

Diagnostic et prise en charge d'un patient avec NASH

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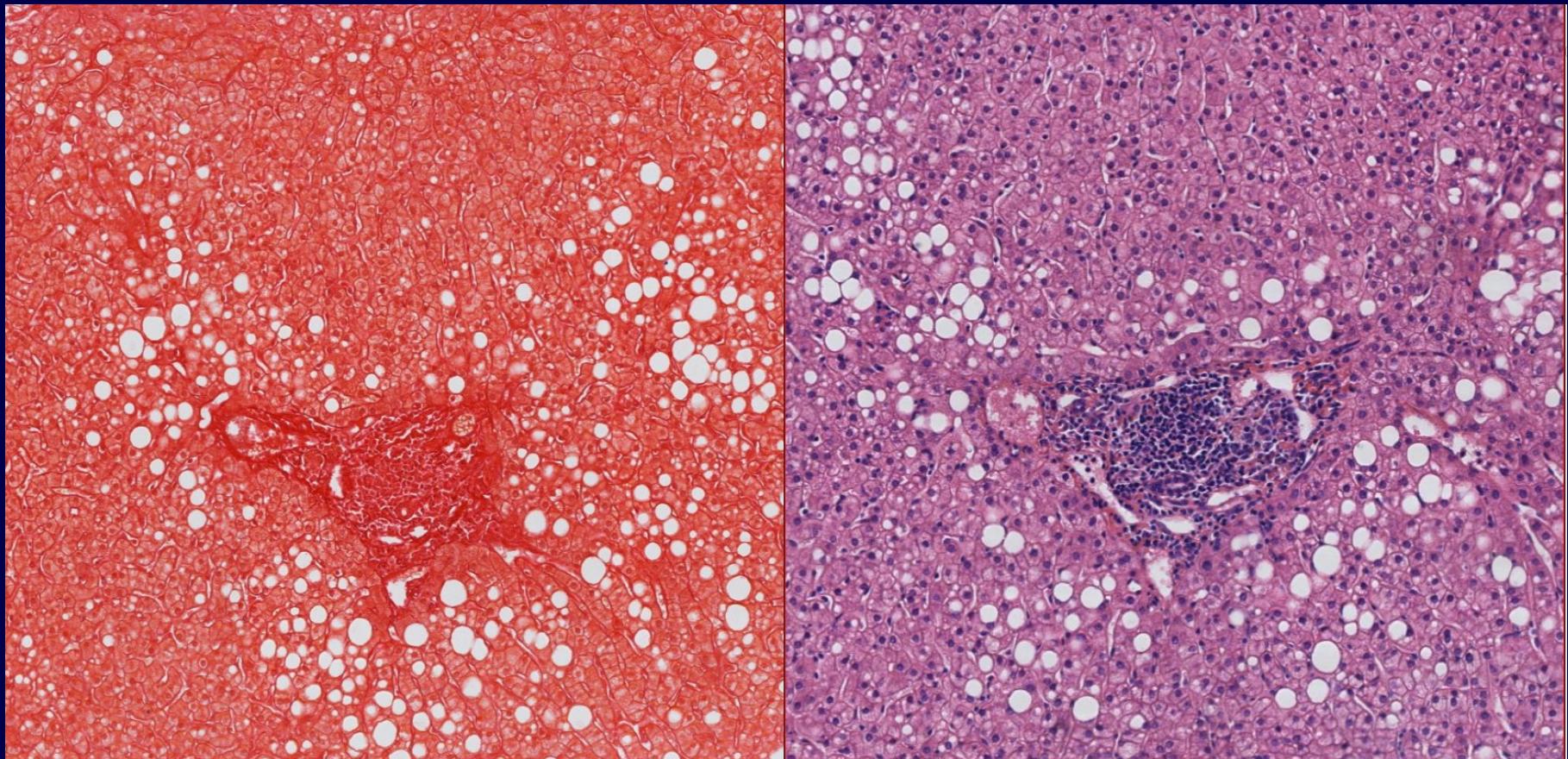
Liens d'Intérêts

Abbvie
Gilead
Intercept
MSD

Cas 2 : Femme agée de 52 ans adressée en octobre 2005 pour hépatite chronique virale C

- ATCD: GEU avec transfusions à l'âge de 26 ans
- Alcool= 0
- Medicaments= 0
- Examen normal en dehors d'un IMC à 28 (160 cm/72 Kg)
- ASAT/ALAT (45/61), ARN du VHC 555 000 UI, Genotype1

PBH Decembre 2005



Score METAVIR A1F1
Stéatose (20%)

2006-2007

- Interféron Pégylé + Ribavirine 18 mois

Réponse virologique soutenue

2006 Avant traitement 72 Kg ALAT 1.5N

2007 Fin de traitement 66 Kg ALAT N

2008-2014 (+10 Kg)

2008-2011 72 à 78 Kg ALAT N

2012-2014 80 à 82 Kg ALAT 2N à 3N

2014

Auriez vous réalisé une PBF?

- oui
- non

2014

Auriez vous réalisé une PBF?

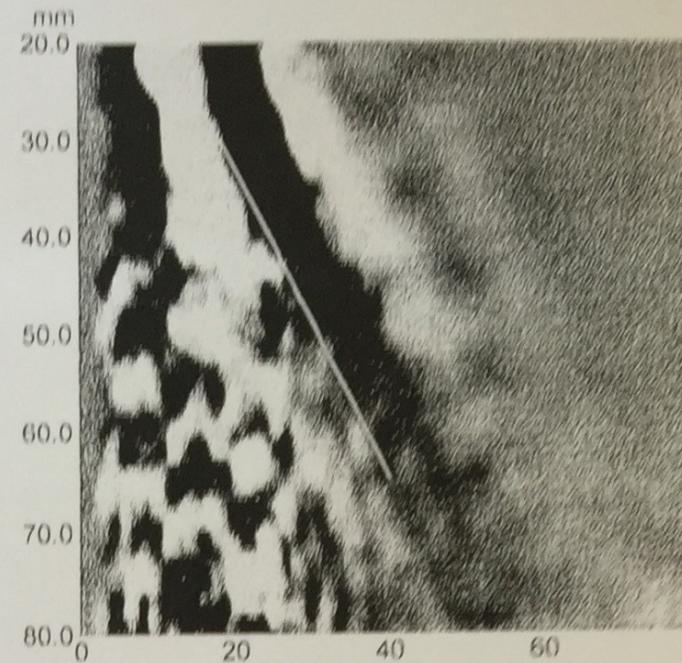
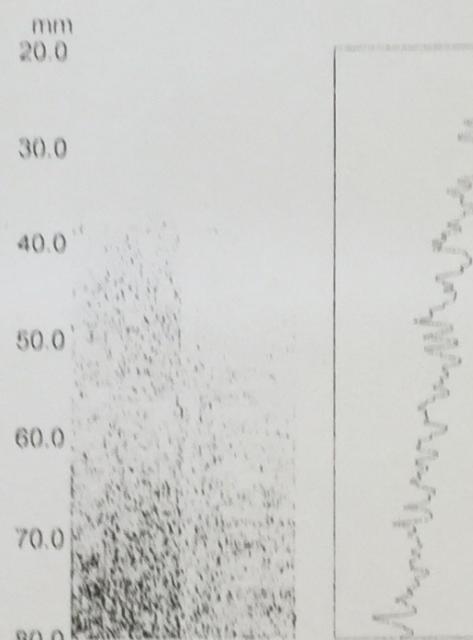
- oui
- non

2014

Auriez vous réalisé un marqueur indirect de fibrose ?

