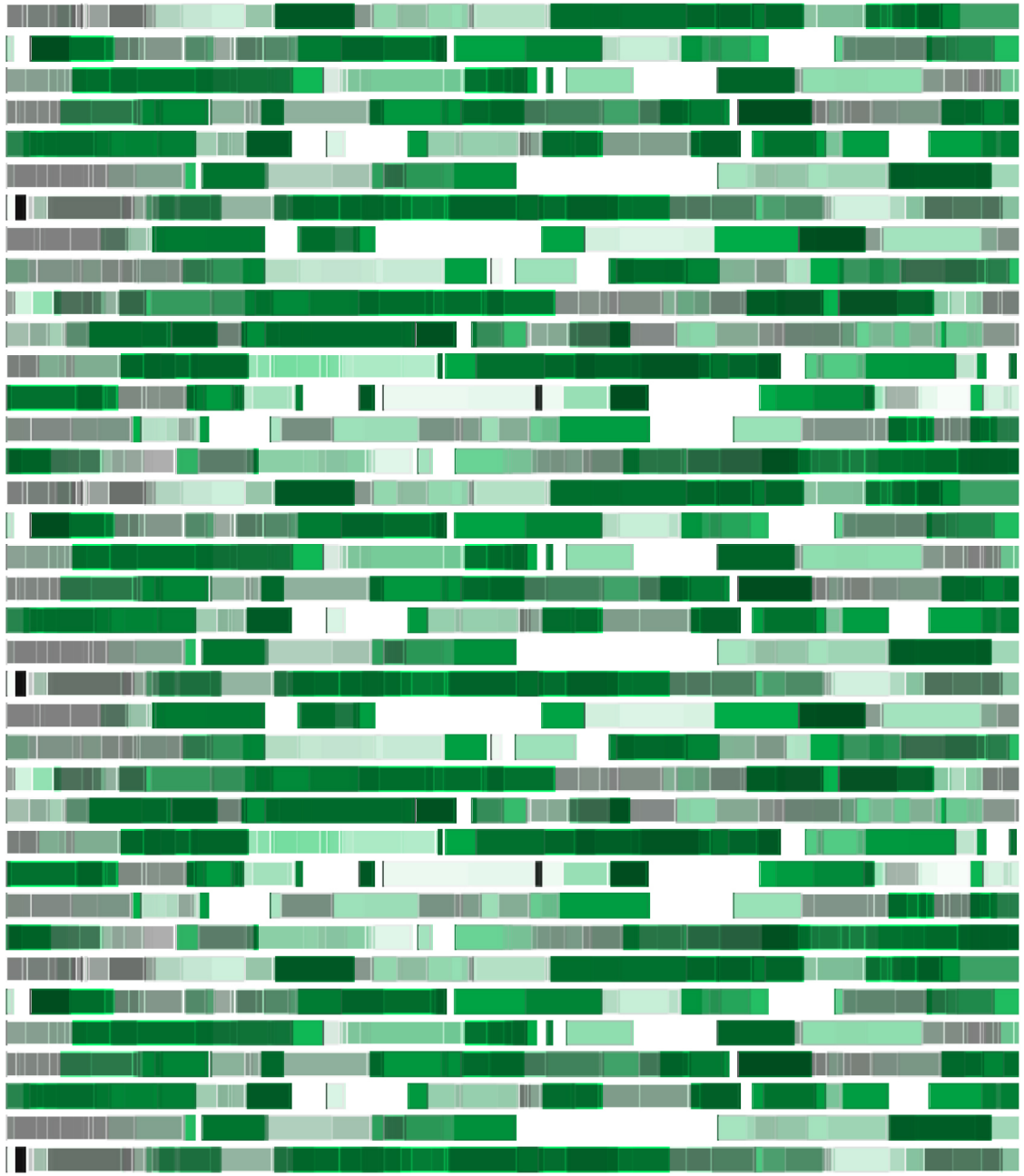
III JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:

A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 12 Y 13 DE FEBRERO DE 2026



¿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

Organizador por:

HENDERE HEALTHCARE

- Consultant or Advisory Role: Novartis, AstraZeneca, Boehringer-Ingelheim, Roche, BMS, Lilly, MSD, Takeda, Phyzer, Kyowa, Sanofi,Jansen
- Research Funding: BMS
- Speaking: Novartis, AstraZeneca, Boehringer-Ingelheim, Roche, BMS, Lilly, MSD, Takeda, Kyowa, Pierre-fabre, Novocure, Sanofi, Jansen

Mutación BRAF en cáncer pulmón. Aspectos controvertidos

.- Inhibidores de BRAF para todos?

.- Cuál es la mejor combinación?

.- Papel de Quimio-inmunoterapia

.- Cual es la mejor estrategia en primera línea?

.- Perfiles determinados de pacientes para QT+IO o BRAF TKI en primera línea?

.- Mecanismos de resistencia

Mutación BRAF en cáncer pulmón. Aspectos controvertidos

.- Inhibidores de BRAF para todos?

.- Cuál es la mejor combinación?

.- Papel de Quimio-inmunoterapia

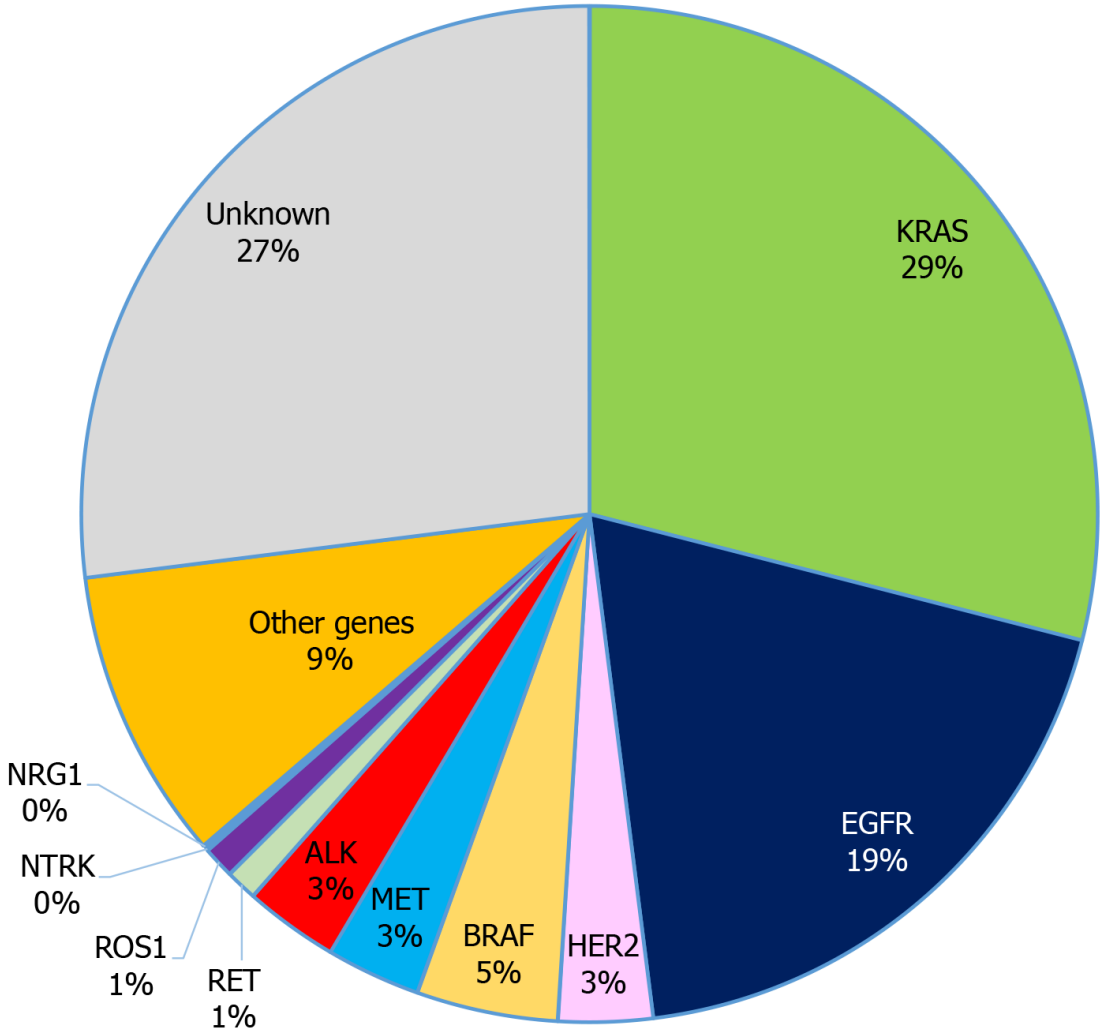
.- Cual es la mejor estrategia en primera línea?

.- Perfiles determinados de pacientes para QT+IO o BRAF TKI en primera línea?

.- Mecanismos de resistencia

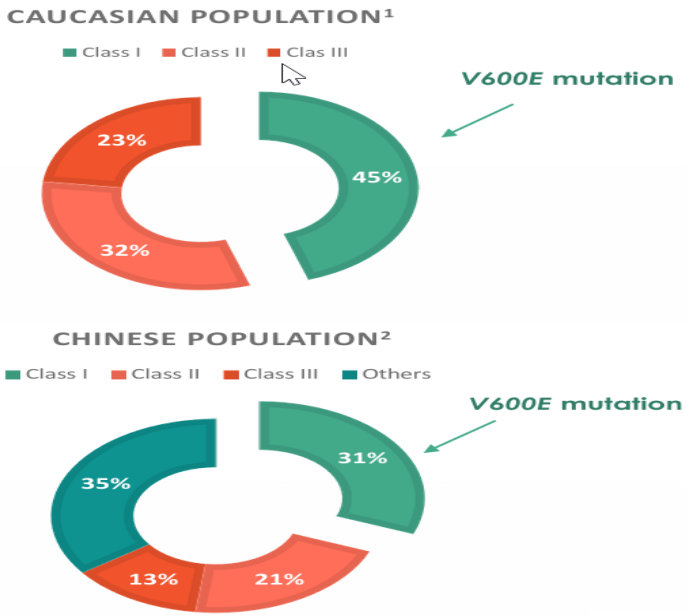
MUTACIONES ONCOGÉNICAS EN NSCLC

- NSCLC es el subtipo de cáncer de pulmón más frecuente (en torno al 80-85% de los casos diagnosticados). 1
- La mutación en **KRAS** es la mutación oncogénica más común en NSCLC. 1
- La mutación **BRAF** tiene una incidencia en torno al 1-5% (~2%) en NSCLC según algunas series. 1-2 El 50% son de clase I tipo **V600E**. 3
- Las mutaciones **BRAFV600** son generalmente mutuamente excluyentes con EGFR y KRAS, así como reordenamientos de ALK y ROS-1. 4



1.Chevallier M, et al. *World J Clin Oncol.* 2021;12(4):217-237; 2. O'Leary CG, et al. Transl Lung Cancer Res. 2019;8(6):1119-1124; 3. Bustamente J. et al. Agents to treat BRAF-mutant lung cancer, Drugs in context, 2019;8:212566; 4. Planchard D, et al. Ann Oncol. 2018;29:iv192-iv237..

CARACTERÍSTICAS CLÍNICAS MUTACIÓN BRAF V600E NSCLC



BRAF V600 NSCLC

Clinical Features
- Never smokers
- Females

Pathological Features
- IV — Late-stage diagnoses
- Micropapillary
- Adenocarcinoma (NOS, SCC, ADC)

Genetic Features
- ~4 mutations/Mb
- Lower median tumor mutational burden
- SETD2, TP53
- Frequent co-occurring mutations

Frequency
- ~1-2% of all NSCLCs

All BRAF mutant
- Poor prognostic impact compared to BRAF WT NSCLC

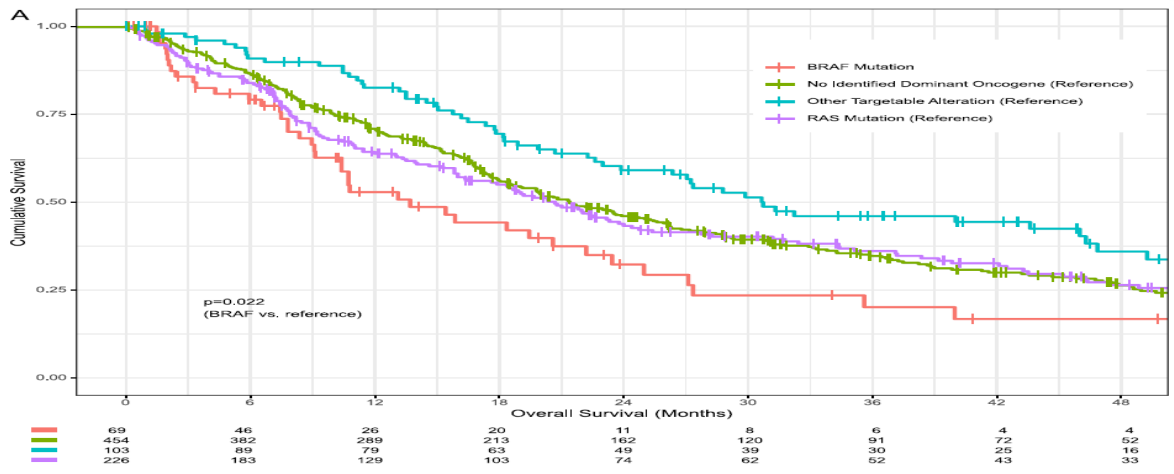
BRAF non-V600 NSCLC

Clinical Features
- Previous/current smokers
- Males

Pathological Features
- I → III — Diagnosed at early stages
- Adenocarcinoma (NOS, SCC, ADC)

Frequency
- ~2-3% of all NSCLCs

Genetic Features
- ~9 mutations/Mb
- Higher median tumor mutational burden
- STK11, KRAS, KEAP1
- Frequent co-occurring mutations



1. Ibiayi D et al. Clin Cancer Res; 25(1) January 1, 2019. 2. Lin Q et al. J transl Med 2019;30;17(1):298. 3Dankner M, Maxwell J, Rose AAN. The evolving treatment landscape for BRAF-mutated non-small cell lung cancer. Transl Lung Cancer Res. 2024;13(4):930.

