A hopeful revolution in cancer care

-explore potential roles of target therapy from tumor agnostic studies

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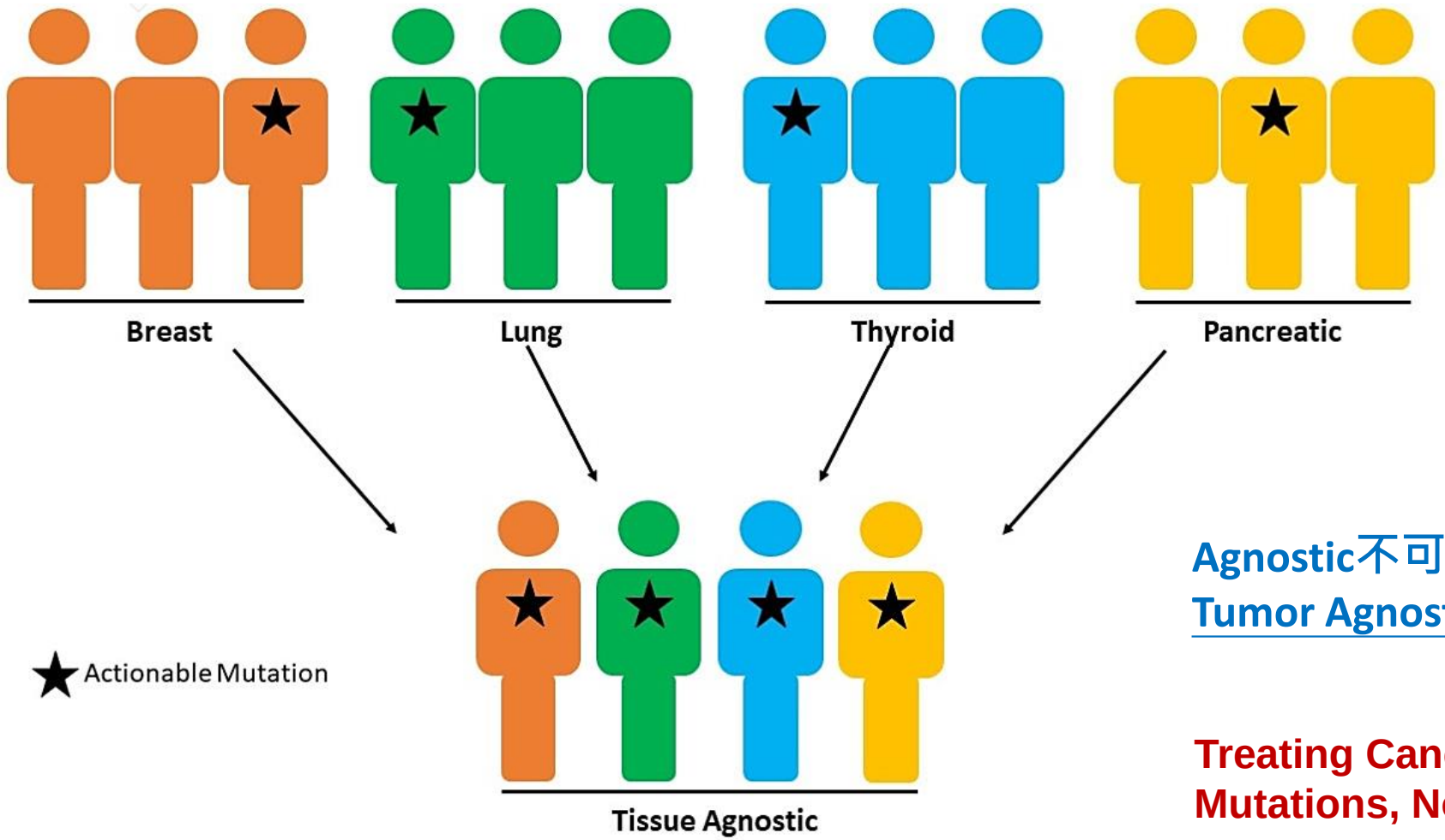
Tumor agnostic therapy or Tissue-agnostic therapy (Drug)

