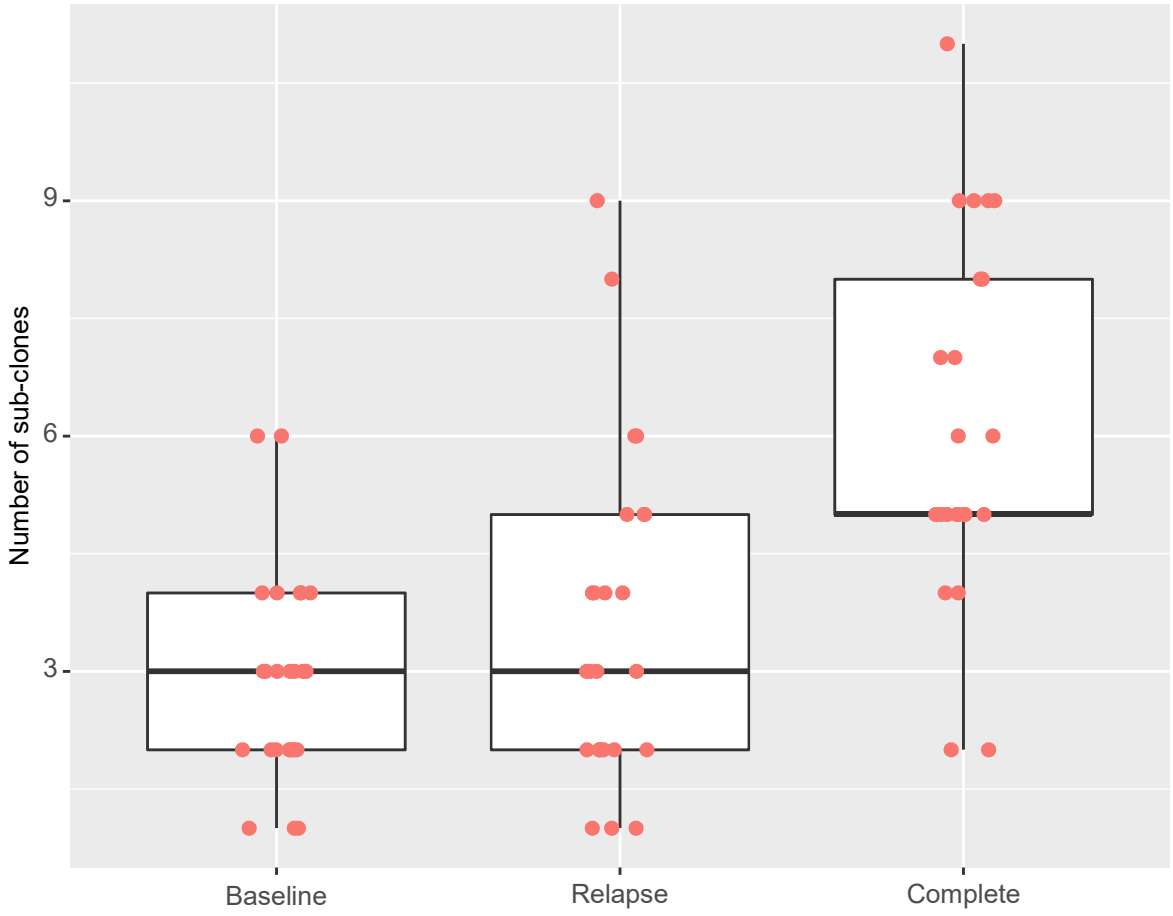
SUPPLEMENTARY INFORMATION

The Spatio-Temporal Evolution of Multiple Myeloma from Baseline to Relapse-Refractory States

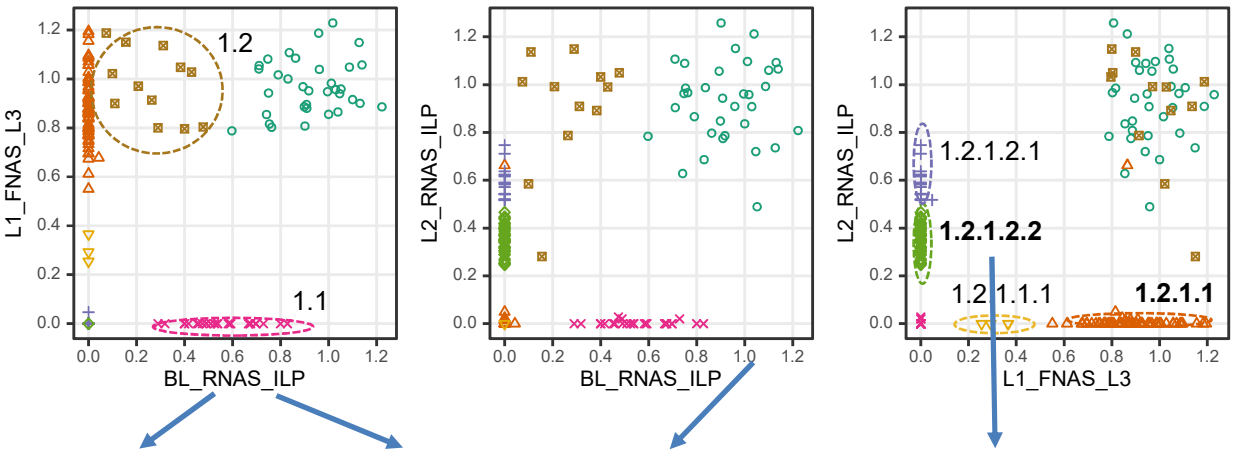
Rasche *et al.*

Supplementary Figures

Supplementary Fig. 1: The number of sub-clones per patient. Boxplots for the number of sub-clones at baseline (iliac crest and focal lesion sub-clones combined), relapse (all follow-up iliac crest and focal lesion samples combined), or during the entire course of the disease (baseline & relapse -> complete). Sub-clones were defined based on SciClone clusters and presence of at least three mutations or at least one copy number aberration.



Supplementary Figure 2: Description of Supplementary Figures 3-27. The figure describes the cancer clonal fraction and mock ongogenetic tree plots shown in Supplementary Figures 3-27. Clonal substructures were inferred using SciClone with default parameters and the filtered set of SNVs. For the manual design of mock phylogenetic trees, the output of SciClone was further interpreted after inclusion of copy number data.

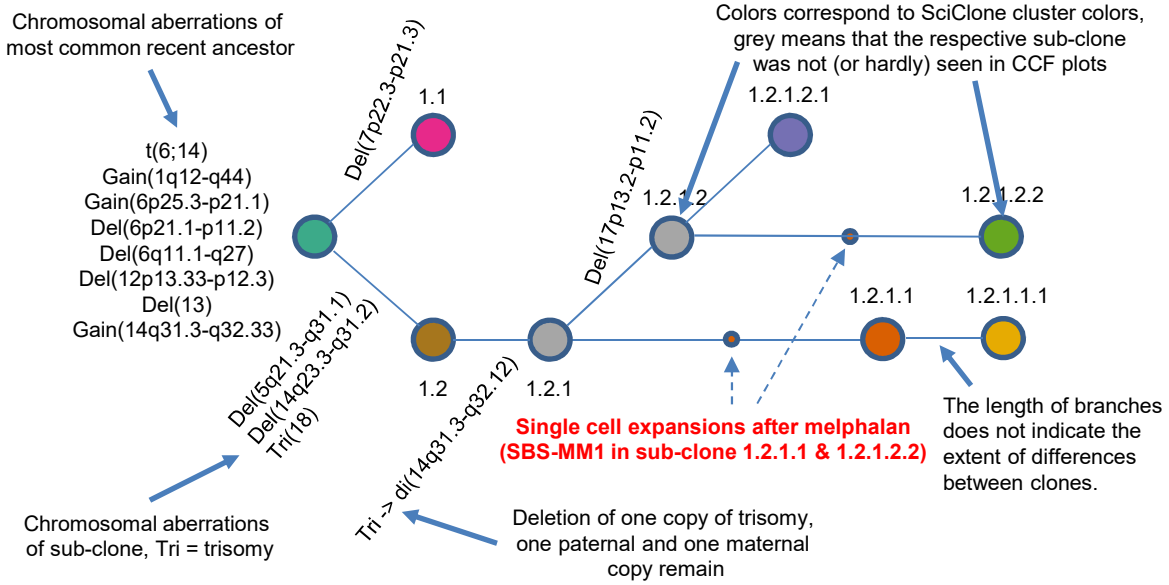


Time point of sample collection, e.g. BL = baseline L1 = after/during first treatment line

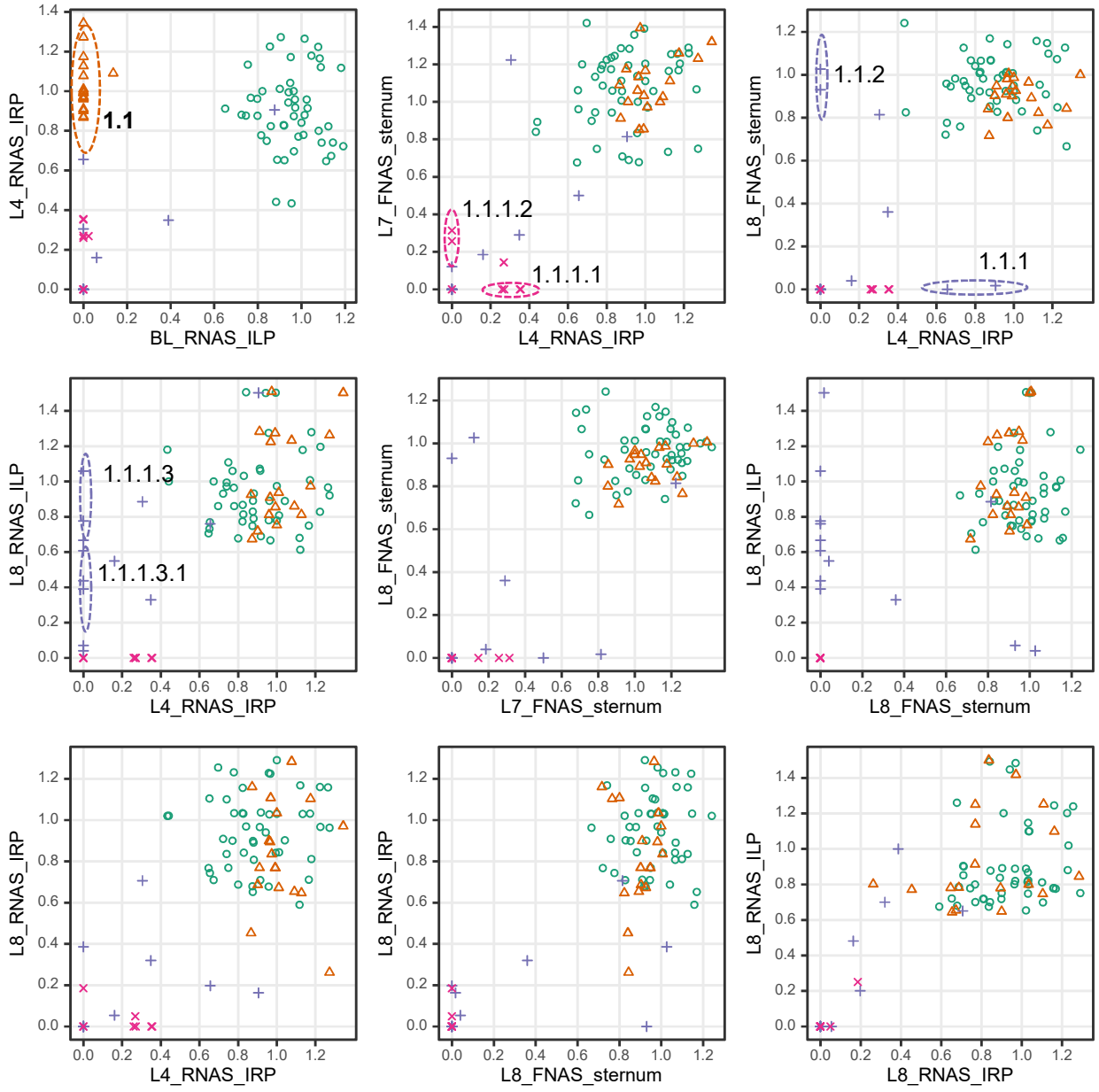
Origin of sample, e.g. RNAS_ILP = random aspirate from left iliac crest, IRP = right iliac crest, FNAS_L3 = fine-needle aspirate from focal lesion at 3rd lumbar vertebra

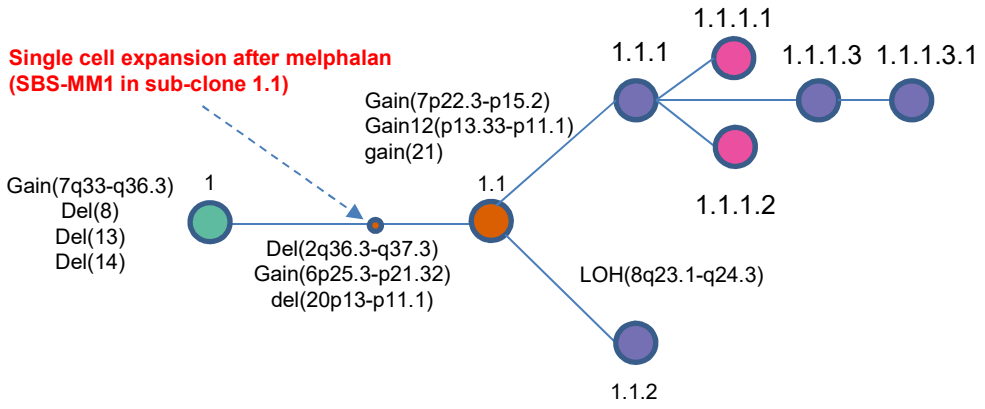
Cancer clonal fraction (CCF)

ID of a sub-clone which was assigned to a SciClone cluster, Sub-clones, which were checked for presence of the melphalan SBS-MM1 signature using *mmsig* and the mSigAct signature presence test, are printed in bold. Test results are shown in Suppl. Table 4.

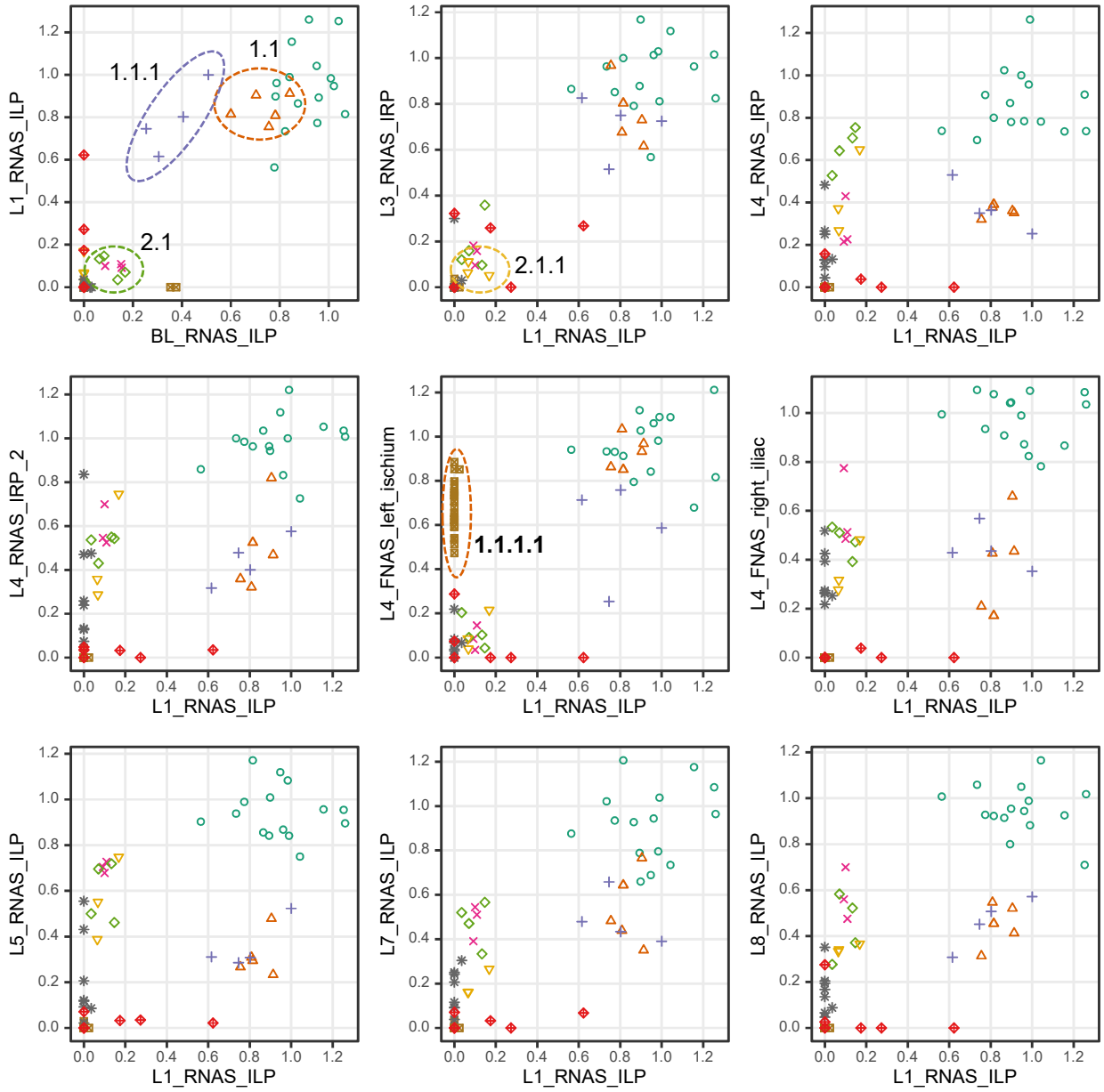


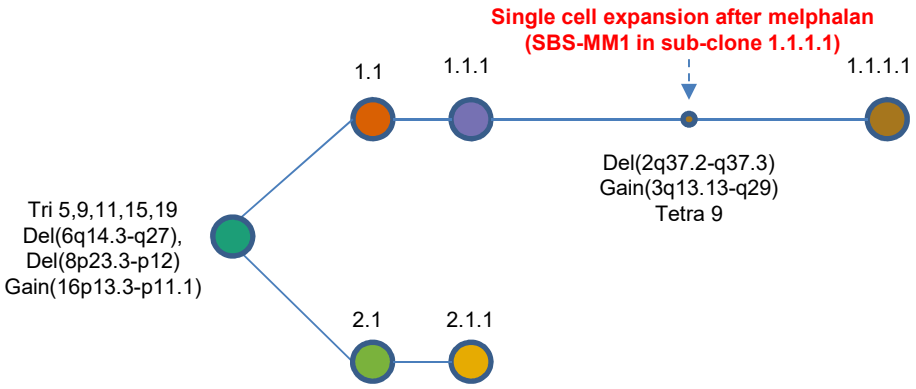
Supplementary Figure 3: Cancer clonal fraction plots and oncogenetic tree for patient #1.
A detailed legend is provided in Suppl. Fig. 2.



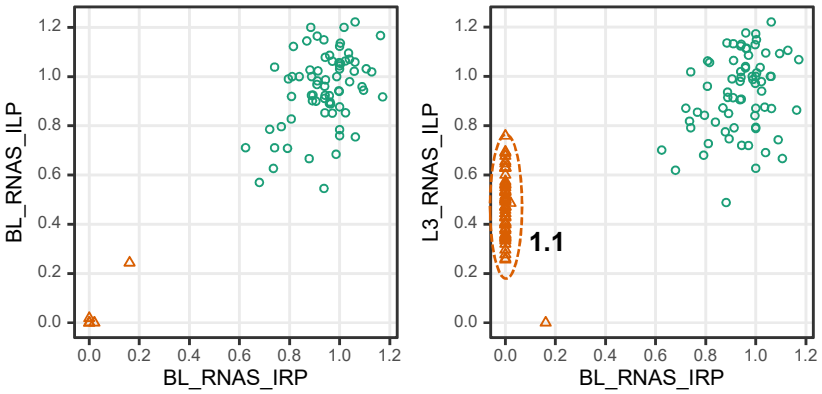


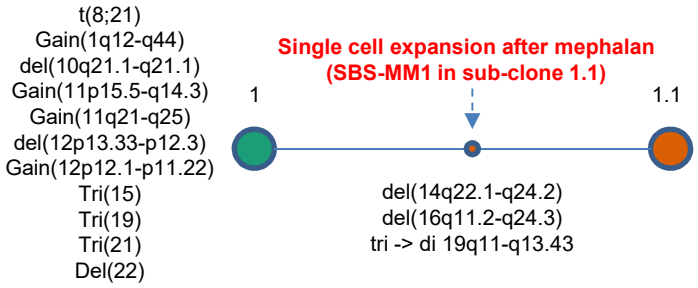
Supplementary Figure 4: Cancer clonal fraction plots and oncogenetic tree for patient #2.
A detailed legend is provided in Suppl. Fig. 2.



