



**PARIS  
MASH  
MEETING**

**10<sup>th</sup> edition**

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Institut Pasteur, Paris**



# **Clinical Considerations in the Design of Combination Therapies**

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# Disclosures

- Scientific advisor or consultant for Akero Therapeutics, BMS, Boehringer Ingelheim, Cytodyn, GSK, Intercept Pharmaceuticals, Madrigal, NGM Biopharmaceuticals, Novo Nordisk, 89Bio, Lilly and Sonic Incytes



*In loving memory of our dear friend, Stephen A. Harrison, who enriched our lives. Your friends and the field will never forget you*

January 2023

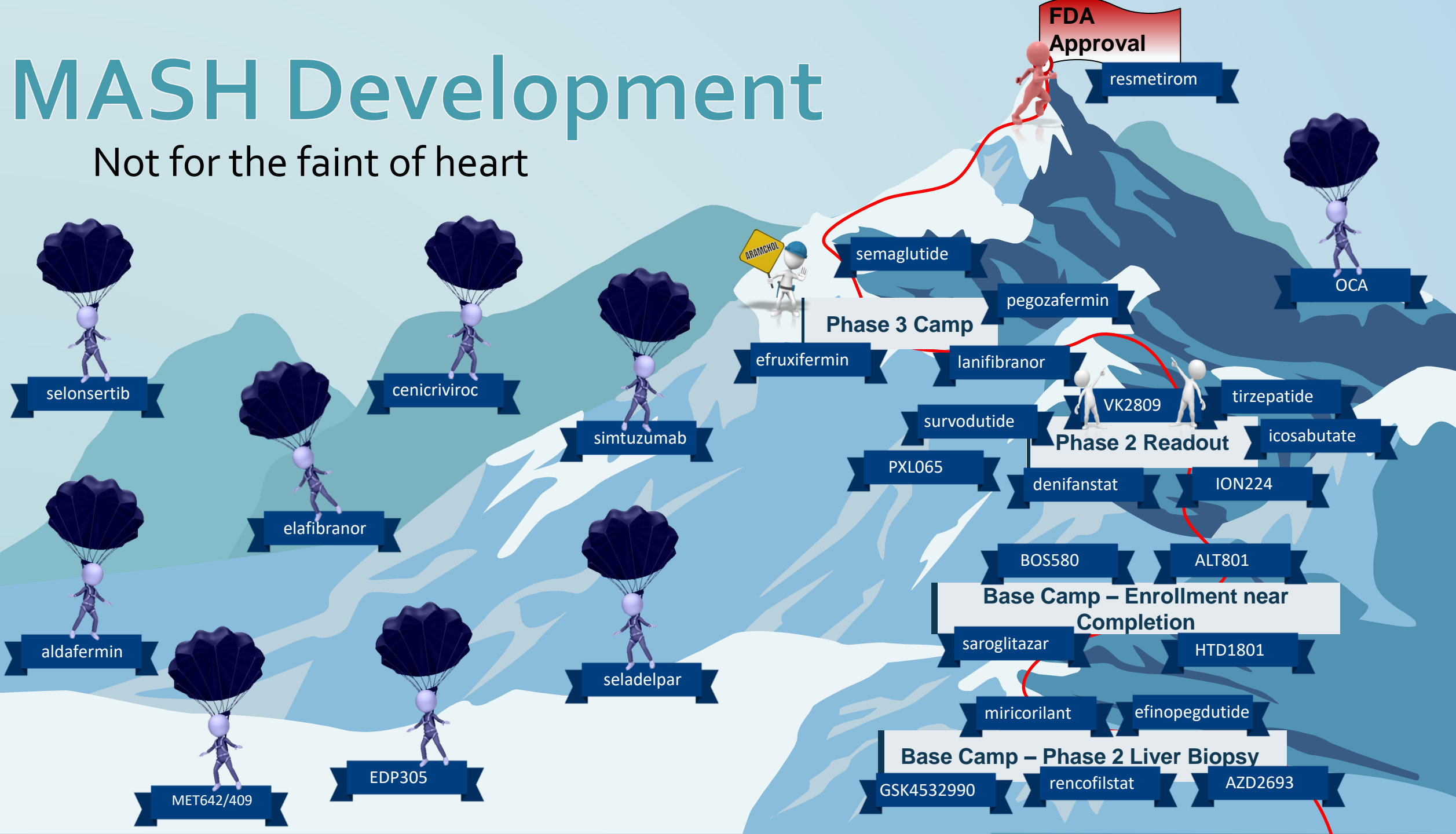


Vienna, 2023

10<sup>th</sup> edition

# MASH Development

Not for the faint of heart



# What does the IDEAL TREATMENT look like?



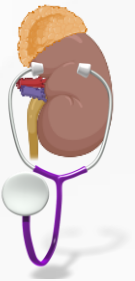
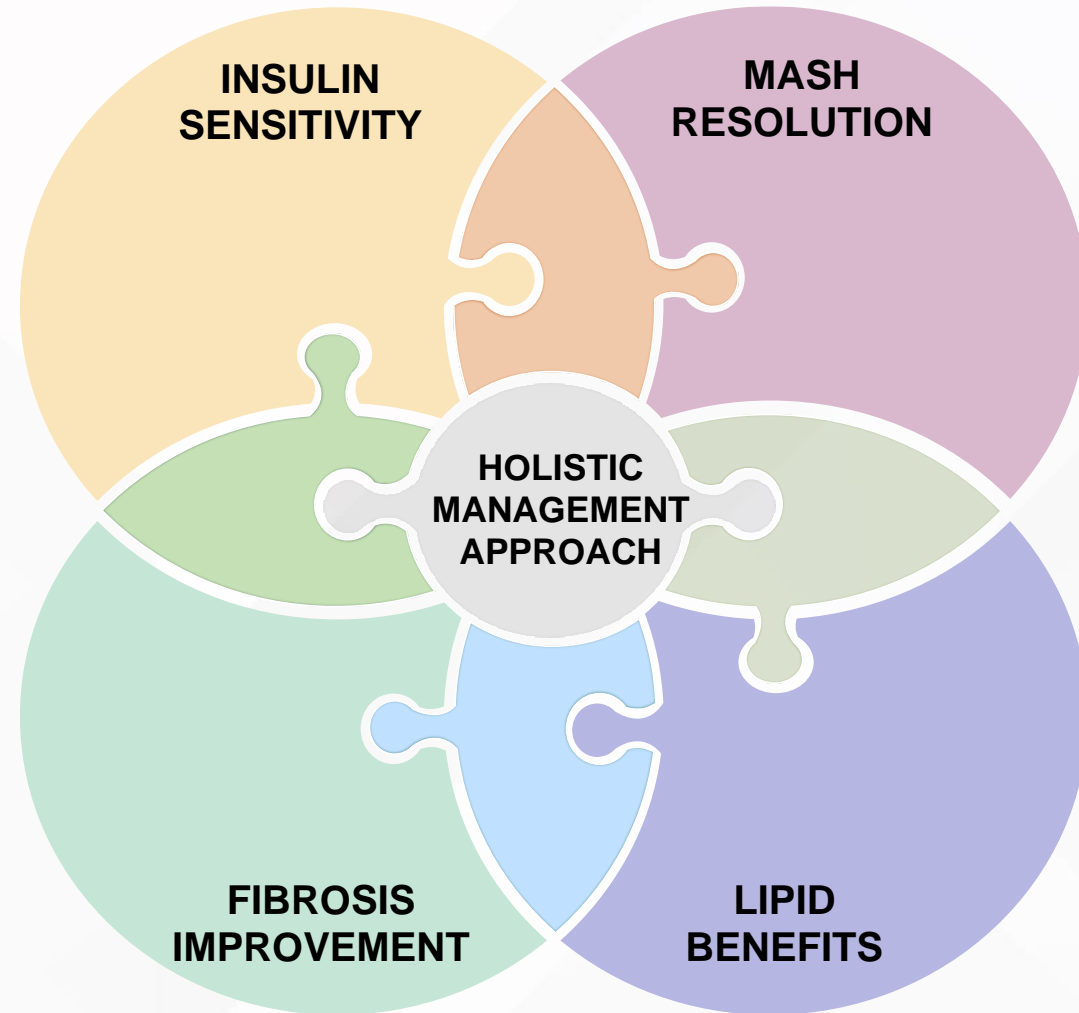
**MACE**  
Major Adverse  
Cardiovascular Events

**1<sup>st</sup> cause**  
**Morbi/Mortality**



**MALO**  
Major Adverse Liver  
Outcomes

**3<sup>rd</sup> cause**  
**Morbi/Mortality**



**Renal Function  
Preservation**

# Thoughts on Non-Cirrhotic MASH

Drugs in Phase 3	Administration	NASH Resolution	Fibrosis Improvement	Insulin Sensitivity	Lipid Benefits	Potential Issues
Resmetirom APPROVED		✓	✓		✓	?GI intolerance
Lanifibranor		✓	✓	✓	✓	GI intolerance peripheral edema, weight gain, anemia
Semaglutide		✓		✓		GI intolerance , pancreatitis?, sarcopenia?
Efruxifermin		✓	✓	✓	✓	GI intolerance , bone loss
Pegozafermin		✓	✓	✓	✓	GI intolerance, bone loss

# Thoughts on Non-Cirrhotic MASH

Completed Phase 2	Administration	NASH Resolution	Fibrosis Improvement	Insulin Sensitivity	Lipid Benefits	Potential Issues
PXL065				✓		GI intolerance
Icosabutate				✓	✓	GI intolerance
Denifanstat		✓	✓		✓	Hair loss
VK2809		✓	✓		✓	GI intolerance
Tirzepatide		✓		✓		GI intolerance , pancreatitis, sarcopenia
Survodutide		✓		✓		GI intolerance , pancreatitis, sarcopenia

