LA EVOLUZIONE DELLA MEDICINA DI PRECISIONE IN ONCOLOGIA: IL MODELLO MUTAZIONALE

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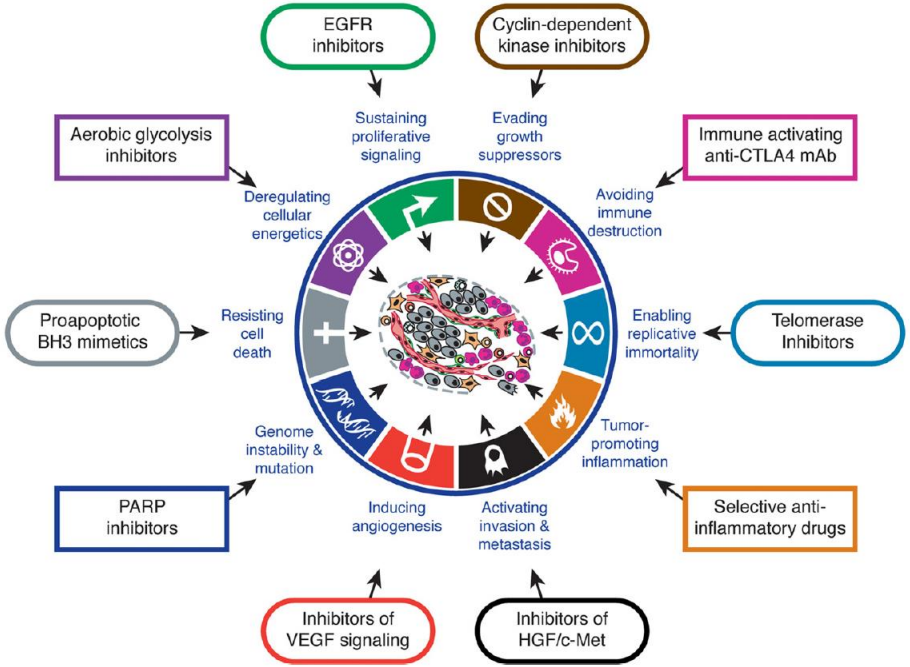
ISTITUTO NAZIONALE PER LO STUDIO E LA CURA DEI TUMORI
FONDAZIONE "G. Pascale" – NAPOLI

SC Biologia Cellulare e Bioterapie

DISCLOSURE SLIDE

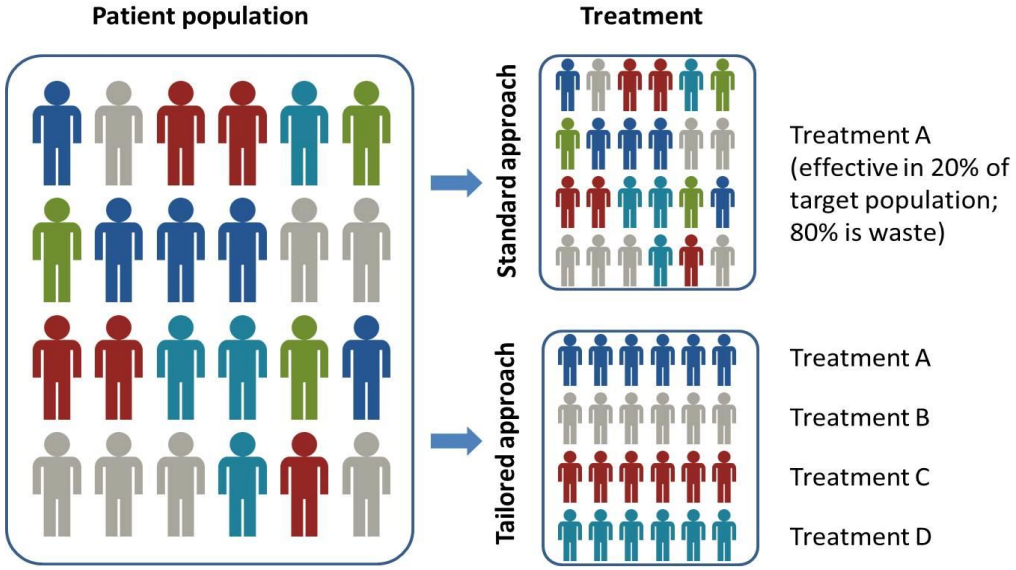
- **Personal financial interests (speaker's fee and/or advisory boards):** MSD, Qiagen, Bayer, Biocartis, Incyte, Roche, BMS, MERCK, Thermofisher, Boehringer Ingelheim, Astrazeneca, Sanofi, Eli Lilly
- **Institutional financial interests (financial support to research projets):** MERCK, Sysmex, Thermofisher, QIAGEN, Roche, Astrazeneca, Biocartis
- **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



Hanahan & Weinberg Cell 2011

Target-based agents + predictive biomarkers: PRECISION MEDICINE



WITHOUT BIOMARKERS

WITH BIOMARKERS

Biomarkers recommended for solid tumors

COLON CANCER: KRAS, NRAS, BRAF, MSI

LUNG CANCER: EGFR, ALK, ROS1, BRAF, PD-L1

MELANOMA: BRAF

GASTRIC CANCER: ERBB2 (HER2)

BREAST CANCER: ERBB2 (HER2)

OVARIAN CANCER: BRCA1/BRCA2

GIST: KIT, PDGFRA, BRAF

TUMOR AGNOSTIC: NTRK

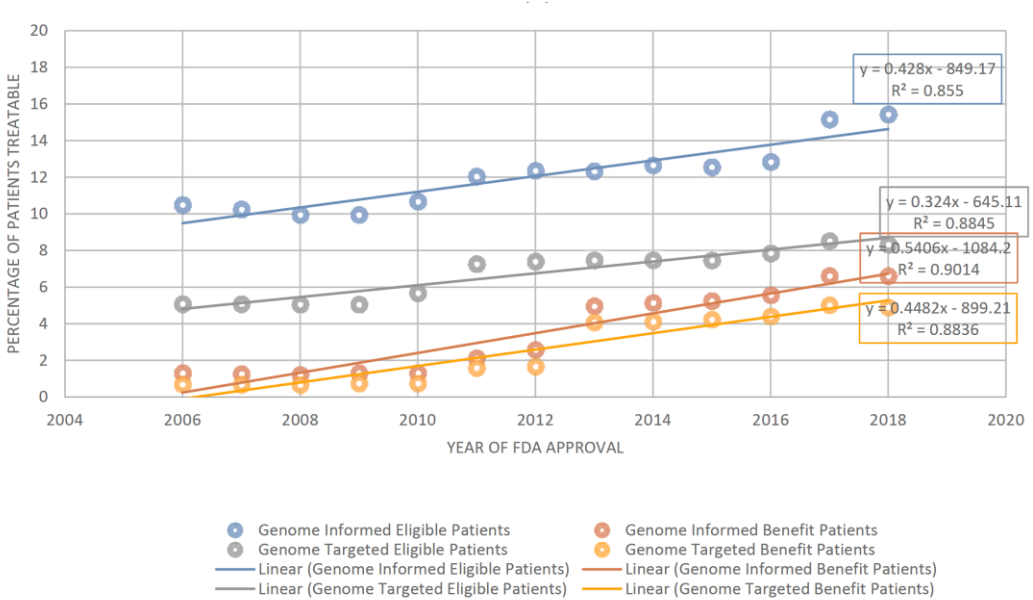
2006-2018 Genomic Therapy	No. (%)
Drugs Overall	
Approved drugs, No.	31
Total indications, No.	38
GT indications	28 of 38 (73.7)
GI indications	38
Drugs per Indication	
NSCLC (GT)	
EGFR	4 (10.5)
ALK	4 (10.5)
ROS1	1 (2.6)
BRAF	1 (2.6)
Breast	
ERBB2/HER2 (GT)	4 (10.5)
BRCA (GI)	1 (2.6)
Melanoma *BRAF* V600 (GT)	5 (13.2)
Colorectal *KRAS* WT (GI)	2 (5.3)
Ovarian *BRCA* (GI)	2 (5.3)
Gastroesophageal *ERBB2/HER2* (GT)	1 (2.6)
GIST (GI)	1 (2.6)
CML Ph+ (GT)	5 (13.2)
CLL 17p (GI)	2 (5.3)
AML (GT)	
IDH2	1 (2.6)
FLT3	1 (2.6)
ALL Ph+ (GT)	1 (2.6)
High-MSI solid tumor (GI)	2 (5.3)

