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# Prospective Study of Drug-induced Interstitial Lung Disease in Advanced Breast Cancer Patients Receiving Everolimus Plus Exemestane

Annelieke E. C. A. B. Willemsen<sup>1</sup> · Jolien Tol<sup>2</sup> · Nielka P. van Erp<sup>3</sup> · Marianne A. Jonker<sup>4</sup> · Maaike de Boer<sup>5</sup> · Bob Meek<sup>6</sup> · Paul C. de Jong<sup>7</sup> · Coline van Moorsel<sup>6,8</sup> · Winald R. Gerritsen<sup>1</sup> · Jan C. Grutters<sup>6,8</sup> · Carla M. L. van Herpen<sup>1</sup>

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## Abstract

**Background** Everolimus-related interstitial lung disease (ILD) (also: pneumonitis) poses a difficulty for physicians, as it is hard to discriminate ILD from other causes of respiratory symptoms and to decide on safe treatment continuation.

**Objective** We investigated the capability of pulmonary function tests (PFT), plasma biomarkers, everolimus pharmacokinetics, and FDG-PET to discriminate between everolimus-related ILD and other causes of respiratory problems and to predict the severity of ILD.

**Patients and methods** Women starting treatment with everolimus plus exemestane for advanced breast cancer were included. At baseline and during the first 3 months, respiratory symptoms, PFT with diffusion capacity of the lungs for carbon monoxide corrected for hemoglobin (DLCOc) and forced vital capacity, serum plasma biomarkers (including SP-D and YKL-40), everolimus trough concentration, and <sup>18</sup>F-FDG-PET were prospectively recorded.

**Results** Twenty-seven (out of 29 included) patients were evaluable for analysis. Fifteen patients (56%) developed everolimus-related respiratory signs or symptoms and four patients (15%) needed everolimus discontinuation and received corticosteroids. Change in DLCOc differentiated ILD from alternative diagnoses with 0.91 sensitivity and 0.78 specificity. Decrease in DLCOc (non-significant) was greatest in patients who needed everolimus discontinuation. Serum SP-D and YKL-40 could differentiate ILD from alternative diagnoses with 0.83 and 0.83 sensitivity, and 0.85 and 0.62 specificity, respectively. <sup>18</sup>F-FDG-PET abnormalities did not precede clinical symptoms. No relationship between ILD and everolimus trough concentration was found.

**Conclusions** This study shows that everolimus-related ILD occurs frequently. Prospective monitoring of DLCOc in combination with measurement of serum SP-D and YKL-40 appear useful to discriminate ILD from other causes of respiratory symptoms. Clinicaltrials.gov identifier: NCT01978171.

## 1 Introduction

In the past decades many novel anti-cancer agents including targeted therapies and immune checkpoint inhibitors have been developed, resulting in significant improvement of treatment outcomes [1, 2]. These new treatments are associated with specific toxicities, including pulmonary toxicities,

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✉ Carla M. L. van Herpen  
carla.vanherpen@radboudumc.nl

Extended author information available on the last page of the article

### Key Points

This is the first study to prospectively investigate drug-induced interstitial lung disease and the value of diverse diagnostic biomarkers to discriminate ILD from alternate diagnoses.

Diffusion capacity and the plasma biomarkers YKL-40 and SP-D can differentiate everolimus-induced ILD from alternate causes.

A rapid decrease in diffusion capacity could be an indication of severe ILD needing treatment discontinuation.

that require adequate management to prevent serious morbidity and even mortality [3, 4]. Interstitial lung disease (ILD), or non-infectious pneumonitis, is an adverse event of special importance, as it is often hard to discriminate between different causes of respiratory symptoms as well as to decide on safe treatment continuation.

An anticancer drug that is associated with frequent occurrence of ILD is the mTOR inhibitor everolimus, with a reported incidence of ILD varying between 3 and 54% [5]. In a meta-analysis of 4,242 cancer patients treated with mTOR inhibitors, the incidence of any grade pneumonitis was 11%, any grade dyspnea 15%, and any grade cough 23% [6]. It is important to note that mTOR inhibitor-induced ILD can be very serious, as respiratory insufficiency and even fatal cases have been described [7–9]. mTOR inhibitor-induced ILD is suspected to be of immunological origin, possibly by exposure of cryptic antigens, delayed-type hypersensitivity, or by an increase in proinflammatory cytokines [10–13].

Everolimus plus exemestane is a valuable treatment option for patients with advanced breast cancer (ABC), but ILD is amongst the most common high-grade adverse events and is a frequent cause of treatment discontinuation [14–17]. In the BOLERO-2 trial, 10% of patients required everolimus dose interruption or reduction because of ILD [18].

