IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A13-09

Vandetanib – Re-assessment of benefit according to § 35a, Paragraph 5b, Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment "Vandetanib – Erneute Nutzenbewertung gemäß § 35a Absatz 5b SGB V" (Version 1.0; Status: 13 June 2013). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Vandetanib – Re-assessment of benefit according to § 35a, Paragraph 5b, Social Code Book V

Contracting agency:
Federal Joint Committee

Commission awarded on:
11 March 2013

Internal Commission No.:
A13-09

Address of publisher:
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Keywords: vandetanib, thyroid neoplasms, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

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[3]Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DOR	Duration of response
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FACT-G	Functional Assessment of Cancer Therapy-General
G-BA	*Gemeinsamer Bundesausschuss* (Federal Joint Committee)
IDR	incidence density ratio
IQWiG	*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (Institute for Quality and Efficiency in Health Care)
MedDRA PT	Medical Dictionary for Regulatory Activities Preferred Terms
MTC	medullary thyroid carcinoma
ORR	objective response rate
PFS	progression-free survival
QTc	time interval between the start of the Q wave and the end of the T wave (corrected for heart rate)
RCT	randomized controlled trial
RET	rearranged during transfection
SAE	serious adverse event
SGB	*Sozialgesetzbuch* (Social Code Book)
SPC	Summary of Product Characteristics
WHO-PS	World Health Organization performance status

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a (5b) Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to re-assess the benefit of the drug vandetanib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to "the company"). The dossier was sent to IQWiG on 11 March 2013.

Research question

The aim of this report is to assess the added benefit of vandetanib compared to *best supportive care* (BSC) as appropriate comparator therapy (ACT) in patients with aggressive and symptomatic medullary thyroid carcinoma (MTC) with unresectable, locally advanced or metastatic disease.

The comparator therapy chosen by the company corresponded to the ACT previously specified by the G-BA.

In the current therapeutic situation, there is a need for all patients to be treated with BSC. Studies that compared vandetanib in combination with BSC with treatment consisting of BSC alone were therefore included in the benefit assessment. If available, studies in which vandetanib as monotherapy was compared with BSC could also be included.

The assessment was based on patient-relevant outcomes. Direct comparative randomized controlled trials (RCTs) were included in the assessment.

Results

One relevant study (D4200C00058, Study 58), the approval study of vandetanib, was available for the assessment.

Study 58 is an ongoing, multicentre, double-blind, placebo-controlled study. Patients were randomized to vandetanib or placebo in a ratio of 2:1. Both the patients in the vandetanib treatment arm and those in the placebo treatment arm received concomitant treatment rated as BSC. The study treatment according to the protocol was continued until progression occurred. If progression occurred, the patients discontinued the randomized treatment phase with the study medication. After the unblinding there was the option to change into an open-label treatment phase with vandetanib (crossover or continued treatment).

Patients diagnosed with an unresectable and locally advanced or metastatic stage of hereditary or sporadic form of MTC were enrolled. According to the Summary of Product Characteristics (SPC), vandetanib is only approved for patients with aggressive and symptomatic course of this disease. However, the study population of Study 58 is not limited

to patients with this course of disease. So the study population is wider than the approval population. Only a subpopulation of Study 58 was therefore relevant for this assessment. The dossier contained analyses for those patients with progressive and symptomatic course of disease. This population was regarded as an adequate approximation to the approval population (patients with aggressive and symptomatic MTC).

Risk of bias

The risk of bias at study level was rated as high. One key aspect was that the patients had the option to change to open-label treatment with vandetanib after progression of the disease and the subsequent discontinuation of the double-blind randomized treatment phase. For all outcomes considered in the benefit assessment, with the exception of overall survival (OS), an analysis was performed that was limited to observations made during the treatment originally assigned. However, the median treatment duration was more than twice as long in the vandetanib + BSC arm (88.6 weeks) than in the comparator arm (37.1 weeks). For this reason, the relative risks estimated on the basis of naive proportions were no adequate analysis. This meant for most outcomes on adverse events (AEs) that no evaluable results were available for the benefit assessment. The time-adjusted analyses on AEs included in the assessment were rated as highly biased due to the uncertainty of the model assumptions, with the direction of the bias being unclear. The risk of bias for the outcome "pain progression", which was analysed on the basis of an analysis of survival time, was also rated as high because of informative censorings and uncertainties regarding the number of the patients considered in the analyses. The direction of the bias was unclear. Potentially highly biased results to the disadvantage of vandetanib result for OS because of the high proportion of patients from the comparator group who changed to the open-label treatment with vandetanib.

Mortality

The treatment with vandetanib + BSC did not result in a statistically significant difference for OS in comparison with the treatment with placebo + BSC. Hence an added benefit of vandetanib + BSC in comparison with the ACT BSC is not proven for this outcome.

Morbidity

The treatment with vandetanib + BSC resulted in a statistically significant prolongation of the time to pain progression in comparison with the treatment with placebo + BSC. The assessment of subgroup characteristics resulted in an indication of an effect modification by the characteristic "age" (< 65 years versus ≥ 65 years) for pain progression. The results on pain progression are therefore regarded in the age subgroups. Because of the high risk of bias with unclear direction based on outcomes, there is a hint of an added benefit of vandetanib + BSC in comparison with the ACT BSC for younger patients (< 65 years). For older patients (≥ 65 years) an added benefit is not proven.

