FUTURE BEGINS NOW

Phase 1 Meeting

Nuevas terapias en desarrollo precoz frente al cáncer

# Breakthrough in phase I: indications through early phase I/II clinical trials

Cinta Hierro Carbó, MD MSc PhD

*Institut Català d'Oncologia (ICO)-Badalona, Barcelona*

# OUTLINE

1. Accelerated approvals hit the target in precision oncology
2. Implementation of Precision Medicine: finding a needle in a haystack
3. Learning from the outliers
4. Messages to take home

# 1. Accelerated approvals hit the target in precision oncology

Cytotoxic drugs have evolved into drugs with more precise targeting effects. Over the past three decades, the FDA has granted more than 120 approvals for novel solid tumors therapeutic drugs and in multiple indications

**Target identification (molecular pre-screening)** and **drug design (early drug development)** have been the core drivers throughout antitumor history, and they have profoundly changed the natural history of tumors with dismal prognosis

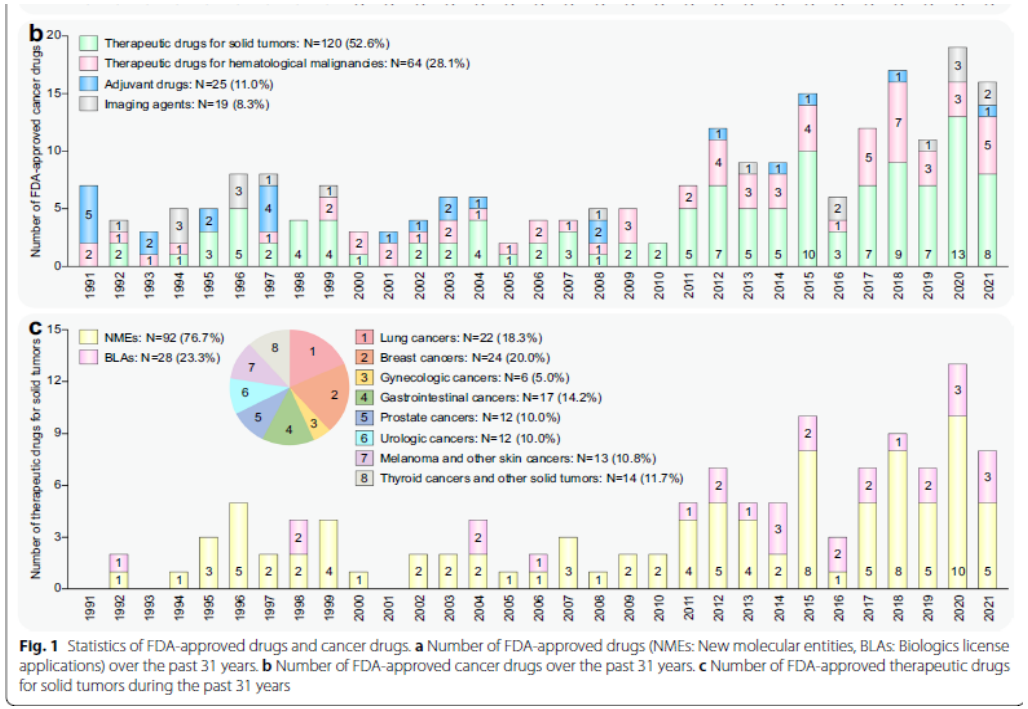
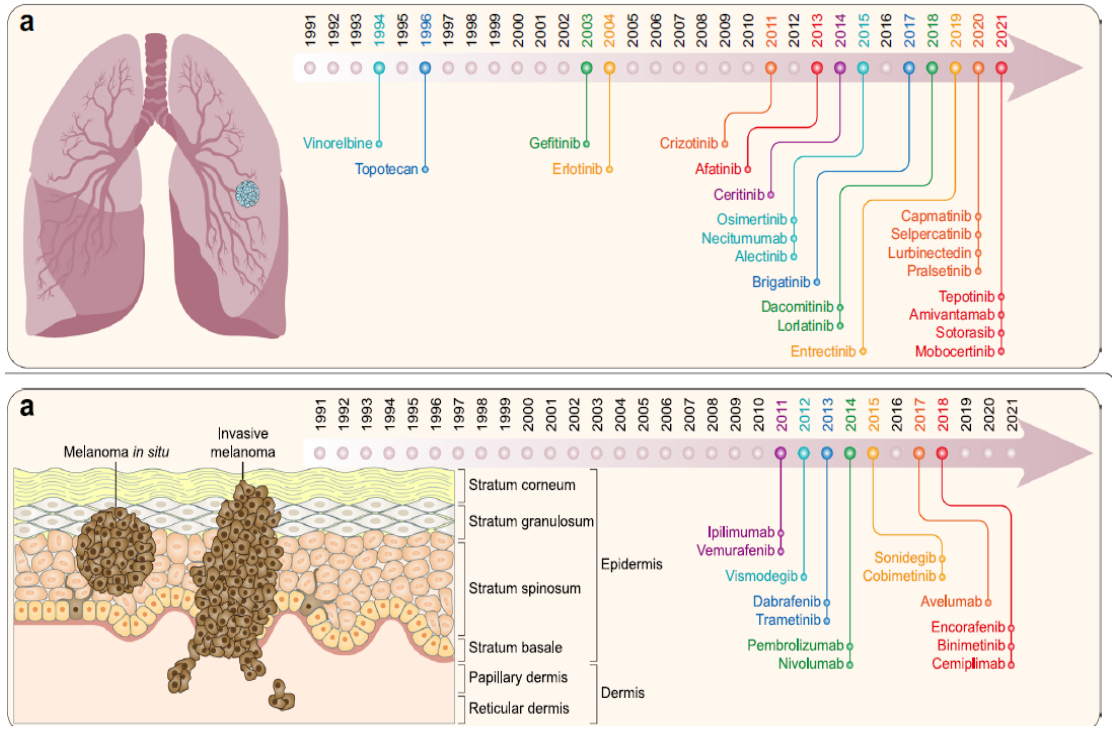



**Fig. 1** Statistics of FDA-approved drugs and cancer drugs. **a** Number of FDA-approved drugs (NMEs: New molecular entities, BLAs: Biologics license applications) over the past 31 years. **b** Number of FDA-approved cancer drugs over the past 31 years. **c** Number of FDA-approved therapeutic drugs for solid tumors during the past 31 years




Wu Q.et al_*JHematolOncol* 2022 Oct 8;15(1):143

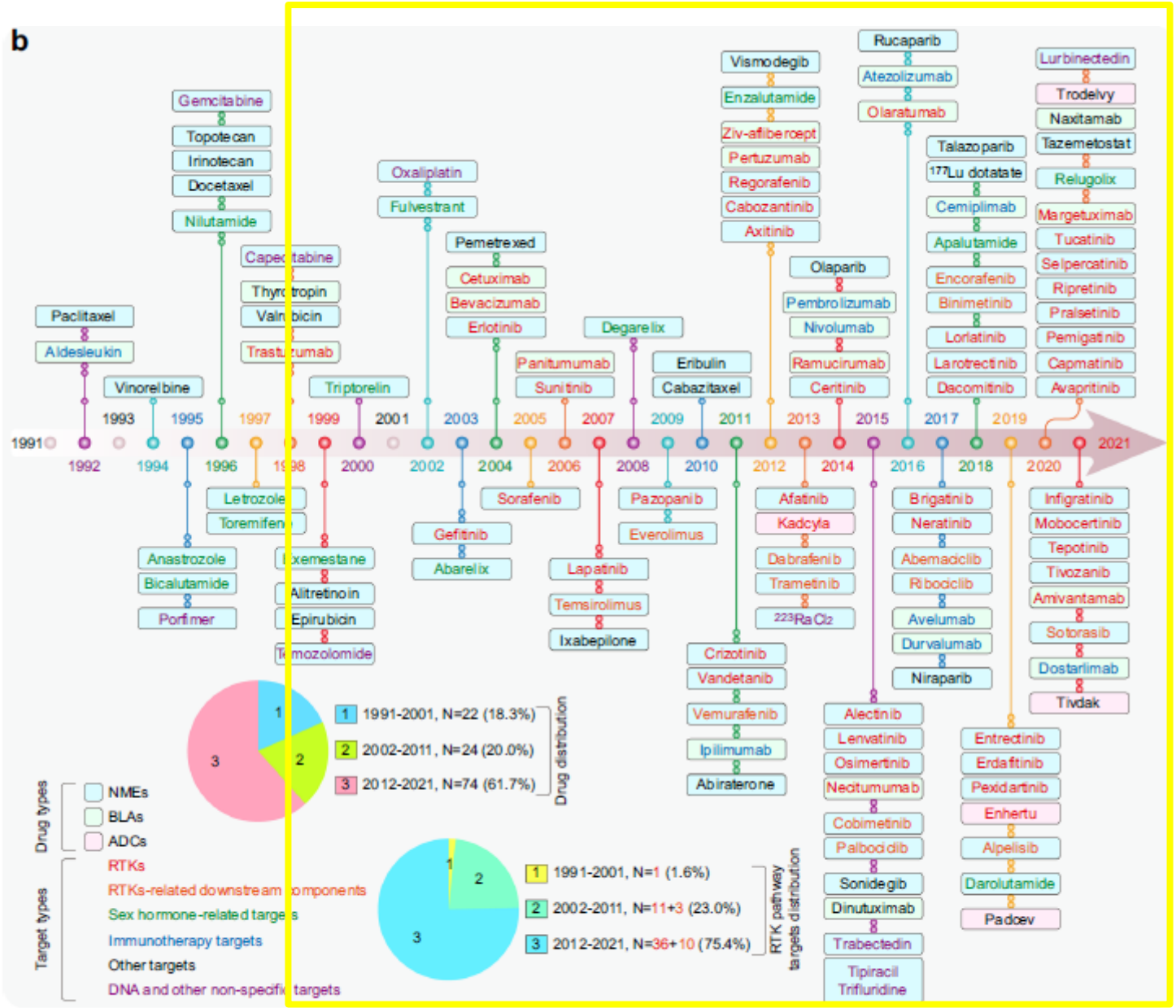
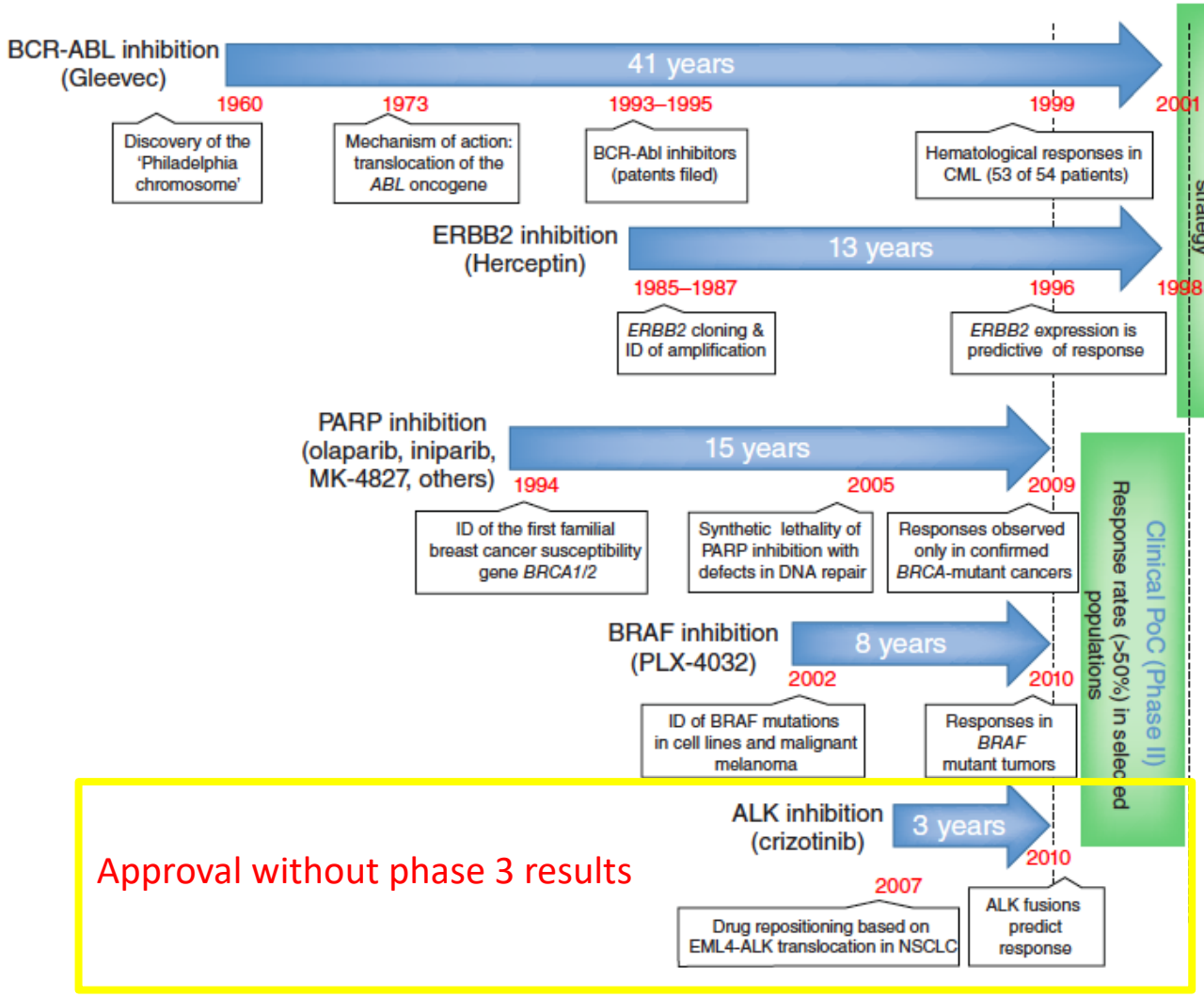



