International Think Tank

Paris NASH Meeting

July 5 & 6, 2018
Institut Pasteur

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With the partnership of

AFEF
SOCIÉTÉ FRANÇAISE D'HÉPATOLOGIE

Société Francophone du diabète

THE FORUM
For Collaborative Research℠

Paris NASH Meeting

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July 5 – 6, 2018, Institut Pasteur

Master protocols in NASH – challenges and opportunities

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Agenda

1. Regulatory pathways/endpoints in NASH trials
2. Determinants of the response rate in NASH trials:
    1. Endpoints/Definition of outcomes
    2. Histological criteria for patients selection
    3. Placebo effect
    4. Multiple pathogenic pathways

3. **Masters protocols**
    1. **Design**
    2. **Pro and Cons**

REGISTRATION PATHWAYS/ENDOPINTS IN NASH CLINICAL TRIALS

TWO STEP APPROACH

1. **Accelerated approval** (FDA) and **conditional approval** (EU) which allows initial marketing approval based on **surrogate endpoints** considered « ***reasonably likely*** » to predict outcomes

- ✓ No evidences that NAS is correlated with outcomes
- ✓ Necroinflammation/activity score ➔ firbosis progression

2. **Final approval** after confirming the clinical benefit in preventing progression to cirrhosis and liver related outcomes (decompensation, HCC, LT, etc.) (confirmatory trial)

- RESOLUTION OF NASH WITHOUT WORSENING OF FIBROSIS
- IMPROVEMENT OF FIBROSIS of ≥ 1 STAGES WITHOUT WORSENING OF NASH

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PRIMARY ENDPOINTS IN NASH CLINICAL TRIALS

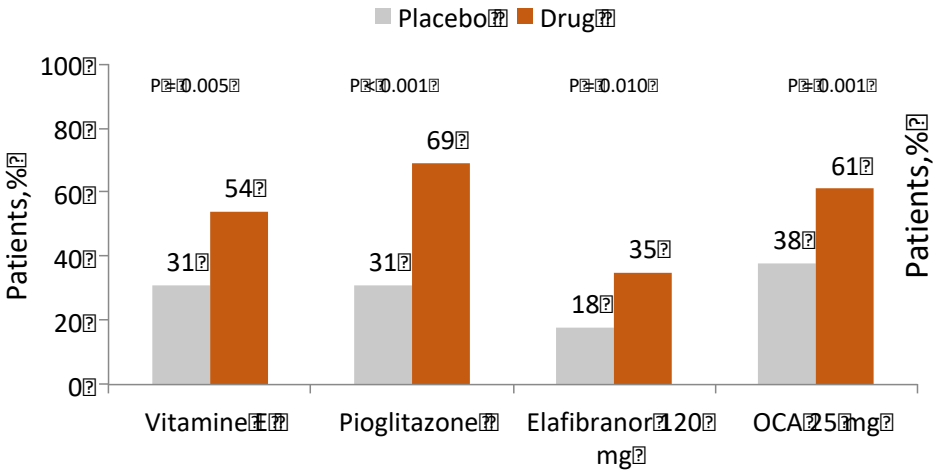
PIVENS	≥ 1 point improvement in ballooning; no increase in fibrosis; **AND** either a decrease in NAS to ≤ 3 OR ≥ 2 points with at least 1 point decrease in either lobular inflammation or steatosis
FLINT	Primary: Decrease in NAS of ≥ 2 point without worsening of fibrosis Secondary: **Resolution of NASH***
GOLDEN	**Resolution of NASH** without worsening of fibrosis**
CENTAUR	Primary: 2-point improvement in NAS with 1-point reduction in either lobular inflammation or hepatocellular ballooning) and no worsening of fibrosis stage Secondary**: Resolution of NASH with no worsening of fibrosis** or improvement of ≥ 1 stage fibrosis without worsening of NASH