Cough and dyspnea are reported frequently and may have several causes, including opportunistic infections such as *Pneumocystis jirovecii* pneumonia [19]. In patients with everolimus-induced ILD it is hard to predict whether or not treatment can be continued safely. Biomarkers leading to better recognition of ILD and to improved prediction of its severity are lacking, but would be of significant clinical value. Biomarkers that may contribute to this are pulmonary function tests (PFTs), plasma biomarkers, everolimus pharmacokinetics, and [<sup>18</sup>F]-fluorodeoxyglucose positron emission tomography with integrated computed tomography (FDG-PET). Two small retrospective studies have shown an association between mTOR inhibitor-induced ILD and a decline in diffusing capacity of the lung for carbon monoxide (DLCO) [20, 21]. In other ILDs, plasma biomarkers such as surfactant protein A (SP-A), surfactant protein D (SP-D), CC16, CCL18, YKL-40, lactate dehydrogenase (LDH), and cancer antigen (CA) 15-3 correlate with pulmonary inflammation [22–27]. Previous studies have demonstrated that a high everolimus trough concentration is associated with a higher risk of toxicity [14, 28]. Increased FDG-avidity in the lungs on FDG-PET scans has been reported in several patients with drug-induced ILD such as bleomycin, rituximab, etoposide, and paclitaxel, mostly as diffuse bilateral FDG-accumulation [29–35]. FDG-PET has been reported to detect ILD earlier than high resolution computed tomography [36]. Therefore, this may be an early marker of ILD.

It is not known yet if PFT can discriminate ILD from other causes or can predict its severity. Also, no biomarkers

in the blood are known to predict or monitor the development and severity of drug-induced ILD. Furthermore, it is not known whether there is an exposure-effect relationship in the development of everolimus-induced ILD, as the pathophysiological mechanism of everolimus-induced ILD is not known.

A prospective analysis of any form of drug-induced ILD following patients from the start of treatment has not been performed yet. In the current study, we prospectively investigated in ABC patients receiving everolimus plus exemestane whether PFT, plasma biomarkers, everolimus trough concentrations, and FDG-PET could discriminate everolimus-induced ILD from other respiratory problems. Furthermore, we determined whether changes in PFT are indicative of the severity of ILD.

## 2 Methods

### 2.1 Patients

The present investigation (PREVENT study) was a prospective, open-label, observational, explorative study carried out in three hospitals in the Netherlands. The study protocol was approved by the Radboudumc ethics committee (reference number 2013-285) and all patients gave written informed consent. Clinicaltrials.gov identifier: NCT01978171.

We included postmenopausal women with ABC before the start of treatment with everolimus plus exemestane. Planned enrollment was 100 patients to guarantee the presence of enough cases of ILD. No formal power analysis was done as this was an exploratory study. Recruitment was considerably slower than anticipated due to reduced use of this treatment when data became available that no survival benefit was demonstrated. Furthermore, CDK4/6 inhibitors became available as an alternative line of treatment. For this reason and considering the high frequency of ILD already observed in the study participants, the study was closed early.

### 2.2 Clinical Evaluation

Patients were evaluated at baseline and at days 14, 35, 60, 90, and 120 after start of therapy. At each visit adverse events were recorded using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Using clinical symptoms, PFT, and imaging, patients were classified as having airway disease, suspected ILD, ILD, or an alternative diagnosis (Table 1), as described in detail previously [5]. In case of respiratory symptoms, infectious analysis was performed with chest X-ray, sputum culture,

PCR for respiratory viruses, serology for atypical pneumonia (*Mycoplasma pneumoniae*, *Chlamydia psittaci*), and legionella antigen test in urine. In case of possible opportunistic infection, a bronchoalveolar lavage for *Pneumocystis jirovecii* pneumonia was performed.

### 2.3 Pulmonary Function Tests (PFTs)

PFTs were performed according to ATS/ERS criteria at every scheduled visit until day 120 and additionally when respiratory symptoms occurred. Forced vital capacity (FVC in liters) and single breath diffusion capacity of the lungs for carbon monoxide (DLCO in mmol/min/kPa) were measured. DLCO was corrected for hemoglobin (DLCOc) [37].

### 2.4 Plasma Biomarkers

Blood was drawn at every scheduled visit until day 120 and at the occurrence of new respiratory symptoms. More information on the measurements is provided in the Electronic Supplementary Methods. Considering the variation in absolute values between individuals, the ratio of plasma biomarkers relative to the baseline value was used.

### 2.5 FDG-PET and Pharmacokinetics

Patients could choose to participate in the FDG-PET imaging part or not. FDG-PET was performed at baseline, day

14, and day 35 after start of treatment. Scans were qualitatively judged by a nuclear medicine physician for FDG-avid abnormalities consistent with ILD. The temporal relationship between FDG-abnormalities and clinical symptoms was evaluated.

Everolimus trough concentrations were measured in whole blood at day 14, 24 h after everolimus administration, by a validated liquid chromatography tandem mass spectrometry technique.

### 2.6 Statistics

To compare groups of patients, for each patient we used the PFT or plasma biomarker measurement at the first moment of the patient's highest severity classification (ILD > suspected ILD > alternative diagnosis > airway disease > no respiratory signs). For patients without respiratory symptoms, the value of PFT closest to the moment of median onset of ILD was used (day 65). Data were analyzed qualitatively, as described in the Electronic Supplementary Methods.