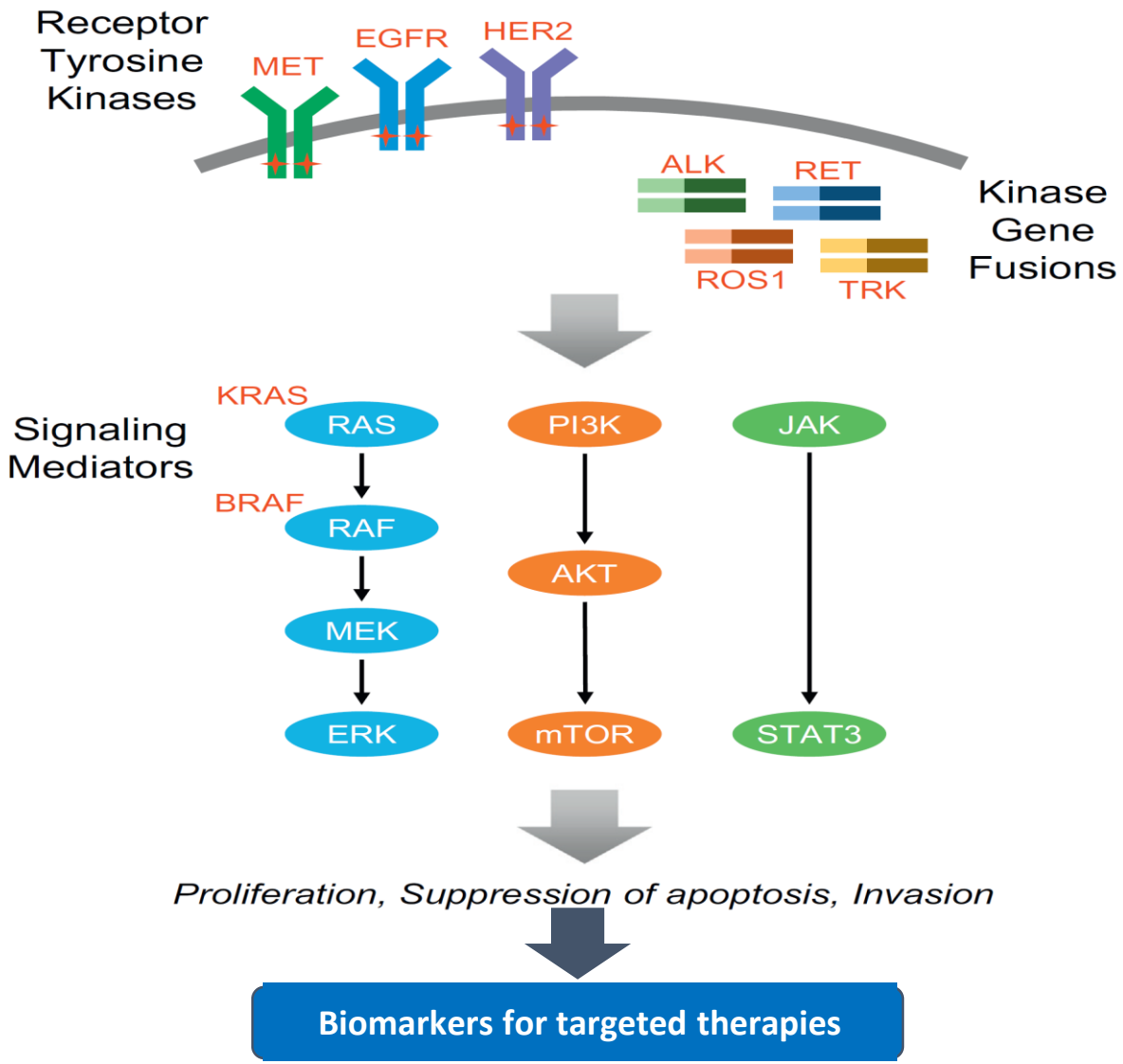


Agnostic不可知論
Tumor Agnostic不定腫瘤類型

Treating Cancer by Mutations, Not by Location

Rosas & Raez. Oncol Ther 2020
https://oncobites.blog/2020/03/06/a-new-paradigm-for-cancer-drug-development/

