IL LABORATORIO IN ONCOLOGIA

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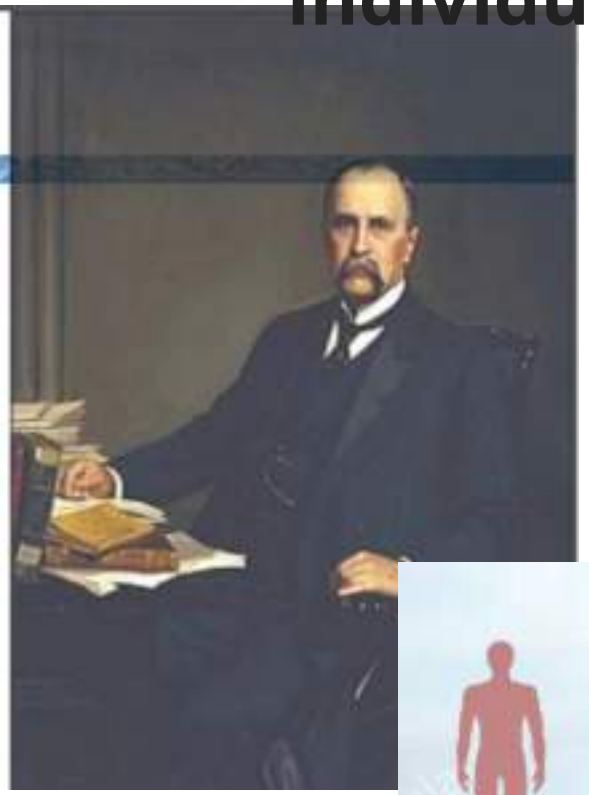
Cambiamento della medicina: dalla popolazione al singolo individuo

Dalla semplificazione osleriana alla complessità del malato.

La visione contemporanea della malattia risale al XIX secolo e si basa sulla correlazione clinico-patologica osleriana.

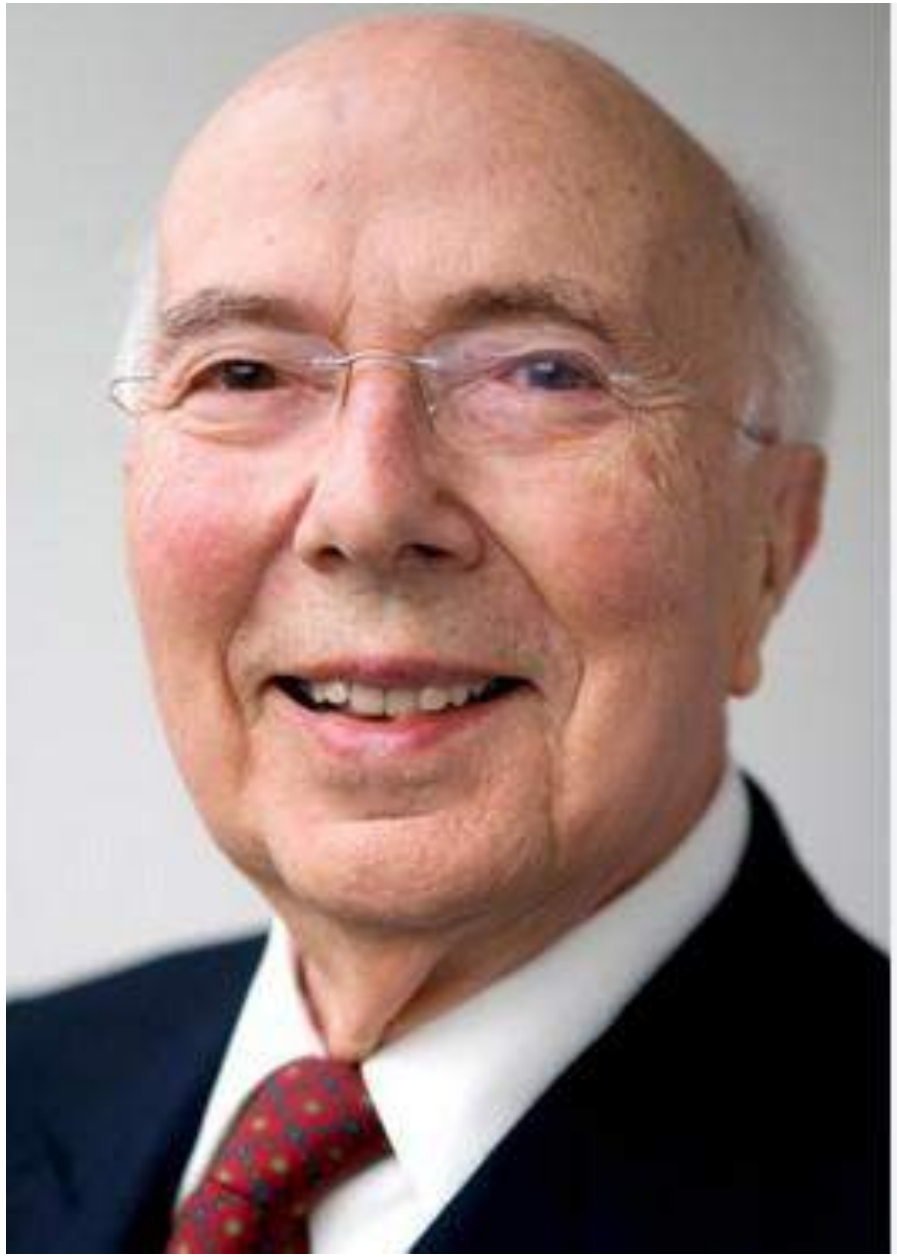
La definizione della malattia è basata sul sistema o organo in cui i sintomi sono manifesti e a cui la patologia è correlata, pur con il limite di generalizzare enormemente i *pato-fenotipi* di malattia.



La **medicina "classica"** più orientata verso la **popolazione rispetto al caso particolare** nel valutare l'efficacia dei farmaci in maniera statisticamente solida.

medicina di precisione

l'insieme di strategie di prevenzione e trattamento che tengono conto della **variabilità individuale** e specifico nella sua interezza



Il modello mutazionale

1

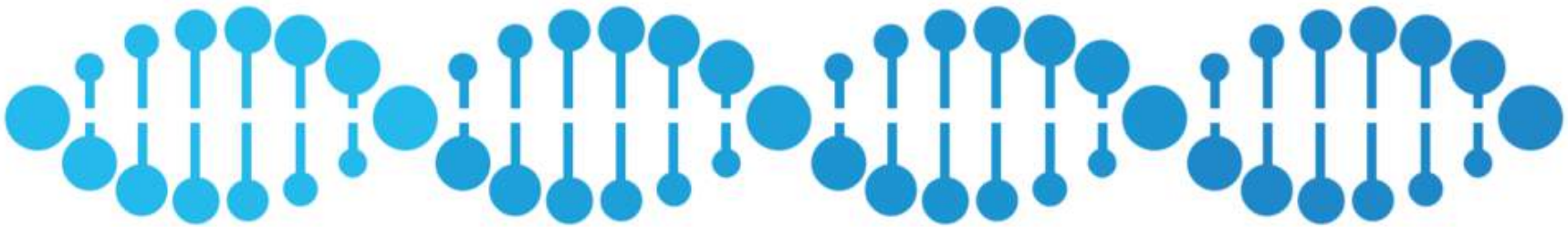
La teoria mutazionale prevede che i tumori si si generino, progrediscano e si diffondano nell'organismo per accumulo di **mutazioni genetiche.**

3

I tumori strettamente dipendenti da mutazioni driver sono definiti **"mutation addicted".**

5

"tumor mutational load"
strumenti diagnostici che forniscano informazioni ampie e multi parametriche in termini quantitativi e qualitativi, per trattare i pazienti con terapie personalizzate.



2

Le **mutazioni "driver"** svolgono un ruolo fondamentale nello sviluppo delle neoplasie.

4

mutazioni "druggable" se bersaglio diretto del farmaco
. **mutazioni "actionable"** se fanno **parte di "pathway"** che possono essere bersaglio di trattamenti specifici.

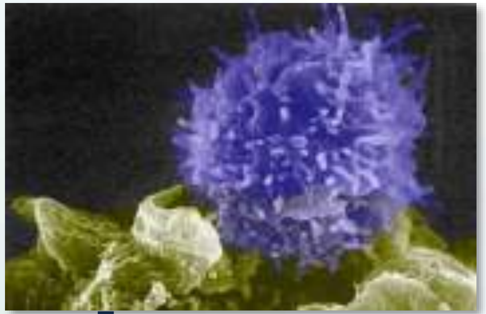
Diverse tipologie di pannelli **NGS - Next Generation Sequencing** per la **CGP - Comprehensive Genomic Profiling** per

- tecnologie impiegate
- dimensioni di campioni utilizzati
- uso di tessuto o biopsia liquida

Treatment Modality for Cancer

Surgery
1846

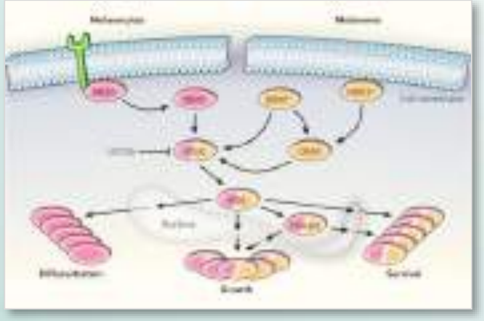
Chemotherapy
1946



Immuno-Oncology
2011

Radiation Therapy
1901

Targeted Therapy
1997



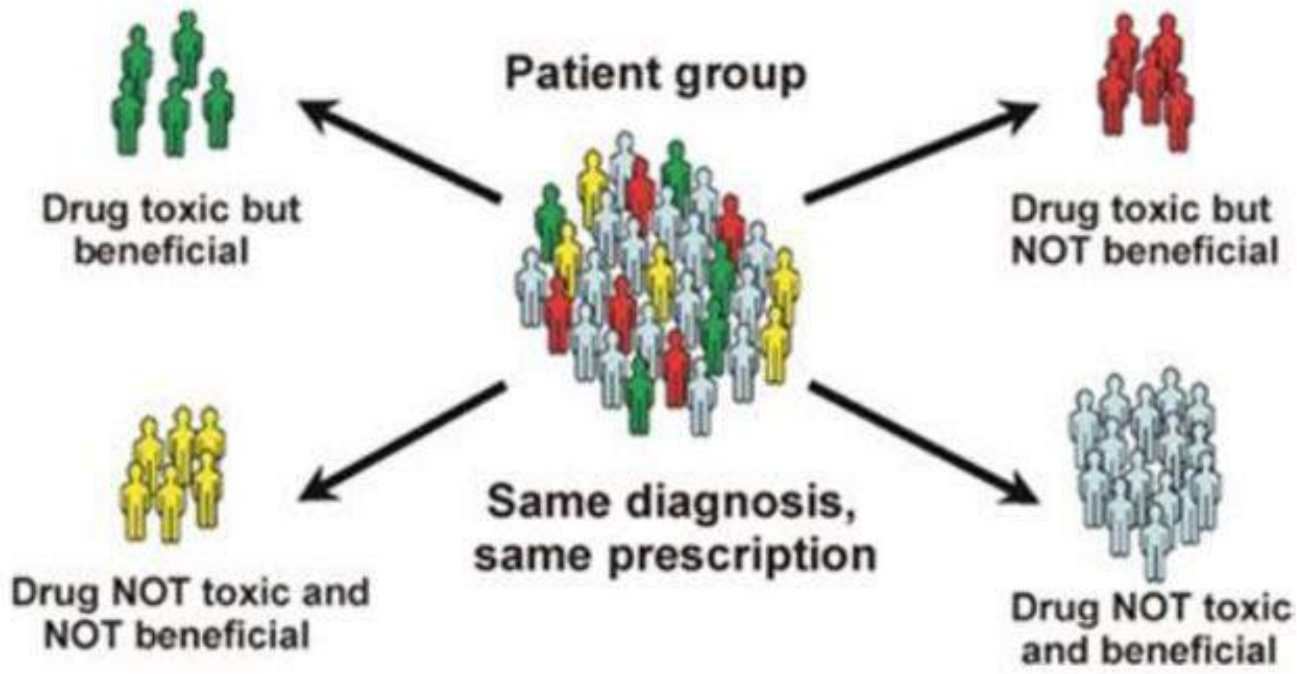
1. DeVita VT Jr, et al. *Cancer Res*. 2008;68:8643–8653; 2. American Cancer Society. http://www.cancer.org/cancer/cancerbasics/thehistoryofcancer/; 3. Hodi FS, et al. *N Engl J Med.* 2010;363:711–723; 4. Sznol M, et al. Presented at ASCO 2013: oral presentation; 5. Kantoff PW, et al. *N Engl J Med*. 2010;363:411–422; 6. Finn OJ. *Ann Oncol*. 2012;23(suppl 8):viii6–viii9.