Genomic Therapy Drugs Approved by the FDA, 2006-2018

GT: genomically targeted therapies
GI: genomically informed therapies

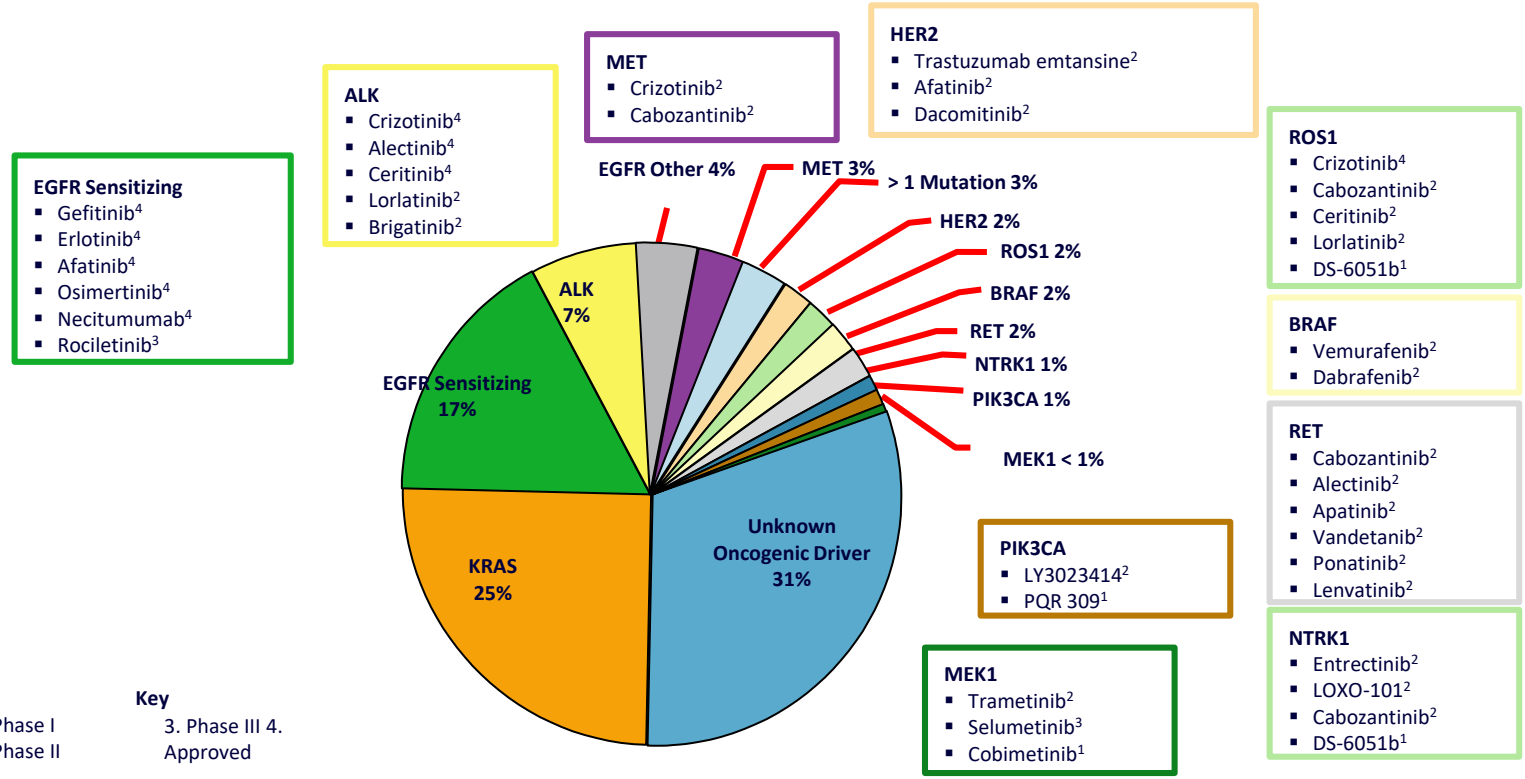
Marquart JAMA Oncol 2018

Estimated US Patient Eligibility and Benefit From Genomically Targeted- and Genomically Informed-Therapies



Marquart JAMA Oncol 2018

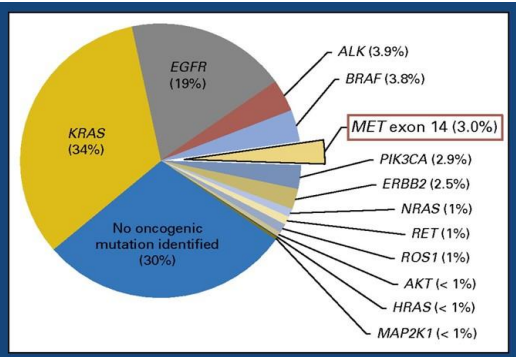
Targeted therapy for adenocarcinoma

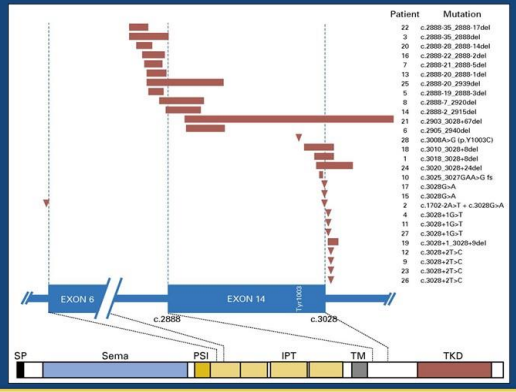


Tsao AS, J Thorac Oncol. 2016

Patients with *MET* ex 14

- Older age, median 72.5y
  - increased comorbidities
  - may not undergo biopsy for additional testing
- Smokers and never smokers
- Sarcomatoid, pleiomorphic histology
- Mutually exclusive with other driver alterations
- Over 100 different genomic variants





Awad MM, et al J Clin Oncol 2016

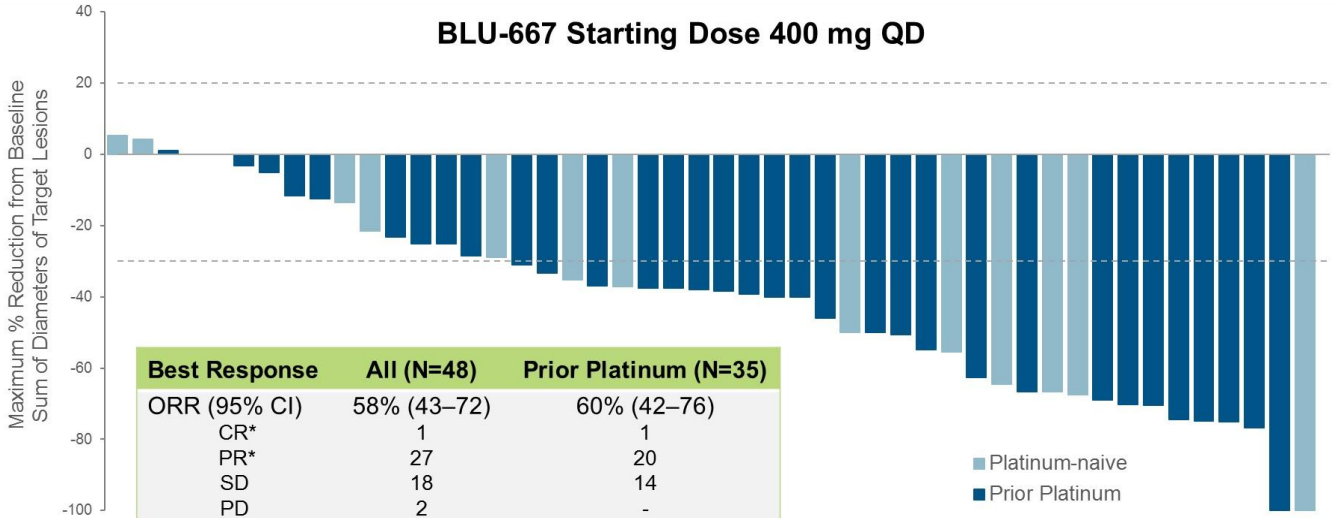
Presented By Karen Reckamp at 2019 ASCO Annual Meeting

