

Supplementary Table S1. Pathological features of cases examined.

N	Age	Sex	Site	Material	Histotype	PD-L1	V600E (Y,N)	Aminoacid change	Co-mutations
1	67	M	hilar lymph node	cytological	adenoca	neg	N	D594N	CHD4
2	63	F	mediastinal lymph node	cytological	adenoca	high	Y	V600E	
3	65	M	bone	biopsy	adenoca	low	N	N581S	
4	74	M	lung	biopsy	adenoca	low	N	G596R	
5	74	M	lung	biopsy	adenoca	high	N	G466V	KRAS, PIK3CA
6	73	F	lung	biopsy	adenoca	low	Y	V600E	KRAS, MET
7	74	M	bone	biopsy	adenoca	low	N	G466A	FGFR3
8	85	M	lung	cytological	adenoca	high	N	D594F	KRAS, PAM2K1
9	83	F	lung	cytological	adenosquamous ca	high	N	N581S	
10	67	M	lung	cytological	adenoca	neg	N	D594N	
11	67	M	lung	biopsy	adenoca	neg	N	N581S	FGFR3
12	77	F	lung	biopsy	adenoca	low	N	L584F	KRAS
13	63	M	stomach (metastasis)	biopsy	adenoca	high	N	D594G	
14	78	M	bone	biopsy	adenoca	low	N	G469V	
15	79	M	pleura	biopsy	adenoca	high	Y	V600E	
16	76	M	hilar lymph node	cytological	adenoca	high	N	G469V	
17	52	M	pericardial effusion	cytological	adenoca	low	N	L597Q	
18	62	M	lung	biopsy	adenoca	neg	N	G466A	
19	71	M	pleura	biopsy	adenoca	low	N	G464V	KRAS
20	72	M	pleura	biopsy	adenoca	low	N	G469A	
21	84	M	lung	surgical	adenoca	low	Y	V600E	
22	45	F	lung	biopsy	adenoca	high	Y	V600E	AKT1, MTOR
23	58	F	mediastinal lymph node	cytological	adenoca	high	Y	V600E	
24	81	F	mediastinal lymph node	cytological	adenoca	low	N	N581S	
25	96	F	lung	cytological	adenoca		Y	V600E	
26	81	F	lung	cytological	adenoca	neg	Y	V600E	
27	64	M	liver (metastasis)	biopsy	adenoca	high	Y	V600E	IDH1
28	79	M	lung	biopsy	adenoca	high	Y	V600E	PIK3CA
29	65	F	lung	biopsy	adenoca	high	Y	V600E	
30	78	M	lung	surgical	adenoca	high	N	K601E	
31	67	M	lung	biopsy	adenoca	low	N	K601E	
32	79	F	mediastinal lymph node	cytological	adenoca	low	N	G469A	ESR1
33	79	M	lung	cytological	adenoca	high	Y	V600E	
34	75	M	lung	surgical	adenoca	low	Y	V600E	
35	68	M	lung	surgical	adenoca	neg	Y	V600E	PIK3CA
36	65	M	lung	biopsy	adenoca	low	Y	V600E	
37	68	F	lung	cytological	adenoca	low	Y	V600E	
38	55	M	lung	biopsy	adenoca	high	N	G464V	KRAS
39	55	F	lung	surgical	adenoca	low	N	G469V	
40	84	F	pleura	biopsy	adenoca	low	Y	V600E	
41	47	M	mediastinal lymph node	cytological	NOS	high	N	G469A	PIK3CA
42	73	F	lung	surgical	adenoca		N	D594N	
43	77	F	lung	cytological	adenoca		N	G469A	PIK3CA
44	55	F	hilar lymph node	surgical	adenoca		Y	V600E	
45	69	F	mediastinal lymph node	cytological	adenoca	high	Y	V600E	
46	68	F	lung	surgical	adenoca		N	G466A	

47	77	F	pleura	biopsy	adenoca	low	N	D594N	
48	74	M	mediastinal lymph node	cytological	adenoca	low	Y	V600E	
49	61	M	mediastinal lymph node	cytological	adenoca	high	N	G466A	
50	79	M	lung	biopsy	adenoca	low	N	E586G	EGFR
51	60	F	lung	biopsy	adenoca	neg	Y	V600E	IDH1
52	70	M	lung	biopsy	NOS		N	G258V	KRAS
53	72	M	lung	biopsy	squamous cell ca	high	N	V471F	
54	68	M	lung	biopsy	adenoca	low	Y	V600E	
55	73	F	lung	biopsy	adenoca	low	N	G466A	
56	83	F	lung	biopsy	adenoca	high	N	G466V	
57	80	M	bone	biopsy	adenoca	low	N	G466V	KRAS, EGFR
58	79	M	pleura	biopsy	adenoca	low	Y	V600E	
59	79	M	lung	surgical	adenoca		Y	V600E	
60	78	M	lung	biopsy	sarcomatoid ca	high	N	N581I	GNAQ

