Comparing Cross-Toxicities and Efficacy of Everolimus and Alpelisib in Different Sequences in Metastatic Breast Cancer Patients

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Introduction

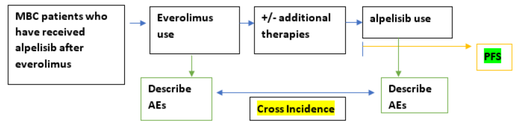
Everolimus (E) and alpelisib (A), both approved for treating HR+/HER2- Metastatic Breast Cancer (MBC), inhibit different steps of the PI3K/AKT/mTOR (PAM) pathway.[1,2] They share unique side effects (SE), many of which are considered class effects (e.g., hyperglycemia). It is unclear if the emergence of an SE during a PAM inhibitor (PAMi) treatment predicts the risk of the same SE during subsequent PAMi treatment. Such cross-incidence (CrIn) of SEs across PAMi is understudied and could help predict and prevent SEs. Similarly, the efficacy of a PAMi on a tumor resistant to a different PAMi hasn't been well established, as these tumors are excluded from new PAMi clinical trials.

Methods and Materials

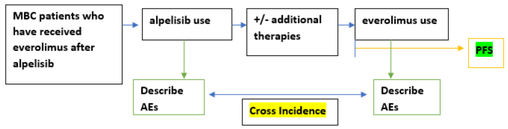
The objectives of the study were to assess 1. CrIn of important AEs between Alpelisib and Everolimus; 2. efficacies of Alpelisib after treatment with Everolimus and vice versa, among patients with HR+/HER2- MBC. A retrospective study was conducted in 3 U.S. cancer institutes (Wilmot, Roswell Park, Duke). Patients with HR+/HER2-MBC with PIK3CA mutation who received both drugs were included. Groups (grps) were defined based on the PAMi sequence: Everolimus followed by Alpelisib (A After E) or reverse, E After A. Progression-free survival (PFS) and Overall Survival (OS) were estimated using Kaplan-Meier method and compared between grps using log-rank test. Survival analyses were conducted for the 2nd PAMi in the sequence. Multivariable analyses were done using Cox Models.

Schema

1. **A after E cohort:**



2. **E after A cohort:**



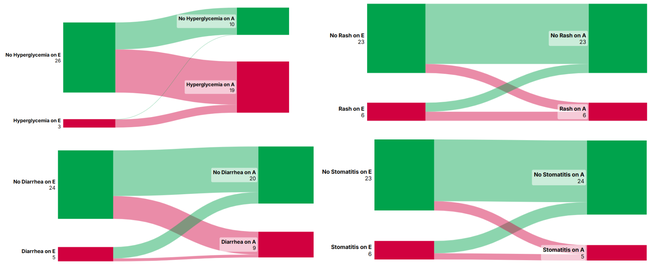
Baseline Characteristics

Characteristic	Total 46 Eligible	A after E N=30	E after A N=16	P-value*
Site				
Duke	11 (23.9)	3 (10.0)	8 (50.0)	0.006
RPCC	20 (43.5)	14 (46.7)	6 (37.5)	
URMC	15 (32.6)	13 (43.3)	2 (12.5)	
Age at first treatment				
mean (SD)	64 (10)	64 (9)	65 (12)	0.906
min - max	32 - 80	34 - 80	32 - 79	
Gender				
Male	1 (2.2)	1 (3.3)	0	>0.999
Female	45 (97.8)	29 (96.7)	16 (100)	
Race				
White	34 (73.9)	21 (70.0)	13 (81.3)	0.382
Black	1 (2.2)	0	1 (6.3)	
Other	1 (2.2)	1 (3.3)	0	
Declined/Unknown	10 (21.7)	8 (26.7)	2 (12.5)	
Ethnicity				
Non-Hispanic	25 (54.4)	13 (43.3)	12 (75.0)	0.040
Declined/Unknown	21 (45.7)	17 (56.7)	4 (25.0)	
ECOG PS				
0	6 (15.0)	4 (15.4)	2 (14.3)	>0.999
1	25 (62.5)	16 (61.5)	9 (64.3)	
2	7 (17.5)	5 (19.2)	2 (14.3)	
3	2 (5.0)	1 (3.9)	1 (7.1)	
Missing	6	4	2	
ER status				
Positive	45 (97.8)	29 (96.7)	16 (100)	>0.999
Negative	1 (2.2)	1 (3.3)	0	
PR status				
Positive	32 (69.6)	20 (66.7)	12 (75.0)	0.740
Negative	14 (30.4)	10 (33.3)	4 (25.0)	
Visceral Disease				
Yes	23 (50.0)	14 (46.7)	9 (56.3)	0.536
No	23 (50.0)	16 (53.3)	7 (43.8)	

