Advanced medullary thyroid cancer: clinical criteria to guide the therapeutical sequence and dose

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CLINICAL CASE 1

- The old one

CLINICAL CASE 1

- 45yom. Lumbar canal stenosis. Depressive syndrome.
- 2004 Sporadic Medullary thyroid carcinoma: Total thyroidectomy + central cervical lymphadenectomy.
- 2008 Relapse: bone metastasis
- 2009 Progression bone disease offer systemic treatment (refuse clinical trial)

CLINICAL CASE 1

Sorafenib 400mg bid

Phase II
(Lam, J Clin Oncol 2010)

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CLINICAL REVIEW

WILEY

Efficacy and toxicity of sorafenib in the treatment of advanced medullary thyroid carcinoma: A systematic review and meta-analysis

Huy Gia Vuong MD, PhD[1] | An Thi Nhat Ho MD[2] | Thao T. K. Tran MD[3] | Jaume Capdevila MD, PhD[4] | Mustafa Benekli MD, PhD[5] | Tadao Nakazawa MD, PhD[1] | Ryohei Katoh MD, PhD[1] | Tetsuo Kondo MD, PhD[1]

101 patients
PR: 21%
SD 58%

CLINICAL CASE 1

- Sorafenib 400mg bid -> 1.5 month because Intolerable Gastritis
- Wait and see.
- 2014: Small liver metastasis. Normal liver function ¿Treatment?

1. In your opinion which is the most important factor to choose this patient's treatment?

- Objective response rate
- Toxicity profile
- Progression-free survival
- Global Survival

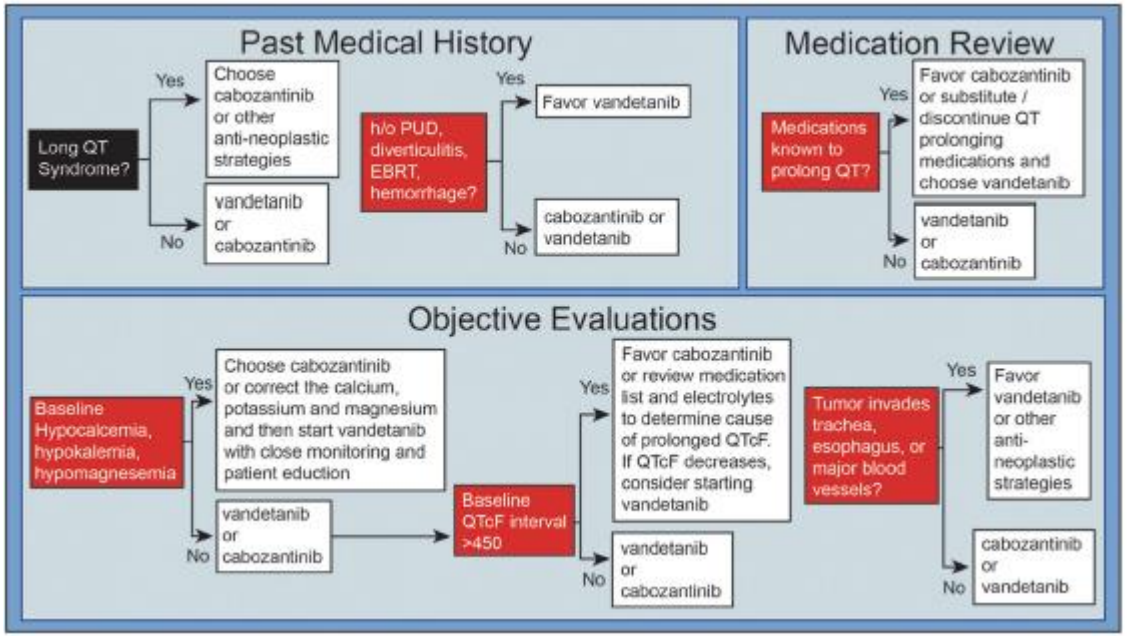
In patient's opinion…

- Objective response rate
- **Toxicity profile**
- Progression-free survival
- Global Survival