Legend: N Number, M male, F female, adenoca adenocarcinoma, ca carcinoma, NOS not otherwise specified, neg negative, Y yes, N no, TPS tumor proportion score). In PD-L1: negative TPS<1%; low TPS 1-49%, high TPS ≥50%.

Supplementary Table S2. Clinical stages and therapeutic regimens of cases examined. TKI therapy against BRAF is highlighted in **red** (alone and/or with CT: total N. 11 cases).

N	Age	Sex	Stage	Adjuvant therapy	Adjuvant regimen	First line therapy	First line regimen	Second line therapy	Second line regimen	Third line therapy	Third line regimen
1	67	M	IIIB			CT	carboplatinum, gemcitabine	none			
2	63	F	IV			none					
3	65	M	IV			CT	carboplatinum, pemetrexed	none			
4	74	M	IIIB			none					
5	74	M	IV			IT	pembrolizumab	CT	carboplatinum, pemetrexed	CT	paclitaxel
6	73	F	IV			CT-IT	carboplatinum, pemetrexed, pembrolizumab	TKI (BRAF)	dabrafenib, trametinib		
7	74	M	IV			CT-IT	carboplatinum, pemetrexed, pembrolizumab	none			
8	85	M	IV			IT	pembrolizumab	none			
9	83	F	IIIA			CT	carboplatinum, gemcitabine	nv			
10	67	M	IV			CT-IT	carboplatinum, pemetrexed, pembrolizumab	CT	carboplatinum, gemcitabine	none	
11	67	M	IV			CT-IT	carboplatinum, pemetrexed, pembrolizumab	CT	docetaxel		
12	77	F	IV			none					
13	63	M	IV			IT	pembrolizumab	CT	carboplatinum, pemetrexed		
14	78	M	IV			none					
15	79	M	IV			TKI (BRAF)	dabrafenib, trametinib				
16	76	M	IV			IT	pembrolizumab	none			
17	52	M	IV			none					
18	62	M	IV			CT-IT	carboplatinum, pemetrexed,	CT	vinorelbine (oral)	none	

							pembrolizumab			
19	71	M	nv			nv				
20	72	M	nv			none				
21	84	M	nv (POR)			none				
22	45	F	nv			TKI (BRAF)	dabrafenib, trametinib	IT	pembrolizuma b	CT pemetrexed, cisplatinu
23	58	F	nv			IT	pembrolizumab	CT	carboplatinu m gemcitabine	none
24	81	F	nv			CT	gemcitabine	IT	atezolizumab	
25	96	F	nv			none				
26	81	F	IV			none				
27	64	M	IV			TKI (BRAF)	dabrafenib, trametinib			
28	79	M	IV			none				
29	65	F	IV			IT	atezolizumab			
30	78	M	nv (POR)			none				
31	67	M	nv			CT	carboplatinu m, paclitaxel	IT	durvalumab	
32	79	F	IV			CT-IT	carboplatinu m, pemetrexed, pembrolizumab	none		
33	79	M	IV			IT	pembrolizumab	none		
34	75	M	IIB *			TKI (BRAF)	dabrafenib, trametinib	nv		
35	68	M	IIB	CT	cisplatinu m, vinorelbine	none		nv		
36	65	M	IV			CT	carboplatinu m, pemetrexed, pembrolizumab	TKI (BRAF)	dabrafeninb, trametinib	
37	68	F	IV			TKI (BRAF)	dabrafenib, trametinib	none		
38	55	M	IV			IT	pembrolizumab	none		
39	55	F	IIA*	CT		none				
40	84	F	IV			TKI (BRAF)	dabrafenib, trametinib			
41	47	M	IV			IT	pembrolizumab	none		
42	73	F	IIIA (POR)			none				
43	77	F	IV			CT	cisplatinu m, pemetrexed	IT	nivolumab	CT carboplatinu m, gemcitabine
44	55	F	IIB*	CT	cisplatinu m, gemcitabine	none				
45	69	F	IIIB			TKI (BRAF)	dabrafenib, trametinib			
46	68	F	IA* (POR)			none				
47	77	F	IV			CT-IT	carboplatinu m, pemetrexed, pembrolizumab	CT	docetaxel (weekly)	
48	74	M	IV			IT	relatlimab, nivolumab, ipilimumab	CT	gemcitabine, carboplatinu m	CT vinorelbine
49	61	M	nv			nv				
50	79	M	IV			TKI (EGFR)	osimertinib	CT	gemcitabine	CT vinorelbine

