Refining the Safe and Effective Use of Targeted Treatments in ER-Positive Advanced Breast Cancer

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No Pain, No Gain? Prevention, Recognition, and Management of Adverse Events

- General thoughts on AEs in ABC
- Targeted therapy-related AEs
  - Endocrine therapy
  - Specific AEs with mTOR inhibition
    - Stomatitis
    - Noninfectious pneumonitis
    - Infection
    - Hyperglycemia

AEs, adverse events; ABC, advanced breast cancer; mTOR, mammalian target of rapamycin

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Advanced Breast Cancer: Treatment Goals

Delay time to disease progression

- **Maximum control of symptoms**
- **Maintain or improve quality of life**
- **Prevent serious complications**

Overall goal is to improve survival duration and quality of life

Roché H, et al. *Ann Oncol*. 2011;22(5):1000-1010.

The Treatment Efficacy vs QoL Balance Is Critical in ABC Management

- **Treatment for distant recurrence of BC can ⬆ OS but is not curative**

Efficacy **Toxicity**

- **QoL is an important treatment goal, therefore therapy should have minimal toxicity and/or manageable adverse events**

QoL, quality of life; OS, overall survival

General Considerations for Patient Management

Thorough medical history
Assess risks prior to initiating systemic therapy

→ **Toxicities associated with sequential therapy may be increased if agents with similar/overlapping safety profiles are used one after another**

Patient awareness and education
Inform of risks, advise of signs and symptoms

→ **Recognition of potential drug interactions**

Treatment recommendations, including dose adjustment or discontinuation as necessary

→
1. **Prevention is the best strategy**
2. **Timely intervention is also key**

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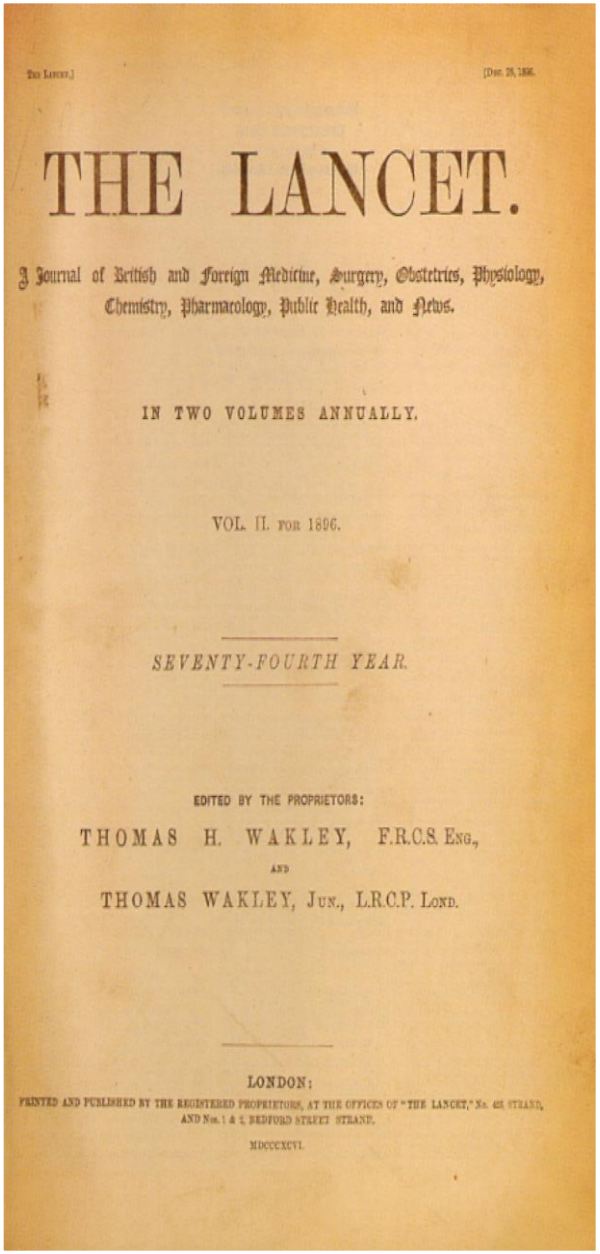

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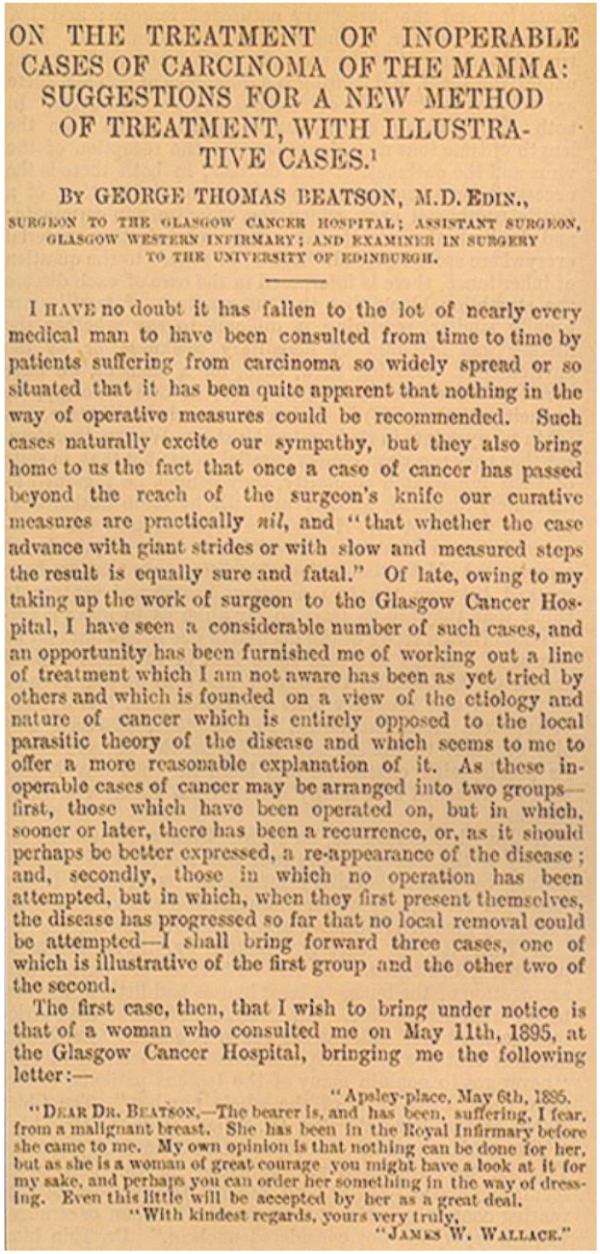


ON THE TREATMENT OF INOPERABLE CASES OF CARCINOMA OF THE MAMMA: SUGGESTIONS FOR A NEW METHOD OF TREATMENT, WITH ILLUSTRATIVE CASES.[1]

BY GEORGE THOMAS BEATSON, M.D. EDIN.,

SURGEON TO THE GLASGOW CANCER HOSPITAL; ASSISTANT SURGEON, GLASGOW WESTERN INFIRMARY; AND EXAMINER IN SURGERY TO THE UNIVERSITY OF EDINBURGH.

