SISTEMA SANITARIO REGIONALE

AZIENDA OSPEDALIERA
SAN CAMILLO FORLANINI

Chieti, 13 settembre 2019

Terapie a Bersaglio Molecolare

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L'Oncologia Moderna

- Targeted Therapy: identificazione di un bersaglio cellulare o extracellulare molecolare ed utilizzo di un farmaco per questo bersaglio (es. HER2 – trastuzumab)

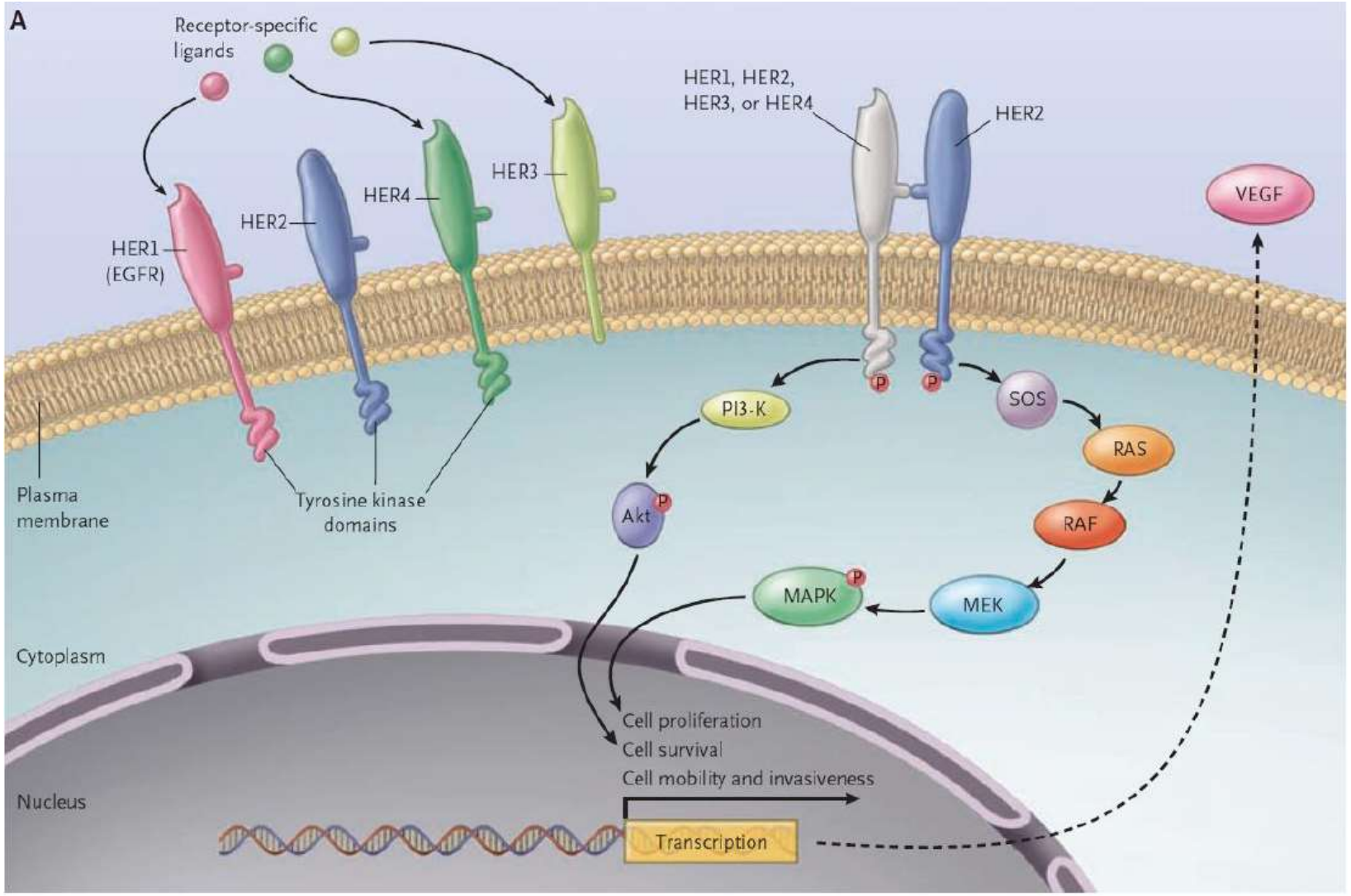
- **Precision Medicine: cucire il trattamento sulle caratteristiche individuali di ogni singolo paziente**

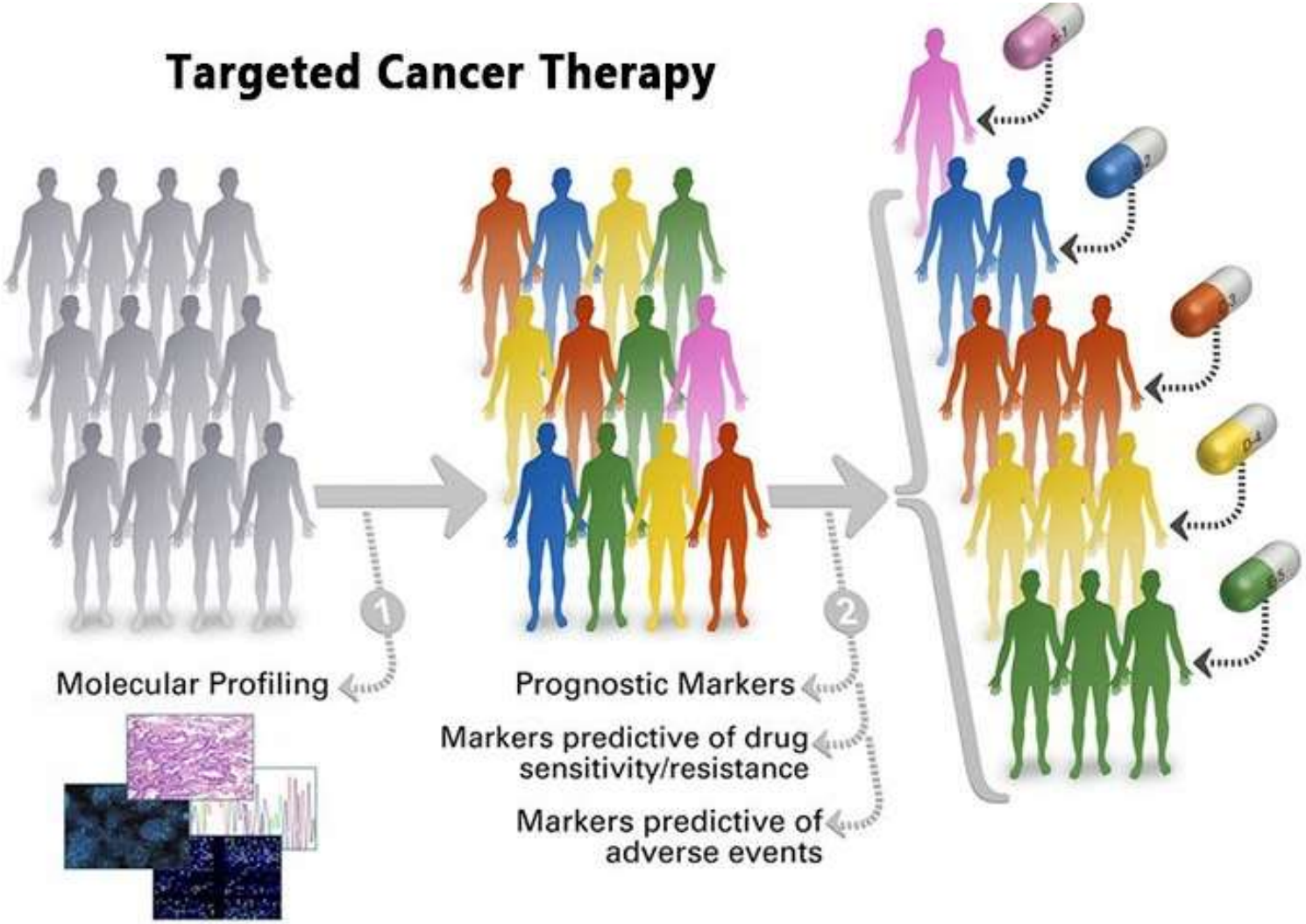
- Synthetic Lethality

- Immunotherapy

Garufi C 2017

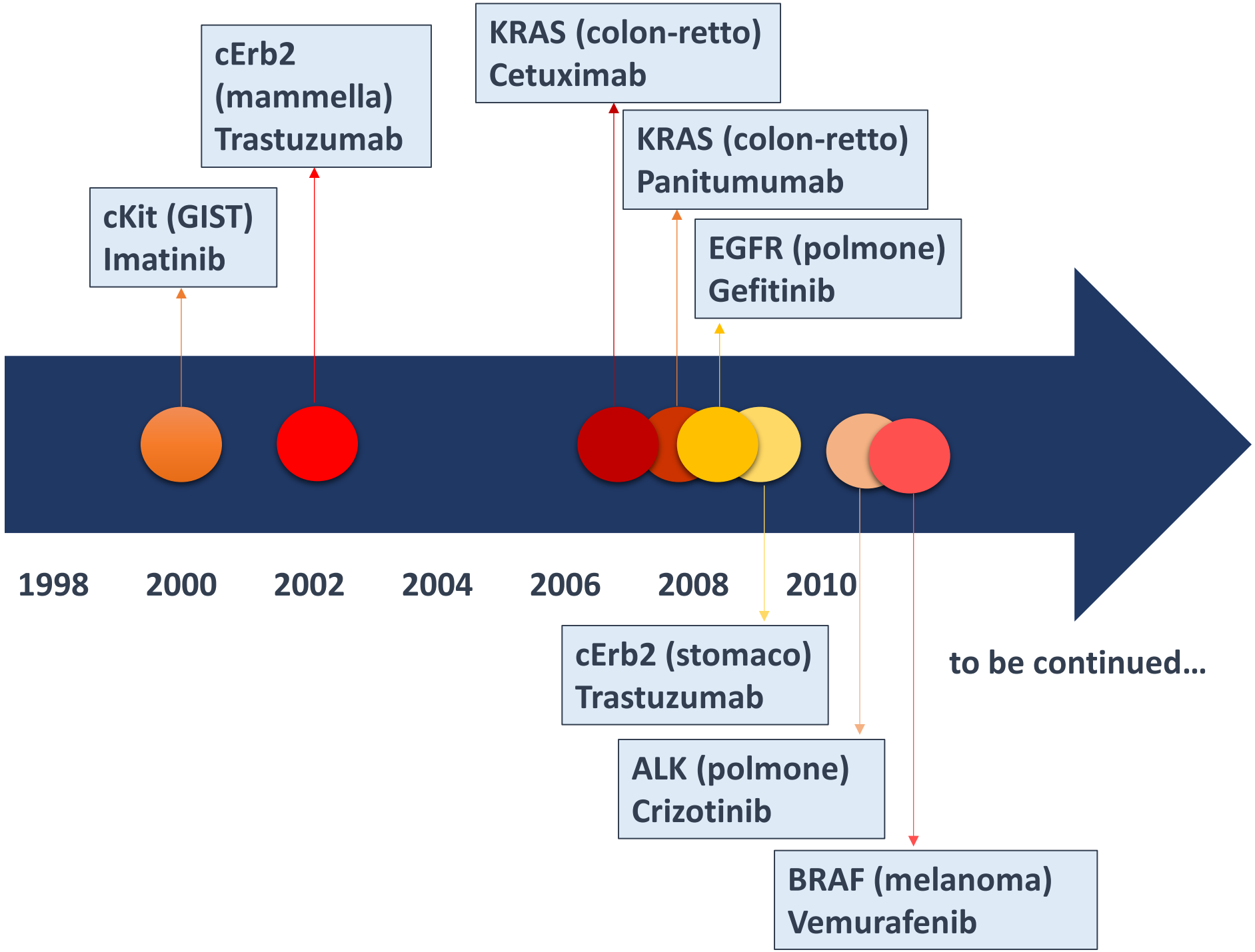
Targeted Therapy





La specifica alterazione molecolare ricercata sul pezzo istologico (e più recentemente nel sangue del paziente) diventa marcatore prognostico e/o predittivo di risposta alla target therapy e permette di selezionare i pazienti candidabili al trattamento

Questo principio della ricerca oncologica prende il nome di **target therapy**



L'utilizzo nella pratica clinica delle targeted therapy ha cambiato la storia naturale di alcune neoplasie
I due esempi più significativi sono rappresentati dal tumore polmonare e dal melanoma

NIH NATIONAL CANCER INSTITUTE

What are targeted cancer therapies?

Targeted cancer therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules ("molecular targets") that are involved in the growth, progression, and spread of cancer. Targeted cancer therapies are sometimes called "molecularly targeted drugs," "molecularly targeted therapies," "precision medicines," or similar names.

From NIH web official site 2019

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29: 30–35, 2018
doi:10.1093/annonc/mdx707
Published online 13 November 2017

SPECIAL ARTICLE

The European Society for Medical Oncology (ESMO) Precision Medicine Glossary

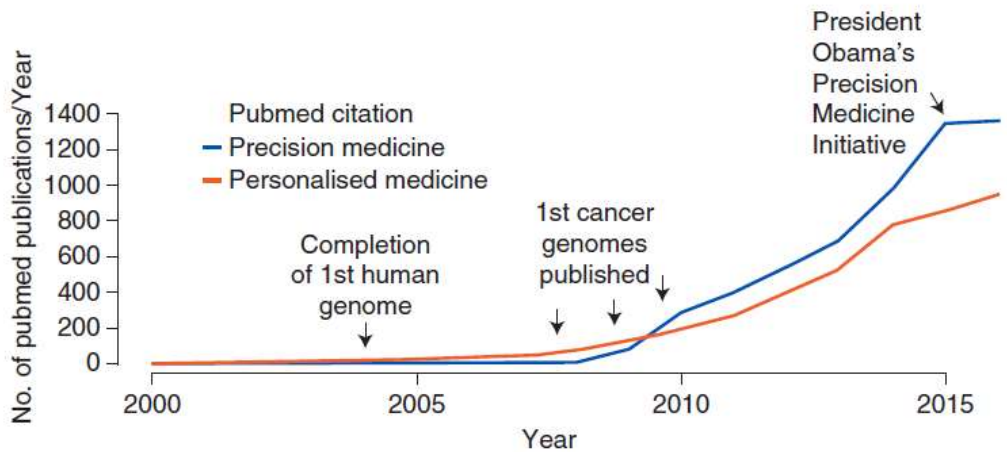


Figure 1. Number of PubMed publications per year including the terms 'precision medicine AND cancer' and 'personalised medicine OR personalised medicine AND cancer'.

Precision Medicine

"Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier."

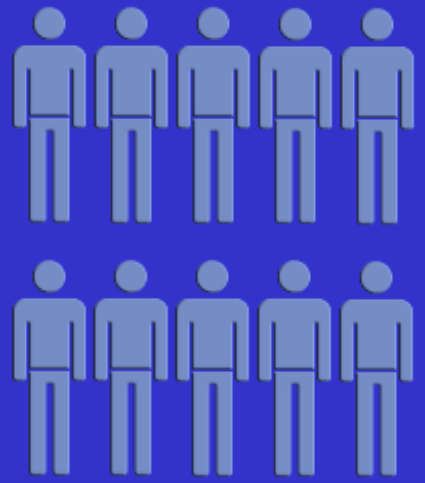
— President Barack Obama, State of the Union Address, January 20, 2015

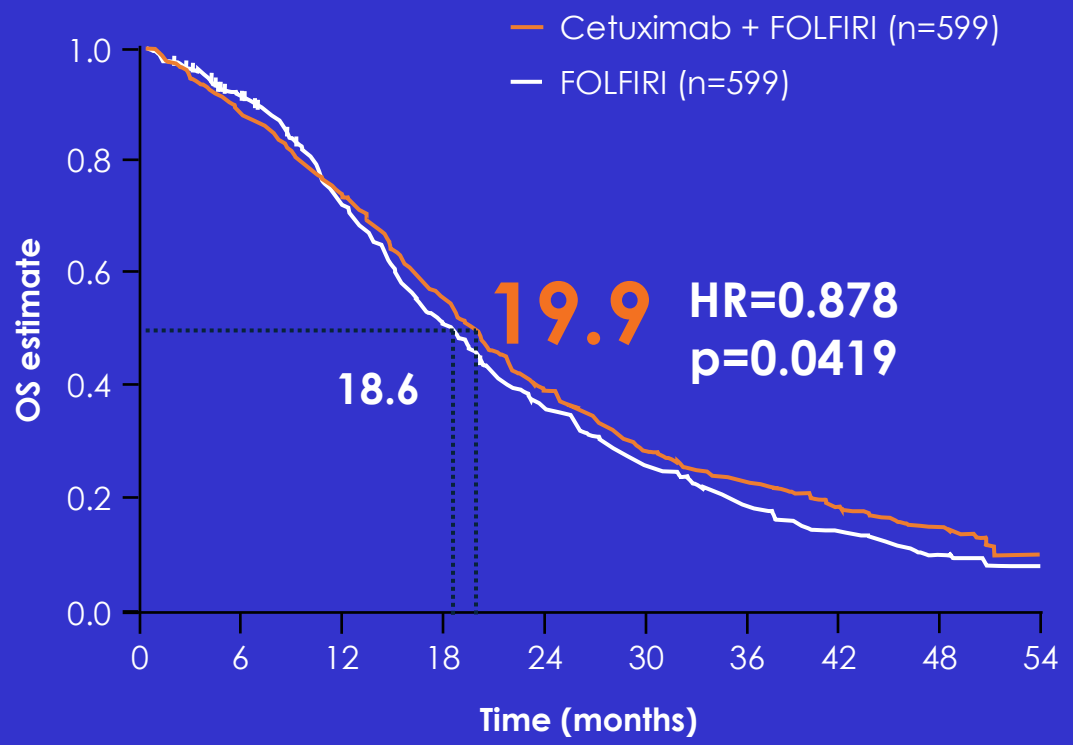
2008 - in assenza di selezione

Δ = + 1,3 mesi

Popolazione dello studio

CRYSTAL





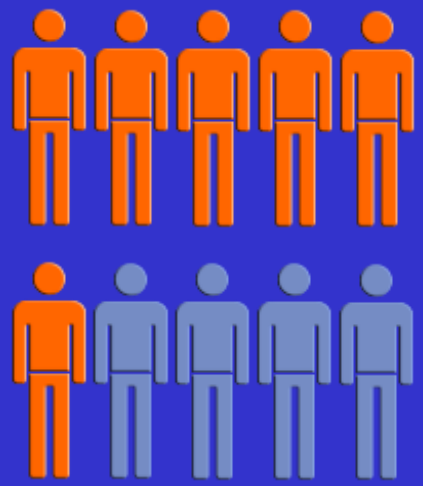
Van Cutsem E et al. J Clin Oncol 2011;29:2011–2019

