FIGARO-BM, a biomarker study of FIGARO-DKD, reveals new insights into the mode-of-action of finerenone

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Introduction

- Finerenone is a selective, non-steroidal antagonist of the mineralocorticoid receptor (nsMRA). Overactivation of the mineralocorticoid receptor (MR) contributes to tissue fibrosis and organ damage found in cardiorenal disease.
- Finerenone was approved in the European Union, the US, Japan, the UK, and several other countries for chronic kidney disease (CKD) in patients with type 2 diabetes (T2D) following results from the phase 3 FIDELIO-DKD and FIGARO-DKD trials[1–4]
- The overall aim of the FIGARO-BM study was to generate insights into the mechanism of disease and the mode-of-action of finerenone in CKD patients with T2D and identifying functional links between treatment-responsive biomarkers

Table 1. Guideline recommendations for finerenone

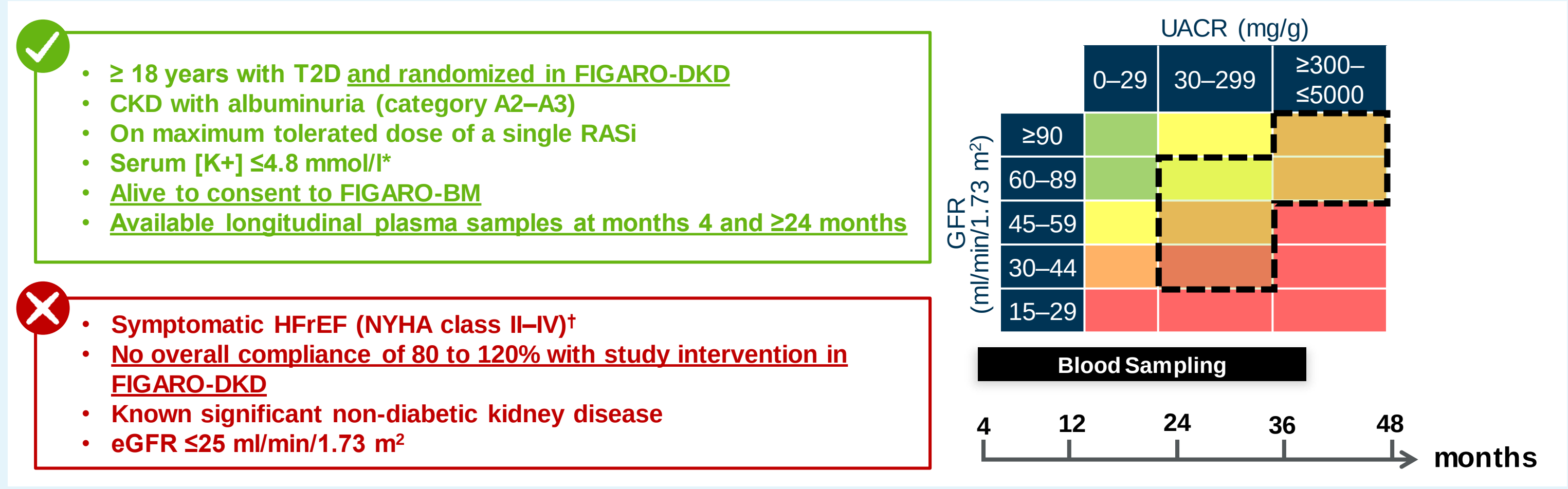
Organization	Guidance	Class/grade	Level
ADA[5]	In patients with CKD who are at increased risk for CV events or CKD progression or are unable to use an SGLT-2i, a non-steroidal MRA (finerenone) is recommended to reduce CKD progression and CV events	A	–
KDIGO[6]	We suggest a nonsteroidal MRA with proven kidney or cardiovascular benefit for patients with T2D, an eGFR ≥25 ml/min/1.73 m^2, normal serum potassium concentration, and albuminuria (≥30 mg/g [≥3 mg/mmol]) despite maximum tolerated dose of RASi	A	2
AACE[7]	A non-steroidal MRA (finerenone) with proven kidney and CV disease benefit is recommended for persons with T2D, an eGFR ≥25 ml/min/1.73 m^2, normal serum potassium concentration, and albuminuria (UACR ≥30 mg/g) despite a maximum tolerated dose of a RASi	A	1
ESC[8]	Finerenone is recommended in addition to an ACEi or ARB in patients with T2D and eGFR >60 ml/min/1.73 m^2 with a UACR ≥300 mg/g, or eGFR 25–60 ml/min/1.73 m^2 and UACR ≥30 mg/g to reduce CV events and kidney failure	1	A
ESC[9]	In patients with T2D and CKD, finerenone is recommended to reduce the risk of HF hospitalization	1	A

