

Oncologia di precisione stato dell'arte *Prof Filippo de Braud*

Ordinario Oncologia Medica Università di Milano

*Direttore Dipartimento Oncologia & Ematologia
Fondazione IRCCS Istituto Nazionale Tumori, Milano*

Prof Filippo de Braud Conflict of interest

Relationship	Company/Organization
Consulting	Pierre Fabre, Mattioli 1885, MCCann Health, MSD, IQVIA, Novartis, Indena, Incyte, Taiho, Menarini, Roche
Advisory arrangements	Sanofi, BMS, Taiho, Incyte
P.I.	AnHeart Therapeutics, Apollomics, AstraZeneca, Basilea Pharmaceutica, Bayer Healthcare, Boehringer Ingelheim, BMS, F. Hoffmann-La Roche, Incyte, Itanet, Janssen-Cilag, Kymab, Loxo Oncology, MedImmune, Merck KGaA, Novartis, Tesaro, Zymeworks
Speakers' bureau	Speaker's fees from Nadirex, ESO, Dephaforum, Ambrosetti, Motore Sanità, Effetti, Events, Fare Comunicazione, Itanet, Nadirex, BMS, Accmed, Idea-z, Dynamicom Education, Sanofi, AstraZeneca
Other interests	Traveling expenses from Incyte, BMS, Novartis, Sanofi, AstraZeneca

When the story of modern Precision Oncology begins....



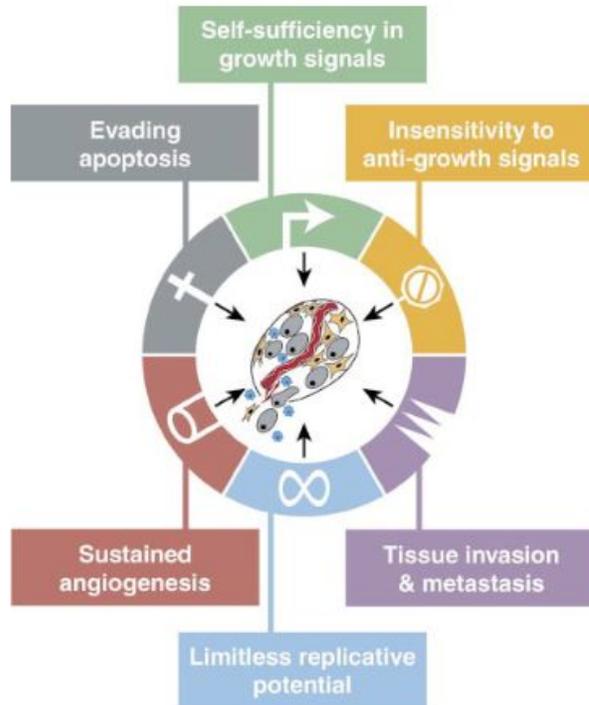
The Hallmarks of Cancer

Review

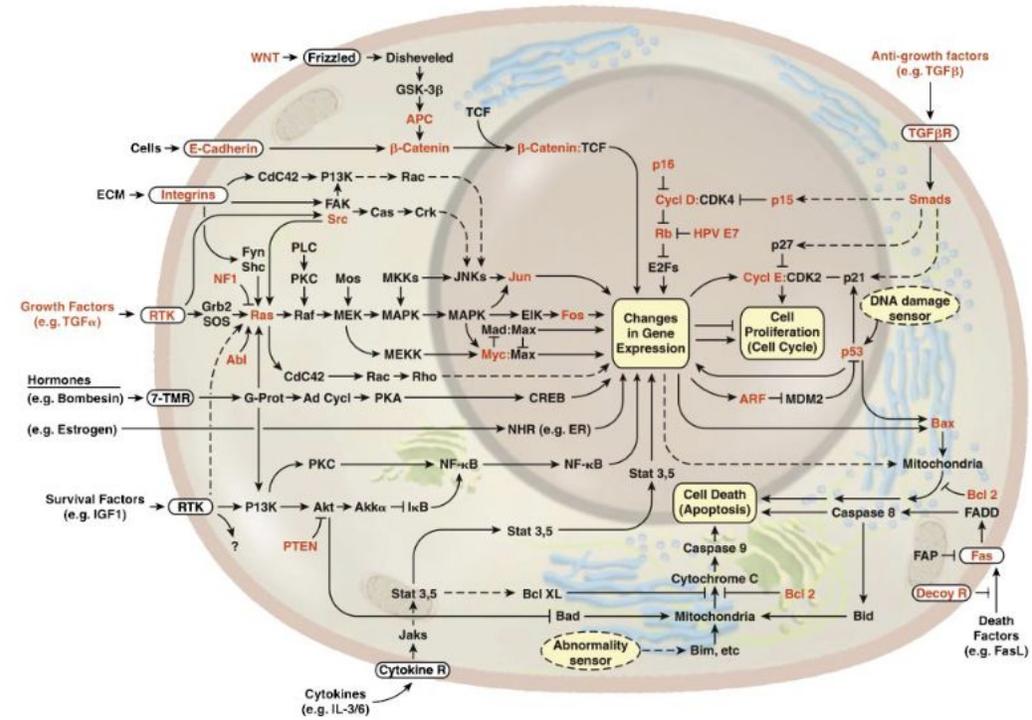
Douglas Hanahan* and Robert A. Weinberg†

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Component	Acquired Capability	Example of Mechanism
	Self-sufficiency in growth signals	Activate H-Ras oncogene
	Insensitivity to anti-growth signals	Lose retinoblastoma suppressor
	Evading apoptosis	Produce IGF survival factors
	Limitless replicative potential	Turn on telomerase
	Sustained angiogenesis	Produce VEGF inducer
	Tissue invasion & metastasis	Inactivate E-cadherin



Aims & Scope

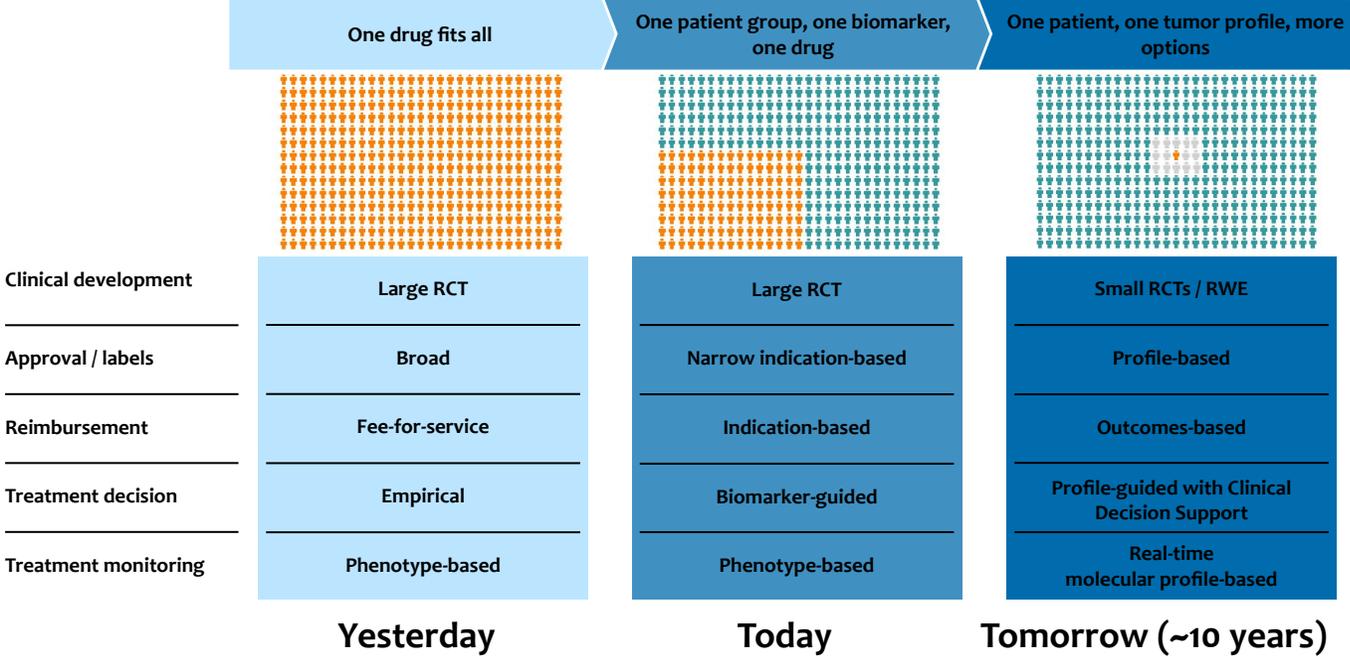
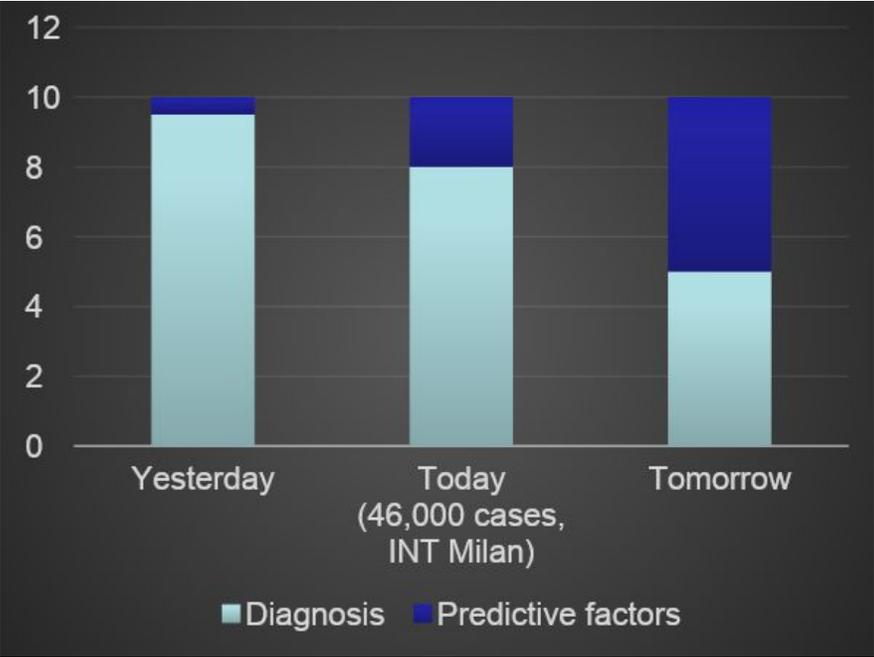
npj Precision Oncology is an international, peer-reviewed journal committed to publishing cutting-edge scientific research in all aspects of precision oncology from basic science to translational applications to clinical medicine.

The journal defines precision oncology as cancer diagnosis, prognosis, prevention and/or treatment tailored specifically to the individual patient based on the genetic and/or molecular profile of the patient. High-impact articles that entail relevant studies using panomics, molecular, cellular and/or targeted approaches in the cancer research field are considered for publication. All areas of precision oncology from basic research to clinical applications will be considered.

Featured topics include carcinogenesis, targeted immunotherapy, mechanism-based therapies targeting specific cellular signaling pathways, genetic risk factors, miRNAs, tumor microenvironment, cancer metabolism and cancer stem cells – all in the context of diagnosis/prognosis/therapy, drug resistance mechanisms, reoccurrence, intervention strategies, emerging clinical and translational aspects.

The journal publishes original basic science, translational and clinical research articles, including clinical trials, especially when informed by genetic/molecular profile data.

