C-CAT
Center for Cancer Genomics and Advanced Therapeutics

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Second Opinion and its management

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What is second opinion(SO)?

- The opinion of a doctor other than the patient's current doctor.
- The second doctor reviews the patient's medical records and gives an opinion about the patient's health problem and how it should be treated.
- A second opinion may confirm or question the first doctor's diagnosis and treatment plan, give more information about the patient's disease or condition, and offer other treatment options.

NCI dictionaries

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

What is second opinion SO for?

- Support the patients' decision-making process
  - Patients are becoming more and more involved in the decision-making process
  - Patients are facing a complex medical issue or difficult treatment decision
  - In Germany, every cancer patient should have access to a free second opinion
- Avoid treatments that are unnecessary from a medical perspective.

What you need for SO?

- Obtain all medical records
  - it is extremely difficult (or unable) to give advices without full information of you past medical history
- May need some more information
  - Sometime, primary physicians may not submit enough information to access your disease. Medical information are so huge that it is unable to submit “all” you records.
  - Doctor will ask you primary physicians for more information (this takes time)

What you (at least) need for the genomic second opinion?

- History of previous treatment
  - Surgery
  - Radiation
  - Medical treatment
    - as detail as possible
    - regimen, when, how long
    - response, toxicity
    - reason of discontinuation
- Genomic report
  - original report is preferrable
  - if local testing: as detail as possible

Can we obtain better health care?

- Changes in diagnosis, treatment recommendations or prognosis as a result of the second opinion occurred in 12-69 % of cases.
- In 43-82 % of cases, the original diagnosis or treatment was verified.
- Patient satisfaction was high, and the second opinion was deemed as helpful and reassuring in most cases.
- Data on patient-relevant outcomes or on the quality of the second opinion are missing.

Ruetters J Cancer Res Clin 2016;142:1521–8

What kind of question shall you ask?

- Is diagnosis appropriate?
  - Especially important in rare cancer
  - May need pathological second opinion
- Is treatment modality appropriate?
  - Surgery, radiation and medicine
- Is treatment sequence appropriate?
  - Multi-modality treatment is a key of oncology
- Is there any other treatment?
  - Indication of radiation and surgery may differ when there is not enough evidence
  - Access to the drug is always a concern globally.

What is genomic report?

- Genomic change in your tumor
  - May report your germ cell mutations (which may be attributed to hereditary tumor)
- Genomic change does not mean that there are always targeted treatments
  - Only limited genomic changes are effectively treated with targeted treatment
  - Clinical trials are limited
- Recommended treatment on genomic testing is not always true
  - they do not consider you past medical history or conditions

Details of medical report

- detected alteration
  - gene
  - changes (mutation, translocation and amplficiatation)
  - %DNA, amplification

  - clinical relevance
    - oncogenic or VUC (variants of uncertain clinical significance)
- approved therapy
- clinical trial availability

