Efficacy and Safety of Everolimus as a Combination Therapy in the Treatment of Metastatic Breast Cancer: A Systemic Review and Meta-analysis

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INTRODUCTION

- Metastatic breast cancer (mBCa) is the most advanced stage of breast cancer affecting the women worldwide.
- The incidence rate of breast cancer is highest in non-Hispanic white women (125.4 per 100,000 women per year) and lowest for Asian Americans/Pacific islander (84.9 cases per 100,000 females).[1]
- Everolimus, a derivative of sirolimus, when combined with endocrine therapy (ET) shows anti-tumor activity in the patients suffering from mBCa.[2] This drug is orally active and has a more favorable pharmacological profile than its predecessors.[3]
- A combination of everolimus and trastuzumab is considered as a first line drug for human epidermal growth factor receptor-2 (HER-2) overexpressing advanced breast cancer.[4-7] In addition, it is a USFDA-approved drug for the treatment of renal cell cancer.[3]
- While the safety of everolimus is debatable as clinicians are feared to recommend due to the negative outcomes of BOLERO-2 studies,[4] the current systematic review scrutinizes the available literatures on safety and efficacy of the drug as a combination therapy.

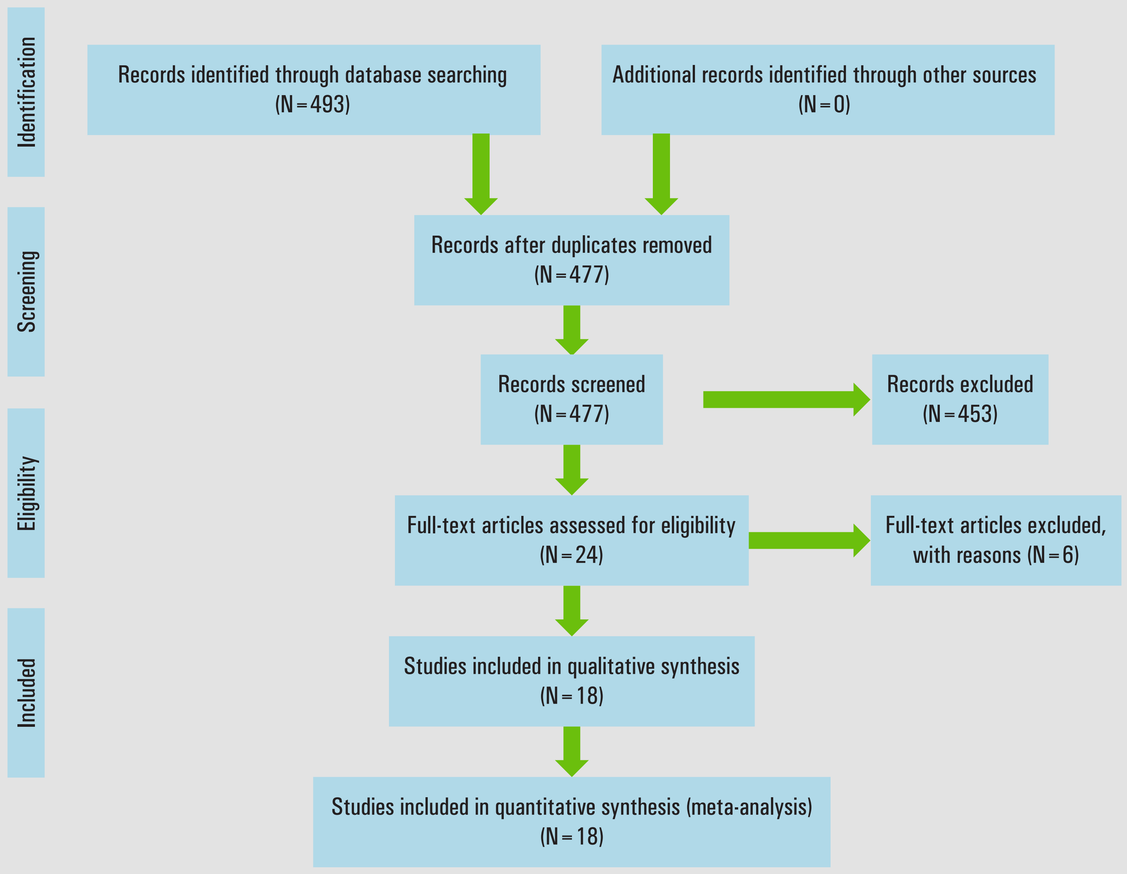
OBJECTIVE

To evaluate the efficacy and safety of everolimus as a combination therapy in the treatment of patients with mBCa.

