Exploratory Subgroup Analysis of the TAMRAD Phase 2 GINECO Trial Evaluating Tamoxifen (TAM) Plus Everolimus (RAD) vs TAM Alone in Patients With Hormone-Receptor–Positive, HER2-Negative Metastatic Breast Cancer (mBC) With Prior Exposure to Aromatase Inhibitors (AIs): Implication for Research Strategies

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Disclosures

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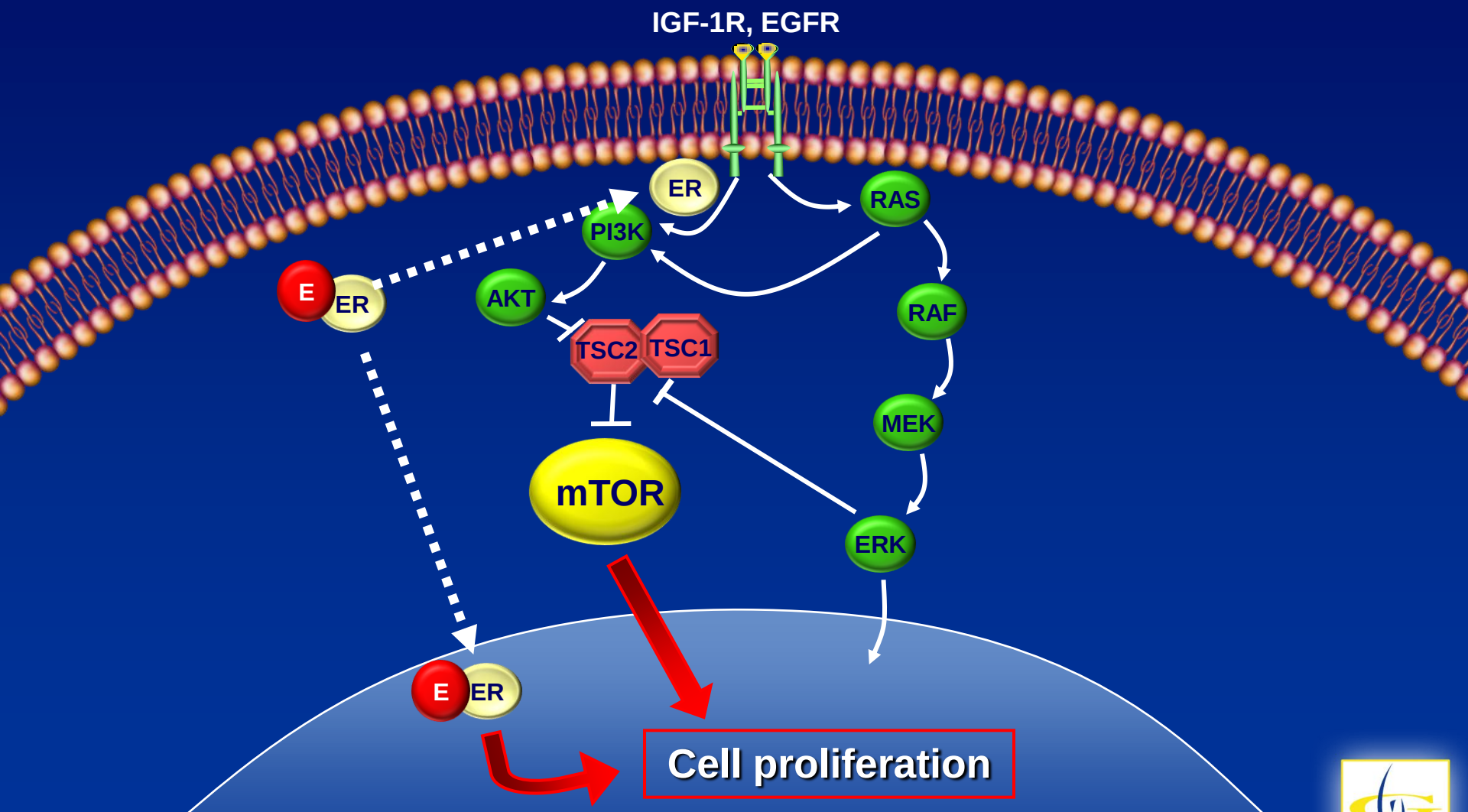
- Dr. Bourgier has no conflicts of interest to disclose

