

Figure 4

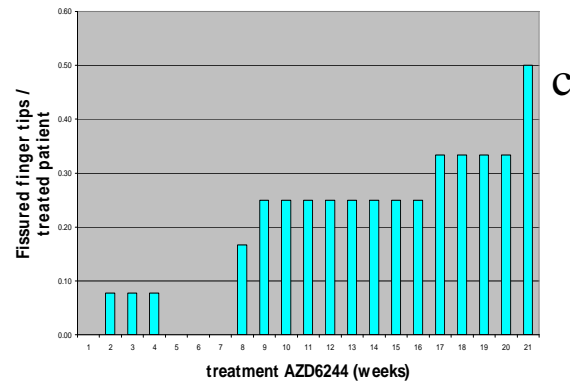
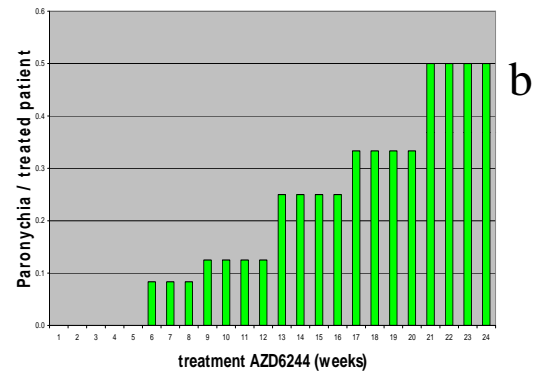
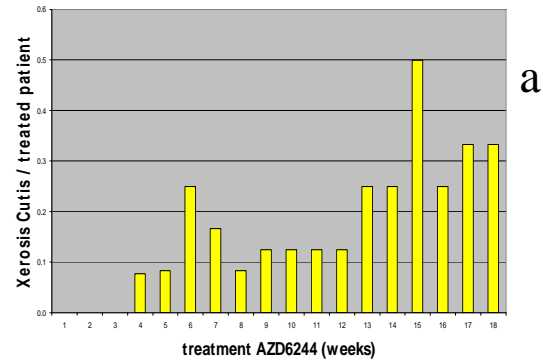


Figure 4
time course of chronic skin changes
a) xerosis cutis
b) paronychia
c) fissured finger tips

Figure 5



Figure 5 chronic skin changes:

- a) left arm with xerosis cutis of 46-year old women, treated with the MEK inhibitor for 15 weeks
- b) fissured finger tips in a 59 year old woman treated with the MEK inhibitor for 8 weeks

Figure 6

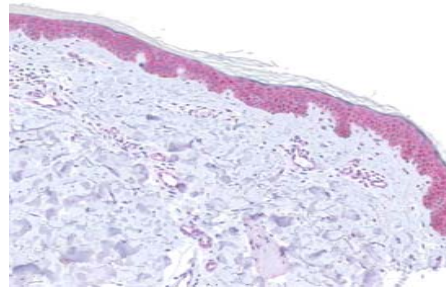
a) Histology of p53 staining in MEK treated patients and matched control

b) Histology of Ki67 staining in MEK treated patients and matched control

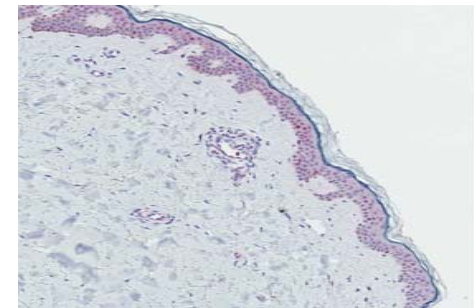
c) Histology measurement of epidermal thickness in HE staining of MEK treated patient and matched control

d) TUNEL staining in MEK treated patient. There was no nuclear signal in the matched control

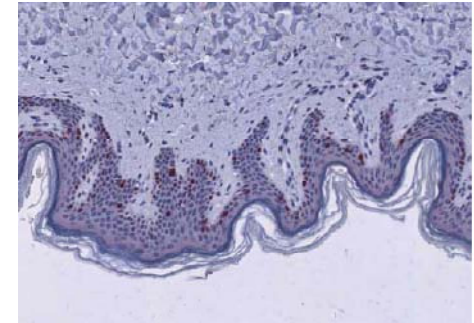
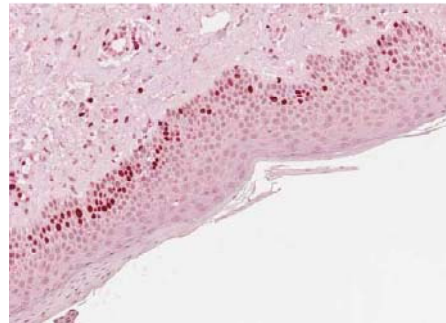
a



