IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Dabrafenib (non-small cell lung cancer) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Dabrafenib (nicht kleinzelliges Lungenkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 July 2017). 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.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BRAF	rapidly accelerated fibrosarcoma – isoform B
BSC	best supportive care
ECOG PS	Eastern Cooperative Oncology Group-Performance Status
EGFR	epidermal growth factor receptor
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IASLC	International Association for the Study of Lung Cancer
IFCT	Intergroupe Francophone de Cancérologie Thoracique
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KRAS	Kirsten rat sarcoma viral oncogene homologue
MEK	mitogen-activated extracellular signal-regulated kinase
NGM	Network Genomic Medicine
NSCLC	non-small cell lung cancer
ORR	objective response rate
PFS	progression-free survival
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
UICC	Union for International Cancer Control

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug dabrafenib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 24 April 2017.

Research question

The aim of this report was to assess the added benefit of dabrafenib in combination with trametinib (hereinafter referred to as "dabrafenib plus trametinib") in comparison with the appropriate comparator therapy (ACT) in adult patients and patients with advanced non-small cell lung cancer (NSCLC) with rapidly accelerated fibrosarcoma – isoform B (BRAF) V600 mutation.

From the G-BA's specification of the ACT, the research questions listed in Table 2 resulted for the benefit assessment of dabrafenib plus trametinib.

Table 2: Research questions of the benefit assessment of dabrafenib + trametinib

Research question	Subindication	ACT[a]
Adult patients with advanced NSCLC with BRAF V600 mutation[b]		
1	Treatment-naive patients	<u>with ECOG PS 0, 1 or 2:</u> ▪ **cisplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) under consideration of the approval status *or* ▪ **carboplatin in combination with a third-generation cytostatic agent** (only for patients with increased risk of cisplatin-induced side effects within the framework of a combination therapy; see Appendix VI to Section K of the Pharmaceutical Directive [3]) *or* ▪ carboplatin in combination with nab-paclitaxel <u>with ECOG PS 2:</u> ▪ as an alternative to the platinum-based combination therapy: monotherapy with gemcitabine or vinorelbine
2	Pretreated patients	<u>Treatment with docetaxel, pemetrexed or nivolumab is indicated:</u> ▪ **docetaxel** or **pemetrexed** or **nivolumab** (pemetrexed: except in mainly squamous cell carcinoma histology) <u>Treatment with docetaxel, pemetrexed and nivolumab is not indicated[c]:</u> ▪ BSC[d]

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: It is assumed for the present therapeutic indication that the NSCLC patients have stage IIIB to IV disease (staging according to IASLC, UICC) without a medical indication for curative resection, radiotherapy or radiochemotherapy.
c: This applies especially to patients for whom nivolumab or cytotoxic chemotherapy is not an option due to their reduced general condition – in particular, these can be patients with ECOG PS 4, 3 or possibly 2.
d: BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve quality of life.
ACT: appropriate comparator therapy; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer

The company principally followed the G-BA's specification of the ACT. Deviations had no consequence for the present benefit assessment.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

The company identified no randomized controlled trials (RCTs) for a direct comparison of dabrafenib plus trametinib versus the ACT or for an indirect comparison based on RCTs for pretreated or treatment-naive patients. For both research questions, the company therefore assessed dabrafenib plus trametinib on the basis of a comparison of individual arms from different studies. For dabrafenib plus trametinib, the company used the non-comparative approval study BRF113928 for both research questions. For the ACT, the company included the retrospective studies Cardarella 2013 and Ding 2017 as well as the data on treatment-naive patients from the Network Genomic Medicine (NGM) Köln register analysis 2017 for research question 1 (treatment-naive patients). For research question 2 (pretreated patients), the company used the results of the pretreated patients from the NGM register analysis Cologne 2017. However, the data presented by the company were overall unsuitable to derive an added benefit of dabrafenib plus trametinib.

Research question 1: treatment-naive patients

The data presented by the company were unsuitable to derive an added benefit of dabrafenib plus trametinib for treatment-naive patients.

The major reason for this is that based on the data on overall survival for dabrafenib plus trametinib (study BRF113928) presented by the company at the time point of the data cut-off on 8 August 2016, and on the data from the 3 retrospective analyses, the median survival time of patients under dabrafenib plus trametinib was about twice as long in comparison with the patients of the 3 retrospective analyses. However, due to a large number of censorings that had largely occurred at an early point in time, the estimation of median survival (24.6 months) on the basis of 36 patients was very imprecise for the treatment-naive patients of the BRF113928 study and was thus unsuitable for the derivation of an added benefit.