# Rationale for Initial Combination Therapy

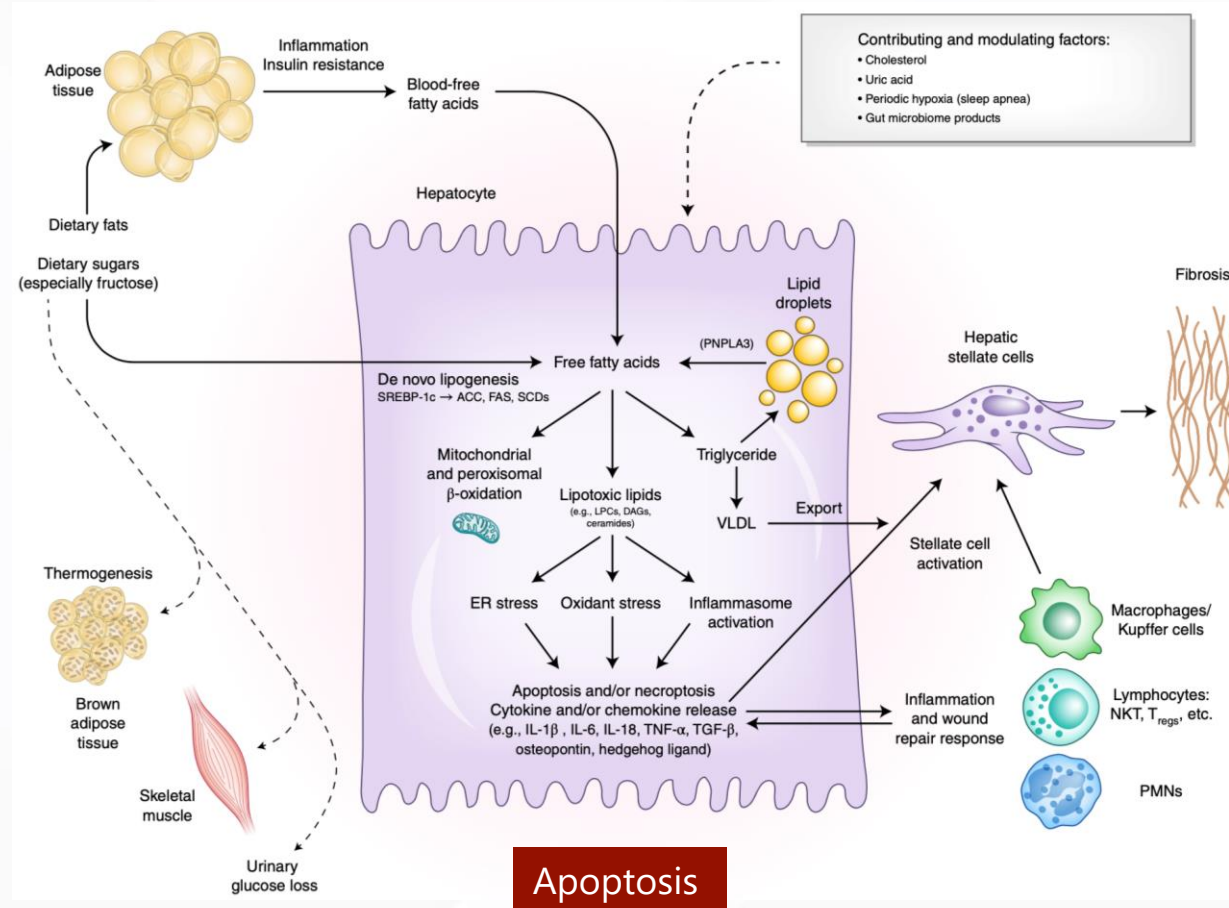
## Multifactorial Disease

Lipogenesis  
Lipid transport

Hepatic insulin resistance  
Gluconeogenesis

Difficult to determine with certainty which pathway is dominant in a particular patient

Use of different classes of medications will increase the chance of controlling/treating the disease faster and more effectively



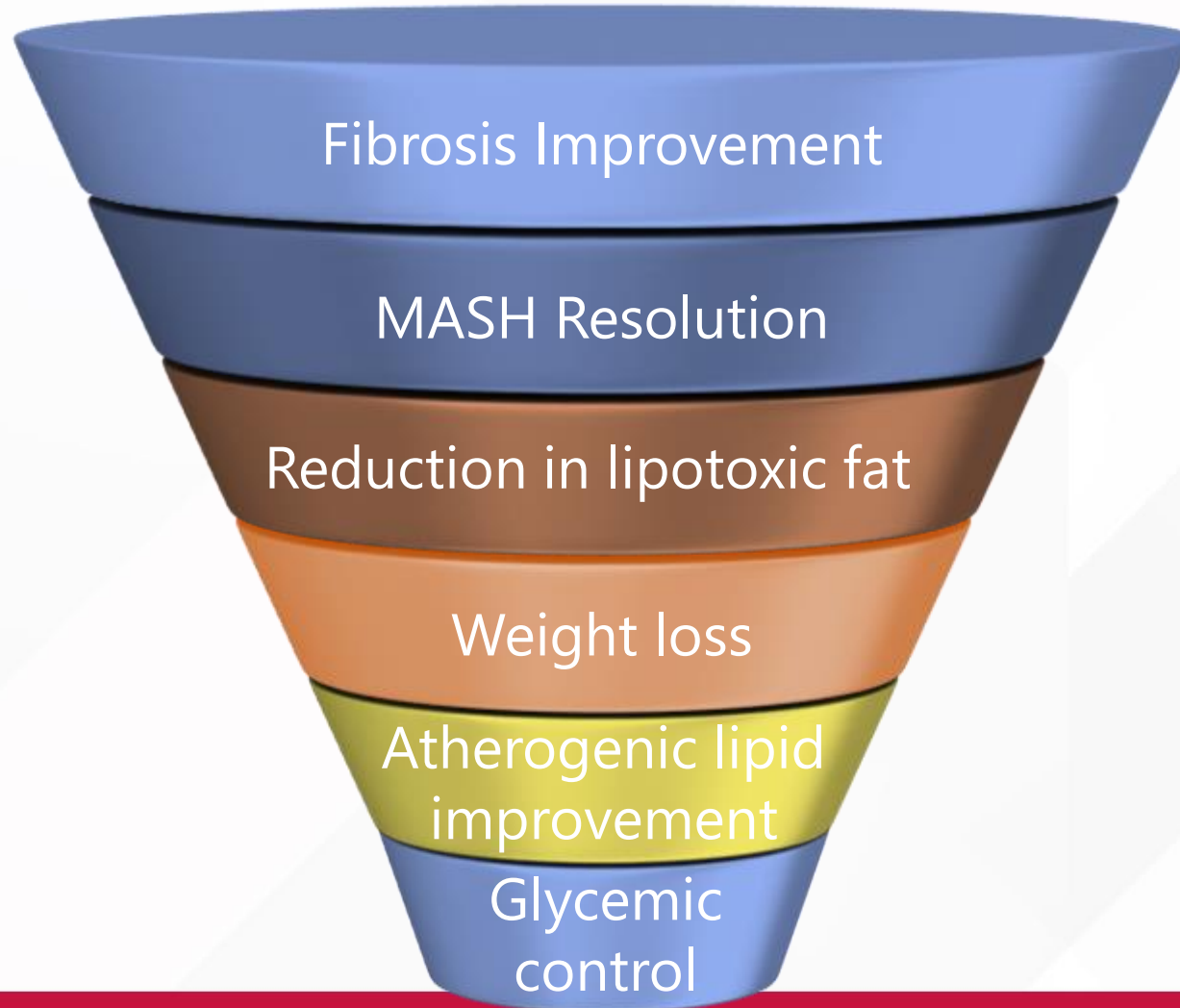
Extracellular  
matrix

Oxidative stress  
Inflammation  
Immune activation

Apoptosis

Friedman et al. Nature Medicine 2018

# A Single Therapy is not Likely to be Enough



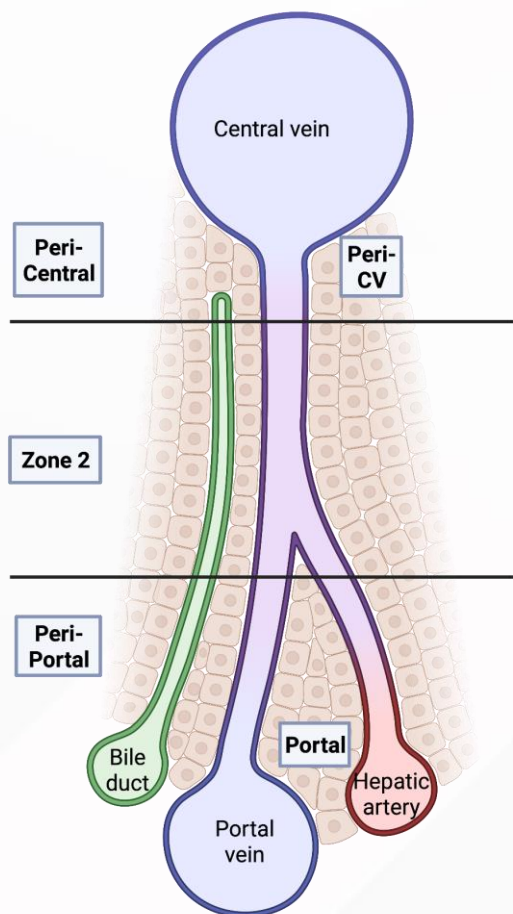
Multifactorial metabolic milieu of MASH warrants potential therapies targeting many pathways

# Approaches to Combination Therapy

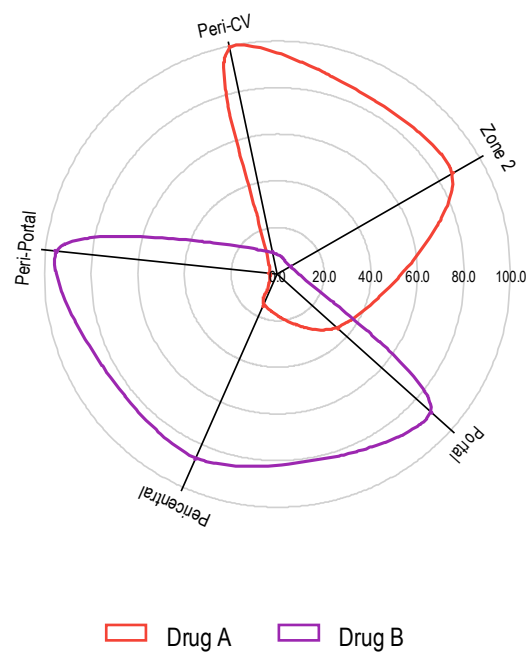
Benefit	Prerequisite	Risk
Single versus multiple drug package - > better compliance > less medical error	Proven synergistic medical benefit Proven safety of the combination	Dosage flexibility