La post-genomica sta cambiando l'industria della salute

Il secolare paradigma «one drug fits for all» è superato

Le nuove **tecnologie di sequenziamento**, permettono di muoversi verso una medicina che oggi viene definita delle **4P**:

Predittiva
Preventiva
Personalizzata
Partecipativa



L'analisi molecolare del genoma di ogni paziente permette di stratificare per sottogruppi

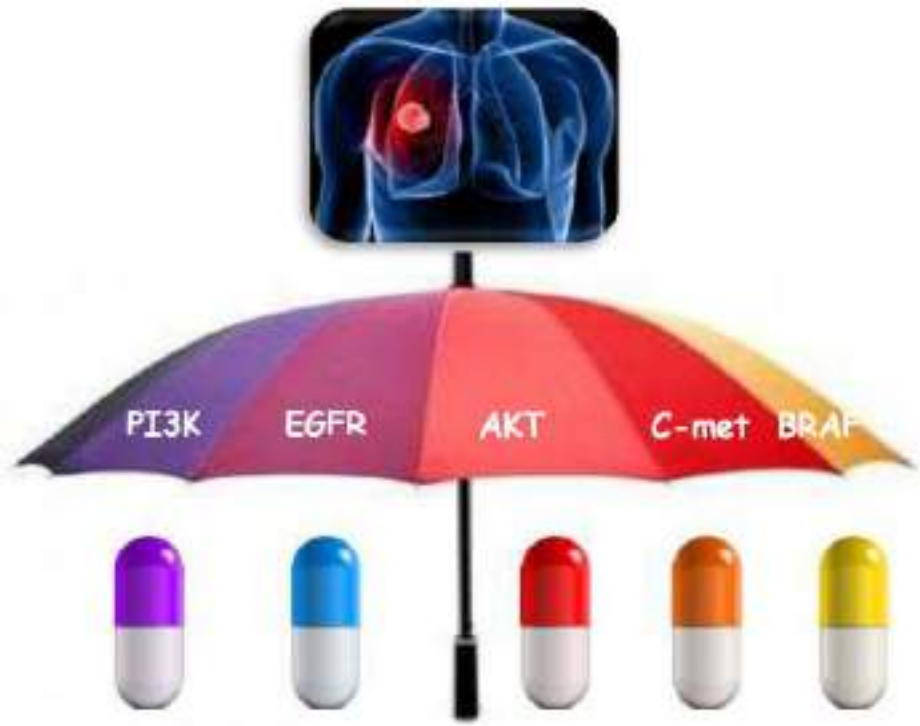
Identifica biomarkers molecolari tumorali target specifico driven decision

Biomarkers in Oncologia medica

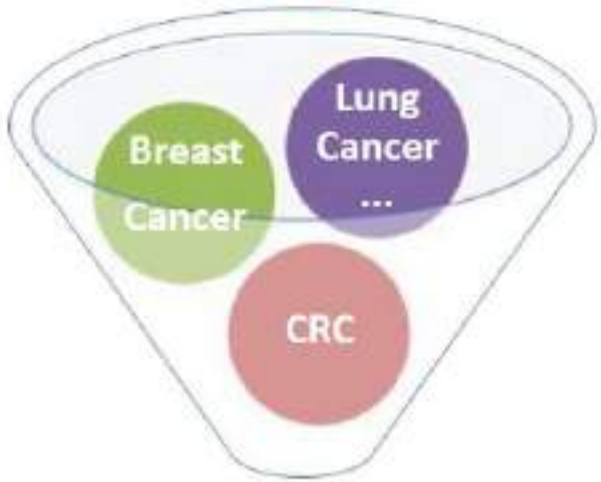
Strategia terapeutica: Target molecolare dipendente

Disegno trial clinici per terapie target

A Single Cancer Type "Umbrella"
Design Right Drug



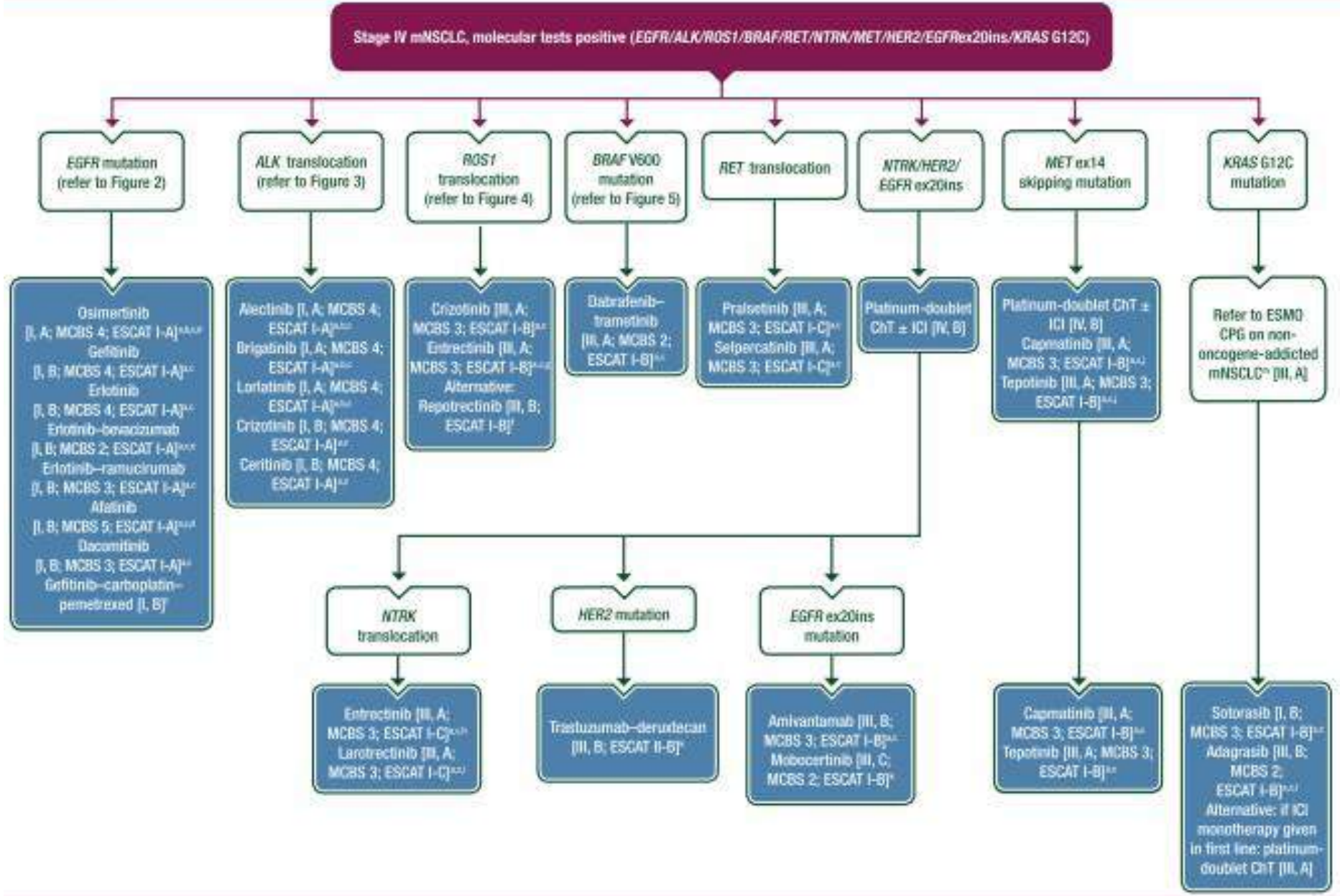
Genetic Aberrations "Basket"
Design Right Person



Targeting molecular aberration

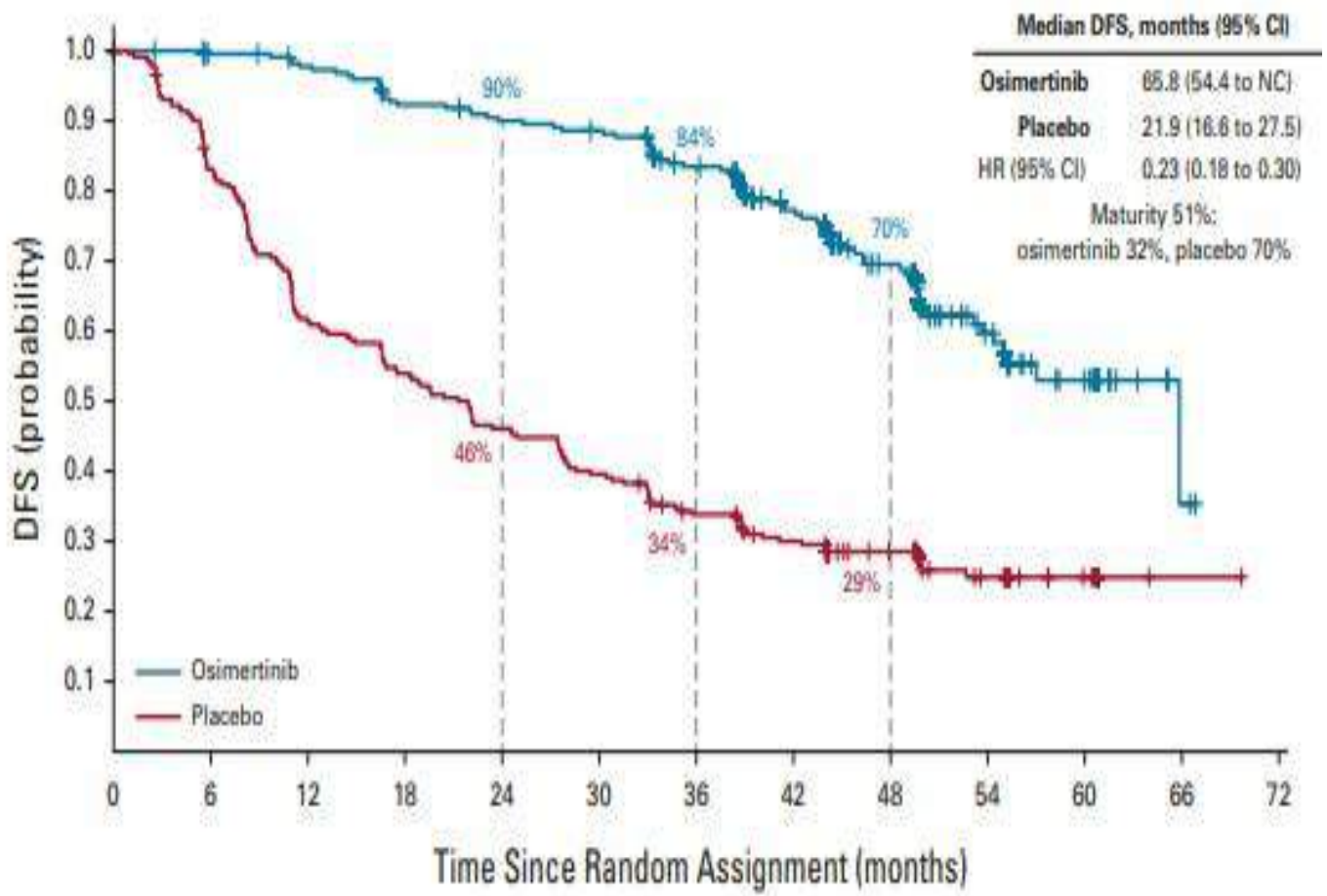
Table 2. List of genomic alterations level I/II according to ESCAT in advanced non-squamous non-small-cell lung c

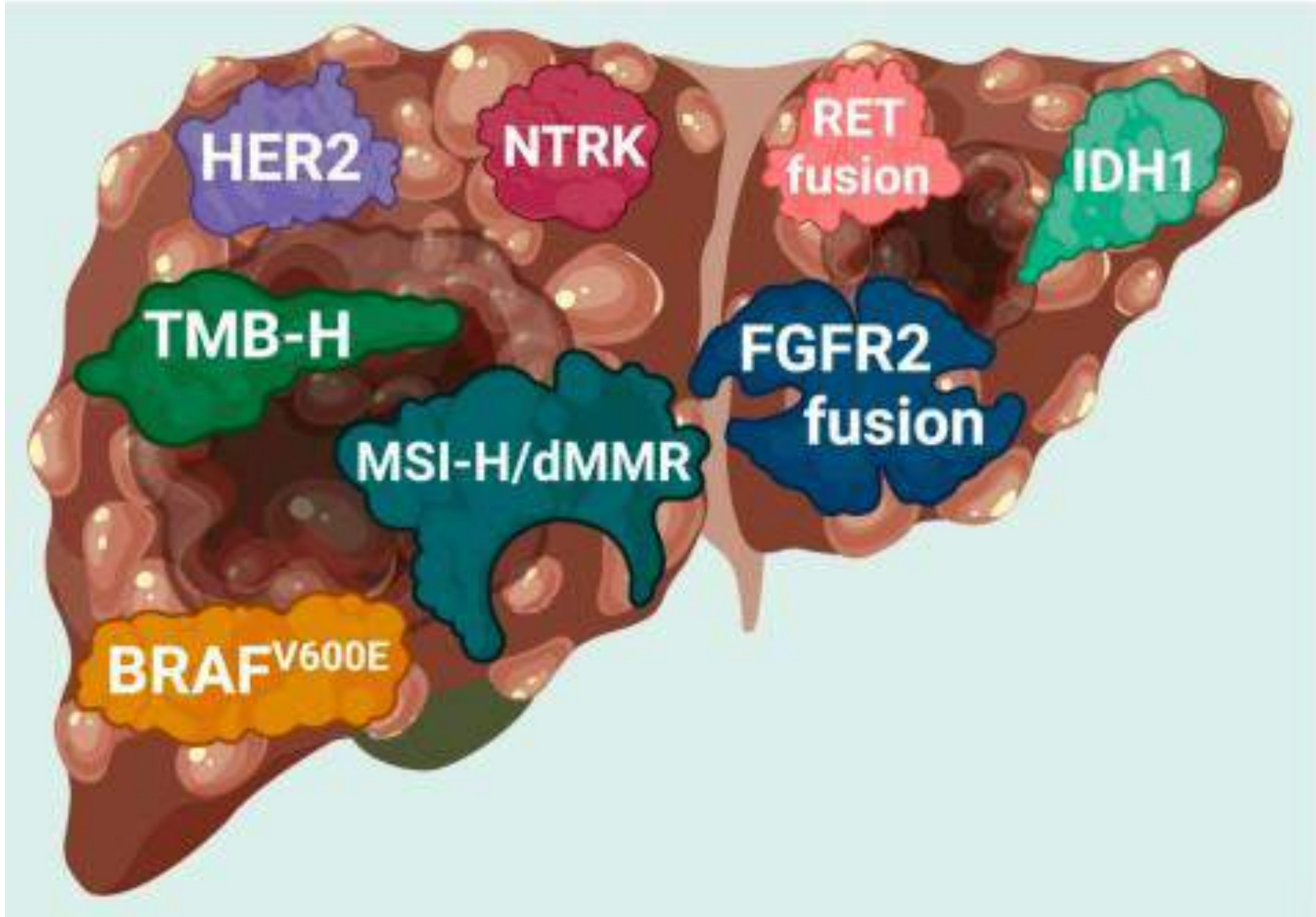
Gene	Alteration	Estimated prevalence	ESCAT score	Drug class matched
EGFR	Common mutations (deletion exon 19, p.L8S8R)	15% Caucasian 50% Asian 30% LATAM	IA	First-, second- and third-generation EGFR TKIs EGFR-MET bispecific antibodies + third-generatio EGFR TKIs EGFR-MET bispecific antibodies + chemotherapy ± EGFR TKIs (after PD on third-generation EGFR TKIs)
	Acquired p.T790M mutation in exon 20	60% after first- or second-generation EGFR TKIs	IA	Third-generation EGFR TKIs
	Exon 20 insertions	2%	IA	EGFR-MET bispecific antibodies or TKIs
	Uncommon mutations (p.G719 variants in exon 18, p.L861Q in exon 21, p.S768I in exon 20)	10%	IB	Second- and third-generation EGFR TKIs
ALK	Fusions	5%	IA	ALK TKIs
KRAS	Mutations (p. G12C)	12%	IA	KRAS ^{G12C} TKIs
RET	Fusions	1%-2%	IA	RET TKIs
ROS1	Fusions	1%-2%	IB	ROS1 TKIs
BRAF	Mutations (p. V600E)	2%	IB	BRAF TKIs + MEK TKIs
MET	Mutations exon 14 skipping	3%	IB	MET TKIs
	Focal amplifications	5% as primary 15% as mechanism of acquired resistance on EGFR TKIs	IIB	MET TKIs + third-generation EGFR TKIs EGFR-MET bispecific antibodies + third-generatio EGFR TKIs
ERBB2	Hotspot mutations	3%	IIB	Pan-HER TKIs Anti-HER2 ADCs
NRG1	Fusions	<1%	IIB	Anti-HER2/HER3 bispecific antibody

