ゲノム情報に基づく臨床試験

国立がん研究センター　先端医療開発センター
トランスレーショナルインフォマティクス分野
土原　一哉

がんゲノム医療がいま必要とされる理由

- がん細胞・微小環境を標的とした合理的な治療法（分子標的療法・免疫チェックポイント療法）の発達
- 個々の症例の分子生物学的背景による治療選択が必須
- 次世代シークエンス技術の一般化により多数遺伝子の同時解析（遺伝子パネル検査）が可能に
- 米国等で遺伝子パネル検査は研究段階から一般臨床へ拡大
- 実地診療で得られる臨床ゲノム情報は今後の治療・診断開発の基礎データに

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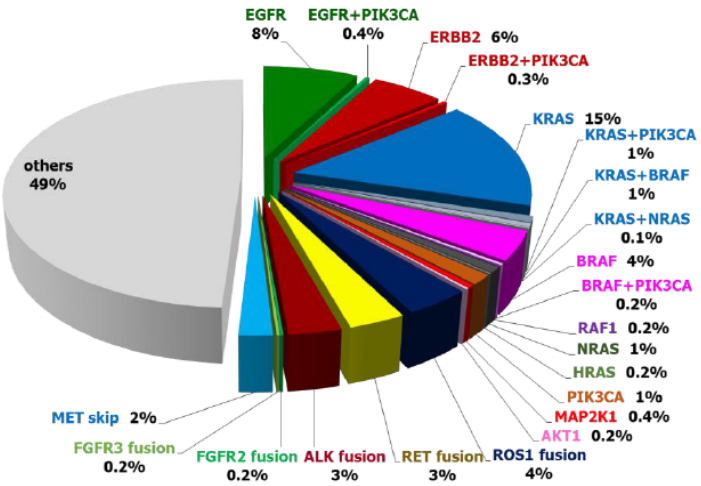
殺細胞性抗がん薬

- 「がん細胞の増殖抑制」を指標としてリード化合物を選択
- 腫瘍縮小効果を確認したのちに作用機序（標的分子）を解明する

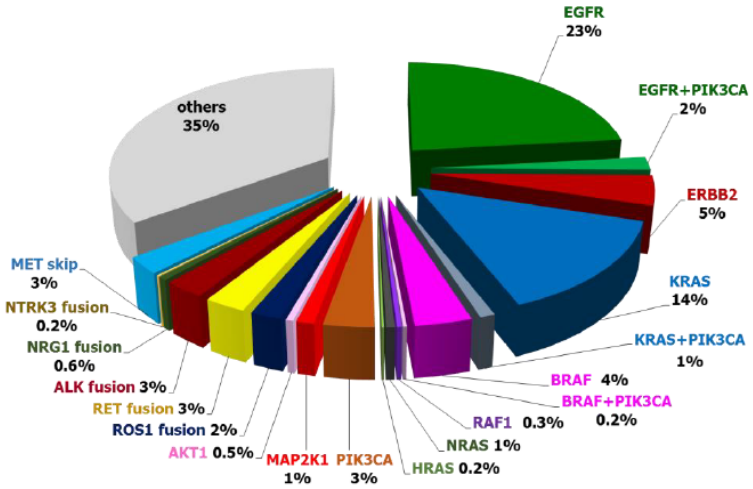
分子標的薬

- がん組織・細胞で活性化している「標的分子の阻害効率」を指標としてリード化合物を選択
- 標的分子を選定したのち腫瘍縮小効果を確認する

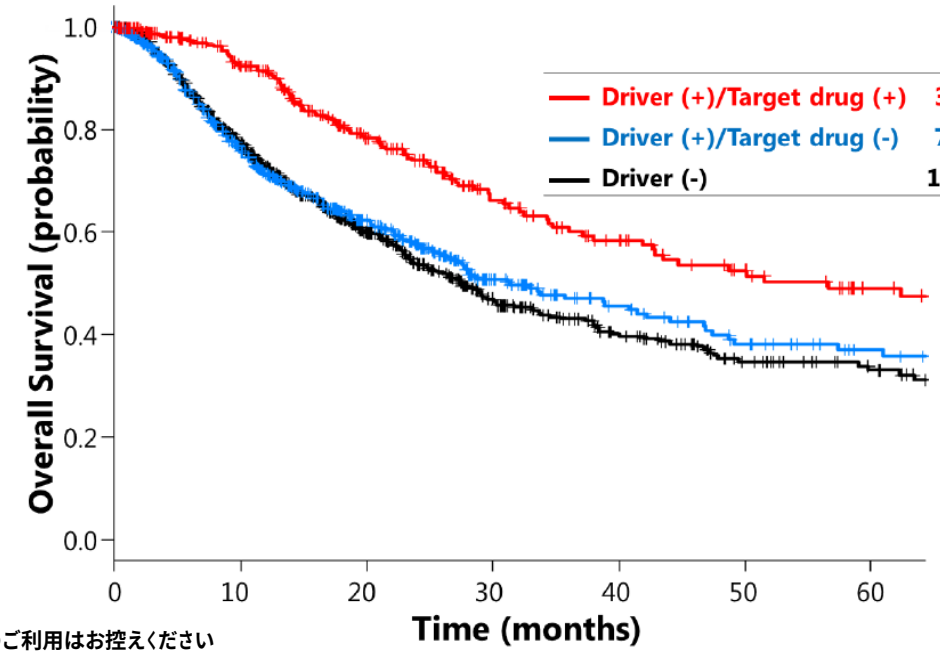
LC-SCRUM-Japanにおける治療標的分子の同定と分子標的薬の治療効果



(n=1,688, OCA ver.1, Mar. 2015~Apr. 2017)



(n=1,316, OCA ver.3, May. 2017~Apr. 2018)



	N	mOS (months)	[95% C.I.]
Driver (+)/Target drug (+)	335	56.6	[41.9-117.3]
Driver (+)/Target drug (-)	714	31.4	[26.4-41.5]
Driver (-)	1159	27.6	[24.0-30.4]

Logrank, p<0.001

Seto, ASCO, 2018

明確なバイオマーカー

分子標的薬はよく効く

分子標的薬は高価

分子標的薬は経済的？

英国での試算

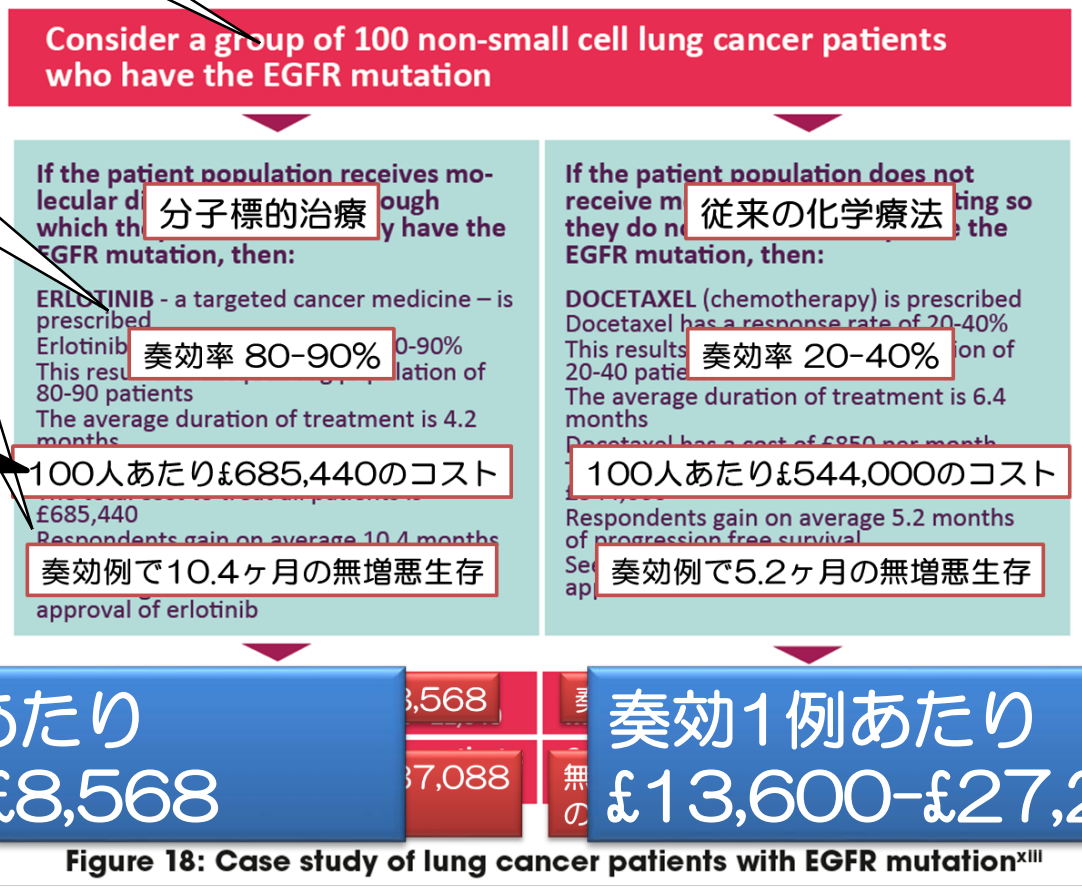


Figure 18: Case study of lung cancer patients with EGFR mutation[xiii]

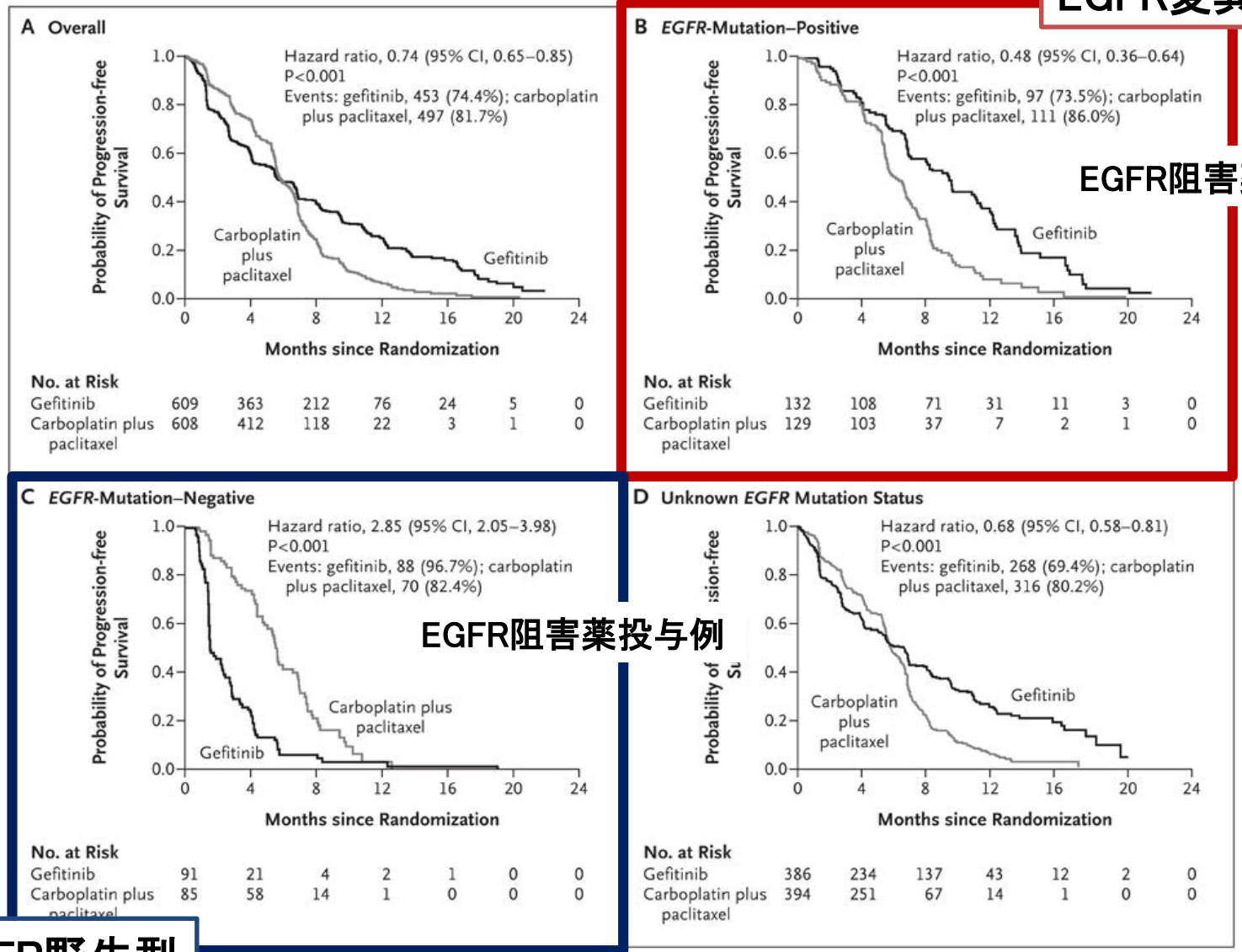
EGFR阻害薬の効果は変異型症例に限定される

EGFR変異型

EGFR阻害薬投与例

EGFR阻害薬投与例

EGFR野生型

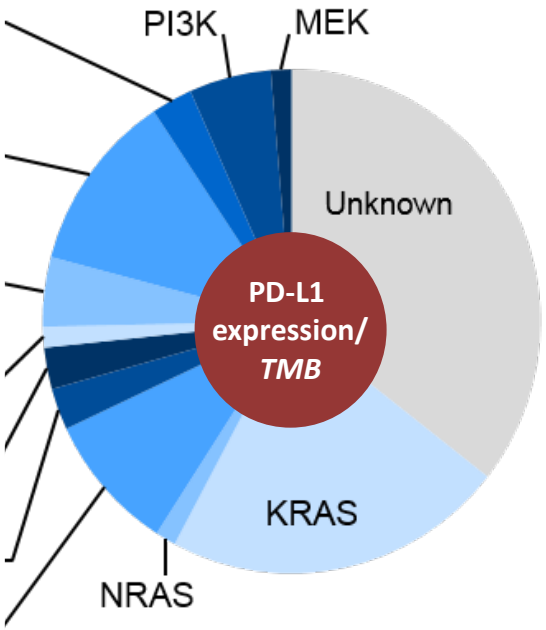


Mok, NEJM, 2009

非小細胞肺がん分子標的薬とバイオマーカー

Genomic alteration-drug associations in NSCLC NCCN guidelines

Base substitutions	BRAF V600E	dabrafenib + trametinib
	EGFR T790M	osimertinib
	EGFR exon 21 L858R EGFR exon 19 deletions	erlotinib | gefitinib| afatinib |dacometinib
Insertions and deletions	HER2 insertions	Ado-trastuzumab emtansine
Copy number alterations	High-level MET amplification MET exon 14 skipping mutation	crizotinib
Rearrangements	*RET rearrangements*	cabozantinib | vandetanib
	ROS1 rearrangements	ceritinib| crizotinib
	ALK rearrangements	crizotinib | ceritinib | alectinib |brigatinib

