希少フラクションの臨床開発
Clinical development for rare fraction cancer

ファイザー株式会社 クリニカルリサーチ統括部　オンコロジー領域部
廣橋　朋子
Tomoko Hirohashi, PhD
Director, Clinical research, Oncology, Pfizer Japan
杉田　潤子（薬事部門）

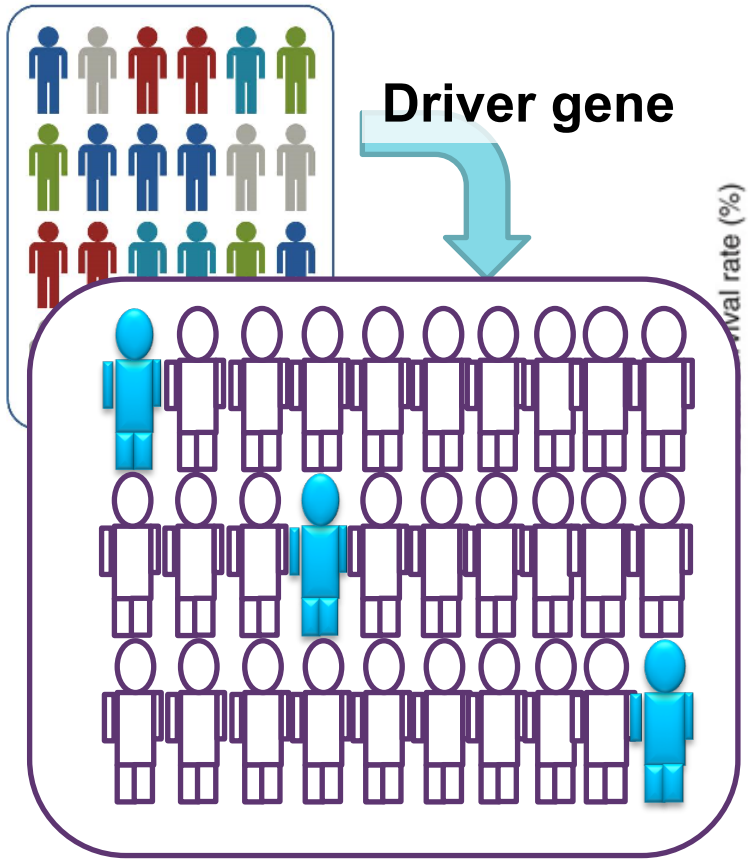
Pfizer
DEVELOPMENT JAPAN
Global Product Development

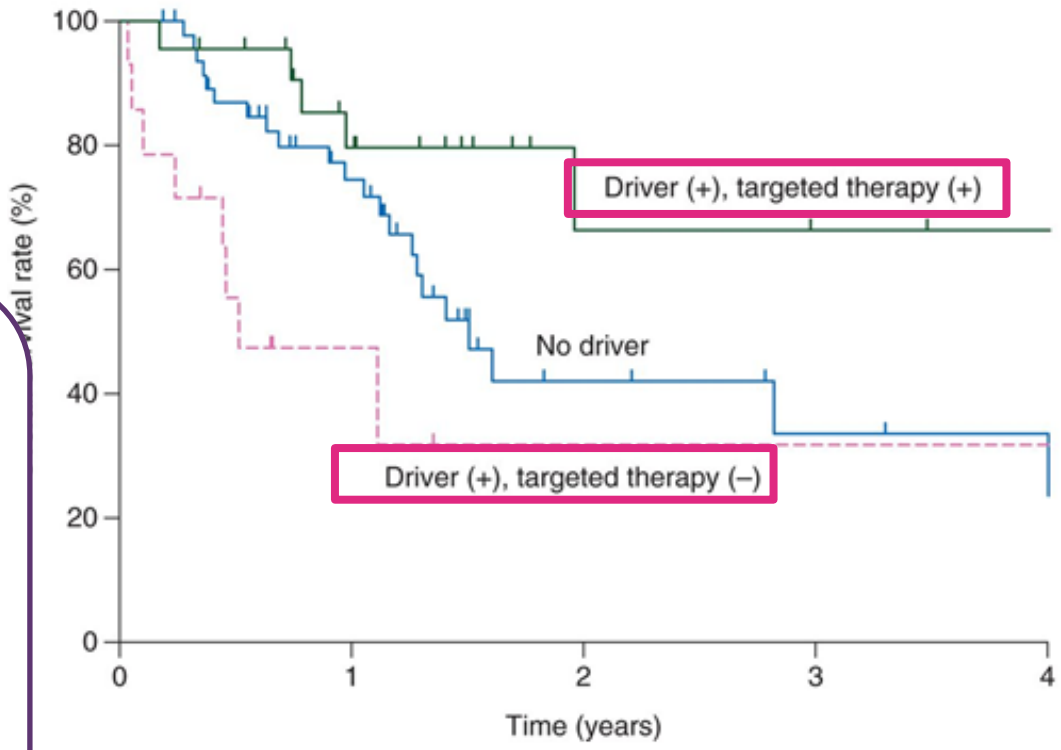
Agenda

- **Background**
- **Successful factors to enhance drug development for a rare fraction cancer**
- **Drug development plan in Japan for rare fraction of cancer**
- **Summary**

