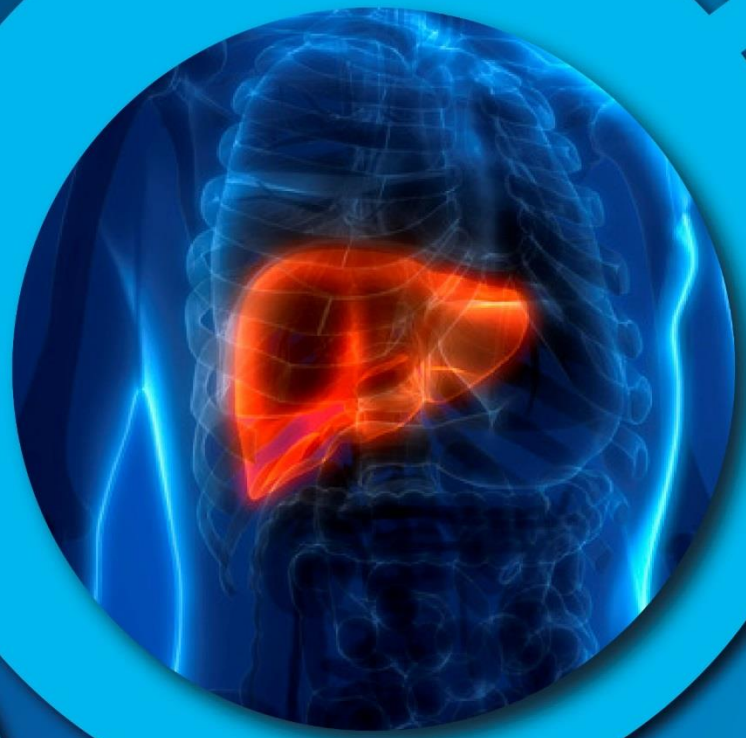


Patient Journey

Approccio personalizzato al paziente e esperienze a confronto: Epatocarcinoma e Colangiocarcinoma

01 Febbraio 2024

VERONA

CROWNE PLAZA

Via Belgio, 16

AIGOM

ASSOCIAZIONE ITALIANA
GRUPPI ONCOLOGICI MULTIDISCIPLINARI

Caratterizzazione Molecolare nel Colangiocarcinoma Avanzato

Giulio Settanni
Laboratorio di Patologia Molecolare
UO Anatomia Patologica (Direttore: Prof. Giuseppe Zamboni)

SACRO CUORE DON CALABRIA I R C C S

1922 - 2022 SACRO CUORE

Cancer Care Center
Numero per la Cura del Tumore
Numero Verde 800 143 143

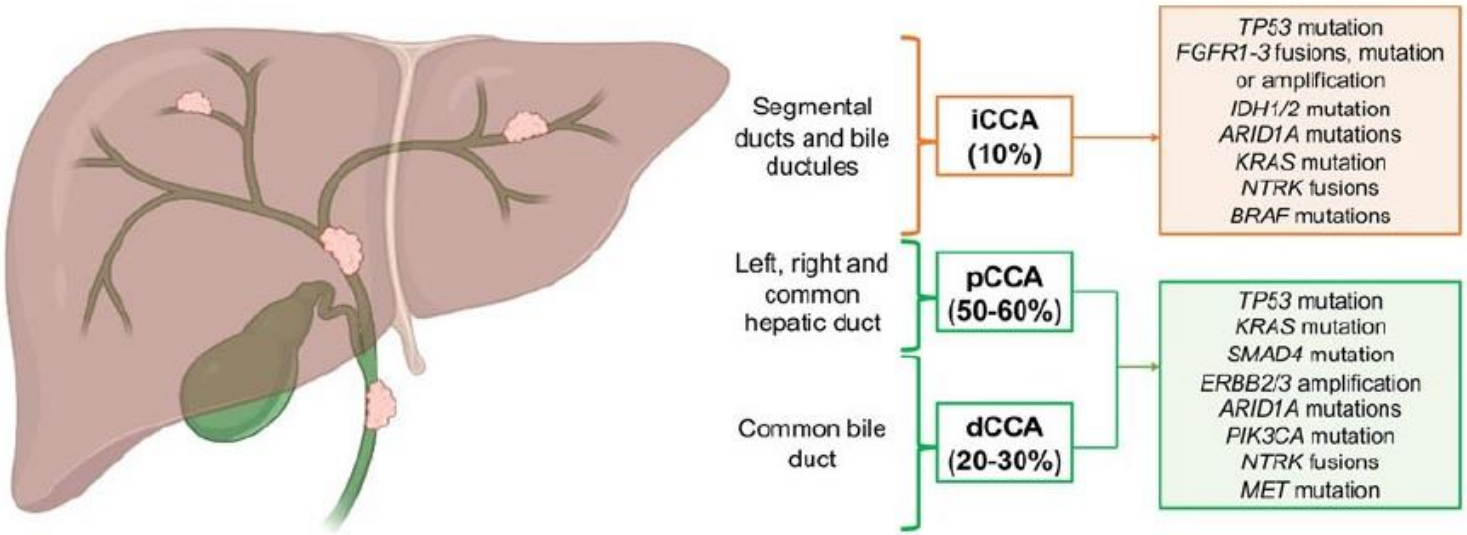
Patient Journey
Approccio personalizzato al paziente e esperienze a confronto:
Epatocarcinoma e Colangiocarcinoma