Drug	Tumor	Phase	Patients (n)	PR (%)	SD>6 months (%)	Median PFS (months)	Median OS (months)	Most frequent AEs (%) (any grade)	References
Vandetanib	MTC	3	331	45	87	30.5*	NE	Weight loss (40) Diarrhea (56) Skin rash (45) Nausea (33) Hypertension (32)	Wells *et al.* (2012)
Cabozantinib	MTC	3	330	28	NE	11.2	NE	Diarrhea (63) Hand-and-foot syndrome (50) Weight loss (47) Anorexia (45) Nausea (43)	Elisei *et al.* (2013)

Medullary Thyroid Cancer in the Era of Tyrosine Kinase Inhibitors: To Treat or Not to Treat—and With Which Drug—Those Are the Questions

Maria E. Cabanillas, Mimi I. Hu, and Camilo Jimenez



J Clin Endocrinol Metab, December 2014, 99(12):4390–4396

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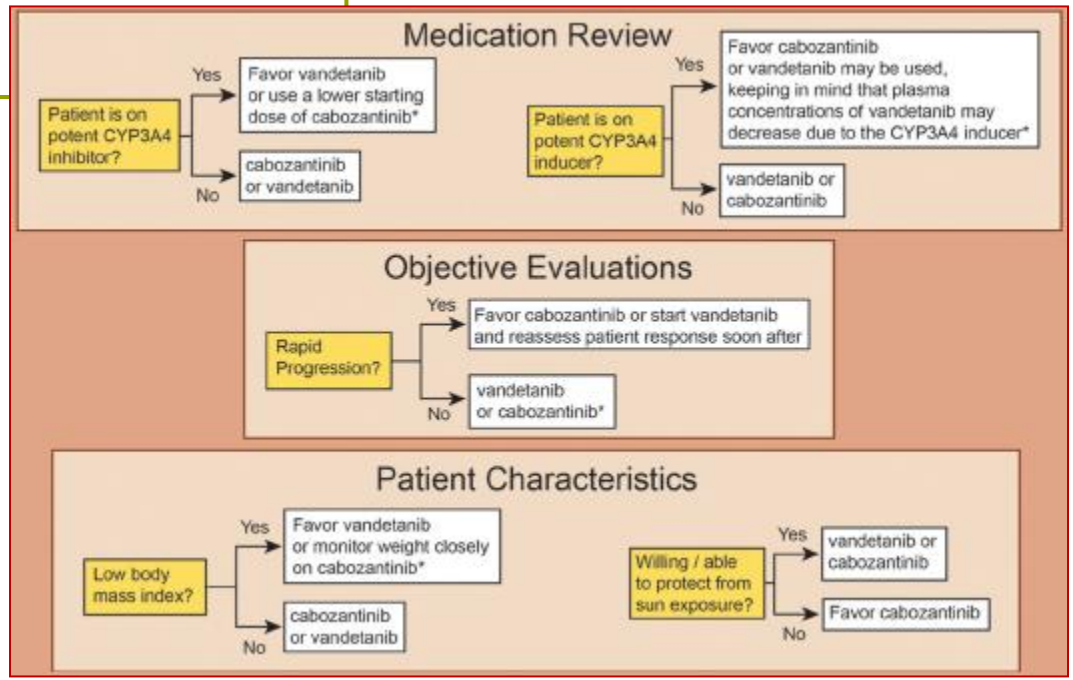

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2. Select a treatment option

- Vandetanib 100mg
- Vandetanib 300mg
- Cabozantinib 140mg
- Cabozantinib 60mg

Study ID	Design	Caprelsa® dose	MTC subtype	Number of patients
ZETA[1]	Randomized (2:1), double-blind, placebo-controlled	300 mg	Sporadic (~90%) Hereditary (10%)	Total: 331 Caprelsa®: 231 Placebo: 100
08[2]	Single arm Open label	300 mg	Hereditary	30
68[3]	Single arm Open label	100 mg	Hereditary	19

