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Original Research

Quality of life assessment of cabozantinib in patients with advanced hepatocellular carcinoma in the CELESTIAL trial

Nick Freemantle [a,*], Patrick Mollon [b], Tim Meyer [a], Ann-Lii Cheng [c], Anthony B. El-Khoueiry [d], Robin K. Kelley [e], Ari D. Baron [f], Fawzi Benzaghou [g], Milan Mangeshkar [h], Ghassan K. Abou-Alfa [i,j]

[a] *University College London, London, UK*
[b] *Ipsen Pharma SAS, Boulogne-Billancourt, France*
[c] *National Taiwan University Hospital and National Taiwan University Cancer Center, Taiwan, Republic of China*
[d] *Norris Comprehensive Cancer Center, Keck School of Medicine of USC, Los Angeles, CA, USA*
[e] *UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA*
[f] *California Pacific Medical Center, San Francisco, CA, USA*
[g] *Ipsen Bioscience, Cambridge, MA, USA*
[h] *Exelixis, Inc., South San Francisco, CA, USA*
[i] *Memorial Sloan Kettering Cancer Center, New York, NY, USA*
[j] *Weill Medical College at Cornell University, New York, NY, USA*

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Visual analog scale

Abstract ***Background:*** The CELESTIAL trial (NCT01908426) demonstrated overall survival benefit for cabozantinib versus placebo in patients with advanced hepatocellular carcinoma (aHCC) who had received prior sorafenib treatment. This analysis of CELESTIAL compared the impact of cabozantinib versus placebo on health-related quality of life (HRQoL).

Materials and methods: Health status was assessed using the EuroQol five-dimension five-level (EQ-5D-5L) questionnaire over the 800-day follow-up period. EQ-5D-5L health states were mapped to health utility scores using reference values for the UK population. Quality-adjusted life years (QALYs) were calculated for each treatment group as the area under the curve for the plot of health utility score over time. The between-treatment group difference in restricted mean QALYs was calculated by generalized linear models and adjusted for baseline differences. A difference of 0.08 in health utility score (or in QALY) was deemed a minimally important difference and to be clinically significant.

* *Corresponding author:* University College London, London, UK.
E-mail address: nicholas.freemantle@ucl.ac.uk (N. Freemantle).

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Results: At week 5, the difference in mean health utility score between cabozantinib and placebo was −0.097 (95% confidence interval [95% CI]: −0.126, −0.067; $p \leq 0.001$). Between-group differences in health utility scores diminished over time and were generally non-significant. The cabozantinib group accrued more QALYs than the placebo group over follow-up. Differences in mean QALYs (cabozantinib minus placebo) were statistically and clinically significant, ranging from +0.092 (95% CI: 0.016, 0.169) to +0.185 (95% CI: 0.126, 0.243) in favour of cabozantinib, depending on the reference value set used.
Conclusions: These HRQoL findings support a positive benefit–risk profile for cabozantinib in previously treated patients with aHCC.

1. Introduction

Most patients with hepatocellular carcinoma (HCC) are diagnosed with advanced disease (aHCC) by which time curative interventions are no longer available [1]. The introduction of targeted therapies in recent years, however, is changing the treatment paradigm for patients with aHCC [2,3]. The goal of these therapies is to prolong life rather than to achieve cure, thus their ability to maintain patients' health-related quality of life (HRQoL) and avoid treatment-related side effects that may be deleterious to HRQoL is highly valued [4,5].

One measure used to evaluate HRQoL is the quality-adjusted life year (QALY), which is a person's length of life weighted by their HRQoL. One QALY is equivalent to 1 year in perfect health [6]. Health technology appraisals often use the EuroQol five-dimension five-level (EQ-5D-5L) questionnaire to evaluate the impact of treatment on QALYs. The EQ-5D-5L assesses five functional symptom dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), and patients respond using a 5-point Likert scale (1, no problems, to 5, unable to perform/extreme problems), resulting in 3125 (i.e. 5^5) possible final health states [7]. The EQ-5D-5L also includes a visual analogue scale (VAS) that provides a single global rating of self-perceived health and is scored on a 0–100 scale, with 0 representing the 'worst', and 100 the 'best', health state imaginable [7]. Utilities are single index values that reflect how 'good' or 'bad' a given health state is, as perceived by a particular reference population (1, best possible health state; 0, death or health states considered interchangeable with death; negative values states, considered worse than death). Utility values are applied to an EQ-5D-5L health status recorded for a population receiving a particular treatment to provide an overall measure of the 'health utility' of that treatment [8–10].