Health-related quality of life

The company's dossier contained no evaluable data on health-related quality of life. An added benefit of vandetanib + BSC in comparison with the ACT BSC is not proven for the outcome "health-related quality of life".

Adverse events

There were no evaluable analyses for most outcomes on AEs. Hence the following outcomes could not be considered in the benefit assessment: rate of serious AEs (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≥ 3), treatment discontinuation due to AEs, and skin rash.

For the specific AEs relevant for the benefit assessment "prolongation of the QTc interval" and "diarrhoea", the differences between the treatment arms were not statistically significant. Overall, a greater or lesser harm from vandetanib + BSC in comparison with BSC is not proven, with the data being highly uncertain.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug vandetanib compared with the ACT is assessed as follows:

Overall, on the basis of the available and evaluable results, a positive effect remains at outcome level for the group of patients aged under 65 years. This effect is a hint of a minor added benefit for an outcome in the category "non-serious/non-severe symptoms" (time to pain progression). For patients who are 65 years or older, an added benefit at outcome level is not proven. When regarding the subgroups it is to be noted, however, that due to a lack of evaluable data on subgroup analyses it cannot be investigated whether possible effect differences across several outcomes, particularly regarding AEs, are consistent. With few exceptions, there were no adequate analyses available for the outcomes regarding harm. Hence no final conclusion can be drawn on harm. Greater harm from vandetanib can also not be excluded. Due to the great uncertainty regarding harm, it can also not be excluded that negative effects outweigh the positive effects.

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1-3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

The uncertainties described lead to the conclusion that, overall, an added benefit of vandetanib + BSC in comparison with the ACT BSC in the treatment of aggressive and symptomatic MTC in patients with unresectable, locally advanced or metastatic disease is not proven.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on added benefit.

2.2 Research question

According to the SPC, vandetanib is approved for the following therapeutic indication [3]:

- Treatment of aggressive and symptomatic MTC in patients with unresectable, locally advanced or metastatic disease

The company designated BSC as the ACT and thereby followed the specification of the G-BA, which named BSC as ACT. BSC is defined as a treatment that ensures the best possible supportive therapy, optimized for the individual patient, for the alleviation of symptoms and improvement in the quality of life (e.g. bisphosphonates for painful bone metastases, external radiotherapy).

The aim of this report is thus to assess the added benefit of vandetanib compared with BSC in patients with aggressive and symptomatic MTC with unresectable, locally advanced or metastatic disease.

In the current therapeutic situation, there is a need for all patients to be treated with BSC. Studies that compared vandetanib in combination with BSC with treatment consisting of BSC alone were therefore included in the benefit assessment. If available, studies in which vandetanib as monotherapy was compared with BSC could also be included.

The assessment was conducted based on patient-relevant outcomes. Only RCTs were to be included in the assessment.

Further information about the research question can be found in Module 3, Section 3.1 and Module 4, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- Study list on vandetanib (studies completed up to 07 January 2013)
- Bibliographical literature search on vandetanib (last search 11 January 2013)
- Search in trial registries for studies on vandetanib (last search 07 January 2013)

The Institute's own search:

- Search in trial registries for studies on vandetanib to check the search results of the company (last search 03 April 2013)

This check produced no deviations from the study pool presented in the dossier.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Studies included

The study listed in Table 2 was included in the benefit assessment.

Table 2: Study pool – RCT, direct comparison: vandetanib + BSC vs. placebo + BSC

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
D4200C00058	yes	yes	no
a: Study for which the company was sponsor, or in which the company was otherwise financially involved BSC: best supportive care; RCT: randomized controlled trial; vs.: versus			

The study pool for the benefit assessment concurred with the study pool of the company.

The Study 58 is an RCT on the comparison of vandetanib + BSC with placebo + BSC.

Section 2.6 contains a reference list for the studies included.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.3.2 Study characteristics

Table 3 and Table 4 describe the Study 58.

Table 3: Characteristics of the studies included – RCT, direct comparison: vandetanib + BSC vs. placebo + BSC

Study	**Study design**	**Population**	**Interventions (number of randomized patients)**	**Study duration**	**Location and period of study**	**Primary outcome; secondary outcomes**[a]
D4200C00058	RCT, double-blind, placebo-controlled	Adult patients with measurable, unresectable, locally advanced or metastatic MTC	Vandetanib + BSC (N = 231) Placebo + BSC (N = 100) Relevant subpopulation with symptomatic and progressive MTC[b]: Vandetanib + BSC (n = 126) Placebo + BSC (n = 60)	Treatment is given until objective progression of the disease, then option for open-label treatment with vandetanib (crossover), follow-up for OS Analysis cut-off July 2009	63 study centres worldwide in 24 countries: Australia, America, Asia and Europe, November 2006 – ongoing (probably up to December 2016)	*Primary:* Progression-free survival *Secondary:* OS, health-related quality of life, time to pain progression, AEs

a: Primary outcomes contain information without consideration of the relevance for the present benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes for the present benefit assessment.
b: This subpopulation is the population relevant for the benefit assessment.