AACE, American Association of Clinical Endocrinologists; ACEi, angiotensin-converting enzyme inhibitor; ADA, American Diabetes Association; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; HF, heart failure; KDIGO, Kidney Disease Improving Global Outcomes; MRA, mineralocorticoid receptor antagonist; N/A, not applicable; RASi, renin–angiotensin system inhibitor; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio

Methods

- Biosamples for FIGARO-BM (NCT05013008) were derived from FIGARO-DKD (NCT02545049), a phase 3 trial which investigated finerenone's efficacy on cardiorenal outcomes and safety in more than 7000 CKD patients with T2D[3]
- FIGARO-BM included 945 patients from 21 countries, overall comparable to the total population in the parent trial and analyzed 2941 biomarkers in more than 4150 longitudinal post-randomization plasma samples using EXPLORE3072® proteomics (Olink Uppsala, Sweden)
- Subjects on treatment with either placebo or finerenone for at least 24 months, and alive to consent, were eligible to participate in FIGARO-BM (Figure 1)
- Biomarkers with a significant difference ($P \leq 0.05$) between treatment arms at more than one study visit (month 4, 12, 24, 36, and 48, based on a linear mixed model) were used for gene enrichment analysis (GSEA). One of the two visits were required to be significant after multiplicity correction ($q \leq 0.05$). Biomarkers with effect estimates below a pre-defined threshold were excluded from GSEA.

Figure 1. Patient characteristics/key enrollment criteria and sampling



- ≥ 18 years with T2D and randomized in FIGARO-DKD
- CKD with albuminuria (category A2–A3)
- On maximum tolerated dose of a single RASi
- Serum [K+] ≤4.8 mmol/l*
- Alive to consent to FIGARO-BM
- Available longitudinal plasma samples at months 4 and ≥24 months

- Symptomatic HFrEF (NYHA class II–IV)†
- No overall compliance of 80 to 120% with study intervention in FIGARO-DKD
- Known significant non-diabetic kidney disease
- eGFR ≤25 ml/min/1.73 m^2

*At run-in or screening visit.;†run-in only; underlined enrollment were added for FIGARO-BM while remaining criteria came from the original study (FIGARO-DKD)
eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association;
RASi, renin–angiotensin system inhibitor; UACR, urine albumin-to-creatinine ratio