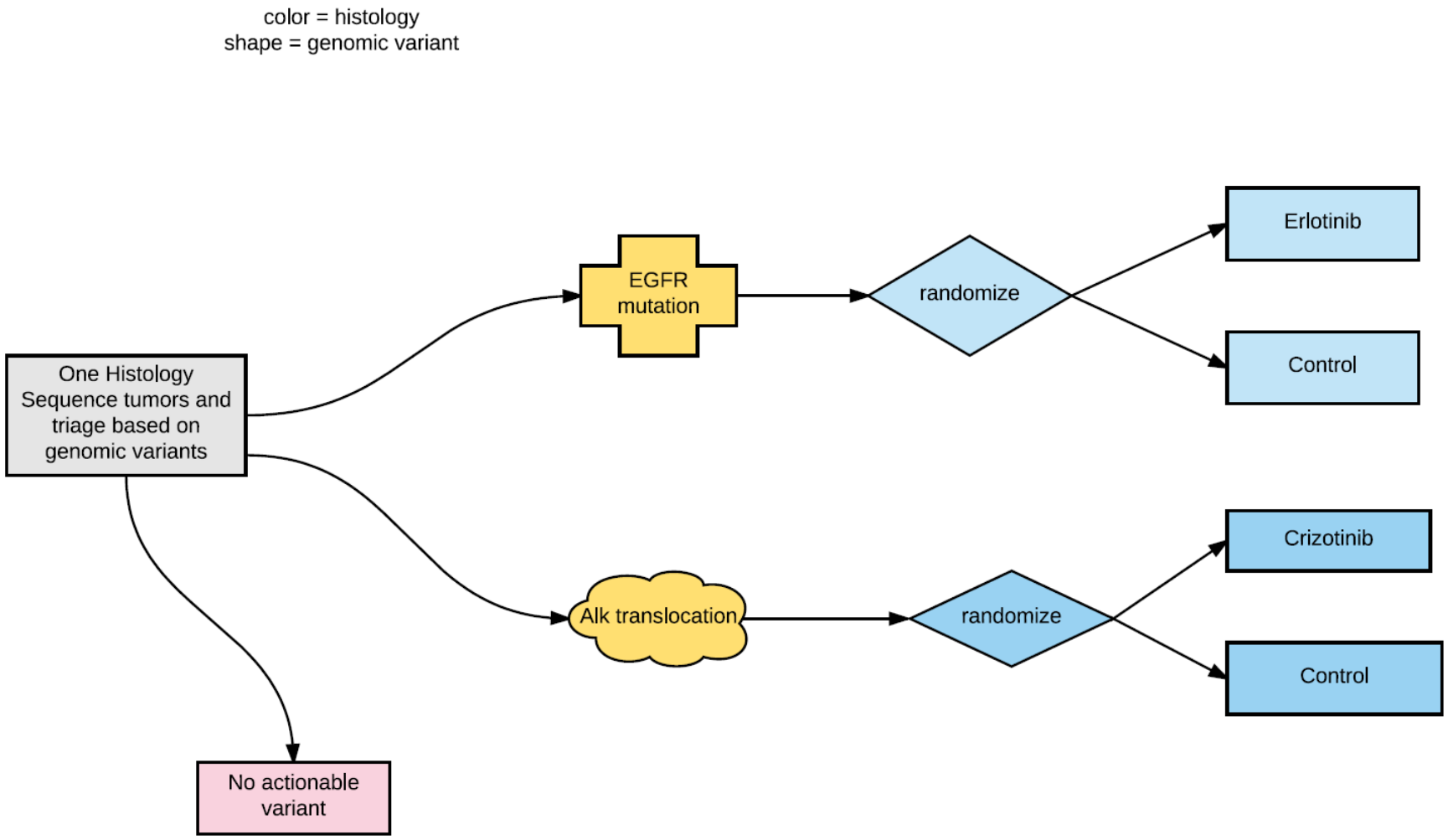


NSCLC NCCN Guidelines version 1.2019;
Image modified from Baumgart, M. (2015) *Am J Hematol Oncol* 11(6):10-13.

- NCCN: National Comprehensive Cancer Network;
- NSCLC: Non-small cell lung cancer.

