V SIMPOSIO GETHI | 18/19 noviembre de 2019

Ilustre Colegio Oficial de Médicos de Madrid. Aula Jiménez Díaz. Madrid

Resultados clínicos de los inhibidores de RET en cáncer de tiroides y otros tumores infrecuentes

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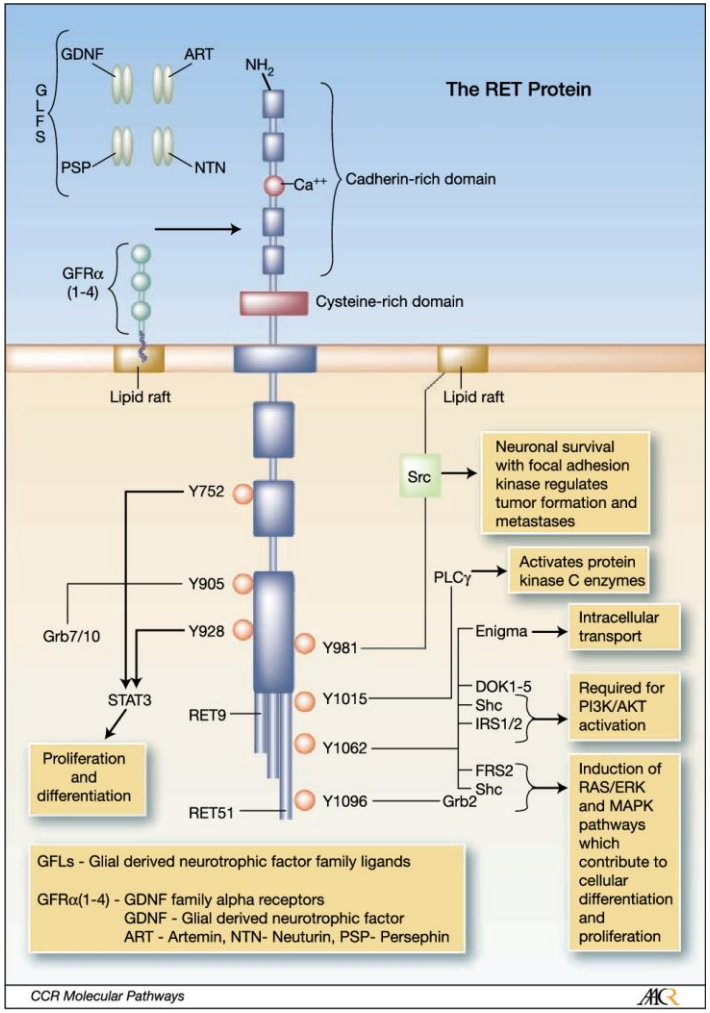
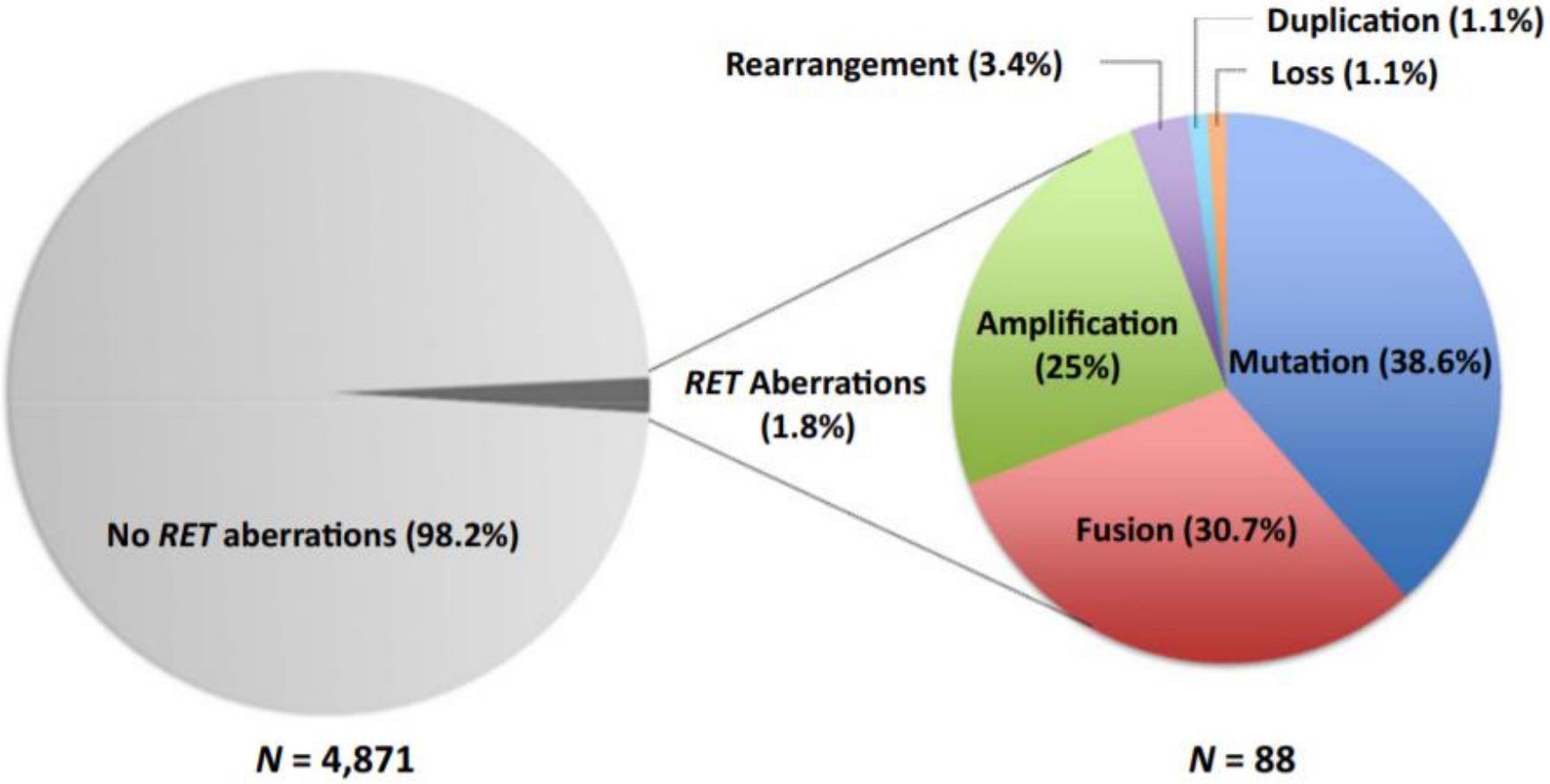
Why develop a RET Specific Kinase inhibitor?

Oncogenic addiction



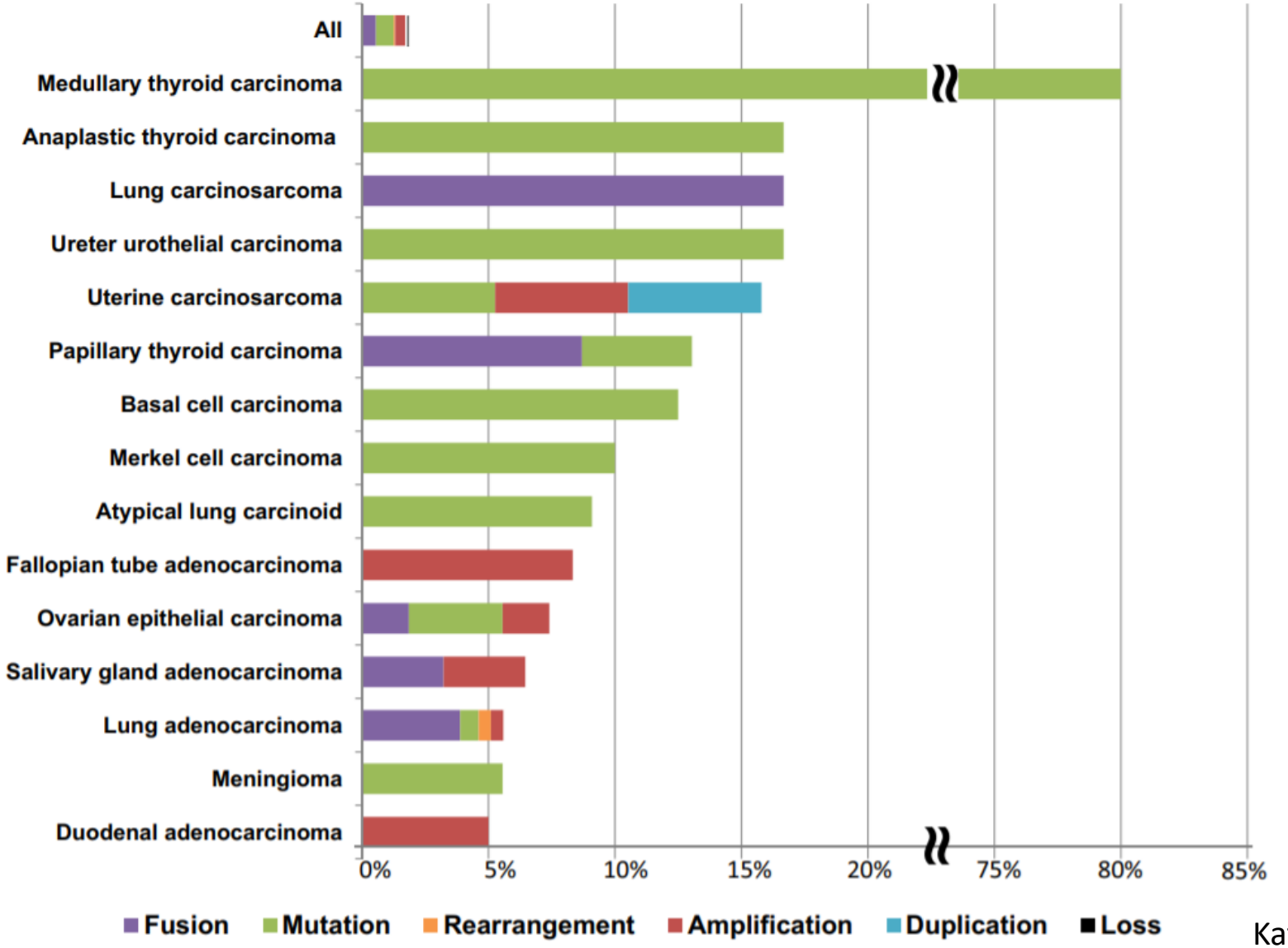
- ✓ REarranged during Transfection (RET) proto-oncogene on chromosome 10q11.2
- ✓ Encodes for a transmembrane receptor with intracelullar kinase domain
- ✓ 1985: RET was identified as a novel trasforming gene
- ✓ RET alterations occur in a mutually exclusive pattern with other oncogenic drivers

Clin Cancer Res 15(23) December 1, 2009



Kato et al CCR 2017

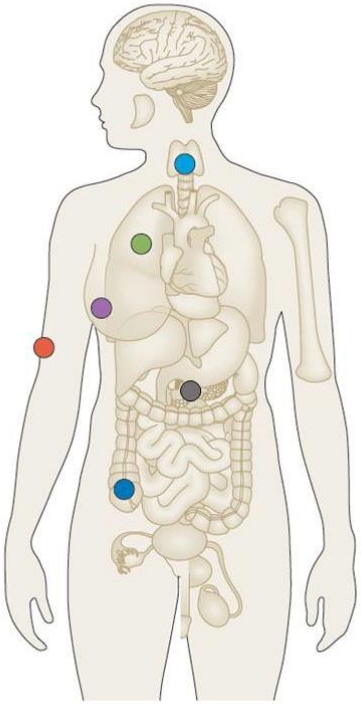
V SIMPOSIO GETHI



Kato et al CCR 2017

RET is activated by two major mechanisms in cancer

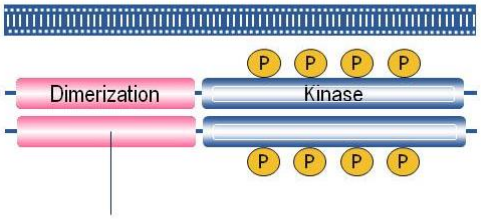
***RET* fusions**



Non-small cell lung cancer (2%)

