

# Biomarker-driven trial design

## バイオマーカーを組み込んだ臨床試験デザイン

JCOGデータセンター  
福田治彦

# 本日の Topics

## ■ 前置き

- Biomarker-driven trial design の `scope`

## ■ 試験デザインに影響する因子

- Credential
- Cross-cancer similarity

## ■ 試験デザインマップ（私家版） - credential

- 探索的試験デザイン
- 検証的試験デザイン

## ■ Master protocol - cross-cancer similarity

- Basket trial
- Umbrella trial
- Platform trial
- NCI-MATCH@NCI, MASTERKEY@NCCH

## ■ 課題

# 前置き

## Biomarker-driven trial design の 'scope'

- 基本的に「有効性」の探索と検証の方法論
  - 第II相試験
  - 第III相試験
  - 第II/III相試験
- 「安全性」・用量設定はスコープ外 – 別のトピック
  - 腫瘍組織のバイオマーカー（somatic mut.）は安全性/毒性に影響しない
  - 推奨用量は毒性のみでは決められず、有効性、標的阻害、PK等により総合的に決められる -- 第I相試験の大規模化の1つの要因
    - Biologically minimal effective dose
    - Biologically optimal dose (BOD)
- 本日はJCOG試験の実例に基づくお話ではありません

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- 試験デザインに影響する因子
  - Credential
  - Cross-cancer similarity
- 試験デザインマップ（私家版）
  - 探索的試験デザインと credential
  - 検証的試験デザインと credential
- Master protocol と cross-cancer similarity
  - Basket trial
  - Umbrella trial
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- 課題

# 試験デザインに影響する因子

## 1. バイオマーカーの「確からしさ」 - **credential** “あてになる度合い”

- 効果がバイオマーカー陽性患者に限られるか否か/限られる度合い
  - マーカー（+）患者では効く かつ マーカー（-）患者では効かない vs.  
マーカー（+/-）によらず効く/効かない ・ ・ 効果との**交互作用の有無/程度**
  - Very strong vs. Strong vs. Weak vs. None

## 2. がん種一標的 / 薬剤の組み合わせ – **cross-cancer similarity**

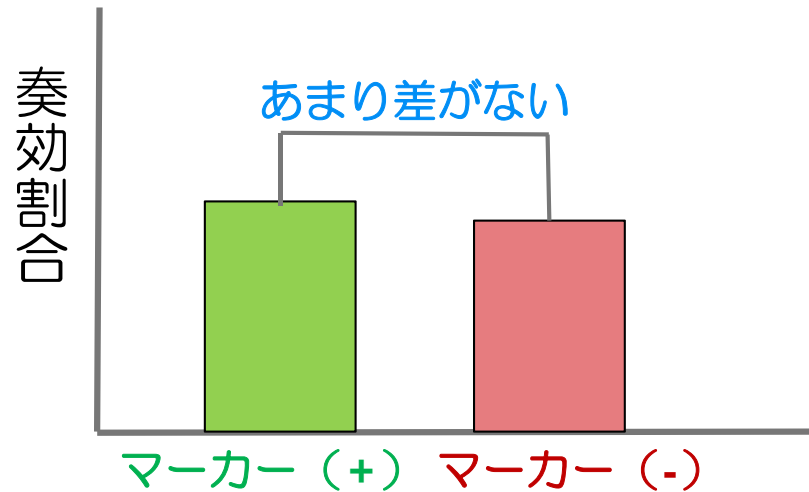
- Single disease – single drug  ふつうの試験
- Single disease – multiple drugs  Umbrella trial
- Multiple diseases – single drug  Basket trial
- Multiple diseases – multiple drugs  NCI-MATCH

## 3. その他

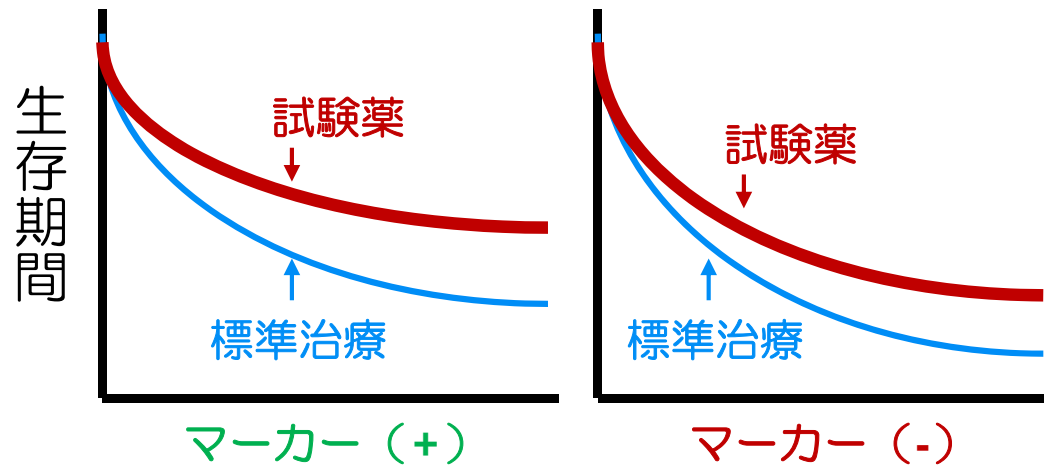
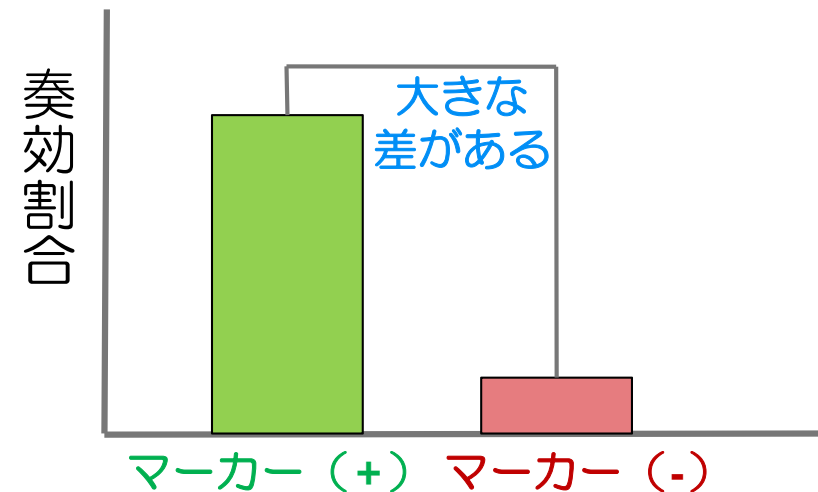
- 相（**phase**） / 目的：第II相 vs. 第III相
- ランダム化の有無 – ただし、相と関連
- バイオマーカーの陽性割合
- 期待される効果の大きさ（**ex.** 奏効割合の絶対値）