Results

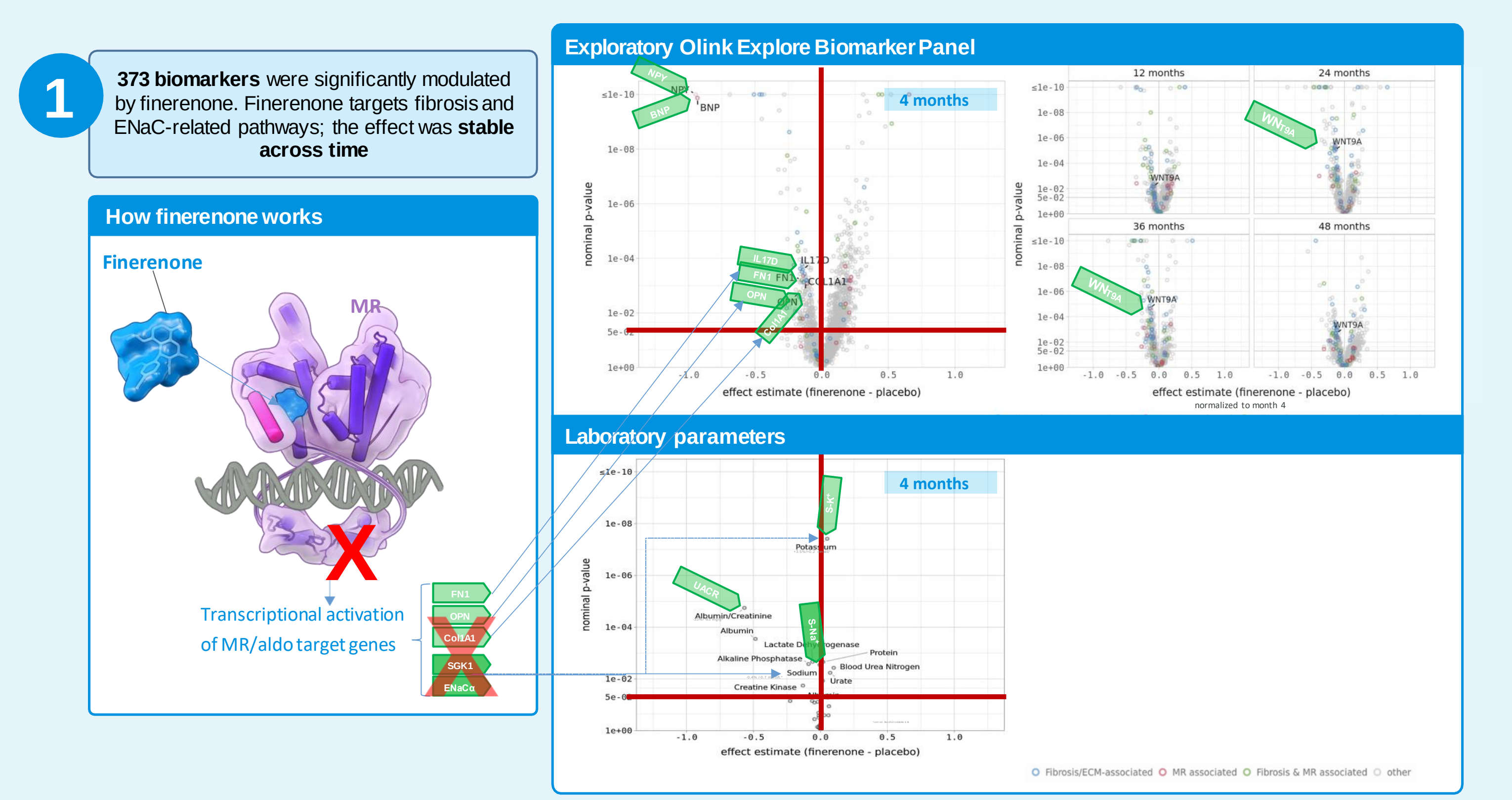
- **Finerenone antagonizes binding of aldosterone (or cortisol) to the MR** and in doing so, it prevents the formation of the active ligand-bound MR transcription factor and its nuclear translocation. Not unexpectedly, a large number of biomarkers (n=373) was significantly modulated by finerenone compared to placebo **(Figure 2)**. This included many known MR target genes such as fibronectin (FN1), osteopontin (SPP1/OPN), the alpha chain of the epithelial sodium channel (ENac), or factors involved in potassium homeostasis thereby recapitulating MR biology
- In addition, markers associated with fibrosis and inflammation pathways were modulated, such as interleukin 17 (IL17) family members or FN1 and WNT9a. Neuropeptide Y (NPY) and BNP showed the largest treatment effect of all investigated lab parameters and Olink biomarkers. Generally, the treatment effect on circulatory biomarker levels was stable across time