Actionable genomic alterations can be major oncogenic drivers

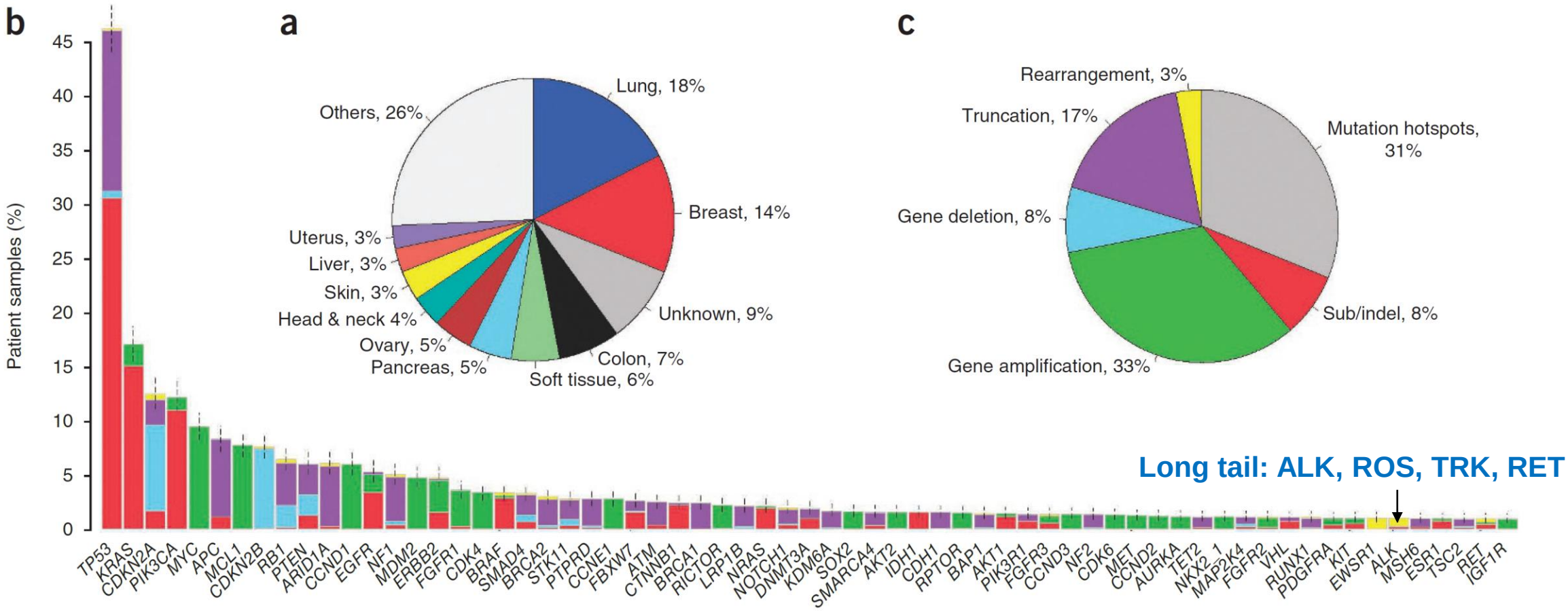


Genomic alterations

- **Gene fusions leading to the expression of chimeric fusion proteins**
- **Point mutations and SNVs**
- **Multiple point mutations: high TMB**

S. Yoda et al. / Pharmacology & Therapeutics 193 (2019) 20–30

Treatments are needed for rare biomarkers and/or rare cancers



Long tail: ALK, ROS, TRK, RET

Clinically actionable alterations in patient samples: Although the number of actionable alterations in any individual cancer patient's sample was low (average, 1.57), a wide variety of alterations was observed across all samples, with 1,579 unique alterations reported.