MET TKI preliminary efficacy in *MET* ex14 NSCLC

Agent	*MET* testing	n	Brain metastases (n)	ORR % (95% CI)	DOR (months)	PFS (months)
Capmatinib (Wolf J et al ASCO 2019)	Tissue RT-PCR	97 **1L**—28 **2/3L**—69	**1L**—3 **2/3L**—11	**1L**—67.9 (47.6, 84.1) **2/3L**—40.6 (28.9, 53.1)	**1L**—11.1 (5.55, NE) **2/3L**—9.7 (5.55, 12.98)	**1L**—9.7 (5.5, 13.86) **2/3L**—5.4 (4.2, 6.97)
Tepotinib (Paik et al ASCO 2019)	Liquid (DNA based NGS) Tissue (RNA based NGS)	73 **Liquid**—48 **Tissue**—51	8	**Liquid**—50 (35.2, 64.8) **1L**—58.8 (32.9, 81.6) **2L**—53.3 (26.6, 78.7) **≥3L**—37.5 (15.2, 64.6) **Tissue**—45 (31.1, 59.7) **1L**—44.4 (21.5, 69.2) **2L**—50 (26, 74) **≥3L**—40 (16.3, 67.7)	**Liquid**—12.4 (5.8, NE) **Tissue**—15.7 (9.0, NE)	**Liquid**—9.5 (6.7, NE) **Tissue**—10.8 (6.9, NE)
Crizotinib (Drilon A et al WCLC 2018)	Tissue-local Prospective central tissue & liquid ctDNA	65	na	32 (21-45)	9.1 (6.4, 12.7)	7.3 (5.4, 9.1)
Savolitinib (Lu S et al AACR 2019)	Tissue	29	5	54.8	na	na

Presented By Karen Reckamp at 2019 ASCO Annual Meeting

BLU-667 Demonstrates Substantial Antitumor Activity in RET Fusion+ Advanced NSCLC



Best Response	All (N=48)	Prior Platinum (N=35)
ORR (95% CI)	58% (43–72)	60% (42–76)
CR*	1	1
PR*	27	20
SD	18	14
PD	2	-
DCR (95% CI)	96% (86–99)	100% (90–100)

* All responses are confirmed on two consecutive assessments as per RECIST 1.1.

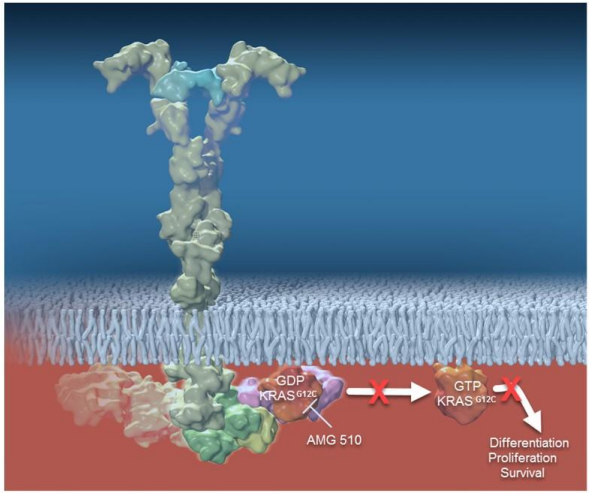
- 5/7 (71%) treatment-naïve patients had confirmed PR

CI, confidence interval; CR, complete response; DCR, disease control rate (best response of SD or better); ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease. Patients enrolled by 14 Nov 18, data cut-off 28 Apr 19. Response-evaluable population includes patients with measurable disease at baseline and ≥1 evaluable post-treatment disease assessment, and excludes 4 patients who previously received >1 cycle of a selective RET inhibitor.

Presented By Justin Gainor at 2019 ASCO Annual Meeting

AMG 510 is a First in Class KRAS^{G12C} Inhibitor

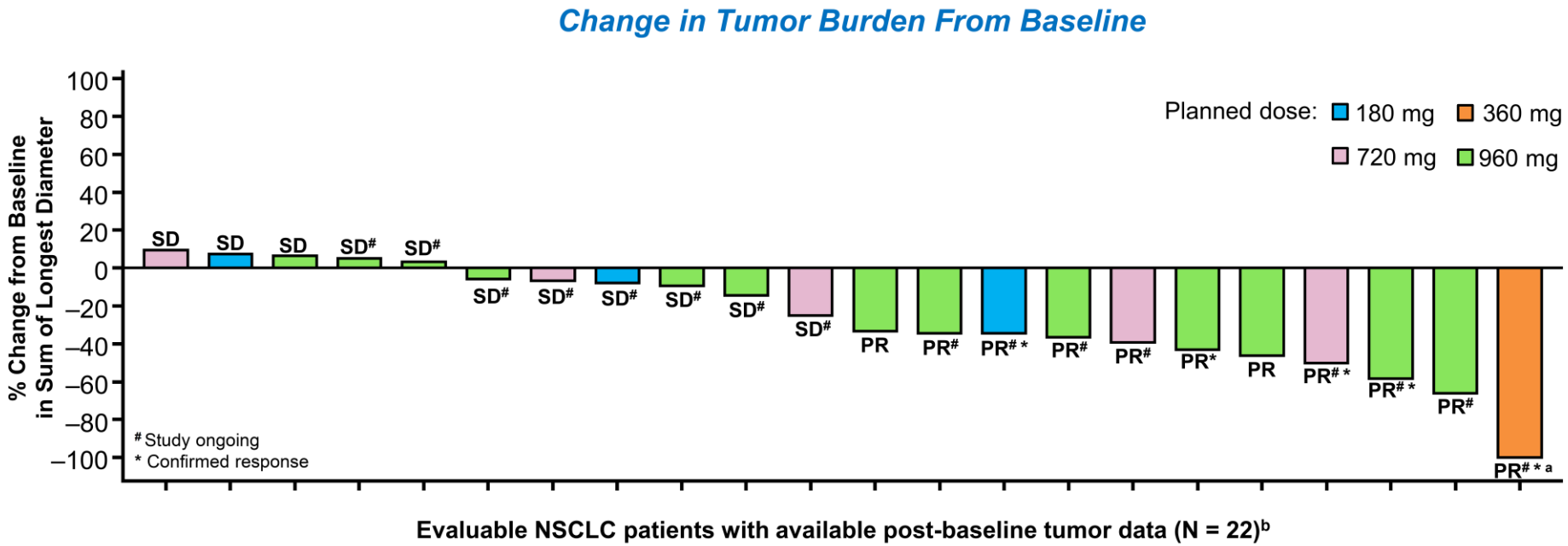
- KRAS is a GTP-binding protein that links receptor tyrosine kinase activation to intracellular signaling [1,2]
- Mutation of KRAS favors the GTP-bound active state and constitutive activation of downstream effects (differentiation, proliferation, survival)[3]
- *KRAS^{G12C}* mutation has been identified as an oncogenic driver of tumorigenesis
- *KRAS^{G12C}* mutation is found in approximately 13% of lung cancer[4], 3% of colorectal (CRC)[5] and appendix cancer, and 1-3% of other solid tumors[6]
- Currently there is no approved therapy targeting this mutation
- AMG 510 is a novel, first in class, small molecule that specifically and irreversibly inhibits KRAS^{G12C} by locking it in an inactive GDP-bound state



1. Prior IA, et al. *Cancer Res*. 2012;72:2457-2467.
2. Ostrem JM, et al. *Nat Rev Drug Discov*. 2016;15:771-785.
3. Ryan MB, et al. *Nat Rev Clin Oncol*. 2018;15:709-720.
4. Biernacka A, et al. *Cancer Genet*. 2016;209:195-198.
5. Neumann J, et al. *Pathol Res Pract*. 2009;205:858-862
6. Zhou L et al. *Med Oncol*. 2016;33:32.

GDP, guanosine diphosphate; GTP, guanosine triphosphate;
KRAS, Kirsten rat sarcoma viral oncogene homolog;
KRAS^{G12C}, KRAS protein with a G12C mutation at the protein level.

