Effect of an Outreach Programme on Vandetanib Safety in Medullary Thyroid Cancer

Lars Bastholt^a Michael C. Kreissl^{b,c} Dagmar Führer^d Ana L. Maia^e
Laura D. Locati^g Léa Maciel^f Yi Wuⁱ Kevin N. Heller^j Alan Webster^k
Rossella Elisei^h

^aDepartment of Oncology R, Odense University Hospital, Odense, Denmark; ^bDepartment of Nuclear Medicine, Augsburg Hospital, Augsburg, ^cDepartment of Nuclear Medicine, University Hospital Würzburg, Würzburg, and ^dDepartment of Endocrinology and Metabolism, University Hospital Essen, Essen, Germany; ^eServiço de Endocrinologia, Hospital de Clínicas de Porto Alegre, Porto Alegre, and ^fHospital das Clínicas de Ribeirão Preto, Ribeirão Preto, Brazil; ^gFondazione IRCCS – Istituto Nazionale dei Tumori, Milan, and ^hEndocrinology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; ⁱDepartment of Head and Neck Surgery, Fudan University Shanghai Cancer Center, Shanghai, China; ^jAstraZeneca, Gaithersburg, Md., USA; ^kAstraZeneca, Macclesfield, UK

Key Words

Vandetanib · Patient outreach · Safety · Adverse events · Medullary thyroid cancer

Abstract

Objectives: Effective management of adverse events (AEs) following vandetanib treatment is important to maximize clinical benefits. We examined whether more frequent contact with vandetanib-treated patients reduced AEs of CTCAE grade 2 or higher. **Study Design:** In this open-label, multicentre, phase III study, patients with locally advanced or metastatic medullary thyroid cancer were randomized to a patient outreach programme (outreach) or a standard AE monitoring schedule (vandetanib control) for 52 weeks. In addition to standard AE monitoring, patients in the outreach arm were contacted every 2 weeks by telephone/during their clinic visit for specific AE questioning related to diarrhoea, nausea, vomiting, fatigue, headache and rash. Patients received vandetanib at 200 or 300 mg/day, depending

on the creatinine levels at screening. **Results:** Altogether, 205 patients were randomized (outreach, n = 103; vandetanib control, n = 102). This study did not meet its primary objective; the mean percentage of time patients experienced at least one AE of grade 2 or higher was higher for the outreach group (51.65%) than for the vandetanib control group (45.19%); the difference was not statistically significant (t statistic: 1.29; 95% CI –3.44 to 16.37%; p = 0.199). The most frequently reported AEs were diarrhoea (56.9% for the outreach group vs. 46.6% for the vandetanib controls), hypertension (36.3 vs. 31.1%), rash (25.5 vs. 24.3%) and nausea (25.5% vs. 18.4%), and the most frequently reported AEs of grade 2 or higher were hypertension (33.3 vs. 23.3%), diarrhoea (26.5 vs. 24.3%) and dermatitis acneiform (11.8 vs. 9.7%). **Conclusions:** Additional outreach to patients treated with vandetanib had no impact on the rate or severity of AEs compared to the standard AE monitoring schedule. AEs were consistent with the known safety profile of vandetanib.

© 2016 European Thyroid Association
Published by S. Karger AG, Basel

Introduction

Medullary thyroid cancer (MTC) is a malignancy of the parafollicular C cells of the thyroid gland, and it accounts for an estimated 4% of thyroid cancers [1, 2]. MTC can only be cured by surgery and, until recently, the treatment options for patients with advanced disease were limited [3, 4]; however, progress in the understanding of the pathogenesis of MTC has led to the development of targeted therapies for this disease.

Several lines of evidence support a role for the rearranged-during-transfection (RET) proto-oncogene as a rational therapeutic target in MTC [1, 5–10]. In addition to RET, vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) likely contribute to the growth and invasiveness of MTC [11, 12].