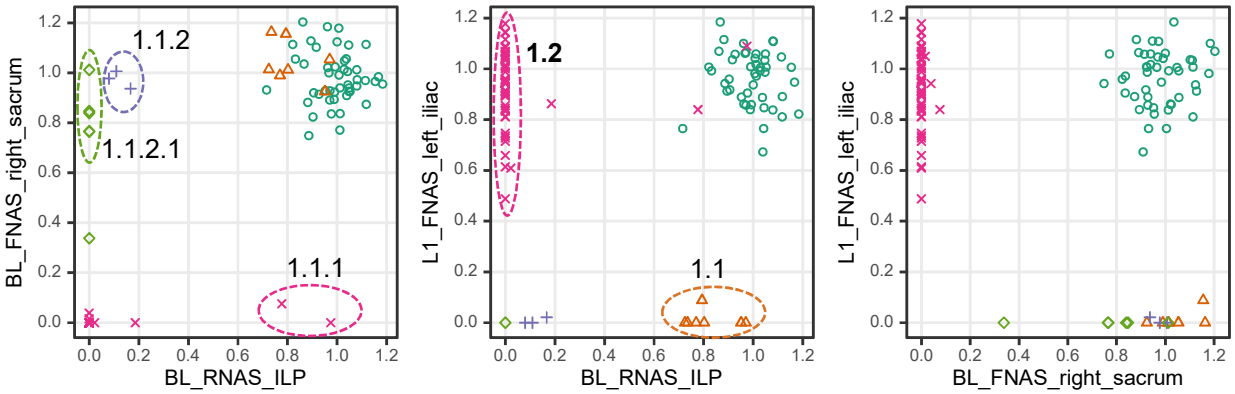


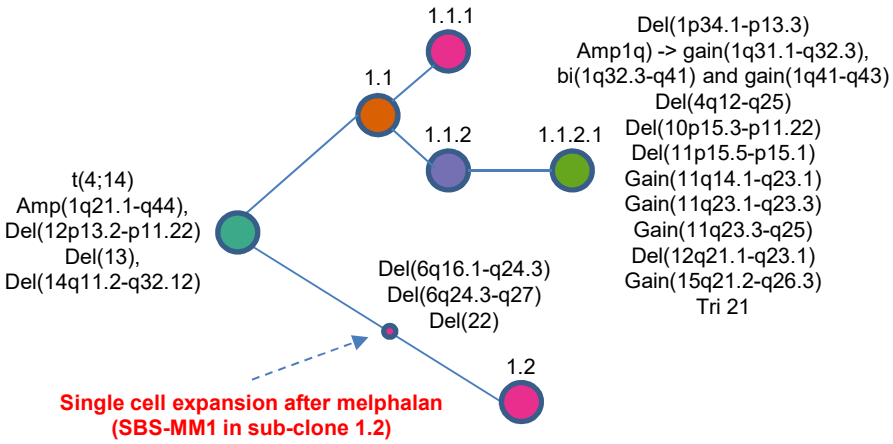
Supplementary Figure 5: Cancer clonal fraction plots and oncogenetic tree for patient #3. A detailed legend is provided in Suppl. Fig. 2.



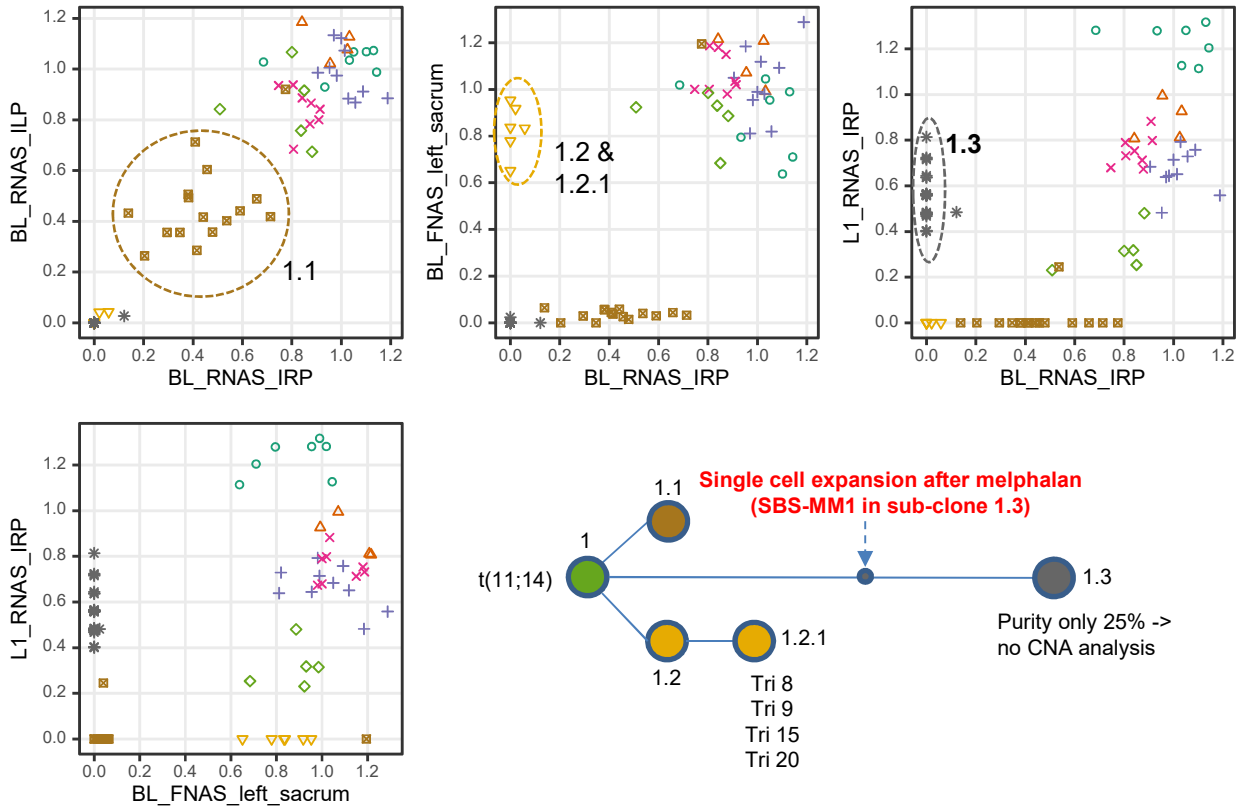


Supplementary Figure 6: Cancer clonal fraction plots and oncogenetic tree for patient #4.
A detailed legend is provided in Suppl. Fig. 2.

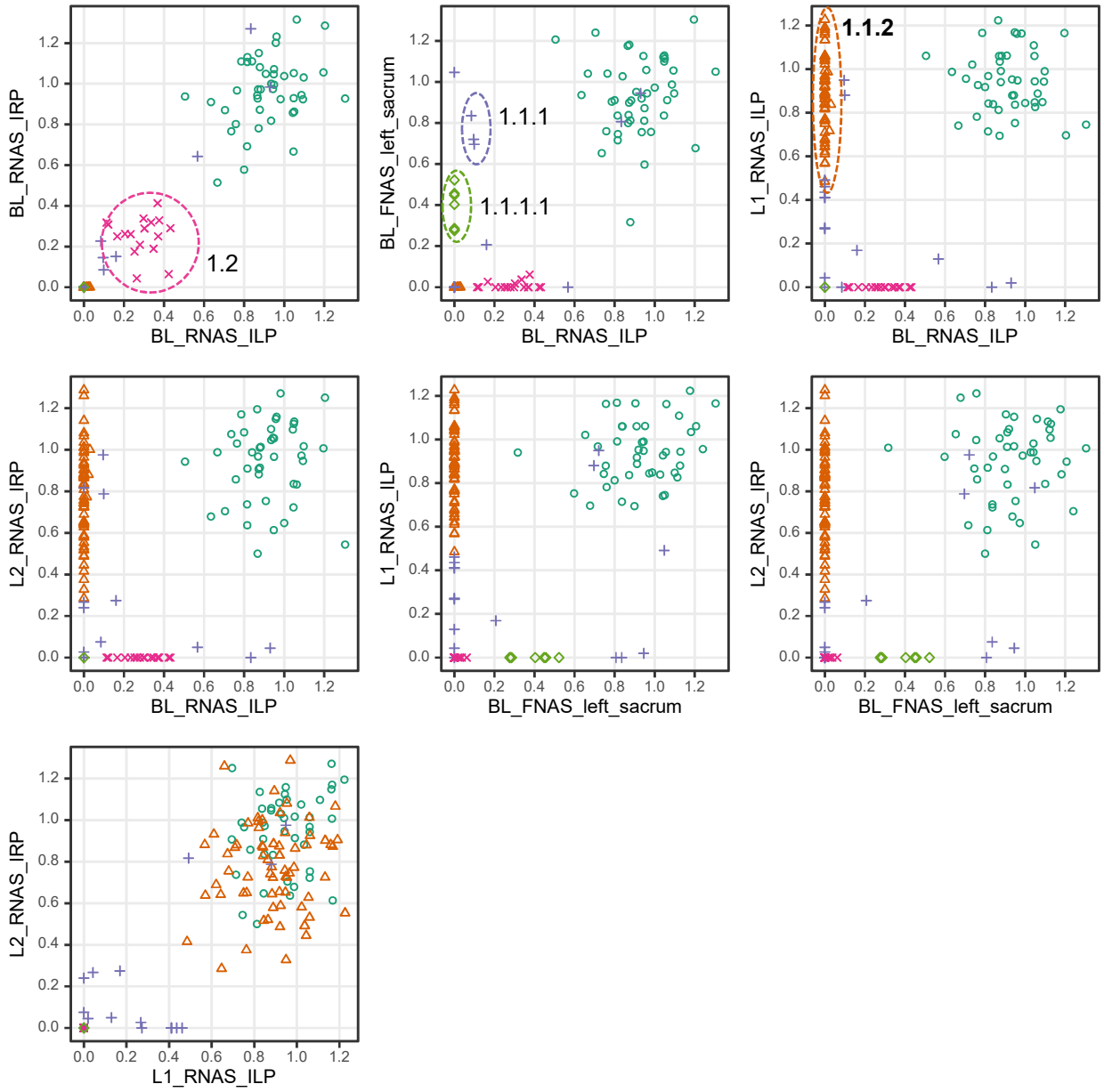


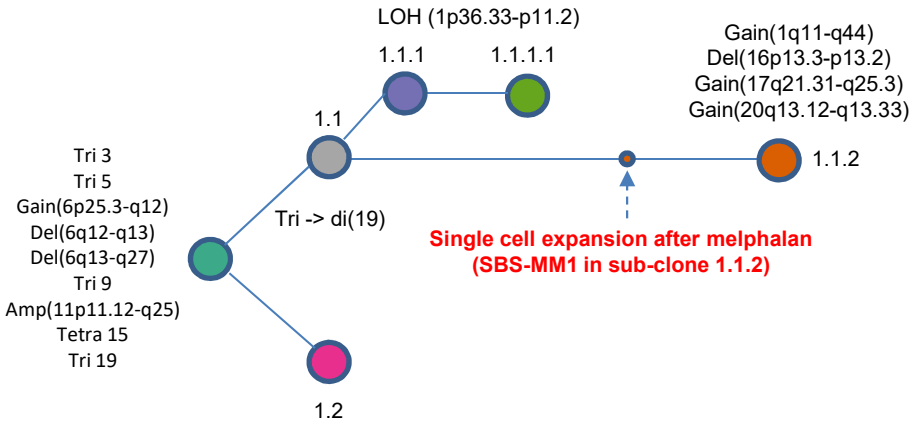


Supplementary Figure 7: Cancer clonal fraction plots and oncogenetic tree for patient #5.
A detailed legend is provided in Suppl. Fig. 2.

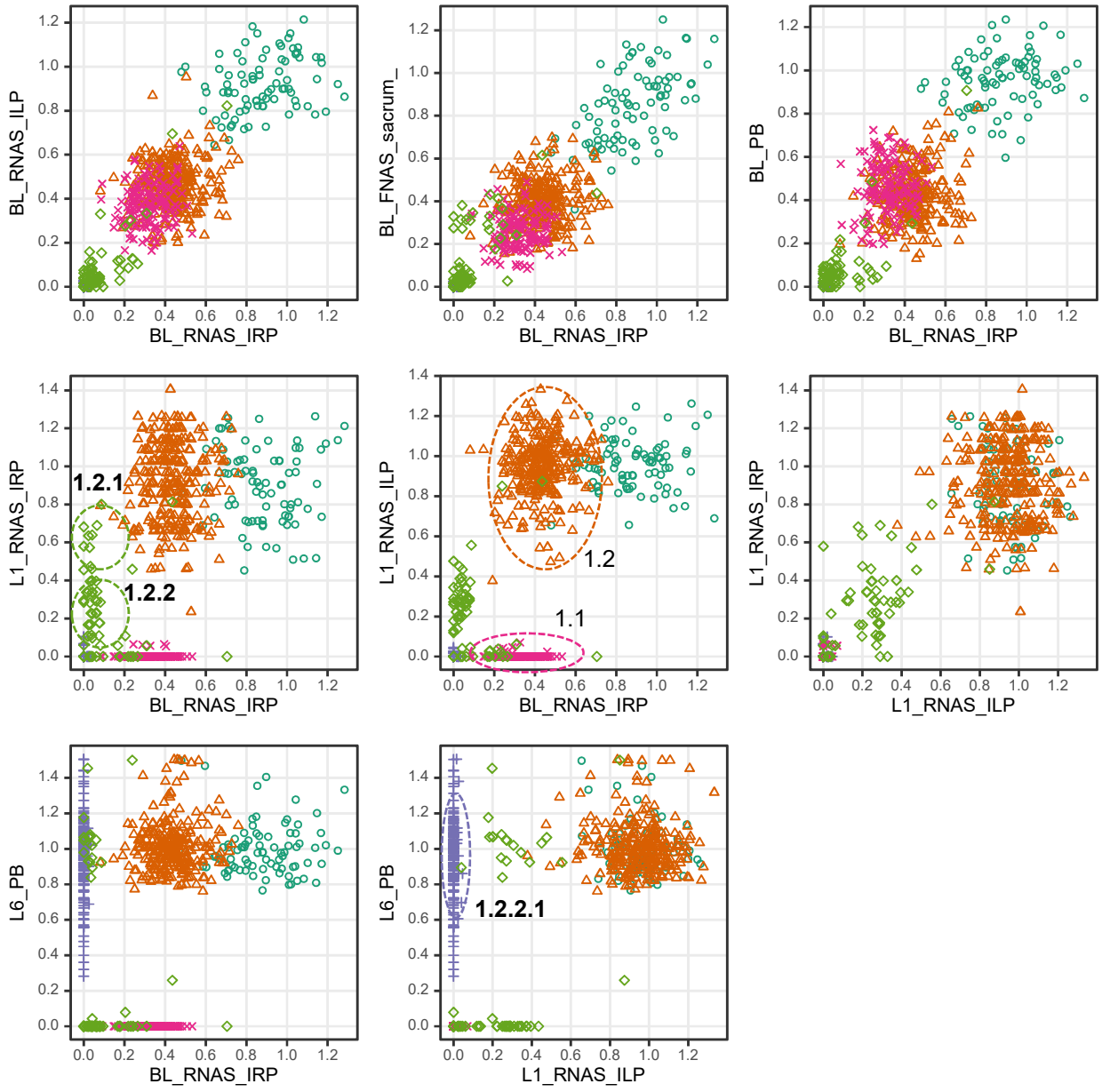


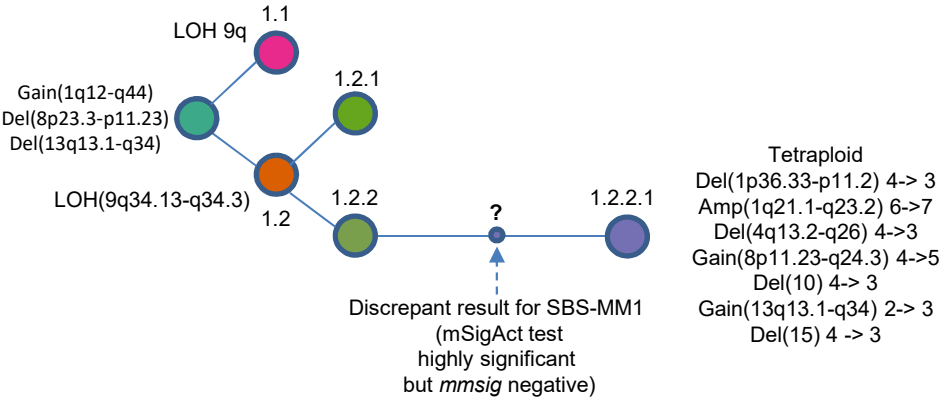
Supplementary Figure 8: Cancer clonal fraction plots and oncogenetic tree for patient #6.
A detailed legend is provided in Suppl. Fig. 2.



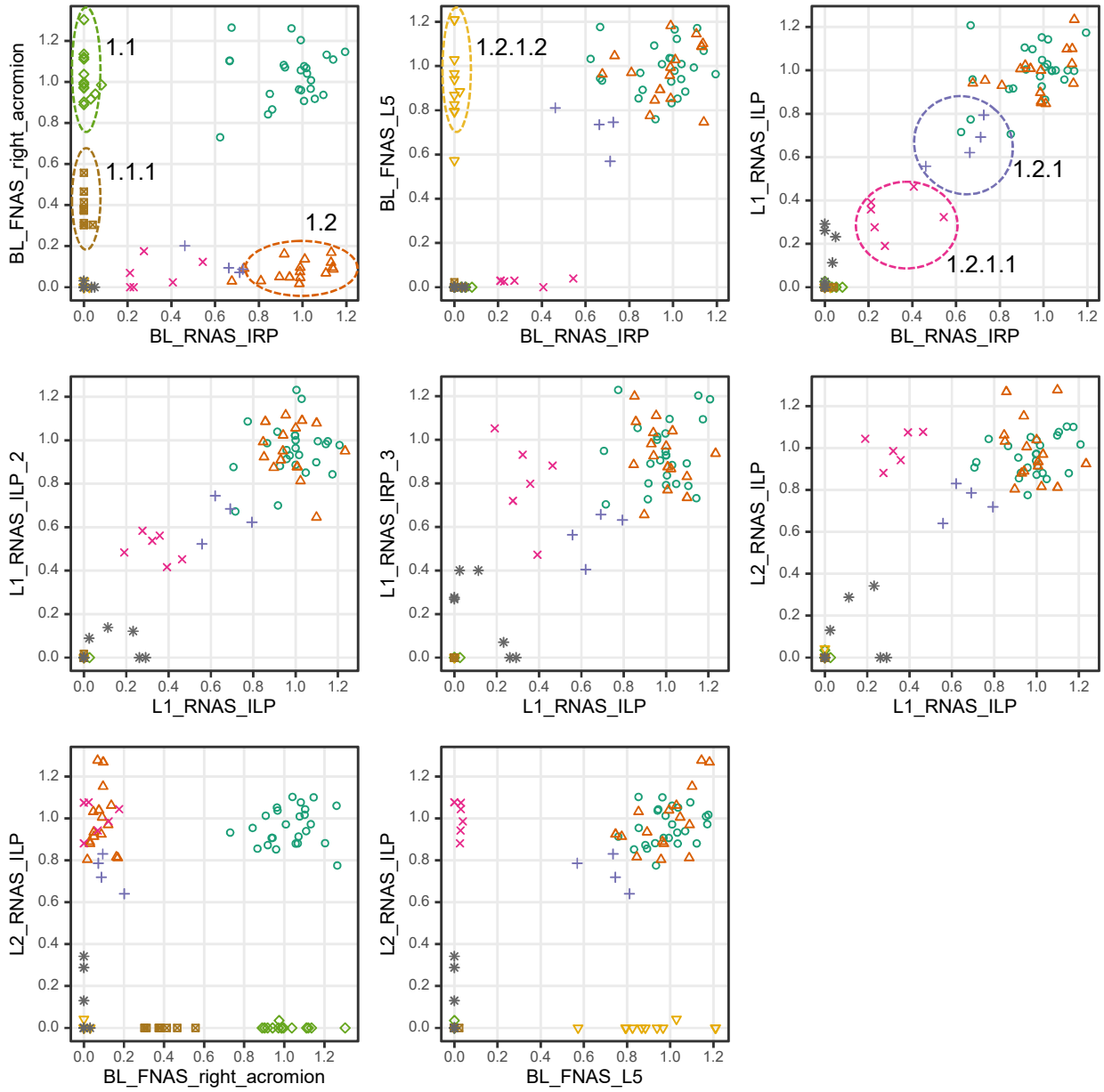


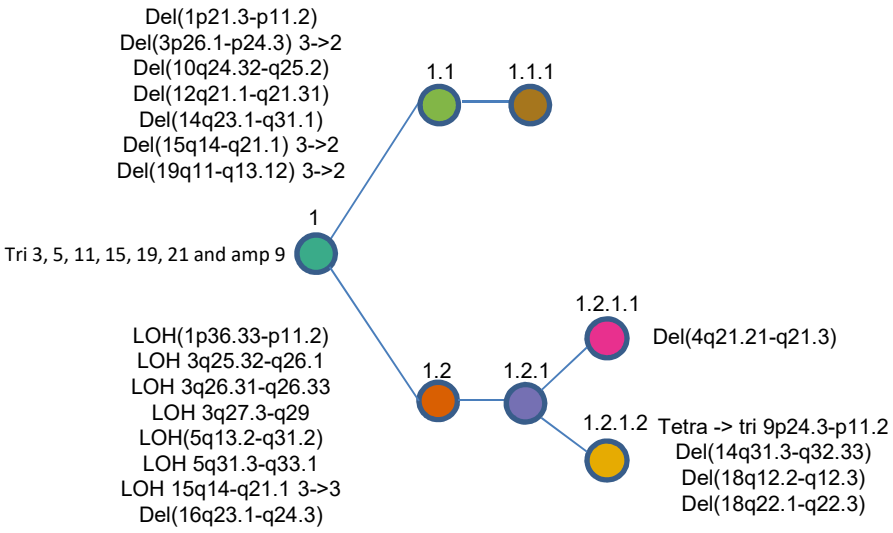
Supplementary Figure 9: Cancer clonal fraction plots and oncogenetic tree for patient #7.
A detailed legend is provided in Suppl. Fig. 2.