- oui
- non

| | |
|--|--|
| Nom ABB | mm 20.0 30.0 40.0 50.0 60.0 70.0 80.0 |
| Prénom FR | |
| Code STEATOSE HCV | |
| Date de naissance 22/04/1965 | |
| Opérateur DR OUZAN | |
| Date 06/03/14 12:01 | |
| Durée de l'examen 00:04:39 | Examen M |
| Elasticité (KPa) 9.7 | |
| IQR (KPa) 1.3 | EC (KPa) 7.7 |
| TdR 91% | |



- (01) E = 7.7 KPa
- (02) E = 9.6 KPa
- (03) E = 10.2 KPa
- (04) E = 10.9 KPa
- (05) E = 9.8 KPa
- (06) E = 7.2 KPa
- (07) E = 9.2 KPa
- (08) E = 10.2 KPa
- (09) E = 11.1 KPa
- (10) E = 8.8 KPa

**82 Kg/1m60
IMC:32**

**Test n° 1
Valide 10
Invalide 1**

2017

Poids 86 Kg IMC: 35 TA 12/8

ALAT 1.8 N

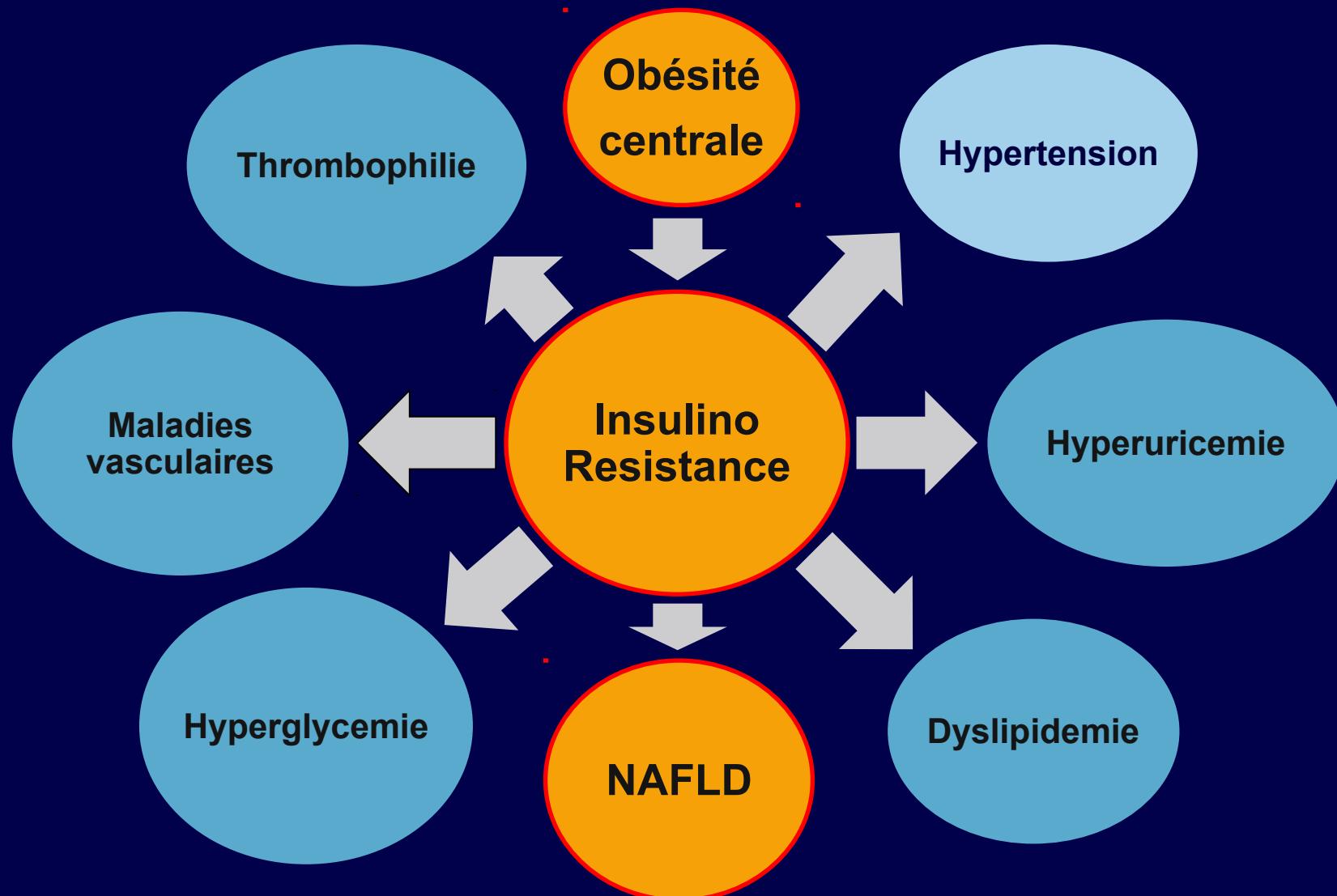
TG: 4.22 g/L

Glycémie: 1g/L

HOMA= 11.9

Fibroscan ininterprétable

Obésité et insulino-résistance



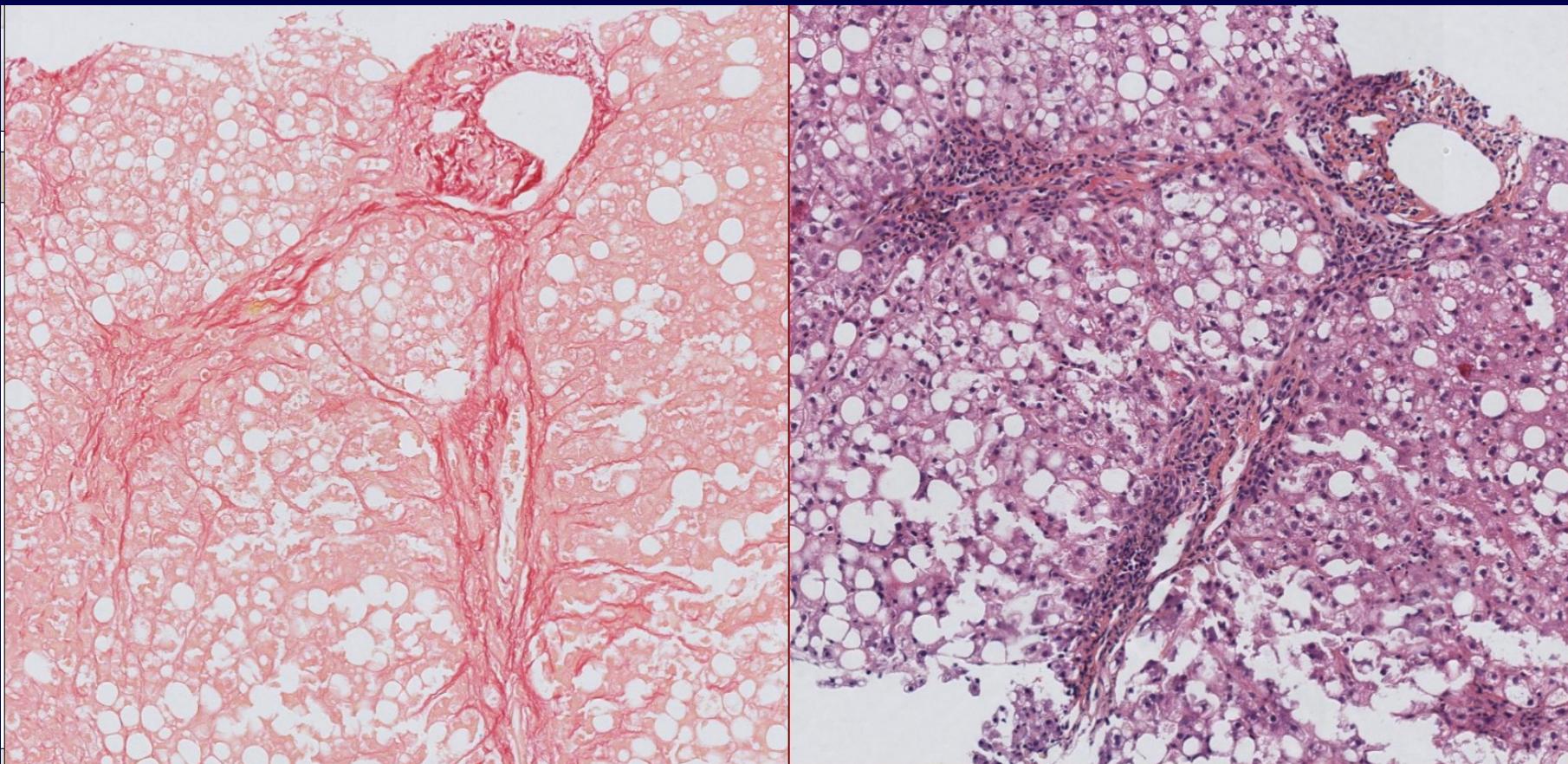
2017

Auriez vous proposer une PBF ?

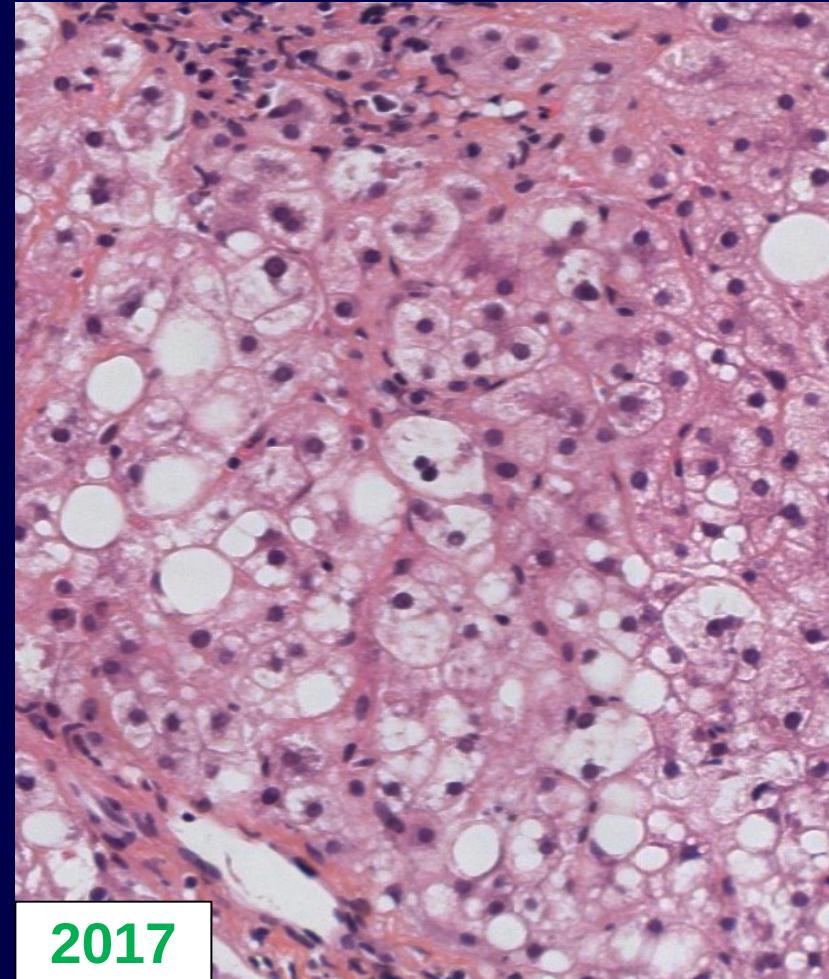
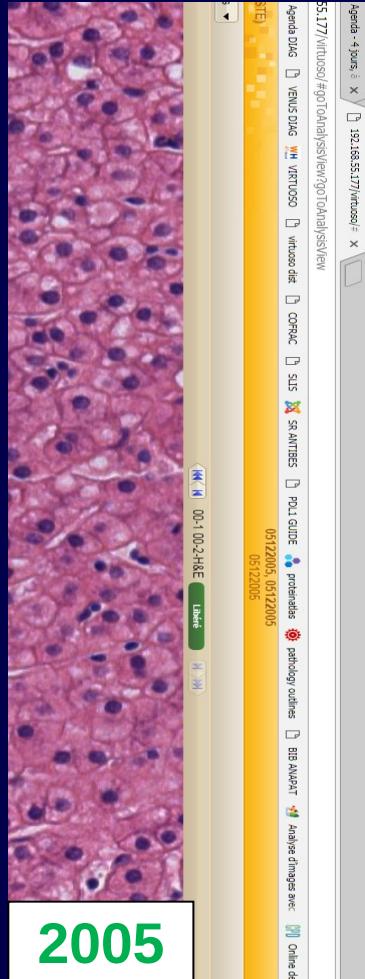
- oui
- non

- **NAS : 7/8**
 - STEATOSE : 3
 - BALLONISATION : 2
 - INFLAMMATION : 2
- **FIBROSE : 3**

PBH 2017



PBH 2005 et 2017 LOBULE



NAFLD Activity Score (NAS)

