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Circulating biomarkers and progression of idiopathic pulmonary fibrosis: data from the INMARK trial

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Abstract

Background: We used data from the INMARK trial to investigate associations between circulating biomarkers of extracellular matrix (ECM) turnover, inflammation, and epithelial dysfunction and disease progression in subjects with idiopathic pulmonary fibrosis (IPF).

Methods: Subjects with IPF and FVC ≥80% predicted were randomised 1:2 to receive nintedanib 150 mg bid or placebo for 12 weeks followed by open-label nintedanib for 40 weeks. Associations between baseline biomarker levels and the proportion of subjects with disease progression (decline in FVC ≥10% predicted or death) over 52 weeks were assessed in subjects randomised to placebo using logistic regression. Associations between baseline demographic/clinical characteristics and biomarker levels and disease progression over 52 weeks were analysed using multivariate models.

Results: Of 230 subjects who received placebo for 12 weeks then open-label nintedanib for 40 weeks, 70 (30.4%) had disease progression over 52 weeks. Baseline levels of CRPM, C3M, CRP, KL-6 and SP-D were not significantly associated with disease progression over 52 weeks in analyses corrected for multiple comparisons. In models including only baseline demographic/clinical characteristics, 61.2% to 64.2% of subjects were correctly classified as having or not having disease progression over 52 weeks. When both demographic/clinical characteristics and biomarker levels were included in the models, 50.0% to 64.5% of the test set were correctly classified.

Conclusions: Among subjects with IPF and preserved FVC, multivariate models based on demographic/clinical characteristics and biomarker levels at baseline did not provide an accurate prediction of which patients would progress.

Trial registration: INMARK trial; NCT02788474. Registered 2 June 2016.

Key words: Biomarkers; interstitial lung diseases; fibrosis; inflammation; extracellular matrix

Take-home message: In patients with idiopathic pulmonary fibrosis, multivariate models based on demographic/clinical characteristics and circulating biomarker levels at baseline did not provide an accurate prediction of disease progression over 52 weeks.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing interstitial lung disease (ILD) associated with high mortality [1]. The pathogenesis of IPF is believed to involve activation of epithelial cells in response to injury, which leads to fibroblast migration and proliferation and the differentiation of fibroblasts into myofibroblasts. Extracellular matrix (ECM) components secreted by myofibroblasts accumulate and lead to aberrant remodelling of the lung architecture and the pathology characteristic of fibrosis [2]. IPF is always progressive but varies in its rate of progression. A number of circulating biomarkers, including those associated with ECM turnover, epithelial injury and inflammation, have been associated with disease progression in subjects with IPF [3-11], but their clinical utility remains to be established.

The INMARK trial investigated circulating biomarkers as predictors of disease progression, and the effect of nintedanib on changes in these biomarkers, in subjects with IPF and preserved FVC [12]. The primary results showed that treatment with nintedanib for 12 weeks did not significantly affect the rate of change in C-reactive protein degraded by MMP-1/8 (CRPM) compared with placebo [12]. Among subjects who received placebo for 12 weeks followed by open-label nintedanib for 40 weeks, there was no significant association between the rate of change in CRPM over 12 weeks and disease progression over 52 weeks; however, rising levels of CRPM over 12 weeks were associated with disease progression over 52 weeks [12]. In these analyses, we investigated associations between circulating biomarkers of ECM turnover, inflammation, and epithelial dysfunction at baseline and over 12 weeks of treatment, changes in FVC over 12 weeks, and disease progression over 52 weeks in the INMARK trial.

Methods

Trial design

The design of the INMARK trial has been published [12]. Briefly, the trial enrolled subjects with IPF diagnosed according to the 2011 international guidelines [13] within the previous 3 years and forced vital capacity (FVC) ≥80% predicted. Subjects were randomised 1:2 to receive nintedanib or placebo for 12 weeks, followed by an open-label period in which all subjects received nintedanib for 40 weeks. These analyses were conducted in subjects who were randomized to receive placebo and who received ≥1 dose of trial medication. The INMARK trial was conducted in accordance with the principles of the Declaration of Helsinki and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization and was approved by local authorities. The clinical protocol was approved by an independent ethics committee or institutional review board at each participating center. All patients provided written informed consent before study entry.

Biomarkers

The following biomarkers were assessed as markers of ECM turnover: CRPM, collagen 1 degraded by MMP-2/9/13 (C1M), collagen 3 degraded by MMP-9 (C3M), biglycan degraded by MMP (BGM), collagen 3 degraded by ADAMTS-1/4/8 (C3A), collagen 5 degraded by MMP-2/9 (C5M), collagen 6 degraded by MMP-2/9 (C6M), citrullinated vimentin degraded by MMP-2/8 (VICM), N-terminal propeptide of type III collagen (pro-C3), N-terminal propeptide of type VI collagen (pro-C6), lysyl oxidase-like 2 (LOXL2) and neutrophil-specific elastin fragments (EL-NE). Krebs von den Lungen-6 (KL-6), surfactant protein D (SP-D), CA-125 and CA19-9 were assessed as markers of epithelial injury. C-reactive protein (CRP) and intercellular adhesion molecule 1 (ICAM-1) were assessed as markers of inflammation.

Sample preparation and analysis

For serum samples, blood was collected with anticoagulant-free, gel-containing serum separation tubes and left to clot at room temperature for approximately 1 hour. The serum was separated by centrifugation and aliquoted before freezing. For plasma samples, blood was collected with K2 EDTA plasma tubes and inverted 8 to 10 times. The plasma was separated by centrifugation and aliquoted before freezing. Samples were shipped from a central laboratory to the sponsor or a contractor for analysis. Serum concentrations of each biomarker of ECM turnover were measured using ELISA [14]. Plasma concentrations of KL-6 and SP-D were measured using commercially available ELISA methods with minor adaptations [KL-6: Sanko Junyaku Co., Ltd./EIDIA Co., Ltd.; SP-D: BioVendor]. Serum concentrations of CA-125 were measured using an electrochemiluminescence immunoassay [Beckman DxI 800]. Serum concentrations of LOXL2 were measured using ELISA [Nordic Bioscience]. Plasma concentrations of ICAM-1 and serum concentrations of CA19-9 were measured using electrochemiluminescence immunoassays [ICAM-1: Merck Sharp & Dohme; CA19-9: Roche Cobas e-601].

Analyses

Biomarker data were not normally distributed and were $\log_{10}$ transformed (or negative reciprocal root transformed for C1M) prior to analysis. Relationships between biomarker levels at baseline and the adjusted rate of decline in FVC (mL) over 12 weeks were assessed by analysing the rate of decline in FVC per unit increase in log value of each biomarker. The rate of decline in FVC (mL) over 12 weeks was analysed using a random coefficient regression model (with random slopes and intercepts) including fixed categorical effects of sex, age, height; fixed continuous effects of baseline FVC (mL) and baseline biomarker value and batch number (only for C1M, EL-NE, Pro-C6) as well as baseline FVC−by−time, baseline biomarker−by−time interactions, and batch number−by−time (only for C1M, EL-NE, Pro-C6). Within−patient errors were modelled by an unstructured variance−covariance matrix. P-values were corrected for multiple comparisons using the Benjamini–Hochberg method [15] to control the false discovery rate (FDR) at 5%.

Correlations between changes from baseline in each biomarker at week 4 and changes from baseline in FVC % predicted at week 12 were assessed using the Spearman correlation coefficient (rho), with Fisher's z-transformation and bias correction. Associations between each biomarker and the proportion of subjects with disease progression (decline in FVC ≥10% predicted or death) over 52 weeks were assessed based on: i) baseline biomarker levels, and ii) baseline biomarker levels plus the rate of change in the biomarker over the first 12 weeks. The rate of change in each biomarker was analysed based on the continuous monthly rate of change and based on rising versus stable or falling levels. Associations were analysed using logistic regression with the baseline value of the biomarker as a linear covariate. Analyses including the rate of change in each biomarker had an additional term for continuous monthly rate of change or rising versus stable or falling levels.
Associations were assessed between baseline FVC % predicted, baseline DLco % predicted, and the baseline value of the biomarker and disease progression over 52 weeks based on logistic regression. The covariates included in the model were the baseline values of FVC % predicted, DLco % predicted and each biomarker, all assessed as continuous covariates, plus batch for C1M, EL-NE and pro-C6 (which were analysed in two batches at baseline). P-values based on a log-rank test compared models with and without the baseline value of the biomarker included as a covariate.

Associations between baseline demographic/clinical characteristics (age, sex, body mass index, race, FVC % predicted, DLco % predicted) and the baseline value of the biomarker and disease progression over 52 weeks were analysed using multivariate LASSO (least absolute shrinkage and selection operator) with stability selection across 100 random subsamples of size 0.5 x size of the data set [16] and random forest regression models. Five sets of demographic/clinical characteristics and biomarkers were chosen. The proportions of subjects correctly classified as having or as not having disease progression over 52 weeks were assessed in a training set (approximately two-thirds of the subjects) and then in a test

set (approximately one-third of the subjects). Mean coefficients across the 100 repetitions of the LASSO or importance values of the random forest regression models for the demographic/clinical characteristics and biomarkers selected in each of the five sets were calculated. Demographic/clinical characteristics and biomarkers with selection frequency ≥25% in the LASSO model with stability selection or with importance values ≥2.5 in the random forest model are presented.

Results

Subjects

A total of 230 subjects received placebo in the double-blind period. Their baseline characteristics have been published [12]. In summary, most were male (73.5%), white (62.6%) and ex-smokers (68.7%). At baseline, mean (SD) age was 70.2 (7.2) years, FVC was 98.0 (12.6) % predicted and DLco was 65.5 (21.2) % predicted.