Irrespective of this, a larger difference between groups than the one observed was required to rule out that this difference was merely based on the bias resulting from a comparison of individual arms of different studies.

In addition, there were further restrictions:

- Due to the small number of patients, the data from the comparative studies for treatment-naive patients presented by the company only had a limited informative value. The analyses on overall survival included 12 (Cardarella 2013), 28 (Ding 2017) and 2332 (NGM Cologne 2017) patients. Moreover, 8 of 22 (40%) patients were censored in the NGM register analysis Cologne 2017; the results of 2 patients were lacking. Information on the number of patients of the relevant subpopulation with BRAF V600E mutation who had died as well as data on censorings were not available for the Cardarella 2013 study. In the Ding 2017 study, the results on overall survival did not exclusively relate to patients with the target mutation BRAF V600.

- Comparability of the study populations was insufficient. The available data demonstrated that the patients of the dabrafenib-trametinib study BRF113928 differed from the patient populations of the respective retrospective analyses particularly with regard to ethnicity, smoking status, ECOG PS, disease stage and disease duration.
- It can further not be assessed with certainty whether the respective ACT specified by the G-BA was used for the retrospective analyses (Cardarella 2013, Ding 2017 and NGM Cologne 2017). In the Cardarella 2013 study, for instance, 5 of the 12 patients who were included in the analysis of overall survival had certainly not received a therapy that corresponded to the ACT.
- The company excluded the study of the Intergroupe Francophone de Cancérologie Thoracique (IFCT) study group with 17.664 patients with advanced NSCLC described in the Barlesi 2016 publication from its assessment. The company did not mention that it had a separate report on this study prepared by the IFCT study group for 189 patients with BRAF V600E mutation. This report included an analysis on overall survival involving 143 of these patients; median survival was 17.2 months. Seventy (49%) of these 143 patients were treated with platinum-based first-line chemotherapy in accordance with the specified ACT. Even if separate analyses for these 70 patients were lacking, it was not comprehensible why the company did not mention this analysis, because, for example, the majority of patients included in the analysis on overall survival in the Cardarella 2013 study used by the company had not been treated in compliance with the ACT either.
- No data on adverse events (AEs) were available for the target population receiving the comparator therapy. The company therefore presented the side effect profile and data on AEs observed under platinum-based chemotherapy in combination with paclitaxel or pemetrexed only as examples. In addition, these data came exclusively from patients without confirmed BRAF V600 mutation.

Research question 2: Pretreated patients

The data presented by the company were unsuitable to derive an added benefit of dabrafenib plus trametinib for pretreated patients.

For dabrafenib plus trametinib, the comparison of individual arms from different studies for pretreated patients conducted by the company was based on the results for 57 patients of the BRF113928 study and 5 patients of the NGM register analysis Cologne 2017. The very small number of patients receiving the comparator therapy did not permit a valid conclusion for the derivation of an added benefit of dabrafenib plus trametinib. It should also be noted that only 3 of the 5 patients had received the ACT specified by the G-BA (docetaxel, nivolumab or pemetrexed). The 2 other patients received docetaxel plus nintedanib combination therapy.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[4]

The result of the assessment of the added benefit of dabrafenib plus trametinib in comparison with the ACT is summarized in Table 3.

[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 to 3 cannot be drawn from the available data). 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). For further details see [1,2].