Table 2. Baseline demographics and patient characteristics in FIGARO-BM*

	FIGARO-DKD[3] (Parent study)	FIGARO-BM (Biomarker study)			
	Total (N = 7352)	Total (N = 945)	Finerenone (n= 481)	Placebo (n = 464)	*P*-value†
Age, years, mean±SD	64.1±9.8	63.9±9.5	63.6±9.5	64.2±9.6	0.3
Male sex, n (%)	5105 (69.4)	706 (74.7)	361 (75.1)	345 (74.4)	0.8
BMI, kg/m^2, mean ±SD	31.4±6.0	30.9±6.1	30.9±6.3	30.9±5.8	0.8
Race or ethnic group, n (%)‡					0.7
White	5277 (71.8)	595 (63.0)	294 (61.1)	301 (64.9)	
Black	258 (3.5)	17 (1.8)	9 (1.9)	8 (1.7)	
Asian	1454 (19.8)	326 (34.5)	174 (36.2)	152 (32.8)	
SBP, mmHg, mean±SD	135.8±14.0	134.3±13.8	134.2±13.9	134.4±13.7	0.8
History of cardiovascular disease, n (%)	3330 (45.3)	322 (34.1)	157 (32.6)	165 (35.6)	0.3
eGFR, ml/min/1.73 m^2, mean±SD	67.8±21.7	66.4±20.7	66.6±20.9	66.2±20.4	0.9
eGFR distribution, n (%)					0.6
≥60	4539 (61.7)	548 (58.0)	281 (58.4)	267 (57.5)	
45 to <60	1534 (20.9)	241 (25.5)	117 (24.3)	124 (26.7)	
25 to <45	1251 (17.0)	156 (16.5)	83 (17.3)	73 (15.7)	
UACR, mg/g, median (IQR)	308 (108–740)	203 (84–503)	219 (85–525)	190 (83–482)	0.4
UACR distribution, n (%)					0.8
≥300 mg/g	3729 (50.7)	368 (38.9)	192 (39.9)	176 (37.9)	
Laboratory values, median (IQR)					
Serum K+, mmol/l	4.3 (4.1–4.6)	4.3 (4.0–4.5)	4.3 (4.0–4.5)	4.3 (4.0–4.5)	0.8
Serum Na+, mmol/l	139 (137–141)	139 (137–140)	139 (137–140)	139 (137–140)	0.7
CRP, mg/l	2.19 (0.97–5.10)	1.63 (0.69–4.40)	1.52 (0.67–4.49)	1.83 (0.71–4.22)	0.5
HbA1c, %	7.5 (6.7–8.5)	7.4 (6.7–8.3)	7.4 (6.7–8.3)	7.4 (6.7–8.2)	>0.9
Baseline medications, n (%)					
ACEi or ARBs	7343 (99.9)	943 (99.8)	480 (99.8)	463 (99.8)	>0.9
Beta blockers	3536 (48.1)	407 (43.1)	211 (43.9)	196 (42.2)	0.6
Diuretics	**3496 (47.6)**	**409 (43.3)**	**226 (47.0)**	**183 (39.4)**	**0.019**
Statins	5184 (70.5)	684 (72.4)	349 (72.6)	335 (72.2)	>0.9
Glucose-lowering therapy	7196 (97.9)	922 (97.6)	468 (97.3)	454 (97.8)	0.6
Insulin	3993 (54.3)	447 (47.3)	219 (45.5)	228 (49.1)	0.3
GLP1 RA	**550 (7.5)**	**111 (11.7)**	**68 (14.1)**	**43 (9.3)**	**0.020**
SGLT-2i	618 (8.4)	93 (9.8)	48 (10.0)	45 (9.7)	0.9

*Percentages may not total 100 because of rounding; †FIGARO-BM treatment arm comparisons were calculated based on Wilcoxon rank sum test for continues variables and Pearson's Chi-squared test or Fisher's exact test for categorial variables (rows highlighted in blue were significant); ‡race and ethnic group were reported by the patients. Other included American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, or multiple. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; BMI, body mass index; CRP, c-reactive protein; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; IQR, interquartile range; SBP, systolic blood pressure; SD, standard deviation; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio

Figure 2. Longitudinal biomarker response to finerenone[10–13]