**Fig. 11** Distribution of therapeutic drugs according to targets and approval years. **a** Distribution of therapeutic drugs according to targets. **b** Distribution of therapeutic drugs according to approval years

1998 FDA-approval of **TRASTUZUMAB**:
*a star is born*

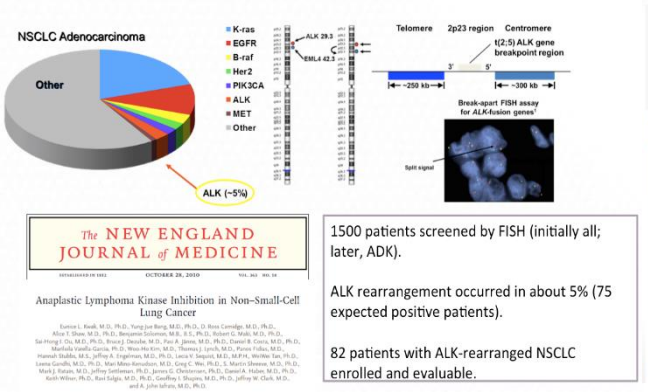
Wu Q.et al_*JHematolOncol* 2022 Oct 8;15(1):143

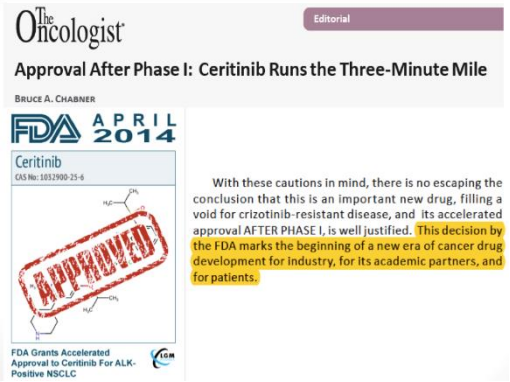



## When Harry met Sally:

FDA approval of imatinib mesylate for CML after 40 years of development, was crucial for fostering the development of MTA in molecularly-selected patient populations

Well designed phase I/II trials might provide strong scientific evidence to support drug approvals

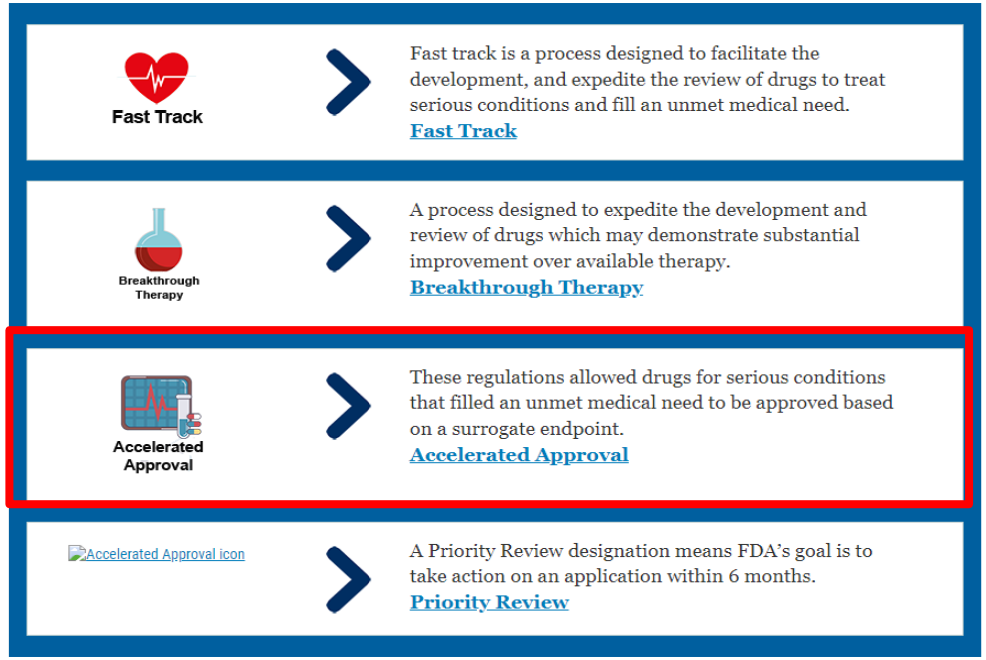



Chin L.et al_*Nature* 2011 Mar;17(3):297-303
Shaw AT. et al_*NEnglJMed* 2014 Mar 27;370(13):1189-97
Chabner BA_*Oncologist* 2017 Jul;22(7):757-758

## → Learning from the Accelerated Approval model

- The FDA's accelerated approval pathway is most frequently used for oncology indications
- Initially developed in 1992 to address the HIV and AIDS crisis
- This pathway expedites access to **drugs that have an effect on clinical endpoints measured earlier than survival** (e.g. ORR), and relies on post-approval studies to verify clinical benefit
- **Rare patient populations and high response rates** in this setting frequently limit the ability to perform randomized clinical trials and compare overall survival, considered the gold standard endpoint in oncology clinical trials




Since 1992, there have been **42 accelerated approvals** in precision oncology for solid tumors

**86% of these approvals were based on ORR**, and so far, none of the indications have been withdrawn

The early clinical benefit predicted has been **verified for 22 indications**, based on confirmatory studies (52%; 3.1 years before)