MATERIALS AND METHODS

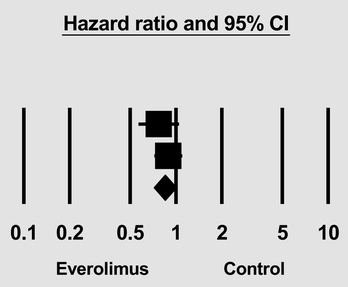
- All the randomized controlled trials (RCTs) examining the efficacy and safety of everolimus as a combination therapy in mBCa patients were included in the study.
- Our primary outcomes were overall survival (OS) and progression-free survival (PFS). Local assessment is the assessment performed by local investigators, whereas central assessment is based on the data available from all the relevant clinical trails.[3]
- Secondary outcomes were response rate (RR), complete response (CR), partial response (PR), stable disease (SD), clinical benefit (CB), stable response (SD), progressive disease (PD) and overall discontinuation.
- Literature searches were conducted using MEDLINE, Cochrane Library, and clinicaltrials.gov. The references of the included studies were considered. No language or date restrictions were imposed.
- Two authors independently selected the papers, extracted the data and assessed the quality of the included studies.
- The study quality of included trails were assessed using the Cochrane Risk of Bias Tool.

RESULTS



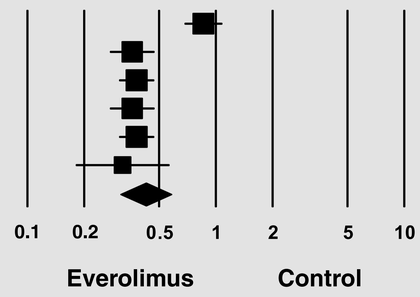
- A total of 18 RCTs involving a total of 11,252 patients were included in this meta-analysis.
- Everolimus regimen showed significant improvement in OS and PFS when compared to control. However, no significant difference was observed in responses including RR (RR = 1.02, 95% CI 0.93-1.12, N = 1512), CR (RR = 1.16, 95% CI 0.70-1.92, N = 1401), PR (RR = 1.01 95% CI 0.91-1.12, N = 1401), and CB (RR = 1.03, 95% CI 0.99-1.08, N = 1401), SD (RR = 1.06, 95% CI 0.91-1.23, N = 1401), and stable response (SD) (RR = 1.06, 95% CI 0.91-1.23, N = 1401) between two groups.
- The overall discontinuation for experimental group was lower than control group.
- Overall, the risk of bias of the included trials was unclear (N = 11) to high (N = 7).
- Most common adverse events of everolimus are stomatitis, diarrhea, rash, and neutropenia, pneumonitis, pneumonia, and pyrexia.

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Piccart 2012	0.770	0.570	1.040	-1.704	0.088
Piccart 2014	0.890	0.725	1.093	-1.114	0.265
	0.850	0.718	1.007	-1.880	0.060



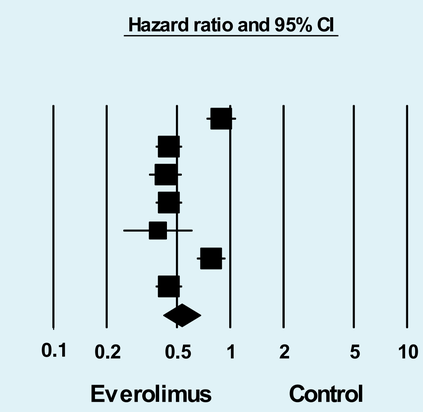
Everolimus regimen showed significant improvement in OS (local assessment) compared to control (HR = 0.85, 95% CI 0.71-1.007)

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Hurvitz 2015	0.860	0.679	1.089	-1.253	0.210
Baselga 2012	0.360	0.273	0.475	-7.225	0.000
Piccart 2012	0.380	0.305	0.473	-8.675	0.000
Beaver 2013	0.360	0.273	0.475	-7.225	0.000
Yardley 2013	0.380	0.305	0.473	-8.675	0.000
Beck 2014	0.320	0.180	0.569	-3.875	0.000
	0.423	0.310	0.577	-5.439	0.000



Everolimus regimen showed significant improvement in PFS (central assessment) compared to control (HR = 0.42, 95% CI 0.31-0.57)

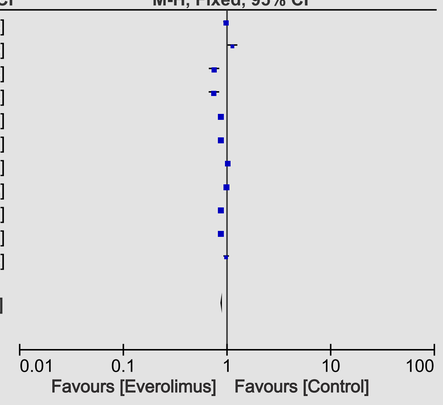
Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Hurvitz 2015	0.890	0.732	1.083	-1.166	0.243
Piccart 2012	0.450	0.377	0.536	-8.908	0.000
Beaver 2013	0.430	0.346	0.534	-7.629	0.000
Yardley 2013	0.450	0.377	0.536	-8.908	0.000
Beck 2014	0.390	0.248	0.614	-4.064	0.000
Andre 2014	0.780	0.645	0.943	-2.566	0.010
Gnant 2013	0.450	0.377	0.536	-8.908	0.000
	0.529	0.416	0.673	-5.196	0.000