01 Febbraio 2024
VERONA

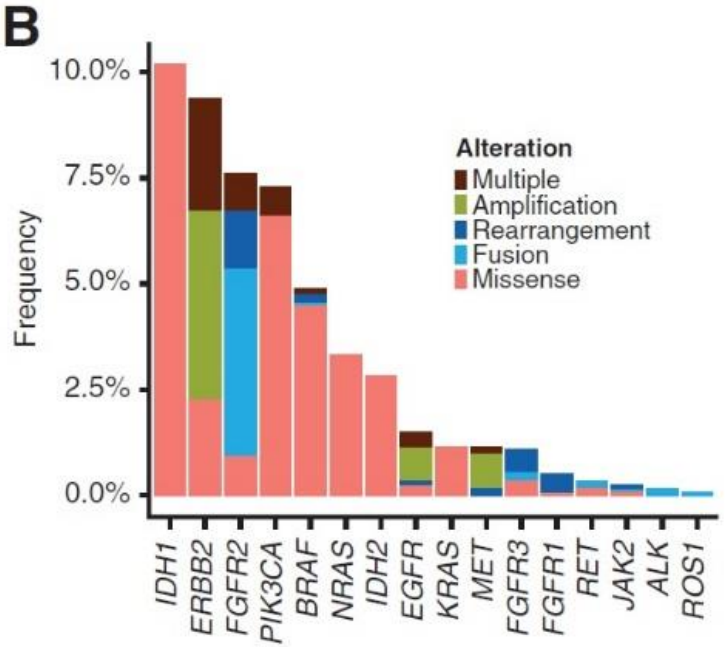
TOPICS

- Potentially actionable genetic alterations in CCAs (ESCAT-1 level)
- NGS as gold standard for Molecular Diagnostics
- Critical aspects in Molecular Typing

