

Supplementary Online Content

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eTable 1. Genes Included in the Cell Cycle and Immune Gene Expression Signature ...	2
eTable 2. Baseline Characteristics	3
eTable 3. Baseline Characteristics in Patients With Available Gene Expression Signature Data	4
eTable 4. Distribution of Gene Expression Signatures by Prognostic Subgroups Identified for PFS in All Pooled Patients With Gene Expression Data (n = 608)	5
eTable 5. Distribution of Gene Expression Signatures by Prognostic Subgroups Identified for OS in All Pooled Patients With Gene Expression Data (n = 608)	6
eTable 6. Objective Response Rate by Prognostic Subgroups Identified for PFS and OS in All Pooled Patients Across Treatment Cohorts.....	7
eTable 7. Duration of Response by Prognostic Subgroups Identified for PFS and OS in All Pooled Patients Across Treatment Cohorts	8
eFigure 1. PFS by Prognostic Subgroup Identified by the Recursive Partitioning Model in All Pooled Patients	9
eFigure 2. Recursive Partitioning Decision Tree and OS Outcomes by Identified Prognostic Subgroups in All Pooled Patients.....	12
eFigure 3. OS by Prognostic Subgroup Identified in the Recursive Partitioning Model in All Pooled Patients	13
eFigure 4. Recursive Partitioning Decision Tree and PFS Outcomes by Identified Prognostic Subgroups in All Patients With Gene Expression Data.....	16
eFigure 5. Recursive Partitioning Decision Tree and Outcomes by Identified Prognostic Subgroups for OS in All Patients With Gene Expression Data.....	17
eFigure 6. Prevalence of Immune or Cell Cycle Gene Expression Signatures by Prognostic Subgroups For PFS (Panel A) and OS (Panel B) in all Pooled Patients With Gene Expression Data (n = 608).....	18
eFigure 7. Objective Response by Prognostic Subgroups.	20

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Genes Included in the Cell Cycle and Immune Gene Expression Signature

Cell cycle genes	Immune signature genes
<i>BRCA1</i>	<i>CCL5</i>
<i>BRIP1</i>	<i>CCND2</i>
<i>CCNB1</i>	<i>CCR5</i>
<i>CCNE1</i>	<i>CD247</i>
<i>FH</i>	<i>CD3E</i>
<i>KDM4A</i>	<i>CD4</i>
<i>MAP2K2</i>	<i>CD86</i>
<i>MTCH1</i>	<i>CD8A</i>
<i>MYC</i>	<i>GZMA</i>
<i>NF2</i>	<i>HAVCR2</i>
<i>PRKDC</i>	<i>IKZF1</i>
<i>PTK2</i>	<i>KIR3DL1</i>
<i>RPTOR</i>	<i>KLRK1</i>
<i>SMARCA4</i>	<i>LAG3</i>
<i>SNAI2</i>	<i>LGALS9</i>
<i>SOX4</i>	<i>MYD88</i>
<i>SRSF2</i>	<i>PDCD1LG2</i>
<i>WDR5</i>	<i>PIK3R5</i>
<i>ZNF703</i>	<i>PTGER4</i>
	<i>PTPRC</i>
	<i>TBX21</i>
	<i>TIGIT</i>
	<i>TNFRSF9</i>

eTable 2. Baseline Characteristics^a

Characteristic	All Pooled Patients (n = 1365)	Cobimetinib Plus Vemurafenib (n = 310)	Vemurafenib Monotherapy (n = 717)	Dacarbazine (n = 338)
Age				
<65 y	1032 (75.6)	232 (74.8)	530 (73.9)	270 (79.9)
≥65 y	333 (24.4)	78 (25.2)	187 (26.1)	68 (20.1)
Sex				
Male	783 (57.4)	181 (58.4)	421 (58.7)	181 (53.6)
Female	582 (42.6)	129 (41.6)	296 (41.3)	157 (46.4)
Race				
White	1325 (97.1)	298 (93.2)	698 (97.4)	338 (100.0)
Nonwhite	40 (2.9)	21 (6.8)	19 (2.6)	0
Region				
North America	389 (28.5)	76 (24.5)	227 (31.7)	86 (25.4)
Europe	774 (56.7)	182 (58.7)	389 (54.3)	203 (60.1)
Australia/New Zealand/Others	202 (14.8)	52 (16.8)	101 (14.1)	49 (14.5)
Baseline disease stage	n = 1364	n = 310	n = 716	n = 338
Unresectable IIIC, M1a, or M1b	500 (36.7)	120 (38.7)	262 (36.6)	118 (34.9)
M1c	864 (63.3)	190 (61.3)	454 (63.4)	220 (65.1)
Baseline ECOG PS	n = 1359	n = 306	n = 715	n = 338
0	911 (67.0)	225 (73.5)	456 (63.8)	230 (68.0)
1	447 (32.9)	80 (26.1)	259 (36.2)	108 (32.0)
2	1 (0.1)	1 (0.3)	0	0
Baseline LDH	n = 1237	n = 285	n = 671	n = 281
Normal	690 (55.8)	155 (54.4)	375 (55.9)	160 (56.9)
Elevated ≤2x ULN	361 (29.2)	95 (33.3)	183 (27.3)	83 (29.5)
Elevated >2x ULN	186 (15.0)	35 (12.3)	113 (16.8)	38 (13.5)
Baseline liver metastasis	n = 1357	n = 310	n = 713	n = 334
Yes	447 (32.9)	100 (32.3)	236 (33.1)	111 (33.2)
No	910 (67.1)	210 (67.7)	477 (66.9)	223 (66.8)
Baseline SLD of target lesions	n = 1347	n = 310	n = 704	n = 333
Mean (SD)	81.7 (70.4)	74.4 (57.8)	86.1 (80.1)	79.2 (57.3)
Median (range)	65.0 (9-1310)	62.5 (10-398)	68.0 (9-1310)	66.0 (9-295)
Gene expression signature	n = 608	n = 143	n = 320	n = 145
Cell cycle	312 (51.3)	71 (49.7)	172 (53.8)	69 (47.6)
Immune	296 (48.7)	72 (50.3)	148 (46.3)	76 (52.4)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; SD, standard deviation; SLD, sum of longest diameter; ULN, upper limit of normal.

