RET como diana terapéutica agnóstica

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4 de noviembre 2021

Conflictos de interés

- Transporte/alojamiento: Roche, Pharmamar, GSK/Tesaro, MSD, Lilly, Medicamenta.
- Inscripciones en congresos: Roche, Pharmamar, GSK/Tesaro, MSD, Novartis, Clovis Oncology.
- Ponencias: Roche, Astra Zeneca, GSK/Tesaro, Clovis Oncology, Medicamenta.
- Advisory board: Pharmamar, Clovis Oncology, GSK/Tesaro, Lilly, Pfizer.

Índice de contenidos

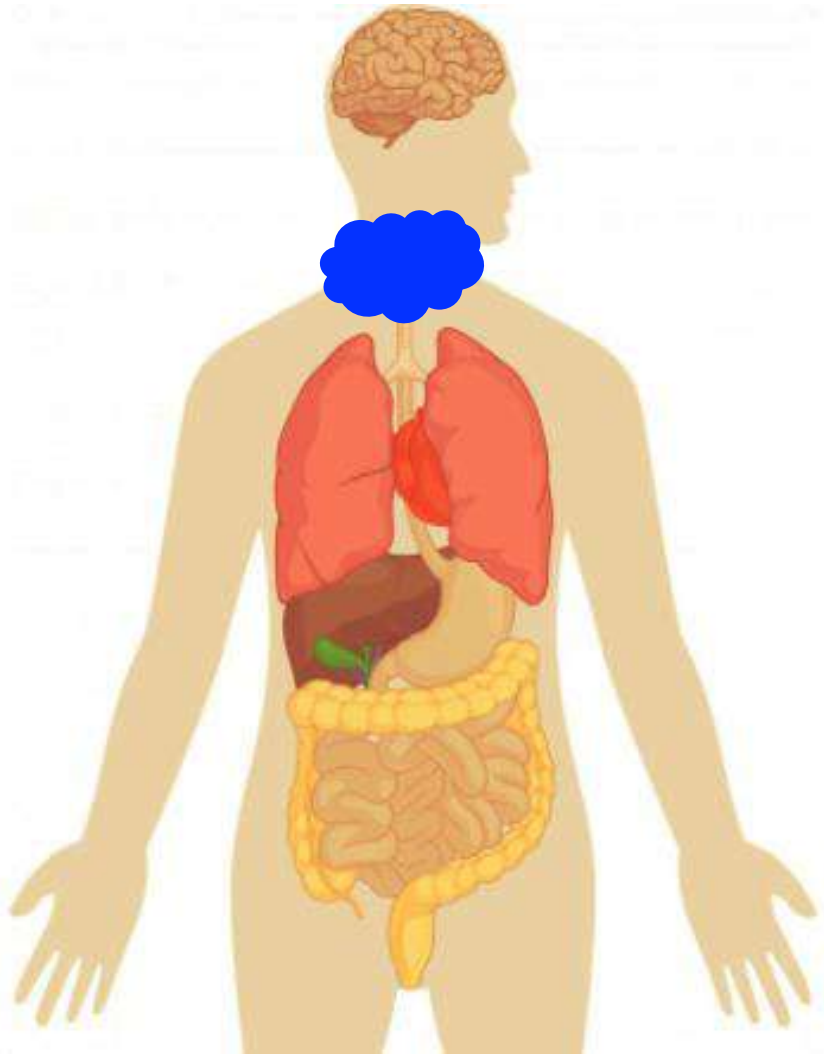
Alteraciones en RET

- Fusiones
- Mutaciones

Mutaciones en RET

Medular

- Hereditario >90%
- Esporádico >60%



RET M918T

Imagen tomada de https://www.freepik.es/vector-premium/anatomia-cuerpo-humano_6975170.htm (ultimo acceso 2 de noviembre 2021). Basado en dibujo de: Li AY, McCusker MG, Russo A, et al. RET fusions in solid tumors. *Cancer Treat Rev*. 2019;81:101911.

Fusiones en RET

Ca. Tiroides	• 10-20%	CCDC6 / NCOA4
Ca. Pulmón No células pequeñas	• 1-2%	KIF5B
Ca. Páncreas Ca. Glándulas salivares Ca. Colorrectal Ca. ovario	• <1%	

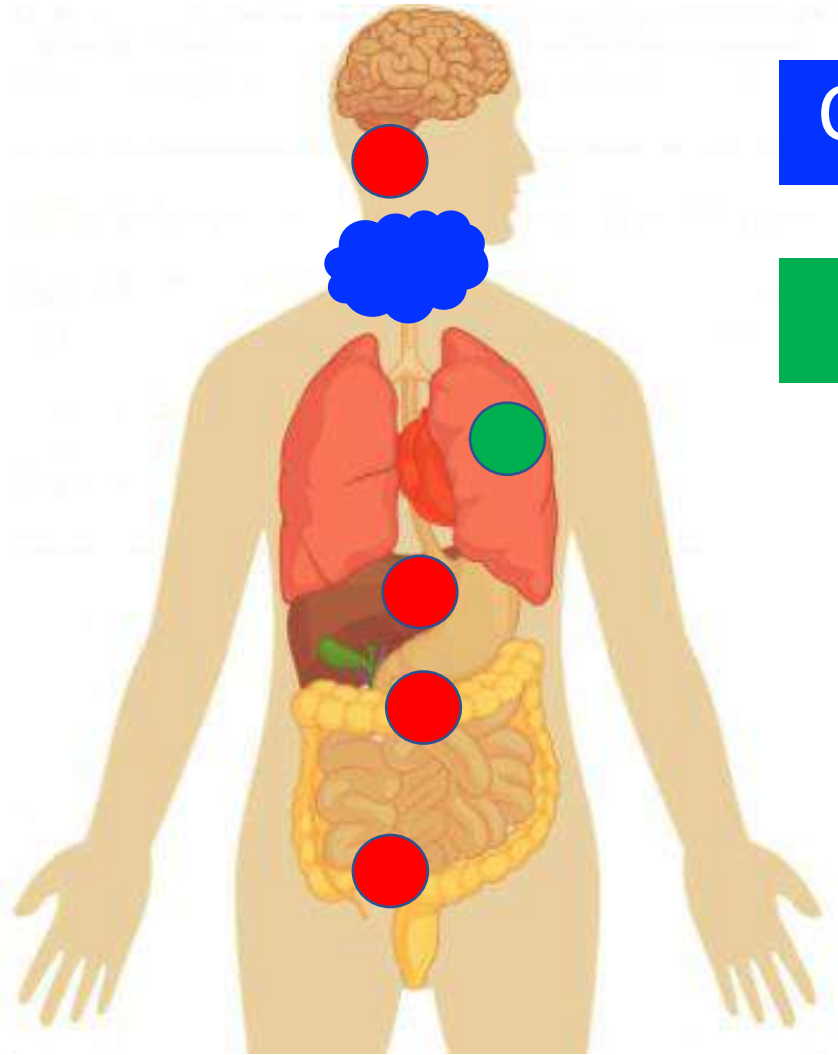
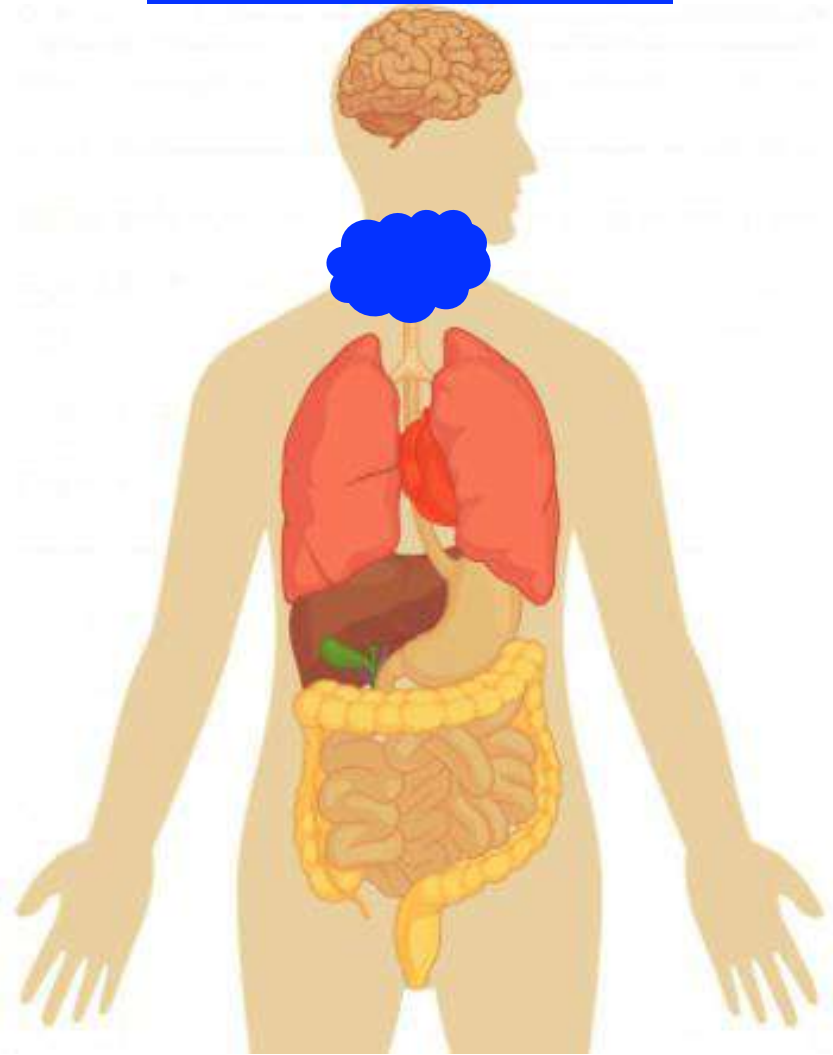


