Bimekizumab reduces systemic inflammation and cardiovascular risk gene signatures in psoriatic disease

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OBJECTIVE

- To understand the early molecular effects of bimekizumab (BKZ) on gene signatures related to systemic inflammation and cardiovascular (CV) risk in psoriatic disease.

Background

- Psoriatic disease is associated with increased **CV disease (CVD) risk,** which may be driven by the release of **proinflammatory cytokines**. An elevation of these cytokines has been detected in both psoriatic tissue and in circulation, demonstrating the systemic nature of this disease.[1–3]
- BKZ, a monoclonal antibody that selectively inhibits both interleukin (IL)-17A and IL-17F, has shown sustained differentiating efficacy in both moderate to severe plaque psoriasis (PSO) and psoriatic arthritis (PsA).[4,5]
- Analysis from phase 3 trials in PSO indicated that **BKZ reduces CVD-associated systemic inflammatory biomarkers**, including neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein.[6–8]

Methods

- **Five CVD risk-related gene signatures** were defined based on previous studies reporting genes dysregulated in the blood of patients with PSO compared with healthy controls, and affected in prevalent and incident CV events (myocardial infarction [MI], major adverse CV or limb events [MACLE]):[9,10]
  - PSO prevalent MI, PSO incident MACLE, PSO combined MI MACLE, PSO CVD key regulators, PSO+CVD (Kvist-Hansen).
- **Blood bulk RNA-seq** data from a previous study that compared patients with PSO to healthy controls was used to understand the extent of **dysregulation of these gene signatures in blood at baseline**.[11]
- **Changes** in these signatures **post-BKZ treatment** were assessed using molecular data from BKZ-treated patients with PSO and PsA.[12–14]
  - **Bulk RNA-seq data** was generated from a phase 2a trial in PSO (skin and blood samples at baseline and Week 8)[15] and from a phase 3 trial in PsA (blood samples at baseline and Week 16).[5]
  - **Proteomics data** was generated from the serum samples of patients with PSO (baseline and Week 8)[15] using the Olink Explore 3072 panel.

1. Garshick MS et al. J Am Coll Cardiol 2021;77:1670–80; **2.** Korman NJ Br J Dermatol 2020;182:840–8; **3.** Polachek A et al. Arthritis Care Res (Hoboken) 2017;69:67–74; **4.** Reich K et al. N Engl J Med 2021;385:142–52 (NCT03536884); **5.** McInnes IB et al. Lancet 2023;401:25–37 (NCT03895203); **6.** Warren RB et al. EADV 2023; Poster 2549; **7.** Angkananard T et al. Biomed Res Int 2018;11:2703518; **8.** Løfblad L et al. Sci Rep 2021;11:15644; **9.** Garshick MS et al. J Eur Acad Dermatol Venereol 2023;37:1361–5; **10.** Kvist-Hansen A et al. Int J Mol Sci 2021;22:10818; **11.** Garshick MS et al. J Invest Dermatol 2022;141:308–15; **12.** Wu D et al. Nucleic Acids Res 2012;40:e133; **13.** Ritchie ME et al. Nucleic Acids Res 2015;43:e47; **14.** Hänzelmann S et al. BMC Bioinformatics 2013;14:714; **15.** Oliver R et al. Br J Dermatol 2022;186:652–63 (NCT03025542). BKZ: bimekizumab; CV: cardiovascular; CVD: CV disease; IL: interleukin; MACLE: major adverse CV or limb events; MI: myocardial infarction; NLR: neutrophil-to-lymphocyte ratio; PsA: psoriatic arthritis; PSO: psoriasis; RNA-seq: ribonucleic acid sequencing.