Subbiah V_*NatMed* 2022 Oct;28(10):1976-1979
fda.gov

**Table 1 | Accelerated approvals for solid tumor indications in precision oncology**

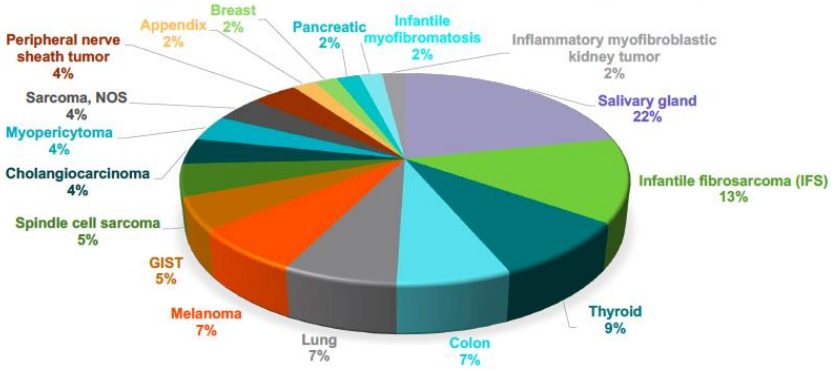
| Drug name | Accelerated approval date | Traditional approval date | Indication |
|---|---|---|---|
| Imatinib mesylate (Gleevec, Novartis) | 02/01/02 | 09/26/08 | KIT (CD117)-positive unresectable and/or metastatic GIST |
| Cetuximab (Erbitux, Imclone) | 02/12/04 | 07/06/12 | In combination with irinotecan for EGFR-expressing metastatic colorectal carcinoma refractory to irinotecan-based chemotherapy |
| Cetuximab (Erbitux, Imclone) | 02/12/04 | 10/02/07 | As a single agent for EGFR-expressing metastatic colorectal carcinoma intolerant to irinotecan-based chemotherapy |
| Panitumumab (Vectibix, Amgen) | 09/27/06 | 05/23/14 | EGFR-expressing metastatic colorectal carcinoma with progression on or after fluoropyrimidine-, oxaliplatin- and irinotecan-containing chemotherapy regimens |
| Imatinib mesylate (Gleevec, Novartis) | 12/19/08 | 01/31/12 | Adjuvant treatment of adults after complete gross resection of KIT (CD117)-positive GIST |
| Lapatinib ditosylate (Tykerb, Novartis) | 01/29/10 | 12/06/18 | In combination with letrozole for post-menopausal women with hormone receptor-positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated |
| Everolimus (Afinitor, Novartis) | 10/29/10 | 01/29/16 | Patients with subependymal giant cell astrocytoma associated with tuberous sclerosis who require therapeutic intervention but are not candidates for curative surgical resection |
| Crizotinib (Xalkori, PF Prism C.V.) | 08/26/11 | 11/20/13 | Locally advanced or metastatic NSCLC that is ALK-positive as detected by an FDA-approved test |
| Everolimus (Afinitor, Novartis) | 04/26/12 | 2/18/16 | Adults with renal angiomyolipma and tuberous sclerosis complex not requiring immediate surgery |
| Pertuzumab (Perjeta, Genentech) | 09/30/13 | 12/20/17 | In combination with trastuzumab and docetaxel for neoadjuvant treatment of HER2-positive locally advanced inflammatory or early-stage breast cancer (either greater than 2 cm in diameter or node-positive) as part of a complete treatment regimen for early early breast cancer |
| Trametinib (Mekinist, Novartis) | 01/08/14 | 11/20/15 | In combination with dabrafenib for unresectable or metastatic melanoma with *BRAF* V600E or V600K mutations, as detected by an FDA-approved test |
| Dabrafenib (Tafinlar, Novartis) | 01/09/14 | 11/20/15 | In combination with trametinib for unresectable or metastatic melanoma with *BRAF* V600E or V600K mutations, as detected by an FDA-approved test |
| Ceritinib (Zykadia, Novartis) | 04/29/14 | 05/26/17 | ALK-positive metastatic NSCLC that progressed on or is intolerant to crizotinib |
| Olaparib (Lynparza, AstraZeneca)[a] | 12/19/14 | 08/17/17 | Deleterious or suspected deleterious germline *BRCA*-mutated advanced ovarian cancer after treatment with three or more lines of chemotherapy |
| Osimertinib mesylate (Tagrisso, AstraZeneca) | 11/13/15 | 03/30/17 | Metastatic *EGFR* T790M mutation-positive NSCLC, as detected by an FDA-approved test, that progressed on or after EGFR TKI therapy |
| Alectinib hydrochloride (Alecensa, Hoffman-La Roche) | 12/11/15 | 11/06/17 | ALK-positive metastatic NSCLC that progressed on or is intolerant to crizotinib |
| Rucaparib camsylate (Rubraca, Clovis Oncology)[a] | 12/19/16 | 04/06/18 | Deleterious *BRCA* mutation (germline and/or somatic) associated advanced ovarian cancer treated with two or more chemotherapies |
| Brigatinib (Alunbrig, Takeda) | 04/28/17 | 05/22/20 | Patients with ALK-positive metastatic NSCLC that have progressed or are intolerant to crizotinib |
| Lorlatinib (Lorbrena, Pfizer) | 11/02/18 | 03/03/21 | ALK-positive metastatic NSCLC that has progressed on: Crizotinib and at least one other ALK inhibitor for metastatic disease; or Alectinib as the first ALK inhibitor therapy for metastatic disease; or Ceritinib as the first ALK inhibitor therapy for metastatic disease |
| Larotrectinib sulfate (Vitrakvi, Bayer Healthcare) | 11/26/18 | N/A | Adult and pediatric patients with solid tumors that have a *NTRK* gene fusion without a known acquired resistance mutation; are metastatic or where surgical resection is likely to result in severe morbidity; and have no satisfactory alternative treatments or that have progressed following treatment |
| Erdafitinib (Balversa, Janssen Biotech) | 04/12/19 | N/A | Locally advanced or metastatic urothelial carcinoma, that has: susceptible *FGFR3* or *FGFR2* genetic alterations, and progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for BALVERSA. |
| Entrectinib (Rozlytrek, Genentech) | 8/15/19 | N/A | Adult and pediatric patients 12 years of age and older with solid tumors that have a *NTRK* gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed after treatment or have no satisfactory alternative therapy. |

**Table 1 (continued) | Accelerated approvals for solid tumor indications in precision oncology**

| Drug name | Accelerated approval date | Traditional approval date | Indication |
|---|---|---|---|
| Fam-trastuzumab deruxtecan-nxki (Enhertu, Daiichi Sankyo) | 12/20/19 | 05/04/22 | Unresectable or metastatic HER2-positive breast cancer who have received two or more previous anti-HER2-based regimens in the metastatic setting |
| Pemigatinib (Pemazyre, Incyte) | 04/17/20 | N/A | Previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangement as detected by an FDA-approved test. |
| Capmatinib hydrochloride (Tabrecta, Novartis) | 05/06/20 | 08/10/2022 | Metastatic NSCLC whose tumors have a mutation that leads to *MET* exon 14 skipping as detected by an FDA-approved test |
| Selpercatinib (Retevmo, Loxo Oncology) | 05/08/20 | 09/21/2022 | Metastatic *RET* fusion-positive NSCLC |
| Selpercatinib (Retevmo, Loxo Oncology) | 05/08/20 | N/A | Adult and pediatric patients 12 years of age and older with advanced or metastatic *RET*-mutant MTC who require systemic therapy |
| Selpercatinib (Retevmo, Loxo Oncology) | 05/08/20 | N/A | Adult and pediatric patients 12 years of age and older with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate). |
| Rucaparib camsylate (Rubraca, Clovis Oncology) | 05/15/20 | N/A | Adult patients with a deleterious *BRCA* mutation (germline and/or somatic)-associated mCRPC who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy |
| Pralsetinib (Gavreto, Blueprint Medicines) | 09/04/20 | N/A | Metastatic *RET* fusion-positive NSCLC as detected by an FDA approved test. |
| Naxitimab-GQGK (Danyelza, Y-mAbs Therapeutics) | 11/25/20 | N/A | In combination with GM-CSF, for the treatment of pediatric patients 1 year of age and older and adult patients with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who have demonstrated a partial response, minor response, or stable disease to prior therapy. |
| Pralsetinib (Gavreto, Blueprint Medicines) | 12/01/20 | N/A | Adult and pediatric patients 12 years of age and older with advanced or metastatic *RET*-mutant MTC who require systemic therapy. |
| Pralsetinib (Gavreto, Blueprint Medicines) | 12/01/20 | N/A | Adult and pediatric patients 12 years of age and older with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate) |
| Tepotinib hydrochloride (Tepmetko, EMD Serono) | 02/03/21 | N/A | Metastatic NSCLC containing *MET* exon 14 skipping alterations. |
| Amivantamab-vmjw (Rybrevant, Janssen Biotech) | 05/21/21 | N/A | Locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion mutations, as detected by an FDA approved test, whose disease has progressed on or after platinum-based chemotherapy. |
| Infigratinib phosphate (Truseltiq, Helsinn Healthcare) | 05/28/21 | N/A | Previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with *FGFR2* gene fusions or other rearrangement as detected by an FDA approved test |
| Sotorasib, (Lumakras, Amgen) | 05/28/21 | N/A | *KRAS* G12C-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least one previous systemic therapy. |
| Mobocertinib succinate (Exkivity, Takeda) | 09/15/21 | N/A | Locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy |
| Dabrafenib (Tafinlar, Novartis) | 06/22/22 | N/A | In combination with trametinib for adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with *BRAF* V600E mutation who have progressed after previous treatment and have no satisfactory alternative treatment options |
| Trametinib (Mekinist, Novartis) | 06/22/22 | N/A | In combination with dabrafenib for adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with *BRAF* V600E mutation who have progressed after previous treatment and have no satisfactory alternative treatment options |
| Fam-trastuzumab deruxtecan-nxki (Enhertu, Daiichi Sankyo) | 08/11/2022 | N/A | Adult patients with unresectable or metastatic NSCLC whose tumors have an activating *HER2* (*ERBB2*) mutation, as detected by an FDA-approved test, and who have received a previous systemic therapy |
| Selpercatinib (Retevmo, Loxo Oncology) | 09/21/2022 | N/A | Adult patients with locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options |

Subbiah V_*NatMed* 2022 Oct;28(10):1976-1979

## Diversity of cancers treated - 17 unique types




**Adult phase I**
- Age ≥18 years
- Advanced solid tumors

n=8

**SCOUT: pediatric phase I/II**
- Age ≤21 years
- Advanced solid tumors

n=12

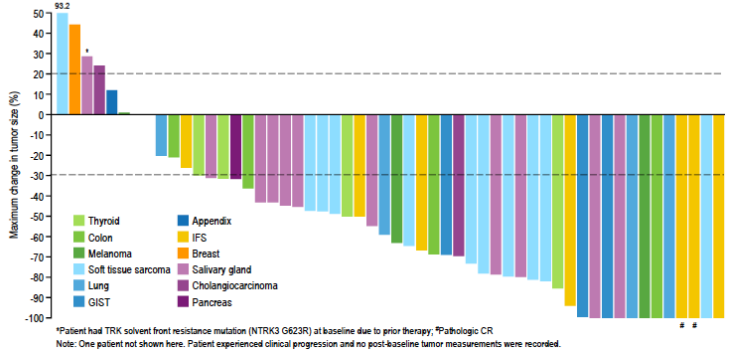
**NAVIGATE: adult/adolescent phase II 'basket' trial**
- Age ≥12 years
- Advanced solid tumors
- TRK fusion positive

n=35

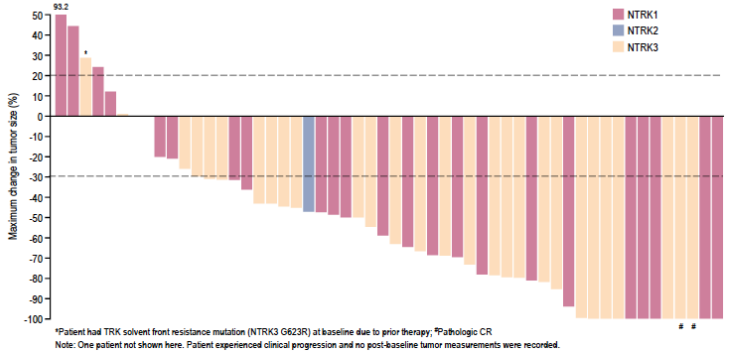
**N=55 TRK fusion patients**

**Data cut-off:** April 14, 2017

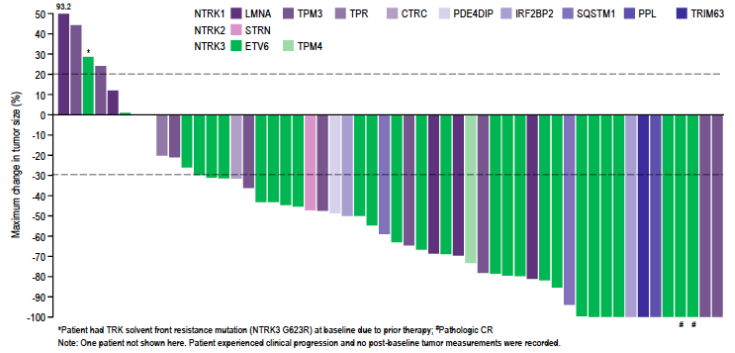
## Efficacy regardless of tumor type




## Efficacy regardless of NTRK gene




## Efficacy regardless of fusion partner




Hong DS_*LancetOncol* 2020 Apr;21(4):531-540

**2018 FDA agnostic-histology approval of larotrectinib** was solely based on 55 patients with NTRKtrans enrolled in adult and paediatric phase I/II trials (global ORR 75% across 12 different histologies)