= NASH incertaine

= NASH certaine

-
-
-

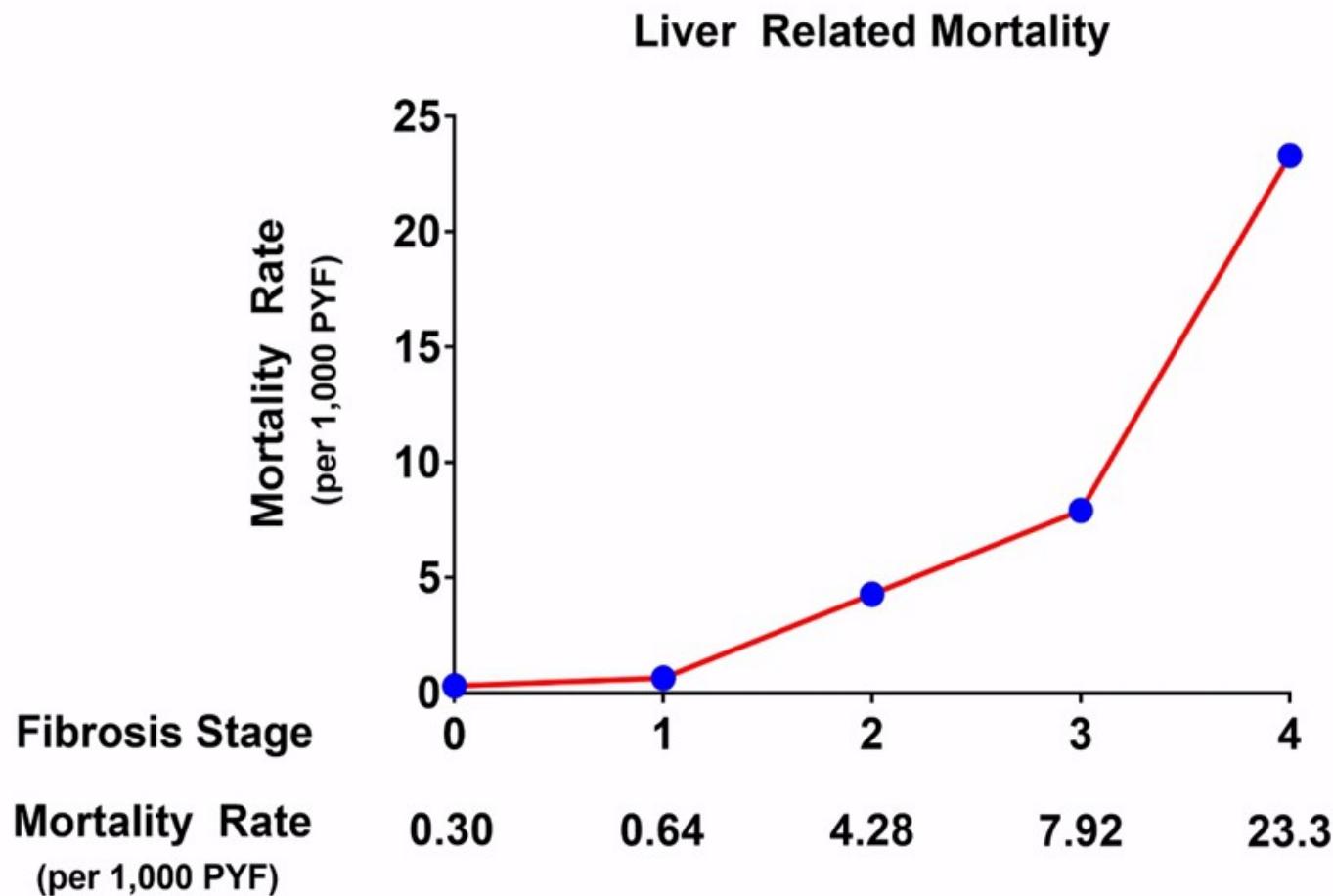
Evaluation de la Fibrose

0-4

F1: sinusoïdale péri centrolobulaire (a: discrète, b:
modérée)
Fibrose portale (c)

