TAMRAD: a GINECO randomized phase II trial of everolimus in combination with tamoxifen versus tamoxifen alone in patients with hormone receptor–positive, HER2-negative metastatic breast cancer with prior exposure to aromatase inhibitors

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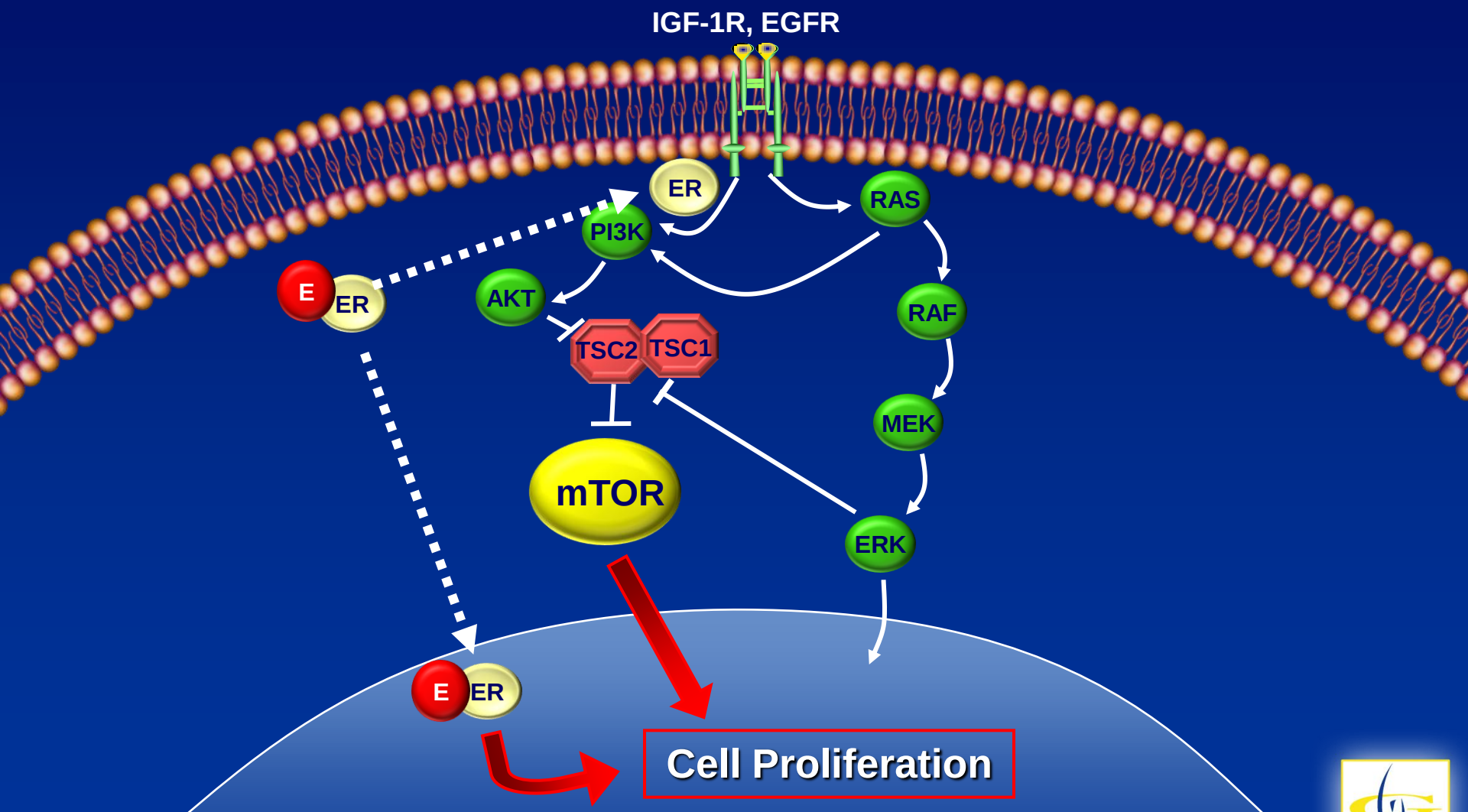
Disclosures