I HAVE no doubt it has fallen to the lot of nearly every medical man to have been consulted from time to time by patients suffering from carcinoma so widely spread or so situated that it has been quite apparent that nothing in the way of operative measures could be recommended. Such cases naturally excite our sympathy, but they also bring home to us the fact that once a case of cancer has passed beyond the reach of the surgeon's knife our curative measures are practically *nil*, and "that whether the case advance with giant strides or with slow and measured steps the result is equally sure and fatal." Of late, owing to my taking up the work of surgeon to the Glasgow Cancer Hospital, I have seen a considerable number of such cases, and an opportunity has been furnished me of working out a line of treatment which I am not aware has been as yet tried by others and which is founded on a view of the etiology and nature of cancer which is entirely opposed to the local parasitic theory of the disease and which seems to me to offer a more reasonable explanation of it. As these inoperable cases of cancer may be arranged into two groups—first, those which have been operated on, but in which, sooner or later, there has been a recurrence, or, as it should perhaps be better expressed, a re-appearance of the disease; and, secondly, those in which no operation has been attempted, but in which, when they first present themselves, the disease has progressed so far that no local removal could be attempted—I shall bring forward three cases, one of which is illustrative of the first group and the other two of the second.

The first case, then, that I wish to bring under notice is that of a woman who consulted me on May 11th, 1895, at the Glasgow Cancer Hospital, bringing me the following letter:—

"Apsley-place, May 6th, 1895.

"DEAR DR. BEATSON,—The bearer is, and has been, suffering, I fear, from a malignant breast. She has been in the Royal Infirmary before she came to me. My own opinion is that nothing can be done for her, but as she is a woman of great courage you might have a look at it for my sake, and perhaps you can order her something in the way of dressing. Even this little will be accepted by her as a great deal.

"With kindest regards, yours very truly,

"JAMES W. WALLACE."

1896: Ovariectomy (Beatson)

1922: Radiation menopause

1940: Estrogens

1951: Adrenalectomy

1960: Androgencs

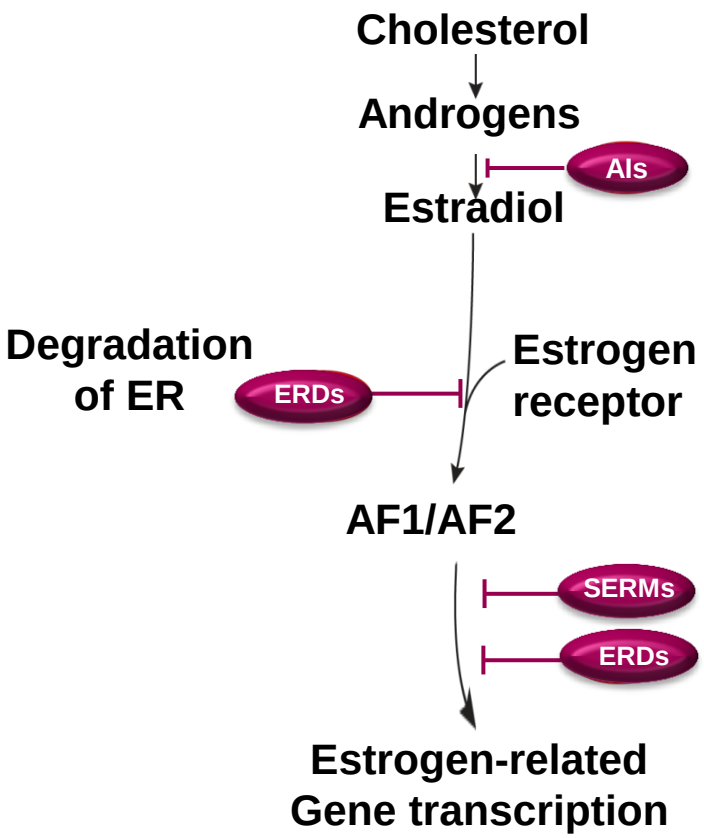
1971: Tamoxifen

1985: GnRH-analogues

1998: Aromatase-inhibitors

2011: m-TOR inhibition

Endocrine Therapy in Postmenopausal Women: Mechanisms of Action



AIs
Block estrogen production by binding and inactivating the aromatase enzyme[1]

SERMs
Modify estrogen-related gene transcription by inducing an alternate ER conformation[1]

ERDs
Attenuate estrogen-regulated transcription by impairing receptor dimerisation, increasing receptor degradation, and disrupting nuclear localization of the receptor[1]

AIs, aromatase inhibitors; ERDs, estrogen receptor downregulators; SERMs, selective estrogen receptor modulators

National Cancer Institute Fact Sheet: Hormone Therapy for Breast Cancer. www.cancer.gov/cancertopics/factsheet/Therapy/hormone-therapy-breast. Accessed December 8, 2014.

Side-Effects and Toxicity of Endocrine Agents

	Visual disturbances	Osteoporosis	Cerebro-vascular events *	Fracture	Cardiac risk	Cognitive functions
SERMs	(+)		+			+
AI 3rd Gen*		+		+	+	(+)
SERD		+		+		
GnRHa		+		+		

	Arthralgia myalgia	Flush	Dysfunctional bleeding*	Endometrial changes	Deep venous thrombosis	Lipid profile impaired
SERMs	(+)	+	+	+	(+)	
	(+)	+	+	+		
AIs	+	(+)				(+) Letrozole anastrozole
SERD						
Goserelin	(+)	+				

Guidelines Breast
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Further Information

References

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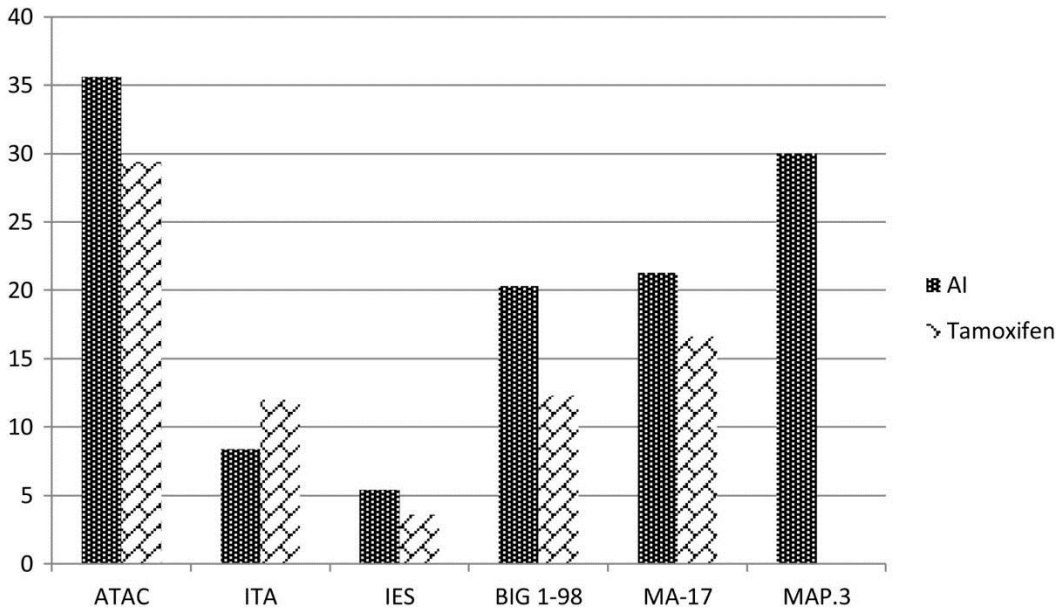
Aromatase Inhibitor-Induced Arthralgia (AIA)

AIA definition

Major criteria
- Currently taking AI therapy
- Joint pain that has developed or worsened since starting AI therapy
- Joint pain improves or resolves within 2 weeks of stopping AI therapy
- Joint pain returns upon resuming AI

