

Supplemental / Appendix

eTable 1. Proportion of patients who first switched to active treatment over the period 2014-2018 according to exposure duration.

eTable 2. First state change among abiraterone new users, by clusters.

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eTable 5. Pair-wise comparison between clusters among enzalutamide new users.

eFigure 1. Clusters in the 13-24 months period among patients still alive for the cluster 'Discontinuation of active treatment' for abiraterone new users (n = 819)

eFigure 2. Clusters in the 13-24 months period among patients still alive for the cluster 'late discontinuation of active treatment' for enzalutamide new users (n = 242)

eFigure 3. Clusters in the 13-24 months period among patients still alive for the cluster 'early discontinuation of active treatment' for enzalutamide new users (n = 210)

eTable 1.

	Switch to active treatment* within			
	0-3 months	3-6 months	6-9 months	9-12 months
Among ABI new users	13.4 %	30.5 %	29.3 %	26.9 %
Among ENZ new users	13.5 %	25.7 %	31.8 %	29.0 %

ABI: abiraterone; ENZ: enzalutamide.

*Switch to abiraterone, enzalutamide or chemotherapy.

eTable 2.

Cluster description	Only ABI	Discontinuation of active treatment	Death	'Late' Switch ABI to ENZ	'Late' switch to docetaxel	Early switch ABI to ENZ	Early switch to docetaxel
N (%)	3538 (53.7)	964 (14.6)	738 (11.2)	472 (7.2)	441 (6.7)	268 (4.1)	164 (2.5)
Nature of the first state change, n (%)							
ABI continuation	2631*	-	-	-	-	-	-
ENZ	138 (15.2)	23 (2.4)	57 (7.7)	389 (82.4)	7 (1.6)	242 (90.3)	4 (2.4)
Docetaxel	1 (0.1)	29 (3.0)	48 (6.5)	6 (1.3)	405 (91.8)	4 (1.5)	152 (92.7)
Cabazitaxel	178 (19.6)	-	-	2 (0.4)	3 (0.7)	-	-
Discontinuation of active treatment	459 (50.6)	912 (94.6)	97 (13.1)	75 (15.9)	26 (5.9)	22 (8.2)	8 (4.9)
Death	131 (14.4)	-	536 (72.6)	-	-	-	-
Median (Q1-Q3) time to 1st state change (only for the main change observed), months							
ENZ				8 [6 - 9]		4 [3 - 5]	
Docetaxel					7 [6 - 8]		4 [3 - 5]
Cabazitaxel							
Discontinuation of active treatment	10 [9 - 11]	5 [4 - 7]					
Death			4 [2 - 5]				

ABI: abiraterone, ENZ: enzalutamide, Q1-Q3: 1st and 3rd quartile, SD: standard deviation.

* Overall, in cluster 1, a change of state occurred for 907 (25.6%) patients and 2631 (74.4%) patients continued abiraterone.

eTable 3.

Cluster description	Only ENZ	Death	'Late' discontinuation of active treatment	'Early' discontinuation of active treatment	Switch to docetaxel	'Late' Switch ENZ to ABI	'Early' switch ENZ to ABI	Switch to ABI then docetaxel
N (%)	2411 (64.8)	349 (9.4)	324 (8.7)	210 (5.6)	166 (4.5)	129 (3.5)	100 (2.7)	34 (0.9)
Nature of the first state change, n (%)								
ENZ continuation	3112*	-	-	-	-	-	-	-
ABI	68 (11.1)	27 (7.7)	11 (3.4)	5 (2.4)	3 (1.8)	114 (88.4)	87 (87.0)	32 (94.1)
Docetaxel	3 (0.5)	4 (1.1)						
Cabazitaxel	122 (20.0)	31 (8.9)	8 (2.5)	2 (1.0)	153 (92.2)	1 (0.8)	1 (1.0)	-
Discontinuation of active treatment	321 (52.5)	53 (15.2)	305 (94.1)	203 (96.7)	10 (6.0)	14 (10.9)	12 (12.0)	2 (5.9)
Death	97 (15.9)	234 (67.0)	-	-	-	-	-	-
Median (Q1-Q3) time to 1st state change (only for the main change observed), months								
ABI						9 [8 - 10]	4 [2 - 6]	5 [4 - 6]
Docetaxel								
Cabazitaxel								
Discontinuation of active treatment	10 [6 - 11]		7 [5 - 8]	5 [3 - 6]				
Death		4 [2 - 5]						

ABI: abiraterone, ENZ: enzalutamide, Q1-Q3: 1st and 3rd quartile, SD: standard deviation.

