

UN NUOVO RUOLO PER LA RICERCA TRASLAZIONALE?

Nicola Normanno



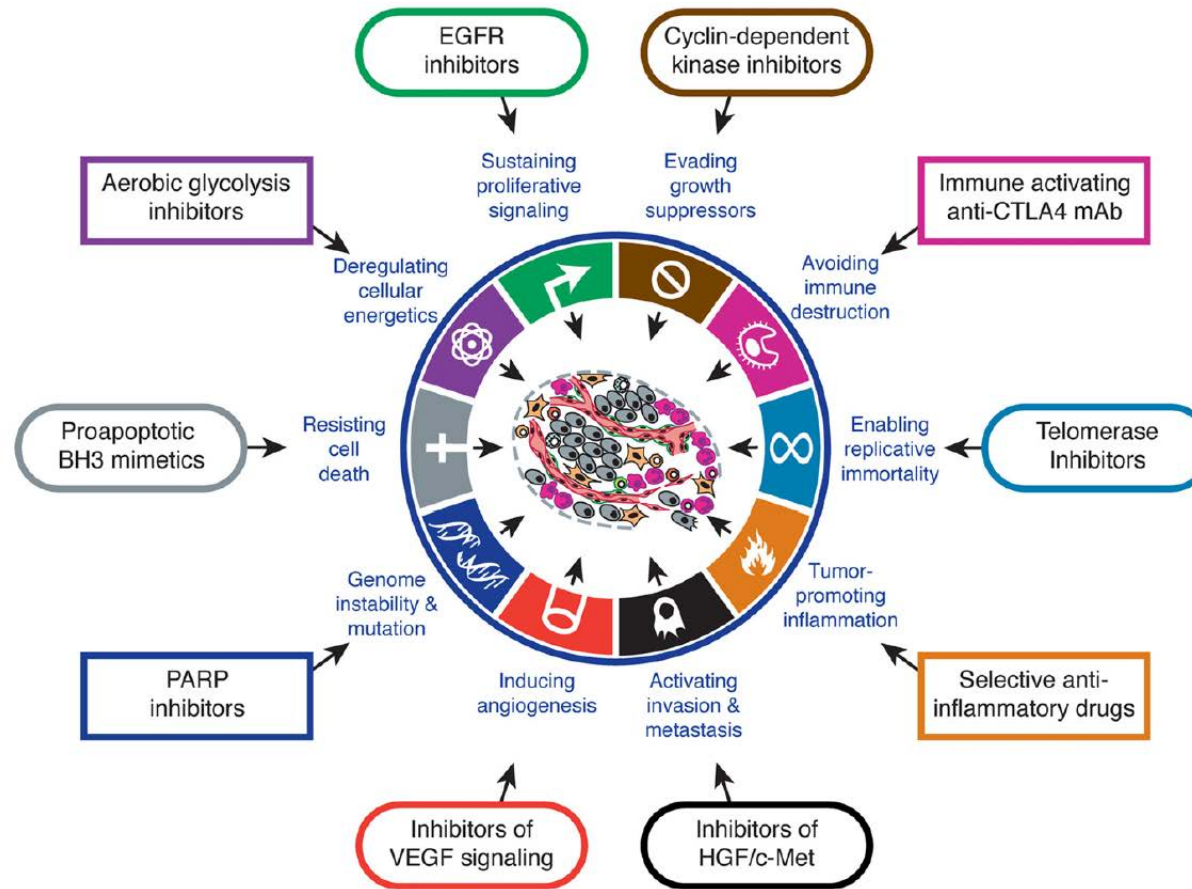
ISTITUTO NAZIONALE PER LO STUDIO E LA CURA DEI TUMORI
FONDAZIONE "G. Pascale" – NAPOLI

SC Biologia Cellulare e Bioterapie

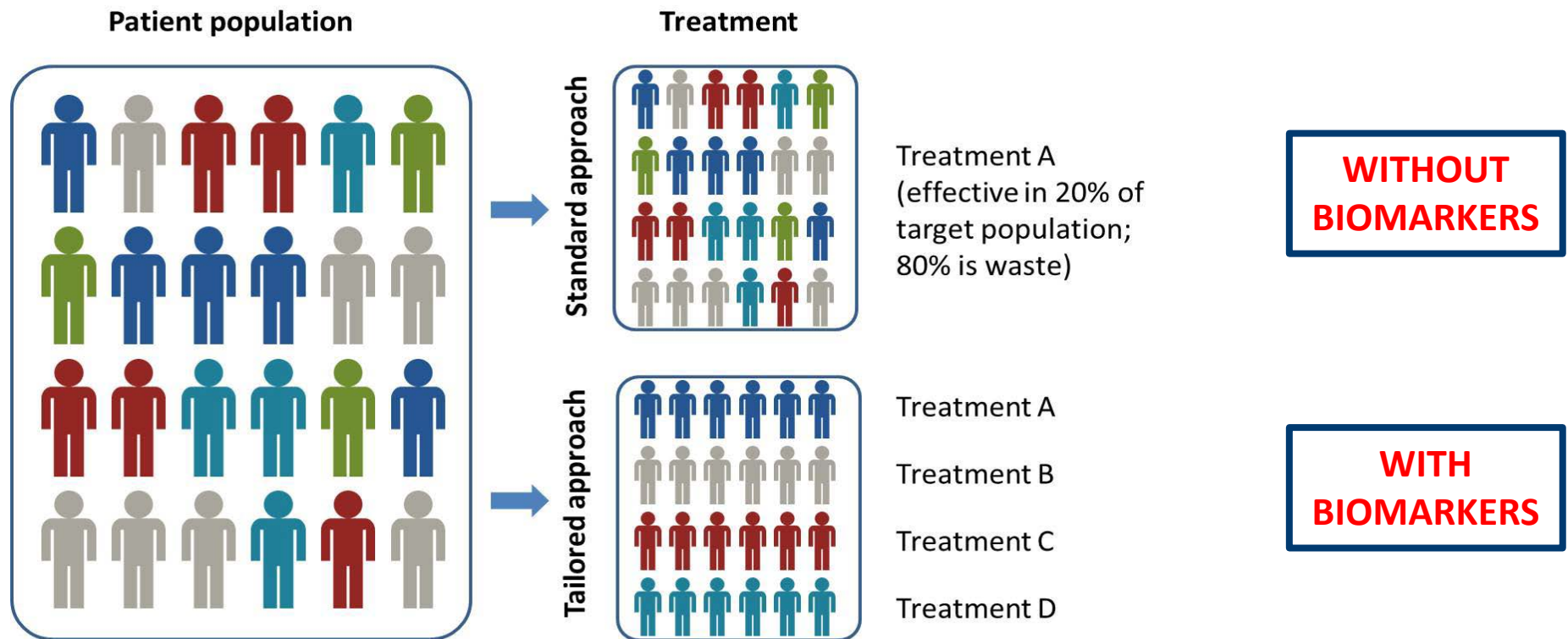
DISCLOSURES

- **Personal financial interests (speaker's fee and/or advisory boards):** MSD, Bayer, Biocartis, Illumina, Incyte, Roche, BMS, MERCK, Thermofisher, Astrazeneca, Eli Lilly, Novartis
- **Institutional financial interests (financial support to research projects):** MERCK, Thermofisher, QIAGEN, Roche, Astrazeneca, Biocartis, Illumina, Blueprint
- **Non-financial interests:** President, International Quality Network for Pathology (IQN Path); President, Italian Cancer Society (SIC)

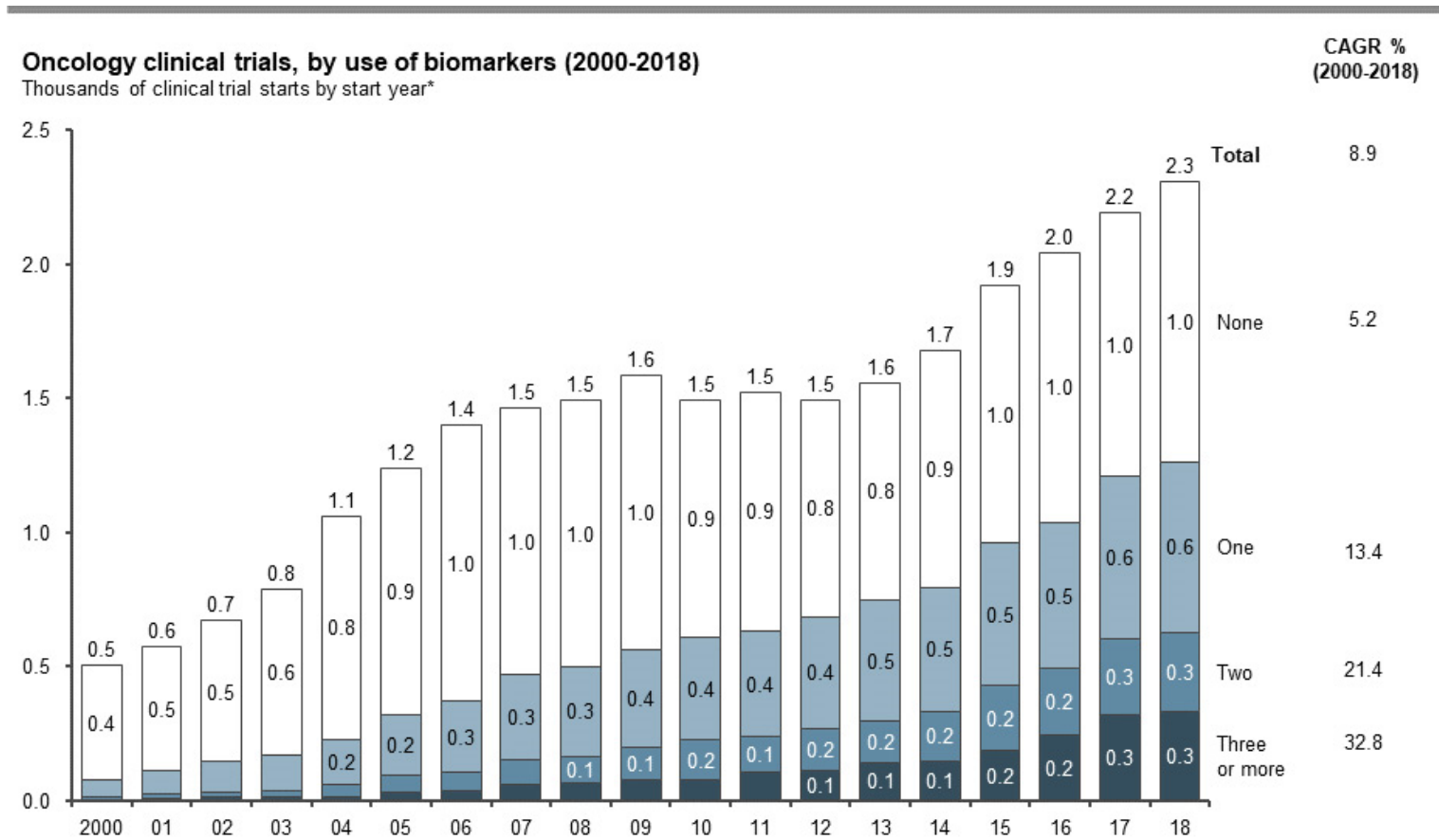
Signal transduction pathways involved in the proliferation and survival of cancer cells