51	60	F	IIIC	CT	carboplatinum, paclitaxel	TKI (BRAF)	dabrafenib, trametinib
52	70	M	nv	none			
53	72	M	nv	CT	gemcitabine, carboplatinum	IT	durvalumab
54	68	M	nv	TKI (BRAF)	dabrafenib, trametinib	none	
55	73	F	nv	CT-IT	carboplatinum, pemetrexed, pembrolizumab		
56	83	F	nv	nv			
57	80	M	IV	nv			
58	79	M	IV	nv			
59	79	M	IA* (POR)	nv			
60	78	M	nv	IT	pembrolizumab		

Legend: N Number, CT chemotherapy, IT immunotherapy, TKIs tyrosine kinase inhibitors, nv not valuable (information not available), none no therapy (no therapy administered during FU), POR postoperative recurrence. * in these cases, the stage was based on the initial pathological diagnosis performed on the surgical specimen.

Supplementary Table S3. Data on OS and PFS.

N	Age	Sex	OS months	OS status	PFS months	PFS status
1	67	M	2	1	2	1
2	63	F	0	1	0	1
3	65	M	6	1	6	1
4	74	M	1	1	1	1
5	74	M	19	1	10	1
6	73	F	23	1	23	1
7	74	M	2	1	2	1
8	85	M	7	1	7	1
9	83	F	4	1	4	1
10	67	M	8	1	5	1
11	67	M	8	1	5	1
12	77	F	6	1	6	1
13	63	M	6	1	6	1
14	78	M	0	1	0	1
15	79	M	6	1	3	1
16	76	M	2	1	2	1
17	52	M	1	1	1	1
18	62	M	4	1	2	1
19	71	M	4	1	4	1
20	72	M	1	1	1	1
21	84	M	1	1	1	1
22	45	F	17	1	17	1
23	58	F	11	1	11	1
24	81	F	10	1	10	1
25	96	F	0	0*	0	0
26	81	F	21	1	21	1
27	64	M	6	1	6	1
28	79	M	1	1	1	1
29	65	F	14	1	14	1
30	78	M	0	1	0	1
31	67	M	9	1	9	1
32	79	F	25	0	20	1
33	79	M	47	0	47	0
34	75	M	10	0	10	0
35	68	M	42	0	42	0

36	65	M	33	0	3	1
37	68	F	33	0	33	0
38	55	M	30	0	30	0
39	55	F	18	0	18	0
40	84	F	13	0	13	0
41	47	M	42	0	23	1
42	73	F	18	0	18	0
43	77	F	10	0	10	0
44	55	F	7	0	7	0
45	69	F	8	0	8	0
46	68	F	2	0	2	0
47	77	F	13	1	3	1
48	74	M	49	0	45	1
49	61	M				
50	79	M				
51	60	F	46	0	1	1
52	70	M	2	1	2	1
53	72	M	27	1	27	1
54	68	M				
55	73	F	4	1	4	1
56	83	F	1	1	1	1
57	80	M				
58	79	M				
59	79	M	20	0	20	0
60	78	M				

Legend: N Number, OS overall survival, PFS progression-free survival. In OS Status and PFS Status: 1 means event and 0 censored.
* OS Status was considered censored (died of other cause), since the patient had 96 years of age when deceased.

Supplementary Table S4. Summary of the Cox regression multivariate analysis.

	OS		PFS	
<i>N. event</i>	23		28	
<i>N. censored</i>	17		12	
<i>N. total</i>	40		40	
Variables	HR (95% CI)	p	HR (95% CI)	p
<i>V600E (Y/N)</i>	0.271 (0.103-0.717)	0.008	0.347 (0.145-0.831)	0.017
<i>Stage (I,II,III,IV,V)</i>	3.044 (1.003-9.238)	0.049	2.453 (0.983-6.121)	0.055
<i>Therapy (TKI, IT, CT and CT-IT)</i>	0.548 (0.356-0.842)	0.006	0.607 (0.417-0.883)	0.009

Legend: N number, OS overall survival, PFS progression-free survival, HR hazard ratio, CI confidence interval, Y yes, N no, CT chemotherapy, IT immunotherapy, TKI tyrosine kinase inhibitor.