2019年3月8日
がんゲノム医療Young Summit

がんゲノム医療“Tumor agnostic”

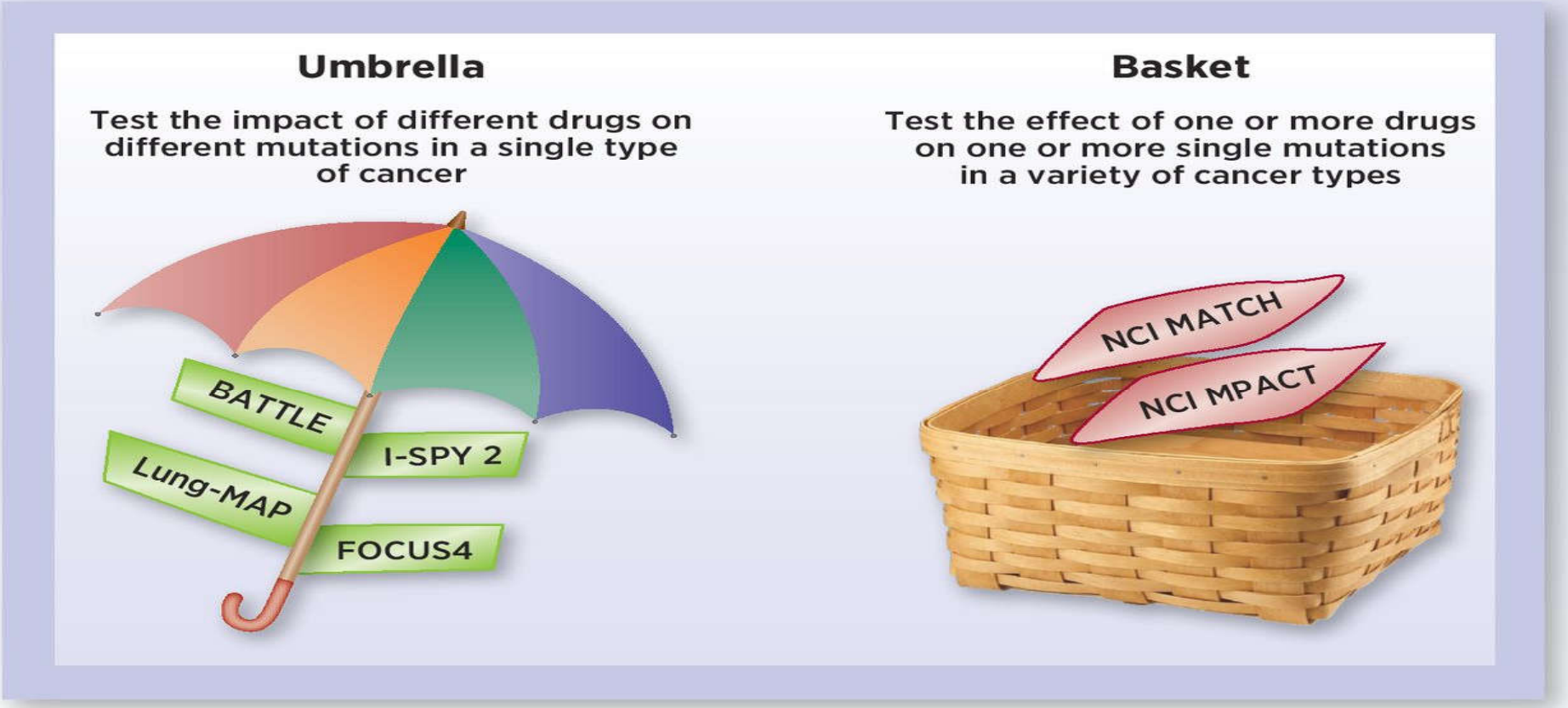
国立がん研究センター東病院
消化管内科　谷口浩也

分子標的治療薬（IOを含む）の登場

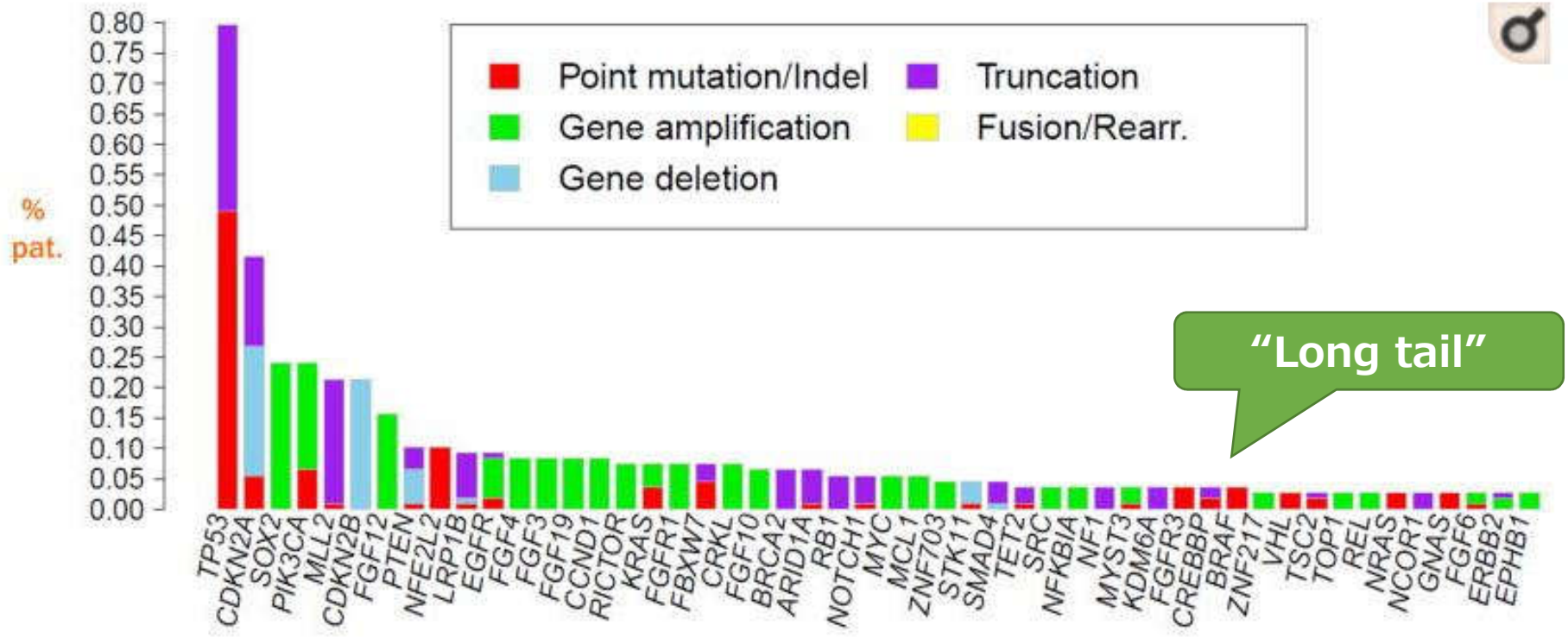
	殺細胞性抗がん剤	分子標的治療薬
Mode of Action	腫瘍に広く作用	特定の分子異常を持つ 腫瘍細胞
第I相試験の目的	推奨用量の決定 有害事象確認	推奨用量の決定 探索的な抗腫瘍効果
推奨用量	用量制限毒性	PK/PDや効果も
第I相試験デザイン	3+3	Basket, Umbrella等
次相試験デザイン	臓器別Phase2試験	治療標的別Phase 2
ゴール	Phase3試験 ⇒承認	Signal finding Fast track

