MATERIAL SUPPLEMENTARY

First line versus second line use of reslizumab in severe uncontrolled asthma.

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Statistical analysis.

The normality of data distribution was checked using the Shapiro-Wilk test. Increases in ACT were compared with ANCOVA using baseline ACT as covariate. For longitudinal comparisons in each group, t-test for matched samples, Wilcoxon and McNemar tests were used. Univariate and multiple logistic regression were applied to establish the relationships between several independent variables (number of exacerbations in the preceding year[1; 2; 3; ≥4], ACT at baseline [due to the non-linearity between the ACT and the logit of the outcome, the ACT was coded into three categories, ≤10; 11-14 and; >14, according to tertiles], chronic OCS [no/yes], last prior biologic treatment [reference omalizumab], and nasal polyposis [no/yes]) and the achievement of control in switchers. The threshold for significance was set at $P<0.05$.

Table S1. Baseline characteristics of the patients. Comparison between first line and second line groups.

Variable	Total (n=159)		First line (n=91)		Second line (n=68)		p
Age (y) (mean, SD)	57.0	10.8	57.3	11.4	56.6	10.0	0.417
Gender (n, % women)	106	66.7%	65	71.4%	41	60.3%	0.141
BMI (mean, SD)	27.4	5.1	27.6	5.2	27.3	4.9	0.375
Smoking history							
-Never (n, %)	112	70.4%	62	68.1%	50	73.5%	0.461
-Current/former (n, %)	47	29.6%	29	31.9%	18	26.5%	
-Pack-years (median, IQR)	15	8-24	15	9-20	6	11-25	0.969
Onset < 12 yrs (n, %)	20	12.6%	10	11.0%	10	14.7%	0.484
Positive skin prick-test (n, %)	63	39.6%	25	27.5%	38	55.9%	<0.001
Comorbidities							
-Rhinitis (n, %)	84	52.8%	44	48.4%	40	58.8%	0.191
-Sinusitis (n, %)	64	40.3%	31	34.1%	33	48.5%	0.066
-Polyposis (n, %)	78	49.1%	43	47.3%	35	51.5%	0.599
-NERD (n, %)	22	13.8%	11	12.1%	11	16.2%	0.460
-ABPA (n, %)	2	1.3%	0	0.0%	2	2.9%	0.181
-Gastroesophageal reflux (n, %)	42	26.4%	22	24.2%	20	29.4%	0.459
-Obesity (n, %)	34	21.4%	17	18.7%	17	25.0%	0.336
-Sleep apnea (n, %)	19	11.9%	9	9.9%	10	14.7%	0.354
-Anxiety (n, %)	30	18.9%	15	16.5%	15	22.1%	0.374
-Depression (n, %)	22	13.8%	13	14.3%	9	13.2%	0.849
-EGPA (n, %)	3	1.9%	2	2.2%	1	1.5%	0.739
Blood eosinophils (cel/µL) (median, IQR)	500	300-800	500	330-795	420	200-818	0.374
FENO (ppb) (median, IQR)	35	12-60	25	7-52	42	21-69	0.460
FEV1 (% predicted) (mean, SD)	70.1	22.3	71.4	21.4	68.4	23.5	0.413
FEV1/FVC (%) (mean, SD)	62.1	16.6	61.1	18.0	63.4	14.6	0.406
FEV1/FVC < 70 (n, %)	92	63.4%	54	65.9%	38	60.3%	0.493

