LUNG CANCER
UPDATES
AACR HIGHLIGHTS
14-18 ABRIL 2018, CHICAGO

Terapias dirigidas (II)

Dr. Manuel Dómine
Fundación Jiménez Díaz

Con el patrocinio de

Bristol-Myers Squibb

Iniciativa científica de:

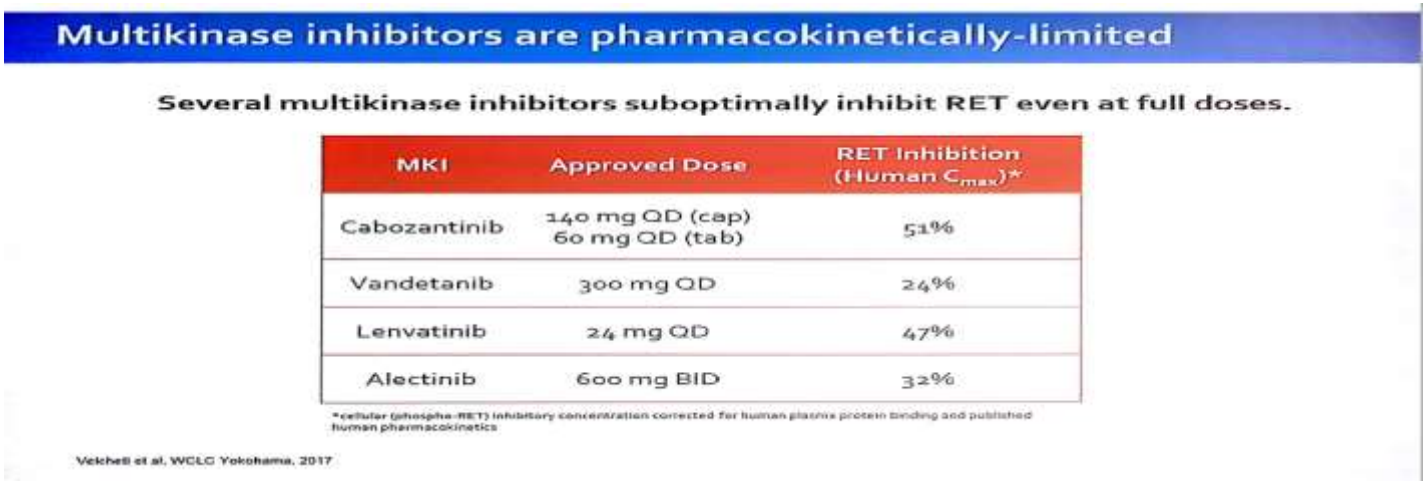
GECP

Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group

Targeted therapy
Nuevo inhibidor selectivo de RET

RET fusion 1-2% NSCLC

Hasta el momento actual no existen fármacos dirigidos aprobados en las fusiones de RET



Multikinase inhibitors are pharmacokinetically-limited

Several multikinase inhibitors suboptimally inhibit RET even at full doses.

MKI	Approved Dose	RET Inhibition (Human C_{max})*
Cabozantinib	140 mg QD (cap) 60 mg QD (tab)	51%
Vandetanib	300 mg QD	24%
Lenvatinib	24 mg QD	47%
Alectinib	600 mg BID	32%

*cellular (phospho-RET) inhibitory concentration corrected for human plasma protein binding and published human pharmacokinetics

Velcheti et al. WCLC Yokohama, 2017

Inhibidores multikinasa: Respuestas bajas y toxicidad alta

Next-generation RET kinase inhibitors are more RET-selective

pre-2017

multikinase inhibitors (with anti-RET activity)

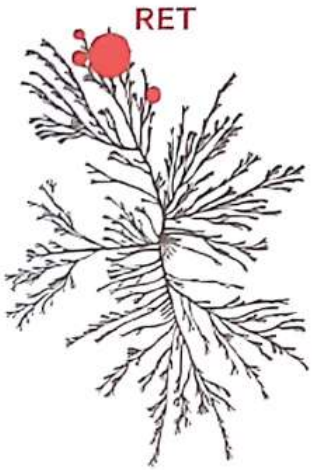
many **repurposed** to focus on RET inhibition