Marcel Weisweg. E J cancer 2021

TIPOS DE MUTACIÓN *BRAF*

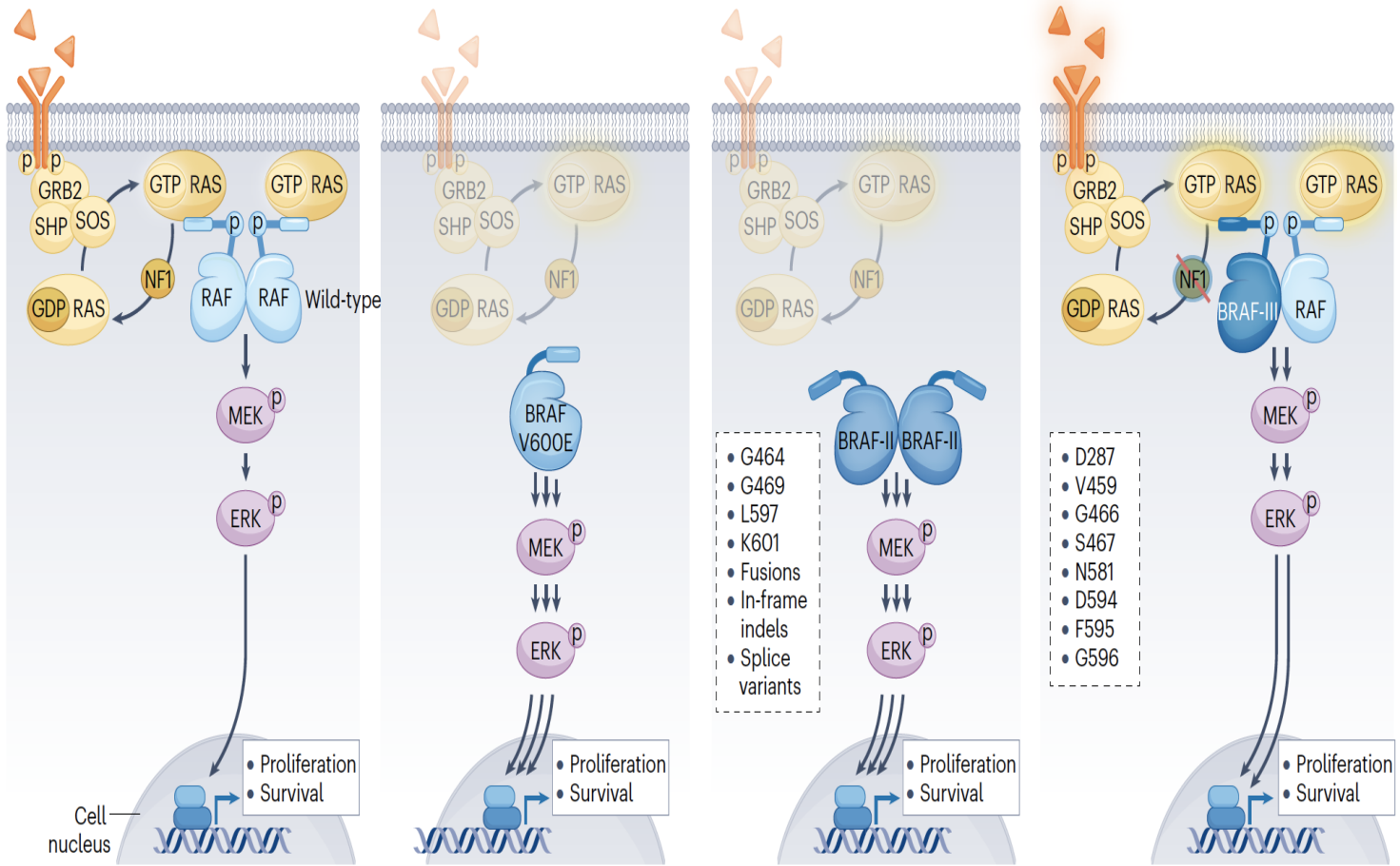
a

Wild-type BRAF
Signals as RAS-dependent dimers following growth factor stimulation of RTKs

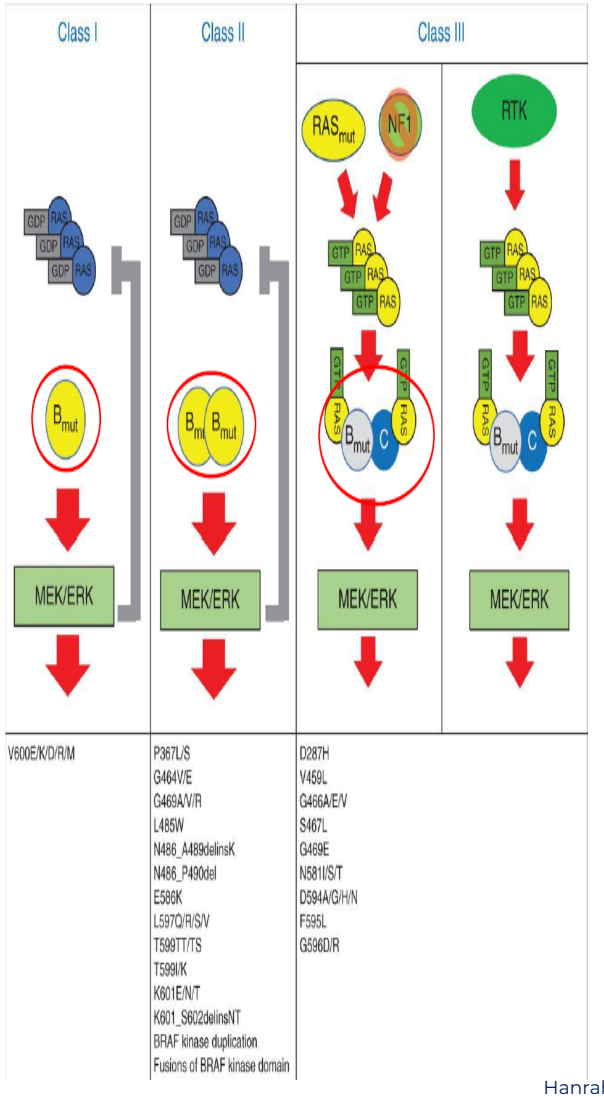
Class I BRAF mutants (V600-mutant)
Signal as high-activity, RAS-independent monomers under conditions of low RAS activity

Class II BRAF mutants (non-V600-mutant)
Signal as intermediate-to-high-activity, RAS-independent dimers

Class III BRAF mutants (non-V600-mutant)
Low-activity or kinase-dead, RAS-dependent mutants that signal as heterodimers with wild-type RAF; often co-occur with RTK or RAS mutations or loss of NF1



Classes of BRAF mutations



Class	BRAF kinase activity	RAS dependent	Dimer dependent
I	High	No	No
II	High/Intermediate	No	Yes
III	Impaired/None	Yes	Yes

High proportion of Braf mutant tumors, particularly Class II and III have co-mutations in other genes.

- TP53, KRAS, KEAP1, etc.

Yaeger, et al, Cancer Discovery 2019

Riudavets, et al,Lung Cancer 2022

Hanrahan et al. Nat Rev Clin Oncol 2024

Mutación BRAF en cáncer pulmón. Aspectos controvertidos

.- Inhibidores de BRAF para todos?

.- Cuál es la mejor combinación?

.- Papel de Quimio-inmunoterapia

.- Cual es la mejor estrategia en primera línea?

.- Perfiles determinados de pacientes para QT+IO o BRAF TKI en primera línea?

.- Mecanismos de resistencia

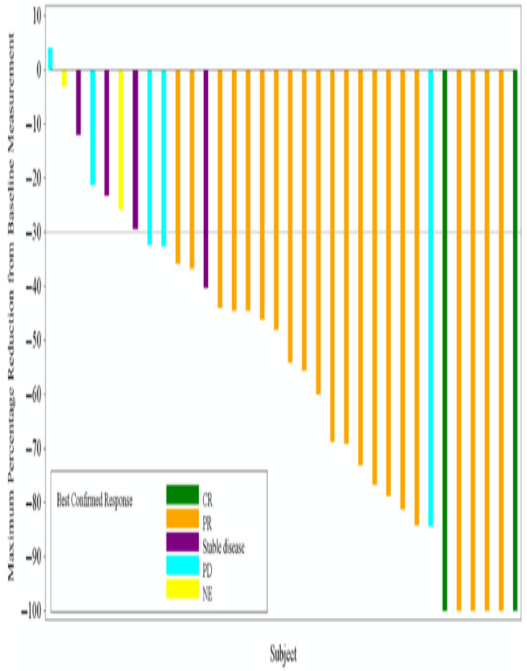
RESUMEN DE LAS CARACTERÍSTICAS DE PK-PD DE TKIs inh BRAF

Parámetros	Encorafenib	Dabrafenib	Vemurafenib	Implicaciones para Encorafenib
$T_{1/2}$ Disociación T1/2, horas[1]	>30	2	0,5	Mayor supresión en la diana
IC50 BRAF BRAF IC50, µM[1]	0,0005	0,0032	0,11	Mayor potencia para inhibir la proliferación en concentraciones más bajas del fármaco
IC50 BRAFV600E BRAFV600E, IC50, µM[1]	0,0004	0,00068	0,035	
Absorción oral[2]	La ingesta de alimentos retrasó la absorción pero no alteró la exposición general al fármaco	Los alimentos disminuyeron la velocidad y el grado de absorción.	Desconocido	Puede ser ingerido independientemente del consumo de alimentos[2]
EC_{80}/IC_{80} Índice paradójico (EC80/IC80)[3]	50	10	5,5	Ventana terapéutica más amplia para lograr la inhibición del tumor sin la activación paradójica de ERK[3]

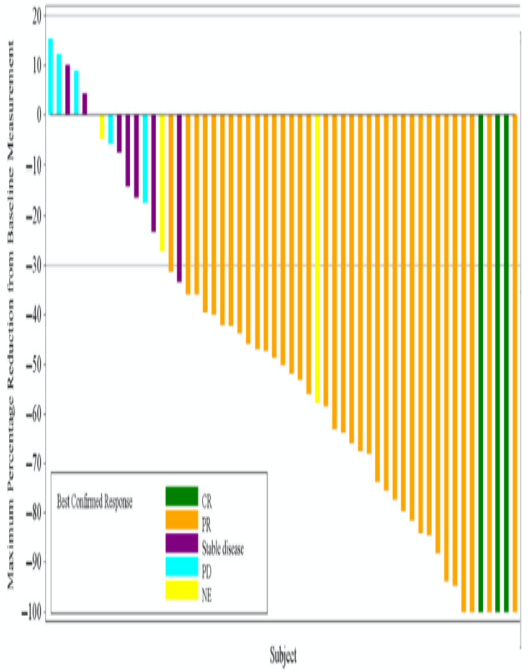
1. Darrin D. Stuart, et al. AACR; Cancer Res 2012;72(8 Suppl):Abstract nr 3790 2.Ouellet D et al., Journal of pharmaceutical sciences, 2013 Sep;102(9):3100-9. 3. Adelmann CH et al. Oncotarget. 2016; 7(21): 30453-60

Clinical Benefit with Dabrafenib + Trametinib in BRAF V600E NSCLC

1st line

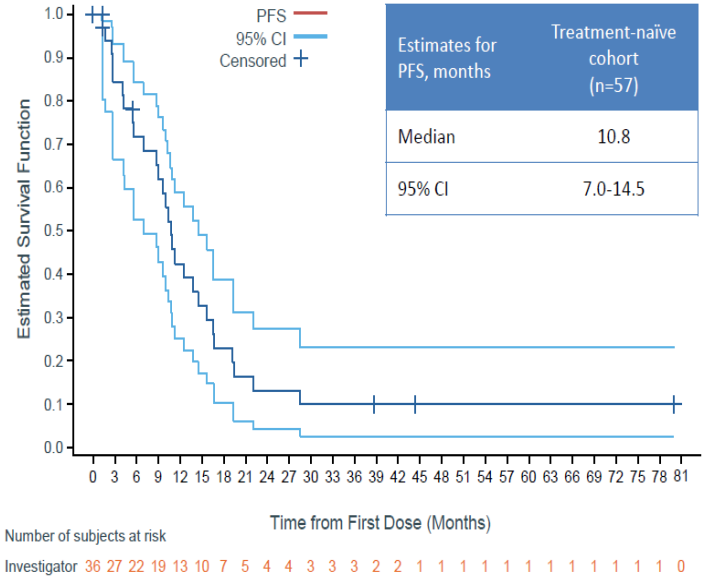


2nd line



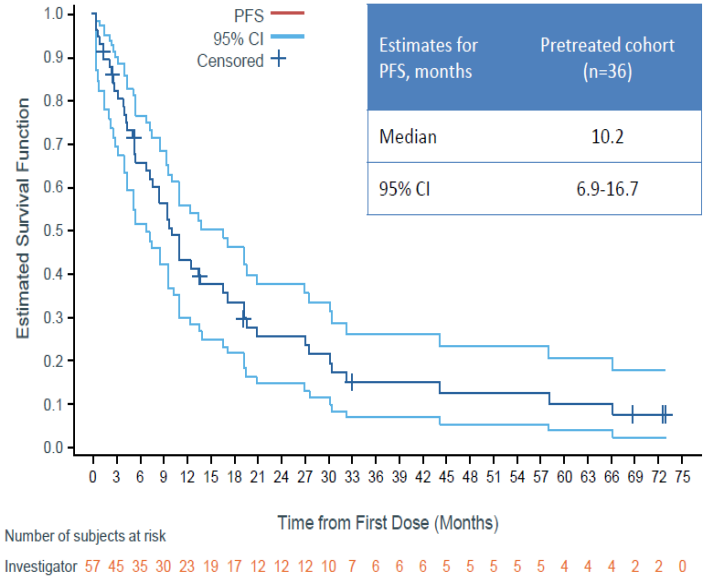
Investigator-assessed best response	Treatment naïve (n=36)	Previously treated (n=57)
ORR (CR + PR), % (95% CI)	**63.9** (46.2-79.2)	**68.4** (54.8-80.1)
DCR (CR + PR + SD), % (95% CI)	**75.0** (57.8-87.9)	**80.7** (68.1-90.0)

Treatment-naïve cohort



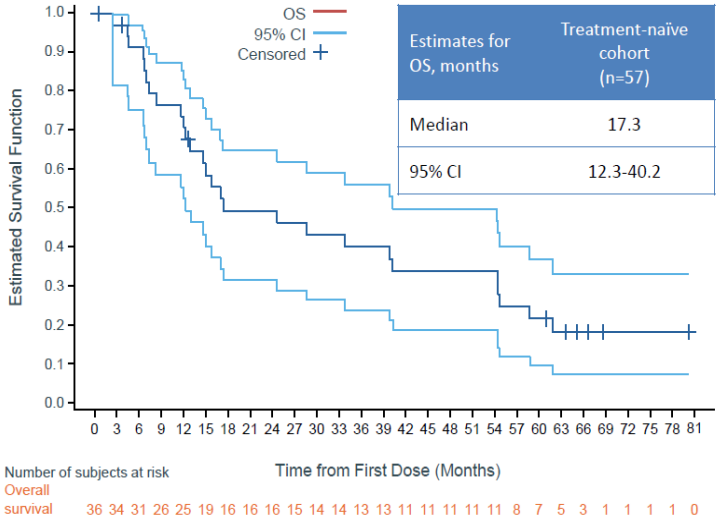
Estimates for PFS, months	Treatment-naïve cohort (n=57)
Median	10.8
95% CI	7.0-14.5

Pretreated cohort



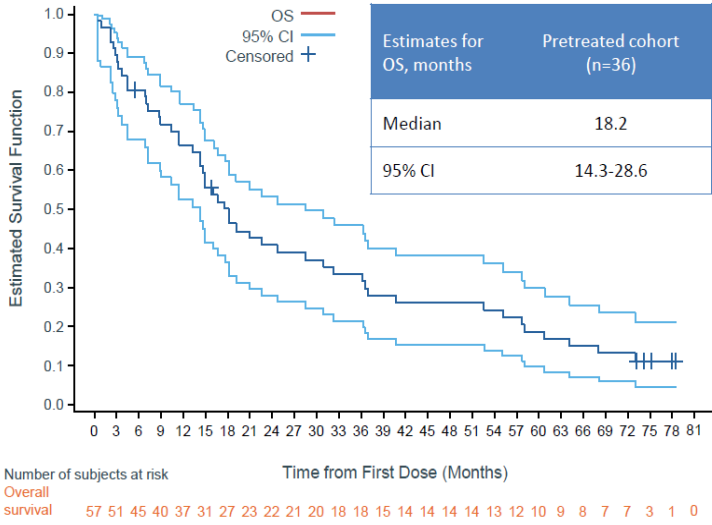
Estimates for PFS, months	Pretreated cohort (n=36)
Median	10.2
95% CI	6.9-16.7

Treatment-naïve cohort



Estimates for OS, months	Treatment-naïve cohort (n=57)
Median	17.3
95% CI	12.3-40.2

Pretreated cohort



Estimates for OS, months	Pretreated cohort (n=36)
Median	18.2
95% CI	14.3-28.6

Planchard D, et al. *J Thorac Oncol.* 2022;17(1):103-115.