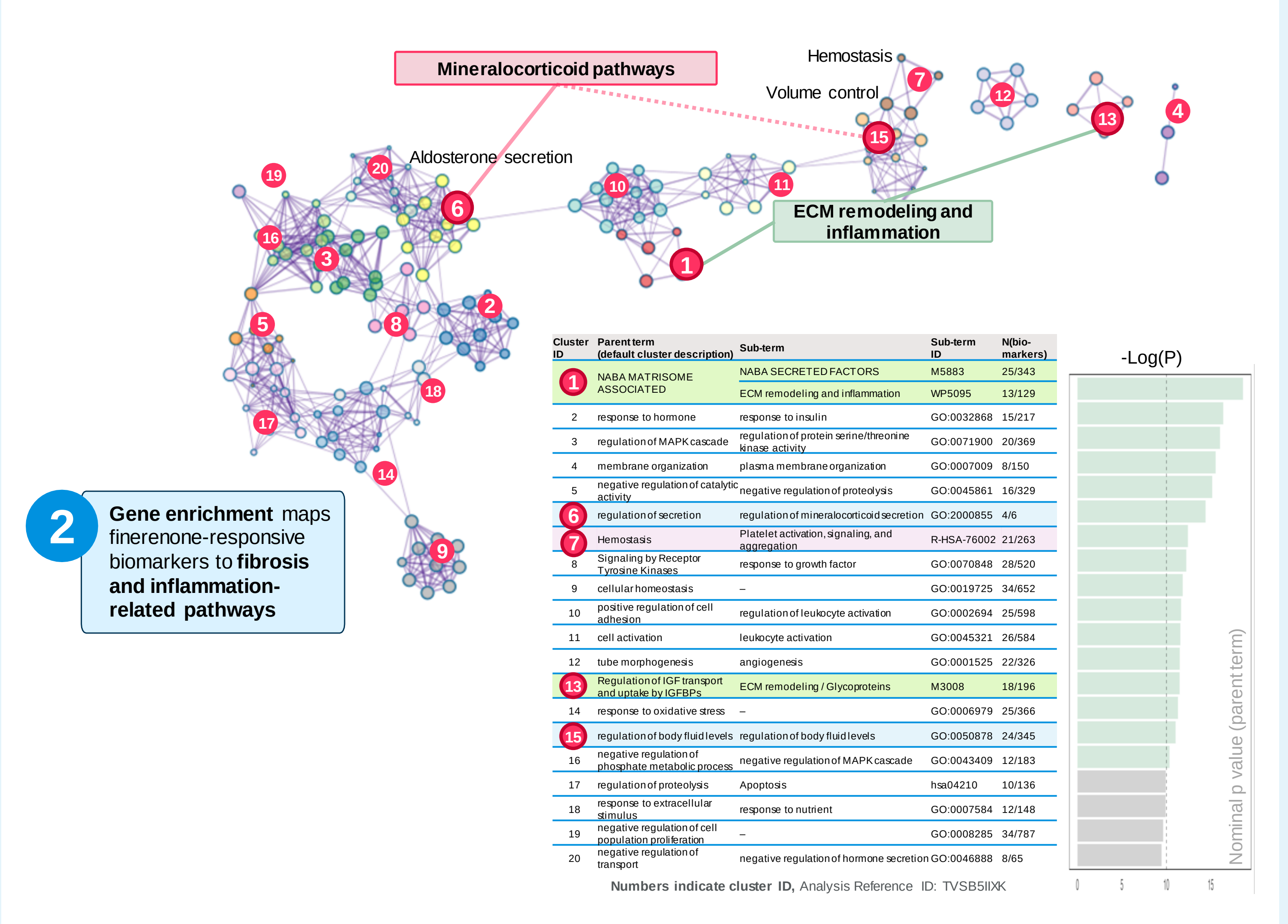


1 **373 biomarkers** were significantly modulated by finerenone. Finerenone targets fibrosis and ENaC-related pathways; the effect was **stable across time**

MR, mineralocorticoid receptor; aldo, aldosterone.

- **Gene set enrichment analysis (Figure 3)** of finerenone-responsive biomarkers identified clusters of extracellular matrix (ECM) remodeling-related pathways, including once again several established markers of inflammation and fibrosis (fibronectin, osteopontin, e.g., IL17C), along with novel markers of ECM remodeling (clusters 1+13 on Figure 3)
- Other clusters (clusters 6+15) are directly linked to mineralocorticoid/aldosterone biology and volume homeostasis reflecting target modulation on pathway level
- Finerenone appears to modulate fibrinolysis/hemostasis (cluster 7)

