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List of abbreviations

Abbreviation	Meaning
BPI-SF	Brief Pain Inventory-Short Form
ACT	appropriate comparator therapy
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	*Gemeinsamer Bundesausschuss* (Federal Joint Committee)
	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MTC	medullary thyroid carcinoma
QTc	time interval between the start of the Q wave and the end of the T wave (corrected for heart rate)
SGB	*Sozialgesetzbuch* (Social Code Book)
SOC	System Organ Class

1 Background

On 23 July 2013, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A13-09 (benefit assessment of vandetanib [new assessment in accordance with § 35a (5) Social Code Book (SGB) V] [1]).

In the commenting procedure on the assessment of vandetanib, on 8 July 2013 the pharmaceutical company (hereinafter abbreviated to "the company") submitted further data to the G-BA that went beyond the information in the dossier [2,3]. These refer to data on Study D4200C00058 (comparison of vandetanib + best supportive care (BSC) versus placebo + BSC). The study was already contained in the company's dossier and was included as relevant by IQWiG in Assessment A13-09. On the basis of the data presented by the company in the dossier, the severity of pain symptoms during the course of the study could not be assessed [4]. Moreover, the majority of the data presented were not evaluable for the outcomes on adverse events (AEs). The data subsequently submitted mainly addressed the uncertainties on these outcomes from the Study D4200C00058 with new analyses.

The G-BA commissioned IQWiG with the assessment of the analyses for Study D4200C00058 subsequently submitted in the commenting procedure. In this context the data were to be assessed with regard to the question as to whether, under consideration of the analyses submitted by the company on pain symptoms as well as on AEs, an added benefit of vandetanib regarding morbidity is proven and uncertainties regarding harm have been dispelled.

In the following Chapter 2 the additional results for Study D4200C00058 are presented and assessed according to the commission. The extent and probability of added benefit of vandetanib are then described under consideration of the analyses subsequently submitted.

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Selection of analyses for the benefit assessment

In its comment [2,3] the company, as proposed in Assessment A13-09 [1], presented on the one hand analyses of AEs on the basis of the time to first event. Deviating from the dossier, the company did not analyse the events with Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 3 but all events for the QTc prolongation. As marginal QTc prolongation is not necessarily patient-relevant, this analysis was not used. Due to the changed choice of events by the company, conclusions on relevant QTc prolongation are lacking in the assessment.

Apart from the data on AEs, the company submitted analyses on the severity of pain in the study with its comment. The analyses newly submitted by the company were assessed in the present addendum.

2.2 Risk of bias

Table 1 shows the risk of bias at study level (for reasons see Dossier Assessment A13-09 [1], as well as the risk of bias for results on the outcomes on AEs for the newly submitted analyses.

The risk of bias of the time to pain progression was not affected by the newly submitted data, which exclusively concerned the rating of the severity of pain progression. As already in the Dossier Assessment A13-09, the risk of bias of the outcome on pain progression was rated as high (for reasons see Dossier Assessment A13-09 [1]).

Table 1: Risk of bias at study and outcome level – RCT, direct comparison: vandetanib + BSC vs. placebo + BSC

Study		Outcomes					
	Study level	AEs	SAEs	Treatment discontinuations due to AEs	Severe AEs (CTCAE Grade ≥ 3)	Diarrhoea	Skin rash
D4200C00058	h	–[a]	h	h	h	h	h

a: Overall rate of AEs not interpretable. Therefore no assessment of risk of bias.
AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; h: high; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The risk of bias at study level was high. The company subsequently submitted survival time analyses (Cox regression) for the outcomes on AEs. Patients without event until disease progression were censored at the time of the last evaluable observation. Due to the possible connection between disease progression and AEs, there were probably informative censorings, which occurred at different frequencies because disease progression occurred later in the vandetanib group. The results for the outcomes on AEs were therefore rated overall as potentially highly biased. Since strength and direction of the connection between disease progression and AEs were unclear, however, no conclusion could be drawn on the direction of the bias.

2.3 Results

Severity of pain symptoms

The severity of pain symptoms could not be evaluated in the dossier assessment because there were no informative data on the grade of pain during the course of the study or at the end of the study. The change of pain by at least 2 points on a 10-point scale of the Brief Pain Inventory-Short Form (BPI-SF), which was chosen as response criterion, was considered insufficient to justify the characterization of pain as severe symptom [1].