Enrolled patients (AcSé trial)

BRAF mutations
n = 194

NSCLC
n = 118

V600 mutations
n = 101
V600E : n=97
V600D : n=1
V600K : n=2
V600M : n=1

Non V600 mutations
n = 17
G466A : n=1
G466V : n=3
G469A : n=3
G469V : n=1
N581S : n=3
G596R : n=1
K601E : n=3
K601N : n=2

Analyzed for efficacy and safety
n = 100

Analyzed for efficacy and safety
n = 15

	ORR	mDoR	mPFS	mOS
BRAF V600 (n=100)	45%	6.4m	5.2m	9.3m
BRAF non V600 (n=17)	0*	2.6 m	1.8m	5.2m

Mazières J et al. WCLC 2018 (OA 12.05)

BRAF non V600 cohort (AcSé Vemu)

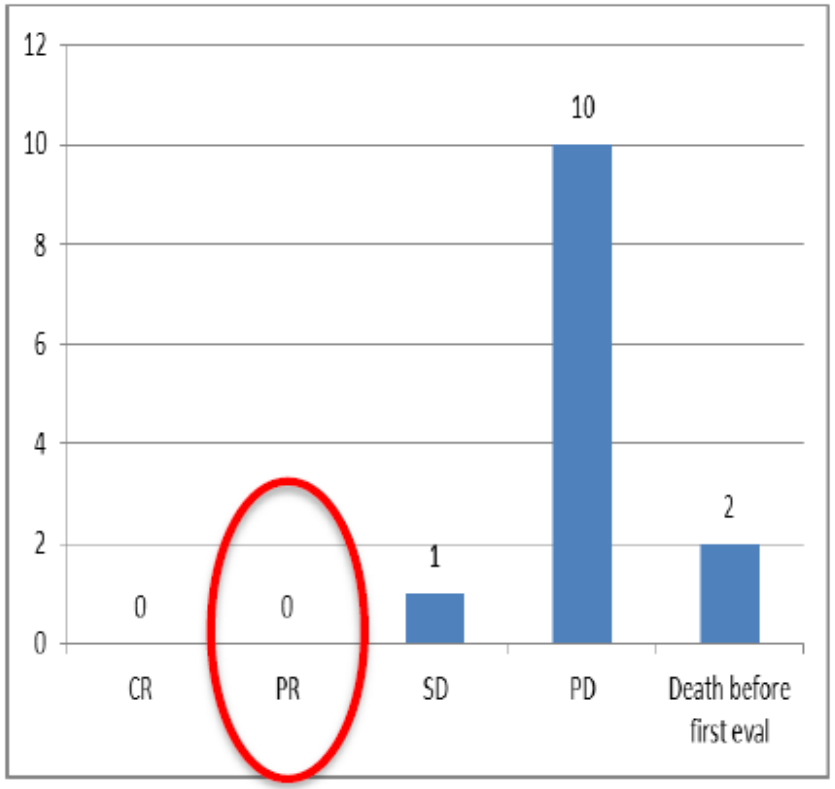
- Mean Bayesian Estimated Success rate : **5.9%** ; credibility 95%CI : [0.2%; 20.6%]
- Prob ORR < futility bound (10%): 81.5% - **study stopped**

Non V600 mutations

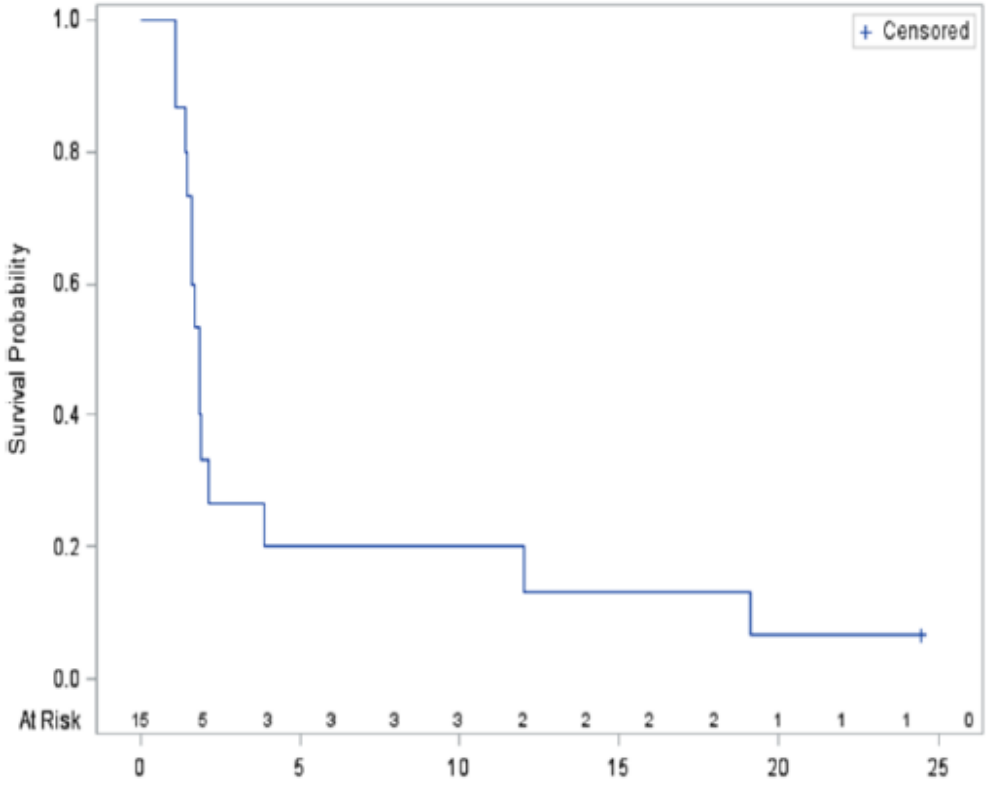
n = 17

G466A : n=1
G466V : n=3
G469A : n=3
G469V : n=1
N581S : n=3
G596R : n=1
K601E : n=3
K601N : n=2

Response rate: 0%



PFS: 1.8 m. [1.4;2.1]



J.Mazieres et al, WCLC 2018

ESTUDIO PHAROS

Objective: To determine the safety, tolerability and efficacy of encorafenib given in combination with binimetinib in patients with *BRAF*^{V600E}-mutant metastatic NSCLC who are either treatment naïve or who have been previously treated with platinum-based chemotherapy and/or anti-PD-1/PD-L1 inhibitor therapy*

Key eligibility criteria

- Metastatic *BRAF*^{V600E}-mutant NSCLC
- ECOG performance status 0 or 1
- No *EGFR* mutation, *ALK* fusion or *ROS1* rearrangement
- No more than 1 prior line of treatment in the advanced setting
- No prior treatment with BRAF or MEK inhibitor
- No symptomatic brain metastases

***BRAF* mutation testing**

- Determined locally by PCR- or NGS-based assay; sent to central laboratory†
- Pleural fluid, fresh and archived tissue, and fine needle aspiration were acceptable[2]

Patients enrolled

- Treatment naïve n=59
- Previously treated n=39

Encorafenib: 450 mg QD
Binimetinib: 45 mg BID
28-day cycles
Treat until progression or unacceptable toxicity

Primary endpoint

- **ORR‡ by IRR**

Secondary endpoints

- ORR by investigator
- DOR, DCR, PFS and TTR (all by IRR and investigator)
- OS
- Safety

Exploratory endpoints

- Biomarker and pharmacokinetic analyses

*PHAROS also allowed for the enrollment of patients with less common BRAFV600 mutations other than V600E in a third arm, but no patients were recruited into this arm so are not shown above. †*BRAF*^{V600} mutations were retrospectively confirmed by FoundationOne CDx (Foundation Medicine, Cambridge, MA). ‡According to RECIST 1.1.

1. Riely GJ, et al. *J Clin Oncol*. 2023;41(21):3700-3711; 2. Riely GJ, et al. *J Clin Oncol*. 2023;41(21, Suppl. Study Protocol):S1-S121.

ESTUDIO PHAROS

	Treatment naïve (n=59)	Previously treated (n=39)	Total (N=98)
Age, years, median (range)	68 (47–83)	71 (53–86)	70 (47–86)
Sex, n (%)			
Women	33 (56)	19 (49)	52 (53)
Men	26 (44)	20 (51)	46 (47)
ECOG PS, n (%)			
0	19 (32)	7 (18)	26 (27)
1	40 (68)	32 (82)	72 (73)
Tumour histology, n (%)			
Adenocarcinoma	57 (97)	38 (97)	95 (97)
Method of BRAF testing, n (%)			
PCR	15 (25)	11 (28)	26 (26)
Tissue NGS	44 (75)	27 (69)	71 (72)
Plasma NGS	0	1 (3)	1 (1)

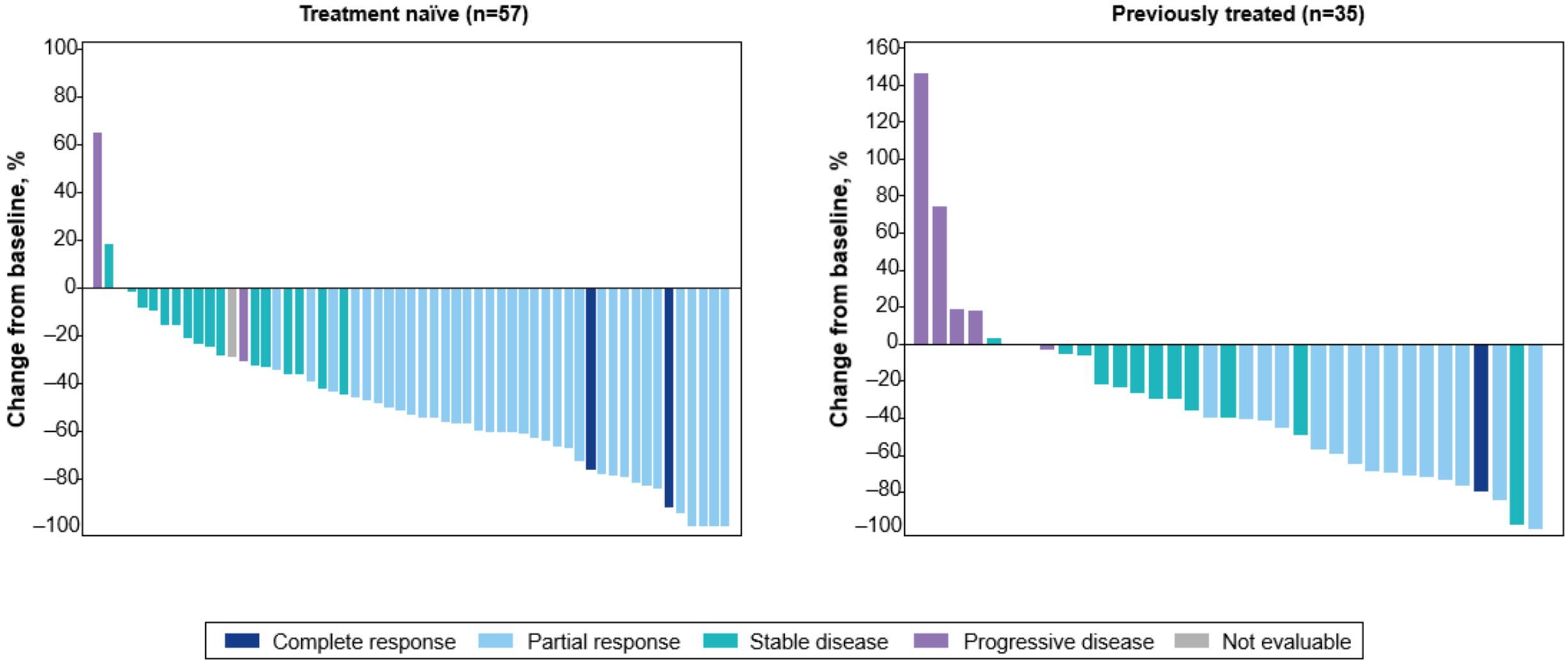
Riely GJ, et al. *J Clin Oncol*. 2023;41(21):3700-3711.

ESTUDIO PHAROS

	Treatment naïve (n=59)	Previously treated (n=39)	Total (N=98)
Smoking status, n (%)			
Current	8 (14)	5 (13)	13 (13)
Former	33 (56)	23 (59)	56 (57)
Never	18 (31)	11 (28)	29 (30)
Brain metastases*, n (%)			
No	55 (93)	35 (90)	90 (92)
Yes	4 (7)	4 (10)	8 (8)
Prior systemic treatment for metastatic disease, n (%)	0	39 (100)	39 (40)
Immunotherapy	NA	23 (59)†	23 (23)†
Monotherapy PD-(L)1	NA	12 (31)	12 (12)
Combination PD-(L)1‡	NA	11 (28)	11 (11)
Chemotherapy	NA	19 (49)	19 (19)
Prior radiotherapy			
No	50 (85)	22 (56)	72 (73)
Yes	9 (15)	17 (44)	26 (27)

Riely GJ, et al. *J Clin Oncol*. 2023;41(21):3700-3711.

ESTUDIO PHAROS - MAXIMUM CHANGE FROM. BASELINE IN THE SUM OF DIAMETERS OF TARGET LESIONS BY INVESTIGATOR ASSESSMENT*



Riely GJ, et al. J Clin Oncol. 2023;41(21):3700-3711.