^a Data are presented as number (percentage) of patients unless otherwise indicated.

eTable 3. Baseline Characteristics in Patients With Available Gene Expression Signature Data^a

	All Pooled Patients (n = 608)	Cobimetinib Plus Vemurafenib (n = 143)	Vemurafenib (n = 320)	Dacarbazine (n = 145)
Baseline ECOG PS	n = 606	n = 143	n = 318	n = 145
0	406 (67.0)	109 (76.2)	202 (63.5)	95 (65.5)
1	200 (33.0)	34 (23.8)	116 (36.5)	50 (34.5)
2	0	0	0	0
Baseline LDH	n = 565	n = 132	n = 300	n = 133
Normal	307 (54.3)	68 (51.5)	165 (55.0)	74 (55.6)
Elevated (≤2× ULN)	169 (29.9)	43 (32.6)	84 (28.0)	42 (31.6)
Elevated (>2× ULN)	89 (15.8)	21 (15.9)	51 (17.0)	17 (12.8)
Baseline liver metastasis	n = 606	n = 143	n = 318	n = 145
Yes	202 (33.3)	51 (35.7)	106 (33.3)	45 (31.0)
No	404 (66.7)	92 (64.3)	212 (66.7)	100 (69.0)
Baseline SLD of target lesions	n = 604	n = 143	n = 316	n = 145
Median, mm (range)	69.7 (9-511)	65.0 (10-332)	70.5 (9-511)	71.0 (10-295)
Gene expression signature	n = 608	n = 143	n = 320	n = 145
Cell cycle	312 (51.3)	71 (49.7)	172 (53.8)	69 (47.6)
Immune	296 (48.7)	72 (50.3)	148 (46.3)	76 (52.4)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; SLD, sum of longest diameters; ULN, upper limit of normal.

^a Data are presented as number (percentage) of patients unless otherwise indicated.

eTable 4. Distribution of Gene Expression Signatures by Prognostic Subgroups Identified for PFS in All Pooled Patients With Gene Expression Data (n = 608)

Genomic signature, n (%)	LDH Normal and LM Absent	LDH Normal and LM Present	LDH Elevated $\leq 2 \times$ ULN, ECOG PS 0, and SLD ≤ 44 mm	LDH Elevated $\leq 2 \times$ ULN, ECOG PS 0, and SLD > 44 mm	LDH Elevated $\leq 2 \times$ ULN and ECOG PS ≥ 1	LDH Elevated $> 2 \times$ ULN
All pooled patients	n = 225	n = 81	n = 23	n = 81	n = 65	n = 89
Cell cycle	93 (41.3)	40 (49.4)	13 (56.5)	43 (53.1)	44 (67.7)	58 (65.2)
Immune	132 (58.7)	41 (50.6)	10 (43.5)	38 (46.9)	21 (32.3)	31 (34.8)
<i>P</i> value ^a	<.0001					
Cobimetinib + vemurafenib	n = 48	n = 20	n = 7	n = 23	n = 13	n = 21
Cell cycle	20 (41.7)	8 (40.0)	2 (28.6)	12 (52.2)	10 (76.9)	13 (61.9)
Immune	28 (58.3)	12 (60.0)	5 (71.4)	11 (47.8)	3 (23.1)	8 (38.1)
<i>P</i> value ^a	.0062					
Vemurafenib	n = 116	n = 48	n = 14	n = 34	n = 36	n = 51
Cell cycle	44 (37.9)	28 (58.3)	9 (64.3)	18 (52.9)	25 (69.4)	36 (70.6)
Immune	72 (62.1)	20 (41.7)	5 (35.7)	16 (47.1)	11 (30.6)	15 (29.4)
<i>P</i> value ^a	<.0001					
Dacarbazine	n = 61	n = 13	n = 2	n = 24	n = 16	n = 17
Cell cycle	29 (47.5)	4 (30.8)	2 (100.0)	13 (54.2)	9 (56.3)	9 (52.9)
Immune	32 (52.5)	9 (69.2)	0	11 (45.8)	7 (43.8)	8 (47.1)
<i>P</i> value ^a	.3146					

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; LM, liver metastases; PFS, progression-free survival; ULN, upper limit of normal.

^aOne-sided Cochrane-Armitage trend test.

eTable 5. Distribution of Gene Expression Signatures by Prognostic Subgroups Identified for OS in All Pooled Patients With Gene Expression Data (n = 608)

Genomic signature, n (%)	LDH Normal and SLD ≤45 mm	LDH Normal and SLD >45 mm	LDH Elevated ≤2x ULN and ECOG PS 0	LDH Elevated ≤2x ULN and ECOG PS ≥1	LDH Elevated >2x ULN
All pooled patients	n = 140	n = 165	n = 104	n = 65	n = 89
Cell cycle	54 (38.6)	78 (47.3)	56 (53.8)	44 (67.7)	58 (65.2)
Immune	86 (61.4)	87 (52.7)	48 (46.2)	21 (32.3)	31 (34.8)
<i>P</i> value ^a	<.0001				
Cobimetinib + vemurafenib	n = 29	n = 39	n = 30	n = 13	n = 21
Cell cycle	10 (34.5)	18 (46.2)	14 (46.7)	10 (76.9)	13 (61.9)
Immune	19 (65.5)	21 (53.8)	16 (53.3)	3 (23.1)	8 (38.1)
<i>P</i> value ^a	.0078				
Vemurafenib	n = 73	n = 90	n = 48	n = 36	n = 51
Cell cycle	29 (39.7)	42 (46.7)	27 (56.3)	25 (69.4)	36 (70.6)
Immune	44 (60.3)	48 (53.3)	21 (43.8)	11 (30.6)	15 (29.4)
<i>P</i> value ^a	<.0001				
Dacarbazine	n = 38	n = 36	n = 26	n = 16	n = 17
Cell cycle	15 (39.5)	18 (50.0)	15 (57.7)	9 (56.3)	9 (52.9)
Immune	23 (60.5)	18 (50.0)	11 (42.3)	7 (43.8)	8 (47.1)
<i>P</i> value ^a	.1051				

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; LM, liver metastases; OS, overall survival; ULN, upper limit of normal.

^aOne-sided Cochrane-Armitage trend test.

eTable 6. Objective Response Rate by Prognostic Subgroups Identified for PFS and OS in All Pooled Patients Across Treatment Cohorts

	Objective response rate, n/N (%)		
	Cobimetinib Plus Vemurafenib	Vemurafenib	Dacarbazine
PFS Prognostic Subgroup			
LDH normal and LM absent	91/118 (77.1)	177/276 (64.1)	25/124 (20.2)
LDH normal and LM present	27/37 (73.0)	60/96 (62.5)	3/36 (8.3)
LDH elevated $\leq 2 \times$ ULN, ECOG PS 0, and SLD ≤ 44 mm	18/23 (78.3)	16/27 (59.3)	2/9 (22.2)
LDH elevated $\leq 2 \times$ ULN, ECOG PS 0, and SLD > 44 mm	35/48 (72.9)	34/71 (47.9)	4/41 (9.8)
LDH elevated $\leq 2 \times$ ULN and ECOG PS ≥ 1	16/24 (66.7)	39/85 (45.9)	3/33 (9.1)
LDH elevated $> 2 \times$ ULN	19/35 (54.3)	37/113 (32.7)	1/38 (2.6)
OS Prognostic Subgroup			
LDH normal and SLD ≤ 45 mm	55/73 (75.3)	114/171 (66.7)	18/79 (22.8)
LDH normal and SLD > 45 mm	63/82 (76.8)	123/193 (63.7)	10/81 (12.3)
LDH elevated $\leq 2 \times$ ULN and ECOG PS 0	53/71 (74.6)	50/98 (51.0)	6/50 (12.0)
LDH elevated $\leq 2 \times$ ULN and ECOG PS ≥ 1	16/24 (66.7)	39/85 (45.9)	3/33 (9.1)
LDH elevated $> 2 \times$ ULN	19/35 (54.3)	37/113 (32.7)	1/38 (2.6)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; LM, liver metastases; OS, overall survival; PFS, progression-free survival; SLD, sum of longest diameters of target lesions; ULN, upper limit of normal.

