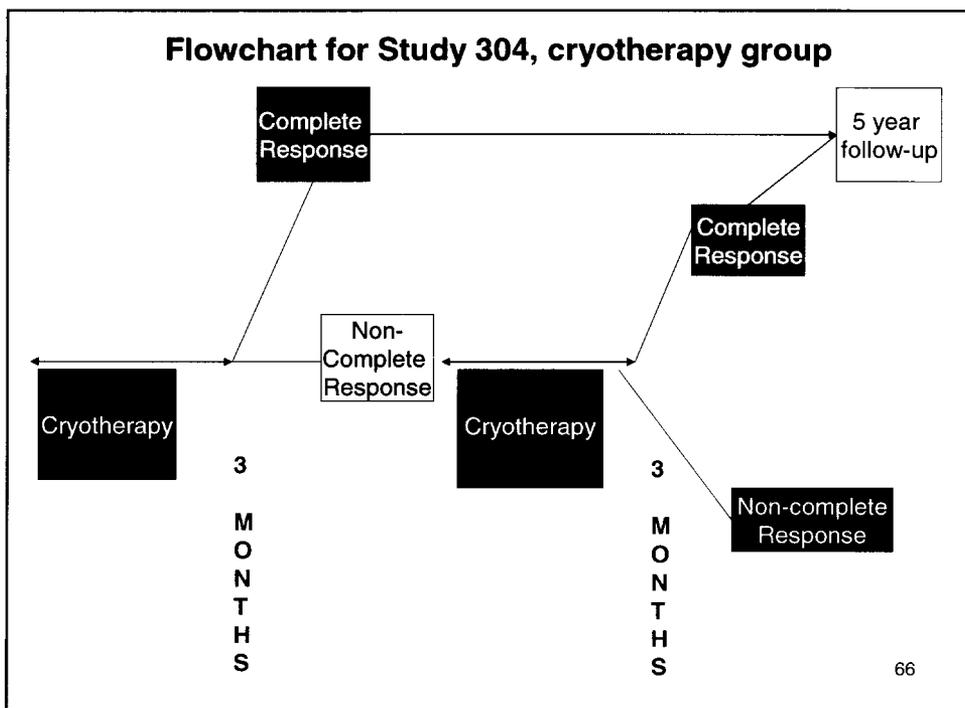
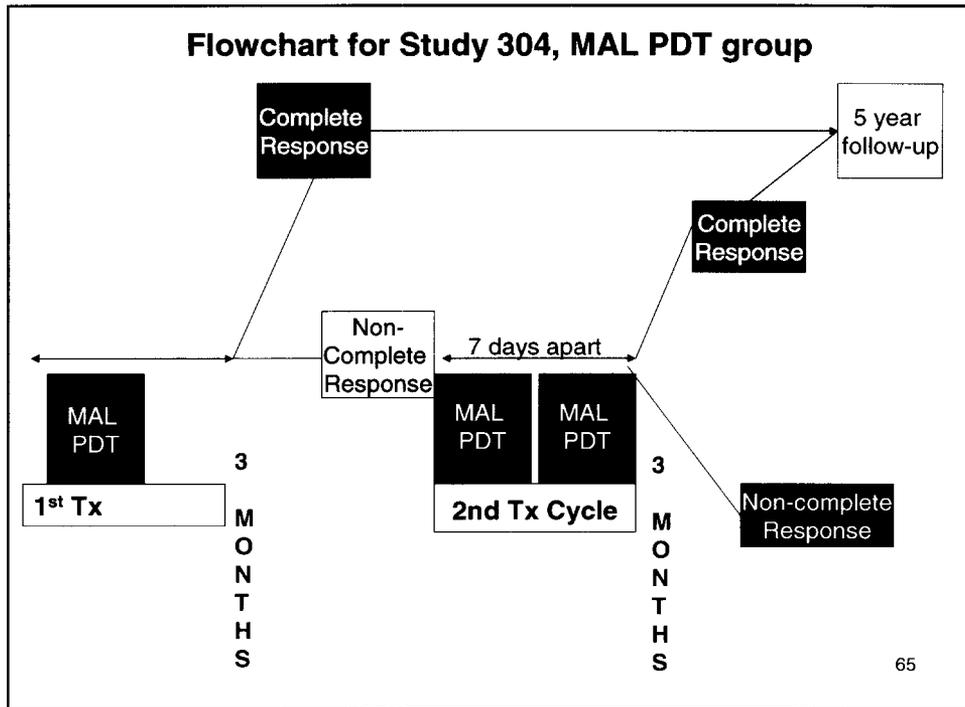
Histologically confirmed diagnosis of previously untreated nodular BCC (study 303) or superficial BCC (study 304) suitable for treatment with the comparator (surgery or cryotherapy, respectively)

### **□ Exclusion criteria:**

High Risk lesions  
Morpheaform  
Infiltrating

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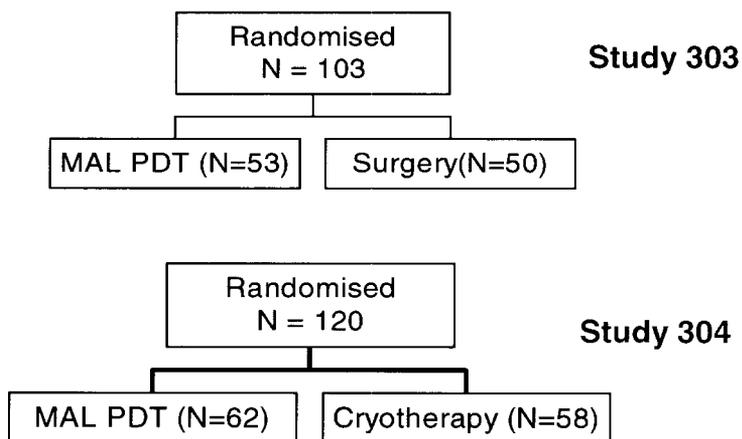