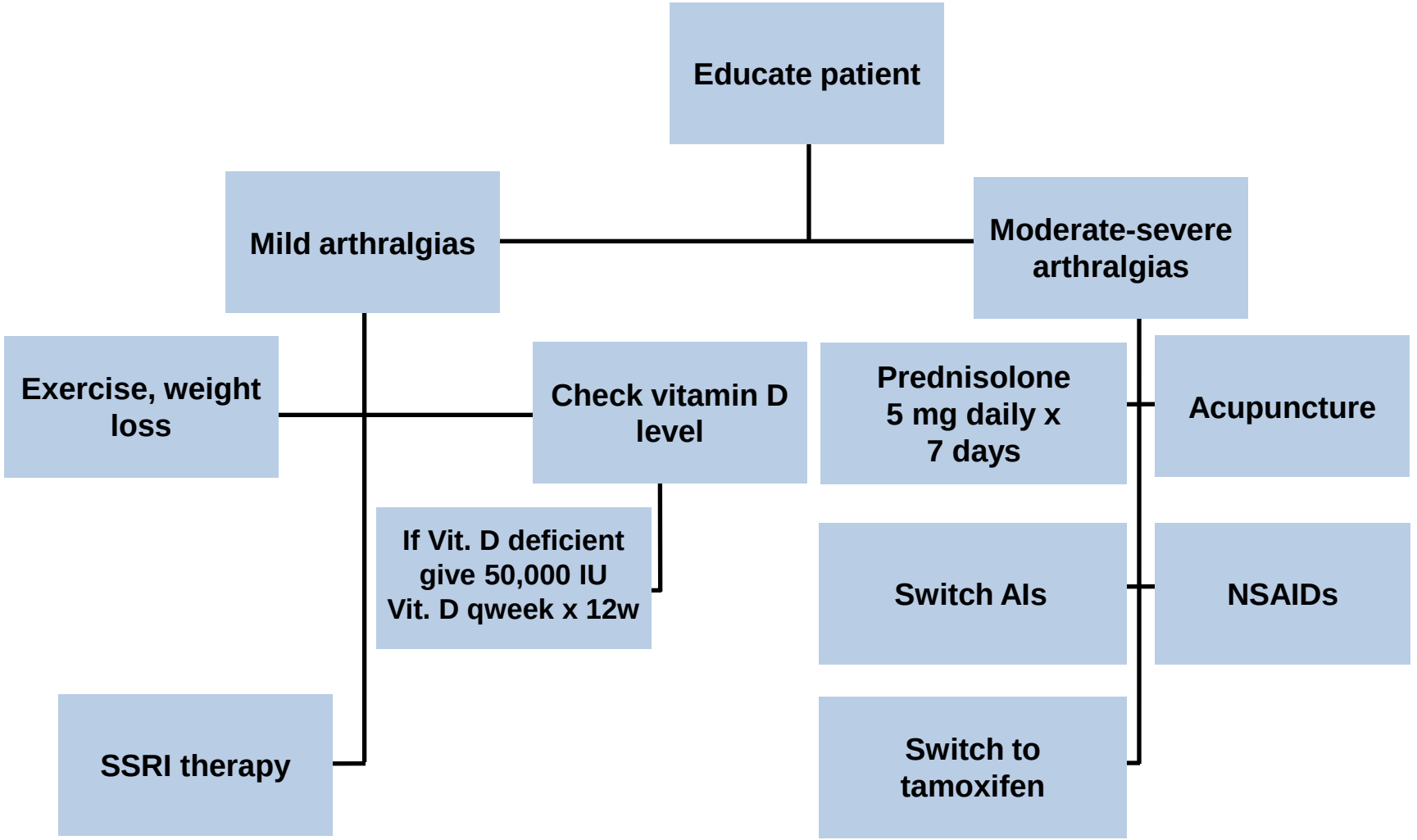
Minor criteria
- Symmetrical joint pains
- Pain in hands and/or wrists
- Carpal tunnel syndrome
- Decreased grip strength
- Morning stiffness
- Improvement in joint discomfort with use or exercise

AIA incidence among large adjuvant trials



Niravath P. *Ann Oncol*. 2013;24(6):1443-1449.