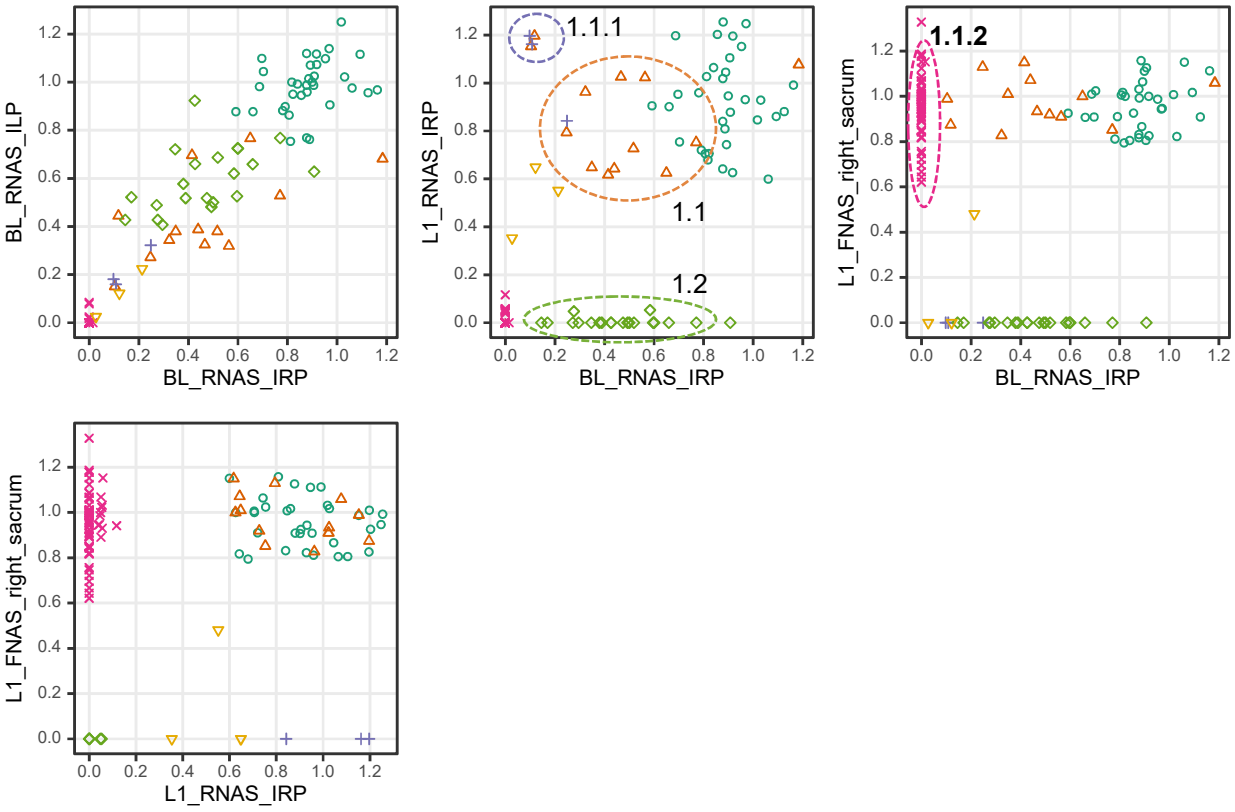


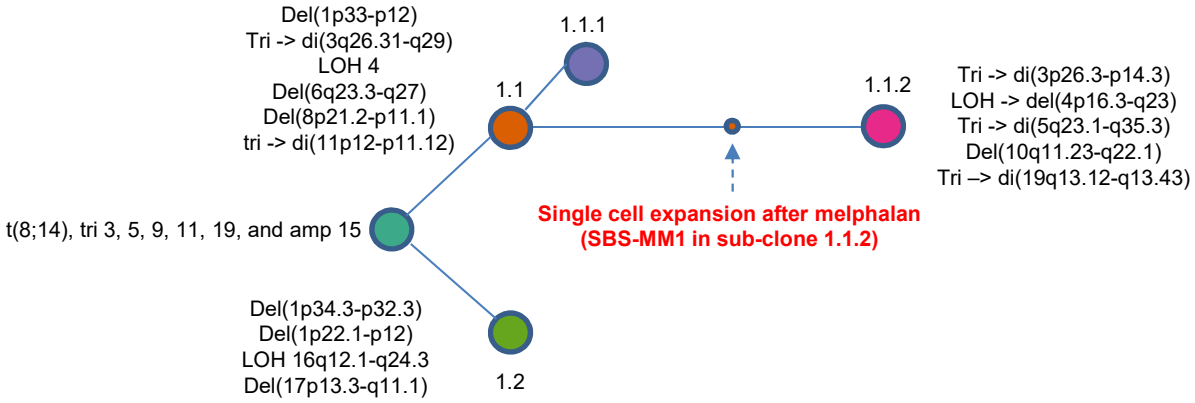
Supplementary Figure 10: Cancer clonal fraction plots and oncogenetic tree for patient #8.
A detailed legend is provided in Suppl. Fig. 2.



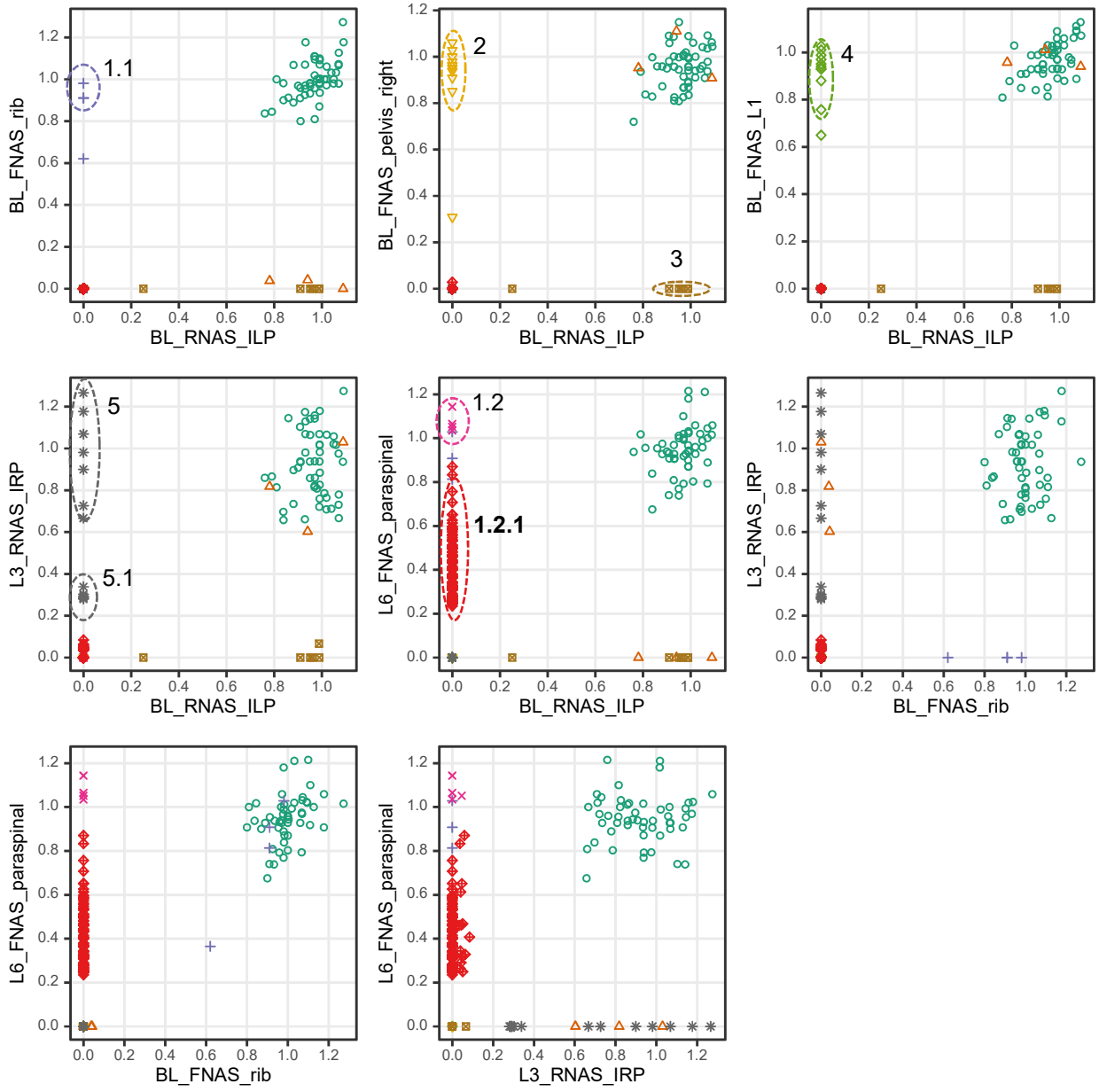


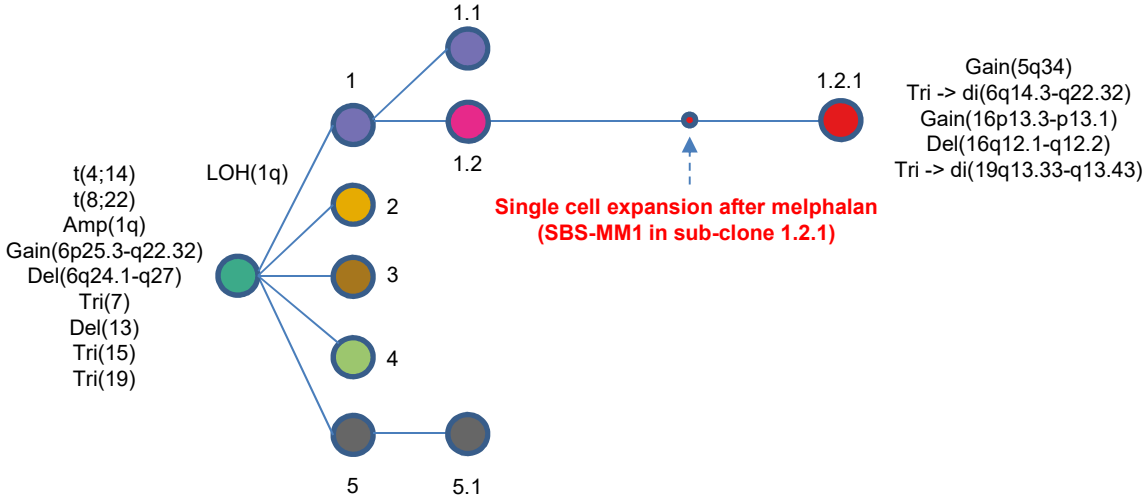
Supplementary Figure 11: Cancer clonal fraction plots and oncogenetic tree for patient #9.
A detailed legend is provided in Suppl. Fig. 2.



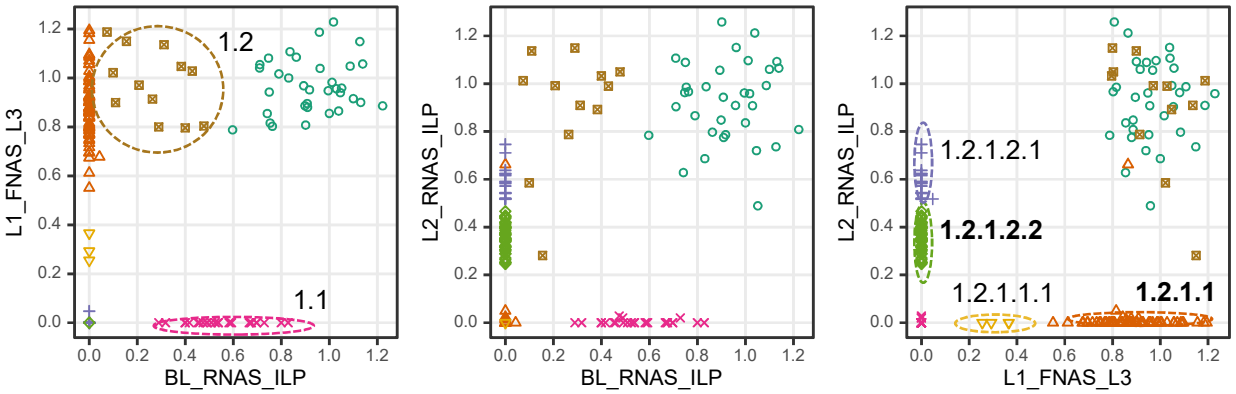


Supplementary Figure 12: Cancer clonal fraction plots and oncogenetic tree for patient #10.
A detailed legend is provided in Suppl. Fig. 2.

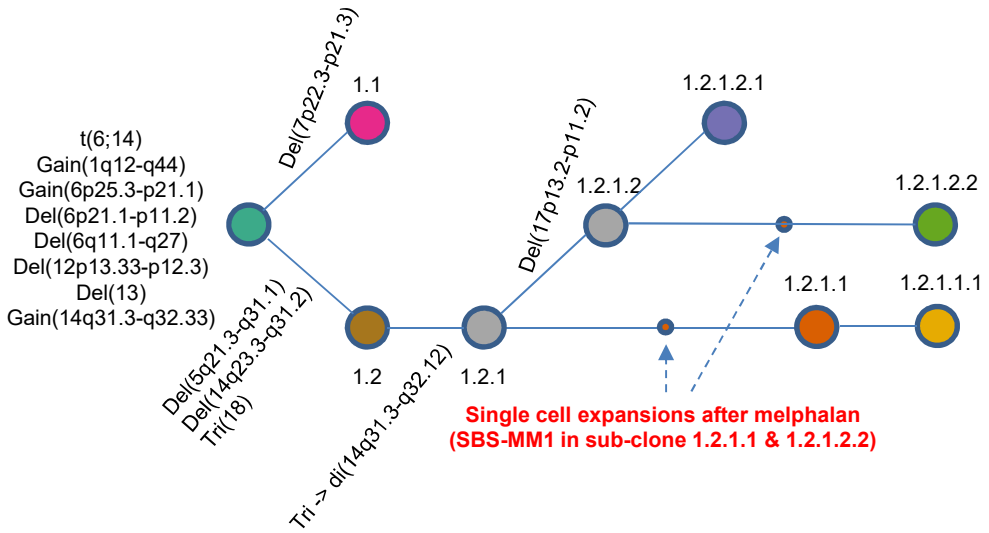




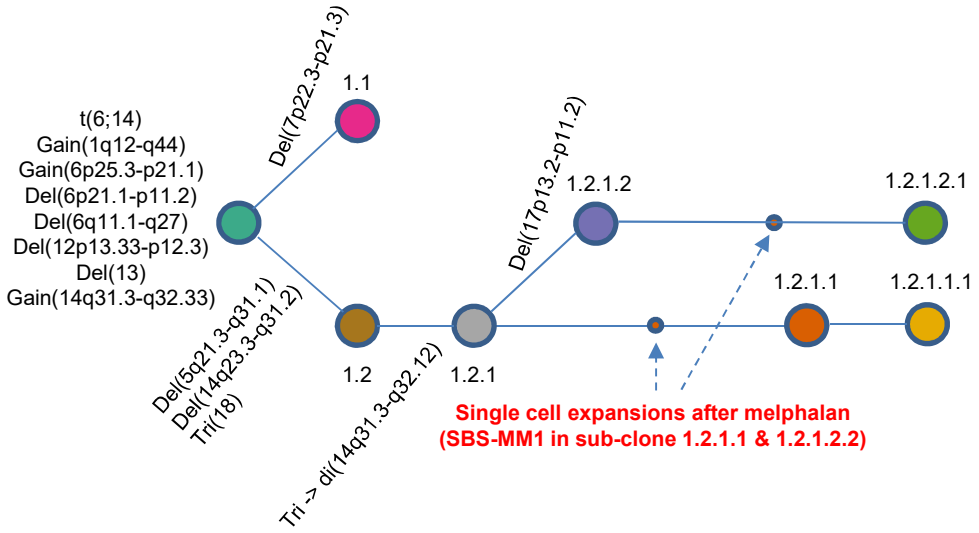
Supplementary Figure 13: Cancer clonal fraction plots and oncogenetic tree for patient #11.
A detailed legend is provided in Suppl. Fig. 2.



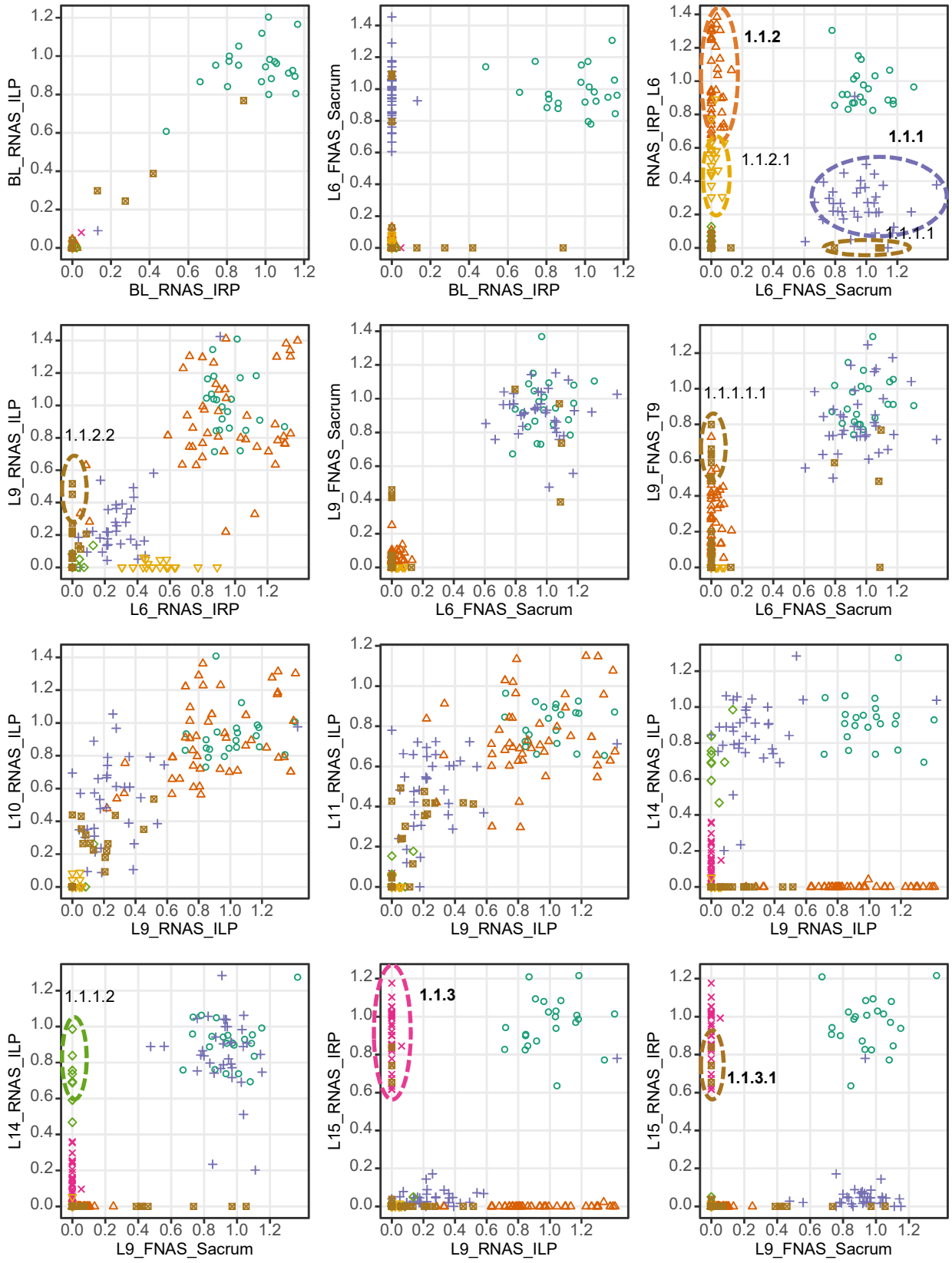
Solution A (green and lilac cluster represent two sub-clones with common ancestor (1.2.1.2))