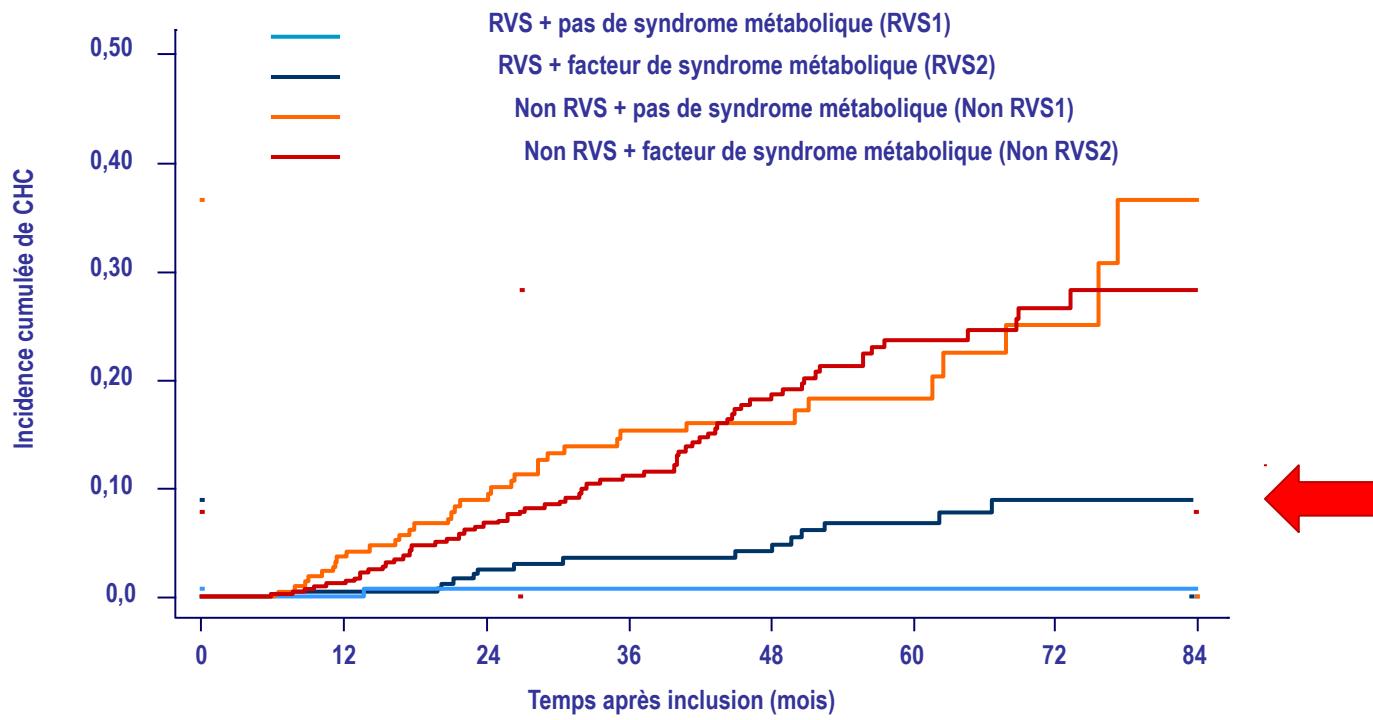
F3: septa fibreux

Quantitative risk of liver mortality by fibrosis stage



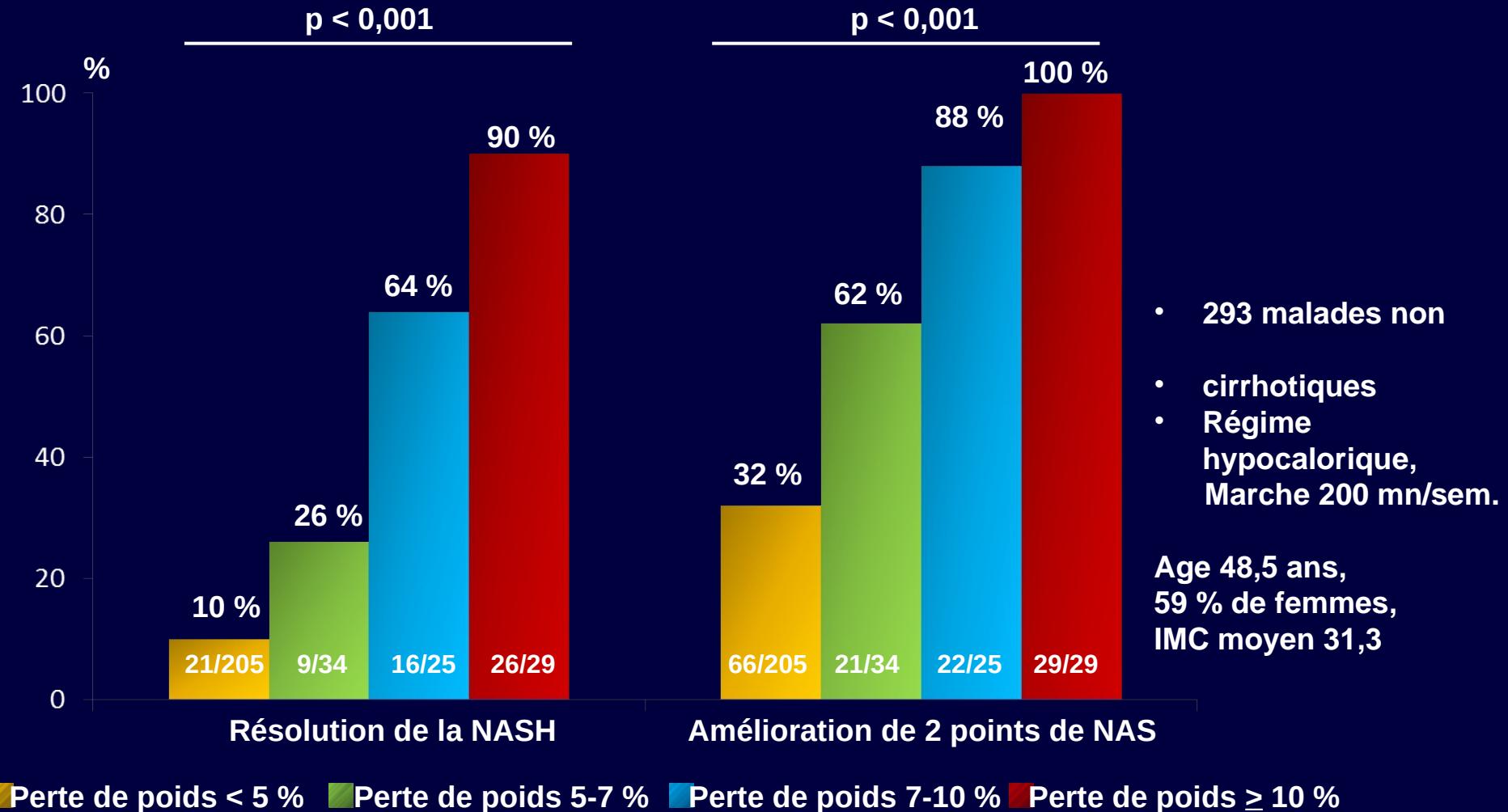
Cirrhose virale C après RVS Le risque de CHC n'est pas nul !

Incidence du CHC en fonction de la RVS et de la présence du syndrome métabolique



Importance de la perte de poids sur l'amélioration de la NASH

Taux de résolution de la NASH et d'amélioration du score NAS en fonction de l'importance de la perte de poids



Emerging Treatments in NASH: Phase III

| Drug | Mechanism of Action | Study Population | Trial | Primary Endpoint(s) |
|------------------|--|--------------------------------|------------|--|
| Elafibranor | PPAR α/δ agonist ^[1] | NASH with fibrosis | RESOLVE-IT | Resolution of NASH w/o fibrosis worsening |
| Obeticholic acid | FXR agonist (bile acid) ^[2] | NASH with fibrosis | REGENERATE | Improvement in fibrosis and NASH; |
| Cenicriviroc | Inhibitor of CCR2/CCR5) ^[3] | NASH with liver fibrosis | AURORA | Improvement in fibrosis w/o NASH worsening |
| Selonsertib | ASK1 inhibitor | NASH with F2-F3 liver fibrosis | STELLAR | Improvement in fibrosis and NASH; |

1. Ratziu V, et al. Gastroenterology. 2016;150:1147-1159.

2. ClinicalTrials.gov. 2015;385:956-965.

3. ClinicalTrials.gov NCT03028740

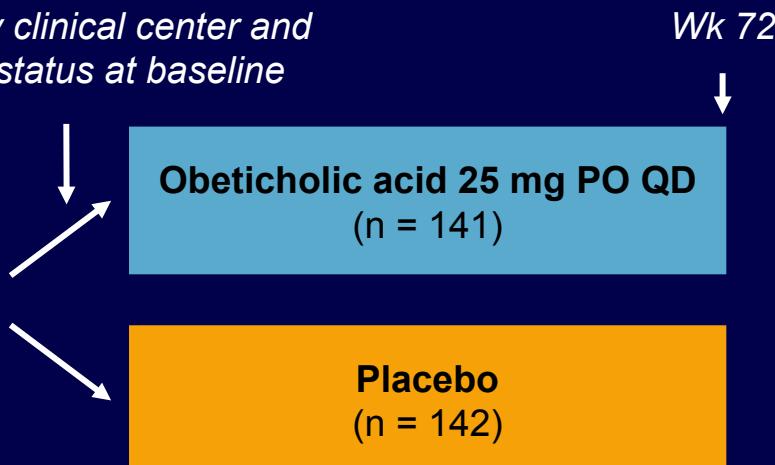
4. ClinicalTrials.gov. NCT03053063.

FLINT: Obeticholic Acid in Noncirrhotic Pts With NASH

- Double-blind, placebo-controlled, randomized, multicenter phase IIb trial

Stratified by clinical center and diabetes status at baseline

Pts with NASH or borderline NASH confirmed by entry biopsy, NAS ≥ 4 (individual scores each ≥ 1), no cirrhosis (N = 283)