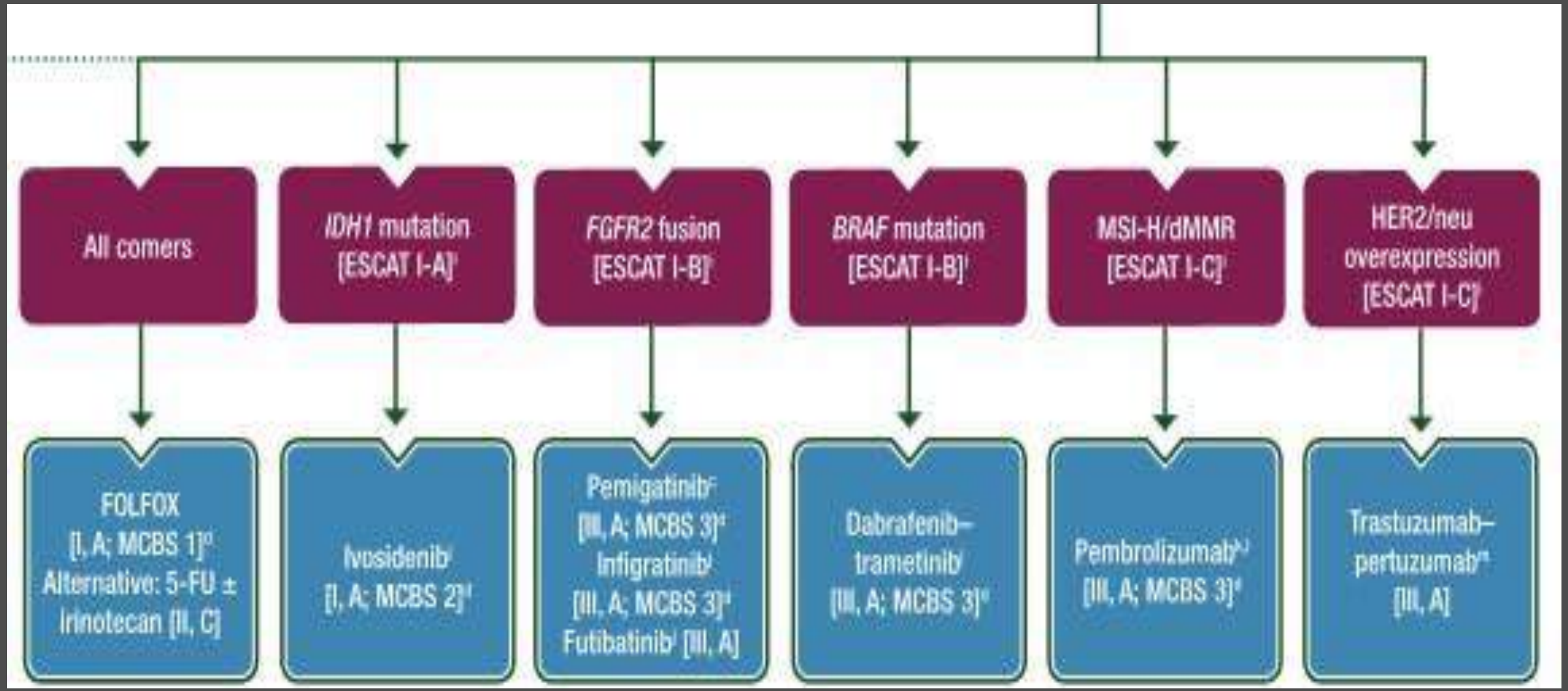

Stage IV mNSCLC, molecular tests positive (EGFR/ALK/ROS1/BRAF/RET/NTRK/MET/HER2/EGFRex20ins/KRAS G12C)
EGFR mutation (refer to Figure 2)
ALK translocation (refer to Figure 3)
ROS1 translocation (refer to Figure 4)
BRAF V600 mutation (refer to Figure 5)
RET translocation
NTRK/HER2/ EGFR ex20ins
MET ex14 skipping mutation
KRAS G12C mutation
Osimertinib [I, A; MCBS 4; ESCAT I-A]
Gefitinib [I, B; MCBS 4; ESCAT I-A]
Erlotinib [I, B; MCBS 4; ESCAT I-A]
Erlotinib–bevacizumab [I, B; MCBS 2; ESCAT I-A]
Erlotinib–ramucirumab [I, B; MCBS 3; ESCAT I-A]
Afatinib [I, B; MCBS 5; ESCAT I-A]
Dacomitinib [I, B; MCBS 3; ESCAT I-A]
Gefitinib–carboplatin–pemetrexed [I, B]
Alectinib [I, A; MCBS 4; ESCAT I-A]
Brigatinib [I, A; MCBS 4; ESCAT I-A]
Lorlatinib [I, A; MCBS 4; ESCAT I-A]
Crizotinib [I, B; MCBS 4; ESCAT I-A]
Ceritinib [I, B; MCBS 4; ESCAT I-A]
Crizotinib [III, A; MCBS 3; ESCAT I-B]
Entrectinib [III, A; MCBS 3; ESCAT I-B]
Alternative: Repotrectinib [III, B; ESCAT I-B]
Dabrafenib–trametinib [III, A; MCBS 2; ESCAT I-B]
Pralsetinib [III, A; MCBS 3; ESCAT I-C]
Selpercatinib [III, A; MCBS 3; ESCAT I-C]
Platinum-doublet ChT ± ICI [IV, B]
Platinum-doublet ChT ± ICI [IV, B]
Capmatinib [III, A; MCBS 3; ESCAT I-B]
Tepotinib [III, A; MCBS 3; ESCAT I-B]
Refer to ESMO CPG on non-oncogene-addicted mNSCLC [III, A]
NTRK translocation
HER2 mutation
EGFR ex20ins mutation
Entrectinib [III, A; MCBS 3; ESCAT I-C]
Larotrectinib [III, A; MCBS 3; ESCAT I-C]
Trastuzumab–deruxtecan [III, B; ESCAT II-B]
Amivantamab [III, B; MCBS 3; ESCAT I-B]
Mobocertinib [III, C; MCBS 2; ESCAT I-B]
Capmatinib [III, A; MCBS 3; ESCAT I-B]
Tepotinib [III, A; MCBS 3; ESCAT I-B]
Sotorasib [I, B; MCBS 3; ESCAT I-B]
Adagrasib [III, B; MCBS 2; ESCAT I-B]
Alternative: if ICI monotherapy given in first line: platinum-doublet ChT [III, A]

clinical tri

Adjuvant Osimertinib for Resected EGFR-Mutated Stage IB-IIIA Non–Small-Cell Lung Cancer: Updated Results From the Phase III Randomized ADAURA Trial




HER2
NTRK
RET fusion
IDH1
TMB-H
FGFR2 fusion
MSI-H/dMMR
BRAFV600E


All comers
IDH1 mutation [ESCAT I-A]
FGFR2 fusion [ESCAT I-B]
BRAF mutation [ESCAT I-B]
MSI-H/dMMR [ESCAT I-C]
HER2/neu overexpression [ESCAT I-C]
FOLFOX [I, A; MCBS 1]
Alternative: 5-FU ± Irinotecan [II, C]
Ivosidenib [I, A; MCBS 2]
Pemigatinib [III, A; MCBS 3]
Infigratinib [III, A; MCBS 3]
Futibatinib [III, A]
Dabrafenib–trametinib [III, A; MCBS 3]
Pembrolizumab [III, A; MCBS 3]
Trastuzumab–pertuzumab [III, A]

TARGET THERAPY IN CHOLANGIOCARCINOMA

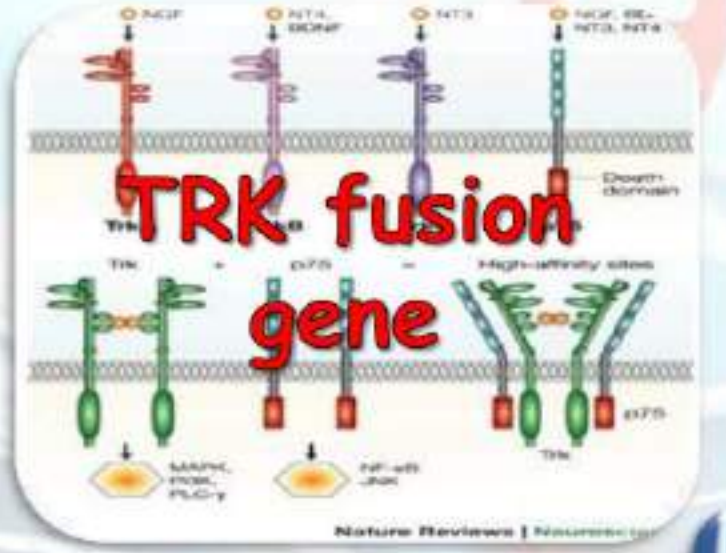
Molecular Abnormality	Prevalence	Drug Name	Study Phase	No. of Patients with Molecular Abnormality	ORR	Disease Control Rate	Median PFS (months)
FGFR2 fusion	10%-15% (primarily ICC)	Pemigatinib (INCB054828)	II	107	35.5%	82.2%	6.9
		Infigratinib (BGJ398)	II	108	23.1%	84.3%	7.3
		Futibatinib (TAS-120)	II	103	41.7%	82.5%	9.0
		Derazantinib (ARQ087)	I/II	103	21.4%	74.8%	8.0
IDH1 R132 mutation	13%-20% (primarily ICC)	Ivosidenib	III	124	2.4%	53.2%	2.7
BRAF V600E mutation	1%-3%	Dabrafenib plus trametinib	II	43	46.5%	85.4%	9.0
		Vemurafenib	II	9	33.3%	NA	NA
HER2 overexpression or amplification	ICC 5% ECC 8%-12% GBC 14%-16%	Trastuzumab plus pertuzumab	II	39	23.1%	51.3%	4.0
		Trastuzumab deruxtecan	II	24	36.4%	81.8%	4.4
		Zanidatamab	I	17	47%	65%	NA
HER2 mutation	2%-3%	Neratinib	II	20	10%	30%	1.8
KRAS G12C mutation	1%	Adagrasib	II	8	50%	100%	NA

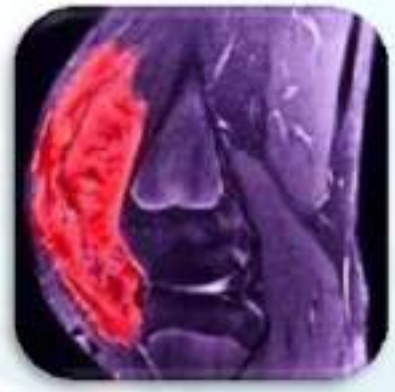
Table 4. List of genomic alterations level I/II according to ESCAT in advanced colorectal cancer

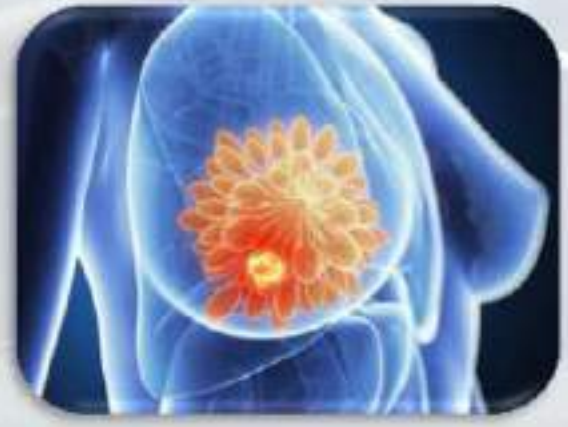
Gene/Signature[a]	Alteration	Estimated prevalence	ESCAT score	Drug class matched
KRAS, NRAS	Mutations (exon 2, 3 and 4)	53%	NA[c]	Anti-EGFR monoclonal antibodies
BRAF	Mutations (p. V600E)	8.5%	IA	BRAF inhibitors + EGFR inhibitors
MSI-H/dMMR[b]	MSI-H/dMMR	4.5%	IA	PD-1 checkpoint inhibitors
KRAS	Mutations (p. G12C)	4%	IA	KRAS ^{G12C} TKIs + anti-EGFR monoclonal antibodies
ERBB2	Amplifications	2%	IIB	Anti-HER2 monoclonal antibodies ± anti-HER2 TKIs Anti-HER2 ADCs
POLE	Mutations	<1%	IIB	PD-1 checkpoint inhibitors

