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Fig. S1. Clinical presentation of hand-foot skin reaction in the course of topical ketoconazole cream (a, b) Patient No. 1: 84-year-old old male, clinical presentation on the whole soles. (c, d) Patient No. 2: 81-year-old male, clinical presentation on the whole soles. (a, c) Before the start of ketoconazole treatment; (b, d) At trial completion. (e) Clinical presentation of Patient No. 1 clinical presentation of the soles and heels at 1-month after start of ketoconazole treatment.

Clinical presentation of Patient No. 2.

clinical presentation of the soles and heels following treatment for: (f) one month, (g) three months, (h) six months. Abbreviations: Pt, patient.

Fig. S1

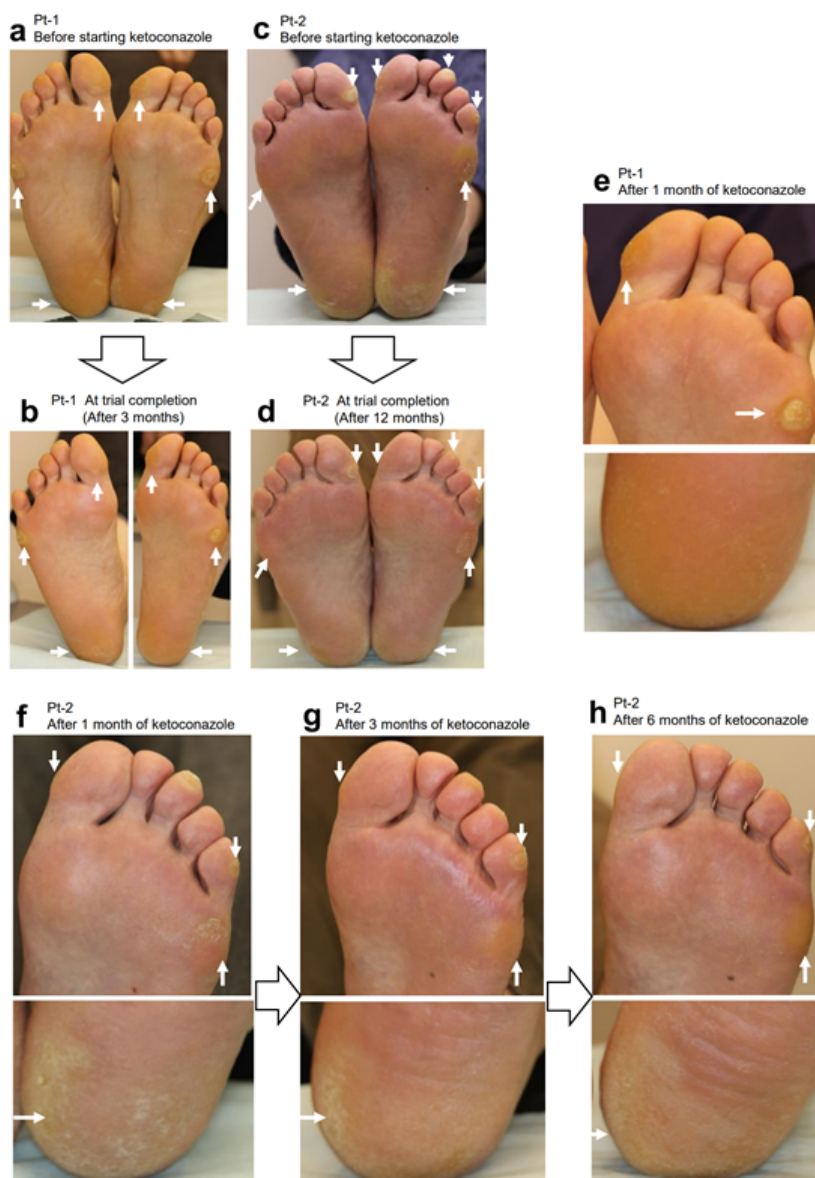


Fig. S2. Cell morphology of NHEK after sorafenib and/or AFD treatment

Phase-contrast images of NHEK cultured under the following condition: (a) vehicle, (b) 7 μ M sorafenib, (c) 1 μ M ketoconazole, (d) ketoconazole + sorafenib, (e) 1 μ M itraconazole, (f) itraconazole + sorafenib. Images were captured at the time western blot samples were collected. Scale bar: 2 mm.

