efpia

European Federation of Pharmaceutical Industries and Associations

イノベーティブな治験デザインによる希少フラクションの開発

中外製薬株式会社
林　盛彦

Today's contents

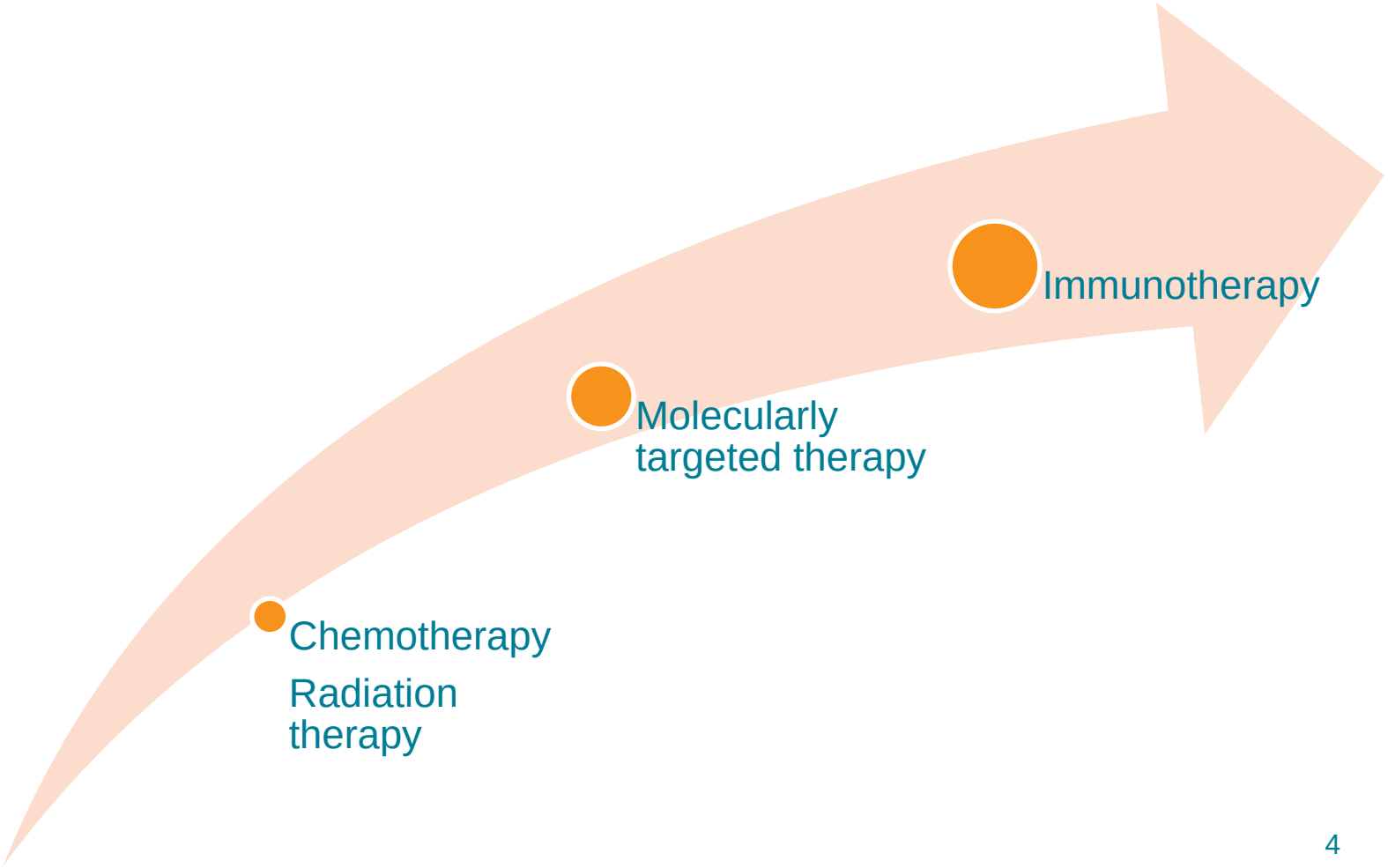
- Background of growing demand of innovative study design
- An example of umbrella trial ~BFAST~
- An example of basket trial ~STARTRK-2~
- Challenges in innovative study

Background of growing demand of innovative study design

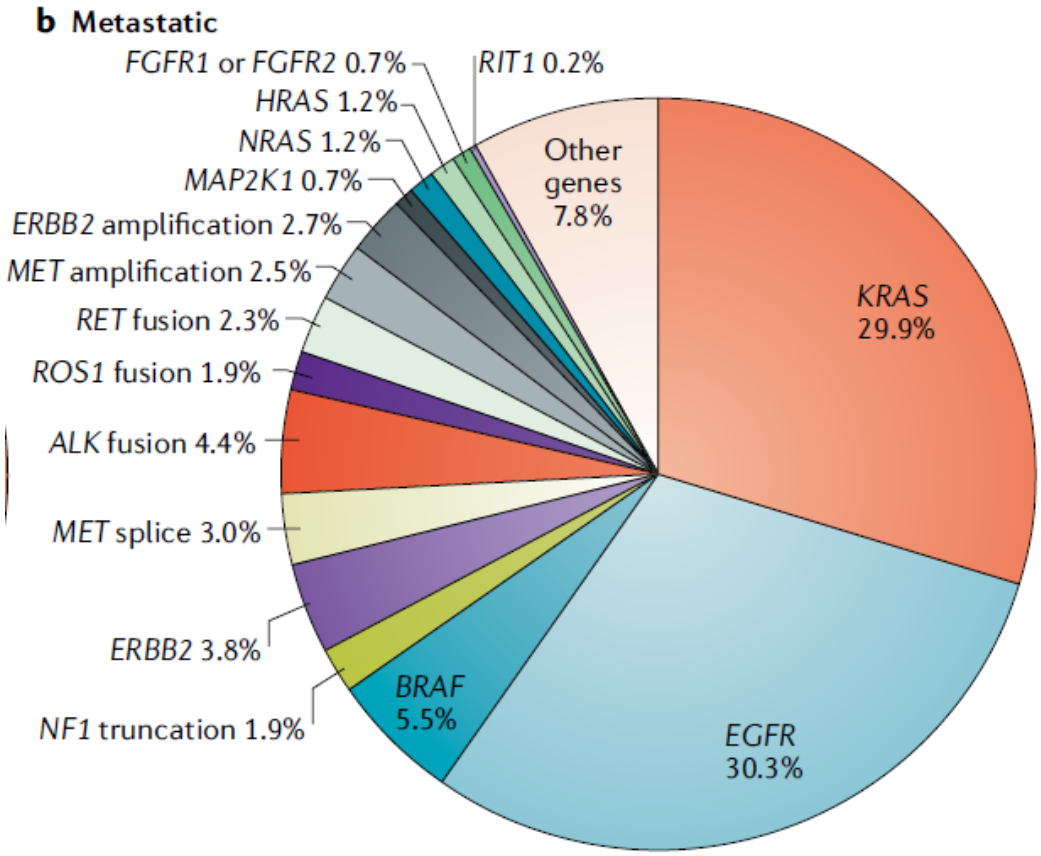
- Appearance of molecularly targeted drugs
- Appearance of cancer genome profile tests
- Growing possibility in developing multiple drugs and/or with multiple cancer subpopulations in parallel under single protocol

Appearance of molecularly targeted drugs

Molecularly targeted therapy is expected to have higher efficacy and have fewer side effects than other types of cancer treatment in specific cancer fraction