AE: adverse event; BSC: best supportive care; MTC: medullary thyroid carcinoma; N: number of randomized patients; n: number of randomized patients in the relevant subpopulation; OS: overall survival; RCT: randomized controlled trial; vs.: versus

Table 4: Characteristics of the interventions – RCT, direct comparison: vandetanib + BSC vs. placebo + BSC

Study	Intervention	Comparison	Concomitant treatment
D4200C00058	Vandetanib tablets 300mg orally once a day[a] + BSC	Placebo tablet orally once a day[a] + BSC	**Concomitant treatment permitted:** ▪ Interventions that were necessary for the safety and wellbeing of the patient could be used at the doctor's discretion (e.g. analgesics or bisphosphonates) **Concomitant treatment prohibited:** ▪ Systemic cancer treatments ▪ Palliative radiotherapy of target lesions and non-target lesions that could be used to monitor tumour growth according to RECIST
After progression of the disease, the patients had the option to change to open-label treatment with vandetanib.			
a: If AEs with CTCAE Grade ≥ 3 occurred, dose reductions to 200 mg/day or 100 mg/day as well as dose interruptions were possible. AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours; vs.: versus			

Study 58 is an ongoing, randomized, double-blind, placebo-controlled study. It is a multi-centre study, with study centres located in countries in Europe, America, Asia and Australia.

Patients diagnosed with an unresectable and locally advanced or metastatic stage of hereditary or sporadic form of MTC were enrolled. According to the SPC [3], vandetanib is only approved for patients with aggressive and symptomatic course of this disease. However, the study population of Study 58 is not limited to patients with this course of disease. So the study population is wider than the approval population. Only a subpopulation of Study 58 was therefore relevant for this assessment. The dossier contained analyses for those patients with progressive and symptomatic course of disease. This population was regarded as an adequate approximation to the approval population (patients with aggressive and symptomatic MTC) (for detailed arguments, see report on the commission A12-09 [4]). Analyses for this subpopulation were not planned a priori for the Study 58, but were demanded by the European Medicines Agency (EMA) during the approval process as an ad-hoc analysis for the outcomes "progression-free survival (PFS)" and "objective response rate (ORR)".

The exclusive consideration of the subpopulation of patients with progressive and symptomatic course of disease deviated from the company's approach, which, besides the results on the relevant subpopulation, also presented the results of the total study population of the Study 58 in its dossier. The company regarded the results of the total population as sufficiently applicable to the population treated according to the approval. This assessment was not accepted (see Section 2.7.2.4.1 of the full dossier assessment).

A total of 331 patients were randomly assigned in a ratio of 2:1, 231 patients to vandetanib + BSC und 100 patients to placebo + BSC. The relevant subpopulation of patients with symptomatic and progressive MTC comprised a total of 186 patients. This concurs with

the information in the European Public Assessment Report (EPAR) on vandetanib [5]. From the relevant subpopulation, 126 patients received vandetanib + BSC und 60 patients received placebo + BSC during the randomized treatment phase.

Vandetanib was administered according to the current approval status [3]. The patients in the vandetanib + BSC arm received 300 mg of vandetanib orally once a day. The patients in the comparator arm received placebo once a day. If AEs with CTCAE Grade ≥ 3 occurred, dose reductions to 200 mg/day or 100 mg/day as well as dose interruptions were possible. In addition, the patients in both treatment arms could receive interventions that were necessary for the safety and wellbeing of the patient at the doctor's discretion. These included analgesics or bisphosphonates, as well as palliative radiotherapy to alleviate symptoms. These were limited to regions outside target lesions and non-target lesions that could be used to assess possible progression of the underlying condition. According to information in the study protocol of the Study 58, bone lesions, which are one of the main indications for palliative radiotherapy, were not used for assessing progression, so that radiotherapy of these lesions was possible during the entire course of the study. Overall, the concomitant treatment used in the Study 58 was accepted as BSC.

The study treatment was continued until progression occurred. If progression occurred, the patients discontinued treatment with the study medication. After the unblinding there was the option to change into an open-label treatment phase with vandetanib (crossover or continued treatment). 38 of the 60 placebo + BSC patients (63.3%) and 26 of the 126 vandetanib + BSC patients (20.6%) from the relevant subpopulation made use of this option.

The primary outcome recorded in the Study 58 was PFS. Patient-relevant secondary outcomes were OS, health-related quality of life, pain progression, and AEs.

