

A Phase 1 Study of XL184, a MET, VEGFR2, and RET Kinase Inhibitor, Administered Orally to Patients (pts) with Advanced Malignancies, Including a Subgroup of Pts with Medullary Thyroid Cancer (MTC)

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INTRODUCTION

- The hepatocyte growth factor (HGF) receptor tyrosine kinase (RTK), MET, is strongly implicated as a mediator of tumor pathobiology, including survival, growth, angiogenesis, invasion, and metastasis.¹⁻³
- Germline or somatic mutations in RET are known to be associated with up to 75% of the cases of medullary thyroid cancer (MTC). Mutations in the MET RTK have also been detected in MTC and transduction of normal human thyroid cells with mutant RET results in upregulation of MET.^{4,5}
- The vascular endothelial growth factor (VEGF) receptors VEGFR-1 and VEGFR-2 are expressed on the surface of vascular endothelial cells and on some bone marrow-derived cells.⁶ VEGF expression is upregulated in many human tumors, and binding and activation of VEGFR-2 by VEGF is likely to be a major driver of tumor neoangiogenesis.
- Preclinical models suggest MET and VEGFR-2 play synergistic roles in promoting tumor angiogenesis and subsequent dissemination.⁷
- Modulation of plasma levels of VEGF-A (↑), placental growth factor (PlGF) (↑) and sVEGFR-2 levels (↓) have been associated with clinical benefit of FDA and EMEA approved antiangiogenic agents.
- Soluble MET (sMET) modulation has been demonstrated in preclinical models of MET pathway inhibition.
- XL184 is a potent RTK inhibitor that targets primarily MET, VEGFR-2, and RET RTKs.
 - XL184 has activity against other RTKs that have been implicated in tumor pathobiology, including KIT, FMS-like tyrosine kinase (FLT3), and Tie-2.

OBJECTIVES

- The primary objectives of this study are:
 - To evaluate the safety and tolerability of XL184,
 - To determine the maximum tolerated dose (MTD) of XL184, and
 - To evaluate the plasma pharmacokinetics of XL184 administered orally to subjects with advanced malignancies.
- The secondary objectives of this study are to evaluate preliminary efficacy and long-term safety and tolerability of XL184.
- Additional secondary objectives in the MTD Expanded Cohort are:
 - To assess the progression-free survival (PFS) and duration of response in subjects with advanced or recurrent MTC, and
 - To correlate the potential pathway dysfunction of thyroid tumor relevant genes such as RET and BRAF and relevant downstream signaling molecules with clinical outcome.
- The exploratory objectives of this study are to evaluate tumor response rate and pharmacodynamic correlates of XL184 activity in plasma and peripheral blood cells.

METHODS

Study Design

This study is a Phase 1, nonrandomized, open-label, dose-finding, first-time-in-humans study.

Key Inclusion Criteria

- Subjects (≥18 years) with histologically confirmed advanced malignancy (solid tumor or lymphoma) that is metastatic or unresectable and for which known effective measures did not exist or were no longer effective
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, life expectancy > 3 months, and adequate hematologic, renal, and hepatic function
- In addition to complying with the above criteria, the MTD Expanded Cohort includes:
 - At least 20 subjects with metastatic and/or locally advanced or locally recurrent MTC not appropriate for surgical resection
 - Subjects who have measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST)
 - Subjects with 15 unstained slides of archival tumor tissue

Key Exclusion Criteria

- Prior chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) before the study
- Prior investigational drug use within 30 days of the first dose of XL184
- Known brain metastases or uncontrolled intercurrent illness

Study Treatments

- Subjects received 2 cycles (cycle length = 14 days) of an oral dose of XL184, either as intermittent (daily for 5 consecutive days followed by a 9-day observation period) or daily administration.
- Subjects were instructed to fast two hours before and one hour after administration of XL184.