Cabozantinib inhibits multiple receptor tyrosine kinases, including vascular endothelial growth factor receptors, the GAS6 receptor (AXL), and the hepatocyte growth factor receptor protein (MET) [11,12]. Based on findings from the pivotal phase 3 CELESTIAL trial (NCT01908426) [3], cabozantinib is approved in Europe and the USA for the treatment of patients with HCC who have been previously treated with sorafenib [11,12].

This analysis of the CELESTIAL trial evaluated the impact of cabozantinib compared with placebo on HRQoL in terms of health utility and QALY assessment.

2. Methods

2.1. Study

Full details of the CELESTIAL study have been published previously [3]. Briefly, patients with HCC (N = 707) were randomized 2:1 to receive cabozantinib 60 mg once daily (n = 470) or placebo plus best supportive care (n = 237). Eligible patients had disease progression despite prior treatment with up to two previous systemic treatments for aHCC, one of which had to be sorafenib. Most CELESTIAL patients received cabozantinib as second-line therapy (71%); 29% received it as third-line therapy.

Study therapy was administered until disease progression, or until the development of unacceptable treatment-related toxicity. The trial was stopped at the time of the second interim analysis because of the clear survival benefit demonstrated by cabozantinib compared with placebo. As a result, 31% of patients were censored from the analysis.

2.2. HRQoL assessments

2.2.1. EuroQol five-dimension (EQ-5D) health status assessment

Patients completed hardcopy EQ-5D-5L questionnaires in their native language at baseline, every 4 weeks until week 25, and then every 8 weeks until radiographic progression or discontinuation of study treatment. Patients were asked to complete the questionnaire regardless of whether their study treatment was given, reduced, interrupted or discontinued.

2.2.2. Health utility assessment

Health utility scores were calculated for each patient by applying the EuroQol crosswalk set of utility index (UK-based) values [13] to their EQ-5D-5L health states.

The National Institute for Health and Care Excellence (NICE) recommends use of these values to enable data interpretation from a UK perspective [9]. Crosswalk values are based on the EQ-5D three-level (EQ-5D-3L) valuation that preceded the EQ-5D-5L and are, therefore, consistent with historical analyses. In cancer populations, the minimally important difference (MID) for the EQ-5D utility index has been established as 0.06 using US population preference values and 0.08 using UK population preference values [14].

Two methods were used to analyse patients' health utility scores. The first method – 'analyses including mortality' – carried over the utility score for each patient from their last recorded study status (i.e., last visit, censorship or death) to the end of the follow-up period (i.e., until death or censorship, up to a maximum of 41 months post randomisation). Where the last recorded status was death, a value of zero was applied and carried over. Where the patient's last status was censorship, their last recorded utility value was carried over until the end of follow-up. The second analysis method – 'analyses excluding mortality' – only used direct measures of utility (obtained while patients were alive); no follow-up data were inferred and carried over.

2.2.3. QALY assessment

Health utility scores were plotted over (follow-up) time and QALYs calculated as the area under the curve [15]. The plot of utility score over time was calculated using linear interpolation of all adjacent scores for each patient, conditional on the number of days for that period. The restricted mean QALYs for each treatment group were calculated by summing the QALYs for each patient in the group over the entire follow-up period and dividing the resultant total QALY by the number of patients in the group. As for the EQ-5D utility index, a MID of 0.08 was used for the QALY analysis.

2.3. Sensitivity analysis

A sensitivity analysis was carried out using an alternative health utility value set developed by Devlin and colleagues for EQ-5D-5L health states using a data sample representative of the general population of England [16].

2.4. Statistical analysis

The mean EQ-5D-5L score in each of the five dimensions was derived using a Poisson mixed-model that included baseline value, randomization group and days from randomization as covariates. The analysis included a random intercept term for patient, and the denominator degrees of freedom were derived from the number of patients. The results were expressed as the exponent of the estimate and were analogous to a relative risk. A score of 2, therefore, implied that the value for the cabozantinib group was, on average, twice that of the placebo group.

Health utility differences at each visit were compared using generalized mixed models with identity link and Gaussian error, parameterized to indicate baseline and randomized periods, and including a random intercept term for each patient to allow grouping of their baseline and follow-up observations.