At the time of the benefit assessment, observation of the patients in the Study 58 was not yet completed. 2 analyses – one interim analysis and the final analysis – were planned. The interim analysis (data cut-off: 31 July 2009) was planned based on the primary outcome "PFS", the final analysis was planned on the basis of OS. The final analysis has not been conducted yet and is to be performed when half of the patients randomized in the Study 58 have died. The median treatment duration (minimum; maximum) at the time of the interim analysis was more than twice as long in the vandetanib + BSC arm (88.6 [2; 133] weeks) than in the comparator arm (37.1 [2; 129] weeks). The outcomes "pain progression" and "health-related quality of life" were recorded until the end of the double-blind treatment phase with the study medication. Deviating from this, those AEs were included in the assessment that started before the beginning of the open-label treatment with vandetanib or up to and including 60 days after the last dose of the randomized study medication at the latest. Data for the outcome "OS" were recorded up to the time of the interim analysis.

Table 5 shows the characteristics of the patients in the study included for the relevant subpopulation.

Table 5: Characteristics of the study populations – RCT, direct comparison: vandetanib + BSC vs. placebo + BSC

Study Group	N	Age [years] mean (SD)	Sex [f/m] %	Prior systemic therapy n (%)	WHO-PS [0/1/2] n (%)			RET mutation status [positive/negative/unknown] n (%)		
D4200C00058										
Vandetanib + BSC	126	53 (14)	37/63	45 (35.7)	74 (59)	45 (36)	7 (6)	75 (59.5)	1 (0.8)	50 (39.7)
Placebo + BSC	60	54 (12)	35/65	29 (48.3)	33 (55)	25 (42)	2 (3)	30 (50.0)	6 (10.0)	24 (40.0)

BSC: best supportive care; f: female; m: male; N: number of randomized patients; n: number of patients in the category; RCT: randomized controlled trial; RET: rearranged during transfection; SD: standard deviation; vs.: versus; WHO-PS: World Health Organization performance status

There were no major differences between the treatment groups with regards to age, sex, and World Health Organization performance status (WHO-PS). Overall, there were considerably more men than women. The proportion of patients who had already received prior systemic therapy before enrolment in the study was smaller in the vandetanib + BSC arm (35.7%) than in the comparator arm (48.3%). The proportion of patients with negative rearranged during transfection (RET) mutation status of their disease was also smaller in the vandetanib + BSC arm (0.8%) than in the comparator arm (10%).

Table 6 shows the risk of bias at study level.

Table 6: Risk of bias at study level – RCT, direct comparison: vandetanib + BSC vs. placebo + BSC

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
D4200C00058	yes	yes	yes	yes	yes	no[a]	high

a: After progression of the disease, the patients had the option to change to open-label treatment with vandetanib. 63.3% of the placebo patients and 20.6% of the vandetanib patients made use of this option. In addition, the median observation duration for all outcomes considered in the benefit assessment, with the exception of OS was 88.6 weeks in the vandetanib group, and only 37.1 weeks in the placebo group.

BSC: best supportive care; RCT: randomized controlled trial; vs.: versus

The risk of bias at study level was rated as high. This deviates from the company's assessment, which derived low risk of bias at study level.

One aspect influencing the risk of bias was that the patients had the option to change to open-label treatment with vandetanib after progression of the disease and the subsequent discontinuation of the double-blind randomized treatment phase. 38 of the 60 patients in the placebo + BSC arm (63.3%) and 26 of the 126 patients in the vandetanib + BSC arm (20.6%) from the approximated target population made use of this option.

For all outcomes considered in the benefit assessment, with the exception of OS, an analysis was performed that was limited to observations made during the treatment originally assigned. However, the median treatment duration was more than twice as long in the vandetanib + BSC arm (88.6 weeks) than in the comparator arm (37.1 weeks). For this reason, the relative risks estimated on the basis of naive proportions were no adequate analysis. This meant for most outcomes on AEs that no evaluable results were available for the benefit assessment. The time-adjusted analyses on AEs included in the assessment were rated as highly biased due to the uncertainty of the model assumptions, with the direction of the bias being unclear. A survival time analysis was conducted for the outcome "pain progression".

Informative censorings can be assumed which occurred at different frequencies because disease progression occurred later in the vandetanib group. It also remains unclear how many and which patients were included in the analysis at the different times. Overall, the results on pain progression are therefore rated as having a high risk of bias with unclear direction. Potentially highly biased results to the disadvantage of vandetanib result for OS because of the high proportion of patients from the comparator group who changed to the open-label treatment with vandetanib.

Further information about the study design, study populations and risk of bias at the study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2, and Appendix 4-G of the dossier and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results on added benefit

The following patient-relevant outcomes were considered in this assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - OS
- Morbidity
  - Pain progression
- Health-related quality of life
  - Adverse events
  - Overall rate of AEs
  - Severe AEs (CTCAE Grade ≥ 3)
  - SAEs
  - Treatment discontinuations due to AEs
  - Specific AEs
    - QTc prolongation
    - Diarrhoea
    - Skin rash

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4). In particular, the outcomes "PFS", "ORR", and "disease control rate (DCR)" as well as the duration of response (DOR) were not used for this assessment since neither the patient relevance postulated in the dossier (in the Study 58, PFS, ORR, DCR and DOR were exclusively recorded using imaging methods) nor the validity of a surrogate characteristic was sufficiently explained. However, additional outcomes were used for this assessment. See Section 2.7.2.4.3 of the full dossier assessment for reasons for the

choice of outcomes. Table 7 shows for which outcomes data for the relevant subpopulation were available in the study included. Table 8 shows the risk of bias for these outcomes.