Pathology lab duties are changing



REVIEW ARTICLE

Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group

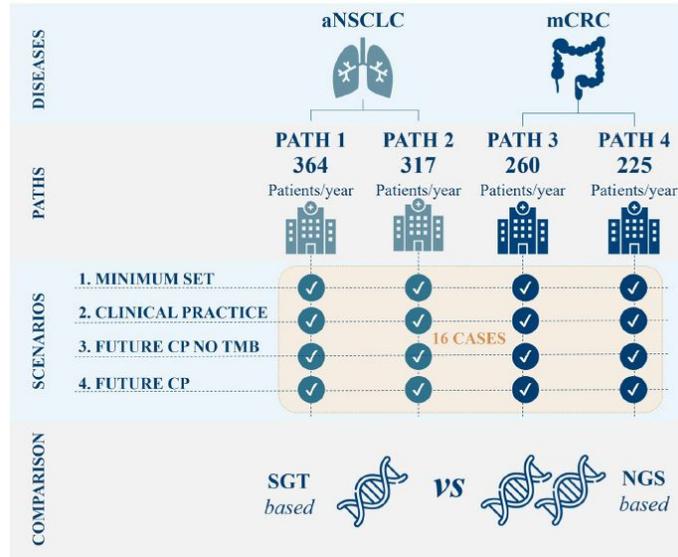
F. Mosele¹, J. Remon², J. Mateo³, C. B. Westphalen⁴, F. Barlesi¹, M. P. Lolkema⁵, N. Normanno⁶, A. Scarpa⁷, M. Robson⁸, F. Meric-Bernstam⁹, N. Wagle¹⁰, A. Stenzinger¹¹, J. Bonastre^{12,13}, A. Bayle^{1,12,13}, S. Michiels^{12,13}, I. Bièche¹⁴, E. Rouleau¹⁵, S. Jezdic¹⁶, J.-Y. Douillard¹⁶, J. S. Reis-Filho¹⁷, R. Dienstmann¹⁸ & F. André^{1,19,20*}



Table 2. Summary recommendations

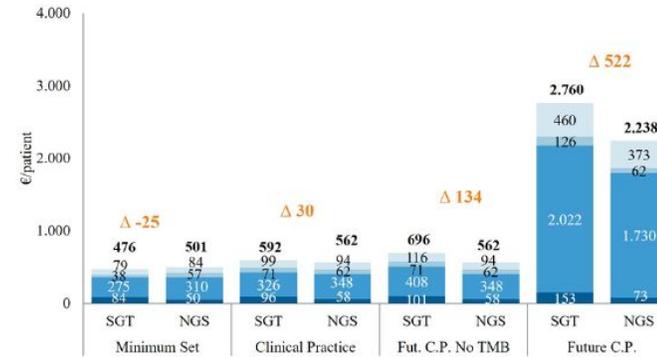
Tumour types	General recommendations for daily practice	Recommendation for clinical research centres	Special considerations for patients
Lung adenocarcinoma	Tumour multigene NGS to assess level I alterations. Larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy (drug included ³) and if they report accurate ranking of alterations. NGS can either be done on RNA or DNA, if it includes level I fusions in the panel.		Using large panels of genes could lead to few clinically meaningful responders, not detected by small panels or standard testings. In this context and outside the diseases where large panels of genes are recommended, ESMO acknowledges that a patient and a doctor could decide together to order a large panel of genes, pending no extra cost for the public health care system, and if the patient is informed about the low likelihood of benefit.
Squamous cell lung cancers	No current indication for tumour multigene NGS		
Breast cancers	No current indication for tumour multigene NGS		
Colon cancers	Multigene tumour NGS can be an alternative option to PCR if it does not result in additional cost.		
Prostate cancers	Multigene tumour NGS to assess level I alterations. Larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy and if they report accurate ranking of alterations.		
Gastric cancers	No current indication for tumour multigene NGS		
Pancreatic cancers	No current indication for tumour multigene NGS		
Hepatocellular carcinoma	No current indication for tumour multigene NGS		
Cholangiocarcinoma	Multigene tumour NGS could be recommended to assess level I alterations. Larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy (drug included ³) and if they report accurate ranking of alterations. RNA-based NGS can be used.		
Others	Tumour multigene NGS can be used in ovarian cancers to determine somatic <i>BRCA1/2</i> mutations. In this latter case, larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy (drug included ³) and if they report accurate ranking of alterations. Large panel NGS can be used in carcinoma of unknown primary. It is recommended to determine TMB in cervical cancer, salivary cancer, thyroid cancers, well-to-moderately differentiated neuroendocrine tumours, vulvar cancer, pending drug access (and in TMB-high endometrial and SCL cancers if anti-PD1 antibody is not available otherwise).		

NGS costs in Italy, single-gene vs. NGS testing



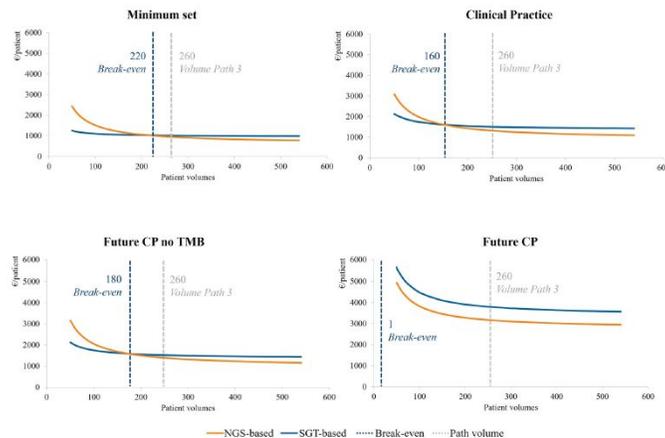
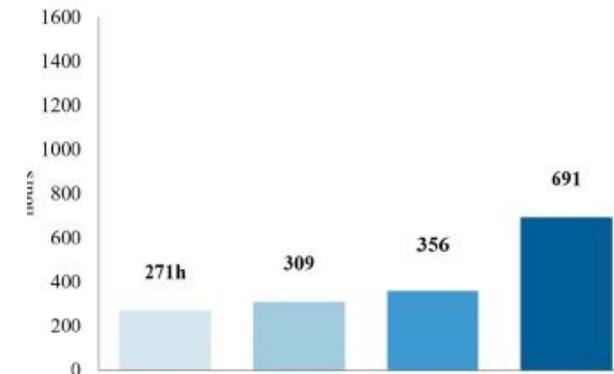
Mean cost per patient

Path 2 - aNSCLC



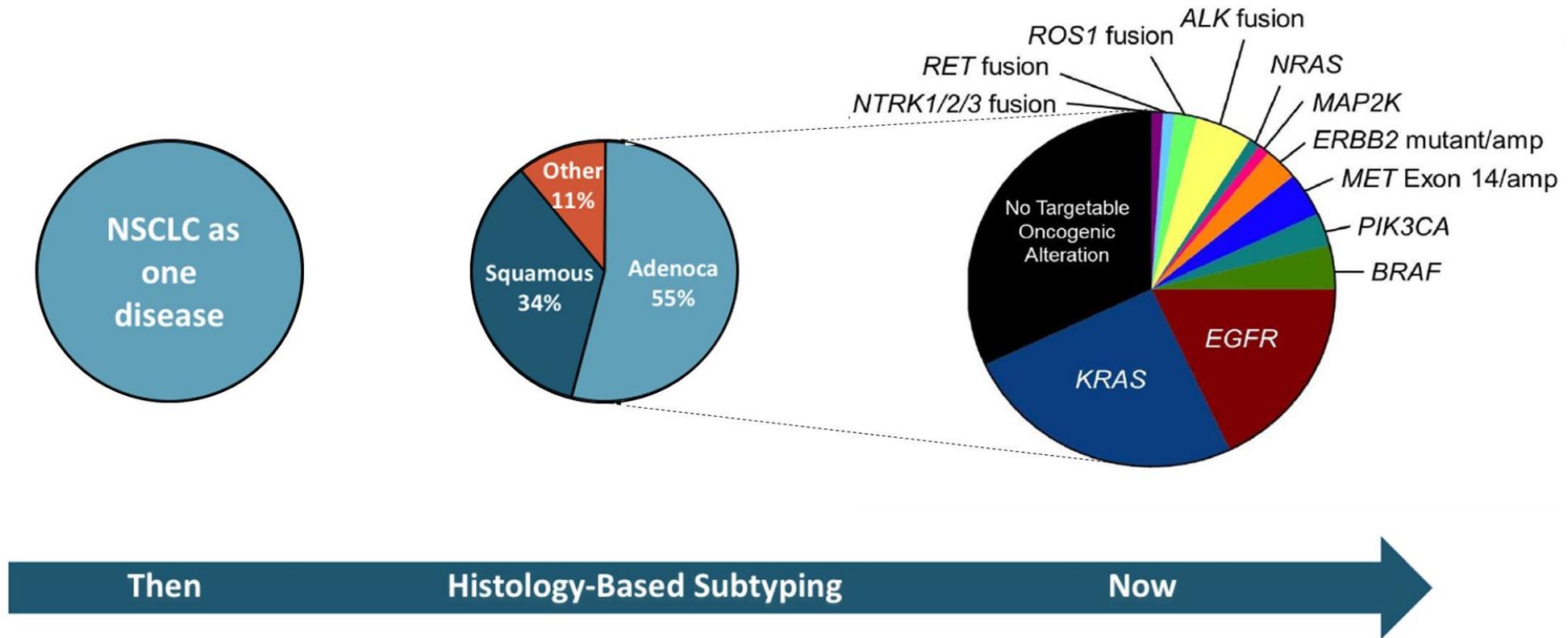
ΔSGT → NGS overall personnel time savings

Path 2 - aNSCLC

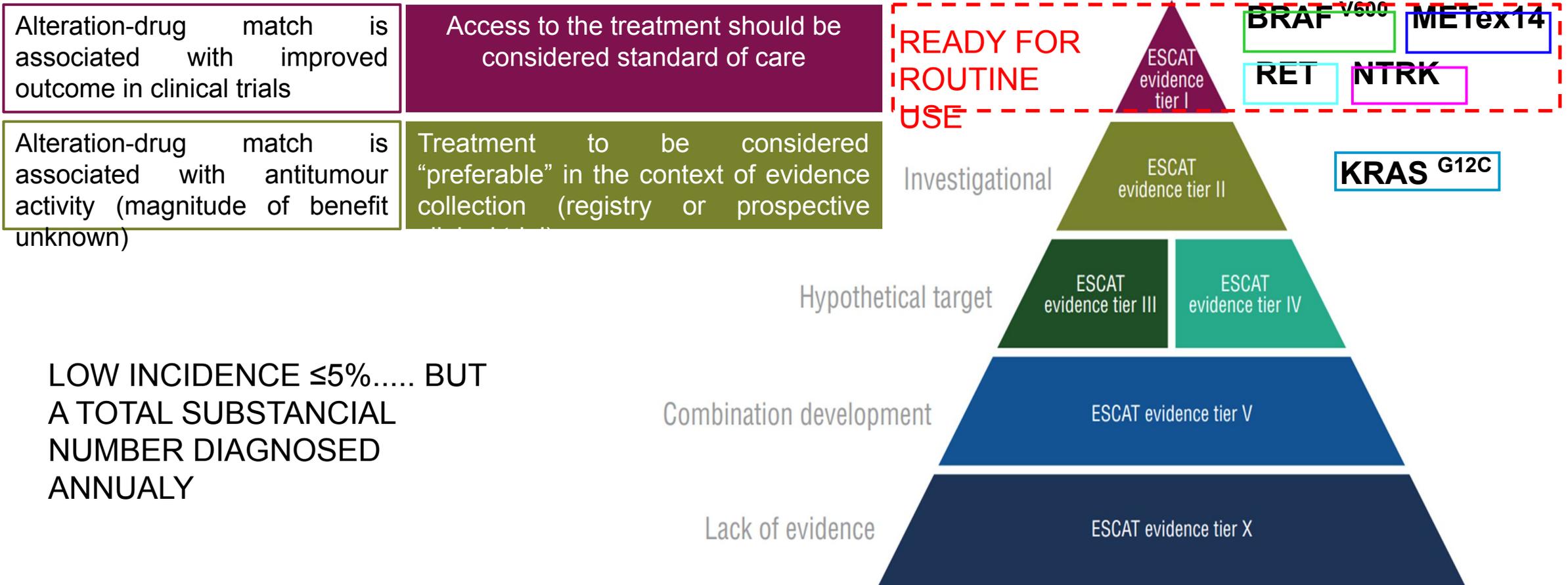


Non small cell Lung Cancer (NSCLC)

NSCLC: NOT one disease but many



ESMO Scale of Clinical Actionability for molecular Targets (ESCAT)

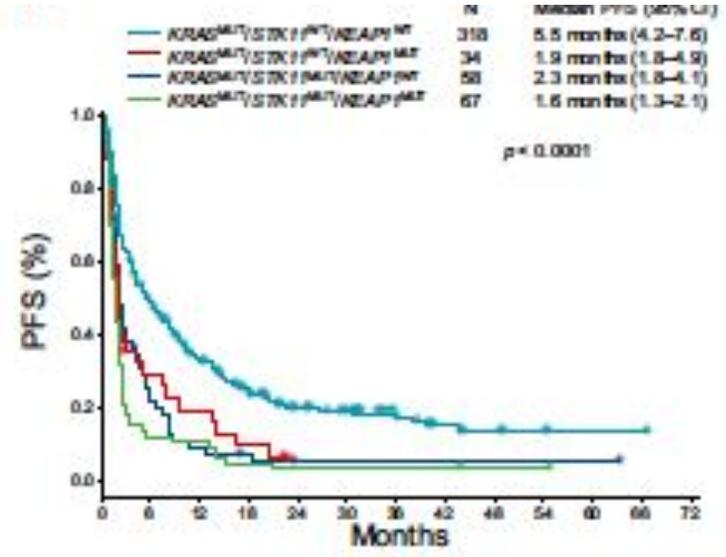
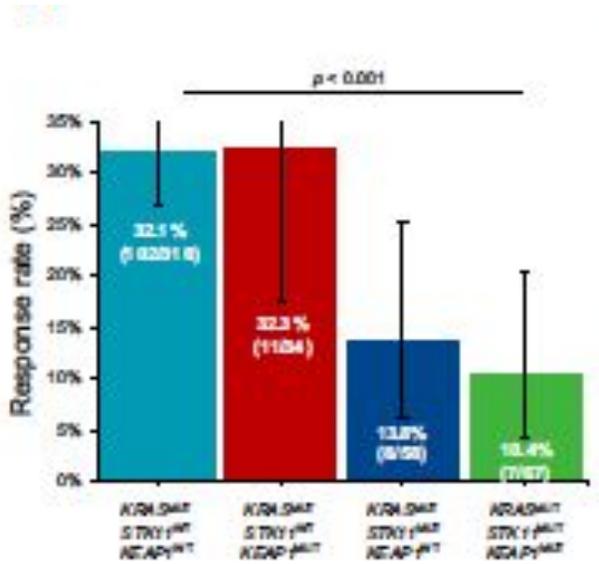