Table 3: Dabrafenib – probability and extent of added benefit

Research question	Subindication	ACT[a]	Extent and probability of added benefit
Adult patients with advanced NSCLC with BRAF V600 mutation[b]			
1	Treatment-naive patients	with ECOG PS 0, 1 or 2: ▪ **cisplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) under consideration of the approval status or ▪ **carboplatin in combination with a third-generation cytostatic agent** (only for patients with increased risk of cisplatin-induced side effects within the framework of a combination therapy; see Appendix VI to Section K of the Pharmaceutical Directive [3]) or ▪ carboplatin in combination with nab-paclitaxel with ECOG PS 2: ▪ as an alternative to the platinum-based combination therapy: monotherapy with gemcitabine or vinorelbine	Added benefit not proven
2	Pretreated patients	Treatment with docetaxel, pemetrexed or nivolumab is indicated: ▪ **docetaxel** or **pemetrexed** or **nivolumab** (pemetrexed: except in mainly squamous cell carcinoma histology) Treatment with docetaxel, pemetrexed and nivolumab is not indicated[c]: ▪ BSC[d]	Added benefit not proven Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: It is assumed for the present therapeutic indication that the NSCLC patients have stage IIIB to IV disease (staging according to IASLC, UICC) without a medical indication for curative resection, radiotherapy or radiochemotherapy.
c: This applies especially to patients for whom nivolumab or cytotoxic chemotherapy is not an option due to their reduced general condition – in particular, these can be patients with ECOG PS 4, 3 or possibly 2.
d: BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report was to assess the added benefit of dabrafenib in combination with trametinib (hereinafter referred to as "dabrafenib plus trametinib") in comparison with the ACT in adult patients and patients with NSCLC with BRAF V600 mutation.

From the G-BA's specification of the ACT, the research questions listed in Table 4 resulted for the benefit assessment of dabrafenib plus trametinib.

Table 4: Research questions of the benefit assessment of dabrafenib + trametinib

Research question	**Subindication**	**ACT**[a]
Adult patients with advanced NSCLC with BRAF V600 mutation[b]		
1	Treatment-naive patients	with ECOG PS 0, 1 or 2: ▪ **cisplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) under consideration of the approval status *or* ▪ **carboplatin in combination with a third-generation cytostatic agent** (only for patients with increased risk of cisplatin-induced side effects within the framework of a combination therapy; see Appendix VI to Section K of the Pharmaceutical Directive [3]) *or* ▪ carboplatin in combination with nab-paclitaxel with ECOG PS 2: ▪ as an alternative to the platinum-based combination therapy: monotherapy with gemcitabine or vinorelbine
2	Pretreated patients	Treatment with docetaxel, pemetrexed or nivolumab is indicated: ▪ **docetaxel** or **pemetrexed** or **nivolumab** (pemetrexed: except in mainly squamous cell carcinoma histology) Treatment with docetaxel, pemetrexed and nivolumab is not indicated[c]: ▪ BSC[d]

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: It is assumed for the present therapeutic indication that the NSCLC patients have stage IIIB to IV disease (staging according to IASLC, UICC) without a medical indication for curative resection, radiotherapy or radiochemotherapy.
c: This applies especially to patients for whom nivolumab or cytotoxic chemotherapy is not an option due to their reduced general condition – in particular, these can be patients with ECOG PS 4, 3 or possibly 2.
d: BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer

The company principally followed the G-BA's specification of the ACT. Deviations are described in Section 2.6.1 of the full dossier assessment. However, they had no consequence for the present benefit assessment.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 Information retrieval and study pool

For both research questions, 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 dabrafenib plus trametinib (status: 13 March 2017)
- bibliographical literature search on dabrafenib plus trametinib (last search on 13 March 2017)
- search in trial registries for studies on dabrafenib plus trametinib (last search on 13 March 2017)
- bibliographical literature search on the ACT (last search on 13 March 2017)
- search in trial registries for studies on the ACT (last search on 13 March 2017)

To check the completeness of the study pool:

- search in trial registries for studies on dabrafenib plus trametinib (last search on 9 May 2017)

In accordance with the company, for pretreated or treatment-naive patients the check of the completeness of the study pool did not produce any RCT on the direct comparison of dabrafenib plus trametinib versus the ACT or on an indirect comparison based on RCTs.

The company therefore searched for further studies on dabrafenib plus trametinib as well as on the ACT. For dabrafenib plus trametinib, the search yielded the study BRF113928 [4-7], and for the comparator therapy, the studies Cardarella 2013 [8] and Ding 2017 [9] and the NGM register analysis Cologne 2017 [10].

The data presented by the company were unsuitable to derive an added benefit of dabrafenib plus trametinib. This was justified for both research questions in Sections 2.3.1 (treatment-naive patients) and 2.3.2 (pretreated patients) respectively. Because the company partly presented data from the same studies for both questions, the evidence provided by the company is at first summarized hereinafter.