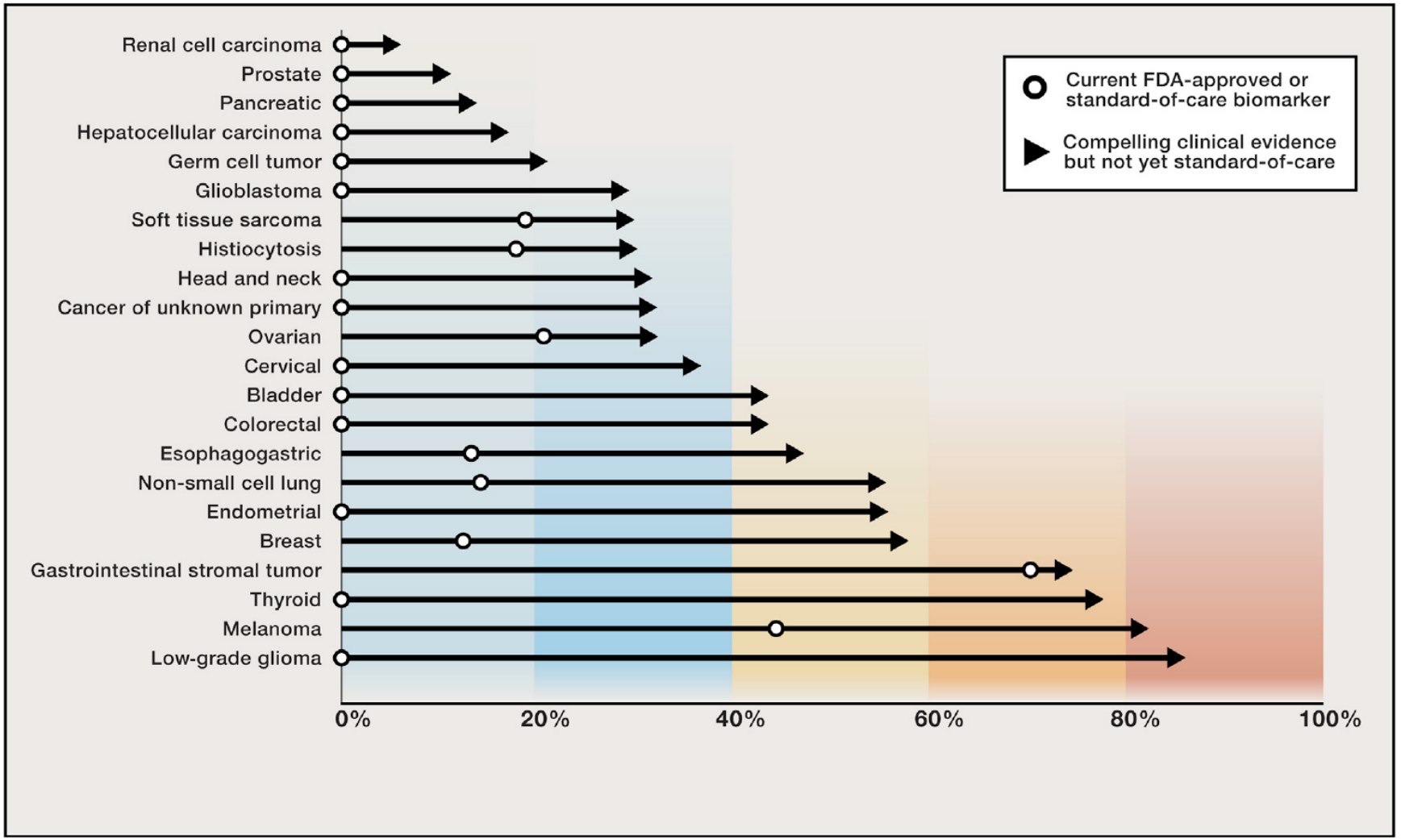
Umbrella Design

One histology
Multiple genomic variants
Separate studies for each variant



Simon, Clin Pharmacol Ther, 2017

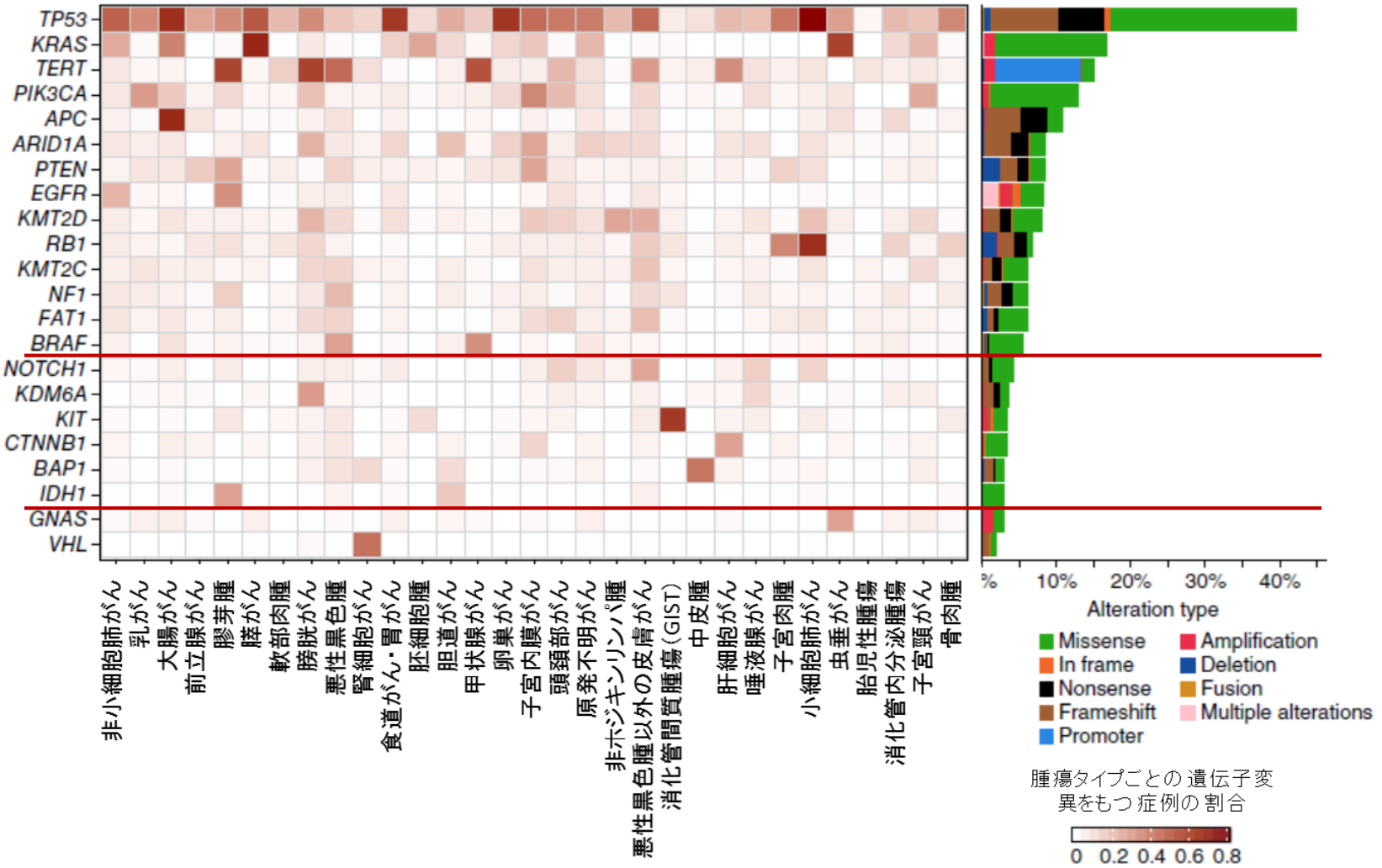
臨床応用されている”Druggable”変異



Hyman, Cell, 2017

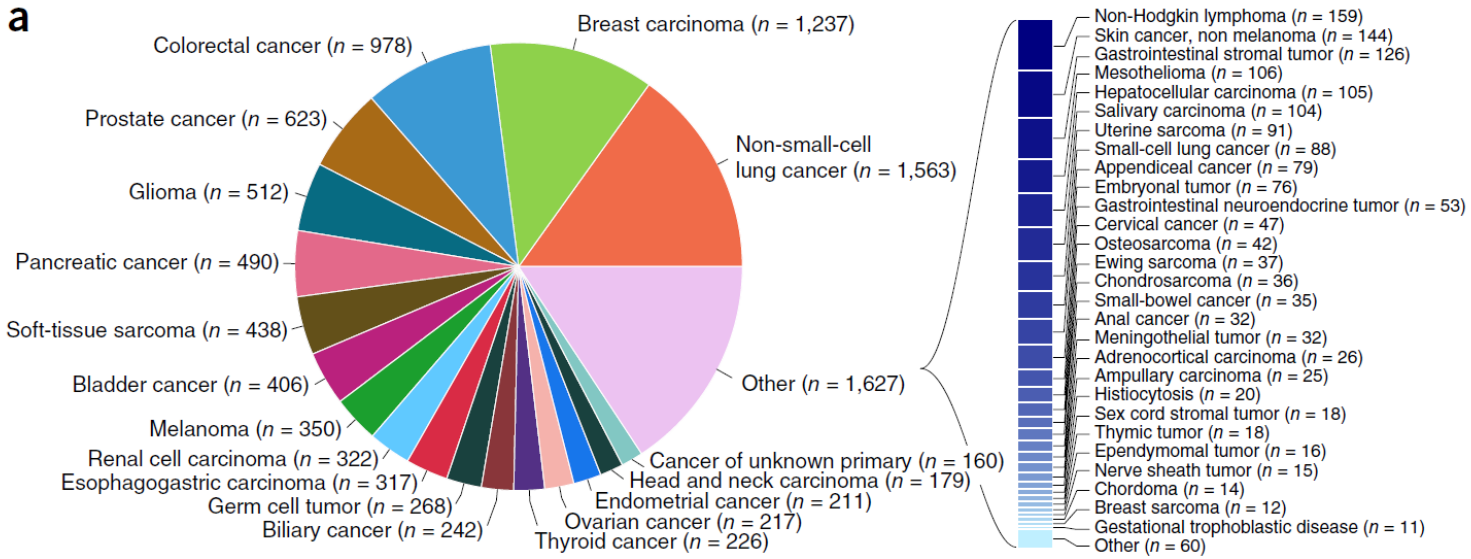
治療標的となるゲノム異常は臓器の壁をこえて存在する

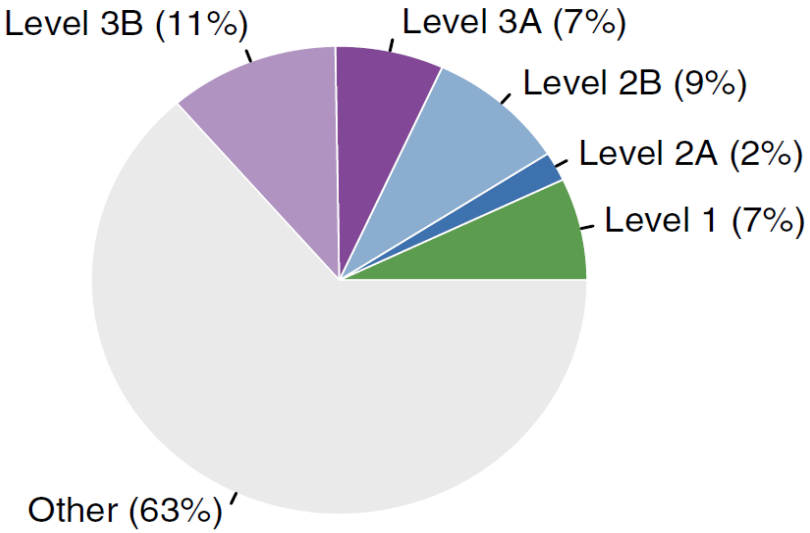
メモリアルスローンケタリングがんセンター·1万例の解析例



Zehir, Nat Med, 2017

MSK-IMPACT：10000例の臨床的有用性



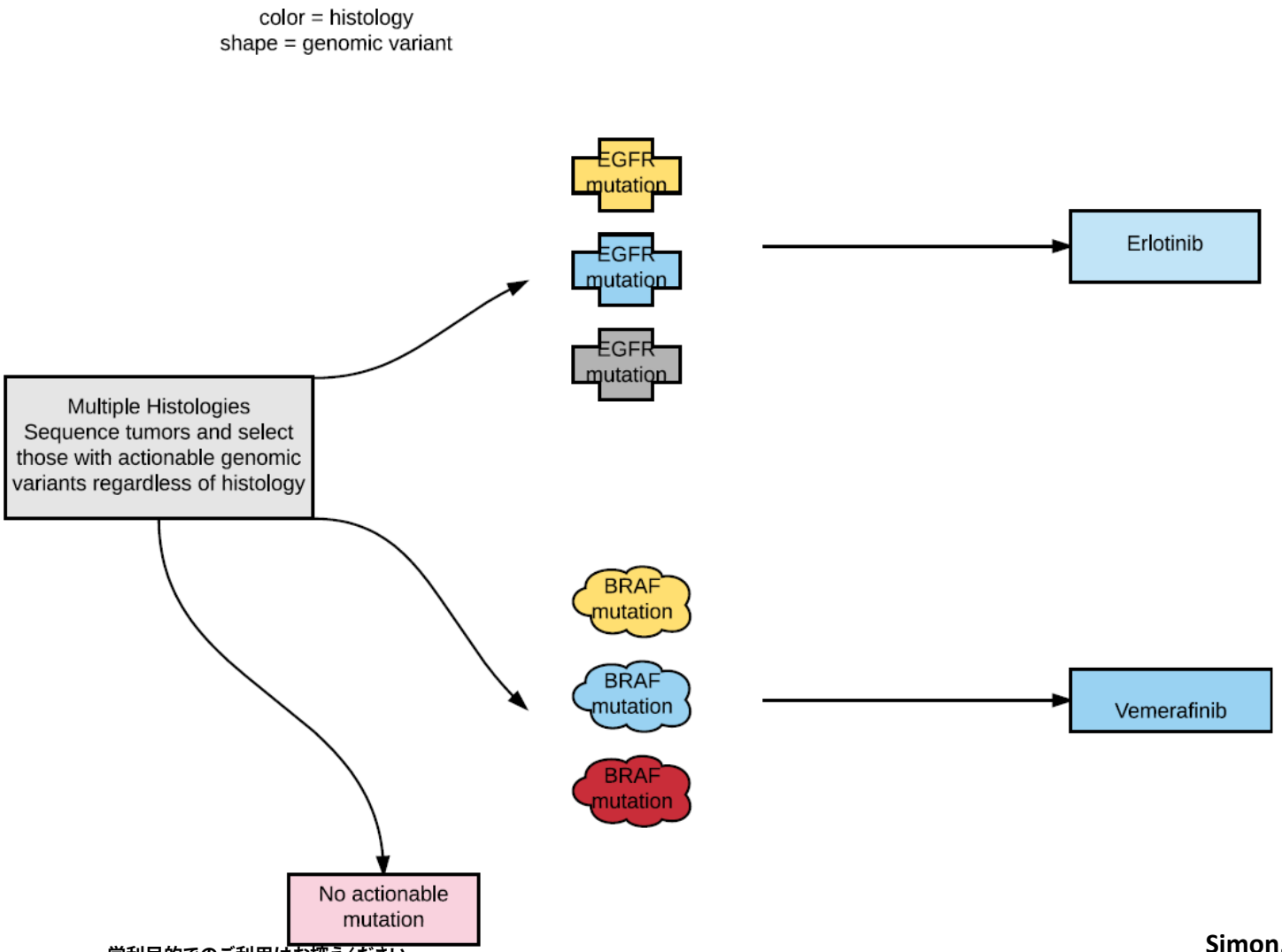


Level 1	FDA-recognized biomarker for an FDA-approved drug in the same indication
Level 2A	Standard of care biomarker for an FDA-approved drug in the same indication
Level 2B	Standard of care biomarker for an FDA-approved drug in another indication
Level 3A	Compelling clinical evidence supporting the biomarker as being predictive of drug response in the same indication
Level 3B	Compelling clinical evidence supporting the biomarker as being predictive of drug response in another indication

Zehir, Nat Med, 2017

Basket Design

Multiple histologies
One genomic variant per treatment



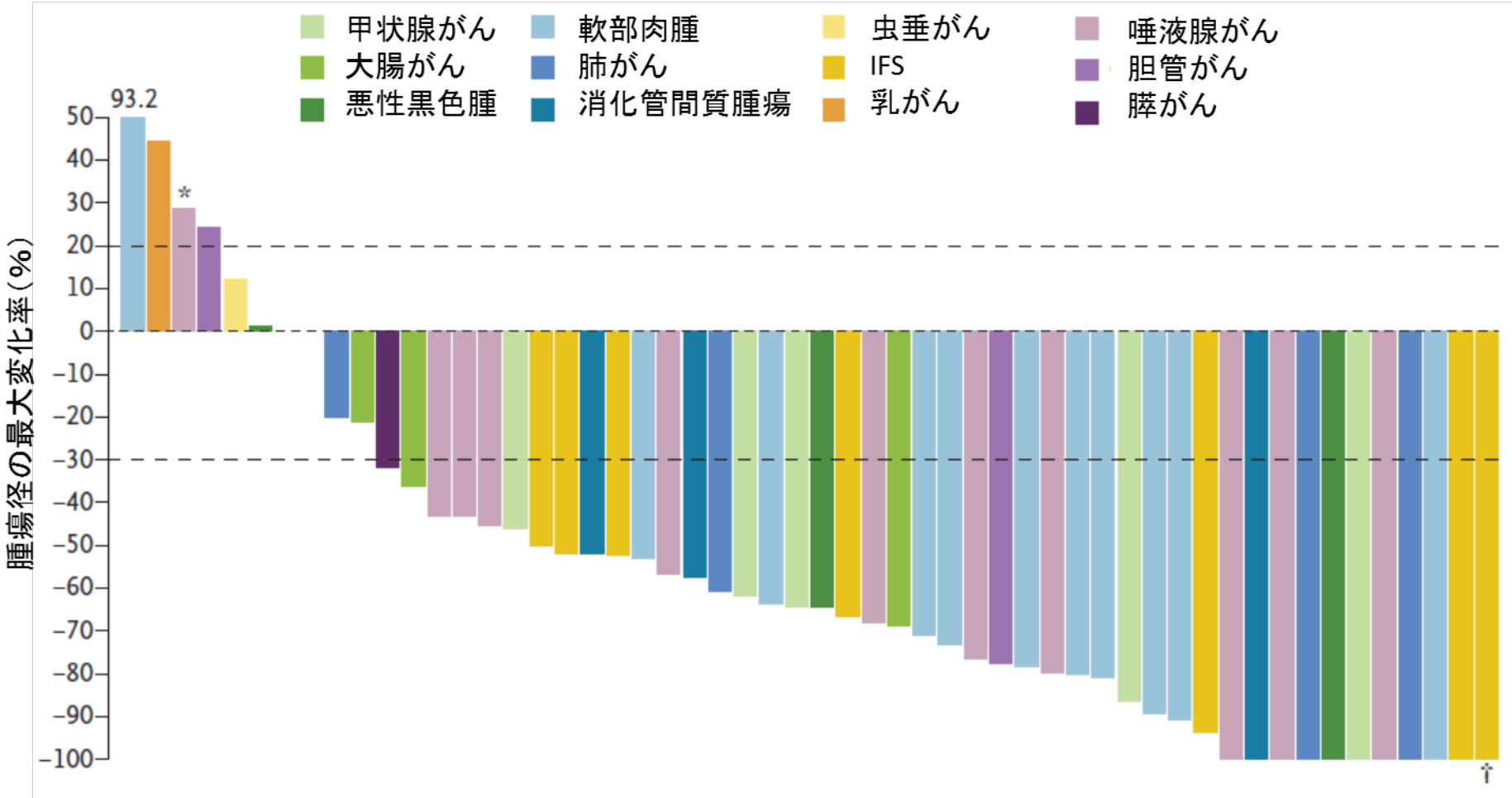
Simon, Clin Pharmacol Ther, 2017

NTRK融合遺伝子陽性例の頻度

Tumor Sample	No. of Samples	No. of Tumors (%)			
		Any *NTRK* Fusion	*NTRK1* Fusion	*NTRK2* Fusion	*NTRK3* Fusion
Adult tumors (TCGA)*					
Total	9,966	31 (0.31)	9 (0.09)	6 (0.06)	16 (0.16)
Thyroid cancer	513	12 (2.34)	5 (0.97)	—	7 (1.36)
Colon adenocarcinoma	310	3 (0.97)	—	—	3 (0.97)
Low-grade glioma	534	5 (0.94)	1 (0.19)	3 (0.56)	1 (0.19)
Sarcoma	263	2 (0.76)	2 (0.76)	—	—
Glioblastoma multiforme	180	1 (0.56)	1 (0.56)	—	—
Pancreatic adenocarcinoma	179	1 (0.56)	—	—	1 (0.56)
Head and neck SCC	522	2 (0.38)	—	1 (0.19)	1 (0.19)
Cervical cancer	306	1 (0.33)	—	—	1 (0.33)
Melanoma	476	1 (0.21)	—	—	1 (0.21)
Breast cancer	1119	2 (0.18)	—	1 (0.09)	1 (0.09)
Lung adenocarcinoma	541	1 (0.18)	—	1 (0.18)	—
Pediatric tumors (St Jude PeCan)†					
Total	3,501	12 (0.34)	5 (0.14)	4 (0.11)	3 (0.09)
Melanoma	9	1 (11.11)	1 (11.11)	—	—
High-grade glioma	132	7 (5.3)	4 (3.03)	2 (1.52)	1 (0.76)
Low-grade glioma	120	3 (2.5)	—	2 (1.67)	1 (0.83)
B-cell ALL	716	1 (0.14)	—	—	1 (0.14)

Okamura, JCO PO, 2018

NTRK融合遺伝子陽性固形がんに対するlarotrectinibの抗腫瘍効果



Drilon, NEJM, 2018

臓器横断的な治療薬開発・承認

NTRK融合遺伝子陽性固形がんに対するNTRK阻害薬

MSI-H/dMMR固形がんに対する抗PD-1抗体薬

LOXO ONCOLOGY

FDA Accepts Larotrectinib New Drug Application and Grants Priority Review

May 29, 2018

– PDUFA date set for November 26, 2018 –

STAMFORD, Conn., May 29, 2018 (GLOBE NEWSWIRE) -- Loxo Oncology, Inc. (Nasdaq:LOXO), a biopharmaceutical company innovating the development of highly selective medicines for patients with genetically defined cancers, today announced that the U.S. Food and Drug Administration (FDA) has accepted the company's New Drug Application (NDA) and granted Priority Review for larotrectinib for the treatment of adult and pediatric patients with locally advanced or metastatic solid tumors harboring an *NTRK* gene fusion. The FDA has set a target action date of November 26, 2018, under the Prescription Drug User Fee Act (PDUFA).

承認

"We are ccepted by FDA and granted Priority Review status," said Josh Bilenker, M.D., ch Larotrectinib treating cancer based on the tumo the body."

The FDA ns of medici e significant improvements in the sa agnosis, or hen compared to standard applicati Breakthrou iatric Disease Designation and Orph

Loxo Oncology and Bayer are engaged in a collaboration for the development and commercialization of larotrectinib. Bayer plans to submit a Marketing Authorization Application (MAA) in the European Union in 2018.