- BRAF, RET, MET, and NTRK are **RARE alterations** in NSCLC, but considered together they represent significant numbers
- Targeted therapies work in these genetic alterations and clinical results obtained emphasize the importance of **MOLECULAR TESTING** at the time of diagnosis
- Randomized studies are unpractical and limited by the poor accrual and evolution of standard-of-care
- The therapeutic strategies after progression are still to be defined
- The **role of IO must be individualized** according to the alteration, to be discussed (no clear benefit in RET/NTRK fusions, potential in some subset of BRAF/METex14, standard in KRASG12C)

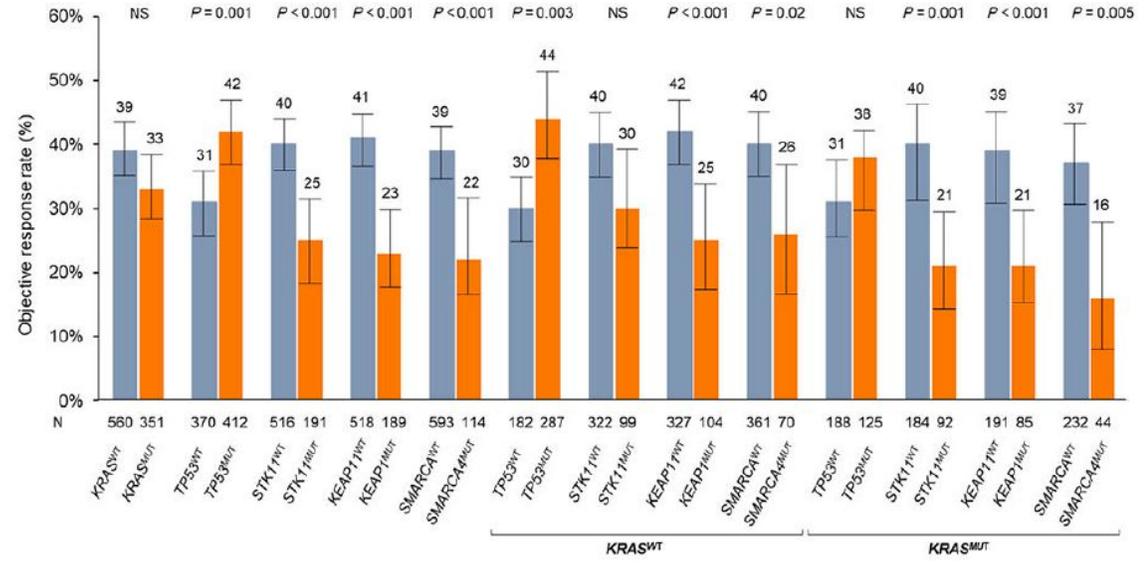
1L Treatment for NSCLC patients with PD-L1 $\geq 50\%$

Who are early progressors ?

PD1 Inhibitors in PD-L1 $\geq 50\%$

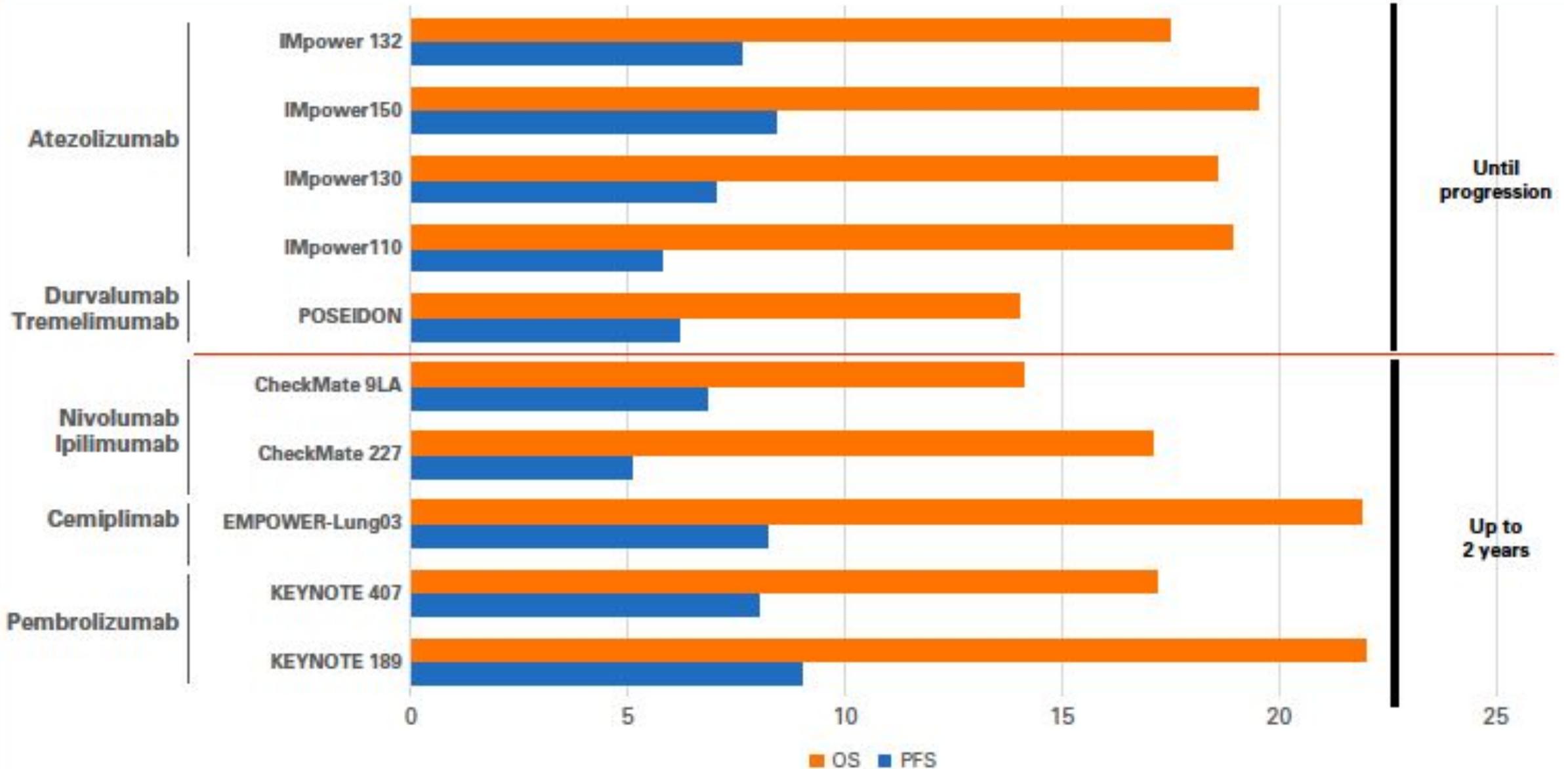


PD1 Inhibitors plus Chemo in PD-L1 all comers



KRAS/STK11/KEAP1 co-mutations predict lower efficacy of Immunotherapy

IO Duration in advanced NSCLC - Trials



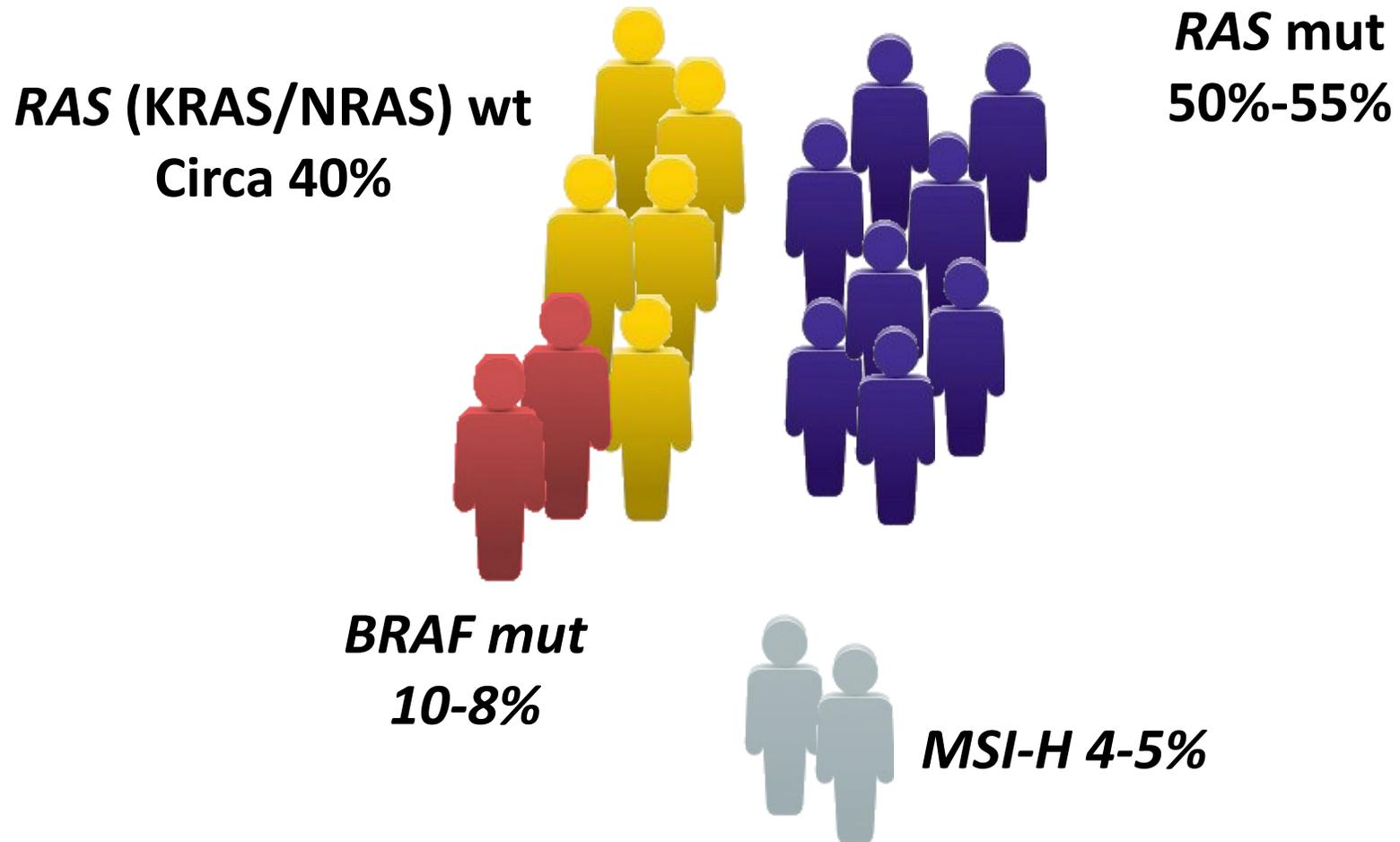
Colon-Rectal Cancer (CRC)

