the timing (and sometimes mechanism) of disease progression or treatment failure.

To date this has been demonstrated in patients with EGFR and KRAS mutations.

Our objective was to determine if this approach could be applied to an unselected cohort of patients with advanced non-small cell lung cancer (adenocarcinoma subtype).

Methods Unselected treatment-naive patients with lung cancer were recruited from thoracic oncology clinics. Paired DNA from tumour biopsies and baseline/longitudinal plasma samples was obtained. Targeted next-generation sequencing (NGS) was performed using a 26-gene panel on biopsy-derived DNA. Primer sets and probes for identified mutations were optimised and validated on a the BioRad-QX100 mdPCR system.

Results The NGS data is summarised in Table 1.

Abstract S105 Table 1 Results of targeted next generation sequencing from cohort of 20 patients

Pt	Biopsy type	Total DNA loaded (ng)	Mutation 1	MAF	Mutation 2	MAF
1	Lung Biopsy	NK	EGFR exon 19 deletion	33		
2	Pleural fluid	NK	KRAS G12R	28		
3	Bronchial biopsy	33	TP53 P152S	20.42		
4	Bronchial biopsy	26	BRAF V600E	35.1		
5	EBUS	25	KRAS G12V	49.33		
6	EBUS	27	EGFR ex 19 del	63.5	TP53 R273L	36.01
7	EBUS	33	TP53 H214R	52.97		
8	EBUS	12	TP53 K132E	40.76		
9	EBUS	12	KRAS G12C	13.75		
10	EBUS	33	TP53 R283P	74.19	KRAS G12V	54.01
11	EBUS	33	KRAS G12C	39.02		
12	Lung biopsy	23	PIK3CA H1047R	28.95		
13	Lung biopsy	3	TP53 R158L	50.69		
14	Lung biopsy	4	TP53 S371Y	28.06		
15	Lung biopsy	16	TP53 1bp del/FM	24.01		
16	Lung biopsy	33	TP53 E258*	12.88		
17	Lung biopsy	33	EGFR ex 19 del	36.51		
18	Brain biopsy	33	KRAS G12L	52.46		
19	Lymph node FNA	8	No mutation	No mutation		
20	Pleural biopsy	33	TP53 C141Y	62.13		

MAF, Mutant Allele Frequency. *Both EGFR and P53 mutation detected in plasma. **Only two reports of G12L in lung cancer on COSMIC out of >20,000.

20 patients in our test cohort had stage IIIB/IV lung adenocarcinoma. These included cytology specimens – EBUS, lymph node FNA and pleural effusion, percutaneous biopsies, pleural biopsies and a brain biopsy. The mean quantity of DNA used for targeted resequencing was 23 ng. The lowest read depth for the identified mutations was 1639; in general coverage was >10,000.

19/20 patients had mutations identified in their diagnostic specimen.

12 of 20 samples had >1 mutation detected and 8 had more than 2 mutations detected at a mutant allele frequency (MAF) >10%.

CtDNA from plasma has been tested for specific mutations including in *PIK3CA*, *TP53*, and *BRAF* as well as *KRAS* and *EGFR* in these patients. In 16 of the 19 patients in which mutations were identified the mutation has also been detected in the plasma. The range of detected MAFs was between <0.1–49.6%.

It was noteworthy that there was discordance between the biomarker response and RECIST1.1 criteria in some patients.

Conclusion It is feasible to perform a targeted NGS analysis on DNA from standard fixed diagnostic lung adenocarcinoma specimens and then validate and use individualised molecular biomarkers for use in a microdroplet digital PCR assay of cell-free circulating tumour DNA. There is potential for this approach to inform clinical decision-making.

This is a robust and low cost means of monitoring treatment response non-invasively and merits further evaluation in a clinical trial.

Nintedanib or pirfenidone?

S106 CONSISTENT EFFECT OF NINTEDANIB ON DECLINE IN FVC IN PATIENTS ACROSS SUBGROUPS BASED ON HRCT DIAGNOSTIC CRITERIA: RESULTS FROM THE INPULSIS® TRIALS IN IPF

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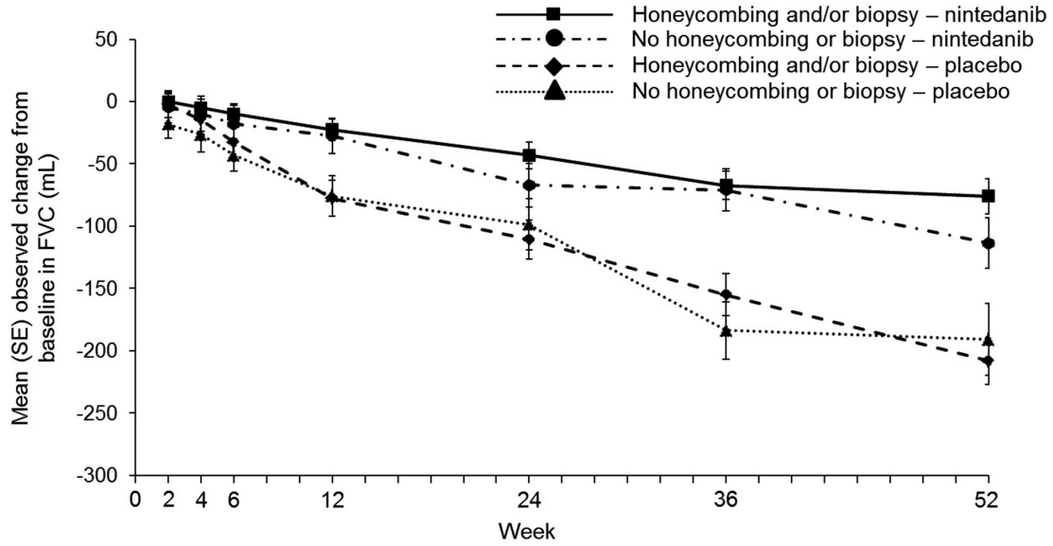
Introduction The two replicate, randomised, placebo-controlled, 52-week INPULSIS® trials assessed the efficacy and safety of nintedanib 150 mg twice daily (bid) in patients with IPF. The primary endpoint was met in both trials; nintedanib significantly reduced the annual rate of decline in FVC compared with placebo, consistent with a slowing of disease progression.

