Dalla biologia molecolare alla terapia di precisione

Bologna, 8 Maggio 2019

Presente e futuro della Medicina di Precisione in Oncologia

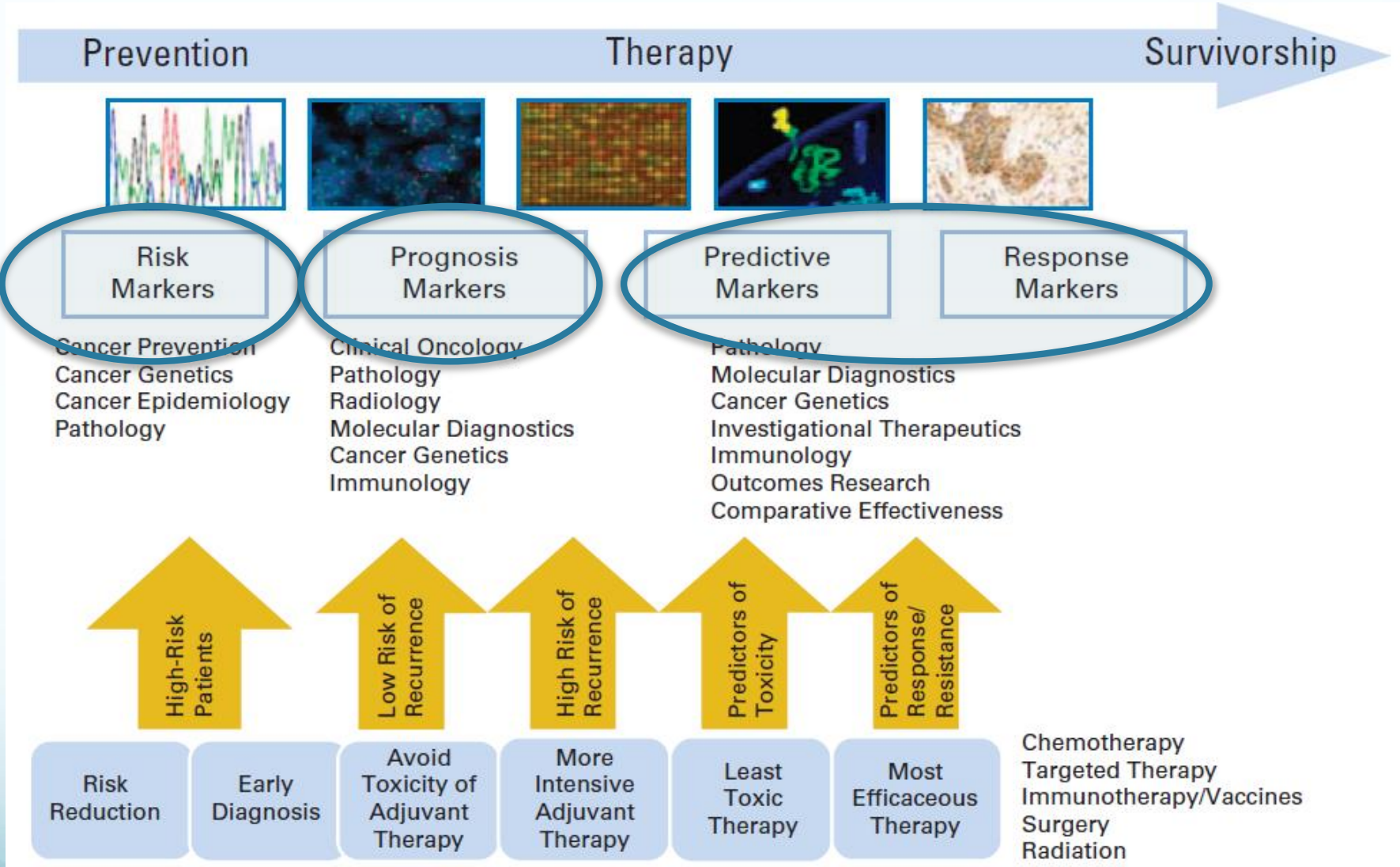
Carmine Pinto

UOC di Oncologia Medica - Clinical Cancer Centre
IRCCS-AUSL di Reggio Emilia

Agenda

- *Target molecolari e test*
- *L'impatto attuale*
- *Tecnologie e test*
- *L'impatto clinico*
- *Le piattaforme*
- *I modelli organizzativi*

The personalized cancer care continuum



Meric-Bernstam et al, J Clin Oncol 2013

Valutazione patologica e molecolare nella scelta di un trattamento oncologico

- *Quali farmaci*
  - *Farmaci a bersaglio molecolare (target terapie)*
  - *Farmaci checkpoint inibitori (immunoterapia)*
- *Selezione dei pazienti*
  - *Identificazione di sensibilità o di resistenza primaria*
  - *Identificazione di resistenza acquisita (secondaria)*
- *Vantaggio clinico*
  - *Maggiore efficacia*
  - *Risparmio di tossicità*
- *Razionalizzazione della spesa*
  - *Ottimizzazione del rapporto costo/beneficio*

Background of molecular personalized therapy

Factors	Evidence
Availability of targets	✔
Availability of validated tests	✔
Availability of data on biological/clinical significance • *Prognostic* • *Predictive of sensitivity* • *Predictive of primary resistance* • *Predictive of secondary resistance*	✔
Availability of drugs • *Efficacy/toxicity ratio* • *Cost/efficacy (effectiveness) ratio*	✔

A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

Ready for routine use	*Alteration-drug associated. Improved outcome in clinical trial*
Investigational	*Alteration-drug associated. Magnitude of benefit unknown*
Hypotetical target	*Alteration-drug suspected. Improve outcome in other tumor types or similar molecular alteration*
Combination development	*Alteration-drug associated with RR but without clinical meaningful benefit. Lack evidence for actionability*

Mateo et al, Ann Oncol 2018

The ESCAT Classification

	ESCAT evidence tier	Required level of evidence	Clinical value class	Clinical implication
Ready for routine use	I: Alteration-drug match is associated with improved outcome in clinical trials	I-A: prospective, randomised clinical trials show the alteration-drug match in a specific tumour type results in a clinically meaningful improvement of a survival end point I-B: prospective, non-randomised clinical trials show that the alteration-drug match in a specific tumour type, results in clinically meaningful benefit as defined by ESMO MCBS 1.1 I-C: clinical trials across tumour types or basket clinical trials show clinical benefit associated with the alteration-drug match, with similar benefit observed across tumour types	Drug administered to patients with the specific molecular alteration has led to improved clinical outcome in prospective clinical trial(s)	Access to the treatment should be considered standard of care
Investigational	II: alteration-drug match is associated with antitumour activity, but magnitude of benefit is unknown	II-A: retrospective studies show patients with the specific alteration in a specific tumour type experience clinically meaningful benefit with matched drug compared with alteration-negative patients II-B: prospective clinical trial(s) show the alteration-drug match in a specific tumour type results in increased responsiveness when treated with a matched drug, however, no data currently available on survival end points	Drug administered to a molecularly defined patient population is likely to result in clinical benefit in a given tumour type, but additional data are needed	Treatment to be considered 'preferable' in the context of evidence collection either as a prospective registry or as a prospective clinical trial

Mateo et al, Ann Oncol 2018

Farmaci registrati e rimborsati dal SSN con richiesta di test biomolecolari

Farmaci	Tumori N.	Tumori Sede	Test ICH	Test molecolari
Anticorpi monoclonali	*6*	*Mammella, stomaco, colon-retto, NSCLC, melanoma, GIST*	*3*	*1*
Piccole molecole	*15*	*NSCLC, melanoma, tiroide*	*0*	*4*
Totale	**21**	**7**	**3**	**5**

1 sola indicazione rimborsata per terapia adiuvante

Farmaci registrati e rimborsati dal SSN con specifici test

Agente	Biomarker	Tumore	Indicazione registrativa in Italia (AIFA)
Imatinib	*c-Kit espressione*	*GIST*	*Metastatico, adiuvante alto rischio*
Vandetanib	*RET mutato (non esclusivo)*	*Carcinoma midollare della tiroide*	*Inoperabile/Metastatico*
Trastuzumab	*HER2 espressione/ amplificazione*	*Carcinoma mammario* *Carcinoma gastrico*	*Adiuvante, neoadiuvante, metastatico in monoterapia o in combinazione con chemioterapia* *Metastatico in combinazione con cisplatino e 5-fluorouracile/capecitabina*
Pertuzumab	*HER2 espressione/ amplificazione*	*Carcinoma mammario*	*Metastatico o ricorrente localmente in I linea in combinazione con docetaxel e trastuzumab*
TDM-1	*HER2 espressione/ amplificazione*	*Carcinoma mammario*	*Metastatico o ricorrente localmente dopo trastuzumab e tassani in monoterapia*
Lapatinib	*HER2 espressione/ amplificazione*	*Carcinoma mammario*	*Metastatico/avanzato in combinazione con capecitabina in pazienti in progressione dopo trastuzumab*
Olaparib	BRCA 1-2 mutazioni	*Carcinoma ovarico*	*Recidive platino-sensibili in risposta dopo chemioterapia a base di platino in monoterapia di mantenimento*
Cetuximab	*RAS wild type*	*Carcinoma del colon-retto*	*Metastatico in combinazione con chemioterapia o in monoterapia*
Panitumumab	*RAS wild type*	*Carcinoma del colon-retto*	*Metastatico pretrattato in monoterapia* *Metastatico in combinazione con chemioterapia*
Pembrolizumab	*PDL-1 espressione*	*NSCLC*	*Metastatico in I e II linea*

Farmaci registrati e rimborsati con specifici test

Agente	Biomarker	Tumore	Indicazione registrativa in Italia (AIFA)
Gefitinib	*EGFR mutato*	*Adenocarcinoma del polmone*	*Localmente avanzato/Metastatico*
Erlotinib	*EGFR mutato*	*Adenocarcinoma del polmone*	*Localmente avanzato/Metastatico*
Afatinib	*EGFR mutato*	*Adenocarcinoma del polmone*	*Localmente avanzato/Metastatico*
Osirmetinib	EGFR mutato T790M	*Adenocarcinoma del polmone*	*Localmente avanzato/Metastatico in PD dopo TKi*
Crizotinib	*ALK fusione* *ROS1 fusione*	*Adenocarcinoma del polmone*	*Stadio avanzato in I linea e pretrattati*
Alectinib	*ALK fusione*	*Adenocarcinoma del polmone*	*Stadio avanzato in I linea e pretrattati con crizotinib*
Ceritinib	*ALK fusione*	*Adenocarcinoma del polmone*	*Stadio avanzato in PD dopo crizotinib*
Vemurafenib	*BRAF mutato*	*Melanoma*	*Inoperabile/Metastatico*
Vemurafenib/Cobimetinib	*BRAF mutato*	*Melanoma*	*Inoperabile/Metastatico*
Dabrafenib	*BRAF mutato*	*Melanoma*	*Inoperabile/Metastatico*
Dabrafenib/Trametinib	*BRAF mutato*	*Melanoma*	*Inoperabile/Metastatico*

Evoluzione dei test nelle terapie target

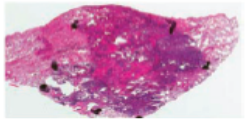
- *Test di sensibilità e Test di resistenza*
- *Test di sensibilità progressivamente incrementata (dal 20% allo 0,01%)*
- *Test per marker indipendenti dalla sede del tumore*
- *Test su tessuto per singolo gene*
- *Test multipli su tessuto – NGS*
- *Test su sangue (biopsia liquida)*

Criticità

- **Non associazione del farmaco al test dell'indicazione registrativa**
  - *Studi registrativi prevedono laboratori centralizzati*
  - *Test validati commerciali disponibili*
- **Accesso al test**
  - *Disponibilità di un test "di qualità" in tutto il territorio nazionale*
- **Non comparabilità del test**
  - *Test con sensibilità differenti*
  - *Test con parametri valutati di positività diversi*
- **Attribuzione della spesa del test**
  - *Test positivi e negativi associati al farmaco*
  - *Differente sede tra esecuzione test e erogazione della terapia*

Genotyping and genomic profiling in personalized medicine

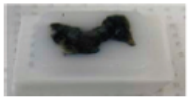
1. Histomorphologic Diagnosis:



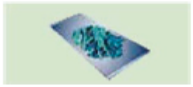
Clinical & Histology-Based Therapy (Compound-Based Therapy): Use clinicopathologic factors to select available drugs for an individual patient

2. Molecular Diagnosis:

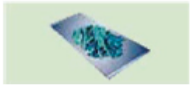
Archival FFPE tumor specimens



Archival cancer specimens



Macro- or microdissection of tumors



Extract tumor nucleic acids:

DNA and RNA

Current Personalized Medicine (Target-Based Therapy V1.0): Use single gene–based molecular tests to select specific drugs for an individual patient

Evolving Personalized Medicine (Target-Based Therapy V2.0): Use multiplexed molecular tests with increased sensitivity and outputs for the therapeutically effective selection of available drugs for an individual patient

Future Personalized Medicine (Patient-Based Therapy): Use an integrated genomic profile from high-throughput next-generation sequencing to tailor targeted treatment for an individual patient

Representative technologies:

Single Biomarker Tests:
- Sanger DNA sequencing or pyrosequencing
- RT-PCR
- FISH
- IHC

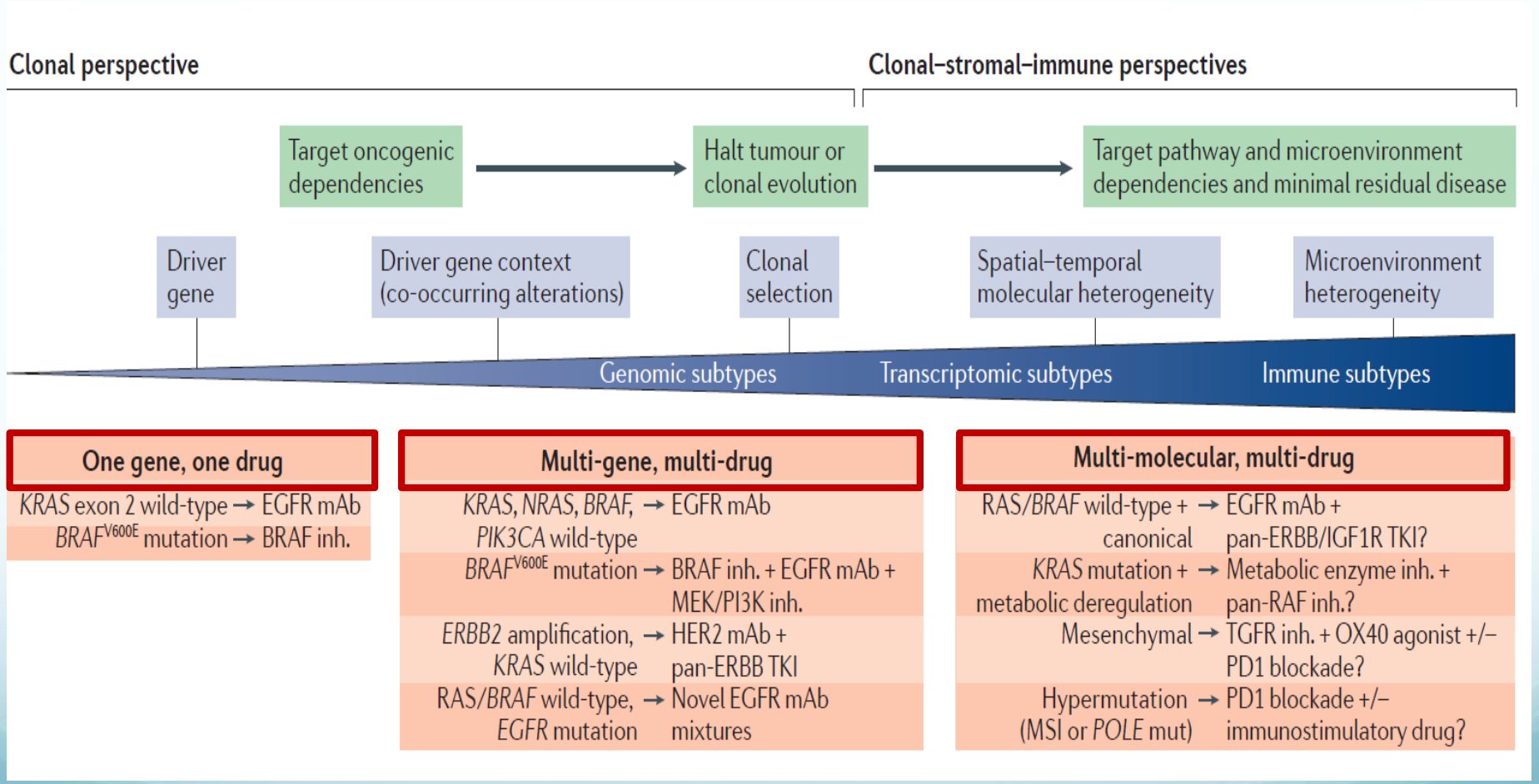
Multiplex, Hotspot Mutation Tests:
- PCR-based SNapShot
- PCR-based Mass Array SNP Sequenom