Using a Mann–Whitney *U* test, the change in PFT was compared between patients with everolimus-related (suspected) ILD and patients with respiratory signs due to an alternative diagnosis. Using a Mann–Whitney *U* test, plasma biomarkers were compared between patients with (suspected) ILD and patients without respiratory symptoms, with airway disease, or with respiratory symptoms due to

**Table 1** Diagnostic classification of respiratory symptoms [5]

CTCAE grade <sup>a</sup> (dyspnea, cough, fever)	PFT decline <sup>b</sup>	Chest CT parenchymal abnormalities	Infectious analysis	Conclusion <sup>c</sup>
0	Non-significant	Absent	–	No ILD
		Present	–	Suspected ILD
	Significant	Absent	General	Inconclusive
		Present	General + consider BAL	ILD
1 or 2	Non-significant	Absent	General	Airway disease
		Present	General + consider BAL	Suspected ILD
	Significant	Absent	General + consider BAL	Suspected ILD
		Present	General + BAL	ILD
3 or 4	Non-significant	Absent	General + consider BAL	Inconclusive
		Present	General + BAL	ILD
	Significant	Absent	General + BAL	Inconclusive
		Present	General + BAL	ILD

CTCAE Common Terminology Criteria for Adverse Events, PFT pulmonary function test, ILD interstitial lung disease, BAL bronchoalveolar lavage, DLCOc diffusion capacity of the lungs for carbon monoxide corrected for hemoglobin

<sup>a</sup>CTCAE pneumonitis NOT included

<sup>b</sup>Significant PFT decline defined as: DLCOc corrected for Hb decline  $\geq 2$  SD compared to baseline AND/OR FVC decline  $\geq 2$  SD compared to baseline

<sup>c</sup>Provided that other possible diagnoses are considered or excluded, such as pulmonary infection, congestive heart failure, pulmonary embolism, carcinomatous lymphangitis or pleuritis, radiation recall pneumonitis, asthma bronchiale, or gastroesophageal reflux

other causes. A receiver-operating-characteristic (ROC) curve analysis was performed, with calculation of the area under the curve (AUC), and testing whether this AUC significantly differed from 0.50. An optimal cut-off value was determined using the Youden index (value with highest sum of sensitivity + specificity – 1) [38]. Sensitivity, specificity, and negative and positive predictive value were calculated.

In patients with (suspected) ILD, the change in DLCOc and FVC at the first moment of the highest classification was compared between patients with and without the need for everolimus discontinuation. In patients who discontinued everolimus due to (suspected) ILD, it was visually evaluated whether discontinuation was preceded by a rise in plasma biomarkers.

As this was an exploratory and hypothesis-generating analysis, no correction for multiple testing was performed.

### 3 Results

#### 3.1 Patients

Between April 2014 and October 2017, 29 subjects were enrolled. Almost all patients who were eligible for the study did participate in the study. Two patients were a screen failure (in one patient after informed consent it was decided to start a different treatment and in the other patient informed consent was withdrawn due to a decline of general wellbeing), and 27 patients could be analyzed. Population demographics are described in Table 2.

#### 3.2 Respiratory Symptoms

From the 27 patients included, 15 patients (56%) developed everolimus-related respiratory problems (symptoms or DLCOc or CT abnormalities): three patients were classified as ILD, 11 with suspected ILD (two patients were asymptomatic, but with CT abnormalities consistent with ILD), and one with airway disease. Eight patients (30%) had an alternative diagnosis (four progression of malignant pleural effusion, three suspected viral respiratory infection, one *Pneumocystis jirovecii* pneumonia). Four patients (15%) had no respiratory symptoms. Details of the classification are described in Electronic Supplementary Table 1.

Median time to onset of (suspected) ILD was 65 days (range 32–119). Four patients discontinued treatment because of (suspected) ILD and were treated according to protocol with prednisolone 60 mg/day followed by tapering, for a mean duration of 69 days (range 50–95) and everolimus was discontinued permanently. In three of these patients corticosteroids were started at the diagnosis of ILD and discontinuation of everolimus, and in

one patient corticosteroids were started 10 days later. This resulted in clinical improvement in all cases. From the four patients who discontinued treatment because of (suspected) ILD, one patient had a history of pulmonary problems (asthma), one patient was a previous smoker, and one patient previously underwent radiation of the breast, but pulmonary abnormalities in this patient were bilateral. In these patients, there was a clear increase in pulmonary symptoms compared to baseline, therefore the symptoms were not attributable to an increase of the pre-existent problems.

#### 3.3 PFTs

Due to logistical reasons no PFTs were done in three patients at day 60 and in three patients at day 90. In the four patients who discontinued everolimus due to (suspected) ILD, DLCOc was better correlated with ILD than FVC. In three out of these four patients, a  $\geq 2$  SD decrease in DLCOc preceded the diagnosis of ILD (Fig. 1). In two out of these four patients the PFT decline was considered significant according to the diagnostic protocol. No other patients had a significant PFT decline.