## Comparative treatments, studies 303 & 304

- ❑ **Study 303:** Simple excision surgery, 5 mm margins
- ❑ **Study 304:** Cryotherapy
  - liquid nitrogen spray
  - initial icefield formation with a 3 mm rim
  - icefield maintained for a minimum of 20 seconds
  - procedure repeated after thaw time of 2-3 times the freeze time.

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## MAL PDT in Low Risk BCC Patient Disposition



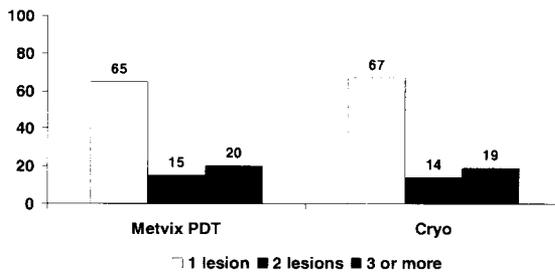
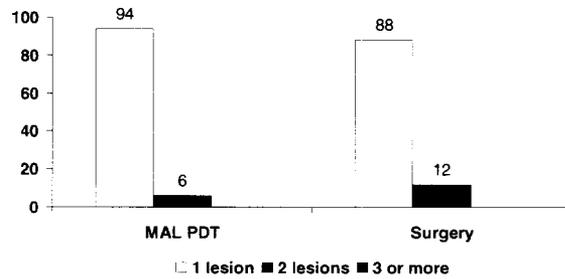
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## DEMOGRAPHICS Studies 303 & 304

Study	Treatment	GENDER						
		AGE			MALE		FEMALE	
		n	Mean	sd	n	%	n	%
303	MAL PDT	52	69	11	32	62	20	38
	Surgery	49	67	11	29	57	20	41
304	MAL PDT	60	63	16	40	67	20	33
	Cryo	58	64	13	30	52	28	48

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### Number of Lesions per Patient (% of patients)



70

## Patient complete response rate, PP

3 months after last treatment

	<b>MAL PDT</b>	<b>Compar- ator</b>	<b>Est. Diff.* (95% CI)</b>
<b>STUDY</b>	<b>N (%)</b>	<b>N (%)</b>	<b>%</b>
<b>303</b>	<b>45/50 (90)</b>	<b>Surgery 46/47 (98)</b>	<b>- 5.1 (-13.8, 3.7)</b>
<b>304</b>	<b>55/58 (95)</b>	<b>Cryo 52/57 (91)</b>	<b>+ 3.4 (- 5.2, 12.0)</b>

\*Mantel-Haenzsel confidence interval adjusted for center

71

## Lesion complete response rate,

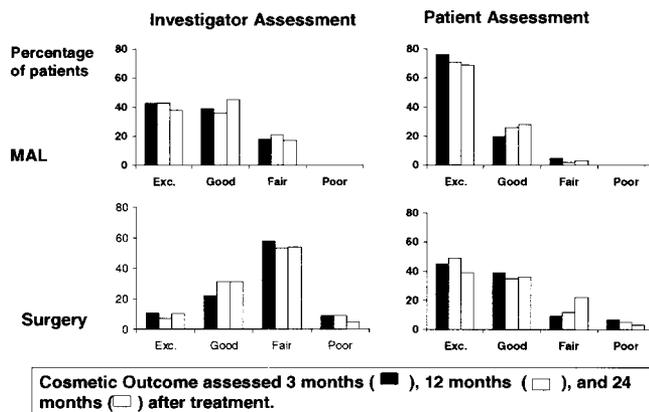
**Studies 303 & 304**

**PP**

<b>STUDY</b>	<b>TREATMENT</b>	<b>n/N</b>	<b>%</b>
<b>303</b>	<b>MAL PDT</b>	<b>48/53</b>	<b>91</b>
	<b>Surgery</b>	<b>51/52</b>	<b>98</b>
<b>304</b>	<b>MAL PDT</b>	<b>99/102</b>	<b>97</b>
	<b>Cryotherapy</b>	<b>93/98</b>	<b>95</b>

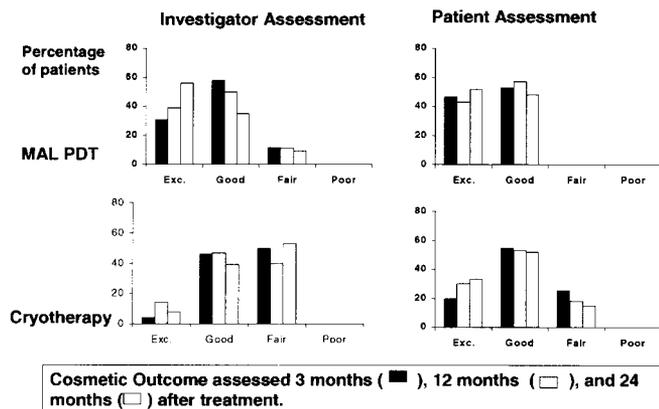
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## Study 303/99: Cosmetic Outcome over time, MAL vs. Surgery



