ESMO 2012 POSTER DISCUSSION

Dirk Schadendorf

Director & Chair
Department of Dermatology
Skin Cancer Center

University Hospital Essen

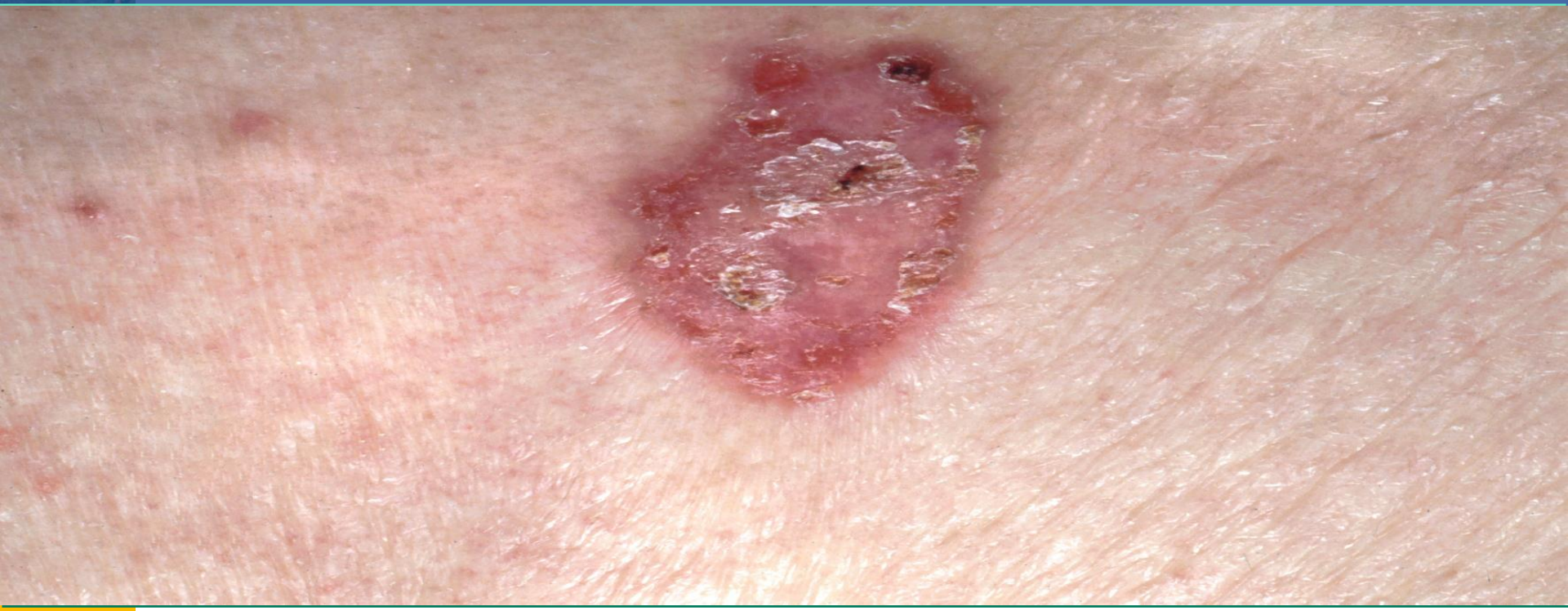
Hauttumorzentrum Essen

DKG KREBSGESELLSCHAFT Zertifiziertes Hautkrebszentrum

TÜV SÜD ISO 9001

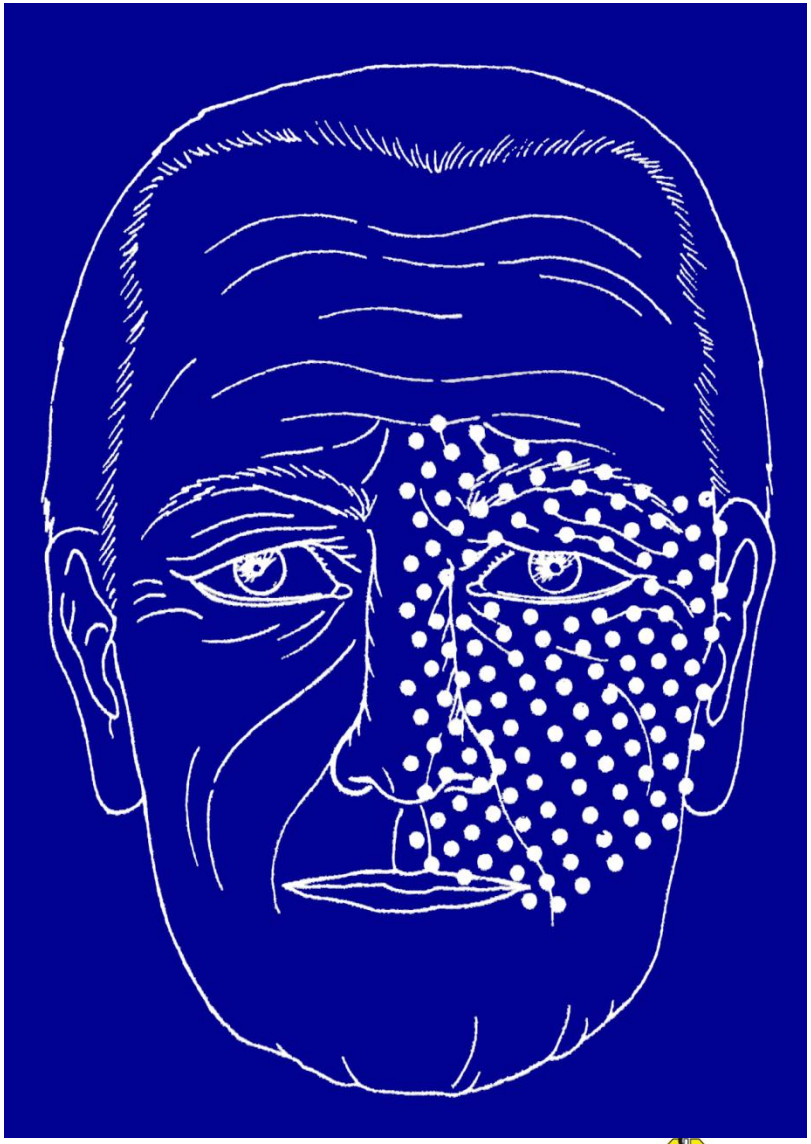
Universitätsklinikum Essen

Clinical Presentation of BCC

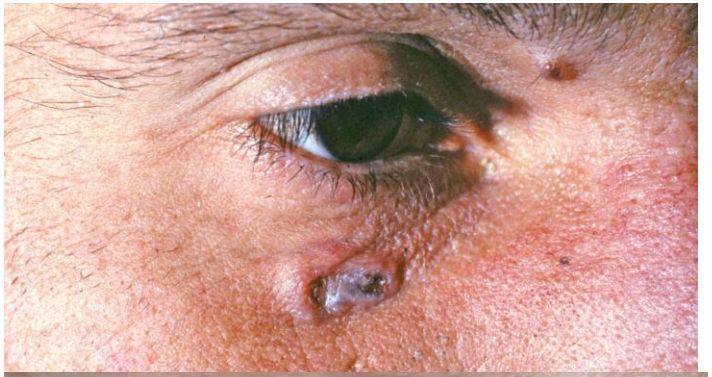


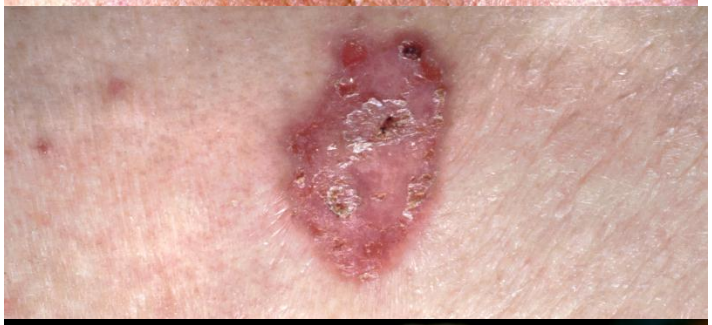
Prevalence and incidence of BCC