Molecular Targets in NSCLC

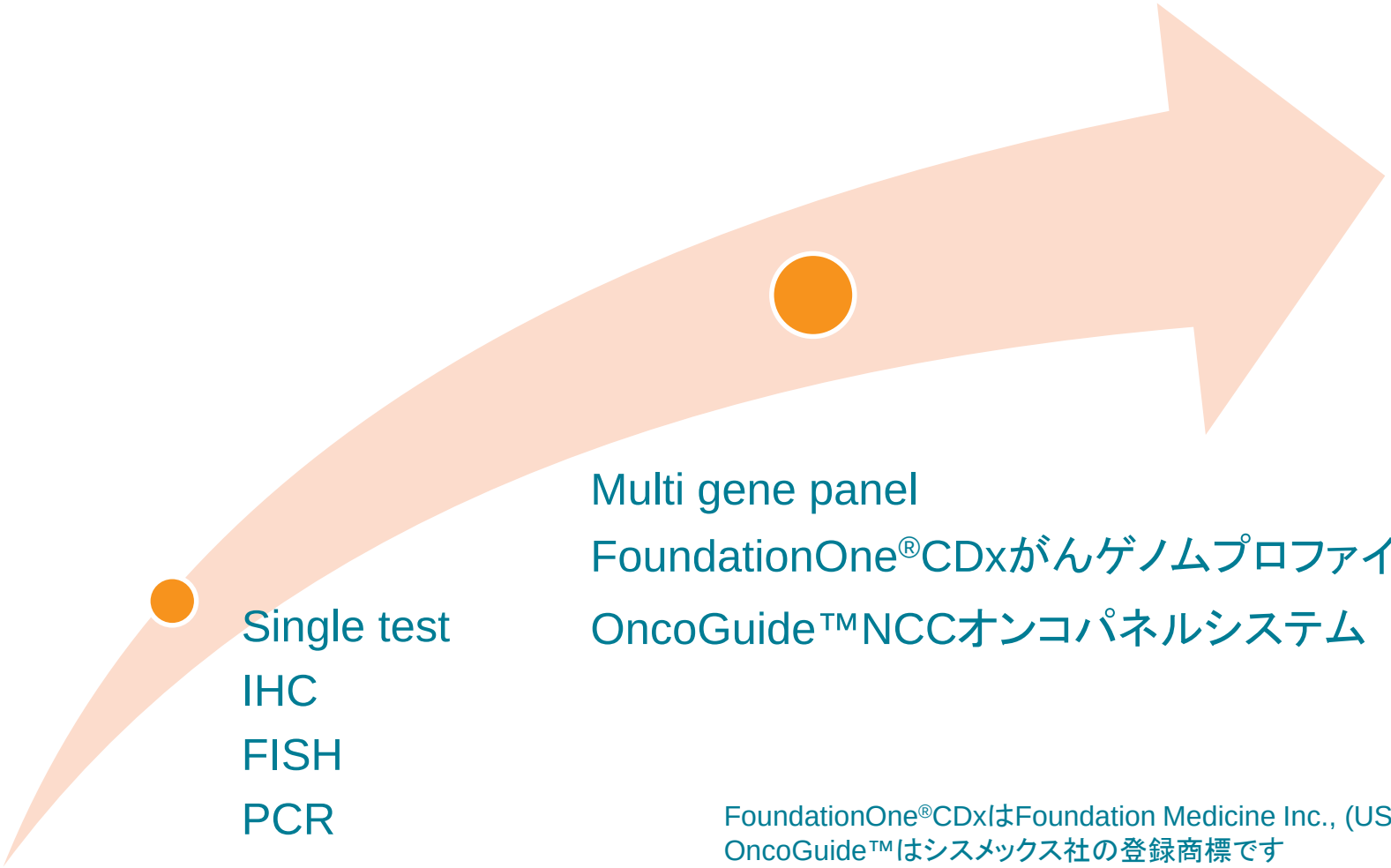


Approved molecularly targeted drugs in NSCLC

- EGFR inhibitors
- ALK inhibitors
- ROS1 inhibitors
- BRAF V600 E inhibitors
- NTRK inhibitors
- MET Ex 14 inhibitors

Nat Rev Cancer 2019;19:495-509

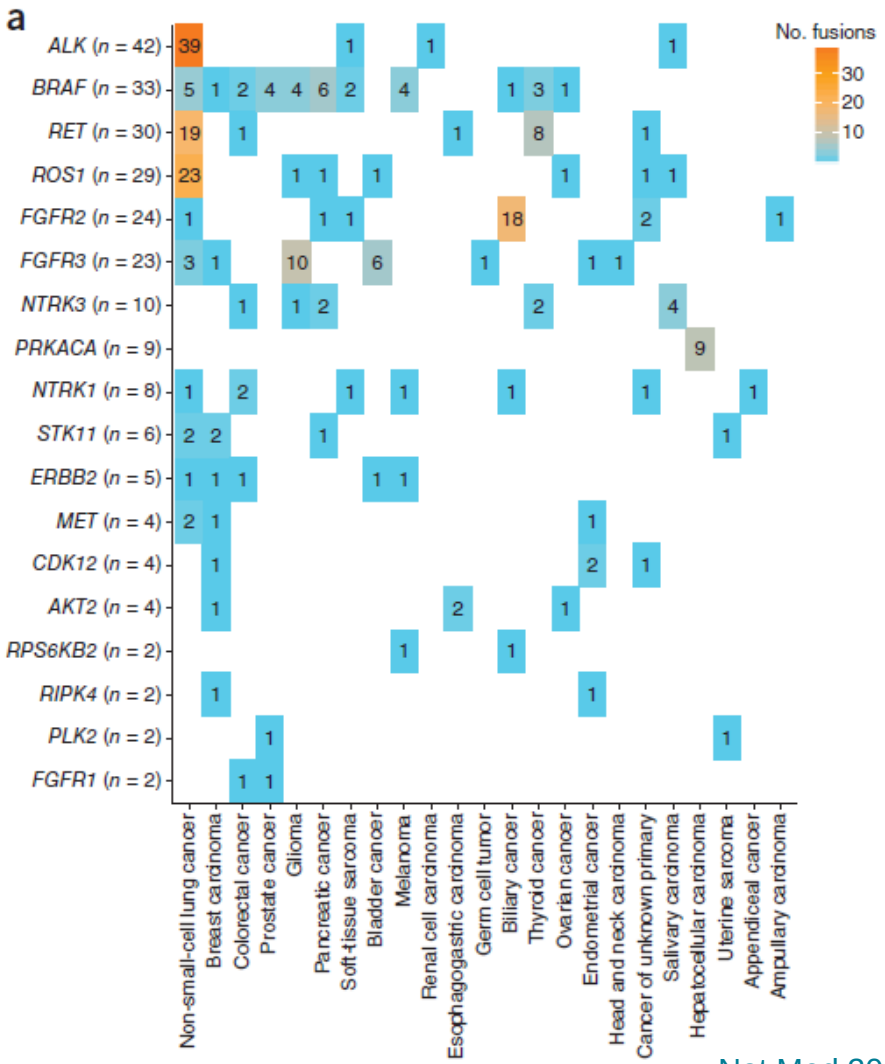
Appearance of cancer genome profile tests



FoundationOne®CDxはFoundation Medicine Inc., (USA)の登録商標,
OncoGuide™はシスメックス社の登録商標です