Relationship between biomarker levels at baseline and rate of decline in FVC over 12 weeks

There was no significant relationship between biomarker levels at baseline and the rate of decline in FVC over 12 weeks (mL/12 weeks) (Table 1). For the biomarkers other than C1M, rates of decline in FVC over 12 weeks per unit increase in log value of the biomarker at baseline ranged from −9.8 to 21.9 mL/12 weeks.

Correlations between changes in biomarkers at week 4 and changes in FVC % predicted at week 12

No or weak correlations were observed between changes in biomarker levels at week 4 and changes in FVC % predicted at week 12 (see Table E1 in the online data supplement). Spearman correlation coefficients ranged from −0.01 to −0.20 and from 0.01 to 0.11.

Associations between biomarker levels and disease progression over 52 weeks

Over 52 weeks, 70 subjects (30.4%) had disease progression. In analyses including the baseline biomarker level as a covariate, baseline levels of CRPM (odd ratio [OR] 1.84 [95% CI: 1.04, 3.25]), C3M (OR 2.04 [95% CI: 1.05, 3.94]), CRP (OR 1.21 [95% CI: 1.01, 1.45]), KL-6 (OR 1.43 [95% CI: 1.05 ,1.95]) and SP-D (OR 1.44 [95% CI: 1.06, 1.96]) were significantly associated with disease progression in uncorrected analyses, but not in analyses corrected for multiple comparisons (Table 2). There were no significant associations between baseline biomarker levels and disease progression over 52 weeks in FDR-corrected analyses adjusted for baseline FVC % predicted and DLco % predicted (see Table E2 in the online data supplement). In FDR-corrected analyses including both the baseline level and the continuous rate of change of the biomarker over 12 weeks as covariates, there were no significant associations between baseline levels of biomarkers and disease progression (Table 3). Adding the rate of change over 12 weeks as a covariate had no influence on the associations between baseline biomarker levels and disease progression. There were no significant associations between rising versus stable or falling levels of biomarkers over 12 weeks and disease progression over 52 weeks in FDR-corrected analyses including baseline levels and rising versus stable or falling levels over 12 weeks as covariates (see Table E3 in the online data supplement).

Fold changes from baseline in each biomarker over 12 weeks in subjects with and without disease progression over 52 weeks are shown in Figure E1 in the online data supplement. There were no significant differences between fold changes in biomarkers over 12 weeks between subjects who did and did not have disease progression over 52 weeks, except for EL-NE. Adjusted mean differences in fold changes from baseline in EL-NE between subjects with versus without disease progression were 1.13 (95% CI: 1.01, 1.26) (p=0.026) at week 8 and 1.13 (95% CI: 1.01, 1.27) (p=0.037) at week 12.

Performance of baseline demographic/clinical characteristics and biomarkers in classifying disease progression over 52 weeks

The proportion of subjects correctly classified as having or not having disease progression over 52 weeks in each of the models are presented in Table 4. In models including only baseline demographic/clinical characteristics, 61.2% to 64.2% of the test set were correctly classified. In models including only baseline biomarker values, 42.6% to 65.6% of the test set were correctly classified. When both demographic/clinical characteristics and biomarker values were included, 50.0% to 64.5% of the test set were correctly classified. The factors that were selected in each of the models are summarized in Table E4. When both demographic/clinical characteristics and biomarker values were included, CRP, ICAM-1, C3A and KL-6 were selected. The performance characteristics of the models are summarised in Table 4.

Discussion

Blood-based biomarkers predictive of short-term progression of IPF would be of clinical value. In the INMARK trial in subjects with IPF and preserved FVC, circulating levels of CRPM, C3M, CRP, KL-6 and SP-D at baseline were not significantly associated with disease progression over 52 weeks in analyses corrected for multiple comparisons. Only 50%–65% of subjects in the test set were correctly classified as having or not having disease progression over 52 weeks in multivariable models that included demographic/clinical characteristics and biomarker levels at baseline.

Prior analyses of data from the INMARK trial showed that rising levels of CRPM over 12 weeks were significantly associated with disease progression over 52 weeks [12]. This was consistent with findings from the PROFILE study, which was conducted in antifibrotic drug-naive subjects with IPF who had greater impairment in FVC [3]. CRPM is generated following the degradation of CRP by matrix metalloproteinases 1 and 8 [17], which have been shown to be elevated in patients with IPF [18,19]. The relevance of the relationship between circulating levels of CRP and CRPM in patients with IPF remains unclear.

The heterogeneity of IPF and the complexity of the biological processes that drive fibrosis complicate the search for prognostic biomarkers, especially in the context of anti-fibrotic therapy. Some studies have suggested that a combination of biomarkers, or of biomarkers and clinical variables, may better identify subjects with IPF at risk of short-term progression than individual factors [4,11,20–24]. In a prospective cohort of 185 subjects with newly diagnosed IPF, the higher the number of neoepitopes with baseline concentrations above the median (out of C3M, C6M, pro-C3, pro-C6), the greater the risk of disease progression or death over 6 months [24]. In a retrospective analysis of data from 118 subjects with IPF, prediction of mortality was more accurate when three circulating biomarkers (MMP-7, KL-6, SP-A) were included in multivariate models in addition to clinical parameters (age, baseline FVC, baseline DLco, change in FVC over 6 months) [20]. In another study, an index based on concentrations of osteopontin, periostin, ICAM-1 and MMP-7 in combination with GAP score more accurately predicted disease progression at 12 months than GAP score alone [23]. However, in our analyses, the addition of baseline biomarker values to multivariate models did not appear to improve the proportion of subjects who were correctly classified as having disease progression over 52 weeks compared with models based on demographic/clinical variables alone. To date, no model for predicting the progression of IPF based on circulating biomarkers has been adequately validated. The challenges of identifying circulating biomarkers that are robustly associated with the progression of IPF using a targeted approach has generated interest in unbiased approaches, such as those based on machine learning or artificial intelligence, but it remains unclear whether such approaches will be more successful [25].

Strengths of our analyses include the prospective design of the INMARK trial that had a 12-week double-blind placebo-controlled period, the inclusion of patients who were naïve to antifibrotic therapy and the assessment of a broad spectrum of biomarkers reflective of ECM remodelling, epithelial injury and inflammation. A limitation of our analyses is that 12 weeks might be too short a period to observe meaningful changes in FVC; thus, correlations

between changes in biomarkers and changes in FVC over 12 weeks may be less informative than changes over a longer period. It should also be noted that all the subjects in the INMARK trial had preserved FVC (FVC ≥80% predicted) at baseline. It is possible that the observations relating to progression over 52 weeks were confounded by patients receiving 9 months of antifibrotic therapy. It is possible that the associations between biomarker levels and disease progression may be different in subjects with more advanced disease or in those who are treatment-naive.

In conclusion, among patients with IPF and preserved FVC in the INMARK trial multivariate models based on a combination of demographic/clinical characteristics and biomarker levels at baseline did not provide an accurate prediction of which patients would progress. Further studies are required to inform the clinical utility of blood biomarkers in subjects with IPF.

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Authors' contributions: TMM, RGJ, VC, YN, IN, MS, SSt, and ESW contributed to the study design. TMM, VC, and YN contributed to data acquisition. CI conducted the data analysis. All authors contributed to the interpretation of the data and to the writing and critical review of this manuscript. All authors read and approved the final manuscript.

Data availability: To ensure independent interpretation of clinical study results and enable authors to fulfil their roles and obligations under the ICMJE criteria, Boehringer Ingelheim

grants all authors access to relevant clinical study data. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data, typically one year after the approval has been granted by major regulatory authorities or after termination of the development programme. Researchers should use https://vivli.org/ to request access to study data and visit https://www.mystudywindow.com/msw/datasharing for further information.

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Table 1. Relationships between baseline biomarker levels and the rate of decline in FVC over 12 weeks.

Biomarker	**N**	**Estimate for relationship between baseline biomarker level and rate of FVC decline over 12 weeks (95% CI)***	**p-value**	**FDR-corrected p-value**
CRPM, ng/mL	228	21.9 (−14.3, 58.0)	0.23	1.00
C1M, ng/mL	227	191.7 (−555.0, 938.4)	0.61	1.00
C3M, ng/mL	228	8.8 (−28.6, 46.1)	0.64	1.00
BGM, ng/mL	226	−8.2 (−36.9, 20.5)	0.57	1.00
C3A, ng/mL	228	0.0 (−25.1, 25.2)	1.00	1.00
C5M, ng/mL	226	−2.6 (−44.1, 38.9)	0.90	1.00
C6M, ng/mL	225	−9.8 (−38.2, 18.5)	0.49	1.00
VICM, ng/mL	228	6.1 (−23.3, 35.4)	0.68	1.00
Pro-C3, ng/mL	220	6.1 (−30.9, 43.1)	0.75	1.00
Pro-C6, ng/mL	218	2.4 (−61.7, 66.4)	0.94	1.00
LOXL2, ng/mL	170	−5.6 (−27.5, 16.3)	0.61	1.00
EL-NE, ng/mL	226	4.2 (−35.7, 44.1)	0.84	1.00
KL-6, U/mL	229	−0.4 (−15.5, 14.8)	0.96	1.00
SP-D, ng/mL	228	6.3 (−10.0, 22.6)	0.45	1.00
CA-125, U/mL	154	5.8 (−25.0, 36.6)	0.71	1.00
CA 19-9, U/mL	141	11.6 (−6.6, 29.7)	0.21	1.00
CRP, mg/L	221	−9.8 (−32.5, 12.9)	0.40	1.00
ICAM-1, ng/mL	228	5.7 (−11.0, 22.4)	0.50	1.00

*Estimates represent the rate of decline in FVC (mL) over 12 weeks per unit increase in log (or negative reciprocal root transformed for C1M) value of the biomarker at baseline. Negative estimates indicate a greater rate of decline in FVC in patients with a higher biomarker value at baseline.