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



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 A 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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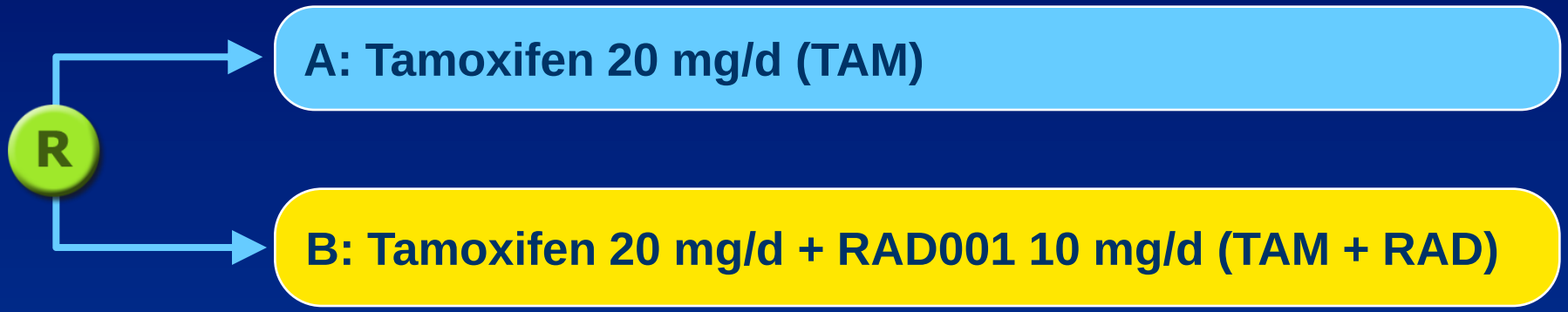
TAMRAD Protocol

Randomized phase II

Metastatic patients with previous exposure to AIs



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

AI = aromatase inhibitor.

Key Inclusion Criteria

- Menopausal condition
- Hormone-receptor positive and HER2 negative
- With or without measurable disease
- Treated with AIs in the 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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Statistical Consideration

- **Primary endpoint : Clinical benefit rate (CBR) at 6 months (*CR + PR + SD at 6 months*)**
- **Secondary endpoints**
  - **Time to disease progression**
  - **Overall survival**
  - **Objective response rate**
  - **Toxicity**
  - **Translational studies**
- **Simon two-stage minimax design, with alpha = 5% and power = 90%**

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

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Study Status as of September 2011

- 111 patients included (March 2008/May 2009)
- Final analysis: May 2011
- Median follow-up 24 month
- Overall survival update: September 2011
- Translational research
  - Initial tumor samples from 48 patients
  - mTOR pathway markers by immunohistochemistry (IHC)
    - pS6K; 4EBP1
  - Mutational analysis
    - PI3K, exon 9 and 20; KRAS exon 2