**Table 4** **Efficacy Results for Patients with Solid Tumors Harboring *NTRK* Gene Fusions**

| Efficacy Parameter | VITRAKVI N = 55 |
|---|---|
| **Overall response rate** (95% CI) | 75% (61%, 85%) |
| Complete response rate | 22% |
| Partial response rate* | 53% |
| **Duration of response**** | **N = 41** |
| Range (months) | 1.6+, 33.2+ |
| % with duration ≥ 6 months | 73% |
| % with duration ≥ 9 months*** | 63% |
| % with duration ≥ 12 months**** | 39% |

**Table 5** **Efficacy Results by Tumor Type**

| Tumor Type | Patients (N=55) | ORR | | DOR |
|---|---|---|---|---|
| | | % | 95% CI | Range (months) |
| Soft tissue sarcoma | 11 | 91% | (59%, 100%) | 3.6, 33.2+ |
| Salivary gland | 12 | 83% | (52%, 98%) | 7.7, 27.9+ |
| Infantile fibrosarcoma | 7 | 100% | (59%, 100%) | 1.4+, 10.2+ |
| Thyroid | 5 | 100% | (48%, 100%) | 3.7, 27.0+ |
| Lung | 4 | 75% | (19%, 99%) | 8.2, 20.3+ |
| Melanoma | 4 | 50% | NA | 1.9, 17.5+* |
| Colon | 4 | 25% | NA | 5.6* |
| Gastrointestinal stromal tumor | 3 | 100% | (29%, 100%) | 9.5, 17.3 |
| Cholangiocarcinoma | 2 | SD, NE | NA | NA |
| Appendix | 1 | SD | NA | NA |
| Breast | 1 | PD | NA | NA |
| Pancreas | 1 | SD | NA | NA |

View full prescribing information for VITRAKVI (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211710s000lbl.pdf).

This indication is approved under accelerated approval and continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. FDA granted this application priority review, breakthrough therapy designation and orphan product designation. A description of FDA expedited programs is in the Guidance for Industry: Expedited Programs for Serious Conditions-Drugs and Biologics. (/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics)

- With accelerated approvals there is renewed **hope for patients with high mortality rates** (e.g. metastatic NSCLC harboring EGFRmut or ALK/ROS1 fusions) and **difficult-to-find cancers** (e.g. advanced thyroid cancers with RETmut or fusions)

- But **many challenges** need to be addressed considering that matching the right therapy to the right patient remains paramount

Accelerated approvals:
THE TIP OF THE ICEBERG

## CHALLENGES

1) As biomarkers becomes more specific, the intended populations become rarer → **subsequent confirmatory randomized trials can become difficult to conduct**

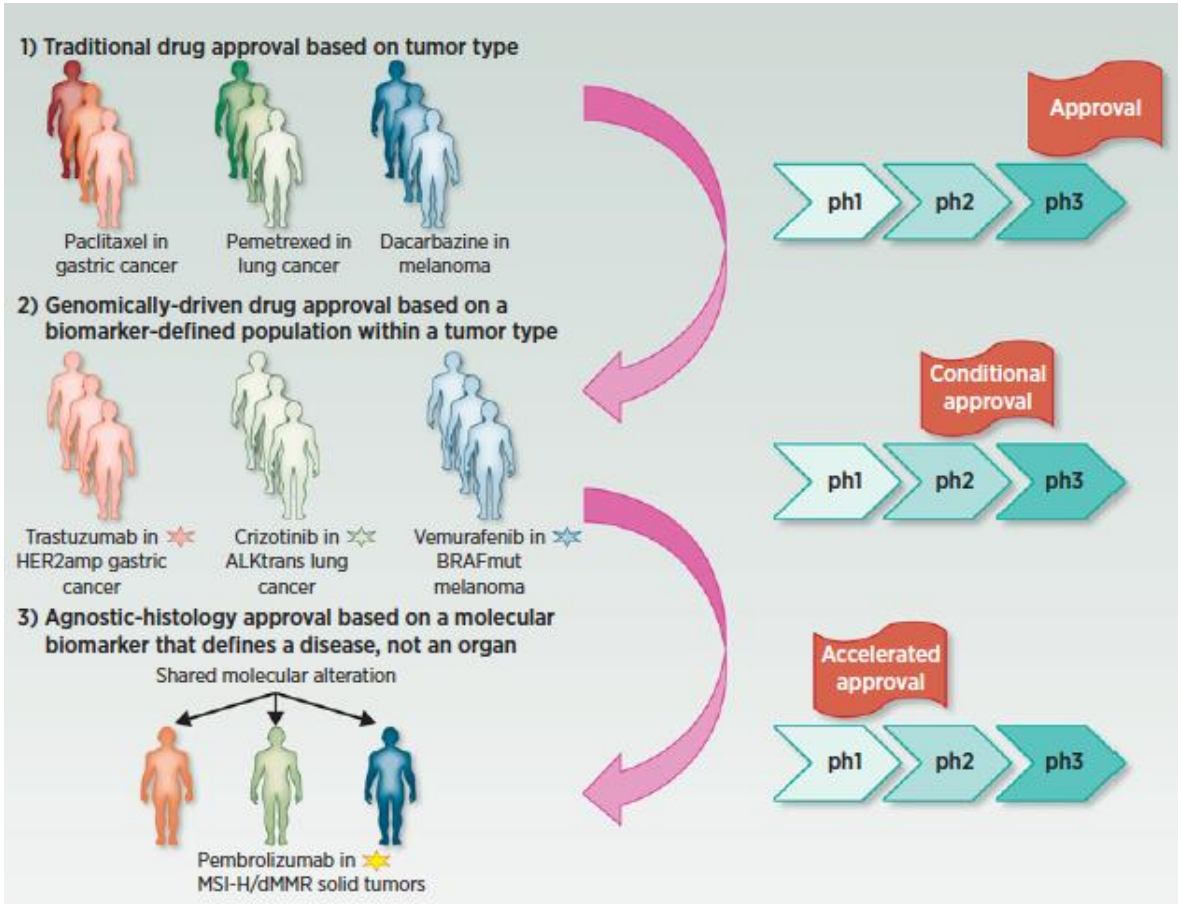
2) Reliance on early clinical endpoints such as ORR creates an uncertainty that clinical benefit may or not may be verified → **this uncertainty must be balanced against the benefit of granting the eaarly access**, as these subsets of patients have limited options

3) Challenges in evaluating the risks of precision therapies, as OS from randomized trials is not only an important efficacy endpoint, but also a key safety measure → **small patient populations further limit the amount of safety data available for new drugs**

4) Use of drugs in biomarker-selected populations may require the development of a validated test to identify this population → **evaluation of these companion diagnostics adds complexity to expedited approval and should be addressed early in the clinical development**

Subbiah V_*NatMed* 2022 Oct;28(10):1976-1979

## Just as precision oncology aims to match the right patient to the right drug, the accelerated approval pathway seems to be the right match for precision oncology



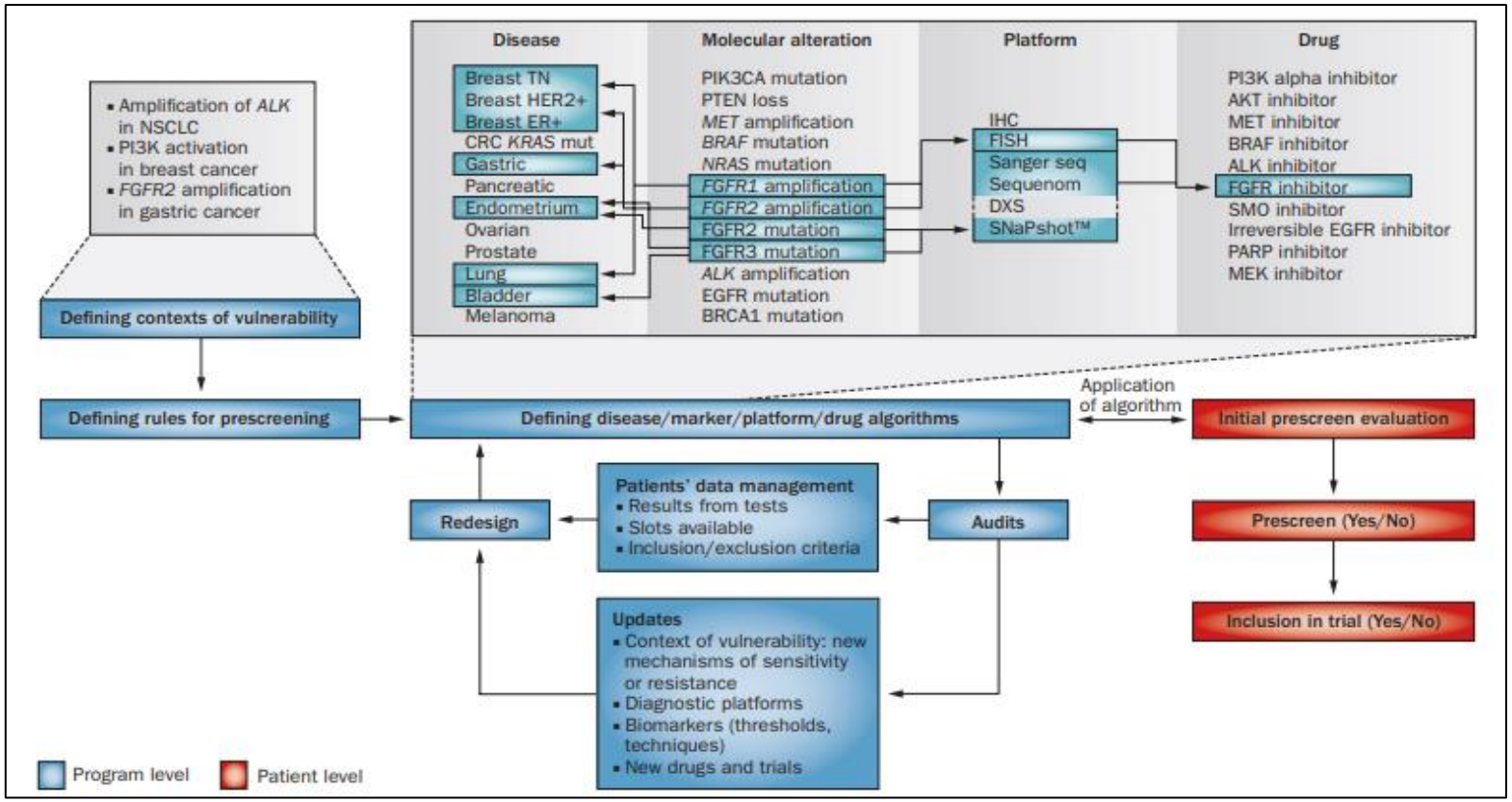

IN CONTRAST…

- **Low response rates from initial single-arm trials with immune checkpoint inhibitors** did not consistently translate to survival advantages in confirmatory trials
- **Withdrawal of some ICI**'s accelerated approvals → WHY?
- ICI differ from MTA as **the populations they treat are largely unselected**, hence randomized studies may be necessary to support marketing approval and predict clinical benefit in future studies of ICI