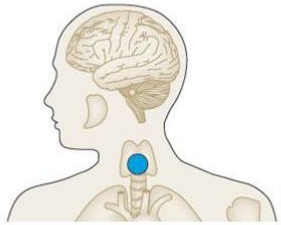
Papillary and other thyroid cancers (10–20%)

Pancreatic cancer (<1%)
Salivary gland cancer (<1%)
Spitz tumors (<1%)
Colorectal cancer (<1%)
Ovarian cancer (<1%)
Myeloproliferative disorders (<1%)
Many others (<1%)



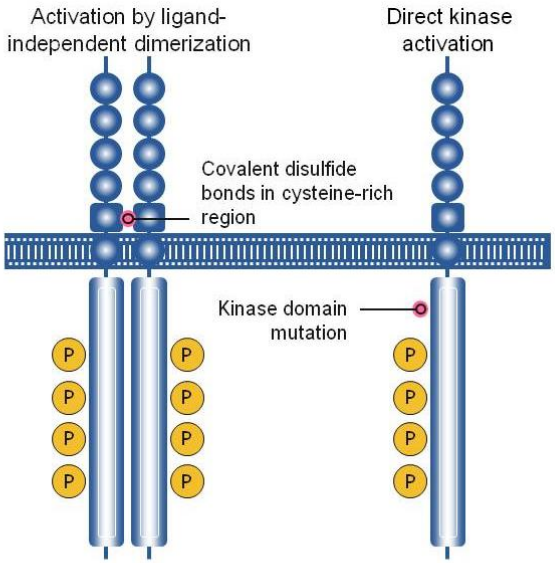
KIF5B (most common in lung cancer)
CCDC6* or *NCOA4 (most common in thyroid cancer)

***RET* mutations**



Medullary thyroid cancer

sporadic (>60%)
hereditary (>90%)



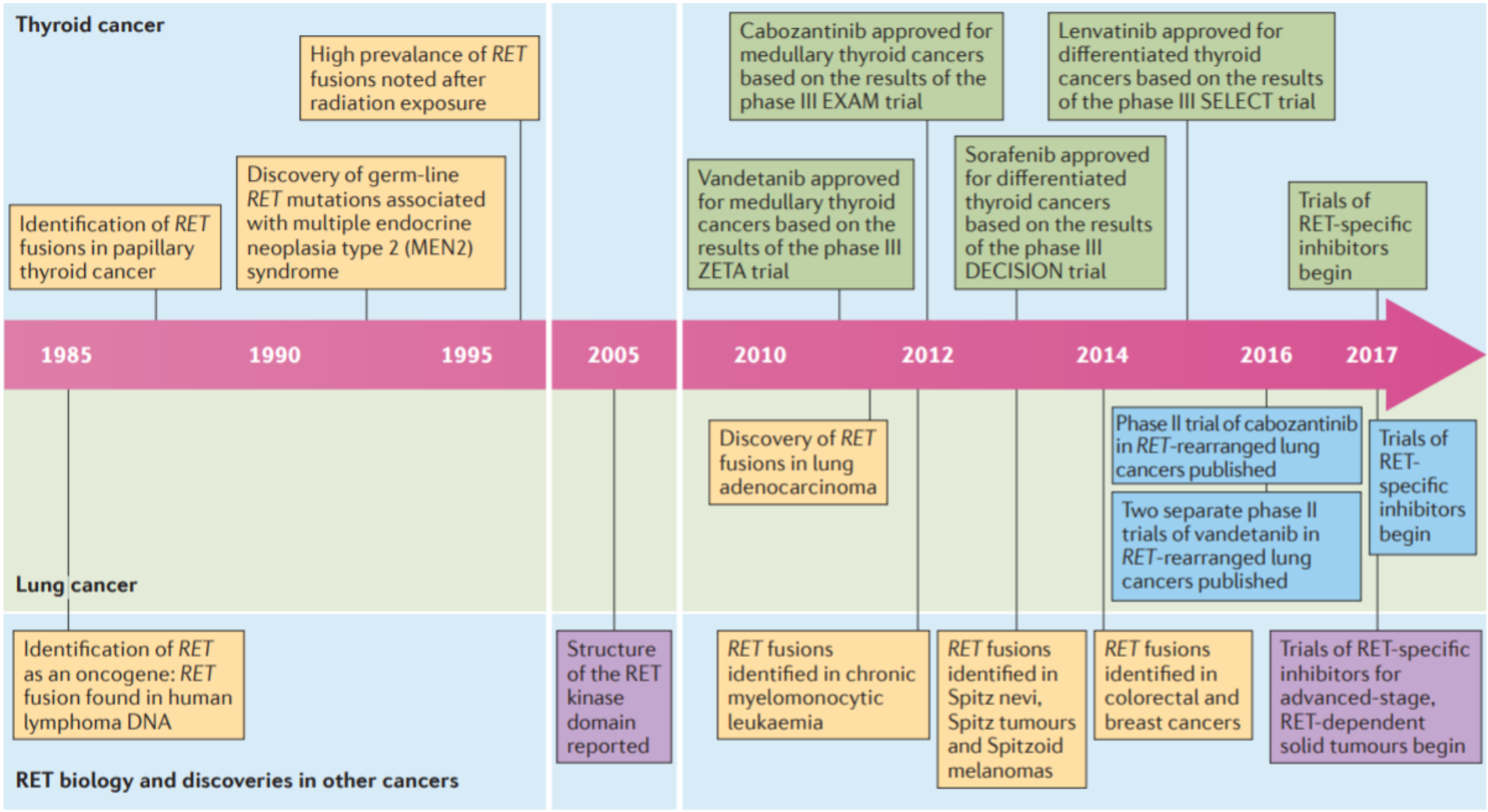
Common mutation: ***RET* M918T**

A. Drilon ASCO 2018

TABLE 4. RELATIONSHIP OF COMMON *RET* MUTATIONS TO RISK OF AGGRESSIVE MTC IN MEN2A AND MEN2B, AND TO THE INCIDENCE OF PHEO, HPTH, CLA, AND HD IN MEN2A

RET *mutation*[a]	*Exon*	*MTC risk level*[b]	*Incidence of PHEO*[c]	*Incidence of HPTH*[c]	*CLA*[d]	*HD*[d]
G533C	8	MOD	+	–	N	N
C609F/G/R/S/Y	10	MOD	+/++	+	N	Y
C611F/G/S/Y/W	10	MOD	+/++	+	N	Y
C618F/R/S	10	MOD	+/++	+	N	Y
C620F/R/S	10	MOD	+/++	+	N	Y
C630R/Y	11	MOD	+/++	+	N	N
D631Y	11	MOD	+++	–	N	N
C634F/G/R/S/W/Y	11	H	+++	++	Y	N
K666E	11	MOD	+	–	N	N
E768D	13	MOD	–	–	N	N
L790F	13	MOD	+	–	N	N
V804L	14	MOD	+	+	N	N
V804M	14	MOD	+	+	Y	N
A883F	15	H	+++	–	N	N
S891A	15	MOD	+	+	N	N
R912P	16	MOD	–	–	N	N
M918T	16	HST	+++	–	N	N

[a]The references for each of the *RET* mutations can be found in the Supplementary Information, where all reported *RET* mutations in MTC are listed.
[b]Risk of aggressive MTC: MOD, moderate; H, high; HST, highest.
[c]Incidence of PHEO and HPTH: + = ~10%; ++ = ~20%–30%; +++ = ~50%.
[d]Y, positive occurrence; N, negative occurrence.



A. Drilon et al Nature 2018

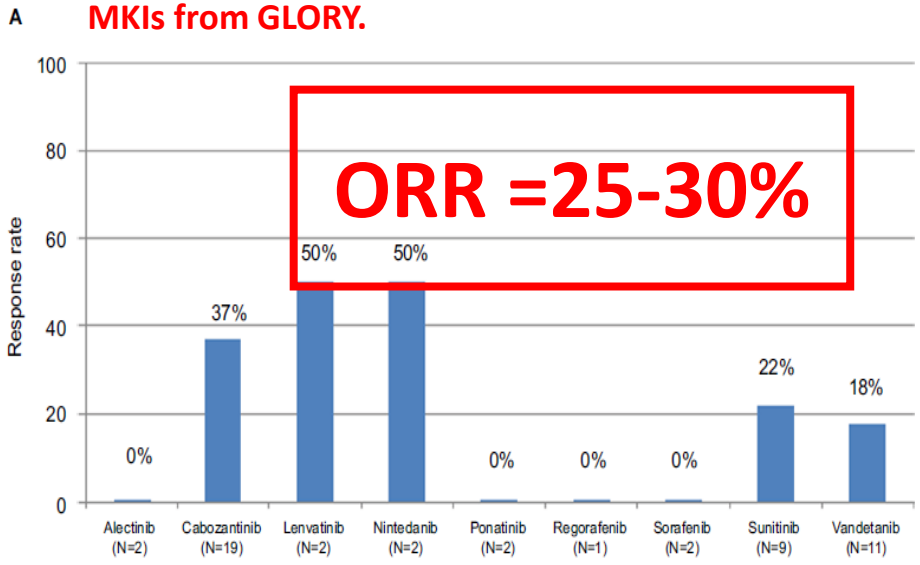
- **Medullary thyroid carcinoma**:

✓ EXAM RCT phase 3 study (cabozantinib vs placebo) – All comers: ORR 28% v 0%, PFS 11.2 v 4 mo, OS 26.6 v 21 mo (NS)
Higher in RET-mutant: 32 v 0%, 13.9 v 4 mo, 44.3 v 18.9 mo
(Schlumberger et al. Annals Oncology 2017)

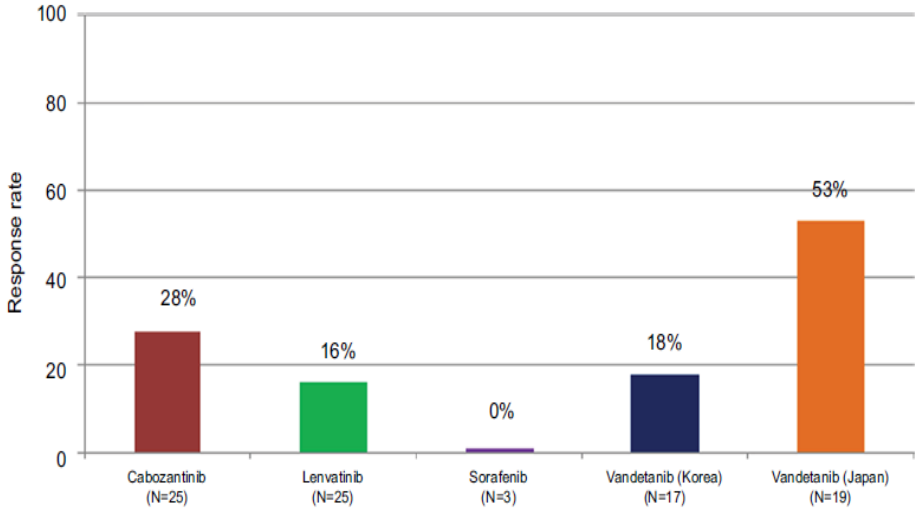
✓ ZETA RCT phase 3 study (vandetanib vs placebo)- All comers: ORR 45% vs 13%, PFS 30.5 vs 19.3 mo, HR 0,46 (Wells et al. JCO 2012)

→**Both trials: no effect on OS**
→**High incidence of side effects leading to drug discontinuation**

Response rates of retrospective analysis on anti-RET MKIs from GLORY.