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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 (range)	14.4 (0.7-102)	13.2 (1.2-94.8)
Disease stage, n (%)		
Bone	45 (78.9)	41 (75.9)
Bone only	14 (24.6)	16 (29.6)
Visceral	28 (49.1)	31 (57.4)
3 or more	16 (28.1)	13 (24.1)
Previous anti-aromatase treatment, n (%)		
Adjuvant only	20 (35.1)	17 (31.5)
Metastatic only	33 (57.9)	33 (61.1)
Adjuvant + metastatic	4 (7)	4 (7.4)
Previous adjuvant TAM treatment, n (%)	24 (42.1)	18 (33.3)
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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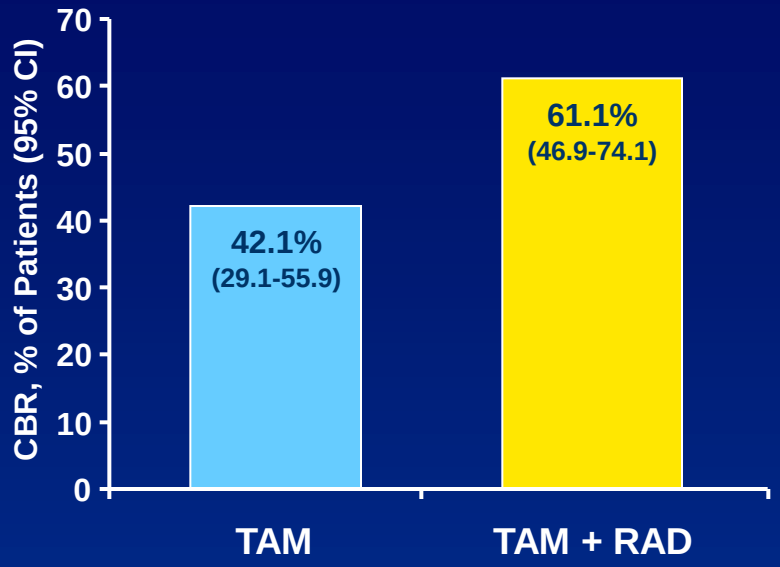
Clinical Benefit Rate and Time to Progression (TTP)