Oncologia di Precisione

Nuova indicazione agnostica



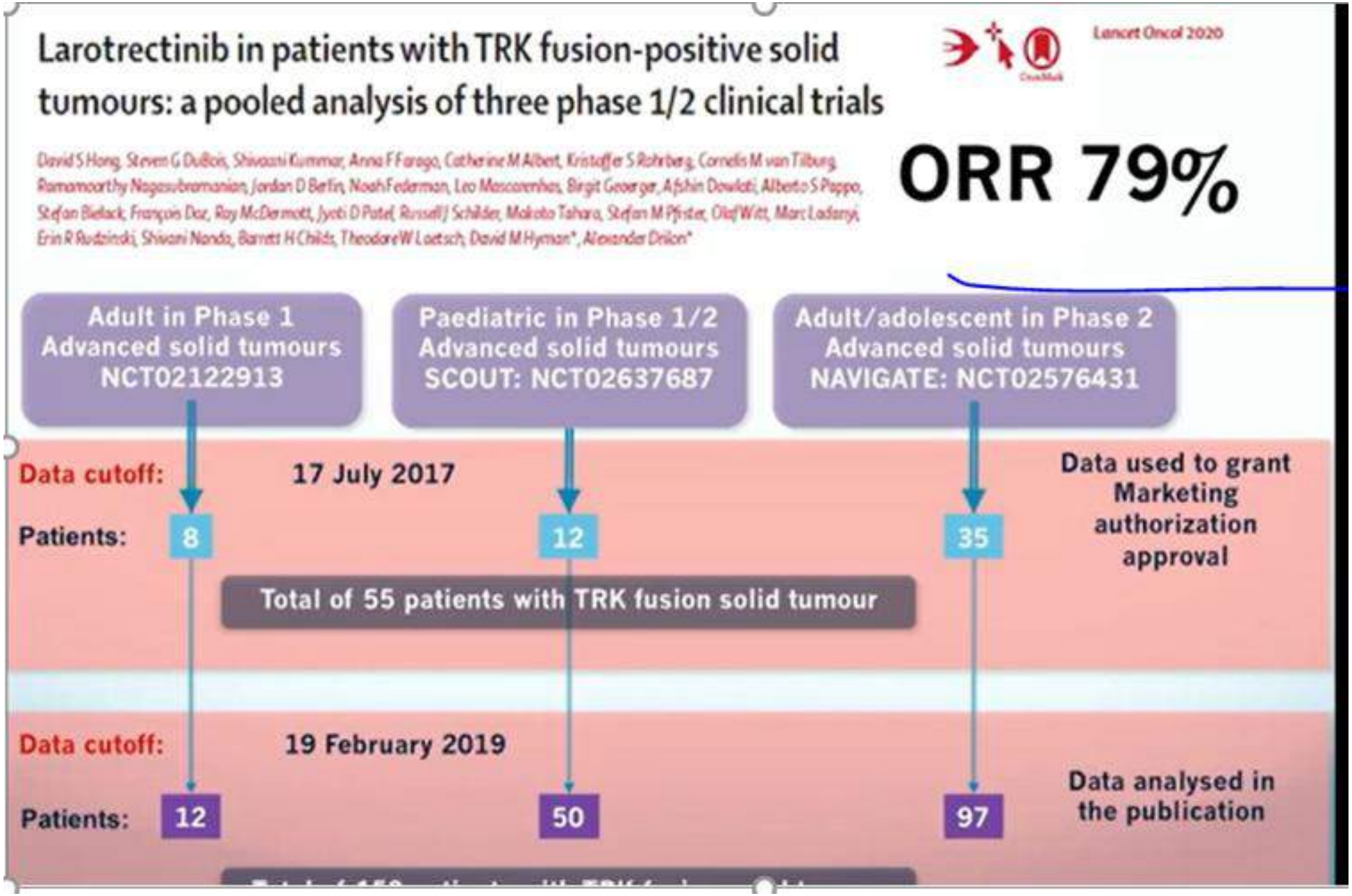




2018

ORIGINAL ARTICLE

Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

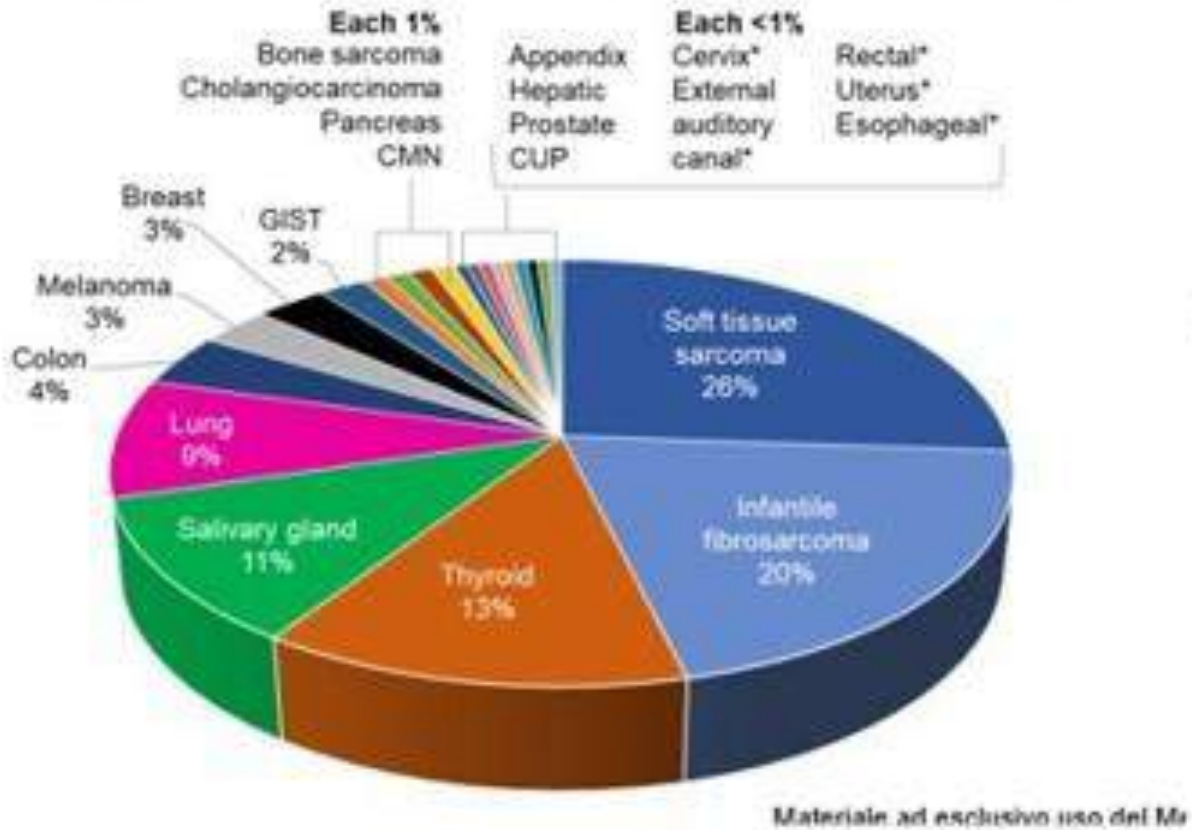

Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials
Lancet Oncol 2020
David S Hong, Steven G DuBois, Shivaani Kumar, Anna F Farago, Catherine M Albert, Kristoffer S Rohrberg, Cornelis M van Tilburg, Ramamoorthy Nagasubramanian, Jordan D Berlin, Noah Federman, Leo Mascarenhas, Birgit Geoerger, Afshin Dowlati, Alberto S Pappo, Stefan Bielack, François Doz, Roy McDermott, Jyoti D Patel, Russell J Schilder, Makoto Tahara, Stefan M Pfister, Olaf Witt, Marc Ladanyi, Erin R Rudzinski, Shivani Nanda, Barrett H Childs, Theodore W Laetsch, David M Hyman*, Alexander Drilon*
ORR 79%
Adult in Phase 1
Advanced solid tumours
NCT02122913
Paediatric in Phase 1/2
Advanced solid tumours
SCOUT: NCT02637687
Adult/adolescent in Phase 2
Advanced solid tumours
NAVIGATE: NCT02576431
Data cutoff:
17 July 2017
Patients:
8
12
35
Data used to grant Marketing authorization approval
Total of 55 patients with TRK fusion solid tumour
Data cutoff:
19 February 2019
Patients:
12
50
97
Data analysed in the publication

Both adult and pediatric patients were included in this analysis; a total of 21 tumor types were represented, including five not previously reported in the previous July 2019 integrated data cut (**Table** and **Figure**)

Table. Baseline characteristics

Characteristics	Integrated dataset (N=218)
Sex, n (%)	
Male	112 (51)
Female	106 (49)
Age, median (range), years	38 (0.1–84)
Pediatric (<18), n (%)	78 (36)
Adult (≥18), n (%)	140 (64)
ECOG or equivalent Lansky PS, n (%)	
0	114 (52)
1	78 (36)
2	23 (11)
3	3 (1)
Known CNS metastases at enrollment, n (%)	19 (9)
Number of prior systemic therapies, median (range)	1 (1–10)
Number of prior systemic regimens, n (%)	
0	59 (27)
1	60 (28)
2	42 (19)
≥3	57 (26)
***NTRK* gene fusion**, n (%)	
NTRK1	97 (44)
NTRK2	6 (3)
NTRK3	115 (53)

Figure. Patient population by tumor type (N=218)