Target-based agents + predictive biomarkers: PRECISION MEDICINE



The number of oncology trials with biomarkers grew at twice the rate of oncology trials overall from 2000 – 2018



nature medicine

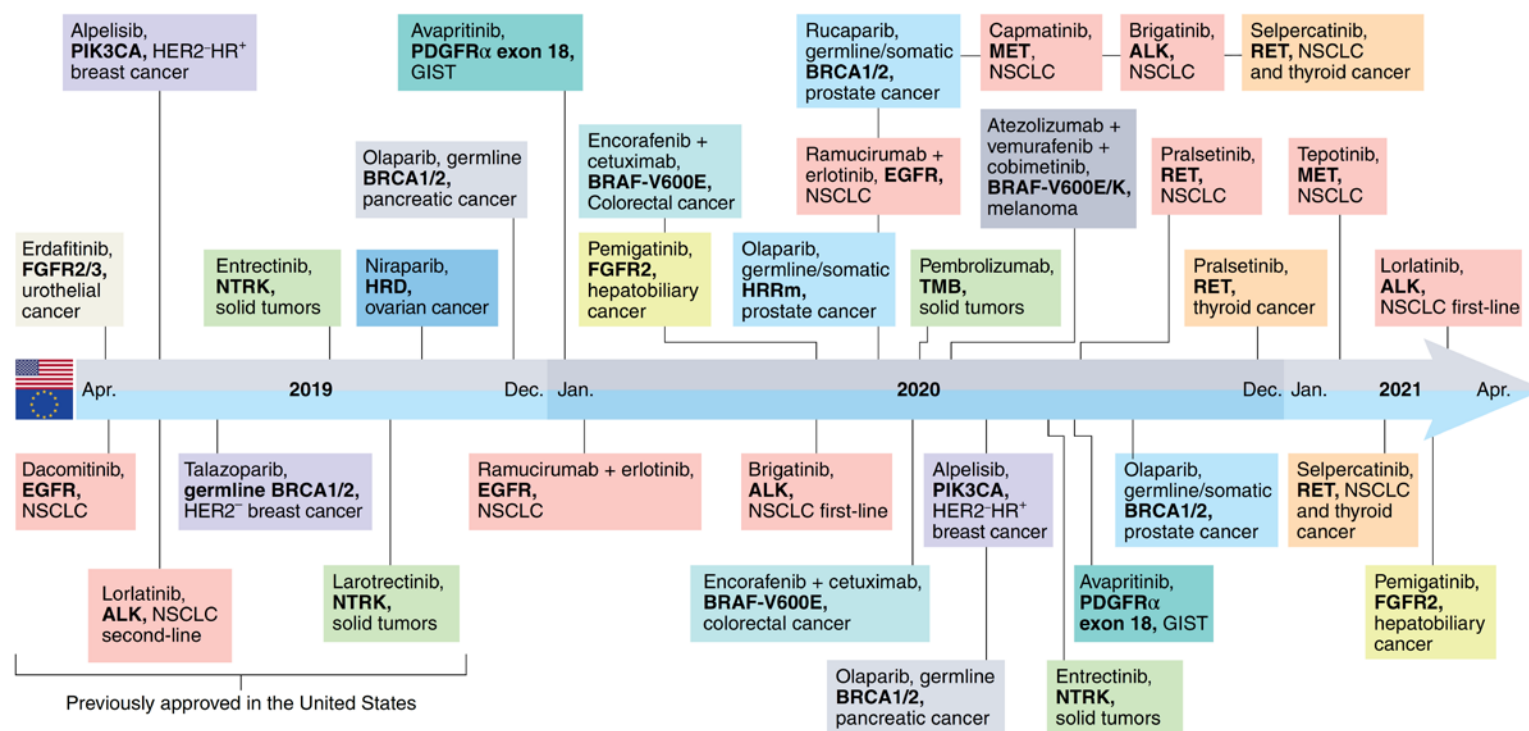
Focus on The Future of Cancer Research



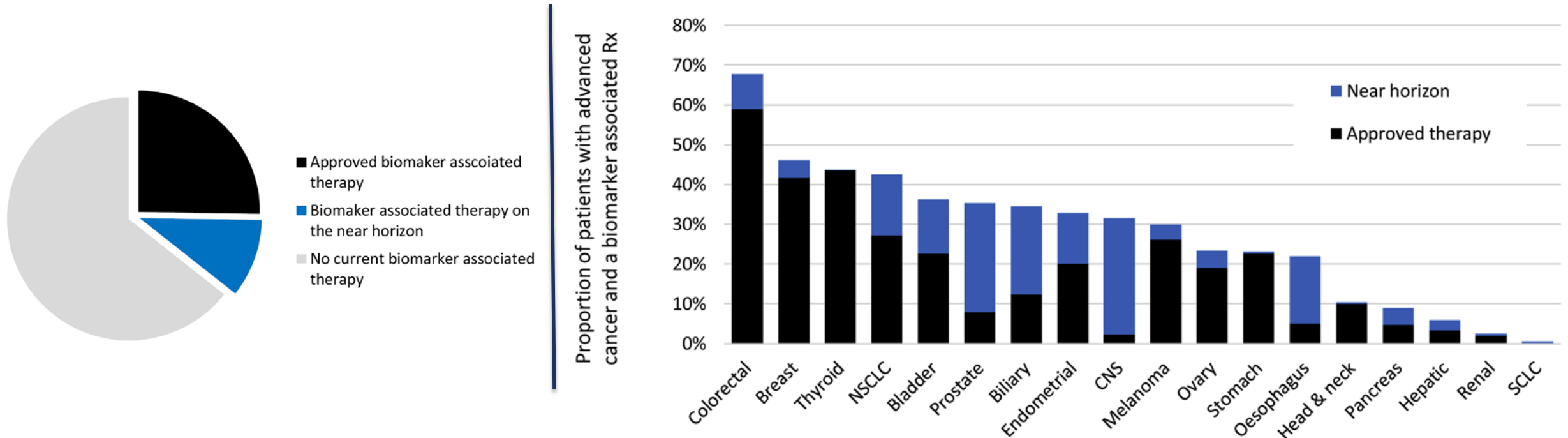
Delivering precision oncology to patients with cancer

Joaquin Mateo, [Lotte Steuten](#), [Philippe Aftimos](#), [Fabrice André](#), [Mark Davies](#), [Elena Garralda](#), [Jan Geissler](#), [Don Husereau](#), [Iciar Martinez-Lopez](#), [Nicola Normanno](#), [Jorge S. Reis-Filho](#), [Stephen Stefani](#), [David M. Thomas](#), [C. Benedikt Westphalen](#) & [Emile Voest](#) ✉

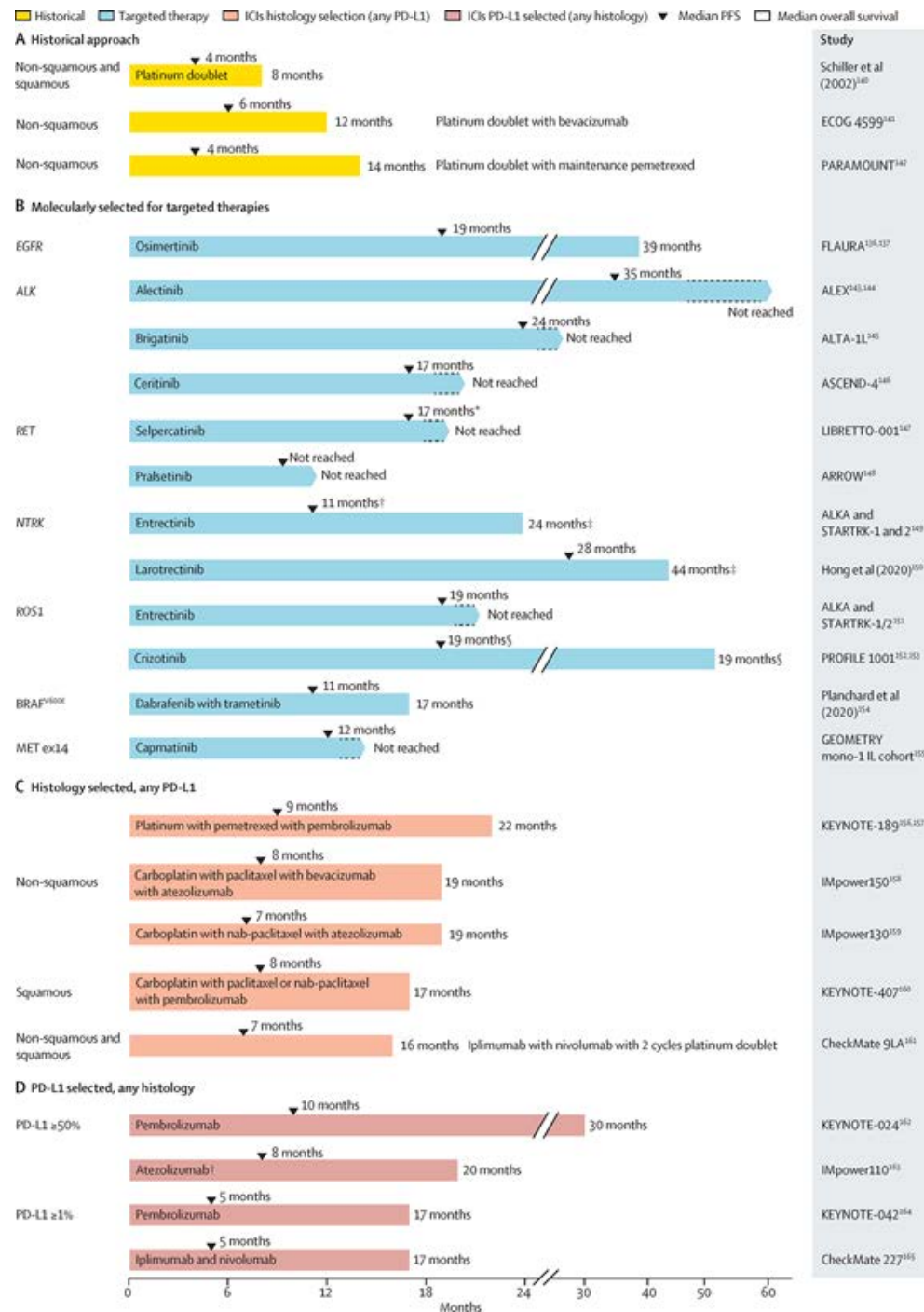
Nature Medicine **28**, 658–665 (2022) |



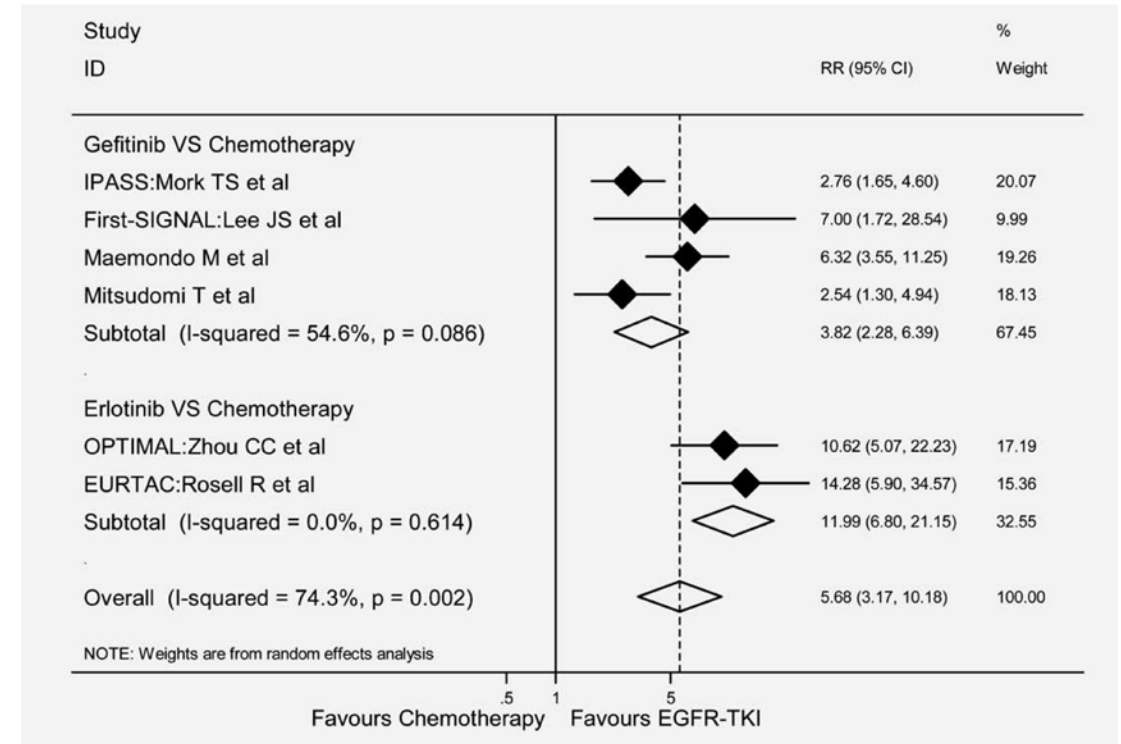
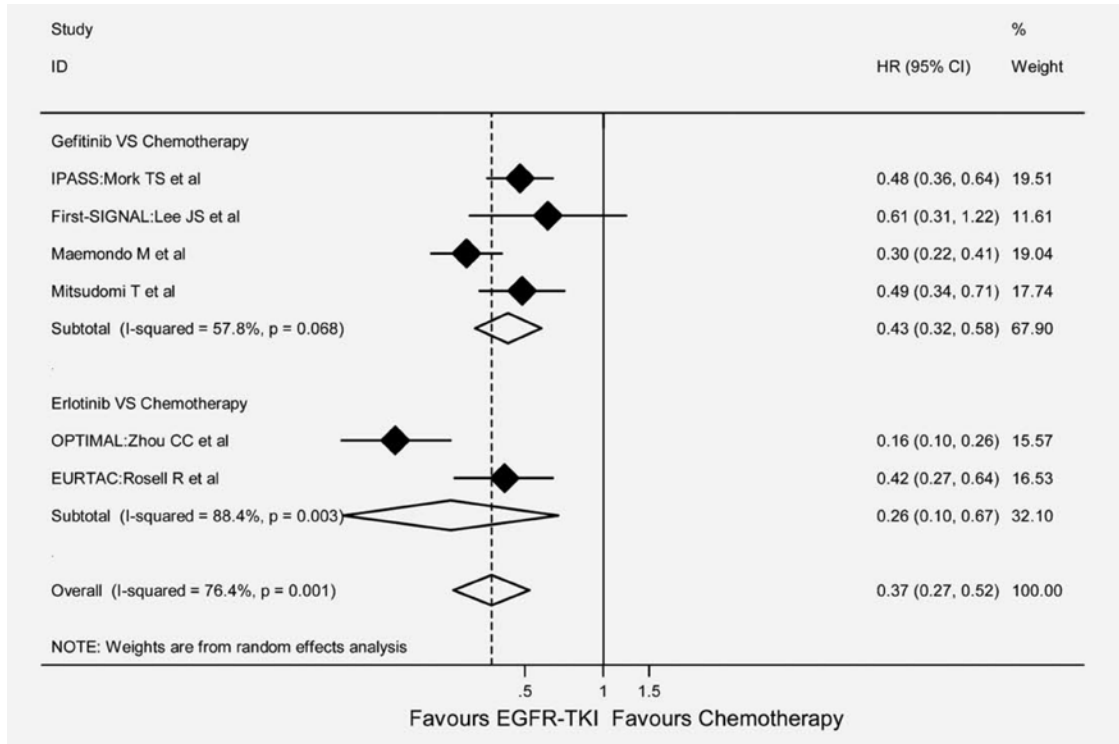
Advanced cancer patients eligible for a biomarker associated therapy