Kinase fusion across tumor types

It has become apparent that gene mutations are shown across tumor types

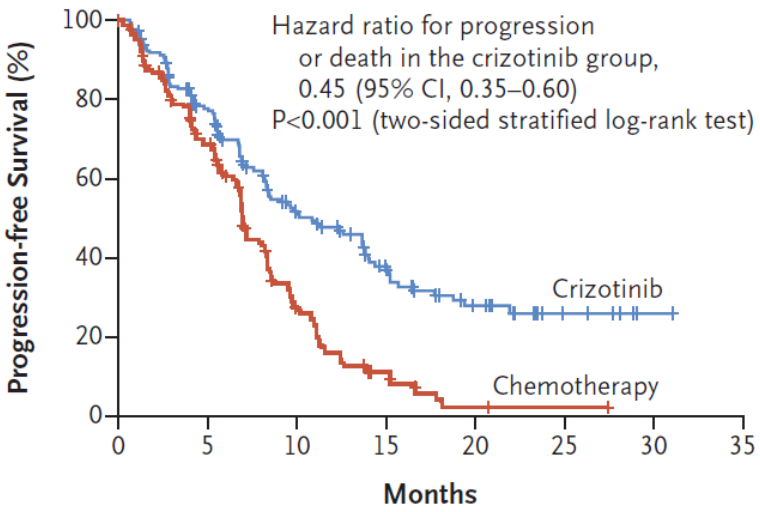


Nat Med 2017;23(6);703-713

Challenges in developing therapies against rare fraction

- Difficulties in
  - Enrolling patients
  - Conducting randomized trials

CRZ vs Chemo in ALK+ NSCLC

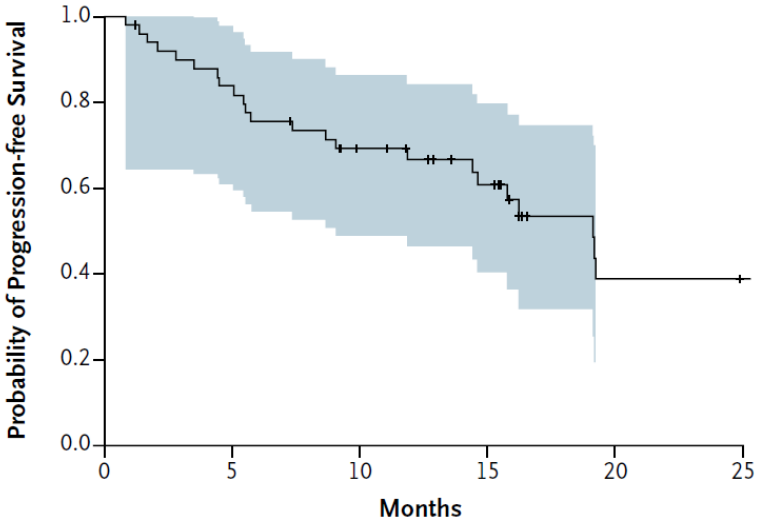


No. at Risk								
Crizotinib	172	120	65	38	19	7	1	0
Chemotherapy	171	105	36	12	2	1	0	0

(n=343)

N Engl J Med 2014; 371:2167-2177

CRZ in ROS1+ NSCLC



No. at Risk						
Crizotinib	50	41	30	21	8	7

(n=50)

N Engl J Med 2014; 371:1963-1971

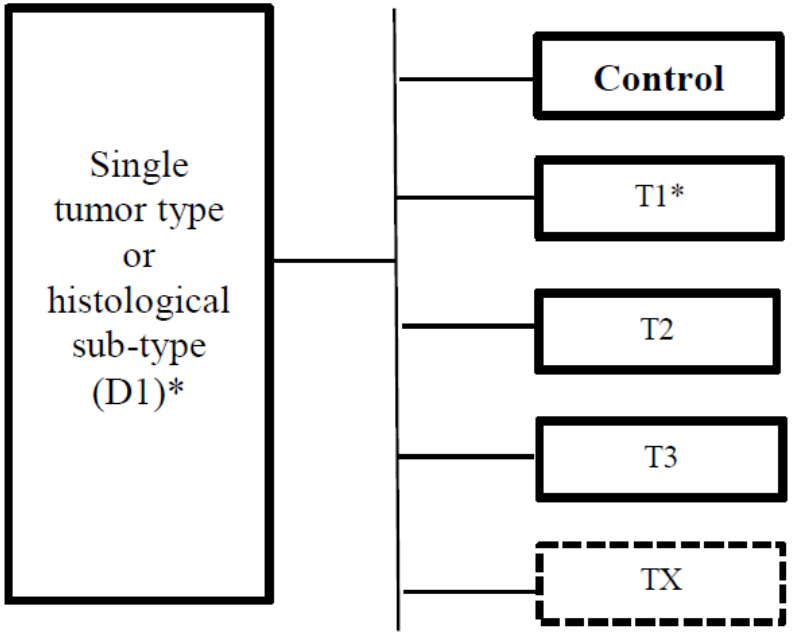
Master protocol

- Definition
  - A protocol designed with multiple substudies, which may have different objectives and involves coordinated efforts to evaluate one or more investigational drugs in one or more disease subtypes within the overall trial structure.
- Advantage
  - Flexibility and efficiency in drug development
- Examples
  - Umbrella
  - Basket

FDA draft guidance. Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics Guidance for Industry, 2018 Sep.

Umbrella trial design

Umbrella trial design is designed to evaluate multiple investigational drugs in a single disease population

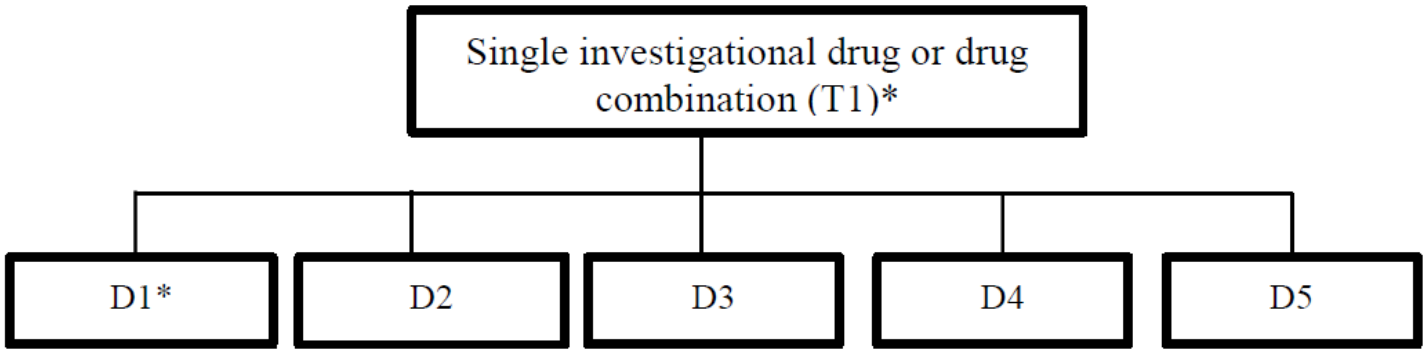


* T = investigational drug; D = protocol defined subpopulation in single disease subtypes; TX = dotted border depicts future treatment arm.

FDA draft guidance. Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics Guidance for Industry, 2018 Sep.

Basket trial design

Basket trial design is designed to test a single investigational drug in different populations



* T = investigational drug; D = protocol defined subpopulation in multiple disease subtypes.

FDA draft guidance. Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics Guidance for Industry, 2018 Sep.