Data presented by the company

The company explained that no RCT was available for dabrafenib plus trametinib in the present therapeutic indication; the only study that had been conducted was the non-randomized non-comparative approval study BRF113928. For both research questions, the company therefore assessed dabrafenib plus trametinib on the basis of a comparison of individual arms from different studies. For the comparator therapy, the company included the studies Cardarella 2013 [8] and Ding 2017 [9] as well as the data on treatment-naive patients from the NGM register analysis Cologne 2017 [10] for research question 1 (treatment-naive patients). For research question 2 (pretreated patients), the company used the results of the pretreated patients from the NGM register analysis Cologne 2017.

Table 5 shows an overview of the data used by the company for research questions 1 and 2.

Table 5: Dabrafenib – data presented by the company

Research question	Subindication	Data presented by the company
Adult patients with advanced NSCLC with BRAF V600 mutation[a]		
1	Treatment-naive patients	Studies on dabrafenib plus trametinib: ▪ BRF113928 Studies on the comparator therapy[b]: with ECOG PS 0, 1 or 2: ▪ Cardarella 2013 ▪ Ding 2017 ▪ NGM Cologne 2017
2	Pretreated patients	Treatment with docetaxel, pemetrexed or nivolumab is indicated: Studies on dabrafenib + trametinib: ▪ BRF113928 Studies on the comparator therapy[c]: ▪ NGM Cologne 2017 Treatment with docetaxel, pemetrexed or nivolumab is not indicated[d]: ▪ No data

a: It was assumed for the present therapeutic indication that the NSCLC patients have stage IIIB to IV disease (staging according to IASLC, UICC) without a medical indication for curative resection, radiotherapy or radiochemotherapy.
b: No data on AEs were available for the approval population. The company therefore presented results on the side effect profile of a platinum-based chemotherapy in combination with paclitaxel [11] or pemetrexed [12] as well as results on the overall rates of AEs based on the data from the PROFILE1014 study "as an example" [13].
c: No data on AEs were available for the approval population. The company therefore presented results on overall AE rates based on the data from the PROFILE1007 [14] study "as an example".
d: This applies especially to patients for whom nivolumab or cytotoxic chemotherapy is not an option due to their reduced general condition – in particular, these can be patients with ECOG PS 4, 3 or possibly 2.
ECOG PS: Eastern Cooperative Oncology Group Performance Status; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; NGM: Network Genomic Medicine; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control

Non-comparative study BRF113928 on dabrafenib plus trametinib

Study BRF113928 was a non-randomized, open-label study with dabrafenib as monotherapy or in combination with trametinib. A total of 3 cohorts (cohort A to C) were examined in the study. Adult patients with metastatic NSCLC (stage IV) and confirmed BRAF V600E mutation were sequentially included in these cohorts. In addition, the patients had to have an ECOG PS of 0, 1 or 2. Since all patients in cohort A received monotherapy with dabrafenib, this cohort was not considered further in the present benefit assessment. 57 and 36 patients who were treated with the combination of dabrafenib plus trametinib were considered in cohorts B and C. The patients in cohort B had been pretreated with at least one platinum-based chemotherapy, while patients in cohort C were included without pretreatment for the metastatic disease. The dosage of both drugs corresponded to the specifications of the Summary of Product Characteristics (SPC) [15]: Dabrafenib was administered twice daily in doses of 150 mg each, trametinib was administered once daily in a dose of 2 mg.

The primary outcome of the study was the objective response rate (ORR). The treatment phase ended with the occurrence of intolerable AEs, death or disease progression. However, patients with disease progression could continue the treatment when the investigator considered it beneficial to them. Median treatment duration was 8.2 months in treatment-naive patients and 10.6 months in pretreated patients. The follow-up observation of the study has not yet been completed. The end of the study and the final analysis are planned when at least 70% of the patients in each cohort have died or 5 years after the last patient was included in the study. Overall survival and selected data on safety are to be assessed in the final analysis.

Further information on the study can be found in Appendix A of the full dossier assessment.

Retrospective studies on the comparator therapy

For the comparator therapy, the company presented the retrospective analyses Cardarella 2013 ([8], patient data from the USA), Ding 2017 ([9], patient data from China) and NGM Cologne 2017 ([10], patient data from Germany).

Cardarella 2013

The Cardarella 2013 study is a retrospective analysis of data of adult patients with NSCLC who had been tested for BRAF mutation in the USA between July 2009 and July 2012. Depending on their mutation status (BRAF V600E, BRAF non-V600E and wild type), the patients were divided into 3 groups. A total of 36 patients had BRAF mutation, whereby 18 of the 36 patients had BRAF V600E mutation. The analysis included patients with metastatic (stage IV) or relapsed metastatic NSCLC for whom at least 4 weeks after the start of a systemic therapy for the advanced stage of their disease suitable scans of the radiological assessments were available. Investigated outcomes of the study are overall survival, progression-free survival (PFS) and tumour response.