- Novartis provided the study drug (everolimus) and research funding for this investigator-sponsored trial
- Thomas Bachelot is a member of an advisory board for Novartis

Strong Evidence Links Hormone Resistance to Cross-Talk Between Signal Transduction Pathways and ER Signalling



Yue W. J Steroid Biochem Mol Biol 2007; 106:102-110

Everolimus (RAD001)

- Oral and potent inhibitor of mammalian target of rapamycin (mTOR)
  - Approved for renal cell carcinoma (multiple countries) and SEGA (US)
- Promising activity on *in vitro* model of hormone resistance[1]
- Promising activity in early clinical trials[2,3]
- Significantly increases neoadjuvant letrozole antitumor activity[4]

SEGA= subependymal giant cell astrocytoma

1. Boulay et al. Clin Cancer Res. 2005; 11:5319-5328.
2. Ellard SL et al. J Clin Oncol. 2009; 27:4536-4541.
3. Awada A et al. Eur J Cancer. 2008; 44:84-91.
4. Baselga J et al. J Clin Oncol. 2009; 27:2630-2637.

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ER and mTOR Inhibition

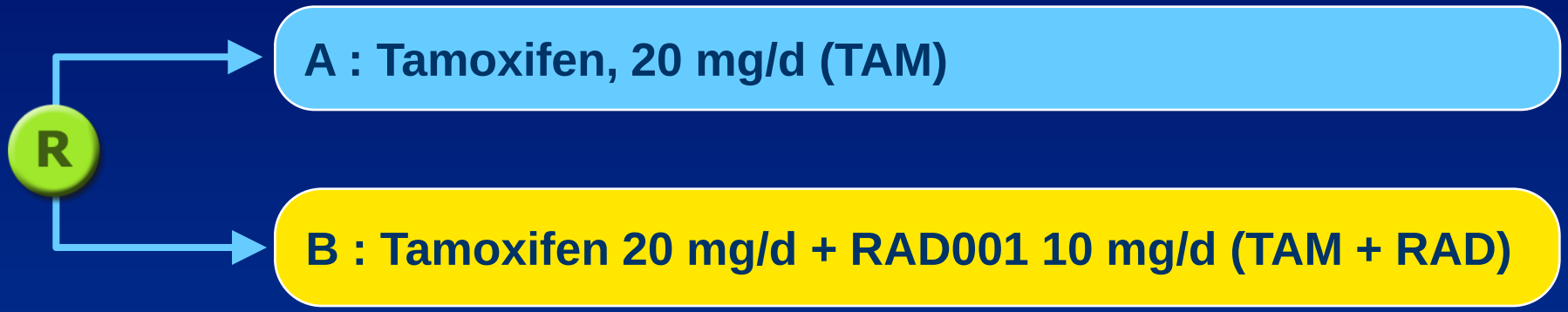
- Previously conducted randomized trials of first-line hormone therapy plus mTOR inhibition in metastatic breast cancer (mBC) have been disappointing[1]
- Selection of aromatase inhibitor (AI)-pretreated mBC patients may enrich the study population with patients whose tumors are driven by activation of the PI3K/AKT/mTOR pathway

1. Chow et al. SABCS meeting 2006, Abstract 6091

TAMRAD PROTOCOL

Randomized Phase II

Metastatic patients with prior exposure to AI



- Stratification: Primary or secondary hormone resistance
  - Primary: Relapse during adjuvant AI; progression within 6 months of starting AI treatment in metastatic setting
  - Secondary: Late relapse (≥ 6 months) or prior response and subsequent progression to metastatic AI treatment
- No crossover planned

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Key Inclusion Criteria

- Menopausal condition
- Hormone receptor positive and HER2 negative
- With or without measurable disease
- Treated with AI in adjuvant and/or metastatic setting
  - May have received tamoxifen in the adjuvant setting
  - May have received chemotherapy in the adjuvant/metastatic setting

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Endpoints

- **Primary: Clinical benefit rate (CBR) at 6 months (*CR + PR + SD at 6 months*)**
- **Secondary:**
  - **Time to progression**
  - **Overall survival**
  - **Objective response rate**
  - **Toxicity**
  - **Translational studies**