A generalized linear model with identity link and Gaussian error was used to analyse the restricted mean QALYs accrued; the summed health utility score was used as the response variable, and the randomization group was used as the explanatory factor. When the model was adjusted for baseline differences, baseline health utility score was included as an additional patient-level explanatory variable. All analyses were undertaken using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. HRQoL assessments

3.1.1. EQ-5D health status assessment

Questionnaire data were available for 82–100% of patients at each assessment point. Median (interquartile range [IQR]) duration of EQ-5D-5L follow-up was 85 (29–169) days for patients receiving cabozantinib and 56 (27–106) days for those receiving placebo (Table 1).

At baseline, mean EQ-5D-5L scores were higher (with corresponding lower utility scores) for cabozantinib compared to placebo across all five health domains (mobility, self-care, usual activity, pain/discomfort, anxiety/depression, and utility) (Supplementary Table 1). As patients were randomly allocated to cabozantinib and placebo groups, such differences were the result of chance; no statistical tests were conducted. Baseline differences between the treatment groups were accounted for by statistical adjustments in all subsequent analyses.

At the end of follow-up, the mean EQ-5D-5L score was significantly higher (indicating greater disease impact) for the cabozantinib group than for the placebo group for four of the five health dimensions: mobility, self-care, usual activities and pain/discomfort (Table 2).

Table 1
Duration of follow-up for EQ-5D-5L measurements.

Treatment	*N*	Follow-up time, days			
		Median	25th percentile	75th percentile	Maximum
Cabozantinib	469[a]	85	29	169	1086
Placebo	237	56	27	106	786

EQ-5D-5L, EuroQol five-dimension five-level.
[a] Baseline data were missing for 1 patient randomly assigned to cabozantinib treatment.

Table 2
EQ-5D-5L dimensions of health at the end of follow-up.

Dimension	Cabozantinib, mean (SD)	Placebo, mean (SD)	Difference (cabozantinib minus placebo)	Lower 95% CI	Upper 95% CI	*p*
Mobility	1.89 (0.95)	1.54 (0.81)	1.24	1.14	1.34	<0.0001
Self-care	1.45 (0.79)	1.25 (0.62)	1.14	1.04	1.24	0.0033
Usual activities	1.93 (0.95)	1.63 (0.87)	1.20	1.10	1.30	<0.0001
Pain/discomfort	2.18 (0.94)	1.93 (0.91)	1.13	1.06	1.21	0.0005
Anxiety/depression	1.62 (0.81)	1.53 (0.72)	1.07	0.99	1.16	0.1104

CI, confidence interval; EQ-5D-5L, EuroQol five-dimension five-level; SD, standard deviation.

The difference in EQ-5D-5L VAS scores for cabozantinib and placebo at each visit is summarized in Supplementary Table 2. Initially, there was a statistically significant decrement for the cabozantinib group compared to the placebo group, but between-group differences ceased to be statistically or clinically significant from week 33 onwards [14].

3.1.2. Health utility assessment

At baseline, the median (IQR) health utility score was 0.80 (0.70–0.91) for cabozantinib and 0.84 (0.74–1.00) for placebo.

At week 5, there was a statistically significant reduction in mean health utility scores for cabozantinib compared with placebo (difference of −0.097) that exceeded the MID of 0.08 [14]. This decrement in the cabozantinib (versus placebo) group remained statistically significant, but below the MID, at each visit from week 5 to week 21 (Fig. 1). During weeks 25–81, the difference ceased to be statistically significant and switched to favouring cabozantinib at weeks 33, 49 and 65. The confidence intervals around the scores were wide, however, making the true clinical significance of the difference difficult to discern. The number of patients reporting outcome data and the statistical significance at each time point are shown in Supplementary Table 3.

3.1.3. QALY assessment

The initial decline in health utility score in the cabozantinib group was reflected in the lower QALY accrual of this group (versus placebo group) up to day 75 on treatment (Fig. 2; Table 3). By day 150, however, patients receiving cabozantinib had begun to accrue more QALYs than patients in the placebo group and continued to do so until treatment discontinuation.

Restricted mean QALYs accrued during follow-up, after adjustment for between-treatment group differences in baseline health utility scores, are shown in Table 4 [16,17]. The analyses including mortality demonstrated a numerically smaller QALY difference (95% confidence interval) favouring cabozantinib over placebo compared with the analysis excluding mortality: 0.092 (0.016–0.169; p = 0.018) compared with 0.164 (0.111–0.217; p < 0.0001), respectively Table 4 [16,17].