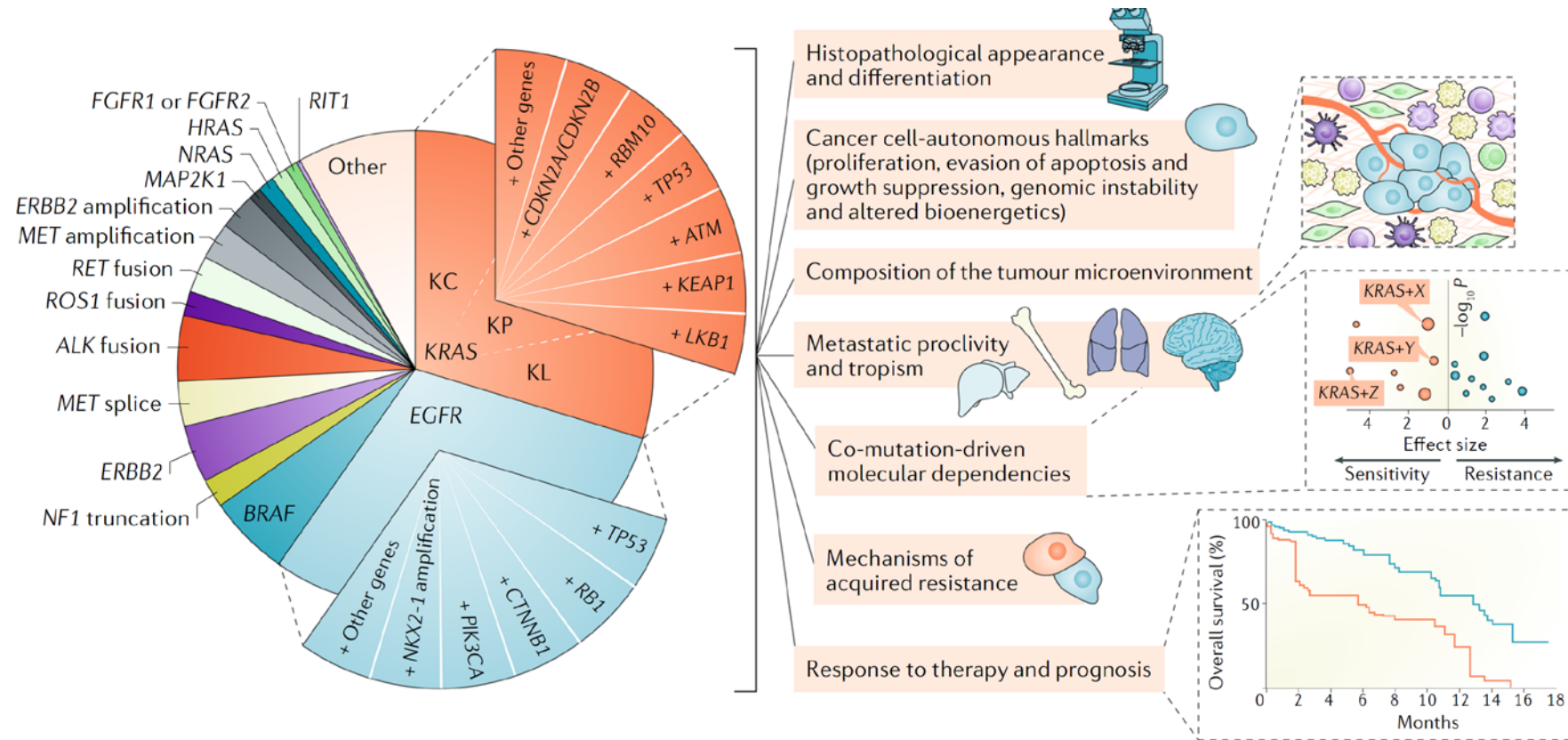
Outcome of NSCLC patients



Meta-analysis of first line EGFR TKIs trials



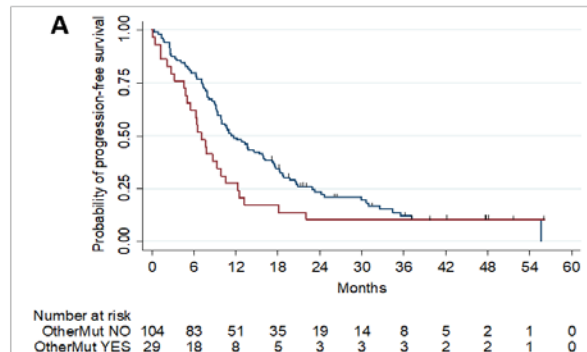
Occurrence of co-mutations in oncogene-addicted NSCLC



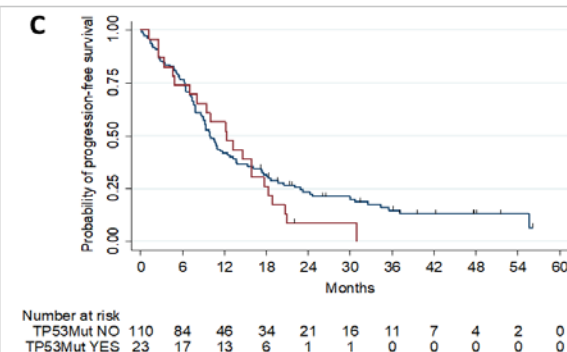
Outcome of EGFR-mutant patients with and without co-mutations

PFS

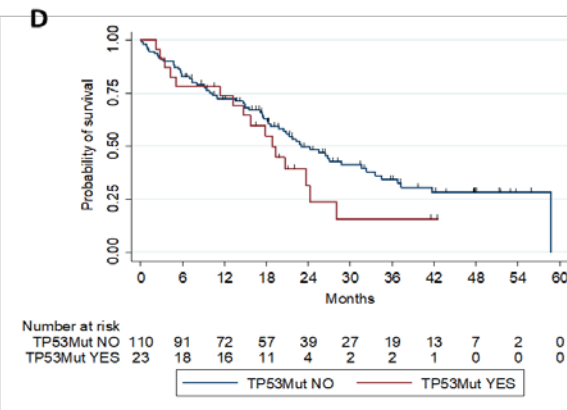
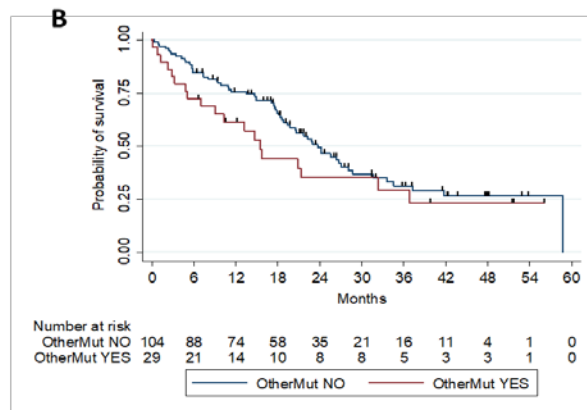
KRAS, NRAS, BRAF,
ERBB2, PIK3CA, MET