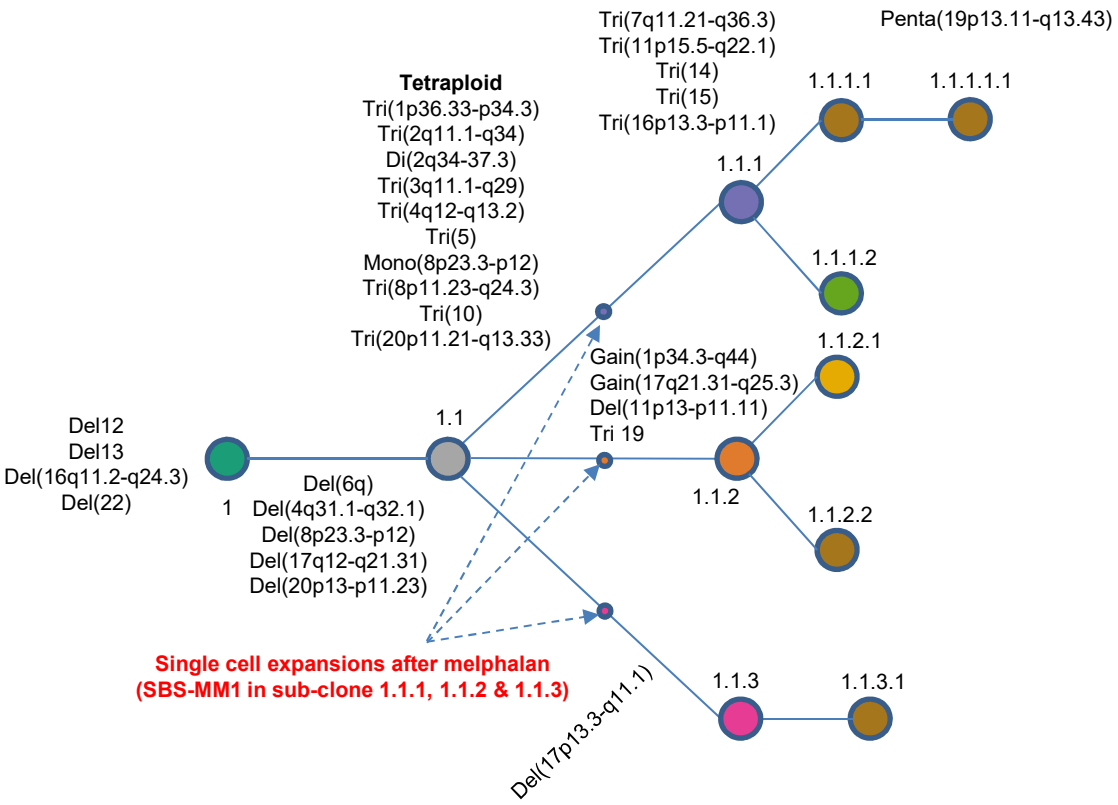


Solution B (green cluster represents descendant of lilac cluster)

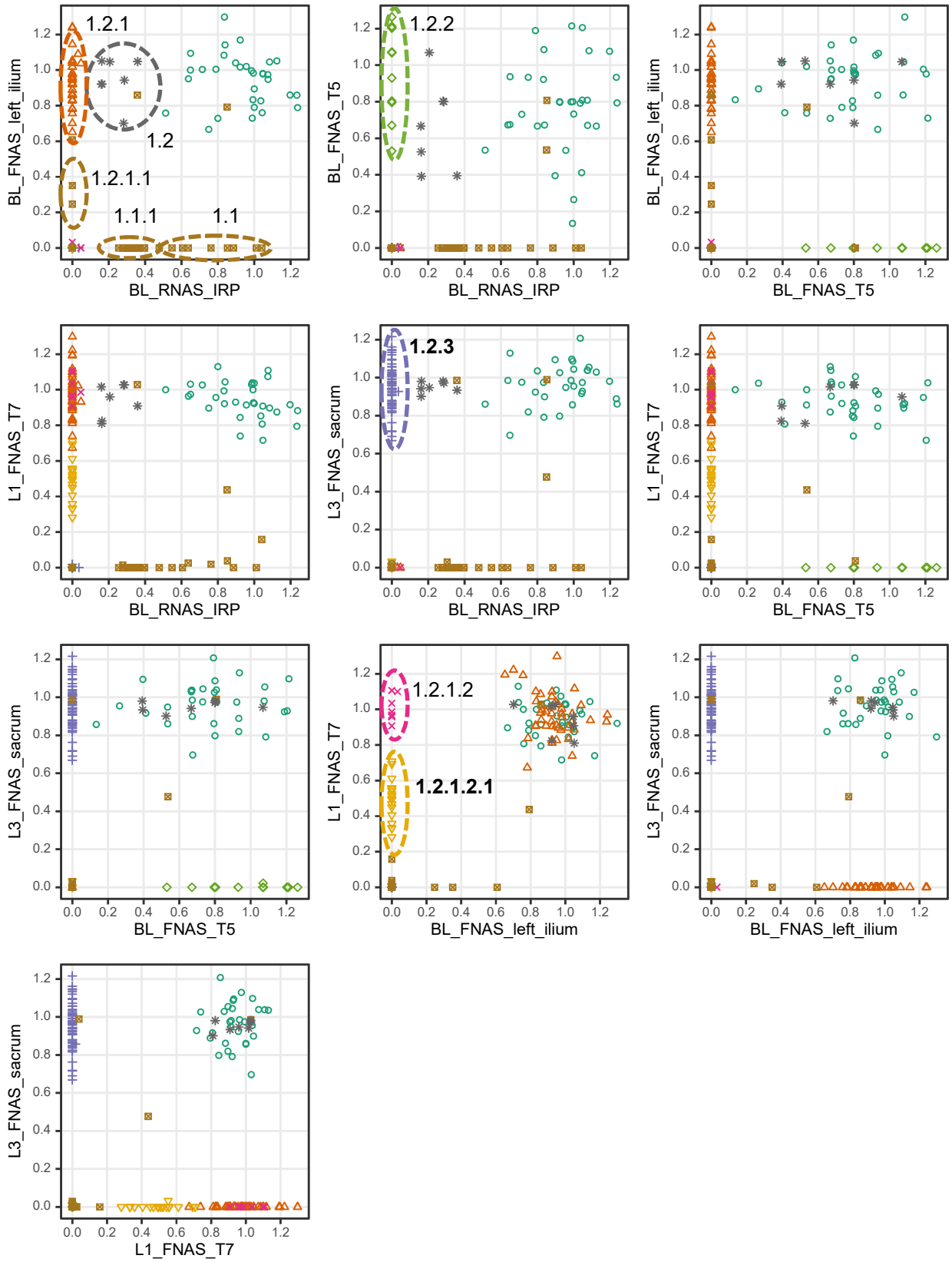


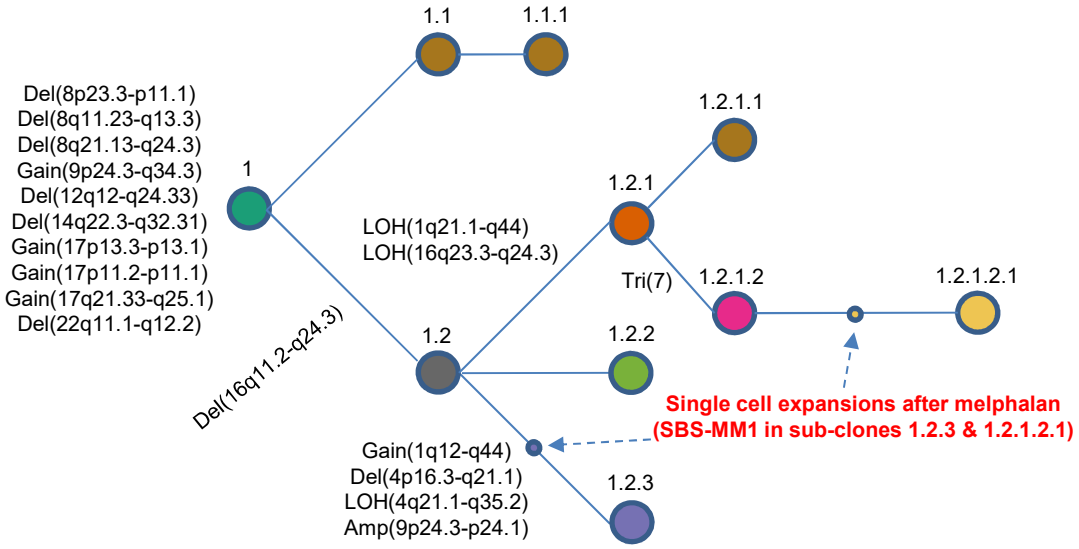
Supplementary Figure 14: Cancer clonal fraction plots and oncogenetic tree for patient #12.
A detailed legend is provided in Suppl. Fig. 2.



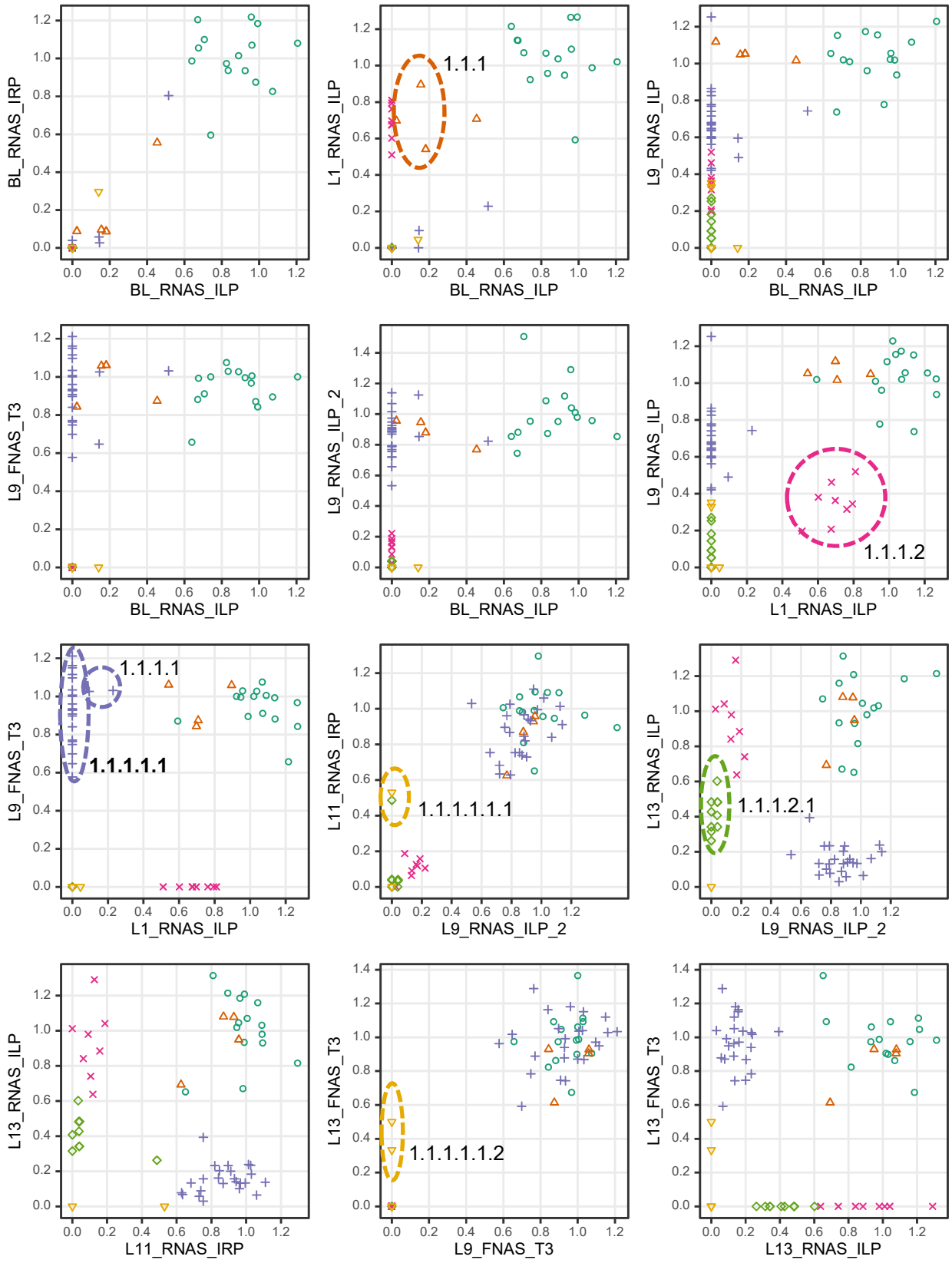

Tri(7q11.21-q36.3)
Tri(11p15.5-q22.1)
Tri(14)
Tri(15)
Tri(16p13.3-p11.1)
Penta(19p13.11-q13.43)
1.1.1.1
1.1.1.1.1
Tetraploid
Tri(1p36.33-p34.3)
Tri(2q11.1-q34)
Di(2q34-37.3)
Tri(3q11.1-q29)
Tri(4q12-q13.2)
Tri(5)
Mono(8p23.3-p12)
Tri(8p11.23-q24.3)
Tri(10)
Tri(20p11.21-q13.33)
1.1.1
1.1.1.2
1.1.2.1
Gain(1p34.3-q44)
Gain(17q21.31-q25.3)
Del(11p13-p11.11)
Tri 19
1.1
Del12
Del13
Del(16q11.2-q24.3)
Del(22)
1
Del(6q)
Del(4q31.1-q32.1)
Del(8p23.3-p12)
Del(17q12-q21.31)
Del(20p13-p11.23)
1.1.2
1.1.2.2
Single cell expansions after melphalan
(SBS-MM1 in sub-clone 1.1.1, 1.1.2 & 1.1.3)
1.1.3
1.1.3.1
Del(17p13.3-q11.1)

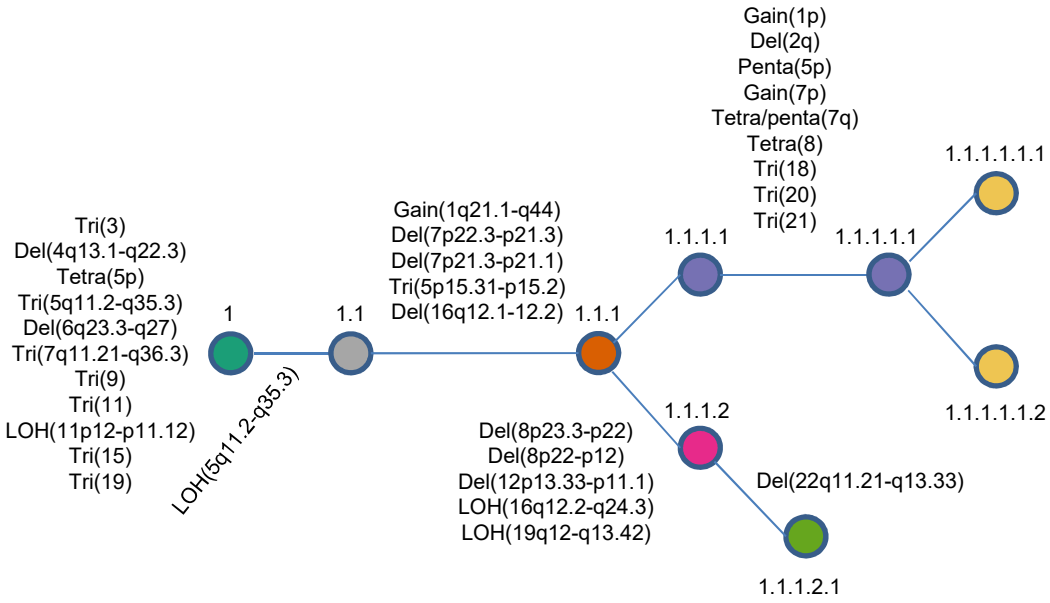
Supplementary Figure 15: Cancer clonal fraction plots and oncogenetic tree for patient #13.
A detailed legend is provided in Suppl. Fig. 2.



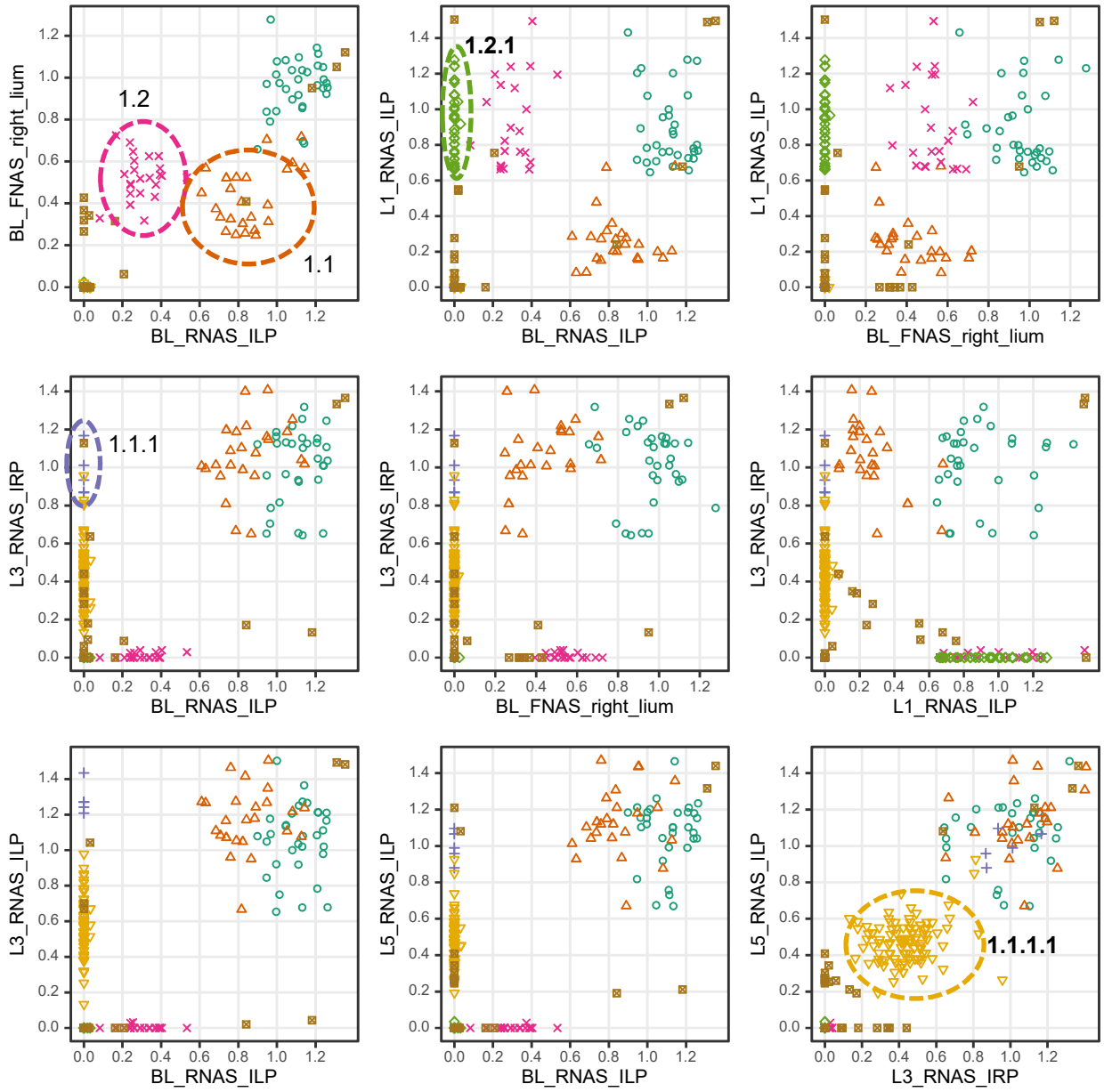

1.1
1.1.1
Del(8p23.3-p11.1)
Del(8q11.23-q13.3)
Del(8q21.13-q24.3)
Gain(9p24.3-q34.3)
Del(12q12-q24.33)
Del(14q22.3-q32.31)
Gain(17p13.3-p13.1)
Gain(17p11.2-p11.1)
Gain(17q21.33-q25.1)
Del(22q11.1-q12.2)
1
1.2.1.1
1.2.1
LOH(1q21.1-q44)
LOH(16q23.3-q24.3)
Tri(7)
1.2.1.2
1.2.1.2.1
Del(16q11.2-q24.3)
1.2
1.2.2
Single cell expansions after melphalan
(SBS-MM1 in sub-clones 1.2.3 & 1.2.1.2.1)
Gain(1q12-q44)
Del(4p16.3-q21.1)
LOH(4q21.1-q35.2)
Amp(9p24.3-p24.1)
1.2.3

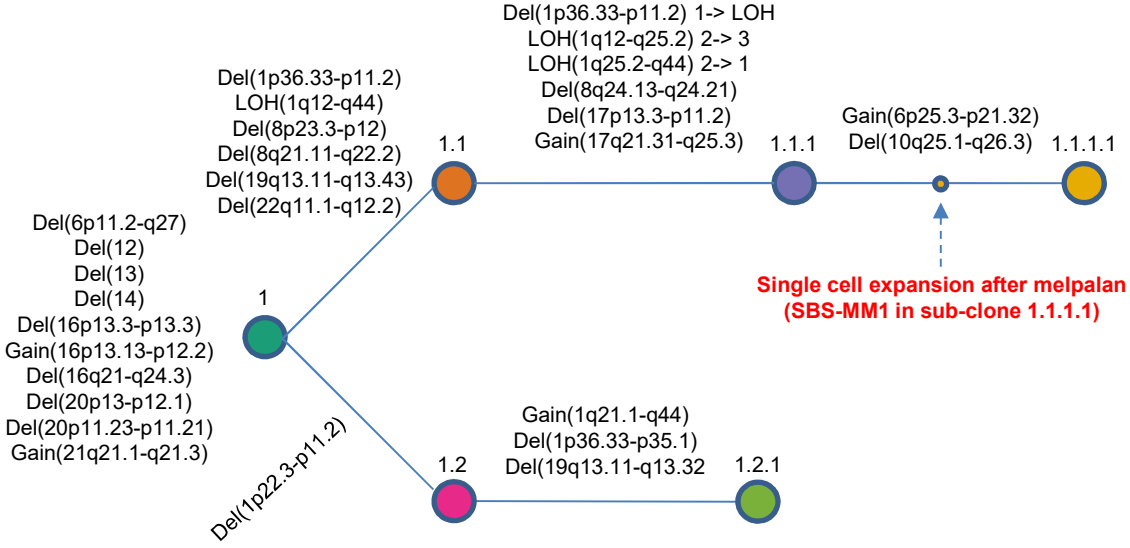
Supplementary Figure 16: Cancer clonal fraction plots and oncogenetic tree for patient #14.
A detailed legend is provided in Suppl. Fig. 2.