Patients with severe exacerbations in the prior 12 months	138	86.8%	80	87.9%	58	85.3%	0.630
Severe exacerbations in the prior 12 months (median, IQR)	3	2-4	3	2-4	2	1-4	0.164
Hospitalized asthma exacerbation (n, %)	53	33.3%	27	29.7%	26	38.2%	0.257
ICU admission	6	6.5%	3	5.5%	3	8.1%	0.613
ACT (mean, SD)	12.8	4.4	12.9	4.2	12.6	4.7	0.652
ACT < 20 (n, %)	150	94.3%	86	94.5%	64	94.1%	0.917
Treatment:							
ICS/LABA (n, %)	159	100%	91	100%	68	100%	-----
LAMA (n, %)	132	83.0%	72	79.1%	60	88.2%	0.130
LTRA (n, %)	112	70.4%	63	69.2%	49	72.1%	0.699
OCS maintenance therapy (n, %)	95	59.7%	55	60.4%	40	58.8%	0.877
OCS burden (mg prednisone eq./day) (median, IQR)[A]	5.5	3.1-13.0	5.2	3.3-10.0	7.4	3.0-18.8	0.331
Switched from another MAB (n, %)	68	42.8%			68	100%	
Last MAB before reslizumab start:							
Omalizumab[B]					52		
- Switched due to lack of efficacy					32		
- Switched due to adverse events					1[C]		
- Switched cause unspecified					19		
Mepolizumab[B]					16		
- Switched due to lack of efficacy					10		
- Switched due to adverse events					1[D]		
- Switched due to cause unspecified					5		

[A]: In 95 patients who received maintenance OCS in the year before reslizumab

[B]: 6 patients received Omalizumab before starting treatment with Mepolizumab

[C]: Myalgias

[D]: Asthenia

Abbreviations: BMI: Body Mass Index; NERD: Nonsteroidal antiinflammatory drug (NSAID)-exacerbated respiratory disease; ABPA: Allergic Broncho Pulmonary Aspergilosis; EGPA: Eosinophilic Granulomatosis with Poliangeithis. FENO: fractional exhaled nitric oxide; FEV1: forced expiratory flow in 1 second; FVC: Forced vital capacity; ICU: intensive care unit; ACT: asthma control test; ICS: inhaled corticosteroids; LABA:

long-acting beta-agonist; LAMA: long-acting muscarinic antagonist; OCS: oral corticosteroids; LTRA: leukotriene receptor antagonists; MAB: monoclonal antibodies.

Table S2. Outcomes in first line and second line patients after 1 year treatment with reslizumab.

First line (n = 91)	Before reslizumab		After 1 year with reslizumab		p
Complete asthma control after 1 year of reslizumab treatment (n, %)	0	0.0%	40	46.0%	
Patients with exacerbations (n, %)	80	87.9%	18	20.5%	<0.001
Number of exacerbations (median, IQR)[A]	4	2-5	1	1-2	0.083
ACT (mean, SD)	12.9	4.2	20.9	4.5	<0.001
ACT ≥ 20 (n, %)	5	5.5%	61	70.1%	<0.001
OCS maintenance therapy (n, %)	55	60.4%	13	14.4%	<0.001
OCS burden (mg prednisone eq./day) (median, IQR)[B]	5.2	3.3-10.0	5.8	2.1-12.3	0.157
Second line (n =68)	Before reslizumab		After 1 year with reslizumab		p
Complete asthma control after 1 year of reslizumab treatment (n, %)	0	0.0%	22	32.4%	
Patients with exacerbations (n, %)	58	85.3%	19	27,9%<	<0.001
Number of exacerbations (median, IQR)[C]	3	2-6	1	1-2	0.317
ACT (mean, SD)	12.6	4.7	18.8	5.7	<0.001
ACT ≥ 20 (n, %)	4	5.9%	39	57.4%	<0.001
OCS maintenance therapy (n, %)	40	58.8%	17	25.0%	<0.001
OCS burden (mg prednisone eq./day) (median, IQR)[D]	7.4	3.0-18.8	7.2	3.8-10.1	0.157

[A] : In 18 patients who presented some exacerbation in the first year with reslizumab

[B]: In 13 patients who used OCS in the first year with reslizumab

[C] : In 19 patients who presented some exacerbation in the first year with reslizumab

[D]: In 17 patients who used OCS in the first year with reslizumab

Abbreviations: ACT: asthma control test; OCS: oral corticosteroids.