CCAs MUTATIONAL LANDSCAPE



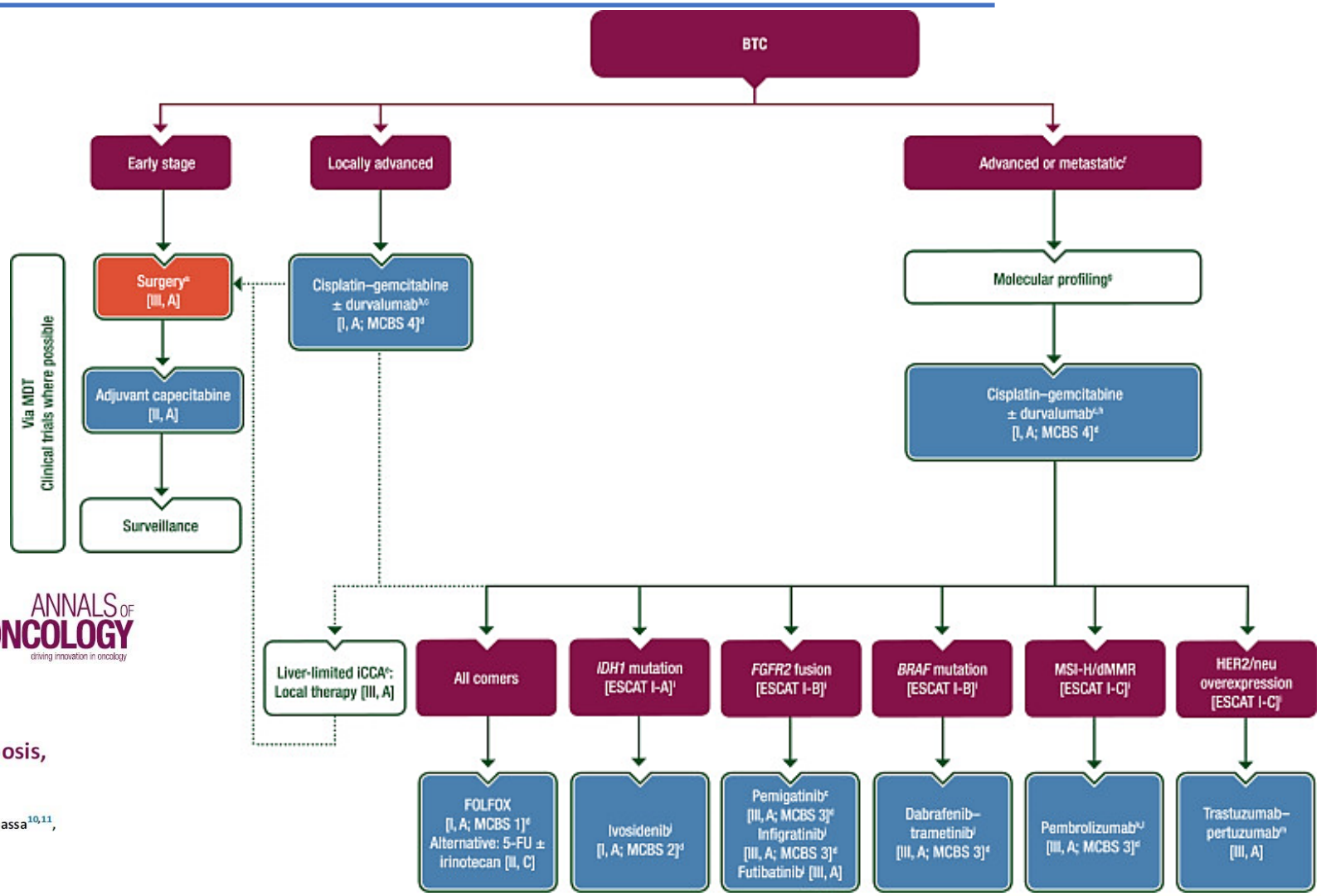
Angerilli et al. 2023



Silverman et al. 2021

~40%
POTENTIALLY ACTIONABLE

MAIN ACTIONABLE TARGETS IN CCAs



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

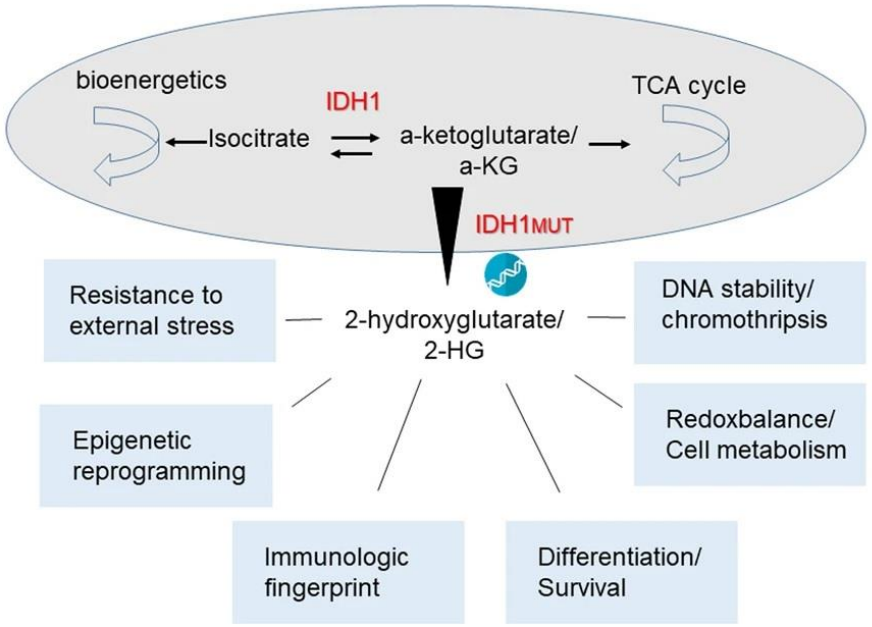
ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