# Potential of AI to Guide Choice of Combinations

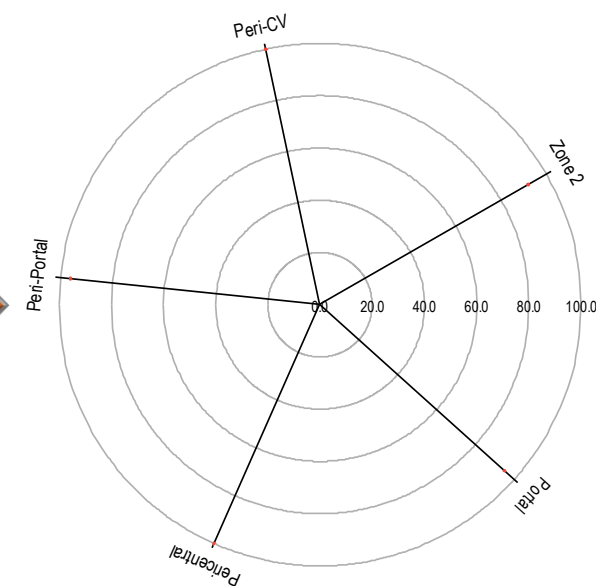


**HistoIndex Zonal Analysis**  
(Percentage of Responders (Regression of Fibrosis) by Zones)



**COMBINATION**

**HistoIndex Zonal Analysis**  
(Percentage of Responders (Regression of Fibrosis) by Zones)



# Regulatory Pathway for Combination

## Study Design

**In vivo & in vitro demonstration of combination rationale**

**For each individual drug**  
*Pharmacology studies – dose finding*

**Need for additional benefits**  
*Greater activity*  
*Better safety profile*

**Drug A + [Placebo or SOC]**

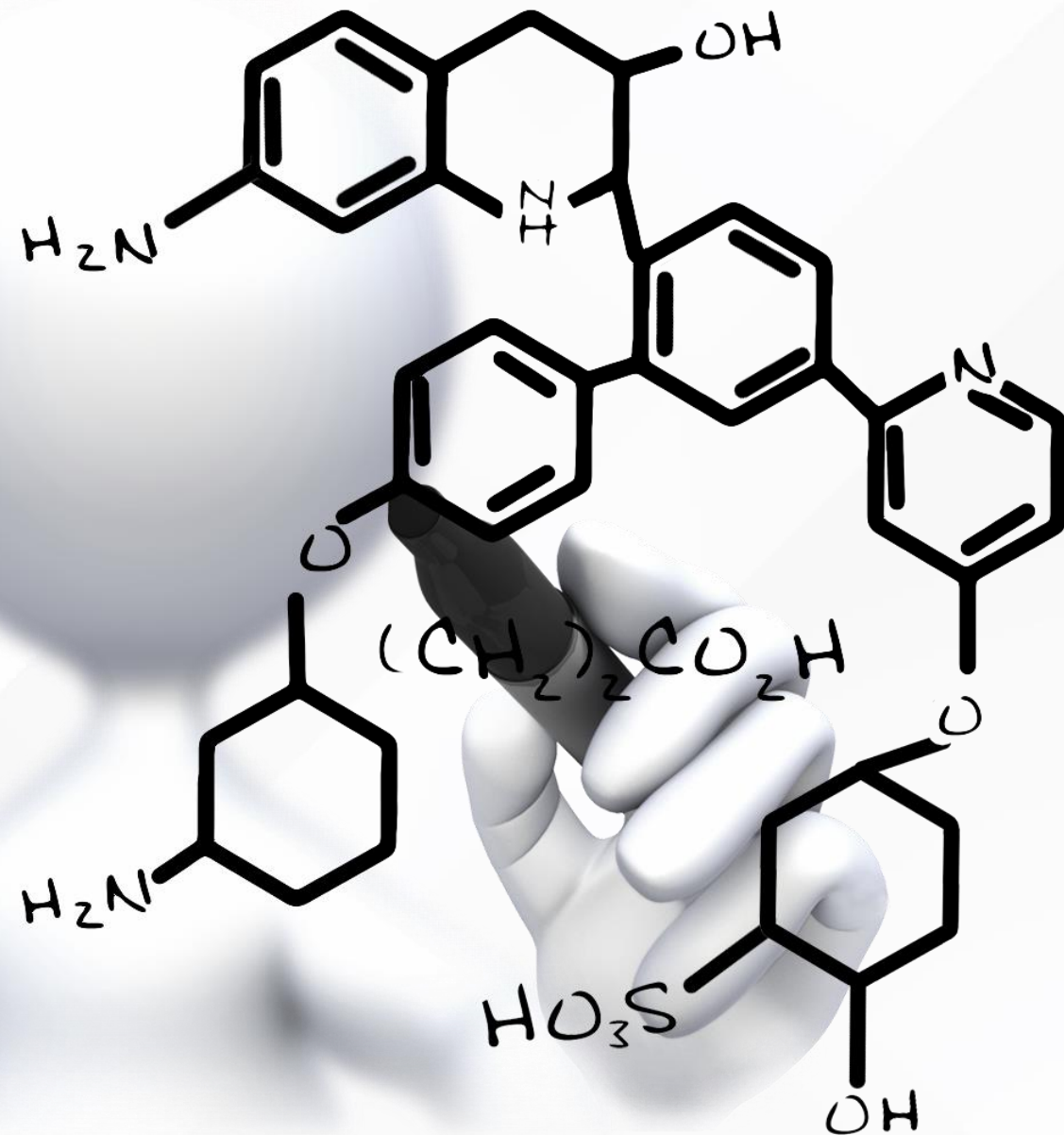
**Drug B + [Placebo or SOC]**

**Drug A + Drug B + [Placebo or SOC]**

**Placebo [+ SOC if applicable]**

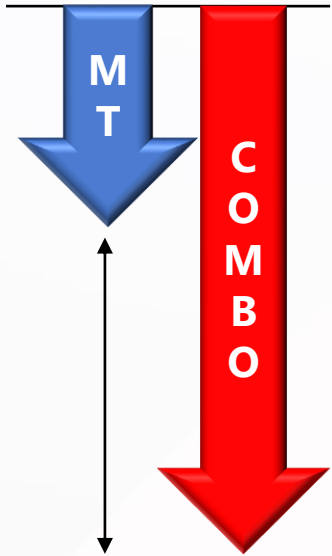
FDA Guidance. Co-development of two or more new investigational drugs for use in combination. June 2013