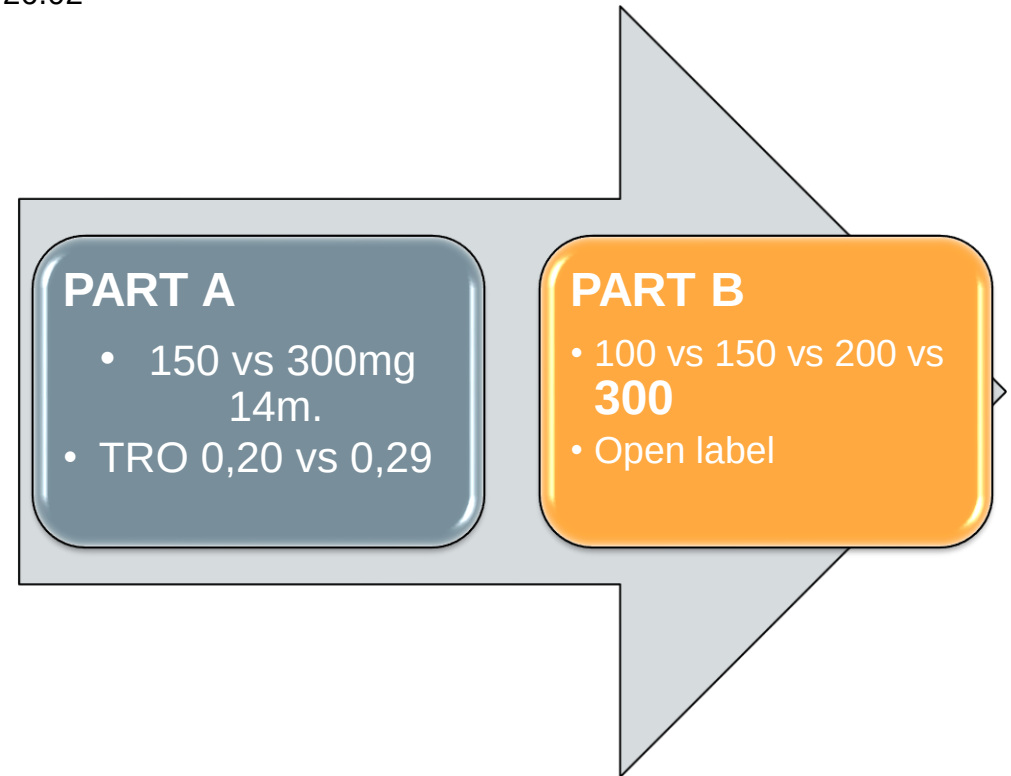
CABOZANTINIB

EXAMINER (NCT01896479)
60mg vs 140mg
Noninferiority
N = 188
RECIST PD
Primary endpoint: PFS.

Safety and efficacy of two starting doses of vandetanib in advanced medullary thyroid cancer

Hu M et al.

Endocrine-related cancer. 2019. 26.02



CLINICAL CASE 1

Vandetanib 100mg. Good tolerance

2017: Progression with lumbar soft tissue mass. Surgery

Vandetanib 300mg (refuse other options)

Vandetanib 200mg due to QT prolongation

CLINICAL CASE 2

- The new one

- 56yom. Former smoker
- MEN2A.
- 1997 bilateral adrenalectomy due to bilateral pheochromocytoma
- 2010 **Medullary thyroid carcinoma**: Total thyroidectomy + central and right cervical lymphadenectomy.
- 2016 **Relapse**: left cervical lymphadenectomy

2019

- Recurrence with **unresectable** cervical and mediastinal involvement (by contacting the trachea)

- **Calcitonin** doubling time 10 months

3. In your opinion which is the most important factor to choose this patient's treatment?

- Objective response rate
- Toxicity profile
- Progression-free survival
- Global Survival

In patient's opinion…

- **Objective response rate**
- Toxicity profile
- Progression-free survival
- Global Survival

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NEXT-GENERATION RET-INHIBITORS

ARROW
BLU-667

Clinical activity of BLU-667, a highly selective RET inhibitor, in advanced *RET*-altered thyroid cancers: updated results from the phase 1 ARROW study

Mimi I. Hu, Matthew Taylor, Lori Wirth, Viola Zhu, Robert Doebele, Dae Ho Lee, Ignacio Matos, Christina Baik, Marcia Brose, Giuseppe Curigliano, Gilberto de Lima Lopes, Dong-Wan Kim, Daniel Tan, Chia-Chi Lin, Michael Palmer, Meera Tugnait, Hui Zhang, Brenton Mar, Corinne Clifford, Beni Wolf, Elena Garralda, Sai-Hong Ignatius Ou, Vivek Subbiah, Justin Gainor