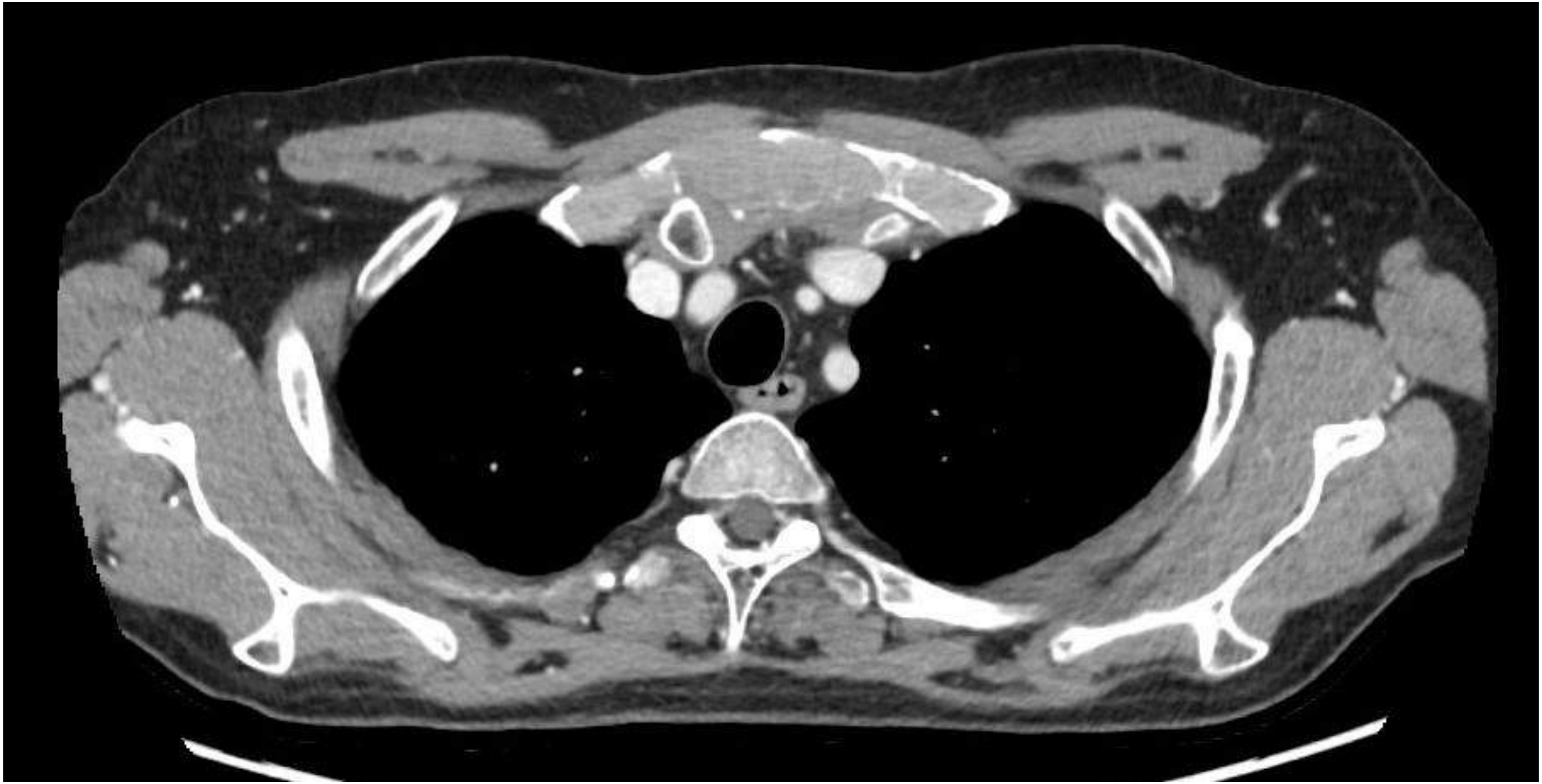
Materiale ad esclusivo uso del Mi

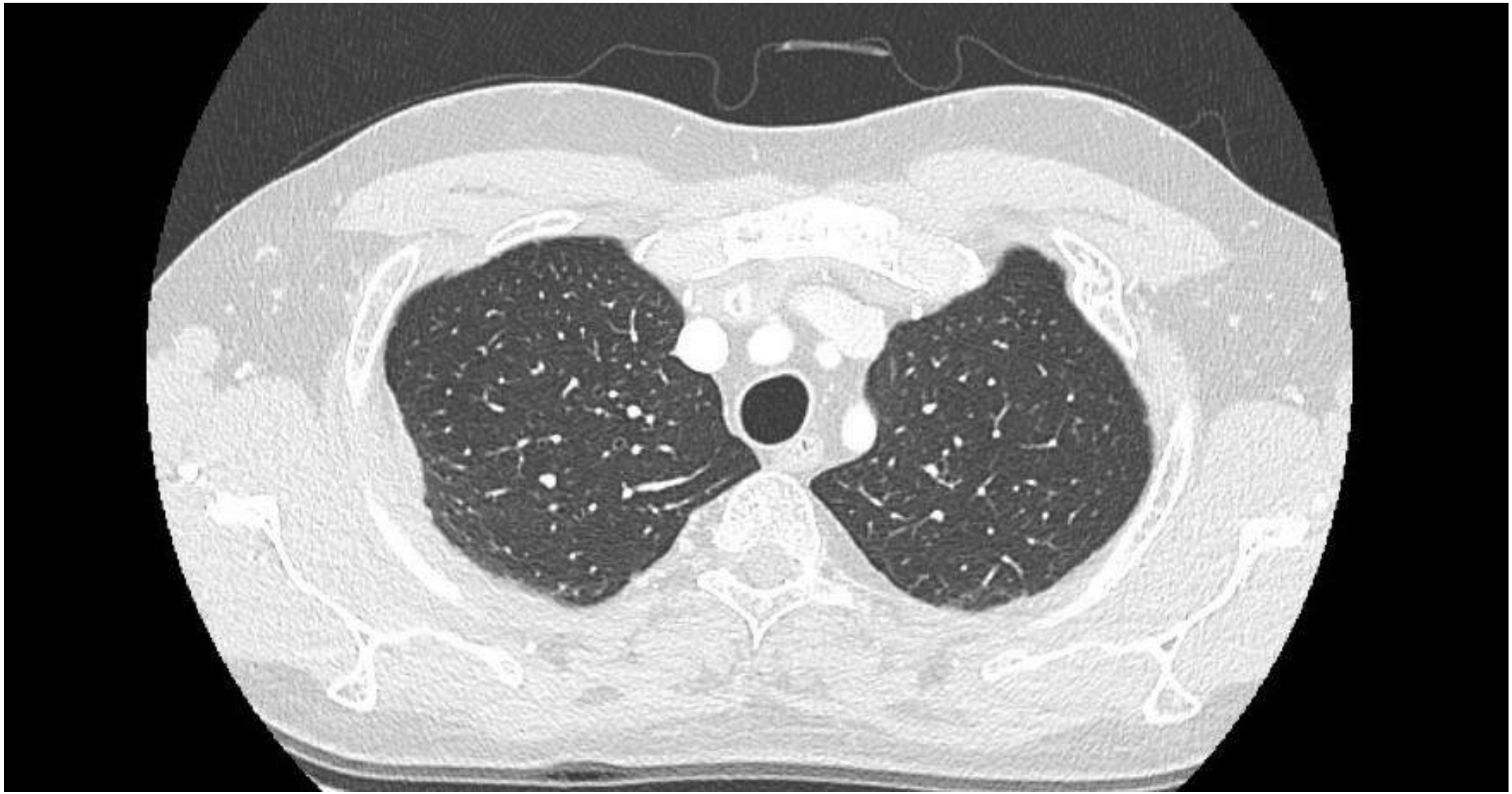
Diagnosi:
A) QUADRO MORFOLOGICO, IMMUNOISTOCHIMICO E MOLECOLARE (cfr BM 1371/2022) COMPATIBILE CON CARCINOMA SECRETORIO DELLA PAROTIDE (pT3; pN1).
INVASIONE VASCOLARE: PRESENTE.
INVASIONE PERINEURALE: PRESENTE.
IPERPLASIA REATTIVA IN LINFONODI INTRAPAROTIDEI (7 REPERITI).
LA NEOPLASIA GIUNGE FOCALMENTE SUL MARGINE CIRCONFERENZIALE.

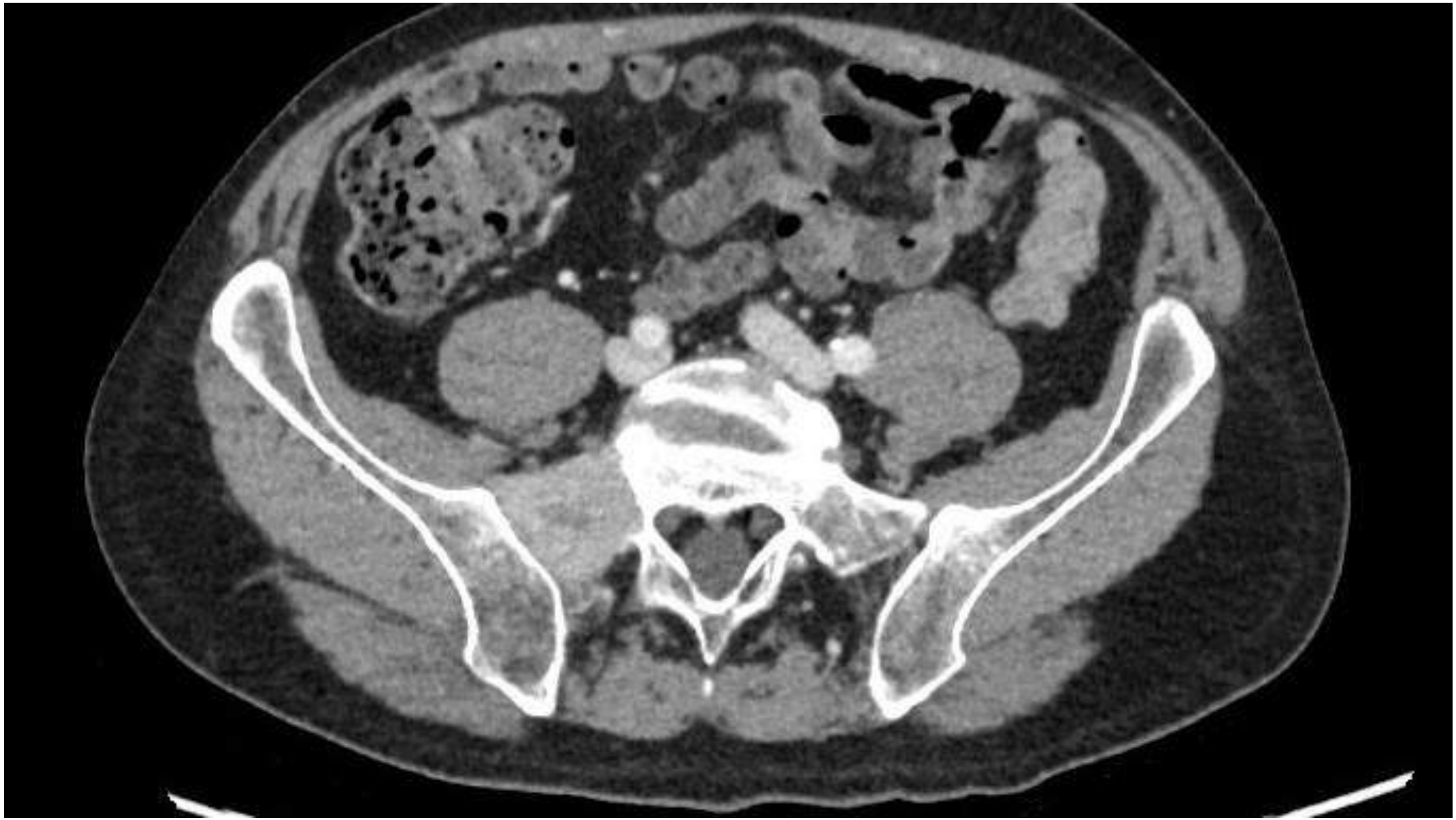
B) IPERPLASIA REATTIVA IN LINFONODI (3 REPERITI).
C) METASTASI DI CARCINOMA IN LINFONODO (1 SU 2 REPERITI; SENZA SUPERAMENTO CAPSULARE).
GHIANDOLA SALIVARE.
D) IPERPLASIA REATTIVA IN LINFONODI (4 REPERITI).
E) IPERPLASIA REATTIVA IN LINFONODI (10 REPERITI).
F) IPERPLASIA REATTIVA IN LINFONODI (6 REPERITI).

Risultato:
E' stata evidenziata la **fusione** (NM_001987.5:r.-454_1009::NM_001012338.2:r.1587_*178) fra i geni **ETV6 (ex5)** - 5' e **NTRK3 (ex15)** - 3' (CAMPIONE CONFORME).

NB. Le fusioni che interessano i geni ETV6 ed NTRK3 sono state descritte nei carcinomi delle ghiandole salivari e sono target potenzialmente terapeutici per gli inibitori di TRK (Hong et al. Lancet Oncol 2020;21(4):531-540).







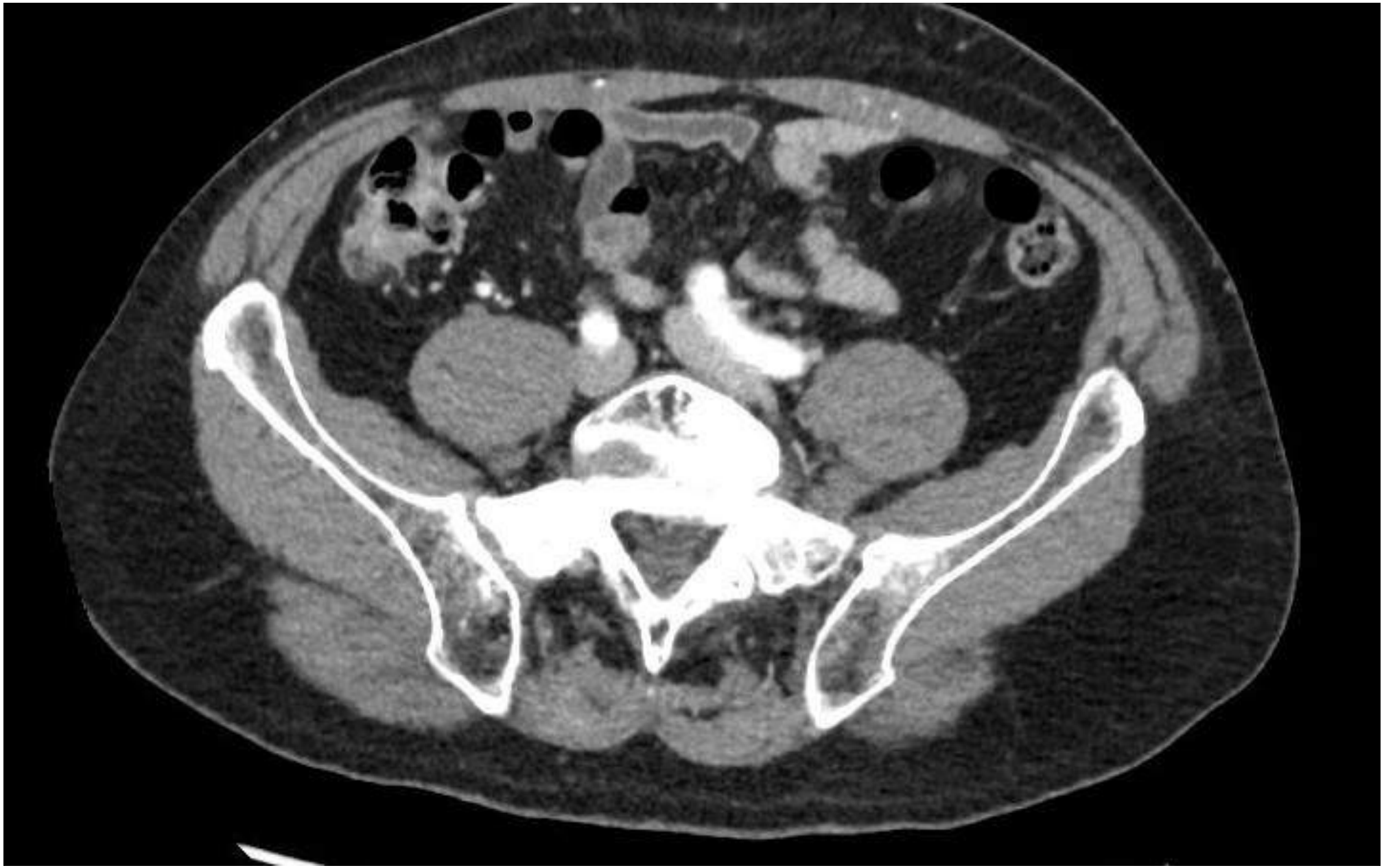
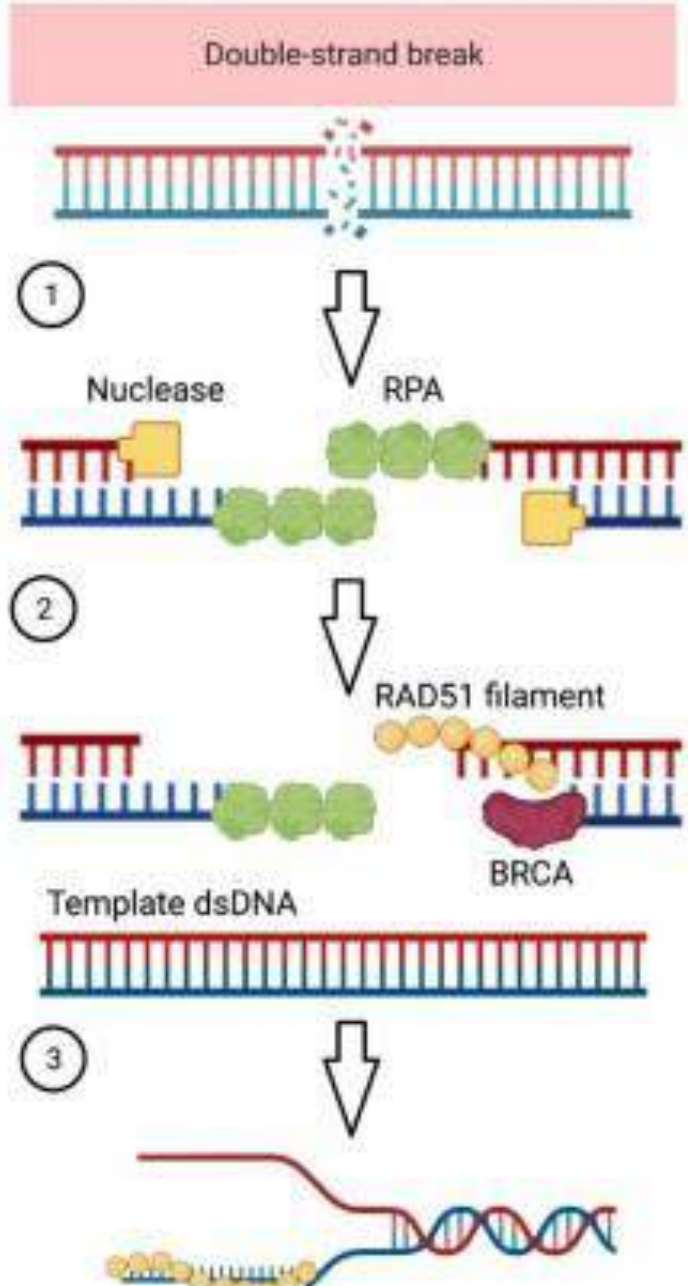


