

# III JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:

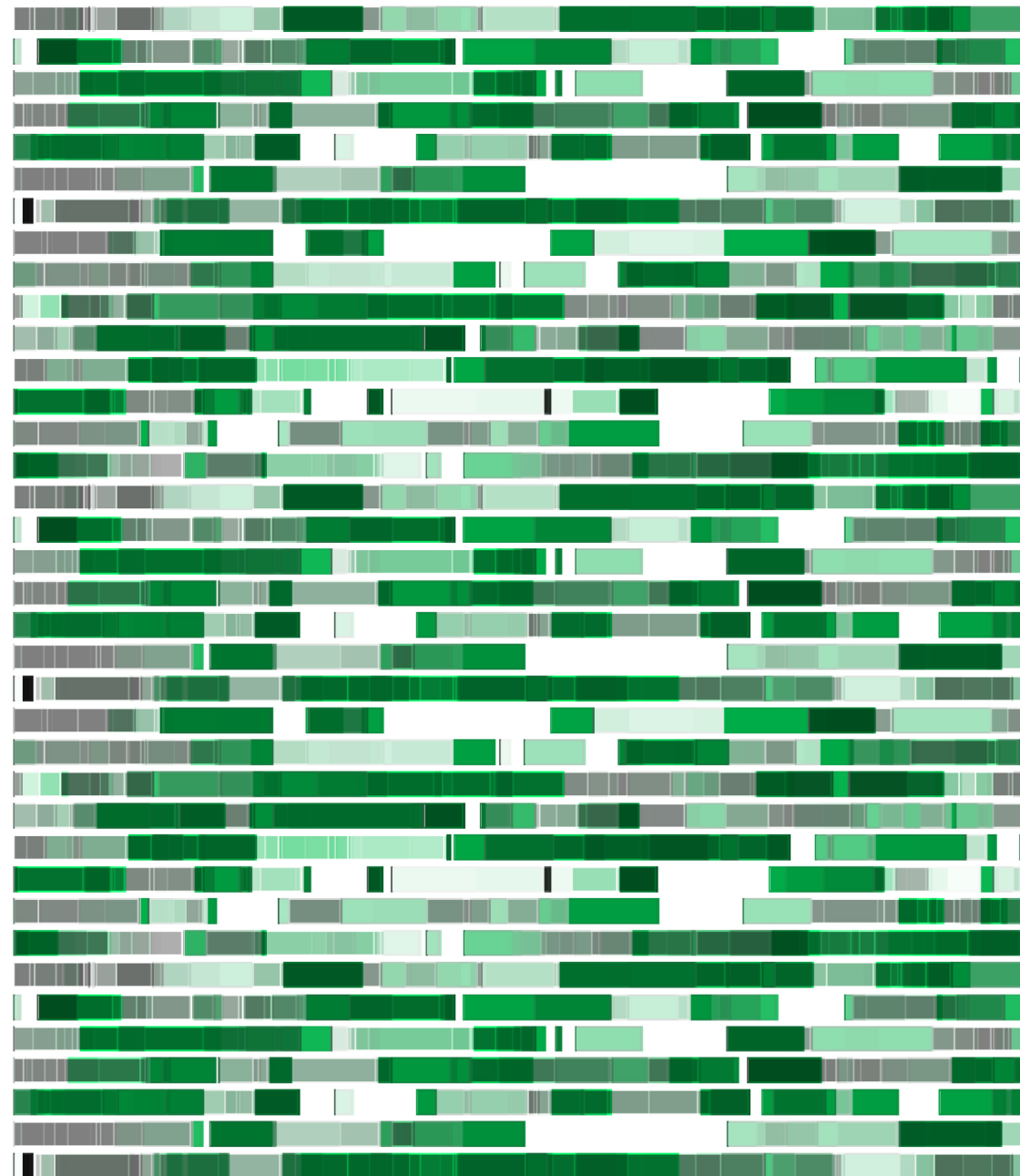
A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN  
SEVILLA, 12 Y 13 DE FEBRERO DE 2026

## Las 3 clases de mutaciones del gen BRAF

Dr. Javier Hernández Losa  
Hospital Universitari Vall d'Hebron

Organizador por:

**HENDERE HEALTHCARE**





## DISCLOSURES

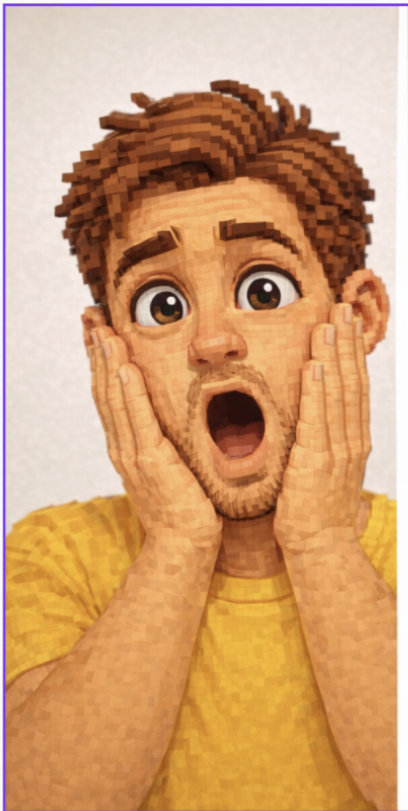
**Advisory Board:** *Pfizer, Lilly, Amgen, Diaceutics, Janssen, Menarini Streamline, Astra Zeneca, Biocartis.*

**Speaker Boureu :** *Lilly, Diaceutics, ThermoFisher , Jannssen, MSD, Roche, Owkin, Takeda, AstraZeneca*

**Grant Support:** Lilly, AstraZeneca



# Las 3 clases de mutaciones del gen BRAF



**MESA 9: Avanzando en el tratamiento dirigido de cáncer de pulmón**

*Moderada:*

Dra. Dolores Isla, Hospital Clínico Universitario Lozano Blesa, Zaragoza

Dr. Sergio Vázquez, Hospital Universitario Lucus Augusti, Lugo

**Nuevas estrategias para la enfermedad EGFR**

Dr. José Manuel Trigo, HC Marbella Internacional Hospital, Málaga

**Importancia de las traslocaciones en el cáncer de pulmón**

Dra. Amparo Sánchez Gastaldo, Hospital Universitario Virgen del Rocío, Sevilla

**Avances en la enfermedad KRAS ¿nuevos inhibidores, monoterapia o asociación con inmunoterapia?**

Dr. Sergio Vázquez, Hospital Universitario Lucus Augusti, Lugo

**Las 3 clases de mutaciones del gen BRAF**

Dr. Javier Hernández, Hospital Universitari Vall d'Hebron, Barcelona

**¿Cómo tratar la enfermedad BRAF? ¿Es posible seleccionar distintos perfiles de pacientes en cáncer de pulmón BRAF?**

Dr. Manuel Cobo, Hospital Regional Universitario de Málaga

**Discusión**

- Mesa de Pulmón.
- Dr. Cobo hablara tratamientos



**Dra. Susana Hernandez**



REVIEW ARTICLE



**Biology and Clinical Management of Non-V600 BRAF Alterations in NSCLC**

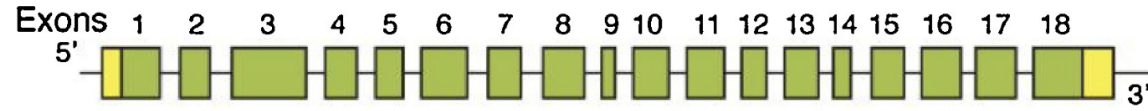
Sandra Ortiz-Cuaran, PhD,<sup>1,2</sup> Laurine Dupriez, MSc,<sup>3</sup> Constance Nicq, MSc,<sup>3</sup> Colin R. Lindsay, MRCP, PhD,<sup>1,2,4</sup> Julien Mazieres, MD, PhD,<sup>1</sup> David Santamaría, PhD,<sup>5</sup> Chiara Ambrogio, PhD,<sup>1</sup> Olivier Galvayrac, PhD,<sup>1</sup> Cristina Teixido, PhD,<sup>1</sup> Luc Friboulet, PhD,<sup>1</sup> Silvia Novello, MD, PhD,<sup>1</sup> Fabrizio Tabbò, MD, PhD,<sup>1,6</sup> Aurélie Swaldutz, MD, PhD,<sup>1,7</sup> Ernest Nadal, MD, PhD,<sup>8</sup> David Planchar, MD, PhD,<sup>1,8</sup> Laura Mezquita, MD, PhD,<sup>1</sup> Marie-Julie Nokin, PhD,<sup>9</sup>, on behalf of the BOLERO Consortium

**Dra. Javier Freire**

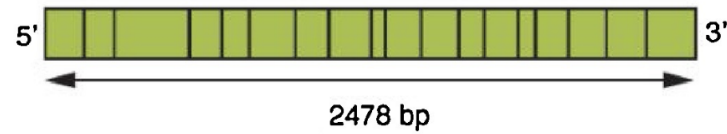




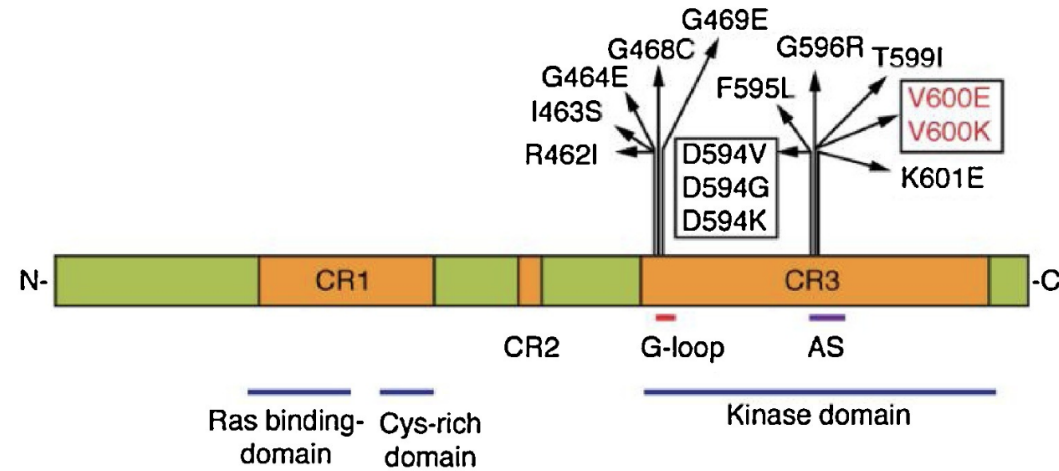
# GEN-BRAF



*BRAF* mRNA



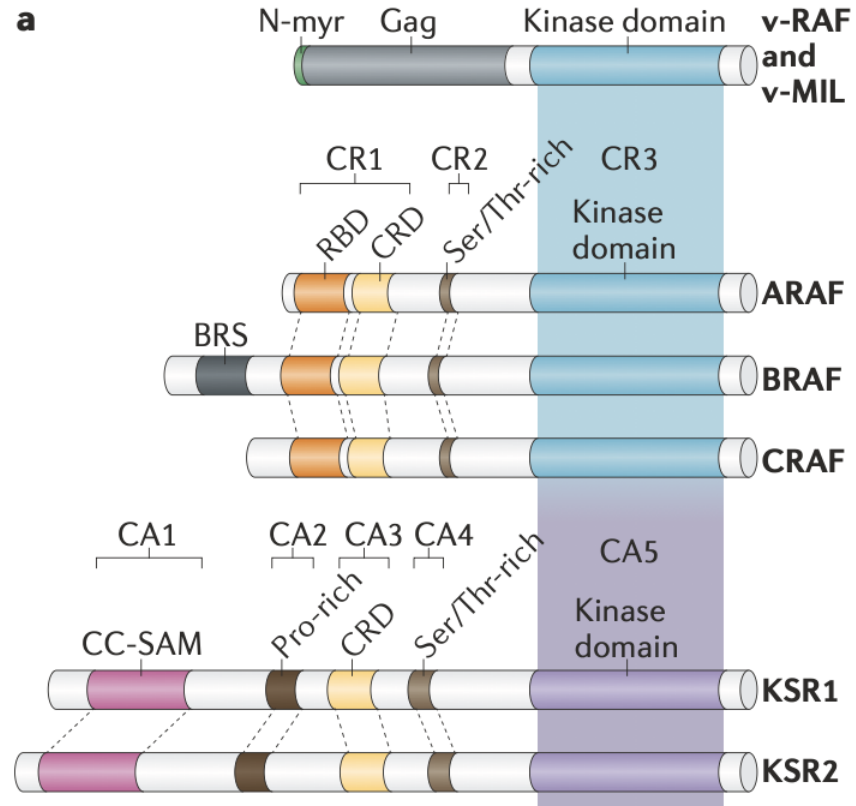
BRAF Protein



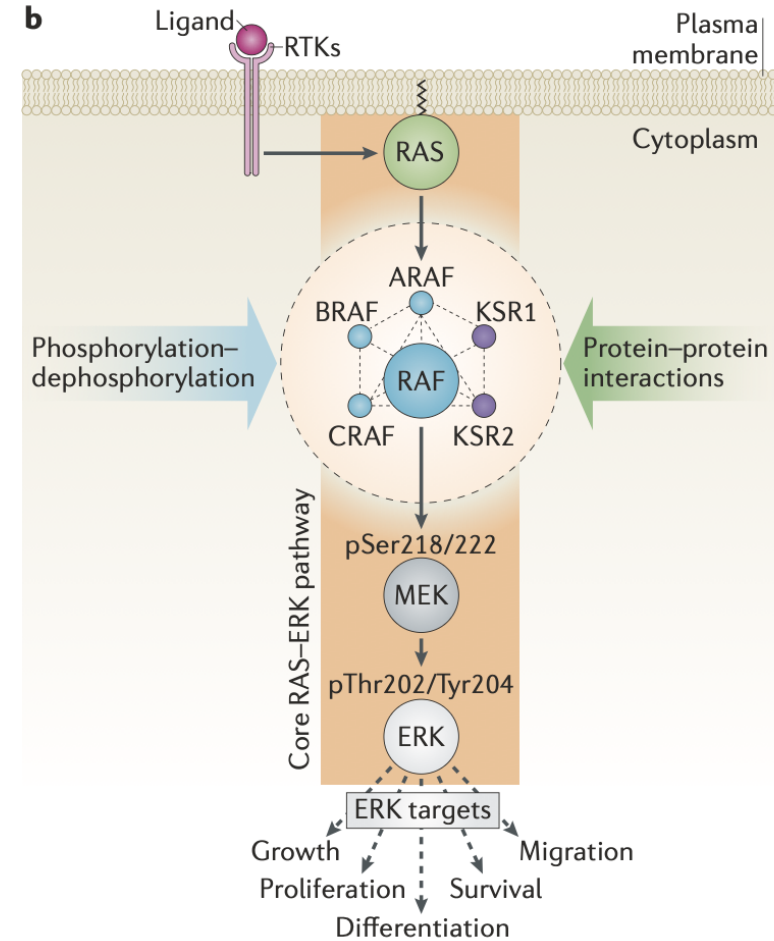
Conserved regions of the proteins BRAF, ARAF and RAF-1