Beaver JA.et al_*NEnglJMed* 2022; 386, 1297-1301
Hierro C. et al_*ClinCancerRes* 2019 Jun 1; 25(11):3210-3219

# 2. Implementation of Precision Medicine: finding a needle in a haystack

**Molecular pre-screening logistics are crucial** for facilitating the identification and interpretation of molecularly-selected patient populations



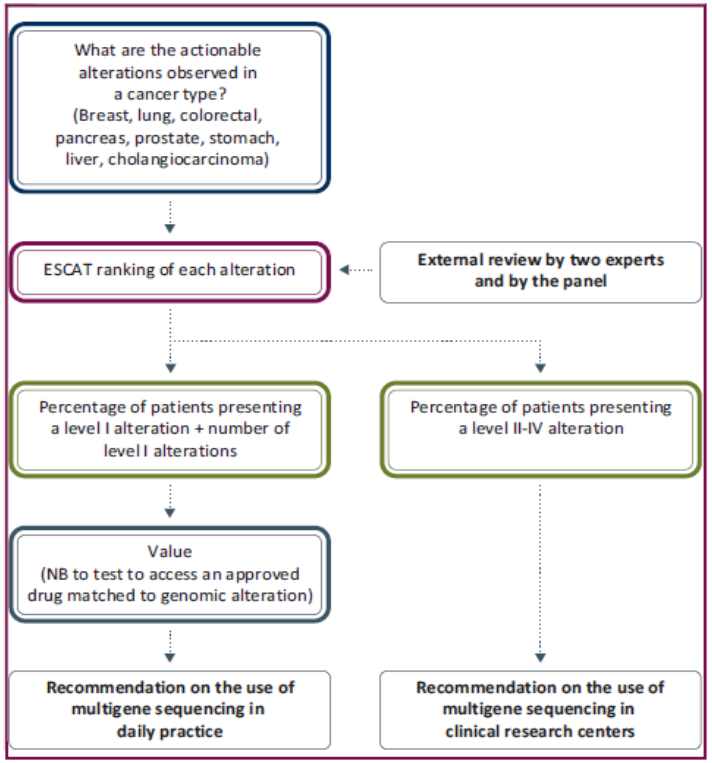




**Figure 1. Method to develop recommendation about NGS in daily practice.**
ESCAT, ESMO Scale for Clinical Actionability of molecular Targets.

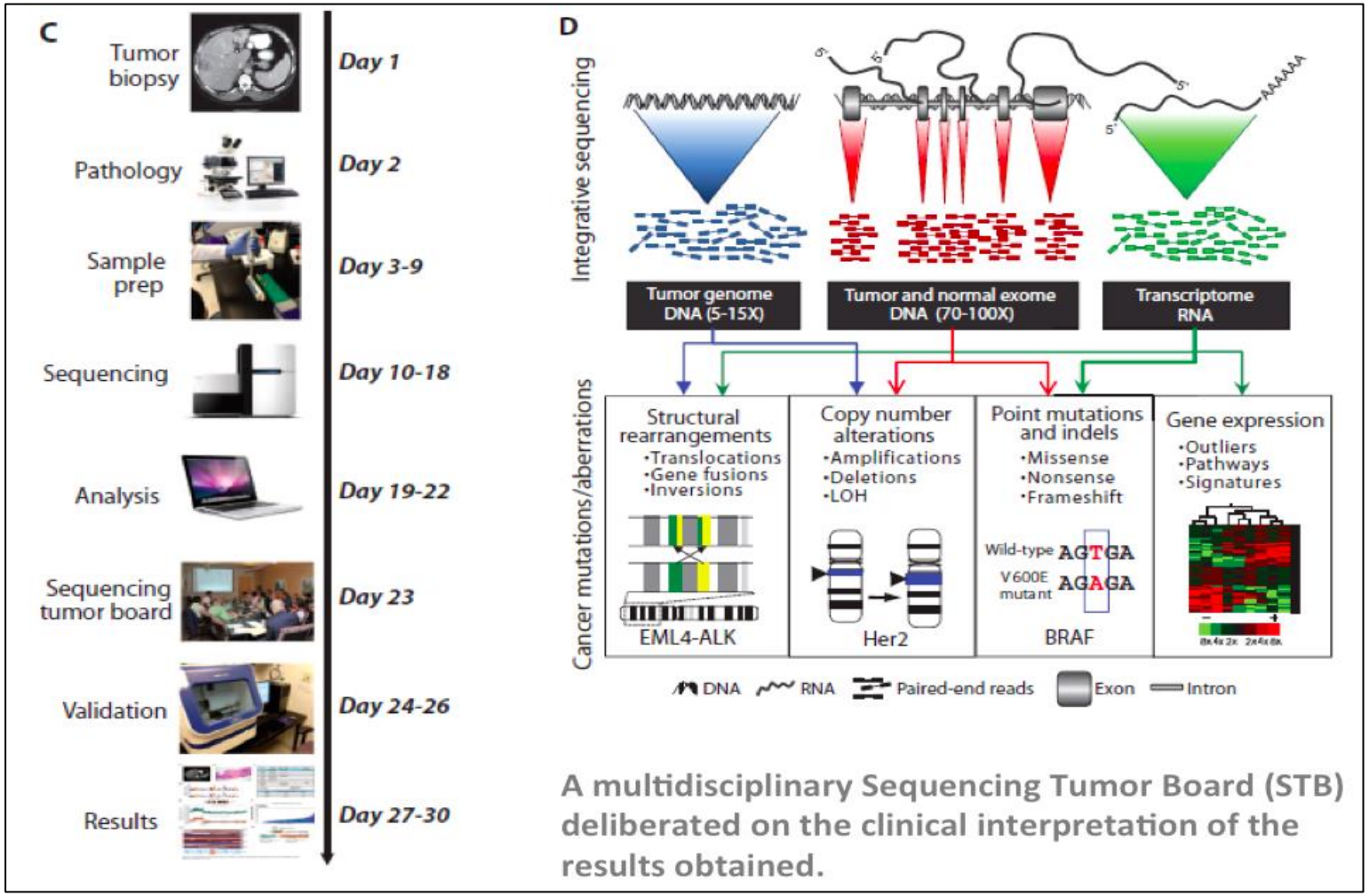
Rodon J.et al_*NatRevClinOncol* 2012 Apr 3;9(6):359-66
Mosele F.et al_*AnnOncol* 2020 Nov;31(11):1491-1505

**Table 1. European Society for Medical Oncology (ESMO) clinical actionability of molecular targets**

| | |
|---|---|
| Tier I | Alteration-drug match is associated with improved outcome in clinical trials |
| Tier II | Alteration-drug match is associated with antitumor activity, but magnitude of benefit is unknown |
| Tier III | Alteration-drug match is suspected to improve outcome based on clinical trial data in other tumor types(s) or with similar molecular alteration |
| Tier IV | Preclinical evidence of actionability |
| Tier V | Alteration-drug match is associated with objective response, but without clinically meaningful benefit |
| Tier X | Lack of evidence for actionability |

**Table 4. Databases with genomic data and where to check for relevance of alterations**

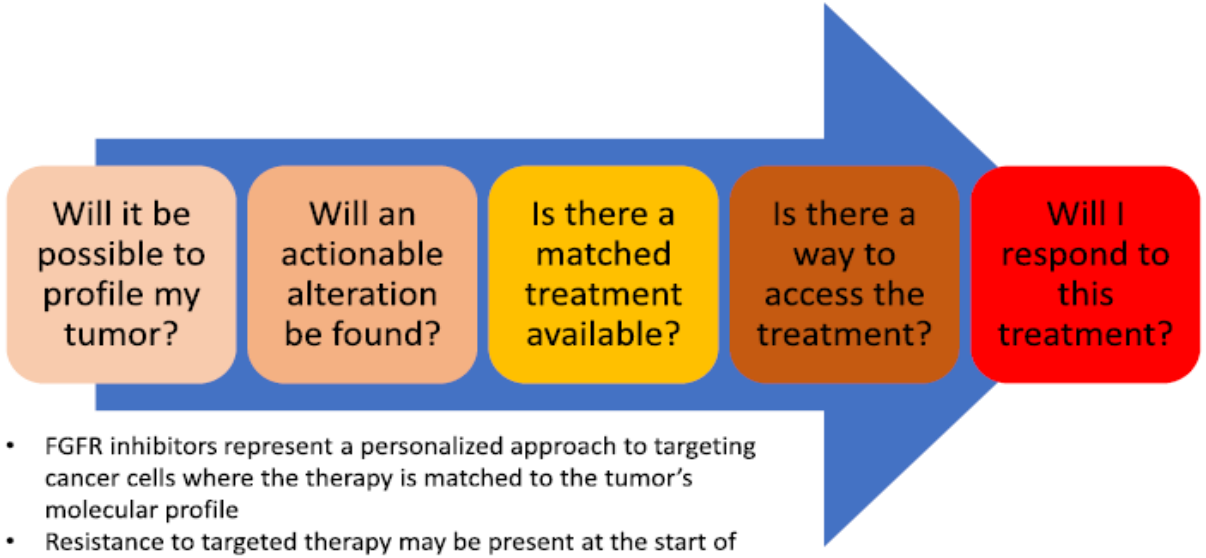
| Database | Comments |
|---|---|
| Cancer Genome Atlas (TCGA) | Large database including cancer-associated genomic alterations of >20 000 cancer patients |
| International Cancer Genome Consortium (ICGC) | Global initiative to build a large database of genomic alterations in the most common tumor types |
| OncoKB | Memorial Sloan Kettering Cancer Centre precision oncology database including link to FDA levels of evidence |
| MyCancerGenome | Large database including cancer-associated genomic alterations of almost 100 000 tumor samples |
| CIViC | Clinical interpretation of variants in cancer, open access open source, community driven |
| COSMIC | Large catalogue of somatic cancer mutations including data from >37 000 genomes |
| ClinVar | Freely accessible, public archive of reports of the relationships among human variations and phenotypes, with supporting evidence |
| Online Mendelian Inheritance in Man (OMIM) | Comprehensive, authoritative compendium of human genes and genetic phenotypes |
| VarSome | Variant knowledge community, data aggregator and variant data discovery tool |
| Breast Cancer Information Core (BIC) Database | Large *BRCA1* and *BRCA2* gene mutation database |
| *ARUP BRCA1* and *BRCA2* mutation databases | Provides information on *BRCA1* and *BRCA2* gene mutations and their impact on risk of developing breast cancer, ovarian cancer and certain other cancers. Two types of databases are provided. One is a list of mutations curated from critical review of literature and family studies. The other provides *in silico* prediction of risk to help understand variants of unknown significance |