Frampton GM et al. Nat Biotechnol. 2013 Nov;31(11):1023-31.

Activity of drugs currently approved with a histology-agnostic indication

Biomarker based

Rare

High clinical efficacy

Drug	Biomarker	Testing method	Biomarker prevalence	Trial type	Population enrolled	Activity
Pembrolizumab	MSI-High/ MMR deficiency	MSI status determined by PCR, MMR status determined by IHC	3.8% of all cancers, enriched in uterine, colorectal and gastric carcinoma	Pooled analysis of five phase 2 studies (KN-012, KN-016, KN-028, KN-158, KN-164)	149 patients, affected by CRC (n = 90) or 15 tumor types	ORR 39% (7% CR), mDOR not reached, mPFS 6 months
Pembrolizumab	TMB-high (>10 mutations/ Mb)	FoundationOne CDx assay	13% of solid tumors enrolled in the Keynote-158 trial (10 different cancer types)	Phase 2 trial (KN-158)	105 TMB-high patients affected by 9 cancer types (anal, cervical, endometrial, mesothelioma, neuroendocrine, salivary, SCLC, thyroid, vulvar)	ORR 29% (4% CR), mDoR not reached, mPFS 2.1 months
Larotrectinib	NTRK fusion	FoundationOne CDx assay	0.3% of solid tumors, enriched in pediatric melanoma, pediatric glioma and adult thyroid cancer	Pooled analysis of a phase 1 trial, the phase 1/2 "SCOUT" trial and the basket phase 2 "NAVIGATE" trial	55 patients affected by 17 different tumor types	ORR 80% (16% CR), mDOR not reached, mPFS not reached
Entrectinib	NTRK fusion	No companion diagnostic yet determined	0.3% of solid tumors, enriched in pediatric melanoma, pediatric glioma and adult thyroid cancer	Pooled analysis of two phase 1 trials (STARTRK-1 and ALKA-372-001) and the phase 2 "STARTRK-2" trial	54 patients affected by 10 different tumor types	ORR 57% (7% CR), mDOR 10.4 months, mPFS 11 months

parallel development in adult and pediatric populations

Durable responses

While these trials and subsequent approvals represent important steps towards personalised oncology treatment, **many patients with tumours harbouring rare biomarkers still have no targeted therapy options**

Pestana et. al., Trends Cancer . 2022 Feb;8(2):135-144.

A paradigm shift to agnostic therapy

Traditional clinical trial programme for cancer drug approval based on tumour type

Participants with **same disease** (line of therapy + tumour type ± genetic mutation)

Multiple by Hamisha from NounProject.com

(Targeted) intervention received as part of **randomised controlled trial (vs standard of care)**, preferably phase 3

Added therapeutic benefit proven compared with standard of care

Drug receives **regulatory approval** for histology dependent indication

Basket trial programme for approval of drugs with a tumour agnostic indication

Participants with the **same genetic anomaly/biomarker** but **different cancer tumour types**

Diversity by Luis Prado from NounProject.com

Targeted intervention received as part of (usually, single-arm) phase 1 or 2 trials

Efficacy based on **surrogate outcomes** i.e. overall response rate (ORR)

Added therapeutic benefit assumed based on primary efficacy endpoint

Conditional marketing authorisation granted for tumour agnostic indication

Factors that influence development of tumor agnostic therapies

Favoring

- Clear understanding of tumor biology that drug is targeting
- Biomarker that can be readily tested in clinical setting
- Ability to run clinical trials across tumor types
- Oncogene-specific advocacy groups
- Regulatory precedent