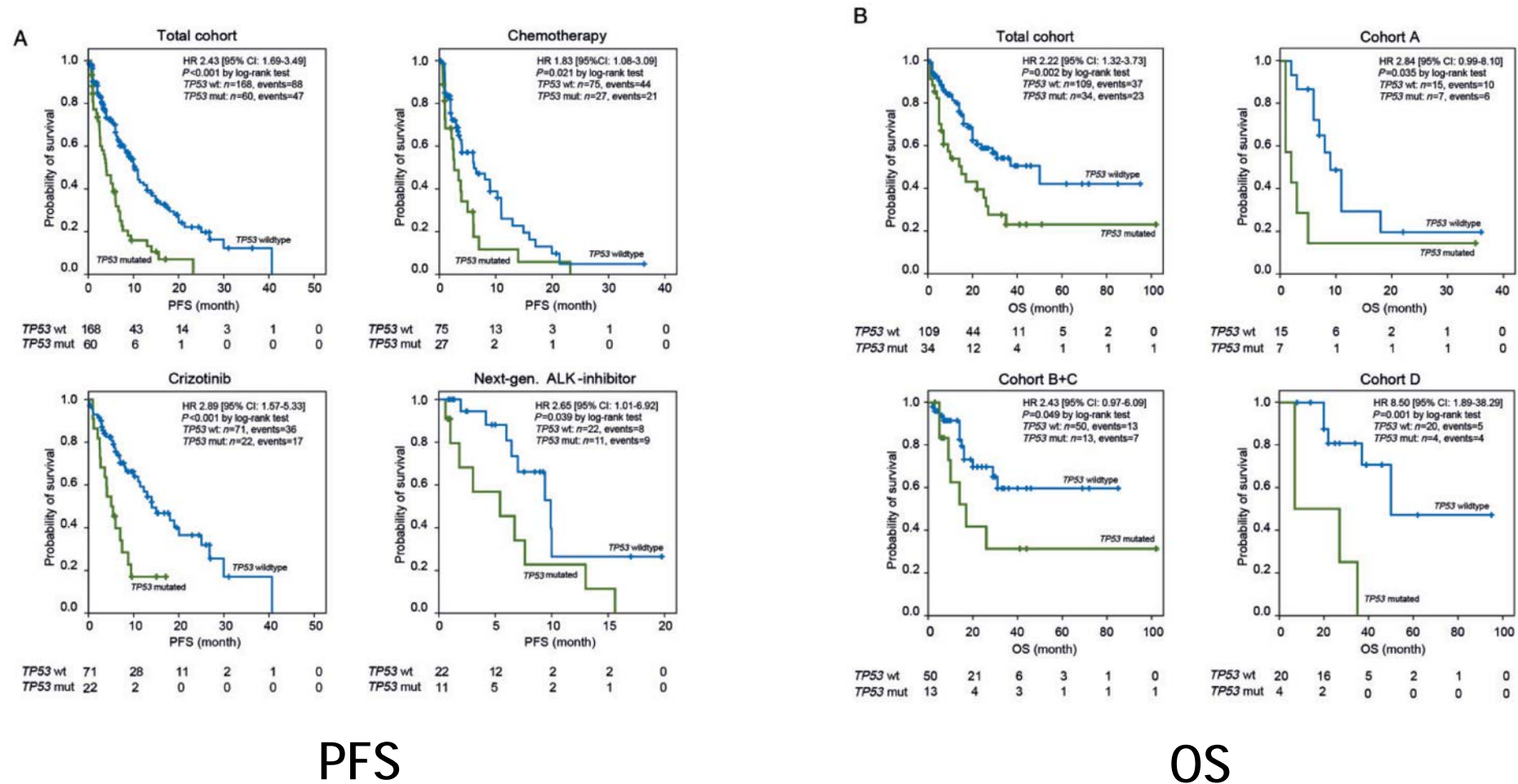
TP53



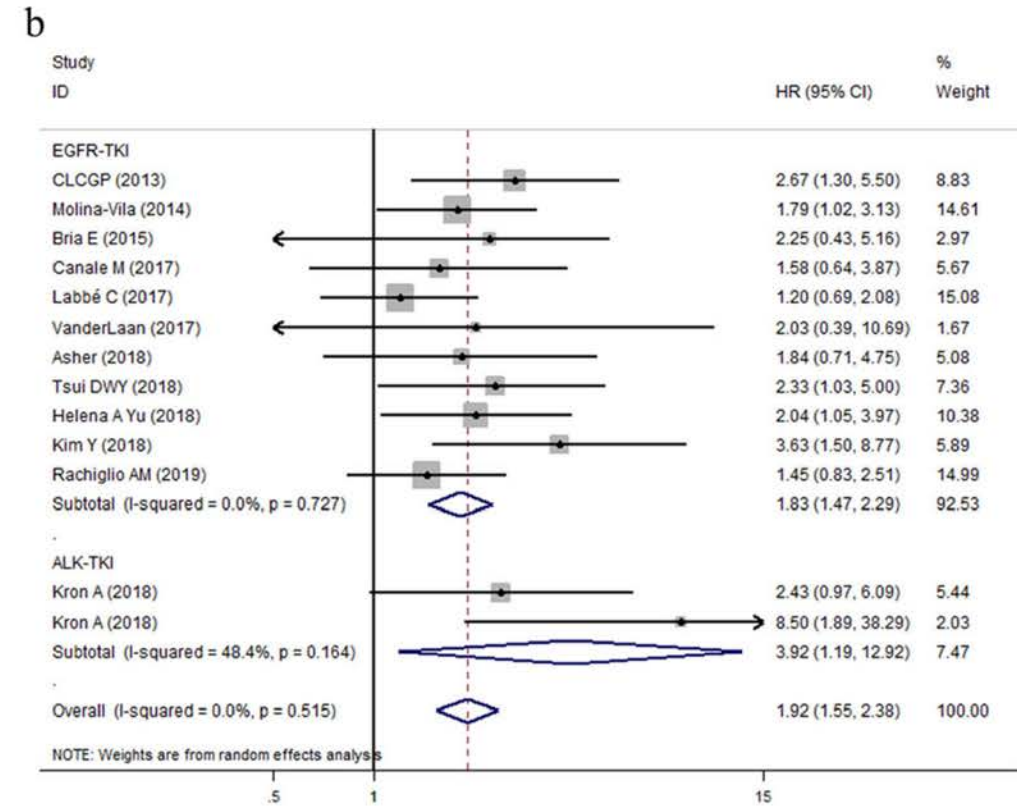
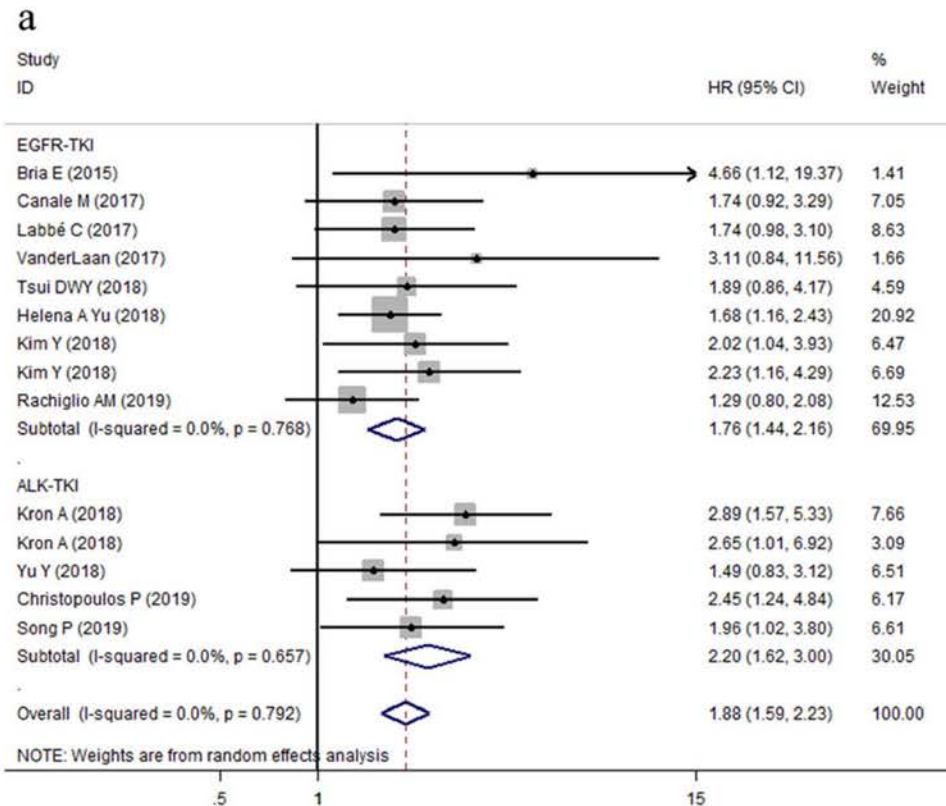
OS



Survival of ALK-positive patients with and without TP53 co-mutations



Outcome of EGFR/ALK-mutant patients with and without TP53 co-mutations



SPECIAL ARTICLE

ESMO expert consensus statements on the management of *EGFR* mutant non-small-cell lung cancer

A. Passaro^{1*}, N. Leigh^{2†}, F. Blackhall^{3,4†}, S. Popat^{5,6,7†}, K. Kerr^{8†}, M. J. Ahn⁹, M. E. Arcila¹⁰, O. Arrieta¹¹, D. Planchard¹², F. de Marinis¹, A. M. Dingemans¹³, R. Dziadziuszko¹⁴, C. Faivre-Finn¹⁵, J. Feldman¹⁶, E. Felip¹⁷, G. Curigliano¹⁸, R. Herbst¹⁹, P. A. Jänne²⁰, T. John²¹, T. Mitsudomi²², T. Mok²³, N. Normanno²⁴, L. Paz-Ares²⁵, S. Ramalingam²⁶, L. Sequist²⁷, J. Vansteenkiste²⁸, I. I. Wistuba²⁹, J. Wolf³⁰, Y. L. Wu³¹, S. R. Yang⁷, J. C. H. Yang³², Y. Yatabe³³, G. Pentheroudakis³⁴ & S. Peters³⁵

7: Is it necessary to test for and report co-mutations occurring with *EGFR* mutation in advanced stage NSCLC?

STATEMENT: The co-mutational landscape found with *EGFR* mutation in advanced NSCLC may be a poor prognostic indicator and may predict relative resistance to *EGFR* TKIs. Investigating the presence of co-occurring alterations can be performed, but is not required, in absence of direct therapeutic implications [I,A].

Precision medicine through biomarkers*

Traditional genetic driver mutations

- Tumour cell¹
- Stable²
- Binary (+/- mutation)³
- *EGFR, BRAF*^{3,4,6,7}

Location

Presence or prevalence

Measurement

Examples

I-O biomarkers

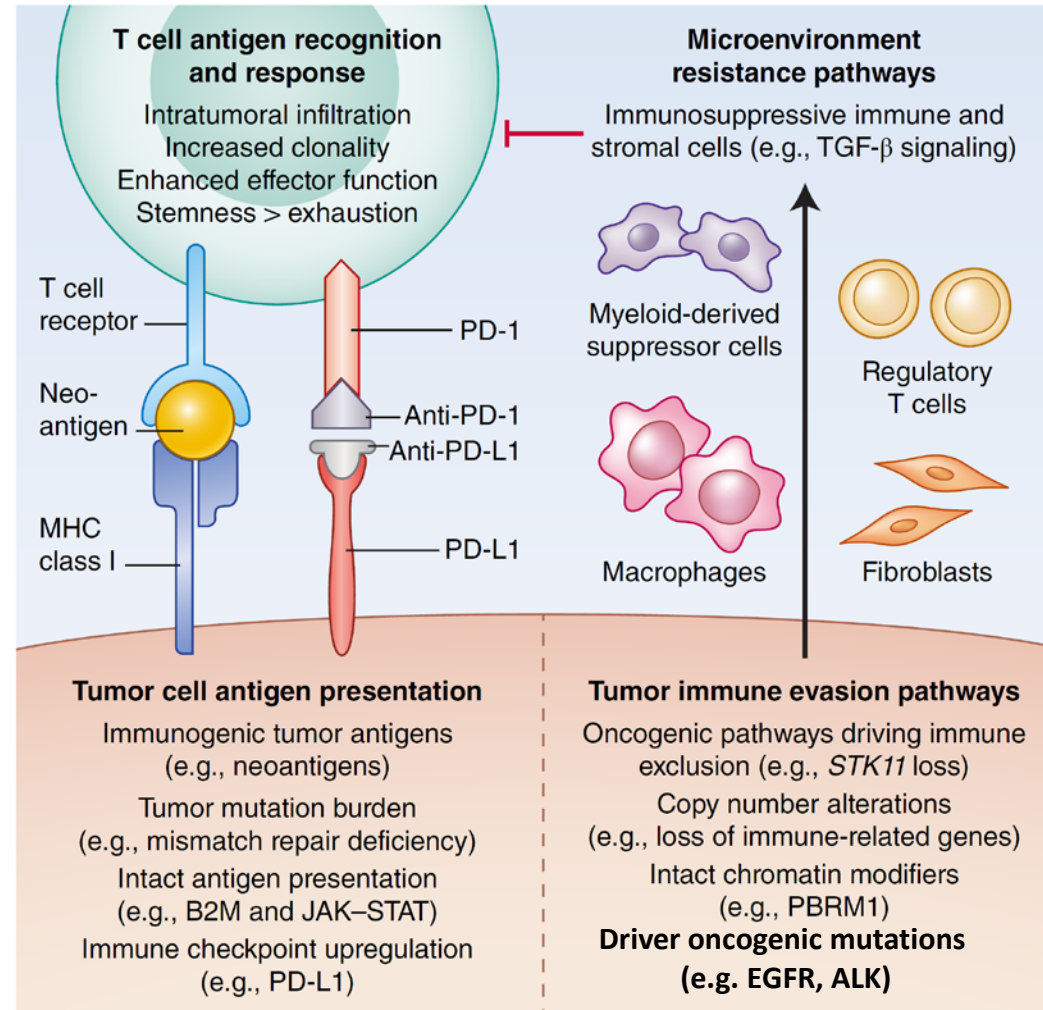
- Tumour and environment⁸
- Dynamic and inducible⁴
- Expression range or magnitude⁹
- PD-L1, tumour-infiltrating immune cells⁹⁻¹¹

*Description of traditional genetic driver mutations and I-O biomarkers represents common features of each group, but are not exhaustive.

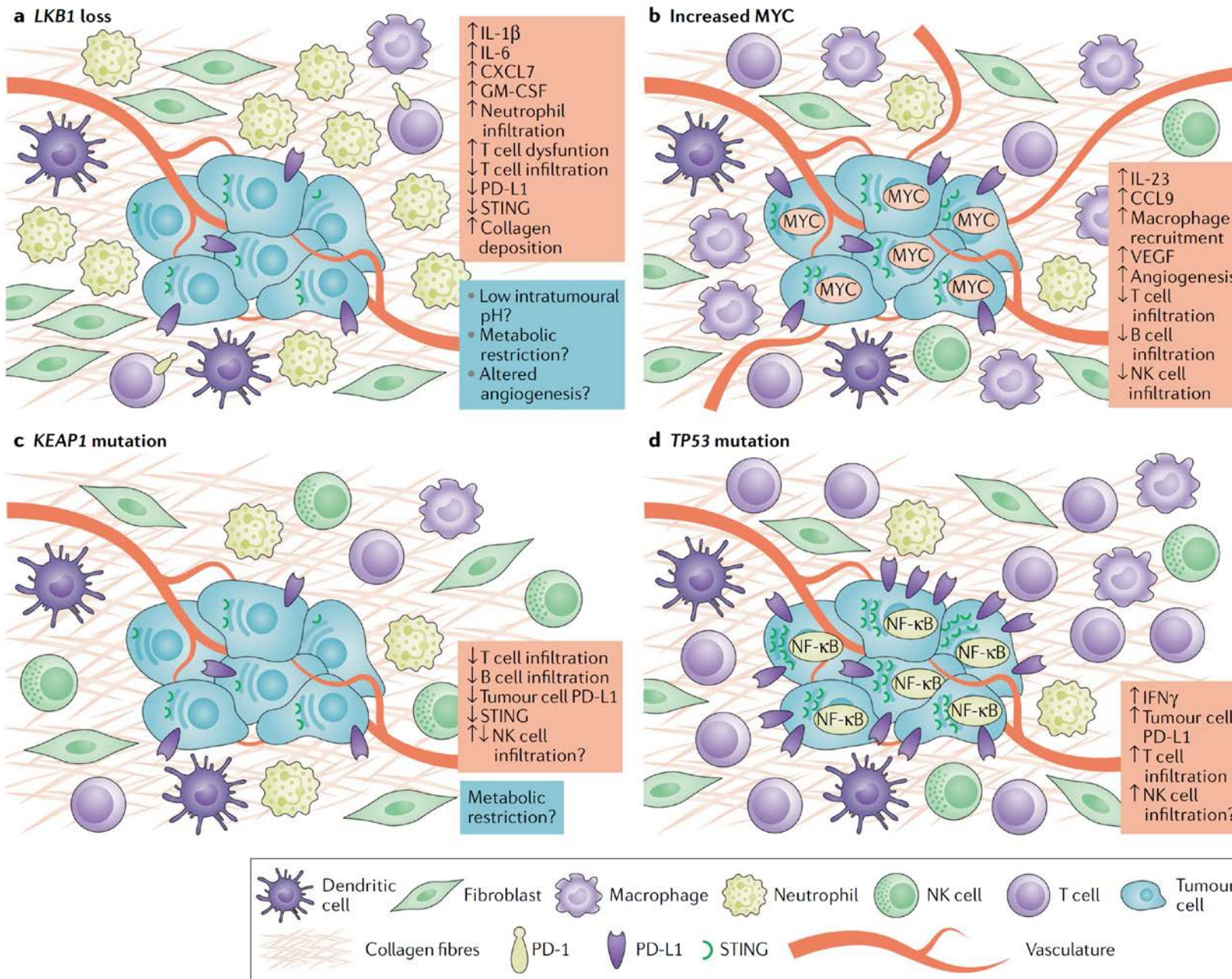
EGFR=epidermal growth factor receptor; PD-L1=programmed death ligand 1.