eTable 7. Duration of Response by Prognostic Subgroups Identified for PFS and OS in All Pooled Patients Across Treatment Cohorts

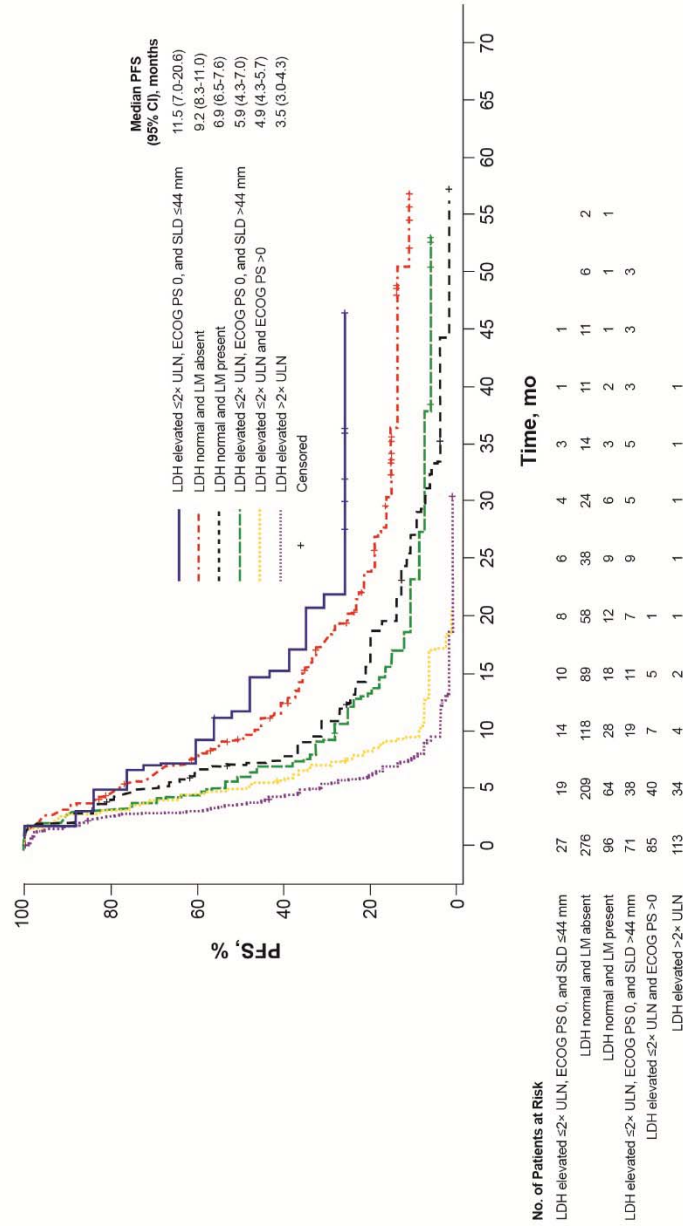
	Duration of response, months, median (95% CI)		
	Cobimetinib Plus Vemurafenib	Vemurafenib	Dacarbazine
PFS Prognostic Subgroup			
LDH normal and LM absent	18.2 (13.4-26.6)	9.7 (8.3-12.9)	20.2 (5.0-35.7)
LDH normal and LM present	15.2 (11.1-28.2)	6.3 (5.6-9.0)	6.4 (4.3-15.6)
LDH elevated $\leq 2\times$ ULN, ECOG PS 0, and SLD ≤ 44 mm	NE (16.6-NE)	11.9 (5.6-NE)	7.0 (3.1-10.8)
LDH elevated $\leq 2\times$ ULN, ECOG PS 0, and SLD >44 mm	12.7 (8.4-17.0)	7.6 (5.6-12.7)	4.8 (3.8-NE)
LDH elevated $\leq 2\times$ ULN and ECOG PS ≥ 1	9.2 (6.0-16.9)	5.1 (3.7-6.7)	7.9 (2.3-20.2)
LDH elevated $>2\times$ ULN	7.9 (5.1-12.5)	4.0 (3.5-4.5)	6.1 (NE-NE)
OS Prognostic Subgroup			
LDH normal and SLD ≤ 45 mm	23.1 (13.6-33.2)	9.2 (8.3-12.9)	20.2 (4.7-35.7)
LDH normal and SLD >45 mm	14.7 (11.1-22.1)	7.6 (6.5-11.6)	11.0 (4.9-NE)
LDH elevated $\leq 2\times$ ULN and ECOG PS 0	13.5 (12.4-20.4)	8.4 (5.7-13.4)	4.8 (3.8-10.8)
LDH elevated $\leq 2\times$ ULN and ECOG PS ≥ 1	9.2 (6.0-16.9)	5.1 (3.7-6.7)	7.9 (2.3-20.2)
LDH elevated $>2\times$ ULN	7.9 (5.1-12.5)	4.0 (3.5-4.5)	6.1 (NE-NE)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; LM, liver metastases; NE, not estimable; OS, overall survival; PFS, progression-free survival; SLD, sum of longest diameters of target lesions; ULN, upper limit of normal.

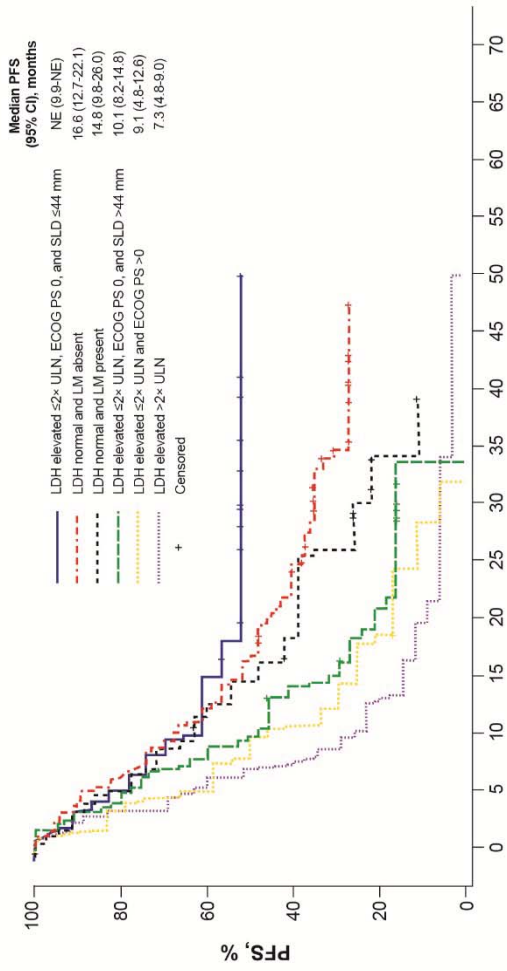
eFigure 1. PFS by Prognostic Subgroup Identified by the Recursive Partitioning Model in All Pooled Patients

A, Pooled vemurafenib cohort. B, Pooled cobimetinib plus vemurafenib cohort. C, Dacarbazine cohort.
 ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; LM, liver metastases; NE, not estimable; PFS, progression-free survival; SLD, sum of longest diameters of target lesions; ULN, upper limit of normal.