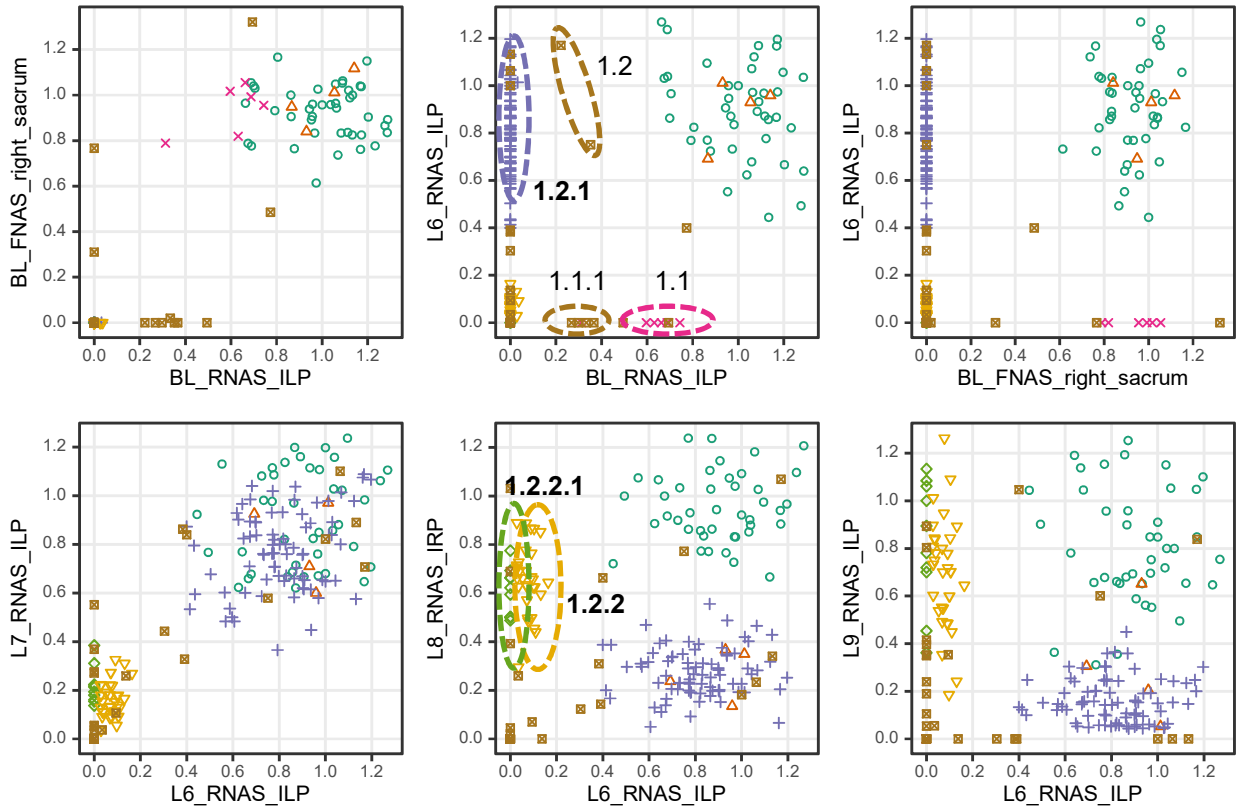

Tri(3)
Del(4q13.1-q22.3)
Tetra(5p)
Tri(5q11.2-q35.3)
Del(6q23.3-q27)
Tri(7q11.21-q36.3)
Tri(9)
Tri(11)
LOH(11p12-p11.12)
Tri(15)
Tri(19)
1
LOH(5q11.2-q35.3)
1.1
Gain(1q21.1-q44)
Del(7p22.3-p21.3)
Del(7p21.3-p21.1)
Tri(5p15.31-p15.2)
Del(16q12.1-12.2)
1.1.1
Del(8p23.3-p22)
Del(8p22-p12)
Del(12p13.33-p11.1)
LOH(16q12.2-q24.3)
LOH(19q12-q13.42)
1.1.1.1
Gain(1p)
Del(2q)
Penta(5p)
Gain(7p)
Tetra/penta(7q)
Tetra(8)
Tri(18)
Tri(20)
Tri(21)
1.1.1.2
Del(22q11.21-q13.33)
1.1.1.2.1
1.1.1.1.1
1.1.1.1.1.1
1.1.1.1.1.2

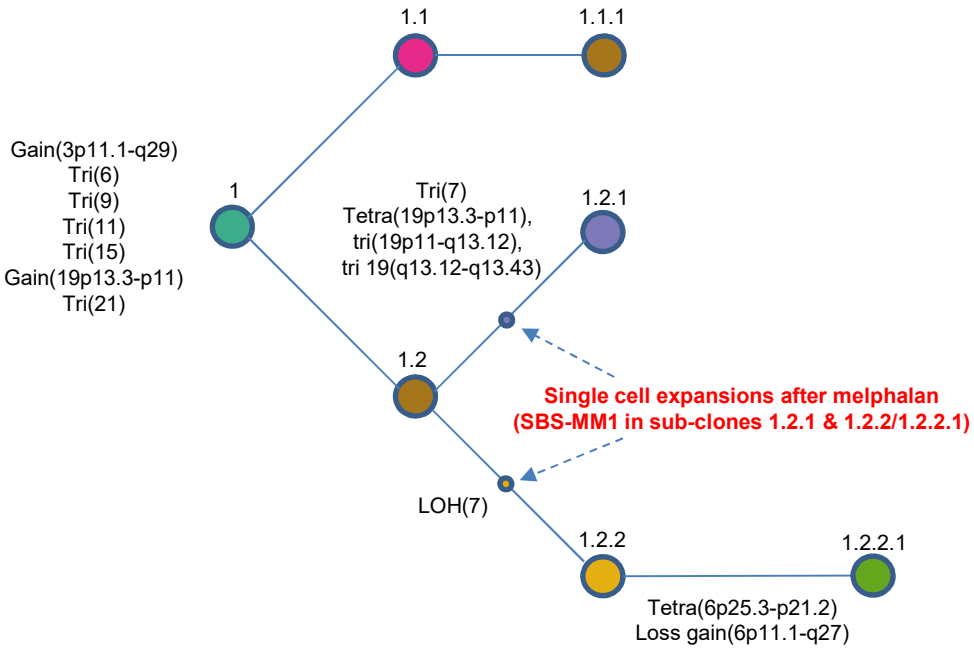
Supplementary Figure 17: Cancer clonal fraction plots and oncogenetic tree for patient #15.
A detailed legend is provided in Suppl. Fig. 2.



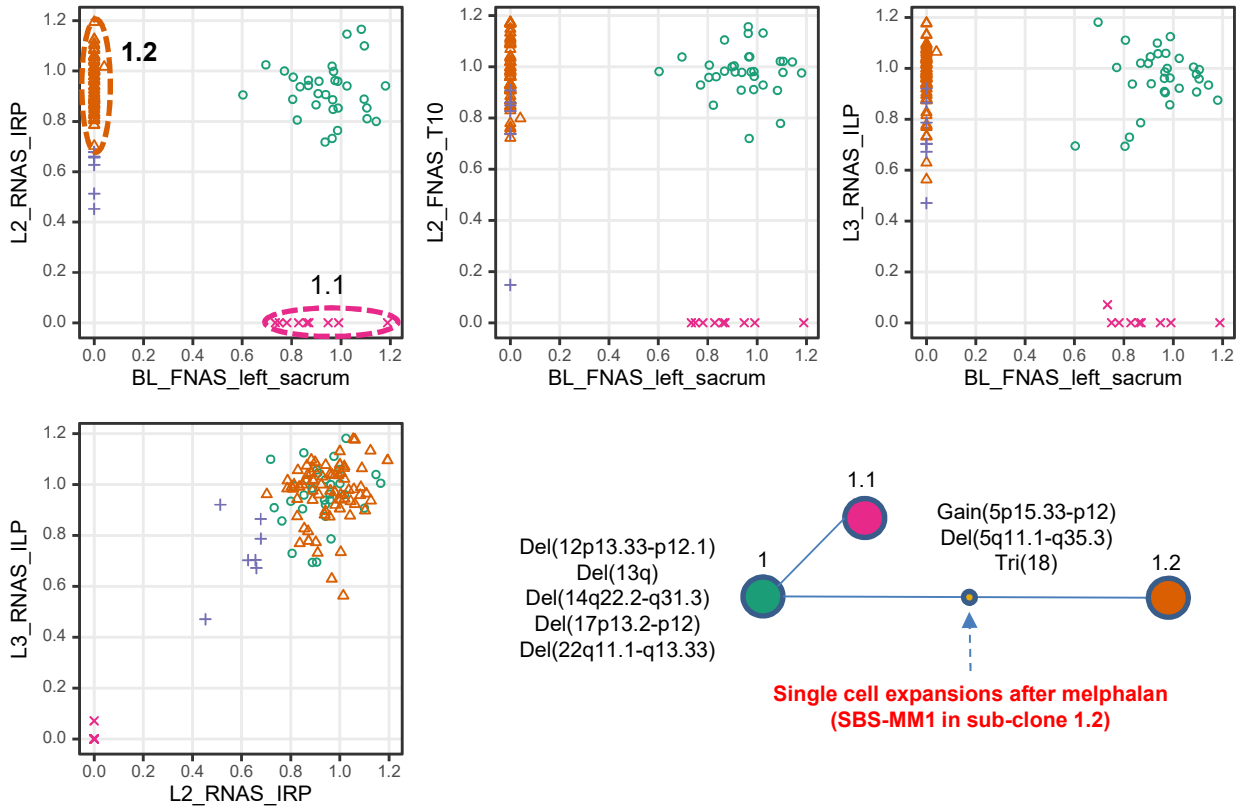


Supplementary Figure 18: Cancer clonal fraction plots and oncogenetic tree for patient #16.
A detailed legend is provided in Suppl. Fig. 2.

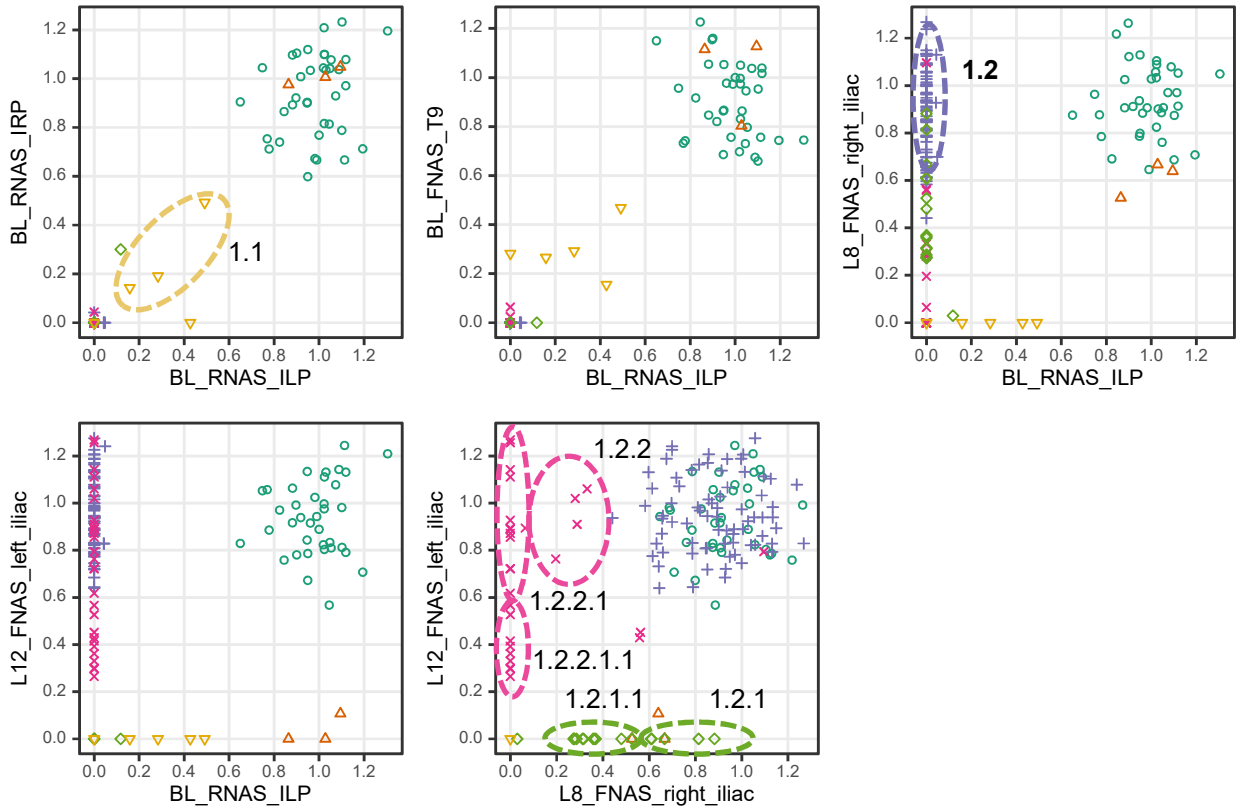


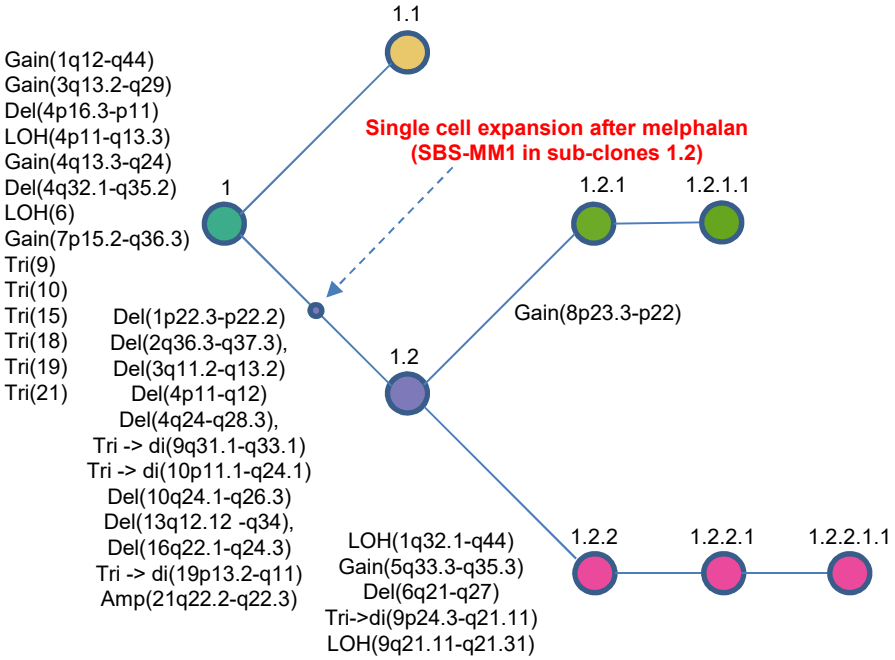


Supplementary Figure 19: Cancer clonal fraction plots and oncogenetic tree for patient #17.
A detailed legend is provided in Suppl. Fig. 2.

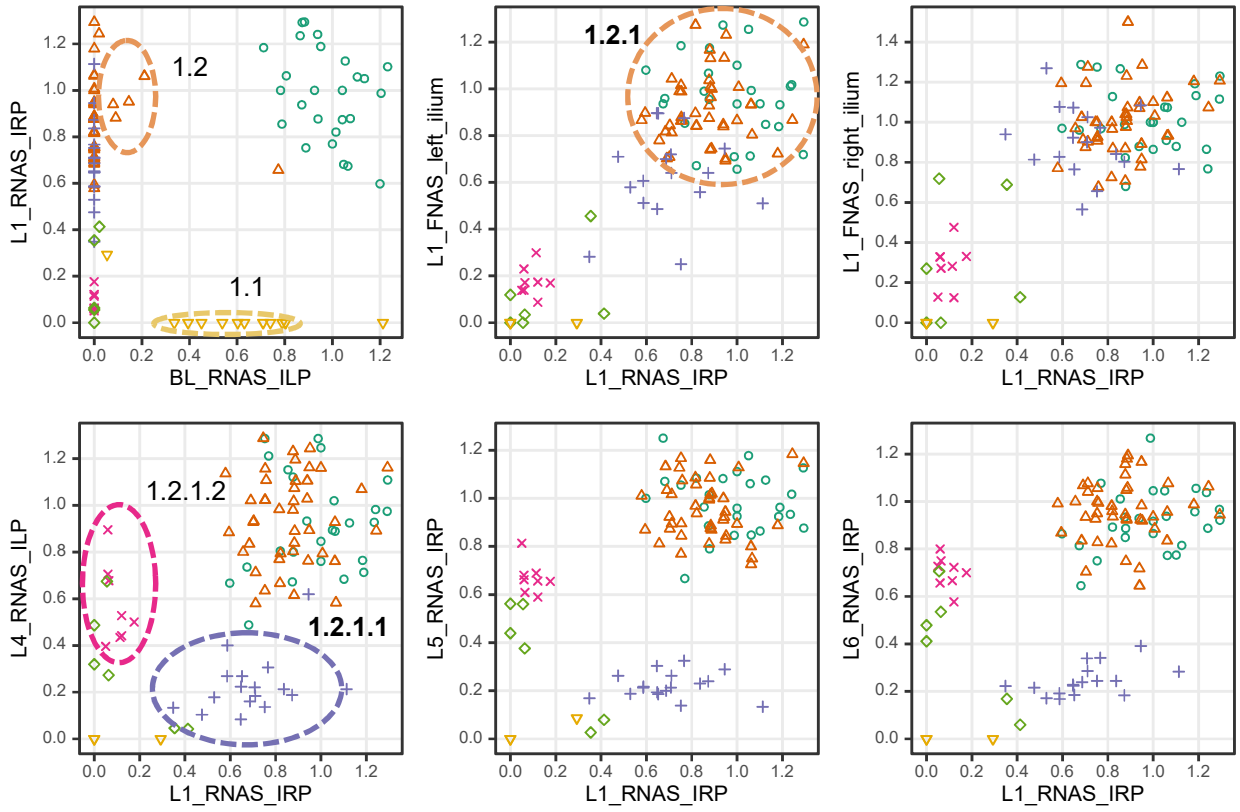


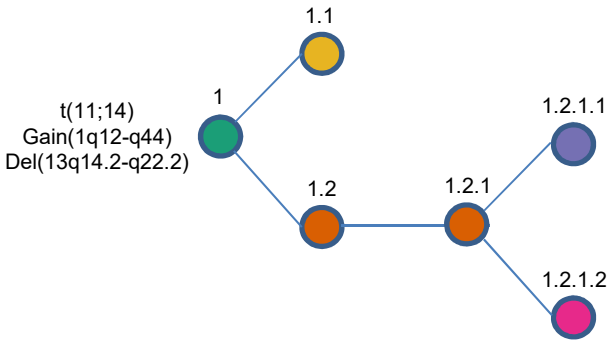
Supplementary Figure 20: Cancer clonal fraction plots and oncogenetic tree for patient #18.
A detailed legend is provided in Suppl. Fig. 2.