Response rates of 5 phase II trials on anti-RET MKIs



NSCLC harbouring RET fusion

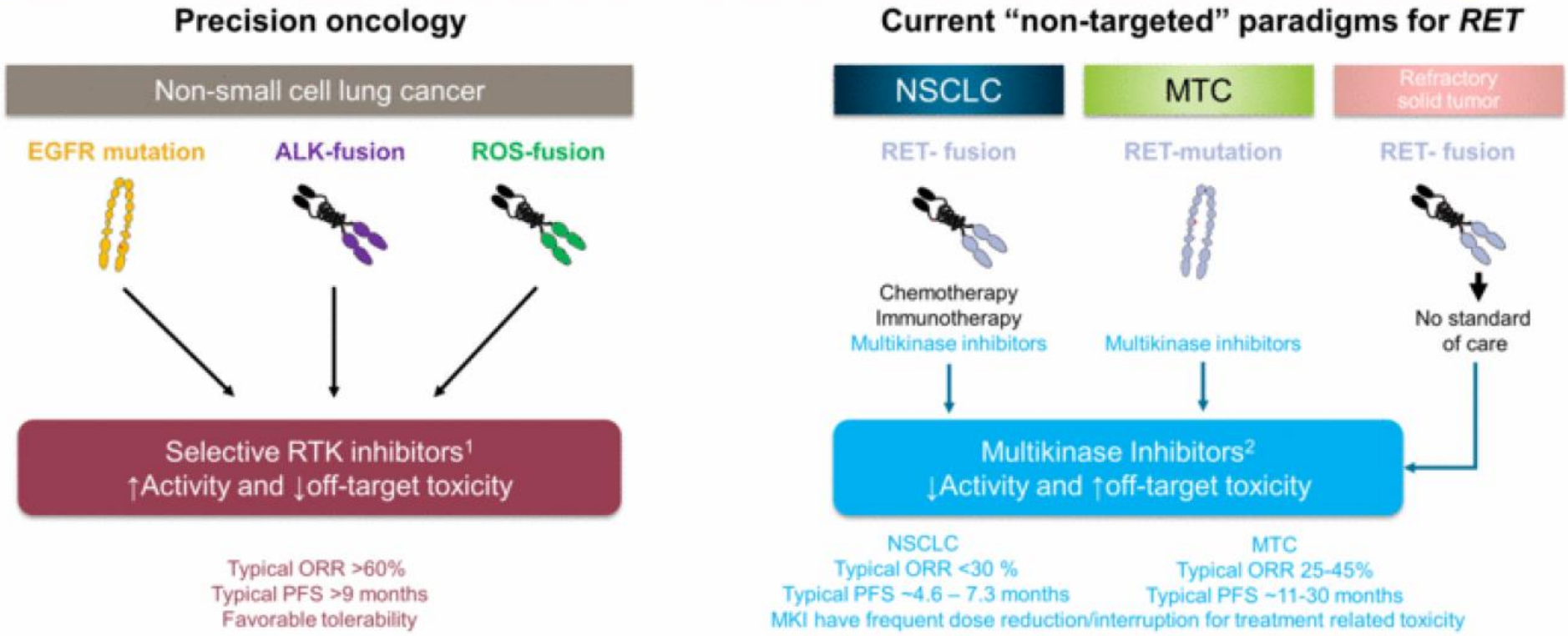
GLORY results (Gautschi et al. JCO 2017):

Multicenter RET registry launched in 2015

RET fusion was seen mainly in adenocarcinoma with minimal to no history of tobacco exposure, good response to platinum and pemetrexed based chemotherapy, 30% of response in retrospective study with carbozantinib, vandetanib lenvatinib etc.

Bronte et al.
Lung Cancer: Targets and Therapy 2019:10 27–36

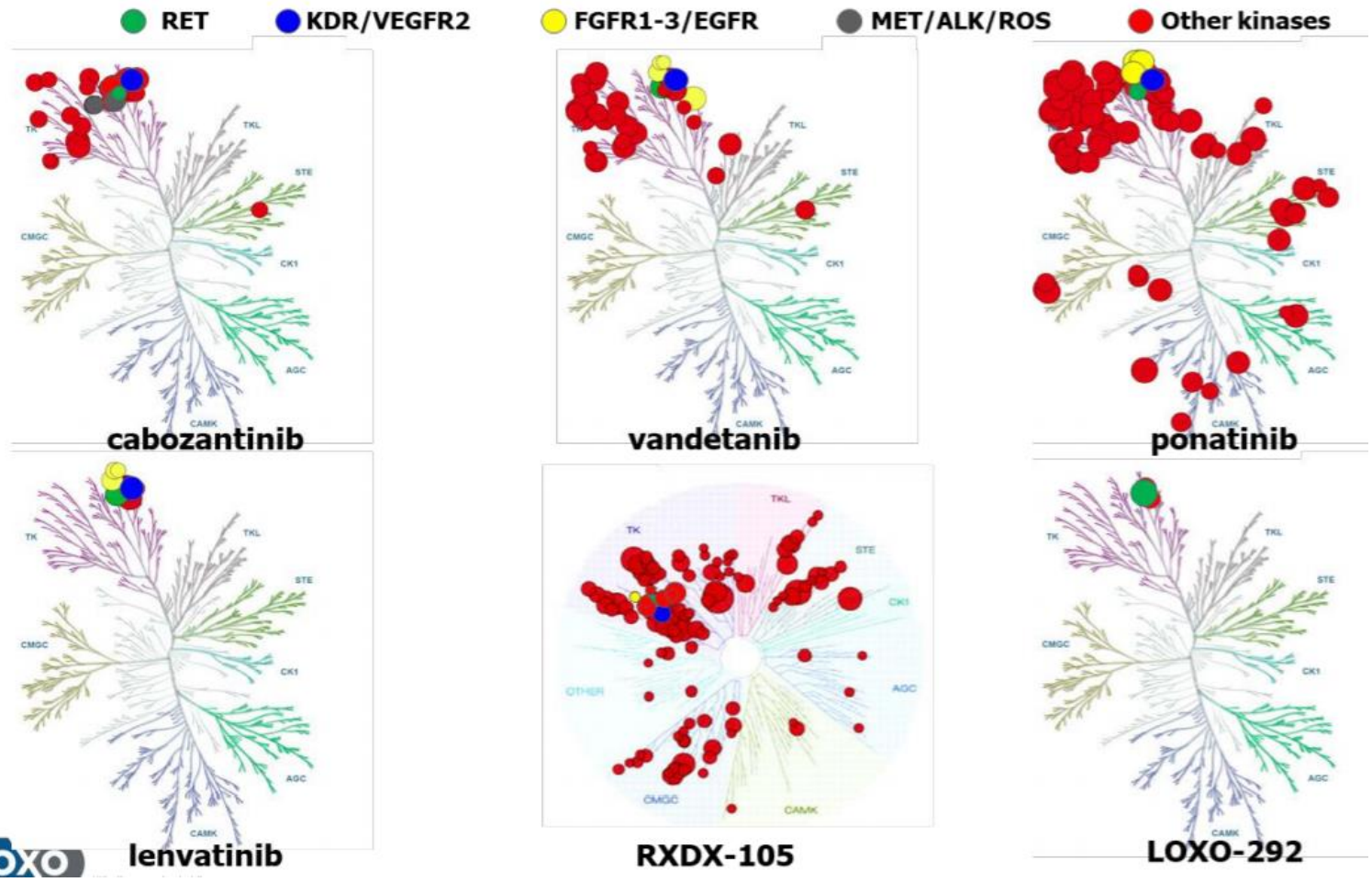
Patients with *RET*-alterations have not benefited from precision oncology



MKI, multikinase inhibitors; MTC, medullary thyroid cancer; NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; RTK, receptor tyrosine kinase

1. Herbst RS et al. *Nature* 2018; 553:446-54; 2. Drilon A et al. *Nat Rev Clin Oncol*. 2018;15:151-67.

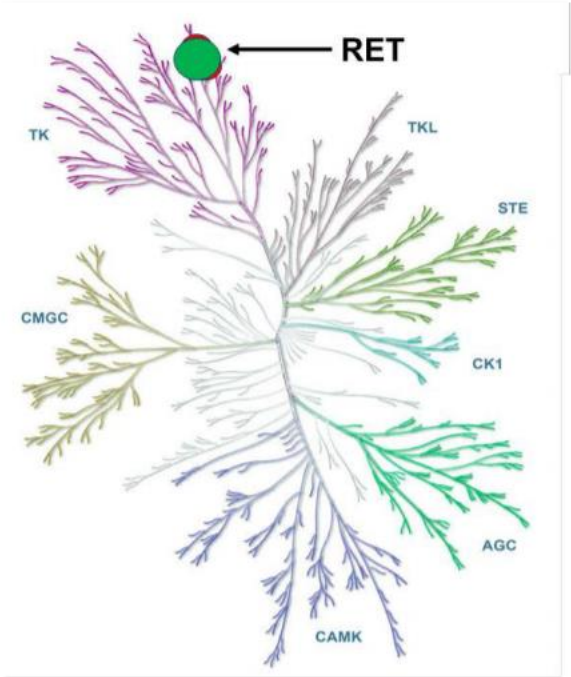
Kinome selectivity for inhibitors with anti-*RET* activity