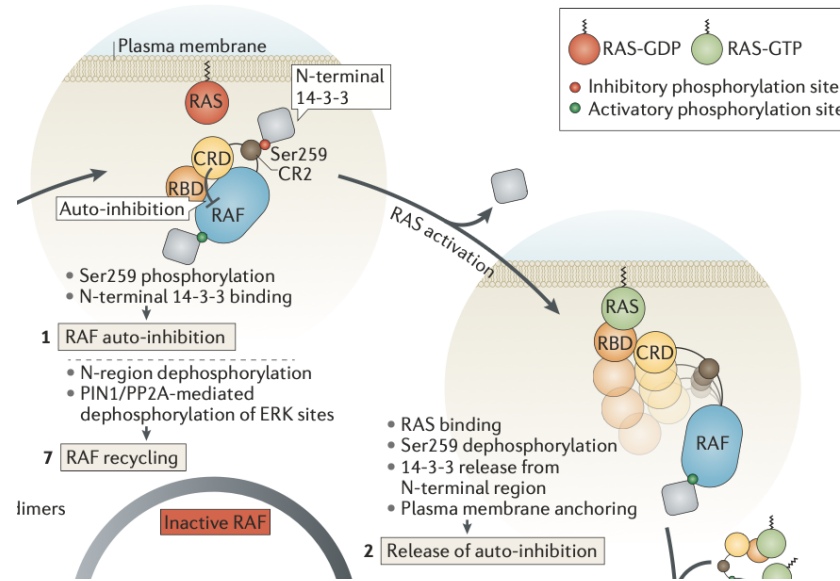


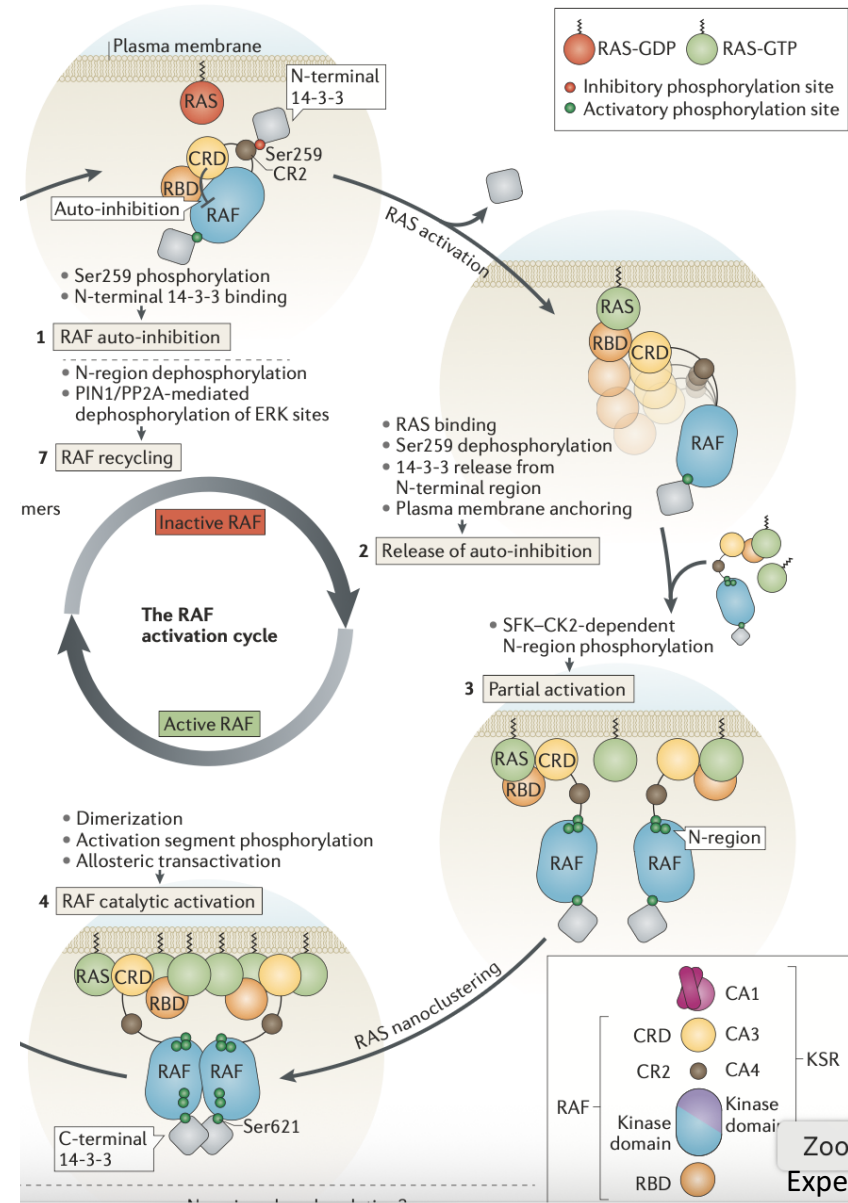
## Mecanismos de acción



KSR. Kinase Suppressor RAS



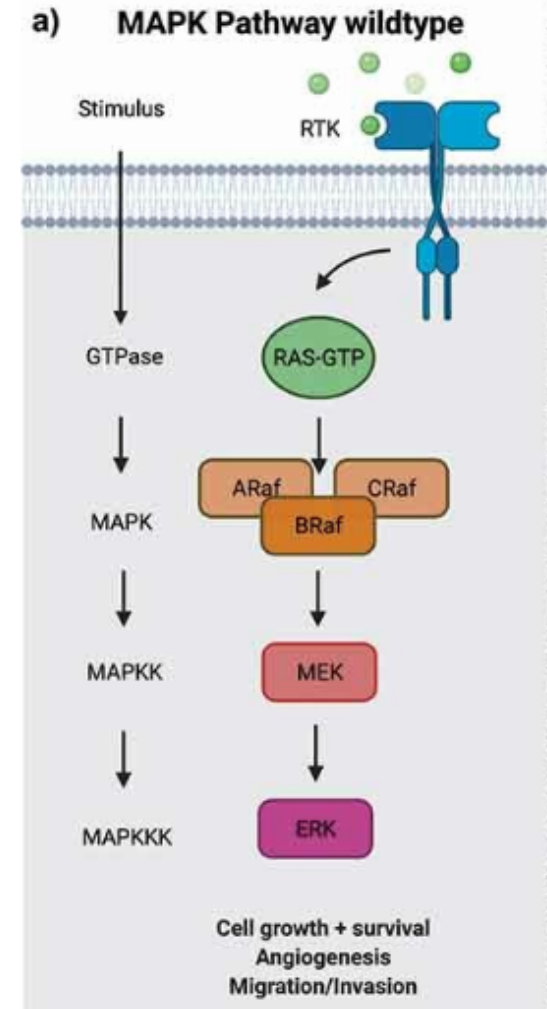
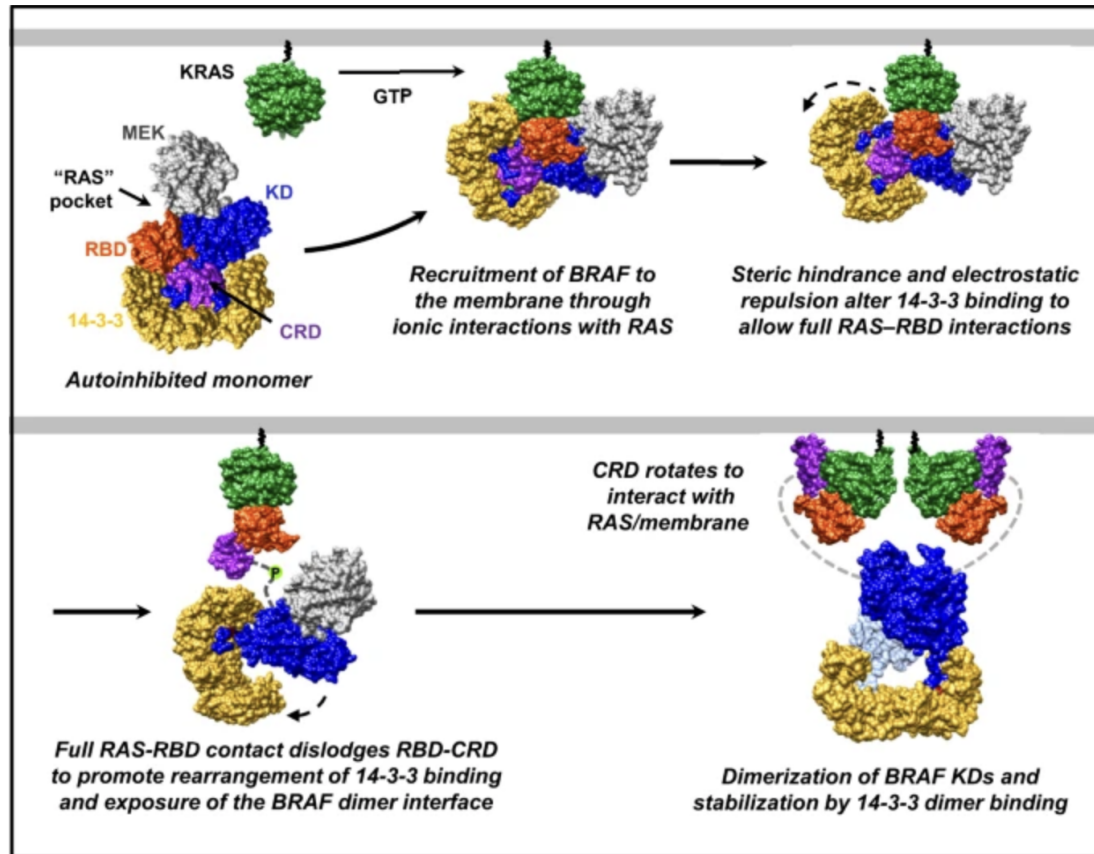






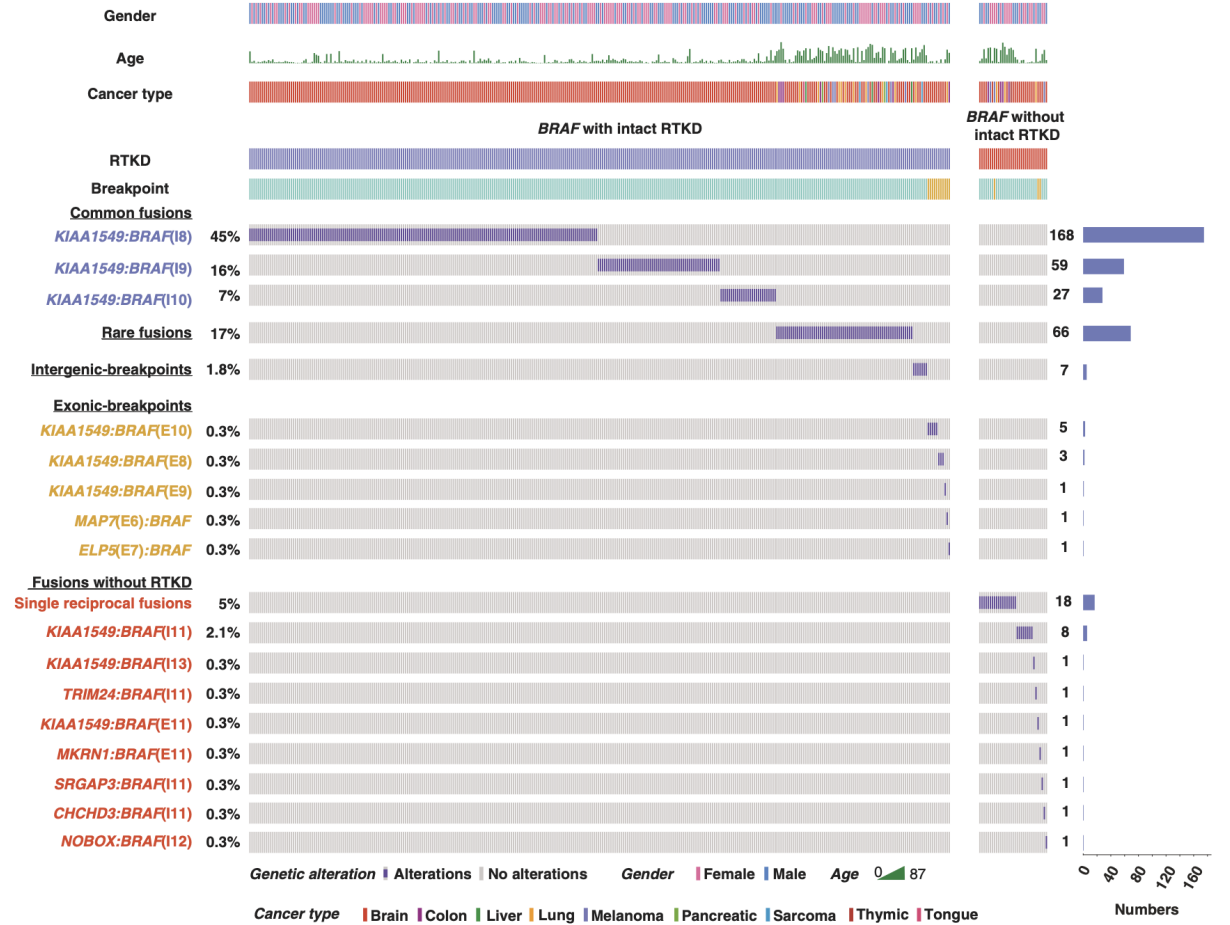
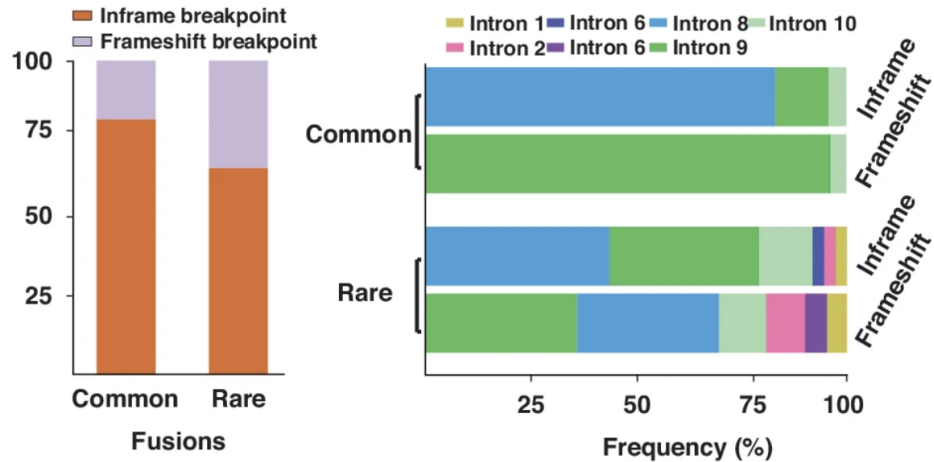
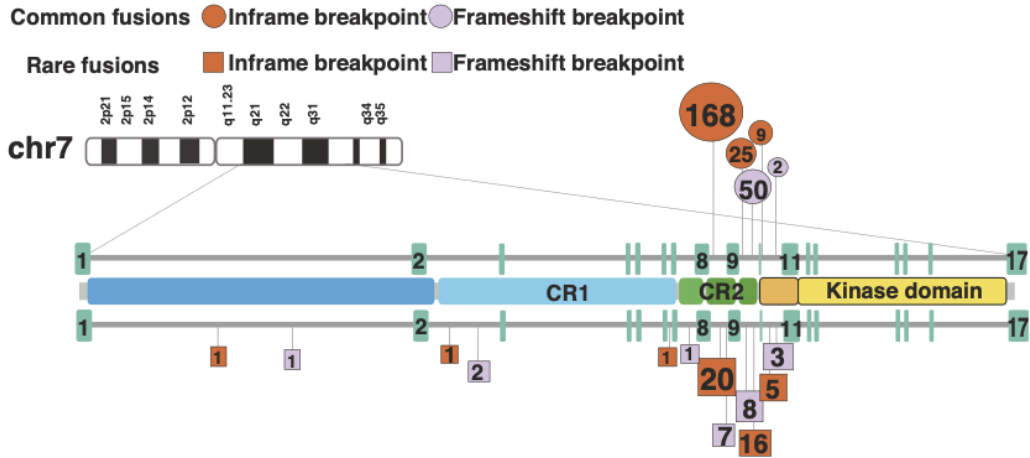