About Larotrectinib (LOXO-101)

Larotrectinib is an oral and highly selective investigational tropomyosin receptor kinase (TRK) inhibitor in clinical development for the treatment of patients with cancers that harbor a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion. Growing research suggests that the *NTRK* genes, which encode for TRKs, can become abnormally fused to other genes, resulting in growth signals that can lead to cancer in many sites of the body. In clinical trials, larotrectinib demonstrated anti-tumor activity in patients with tumors harboring NTRK gene fusions, regardless of patient age or tumor type. In an analysis of 55 RECIST-evaluable adult and pediatric patients with NTRK gene fusions, larotrectinib

U.S. Department of Health and Human Services

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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 grants accelerated approval to pembrolizumab for first tissue/site agnostic indication

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

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

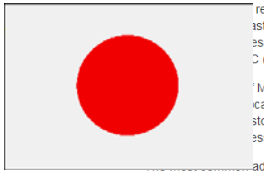
承認

e U.S. Food and Drug Administration granted accelerated approval to pembrolizumab & Co.) for adult and pediatric patients with unresectable or metastatic, microsatellite -H) or mis mors that have progressed following prior ave no s s or with MSI-H or dMMR colorectal cancer that wing trea tin, and irinotecan.

t tissue/s

ased on c MMR cancers enrolled across five uncontrolled, enter, sing ad colorectal cancer and 59 patients were of 14 other cancer types. Patients received either pembrolizumab, 200 mg every 3 weeks, or pembrolizumab, 10 mg/kg every 2 weeks. Treatment continued until unacceptable toxicity, or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or associated with a decline in performance status. A maximum of 24 months of treatment was administered.

The major efficacy outcome measures were objective response rate (ORR) assessed by blinded independent review according to RECIST 1.1, and response duration. ORR was 39.6% (95% CI: 31.7, asted six mo who responded to pembrolizumab. There esponses a ilar irrespective of whether patients were C (36%) or e 14 other cancer types).



承認

MSI-H or c patients (135/149) was prospectively al laborat ase chain reaction (PCR) tests for MSI-H tochemistr 149 patients, MSI-H status was determined in essment of entral laboratory-developed PCR test.

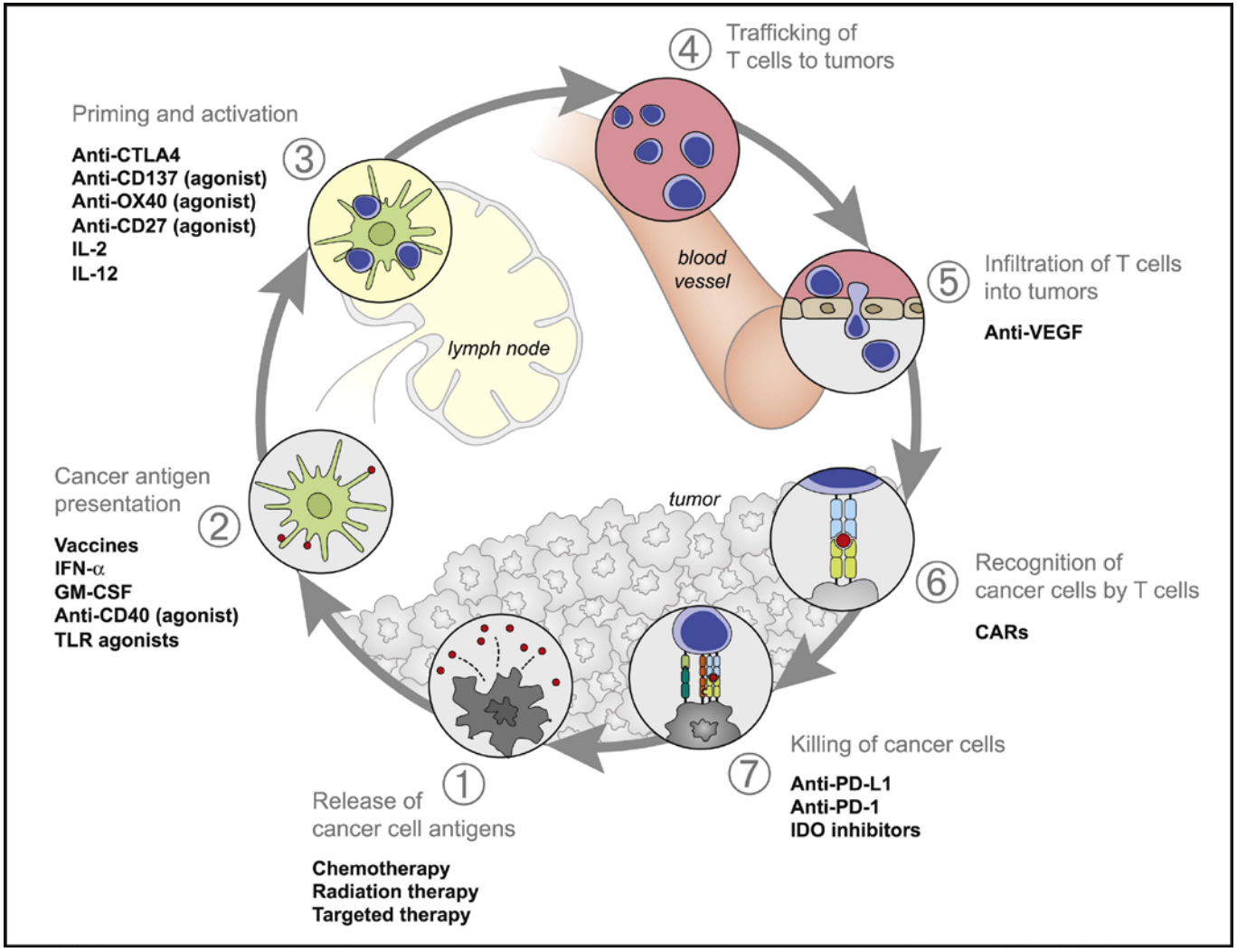
adverse reactions to pembrolizumab include fatigue, pruritus, diarrhea, decreased appetite, rash, pyrexia, cough, dyspnea, musculoskeletal pain, constipation, and nausea. Pembrolizumab is associated with immune-mediated side effects, including pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis.

The prescribing information for pembrolizumab includes a "Limitation of Use" stating that the safety and effectiveness of pembrolizumab in pediatric patients with MSI-H central nervous system cancers have not been established.

The recommended pembrolizumab dose for this indication is 200 mg for adults or 2 mg/kg (up to a maximum of

- 臨床開発の進まない希少がん・希少フラクションが対象
- 治療薬の効果発現の生物学的メカニズムが明確

Therapies that Might Affect the Cancer-Immunity Cycle

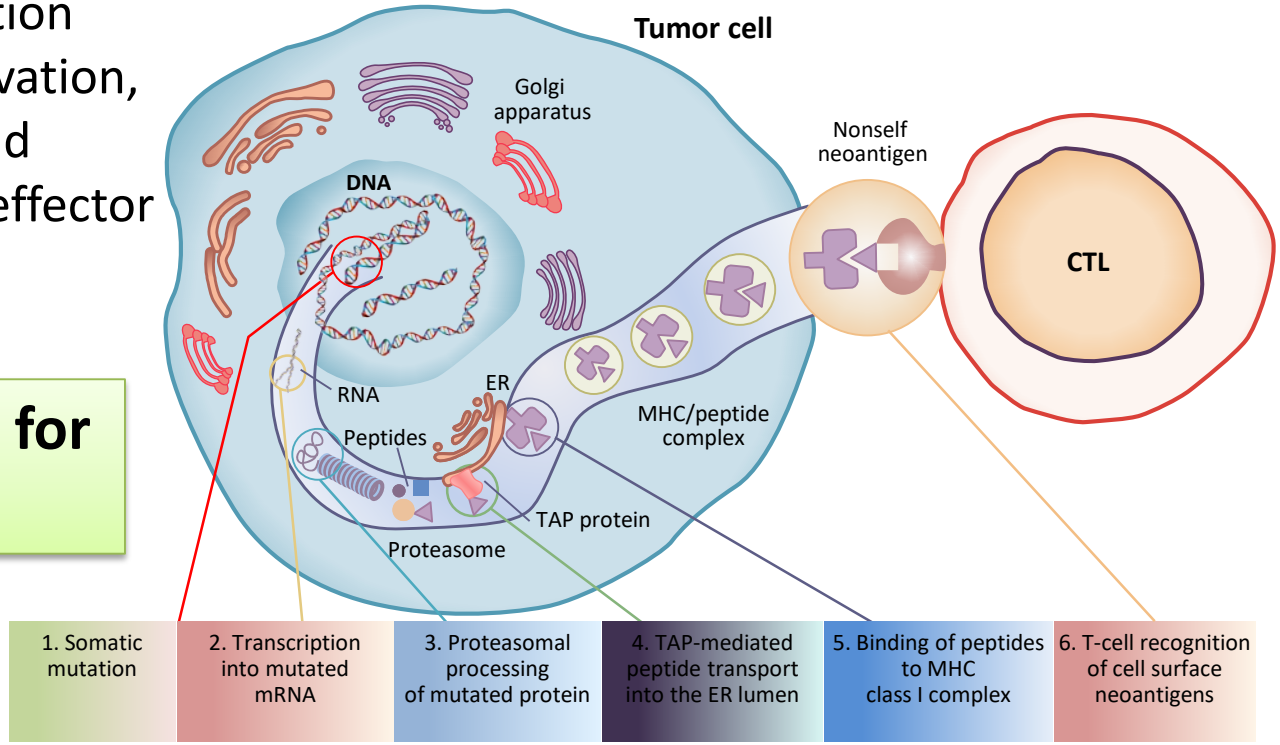


Chen, Immunity, 2013

Tumor Mutational Burden and Neoantigens

- **Tumor mutational burden (TMB)**: number of somatic mutations in the tumor genome
- Somatic mutations may be expressed at the RNA/protein level, resulting in **neoantigens (or neoepitopes)**
- Neoantigen recognition promotes T-cell activation, clonal expansion, and differentiation into effector and memory T cells

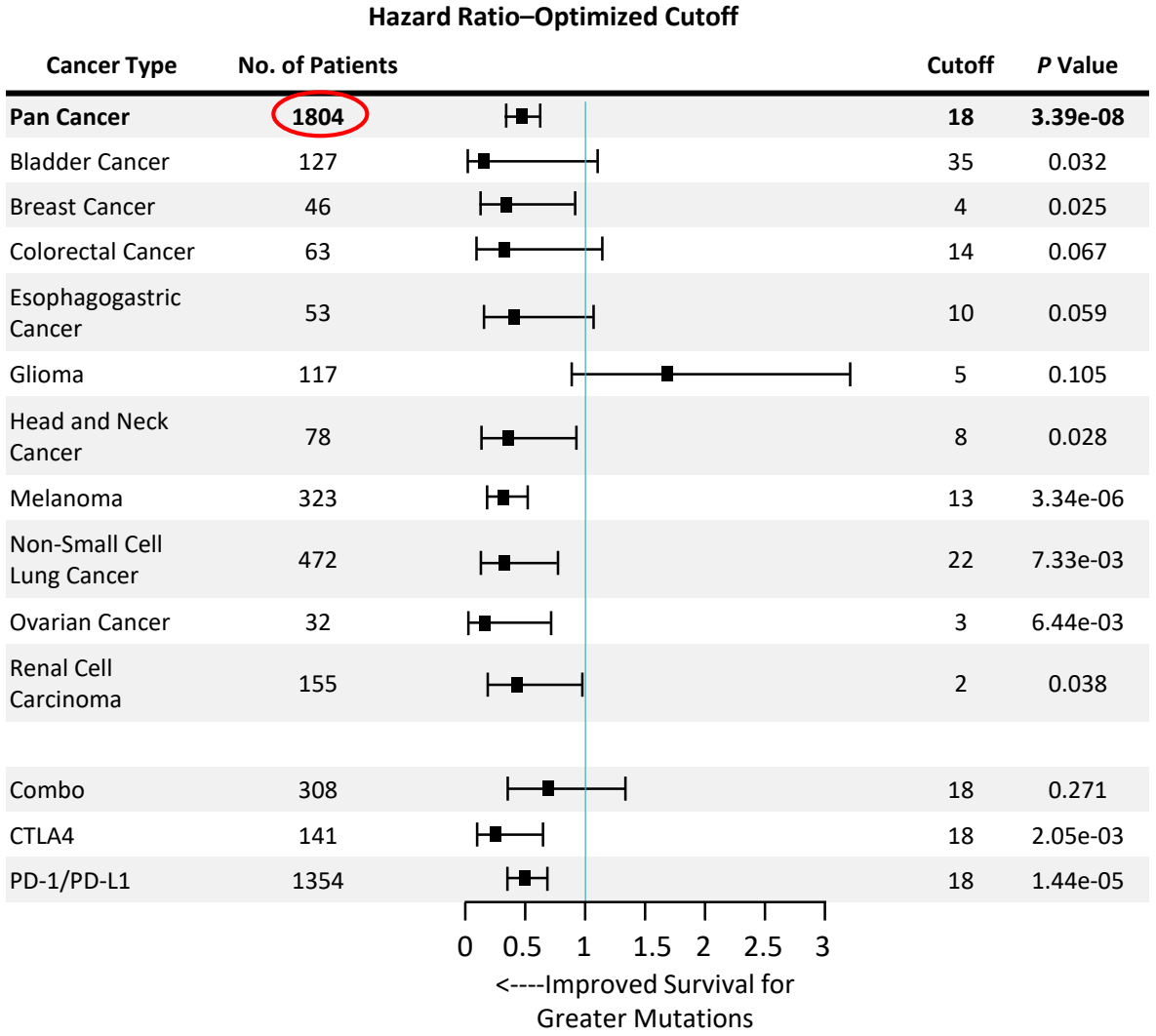
TMB is a surrogate for neoantigen



1. Lawrence MS et al. *Nature*. 2013;499(7457):213-218.
2. Schumacher TN, Schreiber RD. *Science*. 2015;348(6230):69-74.
3. Chabanon RM et al. *Clin Cancer Res*. 2016;22(17):4309-4321.
4. Kim JM, Chen DS. *Ann Oncol*. 2016;27(8):1492-1504.
5. Giannakis M et al. *Cell Rep*. 2016;15:857-865.