Initial High-Throughput Technologies:
- SNP/CNV DNA microarray
- RNA microarray
- Epigenetic modifications

Next-Generation Sequencing:
- Whole genome or exome capture sequencing (DNA)
- Whole or targeted transcriptome sequencing (RNA)
- Epigenetic profiling

Li, J Clin Oncol 2013

Evolution of precision medicine paradigms in colorectal cancer



Dienstmann et al, Nat Rev Cancer 2017

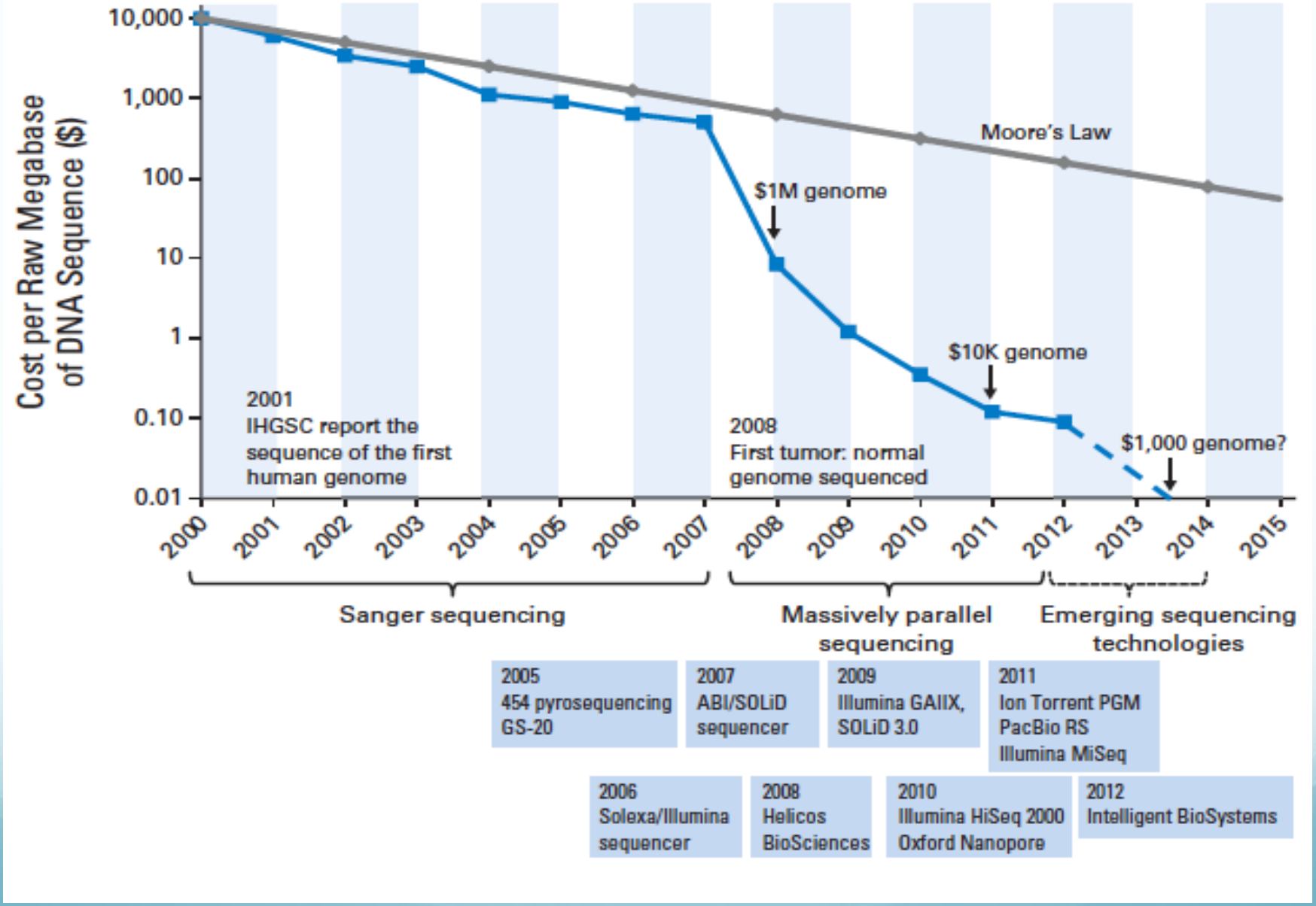
Methods for RAS testing

Study	Method	Sensitivity*	*RAS* mutant**
FIRE-3[1]	Pyrosequencing	≤ 5%[2]	15%[1]
OPUS[3]	Inostics BEAMing technology (detection cut-off 5%)	0.01%[4]	26%[3]
CRYSTAL[5]			15%[5]
CAPRI[6]	NGS: Ion AmpliSeq™ Colon & Lung Cancer Panel	2%[6]	15.9%[6]
PRIME[7]	Bidirectional Sanger sequencing and WAVE-based SURVEYOR® Scan Kits (Transgenomic)	15−20% (Sanger sequencing)[9]	17%[7]
PEAK[8]		1% (WAVE-based SURVEYOR®)[10]	22%[8]
20020408[11]	NGS, Sanger sequencing, and independently conducted WAVE-based SURVEYOR® Scan Kits (Transgenomic)	15–20% (Sanger sequencing)[9]	17.6%[11]
De Roock et al[12]	Sequenom MALDI-TOF MassARRAY multiplex PCR and genotyping	5–15%[12]	11%***

*Values refer to the lowest percentage of MT sequence that is detectable; ***KRAS* exons 3 and 4 and *NRAS* exons 2, 3 and 4; ***selected mutations.

1. Heinemann V, et al. Lancet Oncol 2014 [Epub ahead of print]; 2. Anderson SM. Expert Rev Mol Diagn 2011;11:635–42;
3. Bokemeyer C, et al. J Clin Oncol 2014;32(Supp 5):abstract 3505 (and oral presentation);
4. Aung KL, et al. Hugo J 2010;4:11–21; 5. Ciardiello F, et al. J Clin Oncol 2014;32(Suppl 5):abstract 3506 (and oral presentation);
6. Ciardiello F, et al. Ann Oncol 2014 [Epub ahead of print]; 7. Douillard J-Y, et al. N Engl J Med 2013;369:1023–34;
8. Schwartzberg LS, et al. J Clin Oncol 2014;32:2240−7; 9. Tsiatis AC, et al. J Mol Diagn 2010;12:425−32;
10. Jänne PA, et al. Clin Cancer Res 2006;12:751–8; 11. Peeters M, et al. Ann Oncol 2013;24(Suppl 4):abstract PD-0008 (and poster discussion); 12. De Roock W, et al. Lancet Oncol 2010;11:753–62.

Costs and technologies



MacConaill, J Clin Oncol 2013

Sottogruppi a volume limitato in ambito di patologie neoplastiche a più ampio volume

Neoplasia	N. di nuovi casi stimati nel 2018	Sottogruppi a volume limitato nella malattia avanzata
Carcinoma del polmone	*41.500*	*EGFRm 1.600-1.800* *T790M 600-800* *ALK riarr. 500-600* *ROS1riarr. 100-150*
Carcinoma del colon-retto	*51.300*	*RASwt 5.200-5.800* *BRAFm 1.000-1.100* *H-MSI 600-800*
Melanoma	*13.700*	*BRAFm 800-1.000*
Carcinoma dell'ovaio	*5.200*	*BRCAm 600-800*

AIOM – AIRTUM, I numeri del cancro in Italia 2018

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

OCTOBER 12, 2017

First FDA Approval Agnostic of Cancer Site — When a Biomarker Defines the Indication

Steven Lemery, M.D., M.H.S., Patricia Keegan, M.D., and Richard Pazdur, M.D.

Pembrolizumab Response Rate by Tumor Type.*

Tumor Type	No. of Tumors	Patients with a Response	Range of Response Duration
		no. (%)	*mo*
Colorectal cancer	90	32 (36)	1.6+ to 22.7+
Endometrial cancer	14	5 (36)	4.2+ to 17.3+
Biliary cancer	11	3 (27)	11.6+ to 19.6+
Gastric or gastroesophageal junction	9	5 (56)	5.8+ to 22.1+
Pancreatic cancer	6	5 (83)	2.6+ to 9.2+
Small-intestine cancer	8	3 (38)	1.9+ to 9.1+
Breast cancer	2	2 (100)	7.6 to 15.9
Prostate cancer	2	1 (50)	9.8+
Other cancers	7	3 (43)	7.5+ to 18.2+

FDA approves larotrectinib for solid tumors with NTRK gene fusions

Listen to the FDA D.I.S.C.O. podcast about this approval

On November 26, 2018, the Food and Drug Administration granted accelerated approval to larotrectinib (VITRAKVI, Loxo Oncology Inc. and Bayer) for adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, that are either metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment.

This is the second tissue-agnostic FDA approval for the treatment of cancer.

Approval was based on data from three multicenter, open-label, single-arm clinical trials: LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431). Identification of positive NTRK gene fusion status was prospectively determined in local laboratories using next generation sequencing (NGS) or fluorescence *in situ* hybridization (FISH). NTRK gene fusions were inferred in three pediatric patients with infantile fibrosarcoma who had a documented ETV6 translocation by FISH. The major efficacy outcome measures were overall response rate (ORR) and response duration, as determined by a blinded independent review committee according to RECIST 1.1.

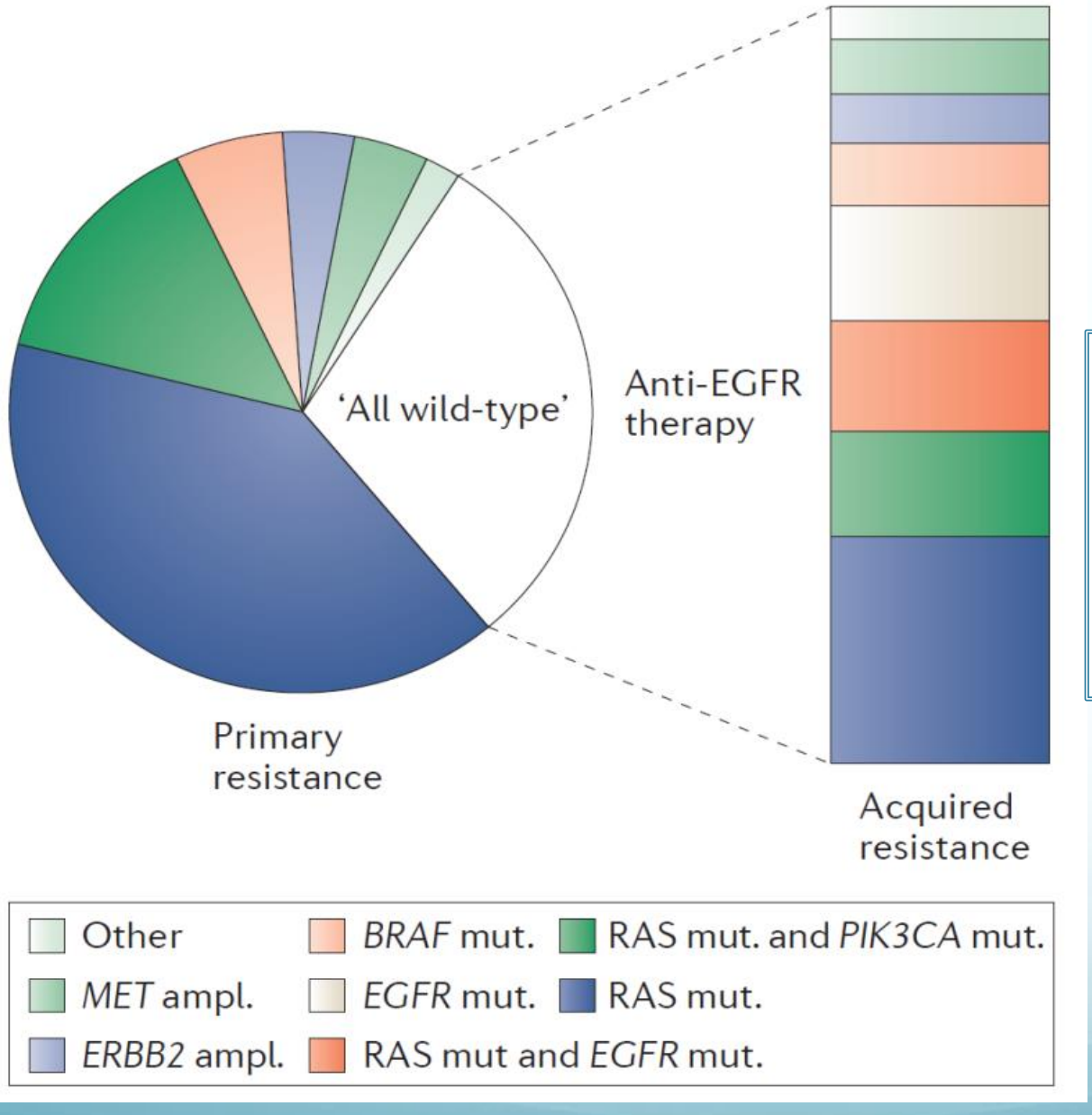
Efficacy was evaluated in the first 55 patients with unresectable or metastatic solid tumors harboring an NTRK gene fusion enrolled across the three trials. All patients were required to have progressed following systemic therapy for their disease, if available, or would have required surgery with significant morbidity for locally advanced disease. Twelve patients were less than 18 years of age. A total of 12 cancer types were represented, with the most common being salivary gland tumors (22%), soft tissue sarcoma (20%), infantile fibrosarcoma (13%), and thyroid cancer (9%).

ORR was 75% (95% CI: 61%, 85%), including 22% complete responses and 53% partial responses. At the time of database lock, median duration of response had not been reached. Response duration was 6 months or longer for 73%, 9 months or longer for 63%, and 12 months or longer for 39% of patients.

The safety of larotrectinib was evaluated in 176 patients enrolled across the three clinical trials, including 44 pediatric patients. The most common adverse reactions (≥20%) with larotrectinib were fatigue, nausea, dizziness, vomiting, increased AST, cough, increased ALT, constipation, and diarrhea.