Selpercatinib* (LOXO-292) is a potent and selective *RET* inhibitor

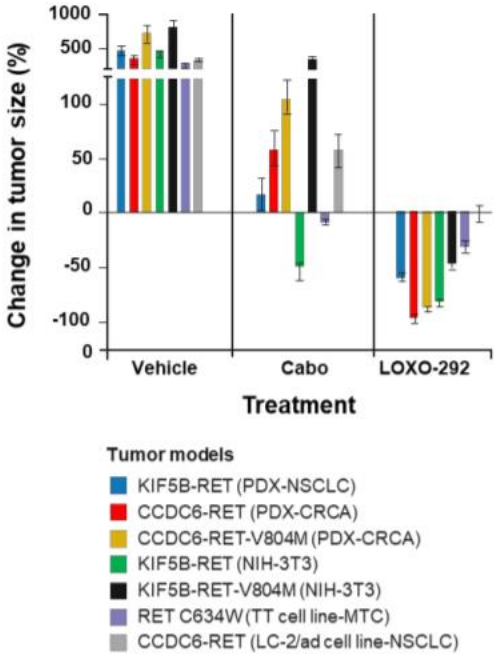
Kinome selectivity

Highly selective for RET



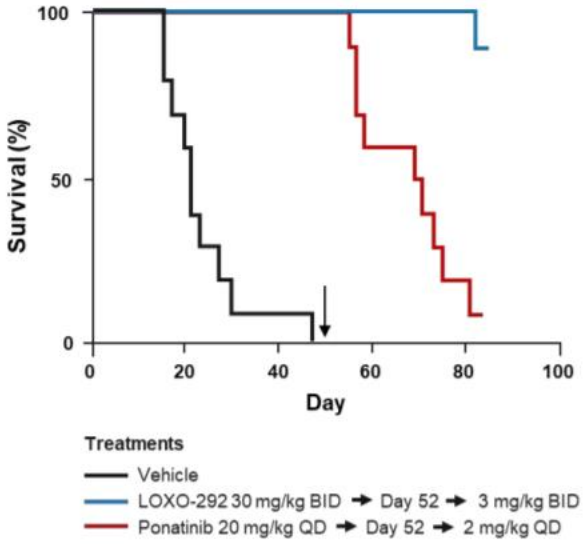
Xenograft models

Multiple fusions/mutations/histologies

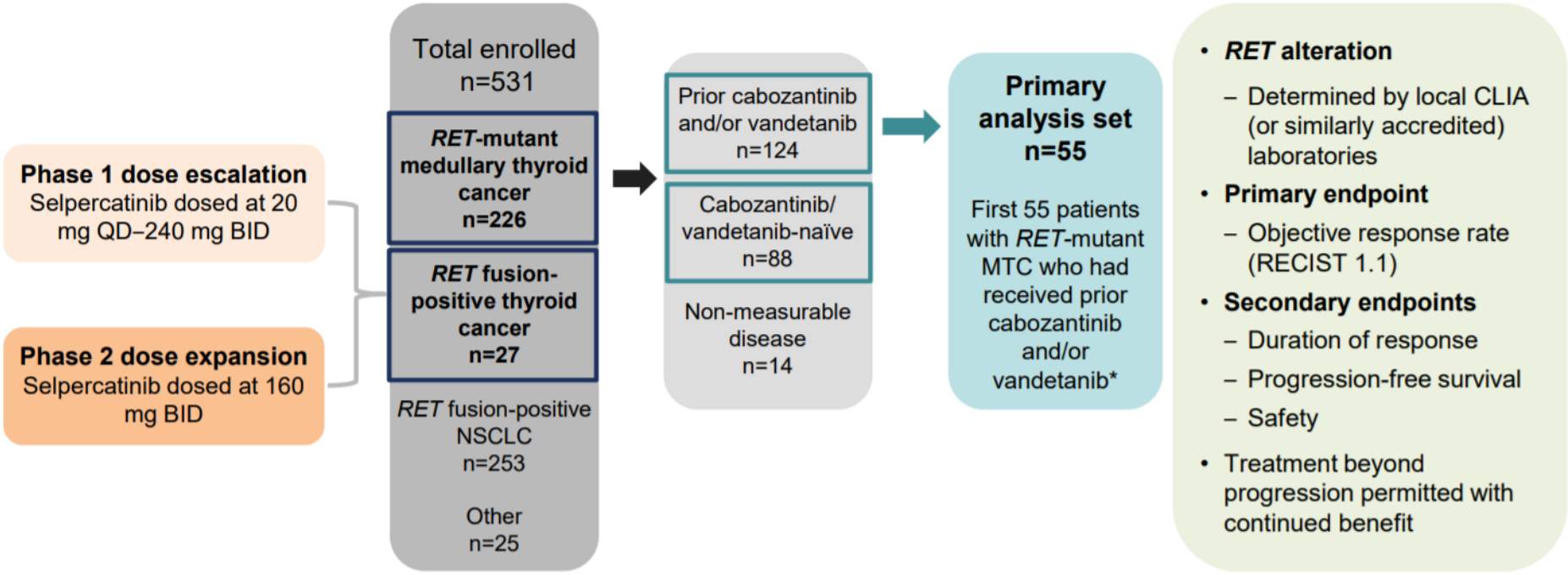


Orthotopic brain model

CCDC6-RET orthotopic brain PDX



LIBRETTO-001: selpercatinib in *RET*-altered cancers



3 populations to be discussed: (1) MTC PAS; (2) MTC, cabozantinib/vandetanib naïve; (3) RET fusion-positive thyroid cancer

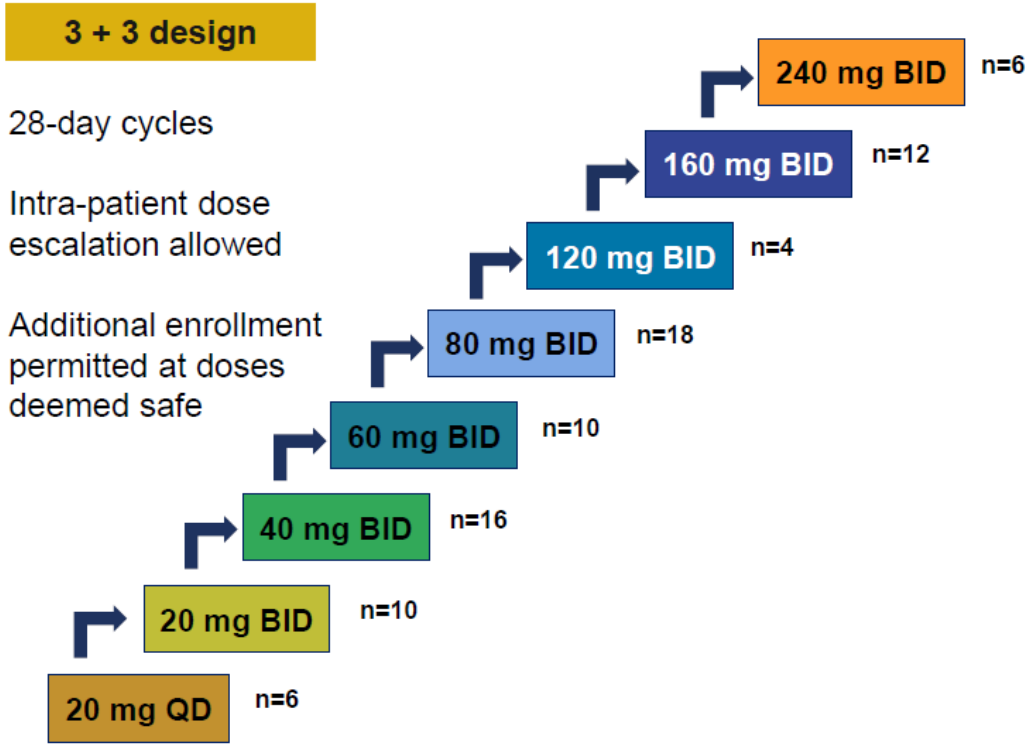
LIBRETTO-001: phase I dose escalation design

Eligibility

- Age ≥12 years
- ECOG 0–2
- Patients with locally advanced or metastatic solid tumors refractory or intolerant to standard therapy
- Any number of prior therapies
- *RET* alteration not required initially ('triggered' by adequate PK)

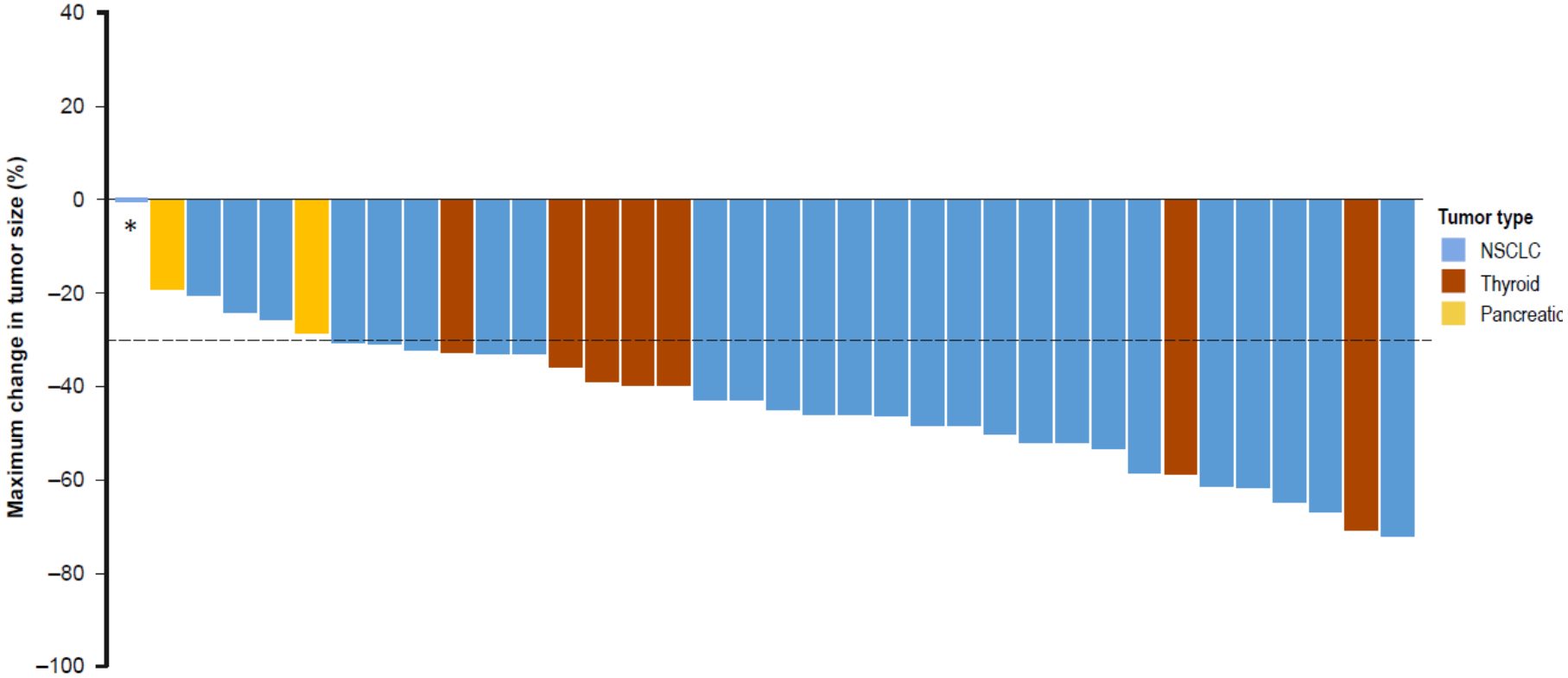
Key endpoints

- Determine MTD or recommended dose
- Safety/tolerability
- PK
- Overall response rate (RECIST v1.1)
- Duration of response



QD = once-daily; BID = twice-daily
PK = pharmacokinetics; MTD = maximum tolerated dose
April 2, 2018 data cut-off date

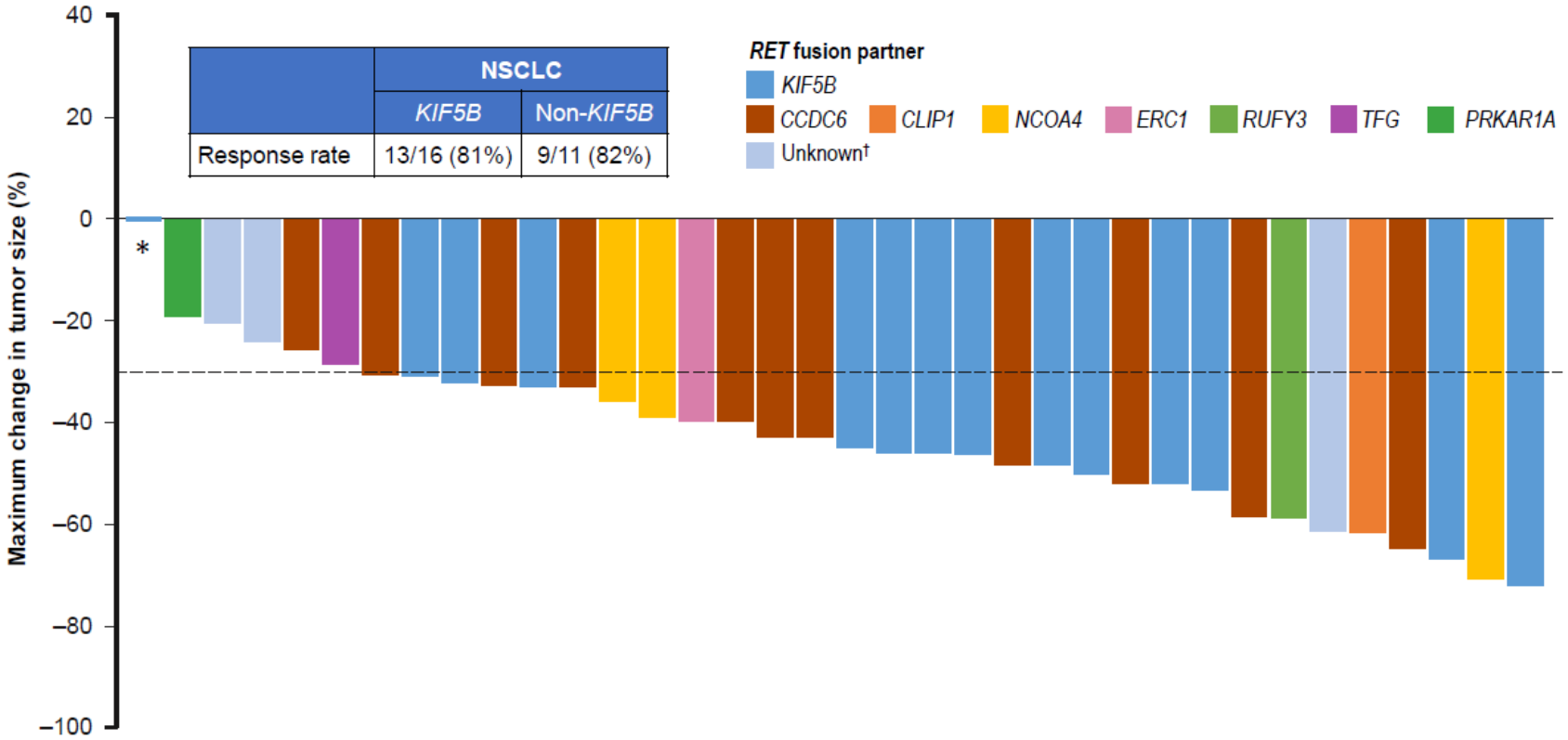
Efficacy of LOXO-292 in *RET* fusion-positive cancers