** The absence (score of 0) of at least 1 of the 3 components of NASH, that is, steatosis, ballooning, and inflammation

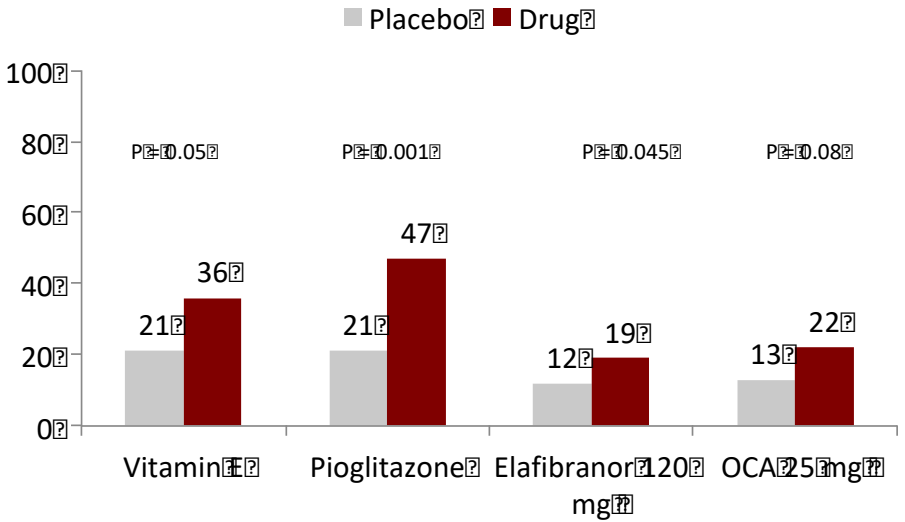
RESOLUTION OF NASH

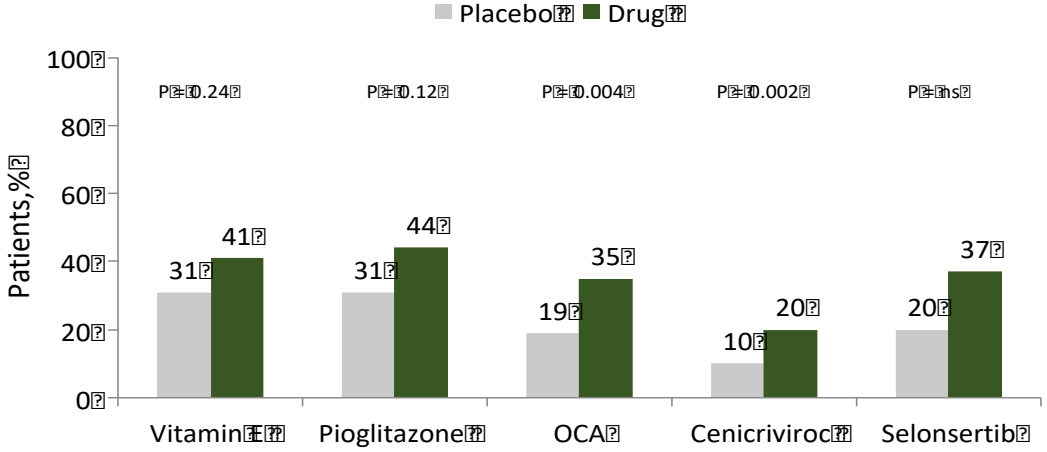
Disappearance of ballooning (score 0), together with either disappearance of lobular inflammation or the persistence of mild lobular inflammation only (score 0 or 1), ➔overall pathologic diagnosis of either steatosis alone or steatosis with mild inflammation

IMPROVEMENT IN STEATOSIS



RESOLUTION OF NASH





IMPROVEMENT IN FIBROSIS

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LOW RESPONSE RATE - 20 – 40%

PLACEBO EFFECT

PIVENS	PLACEBO EFFECT = 19% for primary outcome All subjects were given a standardized set of pragmatic recommendations about lifestyle changes and diet.
FLINT	PLACEBO EFFECT = 21% for primary outcome All patients received standardized recommendations on healthy eating habits, weight reduction, exercise, and the management of hypertension, hypercholesterolemia, and diabetes when indicated.
GOLDEN	PLACEBO EFFECT = 12% for modified primary outcome Very strong placebo effect in patients with mild NASH (NAS = 3): 50% for protocol defined primary outcome; 25% for modified primary outcome

LOW RESPONSE RATE - 20 – 40%

PLACEBO EFFECT

MA of 39 RCT, 1463 patients included

≥ 2 points improvement in NAS in 25 % of patients

≥ 1 point improvement in:

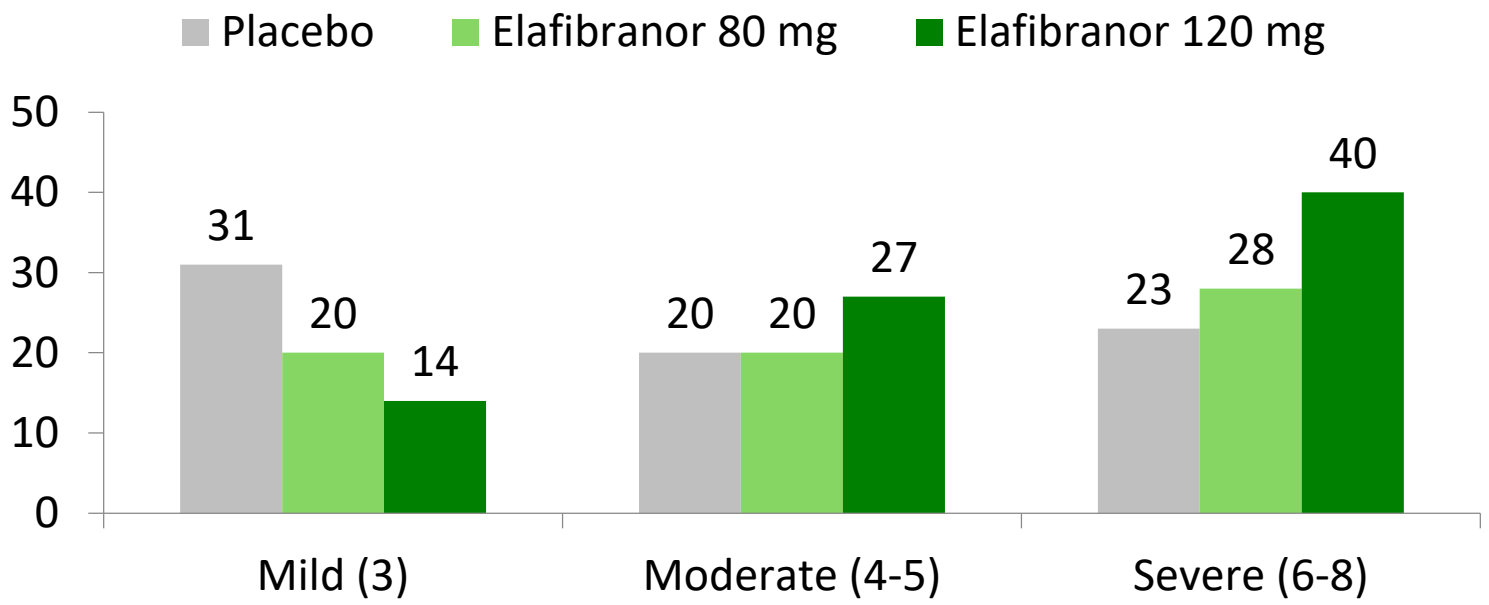
- Steatosis: 33%
- Ballooning: 30%
- Lobular inflammation: 32%
- Fibrosis: 21%

Factors associated with placebo response:

- **Changes in BMI** (reduction of 0.28 ±10 Kg/m^2)
  - Hawthorne effect
  - No of FU visits
- **Baseline NAS** (subjects with higher NAS are more likely to respond to placebo or life style interventions)