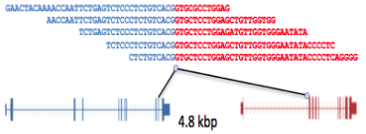

Mateo J.et al_*AnnOncol* 2018 Sep 1;29(9):1895-1902
Schmid S.et al_*ESMOopen* 2022 Oct;7(5):100570

**Multiple limitations** must be addressed **when considering targeted therapy:**

1) Availability of material
2) Accuracy and funding of the pre-screening test
3) Availability and funding of the therapy
4) Dealing with the toxicity whilst achieving efficacy
5) Managing patients' expectations

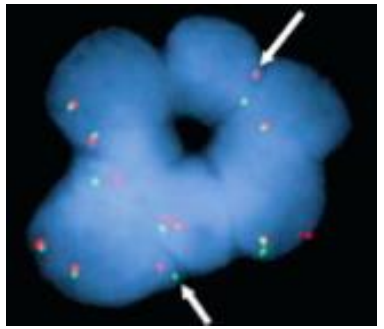



- FGFR inhibitors represent a personalized approach to targeting cancer cells where the therapy is matched to the tumor's molecular profile
- Resistance to targeted therapy may be present at the start of treatment or form over time
- All anticancer treatment approaches can have adverse effects on healthy cells related to the therapy's mechanism of action



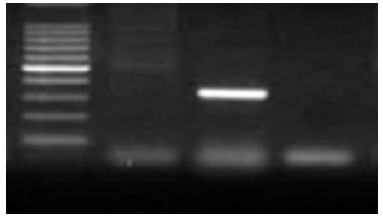

**NGS, Next-Generation Sequencing**

- Detects known and novel fusions with arbitrary breakp in DNA or RNA.



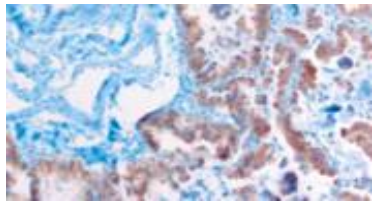
**FISH, Fluorescence In Situ Hybridization**

- Detects gene rearrangements in DNA that *may* generate a fusion transcript.



**RT-PCR, Reverse Transcription Polymerase Chain Reaction**

- Detects known fusion transcripts in RNA.
- Detects 5'/3' imbalance as a fusion signature, but can not determine novel partner.



**IHC, Immunohistochemistry**

- Detects protein expression, which *may* be attributable to a fusion event.

Goyal L.et al_*CancerTreatRev* 2021 Apr;95:102170

# Small molecules, big impact: 20 years of targeted therapy in oncology

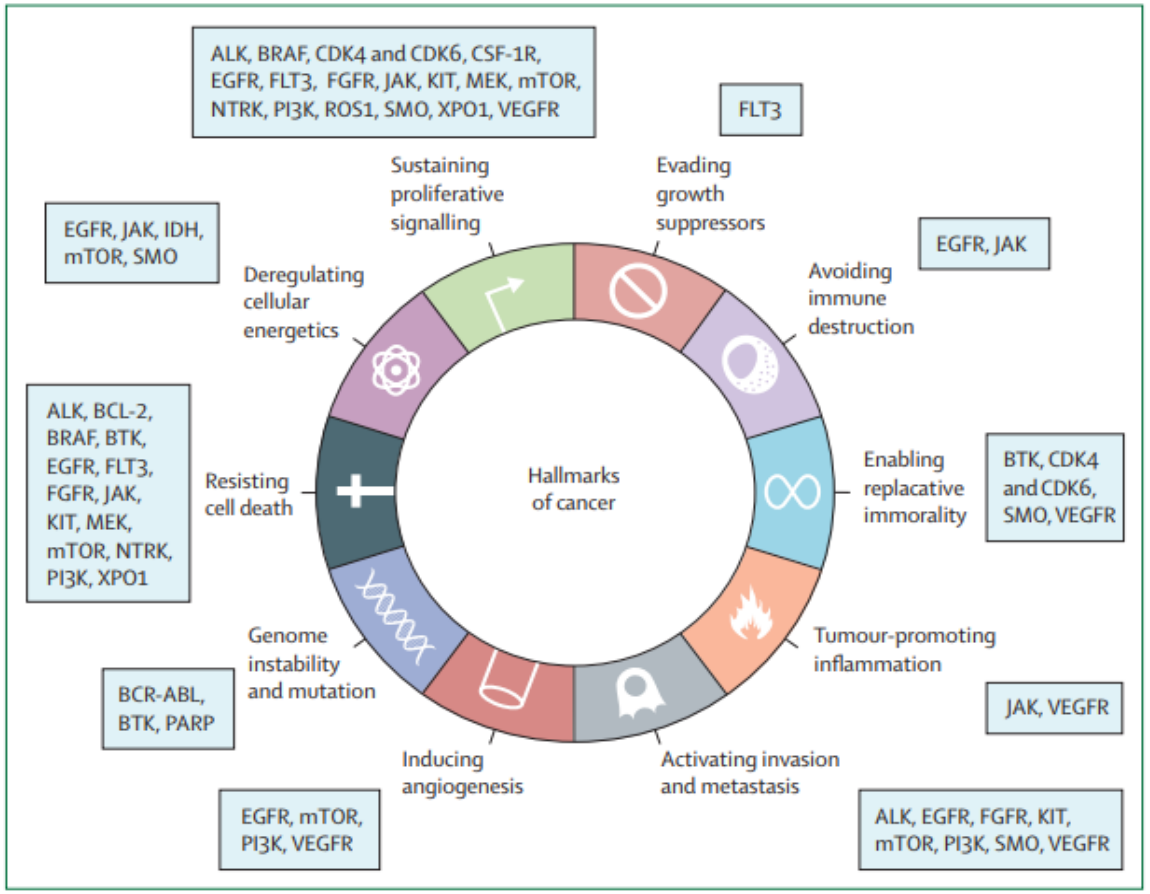


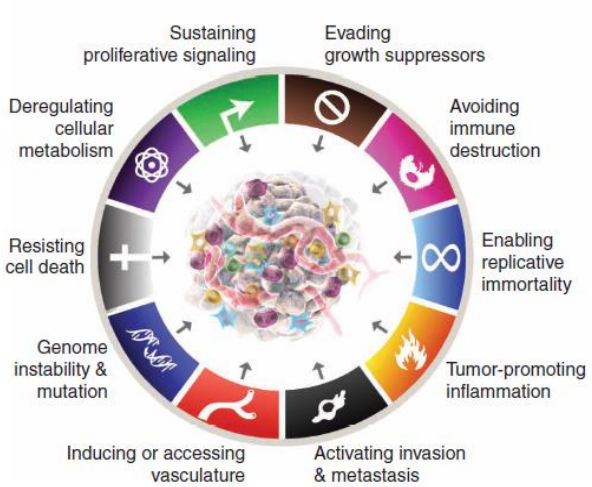

***Figure 1*: Targets of approved small molecule inhibitors**
Targets are mapped to the hallmarks of cancer[1] as annotated by the Cancer Gene Census[2] on the COSMIC website.[3] The hallmarks of cancer are currently not annotated for CSF-1R, IDH, MEK, NTRK, PARP, and SMO in the Cancer Gene Census. These annotations have been added by the authors.

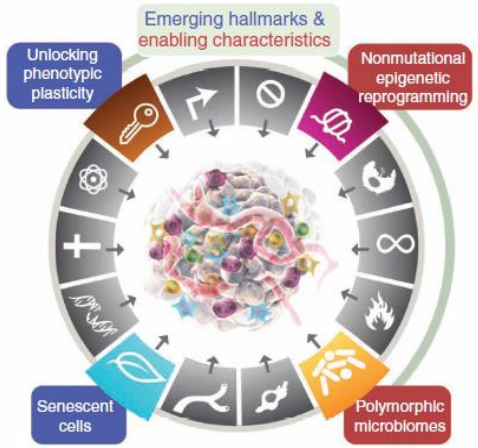
## *Panel:* Lessons learned from small molecule inhibitors in precision medicine

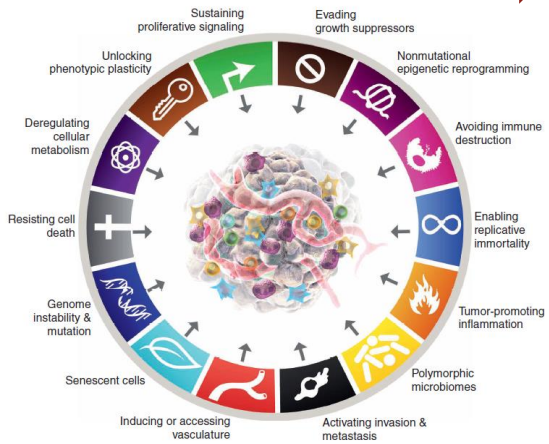
- Degree of target inhibition correlates with efficacy; strategies to increase target inhibition include:
  - More potent inhibitors (excluding targets with narrow therapeutic index)
  - Highly selective inhibitors (minimise so-called off-target toxicity)
  - Combination targeted therapy (more complete pathway inhibition)
  - Mutant selective inhibitors (broaden therapeutic index)
- Identification of tumour-specific vulnerabilities provide opportunities for synthetic lethality
- Small molecule inhibitors with fewer resistance liabilities generally achieve more durable benefit
- Penetrance into sanctuary sites (CNS)
- Early use of next-generation small molecule inhibitors is associated with better outcomes than sequential use of first and subsequent generation agents
- Abrupt treatment discontinuation of small molecule inhibitor in oncogene-addicted cancers after progression might lead to disease flare