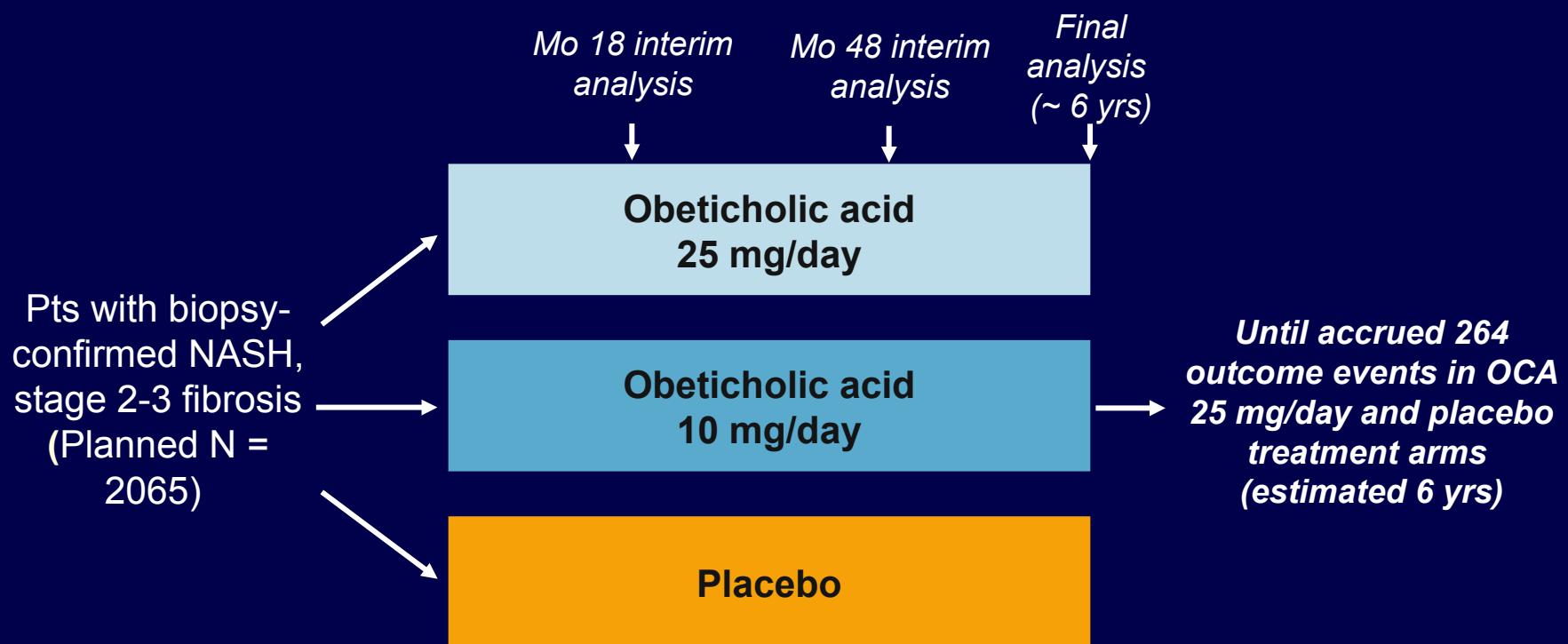


Wk 72
↓

| Primary Endpoint: Wk 72 Improvement in NAS ≥ 2 Points With No Worsening of Fibrosis | Wk 72 Improvement in Fibrosis |
|--|-------------------------------------|
| 45% (50/110) | 35% (36/102) |
| 21% (23/109) | 19% (19/98) |
| <i>P</i> = .0002 | <i>P</i> = .004 |

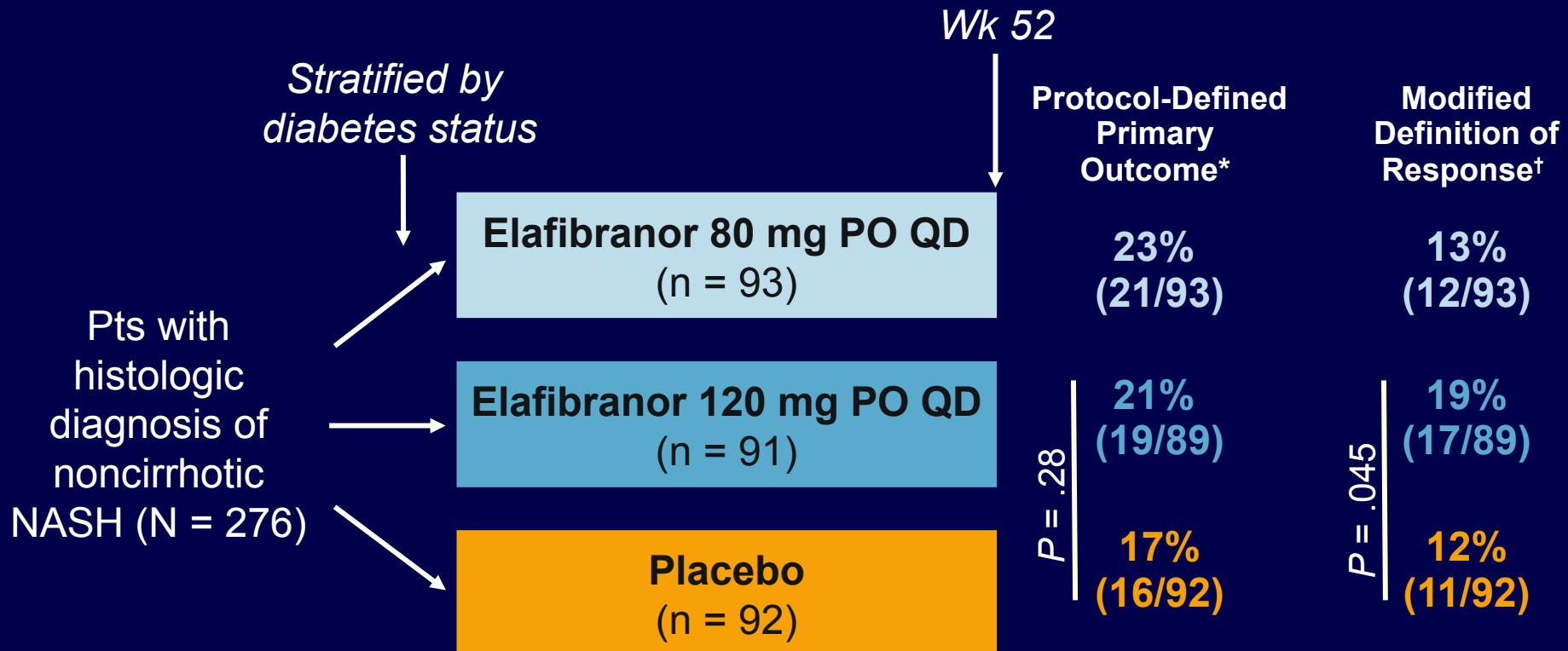
REGENERATE: Long-term Evaluation of Obeticholic Acid for NASH and Fibrosis

- Double-blind, placebo-controlled, randomized, multicenter phase III trial



GOLDEN-505: Elafibranor for 52 Wks

- Double-blind, placebo-controlled, randomized, international phase IIb trial



*Disappearance of steatosis, ballooning, or lobular inflammation.

†Disappearance of ballooning and disappearance or mild persistence of lobular inflammation.