Calvo E, et al 2017 ASCO 改変

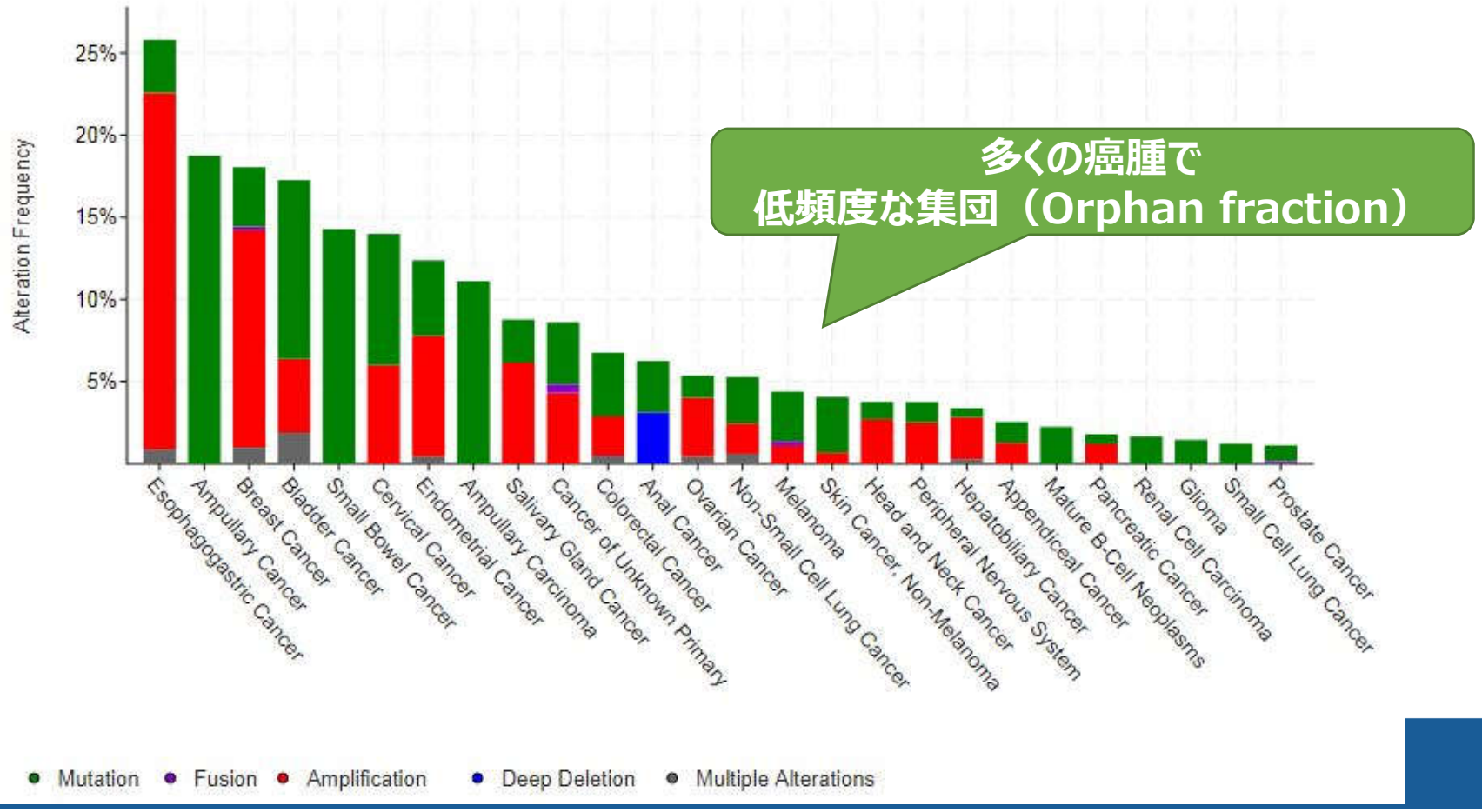
臨床開発デザインの変化



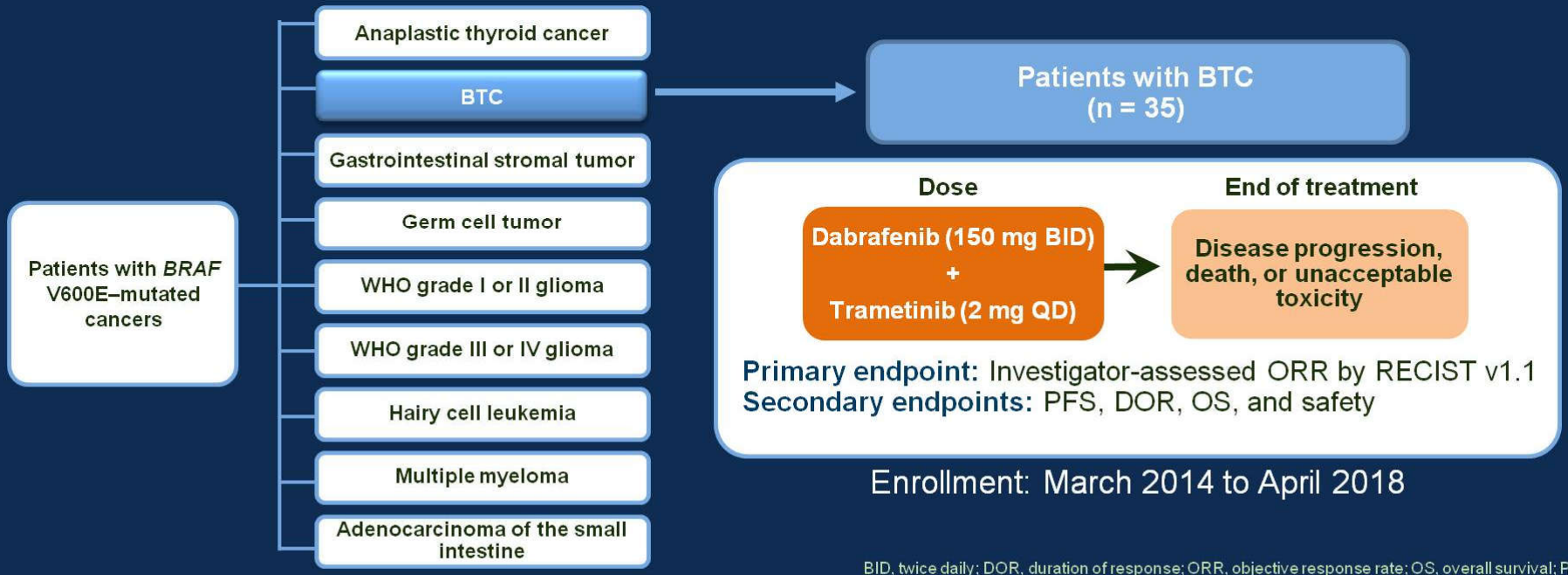
小細胞肺癌の遺伝子異常



癌種別ERBB2遺伝子異常の頻度

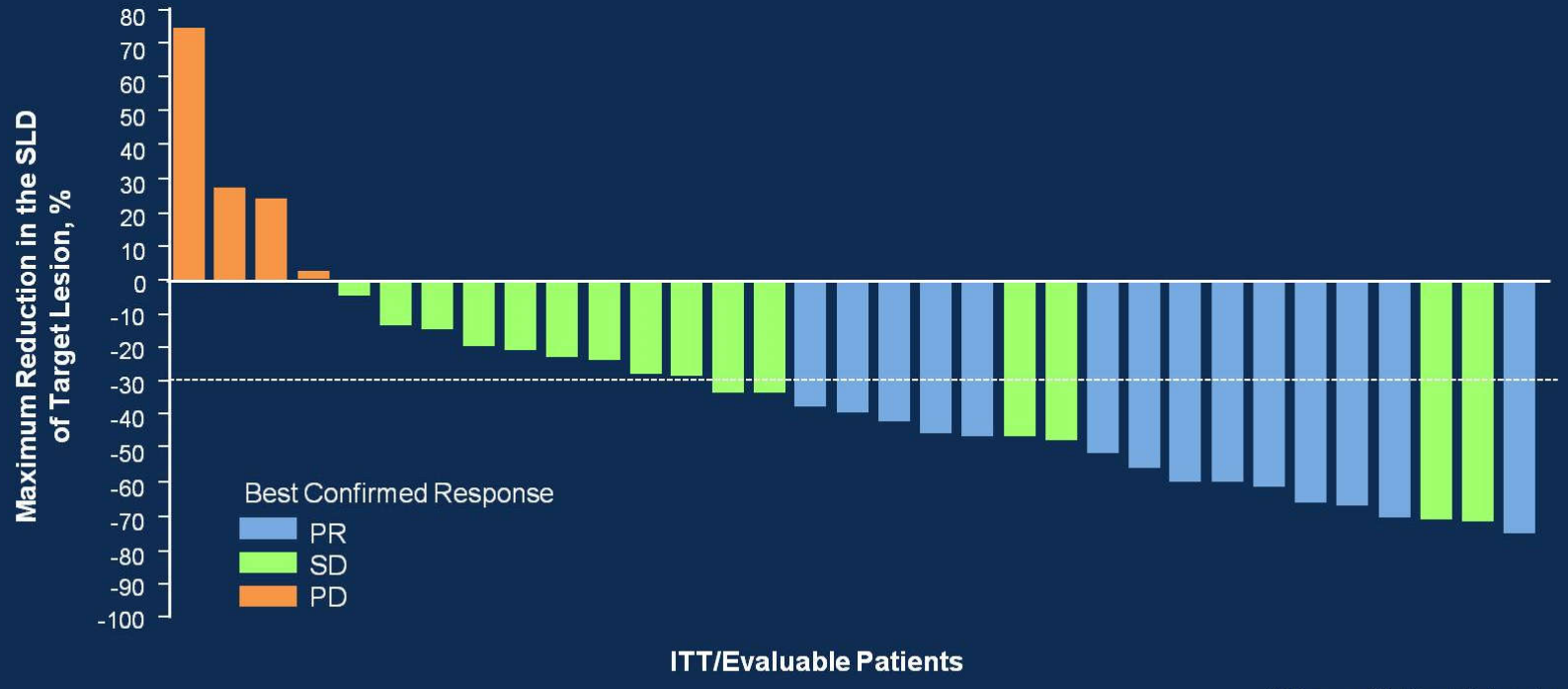


ROAR: A Phase 2, Open-Label, Multicenter Study (NCT02034110)



BID, twice daily; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization.

Investigator-Assessed Maximum Reduction in SLD of Target Lesions



SLD, sum of the longest diameter of the target lesion.