Imagen tomada de https://www.freepik.es/vector-premium/anatomia-cuerpo-humano_6975170.htm (ultimo acceso 2 de noviembre 2021). Basado en dibujo de: Li AY, McCusker MG, Russo A, et al. RET fusions in solid tumors. *Cancer Treat Rev*. 2019;81:101911.

Diana RET “tumor agnóstica”

Un subtipo tumoral



Cualquier subtipo tumoral

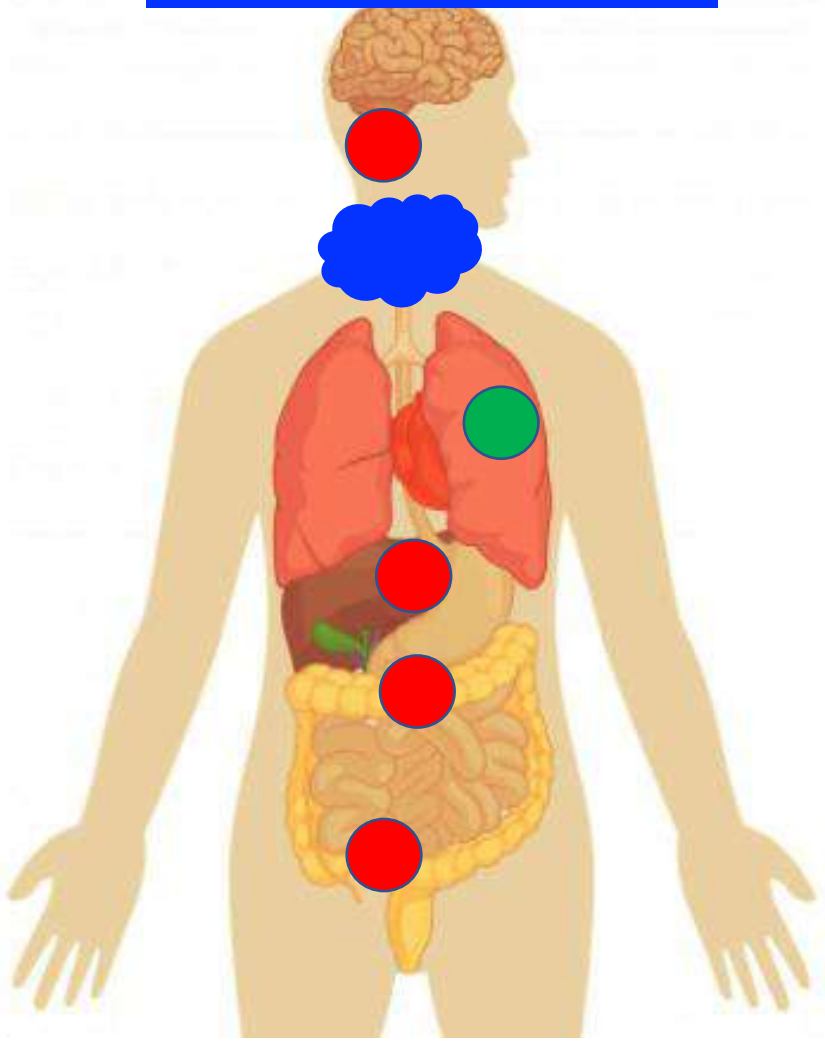
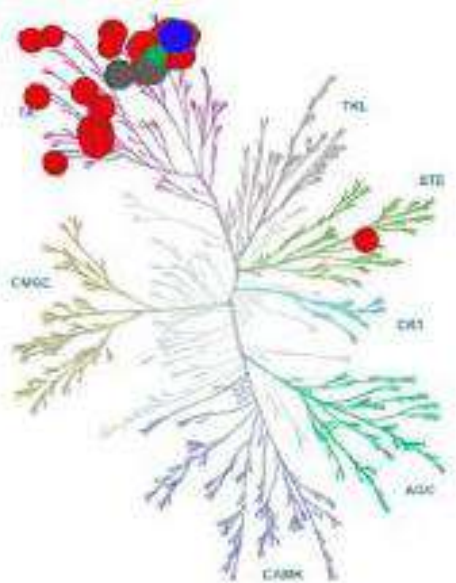


Imagen tomada de https://www.freepik.es/vector-premium/anatomia-cuerpo-humano_6975170.htm (ultimo acceso 2 de noviembre 2021).