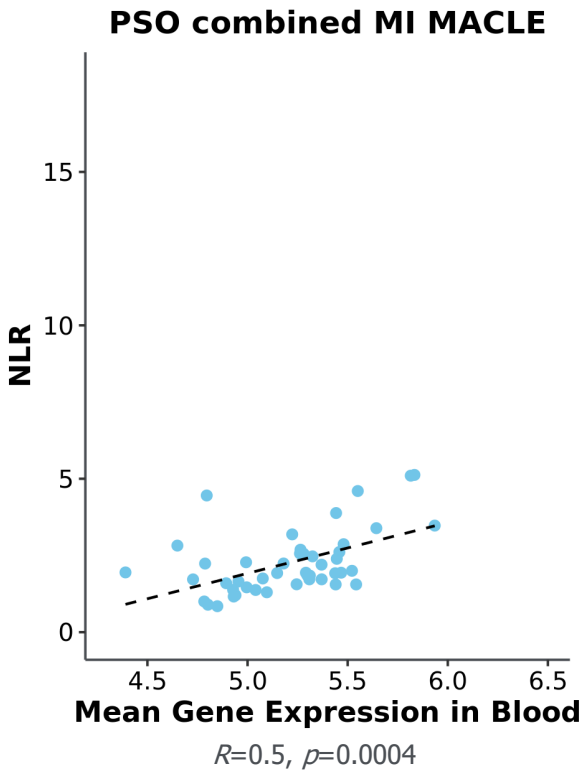
To receive a copy of this poster, and access the full list of genes for each gene set, scan the QR code.
Link expiration: June 09, 2025

CVD Gene Signatures Were Associated With Systemic Effects in Psoriatic Patients

Correlation with NLR in blood at baseline

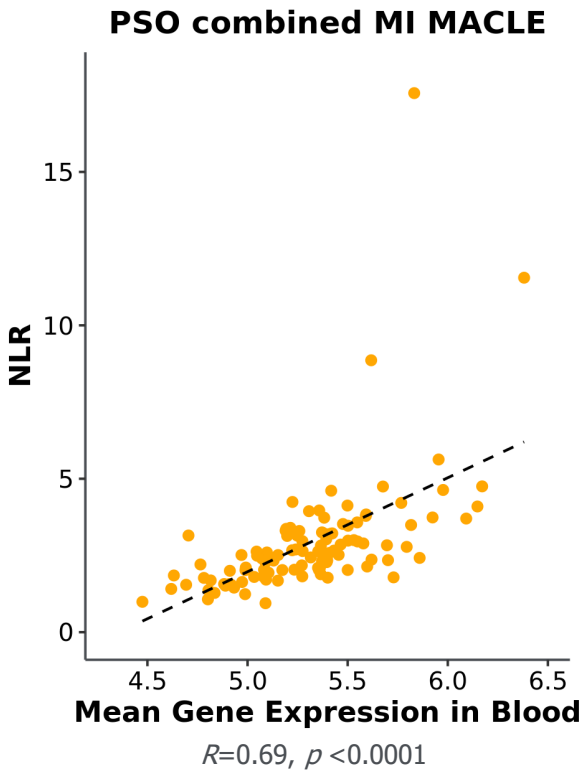
A **positive correlation** was observed between **mean gene expression** in the CVD gene signatures and **NLR levels** at baseline (*R*=0.27–0.51 [PSO], *R*=0.42–0.69 [PsA]; FDR<0.1).

PSO baseline[a,b]



R=0.5, *p*=0.0004

PsA baseline[a,b]