Table 1. List of tumour-agnostic genomic alterations

Gene/Signature[a]	Alteration	Estimated prevalence (illustration of tumours with high prevalence of the alteration)	ESCAT score	Drug class matched
NTRK1/2/3	Fusions	80%-90% secretory breast cancer 15%-20% Spitzoid melanoma	IC	TRK inhibitors
MSI-H/dMMR[a]	MSI-H/dMMR	15%-20% endometrial cancer 15%-20% gastric adenocarcinoma	IC	PD-1 checkpoint inhibitors
RET	Fusions	7% thyroid papillary cancer 2% salivary gland cancer	IC	RET inhibitors
BRAF	Mutations (p.V600E)	40%-45% melanoma 5%-6% small intestinal adenocarcinoma	IC	BRAF inhibitors + MEK inhibitors
FGFR1/2/3	Fusions Mutations	20%-40% bladder cancer 3% glioblastoma multiforme 10%-20% urothelial carcinoma 10% endometrial cancer	IC	Pan-FGFR TKIs
TMB-H[a]	TMB-H	40% small-cell lung cancer	IC	PD-1/PD-L1 checkpoint inhibitors

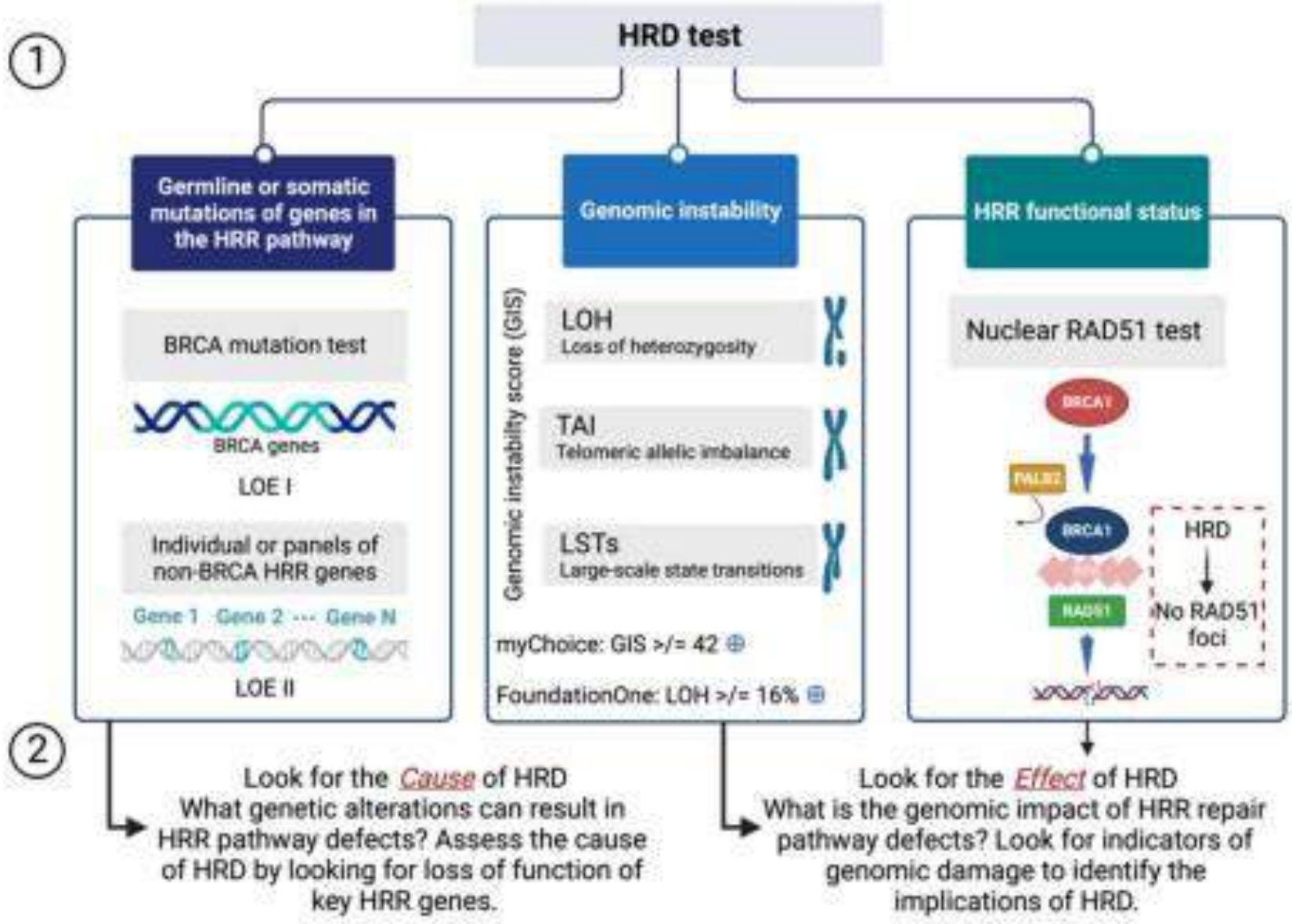

Double-strand break
1
Nuclease
RPA
2
RAD51 filament
BRCA
Template dsDNA
3

HOMOLOGOUS RECOMBINATION DEFICIENCY

- COMPLEX GENOMIC SIGNATURE
- EMERGES WHEN A CELL IS UNABLE TO REPAIR BROKEN DOUBLE-STRANDED DNA VIA HOMOLOGOUS RECOMBINATION REPAIR (HRR) PATHWAY
- CELLS MUST BE ABLE TO REPAIR DNA DAMAGE TO SUSTAIN GENOMIC STABILITY AND CELL FUNCTION
- THIS CAPACITY MANTAINS CHROMOSOME INTEGRITY AND KEEPS CELLS ALIVE

Table 1. Most representative genes involved in the homologous recombination repair pathway [2–6].

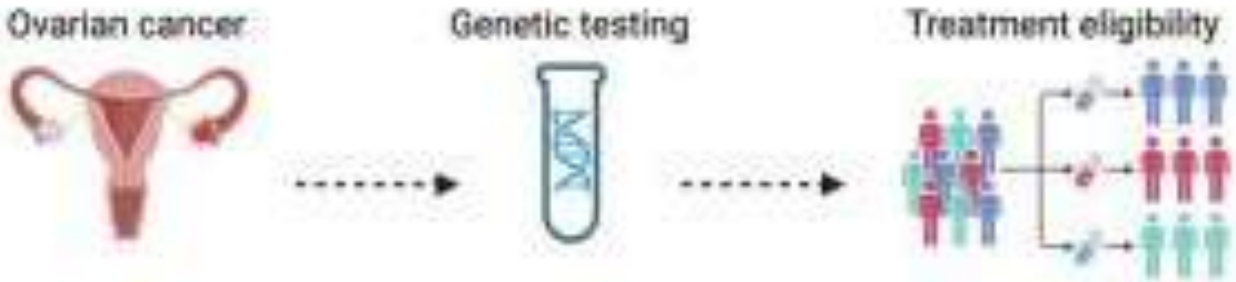
ARID1A	EMSY	MSH2
ATM	FANCA	NBN
ATR	FANCC	PALB2
BRCA1/2	FANCE	PTEN
BARD1	FANCF	RAD50
BAP1	FANCD2	RAD51
BRIP1	FANCG	RAD51B
BLM	FANCI	RAD51C
CDK12	FANCL	RAD51D
CHEK1	H2AX	RAD54L
CHEK2	MRE11	TP53


1
HRD test
Germline or somatic mutations of genes in the HRR pathway
BRCA mutation test
BRCA genes
LOE I
Individual or panels of non-BRCA HRR genes
Gene 1 Gene 2 ··· Gene N
LOE II
Genomic instability
Genomic instability score (GIS)
LOH
Loss of heterozygosity
TAI
Telomeric allelic imbalance
LSTs
Large-scale state transitions
myChoice: GIS >/= 42
FoundationOne: LOH >/= 16%
HRR functional status
Nuclear RAD51 test
BRCA1
PALB2
BRCA1
RAD51
HRD
No RAD51 foci
2
Look for the Cause of HRD
What genetic alterations can result in HRR pathway defects? Assess the cause of HRD by looking for loss of function of key HRR genes.
Look for the Effect of HRD
What is the genomic impact of HRR repair pathway defects? Look for indicators of genomic damage to identify the implications of HRD.

Genomic scar	Description
Loss of heterozygosity (LOH)	One of the two alleles for a gene is lost, resulting in a homozygous cell. Failure of the remaining allele could result in the growth of malignant cells.
Telomeric allelic imbalance (TAI)	The proportion of alleles at the end of the chromosome (telomere) in a pair does not correspond, indicating that one chromosome has more alleles than the other.
Large-scale transitions (LSTs)	Breakpoints between regions of the chromosome cause discrepancies within the chromosome pair.

HRD

- OVARIAN
- BREAST
- PANCREATIC
- UTERINE
- GENITOURINARY
- COLORECTAL
- GASTROINTESTINAL
- HEPATOCELLULAR
- BILIARY
- SARCOMA
- MELANOMA
- PROSTATE



Treatment	Clinical trials	Marker to determine HRD status	FDA-approved diagnostic test
Rucaparib	ARIEL3 (NCT01968213)	BRCA1/2 mutation and/or LOH high	FoundationOne CDx
Olaparib	SOLO-1 (NCT01844986) SOLO-2 (NCT01874353) PAOLA-1 (NCT02477644)	BRCA1/2 mutation and/or positive GIS	MyChoice CDx
Niraparib	PRIMA (NCT02655016) NOVA (NCT01847274)	BRCA1/2 mutation and/or positive GIS	MyChoice CDx

rete
oncologica
Piemonte | Valle d'Aosta

Molecular Tumor Board

CRITERI DI ELIGGIBILITA’

- **ESAURIMENTO DELLE LINEE TERAPUTICHE STANDARD**
- **EVIDENZE CLINICHE E PRECLINICHE DELLA POSSIBILE RILEVANZA DI TARGET NON ROUTINARIAMENTE VALUTATI**
- **PATOLOGIE RARE CON LIMITATE OPZIONI TERAPEUTICHE**
- **PAZ CON TUMORI «ONCOGENE ADDICTED» NON RESPONSIVI AI FARMACI STANDARD**
- **ANALISI FAMILIARE SUGGESTIVA PER MUTAZIONE EREDITARIA AL FINE DI IDENTIFICARE POSSIBILI TARGET**
- **STORIA CLINICA INUSUALE**

FOUNDATIONONE® CDx

PATIENT
03-2024-00114507, IT

TUMOR TYPE
Prostate neuroendocrine carcinoma

COUNTRY CODE
IT

REPORT DATE
29 Jul 2024

ORDERED TEST #
ORD-1925725-01

ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT
DISEASE Prostate neuroendocrine carcinoma
NAME 03-2024-00114507, IT
DATE OF BIRTH 28 July 1960
SEX Male
MEDICAL RECORD # MTB-012

PHYSICIAN
ORDERING PHYSICIAN AIROLDI, MARIO
MEDICAL FACILITY RETE ONCO PIEMONTE VALLE D'AOSTA
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 336652
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Prostate
SPECIMEN ID 2023/I/31641 C1
SPECIMEN TYPE Block
DATE OF COLLECTION 26 September 2023
SPECIMEN RECEIVED 23 July 2024

Genomic Signatures

Microsatellite status - MS-Stable
Tumor Mutational Burden - 2 Muts/Mb

Gene Alterations

For a complete list of the genes assayed, please refer to the Appendix.

BRCA2 **Q2157fs*18**
GNA11 **V344M**
NKX2-1 **amplification**
TMPRSS2 **TMPRSS2-ERG fusion**
TP53 **loss exons 8-11, rearrangement intron 7**

18 Disease relevant genes with no reportable alterations: ***ATM, ATR, BARD1, BRCA1, BRIP1, CDK12, CHEK1, CHEK2, FANCA, FANCL, MLH1, MRE11 (MRE11A), NBN, PALB2, RAD51B, RAD51C, RAD51D, RAD54L***

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***TMPRSS2*** **TMPRSS2-ERG fusion** (p. 7)
- Targeted therapies with potential clinical benefit **approved in this patient's tumor type: Niraparib + Abiraterone** (p. 9), **Olaparib** (p. 10), **Olaparib + Abiraterone** (p. 11), **Talazoparib + Enzalutamide** (p. 11)
- Variants that may inform **nontargeted treatment approaches** (e.g., chemotherapy) in this tumor type: ***BRCA2*** **Q2157fs*18** (p. 5)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 14)
- Variants with **prognostic implications** for this tumor type that may impact treatment decisions: ***BRCA2*** **Q2157fs*18** (p. 5)
- Variants in select cancer susceptibility genes to consider for possible **follow-up germline testing** in the appropriate clinical context: ***BRCA2*** **Q2157fs*18** (p. 5)

GENOMIC SIGNATURES	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Genomic Signatures section
Tumor Mutational Burden - 2 Muts/Mb	**No therapies or clinical trials.** See Genomic Signatures section

GENE ALTERATIONS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
BRCA2 - Q2157fs*18	Niraparib + Abiraterone	Niraparib
	Olaparib	Rucaparib
	Olaparib + Abiraterone	Talazoparib
	Talazoparib + Enzalutamide	

10 Trials see p. 14

Fibromatosi Desmoide

F.D. 37 anni, maschio

Anamnesi familiare positiva per sarcoma di ndd.