Vandetanib is a once-daily oral multikinase inhibitor directed against VEGFR2, RET and EGFR [9, 13]. In the EU, vandetanib is indicated for the treatment of aggressive and symptomatic MTC in patients with unresectable locally advanced or metastatic disease. However, for patients in whom the *RET* mutation is not known or is negative, the product label states that a possible lesser benefit should be taken into account when making individual treatment decisions [14]. Across a number of clinical trials, the most common adverse events (AEs) in vandetanib-treated patients have been diarrhoea, rash, nausea, hypertension and headache [15–20], events consistent with the mechanism of action of VEGFR and EGFR inhibition [17, 18, 20]. In the majority of cases, AEs were managed according to standard clinical practice based on developed algorithms (online suppl. table 1; see www.karger.com/doi/10.1159/000448919 for all online suppl. material) or in combination with vandetanib dose reductions or interruptions. However, because there is a risk of QT prolongation, torsades de pointes, and sudden death in patients who receive vandetanib, the Food and Drug Administration decided that the treatment should only be available through a restricted distribution programme as part of a Risk Evaluation and Mitigation Strategy (REMS). The European Medicines Agency recommended careful monitoring of QT changes during the whole treatment period.

Given the potential of long-term vandetanib treatment, effective management of AEs is crucial in order to maximize the clinical benefit and increase the patient's quality of life [21]. The current study, therefore, set out to investigate whether contacting patients proactively and

repeatedly over relatively frequent, defined periods of time could result in earlier detection of the signs and symptoms of AEs.

Materials and Methods

Study Design

This is an open-label, randomized, multicentre, phase III study (ClinicalTrials.gov No. NCT01298323). Patients were randomized 1:1 to either the experimental arm (inclusion in the patient outreach programme, referred to as 'outreach') or the control arm (standard AE monitoring schedule, referred to as 'vandetanib control') using an integrated voice/web recording system. Once randomized, the patients were followed for 52 weeks unless they met any of the criteria for discontinuation (patients could discontinue this study at any time and for any reason). Scheduled visits for patients in the vandetanib control arm were at weeks 2, 4, 8 and 13 and every 3 months thereafter, supplemented with extra visits as deemed necessary by the patient or the responsible physician. Patients randomized to the outreach group had supplementary phone calls from their physician or an experienced research nurse every second week, with the first contact after 1 week of treatment. Patients completing 52 weeks of treatment were given the option of either continuing to take the study drug or discontinuing the study permanently (refer to the online suppl. material for additional details).

The protocol was approved by the institutional review boards or independent ethics committees of all of the investigational sites. This study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice, and the AstraZeneca policy on bioethics [22, 23]. All patients provided written informed consent, which was based on comprehensive information, including aspects of the clinical trial and a detailed description of most of the potential toxicities that patients might encounter during their treatment. In the consent form, it was stated that patients could contact the department responsible for their treatment in case of toxicity or other concerns.

Patients

Eligible patients were aged 18 years or older, with a histologically confirmed diagnosis of unresectable, locally advanced or metastatic hereditary or sporadic MTC and a performance status of 0–2 [World Health Organization (WHO) or Eastern Cooperative Oncology Group (ECOG)], for whom no standard therapy was available.

Treatments Administered

The starting dose of oral vandetanib was dependent on the patient's creatinine clearance at screening. Patients with a screening creatinine clearance ≥ 50 ml/min started vandetanib at 300 mg (3 $\times$ 100-mg tablets) once daily. Patients with moderate renal impairment, defined as a screening creatinine clearance ≥ 30 to < 50 ml/min, started vandetanib at a reduced dose of 200 mg once daily (2 $\times$ 100-mg tablets). The starting dose was administered throughout this study unless a dose reduction was required (refer to the online suppl. material for additional details).

Objectives

The primary objective of this study was to demonstrate a decrease in the percentage of time patients with locally advanced or

Fig. 1. Patient disposition. * In addition to the standard AE monitoring during scheduled visits, patients in the experimental arm were contacted by study site personnel at week 1 and then every 2 weeks during the first 52 weeks on this study (or prior to discontinuation) to detect and possibly treat AEs sooner than could have occurred without the patient outreach, and at a time of a lower CTCAE grade. Patients who were successfully contacted at least once a week were considered to have taken part in the patient outreach programme (1 patient did not qualify and was included in the control arm for AE reporting). † Standard AE monitoring schedule.

metastatic MTC experienced at least one AE of CTCAE grade 2 or higher in the first 12 months of vandetanib treatment with the use of a patient outreach programme compared to a standard AE monitoring schedule. The secondary objective was to obtain information on the safety and tolerability of vandetanib, which would be compared with data from the pivotal phase III clinical trial [20].