Difficulties of interpretation

C-CAT調査結果

C-CAT Center for Cancer Genomics and Advanced Therapeutics

c-cat-findings_20191219_EC00010200

2 調査結果

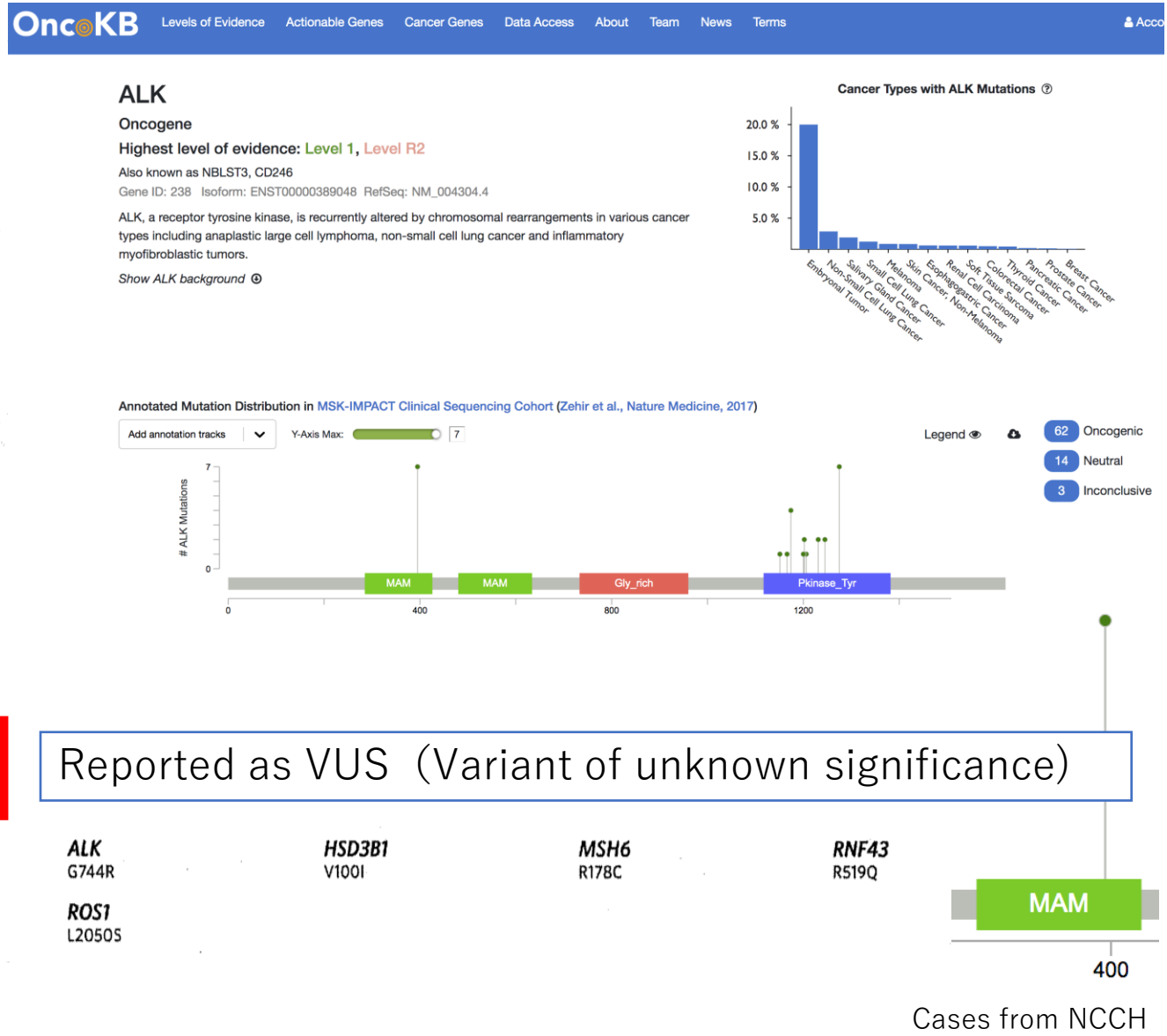
概要

⚠ 薬剤への到達性の指標をご参照ください。

検出変異数	国内承認薬	国内臨床試験中	国内適応外薬	海外臨床試験中	FDA承認薬
体細胞変異：9 生殖細胞系列変異：-	1	1	0	4	1

塩基置換、挿入、欠失（DNA）

No.	マーカー	エビデンスタイプ	臨床的意義	エビデンスレベル	薬剤	薬剤への到達性	米国エビデンスレベル
1	*TP53* Q144*	Predictive	Sensitivity/Response	E	doxorubicin hydrochloride	国内承認薬 FDA承認薬	Tier 2C Pathogenic 海外臨床試験中 (2件)
		Oncogenic	Pathogenic	F			
2	*DNMT3A* R736H	Oncogenic	Likely Oncogenic	F			Tier 2C Pathogenic
3	*RNF43* R519Q	Oncogenic	Likely Pathogenic	F			Tier 3 Uncertain Significance
4	*TET2* Q644*	Oncogenic	Likely Pathogenic	F			Tier 2C Pathogenic
5	*ALK* G744R				alectinib hydrochloride(Trial Condition Match)	国内臨床試験中 (1件)	Tier 3 Uncertain Significance
6	*MSH6* R178C						Tier 3 Uncertain Significance
7	*HSD3B1* V100I						Tier 3 Uncertain Significance
8	*ROS1* L2050S						Tier 3 Uncertain Significance