A



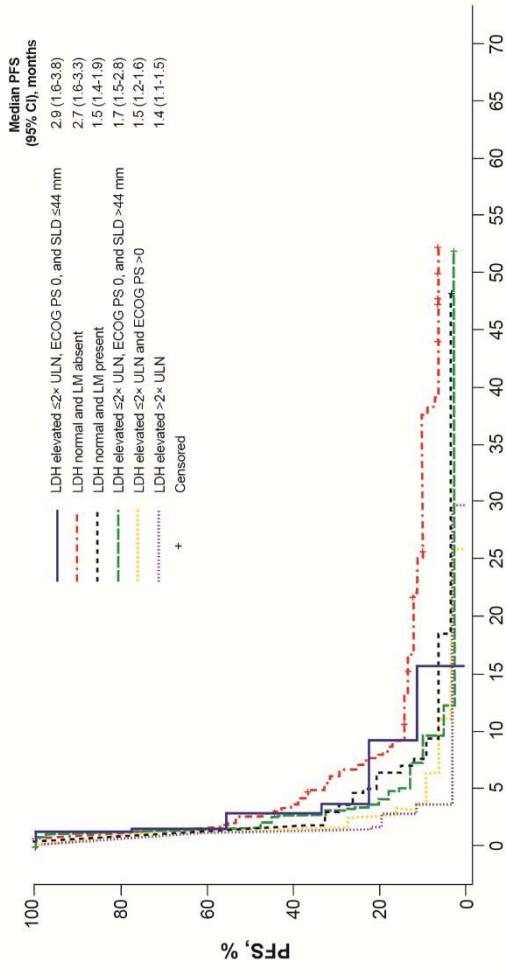
B



No. of Patients at Risk

Time, mo	0	5	10	15	20	25	30	35	40	45	50	55	60	65	70
LDH elevated $\geq 2 \times$ ULN, ECOG PS 0, and SLD ≤ 44 mm	23	19	15	14	10	10	5	4	2	1					
LDH normal and LM absent	118	99	73	56	48	37	29	8	6	1					
LDH normal and LM present	37	30	22	16	12	12	5	1							
LDH elevated $\geq 2 \times$ ULN, ECOG PS 0, and SLD > 44 mm	48	36	22	13	8	6	2								
LDH elevated $\geq 2 \times$ ULN and ECOG PS > 0	24	16	12	6	3	2	1								
LDH elevated $> 2 \times$ ULN	35	23	9	5	3	2	2	1	1	1					

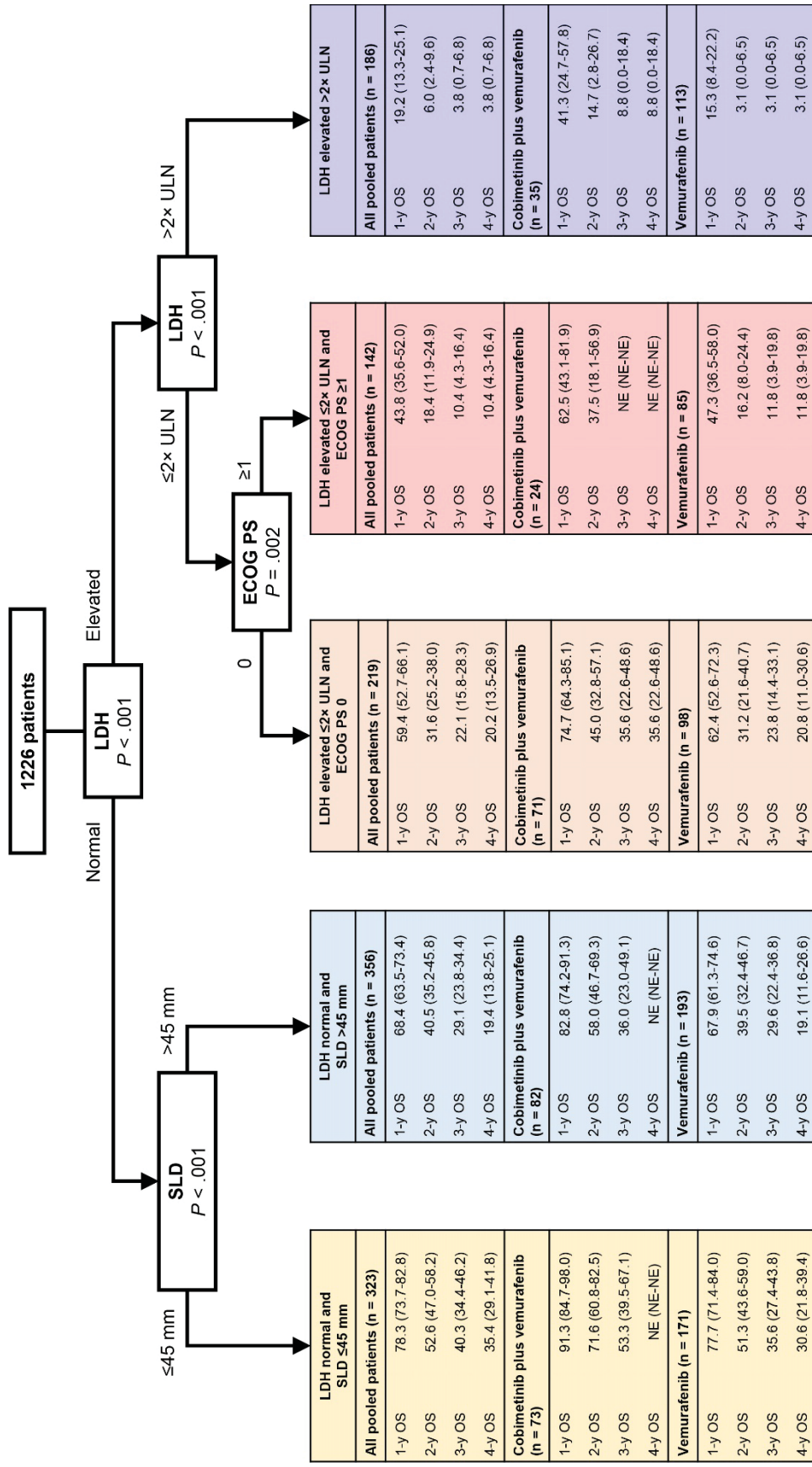
C



No. of Patients at Risk	0	5	10	15	20	25	30	35	40	45	50	55	60	65	70
LDH elevated $\leq 2 \times$ ULN, ECOG PS 0, and SLD ≤ 44 mm	9	2	1	1											
LDH normal and LM absent	124	39	16	14	12	10	8	8	5	4	1				
LDH normal and LM present	36	8	2	2	1	1	1	1	1	1	1				
LDH elevated $\leq 2 \times$ ULN, ECOG PS 0, and SLD > 44 mm	41	7	2	1	1	1	1	1	1	1	1				
LDH elevated $\leq 2 \times$ ULN and ECOG PS > 0	33	3	2	1	1	1	1								
LDH elevated $> 2 \times$ ULN	38	1	1	1	1	1	1								

eFigure 2. Recursive Partitioning Decision Tree and OS Outcomes by Identified Prognostic Subgroups in all pooled patients. A total of 139 (10.2%) were excluded from the OS analysis.

ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; NE, not estimable; SLD, sum of longest diameter; ULN, upper limit of normal.

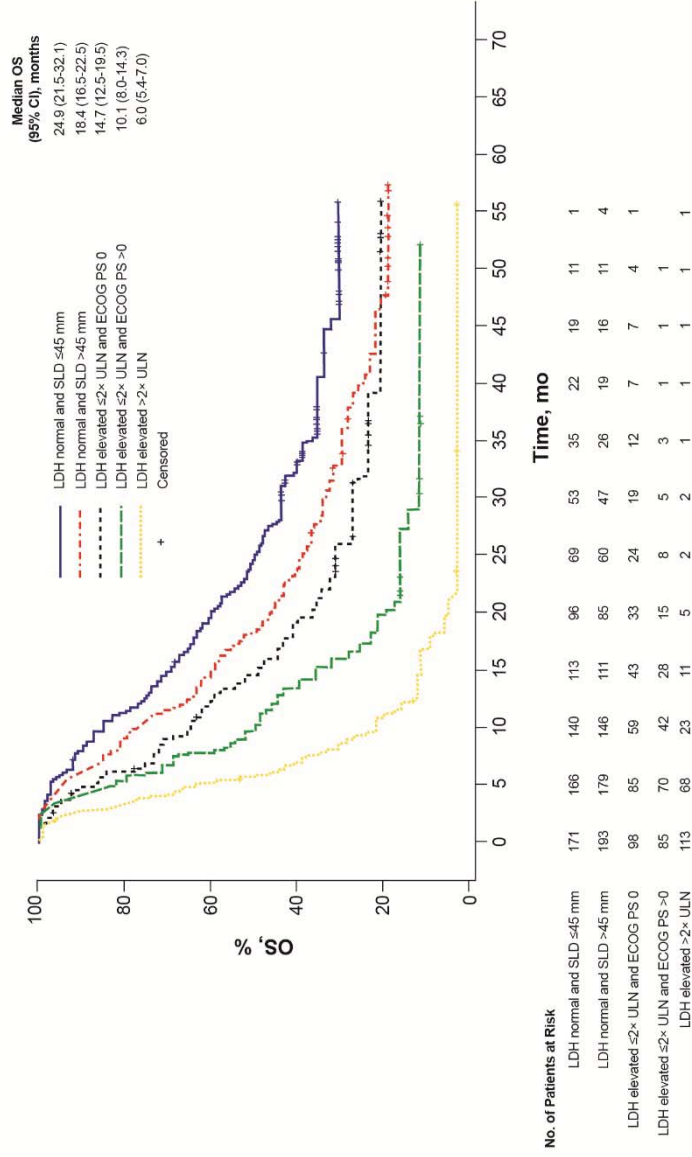


eFigure 3. OS by Prognostic Subgroup Identified in the Recursive Partitioning Model in all Pooled Patients.

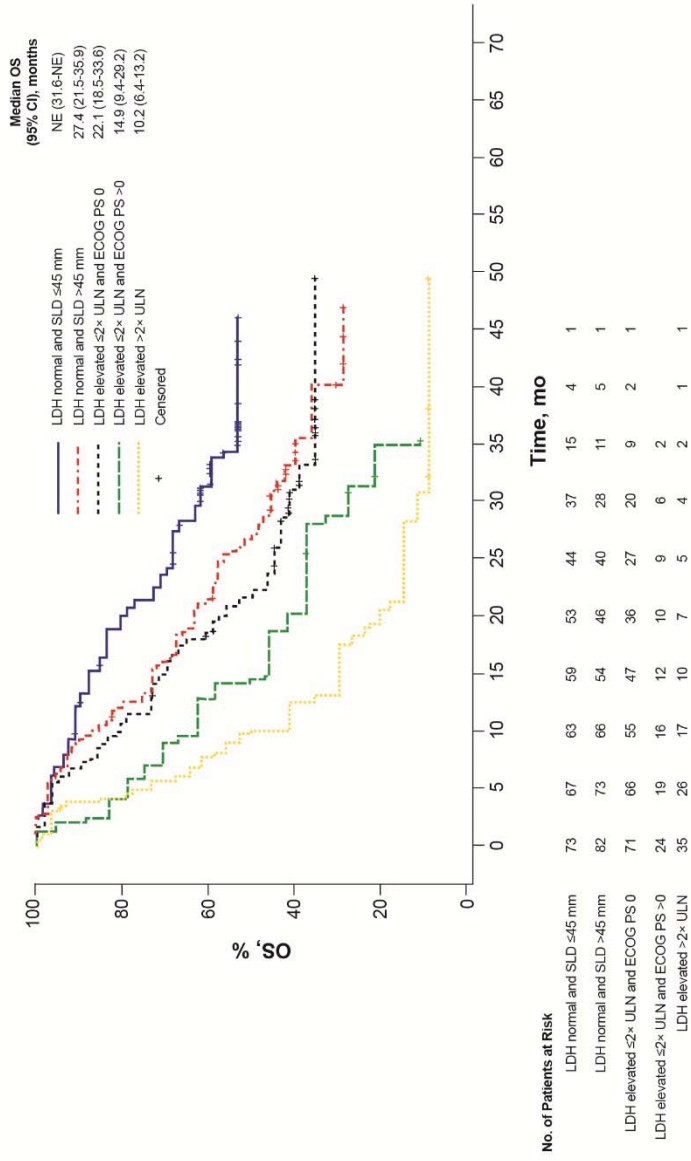
A, Pooled vemurafenib cohort. B, Pooled cobimetinib plus vemurafenib cohort. C, Dacarbazine cohort.

ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; NE, not estimable; OS, overall survival; SLD, sum of longest diameters of target lesions; ULN, upper limit of normal.