1. Merid SK et al. *BMC Bioinformatics*. 2014. doi:10.1186/1471-2105-15-308. 2. Ding J et al. *Nat Commun*. 2015. doi:10.1038/ncomms9554. 3. Van Allen EM et al. *J Clin Oncol*. 2013;31(15):1825-1833. 4. Sharma P, Allison JP. *Science*. 2015;348(6230):56-64. 6. Mok TS. *Nat Rev Clin Oncol*. 2011;8(11):661-668. 7. Davies H et al. *Nature*. 2002;417(6892):949-954. 8. Nelson D et al. *J Immunol Res*. 2014. doi: 10.1155/2014/789069. 9. Kerr KM et al. *J Thorac Oncol*. 2015;10(7):985-989. 10. Anitei MG et al. *Clin Cancer Res*. 2014;20(7):1891-1899. 11. Wang X et al. *Onco Targets Ther*. 2016;9:5023-5039.

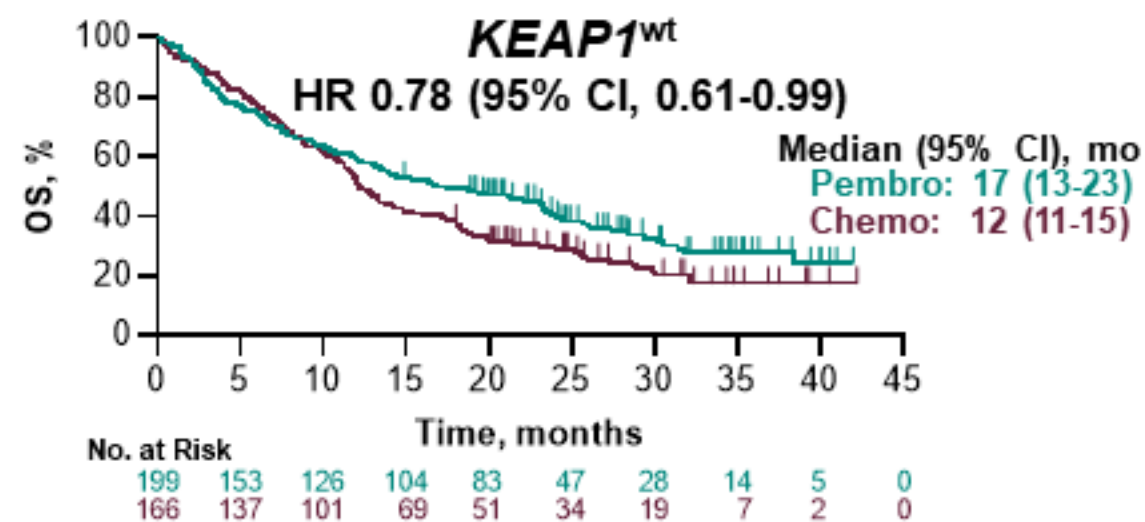
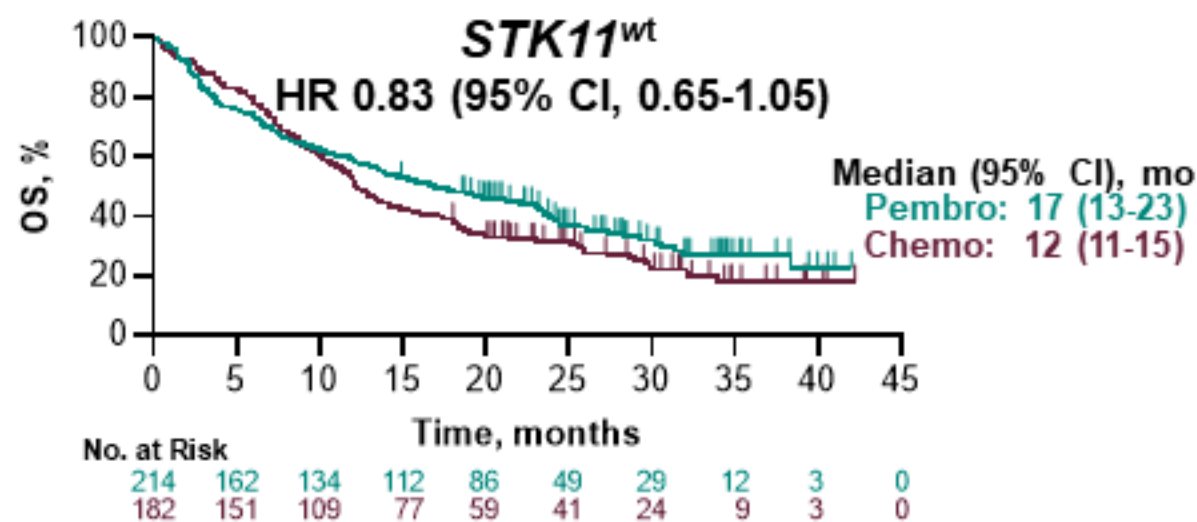
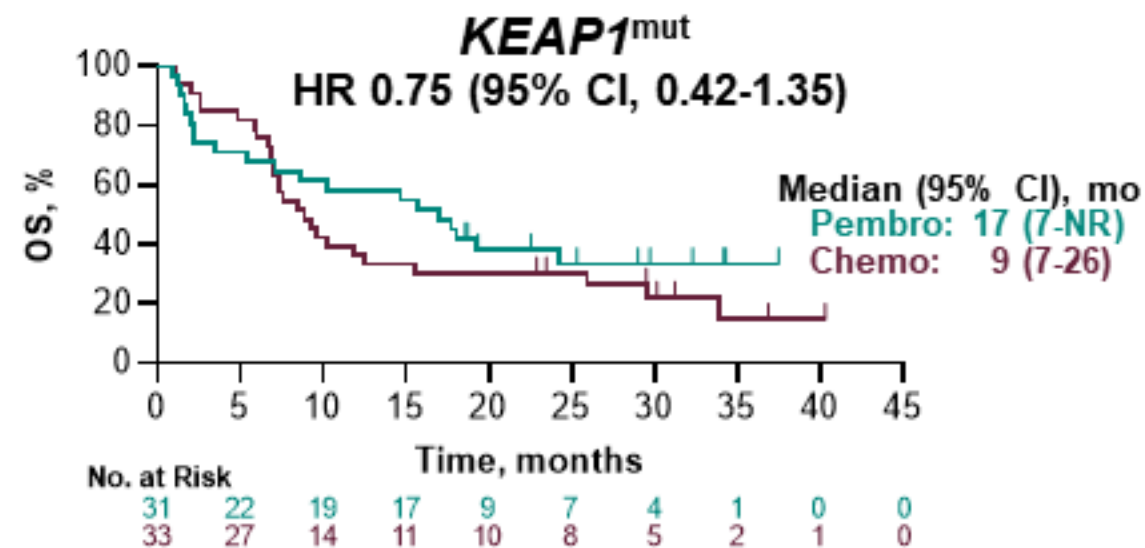
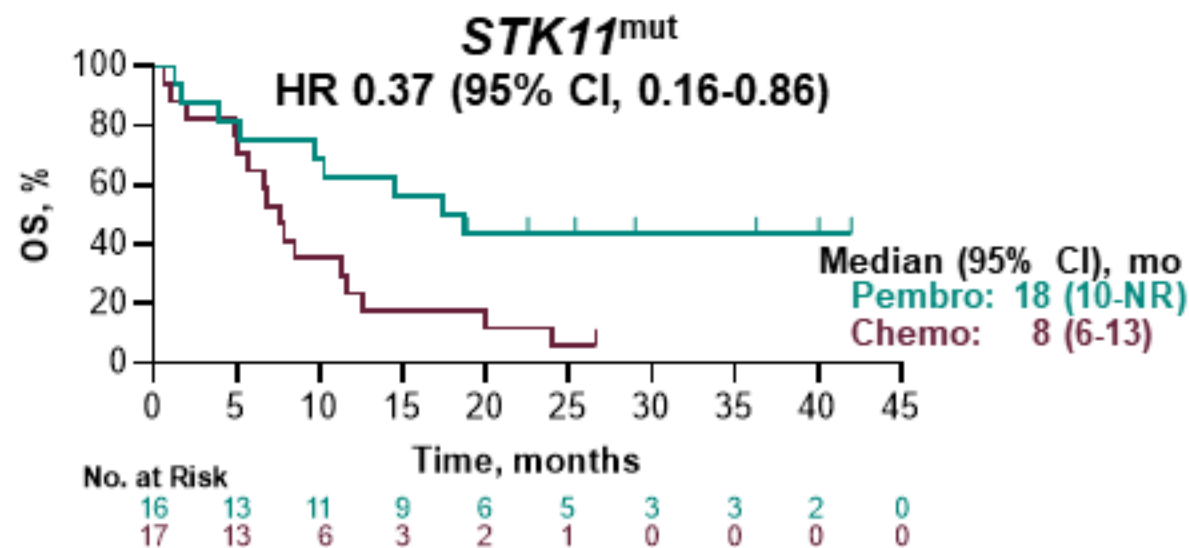
Genomic correlates of response to ICI within the tumor immune microenvironment



Impact of co-mutations on the microenvironment of KRAS- mutant lung adenocarcinoma



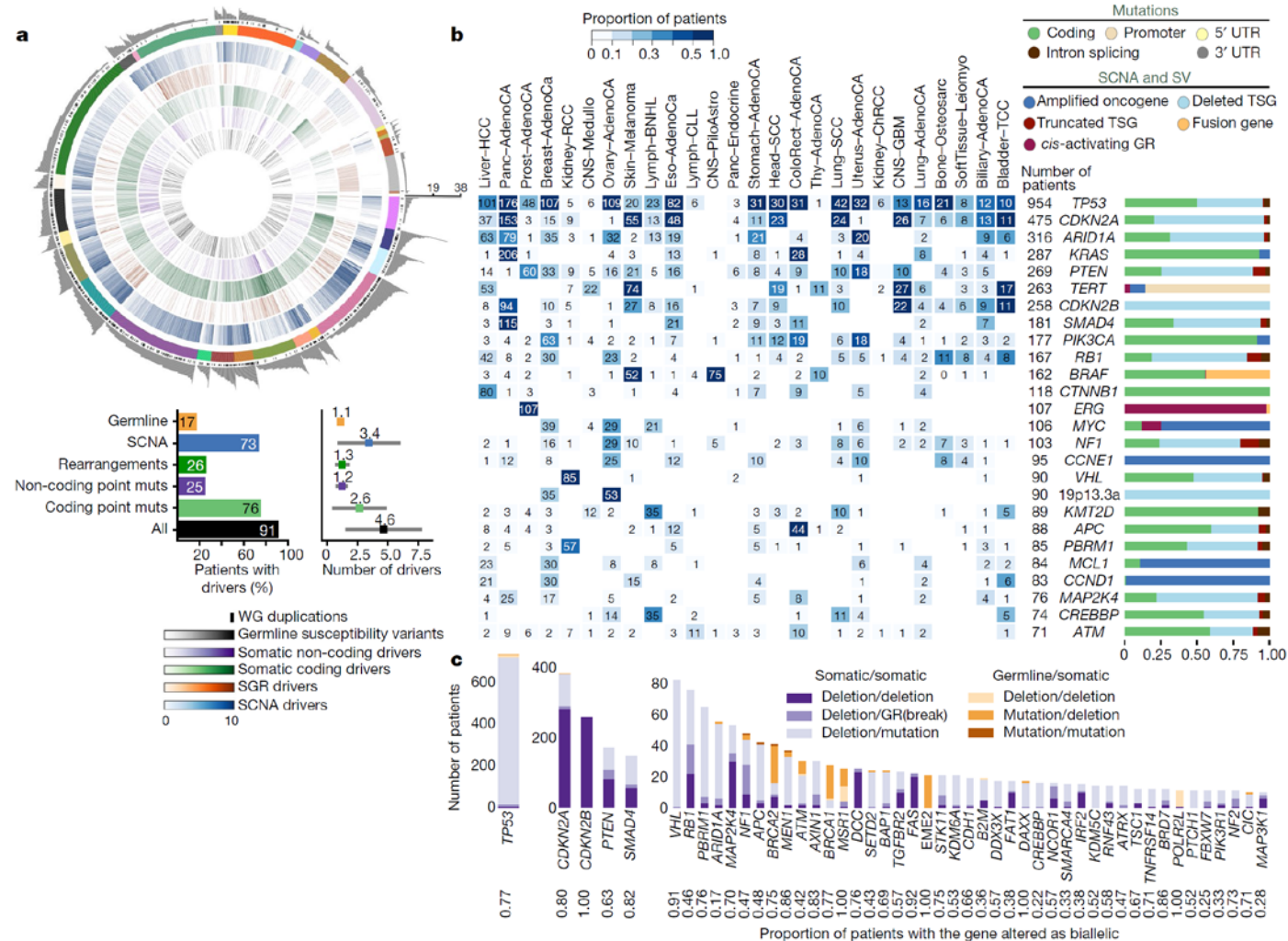
Association of *STK11* and *KEAP1* Status With OS



All participants had PD-L1-positive tumors (TPS $\geq 1\%$).

