

Treatments of Advanced Non-Small-Cell Lung Cancer (NSCLC) in an Italian Center: Drug Utilization and the Treatment Costs of Innovative Drugs

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Status	Treatment line			Mutated			WT-UK			
	1 st line	2 nd line	3 rd line	Adeno	Squamous	Total	Adeno	Squamous	Other	Total
Completed 1st line				12	2	14	82	51	7	140
	Afatinib			3		3				
	Carb+beva+pacli						1		1	2
	Carb+etoposide							1	1	2
	Carb+gem						6	17	2	25
	Carb+nab-paclitaxel							1		1
	Carb+paclitaxel						2		1	3
	Carb+pemetrexed						34		1	35

Status	Treatment line			Mutated			WT-UK			
	1 st line	2 nd line	3 rd line	Adeno	Squamous	Total	Adeno	Squamous	Other	Total
	Carb+vinorelbine							5		5
	Cis+etoposide							1		1
	Cis+gem				1	1	3	9	1	13
	Cis+pemetrexed						15	1		16
	Cis+vinorelbine							2		2
	Cis+vinorelbine os							1		1
	Crizotinib			3		3				
	Docetaxel						1			1
	Erlotinib			1		1	1			1
	Gefitinib			5	1	6				
	Gem						2	12		14
	Pemetrexed						17	1		18
	Ongoing 1st line			11	2	13	27	14	2	43
	Afatinib			1	1	2				
	Carb+beva+pacli						1			1
	Carb+gem			1		1		4		4
	Carb+nab-paclitaxel							2		2
	Carb+paclitaxel								1	1
	Carb+pemetrexed						10	1		11
	Carb+vinorelbine				1	1		1		1
	Cis+gem						1	2		3
	Cis+nab-paclitaxel							1		1
	Cis+pemetrexed						13		1	14
	Crizotinib			2		2				
	Etoposide							1		1
	Gefitinib			7		7				
	Gem							1		1
	Pemetrexed						2	1		3
	Completed 2nd line			12	2	14	37	29	7	73
	Afatinib	Cis+pemetrexed		1		1				
		Osimeertinib		1		1				
	Carb+gem	Crizotinib		1		1				

Status	Treatment line			Mutated			WT-UK			
	1 st line	2 nd line	3 rd line	Adeno	Squamous	Total	Adeno	Squamous	Other	Total
		Docetaxel						1	1	2
		Erlotinib					1	5		6
		Nivolumab						4	1	5
	Carb+nab-paclitaxel	Nivolumab						1		1
	Carb+pemetrexed	Carb+gem					1			1
		Crizotinib		2		2				
		Docetaxel					3			3
		Erlotinib					6		1	7
	Carb+vinorelbine	Carb+pemetrexed						1		1
		Gem					1			1
		Nivolumab						2		2
	Cis+docetaxel	Nivolumab						1		1
	Cis+gem	Afatinib				1	1			
		Carb+pemetrexed						1		1
		Docetaxel						1	1	2
		Erlotinib						1		1
		Nivolumab						6	1	7
	Cis+pemetrexed	Afatinib		1		1				
		Docetaxel					3			3
		Erlotinib					4	1		5
		Nivolumab					4			4
	Cis+vinorelbine	Docetaxel							1	1
		Erlotinib							1	1
	Erlotinib	Cis+pemetrexed		1		1				
	Gefitinib	Carb+pemetrexed		1		1				
		Osimertinib		4		4				
	Gem	Erlotinib					4	1		5
		Gefitinib				1	1			
Nivolumab							4		4	
Pemetrexed	Erlotinib					7	1		8	
	Nivolumab					1			1	
Ongoing 2nd line				2		2	25	22	1	48