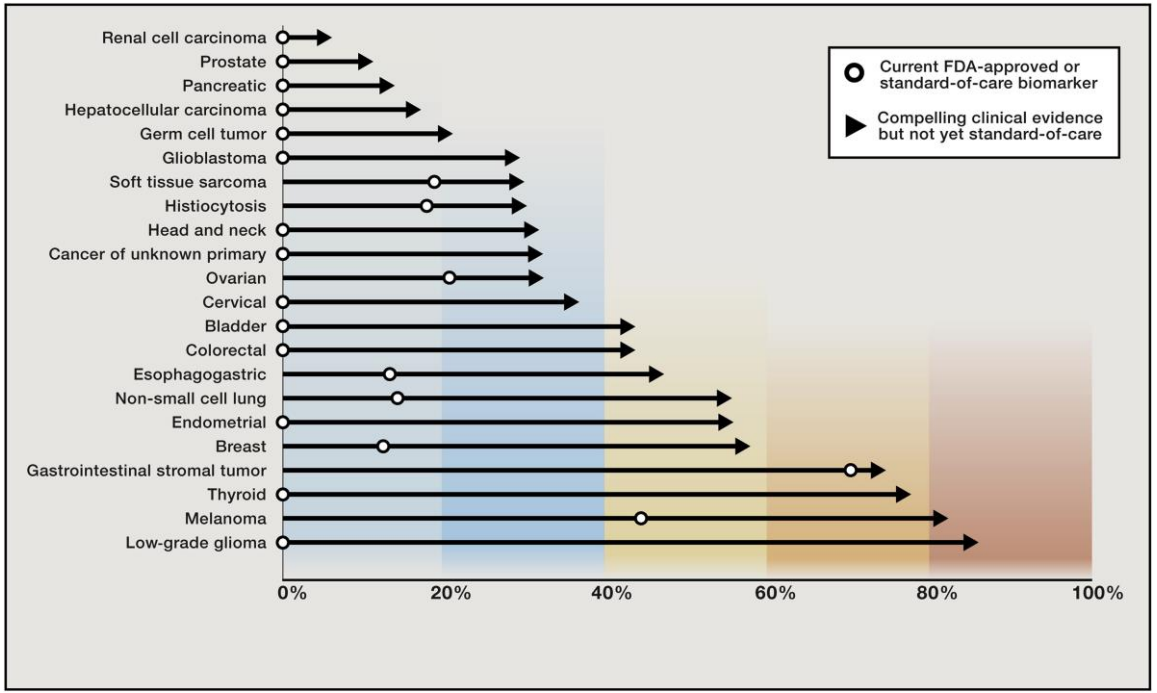
EFFICACY IN NSCLC



[a]Patient had complete response to the target lesion; [b]1 patient discontinued study due to PD prior to the 1st assessment without available post-baseline tumor burden data, and therefore is not shown on the graph.
Evaluable patients: patients who have been followed up for at least 6 weeks; NSCLC = non-small-cell lung cancer; PD = progressive disease; PR = partial response; SD = stable disease