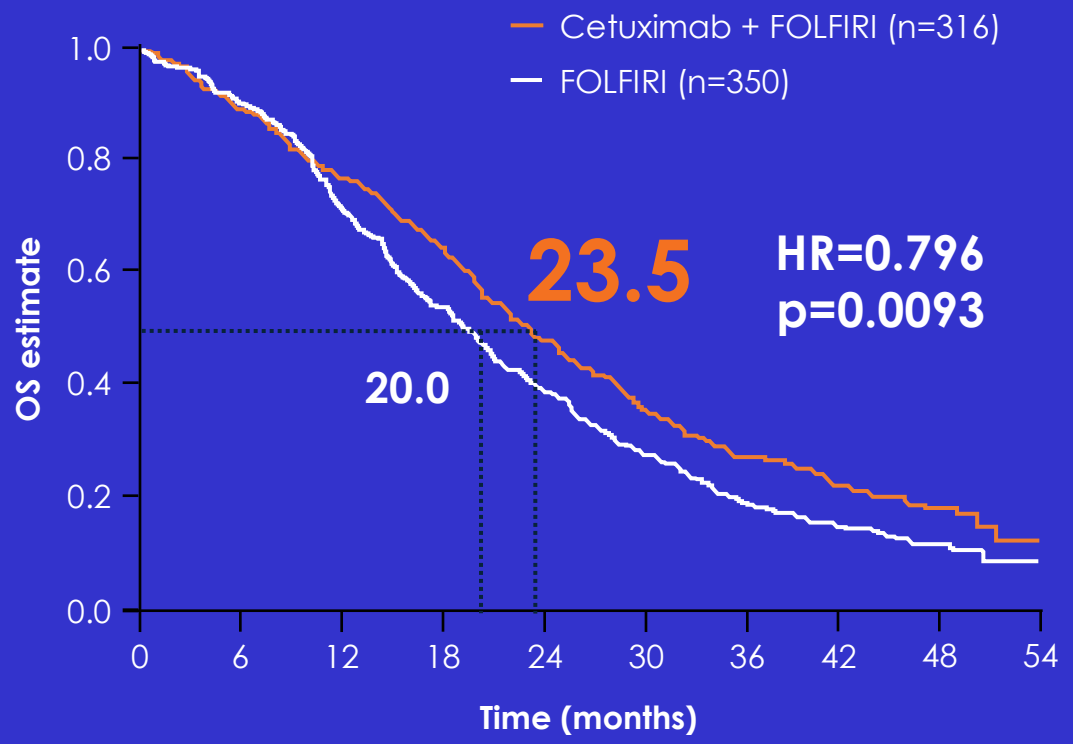
2009 - KRAS

Δ = + 3,5 mesi

Popolazione KRAS *wt*

CRYSTAL





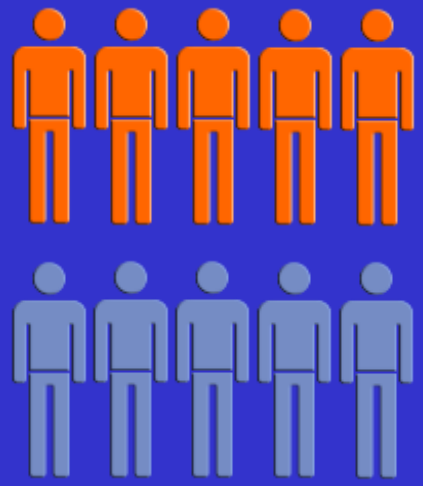
Van Cutsem E et al. J Clin Oncol 2011;29:2011–2019

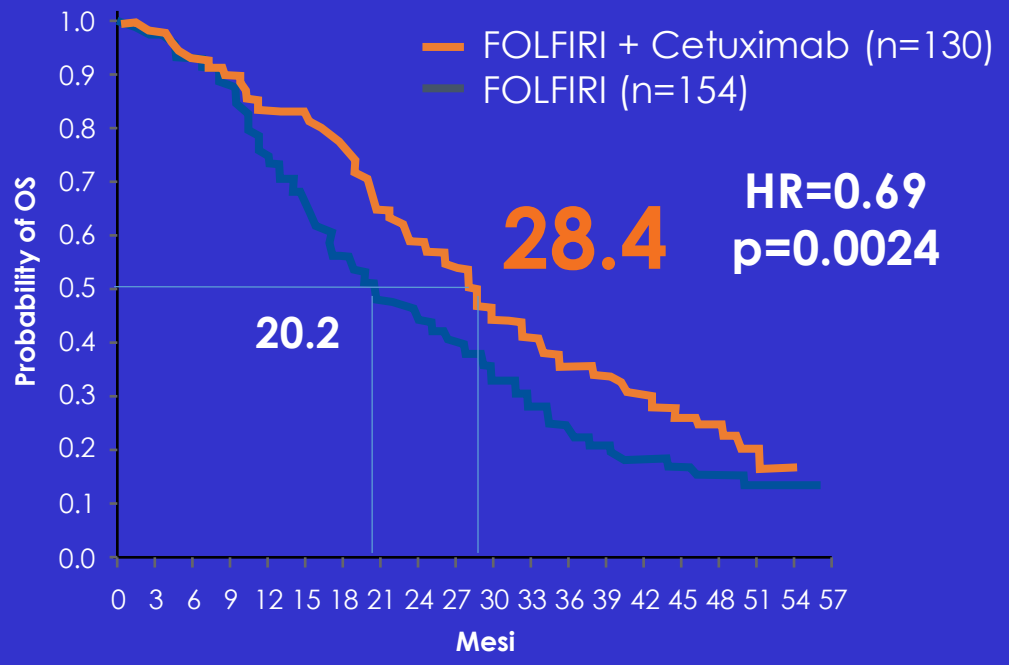
2014 - RAS: selezione del paziente

Δ = + 8,2 mesi

Popolazione RAS *wt*

CRYSTAL





Ciardiello et al., ASCO 2014

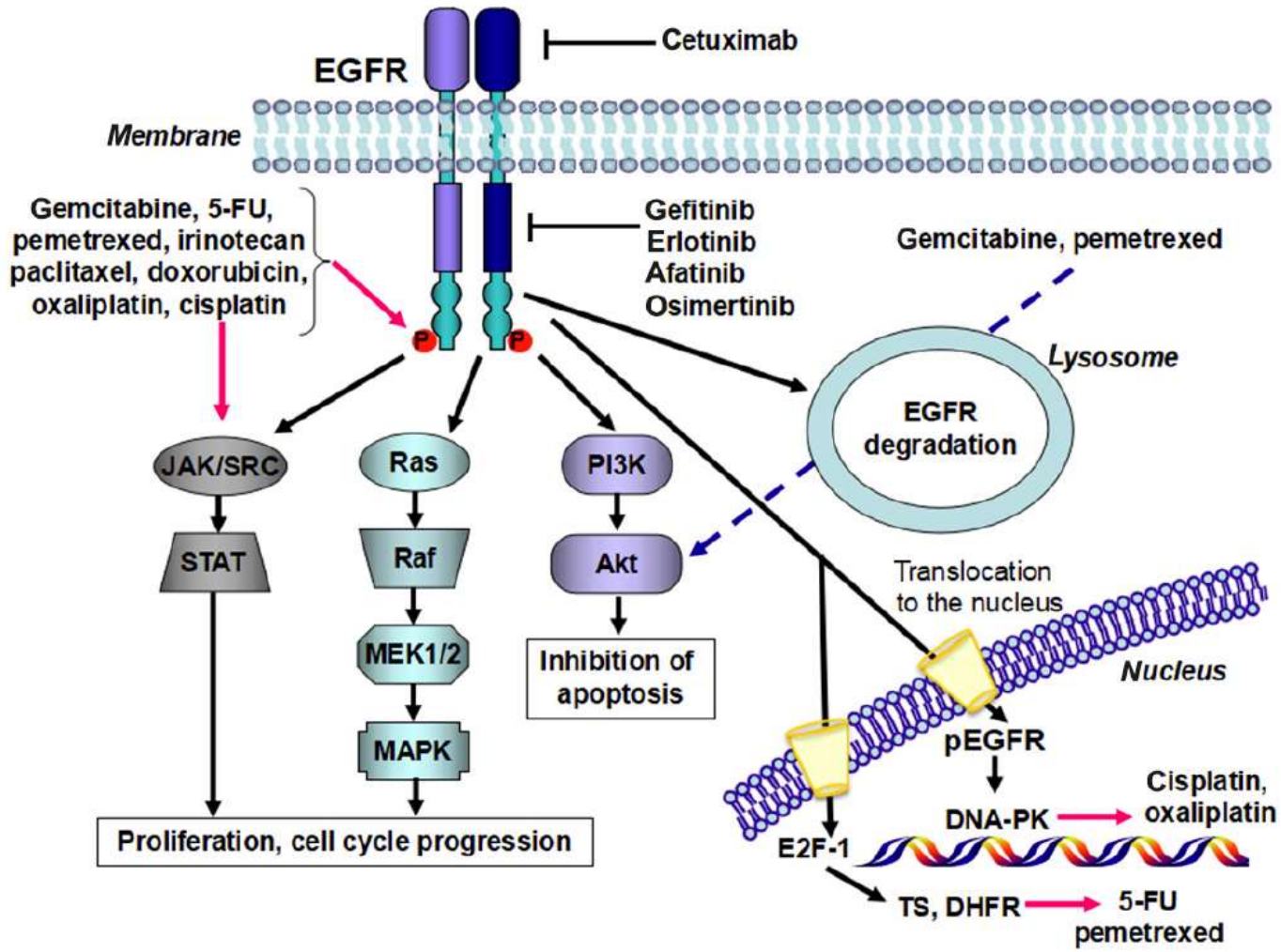
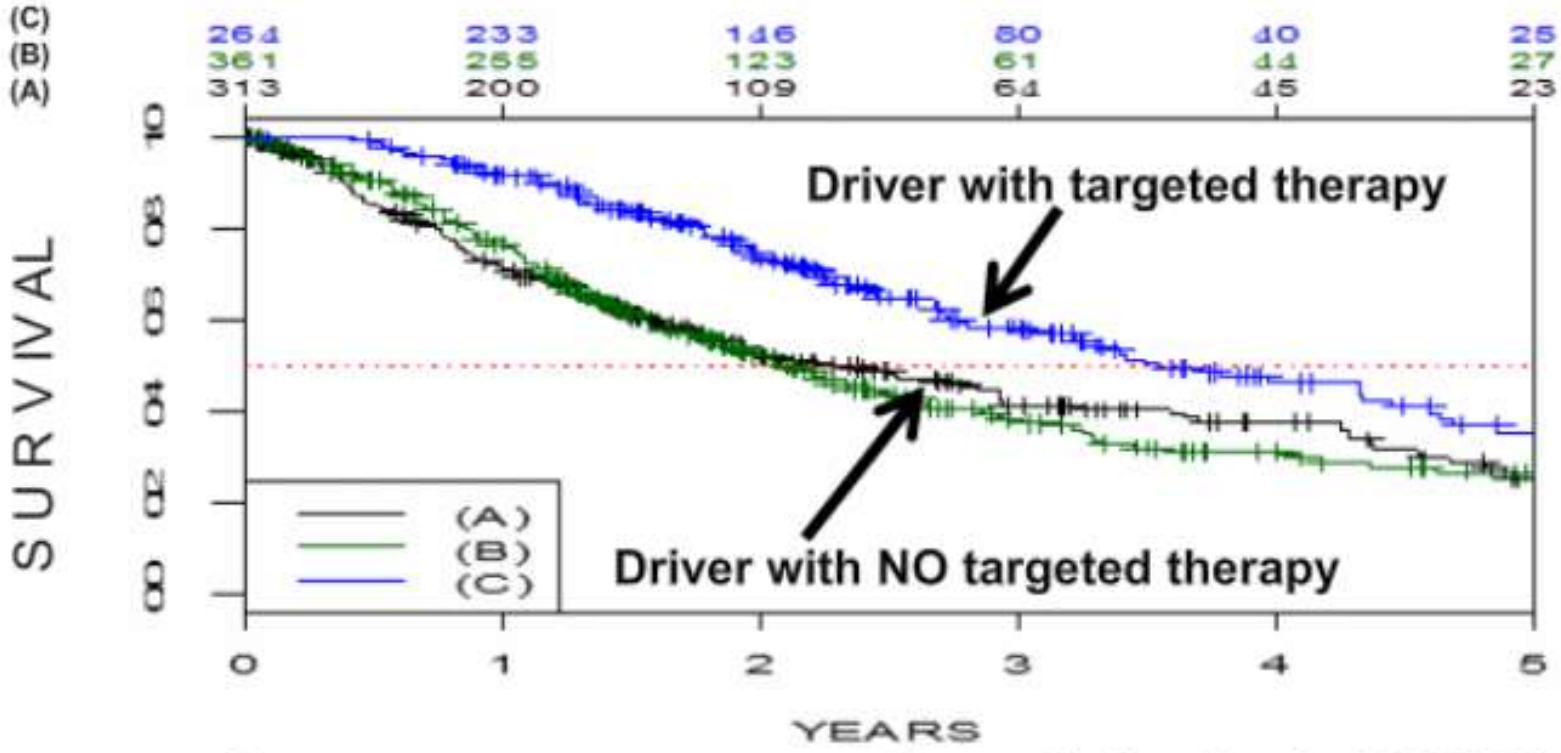


Figure 1. Interaction between chemotherapy and anti-EGFR agents: data from preclinical studies

Survival of Patients with Drivers: Targeted Therapy vs No Targeted Therapy



Group	N	Median Survival (95% CI)
Driver, no targeted therapy (A)	313	2.4 years (1.8 to 2.9)
No driver (B)	361	2.1 years (1.8 to 2.5)
Driver, targeted therapy (C)	264	3.5 years (3.2 to 4.6)

BASKET TRIALS

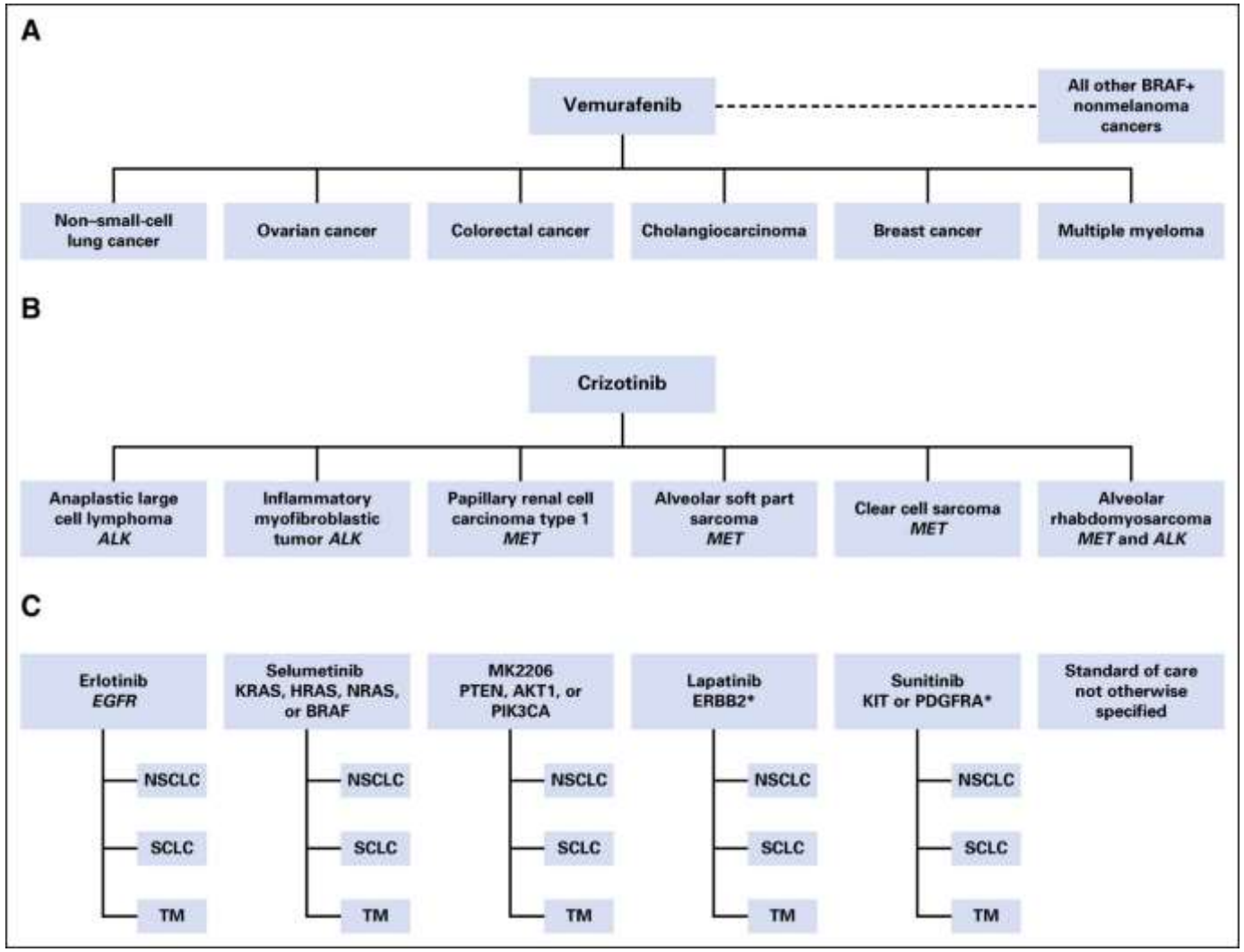
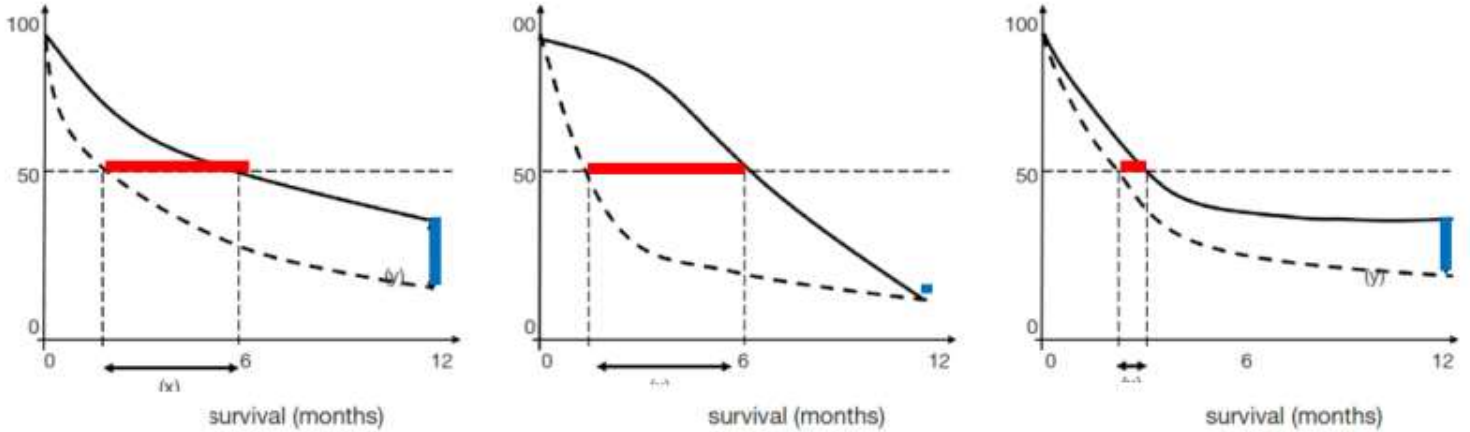