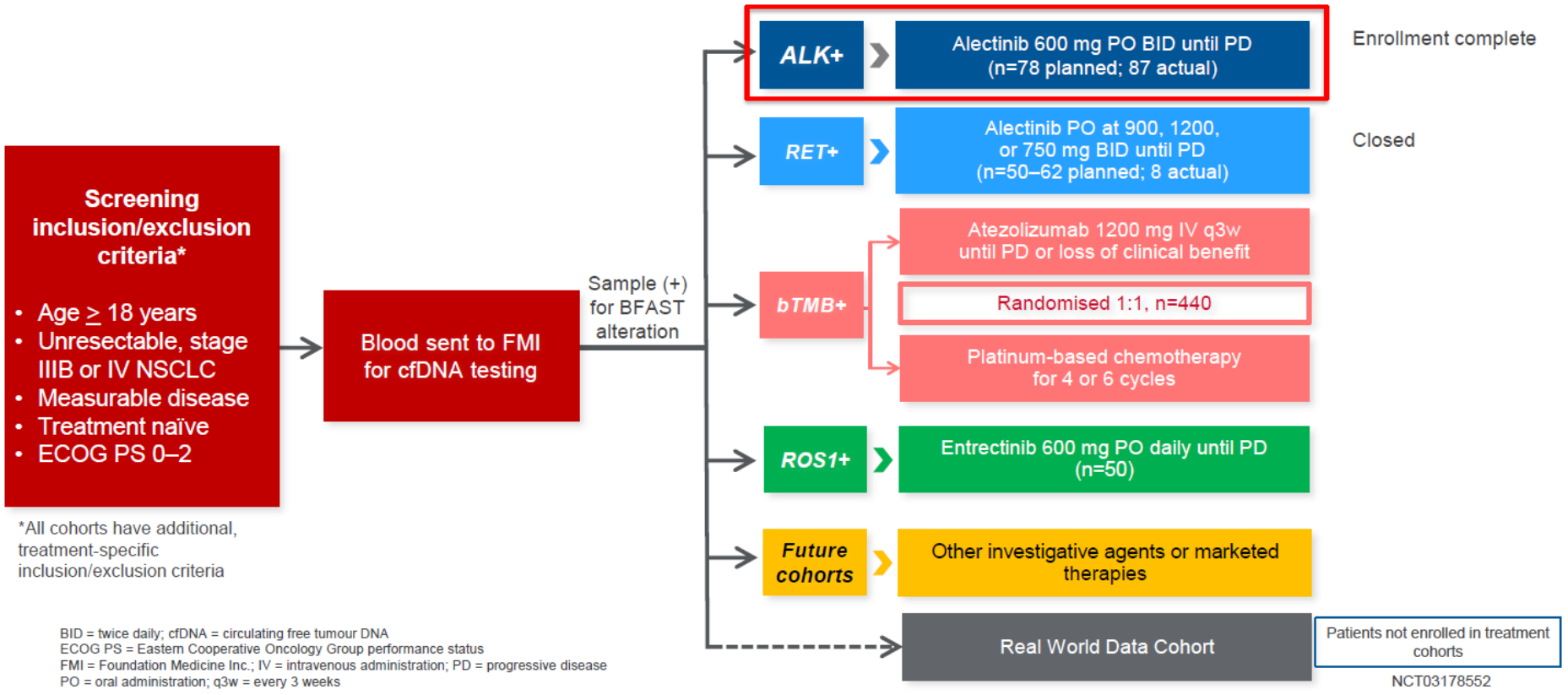
Example of umbrella trial BFAST study design

Umbrella Study

Global phase II/III, multi-cohort study in patients with treatment-naïve advanced/metastatic NSCLC

BARCELONA 2019 ESMO congress

Study design



Shirish M. et al. ESMO 2019

BFAST ALK+ cohort design

Umbrella Study

Goal

Demonstrate consistency of benefit with alectinib in a population selected by blood-based NGS as opposed to tissue-based assay, using ALEX alectinib data as reference

- **Unresectable, stage IIIB or IV NSCLC**
- ***ALK*+ by centralised blood screening only**
- **Treatment naïve**
- **ECOG PS 0–2**

→ **Alectinib 600mg BID** → **Until PD, toxicity, withdrawal or death**

Primary endpoint
Confirmed ORR by investigator

Exploratory endpoint
Confirmed ORR by investigator for patients with baseline CNS metastases

Secondary endpoints

By investigator	By independent review facility
DoR	ORR
PFS	DoR
	PFS

CNS = central nervous system; DoR = duration of response
ORR = overall response rate; PD = disease progression; PFS = progression-free survival
ECOG PS = Eastern Cooperative Oncology Group performance status; NGS = next generation sequencing

NCT03178552

Shirish M. et al. ESMO 2019

What is Entrectinib?

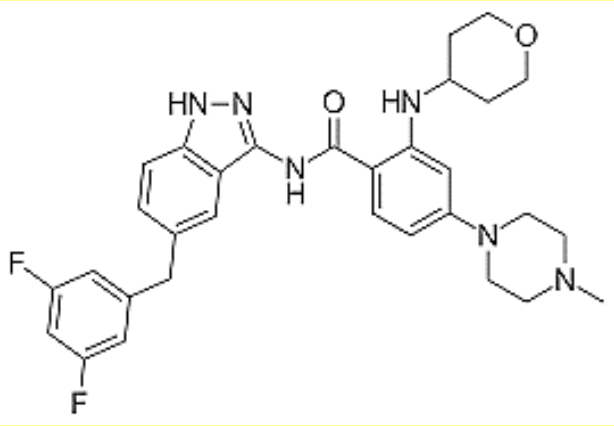
Basket Study

Generic name： Entrectinib

Targets： ROS1 kinase
TRK proteins
（TRKA, TRKB, TRKC）

Indications：

TRK: *NTRK* fusion positive solid tumors
ROS1: *ROS1* fusion positive NSCLC



Entrectinib is an oral, potent and selective inhibitor of TRK proteins and ROS1 tyrosine kinases