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## Cosmetic Outcome over time, MAL PDT vs. Cryotherapy



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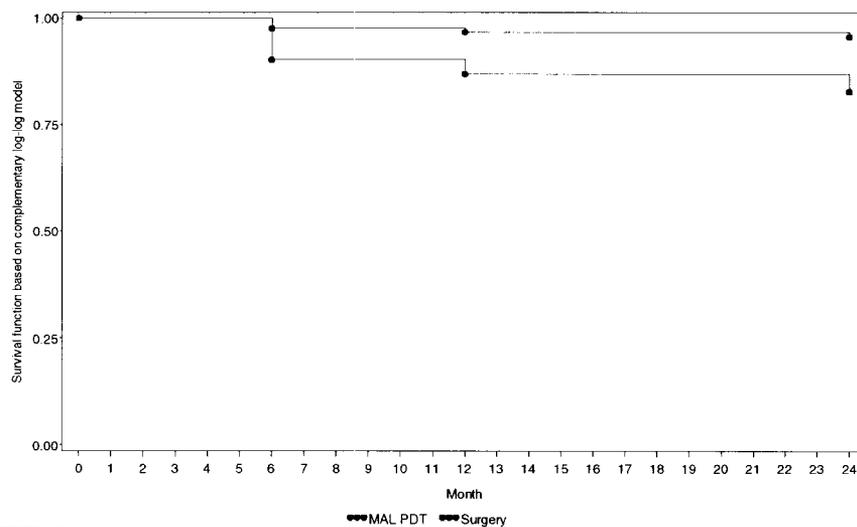
## 2 years follow-up study 303

Treatment	Crude estimate	Life table estimate
<b>MAL-PDT</b>		
Treatment failure	8/53 (15%)	15%
Missing	14/53 (26%)	
<b>Surgery</b>		
Treatment failure	1/52 (2%)	3%
Missing	7/52 (13%)	

75

## Time to treatment failure Nodular BCC, study 303

PP

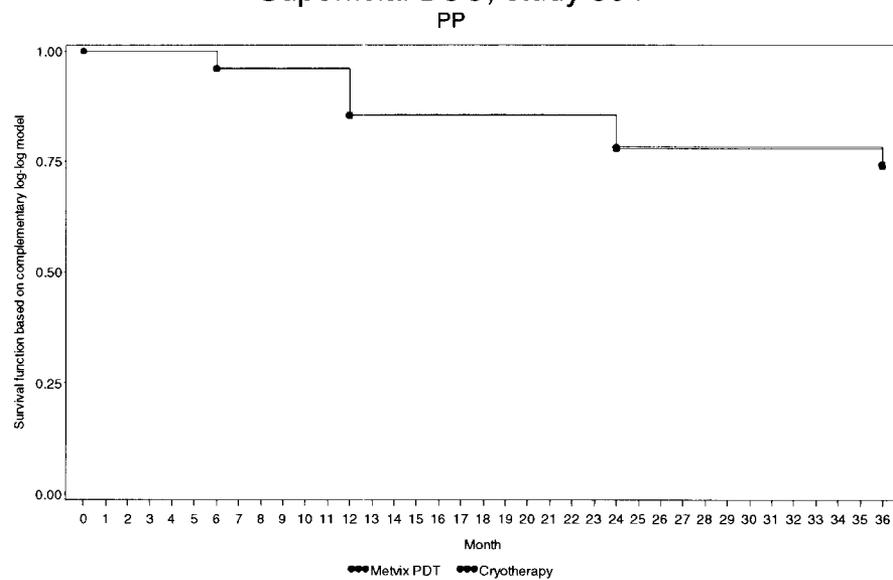


### 3 years follow-up study 304

Treatment	Crude estimate	Life table estimate
<b>MAL-PDT</b>		
Treatment failure	26/103 (25%)	
Missing	9/103 (9%)	25%
<b>Cryotherapy</b>		
Treatment failure	24/98 (24%)	25%
Missing	8/98 (8%)	

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### Time to treatment failure Superficial BCC, study 304



## Conclusions, Studies 303 & 304

- ❑ MAL PDT was shown to give similar initial response and sustained response rates compared with cryotherapy up to 36 months after treatment of superficial BCC
- ❑ MAL PDT was shown to give similar initial response and lower sustained response rates compared with surgery up to 36 months after treatment of nodular BCC
- ❑ MAL PDT was shown to give significantly better cosmetic outcome than either surgery or cryotherapy as assessed by investigators

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## AGENDA - Presentations by Sponsor PhotoCure ASA

Topic	Presenter
Introduction and Rationale for development of photodynamic therapy with methyl aminolevulinate (MAL PDT)	Vidar Hansson, MD, PhD
Regulatory Overview	William A. Clementi, Pharm D, FCP
Overview of Clinical Development Program of MAL PDT in BCC	Kjetil Hestdal, MD, PhD
MAL PDT in low risk basal cell carcinoma; vehicle and active controlled studies	David M. Pariser, MD, FACP
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Safety of MAL-PDT	John Posner, MD, PhD, FRCP
MAL PDT in BCC Benefit/risk	Kjetil Hestdal, MD, PhD

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# **Methyl Aminolevulinate Photodynamic Therapy in Patients with High Risk Basal Cell Carcinoma**