Tissue biomarkers in colorectal cancer

-  Target tx not approved
-  Target tx approved

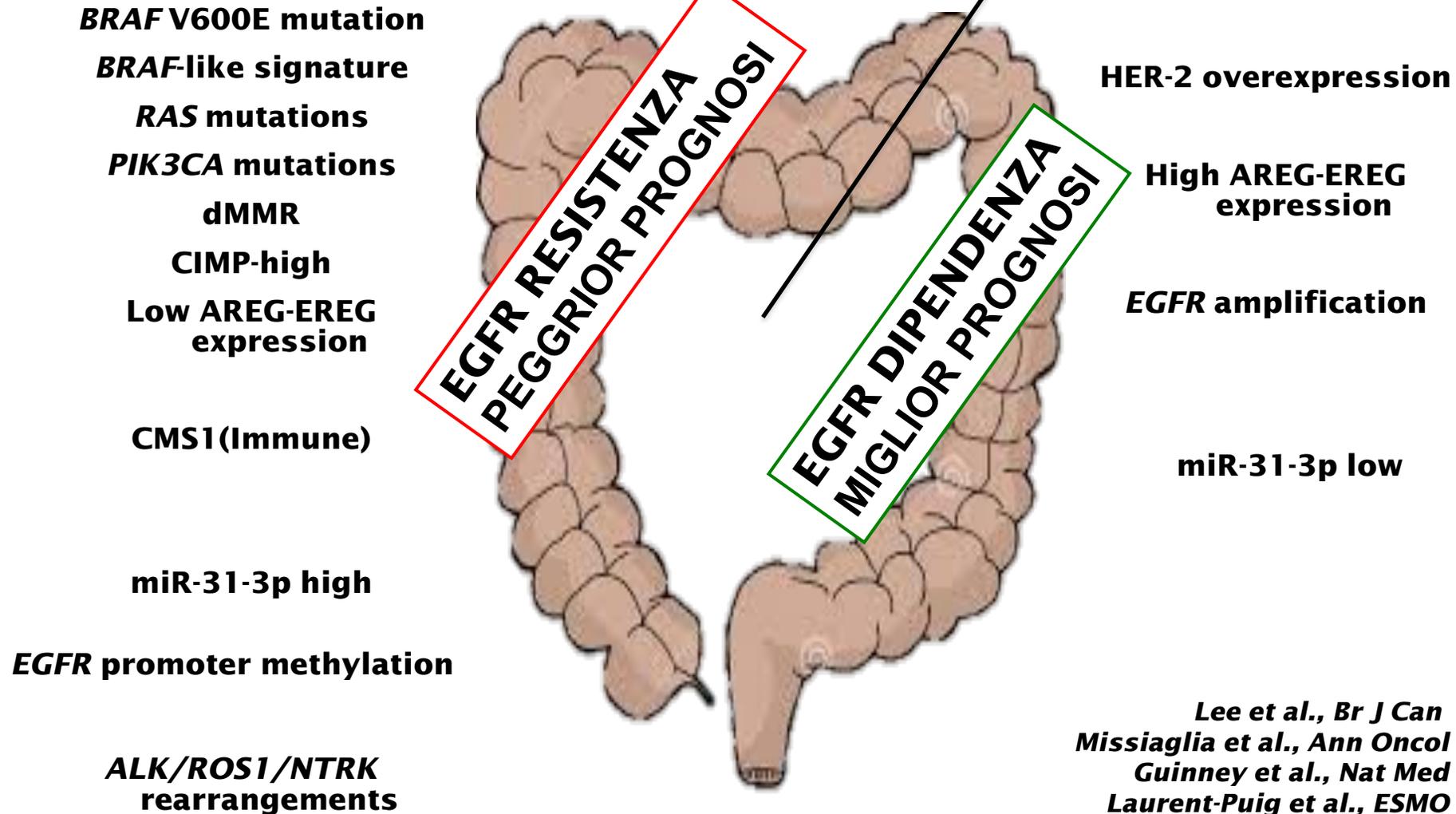
	Alterations	Prevalence	Targetability evidence	Enrichment
	 RAS mutations	55-60%	NO	-
	 KRAS G12C mutation	3%	YES	-
	 BRAF V600E mutation	8-10%	YES	(> if right colon, RAS wt, MSI)
	 PI3K mutations	8%	Probably YES	-
	 Microsatellite instability	5%	YES	(> if right colon, BRAF mut)
	 BRAF non-V600E mutations	2%	NO	(> if left/rectum colon, RAS mut, MSS)
	 HER2 amplification	2%	YES	(> if left/rectum colon, RAS/BRAF wt)
	 MET amplification	2%	Case report	-
	 POLE mutations	1%	YES	(> if right colon, MSS)
	 TRK1-3, ALK, ROS1 translocations	<1%	YES	(> if right colon, RAS/BRAF wt, MSI)
	 RET translocations	<1%	Case report	(> if right colon, RAS/BRAF wt, MSI)
	 MGMT silencing	40%	YES	(> if right colon, RAS mut, MSS)

Molecular Profile mCRC

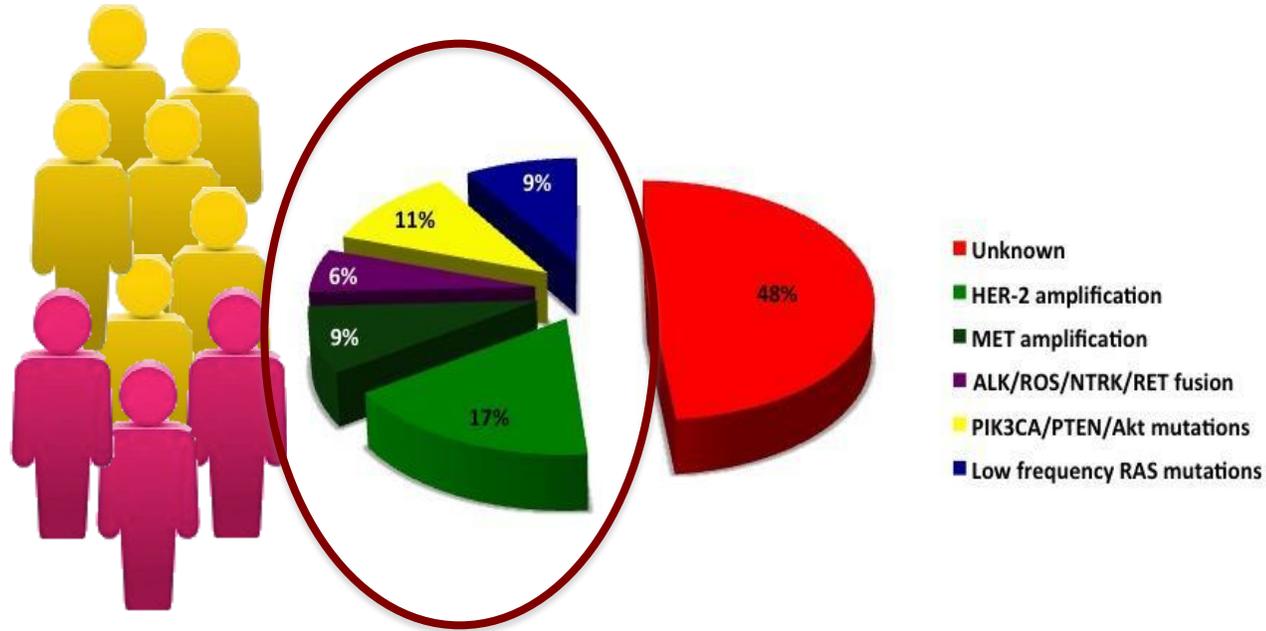


I punti chiave: sede del tumore primitivo

Doppietta + BV o doppietta + anti-EGFR nei pazienti RAS wt: COME SCEGLIERE?



RAS wt

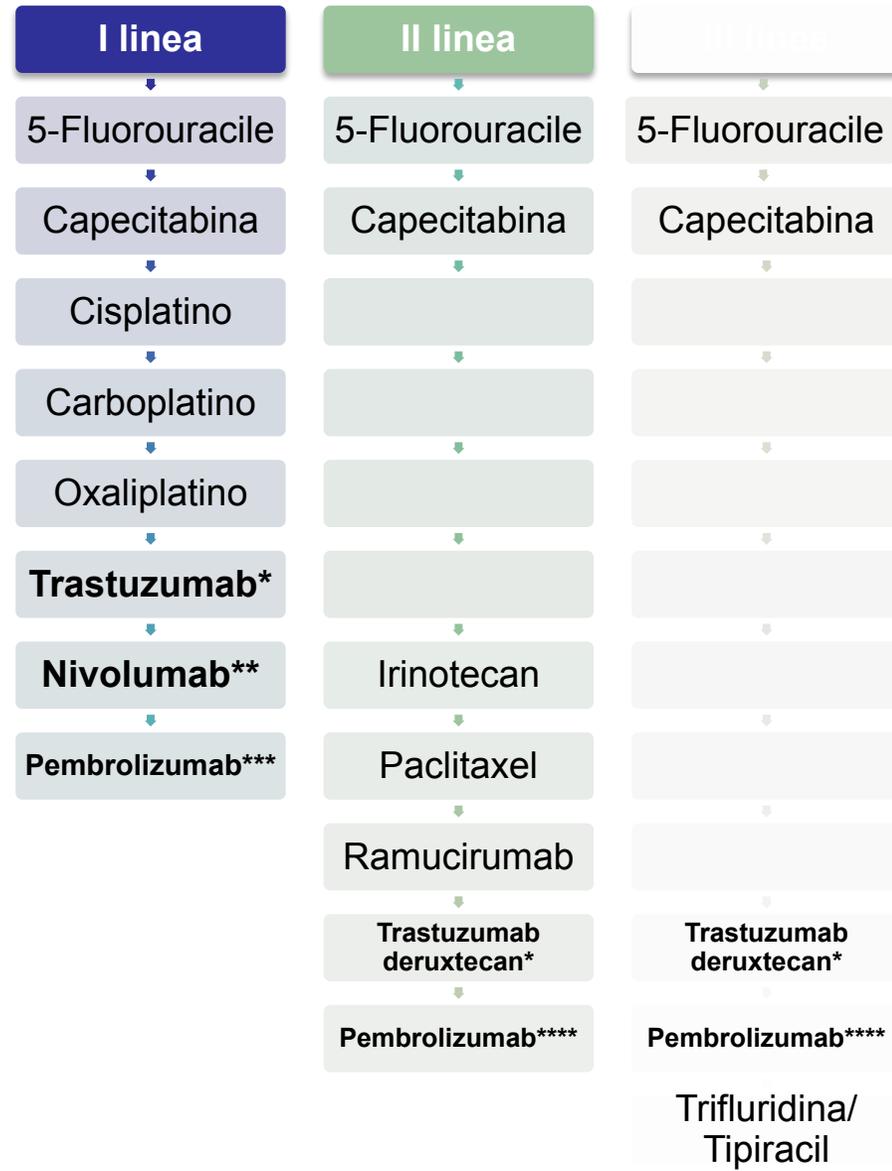


PRESSING Panel:

- **PI3K/PTEN/Akt and MAPks pathway' activating mutations**
- **Her2 amplifications or mutations**
- **MET amplifications**
- **ALK/ROS1/NTRKs and RET fusions**

Gastric Cancer

Farmaci disponibili in pratica clinica e rimborsati nel CG/CGEG avanzato



*HER2+; ** PDL-1CPS \geq 5; **** PDL-1 CPS \geq 1; *****MSI-H

Emerging targets and therapies

FGFR 1-4 and
Monoclonal
Antibodies

Her 3
antibodies and
ADC

KRAS
amplifications
and mutations

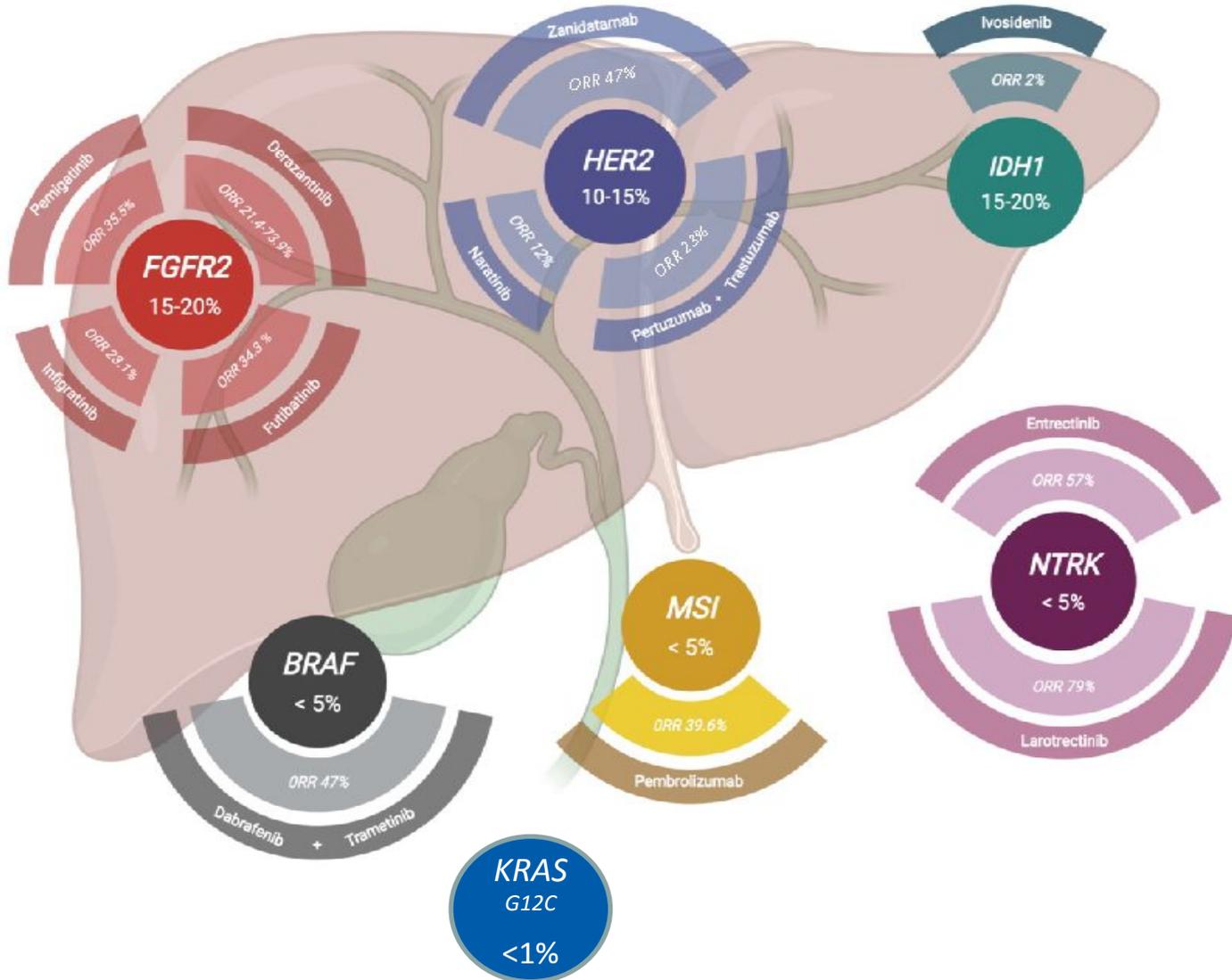
Bispecific
antibody

New immune
checkpoints
(LAG 3)

BiTE and
chemokines

Biliary tract Tumors

In real life: BTC ARE FULL OF **ACTIONABLE TARGETS**



When to sequence?
As Soon As Possible!