Gene		Protein
NTRK1	=	TRKA
NTRK2	=	TRKB
NTRK3	=	TRKC

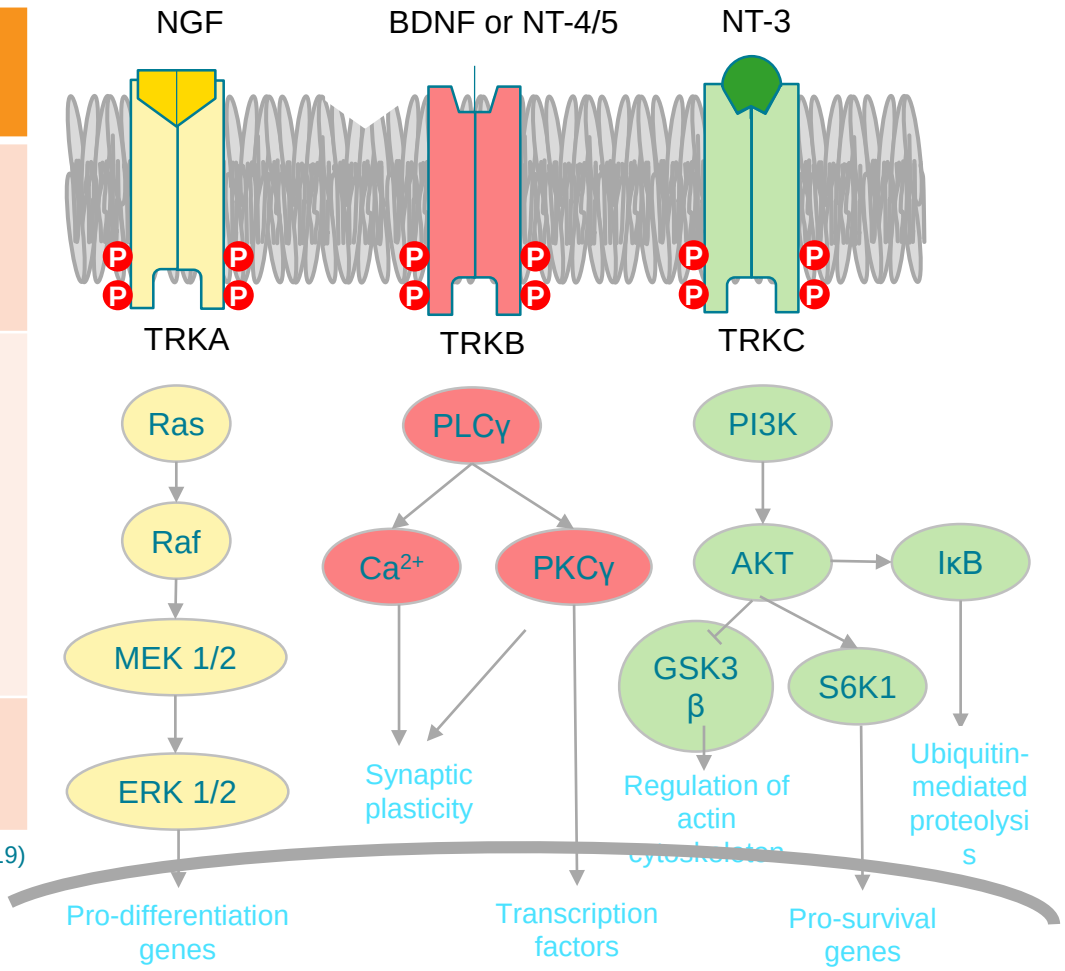
TRK（Tropomyosin receptor kinase）
ROS1（c-ros proto-oncogene 1）

Physiologic function and signal transduction of TRK receptors

Basket Study

Receptor (Gene)	Function
TRKA (*NTRK1*)	Pain Thermoregulation
TRKB (*NTRK2*)	Movement Memory Cognition Mood Appetite Body weight
TRKC (*NTRK3*)	Proprioception

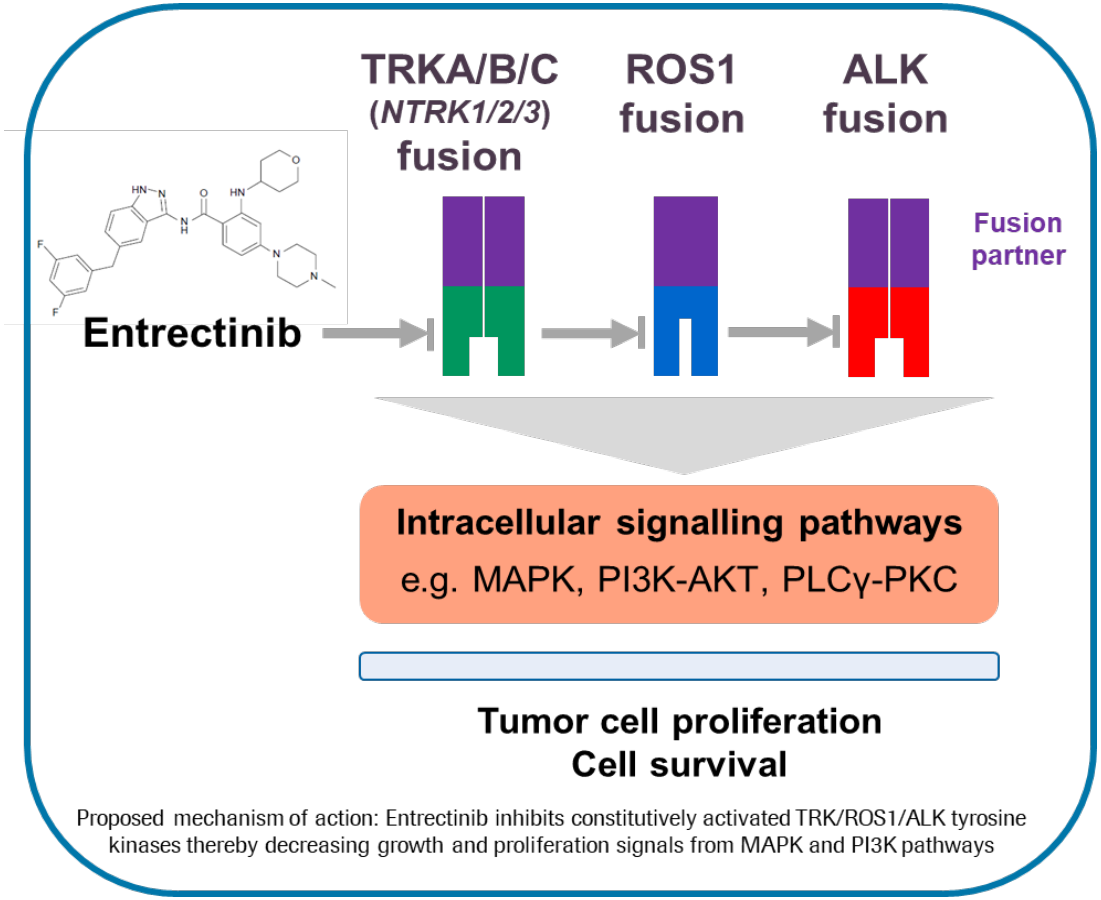
Pathology-reseach and practice 215 (2019)