2017

TKIs more selective for RET

BLU-667
LOXO-292

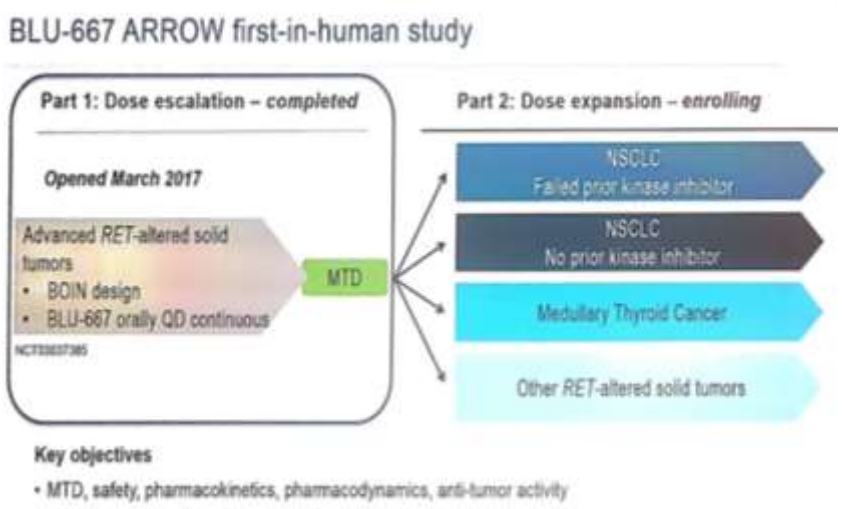
rationally designed or selected to more optimally inhibit RET and target activating *RET* alterations

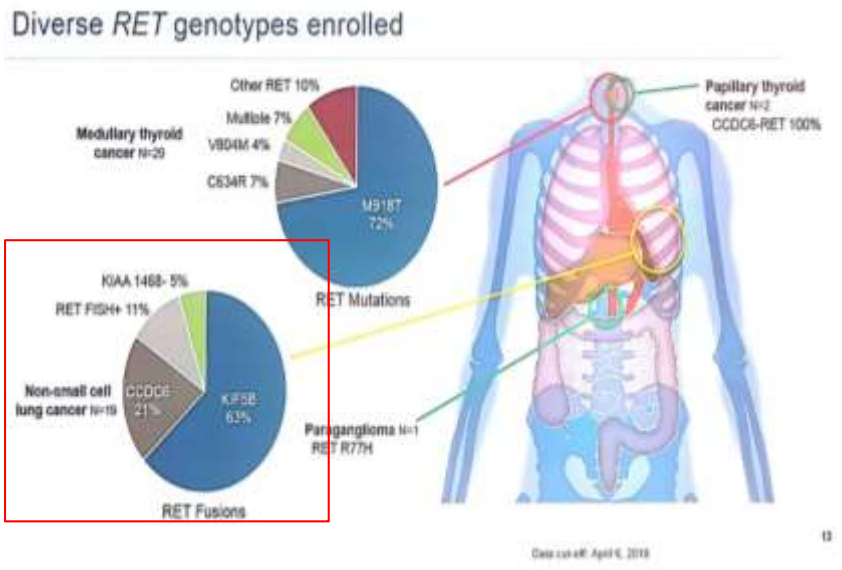


BLU-667

Estudio ARROW: BLU-667, Inhibidor Selectivo de RET (Subbiah V. et al)

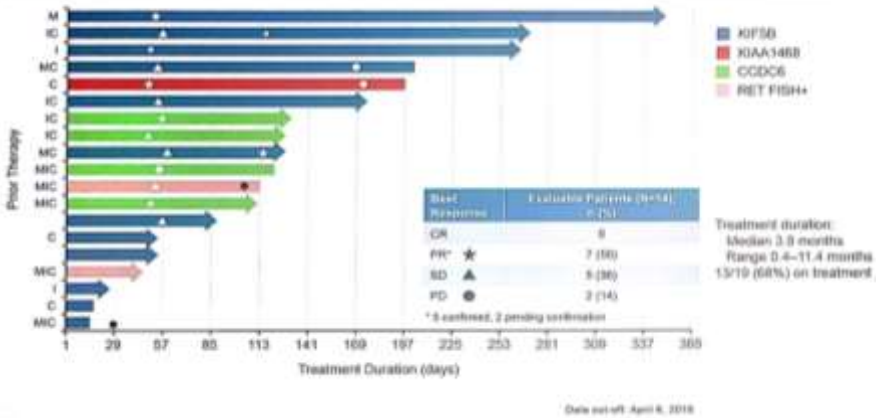
Se presentan los resultados del estudio first-in-human, BLU-667 ARROW, en tumores RET positivos con un nuevo inhibidor oral selectivo de RET (total 56 pacientes)





Response Rate and DOR

BLU-667 has durable activity and high response rate in RET-altered NSCLC



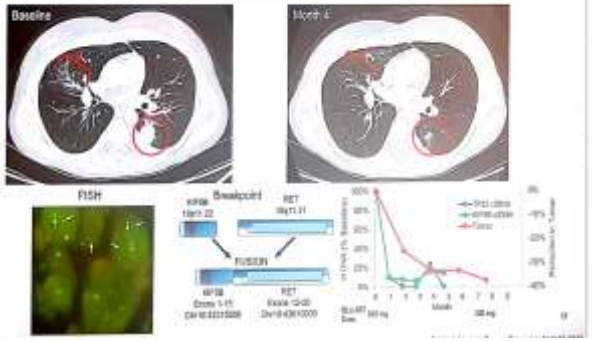
Drug	*RET*-rearranged lung cancers
Cabozantinib	ORR 28%
Vandetanib	ORR 18-47%
BLU-667	ORR 36% (n=5/14)

Best Response	Evaluable Patients (N=14); n (%)
CR	0
PR* ★	7 (50)
SD ▲	5 (36)
PD ●	2 (14)