Precision medicine for rare fraction cancer

Driver geneに対する分子標的治療薬の高い有効性

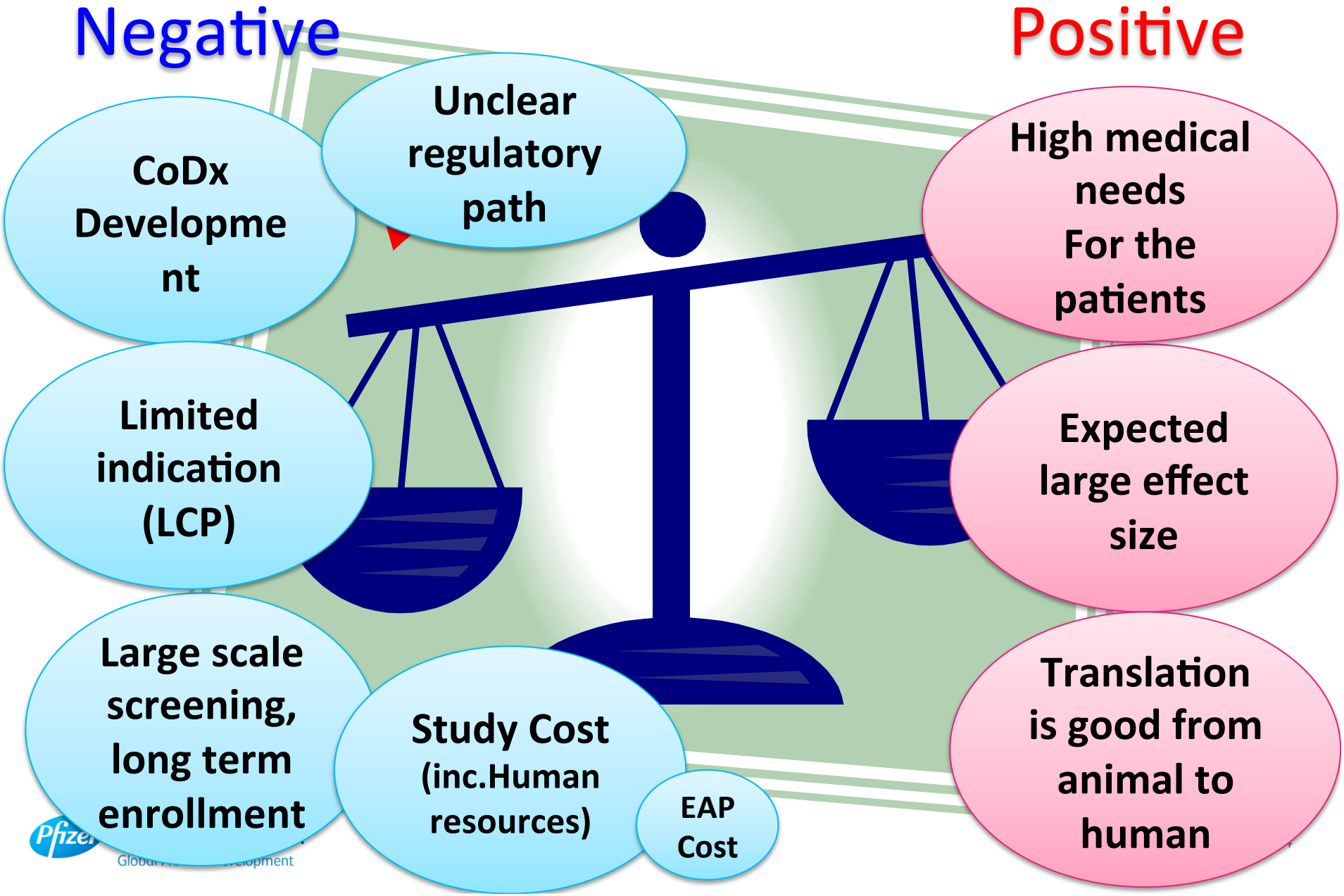




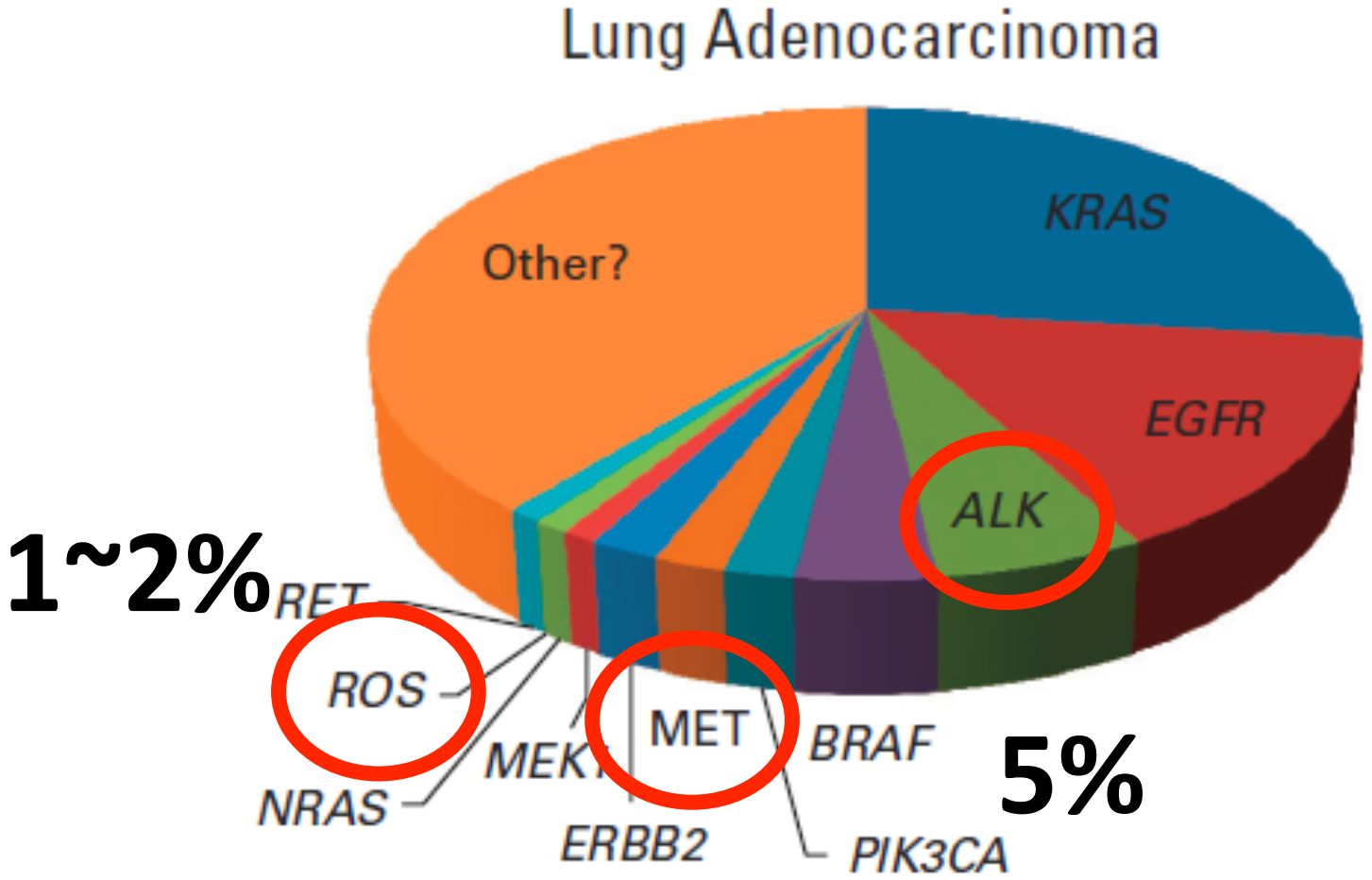
Takeda M. et al., Ann Oncol. 2015 Dec;26(12):2477-82