Reported as VUS（Variant of unknown significance）

ALK
G744R

HSD3B1
V100I

MSH6
R178C

RNF43
R519Q

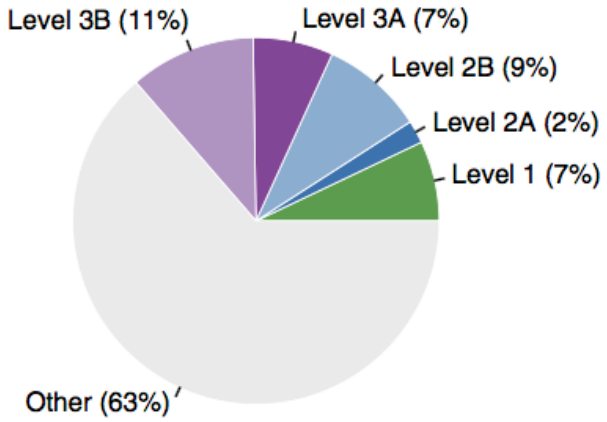
ROS1
L2050S

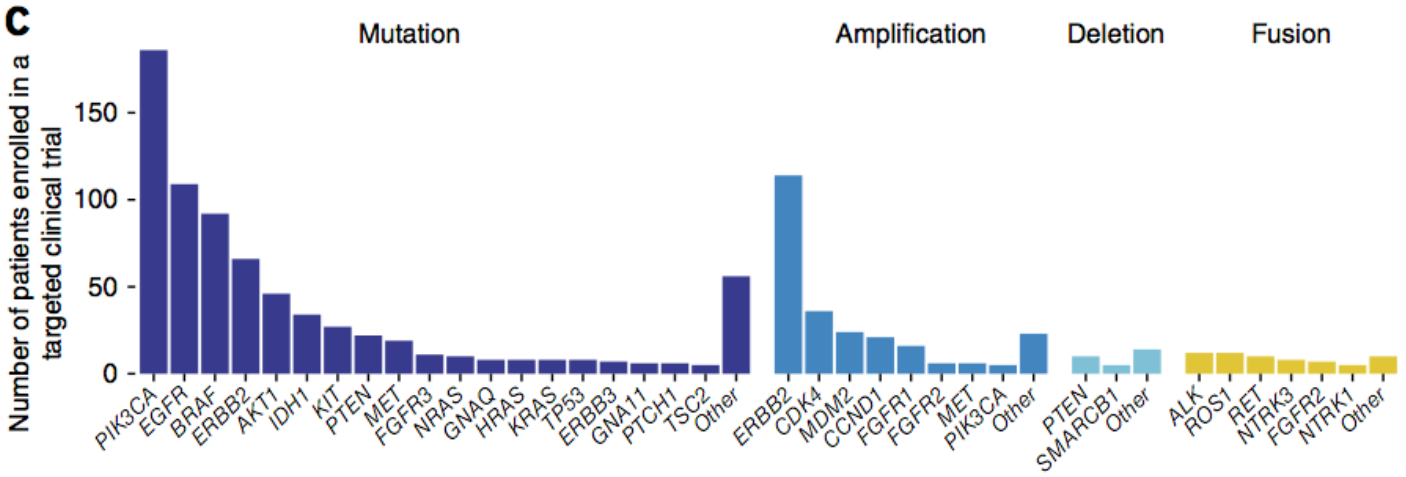
Cases from NCCH

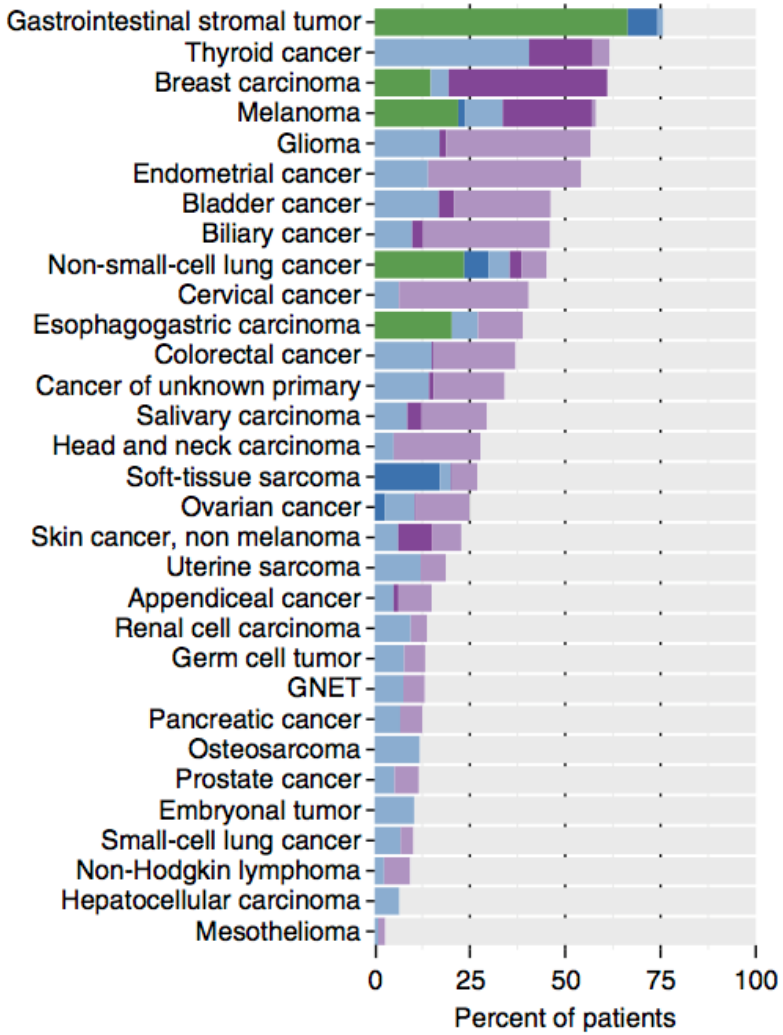
ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

Genomic analysis at Memorial Sloan Kettering hospital 2017

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

Understanding the evidence level

- Level 1　Approved by FDA (EMA, PMDA or other agency) as biomarker for an FDA-approved drug in same indication
- Level 2A　Standard of care biomarker for an FDA-approved drug in same indication
- Level 2B　Standard of care biomarker for and FDA-approved drug in another indication
- Level 3A　Compelling 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

Drug access is practically important

- Reimbursed is most critical for patients
- Some countries may restrict the use, when it is not “approved” but drug approval is not as important as people might think

- Other issues in accessibility may include,
  - location of the treatment: feasibility for patient to regularly visit
  - Emergency response at local hospital: some treatment need special knowledge to its drug

Where to find the clinical trial for your genomic findings?