Fig. S2

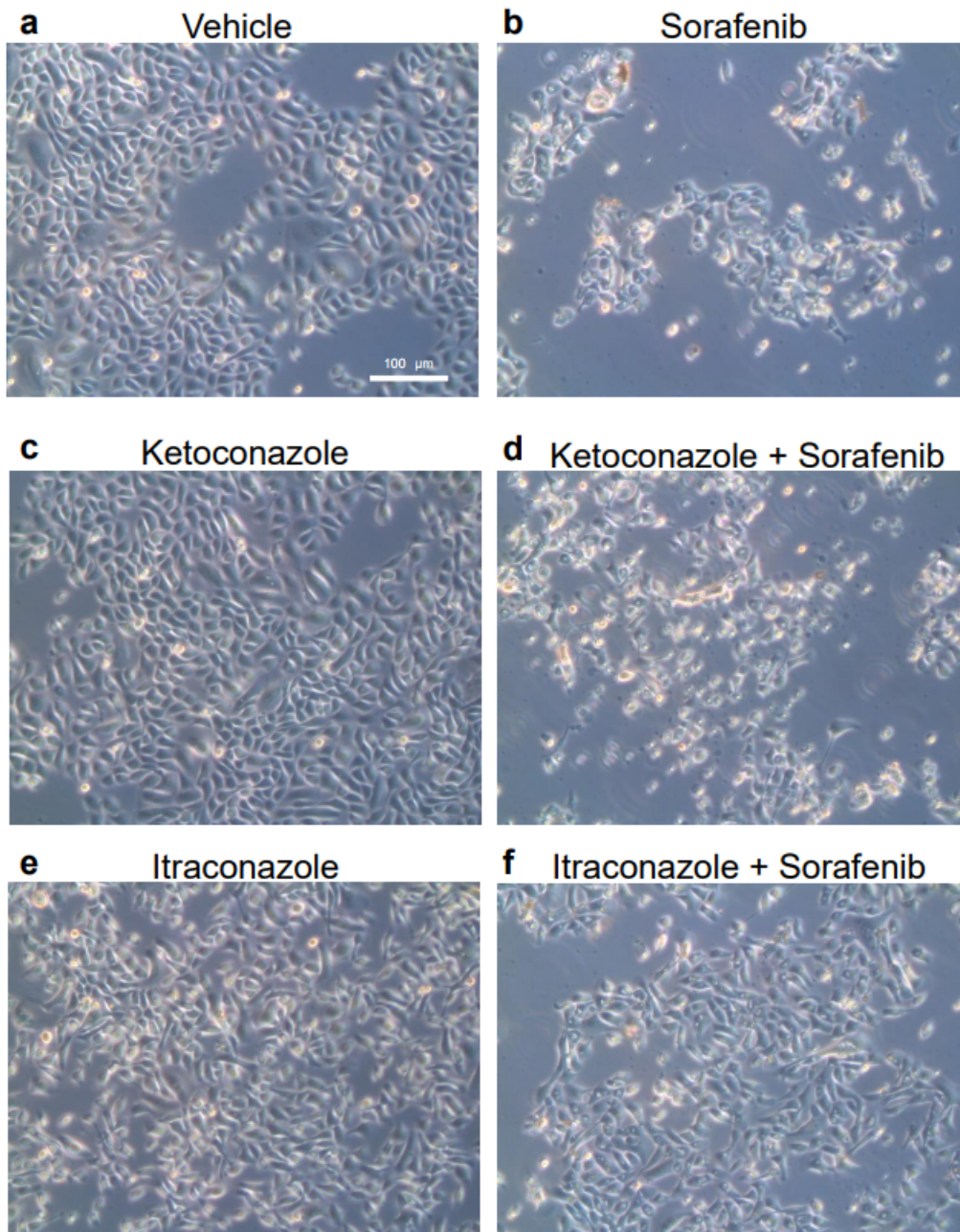


Fig. S3. Staining of annexin V, EthD-III and Hoechst 33342 in sorafenib and/or AFD treated NHEK
After treatment with (a) vehicle, (b) 7 μ M sorafenib, (c) 1 μ M ketoconazole, (d) 1 μ M itraconazole, (e) ketoconazole + sorafenib, (f) and itraconazole + sorafenib, cells were stained using Apoptotic/Necrotic/Healthy Cells Detection Kit and observed under a fluorescence microscope (BZ-X800). Green: annexin V, red: EthD-III, blue: Hoechst 33342. Scale bar: 100 μ m.