Proposed Management Algorithm for AIA



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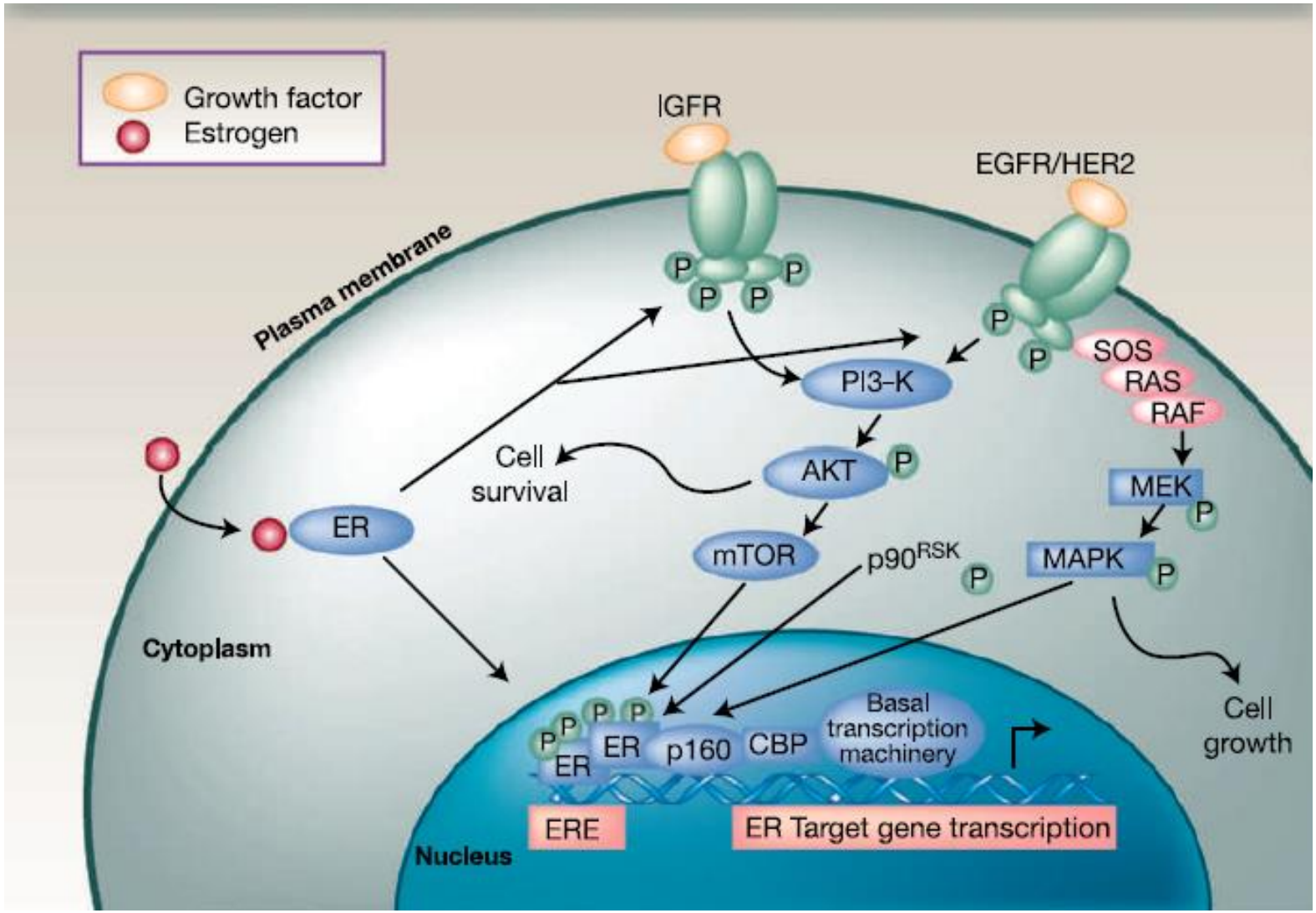
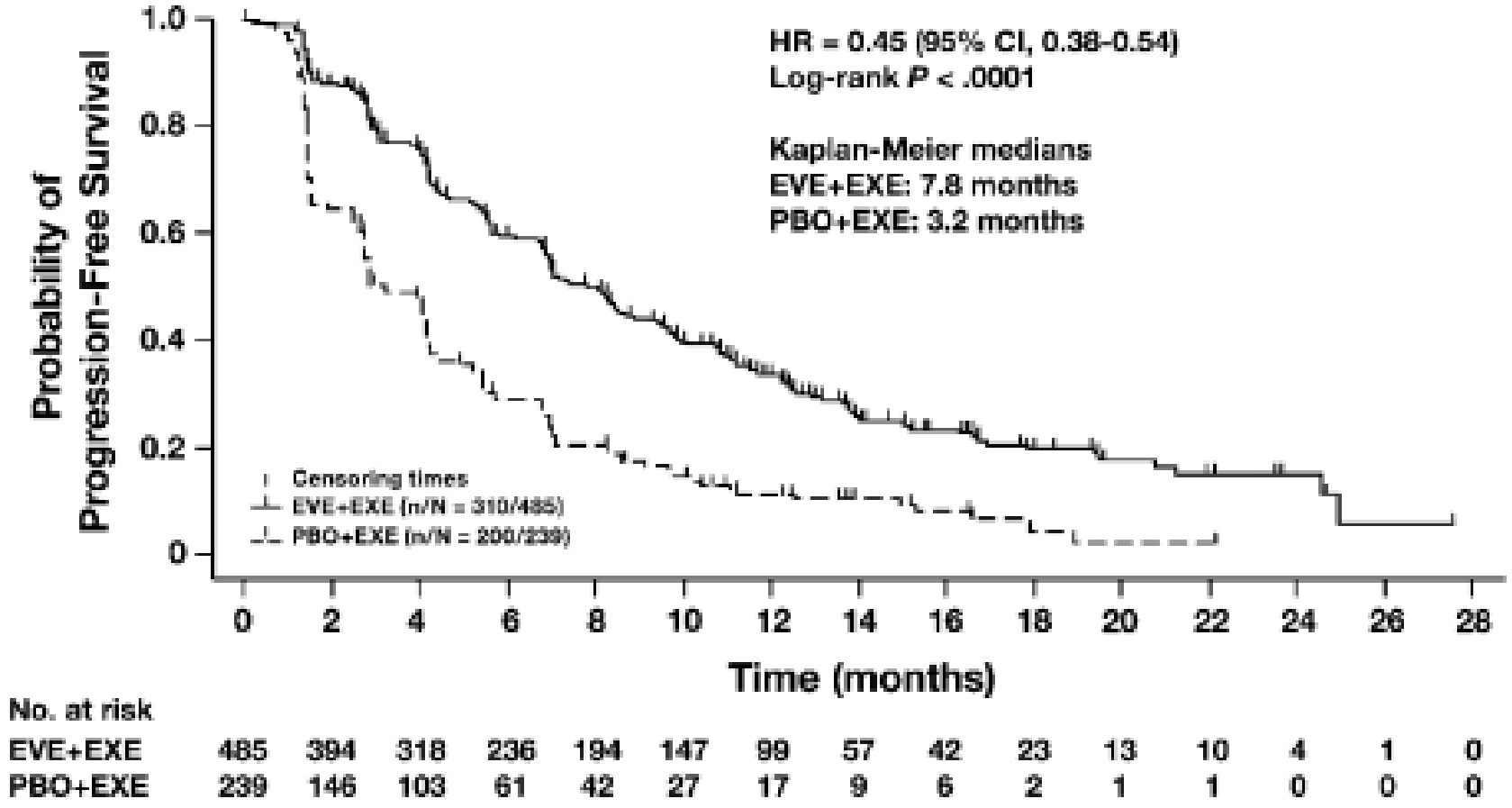
Targeting Signaling Pathways to Overcome Endocrine Resistance



Johnston SRD. *Clin Cancer Res.* 2010;16(7):1979-1987.

BOLERO-2: Final PFS



Yardley DA, et al. *Adv Ther*. 2013;30(10):870-884.

BOLERO-2: Most Common AEs

	Everolimus + exemestane (n = 482), %			Placebo + exemestane (n = 238), %		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Stomatitis	56	8	0	11	1	0
Rash	36	1	0	6	0	0
Fatigue	33	3	<1	26	1	0
Diarrhea	30	2	<1	16	1	0
Appetite decreased	29	1	0	10	0	0
Nausea	27	<1	<1	27	1	0
Noninfectious pneumonitis*	12	3	0	0	0	0
Hyperglycemia*	13	4	<1	2	<1	0

*Adverse events of special interest

Baselga J, et al. *N Engl J Med.* 2012;366(6):520-529.

BOLERO-2: Most Common AEs

	Everolimus + exemestane (n = 482), %			Placebo + exemestane (n = 238), %		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Stomatitis	**56**	**8**	**0**	**11**	**1**	**0**
Rash	36	1	0	6	0	0
Fatigue	33	3	<1	26	1	0
Diarrhea	30	2	<1	16	1	0
Appetite decreased	29	1	0	10	0	0
Nausea	27	<1	<1	27	1	0
Noninfectious pneumonitis*	**12**	**3**	**0**	**0**	**0**	**0**
Hyperglycemia*	13	4	<1	2	<1	0

***Adverse events of special interest**

Baselga J, et al. *N Engl J Med.* 2012;366(6):520-529.