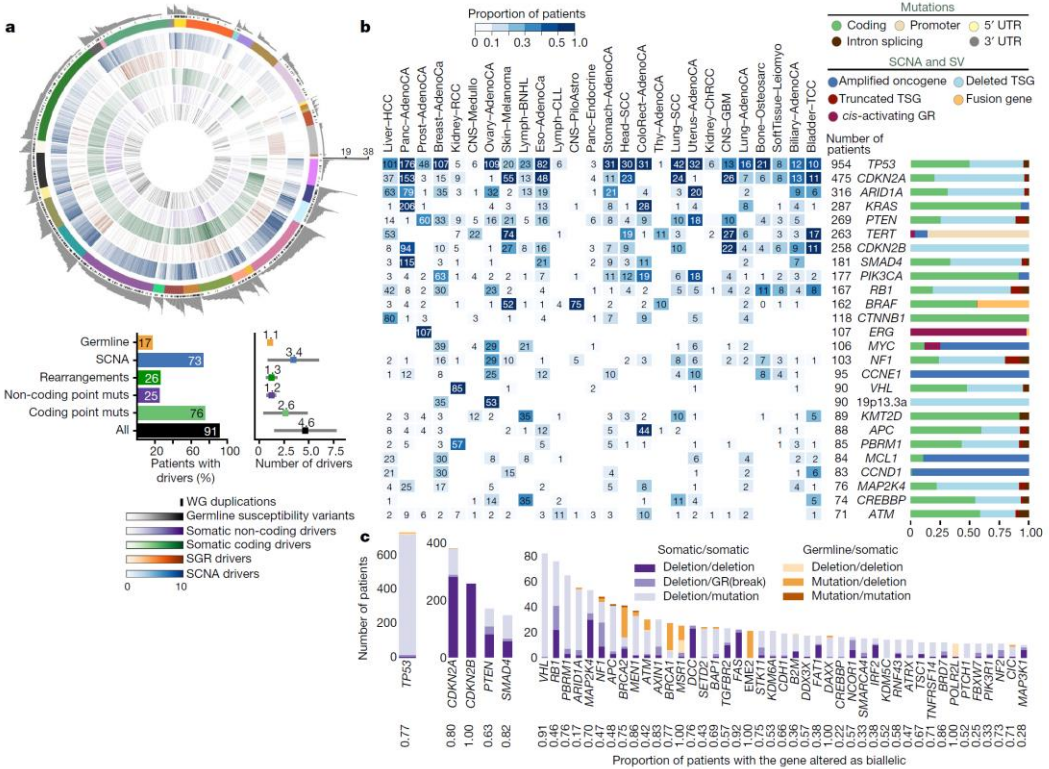
AMGEN

Druggable Alterations in Oncology Today and in the Near Future



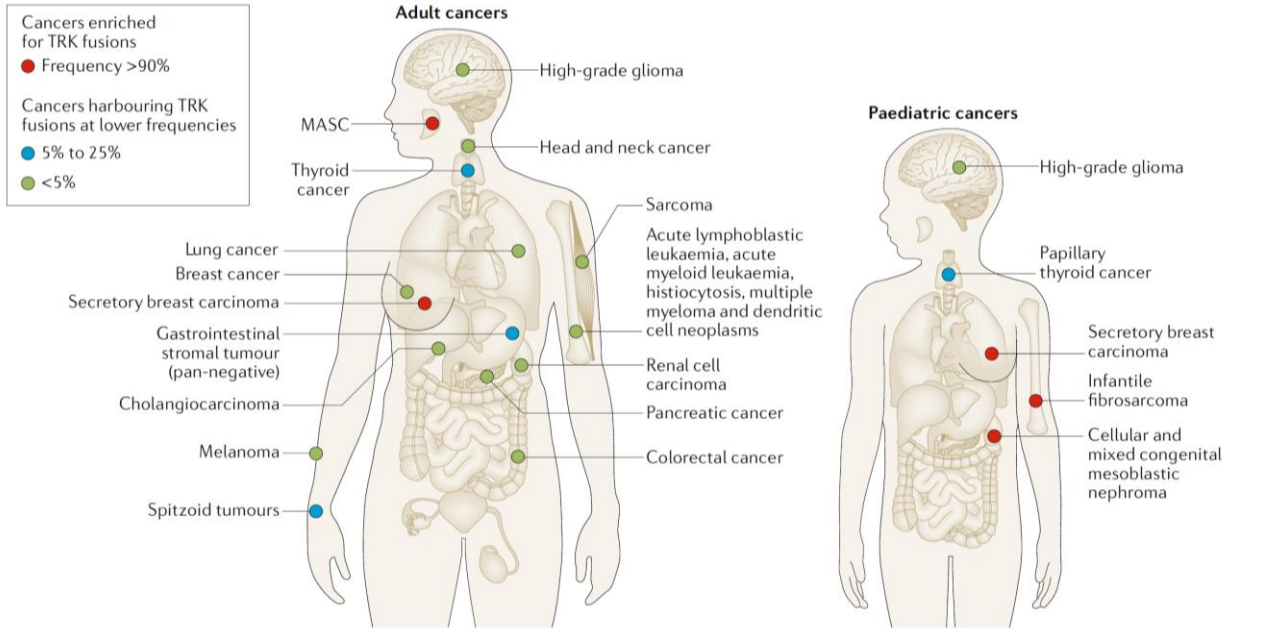
Hyman Cell 2017

Panorama of driver mutations in PCAWG



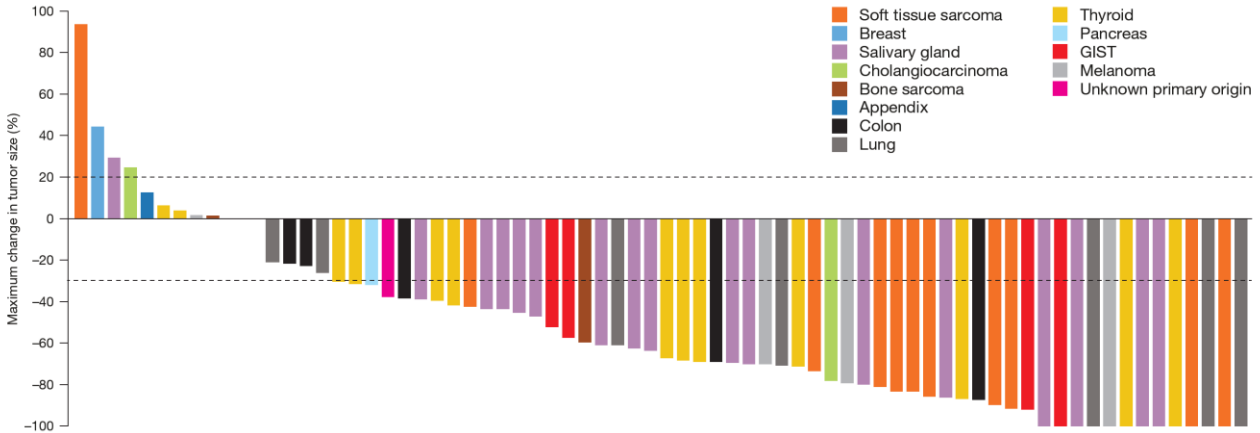
The ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium NATURE 2020

Distribution and frequency of NTRK fusions in adult and paediatric tumours



Cocco Nat Rev Clin Oncol 2018

Best change in tumor size in adult patients with NTRK fusion cancer treated with larotrectinib



Hong ASCO 2019

BRAF mutations in melanoma, CRC and NSCLC

Cancer	Frequency	Prognostic	Predictive§	%V600E
Melanoma	50%	Y/N	Y	90%
CRC	10%	Y	N	90%
NSCLC	3%	Y*	Y	50%

*only V600E

§ for response to class I RAF kinase inhibitors

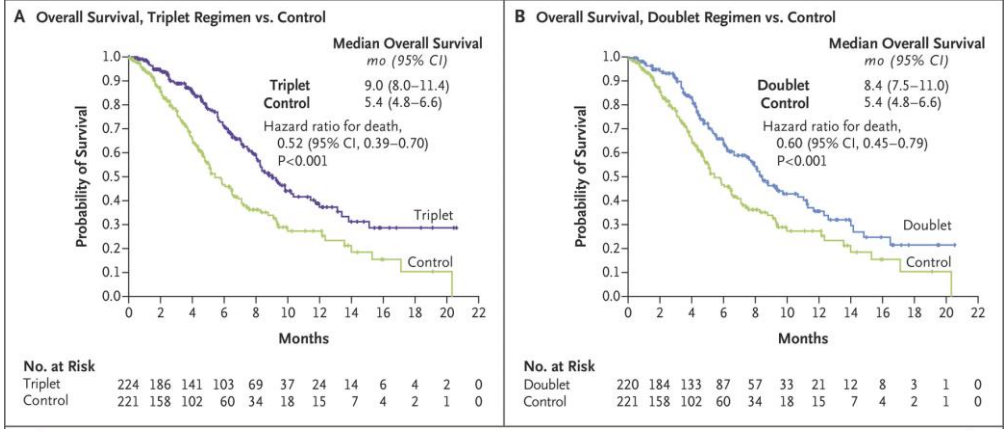


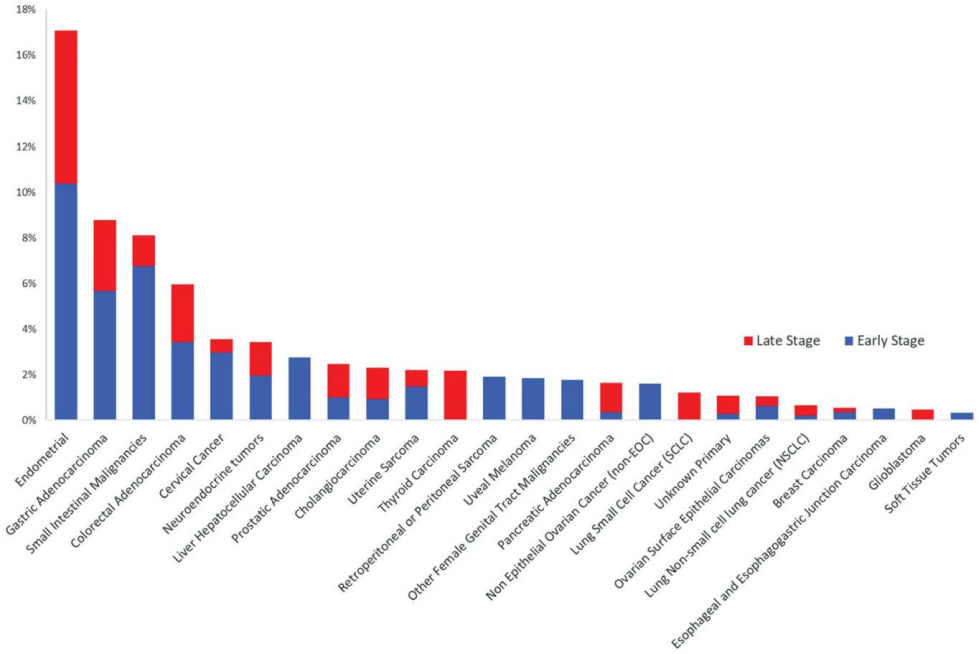
Table 2. Tumor Response in Patients with Metastatic Colorectal Cancer with the *BRAF* V600E Mutation.*

Variable	Triplet Regimen (N=111)	Doublet Regimen (N=113)	Control (N=107)
Objective response			
Patients with a complete or partial response — no. (%)	29 (26)	23 (20)	2 (2)
95% CI	18–35	13–29	<1–7
P value vs. control	<0.001	<0.001	
Best overall response — no. (%)			
Complete response	4 (4)	6 (5)	0
Partial response	25 (23)	17 (15)	2 (2)
Stable disease†	47 (42)	61 (54)	31 (29)
Progressive disease	11 (10)	8 (7)	36 (34)
Could not be evaluated according to RECIST‡	24 (22)	21 (19)	38 (36)
Clinical progression or discontinuation because of adverse event§	15 (14)	19 (17)	17 (16)
Insufficient data to assess response¶	9 (8)	2 (2)	21 (20)
Patients with duration of response ≥6 mo — no./total no. of patients with a response (%)	7/29 (24)	10/23 (43)	1/2 (50)
Patients with ongoing response and <6 mo follow-up — no./total no. of patients with a response (%)	4/29 (14)	1/23 (4)	0

BEACON study: Encorafenib+ Binimetinib+ Cetuximab in previously treated BRAF V600E mutant mCRC pts

Kopetz NEJM 2019

Mismatch repair deficiency across tumors



Le Science 2017

Patient survival and response to pembrolizumab across 12 different tumor types with mismatch repair deficiency

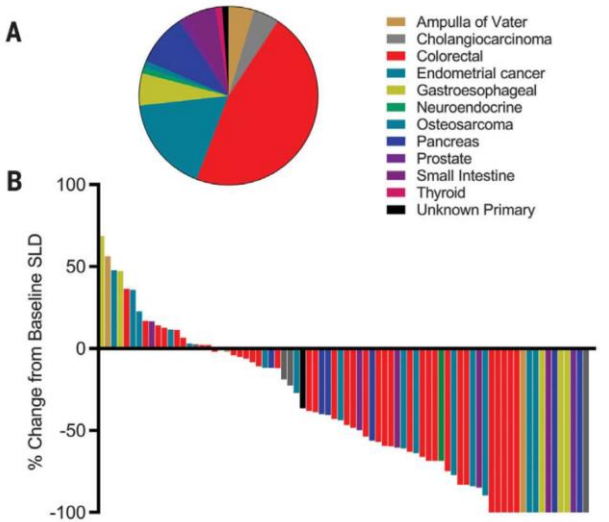


Table 1. Summary of therapeutic response to pembrolizumab (anti–PD-1) treatment. Radiographic responses, progression-free survival (PFS), and overall survival (OS) estimates were measured using RECIST v1.1 guidelines. Patients were considered not evaluable if clinical progression precluded a 12-week scan. The rate of disease control was defined as the percentage of patients who had a complete response, partial response, or stable disease for 12 weeks or more. NR, not reached.