NSCLC = non-small cell lung cancer
Note: Three patients not displayed due to treatment discontinuation prior to first post-baseline response assessment; *Denotes patient with 0% maximum change in tumor size
April 2, 2018 data cut-off date

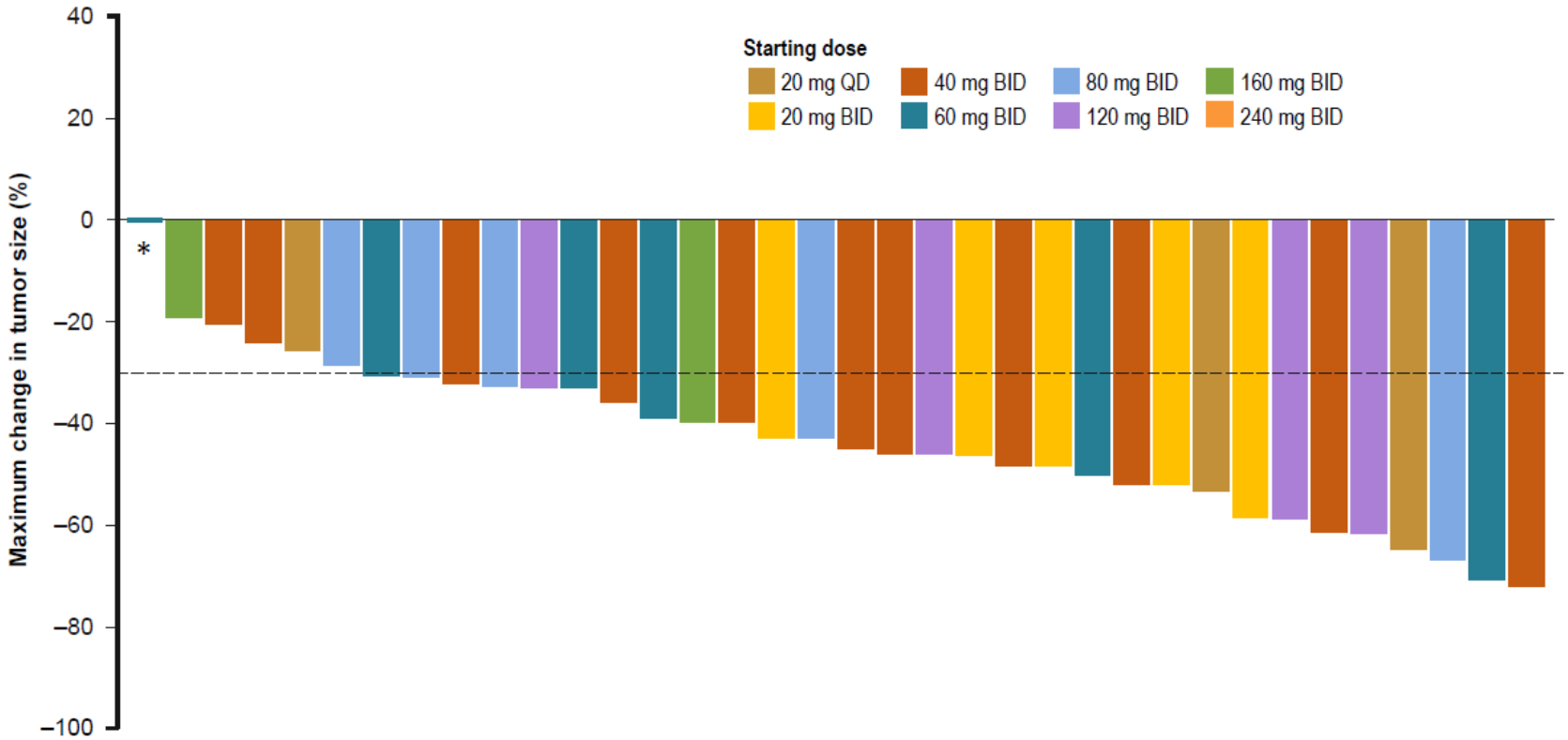
Efficacy of LOXO-292 regardless of *RET* fusion partner

	NSCLC	
	KIF5B	Non-*KIF5B*
Response rate	13/16 (81%)	9/11 (82%)



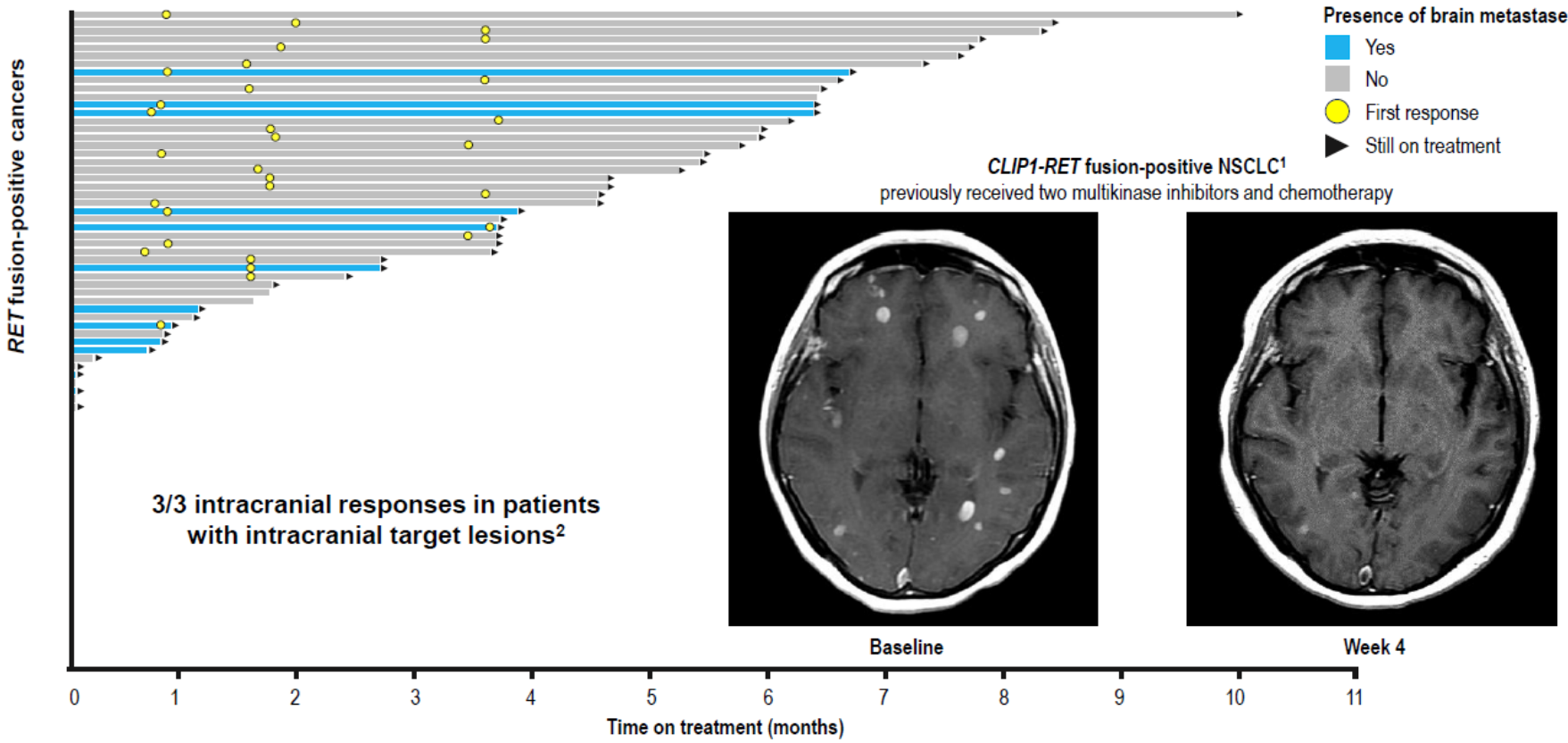
Note: Three patients not displayed due to treatment discontinuation prior to first post-baseline response assessment; *Denotes patient with 0% maximum change in tumor size
†Fusion partner unknown due to FISH+ detection; April 2, 2018 data cut-off date

Efficacy of LOXO-292 regardless of starting dose



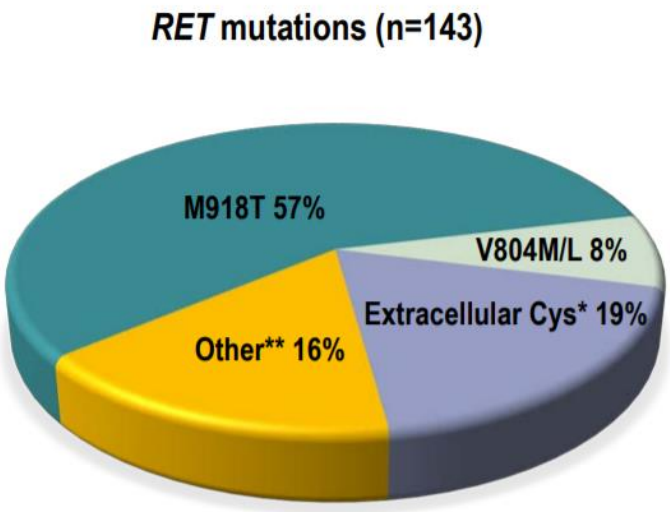
QD = once-daily; BID = twice-daily;
Note: Three patients not displayed due to treatment discontinuation prior to first post-baseline response assessment; *Denotes patient with 0% maximum change in tumor size
April 2, 2018 data cut-off date

Duration of LOXO-292 therapy in patients with brain metastases



NSCLC = non-small cell lung cancer
1. Initiated treatment at 120 mg BID; dose escalated at C5D1 to 160 mg BID; on study in month 4
2. Derived based on investigator assessments of brain metastases per RECIST 1.1
Brain metastases only observed in *RET* fusion-positive cancers; April 2, 2018 data cut-off date