# Combination Therapy Clinical Trials

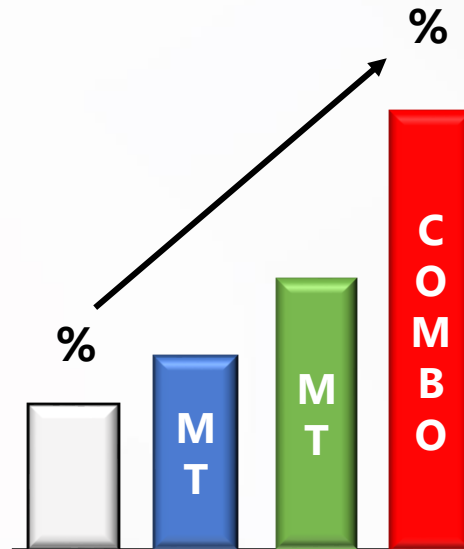


# Advantages of Combination Approaches

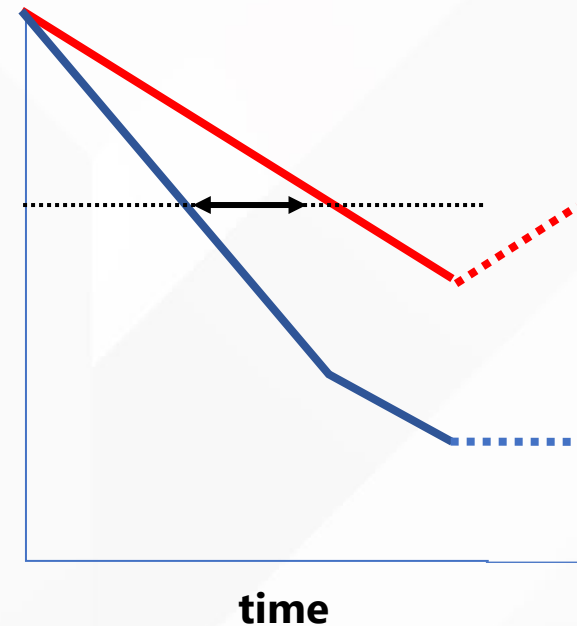
Enhance magnitude of response



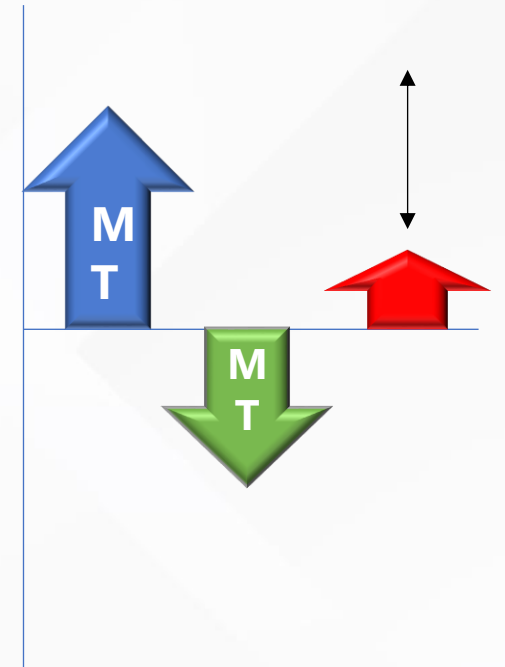
Increase proportion of responders



Accelerate time to response or durability

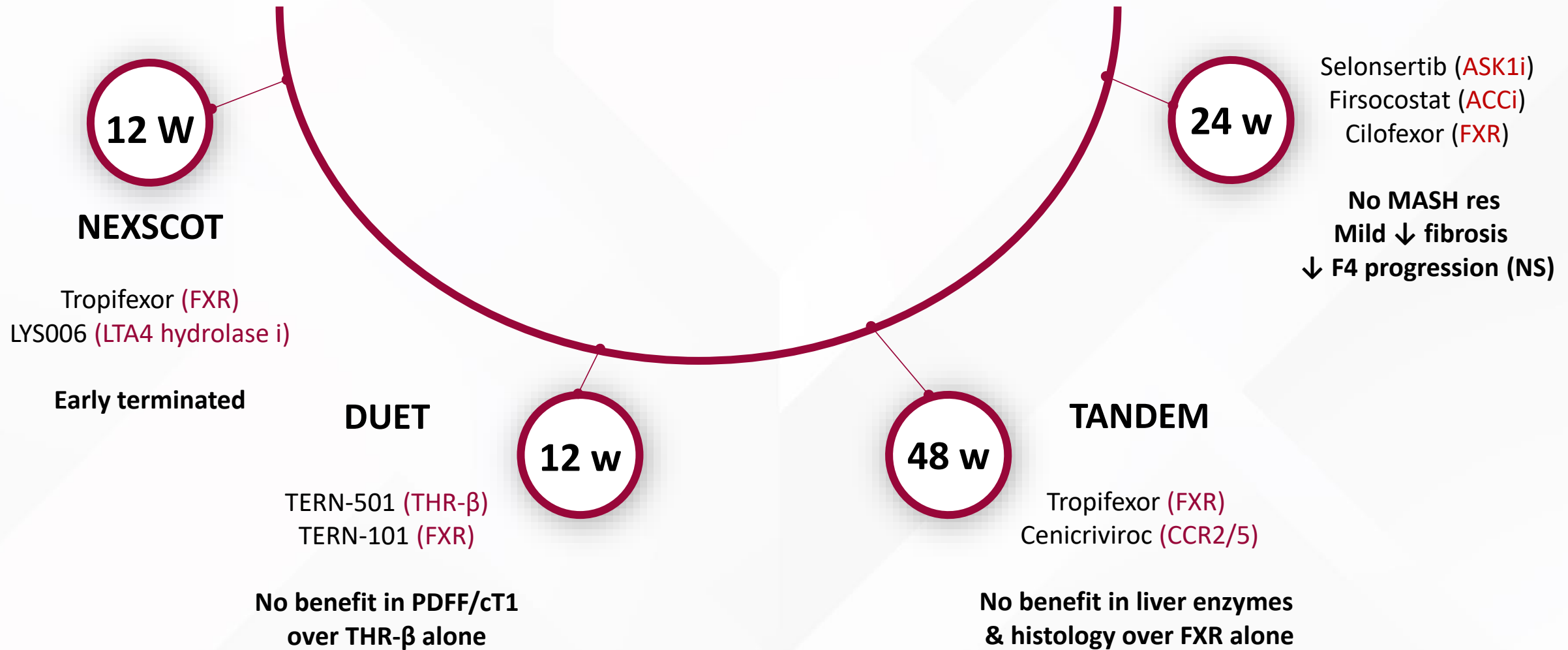


Improved side effect profile



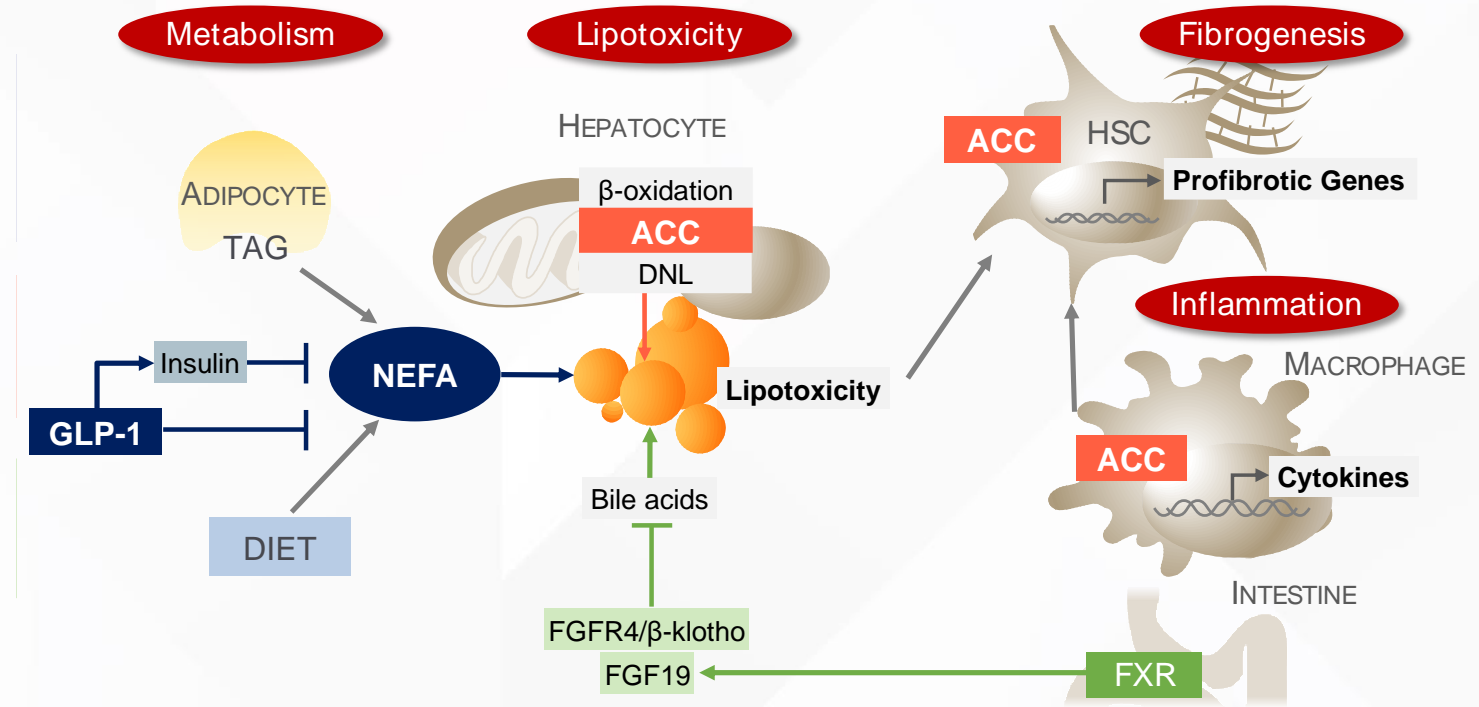
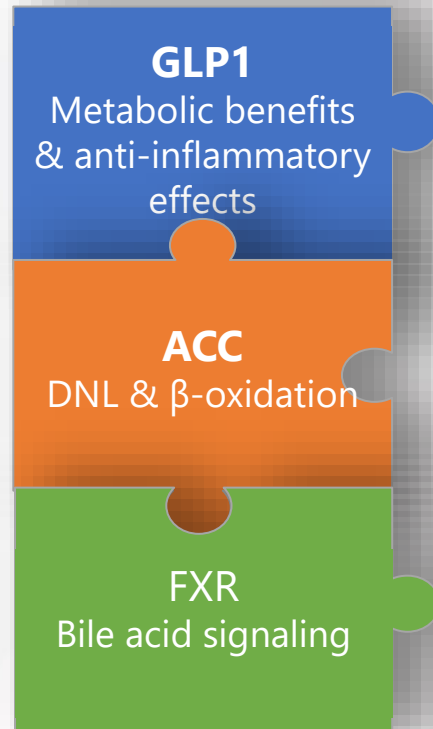
Ratziu and Charlton J Hepatology 2023

# Examples of Failed Combinations



# Semaglutide + Firsocostat + Cilofexor

## Rationale for the combination



**Pathogenesis of MASH is multifactorial and patient population is heterogeneous Semaglutide, firsocostat, and cilofexor target distinct and complementary mechanisms**

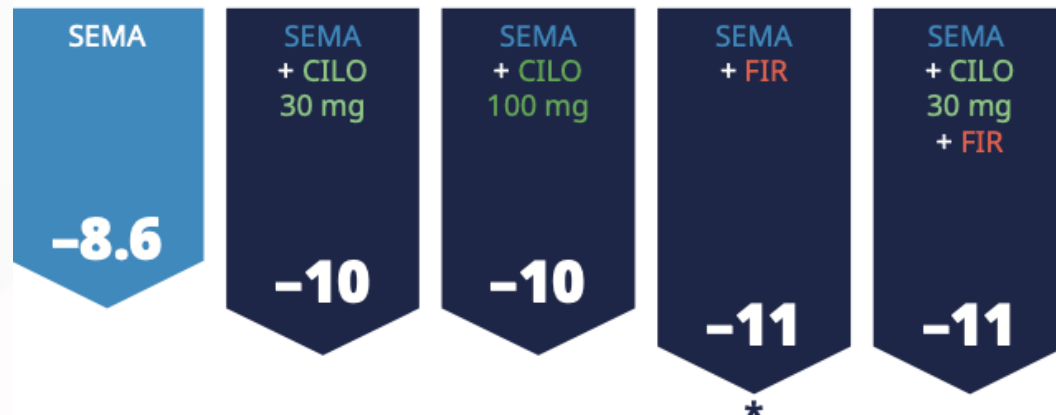
1. Marso SP, et al. N Engl J Med 2016;375:1834-44; 2. Rakipovski G, et al. JACC Basic Transl Sci 2018;3:844-57. 3. Marra F. J Hepatol 2018;68:280-95; 4. Newsome PN, et al. AASLD 2020, abstr 10; 5. Loomba R, et al. Gastroenterology 2018;155:1463-73; 6. Patel K, et al. Hepatology 2020;72:58-71. 7. Alkhouri N et al, J Hepatol 2022;77(3):607-618

# Semaglutide + Firsocostat + Cilofexor

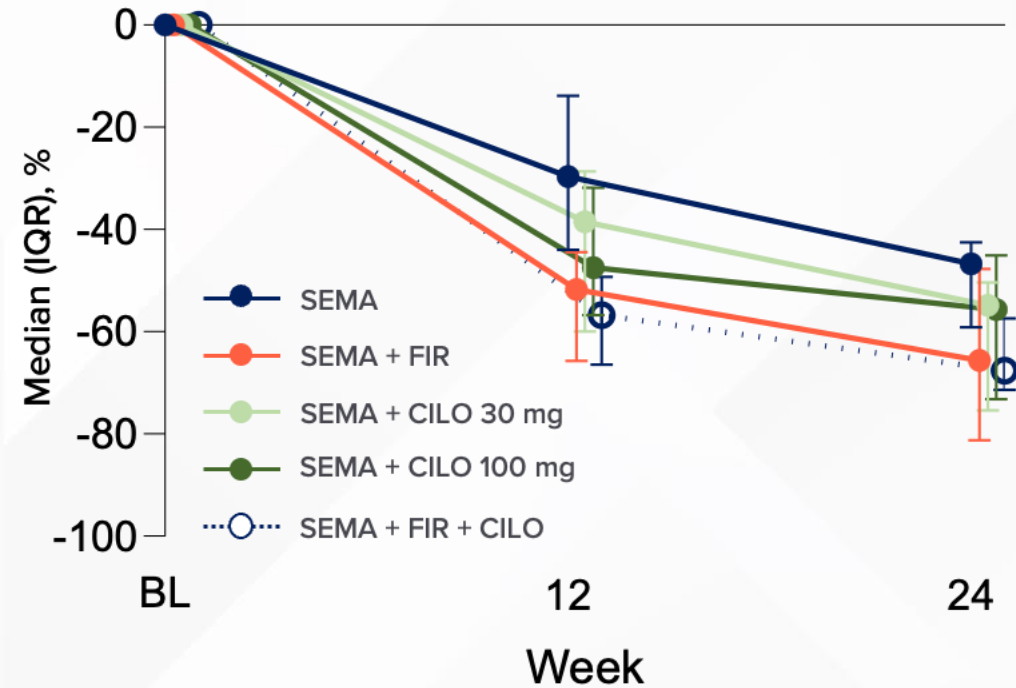
## Absolute Change at Week 24

Greater reductions in **liver fat** in combination groups vs SEMA alone

Absolute change at Week 24 (%) as measured by MRI-PDFF

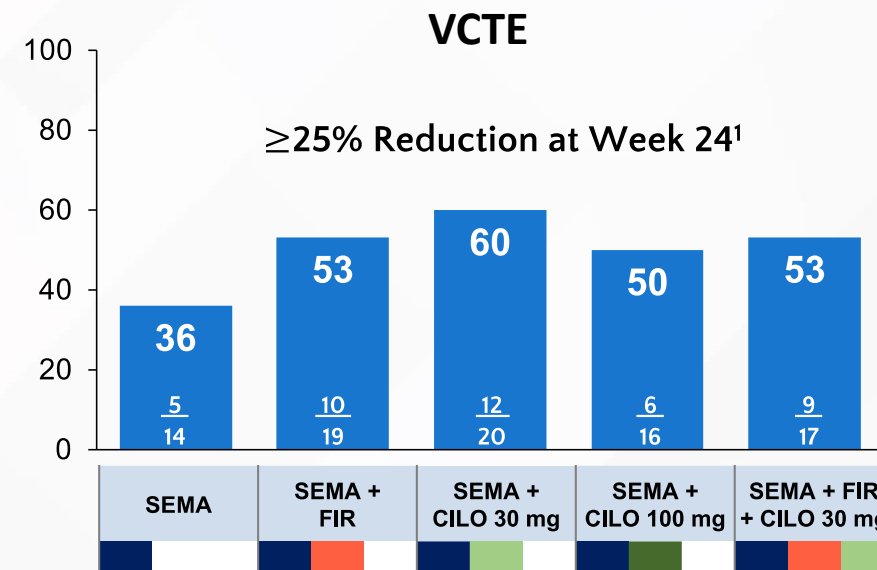


## Relative Change from Baseline



# Results of Combination on other NITs

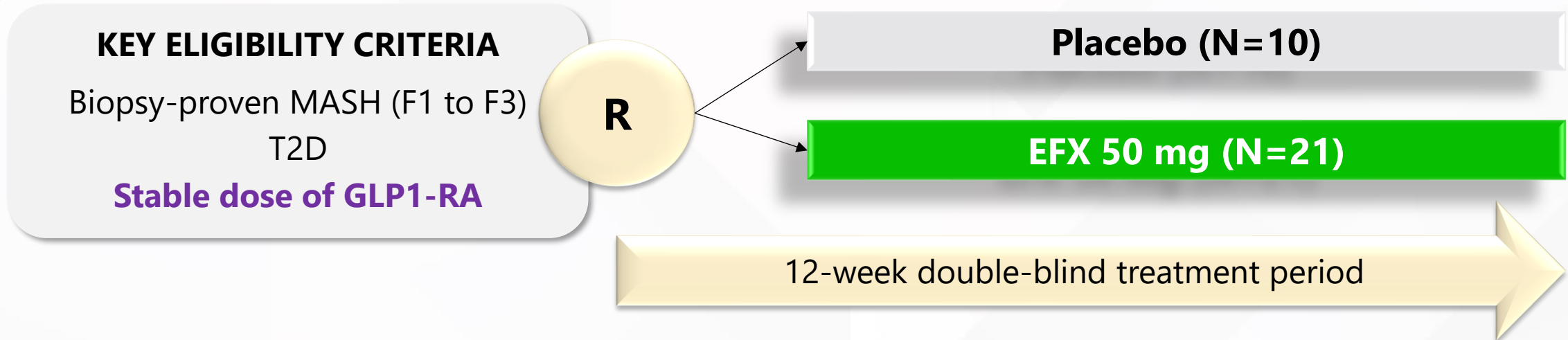
LS <sub>Mean</sub> (95% CI) change from BL at week 24	SEMA n=21	SEMA + FIR n=22	SEMA + CILO 30 mg n=22	SEMA + CILO 100 mg n=22	SEMA + FIR + CILO 30 mg n=21
ALT, U/L	-13 (-23, -3)	-37* (-45, -28)	-32* (-40, -24)	-32* (-40, -23)	-40* (-49, -32)
AST, U/L	-11 (-20, -2)	-26* (-34, -18)	-21 (-29, -14)	-19 (-27, -11)	-26* (-35, -18)
GGT, U/L	-22 (-38, -6)	-21 (-36, -6)	-40 (-54, -26)	-25 (-41, -9)	-23 (-38, -8)
ALP, U/L	-7 (-20, 6)	3 (-8, 15)	-2 (-13, 9)	20* (8, 32)	17* (5, 29)
CK18 M30, U/L	-179 (-252, -107)	-312* (-381, -243)	-259 (-323, -194)	-213 (-284, -143)	-247 (-318, -176)
ELF	-0.56 (-0.86, -0.27)	-0.59 (-0.87, -0.30)	-0.46 (-0.73, -0.19)	-0.47 (-0.76, -0.19)	-0.42 (-0.70, -0.13)