APR:
CEI
Asportazione di osteoma mandibolare
Exeresi cisti sebacea
Multipli noduli sottocutanei

APP:
Intervento in altro centro per aneurisma dell'a. mesenterica con riscontro di multipli noduli mesenterici.
Eseguita biopsia con riscontro di fibromatosi desmoide beta catenina negativa. Avviato follow-up.

All'EO multipli noduli sottocutanei e ossei.

FOUNDATIONONE® CDx

PATIENT
03-2024-00104923, IT

TUMOR TYPE
Soft tissue fibromatosis

COUNTRY CODE
IT

REPORT DATE
14 Mar 2024

ORDERED TEST #
ORD-1830469-01

ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT
DISEASE Soft tissue fibromatosis
NAME 03-2024-00104923, IT
DATE OF BIRTH 05 April 1986
SEX Male
MEDICAL RECORD # MTB-004

PHYSICIAN
ORDERING PHYSICIAN AIROLDI, MARIO
MEDICAL FACILITY OSPEDALE S G BATTISTA MOLINETTE - REPARTO ONCOLOGIA MEDICA 2
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 333537
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Abdominal wall
SPECIMEN ID I 3058 2023 A2
SPECIMEN TYPE Block
DATE OF COLLECTION 06 March 2023
SPECIMEN RECEIVED 01 March 2024

Genomic Signatures

Microsatellite status - MS-Stable
Tumor Mutational Burden - 1 Muts/Mb

Gene Alterations

For a complete list of the genes assayed, please refer to the Appendix.

APC **E422fs*32, D610fs*14, E1464fs*8**

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***APC*** **D610fs*14, E1464fs*8, E422fs*32** (p. 3)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 4)

GENE
APC

ALTERATION
E422fs*32, D610fs*14, E1464fs*8

RATIONALE
Based on preclinical and limited clinical data, APC inactivation may be associated with sensitivity to CBP/beta-catenin interaction inhibitors.

NCT04008797

PHASE 1

A Study of E7386 in Combination With Other Anticancer Drug in Participants With Solid Tumor

TARGETS
CBP, Beta-catenin, FGFRs, RET, PDGFRA, VEGFRs, KIT

LOCATIONS: Lyon (France), Pessac (France), Paris (France), Amiens (France), Texas, Seodaemun (Korea, Republic of), Jongno-gu (Korea, Republic of), Seoul (Korea, Republic of), Songpa-gu (Korea, Republic of)

NCT03264664

PHASE 1

Study of E7386 in Participants With Selected Advanced Neoplasms

TARGETS
CBP, Beta-catenin

LOCATIONS: London (United Kingdom), Manchester (United Kingdom), Glasgow (United Kingdom), Minnesota, Florida, Arizona, California

NCT05949099

PHASE 2

Study of Cryoablation and Nirogacestat for Desmoid Tumor

TARGETS
Gamma-secretase

LOCATIONS: California

GENNAIO 2024

- Progressione encefalica, polmonare, linfonodale e surrenalica

9

MARZO 2023

- Nell'attesa dell'esito dello screening molecolare avviata V linea nab-paclitaxel (I ciclo 11/3/24)

10

12

MARZO 2024

- Screening failure per TAPISTRY Trial c/o Siena
- **NGS FoundationOne***
- **alterazione (somatica) di BRCA1** (p.G1077Afs*8, HGVS Coding effect NM_007294.3: c.3228_3229del; cromosomal position chr17:41244318; VAF 60.9%)
- **mutazione TP53** (p.P191_V197delinsX[1], HGVS Coding effect NM_000546.4:c.572_589del, cromosomal position chr17:7578259, VAF 54%),
- **TMB 11.35 mutation per megabase**
- **MSS**

SINTESI:

Paziente di 38 anni in ottime condizioni generali PS 0 ECOG, affetta da carcinoma mammario metastatico triplo-negativo, sottoposta a molteplici interventi chirurgici e radioterapici encefalici, in attuale V linea con nab-paclitaxel BRCA GER -

Riscontro NGS di mutazione somatica di BRCA (VAF 60.9%)

PATHOLOGIST COMMENTS

Douglas A. Mata, MD, MPH 11-Nov-2024

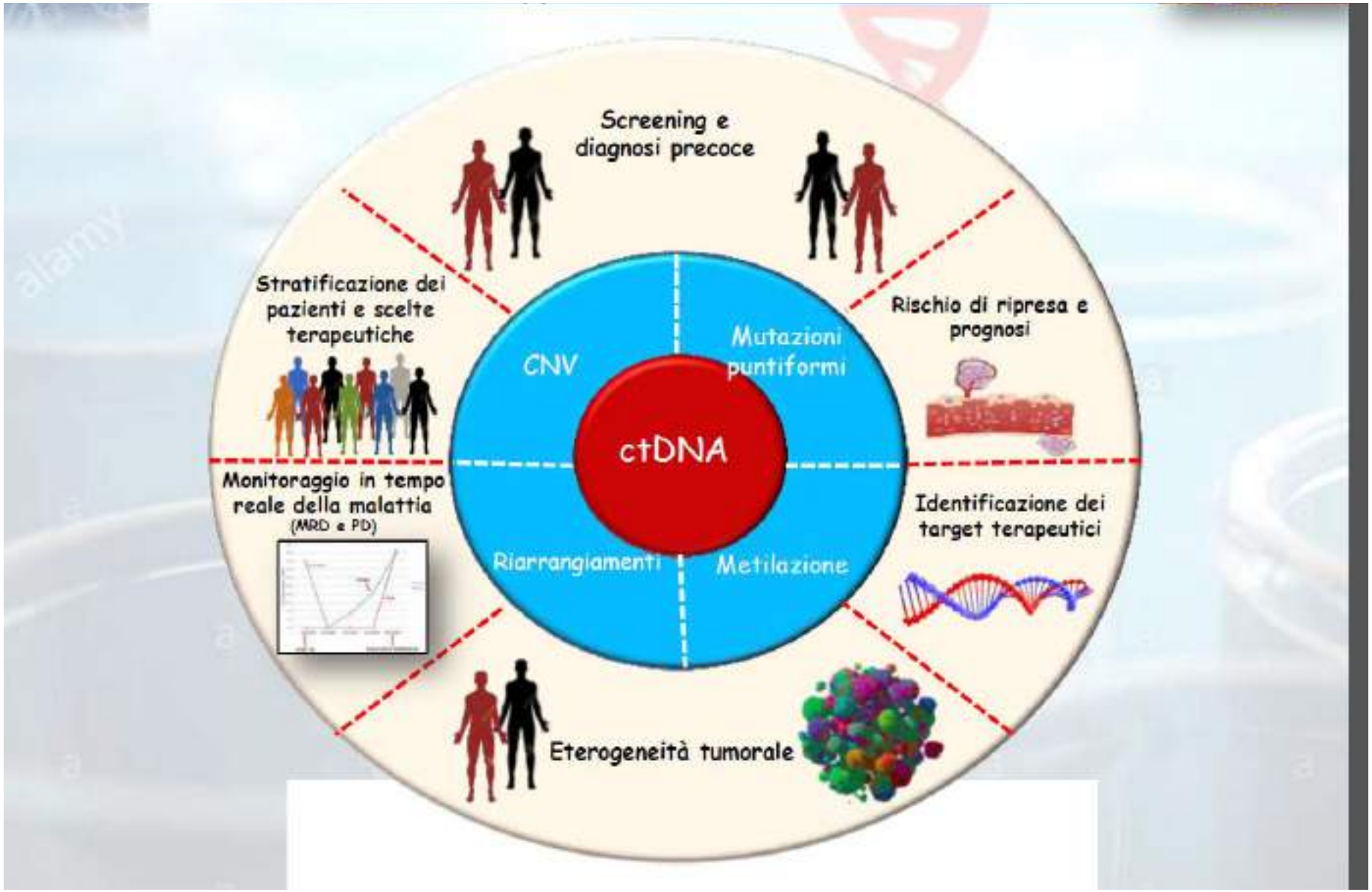
A KIT exon 11 V560del mutation was detected. This particular mutation has been recurrently identified in thymic carcinomas, gastrointestinal stromal tumors, and mucosal melanomas, and less commonly has been reported in non-small-cell lung carcinomas. Clinicopathologic correlation is advised.

GENOMIC SIGNATURES	THERAPY AND CLINICAL TRIAL IMPLICATIONS
HRD signature - HRDsig Negative	**No therapies or clinical trials.** See Genomic Signatures section
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Genomic Signatures section
Tumor Mutational Burden - 2 Muts/Mb	**No therapies or clinical trials.** See Genomic Signatures section

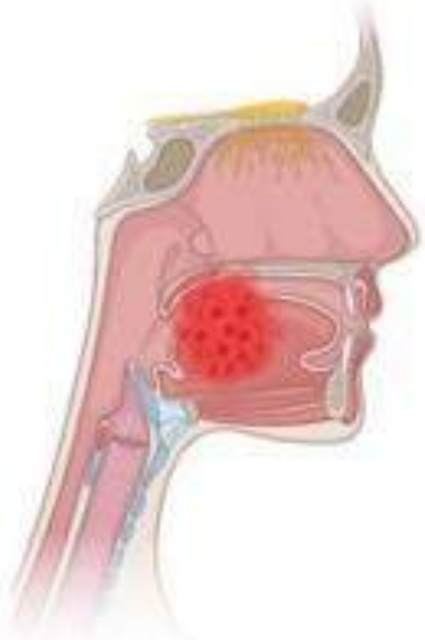
GENE ALTERATIONS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
***KIT* -** exon 11 deletion (V560del)	none	Dasatinib
		Imatinib
		Nilotinib
		Ponatinib
		Sorafenib
		Sunitinib

10 Trials see p. 9

BIOPSIA LIQUIDA E MEDICINA DI PRECISIONE

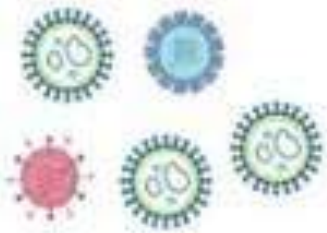


Candidate biomarkers for HNC surveillance

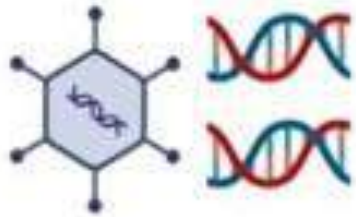


EBV+ nasopharyngeal carcinoma

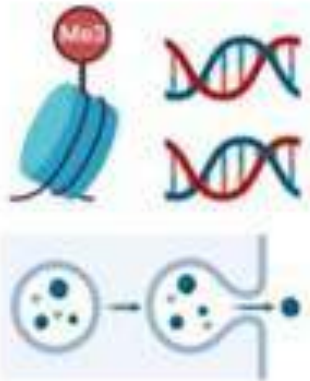
HPV+ oropharyngeal carcinoma



Viral DNA



Other mucosal head and neck squamous cell carcinomas



ctDNA, methylated ctDNA, exosomes…

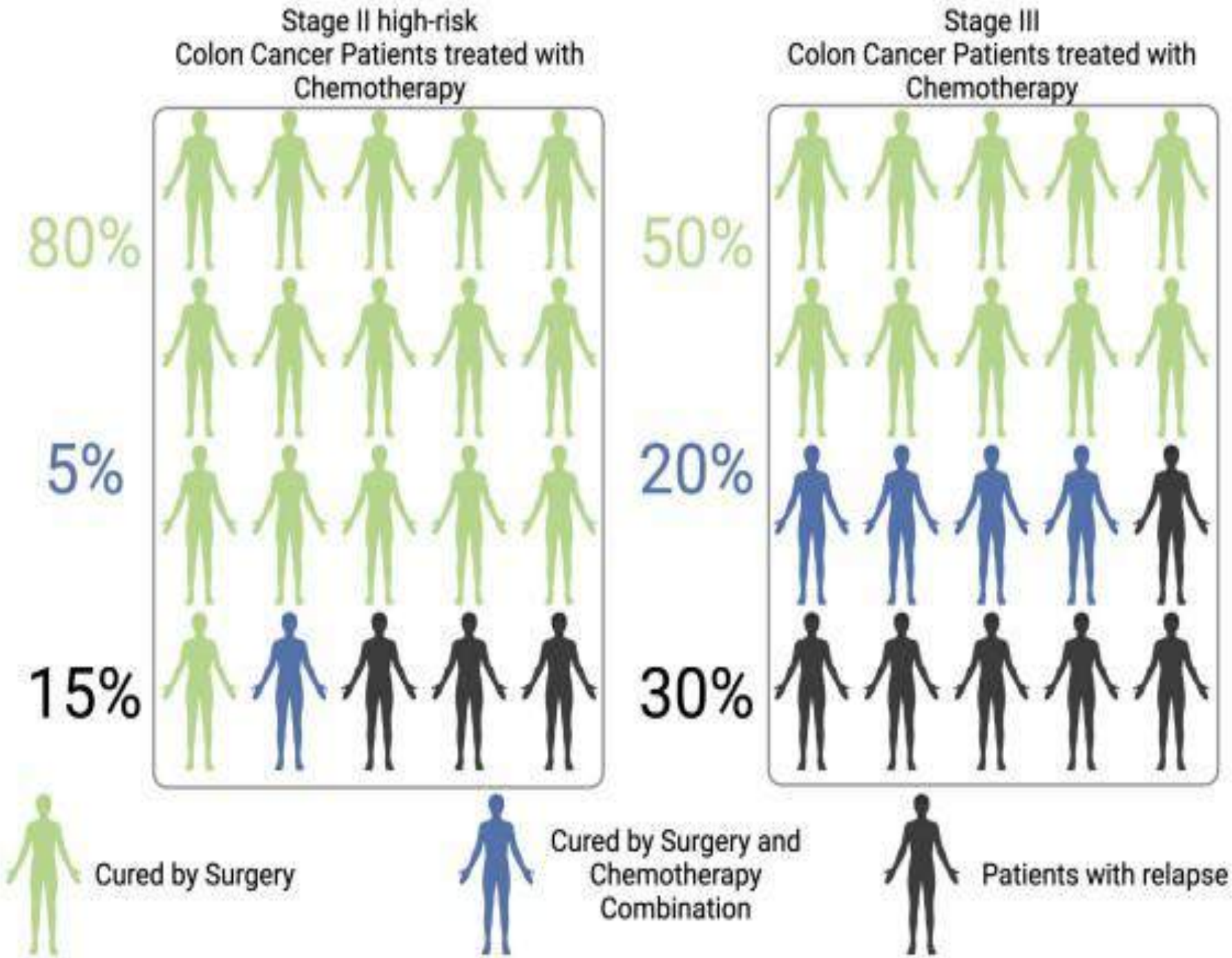
ctHPVDNA and its potential uses

Screening

Guide selection and/or a change in treatment

Detect Recurrence

- Cell free DNA that is tumor-derived released into the circulation through apoptosis, necrosis, or exosomal release from tumor cells
- Measured by quantitative PCR (digital droplet PCR) or NGS