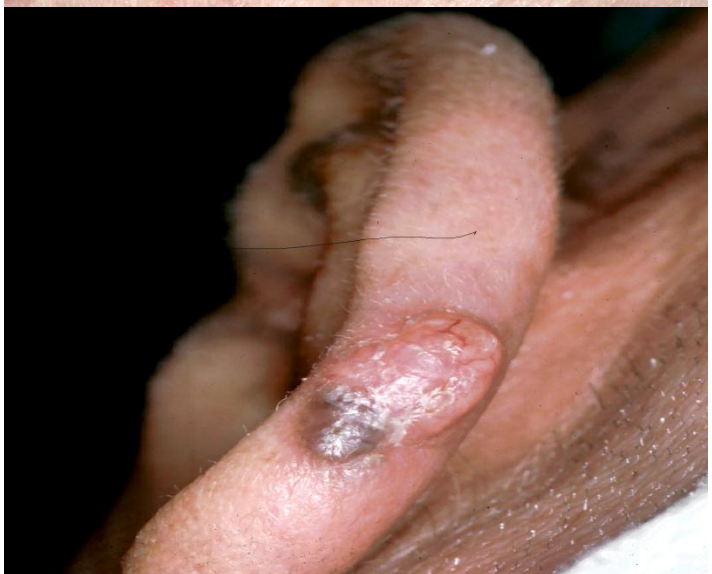
- BCC constitutes ~80% of all NMSCs, accounting for ~2 million cases worldwide each year
- A major cause of BCC is exposure to UV radiation, leading to cumulative DNA damage and gene mutations
- Epidemiological data suggest the overall incidence of BCC is increasing significantly and shows marked geographical variation[2–5]



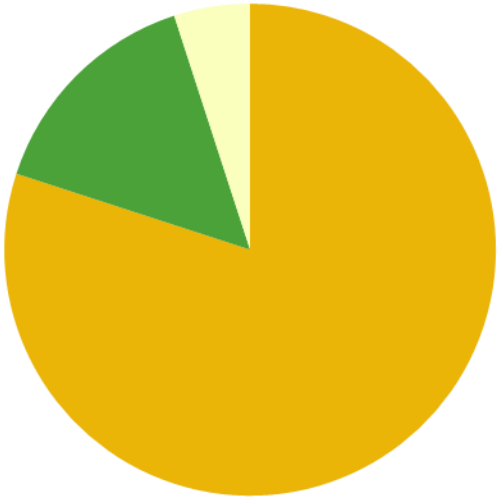
Subtypes of BCC







Most sporadic cases of BCC arise from chronic sun-exposure[1,2]