* Overall, in cluster 1, a change of state occurred in 611 (16.4%) patients and 3112 (83.5%) patients continued enzalutamide.

eTable 4.

Cluster #	1	3	2	5	6	7	8
Cluster description	Only ABI	Discontinuation of active treatment	Death	'Late' Switch ABI to ENZ	'Early' switch ABI to ENZ	'Late' switch to docetaxel	'Early' switch to docetaxel
N (%)	3538 (53.7)	964 (14.6)	738 (11.2)	472 (7.2)	268 (4.1)	441 (6.7)	164 (2.5)
Age, mean ± SD (years)	76.3 ± 8.7	78.2 ± 10.3	82.2 ± 7.0	78.4 ± 8.1	80.1 ± 7.3	73.3 ± 7.9	72.9 ± 7.8
Pair-wise comparison*	2,3,5,6,7,8	1,2,6,7,8	1,3,5,7,8	1,2,7,8	1,7,8	1,2,3,5,6	1,2,3,5,6
ADT duration before ABI initiation, n (%)							
< 2 years	1207 (34.1)	379 (39.3)	375 (50.8)	187 (39.6)	111 (41.4)	231 (52.4)	87 (53.0)
2 - 3 years	611 (17.3)	143 (14.8)	113 (15.3)	85 (18.0)	46 (17.2)	63 (14.3)	28 (17.1)
> 3 years	1656 (46.8)	381 (39.5)	229 (31.0)	191 (40.5)	105 (39.2)	143 (32.4)	48 (29.3)
Not known	64 (1.8)	61 (6.3)	21 (2.8)	9 (1.9)	6 (2.2)	4 (0.9)	1 (0.6)
Pair-wise comparison*§	2,3,5,7,8	1,2,8	1,3,5,6	1,2,8	2	1,4,5,6	1

*p < 0.05 for each pair-wise comparison (versus the group indicated) by one-way analysis of variance for continuous variables and by the chi square test with correction for multiple comparisons across the 7 groups using permutation-style-adjusted p-values; for example, interpretation of two-by-two comparisons for the variable age, 'almost ABI' cluster (cluster #1) was statistically different (p < 0.05) from all other clusters.
 § ADT duration is considered as a continuous variable to enable the chi-square test.

Cluster numbering is similar for new ABI and ENZ users to facilitate cluster comparison.

1. Almost ABI / ENZ
2. Death
3. 'Late' discontinuation active treatment
4. 'Early' discontinuation active treatment
5. 'Late' Switch from ABI to ENZ or vice versa
6. 'Early' Switch from ABI to ENZ or vice versa
7. ('Late') Switch from ABI / ENZ to docetaxel
8. 'Early' Switch from ABI / ENZ to docetaxel
9. Switch from ENZ to ABI then docetaxel.

eTable 5.

Cluster #	1	3	4	2	5	6	7	9
Cluster description	Only ENZ	'Late' discontinuation of active treatment	'Early' discontinuation of active treatment	Death	'Late' Switch ENZ to ABI	'Early' switch ENZ to ABI	Switch to docetaxel	Switch to ABI then docetaxel
N (%)	2411 (64.8)	324 (8.7)	210 (5.6)	349 (9.4)	129 (3.5)	100 (2.7)	166 (4.5)	34 (0.9)
Age, mean ± SD (years)	77.5 ±8.8	81.1 ±8.3	81.6 ±10.2	82.8 ±7.7	80.9 ±8.2	79.2 ±7.8	74.3 ±8.1	77 ±7.6
Pair-wise comparison*	2,3,4,5,7	1,7	1,7	6,7,9	1,7	2,7	1,2,3,4,5,6	2
ADT duration before ENZ initiation, n (%)								
< 2 years	909 (37.7)	124 (38.3)	84 (40.0)	181 (51.9)	71 (55.0)	38 (38.0)	95 (57.2)	14 (41.2)
2 - 3 years	420 (17.4)	50 (15.4)	32 (15.2)	33 (9.5)	16 (12.4)	17 (17.0)	31 (18.7)	6 (17.6)
> 3 years	1038 (43.1)	134 (41.4)	79 (37.6)	129 (37)	41 (31.8)	45 (45.0)	38 (22.9)	14 (41.2)
Unknown	44 (1.8)	16 (4.9)	15 (7.1)	6 (1.7)	1 (0.8)	-	2 (1.2)	-
Pair-wise comparison*§	2,5,7	2,5,7	7	1,3,6	1,3,6	2,5,7	1,3,4,6	NS