- Clinicaltrials.gov
  - https://clinicaltrials.gov/
- NCI
  - Find NCI-Supported Clinical Trials
  - https://www.cancer.gov/about-cancer/treatment/clinical-trials/search
- NHS/NIHR
  - https://bepartofresearch.nihr.ac.uk/
- WHO (International Clinical Trials Registry Platform)
  - https://www.who.int/clinical-trials-registry-platform

Case study:
No oncogene was found by simple plex testing

- Non-smoker, female, 60s
- cTxN3M1a Stage IV
- EGFR/ALK/ROS1 : Negative

Standard treatment

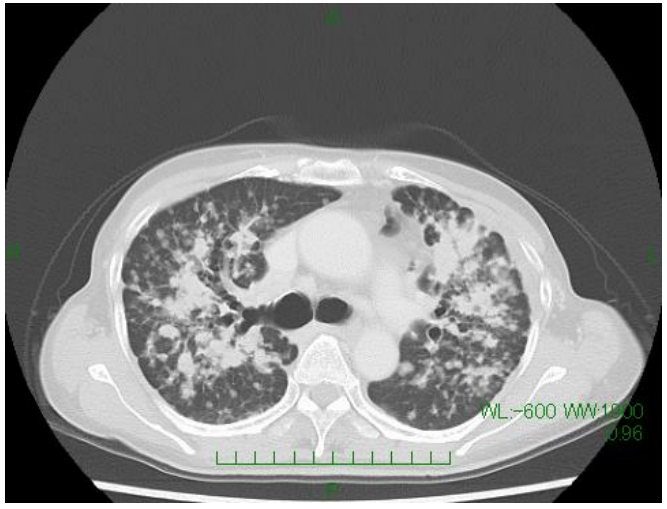
Case from NCCH

CDDP+PEM

Nivolumab

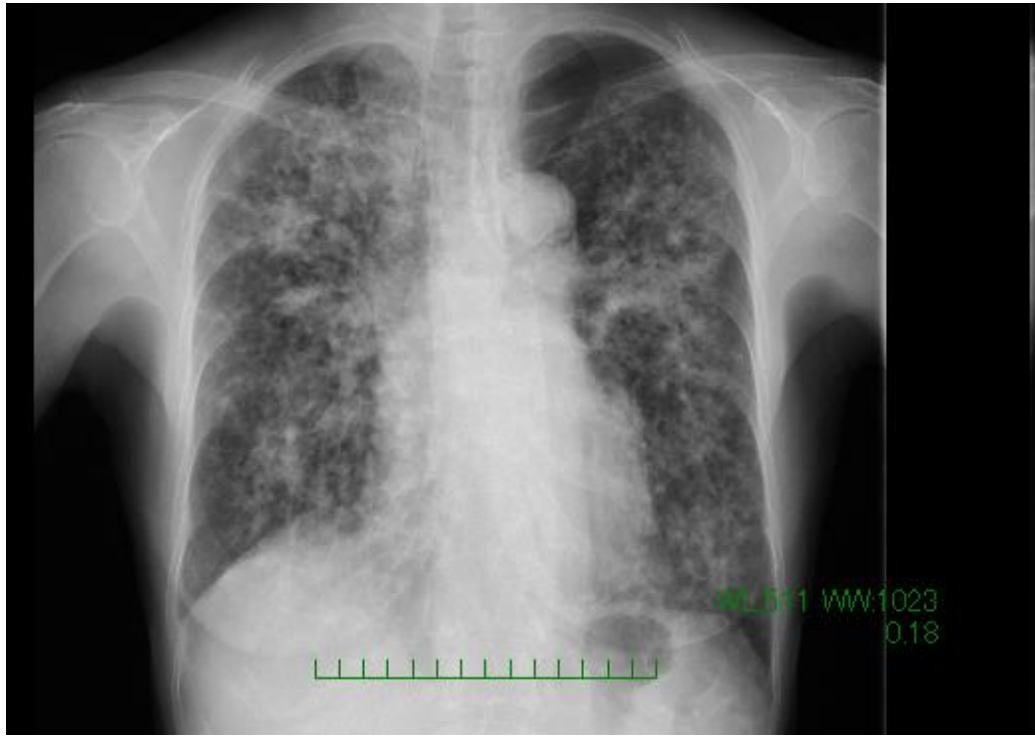
DTX+RAM

BSC

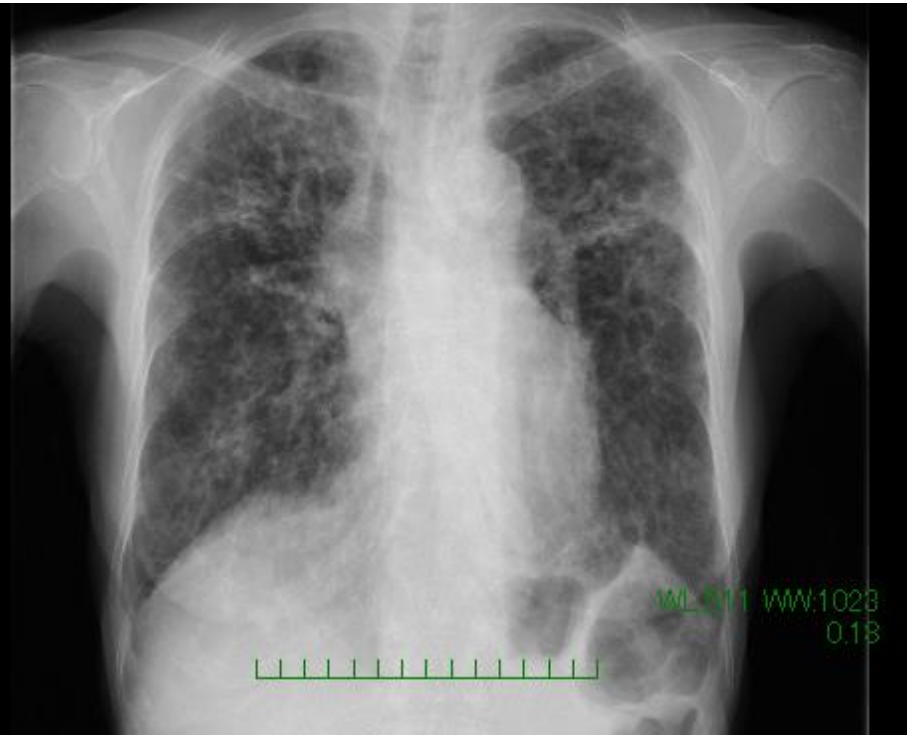


CD74-NRG1

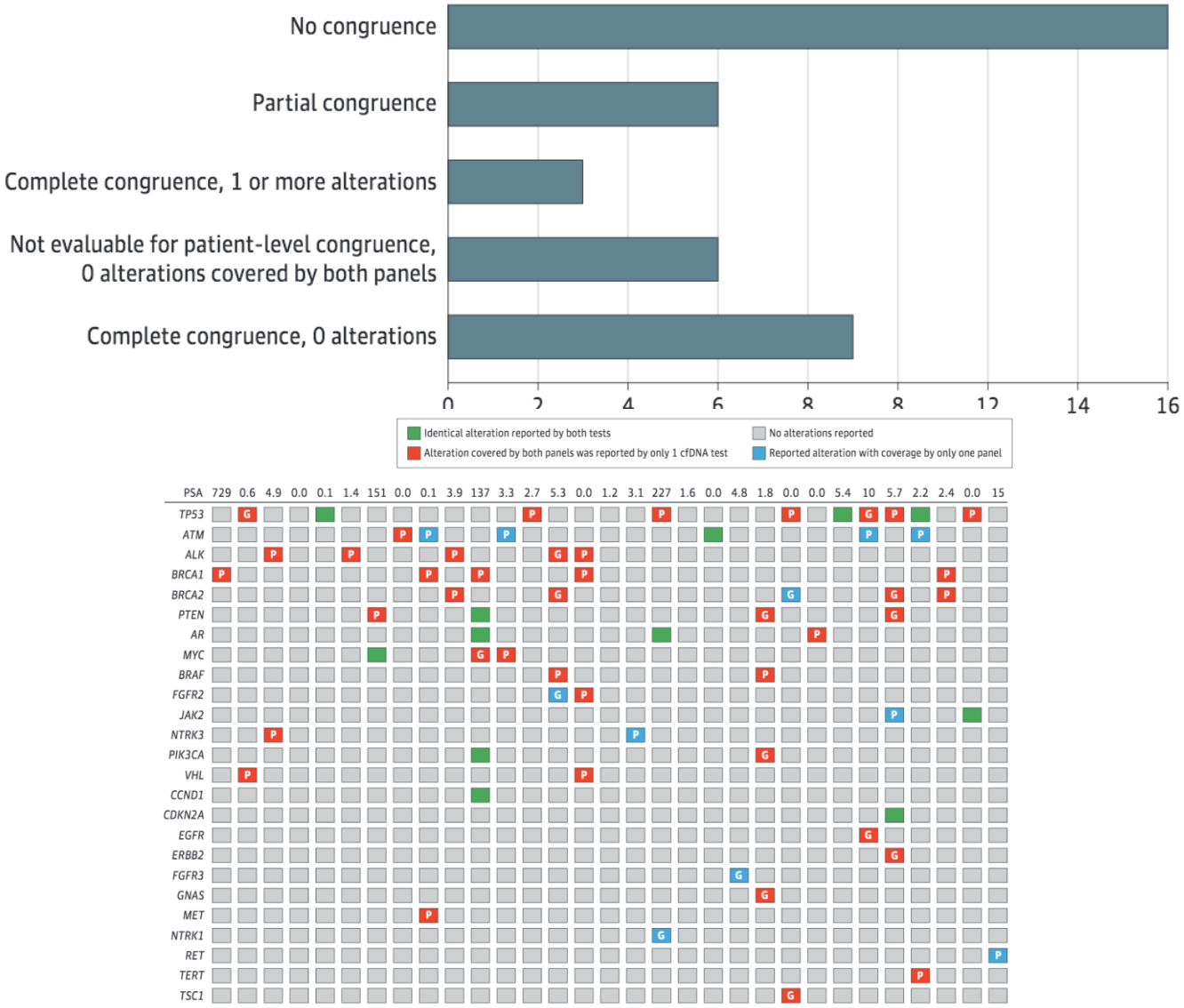
Start of afatinib



2 months



Pitfall in genomic test



- Result may change by testing methods
- Many clinical trials ask for specific test to be positive