In the dossier the company stated that in its analyses based on the Cardarella 2013 study, depending on the outcome, it considered the results of the patients with advanced NSCLC and BRAF V600E mutation who had received standardized platinum-based chemotherapy as first-line treatment for the advanced tumour stage (N = 7, PFS and tumour response) or the results of patients with BRAF V600E mutation who had received no further defined antiproliferative therapy (N = 12, overall survival). Five of the 12 patients included in the analysis on overall survival had received treatment with a BRAF or mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor, which does not comply with the specified ACT. The publication does not definitely indicate whether the ACT had been implemented for the remaining 7 patients. Further information on patient characteristics can be found in Appendix B of the full dossier assessment.

Ding 2017

The Ding 2017 study is a retrospective analysis of data of adult Chinese patients with stage IIIB or IV NSCLC who had been tested for BRAF, Kirsten rat sarcoma viral oncogene homologue (KRAS) and epidermal growth factor receptor (EGFR) mutations between January 2012 and April 2016. Twenty-four of a total of 28 patients with BRAF mutation had BRAF V600E mutation. All examined patients were treated with no further defined platinum-based first-line chemotherapy. Investigated outcomes of the study are overall survival, PFS and tumour response. Further information on patient characteristics can be found in Appendix B of the full dossier assessment.

In the dossier the company stated that in its analyses, depending on the outcome, it considered the results of the patients with advanced NSCLC and BRAF mutation who had received platinum-based chemotherapy as first-line treatment for the advanced tumour stage (N = 28, overall survival and tumour response) or the subgroup of patients with BRAF V600E mutation (N = 24, PFS).

NGM Cologne 2017

The NGM study Cologne 2017 is a register analysis of patient data from German hospitals commissioned by the company that was conducted between January and April 2017. A total of 44 adult patients with advanced NSCLC and confirmed BRAF V600E mutation were included in the register analysis. Twenty-six of these 44 patients received platinum-based first-line chemotherapy (cisplatin or carboplatin) in combination with a third-generation cytostatic agent (gemcitabine, paclitaxel, pemetrexed, vinorelbine), and 5 pretreated patients received treatment with docetaxel, pemetrexed or nivolumab. However, 2 of the 5 pretreated patients received a combination therapy of docetaxel plus nintedanib, which does not correspond to the ACT specified by the G-BA. This study examined the outcomes “overall survival”, “PFS” and “tumour response”. Further information on the characteristics of the treatment-naive patients can be found in Appendix B of the full dossier assessment.

In the dossier the company stated that for the outcome “overall survival” it considered only those patients among the treatment-naive patients who had not received a BRAF or MEK

inhibitor during the course of the treatment (N = 22). For the further outcomes "PFS" and "tumour response", the company included all 26 treatment-naive patients. For the pretreated patients, the company used the results of all 5 patients for all outcomes.

Data presented on AEs

The company described that no data were available on the outcome category "tolerability" of the comparator therapy for the approval population (patients with advanced NSCLC with BRAF V600 mutation). The company therefore presented overall rates of AEs for treatment-naive and pretreated patients based on the PROFILE1014 study [13] or the PROFILE1007 study [14] for NSCLC patients without BRAF V600 mutation "as an example". For treatment-naive patients, the company additionally presented the side effect profile of a platinum-based chemotherapy in combination with paclitaxel [11] or pemetrexed [12] "as an example". For this purpose, the company used the SPCs for pemetrexed [16] and paclitaxel [17] as well as the publications cited [11,12].

2.3.1 Research question 1: treatment-naive patients

Comparison of individual arms from different studies for treatment-naive patients

The company conducted a comparison of individual arms from different studies for treatment-naive patients with advanced NSCLC with BRAF V600 mutation. For dabrafenib plus trametinib, the company used cohort C of the BRF113928 study. For the comparator therapy, the company presented results from the retrospective patient data analyses Cardarella 2013, Ding 2017 and NGM Cologne 2017.