88th Annual Meeting of the American Thyroid Association
Washington, DC • October 6, 2018

Mimi I.Hu et al. ATA meeting 2018

Clinical Activity of LOXO-292, a Highly Selective RET Inhibitor, in Patients with *RET*-Altered Thyroid Cancers: An Update from ASCO 2018

Lori J. Wirth, Maria E. Cabanillas, Eric J. Sherman, Ben Solomon, Sophie LeBoulleux, Bruce Robinson, Matthew H. Taylor, Todd Bauer, Jyoti D. Patel, Karen Reckamp, Jochen H. Lorch, Daniel S. W. Tan, Valentina Boni, Steve Smith, Brian Tuch, Kevin Ebata, Edward Y. Zhu, Michele Nguyen, Xin Huang, Scott Cruickshank, S. Michael Rothenberg, Geoffrey R. Oxnard, Benjamin Besse, Martin Schlumberger, Alexander Drilon, Vivek Subbiah, Manisha H. Shah

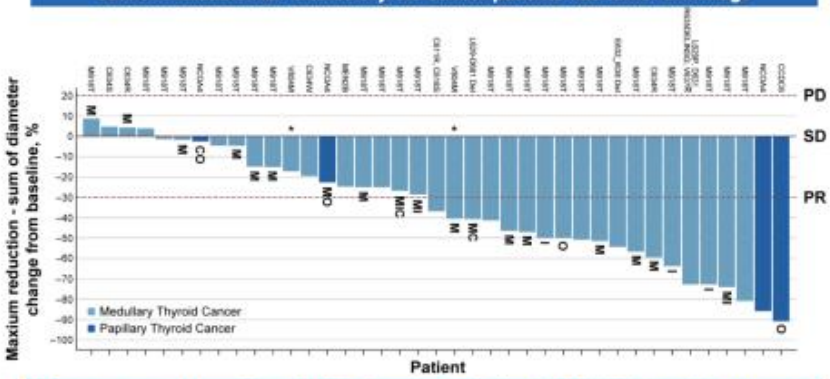
Massachusetts General Hospital Cancer Center, MD Anderson Cancer Center, Memorial Sloan Kettering Cancer Center, Peter MacCallum Cancer Centre, Institut Gustave Roussy, Royal North Shore Hospital, Oregon Health and Science University, Sarah Cannon Research Institute/Tennessee Oncology, University of Chicago, City of Hope National Medical Center, Dana-Farber Cancer Institute, National Cancer Centre Singapore, START Madrid-CIOCC Hospital Universitario Sanchinarro, Loxo Oncology, The Ohio State University Comprehensive Cancer Center

Lori J.Wirth et al. ATA meeting 2018

NEXT-GENERATION RET-INHIBITORS

BLU-667 has profound activity in *RET*-altered thyroid cancer

90% of evaluable *RET*-altered thyroid cancer patients had tumor shrinkage



Responses seen regardless of RET alteration, including RET V804M,* or prior treatment

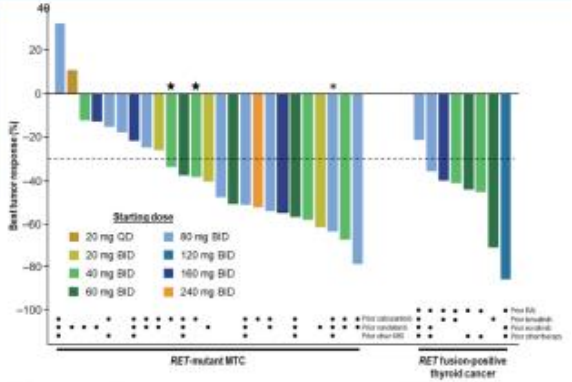
NCOA4, nuclear receptor coactivator 4; CCDC6, coiled-coil domain containing 6; M, prior MKI therapy; C, prior chemotherapy; O, other therapy; I, prior immunotherapy; PD, progressive disease; SD, stable disease; PR, partial response.