Dédée Murrell, MD (Oxford) FAAD (USA)  
Assoc Prof, Derm Dept, Univ of NSW  
Sydney, Australia

81

## **STUDY 205 EUROPE**

### **INVESTIGATORS**

- Wolf P**
- Wulf HC**
- Warloe T**
- Rhodes L**
- Fritsch C**
- Kaufmann R**
- de Rie M**
- Larkö O**

### **SITES (8)**

- Graz, Austria**
- Copenhagen, Denmark**
- Oslo, Norway**
- Liverpool, UK**
- Düsseldorf, Germany**
- Frankfurt, Germany**
- Amsterdam, Netherlands**
- Gothenburg, Sweden**

**INDEPENDENT REVIEWER: Pavel S, MD, Leiden,  
Netherlands**

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## STUDY 310 AUSTRALIA

### INVESTIGATORS

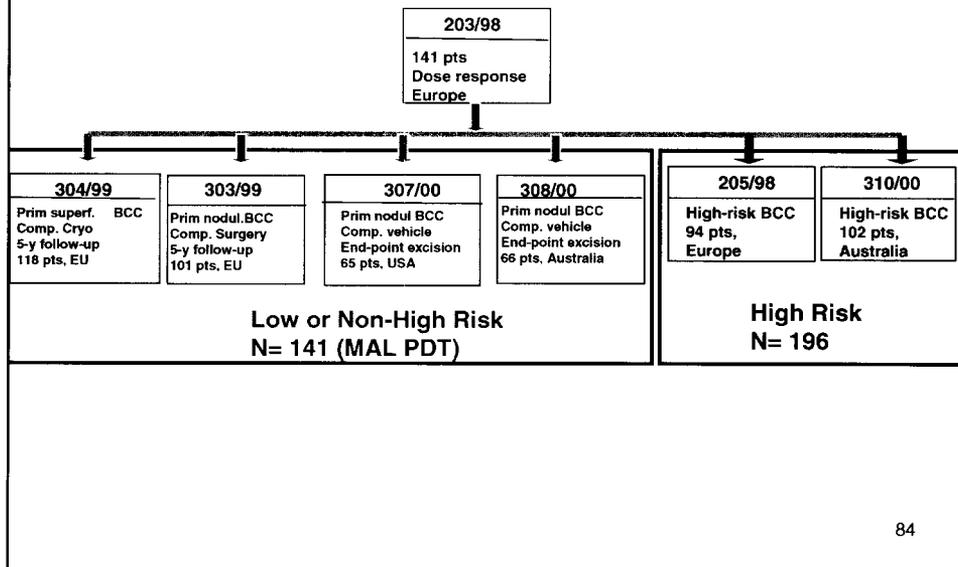
- Murrell D
- Vinciullo C
- Spelman L
- Gebauer K
- Weightman W
- Reid C
- Czarnecki D

### SITES (8)

- Sydney, NSW
- Perth, WA
- Brisbane, QLD
- Fremantle, WA
- Adelaide, SA
- Adelaide, SA
- Melbourne, VIC

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## MAL PDT in superficial and nodular BCC Phase III



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## Definition of “High Risk” BCCs

### Study 205-Europe

- A large BCC, largest diameter >20mm on extremities, >30mm on trunk, >15mm in the face
- A BCC lesion located in mid-face (nose, nasolabial or orbital areas) or ear
- A recurrent BCC lesion: treatment failure after 2 previous treatments within a year
- A BCC lesion in severely sun-damaged skin where surgery or radiation therapy is not suitable due to frequent recurrence/occurrence

### Study 310- Australia

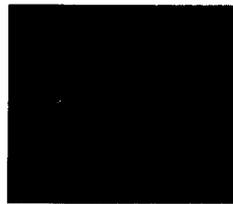
- A large BCC, largest diameter >15mm on extremities, >20mm on trunk, >15mm in the face
- A BCC lesion located in the H-zone as described by Swanson (mid-face, temple or ear)
- A BCC lesion in a patient with high risk of surgical complications due to bleeding abnormalities, anticoagulant medication and/or cardiac risk factors

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## 205 high risk: central face/ear