Methods To qualify for the INPULSIS® trials if a surgical lung biopsy was unavailable, patients needed to have a high-resolution computed tomography (HRCT) scan showing honeycombing and/or a combination of reticular abnormality and traction bronchiectasis, without features suggestive of alternative causes. Surgical lung biopsies, if available, were used to confirm eligibility. A *post-hoc* subgroup analysis of patients with diagnosis based on honeycombing and/or confirmation of usual interstitial pneumonia (UIP) by biopsy versus patients with no honeycombing and no biopsy was undertaken using pooled data from both trials.

Results 723 patients (425 nintedanib, 298 placebo) had honeycombing and/or confirmation by biopsy and 338 (213 nintedanib, 125 placebo) had no honeycombing or biopsy for diagnosis of IPF. Demographics and baseline characteristics were similar between these subgroups. In patients with honeycombing and/or biopsy, the adjusted annual rate of decline in FVC was -108.7 mL/year with nintedanib and -225.7 mL/year with placebo (difference: 117.0 mL/year [95% CI: 76.3, 157.8]); in patients with no honeycombing or biopsy, it was -122.0 mL/year with nintedanib and -221.0 mL/year with placebo (difference: 98.9 mL/year [95% CI: 36.4, 161.5]). The treatment by subgroup interaction



No. of patients							
Honeycombing and/or biopsy – nintedanib	418	409	408	398	385	377	341
No honeycombing or biopsy – nintedanib	208	207	205	206	202	192	178
Honeycombing and/or biopsy – placebo	293	289	291	284	275	267	239
No honeycombing or biopsy – placebo	124	119	116	119	120	116	106

Abstract S106 Figure 1

p-value was not significant for the primary endpoint (p = 0.81) or for the key secondary endpoints of time to first acute exacerbation (p = 0.37) or change from baseline in St George's Respiratory Questionnaire total score (p = 0.67), indicating that the treatment effect of nintedanib was not statistically significantly different between the subgroups.

Conclusion Decline in FVC in placebo arms was virtually identical in patients with A) the presence of honeycombing and/or biopsy confirmation of UIP; and B) the absence of both, but features of "possible UIP" on HRCT. Nintedanib slowed FVC decline equally in both sub-groups. These findings have major implications for diagnosis and clinical trial design.

S107 DISEASE PROGRESSION MODELLING IN IDIOPATHIC PULMONARY FIBROSIS: A PREDICTION OF TIME TO DISEASE PROGRESSION AND LIFE EXPECTANCY WITH PIRFENIDONE

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Objectives Currently, clinical trials in idiopathic pulmonary fibrosis (IPF) are not designed to estimate disease progression and survival over a long period. The objective of this study was to develop a disease progression model in IPF to predict the extent to which treatment with pirfenidone could extend the time to disease progression and improve life expectancy versus best supportive care (BSC) over a patient's lifetime.

Methods A disease progression model was developed categorising disease progression into four health states: progression free; progressed (≥10% decline in FVC or ≥50 m decrease in 6-minute walking distance); lung transplant; and dead. Two cohorts entered the model in the progression-free state: one cohort received pirfenidone (n = 1000), the other received BSC (n = 1000). The proportion of patients in each health state was calculated every 3 months based on parametric survival distributions fitted to data from clinical trials and registries. Distributions calculating progression-free survival (PFS) and overall survival (OS) for pirfenidone were fitted to data from randomised controlled trials (RCTs; Studies 004, 006, 016) and a long-term open-label extension study (Study 012). Distributions calculating PFS and OS for BSC were fitted to data from the RCTs and a US-based IPF registry. Mean PFS and OS were determined for pirfenidone and BSC. Uncertainty was explored by deterministic and probabilistic sensitivity analysis.

Results The model calculated mean PFS as 3.28 years and 2.18 years with pirfenidone and BSC, respectively (Figure). Hence, pirfenidone extended the estimated mean time to disease progression by 1.10 years. Mean OS was calculated as 9.29 years and 6.10 years with pirfenidone and BSC, respectively (Figure 1). Therefore, pirfenidone improved estimated life expectancy by 3.19 years. The extent to which pirfenidone improved PFS and OS was sensitive to choice of parametric survival distribution and method of extrapolation.

Conclusions This disease progression model suggests that treatment with pirfenidone extends the time to disease progression and improves life expectancy, thus preventing early morbidity and deaths in IPF. These conclusions are consistent with expectations for a therapy that has been shown to reduce disease progression and mortality, as measured by a pooled analysis of outcomes in Phase 3 clinical trials.