Figure 3. Linking treatment-responsive biomarkers to biological pathways



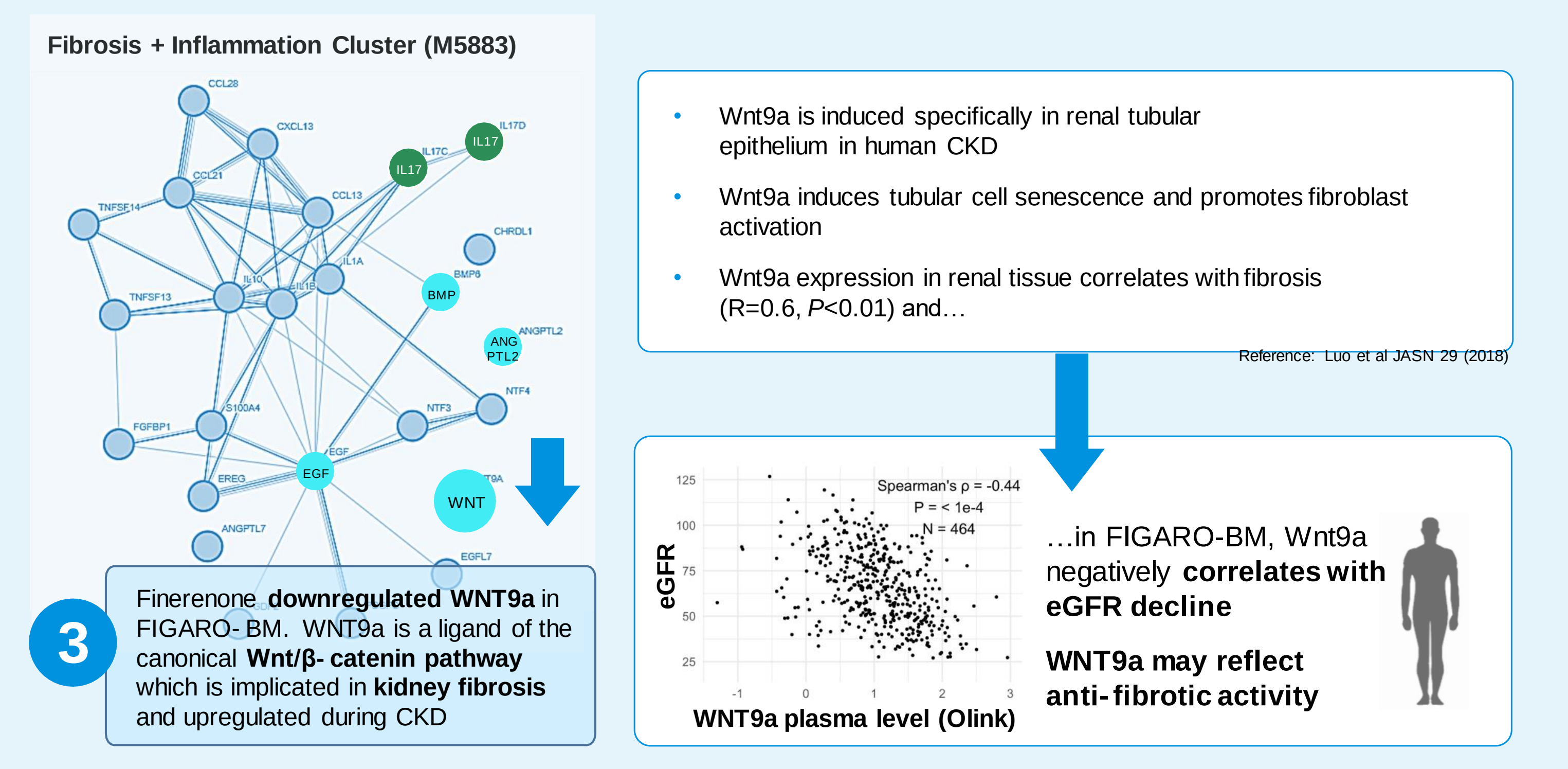
2 **Gene enrichment** maps finerenone-responsive biomarkers to **fibrosis and inflammation-related pathways**