# Credential / 確からしさ / あてになる度合い

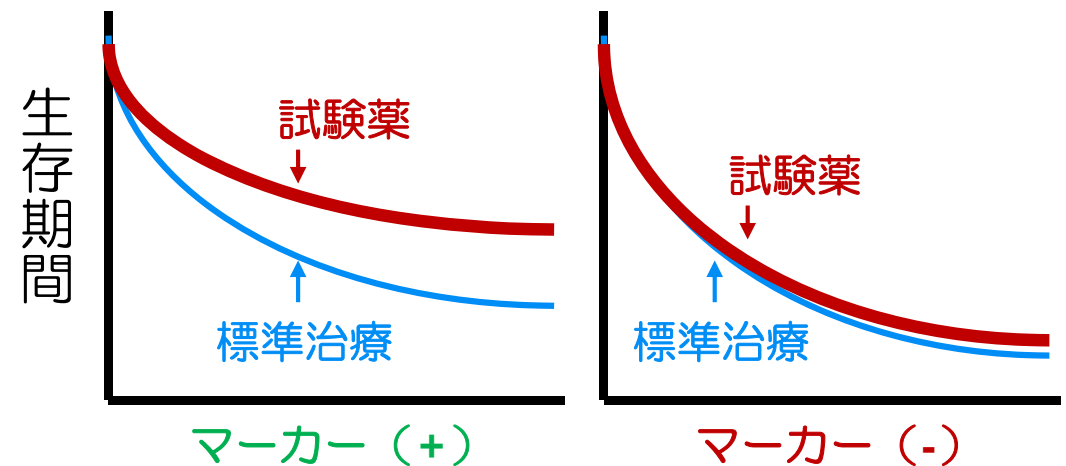
## Credential が弱い



## Credential が強い



マーカー (+) か (-) によらず  
同じくらい効く / 効かない



マーカー (+) だったら効く  
マーカー (-) だったら効かない

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  - Cross-cancer similarity
- 試験デザインマップ（私家版） - **credential**
  - 探索的試験デザイン
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- 課題

# 試験デザインマップ

マーカー (+) だけに効きそう  
マーカー (-) には効かなさそう

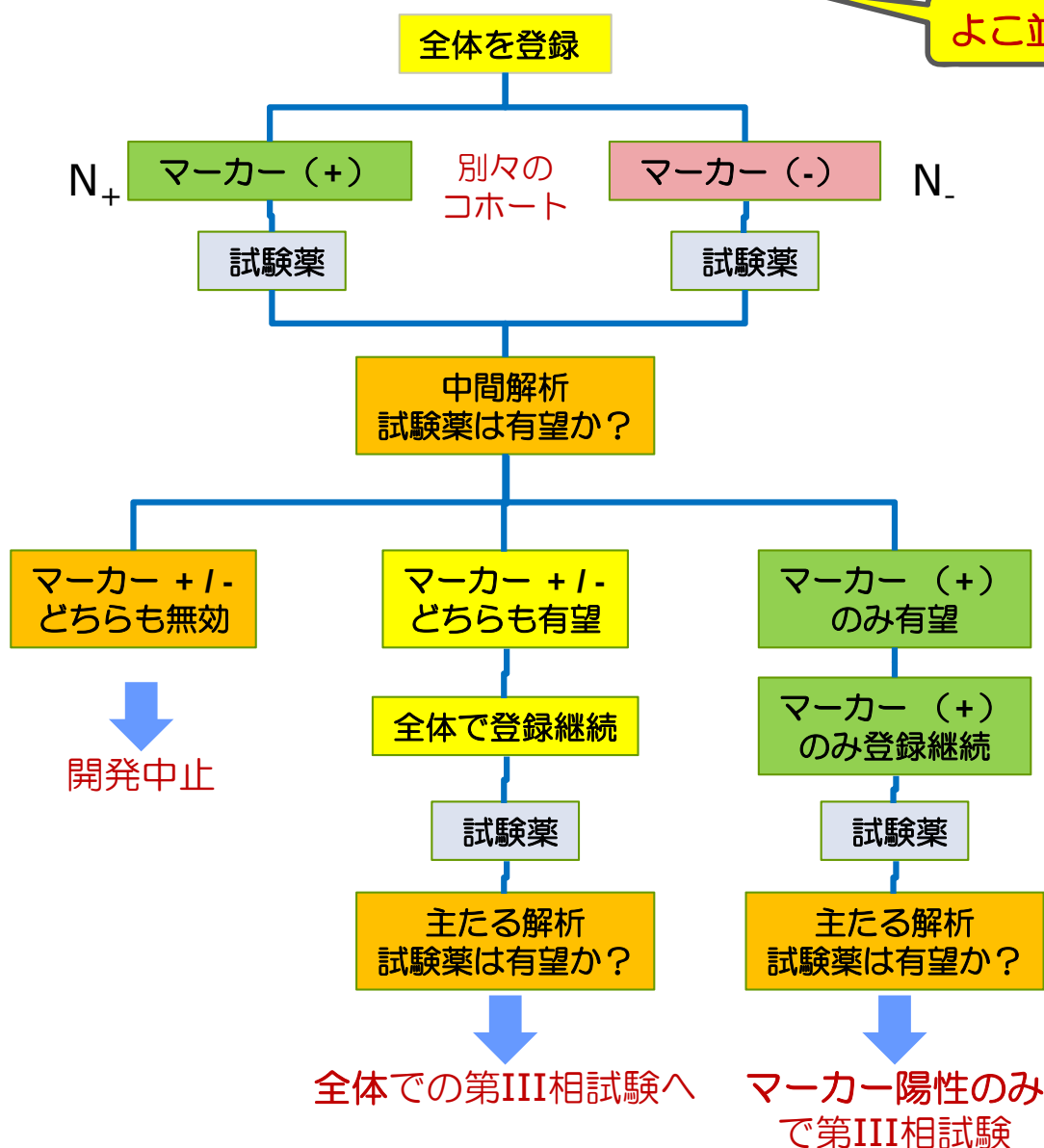
| Phase                                  | Biomarker credentials                                             |                                            |                                                                   |                   |
|----------------------------------------|-------------------------------------------------------------------|--------------------------------------------|-------------------------------------------------------------------|-------------------|
|                                        | none - weak                                                       |                                            | strong                                                            |                   |
| Exploratory phase II<br>non-randomized | Tandem two stage design                                           | (Adaptive) parallel Simon two-stage design | Basket trial design<br>(multiple tumor types, single target/drug) |                   |
| Phase II/III<br>randomized             |                                                                   |                                            | Multi-arm multi-stage (MAMS) design<br>(multiple targets/drugs)   |                   |
| Confirmatory phase III<br>randomized   | weak                                                              | strong                                     |                                                                   | very strong       |
|                                        | Stratified design <i>'all-comers' design</i> とも                   |                                            |                                                                   | Enrichment design |
|                                        | Fallback design                                                   | Marker sequential test (MaST) design       | Subgroup-specific design                                          |                   |
|                                        | Umbrella trial design (single tumor type, multiple targets/drugs) |                                            |                                                                   |                   |

# 試験デザインマップ

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|                                        | Fallback design                                                   | Marker sequential test (MaST) design          | Subgroup-specific design                                          |                   |
|                                        | Umbrella trial design (single tumor type, multiple targets/drugs) |                                               |                                                                   |                   |

# 探索的試験デザイン – credential ありそうな時

## ■ (Adaptive) parallel Simon two-stage design



RESEARCH ARTICLE

### Biomarker-Guided Adaptive Trial Designs in Phase II and Phase III: A Methodological Review

Miranta Antoniou<sup>1,2\*</sup>, Andrea L. Jorgensen<sup>1,2</sup>, Ruwanthi Kolamunnage-Dona<sup>1,2</sup>