Thanda Han MA, Clin Gastroenterol Hepatol 20018, In Press

NAS 2-point reduction according to Baseline NAS severity in the ITT Population (n 274)



Ratziu, Gastroenterology 2016

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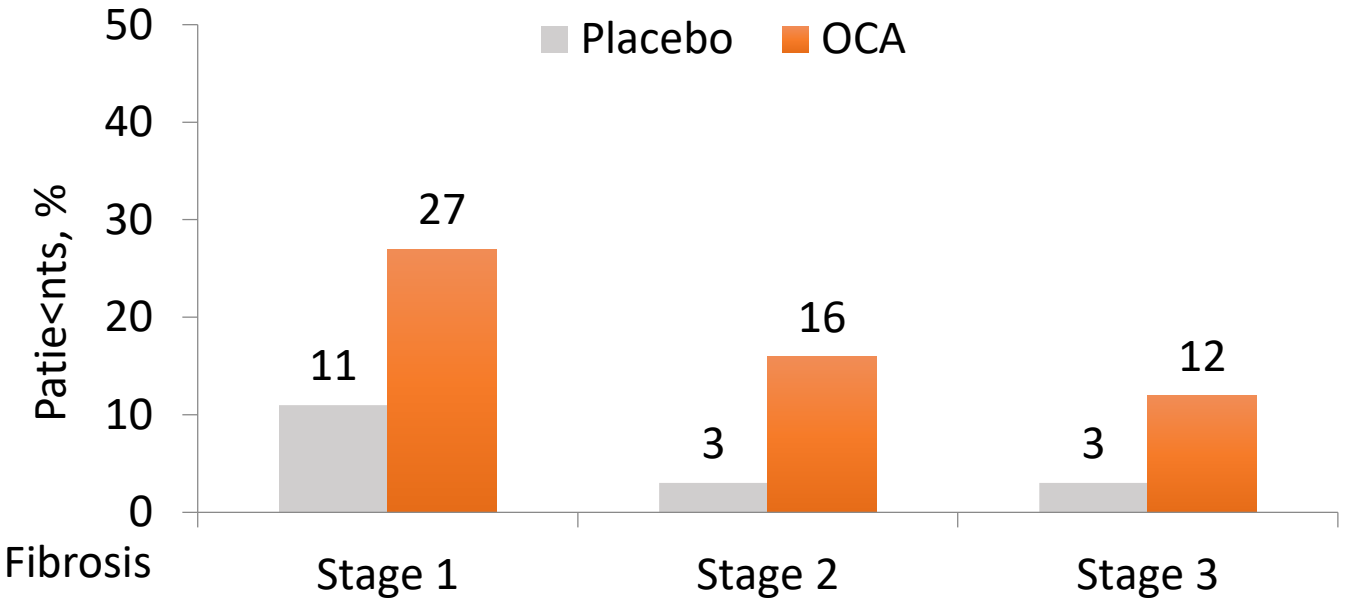
FLINT: Reversion of NASH in high risk subgroup*

*Patients with NAS ≥ 4 and fibrosis stage 2 or 3
or stage 1 with diabetes, BMI≥ 30 kg/m² or ALT ≥ 60 U/l



