PMDA科学委員会

資　料　1

がんのバイオマーカー

名古屋医療センター
直江知樹

2013/07/19

バイオマーカー

- A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention

- 診断バイオマーカー
  - 早期診断
  - 病型診断
- 予想バイオマーカー
  - 薬剤選択 (Efficiency BM)
  - 副作用出現 (Safety BM)
- 代謝バイオマーカー
  - 用量決定
- アウトカムバイオマーカー
  - 反応性
  - 進展
  - 再燃

個別化

- 疾患の性質と個体の特性を生物学的に評価し、患者にとって最適化治療を示す指標

Biomarkers Definitions Working Group. Clin Pharmacol Ther 2001.

様々なBM

Screening method	Detects	Examples
Anatomical screen		
Macrosopic	Tumour masses	Endoscopy, radiology and physical examination
Microscopic	Abnormal cells	Cytology and histology
Molecular biomarker screen		
Carcinogenesis biomarkers	Abnormal molecular species generated by carcinogenesis	Mutated DNA and aberrantly methylated DNA
Released biomarkers	Physiological molecules released in abnormal amounts as a result of the anatomical or metabolic disruptions of carcinogenesis	PSA and stool haeme
Response biomarkers	Molecular species generated in reaction to the presence of a tumour	Antibodies and protein degradation products
Risk biomarkers	Molecular species associated with, or supporting, carcinogenesis	Increased hormone levels and the presence of HPV antigens

HPV, human papilloma virus; PSA, prostate serum antigen.

Nature Reviews Cancer 12, 368、2012

がん診療におけるバイオマーカー

- サンプリング
  - 腫瘍部位
    - DNA・RNA（ゲノム・トランスクリプトーム）
    - タンパク質（プロテオミクス）
    - その他　代謝物（メタボローム）
    - 組織・細胞
  - 非腫瘍部位
    - 循環腫瘍細胞
    - 血中遊離DNA/RNA
    - 血清・血漿
- 非サンプリング
  - イメージング

- Prognostic biomarker (予後バイオマーカー) は、治療の有無にかかわらず予後に影響を及ぼす因子。例えば手術後のがんの再発リスクを予測することで、化学療法や放射線療法などを開発・導入する対象を選択する際など活用される。
- Predictive biomarker (効果予測バイオマーカー) は、薬剤等の治療に対する有効性や副作用を予測する因子。分子標的治療薬などの抗癌剤の開発や使用症例の選択に活用できる。

Published OnlineFirst May 25, 2010; DOI: 10.1158/1078-0432.CCR-10-0880

Clinical Cancer Research

Special Report

AACR-FDA-NCI Cancer Biomarkers Collaborative Consensus Report: Advancing the Use of Biomarkers in Cancer Drug Development

Samir N. Khleif[1], James H. Doroshow[1], and William N. Hait[2]; for the AACR-FDA-NCI Cancer Biomarkers Collaborative

The AACR-FDA-NCI Cancer Biomarkers Collaborative consensus recommendations

- Biospecimens
- Analytic Performance
- Standardization and Harmonization
- Bioinformatics
- Collaboration and Data Sharing
- Regulatory Issues
- Stakeholder Education and Communication
- Science Policy

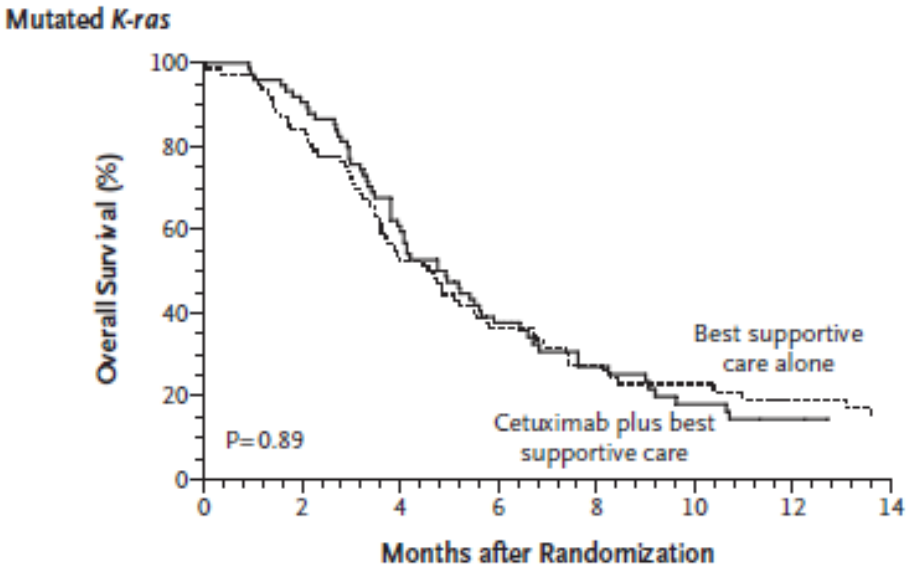
Clin Cancer Res July 1, 2010 16; 3299

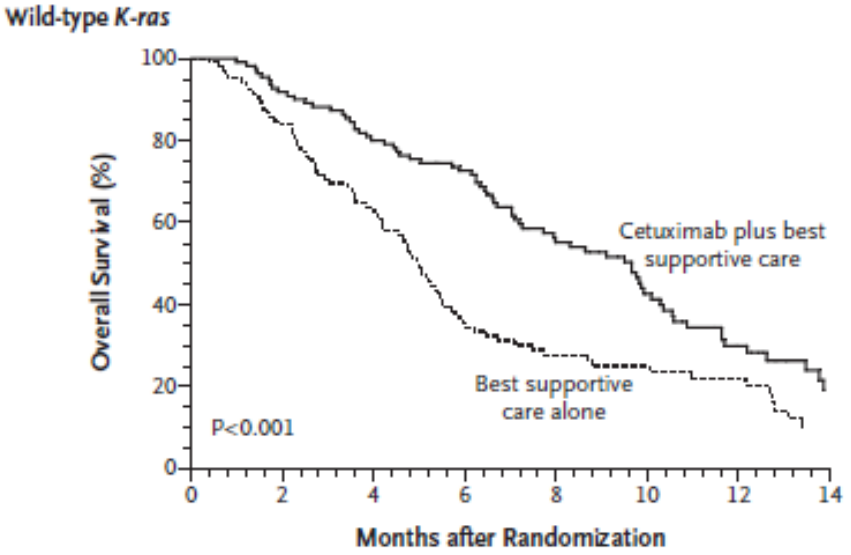
抗体薬におけるPharmacogenomic BM

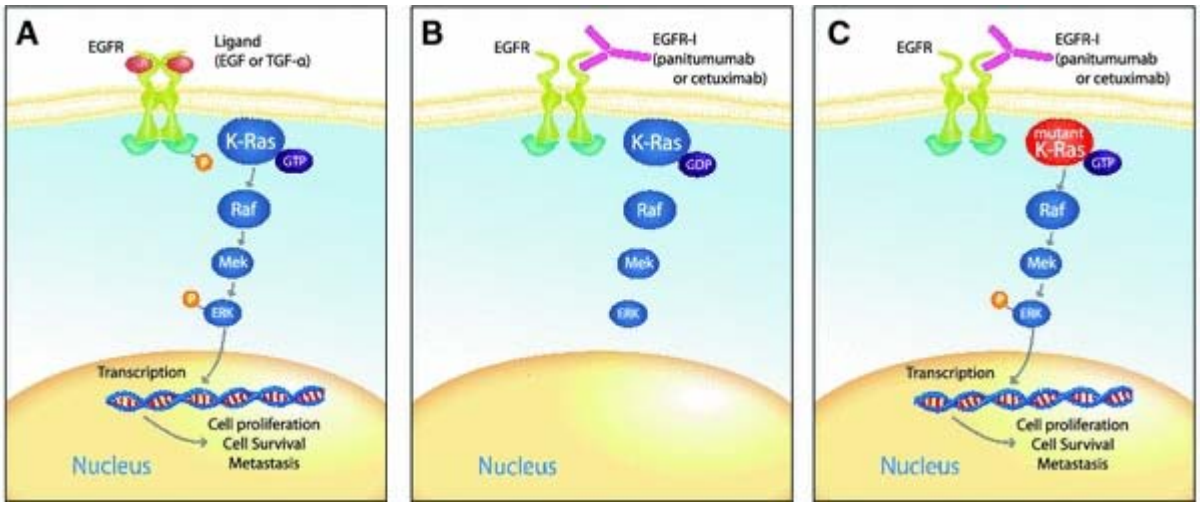
Tositumomab	CD20	Indications and Usage, Clinical Pharmacology
Brentuximab Vedotin	CD30	Indications and Usage, Description, Clinical Pharmacology
Cetuximab (2)	KRAS	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Trastuzumab	ERBB2 (HER2)	Indications and Usage, Precautions, Clinical Pharmacology
Ado-Trastuzumab Emtansine	ERBB2 (HER2)	Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Pertuzumab	ERBB2 (HER2)	Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Studies, Clinical Pharmacology
Panitumumab (1)	EGFR	Indications and Usage, Warnings and Precautions, Clinical Pharmacology, Clinical Studies
Denileukin Diftitox	CD25	Indications and Usage, Warnings and Precautions, Clinical Studies
Cetuximab (1)	EGFR	Indications and Usage, Warnings and Precautions, Description, Clinical Pharmacology, Clinical Studies

FDA HP

K-Ras Mutations and Benefit from Cetuximab in Advanced Colorectal Cancer







Karapetis C et al. NEJM 2008

その他(1)　Pharmacogenomic BM in Drug Labels

Arsenic Trioxide	PML/RARα	Boxed Warning, Clinical Pharmacology, Indications and Usage, Warnings
Rasburicase	G6PD	Boxed Warning, Contraindications
Tretinoin	PML/RARα	Boxed Warning, Dosage and Administration, Precautions
Erlotinib	EGFR	Clinical Pharmacology
Gefitinib	EGFR	Clinical Pharmacology
Cisplatin	TPMT	Clinical Pharmacology, Warnings, Precautions
Busulfan	Ph Chromosome	Clinical Studies
Capecitabine	DPD	Contraindications, Precautions, Patient Information
Mercaptopurine	TPMT	Dosage and Administration, Contraindications, Precautions, Adverse Reactions, Clinical Pharmacology
Thioguanine	TPMT	Dosage and Administration, Precautions, Warnings
Irinotecan	UGT1A1	Dosage and Administration, Warnings, Clinical Pharmacology
Letrozole	ER &/ PGR	Indications and Usage, Adverse Reactions, Clinical Studies, Clinical Pharmacology
Everolimus	ERBB2 (HER2)	Indications and Usage, Boxed Warning, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, Clinical Studies
Dasatinib	Ph Chromosome	Indications and Usage, Clinical Studies, Patient Counseling Information
Imatinib (1)	C-Kit	Indications and Usage, Dosage and Administration Clinical Pharmacology, Clinical Studies

FDA HP

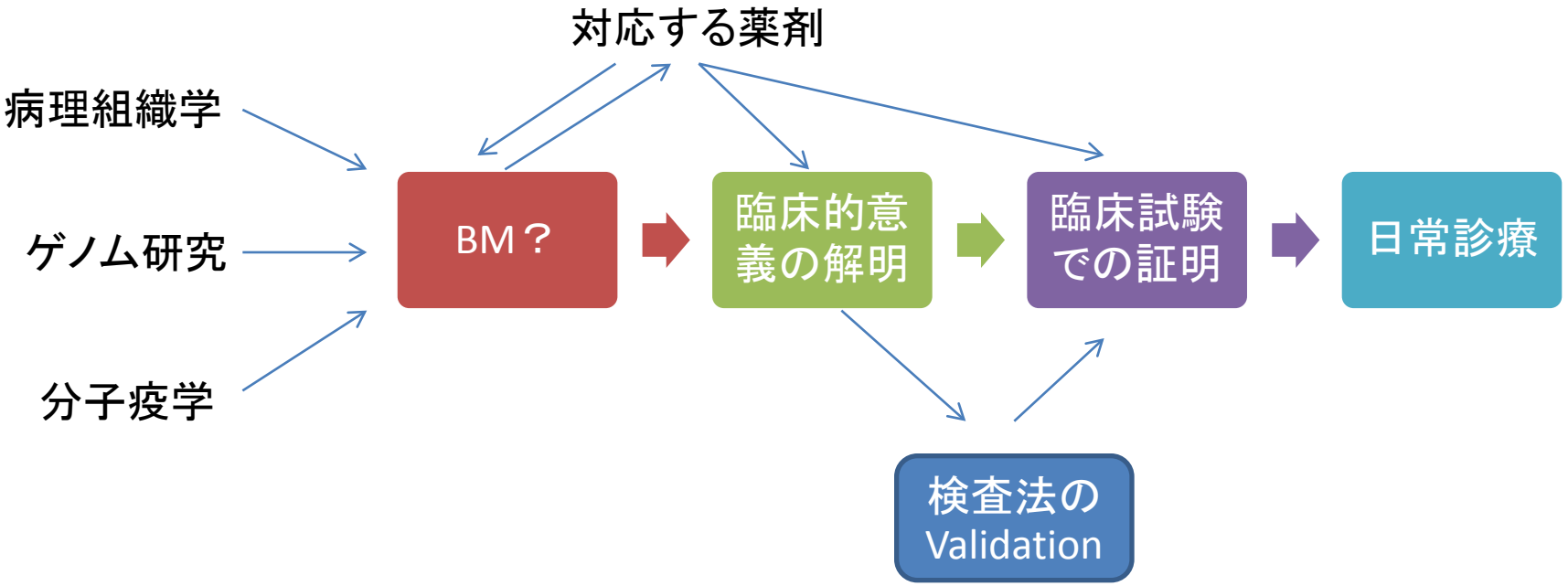
その他(2)　Pharmacogenomic BM in Drug Labels

Imatinib (3)	PDGFR	Indications and Usage, Dosage and Administration, Clincal Studies
Imatinib (2)	Ph Chromosome	Indications and Usage, Dosage and Administration, Clinical Pharmacology, Clinical Studies
Imatinib (4)	FIP1L1-PDGFRα	Indications and Usage, Dosage and Administration, Clinical Studies
Exemestane	ER &/ PGR	Indications and Usage, Dosage and Administration, Clinical Studies, Clinical Pharmacology
Fulvestrant	ER	Indications and Usage, Patient Counseling Information
Nilotinib (1)	Ph Chromosome	Indications and Usage, Patient Counseling Information
Tamoxifen (1)	ER	Indications and Usage, Precautions, Medication Guide
Vemurafenib	BRAF	Indications and Usage, Warning and Precautions, Clinical Pharmacology, Clinical Studies, Patient Counseling Information
Crizotinib	ALK	Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Fluorouracil (2)	DPD	Warnings
Tamoxifen (2)	Factor V Leiden (FV)	Warnings
Tamoxifen (3)	Prothrombin mutations (F2)	Warnings
Nilotinib (2)	UGT1A1	Warnings and Precautions, Clinical Pharmacology