*Fig 1. Three published basket trials. (A) Disease-specific baskets.2 (B) Disease-mutation–specific baskets (CREATE).3 (C) Disease-drug-mutation–specific baskets (CUSTOM).4 *Mutations or amplifications. ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; MET, mesenchymal-epithelial transition factor; NSCLC, non–small-cell lung cancer; SCLC, small-cell lung cancer; TM, thymic malignancy.*

Kunan KM, JCO 2017

Typical survival curves (Kaplan-Meier model) observed in clinical trials

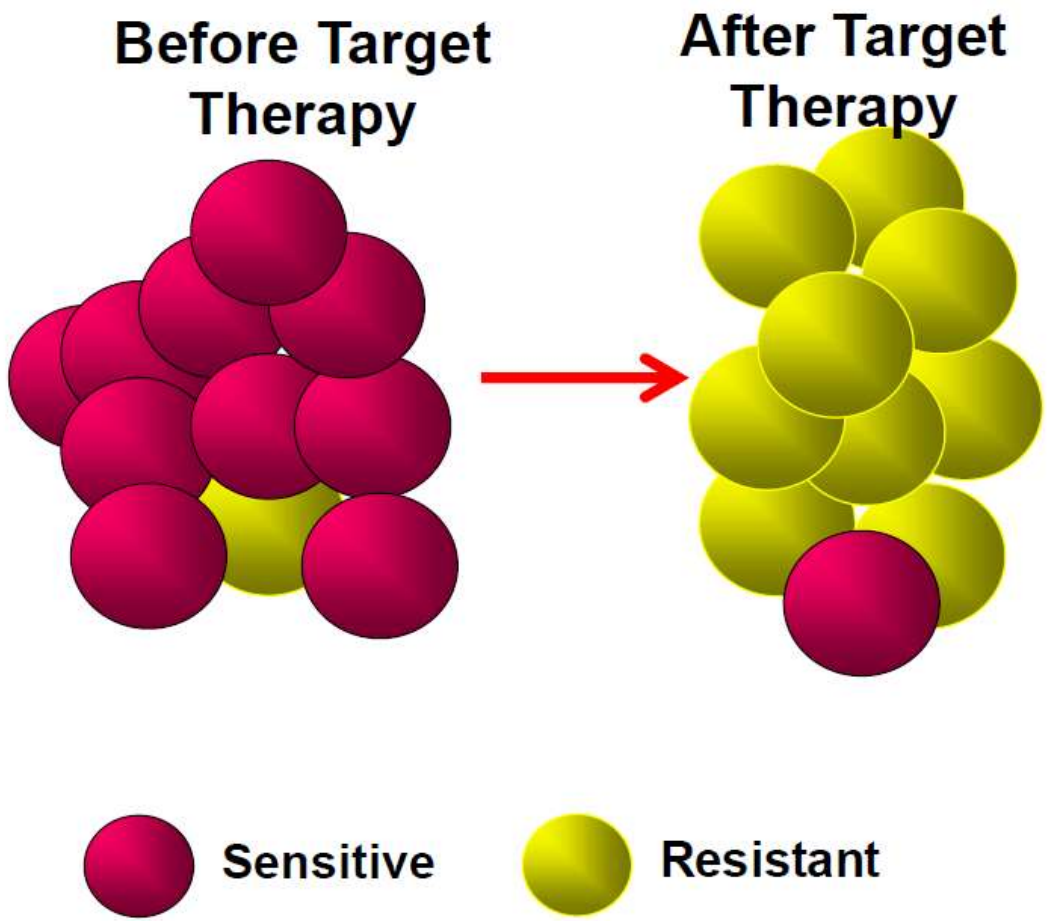
(x) difference in median survival;
(y) 12-month difference in survival rate.



	CHEMOTHERAPY	TARGET THERAPY	IMMUNOTHERAPY
Early Stop for Futility	YES	YES	NO
Correlation with late benefit	YES	NO	NO

S. Pilotto et al. Moving towards a customized approach for drug development: lessons from clinical trials with immune checkpoint inhibitors in lung cancer. Transl Lung Cancer Res. 2015 Dec; 4(6): 704–712.

Resistant cells are selected by treatment with target based agents



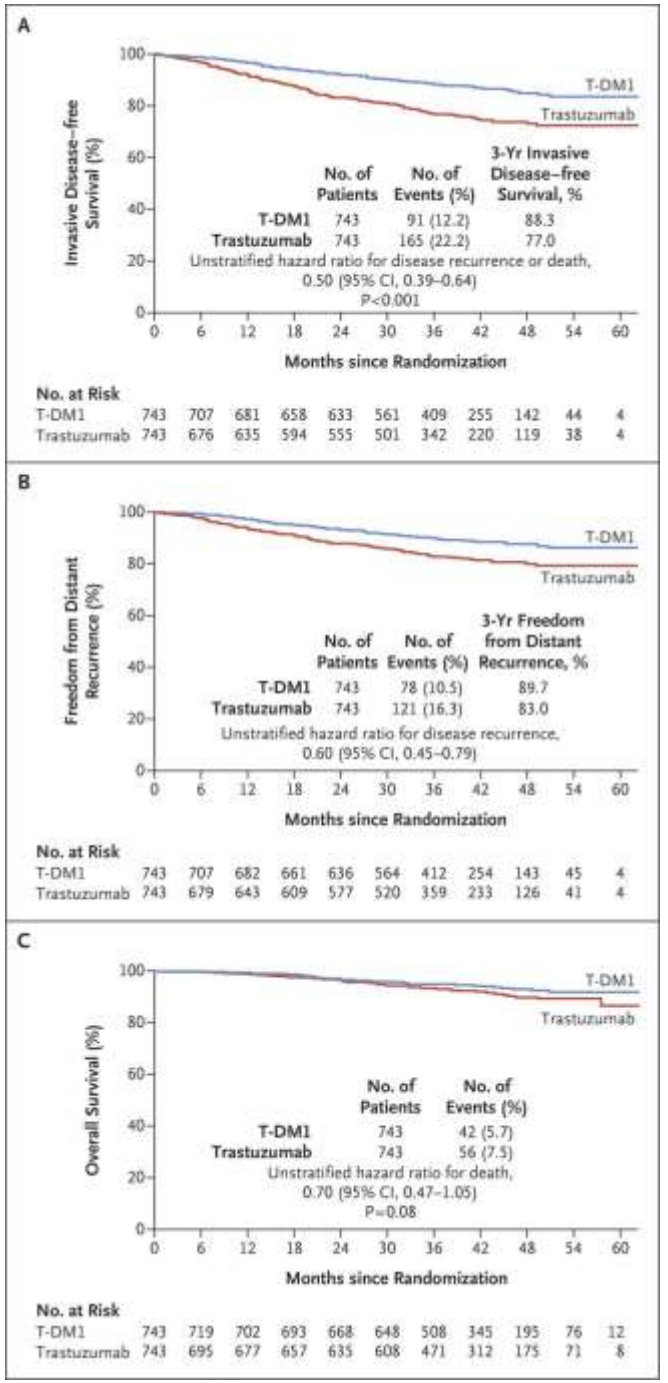
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 14, 2019 VOL. 380 NO. 7

Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer

Kaplan–Meier Estimates of Survival in the Interim Analysis.

G von Minckwitz et al. N Engl J Med 2019;380:617-628.

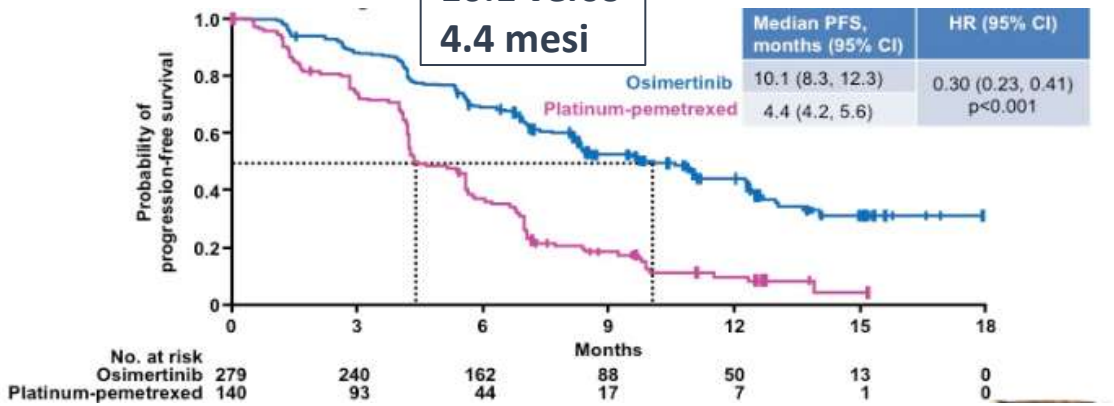


ORIGINAL ARTICLE

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*

10.1 verso 4.4 mesi



E' recentissima la presentazione dello studio che ha valutato l'efficacia di Osimertinib anche in prima linea, indipendentemente dalla mutazione

ESMO 2017: Front-Line Osimertinib Poised to Become Standard of Care in EGFR-Mutation Positive NSCLC

Median PFS with osimertinib was 18.9 months; 95% confidence interval [CI] 15.2, 21.4) compared to 10.2 months; 95% CI 9.6, 11.1 with SoC, hazard ratio [HR] 0.46; 95% CI 0.37, 0.57 ($p < 0.0001$). A total of 136 (49%) versus 206 (74%) patients had a PFS event with osimertinib versus SoC, respectively.

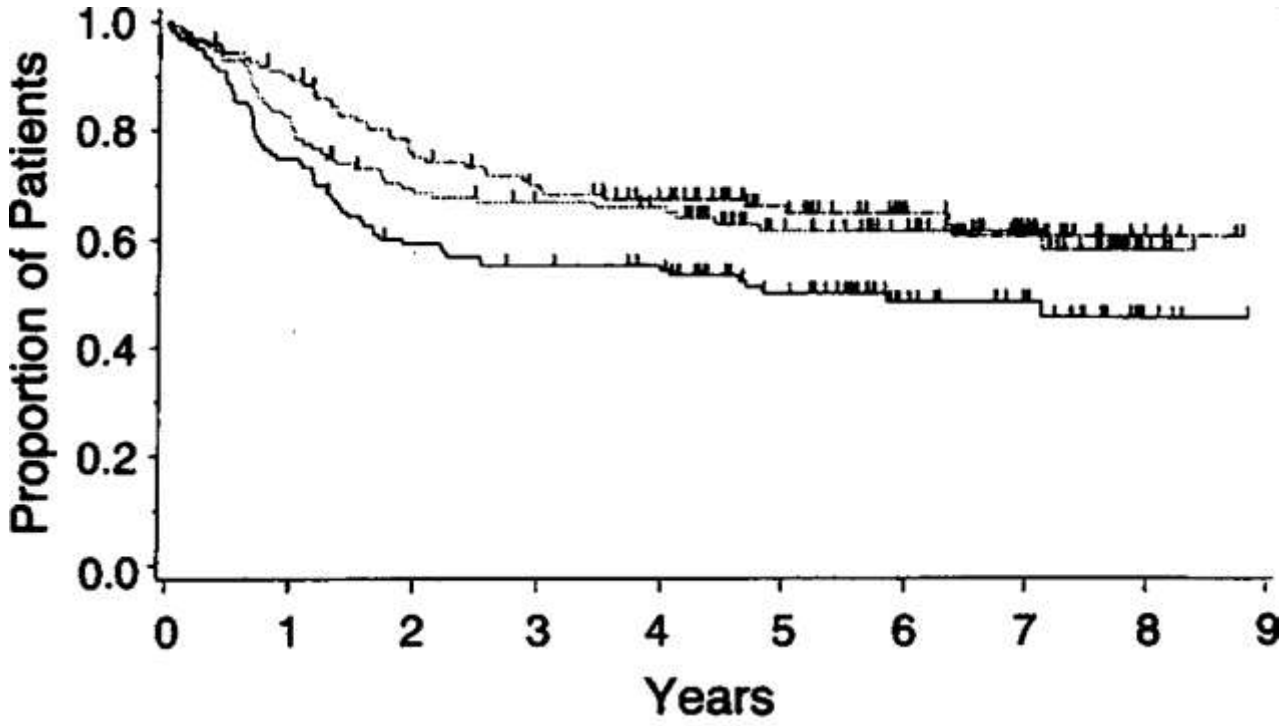
In attesa dell'approvazione del farmaco in prima linea

MADRID 2017 ESMO congress

MADRID Spain
8 -12 September 2017

CHEMOTHERAPY OF ADVANCED HODGKIN'S DISEASE WITH MOPP, ABVD, OR MOPP ALTERNATING WITH ABVD

GEORGE P. CANELLOS, M.D., JAMES R. ANDERSON, PH.D., KATHLEEN J. PROPERT, SC.D., NIS NISSEN, M.D., M. ROBERT COOPER, M.D., EDWARD S. HENDERSON, M.D., MARK R. GREEN, M.D., ARLAN GOTTLIEB, M.D.,* AND BRUCE A. PETERSON, M.D.

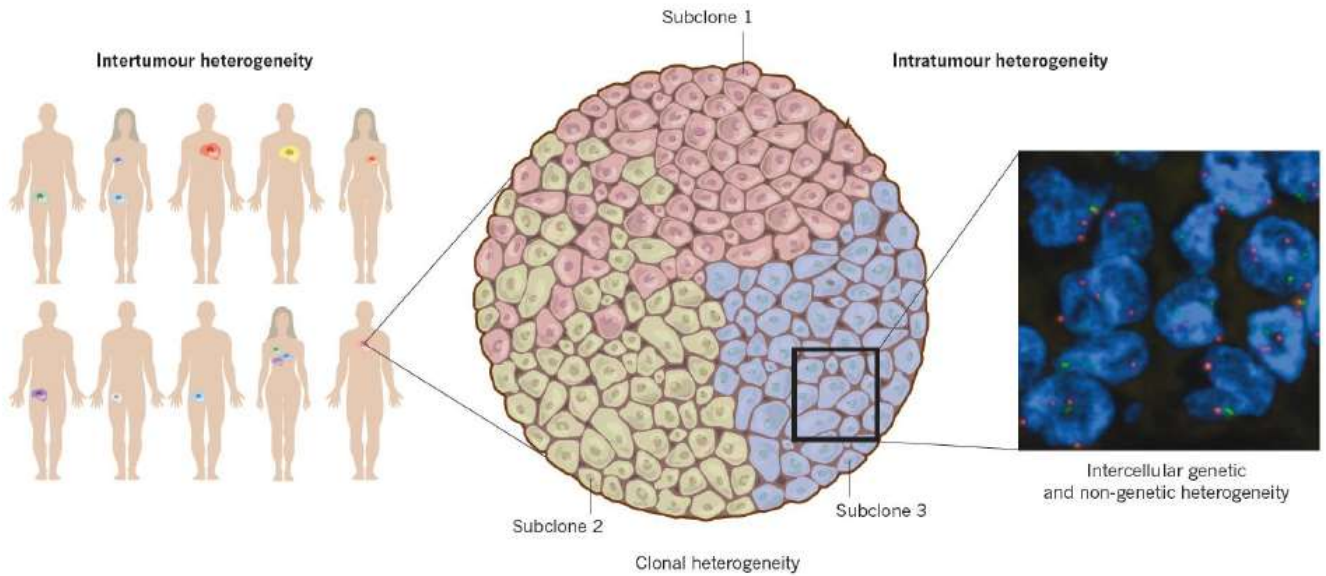


Regimen	No. of Patients	No. (%) of Treatment Failures	Median Survival
—— MOPP	123	62 (50)	4.84
····· ABVD	115	44 (38)	None
-·-·- MOPP–ABVD	123	43 (35)	None
All	361	149 (41)	—

Canellos GP et al. N Engl J Med 1992;327:1478-1484.