Fig. S3

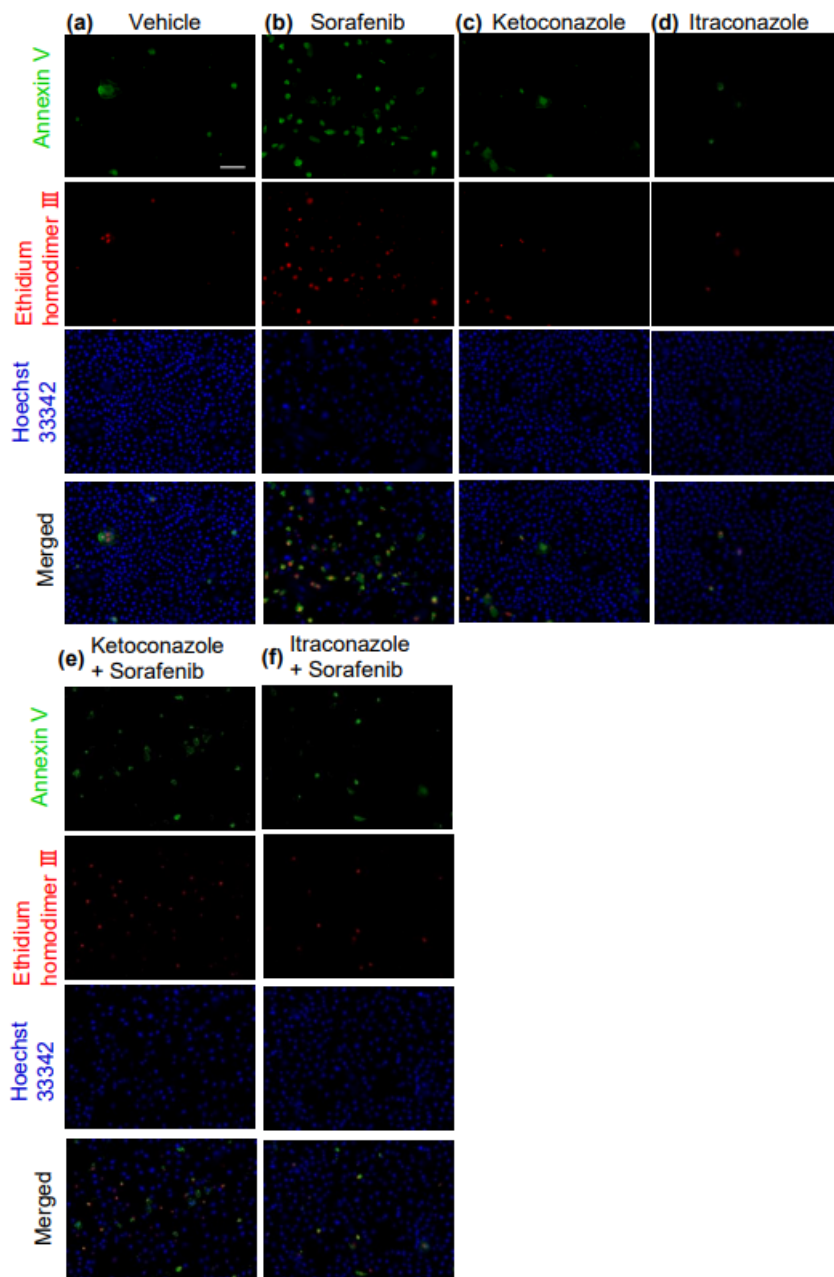


Fig. S4. TUNEL staining in sorafenib and/or AFD treated NHEK

After treatment with (a) vehicle, (b) 7 μ M sorafenib, (c) 1 μ M ketoconazole, (d) 1 μ M itraconazole, (e) ketoconazole + sorafenib, (f) and itraconazole + sorafenib cells were stained using *in situ* Cell Death Detection Kit and observed under fluorescence microscope (BZ-X800). Green: TUNEL positive cells, blue: DAPI. Scale bar: 100 μ m.