Assessments

Safety was assessed throughout this study via monitoring and recording of AEs, 12-lead electrocardiogram (ECG) parameters, vital signs, clinical chemistry, haematology and urinalysis. AEs were classified using the National Cancer Institute's CTCAE (version 4). QTc prolongation was defined as a single value ≥ 550 ms or 2 consecutive measurements (within 48 h of each other), whereby a QTc interval was ≥ 500 but < 550 ms.

Statistical Analysis

The primary endpoint was analysed using a Student independent 2-sample t test. All patients who received at least one dose of vandetanib were included in the safety population (refer to the online suppl. material for additional details).

Results

Patient Characteristics and Disposition

In total, 217 patients were enrolled from 33 centres in 20 countries between February 2011 and April 2012, and 205 patients were randomized to treatment (outreach, $n = 103$; vandetanib control, $n = 102$). Of these, 155 (75.6%) patients (outreach, $n = 78$; vandetanib control, $n = 77$) received the study treatment for 12 months. The patient disposition and reasons for discontinuation are shown in figure 1. Of the 103 patients randomized to the outreach arm, 1 patient did not qualify for the outreach programme. This patient was included in the outreach group demographics, but for the safety analyses this patient was included in the control group.

The demographics and baseline characteristics of the patients are summarized in table 1. The demographic characteristics in the overall population were well balanced between treatment arms. Overall, 194 (94.6%) patients had

Table 1. Patient demographics and disease characteristics

	Outreach (n = 103)	Control (n = 102)	Total (n = 205)
Age, years	55.0 (23–77)	51.5 (20–77)	53.0 (20–77)
Sex			
Male	66 (64.1)	64 (62.7)	130 (63.4)
Female	37 (35.9)	38 (37.3)	75 (36.6)
Race			
White	84 (81.6)	87 (85.3)	171 (83.4)
Asian	19 (18.4)	15 (14.7)	34 (16.6)
Weight, kg	71.8±20.4	70.3±15.7	71.1±18.2
BMI	24.3±5.5	23.9±4.5	24.1±5.0
WHO/ECOG performance status			
0 (normal activity)	72 (69.9)	72 (70.6)	144 (70.2)
1 (restricted activity)	27 (26.2)	28 (27.5)	55 (26.8)
2 (in bed ≥50% of the time)	4 (3.9)	2 (2.0)	6 (2.9)

Values are presented as medians (range), numbers (%) or means ± SD.

Table 2. AEs with a frequency >10% in either treatment arm

	Patients, n (%)		
	outreach (n = 102)	control (n = 103)	total (n = 205)
Any AE	101 (99.0)	93 (90.3)	194 (94.6)
Diarrhoea	58 (56.9)	48 (46.6)	106 (51.7)
Hypertension	37 (36.3)	32 (31.1)	69 (33.7)
Rash	26 (25.5)	25 (24.3)	51 (24.9)
Nausea	26 (25.5)	19 (18.4)	45 (22.0)
Dermatitis acneiform	22 (21.6)	22 (21.4)	44 (21.5)
Fatigue	18 (17.6)	17 (16.5)	35 (17.1)
Decreased appetite	13 (12.7)	19 (18.4)	32 (15.6)
Hypothyroidism	15 (14.7)	15 (14.6)	30 (14.6)
Hypocalcaemia	13 (12.7)	16 (15.5)	29 (14.1)
Asthenia	12 (11.8)	13 (12.6)	25 (12.2)
Decreased weight	12 (11.8)	11 (10.7)	23 (11.2)
Photosensitivity reaction	13 (12.7)	8 (7.8)	21 (10.2)
Headache	12 (11.8)	8 (7.8)	20 (9.8)
Vomiting	9 (8.8)	11 (10.7)	20 (9.8)
Dry skin	7 (6.9)	12 (11.7)	19 (9.3)
Proteinuria	11 (10.8)	8 (7.8)	19 (9.3)

The results include AEs with an onset date on or after the first dose and up to and including 60 days following the last dose. If the patient remained on the study medication after 12 months, only new SAEs were collected until 60 days after the last dose of the study medication.

undergone surgical and medical procedures, with 191 (93.2%) patients having undergone thyroidectomy.