- Significantly greater reductions in ALT in all combination groups vs SEMA alone
- Significant reductions from BL in ELF in all groups ( $p < 0.05$ ); however, no differences vs SEMA

Proportion of patients with  $\geq 25\%$  relative reduction in VCTE higher in combination groups (50-60%) vs SEMA alone (NS)

# Symmetry – Cohort D Design – Add-On to GLP1-RA



## Primary endpoint:

Safety and tolerability of EFX combined with a GLP-1RA

## Secondary endpoints:

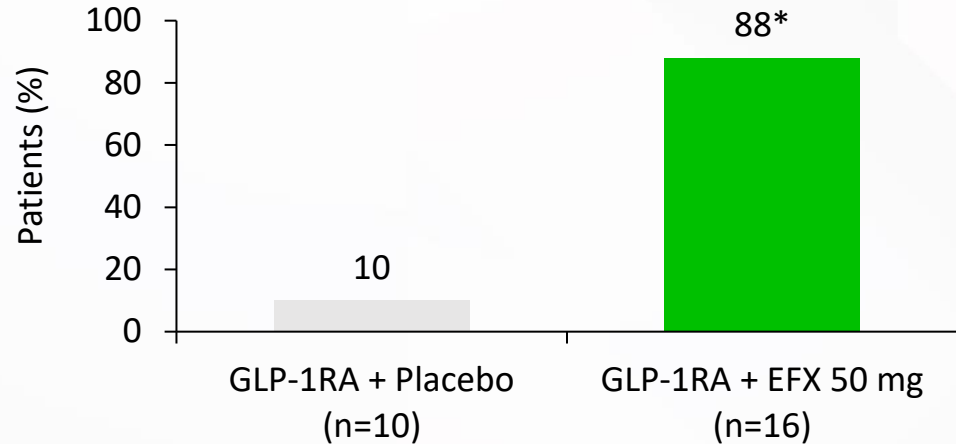
Effects on liver fat, markers of liver injury, markers of glucose and lipid metabolism, and body weight

Baseline characteristics [median dose]	GLP-1RA + Placebo (n=10)	GLP-1RA + EFX 50 mg (n=21)
Semaglutide: [1 mg qw]	60%	43%
Dulaglutide: [3 mg qw]	30%	52%
Liraglutide: [1.5 mg qd]	10%	5%
With 1 exception, all patients remained on baseline GLP-1 therapy through Week 12. Due to unavailability of semaglutide, 1 patient switched to tirzepatide after the Week-10 visit		

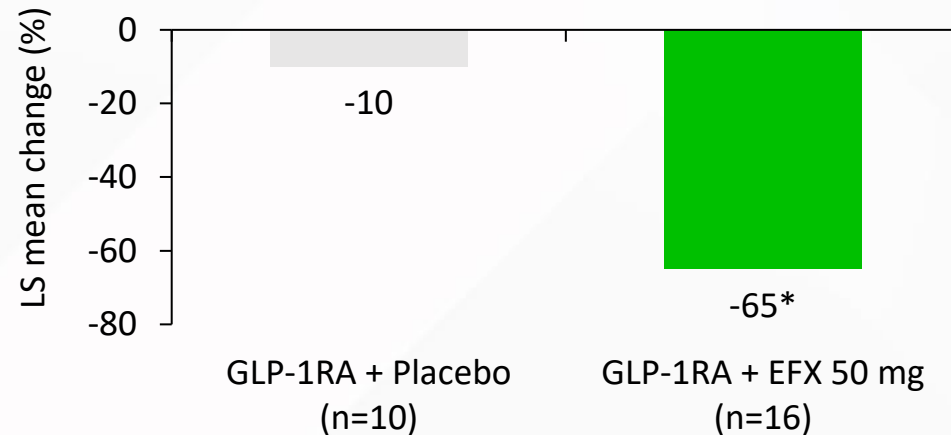
Harrison SA et al. Clin Gastroenterol Hepatol. 2024

# Symmetry – Cohort D Study Results

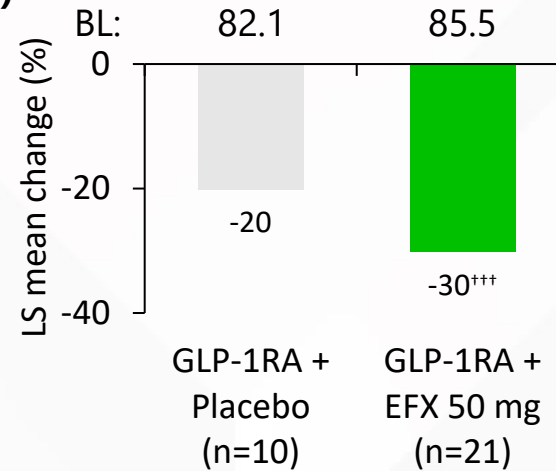
Normalization of liver fat to  $\leq 5\%$  at Week 12 (MRI-PDFF)



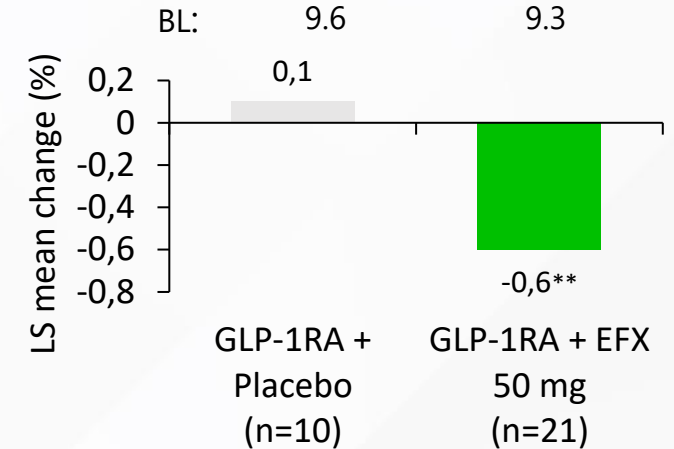
Relative change in liver fat from baseline at Week 12 (MRI-PDFF)