Type of response	Patients (n = 86)
Complete response	18 (21%)
Partial response	28 (33%)
Stable disease	20 (23%)
Progressive disease	12 (14%)
Not evaluable	8 (9%)
Objective response rate	53%
95% CI	42 to 64%
Disease control rate	77%
95% CI	66 to 85%
Median progression-free survival time	NR
95% CI	14.8 months to NR
2-year progression-free survival rate	53%
95% CI	42 to 68%
Median overall survival time	NR
95% CI	NR to NR
2-year overall survival rate	64%
95% CI	53 to 78%

Le Science 2017

The major classes of genomic alterations that give rise to cancer

Approved biomarkers
Biomarkers in clinical trials

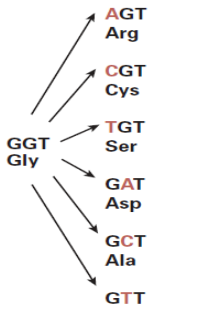
Sequencing, qPCR, NGS, etc

FISH, immunohistochemistry, qPCR, NGS

MSI
MET ex14 skipping
TMB
HRD

Point mutations

EGFR
BRAF
KRAS
NRAS
ERBB2
PIK3CA
AKT1
MAP2K1
STK11
FGFR1-3
IDH1

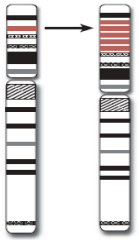


Activation of oncogenes-*RAS* genes in many cancers
Inactivation of TS genes-*TP53* in many cancers

Copy number alterations

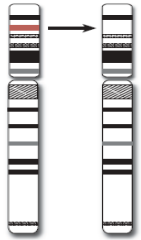
Amplification

ERBB2
EGFR
MET



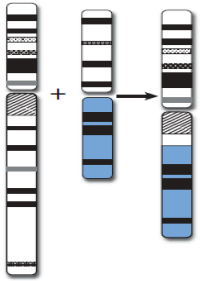
Activation of oncogenes-*ERBB2* in breast cancer

Deletion



Inactivation of TS genes-*RB1* in retinoblastoma

Translocations



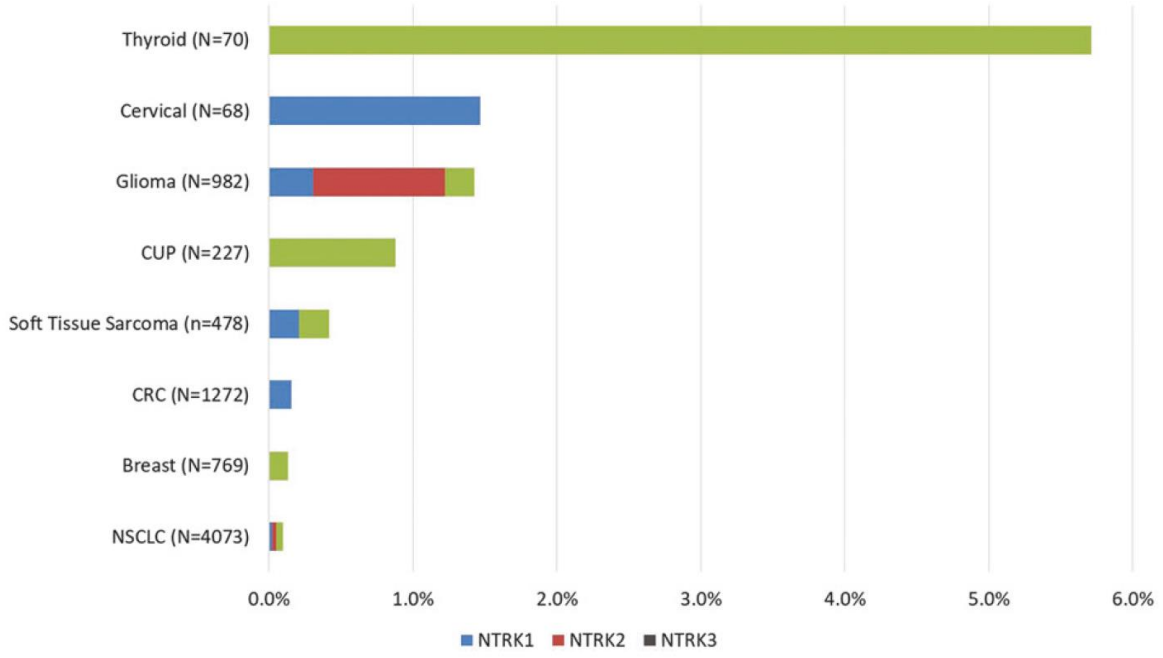
Activation of many genes-*BCR-ABL* in CML

EML4-ALK
ROS-1
NTRK1-2-3
RET
FGFR1-2-3

CML, chronic myeloid leukaemia; FISH, fluorescence *in-situ* hybridisation; MSI, microsatellite instability; NGS, next-generation sequencing; qPCR, quantitative polymerase chain reaction; TMB, tumour mutational burden; TS, tumour suppressor.

Modified from: McConaill LE, Garraway LA. *J Clin Oncol*. 2010;28:5219–28.

Frequency of NTRK fusions across various histologies



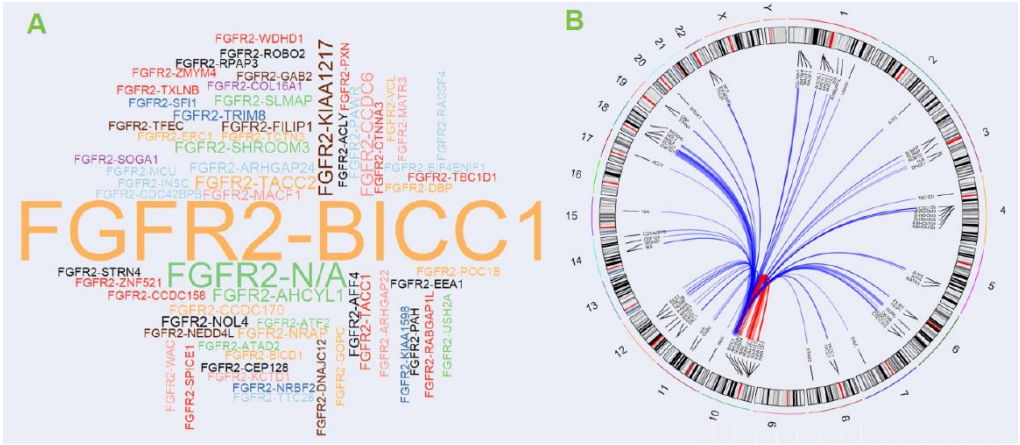
Gatalica Mod Pathol 2019

FGFR2 alterations in primary intrahepatic cholangiocarcinoma – FoundationOne test

***FGFR2*+ rate by country and region**

Region	Country	*FGFR2*+, n	N	Frequency	
				Country	Region
United States	US	21	138	15.2%	15.2%
Europe	France	10	107	9.4%	7.4%
	UK	7	81	8.6%	
	Germany	5	61	8.2%	
	Belgium	4	50	8.0%	
	Italy	13	171	7.6%	
	Spain	3	99	3.0%	
Rest of world	Thailand	2	32	6.2%	2.2%
	Israel	1	25	4.0%	
	Taiwan	1	44	2.3%	
	Korea	5	283	1.8%	
	Japan	2	115	1.7%	

***FGFR2* rearrangements**



Hollebecque A, et al. ESMO poster presentation 2019; abstract #2078.