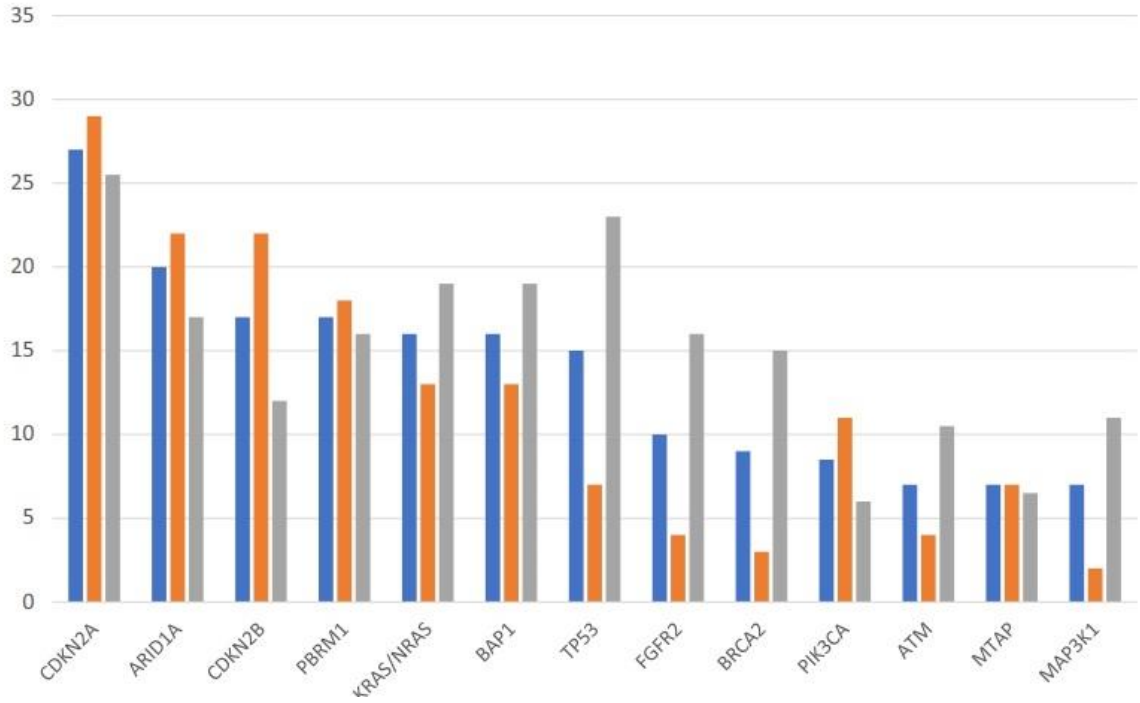
Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up ☆

A. Vogel[1], J. Bridgewater[2], J. Edeline[3,4], R. K. Kelley[5], H. J. Klümpen[6], D. Malka[7,8], J. N. Primrose[9], L. Rimassa[10,11], A. Stenzinger[12], J. W. Valle[13,14] & M. Ducreux[8,15], on behalf of the ESMO Guidelines Committee*