The company derived a non-quantifiable added benefit of dabrafenib plus trametinib on the basis of this comparison. From the company's point of view, the added benefit was shown particularly in respect of the outcome "overall survival". For its conclusion, the company compared the 24.6 months of median overall survival from the BRF113928 study with the 10.8 and 10.5 months of median survival time from the retrospective analyses Cardarella 2013 and NGM Cologne 2017 (see Appendix C of the full dossier assessment). With respect to the median survival time of 14.7 months from Ding 2017, the company pointed out that the outcome in this study was recorded for the period as of the first diagnosis and not for the time as of the start of treatment as in the other included studies.

Based on the data on overall survival from the BRF113928 study presented by the company for dabrafenib plus trametinib at the time point of the data cut-off on 8 August 2016, and on the data of the 3 retrospective analyses, the median survival time of patients under dabrafenib plus trametinib was about twice as long in comparison with patients of the 3 retrospective analyses. However, the estimation of median overall survival was very imprecise for the treatment-naive patients of the BRF113928 study and was thus unsuitable for the derivation of the added benefit. It could be inferred from the documents presented by the company, including Module 4 A Table 4-35, that at the time point of the data cut-off on 8 August 2016 10 of the 36 treatment-naive patients had died and 26 patients had been censored (only 2 of

them after termination of the follow-up). The high number of censorings can also be seen in the Kaplan-Meier analysis (see Figure 1). However, deviating from this, the company only mentioned 18 censored patients at one point in Module 4 A of its dossier. The origin of this number is unclear. Besides the number of censored patients, the time point at which these censorings occurred over time was of particular importance for the assessment of the informative value of the data. For instance, based on the number of patients at risk, Figure 1 shows that the proportion of patients at risk was drastically reduced over time. At the time point of 12 months, only one third of the patients were at risk, at 14 months one sixth of the patients were at risk and as of month 16 a total of only 2 patients (approx. 5%) were at risk. The median of overall survival arose from the fact that the Kaplan-Meier estimate was reduced from approx. 70% to approx. 40% by one single event at the time point of 24.6 months. This means that the right hand side of the Kaplan-Meier curve and thus also the median of overall survival are subject to very high uncertainty.

Irrespective of this, a larger difference between groups than the one observed was required to rule out that this difference was merely based on the bias resulting from a comparison of individual arms of different studies.

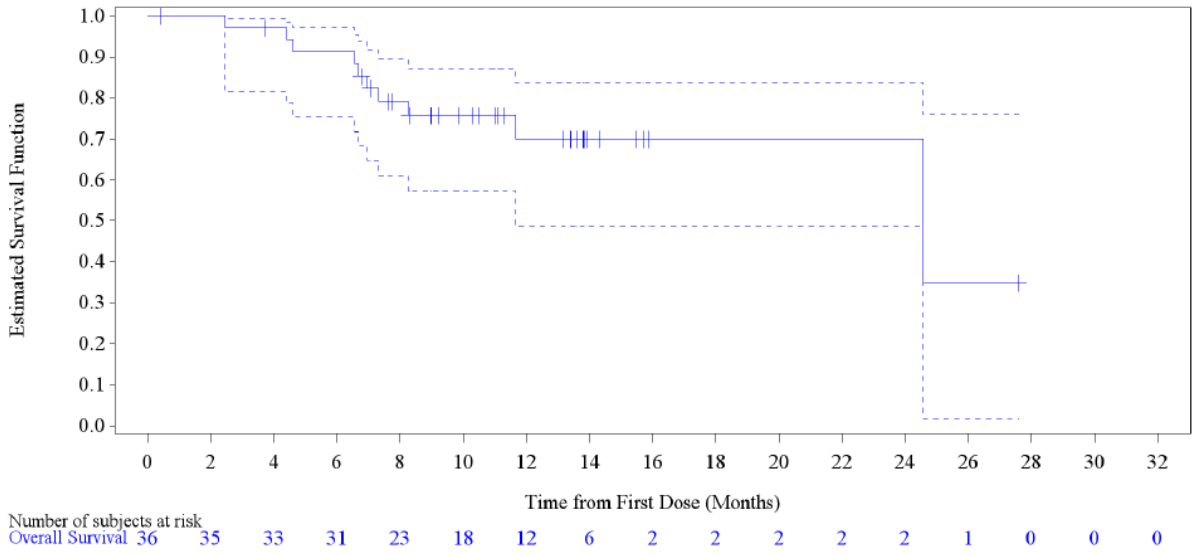

Figure 1: Kaplan-Meier curve for overall survival of treatment-naive patients of the BRF113928 study