How?
DNA-based NGS
(+/-RNA-based NGS, **preferred**)
Liquid biopsy only for selected cases

DOES **SYSTEMIC NGS** FOR BTC IMPROVE CARE?

Multicentric study assessing **real-life clinical actionability** of molecular alterations identified with expanded NGS for **587 patients (pts)** affected by advanced BTCs treated at 5 Italian institutions (2016-2022)

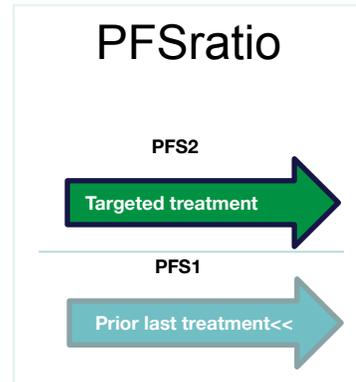
FGFR2i
[n=63 (66%)]

Ivosidenib
[n=15 (16%)]

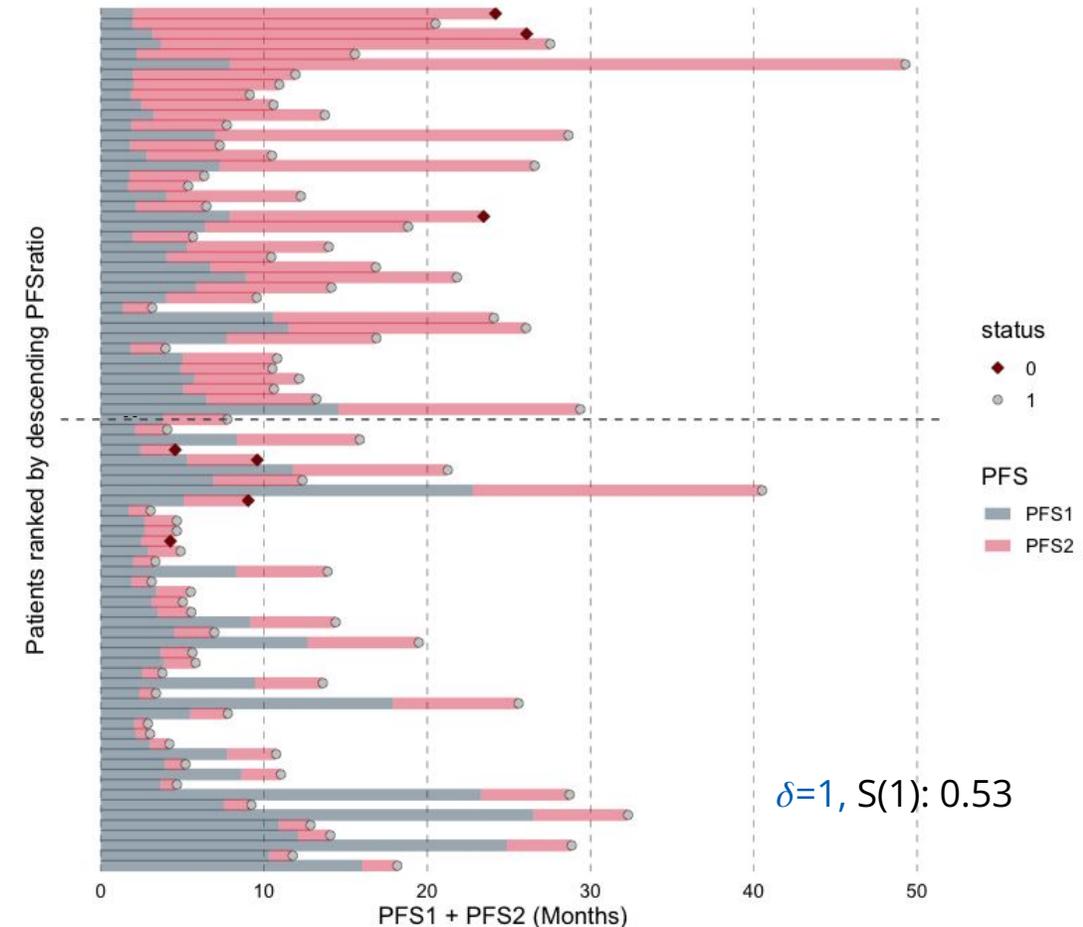
BRAFi-MEKi
[n=9 (9%)]

ERBB2i
[n=4 (4%)]

ICIs
[n=3 (3%)]



δ parameter = 1



Melanoma

Checkpoint inhibitors in high-risk stage III resectable melanoma

Standard of care pre-2010		Surgery	Observation	Med RFS 25.6 mo ¹ 5-yr RFS ~35%
		Surgery	Adjuvant IFN- α	HR 0.82 vs obn (DFS) ²
2015 EORTC 18071		Surgery	Adjuvant CTLA-4	HR 0.75 vs obn (RFS) ³ 5-yr RFS ~41%
2017-18 KEYNOTE 054 CheckMate 238		Surgery	Adjuvant PD-1	HR 0.57 vs surgery alone (RFS) ⁴ HR 0.65 vs CTLA-4 (RFS) ⁵ 5-yr RFS ~55%
2022 SWOG S1801	Neoadjuvant PD-1	Surgery	Adjuvant PD-1	HR 0.58 vs adjuvant PD-1 (EFS) ⁶
2024 NADINA	Neoadjuvant PD-1 plus CTLA-4	Surgery	Response-directed adjuvant PD-1 or BRAF/MEK	HR 0.32 vs adjuvant PD-1 (EFS) ⁷

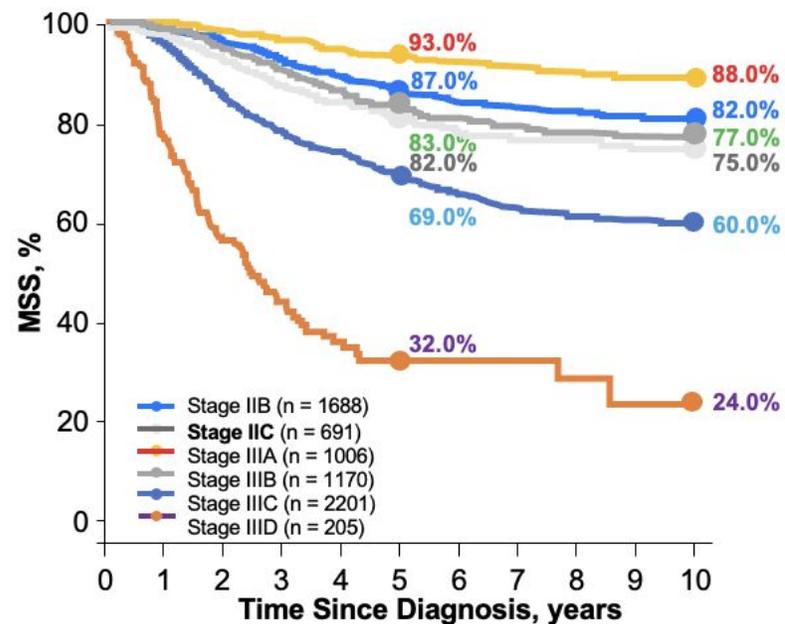
Prognosis of localized cutaneous melanoma

Despite curative intent surgery, 12-76% of patients still died due to metastatic disease

8th Ed		
Stage	5y MSS*	10y MSS*
IA	99%	98%
IB	97%	94%
IIA	95%	88%
IIB	87%	82%
IIC	82%	75%
IIIA	93%	88%
IIIB	83%	77%
IIIC	69%	60%
IIID	32%	24%

* Melanoma-specific survival

Melanoma Specific Survival by Subgroup (AJCC 8)^{1,2}

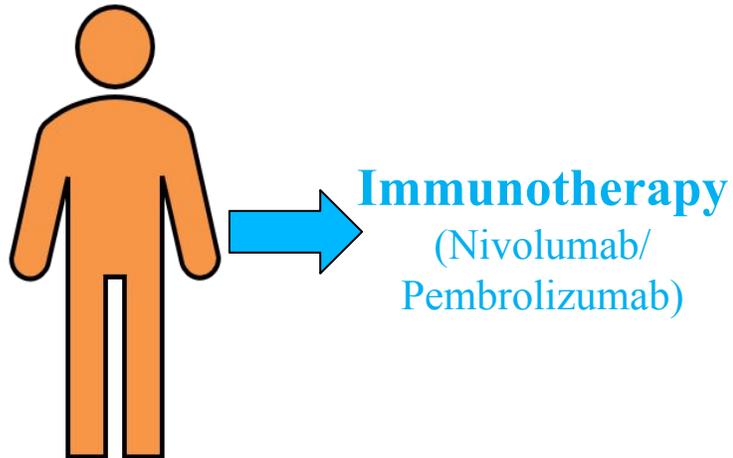


AJCC, American Joint Committee on Cancer; AJCC 8, American Joint Committee on Cancer's *Cancer Staging Manual*, 8th edition; MSS, melanoma-specific survival.

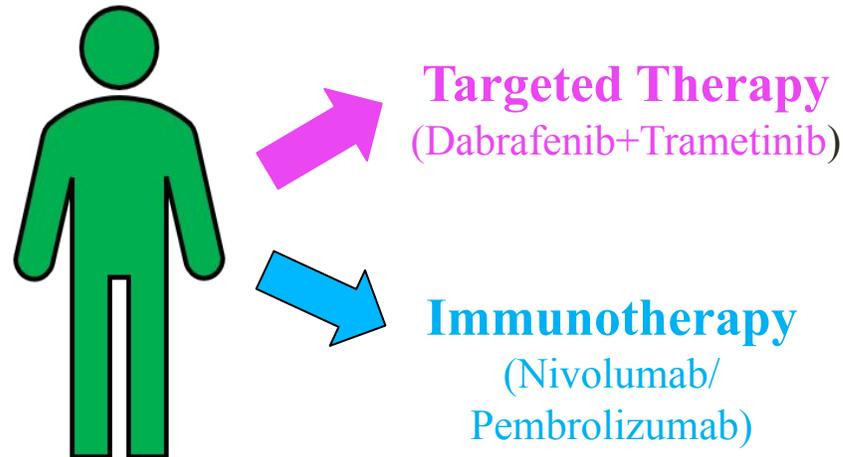
1. Amin MB, Edge S, Greene F, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer International Publishing; 2017; 2. Gershenwald JE, et al. *CA Cancer J Clin*. 2017;67:472-492.