Difficult to initiate clinical study for rare fraction cancer

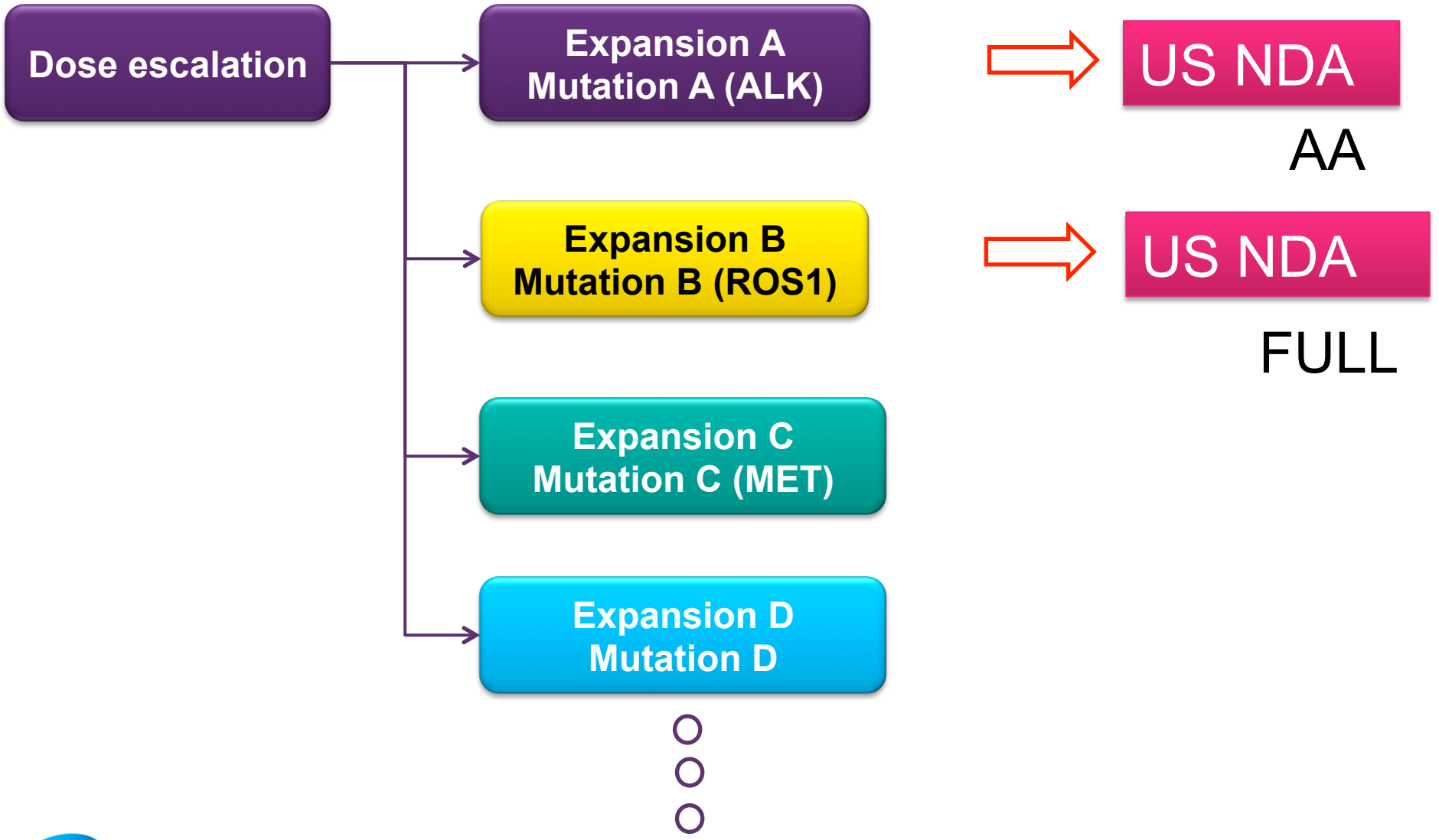
Points to be considered to pursue clinical development for rare fraction cancer