Bedard PL.et al_*Lancet* 2020 Mar 28;395(10229):1078-1088

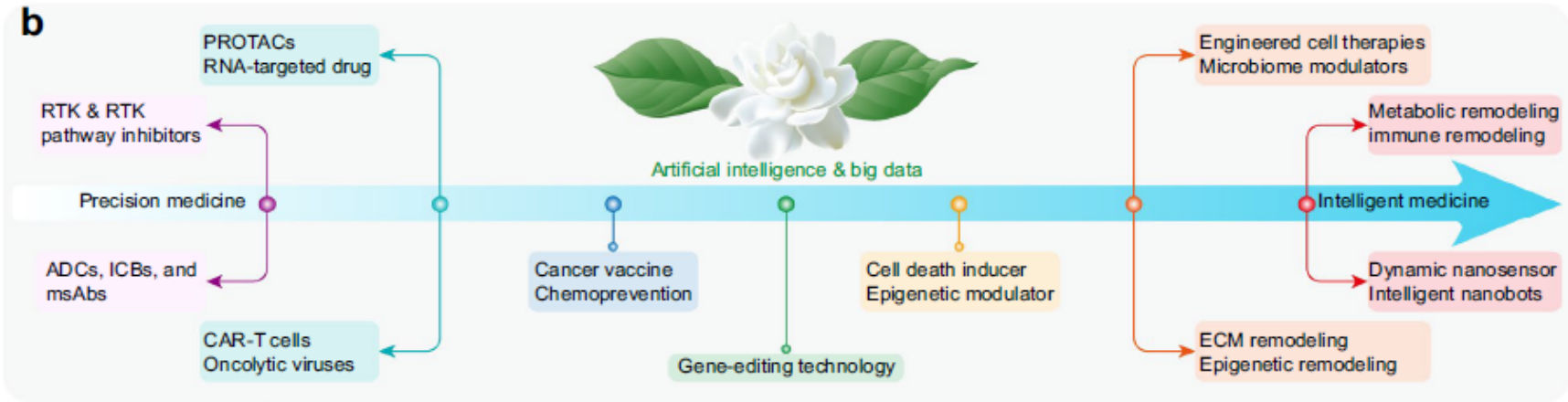
2000 **Hallmarks of Cancer: New Dimensions** 2022



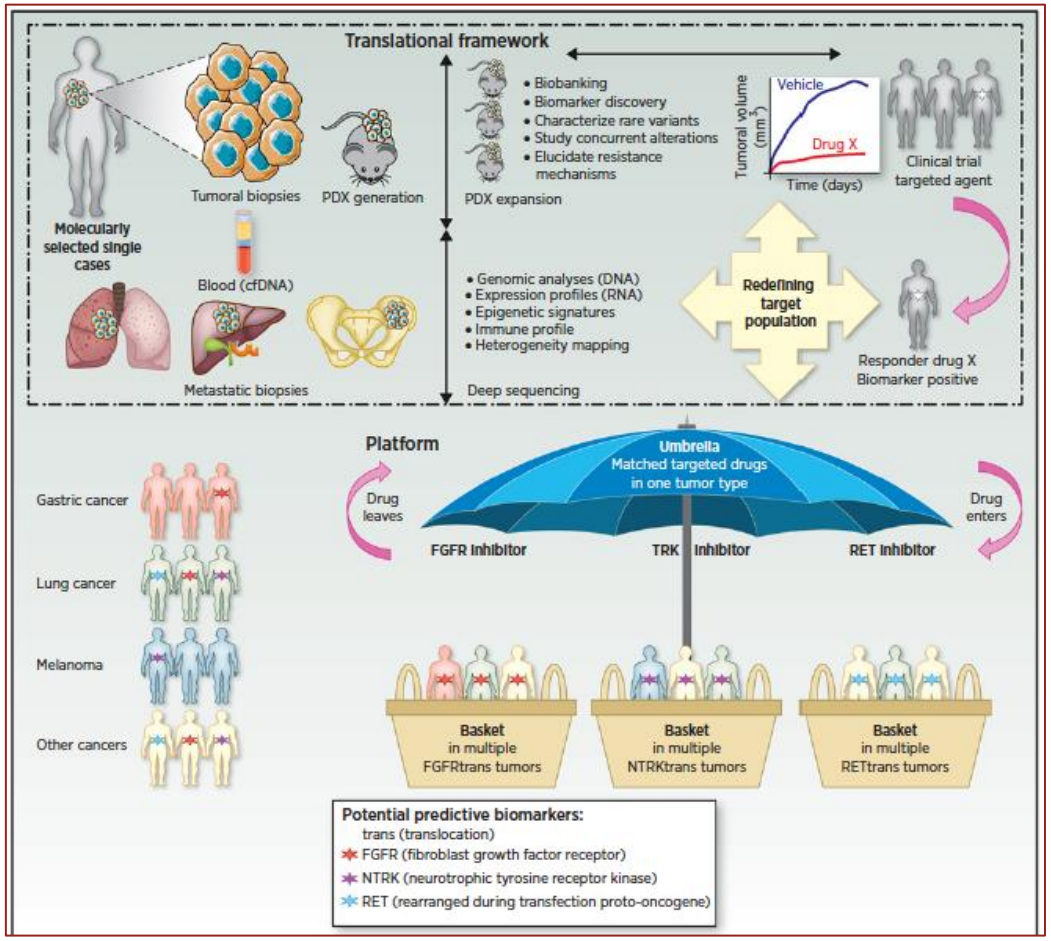

## FUTURE PERSPECTIVES



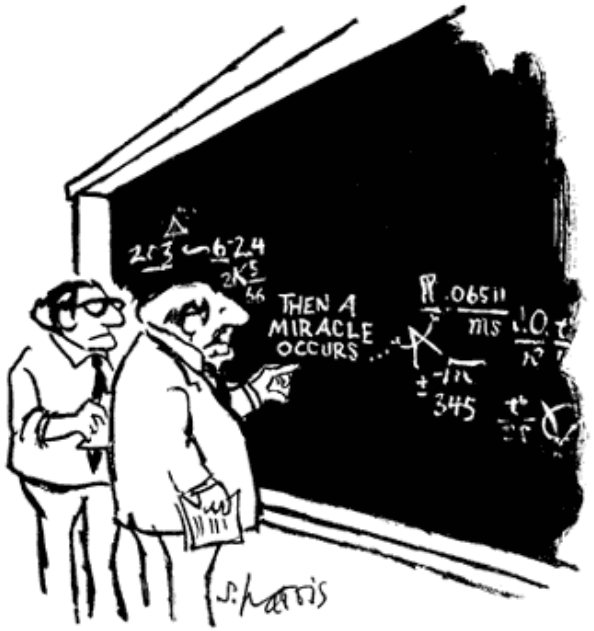

Hanahan D. *CancerDiscov* 2022 Jan;12(1):31-46
Wu Q.et al_*JHematolOncol* 2022 Oct 8;15(1):143

# 3. Learning from the outliers

Early phase I/II clinical trials have emerged as the **ideal scenario to gain more data from the exceptional responders**




**"The devil is in the details"**




"I think you should be more explicit here in step two."

Hierro C. et al_*ClinCancerRes* 2019 Jun 1; 25(11):3210-3219

Several molecular alterations are found in a wide range of cancers, and early phase I/II studies have been crucial **to define the biologic and therapeutic effect of new aberrations in multi-histology genomically selected basket trials**

**Futibatinib, an Irreversible FGFR1–4 Inhibitor, in Patients with Advanced Solid Tumors Harboring *FGF/FGFR* Aberrations: A Phase I Dose-Expansion Study**

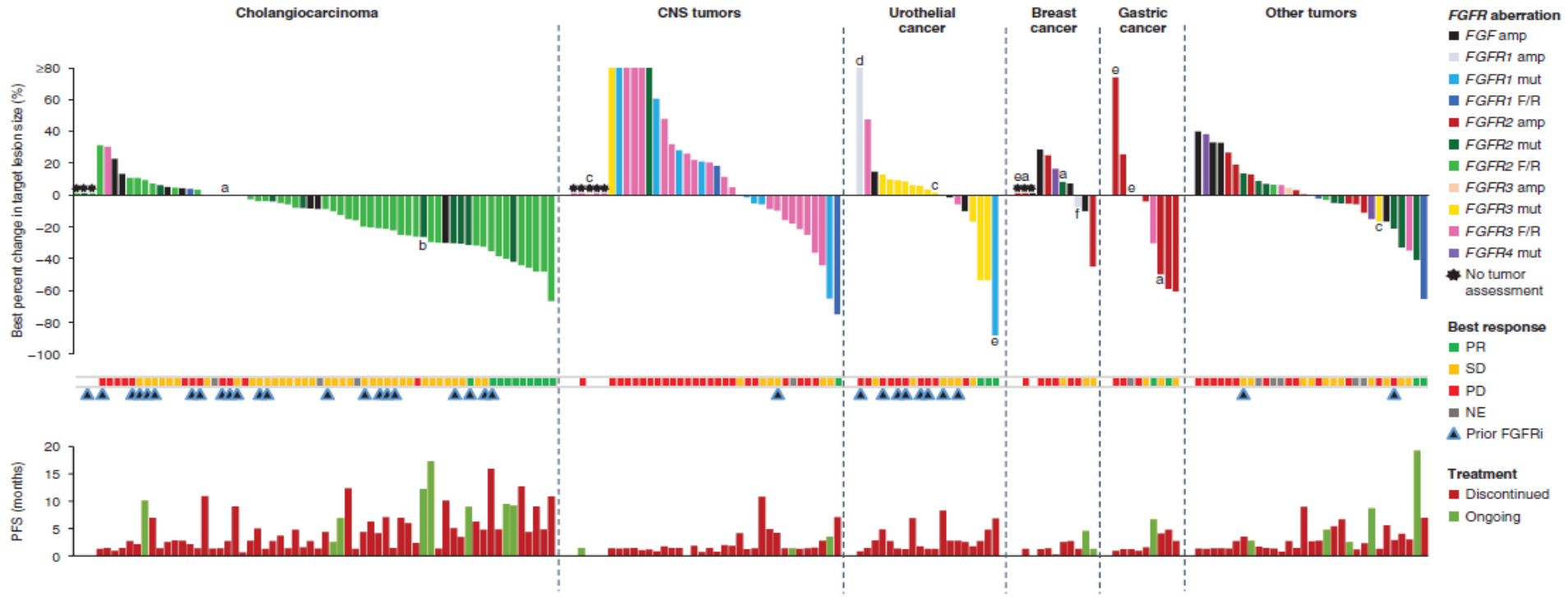



**Figure 2.** Individual response and treatment outcome by tumor type in patients who received futibatinib 20 mg once daily.