ANTITUMOR ACTIVITY ENDPOINTS AND DURATION OF RESPONSE BY

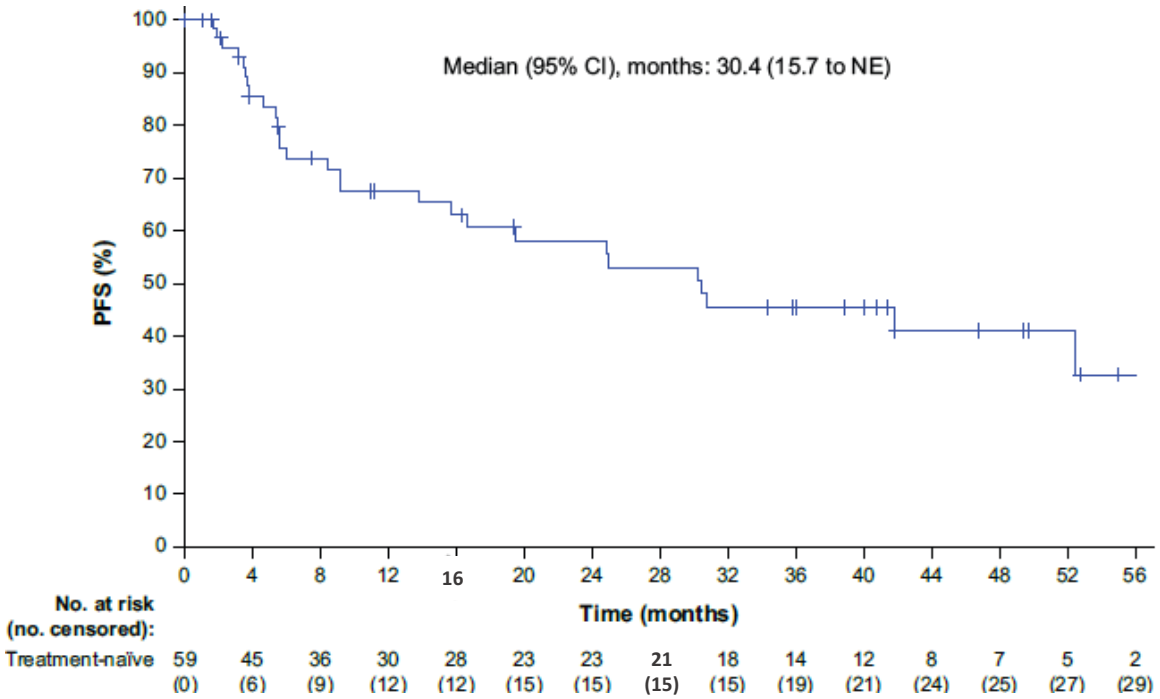
Endpoint by IRR	Treatment naïve (n=59)	Previously treated (n=39)
Objective response rate (95% CI), %[a]	**75 (62, 85)**	**49 (32 to 65)**
Complete response, n (%)	12 (20)	5 (13)
Partial response, n (%)	32 (54)	14 (36)
Stable disease, n (%)	10 (17)	12 (31)
Progressive disease, n (%)	2 (3)	3 (8)
Not evaluable	3 (5)	5 (13)
DOR, median (95% CI), months[a]	**40.0 (23.2, NE)**	**16.7 (7.4 to NE)**
DOR ≥6, months, No. (%)	33 (75)	14 (74)
DOR ≥12, months, No. (%)	28 (64)	8 (42)
DOR ≥24, months, No. (%)	20 (45)	5 (26)
Time to response, median (range), months[a]	1.9 (1.1-5.6)	1.7 (1.2-16.5)

Johnson ML et al. J Clin Oncol. 2025. DOI:10.1200/JCO-25-02023.

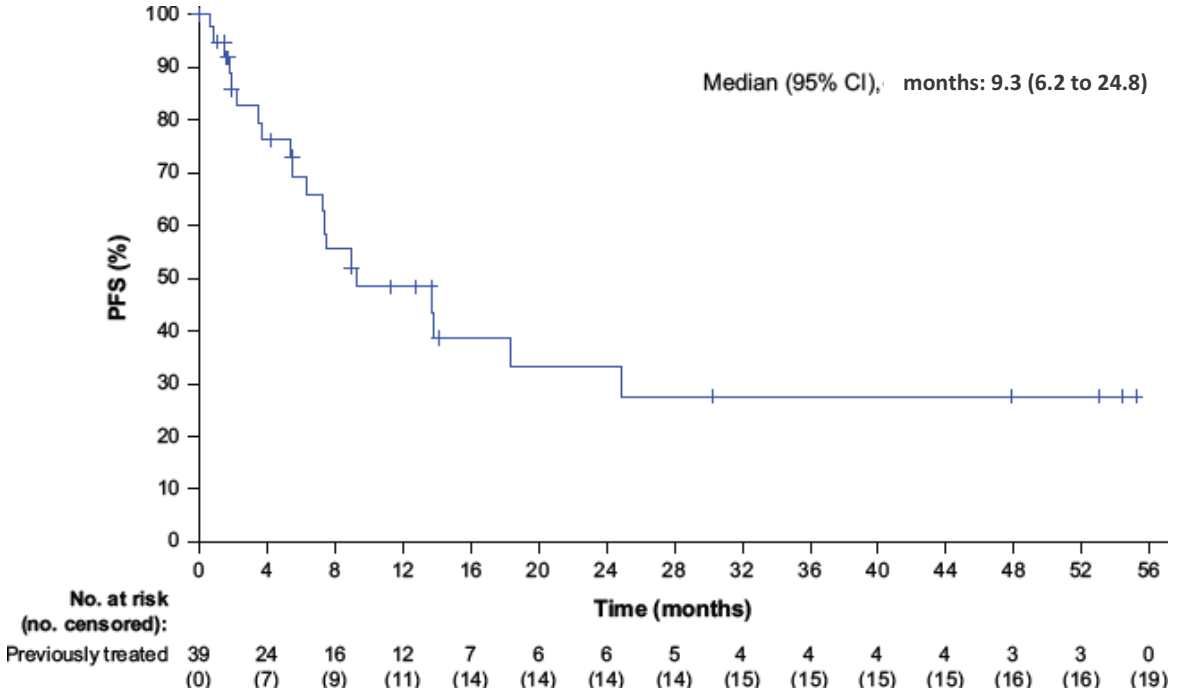
DOR, duration of response; IRR, independent radiology review; NE, not estimable

ESTUDIO PHAROS ESMO 2025 UPDATE: PROGRESSION-FREE SURVIVAL BY IRR (DATA CUTOFF: MARCH, 2025)

Primera línea de tratamiento



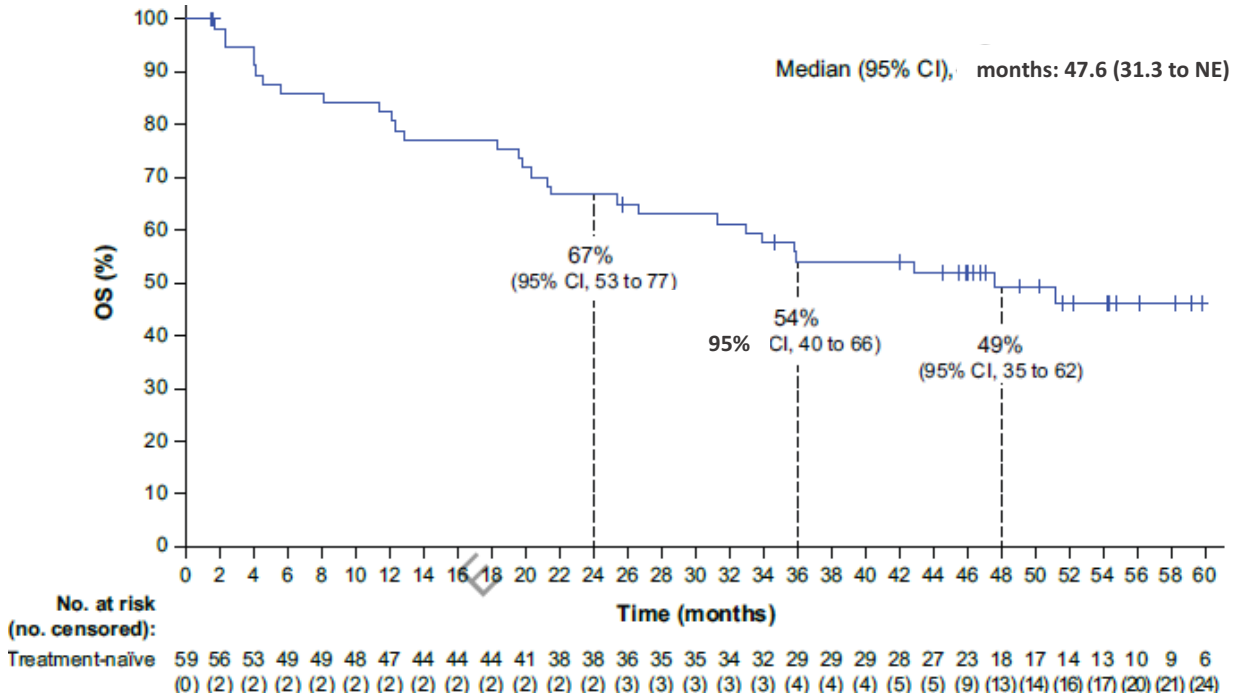
Segunda línea de tratamiento



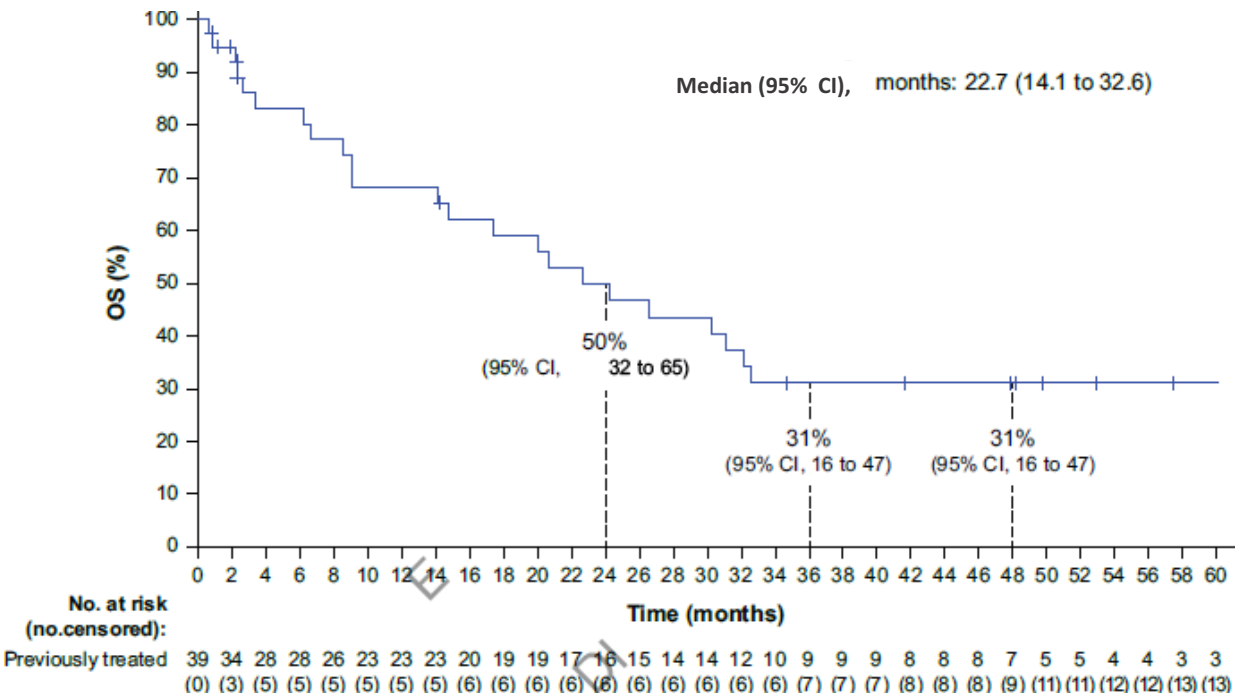
Johnson ML et al. J Clin Oncol. 2025. DOI:10.1200/JCO-25-02023

ESTUDIO PHAROS ESMO 2025 UPDATE: OVERALL SURVIVAL (DATA CUTOFF: MARCH, 2025)

Primera línea de tratamiento



Segunda línea de tratamiento



Johnson ML et al. J Clin Oncol. 2025. DOI:10.1200/JCO-25-02023

ESTUDIO PHAROS – ORR, SLP and OS BY IRR IN PATIENT SUBGROUPS: AGE. SEX. ECOG PS

Characteristic	Treatment naïve				Previously treated			
	n	ORR, % (95% CI)	mPFS (95% CI), months	mOS (95% CI), months	n	ORR, % (95% CI)	mPFS (95% CI), months	mOS (95% CI), months
Age group, years								
<65	23	74 (52 to 90)	24.9 (5.6 to NE)	51.2 (19.8 to NE)	13	38 (14 to 68)	9.0 (1.9 to NE)	32.6 (3.4 to NE)
≥65	36	75 (58 to 88)	30.4 (15.7 to NE)	39.3 (25.4 to NE)	26	54 (33 to 73)	9.3 (6.2 to 24.8)	22.7 (14.1 to 31.1)
Sex								
Women	33	70 (51 to 84)	30.7 (15.7 to NE)	47.6 (21.5 to NE)	19	53 (29 to 76)	9.3 (7.4 to 24.8)	30.3 (20.7 to NE)
Men	26	81 (61 to 93)	30.2 (9.2 to NE)	51.2 (19.6 to NE)	20	45 (23 to 69)	7.3 (3.6 to NE)	14.7 (6.7 to NE)
ECOG PS								
0	19	74 (49 to 91)	30.7 (15.7 to NE)	NE (35.7 to NE)		86 (42 to 100)	18.4 (7.4 to NE)	32.2 (22.7 to NE)
1	40	75 (59 to 87)	30.4 (9.2 to NE)	32.9 (20.3 to 61.4)		41 (24 to 59)	7.5 (5.4 to 24.8)	20.0 (9.1 to 32.6)

Johnson ML et al. J Clin Oncol. 2025. DOI:10.1200/JCO-25-02023

- Most prominent TRAEs include GI, asthenia, pirexia, and eye tox.

Dabrafenib + Trametinib

	Grade 1-2	Grade 3	Grade 4	Grade 5
Pyrexia	25 (44%)	1 (2%)	0	0
Nausea	23 (40%)	0	0	0
Vomiting	20 (35%)	0	0	0
Diarrhoea	18 (32%)	1 (2%)	0	0
Decreased appetite	17 (30%)	0	0	0
Asthenia	16 (28%)	2 (4%)	0	0
Dry skin	14 (25%)	1 (2%)	0	0
Peripheral oedema	13 (23%)	0	0	0
Chills	12 (21%)	1 (2%)	0	0
Cough	12 (21%)	0	0	0
Rash	11 (19%)	1 (2%)	0	0
Arthralgia	11 (19%)	0	0	0
Constipation	10 (18%)	0	0	0
Fatigue	9 (16%)	1 (2%)	0	0
Blood alkaline phosphatase increased	9 (16%)	0	0	0
Dyspnoea	8 (14%)	2 (4%)	0	0
Pruritus	8 (14%)	1 (2%)	0	0
Dizziness	8 (14%)	0	0	0

Pyrexia (56%)
Nausea (51%)
Vomiting (41%)

- Dose reduction: 35%
- Dose interruption: 61%
- Discontinuation: 12%

Encorafenib + Binimetinib

TABLE 3. Incidence of TRAEs of Any Grade ≥10% in All Patients

	Overall (N = 98)		
AE Preferred Term	Any Grade	Grade 3	Grade 4
Any TRAEs, No. (%)	92 (94)	37 (38)	3 (3)[a]
Nausea	49 (50)	3 (3)	0
Diarrhea	42 (43)	4 (4)	0
Fatigue	31 (32)	2 (2)	0
Vomiting	28 (29)	1 (1)	0
Anemia	18 (18)	3 (3)	0
Vision blurred	17 (17)	1 (1)	0
Constipation	13 (13)	0	0
ALT increased	12 (12)	5 (5)	0
AST increased	12 (12)	7 (7)	0
Pruritus	12 (12)	0	0
Blood creatine phosphokinase increased	11 (11)	0	0
Peripheral edema	11 (11)	0	0
Abdominal pain	10 (10)	0	0
Alopecia	10 (10)	0	0
Asthenia	10 (10)	3 (3)	0
Dry skin	10 (10)	0	0

Nausea (50%)
Diarrhea (43%)
Fatigue (32%)
Vomiting (29%)
Pyrexia (22%)

- Dose reduction 24%
- Dose interruption 44%
- Discontinuation 15%

Drug	n	Response rate	PFS (months)	OS (months)
Dabrafenib + trametinib 1L	36	64%	10.8	17.3
Dabrafenib + trametinib 2L	57	68%	10.2	18.2
Encorafenib + binimetinib 1L	59	75%	30.2	NE
Encorafenib + binimetinib 2L	39	46%	9.3	22.7

Similar outcomes between treatment-näive and pre-treated patients

Better outcomes in treatment-näive patients

Riely GJ, et al. J Clin Oncol. 2023; Planchard D, et al. Lancet Oncol 2017.