IDH1



Mehrjardi et al. 2020

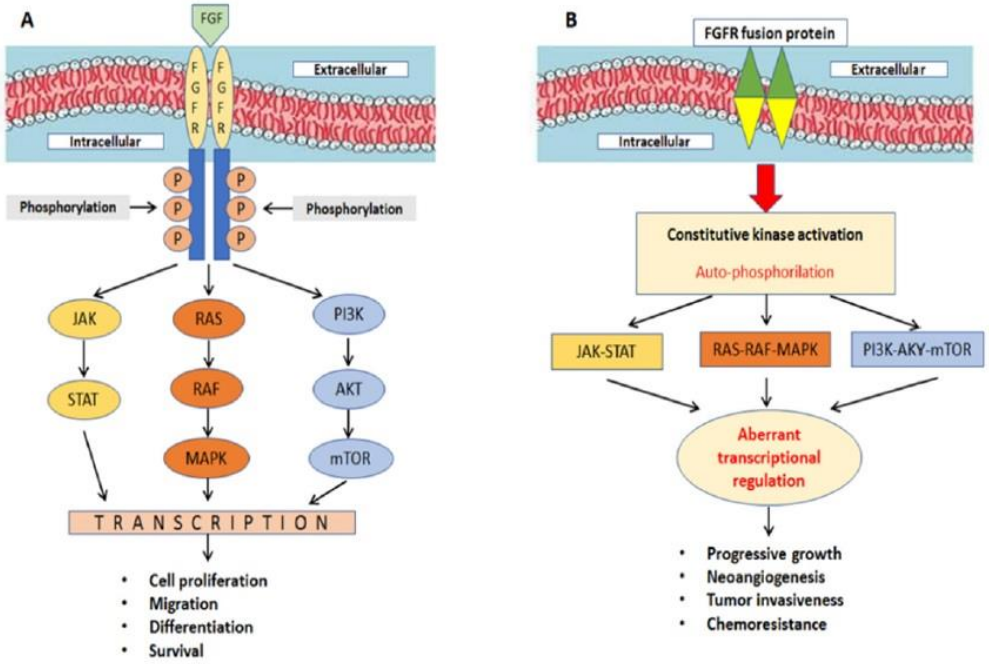


Rimini et al. 2022

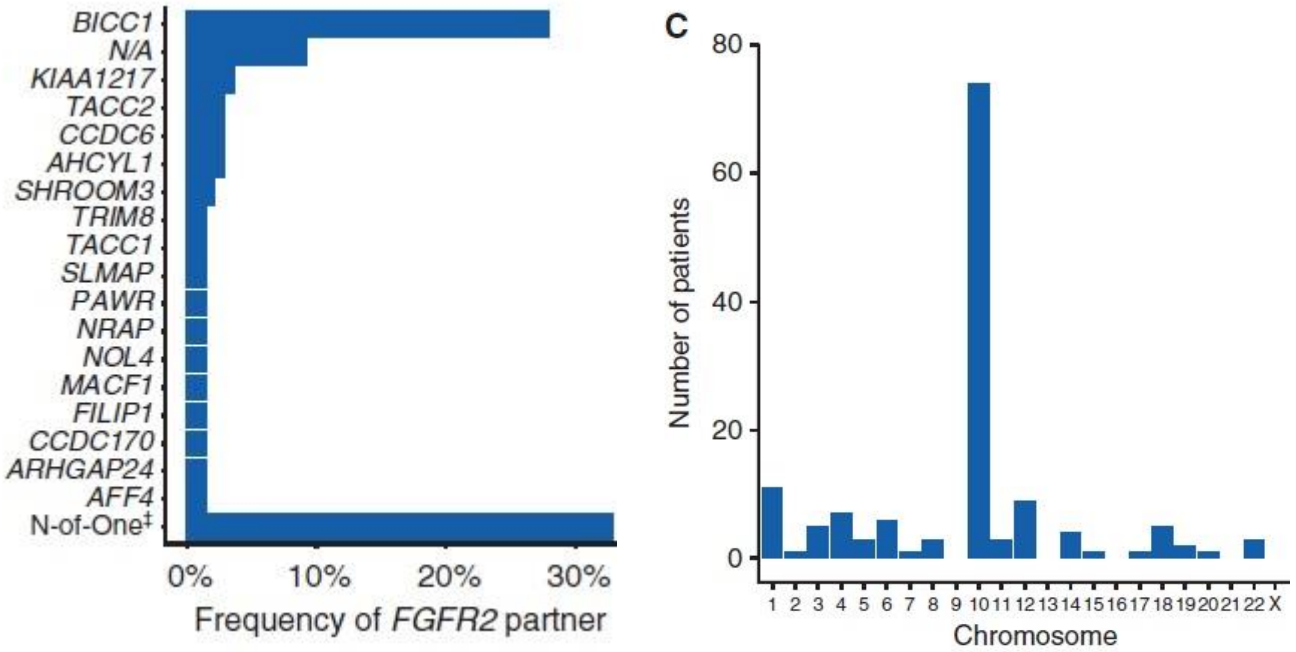
- IDH1 altered in ~15% iCCA;
- Most common alteration: codon R132 Missense;
- Treatment: Ivosidenib.

- Common associations: CDKN2A-B, PBRM1; KRAS;
- Less common associations: TP53, BRCA2, FGFR2;
- Prognostic value?

FGFR2



Capuozzo et al. 2022



Silverman et al. 2021

- FGFR2 altered in ~10% iCCA;
- Most common alteration: FGFR2 fusions;
- Treatment: Pemigatinib.