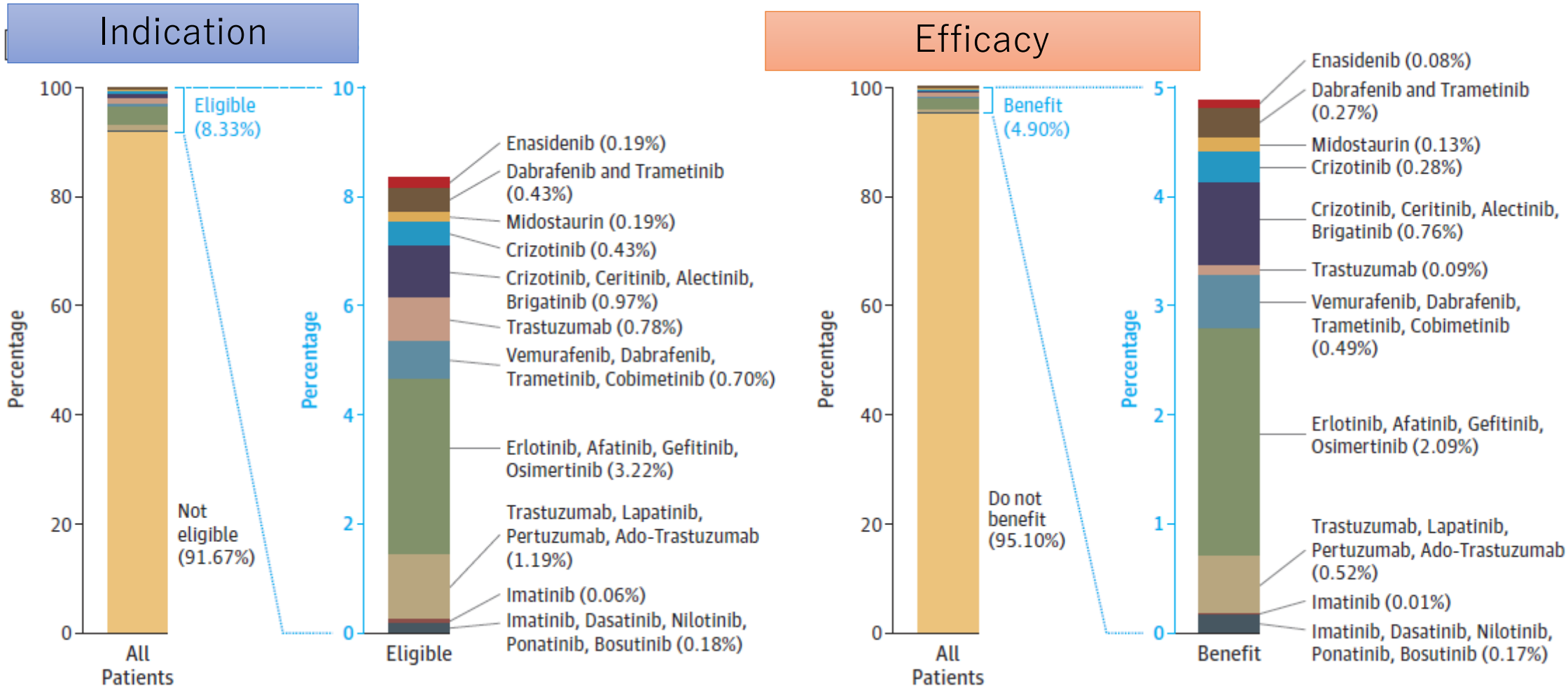
Torga JAMA Oncol 2018

Pitfall in clinical trials

- Many trials do not reveal their targets (genes) in public
- Progress of clinical trials are by the day, and availability is not on public
- Clinical trials are regulated not only by the sponsor (mainly pharmaceutical) but regulatory agency, and ethnicity may be a problem
  - readability of the briefing paper, agreement

Value of genomic medicine

2006-2018・31agents・38indication（FDA）



Marquart JAMA Oncology 2018

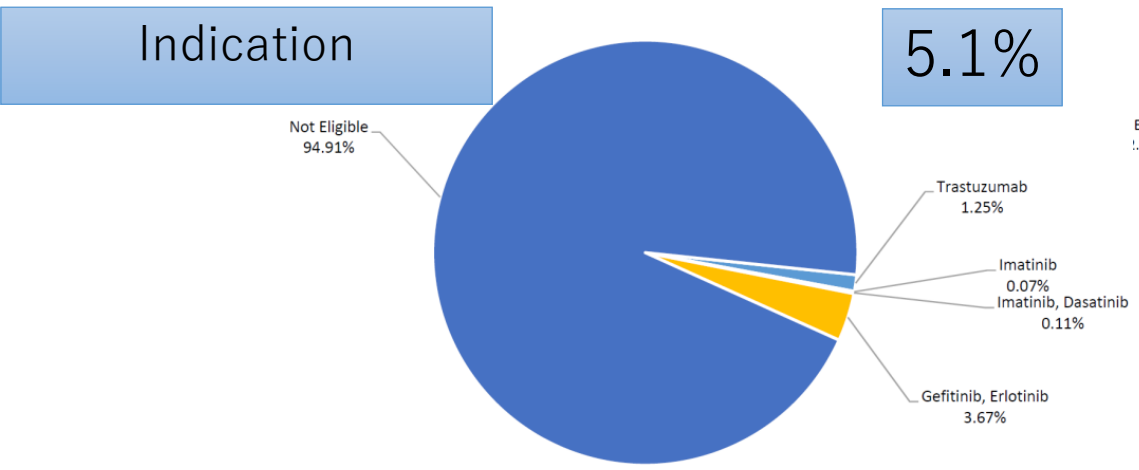
How genomic medicine has evolved?