Mutación BRAF en cáncer pulmón. Aspectos controvertidos

.- Inhibidores de BRAF para todos?

.- Cuál es la mejor combinación?

.- Papel de Quimio-inmunoterapia

.- Cual es la mejor estrategia en primera línea?

.- Perfiles determinados de pacientes para QT+IO o BRAF TKI en primera línea?

.- Mecanismos de resistencia

Table 2 Immune checkpoint inhibitor efficacy outcomes in various molecular alterations

		Best response (%)			PFS			OS
Driver	n	CR/PR	SD	PD	Median (months)	6 month PFS (%)	1 year PFS (%)	Median (months)
BRAF	38	28.1	28.1	43.8	3	35	19	13.6
KRAS	252	27.2	23.1	49.8	3.2	39	26	13.5
ROS1	5	20	0	80	NA	NA	NA	NA
MET	36	15.6	34.4	50	3.4	33	23	18.4
EGFR	110	11	18	71	2	16	6	8.8
HER2	23	9.5	28.6	61.9	3.5	34	17	10
RET	14	7.1	21.4	71.4	2.2	16	8	6.5
ALK	18	0	21.4	78.6	2.1	16	8	17

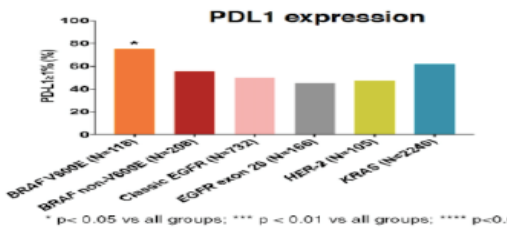
 Mazieres J, Drilon AE, Mhanna LJ *et al*. Efficacy of immune-checkpoint inhibitors in non-small cell lung cancer patients harbouring activating molecular alterations (ImmunoTarget). *J Clin Oncol* 2018; 36, suppl:abstr 9010.

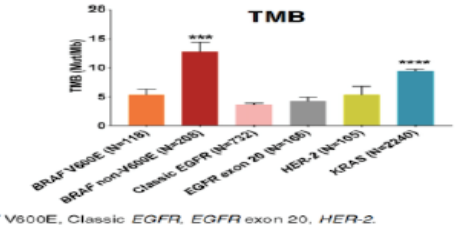
CR, complete response; NA, not available; PFS, progression-free survival; PR, partial response.

Mazières J, Drilon A, Lusque A, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. Ann Oncol. 2019 May 24. pii: mdz167. doi: 10.1093/annonc/mdz167

ICI activity in BRAFmut NSCLC: Evidence from retrospective series

- High level of PD-L1 expression
- Low/intermediate TMB
- Microsatellite-stable status





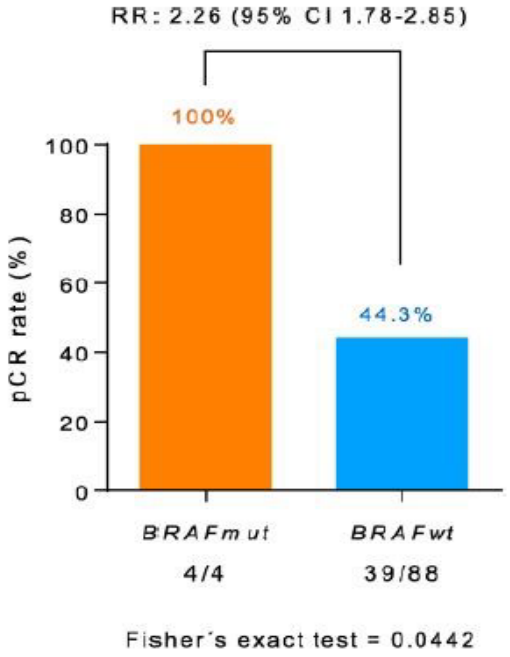
* p< 0.05 vs all groups; *** p < 0.01 vs all groups; **** p<0.01 vs *BRAF* V600E, Classic *EGFR*, *EGFR* exon 20, *HER-2*.

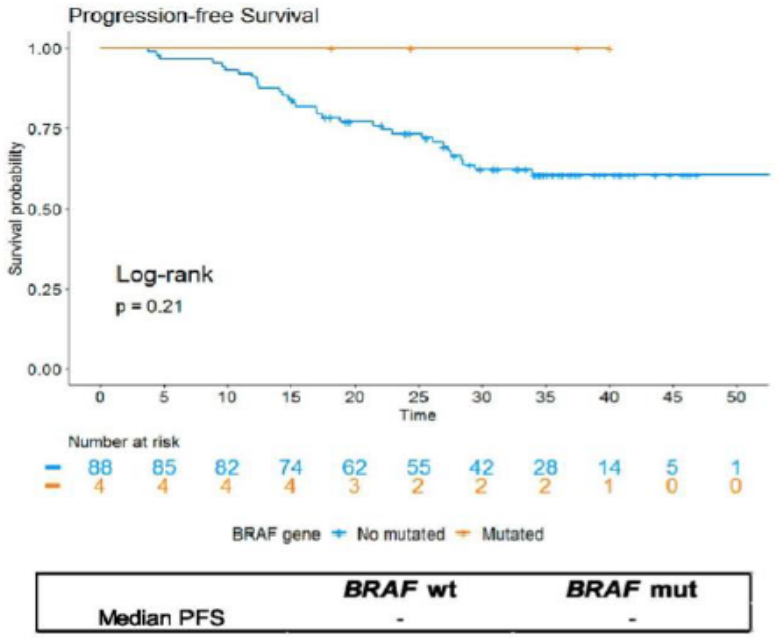
Study	Previous TKI	BRAF	n	ORR (%)	PFS (months)	OS	Efficacy
Europe IMMUNOTARGET (N=34)	NA	All *V600E* *Non-V600*	 14 14	24%	3.1 1.8 4.1	13.6m 8.2m 17.2m	Smokers
US MSK-IMPACT (n=46)	NA	*V600E* *Non-V600*	10 36	10% 22%	1.4 3.2	2.5y 1.7y	Better OS in Non-V600 receiving ICI vs not
Israel (n=39)	NA	*V600E* *Non-V600E*	21 18	25% 33%	3.7 4.1	NR	Efficacy not PD-L1 related
Italian EAP nivolumab (n=11)	NA	NA	14	9.1%		10.3m	No OS differences to WT-population

Mazières J, *et al. Annals of Oncology* 2019; Offin M, *et al. J Thor Oncol* 2019; Myall et al. J Thor Oncol 2019; Rihawi et al. J Thor Oncol 2019;

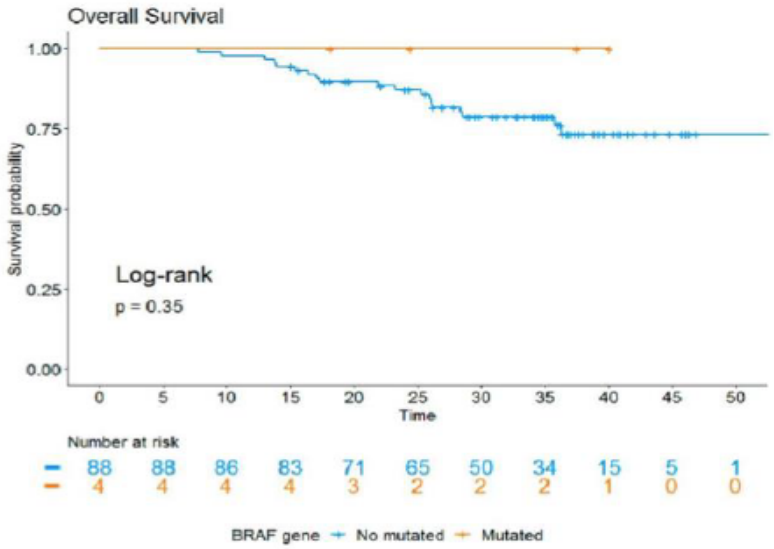
Efficacy of chemo-IO in *BRAF*mut NSCLC

Pathological complete response and survival after neoadjuvant chemo-IO, in stage III NSCLC patients (NADIM cohort)





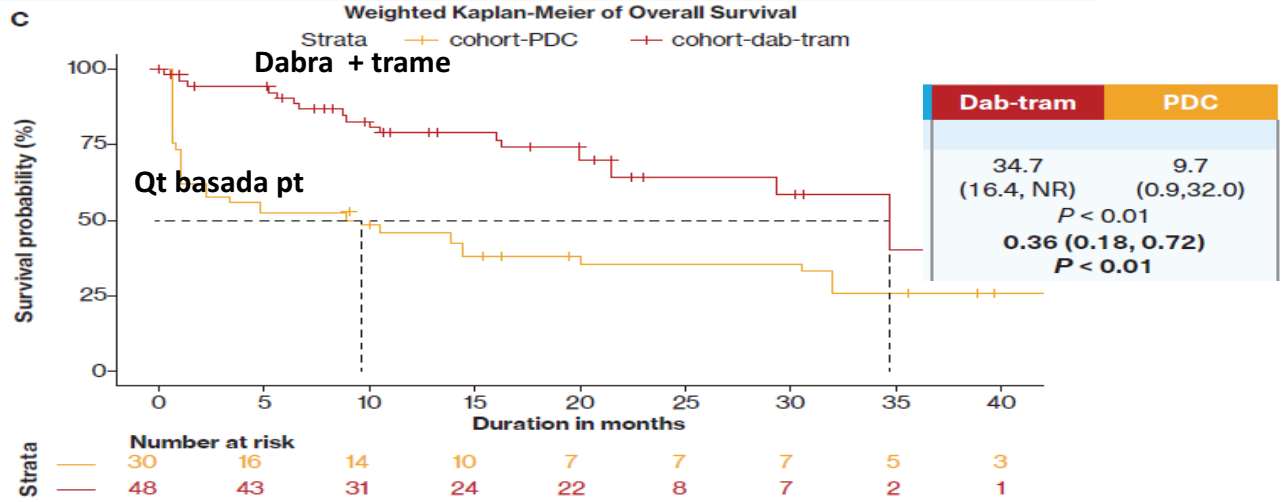
	BRAF wt	*BRAF* mut
Median PFS	-	-

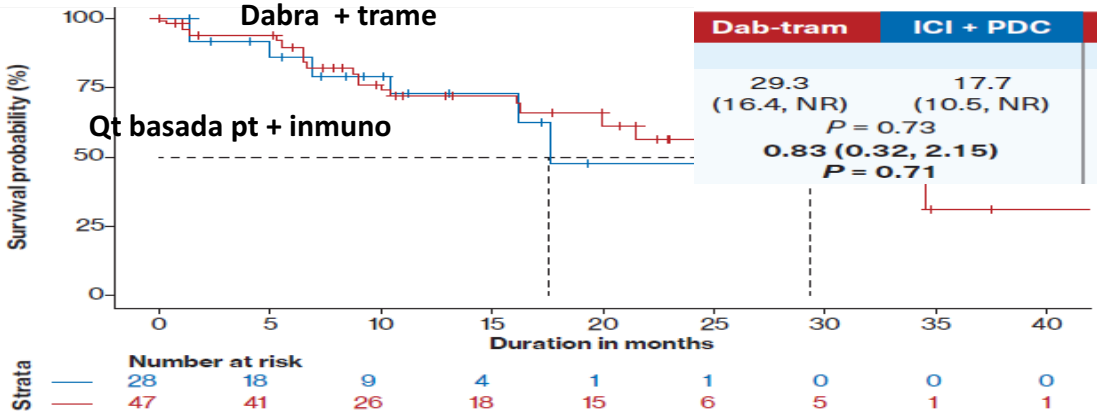


	BRAF wt	*BRAF* mut
Median OS	-	-

Provencio et al. Lung Cancer 2024

Clinical outcomes of patients with BRAF^{V600}-mutated metastatic NSCLC (mNSCLC) receiving first-line (1L) dabrafenib+trametinib vs other standard of care in real-world practice. Roll of immunotherapy





*Pre-weighted data can be viewed by scanning the QR code
dab-tram, dabrafenib plus trametinib; ICI, immune-checkpoint inhibitor; PDC, platinum-doublet chemo

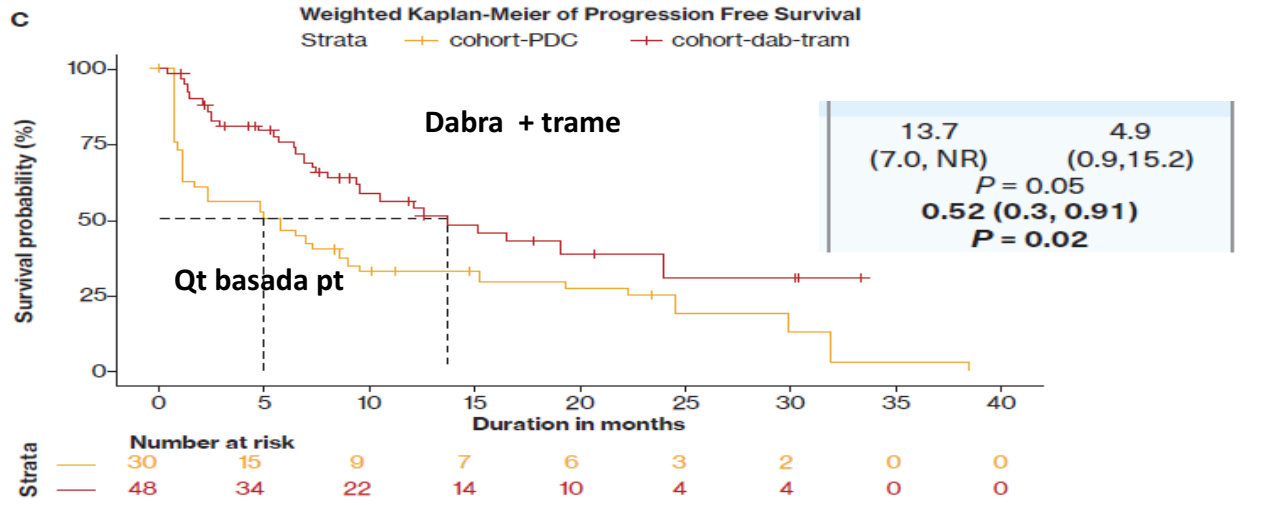
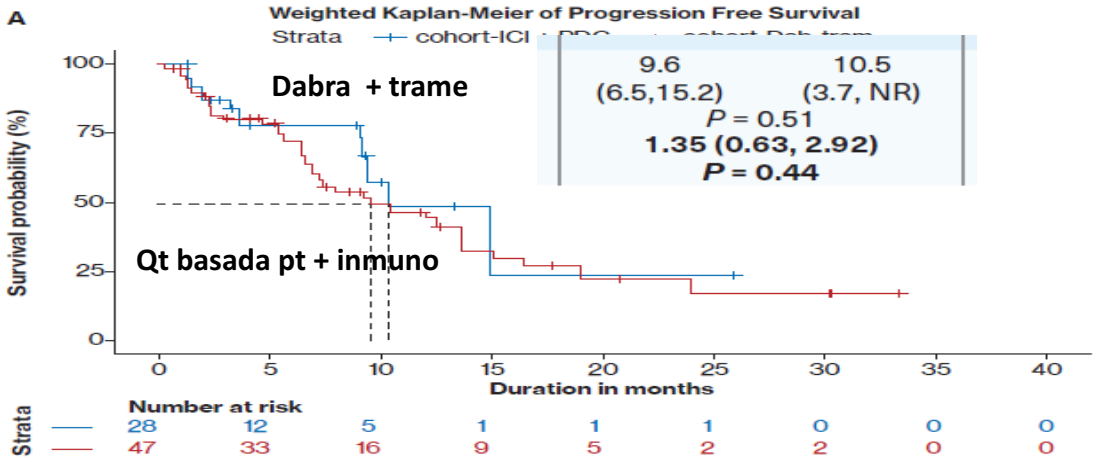