- Common partner: BICC1 (30%);
- Intrachromosomic Re-arrangement is common;
- Difficult molecular testing.

HER2, BRAF

HER2 Amplification
(~10% CCA)

Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway): a multicentre, open-label, phase 2a, multiple basket study

Milind Javle, Mitesh J Borad, Nilofer S Azad, Razelle Kurzrock, Ghassan K Abou-Alfa, Ben George, John Hainsworth, Funda Meric-Bernstam, Charles Swanton, Christopher J Sweeney, Claire F Friedman, Ron Bose, David R Spigel, Yong Wang, Jonathan Levy, Katja Schulze, Vaikunth Cuchelkar, Arisha Patel, Howard Burris

Lancet 2021

PERTUZUMAB/TRASTUZUMAB

BRAF V600E Mutation
(~5% CCA)

Dabrafenib plus trametinib in patients with *BRAF*^{V600E}-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial

Vivek Subbiah, Ulrik Lassen, Elena Élez, Antoine Italiano, Giuseppe Curigliano, Milind Javle, Filippo de Braud, Gerald W Prager, Richard Greil, Alexander Stein, Angelica Fasolo, Jan H M Schellens, Patrick Y Wen, Kert Viele, Aislyn D Boran, Eduard Gasal, Paul Burgess, Palanichamy Ilankumaran, Zev A Wainberg

Lancet 2021

DABRAFENIB/TRAMETINIB

NTRK, MSI

NTRK1,2,3 Fusions
(<1% CCA)

Entrectinib in patients with advanced or metastatic *NTRK* fusion-positive solid tumours: integrated analysis of three phase 1–2 trials

Robert C Doebele, Alexander Drilon*, Luis Paz-Ares, Salvatore Siena, Alice T Shaw, Anna F Farago, Collin M Blakely, Takashi Seto, Byung Chul Cho, Diego Tosi, Benjamin Besse, Sant P Chawla, Lyudmila Bazhenova, John C Krauss, Young Kwang Chae, Minal Barve, Ignacio Garrido-Laguna, Stephen V Liu, Paul Conkling, Thomas John, Marwan Fakih, Darren Sigal, Herbert H Loong, Gary L Buchschacher Jr, Pilar Garrido, Jorge Nieva, Conor Steuer, Tobias R Overbeck, Daniel W Bowles, Elizabeth Fox, Todd Riehl, Edna Chow-Maneval, Brian Simmons, Na Cui, Ann Johnson, Susan Eng, Timothy R Wilson, George D Demetri, on behalf of the trial investigators*

Lancet 2020

ENTRECTINIB/LAROTRECTINIB

dMMR/MSI
(<1% CCA)

Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/ Mismatch Repair–Deficient Cancer: Results From the Phase II KEYNOTE-158 Study

Aurelien Marabelle, MD, PhD[1]; Dung T. Le, MD[2]; Paolo A. Ascierto, MD[3]; Anna Maria Di Giacomo, MD[4]; Ana De Jesus-Acosta, MD[2]; Jean-Pierre Delord, MD, PhD[5]; Ravit Geva, MD, MSc[6]; Maya Gottfried, MD[7]; Nicolas Penel, MD, PhD[8]; Aaron R. Hansen, MBBS[9]; Sarina A. Piha-Paul, MD[10]; Toshihiko Doi, MD, PhD[11]; Bo Gao, MBBS, PhD[12]; Hyun Cheol Chung, MD, PhD[13]; Jose Lopez-Martin, MD, PhD[14]; Yung-Jue Bang, MD, PhD[15]; Ronnie Shapira Frommer, MD[16]; Manisha Shah, MD[17]; Razi Ghori, PhD[18]; Andrew K. Joe, MD[18]; Scott K. Pruitt, MD, PhD[18]; and Luis A. Diaz Jr, MD[19]

JCO 2019

PEMBROLIZUMAB

MOLECULAR TYPING OF CCAs: NGS

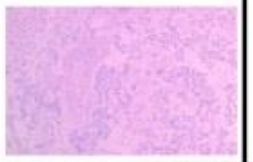
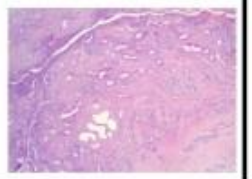
- Parallele Analysis of SNPs, InDels, Fusions, CNVs;
- Low Input DNA/RNA;
- Ready to Use Gene Panels;
- High Multiplexing capacity.

