Supplementary material

Prospective study of drug-induced interstitial lung disease in advanced breast cancer patients receiving everolimus plus exemestane

Targeted Oncology

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METHODS

Clinical evaluation

In case of (suspected) ILD the decision for treatment discontinuation was based on the discretion of the treating physician. Follow-up stopped if a patient discontinued everolimus due to progressive disease. If discontinuation was due to ILD, evaluation was continued during the recovery of ILD.

Pulmonary function tests

Before quantative analysis, we depicted our data graphically. In patients who discontinued everolimus due to ILD it was visually evaluated if a decrease in DLCOc or FVC preceded discontinuation. The relationship between the severity of respiratory symptoms at the first moment of the patient's highest severity classification and the degree of decrease in DLCOc at that moment was studied visually. Spaghetti plots were constructed showing the change in DLCOc in patients with (suspected) ILD to compare patients with and without the need for discontinuation of everolimus treatment. As changes in PFT in the period before discontinuation are of main interest, this plot is constructed with on the x-axis the number of days before "day zero": the day of everolimus discontinuation or maximally the 120st day of treatment in patients who continued treatment. The slopes in the period of the last six weeks of these groups were compared by measuring the absolute change in DLCOc divided by the number of days. The period of six weeks was chosen by clinical experience, as this is the time over which ILD often develops and deteriorates.

Pneumoproteins

One 9ml lithium-heparine tube and one 9ml serum tube with clot activator were collected. Following centrifugation, plasma and serum were collected and dispersed over three aliquots, which were stored at - 80°C. YKL-40, CCL18, SP-D, and CA 15-3 levels were determined by two separate duplex bead-based immunoassays (R&D Systems) in accordance with the manufacturer's instructions. Pneumoprotein concentrations were measured on a Bio-Plex System 100 (Bio-Rad). Enzyme-linked

immuno sorbent assay (ELISA) (BioVendor) was used for quantification of surfactant protein A (SP-A) and was performed in accordance with the manufacturer's instructions.

Supplementary table 1: diagnostic classification per patient at first moment of maximal classification

Study id	Number of treatment days	CTCAE grade	Significant PFT decline?	CT abnormalities	Conclusion
1	14	2 cough	0	no new pulmonary abnormalities	alternative diagnosis: suspected viral upper respiratory infection
2	91	2 dysnea	1	ground glass opacities	ILD
3	84	0	0	no new pulmonary abnormalities	no respiratory symptoms
4	11	2 cough, 2 dyspnea	0	consolidations	suspected ILD
5	35	2 dysnea	0	pleural effusion	alternative diagnosis: pleuritis carcinomatosa
6	112	1 cough	0	pleural effusion	alternative diagnosis: pleuritis carcinomatosa
7	46	3 dyspnea, 2 cough	0	infiltrative abnormalities, pleural effusion, and reticular thickening basal	ILD
8	89	1 cough, 1 dyspnea	0	ground glass opacities and reticular thickening	suspected ILD
9	17	1 cough, 1	0	no new pulmonary abnormalities	alternative diagnosis: PCR positive for

		fever			rhinovirus
10	34	1 cough, 1 dyspnea	0	infiltrative abnormalities	suspected ILD
11	34	0	0	infiltrative abnormalities	suspected ILD
12	79	2 cough, 2 dyspnea	0	infiltrative abnormalities, ground glass opacities, and thickening of interlobular septae	suspected ILD
13	62	1 dyspnea	0	Ground glass opacities	suspected ILD
14	13	1 cough, 1 dyspnea	0	pleural fluid and pleuritis carcinomatosa	alternative diagnosis: pleuritis carcinomatosa and possible lymphangitic carcinomatosa
15	62	0	0	no new pulmonary abnormalities	no respiratory symptoms
16	119	2 cough	0	infiltrative abnormalities, ground glass opacities	suspected ILD
17	48	2 dysnea	0	no new pulmonary abnormalities	alternative diagnosis: suspected viral upper respiratory infection
18	57	0	0	no new pulmonary abnormalities	no respiratory symptoms

19	55	0	0	no new pulmonary abnormalities	no respiratory symptoms
20	32	0	0	infiltrative abnormalities	suspected ILD
21	60	0	0	no new pulmonary abnormalities	no respiratory symptoms
22	45	2 dyspnea, 1 cough	0	consolidation	alternative diagnos: proven Pneumocystis jirovecii pneumonia
23	51	2 cough, 2 dyspnea	1	consolidations and ground glass opacities	ILD
24	89	2 dysnea	0	consolidation and pleural effusion	suspected ILD
25	90	1 cough	0	consolidations, ground glass opacities and reticular thickening	suspected ILD
26	14	1 cough	0	no new pulmonary abnormalities	alternative diagnosis: suspected viral upper respiratory infection
27	35	0	0	consolidations	suspected ILD