Meric-Bernstam F.et al_*CancerDiscov* 2022 Feb;12(2):402-415

Furthermore, **primary and acquired resistance mechanisms can be early described** in molecularly-selected patients enrolled in phase I/II trials and guide subsequent targeted therapies

## TAS-120 Overcomes Resistance to ATP-Competitive FGFR Inhibitors in Patients with FGFR2 Fusion–Positive Intrahepatic Cholangiocarcinoma

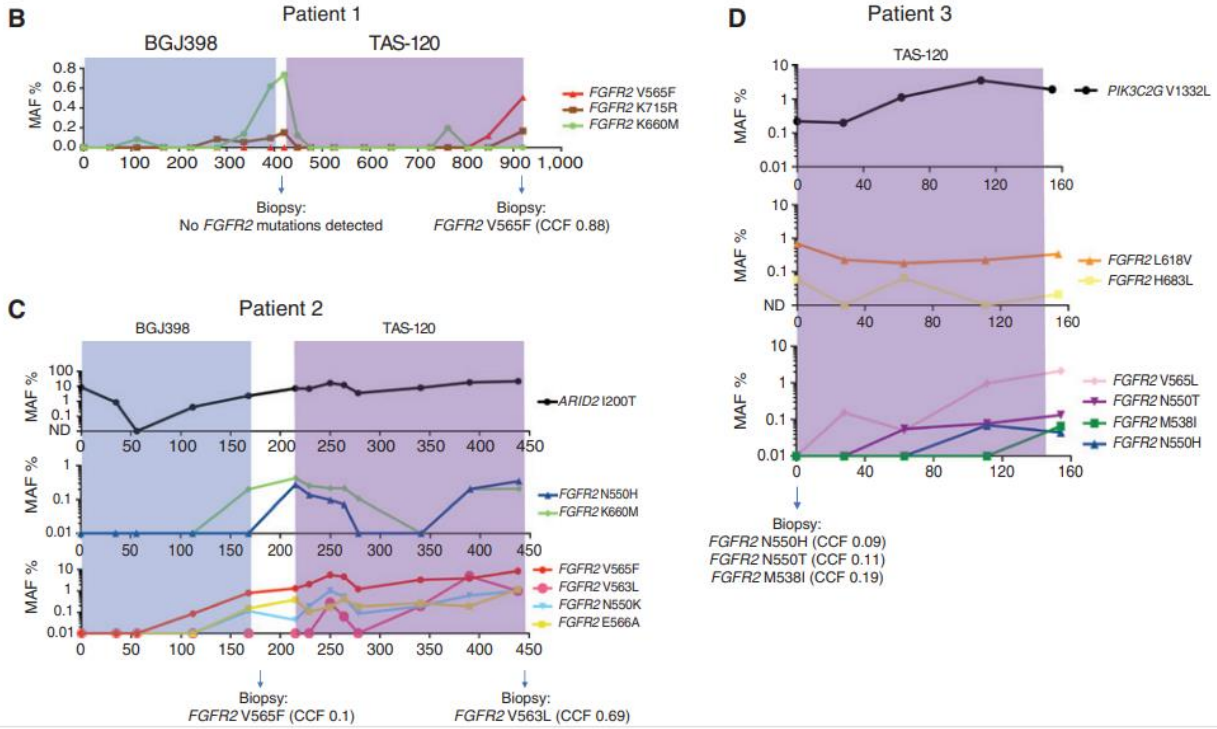



**Table 1A. Clinical data of patients with FGFR2 fusion–positive cholangiocarcinoma receiving FGFR inhibitors**

| Patient ID | FGFR2 fusion | First FGFR inhibitor | PFS (months) | BOR | Intervening therapies between 1st and 2nd FGFR inhibitor | Interval between 1st and 2nd FGFR inhibitor (months) | Second FGFR inhibitor | PFS (months) | BOR |
|---|---|---|---|---|---|---|---|---|---|
| 1 | *FGFR2-SORBS1* | BGJ398 | 12.6 | –68.2% | None | 1.2 | TAS-120 | 15.8 | –76.7% |
| 2 | *FGFR2-ZMYM4* | BGJ398 | 5.6 | –49.9% | None | 1.6 | TAS-120 | 7.2 | +8.3% |
| 3 | *FGFR2-INA* | Debio 1347 | 11.4 | –49.5% | Gemcitabine/ docetaxel, T11 palliative radiation | 3.0 | TAS-120 | 5.1 | –22.1% |
| 4 | *FGFR2-NRAP* | BGJ398 | 7.1 | –40.0% | T8 palliative radiation, pembroli-zumab, resec-tion of T8 metastasis, FOLFOX | 7.4 | TAS-120 | 17.2 | –47.7% |

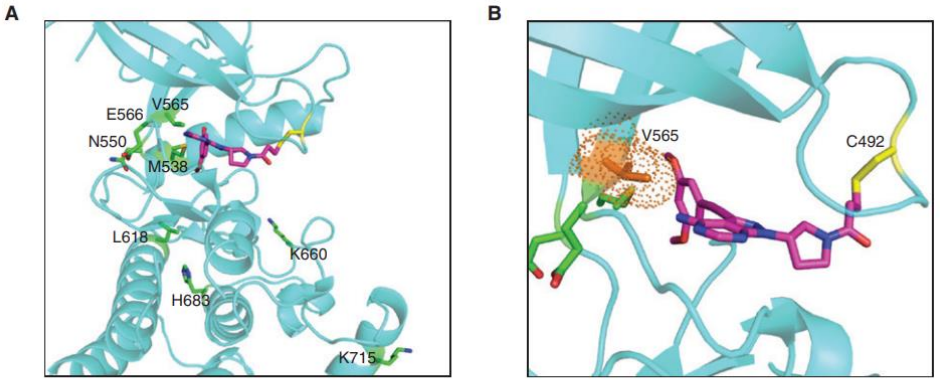



**Figure 4.** Structural modeling of secondary FGFR2 kinase domain mutations with TAS-120. **A,** Model showing TAS-120 docked into the binding pocket of WT FGFR2. Amino acid residues corresponding to mutations conferring resistance to ATP-competitive FGFR inhibitors are highlighted. Structural representations were prepared using PyMOL. **B,** A close-up view of TAS-120 in ATP-binding pocket of WT FGFR2. The gatekeeper residue (V565) is in close proximity to the dimethoxy phenyl group of TAS-120.

Goyal L.et al_*CancerDiscov* 2019 Aug;9(8):1064-1079

# 4. Messages to take home

- **Early ph1/2 clinical trials have evolved**, shifting from tumor type-centered to gene-directed, histology-agnostic, with innovative adaptive design tailored **to biomarker profiling with the goal to improve treatment outcomes**

- To improve the implementation of Precision Medicine, this approach should be used early in the course of the disease, and **patients should have complete tumor profiling and access to effective matched therapy**

- Innovative trial designs (umbrella or basket studies) are emerging as patient-centric approaches and public-private partnerships, cross-industry, government and non-profit sector collaborations are enabling implementation. **Success will require new paradigms in oncology drug development and market approval and continued collaboration**

# THANK YOU FOR YOUR ATTENTION


FUTURE BEGINS NOW
Fase 1 Meeting
Nuevas terapias en desarrollo precoz frente al cáncer

09:00 - 09:15 **Introducción y bienvenida**
Dr. Ignacio Matos García, Clínica Universidad de Navarra, Madrid
Dr. Eduardo Castañón Álvarez, Clínica Universidad de Navarra, Madrid
Dr Antonio González Martín, Clínica Universidad de Navarra, Madrid

**09:15-10:35 SESIÓN 1 - TERAPIAS DIANA**
Moderadores: Dra. Valentina Boni, NEXT Oncology, Madrid
Dr. Luis Paz-Ares Rodríguez, Hospital Univ. 12 de Octubre, Madrid

09:15 - 09:20 **Presentación sesión**
09:20 - 09:40 **Breakthrough en fases I. Indicaciones a través de fases I/II**
Dra. Cinta Hierro Carbó, ICO Badalona
09:40 - 10:00 **Estudios UMBRELLA. Diseño y retos**
Dr. Emiliano Calvo Aller, START Madrid-CIOCC, Madrid
10:00 - 10:20 **Novedades 2022 en terapias diana**
Dr. Federico Longo Muñoz., Hospital Univ. Ramón y Cajal, Madrid
10:20 - 10:35 **Discusión**

**10:35-11:55 SESIÓN 2 - ADC**
Moderadores: Dra. Aitana Calvo Ferrández, Hospital General Univ. Gregorio Marañón, Madrid
Dr. Ignacio Ortego Zabalza, MD Anderson Cancer Center Madrid, Madrid

10:35 - 10:40 **Presentación sesión**
10:40 - 11:00 **Tipos y mecanismo de acción de los ADCs**
Dr. Alberto Ocaña Fernández , Hospital Clínico San Carlos, Madrid
11:00 - 11:20 **Novedades de 2022 en ADCs**
Dr. Víctor Moreno García, Hospital Univ. Fundación Jiménez Díaz, Madrid
11:20 - 11:40 **ADCs como terapia agnóstica: ¿Mito o realidad?**
Dra. Desamparados Roda Pérez, Hospital Clínico Univ. de Valencia
11:40 - 11:55 **Discusión**
11:55 - 12:25 **Pausa café**

**12:25-13:45 SESIÓN 3 - ANTICUERPOS BIESPECÍFICOS/T CELL ENGAGERS**
Moderadores: Dra. María Rodríguez Ruiz, Clínica Universidad de Navarra, Pamplona
Dr. Ignacio Melero Bermejo Clínica Universidad de Navarra, Pamplona

12:25 - 12:30 **Presentación sesión**
12:30 - 12:50 **Diseño y mecanismo de acción**
Dr. Pedro Berraondo López, CIMA, Universidad de Navarra, Pamplona
12:50 - 13:10 **Novedades 2022 en anticuerpos biespecíficos y T-cell engagers**
Dr. Iván Victoria Ruiz, Hospital Clínic de Barcelona
13:10 - 13:30 **Estrategias de desarrollo de anticuerpos biespeficos y T-cell engagers**
Dra. Elena Garralda Cabanas, Vall d'Hebron Instituto de Oncología, Barcelona
13:30 - 13:45 **Discusión**
13:45 - 15:00 **Almuerzo**

**15:00 - 16:20 SESIÓN 4 - TERAPIA CELULAR**
Moderadores: Dr. Juan Martín Liberal, Institut Català d'Oncologia, Barcelona
Dr. Mariano Ponz-Sarvisé, Clínica Universidad de Navarra, Pamplona

15:00 - 15:05 **Presentación sesión**
15:05 - 15:25 **Optimización de la terapia celular, del laboratorio a la clínica**
Dra. Alena Gross Vidal, Vall d'Hebron Instituto de Oncología, Barcelona
15:25 - 15:45 **Novedades 2022 en terapia celular**
Dra. María Ochoa de Olza, Centre Hospitalier Universitaire Vaudois, Laussane
15:45 - 16:05 **Nuevas estrategias y biomarcadores**
Dr. Sergio Quezada, UCL Cancer Institute, Londres
16:05 - 16:20 **Discusión**

**16:20 - 17:25 SESIÓN 5 - COLABORACIÓN, MEJORA DEL ENSAYO CLÍNICO PRECOZ EN ESPAÑA**
Moderadores: Dr. Ignacio Matos García, Clínica Universidad de Navarra, Madrid
Dr. Eduardo Castañón Álvarez, Clínica Universidad de Navarra, Madrid

16:20 - 16:25 **Presentación sesión**
16:25 - 17:25 **¿Dónde estamos y hacia dónde vamos? Presente y futuro de los ensayos precoces en Oncología en España**
Amelia Martín Uranga, Farmaindustria
AEMPS
Dr. Santiago Ponce Aix, Hospital Gustave Roussy, Villejuif
Dr. Emiliano Calvo Aller, START Madrid-CIOCC, Madrid
Dra. Elena Garralda Cabanas, Vall d'Hebron Instituto de Oncología, Barcelona
17:25 - 17:30 **Clausura**

*chierro@iconcologia.net*