Table 2. Associations between baseline levels of biomarkers and disease progression over 52 weeks.

Biomarker	**Odds ratio (95% CI) for disease progression for baseline level**
CRPM, ng/mL	1.84 (1.04, 3.25)*
C1M, ng/mL	27.53 (0.10, >999.99)
C3M, ng/mL	2.04 (1.05, 3.94)*
BGM, ng/mL	1.21 (0.88, 1.66)
C3A, ng/mL	1.20 (0.70, 2.06)
C5M, ng/mL	0.89 (0.58, 1.36)
C6M, ng/mL	1.13 (0.80, 1.59)
VICM, ng/mL	0.98 (0.77, 1.24)
Pro-C3, ng/mL	1.05 (0.61, 1.80)
Pro-C6, ng/mL	0.97 (0.62, 1.53)
LOXL2, ng/mL	1.11 (0.81, 1.53)
EL-NE, ng/mL	0.85 (0.63, 1.13)
KL-6, U/mL	1.43 (1.05 ,1.95)*
SP-D, ng/mL	1.44 (1.06, 1.96)*
CA-125, U/mL	0.98 (0.66, 1.46)
CA 19-9, U/mL	1.07 (0.88, 1.31)
CRP, mg/L	1.21 (1.01, 1.45)*
ICAM-1, ng/mL	1.53 (0.74, 3.18)

*$p<0.05$ in uncorrected analyses. $p>0.05$ in FDR-corrected analyses.

Table 3. Associations between baseline levels plus continuous rate of change in biomarkers over 12 weeks and disease progression over 52 weeks.

Biomarker	**Odds ratio (95% CI) for disease progression for baseline level**
CRPM, ng/mL	2.00 (1.10, 3.65)*
C1M, ng/mL	26.39 (0.005, >999.99)
C3M, ng/mL	2.65 (1.07, 6.58)*
BGM, ng/mL	1.50 (0.95, 2.37)
C3A, ng/mL	1.22 (0.70, 2.10)
C5M, ng/mL	0.90 (0.59, 1.38)
C6M, ng/mL	1.14 (0.76, 1.70)
VICM, ng/mL	0.99 (0.78, 1.25)
Pro-C3, ng/mL	1.04 (0.60, 1.80)
Pro-C6, ng/mL	0.83 (0.49, 1.39)
LOXL2, ng/mL	1.18 (0.81, 1.72)
EL-NE, ng/mL	0.93 (0.67, 1.30)
KL-6, U/mL	1.47 (1.07, 2.01)*
SP-D, ng/mL	1.42 (1.04, 1.94)*
CA-125, U/mL	0.97 (0.66, 1.44)
CA 19-9†, U/mL	1.07 (0.88, 1.31)
CRP†, mg/L	1.21 (1.01, 1.45)*
ICAM-1, ng/mL	1.55 (0.75, 3.22)

*$p<0.05$ in uncorrected analyses. $p>0.05$ in FDR-corrected analyses. †Model includes only baseline levels of the biomarker since no individual slopes could be estimated in the placebo group.

Table 4. Performance of multivariate models for classifying subjects in the test set as having or not having disease progression over 52 weeks.

	All biomarkers at baseline (n=32)	**Selected biomarkers* at baseline (n=61)**	**Demographic/ clinical characteristics at baseline (n=67)**	**Demographic/ clinical characteristics and all biomarkers at baseline (n=31)**	**Demographic/ clinical characteristics and selected biomarkers* at baseline (n=58)**
LASSO					
Subjects correctly classified as not having disease progression	14 (43.8)	26 (42.6)	31 (46.3)	13 (41.9)	18 (31.0)
Subjects correctly classified as having disease progression	7 (21.9)	8 (13.1)	10 (14.9)	5 (16.1)	11 (19.0)
Total subjects correctly classified	21 (65.6)	34 (55.7)	41 (61.2)	18 (58.1)	29 (50.0)
Sensitivity	5.0	44.4	43.5	35.7	61.1
Specificity	77.8	60.5	70.5	76.5	45.0
Positive predictive value	63.6	32.0	43.5	55.6	33.3
Negative predictive value	66.7	72.2	70.5	59.1	72.0
LASSO (with selection frequency ≥25%)					
Subjects correctly classified as not having disease progression	–	16 (26.2)	34 (50.7)	–	24 (41.4)
Subjects correctly classified as having disease progression	–	10 (16.4)	9 (13.4)	–	8 (13.8)

Total subjects correctly classified	–	26 (42.6)	43 (64.2)	–	32 (55.2)
Sensitivity	–	55.6	39.1	–	44.4
Specificity	–	37.2	77.3	–	60.0
Positive predictive value	–	27.0	47.4	–	33.3
Negative predictive value	–	66.7	70.8	–	70.6
Random forest					
Subjects correctly classified as not having disease progression	17 (53.1)	34 (55.7)	43 (64.2)	17 (54.8)	31 (53.4)
Subjects correctly classified as having disease progression	1 (3.1)	4 (6.6)	0	3 (9.7)	1 (1.7)
Total subjects correctly classified	18 (56.3)	38 (62.3)	43 (64.2)	20 (64.5)	32 (55.2)
Sensitivity	7.1	22.2	0	21.4	5.6
Specificity	94.4	79.1	97.7	100	77.5
Positive predictive value	50.0	30.8	0	100	10.0
Negative predictive value	56.7	70.8	65.2	60.7	64.6

Data are n (%) of subjects or %. *BGM, C1M, C3A, C3M, C5M, C6M, CRP, CRPM, ICAM-1, KL-6, pro-C3, pro-C6, SP-D and VICM were selected as these biomarkers had an adequate number of samples for statistical testing.

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Table E1. Correlations between change from baseline in each biomarker at week 4 and change from baseline in FVC % predicted at week 12.

	Placebo
CRPM, n	220
Spearman coefficient (95% CI)	−0.04 (−0.17, 0.09)
p-value	0.53
C1M, n	221
Spearman coefficient (95% CI)	−0.05 (−0.19, 0.08)
p-value	0.42
C3M, n	210
Spearman coefficient (95% CI)	−0.05 (−0.19, 0.08)
p-value	0.44
BGM, n	218
Spearman coefficient (95% CI)	0.11 (−0.03, 0.24)
p-value	0.11
C3A, n	221
Spearman coefficient (95% CI)	−0.01 (−0.15, 0.12)
p-value	0.83
C5M, n	219
Spearman coefficient (95% CI)	−0.08 (−0.22, 0.05)
p-value	0.21
C6M, n	201
Spearman coefficient (95% CI)	−0.04 (−0.18, 0.10)
p-value	0.54
VICM, n	221
Spearman coefficient (95% CI)	−0.14 (−0.26, 0.00)
p-value	0.044
Pro-C3, n	208
Spearman coefficient (95% CI)	0.01 (−0.13, 0.14)
p-value	0.91

Pro-C6, n	207
Spearman coefficient (95% CI)	−0.03 (−0.17, 0.11)
p-value	0.66
LOXL2, n	154
Spearman coefficient (95% CI)	−0.10 (−0.25, 0.06)
p-value	0.23
EL-NE, n	220
Spearman coefficient (95% CI)	−0.06 (−0.19, 0.07)
p-value	0.38
KL-6, n	220
Spearman coefficient (95% CI)	−0.08 (−0.21, 0.05)
p-value	0.24
SP-D, n	221
Spearman coefficient (95% CI)	−0.10 (−0.23, 0.03)
p-value	0.13
CA-125, n	112
Spearman coefficient (95% CI)	−0.07 (−0.25, 0.12)
p-value	0.48
CRP, n	212
Spearman coefficient (95% CI)	−0.20 (−0.32, −0.06
p-value	0.0037
ICAM-1, n	221
Spearman coefficient (95% CI)	−0.17 (−0.30, −0.04)
p-value	0.011

Table E2. Association between baseline FVC % predicted, DLco % predicted and biomarker values, and disease progression over 52 weeks.