CR=complete response; PR=partial response; SD=stable disease

Statistical Considerations

- ***Simon*** **two-stage** ***Minimax*** **design, with alpha = 5% and power = 90%**
- **Considering a gain in CBR of 20% as the minimum needed to warrant further study for the combination**
- **Assuming a CBR of 50% in the TAM arm[1], 53 evaluable patients were needed in both arms**

1. Thurlimann et al. Breast Cancer Res Treat 2004; 85:247-254

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Study Status

- 111 patients included from March 2008 to May 2009
  - First analysis: April 2010
  - Final analysis: October 2010
  - Translational research is ongoing
    - PI3K/mTOR pathway markers

Follow-up	TAM n = 57	TAM + RAD n = 54
Median, months (range)	22.6 (0.9-29.7)	22.3 (2.6-29.3)

Patient Characteristics

	TAM n = 57	TAM + RAD n = 54
Median age, years (range)	66 (42-86)	62.5 (41-81)
Median duration of metastatic disease (months)	14.4 (0-102)	13.2 (1.2-94.8)
Disease stage, n (%)		
Bone	45 (78.9)	41 (75.9)
Bone only	13 (22.8)	16 (29.6)
Visceral	30 (52.6)	31 (57.4)
3 or more	16 (28.1)	14 (25.9)
Previous anti-aromatase treatment, n (%)		
Adjuvant only	19 (33.3)	15 (27.8)
Metastatic only	33 (57.9)	34 (63.0)
Adjuvant + metastatic	5 (8.8)	5 (9.2)
Previous adjuvant TAM treatment, n (%)	23 (40.4)	17 (31.5)
Previous chemotherapy, n (%)		
Adjuvant	32 (56.1)	25 (46.3)
Metastatic	15 (26.3)	13 (24.1)
Primary hormone resistance, n (%)	28 (49.1)	26 (49.1)
Secondary hormone resistance, n (%)	29 (50.9)	27 (50.9)