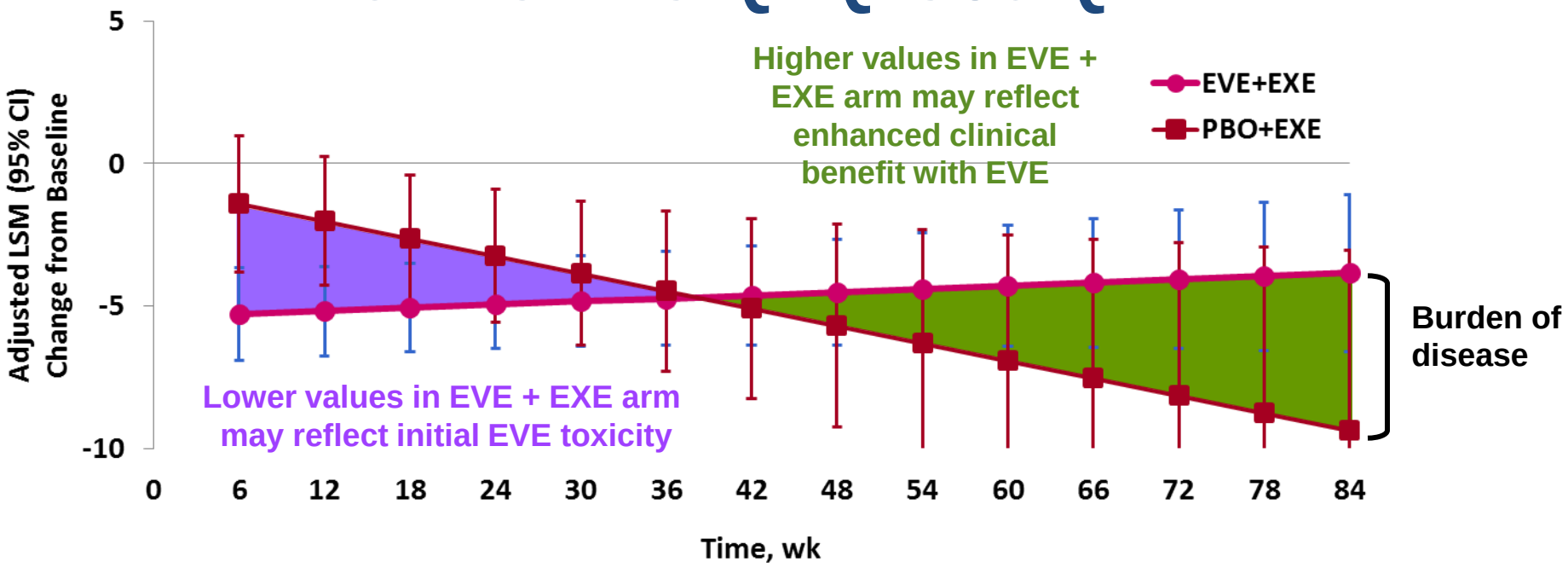
BOLERO-2: Patients Receiving First Therapy for Metastatic BC Safety

	Everolimus + exemestane (n = 100), %			Placebo + exemestane (n = 37), %		
	Grade			Grade		
AE (preferred term)	All	3	4	All	3	4
Stomatitis	68	4	0	22	0	0
Diarrhea	40	3	1	22	0	0
Rash	37	0	0	8	0	0
Fatigue	32	3	0	16	3	0
Weight decrease	30	1	0	11	0	0
Decreased appetite	28	0	0	11	0	0
Nausea	28	0	1	30	3	0
Cough	26	0	0	8	0	0
Pneumonitis*	22	1	0	0	0	0
Hyperglycaemia*	17	7	1	3	3	0

*Incidence <25%, but AE of special interest

Beck J, et al. *Breast Cancer Res Treat.* 2014;143(3):459-467.

Managing AEs May Help Maintain HRQOL in Patients: Linear Mixed-Effects Model for EORTC QLQ-C30 QL2



Patients, n														
EVE + EXE	376	324	270	224	205	173	149	123	99	73	54	43	28	20
PBO + EXE	178	129	95	66	52	37	29	21	17	12	9	5	3	1

- Early management of AEs may result in patients deriving full clinical benefit from EVE + EXE and ensure maintenance of long-term QOL

EVE, everolimus; EXE, exemestane; PBO, placebo; HRQOL, Health related quality of life; LSM, least squares mean; QL2, Global Health Status; SE, standard error.

Campone M, et al. *Curr Med Res Opin*. 2013;29(11):1463-1473.

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AEs, adverse events; ABC, advanced breast cancer; mTOR, mammalian target of rapamycin

Stomatitis: Clinical Presentation

- **mTOR inhibitor-associated stomatitis[1,2]**
  - **Distinct from chemotherapy-induced mucositis**
  - **Aphthous-like ulcers characterized by discrete, ovoid, superficial, well-demarcated ulcerations with a grayish-white pseudomembrane**
  - **Ulcers typically develop acutely in the first cycle of therapy[3]**
  - **Severity usually peaks within the first 2 weeks of therapy[3]**

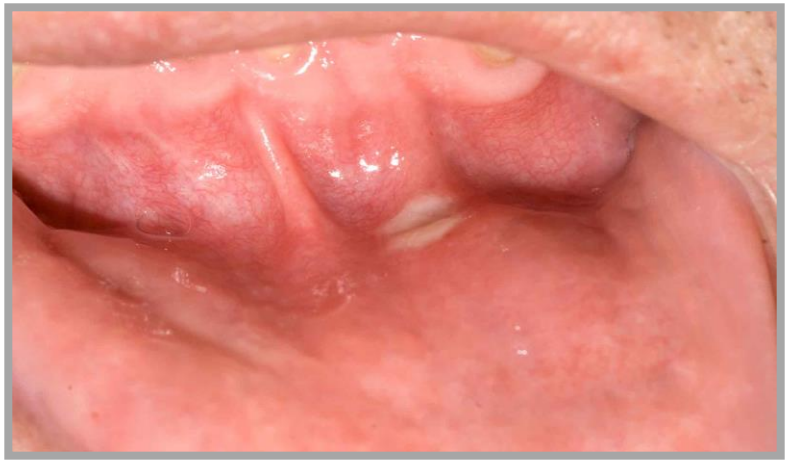

Image reprinted from Porta C, et al. *Eur J Cancer.* 2011;47(9):1287-1298.

1. de Oliveira MA, et al. *Oral Oncol.* 2011;47(10):998-1003. 2. Wojtaszek C. *Clin J Oncol Nurs*. 2000;4(6):263-270.
3. Rugo H, et al. *J Clin Oncol.* 2014;32(5s): Abstract 645.

Stomatitis: Clinical Management Strategy

Grade	Symptoms	Treatment and management	Everolimus dose modification
1	Minimal: Can maintain normal diet	• Nonalcoholic or 0.9% salt water mouthwash several times daily	• No change
2	Symptomatic but can eat and swallow modified diet	• Topical analgesic mouth treatments with or without topical corticosteroids • Avoid agents containing hydrogen peroxide, iodine, and thyme derivatives	• Temporarily interrupt dose until recovery to grade ≤1, then restart at same dose • If stomatitis recurs at grade 2, then temporarily interrupt dose until recovery to grade ≤1, and restart at reduced dose
3	Symptomatic and unable to adequately aliment or hydrate orally	• Topical analgesic mouth treatments with or without topical corticosteroids • Avoid agents containing hydrogen peroxide, iodine, and thyme derivatives	• Temporarily interrupt dose until recovery to grade ≤1, then restart at reduced dose
4	Associated with life-threatening consequences	• Treat with appropriate medical therapy	• Discontinue treatment

Afinitor® (everolimus) [prescribing information]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation; 2014. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022334s025203985s007lbl.pdf. Accessed December 8, 2014.

Stomatitis: Patient Education

- **Patient awareness and early intervention are important[1,2]**
  - **Consider evaluation for herpes virus or fungal infection[1]**
  - **Oral hygiene: Educate patients about good oral hygiene[1,2]**
    - **Rinse with nonalcoholic mouthwash**
    - **Floss after each meal**
    - **Use mild toothpaste and soft-bristled toothbrush**
    - **Avoid agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives**
      - **Note: Preventive treatment with sodium bicarbonate-based mouthwash has been shown to be ineffective[3]**
  - **Advise patients to avoid foods that are spicy/acidic/salty[4]**
  - **Prompt reporting: Advise patients to promptly report any signs or symptoms[1]**
    - **>3 lesions**
    - **Lesions lasting >3 days**
    - **Lesions interfering with eating and drinking**

1. Porta C, et al. *Eur J Cancer.* 2011;47(9):1287-1298. 2. Pilotte AP, et al. *Clin J Oncol Nurs.* 2011;15(5):E83-E89.
3. Ferté C, et al. *Eur J Cance*r. 2011;47(15):2249-2255. 4. Eisen T, et al. *J Natl Cancer Inst.* 2012;104(2):93-113.

