Trametinib in combination with dabrafenib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID661]

Novartis response to clarification questions

Section A: Clarification on effectiveness data

A1. In the company submission, the results for the subgroup analyses are presented in figures 19 and 20 for the COMBI-d trial and figures 21 and 22 for the COMBI-v trial. Please provide the p values for the tests for interaction for all subgroup analyses for overall survival (OS) and progression-free survival (PFS).

Novartis response:

Please refer to tables: [redacted];

[redacted]

Please note that COMBI-v and COMBI-d were not powered to assess differences in PFS and OS between treatment groups in subgroups of patients presented in figures 21 and 22 of the submission. Accordingly, p-values for these comparisons should be interpreted cautiously. Furthermore, because the numbers of patients within subgroups may be small, the estimates of treatment effect may be associated with substantial uncertainty and should also be interpreted cautiously. On the other hand, to the extent that multiple subgroup analyses are performed, it increases the likelihood of observing a spurious statistically significant interaction between treatment group and the factors defining the subgroups. We therefore suggest that these data are not used to inform alternative health economics analyses as they are likely to lead to misleading and uncertain cost effectiveness results.

A2. On page 127 (section 4.8.2) of the company submission, a list of planned exploratory subgroup analyses is presented. This list includes a subgroup analysis according to 'prior immunotherapy (yes or no)'. Please provide the OS and PFS results for the subgroups of patients in the COMBI-d trial who did, and did not, receive prior immunotherapy treatment.

Novartis response:

Please refer to tables: [redacted];
Also, please note COMBI-d was not powered to assess differences in PFS and OS between treatment groups according to whether patients had or had not received prior immunotherapy. Accordingly, PFS and OS data reported in [redacted]

[redacted] for these comparisons should be interpreted cautiously. Furthermore, because the numbers of patients within subgroups may be small, the estimates of treatment effect may be associated with substantial uncertainty and should also be interpreted cautiously. We therefore suggest that these data are not used to inform alternative health economics analyses as they are likely to lead to misleading and uncertain cost effectiveness results.

A3. Across all the trials reported in the company submission, the Pike estimator is used to conduct the stratified log-rank test for PFS and OS. Please explain why the Pike estimator was chosen in preference to the Cox proportional hazards model.

Novartis response:

The Pike estimator, which is a nonparametric estimator of the HR, has been specifically developed for survival data and is used as a measure of the relative survival experience of two groups. Within the range of values of the ratio of the hazard rates of interest in clinical trials, Pike estimator is more efficient in terms of mean square error than the Cox proportional hazard method. Please refer to the paper by Bernstein *et al* (1981) for further information.

A4. The Reporting and Analysis Plan (RAP) provided in the company submission for the COMBI-v trial is stated to be the latest version (amendment number 4). It is not clear when the first version of the RAP was finalised, or what changes have been made between version 1 and version 4. Please provide either the first version of the RAP or a RAP revision history table, so that comparisons can be made between the first and the current version.

Novartis response:

Please refer to file [redacted], which contains the original RAP for combi-v.

<u>Section B: Clarification on cost-effectiveness data</u>

<u>B1. Priority question: Revised Kaplan-Meier (K-M) analyses</u>

Please provide the K-M analyses detailed in points 1a, 1b, 2a and 2b for the ITT populations including all patients who were lost to follow-up, or who withdrew from the trials. Please censor patients lost to follow-up, and those who withdrew from the trials at the date recorded. Patients alive and still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off, not at the point when last known to be alive (for OS and post-progression survival [PPS]), or at the date of the last tumour assessment (for PFS).