Rare fraction cancer



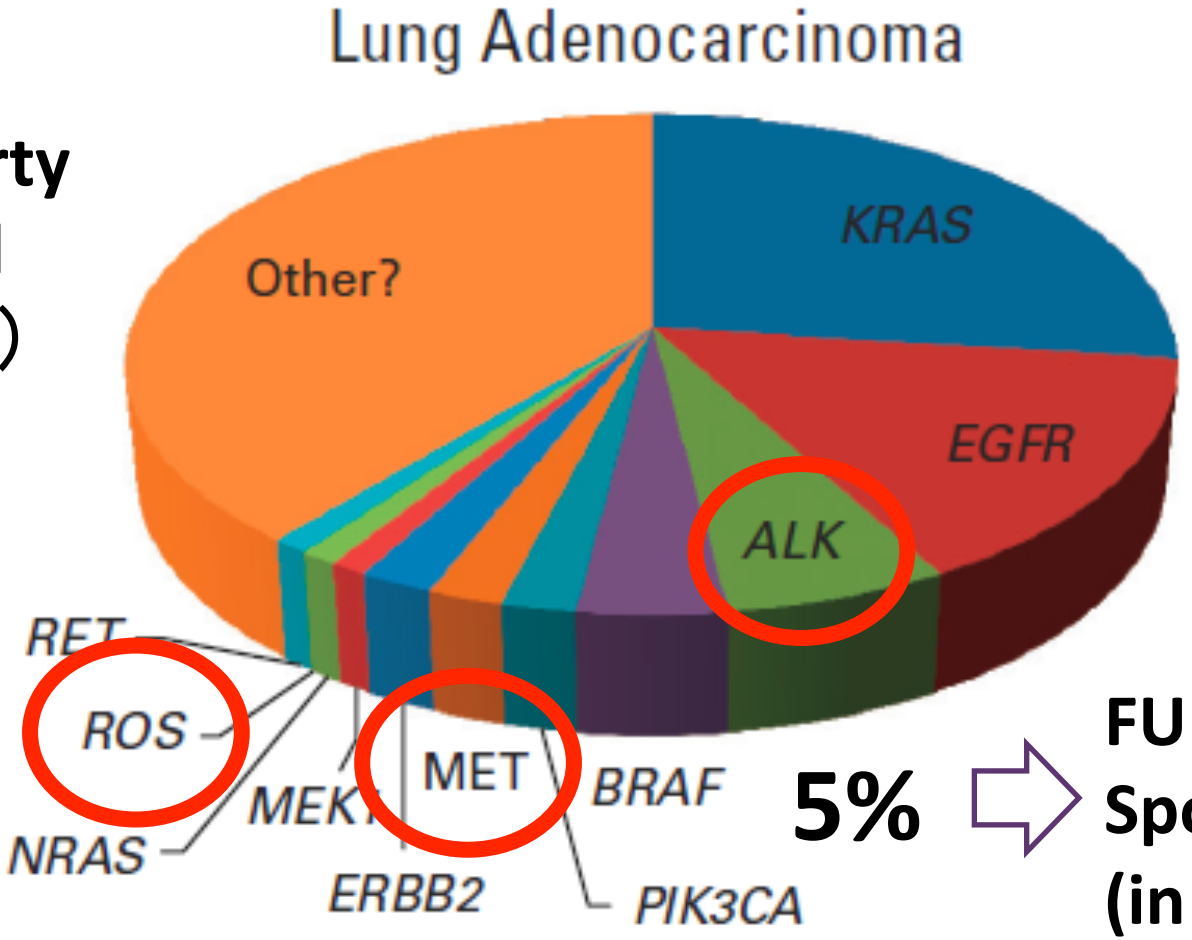
General Basket Trial (In case of G-FIH study)