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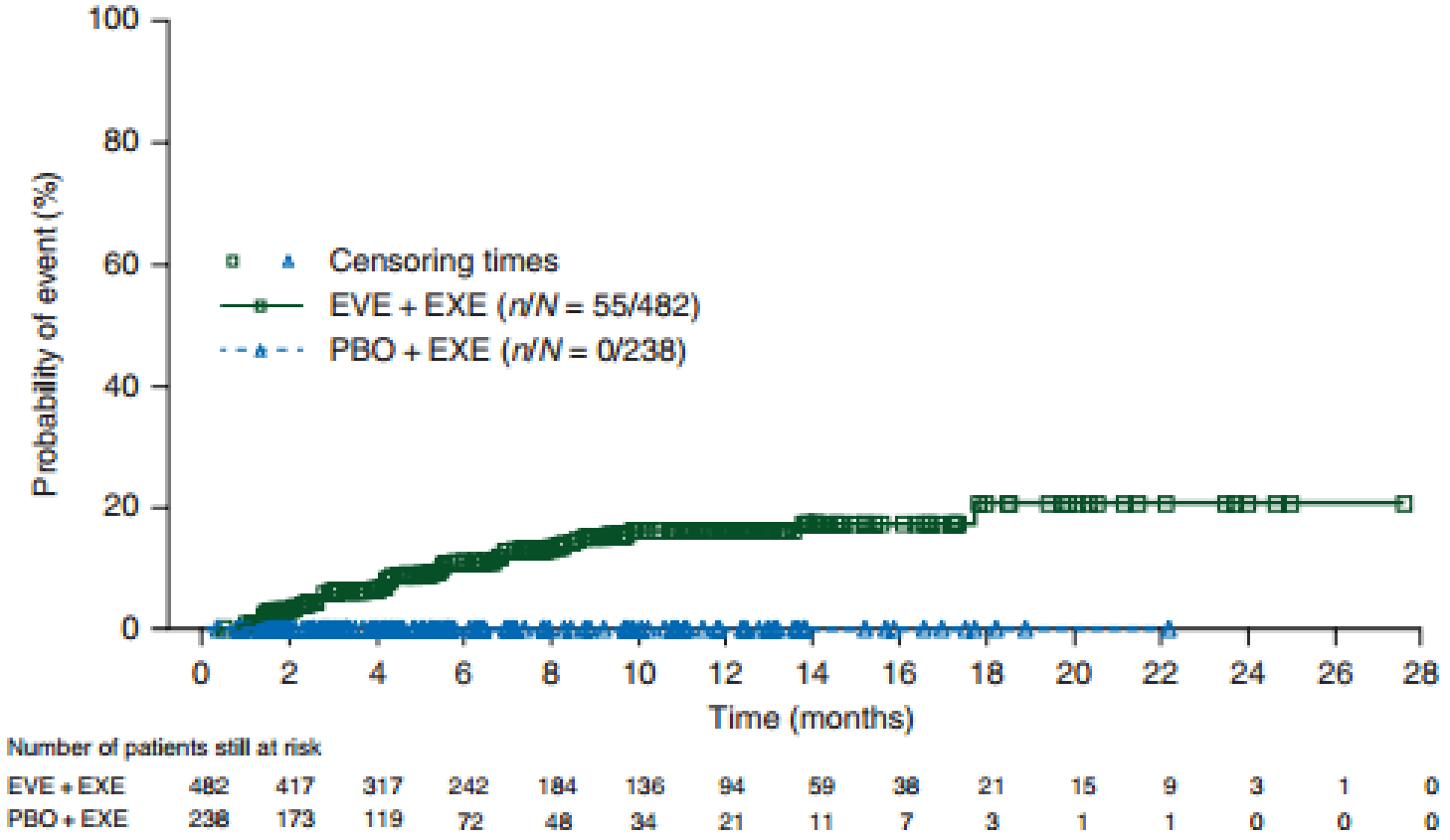
AEs, adverse events; ABC, advanced breast cancer; mTOR, mammalian target of rapamycin

Noninfectious Pneumonitis: Clinical Presentation

- **Noninfectious, nonmalignant infiltration of the lungs[1,2]**
  - **Class effect associated with rapamycin derivatives[1.2]**
- **Presents with no symptoms or with nonspecific signs and symptoms[1]**
  - **Cough, shortness of breath/dyspnea, nonspecific radiologic changes, pleural effusion, or hypoxia**
- **Symptomatic cases are usually mild to moderate in severity and reversible; however, a small proportion may be severe[2,3]**
- **Baseline radiographic assessment of the chest is critical for on-treatment diagnosis**

1. Porta C, et al. *Eur J Cancer.* 2011;47(9):1287-1298. 2. White DA, et al. *Am J Respir Crit Care Med.* 2010;182(3):396-403. 3. Afinitor® (everolimus) [Web page]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation; 2014. http://www.afinitor.com/global/side-effect-management. Accessed December 7, 2014.

Cumulative Risk Estimates for Initial Onset of Grade ≥2 Pneumonitis in BOLERO-2



Rugo HS, et al. *Ann Oncol*. 2014;25(4):808-814.

Noninfectious Pneumonitis: Clinical Management Strategy

Grade	Symptoms	Treatment and management	Everolimus dose modification
1	Asymptomatic, radiographic findings only	• Initiate appropriate monitoring	• No change
2	Symptomatic, not interfering with ADL	• Perform diagnostics to exclude infectious causes • Consider treatment with corticosteroids	• Consider dose interruption until recovery to grade ≤1, then restart at reduced dose • If no recovery to grade ≤1 within 4 weeks, discontinue treatment
3	Symptomatic, interfering with ADL, O_2 required	• Perform diagnostics to exclude infectious causes • Consider treatment with corticosteroids	• Dose interruption until recovery to grade ≤1, then restart at reduced dose • If noninfectious pneumonitis recurs at grade 3, consider treatment discontinuation
4	Life threatening, ventilatory support indicated	• Perform diagnostics to exclude infectious causes • Consider treatment with corticosteroids	• Discontinue treatment

ADL, activities of daily living

Afinitor® (everolimus) [prescribing information]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation; 2014. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022334s025203985s007lbl.pdf. Accessed December 8, 2014.