Novartis response:

The censoring method used in both the combi-v and the combi-d trials (that is, to censor patients the earliest of the event date or the date of last observation) represents the conventional approach to censoring of survival endpoints in clinical trials in oncology (Green S, Benedetti J, Smith A, et al. Clinical Trials in Oncology, Second Edition. Taylor & Francis, (2002). This approach is premised on the assumption that the likelihood of experiencing an event after censoring is the same for patients who were censored (for whom the events would be unobserved) and those who were not (for whom the events would be observed). This assumption would be violated, and censoring would be informative, if the actual (unobserved) risk of the event between the last observation and the data cut-off for patients who were censored was actually zero. This would be true if all events during that period are recorded spontaneously for all patients.

The approach proposed by the ERG is premised on the assumption that the risk of an event between the last observation and the data cut-off is known and is zero for those without a recorded event.

Stated differently, it assumes that all events that occurred between the last observation and the data cut-off are recorded.

If all patients who experience an event after the last assessment are captured by spontaneous reporting, then the use of the conventional censoring rule may yield Kaplan Meier estimates that overestimate the risk of the event and underestimate survival. On the other hand, if there are some events that occur after the last observation, but which are not captured by spontaneous reporting, then the censoring rule proposed by the ERG may yield Kaplan Meier estimates that underestimate the risk of the event and overestimate survival. The relative magnitude of the potential biases depend on the likelihood that events between the last observation and the data cut-off are recorded.

Because most PFS events represent disease progression (rather than death), and determination of disease progression can only be made by assessment, it is clear that the censoring rule proposed by the ERG would lead to an underestimation of the risk of progression or death. If a material share PFS events are deaths, and all death are spontaneously reported, then the conventional approach may overestimate the risk of progression or death to some degree. While the relative magnitude of the bias depends on the proportion of events that are deaths and the proportion of deaths that are spontaneously reported, it seems likely that the conventional approach would be less biased for PFS.

Regarding OS, there may be reporting requirements for clinical trials that increase the likelihood that events which occur between the last assessment and the end of data cut-off are recorded (for examples, according to FDA requirements, serious adverse events, including deaths potentially related to treatment, must be reported within a few weeks). Accordingly, the likelihood of bias associated with the conventional approach may be greater with OS than with PFS. However, if there is any probability that deaths occurring after the last observation but before the data cut-off are not recorded, then the approach proposed by the ERG may also be associated with bias. Again, the relative magnitude of these potential biases is unknown.

In their discussion of the potential limitation of the conventional censoring rule, Bagust and Beale (2013) point out that, due to the few patients at risk generally witnessed at that specific point, the conventional approach to censoring may result in sudden downward shift of the Kaplan Meier curves at the end of the observed data. It is important to note that no such shifts were observed in the Kaplan-Meier curves for PFS for combi-v, combi-d, or the pooled data from the two trials. These results suggest that the magnitude of any bias associated with the conventional censoring rule is likely to be small.

In consideration of the reasons discussed above, Novartis presents the required analyses using the conventional approach to censoring (i.e., patients censored at last observation or event).

1. Trial data set: COMB-d; 12th January 2015 data cut (if available, otherwise the most recent data):

a. Time to death from any cause (OS), time to disease progression or death based on investigator assessment (investigator-assessed PFS), and time from disease progression by investigator assessment to death from any cause (PPS), stratified by treatment arm (trametinib plus dabrafenib compared with dabrafenib).

Novartis response:

Please refer to tables [redacted]

b. Time to treatment discontinuation, stratified by treatment arm (trametinib plus dabrafenib compared with dabrafenib).

Novartis response:

Please refer to tables [redacted]

2. Trial data set: COMB-v; un-crossed data, 13th March 2015 data cut (if available, otherwise the most recent data):

a. Time to death from any cause (OS), time to disease progression or death based on investigator assessment (investigator-assessed PFS), and time from disease progression by investigator assessment to death from any cause (PPS), stratified by treatment arm (trametinib plus dabrafenib compared with vemurafenib).

Novartis response:

Please refer to [redacted]

b. Time to treatment discontinuation, stratified by treatment arm (trametinib plus dabrafenib compared with vemurafenib).