3.2. Sensitivity analysis

Restricted mean QALY accrual for the cabozantinib group was greater (versus placebo) using the Devlin

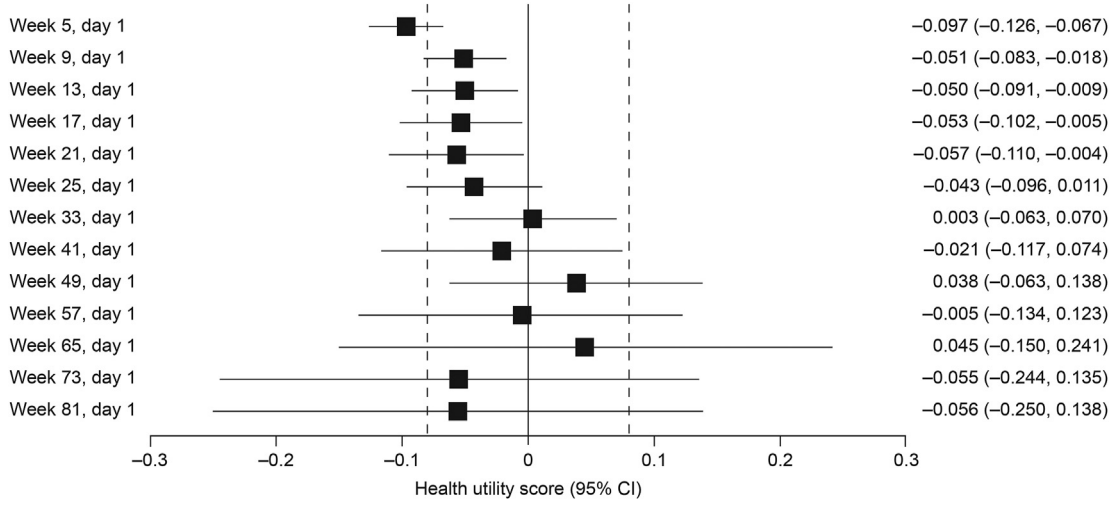

Fig. 1. Differences between cabozantinib and placebo in utilities at each follow-up visit. Utilities were assigned using the crosswalk value set and adjusted for baseline differences. (NB: scores <0 favour placebo). Data are presented as mean and 95% confidence interval. Dashed lines indicate MID threshold of ±0.08. CI, confidence interval; MID, minimally important difference.

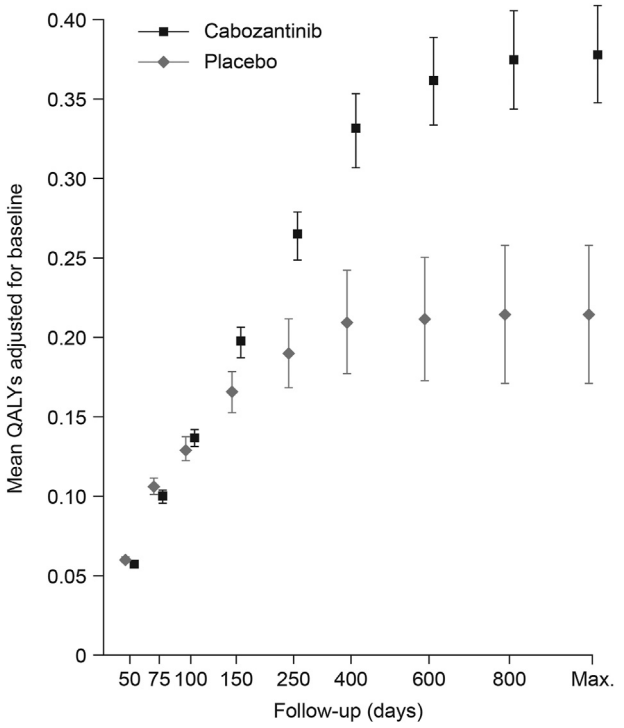

Fig. 2. Mean (95% CI) QALYs[a] accrued at different assessment points with cabozantinib or placebo (analysis excluding mortality). CI, confidence interval; QALY, quality-adjusted life year; Max., maximum follow-up date[b] a QALYs were calculated using the area under the curve of the plot of utility over time, and analyses were adjusted for between-treatment group differences in baseline differences in health utility score. Health utility scores were calculated using the crosswalk value set. [b] The follow-up period continued until death or censorship, up to a maximum of 41 months.

health utility value set than with the crosswalk value set. Overall, QALY accrual in the cabozantinib group was statistically significantly higher than in the placebo group, with a magnitude of difference that exceeded the MID. This finding was consistent for the analyses including and excluding mortality (Table 4) [16,17].