Safety Results

Primary Outcome

The mean percentage of time patients experienced at least one AE of CTCAE grade 2 or higher was 51.65% (SD 35.55) for the outreach arm versus 45.19% (SD 36.35) for the vandetanib control arm. This difference was not statistically significant (t statistic 1.29; 95% CI –3.44% to 16.37%; p = 0.199).

Extent of Exposure

The mean duration of treatment in the outreach arm (actual treatment exposure: 14.13 months) was slightly longer than that in the vandetanib control arm (actual treatment exposure: 13.87 months). Apart from 1 patient in the outreach arm who received vandetanib at 200 mg, all patients received a starting dose of vandetanib of 300 mg.

Dose interruptions occurred in 112 (54.6%) patients (60.8% of the outreach group vs. 48.5% of the vandetanib control group) and dose reductions occurred in 82 (40.0%) patients (43.1% of the outreach group vs. 36.9% of the vandetanib control group). Dose interruptions due to AEs occurred in 92 patients (44.9%) and dose reductions due to AEs occurred in 78 patients (38.0%). The most common AEs leading to dose interruptions were diarrhoea (n = 3; 1.5%), decreased appetite (n = 3; 1.5%) and hypertension (n = 6; 2.9%); all other AEs leading to dose interruptions were reported by 2 patients or fewer.

Table 3. AEs of CTCAE grade 2 or higher occurring with a frequency >3% in either treatment arm

	Patients, n (%)		
	outreach (n = 102)	control (n = 103)	total (n = 205)
Any AE of CTCAE grade 2 or higher	90 (88.2)	83 (80.6)	173 (84.4)
Hypertension	34 (33.3)	24 (23.3)	58 (28.3)
Diarrhoea	27 (26.5)	25 (24.3)	52 (25.4)
Dermatitis acneiform	12 (11.8)	10 (9.7)	22 (10.7)
Rash	8 (7.8)	10 (9.7)	18 (8.8)
Hypocalcaemia	9 (8.8)	8 (7.8)	17 (8.3)
Nausea	9 (8.8)	6 (5.8)	15 (7.3)
Decreased appetite	6 (5.9)	7 (6.8)	13 (6.3)
Proteinuria	8 (7.8)	4 (3.9)	12 (5.9)
Increased ALT	6 (5.9)	6 (5.8)	12 (5.9)
Prolonged QT	7 (6.9)	5 (4.9)	12 (5.9)
Fatigue	4 (3.9)	7 (6.8)	11 (5.4)
Decreased weight	5 (4.9)	5 (4.9)	10 (4.9)
Urinary tract infection	5 (4.9)	3 (2.9)	8 (3.9)
Asthenia	3 (2.9)	5 (4.9)	8 (3.9)
Headache	5 (4.9)	2 (1.9)	7 (3.4)
Increased blood creatinine	3 (2.9)	4 (3.9)	7 (3.4)
Insomnia	2 (2.0)	4 (3.9)	6 (2.9)
Dyspnoea	4 (3.9)	2 (1.9)	6 (2.9)
Abdominal pain	4 (3.9)	2 (1.9)	6 (2.9)
Dry skin	2 (2.0)	4 (3.9)	6 (2.9)

The results include AEs with an onset date on or after the first dose and up to and including 60 days following the last dose. If the patient remained on the study medication after 12 months, only new SAEs were collected until 60 days after the last dose of the study medication.

The most common AEs leading to dose reductions were diarrhoea (n = 10; 4.9%), increased alanine aminotransferase (ALT) (n = 4; 2.0%), rash (n = 11; 5.4%) and hypertension (n = 12; 5.9%).

Adverse Events

Most patients reported at least one AE [n = 101 (99%) in the outreach arm vs. n = 93 (90.3%) in the vandetanib control arm]. The most frequently reported AEs were diarrhoea, hypertension, rash and nausea (table 2).