The efficacy of targeted therapy depends on

TUMOR HETEROGENEITY



Burrell Nature 2013

Clinical Lung Cancer

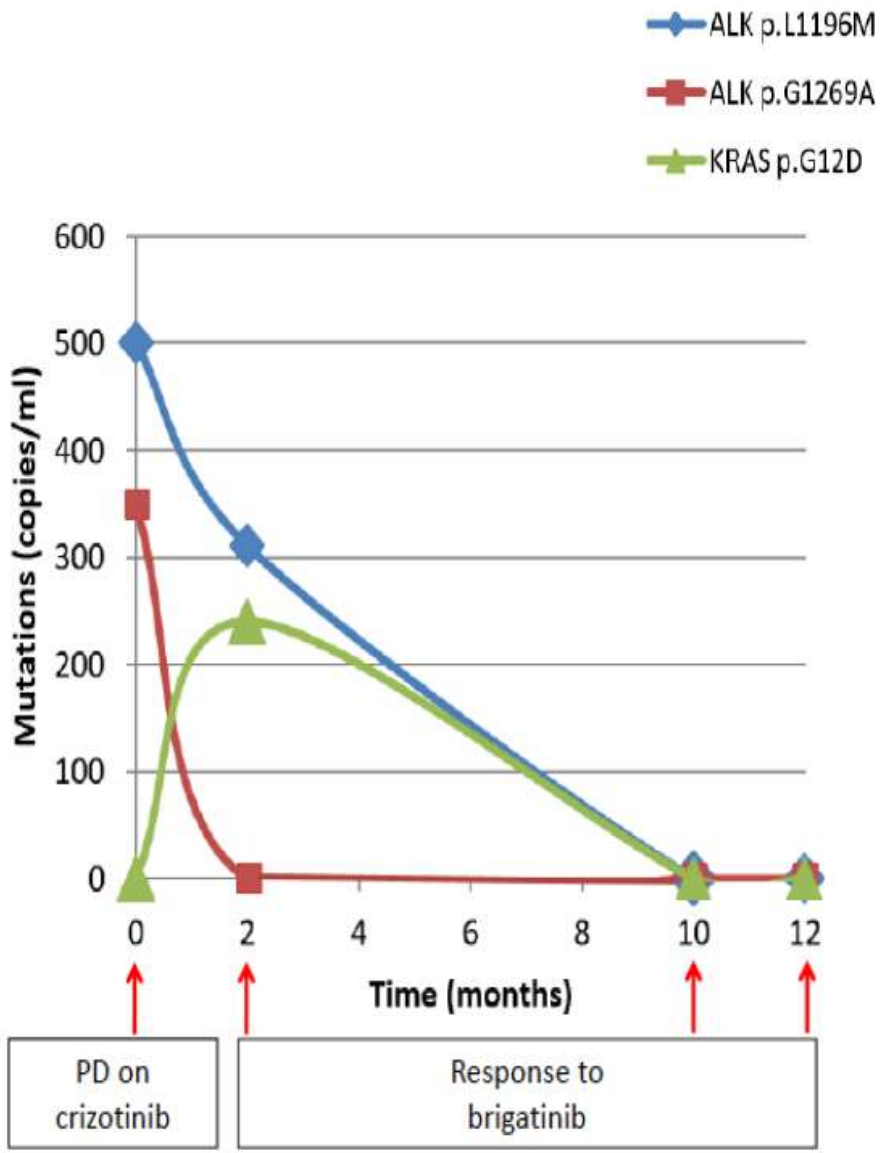
Available online 18 May 2017

In Press, Corrected Proof

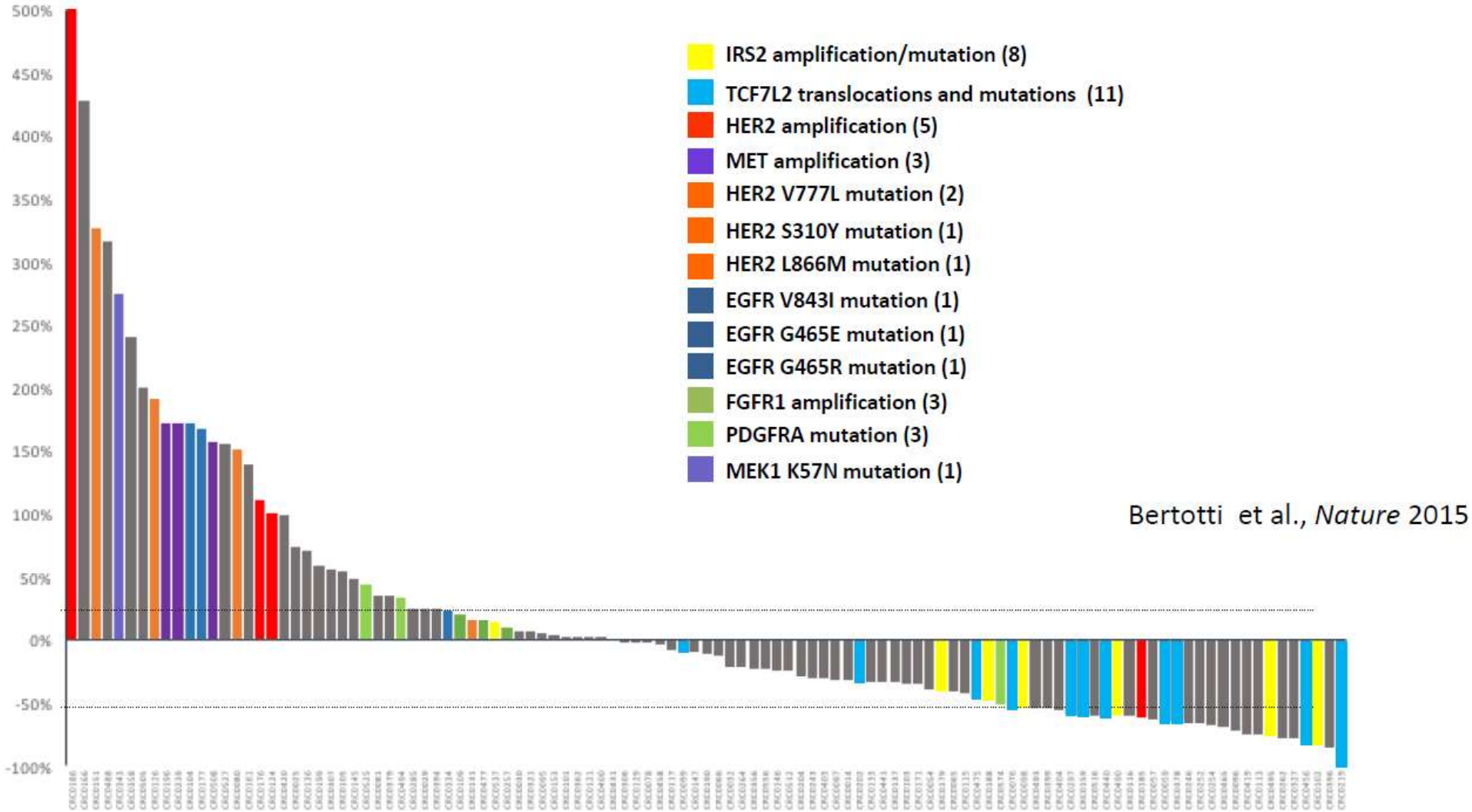
Original Study

Detection of *ALK* and *KRAS* Mutations in Circulating Tumor DNA of Patients With Advanced ALK-Positive NSCLC With Disease Progression During Crizotinib Treatment

Paola Bordi [1], Marcello Tiseo [1] ✉, Eleonora Rofi [2], Iacopo Petrini [3], Giuliana Restante [2], Romano Danesi [2], Marzia Del Re [2]

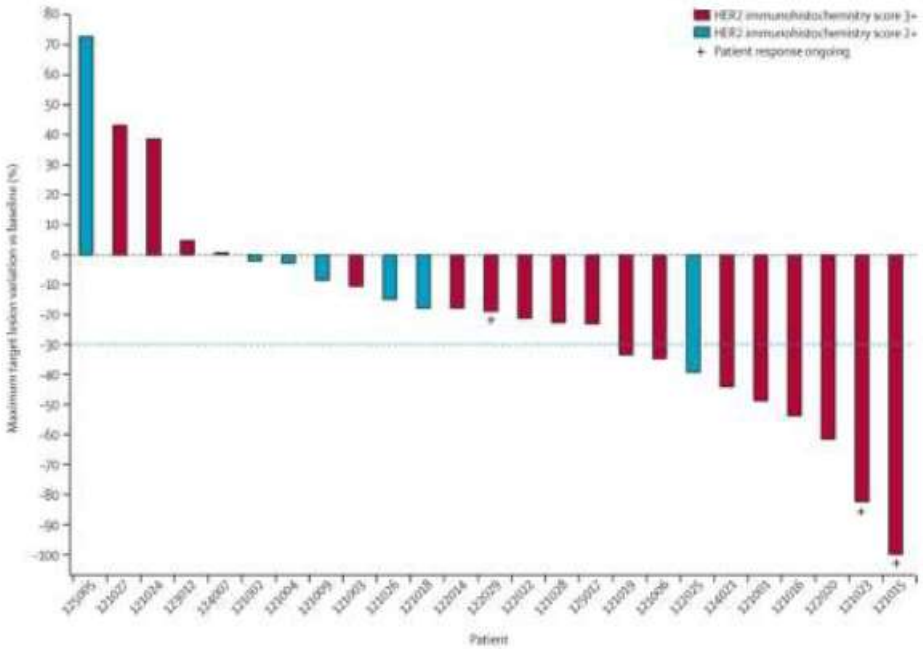


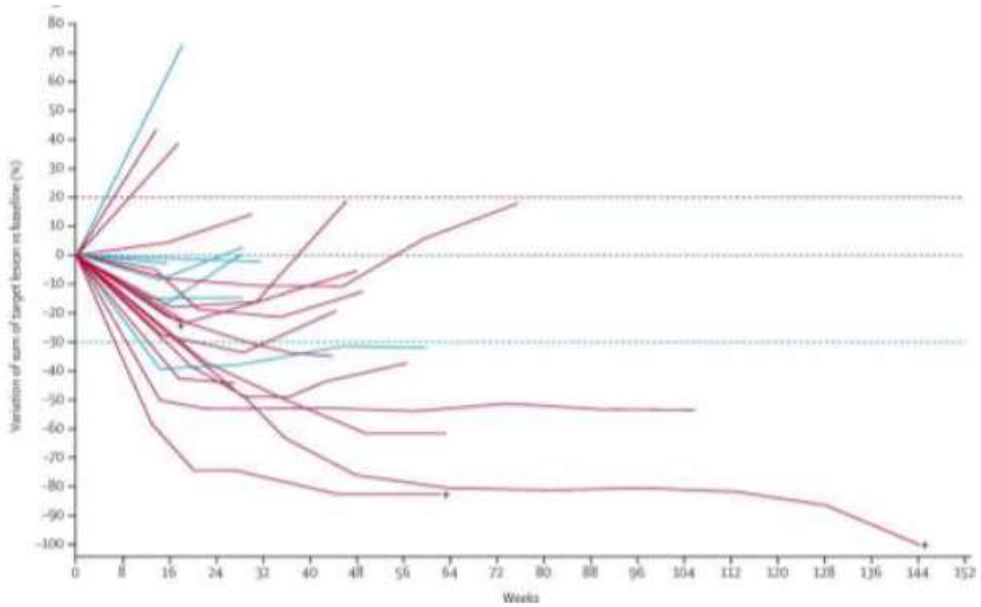
Resistance: Discovery of actionable biomarkers



Bertotti et al., *Nature* 2015

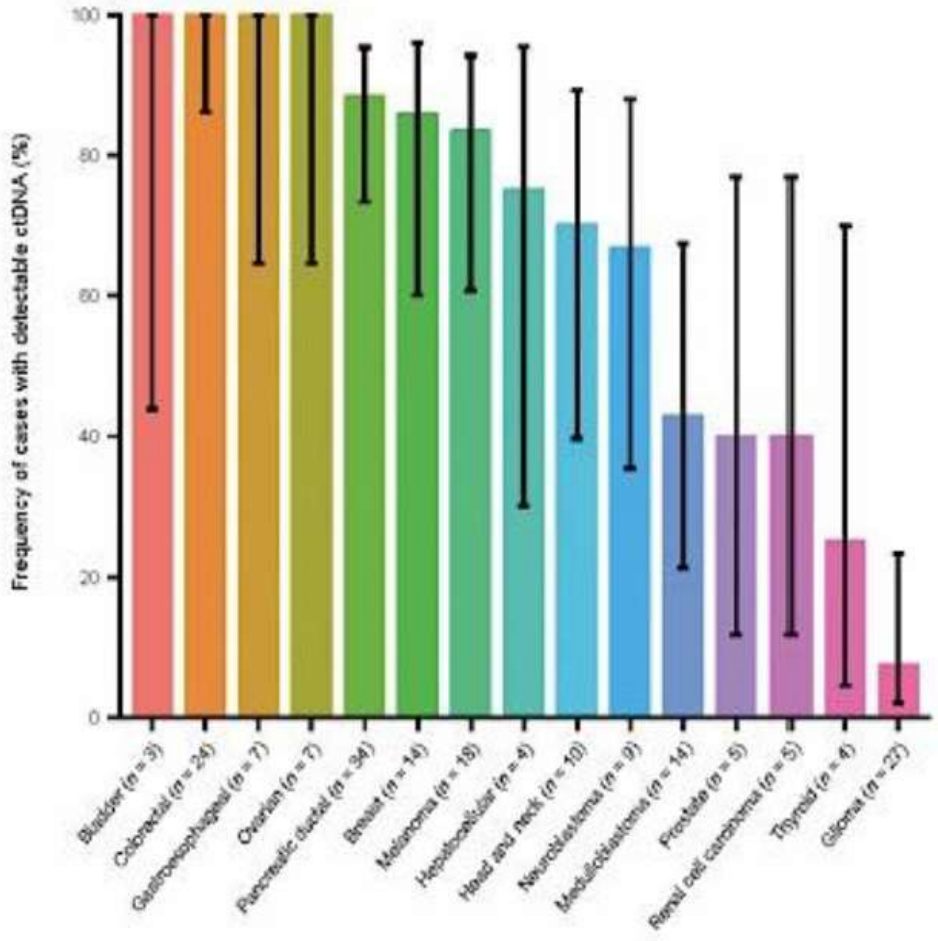
The HERACLES Trial: From xenopatients to patients





Sartore-Bianchi, Trusolino et al., *Lancet Oncology* 2016

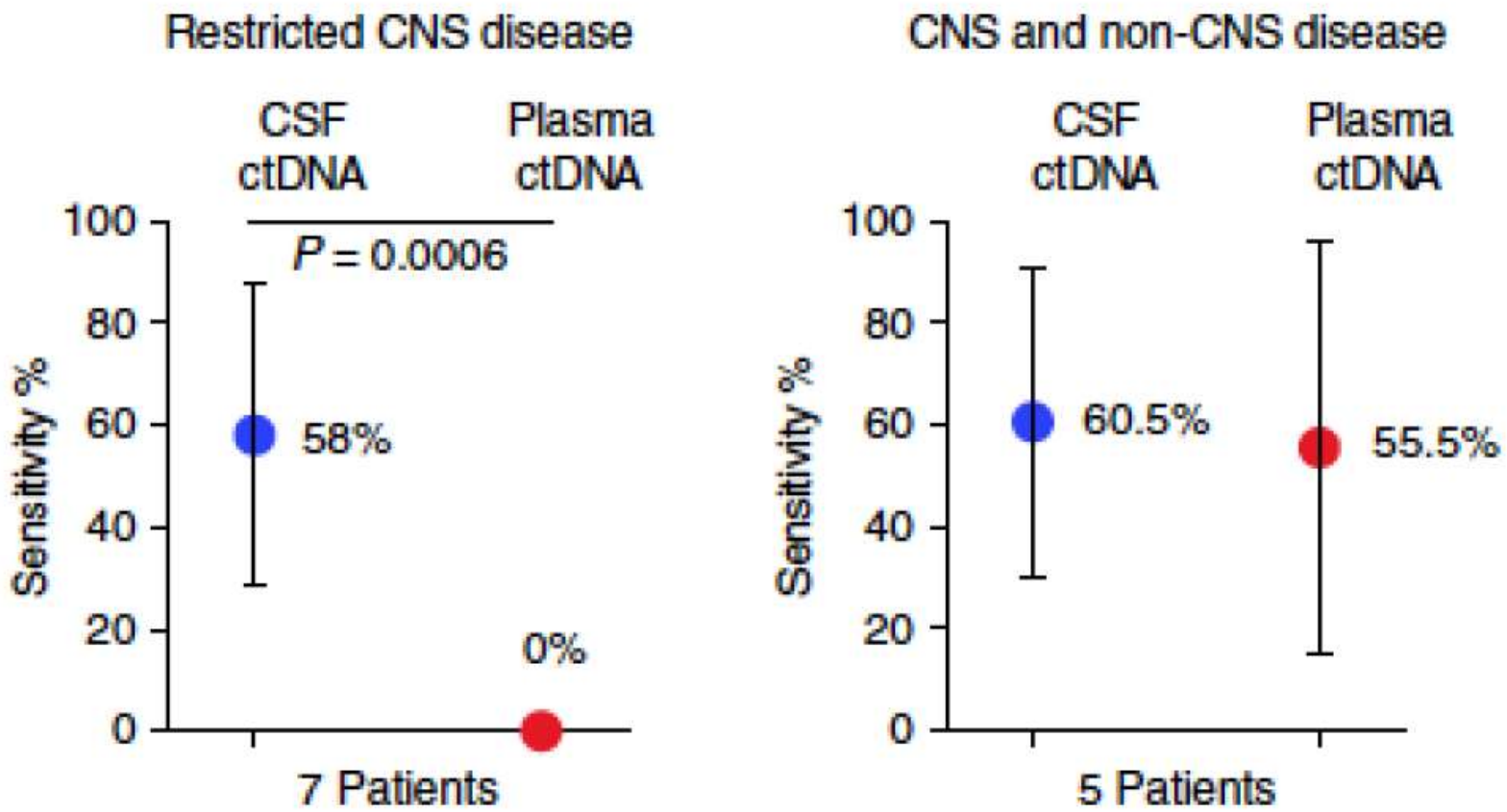
Applications of liquid biopsy in precision medicine: CHALLENGES