Rare Fraction Cancer

The 3rd Party Sponsored（Asia only）

1~2%



5% ⇨ **FULL PFE Sponsored (in the world)**

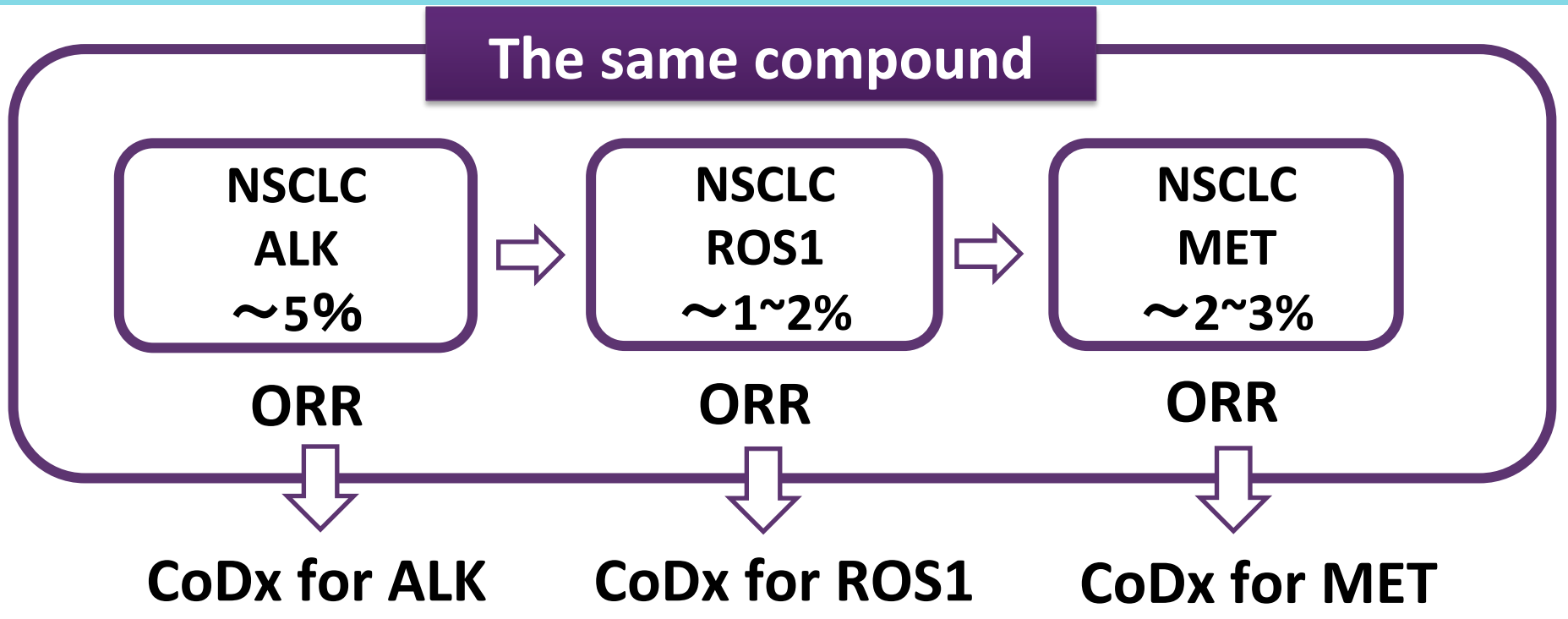
2~3% ⇨ **Under discussion Mixed Model?**

The 3rd PartySponsored:
Investigator initiated clinical trial (IICT) or External funding