Biomarker	Subjects with baseline biomarker value, n	Subjects with disease progression, %	Odds ratio (95% CI) for baseline FVC % predicted	Odds ratio (95% CI) for baseline DLco % predicted	Odds ratio (95% CI) for baseline biomarker level
CRPM, ng/mL	228	30.3	1.02 (1.00, 1.05)	0.99 (0.98, 1.01)	1.75 (0.99, 3.27)
C1M, ng/mL	227	30.4	1.03 (1.00, 1.05)	0.99 (0.97, 1.00)	27.7 (0.1, 11418)
C3M, ng/mL	228	30.3	1.02 (1.00. 1.05)	0.99 (0.98, 1.01)	1.91 (1.00, 3.82)*
BGM, ng/mL	226	30.5	1.02 (1.00, 1.05)	0.99 (0.98, 1.01)	1.14 (0.83, 1.60)
C3A, ng/mL	228	30.3	1.02 (1.00, 1.05)	0.99 (0.98, 1.01)	1.06 (0.65, 1.99)
C5M, ng/mL	226	30.5	1.02 (1.00, 1.05)	0.99 (0.98, 1.00)	0.89 (0.58, 1.39)
C6M, ng/mL	225	30.7	1.02 (1.00, 1.05)	0.99 (0.98, 1.01)	1.06 (0.74, 1.51)
VICM, ng/mL	228	30.3	1.02 (1.00, 1.05)	0.99 (0.98, 1.00)	0.99 (0.78, 1.25)
Pro-C3, ng/mL	220	30.9	1.03 (1.00, 1.05)	0.99 (0.98, 1.01)	1.07 (0.62, 1.85)
Pro-C6, ng/mL	218	30.7	1.03 (1.00, 1.05)	0.99 (0.98, 1.01)	0.97 (0.61, 1.53)
LOXL2, ng/mL	170	32.9	1.02 (0.99, 1.05)	0.99 (0.97, 1.00)	1.06 (0.76, 1.48)
EL-NE, ng/mL	226	30.5	1.03 (1.00, 1.05)	0.99 (0.97, 1.00)	0.81 (0.60, 1.08)
KL-6, U/mL	229	30.6	1.03 (1.00, 1.05)	1.00 (0.98, 1.01)	1.50 (1.07, 2.12)*
SP-D, ng/mL	228	30.3	1.03 (1.00, 1.05)	1.00 (0.98, 1.01)	1.49 (1.07, 2.12)*
CA-125, U/mL	154	32.5	1.04 (1.01, 1.07)	0.99 (0.98, 1.01)	0.97 (0.65, 1.47)
CA 19-9, U/mL	141	29.8	1.03 (1.00, 1.06)	1.00 (0.98, 1.01)	1.10 (0.90, 1.36)
CRP, mg/L	221	31.2	1.03 (1.00, 1.05)	1.00 (0.98, 1.01)	1.23 (1.01, 1.51)*
ICAM-1, ng/mL	228	30.3	1.03 (1.00, 1.05)	0.99 (0.98, 1.01)	1.62 (0.75, 3.55)

*$p<0.05$ in uncorrected analyses. $p>0.05$ in FDR-corrected analyses.

Table E3. Associations between baseline plus rising versus stable/falling levels of biomarkers over 12 weeks and disease progression over 52 weeks.

Biomarker	**Odds ratio (95% CI) for disease progression**	
	for baseline level	**for rising vs stable/falling levels**
CRPM, ng/mL	2.12 (1.18, 4.12)*	1.87 (1.02, 3.44)*
C1M, ng/mL	10.77 (0.02, >999.99)	1.37 (0.50, 3.76)
C3M, ng/mL	2.30 (1.10, 5.04)*	1.24 (0.63, 2.45)
BGM, ng/mL	1.14 (0.81, 1.64)	0.78 (0.41, 1.50)
C3A, ng/mL	1.17 (0.73, 2.20)	0.71 (0.36, 1.35)
C5M, ng/mL	0.89 (0.59, 1.39)	1.04 (0.58, 1.85)
C6M, ng/mL	1.28 (0.88, 1.88)	2.62 (0.80, 8.54)
VICM, ng/mL	0.98 (0.77, 1.24)	0.89 (0.47, 1.73)
Pro-C3, ng/mL	1.05 (0.61, 1.80)	1.04 (0.57, 1.86)
Pro-C6, ng/mL	0.99 (0.62, 1.58)	1.06 (0.57, 1.98)
LOXL2, ng/mL	1.05 (0.75, 1.50)	0.76 (0.38, 1.52)
EL-NE, ng/mL	0.78 (0.57, 1.07)	0.64 (0.32, 1.27)
KL-6, U/mL	1.48 (1.08, 2.04)*	1.37 (0.77, 2.49)
SP-D, ng/mL	1.44 (1.07, 1.97)*	0.92 (0.51, 1.67)
CA-125, U/mL	0.96 (0.65, 1.44)	1.62 (0.76, 3.60)
CA 19-9, U/mL	1.07 (0.88, 1.31)	NC
CRP, mg/L	1.21 (1.02, 1.45)*	NC
ICAM-1, ng/mL	1.57 (0.76, 3.31)	0.81 (0.45, 1.45)

*p<0.05 in uncorrected analyses. p>0.05 in FDR-corrected analyses. NC, not calculated (no individual slopes could be estimated in the placebo group).

Table E4. Mean coefficients or importance values for the baseline characteristics and biomarkers selected in multivariate models.

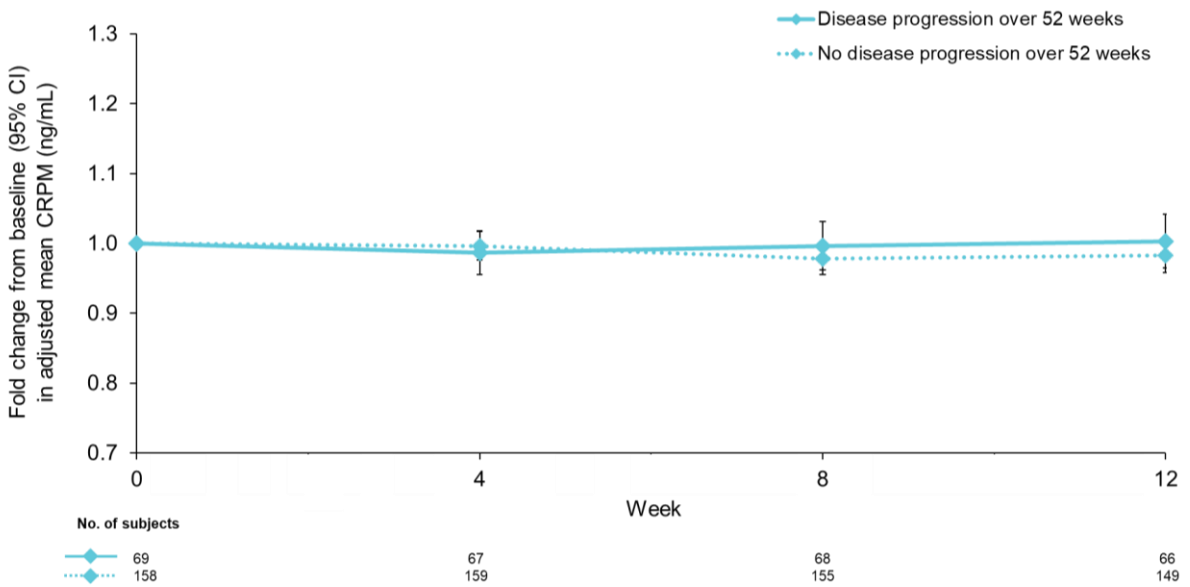
	All biomarkers at baseline		**Selected biomarkers* at baseline**		**Demographic/ clinical characteristics at baseline**		**Demographic/clinical characteristics and all biomarkers at baseline**		**Demographic/clinical characteristics and selected biomarkers* at baseline**	
	Variable selected	Mean coefficient or importance value	Variable selected	Mean coefficient or importance value	Variable selected	Mean coefficient or importance value	Variable selected	Mean coefficient or importance value	Variable selected	Mean coefficient or importance value
LASSO	No variables with selection frequency ≥25%		SP-D	0.13	Sex	0.19	No variables with selection frequency ≥25%		C3M	0.13
			C3M	0.09	Race	0.12			BMI	−0.22
					BMI	−0.10			Sex	0.12
									CRP	0.15
									SP-D	0.09
									ICAM-1	0.08
									FVC % predicted	0.10
Random forest	CRP	10.0	SP-D	10.0	Sex	10.0	CRP	10.0	C3M	10.0
	C3M	6.7	CRPM	8.6	Race	4.5	ICAM-1	2.7	ICAM-1	9.3
	SP-D	5.6	KL-6	3.9	FVC % predicted	4.3	C3A	2.6	FVC % predicted	8.9
	C6M	4.8	C3M	3.4			KL-6	2.6	Sex	6.0

	VICM	4.7	C3A	3.3				CRPM	5.3
	BGM	2.8	C6M	2.6				BMI	5.3
	Pro-C3	2.6						KL-6	3.9
								CRP	3.7
								Race	2.7

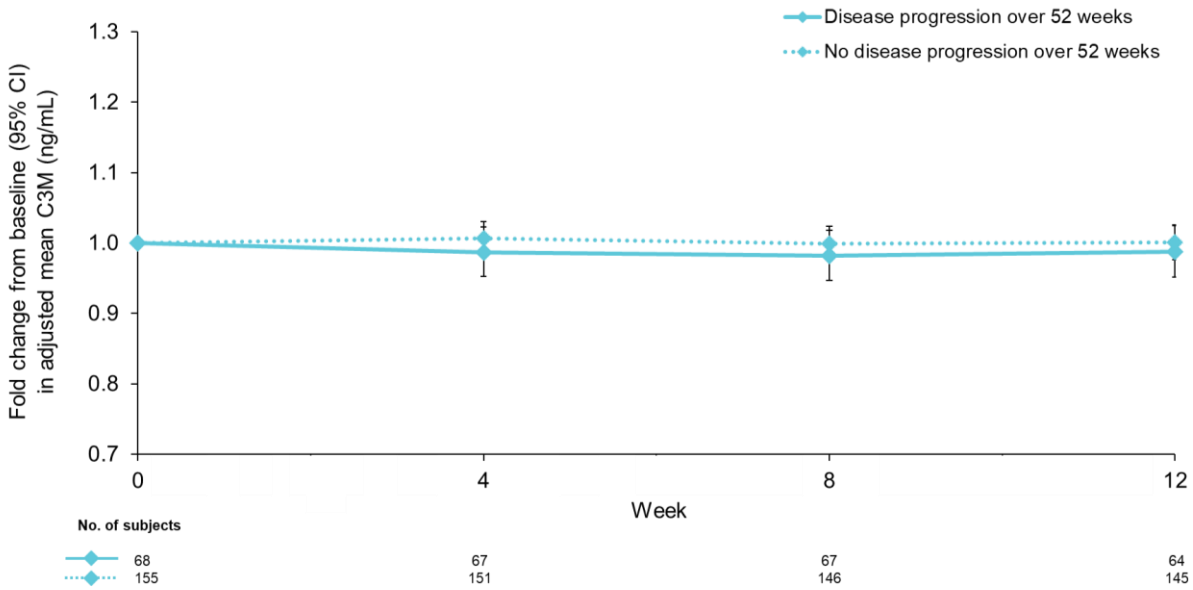
*BGM, C1M, C3A, C3M, C5M, C6M, CRP, CRPM, ICAM-1, KL-6, pro-C3, pro-C6, SP-D and VICM were selected as these biomarkers had an adequate number of samples for statistical testing. Variables had selection frequency ≥25% in the LASSO model with stability selection or importance values ≥2.5 in the random forest model. Importance values were standardized to a range from 0 to 10, *i.e.,* displayed according to their position within this range.