<sup>1</sup> MRC North West Hub For Trials Methodology Research, Liverpool, United Kingdom, <sup>2</sup> Department of Biostatistics, Institute of Translational Medicine, University of Liverpool, L69 3GL, Liverpool, United Kingdom

Antoniou et al., PLOS ONE, 2016

バイオマーカー陽性・陰性それぞれで  
閾値、期待値、 $\alpha$ 、 $\beta$ 、サンプルサイズ、  
中間解析の decision rule を設定  
→ 2つの単群第II相試験を並行して行うイメージ  
Primary endpoint は %response や %6m-PFS

マーカーの credential ありそうな時？  
(マーカー (-) だと効かなさそうな時)  
HER2 のような場合？  
マーカー陽性割合が半分くらいの時？

Pros:

ロジックがシンプル、マーカー (-) も調べる

Cons:

登録ペースが予想と異なった場合、  
片方のコホートでの登録休止が長くなる？

「マーカー (+) に期待・あわよくば (-) も」  
デザイン

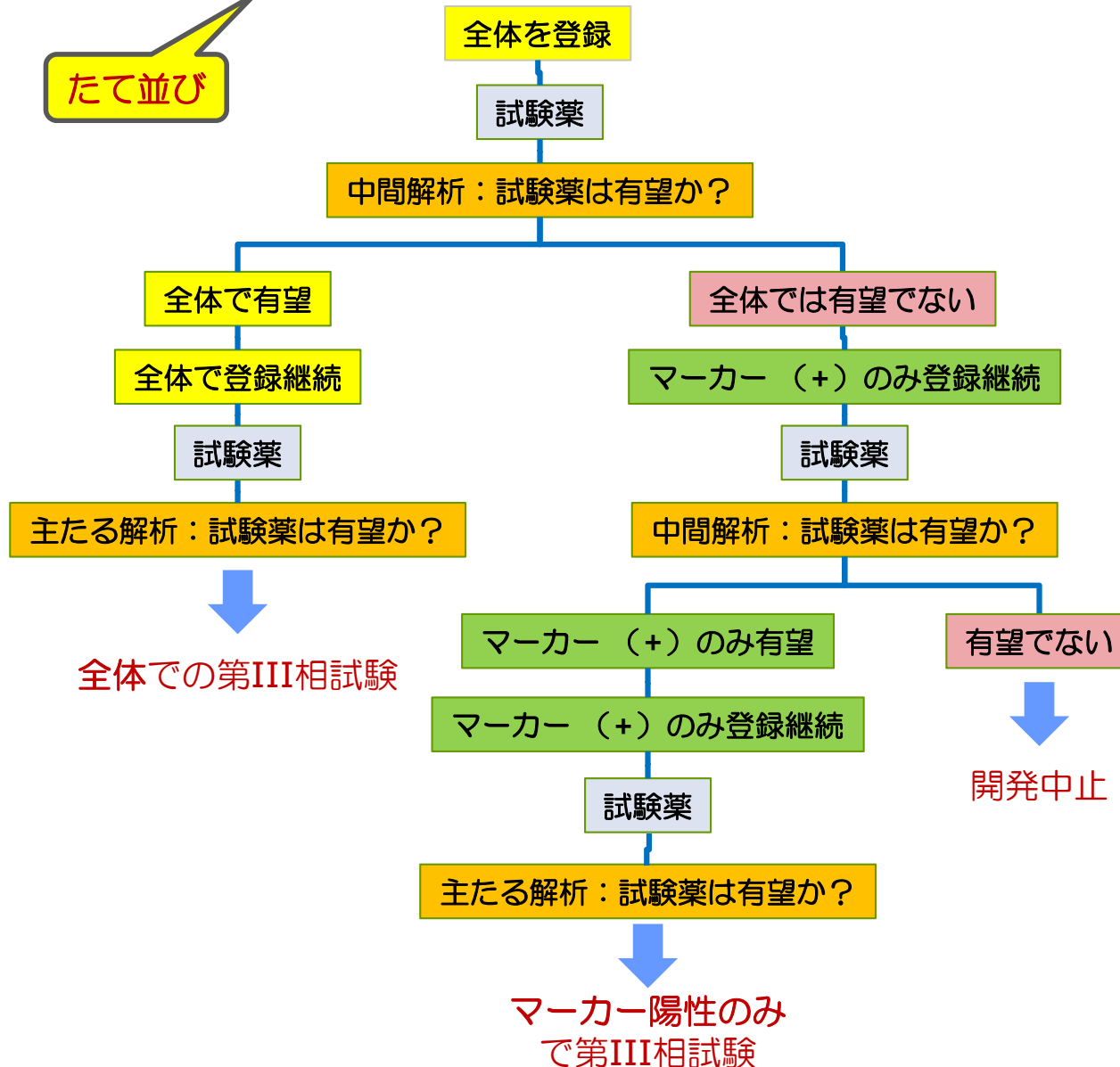
# 試験デザインマップ

| Phase                                   | Biomarker credentials                                             |                                                  |                                                                      |                      |
|-----------------------------------------|-------------------------------------------------------------------|--------------------------------------------------|----------------------------------------------------------------------|----------------------|
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| Exploratory phase II<br>non-randomized  | Tandem<br>two stage<br>design                                     | (Adaptive)<br>parallel Simon<br>two-stage design | Basket trial design<br>(multiple tumor types,<br>single target/drug) |                      |
| Phase II/III<br>randomized              |                                                                   |                                                  | Multi-arm multi-stage<br>(MAMS) design<br>(multiple targets/drugs)   |                      |
| Confirmatory<br>phase III<br>randomized | weak                                                              | strong                                           |                                                                      | very strong          |
|                                         | Stratified design                                                 |                                                  |                                                                      | Enrichment<br>design |
|                                         | Fallback<br>design                                                | Marker<br>sequential test<br>(MaST) design       | Subgroup-<br>specific design                                         |                      |
|                                         | Umbrella trial design (single tumor type, multiple targets/drugs) |                                                  |                                                                      |                      |

# 探索的試験デザイン – credential なさそうな時

## ■ Tandem two stage design

たて並び



RESEARCH ARTICLE

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Miranta Antoniou<sup>1,2\*</sup>, Andrea L Jorgensen<sup>1,2</sup>, Ruwanthi Kolamunnage-Dona<sup>1,2</sup>

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Antoniou et al., PLOS ONE, 2016

マーカーの credential なさそうな時？  
(マーカー (-) でも効きそうな時)  
マーカー陽性割合が低い時？  
Nivolumab のような場合？

Pros:

真に全体で有効なら効率的  
(実際に credential が弱かったら  
試験は早く終わる)

Cons:

マーカー (-) での効果はわからない  
マーカー (-) でも実はそこそこ効く  
のを見落とす可能性あり

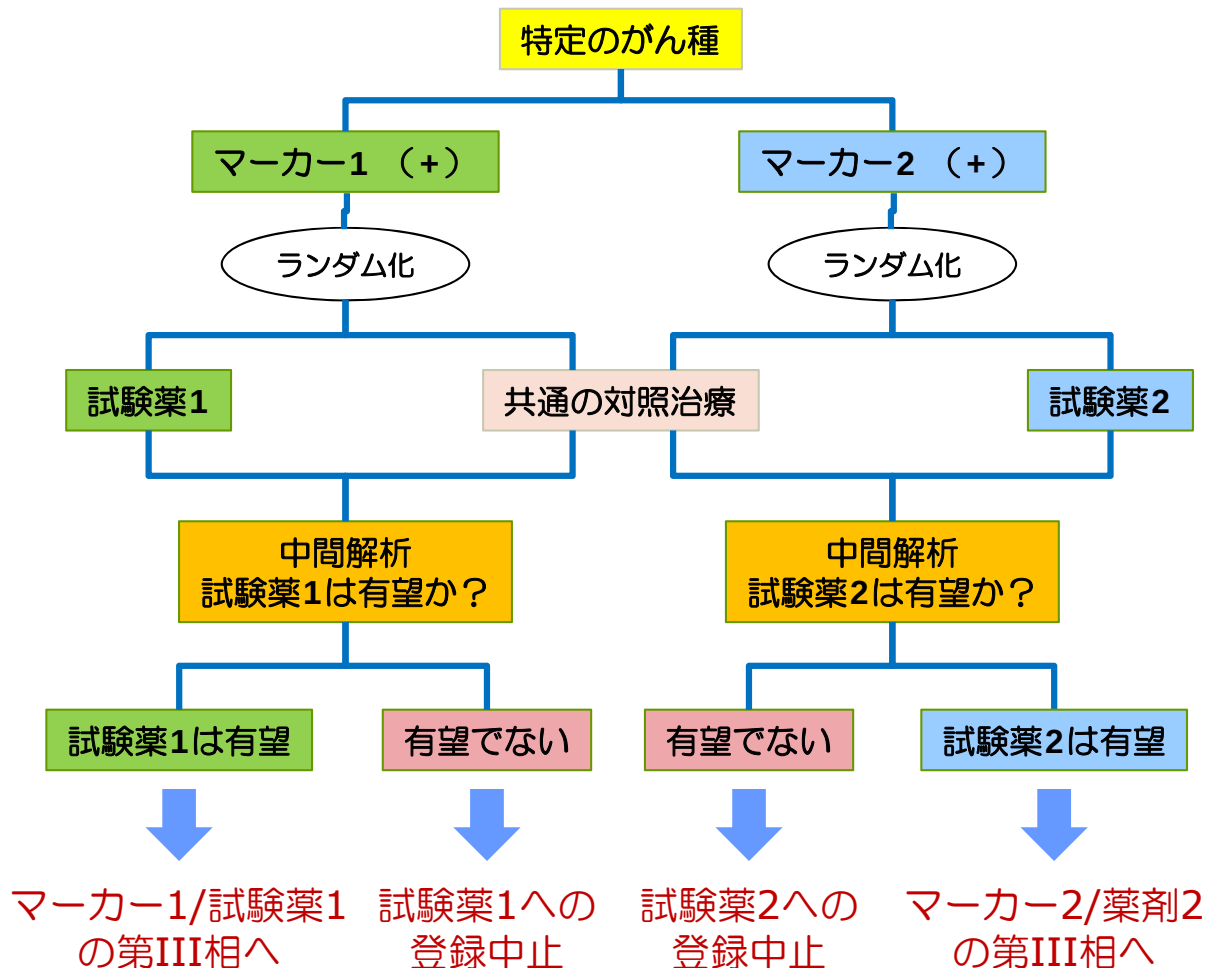
「全体の方がいけるんじゃないか」  
デザイン

# 試験デザインマップ

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# Phase II / III デザイン

## ■ Multi-arm multi-stage (MAMS) design



- 有望な試験薬が複数ある場合
- 共通の対照群を置くことで効率アップ
- **Randomized screening phase II study**を同時並行で行うイメージ
- マーカーの **credential** が強い時 (**enrichment design**)

1つの企業が同時に同一疾患に複数の試験薬を開発することは考えにくい・・・  
研究者 (**Cooperative Group**や医療機関) 主導で行われること (**academic trial**) が多いと思われる

「いっぺんにたくさん調べよう」  
デザイン

Ex) GOG-182, STAMPEDE, ICON6  
Bayesian variants) I-SPY2, FOCUS4

これを大規模・継続的に行うのが '**platform**' trial (後述)  
(Woodcock & LaVange, N Eng J Med 2017)

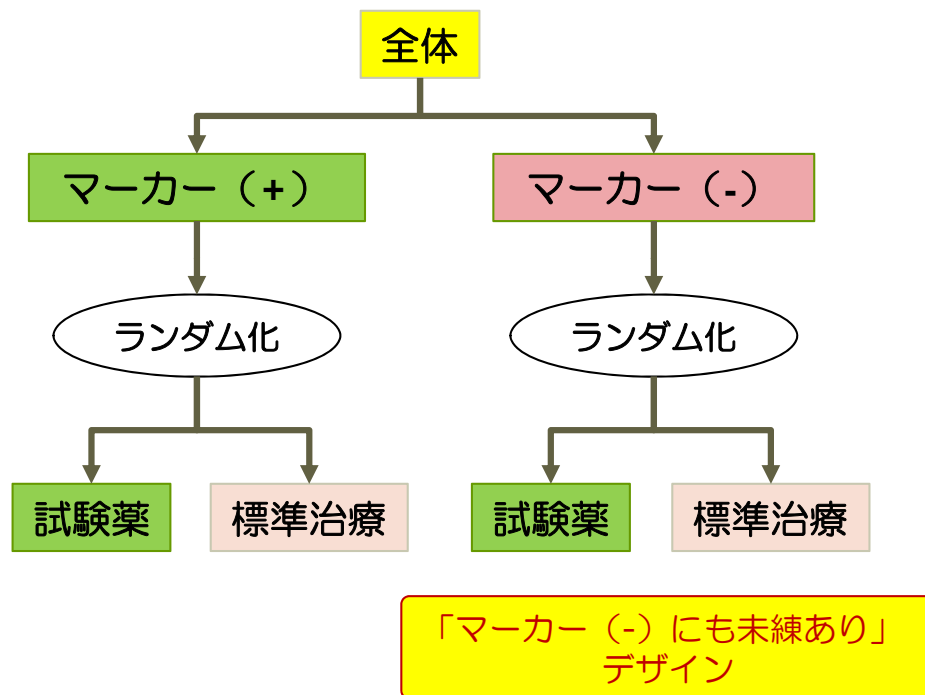
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|                                        | Fallback design                                                   | Marker sequential test (MaST) design       | Subgroup-specific design                                          |                   |
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# 検証的試験デザイン