Patients Enrolled as of 9 May 2018, Follow-up as of 14 Se

Efficacy of LOXO-292 in *RET*-mutant MTC and *RET* fusion-positive thyroid cancer (RECIST 1.1)

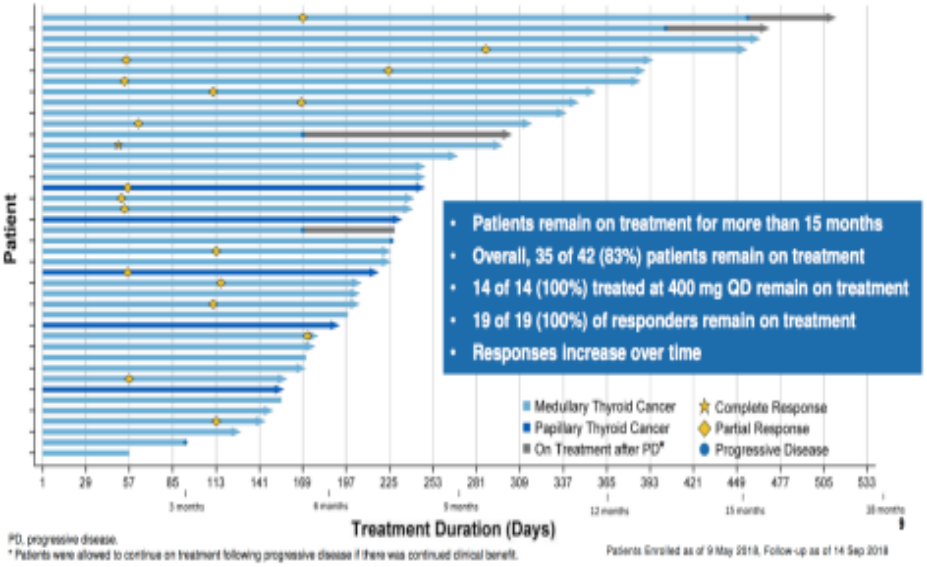
	RET-mutant MTC[a]	*RET* fusion-positive thyroid cancer[b]
ORR (95% CI)	59% (17/29) (39–77%)	78% (7/9) (40–97%)
Confirmed ORR (95% CI)	56% (15/27)[c] (35–75%)	78% (7/9) (40–97%)
CR	2	–
PR[d]	15	7
SD	8	2
PD	2	–
NE	2	–

- All unconfirmed responses at ASCO have since been confirmed
- 17/24 (71%) responding patients responded at patient's starting dose
- Activity independent of prior therapy
- 1/1 intracranial response (1 PR, pending confirmation) in *RET* fusion-positive thyroid patient with measurable CNS lesions



★pending confirmation; ★ complete response. Patients enrolled as of April 2, 2018. Follow-up as of July 19, 2018. a. Includes 2 patients with non-measurable disease (confirmed CR and SD); b. Includes 1 patient with non-measurable disease (SD); c. Excludes two patients with unconfirmed PRs pending confirmation at time of data cut-off; d. RET-mutant MTC includes 13 confirmed PR, 2 unconfirmed PRs pending confirmation.
Note: The three patients with non-measurable disease are not shown on the waterfall plots.

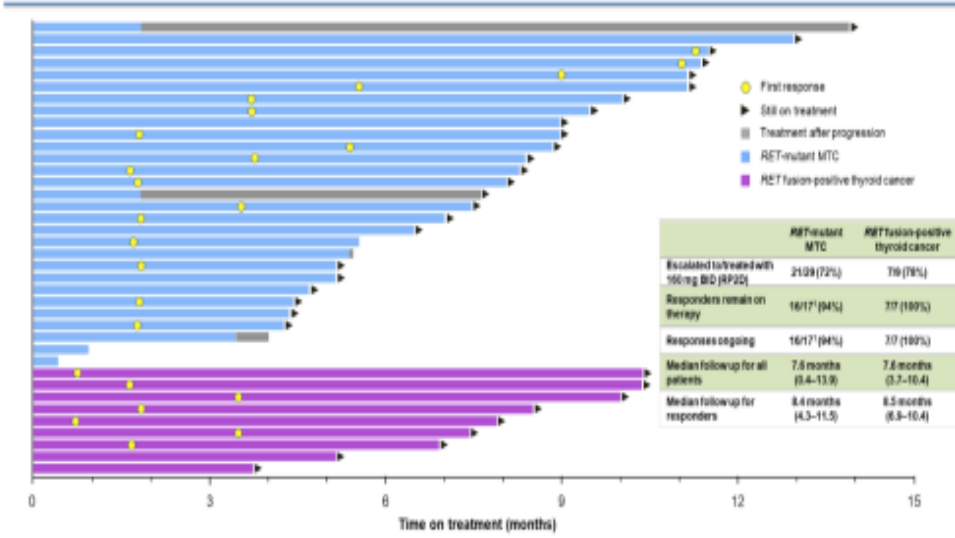
BLU-667 shows durable responses in thyroid cancer patients



PD, progressive disease.
* Patients were allowed to continue on treatment following progressive disease if there was continued clinical benefit.

Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018

Duration of LOXO-292 treatment in *RET*-mutant MTC and *RET* fusion-positive thyroid cancer



	RET-mutant MTC	RET fusion-positive thyroid cancer
Escalated to/treated with 160 mg BID (RP2D)	21/29 (72%)	7/9 (78%)
Responders remain on therapy	16/17[1] (94%)	7/7 (100%)
Responses ongoing	16/17[1] (94%)	7/7 (100%)
Median follow-up for all patients	7.6 months (0.4–13.9)	7.6 months (3.7–10.4)
Median follow-up for responders	8.4 months (4.3–11.5)	8.5 months (6.9–10.4)

1. One patient withdrew consent from study treatment while in response.
Patients enrolled as of April 2, 2018. Follow-up as of July 19, 2018.

Safety - BLU-667 is well tolerated

All doses and patients, N=69							
		Treatment-emergent AEs (≥15% overall)				Treatment-related AEs	
Adverse Event	Any event n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3	Grade 4
Constipation	24 (35)	22 (32)	2 (3)	-	-	-	-
Aspartate aminotransferase increased	23 (33)	20 (29)	3 (4)	-	-	-	-
Anemia	21 (30)	8 (12)	7 (10)	6 (9)	-	4 (6)	-
Hypertension	21 (30)	5 (7)	5 (7)	11 (16)	-	6 (9)	-
White blood cell count decreased	20 (29)	7 (10)	10 (15)	3 (4)	-	3 (4)	-
Diarrhea	19 (28)	11 (16)	3 (4)	5 (7)	-	4 (6)	-
Neutropenia	19 (28)	5 (7)	5 (7)	6 (9)	3 (4)	5 (7)	2 (3)
Alanine aminotransferase increased	17 (25)	16 (23)	-	1 (1)	-	1 (1)	-
Blood creatinine increased	16 (23)	15 (28)	1 (1)	0	-	0	-
Fatigue	13 (19)	9 (13)	3 (4)	1 (1)	-	1 (1)	-
Headache	12 (17)	9 (13)	2 (3)	1 (1)	-	1 (1)	-

Most AEs were Grade 1

Only 2 discontinuations for related AEs*

AE, adverse event; ALT, alanine aminotransferase.
*Discontinuations for related AEs: 1ALT (gr3) and pneumonitis (gr2)

Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018

- 8 treatment-emergent AEs, regardless of attribution, in ≥10% of patients; most were Grade 1 and judged not related to LOXO-292

	All doses and patients, n=82							
	Treatment-emergent AEs (≥10% overall)					*Treatment-related* AEs		
	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total
Diarrhea	15%	7%	1%	–	23%	1%	–	11%
Fatigue	9%	13%	–	–	22%	–	–	17%
Dry Mouth	21%	–	–	–	21%	–	–	13%
Constipation	17%	2%	–	–	20%	–	–	4%
Hypomagnesemia	12%	1%	–	–	13%	–	–	2%
Cough	11%	1%	–	–	12%	–	–	1%
Headache	10%	1%	1%	–	12%	–	–	1%
Nausea	9%	4%	–	–	12%	–	–	5%

- Four patients experienced *treatment-related* AEs ≥ grade 3 (all grade 3): diarrhea, increased ALT/AST, thrombocytopenia (DLT @ 240mg BID), tumor lysis syndrome (DLT @ 240mg BID); all were reversible with dose interruption
- 160mg BID selected as RP2D, with dose exploration ongoing at 200 mg BID to further characterize LOXO-292 safety and efficacy

AE = adverse event; DLT = dose limiting toxicity; ALT = alanine aminotransferase; AST = aspartate aminotransferase; RP2D = recommended phase 2 dose;
Note: Total %s for any given AE may be different than the sum of the individual grades, due to rounding. Patients enrolled as of April 2, 2018. Follow-up as of July 19, 2018.