## PROCESO DE DIMERIZACIÓN DE BRAF



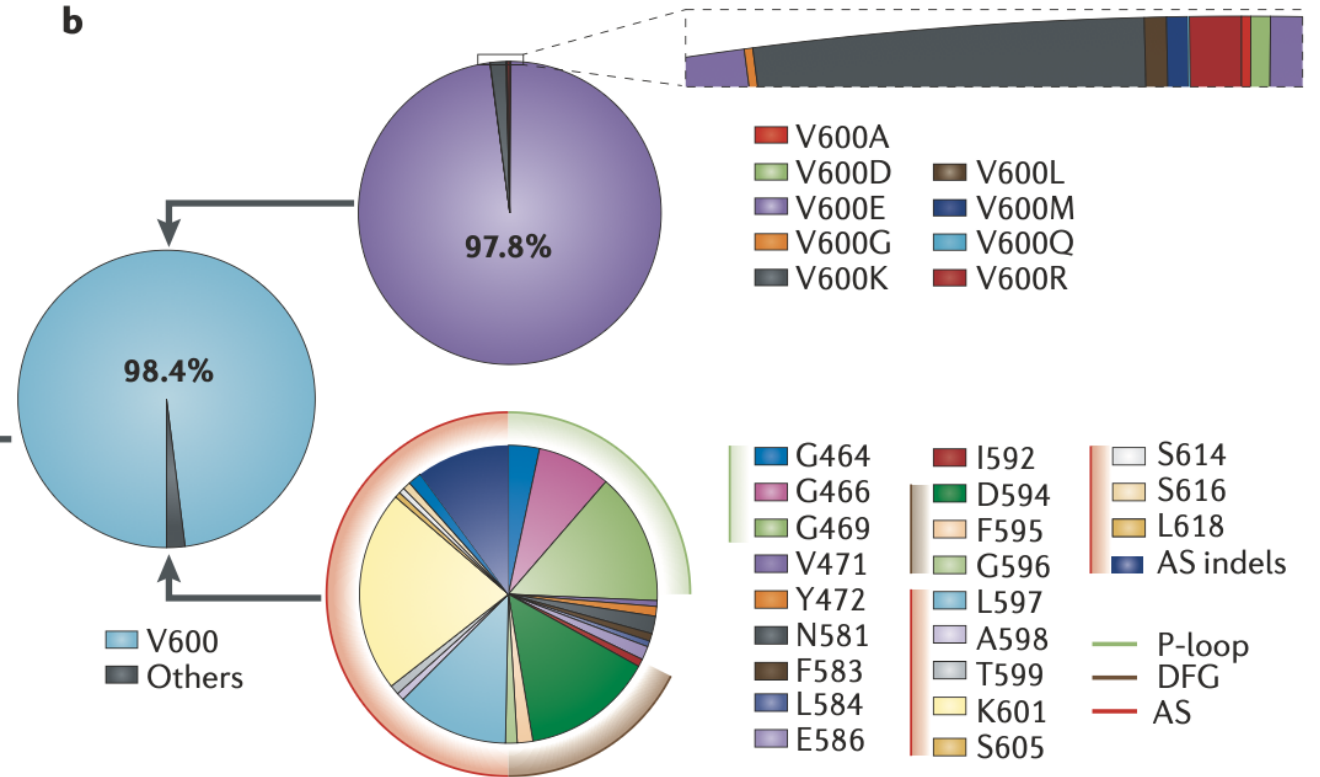
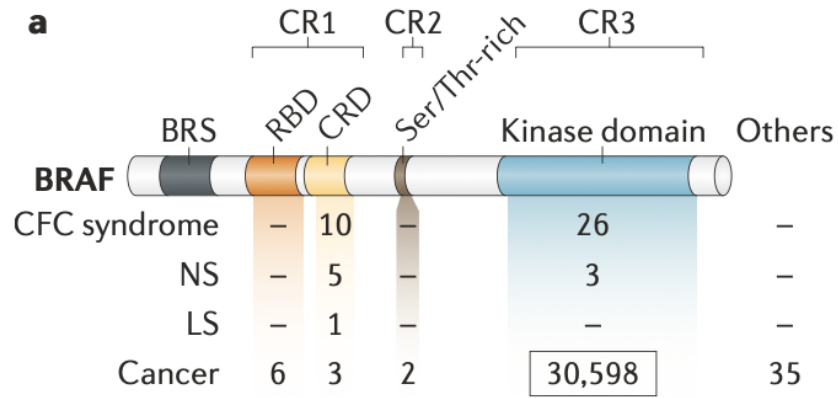


# REORDENAMIENTOS DE BRAF EN CÁNCER



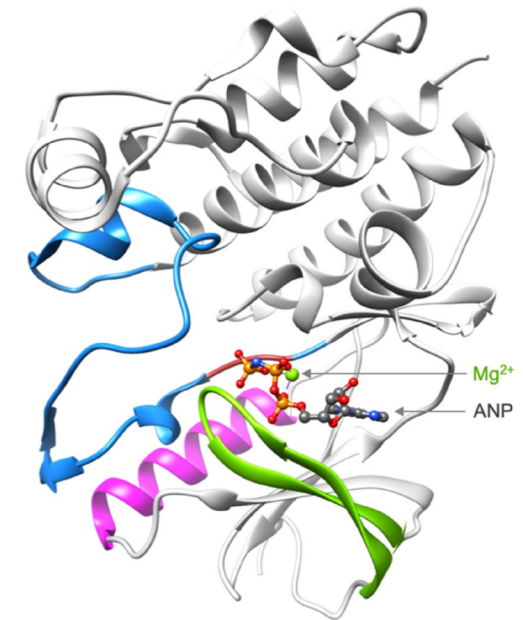
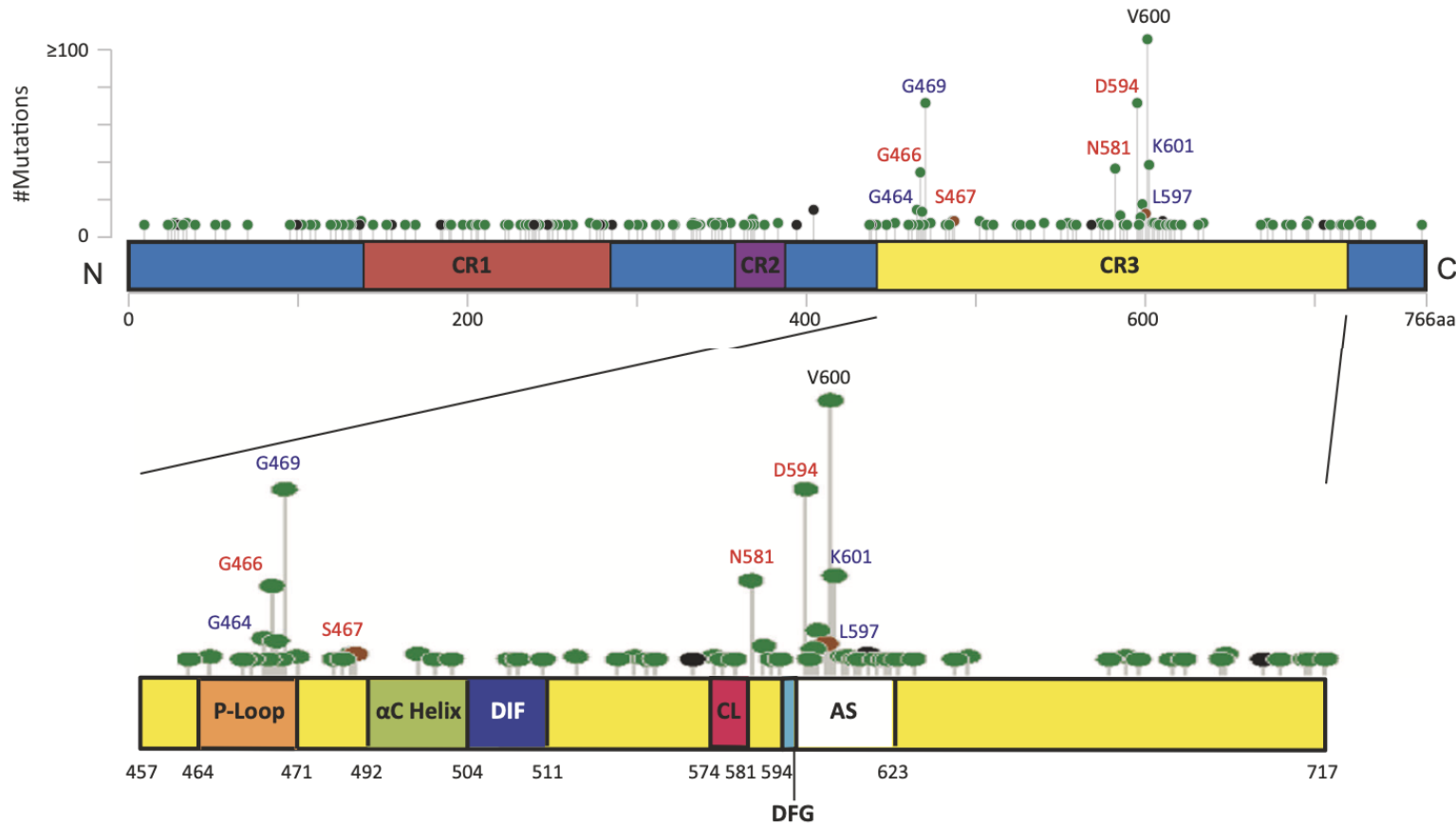


# MUTACIONES DE BRAF





# Estructura del gen BRAF



■ P-loop  
■ C-helix  
■ Activation loop

Dankner M et al. *Oncogene* (2018) 37:3183–3199

Krebs et al. *Scientific Reports*. (2022) 12:12528



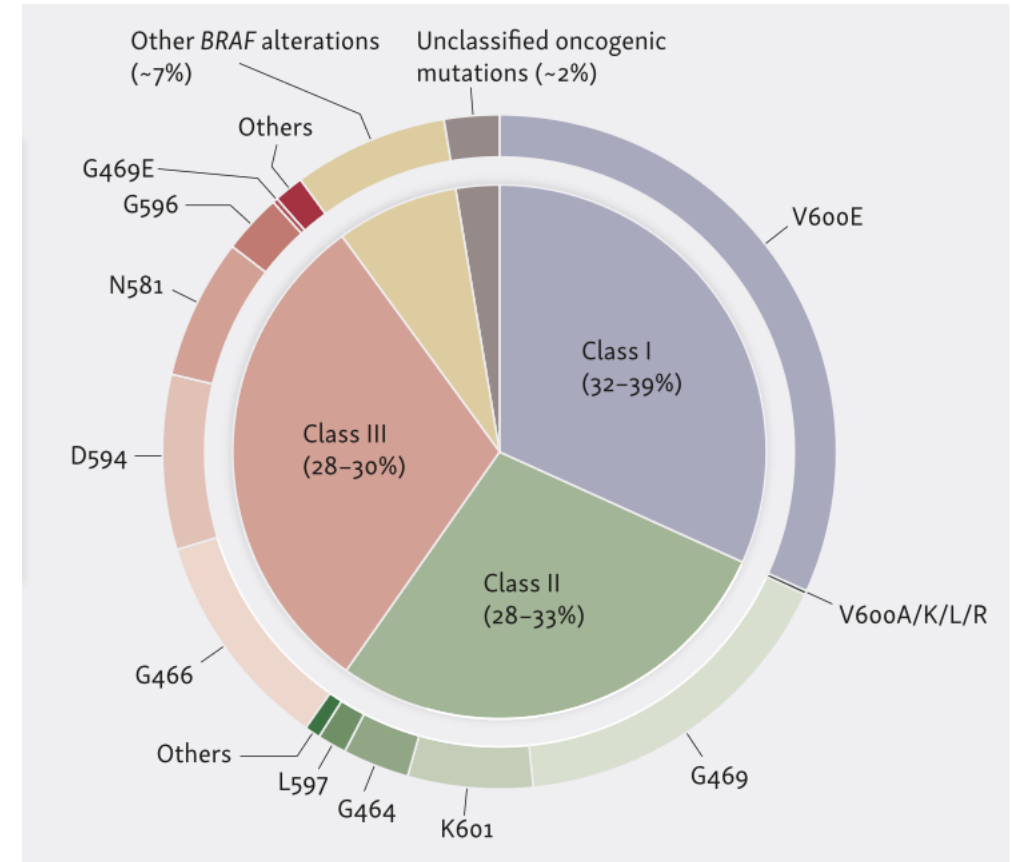
# Frecuencia de mutaciones del gen BRAF en NSCLC