Barriers

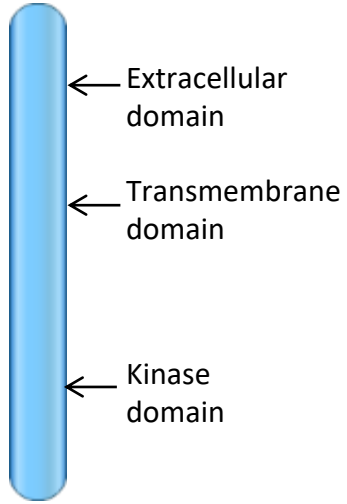
- **Historical/empiric approach to therapy**
- **Disrupts treatment algorithms for disease type**
  - Physicians
  - Clinical trial groups
  - Tumor-specific advocacy group
- **Lack of widespread tumor testing**
  - Need routine use of broad NGS panels.

Adopt from 2019 WCLC plenary seminar for tumor agnostic therapy

Anaplastic lymphoma kinase (ALK) 間變性淋巴瘤激酶

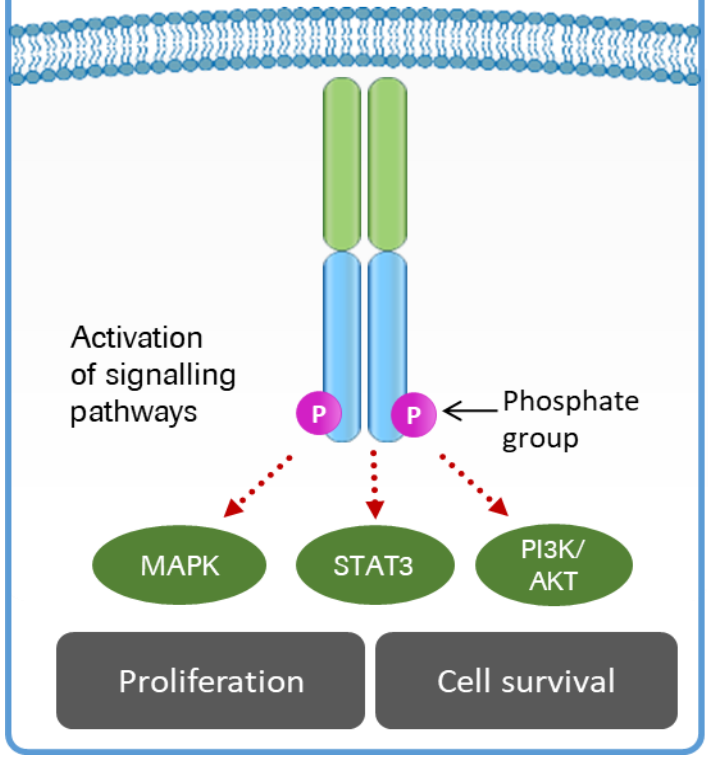
Adenocarcinoma
Age: early 50s
Never/light smoker