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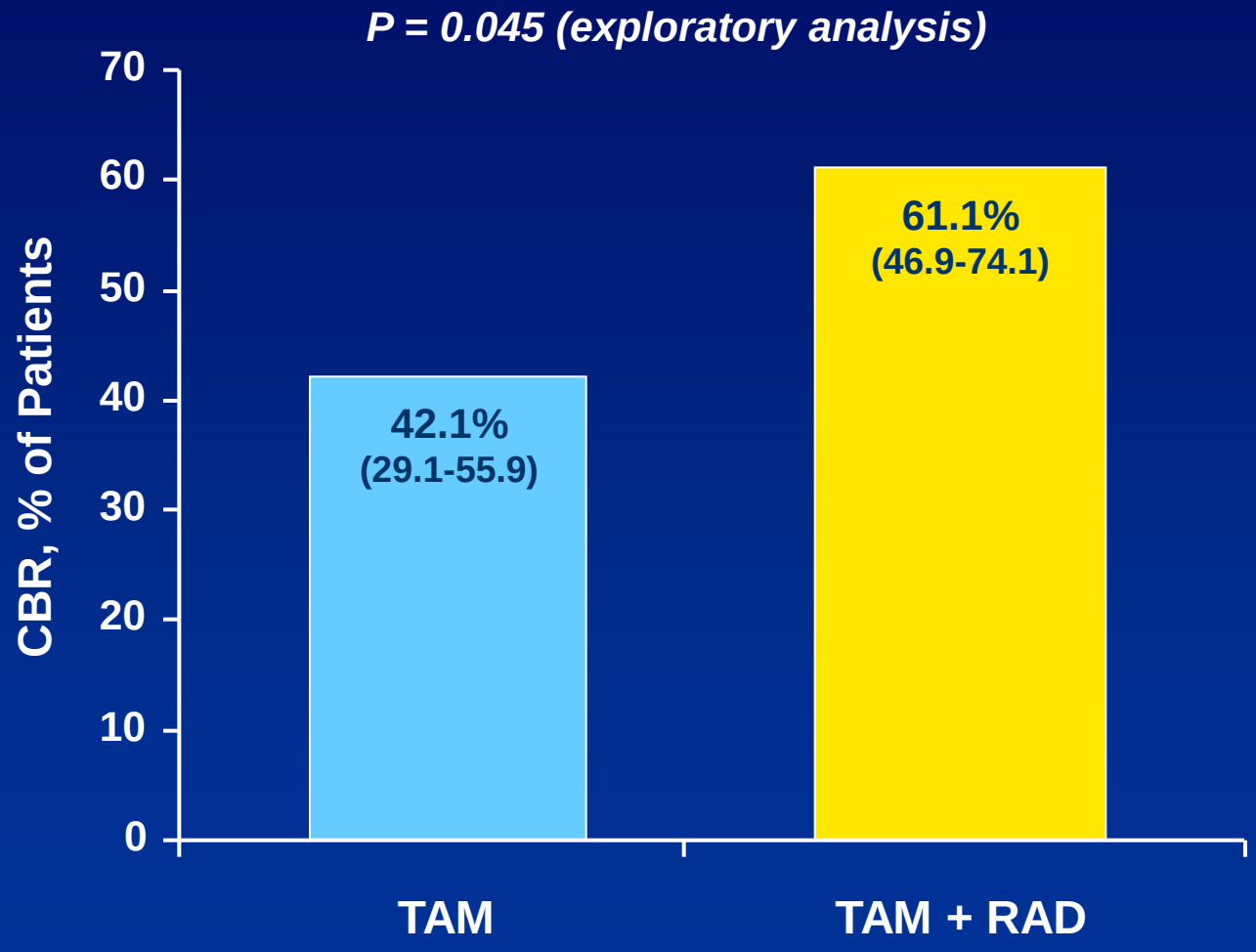
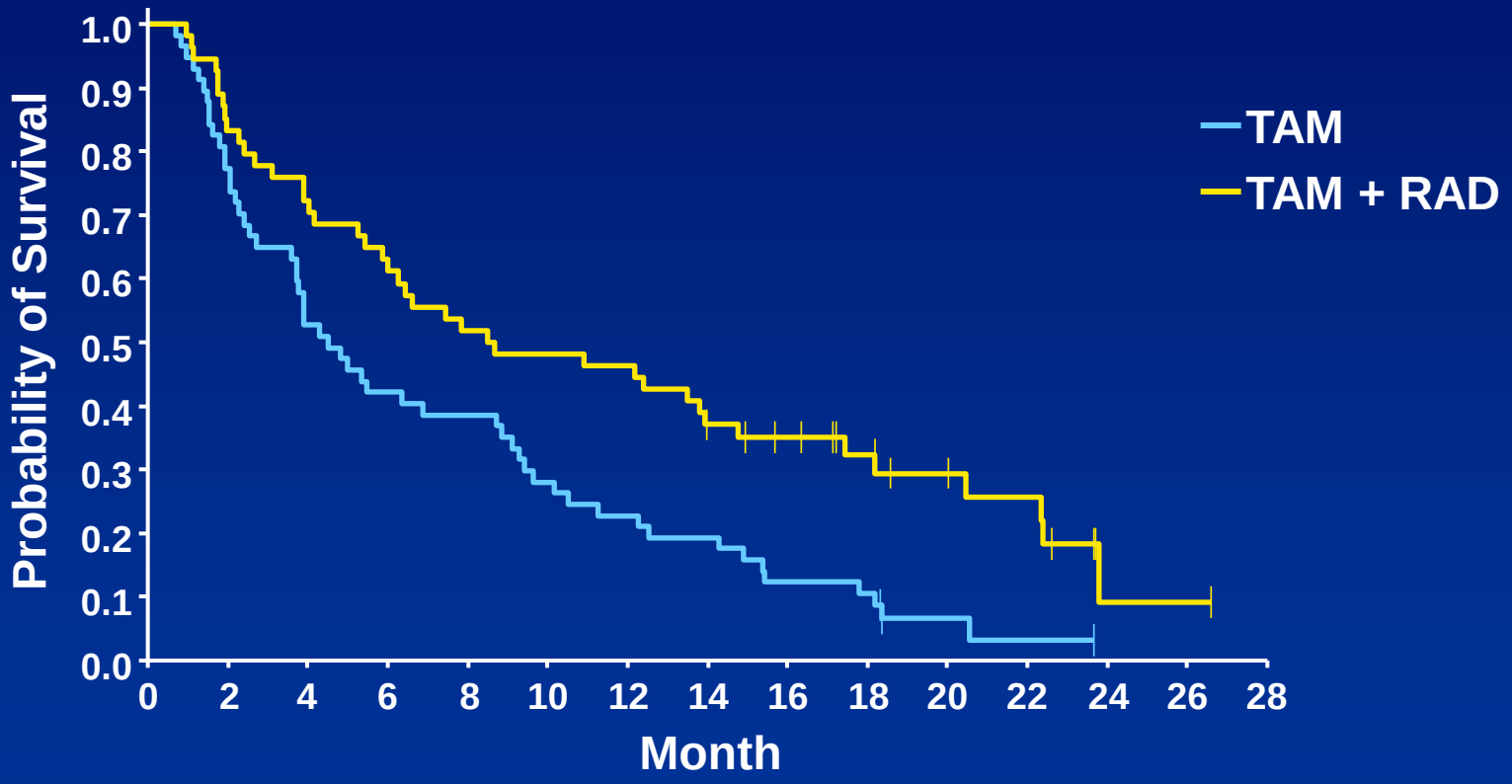
Primary Endpoint: Clinical Benefit Rate