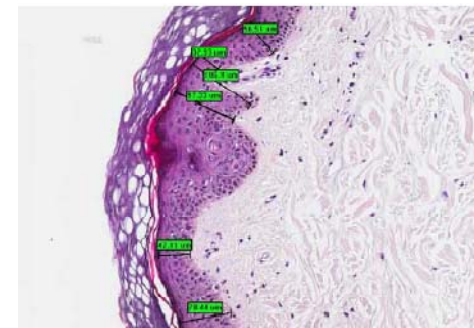
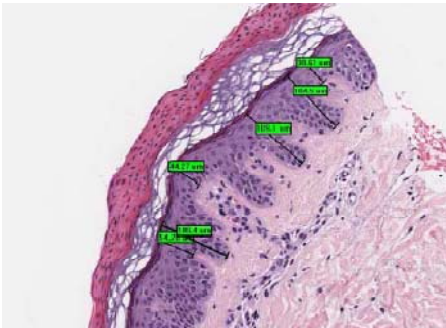
Matched controls



b



c



d

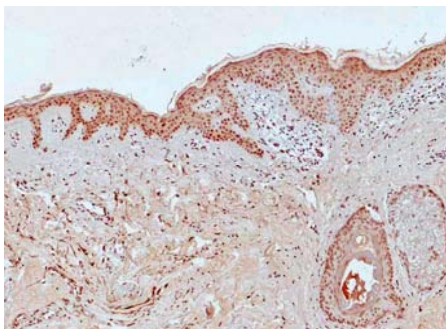


Figure 7

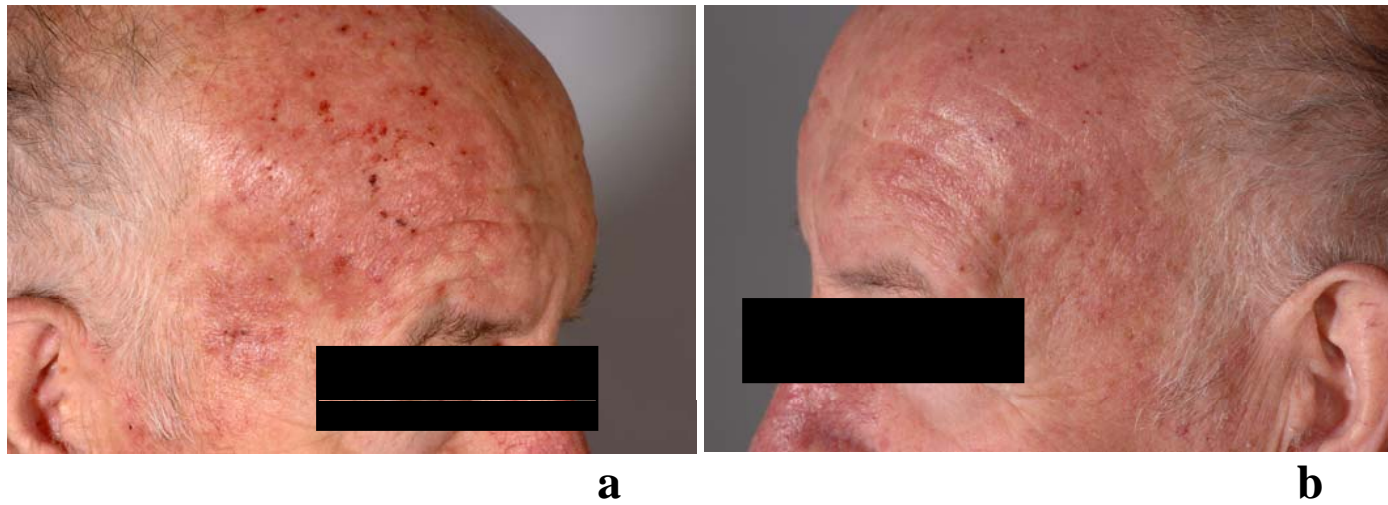


Figure 7

Image of half side treatment experiment in a 72-year old man, treated with the MEK inhibitor for 4 weeks

a) under treatment with the antibiotic acne therapeutic Erythromycin gel 4% for 1 week

b) under treatment with Halomethason-Monohydrat 0,5 mg/1g, Triclosan 10 mg/1g cream for 1 week

Figure 8



Figure 8 Photodistribution of skin eruption in a patient treated with AZD6244

Table 2 p53 positive cells significantly elevated in MEK treated patients compared to matched controls (p=0.00080)

MEK treated patients	p53 pos cells total Mean	Matched controls	p53 pos cells total Mean
M1	3.7	C1	1.3
M2	0.3	C2	0.3
M3	3.7	C3	1.3
M4	12.0	C4	0.7
M5	2.3	C5	0.3
M6	1.7	C6	1.0
M7	7.7	C7	0.7
M8	11.0	C8	3.3
M9	16.3	C9	0.7
M10	5.0	C10	0.3
M11	5.7	C11	1.3
M12	8.7	C12	0.7
M13	10.3	C13	1.3

Table 3 shift of Ki67 positive cells from the basal to the suprabasal keratinocyte-layers in MEK treated patients compared to matched controls (p=1.242 E-10)

MEK treated patients	MEK Quotient Ki67 suprabasal vs total	Matched controls	Matched Controls Quotient Ki67 suprabasal vs total
M1	0.85	C1	0.22
M2	0.93	C2	0.23
M3	0.93	C3	0.47
M4	0.71	C4	0.34
M5	0.96	C5	0.21
M6	0.85	C6	0.25
M7	0.68	C7	0.15
M8	0.57	C8	0.33
M9	0.75	C9	0.10
M11	0.62	C11	0.29
M12	0.72	C12	0.20
M13	0.88	C13	0.11