Stage II high-risk
Colon Cancer Patients treated with
Chemotherapy
80%
5%
15%
Stage III
Colon Cancer Patients treated with
Chemotherapy
50%
20%
30%
Cured by Surgery
Cured by Surgery and
Chemotherapy
Combination
Patients with relapse

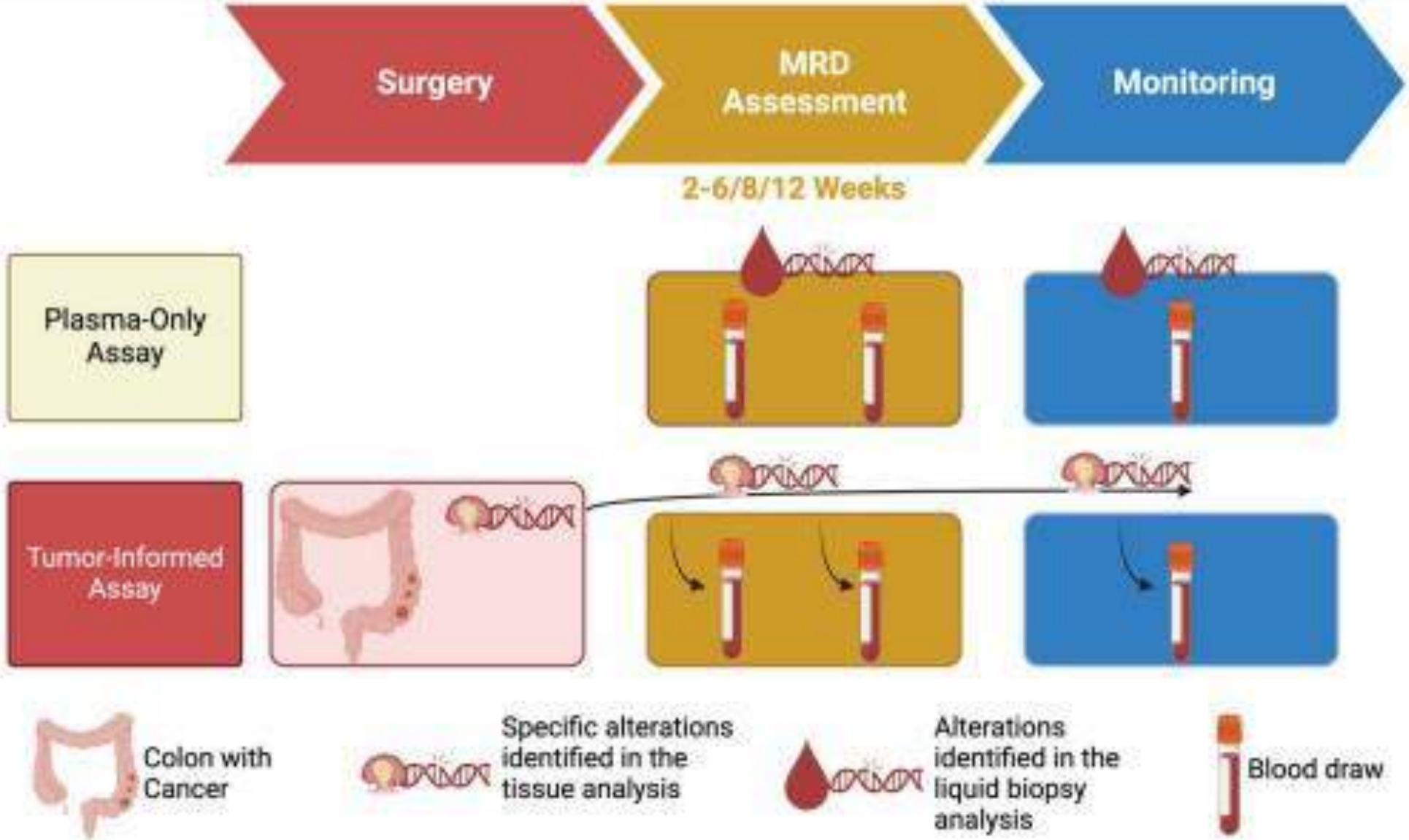

Surgery
MRD Assessment
Monitoring
2-6/8/12 Weeks
Plasma-Only Assay
Tumor-Informed Assay
Colon with Cancer
Specific alterations identified in the tissue analysis
Alterations identified in the liquid biopsy analysis
Blood draw

Table 3. List of genomic alterations level I/II according to ESCAT in advanced breast cancer

Gene	Alteration	Estimated prevalence	ESCAT score	Drug class matched
ERBB2	Amplifications	15%-20%	IA	Anti-HER2 monoclonal antibodies HER2 TKIs Anti-HER2 ADCs
	Hotspot mutations	4%	IIB	Pan-HER TKIs Anti-HER2 ADCs
PIK3CA	Hotspot mutations	30%-40%	IA (ER-positive HER2-negative ABC)	α-specific PI3K inhibitors*
ESR1	Mutations	30%-40%	IA (ER-positive HER2-negative ABC resistant to AI)	SERDs
BRCA1/2	Germline pathogenic/likely pathogenic variants	4%	IA	PARP inhibitors
	Somatic mutations	3%	IIB	PARP inhibitors
PTEN	Mutations/deletions	7%	I/II	AKT inhibitors
AKT1	Mutations (p. E17K)	5%	I/II	AKT inhibitors
PALB2	Germline pathogenic/likely pathogenic variants	1%	IIB	PARP inhibitors

Almost all ABC patients on CDK4/6i will progress

Endocrine sensitivity compromise – Fulvestrant single agent achieves mPFS of 1,8 – 4,5

Endocrine Strategies based on acctionable mutations &/or doublets

- mTORi: **everolimus** and second generation mTOR
- PI3K*mut*: **alpelisib, inavolisib**
- AKT/PI3K/P-TEN: **Capivasertib,** ipatasertib
- gBRCA1/2*mut*: **Olaparib, talazoparib**
- ESR1*mut*: **Elacestrant, camicestrant, giredestrant**/PROTAC/Progestagens
- CDK4/6i rechalenge: Ribociclib, abemaciclib & new CDK4/6i
- CDK2 / CDK4 selective inhibitors

Non-endocrine approaches = ADCs / Chemotherapy

- HER2-low: **Trastuzumab-deruxtecan**
- TROP2: **Sacituuzmab-govitecan, datopotamab-deruxtecan**

"Network Medicine"

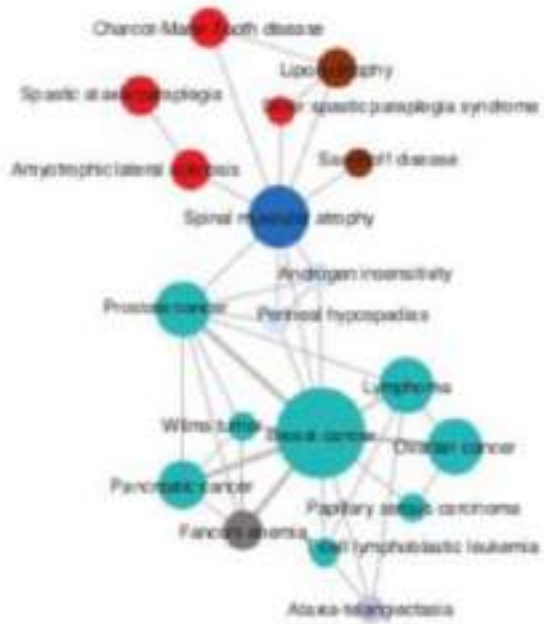
- I network al momento più conosciuti e studiati sono quelli molecolari, ossia
  - **network di interazione proteica** (i cui nodi sono proteine legate tra loro da interazioni fisiche),
  - **network metabolici** (i cui nodi sono costituiti da metaboliti, legati tra loro se coinvolti nella stessa reazione biochimica),
  - **network regolatori** (i cui legami sono costituiti, a livello trascrizionale, dalla interazione regolatoria tra fattore trascrizionale e gene, mentre a livello post trascrizionale, i legami si stabiliscono tra chinasi e loro substrati),
  - **network di RNA** (i cui nodi sono costituiti da miRNAs e lncRNA).


The human disease network

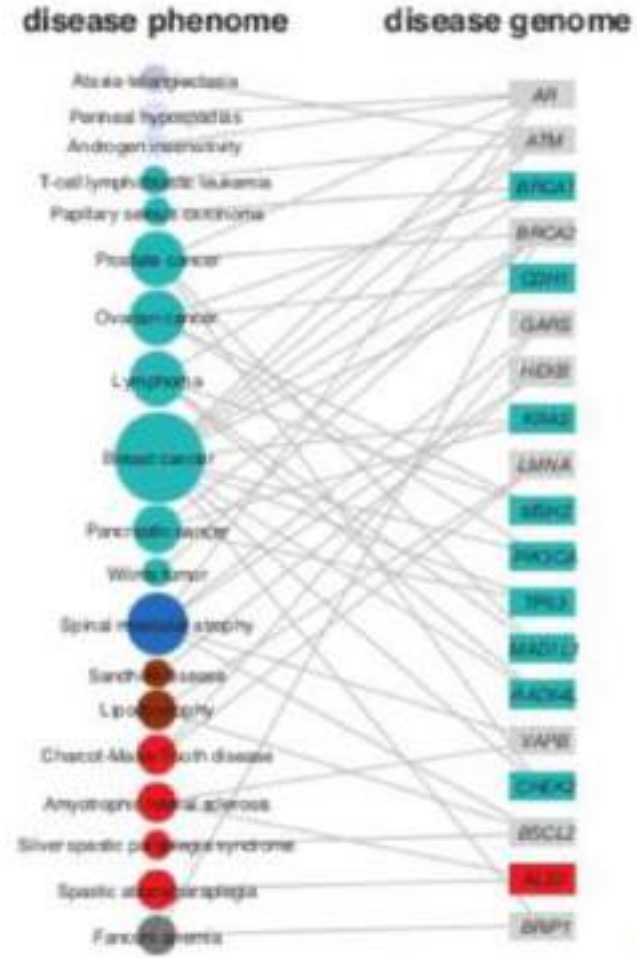
Goh et al., PNAS 2007

La malattia come perturbazione di un network

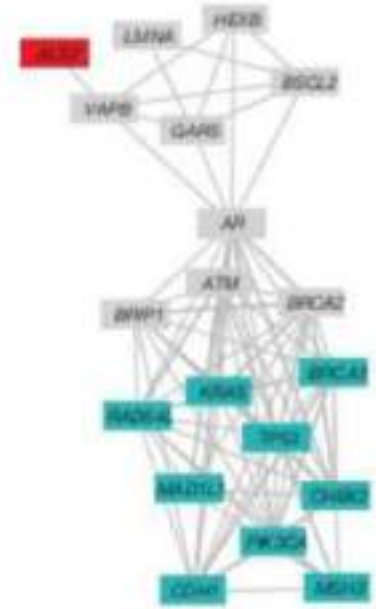
Human Disease Network (HDN)



DISEASOME



Disease Gene Network (DGN)



LA SFIDA ORGANIZZATIVA

- TECNICHE BIOPTICHE ADEGUATE
- LABORATORI CERTIFICATI (LABORATORI HUB)
- INDICARE I PERCORSI CON I TEMPI DEI CAMPIONI DI TESSUTO E SANGUE
- DISCUTERE COLLEGIALMENTE LE SCELTE TERAPUTICHE
- INDICARE E REPERIRE IL FARMACO ADEGUATO
- PERIFERIZZARE LE TERAPIE
- RACCOGLIERE GLI ESITI TERAPEUTICI

ABBIAMO UN MODELLO ADEGUATO ?

- **NON ANCORA**
- **ABBIAMO LABORATORI HUB CERTIFICATI**
- **STIAMO CHIARENDO CHI FA CHE COSA , IN QUANTO TEMPO E CON QUALE TARIFFA**
- **ABBIAMO UN MTB REGIONALE**
- **ABBIAMO GIC E ONCOLOGI SUL TERRITORIO**
- **DOBBIAMO POTENZIARE GENETICA ONCOLOGICA**