A



B



C

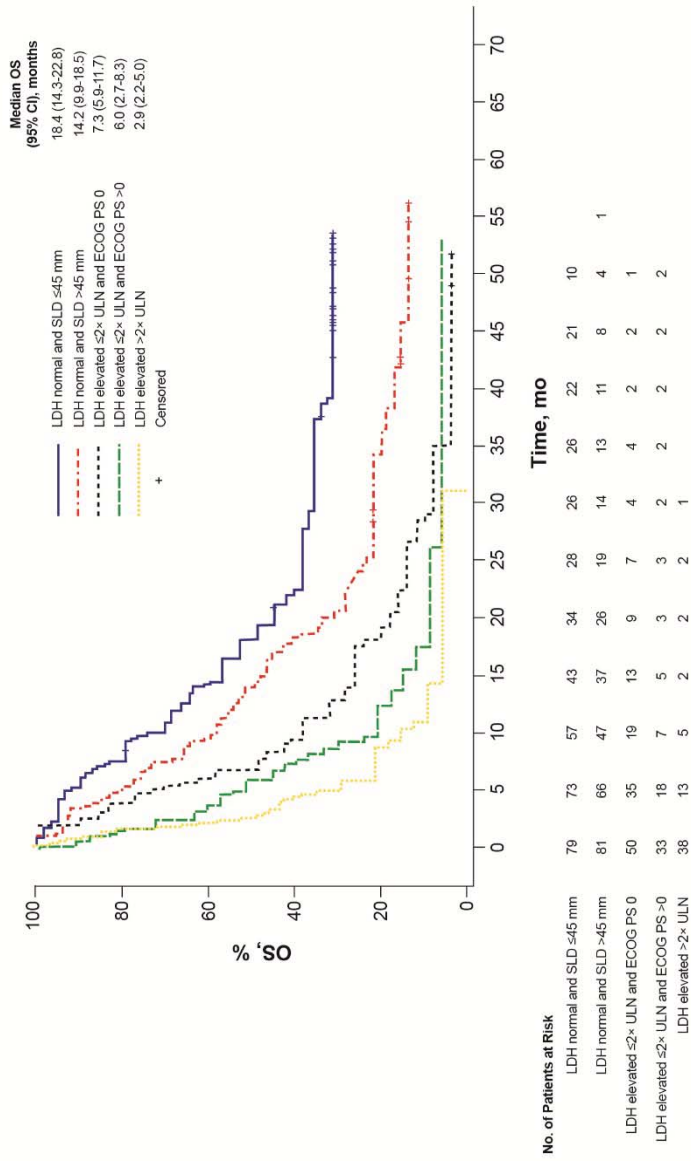


Figure 4. Recursive Partitioning Decision Tree and PFS Outcomes by Identified Prognostic Subgroups in all patients with gene expression data. Patients with missing data for one or more parameters of interest were excluded from these analyses. A total of 44 (7.2%) patients were excluded from the gene signature analyses.

ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; NE, not estimable; SLD, sum of longest diameter; ULN, upper limit of normal.