ALK protein

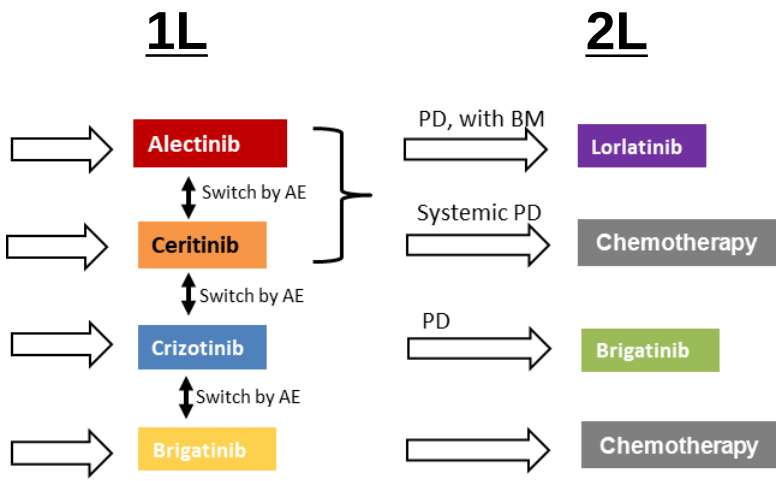


***ALK* is NOT expressed in normal lung tissue**

EML4-ALK fusion protein signaling



Taiwan NHIA reimbursed ALK TKIs

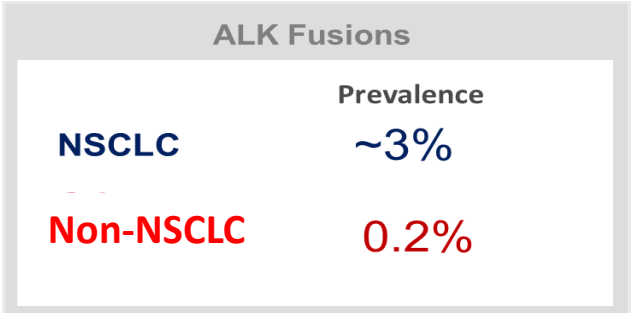


1. Clin Pharmacol Ther. 2014 Jan;95(1):15-23 2. Cancer Sci 2008; 99: 2349–2355
3.Ou SH et al. Oncologist 2012;17:1351-75 4全民健康保險藥物給付項目及支付標準－第六編第八十三條之藥品給付規定第9節 抗癌瘤藥物

ALK fusion is less frequent in non-NSCLC

Clinical and genomic features of ALK fusion-positive and ALK fusion-negative NSCLC and non-NSCLC cases

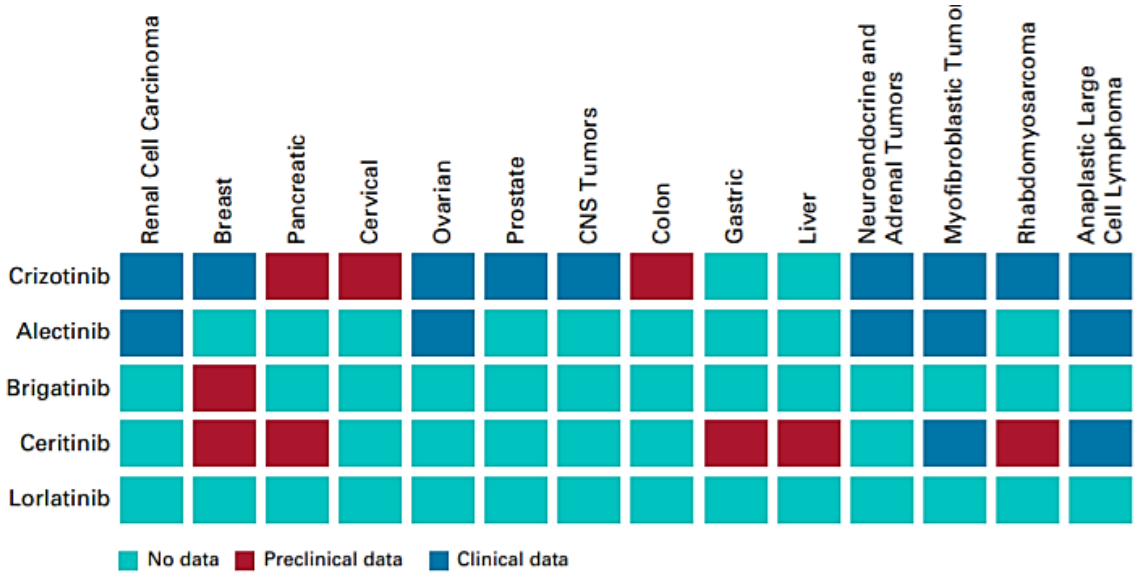
Parameter	NSCLC	Non-NSCLC	Total
Total cases sequenced, n (%)	21,522 (18.8%)	92,678 (81.2%)	114,200
Gender, female/male	52.6%/47.4%	59.2%/40.8%	
Age			
Mean	55.4	43.0	
Median	56	47	
Range	15–95	0–87	
Number of cases with *ALK* rearrangements	675 (3.1%)	201 (0.2%)	876 (0.8%)
Total number of ALK rearrangements	680	204	884
Fusions	615 (90.4%)	173 (84.8%)	788 (89.1%)
Other rearrangements	65 (9.6%)	31 (15.2%)	96 (10.9%)
EML4 fusion partner frequency	568 (83.5%)	63 (30.9%)	631 (71.4%)



Outside of NSCLC, ALK rearrangements were most often found in carcinomas, sarcomas, and hematolymphoid malignancies.