ESMO 2018

Tumor cell proliferation by *NTRK* fusion gene

Basket Study

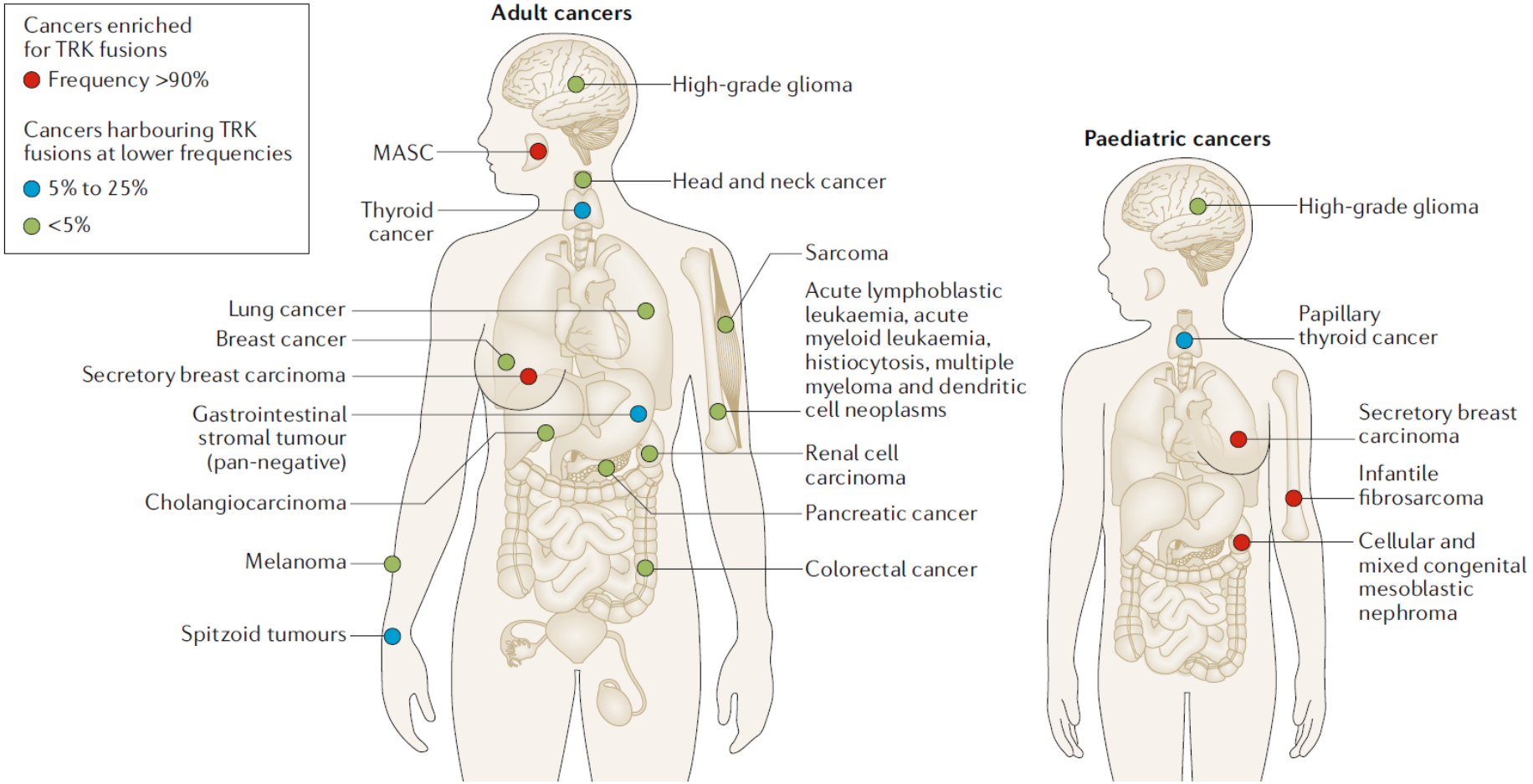


Robinson GW et al. ISPNO 2020.

Distribution and frequency of NTRK fusion positive tumors

Basket Study

High frequencies in rare cancers, low frequencies in common tumors



Nat Rev Clin Oncol. (2018)

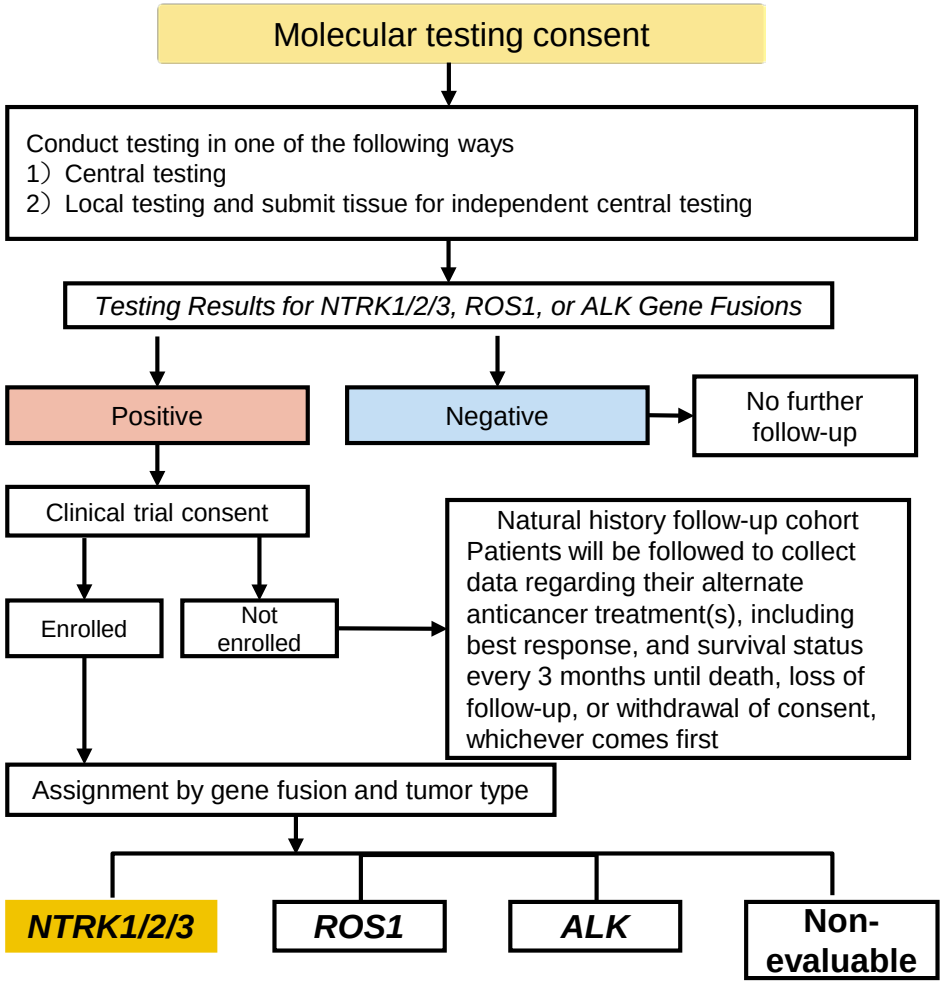
STARTRK-2 study
（An open-label, multicenter, global Phase II Basket study）

Basket Study

An open-label, multicenter, global phase 2 basket study of Entrectinib for the treatment of patients with locally advanced or metastatic solid tumors that harbor *NTRK1/2/3, ROS1, or ALK* gene reaarangements

- **Primary endpoint**
  - ORR by BICR
- **Secondary endpoints**
  - CBR, DOR
    PFS, OS
    Intracranial (IC)-ORR, IC-PFS etc.