Time to Progression

TAM: 4.5 mo.
TAM + RAD: 8.6 mo.

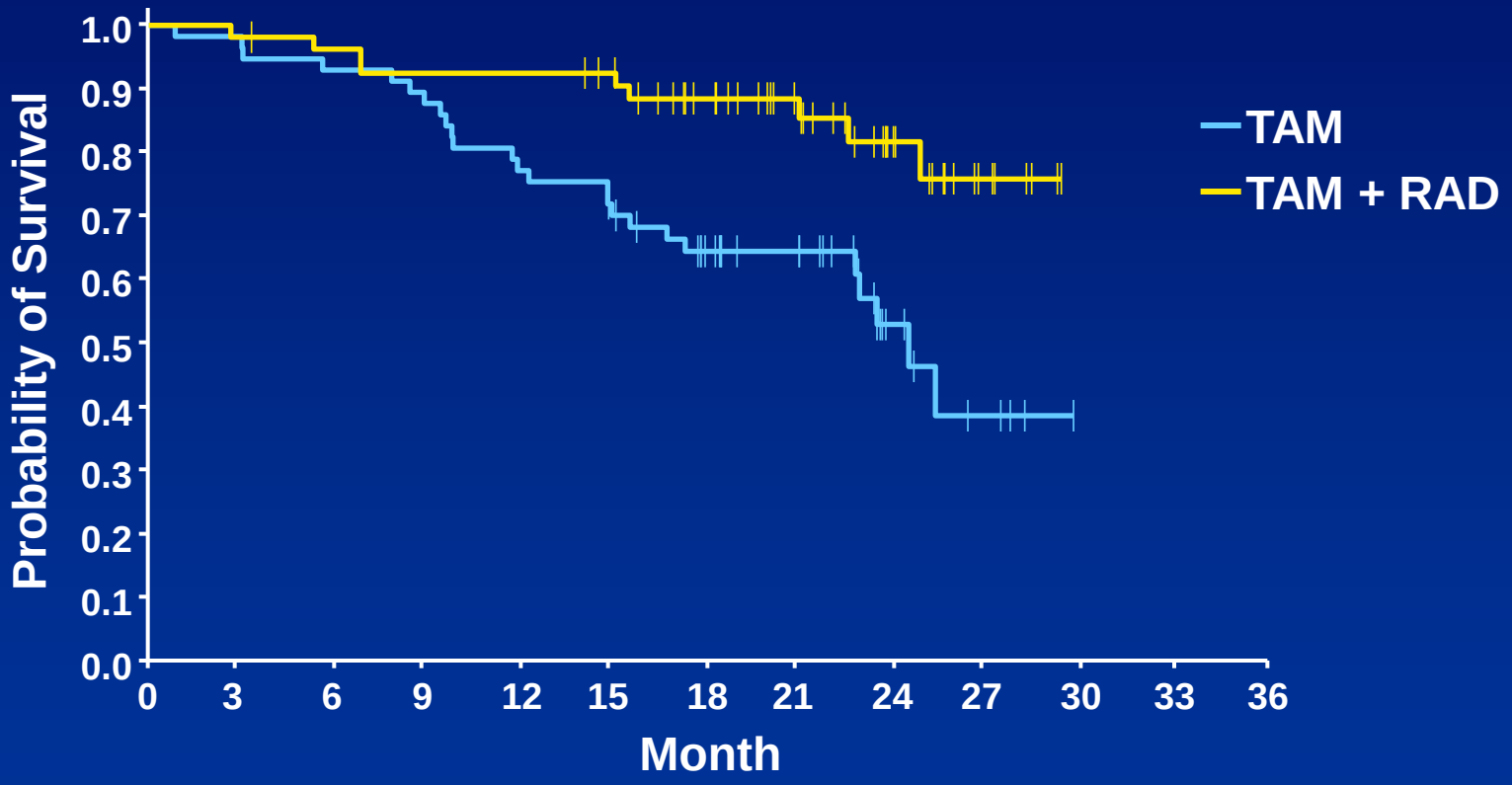
Hazard Ratio (HR) = 0.53; 95% CI (0.35-0.81)
Exploratory log-rank: *P* = 0.0026