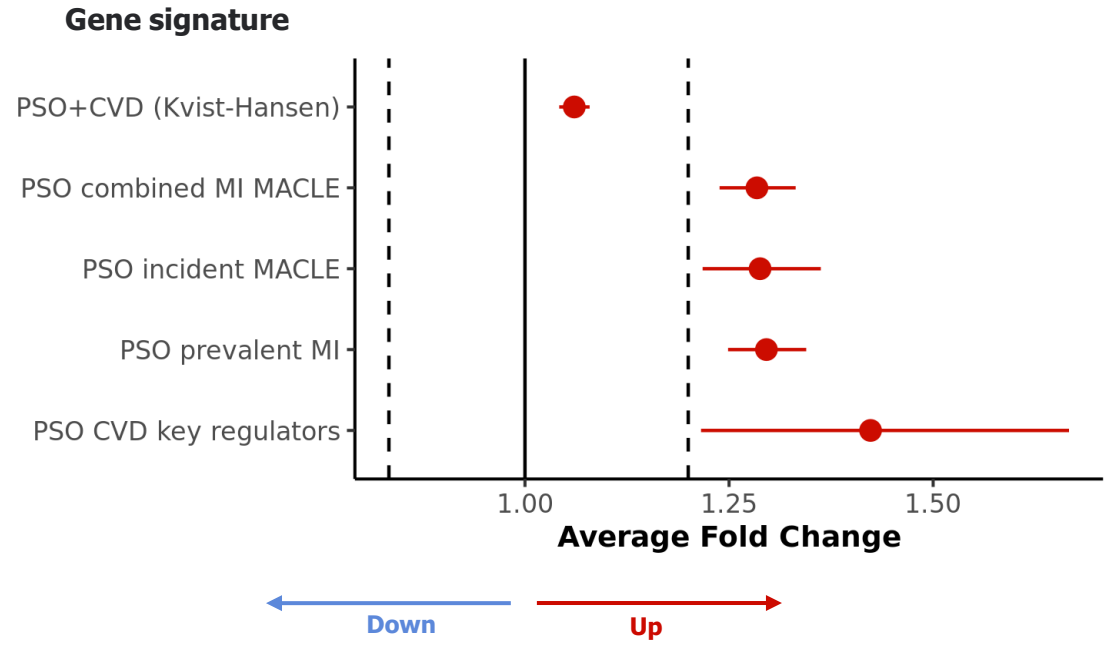


R=0.69, *p* <0.0001

Changes at baseline in PSO versus healthy blood

Baseline data from a published study[1] showed an **increase** in these **gene signatures** in the blood of patients with PSO versus healthy controls (average fold-change: 1.06–1.42).

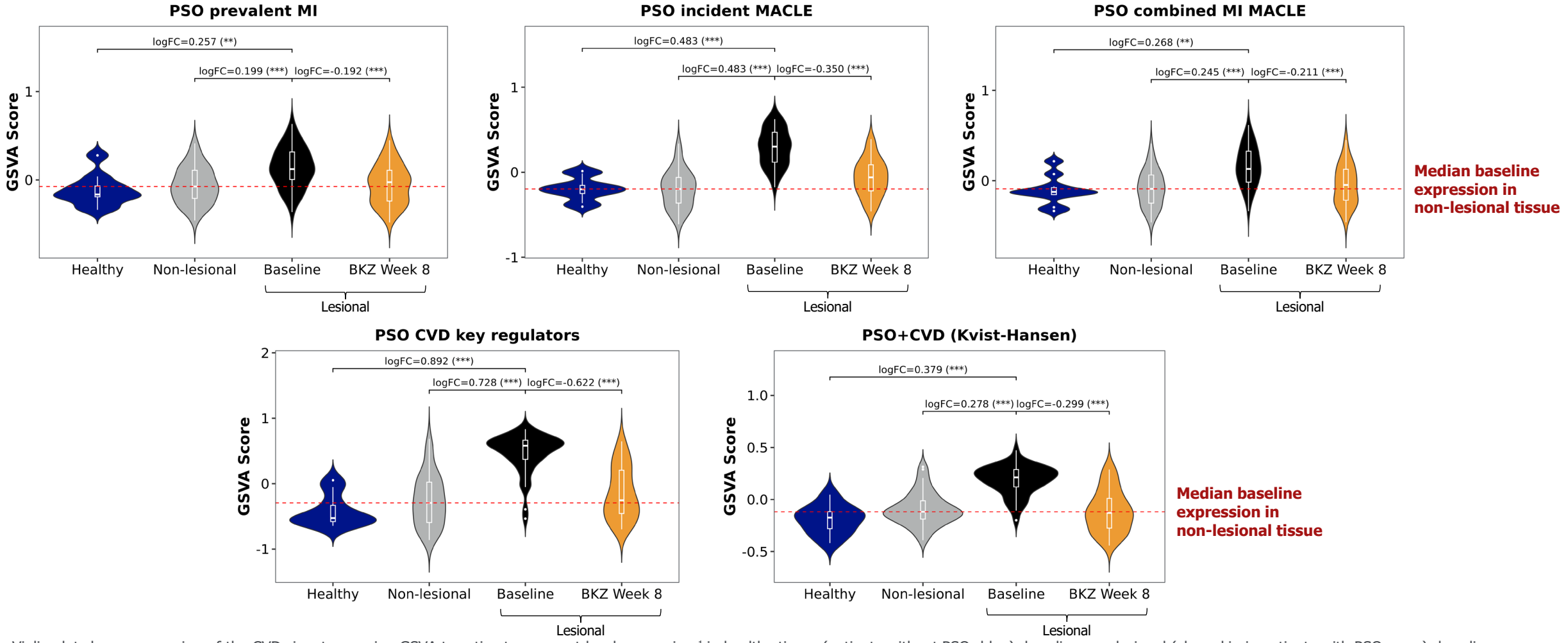
PSO baseline[c]