Data cutoff date: Sep 4, 2018.

I biomarcatori tumorali agnostici



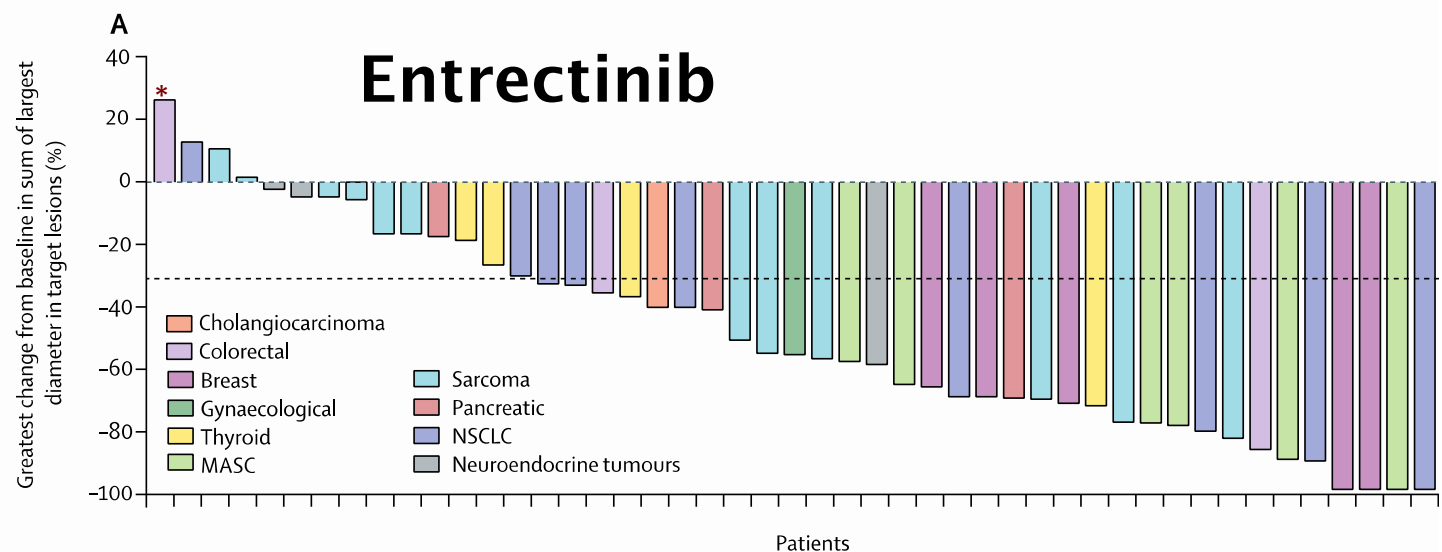
Molecular alterations with potential for future histology-agnostic designation

Molecular alteration	Therapeutic agent	Trial characteristics ^a	Study population	Preliminary efficacy results
RET fusions	Selpercatinib ¹³⁰	Phase I/II trial (LIBRETTO-001)	n = 531; NSCLC (n = 253); MTC (n = 226); PTC (n = 27); other (n = 25)	ORR: 66% for NSCLC, 51% for MTC, 62% for PTC; CRs: 2% for NSCLC, 6% for MTC, 0% for PTC; DCR: 98% for NSCLC, 95% for MTC, 100% for PTC; mDOR: 20 months for NSCLC, NR for MTC and PTC; mPFS: NR
	Pralsetinib ¹⁴⁷	Phase I/II trial (ARROW)	n = 144; three tumour types: NSCLC (n = 79); MTC (n = 60); PTC (n = 5)	ORR: 58% for NSCLC, 46% for MTC, 50% for PTC; CRs: 1% for NSCLC, 1% for MTC, 0% for PTC; DCR: 96% for NSCLC, 97% for MTC, 100% for PTC; mDOR: NR; mPFS: NR
	RXDX-105 (REF. ¹⁴⁸)	Phase I/Ib trial	Study completed	NA
FGFR mutations	Debio 1347 (REF. ¹⁴⁹)	Phase II basket trial (FUZE)	Enrolment ongoing	NA
	TAS-120 (REF. ¹⁵⁰)	Phase II basket trial (TiFFANY)	Enrolment ongoing	NA
KRAS ^{G12C} mutation	AMG 510 (REF. ¹³¹)	Phase I trial in adult patients	n = 35; three tumour types: NSCLC (n = 19); CRC (n = 14); appendix (n = 2)	ORR: 17% overall, 50% for NSCLC; CRs: 0%; DCR: 69%; mDOR: NR; mPFS: NR
	MRTX849 (REF. ¹³⁵)	Phase I trial in adult patients	n = 17; four tumour types: NSCLC (n = 10); CRC (n = 4); appendix (n = 2); duodenal (n = 1)	ORR: 30% overall, 50% for NSCLC, 25% for CRC; CRs: 0%; DCR: 91%; mDOR: NR; mPFS: NR
NRG1 fusion	Zenocutuzumab ¹⁵¹	Phase I/II basket trial	Enrolment ongoing	NA
	Tarloxotinib ¹⁵²	Phase II basket trial (RAIN)	Enrolment ongoing	NA

CR, complete response; CRC, colorectal cancer; DCR, disease-control rate; DOR, duration of response; m, median; MTC, medullary thyroid cancer; NA, not available; NR, not reported; NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; PTC, papillary thyroid carcinoma.

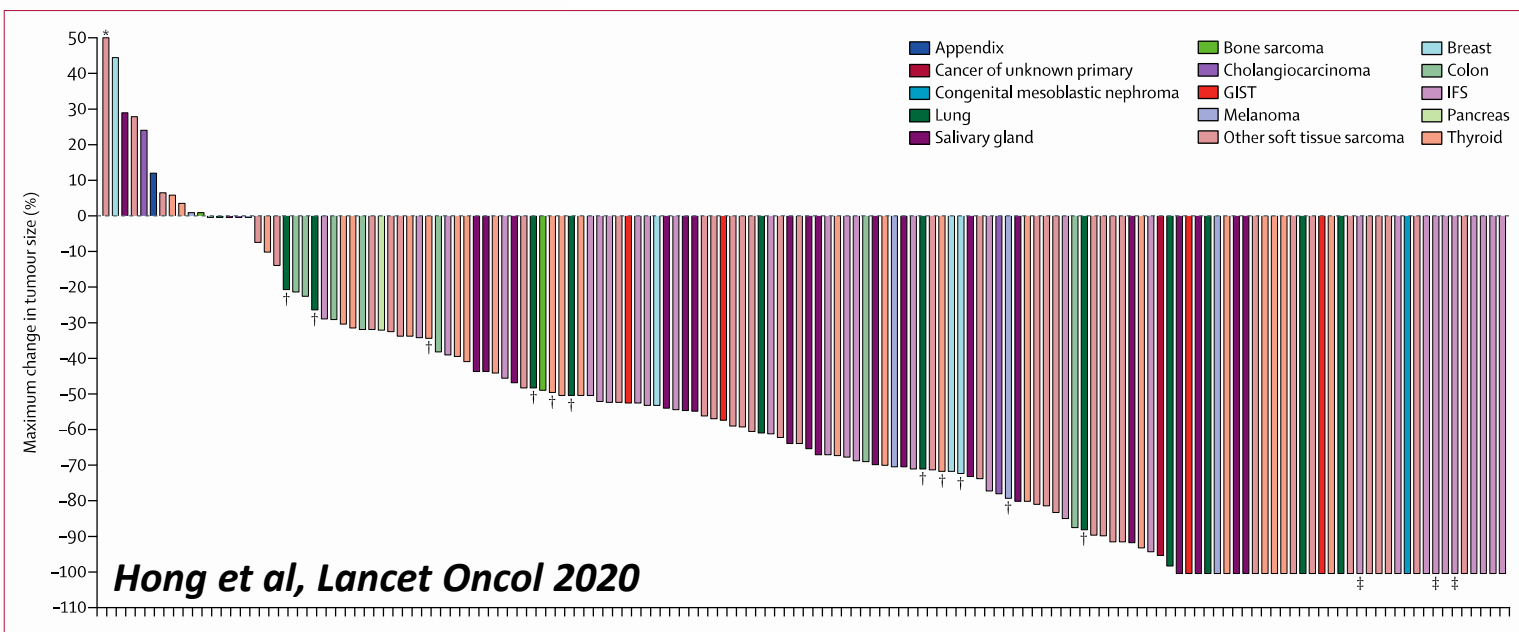
^aAs of 8 February 2020 in clinicaltrials.gov.