第III相までに対象が絞れていない場合

## (Biomarker-) stratified Design

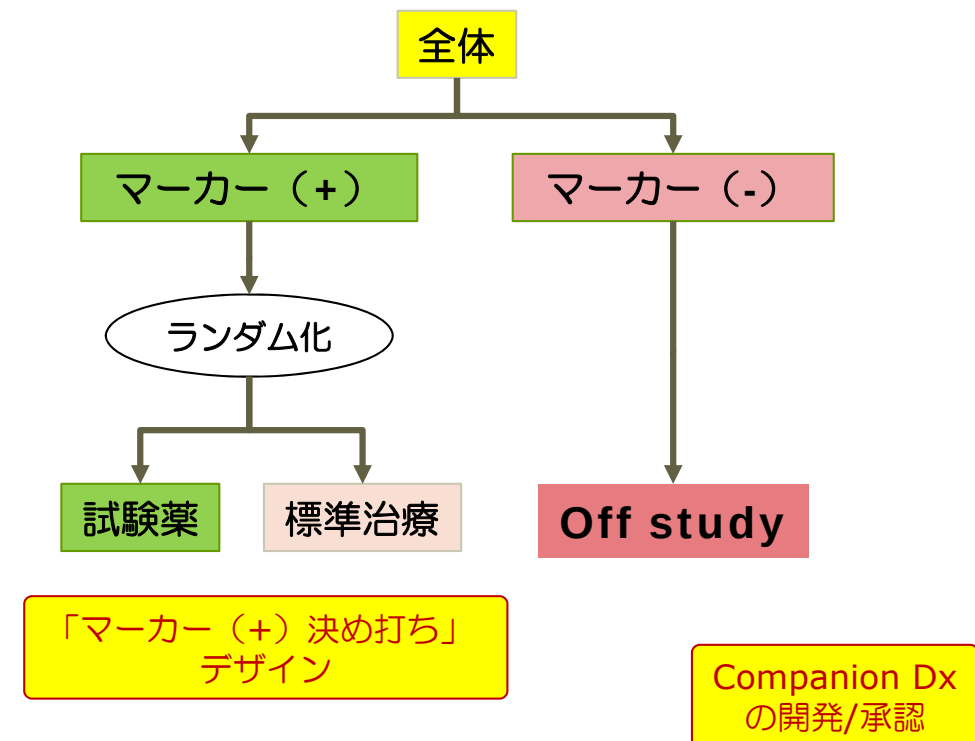


検定のしかたによってオプションあり：

- Subgroup-specific testing design
- Marker sequential test (MaST) design
- Fall-back trial design
- Biomarker-positive and overall design

第III相までにマーカー (+) に効果が限られるとわかっている場合 (マーカー (-) には効かない)

## Enrichment Design



Ex)

CRYSTAL: cetuximab / colorectal cancer with EGFR expression  
 BRIM 3: vemurafenib / melanoma with BRAF<sup>V600E</sup> mutation  
 EURTAC: erlotinib / NSCLC with EGFR mutation  
 CLEOPATRA: pertuzumab / breast cancer with HER2 expression  
 PROFILE 1007: crizotinib / NSCLC with ALK rearrangement  
 LUX-LUNG3: afatinib / NSCLC with EGFR mutation

# 試験デザインマップ

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検定のしかたの違い

# Stratified design options

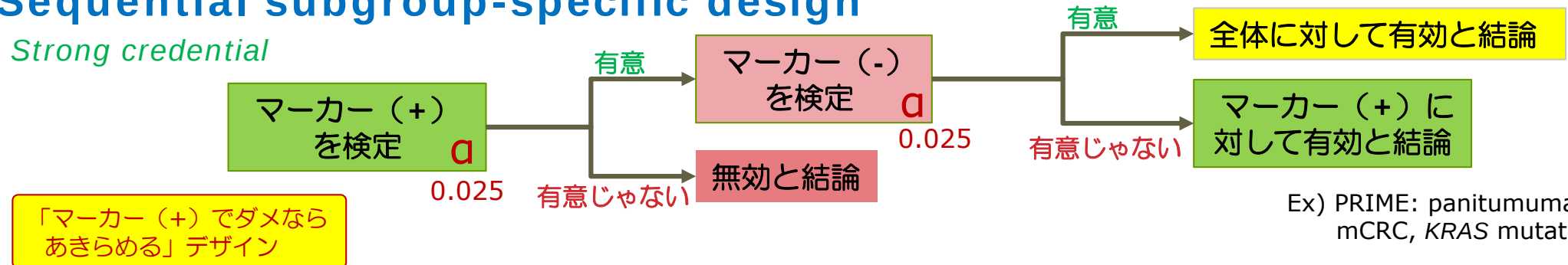
Biomarker enrichment strategies: matching trial design to biomarker credentials

Boris Freidlin and Edward L. Korn

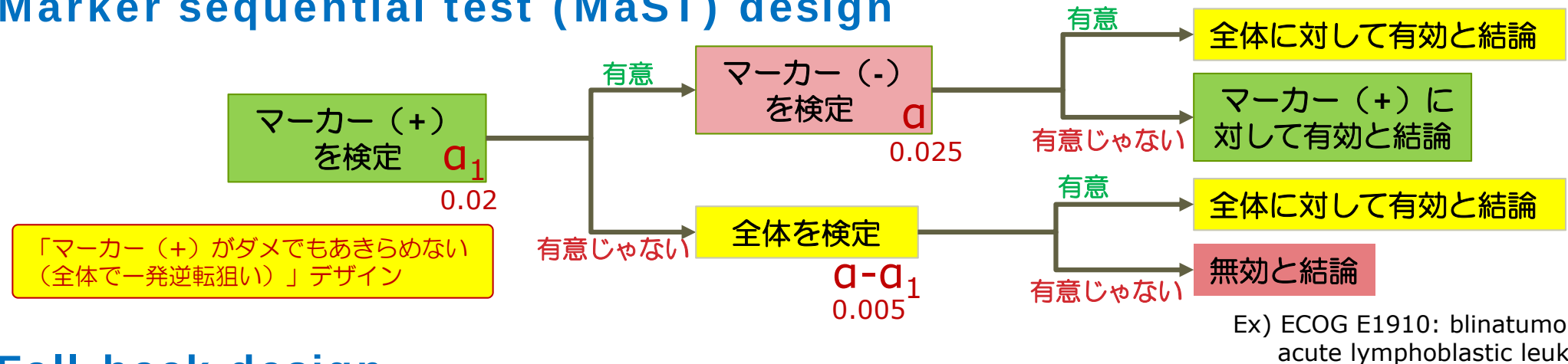
Freidlin & Korn., NATURE REVIEWS Clinical Oncology 2014