Bettegowda C, et al. Sci Transl Med. 2014;6(224):224ra24

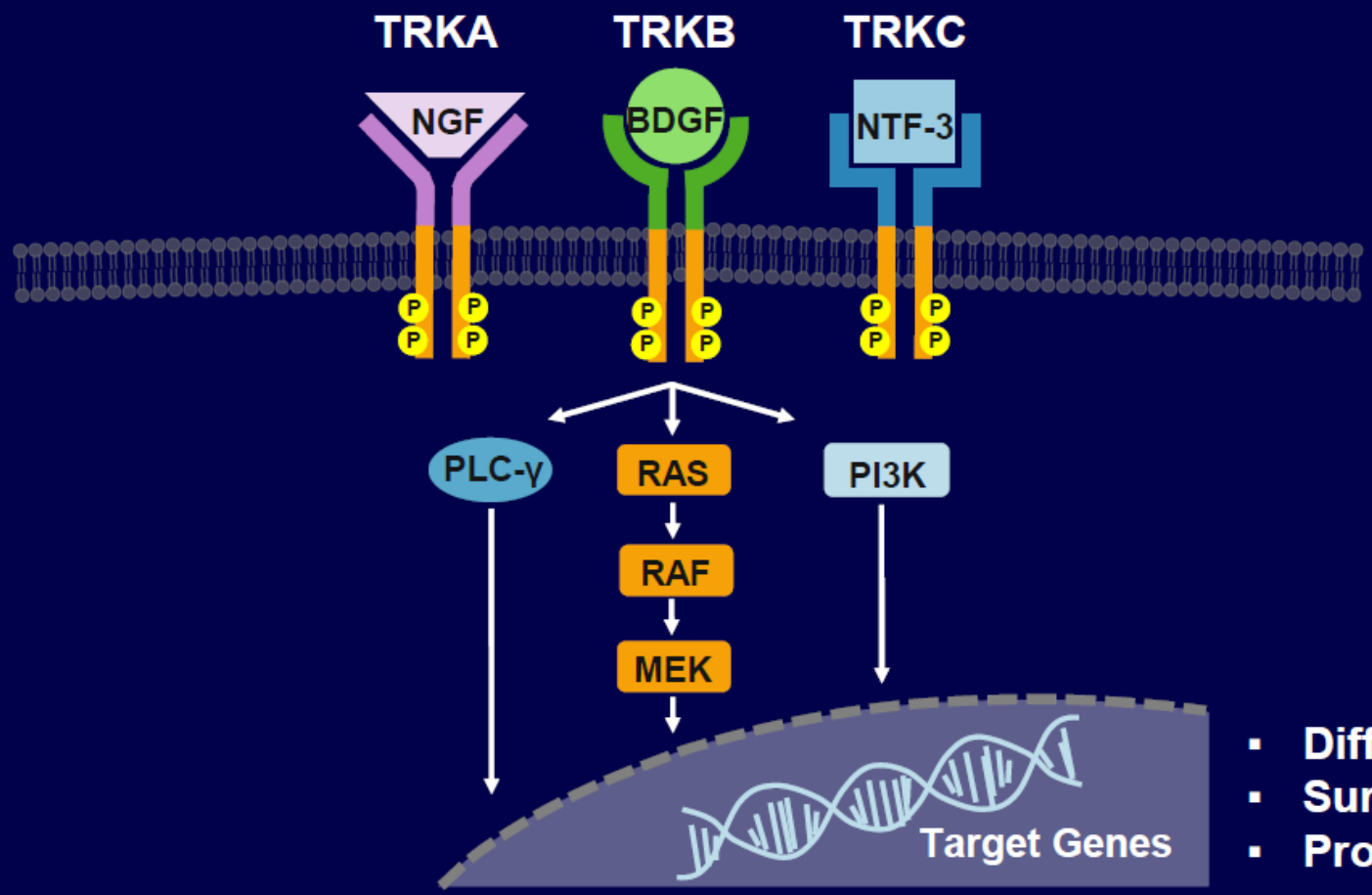
- Biology and tissue of origin are not fully elucidated (anatomic barriers to ctDNA release)
- The amount of ctDNA in blood can be extremely low, which requires super-sensitive technologies to detect mutations of low allelic frequencies
- Heterogeneity

Sensitivity analysis of CSF ctDNA and plasma ctDNA



Del Re M, 2018

Tropomyosin Receptor Kinase Signaling Pathway



- Differentiation
- Survival
- Proliferation

Amatu A, et al. ESMO Open. 2016;1:e000023.

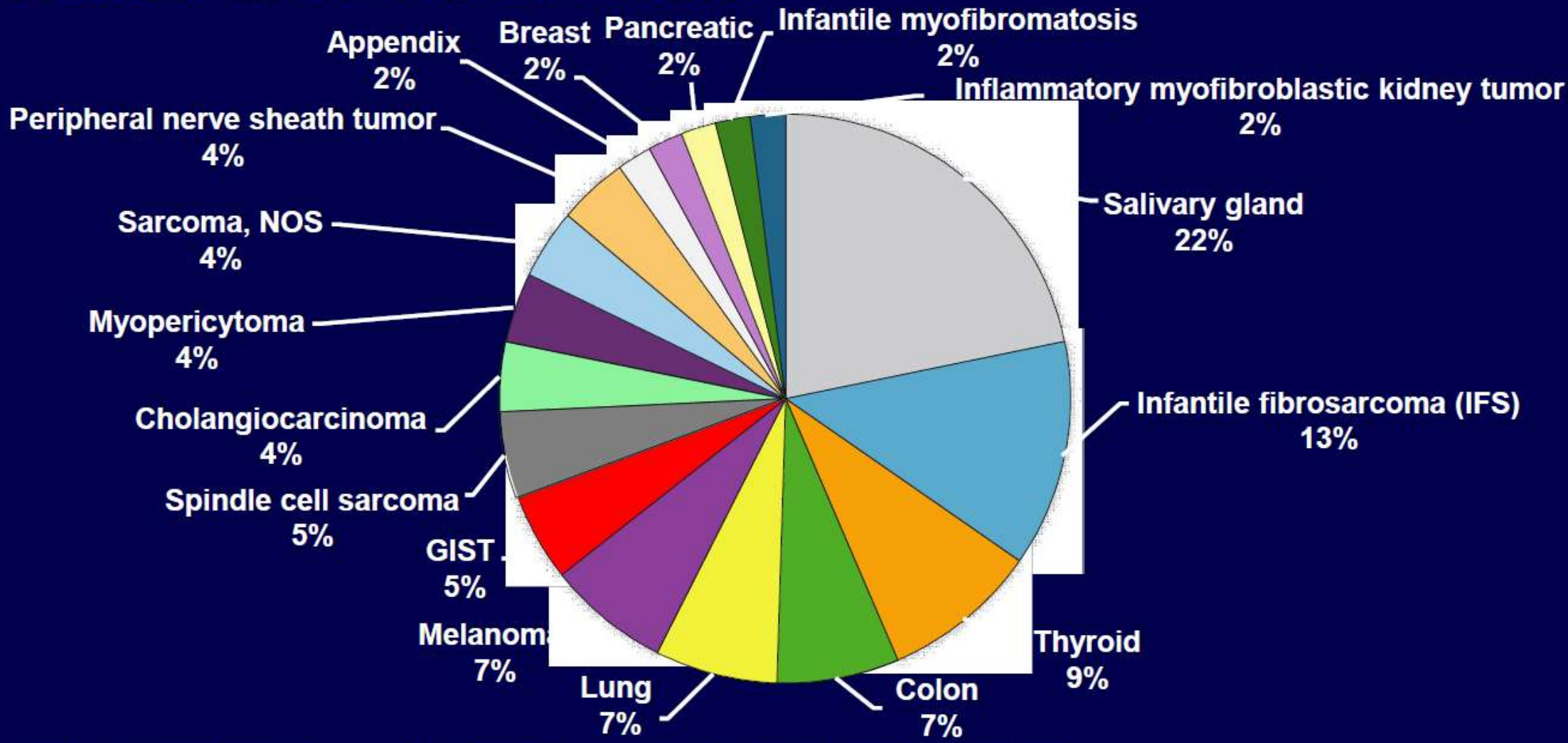
NTRK Fusion vs *NTRK* Mutation

- Gene fusion:
  - No change to DNA sequence
  - Change to the location of the gene on the chromosome
  - Typically results in an overactive receptor
- For *NTRK* genes, **FUSIONS** are activating and predictive of response
  - Target for cancer therapy

- Gene mutation:
  - Change to DNA sequence
  - Location on chromosome unchanged
  - Typically results in an abnormal protein product
- For *NTRK* genes, mutations do not appear to be oncogenic driver events

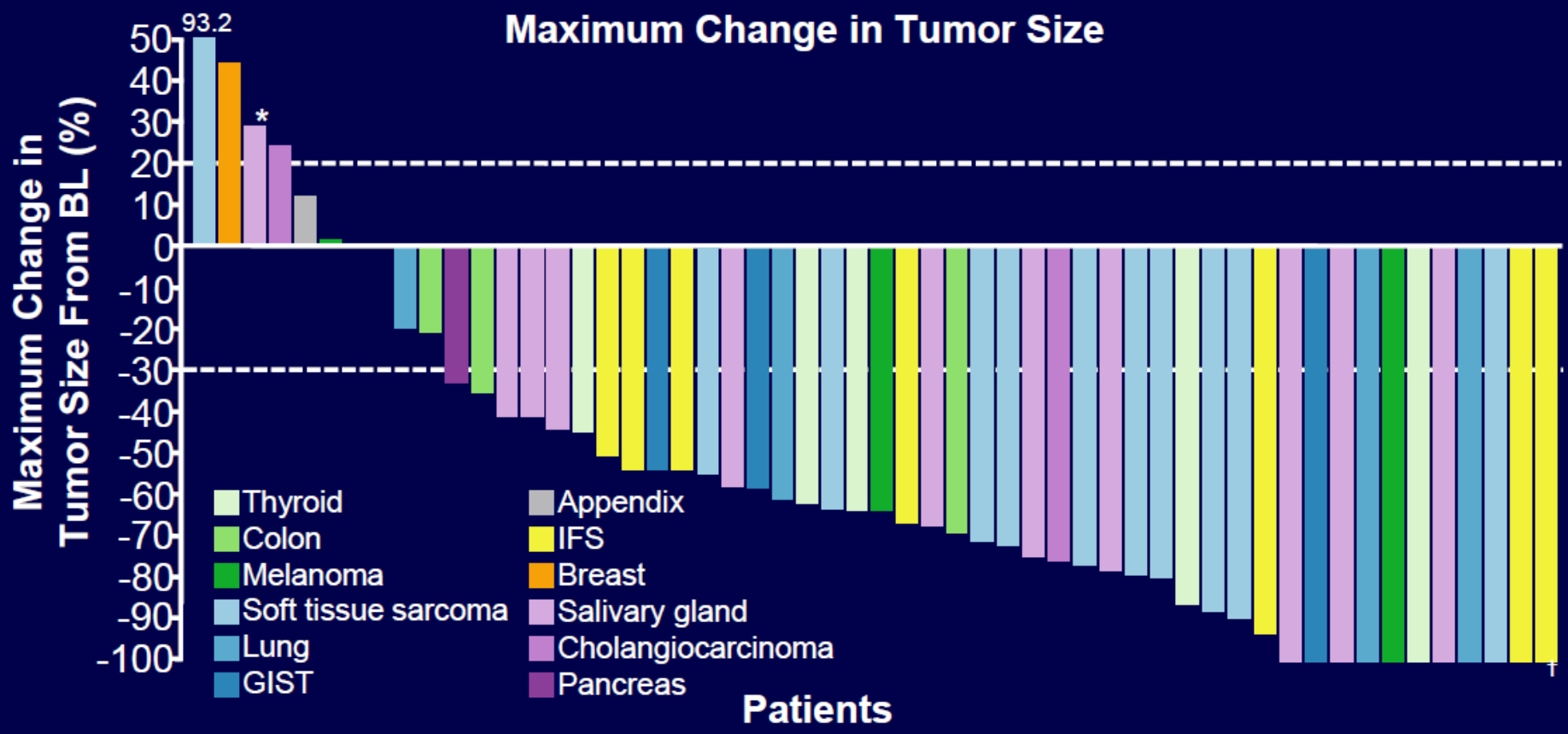
Latysheva NS, et al. Nucleic Acids Res. 2016;44:4487-4503. Supek F, et al. Cell. 2014;156:1324-1335. Amatu A, et al. ESMO Open. 2016;1:e000023.

17 Unique Cancer Types Positive for TRK Fusions Treated with Larotrectinib



Hyman DM, et al. ASCO 2017. Abstract LBA2501. Drilon A, et al. N Engl J Med. 2018;378:731-739.

Larotrectinib Antitumor Activity Irrespective of Tumor Type



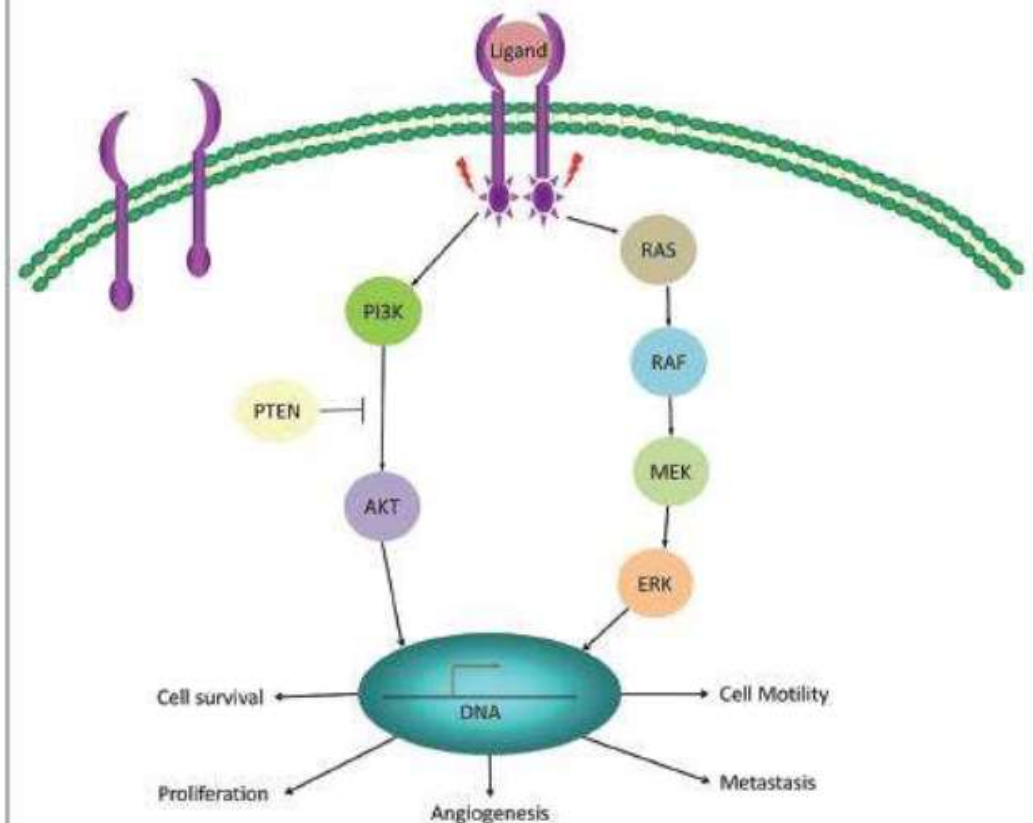
Data omitted for 1 patient who experienced PD and had no recorded post-BL tumor measurements.
*Patient with BL TRK resistance mutation (*NTRK3* G623R) due to previous treatment. †Pathologic CR.

Drilon A, et al. N Engl J Med. 2018;378:731-739.

BRAF GENE

- BRAF (v-raf murine sarcoma viral oncogene homolog B; B-type raf kinase) gene is located on chromosome 7 (KRAS gene on chromosome 12)
- *BRAF* V600 mutations lead to
  - Constitutive BRAF kinase activity phosphorylation of MEK and ERK kinases
  - Sustained MAPK pathway signaling

Fig. 1. Overview of MAPK Signaling Pathway

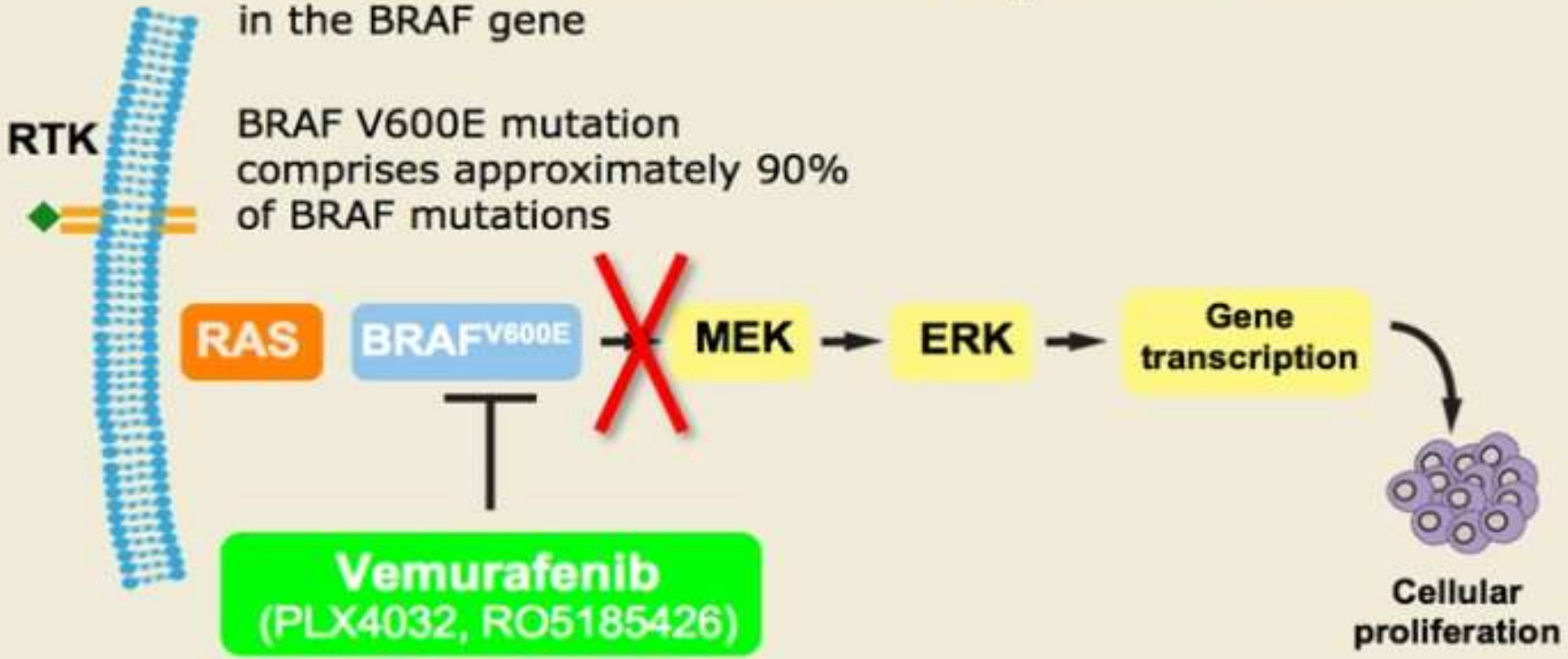


Abbreviations: AKT, protein kinase B; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; RAF, rapid accelerated fibrosarcoma; RAS, rat sarcoma.