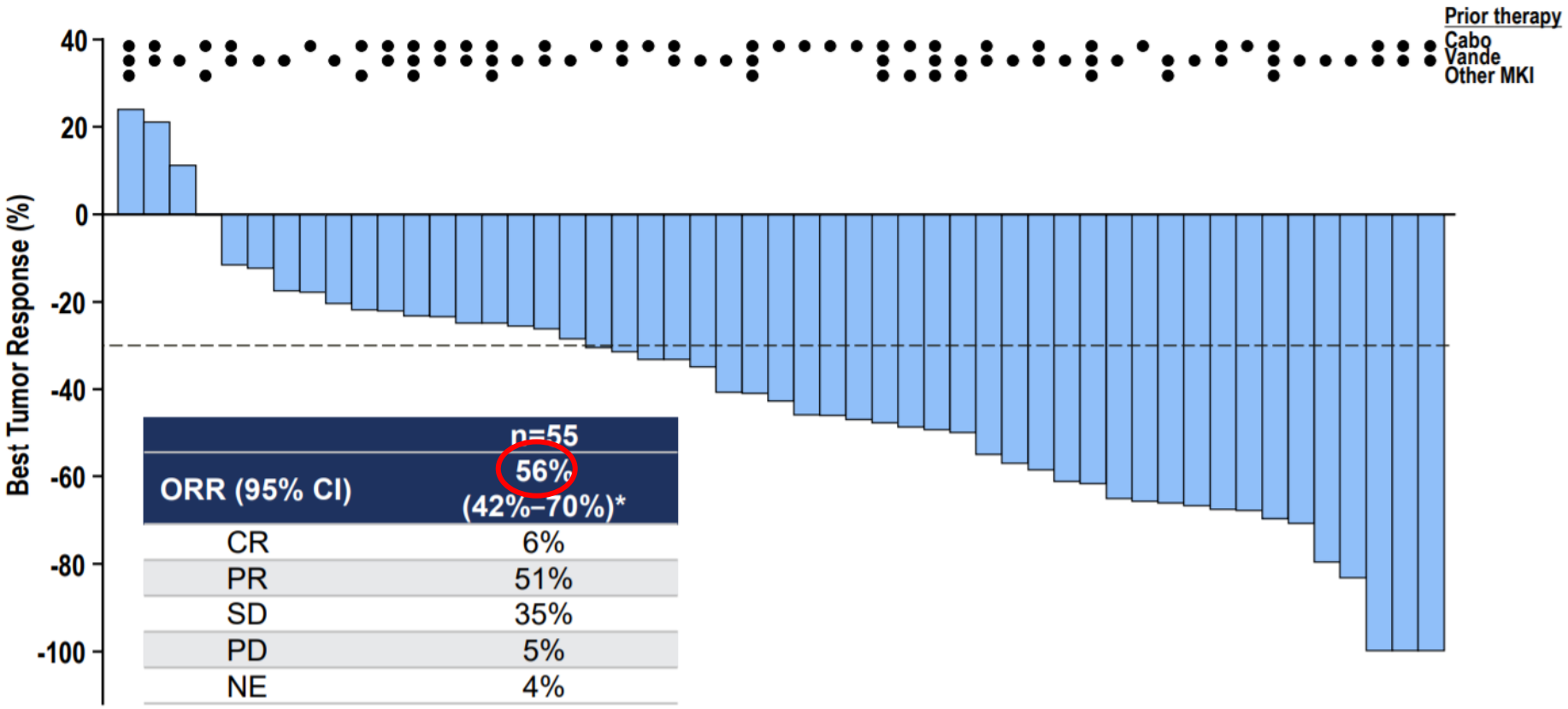
Patient characteristics: *RET*-mutant MTC



Characteristic	PAS (n=55)	Cabo/Vande-Naïve (n=88)
Female / Male, n (%)	19 (35) / 36 (65)	30 (34) / 58 (66)
Median age (range), years	57 (17–84)	58 (15–82)
ECOG performance status, n (%)		
0	11 (20)	43 (49)
1	41 (75)	42 (48)
2	3 (5)	3 (3)
Median prior systemic regimens (range)	2 (1–8)	0 (0–2)
Prior cabozantinib and/or vandetanib, n (%)	55 (100)	-
Cabozantinib only	13 (24)	-
Vandetanib only	18 (33)	-
Cabozantinib and vandetanib	24 (44)	-
Prior multikinase inhibitor (MKI), n (%)	55 (100)	7 (8)
1	26 (47)	6 (7)
≥2	29 (53)	1 (1)
Prior non-MKI systemic therapy, n (%)	17 (31)	9 (10)
Brain metastases, n (%)‡	4 (7)	2 (2)
Measurable disease, n (%)	53 (96)	86 (98)

Presented by L. Wirth et al. ESMO 2019

Activity of selpercatinib: *RET*-mutant MTC PAS (n=55)



	n=55
ORR (95% CI)	56% (42%–70%)*
CR	6%
PR	51%
SD	35%
PD	5%
NE	4%

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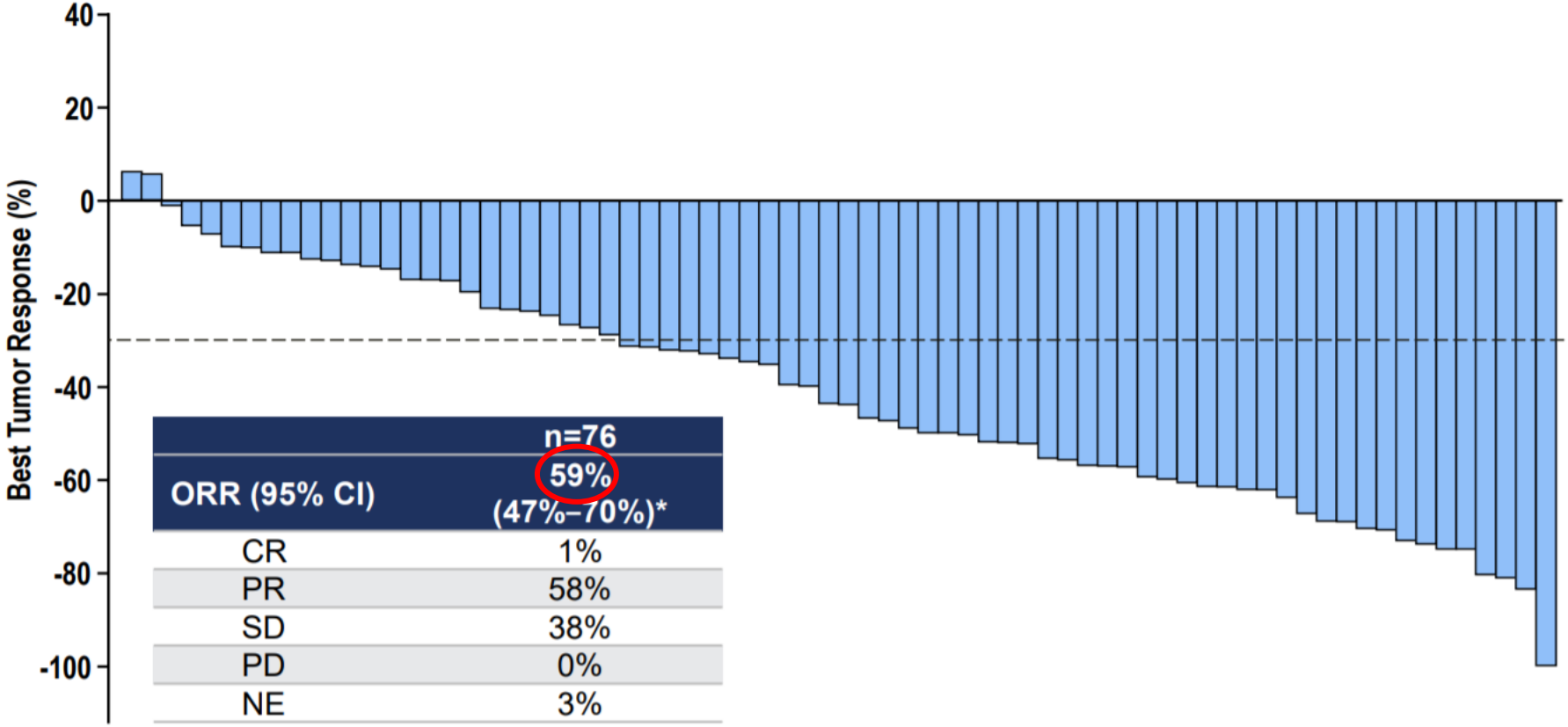
Activity of selpercatinib: cabozantinib/vandetanib-naïve *RET*-mutant MTC (n=76)



	n=76
ORR (95% CI)	59% (47%–70%)*
CR	1%
PR	58%
SD	38%
PD	0%
NE	3%

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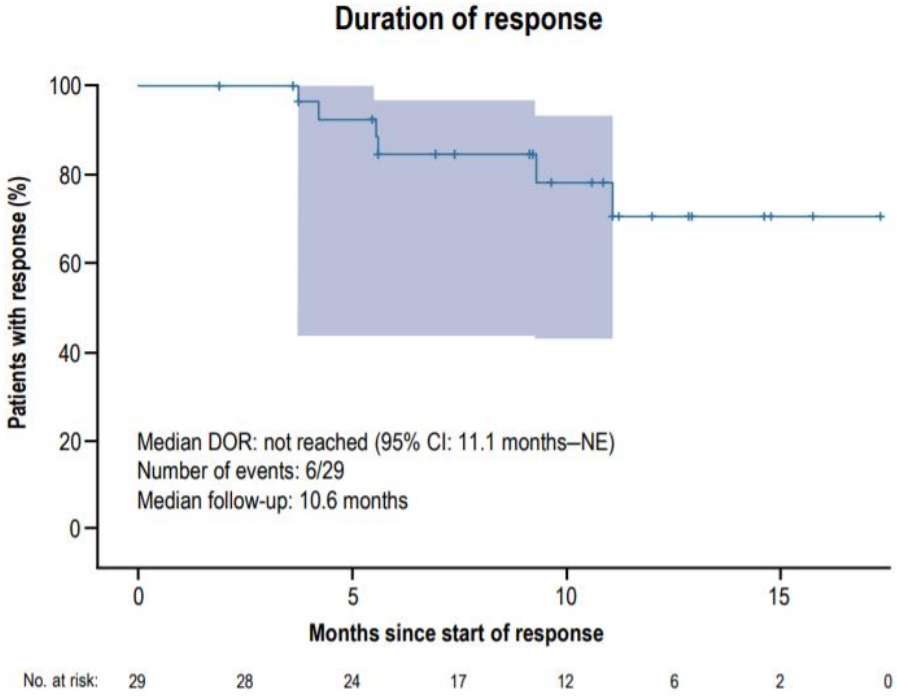
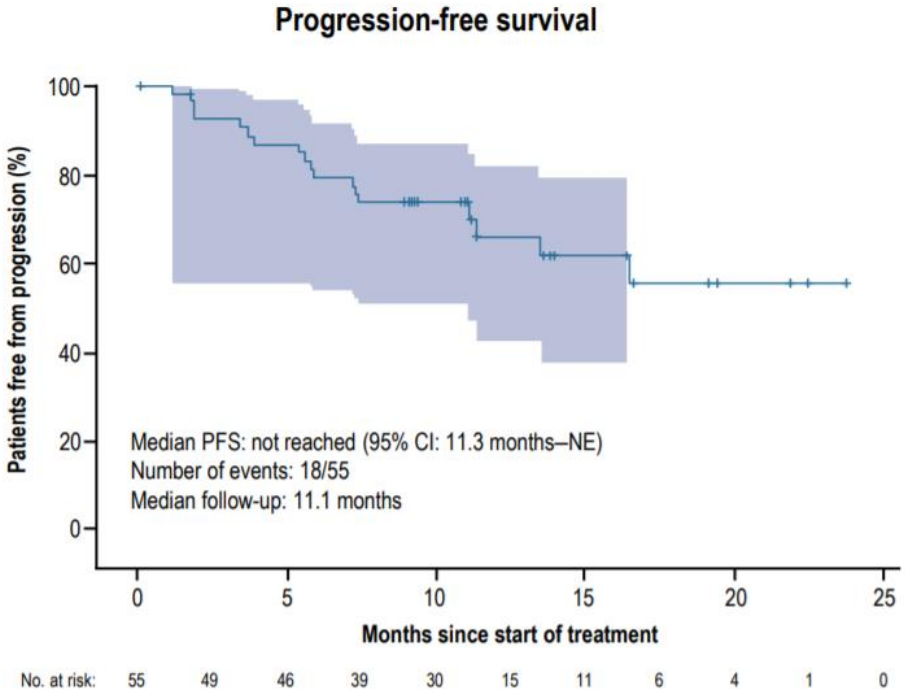
Durability of selpercatinib benefit: primary analysis set