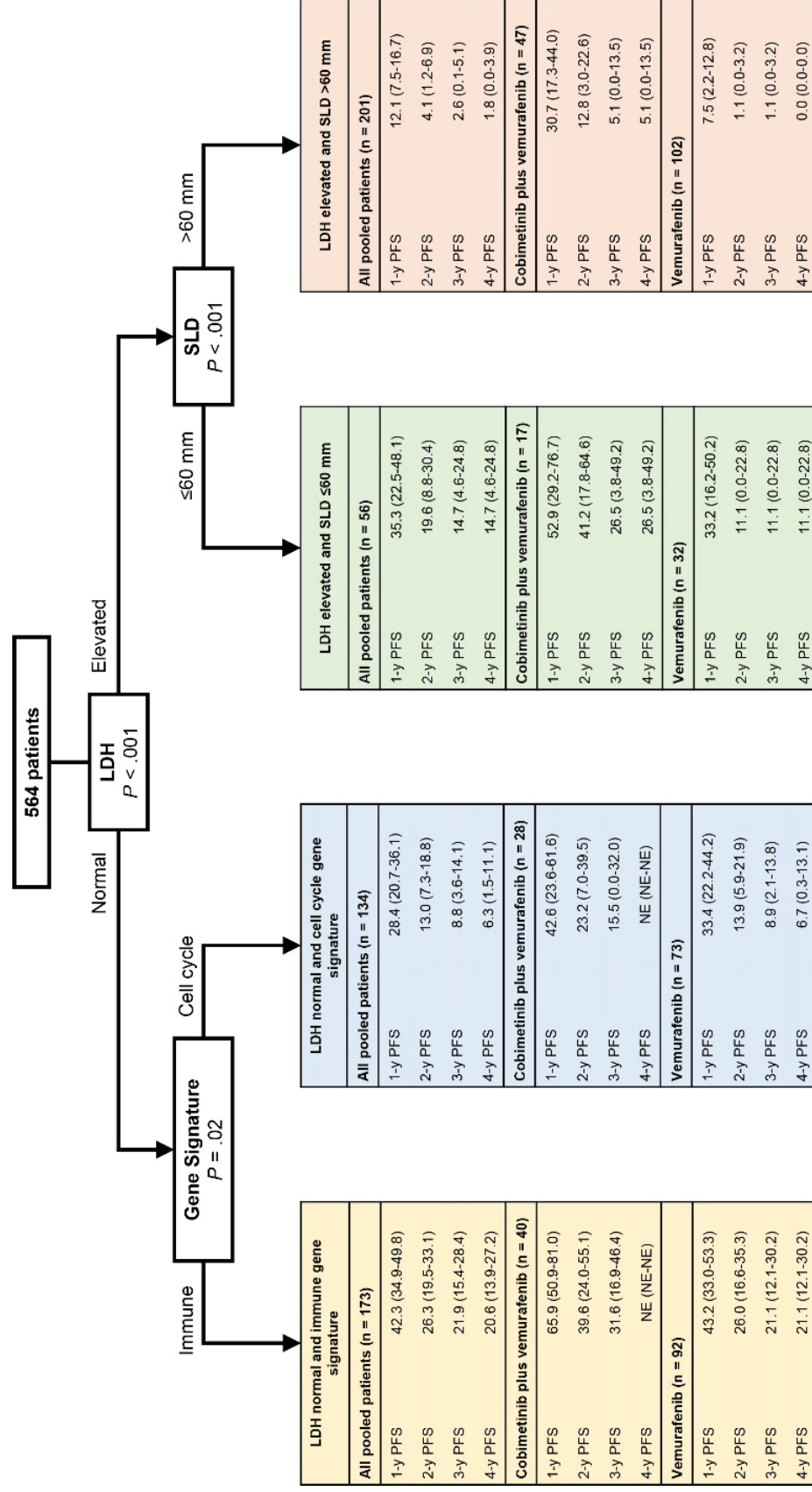
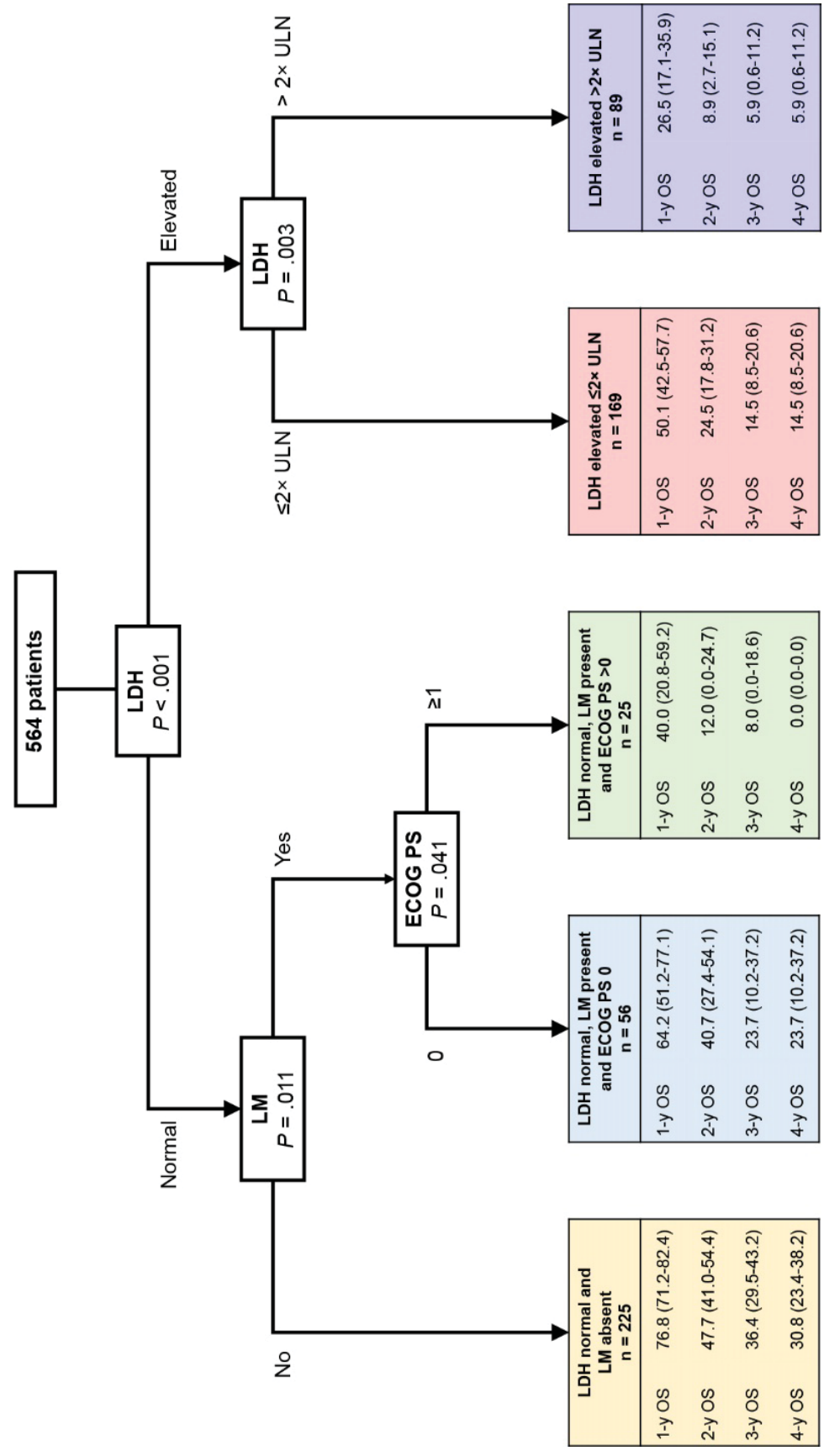
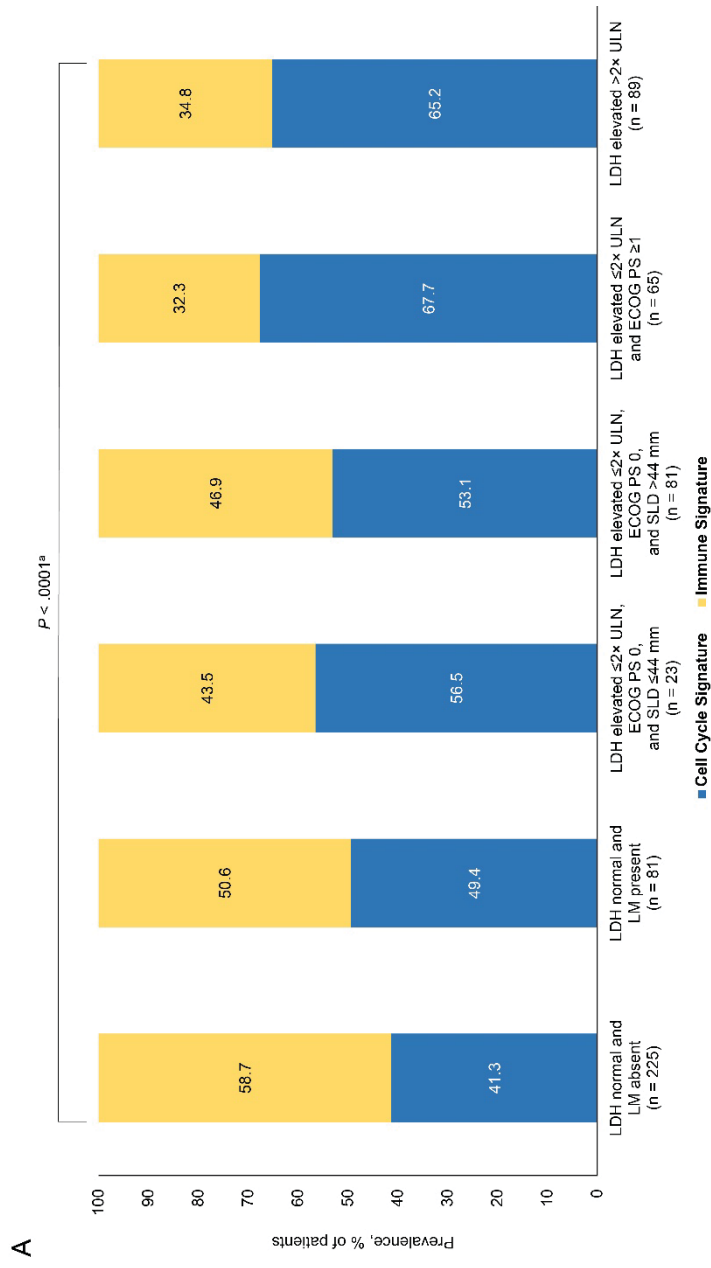


Figure 5. Recursive Partitioning Decision Tree and Outcomes by Identified Prognostic Subgroups for OS in All Patients With Gene Expression Data. Patients with missing data for one or more parameters of interest were excluded from these analyses. A total of 44 (7.2%) patients were excluded from the gene signature analyses. Data are % (95% CI). ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; LM, liver metastases; ULN, upper limit of normal.