Further restrictions of the presented comparison

The data of the comparative studies for treatment-naive patients presented by the company only had a limited informative value. For instance, only few patients were included in the analyses on overall survival (Cardarella 2013: N = 12, Ding 2017: N = 28 and NGM Cologne 2017: N = 22). Moreover, 8 of 22 patients (40%) of the NGM register analysis Cologne 2017 had been censored (see Figure 2 in Appendix C of the full dossier assessment); the results of 2 patients were lacking. Information on the number of patients of the relevant subpopulation

with BRAF V600E mutation who had died as well as data on censorings were not available at all for the Cardarella 2013 study. In the Ding 2017 study, the results on overall survival did not exclusively relate to patients with the target mutation BRAF V600 (see Figure 3 in Appendix C of the full dossier assessment).

Moreover, comparability of the study populations was insufficient; many data were missing particularly in the publication on the Cardarella 2013 study. However, the available data demonstrated that the patients of the dabrafenib-trametinib study BRF113928 had differed from the patient populations of the respective retrospective analyses. This applied particularly to parameters such as ethnicity, smoking status, ECOG PS, disease stage and disease duration (see Appendix B of the full dossier assessment, Table 12). The comparability of the patient characteristics is a necessary precondition for conclusions based on the comparison of study arms.

It can further not be assessed with certainty whether the respective ACT specified by the G-BA was used for the retrospective analyses (Cardarella 2013, Ding 2017 and NGM Cologne 2017). The Ding 2017 study provided the information that a platinum-based therapy was administered, however, without specifying the used substances. In the Cardarella 2013 study, for example, the 12 patients who were included in the analysis on overall survival received an antiproliferative therapy that was not further specified. Five (42%) of these patients received treatment with a BRAF or MEK inhibitor. This did not correspond to the specified ACT. The publication did not clearly reveal whether the remaining 7 patients had received treatment corresponding to the ACT. The available documents on the NGM register analysis Cologne 2017 showed that 55% of the patients who were included in the analysis on overall survival had been treated with a carboplatin-based combination chemotherapy with a third-generation cytostatic agent. It is not clear from the available data whether these patients fulfilled the prerequisite of an increased risk of cisplatin-induced side effects in accordance with Appendix VI to Section K of the Pharmaceutical Directive [3].

Within the framework of its bibliographical search for the comparator therapy, the company identified the publication on the Barlesi 2016 retrospective study [18] including 17.664 patients with advanced NSCLC. Exclusion on the basis of this publication was adequate. But the company did not mention that it had a separate report on this study for 189 patients with BRAF V600E mutation. This report had been prepared by the group that had conducted the study, the IFCT. This report included an analysis on overall survival involving 143 of these patients; median survival was 17.2 months. Seventy (49%) of these 143 patients were treated with platinum-based first-line chemotherapy in accordance with the specified ACT. Even if separate analyses for these 70 patients were lacking, it was not comprehensible why the company did not mention this analysis, because the majority of the patients included in the analysis on overall survival in the Cardarella 2013 study used by the company, for example, had not been treated in compliance with the ACT either. Section 2.6.2.3.2 of the full dossier assessment provides a detailed commentary on the exclusion of the Barlesi 2016 study by the company.

No relevant data on AEs were available for the target population receiving the comparator therapy. Therefore, the company presented the side effect profile of a platinum-based chemotherapy in combination with paclitaxel or pemetrexed based on the Gatzemeier 2000 [11] and Shepherd 2001 [12] publications and results on overall AE rates based on the data of the PROFILE1007 [14] and PROFILE1014 [13] studies as examples. The company did not conduct a systematic search for this purpose. All results on AEs of the comparator therapy presented by the company came from patients without confirmed BRAF V600 mutation.

Summary

Due to the uncertainties described, the data presented by the company are unsuitable for the derivation of an advantage or disadvantage of dabrafenib plus trametinib in treatment-naive patients. Moreover, comparability of the study populations is insufficient due to the uncertainty of the implementation of the ACT. Accordingly, no added benefit of dabrafenib plus trametinib versus the ACT can be derived from the comparison for research question 1 presented by the company.