BMの様々な用途

	BCR-ABL mRNA定量	HER2陽性	CD20陽性	EGFR変異	WT1mRNA定量
生物学的意義（特異性・安定性）	◎	○	×	○	△
診断・病型マーカー	○	△	△	△	×
予後マーカー	◎	○	×	×	×
薬剤選択マーカー	◎	◎	◎	◎	×
治療効果マーカー	◎	×	×	×	○
検査法の定量性・簡便性・標準化	◎	△	△	△	◎

各BMの科学的確からしさの程度



バイオマーカーのエビデンスレベル

Table 2. Revised determination of Levels of Evidence using elements of tumor marker studies*

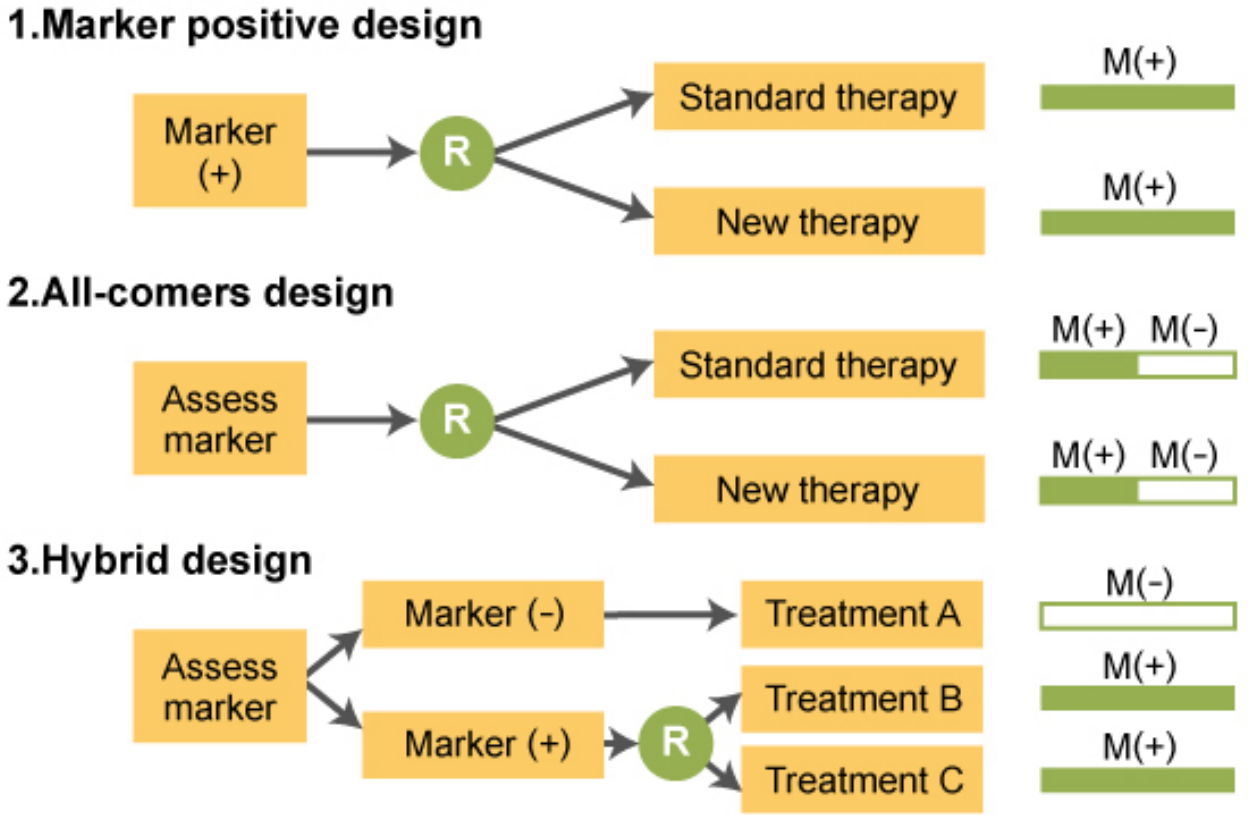
Level of evidence	Category from Table 1	Validation studies available
I	A	None required
I	B	One or more with consistent results
II	B	None or inconsistent results
II	C	2 or more with consistent results
III	C	None or 1 with consistent results or inconsistent results
IV–V	D	NA†

* Levels of Evidence (LOEs) revised from those originally proposed by Hayes et al. (3).

† NA = not applicable because LOE IV and V studies will never be satisfactory for determination of medical utility.

前向き研究での実証

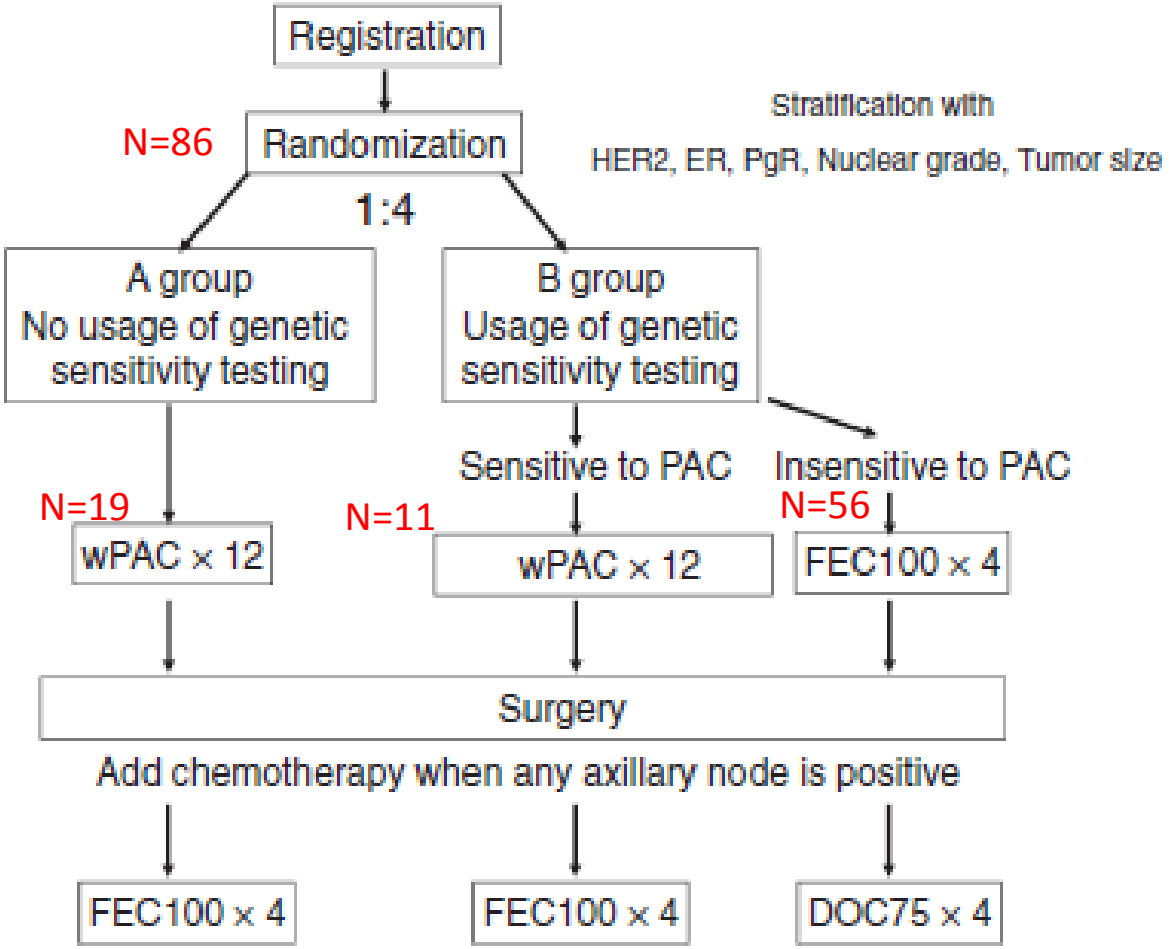
図2 バイオマーカーを用いた臨床試験のデザイン



Mandrekar SJ, et al.: J Clin Oncol. 27(24): 4027-4034, 2009をもとに作図

Prospective randomized phase II study determines the clinical usefulness of genetic biomarkers for sensitivity to primary chemotherapy with paclitaxel in breast cancer

Yoshinori Ito,[1,6] Koichi Nagasaki,[2] Yoshio Miki,[2] Takuji Iwase,[3] Futoshi Akiyama,[4] Masaaki Matsuura,[2] Rie Horii,[4] Masujiro Makita,[3] Nahomi Tokudome,[1] Masaru Ushijima,[2] Masataka Yoshimoto,[5] Shunji Takahashi,[1] Tetsuo Noda[2] and Kiyohiko Hatake[1]

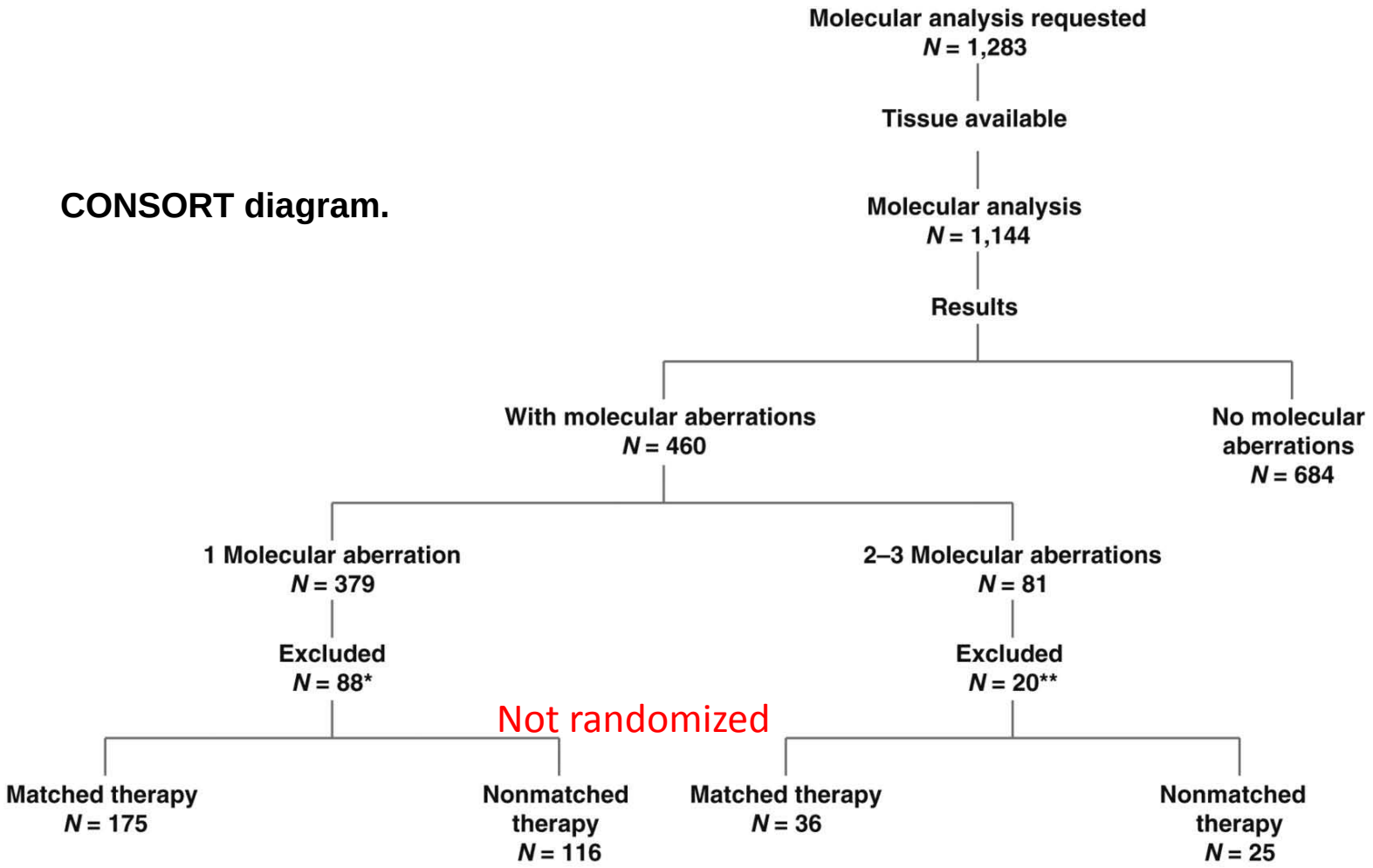


Clinical Response

10(53%) 5(55%) 30(54%)

分子マーカーに基づく治療が本当に有効か？

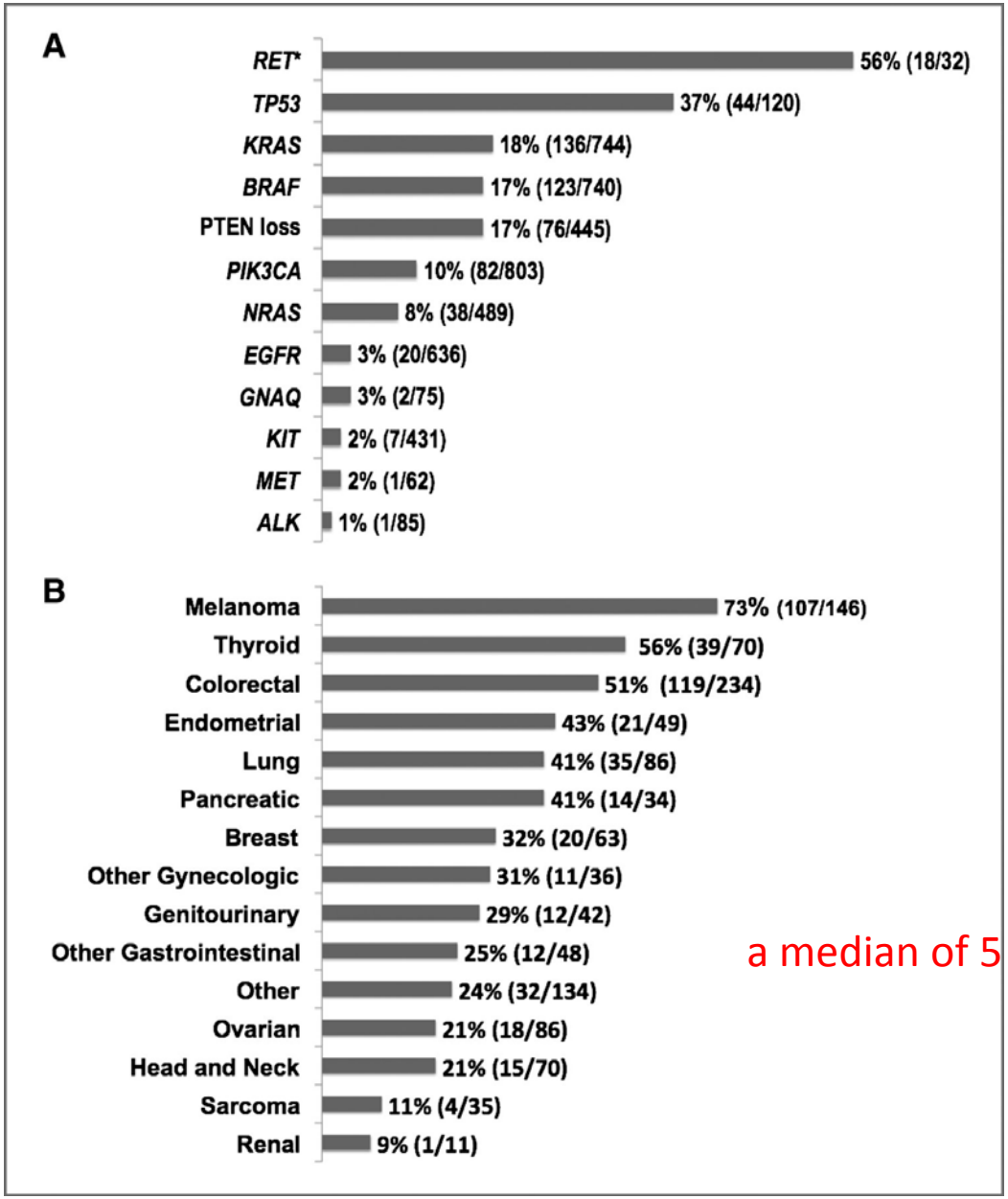
CONSORT diagram.