Cluster ID	Parent term (default cluster description)	Sub-term	Sub-term ID	N(bio-markers)
1	NABA MATRISOME ASSOCIATED	NABA SECRETED FACTORS ECM remodeling and inflammation	M5883 WP5095	25/343 13/129
2	response to hormone	response to insulin	GO:0032868	15/217
3	regulation of MAPK cascade	regulation of protein serine/threonine kinase activity	GO:0071900	20/369
4	membrane organization	plasma membrane organization	GO:0007009	8/150
5	negative regulation of catalytic activity	negative regulation of proteolysis	GO:0045861	16/329
6	regulation of secretion	regulation of mineralocorticoid secretion	GO:2000855	4/6
7	Hemostasis	Platelet activation, signaling, and aggregation	R-HSA-76002	21/263
8	Signaling by Receptor Tyrosine Kinases	response to growth factor	GO:0070848	28/520
9	cellular homeostasis	–	GO:0019725	34/652
10	positive regulation of cell adhesion	regulation of leukocyte activation	GO:0002694	25/598
11	cell activation	leukocyte activation	GO:0045321	26/584
12	tube morphogenesis	angiogenesis	GO:0001525	22/326
13	Regulation of IGF transport and uptake by IGFBPs	ECM remodeling / Glycoproteins	M3008	18/196
14	response to oxidative stress	–	GO:0006979	25/366
15	regulation of body fluid levels	regulation of body fluid levels	GO:0050878	24/345
16	negative regulation of phosphate metabolic process	negative regulation of MAPK cascade	GO:0043409	12/183
17	regulation of proteolysis	Apoptosis	hsa04210	10/136
18	response to extracellular stimulus	response to nutrient	GO:0007584	12/148
19	negative regulation of cell population proliferation	–	GO:0008285	34/787
20	negative regulation of transport	negative regulation of hormone secretion	GO:0046888	8/65

Numbers indicate cluster ID, Analysis Reference ID: TVSB5IIXK

- **WNT9a** is one interesting biomarker within the highest-ranking gene list of cluster 1 (Term ID M5883). All 25 treatment-responsive pathway members (from the 373 panel) are depicted in the protein-protein network (using STRING) in **Figure 4**.
- WNT9a is a ligand of the canonical Wnt/β-catenin pathway which is implicated in kidney fibrosis and upregulated during CKD. Zhou et al, found that activation of WNT receptors by Wnt ligands (including WNT9a) directly induced the expression of multiple RAS effector genes[14]
- Pharmacological Wnt-blockade not only abolished RAS induction but also restored podocyte integrity, ameliorated albuminuria, tissue fibrosis and overall renal function in a mouse model of kidney disease[14]

Figure 4. Deep dive into fibrosis-related markers – WNT9a



3 Finerenone **downregulated WNT9a** in FIGARO- BM. WNT9a is a ligand of the canonical **Wnt/β- catenin pathway** which is implicated in **kidney fibrosis** and upregulated during CKD

- Wnt9a is induced specifically in renal tubular epithelium in human CKD
- Wnt9a induces tubular cell senescence and promotes fibroblast activation
- Wnt9a expression in renal tissue correlates with fibrosis (R=0.6, $P<0.01$) and…

Reference: Luo et al JASN 29 (2018)

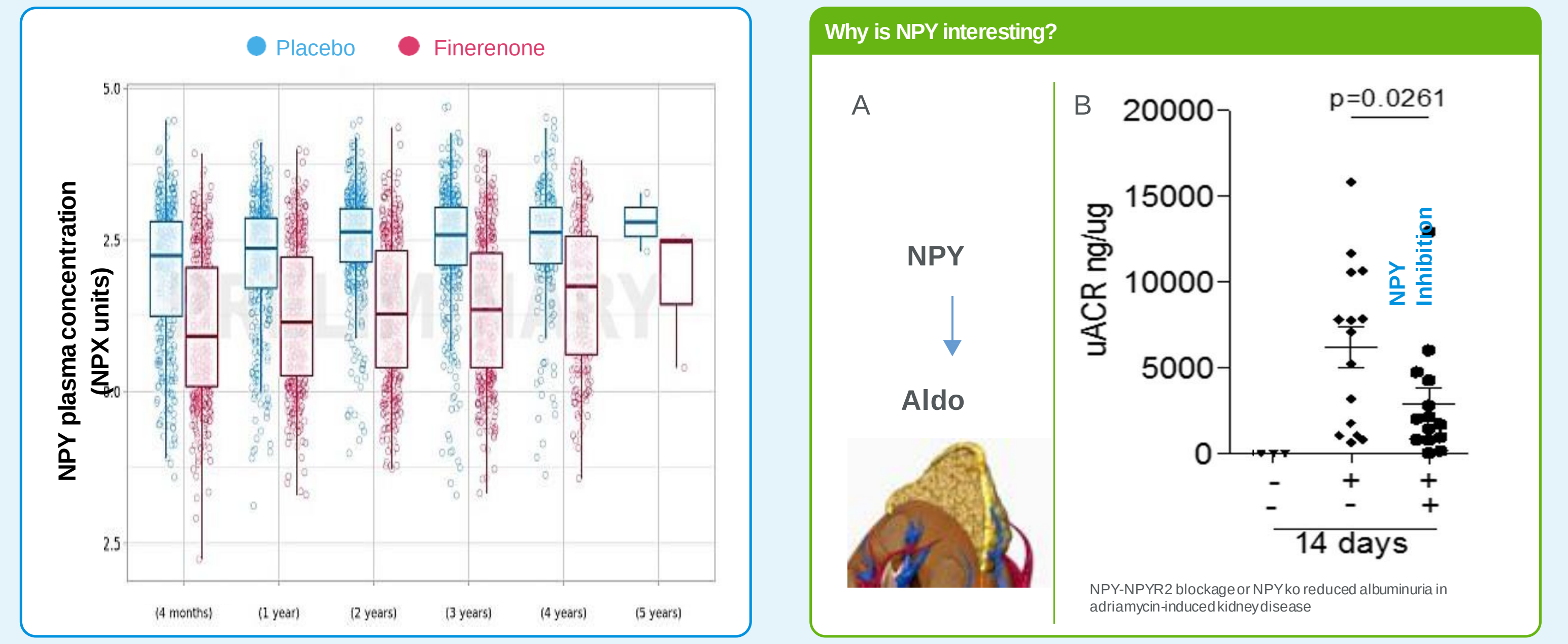
…in FIGARO-BM, Wnt9a negatively **correlates with eGFR decline**