In its comment on the dossier assessment, the company presented an analysis of the degree of pain in patients with pain progression. This analysis described the mean pain patients experienced at the start of the study and at the time at which the event "pain progression" occurred. Patients who showed pain progression during the course of the study had a mean pain intensity of 3 to 4 points on the scale at the start of the study (vandetanib + BSC: mean (standard deviation) 3.18 (2.7); placebo + BSC: 3.85 (2.18)). At the time of pain progression, a mean pain of approximately 6 points was documented (vandetanib + BSC: 5.64 (2.13); placebo + BSC: 6.09 (2.19)) [2]. Under consideration of the fact that opiates could also be additionally used in the study if required, and appraising the literature presented by the company [5-7], this degree of pain in patients with pain progression was no longer rated as non-severe symptoms. The results on pain progression were classified into the category "severe/serious symptoms" instead and considered accordingly when determining the extent of added benefit (see Section 2.4.1 of this addendum).

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 (see Table 3). 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 (p-value of the interaction 0.198). 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 appropriate comparator therapy (ACT) BSC for younger patients (< 65 years). For older patients (≥ 65 years), the group difference was not statistically significant. Moreover, the estimate for the relative risk had a

different direction of effect than the estimates of the subgroup of younger patients and the total population. An added benefit regarding pain progression is not proven for older patients.

Adverse events

Table 2 presents the results of the analyses on AEs submitted with the comments [2,3].

Table 2: Results on AEs – RCT, direct comparison: vandetanib + BSC vs. placebo + BSC

Study Outcome category Outcome	Vandetanib + BSC		Placebo + BSC		Vandetanib + BSC vs. placebo + BSC
	N	Median survival time [95% CI] (months)	N	Median survival time [95% CI] (months)	HR [95% CI]; p-value
AEs					
Overall rate of AEs	126	n.d.	59	n.d.	–[a]
SAEs	126	n.d.	59	n.d.	1.40 [0.74; 2.63] n.d.
Severe AEs (CTCAE Grade ≥ 3)	126	n.d.	59	n.d.	2.27 [1.47; 3.52] n.d.
Treatment discontinuations due to AEs	126	n.d.	59	n.d.	2.75 [0.88; 8.60] n.d.
Diarrhoea (SAE)[b]	126	n.d.	59	n.d.	n.c.[c]
Skin rash	126	n.d.	59	n.d.	4.33 [3.04; 6.18] n.d.

a: Overall rate of AEs not interpretable, therefore HR not provided.
b: Proportion of patients with at least one SAE in the PT "diarrhoea".
c: According to information provided by the company.
AE: adverse event; BSC: best supportive care; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; N: number of analysed patients; n.c.: not calculable; n.d.: no data; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The time-adjusted analyses of AEs showed statistically significant results to the disadvantage of vandetanib for the outcomes "severe AEs (CTCAE Grade ≥ 3)" and "skin rash". Under consideration of the high risk of bias, there is a hint of greater harm from vandetanib + BSC in comparison with BSC for these outcomes. Further characterization of the AEs CTCAE Grade ≥ 3 is not possible because the company did not provide any data according to System Organ Classes (SOC) and Preferred Term (PT) in the population of patients with aggressive and symptomatic medullary thyroid carcinoma (MTC).

The comparison of vandetanib + BSC versus placebo + BSC did not result in a statistically significant difference for the SAEs and the treatment discontinuations due to AEs. Lesser or greater harm from vandetanib + BSC is not proven for these outcomes.

Age was investigated as a possible effect modifier in the survival time analyses. There was no indication of interaction for any of the outcomes on AEs used in the assessment. Other possible effect modifiers were not investigated here.

2.4 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 [8].

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 the added benefit.

2.4.1 Assessment of added benefit at outcome level

Overall, the data availability presented in Section 2.4 of the assessment A13-09 [1] and in Section 2.3 of this addendum resulted in a hint of an added benefit regarding the time to pain progression for patients under the age of 65 years. For older patients (≥ 65 years) an added benefit is not proven. This is offset by a hint of greater harm for severe AEs (CTCAE Grade ≥ 3) and skin rash.