Status	Treatment line			Mutated			WT-UK			
	1 st line	2 nd line	3 rd line	Adeno	Squamous	Total	Adeno	Squamous	Other	Total
	Afatinib	Cis+pemetrexed					1			1
	Carb+docetaxel	Nivolumab						1		1
	Carb+gem	Nivolumab					1	7		8
		Vinorelbine						1		1
	Carb+pemetrexed	Docetaxel					1			1
		Nivolumab					9	1		10
	Carb+vinorelbine	Nivolumab						3		3
	Cis+gem	Nivolumab						5	1	6
	Cis+pemetrexed	Cis+pemetrexed					2			2
		Erlotinib		1		1				
		Nivolumab					9			9
	Cis+vinorelbine	Nivolumab						1		1
	Gefitinib	Osimertinib		1		1				
	Gem	Nivolumab					1	3		4
	Pemetrexed	Cis+gem					1			1
	Completed 3rd line			4		4	11	6		17
	Carb+gem	Carb+pemetrexed	Docetaxel					1		1
			Nivolumab					1		
		Docetaxel	Nivolumab					1		1
		Nivolumab	Docetaxel					1		1
			Erlotinib						1	
	Carb+pemetrexed	Carb+gem	Erlotinib				1			1
		Erlotinib	Carb+gem				1			1
		Gem					1			1
		Nivolumab	Docetaxel				1			1
	Carb+vinorelbine	Crizotinib	Alectinib	1		1				
	Cis+gem	Docetaxel	Erlotinib					1		1
		Gem	Nivolumab				1			1
	Cis+pemetrexed	Docetaxel	Erlotinib				1			1
		Gefitinib	Osimertinib	1		1				
		Nivolumab	Docetaxel					1		1
			Erlotinib					1		

Status	Treatment line			Mutated			WT-UK			
	1 st line	2 nd line	3 rd line	Adeno	Squamous	Total	Adeno	Squamous	Other	Total
	Gefitinib	Cis+docetaxel	Osimertinib	1		1				
	Gem	Erlotinib	Docetaxel				1			1
	Pemetrexed	Carb+gem	Crizotinib	1		1				
		Carb+pemetrexed	Erlotinib				1			1
	Gem	Erlotinib				1			1	
Ongoing 3 rd line				3		3	6	3		9
	Carb+gem	Carb+gem	Nivolumab					1		1
		Carb+vinorelbine	Nivolumab					1		1
		Gem	Nivolumab	1		1				
	Carb+pemetrexed	Crizotinib	Alectinib	1		1				
		Docetaxel	Nivolumab				1			1
		Gem	Nivolumab				1			1
	Cis+pemetrexed	Crizotinib	Alectinib	1		1				
Docetaxel		Nivolumab				4	1		5	
Total				44	6	50	188	125	17	330

Table I-suppl. Therapeutic regimens in non-surgical patients. "Adeno" category includes adenocarcinoma and adenosquamous carcinoma. "Other" category includes lung carcinoma NOS, anaplastic carcinoma, and anaplastic sarcomatoid carcinoma

Beva = bevacizumab; Carb = carboplatin; Cis = cisplatin; Gem = gemcitabine; Os = *per os*; Pacli = paclitaxel; NOS = not otherwise specified

TTNT1	Complete model				Reduced model			
	Effect (95% CI)			p-value	Effect (95% CI)			p-value
Male	-1.24	-3.17	0.69	0.2	-1.25	-3.04	0.54	0.17
Age (per year)	0.06	-0.03	0.15	0.18				
PS 1 vs 0	-1.34	-3.11	0.43	0.14				
PS 2 vs 0	-1.62	-4.22	0.97	0.22				
PS 3 vs 0	-5.06	-12.93	2.82	0.21				
Former smoker vs nonsmoker	-0.46	-3.32	2.41	0.75				
Smoker vs nonsmoker	-0.81	-3.71	2.09	0.58				
Stage III vs IV	-1.17	-2.99	0.66	0.21				
Other histotype vs adeno	0.36	-3.45	4.16	0.85				
Squamous vs adeno	-0.24	-2.13	1.65	0.8				
Mutated vs WT/UK	0.35	-3.07	3.76	0.84				
Maintenance	4.61	2.46	6.76	<0.001	4.83	2.86	6.80	<0.001
TT vs chemo 1L	7.10	2.41	11.79	<0.005	8.06	4.27	11.85	<0.001

Table II-suppl. Results of the multivariate analysis of the TTNT1. Complete and reduced model, after a LASSO regression, are reported. All variables with a p value <0.05 are statistically associated with TTNT1. "Adeno" includes both adenocarcinoma and adenosquamous carcinoma.