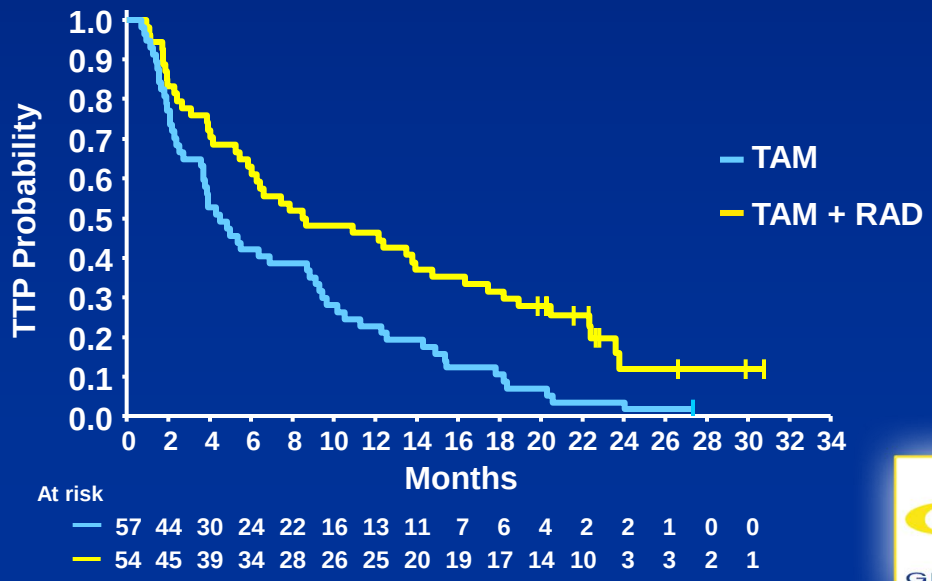
Clinical benefit rate

***P* = 0.045 (exploratory analysis)**

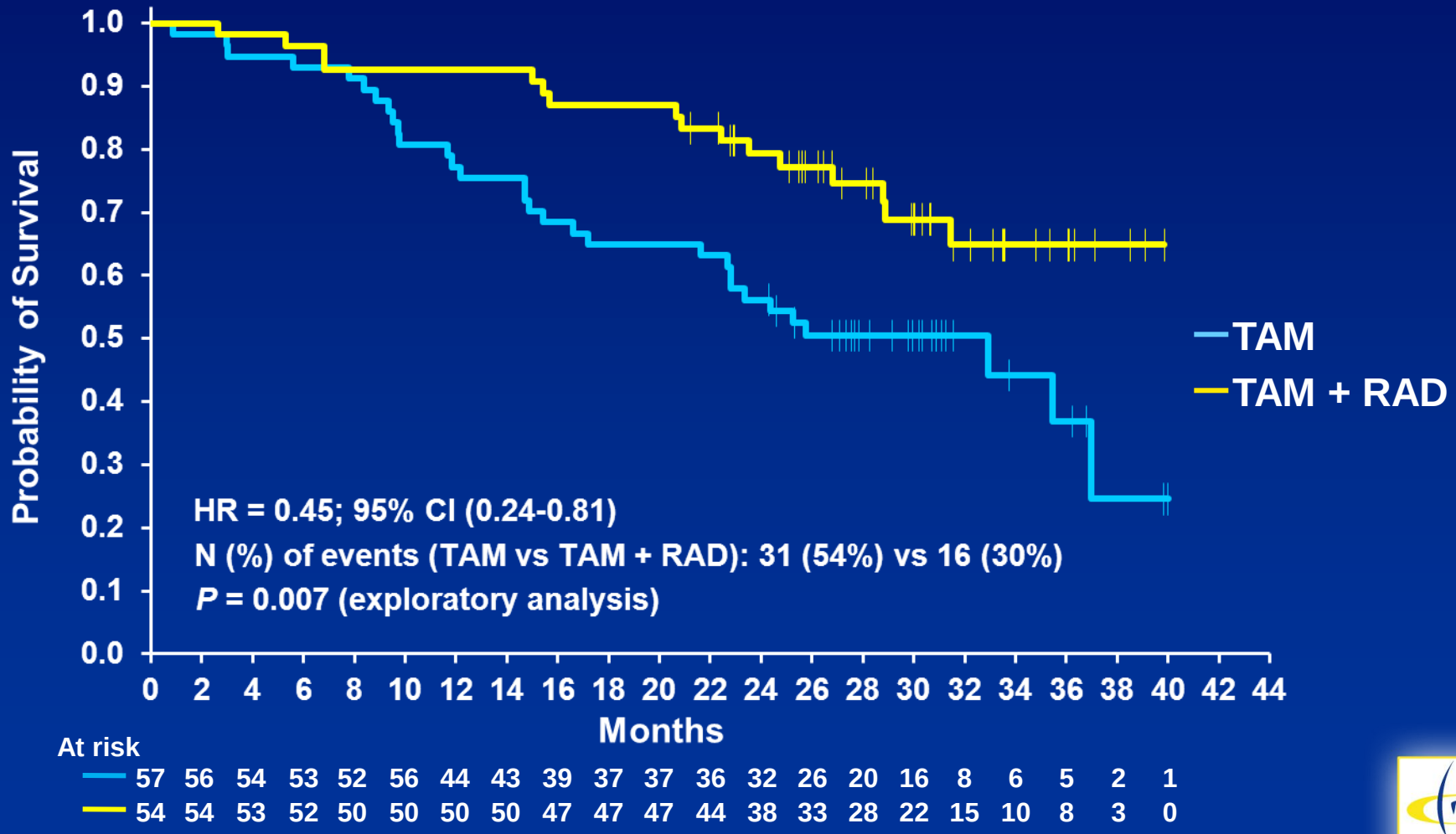


Time to progression

- **TAM: 4.5 months**
- **TAM + RAD: 8.6 months**
- **HR (95% CI) = 0.54 (0.36-0.81)**
- ***P* = 0.0021 (exploratory analysis)**



Overall Survival (as of September 2011)



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	11/28 (39.3)	19/31 (61.3)
No visceral metastases	13/29 (44.8)	14/23 (60.9)
Previous adjuvant tamoxifen	9/24 (37.5)	12/18 (66.7)
No previous adjuvant tamoxifen	15/33 (45.5)	21/36 (58.3)
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	10/28 (35.7)	12/26 (46.2)
Secondary hormone resistance	14/29 (48.3)	20/27 (74.1)