*Eighty-eight patients were excluded from the analyses of clinical outcomes (regional therapy, *n* = 18; ineligible for study participation, *n* = 26; too early, *n* = 44).
**Twenty patients were excluded (regional therapy, 8; too early, *n* = 2; ineligible for study participation, *n* = 10).

Tsimberidou A et al. Clin Cancer Res 2012;18:6373-6383

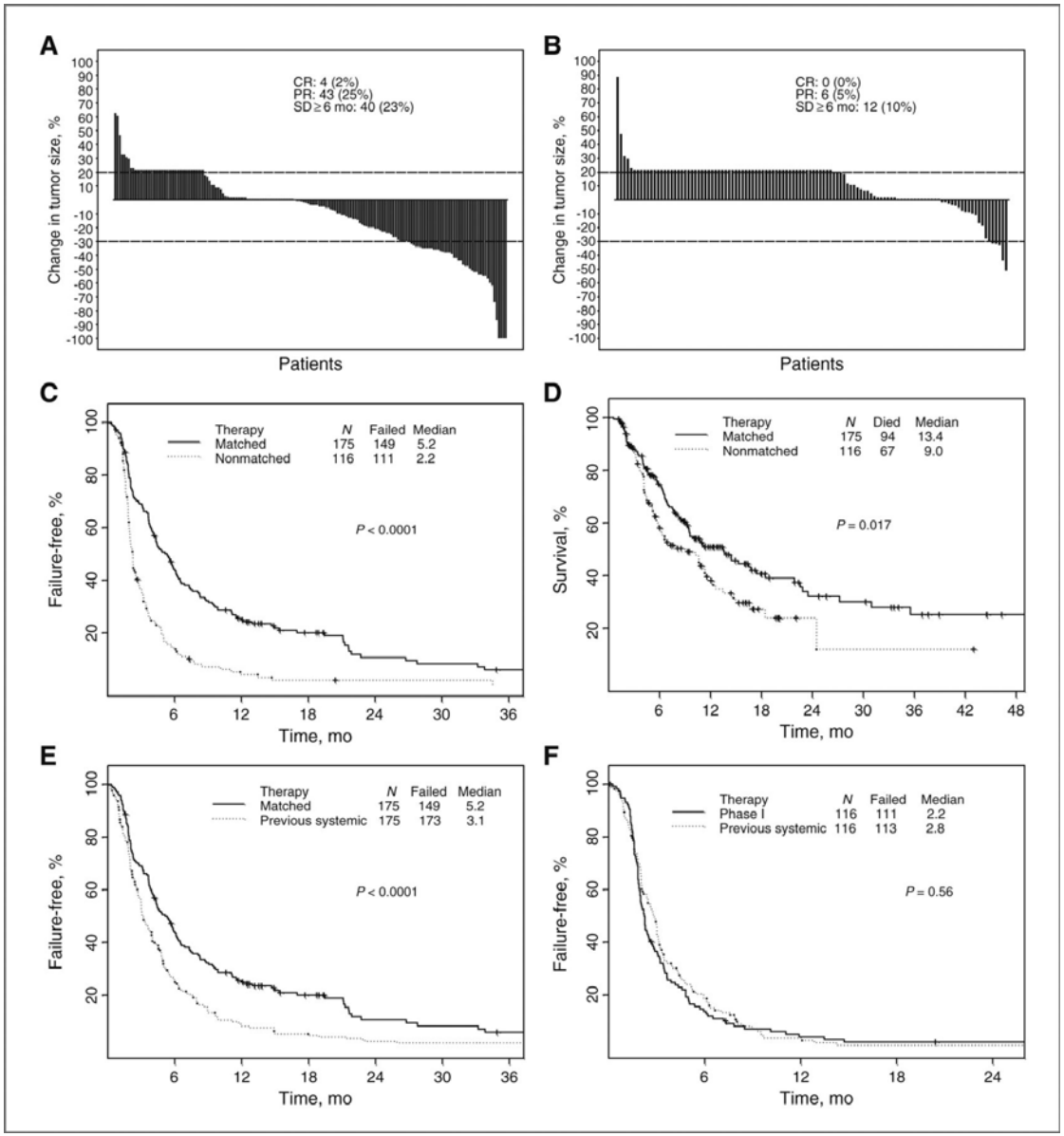
A, proportions of molecular aberrations (N = 1,144).



a median of 5 prior therapies

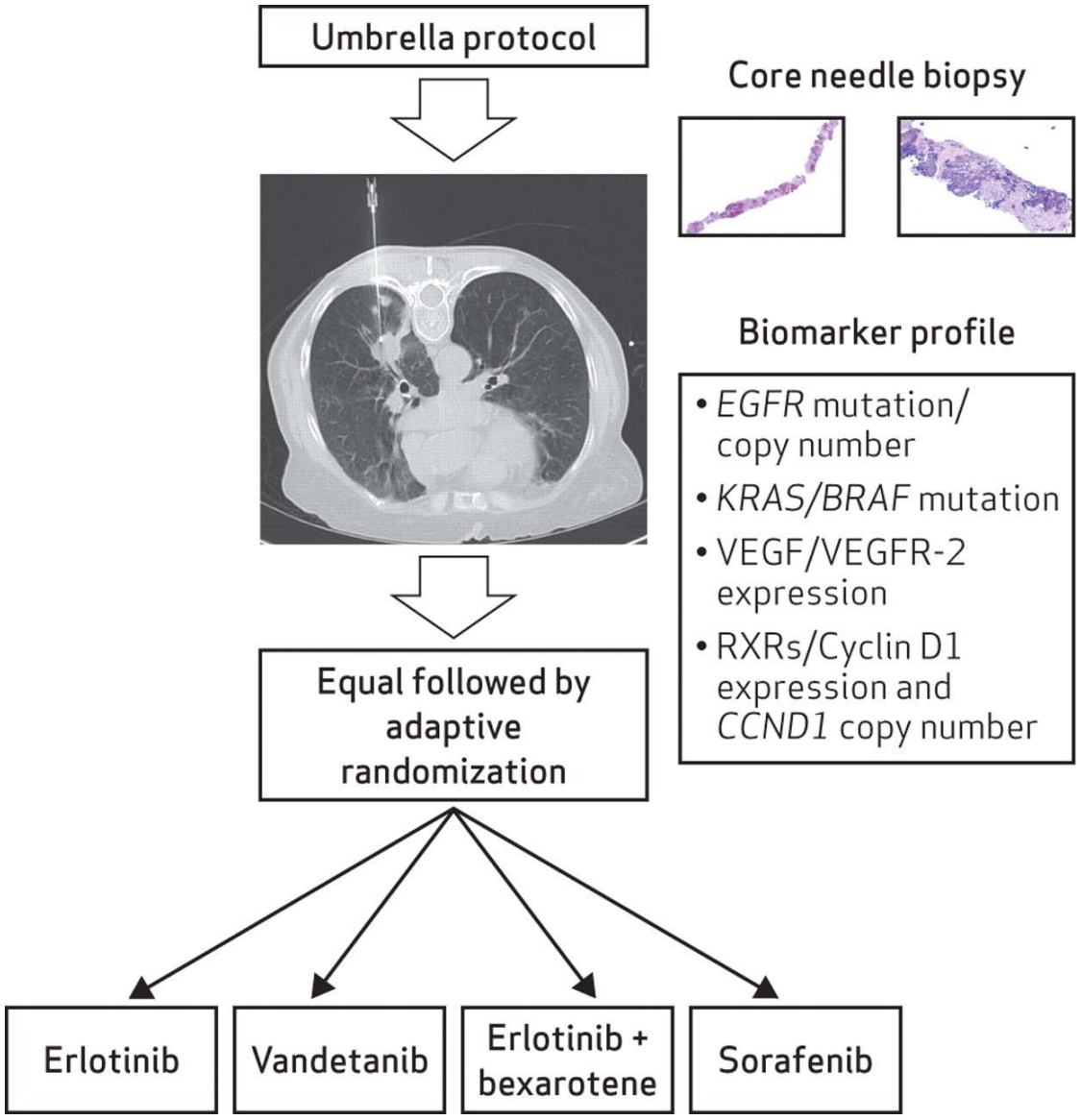
Tsimberidou A et al. Clin Cancer Res 2012;18:6373-6383

A, best response by RECIST of 175 patients with one molecular aberration treated with matched therapy: changes from baseline in tumor measurements (waterfall plot).



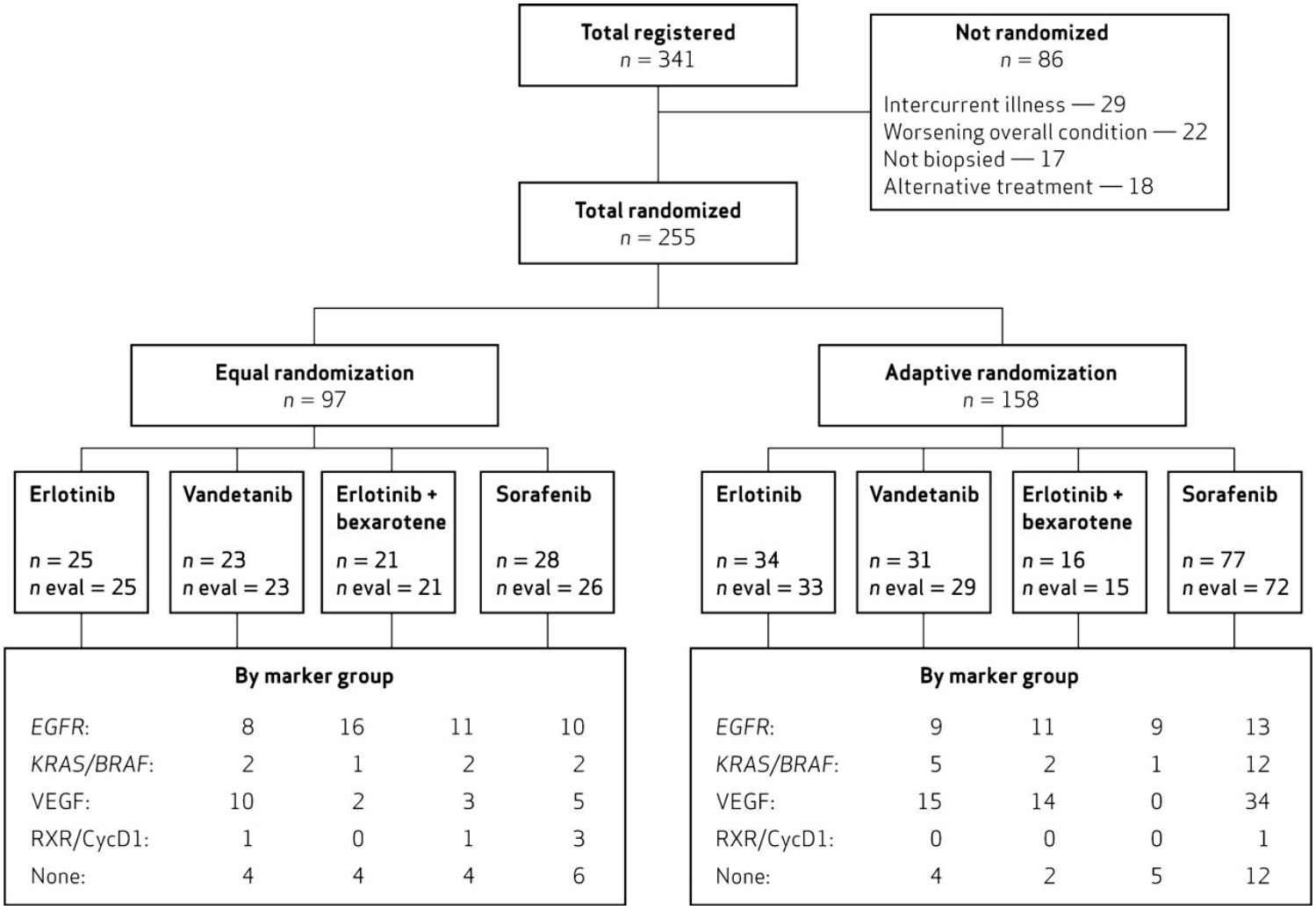
Tsimberidou A et al. Clin Cancer Res 2012;18:6373-6383

Schema for BATTLE study.



Kim E S et al. Cancer Discovery 2011;1:44-53

CONSORT diagram of the BATTLE study.