NGS panels for comprehensive genomic profiling: tissue

Assay name	FoundationOne CDx™	MSK-IMPACT™	Molecular Intelligence®	Tempus xT	ACE ImmunoID™16-18	TruSight Oncology 500 (assay under development)	Oncomine™ Tumour Mutational Load assay	NeoTYPE® Discovery Profile	CANCERPLEX
Sequencing platform	Illumina HiSeq 4000	Illumina HiSeq 2500	Illumina NextSeq	Illumina HiSeq 4000	Illumina NovaSeq 600	Illumina NextSeq 550Dx	Ion GeneStudio S5 series	Not reported	Illumina NextSeq
No. of genes	324	468	592	595	>20,000	523	409	326	435
Types of alterations	Substitutions, indels, CNVs, rearrangements	Somatic SNVs, indels, CNVs, rearrangements	Somatic non-synonymous missense mutations	SNVs, indels, CNVs, rearrangements	SNVs, indels, fusions	SNVs, MNVs, indels	Nonsynonymous and synonymous SNVs	SNPs, indels, rearrangements	SNVs, indels, CNVs, rearrangements
Tumour slide specifications	10 FFPE slides (20% tumour nuclei)	FFPE tissue (50–250 ng)	15 FFPE slides	FFPE slides (20% tumour nuclei)	FFPE tissue (50 ng DNA)	Not reported	FFPE tissue (20 ng DNA)	FFPE tissue	FFPE slides/blocks, CNB, FNA (>20% tumour nuclei) (>50 ng DNA)
Patient-matched normal sample	No	Yes	No	Yes	No	No	No	No	No
Reported TMB value (determination for TMB high)	mut/Mb (≥20)	mut/Mb (≥13.8)	mut/Mb (≥17)	mut/Mb (not reported)	Non-synonymous mut/Mb (not reported)	mut/Mb (≥15)	mut/Mb (not reported)	mut/Mb (not reported)	Not reported
Turnaround time	<2 weeks	<3 weeks	10–14 days	2–3 weeks	2–4 weeks	Not reported	2–3 days	14–22 days	7–10 days

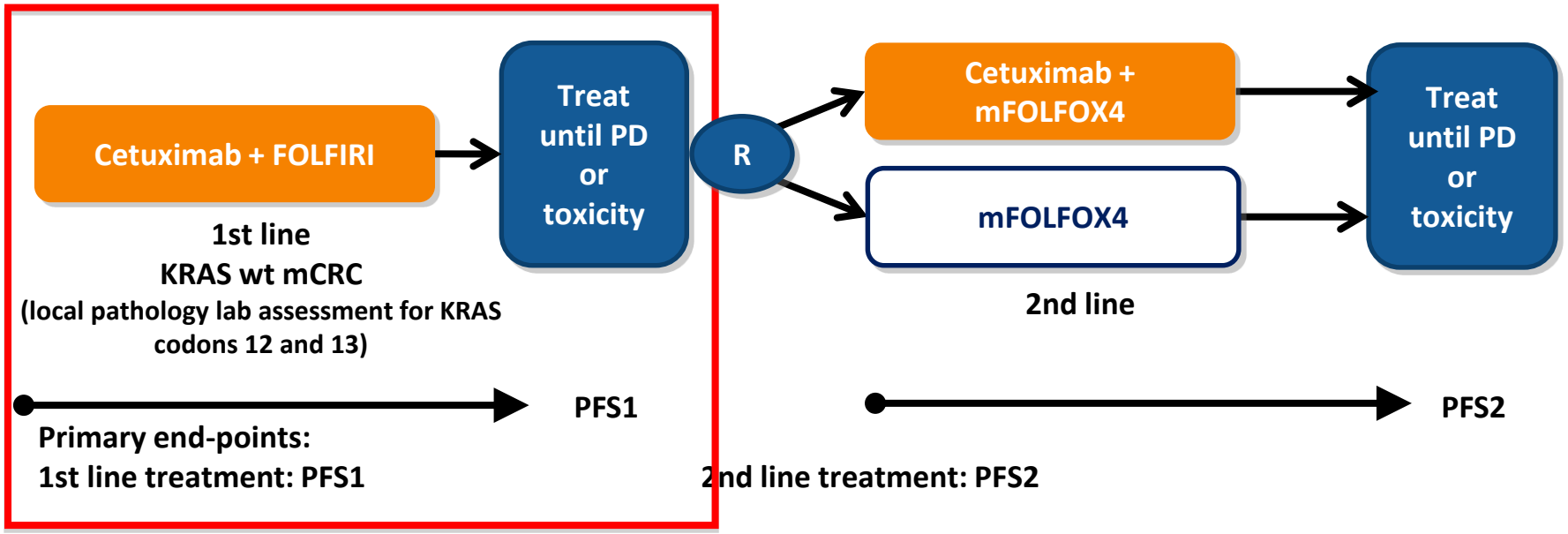
CNB=core needle biopsy; CNV=copy number variation; FFPE=formalin-fixed paraffin-embedded; FNA=fine needle aspirate; indel=insertion and deletion; Mb=megabase; MNV=multi-nucleotide variants; mut=mutations; no=number; SNV=single-nucleotide variant; TMB=tumour mutational burden

NGS panels for comprehensive genomic profiling: liquid biopsy

Test name*	FoundationOne® Liquid/bTMB	Guardant360/ GuardantOMNI™	MutatorDETECT	Unnamed	PredicineATLAS	Oncomine Pan-Cancer Cell-Free Assay	AVENIO ctDNA Kits
No. of genes measured	70/394	73/500+	64	508	600	52	17/77/197
Sequencing platform	Illumina HiSeq 4000	Guardant Health Digital Seq Platform	Illumina NGS‡	Illumina NGS	Not reported	Ion GeneStudio S5 series	Illumina NextSeq
Types of alterations	SNVs, indels, fusions, CNAs	SNVs, indels, fusions, CNAs	SNVs, indels, fusions, CNVs	SNVs, indels, CNVs	SNV, CNV, rearrangements§	SNVs, indels, fusions, CNVs	SNVs, indels, fusions, CNVs
Sample requirement	(20 ng cfDNA)	1–2 mL plasma (5–30 ng cfDNA)	Two 10 mL tubes of peripheral whole blood or 6–10 mL plasma‡	Plasma (single blood draw)	Plasma (5 mL)§	20 ng cfNA	10-50 ng cfDNA

bTMB=blood TMB; cfDNA=cell-free DNA; CNA=copy number alteration; CNV=copy number variation; indel=insertion and deletion; NGS=next-generation sequencing; no=number; seq=sequencing; SNV=single nucleotide variant; TMB=tumour mutational burden

CAPRI GOIM trial



- From July 2009 to June 2013: 340 patients enrolled for 1st line
- As of 31 August 2013, 151 pts have progressed and were randomized to ongoing 2nd line therapy (cetuximab + mFOLFOX4, n=76; mFOLFOX4, n=75)

Ciardiello, Normanno et al Ann Oncol 2014

Gene mutations assessed by NGS in mCRC patients enrolled in the CAPRI-GOIM trial

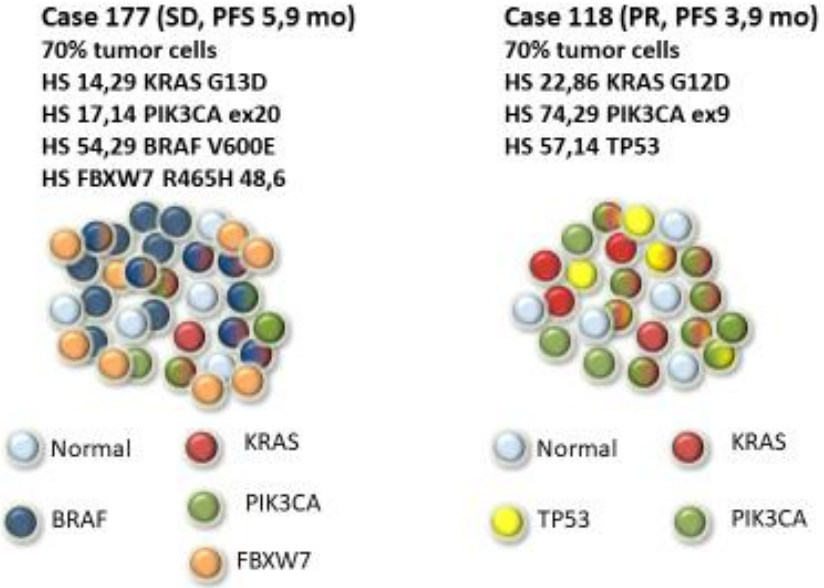
Genes with >10 mutated cases	Total mutated cases, n (N=182 analyzed)	Cases with multiple mutations, n	Types of concomitant mutations (n)
KRAS	45	30*	TP53 (18), PIK3CA ex9 (9), PIK3CA ex20 (5), FBXW7 (5), BRAF (4), MET (1), EGFR (1), SMAD4 (1), FGFR3 (1), ERBB2 (1), PTEN (1)
NRAS	13	5	TP53 (3), PIK3CA ex9 (1), MET (1)
BRAF	15	12†	TP53 (9), KRAS (4), PIK3CA ex20 (3), FBXW7 (2), PIK3CA ex9 (1), SMAD4 (1), FGFR3 (1), FGFR2 (1)
PIK3CA ex9	16	14‡	KRAS (9), TP53 (8), PIK3CA ex 20 (2), NRAS (1), BRAF (1), MET (1), EGFR (1), ERBB2 (1)
PIK3CA ex20	10	7‡	KRAS (5), BRAF (3), TP53 (3), PIK3CA ex9 (2), FBXW7 (2), ERBB2 (1)
TP53	72	36	KRAS (18), BRAF (9), PIK3CA ex9 (8), FBXW7 (5), NRAS (3), PIK3CA ex20 (3), MET (1), EGFR (1), SMAD4 (1), CTNNB1 (1), FGFR3 (1), ERBB2 (1)