REVIEW ARTICLE



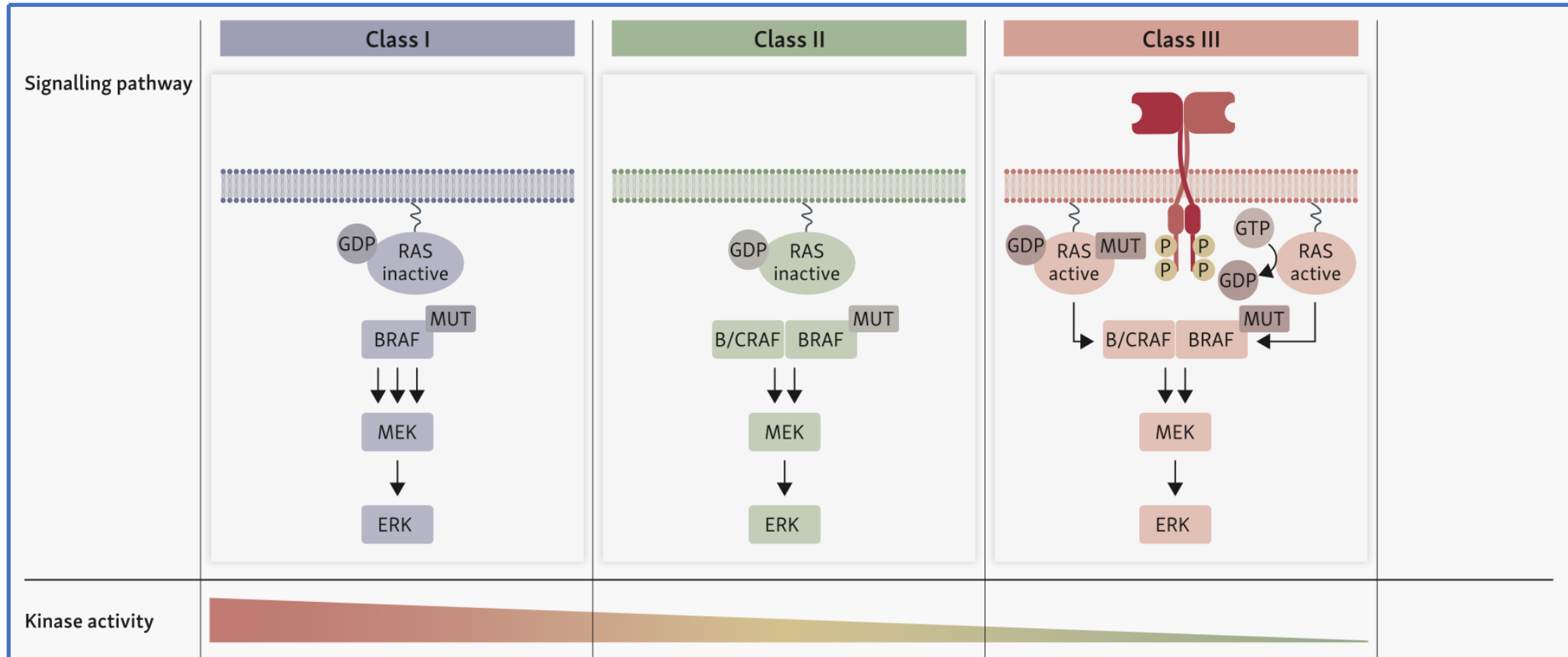
## Biology and Clinical Management of Non-V600 BRAF Alterations in NSCLC

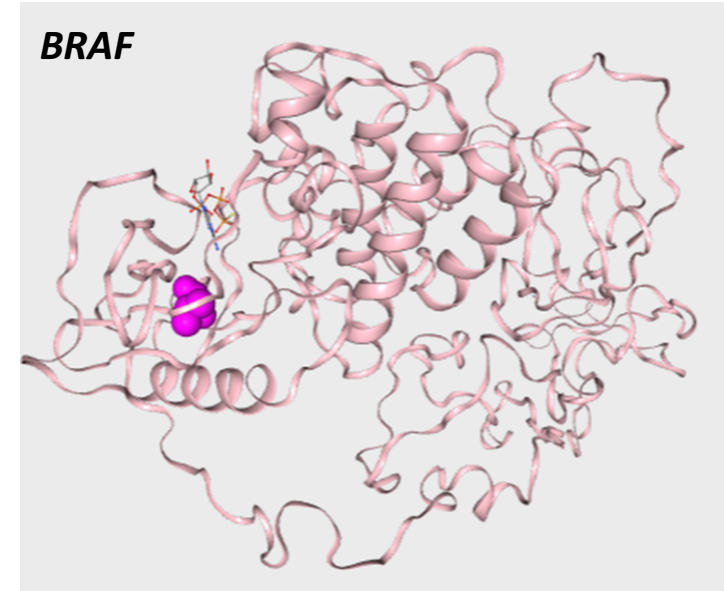
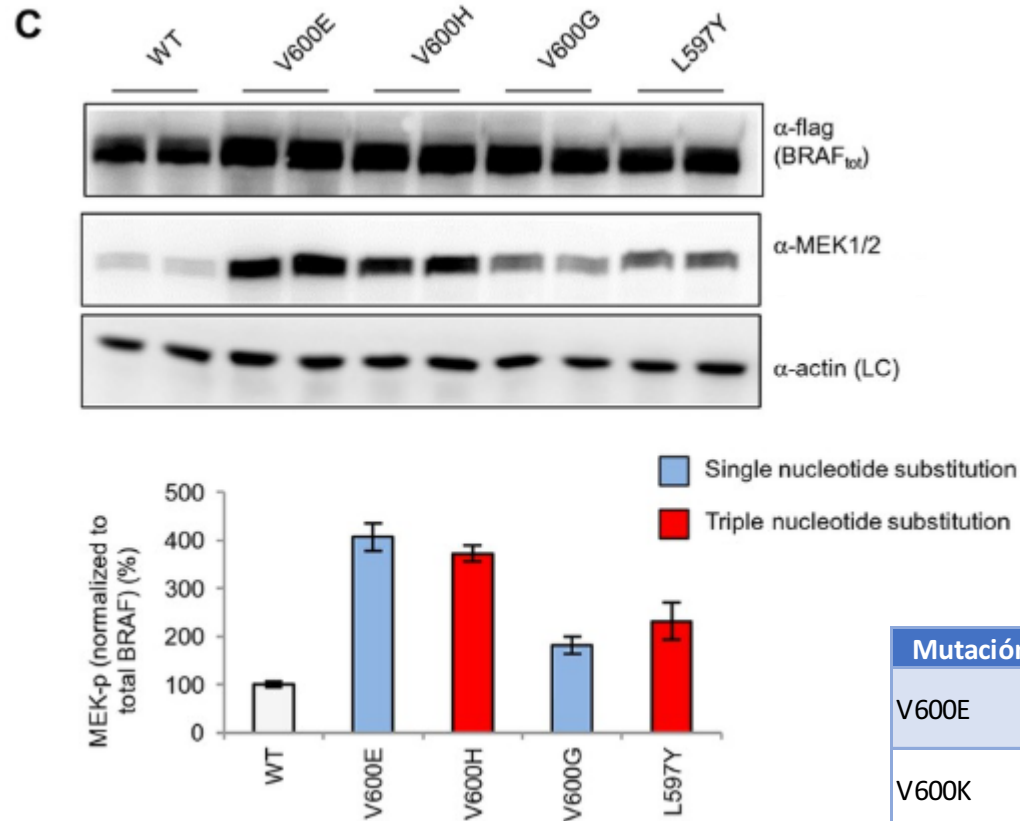
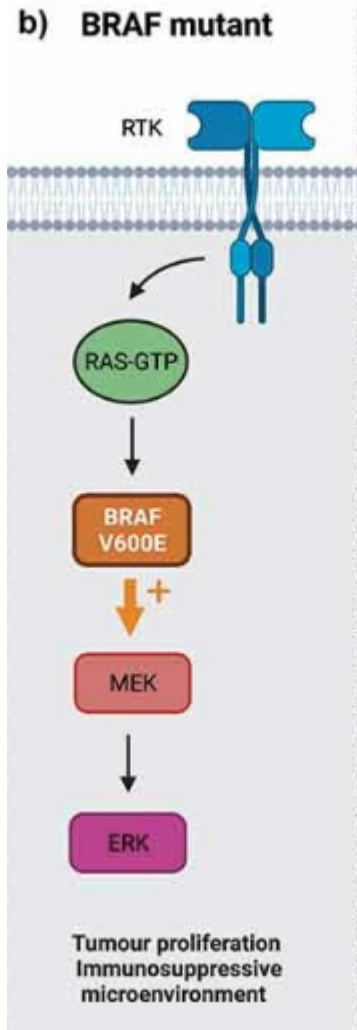
Sandra Ortiz-Cuaran, PhD,<sup>a,\*</sup> Laurine Dupriez, MSc,<sup>b</sup> Constance Nicq, MSc,<sup>a</sup>  
Colin R. Lindsay, MRCP, PhD,<sup>c,d,e</sup> Julien Mazieres, MD, PhD,<sup>f</sup>  
David Santamaría, PhD,<sup>g</sup> Chiara Ambrogio, PhD,<sup>h</sup> Olivier Calvayrac, PhD,<sup>i</sup>  
Cristina Teixido, PhD,<sup>j</sup> Luc Friboulet, PhD,<sup>k</sup> Silvia Novello, MD, PhD,<sup>l</sup>  
Fabrizio Tabbò, MD, PhD,<sup>m</sup> Aurélie Swalduz, MD, PhD,<sup>a,n</sup> Ernest Nadal, MD, PhD,<sup>o</sup>  
David Planchard, MD, PhD,<sup>p,q</sup> Laura Mezquita, MD, PhD,<sup>r</sup>  
Marie-Julie Nokin, PhD,<sup>b</sup>, on behalf of the BOLERO Consortium





# Diferentes clases de mutaciones del gen BRAF





| Mutación   | Activación de BRAF | Autofosforilación | Comentarios                        |
|------------|--------------------|-------------------|------------------------------------|
| V600E      | Alta               | Sí                | Mutación más frecuente y potente   |
| V600K      | Moderada-alta      | Sí, pero variable | Segunda más común, diferente carga |
| V600D      | Variable           | Puede variar      | Menos frecuente                    |
| Otras V600 | Variable           | Variable          | Depende del aminoácido sustituido  |

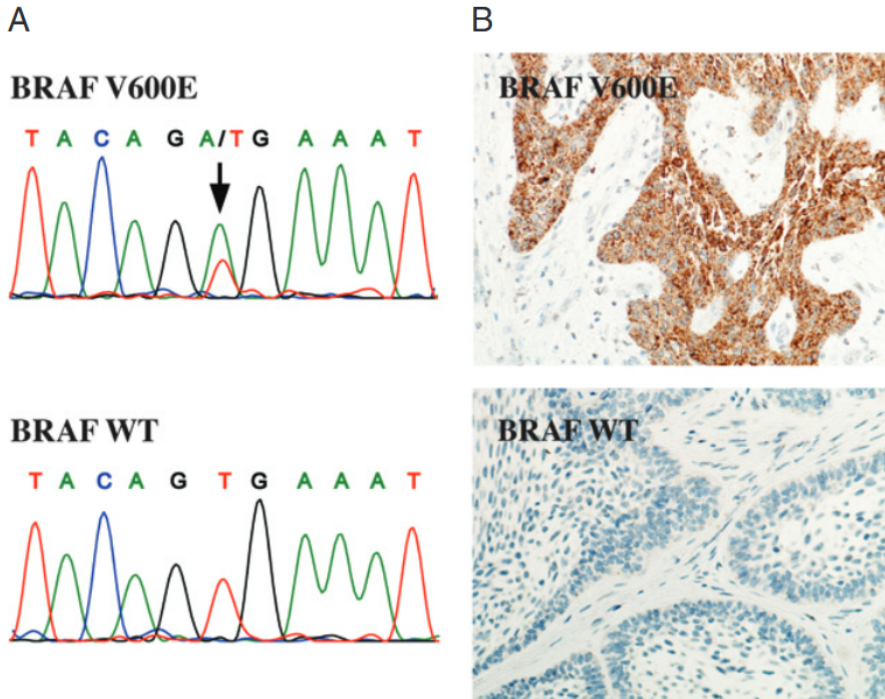
Karoulia Z, et al. An Integrated Model of RAF Inhibitor Action Predicts Inhibitor Activity against Oncogenic BRAF Signaling. *Cancer Cell*. 2016 Sep 12;30(3):485-498.

Heidorn SJ, et al. Kinase-dead BRAF and oncogenic RAS cooperate to drive tumor progression through CRAF. *Cell*. 2010 Jan 22;140(2):209-21.

Adams R, et al. BRAF inhibitors and their immunological effects in malignant melanoma. *Expert Rev Clin Immunol*. 2022 Apr;18(4):347-362

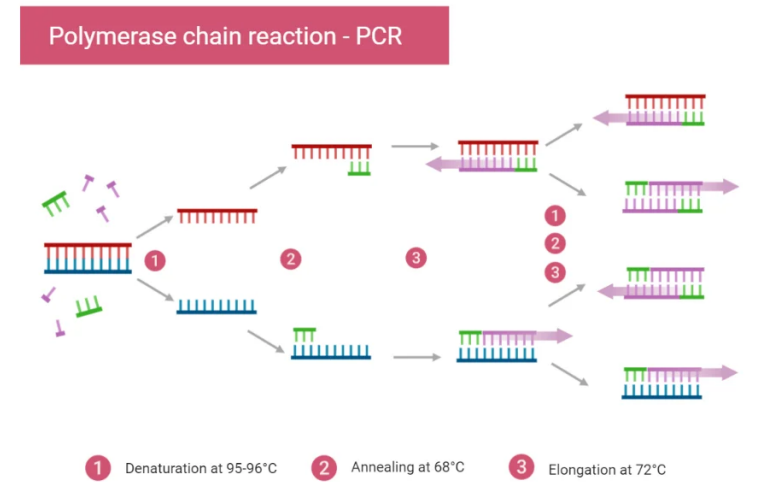


# Como se determinan las mutaciones del gen BRAF



**VS**

## Real Time PCR / quantitative PCR (qPCR)





## Como se determinan las mutaciones de BRAF

| Kit Comercial                                      | Mutaciones detectadas   | Comentarios adicionales  |
|--|---|--|
| <b>Idylla BRAF Mutation Test (Biocartis)</b>       | V600E (también c.1799_1800delinsAA)* - V600D- V600K- V600R- V600M- <b>K601E</b> | Detecta mutaciones principales en codón 600 y K601<br>análisis rápido (~90 min) sin extracción IVD         |
| <b>Cobas BRAF V600 Mutation Test (ROCHE)</b>       | V600E (también c.1799_1800delinsAA)*- V600K- V600D - V600R                      | Detecta mutaciones principales en codón 600<br>Con extracción de ADN y preparación de reactivos IVD        |
| <b>BRAF Mutation Detection Kit (AmoyDx)</b>        | V600E- V600K- V600D- V600R- V600M   | Detecta mutaciones principales en codón 600<br>Con extracción de ADN y reactivos predispensados IVD        |
| <b>Easy® BRAF (Diatech)</b>                        | V600E- V600K- V600D- V600R- V600M- <b>K601E</b>                                 | Detecta mutaciones principales en codón 600 y K601<br>Con extracción de ADN y preparación de reactivos IVD |
| <b>therascreen BRAF RGQ/ Pyro PCR Kit (Qiagen)</b> | V600E (también c.1799_1800delinsAA)*- V600K- V600D - V600R, <b>G464 y G469</b>  | Detecta mutaciones principales en codón 600 y K601<br>Con extracción de ADN y preparación de reactivos IVD |