Neuschwander Tetri, Lancet 2014

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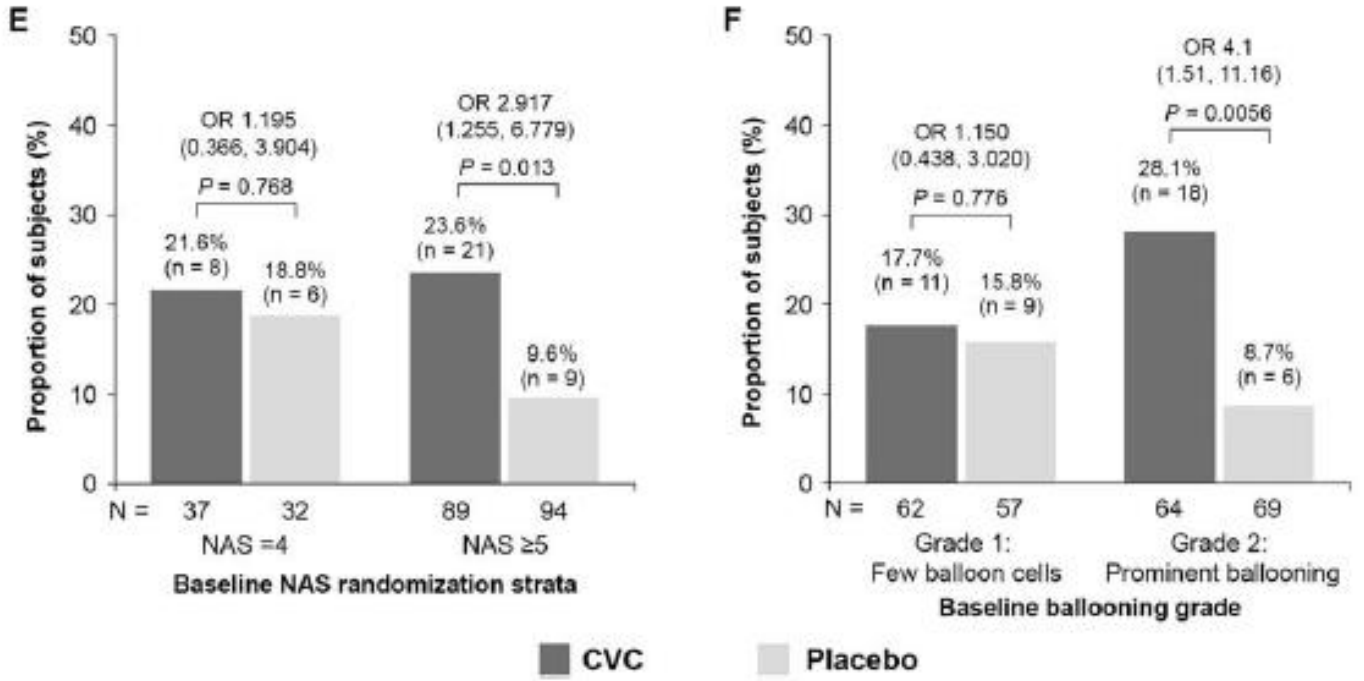
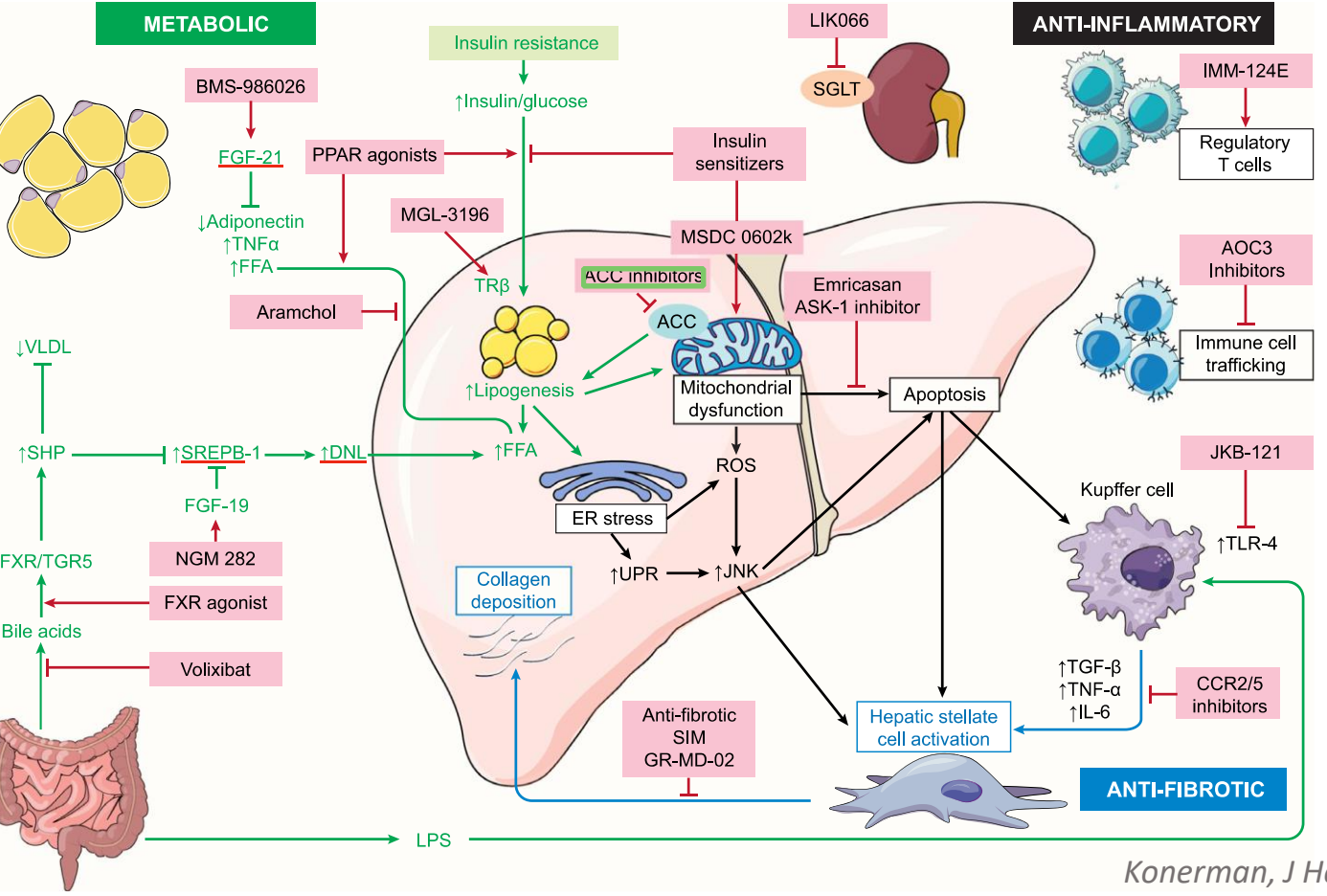
IMPROVEMENT IN FIBROSIS BY ≥ 1 POINT AND NO WORSENING OF NASH



Friedman, Hepatology 2018

MULTIPLE PATHOGENIC PATHWAYS AND THERAPEUTIC TARGETS



Konerman, J Hepatol 2018

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LOW RESPONSE RATE (20 – 40%)

- Heterogeneity in primary/secondary endpoints
- Patients selection
- Placebo effect
- Multiple pathogenic pathways