Successful factors

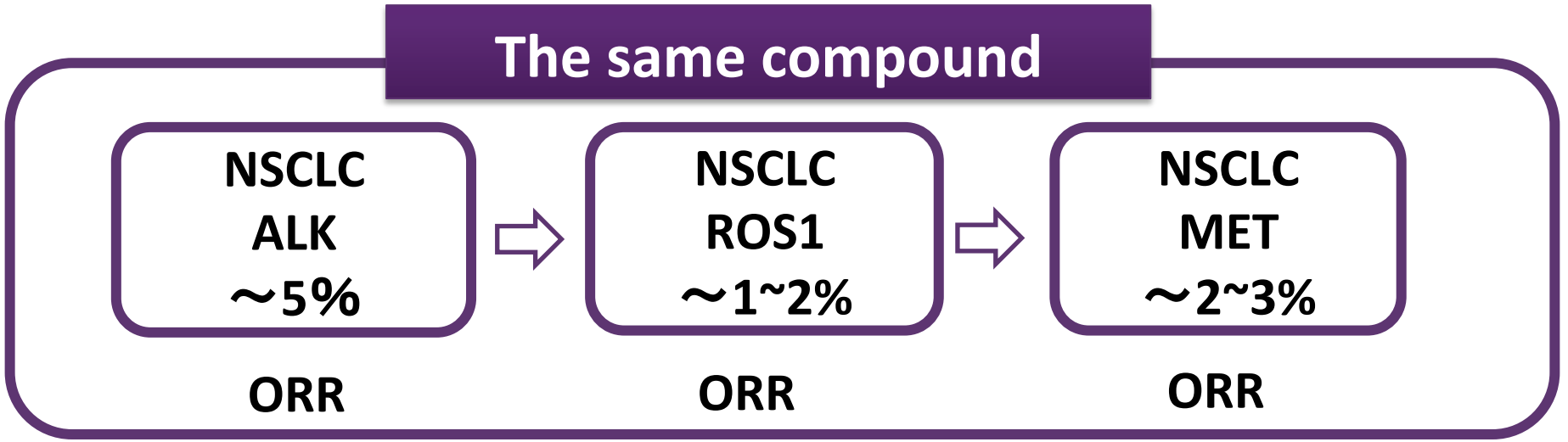
- **Focused on of a particular compound (anchor drug) or in a particular area (home ground)**
- **Efficient drug development strategy was available**
- **Flexible concept drug approval is existed (Pink sheet)**

Efficient drug development strategy



- Large effect size is expected from preclinical data (all targets are “driver gene” , KEY factor)
- ORR can be a primary endpoint
- Basket trial is easily available
- NGS will resolve the issue of multiple CoDx

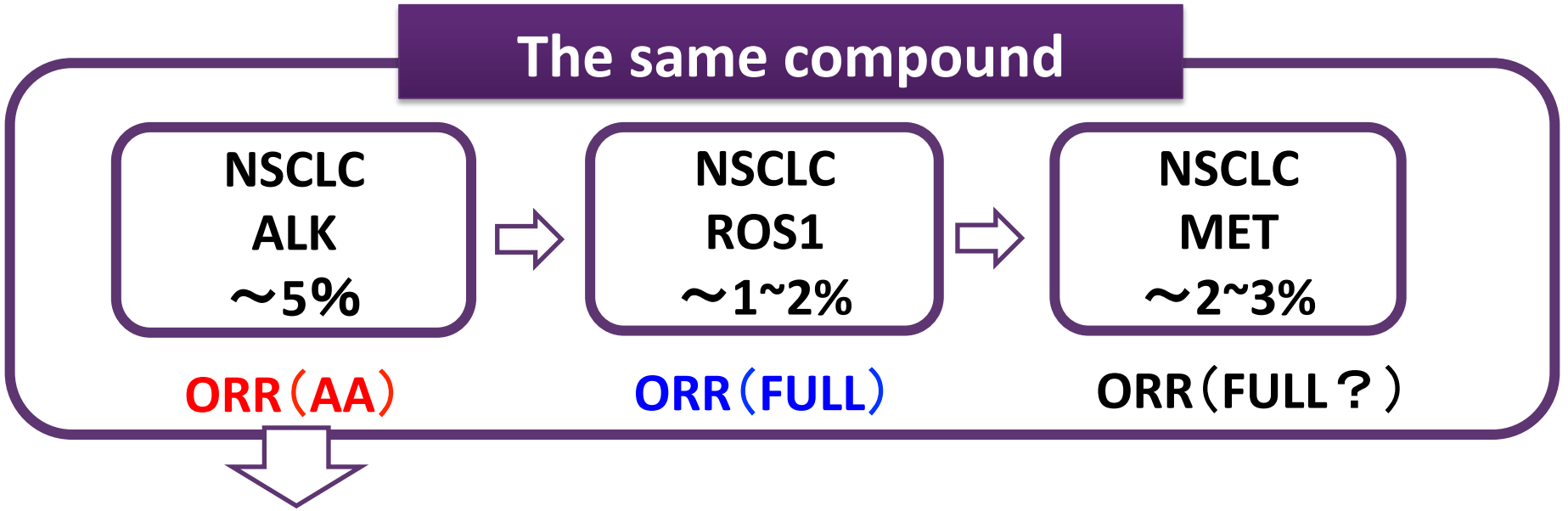
Efficient drug development strategy



- **No randomized trials for each indication are required BEFORE approval**

For while 20% if a population of the patients with a common tumor types may continue to represent a relatively large patient group such that it is realistically possible to conduct " transitional" regulatory agency-mandated randomized trial (M. Maurie et.al. Oncology 2016;91:299-301)

Efficient drug development strategy



Randomized trial G-P3 was required for full approval

- **No randomized trials for each indication are required from 2nd indication**

Flexible drug approval concept in the US

"The Pink Sheet"

The Next Phase In Oncology: FDA's Pazdur Has New Vision For Drug Development

- November 11 2013 12:00 AM

Executive Summary

FDA's top cancer drug reviewer has taken to the podium to paint a picture of the next phase in cancer drug development, which includes new business models, a return to single-arm trials and a new emphasis on safety.

