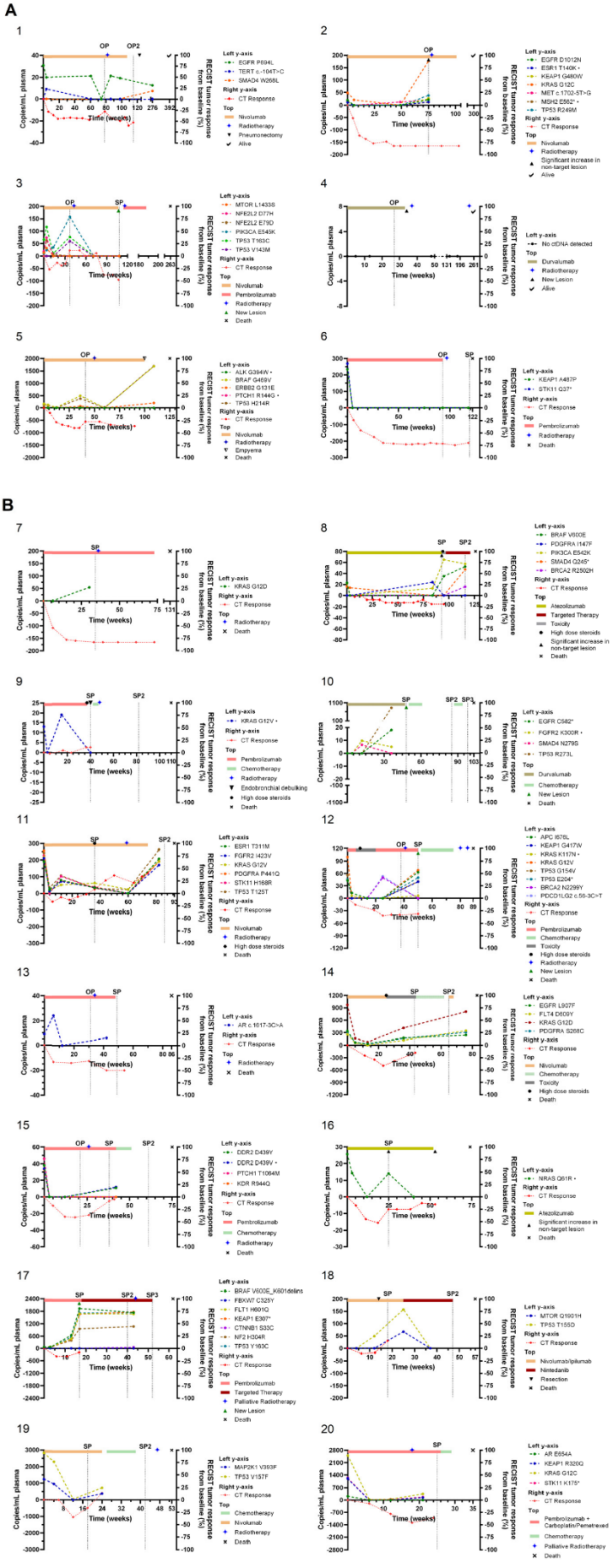

A
1
OP
OP2
Copies/mL plasma
RECIST tumor response from baseline (%)
Time (weeks)
Left y-axis
EGFR P694L
TERT c.-104T>C
SMAD4 W356L
Right y-axis
CT Response
Top
Nivolumab
Radiotherapy
Pneumonectomy
Alive
2
OP
Left y-axis
EGFR D1012N
ESR1 T140K
KEAP1 G480W
KRAS G12C
MET c.1703-5T>G
MSH2 E562*
TP53 R249M
Right y-axis
CT Response
Top
Nivolumab
Radiotherapy
Significant increase in non-target lesion
Alive
3
OP
SP
Left y-axis
MTOR L1433S
NFE2L2 D77H
NFE2L2 E79D
PIK3CA E545K
TP53 T163C
TP53 V143M
Right y-axis
CT Response
Top
Nivolumab
Pembrolizumab
Radiotherapy
New Lesion
Death
4
OP
Left y-axis
No ctDNA detected
Top
Durvalumab
Radiotherapy
New Lesion
Alive
5
OP
Left y-axis
ALK G394W
BRAF G469V
ERBB2 G131E
PTCH1 R144G
TP53 H214R
Right y-axis
CT Response
Top
Nivolumab
Radiotherapy
Empyema
Death
6
OP
SP
Left y-axis
KEAP1 A487P
STK11 Q37*
Right y-axis
CT Response
Top
Pembrolizumab
Radiotherapy
Death
B
7
SP
Left y-axis
KRAS G12D
Right y-axis
CT Response
Top
Radiotherapy
Death
8
SP
SP2
Left y-axis
BRAF V600E
FDGFRA I147F
PIK3CA E542K
SMAD4 Q245*
BRCA2 R2502H
Right y-axis
CT Response
Top
Atezolizumab
Targeted Therapy
Toxicity
High dose steroids
Significant increase in non-target lesion
Death
9
SP
SP2
Left y-axis
KRAS G12V
Right y-axis
CT Response
Top
Pembrolizumab
Chemotherapy
Radiotherapy
Endobronchial debulking
High dose steroids
Death
10
SP
SP2
SP3
Left y-axis
EGFR C582*
FGFR2 K300R
SMAD4 N276S
TP53 R273L
Top
Durvalumab
Chemotherapy
New Lesion
Death
11
SP
SP2
Left y-axis
ESR1 T311M
FGFR2 I423V
KRAS G12V
PDGFRA P441Q
STK11 H168R
TP53 T125T
Right y-axis
CT Response
Top
Nivolumab
Radiotherapy
High dose steroids
Death
12
OP
SP
Left y-axis
APC I676L
KEAP1 G417W
KRAS K117N
KRAS G12V
TP53 D154V
TP53 E204*
BRCA2 N2299Y
PDCD1LG2 c.66-3C>T
Right y-axis
CT Response
Top
Pembrolizumab
Chemotherapy
Toxicity
High dose steroids
Radiotherapy
New Lesion
Death
13
OP
SP
Left y-axis
AR c.1617-3C>A
Right y-axis
CT Response
Top
Radiotherapy
Death
14
SP
SP2
Left y-axis
EGFR L907F
FLT4 D859Y
KRAS G12D
PDGFRA S268C
Right y-axis
CT Response
Top
Nivolumab
Chemotherapy
Toxicity
High dose steroids
Death
15
OP
SP
SP2
Left y-axis
DDR2 D439Y
DDR2 D439V
PTCH1 T1064M
KDR R944Q
Right y-axis
CT Response
Top
Pembrolizumab
Chemotherapy
Radiotherapy
Death
16
SP
Left y-axis
NRAS Q61R
Right y-axis
CT Response
Top
Atezolizumab
Significant increase in non-target lesion
Death
17
SP
SP2
SP3
Left y-axis
BRAF V600E_K601delins
FBXW7 C325Y
FLT1 H601Q
KEAP1 E307*
CTNNB1 S33C
NF2 H304R
TP53 Y163C
Right y-axis
CT Response
Top
Pembrolizumab
Targeted Therapy
Palliative Radiotherapy
New Lesion
Death
18
SP
SP2