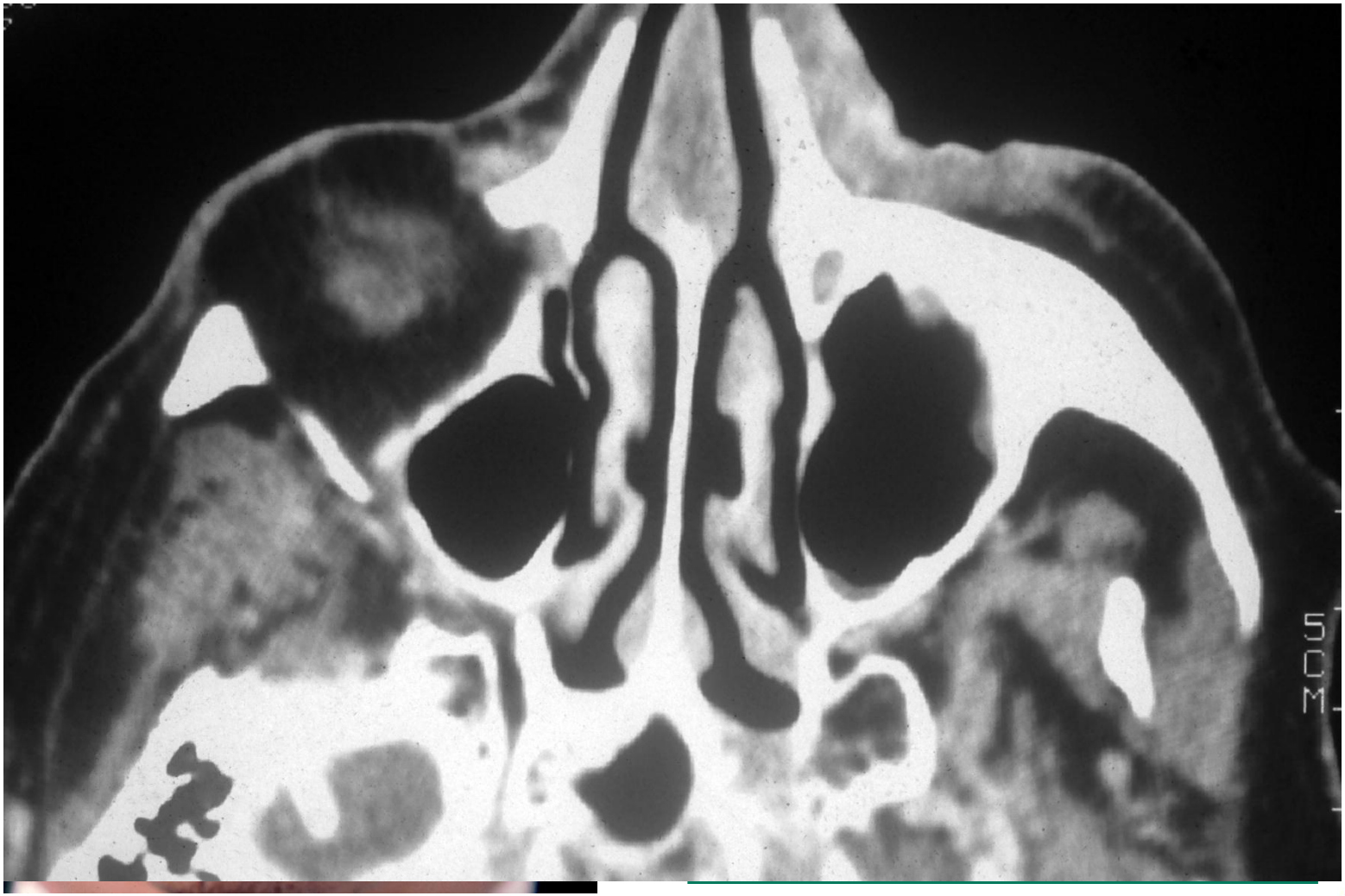


80% occur on the head and neck

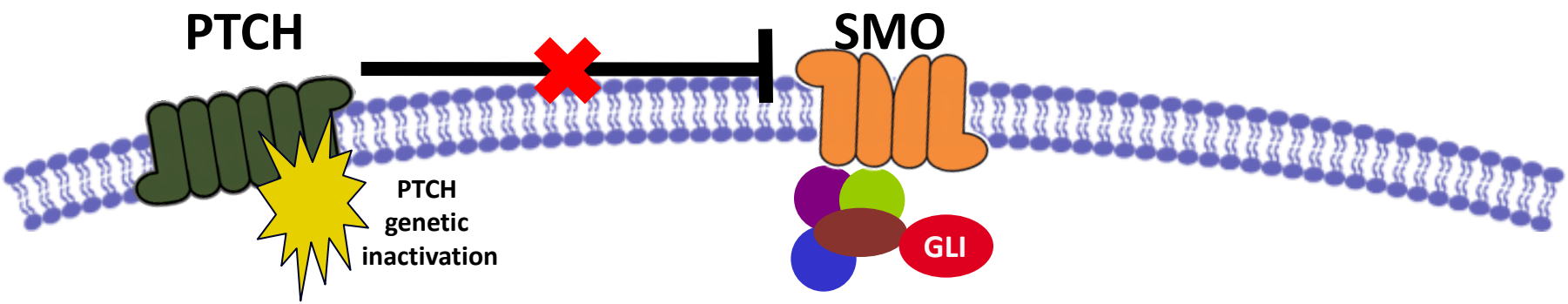
15% occur on the trunk

5% occur on the arms, legs or other sites

Limitation of Surgery



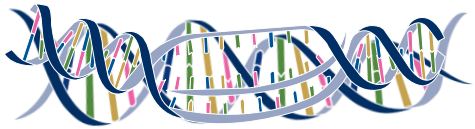
Mutation-driven Hedgehog signalling is involved in BCC: Inactivating PTCH mutations



Inactivating genetic alterations of PTCH (e.g. mutations, methylation, etc.) prevent inhibition of SMO, leading to constitutive activation of the Hedgehog signalling pathway

CONSITUTIVE SIGNAL

Transcription of target genes



Tumour cell proliferation

Inhibitors of SMO – central mediators of Hedgehog pathway signalling

vismodegib
GDC-0449
LDE225

PTCH

SMO

Inhibition

PTCH genetic inactivation

GLI

NO SIGNAL

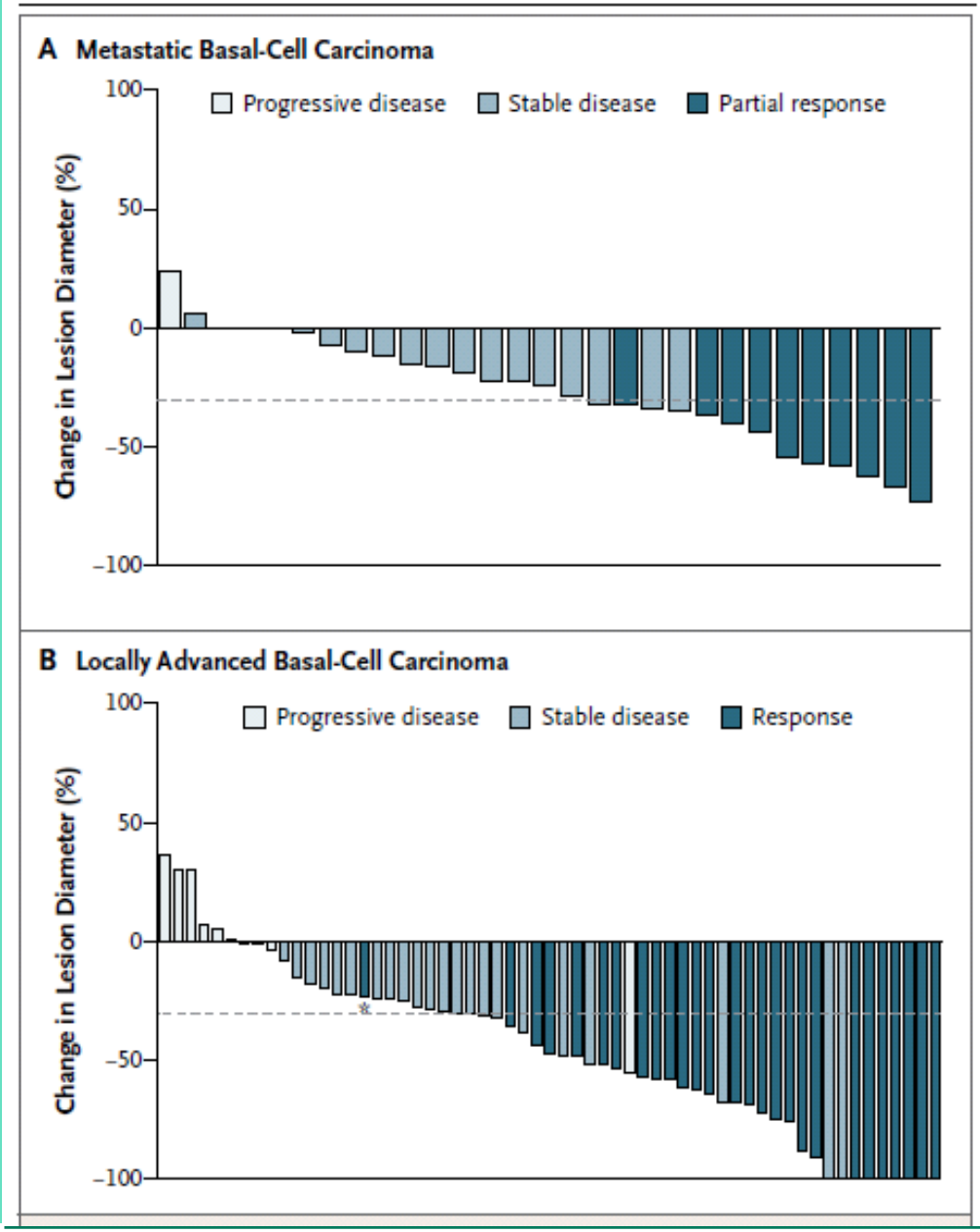
Inhibition of tumour growth

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2012;366:2171-9.

degib
noma

n, M.D.,
D. Lewis, M.D.,
Simon Yoo, M.D.,
Ellen Marmur, M.D.,
g, M.D.,
ert L. Yauch, Ph.D.,
kel Hauschild, M.D.