Richard Pazdur: FDA Office of Hematology and Oncology Products Director

Flexible drug approval concept in the US

…So profound that FDA's primary advocate for randomized trials in oncology now acknowledges that **randomized trials may be unnecessary**, if not impossible, given the dramatic response rates shown by some of these targeted agents.

前例のない効果が示された場合は、
必ずしもP3が必要であるとは限らない。
(特に希少の場合)

Flexible drug approval concept in the US

- **Pazdur explained that many cancer patients enroll in randomized trials to cross over to the experimental drug at the time of disease progression. That suggests a "loss of equipoise and clearly the trial should not have been done."**
- **"Single-arm trials do not give us comparative safety data. They give us a snapshot in time of the safety of a particular population or adverse events that occur. But one doesn't know whether these are associated with the drug, one doesn't know whether they are associated with the underlying disease," he explained.**

比較試験はむしろSafety評価として重要となる

→ 最初のIndication（肺がん）でP3が実施され安全性が確認されていていれば，同一癌腫のMutation違いの場合はP3の比較試験は必要がない

Flexible drug approval concept in the US

…FDA could approve **a drug indicated not for a particular type of cancer but for inhibiting a particular molecular pathway**. "There is nothing in the legislation that would prohibit us from approving a drug for inhibiting pathway X or inhibiting pathway Y without any reference to a known established disease here. So that is open, we do have that degree of flexibility."

臓器ごとの承認ではなく標的分子別の適応で承認する可能性もある。

ALCOMAでの適応取得を支持する考え方？

- **If successful factors are exited, drug development for rare fraction cancer can be enhanced and activated**

How about Japan?

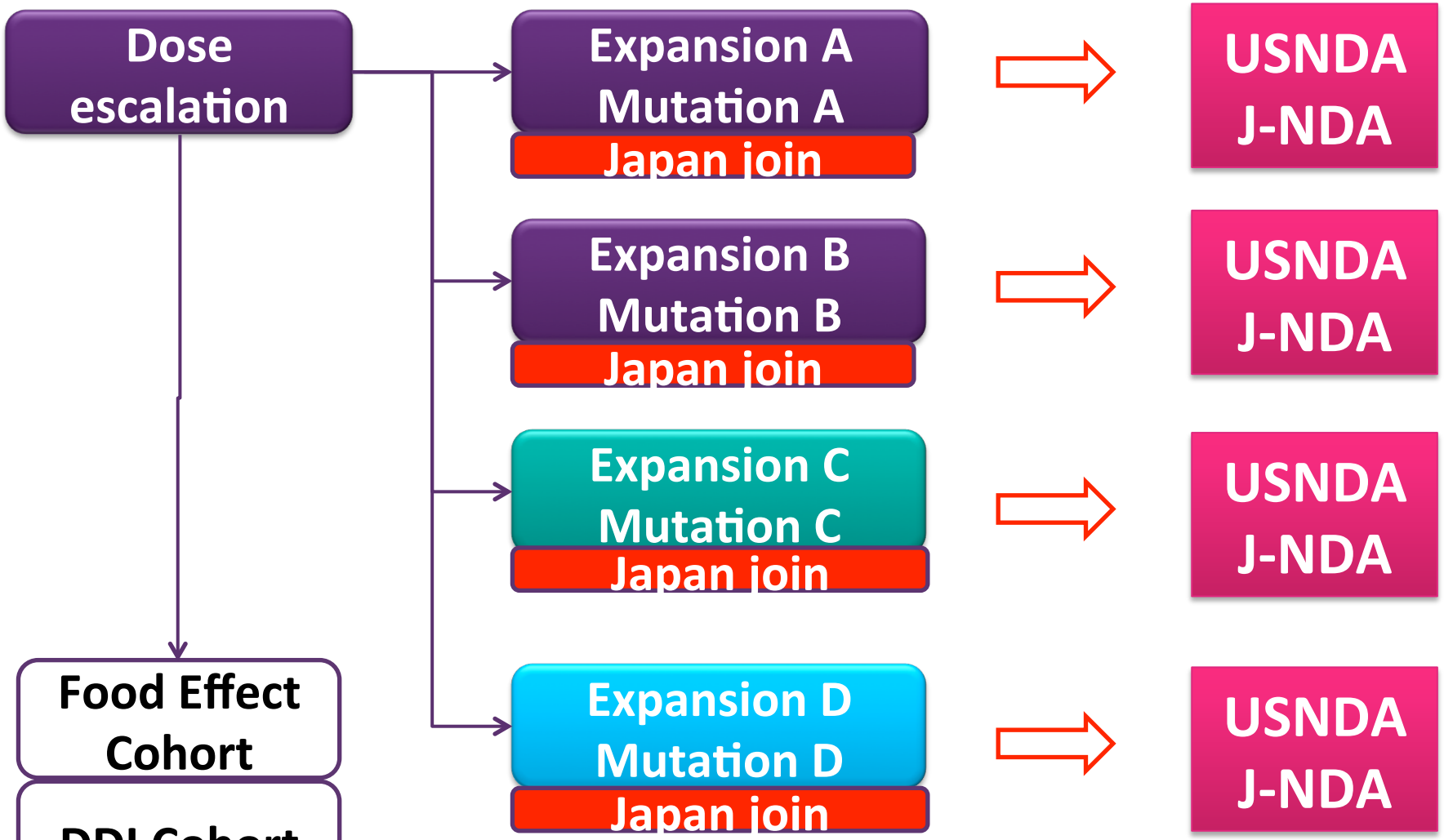
How to establish drug development plan in Japan for rare fraction cancer