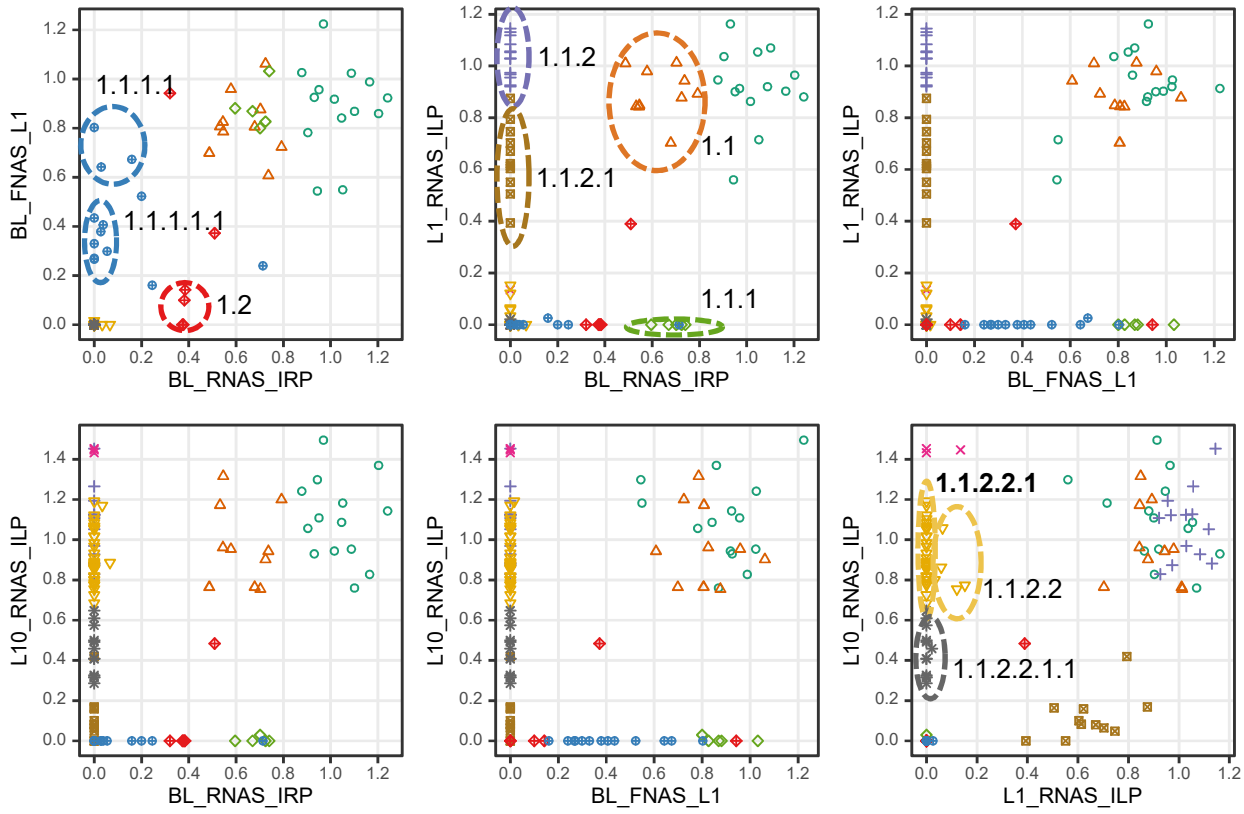


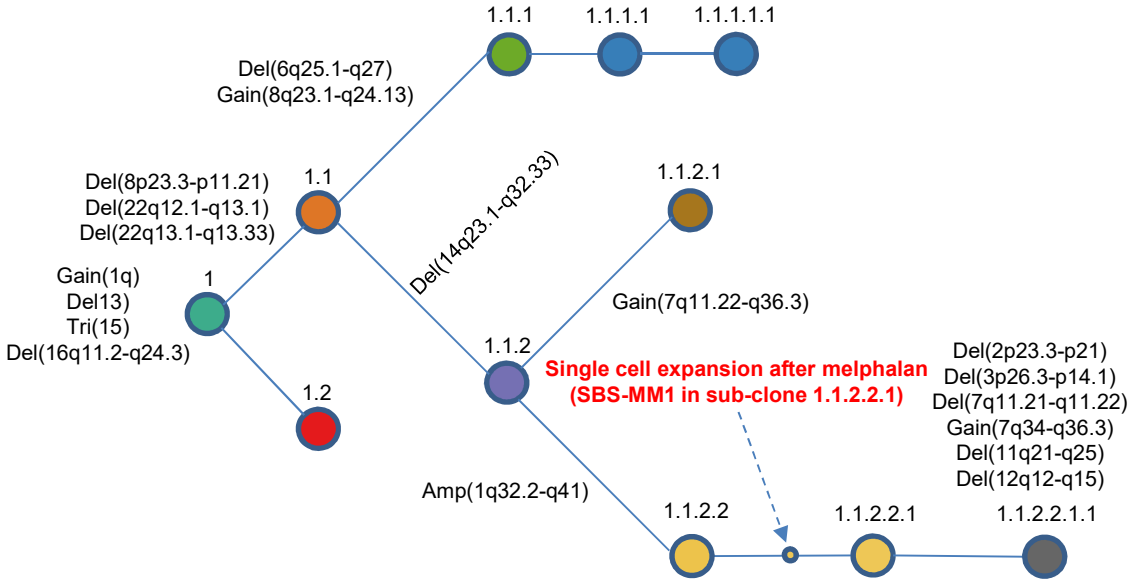
Supplementary Figure 21: Cancer clonal fraction plots and oncogenetic tree for patient #19.
A detailed legend is provided in Suppl. Fig. 2.



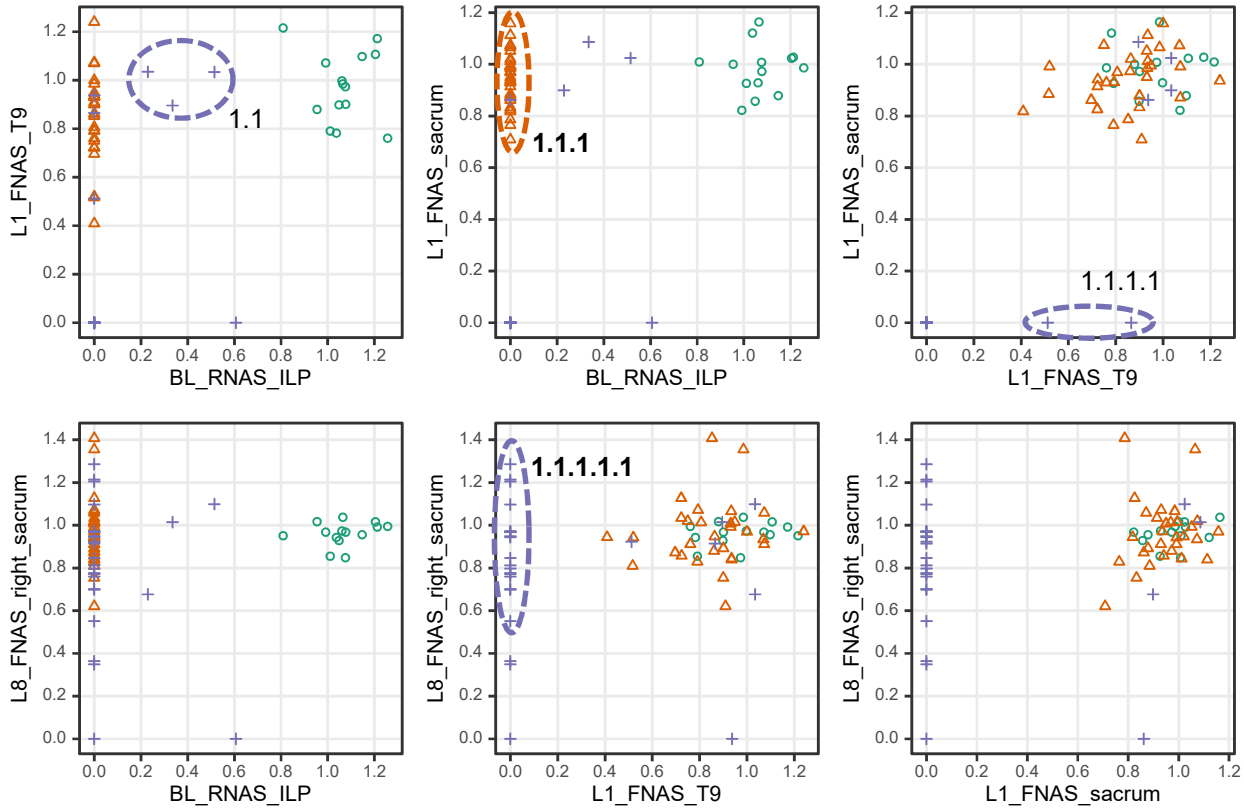


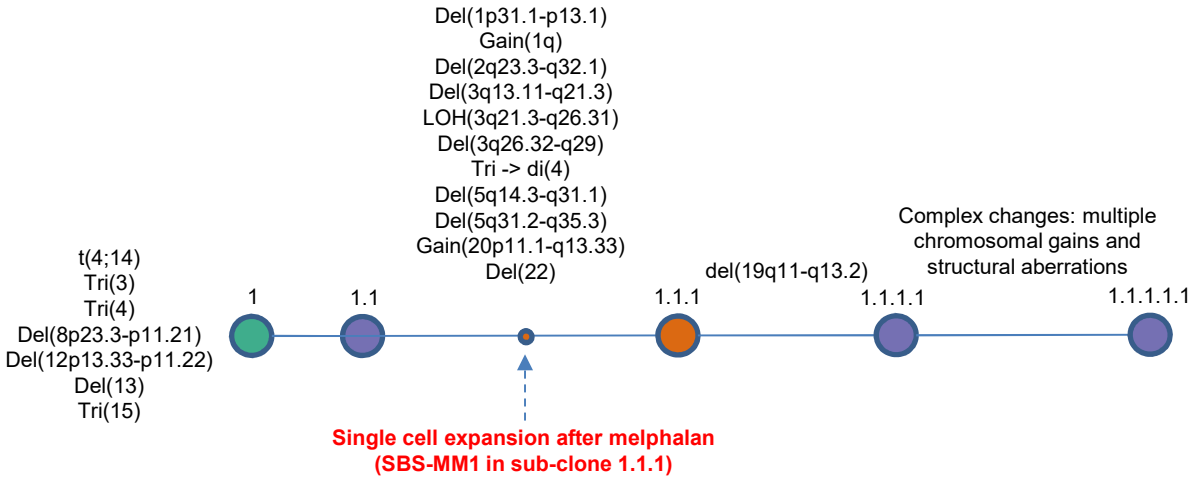
Supplementary Figure 22: Cancer clonal fraction plots and oncogenetic tree for patient #20.
A detailed legend is provided in Suppl. Fig. 2.



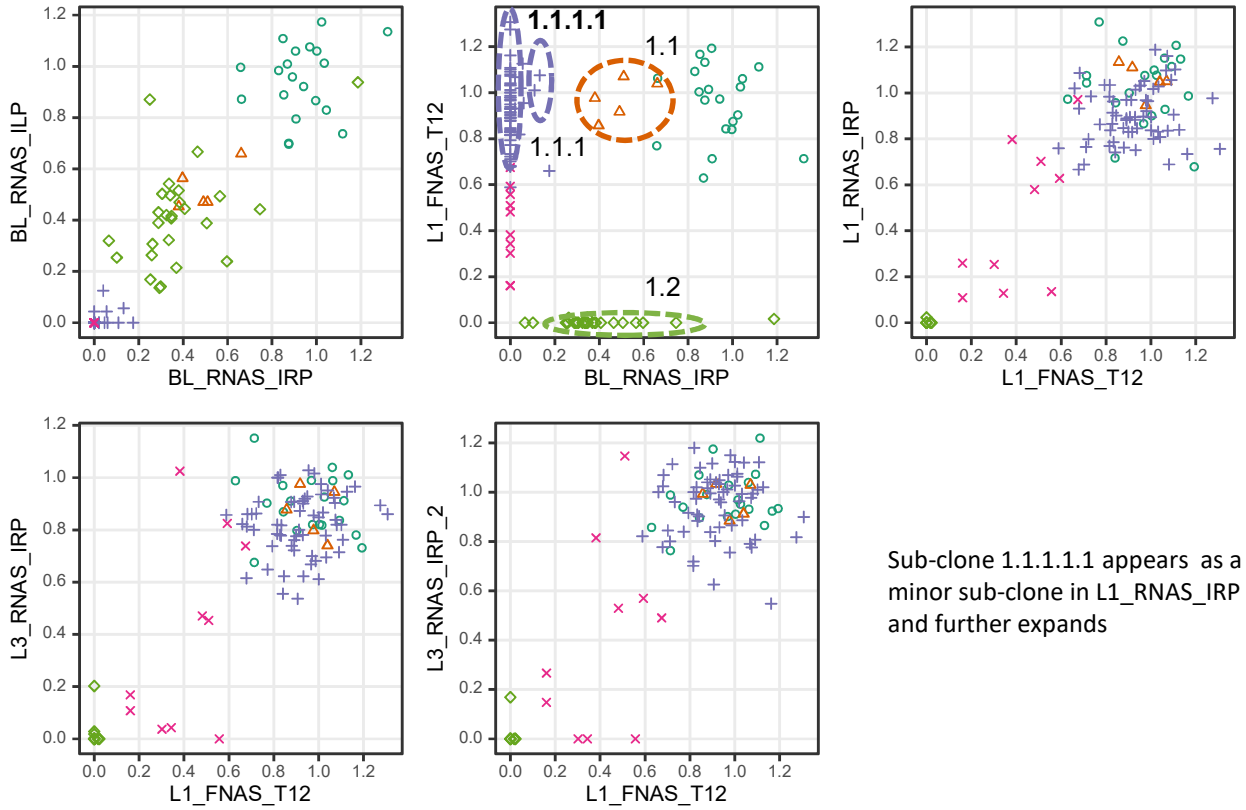


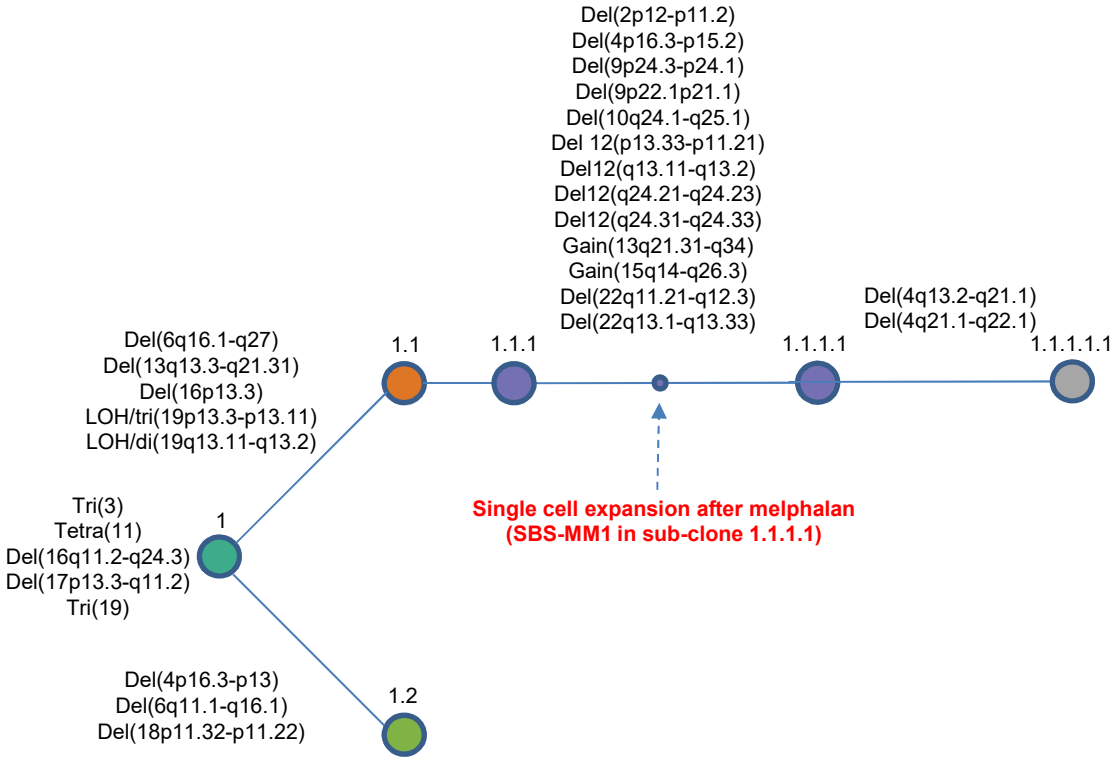
Supplementary Figure 23: Cancer clonal fraction plots and oncogenetic tree for patient #21.
A detailed legend is provided in Suppl. Fig. 2.



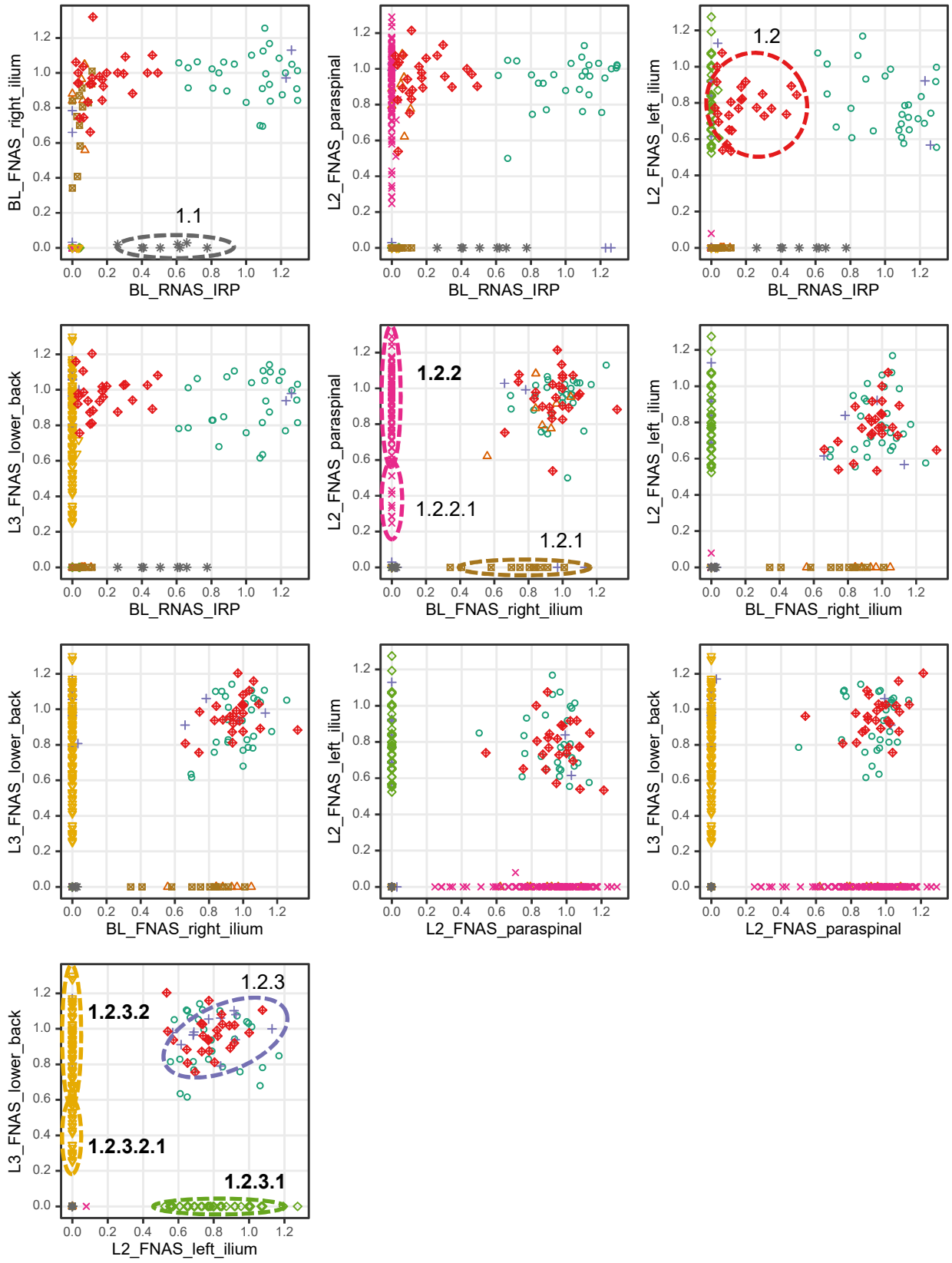


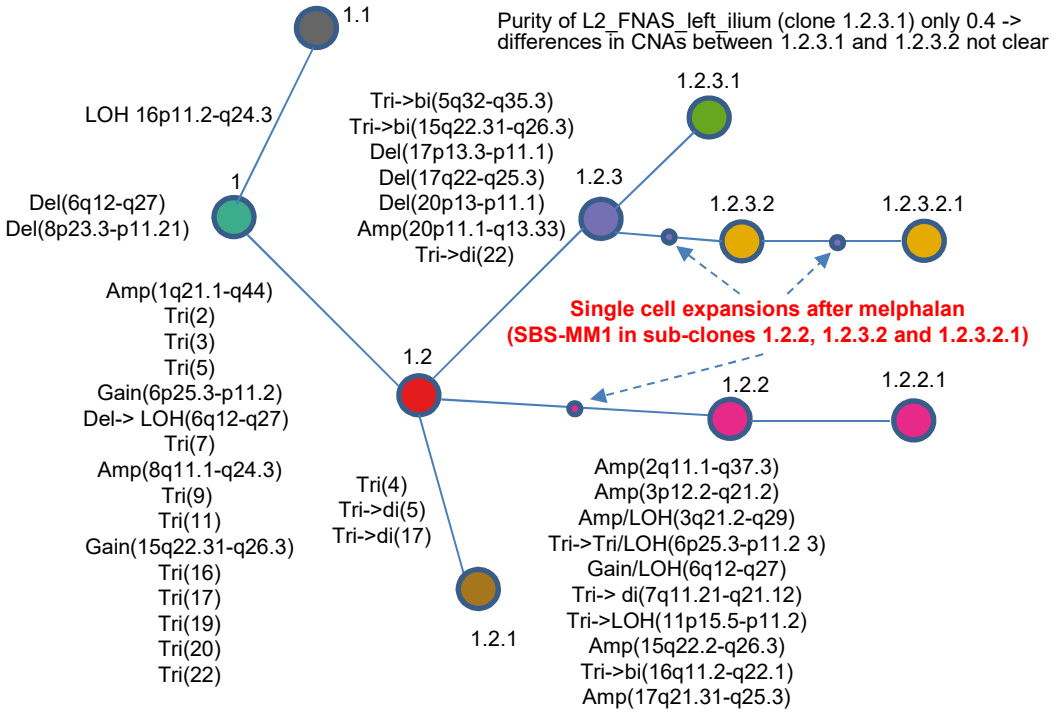
Supplementary Figure 24: Cancer clonal fraction plots and oncogenetic tree for patient #22.
A detailed legend is provided in Suppl. Fig. 2.