- Based on nonclinical data, the starting dose was 0.08 mg/kg.
 - Doses were escalated with cohorts of 3 to 6 subjects (100% dose escalations in the absence of any drug-related adverse events (AEs) of Grade ≥ 2 or until an MTD was determined).
 - Intermittent doses of 0.08, 0.16, 0.32, 0.64, 1.28, 2.56, 5.12, 7.68, 11.52 mg/kg powder-in-bottle (PIB) formulation and daily doses of 175 mg (PIB), 265 mg (PIB), 175 mg (capsule), and 250 mg (capsule) were administered.

Pharmacokinetic Assessments

- During each cycle, blood samples were collected at the following timepoints:
 - Cohorts 1-5: at pre-dose and at nine timepoints out to 72 hours after Day 1 dosing or 96 hours after Day 8 dosing, respectively.
 - Cohorts 6-9: at pre-dose and at eight timepoints out to 168 hours after Day 5 dosing.
 - Cohorts 10-11: at pre-dose and at six timepoints out to 24 hours after Days 1, 5, and 19 dosings, respectively.
 - Cohorts 12-13 and 99: at pre-dose and at six timepoints out to 24 hours after Days 1 and 19 dosings, respectively.

- Pharmacokinetic (PK) parameters were obtained by noncompartmental analysis.

Translational Medicine Assessments

- Plasma samples collected on Days 1, 2, and 8 (Cohorts 1-5, pre- and post-dose) and on Days 1, 5, 15, 19, and 29 (Cohorts 6-13 and 99, all pre-dose except Day 5, 4 hours post-dose) were analyzed by ELISA (Pathway Diagnostics, Malibu, CA, USA and Exelixis).
- Plasma samples from 13 subjects enrolled in Cohorts 1-5 and 26 subjects enrolled in Cohort 6-13 and 99 have been analyzed.
- Whole blood samples (n = 21) to determine the hereditary RET status in MTC subjects and tumor samples (n = 19) to determine the RET status of sporadic MTC subjects were analyzed (Exelixis, Clinical Collaborators).

Tumor Response

- Tumors were assessed at baseline, Day 28, and then every 8 weeks. Subjects with measurable lesions were assessed by the site radiologists using RECIST criteria.

RESULTS

- To date, 84 subjects have been enrolled. Reported safety data include subjects who received ≥ 1 dose of XL184. Reported efficacy data include subjects with ≥ 3 month follow-up. This is an analysis of preliminary data from an ongoing study.
- As of 02 September 2008:
 - Safety data from 71 subjects are reported.
 - Pharmacokinetic data are available for 64 subjects.
- As of 11 September 2008:
 - Efficacy data are available for 74 subjects with at least 2 post-baseline efficacy assessments.
 - Baseline characteristics and treatment status are shown in Tables 1 and 2.

Table 1. Baseline Characteristics

Characteristic	Subjects (n = 84)*
Median age, years (range)	54 (29-89)
Gender (male/female)	64/20
Race	
White	71
Black	6
Asian	3
Other	4
Diagnosis/primary site	
Medullary thyroid cancer (MTC)	36
Colorectal cancer, Melanoma	6 each
Sarcoma	4
Carcinoid, Pancreatic, GE junction	3 each
Papillary renal cell, Parotid, Gastric, Mesothelioma, SCC, HCC	2 each
Breast, Cutaneous T-cell lymphoma, Head and Neck, Appendiceal, Laryngeal, Neuroendocrine, Adenocystic, Rectal, PTC, FTC, Adenoma of salivary glands	1 each
ECOG performance status	
0	38
1	43
2	3
Prior chemotherapy ^b	
Median number of regimens (range)	3 (1-10)

FTC, follicular thyroid cancer; GE, gastroesophageal; HCC, Hurtle cell cancer; PTC, papillary thyroid cancer; SCC, squamous cell cancer.

