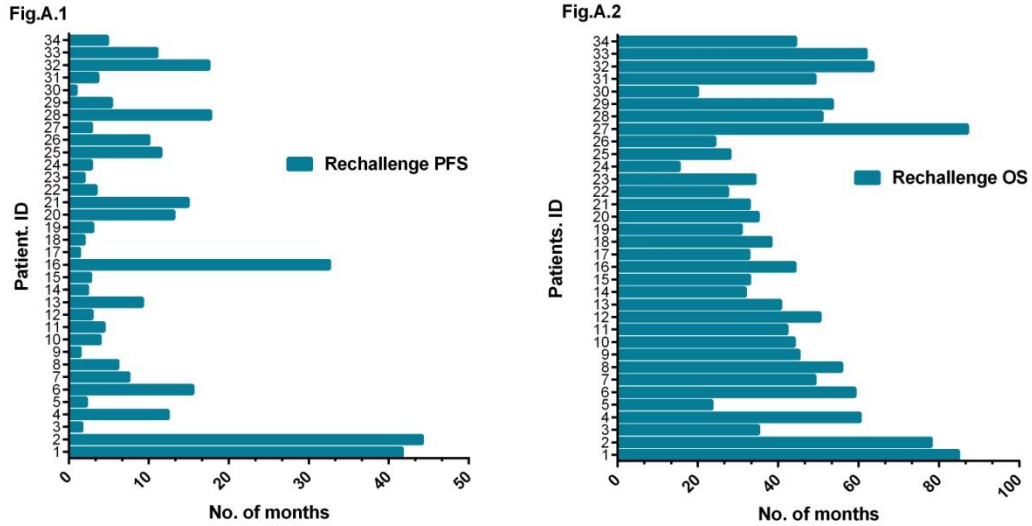


**Supplementary Figure 1:** The survival analysis for all patients with pemtrexed-based rechallenge therapy of this study. A1: Median rechallenge PFS; A2: Median rechallenge OS. OS: Overall survival; PFS: Progression-free survival.



**Supplementary Table 1:** Baseline patients' clinical characteristics and treatment stratification.

Characteristic	Number of patients ( <i>n</i> = 34)	%
<b>Age, y ±SD</b>	57.4 ±9.9	
≥60 years	15	44.1
<b>Male sex</b>	13	38.2
<b>ECOG PS</b>		
0–1	19	55.9
2–3	15	44.1
<b>Smoking status</b>		
Never	23	67.6
Current	4	11.8
Former	7	20.6
<b>Comorbidities</b>		
Yes	19	55.9
<b>Histology</b>		
Adenocarcinoma	34	100
<b>Driver mutation</b>		
EGFR positive	12	35.3
T790M	1	2.9
ALK positive	4	11.8
<b>Weight loss &gt;5%</b>	4	11.8
<b>TKI therapy</b>	16	47.1
<b>Previous surgery</b>	8	23.5
<b>Radiotherapy</b>	10	29.4
<b>Initial PBC regimens</b>		
Carboplatin and pemetrexed	12	35.3

Cisplatin and pemetrexed	19	55.9
Nedaplatin and pemetrexed	3	8.8
<b>Initial maintenance treatment</b>		
Yes	16	47.1
<b>Response to initial PBC</b>		
PR	15	44.1
SD	19	55.9
<b>TFS after initial PBC, months</b>		
<15	17	50.0
≥15	17	50.0
<b>PFS after initial PBC, months</b>		
<10	11	32.4
≥10	23	67.6
<b>Line of rechallenge therapy</b>		
2nd	10	29.4
3rd	12	35.3
≥4th	12	35.3
<b>PBC rechallenge regimens</b>		
Carboplatin and pemetrexed	11	32.4
Cisplatin and pemetrexed	9	26.5
Nedaplatin and pemetrexed	2	5.9
Taxane and pemetrexed	4	11.8
Pemetrexed alone	8	23.5
<b>Maintenance treatment</b>		
Yes	8	23.5
<b>Bevacizumab regimens</b>		
Yes	13	38.2

ECOG PS: Eastern Cooperative Oncology Group Performance Status; PBC: Pemetrexed-based chemotherapy; PD: Progressive disease; PFS: Progression-free survival; PR: Partial response; SD: Stable disease; TFS: Treatment-free survival; TKI: Tyrosine kinase inhibitors.

**Supplementary Table 2: Univariate Cox regression analyses for PFS and OS in PBC rechallenge.**

Characteristic	PFS			OS		
	HR	95% CI	P value	HR	95% CI	P value
<b>Age</b>						
≥60 years	0.704	0.305–1.624	0.410	0.564	0.211–1.508	0.254
<b>Gender</b>						
Female (vs. male)	1.356	0.591–3.110	0.472	2.496	0.972–6.408	0.057
<b>Smoking history</b>						
Yes	1.376	0.593–3.189	0.457	2.177	0.856–5.536	0.102
<b>Comorbidities</b>						
Yes	0.586	0.256–1.341	0.206	1.446	0.557–3.749	0.448
<b>ECOG PS</b>						

≥2	0.096	0.010–0.925	0.043*	0.352	0.044–2.790	0.323
<b>Driver mutation</b>						
EGFR positive	1.528	0.672–3.476	0.312	1.397	0.535–3.644	0.495
ALK positive	1.462	0.427–5.004	0.545	2.233	0.632–7.892	0.212
<b>Weight loss &gt;5%</b>						
Yes	0.905	0.260–3.144	0.875	1.276	0.287–5.684	0.749
<b>Maintenance treatment</b>						
Yes	0.674	0.265–1.714	0.408	0.340	0.096–1.201	0.094
<b>Bevacizumab regimens</b>						
Yes	1.009	0.438–2.323	0.983	0.822	0.317–2.135	0.688
<b>Previous surgery</b>						
Yes	0.795	0.311–2.032	0.631	0.776	0.254–2.369	0.656
<b>Radiotherapy</b>						
Yes	0.958	0.377–2.434	0.928	1.756	0.632–4.877	0.280
<b>Initial maintenance</b>						
Yes	1.053	0.471–2.354	0.900	0.852	0.334–2.175	0.738
<b>Response to initial PBC</b>						
PR (vs. SD)	0.713	0.314–1.620	0.419	1.326	0.494–3.559	0.575
<b>TFS after initial PBC</b>						
≥15 (vs. <15) months	0.815	0.358–1.860	0.628	1.108	0.425–2.886	0.834
<b>PFS after initial PBC</b>						
≥10 (vs. <10) months	1.775	0.763–4.129	0.183	1.077	0.421–2.757	0.877
<b>Line of rechallenge therapy</b>						
2nd, 3rd (vs. ≥4 <sup>th</sup> )	1.963	0.862–4.470	0.108	1.326	0.494–3.559	0.575

CI: Confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: Hazard ratio; OS: Overall survival; PBC: Pemetrexed-based chemotherapy; PFS: Progression-free survival; PR: Partial response; SD: Stable disease; TFS: Treatment-free survival.