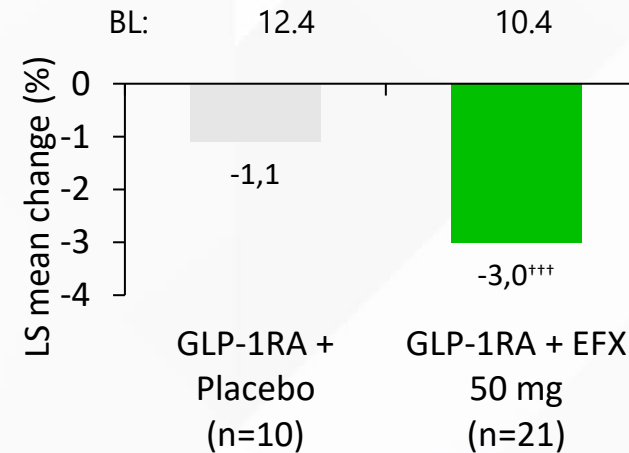
Pro-C3



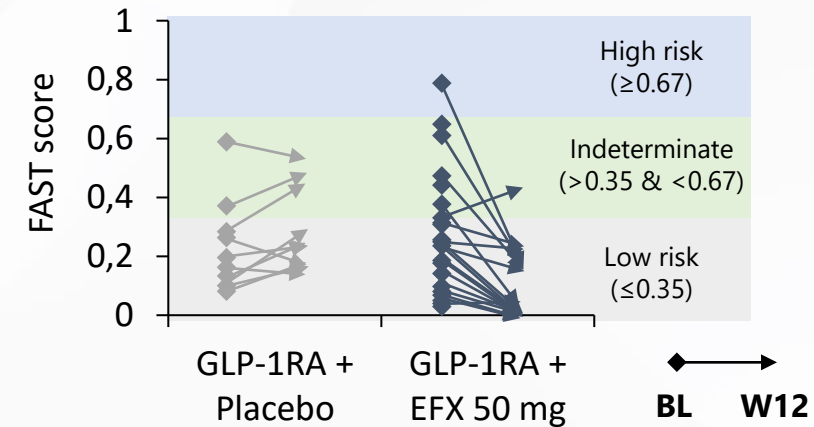
ELF score



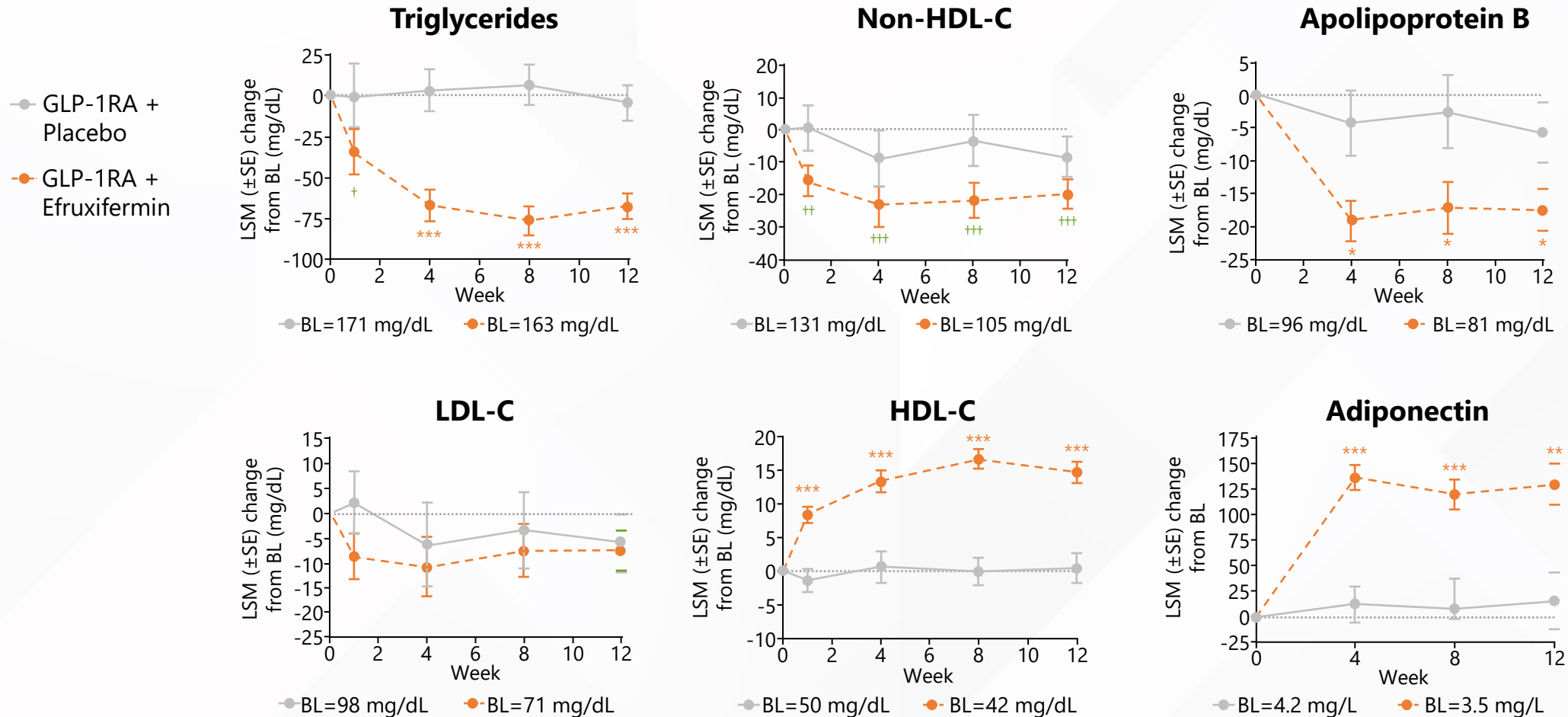
Liver stiffness



FAST score



# Symmetry – Cohort D Study Results



Harrison SA et al. Clin Gastroenterol Hepatol. 2024

# Akero – Cohort D Study Results - Add-on to GLP1-RA

## Safety & Tolerability

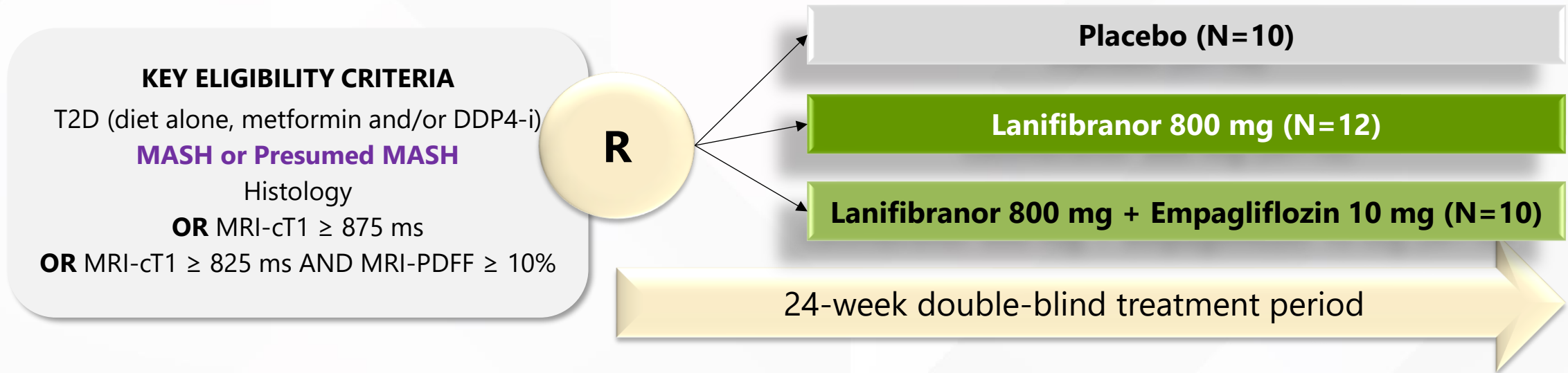
TEAEs	Placebo (N=10)	EFX 50 mg (N=21)
TEAE leading to death	0	0
Drug-related SAE	0	0
Drug related TEAE leading to discontinuation	0	1 (5%)

Most frequent (≥15%) Drug-Related TEAEs	Placebo (N=10)	EFX 50 mg (N=21)
Diarrhea	3 (30%)	4 (19%)
Nausea	1 (10%)	7 (33%)
Increased Appetite	0	5 (24%)
Decreased Appetite	2 (20%)	3 (14%)

- The most frequent drug-related AEs were mild or moderate diarrhea, nausea, or increased appetite
- There were 2 SAEs; neither were deemed drug related
- One patient discontinued due to a drug-related AE of Grade 2 nausea

Harrison SA et al. Clin Gastroenterol Hepatol. 2024

# LEGEND – Combination Pan-PPAR & SGLT2-i



## Primary endpoint at Week 24:

Absolute change from baseline in HbA1c  
**Benefits of combination over lani alone**

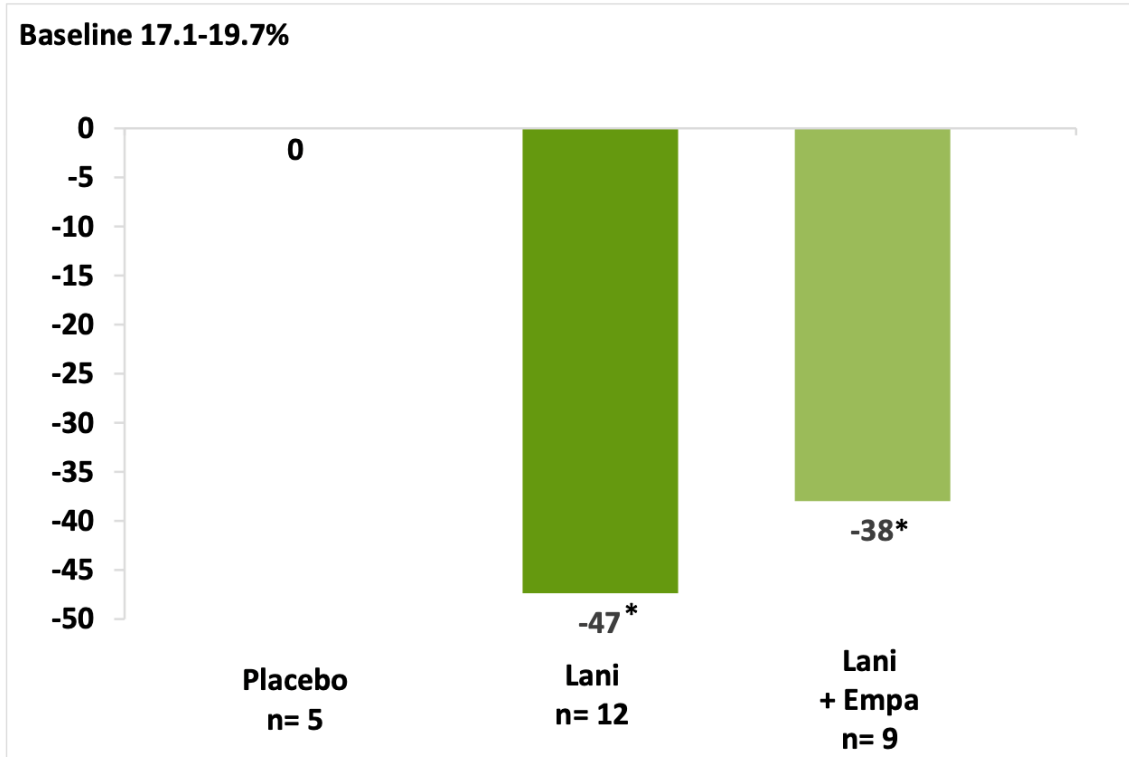
Placebo: +0.26%  
Lani: -1.14%  
Lani + Empa: -1.59%

## Secondary endpoints:

MRI-PDFF, MRI-cT1, weight

# LEGEND – Combination Pan-PPAR & SGLT2-i

Relative Change from Baseline (PDFF)

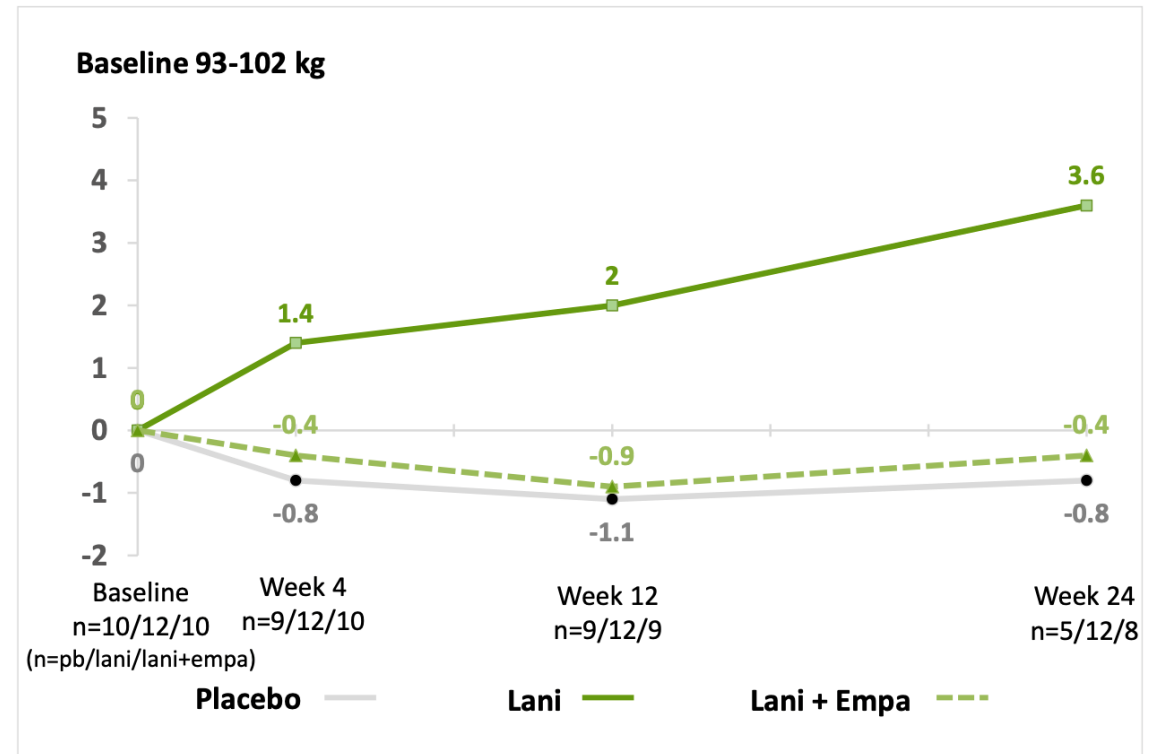


\*p≤0.05, versus placebo (ANCOVA – Analysis of Covariance)

Six patients were not considered in the FAS because no MRI-PDFF values available at Week 24:

- 5 patients under placebo who prematurely stopped before Week 24
- 1 patient under lani+empa who significantly modified his/her diet (intercurrent event) before Week 24