Figure E1. Fold change in each biomarker over 12 weeks in subjects with and without disease progression over 52 weeks.

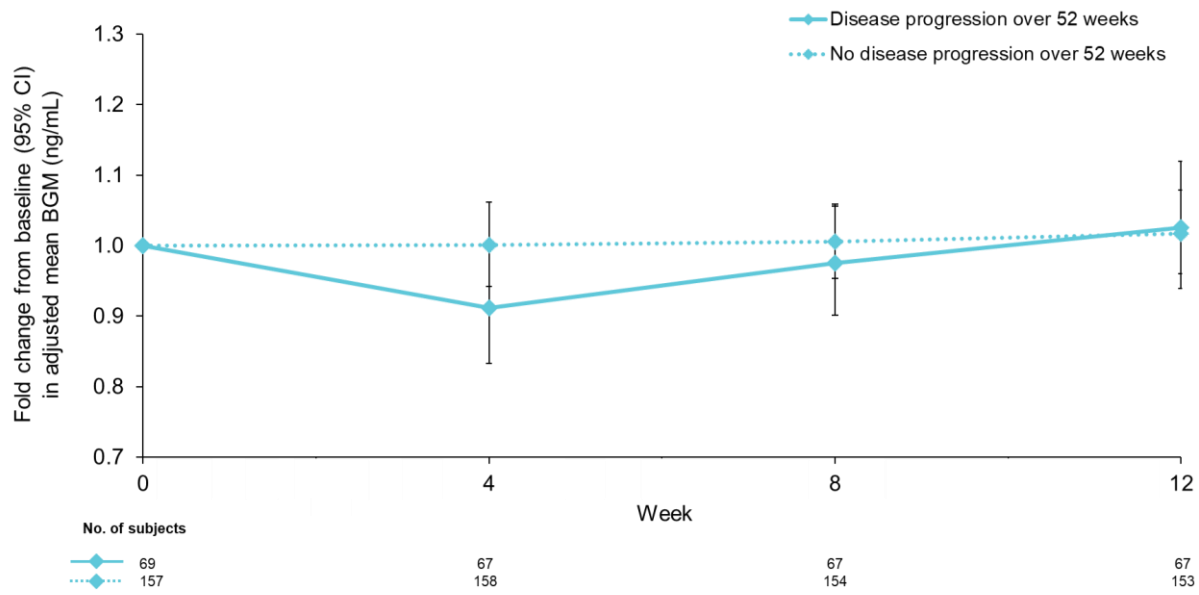
CRPM



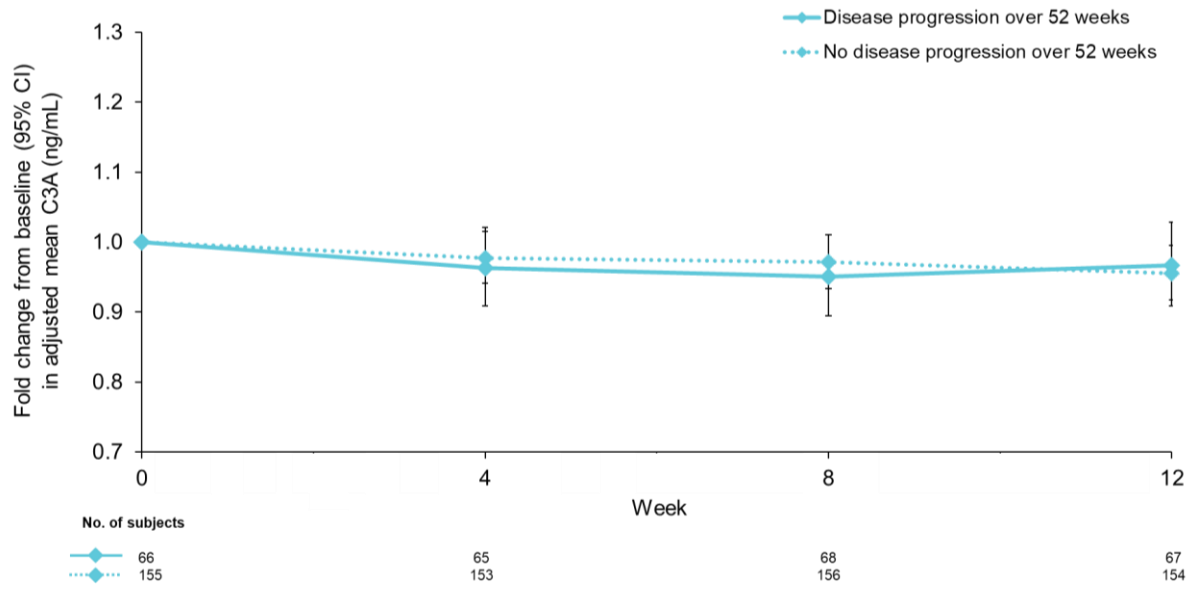
C3M



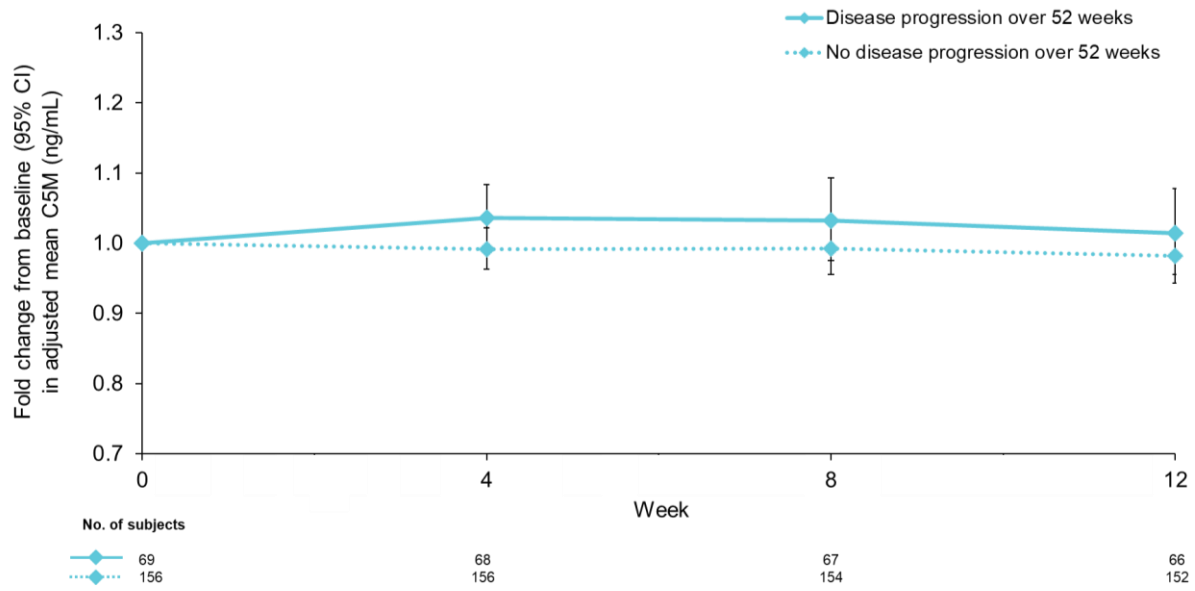
BGM


Disease progression over 52 weeks
No disease progression over 52 weeks
Fold change from baseline (95% CI) in adjusted mean BGM (ng/mL)
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0
4
8
12
Week
No. of subjects
69
157
67
158
67
154
67
153

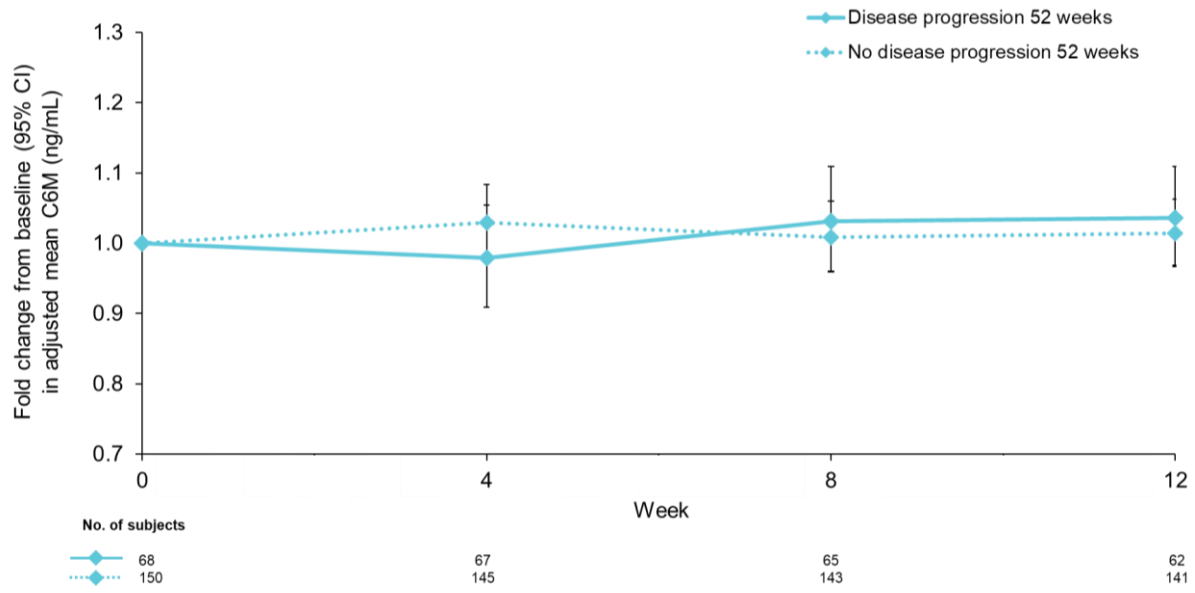
C3A


Disease progression over 52 weeks
No disease progression over 52 weeks
Fold change from baseline (95% CI) in adjusted mean C3A (ng/mL)
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0
4
8
12
Week
No. of subjects
66
155
65
153
68
156
67
154