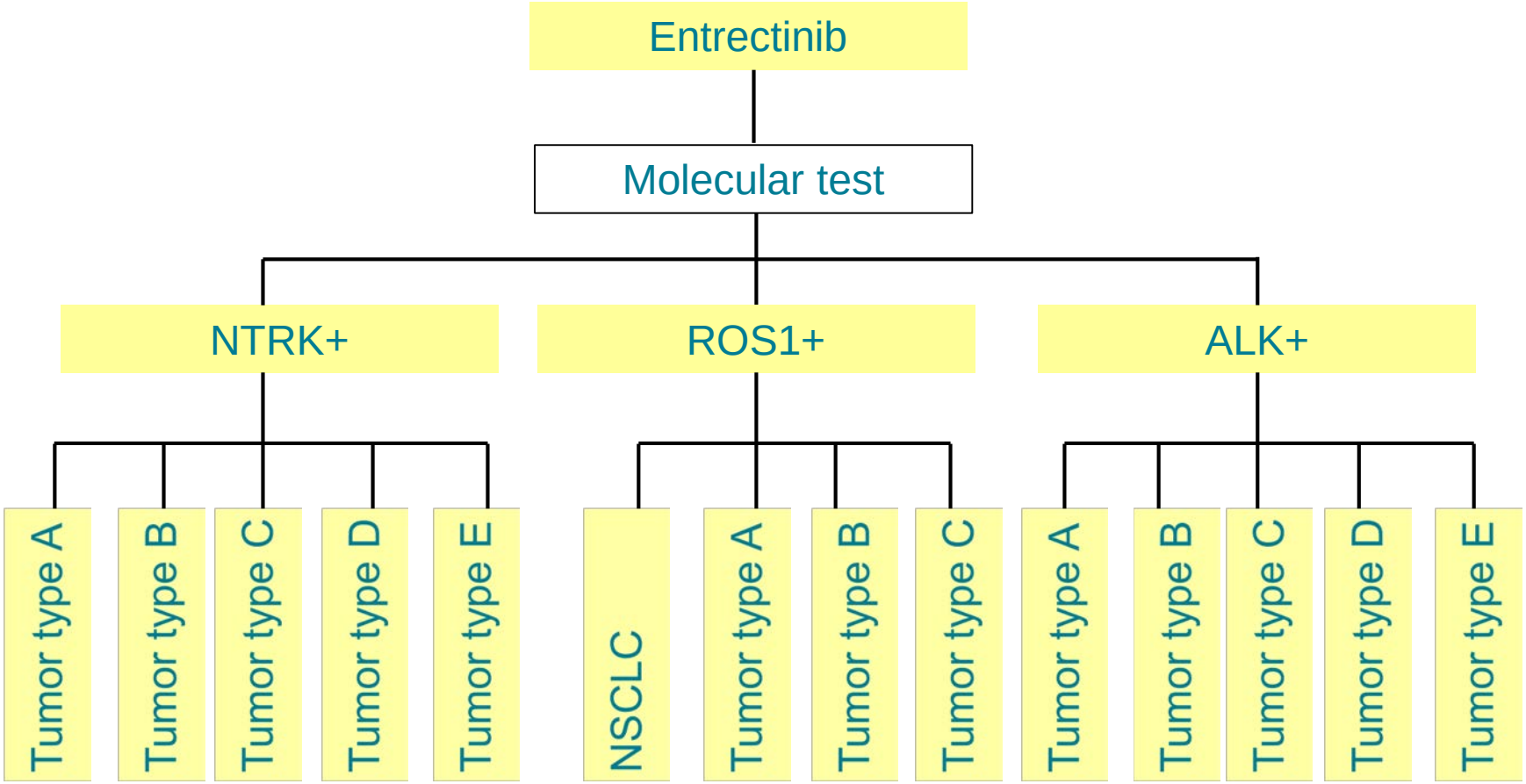
    Subgroup analysis of patients with brain metastasis at baseline and tumor types was preplanned
- **Analysis population**
  - *NTRK* efficacy analysis population：
    51 adult patients with NTRK fusion-positive, TRK inhibitor-naïve solid tumors
  - Safety analysis population：
    206 patients overall have received Entrectinib (all tumor types and gene rearrangements)
- **Methods**
  - 600 mg QD, 28-day cycle
  - Study treatment until PD by BICR, unacceptable toxicity or withdrawal of consent



CTD

STARTRK-2 study
Multi basket trial

Basket Study



STARTRK-2
Primary enrollment (except for ROS1 fusion positive NSCLC)

Basket Study

- Patients were enrolled under a 2-stage sequential testing design
- Threshold ORR: 20%
- Expected ORR: 40%
- 1st stage
  - Enroll up to 13 patients per basket
  - Patients are enrolled sequentially and the stage is deemed successful on the 4th responder
  - If the first stage is not successful, then enrollment in that basket will be terminated
- 2nd stage
  - Up to an additional 49 patients will be enrolled into the second stage

STARTRK-2
Primary enrollment (ROS1 fusion positive NSCLC)

Basket Study

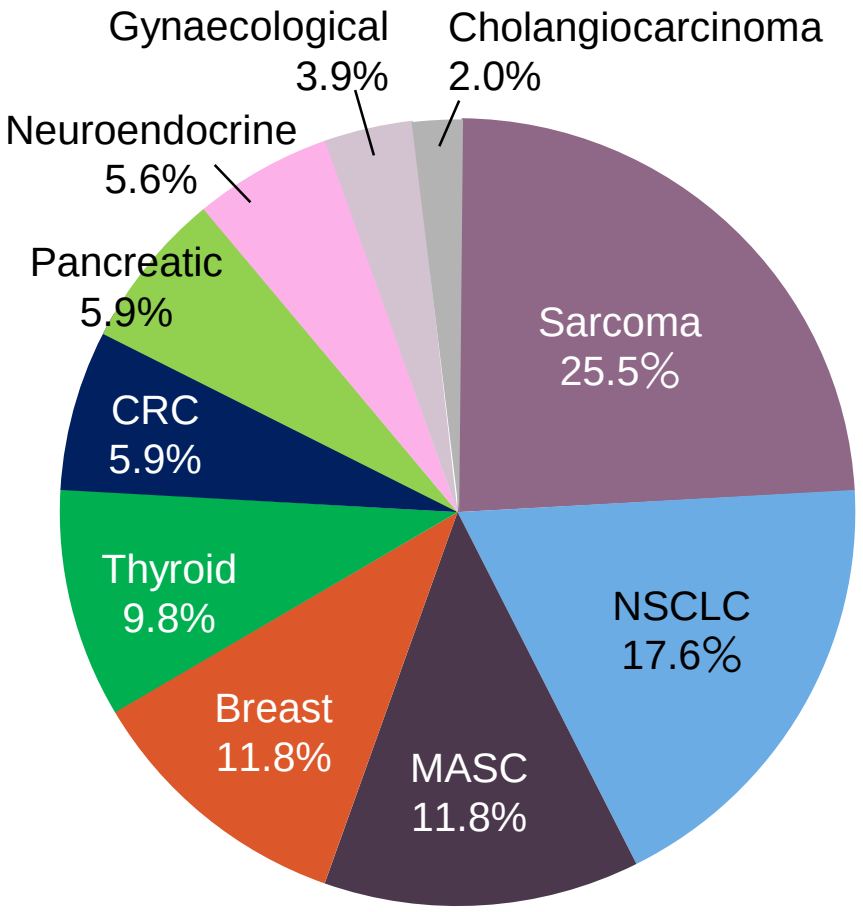
- Part A: the same as except for ROS1 fusion positive NSCLC
- Part B: set based on crizotinib clinical data
  - Threshold ORR: 50%
  - Expected ORR: 65%
  - Up to an additional 90 patients will be enrolled

Baseline characteristics (NTRK efficacy analysis population)

Basket Study

Tumor types

n（%）	*NTRK* efficacy analysis population（n=51）
Sarcoma	13（25.5%）
NSCLC	9（17.6%）
MASC	6（11.8%）
Breast	6（11.8%）
Thyroid	5（9.8%）
CRC	3（5.9%）
Pancreatic	3（5.9%）
Neuroendocrine	3（5.9%）
Gynaecological*	2（3.9%）
Cholangiocarcinoma	1（2.0%）



*ovarian and endometrioid carcinoma

Data cut off date: 31 May 2018

CRC: colorectal cancer
MASC: mammary analogue secretory carcinoma
NSCLC: non-small cell lung cancer

ORR and best overall response by BICR (NTRK efficacy analysis population)

Basket Study

ORR and best overall response （n=51）

	N	%
ORR [95%CI]	29	56.9% [42.3,70.7]
CR	4	7.8%
PR	25	49.0%
SD	9	17.6%
PD	3	5.9%
Non CR/PD	3	5.9%
Missing or unevaluable	7	13.7%

ORR by tumor types（n=51）

Tumor types	Responders/n	ORR (%)
Sarcoma	6/13	46.2%
NSCLC	6/9	66.7%
Breast	5/6	83.3%
MASC	5/6	83.3%
Thyroid	1/5	20.0%
CRC	1/3	33.3%
Neuroendocrine	1/3	33.3%
Pancreatic	2/3	66.7%
Gynaecological	1/2	50.0%
Cholangiocarcinoma	1/1	100.0%