Left y-axis
MTOR Q1931H
TP53 T155D
Right y-axis
CT Response
Top
Nivolumab/Ipilumab
Nintedanib
Resection
Death
19
SP
SP2
Left y-axis
MAP2K1 V393F
TP53 V157F
Right y-axis
CT Response
Top
Chemotherapy
Nivolumab
Radiotherapy
Death
20
SP
Left y-axis
AR E654A
KEAP1 R320Q
KRAS G12C
STK11 K175*
Right y-axis
CT Response
Top
Pembrolizumab + Carboplatin/Pemetrexed
Chemotherapy
Palliative Radiotherapy
Death

Supplementary Figure S1: Detailed individual patient monitoring using ctDNA. Each profile combines mutant ctDNA levels with sum of target lesions change measured by CT scan (RECIST v1.1) of patients with OP (A) and SP (B). Patient numbers match with the numbers shown in Figure 1. Mutant ctDNA levels are plotted on the left y-axis. Variants marked with a dot had a variant depth < 10 but were detected at multiple timepoints within the same patient. Changes in tumor size (as sum of target lesions) are plotted on the right y-axis, in case of tumor progression due to new lesions or significant progression of non-target lesions this was indicated with a triangle at the moment of OP or SP. The bar on top shows which treatments the patients received over time, key clinical procedures, moment of OP, SP, SP2, SP3 (systemic progression for the respective second- or third time after subsequent systemic therapy) and final survival status. Each figure (1-20) depicts an individual patient, sorted by OS and patient grouping as described in table 2. Patients 12, 13, and 15 were initially treated as OP, but turned out to be SP. Patients 4 and 10 had no target lesions according to RECIST as they were treated with chemoradiotherapy preceding durvalumab treatment for stage 3 disease.

Supplementary Table S1: Local ablative treatment during ICI-treatment in study cohort

Patient	Site of progression	Local treatment	Duration to second progression* (weeks)
OP			
1	Primary tumor left lung	RT 10x3Gy	35 weeks
	2nd time OP: primary tumor	Pneumonectomy	Not reached
2	Rib metastasis (solitary)	RT 1x8Gy	Not reached
3	Primary tumor right lung	RT 17x3Gy	67
	2nd time OP: lymph nodes Naruke 8 +11/12L	RT 10x3Gy	Not reached/ died due to other cancer
4	Brain metastasis (solitary)	RT 1x 20Gy	149
	2nd time: 4 brain metastases	Gamma Knife	Not reached
5	Primary tumor left lung	RT 17x13Gy	68
6	Brain metastasis (solitary)	RT 24G in 3 fraction 3x8Gy	26
SP cases initially treated as OP			
12	lymph nodes paratracheal (1) and low cervical (1)	RT 5x4Gy	12
13	Primary tumor right lung	RT 8x7,5Gy	18
15	Left lung (nodule)	RT 1x 20Gy	17

RT = radiotherapy, Gy = gray

*Either systemic progression or oligoprogression occurring for the second time.