Nodal target of strategic importance

Individual approaches to Individual patient

MASTER PROTOCOLS

Combination therapy

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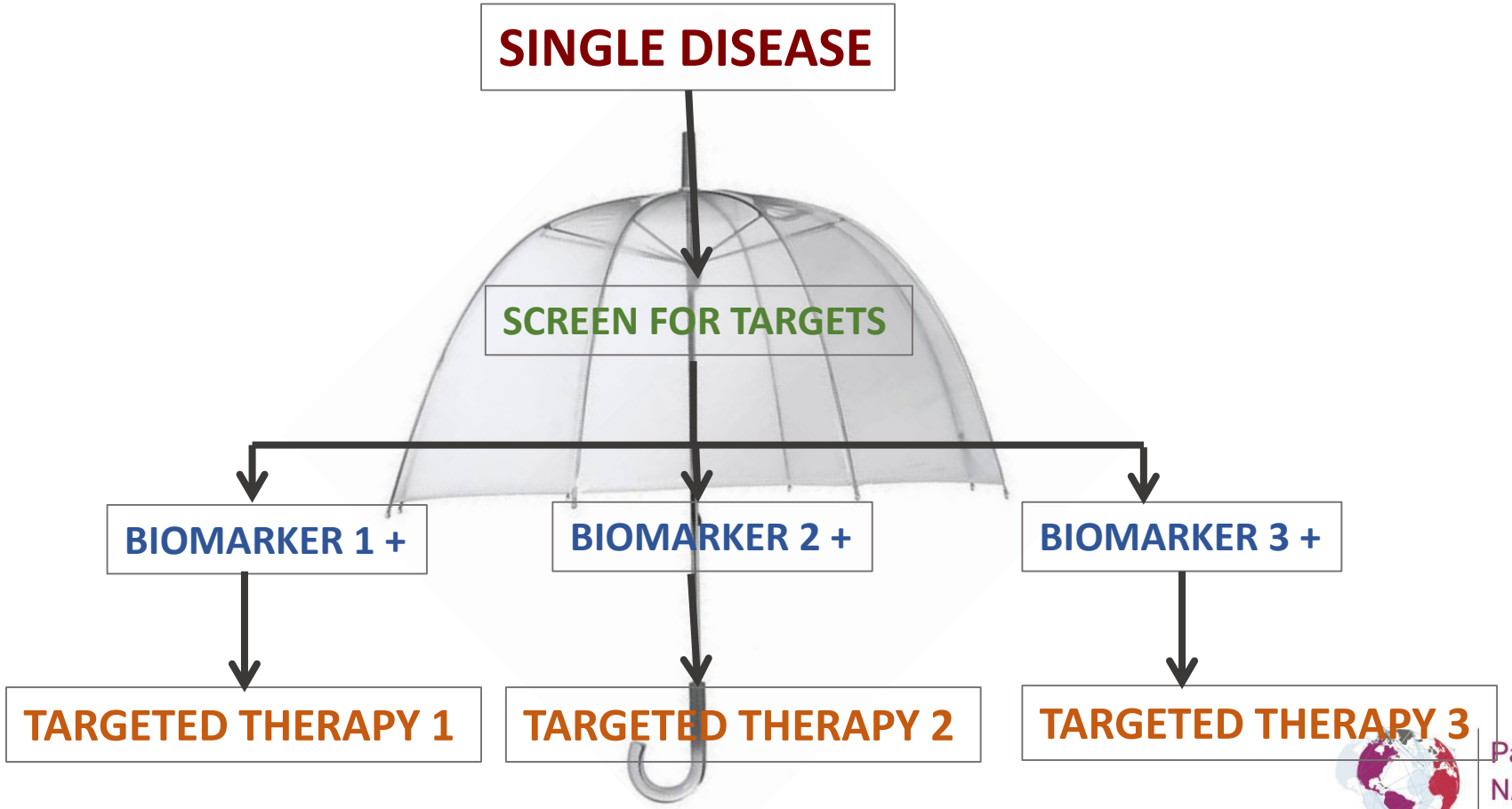
MASTERS PROTOCOLS

1. UMBRELLA TRIALS
2. BASKET TRIALS
3. PLATFORM TRIALS

UMBRELLA TRIAL DESIGN



Woodcock, NEJM 2017

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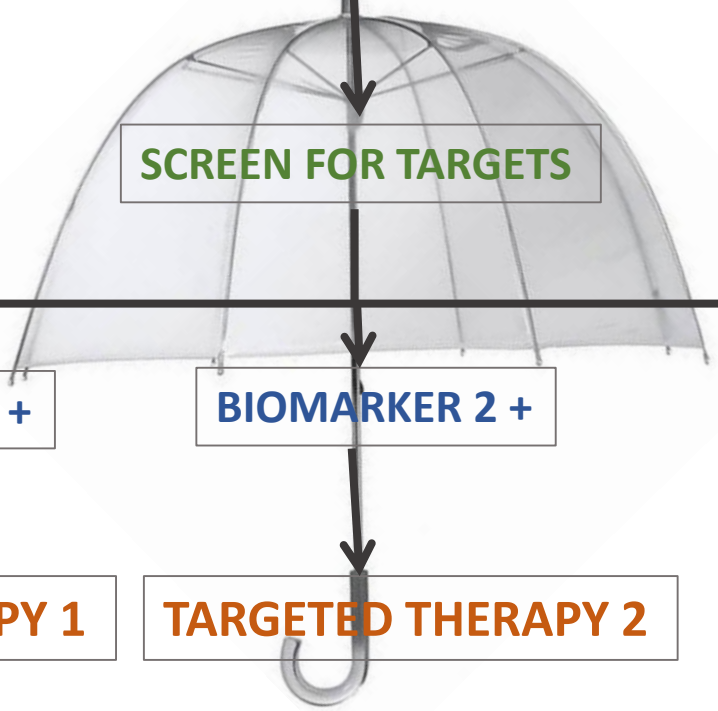
UMBRELLA TRIAL DESIGN → INDIVIDUAL APPROACH TO INDIVIDUAL PATIENT