*Includes data from 70 subjects reported in the 02 Sep 2008 data transfer and 14 additional subjects not included in the 02 Sep 2008 data transfer.

^bIncludes data from 70 subjects reported in the 02 Sep 2008 data transfer.

Table 2. Summary of Treatment Status

Status	Subjects (n)
On treatment	27
Off treatment	57
Reason for withdrawal ^a	
Progressive disease	39
Investigator decision	3
Withdrew consent	2
Adverse events	12
Other (radiation treatment given)	1

Cohort Number	Formulation	Original XL184 Dose Level	Subjects, (n)	Months on Study ^b
1	PIB	0.08 mg/kg	4	1-9
2	PIB	0.16 mg/kg	4	1-21
3	PIB	0.32 mg/kg	4	1-5
4	PIB	0.64 mg/kg	3	1-4
5	PIB	1.28 mg/kg	3	2-26+ (1 active)
6	PIB	2.56 mg/kg	3	3-8
7	PIB	5.12 mg/kg	5 ^c	1-20+ (2 active)
8	PIB	7.68 mg/kg	3	1-7
9	PIB	11.52 mg/kg	3	1-5
10	PIB	175 mg daily	3	2-8
11	PIB	265 mg daily	10	1-15+ (4 active)
12	Capsule	175 mg daily	6	1-11+ (3 active)
13	Capsule	250 mg daily	5	1-9+ (1 active)
99	Capsule	175 mg daily	28	1-7+ (16 active)
Total			84^d	

^aData available for 70 subjects reported in the 02 Sep 2008, data transfer and 14 additional subjects not included in the 02 Sep 2008 data transfer.

^bThis includes subjects with date of withdrawal. Data are preliminary because the study is ongoing.

^cNine subjects (11%) underwent intrapatient dose escalation to a dose at or below the capsule MTD of 175 mg.

^dOne subject has two ID numbers (withdrew consent and later re-enrolled).

SAFETY

- Eight dose-limiting toxicities (DLTs) in six subjects during dose escalation occurred:
 - Cohort 9 (11.52 mg/kg, PIB): 1 Grade 3 palmar/plantar erythema (PPE), 1 Grade 3 AST (aspartate aminotransferase), 1 Grade 3 ALT (alanine aminotransferase), 1 Grade 3 lipase elevation
 - Cohort 11 (265 mg/day, PIB): Grade 2 and Grade 3 mucositis, 1 Grade 3 AST elevation
 - Cohort 13 (250 mg/day, capsule): 1 Grade 3 PPE.
- As of 10 Oct 2008, 71 SAEs have been reported in 38 subjects. Of the 71 events, seven were assessed as related to study treatment in six subjects: Grade 4 Pulmonary embolism, Grade 3 Nausea and Grade 3 Skin infection, Grade 2 Ileus, Grade 3 Hypothyroidism, Grade 3 Hyperbilirubinemia, and Grade 2 Diverticulitis, respectively.

Table 3. Most Frequently Reported (≥10% of Subjects) Adverse Events Considered Possibly or Probably Related to Study Treatment

Adverse Event ^{a,b,c}	Subjects (n = 71)		
	Total, n (%)	Grade 1 or 2	Grade 3
Diarrhea	17 (24)	13	1
Nausea	13 (18)	11	1
Fatigue	11 (15)	6	0
Anorexia	9 (13)	6	0
Mucosal inflammation	9 (13)	7	1
Increased AST	8 (11)	2	2
Hypertension	7 (10)	0	1
Vomiting	7 (10)	6	0

^aAdverse event data include one subject who elected to withdraw from the study and later re-enrolled under a unique study subject number.

^bNone of the listed adverse events were > Grade 3.

^cAccording to the Common Terminology Criteria for Adverse Events Version 3.0.