Fig. S4

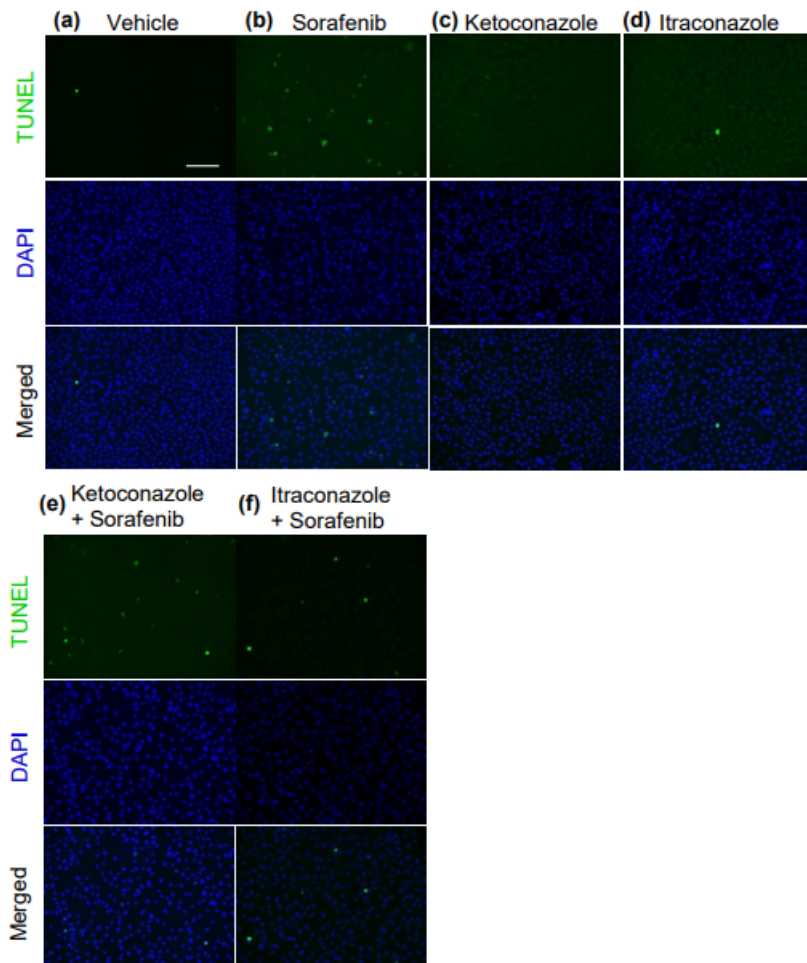


Fig. S5. Detection of apoptosis-related factors in cell lysates by apoptosis antibody array

(a) After treatment with sorafenib and/or AFD, cells were lysed and analyzed using an apoptosis array. Squares indicate altered molecules. (b) cleaved caspase-3, (c) procaspase-3, (d) cIAP-1, (e) TRAIL R1, (f) TRAIL R2, (g) Fas, (h) TNF R1. Data for (b-h) were semi-quantified using Image J and evaluated by one-way ANOVA followed by Tukey's test, * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$; ns, not significant. Abbreviations: Sora or S: sorafenib, Keto: ketoconazole, Itra: itraconazole.