The recommended larotrectinib doses are 100 mg orally twice daily for adults and 100 mg/m2 orally twice daily

Genomic landscape before and after anti-EGFR therapy

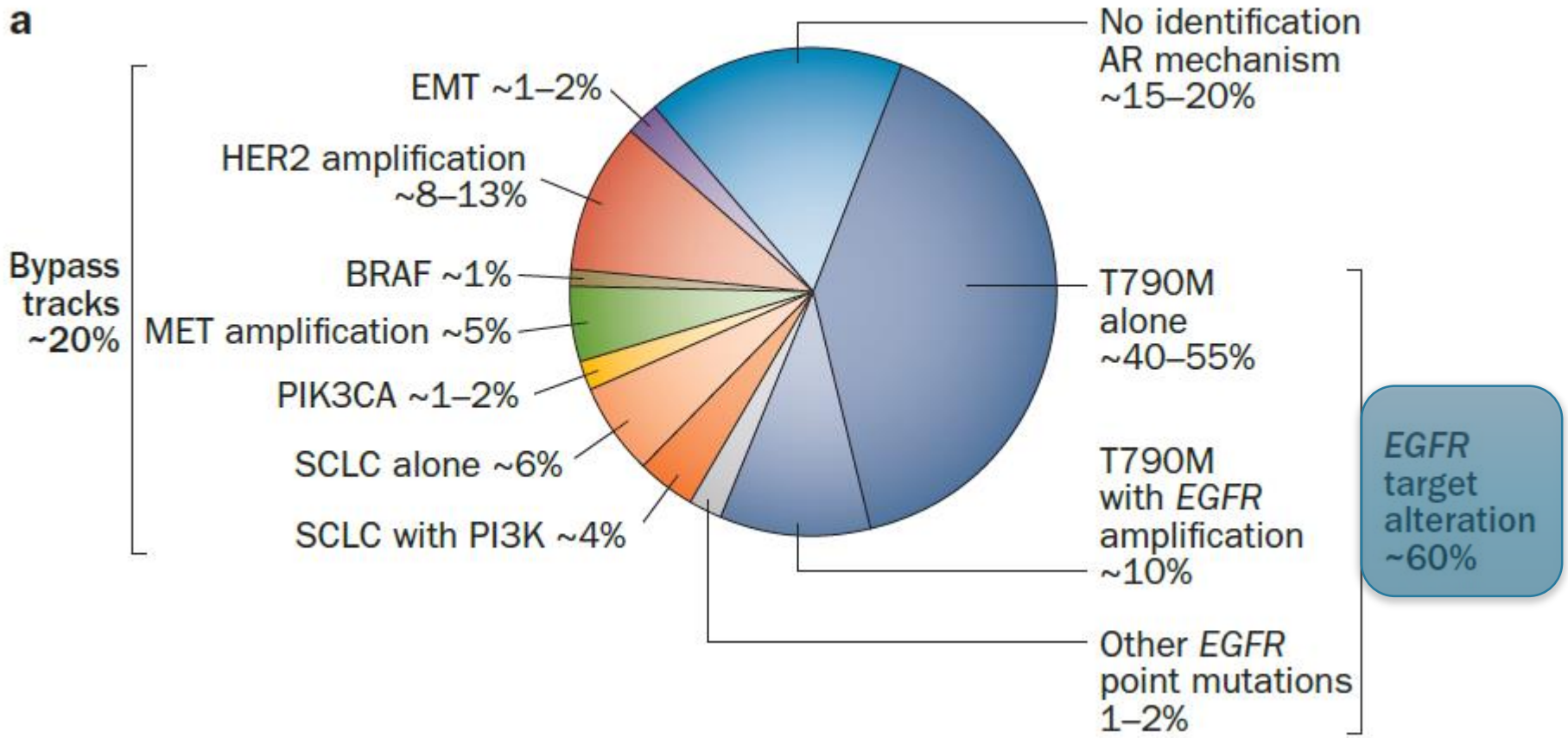


Anti-EGFR therapy in mCRC

- ***Primary resistence***
- ***Acquired resistence***

Dienstmann et al, Nat Rev Cancer 2017

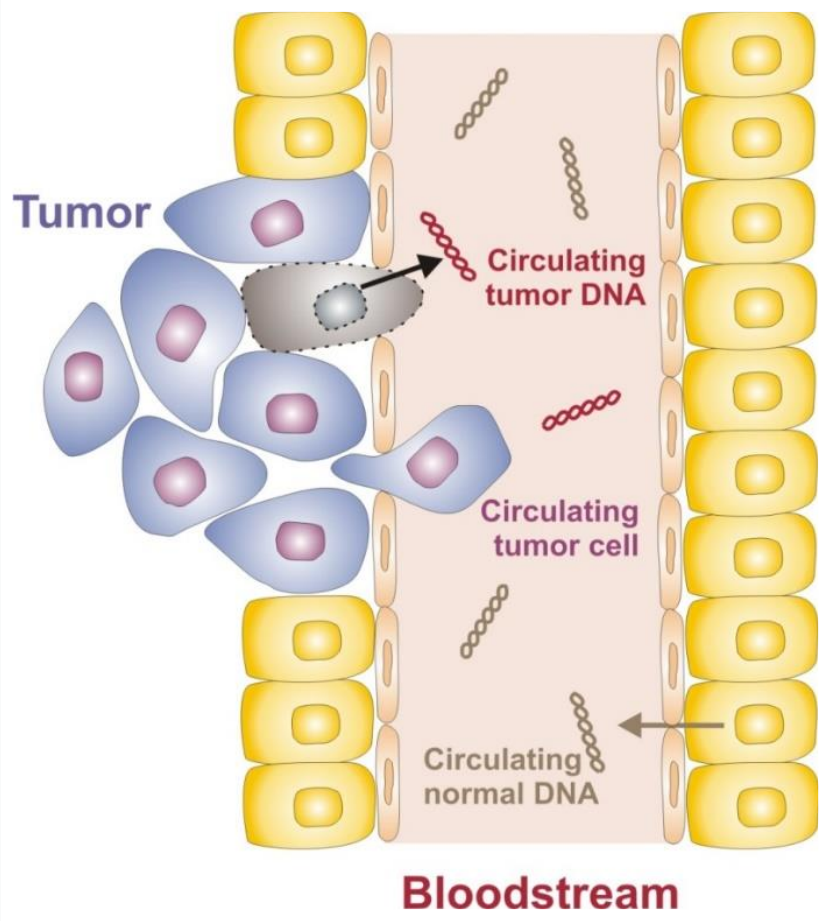
Mechanisms of acquired biological resistance to EGFR TKIs in NSCLC



Camidge et al, Nat Rev Clin Oncol 2014

Liquid Biopsy

Concept of Liquid Biopsy:



Advantages of Liquid Biopsy:

- Highly compliant and minimally invasive
- Always accessible
  - *Tissue is not always accessible*
- Fresh DNA profile
  - *Archival tissue can have a different mutation profile*
- No selection bias
  - *Liquid biopsy accounts for tumor heterogeneity at primary and metastatic sites*
- Monitoring is possible
- Reduced turn around time compared to tissue biopsy

Cancer Treatment Reviews 70 (2018) 1–8

Contents lists available at ScienceDirect

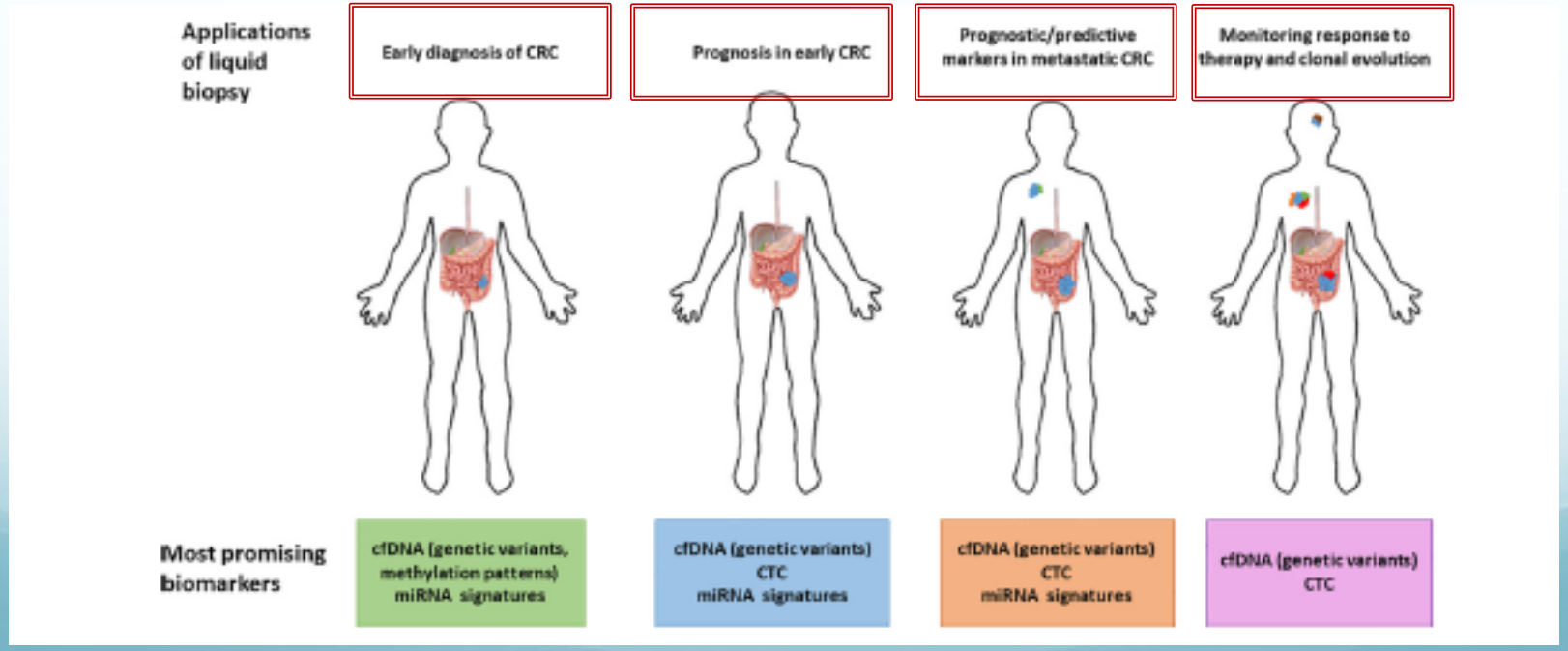
Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

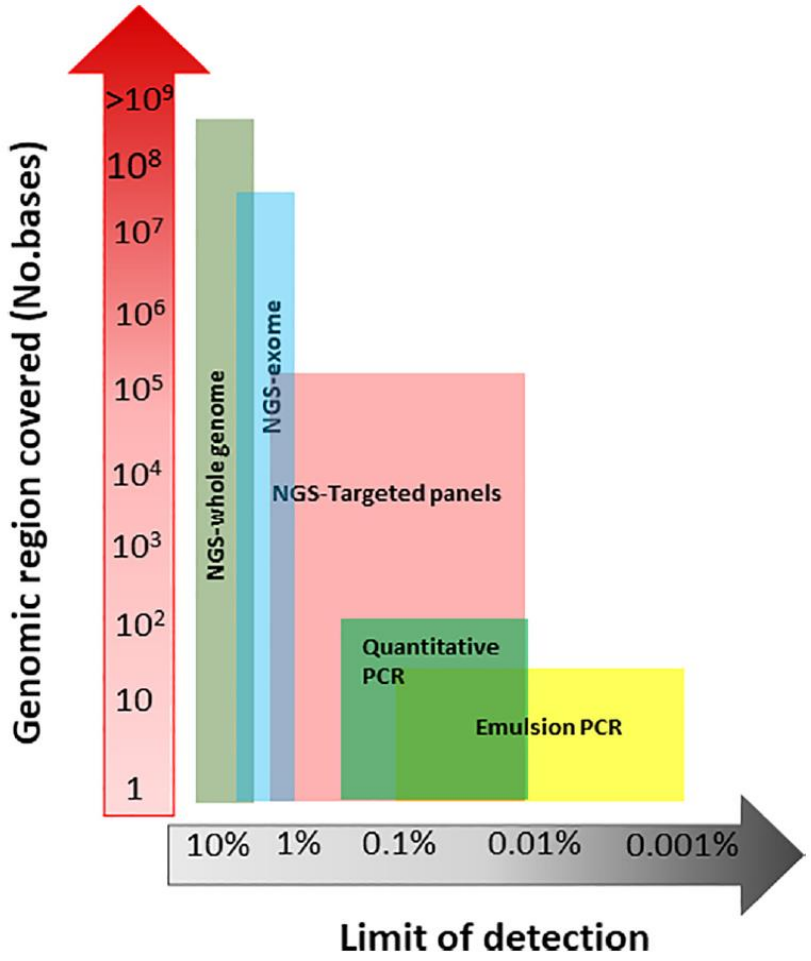
Laboratory-Clinic Interface

The liquid biopsy in the management of colorectal cancer patients: Current applications and future scenarios

Nicola Normanno[a,*], Andres Cervantes[b], Fortunato Ciardiello[c], Antonella De Luca[a], Carmine Pinto[d]



Analytical Sensitivity of the Different Approaches Used for cfDNA Analysis



- *Methods based on quantitative PCR have a limit of detection (LoD) up to 0.005%*
- *The Emulsion PCR-based technologies [Droplet Digital PCR (ddPCR) and Beads, Emulsion, Amplification, and Magnetics (BEAMing)] have a LoD ranging from 0.01 to 0.001%*
- *Technologies based on quantitative PCR and emulsion PCR can analyze up to hundreds bases and interrogate a limited number of loci, usually up to 10*
- *Massively parallel or next-generation sequencing (NGS) technologies allow sequencing from 200 Kb to 3.2 Gb with a sensitivity up to 0.01% for targeted panels*

Normanno et al, Clin Treat Rev 2018

ALLEGATO I

RIASSUNTO DELLE CARATTERISTICHE DEL PRODOTTO

4.4 Avvertenze speciali e precauzioni di impiego

Quando si considera l'uso di IRESSA per il trattamento del NSCLC localmente avanzato o metastatico, è importante che la valutazione della mutazione dell'EGFR del tessuto tumorale sia effettuata per tutti i pazienti. Se un campione del tumore non è valutabile, allora può essere utilizzato il DNA tumorale circolante (ctDNA) ottenuto da un campione di sangue (plasma).

Devono essere usati solo test robusti, affidabili e sensibili con utilità dimostrata per la determinazione dello stato di mutazione dell'EGFR sul tessuto tumorale o ctDNA, questo al fine di evitare risultati falsi negativi o falsi positivi (vedere paragrafo 5.1).

Centri in Italia che refertano EGFRm per indicazioni terapeutiche nel NSCLC su biopsia liquida

Regione	Numero di centri
Campania	*2*
Emilia Romagna	*5*
Friuli Venezia Giulia	*2*
Lazio	*1*
Liguria	*1*
Lombardia	*7*
Marche	*1*
Piemonte	*3*
Puglia	*1*
Sardegna	*1*
Sicilia	*1*
Umbria	*1*
Veneto	*1*
Tutte le regioni	**27**

Biopsia liquida: criticità e sviluppo

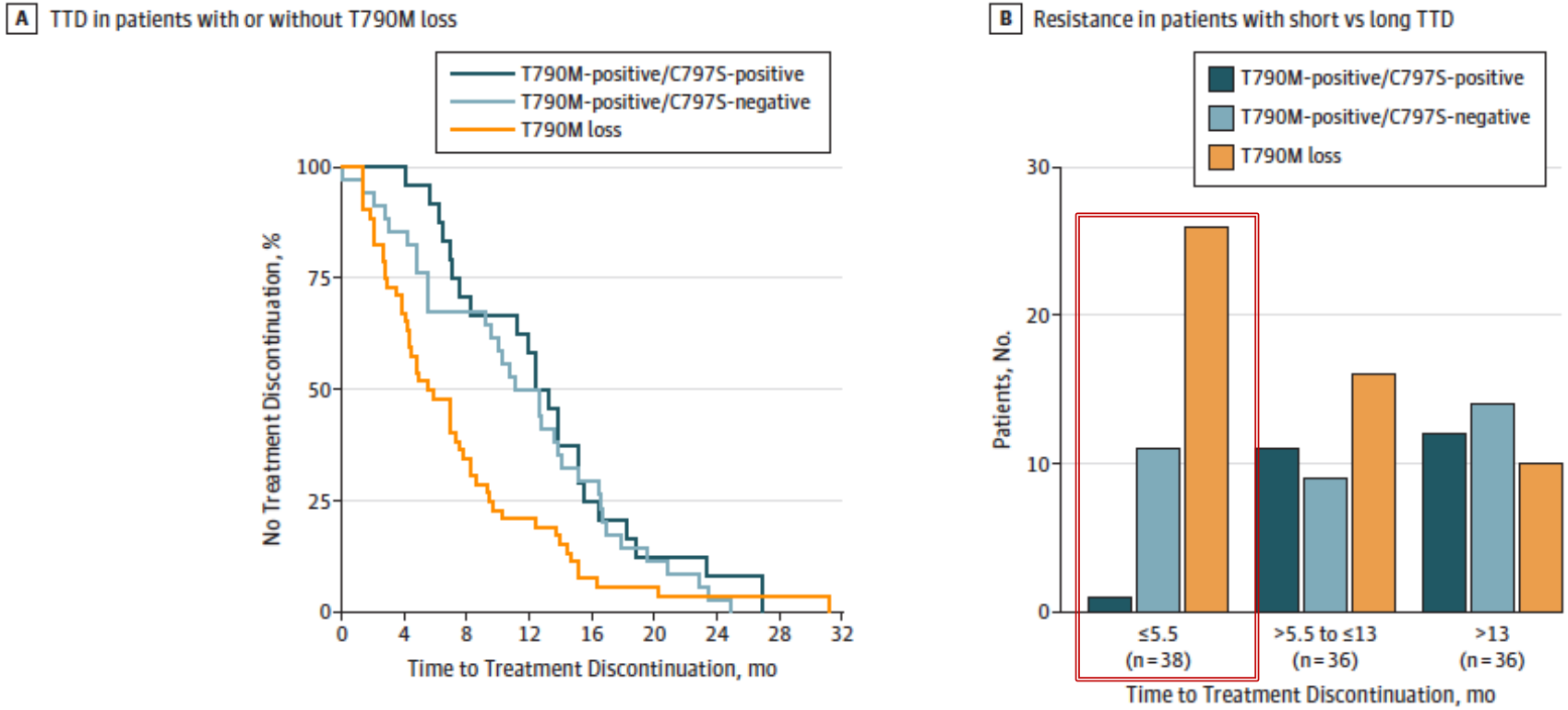
- **Definire le indicazioni**
  - *Cliniche (richiesta per prescrizione e rimborsabilità)*
  - *Ricerca (finalità differenti)*
- **Definire i requisiti per i laboratori**
  - *Caratteristiche e volume dei laboratori*
- **Definire il processo pre-analitico**
  - *Timing nella storia naturale e clinica della malattia*
  - *Tempi e modalità di prelievo, conservazione e trasporto*
- **Definire il processo analitico e di refertazione**
  - *Metodiche, test e sensibilità*
  - *Requisiti di refertazione*
- **Controllo di qualità**
  - *Progetto Europeo e Italiano in corso*