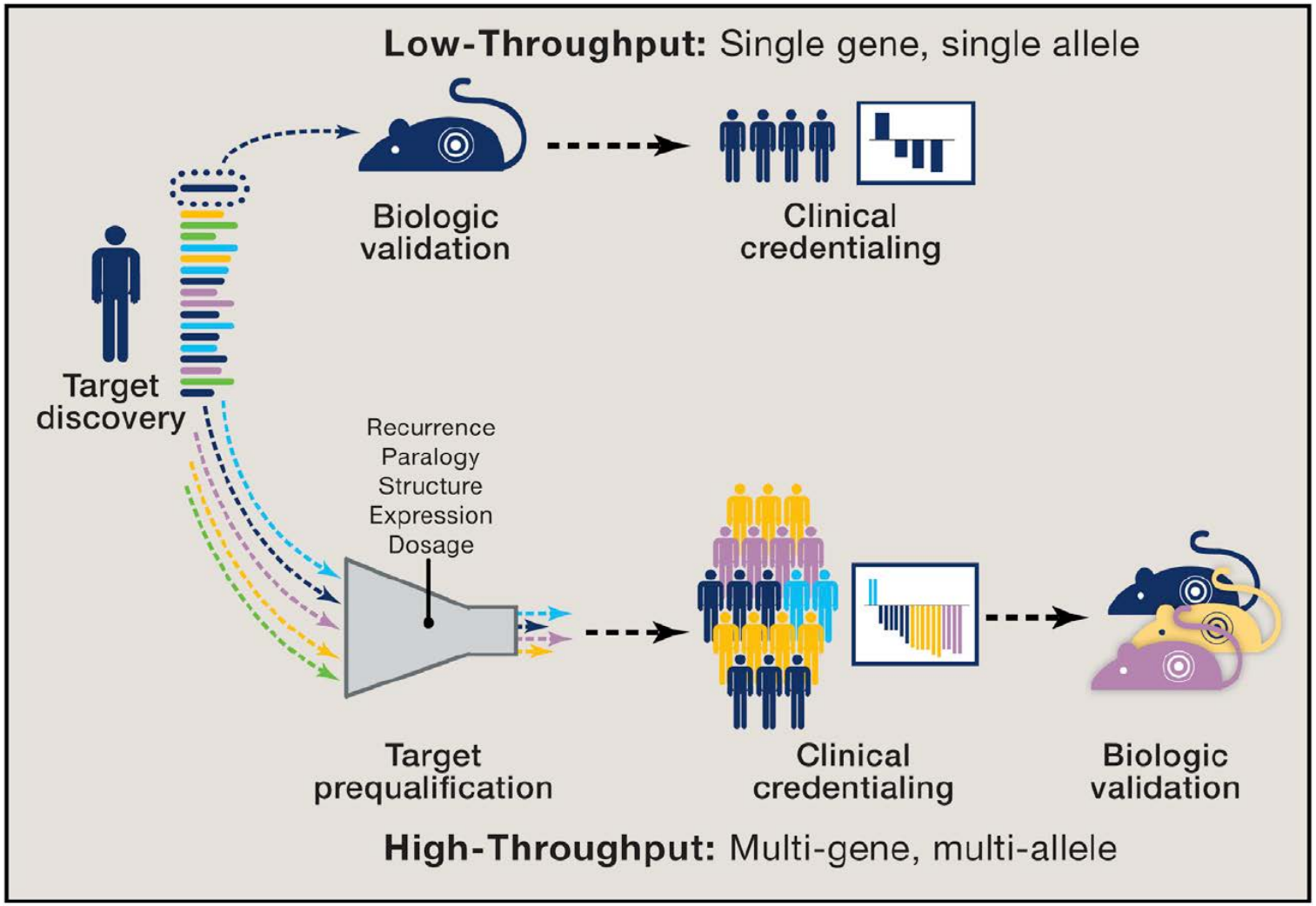
Pan-Tumor Assessment of TMB and Clinical Benefit with Checkpoint Inhibitors

- MSKCC cohort: ~1800 patients across 10 tumor types received commercial PD-(L)1 and/or CTLA-4 inhibitor therapy[1]
- TMB was assessed using the MSKCC-IMPACT™ NGS gene panel[1,2]
- Data demonstrated improved survival / outcome with greater mutations across all tumor types except glioma[1]



1. Chan TA. Oral presentation at ASCO-SITC 2017. 2. Cheng DT et al. *J Mol Diagn*. 2015;17:251-264.

Approaches to Novel Target Validation



Hyman, Cell, 2017

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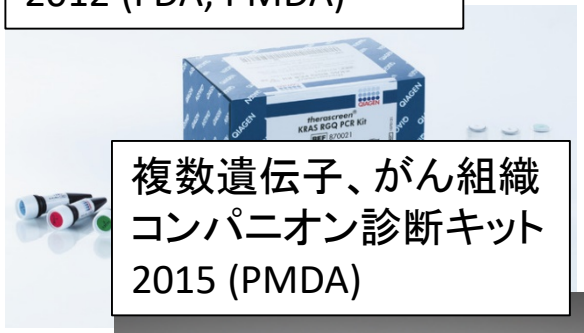
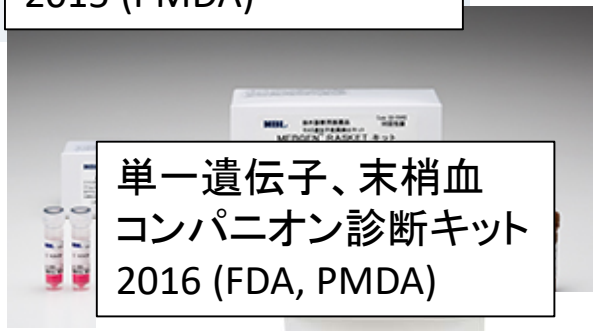
がん遺伝子関連検査の薬事承認

単一遺伝子、がん組織
コンパニオン診断キット
2012 (FDA, PMDA)



複数遺伝子、がん組織
コンパニオン診断キット
2015 (PMDA)



単一遺伝子、末梢血
コンパニオン診断キット
2016 (FDA, PMDA)

がん組織、NGS
コンパニオン診断システム
2017 (FDA), 2018 (PMDA)

がん組織、NGS
遺伝子プロファイル検査システム
2017 (FDA), 2018 (PMDA)

がん組織、NGS
遺伝子プロファイル検査システム/
コンパニオン診断システム
2017 (FDA), 2018 (PMDA)

コンパニオン診断（CDx）と遺伝子プロファイル検査（Comprehensive Gene Profile, CGP）の比較

	CDx	CGP
診断に基づく治療	確実なエビデンスに基づいた承認薬	医学的に効果が期待できる未承認薬（臨床試験）、適応外使用
診断のプロセス	対応する承認薬の使用可否を直接決定	臨床的意義を専門家が総合的に判断
実施施設	―	専門家会議が開催可能な施設（がんゲノム医療中核拠点病院・連携病院）
規制上のポイント	陽性・陰性反応的中度	分析学的妥当性

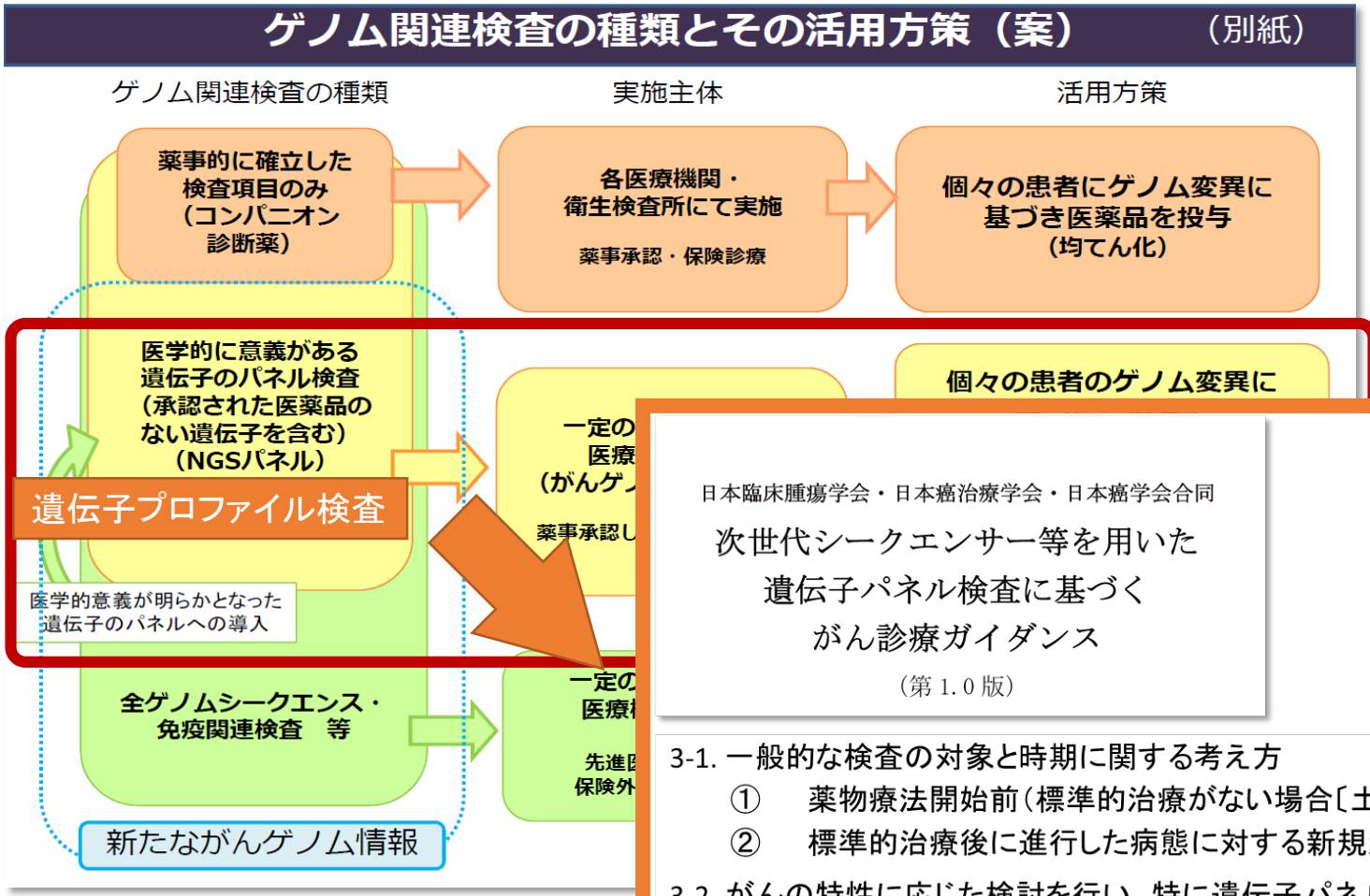
PMDA矢花直幸博士の資料（第25回抗悪性腫瘍薬開発フォーラム 2018）を改変

Comparison of the MSK-IMPACT™ and FoundationOne CDx™ Panels

	MSK-IMPACT[1-3]	FoundationOne® CDx[3-7]
Median depth of coverage	718x	500x
Number of genes	468	324
Molecular signatures part of intended use	MSI*	TMB and MSI
Agency approval	FDA granted marketing authorization	FDA and CMS approval as a companion diagnostic
Testing locations	Single-site assay performed at MSKCC	Single-site assay performed at Foundation Medicine, Inc.
Concordance	> 92% in detecting MSI	> 94% in detecting select mutations
Biomarker reporting tier	Level 2: Cancer Mutations with Evidence of Clinical Significance	Level 1: Companion Diagnostic

1. US Food and Drug Administration. https://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm584603.pdf. Accessed December 05, 2017. 2. Zehir A, et al. *Nature Medicine*. 2017. 3. US Food and Drug Administration. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm585347.htm. Accessed December 05, 2017. 4. US Food and Drug Administration. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ ucm587273.htm. Accessed December 05, 2017. 5. Foundation Medicine Inc. http://investors.foundationmedicine.com/releasedetail.cfm?ReleaseID=1050380. Accessed December 05, 2017. 6. Hoffmann-La Roche. https://www.roche.com/investors/updates/inv-update-2017-12-04.htm. Accessed December 05, 2017. 7. Frampton GM, et al. *Nature Biotechnology*. 2013;31(11):1023-1031.

がんゲノム医療体制でのCDxとCGPの切り分け



日本臨床腫瘍学会・日本癌治療学会・日本癌学会合同

次世代シークエンサー等を用いた
遺伝子パネル検査に基づく
がん診療ガイダンス

（第 1.0 版）

3-1. 一般的な検査の対象と時期に関する考え方

① 薬物療法開始前（標準的治療がない場合〔土原註〕）

② 標準的治療後に進行した病態に対する新規治療の探索

3-2. がんの特性に応じた検討を行い、特に遺伝子パネル検査が活用されるべきがん種について

① 小児がん・希少がん

② 原発不明がん

③ その他のがん

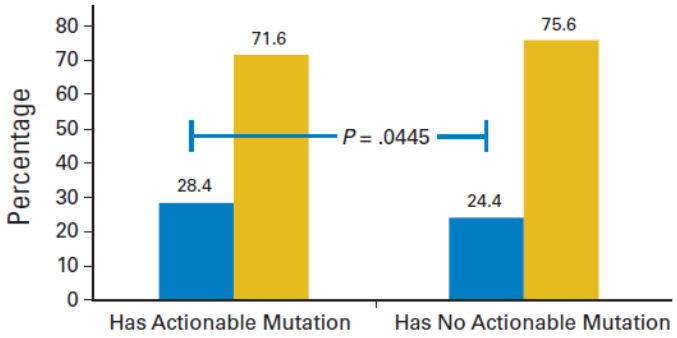
内を担う。平成30年度は先進医療B、

薬事承認されたコンパニオン診断、個別の

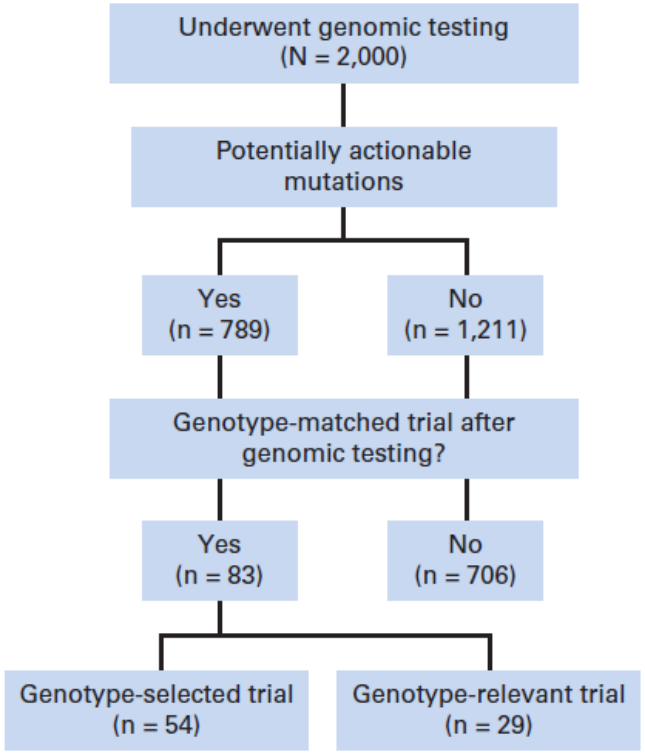
がんゲノム医療がいま必要とされる理由

- がん細胞・微小環境を標的とした合理的な治療法（分子標的療法・免疫チェックポイント療法）の発達
- 個々の症例の分子生物学的背景による治療選択が必須
- 次世代シークエンス技術の一般化により多数遺伝子の同時解析（遺伝子パネル検査）が可能に
- 米国等で遺伝子パネル検査は研究段階から一般臨床へ拡大
- 実地診療で得られる臨床ゲノム情報は今後の治療・診断開発の基礎データに

MD Anderson Cancer Center (2012-2013)



C



PRECISION MEDICINE OUTLOOK

PERSPECTIVE

がんゲノム医療は幻想?!