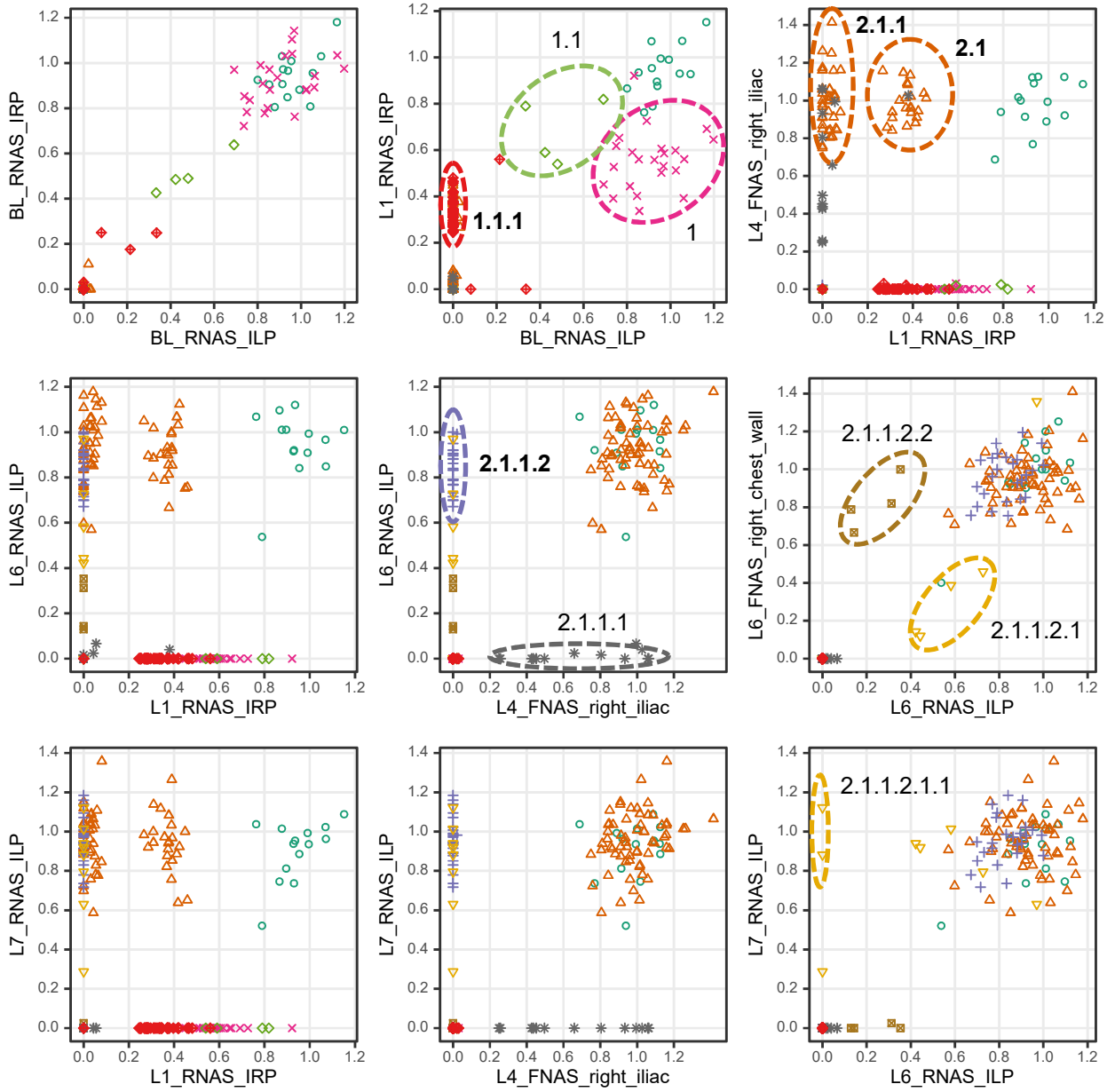
Supplementary Figure 25: Cancer clonal fraction plots and oncogenetic tree for patient #23.
A detailed legend is provided in Suppl. Fig. 2.

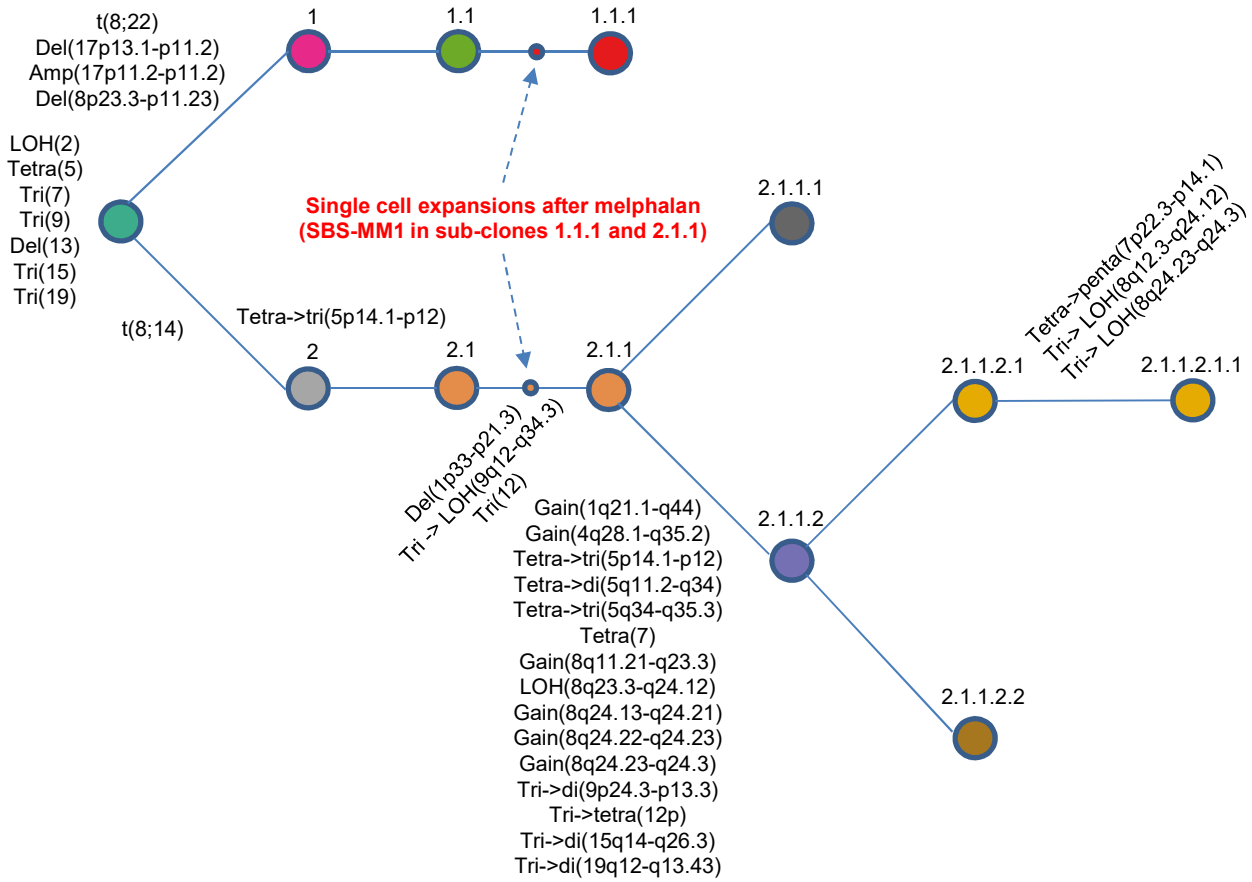




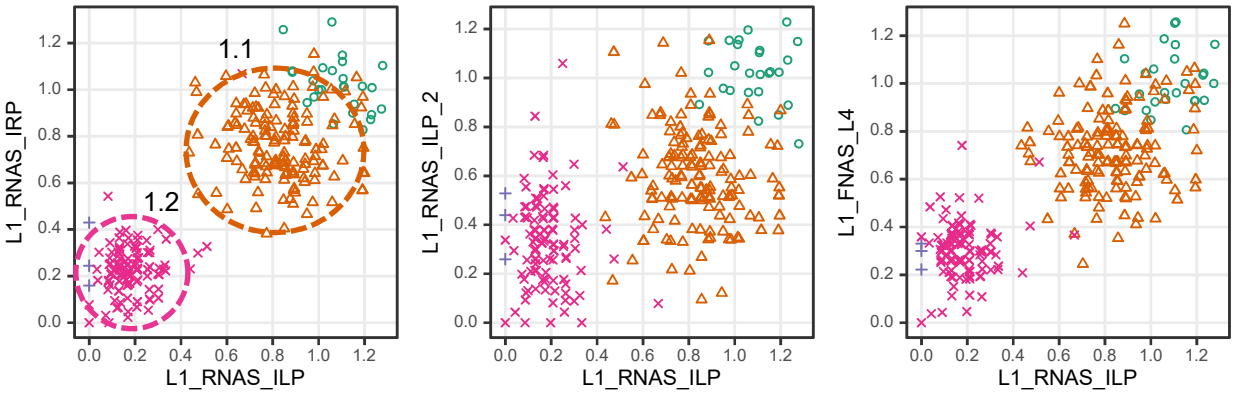
Relationship between 1.2.1, 1.2.2 and 1.2.3 uncertain:
LOH(3p26.3-p14.1) shared between 1.2.1 and 1.2.3 and absent in 1.2.2,
but cluster ▲ in CCF plots shared between 1.2.1 and 1.2.2 and absent in 1.2.3.

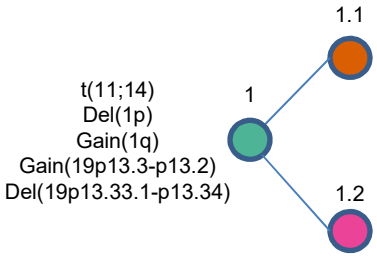
Supplementary Figure 26: Cancer clonal fraction plots and oncogenetic tree for patient #24.
A detailed legend is provided in Suppl. Fig. 2.



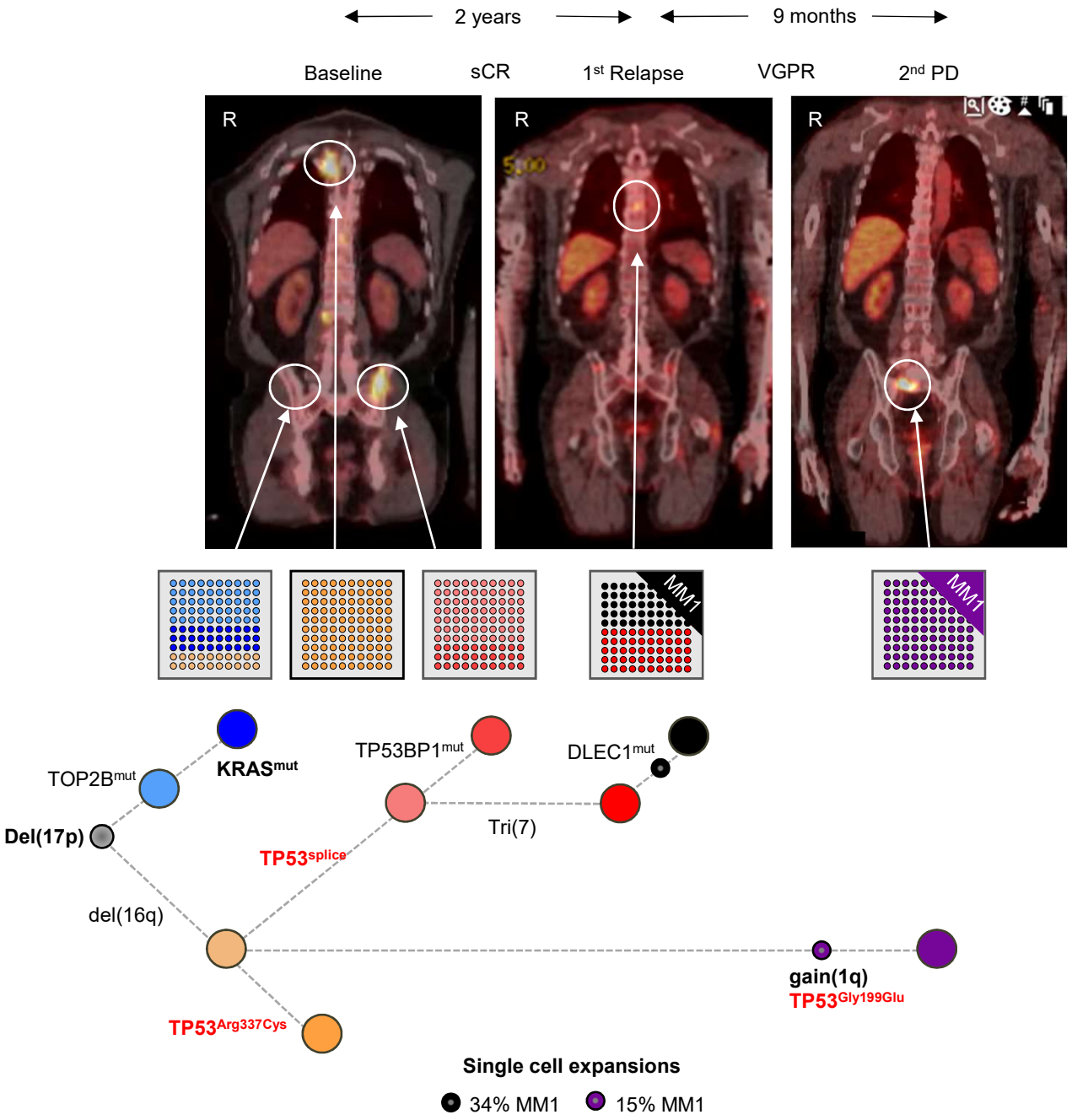

t(8;22)
Del(17p13.1-p11.2)
Amp(17p11.2-p11.2)
Del(8p23.3-p11.23)
1
1.1
1.1.1
LOH(2)
Tetra(5)
Tri(7)
Tri(9)
Del(13)
Tri(15)
Tri(19)
Single cell expansions after melphalan
(SBS-MM1 in sub-clones 1.1.1 and 2.1.1)
2.1.1.1
t(8;14)
Tetra->tri(5p14.1-p12)
2
2.1
2.1.1
Del(1p33-p21.3)
Tri -> LOH(9q12-q34.3)
Tri(12)
Gain(1q21.1-q44)
Gain(4q28.1-q35.2)
Tetra->tri(5p14.1-p12)
Tetra->di(5q11.2-q34)
Tetra->tri(5q34-q35.3)
Tetra(7)
Gain(8q11.21-q23.3)
LOH(8q23.3-q24.12)
Gain(8q24.13-q24.21)
Gain(8q24.22-q24.23)
Gain(8q24.23-q24.3)
Tri->di(9p24.3-p13.3)
Tri->tetra(12p)
Tri->di(15q14-q26.3)
Tri->di(19q12-q13.43)
2.1.1.2
2.1.1.2.1
Tetra->penta(7p22.3-p14.1)
Tri-> LOH(8q12.3-q24.12)
Tri-> LOH(8q24.23-q24.3)
2.1.1.2.1.1
2.1.1.2.2

Supplementary Figure 27: Cancer clonal fraction plots and oncogenetic tree for patient #25.
A detailed legend is provided in Suppl. Fig. 2.

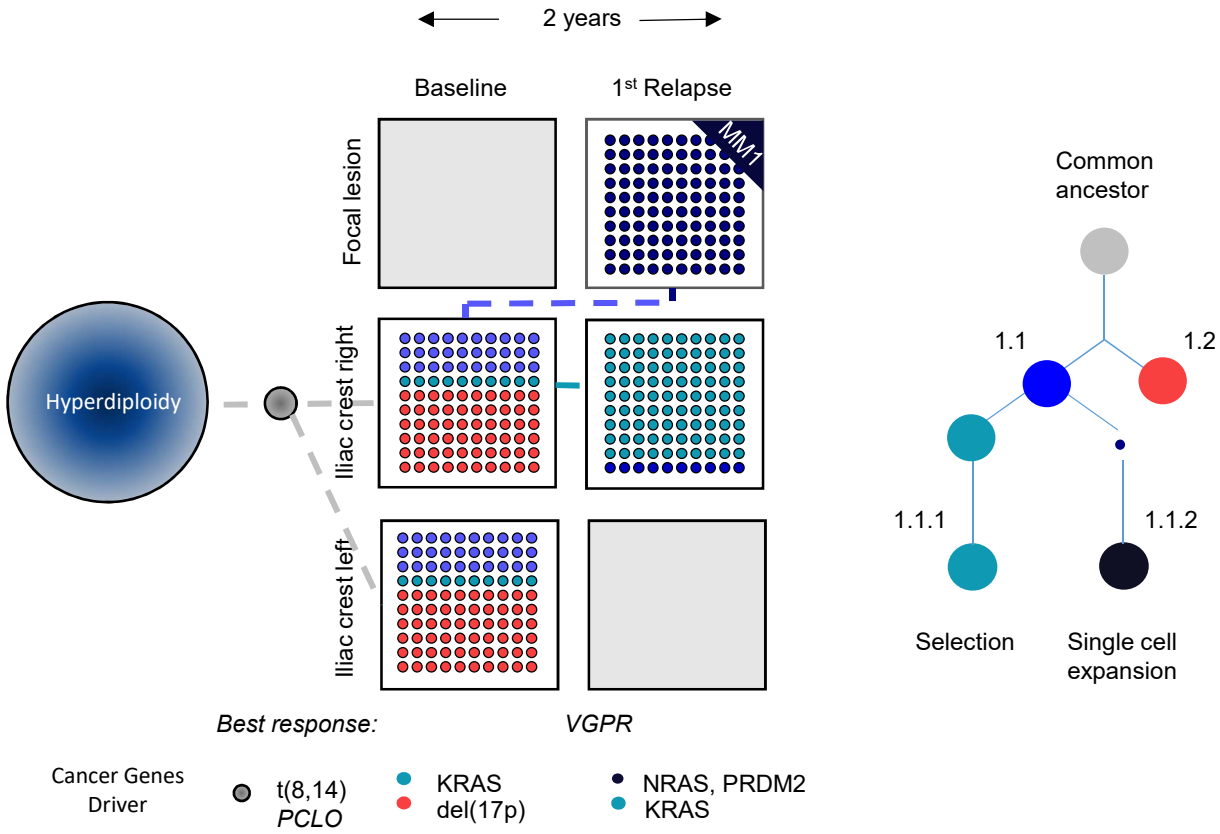




Supplementary Fig. 28: Alternating spatial clonal dominance of TP53-mutated sub-clones. PET-CT images for patient #13 at baseline and at two follow-up time points as well as the corresponding mock phylogenetic tree. In this patient, unique sub-clones were seen at distinct locations both at baseline and after relapse. The patient presented with three unique T*P53* double-hit events which are marked in red in the tree. Other known myeloma drivers are marked in bold. The length of branches corresponds to the time point of first appearance of respective clones.



Supplementary Fig. 29: Concomitant selection of pre-existing disease and single-cell expansion. In patient #9 we observed selection of a pre-existing clone with a *KRAS* mutation at the right iliac crest and a concomitant expansion of a single-cell with an *NRAS* mutation at the right sacrum. The single-cell expansion was predicted based on the presence of the MM1 melphalan signature. Grey boxes/cards indicate that tumor data is not available for the respective timepoints and sites. The corresponding mock phylogenetic tree is shown on the right. The length of branches does not indicate the extent of differences between sub-clones.