NIMBLE
Non-Invasive BioMarkers of MetaBolic Liver DiseasE

FNIH
Foundation for the National Institutes of Health

LITMUS

imi innovative medicines initiative



SINGLE DISEASE

SCREEN FOR TARGETS

BIOMARKER 1 +

BIOMARKER 2 +

BIOMARKER 3 +

TARGETED THERAPY 1

TARGETED THERAPY 2

TARGETED THERAPY 3

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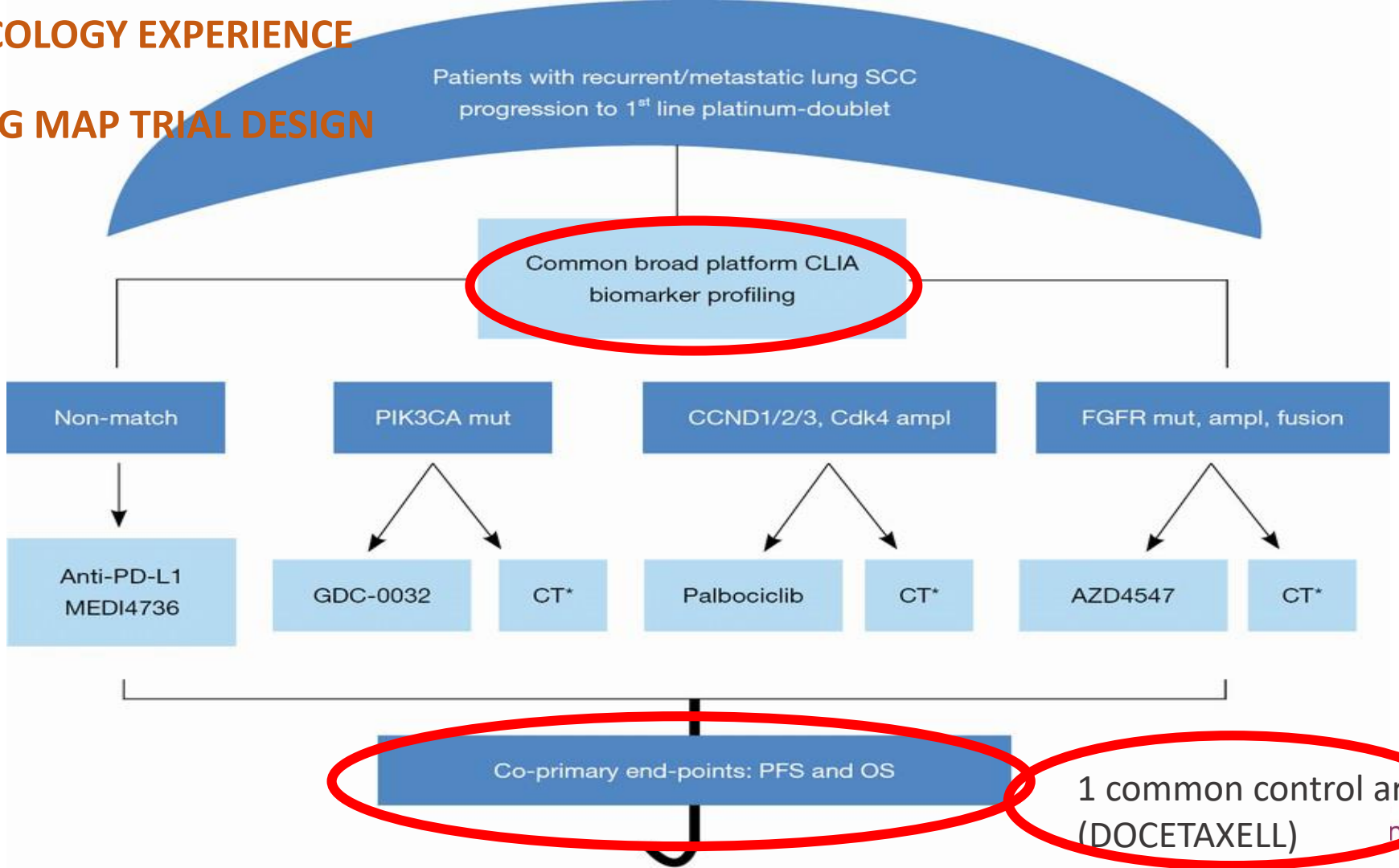
MASTER PROTOCOLS – UMBRELLA VS. BASKET TRIALS

UMBRELLA TRIAL

- Test the impact of **different drugs** on **different biomarkers**/mutations in a **single disease**/type of cancer
  - BATTLE (NSCLC – EGFR mutation, KRAS/BRAF mutation, VEGF expression, etc)
  - ISPY2 (Breast cancer)
  - Lung MAP Squamous Lung Master (Squamous cell NSCLC)