AEs of CTCAE grade 2 or higher were reported in 90 (88.2%) patients in the outreach arm and in 83 (80.6%) patients in the vandetanib control arm. The most frequently reported AEs of CTCAE grade 2 or higher were hypertension (33.3 vs. 23.3%), diarrhoea (26.5 vs. 24.3%) and dermatitis acneiform (11.8 vs. 9.7%; table 3).

Table 4. SAEs occurring with a frequency >1% in either treatment arm

	Patients, n (%)		
	outreach (n = 102)	control (n = 103)	total (n = 205)
Any SAE	27 (26.5)	30 (29.1)	57 (27.8)
Death	4 (3.9)	2 (1.9)	6 (2.9)
Hypertension	2 (2.0)	2 (1.9)	4 (2.0)
Diarrhoea	3 (2.9)	0	3 (1.5)
Hypocalcaemia	0	2 (1.9)	2 (1.0)
Pancreatitis	0	2 (1.9)	2 (1.0)
Chest pain	0	2 (1.9)	2 (1.0)

The results include AEs with an onset date on or after the first dose and up to and including 60 days following the last dose. If the patient remained on the study medication after 12 months, only new SAEs were collected until 60 days after the last dose of the study medication.

AEs of CTCAE grade 3 or higher were reported in 54 (52.9%) patients in the outreach arm versus 47 (45.6%) patients in the vandetanib control arm. The most frequently reported AEs of CTCAE grade 3 or higher were hypertension (16.7 vs. 10.7%), diarrhoea (6.9 vs. 2.9%), prolonged QT (3.9 vs. 4.9%), fatigue (2.0 vs. 2.9%) and rash (2.9 vs. 1.9%).

Of the 194 (94.6%) patients who experienced AEs during this study, 179 (87.3%) had a drug-related AE [n = 91 (89.2%) in the outreach arm vs. n = 88 (85.4%) in the vandetanib control arm]. Serious AEs (SAEs) were reported in 57 (27.8%) patients; the number of patients who reported at least one SAE was smaller in the outreach arm (n = 27; 26.5%) versus the vandetanib control arm (n = 30; 29.1%). Drug-related SAEs were reported in 21 (10.2%) patients. The most frequently reported SAE was hypertension, which was reported by 2 patients in each group (table 4).

AEs with an outcome of death were reported in 6 (2.9%) patients – 4 patients in the outreach arm and 2 patients in the vandetanib control arm (details for each patient are available in the online suppl. material).

Clinical Laboratory Evaluation, Vital Signs and ECG Changes

No clinically significant laboratory abnormalities, vital sign abnormalities, or ECG changes other than QT prolongations were observed in this study.

Discussion

There is a need to anticipate and effectively manage therapy-related AEs with vandetanib in order to maximize the clinical benefit [21]. The REMS programme exists to ensure that only certified prescribers may prescribe vandetanib. Early detection, intervention and coordinated management of vandetanib-associated AEs, together with patient awareness of AEs, are also crucial for successful treatment. The current study investigated whether more frequent contact with patients would decrease the percentage of time patients experienced AEs of CTCAE grade 2 or higher in the first 12 months of treatment with vandetanib. Results indicated that additional outreach from certified prescribers to patients treated with vandetanib had no significant impact on either the rate or the severity of AEs, consistent with the predictable AE profile of this treatment.

The strengths of this study are its randomized design and large sample size. As such, the trial population recruited for this study is similar to that expected in clinical reality.

As an open-label study, it is possible that the findings of the primary endpoint may reflect an ascertainment bias associated with the more frequent patient contact in the outreach arm. The number of patients who reported at least one AE was slightly larger for those patients participating in the outreach programme than for those who did not take part in the programme (99 vs. 90%). The possibility that intervention in this study could have encouraged participants to be more aware of their signs and symptoms, thereby increasing the likelihood of reporting of an AE, cannot be discounted. It is well known that the use of patient-reported outcomes leads to increases in the number of toxicities reported [24]. This is also supported by the fact that the pattern of AEs in the outreach arm is fully comparable to the pattern reported in the pivotal phase III study, for which the reporting of AEs was more meticulous because the study was a registration study [20]. Similarly, a heightened awareness of AEs among the patients participating in the outreach programme may have increased the likelihood of vandetanib discontinuation. The fact that only centres experienced in the treatment of patients with vandetanib were involved in this study may have also resulted in some bias in the results; these centres have dedicated and experienced study nurses who can easily be contacted by patients with problems. As such, more AEs may have been reported in the outreach arm. Indeed, findings from other studies have shown increased reporting rates for AEs with the use of solicited versus spontaneously reported collection meth-