Tumor/plasma EGFR status concordance in the IFUM study

Tumour and plasma 1 – screened patients evaluable for both samples (*N* = 652)					
	Plasma 1 *EGFR* mutation status (*n*)				
	Positive		Negative		Total
Adjusted baseline tumour *EGFR* mutation status, *n*					
Positive	69		36		105
Negative	1		546		547
Total	70		582		652
	Exon 19 deletions	L858R	L858R and T790M	Negative	Total
Exon 19 deletions	48	0	0	23	71
L858R	0	21	0	12	33
L858R and T790M	0	0	0	1	1
Negative	0	1	0	546	547
Total	48	22	0	582	652
	N		Rate (%)		95% CI
Concordance	652		94.3		92.3–96.0
Sensitivity	105		65.7		55.8–74.7
Specificity	547		99.8		99.0–100.0
PPV	70		98.6		92.3–100.0
NPV	582		93.8		91.5–95.6

Douillard et al, Br J Cancer 2014

Acquired resistence to osirmetinib in a validation cohort (N.=110) from the AURA Study



Oxnard et al, JAMA Oncol 2018

CAPRI *Study*

340 RAS exon 2 wild type mCRC patients enrolled

182 patients (53.5%) with tissue available for NGS analysis

92 patients (27%) with baseline plasma sample available

Tissue and plasma KRAS and NRAS status

Tissue KRAS/NRAS mutational status*, n		Plasma KRAS/NRAS mutational status** (n) Mutated	Wild type
Mutated	*33*	**23**	**10**
Wild Type	*59*	*10*	*49*
Total	*92*	*33*	*59*

* NGS; ** BEAMing

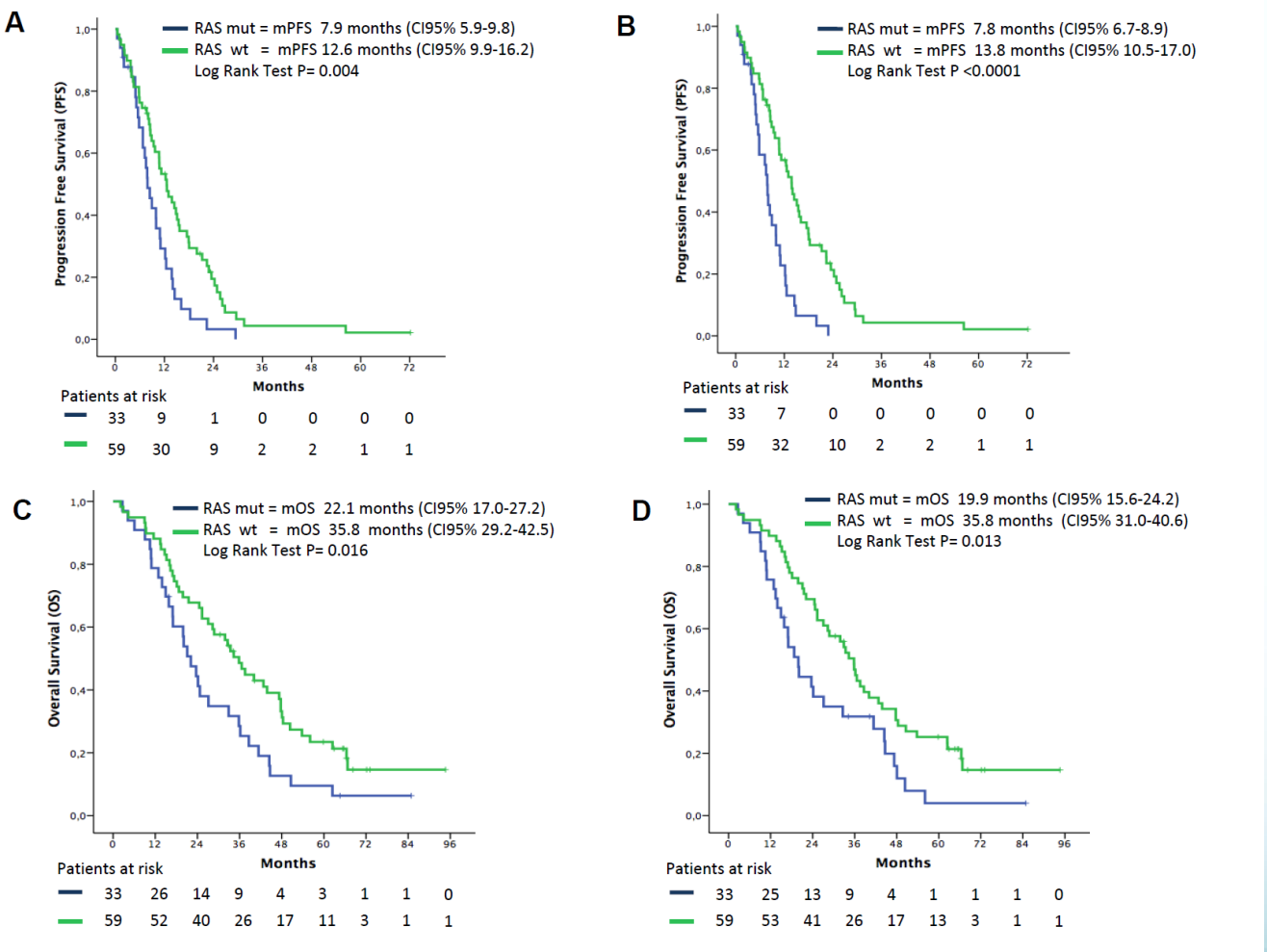
The concordance rate of plasma and tissue testing was 78.3%

Normanno et al, Ann Oncol 2017

PFS and OS of mCRC patients according to RAS test performed on tissue or liquid biopsy

Tissue Testing

Liquid Biopsy Testing



Normanno et al, Ann Oncol 2017

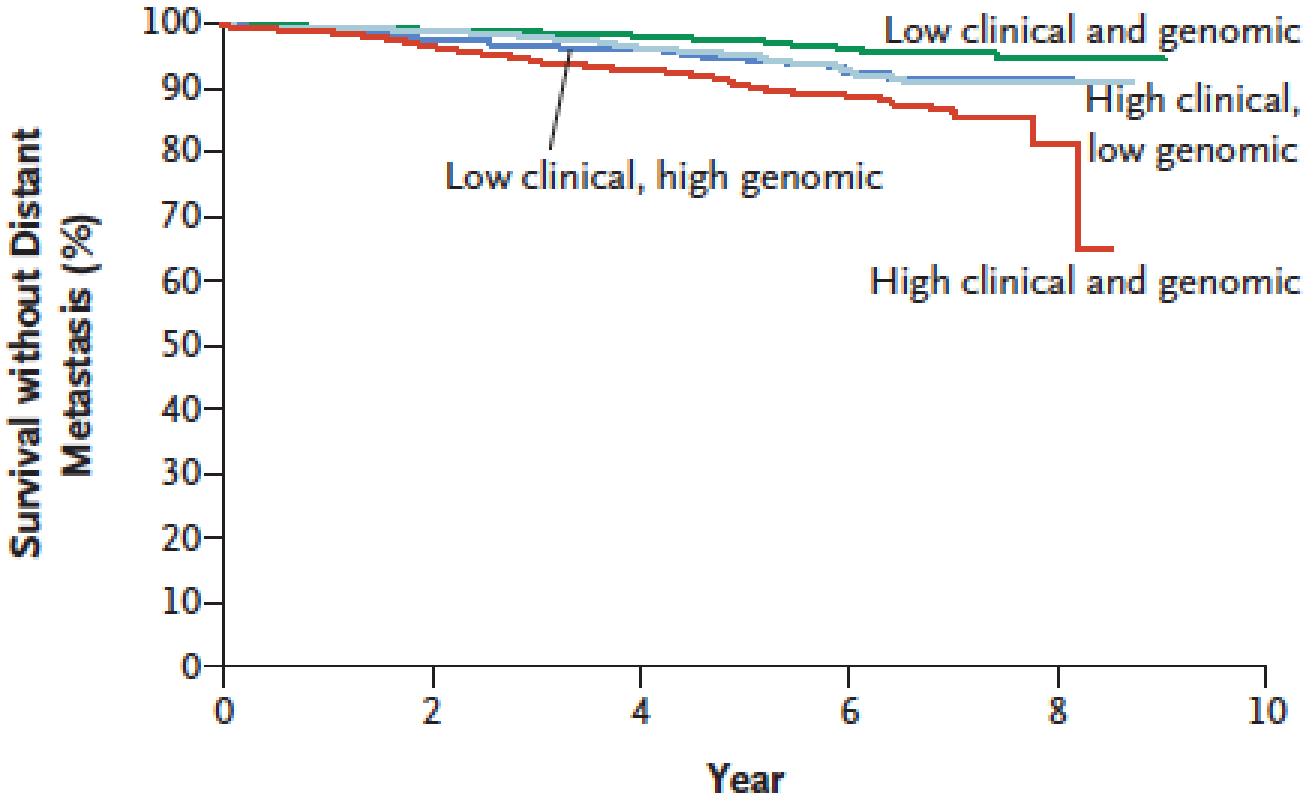
A negative liquid biopsy might suggest a better outcome in RAS mutant patients

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 25, 2016 VOL. 375 NO. 8

70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer

F. Cardoso, L.J. van't Veer, J. Bogaerts, L. Slaets, G. Viale, S. Delaloge, J.-Y. Pierga, E. Brain, S. Causeret, M. DeLorenzi, A.M. Glas, V. Golfinopoulos, T. Goulioti, S. Knox, E. Matos, B. Meulemans, P.A. Neijenhuis, U. Nitz, R. Passalacqua, P. Ravdin, I.T. Rubio, M. Saghatchian, T.J. Smilde, C. Sotiriou, L. Stork, C. Straehle, G. Thomas, A.M. Thompson, J.M. van der Hoeven, P. Vuylsteke, R. Bernards, K. Tryfonidis, E. Rutgers, and M. Piccart, for the MINDACT Investigators*



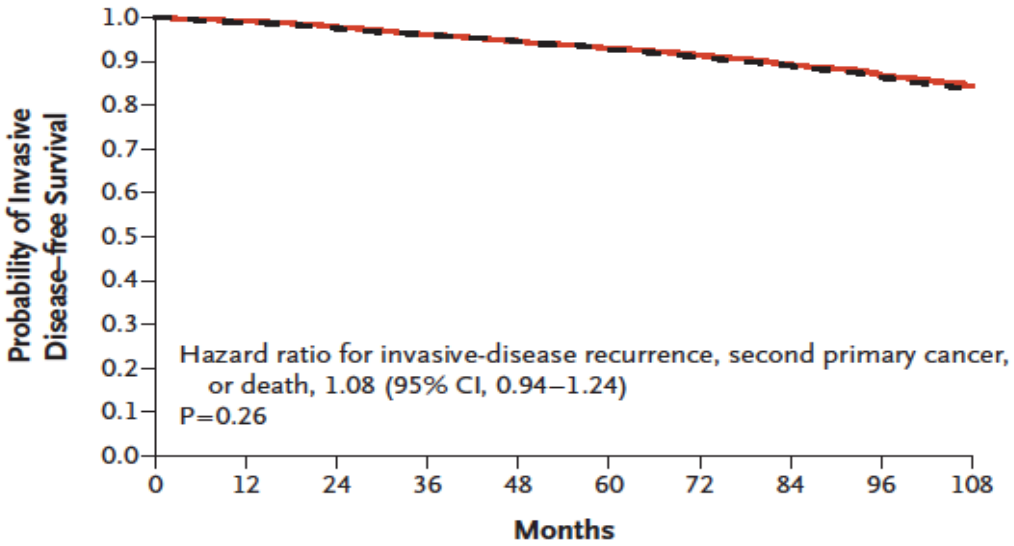
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 12, 2018 VOL. 379 NO. 2

Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

J.A. Sparano, R.J. Gray, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, M.P. Goetz, J.A. Olson, Jr., T. Lively, S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood, P.M. Ravdin, M.M. Keane, H.L. Gomez Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky, D.L. Toppmeyer, V.G. Kaklamani, J.L. Berenberg, J. Abrams, and G.W. Sledge, Jr.

A Invasive Disease–free Survival



No. at Risk										
Chemoendocrine therapy	3312	3204	3104	2993	2849	2645	2335	1781	1130	523
Endocrine therapy	3399	3293	3194	3081	2953	2741	2431	1859	1197	537

Evoluzione delle terapie target e indicazioni registrative

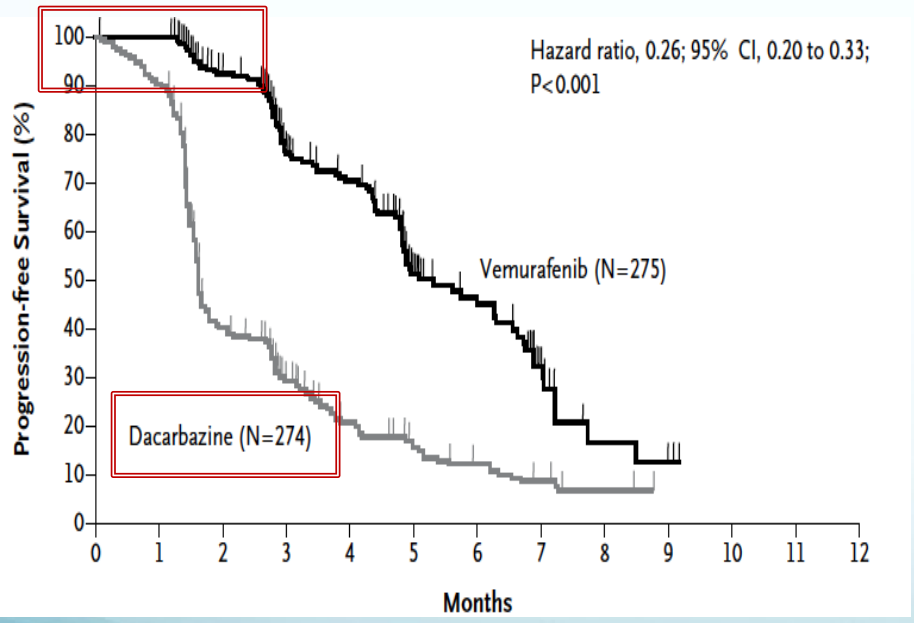
- *Monoterapia in malattia avanzata in I e II linea*
- *Monoterapia in malattia avanzata resistente ad una precedente terapia target*
- *Sviluppo di combinazioni*
- *Terapia di mantenimento*
- *Terapia adiuvante*
- *Indicazioni off label*

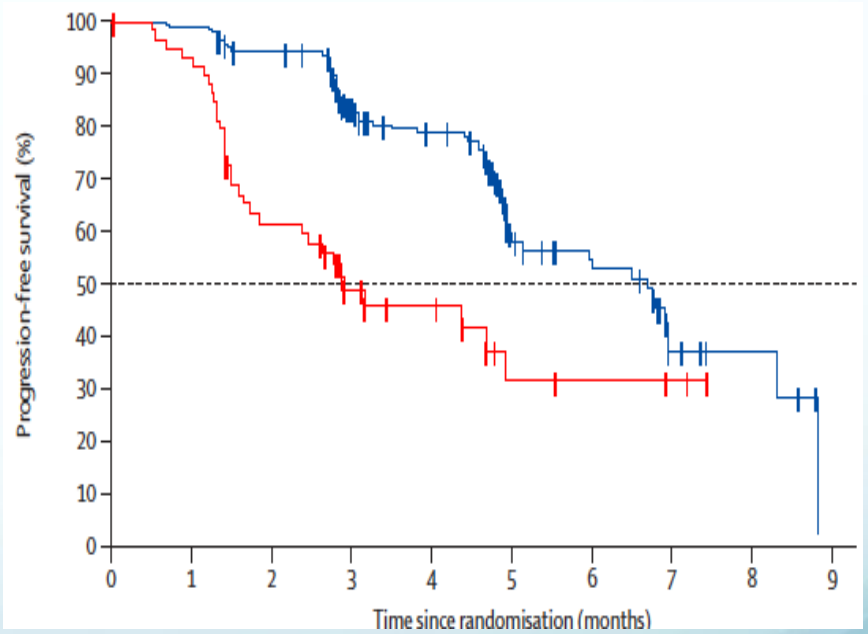
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Dabrafenib in *BRAF*-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial





Chapman et al, N Eng J Med 2011; Haushild et al, Lancet 2012

The NEW ENGLAND JOURNAL of MEDICINE

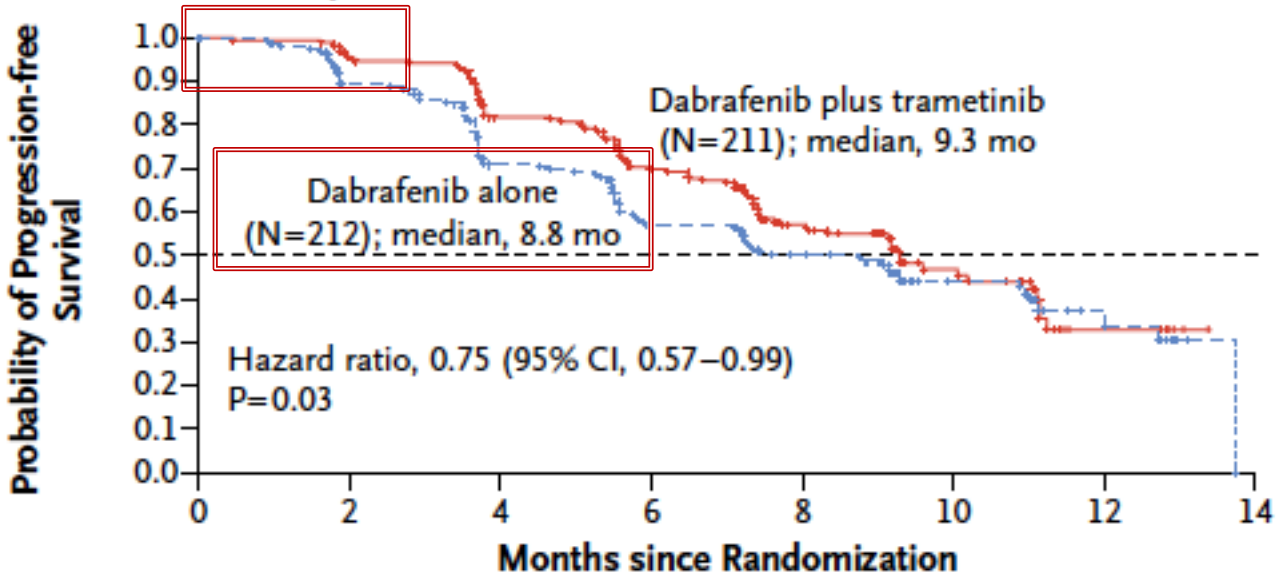
This article was published on September 29, 2014, at NEJM.org.

ORIGINAL ARTICLE

Combined BRAF and MEK Inhibition versus BRAF Inhibition Alone in Melanoma

G.V. Long, D. Stroyakovskiy, H. Gogas, E. Levchenko, F. de Braud, J. Larkin, C. Garbe, T. Jouary, A. Hauschild, J.J. Grob, V. Chiarion Sileni, C. Lebbe, M. Mandalà, M. Millward, A. Arance, I. Bondarenko, J.B.A.G. Haanen, J. Hansson, J. Utikal, V. Ferraresi, N. Kovalenko, P. Mohr, V. Probachai, D. Schadendorf, P. Nathan, C. Robert, A. Ribas, D.J. DeMarini, J.G. Irani, M. Casey, D. Ouellet, A.-M. Martin, N. Le, K. Patel, and K. Flaherty

Progression-free Survival, Intention-to-Treat Population



No. at Risk

Dabrafenib plus trametinib	211	196	164	138	82	33	9	0
Dabrafenib alone	212	173	136	107	68	31	10	0

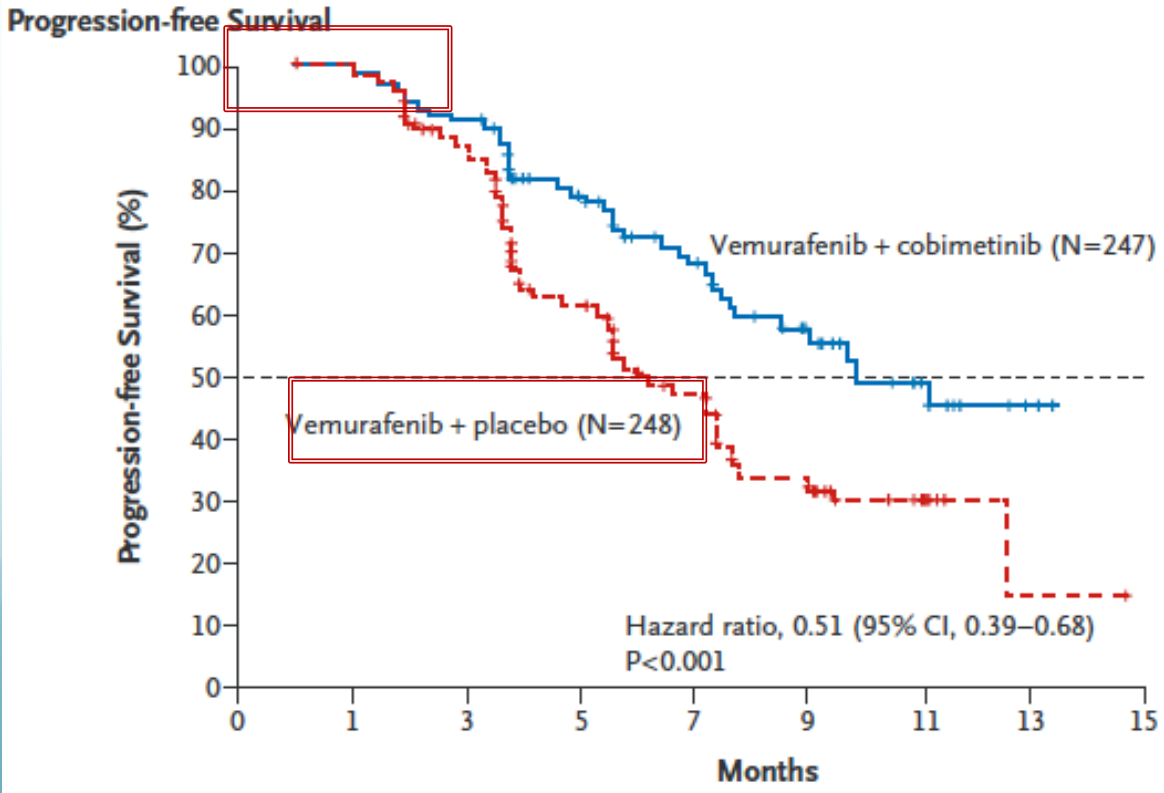
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 13, 2014 VOL. 371 NO. 20

This article was published on September 29, 2014, at NEJM.org.

Combined Vemurafenib and Cobimetinib in *BRAF*-Mutated Melanoma

James Larkin, M.D., Ph.D., Paolo A. Ascierto, M.D., Brigitte Dréno, M.D., Ph.D., Victoria Atkinson, M.D., Gabriella Liszkay, M.D., Michele Maio, M.D., Mario Mandalà, M.D., Lev Demidov, M.D., Daniil Stroyakovskiy, M.D., Luc Thomas, M.D., Ph.D., Luis de la Cruz-Merino, M.D., Caroline Dutriaux, M.D., Claus Garbe, M.D., Mika A. Sovak, M.D., Ph.D., Ilsung Chang, Ph.D., Nicholas Choong, M.D., Stephen P. Hack, M.D., Ph.D., Grant A. McArthur, M.B., B.S., Ph.D., and Antoni Ribas, M.D., Ph.D.



	Patients Who Died or Had Disease Progression	Median Progression-free Survival
	no.	*mo*
Vemurafenib + cobimetinib	79	9.9 (9.0–NR)
Vemurafenib + placebo	128	6.2 (5.6–7.4)

Resistenza a I linea- HER2 mammella

The New England Journal of Medicine

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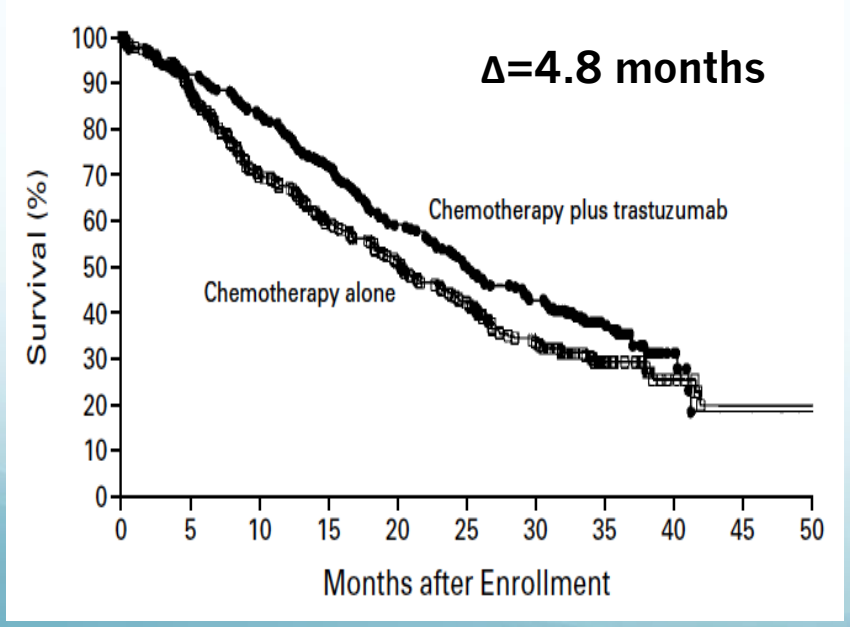
VOLUME 344 MARCH 15, 2001 NUMBER 11

USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

DENNIS J. SLAMON, M.D., PH.D., BRIAN LEYLAND-JONES, M.D., STEVEN SHAK, M.D., HANK FUCHS, M.D., VIRGINIA PATON, PHARM.D., ALEX BAJAMONDE, PH.D., THOMAS FLEMING, PH.D., WOLFGANG EIERMANN, M.D., JANET WOLTER, M.D., MARK PEGRAM, M.D., JOSE BASELGA, M.D., AND LARRY NORTON, M.D.*

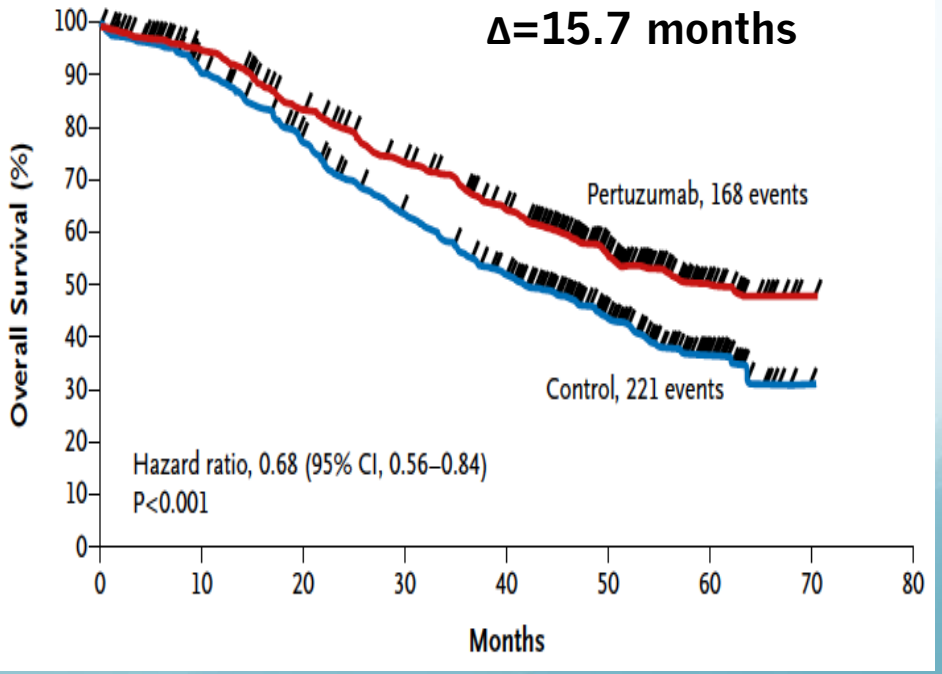


The NEW ENGLAND JOURNAL of MEDICINE FEBRUARY 19, 2015

ORIGINAL ARTICLE

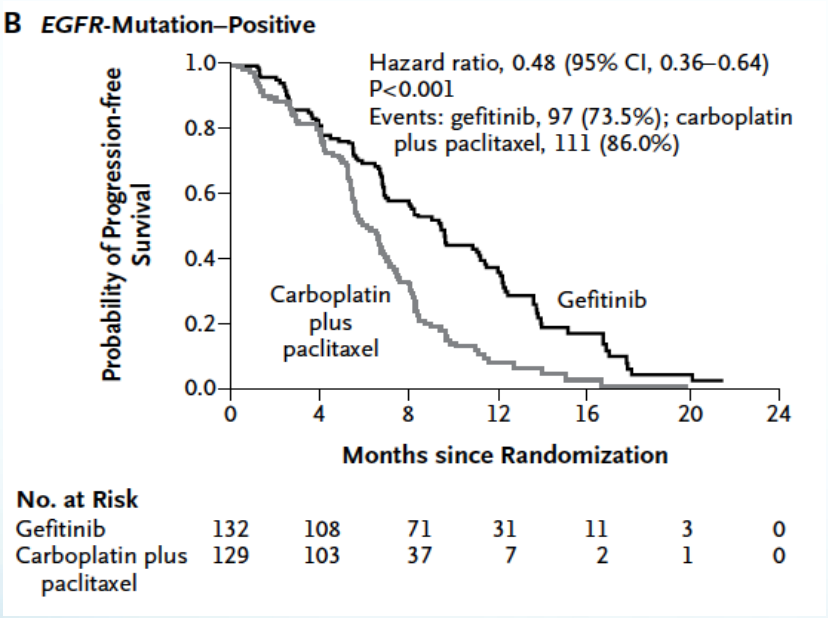
Pertuzumab, Trastuzumab, and Docetaxel in HER2-Positive Metastatic Breast Cancer

Sandra M. Swain, M.D., José Baselga, M.D., Sung-Bae Kim, M.D., Jungsil Ro, M.D., Vladimir Semiglazov, M.D., Mario Campone, M.D., Eva Ciruelos, M.D., Jean-Marc Ferrero, M.D., Andreas Schneeweiss, M.D., Sarah Heeson, B.Sc., Emma Clark, M.Sc., Graham Ross, F.F.P.M., Mark C. Benyunes, M.D., and Javier Cortés, M.D., for the CLEOPATRA Study Group*