[a] Figure shows only 'PSO combined MI MACLE' signature as an example; **[b]** *R* is the Spearman correlation coefficient; **[c]** Dotted vertical lines correspond to a fold change of 0.83 and 1.2; the error bars represent 95% CIs. **1.** Garshick MS et al. J Invest Dermatol 2022;141:308–15. CI: confidence interval; CVD: cardiovascular disease; FDR: false discovery rate; MACLE: major adverse cardiovascular or limb events; MI: myocardial infarction; NLR: neutrophil-to-lymphocyte ratio; PsA: psoriatic arthritis; PSO: psoriasis.

BKZ Treatment Led to Rapid Normalization of CVD Gene Signatures in Psoriatic Skin

In **skin** of patients with PSO, CVD signatures were **rapidly normalized** after BKZ treatment **by Week 8** (two BKZ doses; median percentage improvement: **93%–100%**).

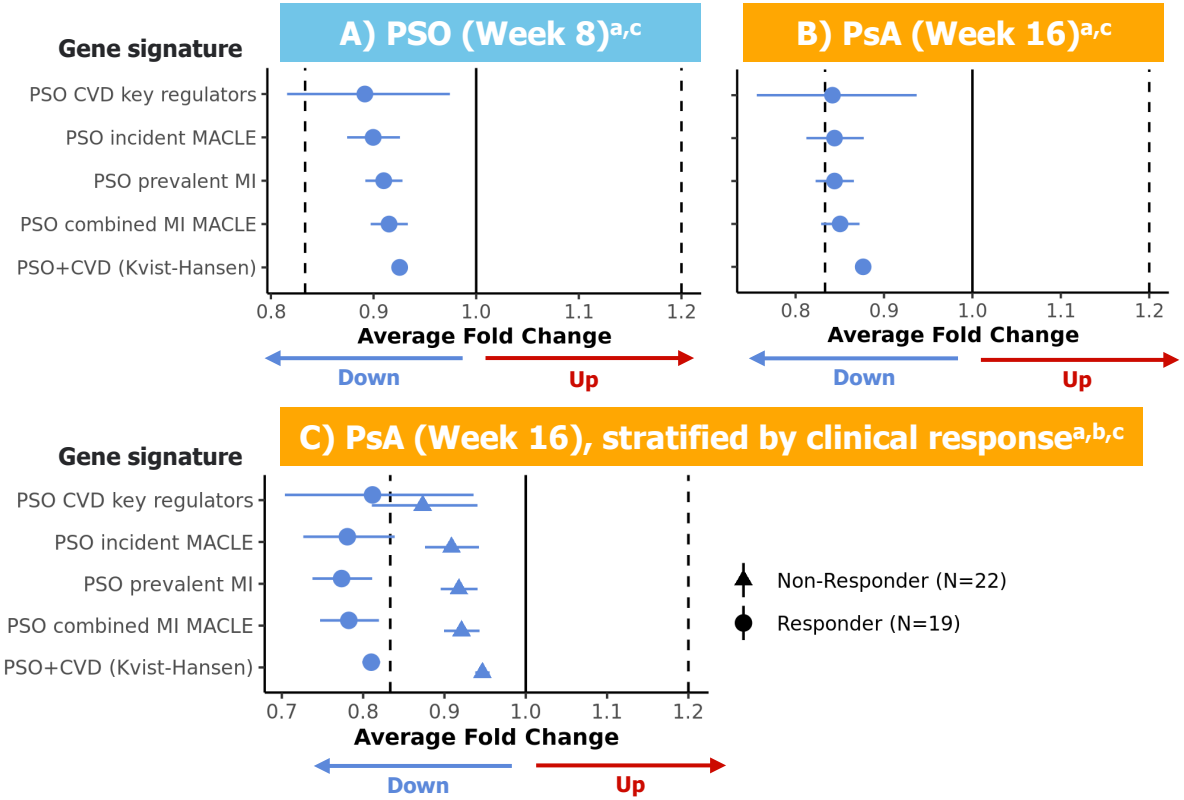