Treatment Strategies for Adjuvant Melanoma

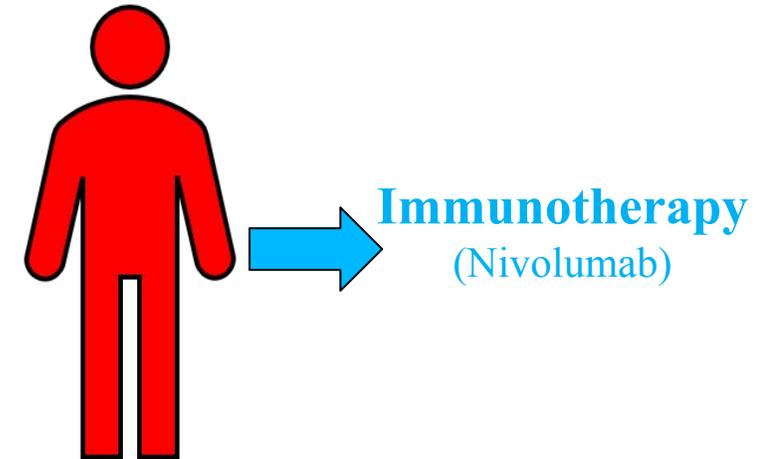
Wild-Type Stage III



BRAF^{V600} Stage III

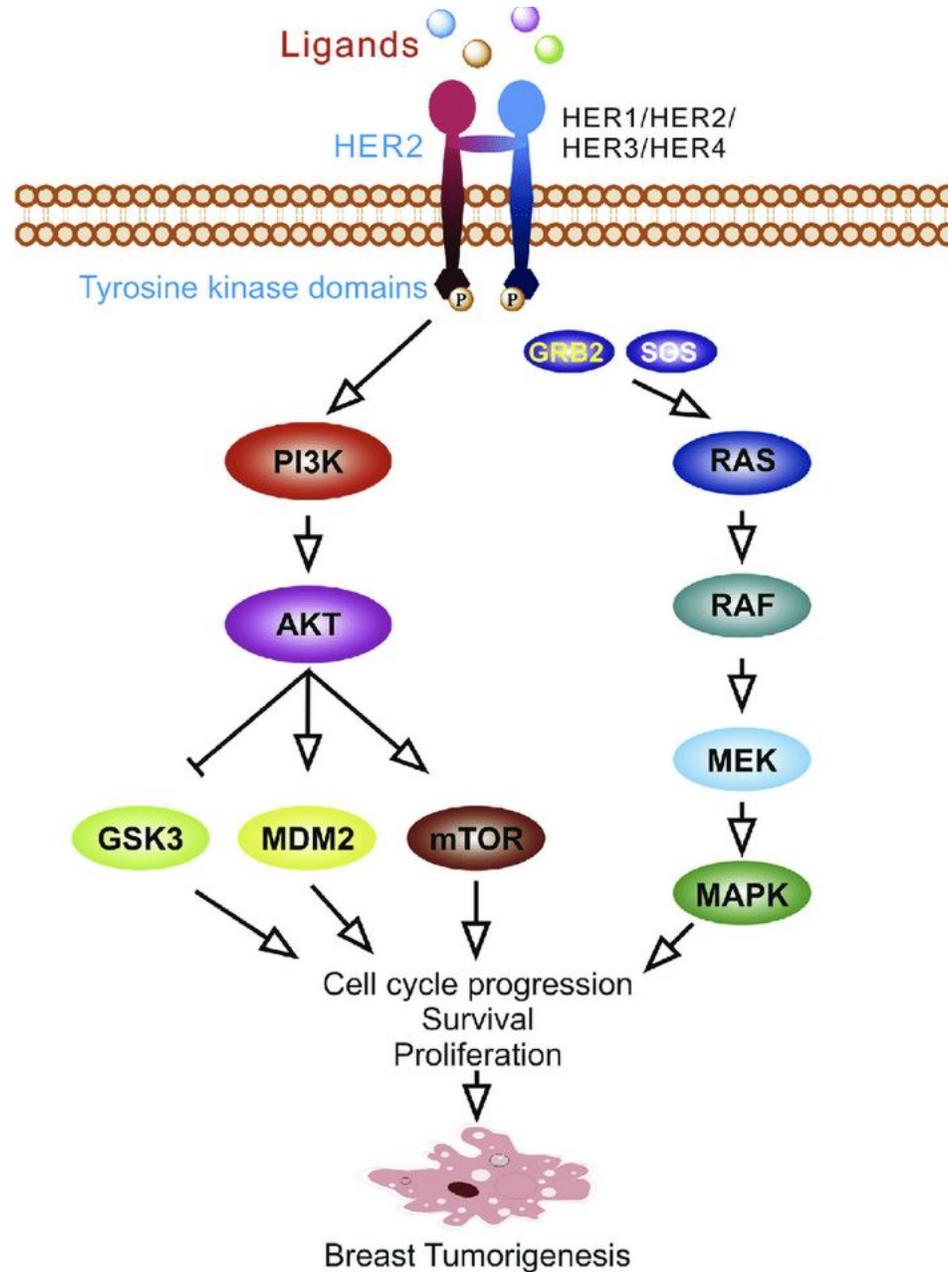


Stage IV NED
(Wild-Type/BRAF^{V600})



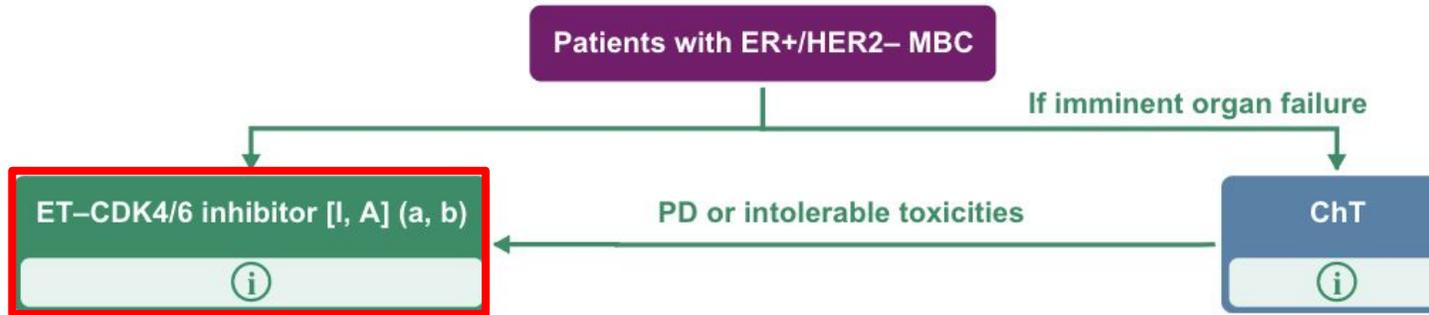
Breast Cancer

HER2 signalling in breast cancer



First-line treatment

v1.1 - May 2023



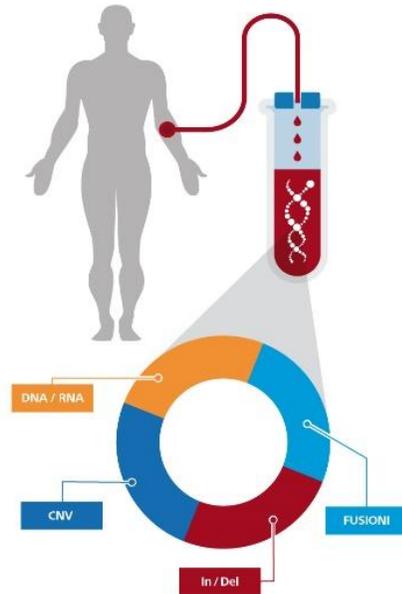
Current treatment landscape and outcomes: mPFS*

1L	ET + CDK4/6i	No prior CDK4/6i	24.8–28.2 mo ^{1–3}
2L+	ET + targeted therapies	Prior CDK4/6i	5.5 mo ⁴
	ET monotherapy	Prior CDK4/6i	1.9–2.6 mo ^{4,5}
3L+	Single-agent CT	Mostly CT naïve (mBC)	6.2–7.1 mo ^{6–8}
	T-DXd (HER2-low)	Prior ET and CT	10.1 mo ⁹

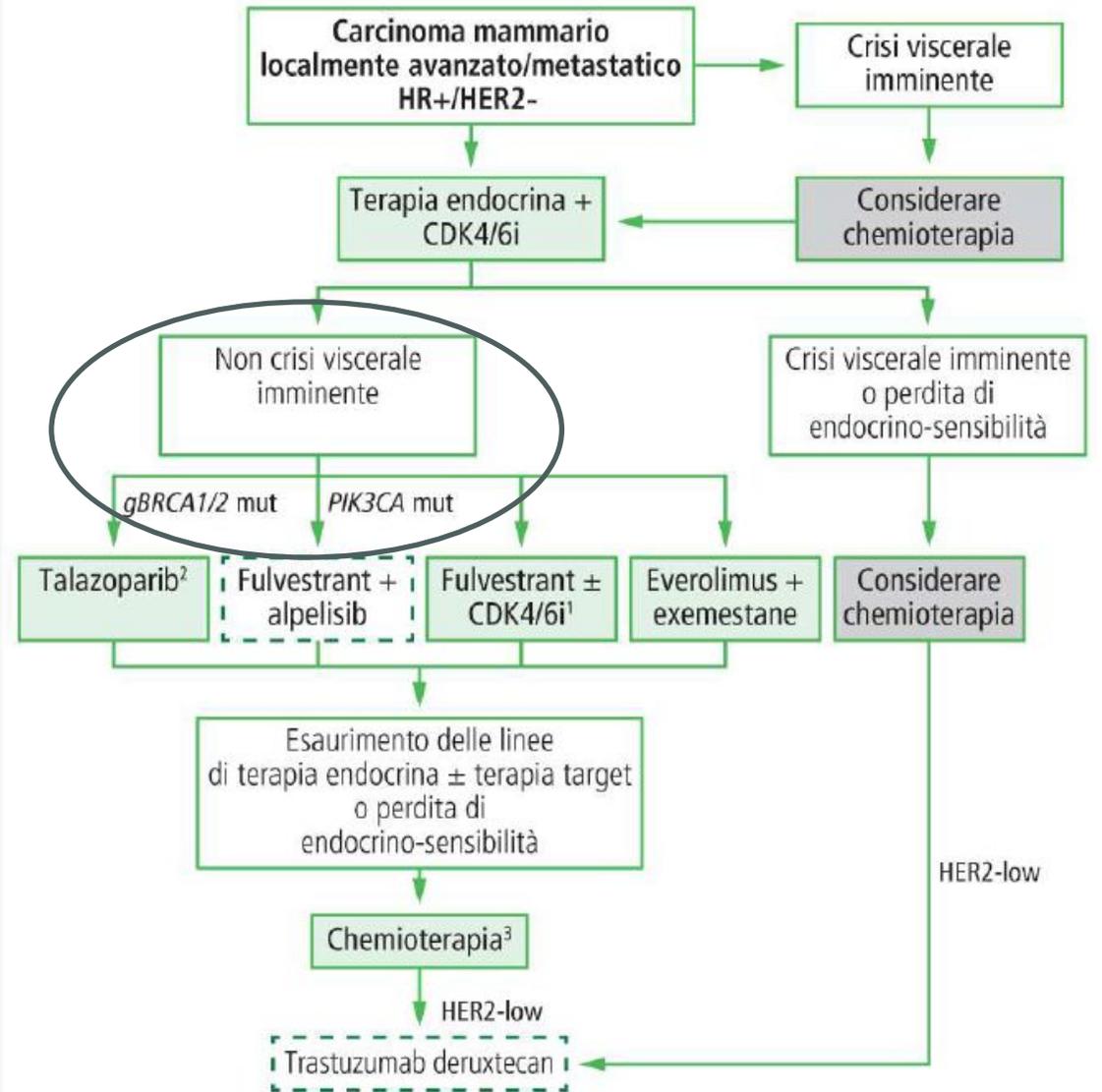
Adapted from G. Curigliano, ASCO 2024 meeting

Tumori ormonopositivi o 'luminal-like' (ER+ ed HER2-) in stadio avanzato

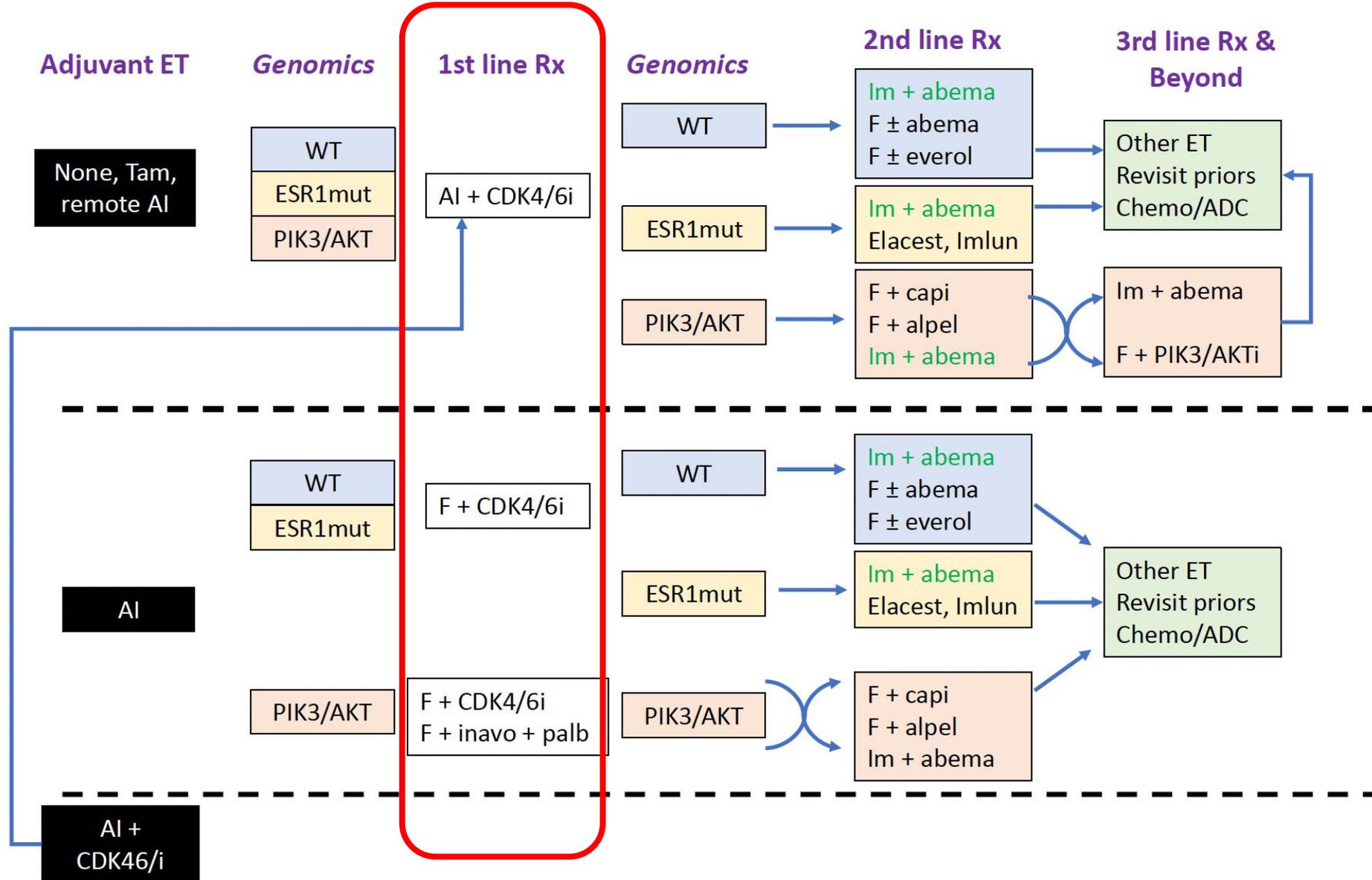
Sempre valutare **biopsia di ricaratterizzazione a progressione di malattia** (per la ricerca target e meccanismi di resistenza e per escludere switch di istotipo)