PHARMACOKINETICS

- Systemic exposure (C_{max} and AUC₀₋₂₄) values increased generally dose-proportionally with increasing XL184 dose.
- Terminal-phase half-life (t_{1/2}) values were long (range: 59.1 to 136 hours).
- XL184 was orally bioavailable, with a t_{max} value of 5 hours on Day 1 for Cohort 12 and 99 (175 mg capsule, Figure 1).
- Pre-dose XL184 concentration data suggest that steady-state plasma drug levels occurred by Day 15.
- The accumulation ratio at steady-state after daily dosing is approximately 4- to 6-fold.

PHARMACODYNAMICS

- Pharmacodynamic plasma markers of response to anti-angiogenic treatment were assessed:
 - Combined data from MTD Expanded Cohort subjects (n = 7; Cohorts 12 and 99) demonstrated statistically significant changes in placental growth factor (↑), VEGF-A (↑), and sVEGFR2 (↓, Fig 2).
 - sMET, a potential biomarker of MET inhibition, was increased upon XL184 treatment in 4 of 7 subjects as well.

TUMOR RESPONSE IN MTC SUBJECTS

- Best overall response rate (RR) = 55%
- Median treatment duration not reached (range, 1+ -25+)
- MTC disease control rate (DCR) (PR + SD ≥ 3 months) = 84%

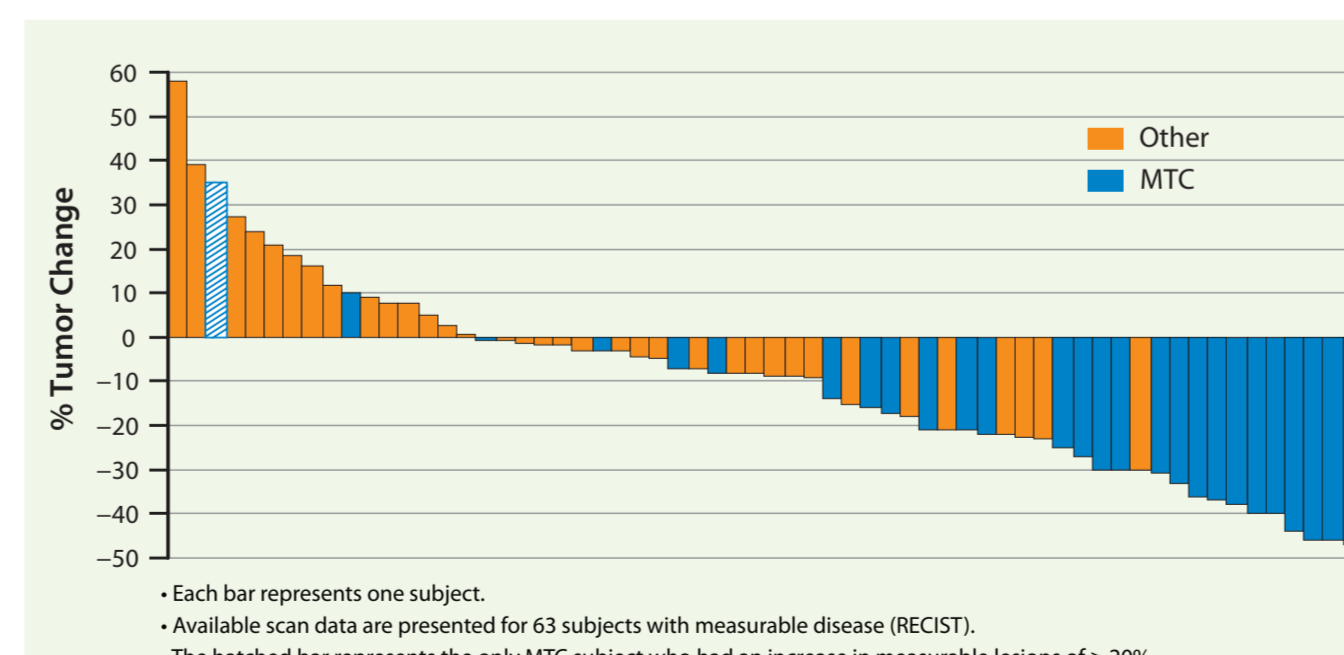


Figure 3. Best radiographic response in subjects with ≥ 1 post-baseline scan.