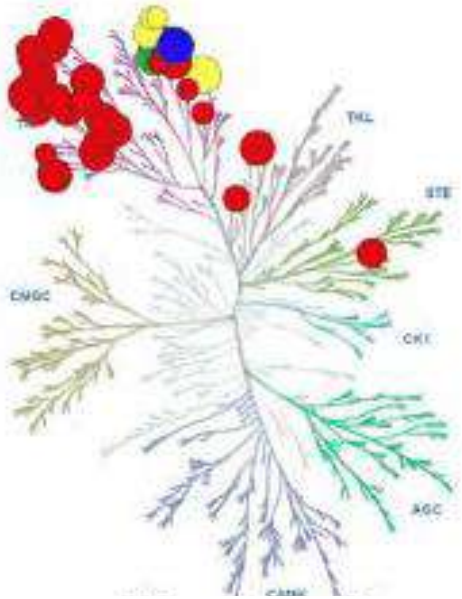
Inhibidor multikinasa

Inhibidor selectivo RET

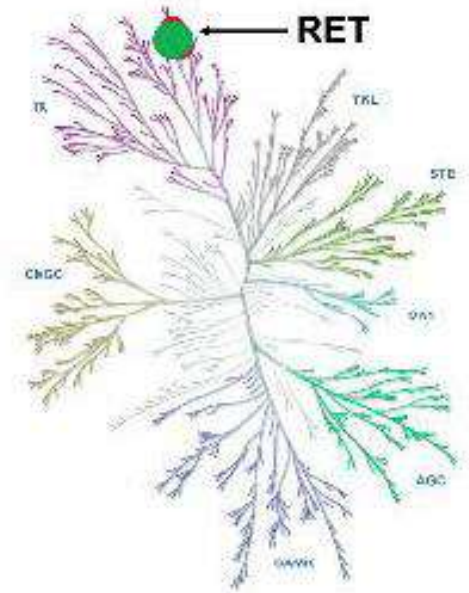
Carbozantinib



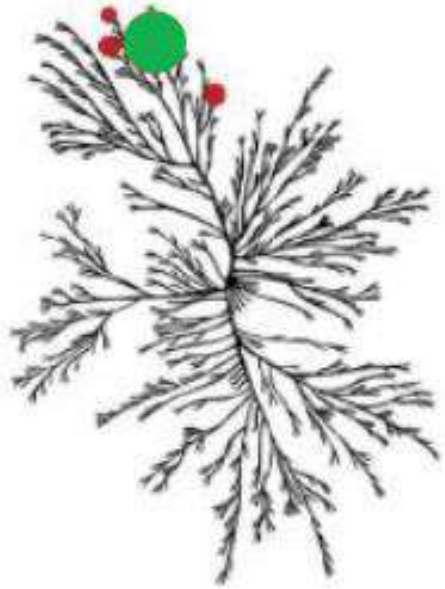
Vandetanib



Selpercatinib (LOXO-292)



Pralsetinib (BLU-667)



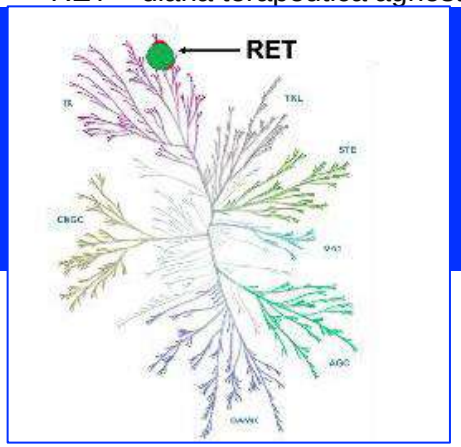
- RET
- KDR/VEGFR2
- FGFR1-3/EGFR
- MET/ALK/ROS
- Other kinases

Drilon A. RET fusions and mutations. ESMO 2020; Loong HH. 'Opening New Horizons' RET, NTRK, MET, HER2 … ESMO 2021

Inhibidores selectivos de RET

- Selpercatinib
- Pralsetinib

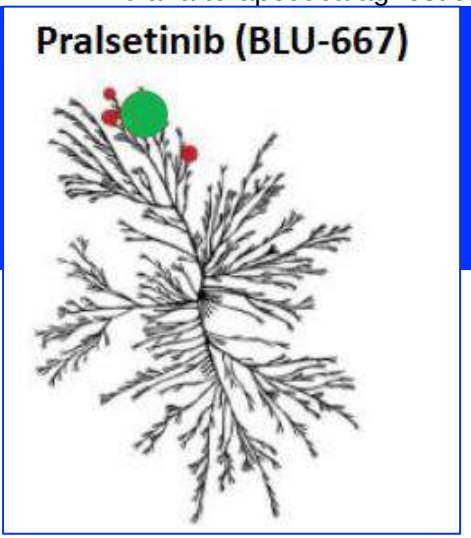
Selpercatinib (Loxo-292)



- Pequeña molécula.
- Oral
- Potente frente a alteraciones en RET: fusiones, mutaciones activadoras, mutaciones de resistencia adquirida…
- Penetra SNC.
  - Actividad demostrada en modelos preclínicos
- Previene autoactivación de RET y señales “downstream” (unión con el sitio de unión de ATP)

Drilon A. RET fusions and mutations. ESMO 2020

Pralsetinib (BLU-667)