Fig. S5

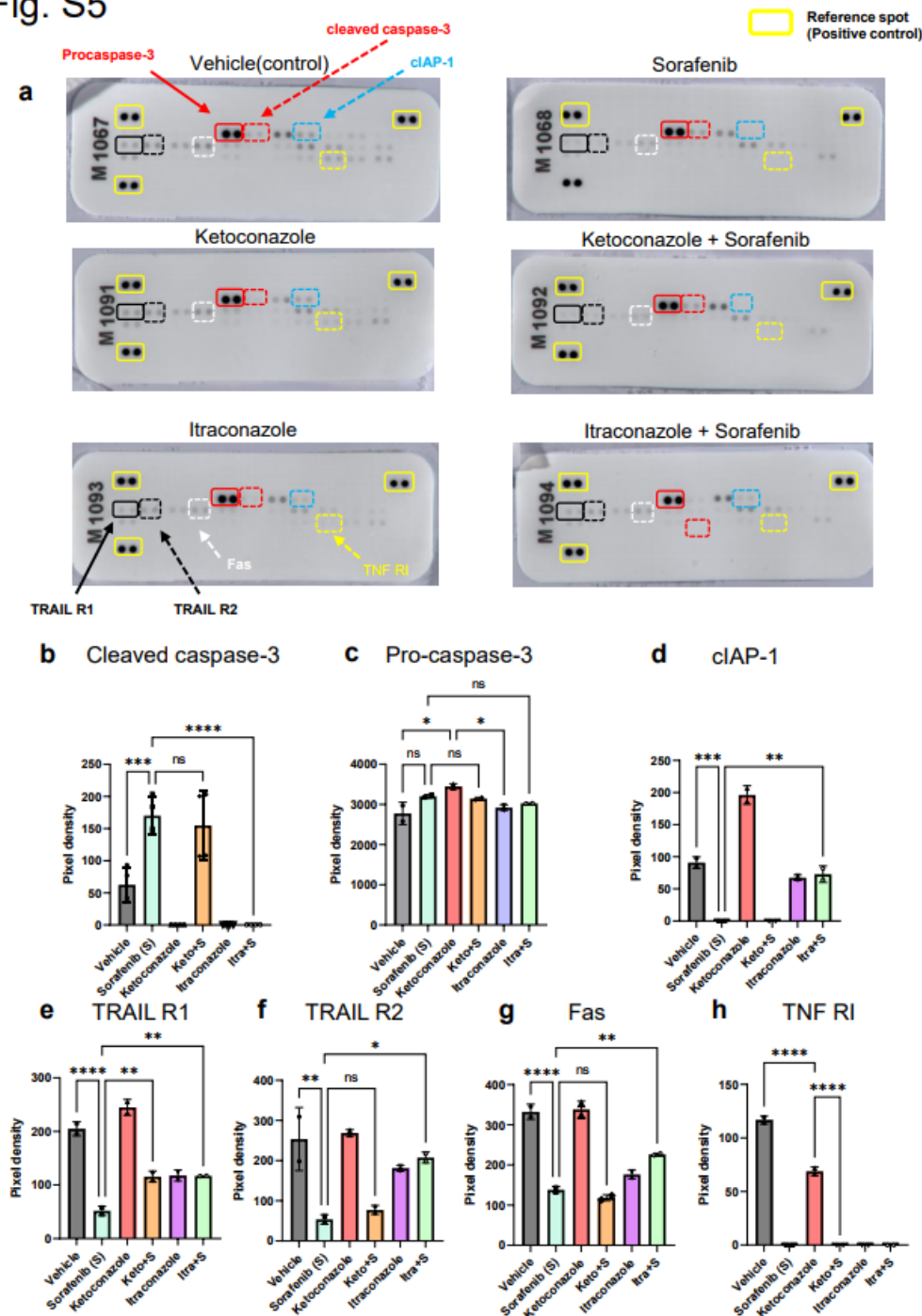


Fig. S6. Detection of apoptosis-related factors in cell lysates after sorafenib treatment

The results of western blot analysis for caspase-1 (48 kDa) (a), caspase-8 (57 kDa) (b), Fas (40-50 kDa) (c), TNFR1 (55 kDa) (d), TRAIL R1(35-55 kDa) (e), and TRAIL R2 (40 and 48 kDa) (f) in the cell lysates are shown. Bands were semi-quantified using Image J and data were expressed as relative ratios of caspase-1, caspase-8, Fas, TNFR1, TRAILR1, TRAILR2 / β -actin. Data were evaluated by one-way ANOVA followed by Tukey's test, $**P < 0.01$, $*P < 0.05$, *ns*, not significant. Abbreviations: Sora or S, sorafenib; Keto, ketoconazole; Itra, itraconazole. Results are presented as the mean $\pm$ SD of triplicate experiments.