Precision oncology promises drugs that target the specific mutations in their tumour, the hope of producing long-lasting remission and extending their survival. The basic idea is to use genetic testing to link patients with the drugs that will work best for them, irrespective of the tissue of origin of their tumour. Enthusiasm has been fuelled by reports of exceptional or super responders — individuals for whom experimental therapies seem to work spectacularly well.

In one such example, an individual with metastatic bladder cancer showed a dramatic response to the drug everolimus[1]. Sequencing later revealed that the patient had a mutation that affects the mTOR pathway, which is the mechanism of action of everolimus. Yet despite the hype surrounding rare cases such as these, most people with cancer do not benefit from the precision strategy, nor has this approach been shown to improve outcomes in controlled studies. Precision oncology remains a hypothesis in need of verification.

Few patients benefit from precision oncology. Data from some 2,600 people enrolled in a sequencing programme at the MD Anderson Cancer Center in Houston, Texas, showed that just 6.4% were paired with a targeted drug for identified mutations[2]. Similarly, the Molecular Analysis for Therapy Choice (NCI-MATCH) trial at the US National Cancer Institute has enrolled 795 people who have relapsed solid tumours and lymphoma, but as of May 2016 it had only been able to pair 2% of patients with a targeted therapy[3].

NOT SO EXCEPTIONAL

But being assigned such a therapy is not proof of benefit. When patients with diverse, relapsed cancers are given drugs based on biological markers, only around 30% respond at all, and the median progression-free survival is just 5.7 months[4]. Multiplying the percentage of patients receiving targeted therapies by this response rate, I estimate that precision oncology will benefit around 1.5% of patients with relapsed and refractory solid tumours.

It is on this tiny proportion of patients that the hopes for precision oncology have been built. Although many patients have undergone sequencing in the past decade (Foundation Medicine, a commercial provider of tumour profiling, has sequenced at least 18,000 patients), the number of reported cases of exceptional and super responders over that time are few. In a search of the biomedical literature with a colleague, we identified only 32 cases[5].

Moreover, even when vignettes such as these are reported, they often have major gaps. The number and duration of responses to previous therapies, and the number of patients who were treated to identify the super responder[5], are often omitted. Because even the most serious malignancies, such as pancreatic cancer, exist along a continuum, some patients are already destined to outlive the average. Indeed, we found several cases in which the 'exceptional' responders had already experienced exceptional responses to conventional chemotherapy before their actually miraculous response to precision oncology[5]. It is hard to avoid the unsettling conclusion that such cases do not reflect the success of precision oncology, but rather the selective reporting of individuals who were always likely to do well.

When considered objectively, the prospects and potential of precision oncology are sobering. At best, we may expect short-lived responses in a tiny fraction of patients, with the inevitable toxicity of targeted therapies and inflated cost that this approach guarantees.

PRECISION ONCOLOGY ON TRIAL

In medical science, the ultimate judge of a therapeutic strategy is the randomized controlled trial. So far, precision oncology has been tested in only one such published study[6]. The SHIVA trial assigned 99 patients with cancer to therapies based on an identified mutation or mutations, and 96 patients to the treatment selected by their physicians. Median progression-free survival, the primary endpoint, was almost equally poor in both cases (2.3 and 2.0 months, respectively).

No single trial can prove that a therapy does not work in any circumstances, and SHIVA is no exception. It paired patients with drugs for 'pathway' mutations, not just for mutations that can be targeted with drugs, allowing those running the trial to enrol more than a quarter of screened patients. But further randomized controlled trials are needed to test alternative hypotheses, and the use of different medications and alternative pathways. These trials will have to balance applicability and generalizability (the percentage of screened patients that can be enrolled) against the strength of the biological rationale. Several more trials are needed before we can judge whether this strategy is viable.

WHEN CONSIDERED OBJECTIVELY, THE PROSPECTS AND POTENTIAL OF PRECISION ONCOLOGY ARE SOBERING.

Precision oncology is inspirational. What doctor or patient would not want to harness genetics to tailor a therapy to an individual? But travelling back in a time machine is also inspirational. Who would not want to wind back the clock to remove their cancer before it spreads? In both cases, however, as of 2016, the proposal is neither feasible, cost-effective nor assured of future success. Yet in only one of these cases does the rhetoric so far outpace the reality that we risk fooling even ourselves. ■

Vinay Prasad *is a haematologist–oncologist at the Knight Cancer Institute, Oregon Health and Science University, Portland, Oregon, USA.*
e-mail: prasad@ohsu.edu

1. Iyer, G. *et al. Science* **338,** 221 (2012).
2. Meric-Bernstam, F. *et al. J. Clin. Oncol.* **33,** 2753–2762 (2015).
3. ECOG-ACRIN Cancer Research Group http://ecog-acrin.org/nci-match-eay131/interim-analysis (2016).
4. Schwaederle, M. *et al. JAMA Oncol.* http://dx.doi.org/10.1001/jamaoncol.2016.2129 (2016).
5. Prasad, V. & Vandross, A. *Mayo Clin. Proc.* **90,** 1639–1649 (2015).
6. Le Tourneau, C. *et al. Lancet Oncol.* **16,** 1324–1334 (2015).

Meric-Bernstein F, J Clin Oncol, 2015

SCRUM-Japan

Cancer Genomic Screening Project for Individualized Medicine in Japan

Atsushi Ohtsu
NCCHE

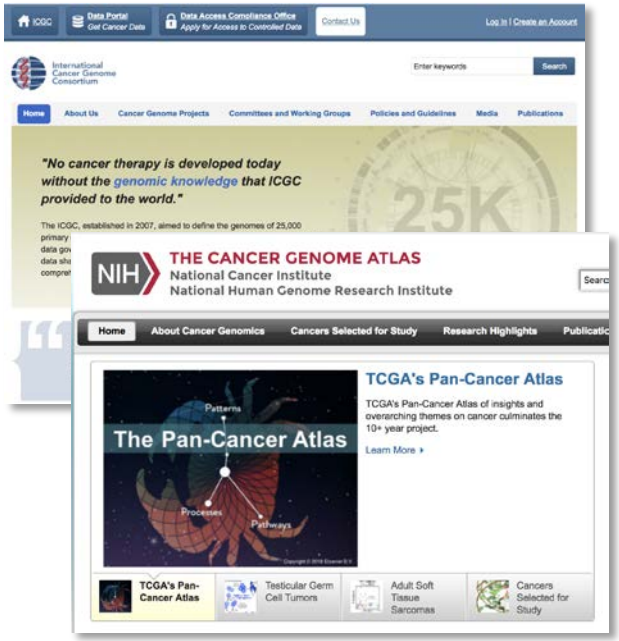
1st stage: Feb 2015-Mar 2017
2nd stage: Apr 2017-

Koichi Goto
NCCHE

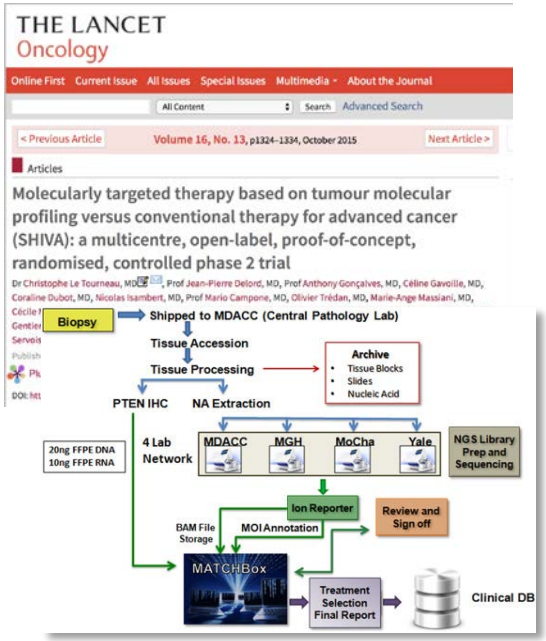
Takayuki Yoshino
NCCHE

Cancer genomics and drug development: Before SCRUM-Japan

Molecular epidemiology



Master protocol-based Clinical Trials



Cancer genomics and drug development: Before SCRUM-Japan

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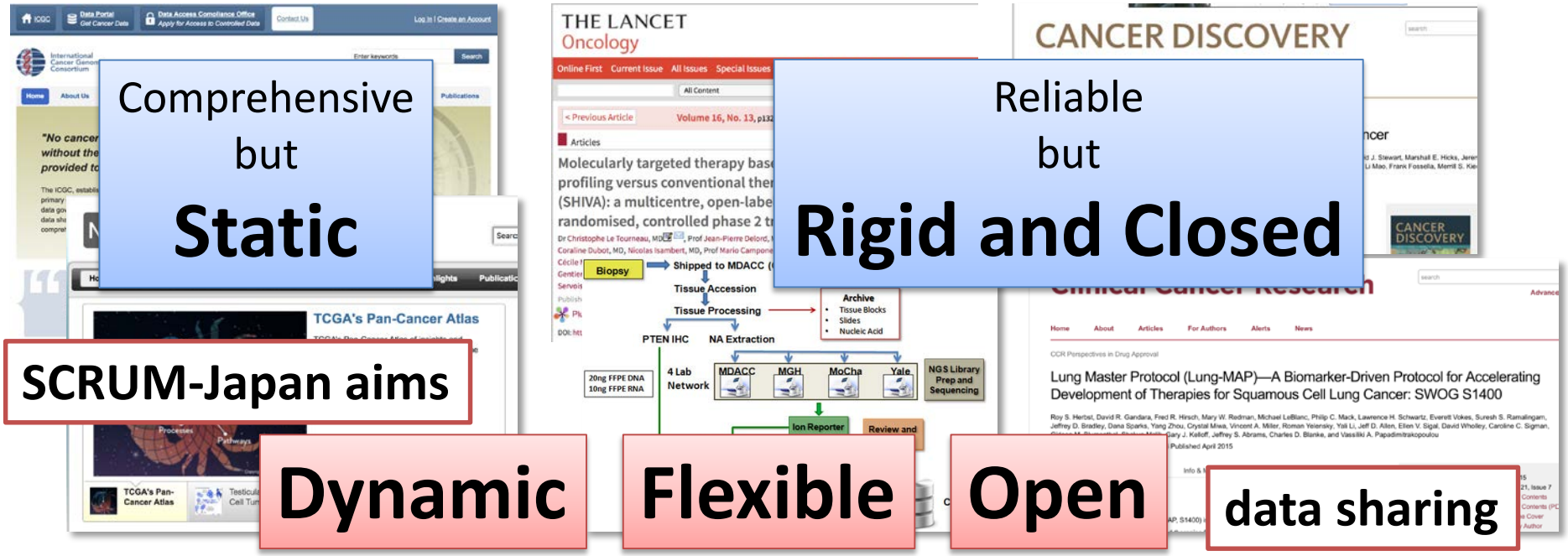
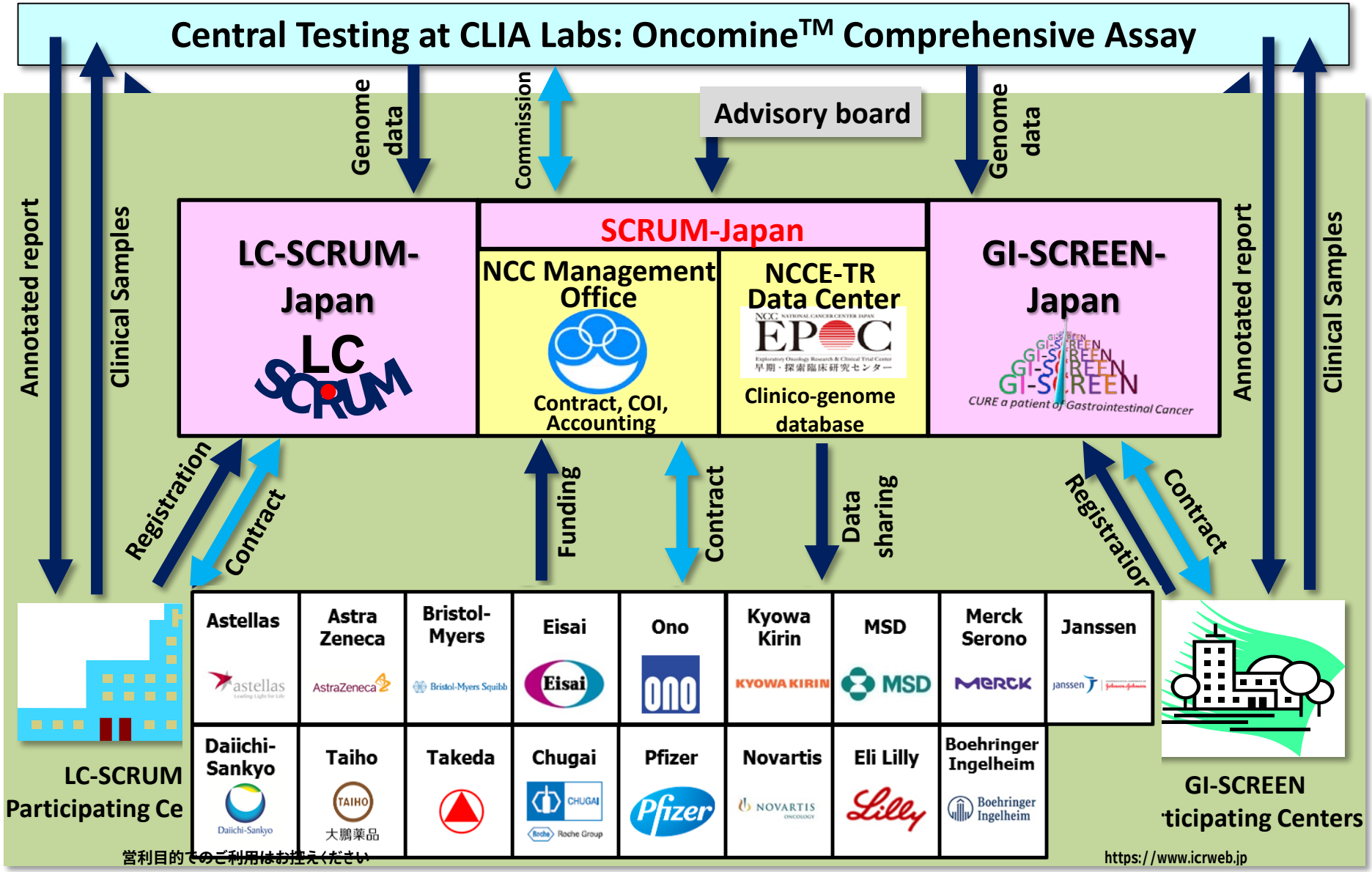
Master protocol-based Clinical Trials