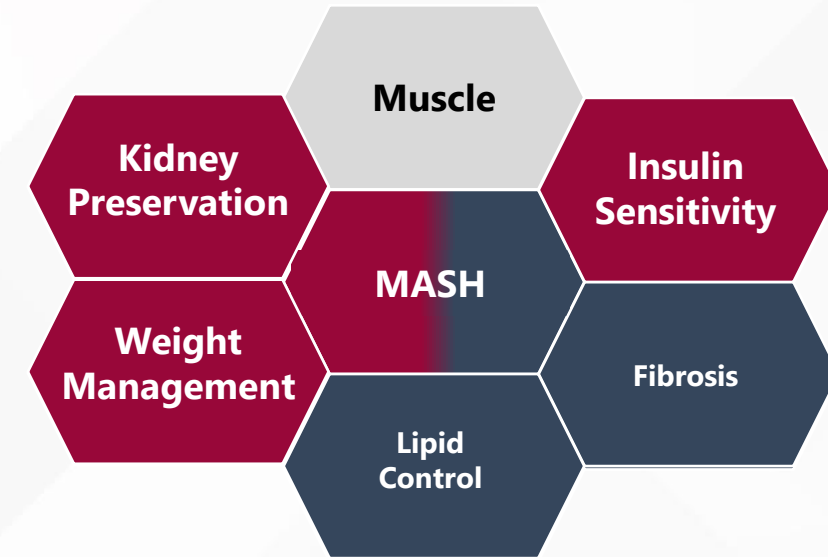
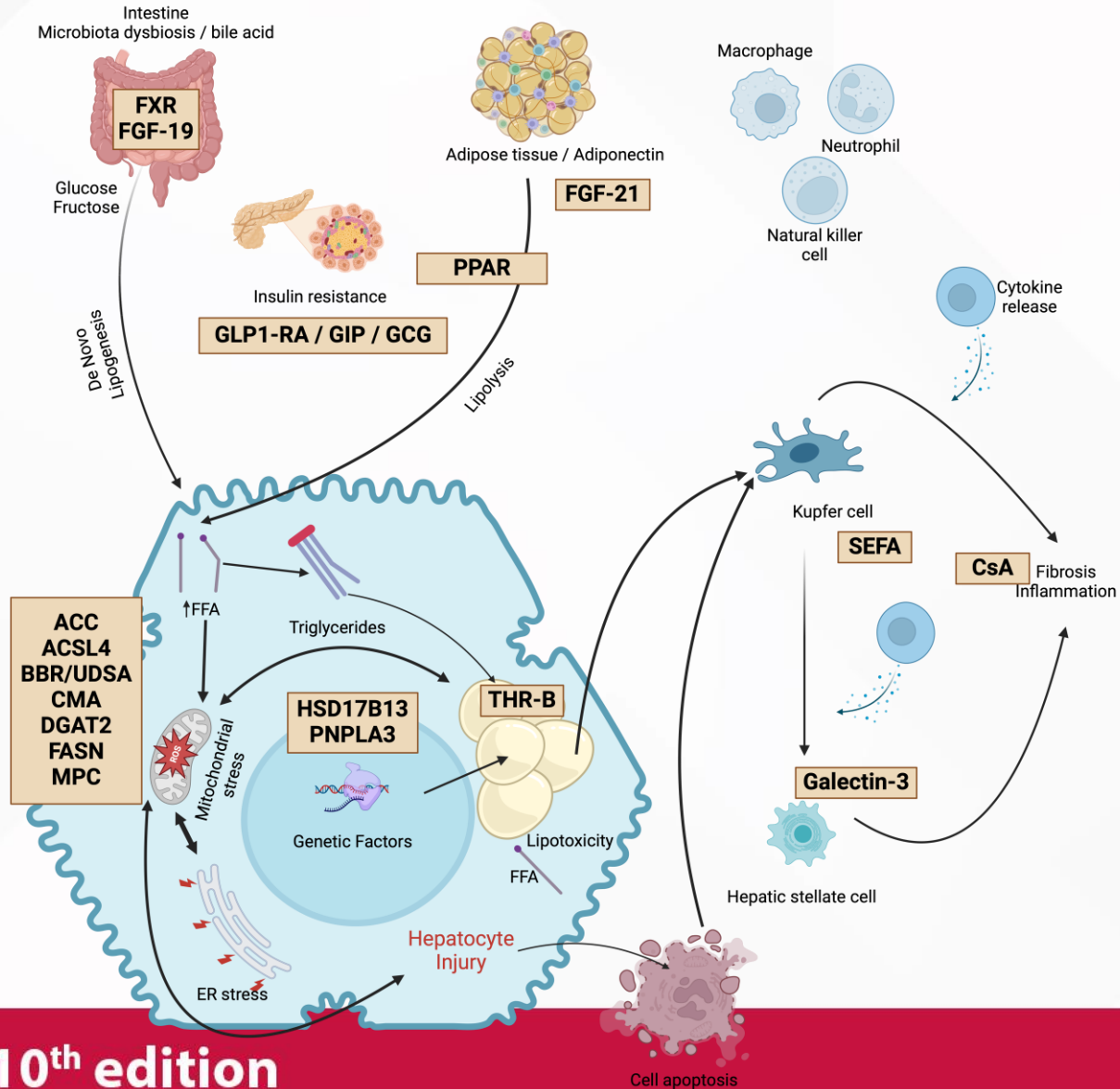
Relative Change from Baseline (Weight)



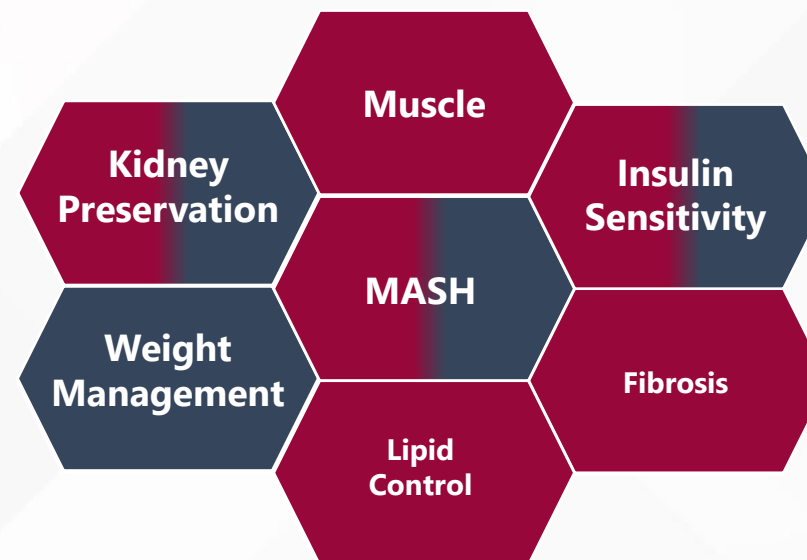
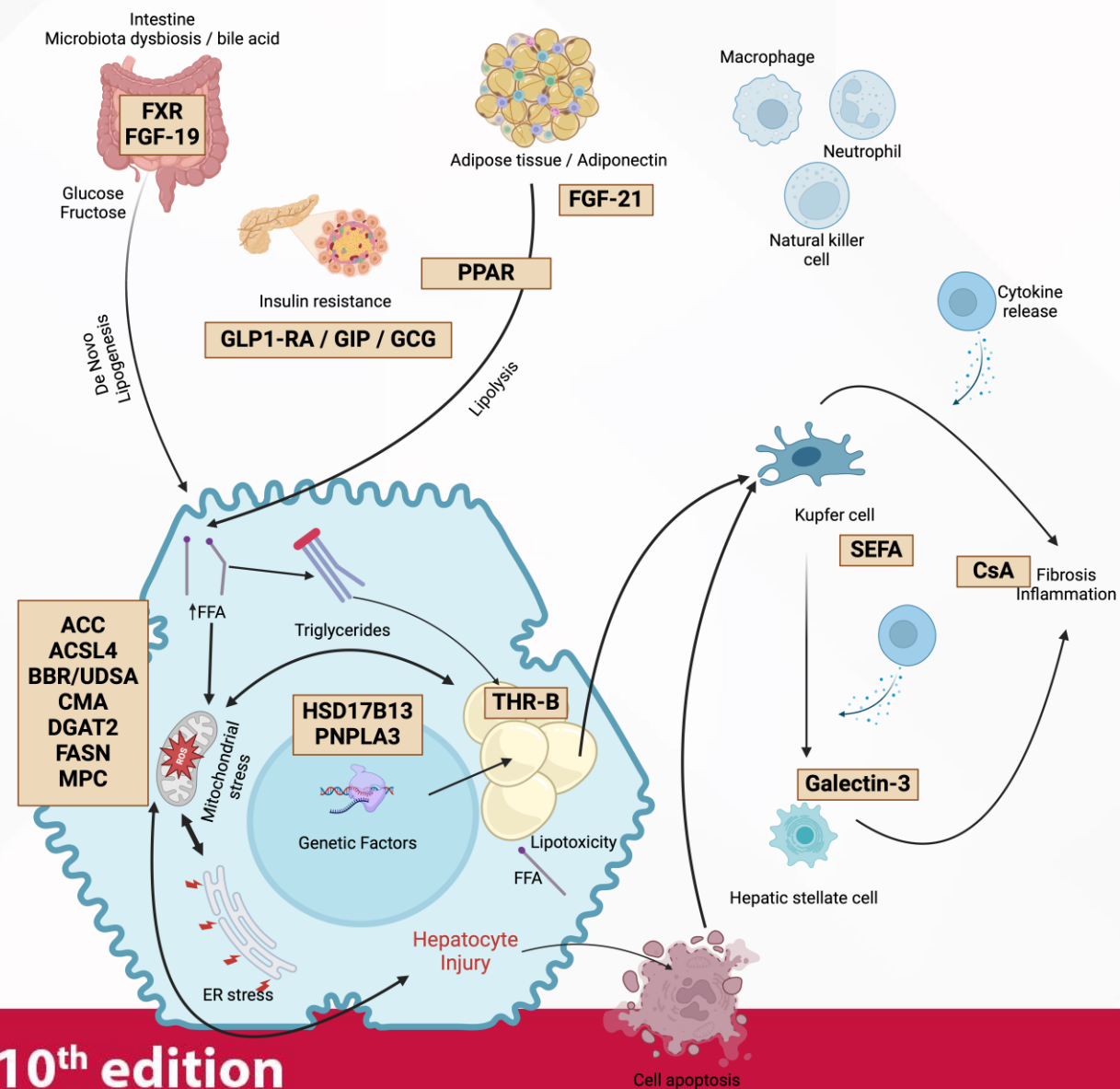
At Week 24, 7 patients without weight values available :

- 5 patients under placebo who prematurely stopped before Week 24
- 1 patient under lani+empa with missing data at Week 24, and 1 patient under lani+empa who significantly modified his/her diet (intercurrent event) before Week 24.