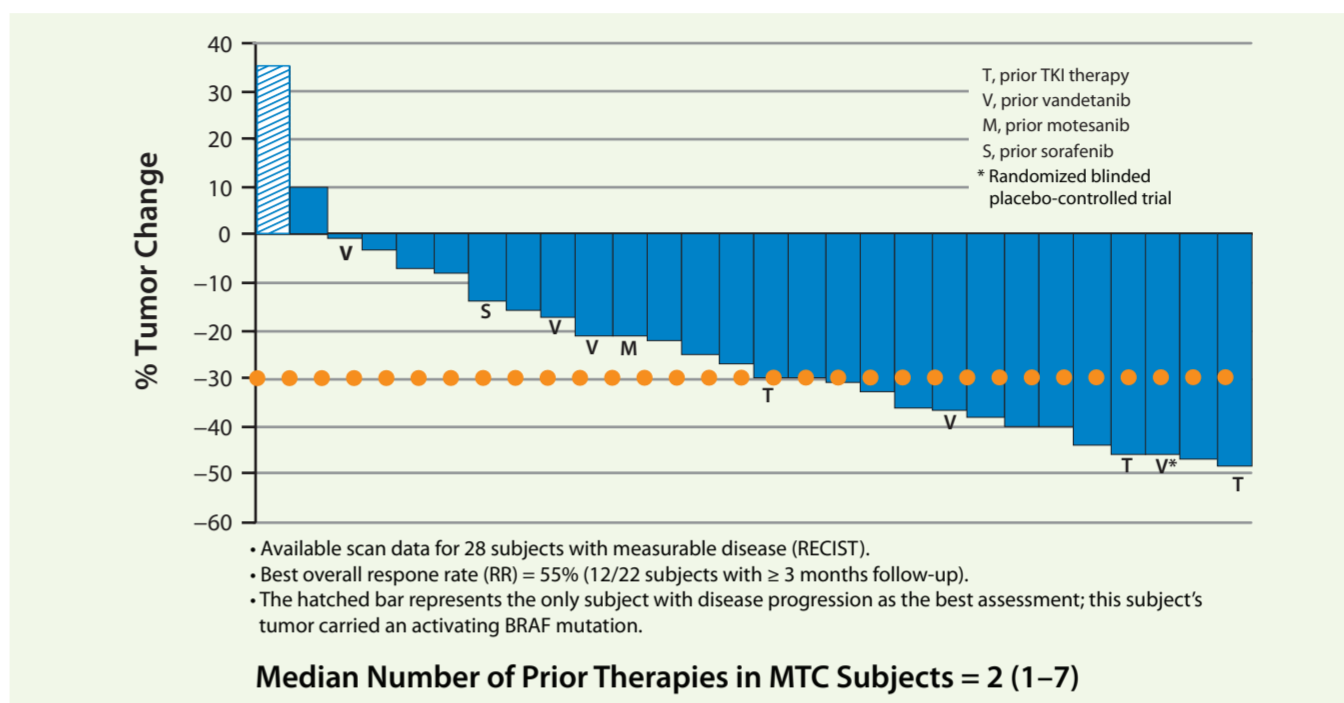


Figure 4. Best radiographic response in MTC subjects with ≥ 1 post-baseline scan.