ods [25, 26], and solicitation of AEs is thought to be more sensitive since questionnaires or checklists prompt patients to report events [25]. Given that a number of AEs are typically seen in the first 3 months of vandetanib treatment [27], another explanation for the findings of the current study is that the benefits of frequent patient contact might not be apparent over a prolonged treatment period of 12 months. It is noteworthy that there was a slight reduction in the number of SAEs reported in the outreach arm (26.5 vs. 29.1%); it is possible that this is because AEs were reported and treated earlier before becoming more serious in nature.

The duration of vandetanib treatment was similar across the 2 study arms. The types and severity of AEs were generally similar in both treatment arms and consistent with the known safety profile of vandetanib [17, 18, 20] and the mechanism of action of VEGFR and EGFR inhibition [28, 29]. The most common AEs with vandetanib treatment were diarrhoea, hypertension, rash and nausea; these AEs were also the most commonly reported events in the phase III registration trial of vandetanib [20]. In the current study, we found that the overall incidences of diarrhoea and hypertension for patients receiving vandetanib were similar to those in the ZETA trial (diarrhoea, 51.7 vs. 56%, and hypertension, 33.7 vs. 32%, respectively), whereas rash, nausea and prolonged QT were reported at a lower rate (rash, 24.9 vs. 45%; nausea, 22 vs. 33%, and prolonged QT, 7.8 vs. 14%, respectively) [20]. Similarly to the phase III registration trial [20], a protocol-defined QTc prolongation was observed in 8% of the patients and there were no reports of torsades de pointes. No clinically significant laboratory abnormalities, vital sign abnormalities or ECG changes were observed in the study. AEs were managed through the use of standard medical care, dose reduction, dose interruption, or permanent discontinuation of the treatment. The number of patients who discontinued treatment because of AEs was small (5.4%). It should be noted that prevention of AEs is an important part of treatment management with vandetanib. Two particular examples are: the use of protective clothing, such as gloves and hats, in addition to the use of sunscreens to prevent skin rashes; frequent blood pressure monitoring, as well as dietary recommendations on salt intake, for patients with normal to moderately high blood pressure is also indicated.

In conclusion, intervention via an outreach programme from certified prescribers did not show any additional benefits in terms of the percentage of time patients experienced at least one AE of grade 2 or higher compared to a standard AE monitoring schedule. Addi-

tional outreach to patients treated with vandetanib had no impact on either the rate or the severity of AEs. AEs were predictable and consistent with the known safety profile of vandetanib. Standard medical care of patients treated with vandetanib, including algorithms for the handling of AEs, is efficient to ensure the safety of treatment with vandetanib in patients with MTC. This study has provided further evidence to show that, when the REMS measures are applied, vandetanib has a predictable AE profile. For those patients for whom frequent visits to the clinic may pose a problem, a schedule of less frequent visits combined with an outreach programme may be appropriate as part of their standard of care.

Acknowledgements

The authors would like to thank the patients who took part in this study. Medical writing assistance was provided by Claire Routley, PhD, from Mudskipper Business Ltd., funded by AstraZeneca. This study was sponsored by AstraZeneca.