Violin plot shows expression of the CVD signature, using GSVA to estimate gene set level expression,[1] in healthy tissue (patients without PSO; blue), baseline non-lesional (clear skin in patients with PSO; grey), baseline lesional (black), and BKZ-treated lesional tissue at Week 8 (orange). Wider sections of the violin plot indicate higher density of data at the respective y-axis value. White box plots show median and IQR normalized expression. LogFC and FDR-adjusted p-values were calculated using *limma* moderated t-test.[2] ***FDR<0.001, **FDR<0.01. **1.** Hänzelmann S et al. BMC Bioinformatics 2013;14:7; **2.** Ritchie ME et al. Nucleic Acids Res 2015;43:e47. BKZ: bimekizumab; CVD: cardiovascular disease; FC: fold change; FDR: false discovery rate; GSVA: gene set variation analysis; IQR: interquartile range; MACLE: major adverse CV or limb events; MI: myocardial infarction; PSO: psoriasis.

BKZ Treatment Reduced CVD Gene Signatures in Blood of Psoriatic Patients

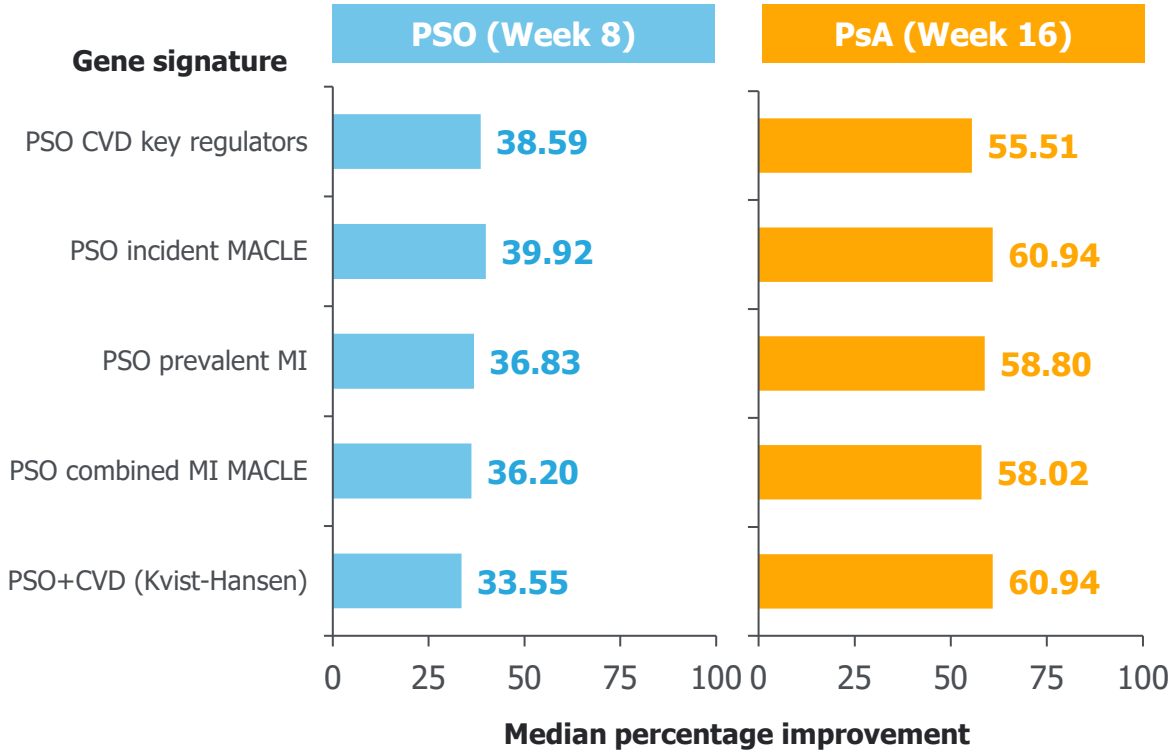
Effects in blood of patients with PSO and PsA