205-1003-200499-1



205-0904-140100-2



205-802-270599-2



205-0508-0207799-2

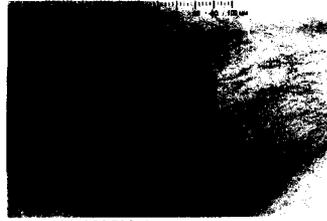
205-0508-130100-2

86

## 205 large BCCs, multiple



205-308-250599-2



205-308-250599-1

87

## 205 severely sun-damaged patients



205-310-270599-6



205-310-270599-8



205-301-248499-1



205-306-170599-4

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## 310 H zone lesions



89

## 310 large BCCs, lower legs



65yo diabetic-CR

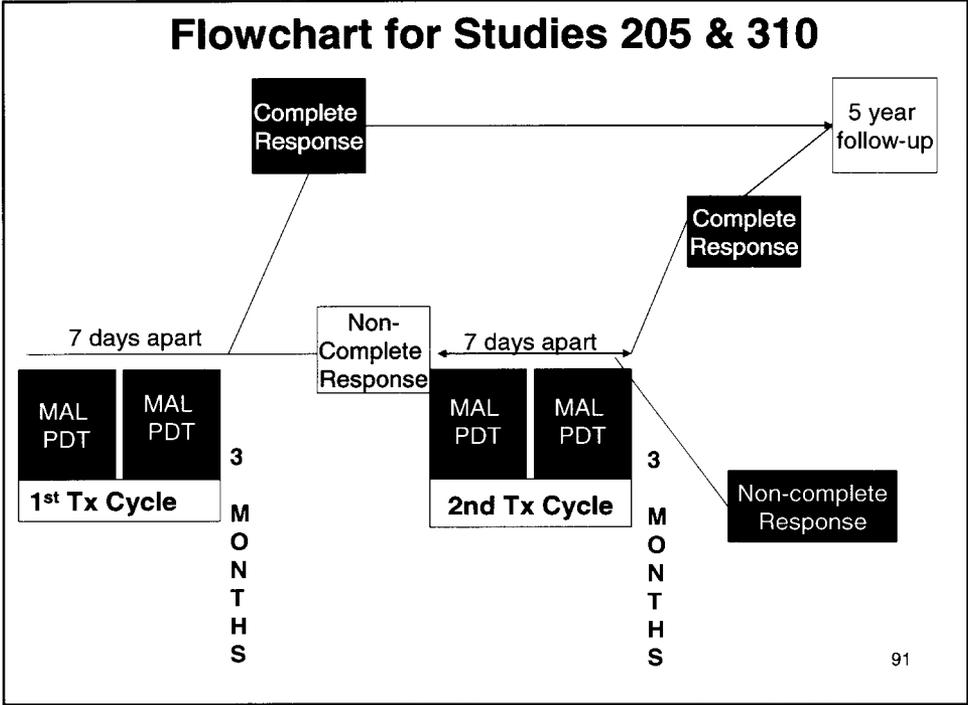


80yo F -CR



47yo AIDS pt  
Hep B +ve- CR

90



### Histologic verification of complete response

**Study 205:**  
One biopsy per lesion

**Study 310:**  
Histologic verification  
3 months after last  
treatment with multiple  
biopsies

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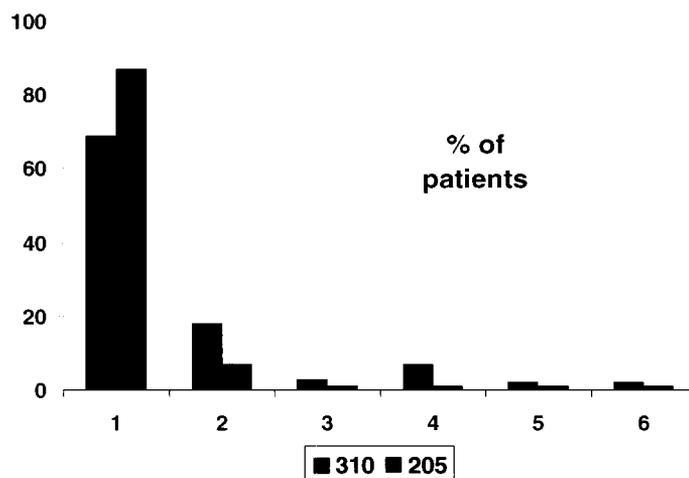
## Role of independent reviewer

### Study 205: Independent Reviewer reviewed photos and histology reports

- Baseline to confirm adherence to inclusion criteria
- 3 months after last PDT to assess response and cosmetic outcome

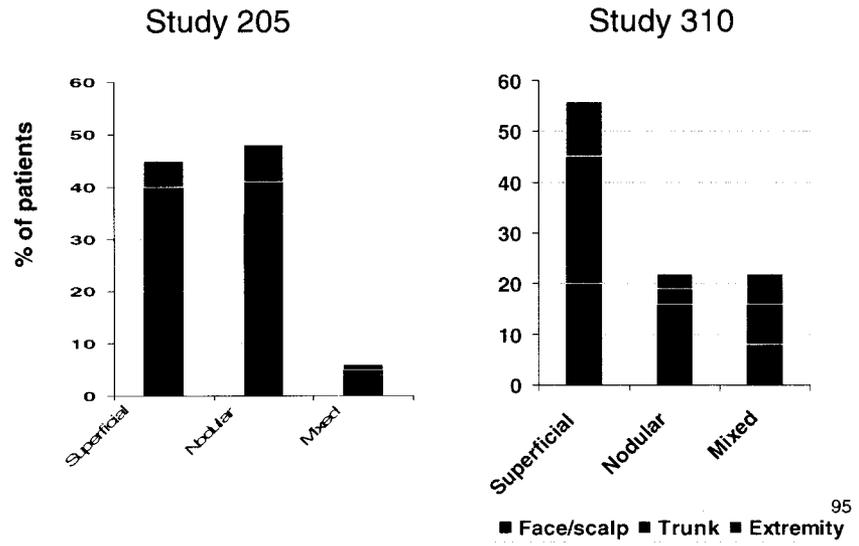
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## Number of lesions per patient



94

### LESION TYPE AND LOCATION



### Lesion diameter

Study	Longest Lesion Diameter (mm)			
	N	Mean	STD	Range
205	123	23.0	17.0	3 - 110
310	165	19.7	11.4	3 - 62

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## Distribution of “high risk” criteria