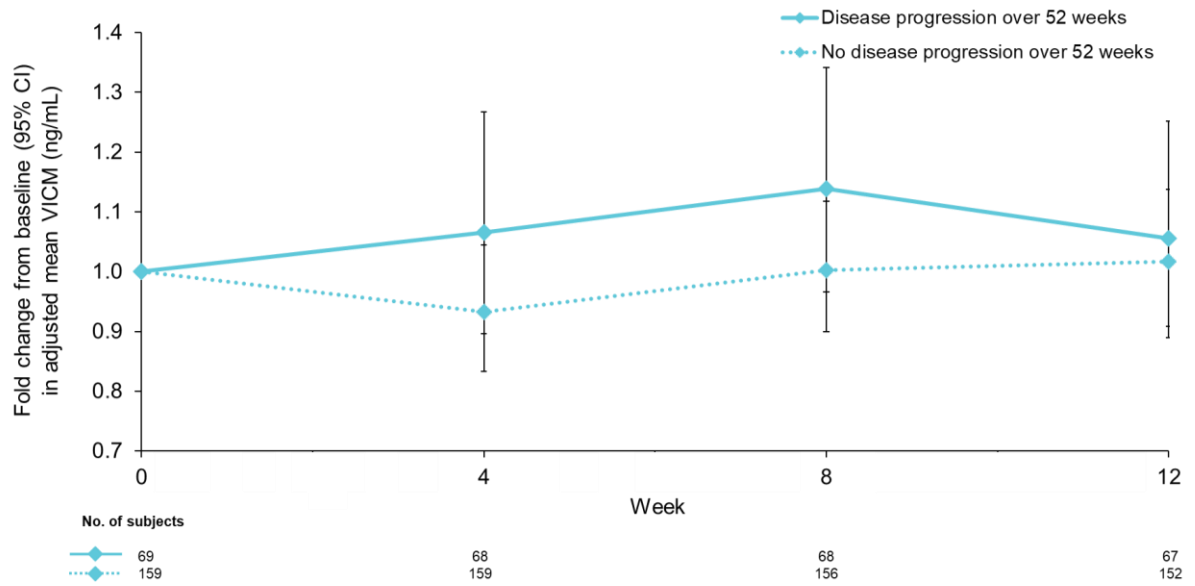
C5M


Disease progression over 52 weeks
No disease progression over 52 weeks
Fold change from baseline (95% CI) in adjusted mean C5M (ng/mL)
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0
4
8
12
Week
No. of subjects
69
156
68
156
67
154
66
152

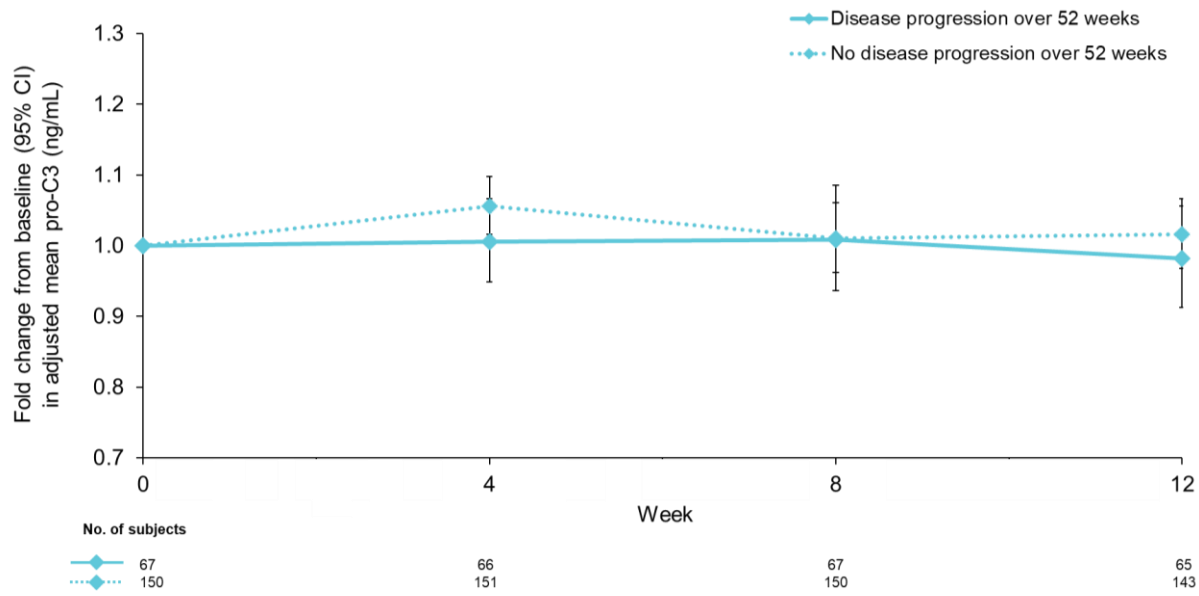
C6M


Disease progression 52 weeks
No disease progression 52 weeks
Fold change from baseline (95% CI) in adjusted mean C6M (ng/mL)
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0
4
8
12
Week
No. of subjects
68
150
67
145
65
143
62
141

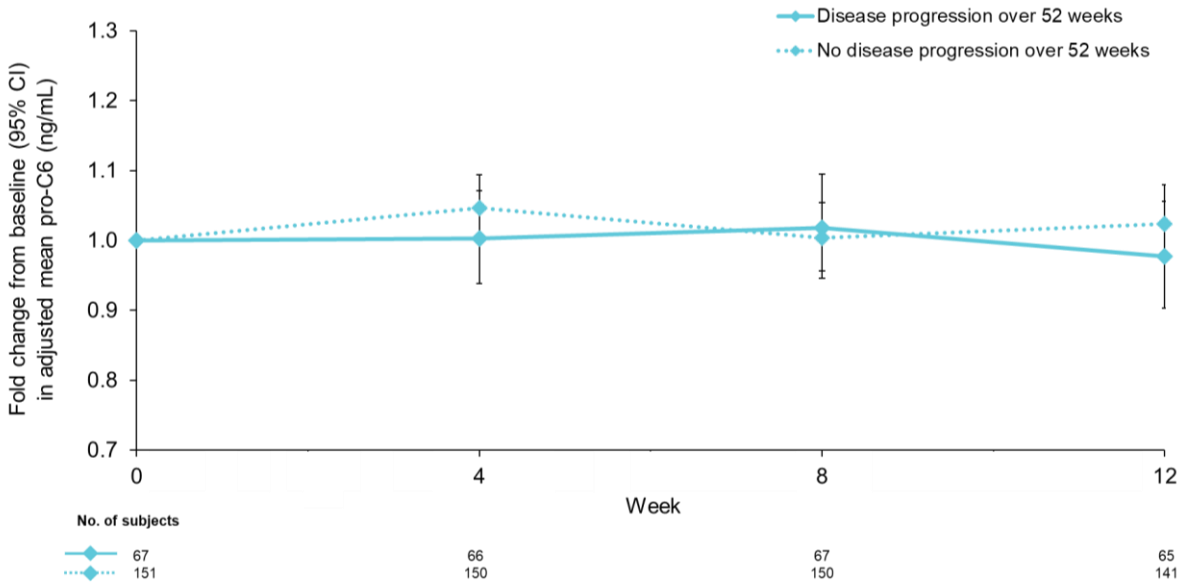
VICM


Disease progression over 52 weeks
No disease progression over 52 weeks
Fold change from baseline (95% CI) in adjusted mean VICM (ng/mL)
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0
4
8
12
Week
No. of subjects
69
159
68
159
68
156
67
152