Fig. S6

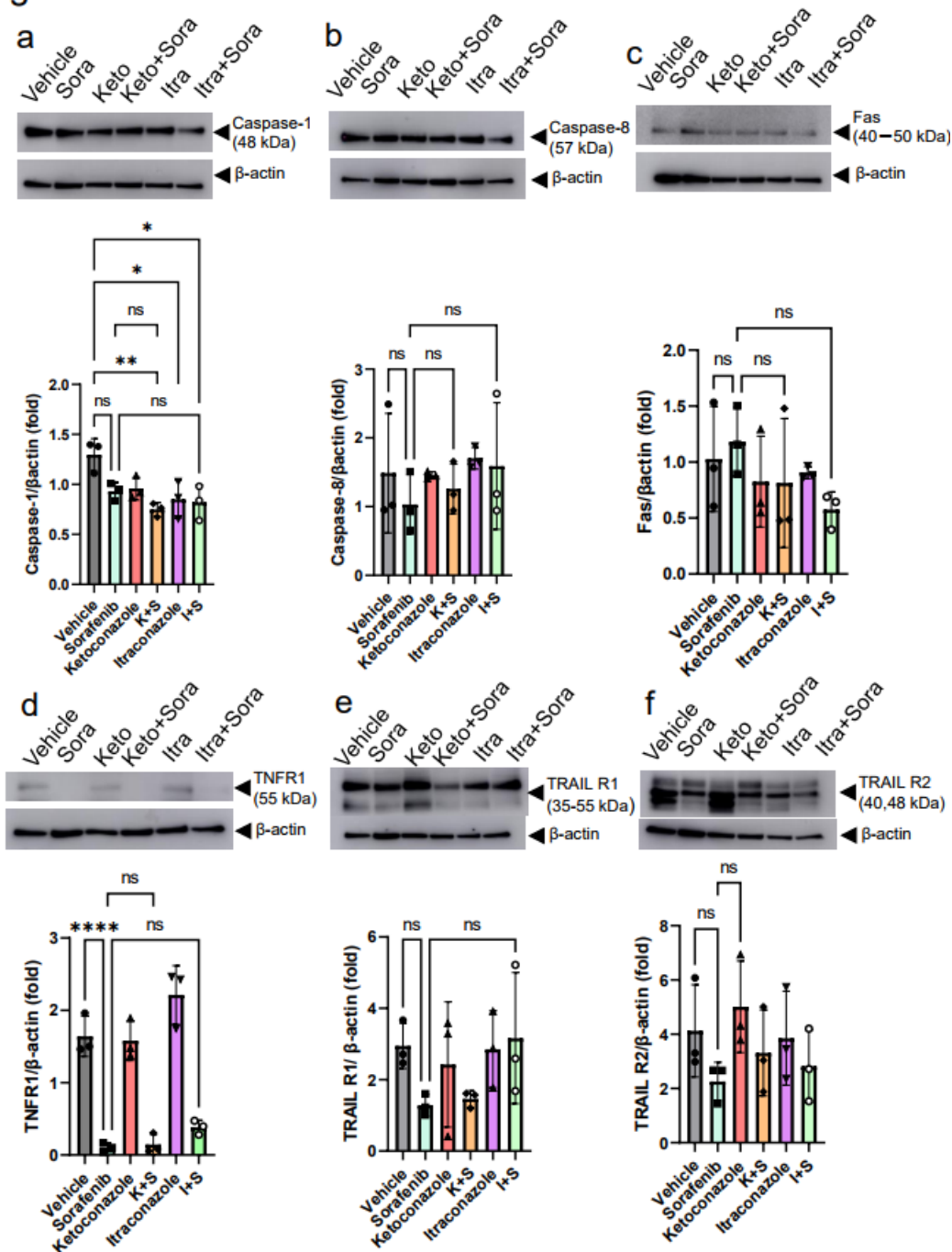


Fig. S7. Detection of cleaved caspase-1 and -8 in cell lysates after sorafenib treatment

The western blot images show caspase-1 (48 kDa) (a) and caspase-8 (57 kDa) in the cell lysates. Cleaved caspase-1 and -8 fragments (p10) were not detected on the membrane. Abbreviations: Sora or S, sorafenib; Keto, ketoconazole; Itra, itraconazole.