### STUDY 205

- Large 52%
- Mid-face 43%
- Recurrent 13%
- Severely sun-damaged skin 15%

### STUDY 310

- Large 55 %
- H-zone 29 %
- Surgical risk only 16 %

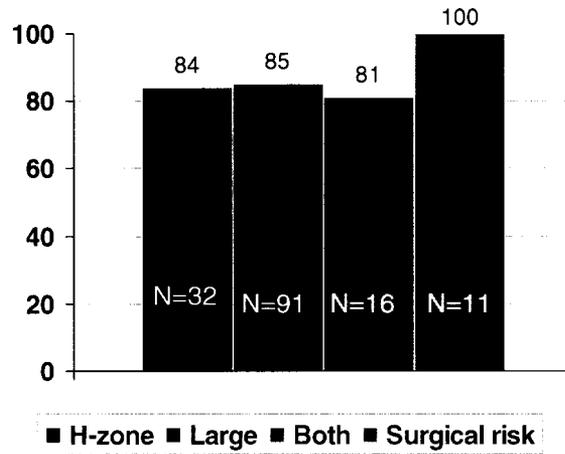
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## Primary Efficacy Endpoint High Risk BCC

STUDY	PATIENT COMPLETE RESPONSE RATE	
	ITT	PP
PC T205/98	68/94 (72% )	61/85 (72%)
PC T310/00	82/102 (80% )	81/95 (85%)

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**% Complete response by lesion inclusion criteria,  
Study 310 (ITT)**



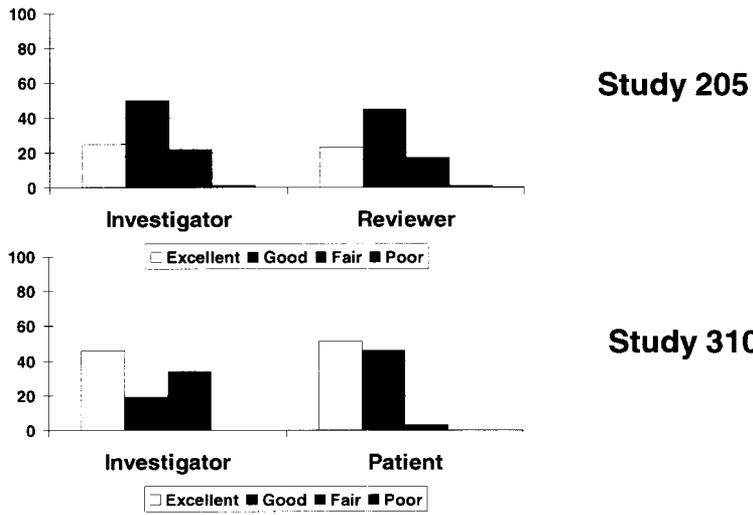
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**Lesion Complete Response Rate**

STUDY	LESION COMPLETE RESPONSE RATE (n/N (%))	
	ITT	PP
PC T205/98	92/123 (75%)	80/108 (74%)
PC T310/00	141/165 (85%)	131/148 (89%)

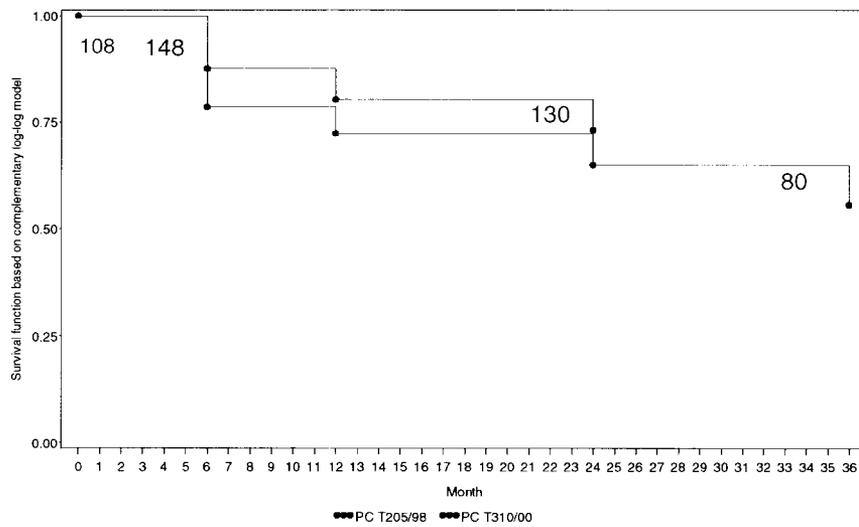
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## Cosmetic Outcome



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## Time to treatment failure High Risk BCC, studies 205 and 310



## Efficacy Conclusions Uncontrolled Studies 205 & 310 in “high risk” BCCs

- Supportive evidence of efficacy & utility in patients with high risk superficial and nodular BCC
- MAL-PDT offers an alternative treatment for BCCs where Mohs is not usually used
  - large superficial BCCs
  - lower leg lesions
  - Patients with medical contraindications
- Good to excellent cosmetic outcome demonstrated in patients with
  - Central facial & ear lesions
  - Large superficial BCCs

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## AGENDA - Presentations by Sponsor PhotoCure ASA

Topic	Presenter
<b>Introduction and Rationale for development of photodynamic therapy with methyl aminolevulinate (MAL PDT)</b>	Vidar Hansson, MD, PhD
<b>Regulatory Overview</b>	William A. Clementi, Pharm D, FCP
<b>Overview of Clinical Development Program of MAL PDT in BCC</b>	Kjetil Hestdal, MD, PhD
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<b>MAL PDT in BCC Benefit/risk</b>	Kjetil Hestdal, MD, PhD