*11 cases with KRAS mutated tumors had >2 concomitant mutations (maximum 5 mutations); †5 cases with BRAF mutated tumors had >2 concomitant mutations (maximum 4 mutations); ‡9 cases with PIK3CA mutated tumors had >2 concomitant mutations (maximum 4 mutations)

Ciardiello, Normanno et al Ann Oncol 2014

Heterogeneity Score (HS) in mCRC patients enrolled in the CAPRI trial

- The heterogeneity score (HS) was obtained by normalizing the frequency of mutant alleles for the fraction of neoplastic cells
- The HS virtually corresponds to the fraction of neoplastic cells that carry a specific mutation



Normanno et al Ann Oncol 2015

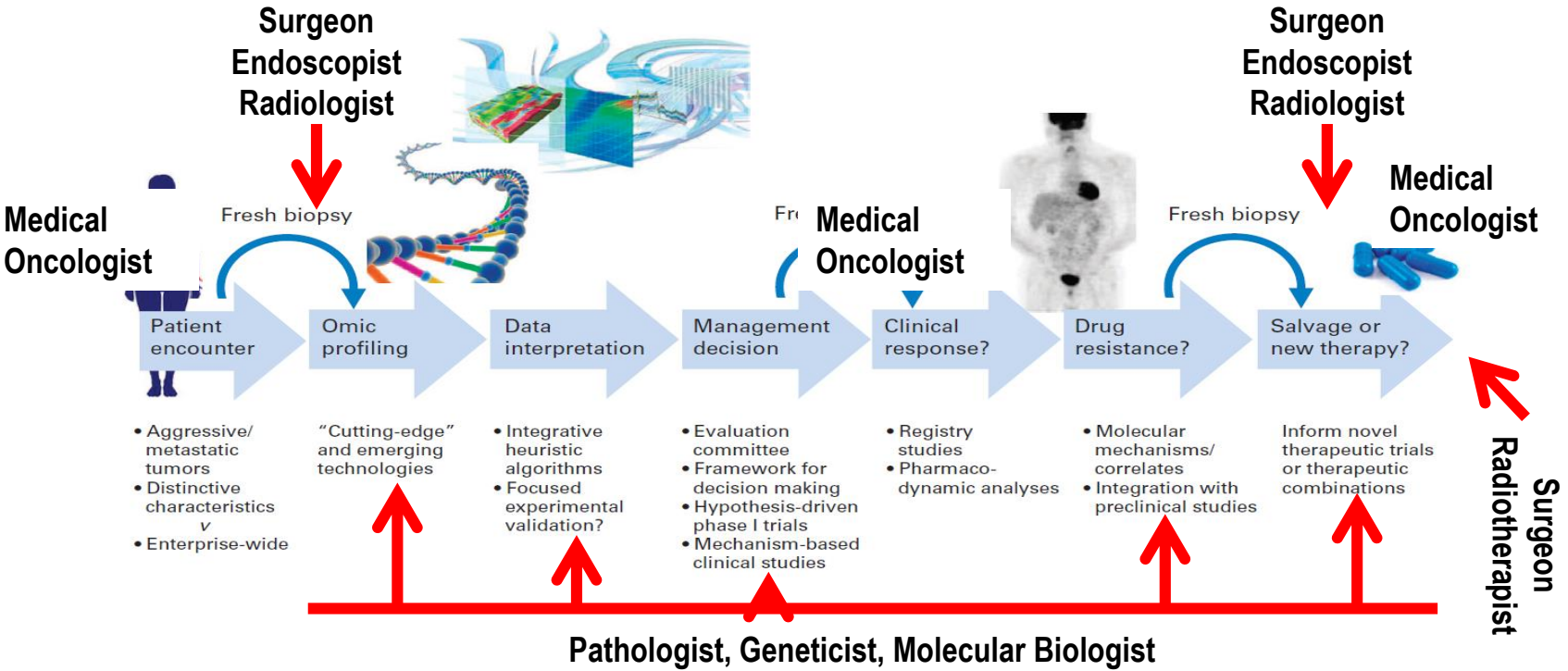
Open questions

- **Which patients should receive a comprehensive genomic profiling (CGP)?**
  - **Advanced or metastatic, failure of previous lines of standard therapy, progression after target therapy….**
  - **At first diagnosis in**
    - **NSCLC (non squamous)**
    - **Young patients, rare diseases, unusual clinical presentation, CUP…..**
- **How should the result of a CGP test be interpreted with respect to tumor heterogeneity (target priority)?**
  - **Clonal vs sub-clonal driver alterations**
  - **Tissue and cfDNA testing to assess clonal architecture of the disease**
  - **Monitoring clonal evolution of the disease**

Open questions (continued)

- How to offer a therapeutic opportunity for cancer patients undergoing CGP?
  - Using large NGS panels will increase the number of patients with mutations that might be targeted with drugs not approved for the tumor type
  - Need to organize a large set of clinical trials to offer the possibility of treatment within a framework approved by regulatory bodies
  - In addition, access to drugs already approved for other indications should be guaranteed in an adequately regulated context and under agreements with pharmaceutical companies
- How to handle incidental findings such as germline mutations that are occasionally detected?
  - Some mutations identified in the tumor tissue could also be of a germinal nature

Precision Oncology: The role of the Molecular Tumor Board



Garraway JCO 2013

DECRETO COMMISSARIO AD ACTA N. 99 DEL 14.12.2018

2. Realizzazione della Rete della Medicina di Precisione

Obiettivi e Indicatori

a. Incrementare la cultura dell'approccio multidisciplinare per la medicina di precisione

- Costituzione del Molecular Tumor Board regionale

b. Garantire l'accesso ai test per i biomarcatori approvati nella pratica clinica

- Incremento del numero dei pazienti analizzati per biomarcatori approvati nella pratica clinica

c. Incrementare l'impiego di farmaci molecolari approvati per la pratica clinica

- Incremento dei pazienti trattati con farmaci molecolari approvati in pratica clinica

d. Attuare programmi di screening genetico-molecolare esteso per pazienti selezionati

- Incremento dei pazienti sottoposti a screening genetico-molecolare esteso

e. Sviluppare studi clinici con farmaci a bersaglio molecolare per pazienti con specifiche alterazioni genetico-molecolari

- Incremento del numero di pazienti arruolati in studi clinici con farmaci a bersaglio molecolare

Rete della Medicina di Precisione

- **Molecular Tumor Board come strumento di governance della applicazione clinica della medicina di precisione**
  - **Molecular Tumor Board Regionale responsabile della realizzazione della rete, della armonizzazione delle procedure e del monitoraggio dei risultati**
- **Molecular Tumor Board dei CORP e CORPUS responsabili della implementazione a livello dei GOM**
  - **Propone azioni per la ottimizzazione dei percorsi per i test per i biomarcatori nell'ambito del CORP/CORPUS**
  - **Monitora l'andamento e l'appropriatezza dei test per biomarcatori nell'ambito dei GOM del CORP/CORPUS**
  - **Valuta la appropriatezza della richiesta di test di NGS per CGP**
  - **Discute i risultati dei test di CGP e propone raccomandazioni terapeutiche**