## DIFERENTES MANERAS DE MIRAR ALTERACIONES DE BRAF

**Table 1**

**Characteristics of the studies included in this meta-analysis.**

| First author | Year | Source of Pts | Methods                | No. of Pts | Mut BRAF (%) | Female (%) | Smokers (%) | ADC (%)     | Stage III/IV (%) |
|--------------|------|---------------|------------------------|------------|--------------|------------|-------------|-------------|------------------|
| Pratilas     | 2008 | 4 countries   | PCR + SEQ/MALDI-TOF MS | 916        | 17 (1.9)     | 577 (63.0) | 614 (67.0)  | 623 (68.0)  | NA               |
| Schmid       | 2009 | Austria       | PCR + SEQ              | 96         | 2 (2.1)      | 38 (39.6)  | 74 (77.1)   | NA          | NA               |
| Lee          | 2010 | Korea         | PCR + SEQ              | 173        | 2 (1.2)      | 60 (34.7)  | 117 (67.6)  | 117 (67.6)  | NA               |
| Kobayashi    | 2011 | Japan         | PCR + SEQ/SSCP         | 581        | 5 (0.9)      | 204 (35.1) | NA          | 382 (65.7)  | 124 (21.3)       |
| Marchetti    | 2011 | Italy         | PCR + SEQ/HRMA         | 1046       | 37 (3.5)     | 187 (25.3) | 542 (73.3)  | 739 (70.7)  | 218 (29.5)       |
| Paik         | 2011 | USA           | MALDI-TOF MS           | 697        | 18 (2.6)     | 452 (65.8) | 386 (56.2)  | NA          | NA               |
| An           | 2012 | China         | HRMA                   | 452        | 7 (1.5)      | NA         | 192 (42.5)  | 307 (67.9)  | NA               |
| Sasaki       | 2012 | Japan         | PCR + SEQ              | 305        | 6 (2.0)      | 148 (56.7) | NA          | NA          | NA               |
| Cardarella   | 2013 | USA           | PCR + SEQ              | 883        | 36 (4.1)     | 148 (50.5) | 229 (78.4)  | 256 (87.4)  | 237 (80.9)       |
| Llie         | 2013 | France        | PCR + SEQ              | 450        | 40 (8.5)     | 158 (35.1) | 403 (89.6)  | NA          | 352 (78.2)       |
| Brustugun    | 2014 | Norway        | PCR                    | 979        | 17 (1.7)     | 476 (48.6) | NA          | 646 (66.0)  | NA               |
| Kinno        | 2014 | Asian         | PCR + SEQ/HRMA         | 2001       | 26 (1.3)     | 935 (46.7) | 844 (42.2)  | 1835 (91.7) | 304 (15.3)       |
| Costa        | 2015 | Spain         | PCR                    | 80         | 2 (2.5)      | 28 (35)    | 64 (80)     | 71 (88.7)   | NA               |
| Luk          | 2014 | Australia     | MALDI-TOF MS           | 273        | 7 (2.6)      | 129 (47.3) | NA          | NA          | NA               |
| Shao         | 2015 | China         | SARMS-PCR              | 89         | 1 (1.1)      | 35 (39.3)  | 39 (43.8)   | 88 (98.9)   | 16 (18.0)        |
| Tissot       | 2016 | France        | PCR + SEQ              | 2690       | 80 (3.0)     | NA         | NA          | NA          | NA               |

**11711 270 (2,3%)**

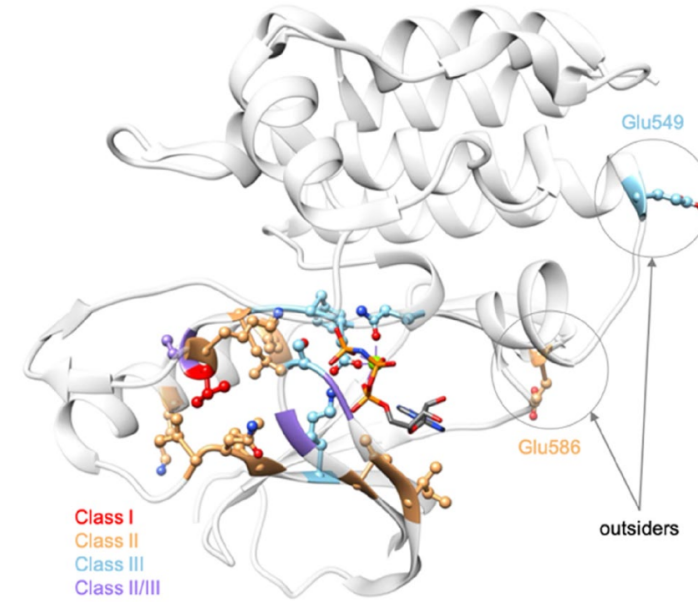
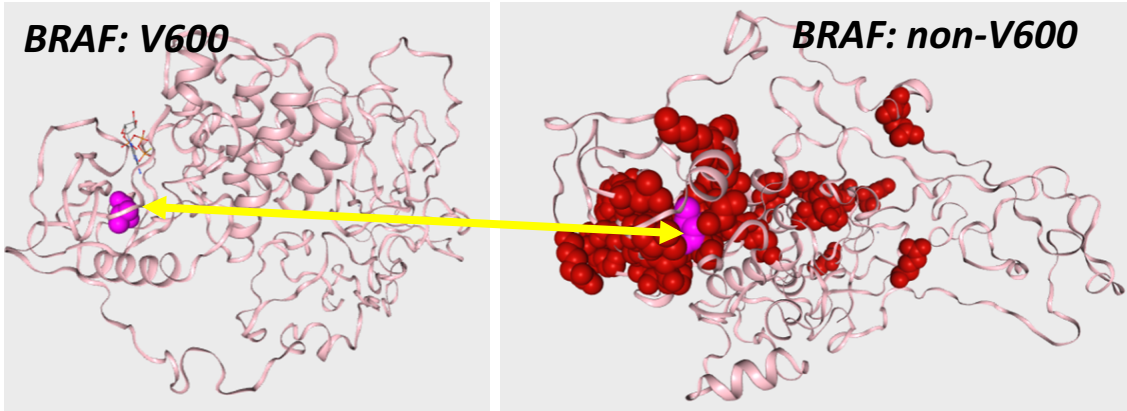
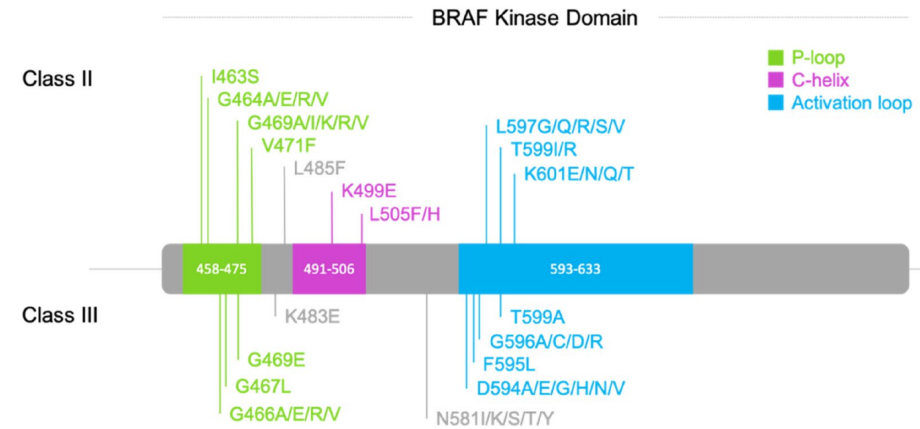


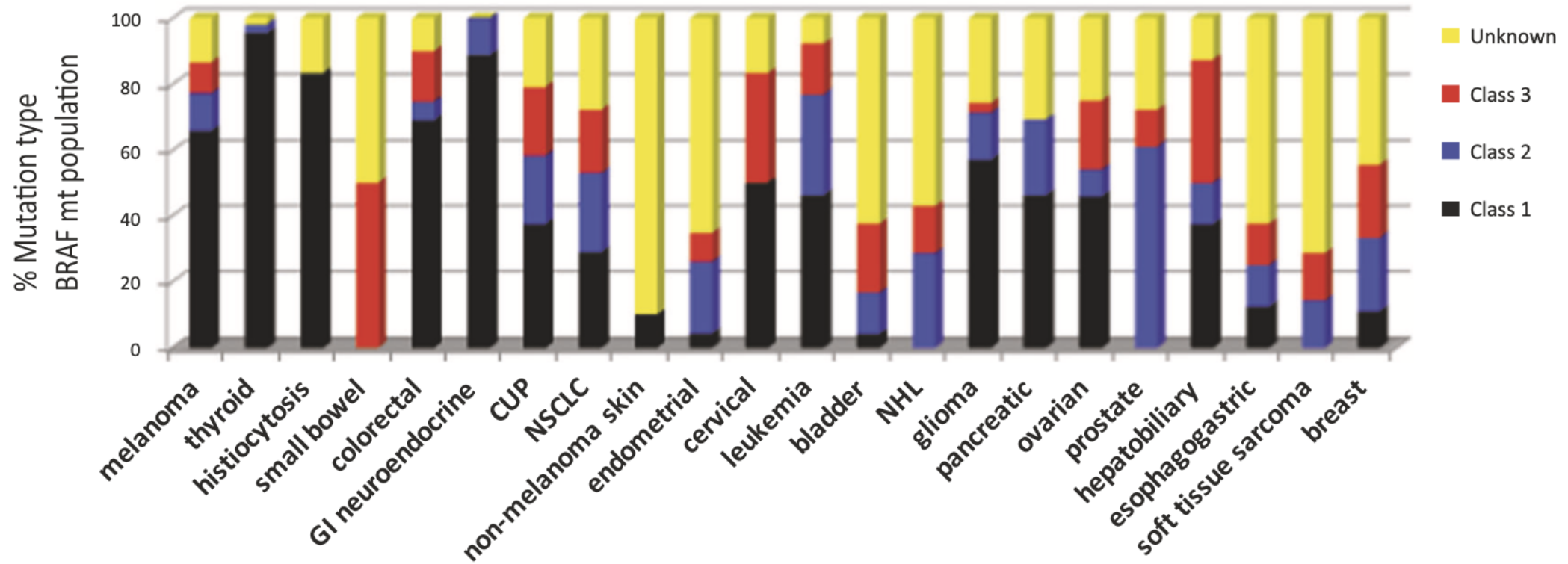
Table 1. Most frequent BRAF mutations in NSCLC.

| Mutation | Class | Nucleotide Change | AA Change | Location in the Protein | Effect                   |
|----------|-------|-------------------|-----------|-------------------------|--------------------------|
| V600E    | I     | 1799              | T>A       | Activation segment      | Activate kinase activity |
| V600K    | I     | 1798_1799         | delinsAA  | Activation segment      | Activate kinase activity |
| V600R    | I     | 1798_1799         | GT>AG     | Activation segment      | Activate kinase activity |
| L597Q    | II    | 1790              | T>A       | Activation segment      | Activate kinase activity |
| L597R    | II    | 1790              | T>G       | Activation segment      | Activate kinase activity |
| K6001E   | II    | 1801              | A>G       | Activation segment      | Activate kinase activity |
| G464V    | II    | 1391              | G>T       | P-loop                  | Activate kinase activity |
| G469A    | II    | 1406              | G>C       | Glycine-rich region     | Activate kinase activity |
| G469E    | II    | 1406              | G>A       | Glycine-rich region     | Unknown                  |
| G469R    | II    | 1405              | G>A       | Glycine-rich region     | Unknown                  |
| G466R    | III   | 1396              | G>A       | P-loop                  | Impaired kinase activity |
| G466A    | III   | 1397              | G>C       | P-loop                  | Activate kinase activity |
| G466V    | III   | 1397              | G>T       | P-loop                  | Impaired kinase activity |
| D594E    | III   | 1782              | T>G       | DFG motif               | Impaired kinase activity |
| D594G    | III   | 1781              | A>G       | DFG motif               | Impaired kinase activity |
| D594H    | III   | 1780              | G>C       | DFG motif               | Impaired kinase activity |
| D594N    | III   | 1780              | G>A       | DFG motif               | Impaired kinase activity |
| N581Sa   | III   | 1742              | A>G       | Catalytic loop          | Activate kinase activity |
| G596R    | III   | 1786              | G>C       | DFG motif               | Impaired kinase activity |



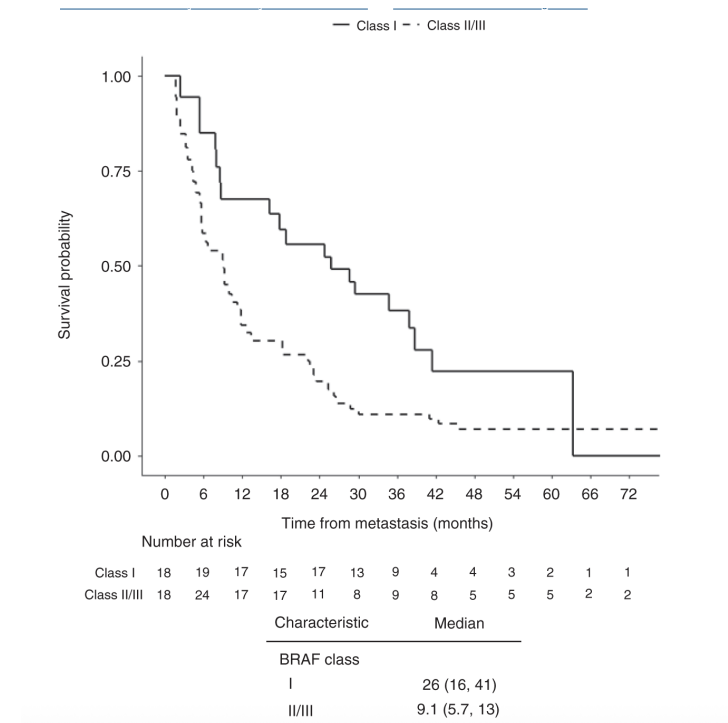
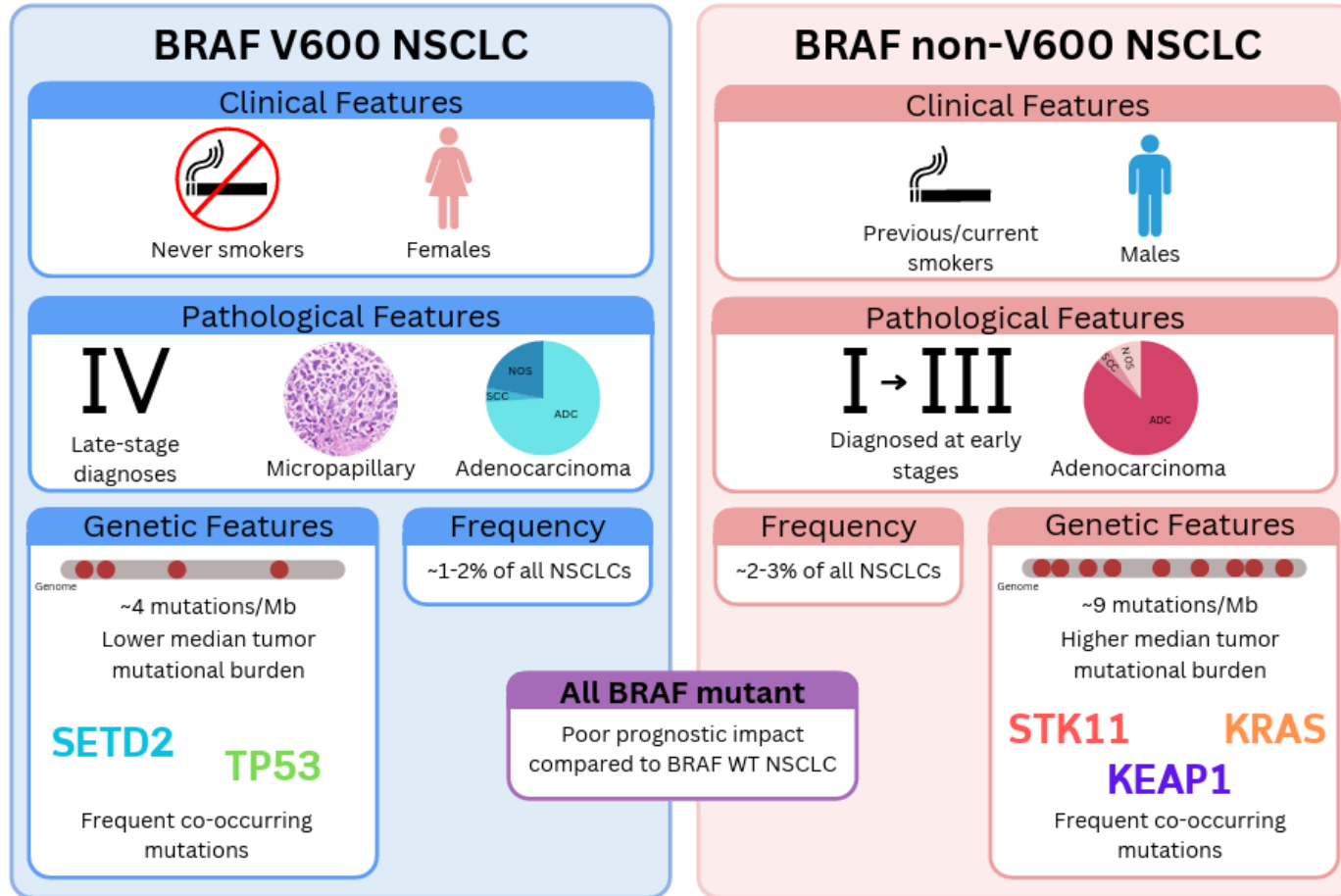