Novartis response:

Please refer to tables [redacted]

B2. Priority question: Please provide results for EQ-5D utility scores (using UK valuation) in the COMI-d and COMBI-v trials (January 2015 and March 2015 data cut if available, otherwise the most recent data), showing (i) the number of valid patient responses (at baseline and every 8 weeks thereafter through to week 56, and then every 12 weeks until progression, at progression and 5 weeks post-progression), and (ii) the mean and standard deviation of the EQ-5D values every time these data were recorded, stratified by treatment (COMBI-d: trametinib plus dabrafenib compared with dabrafenib; COMBI-v: trametinib plus dabrafenib compared with vemurafenib).

Novartis response:

Please refer to tables [redacted]

B3. Priority question: Please repeat the analyses in question B2, for each of the 3 subgroups defined by country of origin:

a. USA and Canada

b. Europe

c. Other

Novartis response:

Please refer to tables [redacted];

Please note that COMBI-v and COMBI-d were not powered to assess differences in EQ-5Ds scores in the subgroups defined by country of origin. Accordingly, these comparisons should be interpreted cautiously. Furthermore, because the numbers of patients within subgroups may be small, the estimates of treatment effect may be associated with substantial uncertainty and should also be interpreted cautiously. We therefore suggest that these data are not used to inform alternative health economics analyses as they are likely to lead to misleading and uncertain cost effectiveness results.

B4. Priority question: Using the latest available data from the COMBI-d and COMBI-v trials, and omitting any patient who switched treatment, please provide a table for each trial showing the number of patients in each treatment arm who continued to receive their assigned study treatment after disease progression. Please also include the median time between progression and treatment discontinuation for these patients.

Novartis response:

Please refer to tables [redacted] and [redacted]. Please also note that, while the protocol allowed for treatment beyond progression at the discretion of the physician, the CRF did not explicitly capture when this course of action was taken. Given that the treatment was administered daily and that there is a natural lag between scanning and progression determination, a 15-day time "window" was used to determine which patients were treated post-progression. Any treatment continuation beyond 15 days after the progression date was considered to be intentional.

B5. Please clarify whether patients in the COMBI-d and COMBI-v trials, whose disease had progressed but who remained on study treatment, were categorised as having had disease progression in all analyses undertaken after the point at which progression was identified.

Novartis response: Yes, that is correct.

B6. Please provide details of the criteria that were used to stop treatment in patients whose disease had progressed but who remained on study treatment.

Novartis response:

The criteria used were the following:

- Achieve an objective response (partial or complete response) according to RECIST, version 1.1, or have stable disease with imaging evidence of tumor reduction lasting at least 8 weeks while receiving study treatment
- No treatment-related AEs of CTCAE grade 4 during the last four weeks of study treatment
- No signs and symptoms of clinical disease progression that decrease ECOG performance status to ≥ 2
- No severe clinical conditions that require immediate surgical or radiotherapeutical intervention, subjects who required palliative radiation of bone lesions or limited surgical removal of isolated tumor lesions may be considered after completion of the procedure (radiotherapy or surgery) and review by the GSK Medical Monitor

If all of the above conditions were met, the following steps were implemented prior to continuation of study treatment:

- The investigator consulted with and received approval from the Medical Monitor.
- The subject signed an informed consent that specified alternative therapies (e.g., FDA-approved therapies) that the subject may be foregoing by continuing study treatment

References

Bagust, A. and S. Beale “Survival Analysis and Extrapolation Modeling of Time-to-Event Clinical Trial Data for Economic Evaluation: An Alternative Approach” Med Decis Making 2014 34: 343

Bernstein L., Anderson J., Pike M.C. “Estimation of the Proportional Hazard in Two-Treatment-Group Clinical Trials”. Biometrics. 1981; 37: 513-519.

Green S, Benedetti J, Smith A, et al. Clinical Trials in Oncology, Second Edition. Taylor & Francis, (2002).