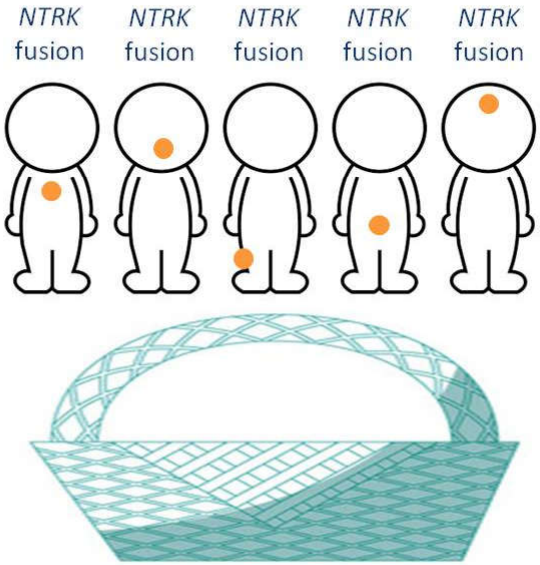
Tumor agnostic drug development can address the 'long tail'

Histology-specific drug development → **Alteration-specific drug development (agnostic of tumor type)**

- Traditional designs
- Umbrella trials

BASKET TRIAL

- One qualifying group of alterations
- Tumor agnostic patient accrual



Tumor agnostic trialの問題点

VE-BASKET study design

Patients and treatment

- *BRAF*^{V600} mutation-positive (documented by local testing)
- 208 patients treated
- Vemurafenib 960 mg bid

Primary endpoint

- Response rate at week 8

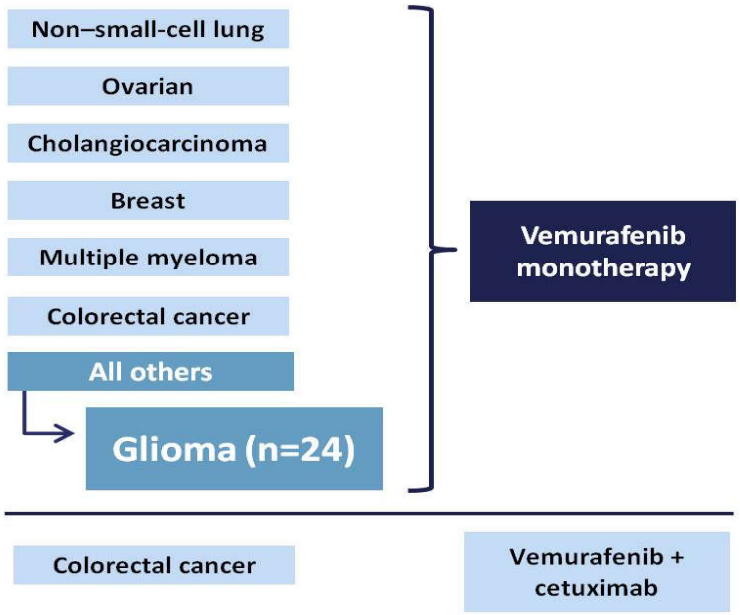
Secondary endpoints

- ORR, BOR, TTR, DOR, CBR
- PFS, TTP, OS
- Safety

Simon 2-stage design

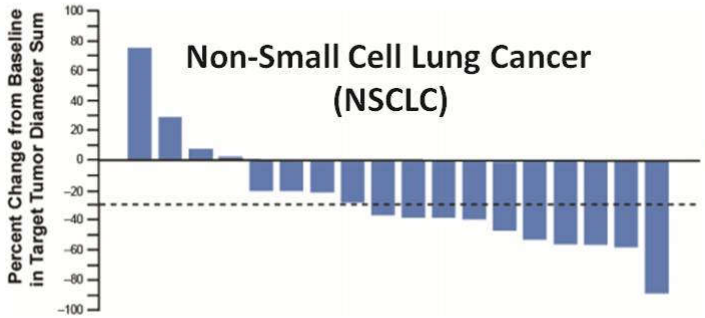
Tumor assessment: RECIST v1.1

Database lock: January 12, 2017

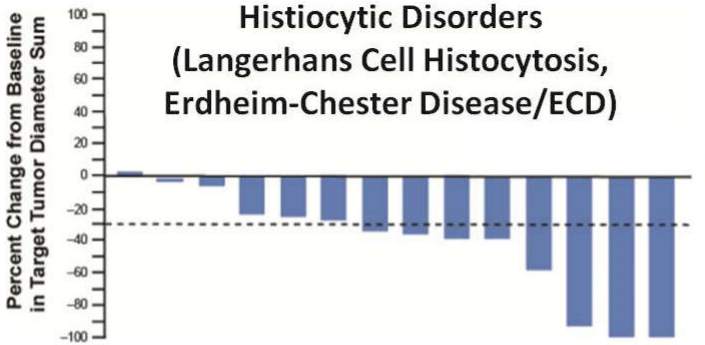


bid, twice daily; BOR, best overall response; CBR, clinical benefit rate; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to progression; TTR, time to response

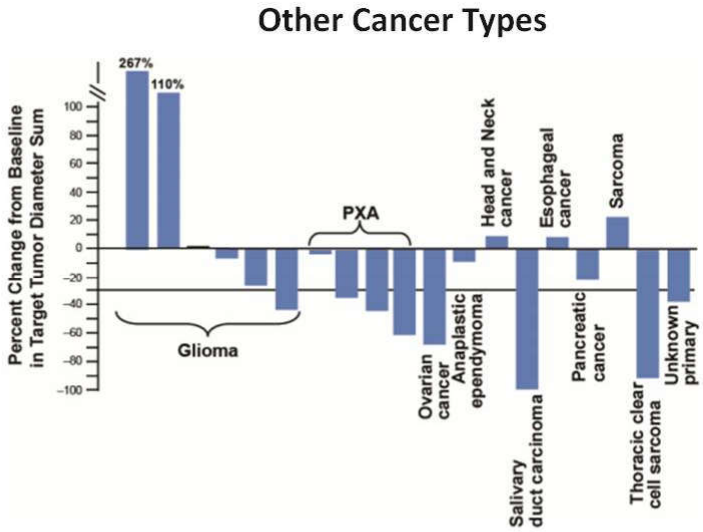
Vemurafenib basket addresses the long tail of BRAF^{V600E} alterations



NCCN Guidelines for NSCLC



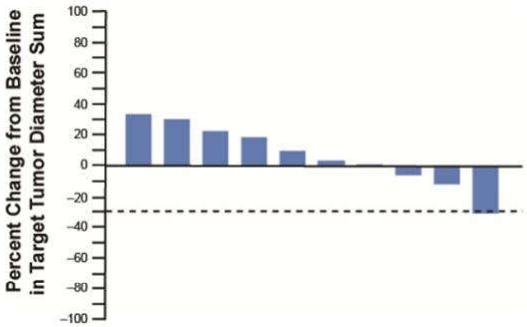
FDA Approval for ECD



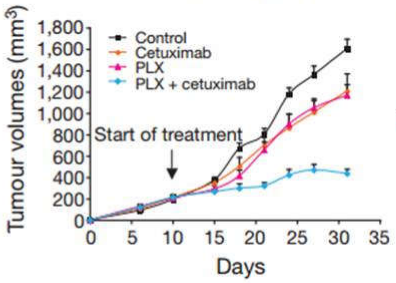
Hyman DM et al. N Engl J Med 2015;373:726-736.

Basket trials are adaptable: the platform trial concept

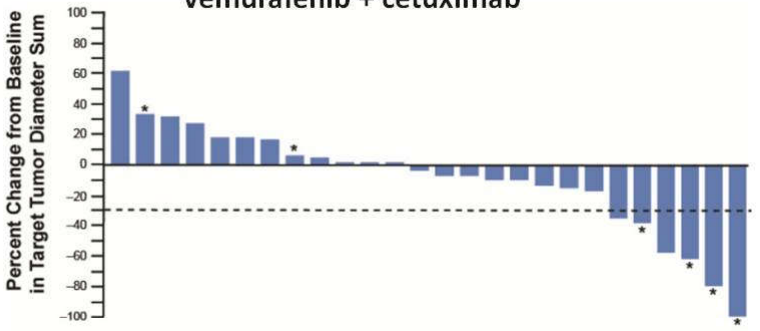
Colorectal Cancer
vemurafenib monotherapy



WiDr xenografts



Colorectal Cancer
vemurafenib + cetuximab



Novel therapeutic strategy enters the study design

Former therapeutic strategy leaves the study design

Prahallad A et al, Nature. 2012 Jan 26;483(7387):100-3.
Hyman DM et al. N Engl J Med 2015;373:726-736.