DNA							RNA	
Deletions, insertions, and substitutions					Copy number alternations		Fusions and splicing variants	
AKT1	*CTNNB1*	*FGFR4*	*MAP2K1*	*PTEN*	***AR***	***FGFR2***	*ALK*	***NRG1***
AKT2	*EGFR*	*FLT3*	*MAP2K2*	*RAF1*	***EGFR***	***FGFR3***	***AR***	*NTRK1*
AKT3	*ERBB2*	*GNAS*	*MET*	*RET*	***ERBB2***	***KRAS***	***BRAF***	*NTRK2*
ALK	*ERBB3*	*HRAS*	*NRAS*	*ROS1*	***ERBB3***	***MET***	***EGFR***	*NTRK3*
AR	*ERBB4*	*IDH1*	*NTRK1*	*STK11*	***FGFR1***	***PIK3CA***	***ESR1***	***NUTM1***
ARAF	*ESR1*	*IDH2*	*NTRK2*	*TP53*			***FGFR1***	*RET*
BRAF	*FGFR1*	*KEAP1*	*NTRK3*				***FGFR2***	*ROS1*
CDK4	*FGFR2*	*KIT*	*PDGFRA*				***FGFR3***	***RSPO2***
CHEK2	*FGFR3*	*KRAS*	*PIK3CA*				*MET*	***RSPO3***