Patients at risk															
TAM + RAD: n =	54	45	39	34	28	26	25	19	16	12	9	7	1	1	0
TAM : n =	57	44	30	24	22	16	13	11	7	6	2	1	0	0	0

Overall Survival (as of October 2010)

HR = 0.32; 95% CI (0.15-0.68)
Exploratory log-rank: *P* = 0.0019



Patients at risk											
TAM + RAD: n =	54	53	51	49	49	45	38	26	14	6	0
TAM : n =	57	55	53	50	44	38	30	22	9	4	0

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Adverse Events

Incidence, n (%)	TAM n = 57		TAM + RAD n = 54	
Grade	**Any**	***3/4***	**Any**	***3/4***
Most Common Adverse Events (AE)				
Fatigue	30 (52.6)	*6 (10.5)*	40 (74.1)	*3 (5.6)*
Stomatitis	4 (7.0)	*0*	28 (51.9)	*6 (11.1)*
Rash	3 (5.3)	*1 (1.8)*	21 (38.9)	*3 (5.6)*
Anorexia	10 (17.5)	*2 (3.5)*	24 (44.4)	*5 (9.3)*
Diarrhea	5 (8.8)	*0*	21 (38.9)	*1 (1.9)*
Nausea	19 (33.3)	*0*	18 (33.3)	*2 (3.7)*
Vomiting	7 (12.3)	*2 (3.5)*	9 (16.7)	*0*
Pneumonitis	2 (3.5)	*2 (3.5)*	9 (16.7)	*1 (1.9)*
Thromboembolic	4 (7.0)	*4 (7.0)*	7 (13.0)	*3 (5.6)*
Pain	48 (84.2)	*11 (19.3)*	42 (77.8)	*5 (9.3)*
Dose reduction due to AE	**0 (0)**		**15 (28)**	
Treatment discontinuation due to AE	**4 (7.0)**		**3 (5.6)**	

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Clinical Benefit in Selected Subgroup

CBR, n (%)	TAM n = 57	TAM + RAD n = 54
ALL	*24/57 (42.1)*	*33/54 (61.1)*
Visceral metastases	12/30 (40.0)	19/31 (61.3)
No visceral metastases	12/27 (44.4)	14/23 (60.9)
Previous adjuvant tamoxifen	9/23 (39.1)	11/17 (64.7)
No previous adjuvant tamoxifen	15/34 (44.1)	22/37 (59.5)
Previous metastatic chemotherapy	4/15 (26.7)	6/13 (46.2)
No previous metastatic chemotherapy	20/42 (47.6)	27/41 (65.9)
Primary hormone resistance	11/28 (39.3)	12/26 (46.2)
Secondary hormone resistance	13/29 (44.8)	21/27 (77.8)