Emerging Treatments in NASH: Phase II

| Drug | Mechanism of Action | Study Population | Trial | Primary Endpoint(s) |
|--------------|---|--|---------------------------|--|
| Cenicriviroc | Inhibitor of CCR2/CCR5 | NASH with liver fibrosis | CENTAUR*[1,2] | Improvement in NAS w/o fibrosis worsening |
| Simtuzumab | Monoclonal antibody to LOXL2 ^[3] | Liver fibrosis secondary to NASH | NCT01672866*[4] | Morphometric quantitative collagen change; EFS |
| Aramchol | Fatty acid–bile acid conjugate ^[5] | NASH | Aramchol_005*[6] | Change in liver triglycerides by NMRS |
| Liraglutide | GLP-1 analogue | Overweight NASH | LEAN ^[7,8] | Resolution of NASH w/o fibrosis worsening |
| GR-MD-02 | Galectin-3 inhibitor ^[9] | Liver fibrosis and portal hypertension in NASH cirrhosis | NASH-CX ^[10] | Improvement in HVPG |
| Emricasan | Caspase inhibitor | NASH with liver fibrosis | ENCORE-NF ^[11] | Improvement in fibrosis w/o NASH worsening |

1. ClinicalTrials.gov. NCT02217475. 2. Friedman S, et al. Contemp Clin Trials. 2016;47:356-365.

3. Meissner EG, et al. Liver Int. 2016;[Epub ahead of print]. 4. ClinicalTrials.gov. NCT01672866.

5. Safadi R, et al. Clin Gastroenterol Hepatol. 2014;12:2085-2091. 6. ClinicalTrials.gov. NCT02279524.

7. Armstrong MJ, et al. Lancet. 2016;387:679-690. 8. ClinicalTrials.gov. NCT01237119.

9. Harrison SA, et al. Aliment Pharmacol Ther. 2016;[Epub ahead of print].

10. ClinicalTrials.gov. NCT02462967. 11. ClinicalTrials.gov. NCT02686762.

Emerging Treatments in NASH: Phase II

| Drug(s) | Mechanism(s) of Action | Study Population | Trial | Primary Endpoint(s) |
|---------------------|-------------------------------|--------------------------------|---------------------------------|--|
| Selonsertib | ASK1 inhibitor | NASH with F2-F3 liver fibrosis | GS-US-384-1497 ^[1,2] | Safety and tolerability |
| JKB-121 | TLR-4 antagonist | NASH | Pro00062677 ^[3] | Safety and tolerability; change in ALT, hepatic fat; TTP |
| NGM-282 | FGF-19 agonist ^[4] | NASH | 15-0105 ^[5] | Change in hepatic fat |
| BMS-986036 | FGF-21 agonist | NASH | MB130-045 ^[6] | Safety and tolerability; change in hepatic fat |
| GS-0976 | ACC inhibitor | NASH | GS-US-426-3989 ^[7] | Safety and tolerability |
| GS-9674, GS-0976 | FXR agonist (bile acid) | NAFLD | GS-US-384-3914 ^[8] | Safety and tolerability |
| | ACC inhibitor | | | |
| Volixibat | ASBT inhibitor | NASH | NCT02787304 ^[9] | Improvement in NAS w/o fibrosis worsening |

1. Loomba R, et al. AASLD 2016. Abstract LB-3. 2. ClinicalTrials.gov. NCT02466516.

3. ClinicalTrials.gov. NCT02442687 4. Hegade VS, et al. Therap Adv Gastroenterol. 2016;9:376-391.

5. ClinicalTrials.gov. NCT02443116.6. ClinicalTrials.gov. NCT02413372.

7. ClinicalTrials.gov. NCT02856555.8. ClinicalTrials.gov. NCT02781584.

9. ClinicalTrials.gov. NCT02787304.

Indications de la chirurgie bariatrique

- IMC $\geq 40 \text{ kg/m}^2$
- IMC $\geq 35 \text{ kg/m}^2$ et une comorbidité:
 - Cardio-vasculaire
 - Respiratoire (SAHOS)
 - Diabète de type 2
 - NASH
 - Maladies ostéo-articulaires invalidantes

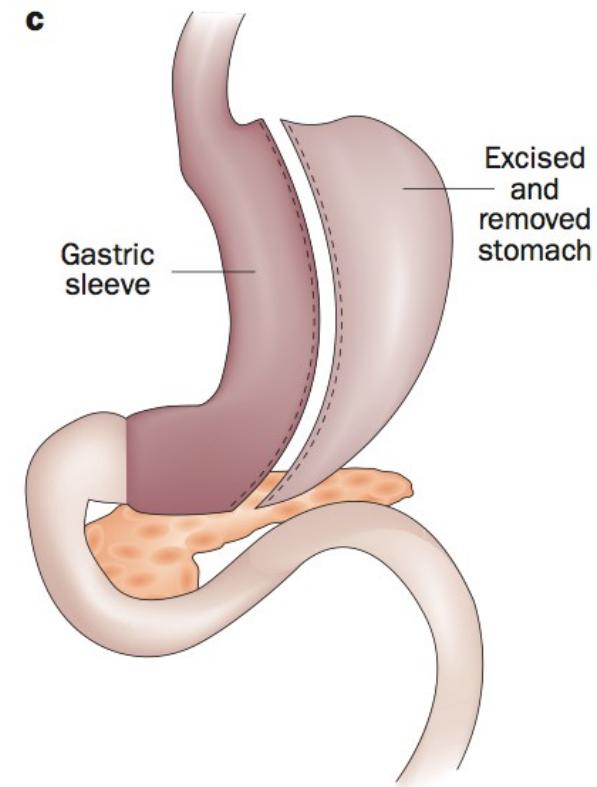
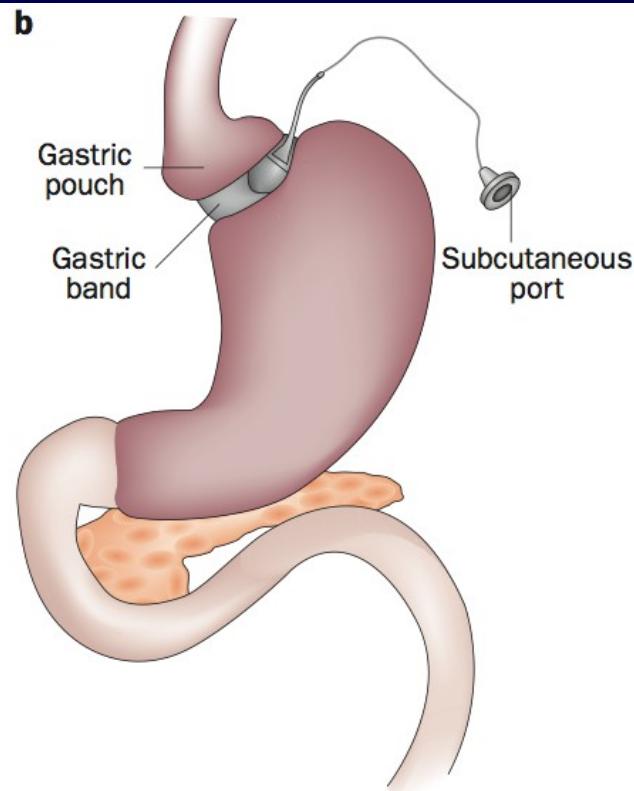
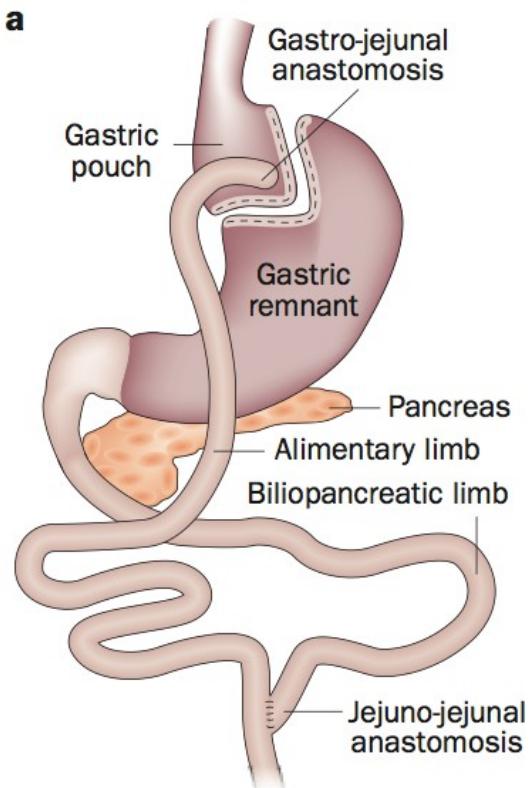
Indications de la chirurgie bariatrique