## Sequential subgroup-specific design

*Strong credential*

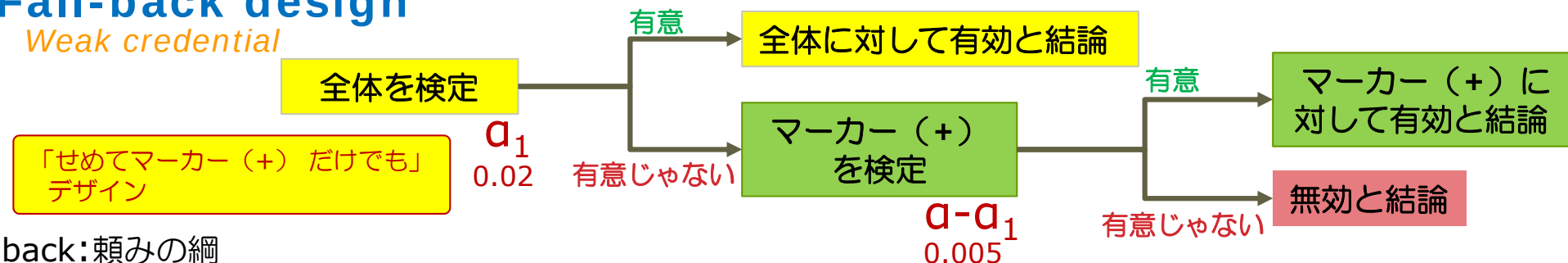


## Marker sequential test (MaST) design



## Fall-back design

*Weak credential*



\*fallback: 頼みの綱

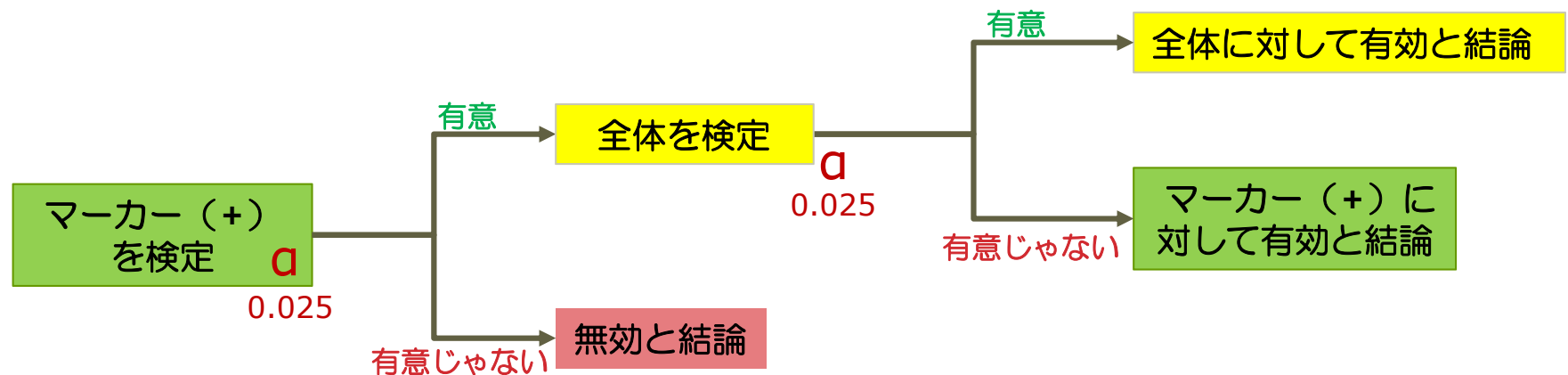
営利目的でのご利用はご遠慮ください

ICRweb臨床研究入門 <http://www.icrweb.jp>

# Stratified designs

## ■ 推奨できないデザイン

### Sequential biomarker-positive and overall population design



統計的 / 数学的には問題はないが（閉検定の手法）・・・  
 マーカー（-）で全く効果がなくてもマーカー（+）での効果が  
 大きければそれに引っ張られて全体が有意になってしまう  
 ・・・臨床的には問題

Ex)  
 ECOG0147, ZODIAC,  
 MONET1, ARCHER,  
 MERiDiAN

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  - 探索的試験デザイン
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- **Master protocol - cross-cancer similarity**
  - Basket trial
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  - Platform trial
  - NCI-MATCH@NCI, MASTERKEY@NCCH
- 課題

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# Cross-cancer similarity – tumor agnostic approach

## FDA Approves Pembrolizumab for Microsatellite Instability-High and Mismatch Repair Deficient Cancers

Jason M. Broderick @jasoncology

Published Online: Tuesday, May 23, 2017



Richard Pazdur, MD

The FDA has granted an accelerated approval to pembrolizumab (Keytruda) for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) solid tumors that have progressed after prior treatment and who have no satisfactory alternative treatment options, as well as patients with MSI-H or dMMR colorectal cancer following progression on a fluoropyrimidine, oxaliplatin, and irinotecan.

しかし・・・

ということもある

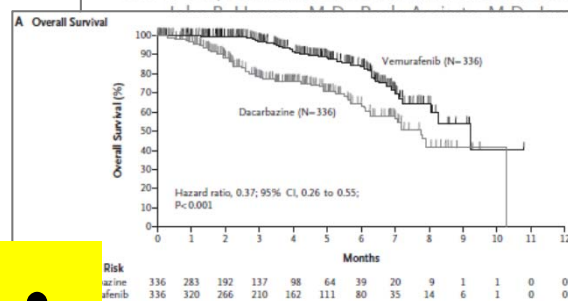
FDAが初めて、がん種を限らずに  
MSI-H / dMMRの固形がんに対する  
ペムブロリズマブを承認  
- Tumor agnostic approval

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

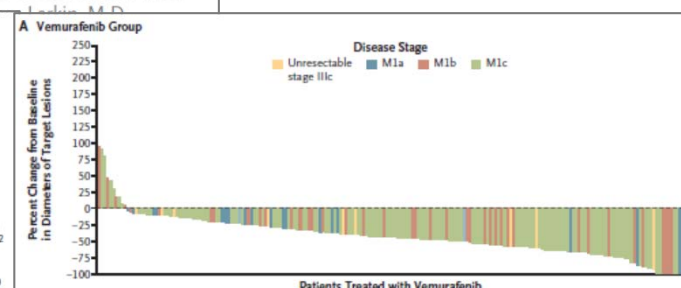
## Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D., et al.



ベムラフェニブはBRAF<sup>V600E</sup>変異  
メラノーマにはよく効くが・・・

Chapman et al.,  
N Eng J Med 2011

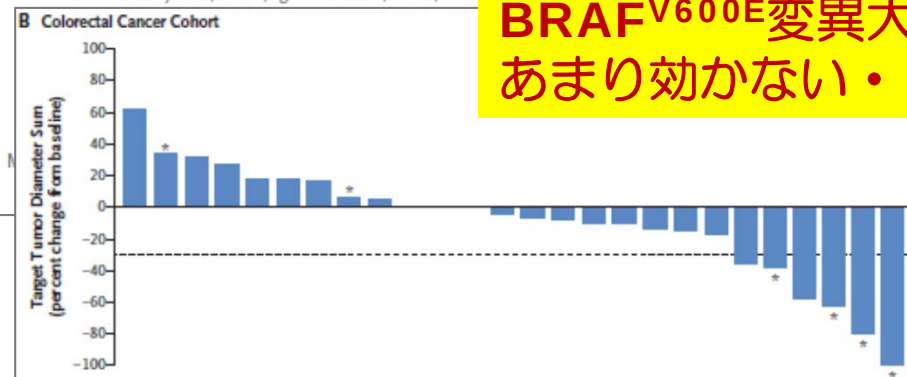


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations

David M. Hyman, M.D., Igor Puzanov, M.D., Vivek R. Anand, M.D., et al.



BRAF<sup>V600E</sup>変異大腸癌には  
あまり効かない・・・

Hyman et al.,  
N Eng J Med 2015

# Master protocols

Woodcock & LaVange,  
N Eng J Med 2017

THE NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS  
Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D.,  
and Janet Woodcock, M.D., Editors

Master Protocols to Study Multiple  
Therapies, Multiple Diseases, or Both

Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.