Fig. S7

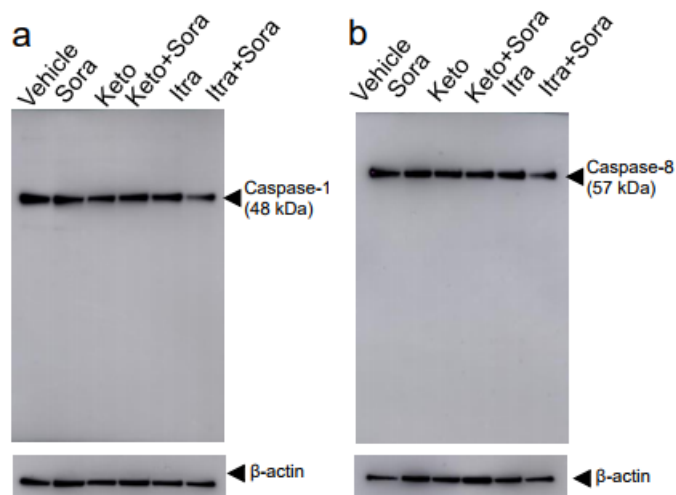


Fig. S8. Detection of phospho-NFκB p65 in cell lysates of NHEK after sorafenib treatment

Western blot analysis of NFκB p65 phosphorylation in cell lysates. NHEK were incubated for 6 hours with 0, 7 or 10 μM sorafenib, and the cell lysates were prepared using M-PER. Bands were semi-quantified using Image J. Data are presented as the relative ratio of phosphorylated NFκB p65/ NFκB p65. Data were evaluated by one-way ANOVA followed by Tukey's test; * $P < 0.05$, ns, not significant.

Fig. S8

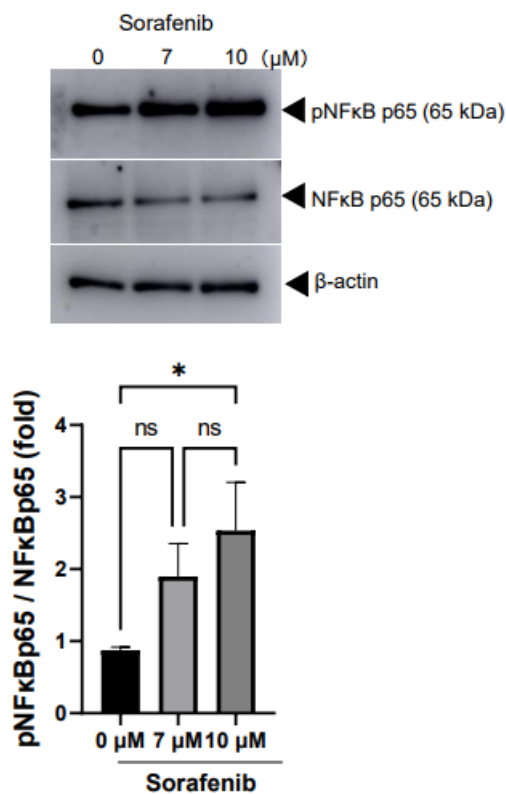


Fig. S9. Detection of cytokines in culture supernatants and cell lysates by cytokine antibody array

(a) After treatment with or without sorafenib, cells were lysed and subjected to cytokine array. Squares indicate altered molecules. (b) IL-1 α (supernatant). (c) IL-1RA (supernatant). (d) MIF (supernatant). (e) PAI-1 (supernatant). (f) IL-1 α (lysate). (g) IL-1RA (lysate). (h) MIF (lysate). (i) PAI-1 (lysate). (b-i) Each spot was semi-quantified using Image J. Data were evaluated by one-way ANOVA followed by Tukey's test; **** $P < 0.0001$; ns, not significant. Abbreviations: Sora or S, sorafenib; Keto, Ketoconazole; Itra, itraconazole.