SUMMIT試験：HER2/3変異陽性癌へのNeratinib

Extended Data

***HER2* or *HER3* mutations (documented by local testing)**

Primary endpoint

- Objective response rate at week 8 (ORR_8)

Secondary endpoints

- ORR (confirmed)
- Clinical benefit rate (CBR)
- Progression-free survival (PFS)
- Safety
- Biomarkers

Simon 2-stage design

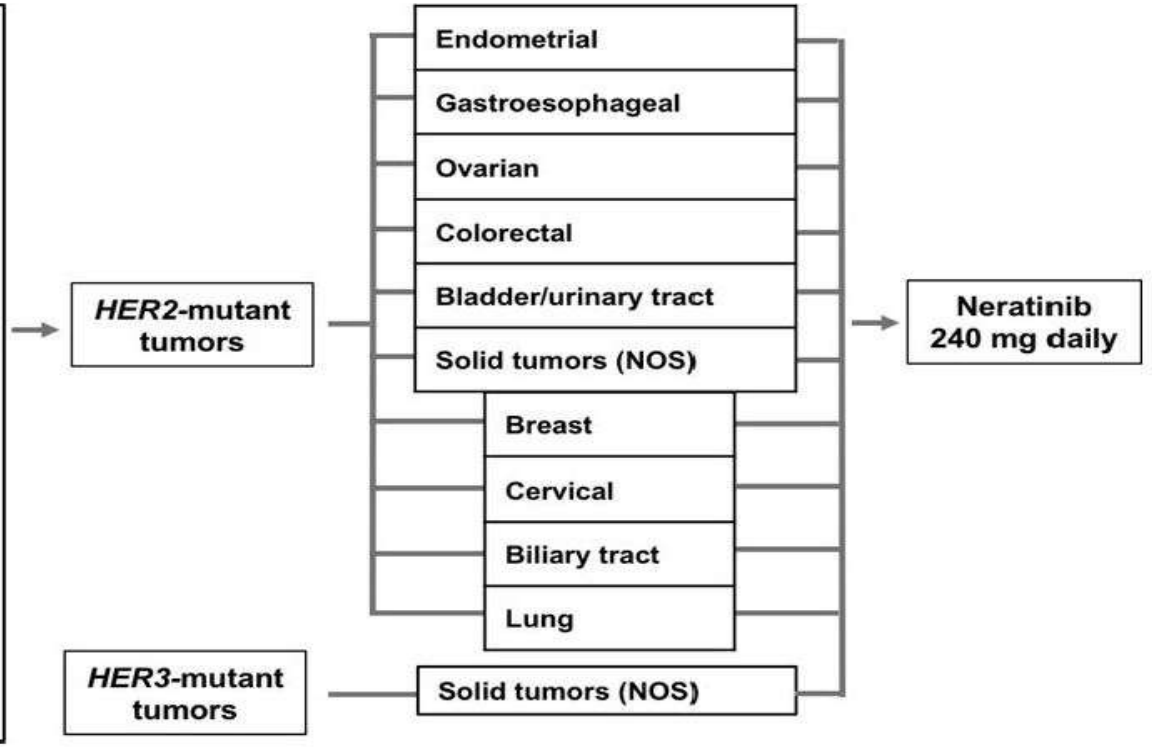
- If ≥1 response in first evaluable 7 patients, expand cohort to Stage 2 (N=18)
- If ≥4 responses in Stage 2, expand or breakout

Tumor assessments

- RECIST v1.1 (primary criteria)
- PET response criteria (RECIST non-evaluable)

Statistical methods

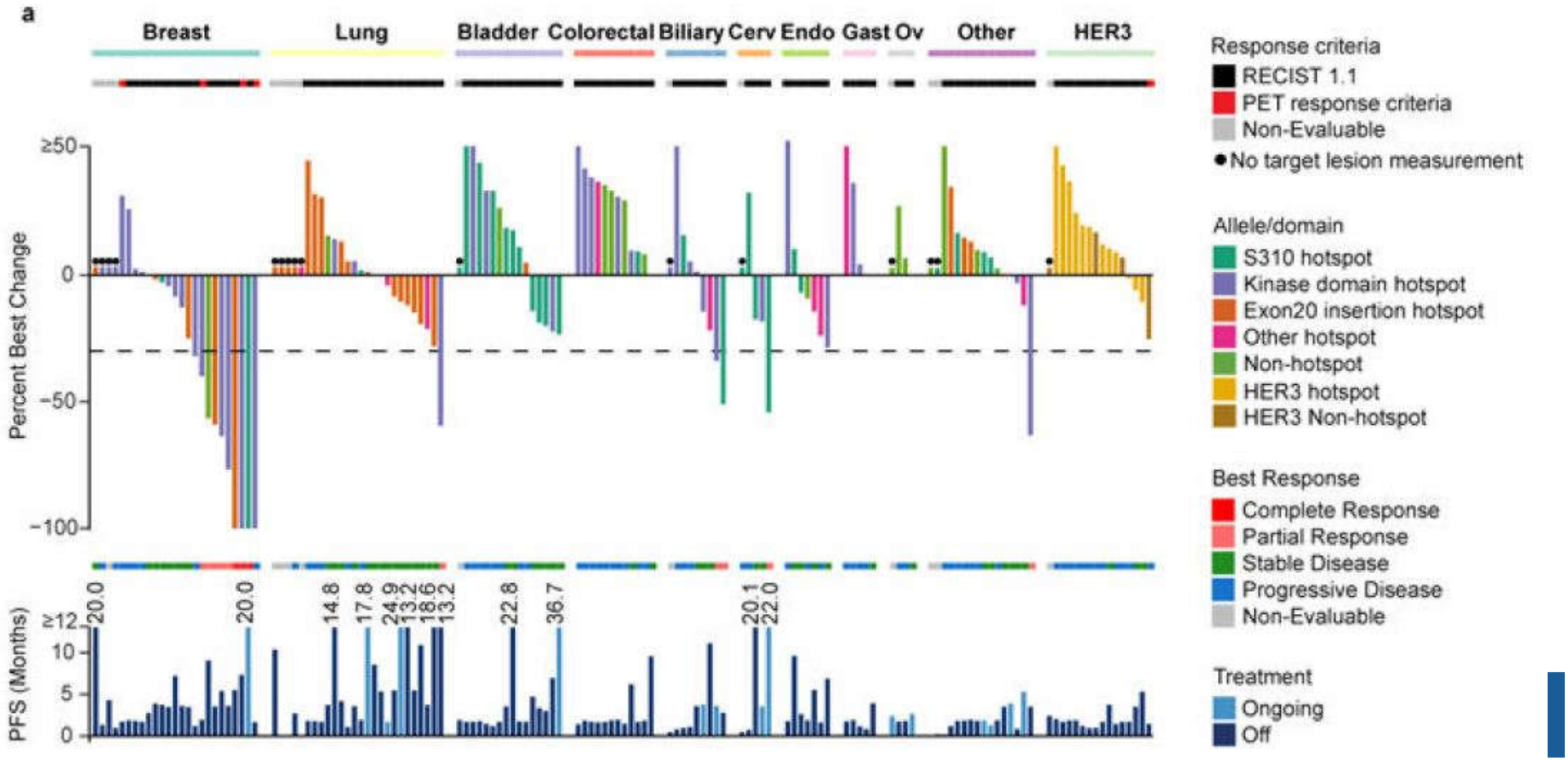
- ORR_8, ORR, CBR: associated 95% CI
- Median PFS: Kaplan-Meier estimate with 95% CI



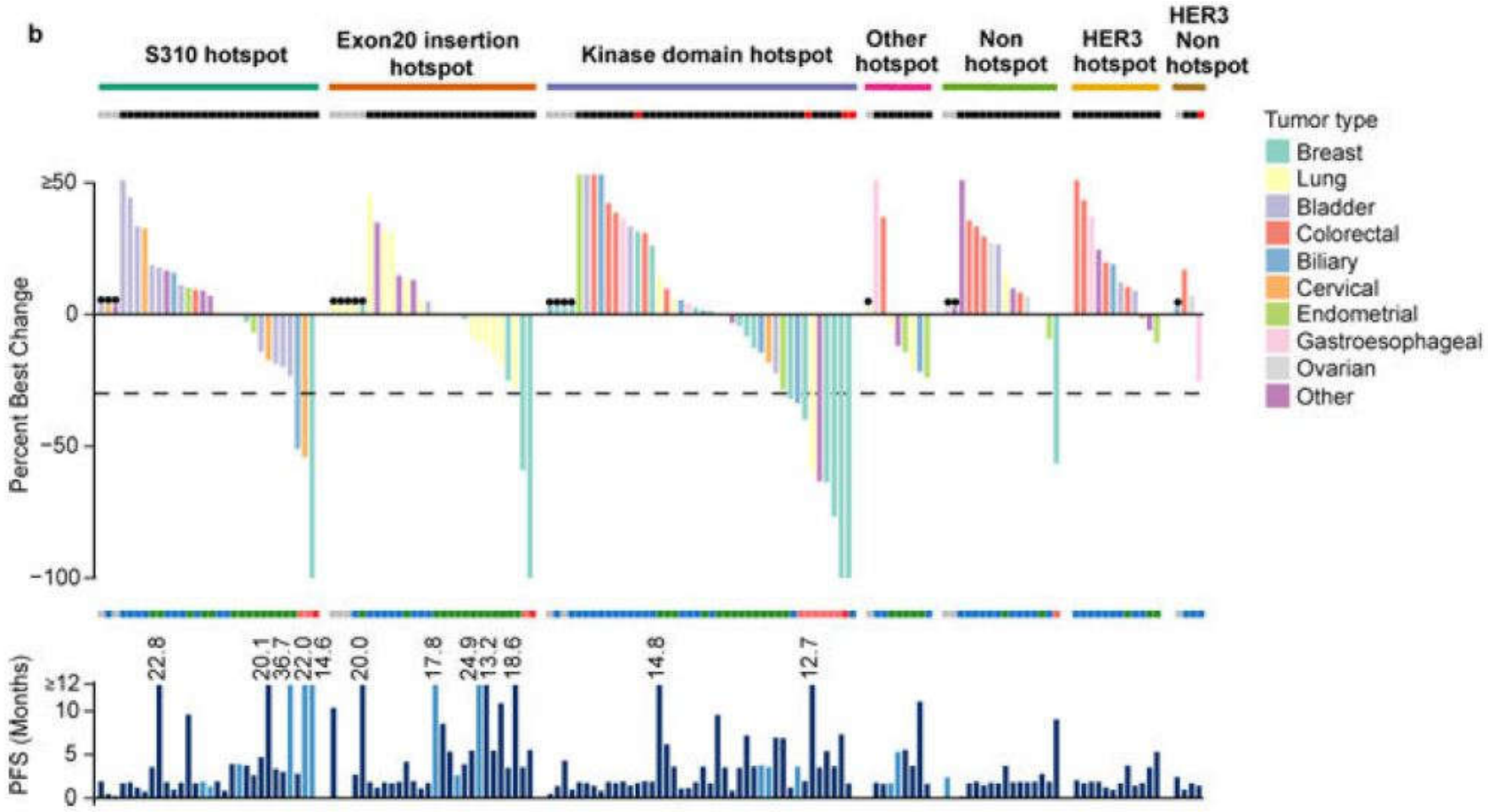
Nature. 2018 Feb 8; 554(7691): 189–194.