Kim E S et al. Cancer Discovery 2011;1:44-53

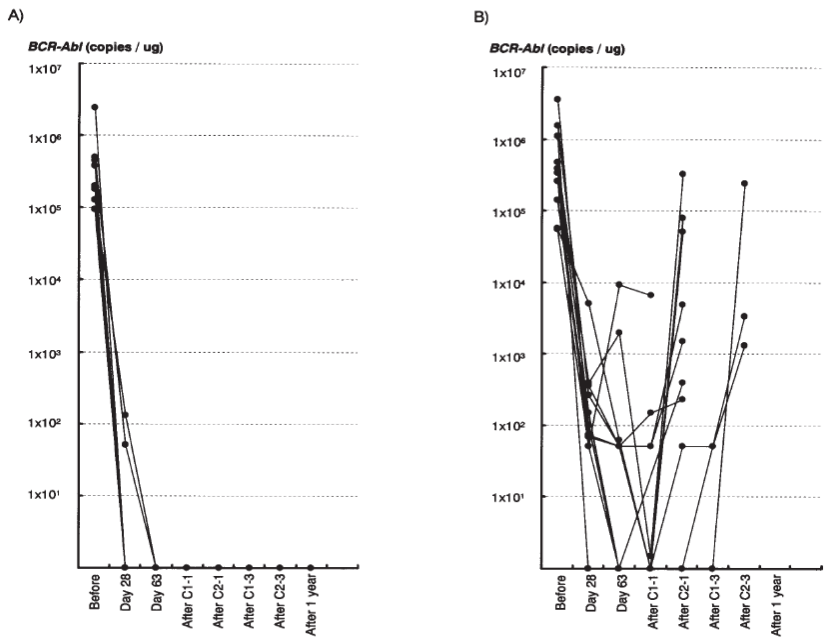
KRAS変異による抗EGFR抗体薬の有用性

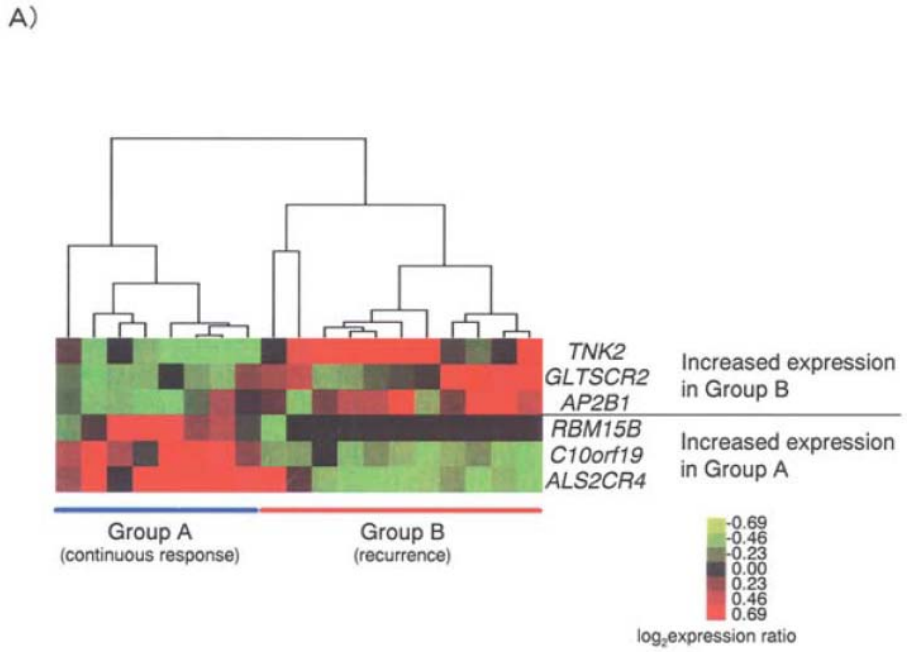
	Cetuximab								Panitumumab	
試験名	CRYSTAL		OPUS		COIN		NORDIC VII		PRIME	
KRAS statusの検討	後ろ向き		後ろ向き		前向き		前向き		前向き	
Phase	第III相		第II相		第III相		第III相		第III相	
化学療法	FOLFIRI		FOLFOX4		FOLFOX/XELOX		FLOX		FOLFOX4	
KRAS 評価症例	1,063 (89%)		315 (93%)		1,316 (81%)		498 (88%)		1,096 (93%)	
KRAS 野生型	併用群 316	単独群 350	併用群 82	単独群 97	併用群 362	単独群 367	併用群※ 97	単独群 97	併用群 325	単独群 331
PFS中央値 (月)	**9.9**	**8.4**	8.3	7.2	8.6	8.6	**7.9**	**8.7**	**10.0**	**8.6**
HR (95% CI)	**0.696 (0.558-0.867)**		0.567 (0.375-0.856)		0.96 (0.82-1.12)		**1.07 (0.79-1.45)**		**0.80 (0.67-0.97)**	
p値	**0.0012**		0.0064		0.60		**0.66**		**0.01**	
OS中央値 (月)	23.5	20.0	22.8	18.5	**17.0**	**17.9**	22.0	20.1	23.9	19.7
HR (95% CI)	0.796 (0.670-0.946)		0.855 (0.599-1.219)		**1.04 (0.87-1.23)**		1.14 (0.80-1.61)		0.88 (0.73-1.06)	
p値	0.0093		0.39		**0.67**		0.66		0.17	

太字は主要評価項目　単独群＝化学療法単独群　※NORDIC VII は3群比較試験。表中の併用群はCetuximab 継続投与群の数値

[CRYSTAL] Van Cutsem E, et al.: J Clin Oncol. 29(15): 2011-2019, 2011 [OPUS] Bokemeyer C, et al.: Ann Oncol. 22(7): 1535-1546, 2011 [COIN] Maughan TS, et al.: Lancet. 377(9783): 2103-2114, 2011; [NORDIC VII] Tveit KM, et al.: ESMO 2010: 20LBA; [PRIME] Douillard JY, et al.: ASCO 2011: abst #3510

Prediction of risk of disease recurrence by genome-wide cDNA microarray analysis in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia treated with imatinib-combined chemotherapy

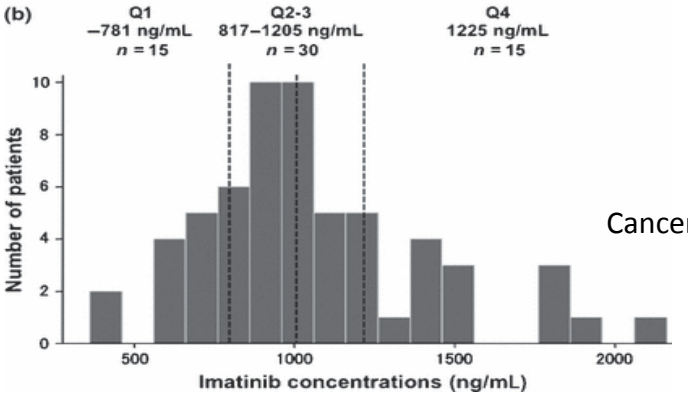




Int J Oncol 2007

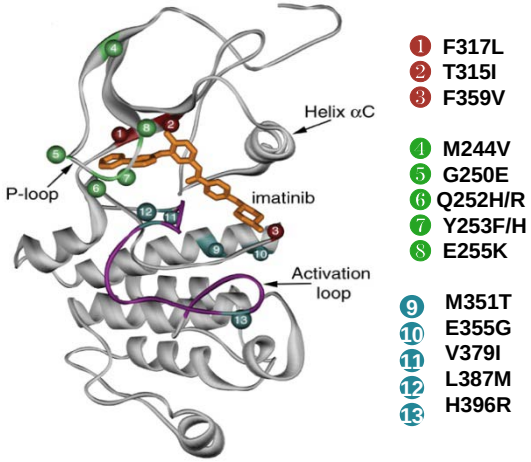
その後進まなかった理由

- PK profile



Cancer Science 2010

- TKI-resistance (Point mutation of Abl kinase domain)

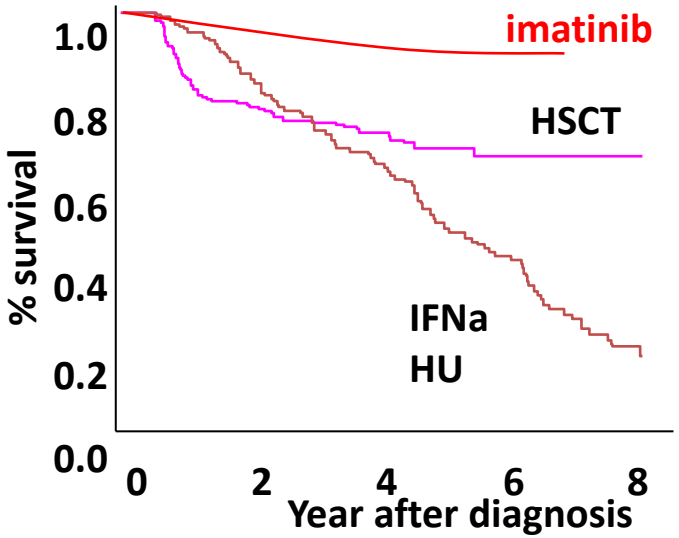


- Additional genetic abnormality
- Generation of second TKI

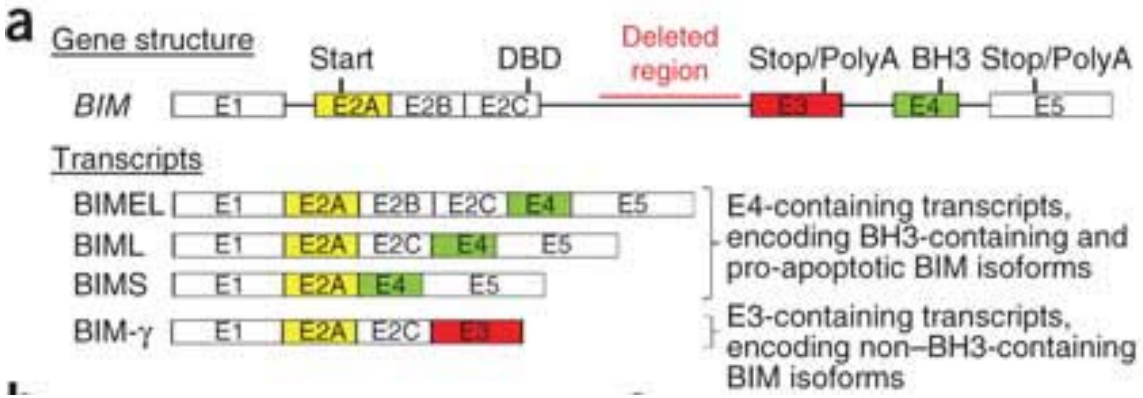
Resistance mechanism to TKIs in CML

- Pharmacokinetics
  - α-1-acid glycoprotein
  - P-glycoprotein
  - *UGT1A1 (Nilotinib)*
- Change of target molecule（BCR/ABL-dependent）
  - Point mutation
  - Amplification
  - Altered splicing of *ABL*
- Alternative signals
  - Lyn, NUP98/DDX10, TEL/MDS/EVI1
- Quiescent Stem cell

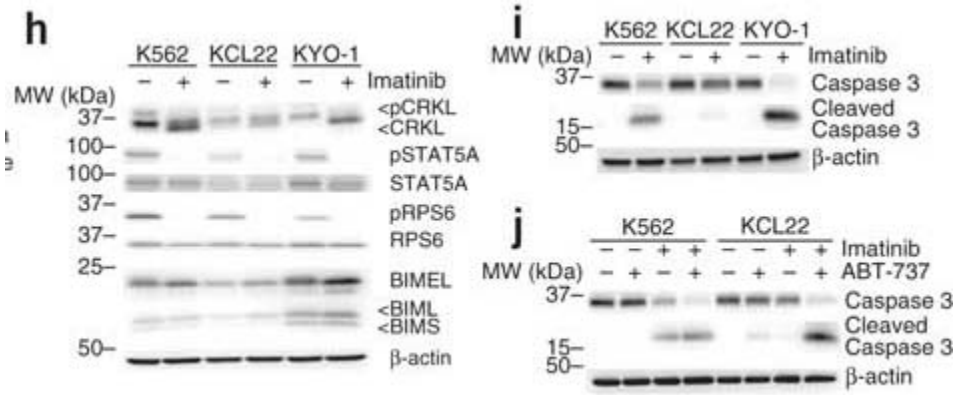
- Polymorphism
  - *BIM*



Polymorphism of *BIM* associated with TKI responsiveness



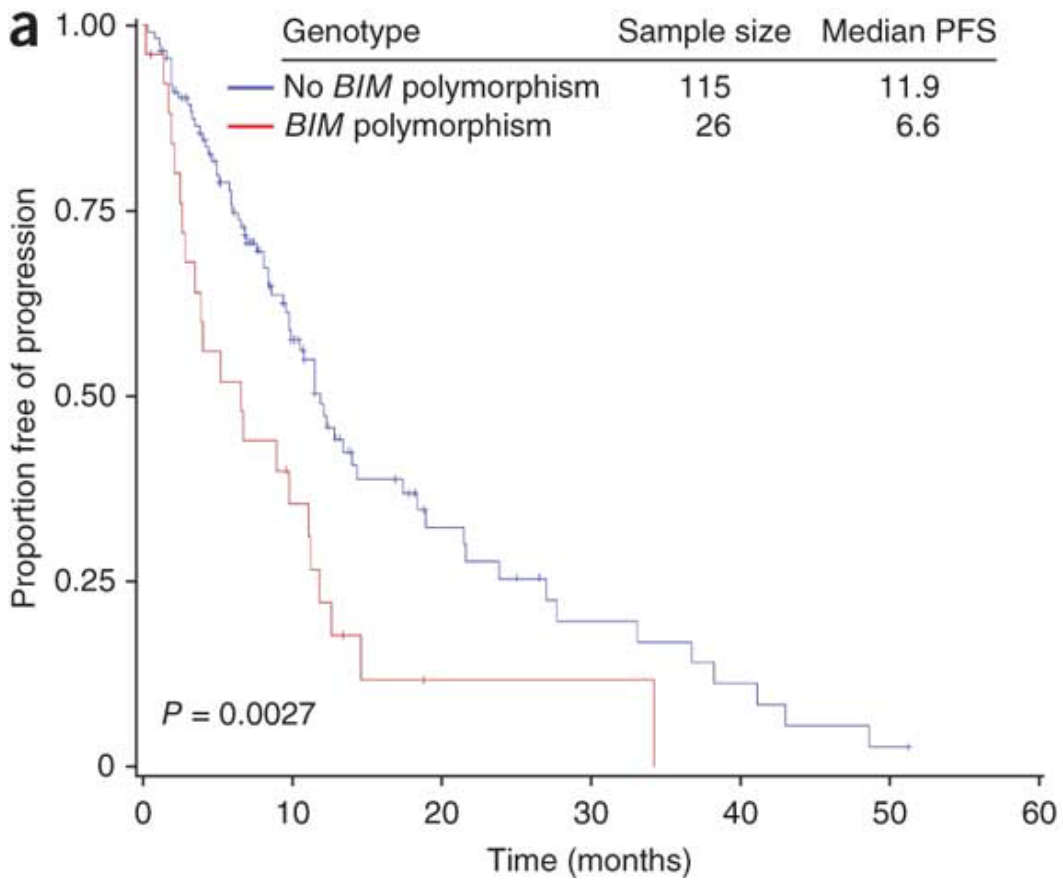
- Slicing of E2–E3 and E2–E4 is mutually exclusive
- Deletion polymorphism increases E3:E4 transcripts ratio
- E2–E3 products have no BH3 domain, a death agonist