**Table 2** Population demographics

Characteristic	
Age (years; median and range)	62 (35–76)
Race	All Caucasian
Eastern Cooperative Oncology Group Performance Status score (n, %)	
0	18/27 (67)
1	8/27 (30)
2	1/27 (4)
Follow-up time (days, median)	95
Current or ex-smokers (n)	8/27
History of pulmonary disease (n)	3
Chronic obstructive pulmonary disease	1
Asthma bronchiale	1
Bronchiectases	1
History of radiation of the breast region (n, %)	15/27 (56%)
Number of previous treatments (mean)	
In adjuvant setting	1.1
In metastatic setting	2.1
Total	3.2
Lymphocyte count < 500/mm <sup>3</sup> during treatment	1 patient at two time-points

### 3.3.1 PFTs to Discriminate (Suspected) Interstitial Lung Disease (ILD) from an Alternative Diagnosis in Patients with Respiratory Symptoms

The median decrease in FVC was 0.21L (8%) in the 14 patients with everolimus-related (suspected) ILD, compared to 0.20 L (6%) in the eight patients with respiratory symptoms due to an alternative cause ( $p=0.328$  and  $p=0.328$ , respectively). DLCOc decrease was 1.02 mmol/min/kPa (16%) in everolimus-related (suspected) ILD versus a 0.10 mmol/min/kPa increase (1%) in patients with other causes ( $p=0.004$  and  $p=0.005$ , respectively) (Fig. 2). ROC analysis using the absolute decrease in DLCOc to predict (suspected) ILD showed an AUC of 0.90 ( $p=0.003$ ). At the optimal cut-off point of a 0.16 mmol/min/kPa decrease in DLCOc, this had a sensitivity of 0.92 and a specificity of 0.86, with a positive and negative predictive value of 0.92 and 0.86, respectively. Alternatively, if a cut-off of a  $>0.0$  mmol/min/kPa DLCOc change is used to diagnose alternative causes and a  $>1.0$  mmol/min/kPa DLCOc decrease for (suspected) ILD, 67% of patients can be diagnosed and this is correct in 93% of cases.

### 3.3.2 PFTs to Predict the Need for Treatment Discontinuation in Patients with (Suspected) ILD

Patients with (suspected) ILD with the need for treatment discontinuation showed a stronger DLCOc decrease compared to patients without the need for discontinuation (Fig. 3a, b), but this difference was not statistically significant. The median slopes of the 6 weeks before day zero were  $-0.042$  and  $-0.00063$ , respectively. However, the DLCOc decrease was not statistically significantly different in patients with ( $-1.78$  mmol/min/kPa, 27%) versus without ( $-0.73$  mmol/min/kPa, 14%) everolimus discontinuation ( $p=0.26$  and  $p=0.15$ , respectively). No significant difference was observed in FVC decrease in patients with (0.21 L, 7%) or without everolimus discontinuation (0.19 L, 8%), ( $p=0.70$  and  $p=0.94$ , respectively).

### 3.3.3 Correlation between Diffusion Capacity of the Lungs For Carbon Monoxide Corrected for Hemoglobin (DLCOc) Decrease and Severity of Respiratory Symptoms

In the total group of patients as well as in the group of patients with (suspected) ILD, no significant correlation