# MUTACIONES DE BRAF EN DIFERENTES TIPOS TUMORALES





# FENOTIPO DIFERENTE EN CANCER DE PULMON





## Case reports of BRAF non-V600 NSCLC.

| BRAF Mutation    | Co-Mutations  | Drug                  | Line | Best Response | PFS             | Case Report                                 |
|------------------|---|-----------------------|------|---------------|-----------------|---|
| <b>G469L</b>     | NR  | Vemurafenib           | 1    | PD            | 2 weeks         | <a href="#">Gautschi et al. [27]</a>        |
| <b>G469A</b>     | TP53  | Dabrafenib/tramet     | 4    | SD            | 6 months        | <a href="#">Dagogo-Jack et al. [28]</a>     |
| <b>G469V</b>     | <i>APC</i> and <i>CHD2</i> mutations;<br><i>NFKBIA</i> and <i>NKX2-1</i> ampl.  | Dabrafenib/trametinib | 2    |               | 9 weeks         | <a href="#">Negrao et al. [18]</a>          |
| <b>L597R</b>     | none  | Dabrafenib/trametinib | 2    | PR            | NR at 12 months | <a href="#">Negrao et al. [18]</a>          |
| <b>D594G</b>     | <i>TP53</i> H193L   | trametinib            | 4    | SD            | 4 months        | <a href="#">Negrao et al. [18]</a>          |
| <b>W604C</b>     | none  | Dabrafenib/trametinib | 1    | PR            | NR at 15 months | <a href="#">Reyes et al. [29]</a>           |
| <b>G469R</b>     | <i>TP53</i> , <i>STK11</i> , <i>ATK11</i> mutations;<br><i>PI3KCA</i> , <i>PDGFRA</i> , <i>Kit</i> , <i>KDR</i> <i>CDKN2A</i><br>ampl/loss. | Sorafenib             | 8    | PR            | 6 months        | <a href="#">Sereno et al. [30]</a>          |
| <b>p.T599dup</b> | none  | Dabrafenib/trametinib | 1    | PR            | NR at 4 months  | <a href="#">Turshudzhyan et al. [31]</a>    |
| <b>p.T599dup</b> | <i>TP53</i> , <i>BRCA2</i> and <i>CTNNB1</i>  | Dabrafenib/trametinib | 1    | SD            | 8 months        | <a href="#">Jiang et al. [32]</a>           |
| <b>G596R</b>     | NR  | CT-IO                 | 1    | PR            | 6 months        | <a href="#">Lazar et al. [33]</a>           |
| <b>G464V</b>     | NR  | CT                    | 1    | PD            | 2 weeks         | <a href="#">Lazar et al. [33]</a>           |
| <b>G469V</b>     | NR  | CT-IO                 | 1    | PR            | NR at 18 weeks  | <a href="#">Lazar et al. [33]</a>           |
| <b>G469A</b>     | NR  | IO                    | 2    | PR            | NR at 4 years   | <a href="#">Rittberg et al. [34]</a>        |
| <b>E501Q</b>     | none  | CT-IO                 | 1    | PR            | NR at 3 years   | <a href="#">Do et al. [35]</a>              |
| <b>K601E</b>     | <i>EGFR</i> , <i>RICTOR</i>   | Dabrafenib/trametinib | 1    | PR            | 9 months        | <a href="#">Su et al. [36]</a>              |
| <b>G469V</b>     | none  | Sorafenib             | 2    | PR            | 13 months       | <a href="#">Casadei-Gardini et al. [37]</a> |
| <b>K601E</b>     | <i>FGFR4</i> and <i>ALK VUS</i>   | trametinib            | 3    | PR            | 4 months        | <a href="#">Saalfeld et al. [38]</a>        |
| <b>G466R</b>     | <i>NF1</i> <i>I70fs*15</i>  | Dabrafenib/trametinib | 3    | PD            | 3 months        | <a href="#">Citarella et al. [39]</a>       |

PFS = progression-free survival, PD = progression disease, SD = stable disease, PR = partial response, CR = complete response, NGS = next-generation sequencing, NR = not reached



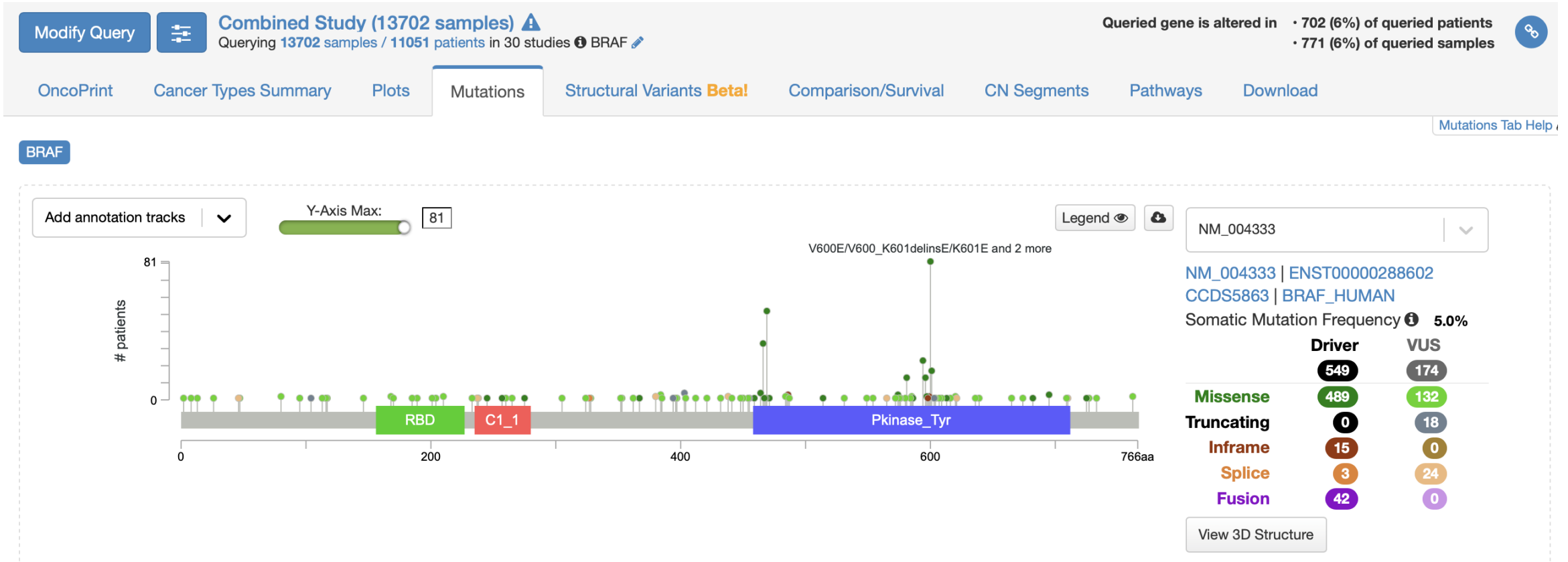
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| Kit Comercial  | Mutaciones detectadas  | Comentarios adicionales   |
|--|--|---|
| <b>Idylla BRAF Mutation Test (Biocartis)</b>               | V600E (también c.1799_1800delinsAA)* - V600D- V600K- V600R- V600M- <b>K601E</b>                      | Detecta mutaciones principales en codón 600 y K601<br>análisis rápido (~90 min) sin extracción<br>IVD         |
| <b>Cobas BRAF V600 Mutation Test (ROCHE)</b>               | V600E (también c.1799_1800delinsAA)*- V600K- V600D - V600R   | Detecta mutaciones principales en codón 600<br>Con extracción de ADN y preparación de reactivos<br>IVD        |
| <b>BRAF Mutation Detection Kit (AmoyDx)</b>                | V600E- V600K- V600D- V600R- V600M-V600A<br>V600E2-V600D2   | Detecta mutaciones principales en codón 600<br>Con extracción de ADN y reactivos predispensados<br>IVD        |
| <b>Easy® BRAF (Diatech)</b>                                | V600E- V600K- V600D- V600R- V600M- <b>K601E</b>  | Detecta mutaciones principales en codón 600 y K601<br>Con extracción de ADN y preparación de reactivos<br>IVD |
| <b>therascreen BRAF RGQ/ Pyro PCR Kit (Qiagen)</b>         | V600E (también c.1799_1800delinsAA)*- V600K- V600D - V600R, <b>K601E, G464 y G469</b>                | Detecta mutaciones principales en codón 600 y K601<br>Con extracción de ADN y preparación de reactivos<br>IVD |
| <b>NRAS-BRAF Mutation Test™ (Roche Diagnostics)(ROCHE)</b> | V600E (también c.1799_1800delinsAA)*- V600K- V600D - V600R, <b>G466A, G466V, G469A, G469R, G469V</b> | Detecta mutaciones principales en exón 11 y 15<br>Con extracción de ADN y preparación de reactivos<br>RUO     |





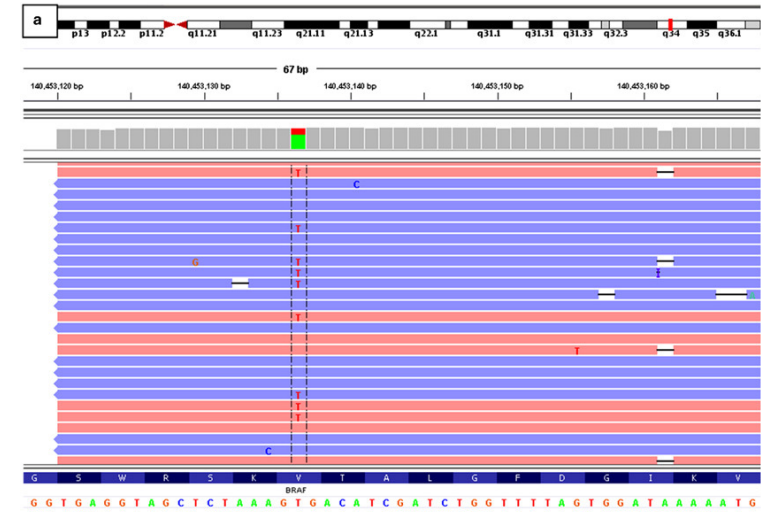
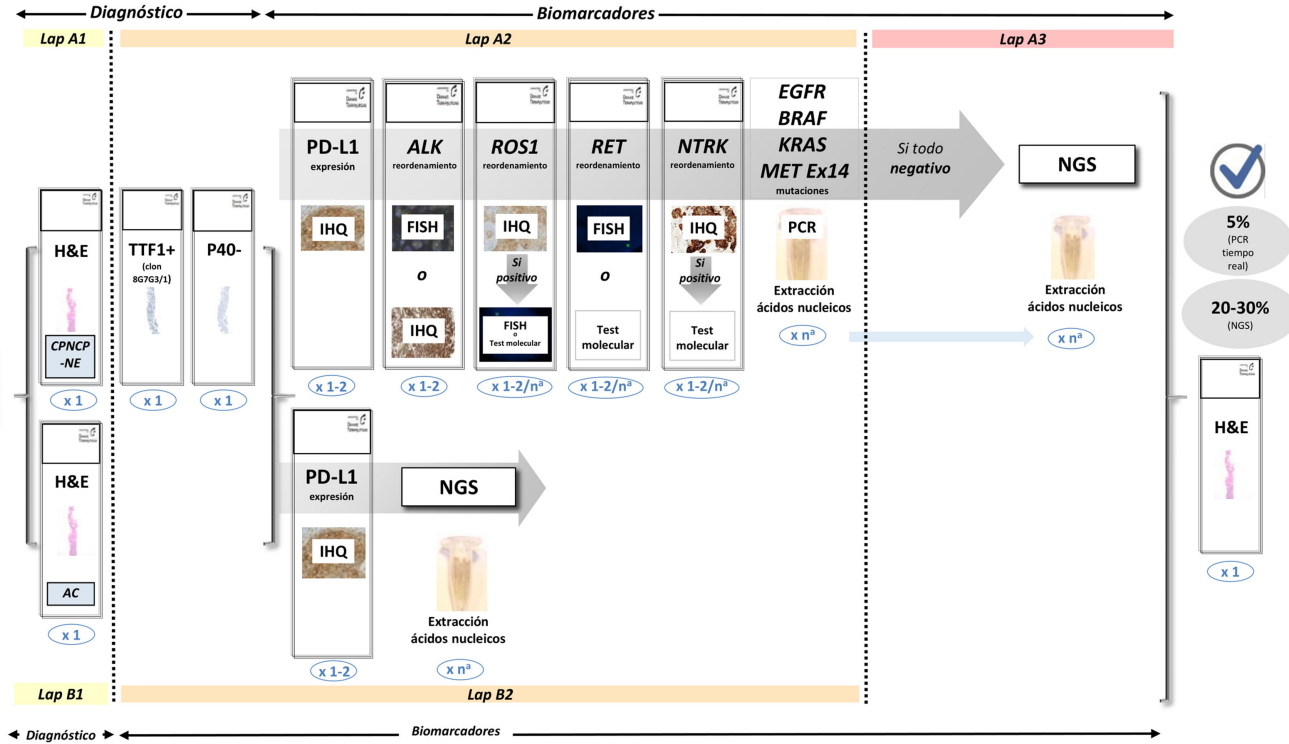
# Mutaciones del gen BRAF en Cancer de pulmón