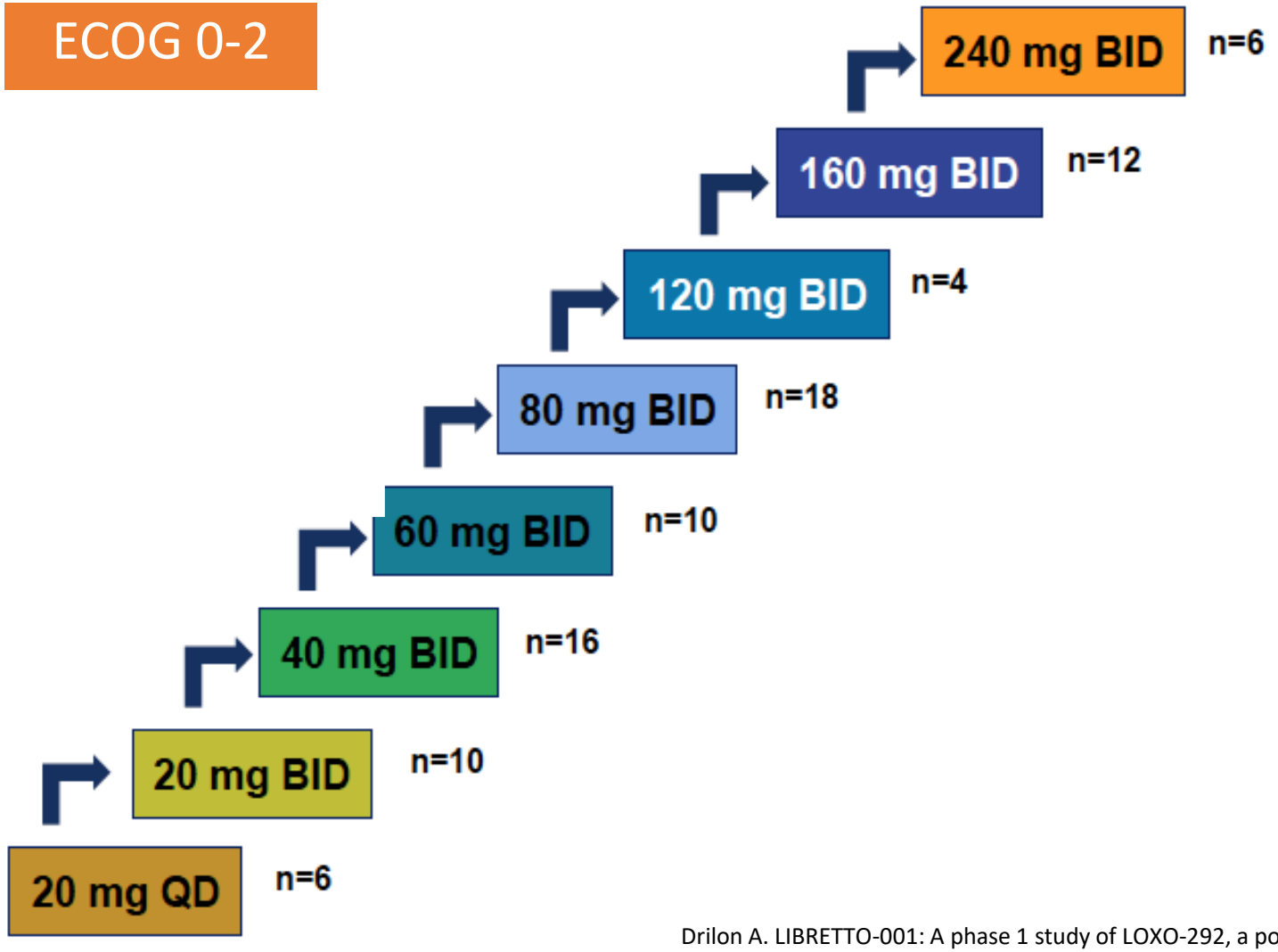
- Inhibidor selectivo y potente de RET
- Oral
- Eficaz frente a mutación de resistencia en RET V804 M/L
- Eficaz a nivel de SNC.

Gainor J. Clinical Activity and Tolerability of BLU-667 a Highly Potent and Selective RET Inhibitor in Patients with Advanced RET-Fusion+ Non-small Cell Lung Cancer. ASCO 2019

SELPERCATINIB → LIBRETO 001

Diseño del estudio

ECOG 0-2



Cohortes fase II 160 mg/12h

1: Tumores sólidos con fusión en RET tras 1ª línea o intolerante

2: Tumores sólidos con fusión en RET sin 1ª línea

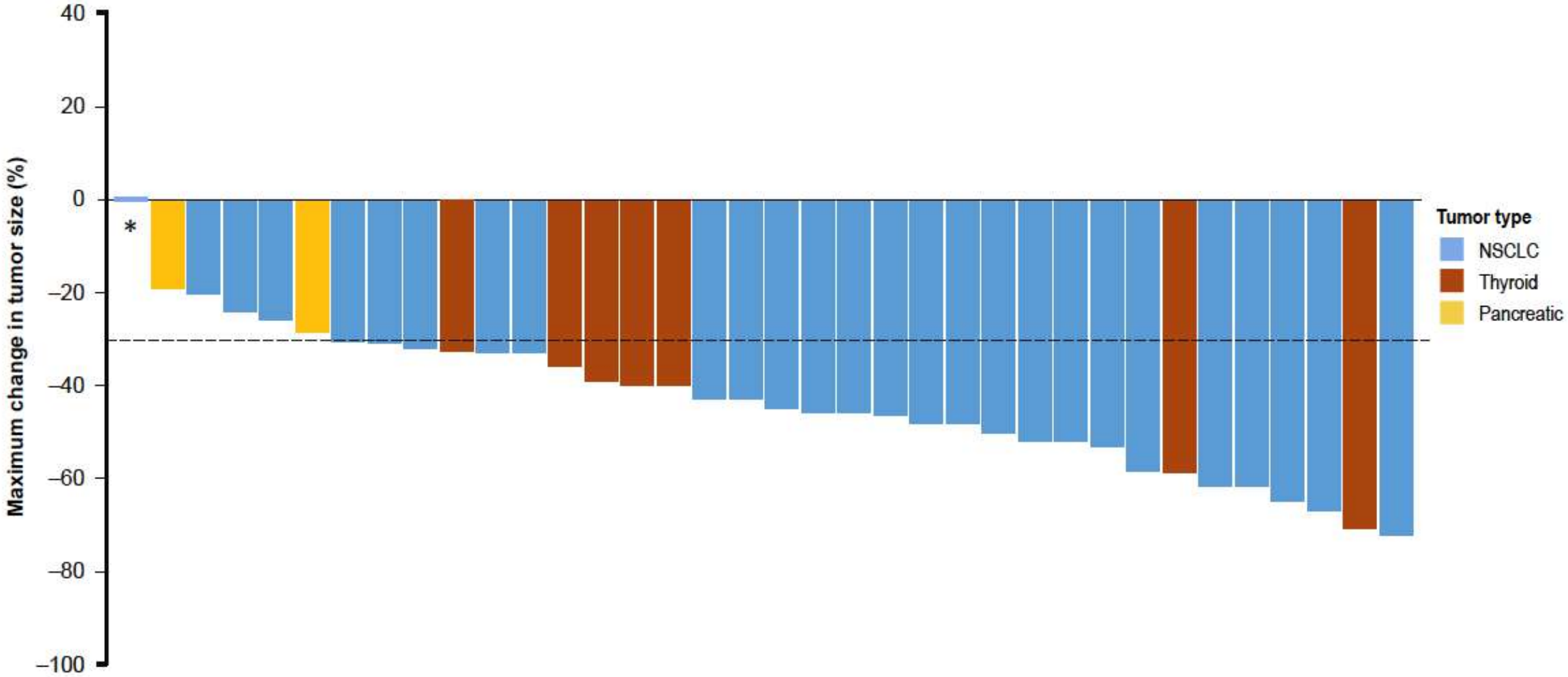
3: Ca. Medular con mutación en RET tras 1ª línea o intolerante