- ORR, DOR, PFS similar regardless of prior therapy (e.g. cabozantinib only, vandetanib only, or cabozantinib and vandetanib) or *RET* mutation status (M918T vs other)
- Of 15 patients in the PAS that progressed, 13 continued treatment post-progression, for 1.0–19.9 months

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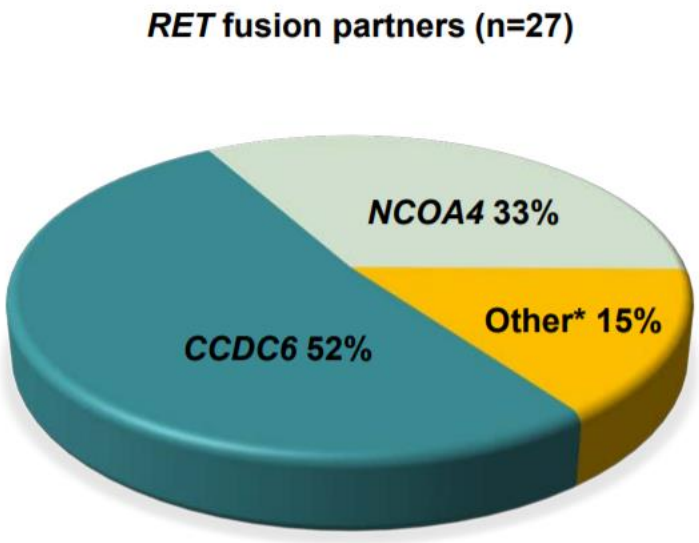
Patient characteristics: *RET* fusion-positive thyroid cancer



Characteristic	*RET* fusion-positive thyroid cancer (n=27)
Female / Male, n (%)	13 (48) / 14 (52)
Median age (range), years	54 (20–88)
ECOG performance status, n (%)	
0	8 (30)
1	16 (59)
2	3 (11)
Histology, n (%)	
Papillary	21 (78)
Hürthle cell	1 (4)
Poorly differentiated	3 (11)
Anaplastic	2 (7)
Median prior systemic regimens (range)	3 (1–7)
Prior radioactive iodine (RAI), n (%)	24 (89)
Prior systemic therapy other than RAI, n (%)	19 (70)
Prior lenvatinib and/or sorafenib, n (%)	13 (48)
Brain metastases, n (%)**	7 (26)
Measurable disease, n (%)	26 (96)

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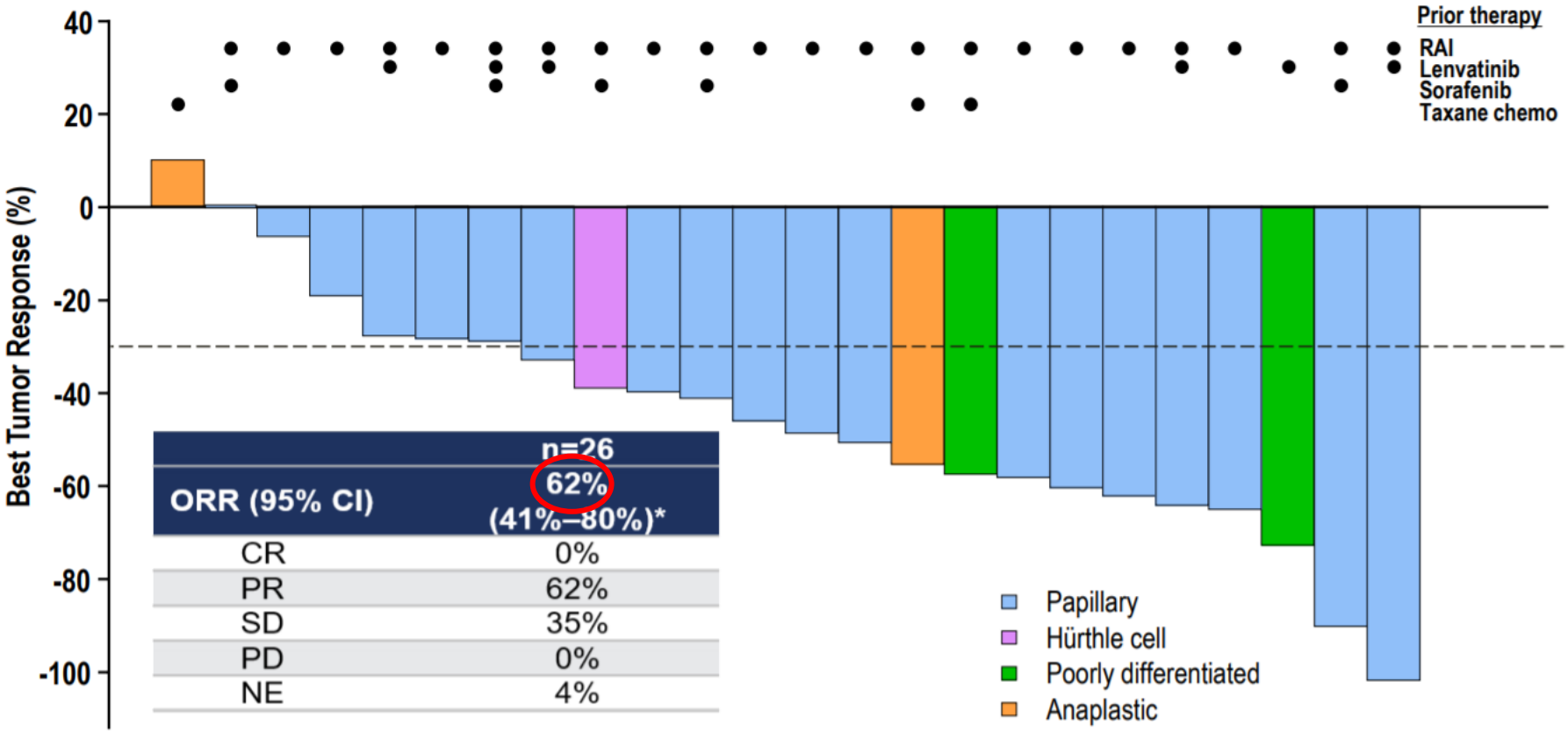
Activity of selpercatinib: *RET* fusion-positive thyroid cancer (n=26)



	n=26
ORR (95% CI)	62% (41%–80%)*
CR	0%
PR	62%
SD	35%
PD	0%
NE	4%

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Selpercatinib safety profile

Adverse event	LIBRETTO-001 safety database, n=531							
	Treatment-emergent AEs (≥15% overall)					Treatment-related AEs		
	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total
Dry mouth	29%	4%	–	–	32%	–	–	27%
Diarrhea	21%	8%	2%	–	31%	1%	–	16%
Hypertension	4%	11%	14%	<1%	29%	8%	<1%	18%
Increased AST	17%	5%	6%	1%	28%	4%	1%	22%
Increased ALT	13%	4%	7%	1%	26%	6%	1%	21%
Fatigue	15%	9%	1%	–	24%	<1%	–	14%
Constipation	19%	3%	<1%	–	22%	<1%	–	11%
Headache	15%	4%	1%	–	20%	<1%	–	7%
Nausea	15%	4%	<1%	–	19%	<1%	–	8%
Peripheral edema	16%	4%	<1%	–	19%	–	–	10%
Increased creatinine	14%	4%	–	<1%	18%	–	–	10%

- 9 patients (1.7%) discontinued due to treatment-related toxicity

Tumor Lysis Syndrome!

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Conclusions

- **Selpercatinib demonstrated robust and durable anti-tumor activity in *RET*-mutant MTC and *RET* fusion-positive thyroid cancer**
  - Prior cabozantinib and/or vandetanib MTC (n=55):
    - Heavily pre-treated population (53% with ≥2 MKIs)
    - ORR 56% (95% CI: 42–70)
    - Median DOR not reached (95% CI: 11.1–NE), median PFS not reached (95% CI: 11.3–NE)
    - Significant and stable reductions in calcitonin and CEA in most patients
  - Cabozantinib/vandetanib-naïve MTC (n=76): ORR 59% (95% CI 47–70), median DOR, PFS not reached
  - *RET* fusion-positive thyroid cancer (n=26): ORR 62% (95% CI 41–80), median DOR, PFS not reached

- **Favorable safety profile**
  - Safety database (n= 531):
    - Most AEs low grade and unrelated to selpercatinib
    - Only 1.7% discontinued therapy for treatment-related AEs

- **Outcomes with selpercatinib after treatment with approved MKIs comparable to outcomes with MKIs when they are used in first line, and less toxic**

- **New Drug Application (NDA) submission to US FDA planned by the end of 2019**

- **Randomized, global phase 3 trial:** selpercatinib vs. cabozantinib or vandetanib (investigator's choice) in kinase inhibitor-naïve *RET*-mutant MTC (in the coming months)

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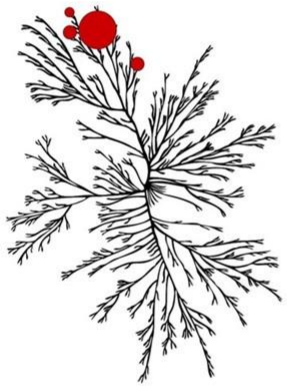
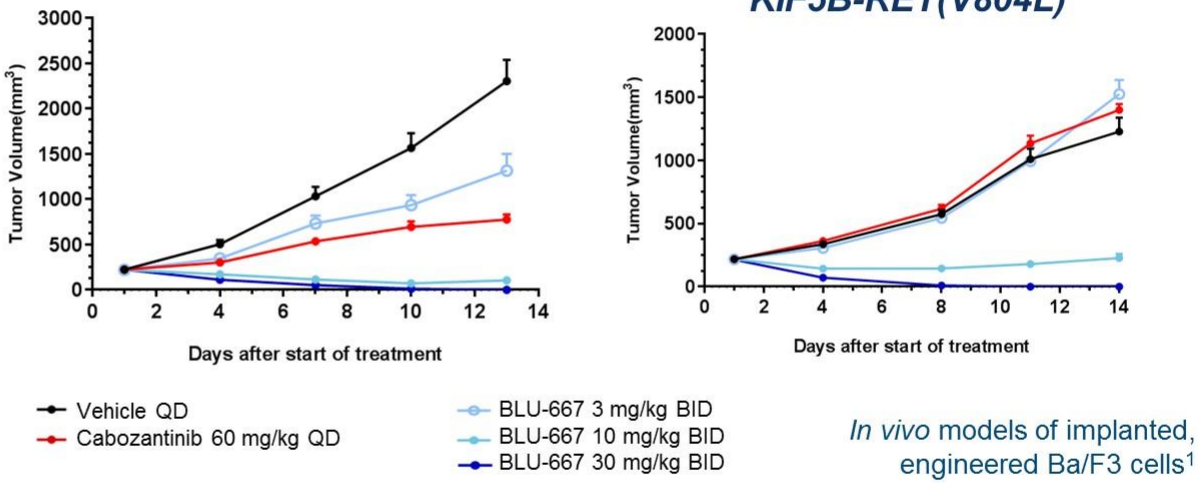
BLU-667 Potently and Selectively Inhibits RET Alterations and Resistance Mutants