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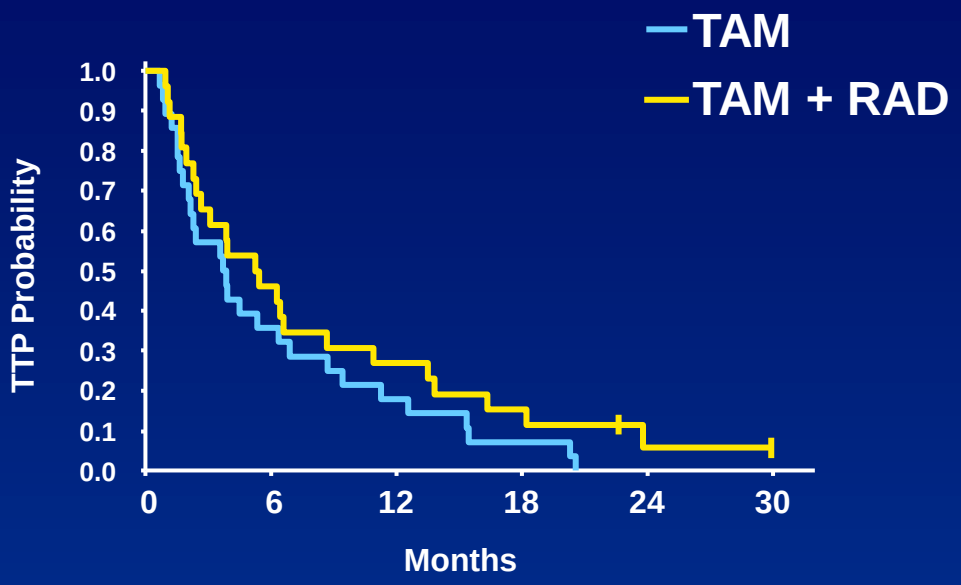
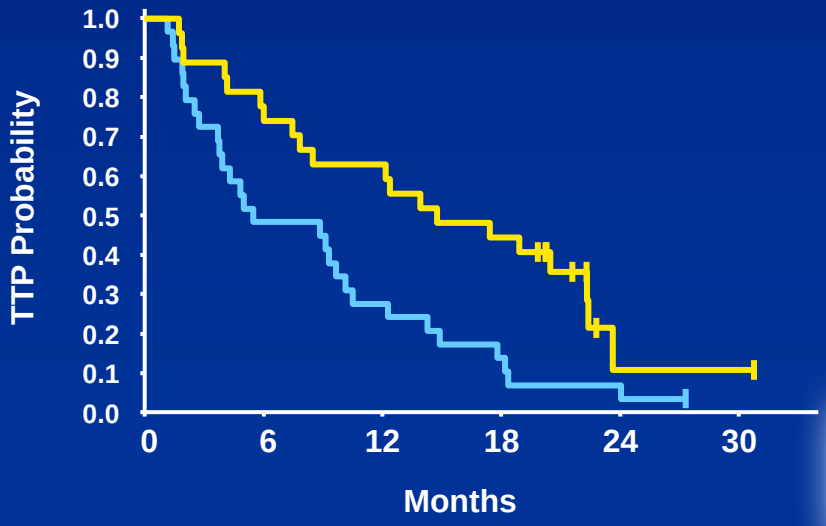
Time to Progression as a Function of Intrinsic Hormone Resistance

- **Primary resistance**
  - TAM: 3.8 months
  - TAM + RAD: 5.4 months
  - HR = 0.70 (0.40-1.21)
  - *P* = NS (exploratory analysis)



- **Secondary resistance**
  - TAM: 5.5 months
  - TAM + RAD: 14.8 months
  - HR = 0.46 (0.26-0.83)
  - *P* = 0.0087 (exploratory analysis)