Table 7: Matrix of outcomes – RCT, direct comparison: vandetanib + BSC vs. placebo + BSC

Study	Outcomes									
	OS	Pain progression	Health-related quality of life	AEs	SAEs	Treatment discontinuations due to AEs	Severe AEs (CTCAE Grade ≥ 3)	QTc prolongation	Diarrhoea	Skin rash
D4200C00058	y	y	n[a]	n[a]	n[a]	n[a]	n[a]	y[b]	y[c]	n[a]

a: No evaluable data available; for reasons, see Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment
b: AEs with CTCAE Grade ≥ 3 according to SMQ "torsade de pointes/QTc prolongation"
c: SAEs diarrhoea according to preferred term

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; OS: overall survival; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized Medical Dictionary for Regulatory Activities Query; vs.: versus

Table 8: Risk of bias at study and outcome level – RCT, direct comparison: vandetanib + BSC vs. placebo + BSC

Study	Study level	Outcomes									
		OS	Pain progression	Health-related quality of life	AEs	SAEs	Treatment discontinuations due to AEs	Severe AEs (CTCAE Grade ≥ 3)	QTc prolongation	Diarrhoea	Skin rash
D4200C00058	h	h	h	–[a]	–[a]	–[a]	–[a]	–[a]	h	h	–[a]

a: No evaluable data available

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; h: high; OS: overall survival; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

There were no evaluable data on health-related quality of life, overall rate of AEs, SAEs, treatment discontinuations due to AEs, severe AEs (CTCAE Grade ≥ 3) and skin rashes. Therefore no further outcome-specific assessment of the risk of bias was conducted.

The risk of bias for the outcomes "OS" and "pain progression" was rated as high. For the outcome "pain progression", this deviated from the company's assessment (see Section 2.7.2.4.2 of the full dossier assessment).

There were no evaluable data for a large proportion of the outcomes on AEs. The company exclusively presented analyses on the basis of the naive proportion of the patients with at least one event in Module 4 of the dossier. These analyses were not evaluable for the benefit assessment because the observation duration in the 2 treatment arms differed considerably (median treatment duration of 88.6 weeks in the vandetanib + BSC arm, and of 37.1 weeks in the comparator arm). The rate of patients with at least one event per 1000 patient years (incidence density), which the company partially included in the analyses on the relevant subpopulation, could also not be considered because of unverifiable contradictions (see Section 2.7.2.4.2 of the full dossier assessment). In the case of rare events, the Institute performed its own calculations of the incidence density. For rare events, this analysis can serve as an approximation for the analysis of the time to an event. The risk of bias for these analyses was also rated as high, however.

Table 9 and Table 10 summarize the results on the comparison of vandetanib + BSC and placebo + BSC in patients in the therapeutic indication. The data from the company's dossier were supplemented, where necessary, by the Institute's own calculations. In addition, data from Module 5 of the dossier were added.

Table 9: Results on morbidity and quality of life – RCT, direct comparison: vandetanib + BSC vs. placebo + BSC

Study **Outcome category** **Outcome**	**Vandetanib + BSC**		**Placebo + BSC**		**Vandetanib + BSC vs. placebo + BSC**	
	N	**Median time to pain progression [95% CI] (months)**	**N**	**Median time to pain progression [95% CI] (months)**	**HR [95% CI]**	**p-value**
D4200C00058						
Morbidity						
Time to pain progression	126	11.07 [no data]	60	3.42 [no data]	0.62 [0.39; 0.99]	0.045
Health-related quality of life	No evaluable data					

BSC: best supportive care; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

Table 10: Results on mortality and AEs – RCT, direct comparison: vandetanib + BSC vs. placebo + BSC

Study **Outcome category**	**Vandetanib + BSC**		**Placebo + BSC**		**Vandetanib + BSC vs. placebo + BSC**
Outcome	**N**	**Median survival time [95% CI] (months)**	**N**	**Median survival time [95% CI] (months)**	**HR [95% CI]; p-value**
D4200C00058					
Mortality					
OS	126	no data[a]	60	no data[a]	1.06 [0.50; 2.23][b]; 0.879
	N	**Patients with event n (n/1000 patient years)[c]**	**N**	**Patients with event n (n/1000 patient years)[d]**	**IDR [95% CI]; p-value**
Adverse events					
Overall rate of AEs	No evaluable data				
SAEs	No evaluable data				
Severe AEs (CTCAE Grade ≥ 3)	No evaluable data				
Treatment discontinuations due to AEs	No evaluable data				
QTc prolongation (CTCAE Grade ≥ 3)[e]	126	10 (55.2)[f]	60	0 (0)[f]	6.79 [0.40; 115.83]; 0.186[g]
Diarrhoea (SAE)[h]	126	3 (16.6)[f]	60	0 (0)[f]	2.26 [0.12; 43.80]; 0.589[g]
Skin rash	No evaluable data				