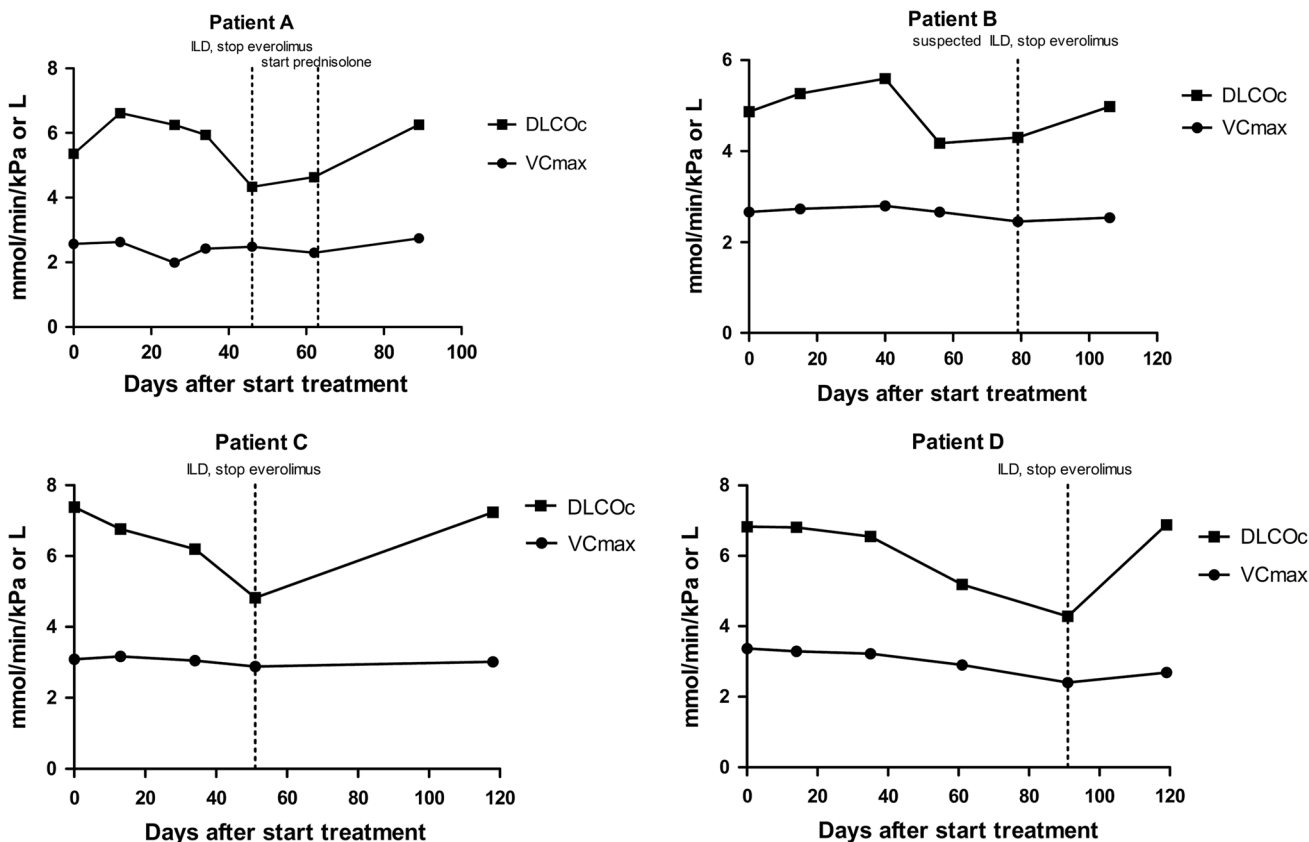
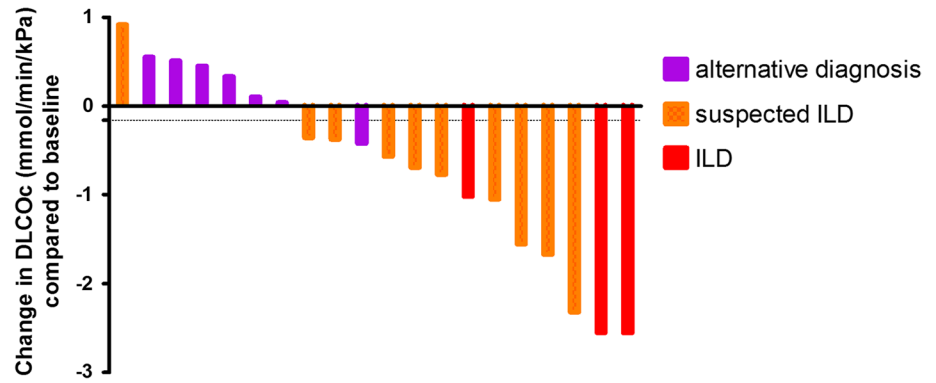


Fig. 1 Pulmonary function tests in patients who discontinued everolimus due to (suspected) interstitial lung disease (ILD)



**Fig. 2** Change in DLCOc at the first moment of the patient's highest severity classification compared to baseline per classification in patients with respiratory symptoms. Each bar represents one patient



was observed between the severity of symptoms and DLCOc decrease, Spearman  $r = -0.26$  [95% confidence interval (CI)  $-0.60, 0.16$ ] and  $-0.44$  (95% CI  $-0.80, 0.17$ ).

### 3.4 Plasma Biomarkers

Plasma biomarkers were collected from 25 patients, with a total of 123 samples. Due to logistical problems, from two patients no samples could be collected and from the other 25 patients, one sample on day 14 and two samples on day 35 were not collected. One sample had to be discarded due to pre-analytical errors.

#### 3.4.1 Plasma Biomarkers to Discriminate Between Patients With and Without (Suspected) ILD

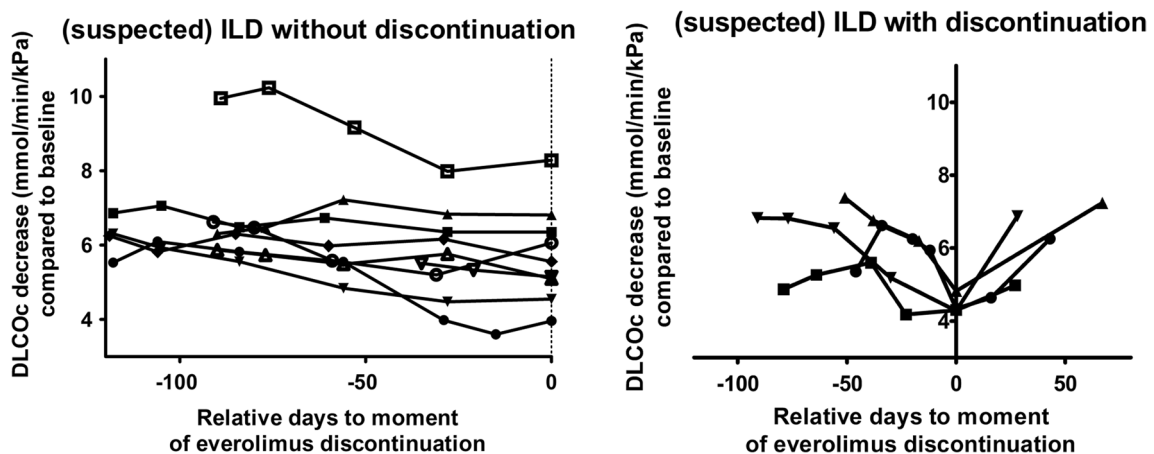
Patients with (suspected) ILD were compared to patients without respiratory symptoms, airway disease, or respiratory symptoms due to an alternative cause. Concentrations of YKL-40 and SP-D in patients with (suspected) ILD were significantly higher compared to patients without (suspected) ILD (Table 2), median ratio 1.31 versus 0.94 and 1.27 versus 0.64, respectively. No significant difference between the ILD