Efficacy and safety of vismodegib in patients with advanced basal cell carcinoma (BCC): 12-month update of the ERIVANCE BCC study

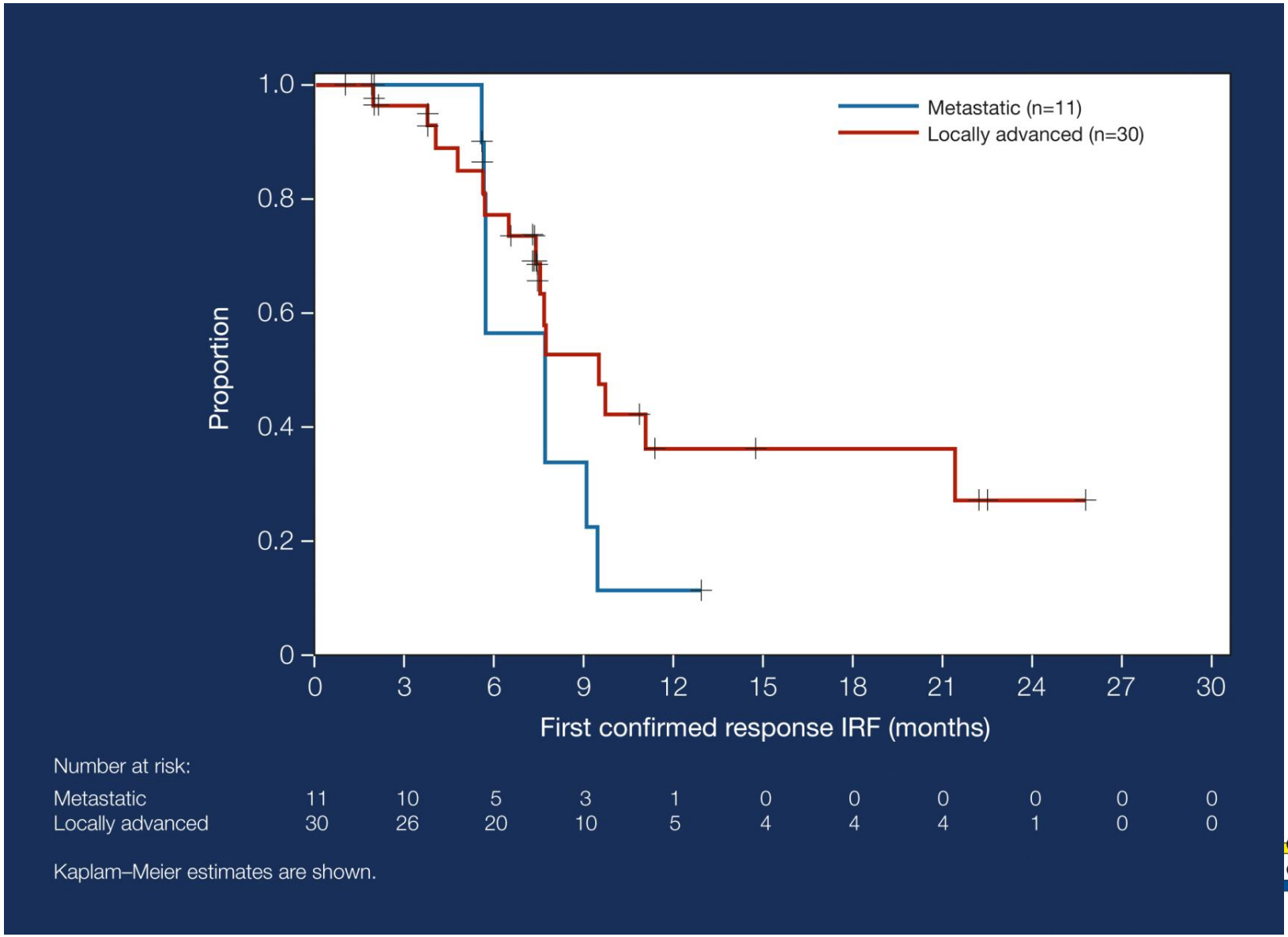
Presented as a poster at ESMO 2012

Aleksandar Sekulic, MD, PhD

On behalf of: Michael R. Migden, Anthony E. Oro, Karl Lewis, John D. Hainsworth, James A. Solomon, Simon Yoo, Sarah T. Arron, Philip A. Friedlander, Ellen Marmur, Charles M. Rudin, Anne Lynn S. Chang, Luc Dirix, Jeannie Hou, Huibin Yue, and Axel Hauschild, and the

ERIVANCE BCC study investigators

Duration of response by Independent Review Facility (efficacy evaluable patients)



Median duration of response by Independent Review Facility

- **Median DOR remained similar to the primary analysis**

	mBCC (n=33)		laBCC (n=63)	
	Nov 26, 2010	Nov 28, 2011	Nov 26, 2010	Nov 28, 2011
Median DOR, months [95% CI]	7.6 [5.6–NE]	7.6 [5.5–9.4]	7.6 [5.7–9.7]	9.5 [7.4–21.4]

- Data from the 12-month update further support the durability of response observed in vismodegib-treated patients with advanced BCC, and also confirm the manageable safety profile of vismodegib
- These updated results with 12 additional months of follow-up confirm durable tumor responses with vismodegib treatment, which is clinically meaningful in this population of advanced BCC with a high unmet medical need

Expanded access study of laBCC and mBCC patients treated with the Hedgehog-pathway inhibitor vismodegib

Glen J. Weiss, Anthony E. Oro, Anne Lynn S. Chang, James A. Solomon, Patricia LoRusso, Omid Hamid, Bann-mo Day, Edward McKenna, Diana M. Chen, John D. Hainsworth