Conduct/Participate into basket trial (G-FIH)

vs

Conduct local/regional phase 2 study

Japan participation into basket Trial (G-FIH study)



Pfizer DEVELOPMENT JAPAN
Global Product Development

Points to be considered

- **How to set enough sample size of J-pts for each cohort for JNDA ?**
  - **Need to show consistency between non-Japanese and Japanese on the primary endpoint?**
  - **Additional clinical study is required?**
- **From Japan regulatory perspective, Phase 1 is considered as "for safety"**
  - **Endpoint can be acceptable from Japan regulatory authority?**
- **Can we meet CoDx development (approval and launch)?**

Flexible action in the US for CoDx approval

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

3036-1 Commitment to support the availability, through the use of clinical trial data, of an in-vitro diagnostic device that is essential to the safe and effective use of crizotinib for patients with ROS1 rearrangements in metastatic non-small cell lung cancer (mNSCLC) tumor specimens.

The timetable you submitted on Mar 02, 2016, states that you will support the submission of a Premarket Approval (PMA) Application to FDA/CDRH according to the following schedule:

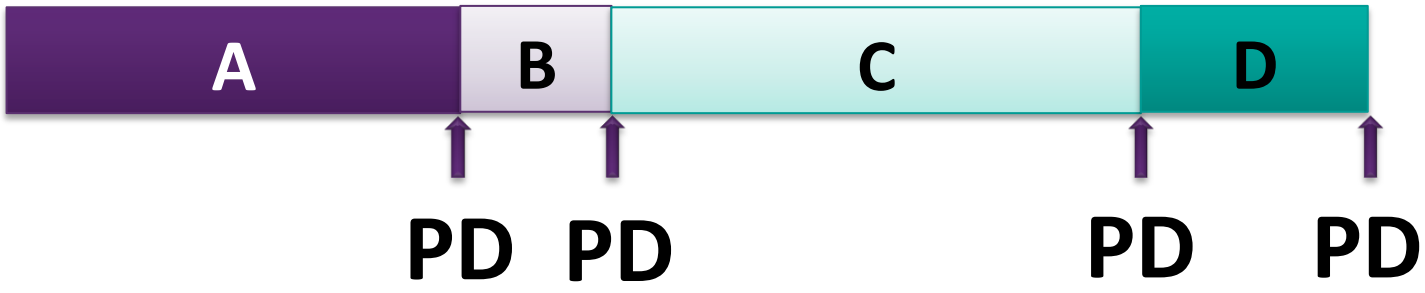
- Final Report Submission: December 2017

http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/202570Orig1s016ltr.pdf

Conduct local/regional phase 2 study(Concept)

In case of rare fraction cancer, "N-of-1 Trial" for rare disease can be applicable if;

- ***a primary endpoint can be ORR***
- ***indication will be obtained regardless of line***



If same approach is used in single arm study, robust data packaged (compared with standard of care) can be obtained

Single arm study having a SOC data at maximum

1	1st Regimen	2nd Regimen	3rd Regimen	4th Regimen
2	1st Regimen	2nd Regimen	3rd Regimen	4th Regimen
3	1st Regimen	2nd Regimen	3rd Regimen	4th Regimen
4	1st Regimen	2nd Regimen	3rd Regimen	4th Regimen
5	1st Regimen	2nd Regimen	3rd Regimen	4th Regimen
6	1st Regimen	2nd Regimen	3rd Regimen	4th Regimen
7	1st Regimen	2nd Regimen	3rd Regimen	4th Regimen

	1st regimen	2nd regimen	3rd regimen	4th regimen
SOC	50%	40%	30%	20%
治験薬	70%	60%	70%	60%

Points to be considered

- The regulatory success rate might be higher than joining basket trial
  - Robust data packages can be obtained such, including a certain level of SOC data
- Drug lag must be existed
- Difficult to get endorsement for an additional regional study

(Mitigation plan)

  - Then the 3rd party collaboration (IICT or external funding) will be effectively used
  - If SOC data can be obtained from real world data (both safety and efficacy), the sample size can be minimized

Summary

- In global perspective, drug development for rare fraction cancer can be enhanced and activated, if successful factors are exited
  - Efficient drug development strategy is available
  - Flexible concept drug approval is existed (Pink sheet)
- On the other hand, still some difficulties are existed in Japan
  - Less experiences of the 3rd party collaboration
  - Regulatory path for clinical development of rare fraction cancer has not been established yet
- Japan requires a regulatory scheme for drug development/approval for rare fraction cancer
  - Flexibility for both drug and CoDx approvals
  - Additional regulatory value
    - NOTE: Current SAKIGAKE is not applicable for LCM (Expansion of indication).
  - Effective use of real world data (using patient registry initiative)