Ongoing MKI trials

Drug	Trial	Phase	N	Setting	Primary outcome
Anlotinib	NCT02586337 (ALTER01032)	III (vs placebo)	120	1st line	PFS
Nintedanib	NCT01788982	II (vs placebo)	143	2nd line	PFS
Ponatinib	NCT03838692	II	31	2nd line	ORR
Regorafenib	NCT02657551	II	33	2nd line	ORR / PFS
Sulfatinib	NCT02614495	II	50 (MTC & DTC)	1st/2nd line	ORR

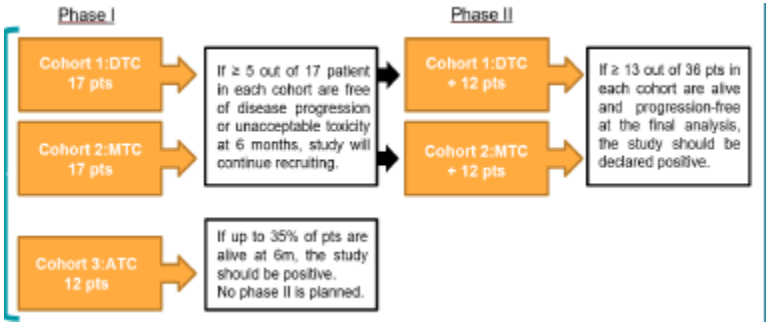
Courtesy of J.Hernando

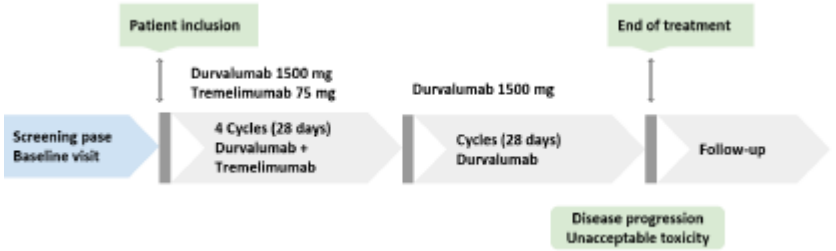
Inmunotherapy

GETNE
Grupo Español de Tumores Neuroendocrinos y Endocrinos

Study title: A phase II study of durvalumab (MEDI4736) plus tremelimumab for the treatment of patients with progressive, refractory advanced thyroid carcinoma - The DUTHY trial

Study number: GETNE - T1812





4. What do you think is the best option for this patient?

- Vandetanib
- Cabozantinib
- Clinical trial (RET inhibitors)
- Clinical trial (inmunotherapy)
- Other

ARROW trial: first-in-human study with BLU-667

PART 1: Dose escalation – *complete*

Objective: *Determine MTD/RP2D* ✓

Proof of concept ✓

BOIN design
Advanced MTC, NSCLC*, or other solid tumor*

MTD/RP2D 400 mg PO daily

*All NSCLC and other solid tumors were RET-altered in cohorts higher than 30 mg QD

Part 1: *62 patients treated*
53 treated at 30 – 600 mg QD
9 treated at 200 – 300 mg divided BID dosing

PART 2: Dose expansion – ongoing

Objective: *Determine Overall Response Rate*

- ***RET*-altered NSCLC with prior MKI**
- ***RET*-altered NSCLC with no prior MKI**
- **MTC with prior MKI**
- **MTC with no prior MKI**
- **Other *RET*-altered solid tumors (including PTC)**
- ***RET*-altered solid tumors with prior selective RET TKI**

MTD, maximum tolerated dose; RP2D, recommended Part 2 dose; BOIN, Bayesian optimal interval; MTC, medullary thyroid cancer; NSCLC, non-small cell lung cancer; QD, once daily; BID, twice daily; PO, orally; ORR, overall response rate; MKI, multikinase inhibitor; PTC, papillary thyroid cancer; TKI, tyrosine kinase inhibitor. NCT03037385

Patients Enrolled as of 9 May 2018. Follow-up as of 14 Sep 2018

GRACIAS !!!

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