## ■ Basket

単一薬剤

- To study a **single targeted** therapy in the context of **multiple diseases** or disease subtypes

複数がん種

## ■ Umbrella

複数薬剤

- To study **multiple targeted** therapies in the context of a **single disease**

単一がん種

# Basket & Umbrella

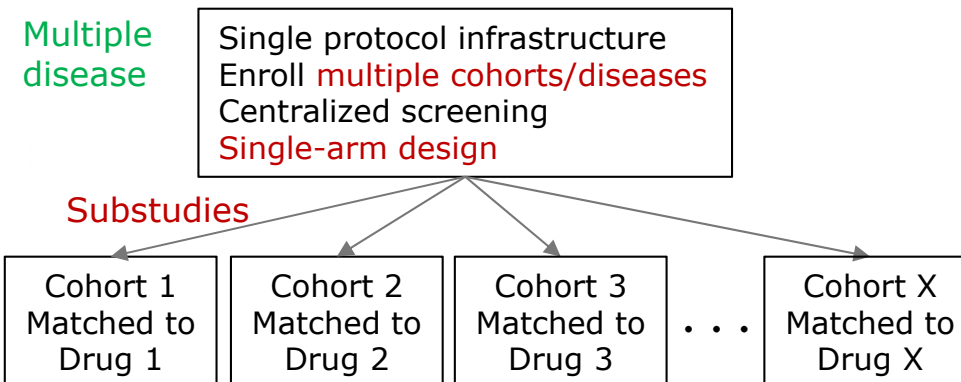
## Improving Clinical Trial Efficiency: Thinking outside the Box

Sumithra J. Mandrekar, PhD, Suzanne E. Dahlberg, PhD, and Richard Simon, DSc

Mandrekar S et al., 2015 ASCO Educational Book

### Basket (bucket) trial

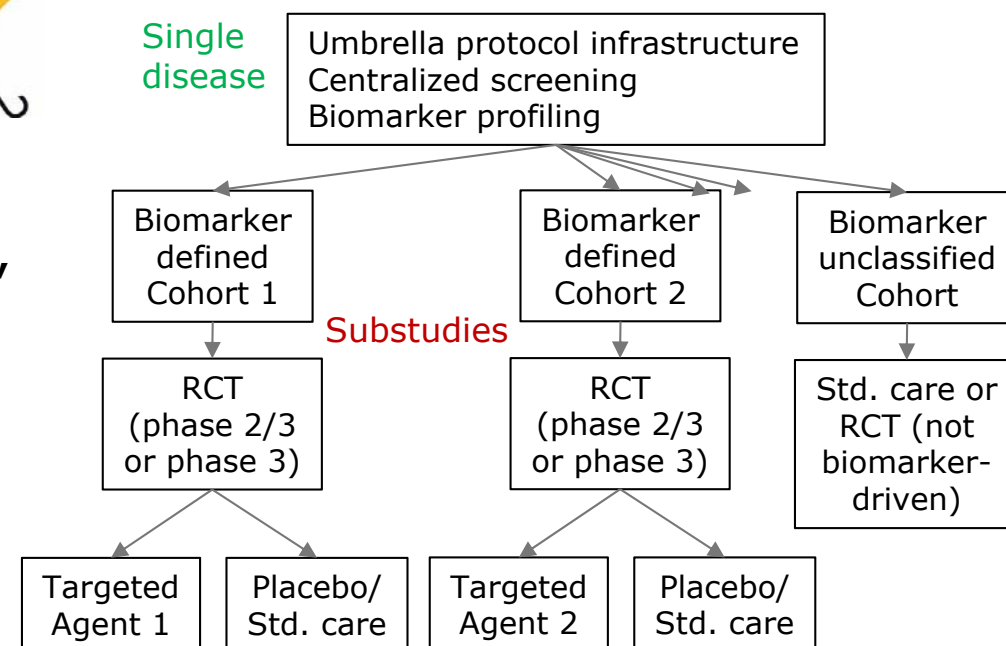
- 複数がん種 (*tumor-agnostic*)
- 単一薬剤
  - 単群 phase II の集合
  - Ex) SIGNATURE
- ある薬剤がどのがんに効くかを見たい
  - 通常は企業治験 – seeds-oriented



がん種が異なるので共通の対照群は置けない

### Umbrella trial

- 単一がん種
  - Ex) FOCUS4(mCRC),  
ALCHEMIST(Ad NSCLC adjvant),  
Lung-MAP(Sq NSCLC)
- 複数薬剤
  - Phase III, phase II/III の集合
    - 単群検証コホートもあり得る
- あるがん種にどの薬剤が効くかを見たい
  - academic trial – needs-oriented



がん種が1つなので共通の対照群が置ける

# Master protocols

Woodcock & LaVange,  
N Eng J Med 2017

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS  
Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D.,  
and Janet Woodcock, M.D., Editors

Master Protocols to Study Multiple  
Therapies, Multiple Diseases, or Both

Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.

## ■ Basket

単一薬剤

- To study a **single targeted** therapy in the context of **multiple diseases** or disease subtypes

複数がん種

## ■ Umbrella

複数薬剤

- To study **multiple targeted** therapies in the context of a **single disease**

単一がん種

## ■ Platform

複数薬剤

- To study **multiple targeted** therapies in the context of a **single disease** in a **perpetual manner**, with therapies **allowed to enter or leave the platform** on the basis of a decision algorithm

単一がん種

継続的に行って、治療を足したり減らしたり

- 「master protocol」の一種

The NEW ENGLAND JOURNAL of MEDICINE

## REVIEW ARTICLE

## THE CHANGING FACE OF CLINICAL TRIALS

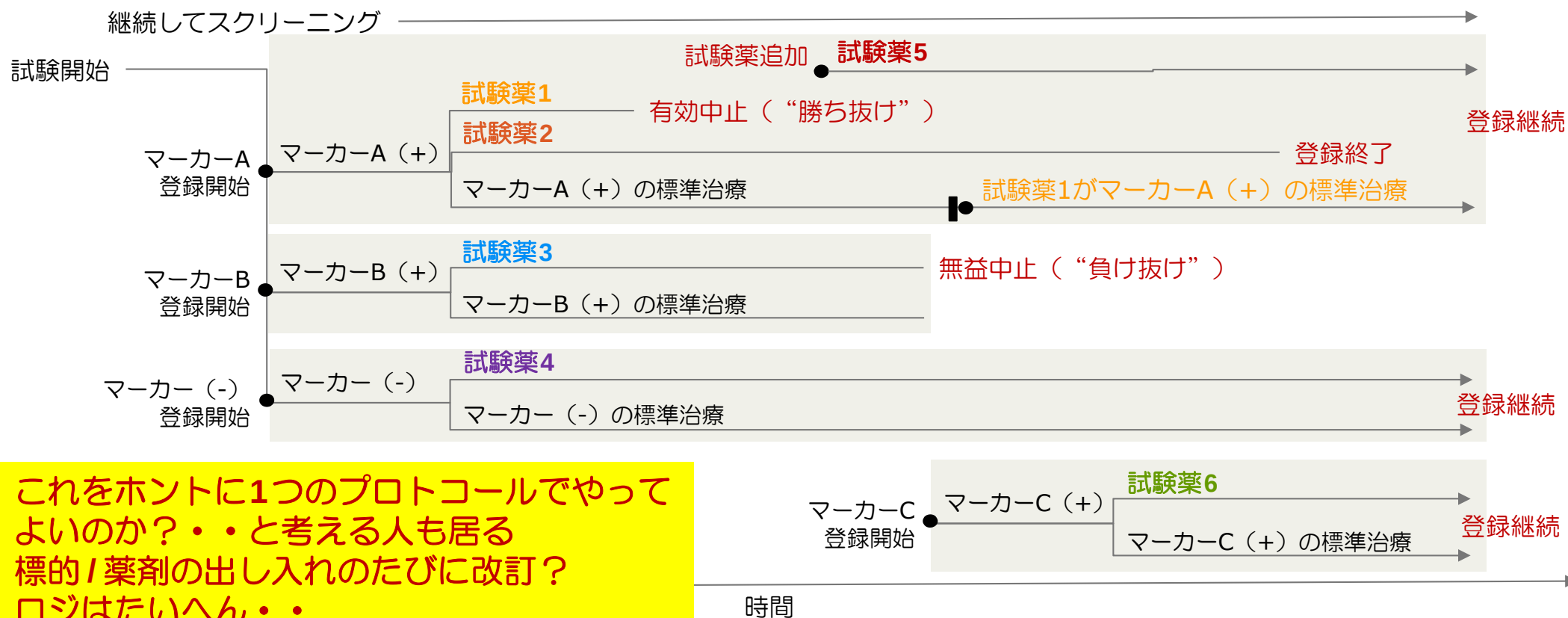
Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D.,  
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## Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.