BLU-667: High kinome selectivity for RET[a]



BLU-667 vs. pharmacologically relevant kinases:

- ~90-fold more selective for RET than VEGFR2
- 20-fold more selective for RET than JAK1



BLU-667 Cellular activity in KIF5B-RET[2]

	KIF5B-RET	KIF5B-RET V804L	KIF5B-RET V804M	KIF5B-RET V804E
BLU-667	10.1 nM (1x)	8.1 nM (0.8x)	14.1 nM (1.4x)	8.1 nM (0.8x)

[a]Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content. BLU-667 is an investigational agent discovered and currently in development by Blueprint Medicines Corporation (Blueprint Medicines). 1. Subbiah, et al. *Cancer Discovery* 2018; 2. Blueprint internal data

ARROW: BLU-667 Dose-Escalation and Expansion Study

Part 1: Dose-Escalation (N=62; Complete)[1]

RET-altered advanced solid tumors

BLU-667: 30-600 mg by daily oral administration (QD or BID)

Phase 2 dose determined (400 mg QD)

ARROW is registered with clinicaltrials.gov (NCT03037385)

Part 2: Expansion Cohorts (Ongoing)

BLU-667 400 mg QD

- Unresectable, advanced solid tumor
- RET alteration status by local tumor testing
- No additional driver mutation
- ECOG PS 0-1
- Asymptomatic brain metastases allowed
- Progressive disease or intolerant to SOC therapy, or not a candidate

Primary objectives:

Overall response rate (RECIST 1.1)

Safety

- RET fusion+ NSCLC, prior platinum (n=80)
- RET fusion+ NSCLC, platinum naïve (n=40)
- MTC, prior cabozantinib or vandetanib (n=60)
- MTC, no prior cabozantinib or vandetanib (n=40)
- Other RET fusion+ tumors (n=40)
- Other RET-mutated tumors (n=20)
- RET-altered, prior selective RET inhibitor (n=20)

Presented by J.F. Gainor et al. ASCO 2019

BLU-667 has Activity in Other RET Fusion+ Malignancies

- PR in 2/2 patients with metastatic pancreatic cancer
  - 67 yo male, CCDC6-RET fusion, continues with confirmed PR (53% shrinkage) at ~6 months
  - 31 yo male, TRIM33-RET and JMJD1C-RET fusions, continues treatment after PR (41% shrinkage) at first response assessment
- PR in a patient with intrahepatic bile duct carcinoma
  - 51 yo female, NCOA4-RET fusion, continues with confirmed PR (67% shrinkage) at ~15 months
- ORR 83% (5/6)* in RET-fusion PTC (Abstract 6018 presented June 1, 2019)
- Safety profile similar to what was seen in RET fusion+ NSCLC

* Confirmation of response is pending for two patients. Data cut-off date: 28 Apr 2019.

Conclusions

- BLU-667 demonstrates broad and durable antitumor activity in patients with RET fusion+ advanced NSCLC
  - 60% ORR and 100% DCR in patients previously treated with platinum chemotherapy, and 58% ORR in all RET fusion+ patients
  - Responses observed regardless of treatment history, RET fusion partner or CNS involvement
  - Active against intracranial metastases
  - Well tolerated at 400 mg QD with most AEs grade 1/2
- BLU-667 has FDA breakthrough therapy designation in RET fusion+ NSCLC that progressed following platinum based chemotherapy
- Data support expansion of ARROW trial in treatment-naïve NSCLC patients and continued enrollment of other RET-altered solid tumor groups

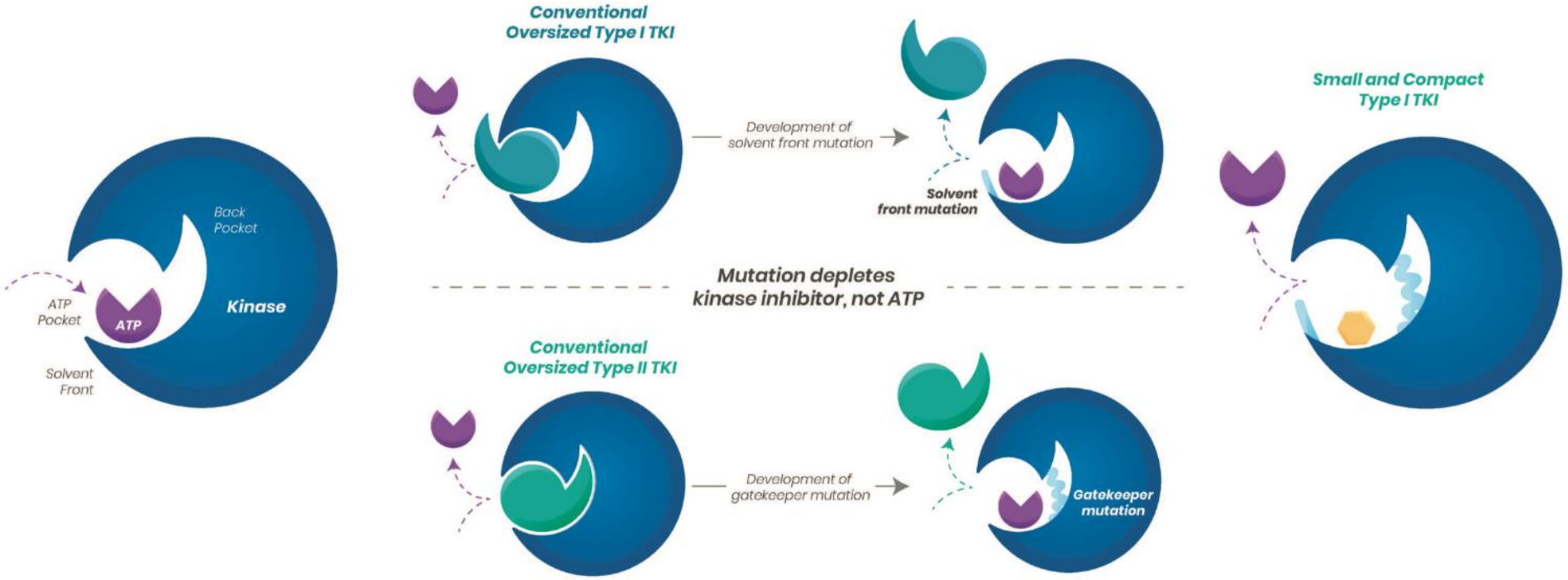
RP2D, recommended phase 2 dose.
Data are preliminary and based on a data cut-off date of April 28, 2019.

LOXO-292 (selpercartinib) vs BLU-667 (praseltinib)

	Selpercatinib	Pralsetinib
ORR % NSCLC naive RET fusion	85% (69-95)	71% (NA)
ORR% NSCLC chemo pretreated	68% (58-76)	60% (42-76)
PFS NSCLC RET fusion (months)	18,4	NR
DoR (months)	20,3	NR
Intracraneal Activity	91 (59-100%)	78% (NA)
ORR % RET Mutant Thyroid naive	59% (47-70%)	56%(38-74%)
ORR% RET mutantThyroid MKI pretreated	56% (42-70%)	63% (35-85)
ORR% RET fusion positiveThyroid	62% (41-80%)	83% (5/6 pts)
Safety (G3)		
HTN	14%	13%
Transaminitis	6%-7%	3%
Anemia, Neutropenia	NA	7%-13%
Drug Discontinuation rate	1,7	4%
Tumor Agnostic RET altereted cancer activit	yes	yes

- ✓ More specific and potent RET inhibitors in comparison to MKIs
- ✓ Similar ORR and PFS, however BLU-667 data are less mature
- ✓ Less toxic with a low discontinuation rate (vandetanib 13%)
- ✓ Both shown intracraneal activity and afficacy on RET gatekeeper mutations acquired as MoR to MKIs

- **Need to define mechanism of resistance to newest generation RET inhibitors**
- **Cross sensitivity? No data reported**


Back Pocket
ATP Pocket
ATP
Kinase
Solvent Front
Conventional Oversized Type I TKI
Development of solvent front mutation
Solvent front mutation
Small and Compact Type I TKI
Mutation depletes kinase inhibitor, not ATP
Conventional Oversized Type II TKI
Development of gatekeeper mutation
Gatekeeper mutation

RET alterations emerged as a new mechanism of resistance in EGFR mutant NSCLC treated with osimertinib

Characteristics of the patients with fusion-positive *EGFR*-mutant NSCLC

Patient ID[a]	Institution	T/P[b]	Testing[c]	Acquired fusion	Founder *EGFR* mutation	Treatment history prior to detection of fusion	T790M status[d]	Other molecular findings[d]	Treatment after fusion detection	Response (RECIST 1.1)
1	MGH	T	SFA	***CCDC6–RET***	Del19	1. Afatinib 2. Osimertinib	–	–	Osimertinib + BLU-667	PR (–78%)
2	MGH	T	SFA	***PCBP2–BRAF***	Del19	1. Erlotinib 2. Carbo/pem 3. Osimertinib	–	*TP53*	–	–
3	MGH	T	FO	***AGK–BRAF***	Del19	1. Erlotinib 2. Osimertinib	–	*CTNNB1, APC, CDKN2A/B*	–	–
33	MGH	P	G360	***CCDC6–RET + TPM3–NTRK1***	Del19	1. Erlotinib 2. Osimertinib	–	$EGFR^{Amp}$, $BRAF^{Amp}$, MET^{Amp}, $CKD6^{Amp}$, $CCNE1^{Amp}$, *TP53, TERT*	–	–
42	MGH	T	SFA	***CCDC6–RET***	Del19	1. Cisplatin/ pemetrexed 2. Afatinib	–	*TP53*	Afatinib + cabozantinib	SD (–6%)
43	MGH	T	SFA	***BAIAP2L1–BRAF***	Del19	1. Erlotinib 2. Osimertinib 3. Carbo/pem 4. Osimertinib/ gemcitabine	+	*SMAD4, PTCH1, TP53*	–	–
44	UC-Irvine	T	SFA	***NCOA4–RET***	Del19	1. Cisplatin/ pemetrexed (adjuvant) 2. Afatinib/ cetuximab	–	*RNF43, CDKN2A*	Osimertinib + BLU-667	PR (–78%)

Abbreviations: PR, partial response; SD, stable disease.

[a]Patients 1–41 correspond to patients in the osimertinib-resistant cohort, with molecular findings shown in Fig. 1. Patients 42, 43, and 44 are not included in Fig. 1 because their biopsies were obtained at progression on therapies other than single-agent osimertinib.

[b]T, tissue testing (from biopsies of progressing lesions); P, plasma ctDNA testing (as indicated in next column).

[c]Testing: SFA, MGH Solid Fusion Assay; FO, FoundationOne NGS Panel; G360, Guardant 360 ctDNA NGS Panel.

[d]T790M and other molecular findings refer to the time of fusion detection.

S. Piotrowska et al. Cancer Discovery 2018

Other RET inhibitors in development:

BOS172738: Safety, Efficacy, and Tolerability of BOS172738 in Patients With Advanced Rearranged During Transfection (RET) Gene-Altered Tumors
https://clinicaltrials.gov/ct2/show/NCT03780517
Escalation phase ongoing

RXDX-105: Study of RXDX-105, Potent RET Inhibitor in Patients With Advanced Lung Cancer and Other Solid Tumors
Discontinued

TPX-0046 (Turning Point) targeting RET and SRC with activity on solvent mutations
Phase 1 trial not yet opened

What ‘s Next?

TARGETED THERAPIES

Time to shift the burden of proof for oncogene-positive cancer?

Robert C. Doebele

“…Do we still need to run randomized phase III trials of oncogene-directed therapies against standard chemotherapy drugs?..”

Should expensive clinical testing continue when there is early, obvious benefit of a targeted cancer drug?


THANK
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