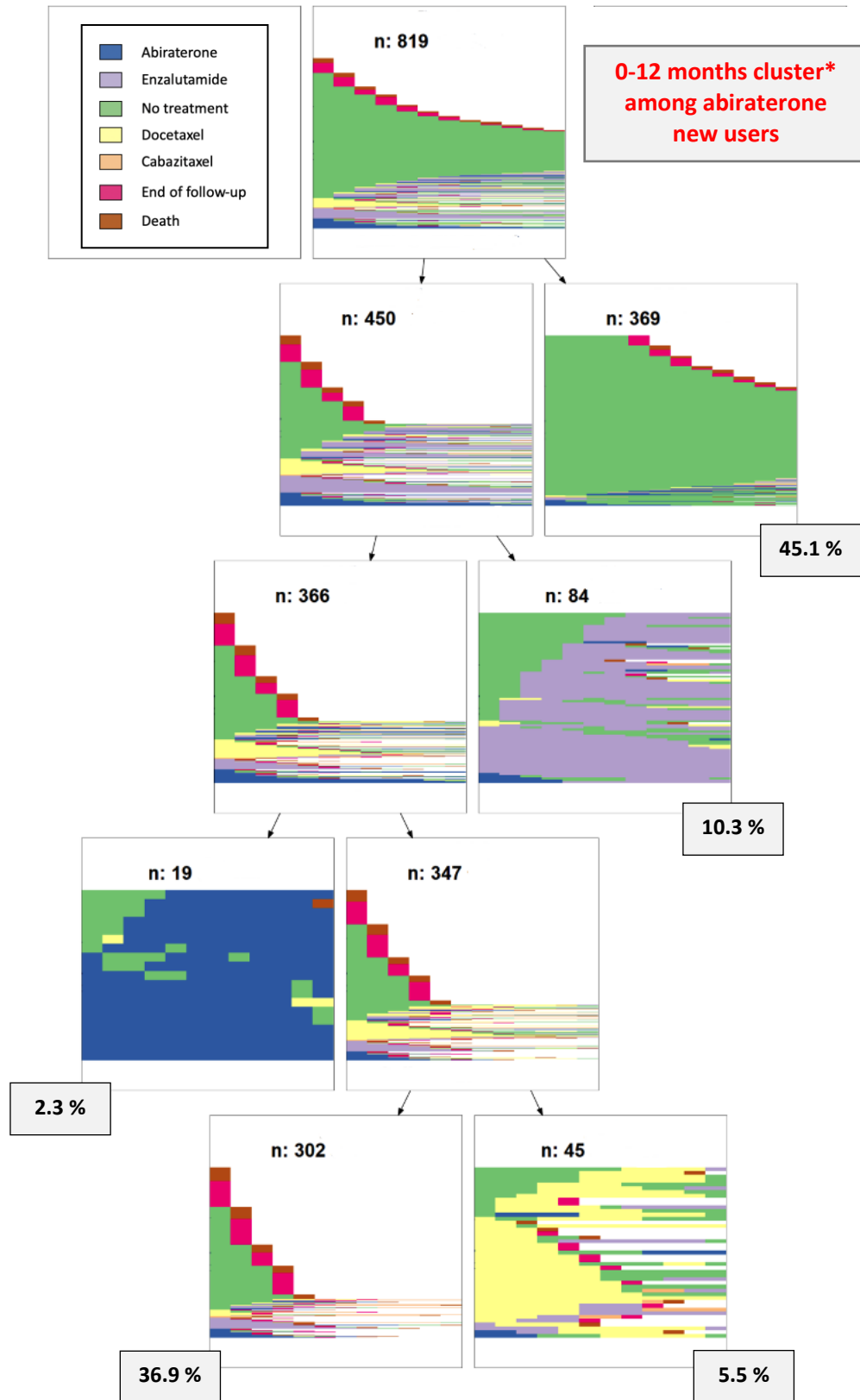
*p < 0.05 for each pair-wise comparison (versus the group indicated) by one-way analysis of variance for continuous variables and by the chisquare test with correction for multiple comparisons across the 7 groups using permutation-style-adjusted p-values; for example, interpretation of two-by-two comparisons for the variable age, 'almost ABI' cluster (cluster #1) was statistically different (p < 0.05) from all other clusters.