ROSS et al., Oncologist 2017

Data for the use of ALK-inhibitors in non-NSCLC tumor types



	Renal Cell Carcinoma	Head and Neck	Breast	Pancreatic	Bladder	Uterine	Vaginal	Vulvar	Cervical	Ovarian	Prostate	CNS Tumors	Colon	Gastric	Liver	GIST	Neuroendocrine and Adrenal Tumors	Rectal
Crizotinib	2	0	2	1	0	0	0	0	1	2	2	2	1	0	0	0	2	0
Alectinib	2	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	2	0
Brigatinib	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ceritinib	0	0	1	1	0	0	0	0	0	0	0	0	0	1	1	0	0	0
Lorlatinib	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

No data (0) Pre-clinical data (1) Clinical data (2)

https:// doi.org.10.1200/ PO.20.00383

Alectinib/TKI treated solid cancers harbor ALK alteration

	Cancer type	ALK Fusion partner (Detected Method)	Clinical benefits, treatment (PFS)	Ongoing trials
1	Esophageal cancer 食道癌	STRN (ARMS)	1 crizotinib, CR (22mos PFS, 43mos OS)	
2	Gallbaldder cancer 膽囊癌	AMBRA1 (NGS +>IHC-ALK+)	1 crizotinib, PR (7 mos)	
3	Extrahepatic Cholangiocarcinoma 肝外膽管癌	NA	NA	NCT03768375 NCT02836847 with Crizotinib but no data
4	Gastric cancer 胃癌	HMBOX(NGS)	1 Alectinib, PR (6 mos)	
5	Pancreatic cancer 胰臟癌	• EML4*5,STRN,PPF1B, DCTN1 • KANK4 (NGS) • Intron19, EML4	• 8 cases: 1 PR, 3 SD, 2PD, 2 Unknown • 1case: 1 Alectinib, CR • 3 cases: Alectinib 1SD(5.4 mos), 1PD(0.9 mos), 1 UK(1.6 mos)	

CR, complete remission; PD, progressive disease; SD, stable disease; PR, partial response; mos, months. UK, unknown

1.Zhang et al. 2021 2. Zhou et al. 2020 4. Ambrosini et al.2022 Wen et al.2021
5. Singhi et al.2017;Ou K et al.2021;Gaule et al., 2022 ;Ambrosini et al.2022