Woodcock & LaVange, N Eng J Med 2017

より、図を日本語化



## ■ 多がん種・多薬剤の basket trial

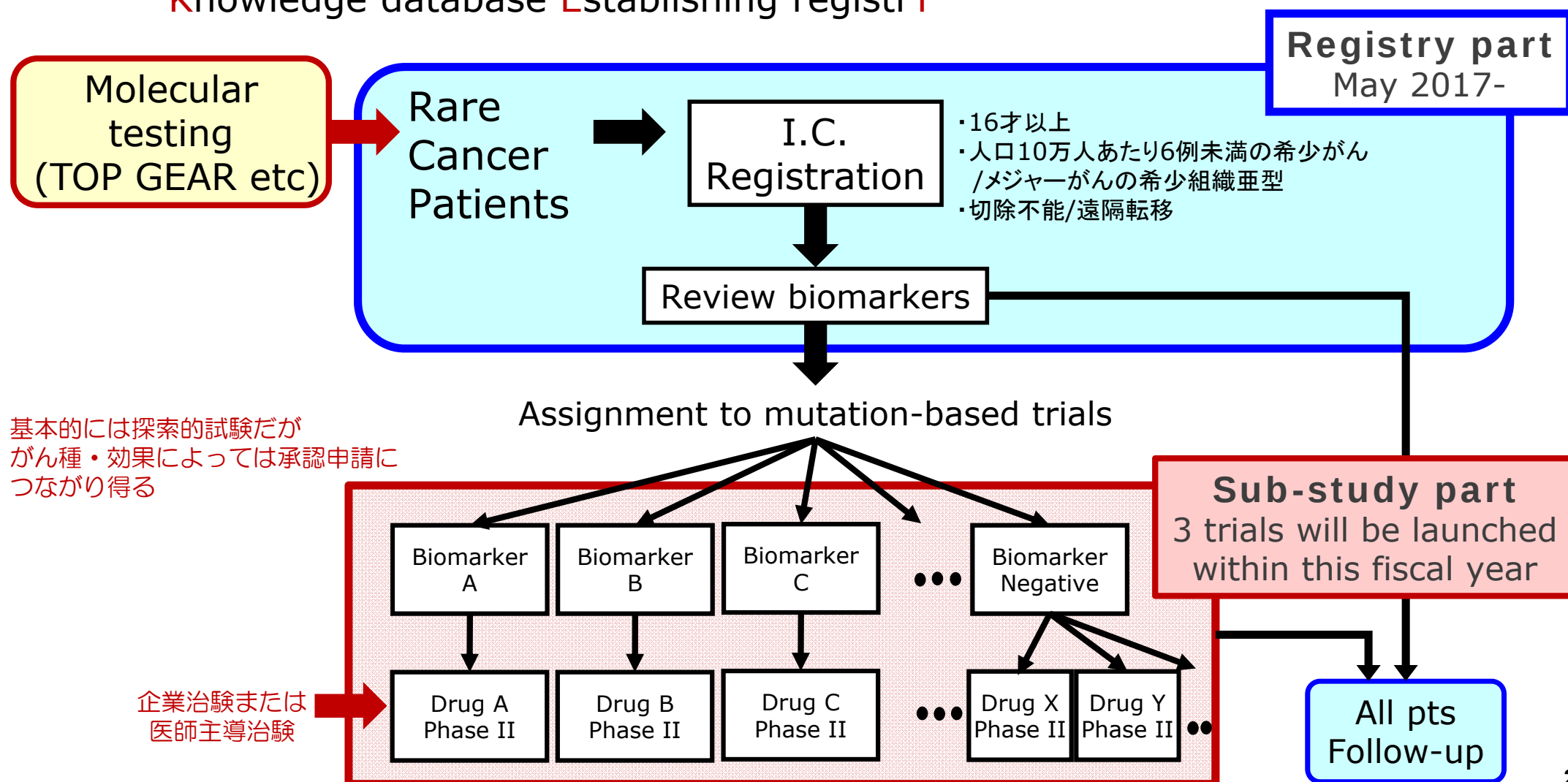
- 繰り返す

□ジはもっとたいへん・・・NCIくらいしかできない？



# MASTER KEY Project @NCCH

- 希少がんを対象とした **basket trial** - 多がん種・多薬剤
  - Marker Assisted Selective ThERapy in Rare cancers:  
Knowledge database Establishing registry



# Biomarker-driven trials の課題@各種総説

## ■ Credentials - More precise biomarkers

- 全ゲノム、RNA、メチル化、その他の 'omics' 解析
- 機能不明の遺伝子変異の探索
- 同一患者内・同一腫瘍内の heterogeneity の本態解明
- 画像検査: FDG-PET/CT, FLT-PET, dynamic/diffusion-weighted MRI

## ■ Cross-cancer similarity - Tumor agnostic approach

- 異なるがん種に共通する遺伝子異常と有効性の探索 — 多くのがん種で検討
  - More 'imatinib CML-GIST story' in *BCR-ABL*
- ただし、がん種による違いの過度の軽視にも注意
  - すべてが tumor-agnostic にうまくいくとは限らない - がん種毎の検討は残る

## ■ Logistics & Costs

- 薬剤の調達、検査結果返却までの時間 (Turn Around Time) の短縮
- 高度なプロジェクト管理能力・多くの組織の協同が必要
  - 特に platform trial, NCI-MATCH etc.
- お金もかかる

# 試験デザインマップ：赤字の6つが基本形

| Phase                                  | Biomarker credentials                                             |                                            |                                                                   |                   |
|----------------------------------------|-------------------------------------------------------------------|--------------------------------------------|-------------------------------------------------------------------|-------------------|
|                                        | none - weak                                                       |                                            | strong                                                            |                   |
| Exploratory phase II<br>non-randomized | Tandem two stage design                                           | (Adaptive) parallel Simon two-stage design | Basket trial design<br>(multiple tumor types, single target/drug) |                   |
| Phase II/III<br>randomized             |                                                                   |                                            | Multi-arm multi-stage (MAMS) design<br>(multiple targets/drugs)   |                   |
| Confirmatory phase III<br>randomized   | weak                                                              | strong                                     |                                                                   | very strong       |
|                                        | Stratified design                                                 |                                            |                                                                   | Enrichment design |
|                                        | Fallback design                                                   | Marker sequential test (MaST) design       | Subgroup-specific design                                          |                   |
|                                        | Umbrella trial design (single tumor type, multiple targets/drugs) |                                            |                                                                   |                   |