Vemurafenib Inhibits BRAF^{V600E} Kinase

40-60% of cutaneous melanomas are positive for mutations in the BRAF gene

BRAF V600E mutation comprises approximately 90% of BRAF mutations



Adapted from Chapman PB et al. *Proc ASCO* 2011;Abstract LBA4.

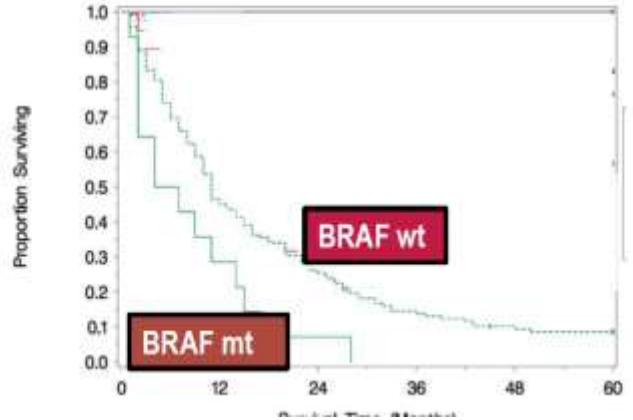
BRAF and Advanced MSS Colon Cancer

PROGNOSTIC EFFECT OF BRAF V600E MUTATION

Poor Survival Associated with the *BRAF* V600E Mutation in Microsatellite-Stable Colon Cancers

Wade S. Samowitz,[1] Carol Sweeney,[2] Jennifer Herrick,[2] Hans Albertsen,[2] Theodore R. Levin,[3] Maureen A. Murtaugh,[2] Roger K. Wolff,[2] and Martha L. Slattery[2]

6063 Cancer Res 2005; 65: (14). July 15, 2005

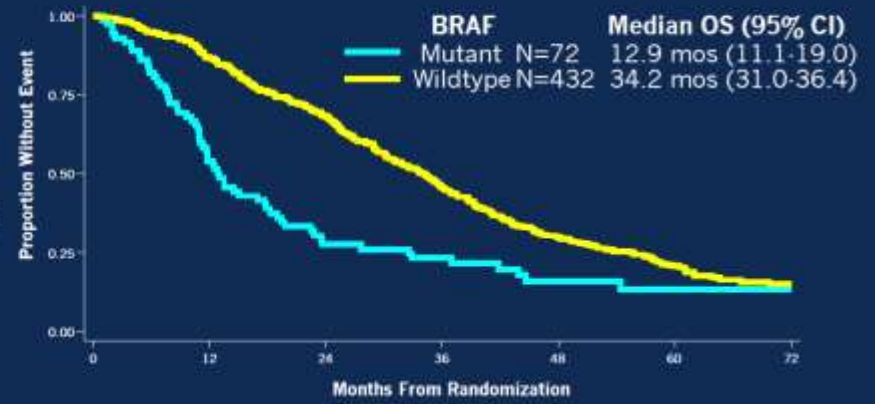


Samowitz WS, et al. Cancer Res 2005;65(14):6063–6069.

CALGB study: OS is affected by BRAF mutations (72/504, 14%) (adjusted on sidedness)

HR_{adj} 1.67
(95% CI 1.20-2.33)
p 0.0035

Without adjusting for sidedness:
HR_{adj} 1.82
(95% CI 1.37-2.44)
p 0.0001



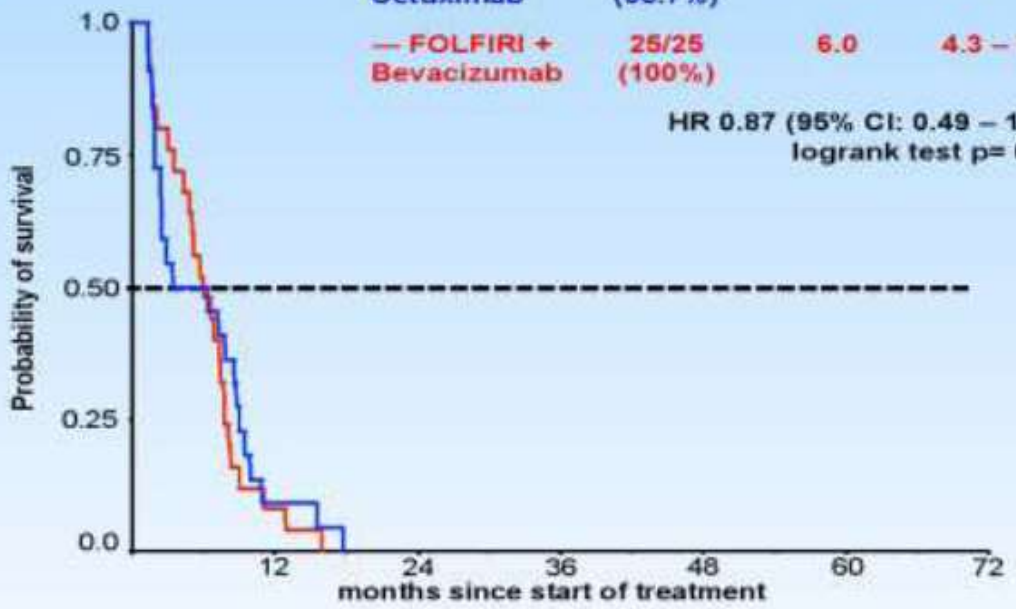
MORE RECENT DATA: FIRE 3

BRAF mutant patients

Progression free Survival

	Events n/N (%)	Median (months)	95% CI
— FOLFIRI + Cetuximab	22/23 (95.7%)	4.9	2.4 – 8.8
— FOLFIRI + Bevacizumab	25/25 (100%)	6.0	4.3 – 7.8

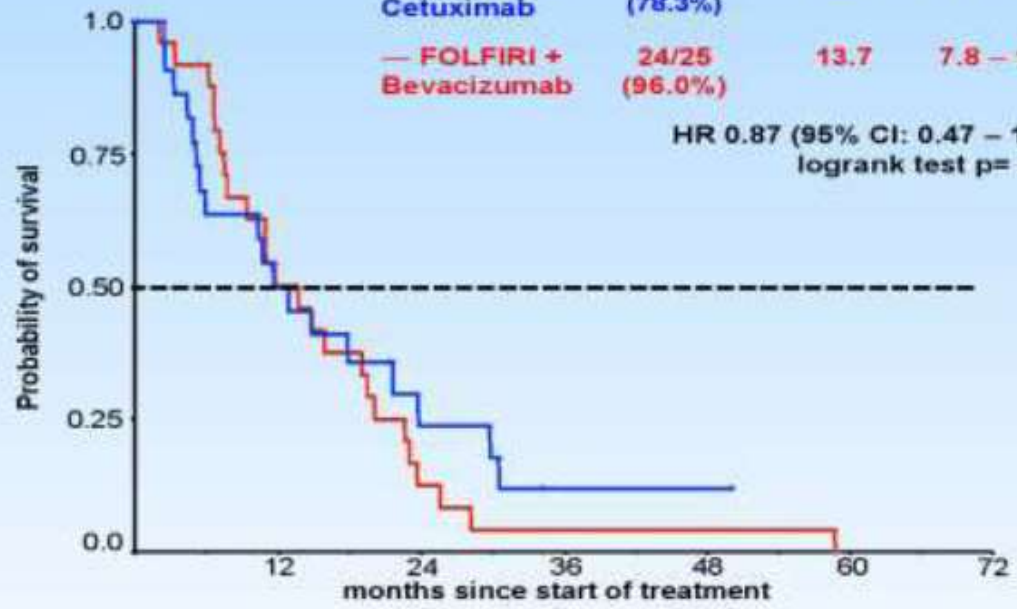
HR 0.87 (95% CI: 0.49 – 1.57)
logrank test p= 0.65



Overall Survival

	Events n/N (%)	Median (months)	95% CI
— FOLFIRI + Cetuximab	18/23 (78.3%)	12.3	5.5 – 21.7
— FOLFIRI + Bevacizumab	24/25 (96.0%)	13.7	7.8 – 19.5

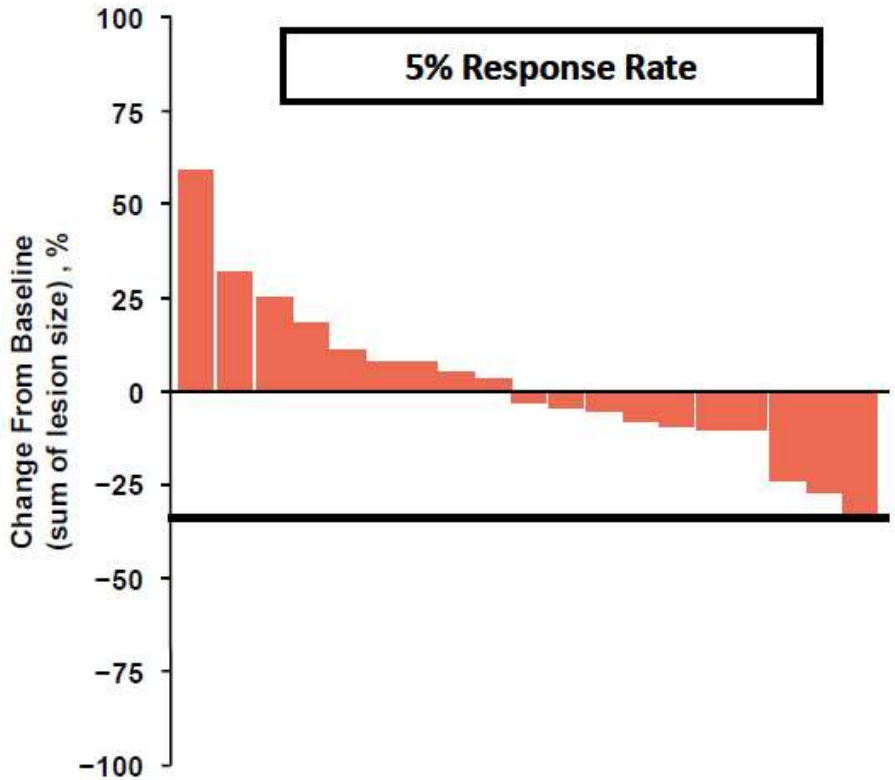
HR 0.87 (95% CI: 0.47 – 1.61)
logrank test p= 0.65

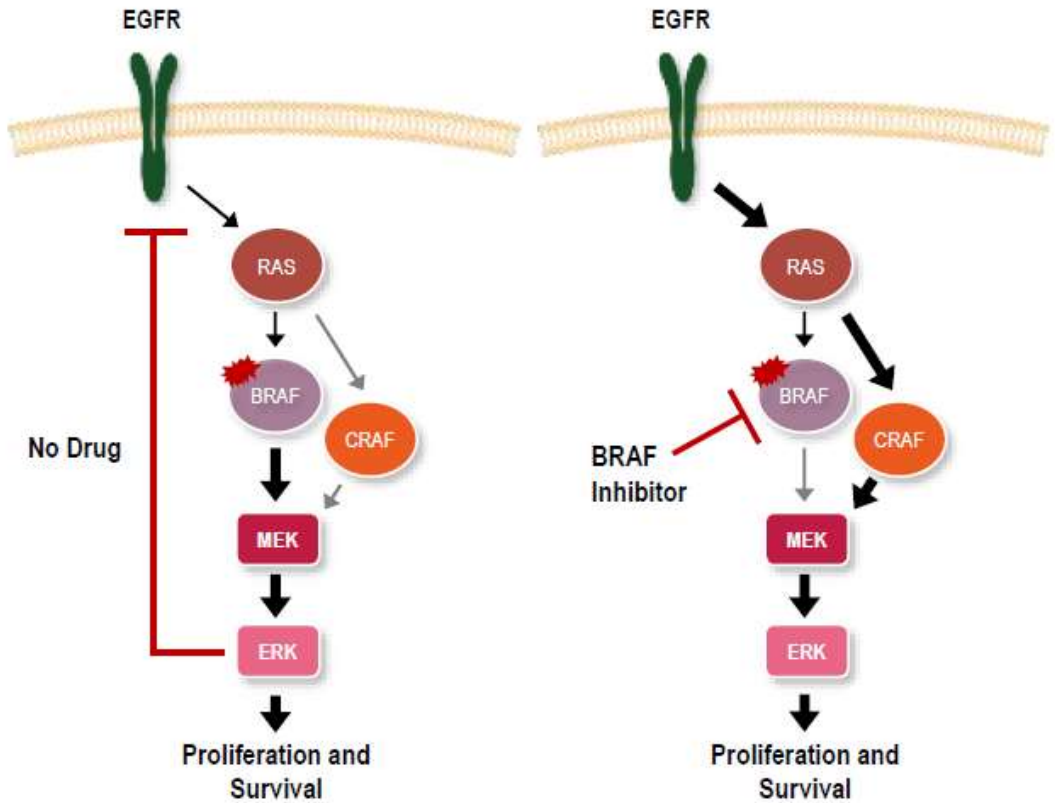


	FOLFIRI + Cetuximab		FOLFIRI + Bevacizumab			
ORR	%	95%-CI	%	95%-CI	Odds ratio	p (two sided Fisher test)
BRAF mutant (N= 48)	52.2	30.6 – 73.2	40.0	21.1 – 61.3	1.64 (0.52-5.14)	0.29

Stintzing S et al. Eur J Cancer 2017;in press

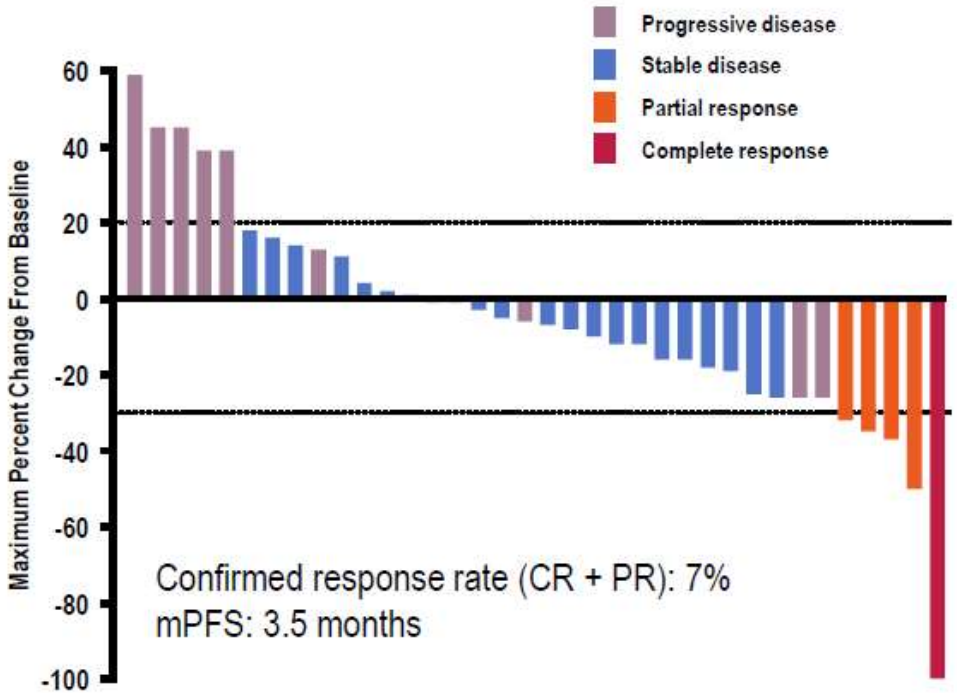
VEMURAFENIB MONOTHERAPY: NOT EFFECTIVE IN *BRAF*–MUTANT CRC

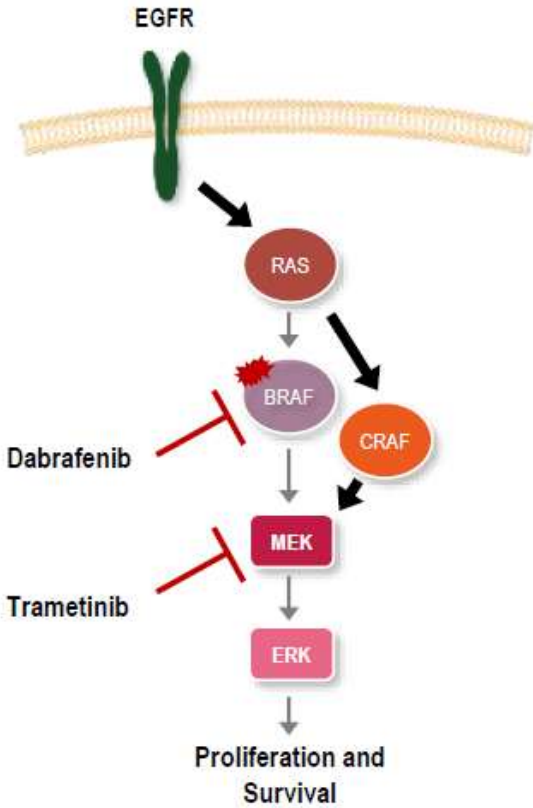




Corcoran RB, et al. *Cancer Discov*. 2012;2:227-235; Kopetz S, et al. *J Clin Oncol*. 2010;28:453-459; Montero-Conde C, et al. *Cancer Discov*. 2013;3:520-533; Prahallad A, et al. *Nature*. 2012;483:100-103.