Tasa de mutación BRAF en pulmón: 6%

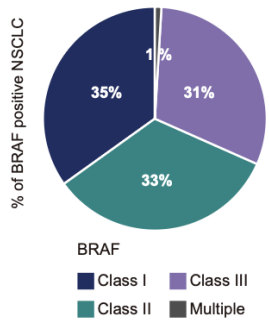
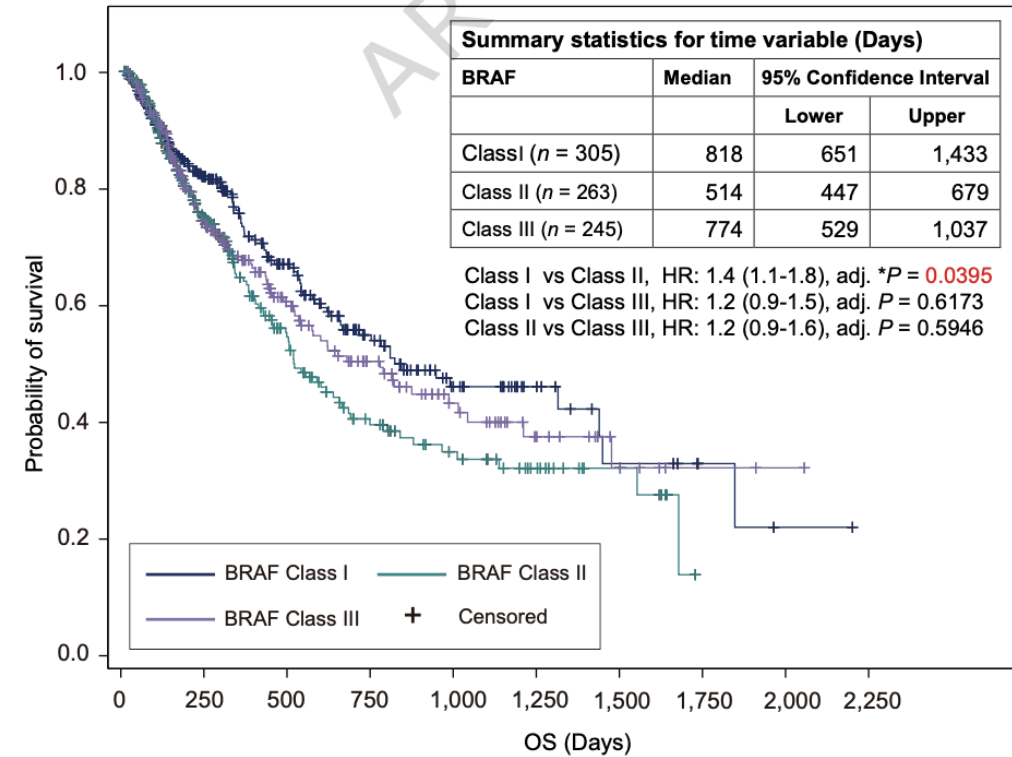
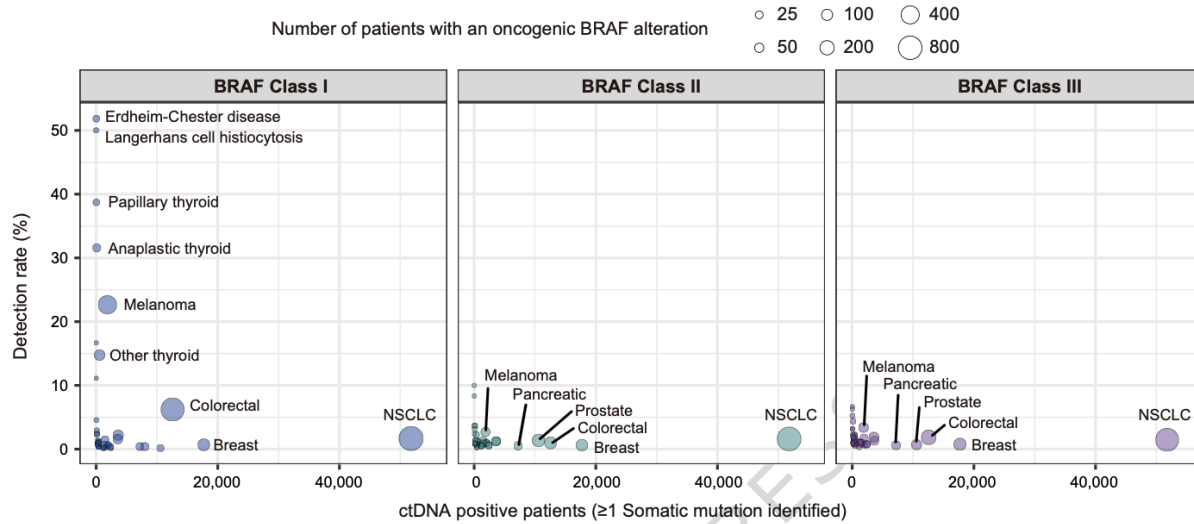


# NGS





# NGS EN BIOPSIA LIQUIDA



**d**

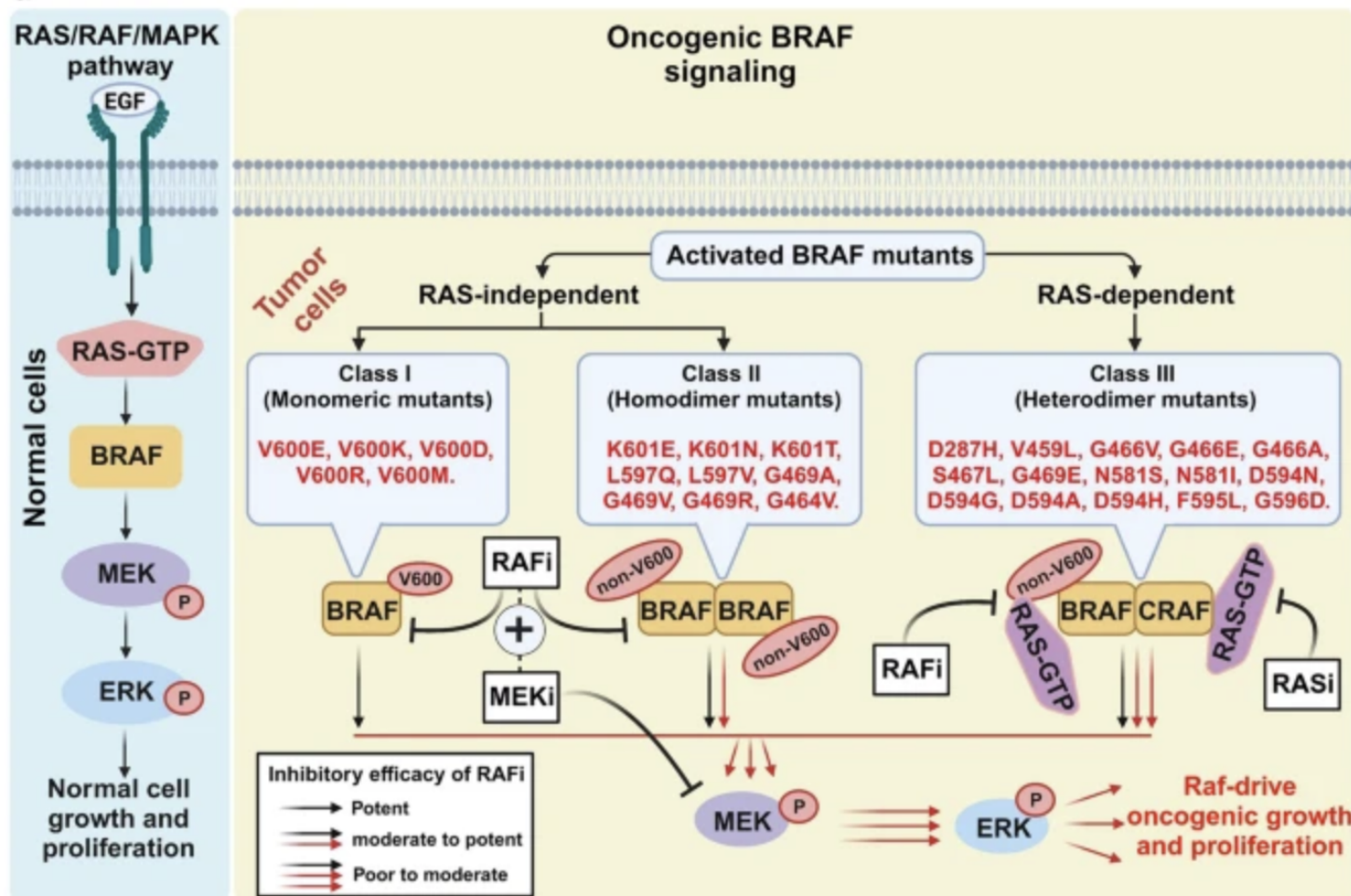
| BRAF Class          | First Line Regimen (top 3)               | Frequency | Percent |
|---------------------|--|-----------|---------|
| Class I (n = 307)   | trametinib + dabrafenib                  | 73        | 23.8    |
|                     | pembrolizumab                            | 45        | 14.7    |
|                     | carboplatin + pemetrexed + pembrolizumab | 33        | 10.8    |
| Class II (n = 271)  | carboplatin + pemetrexed + pembrolizumab | 53        | 19.6    |
|                     | pembrolizumab                            | 41        | 15.1    |
| Class III (n = 271) | carboplatin + pemetrexed                 | 27        | 10.0    |
|                     | carboplatin + pemetrexed + pembrolizumab | 45        | 17.9    |
|                     | pembrolizumab                            | 44        | 17.5    |
|                     | carboplatin + pemetrexed                 | 27        | 10.8    |

51,783 lung cancer patients with detectable ctDNA  
 2,398 patients (4.63%)

Manabe, T., et al. Nat Commun (2026).



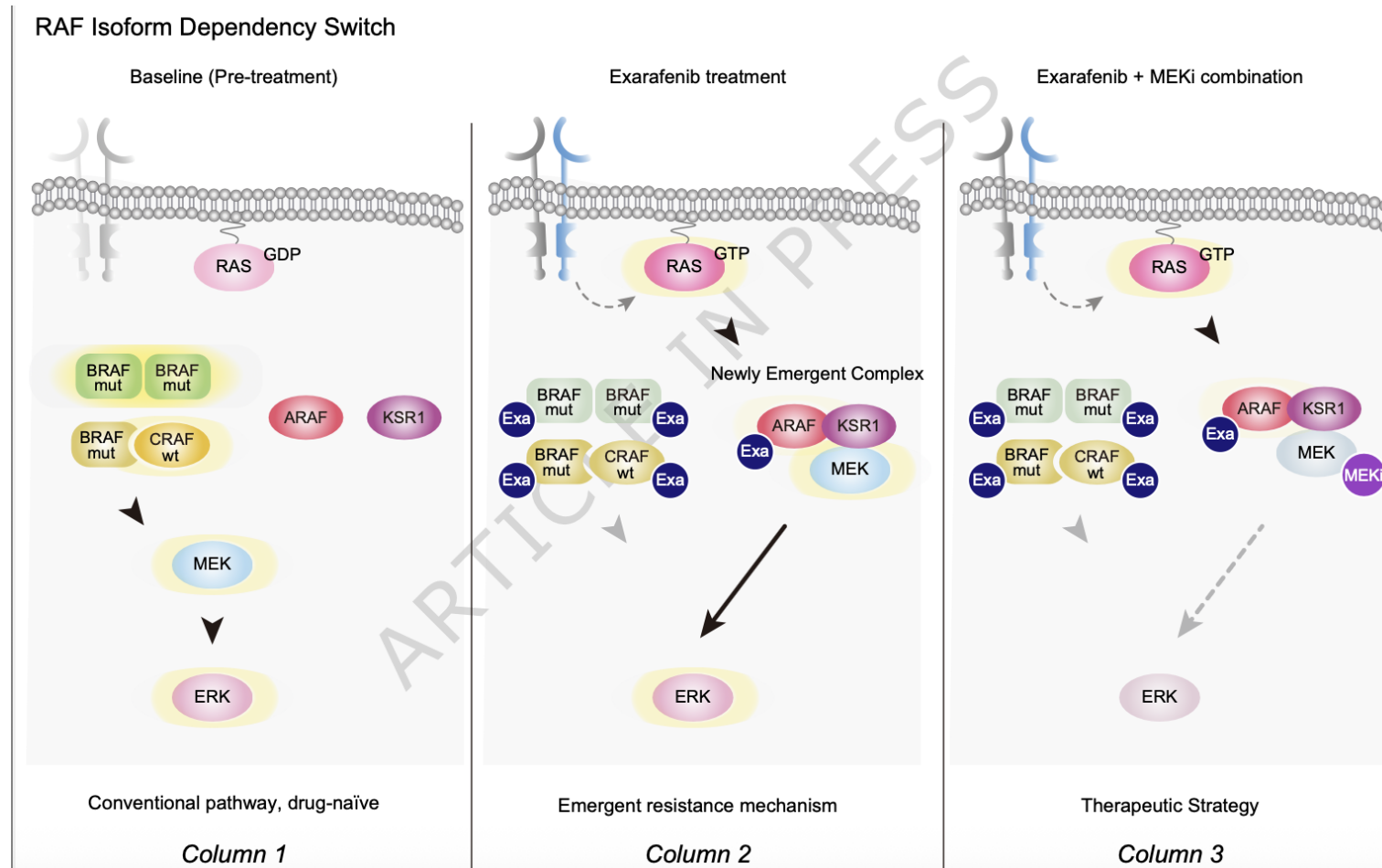
## Tratamientos dirigidos dependiendo del tipo de mutación de BRAF