Significant downregulation[a] of the CVD gene signatures was observed as early as Week 8 in PSO (A) and Week 16 in PsA (B). This effect was **associated with clinical response**[b] in PsA, with greater reduction in patients that responded to treatment compared to non-responders (C). It is expected that in blood gene dysregulation is weaker than in disease tissue.[1]



Median percentage improvements in CVD gene signatures

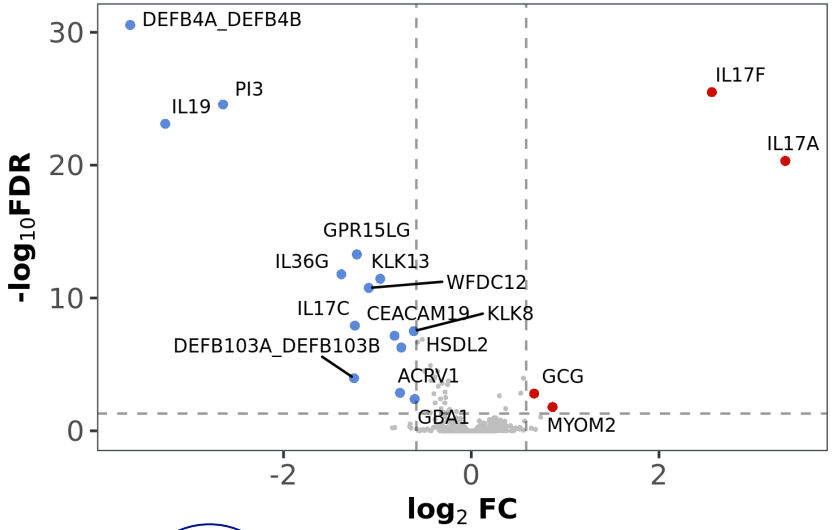
Placed in the context of baseline dysregulation in blood of PSO patients,[2] BKZ led to a median percentage **improvement** ranging from 33.55–39.92% (Week 8; PSO) and 55.51–60.94% (Week 16; PsA), demonstrating **early reversal of CVD-related gene signatures**.



[a] CAMERA analysis,[3] FDR<0.05; **[b]** Responders were defined as study participants achieving ACR70 and having high improvement in DAPSA actual score and change from baseline; non-responders had no/minimal DAPSA improvement from baseline; **[c]** Dotted vertical lines correspond to a fold change of 0.83 and 1.2; the error bars represent 95% CIs. **1.** Dolcino M et al. PLoS ONE 2015;10:e0128262; **2.** Garshick MS et al. J Invest Dermatol 2022;141:308–15; **3.** Wu D et al. Nucleic Acids Res 2012;40:e133. ACR70: ≥70% improvement in American College of Rheumatology response; BKZ: bimekizumab; CI: confidence interval; CVD: cardiovascular disease; DAPSA: disease activity in psoriatic arthritis score; FDR: false discovery rate; MACLE: major adverse cardiovascular or limb events; MI: myocardial infarction; PsA: psoriatic arthritis; PSO: psoriasis.

BKZ Treatment Reduced Serum Proteins Related to Systemic Inflammation in Patients with PSO

By Week 8, in the serum of patients with PSO, proteomics analysis demonstrated **significant reduction**[1] (FDR<0.05) of several **IL-17-related** proteins,[a] some of which are also linked to CVD (e.g. PI3).[2]



CONCLUSIONS

At early timepoints, bimekizumab treatment was associated with molecular reduction in systemic inflammation/cardiovascular disease risk signatures in both blood and skin, which is consistent with the reduction in the neutrophil-to-lymphocyte ratio observed in clinical data.

Further studies are being undertaken to assess longer term molecular effects post-bimekizumab treatment.

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All proteins with $|\log_2 FC| >= \log_2(1.5)$ and FDR<0.05 are labelled. LogFC and FDR-adjusted p-values were calculated using *limma* moderated t-test.[1] **[a]** Measured IL17A and IL17F in serum are the antibody-bound proteins and are expected to be increased post-treatment due to target engagement. **1.** Ritchie ME et al. Nucleic Acids Res 2015;43:e47; **2.** Kvist-Hansen A et al. Int J Mol Sci 2021;22:10818. BKZ: bimekizumab; CVD: cardiovascular disease; FC: fold change; FDR: false discovery rate; IL: interleukin; PI3: peptidase inhibitor 3; PSO: psoriasis.