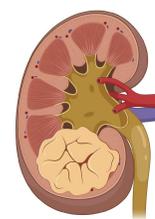
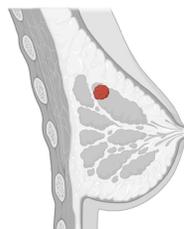
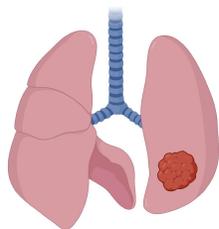
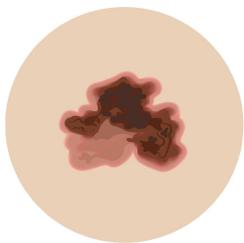
Valutare **biopsia liquida** per la ricerca di mutazioni di ESR1 (mutazione di resistenza sensibile a trattamento con Elacestrant)



Median PFS in recent RCTs of endocrine therapy: sub-analysis in patients with prior CDK4/6i therapy



How to improve Cure Rate !



ICIs

Adj.
Pembrolizumab

Periop.
Pembrolizumab

Periop.
Pembrolizumab

Adj.
Pembrolizumab

Neoadj.
Dostarlimab

Periop.
Durvalumab

Adj.
Nivolumab

Neoadj.
Nivolumab

Periop.
Pembrolizumab

Adj.
Atezolizumab

Periop.
Nivolumab+Ipilimumab

Periop.
Durvalumab

Target therapies

Adj.
Dabrafenib+Trametinib

Adj.
Osimertinib

Adj.
Alectinib

Neoadj. Trastuzumab
(+ Pertuzumab)

Adj. Trastuzumab
(+ Pertuzumab)

Adj. T-DM1

Adj. Olaparib

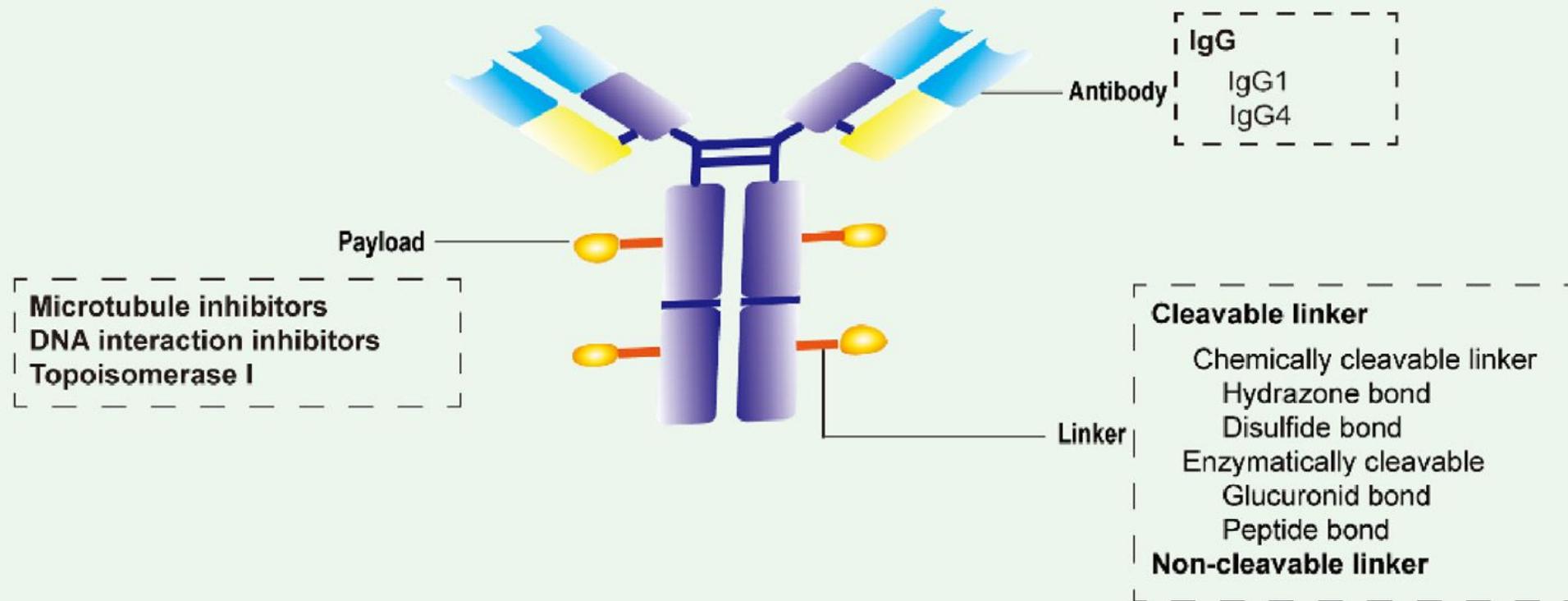
Adj. Abemaciclib

Adj. Ribociclib

Legend

- AIFA^a reimbursed
- L. 648/96
- E.A.P.

ADC



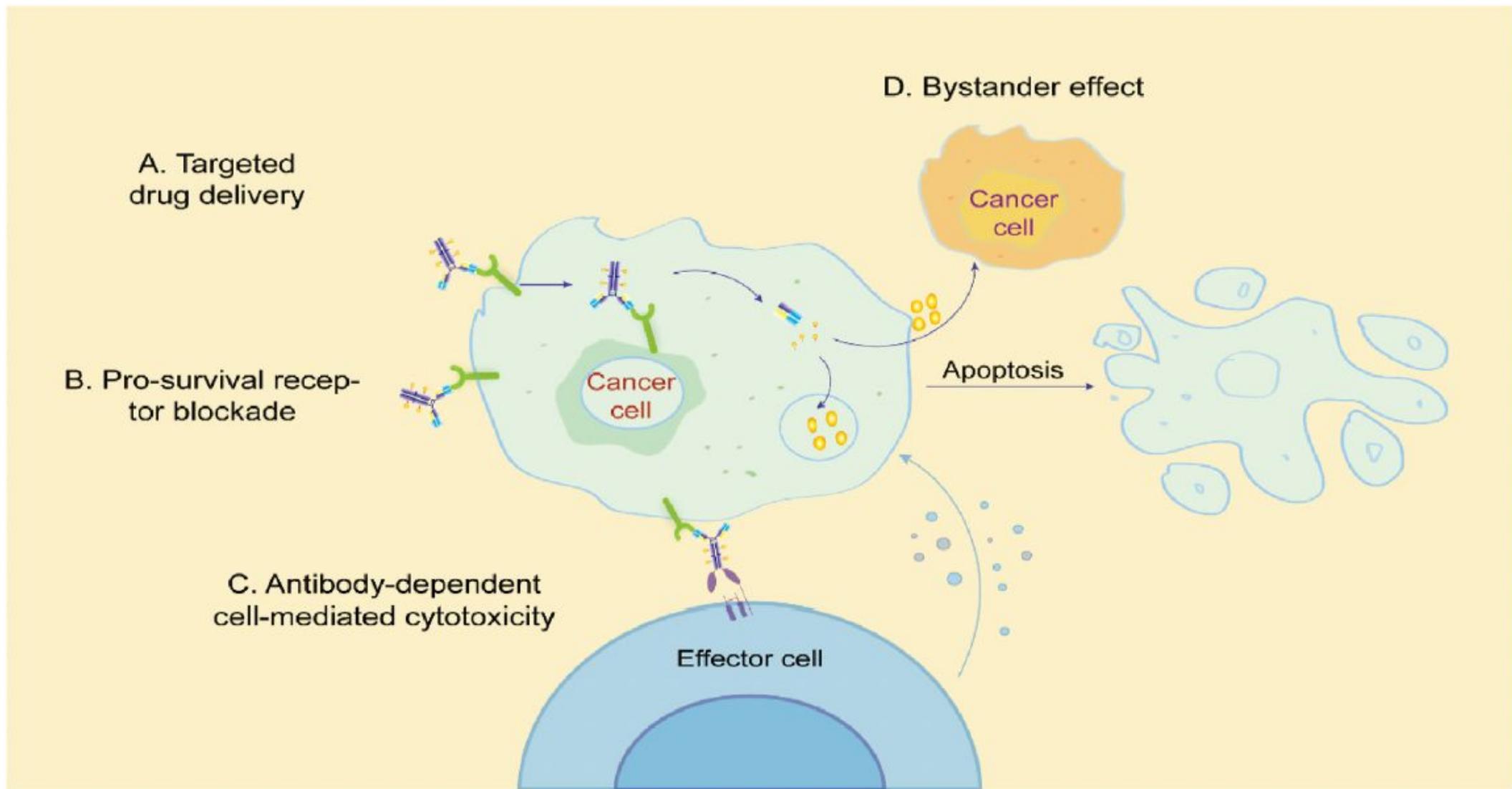
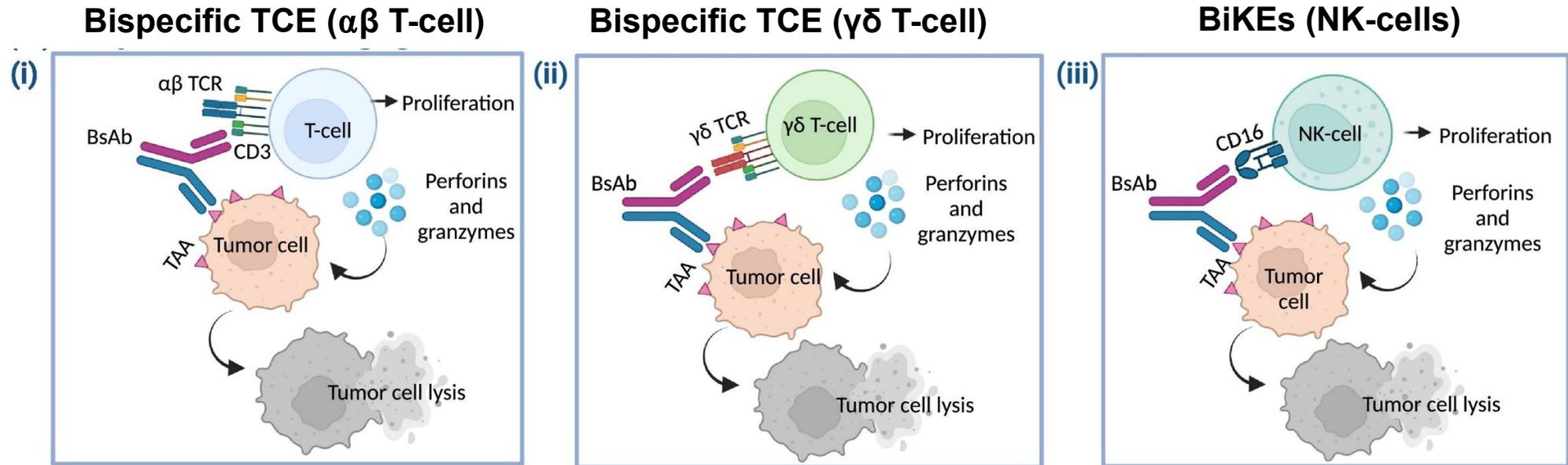


Figure 2 The mechanism of ADCs. After ADCs enter the body, the antibody targets the surface antigen of cancer cells, and endocytosis occurs to release the payloads. At the same time, ADCs can also produce the ADCC and bystander effects. Created with Adobe Illustrator.