and no-ILD group was seen regarding CA 15-3, uteroglobin, CCL18, SP-A, and LDH concentrations. YKL-40 and SP-D showed the highest ROC AUC. At the optimal cut-off points ( $> 1.10$  and  $> 1.00$ , respectively), these plasma biomarkers had high sensitivity and specificity and positive and negative predictive values (Table 3).

The optimal cut-offs for DLCOc and SP-D were combined, and patients were classified as with or without (suspected) ILD when both tests indicated the same direction. This could classify 70% of patients, with positive and negative predictive values of 1.0 and 0.80, respectively.

#### 3.4.2 Plasma Biomarkers to Predict the Need for Treatment Discontinuation in Patients with (Suspected) ILD

In three out of four patients who discontinued everolimus treatment due to ILD, plasma biomarker data were available. In these three patients, changes in concentration of plasma biomarkers SP-A, SP-D, and YKL-40 paralleled the development of ILD best (Fig. 4). However, plasma biomarker concentrations did not allow discrimination between patients with and without the need for treatment discontinuation. In patients with (suspected) ILD, the median ratio of YKL-40



**Fig. 3** Spaghetti plots of DLCOc for patients with (suspected) interstitial lung disease (ILD) with versus without the need for discontinuation

was 1.29 in patients without the need for discontinuation, compared to 1.32 in the patients with the need for discontinuation ( $p=1.00$ ). For SP-D, medians were 1.09 and 1.52, respectively ( $p=0.11$ ).

### 3.5 Everolimus Pharmacokinetics

Everolimus trough concentrations were measured in 26 patients. There was no difference in everolimus concentrations of patients with versus without (suspected) ILD, with geometric mean concentrations of 10.3 and 10.1  $\mu\text{g/L}$ , respectively ( $p=0.94$ ).

### 3.6 FDG-PET

Four patients did not participate in the FDG-PET imaging part, and therefore FDG-PET data were available from 11/15 patients with everolimus-related respiratory symptoms. From these patients, none had enhanced FDG uptake at day 14, while 7/11 patients showed an FDG-uptake pattern consistent with ILD on day 35. In these patients, FDG-uptake was most often focal consolidations, either unilateral or bilateral. From these seven patients with respiratory symptoms and FDG-PET abnormalities, six patients were classified as (suspected) ILD at or before day 35. The seventh patient showed pulmonary abnormalities consistent with ILD at day 35 and developed suspected ILD at day 89. As such, FDG-PET abnormalities mostly did not precede the clinical diagnosis. No enhanced FDG uptake was seen in patients without everolimus-related respiratory symptoms.

## 4 Discussion

To the best of our knowledge, this is the first prospective study investigating drug-induced ILD. We demonstrated that in ABC patients treated with everolimus, DLCOc decline

and the plasma biomarkers YKL-40 and SP-D seem to discriminate patients with versus without (suspected) ILD. DLCOc shows a much better diagnostic performance for detecting ILD than FVC. The amount of DLCOc decline seems to be different for (suspected) ILD and alternative causes, such as malignant pleural effusion and respiratory infections. However, as DLCOc is foremost a marker of disease severity, analysis in more patients is needed to confirm the discriminative capability of DLCOc. A rapid decrease in absolute DLCOc could be an alarming indicator for severe toxicity necessitating treatment discontinuation. Furthermore, this study shows that the grade of respiratory symptoms is not a good reflection of the decrease in diffusion capacity. As such, measurement of DLCOc could be used as an indication of the severity of parenchymal changes. As the change in PFT compared to baseline is more informative than the absolute value, PFT is preferably performed at baseline and during follow-up.

SP-D is a protein involved in pulmonary immune and inflammatory regulation and in surfactant homeostasis, and has previously shown its value in hypersensitivity pneumonitis and idiopathic pulmonary fibrosis [39–41]. YKL-40 is involved in tissue remodeling after an inflammatory response and has been associated with idiopathic pulmonary fibrosis, sarcoidosis, and hypersensitivity pneumonitis [42]. However, YKL-40 is also known to be associated with breast cancer markers [43]. We demonstrate that these proteins also increase in drug-induced ILD. SP-A, uteroglobin, CCL18, and LDH showed a non-significant increase in everolimus-induced ILD.