§ The ADT duration has been considered as a continuous variable to enable the chisquare test. NS: non-significant.

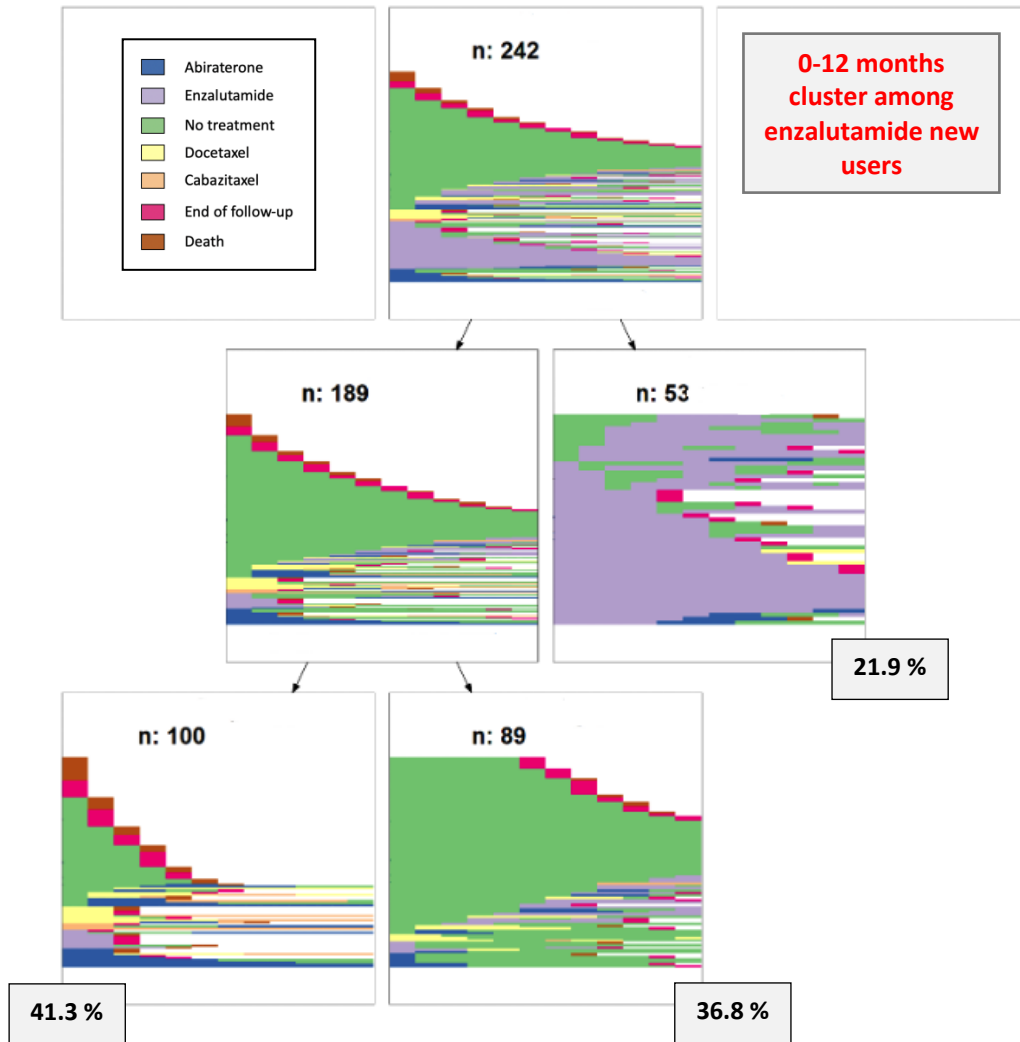
Cluster numbering was similar among new ABI or ENZ users; this was used to facilitate cluster comparison.

1. Almost ABI / ENZ
2. Death
3. 'Late' discontinuation active treatment
4. 'Early' discontinuation active treatment
5. 'Late' Switch from ABI to ENZ or vice versa
6. 'Early' Switch from ABI to ENZ or vice versa
7. 'Late' Switch from ABI / ENZ to docetaxel
8. 'Early' Switch from ABI / ENZ to docetaxel
9. Switch from ENZ to ABI then docetaxel.

eFigure 1. Clusters in the 13-24 months period among patients still alive for the cluster 'Discontinuation of active treatment' for abiraterone new users (n = 819).