Supplementary Table S2A: Key ctDNA measurements in the OP group

	Baseline		OP			Sample before OP		
Patient	Mutant copies	Number of mutations	Mutant copies	Number of mutations	ctDNA change between baseline and OP	Mutant copies	Number of mutations	ctDNA change between this sample and OP
1	30,9	1	0	0	-100%	21	1	-100%
2	133,5	6	308,7	7	131%	12,7	1	2331%
3	137	5	295	3	115%	54	3	446%
4	0	0	0	0	N/A	0	0	N/A
5	312	4	943	5	202%	17	1	5447%
6	503	2	0	0	-100%	0	0	0%

Supplementary Table S2B: Key ctDNA measurements in the SP group

	Baseline		SP			Sample before SP		
Patient number	Mutant copies	Number of mutations	Mutant copies	Number of mutations	ctDNA change between baseline and SP	Mutant copies	Number of mutations	ctDNA change between this sample and SP
7	0	0	54	1	100%	0	0	100%
8	60	3	100	2	67%	37	2	170%
9	27	1	0	0	-100%	19	1	-100%
10	0	0	842	3	100%	16,3	2	5066%
11	1344	6	231	6	-83%	490	6	-53%
12	245	4	268	6	9%	103	2	160%
13	9	1	6	1	-33%	0	0	100%
14	2160	4	868	4	-60%	138	3	529%
15	151	4	23	2	-85%	0	0	100%
16	25,7	1	14,2	1	-45%	0	0	100%
17	295	6	7914	5	2583%	2485	5	218%
18	0	0	224	2	100%	0	0	357%
19	4714	2	1125	2	-76%	52	1	2063%
20	5169	4	653	3	-87%	73	2	795%

Supplementary Table S3: Overview of variants found in each patient

Patient	Variants detected in each patient							
1	*EGFR* p.P694L	*TERT* c.-104T>C	*SMAD4* p.W268L					
2	***TP53* p.R249M**	*EGFR* p.D1012N	*ESR1* p.T140K	***KEAP1* p.G480W**	***KRAS* p.G12C**	*MET* c.1702-5T>G	***MSH2* p.E562***	
3	***TP53* p.V143M**	***PIK3CA* p.E545K**	***TP53* p.T163C**	***MTOR* p.L1433S**	***NFE2L2* p.D77H**	***NFE2L2* p.E79D**		
4	No variants detected							
5	*PTCH1* p.R144G	*ALK* p.G394W	***BRAF* p.G469V**	*ERBB2* p.G131E	***TP53* p.H214R**			
6	*KEAP1* p.A487P	***STK11* p.Q37***						
7	***KRAS* p.G12D**							
8	***BRAF* p.V600E**	***PIK3CA* p.E542K**	*BRCA2* p.R2502H	*PDGFRA* p.I147F	***SMAD4* p.Q245***			
9	***KRAS* p.G12V**							
10	*EGFR* p.C582*	***TP53* p.R273L**	*FGFR2* p.K300R	*SMAD4* p.N279S				
11	*ESR1* p.T311M	*FGFR2* p.I423V	***KRAS* p.G12V**	*PDGFRA* p.P441Q	***STK11* p.H168R**	***TP53* p.T125T**		
12	*KEAP1* p.G417W	*APC* p.I676L	***KRAS* p.G12V**	***KRAS* p.K117N**	***TP53* p.G154V**	***TP53* p.E204***	*BRCA2* p.N2299Y	*PDCD1LG2* c.56-3C>T
13	*AR* c.1617-3C>A							
14	*EGFR* p.L907F	*FLT4* p.D609Y	***KRAS* p.G12D**	*PDGFRA* p.S268C				
15	*DDR2* p.D439Y	*DDR2* p.D439V	*KDR* p.R944Q	*PTCH1* p.T1064M				
16	***NRAS* p.Q61R**							
17	***BRAF* p.V600E_K601delins**	*FLT1* p.H601Q	***KEAP1* p.E307***	*NF2* p.H304R	***TP53* p.Y163C**	*CTNNB1* p.S33C	*FBXW7* p.C325Y	
18	*MTOR* p.Q1901H	***TP53* p.T155D**						
19	*MAP2K1* p.V393F	***TP53* p.V157F**						
20	*KEAP1* p.R320Q	***KRAS* p.G12C**	***STK11* p.K175***	*AR* p.E654A				

Supplementary Table S3: Variants exclusively found at the moment of OP are marked red, variants found at OP and other timepoints are marked pink. Variants found exclusively at SP are marked dark blue, variants found at SP and other timepoints are marked light blue. Variants marked white were not detected at the moment of OP or SP. Variants in bold text are considered pathogenic or likely pathogenic.