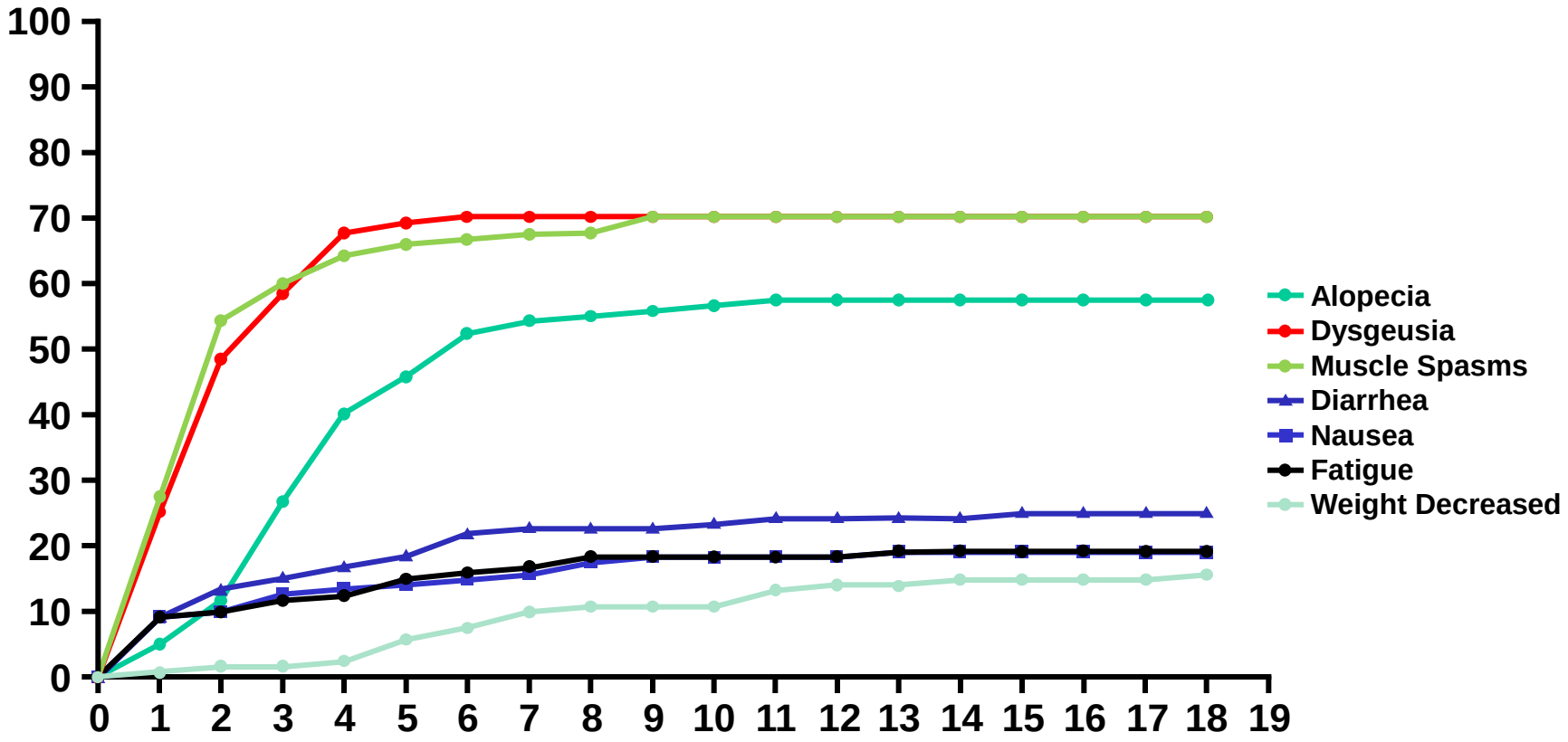
Overall response (RECIST) to vismodegib therapy in advanced BCCs at study termination

	laBCC (n=57)	mBCC (n=39)
Objective response, n (%)	26 (45.6)	12 (30.8)
(95% CI)	(32.4–59.3)	(17.0–47.6)
Complete response, n (%)	6 (10.5)	2 (5.1)
Partial response, n (%)	20 (35.1)	10 (25.6)
Stable disease, n (%)	28 (49.1)	20 (51.3)
Progressive disease, n (%)	0	3 (7.7)
Unevaluable/missing, n (%)	3 (5.3)	4 (10.3)
Median (range) time to response, months[a]	2.6 (1.0–11.0)	2.6 (1.4–12.6)

Patients determined at baseline to have measurable disease by RECIST version 1.0.

[a]Response assessments q4–8 weeks by physical exam; q8–16 weeks by radiographic.

Cumulative occurrence of selected AEs by cycle



Conclusions

- Safety findings are similar to those reported in the pivotal study in patients with advanced BCC
- Most common AEs occur by Day 60 after treatment initiation, but alopecia and weight decreased have a more gradual onset
- Targeted inhibition of Hedgehog signaling with vismodegib demonstrated substantial clinical activity for patients with advanced BCC who cannot be treated by surgical resection or radiotherapy

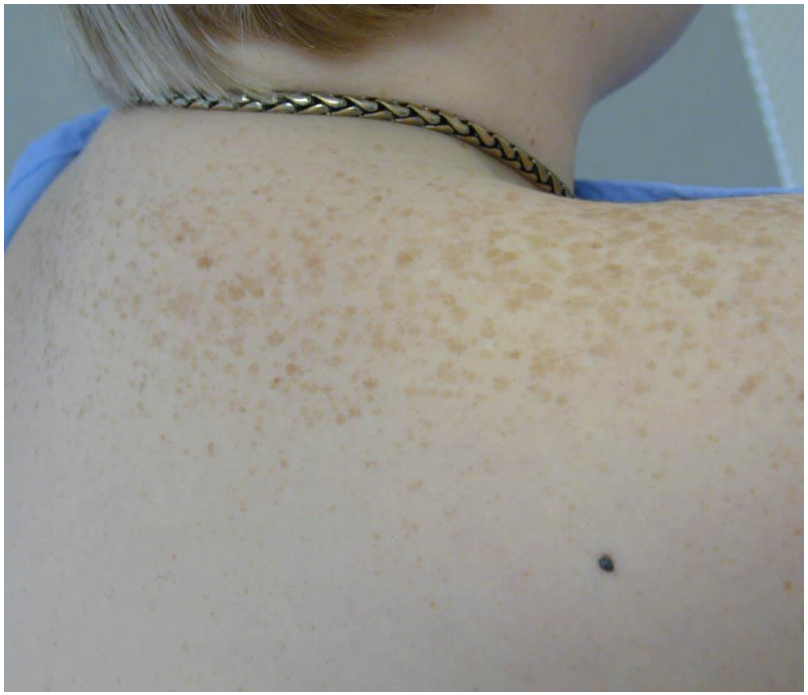
Melanoma – Open Questions

- who will be affected by melanoma?
- who is at risk of metastasizing?
- who will benefit from which therapy?