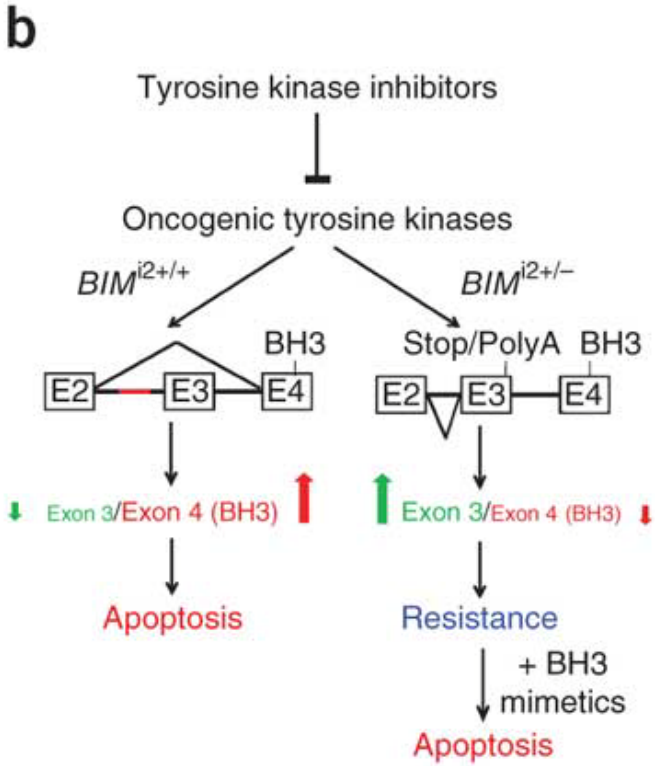


KCL22 carries the deletion polymorphism

Ng KP, et al. Nature Medicine 2012

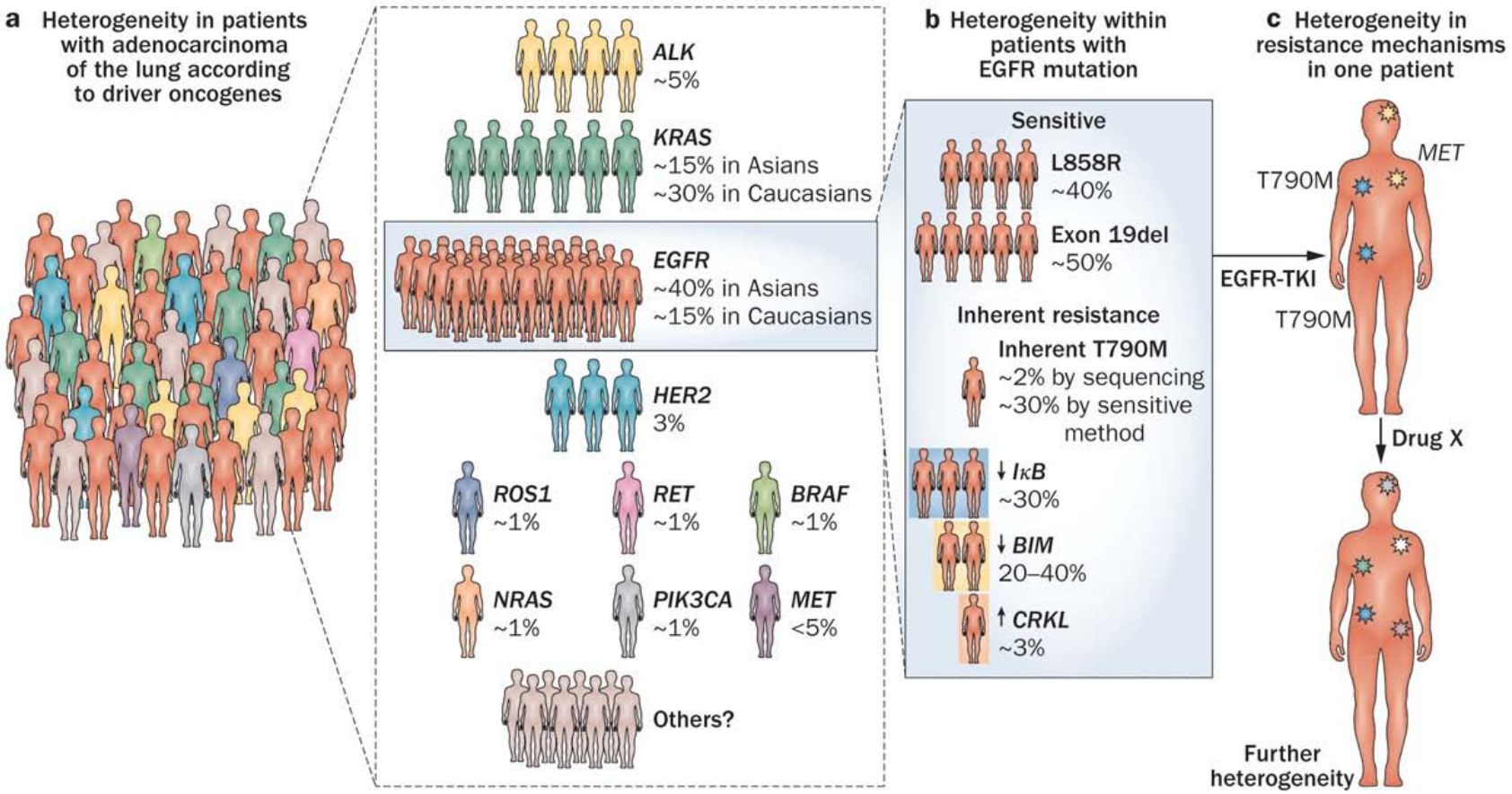
BIM deletion is associated with shorter PFS in EGFR mut+ NSCLC patients treated with TKI





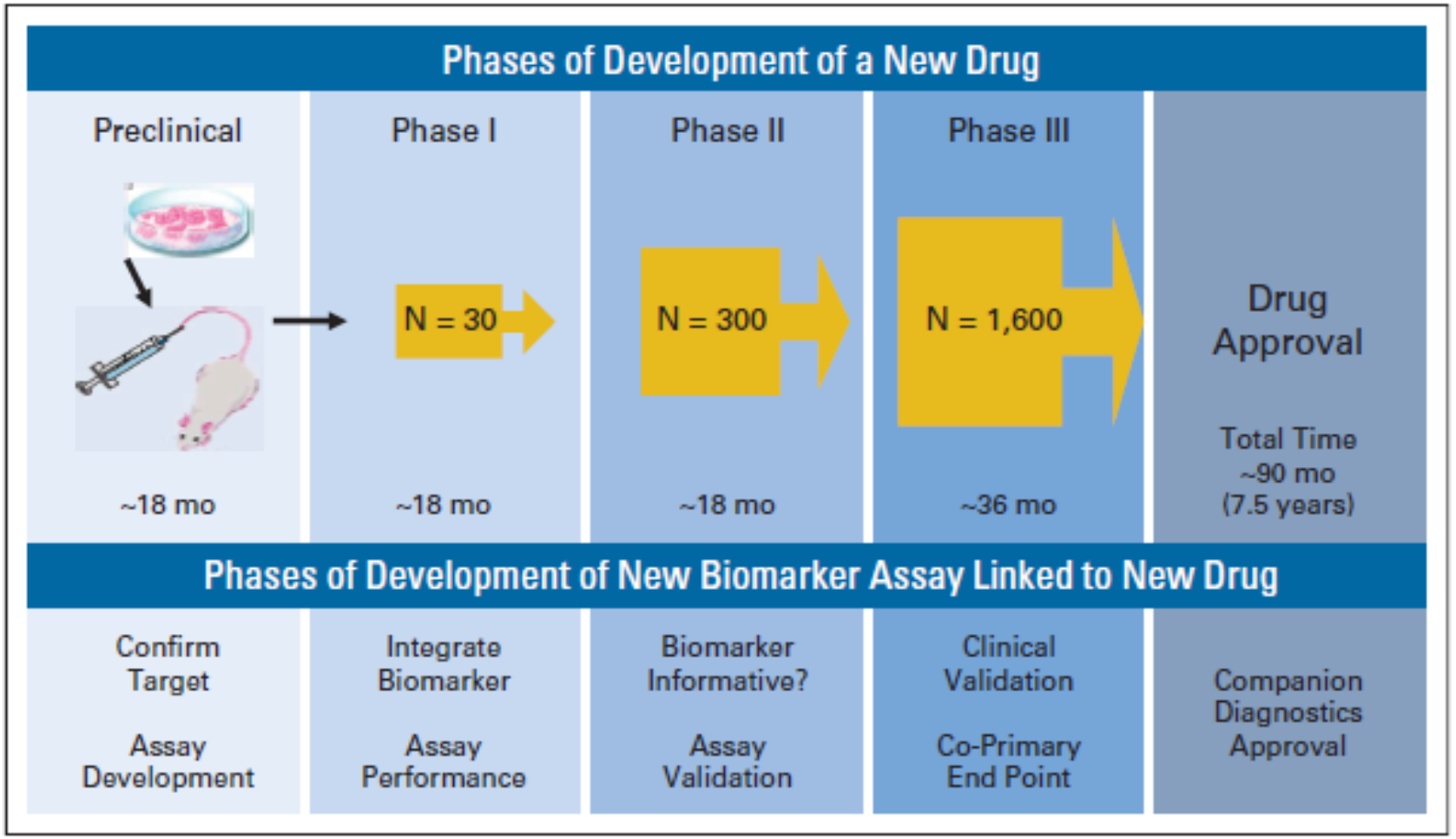
Ng KP, et al. Nature Medicine 2012

Various classes of tumour heterogeneity in adenocarcinoma of the lung

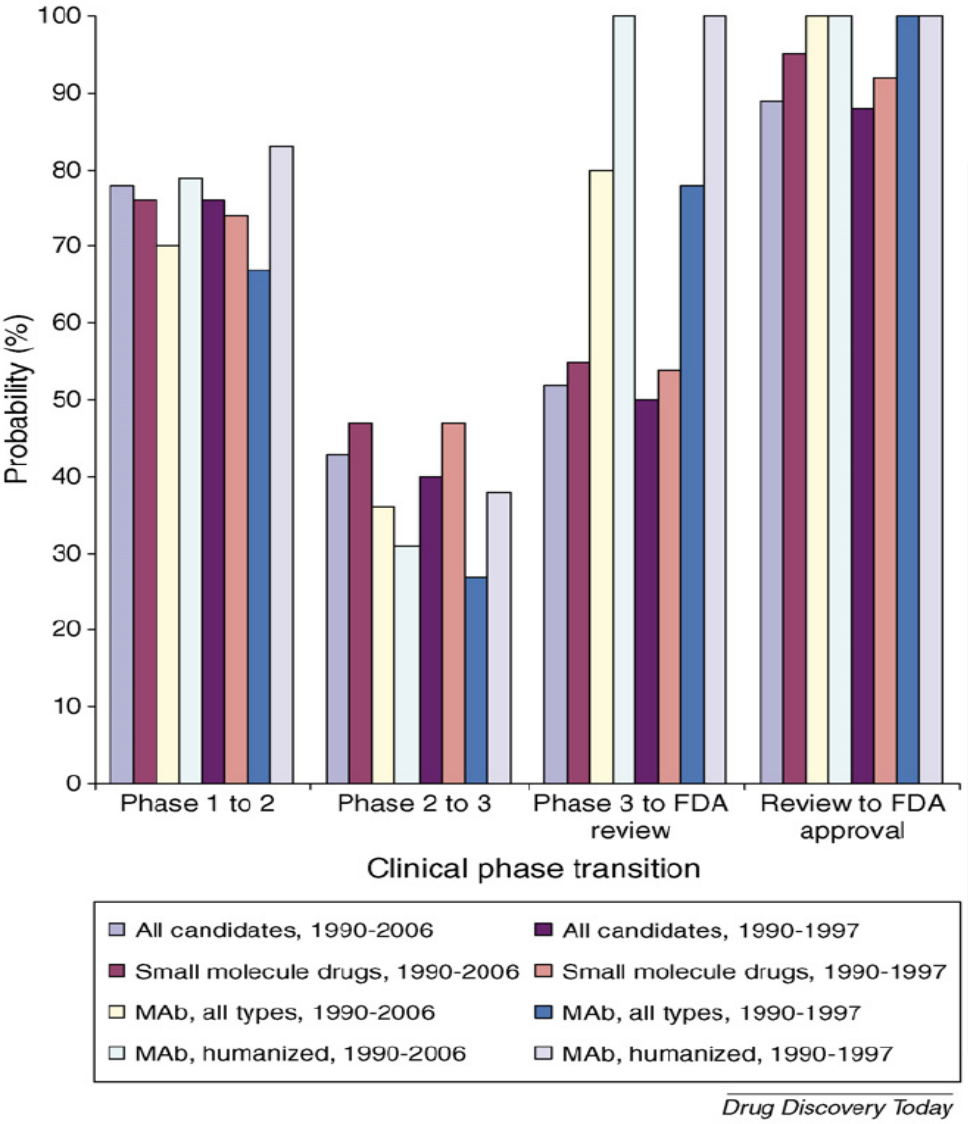


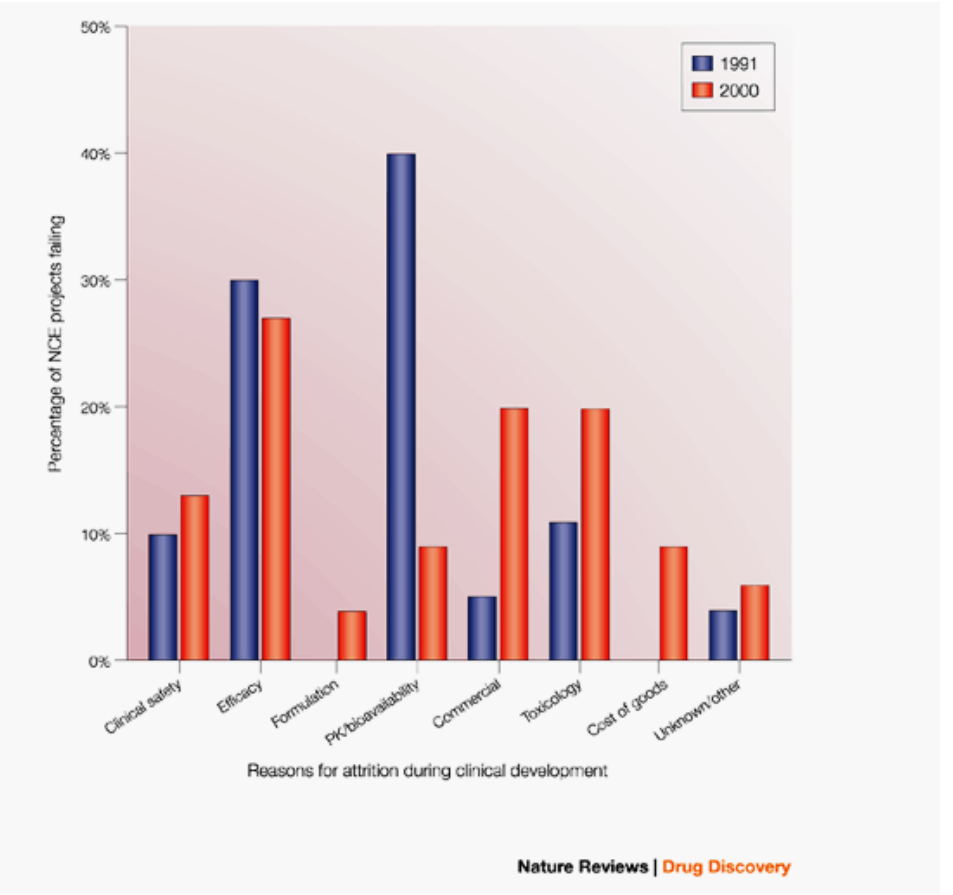
Mitsudomi, T. *et al*. (2013) *Nat. Rev. Clin. Oncol.*