BISPECIFIC

bsAbs: mechanism of action (I)

1) Immune cell engagers:



- simultaneous binding of the **CD3e** of the TCR complex and the selected tumor associated antigen (**TAA**)
- Activation of T cells with **cytotoxic/proinflammatory** activity against tumor cells
- Role in TME reshape
- Unclear role in memory formation

- New immune cells are in development
- **LAVA-051** ($\gamma\delta 9V\delta 2$ -T \times CD1d, bispecific nanobody, Gammabody) in leukemia and myeloma cells

- Simultaneous binding of **CD16** (activating receptor on NK cells) and **TAA**
- MHC-I deficient tumor cells **killing**
- **AFM13** (CD30 \times CD16A, TandAb) in CD30+ lymphoma
- **RO7297089** (BCMA \times CD16A, IgG-scFv2) in multiple myeloma

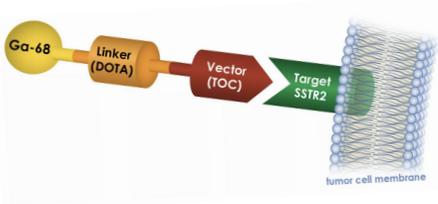
Theranostics

What is Theranostics?

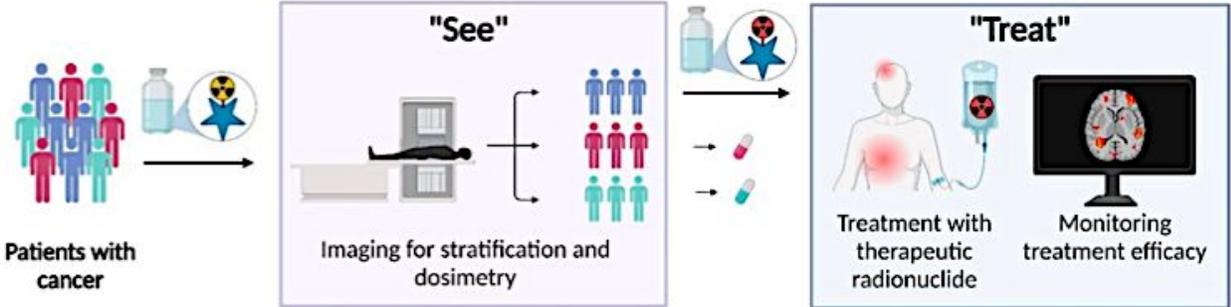
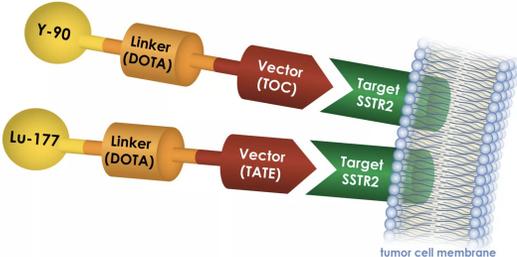
THERANOSTICS is a combination of the terms **THERA**peutics and **diagNOSTICS**. It is used to describe the combination of using one radioactive drug to identify (diagnose) with NM techniques (e.g. SPECT, PET) a target and a second radioactive drug to deliver therapy to treat the main tumor and any metastatic tumors.

Two phases:

1. Diagnostic phase

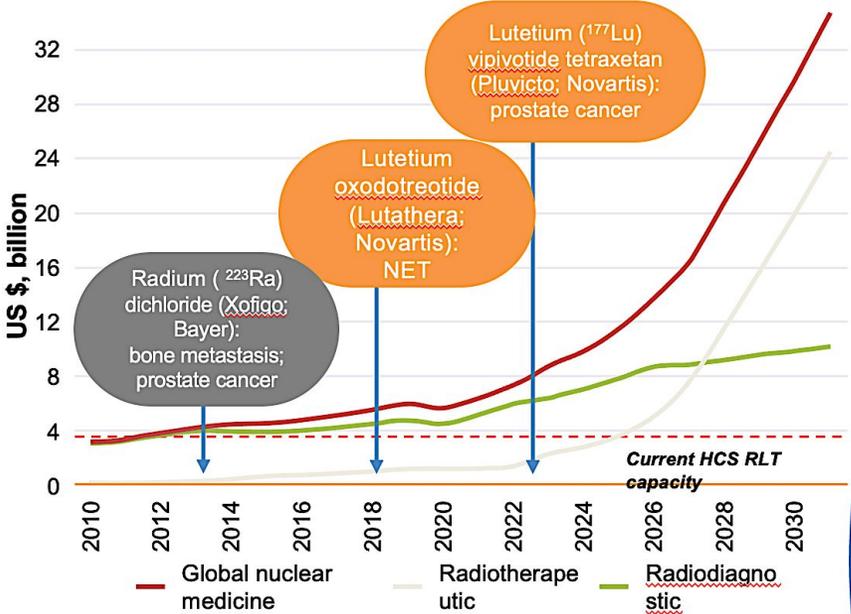


2. Therapeutic phase

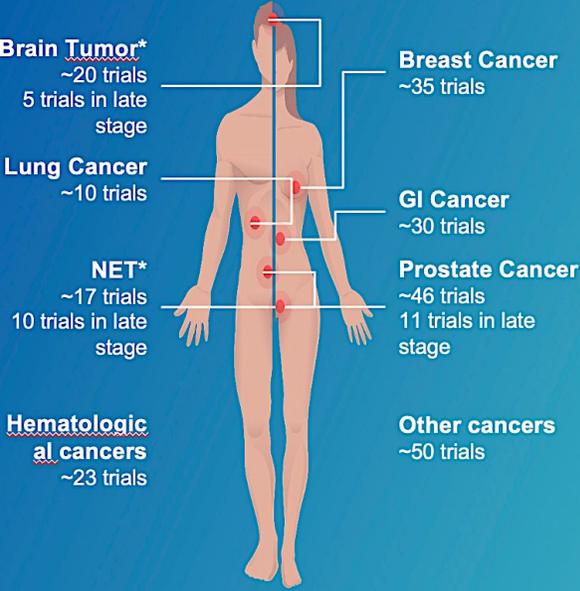


Demand for RL-Imaging and RL-Therapy will potentially outstrip current HCS capacity in the next few years in many countries

Radioligand theranostics market 2010-2031¹

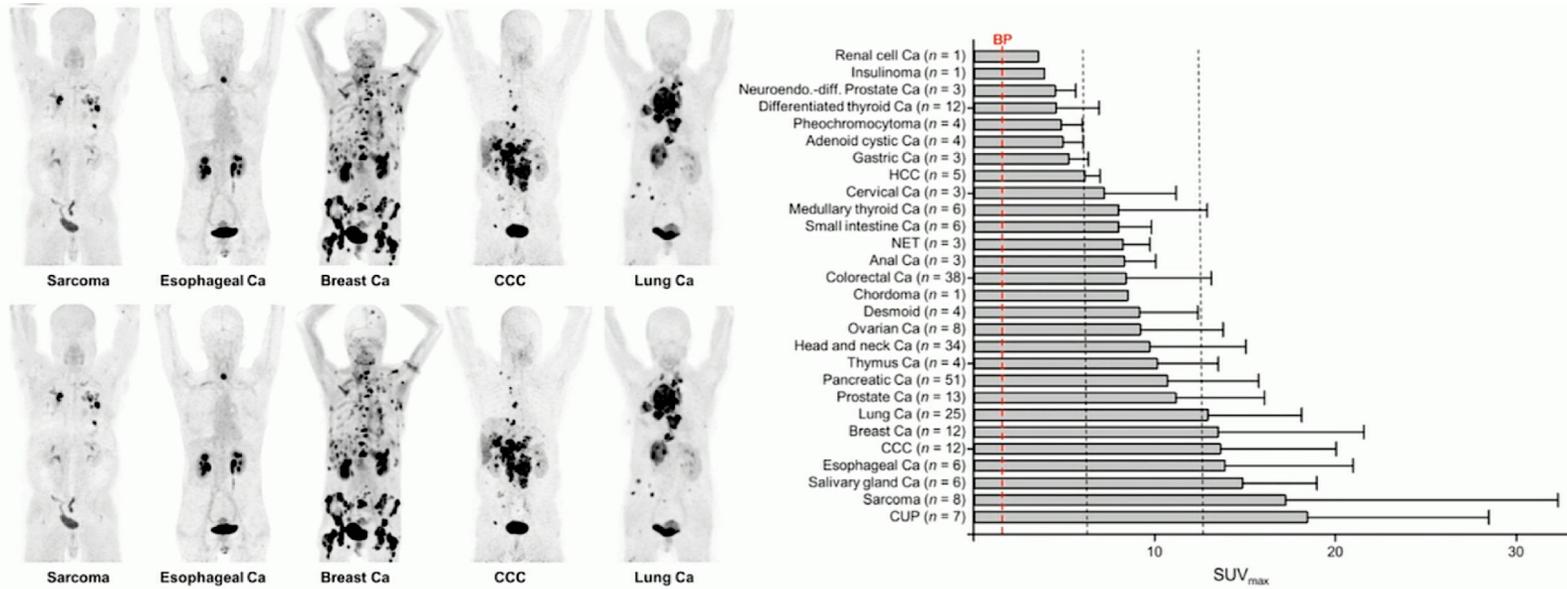


~225 clinical trials underway to evaluate RLT in various cancers²



GI, gastrointestinal; HCS, healthcare system; NET, neuroendocrine tumors; RLI, radioligand imaging; RLT, radioligand therapy
¹Estimated using projected global incidence of cancers with pipeline RLT products. HCS, healthcare systems; NEN, neuroendocrine tumors; RLT, radioligand therapy.
²References: 1. MEDrainsintell, Nuclear Medicine Report & Directory Edition 2022 (Part 1 & 2); 2. IQVIA: Succeeding with Innovation: The State of Radioligand Therapy Readiness in Europe (Video). Available from: [ess-europe](https://www.ess-europe.com). Last accessed: June 4,

FAPi PET – The Pan-Tumoral Tracer



Kratochwil C et al. ⁶⁸Ga-FAPi PET/CT: Tracer Uptake in 28 Different Kinds of Cancer. JNM Apr 2019

Many inhibitors of FAP (FAPi) have been synthesized for diagnosis and therapy

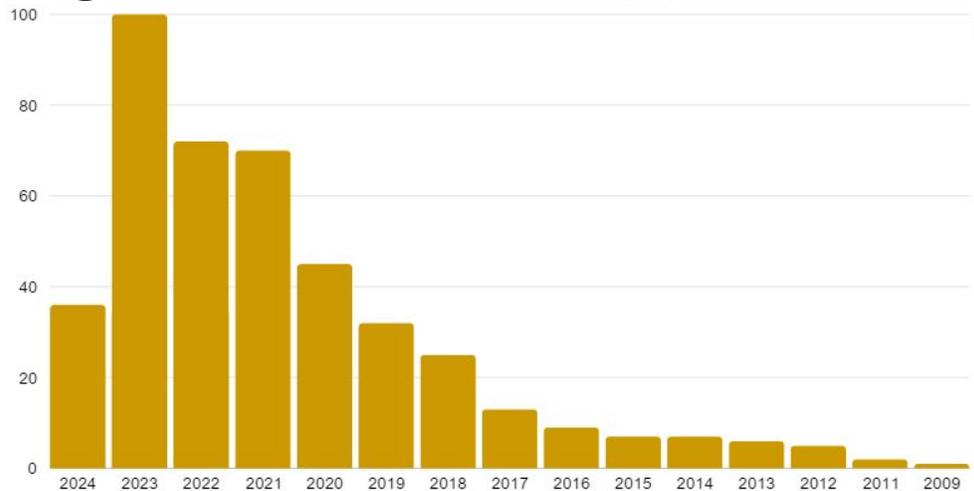
FAPi (FAPi-02, FAPi-04, FAPi-42, FAPi-46, FAPi-74, Onco-FAP, FAPi-2286.....)

- **Chelator** (DOTA, DATA, NOTA.....)
- **Radioisotopes** for imaging and therapy

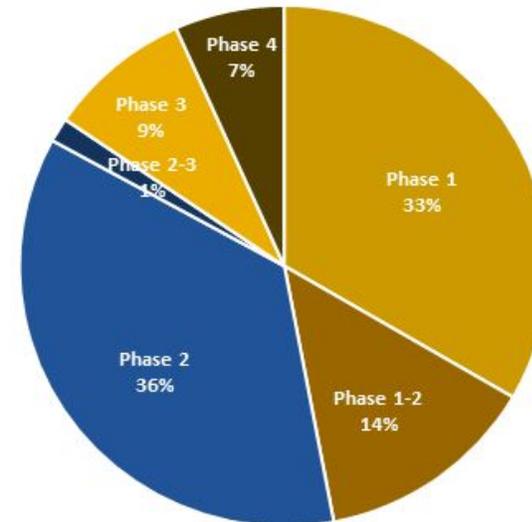
Ga, 18F, 99mTc, 90Y, 177Lu, 131I, 225Ac, 188Re, Sm...

Radiopharmaceutical trials are an increasing focus in new research

Planned & ongoing study with RF vs biological target of cancer starts by year



Citeline, Trial Trove 2024



a significant number of trials in early development with over 80% of trials in Phase 1, Phase 1-2, or Phase 2