Figure 3. rwPFS with A) Dab-tram vs ICI + PDC, B) Dab-tram vs



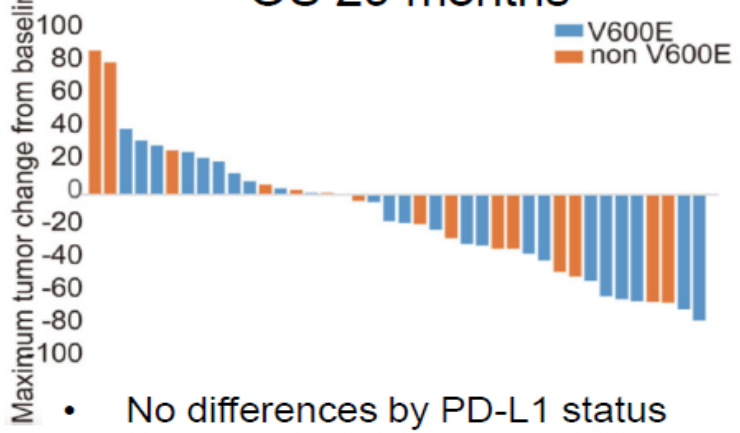
*Pre-weighted data can be viewed by scanning the QR code
dab-tram, dabrafenib plus trametinib; ICI, immune-checkpoint inhibitor; PDC, platinum-doublet chemo

Barbara Melovsky. ESMO 2021

Efficacy of chemo-IO in *BRAF*mut NSCLC

Retrospective RWE

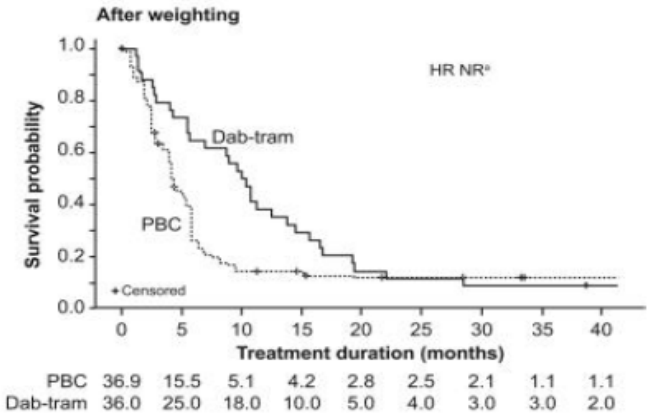
- **1L (n=25)**
  ORR 41%
  DCR 78%
  PFS 9 months
  OS 29 months



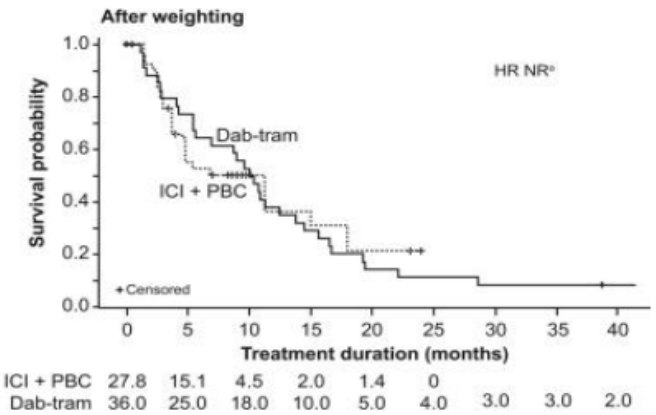
- No differences by PD-L1 status
- Better outcomes in 1L vs. later lines

Phase 2 D+T trial vs. RWE

1L D+T vs. PBC



1L D+T vs. ICI+PBC



Outcome	Dabra + Trame (n=36)	PBC (n=37)	ICI + PBC (n=28)
Median OS, mo (95% CI)	**17.3** (14.6-NR)	**9.7** (6.4-19.6)	**18.0** (5.1-NR)
After weighting		**P= 0.01**	**P= 0.15**
Median PFS/rwPFS, mo (95% CI)	**10.2** (7.0-14.5)	**4.2** (3.0-5.8)	**11.3** (3.7-NR)

Yan et al. Front Oncol 2024; Johnson et al. JTO Clin Res Rep 2022

Mutación BRAF en cáncer pulmón. Aspectos controvertidos

.- Inhibidores de BRAF para todos?

.- Cuál es la mejor combinación?

.- Papel de Quimio-inmunoterapia

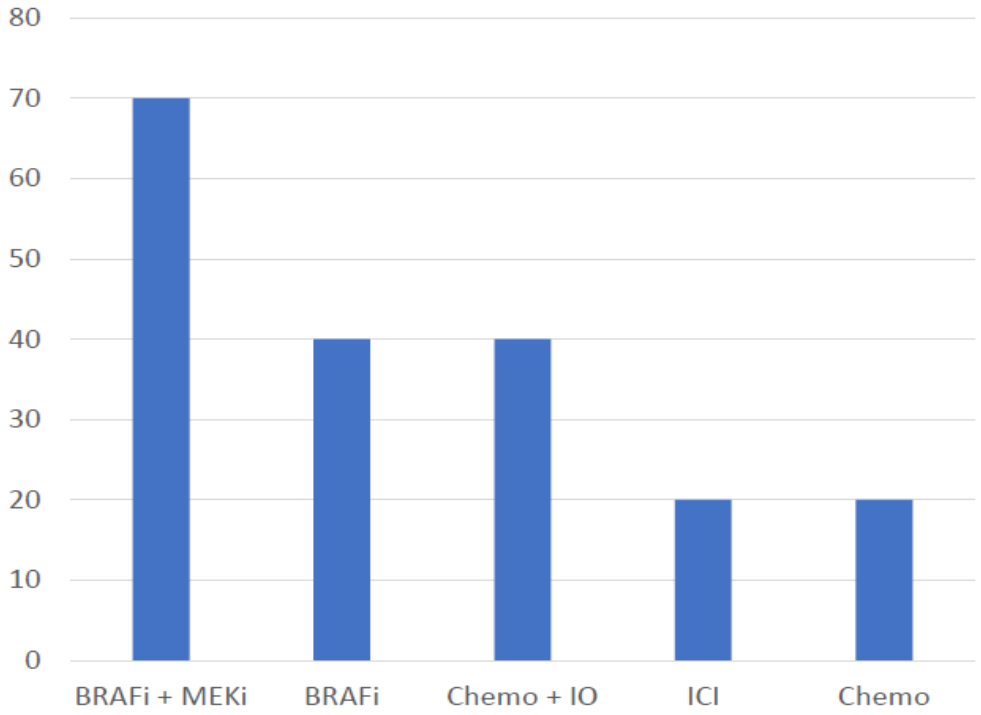
.- Cual es la mejor estrategia en primera línea?

.- Perfiles determinados de pacientes para QT+IO o BRAF TKI en primera línea?

.- Mecanismos de resistencia

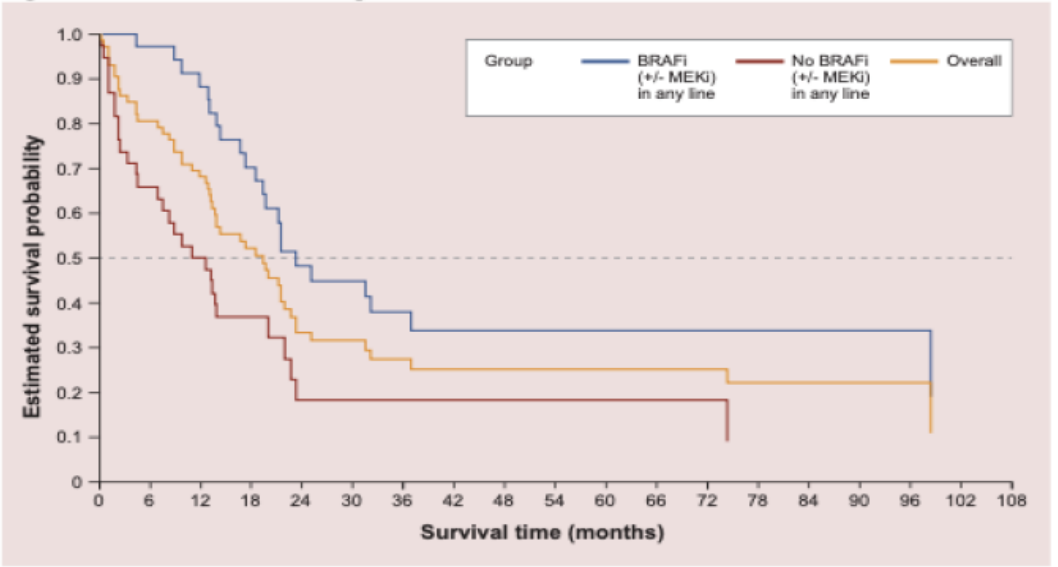
Outcomes by treatments available in *BRAF*mut NSCLC

Estimated RR by different available treatments



Improved OS in patients who received BRAFi (+/-MEKi)[1,2]

Figure 2. OS From the First Diagnosis of mNSCLC



BRAFi vs not
OS 23.4m vs 11.8m

What's the best sequence of treatment?

. Goyal, ESMO 2018; 2. Horn et al. Lung Cancer 2019

ESTUDIO PHAROS - ORR, SLP and OS BY IRR IN PATIENT SUBGROUPS: PREVIOUSLY TREATED

Characteristic	Treatment naïve				Previously treated			
	n	ORR, % (95% CI)	mPFS (95% CI), months	mOS (95% CI), months	n	ORR, % (95% CI)	mPFS (95% CI), months	mOS (95% CI), months
Previously treated with IO								
No		N/A			15	33 (12 to 62)	9.0 (3.6 to 18.4)	20.7 (8.6 to NE)
Yes		N/A			24	58 (37 to 78)	13.8 (6.2 to NE)	26.6 (14.1 to NE)

Johnson ML et al. J Clin Oncol. 2025. DOI:10.1200/JCO-25-02023

Pharos: Subsequent anticancer

Patients, n (%)	Treatment naive (n=59)	Previously treated (n=39)
Received at least 1 subsequent anticancer systemic treatment	34 (58)	10 (26)
First subsequent therapy[a]		
Immunotherapy-based regimen	19 (56)	4 (40)
Monotherapy	7 (21)	2 (20)
Combination with chemotherapy or other immunotherapy	12 (35)	2 (20)
Chemotherapy-based régimen without immunotherapy	5 (15)	3 (30)
BRAF ± MEK inhibitor	10 (29)	3 (30)
Received ≥1 subsequent BRAF ± MEK inhibitor[a]	13 (38)	3 (30)
Received ≥1 subsequent anticancer radiotherapy treatment	9 (15)	4 (10)

[a]Calculated out of the patients who received at least 1 subsequent anticancer systemic treatment (34 treatment-naive patients and 10 previously treated patients).

Johnson ML et al. J Clin Oncol. 2025. DOI:10.1200/JCO-25-02023

Mutación BRAF en cáncer pulmón. Aspectos controvertidos

.- Inhibidores de BRAF para todos?

.- Cuál es la mejor combinación?

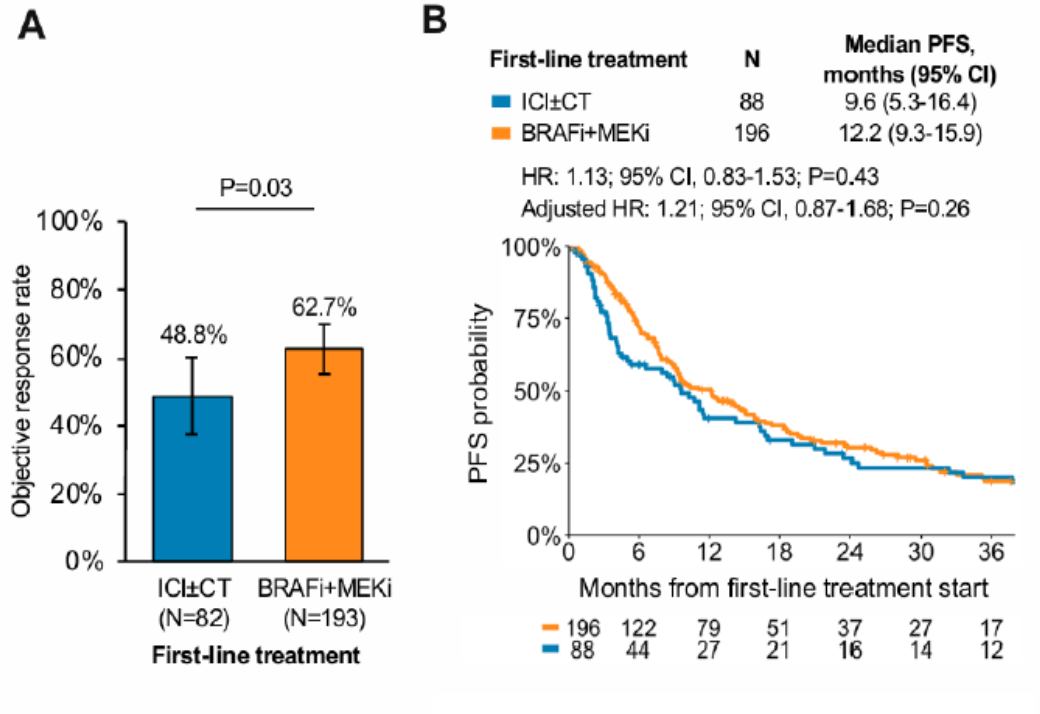
.- Papel de Quimio-inmunoterapia

.- Cual es la mejor estrategia en primera línea?

.- Perfiles determinados de pacientes para QT+IO o BRAF TKI en primera línea?