DABRAFENIB + TRAMETINIB: LIMITED ACTIVITY IN *BRAF*-MUTANT CRC





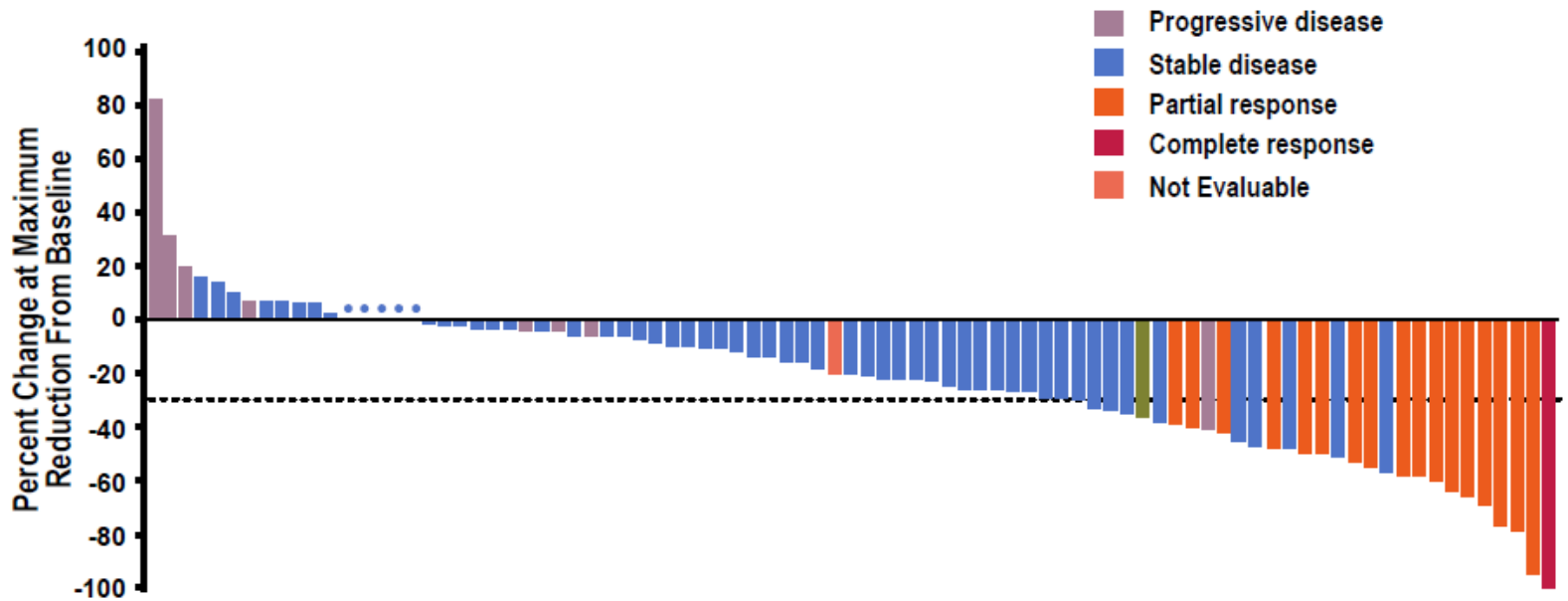
CR, complete response; PR, partial response.

Corcoran RB, et al. *J Clin Oncol*. 2014;32(suppl) [abstract 3517].

CONFIRMED BEST RESPONSE IN *BRAF* V600E COHORT (CONT)

D + T + P (n = 91)

Confirmed CR/PR: 19 (21%)
Stable disease: 59 (65%)
Disease control: 78 (86%)



Color: confirmed response.
Height of bar: best unconfirmed response.

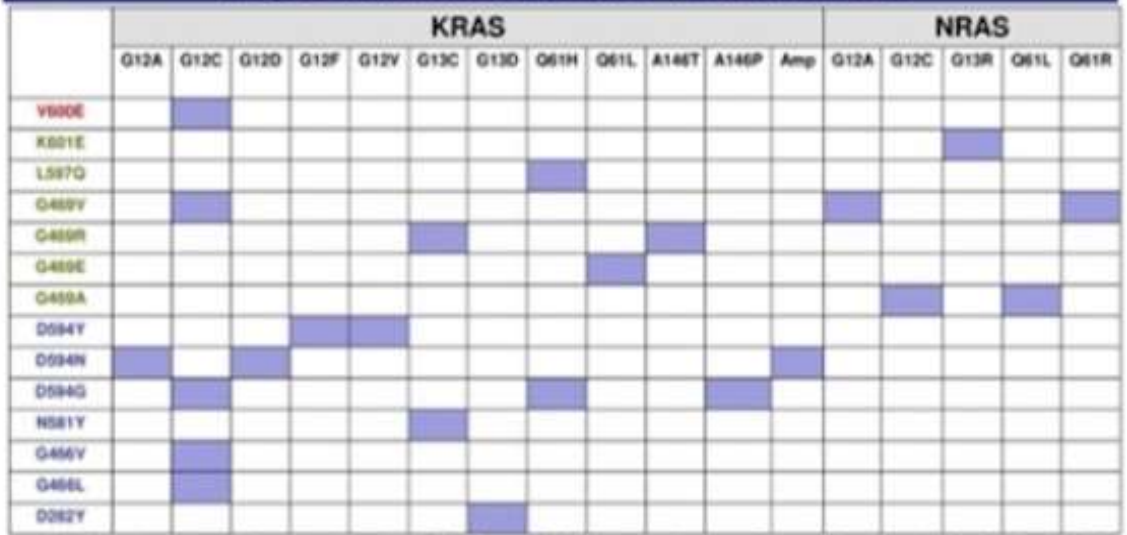
Bar color indicates best confirmed response and bar height indicates best unconfirmed response. Dot indicates maximum reduction from baseline is 0%.

BRAF-mutant in NSCLC

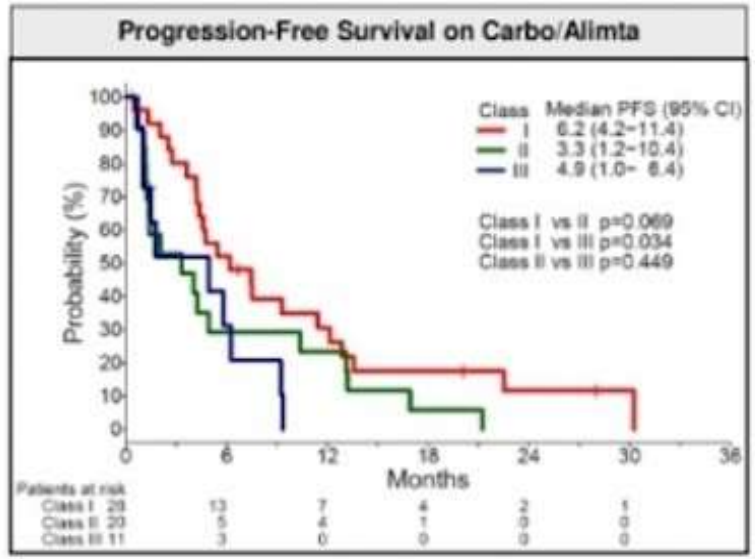
Mutations Identified in Cohort

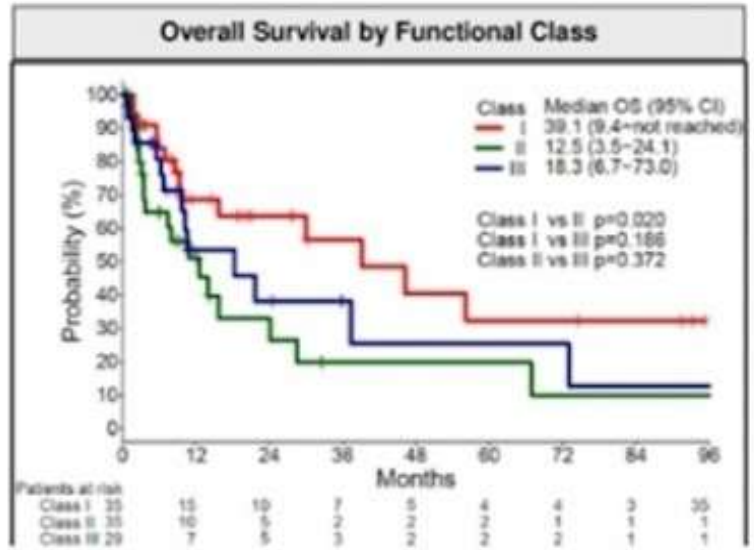
Mutation Class	Mutations
Class I	V600E
Class II	L601G, K601E, L597V/Q/R, G469V/S/R/E/A, G464V
Class II	G596R, D594Y/N/G/E, N581Y/S/I, G466V/L/E/A, D287Y

RAS Co-Alterations in BRAF-Mutant NSCLC



- We detected genetic alteration in *KRAS* or *NRAS* in specimens from 23 patients, including *KRAS* mutations (n=17), *NRAS* mutations (n=5), and one case of high-level *KRAS* amplification (> 25 copies).
- The breakdown of overlapping BRAF/RAS alterations by mutation class was:
  - Class I: 1 (1%) of 107, Class II: 10 (13%) of 75, and Class III: 12 (22%) of 54 tumors
- Class I *BRAF* mutations were significantly less likely to co-occur with *RAS* alterations
  - (class I vs II, p=0.001; class I vs III, p<0.001)

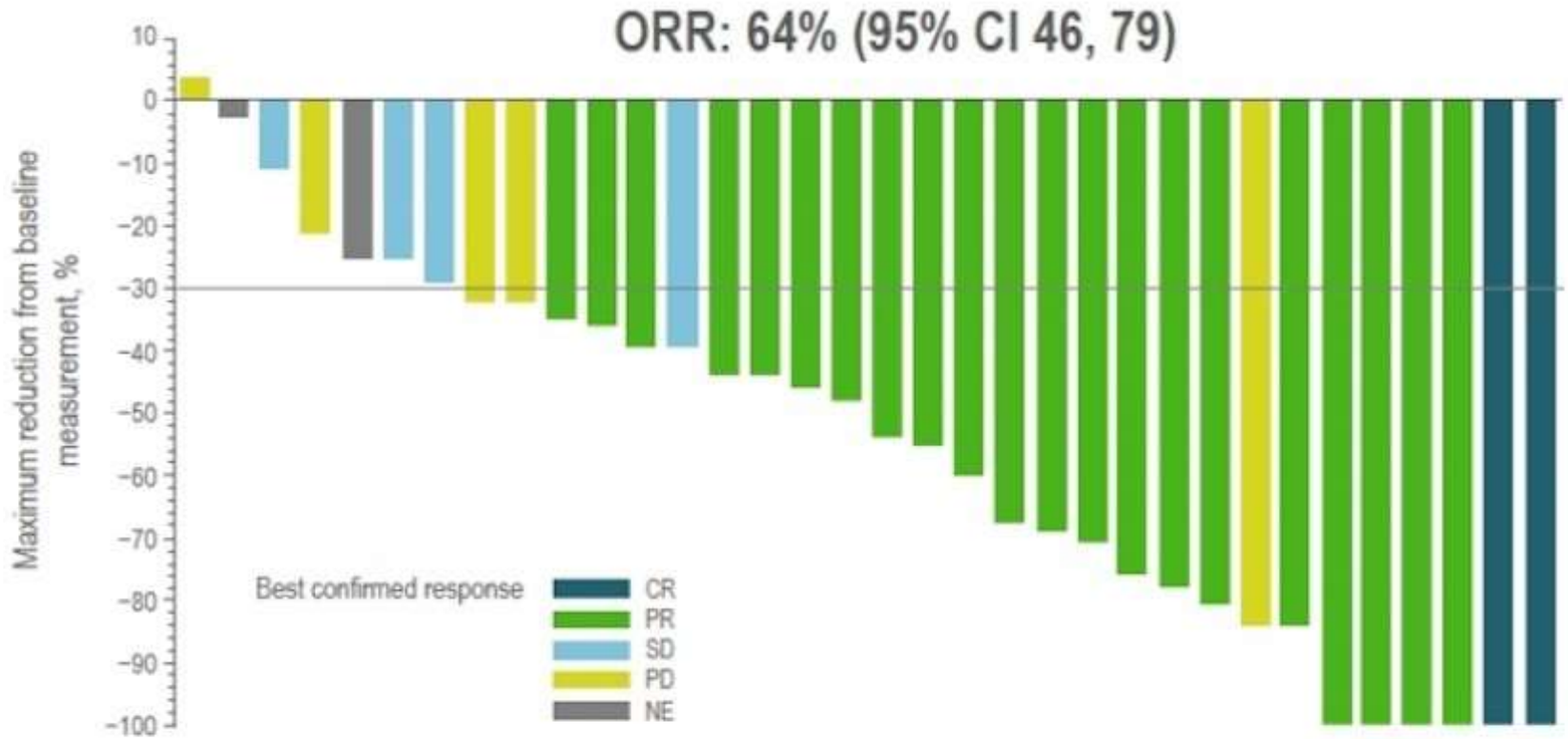




Dogogo-Jack et al, ASCO 18

MAXIMUM CHANGE IN TARGET LESION BY BEST CONFIRMED RESPONSE WITH DABRAFENIB + TRAMETINIB IN 1ST LINE

Cohort C



Planchard D *et al. Lancet Oncol* 2017;18:1307–1316

NOTE: Dabrafenib + trametinib is not approved for the treatment of *BRAF*+ NSCLC in Japan

BRAIN Tumors and BRAF

DISCOVERY MEDICINE

Table 1. Prevalence of *BRAF*-V600E mutation and *KIAA1549-BRAF* fusion in primary brain tumors in children and adults.		
Tumor Type		**% *BRAF*-V600E Mutation**
Pleomorphic xanthoastrocytoma (PXA)		42-66%
Astroblastoma		38%
Ganglioglioma grade I		18-50%
Pilocytic astrocytoma (PA)		5-16%
Dysembryoplastic neuroepithelial tumor (DNET)		0-9%
Astrocytoma	Glioblastoma multiforme (GBM)	1-8% (mainly epithelioid and giant cell subtype)
	Gliosarcoma	0-22%
	Diffuse astrocytoma	0-14%
	Anaplastic astrocytoma	0-3%
Meningioma		0-3% (mainly rhabdoid subtype)
Oligodendroglioma II		0-3%
Tumor Type		**% *KIAA1549-BRAF* fusion**
Pilocytic astrocytoma (PA)		51-66%
Diffuse astrocytoma		8%

Table 1. Prevalence of *BRAF*-V600E mutation and *KIAA1549-BRAF* fusion in primary brain tumors in children and adults.

Maraka S, Discovery Medicine 2019

BRAIN Tumors and BRAF

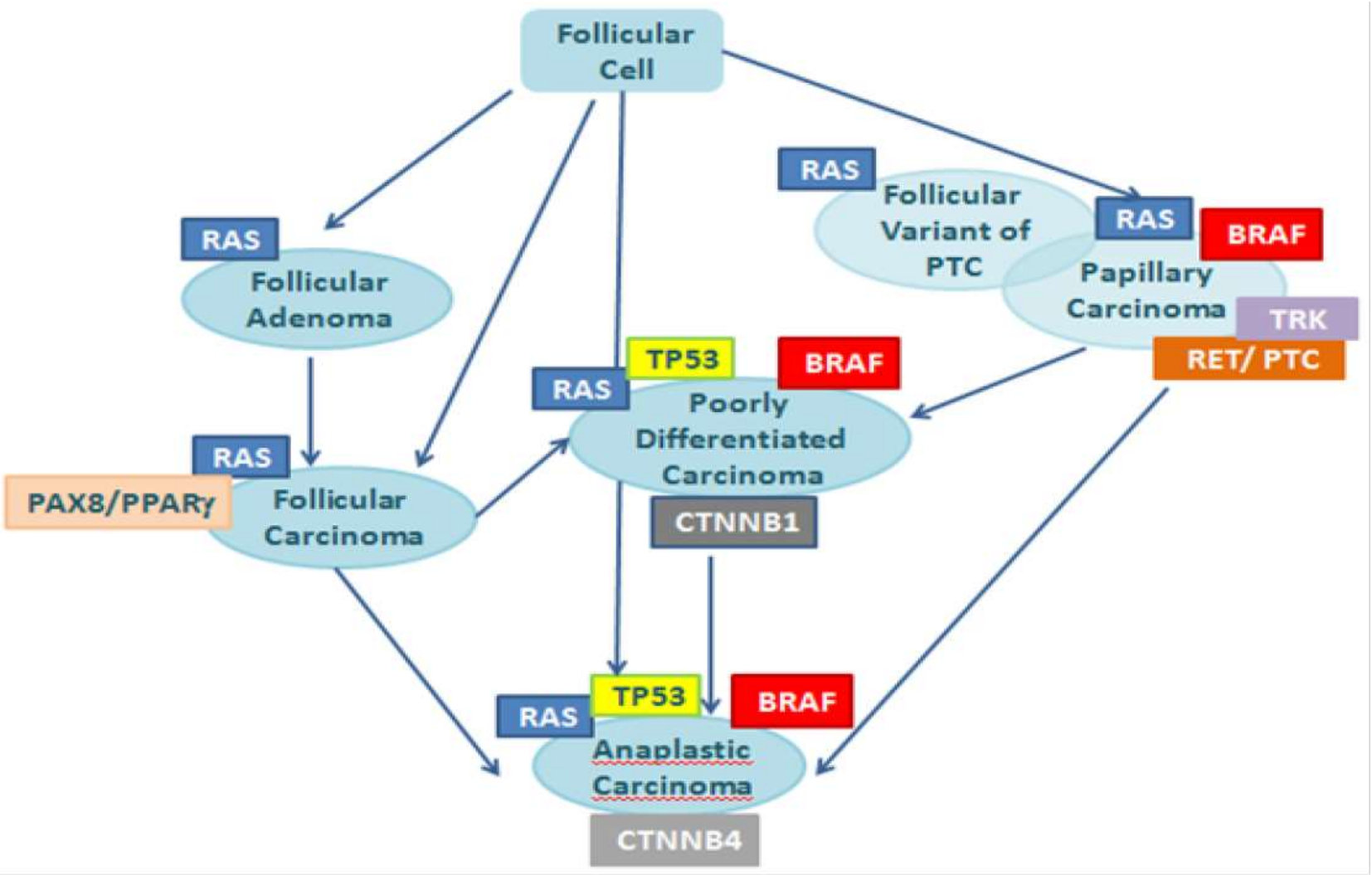
Table 2. Published reports of BRAF inhibition treatment in adult primary brain tumors with *BRAF*-V600E mutation.