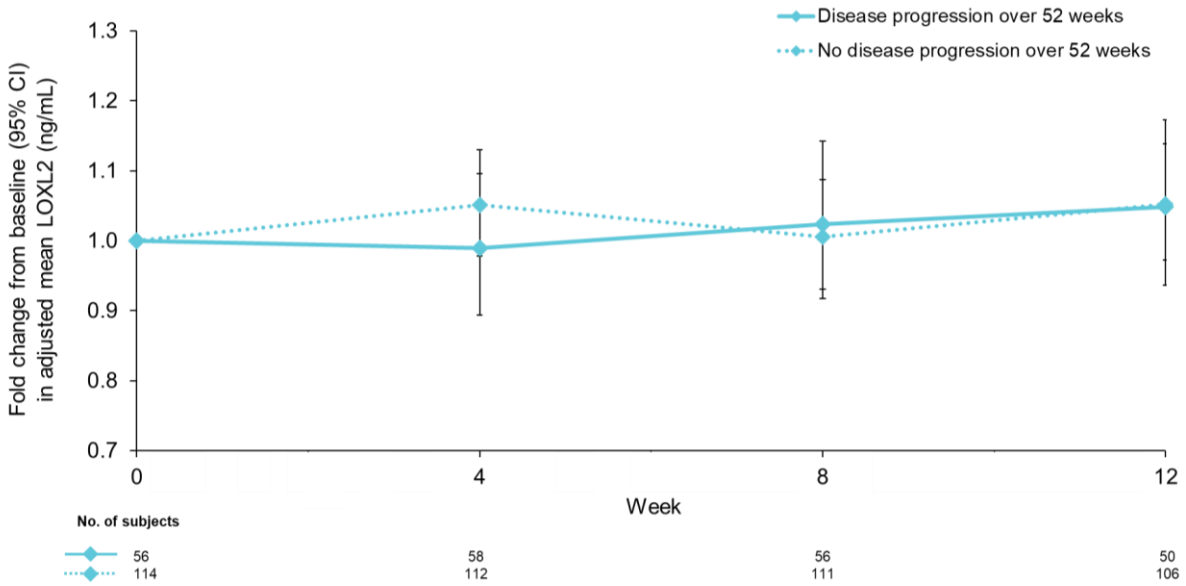
Pro-C3


Disease progression over 52 weeks
No disease progression over 52 weeks
Fold change from baseline (95% CI) in adjusted mean pro-C3 (ng/mL)
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0
4
8
12
Week
No. of subjects
67
150
66
151
67
150
65
143

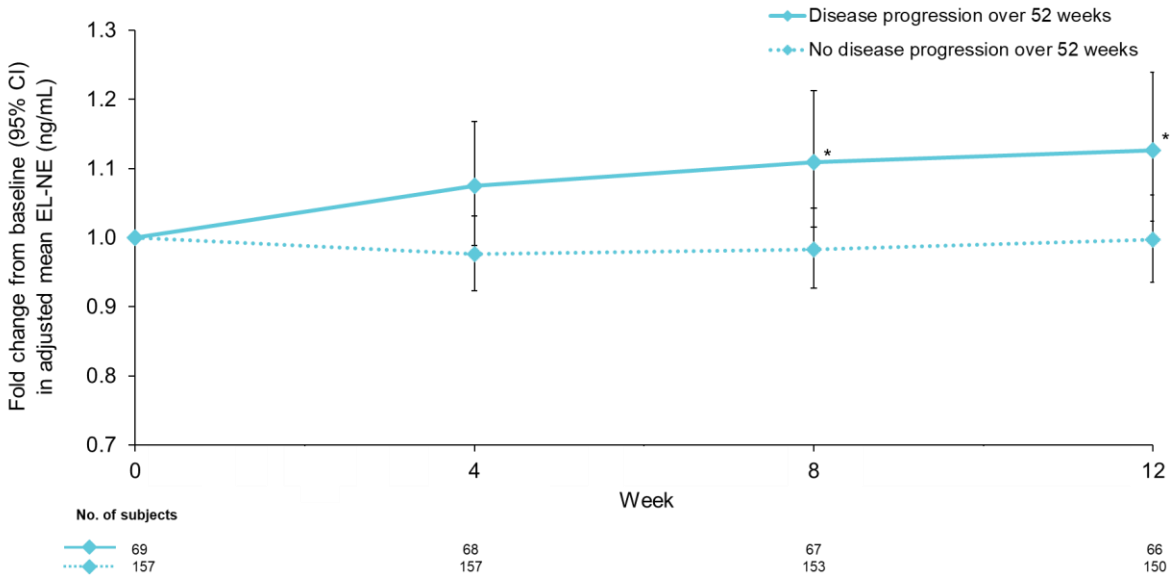
Pro-C6


Disease progression over 52 weeks
No disease progression over 52 weeks
Fold change from baseline (95% CI) in adjusted mean pro-C6 (ng/mL)
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0
4
8
12
Week
No. of subjects
67
151
66
150
67
150
65
141

LOXL2

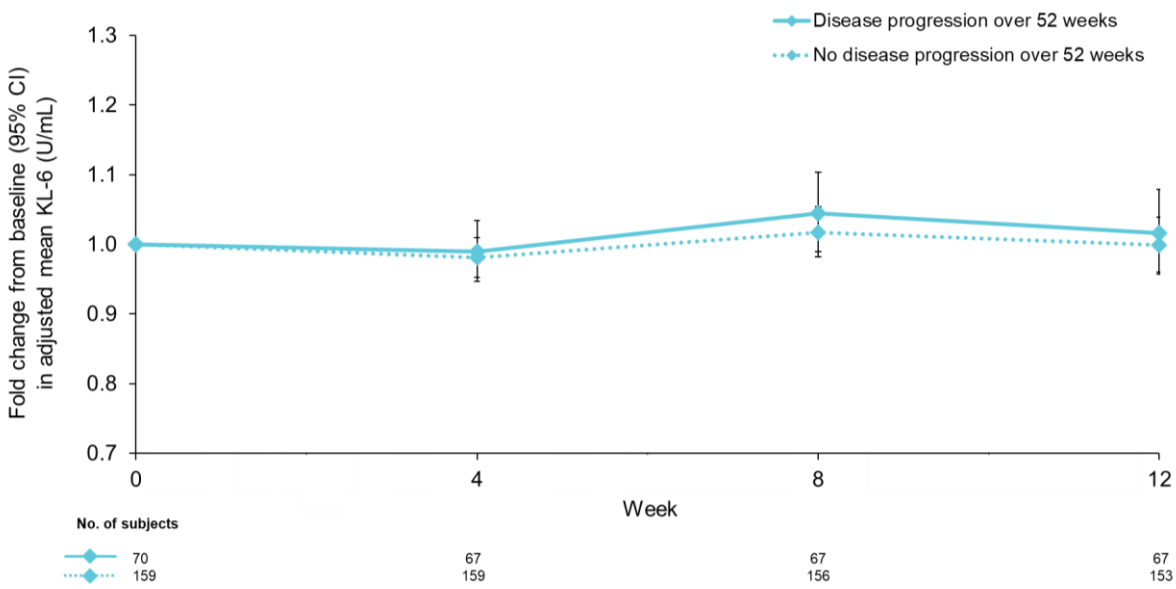

Disease progression over 52 weeks
No disease progression over 52 weeks
Fold change from baseline (95% CI) in adjusted mean LOXL2 (ng/mL)
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0
4
8
12
Week
No. of subjects
56
114
58
112
56
111
50
106

EL-NE

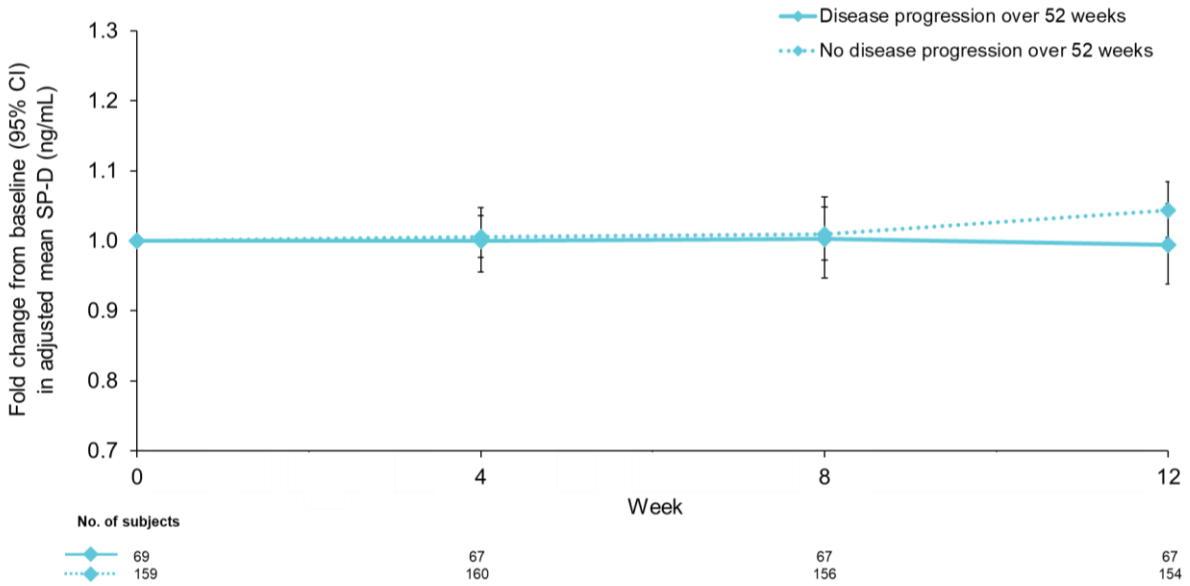


*p<0.05 for the comparison with no disease progression.