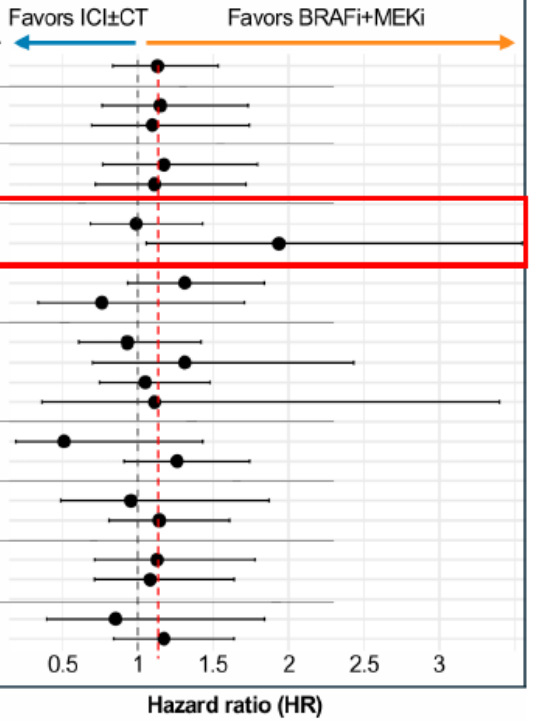
.- Mecanismos de resistencia

Objective response rate and progression-free survival by first-line treatment BRAF V600E



C

Subgroup		N	PFS HR (95% CI)	P value
Overall		284	1.13 (0.83-1.53)	0.43
Age (years)	<70	159	1.15 (0.76-1.73)	0.51
	≥70	125	1.10 (0.69-1.74)	0.70
Sex	Male	136	1.17 (0.77-1.79)	0.46
	Female	148	1.11 (0.72-1.71)	0.63
Smoking status	Ever	191	0.99 (0.68-1.43)	0.95
	Never	91	1.94 (1.06-3.55)	0.03
ECOG PS	0-1	228	1.31 (0.93-1.84)	0.12
	≥2	44	0.76 (0.34-1.71)	0.51
PD-L1 TPS	≥50%	134	0.93 (0.61-1.42)	0.74
	1-49%	83	1.31 (0.70-2.43)	0.40
	≥1%	217	1.05 (0.75-1.48)	0.78
	<1%	39	1.11 (0.36-3.40)	0.86
Metastatic sites	>3	32	0.51 (0.19-1.43)	0.20
	≤3	252	1.26 (0.91-1.74)	0.16
Brain metastasis	Yes	48	0.95 (0.49-1.87)	0.89
	No	236	1.14 (0.81-1.61)	0.45
Bone metastasis	Yes	106	1.13 (0.72-1.77)	0.61
	No	178	1.08 (0.71-1.64)	0.71
Liver metastasis	Yes	48	0.85 (0.40-1.84)	0.68
	No	236	1.17 (0.84-1.64)	0.35



(A) Objective response rate, and (B) progression-free survival by first-line treatment. (C) Subgroup analysis of progression-free survival by first-line treatment.

Overall Survival was superior with Chemo+IO, especially in smokers

Di Frederico, et al ASCO 2025

Smoking status influences responses to BRAFi + MEKi

Encorafenib + Binimetinib	Treatment naïve		Previously treated	
Characteristic	n	ORR, % (95% CI)	n	ORR, % (95% CI)
Smoking status				
Current	8	50.0 (15.7, 84.3)	5	20.0 (0.5, 71.6)
Former	33	75.8 (57.7, 88.9)	23	52.2 (30.6, 73.2)
Never	18	83.3 (58.6, 96.4)	11	45.5 (16.7, 76.6)

- **Smoking can induce CYP1A2 isoform, which has been shown to lower the exposure to binimetinib and may explain the lower response in this study.**
- **Smoking history often have more co mutations which may impact response to treatment**

Riely GJ, et al. J Clin Oncol. 2023

ESTUDIO PHAROS – ORR, SLP and OS BY IRR IN PATIENT SUBGROUPS: SMOKING STATUS[1]

Characteristic	Treatment naïve				Previously treated			
	n	ORR, % (95% CI)	mPFS (95% CI), months	mOS (95% CI), months	n	ORR, % (95% CI)	mPFS (95% CI), months	mOS (95% CI), months
Smoking status								
Current/former	41	71 (55 to 84)	24.8 (9.2 to NE)	35.7 (20.3 to NE)	28	46 (28 to 66)	9.0 (6.2 to NE)	20.0 (9.1 to 32.6)
Never	18	83 (59 to 96)	41.8 (16.6 to NE)	61.4 (61.4 to NE)	11	55 (23 to 83)	18.4 (3.6 to NE)	32.2 (8.6 to NE)

Tanto entre los pacientes sin tratamiento previo como entre los que habían recibido tratamiento anteriormente, la SLP y la SG fueron numéricamente más prolongadas en los pacientes sin antecedentes de tabaquismo que en los que tenían antecedentes.[1]

El tabaquismo se relaciona con una mayor mortalidad en pacientes oncológicos[2]

Rº pembrolizumab + pemetrexed + platino en KEYNOTE 189: ORR: 48% / mPFS: 9,0 meses / mOS: 22 meses[3]

Rº cemiplimab + QT en EMPOWER-Lung 3 (adenocarcinoma): ORR: 41,3% / mPFS: 7,9 meses / mOS: 19,4 meses[4]

Rº tislelizumab + QT en RATIONALE 304: ORR: 57,4% / mPFS: 9,8 meses/ mOS: 21,4 meses[5]

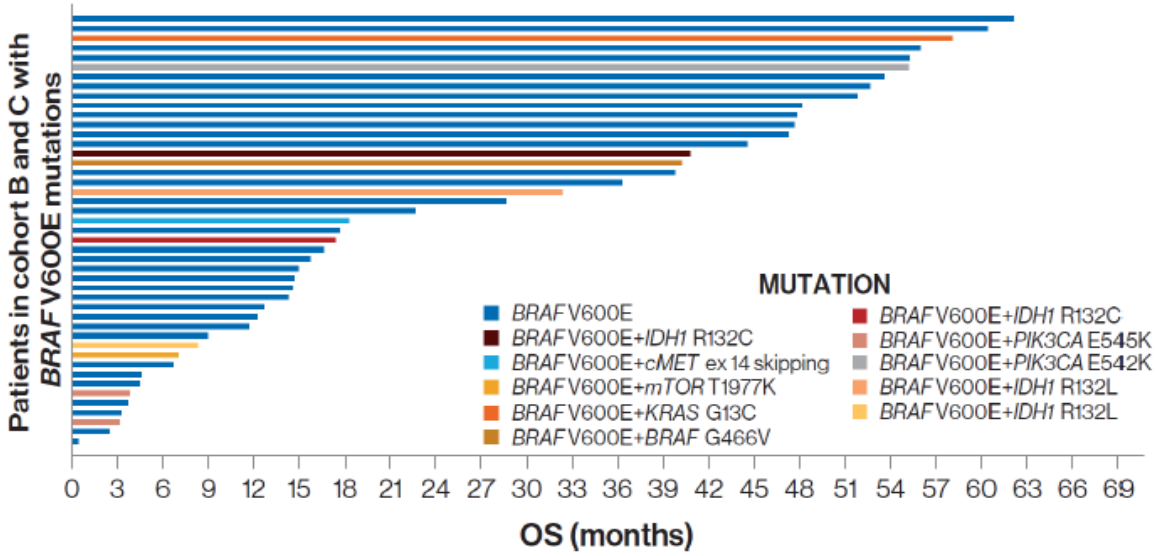
1. Johnson ML et al. J Clin Oncol. 2025. DOI:10.1200/JCO-25-02023. 2 Jassem J. Tobacco smoking after diagnosis of cancer: clinical aspects. Transl Lung Cancer Res. 2019 May;8(Suppl 1):S50-S58. doi: 10.21037/tlcr.2019.04.01 3. Garassino MC et al. J Clin Oncol 41, 1992-1998(2023).DOI:10.1200/JCO.22.01989. 4. Baramidze A et al. World Conference on Lung Cancer (WCLC 2025), Barcelona, España. 5. Lu, S. et al. Tislelizumab plus chemotherapy as first-line treatment of locally advanced or metastatic nonsquamous non-small-cell lung cancer (final analysis of RATIONALE-304: a randomized phase III trial). ESMO Open, Volume 9, Issue 10, 103728.

Genomic background in BRAF V600E NSCLC treated with RAFi + MEKi

Dabrafenib + Trametinib

N=86 (29 Rx-näive, 57 previously-Rx)

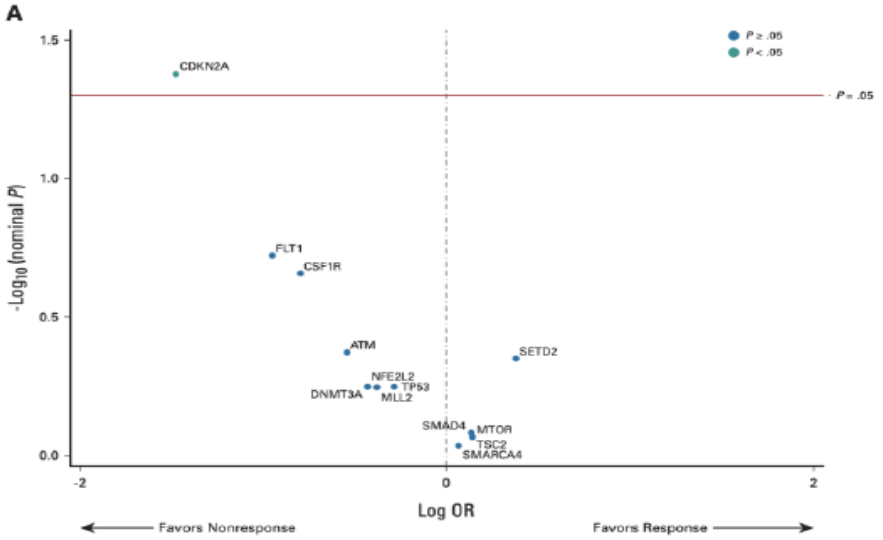
- Concomitant mutation found in 11 patients (22%): PIK3CA, IDH1, mTOR, KRAS, BRAF



Encorafenib + Binimetinib

N=80 (48 Rx-näive, 32 previously-Rx)

- Most frequent genes found altered: ETD2 and TP53 (43% each), SMAD4 (21%), ATM, MLL2, CSF1R, SMARCA4 (14% each), and CDKN2A (11%)



Not definitively associated with patient outcomes

Riely GJ, et al. *J Clin Oncol*. 2023; Planchard D, et al. *J Thorac Oncol*. 2022;17(1):103-115.

Limited evidence on RAFi + MEKi activity in patients with BRAF V600E NSCLC and CNS involvement

Dabrafenib + Trametinib

Asymptomatic untreteated <1 cm, or previously treated, and stable

"The patient with non-measurable brain metastasis at baseline had a non-complete response and non-progressive disease response in the brain lesion."

Encorafenib + Binimetinib

Untreated small brain metastases (<5 mm) and previously treated brain metastases allowed

	Treatment naïve		Previously treated	
Characteristic	n	ORR, % (95% CI)	n	ORR, % (95% CI)
Brain metastases				
No	55	72.7 (59.0, 83.9)	35	51.4 (34.0, 68.6)
Yes	4	100 (39.8, 100.0)	4	0

In patients with baseline brain metastases noted by the investigator, all four treatment-naïve patients had a systemic CR or PR, but none of the four previously treated patients had a systemic objective response by IRR

Riely GJ, et al. *J Clin Oncol*. 2023; Planchard D, et al. *J Thorac Oncol*. 2022;17(1):103-115.

Post-immunotherapy treatment with RAFi + MEKi in patients with BRAF V600E NSCLC

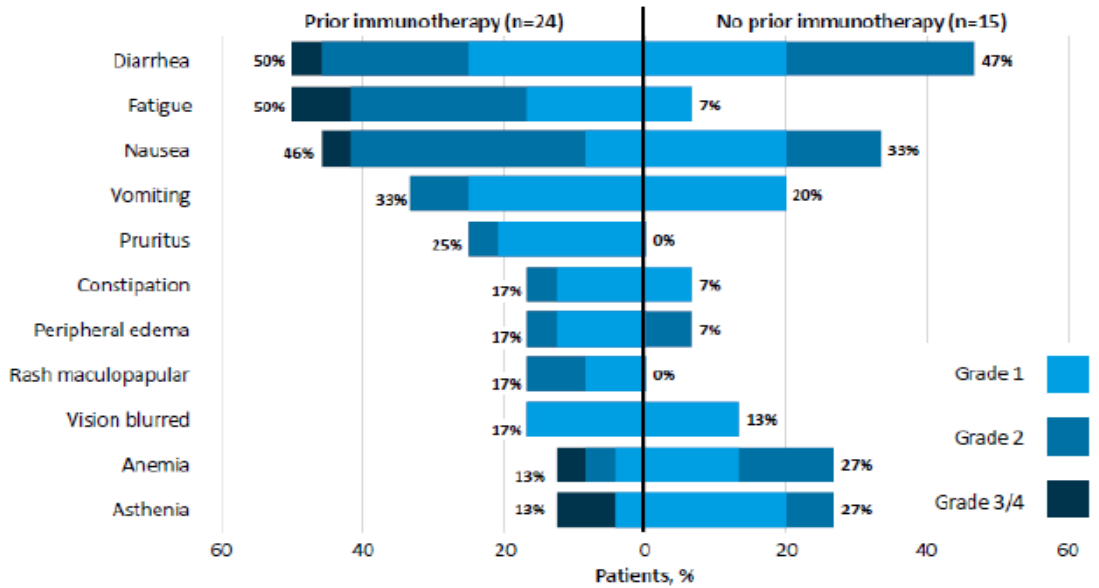
Potentially higher efficacy

- ORR by Independent Radiology Review

Characteristic	Previously treated	
	n	ORR, % (95% CI)
Previously treated with immunotherapy		
Yes	23	56.5 (34.5, 76.8)
No	16	31.3 (11.0, 58.7)

Numerically higher toxicity

- TRAEs (≥15%) in previously treated patients with or without prior immunotherapy



Riely GJ, et al. *J Clin Oncol*. 2023; Planchard D, et al. *J Thorac Oncol*. 2022;17(1):103-115.

Mutación BRAF en cáncer pulmón. Aspectos controvertidos

.- Inhibidores de BRAF para todos?