4: Ca. Medular con mutación en RET sin 1ª línea

5: Otros tumores sólidos con alteraciones en RET

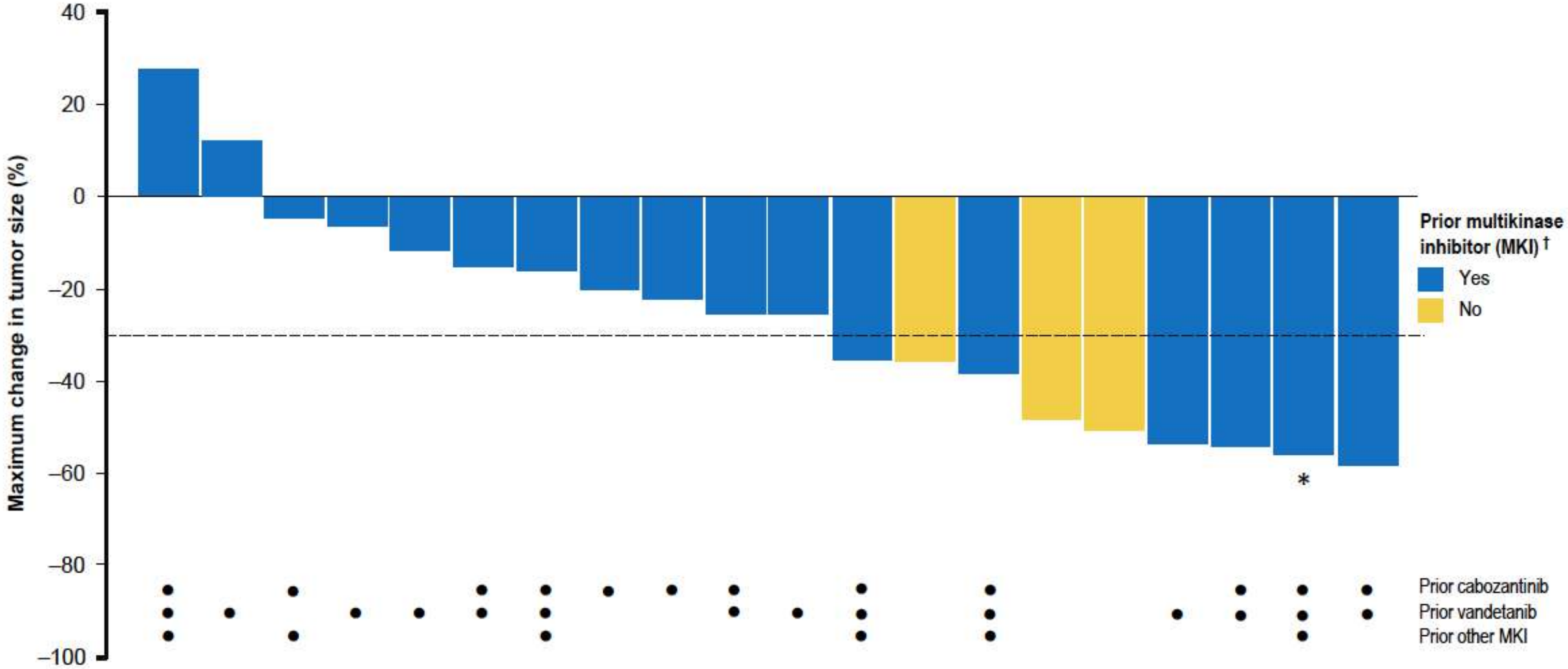
Drilon A. LIBRETTO-001: A phase 1 study of LOXO-292, a potent and highly selective RET inhibitor, in patients with RET-altered cancers. ASCO 2018

Eficacia – tumores con fusión en RET



Drilon A. LIBRETTO-001: A phase 1 study of LOXO-292, a potent and highly selective RET inhibitor, in patients with RET-altered cancers. ASCO 2018

Eficacia – tumores con mutación en RET



Drilon A. LIBRETTO-001: A phase 1 study of LOXO-292, a potent and highly selective RET inhibitor, in patients with RET-altered cancers. ASCO 2018

Eficacia – cohorte Ca. Pulmón no células pequeñas

96/253 M1 cerebral

	Prior Platinum PAS (n=105)	Prior Platinum IAS (n=218)	Treatment Naive (n=48)
Objective Response Rate (95% CI)	63.8% (53.9, 73)	56.9% (50.0, 63.6)	85.4% (72.2, 93.9)
Complete Response	1.9%	4.1%	2.1%
Partial Response	61.9%	52.8%	83.3%
Stable Disease	28.6%	37.2%	8.3%
Median Duration of Response (95% CI)	17.5 mo (12.1, NE)	17.5 mo (12.1, NE)	NE (12.0, NE)
Median Progression Free Survival (95% CI)	19.3 mo (13.9, NE)	19.3 mo (16.5, NE)	NE (13.8, NE)

Cortesía de Lilly

Eficacia – cohorte Ca. medular tiroides

	Prior Cabo/Vande (PAS) (n=55)	Prior Cabo/Vande (IAS) (n=143)	Cabo/Vande-Naive (n=112)
Objective Response Rate (95% CI)	69.1% (55.2, 80.9)	69.2% (61.0, 76.7)	71.4% (62.1, 79.6)
Complete Response	10.9%	4.2%	8.9%
Partial Response	58.2%	65.0%	62.5%
Stable Disease	25.5%	24.5%	25.0%
Median Duration of Response (95% CI)	NE (19.1, NE)	NE (19.1, NE)	22.0 mo (21.9, NE)
Median Progression Free Survival (95% CI)	NE (24.4, NE)	NE (20.0, NE)	NE (23.6, NE)

Cortesía de Lilly

Seguridad

	Selpercatinib N=746	
Adverse Reaction	All Grades (%)	Grades 3-4 (%)
Hypersensitivity†,‡	5.2	1.7*
Decreased Appetite	14.1	0.1*
Headache‡	24	1.5*
Dizziness‡	14.6	0.1*
ECG QT Prolonged‡	18.1	4.0
Hypertension‡	37.4	19.4
Abdominal Pain‡	25.5	1.9*
Diarrhoea‡	39.0	3.5*
Nausea	23.5	0.7*
Vomiting	16.2	0.9*
Constipation	27.1	0.5*
Dry Mouth‡	40.3	0

	Selpercatinib N=746	
Adverse Reaction	All Grades (%)	Grades 3-4 (%)
Rash‡	28.7	0.7*
Pyrexia	14.3	0.1*
Fatigue‡	38.2	2.3*
Oedema‡	38.7	0.5*
ALT increased†	49.5	10.6
AST increased†	55.0	9
Platelets decreased†	34.5	3.0
Lymphocyte count decreased†	46.2	16.1
Magnesium decreased†	25.6	0.5
Creatinine increased†	39.1	1.2
Haemorrhage	16.6	2.4