ONCOLOGY EXPERIENCE

LUNG MAP TRIAL DESIGN



Disease/hist ological feature 1

Disease/hist ological feature 2

Disease/hist ological feature 3

SCREEN FOR TARGET

Target positive patients

Trial of one targeted therapy

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MASTER PROTOCOLS – UMBRELLA VS. BASKET TRIALS

UMBRELLA TRIAL

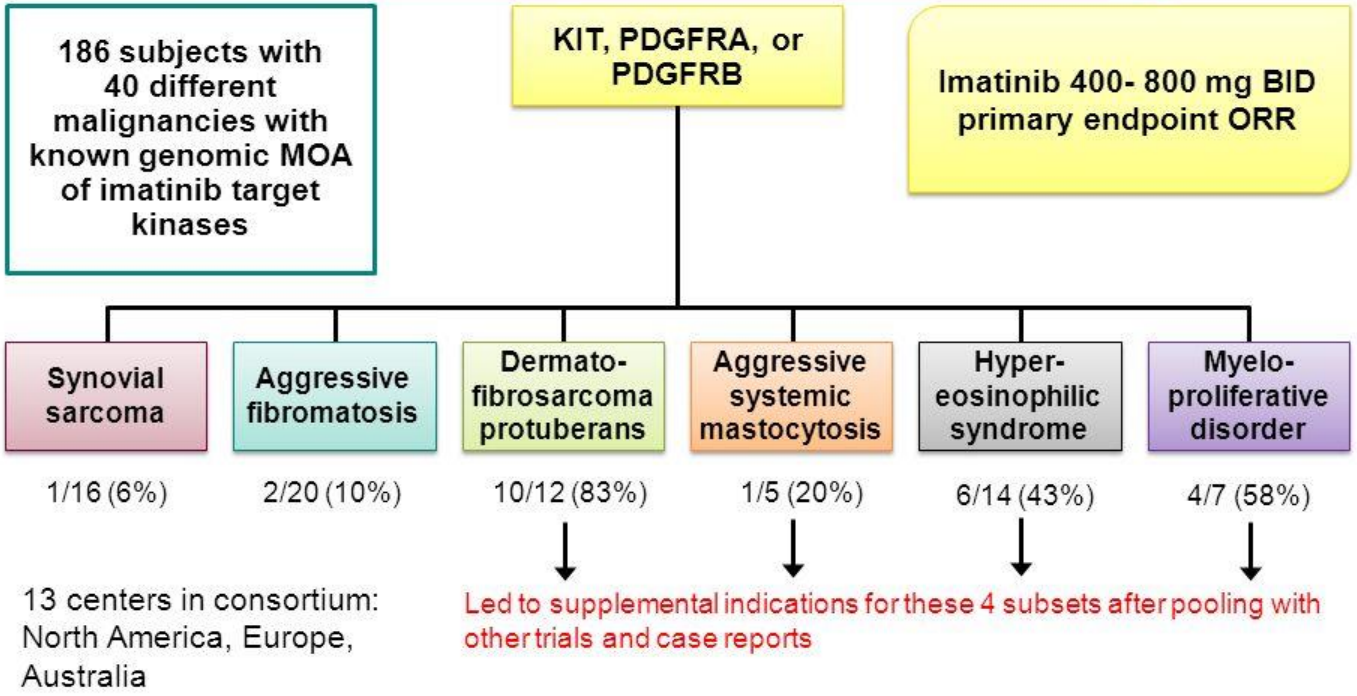
- Test the impact of **different drugs** on **different biomarkers**/mutations in a **single disease**/type of cancer
  - BATTLE (NSCLC – EGFR mutation, KRAS/BRAF mutation, VEGF expression, etc)
  - ISPY2 (Breast cancer)
  - Lung MAP Squamous Lung Master (Squamous cell NSCLC)

BASKET TRIAL

- Test the effect of **one drug** on a **single mutation** in a **variety of cancer types**
  - Imatinib Basket B 2225 : 40 cancers – solid tumours and hematologic cancers
  - BRAF + : Multiple nonmelanoma cancers with *BRAF* V600 mutations;
  - NCI MATCH: Advanced solid tumor, lymphoma, or myeloma;

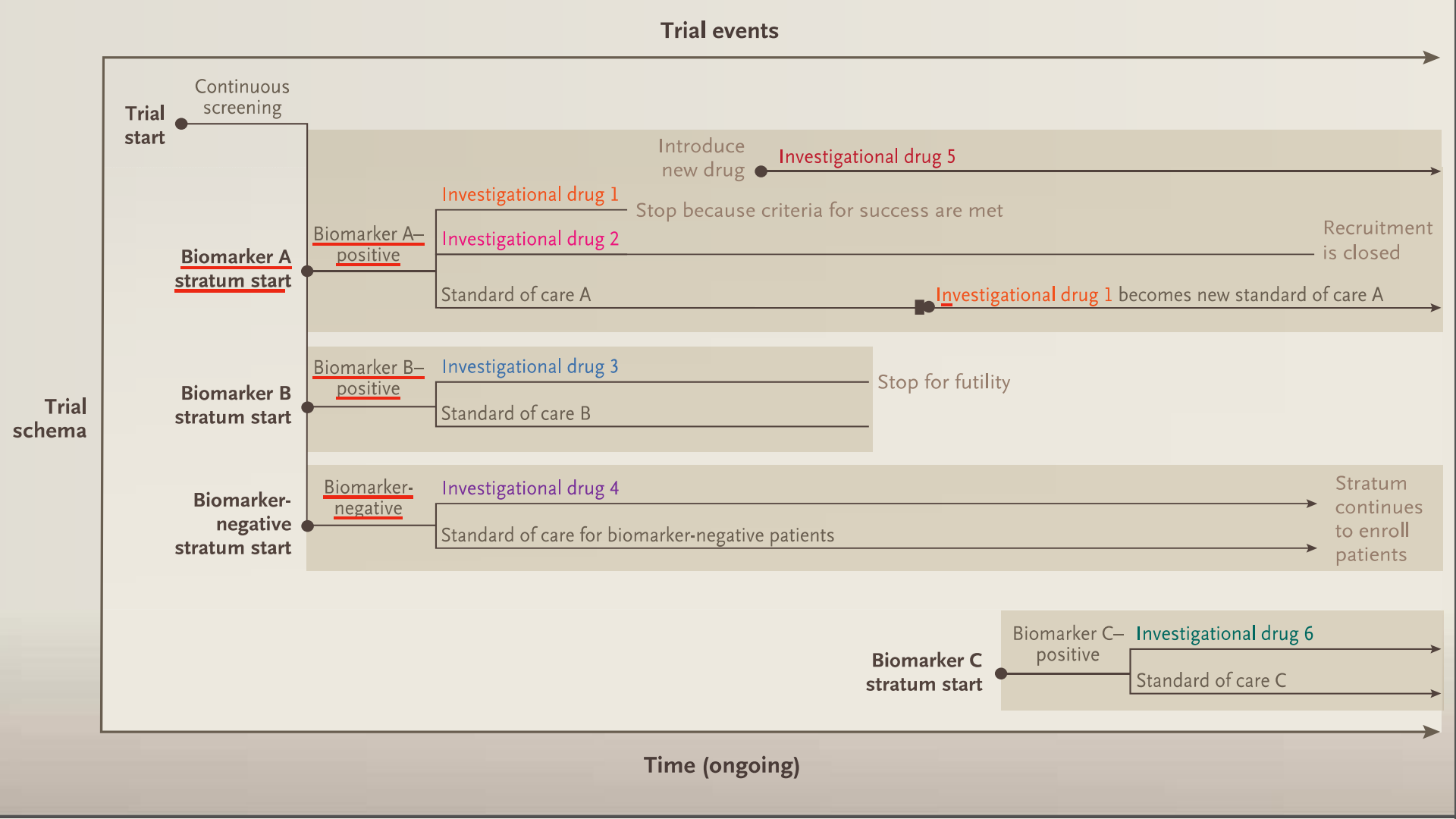
The First Basket: Imatinib B2225

Phase 2 multi center open label non comparative trial



Blumenthal. Innovative trial designs to accelerate the availability of highly effective anti-cancer therapies: an FDA perspective, AACR 2014