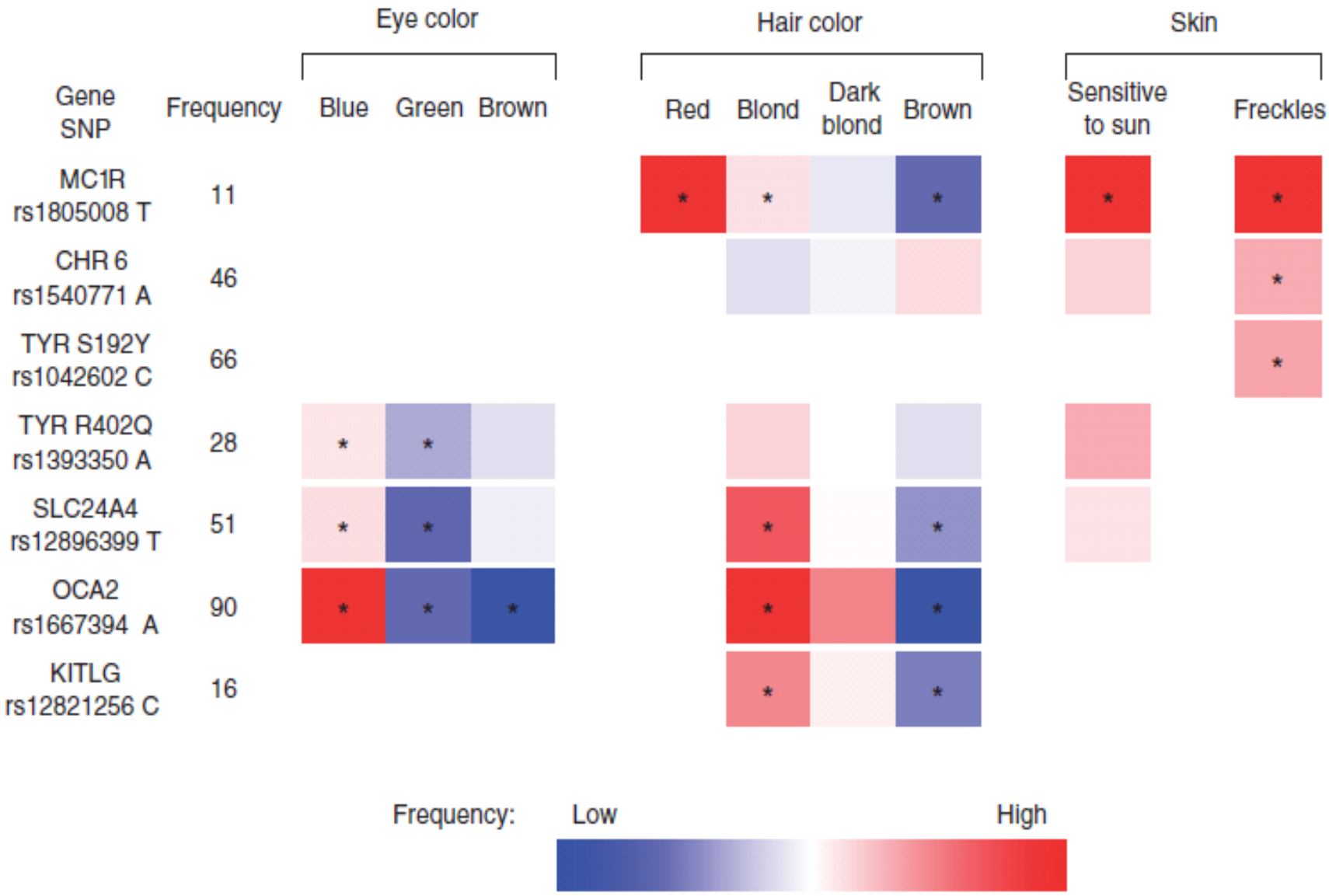
Who will be affected?

- Keltic origin, „fair complexion“
  - high sun sensitivity
  - freckles
- UV exposure
  - intermittent-excessive
  - sun burns in childhold
- MM in own and/or familiy
- high nevus counts (>50):

  RR 5x increased
- multiple dysplastic nevi (>5)
- actinic lentigenes
- geographic localisation / place of living