No correlation was seen between everolimus trough concentration and the development of (suspected) ILD, whereas other everolimus-related toxicities have been related to trough concentration [14, 28]. This observation is in line with other studies that have indicated that the development of ILD is not exposure-related [44, 45]. Most patients with (suspected) ILD had FDG-avid pulmonary abnormalities.

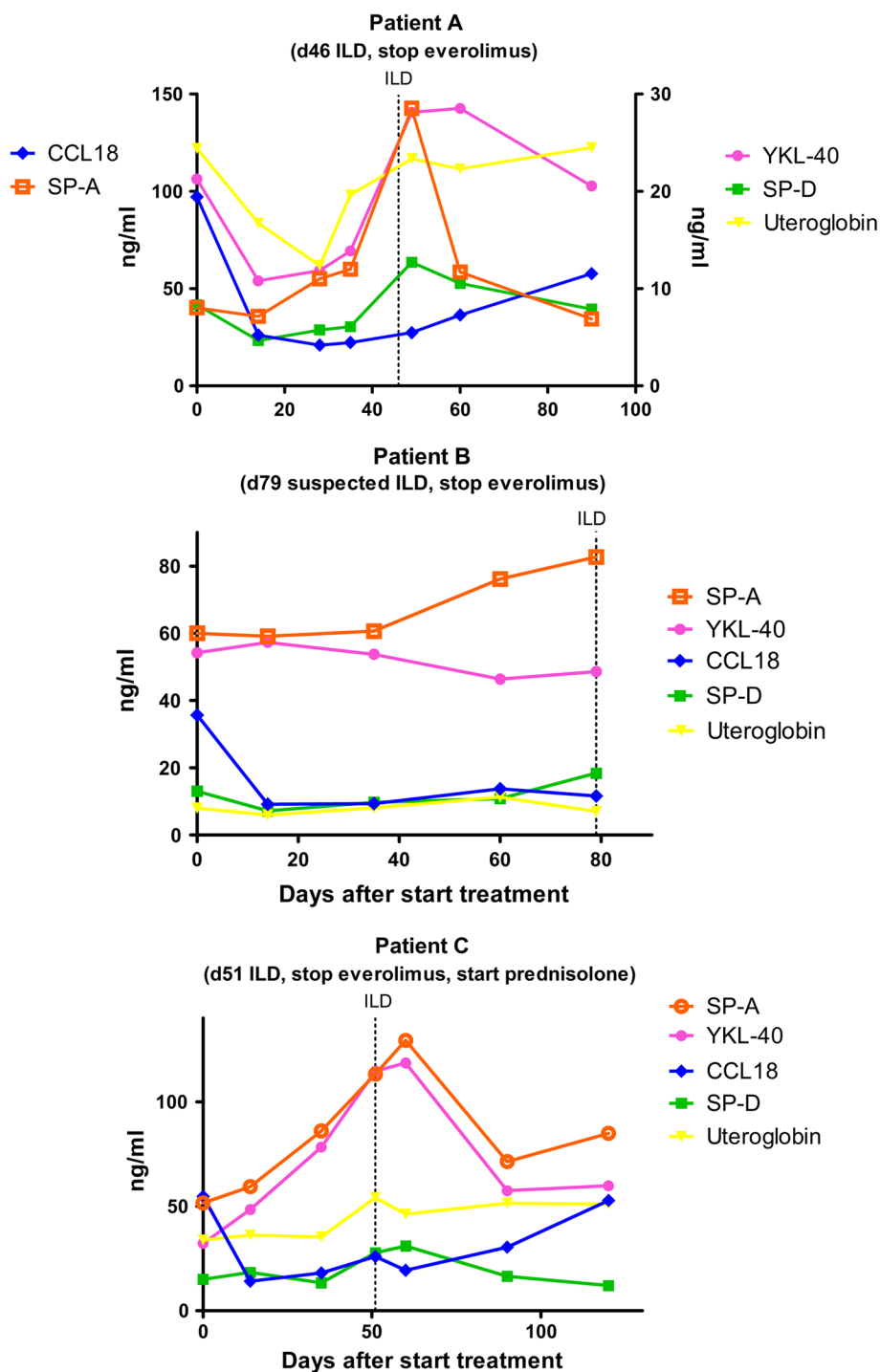
**Table 3** Diagnostic performance of change of plasma biomarkers from baseline to discriminate patients with and without (suspected) interstitial lung disease (ILD)

Plasma biomarker	Median ratio for patients without (suspected) ILD ( $n=13$ )	Median ratio for patients with (suspected) ILD ( $n=12$ )	$p$ value	Area under the ROC curve	Sensitivity	Specificity	Positive predictive value	Negative predictive value
YKL-40	0.94	1.31	0.039	0.75	0.83	0.62	0.67	0.80
SP-D	0.64	1.27	0.003	0.85	0.83	0.85	0.83	0.85
SP-A	1.07	1.63	0.077	0.71				
Uteroglobin	1.23	1.29	0.849	0.53				
CCL18	0.27	0.38	0.231	0.64				
CA 15.3	1.19	1.02	0.479	0.59				
LDH	1.37	1.47	0.735	0.55				

ROC receiver-operating characteristic



**Fig. 4** Plasma biomarkers in patients who discontinued everolimus due to (suspected) interstitial lung disease (ILD)



However, as these FDG-PET abnormalities mostly did not precede the clinical symptoms, FDG-PET does not seem to have significant predictive value for ILD.