Tumor agnostic trialの難しさ:癌腫の違い

Nature. 2018 Feb 8; 554(7691): 189–194.



Tumor agnostic trialの難しさ:変異タイプの違い



Tumor agnostic “trial” から “approval”へ

Pembro for MSI-H/dMMR solid tumors

MERCK

Published on *Merck Newsroom Home* (https://www.mrknewsroom.com) on 5/25/17 7:00 pm EDT

FDA Approves Merck’s KEYTRUDA® (pembrolizumab) for Adult and Pediatric Patients with Unresectable or Metastatic, Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors

Release Date:
Thursday, May 25, 2017 7:00 pm EDT

Dateline City:
KENILWORTH, N.J.

KEYTRUDA Now Approved for MSI-H or dMMR Patients Whose Disease Has Progressed Following Prior Treatment and Who Have No Satisfactory Alternative Treatment Options, Which Includes Patients with Colorectal Cancer That Has Progressed Following Treatment with Fluoropyrimidine, Oxaliplatin, and Irinotecan

With this Unique Indication, KEYTRUDA is the First Cancer Therapy Approved for Use Based on a Biomarker, Regardless of Tumor Type

Larotrectinib for solid tumors with NTRK fusions

FDA U.S. FOOD & DRUG ADMINISTRATION

A to Z Index | Follow FDA | En Español

Search FDA

Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Tobacco Products

Drugs

Home > Drugs > Drug Approvals and Databases > Approved Drugs

Approved Drugs

Hematology/Oncology (Cancer) Approvals & Safety Notifications

Drug Information Soundcast in Clinical Oncology (D.I.S.C.O.)

Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)

FDA approves larotrectinib for solid tumors with NTRK gene fusions

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

Listen to the FDA D.I.S.C.O. podcast about this approval

On November 26, 2018, the Food and Drug Administration granted accelerated approval to larotrectinib (VITRAKVI, Loxo Oncology Inc. and Bayer) for adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, that are either metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment.

This is the second tissue-agnostic FDA approval for the treatment of cancer.

Approval was based on data from three multicenter, open-label, single-arm clinical trials: LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431). Identification of positive NTRK gene fusion status was prospectively determined in local laboratories using next generation sequencing (NGS) or fluorescence *in situ* hybridization (FISH). NTRK gene fusions were inferred in three pediatric patients with infantile fibrosarcoma who had a documented ETV6 translocation by FISH. The major efficacy outcome measures were overall response rate (ORR) and response duration, as determined by a blinded independent review committee according to RECIST 1.1.

Efficacy was evaluated in the first 55 patients with unresectable or metastatic solid tumors harboring an NTRK gene fusion enrolled across the three trials. All patients were required to have progressed following systemic therapy for their disease, if available, or would have required surgery with significant morbidity for locally advanced disease. Twelve patients were less than 18 years of age. A total of 12 cancer types were represented, with the most common being salivary gland tumors (22%), soft tissue sarcoma (20%), infantile fibrosarcoma (13%), and thyroid cancer (9%).

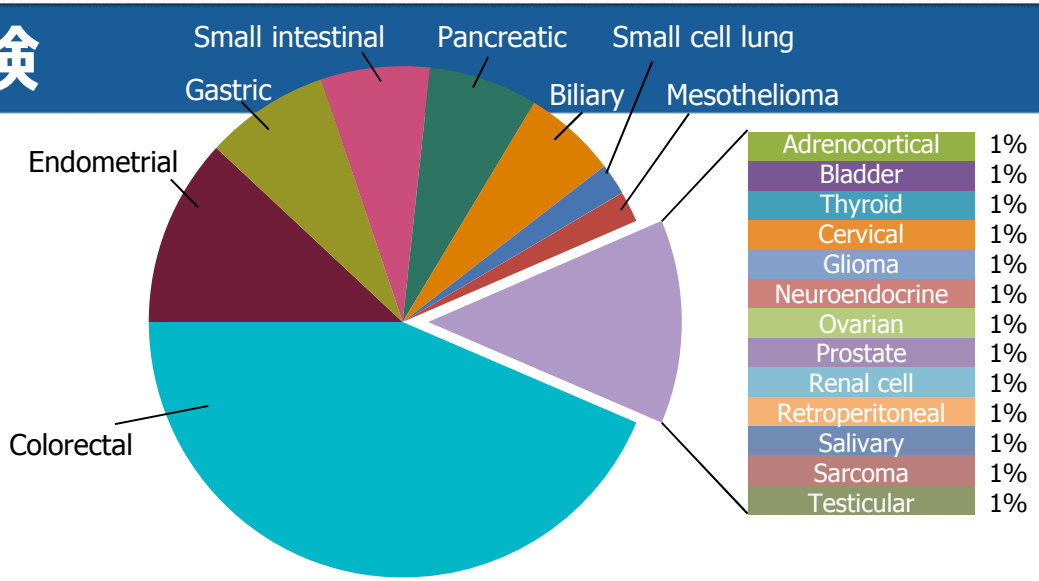
Tumor agnostic (TA) trial ⇒ TA development↖

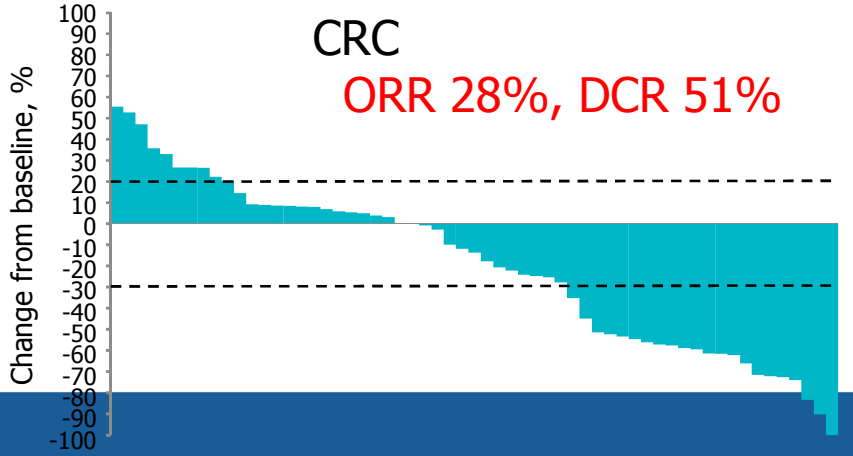
- Heterogeneity of effects?
- Differences in CNS penetration
- How will treatment effects be measured?
- Does the drug work best in combination?
- Unmet need?

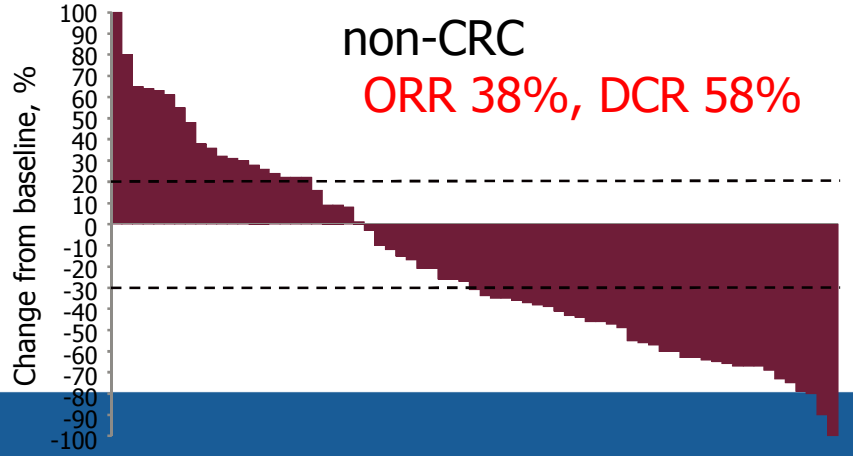
- How will patients be identified?
- Pediatric formulation necessary?