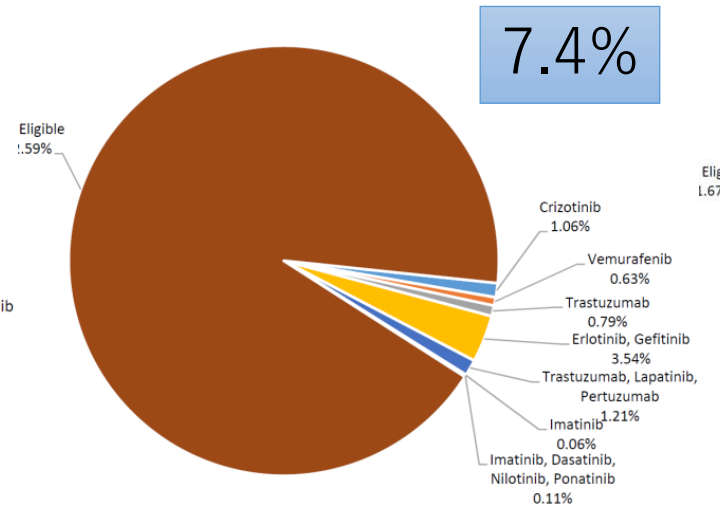
2006

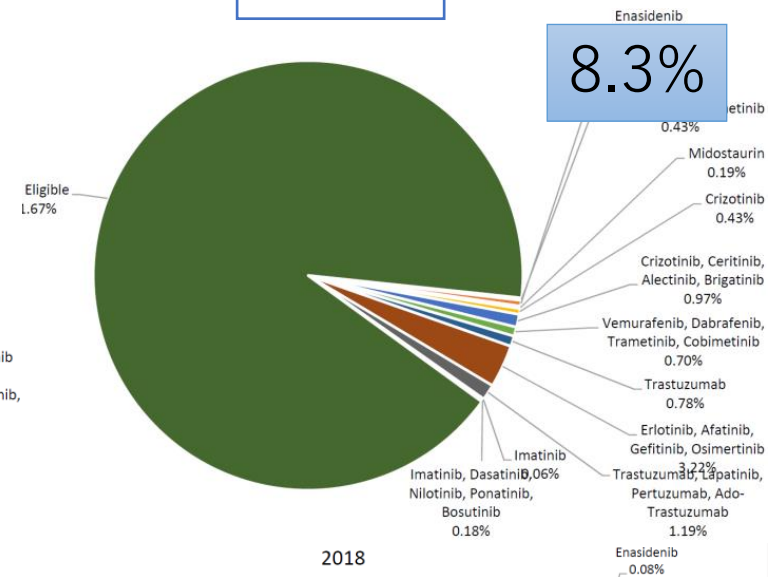
2012

2018

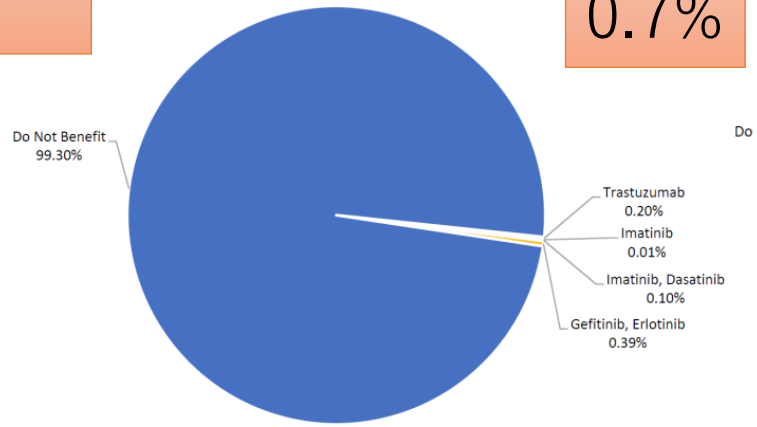
Indication

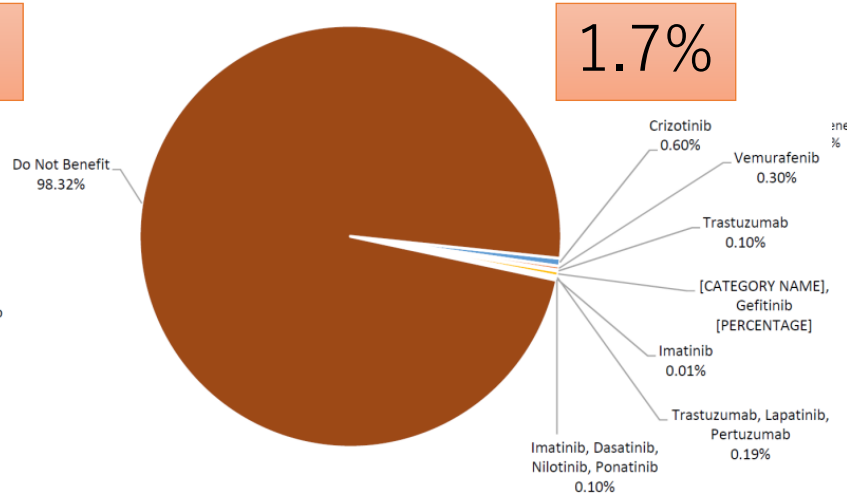


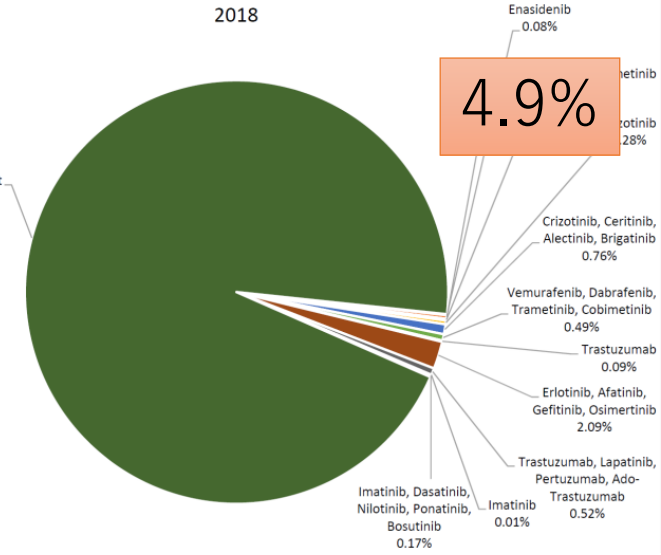




Efficacy







ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

Marquart JAMA Oncology 2018

Pitfalls and expectation in SO

- Doctors are unable to compass all the availability of the treatment at each region
  - surgical indication
  - radiation modality: IMRT/3D
  - drug access
- General understanding of the disease is important in the treatment journey
  - better care is not only provided by the specific treatment
  - information of the disease and treatment will elevate the level of satisfaction
- Advance in genomic medicine may change your treatment within years