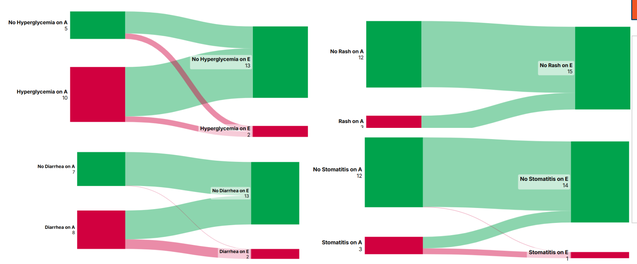
Characteristic	Total 46 Eligible	A after E N=30	E after A N=16	P-value*
Combined with Alpelisib				0.420
Tamoxifen	0	0	0	
Anastrozole	1 (2.2)	1 (3.3)	0	
Letrozole	0	0	0	
Fulvestrant	42 (91.3)	27 (90.0)	15 (93.8)	
Exemestane	2 (4.4)	2 (6.7)	0	
Other	1 (2.2)	0	1 (6.3)	
Combined with Everolimus				0.478
Tamoxifen	3 (6.5)	3 (10.0)	0	
Anastrozole	1 (2.2)	0	1 (6.3)	
Letrozole	1 (2.2)	1 (3.3)	0	
Fulvestrant	9 (19.6)	6 (20.0)	3 (18.8)	
Exemestane	32 (69.6)	20 (66.7)	12 (75.0)	
Other	0	0	0	
Chemotherapy in Metastatic Setting				0.036
Yes	33 (71.7)	25 (83.3)	8 (50.0)	
No	13 (28.9)	5 (17.2)	8 (50.0)	
Lines of Chemotherapy				0.073
0	13 (28.3)	5 (16.7)	8 (50.0)	
1	11 (23.9)	7 (23.3)	4 (25.0)	
2	13 (28.3)	11 (36.7)	2 (12.5)	
>2	9 (19.6)	7 (23.3)	2 (12.5)	
Lines of Endocrine therapy				0.760
0	0	0	0	
1	6 (13.0)	3 (10.0)	3 (18.8)	
2	17 (37.0)	11 (36.7)	6 (37.5)	
>2	23 (50.0)	16 (53.3)	7 (43.8)	
Prior CDK4/6 Inhibitor				>0.999
No	1 (2.2)	1 (3.3)	0	
Yes	45 (97.8)	29 (96.7)	16 (100)	
If yes, duration (months)				0.695
Median (IQR)	14.0 (6.0, 27.0)	11.0 (6.0, 24.0)	16.0 (5.0, 32.5)	
Min - Max	2.0 – 93.0	2.0 – 48.0	2.0 – 93.0	
ET Sensitivity				0.325
Yes	41 (89.1)	28 (93.3)	13 (81.3)	
No	5 (10.9)	2 (6.7)	3 (18.8)	

Cross Incidence of AEs:

A After E Cohort:



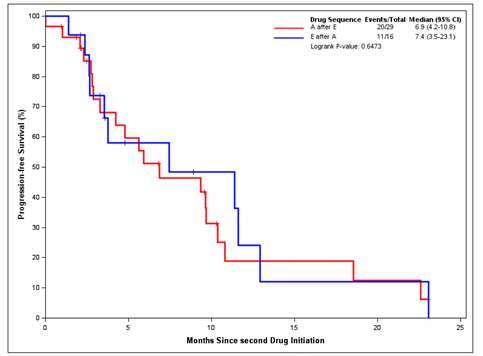
E After A Cohort:

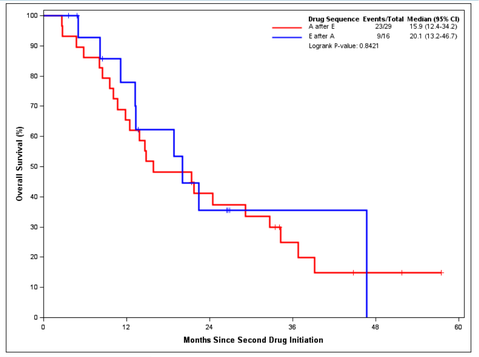


Conclusion:

All patients who developed hyperglycemia and half who developed rash on Everolimus also developed them again on Alpelisib in this study. These results could help clinicians use preemptive strategies (like metformin, topical steroids) while using 2nd PAMi. Alpelisib and Everolimus therapy were each associated with mPFS >6m when used as 2nd PAMi, suggesting meaningful activity. No significant differences were observed in PFS or OS between these two drugs when used as the 2nd PAMi. Further validation these results is needed in a larger dataset.

Efficacy:





Cox Model for PFS:

Parameter	Hazard Ratio	95% Hazard Ratio Confidence Limits		P-value
drug_sequence: E after A vs A after E	0.950	0.372	2.430	0.9151
chemo_met_setting: Yes vs No	2.464	0.883	6.877	0.0851
lines_ET >2 vs <=2	0.738	0.354	1.536	0.4158
ET_sensitivity Yes vs No	0.314	0.092	1.074	0.0649

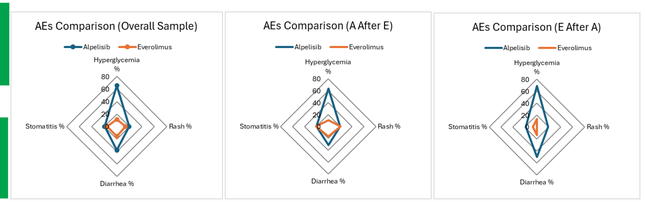
Duration of Use of Study Drugs:

Characteristic	Total 46 Eligible	A after E N=30	E after A N=16	P-value*
Alpelisib Use (months)				0.150
Median (IQR)	4.7 (2.2, 9.7)	5.3 (2.5, 9.8)	4.5 (1.2, 6.9)	
Min - Max	0.5 – 27.3	1.0 – 27.3	0.5 – 12.9	
Everolimus Use (months)				0.762
Median (IQR)	5.9 (3.1, 9.5)	6.3 (2.8, 8.5)	3.8 (3.3, 11.4)	
Min - Max	0.8 – 23.3	0.8 – 16.7	1.2 – 23.3	
Missing	2	0	2	

Cox Model for PFS:

Parameter	Hazard Ratio	95% Hazard Ratio Confidence Limits		P-value
drug_sequence: E after A vs A after E	0.922	0.391	2.173	0.8519
chemo_met_setting: Yes vs No	1.086	0.429	2.745	0.8621
lines_ET >2 vs <=2	0.972	0.469	2.013	0.9392
ET_sensitivity Yes vs No	0.719	0.244	2.115	0.5484

Incidence of AEs:



Contact

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