MERCK


Trial events
Trial schema
Trial start
Continuous screening
Introduce new drug
Investigational drug 5
Biomarker A stratum start
Biomarker A–positive
Investigational drug 1
Stop because criteria for success are met
Investigational drug 2
Recruitment is closed
Standard of care A
Investigational drug 1 becomes new standard of care A
Biomarker B stratum start
Biomarker B–positive
Investigational drug 3
Stop for futility
Standard of care B
Biomarker-negative stratum start
Biomarker-negative
Investigational drug 4
Stratum continues to enroll patients
Standard of care for biomarker-negative patients
Biomarker C stratum start
Biomarker C–positive
Investigational drug 6
Standard of care C
Time (ongoing)

MASTERS PROTOCOLS

PROS AND CONS

SCREENING

INDIVIDUAL TRIALS	MASTER PROTOCOLS

• Patients are screened for one protocol and if they don't meet the inclusion criteria they either get screened for another trial or miss the opportunity to participate altogether.
• For each separate trial, the process of data collection and testing is repeated, with overlapping information gathered for multiple trials but not shared among them.
	• Use of a **common screening platform** to identify all trials for which a patient is eligible:
	  • streamlined recruitment process
	  • fewer screening failures
	  • shorter recruitment times
	  • Patients - more opportunities to participate in investigational research and earlier access to potentially beneficial therapies

MASTERS PROTOCOLS – Infrastructure Innovation

- ✓ Centralized shared governance (steering committee, institutional review board)

→ Uniform decisions for all trials conducted under a protocol
Quality control

MASTERS PROTOCOLS – Trials Design Innovation

- ✓ **Similar study designs** (schedule of visits, clinical examination components, measurement procedures, outcome definitions, and ascertainment procedures) with differences dictated only by peculiarities of the individual therapies under investigation
- ✓ **Adaptive randomization** and other **adaptive design** features
  - ✓ **Adaptation to statistical aspects of design**:
    - ✓ Group sequential design
    - ✓ Adaptation to sample size/statistical information, analysis schedule, decision criteria, randomization ratio

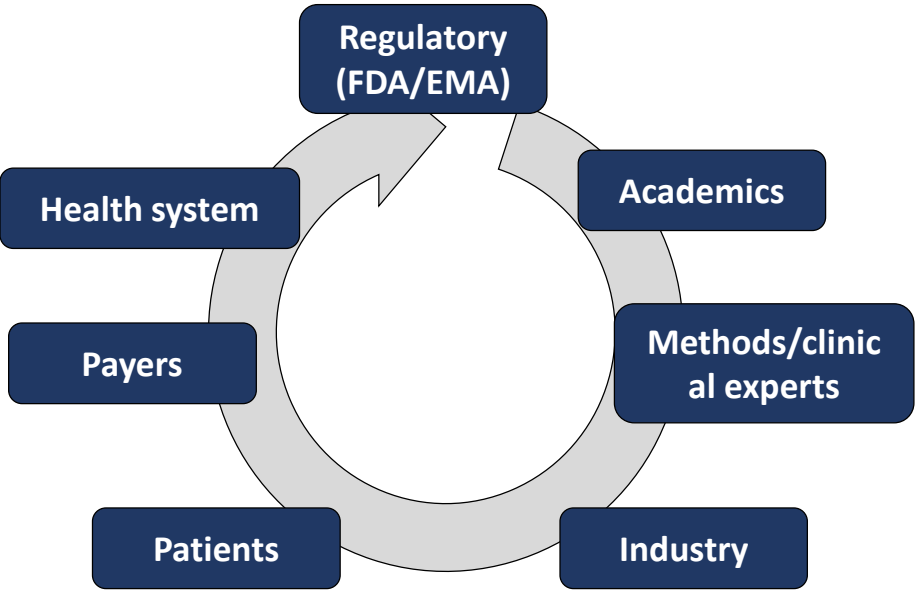
      - Interim analysis ➔ react to negative/positive results, make decisions, corrective actions
      - Combined analysis (data collected at different stages)
      - Shorten the trial duration

MASTERS PROTOCOLS – Trials Design Innovation

- ✓ **Similar study designs** (schedule of visits, clinical examination components, measurement procedures, outcome definitions, and ascertainment procedures) with differences dictated only by peculiarities of the individual therapies under investigation
- ✓ **Adaptive randomization** and other **adaptive design** features
  - ✓ **Adaptation to statistical aspects of design**:
    - ✓ Group sequential design
    - ✓ Adaptation to sample size/statistical information, analysis schedule, decision criteria, randomization ratio
  - ✓ **Adaptations to *scientific* aspects of design –** adaptation to patients population, treatment arm selection, endpoint selection
- ✓ Longitudinal modeling to determine probabilities of success/failure
- ✓ **Shared control group** ➔ reduce the overall sample size
- ✓ **Natural history cohort**

Low response rate in NASH Clinical trial

MASTER PROTOCOLS ➔ THE KEY TO PERSONALIZED TREATMENT



- Bring additional therapeutic options to patients earlier without compromising the quality of the evidence needed to establish the efficacy and safety of therapeutic agents.
- Maintain patients in long- term clinical trials by progressing them through the various stages of the development program ➔offers prolonged drug exposure with the flexibility of enabling additional patients to be enrolled at each stage of the study
- Reduce the need to find full cohorts of new patients with histologically confirmed NASH