Based on these results, the extent of added benefit was estimated at outcome level. The following Tables (Table 3 and Table 4) are an update of the Tables 12 and 13 of the assessment A13-09, which were supplemented with the results considered in the present addendum.

Table 3: Extent of added benefit at outcome level (beneficial outcomes): vandetanib + BSC vs. BSC

Outcome	**Effect estimates [95% CI] p-value time to event (months) vandetanib + BSC vs. BSC probability[a]**	**Derivation of extent[b]**
Mortality		
OS	HR 1.06 [0.50; 2.23][c] p = 0.879 n.d.[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 probability: "hint"	Outcome category: severe/serious symptoms $CI_o < 1.00$ added benefit, extent: "minor"
Age < 65 years	*HR 0.52 [0.31; 0.88]* *p = 0.014* *n.d.*[e] *probability: "hint"*	*Outcome category: severe/serious symptoms* *$CI_o < 0.90$* *added benefit, extent: "considerable"*
Age ≥ 65 years	*HR 1.19 [0.41; 3.49]* *p = 0.747* *n.d.*[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 CIo.
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: In relation to the relevant subpopulation, 21 (16.7%) (vandetanib + BSC) and 10 (16.7%) (placebo + BSC) patients died 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; CIo: upper limit of confidence interval;
FACT-G: Functional Assessment of Cancer Therapy-General; HR: hazard ratio; n.d.: no data; vs.: versus

Table 4: Extent of added benefit at outcome level (harmful outcomes): vandetanib + BSC vs. BSC

Outcome	**Effect estimates [95% CI] p-value time to event (months) vandetanib + BSC vs. BSC probability[a]**	**Derivation of extent[b]**
AEs		
Overall rate of SAEs	HR 1.40 [0.74; 2.63] n.d. n.d.	Greater/lesser harm not proven
Severe AEs (CTCAE Grade ≥ 3)	HR 2.27 [1.47; 3.52] HR 0.44 [0.28; 0.68][c] n.d. n.d. probability: "hint"	Outcome category: severe/serious AEs greater harm extent "major"
Treatment discontinuations due to AEs	HR 2.75 [0.88; 8.60] n.d. n.d.	Greater/lesser harm not proven
Diarrhoea[d] (SAE)	not calculable[e]	Greater/lesser harm not proven
Skin rash	HR 4.33 [3.04; 6.18] HR 0.23 [0.16; 0.33][c] n.d. n.d. probability: "hint"	Outcome category: non-severe/non-serious AEs greater harm extent: “considerable”

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 CIo.
c: Institute's calculation (reversed direction of effect to enable use of threshold values for the extent of added benefit).
d: According to PT.
e: According to information provided by the company.
AE: adverse event; BSC: best supportive care; CI: confidence interval; CIo: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; SAE: serious adverse event; vs.: versus

2.4.2 Overall conclusion on added benefit

Table 5 and Table 6 summarize the results that were considered in the overall conclusion on the extent of added benefit for the subgroups based on age.

Table 5: 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: "considerable" (morbidity, severe/serious symptoms: time to pain progression)	Hint of greater harm – extent: "major" (severe/serious AEs: AEs CTCAE Grade ≥ 3) Hint of greater harm – extent "considerable" (non-severe/non-serious AEs: skin rash)

For younger patients (< 65 years) positive and negative effects remain. The considerable added benefit is offset by greater harm of major and considerable extent. Since the added benefit describes a delay in disease progression measured with patient-relevant symptoms, it is not completely offset by the major and considerable harm, but downgraded. Overall, there is a hint of a minor added benefit of vandetanib + BSC in comparison with BSC for younger patients with aggressive and symptomatic MTC.

Table 6: Positive and negative effects from the assessment of vandetanib + BSC compared with the ACT BSC, age ≥ 65 years

Positive effects	**Negative effects**
-	Hint of greater harm – extent: "major" (severe/serious AEs: AEs CTCAE Grade ≥ 3) Hint of greater harm – extent "considerable" (non-severe/non-serious AEs: skin rash)

For older patients (≥ 65 years), only negative effects remain. Overall, there is therefore a hint of lesser benefit of vandetanib + BSC in comparison with BSC alone for older patients with aggressive and symptomatic MTC.

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