Lemery S, et al. Regulatory Considerations ASCO 2018

KN164/158試験

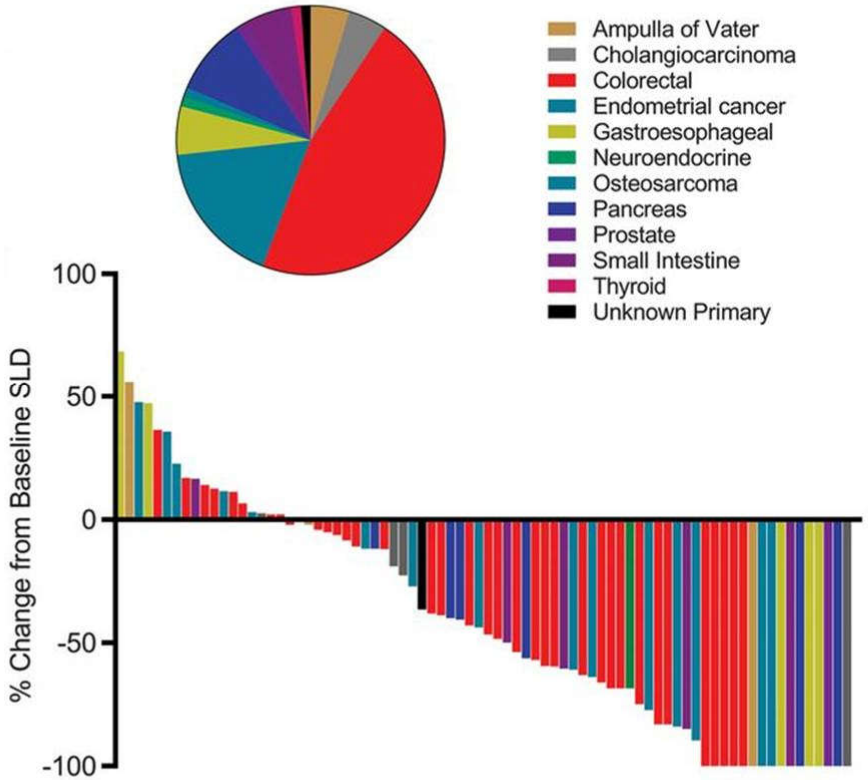


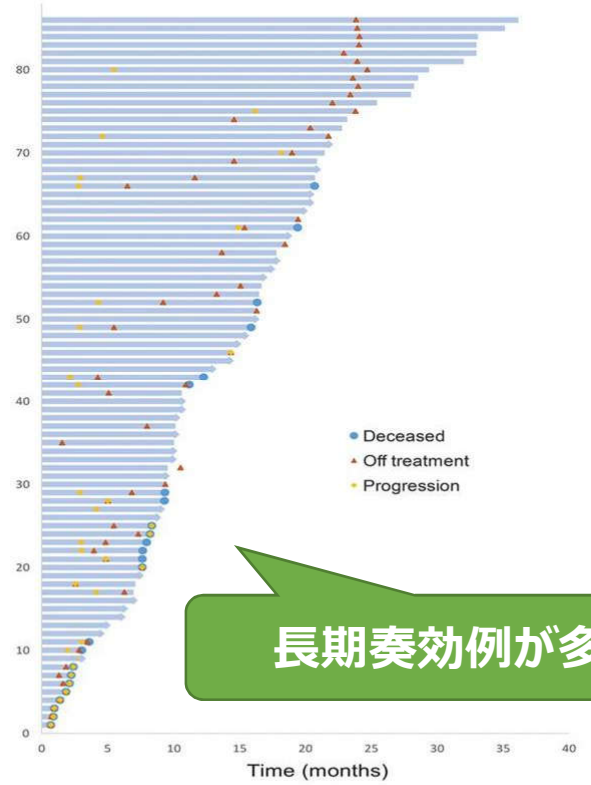




Diaz LA Jr, et al: 2017 ASCO #3071.