a: 21 (16.7%) (vandetanib + BSC) and 10 (16.7%) (placebo + BSC) patients died with regard to the relevant subpopulation in the two treatment groups. It is therefore not possible to provide the median survival time or the 25% quantile of the time to death.
b: Institute's calculation; the company cited 99.98% CI (α adjustment based on interim analysis) although reported as 95% CI in the dossier
c: Treatment time with study medication in the vandetanib + BSC arm: 181.0 years
d: Treatment time with study medication in the placebo + BSC arm: 58.5 years
e: Proportion of patients with at least one severe AE (CTCAE Grade ≥ 3) in the SMQ "torsade de Pointes/QTc prolongation"
f: Patients with event per 1000 patient years; Institute's calculation
g: Institute's calculation of estimator, corresponding CI and p-value; calculation with continuity correction of 0.5 in both treatment arms because of lack of events in the comparator group
h: Proportion of patients with at least one SAE in the PT "diarrhoea"

AE: adverse event; BSC: best supportive care; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; IDR: incidence density ratio; N: number of analysed patients; n: number of patients with event; OS: overall survival; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized Medical Dictionary for Regulatory Activities Query; vs.: versus

The Study 58 did not meet the particular requirements placed on the derivation of "proof" from a single study (see Section 2.7.2.8.1 of the full dossier assessment). Hence, at most "indications" – e.g. of an added benefit – could be derived from the data.

This assessment deviates from that of the company, which derived "proof" of added benefit for the relevant subpopulation from the Study 58.

Mortality

Overall survival

The treatment with vandetanib + BSC did not result in a statistically significant difference for OS in comparison with the treatment with placebo + BSC. Hence an added benefit of vandetanib + BSC in comparison with the ACT BSC is not proven for this outcome.

Morbidity

Pain progression

The outcome "pain progression" was operationalized as "time to pain progression" in the Study 58. The treatment with vandetanib + BSC resulted in a statistically significant prolongation of the time to pain progression in comparison with the treatment with placebo + BSC for the relevant subpopulation of patients with progressive and symptomatic course of disease. The assessment of subgroup characteristics resulted in an indication of an effect modification by the characteristic "age" (< 65 years versus ≥ 65 years) for pain progression. The results on pain progression are therefore regarded in the age subgroups. Because of the high risk of bias based on outcomes, there is a hint of an added benefit of vandetanib + BSC in comparison with the ACT BSC for younger patients (< 65 years). For older patients (≥ 65 years) an added benefit is not proven (see end of this Section for details).

Health-related quality of life

Health-related quality of life was recorded in the Study 58 using the questionnaire Functional Assessment of Cancer Therapy-General (FACT-G). However, results were only available as changes of the mean values of the total score or as changes in comparison with the baseline value during the course of the study. The results were regarded as non-evaluable because of the high proportion of patients per recording period who were not considered. The company's dossier therefore contained no evaluable data on health-related quality of life. Hence an added benefit of vandetanib + BSC in comparison with the ACT BSC for the outcome "health-related quality of life" is not proven.

Adverse events

Module 4 of the dossier did not contain any valid analyses for the assessment of AEs, which could be considered in the benefit assessment. The data based on naive proportions (proportion of patients with at least one event) presented by the company did not constitute an adequate analysis due to the considerably different treatment durations with the study medication (and hence also observation durations) in both treatment arms (median treatment

duration with the study medication: 88.6 weeks in the vandetanib + BSC arm, and 37.1 weeks in the comparator arm). The rates of patients with at least one event per 1000 patient years (incidence density), which the company partially presented in the analyses on the relevant subpopulation, could also not be considered because of unverifiable contradictions (see Section 2.7.2.4.2 of the full dossier assessment).

Therefore the analysis of the incidence density on the basis of the Institute's calculations was used for this benefit assessment, but only in case of rare events (see Section 2.7.2.4.2 of the full dossier assessment). The incidence density ratio (IDR) was calculated as related effect measure. It was not possible to conduct a valid analysis for non-rare events on the basis of the data presented in the dossier. No evaluable analyses were available for the overall rate of AEs, SAEs, discontinuations due to AEs, severe AEs (CTCAE Grade ≥ 3) as well as the specific AE "skin rash", due to the reasons described above. For these outcomes, greater or lesser harm from vandetanib + BSC than from the ACT BSC is not proven.

Results were available for the specific AEs "prolongation of the QTc interval" and "diarrhoea", on the basis of which the Institute could calculate the IDR. The results of the AE "prolongation of the QTc interval" were based on the Standardized Medical Dictionary for Regulatory Activities Query (SMQ) "torsade de pointes/QTc prolongation" of those AEs with CTCAE Grade ≥ 3. There was no statistically significant difference between the treatment arms. There were no corresponding results of an SMQ for severe AEs for the AE "diarrhoea". Therefore diarrhoea that was classified as SAE on the basis of the Medical Dictionary for Regulatory Activities Preferred Terms (MedDRA PT) "diarrhoea" had to be used. There was also no statistically significant difference between the treatment arms, with serious diarrhoea being observed in very few patients.

Overall, a greater or lesser harm from vandetanib + BSC in comparison with BSC is not proven, with the data being highly uncertain.