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## **Safety of MAL-PDT**

John Posner MD PhD FRCP  
Consultant in Pharmaceutical Medicine

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## **Safety of MAL-PDT**

John Posner MD PhD FRCP  
Consultant in Pharmaceutical Medicine

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## Contents

Definitions and Methodology  
Safety Patient Population  
Adverse Events (AE's)  
Clinical Laboratory evaluation  
Irritancy and Sensitization

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## Adverse Events - Methodology

### **AE's and Serious AE's:**

defined in accordance with ICH guidelines on GCP

**Treatment related** = 'Yes' or 'Uncertain'

### **Period of recording:**

AK: from randomization to 3 months after last treatment

BCC: from randomization to 6 months and for SAE's up to 3 years after last treatment

### **AE coding and classification:**

Local (WHO: skin and appendages with additional terms)

Non-local (all other WHO system organ classes)

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## Safety Patient Population

Clinical Trials in BCC	538
Clinical Trials in AK	383
Compassionate Use Norway	1012
Postmarketing Experience	c.35,079

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## Clinical Trial Safety (ITT) Population

**Safety Population:** all patients randomized to treatment who received at least 1 dose of randomized medication or who underwent at least 1 of the other interventions.

	BCC	AK	BCC+AK
Patients	538	383	921
Lesions	857	1505	2362
PDT sessions	1613	2260	3873

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### Number of Patients in Clinical Trials with Treatment Emergent AE's

Number of Patients	BCC	AK	BCC+AK
<b>Total</b>	538	383	921
Any AE	434 (81%)	297 (78%)	731 (79%)
Non Local	146 (27%)	83 (22%)	229 (25%)
Local	405 (75%)	282 (74%)	687 (75%)

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### Deaths and Serious AEs

	BCC	AK	BCC+AK
<b>Number of Patients</b>	538	383	921
Deaths	18	1	19
Any SAE	26 (5%)	10 (3%)	36 (4%)
Local SAE	1	0	1

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## **Non-Local Adverse Events**

Most non-local AE's were not systemic. Highest frequency were BCC at another site (coded as neoplasm) and surgical intervention for pre-existing skin lesion

There were reports of influenza like symptoms, dizziness, headache, blurred vision

**Conclusion:** No evidence of systemic effects

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## **Local AE's - Phototoxicity**

Phototoxic symptoms and signs (localized to treatment area):

Pain / Burning / Stinging skin

Erythema skin

Edema skin

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## Local AE's with MAL-PDT BCC and AK

Total Patients	921
Any Local AE	73%
Erythema	42%
Pain Skin	34%
Burning skin	31%
Edema skin	16%
Pruritus	14%
Crusting	11%
Stinging skin	10%
Skin ulceration	7%
Blisters	6%
Suppuration	5%

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## Local AE's – Severity and Discontinuations

### Severity

Mild 53%, Moderate 37%, Severe 10%  
No difference between BCC and AK

### Discontinuations

BCC 4/538 (0.7%)  
AK 9/383 (1.3%)

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## Duration of Local AE's

### 1 day or less:

Skin pain, burning sensation, stinging, tingling

### Up to 1 week:

Skin edema, peeling, bleeding, infection pruritus, itching,

### 1 to 2 weeks:

Erythema, crusting, skin ulceration, blisters, suppuration

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## Local AE's vs Number of MAL-PDT Sessions in Patients with BCC

PDT's	Number of Patients	
	Total	With AE's
1 <sup>st</sup> of 1	169	86%
1 <sup>st</sup> of 2	250	55%
2 <sup>nd</sup> of 2	250	35%
1 <sup>st</sup> of 3	25	60%
2 <sup>nd</sup> of 3	25	20%
3 <sup>rd</sup> of 3	25	12%
1 <sup>st</sup> of 4	94	64%
2 <sup>nd</sup> of 4	94	41%
3 <sup>rd</sup> of 4	94	22%
4 <sup>th</sup> of 4	94	24%

**Conclusion: No increase in number or severity of AE's with repeated application**

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### AE's in vehicle-controlled studies of nodular BCC

Number of Patients	MAL-PDT N=66	Placebo-PDT N=65
Any AE	60 (91%)	43 (66%)
Local AE	49 (74%)	30 (46%)
Non-Local AE	38 (58%)	28 (43%)

Related Local AE's

- MAL-PDT : mild 47%, moderate 53%, severe 0%
- Placebo: mild 57%, moderate 40%, severe 3%

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### AE's in surgery-controlled study of nodular BCC

Number of Patients	MAL-PDT N=52	Surgery* N=49
Any AE	27 (52%)	14 (29%)
Local AE	26 (50%)	8 (16%)
Non-Local AE	7 (13%)	9 (18%)

\* Patients received local anesthesia

Related Local AE's

- MAL-PDT : mild 72%, moderate 24%, severe 4%
- Surgery: mild 100%, moderate 0%, severe 0%

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### AE's in cryotherapy-controlled study of superficial BCC

Number of Patients	MAL-PDT N=60	Cryotherapy N=58
Any AE	45 (75%)	46 (79%)
Local AE	42 (70%)	45 (78%)
Non-Local AE	17 (28%)	21 (36%)

**Related Local AE's**

- MAL-PDT : mild 74%, moderate 17%, severe 10%
- Cryotherapy: mild 61%, moderate 36%, severe 2%