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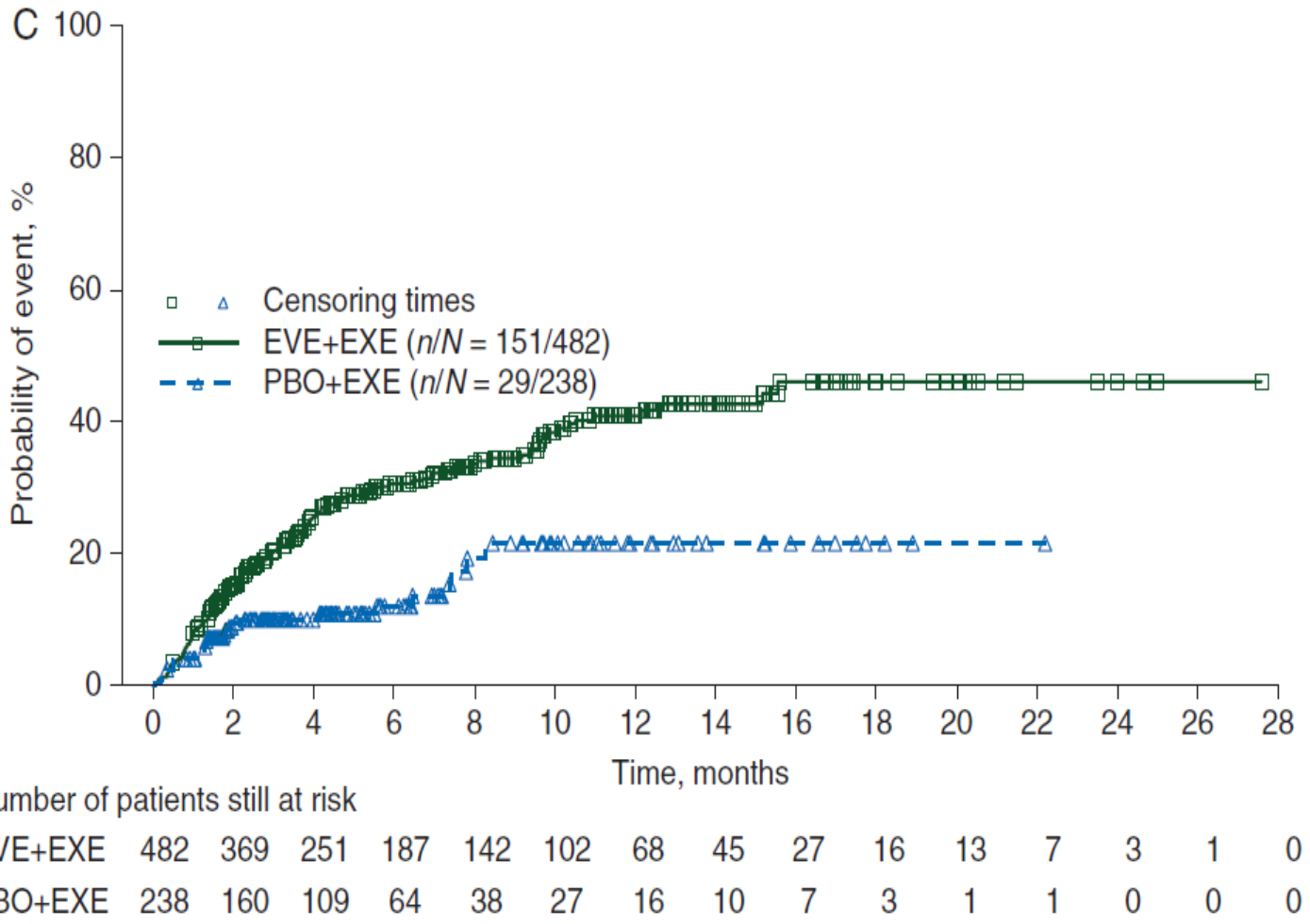
AEs, adverse events; ABC, advanced breast cancer; mTOR, mammalian target of rapamycin

Infection: Introduction

- The immunosuppressive properties of mTOR inhibition may increase susceptibility to infection (eg, bacterial, fungal, or viral)[1]
- In breast cancer, the most common mTOR inhibitor-associated infections include
  - Nasopharyngitis (10%)
  - Urinary tract infection (10%)
  - Upper respiratory tract infection (6%)
  - Pneumonia (4%)[2]

1. Porta C, et al. *Eur J Cancer.* 2011;47:1287-1298.
2. Afinitor® (everolimus) [prescribing information]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation; 2014. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022334s025203985s007lbl.pdf. Accessed December 8, 2014.

BOLERO-2: Incidence of Infections (Grade ≥2)



Aapro M, et al. *Ann Oncol.* 2014;25:763-773.

Infection: Clinical Management Strategy

- Prompt diagnosis and treatment with antibiotic, antifungal, or antiviral agents[1-3]
  - mTOR inhibitor drug-drug interactions (eg, with CYP3A4 inducers or inhibitors) should be considered
- Active monitoring for infections
- Maintenance of personal hygiene[4]
- Medical attention for signs of infections (fever, cough)[4]
- Grade 2 or 3 infections
  - Dose interruption until infection is grade ≤1
  - Treatment is re-initiated either at the same dose (grade 2) or a lower dose (grade 3)

1. Afinitor® (everolimus) [prescribing information]. Horsham, UK: Novartis Europharm Limited, 2012. ec.europa.eu/health/documents/community-register/2009/2009080361990/anx_61990_en.pdf. Accessed December 8, 2014.
2. Afinitor® (everolimus) [prescribing information]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation; 2014. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022334s025203985s007lbl.pdf. . Accessed December 8, 2014.
3. Porta C, et al. *Eur J Cancer.* 2011;47:1287-1298. 4. Moldawer N,P et al. *Kidney Cancer J.* 2010;8:51-59.

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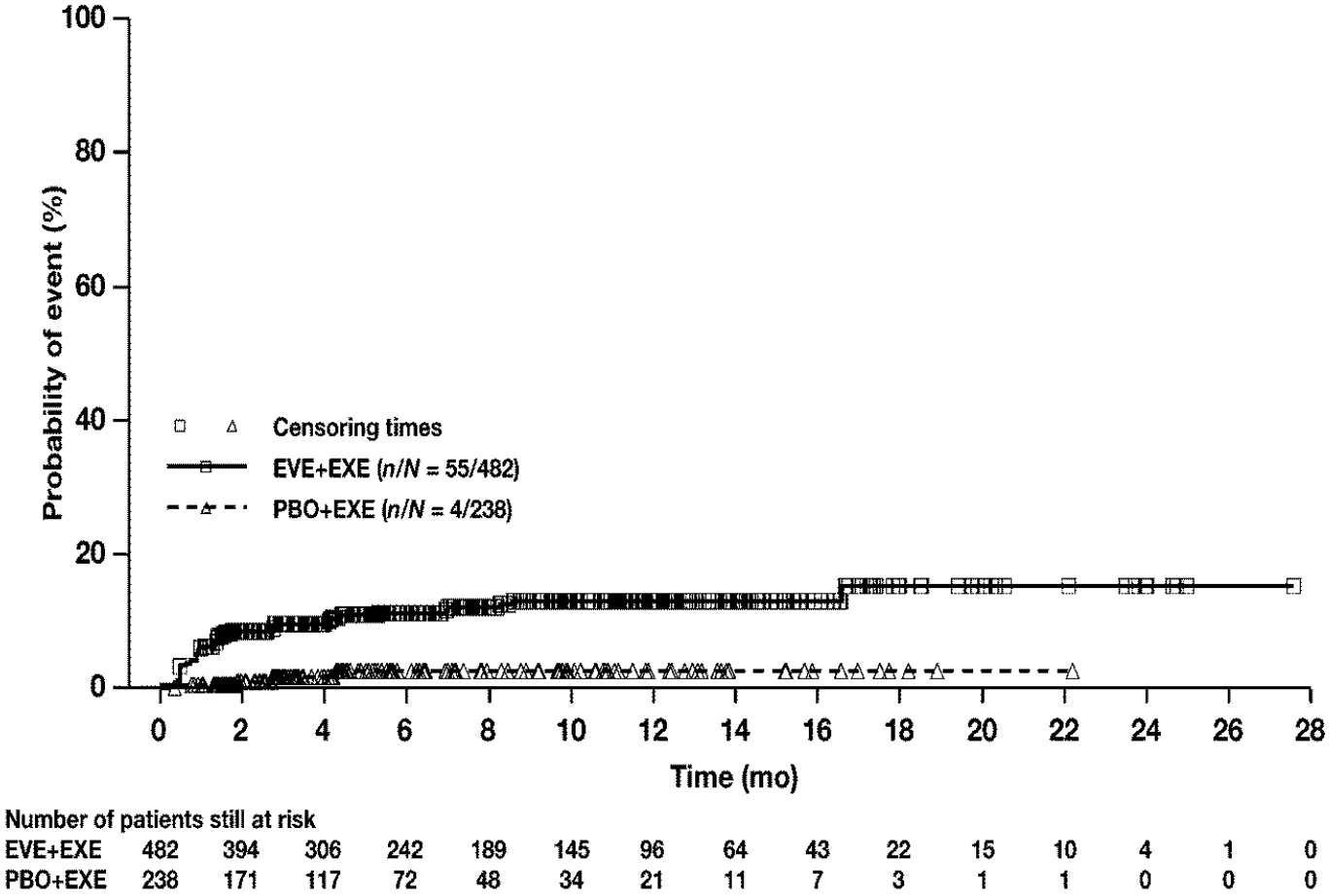
Inhibition of PI3K/AKT/mTOR Signaling Affects Glucose Homeostasis