薬剤開発とバイオマーカー



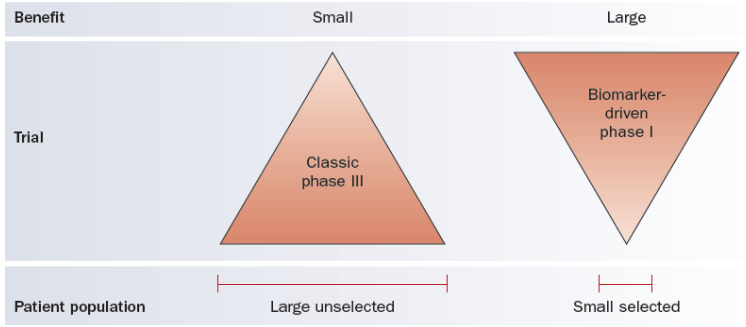
薬剤開発：どのPhaseで中止になるか、その理由は？





新規薬剤開発におけるBMの意義

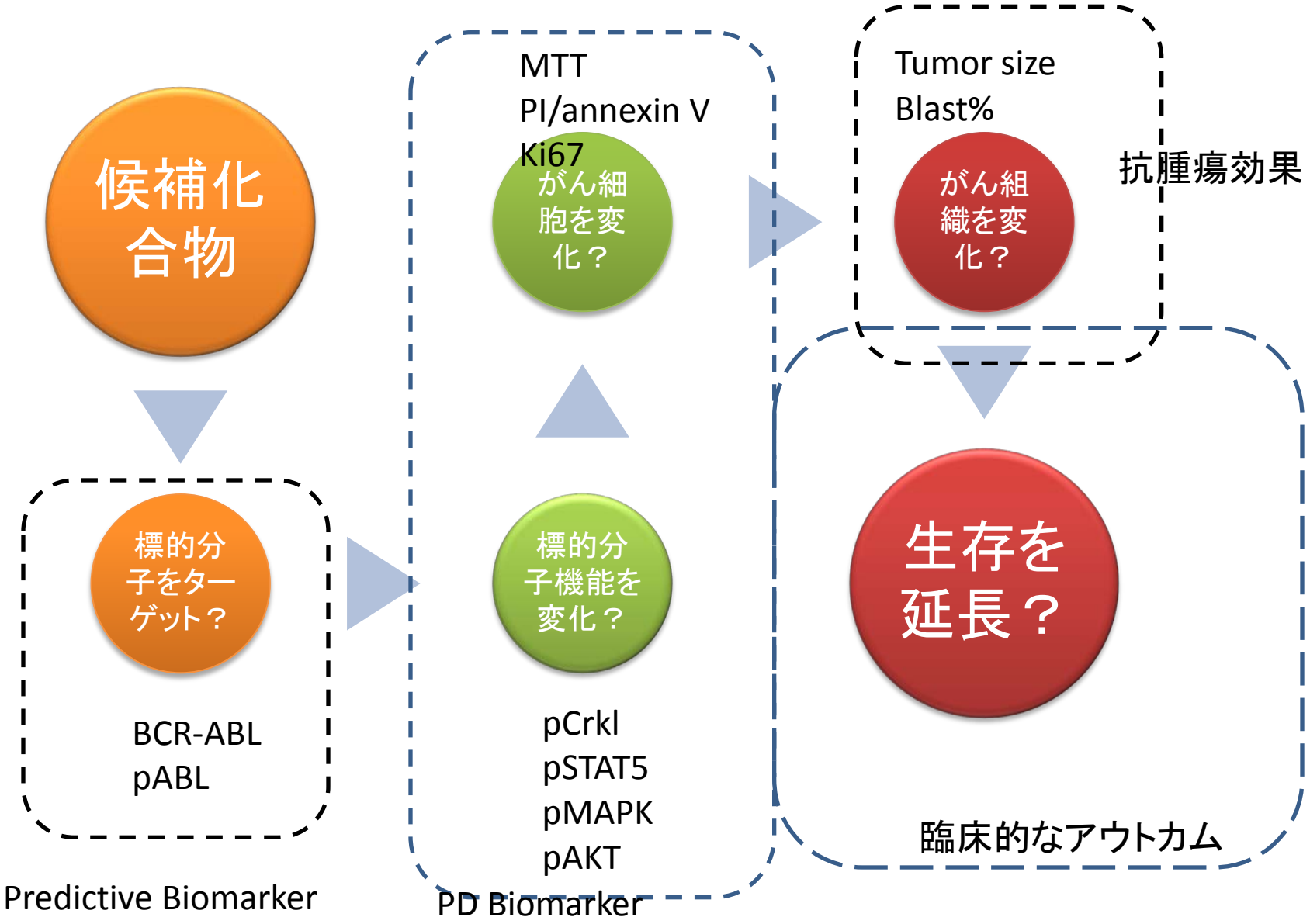
- 被験者（対象疾患）を絞る



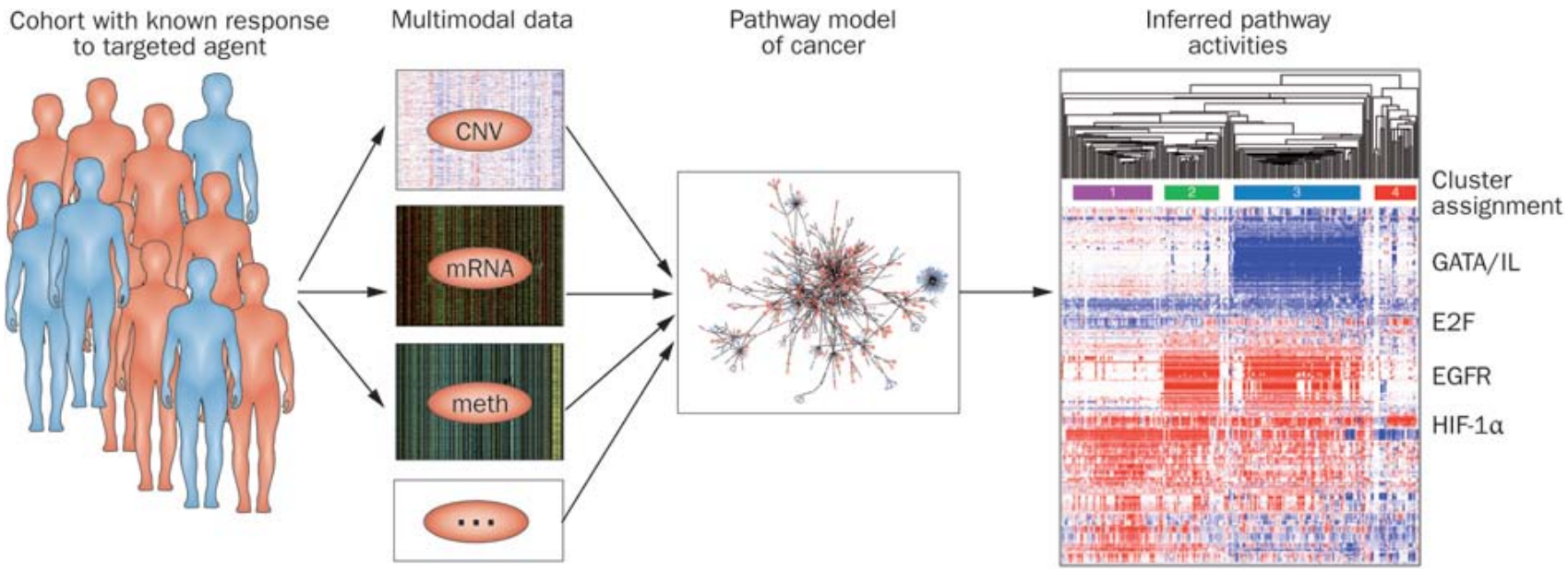
Nat Rev Clin Oncol. 2011

- 適正な薬剤濃度を決定する　Optimal biological dose（OPD) vs MTD
- 臨床でのProof-of-Concept (POC) を確認する
- （有効な対照群をさらに絞り込む、副作用出現に関連するBMを探索するなど）

ドライバーを標的としたバイオマーカー

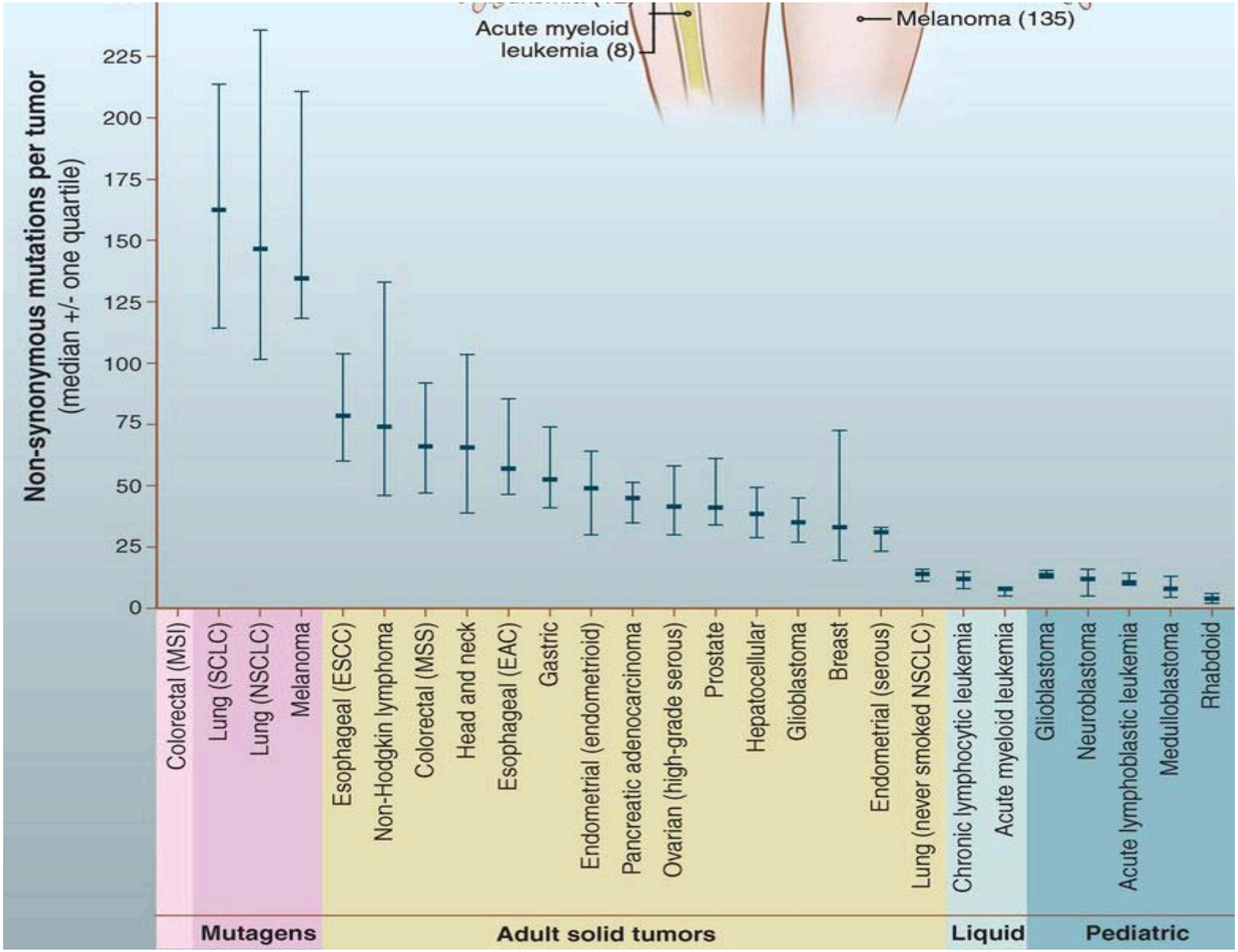


An example of an integrative approach to pathway analysis of a drug-sensitive versus drug-resistant population of patients.



Nat. Rev. Clin. Oncol..2012.159

Number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies.



B Vogelstein et al. Science 2013;339:1546-1558

指定シーズ1：白血病ゲノムに基づく層別化治療の確立（直江）

JALSG AML201試験

- CBF-AMLに対するHD-ACの有用性（*BLOOD 2011*）
- 高用量DNR療法のIDRとの同等性（*BLOOD 2011*）

- 230症例検体集積
- DNA、RNA中央保存→連結不可能匿名化
- 検体提出機関の倫理委員会承認完了（2011年4月）

網羅的遺伝子変異解析

- AMLの発症に関与する分子異常
- AMLの予後予測因子となる分子異常
- CBF-AMLの進展・薬剤感受性に関与する分子異常
- HD-AC、DNR、IDRの副作用に関係する分子異常

分子層別化モデル

JALSG AML209試験

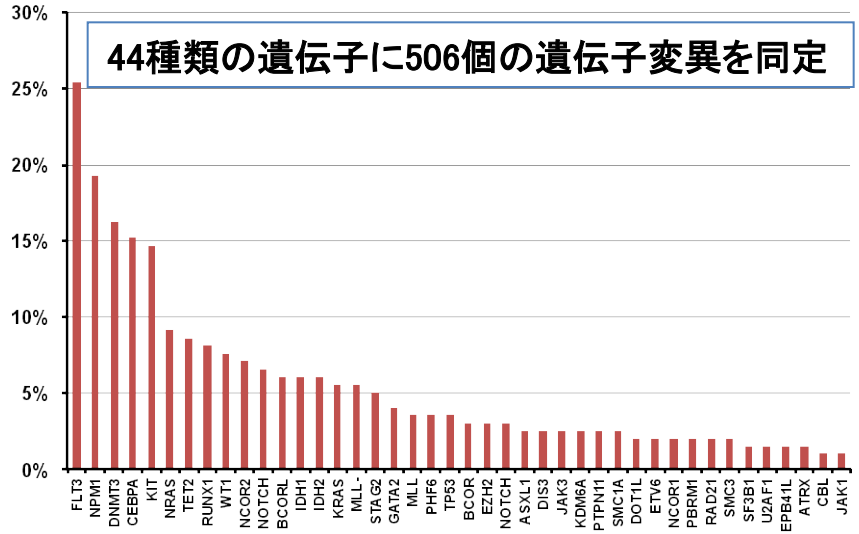
- 未治療成人AML：1500例予定
- 染色体核型・キメラ遺伝子
- 網羅的遺伝子変異解析
- 分子病型別のDFS・OS・CR率
- 遺伝子変異に基づく個別化治療の有効性の検証
- 残余検体中央保存同意
- 登録終了予定：2015年2月