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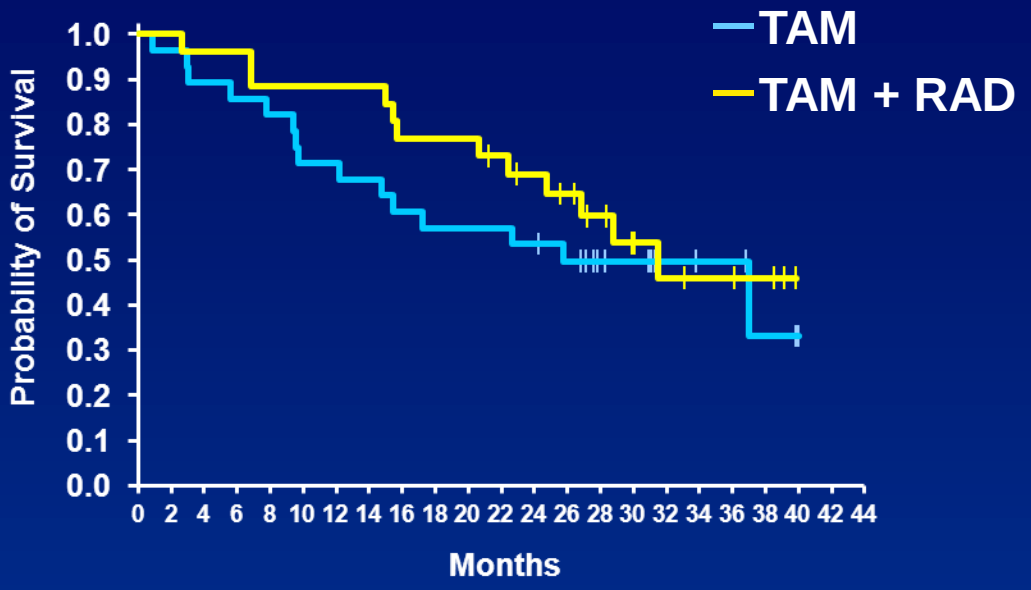
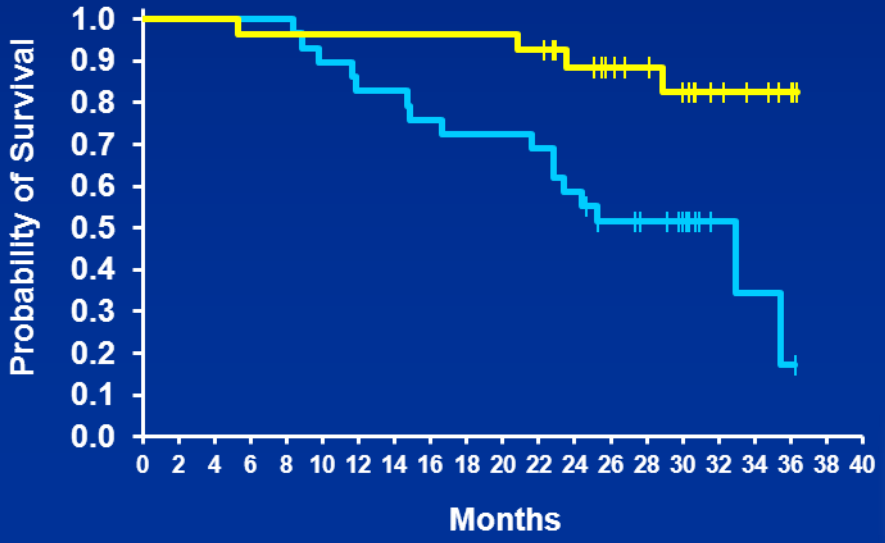
Survival as a Function of Intrinsic Hormone Resistance

- Primary resistance
  - N (%) of events
    - TAM: 15 (54%)
    - TAM + RAD: 12 (46%)
  - HR = 0.73 (0.34-1.55)
  - *P* = 0.41 (exploratory analysis)