Analysis of RET Mutational Status in MTC Subjects

- Three MTC subjects have been identified who carry hereditary activating RET mutations. Two subjects demonstrated a germline RET mutation of uncharacterized function that might be a polymorphism.⁸ (Table 4)
 - The incidence of germline mutation is thus 18%. In addition, the G691S RET polymorphism was sequenced from 7 of 17 (41%) of the germline samples.
- RET mutations have been detected in 12 of 17 tumor samples analyzed by sequencing of the RET gene (Table 4). These included two novel mutations of unknown function, G29-630 Del Exon 11, and R982C, in the extracellular domain of RET. The latter mutation might be a polymorphism.⁸
 - Among the tumors from the subjects without a confirmed RET abnormality, two were found to have amplification of the MET gene: 1.7 and 2.2 fold. The latter tumor also contained an activating BRAF mutation, G469A, in the kinase P-loop. While this mutation has been reported in other tumor types, it has not been previously reported in association with MTC.
- Overall, RET mutations (including novel mutations of unknown function) are associated with at least 14 of 18 (78%) of the MTC cancers evaluated to date.

Table 4. Summary of the Genotyping Results in Whole Blood and Archival Tumor Samples of MTC Subjects.

Subject ID	RET Status in Blood (germline)	Tumor Mutation Status (somatic)	Maximal Tumor Response (%)
1	NMD	RET 629-630 del	-48
2	NMD	RET M918T	-46
3	G691S	RET G691S (polymorphism); 1.7x MET amplification	-43
4	NMD	NMD	-40
5	G691S	RET C620W	-40
6	G691S	RET C634R, G691S	-38
7	NMD	RET M918T	-33
8	NMD	RET M918T	-30
9	G691S	RET M918T ^a	-30
10	G691S	NMD	-25
11	Not determined	RET D898-E901 del	-21
12	C634Y	RET C634Y	-17
13	R982C (uncharacterized); G691S	RET M918T; R982C; G691S	-14
14	NMD	RET C634R	-14
15	C611R	Not determined	NM
16	C620R	RET C620R; K808E; K821E ^a	NM
17	R982C (uncharacterized), G691S (polymorphism)	NMD	Scan not done
18	NMD	RET NMD; BRAF G469A; 2.2x MET amplification	+35

NM, non-measurable disease; NMD, no mutations detected.

RET hot spot analysis:

red: known activating mutations; G691S represents a known polymorphism

Exelixis report (exons 10-20); external reports (including MDACC Gagel lab: exons 10,11, 13-16)

MET hot spot analysis: exons 2, 14-19

BRAF hot spot analysis: exons 2, 11, 15

Table 5. Response to Treatment in Subjects with at Least 3 Months of Follow-Up			
Response	Subjects (n)	Primary Diagnosis	Duration of Status (months)
Confirmed partial response (n = 7)	7	MTC	18+, 17+, 6+, 5+, 5, 4, 2+
Unconfirmed partial response (n = 6)	5	MTC	3+, 3, 1+, 1, 1
	1	Neuroendocrine carcinoma	2
Stable disease (SD) ≥ 3 months (n = 28)	2	Carcinoid	15, 7
	1	Cutaneous T-cell lymphoma	20
	1	Parotid	4
	1	Appendiceal	3
	9	MTC	13+, 10+, 10+, 9, 8+, 7, 6+, 5, 3
	2	Sarcoma	5, 4
	2	CRC	5, 4
	1	Papillary RCC	6
	1	Melanoma	3, 3
	2	Mesothelioma	6
	1	Adenocystic	7
	1	Follicular thyroid	8+
	1	GE junction	3
	1	Papillary thyroid	8+
	1	HCC	6+
	1	Rectal	4
Progressive disease (n = 39)	39	Various	-

Clinical Observations in Subjects with MTC

Based upon limited preliminary data, no clear association exists between the magnitude of maximum calcitonin level reduction and the magnitude of maximum tumor reduction among MTC subjects who had a reduction in tumor size (Figure 5). Figure 6 presents the scans of a MTC subject dosed at 5.12 mg/kg PIB who achieved a confirmed partial response after less than 4 months of study treatment.