Cortesía de Lilly

PRALSETINIB → ARROW

Diseño del estudio

ECOG 0-1

Tumores con alteraciones en RET

Escalado dosis

30 mg

↓

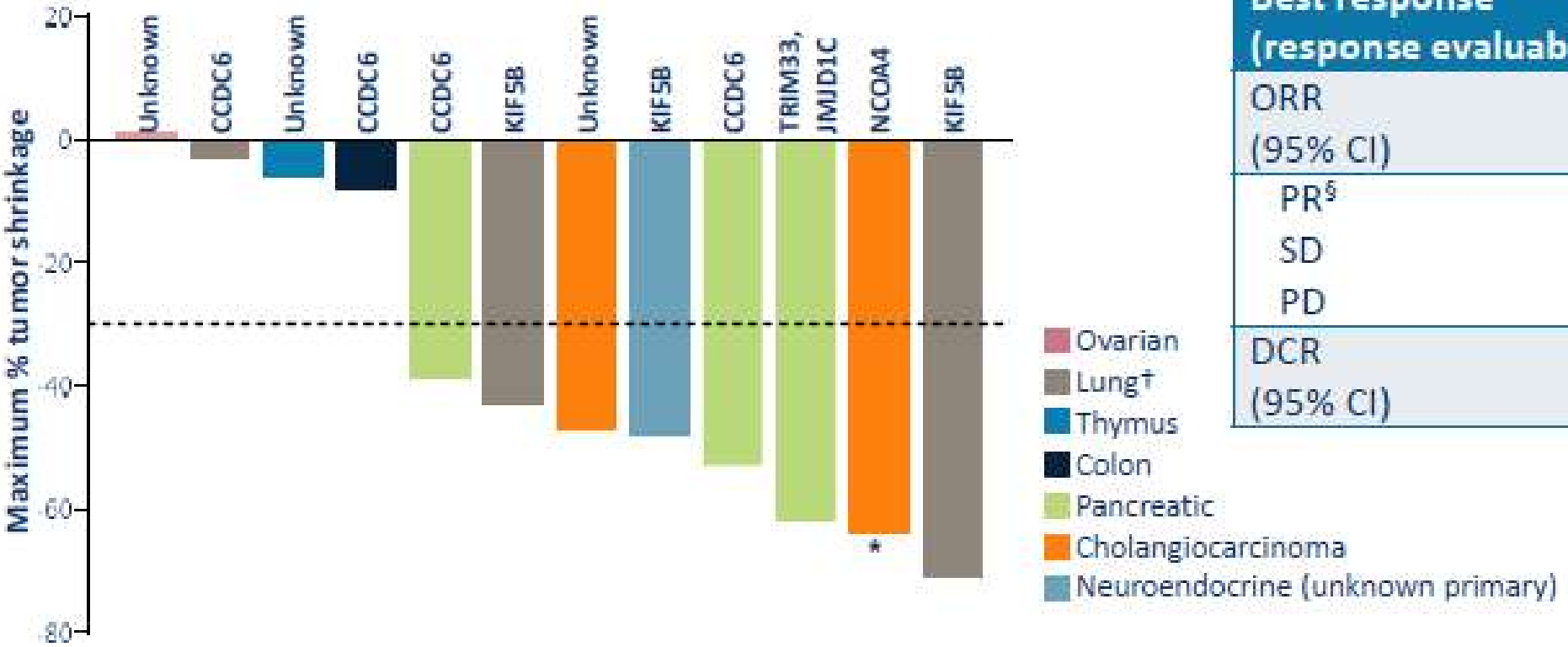
600 mg

Cohortes fase II 400 mg/12 h

- CPNCP con fusión en RET –platino previo (80)
- CPNCP con fusión en RET sin platino previo (40)
- Ca. Medular de tiroides con tratamiento previo (60)
- Ca. Medular de tiroides sin tratamiento previo (40)
- Tumores con fusiones en RET (20)
- Otros tumores con mutaciones en RET (20)

Gainor J. Clinical Activity and Tolerability of BLU-667 a Highly Potent and Selective RET Inhibitor in Patients with Advanced RET-Fusion+ Non-small Cell Lung Cancer. ASCO 2019

Eficacia – tumores con fusión en RET



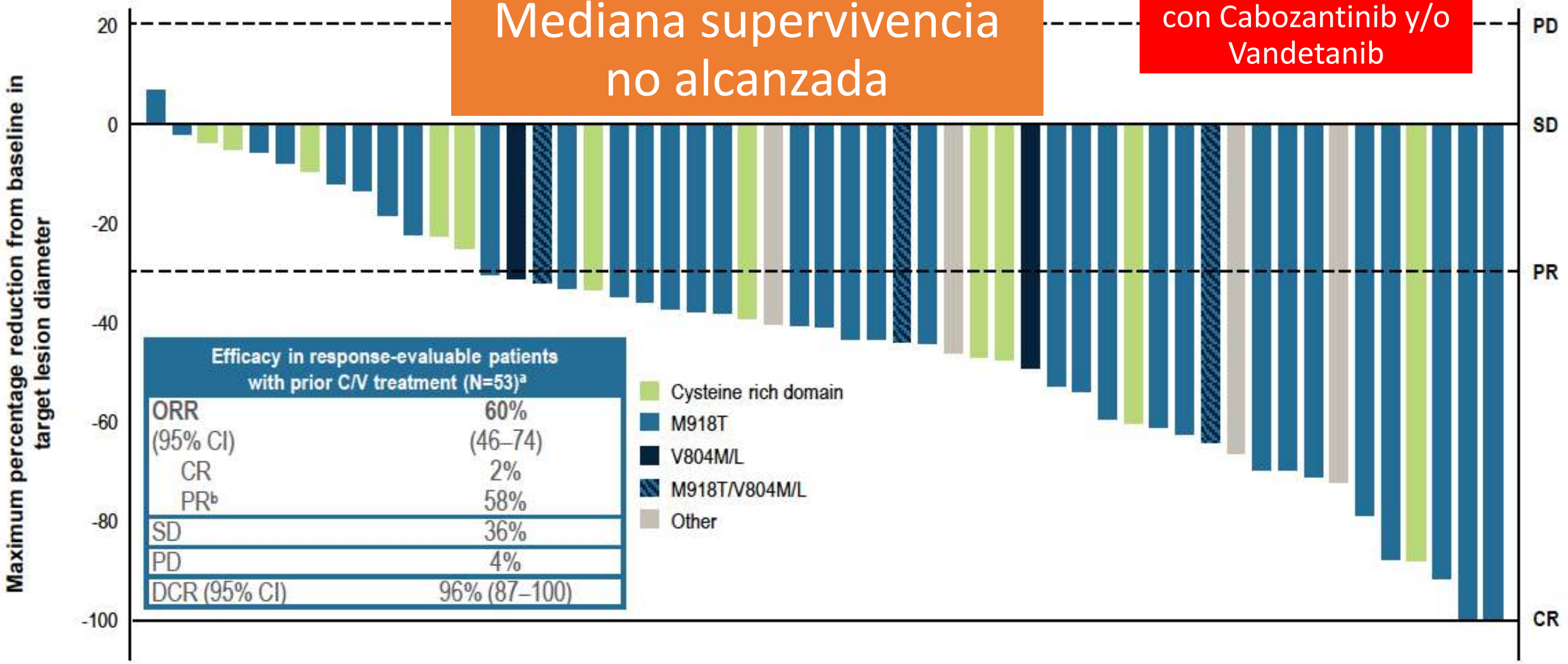
Best response (response evaluable), %	RET fusion-positive tumor (n=12)‡
ORR (95% CI)	50 (21–79)
PR§	50
SD	42
PD	8
DCR (95% CI)	92 (62–100)

Subbiah V, et al . Clinical activity of the RET inhibitor pralsetinib (BLU-667) in patients with RET fusion+ solid tumors. ASCO 2020