Table S3. Outcomes in naïve first line and second line switchers patients after 6 months.

Variable	Total (n=159)		First line (n=91)		Second line (n=68)		p
Complete asthma control after 6-month of reslizumab treatment (n, %)	64	41.0%	37	42.0%	27	39.7%	0.768
Patients with exacerbations (n, %)	30	19.2%	17	19.3%	13	19.1%	0.975
Number of exacerbations (median, IQR)[A]	1	1-2	1	1-2	1	1-2	0.967
ACT (mean, SD)	19.3	5.1	20.0	4.7	18.7	5.5	0.193
ACT ≥ 20 (n, %)	89	57.1%	52	59.1%	37	54.4%	0.558
ACT increase from baseline ≥ 3 (n, %)	123	78.8%	74	84.1%	49	72.1%	0.068
OCS maintenance therapy (n, %)	47	30.3%	24	27.6%	23	33.8%	0.402
FEOS score (mean, SD)	75.0	22.1	76.4	22.6	73.2	21.4	0.409

[A] : In 30 patients who presented ≥1 exacerbation during the first year after reslizumab initiation.

Table S4. Univariate and multiple regression logistic models in second line patients.

Logistic regression	Univariate				Multiple (last step forward)			
			CI95%				CI95%	
Independent variables	p	OR	Botton	Upper	p	OR	Botton	Upper
Nº exacerbations (ref. 0)	0.046							
1 exacerbation	0.069	0.143	0.018	1.161				
2 exacerbations	0.161	0.312	0.061	1.592				
3 exacerbations	0.024	0.095	0.012	0.735				
≥ 4 exacerbations	0.006	0.076	0.012	0.470				
ACT (reference ≤ 10)	0.018				0.017			
ACT 11-14	0.101	3.667	0.775	17.348	0.089	4.039	0.809	20.165
ACT >14	0.005	7.944	1.884	33.498	0.004	8.786	1.965	39.292
Last MAB (ref. omalizumab)	0.193	0.401	0.101	1.588				
Chronic OCS (ref. no)	0.041	0.989	0.979	1.000	0.038	0.988	0.977	0.999
Polyposis (ref. no)	0.168	2.083	0.733	5.921				

Abbreviations: CI95%: confidence interval of 95%; OR: odds ratio; ACT: asthma control test; MAB: monoclonal antibodies; OCS: oral corticosteroids.

Table S5. Differential response to reslizumab in patients with previous failure to ompalizumab or mepolizumab.

Last MAB omalizumab (n = 52)	Before reslizumab		After 1 year with reslizumab		p
Complete asthma control after 1 year of reslizumab treatment (n, %)	0	0.0%	19	36.5%	
Patients with exacerbations (n, %)	43	82.7%	12	23.1%	<0.001
Number of exacerbations (median, IQR)[A]	3	2-5	0	0-1	<0.001
ACT (mean, SD)	12.3	4.3	19.3	5.8	0.003
ACT ≥ 20 (n, %)	2	3.8%	31	59.6%	<0.001
OCS maintenance therapy (n, %)	31	59.6%	12	23.1%	<0.001
Last MAB mepolizumab (n = 16)	Before reslizumab		After 1 year with reslizumab		p
Complete asthma control after 1 year of reslizumab treatment (n, %)	0	0.0%	3	18.8%	
Patients with exacerbations (n, %)	15	93.8%	7	43,8%	0.005
Number of exacerbations (median, IQR)[B]	3	2-4	0	0-1	0.001
ACT (mean, SD)	13.8	5.9	17.4	5.1	0.009
ACT ≥ 20 (n, %)	2	12.5%	8	50.0%	0.034
OCS maintenance therapy (n, %)	9	56.3%	5	31.3%	0.102

[A] : In 12 patients who presented some exacerbation in the first year with reslizumab
[B] : In 7 patients who presented some exacerbation in the first year with reslizumab
Abbreviations: ACT: asthma control test; MAB: monoclonal antibody. OCS: oral corticosteroids.