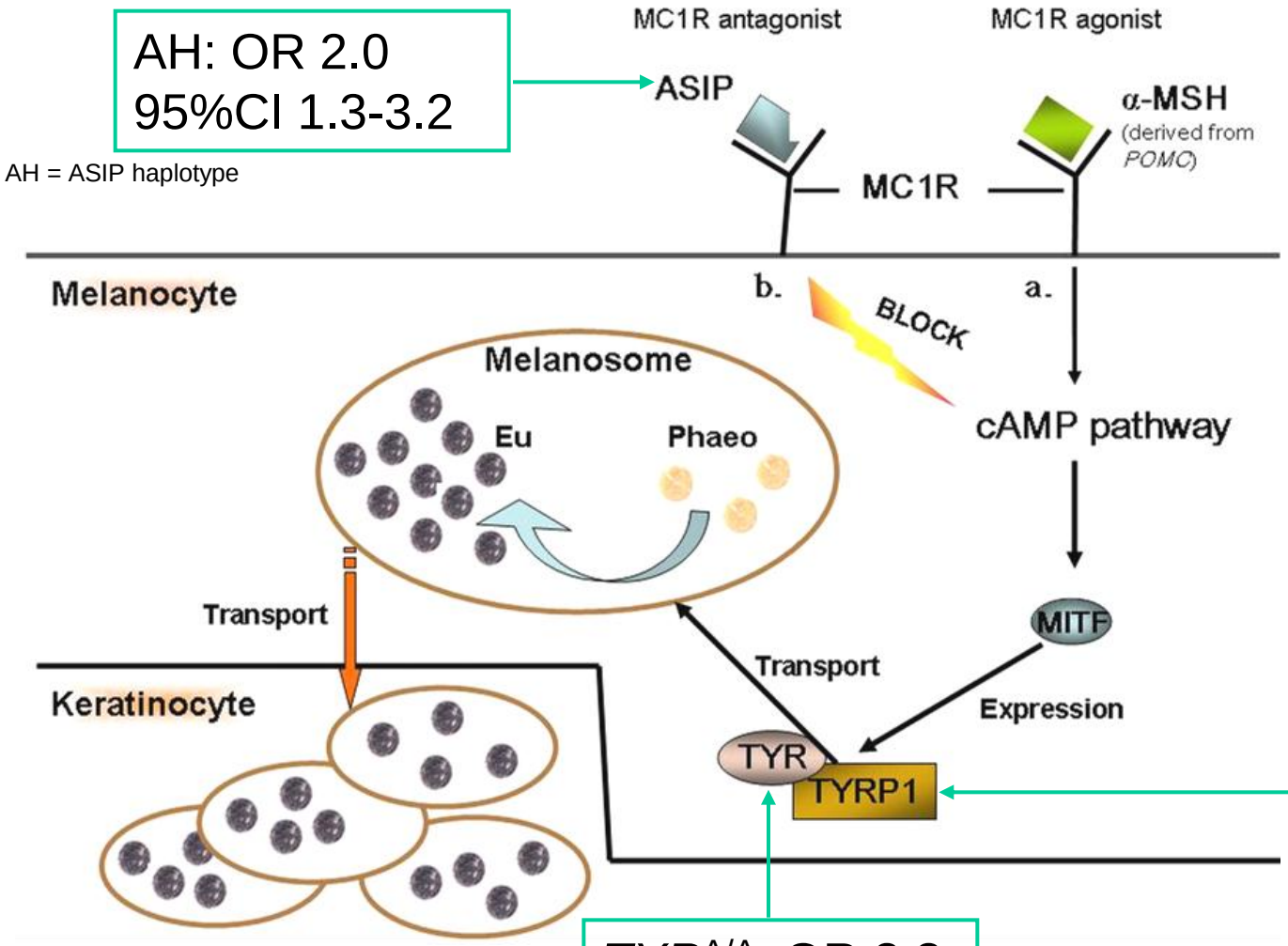
Genes and SNPs affecting Phenotype



Pigmentation Genes & Melanoma Risk

AH: OR 2.0
95%CI 1.3-3.2

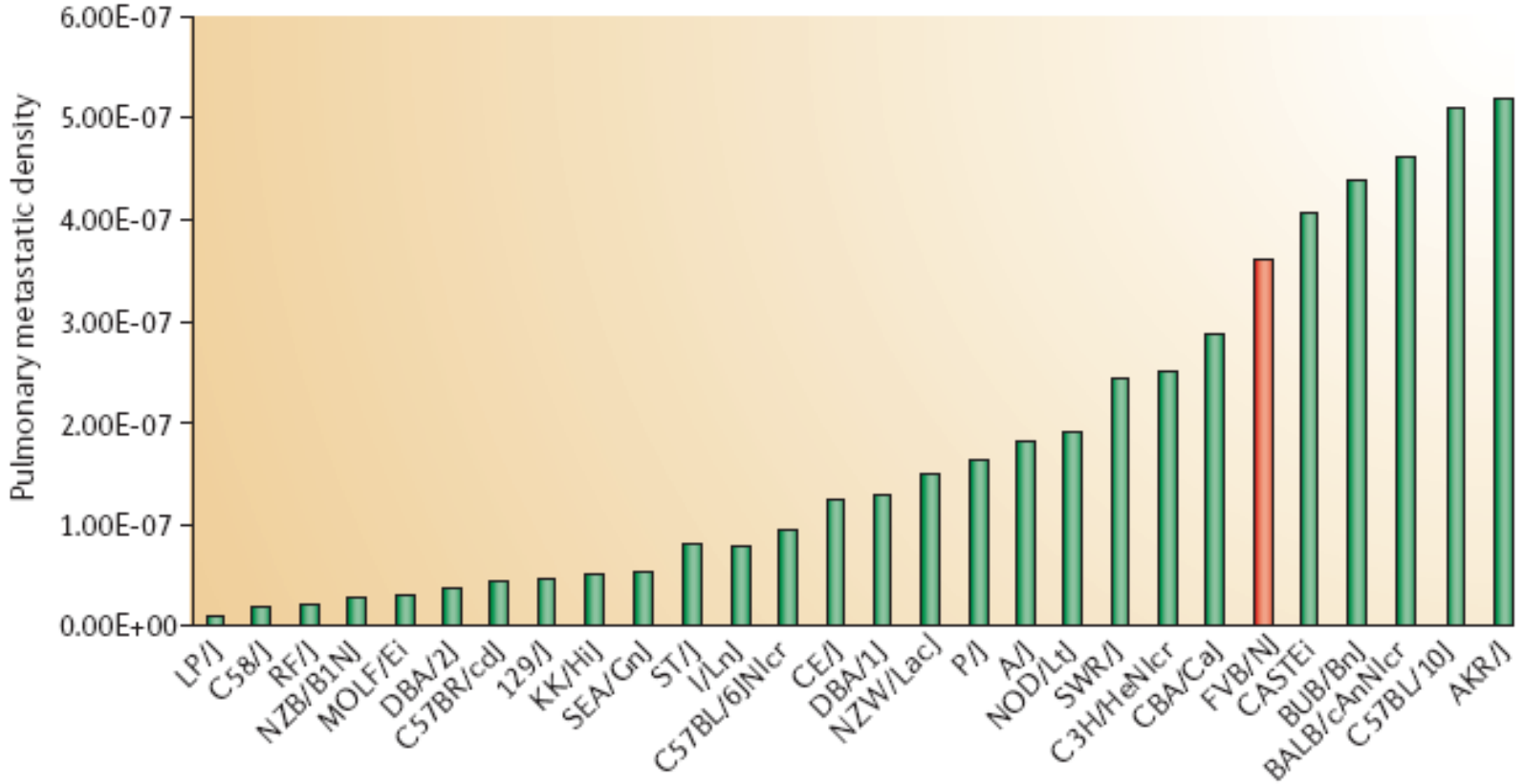
AH = ASIP haplotype



TYRP1$^{T/T}$: OR 0.8
95%CI 0.5-1.2

TYR$^{A/A}$: OR 2.3
95%CI 1.3-4.0

Genetic Background and Clinical Course



Genetic predisposition has profound effect on clinical outcome!

quantified (y axis) in the transgene-positive F1 female progeny. The red bar represents the metastatic efficiency of the polyoma middle-T antigen-expressing tumour in the original FVB/NJ homozygous inbred background.

Hunter 2006 Nat Rev Cancer

The melanoma risk loci as determinants of melanoma prognosis.

Tomas Kirchhoff, Justin Rendleman, Shulian Shang, Christine Brocia, Michelle W. Ma, Richard L. Shapiro, Russell S. Berman, Anna C. Pavlick, Yongzhao Shao, Iman Osman,

NYU Langone Medical Center,

New York University School of Medicine, New York, NY

BACKGROUND.

•The goal of this study is to assess the association of *108 established melanoma genetic susceptibility* loci, found by recent GWAS, with melanoma progression, clinical outcome, and prognosis

METHODS.