Everolimus regimen showed significant improvement in PFS (local assessment) compared to control (HR = 0.52, 95% CI 0.41-0.67)

Study or Subgroup	Everolimus Events	Everolimus Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Andre 2014	247	284	254	285	9.6%	0.98 [0.92, 1.04]
Bachelot 2012	56	57	47	54	1.8%	1.13 [1.01, 1.26]
Baselga 2012	258	482	170	238	8.6%	0.75 [0.67, 0.84]
Beaver 2013	258	485	170	239	8.6%	0.75 [0.67, 0.84]
Campone 2013	404	485	229	239	11.6%	0.87 [0.83, 0.91]
Gnant 2013	404	482	229	238	11.6%	0.87 [0.83, 0.91]
Hurvitz 2015	426	472	211	238	10.6%	1.02 [0.96, 1.07]
Piccart 2014	474	485	237	239	12.0%	0.99 [0.97, 1.00]
Rugo 2014	404	485	229	239	11.6%	0.87 [0.83, 0.91]
Yardley 2013	404	485	229	239	11.6%	0.87 [0.83, 0.91]
Yardley 2015	54	56	56	57	2.1%	0.98 [0.92, 1.04]
Total (95% CI)		**4258**		**2305**	**100.0%**	**0.90 [0.88, 0.91]**
Total events	3389		2061			

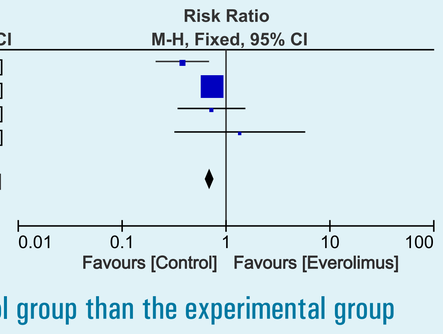
Heterogeneity: Chi² = 188.78, df = 10 (P < 0.00001); I² = 95%
Test for overall effect: Z = 11.16 (P < 0.00001)



The overall discontinuation was lower in the experimental group compared to control group (RR = 0.90, 95% CI 0.88-0.91, N = 6563)

Study or Subgroup	Everolimus Events	Everolimus Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Andre 2014	14	284	37	285	11.5%	0.38 [0.21, 0.69]
Gnant 2013	294	485	198	239	82.9%	0.73 [0.67, 0.80]
Hurvitz 2015	16	480	11	239	4.6%	0.72 [0.34, 1.54]
Yardley 2015	4	56	3	57	0.9%	1.36 [0.32, 5.79]
Total (95% CI)		**1305**		**820**	**100.0%**	**0.70 [0.63, 0.77]**
Total events	328		249			

Heterogeneity: Chi² = 5.95, df = 3 (P = 0.11); I² = 50%
Test for overall effect: Z = 6.99 (P < 0.00001)



The progression of the disease (PD) was higher for the control group than the experimental group (RR 0.70, 95% CI 0.63-0.77, N = 2125)

DISCUSSION

- Everolimus is a derivative of natural macrocyclic lactone sirolimus that binds to immunophilin FK Binding Protein-12 (FKBP-12) generating an immunosuppressive complex which inhibits the activation of mechanistic target of rapamycin (mTOR), a key regulatory kinase.[3]
- Inhibition of mTOR results in the inhibition of T lymphocyte and prevents the proliferation associated with antigen and cytokine (IL-2, IL-4, and IL-15) stimulation.[3]
- The BOLERO-2 trials on the drug efficacy demonstrated a significant benefit in PFS (72.9%, total N = 724) for the combination therapy in the patients with estrogen receptor-positive advanced breast cancer who relapse or progresses during or shortly after non-steroidal aromatase inhibitor therapy.[4]
- Patients with HER-2 positive advanced breast cancer having tumors with PIK3CA mutations, PTEN (tumor suppressor gene) loss, or hyperactive PI3K/mTOR pathway could derive PFS benefit from everolimus.[5] However, clinicians unfamiliarity to everolimus treatment for breast cancer might be the reason of previous discontinuations.[4]
- A number of studies showed that addition of everolimus to ET did not significantly affect the safety profile.[3-4,8-10]
- In addition, the efficacy and safety of everolimus plus trastuzumab and paclitaxel as a first-line treatment for HER-2 positive advanced breast cancer in Asian patients was consistent with the previous reports.[7]

CONCLUSION

- Everolimus showed significant improvement in OS and PFS in patients with mBCa when compared to control. In addition, everolimus was associated with lower overall discontinuation compared to control.
- The data supports the safety and efficacy of everolimus in the combination therapies, such as with ET or trastuzumab.
- Further analysis on more RCTs with adequate power is needed to support the current finding.

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Poster presented at ISPOR 23rd Annual International Meeting, 19-23 May, 2018, Baltimore Convention Center, Baltimore, MD, USA