2.3.1.1 Results on added benefit

In its dossier, the company did not present any suitable data for the assessment of the added benefit of dabrafenib plus trametinib in adult treatment-naive patients with advanced NSCLC with BRAF V600 mutation versus the ACT. Hence, there is no hint of an added benefit of dabrafenib plus trametinib in comparison with the ACT; an added benefit is therefore not proven.

2.3.1.2 Probability and extent of added benefit

Since the company did not present any suitable data for the assessment of the added benefit of dabrafenib plus trametinib in comparison with the ACT in adult treatment-naive patients with advanced NSCLC with a BRAF V600 mutation, an added benefit of dabrafenib plus trametinib is not proven for these patients.

This deviates from the approach of the company that derived a non-quantifiable added benefit of dabrafenib plus trametinib for both treatment-naive and pretreated patients without providing information on the probability of the added benefit.

2.3.2 Research question 2: Pretreated patients

Comparison of individual arms from different studies for pretreated patients

The company conducted a comparison of individual arms from different studies for pretreated patients with advanced NSCLC with a BRAF V600 mutation. For dabrafenib plus trametinib, the company used the results of cohort B of the BRF113928 study that included 57 pretreated patients. For the comparator therapy, the company presented results on 5 pretreated patients from the NGM Cologne 2017 register analysis [10] (see also Section 2.3).

The company pointed to the limited validity of the results due to the small number of patients, but derived a non-quantifiable added benefit for dabrafenib plus trametinib for pretreated patients on the basis of these data.

The approach of the company was not followed. The very small number of patients receiving the comparator therapy did not permit a valid conclusion for the derivation of an added benefit of dabrafenib plus trametinib. It should also be noted that only 3 of the 5 patients had received the ACT specified by the G-BA (docetaxel, nivolumab or pemetrexed). The 2 other patients received docetaxel plus nintedanib combination therapy. No added benefit of dabrafenib plus trametinib versus the ACT can therefore be derived from the comparison for pretreated patients presented by the company.

2.3.2.1 Results on added benefit

In its dossier, the company did not present any suitable data for the assessment of the added benefit of dabrafenib plus trametinib in adult pretreated patients with advanced NSCLC with BRAF V600 mutation versus the ACT. Hence, there is no hint of an added benefit of dabrafenib plus trametinib in comparison with the ACT; an added benefit is therefore not proven.

2.3.2.2 Probability and extent of added benefit

Since the company did not present any suitable data for the assessment of the added benefit of dabrafenib plus trametinib in comparison with the ACT in adult pretreated patients with advanced NSCLC with a BRAF V600 mutation, an added benefit of dabrafenib plus trametinib is not proven for these patients.

This deviates from the approach of the company that derived a non-quantifiable added benefit of dabrafenib plus trametinib for both treatment-naive and pretreated patients without providing information on the probability of the added benefit.

2.4 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of dabrafenib plus trametinib in comparison with the ACT is summarized in Table 6.

Table 6: Dabrafenib – probability and extent of added benefit

Research question	Subindication	ACT[a]	Extent and probability of added benefit
Adult patients with advanced NSCLC with BRAF V600 mutation[b]			
1	Treatment-naive patients	with ECOG PS 0, 1 or 2: ▪ **cisplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) under consideration of the approval status or ▪ **carboplatin in combination with a third-generation cytostatic agent** (only for patients with increased risk of cisplatin-induced side effects within the framework of a combination therapy; see Appendix VI to Section K of the Pharmaceutical Directive [3]) or ▪ carboplatin in combination with nab-paclitaxel with ECOG PS 2: ▪ as an alternative to the platinum-based combination therapy: monotherapy with gemcitabine or vinorelbine	Added benefit not proven
2	Pretreated patients	Treatment with docetaxel, pemetrexed or nivolumab is indicated: ▪ **docetaxel** or **pemetrexed** or **nivolumab** (pemetrexed: except in mainly squamous cell carcinoma histology) Treatment with docetaxel, pemetrexed and nivolumab is not indicated[c]: ▪ BSC[d]	Added benefit not proven Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: It is assumed for the present therapeutic indication that the NSCLC patients have stage IIIB to IV disease (staging according to IASLC, UICC) without a medical indication for curative resection, radiotherapy or radiochemotherapy.
c: This applies especially to patients for whom nivolumab or cytotoxic chemotherapy is not an option due to their reduced general condition – in particular, these can be patients with ECOG PS 4, 3 or possibly 2.
d: Best supportive care (BSC) refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control

The G-BA decides on the added benefit.

2.5 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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