The assessments on results on AEs deviate from those of the company, which derived a proof of greater harm from vandetanib + BSC versus the ACT BSC for the overall rate of AEs, SAEs and discontinuations due to AEs. It is to be noted that the company's assessment was only based on the results on the basis of the naive proportions.

Subgroup analyses

Subgroup analyses on the following characteristics were considered for this benefit assessment: age (< 65 years versus ≥ 65 years), sex (male versus female), WHO-PS at the start of the study (0 versus ≥ 1), RET mutation status (positive versus negative), disease status (locally advanced versus metastatic), opioid use at the start of the study (< 10 mg/day versus ≥ 10 mg/day of morphine sulfate equivalent). Module 4 of the dossier only contained subgroup analyses on all characteristics for the outcome "pain progression". Subgroup analyses were only included in the analyses on the relevant subpopulation, and only for some of the relevant characteristics, for the outcomes "overall rate of AEs", "SAEs", "severe AEs

(CTCAE Grade ≥ 3)", and "treatment discontinuations due to AEs". These were not evaluable, however, as they were based on the raw proportions of patients with at least one event or the calculation of the incidence densities was subject to unverifiable contradictions (see Section 2.7.2.4.2 of the full dossier assessment). Results on subgroups for the outcome "health-related quality of life" (measured with the FACT-G) were also only included in the study documents on the relevant subpopulation. They only comprised graphic representations of the courses of the mean values over time, and were also not evaluable for the benefit assessment (see Section 2.7.2.4.3 of the full dossier assessment). There were no subgroup analyses for the outcome "OS".

Regarding the outcome "pain progression", there was an indication of an effect modification for the characteristic "age". There was no effect modification for any of the other characteristics. Table 11 shows the results of the subgroup analyses according to age.

Table 11: Subgroups: outcome "time to pain progression" according to age – RCT, direct comparison: vandetanib + BSC vs. placebo + BSC

Study Characteristic / Subgroup	Vandetanib + BSC		Placebo + BSC		Vandetanib + BSC vs. placebo + BSC	
	N	Median time to pain progression [95% CI] (months)	N	Median time to pain progression [95% CI] (months)	HR [95% CI]	p-value
D4200C00058						
Age[a]						
< 65 years	93	no data[b]	48	no data[b]	0.52 [0.31; 0.88]	0.014
≥ 65 years	33	no data[c]	12	no data[c]	1.19 [0.41; 3.49]	0.747
					Interaction test:	0.198

a: Defined post-hoc as part of the approval process
b: For the relevant subpopulation, there were only data available on the proportion of patients with at least one event (n [%]): vandetanib + BSC: 45 (48.4); placebo + BSC: 29 (60.4).
c: For the relevant subpopulation, there were only data available on the proportion of patients with at least one event (n [%]): vandetanib + BSC: 15 (45.5); placebo + BSC: 4 (33.3).
BSC: best supportive care; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; vs.: versus

There was an indication of effect modification for the characteristic "age" (interaction test: p = 0.198). With regard to the individual subgroups, there was a statistically significant difference between the treatment groups in favour of vandetanib + BSC for younger patients (< 65 years). For older patients (≥ 65 years) the result was not statistically significant.

Because of the high risk of bias based on outcomes, there is therefore a hint of an added benefit of vandetanib + BSC in comparison with the ACT BSC for younger patients (< 65 years). For older patients (≥ 65 years) an added benefit is not proven.

Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in Appendix A of Benefit Assessment A11-02 [2].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on added benefit.

2.5.1 Assessment of added benefit at outcome level

The data presented in Section 2.4 resulted in a hint of an added benefit of vandetanib + BSC versus the ACT BSC for patients < 65 years for the outcome "pain progression". The extent of the added benefit at outcome level was estimated from these results (see Table 12).

Table 12: Extent of added benefit at outcome level (beneficial outcomes): vandetanib + BSC vs. BSC

Outcome	**Effect estimator [95% CI] p-value time to event (months) vandetanib + BSC vs. BSC probability**	**Derivation of extent[b]**
Mortality		
Overall survival	HR 1.06 [0.50; 2.23][c] p = 0.879 no data[d]	Lesser benefit/added benefit not proven
Morbidity		
Time to pain progression	HR 0.62 [0.39; 0.99] p = 0.045 median: 11.07 vs. 3.42	Outcome category: non-serious/non-severe symptoms CIo > 0.9 Added benefit not proven
Age < 65 years	*HR 0.52 [0.31; 0.88]* *p = 0.014* *no data[e]* *Probability: "hint"*	*Outcome category: non-severe symptoms* *0.80 < CIo < 0.90* *Added benefit, extent: "minor"*
Age ≥ 65 years	*HR 1.19 [0.41; 3.49]* *p = 0.747* *no data[f]*	*Lesser benefit/added benefit not proven*
Health-related quality of life		
FACT-G	No evaluable data were available in the company's dossier.	Lesser benefit/added benefit not proven