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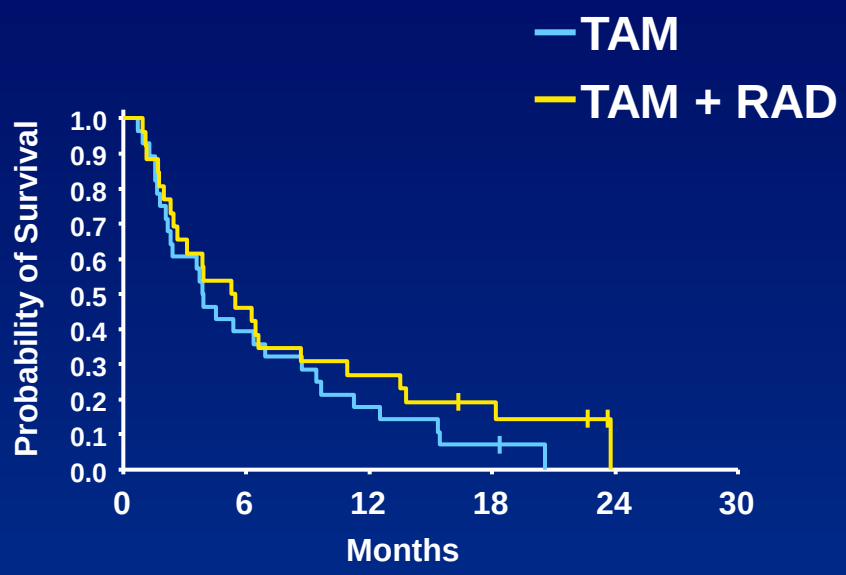
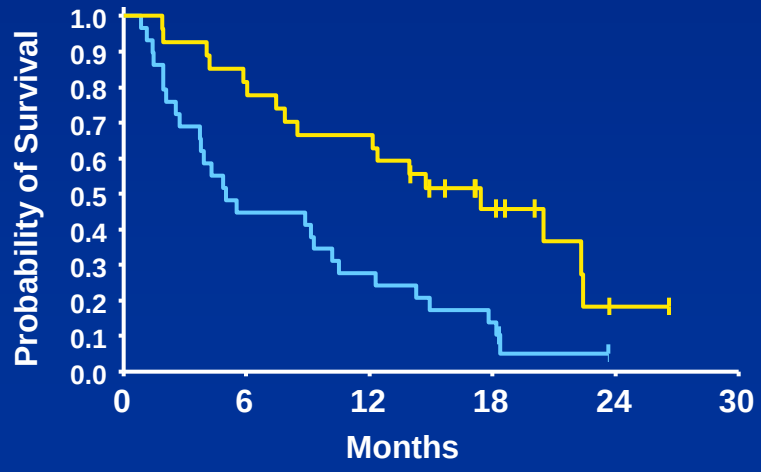
Time to Progression As a Function of Intrinsic Hormone Resistance

- **Primary hormone resistance (n = 54)**
  - **TAM: 3.9 mo.**
  - **TAM + RAD: 5.4 mo.**
  - ***HR = 0.74 (0.42-1.3)***



- **Secondary hormone resistance (n = 56)**
  - **TAM: 5.0 mo.**
  - **TAM + RAD: 17.4 mo.**
  - ***HR = 0.38 (0.21-0.71)***



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Conclusions

- In this randomized phase II trial of an mTOR inhibitor and anti-estrogen combination in AI-pretreated patients:
  - Everolimus combined with tamoxifen allowed for a 61% CBR, as compared with 42% for tamoxifen alone
  - Time to progression and survival increased with the addition of everolimus to tamoxifen compared with tamoxifen alone
    - TTP: HR = 0.53; 95% CI, 0.35-0.81
    - Survival: HR = 0.32; 95% CI, 0.15-0.68
  - Toxicity was manageable and consistent with previous studies
  - Clinical benefit may favor patients with secondary hormone resistance

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