1L = patients who didn't undergo second-line therapy; PS = performance status; TT = target therapy; TTNT1 = time between diagnosis and therapy reassessment after failure of first-line treatment; UK = unknown; WT = wild-type

TTNT2	Complete model				Reduced model			
	Effect (95% CI)			p-value	Effect (95% CI)			p-value
Male	0.69	-3.27	4.65	0.73				
Age (per year)	-0.03	-0.21	0.15	0.76				
PS 1 vs 0	-4.23	-7.91	-0.55	<0.05	-4.08	-7.64	-0.52	<0.05
PS 2 vs 0	-5.69	-10.47	-0.91	<0.05	-5.29	-9.77	-0.82	<0.05
PS 3 vs 0	-8.68	-19.78	2.43	0.12	-8.57	-19.46	2.32	0.12
Former smoker vs nonsmoker	1.85	-3.20	6.90	0.47	1.80	-2.97	6.58	0.46
Smoker vs nonsmoker	-0.30	-5.55	4.96	0.91	-0.17	-5.12	4.78	0.95
Stage III vs IV	-0.87	-4.78	3.04	0.66				
Other histotype vs adeno	6.47	-0.10	13.05	0.05	6.19	-0.19	12.56	0.06
Squamous vs adeno	0.31	-3.35	3.97	0.87	0.22	-3.31	3.75	0.90
Mutated vs WT/UK	1.53	-3.82	6.89	0.57	1.36	-3.52	6.24	0.58
Maintenance	3.11	-2.49	8.71	0.27	3.19	-2.12	8.49	0.24
TT vs chemo 1L	16.12	5.95	26.30	<0.005	16.44	6.62	26.27	<0.005
ICI vs chemo 2L	0.08	-4.25	4.40	0.97	0.27	-3.91	4.44	0.90
TT vs chemo 2L	4.85	0.98	8.73	<0.05	4.88	1.23	8.52	<0.01

Table III-suppl. Results of the multivariate analysis of the TTNT2. Complete and reduced model, after a LASSO regression, are reported. All variables with a p value <0.05 are statistically associated with TTNT2. "Adeno" includes both adenocarcinoma and adenosquamous carcinoma.

1L = patients who didn't undergo second-line therapy; 2L = patients who didn't undergo third-line therapy; ICI = immune checkpoint inhibitors; PS = performance status; TT = target therapy; TTNT2 = time between diagnosis and therapy reassessment after failure of second-line treatment; UK = unknown; WT = wild-type

Length of therapy (months)	661	541	780	<0.001	1,050	711	1,388	<0.001	1,383	628	2,137	<0.001
Former smoker vs nonsmoker	1,569	-159	3,297	0.07	-4,116	-13,258	5,026	0.37	6,211	-11,708	24,130	0.48
Smoker vs nonsmoker	1,473	-271	3,217	0.1	-4,744	-14,537	5,049	0.34	7,842	-13,688	29,373	0.46
Stage III vs IV					8,988	3,280	14,696	<0.005	-10,347	-24,161	3,466	0.14
Other histotype vs adeno	-5,519	-8,459	-2,579	<0.001	-8,451	-20,246	3,344	0.16	-12,232	-29,127	4,664	0.15
Squamous vs adeno	-4,015	-5,174	-2,856	<0.001	-2,442	-8,794	3,910	0.45				
Mutated vs WT/UK					10,069	923	19,214	<0.05	17,256	870	33,641	<0.05
Ongoing vs completed therapy	3,062	1,882	4,242	<0.001	9,316	2,691	15,941	<0.01	28,904	14,734	43,074	<0.001
Maintenance	6,231	4,637	7,824	<0.001	4,352	-4,121	12,826	0.31	5,767	-12,560	24,094	0.52
TT vs chemo 1L	5,977	4,037	7,916	<0.001								
ICI vs chemo 2L					11,300	3,583	19,016	<0.005	25,202	8,106	42,297	<0.01
TT vs chemo 2L					3,673	-3,872	11,217	0.34	1,447	-14,464	17,359	0.85
ICI vs chemo 3L												
TT vs chemo 3L												
Adjusted R ²	0.6458			<0.001	0.428			<0.001	0.6667			<0.001

Table IV-suppl. Results of the multivariate analysis of the TTNT2. Complete and reduced model, after a LASSO regression, are reported. All variables with a p value <0.05 are statistically associated with total costs. "Adeno" includes both adenocarcinoma and adenocarcinoma.

1L = patients who didn't undergo second-line therapy; 2L = patients who didn't undergo third-line therapy; 3L = patients who received a complete or partial third-line therapy; ICI = immune checkpoint inhibitors; PS = performance status; TT = target therapy; TTNT2 = time between diagnosis and therapy reassessment after failure of second-line treatment; UK = unknown; WT = wild-type