AML209登録症例（1500例）での検証

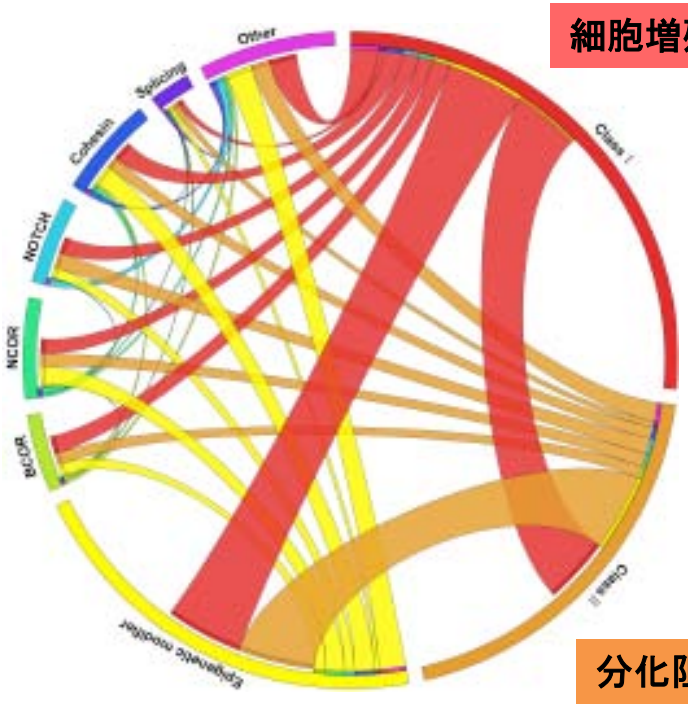
分子病態に基づく予後層別化システムの確立
治療標的分子・副作用関連分子の同定
全年齢層に対し有効かつ安全な薬剤開発シーズの提供

指定シーズ1：白血病ゲノムに基づく層別化治療の確立（直江）

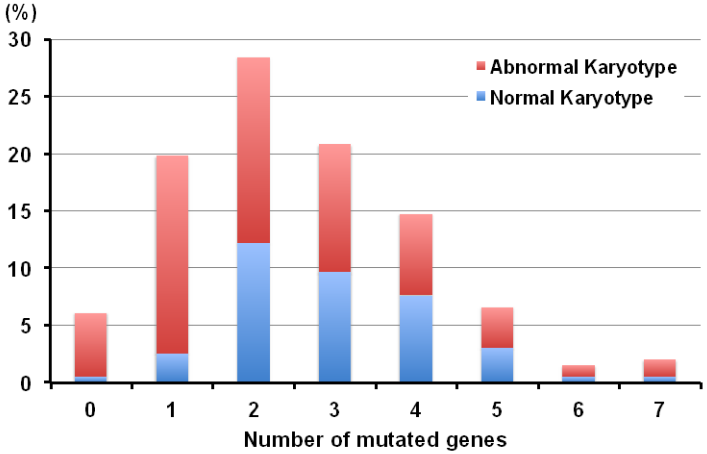
JALSG AML201試験登録例における網羅的遺伝子変異解析



AMLでは細胞増殖、分化阻害、エピゲノムに影響を及ぼす遺伝子変異が同時に獲得される



AMLでは平均2.54個/例の遺伝子変異を獲得

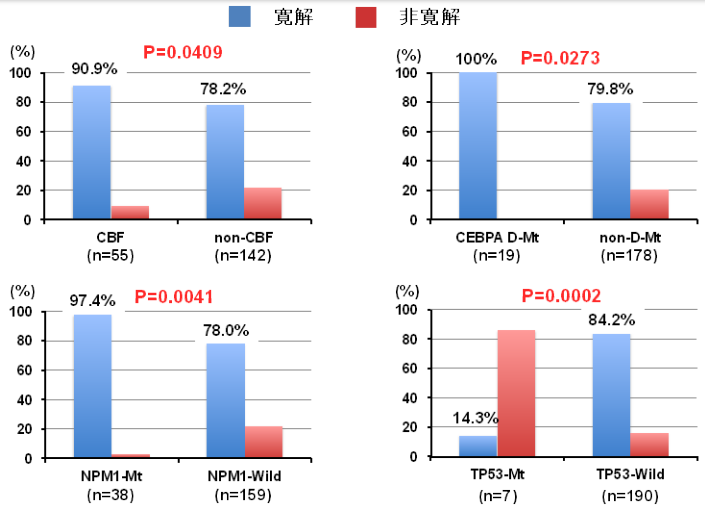


Kihara et al. EHA 2013, paper in preparation

指定シーズ1：白血病ゲノムに基づく層別化治療の確立（直江）

JALSG AML201試験登録例における網羅的遺伝子変異解析

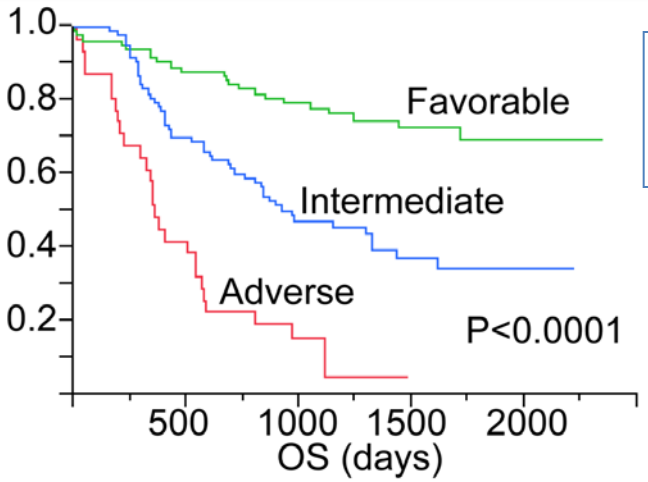
寛解達成に影響を及ぼす4種類の遺伝子病型を同定



生存率に影響を及ぼす6種類の遺伝子病型を同定

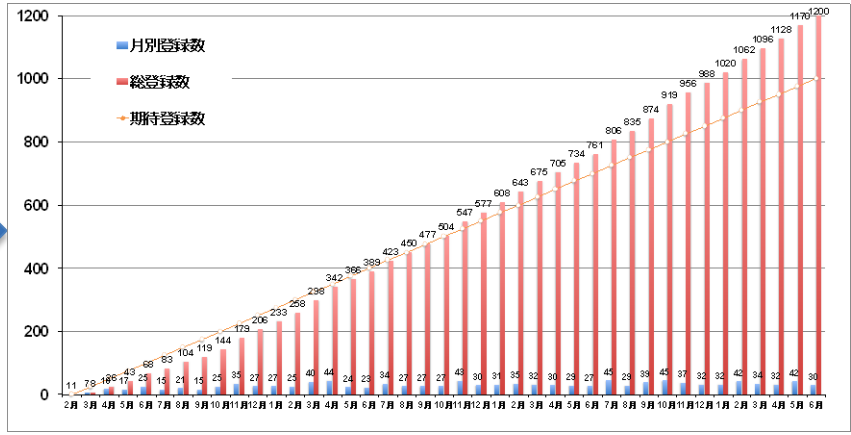
Variables	HR	95% CI	P value
TP53 Mt.	15.167	6.555 – 35.094	< 0.0001
MLL-PTD	3.843	1.964 – 7.522	< 0.0001
CBF-AML	0.359	0.207 – 0.622	0.0003
RUNX1 Mt.	2.301	1.278 – 4.146	0.0055
FLT3-ITD	1.805	1.130 – 2.885	0.0135
DNMT3A Mt.	1.696	1.055 – 2.725	0.0291