Pembrolizumab: histology-agnostic activity in MSI-high cancers



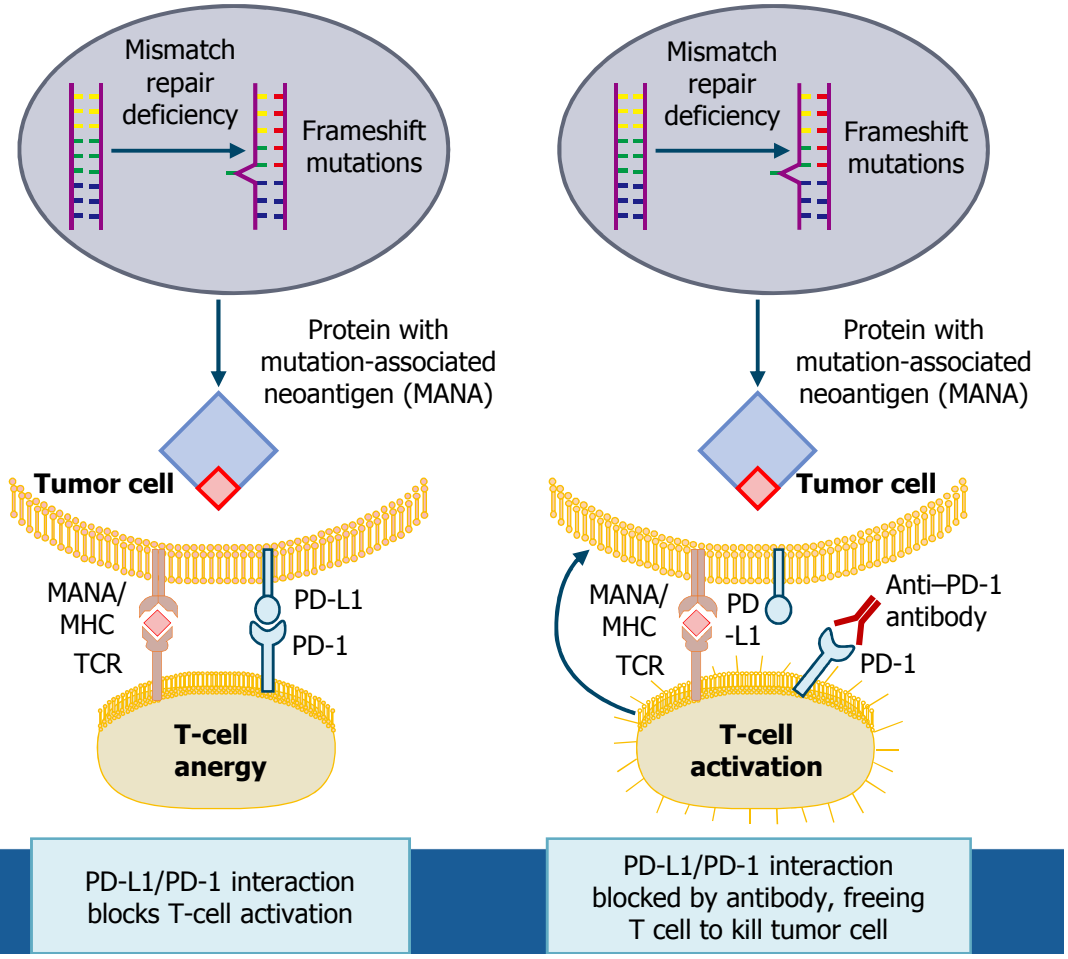


長期奏効例が多い

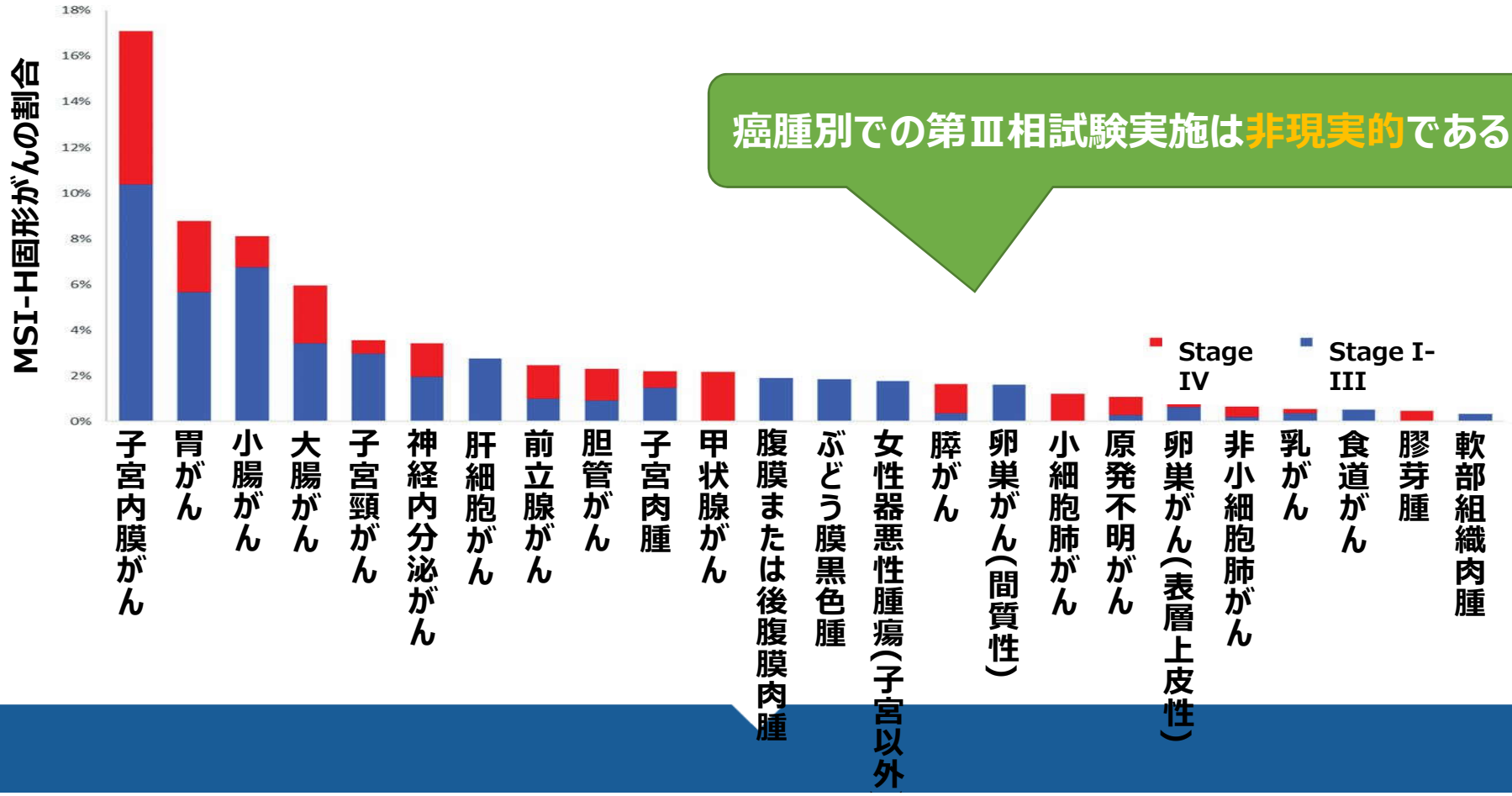
Dung TL et al. Science 2017

共通の抗腫瘍メカニズム

- MSI-H癌は腫瘍組織によらずTMB-Hである(hypermutated phenotype)
- TMB-Hはneoantigen高発現である
- Neoantigen高発現は腫瘍細胞の自己免疫認識 (autologous immune recognition)に繋がる
- 腫瘍neoantigen特異T細胞上のPD-1をブロックすることにより抗PD1抗体は抗腫瘍免疫応答を活性化する
- **MSI-H癌におけるPD-1のブロックは癌腫によらず有効な抗腫瘍免疫に繋がる可能性がある**



希少フラクションである

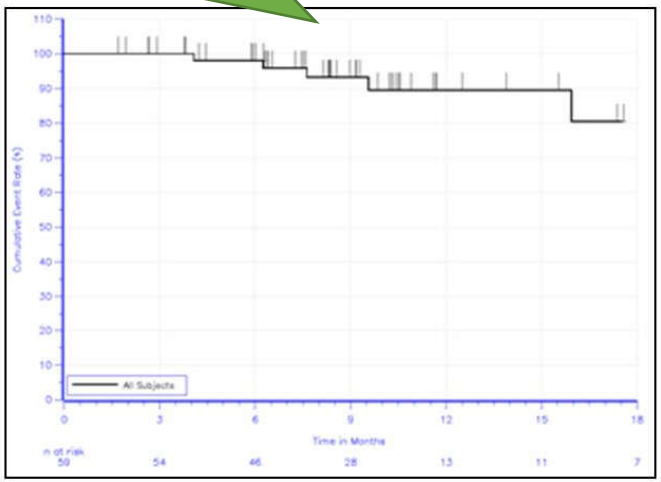


多数の癌種で効果が認められた

14癌種で奏効が認められた

	N	Objective response rate n (%)	95% CI
CRC	90	32 (36%)	(26%, 46%)
Non-CRC	59	27 (46%)	(33%, 59%)
Endometrial cancer	14	5 (36%)	(13%, 65%)
Biliary cancer	11	3 (27%)	(6%, 61%)
Gastric or GE junction cancer	9	5 (56%)	(21%, 86%)
Pancreatic cancer	6	5 (83%)	(36%, 100%)
Small intestinal cancer	8	3 (38%)	(9%, 76%)
Breast cancer	2	PR, PR	
Prostate cancer	2	PR, SD	
Bladder cancer	1	NE	
Esophageal cancer	1	PR	
Sarcoma	1	PD	
Thyroid cancer	1	NE	
Retroperitoneal adenocarcinoma	1	PR	
Small cell lung cancer	1	CR	
Renal cell cancer	1	PD	