References

- Mulligan LM, Kwok JB, Healey CS, Elsdon MJ, Eng C, Gardner E, Love DR, Mole SE, Moore JK, Papi L, Ponder MA, Telenius H, Tunnacliffe A, Ponder BA: Germ-line mutations of the RET proto-oncogene in multiple endocrine neoplasia type 2A. *Nature* 1993; 363:458–460.
- Lakhani VT, You YN, Wells SA: The multiple endocrine neoplasia syndromes. *Annu Rev Med* 2007;58:253–265.
- Martins RG, Rajendran JG, Capell P, Byrd DR, Mankoff DA: Medullary thyroid cancer: options for systemic therapy of metastatic disease? *J Clin Oncol* 2006;24:1653–1655.
- Kloos RT, Eng C, Evans DB, Francis GL, Gargel RF, Gharib H, Moley JF, Pacini F, Ringel MD, Schlumberger M, Wells SA Jr: Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid* 2009;19:565–612.
- Donis-Keller H, Dou S, Chi D, Carlson KM, Toshima K, Lairmore TC, Howe JR, Moley JF, Goodfellow P, Wells SA Jr: Mutations in the RET proto-oncogene are associated with MEN 2A and FMTC. *Hum Mol Genet* 1993; 2:851–856.
- Carlson KM, Dou S, Chi D, Scavarda N, Toshima K, Jackson CE, Wells SA Jr, Goodfellow PJ, Donis-Keller H: Single missense mutation in the tyrosine kinase catalytic domain of the RET protooncogene is associated with multiple endocrine neoplasia type 2B. *Proc Natl Acad Sci USA* 1994;91:1579–1583.
- Marsh DJ, Learoyd DL, Andrew SD, Krishnan L, Pojer R, Richardson AL, Delbridge L, Eng C, Robinson BG: Somatic mutations in the RET proto-oncogene in sporadic medullary thyroid carcinoma. *Clin Endocrinol (Oxf)* 1996;44:249–257.
- Elisei R, Cosci B, Romei C, Bottici V, Renzini G, Molinaro E, Agate L, Vivaldi A, Faviana P, Basolo F, Miccoli P, Berti P, Pacini F, Pinchera A: Prognostic significance of somatic RET oncogene mutations in sporadic medullary thyroid cancer: a 10-year follow-up study. *J Clin Endocrinol Metab* 2008;93:682–687.
- Carlomagno F, Vitagliano D, Guida T, Ciardiello F, Tortora G, Vecchio G, Ryan AJ, Fontanini G, Fusco A, Santoro M: ZD6474, an orally available inhibitor of KDR tyrosine kinase activity, efficiently blocks oncogenic RET kinases. *Cancer Res* 2002;62:7284–7290.
- Vitagliano D, De Falco V, Tamburrino A, Coluzzi S, Troncone G, Chiappetta G, Ciardiello F, Tortora G, Fagin JA, Ryan AJ, Carlomagno F, Santoro M: The tyrosine kinase inhibitor ZD6474 blocks proliferation of RET mutant medullary thyroid carcinoma cells. *Endocr Relat Cancer* 2011;18:1–11.
- Rodriguez-Antona C, Pallares J, Montero-Conde C, Inglada-Perez L, Castelblanco E, Landa I, Leskela S, Leandro-Garcia LJ, Lopez-Jimenez E, Leton R, Cascon A, Lerma E, Martin MC, Carralero MC, Mauricio D, Cigudosa JC, Matias-Guiu X, Robledo M: Overexpression and activation of EGFR and VEGFR2 in medullary thyroid carcinomas is related to metastasis. *Endocr Relat Cancer* 2010;17:7–16.
- Schlumberger M, Carlomagno F, Baudin E, Bidart JM, Santoro M: New therapeutic approaches to treat medullary thyroid carcinoma. *Nat Clin Pract Endocrinol Metab* 2008;4: 22–32.
- Wedge SR, Ogilvie DJ, Dukes M, Kendrew J, Chester R, Jackson JA, Boffey SJ, Valentine PJ, Curwen JO, Musgrove HL, Graham GA, Hughes GD, Thomas AP, Stokes ES, Curry B, Richmond GH, Wadsworth PF, Bigley AL, Hennequin LF: ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. *Cancer Res* 2002;62:4645–4655.
- AstraZeneca: Caprelsa (vandetanib) tablets – prescribing information. 2011.
- Holden SN, Eckhardt SG, Bassar R, de Boer R, Rischin D, Green M, Rosenthal MA, Wheeler C, Barge A, Hurwitz HI: Clinical evaluation of ZD6474, an orally active inhibitor of VEGF and EGF receptor signaling, in patients with solid, malignant tumors. *Ann Oncol* 2005;16: 1391–1397.