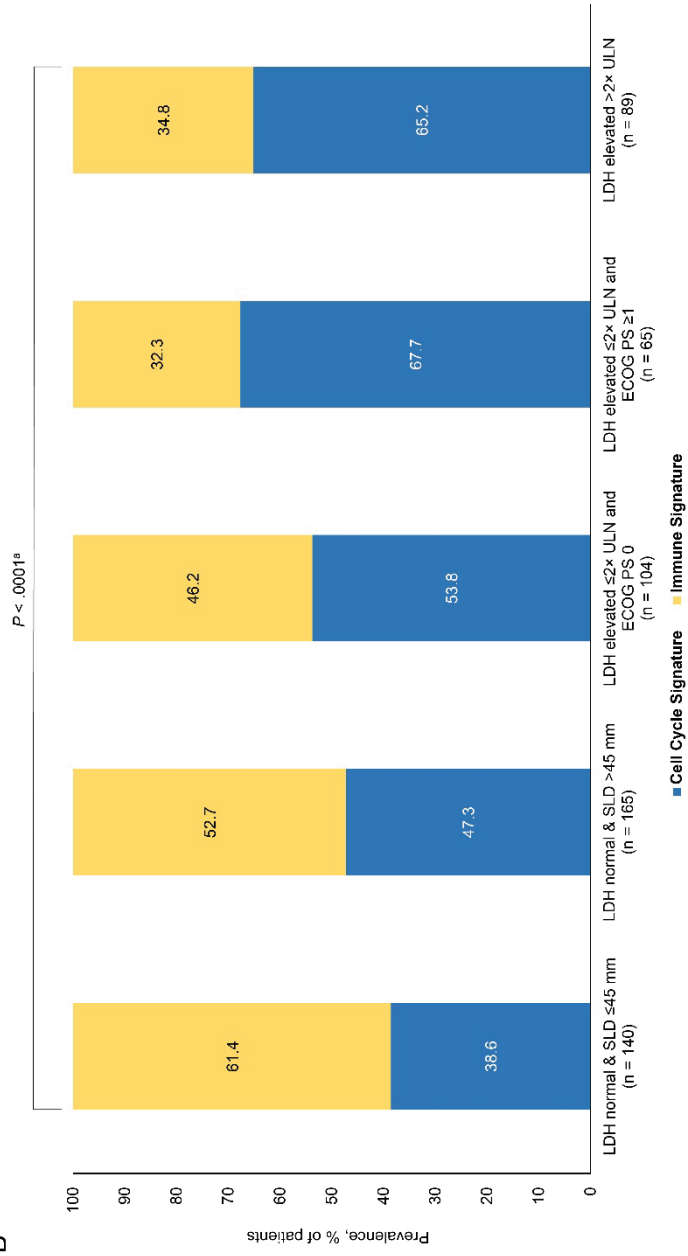


eFigure 6. Prevalence of Immune or Cell Cycle Gene Expression Signatures by Prognostic Subgroups For PFS (Panel A) and OS (Panel B) in all Pooled Patients With Gene Expression Data (n = 608).
 a One-sided Cochrane-Armitage trend test.

ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; LM, liver metastases; OS, overall survival; PFS, progression-free survival; SLD, sum of longest diameters of target lesions; ULN, upper limit of normal.

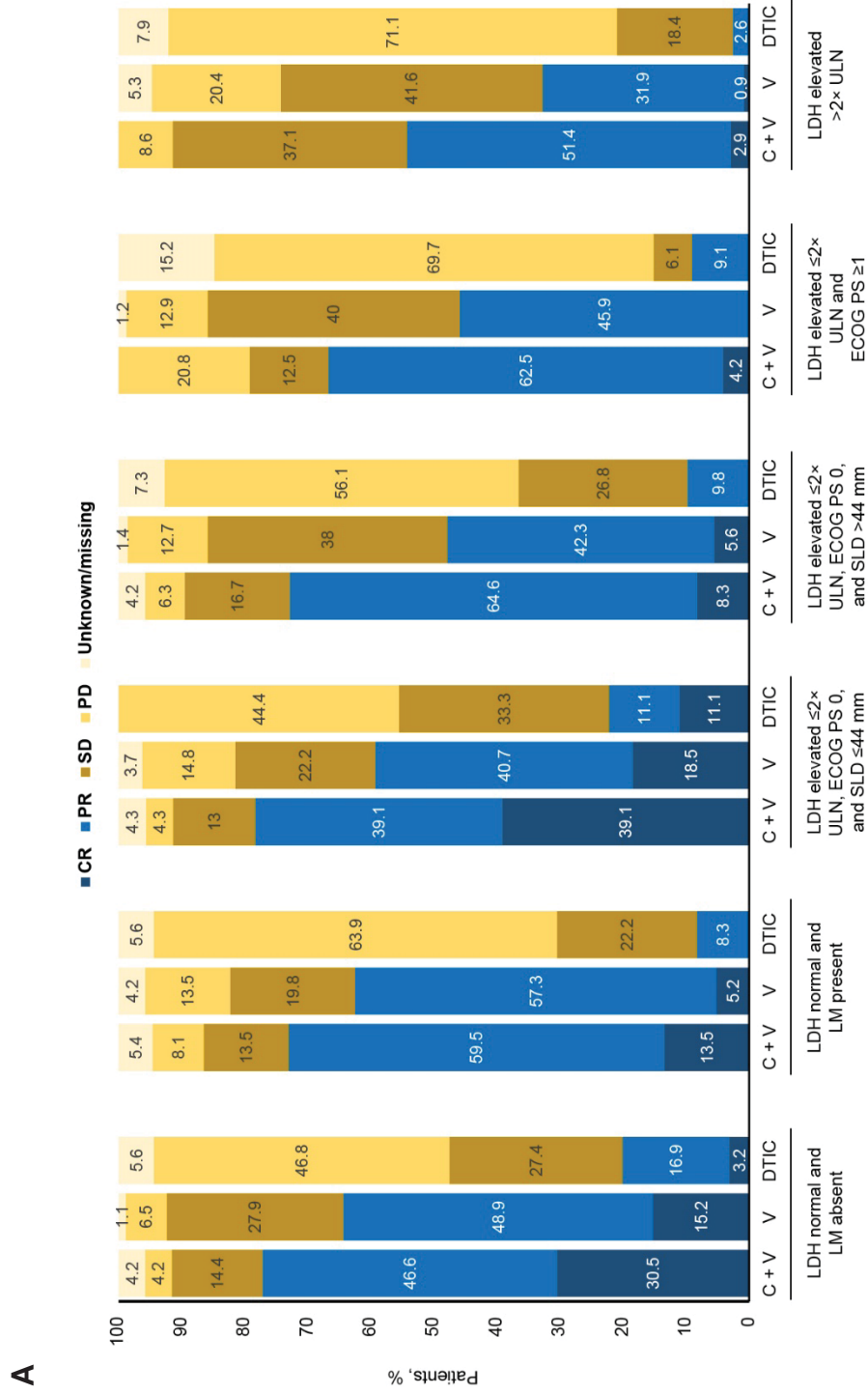


B



eFigure 7. Objective Response by Prognostic Subgroups.

A, Progression-free survival (PFS) and B, overall survival (OS) in all pooled patients across treatment cohorts.
 C+V, cobimetinib combined with vemurafenib; CR, complete response; DTIC, dacarbazine; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; LM, liver metastases; OS, overall survival; PFS, progression-free survival; PD, progressive disease; PR, partial response; SD, stable disease; SLD, sum of longest diameters of target lesions; ULN, upper limit of normal; V, vemurafenib.



B