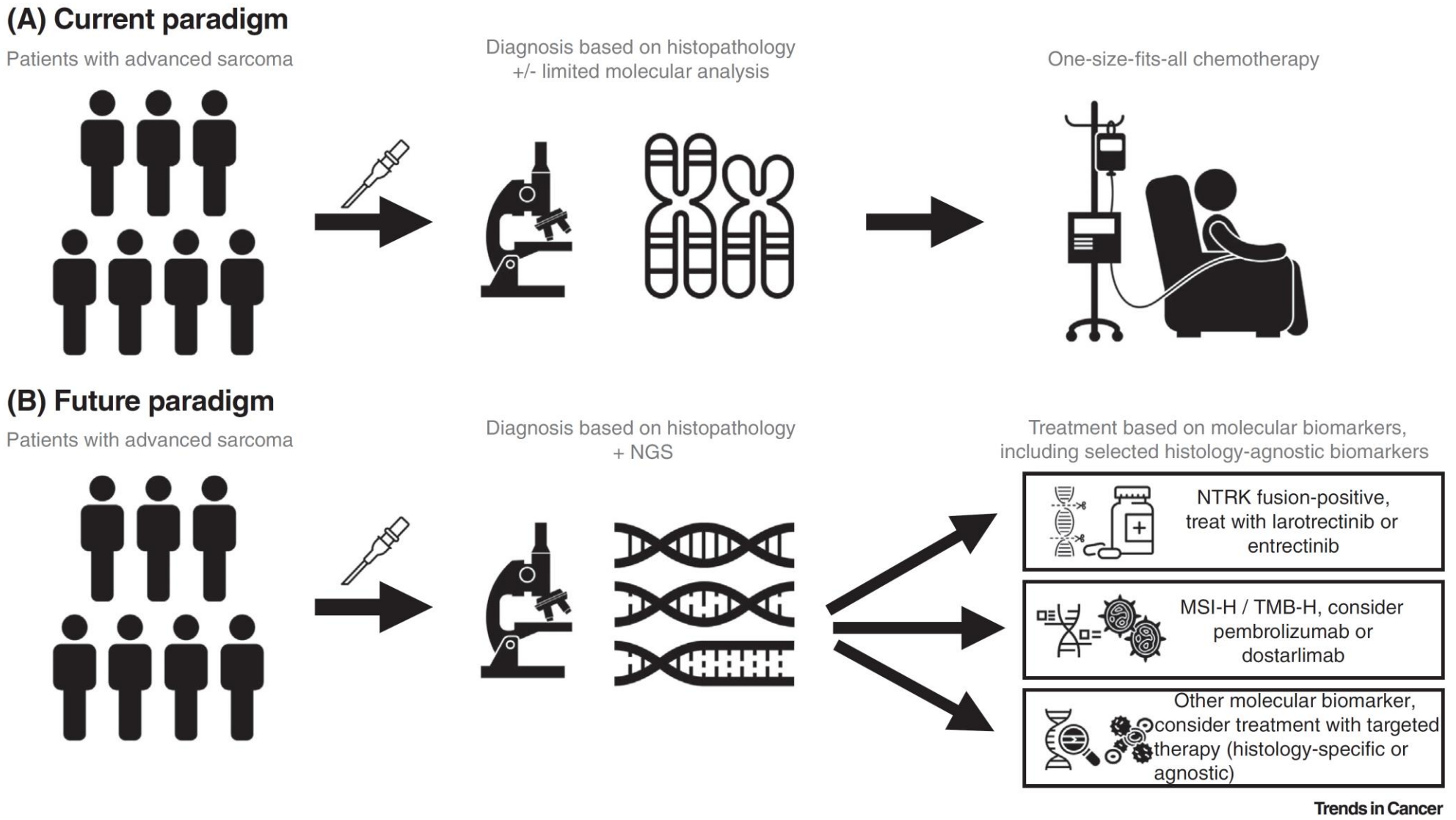
Chugai participates in NBCT project

Alectinib compassionate use
For ALK+ ~5-10 pts
(0.2%> 2pt)

patient central
RWD

https://nbct.nhri.org.tw/docDetail.aspx?uid=10143&pid=10142&docid=10208&rn=15732

Efforts are under way to move toward a biomarker-driven approach



MSI-H microsatellite instability-high; NGS, next-generation sequencing; NTRK, neurotrophic tyrosine receptor kinase.

Pestana et al.,Trends Cancer. 2022 Feb;8(2):135-144.

Key points

1. **Tumor-agnostic therapies** that uses drugs to treat cancer based on the cancer's genetic and molecular features (biomarkers) without regard to the cancer type or where the cancer started in the body.
2. Regulatory approval of medicines of histology-independent indications (agnostic therapy) represents an important **paradigm shift**.
3. Tumor-agnostic therapies will play an important role in a new era of personalized healthcare, **challenging existing diagnostic and value assessment frameworks**
4. This pioneer project with opportunities for **multi-stakeholder collaboration**—identifies ways in which industry, policymakers, regulators, payers, clinicians and patient representatives can work together to improve patient care in oncology

INNOVATION BEYOND IMAGINATION