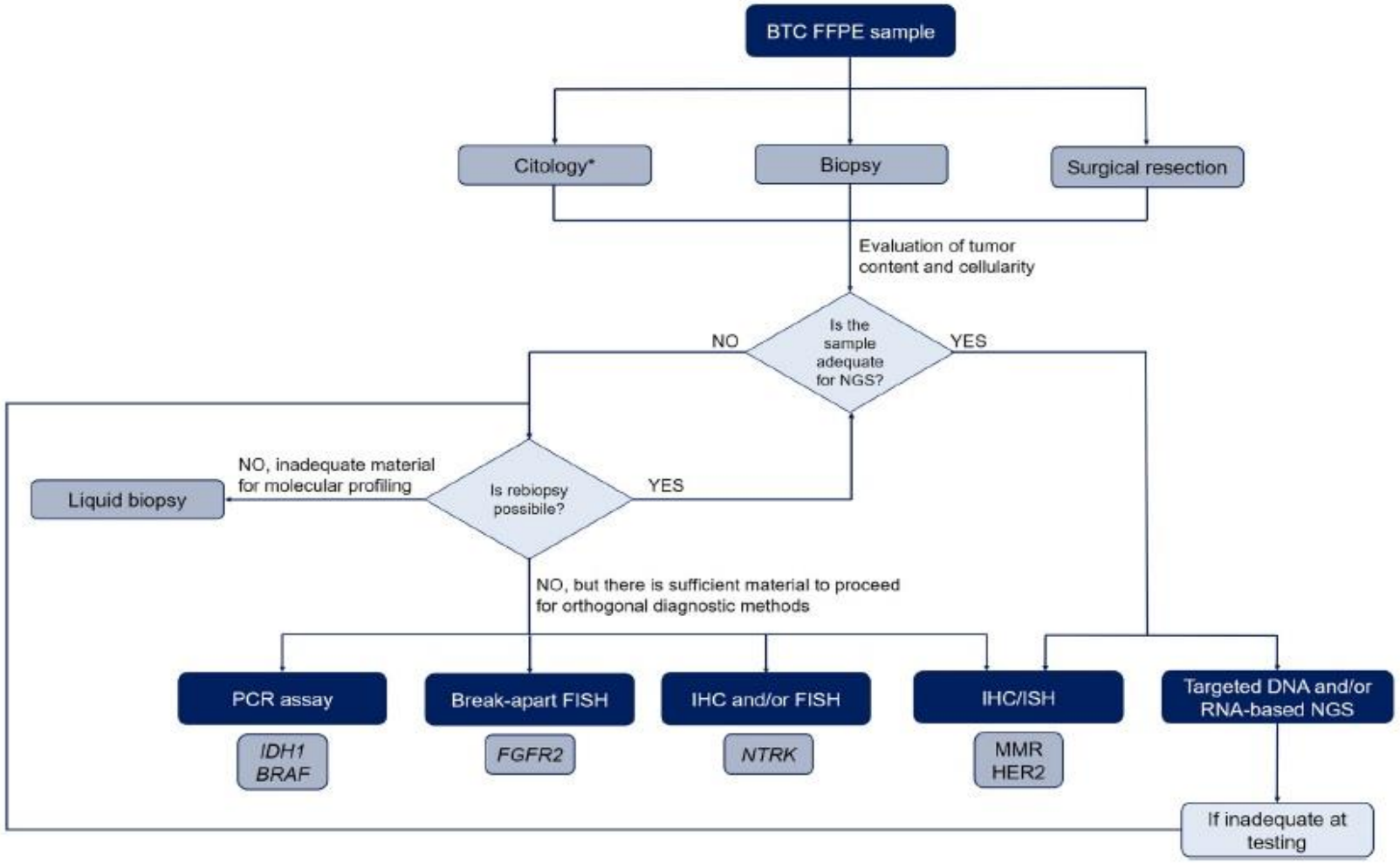
Oncomine Express Test IVDR

2 Patologi Molecolari
3 Biologi Molecolari
1 Genetista Medico
2 TSLB Dedicati

THE ROLE OF THE PATHOLOGIST

TYPE OF TISSUE AVAILABLE FOR TESTING		ANALYTIC PROBLEMS
Needle biopsy		Small sample size Low cellularity Marked desmoplasia/necrosis
Surgical resction specimen		Problems in pre-analytic variables (fixation, cold ischaemia etc)
Biliary brushing or microbiopsy		Difficulty of diagnosis Extremely low cellularity
Surgical resction specimen		Problems in pre-analytic variables (fixation, cold ischaemia etc)

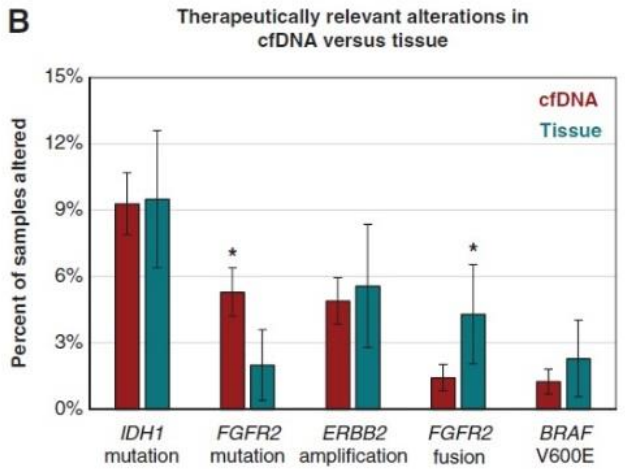
Fassan et al. 2024



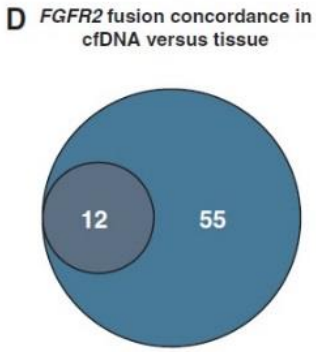
Best NGS Practice

	Known partner	Unknown partner	Partner not in frame	Intergenic	Close partner	C-terminal deletion
Dual fusion probe FISH	✓	✗	✓	✗	✗	✗
Break-apart FISH	✓	✓	✓	✓	✗	✗
Imbalance assay NGS	✓	✓	✓	✓	✓	✓
Amplicon-based NGS	✓	✗	✓	✗	✓	✗
Single primer extension-based NGS	✓	✓	✓	✓	✓	✓
Hybrid capture-based RNA NGS	✓	✓	✓	✓	✓	✓
Hybrid capture-based DNA NGS	✓	✓	✓	✓	✓	✓

Angerilli et al. 2023



Berchuck et al. 2022



18%

NGS technology Should be Carefully selected: FGFR2 docet!

Liquid Biopsy: Poor performances in FGFR2 fusions detection.

Take Home Message

- Virtually, 40% of genetic alterations in CCA are actionable;
- ESCAT-1 level alterations in IDH1, FGFR2, HER2, BRAF, NTRK, MSI;
- NGS is the suggested standard for molecular diagnostics in CCAs;
- Gene associations may be helpful in molecular diagnostics;
- If material inadequate for NGS ortogonal tecniques are required;
- Liquid Biopsy not still reliable for FGFR2 fusions.

THANK YOU!

SACRO CUORE DON CALABRIA I R C C S

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Cancer Care Center
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Numero Verde
800 143 143