Study	Grade	Location	Age (y)	Sex	Stage of Disease	Treatment	Radiographic Response	Duration of Response
Pleomorphic Xanthoastrocytoma (PXA) studies								
Chamberlain, 2013	II	L Temporal	34	F	Recurrent	Vemurafenib	SD	4 mo
	III	R Frontal	43	M	Recurrent	Vemurafenib	PD	NR
	II	L Frontal	47	F	Recurrent	Verumafenib	SD	6 mo
	II	R Temporal	53	M	Recurrent	Verumafenib	PR	10 mo
Usubalieva *et al.*, 2015	III	+LMD	35	F	Recurrent	Dabrafenib	PR	3 mo
Hofer *et al.*, 2016	III	R Temporal+ LMD	29	F	Recurrent	Vemurafenib	PR	12 mo
Leaver, 2016	III*	L Occipital	39	M	Recurrent	Verumafenib	CR	2 mo
Lee *et al.*, 2016	III	R Frontal-Parietal	41	M	Recurrent	Verumafenib	PR	>12 wks
Amayiri *et al.*, 2017	III	L Parietal	16	F	Recurrent	Dabrafenib+Trametinib	PR	30 mo
Brown *et al.*, 2017	III	R Temporal	48	F	Recurrent	Dabrafenib+Trametinib	PR, CR	>8 mo
	III	R Temporal	21	F	Recurrent	Dabrafenib	CR	20 mo
	III	R Temporal	21	F	Recurrent	Dabrafenib+Trametinib	CR	>4 mo
Burger *et al.*, 2017	III	R Temporal+ LMD	24	M	Recurrent	Dabrafenib	CR	>27 mo
	III	L Temporal+ LMD	50	M	Recurrent	Dabrafenib	PR	>8 mo
Migliorini *et al.*, 2017	III	R Parietal	32	F	Recurrent	Dabrafenib+Trametinib	PR	12 mo
Johanns *et al.*, 2018	High grade glioma/PXA	L Frontal	24	M	Recurrent	Dabrafenib+Trametinib	PR	>3 mo**
Schreck *et al.*, 2018	III	L Temporal	16	M	Recurrent	Dabrafenib+Trametinib	PR	16 mo
Glioblastoma studies								
Leaver, 2016	IV* (epithelioid)	R Temporal	26	M	Recurrent	Vemurafenib	PR	7 days
Burger *et al.*, 2017	IV	L Temporal+ LMD	25	M	Recurrent	Dabrafenib	CR	>3 mo
Johanns *et al.*, 2018	IV (epithelioid)	L Temporal	28	F	Recurrent	Dabrafenib+Trametinib	PR	11 mo
Schreck *et al.*, 2018	IV (epithelioid)	L Frontal	23	F	Recurrent	Dabrafenib+Trametinib	SD	>16 mo
Ganglioglioma								
Shih *et al.*, 2015	I	L Temporal+ Brainstem	21	M	Recurrent	Dabrafenib	PR	>3 mo***
Chamberlain, 2016	I	Frontal	26	F	Recurrent	Dabrafenib	SD	4 mo
	I	Frontal	34	K	Recurrent	Dabrafenib	SD	7 mo
	J	Temporal	45	L	Recurrent	Dabrafenib	PR	10 mo
Meletath *et al.*, 2016	III	L Parietal	25	M	Recurrent	Dabrafenib	CR	>24 mo
Beland *et al.*, 2018	III	R Temporal-parietal+LMD	51	F	Recurrent	Dabrafenib+Trametinib	CR	>6 mo
Marks *et al.*, 2018	III	R Temporal	16	F	Recurrent	Dabrafenib+Trametinib	CR	>6 mo
Papillary Craniopharyngioma studies								
Aylwin *et al.*, 2016	I	Supracellar	27	F	Recurrent	Vemurafenib	Near CR	7 mo
Brastianos & Santagata, 2016	I	Supracellar	39	M	Recurrent	Dabrafenib+Trametinib	PR	>7 mo
Roque & Oda, 2017	I	Supracellar	47	F	Recurrent	Dabrafenib+Trametinib	PR	>7 mo
Himes *et al.*, 2018	I	Supracellar	47	M	Recurrent	Dabrafenib	PR	>24 mo

Table 2. Published reports of BRAF inhibition treatment in adult primary brain tumors with *BRAF*-V600E mutation.

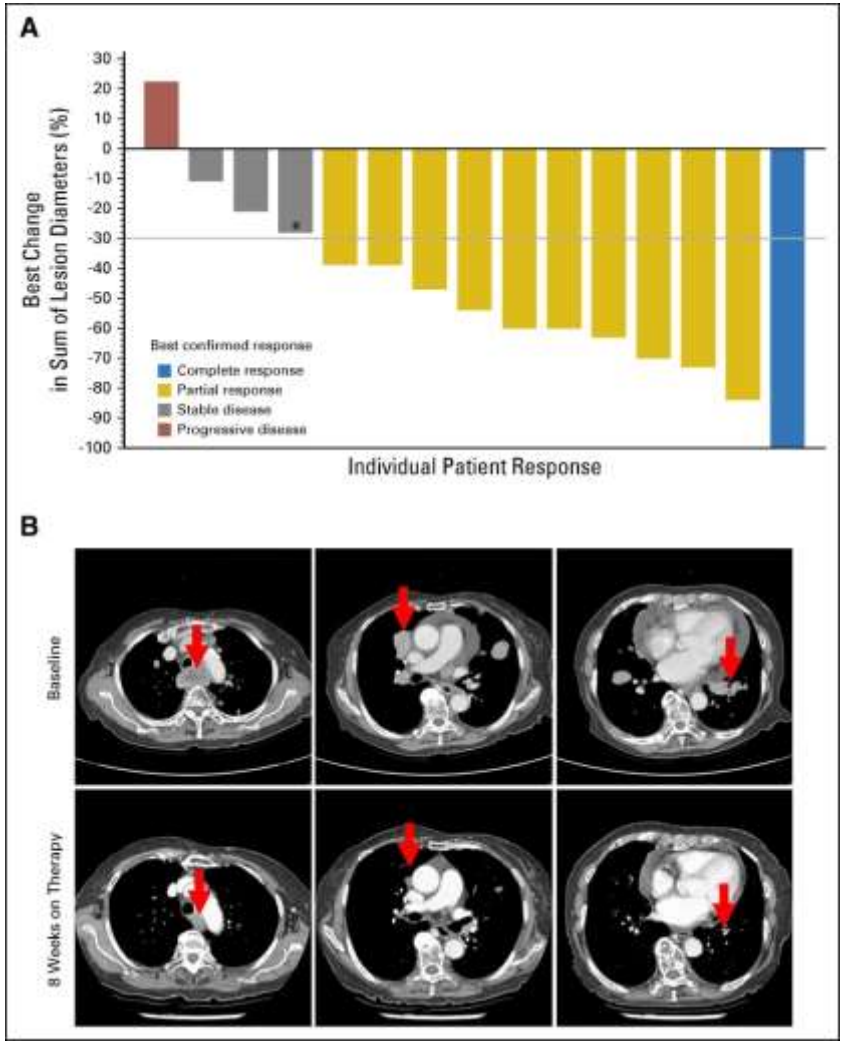
Maraka S, Discovery Medicine 2019

Thyroid Cancer and BRAF

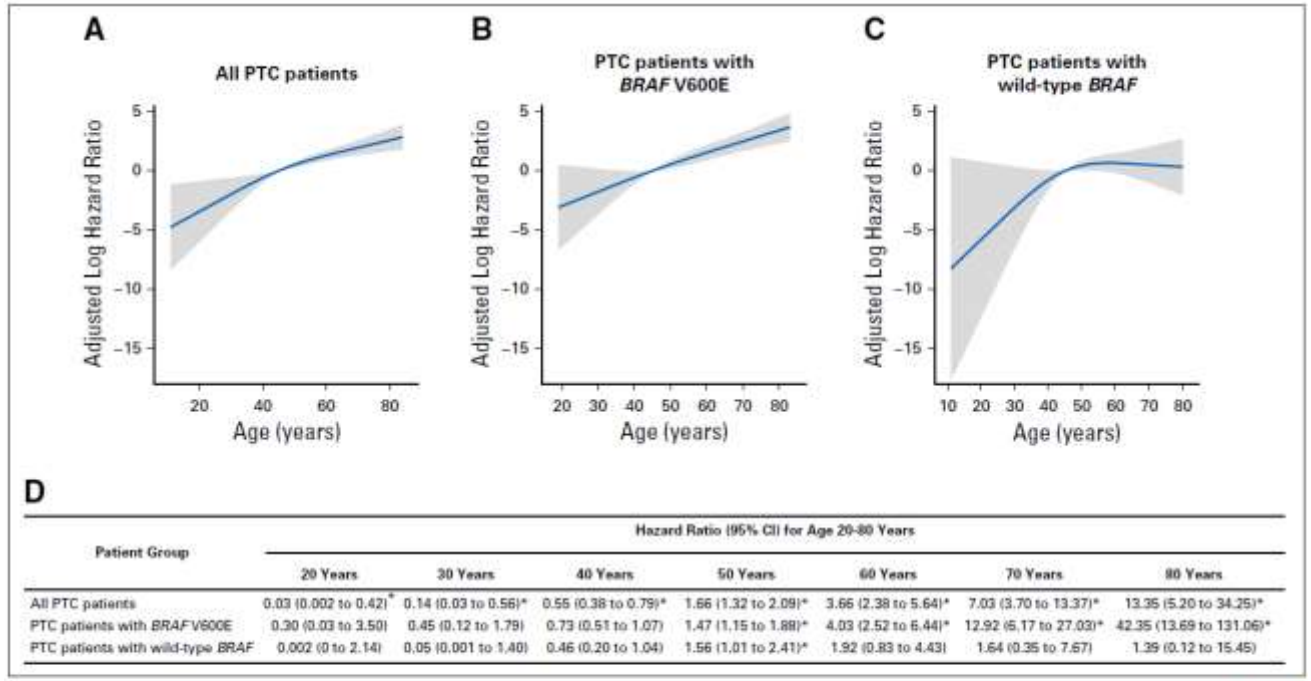


F. Khatami 2018

BRAF and Thyroid Cancer



Subbiah V et al JCO 2018



D

Patient Group	Hazard Ratio (95% CI) for Age 20-80 Years						
	20 Years	30 Years	40 Years	50 Years	60 Years	70 Years	80 Years
All PTC patients	0.03 (0.002 to 0.42)*	0.14 (0.03 to 0.56)*	0.55 (0.38 to 0.79)*	1.66 (1.32 to 2.09)*	3.66 (2.38 to 5.64)*	7.03 (3.70 to 13.37)*	13.35 (5.20 to 34.25)*
PTC patients with *BRAF* V600E	0.30 (0.03 to 3.50)	0.45 (0.12 to 1.79)	0.73 (0.51 to 1.07)	1.47 (1.15 to 1.88)*	4.03 (2.52 to 6.44)*	12.92 (6.17 to 27.03)*	42.35 (13.69 to 131.06)*
PTC patients with wild-type *BRAF*	0.002 (0 to 2.14)	0.05 (0.001 to 1.40)	0.46 (0.20 to 1.04)	1.56 (1.01 to 2.41)*	1.92 (0.83 to 4.43)	1.64 (0.35 to 7.67)	1.39 (0.12 to 15.45)

Fig 4. Multivariate Cox proportional hazards regression analysis of papillary thyroid cancer (PTC)–specific mortality risk with restricted cubic splines (RCS). Continuous linea association between patient age and PTC-specific mortality was observed (A) in the analysis of all patients and (B) even more significantly in patients with *BRAF* V600E, bu CI not in patients with wild-type *BRAF*. The blue line represents the fitted line of the association between patient age and the estimated hazard ratio (HR) of mortality afte adjustment; the shaded region represents the 95% CI. The models were adjusted for the following clinicopathologic characteristics: patient sex, tumor size, extrathyroidal extension ymph node metastasis, distant metastases, administered activities of radioactive iodine, and study center. The RCS plots were performed with the age of 45 years as the reference or HR calculation. (D) Specific HRs and 95% CIs are presented for the indicated patient age points. (*) Significantly different HRs in reference to patient age of 45 years.

Shen X et al, JCO 2018

Decision Flow

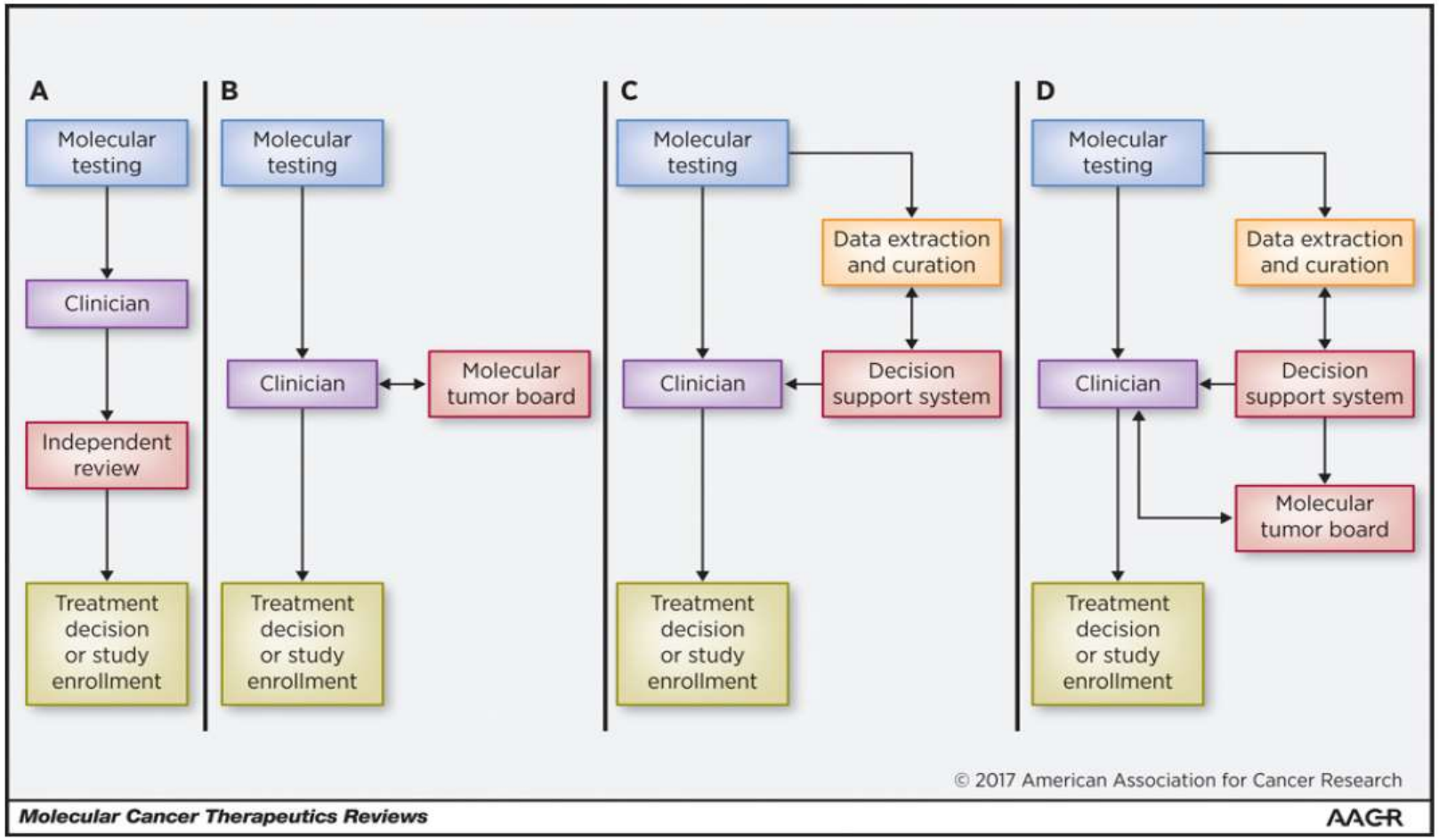


Figure 1.
Patient management workflow strategies. Patient management workflow strategies with an (**A**) independent review model, (**B**) molecular tumor board model, (**C**) decision support system model, and (D) integrated model. In **A**, clinicians filter through scientific literature and public databases to reach treatment decisions for patients. **B** and **C** provide clinicians with support for making informed treatment decisions. In **B**, clinicians present cases to molecular tumor boards and a recommended course of action is provided. In **C**, decision support systems provide "curated" information to help clinicians make treatment decisions. In **D**, extracted and curated data are reviewed by clinicians and, if necessary, with the support of molecular tumor boards.

Mol Cancer Ther; 16(12) December 2017

”Targeted Therapy”: Questioni Aperte (1)

- In differenti neoplasie gli stessi target hanno **rilevanza diversa**

HER2 : mammella *versus* stomaco

- **Eterogeneità Tumorale e Resistenza**

a) I meccanismi di resistenza primaria rimangono la causa di fallimento

b) I meccanismi di resistenza secondaria non sono facilmente diagnosticabili ed aggredibili

”Targeted Therapy”: Questioni Aperte (2)

- **Metodologia**

a) Biopsia liquida: «ready for prime time?»
b) NGS: subito a tutti ed a progressione?

- **Problemi Etici ed Organizzativi**

a) A chi cercare le mutazioni rare?
b) Creare dei Tumor Boards
c) Chi le cerca? Un solo centro, ogni Ospedale?

Pescara, città dai mille volti, dalle mille facce, tenera ed accogliente con il suo profumo di mare, tenace e forte come le montagne che la circondano, mai banale, con i suoi cittadini, spesso polemici, ma con il cuore tra il ruvido ed il tenero.

Bridging the gap between bench and bedside