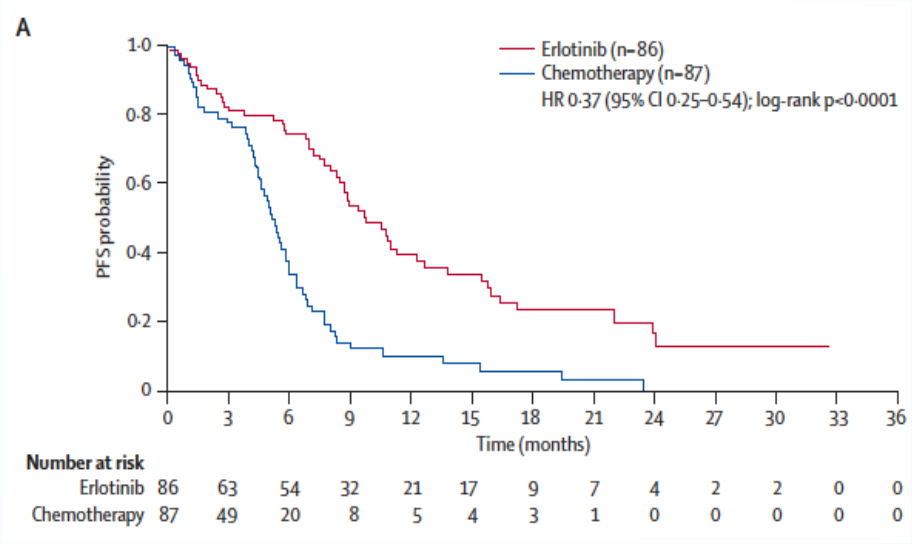


TKi in EGFRm NSCLC

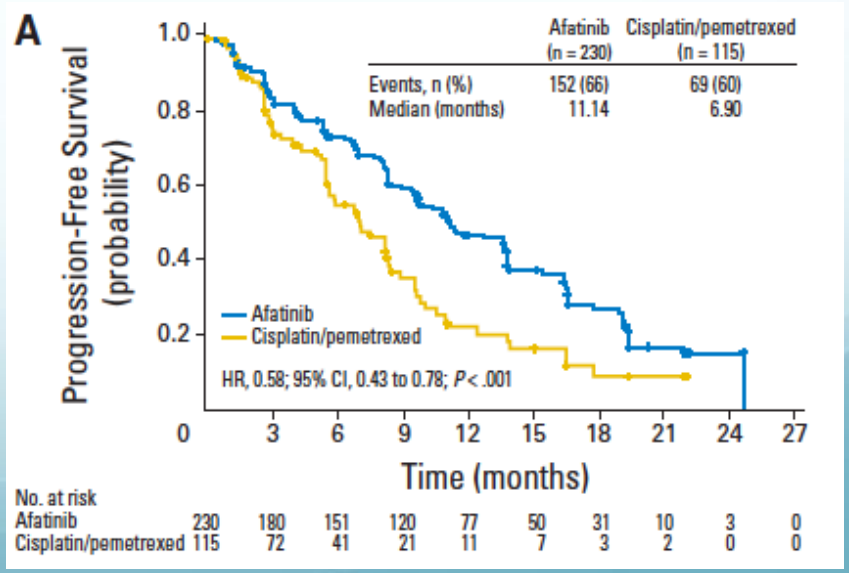
Gefitinib - Studio IPASS



Erlotinib – Studio EURTAC



Afatinib - Studio LUX-Lung 3



Mok et al, NEJM 2009
Rosell et al, Lancet Oncology 2012
Sequist et al, J Clin Oncol 2013

The NEW ENGLAND JOURNAL of MEDICINE

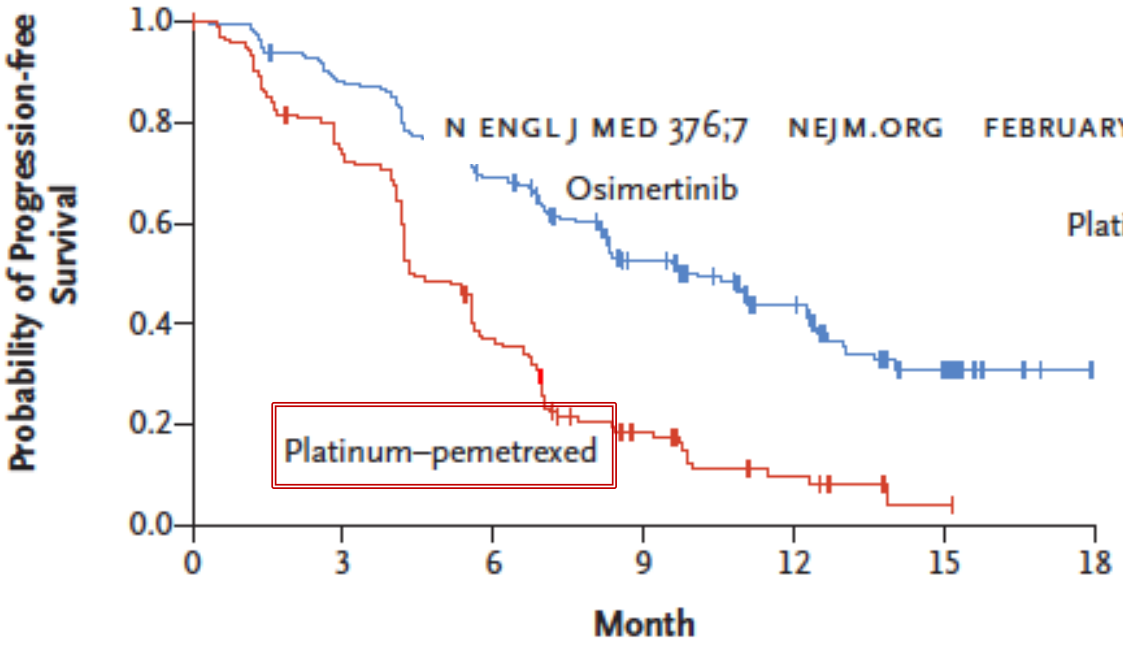
N ENGL J MED 376;7 NEJM.ORG FEBRUARY 16, 2017

ORIGINAL ARTICLE

Osimertinib or Platinum–Pemetrexed in *EGFR* T790M–Positive Lung Cancer

T.S. Mok, Y.-L. Wu, M.-J. Ahn, M.C. Garassino, H.R. Kim, S.S. Ramalingam, F.A. Shepherd, Y. He, H. Akamatsu, W.S.M.E. Theelen, C.K. Lee, M. Sebastian, A. Templeton, H. Mann, M. Marotti, S. Ghiorghiu, and V.A. Papadimitrakopoulou, for the AURA3 Investigators*

Patients in Intention-to-Treat Population



No. at Risk							
Osimertinib	279	240	162	88	50	13	0
Platinum–pemetrexed	140	93	44	17	7	1	0

	No. of Patients	Median Progression-free Survival *mo (95% CI)*
Osimertinib	279	10.1 (8.3–12.3)
Platinum–pemetrexed	140	4.4 (4.2–5.6)

Hazard ratio for disease progression or death, 0.30 (95% CI, 0.23–0.41)
P<0.001

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 11, 2018 VOL. 378 NO. 2

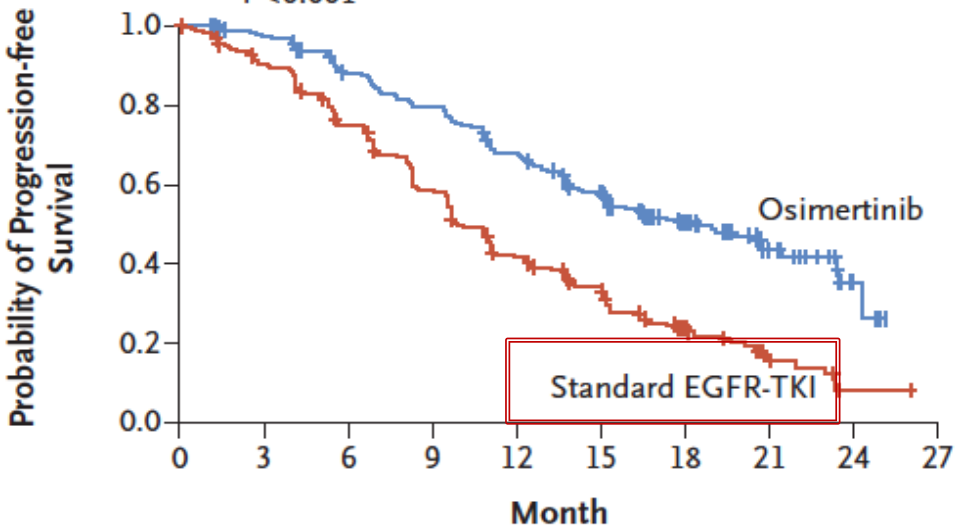
Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

J.-C. Soria, Y. Ohe, J. Vansteenkiste, T. Reungwetwattana, B. Chewaskulyong, K.H. Lee, A. Dechaphunkul, F. Imamura, N. Nogami, T. Kurata, I. Okamoto, C. Zhou, B.C. Cho, Y. Cheng, E.K. Cho, P.J. Voon, D. Planchard, W.-C. Su, J.E. Gray, S.-M. Lee, R. Hodge, M. Marotti, Y. Rukazenkov, and S.S. Ramalingam
for the FLAURA Investigators*

A Progression-free Survival in Full Analysis Set

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	279	18.9 (15.2–21.4)
Standard EGFR-TKI	277	10.2 (9.6–11.1)

Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57)
P<0.001



The NEW ENGLAND JOURNAL of MEDICINE

This article was published on June 6, 2017, at NEJM.org.

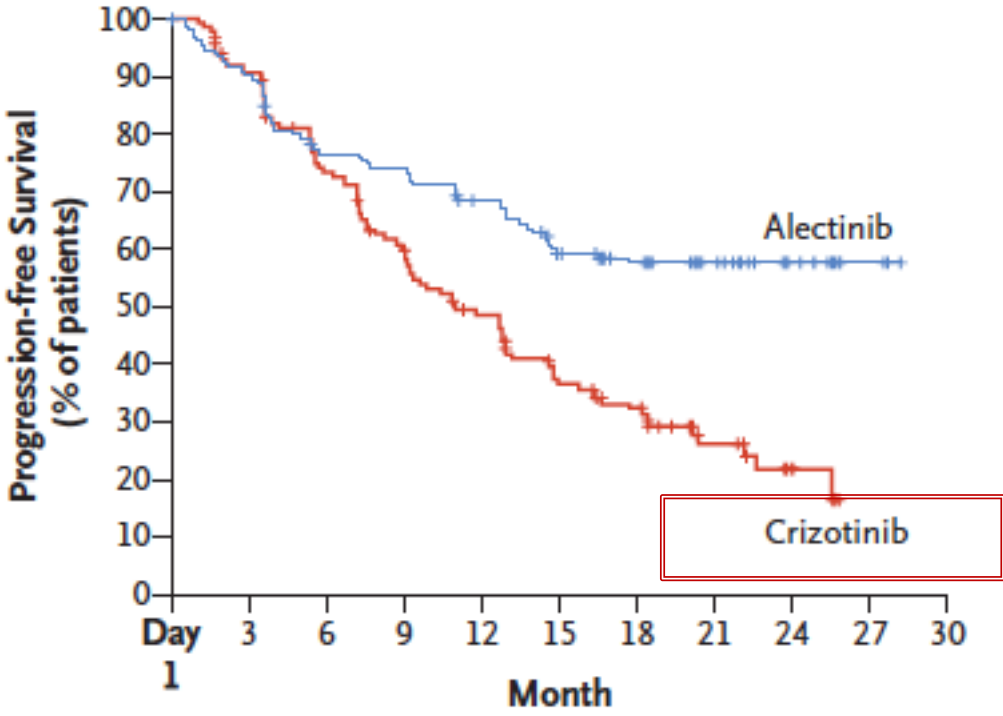
ORIGINAL ARTICLE

Alectinib versus Crizotinib in Untreated *ALK*-Positive Non–Small-Cell Lung Cancer

Solange Peters, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Alice T. Shaw, M.D., Ph.D., Shirish Gadgeel, M.D., Jin S. Ahn, Dong-Wan Kim, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Maurice Rafal Dziadziuszko, M.D., Rafael Rosell, M.D., Ph.D., Ali Zeaite Emmanuel Mitry, M.D., Ph.D., Sophie Golding, M.Sc., Bogdana Ba Johannes Noe, Ph.D., Peter N. Morcos, Pharm.D., and Tony Mo for the ALEX Trial Investigators*

A Progression-free Survival

Hazard ratio for disease progression or death, 0.47 (95% CI, 0.34–0.65)
P<0.001 by log-rank test



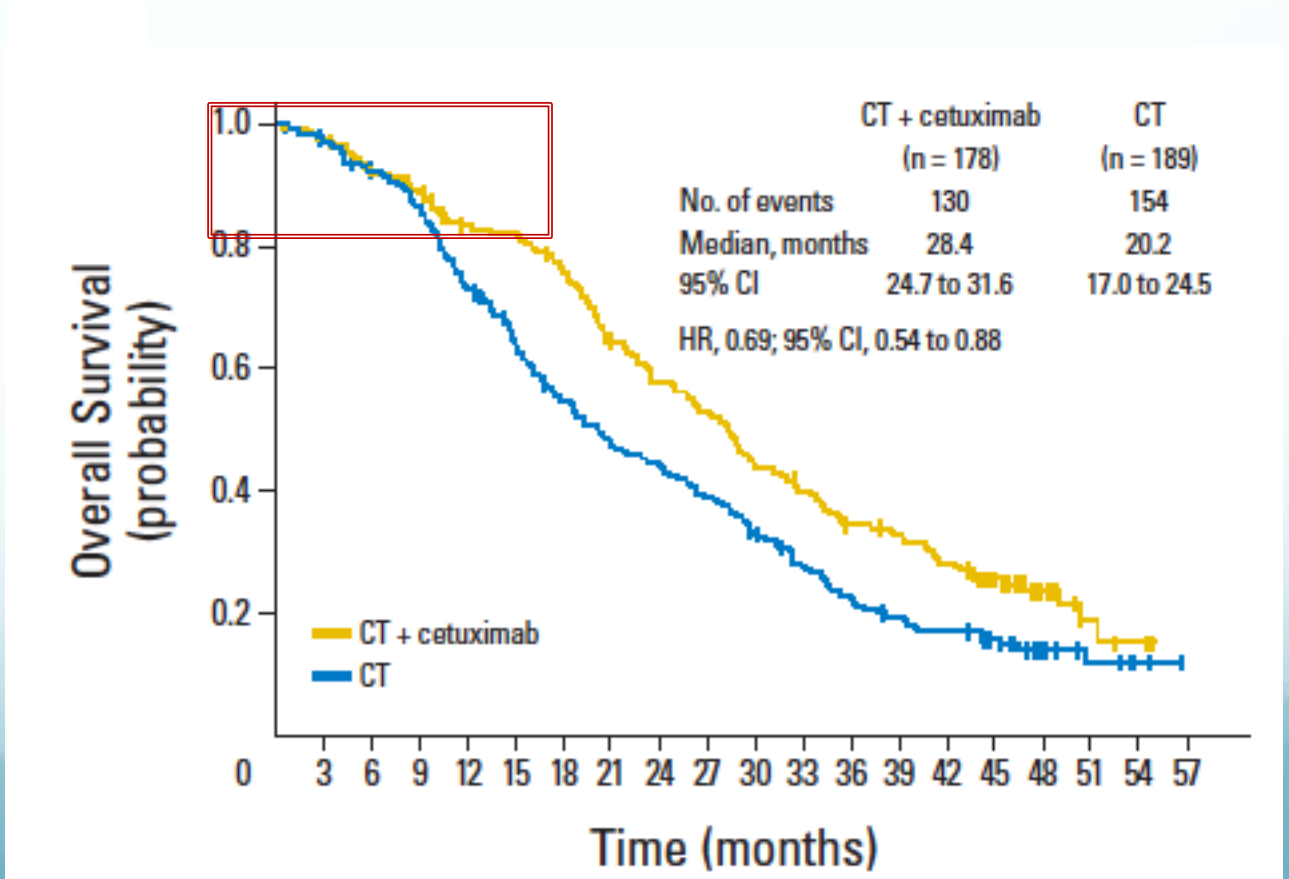
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Published online ahead of print at www.jco.org on January 20, 2015.