Activity of NTRK inhibitors in solid tumors

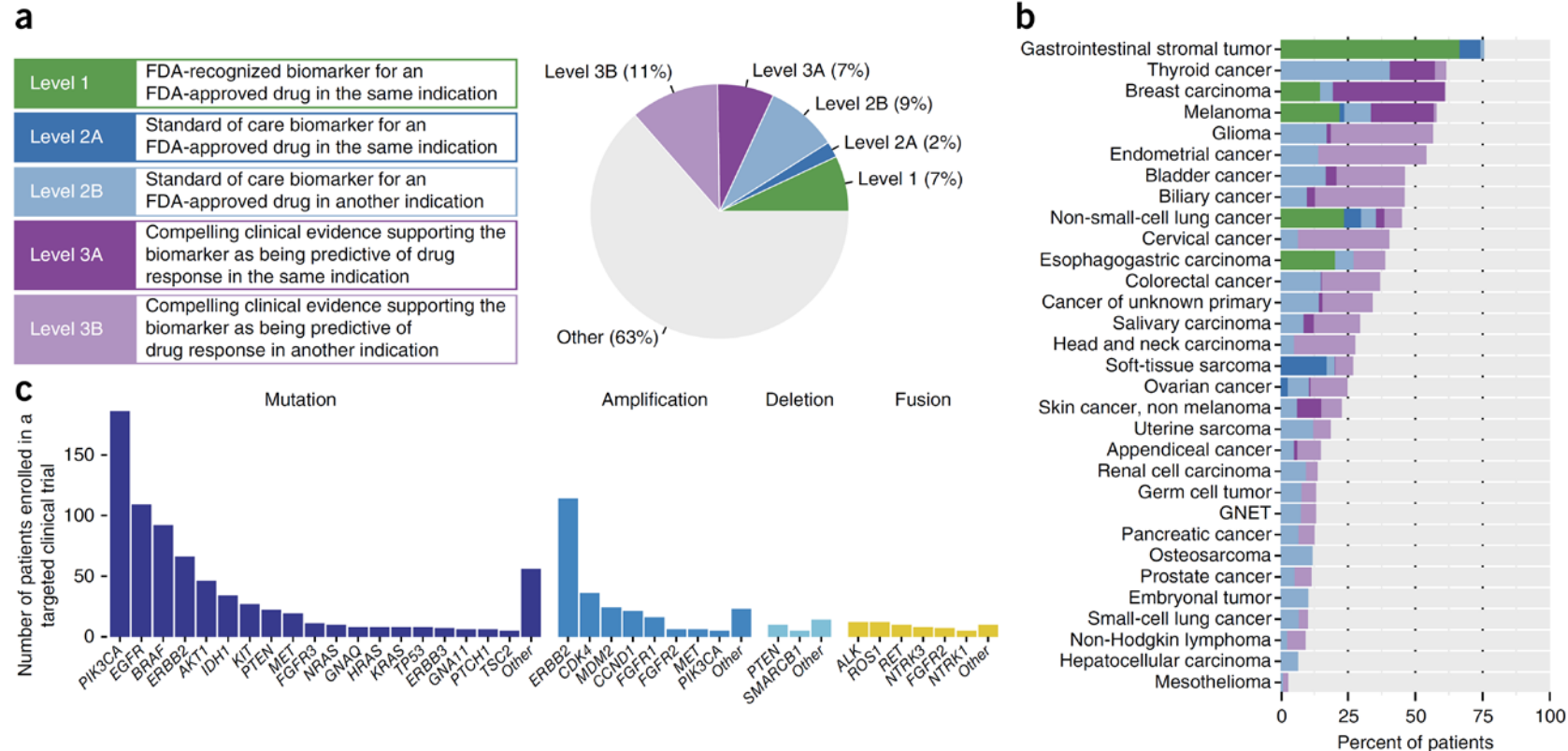


Doebele et al, Lancet Oncol '20

Larotrectinib



Clinical actionability of somatic alterations revealed by MSK-IMPACT



Study	Setting	Assay(s)	Number of Patients	Number of Assays	Number of Patients Matched	Match Rate, % ^a	Reference
North America							
MSK-IMPACT	Single-center	DNA: 341- to 410-gene NGS panel (all exons and selected introns)	10,336	10,945	527 ^b	11 ^b	12
MD Anderson Personalized Cancer Therapy Program	Single-center	DNA: 10-gene NGS panel (hotspot)	1,144	1,144	211	18	13
MD Anderson Personalized Cancer Therapy Program	Single-center	DNA: 11- to 50-gene NGS panel (hotspot)	2,000	2,000	83	4	14
MD Anderson Personalized Cancer Therapy Program	Single-center	DNA: 236 genes	339	339	122	36	15
PREDICT	Single-center	DNA: 182- to 236-gene NGS panel (Foundation Medicine)	347	347	87	25	16
IMPACT/COMPACT	Single-center	DNA: 23- to 50-gene NGS panel (hotspot); Protein: PTEN IHC	1,640	1,640	89	5	17
NCI-MATCH	Multicenter	DNA: 143-gene NGS panel (hotspot); Protein: PTEN, MLH1, MSH2, and Rb IHC	5,540	5,540	686	12	18
Europe							
MOSCATO	Single-center	DNA: 40- to 75-gene NGS panel (hotspot), CGH, WES in limited number of cases; RNA: RNAseq; Protein: MET and phospho-MET IHC	843	843	199	24	19
Asia							
IMPACT-SG	Single-center	DNA: NGS panel (variable number of genes, hotspot); Protein: ALK, cMET, cMYC, FGFR2, HER2, HGF, MMR, NTRK, PTEN, ROS1, and PD-L1 IHC	1,015	1,064	53	5	
IMAC	Single-center	DNA: 50-gene NGS panel (hotspot)	365	365	23	6	20
NEXT 1	Single-center	DNA: 83- to 381-gene NGS panel (hotspot); Protein: PTEN, MET, and HER2 IHC	588	588	60	10	21
TOP-GEAR	Single-center	DNA: 114-gene NGS panel (all exons and selected introns)	187	187	25	13	22
Kyoto University Hospital Study	Single-center	DNA: 215-gene NGS panel (all exons and selected introns)	73	73	9	12	23

Precision Oncology Efforts Across the Globe

Italian Register of Actionable Mutations - RATIONAL study

Study design

Protocol version 2.0 of 08/06/2020

- *Multicenter, observational (primary data collection) and prospective.*
- Sponsor: Federation of Italian Cooperative Oncology Groups (FICOG)
- Coordinating center: National Cancer Institut "Fondazione G. Pascale"- IRCCS, Naples
- PI: Dr. Nicola Normanno;

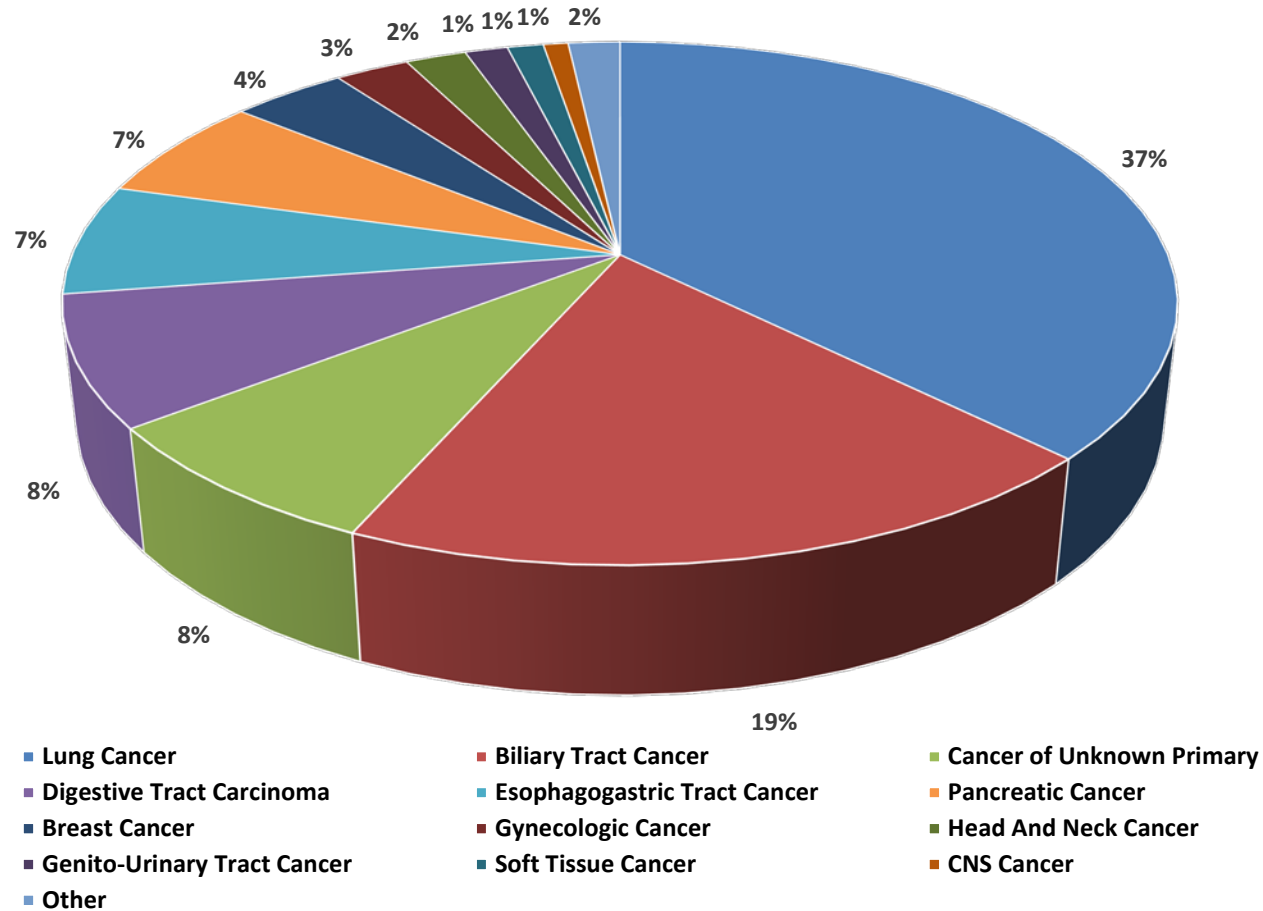
The goal of the study is the creation of a national network for personalized medicine that might offer Italian patients with solid malignancies the chance to access innovative therapies through clinical trials.

The primary aim of the study is:

Description of the frequency of actionable mutations within those patients receiving a genetic and molecular characterization with high throughput methods.

The Italian National Registry of Actionable Mutations The RATIONAL Study

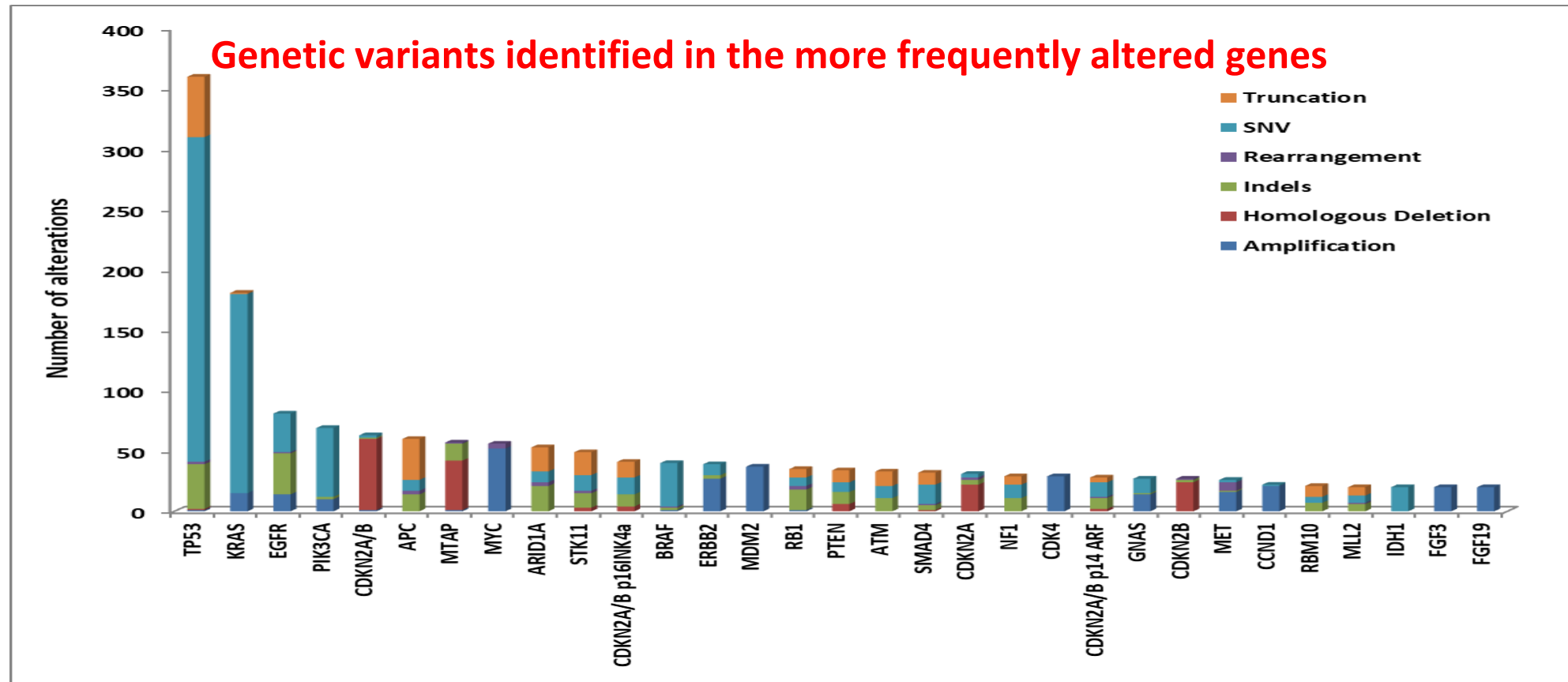
Distribution of tumor types among 1280 patients enrolled in Pathways A (n. 263) and B (n. 1017)