産学連携全国がんゲノムスクリーニング（SCRUM-Japan）

- **新薬開発を目指した世界最大規模のゲノムスクリーニングコンソーシアム**
  - 製薬企業17社との共同研究契約（企業資金はNGS解析費用のみ。データセンター、レジストリ、医師主導治験は公的研究費により実施）
  - 全国250を超える医療機関の参加
- **十分な規制面への対応と詳細な臨床情報**
  - CLIA認証ラボ（日米2箇所）での国際的互換性を有するNGSパネル解析
  - 薬事承認申請データに使用可能な企業・医師主導治験での実施
- **新薬へのがん患者アクセスの最大化**
  - 治験情報の公開と患者紹介ネットワークの構築
- **NCC、企業、参加施設代表者による公平な運営**
  - アカデミア代表者・企業代表者同数による運営委員会
  - 一次利用の知財は国がんに帰属。二次利用は実施研究者・企業
- **ゲノム情報のリアルタイムでの共有**
  - 各参加施設・企業が自由に閲覧・集計可能

SCRUM-Japan; an Academia-industrial Collaboration Program

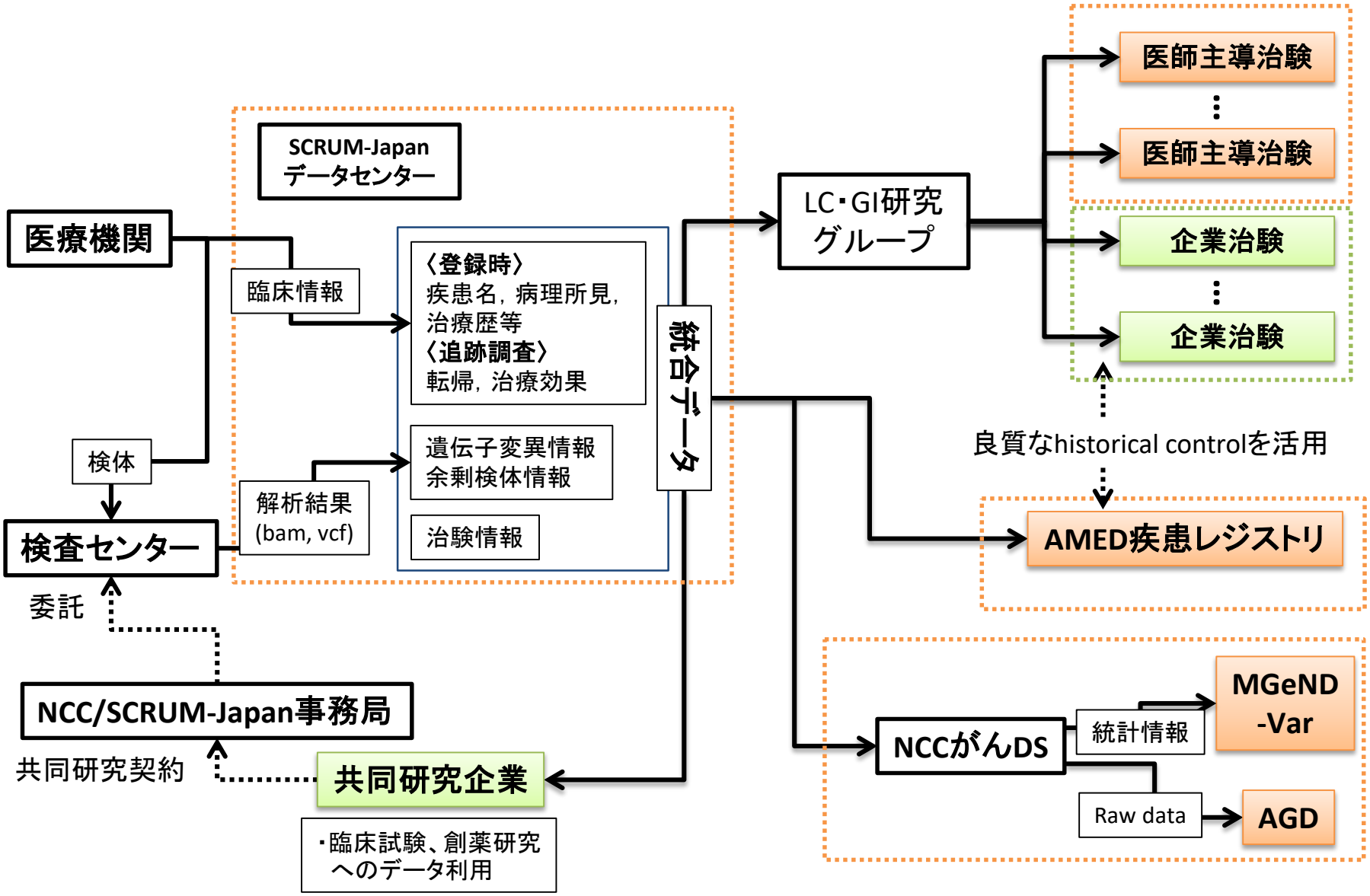


Gene List for OCAv3 (161 genes)

Hotspot Genes				Full-Length Genes		Copy Number Genes		Gene Fusions (Inter and Intragenic)	
AKT1	FGFR1	MAP2K1	RAF1	ARID1A	NOTCH1	AKT1	IGF1R	AKT2	MYB
AKT2	FGFR2	MAP2K2	RET	ATM	NOTCH2	AKT2	KIT	ALK	MYBL1
AKT3	FGFR3	MAP2K4	RHEB	ATR	NOTCH3	AKT3	KRAS	AR	NF1
ALK	FGFR4	MAPK1	RHOA	ATRX	PALB2	ALK	MDM2	AXL	NOTCH1
AR	FLT3	MAX	ROS1	BAP1	PIK3R1	AR	MDM4	BRAF	NOTCH4
ARAF	FOXL2	MDM4	SF3B1	BRCA1	PMS2	AXL	MET	BRCA1	NRG1
AXL	GATA2	MED12	SMAD4	BRCA2	POLE	BRAF	MYC	BRCA2	NTRK1
BRAF	GNA11	MET	SMO	CDK12	PTCH1	CCND1	MYCL	CDKN2A	NTRK2
BTK	GNAQ	MTOR	SPOP	CDKN1B	PTEN	CCND2	MYCN	EGFR	NTRK3
CBL	GNAS	MYC	SRC	CDKN2A	RAD50	CCND3	NTRK1	ERBB2	NUTM1
CCND1	H3F3A	MYCN	STAT3	CDKN2B	RAD51	CCNE1	NTRK2	ERBB4	PDGFRA
CDK4	HIST1H3B	MYD88	TERT	CHEK1	RAD51B	CDK2	NTRK3	ERG	PDGFRB
CDK6	HNF1A	NFE2L2	TOP1	CREBBP	RAD51C	CDK4	PDGFRA	ESR1	PIK3CA
CHEK2	HRAS	NRAS	U2AF1	FANCA	RAD51D	CDK6	PDGFRB	ETV1	PPARG
CSF1R	IDH1	NTRK1	XPO1	FANCD2	RB1	EGFR	PIK3CA	ETV4	PRKACA
CTNNB1	IDH2	NTRK2		FANCI	RNF43	ERBB2	PIK3CB	ETV5	PRKACB
DDR2	JAK1	NTRK3		FBXW7	SETD2	ESR1	PPARG	FGFR1	PTEN
EGFR	JAK2	PDGFRA		MLH1	SLX4	FGF19	RICTOR	FGFR2	RAD51B
ERBB2	JAK3	PDGFRB		MRE11A	SMARCA4	FGF3	TERT	FGFR3	RAF1
ERBB3	KDR	PIK3CA		MSH2	SMARCB1	FGFR1		FGR	RB1
ERBB4	KIT	PIK3CB		MSH6	STK11	FGFR2		FLT3	RELA
ERCC2	KNSTRN	PPP2R1A		NBN	TP53	FGFR3		JAK2	RET
ESR1	KRAS	PTPN11		NF1	TSC1	FGFR4		KRAS	ROS1
EZH2	MAGOH	RAC1		NF2	TSC2	FLT3		MDM4	RSPO2
								MET	RSPO3
									TERT

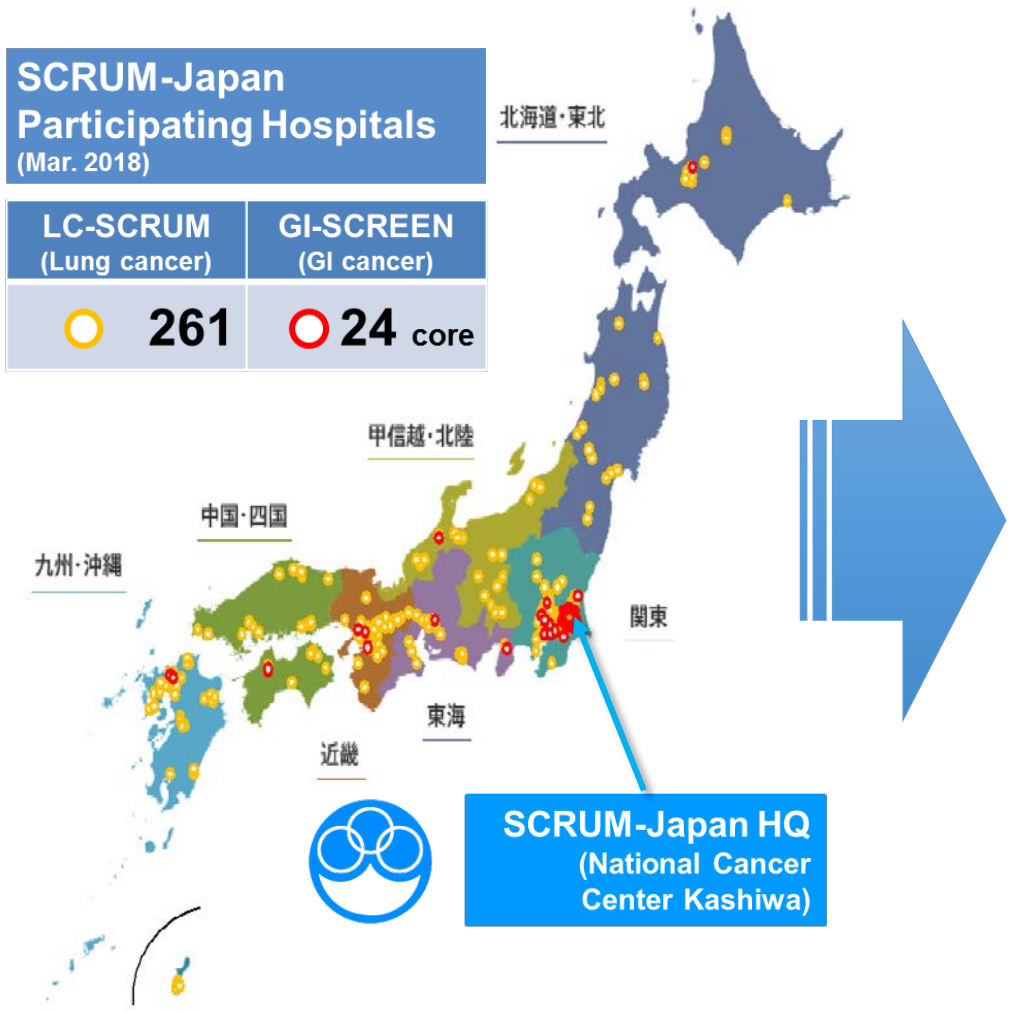
Assay	Configuration	Unique Genes	DNA	RNA
OCAv3	OCAv3 DNA + OCAv3 RNA	161	146	51

SCRUM-Japanにおけるデータのながれ



SCRUM-Japanへの登録状況

(2015年2月 – 2018年6月)



	No.
非小細胞肺がん	**4,346**
非扁平上皮がん	3,701
扁平上皮がん	645
消化器がん	**5,284**
食道がん	370
胃がん	1,142
小腸がん	93
大腸がん	2,329
肝細胞がん	67
胆道がん	418
膵がん	653
神経内分泌腫瘍	73
GIST	79
その他	60
計	**9,630**

臨床試験における被験者選定システムの利用

Umbrella type study

臓器	標的	薬剤	相	主導
肺がん	RET	RET阻害剤A	II	IIT (国がん東)
肺がん	RET	RET阻害剤B	I /II	IIT (金沢大)
肺がん	RET	RET阻害剤C	II	企業(内資)
肺がん	ROS1	ROS1阻害剤A	I /II	企業(外資)
肺がん	ROS1	ROS1阻害剤B	II	企業(外資)
肺がん	ROS1	ROS1阻害剤B	EAP	企業(外資)
肺がん	ROS1	ROS1阻害剤C	I	企業(内資)
肺がん	ROS1/ALK	ROS1阻害剤D	I	企業(外資)
肺がん	MET	MET阻害剤A	II	企業(外資)
肺がん	MET	MET阻害剤B	II	企業(外資)
肺がん	MET	MET阻害剤C	I	企業(外資)
肺がん	MET	MET阻害剤D	II	IIT (九州がんC)
肺がん	ALK	ALK阻害剤A	II	企業(外資)
肺がん	ALK	ALK阻害剤B	II	IIT (国がん東)
肺がん	ALK	ALK阻害剤C	I /II	企業(外資)
肺がん	ALK	ALK阻害剤D	III	企業(内資)
肺がん	HER2	HER2阻害剤A	II	IIT (岡山大)
肺がん	HER2	HER2阻害剤B	II	IIT (北大)
肺がん	KRAS	RAS阻害剤	III	企業(外資)
肺がん	BRAF	治験薬X+Y	II	企業(外資)
肺がん	PI3K/AKT/mTOR	PI3K/mTOR阻害剤	II	IIT (国がん東)
大腸がん	MSI-H	抗PD-1抗体	III	企業(外資)
大腸がん	HER2	HER2阻害剤C+D	II	IIT (国がん東)
大腸がん	BRAF V600E	治験薬Z	II	IIT(愛知県がんC)
大腸がん	BRAF nonV600E	治験薬U+V+W	II	IIT (国がん東)
胆道がん	HER2	HER2阻害剤E	II	IIT (国がん東)