日本人AMLにおける分子層別化モデルを構築

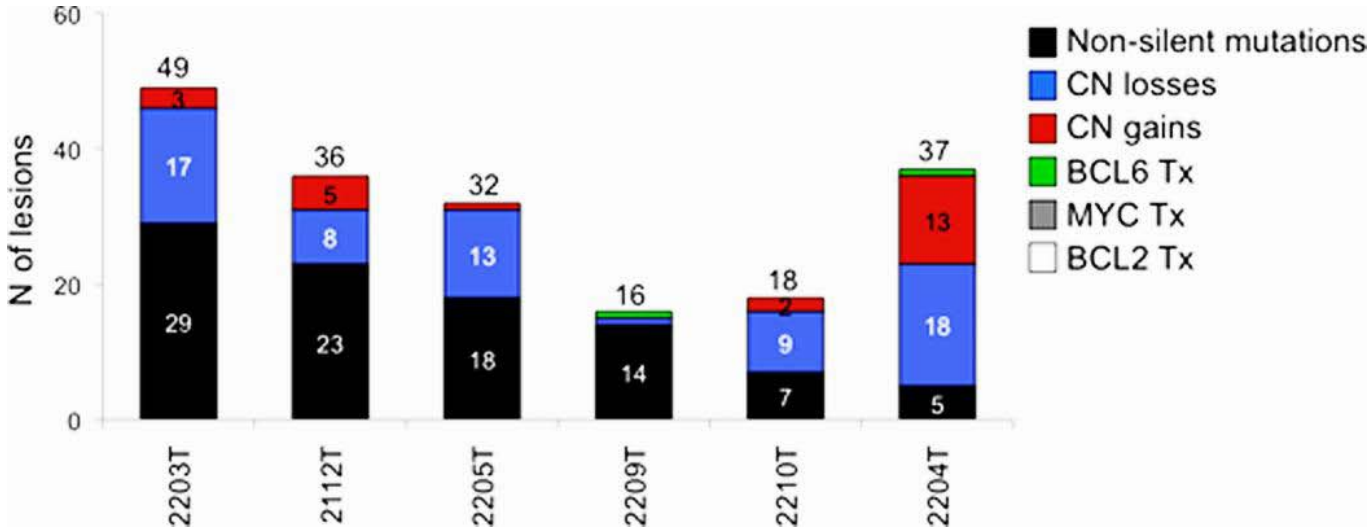


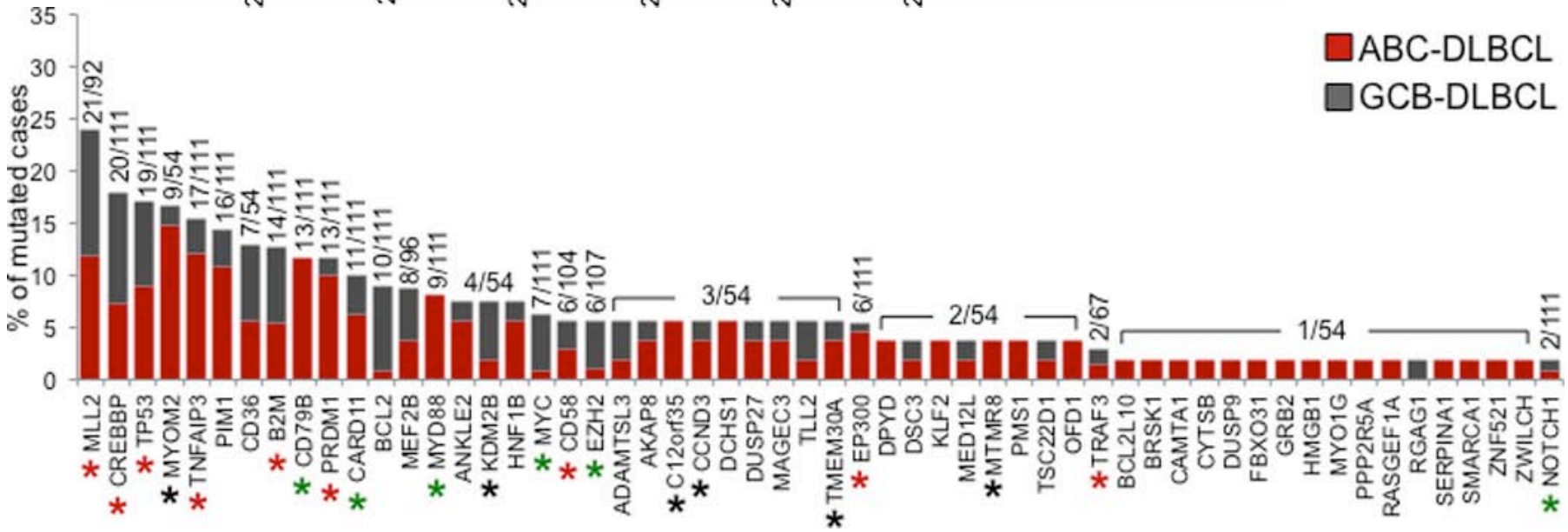
大規模コホート（AML209 1500例）で検証

1200例の検体収集を達成
計画よりも9ヶ月早く目標数達成予定



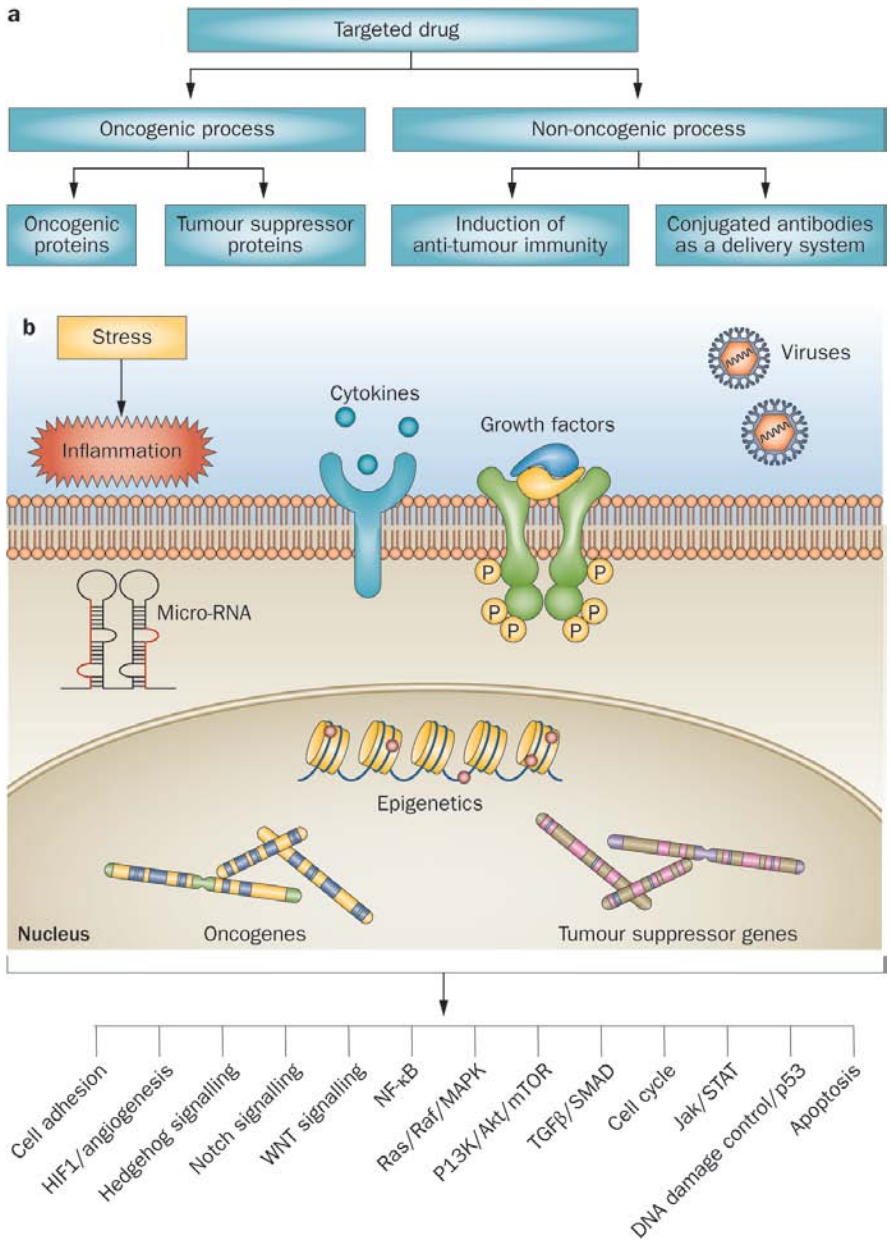
Complex molecular pathogenesis of DLBCL





Pasqualucci, et al. Nat Genet. 2011

Figure 1 Targeted therapy of lymphoma



Younes, A. & Berry, D. A. (2012)
Nat. Rev. Clin. Oncol. 2012

Figure 2 Clinical rationale for targeting oncogeneic pathways

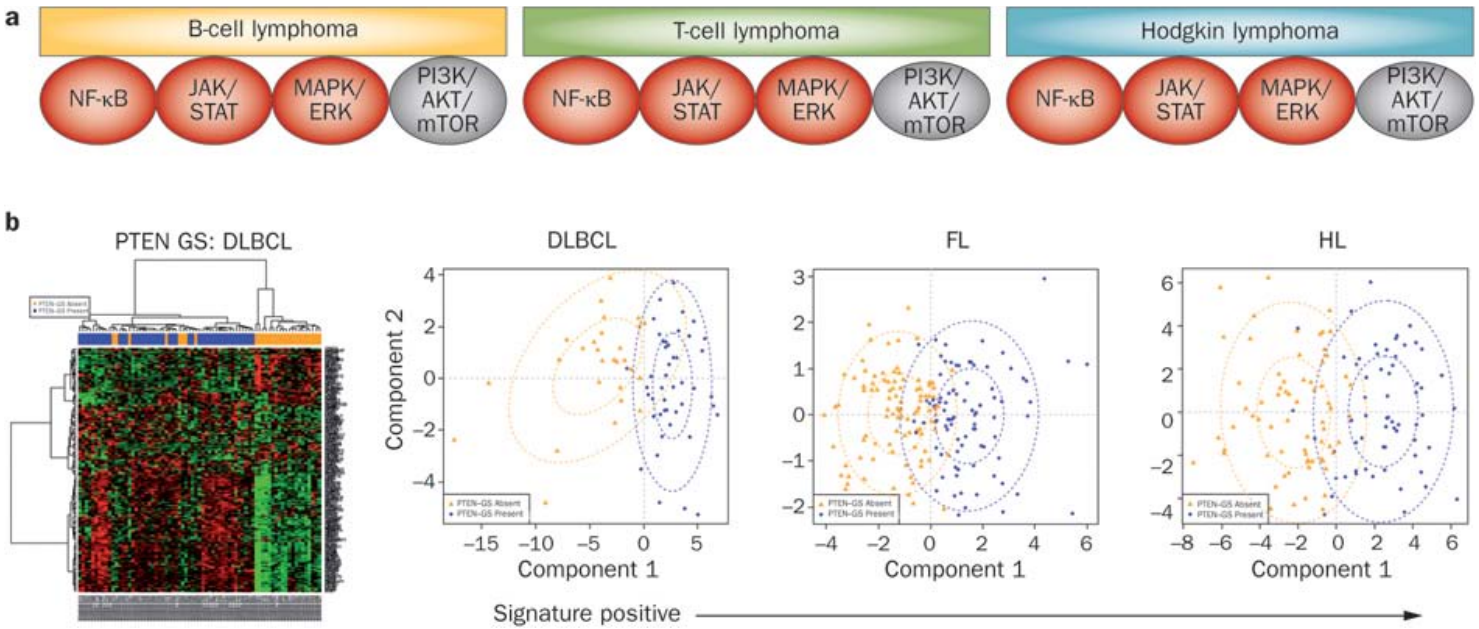


Table 1 Response rates according to histology

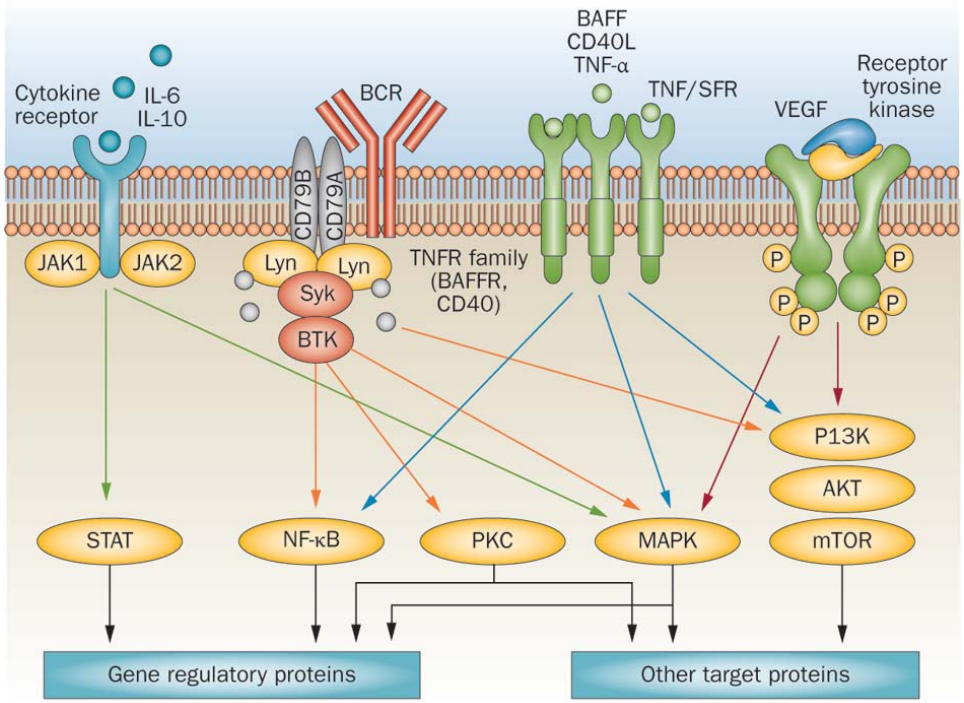
Table 1 | Response rates according to histology

Pathway	Drug	Target	Response rate in different histologies (%)					
			DLBCL	FL	MCL	SLL/CLL	T-cell	HL
PI3K/ AKT/ mTOR	Everolimus	mTOR	30	50	32	18	63	53
	Temsirolimus	mTOR	36	56	38	10	–	–
	CAL-101	PI3K	0	55	67	30	–	–
B-cell receptor	Fostamatinib	Syk	22	10	11	55	0	–
	PC132765	Btk	17	23	69	67	–	–

Abbreviations: CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; MCL, mantle-cell lymphoma; SLL, small lymphocytic lymphoma.

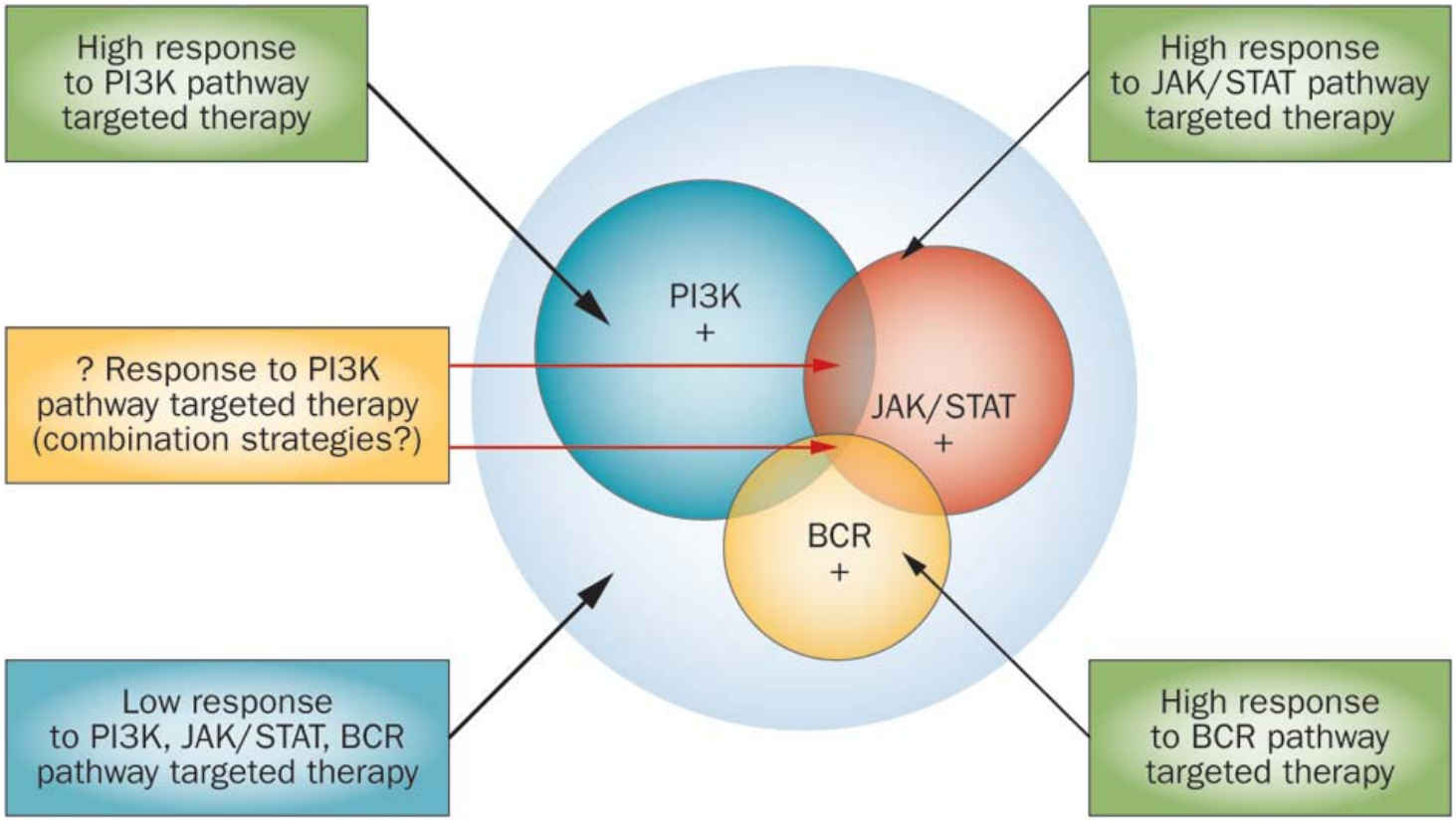
Younes, A. & Berry, D. A. (2012) From drug discovery to biomarker-driven clinical trials in lymphoma
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2012.156

Figure 3 Rationale for combination therapy in lymphoma



Younes, A. & Berry, D. A. (2012) From drug discovery to biomarker-driven clinical trials in lymphoma *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2012.156

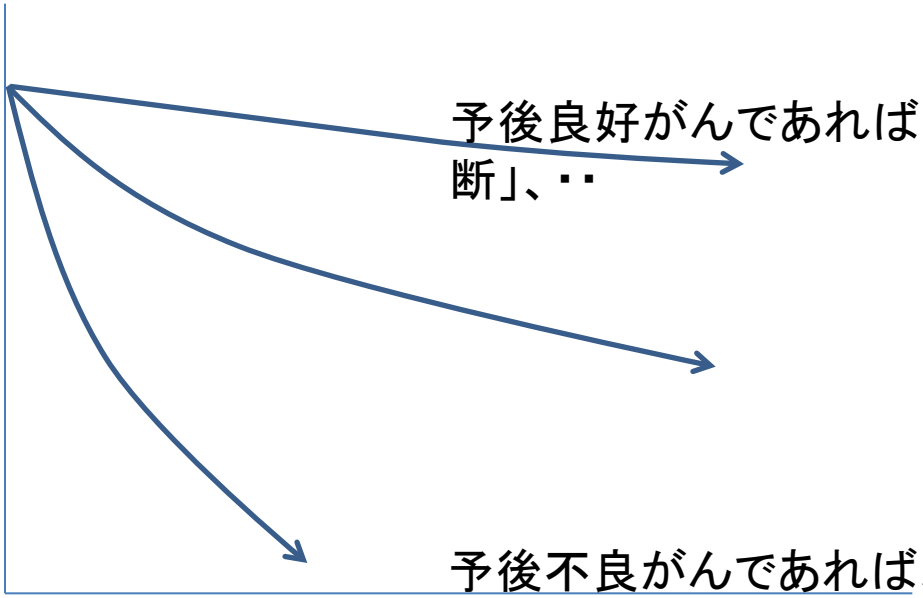
Figure 4 Defining lymphoma subsets based on biomarkers of activated pathways



“がん”における真のエンドポイントは何か？

生存割合

治療行為の有効性を示す評価項目



予後良好がんであれば、「QOL」「医療コスト」「治療中断」、・・

予後不良がんであれば、「生存」、高齢者は？

医療者・患者が実感でき、かつ客観的な有効性：　多くの場合、死亡率の低下

BM: 安全性予測にどの程度有用か？

TPMT
UGT1A1
CYP2C9
CYP2D6

G6PD
DPD
Factor V
Leiden
Prothrombin
mutations

Journal of Clinical Oncology, 2011 ASCO Annual Meeting Proceedings

Genetic associations with **taxane-induced neuropathy** by a genome-wide association study (GWAS) in E5103.

B. P. Schneider, et al.

まとめ（1）

- 優れたPredictive marker　↔　優れた薬剤

（ドライバー変異がBMであることは論を待たないであろう）

- これ以外でのBM有効性の検証は意外と難しい
- ゲノムレベルの情報が急速に蓄積する中で、BMは組み合わされ複雑化している

まとめ（2）
これからBMが求められる領域は？

- 分子標的治療

- “抗がん剤”“放射線治療”

- MOA／POC不明　（ex.サリドマイド)
  – → 統計解析
- 免疫療法におけるBM


Published OnlineFirst August 27, 2012; DOI: 10.1158/1078-0432.CCR-12-1206

Predictive Biomarkers and Personalized Medicine

Clinical Cancer Research

Developing and Validating Continuous Genomic Signatures in Randomized Clinical Trials for Predictive Medicine

Shigeyuki Matsui[1], Richard Simon[2], Pingping Qu[3], John D. Shaughnessy Jr[4], Bart Barlogie[4], and John Crowley[3]

まとめ（3）
バイオマーカー臨床開発の問題点

- 誰が主体的に進めるのか？（メーカーVsアカデミア）
- ヒト検体の収集・保存に関わる問題
  - ICやゲノム指針対応など倫理問題
  - 治験における探索的研究
- 臨床的有用性・エビデンスーいかに実証するか？
- 解析方法の標準化・知財問題－複数利害関係者にまたがる問題
- 出口戦略： コスト負担、保険承認など