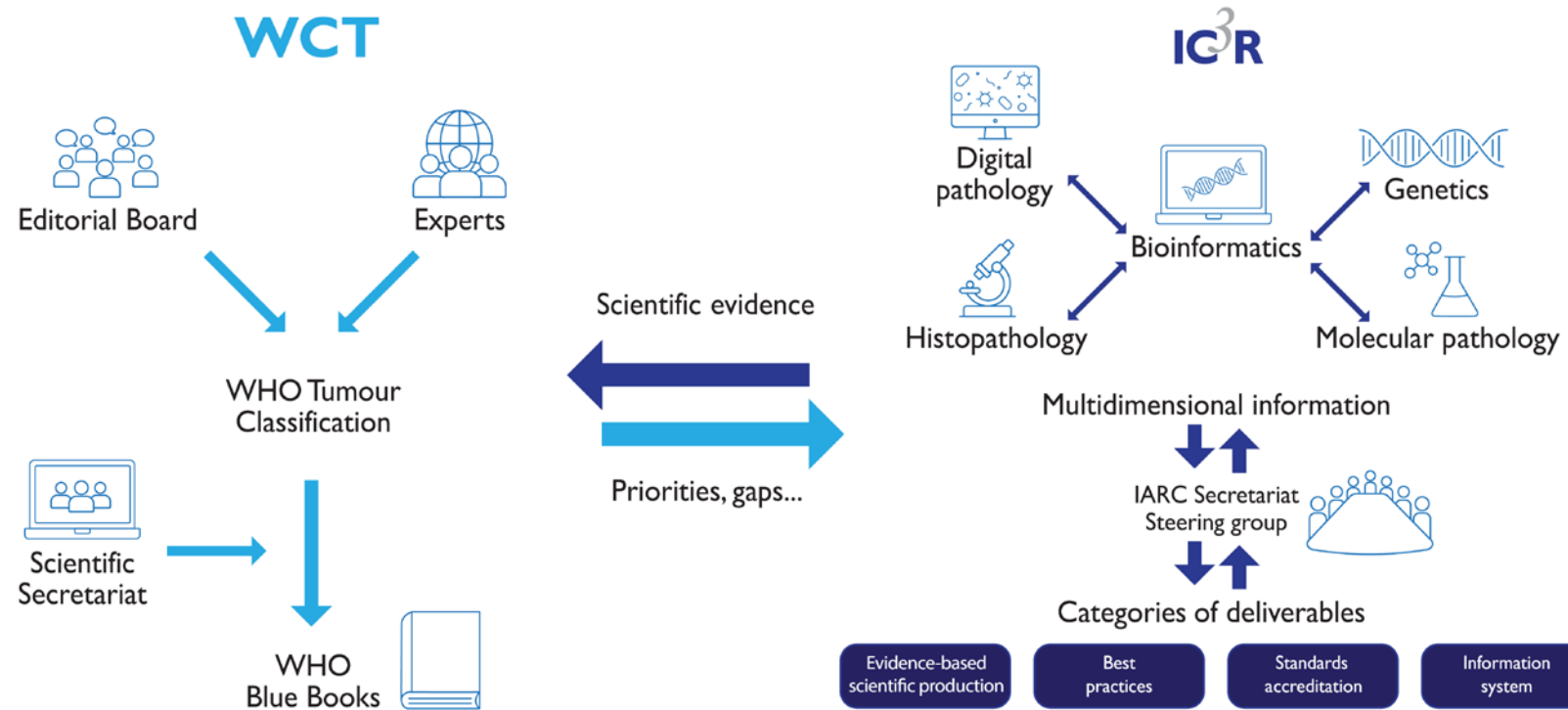
Tumor Type	N
Lung Cancer	479
Biliary Tract Cancer	246
Digestive Tract Carcinoma	103
Cancer of Unknown Primary	101
Esophagogastric Tract Cancer	88
Pancreatic Cancer	83
Breast Cancer	51
Gynecologic Cancer	33
Head And Neck Cancer	27
Other	23
Genito - Urinary Tract Cancer	19
Soft Tissue Cancer	16
CNS Cancer	11

Genetic variants identified in the whole cohort of patients enrolled in pathways A and B

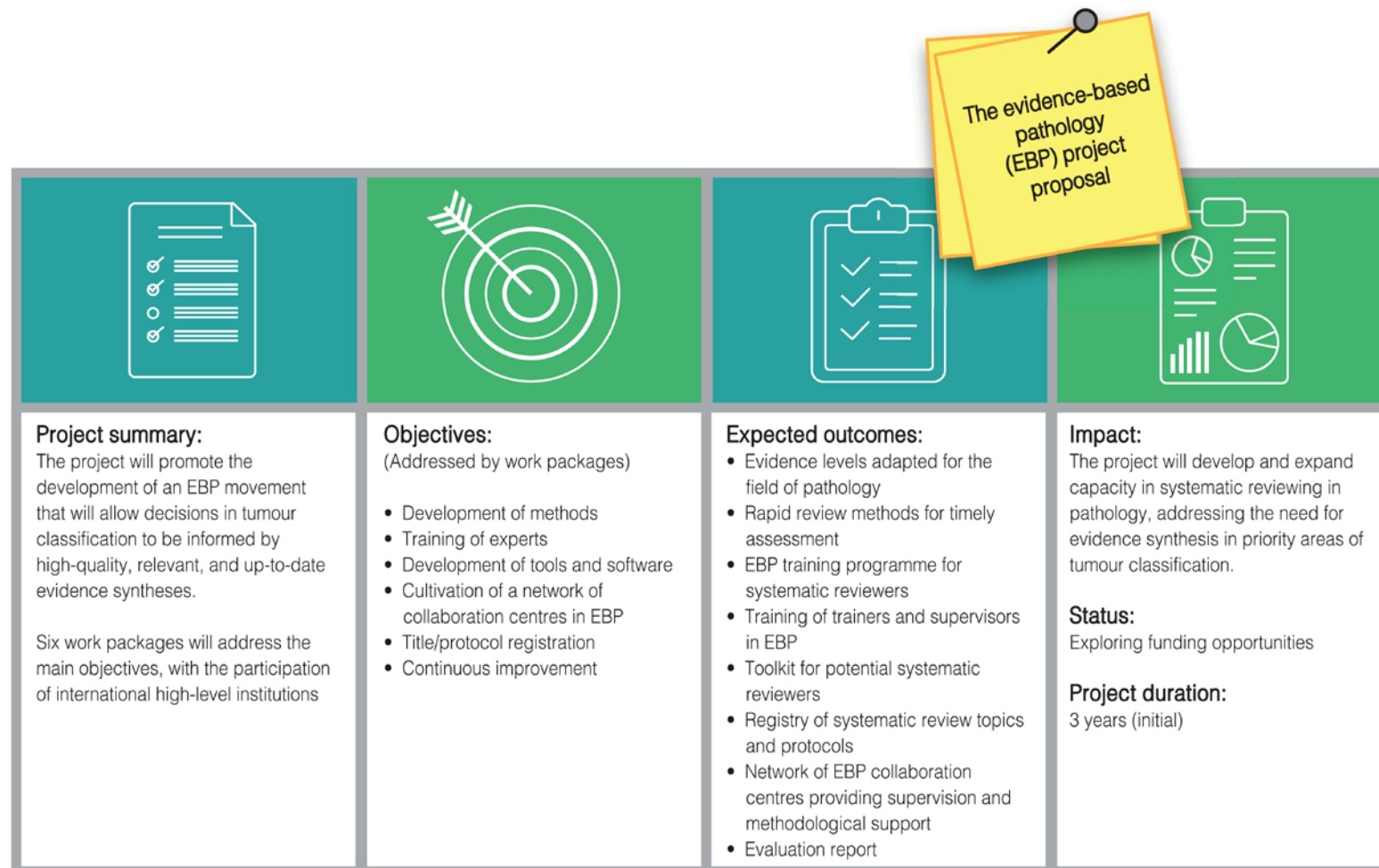
In 688 successfully sequenced samples, 2917 genomic alterations in 262 genes were identified



The International Collaboration for Cancer Classification and Research (IC3R)



The evidence-based pathology project proposal



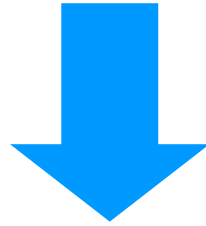
Principali applicazioni dei campioni biologici nella ricerca oncologica

- Per l'identificazione e lo studio di biomarcatori
- Per lo studio dei meccanismi responsabili della patogenesi e progressione dei tumori umani
- Per lo studio dei meccanismi coinvolti nella sensibilità/resistenza al trattamento e nell'outcome clinico

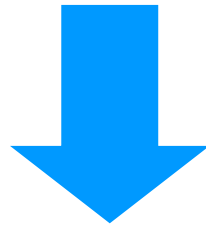
Il ciclo del campione biologico



Standardizzazione dei metodi di raccolta e di pre-trattamento del campione



Conservazione delle proprietà chimiche, biologiche e morfologiche del campione



CAMPIONI BIOLOGICI DI ELEVATA
QUALITA'



Utilizzo del campione per usi non previsti

I campioni non sono quasi mai raccolti in funzione di un unico progetto di ricerca, ma in vista di un numero indeterminato di ricerche future

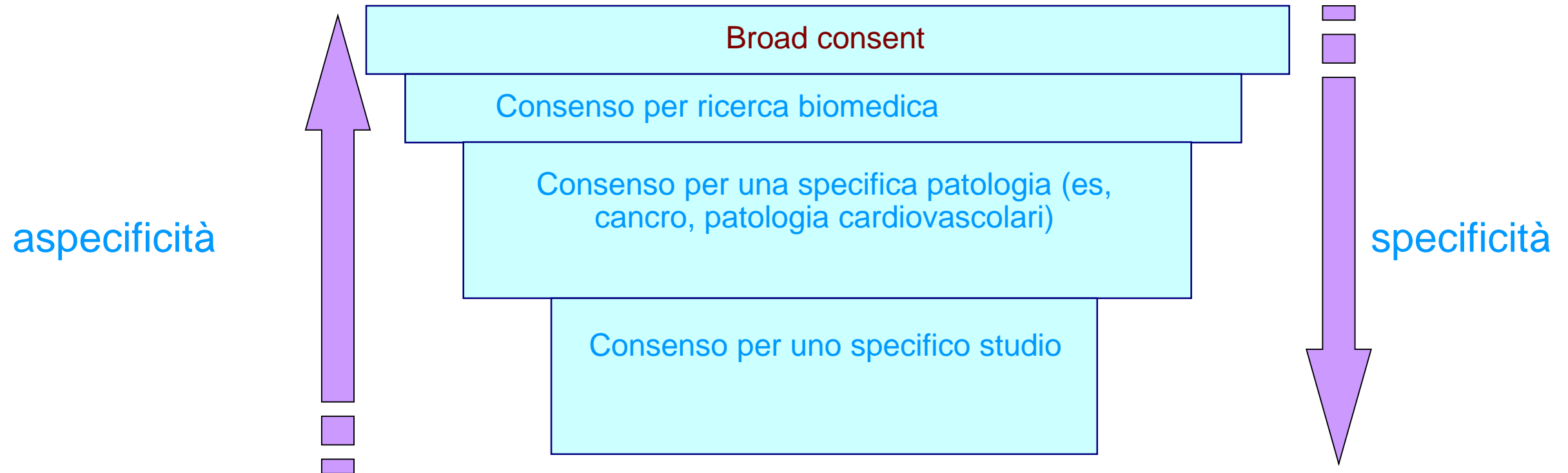
Molte indagini non sono prevedibili, in quanto spesso correlate allo sviluppo delle conoscenze scientifiche; altre vengono pianificate solo in momenti successivi

Occorre avere un nuovo consenso?

Tipologie di consenso informato

- A) Consenso specifico** il campione può essere utilizzato solo per la singola ricerca cui la donazione è finalizzata
- B) Consenso ristretto** il campione può essere utilizzato solo per ricerche omologhe a quelle cui la donazione è finalizzata
- C) Consenso ampio** secondo cui il campione può essere sempre utilizzato

Consenso informato



Tanto più ampio è il consenso, tanto più aumenta l'autonomia dello sperimentatore



Autorizzazione generale al trattamento di dati personali effettuato per scopi di ricerca scientifica; Garante per la protezione dei dati personali, 15 dicembre 2016

Nel caso in cui, successivamente alla raccolta del consenso, si voglia utilizzare il campione per uno studio diverso da quello per cui si è ottenuto il consenso, occorrerà **ricontattare il soggetto** a cui il campione si riferisce e ottenere **un nuovo consenso**

Centro di coordinamento nazionale dei comitati etici

26/07/2022 – Versione n. 1

Ricerca osservazionale: un pilastro nel processo di produzione di conoscenza

Premessa

Questo documento ha come oggetto gli studi osservazionali intesi nel loro significato di studi caratterizzati dall'assenza di intervento attivo da parte dei ricercatori, quindi definiti, in questa sede, come studi nei quali il ricercatore non determina l'assegnazione dei soggetti ai diversi gruppi di studio, ma si limita a registrare (osservare) quello che avviene nella realtà.

A) Per quanto riguarda **il trattamento dei dati personali**, appare opportuno raccomandare la **massima semplificazione degli adempimenti relativi**, rimuovendo o limitando il più possibile gli ostacoli formali che un'interpretazione della normativa, improntata ad un approccio prevalentemente "interventistico" e "monouso", tuttora frapponne all'utilizzo e riutilizzo dei dati di ricerca.

In quanto "fonte" di conoscenze significative per la comunità scientifica, tali dati debbono poter circolare il più liberamente possibile all'interno di essa. Soprattutto quando le finalità della ricerca siano osservazionali (nel senso qui considerato), dovrebbe quindi potersi **fare ricorso a basi giuridiche alternative per agevolare il (ri)trattamento dei dati de quibus**, senza dovere ogni volta dipendere da un nuovo consenso dell'interessato – con l'unico limite di una preventiva idonea pseudonimizzazione/cifratura dell'identità del paziente - **venendosi così a contemperare ragionevolmente ed efficacemente "diritto dell'individuo e interesse della collettività" (art. 32 Cost.).**

La medicina di precisione nel 2030