Eficacia – tumores con mutación en RET

Mediana supervivencia no alcanzada

Tratamiento previo con Cabozantinib y/o Vandetanib



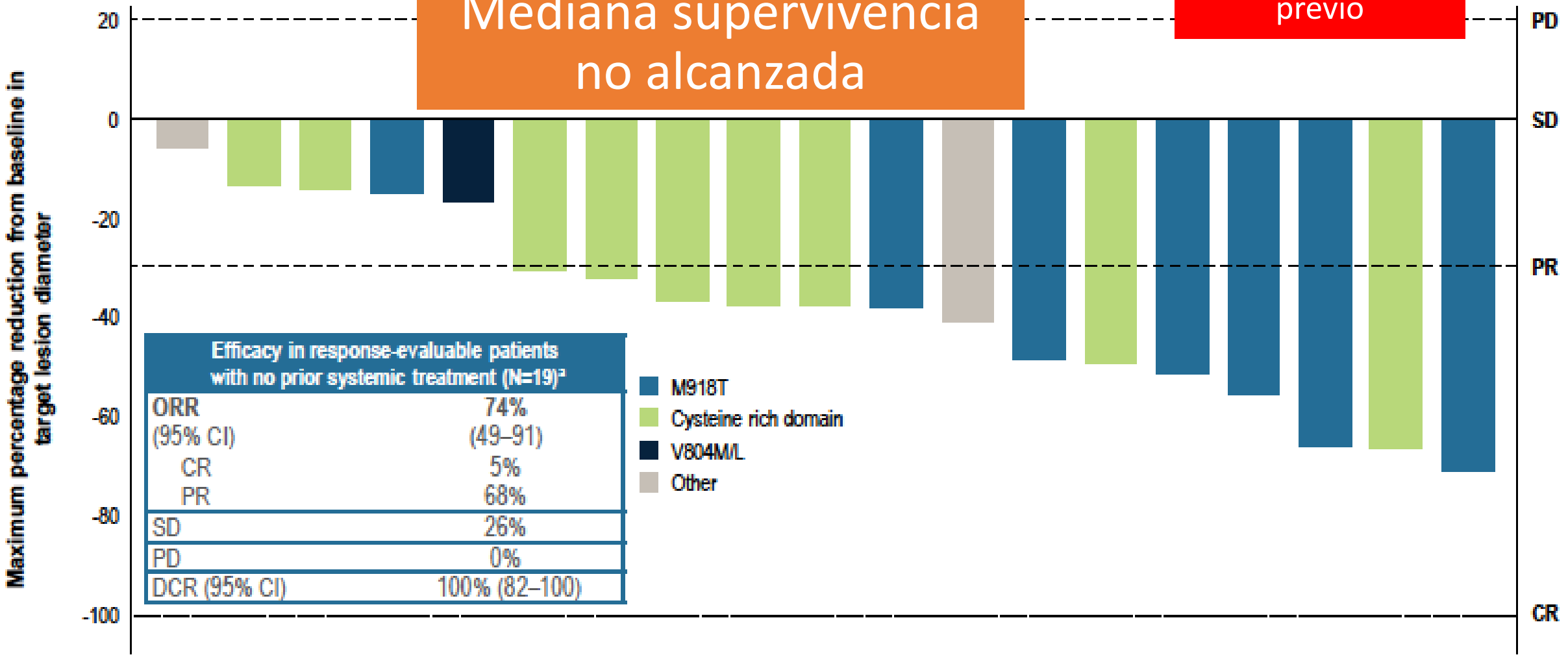
Efficacy in response-evaluable patients with prior C/V treatment (N=53)[a]	
ORR	60%
(95% CI)	(46–74)
CR	2%
PR[b]	58%
SD	36%
PD	4%
DCR (95% CI)	96% (87–100)

Hu ML, et al. Results from the registrational phase 1/2 ARROW trial of pralsetinib (BLU-667) in patients with advanced RETmutation-positive medullary thyroid cancer. ESMO 2020

Eficacia – tumores con mutación en RET

Mediana supervivencia no alcanzada

SIN tratamiento previo

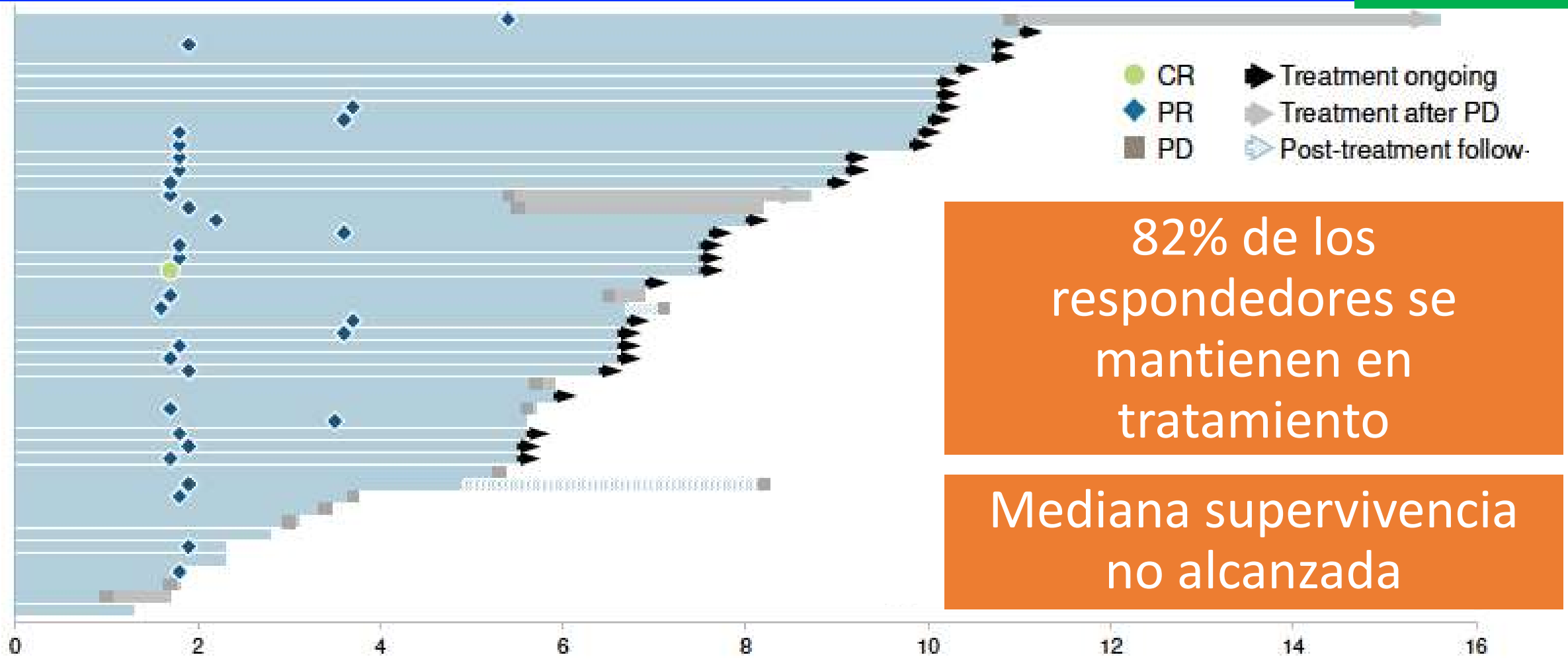


Efficacy in response-evaluable patients with no prior systemic treatment (N=19)[a]	
ORR	74%
(95% CI)	(49–91)
CR	5%
PR	68%
SD	26%
PD	0%
DCR (95% CI)	100% (82–100)