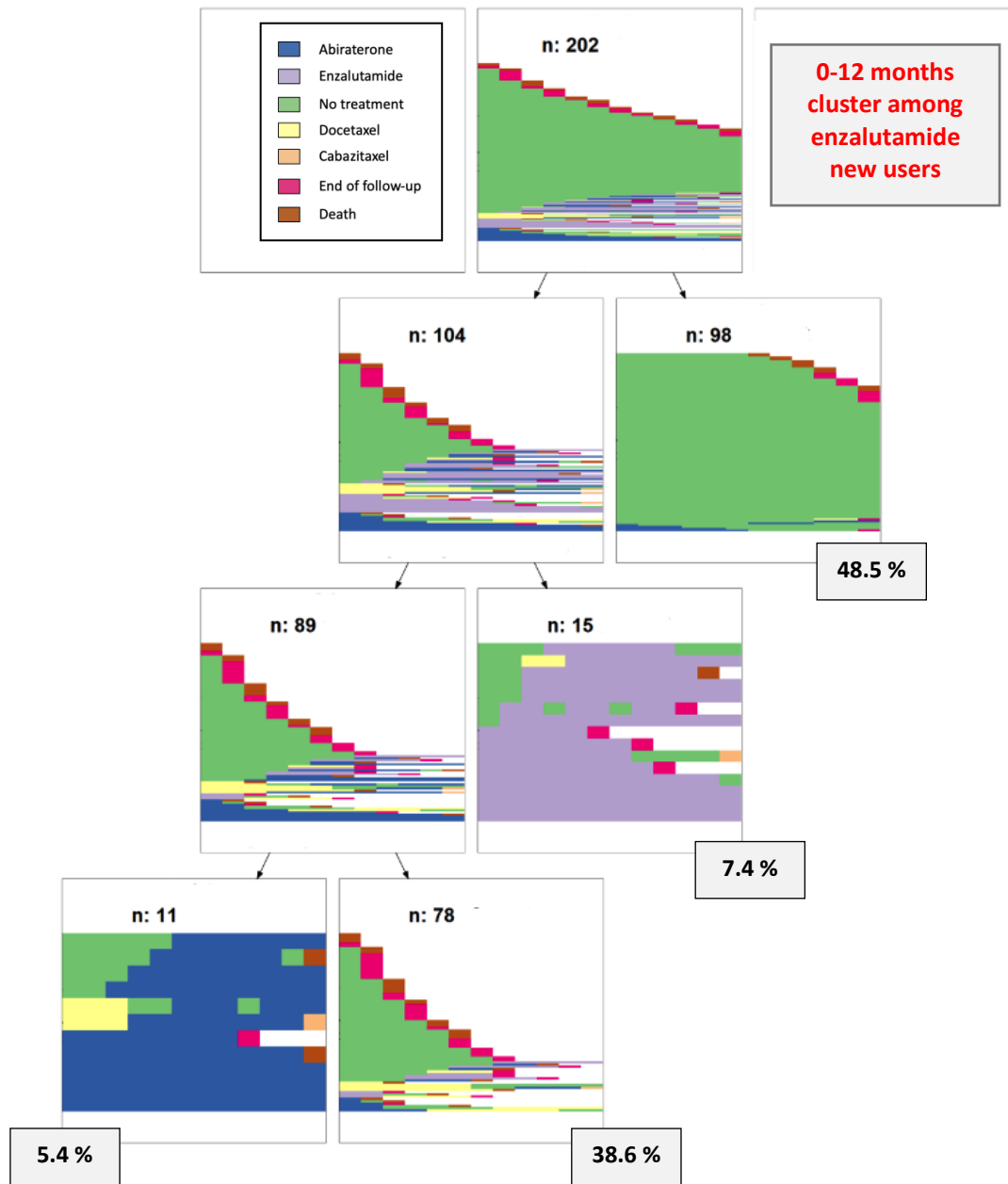


eFigure 2. Clusters in the 13-24 months period among patients still alive for the cluster 'late discontinuation of active treatment' for enzalutamide new users (n = 242)



*Patients still alive

eFigure 3. Clusters in the 13-24 months period among patients still alive for the cluster 'early discontinuation of active treatment' for enzalutamide new users (n =202)



*Patients still alive