- mTOR is a downstream effector of insulin signaling and subsequent gluconeogenesis and glycogen synthesis[1]
- As a consequence, mTOR inhibition can disrupt these physiologic processes to varying degrees[1]
- Hyperglycemia can occur with everolimus use[1]
- Median time of onset of hyperglycemia is within 6 weeks after initiation of mTOR inhibitor treatment[2]

1. Zoncu R, et al. *Nat Rev Mol Cell Biol*. 2011;12(1):21-35. 2. Rugo HS, et al. *Ann Oncol*. 2014; 25(4):808-815.

BOLERO-2: Cumulative Risk of Hyperglycemia (Grade ≥2)



Number of patients still at risk

EVE+EXE	482	394	306	242	189	145	96	64	43	22	15	10	4	1	0
PBO+EXE	238	171	117	72	48	34	21	11	7	3	1	1	0	0	0

Rugo HS, et al. *Ann Oncol*. 2014; 25(4):808-815.

Everolimus-Associated Hyperglycemia: Guidance for Practical Management

- Monitor fasting serum glucose levels before starting everolimus therapy and monitor serum glucose periodically thereafter[1,2]
- Achieve optimal glycemic control before starting everolimus[1,2]
- Manage according to standard consensus guidelines[3]

Grade	Lab Values	Treatment and Management	Everolimus Dose Modification
1	Glucose: >ULN-160 mg/dL	• None	• No change
2	Glucose: >160-250 mg/dL	• Manage with appropriate medical therapy according to American Diabetes Association and European Association for the Study of Diabetes standard guidelines and monitor	• No dose adjustment required
3	Glucose: >250-500 mg/dL		• Temporary dose interruption until recovery to grade ≤1 • Restart dose at a lower dose
4	Glucose: >500 mg/dL		• Discontinue everolimus

ULN, upper limit of normal.

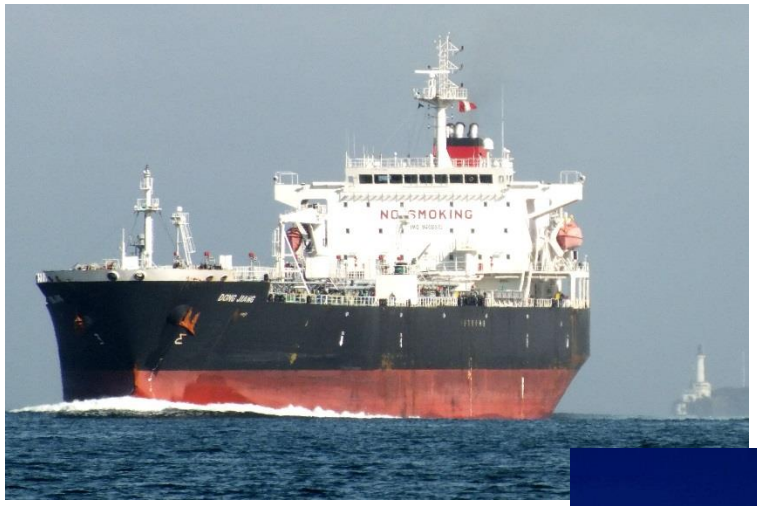
1. Afinitor® (everolimus) [prescribing information]. Horsham, UK: Novartis Europharm Limited, 2012. ec.europa.eu/health/documents/community-register/2009/2009080361990/anx_61990_en.pdf. Accessed December 8, 2014.
2. Eisen T, et al. *J Natl Cancer Inst.* 2012;104(2):93-113. 3. Nathan DM, et al. *Diabetes Care.* 2009;32(1):193-203.

Therapy Management Strategies

- **Patient:**
  - **Patient awareness and early intervention are important**
  - **Advise patients to promptly report any new or worsening symptoms**
  - **Stomatitis: Consider evaluation for herpes virus or fungal infection; educate patients about good oral hygiene; advise patients to avoid foods that are spicy, acidic, salty**
- **Physician:**
  - **Monitoring of renal function, fasting serum glucose, lipid profile and complete blood count is recommended prior to use of everolimus**
  - **Possibility of dose modifications to manage occurrence and intensity of side effects**

Conclusions

- **Physical and mental integrity as well as quality of life are the main goals of ABC treatment**
- **Minimizing side effects has even higher priority in ABC than in early breast cancer**
- **Close interaction and intensified communication between patient and physician necessary**
- **Arthralgia in AI can reduce compliance**
- **Everolimus + AI leads to higher efficacy with manageable toxicity (caveat stomatitis)**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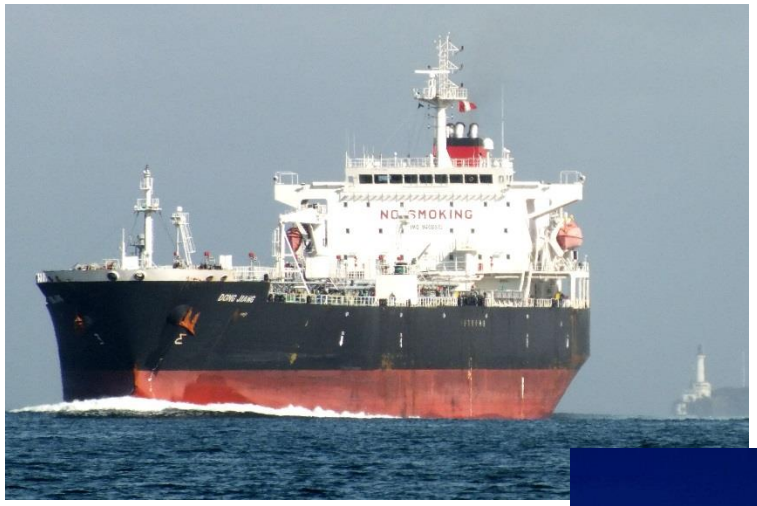
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The whole of science is nothing more than a refinement of everyday thinking

Albert Einstein

Striking Success:

The Emergence of New Targeted Treatment Strategies for Advanced Breast Cancer