- en deuxième intention après échec d'un traitement médical, nutritionnel, diététique et psychologique ;
- en l'absence de perte de poids suffisante ou en l'absence de maintien de la perte de poids ;
- patients informés, ayant bénéficié d'une évaluation et d'une prise en charge pluridisciplinaire ;
- risque opératoire acceptable.

Mme Abb...

- Juillet 2017 consultation de chirurgie bariatrique
- Sept 2017 évaluation cœur RAS, SAHOS, pas de VO
- Octobre 2017 RCP et accord CPAM
- Janvier 2018 Gastrectomie de Type Sleeve

Chirurgie bariatrique



Gastric-by-pass

Anneau ajustable

Sleeve gastrectomy

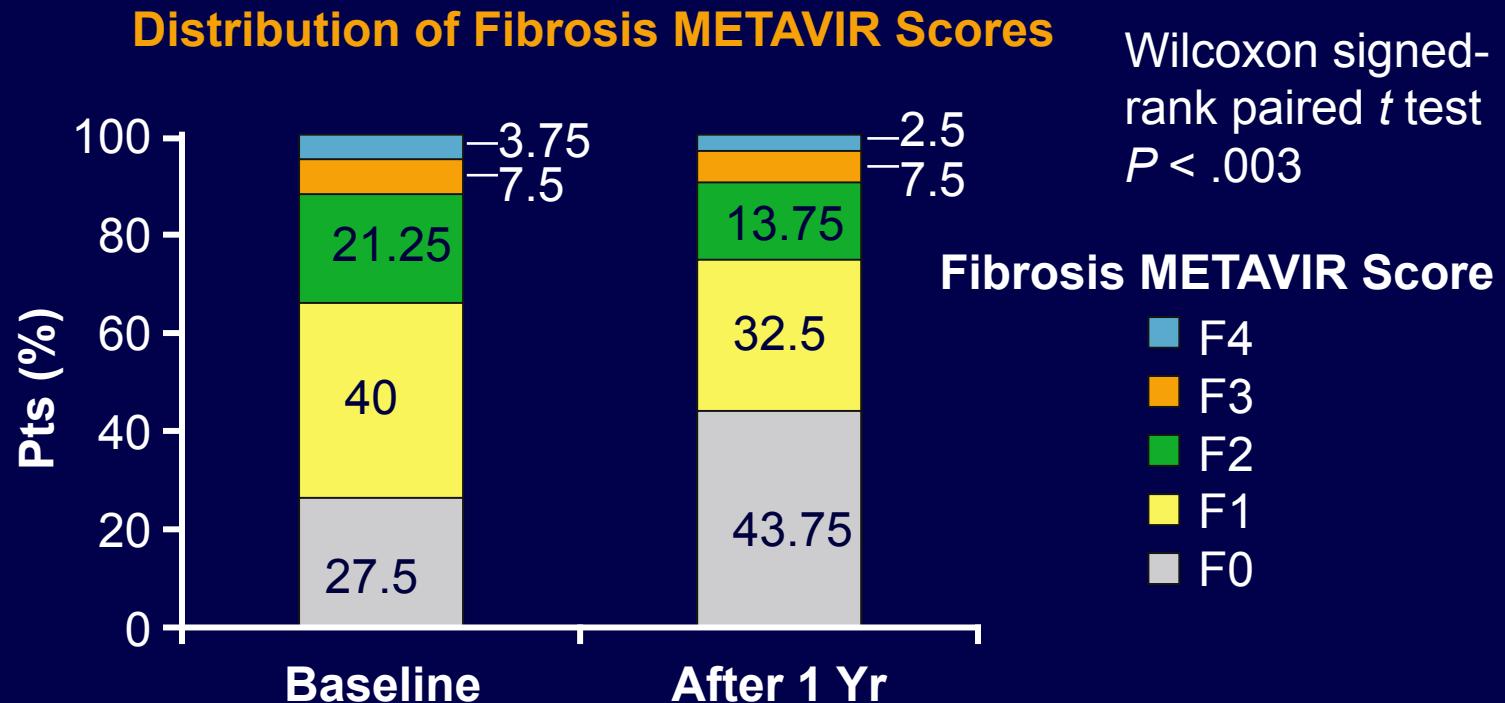
Bariatric Surgery Improves Clinical Parameters

- Prospective study following bariatric surgery in pts who are severely obese (N = 381) with ≥ 1 comorbidity, no excessive drinking < 2 yrs, no chronic liver diseases
 - Liver biopsies assessed by 2 blinded reviewers for fibrosis (F0-4), NAFLD scoring to determine NASH (≥ 3 , probable or definite; ≥ 5 , definite)

| Parameter | Before Surgery | After 5 Yrs | P Value |
|---------------------------------|----------------|-------------|---------|
| Diabetes mellitus, n (%) | 94 (24.8) | 24 (10.8) | .00001 |
| Arterial hypertension, n (%) | 185 (48.8) | 85 (37.0) | .0005 |
| Serum triglycerides, mean (g/L) | 1.67 | 1.06 | .00001 |
| Fasting glucose, mean (g/L) | 1.18 | 0.94 | .00001 |
| Insulin resistance index, mean | 3.2 | 2.83 | .00001 |
| ALT, mean (IU/L) | 30.1 | 22.8 | .00003 |
| GGT, mean (IU/L) | 39.9 | 29.2 | .00001 |

Bariatric Surgery Improves Fibrosis in Pts With NASH

- Prospective study of bariatric surgery in pts who are morbidly obese with biopsy-validated NASH, ≥ 1 comorbidity factor for > 5 yrs, no chronic liver disease (N = 109)



Conclusions

- Rechercher devant toute pathologie hépatique une comorbidité de type NASH
- Appliquer les règles hygiéno-diététiques (régime ,exercice) systématiquement, de façon personnalisée et continue
- En cas d'échec, persévérer et envisager une association à un traitement médicamenteux en cours d'évaluation ou une chirurgie bariatrique

NAFLD: Recommandations françaises (AEFF et