Fig. S9

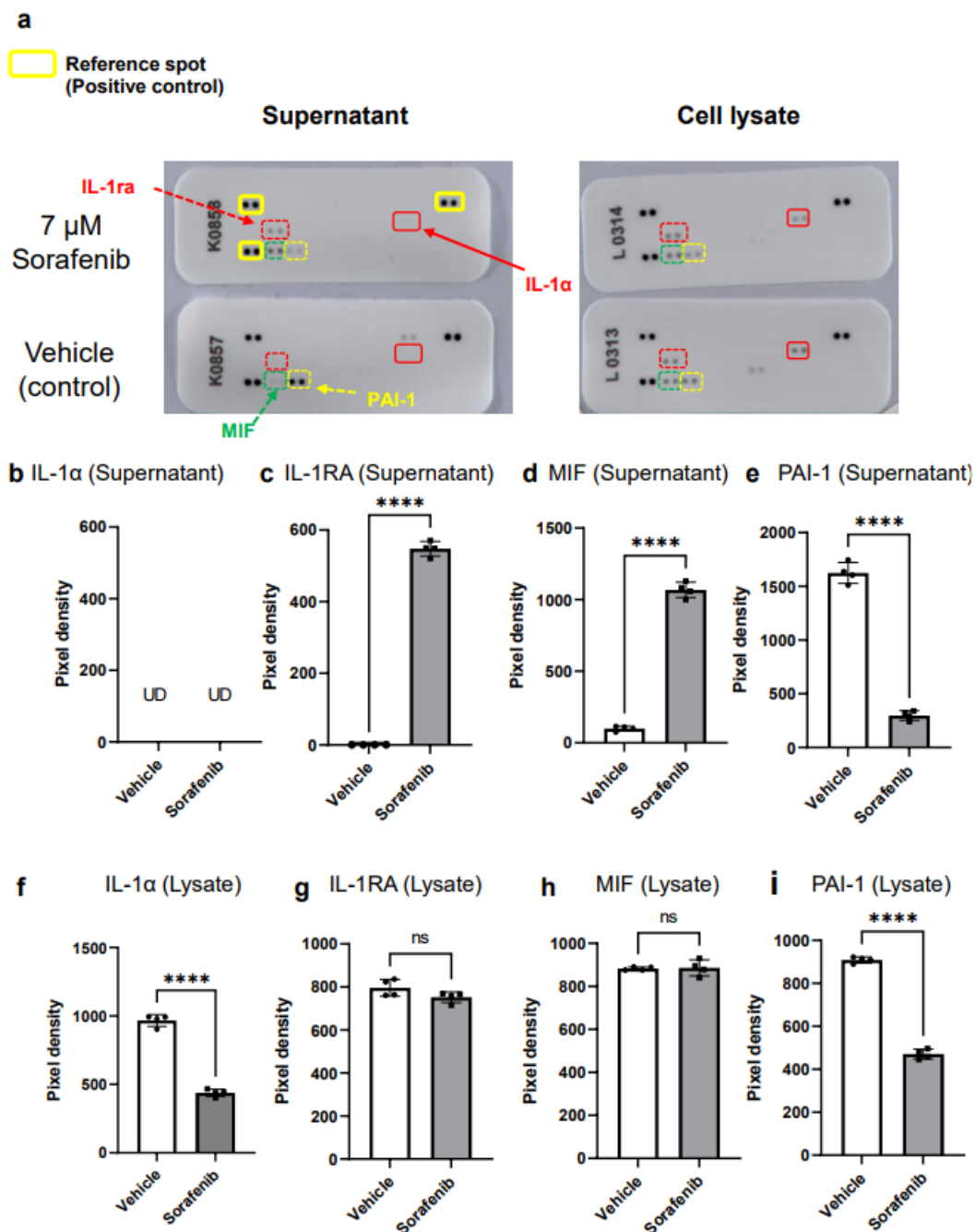


Fig. S10. Detection of IL-1 α , IL-1RA, MIF, and PAI-1 in cell lysates of NHEK after sorafenib treatment. Western blot analysis of IL-1 α (proIL-1 α : 31 kDa, cleaved IL-1 α : 17 kDa) (a), IL-1RA (20-25 kDa) (b), MIF (12 kDa) (c), PAI-1(48 kDa) (d) in the cell lysates, and PAI-1 (e) in the supernatants. Bands were semi-quantified using Image J. Data are presented as the relative ratio of IL-1 α , IL-1RA, MIF, or PAI-1/ β -actin (a-d), and pixel density for PAI-1(e). Data were evaluated by one-way ANOVA followed by Tukey's test; ns, not significant. Abbreviations: Sora or S, sorafenib; Keto, ketoconazole; Itra, itraconazole. All results represent the mean $\pm$ SD from triplicate experiments.

Fig. S10