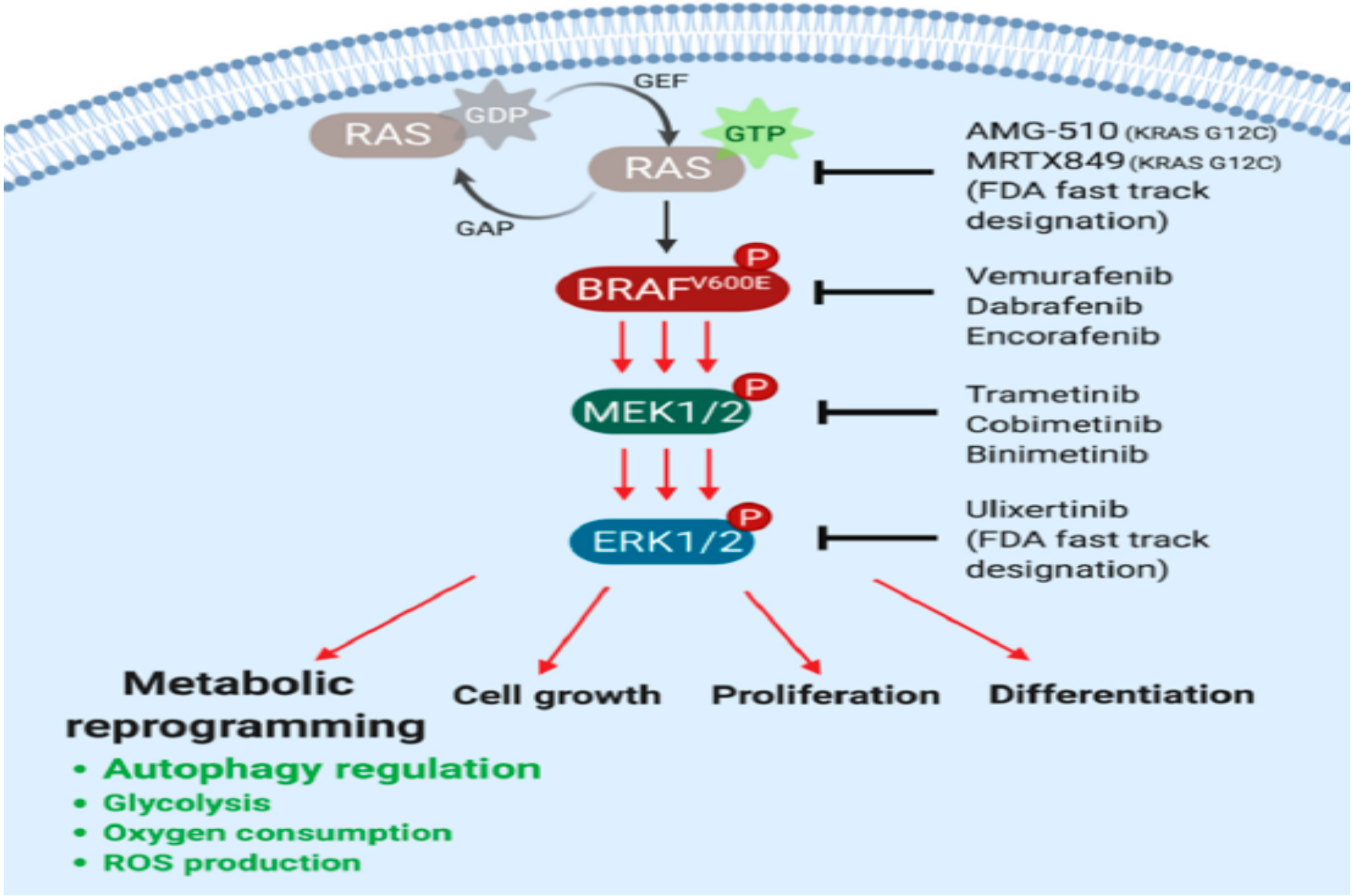
.- Cuál es la mejor combinación?

.- Papel de Quimio-inmunoterapia

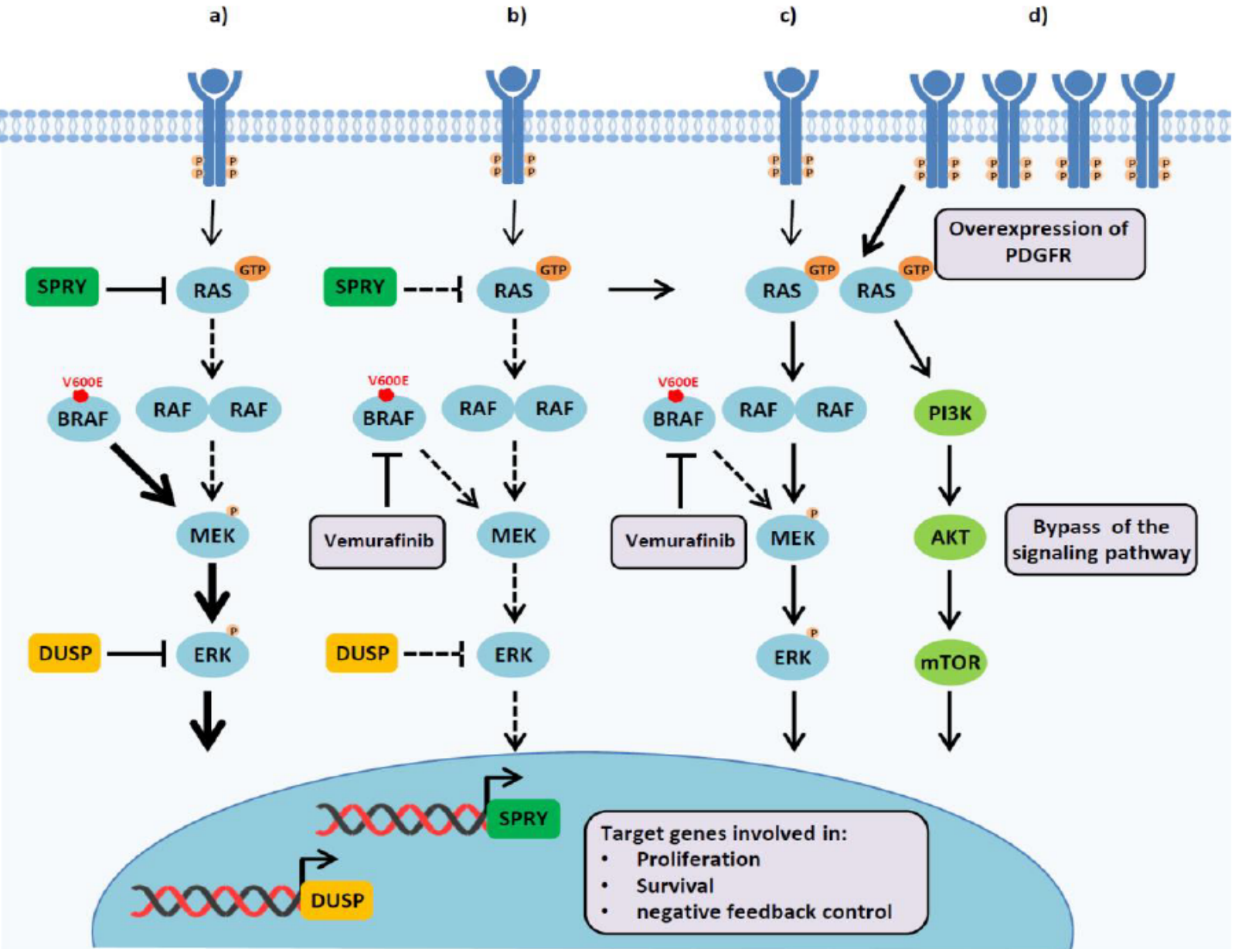
.- Cual es la mejor estrategia en primera línea?

.- Perfiles determinados de pacientes para QT+IO o BRAF TKI en primera línea?

.- Mecanismos de resistencia


GEF
RAS
GDP
GTP
RAS
GAP
AMG-510 (KRAS G12C)
MRTX849 (KRAS G12C)
(FDA fast track designation)
P
BRAF V600E
Vemurafenib
Dabrafenib
Encorafenib
P
MEK1/2
Trametinib
Cobimetinib
Binimetinib
P
ERK1/2
Ulixertinib
(FDA fast track designation)
Metabolic reprogramming
• Autophagy regulation
• Glycolysis
• Oxygen consumption
• ROS production
Cell growth
Proliferation
Differentiation

Tolerant/Persister Cancer Cells and the Path to Resistance to Targeted Therapy anti BRAF



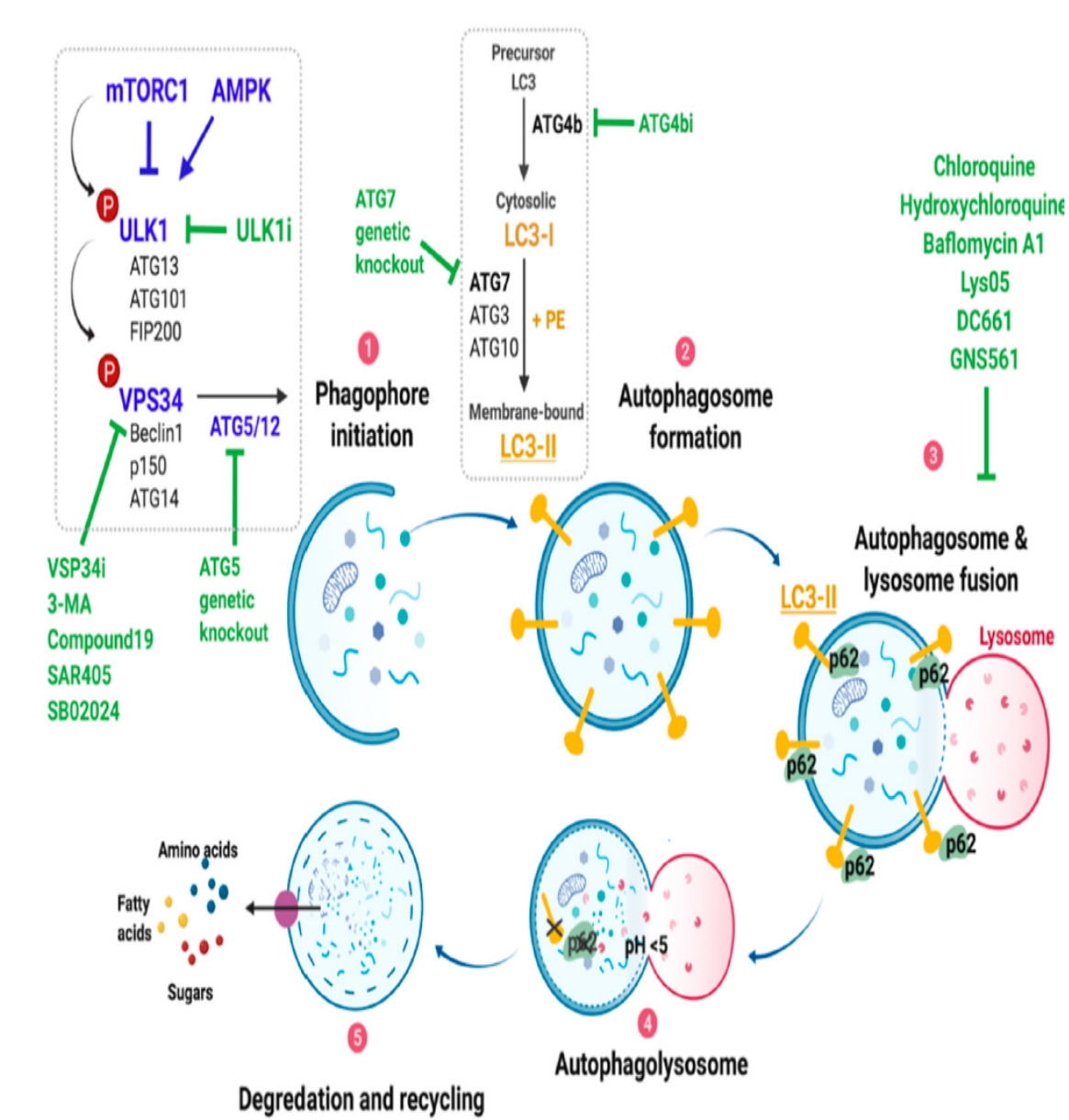
.- Pharmacological inhibition of the MAPK pathway with BRAF inhibitor provokes downregulation of DUSP and SPRY promoting cell proliferation and survival

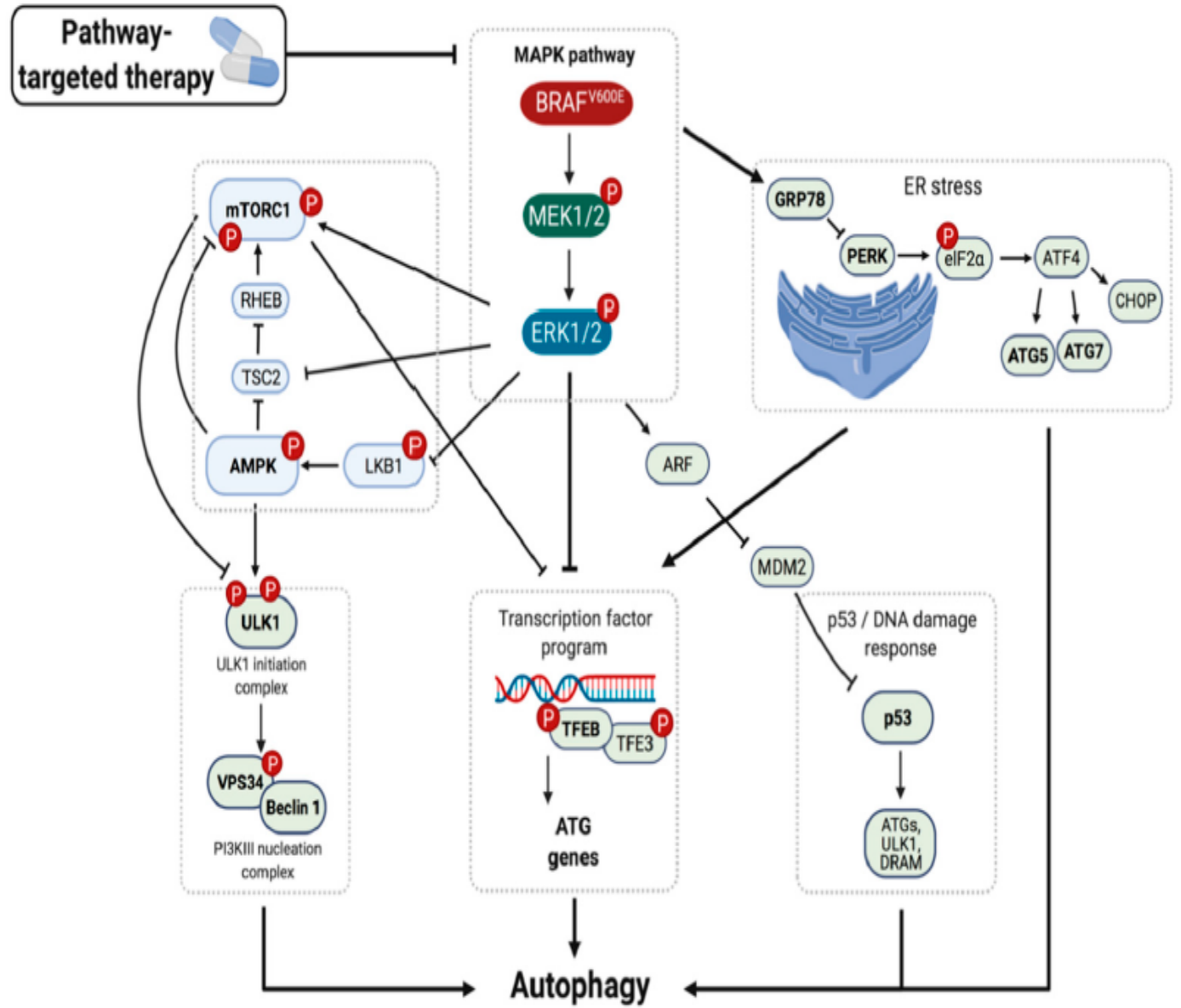
.- Relieving the negative feedback loop

.- Overexpression of PDGFR, resulting in an upstream activation of the pathway that bypasses mutant BRAF

Mirna Swayden. Cells 2021

New mechanism iBRAF resistenat Autophagy Inhibition in BRAF-Driven Cancers





Mona Foth. Cancers 2021

Resumen y conclusiones

- Heterogeinedad en mutación BRAF Clase I-III
- Mediana de seguimiento de 4 años, la combinación de encorafenib + binimetinib mostró una mediana de SG prolongada con 50% supervivientes mutación BRAF V600E sin tratamiento previo.
- La seguridad a largo plazo fue consistente con análisis previos[1,2], sin que se observaran nuevas señales de seguridad con un seguimiento más prolongado.
- En l ausencia de estudios randomizados, diversos grupo de pts se podrían beneficiar de QT-IO 1º linea. Fumadores activos, BRAF noV600E, alta carga murtacional
- Pero con los datos actualizados 1 línea encorafenib + binimetinib, se deberia considerar la primera opción en la mayoría de los pacientes BARF V600E