Phase I/Basket type study

臓器	標的	薬剤	相	主導
固形がん	MET	MET阻害剤	I	企業(外資)
固形がん	FGFR	FGFR阻害剤a	I	企業(内資)
固形がん	FGFR	FGFR阻害剤b	I	企業(内資)
固形がん	EGFR/HER2	HER1/2阻害剤	I	企業(外資)
固形がん	HER2	HER2阻害剤	I	企業(内資)
固形がん	NTRK1/2/3	NTRK阻害剤a	I	企業(外資)
固形がん	NTRK1/2/3	NTRK阻害剤b	I	企業(外資)
固形がん	NTRK1/2/3	NTRK阻害剤c	I	企業(内資)
固形がん	ROS1/ALK	治験薬a	I	企業(外資)
固形がん	PI3K/AKT/mTOR	AKT阻害剤a	I	企業(内資)
固形がん	PI3K/AKT/mTOR	AKT阻害剤b	I	企業(外資)
固形がん	PI3K/AKT/mTOR	AKT阻害剤c	I	企業(外資)
固形がん	FGFR	FGFR阻害剤c	I	企業(内資)
固形がん	FGFR	FGFR阻害剤d	I	企業(外資)
固形がん	FGFR	FGFR阻害剤e	I	企業(外資)
固形がん(GI)	TMB-H	抗PD-1抗体	II	IIT (国がん東)

新薬開発治験合計42試験：
企業治験 30 & 医師主導治験 12
umbrella 26 & basket 16

IIT: 医師主導治験

SCRUM-Japanプラットフォーム利用による各種治験への登録状況

Organ	Genetic alterations	Screened No.	Enrolled No. (%)
NSCLC	ROS1 fusion	149	51 (34)
	RET fusion	117	53 (45)
	ALK fusion	104	7 (7)
	NTRK3 fusion	2	1 (50)
	ERBB2 mut/amp	210	12 (6)
	MET amp/ex14 skip	92	18 (20)
	PIK3CA mut	77	1 (1)
	BRAF mut (V600E)	48	3 (6)
	FGFR1 amp	47	2 (5)
	Total	846	148 (17)
CRC	BRAF mut	165	18 (11)
	ERBB2 amp	54	16 (30)
	FGFR amp	33	4 (12)
	AKT1 mut	15	1 (7)
	MSH6	18	1 (6)
	MSI-H*	51	19 (37)

*GI-SCREEN CRC-MSI

Organ	Genetic alterations	Screened No.	Enrolled No. (%)
GC	FGFR amp	30	3 (10)
	MET amp	13	2 (15)
	AKT mut	2	1 (50)
	ERBB2 amp	90	1 (1)
	ROS1 fusion	2	1 (50)
EC	FGFR amp/fusion	8	3 (38)
	FGF amp	68	2 (3)
	PIK3CA mut	21	3 (14)
	EGFR amp	16	1 (6)
	ERBB2 amp	6	1 (17)
BTC	FGFR mut/amp/fusion	15	5 (33)
	ERBB2 mut/amp	25	2 (8)
	ERBB3 amp	9	1 (11)
	PIK3CA mut	24	2 (8)
	IDH1 mut	11	1 (9)
	PTEN mut	5	1 (20)
	MLH1	1	1 (100)
PC	BRCA2 mut	11	1 (9)
Small Int	ROS1 fusion	1	1 (100)
NEC	PIK3CA mut	5	1 (20)
	Total	699	93 (15)

総計　241例（2018年6月現在）

登録が終了したSCRUM-Japan関連試験：17試験

Organ	Target	Agent	Phase	Sponsor	n	ORR	Status
NSCLC	RET	vandetanib	II	IIT (NCCE)	17	53%	In preparation
NSCLC	RET	lenvatinib	II	Eisai	25	16%	-
NSCLC	BRAF	dabra+trame	II	Novartis	57	63%	Approved
NSCLC	ROS1	crizotinib	II	Pfizer	127	77%	Approved
NSCLC	HER2	T-DM1	II	IIT (Okayama U)	15	7%	-
NSCLC	KRAS	abemaciclib	III	Lilly	OS: negative		
NSCLC	ROS1	DS6051b	I	Daiichi-Sankyo	NR		
NSCLC	ROS1/ALK	PF06463922	I	Pfizer	NR		
NSCLC	MET	AZD6049	I	AZD	NR		
NSCLC	HER2	trastuzumab	II	IIT (Hokkaido U)	NR		
NSCLC	KRAS	abemaciclib	III	Lilly	NR		
Solid tumor	HER2	DS8201a	I	Daiichi-Sankyo	24	43%	Phase II on-going
Solid tumor	MET	merestuinib	I	Lilly	NR		
Solid tumor	FGFR	DS1123	I	Daiichi-Sankyo	NR		
Solid tumor	MET	merestuinib	I	Lilly	NR		
Solid tumor	PI3K/AKT/mTOR	BYL719	I	Bayer	NR		
Solid tumor	FGFR	BGJ398	I	Novartis	NR		
Solid tumor	FGFR	ASP5878	I	Astellas	NR		

Yoh K, et al. Lancet Respir Med 2017
Velcheti V, et al. ESMO 2016
Planchard D, et al. Lancet Oncology 2016
Goto K, et al. J Clin Oncol, 2018
Hotta K, et al. J Thorac Oncol, 2018
Doi T, et al. Lancet Oncol, 2017

RWDを有効性評価の比較対照群として用いる際の問題点

- 臨床データの質保証がない
- 患者背景が不均一
- 治療ラインが不均一
- 画像評価間隔が不均一（＝ORR/PFS評価が困難）
- 経過追跡が不十分な症例（消息不明例）が多い（＝OS評価も難しい）

質保証された前向きでの臨床データ収集の必要性

SCRUM-Japan 疾患レジストリを活用した
新薬承認審査時の治験対照群データ作成のための前向き多施設共同研究
（SCRUM-Japan Registry）

◆目的

産学連携全国がんゲノムスクリーニング事業（SCRUM-Japan）に登録された症例の中で、対象となる遺伝子異常に対する新薬開発試験が実施されており、近い将来その新薬承認申請が見込まれる遺伝子異常陽性例での治療効果データなどを前向きに集積し、**当該新薬の承認審査時に比較可能な治験対照群のデータ**を作成する。

承認審査時の「評価資料」とすることを目指す

＝

質保証（信頼性保証）されたデータの収集、マネジメント

施設数を限定（登録上位約50施設）
治験対象となりうる変異陽性例に限定

希少フラクション治験対照群データ作成に向けた前向きレジストリの構築

◆　評価項目

対象とする遺伝子異常陽性例ごとに、以下の項目を算出する。

① 各治療ライン及び治療レジメンにおける以下の項目

- 奏効率 （ORR：Objective Response Rate）
- 奏効持続期間 （DoR：Duration of Response）
- 病勢コントロール率 （DCR：Disease Control Rate）
- 無増悪生存期間 （PFS：Progression Free Survival）
- 治療成功期間 （TTF：Time to Treatment Failure）

② 全生存期間 （OS：Overall Survival）

◆ 参加予定施設数：57施設

● **進捗状況**

- IRB承認・契約締結施設数： 41施設
- 登録開始: 2017年11月30日
- 登録数（6/19現在）: 66例

	Gene alteration
Non-sq NSCLC	RET fusion gene MET ex14 skip / amplification
Sq NSCLC	FGFR1/2/3 amplification/fusion PIK3CA mutation/amplification
CRC	BRAF V600E/non-V600E mutation ERBB2 amplification
Gastric cancer	FGFR2 amplification MET amplification
Esophageal cancer	ERBB2 amplification PIK3CA mutation/ amplification
Biliary tract cancer	FGFR2 fusion ERBB2 amplification IDH1 mutation
Pancreatic cancer	BRCA2 mutation PALB2 mutation ATM mutation

SCRUM-J RWD とSCRUM-J 前向き(規制対応)レジストリ

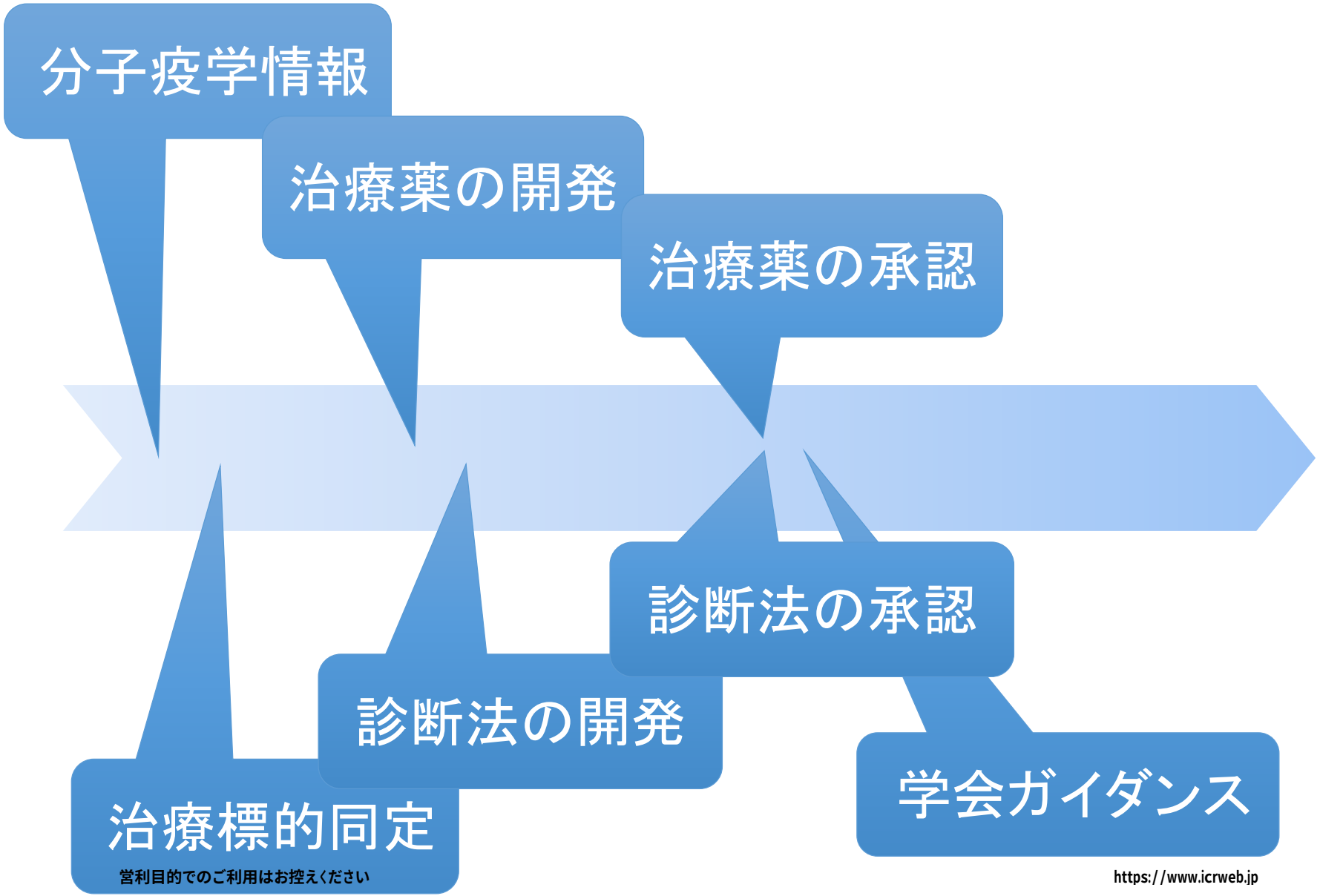
		SCRUM-J RWD (LC-SCRUM)	SCRUM-Japan Registry
参加施設数		260施設	57施設
PS,年齢、転移部位	データ収集タイミング	登録時点のみ	各治療ライン開始時
薬物療法歴	治療目的	-	各治療ごとの内訳 ・neoadjuvant/adjuvant/palliative
	治療中止理由	-	治療中止理由の内訳
	増悪日	-	画像での増悪判定日
画像評価	収集データ	Best response (RECIST ver1.1) のみ	各画像評価時点(RECIST ver1.1)
	評価間隔	不均一(担当医ごと)	6ー10週(プロトコール規定)
	標的病変区分	-	・測定可能病変 ・評価可能病変
QC/QA	モニタリング	-	中央モニタリング On-siteサンプリングSDV
	システム	EDC	EDC, Storage システム
	その他	-	規制ガイドラインに沿ったSOPおよび監査
データフォーマット		CDISC 非標準	CDISC 標準 (SDTM変換)
企業へのデータ提供		参加全企業との共有	個別契約企業のみ

SCRUM-Japanに期待される成果

- 全国規模の遺伝子スクリーニングによる新薬開発治験の推進
- NGSパネル等のMultiplex診断薬、ゲノム医療の臨床応用推進
- がんの病態解明、新規治療標的の同定のための研究推進
- レジストリデータを利用して作成した治験対照群データ（Natural History Data)の活用による新薬審査・承認の効率化
- 収集データの国際規格標準化によるデータ統合・シェアリングの推進

がん新薬への患者アクセスの最適化が実現！

(理想的な)最適化医療開発プロセス



The Hallmarks of a Precision Oncology Study

Hyman, Cell, 2017

がん薬物療法を最適化するには

- 良質な臨床情報が附随した分子疫学情報
- がんの多様性を反映した非臨床実験系
- グローバルの開発競争の先頭にたつ
  - いち早く情報を収集，情報の良否を吟味する
- バイオマーカー診断の均てん化
  - 全国どこにいても良質な検査が受けられる
- 小回りのきく診断開発
  - 実地臨床に即した診断キットのカスタマイズ

基礎・臨床研究者、治療薬・診断薬メーカーの緊密な連携