"Durable" response

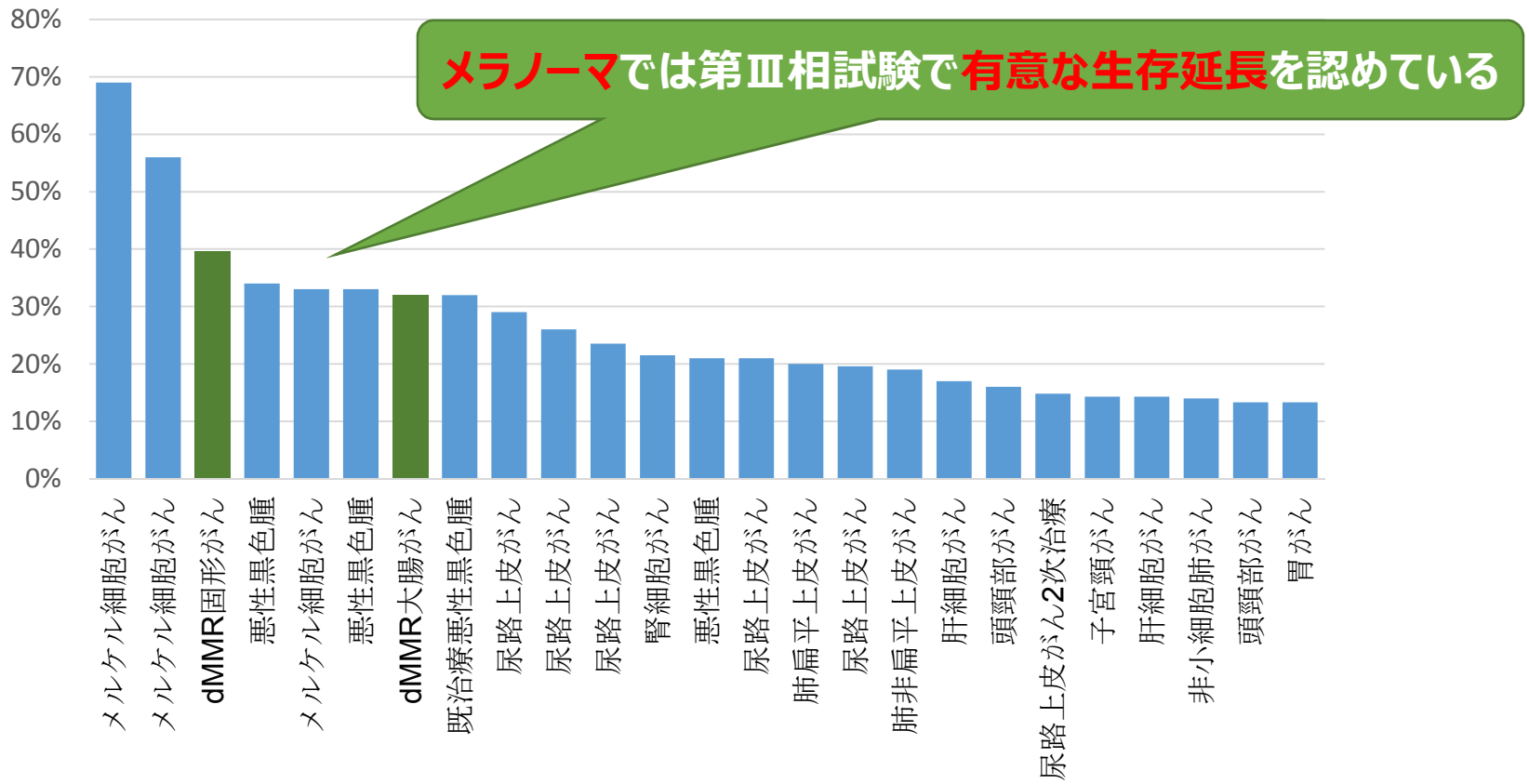


KM-DOR in 59 responding patients

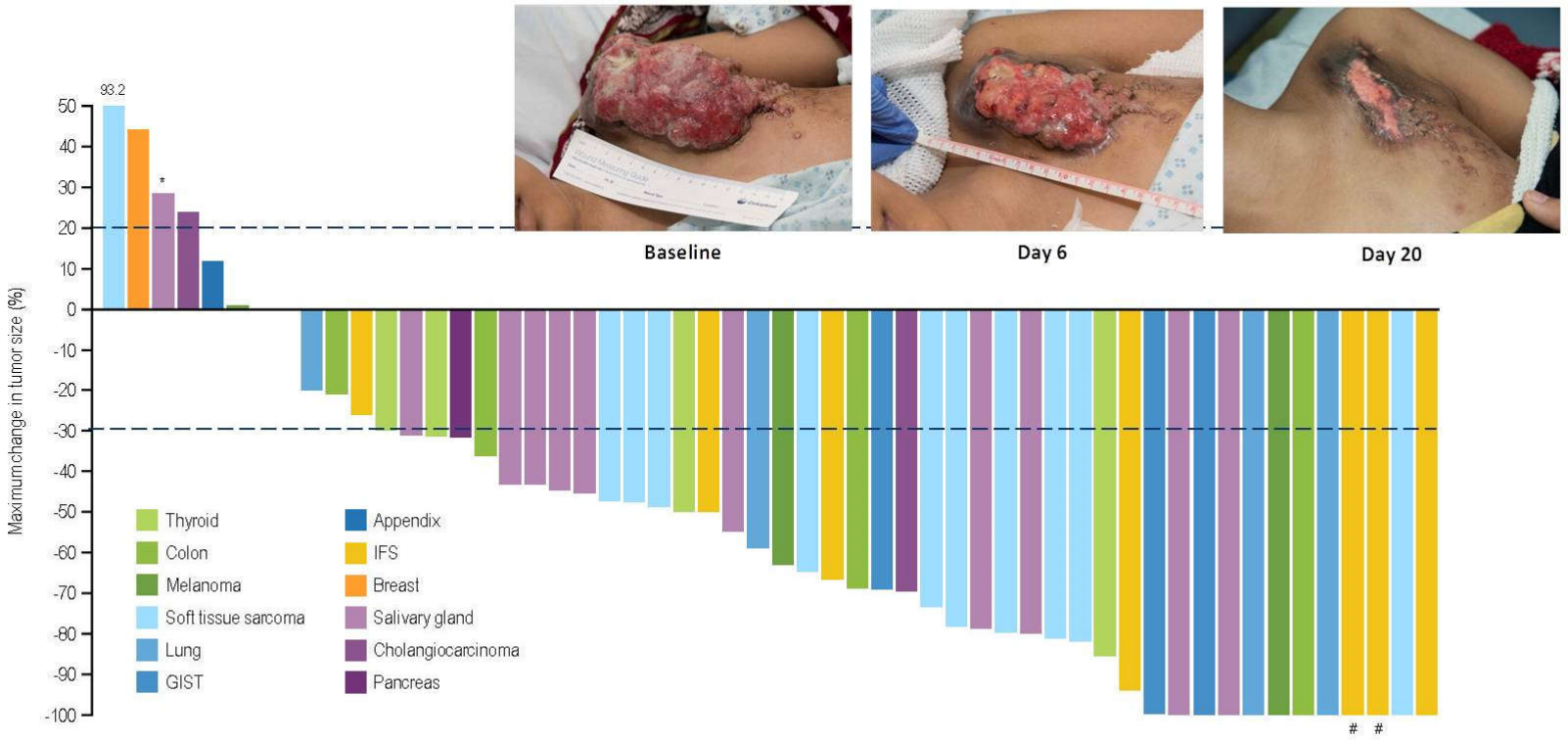
Source: Keytruda labeling, BLA submission, FDA review documents

生存への効果は課題があるが・・・

奏効割合

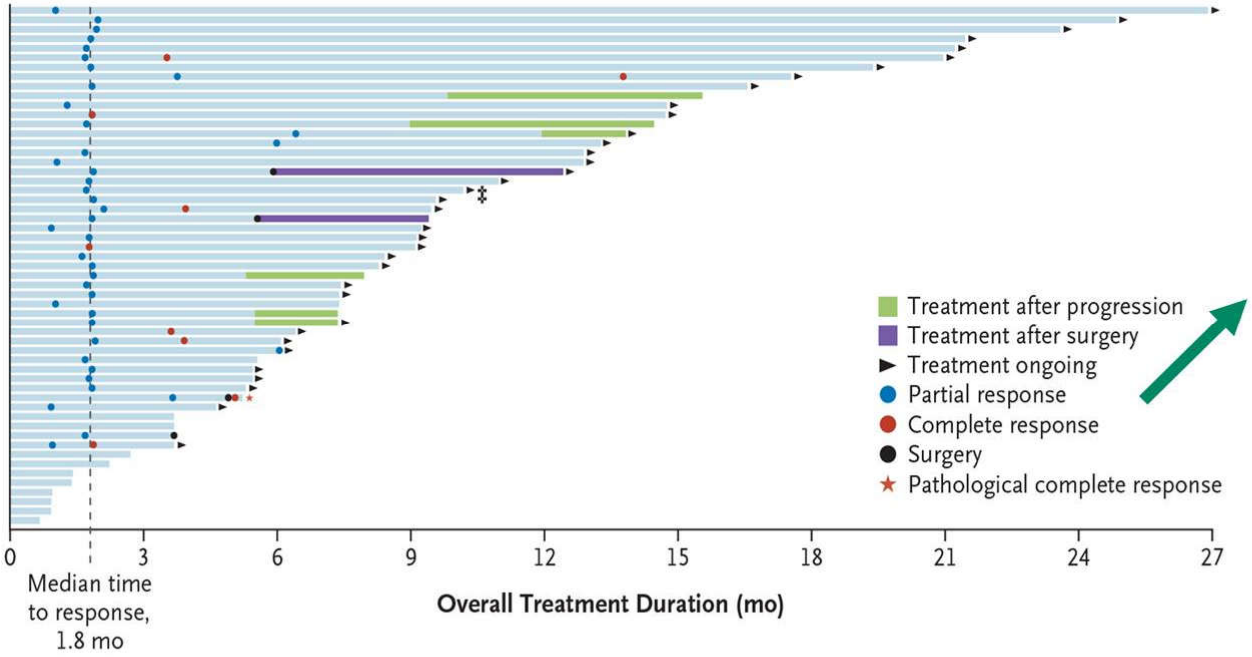


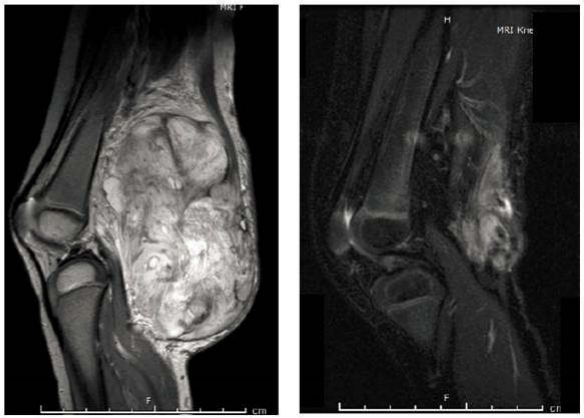
Larotrectinib: histology-agnostic activity in TRK fusion+ cancers



Drilon A et al. N Engl J Med 2018; Shukla N et al, J Clin Oncol PO 2017

Larotrectinib trial uncovers the potential for neoadjuvant therapy





Baseline Cycle 3

2 year-old requiring leg amputation for TRK fusion-positive sarcoma

- dramatic response to larotrectinib
- underwent limb-sparing surgery with no functional deficits
- pathologic complete response

Drilon A et al. N Engl J Med 2018

GOZILA Project

•Each arm to have a junior/senior investigator leadership team
•Flexible design: arms open and close with best available science

GOZILA Project
Guardant **O**riginates in **Z**ipangu **L**iquid biopsy **A**rrival

Nationwide Genome Screening Project
SCRUM-Japan GI-SCREEN
26 sites

CRC cohort, N = 1,500
- Before anti-EGFR, N = 500
- Refractory to anti-EGFR, N = 500

CRC Only

Non-CRC cohort, N = 1,500
- Gastric cancer, N = 300
- Esophageal cancer, N = 150
- Hepatocellular carcinoma, N = 100
- Biliary tract cancer, N = 150
- Pancreatic cancer, N = 100
- Neuroendocrine tumor/carcinoma, N = 50
- GIST, N = 100
- Others, N = 50

Non-GI Cancer cohort, N = 1,000

Pan Cancer

Organ-Specific approach

ctDNA analysis

- HER2 Positive → Trastuzumab + Pertuzumab (TRIUMPH)
- *BRAF* V600E MT → Eribulin (BRAVERY)
- *BRAF* Non-V600E MT → Binimetinib+ Encorafenib + Cetuximab (BIG BANG)
- *MET* Amplification* → MET-targeted Tx (METBEIGE)
- All WT** → Re-challenge with anti-EGFR mAb

HER2 Positive* → HER2-targeted Tx

Tumor-agnostic approach

ctDNA analysis

- bTMB-High Cancer → Nivolumab (TMB-H basket)
- Any FGFR alteration** → FGFR-targeted Tx
- Any HER2 alteration** → HER2-targeted Tx
- ROS1 alteration** → ROS1-targeted Tx

まとめ：”Tumor agnostic” development

- 分子標的治療薬の登場により、新たな治療開発のスキームが生まれた
  - Phase I expansion cohorts, phase II basket trials..
  - これらのデザインを用いたpivotal trialsが実施されている
  - 実例：MSI-H/dMMR固形がんへのPembro、TRK阻害剤..

- Tumor agnostic trialsは新しい研究へのプラットフォームでもある
  - 未知のrare variantへの有効性の確認
  - 早い治療ラインや補助療法への展開
  - 耐性メカニズムへの理解
  - 耐性克服のための新しい治療