WNT9a may reflect anti-fibrotic activity

- **NPY** is strongly downregulated in plasma after several weeks of treatment with finerenone **(Figure 5).** Among all analyzed Olink biomarkers, NPY demonstrated the highest effect size in response compared to placebo.
- NPY has increasingly been implicated in the pathogenesis of cardiorenal diseases (CKD, arrhythmia, heart failure or myocardial infarction) and atherosclerosis. Downmodulation of NPY is likely beneficial to a broad population of CVD patients.[14]
- In rodent models of glomerulosclerotic kidney disease, pharmacological inhibition or knock-out of NPY was shown previously to reduce albuminuria suggesting a direct pathogenic role of NPY in albuminuria[15]

Figure 5. Linking treatment-responsive biomarkers to biological pathways

4 Biomarkers with largest effect size included the neurohormonal peptide, **NPY,** which has been implicated in aldosterone secretion and may play a causal role in **albuminuria**



NPY-NPYR2 blockage or NPY ko reduced albuminuria in adriamycin-induced kidney disease

Box plot illustrates NPY plasma levels (in absolute, non-adjusted NPX units on original log2 scale) across time per treatment arm up to 5 years after randomization into FIGARO-DKD. Boxes indicate median+IQR. Whiskers = 95% CI)

References: A:[16] Renshaw, Endocrinol, 141 (2000), B:[17] Lay AC et al, PNAS, 117 (27):2020 (B: modified, with permission from the author)

Abbreviations: NPY, neuropeptide Y; uACR, urine albumin-to-creatinine ratio in ng per ug creatinine, NPX, normalized expression unit (Olink) on log2 scale

Conclusions

- FIGARO-BM provides human biomarker evidence that finerenone acts on inflammation and fibrosis pathways and counteracts multiple aspects of aldosterone-driven adverse effects
- Finerenone reduces markers involved in inflammation and (cardiorenal) fibrosis such as fibronectin (FN1), osteopontin (SPP1/OPN), Col1A1, IL17C, and IL17D thereby confirming findings from animal studies
- FIGARO-BM reveals novel biomarkers (e.g. NPY, WNT) which may mediate beneficial cardiorenal effects of finerenone observed in clinical trials
- Future studies are needed to validate these findings

Summary

- This study investigated the circulatory biomarker profile of finerenone in a subset of almost 1000 patients with CKD and T2D from the phase III trial FIGARO-DKD.
- Out of ~3000 biomarkers measured with Olink technology, 373 markers were considered treatment responsive compared to placebo-treated subjects.
- The study supports previously reported preclinical findings from animal models and provides new insights to mechanisms leading to clinical benefits in a broad cardiorenal patient population

This study was initially presented on November 2nd at ASN Kidney Week 2023

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Disclosures

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