Hu ML, et al. Results from the registrational phase 1/2 ARROW trial of pralsetinib (BLU-667) in patients with advanced RETmutation-positive medullary thyroid cancer. ESMO 2020

Duración de respuesta – Ca. Pulmón no células pequeñas

400 mg/12 h



82% de los respondedores se mantienen en tratamiento

Mediana supervivencia no alcanzada

Gainor JF, et al. Clinical Activity and Tolerability of BLU-667, a Highly Potent and Selective RET Inhibitor, in Patients with Advanced RET-Fusion+ Non-small Cell Lung Cancer. ASCO 2019

Seguridad

TRAEs in ≥15% of patients	Pralsetinib 400 mg QD (N=438)	
	All grades	Grade ≥3
Aspartate aminotransferase increased	34%	2%
Anemia	24%	8%
Alanine aminotransferase increased	23%	2%
Hypertension	22%	11%
Constipation	23%	1%
White blood cell count decreased	18%	3%
Neutropenia	18%	10%
Neutrophil count decreased	16%	6%
Hyperphosphatemia	15%	1%

Hu ML, et al. Results from the registrational phase 1/2 ARROW trial of pralsetinib (BLU-667) in patients with advanced RETmutation-positive medullary thyroid cancer. ESMO 2020

Aprobaciones actuales

FDA approves selpercatinib for lung and thyroid cancers with RET gene mutations or fusions

Resources for Information | Approved Drugs

Oncology (Cancer) / Hematologic Malignancies Approval Notifications

Ongoing | Cancer Accelerated Approvals

Verified Clinical Benefit |

On May 8, 2020, the Food and Drug Administration granted accelerated approval to selpercatinib (RETEVMO, Eli Lilly and Company) for the following indications:

- Adult patients with metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC);
- Adult and pediatric patients ≥12 years of age with advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy;
- Adult and pediatric patients ≥12 years of age with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

Content current as of:
05/11/2020

Regulated Product(s)
Drugs
Prescription Drugs

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-selpercatinib-lung-and-thyroid-cancers-ret-gene-mutations-or-fusions; https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pralsetinib-lung-cancer-ret-gene-fusions; https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pralsetinib-ret-altered-thyroid-cancers Último acceso 2 de noviembre 2021

FDA approves pralsetinib for lung cancer with RET gene fusions

Resources for Information | Approved Drugs

Oncology (Cancer) / Hematologic Malignancies Approval Notifications

Ongoing | Cancer Accelerated Approvals

Verified Clinical Benefit | Cancer Accelerated Approvals

On September 4, 2020, the Food and Drug Administration granted accelerated approval to pralsetinib (GAVRETO, Blueprint Medicines Corporation) for adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test.

Today, FDA also approved the Oncomine Dx Target (ODxT) Test (Life Technologies Corporation) as a companion diagnostic for pralsetinib.

Efficacy was investigated in a multicenter, open-label, multi-cohort clinical trial (ARROW, NCT03037385) in patients whose tumors had RET alterations. Identification of RET gene alterations was prospectively determined in local laboratories using either next generation sequencing, fluorescence in situ hybridization, or other tests. The main efficacy outcome

Content current as of:
09/08/2020

Regulated Product(s)
Drugs
Oncology

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-selpercatinib-lung-and-thyroid-cancers-ret-gene-mutations-or-fusions; https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pralsetinib-lung-cancer-ret-gene-fusions; https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pralsetinib-ret-altered-thyroid-cancers Último acceso 2 de noviembre 2021

FDA approves pralsetinib for RET-altered thyroid cancers

Resources for Information | Approved Drugs

Oncology (Cancer) / Hematologic Malignancies Approval Notifications

Ongoing | Cancer Accelerated Approvals

Verified Clinical Benefit | Cancer Accelerated Approvals

On December 1, 2020, the Food and Drug Administration approved pralsetinib (GAVRETO, Blueprint Medicines Corporation) for adult and pediatric patients 12 years of age and older with advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy or *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

Efficacy was investigated in a multicenter, open label, multi-cohort clinical trial (ARROW, NCT03037385) in patients whose tumors had *RET* gene alterations. Identification of *RET* gene alterations was prospectively determined in local laboratories using either next generation sequencing, fluorescence *in situ* hybridization, or other tests.

The main efficacy outcome measures were overall response rate (ORR) and response duration determined by a blinded independent review committee using RECIST 1.1.

Content current as of:
12/01/2020

Regulated Product(s)
Drugs
Prescription Drugs

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-selpercatinib-lung-and-thyroid-cancers-ret-gene-mutations-or-fusions; https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pralsetinib-lung-cancer-ret-gene-fusions; https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pralsetinib-ret-altered-thyroid-cancers Último acceso 2 de noviembre 2021

Retsevmo

Share RSS

selpercatinib

AUTHORISED
This medicine is authorised for use in the European Union.

Table of contents

Overview

Retsevmo is a cancer medicine for use in patients whose cancer is caused by changes in a gene called *RET*. It can be used for:

- advanced non-small cell lung cancer in adults who had previously received immunotherapy or platinum-based cancer medicines or both;
- advanced thyroid cancer in adults who had previously been treated with the cancer medicines sorafenib or lenvatinib or both;
- advanced medullary thyroid cancer in patients aged from 12 years who had previously been treated with the cancer medicines cabozantinib or vandetanib or both.

https://www.ema.europa.eu/en/medicines/human/EPAR/retsevmo; https://www.ema.europa.eu/en/medicines/human/summaries-opinion/gavreto Último acceso 2 de noviembre 2021

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Gavreto

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pralsetinib

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Opinion

On 16 September 2021, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a conditional2 marketing authorisation for the medicinal product Gavreto, intended for the treatment of patients with rearranged during transfection (RET)-fusion positive non-

https://www.ema.europa.eu/en/medicines/human/EPAR/retsevmo; https://www.ema.europa.eu/en/medicines/human/summaries-opinion/gavreto Último acceso 2 de noviembre 2021

CONCLUSIONES

- Selpercatinib y pralsetinib son dos inhibidores de RET que han demostrado seguridad y eficacia en pacientes con tumores con fusiones y mutaciones en RET, independientemente de la histología.
- Los pacientes con tumores y alteraciones en RET son poco frecuentes pero, de tenerlas, se pueden beneficiar del tratamiento con inhibidores selectivos en RET.
- Es fundamental el testado de RET, sobre todo en cáncer de tiroides y en cáncer de pulmón no de células pequeñas (aprobaciones FDA/EMA).

Gracias

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4 de noviembre 2021