a: Probability provided if statistically significant differences were present
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_o.
c: Institute's calculation; the company cited 99.98% CI (α adjustment based on interim analysis) although reported as 95% CI in the dossier
d: 21 (16.7%) (vandetanib + BSC) and 10 (16.7%) (placebo + BSC) patients died with regard to the relevant subpopulation in the 2 treatment groups. It is therefore not possible to present the median survival time or the 25% quantile of the time to death.
e: For the relevant subpopulation, there were only data available on the proportion of patients with at least one event (n [%]): vandetanib + BSC: 45 (48.4); placebo + BSC: 29 (60.4).
f: For the relevant subpopulation, there were only data available on the proportion of patients with at least one event (n [%]): vandetanib + BSC: 15 (45.5); placebo + BSC: 4 (33.3).
BSC: best supportive care; CI: confidence interval; CI_o: upper limit of confidence interval;
FACT-G: Functional Assessment of Cancer Therapy-General; HR: hazard ratio; vs.: versus

Table 13: Extent of added benefit at outcome level (harmful outcomes): vandetanib + BSC vs. BSC

Outcome	**IDR [95% CI] p-value number of patients with event n (n/1000 patient years)[a, b] vandetanib + BSC vs. BSC probability[c]**	**Derivation of extent[d]**
AEs		
Overall rate of SAEs	No evaluable data available	Lesser/greater harm not proven
Severe AEs (CTCAE Grade ≥ 3)	No evaluable data available	Lesser/greater harm not proven
Treatment discontinuations due to AEs	No evaluable data available	Lesser/greater harm not proven
QTc prolongation[e] (CTCAE Grade ≥ 3)	IDR: 6.79 [0.40; 115.83] p = 0.186[f] 10 (55.2)[g] vs. 0 (0)[g]	Lesser/greater harm not proven
Diarrhoea[h] (SAE)	IDR: 2.26 [0.12; 43.80] p = 0.589[f] 3 (16.6)[g] vs. 0 (0)[g]	Lesser/greater harm not proven

a: Treatment time with study medication in the vandetanib + BSC arm: 181.0 years
b: Treatment time with study medication in the BSC arm: 58.5 years
c: Probability provided if statistically significant differences were present
d: Estimations of effect size are made depending on the outcome category with different limits based on the CI_o.
e: according to SMQ "torsade de pointes/QTc prolongation"
f: Institute's calculation of estimator, corresponding CI and p-value; calculation with continuity correction of 0.5 in both arms because of lack of events in the comparator group
g: Patients with event per 1000 patient years, Institute's calculation
h: according to PT

AE: adverse event; BSC: best supportive care; CI: confidence interval; CI_o: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; IDR: incidence density ratio; PT: preferred term; SAE: serious adverse event; SMQ: Standardized Medical Dictionary for Regulatory Activities Query; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 14 summarizes the results that were considered in the overall conclusion on the extent of added benefit for the subgroups based on age.

Table 14: Positive and negative effects from the assessment of vandetanib + BSC compared with the ACT BSC, age < 65 years

Positive effects	**Negative effects**
Hint of an added benefit – extent: “minor” (morbidity, non-serious/non-severe symptoms/time to pain progression)	

Overall, on the basis of the available and evaluable results, only a positive effect remains at outcome level for the group of patients aged under 65 years. This effect is a hint of a minor added benefit for an outcome in the category "non-serious/non-severe symptoms" (time to pain progression). For patients who are 65 years or older, there is no proof of an added benefit at outcome level. When regarding the subgroups it is to be noted, however, that due to a lack of evaluable data on subgroup analyses it cannot be investigated whether possible effect differences across several outcomes, particularly regarding AEs, are consistent. With few exceptions, there were no adequate analyses available for the outcomes regarding harm. Hence no final conclusion can be drawn on harm. Greater harm from vandetanib can also not be excluded. Due to the great uncertainty regarding harm, it can also not be excluded that negative effects outweigh the positive effects.

The uncertainties described lead to the conclusion that, overall, no proof of added benefit of vandetanib + BSC in comparison with the ACT BSC in the treatment of aggressive and symptomatic MTC in patients with unresectable, locally advanced or metastatic disease can be derived.

2.6 List of included studies

D4200C00058

AstraZeneca. An international, phase III, randomized, double-blinded, placebo-controlled, multi-centre study to assess the efficacy of ZD6474 versus placebo in subjects with unresectable locally advanced or metastatic medullary thyroid cancer: study D4200C00058; clinical study report [unpublished]. 2010.

AstraZeneca. An efficacy study comparing ZD6474 to placebo in medullary thyroid cancer: full text view [online]. In: Clinicaltrials.gov. 22.02.2012 [accessed 11.02.2013]. URL: http://www.clinicaltrials.gov/ct2/show/NCT00410761.

AstraZeneca Pharmaceuticals. An international, phase III, randomized, double-blinded, placebo-controlled, multi-centre study to assess the efficacy of ZD6474 versus placebo in subjects with unresectable locally advanced or metastatic medullary thyroid cancer: consolidated post-hoc analyses for benefit assessment pursuant to Section 35a of the German Social Code Book V (SGB V); study D4200C00058; post-hoc analyses [unpublished]. 2013.

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References for English extract

Please see full dossier assessment for full reference list.

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