Data cut off date: 31 May 2018

ORR and best overall response by BICR (ROS1 efficacy analysis population)

Basket Study

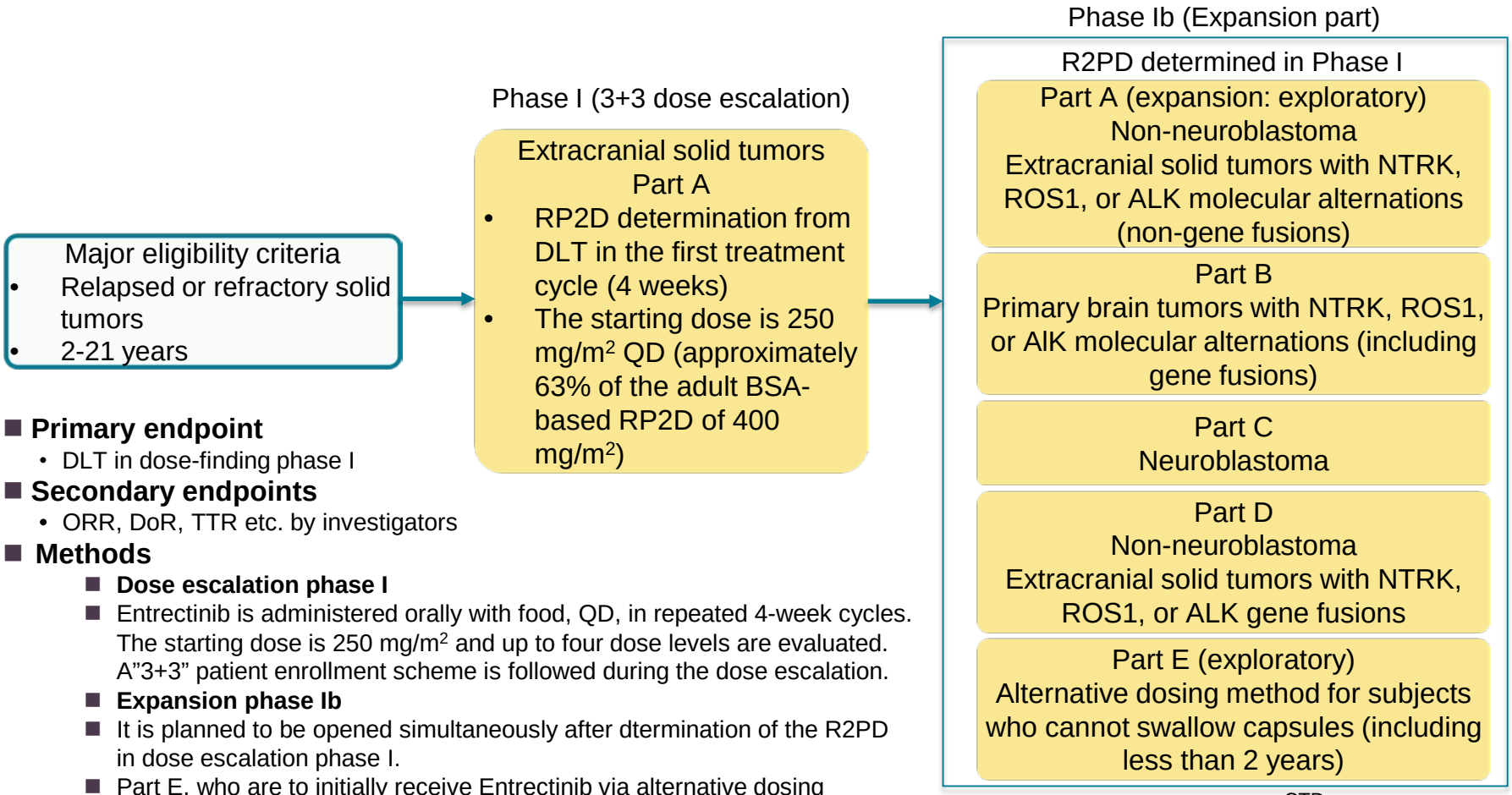
ORR and best overall response （n=33）

	N	%
ORR [95%CI]	25	75.8% [57.7,88.9]
CR	1	3.0%
PR	24	72.7%
SD	0	-
PD	2	6.1%
Non CR/PD	3	9.1%
Missing or unevaluable	3	9.1%

STARTRK-NG study
（An open-label, multicenter, global Phase I/Ib study）

Basket Study

A phase 1/2, open-label, dose-escalation and expansion study of Entrectinib in children and adolescents with no curative first-line treatment option, recurrent or refractory solid tumors and primary CNS tumors, with or without TRK, ROS1, or ALK fusions



- **Primary endpoint**
  - DLT in dose-finding phase I
- **Secondary endpoints**
  - ORR, DoR, TTR etc. by investigators
- **Methods**
  - **Dose escalation phase I**
  - Entrectinib is administered orally with food, QD, in repeated 4-week cycles. The starting dose is 250 mg/m^2 and up to four dose levels are evaluated. A"3+3" patient enrollment scheme is followed during the dose escalation.
  - **Expansion phase Ib**
  - It is planned to be opened simultaneously after dtermination of the R2PD in dose escalation phase I.
  - Part E, who are to initially receive Entrectinib via alternative dosing methods at a-1 dose level de-escalation from the RP2D.

Results of STARTRK-NG

Basket Study

- DLT
  - The 550 mg/m^2 dose level was determined as MTD and was selected as RP2D
    - Three patients experienced DLTs at 750 mg/m^2
    - One patient experienced a DLT at 550 mg/m^2

Part	Age (y)	Tumor type	Dose (mg/m^2)	BoR*	DoR* (months)	TTR (months)
A	4	Infantile fibrosarcoma	750	PR	9.1	1.91
B	3	Epitheliod glioblastoma	550	CR	3.94**	1.91
E	4	High grade glioma	400	PR	6.47**	1.91
E	4	Malignant melanoma	400	PR	6.47**	1.87
E	4.5 m	Infantile fibrosarcoma	400	SD	-**	-

*: Evaluated by investigators based on RECIST ver. 1.1 except for epitheliod glioblastoma and high grade glioma

Data cut off date: 31 Oct 2018

**: On treatment at data cut of date

Operational challenges in innovative study

- Challenges
  - Common
    - Low screening hit rate (dependent on number of cohorts and prevalence of each cohorts)
    - Possibility of low number of screening (dependent on screening hit rate)
    - Contract extension with CRO by adding cohort
    - No standardized contractual or cost estimating method at sites
    - Different policy applied per site for disclosure of genetic information from screening test to patients

Operational challenges in innovative study (Cont'd)

- Challenges
  - Umbrella trial
    - Required many CTNs
    - Management of larger volume of safety information than conventional trials
  - Basket trial
    - Selection of principal investigator
    - Search for potential patients in each site

Regulatory challenges in innovative study

- Challenges
  - Limited number of patients to evaluate efficacy and safety
  - No control arm

- Solution
  - Post marketing survey, PMR
  - RWD, registry

Summary

- Innovative study design is in a growing demand for developing investigational drugs for rare cancer or rare fraction
- Entrectinib was successfully approved by the results from a basket trial for indications of NTRK+ solid tumor and ROS1+ NSCLC
- There are still some challenges to solve regarding studies applying innovative design