Table 4
Overall differences between cabozantinib and placebo in restricted mean QALYs accrued over the follow-up period calculated using the (primary) crosswalk and (sensitivity) Devlin value sets, adjusted for baseline differences [16,18].

	Mean QALY difference (cabozantinib − placebo)[a]	Lower 95% CI	Upper 95% CI	*p*
Crosswalk value set				
Analysis including mortality	0.092	0.016	0.169	0.018
Analysis excluding mortality	0.164	0.111	0.217	<0.0001
Devlin value set (sensitivity analysis)				
Analysis including mortality	0.115	0.032	0.198	0.007
Ana[a]ysis excluding mortality	0.185	0.126	0.243	<0.0001

CI, confidence interval; QALY, quality-adjusted life year.
[a] Adjusted for between-treatment group differences in baseline health utility scores. Not adjusted for dose reductions and interruptions during follow-up.

4. Discussion

This analysis compared measures of HRQoL for patients with aHCC randomized to receive cabozantinib or placebo after prior sorafenib treatment in the phase 3 CELESTIAL trial [3]. Initial reductions in mean health utility scores for cabozantinib compared with placebo diminished over time and were generally non-significant; overall QALY accrual was greater for the cabozantinib (versus placebo) group.

In the initial weeks of treatment, patients receiving cabozantinib had lower mean health utility scores than those receiving placebo, a decrement that was greater than the MID up to week 5. Thereafter, the difference was less than the MID, and from week 33 onwards, the difference in mean health utility score (cabozantinib minus placebo) diminished, and favoured cabozantinib at later time points (weeks 49 and 65). The transient reduction in health utility score among patients

Table 3
Difference in mean total QALYs accrued at different follow-up times (crosswalk weightings; analysis not including mortality).

Day	Number of patients		Difference (cabozantinib minus placebo)	Lower 95% CI	Upper 95% CI	*p*
	Cabozantinib	Placebo				
50	389	212	−0.003	−0.005	−0.002	≤0.001
75	405	217	−0.006	−0.010	−0.001	0.021
100	410	217	0.007	−0.001	0.015	0.103
150	412	217	0.032	0.017	0.047	≤0.001
250	414	217	0.074	0.049	0.099	≤0.001
400	414	217	0.121	0.082	0.161	≤0.001
600	414	217	0.150	0.103	0.197	≤0.001
800	414	217	0.160	0.108	0.212	≤0.001
Max.	414	217	0.164	0.111	0.217	≤0.001

AUC, area under the curve; CI, confidence interval; max., maximum; QALY, quality-adjusted life year.
Mean total QALYs are based on AUCs. Analysis corrected for baseline utility differences.
Max. corresponds to the entire follow-up period observed.

receiving cabozantinib may have been driven by a higher rate of treatment-emergent adverse events (TEAEs, versus placebo), particularly the grade 3 and 4 TEAEs, during the initial period when tolerability-related dosing adjustments are often made [18]. In CELESTIAL, 62% of patients receiving cabozantinib had at least one dose reduction, with a median time to first dose reduction of 38 days [12]. The most common (any grade) TEAEs reported in CELESTIAL, which may have negatively affected health utility score were: palmar–plantar erythrodysesthesia (22%), diarrhoea (10%), fatigue (7%) [3]. Similar rates of TEAEs have been reported in other trials of cabozantinib (e.g. METEOR) and for other tyrosine kinase inhibitors, such as sorafenib or regorafenib [19–21]. In the phase 3 RESORCE trial of 2L regorafenib versus placebo in patients with HCC who had received prior sorafenib treatment, no significant differences in EQ-5D or Functional Assessment of Cancer Therapy–Hepatobiliary questionnaire scores were reported. The least-squares mean time-adjusted area under the curve analyses for both HRQoL measures, however, were statistically (but not clinically significantly) lower for the regorafenib (versus placebo) group [21]. When interpreting these results, it is relevant to note that sorafenib intolerant patients were excluded from RESORCE, but not from CELESTIAL, resulting in a possible bias towards higher rates of tyrosine kinase inhibitor intolerance in the CELESTIAL population.

Although cabozantinib was associated with an initial reduction in the health utility score compared with placebo, patients receiving cabozantinib benefited from longer overall survival and greater QALY accrual over time. The difference in restricted mean QALY accrual was statistically significant and similar or greater than the MID, supporting a positive benefit–risk profile for cabozantinib. Further analyses by line of therapy were not possible due to insufficient sample sizes.