Supplementary Table 1: Treatment and samples

ID	Treatment at UAMS	Line	Best response	Sample 1	Sample 2	Sample 3	Sample 4
1	1st ASCT	1	CR	RNAS ILP			
1	KRD	2	PD				
1	PACMED	3	SD				
1	Metronomic 28 day (Vel/Dex/Dox/Cis/Pom/Rev +/- Thal)	4	PR	RNAS IRP			
1	Pom	5	continuous PR				
1	Trametinib	6	PD				
1	VRD	7	PD				
1				FNAS sternum			
1	PACMED	8	PD				
1				RNAS ILP	FNAS sternum		
1	Metronomic 28 day	9	SD				
1				RNAS ILP	RNAS IRP		
2	VDTPACE	1		RNAS ILP			
2	Tandem ASCT	1					
2	Consolidation 1 & 2	1					
2	VDT Maintenance	1	PR				
2				RNAS ILP			
2	Vel/Dex	2					
2	Rev/Dex	3	SD				
2				RNAS IRP			
2	Pom/Vel/Dex	4	SD				
2				RNAS IRP			
2	Pom/Vel	4	SD				
2				RNAS IRP	FNAS left ischium	FNAS right iliac	
2	Metronomic 28 day	5	PR				
2				RNAS ILP			
2	Trametinib	6	PR				
2	Pom/Vel/Cyclo	7					
2				RNAS ILP			
2	Pom/Vel/Cyclo	7					
2	Carfilzomib	8	PR				

ID	Treatment at UAMS	Line	Best response	Sample 1	Sample 2	Sample 3	Sample 4
2				RNAS ILP			
3	MVTDPACE	1		RNAS IRP	RNAS ILP		
3	1st ASCT	1					
3	MVDTPACE	1					
3	2nd ASCT	1					
3	VRD Maintenance	1	CR				
3	Pomalidomide	2	PR				
3	VDTPACE	3	SD				
3				RNAS ILP			
4	VDTPACE	1		RNAS ILP	FNAS right sacrum		
4	Tandem ASCT	1					
4	Consolidation 1 & 2	1					
4	VRD Maintenance	1	CR				
4				FNAS left iliac			
5	MVTDPACE	1		RNAS ILP	RNAS IRP	FNAS left sacrum	
5	1st ASCT	1					
5	Rituximab	1					
5	Vel/Rev Maintenance	1					
5	Vel/Dex Maintenance	1	CR				
5				RNAS IRP			
6	MVTDPACE	1		RNAS ILP	RNAS IRP	FNAS right ilium	
6	1st ASCT	1					
6	MVDTPACE	1					
6	2nd ASCT	1					
6	VRD Maintenance	1	VGPR				
6				RNAS ILP			
6	KRD	2	SD				
6				RNAS IRP			

ID	Treatment at UAMS	Line	Best response	Sample 1	Sample 2	Sample 3	Sample 4
7	MVTDPACE	1		RNAS IRP	PB	FNAS sacrum	RNAS ILP
7	1st ASCT	1					
7	MVDTPACE	1					
7	2nd ASCT	1					
7	VRD Maintenance	1					
7	VTD Maintenance	1	CR				
7				RNAS IRP	RNAS ILP		
7	Carf/Dex	2	PR				
7	Metronomic 28 day	3	SD				
7	Trametinib	4	PR				
7	Pomalidomide	5	PD				
7	Vel/Dex	6	PD				
7				PB			
8	MVTDPACE	1	SD	FNAS right acromion	RNAS IRP	FNAS L5	
8				RNAS ILP			
8	MVTDPACE	1	SD				
8				RNAS ILP			
8	1st ASCT	1	PR				
8				RNAS IRP			
8	Rev/Dex	2	SD				
8				RNAS ILP			
9	MVTDPACE	1		RNAS IRP	RNAS ILP		
9	1st ASCT	1					
9	VRD Maintenance	1	VGPR				
9				RNAS IRP	FNAS right sacrum		
10	MVTDPACE	1		RNAS ILP	FNAS L1	FNAS pelvis right	FNAS rib
10	1st ASCT	1					
10	MVDTPACE	1					
10	2nd ASCT	1					
10	VDTPACE	1					

ID	Treatment at UAMS	Line	Best response	Sample 1	Sample 2	Sample 3	Sample 4
10	VRD Maintenance	1	sCR				
10	Metronomic 28 day	2	PD				
10	Vincristine	3	PD				
10				RNAS IRP			
10	PACMED + Mel	4					
10	3rd ASCT	4	PD				
10	Carf/Dex	5	PD				
10	PACMED	6					
10	4th ASCT	6	PD				
10				FNAS paraspinal			
11	MVTDPACE	1		RNAS ILP			
11	1st ASCT	1					
11	MVDTPACE	1					
11	2nd ASCT	1					
11	VRD Maintenance	1	CR				
11				FNAS L3			
11	Pom/Carf/Dex	2	PD				
11				RNAS ILP			
12	DTPACE	1		RNAS IRP	RNAS ILP		
12	Interim Thal/Dex 1	1					
12	1st ASCT	1					
12	Interim Thal/Dex 2	1					
12	2nd ASCT	1					
12	Interim Thal/Dex 3	1					
12	DTPACE Consolidation	1					
12	Thal/Dex Maintenance	1	VGPR				
12	VTD (Vel/Thal/Dex)	2	PR				
12	VRD (Vel/Rev/Dex)	3	VGPR				
12	Velcade	4	SD				
12	Pom/Vel/Dex	5	SD				
12	Carf/Dex	6	PR				

ID	Treatment at UAMS	Line	Best response	Sample 1	Sample 2	Sample 3	Sample 4
12				FNAS Sacrum			
12				RNAS IRP			
12	Metronomic 28 day	7	SD				
12	Trametinib	8	SD				
12				RNAS ILP			
12	Pomalidomide	9	PD				
12				RNAS ILP	FNAS Sacrum	FNAS T9	
12	PACMED+VT	10	SD				
12				RNAS ILP	RNAS IRP		
12	Trametinib	11	PD				
12	Thalidomide	11					
12				RNAS ILP			
12	3rd ASCT	12	CR				
12	Carf/Dex	13	PD				
12	Carf/Rev/Dex	14	PD				
12				RNAS ILP			
12	Daratumumab	15	PD				
12				RNAS IRP			
13	MVTDPACE	1		RNAS IRP	FNAS T5	FNAS left ilium	
13	1st ASCT	1					
13	MVDTPACE	1					
13	2nd ASCT	1					
13	VRD Maintenance	1	sCR				
13				FNAS T7			
13	Dara/Pom/Cyclo	2	VGPR				
13	KRD	3	continuous VGPR				
13				FNAS sacrum			
14	MVTDPACE	1		RNAS IRP	RNAS ILP		
14	VTD	1	PR				
14				RNAS ILP			
14	Vel/Dex	2	SD				

ID	Treatment at UAMS	Line	Best response	Sample 1	Sample 2	Sample 3	Sample 4
14	VDTPACE	3	SD				
14	Carf/Dex	4	SD				
14	Carf/Dex/Dox/Cis/Thal	5	SD				
14	KRD	6	SD				
14	Thal/Rev	7	SD				
14	Pom/Carf/Dex	8	SD				
14	Pom/Vel/Dex	9	PD				
14				RNAS ILP	FNAS T3	RNAS ILP	
14	Vincristine	10					
14	Metronomic 28 day	10	PD				
14	Pom/Carf/Dex	11	PD				
14				RNAS IRP			
14	Trametinib	12	PR				
14	Pomalidomide	13	PD				
14				FNAS T3	RNAS ILP		
15	MVTDPACE	1		RNAS ILP	FNAS right ilium		
15	1st ASCT	1					
15	MVDTPACE	1					
15	2nd ASCT	1					
15	VRD Maintenance	1					
15	VTD Maintenance	1	sCR				
15				RNAS ILP			
15	Vel/Pom/Dex	2	CR				
15	KRD	3	SD				
15				RNAS IRP			
15				RNAS ILP			
15	VD-PACE	4					
15	VTD-BEAM	4					
15	3rd ASCT	4	VGPR				
15	Carf/Cyclo/Dex	4					
15	Carf/Dex + Trametinib	5	SD				
15				RNAS ILP			

ID	Treatment at UAMS	Line	Best response	Sample 1	Sample 2	Sample 3	Sample 4
16	MVTDPACE	1		RNAS ILP	FNAS right sacrum		
16	1st ASCT	1					
16	VTDPACE Consolidation	1					
16	VRD Maintenance	1	sCR				
16	Carf/Dex	2	SD				
16	Vel/Dex	3	PD				
16	Metronomic 28 day	4	SD				
16	Pom/Dex	5	SD				
16	Trametinib	6	SD				
16				RNAS ILP			
16	Thalidomide	7	SD				
16				RNAS ILP			
16	Lenalidomide	8	PD				
16				RNAS IRP			
16	2nd ASCT	9	PD				
16				RNAS ILP			
17	VDTPACE	1		FNAS left sacrum			
17	1st ASCT	1					
17	Consolidation 1 & 2	1					
17	VRD Maintenance	1	CR				
17	KRD	2	PD				
17				RNAS IRP	FNAS T10		
17	Pom/Cyclo/Dex	3	PD				
17				RNAS ILP			
18	VDTPACE	1		RNAS ILP	RNAS IRP	FNAS T9	
18	Tandem ASCT	1					
18	Consolidation 1 & 2	1					
18	VRD Maintenance	1	CR				
18	VRD	2	SD				
18	VTDR	3	SD				

ID	Treatment at UAMS	Line	Best response	Sample 1	Sample 2	Sample 3	Sample 4
18	VDTPACE	4	PR				
18	Metronomic 28 day	5	SD				
18	Arsenic Trioxide+ ATRA	6	SD				
18	Metronomic 28 day	7	PD				
18	PACMED	8					
18	3rd ASCT	8	PR				
18				FNAS right iliac			
18	PACMED	9	PR				
18	Melphalan	10	PR				
18	Vincristine	11	continuous PR				
18	BEAM + VTD	12					
18	4th ASCT	12	PR				
18				FNAS left iliac			
19	VDTPACE	1		RNAS ILP			
19	Tandem ASCT	1					
19	VRD Maintenance	1	CR				
19				RNAS IRP	FNAS left ilium	FNAS right ilium	
19	PACMED	2					
19	3rd ASCT	2	PD				
19	Trametinib	3	VGPR				
19	Pom/Dex	4	continuous VGPR				
19				RNAS ILP			
19	VTD	5	PD				
19				RNAS IRP			
19	Vincristine	6					
19	Metronomic 28 day	6	PD				
19				RNAS IRP			
20	MVTDPACE	1		RNAS IRP	FNAS L1		
20	1st ASCT	1					
20	MVDTPACE	1					
20	2nd ASCT	1					

ID	Treatment at UAMS	Line	Best response	Sample 1	Sample 2	Sample 3	Sample 4
20	VRD Maintenance	1	CR				
20				RNAS ILP			
20	MVDRPACE	2	PD				
20	Carfilzomib	3	PD				
20	Thal/Cyclo/Dex	4					
20	3rd ASCT	4	PD				
20	BEAM	5	SD				
20	VTD	6	PR				
20	Bevacizumab + Vel	7	continuous PR				
20	Bevacizumab + VTD	8	VGPR				
20	Bevacizumab + VTCD + Eto	9	continuous VGPR				
20	VDTPACE	10	PD				
20				RNAS ILP			
21	VDTPACE	1		RNAS ILP			
21	MVDRPACE	1					
21	Tandem ASCT	1					
21	VDTPACE	1					
21	VRD Maintenance	1	sCR				
21				FNAS T9	FNAS sacrum		
21	PACMED	2					
21	Ara-C/Eto/BCNU + ASCT	2	PR				
21	Vincristine	3					
21	Metronomic 28 day	3	PD				
21	Pom/Carf/Dex	4	PD				
21	VRD	5	PD				
21	Trametinib	6	PD				
21	PACMED + ASCT	7	PD				
21	PACMED	8	PD				
				FNAS right sacrum			
22	VDTPACE	1		RNAS IRP			
22				RNAS ILP			

ID	Treatment at UAMS	Line	Best response	Sample 1	Sample 2	Sample 3	Sample 4
22	Tandem ASCT	1					
22	Consolidation 1 & 2	1					
22	Thal/Dex Maintenance	1					
22	Lenalidomide Maintenance	1	CR				
22				RNAS IRP	FNAS T12		
22	Metronomic	2	no reponse				
22	KRD	3	PR				
22			continous PR	RNAS IRP			
22			continous PR	RNAS IRP			
23	1st ASCT	1		RNAS IRP	FNAS right ilium		
23	2nd ASCT	1					
23	VDT-PACE	1	CR				
23	VRD	2	PD				
23				FNAS paraspinal	FNAS left ilium		
23	BCNU + 3rd ASCT	3					
23	CRD	3	nCR				
23				FNAS lower back			
24	MVTDPACE	1		RNAS IRP	RNAS ILP		
24	Tandem ASCT	1					
24	VTDPACE Consolidation	1					
24	VRD Maintenance	1	CR				
24				RNAS IRP			
24	Metronomic 28 day	2	PR				
24	Trametinib	3	CR				
24	Pom/Dex	4	PD				
24				FNAS right iliac			
24	PACMED + 3rd ASCT	5	CR				
24	Pom/Carf/Dex	6	PD				
24				RNAS ILP	FNAS right chest wall		
24	PACMED	7	PD				
24				RNAS ILP			

ID	Treatment at UAMS	Line	Best response	Sample 1	Sample 2	Sample 3	Sample 4
25	DTPACE (Dex /Thal / Cis / Dox/ Cyclo / Eto)	1					
25	Tandem ASCT	1	CR				
25				RNAS ILP	FNAS L4		
25				RNAS IRP	RNAS ILP		

Supplementary Table 2: Evolution pattern

ID	Excluded	Single-cell expansion	Coexisting subclones	Spatial dominance	PET FL	Response	SG	GEP70 baseline
1	-	x	-	-	2	CR	PR	low risk
2	-	-	x	-	140	PR	HY	low risk
3	only one FU sample	NA	NA	NA	masked	CR	PR	high risk
4	only one FU sample	NA	NA	NA	30	CR	t(4;14)	high risk
5	only one FU sample	NA	NA	NA	0	CR	CD-2	low risk
6	-	-	x	-	11	VGPR	HY	low risk
7	-	-	x	-	0	CR	MF	high risk
8	-	-	x	-	35	PR	HY	low risk
9	-	-	x	-	4	VGPR	HY	low risk
10	-	-	-	x	50	CR	MS	high risk
11	-	-	-	x	11	CR	t(6;14)	low risk
12	-	-	x	-	1	VGPR	MS	NA
13	-	-	-	x	21	CR	HY	low risk
14	-	-	x	-	3	PR	HY	low risk
15	-	-	x	-	4	CR	PR	low risk
16	-	-	x	-	2	CR	HY	low risk
17	-	x	-	-	1	CR	CD-1	low risk
18	-	x	-	-	1	CR	LB	low risk
19	-	x	-	-	1	CR	CD-2	low risk
20	-	x	-	-	1	CR	PR	high risk
21	-	x	-	-	0	CR	MS	low risk
22	-	x	-	-	0	CR	HY	low risk
23	-	-	-	x	25	CR	MS	low risk
24	-	-	x	-	20	CR	HY	low risk
25	no treatment	NA	NA	NA	2	CR	NA	NA

Supplementary Table 3: Contribution of SBS-MM1 signature to sub-clonal mutations

ID	Clone ID	# Mutations	SBS-MM1 contribution (mmsig)	*P* (mSigAct)	SBS-MM1
1	1.1	25	0.42 (0-0.62)	1.46E-03	yes
2	1.1.1.1	44	0.43 (0-0.62)	6.07E-05	yes
3	1.1	62	0.56 (0.42-0.68)	5.83E-09	yes
4	1.2	54	0.44 (0.34-0.6)	8.94E-06	yes
5	1.3	34	0.37 (0.09-0.57)	3.37E-04	yes
6	1.1.2	86	0.33 (0.14-0.46)	4.37E-06	yes
7	1.2.1 & 1.2.2 combined	58	0 (0-0.08)	0.20	no
7	1.2.2.1	405	0 (0-0)	3.80E-05	no
9	1.1.2	87	0.48 (0.32-0.62)	2.93E-09	yes
10	1.2.1	126	0.35 (0.26-0.47)	4.61E-07	yes
11	1.2.1.1	83	0.3 (0.09-0.37)	4.30E-06	yes
11	1.2.1.2.2	64	0.52 (0.27-0.65)	1.37E-07	yes
12	1.1.1	53	0.58 (0.43-0.78)	2.02E-09	yes
12	1.1.2	60	0.32 (0.05-0.53)	7.91E-04	yes
12	1.1.3	48	0.32 (0-0.45)	2.91E-04	yes
13	1.2.1.2.1	25	0.41 (0.08-0.61)	5.95E-03	yes
13	1.2.3	70	0.12 (0-0.37)	4.18E-02	yes
14	1.1.1.1.1	35	0 (0-0)	1.00	no
15	1.1.1.1	111	0.43 (0.28-0.55)	1.20E-08	yes
15	1.2.1	40	0 (0-0.31)	0.28	no
16	1.2.1	98	0.5 (0.38-0.62)	1.28E-13	yes
16	1.2.2 & 1.2.2.1 combined	52	0.46 (0.3-0.55)	2.40E-05	yes
17	1.2	91	0.21 (0-0.32)	2.71E-02	yes
18	1.2	81	0.23 (0.07-0.33)	2.46E-03	yes
19	1.2.1	48	0 (0-0.28)	0.42	no
19	1.2.1.1	26	0 (0-0.2)	1.00	no
20	1.1.2.2.1	66	0.38 (0.26-0.48)	6.68E-07	yes
21	1.1.1	47	0.19 (0.04-0.44)	3.11E-02	yes
21	1.1.1.1.1	32	0 (0-0)	1.00	no
22	1.1.1.1	80	0.3 (0.12-0.4)	2.19E-05	yes
23	1.2.2	147	0.23 (0.19-0.35)	7.86E-06	yes
23	1.2.3.1	55	0.1 (0-0.28)	0.19	no
23	1.2.3.2	111	0.14 (0.04-0.31)	4.25E-03	yes
23	1.2.3.2.1	35	0.41 (0-0.55)	2.21E-04	yes
24	1.1.1	63	0.28 (0.17-0.5)	6.27E-04	yes
24	2.1	33	0 (0-0.13)	0.93	no
24	2.1.1	46	0.49 (0.3-0.6)	1.16E-08	yes
24	2.1.1.2	34	0 (0-0)	1.00	no

ID: patient ID, Clone ID corresponds to sub-clone ID in Supplementary Figures 3-26.

ID	Sweep 1	Prior response	Sweep 2	Prior response	Sweep 3	Prior response
1	x	CR	x	PR	x	PD
2	-		-		-	
6	x	VGPR	-		-	
7	x	CR	-		-	
8	x	PR	-		-	
12	x	VGPR	x	CR	x	PD
14	x	PR	x	PR	-	
15	x	CR	x	CR	-	
16	x	CR	x	PD	-	
17	x	CR	-		-	
19	x	CR	-		-	
20	x	CR	x	VGPR	-	
22	x	CR	x	PR	-	
24	x	CR	x	PD	-	

Supplementary Table 5: Mutations in epigentic modifiers of KDM/KMT family

ID	Gene	Chr	Pos	Ref	Alt	Mut.- type	Change	Sub-clone*
3	KMT2B	19	36223964	G	T	missense	Val2172Phe	1.1
6	KDM2A	11	67010546	T	G	missense	Trp516Gly	1.1.2
7	KDM3A	2	86683616	C	T	missense	Ser203Phe	1.1
7	KDM3B	5	137760018	G	A	stop gained	Trp1409*	1.2.2.1
7	KDM5B	1	202700034	C	T	splice site	-	1.1
7	KDM5B	1	202727542	C	A	missense	Asp428Tyr	1.2.2.1
7	KMT2C	7	151833961	G	T	missense	Pro4955Thr	1.2.2.1
10	KDM2A	11	66982864	C	A	missense	Ser180Arg	1.2.1
12	KDM4B	19	5131419	G	A	missense	Ala584Thr	1.1.1
12	KMT2D	12	49424479	C	G	missense	Gly4582Arg	1.1.3
14	KMT2C	7	151853012	G	C	missense	Asn4038Lys	1.1.1.1.1
15	KDM4C	9	6793039	G	C	missense	Met17Ile	1.2.1
15	KMT2D	12	49432602	C	T	missense	Gly2846Asp	1.1
18	KDM5B	1	202700030	C	T	splice site	-	1.2.2.1
20	KMT2D	12	49424767	T	G	missense	Lys4527Thr	1.1.2.2.1
24	KDM3B	5	137715291	G	T	missense	Gly200Val	2.1

ID: patient ID; *please refer to Supplementary Figures 3-27.

Supplementary Table 6: Sample inclusion

	Baseline comparison		Relapse comparison			Clonal relationship			
ID	Iliac/Iliac	Iliac/FL	Iliac/Iliac	Iliac/FL or FL/FL	First/last sample	Paired Iliac/FL	Only Iliac	Evolution pattern	Sweeps
1			x	x	x		x	x	x
2				x	x		x	x	x
3	x				x		x		
4		x			x	x	x		
5	x	x			x	x	x		
6	x	x			x	x	x	x	x
7	x	x	x		x	x	x	x	x
8		x			x	x	x	x	x
9	x				x		x	x	
10					x	x	x	x	
11					x		x	x	
12	x		x		x		x	x	x
13					x	x	x	x	
14	x			x	x		x	x	x
15		x			x	x	x	x	x
16					x	x	x	x	x
17				x	x			x	x
18	x	x			x	x	x	x	
19				x	x		x	x	x
20		x			x	x	x	x	x
21					x		x	x	
22					x		x	x	x
23				x	x	x	x	x	
24	x				x		x	x	x
25			x						