•891 melanoma patients prospectively accrued and followed were studied

•Univariate and multivariate Cox proportional hazards models were used to test the association between each SNP and **recurrence-free survial (RFS) and overall survival (OS)**

•Multivariate analyses were stratified by tumor stage and adjustments included age, gender, ethnicity, histological type, thickness, ulceration status, and anatomic site.

•Associations with RFS and OS were also analyzed among different clinicopathological subgroups including:

- ➢histological subtype (superficial spreading melanoma, nodular melanoma)
- ➢primary tumor ulceration status (present, absent)
- ➢primary tumor thickness (<1mm, 1mm-4mm, >4mm)

•ROC curves were used to measure utility of SNPs in classifying 3-year recurrence

RESULTS.

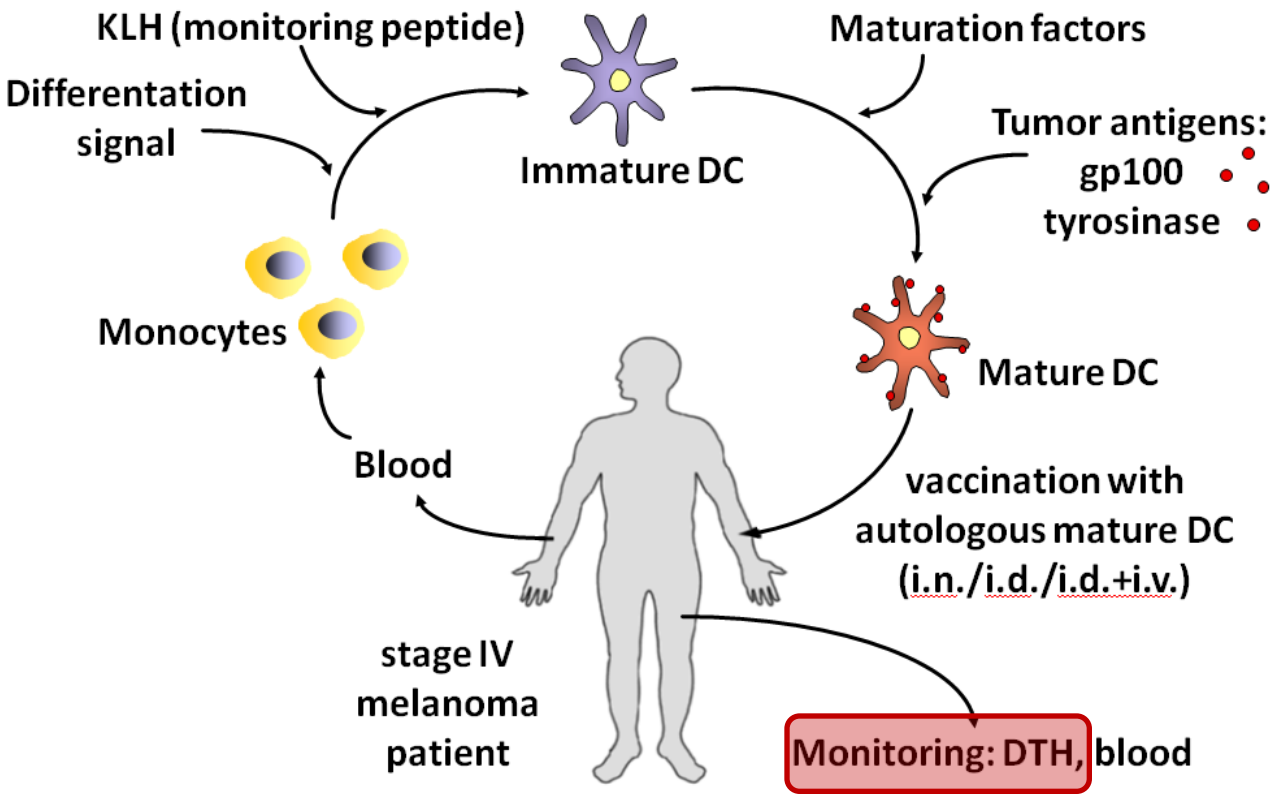
- The most promising associations were observed from the multivariate analysis for:
  - rs7538876 with RFS (HR=1.48, 95% CI 1.20–1.83, p=0.0002, Table 2)
  - rs9960018 with RFS (HR=1.43, 95% CI=1.07-1.91, p=0.0159, Table 2)
  - rs9960018 with OS (HR=1.52, 95% CI=1.09-2.13, p=0.0138, Table 2)
- **rs7538876 passed the correction for multiple testing (p=0.01)**

PROBLEMS:

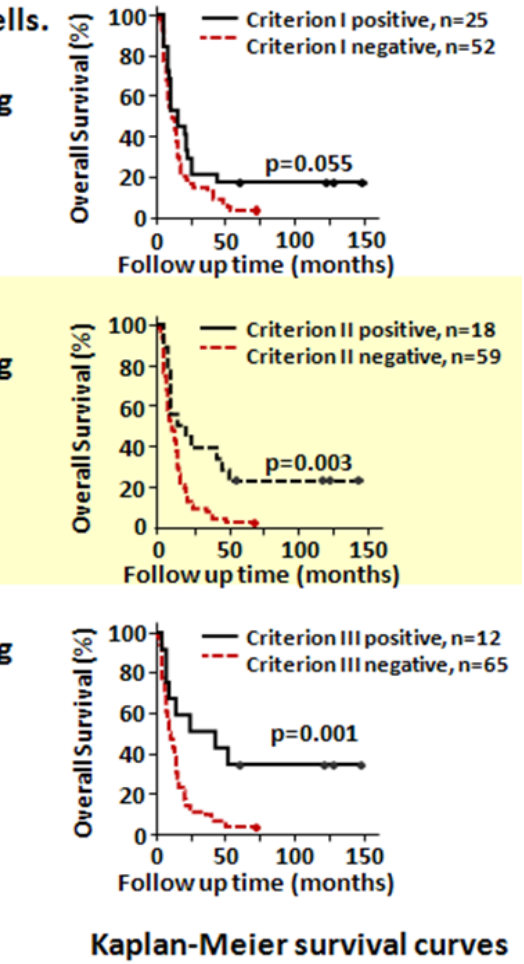
- small patient group
- no validation!!!!

Skin-test infiltrating lymphocytes predict clinical outcome of dendritic cell based vaccination in metastatic melanoma

Dendritic cell vaccination protocol



Skin-test infiltrating lymphocytes predict clinical outcome of dendritic cell based vaccination in metastatic melanoma



Kaplan-Meier survival curves

- Test #1 (n=77pts) : **Tetramer binding** (3 TAA); 25 pts +
- Test #2 (n=25pts) : **peptide recognition**; 18 pts +
- Test #3 (18=pts) : **natural TAA processing**; 12 pts +

Open questions

- T cell infiltration and functionality really dependent on vaccine?
- What is needed to increase T cell functionality?

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