The sensitivity analysis using the Devlin reference utility value set showed a greater HRQoL benefit (in terms of health utility score and accrued QALYs) with cabozantinib than was shown in the primary (crosswalk) analysis. This may be because the Devlin value set allows full use of the EQ-5D-5L health-status data while the crosswalk values have been adapted from an EQ-5D-3L value set. However, NICE have raised concerns over the validity of the source data used to generate the Devlin value set [9].

Two approaches were used to estimate accrued QALYs for patients who died during the trial; both showed a benefit of cabozantinib over placebo, but both may be subject to potential bias. The method that excluded mortality has the potential to overestimate the treatment effect of cabozantinib on QALYs, while the analysis that included mortality has the potential to underestimate the full QALY accrual (versus placebo) of treatments with proven survival benefit. The latter (more conservative) approach is recommended by NICE and goes some way to mitigating the potential overestimates in the analyses excluding mortality [6].

The results of this HRQoL analysis are limited by the early cessation of CELESTIAL for clinical benefit, which resulted in a truncated follow-up period and the need to 'project' health state values for the remainder of the outcome period for a substantial number of patients. Overall, 9% of patients were censored within 100 days of randomization and 25% of patients in the cabozantinib and placebo groups had less than 5.3 months and 4.3 months of follow-up data, respectively [3]. Towards the end of follow-up, the number of patients with available HRQoL data was also lower in the placebo group than in the cabozantinib group owing to the shorter overall survival among placebo patients; this introduced a potential source of bias and may have compromised the precision of the HRQoL estimates. Another limitation is that utility values were derived using the EQ-5D, a generic measure that may potentially lack sensitivity in patients with cancer [16]. In addition, health-status data were converted to health utility scores using index value sets for the UK, irrespective of their actual country of origin. Furthermore, the primary analysis used the EuroQol crosswalk value set, which was originally developed for use with the EQ-5D-3L questionnaire [10,13]. The consistency of the Devlin analysis and the crosswalk analysis, however, contributes to confidence in the results.

5. Conclusion

This analysis of the HRQoL data from the CELESTIAL trial found that second- or third-line treatment with cabozantinib after sorafenib in patients with aHCC was associated with a small initial reduction in health utility compared with placebo, but that the initial difference quickly ceased to be clinically significant. This finding is consistent with clinical experience where there can be early onset of cabozantinib-related adverse events that are subsequently managed with dose adjustments and/or supportive care.

With prolonged follow up, cabozantinib was associated with a statistically significant and clinically meaningful increase in mean QALYs compared with placebo.

Together with the data demonstrating overall survival benefit with cabozantinib compared with placebo, the present analysis supports a positive benefit–risk profile for cabozantinib in previously treated patients with aHCC.

CRediT author statement

Nick Freemantle: Conceptualization, Methodology, Formal analysis, Writing – Original Draft, Writing – Review & Editing, Visualizatio, **Patrick Mollon:** Conceptualization, Methodology, Formal analysis,

Writing – Original Draft, Writing – Review & Editing, Visualization, **Tim Meyer:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – Review & Editing, Visualization, **Ann-Lii Cheng:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – Review & Editing, Visualization, **Anthony B. El-Khoueiry:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – Review & Editing, Visualization, **Robin Kate Kelley:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – Review & Editing, Visualization, **Ari D. Baron:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – Review & Editing, Visualization, **Fawzi Benzaghou:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – Review & Editing, Visualization, **Milan Mangeshkar:** Conceptualization, Methodology, Formal analysis, Writing – Review & Editing, **Ghassan K. Abou-Alfa:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – Review & Editing, Visualization

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: NF has received research grants (to institution) from the European Association of Cardiothoracic Surgery; consultancy fees from ALK, Allergan, Aimmune, AstraZeneca, Gilead, Grifols, Ipsen, MSD, Novo Nordisk, Novartis, Sanofi Aventis and Vertex; speaker fees from Abbott Singapore and Sanofi Aventis.

PM is an employee of Ipsen.

TM has received research grants from Bayer and BTG; consultancy fees from AstraZeneca, Bayer, Eisai, Ipsen, and Roche.

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Data sharing

Where patient data can be anonymized, Ipsen will share all individual participant data that underlie the results reported in this article with qualified researchers who provide a valid research question. Study documents, such as the study protocol and clinical study report, are not always available. Proposals should be submitted to DataSharing@Ipsen.com and will be assessed by a scientific review board. Data are available beginning 6 months and ending 5 years after publication; after this time, only raw data may be available.

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Appendix A. Supplementary data

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