Uso de diferentes Inhibidores  
RAF  
MEK  
RAS

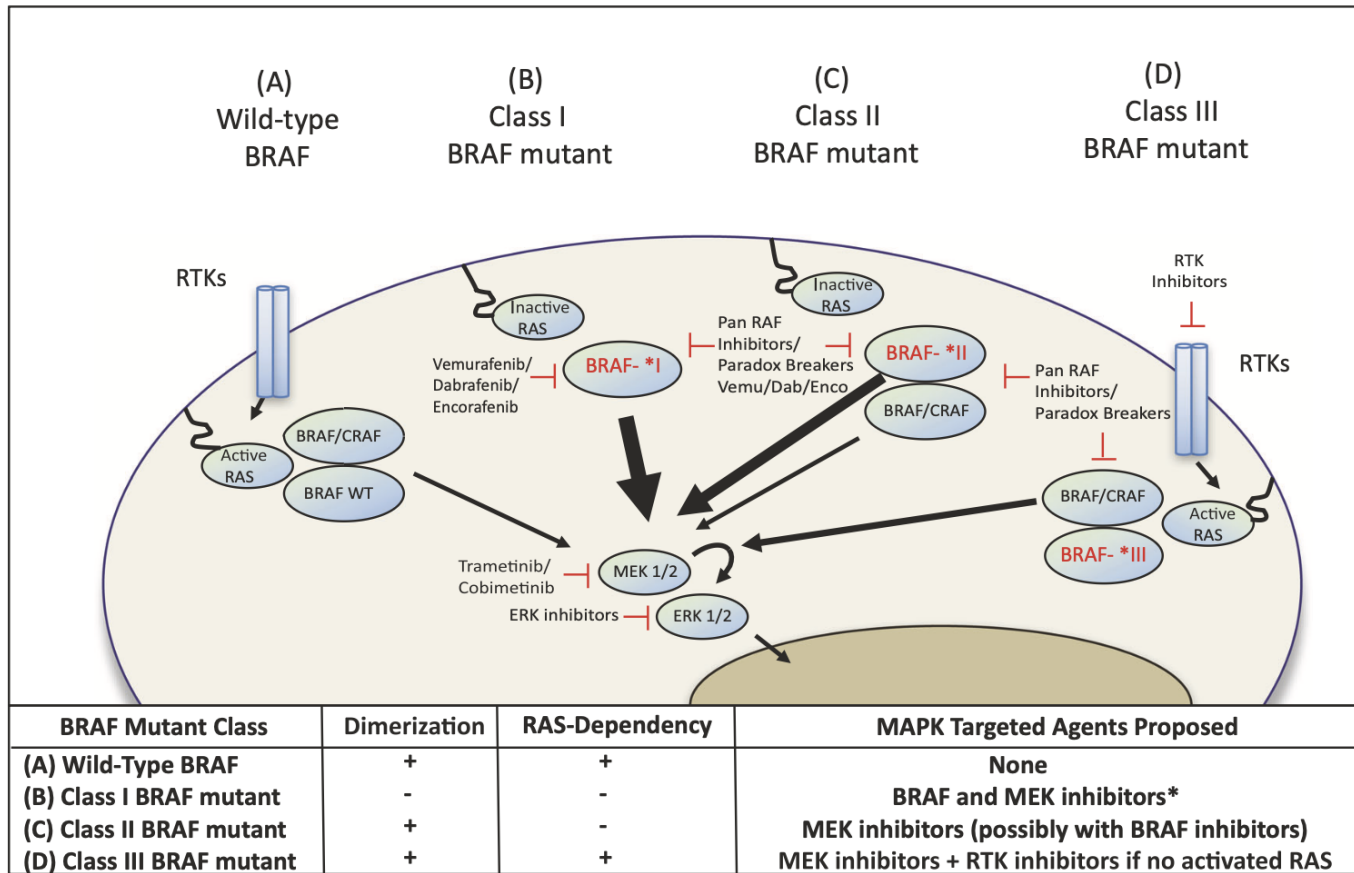


## Tratamientos dirigidos frente a BRAF, atención a las resistencias

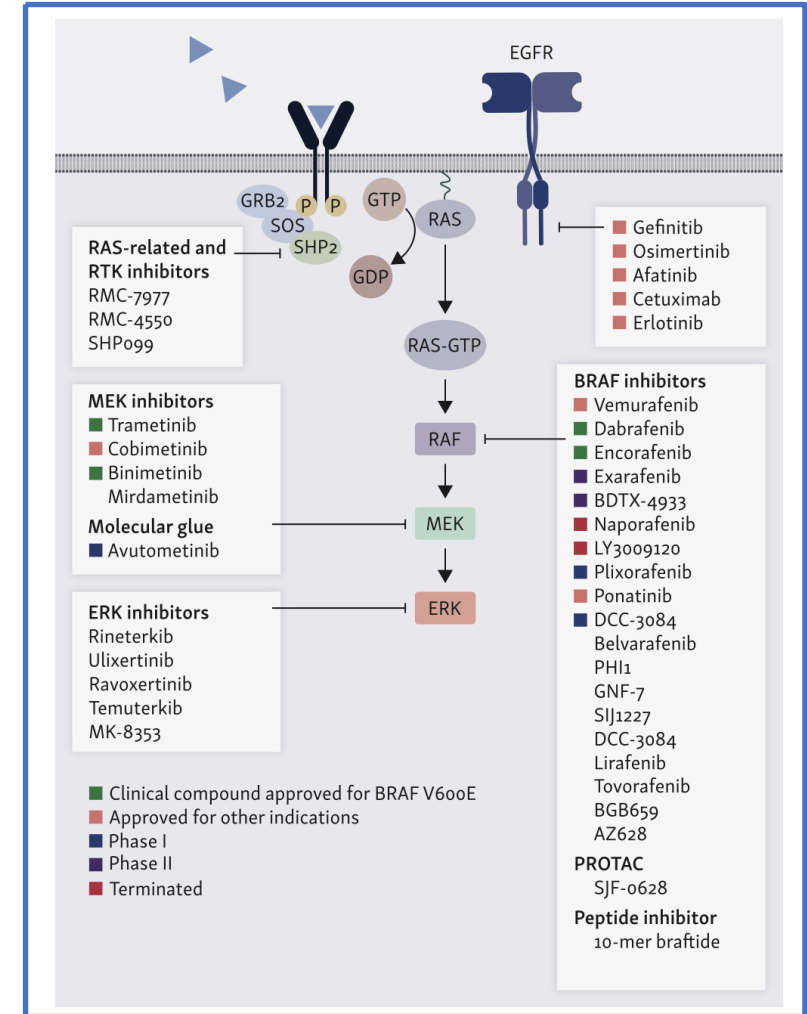




# NUEVOS ABORDAJES TERAPEUTICOS

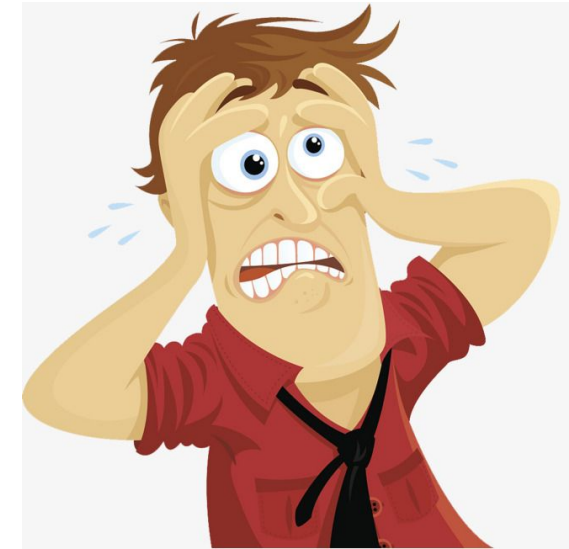
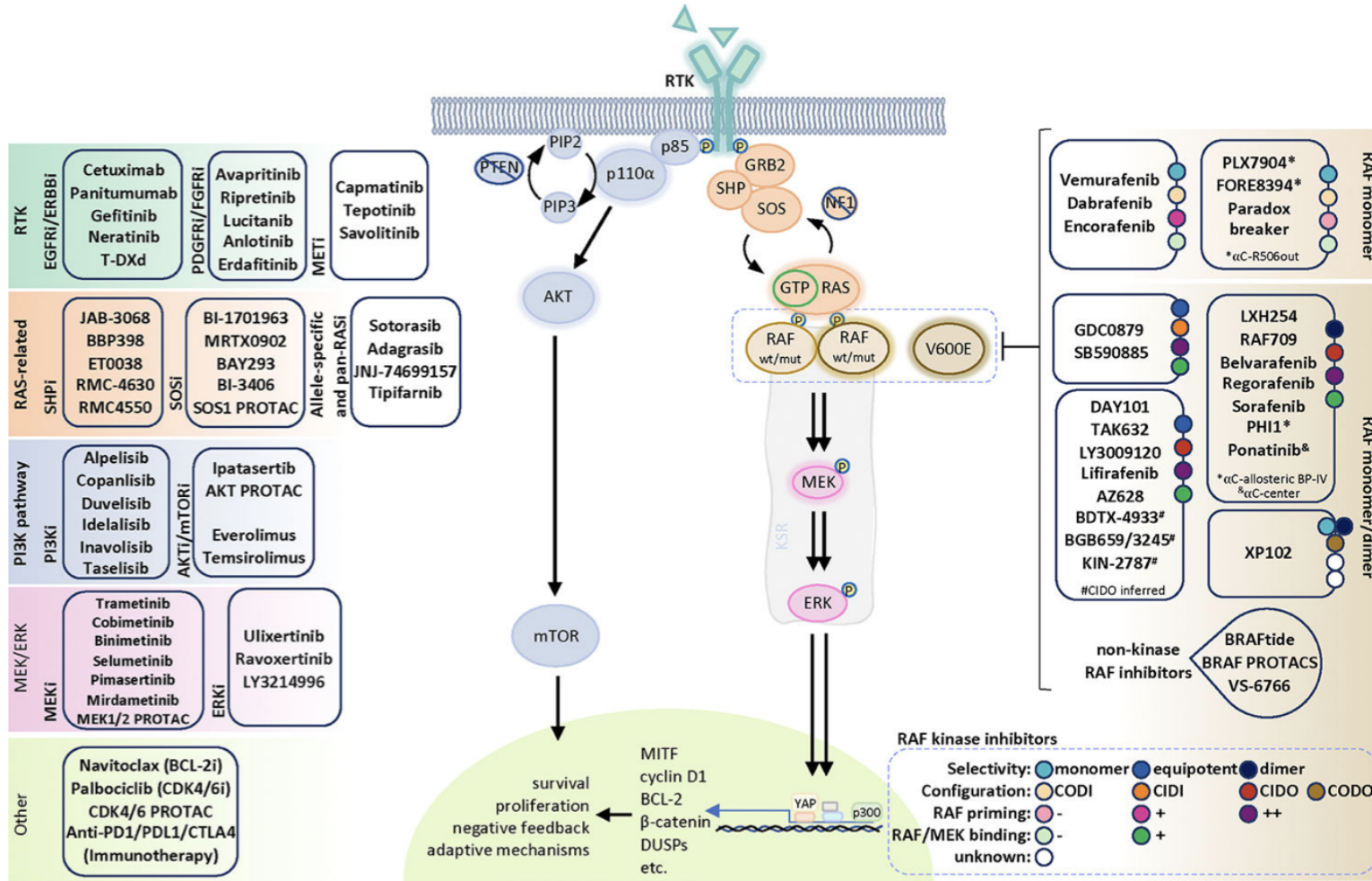


\*CRC is an exception due to frequent upstream activation of RAS by receptor tyrosine kinases that promotes BRAF dimerization. Class I BRAF mutant CRC are refractory to BRAF inhibitors for this reason.



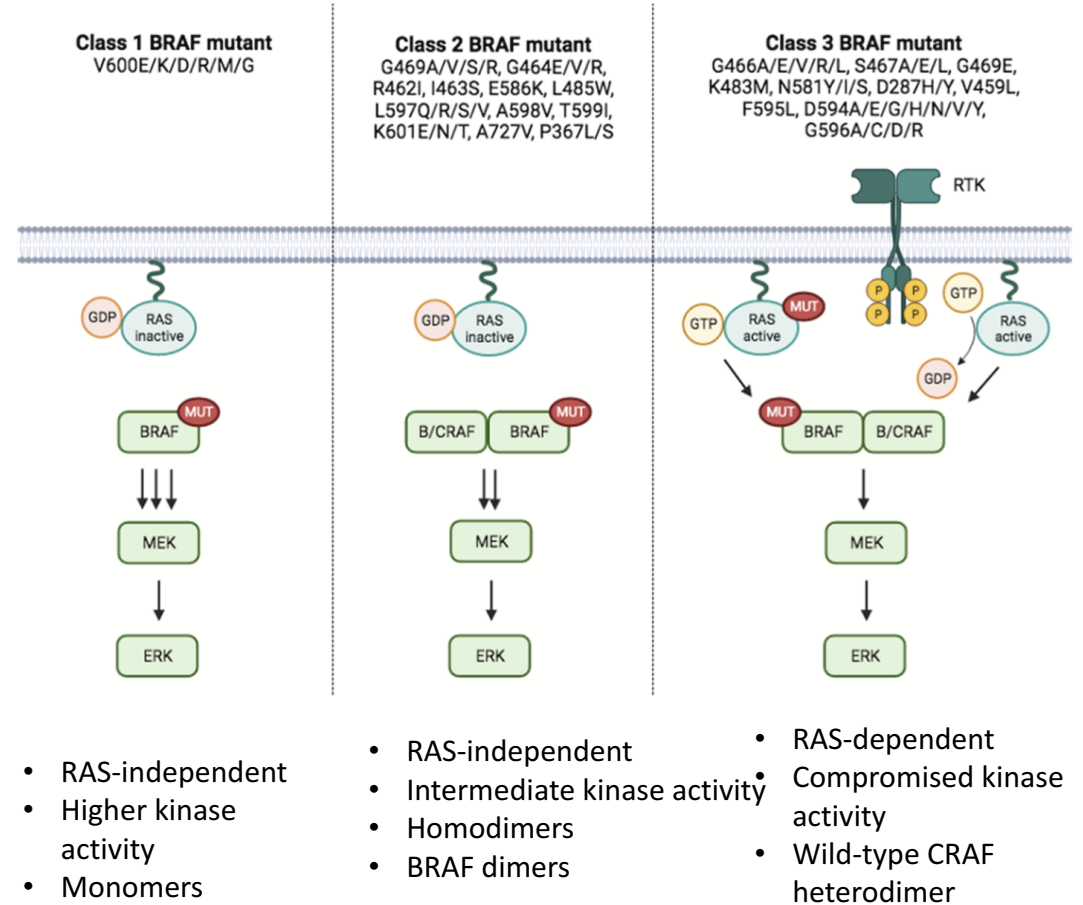


# NUEVOS ABORDAJES TERAPEUTICOS



# CONCLUSIONES

- Existen 3 clases de mutaciones del gen BRAF
- La detección de dichas mutaciones se debe hacer mediante técnicas basadas en NGS tanto en tumor solido como biopsia Liquida
- Conocer dichas alteraciones, abre la puerta para el uso de fármacos dirigidos de manera combinada a dichas vias de señalización.



# GRACIAS!

II JORNADA TRASLACIONAL  
DE ONCOLOGÍA DE PRECISIÓN: A TRAVÉS DE LAS VÍAS  
DE SEÑALIZACIÓN  
SEVILLA, 6 Y 7  
DE FEBRERO DE 2025