The incidence of ILD was high, as 56% of patients developed everolimus-related respiratory problems, and 15% had to discontinue treatment because of drug-induced ILD. This high incidence is in contrast with earlier studies, such as the BOLERO-2 [16], which demonstrates that the incidence

of ILD is higher when awareness is high. Furthermore, it illustrates that the incidence of ILD is very variable as there are no generally accepted criteria for its diagnosis. It is important to note that patients with CT abnormalities or a DLCOc decrease may have no or only minor symptoms and the majority of patients with suspected ILD continued everolimus without further deterioration. Everolimus discontinuation and treatment with prednisolone resulted in

good recovery of symptoms and PFT in our patients with severe ILD.

The strong point of this study is the prospective collection of a comprehensive dataset. A prospective study of drug-induced ILD following patients from start of treatment has not been published before. A limitation of this study is the limited sample size. Despite this, however, clear observations could be made because of the high incidence of everolimus-induced ILD. Another limitation is that as yet the diagnosis of drug-induced ILD is largely made per exclusion. In patients with respiratory symptoms, analysis for viral, bacterial, and yeast infections was performed on clinical suspicion and therefore was not performed in all patients. As such, it is possible that cases have been assessed as ILD when an alternative diagnosis was missed. Also, the criteria we used have not yet been externally validated. However, to date, no validated criteria exist. The criteria we used are detailed and use multiple sources of information. Therefore, we believe this is preferable above for instance the CTCAE criteria, which are very non-specific. Furthermore, we acknowledge the risk that PFT is not a fully independent biomarker, as a significant PFT decline is part of the diagnostic criteria for ILD. However, only two patients had a significant PFT decline and patients were only diagnosed with ILD if other causes were excluded. In this study everolimus was used in combination with exemestane. Exemestane is not associated with ILD [46], and therefore this does not seem to influence ILD incidence.

Our data should be considered explorative and hypothesis-generating. Although our results will have to be confirmed in another study, we do suggest that a rise in SP-D combined with a decrease in DLCOc ( $>0.16$  mmol/min/kPa) is suggestive of everolimus-induced lung injury. DLCOc and plasma biomarker measurements could be useful in monitoring other forms of drug-induced ILD, especially for targeted therapies such as PI3 K inhibitors and Akt inhibitors, with similar class-related pneumonitis. However, the use of the biomarkers identified in our study need to be confirmed for these other anticancer therapies.

In summary, we report a high incidence of everolimus-related ILD and have prospectively shown that DLCOc and SP-D and YKL-40 provide valuable tools for the early diagnosis of everolimus-induced lung toxicity. If after validation these tests can be applied in a clinical algorithm this could help to keep patients on treatment when possible, while also preventing drug-induced morbidity.

## Compliance with Ethical Standards

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**Conflict of Interest** Nielka P. van Erp and Carla M.L. van Herpen have received an Investigator Driven Research Grant from Novartis from

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## Affiliations

Annelieke E. C. A. B. Willemsen<sup>1</sup> · Jolien Tol<sup>2</sup> · Nielka P. van Erp<sup>3</sup> · Marianne A. Jonker<sup>4</sup> · Maaike de Boer<sup>5</sup> · Bob Meek<sup>6</sup> · Paul C. de Jong<sup>7</sup> · Coline van Moorsel<sup>6,8</sup> · Winald R. Gerritsen<sup>1</sup> · Jan C. Grutters<sup>6,8</sup> · Carla M. L. van Herpen<sup>1</sup>

<sup>1</sup> Department of Medical Oncology, Radboud university medical center, route 452, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

<sup>2</sup> Department of Medical Oncology, Jeroen Bosch Hospital, P.O. Box 90153, 5200 ME 's Hertogenbosch, The Netherlands

<sup>3</sup> Department of Pharmacy, Radboud university medical center, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

<sup>4</sup> Department for Health Evidence, Radboud university medical center, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

<sup>5</sup> Division of Medical Oncology Department of Internal Medicine, GROW-School of Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands

<sup>6</sup> Department of Pulmonology, St. Antonius Hospital, Centre of Interstitial Lung Diseases, Nieuwegein, The Netherlands

<sup>7</sup> Department of Medical Oncology, St. Antonius Hospital, Nieuwegein, The Netherlands

<sup>8</sup> Division Heart & Lungs, University Medical Center Utrecht, Utrecht, The Netherlands