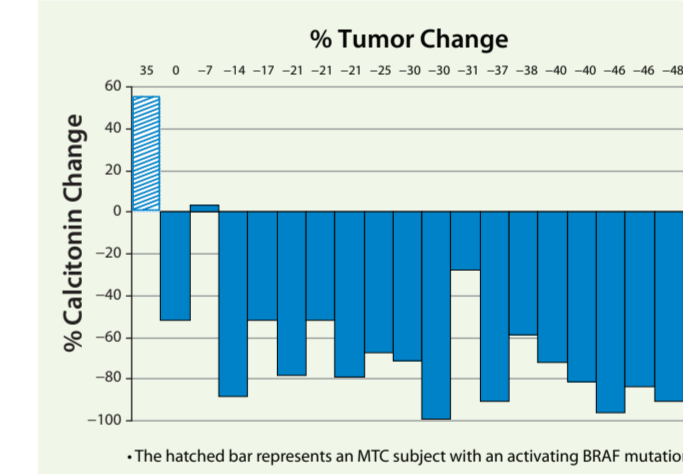


Figure 5. Analysis of maximal changes in plasma calcitonin versus maximal tumor reduction.

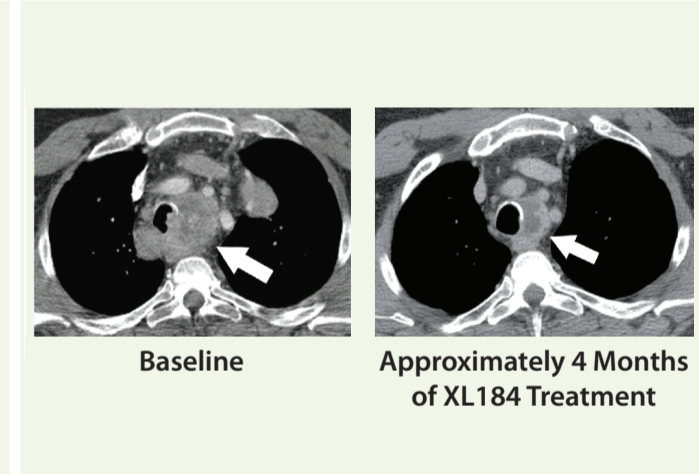


Figure 6. cPR in a subject with MTC.

CONCLUSIONS

- XL184 is generally well tolerated. The most commonly reported XL184-related AEs include diarrhea, nausea, and fatigue. DLTs include AST, ALT, and lipase elevations, PPE, and mucositis.
- Antitumor activity has been observed in subjects with various cancers including MTC:
 - 13 PRs (7 PRc, 6 PRu) and 28 subjects with SD ≥ 3 months (including 16 with SD ≥ 6 months)
 - 55% best overall RR in MTC subjects with ≥ 3 month follow-up, 12 PRs (7 confirmed)
 - 84% MTC DCR (PR + SD ≥ 3 months)
- Preliminary sequencing data suggest that XL184 has activity in MTC subjects independent of their RET mutational status.
- Statistically significant changes in pharmacodynamic biomarkers are consistent with the anti-angiogenic target profile of this agent.
- A Phase 3 Pivotal study in MTC and Phase 2 studies in NSCLC and GBM are ongoing.

References

- Bischmeier C, et al. Nat Rev Mol Cell Biol. 2003;4:915-925.
- Jiang WG, et al. Crit Rev Oncol Hematol. 2005;53(1):35-69.
- Sattler M, et al. Cancer Treat Res. 2004;119:121-138.
- Wassenaar VM, et al. Am J Surg Pathol. 2005;29:544-9.
- Ivan M, et al. Oncogene. 1997;14(20):2417-23.
- Ferrara N, et al. Nat Med. 2003;9:669-676.
- Bottaro DP, Liotta LA. Nature. 2003;423:593-595.
- Hofstra RM, et al. J Clin Endocrinol Metab. 1996;81(8):2881-4.

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