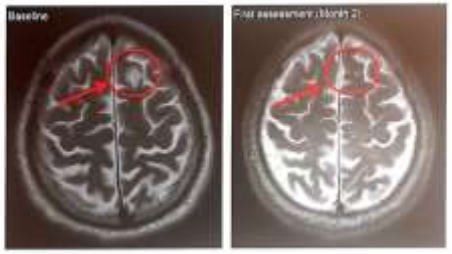
* 5 confirmed, 2 pending confirmation

Potent activity against KIF5B-RET NSCLC – post-vandetinib+everolimus

Potent activity against KIF5B-RET NSCLC – post chemotherapy



Activity against KIF5B-RET NSCLC brain metastases



Toxiciy

Understanding the safety profile of BLU-667

Maximum Tolerated Dose – 400 mg QD

Dose (mg QD)	# Evaluable (N=49)	Dose limiting toxicity
30	1	None
60	6	None
100	5	Alanine transaminase increased (1)
200	12	None
300	11	Tumor lysis syndrome (1) Hypertension (1)
400	10	Asthenia (1) Hypertension (1)
600	4	Hyponatremia (1) Hypertension (1)

Treatment-emergent Adverse Events ≥10% per CTCAE
(30-400 mg Safety Population, N=49)

Adverse event, n (%)	Grade 1	Grade 2	Grade 3
Constipation	10 (20)	2 (4)	0
ALT increased	10 (20)	0	1 (2)
AST increased	8 (16)	2 (4)	0
Hypertension	3 (6)	2 (4)	4 (8)
Fatigue	5 (10)	1 (2)	1 (2)
Edema peripheral	6 (12)	1 (2)	0
Diarrhea	4 (8)	1 (2)	1 (2)
Blood creatinine increased	6 (12)	0	0
Hyperphosphatemia	4 (8)	2 (4)	0
Nausea	5 (10)	1 (2)	0
Leukopenia	5 (10)	0	0
Neutropenia	2 (4)	1 (2)	2 (4)
White blood cell decreased	2 (4)	2 (4)	1 (2)
Insomnia	5 (10)	0	0
Cough	3 (6)	2 (4)	0

Most adverse events were Grade 1

8 (16%) patients had Grade 3 treatment-related AE

No Grade 4/5 treatment-related AEs

Overall toxicity comparison of BLU-667 with older RET inhibitors

Drug	Dose Reduction Rate	Drug Discontinuation Rate	Diarrhea (any grade)	Rash (any grade)	Liver dysfunction (any grade)	Drug-related AE (≥grade 3)
Cabozantinib	73%	8%	61%	62%	97%	46%
Vandetanib	53%	21%	79%	63%	21%	-
BLU-667	Await further treatment at RP2D	Await further treatment at RP2D (2%*)	12%**	none reported	22%**	16%

*n=1/49 patients in escalation with transaminitis **treatment-emergent adverse event (AE)

No grade 4 or 5 treatment-related AEs.

Estudio ARROW: BLU-667, Inhibidor Selectivo de RET (Subbiah V. et al)

- Mayor capacidad de inhibición selectiva y mejor perfil de toxicidad que los inhibidores RET multikinasa
- En NSCLC-RET+, BLU-667 consigue 50% de respuestas (7/14) con 36% respuestas confirmadas (5/14)
- Respuestas en pacientes pretratados así como no tratados previamente con TKIs
- Se confirma actividad preliminar intracranial
- Fase expansion del estudio en marcha

Estudio ARROW: BLU-667, Inhibidor Selectivo de RET (Subbiah V. et al)

CANCER DISCOVERY

search

Advanced Search

Home About Articles For Authors Alerts News

Research Articles

Precision Targeted Therapy With BLU-667 for RET-Driven Cancers

Vivek Subbiah, Justin F. Gainor, Rami Rahal, Jason D. Brubaker, Joseph L. Kim, Michelle Maynard, Wei Hu, Qiongfang Cao, Michael P. Sheets, Douglas Wilson, Kevin J. Wilson, Lucian DiPietro, Paul Fleming, Michael Palmer, Mimi I. Hu, Lori Wirth, Marcia S. Brose, Sai-Hong Ignatius Ou, Matthew Taylor, Elena Garralda, Stephen Miller, Beni Wolf, Christoph Lengauer, Timothy Guzi, and Erica K. Evans

DOI: 10.1158/2159-8290.CD-18-0338 Check for updates

Article Figures & Data Info & Metrics PDF

Published OnlineFirst April 15, 2018
doi: 10.1158/2159-8290.CD-18-0338

Abstract

Otros inhibidores selectivos de RET presentados

4784 / 13 - TAS0286/HM05, a novel highly selective RET inhibitor, prominently inhibits various RET defective tumor growth. H. Fujita

4785 / 14 - NMS-E668, a highly potent orally available RET inhibitor with selectivity towards VEGFR2 and demonstrated antitumor efficacy in multiple RET-driven cancer models. E. Ardini