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### Compassionate Use Study

1012 patients with 3457 BCC + 1470 AK lesions + some other non-melanoma skin cancers treated in Norway with formal collection of solicited data on pain / erythema and other AE's recorded

**Main findings:**

Majority of patients had evidence of phototoxicity  
3 non-local AE's

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## Post Marketing Experience

First marketed in October 2001 (Sweden) and recently launched in 3 other Nordic countries, UK and Germany. By June 2003 c.35,079 patients exposed to MAL-PDT in routine clinical use (probably most had 2 PDT sessions)

### **5 patients** - unexpected ADRs

1 herpes zoster, 1 dizziness, 1 headache, 2 eczema

### **3 patients** – serious expected ADRs

2 facial edema, 1 second degree burn

### **5 patients** – non-serious and expected ADRs

Phototoxic reactions

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## Clinical Laboratory AK and BCC (Phase 1 and 2 studies)

CBC's and plasma biochemistry examined in 375 patients in 5 Phase I/II studies

In Study 205/98 in which all 78 patients with High-Risk lesions were treated with standard regimen LFTs, ALT, AST, Bilirubin:

Uniform distribution of changes from baseline

No patient had increase > 2 x baseline

Remainder had changes of < 40%

1-3 % had increases or decreases of 40-80%

**Conclusion: No clinically relevant findings in LFTs or other laboratory parameters**

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## Skin irritancy, sensitization and cross-sensitization to 5-ALA

### Study 110/03

“A double-blind, within-subject, vehicle-controlled, randomized, single center study in healthy volunteers, assessing sensitization by MAL cream and it’s vehicle, and cross-sensitization to 5-ALA and it’s vehicle.”

Day	-7 - 0	1-22	23-36	37-39	39-41	42-45
	Screen	Induction	Rest	Challenge	Assess	Follow-up
		MAL / V		MAL / V ALA / V	48, 72, 96 h post start of challenge	
<b>Number of HV's</b>	224	156		58 both 40 ALA / V		

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## Skin irritation and sensitization

### Irritancy

All but one subject reacted with erythema during the 3 week induction period of exposure to MAL.

The earliest reaction of moderate severity occurred after 4 days of constant exposure.

Very little reaction observed on sites exposed to vehicle.

### Sensitization

30 of 58 (52%) subjects had positive reactions to challenge with MAL vs 1 subject with Vehicle

0 of 98 subjects had positive reactions to ALA

### Conclusion

MAL can cause irritation and contact sensitization with no evidence of cross-sensitization to 5-ALA

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## **Clinical Relevance of findings**

**The clinical relevance of these findings is questionable:**

Sensitization in clinical practice is rare

- 1 confirmed case report post-marketing
- no definite case in 921 patients in Clinical Trials

Conditions in clinical practice are very different:

- Short exposure (3 hours vs 3 weeks continuous)
- No irritancy seen in normal clinical use
- Illumination (Photobleaching / Phototoxicity)
- Different occlusive dressing (Tegaderm vs aluminium Finn chamber + opaque adhesive tape)

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## **Overall Safety Conclusions 1**

**Clinical Trials of MAL-PDT in > 900 patients, compassionate use in > 1000 patients and post-marketing data in >35,000 patients indicate:**

**No evidence of systemic effects of MAL-PDT**

**MAL-PDT does not cause generalized photosensitivity**

**MAL-PDT is well tolerated, despite frequent local phototoxic reactions**

- Very low (1%) incidence of discontinuation due to phototoxic reactions and only one leading to hospitalization (SAE) in clinical trials

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## Overall Safety Conclusions 2

**MAL can cause local irritation and contact sensitization in an intensified and prolonged exposure with no cross-sensitivity to ALA**

**Definite cases of sensitization in clinical practice appear to be rare (only 1 definite case post-marketing)**

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## AGENDA - Presentations by Sponsor PhotoCure ASA

Topic	Presenter
Introduction	Hilde Morris, DVM
Regulatory Overview	William A. Clementi, Pharm D, FCP
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## **MAL PDT in BCC Benefit Risk**

Kjetil Hestdal, MD, PhD

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### **Demonstrated benefits of MAL PDT**

- Safety and efficacy have been established in two vehicle controlled studies based on histological end points
- Initial and sustained response rates were similar to cryotherapy through 3 years of follow up
- A favorable safety profile has been established in clinical trials and post marketing experience
- Cosmetic outcome is superior to that of cryotherapy and excisional surgery

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## Manageable risks of MAL PDT

- ❑ MAL PDT was shown to give similar initial response and lower sustained response rates compared with surgery up to 36 months after treatment of nodular BCC
  - There is retained ability to treat with other modalities
- ❑ Treatment success may require second course of treatment at 3 months in some individuals
  - Data indicate similar rate of retreatment with cryotherapy
  - BCC treatment guidelines already incorporate follow up
- ❑ Mild to moderate local phototoxic reactions
  - Very few patients (<1%) withdrawn due to phototoxic reactions
- ❑ Skin sensitization potential
  - Low rate expected in clinical use based on clinical trial and post marketing data

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## MAL PDT in BCC

- ❑ New and unique non-surgical treatment option for BCC with a favorable benefit to risk ratio
- ❑ Indicated for treatment of nodular and superficial BCC where surgery is not desirable

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Photodynamic therapy for BCC with methyl  
aminolevulinate and CureLight 01

NDA 21-576

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