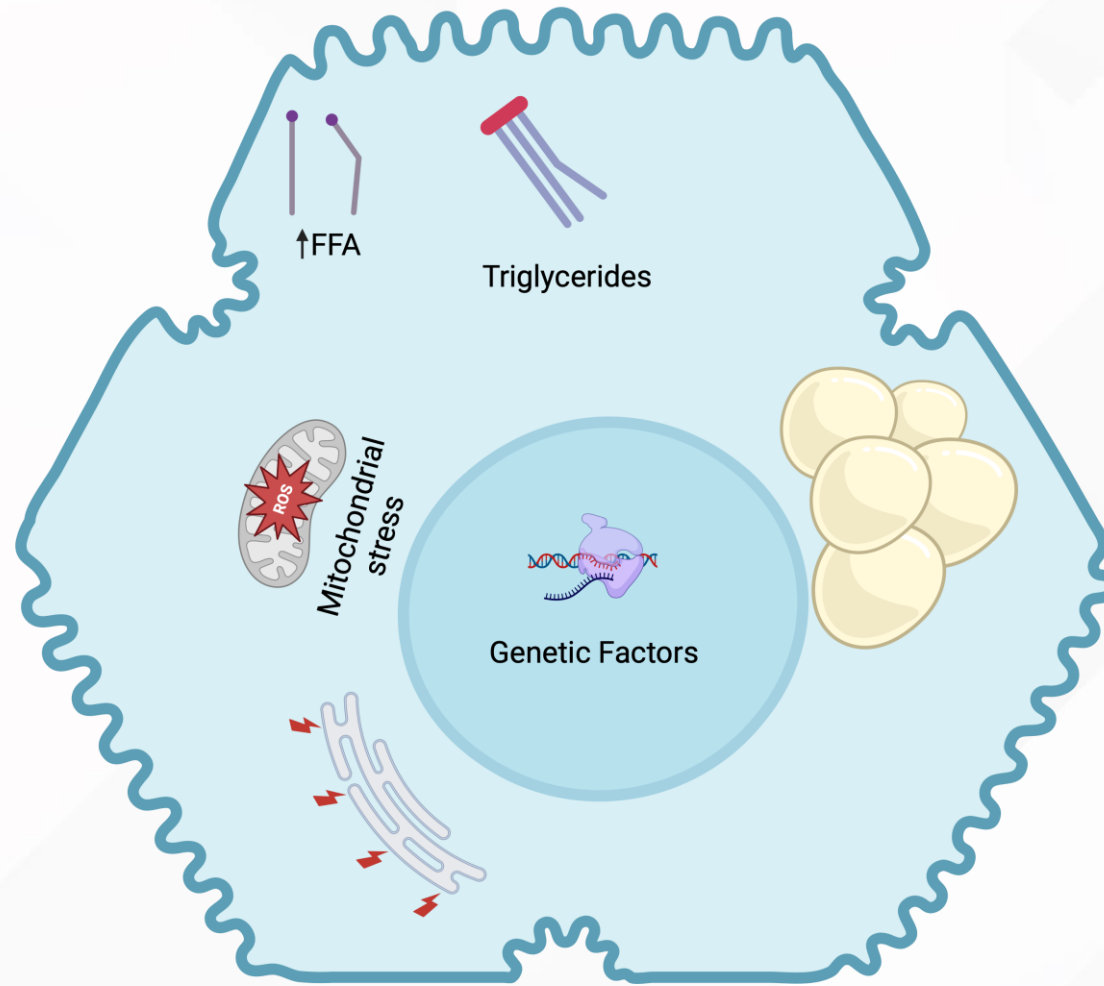
# Potential Combinations



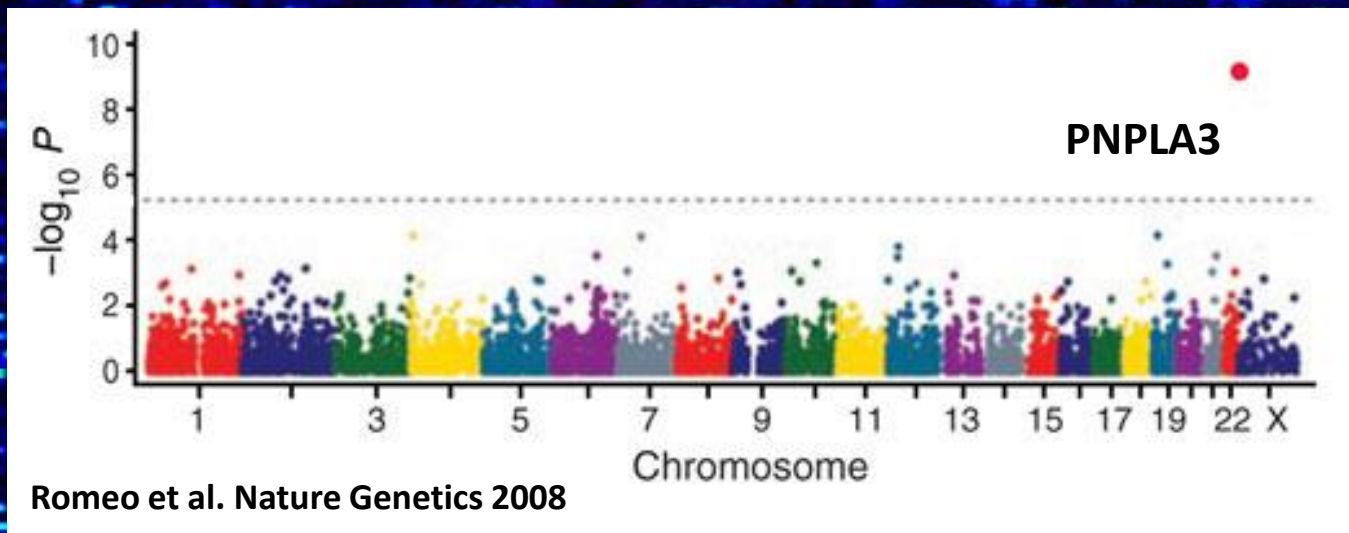
# Potential Combinations



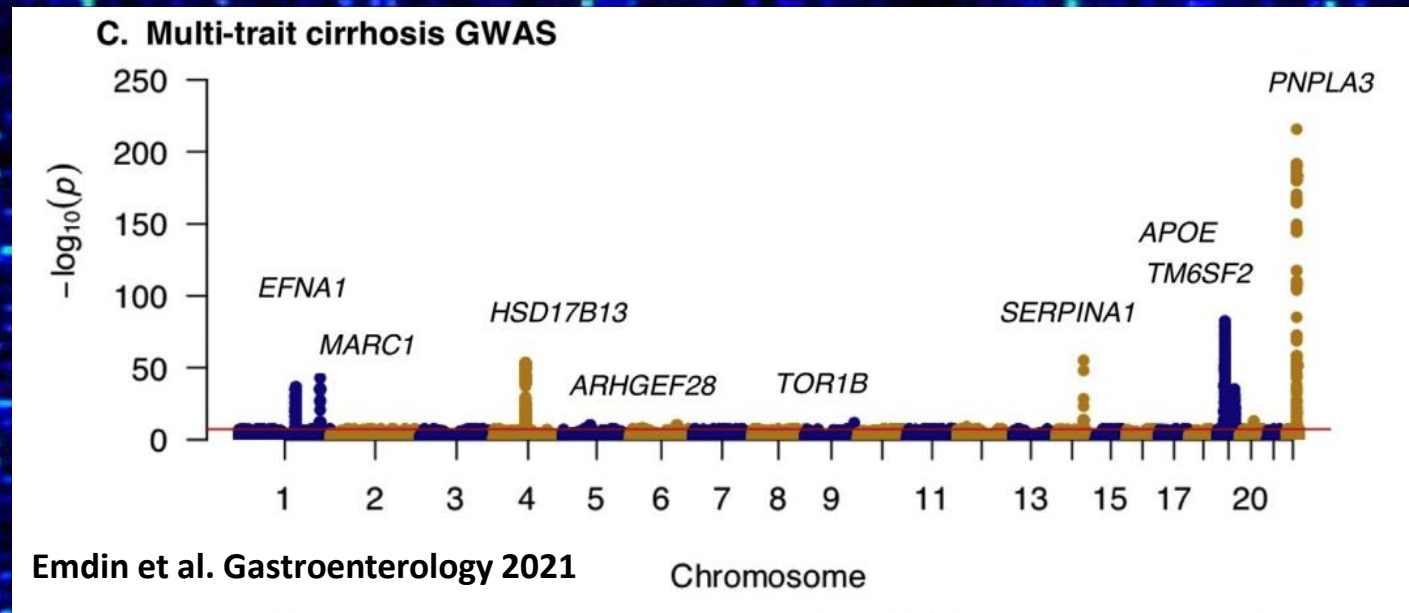
# Potential Combinations – Genetics & Precision Medicine



# GeneChip HUMAP Xba131

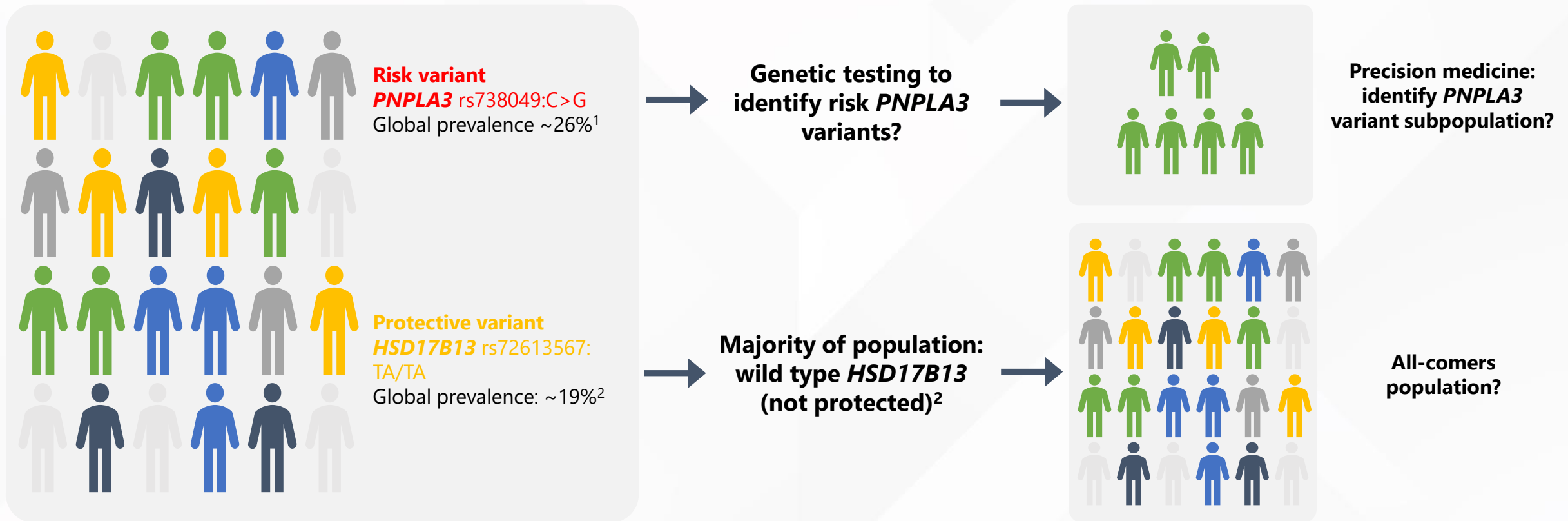


- PNPLA3**
- TM6SF2**
- MBOAT7**
- HSD17B13**



# What the Future may hold for Precision Medicine?

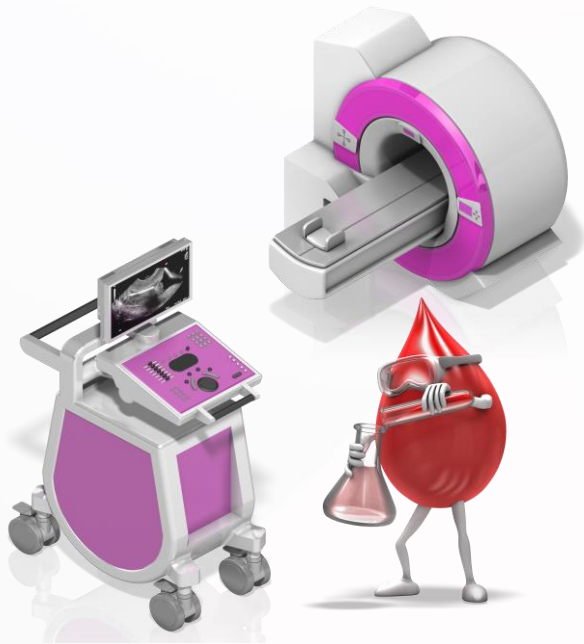
## General population (all-comers)



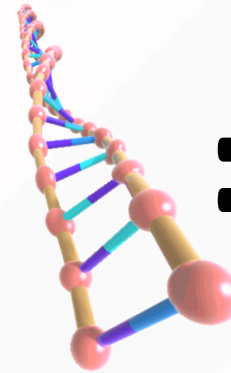
1. Yip TC-F et al. Hepatology. 2023; 2. <https://gnomad.broadinstitute.org/variant/4-87310240-T-TA>. Accessed May 10, 2024

# A Future Towards Precision Medicine

Guiding the Choice of the Most Appropriate Combination at the Individual Patient Level



**Non-Invasive Testing**



**Right  
combination for  
right patient**

**Metabolic Factors**

(Weight, blood pressure, lipid & glycemic profile)

**Genetic Variants**

(HSD17B13, PNPLA3, GCKR, TM6SF2)

# Summary

- Combination therapy will likely be required to achieve higher response rates
- Combinations must be purposeful: Synergistic, provide more wholistic treatment or mitigate side effects (least optimal)
- A personalized approach will allow for tailoring to the individual patient's dominant driving factors



**Thank you for your attention**

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