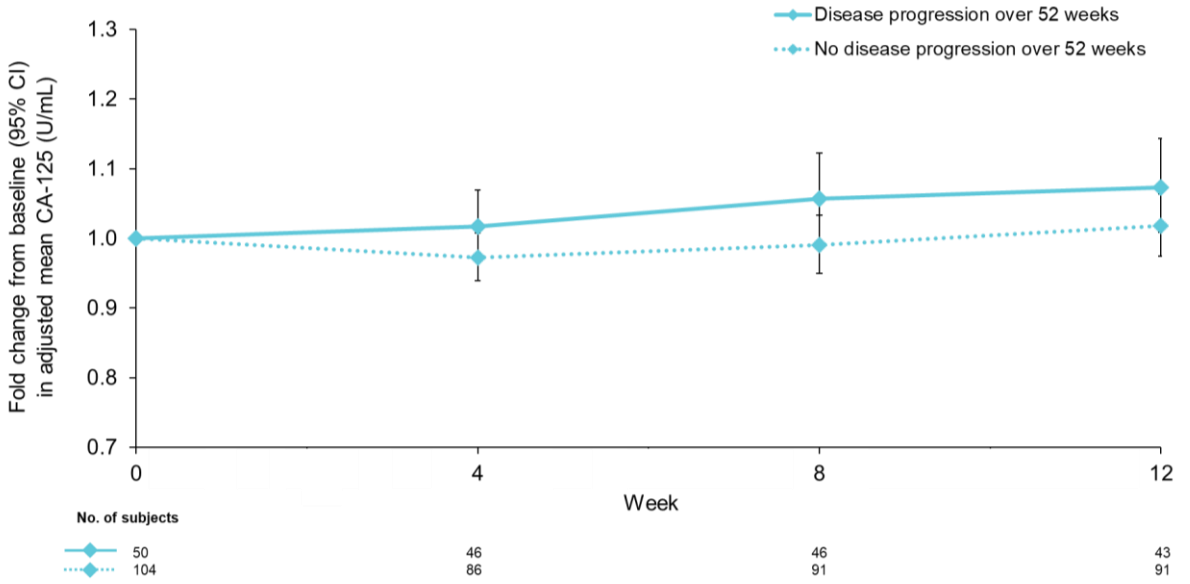
KL-6



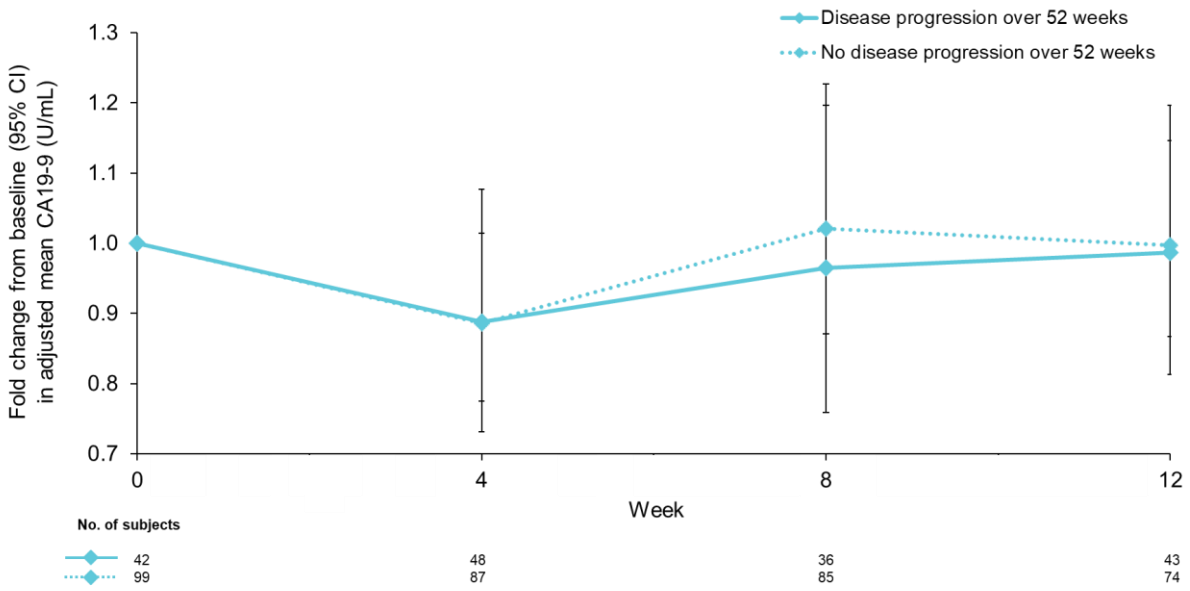
SP-D


Disease progression over 52 weeks
No disease progression over 52 weeks
Fold change from baseline (95% CI) in adjusted mean SP-D (ng/mL)
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0
4
8
12
Week
No. of subjects
69
159
67
160
67
156
67
154

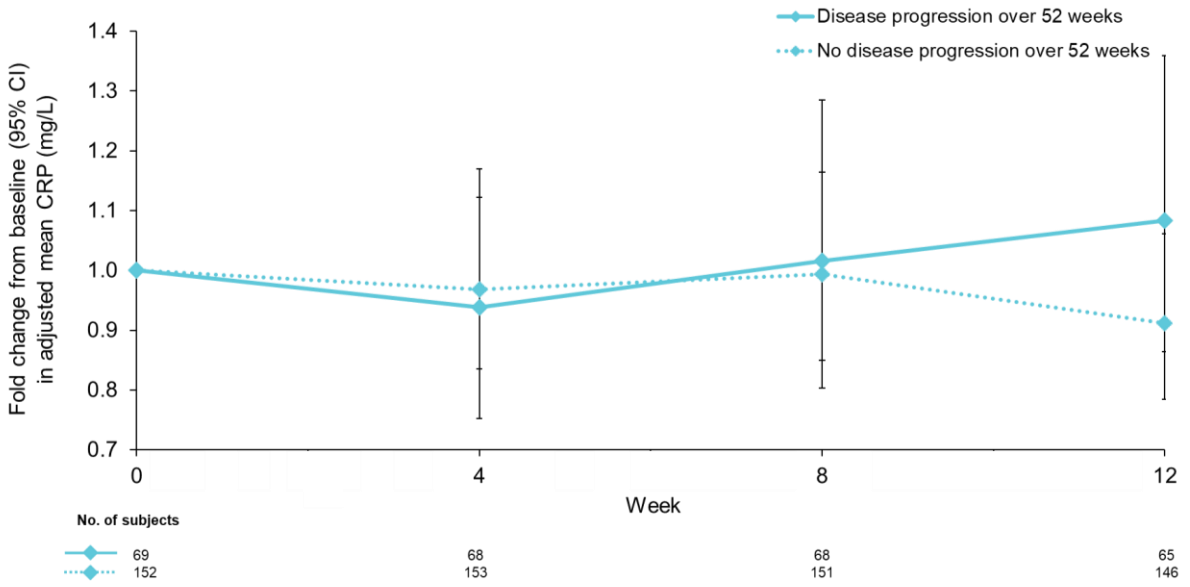
CA-125


Disease progression over 52 weeks
No disease progression over 52 weeks
Fold change from baseline (95% CI) in adjusted mean CA-125 (U/mL)
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0
4
8
12
Week
No. of subjects
50
104
46
86
46
91
43
91

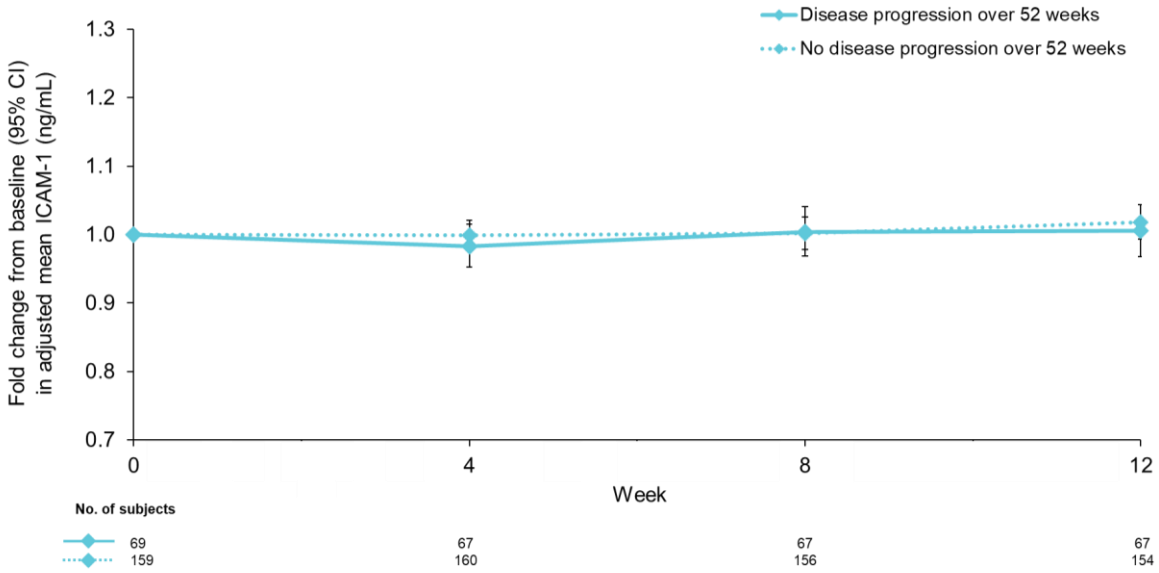
CA19-9


Disease progression over 52 weeks
No disease progression over 52 weeks
Fold change from baseline (95% CI) in adjusted mean CA19-9 (U/mL)
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0
4
8
12
Week
No. of subjects
42
48
36
43
99
87
85
74

CRP


Disease progression over 52 weeks
No disease progression over 52 weeks
Fold change from baseline (95% CI) in adjusted mean CRP (mg/L)
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0
4
8
12
Week
No. of subjects
69
68
68
65
152
153
151
146

ICAM-1


Disease progression over 52 weeks
No disease progression over 52 weeks
Fold change from baseline (95% CI) in adjusted mean ICAM-1 (ng/mL)
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0
4
8
12
Week
No. of subjects
69
159
67
160
67
156
67
154