Fluorouracil, Leucovorin, and Irinotecan Plus Cetuximab Treatment and *RAS* Mutations in Colorectal Cancer

Eric Van Cutsem, Heinz-Josef Lenz, Claus-Henning Köhne, Volker Heinemann, Sabine Tejpar, Ivan Melezínek, Frank Beier, Christopher Stroh, Philippe Rougier, J. Han van Krieken, and Fortunato Ciardiello

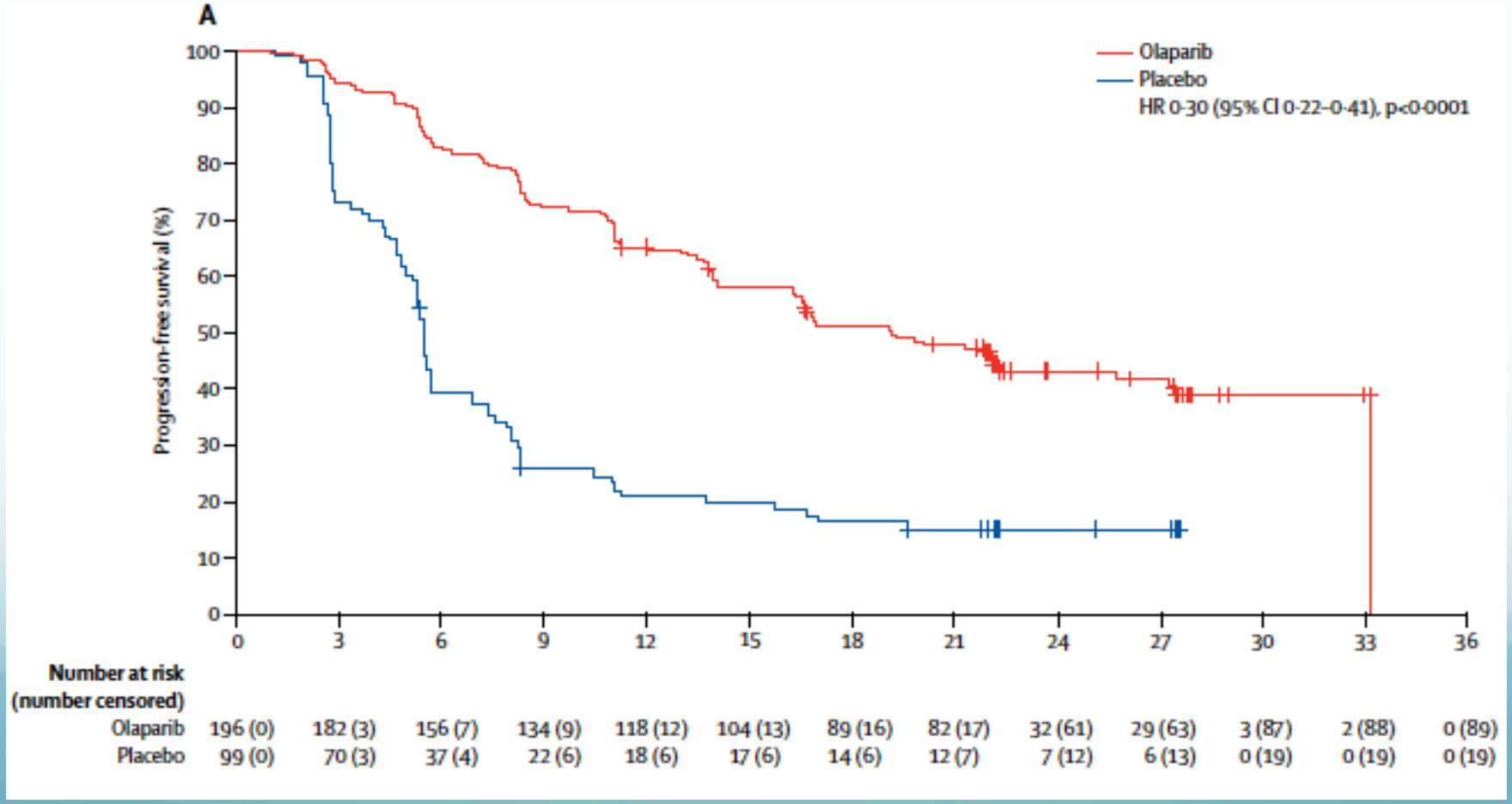


Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial

Lancet Oncol 2017

Published Online
July 25, 2017

*Eric Pujade-Lauraine, Jonathan A Ledermann, Frédéric Selle, Val Gebski, Richard T Penson, Amit M Oza, Jacob Korach, Tomasz Huzarski, Andrés Poveda, Sandro Pignata, Michael Friedlander, Nicoletta Colombo, Philipp Harter, Keiichi Fujiwara, Isabelle Ray-Coquard, Susana Banerjee, Joyce Liu, Elizabeth S Lowe, Ralph Bloomfield, Patricia Pautier, the SOLO2/ENGOT-Ov21 investigators**

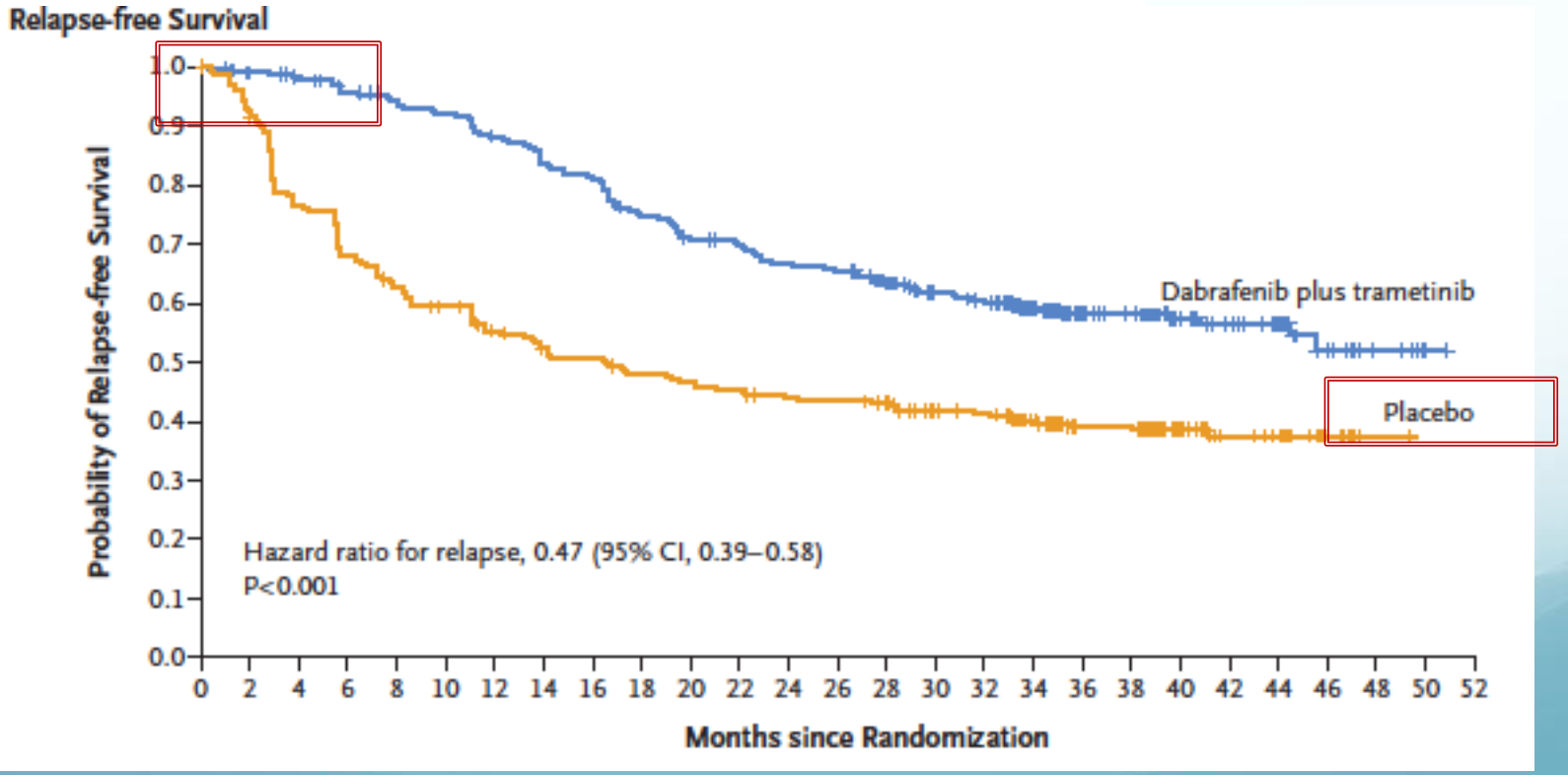


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 9, 2017 VOL. 377 NO. 19

Adjuvant Dabrafenib plus Trametinib in Stage III *BRAF*-Mutated Melanoma

G.V. Long, A. Hauschild, M. Santinami, V. Atkinson, M. Mandalà, V. Chiarion-Sileni, J. Larkin, M. Nyakas, C. Dutriaux, A. Haydon, C. Robert, L. Mortier, J. Schachter, D. Schadendorf, T. Lesimple, R. Plummer, R. Ji, P. Zhang, B. Mookerjee, J. Legos, R. Kefford, R. Dummer, and J.M. Kirkwood



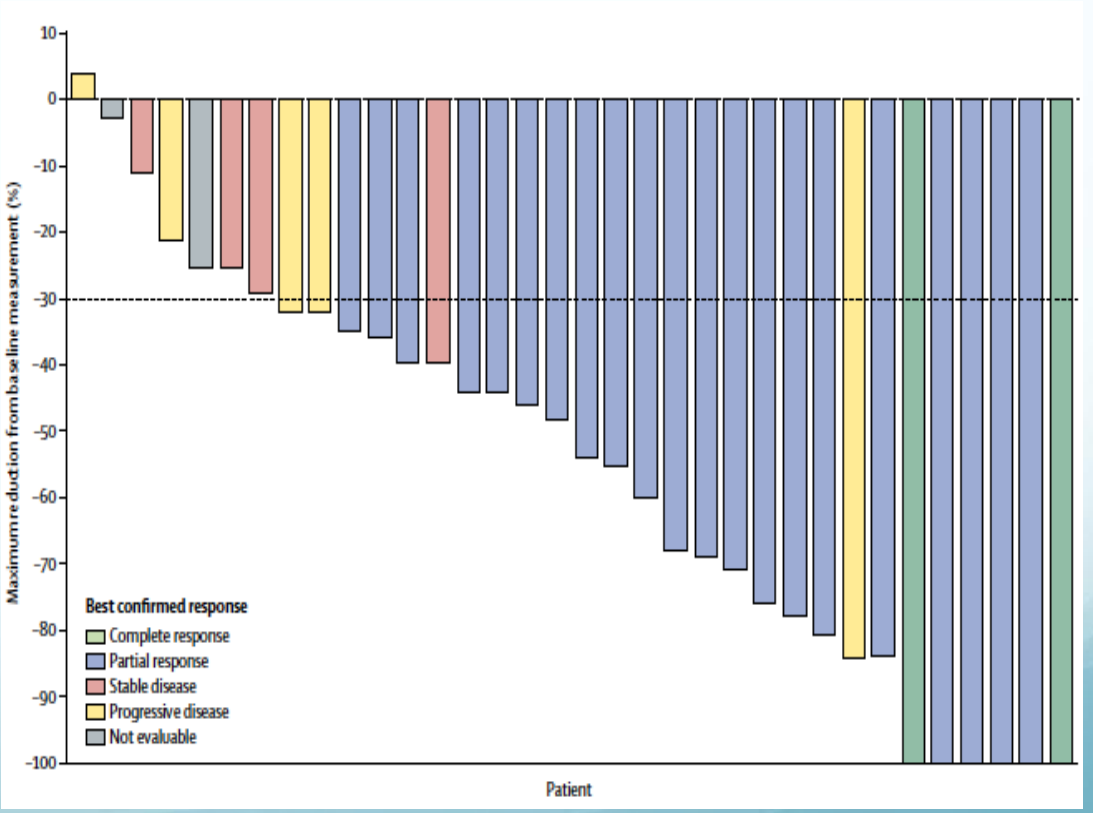
Lancet Oncol 2017; 18: 1307–16

Dabrafenib plus trametinib in patients with previously untreated *BRAF*^{V600E}-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial

David Planchard, Egbert F Smit, Harry J M Groen, Julien Mazieres, Benjamin Besse, Åslaug Helland, Vanessa Giannone, Anthony M D'Amelio Jr, Pingkuan Zhang, Bijoyesh Mookerjee, Bruce E Johnson

	Investigator assessed (n=36)	Independent review committee assessed (n=36)
Overall response (complete and partial responses)	23 (64%; 46–79)	23 (64%; 46–79)
Disease control (complete responses, partial responses, and stable disease)	27 (75%; 58–88)	26 (72%; 55–86)
Complete response	2 (6%)	2 (6%)
Partial response	21 (58%)	21 (58%)
Stable disease	4 (11%)	3 (8%)
Progressive disease	5 (14%)	7 (19%)
Not evaluable	4 (11%)	3 (8%)

Data are n (%; 95% CI) or n (%).



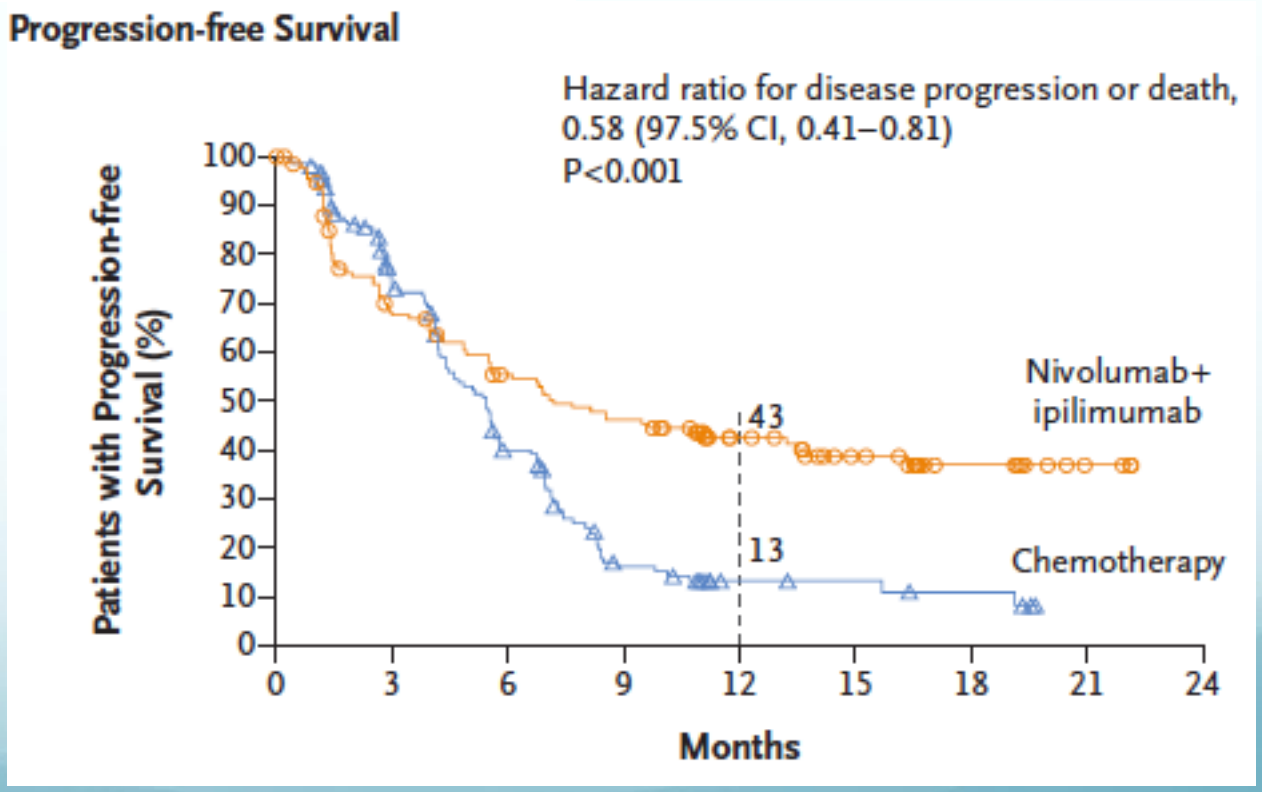
The NEW ENGLAND JOURNAL of MEDICINE

This article was published on April 16, 2018, at NEJM.org.

ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden

M.D. Hellmann, T.-E. Ciuleanu, A. Pluzanski, J.S. Lee, G.A. Otterson, C. Audigier-Valette, E. Minenza, H. Linardou, S. Burgers, P. Salman, H. Borghaei, S.S. Ramalingam, J. Brahmer, M. Reck, K.J. O'Byrne, W.J. Geese, G. Green, H. Chang, J. Szustakowski, P. Bhagavatheeswaran, D. Healey, Y. Fu, F. Nathan, and L. Paz-Ares



Commercial profile analyses

Assays conducted	Foundation Medicine	Tempus	Nanthealth GPS	Caris Life Sciences	Ambry & Myriad
DNA NGS	324 genes	596 genes, 1714 genes, WES	WES & WGS	596 genes	HRD assays; Lynch Tumor Next
Matched normal sample	No	Suggested not imperative	Yes	No	Yes
IHC	PD-L1	MMR genes PD-1/PD-L1	No	MMR genes, PD-1/L1, ER/PR, etc	No
RNA	No	Limited RNA	Whole transcriptome	53 gene assay; soon whole transcriptome	No
Methylation	No	No	No	MGMT	No
Other and/or future tests	Liquid biopsy, heme DNA/RNA panel	Adding liquid biopsy	Liquid biopsy circulating DNA and RNA	2019: WES, methylation	Hereditary panels

WES = Whole Exome Sequencing; WGS = Whole Genome Sequencing

Genetic Screening Programs

Institution	N. Genes	Cancer Type	Tissue type
EORTC - SPECTA Colon/Lung	*360*	*All*	*Archival*
Gustave Roussy - MOSCATO	*50/75 + aCGH*	*All*	*Biopsy*
MSK-IMPACT	*347*	*All*	*Archival*
Dana Farber - PROFILE	*305*	*All*	*Archival*
UCSF – GENOMIC MEDICINE	*>500*	*All*	*Archival*
MD Anderson – IMPACT2	*315+28*	*All*	*Archival*
NCI-MATCH	*143*	*All*	*Archival*

M-PACT

4 Treatment Regimens, 3 Pathways, and 20 Targeted Genes

	Gain of Function	Loss of Function
RAS pathway: GSK 1120212 MEK inhibitor	*BRAF, KRAS NRAS, HRAS*	*NF1*
PI3K pathway: Everolimus mTOR inhibitor	*AKT1, PIK3CA, MTOR*	*PTEN FBXW7*
DNA repair pathways: Veliparib (PARP inhibitor) + TMZ		*ATM, ATR, ERCC1, MLH1, MSH2, NBN, RAD51*
MK1775 (Wee1 inhibitor) + carboplatin		*PARP1, PARP2, TP53*

National Cancer Institute

391 aMOIs (with COSMIC ID) selected

http://dctd.cancer.gov/MajorInitiatives/M-PACT_Slides.pdf

TAPUR Matching Rules

- Specific genomic inclusion and exclusion criteria included for each drug
- Matching at variant level if possible
- Automated rules engine approves/rejects match proposed by treating MD
- If no match proposed or match rejected, treating MD may consult TAPUR Molecular Tumor Board (MTB)
- MTB identifies TAPUR drugs or other options based on tumor genomics

Drugs Available in TAPUR

Pharmaceutical Company (Number of Drugs)	Drug(s) Provided for TAPUR Study
AstraZeneca (1)	Olaparib
Bayer (1)	Regorafenib
Bristol-Meyers Squibb (1)	Dasatinib
Eli Lilly (1)	Cetuximab
Genentech (6)	Erlotinib, Trastuzumab + Pertuzumab, Vemurafenib + Cobimetinib, Vismodegib
Merck (1)	Pembrolizumab
Pfizer (6)	Axitinib, Bosutinib, Crizotinib, Palbociclib, Sunitinib, Temsirolimus

The National Registry of "actionable" mutations – RATIONAL Study

- *Prospective, multicenter, observational, non-interventional study*
- *Endorsed by AIOM and SIAPEC*
- *Sponsor: AIOM*
- *PI: Nicola Normanno*
- *Coordinating Center: Istituto Nazionale Tumori "Fondazione G. Pascale"-IRCCS, Naples, Italy*
- *All Italian academic institutions and regional hospitals*

The National Registry of “actionable” mutations - RATIONAL Study

- *The aim of this project is the creation of a national network of personalized medicine that allows Italian patients with solid tumors to access the most innovative therapies through clinical trials*
- *A national register of "actionable" mutations will be created in patients with advanced malignancies, in which the various local and regional genomic cancer screening initiatives can be merged (Path A)*
- *A limited and selected number of patients who do not have access to pharmacogenetic characterization tests for their neoplasm and who meet specific criteria will be offered the possibility of free access to the FoundationOne pharmacogenetic screening test (Path B)*

RATIONAL Study - Criteria for the test FoundationOne

One of the following criteria

- *Patients diagnosed with advanced non-small cell lung cancer (NSCLC) negative for EGFR mutations and ALK rearrangements;*
- *Patients with any tumor type (included NSCLC) at disease progression after targeted therapy;*
- *Patients with unknown primary tumor (CUP)*
- *Patients with bile duct cancer*

Molecular diagnostics

Objectives

- *Access*
- *Equity*
- *Quality*
- *Time*
- *Performance*
- *Effectiveness*

First phase before 2017

Clinical needs	*Objectives*	*Actions*
• *AIFA registered drug related to molecular test*	• *Test availability and access* • *Sample management* • *Laboratory training*	• *Scientific Society (AIOM, SIAPEC) activity* • *National Recommendations* • *National External Quality Assurance (EQA)*

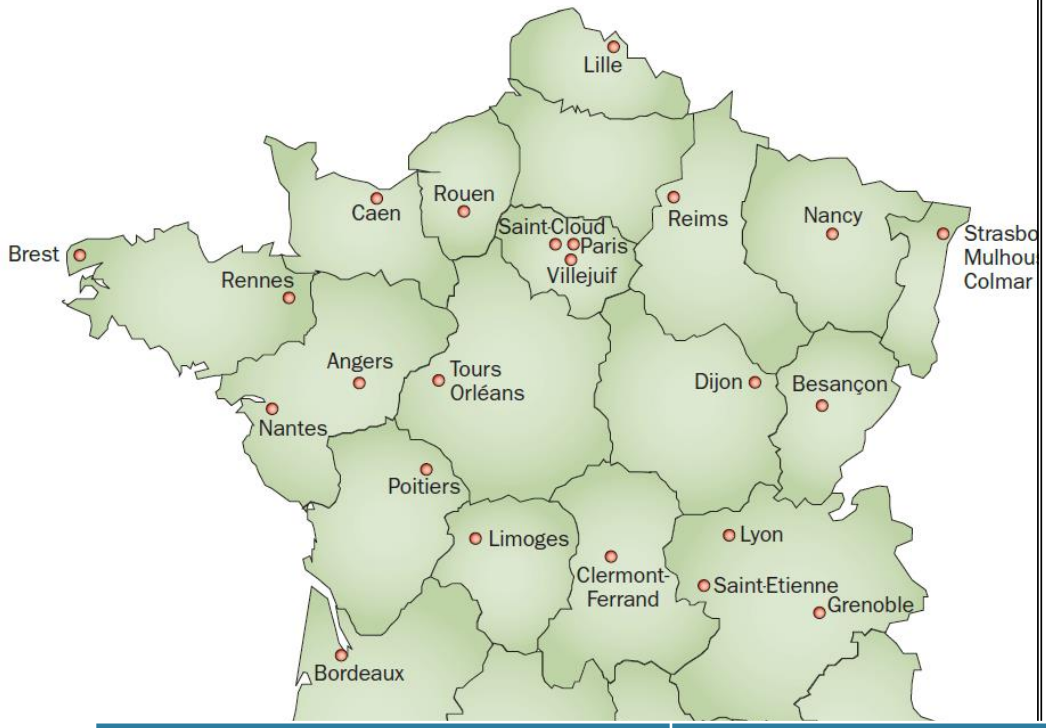
Second phase after 2017

Clinical needs	*Objectives*	*Actions*
• *Improvement of molecular selection* • *From to gene one drug to multimolecular multidrug request* • *Liquid biopsy*	• *New organization models* • *Costs* • *Management* • *Time of test result*	• *National Agencies* • *Regional Institutions* • *Network* • *Two level model* • *Hub model*

Italian External Quality Asurance (AIOM-SIAPEC)

Test	Year	Registered Centres N.	Successful Centres N. (%)
KRAS mCRC	*2012*	*83*	**79 (95)**
BRAF Melanoma	*2012*	*80*	**73 (91)**
RAS-BRAF mCRC	*2014*	*88*	**79 (90)**
BRAF Melanoma	*2014*	*92*	**75 (69)**
RAS-BRAF mCRC-Melanoma	*2017*	*102*	**82 (80)**

Molecular genetics platforms in France



- *The 28 molecular genetics centers are regional hubs for expert molecular testing. The centers were selected through competitive calls for proposals*
- *The centers are located throughout the country, with an average of one center per administrative region; their number is not expected to increase.*
- *Each molecular genetics center is a partnership between several*

Country	Population	Molecular Lab Center
France	*67,000,000*	*28*
Italy	*61,000,000*	*82*

Nowak et al, Nat Rev Clin Oncol 2012

The most organized oncology testing structures in the world

28 INCa genetic molecular platforms

- ***Melanoma***
  - *BRAF/c-KIT*
- ***Lung***
  - *Perform EGFR and ALK*
  - *Perform* **reflex testing** *for some "Emerging Biomarkers", including KRAS, BRAF and HER2 This testing list is imposed by INCa in guidelines**
- **Testing results are included in the pathology report**, *generally including an indication of which treatment type may benefit the patient*
- **No testing technique imposed** *(both kits and LDTs are used)*

IHC

- ***Actual coverage of ICH machines within Inca platforms***
  - *Dako ~38% / Ventana ~60-65% / Leica ~38%*
- ***The majority of IHC testing is however carried out by non INCa platforms***

Types of Testing Centers	# of Testing Centers
Major labs – INCa molecular genetic platforms • *Specialized Oncology Centers* • *University Hospitals*	*28* *20* *8*
Major Private Labs (Cerba, Biomnis)	*2*
Community based labs	*2000*
Public hospitals	*350*

* ROS1, CMET & NRAS can also sometimes be included in panel of tests performed reflexively, but are not included in INCa guidelines

Revisione delle Linee guida organizzative e delle raccomandazioni per la Rete Oncologica che integra l'attività ospedaliera per acuti e post acuti con l'attività territoriale

D.M. n.70/2015

06.11.2017

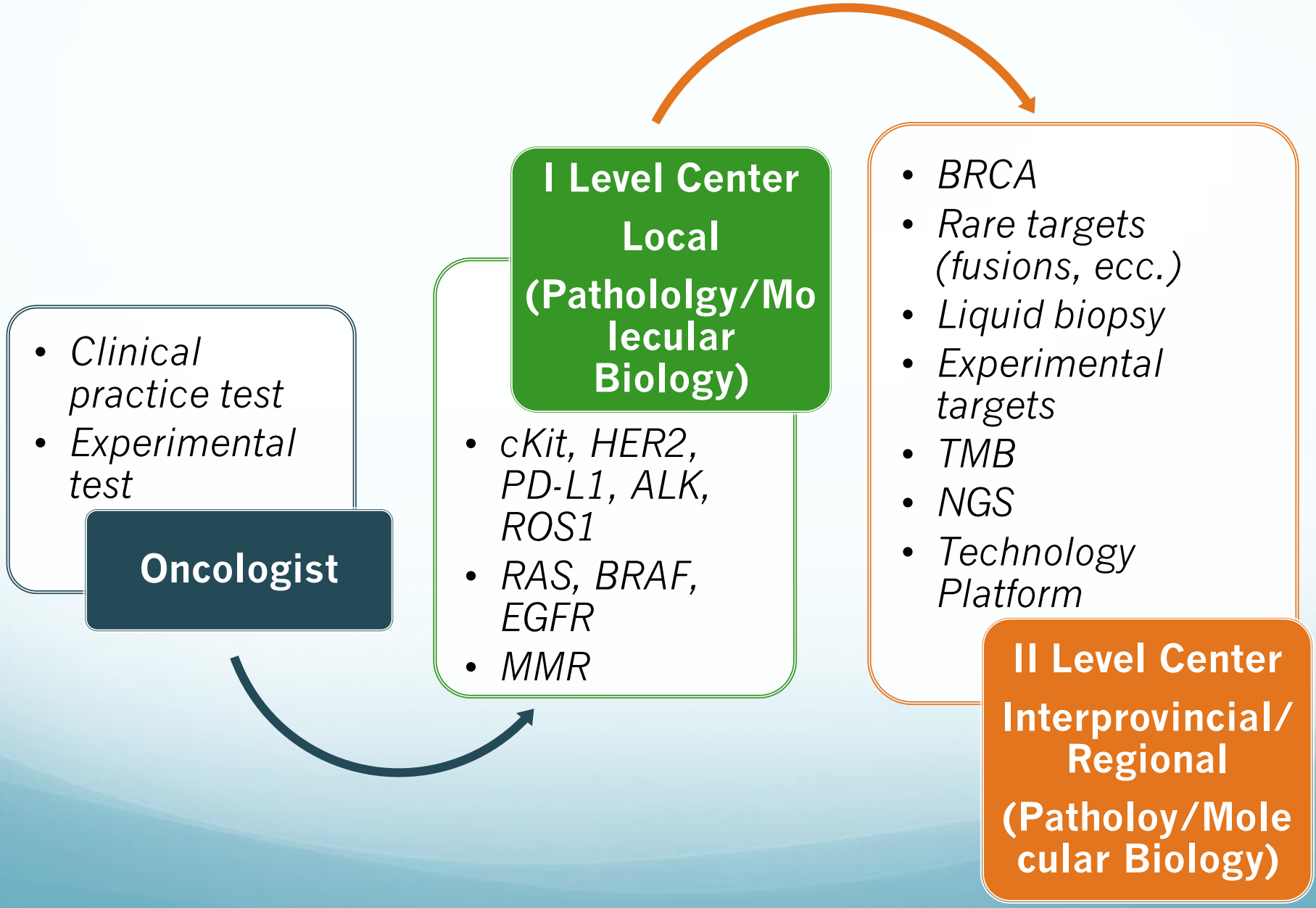
I costi delle nuove tecnologie impongono la individuazione di centri di riferimento a livello regionale nel contesto delle reti oncologiche. Il numero di laboratori che offre test predittivi in Italia sta infatti aumentando in maniera progressiva ed ingiustificata. Le nuove tecnologie di NGS richiedono la centralizzazione dei test sia per ridurre i costi che per garantire una adeguata specializzazione.

agenas.
sede centrale: via Piemonte 60 - 00187 Roma
sede legale: via Puglie 23 - 00187 Roma
cod. fisc. 97113690586
tel 06 42749700 - fax 06 42749488
agenas@pec.agenas.it
www.agenas.it

Funzione della Rete Interprovinciale/Regionale

- *Identificare centri con adeguata esperienza e dotazione tecnologica in grado di rispondere alle esigenze presenti e future di test per biomarcatori nella pratica clinica*
- *Stabilire le modalità di interazione tra laboratori di riferimento inter-provinciale, regionale e centri periferici*
- *Definire le procedure di raccolta di campioni biologici adeguati ai test per biomarcatori*
- *Armonizzare procedure di analisi e di refertazione*
- *Definire un sistema comune di rimborso dei test*
- *Creare un database regionale per la raccolta dei dati delle analisi molecolari*
- *Monitorare l'andamento dei test per i biomarcatori in funzione della epidemiologia regionale e dell'appropriatezza dell'impiego di farmaci biologici*

Model 1 – Two Level Centers



Model 2 - High Volume Center

- *Clinical practice test*
- *Experimental test*

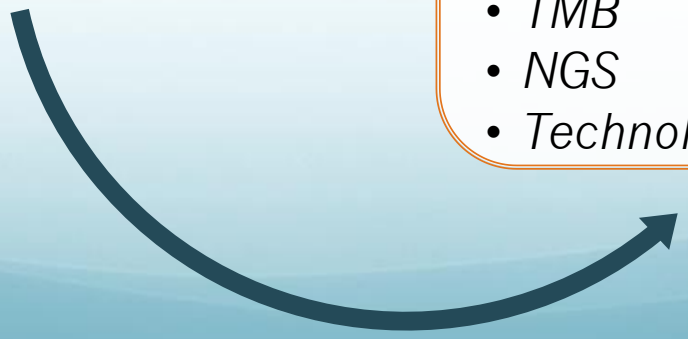
Oncologist

High Volume Center

Interprovincial/Regional

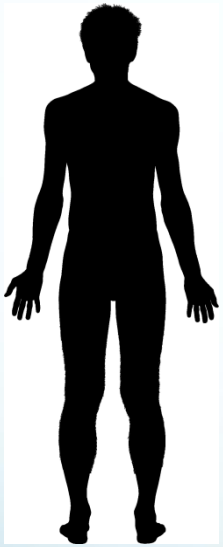
(Pathology/Molecular Biology)

- *cKit, HER2, PD-L1, ALK, ROS1*
- *RAS, BRAF, EGFR*
- *MMR*
- *BRCA*
- *Rare targets (fusions, ecc.)*
- *Liquid biopsy*
- *Experimental targets*
- *TMB*
- *NGS*
- *Technology Platform*



Molecular Tumor Board

Genetics experts oncologists, pathologists, pharmacologists, pharmacists, cancer researchers



Recommendations

- *Clinical trial*
- *Off-label treatment*
- *Standard treatment (not targeted)*

Submit pathology or genomics analysis

Objectives of Inter-Provincial/Regional Molecular Tumor Board

- *Trend and results evaluation of test and correlation to epidemiological data biological drug*
- *New target and test, new technologies, clinical and traslational studies*
- *Regional database*
- *Quality Assurance System*