Disclosure Statement

L.B. has been on advisory boards for: AstraZeneca, Bayer, Eisai and SOBI. He has given lectures for: AstraZeneca, Bayer, Genzyme and SOBI, and he has been reimbursed for conference attendance by AstraZeneca. M.C.K. has been on advisory boards for: AstraZeneca, Bayer, Eisai and SOBI. He has given lectures for: AstraZeneca, Bayer, Genzyme and Sanofi, and he has been reimbursed conference attendance by AstraZeneca and SOBI. D.F. has been on advisory boards and given lectures for: AstraZeneca, Bayer, Eisai, SOBI and Genzyme. A.L.M. has been a consultant for Bayer and AstraZeneca, and she has been on the advisory board for AstraZeneca Brazil. L.M. is a consultant for Bayer. K.N.H. and A.W. were employees of AstraZeneca at the time of the conduction of this study. L.D.L. and Y.W. have no conflict of interests. R.E. has been a consultant for: Bayer, AstraZeneca, EISAI, Exelixis and Novartis.

- 16 Tamura T, Minami H, Yamada Y, Yamamoto N, Shimoyama T, Murakami H, Horiike A, Fujisaka Y, Shinkai S, Tahara M, Kawada K, Ebi H, Sasaki Y, Jiang H, Saijo N: A phase I dose-escalation study of ZD6474 in Japanese patients with solid, malignant tumors. *J Thorac Oncol* 2006;1:1002–1009.
- 17 Wells SA, Gosnell JE, Gagel RF, Moley J, Pfister D, Sosa JA, Skinner M, Krebs A, Vasselli J, Schlumberger M: Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer. *J Clin Oncol* 2010;28:767–772.
- 18 Robinson BG, Paz-Ares L, Krebs A, Vasselli J, Haddad R: Vandetanib (100 mg) in patients with locally advanced or metastatic hereditary medullary thyroid cancer. *J Clin Endocrinol Metab* 2010;95:2664–2671.
- 19 Wells SA, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, Baudin E, Vasselli JR, Read J, Schlumberger M: Vandetanib (VAN) in locally advanced or metastatic medullary thyroid cancer (MTC): a randomized, double-blind phase III trial (ZETA). *J Clin Oncol* 2010;28:15S.
- 20 Wells SA, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, Baudin E, Elisei R, Jarzab B, Vasselli JR, Read J, Langmuir P, Ryan AJ, Schlumberger MJ: Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol* 2012;30:134–141.
- 21 Grande E, Kreissl MC, Filetti S, Newbold K, Reinisch W, Robert C, Schlumberger M, Tolstrup LK, Zamorano JL, Capdevila J: Vandetanib in advanced medullary thyroid cancer: review of adverse event management strategies. *Adv Ther* 2013;30:945–966.
- 22 World Medical Association: Declaration of Helsinki – ethical principles for medical research involving human subjects. <http://www.wma.net/en/30publications/10policies/b3/index.html>.
- 23 AstraZeneca: Global policy: bioethics. 2015. <http://www.astrazeneca.com/Responsibility/Code-policies-standards/Our-global-policies>.
- 24 Basch E: The missing voice of patients in drug-safety reporting. *N Engl J Med* 2010;362:865–869.
- 25 Wernicke JF, Faries D, Milton D, Weyrauch K: Detecting treatment emergent adverse events in clinical trials: a comparison of spontaneously reported and solicited collection methods. *Drug Saf* 2005;28:1057–1063.
- 26 Molokhia M, Tanna S, Bell D: Improving reporting of adverse drug reactions: systematic review. *Clin Epidemiol* 2009;1:75–92.
- 27 Langmuir PB, Yver A: Vandetanib for the treatment of thyroid cancer. *Clin Pharmacol Ther* 2012;91:71–80.
- 28 Izzedine H, Rixe O, Billefont B, Baumelou A, Deray G: Angiogenesis inhibitor therapies: focus on kidney toxicity and hypertension. *Am J Kidney Dis* 2007;50:203–218.
- 29 Herbst RS: Toxicities of antiangiogenic therapy in non-small-cell lung cancer. *Clin Lung Cancer* 2006;8(suppl 1):S23–S30.