- Secondary resistance
  - N (%) of events
    - TAM: 16 (55%)
    - TAM + RAD: 4 (15%)
  - HR = 0.21 (0.07-0.63)
  - *P* = 0.002 (exploratory analysis)



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PI3K and KRAS Mutational Status

- Mutational analysis was performed for PI3K and KRAS in 48 patients (primary tumor)
  - PI3K, exon 9 mutation: 1/48 (2%)
  - PI3K, exon 20 mutation: 2/47 (4.2%)
  - KRAS mutation: 4/48 (8.3%)

- Incidence of PI3K and KRAS mutation was lower than expected; no statistical analysis was performed

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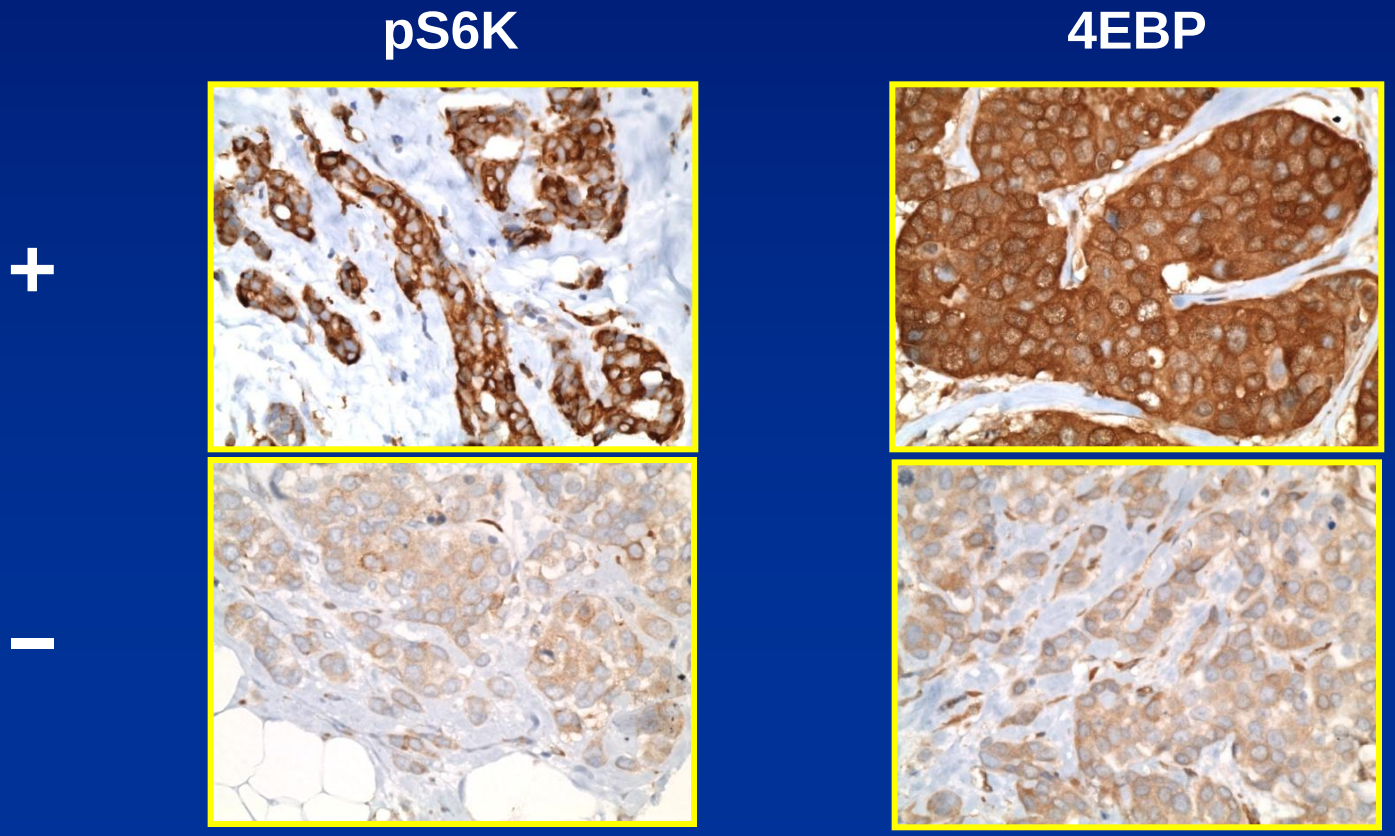
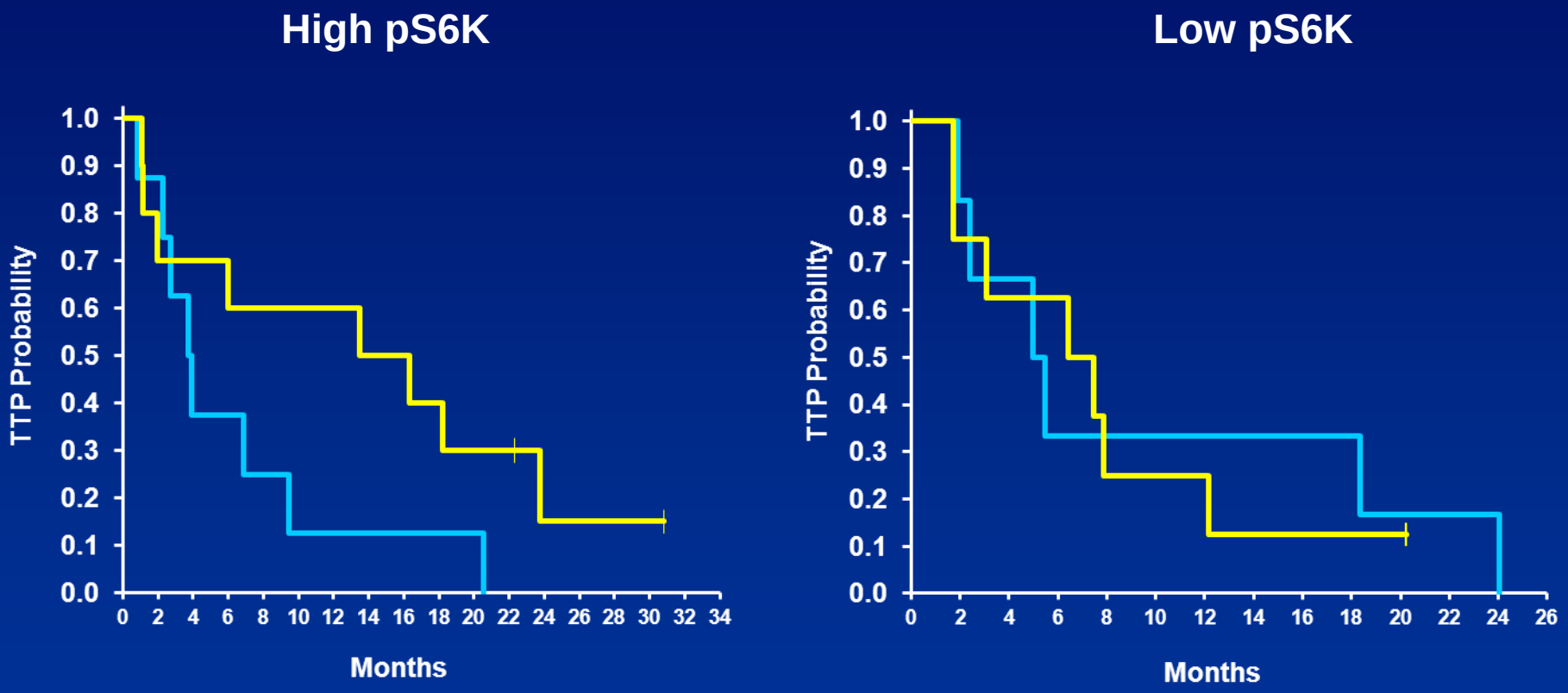
mTOR Activation Biomarker

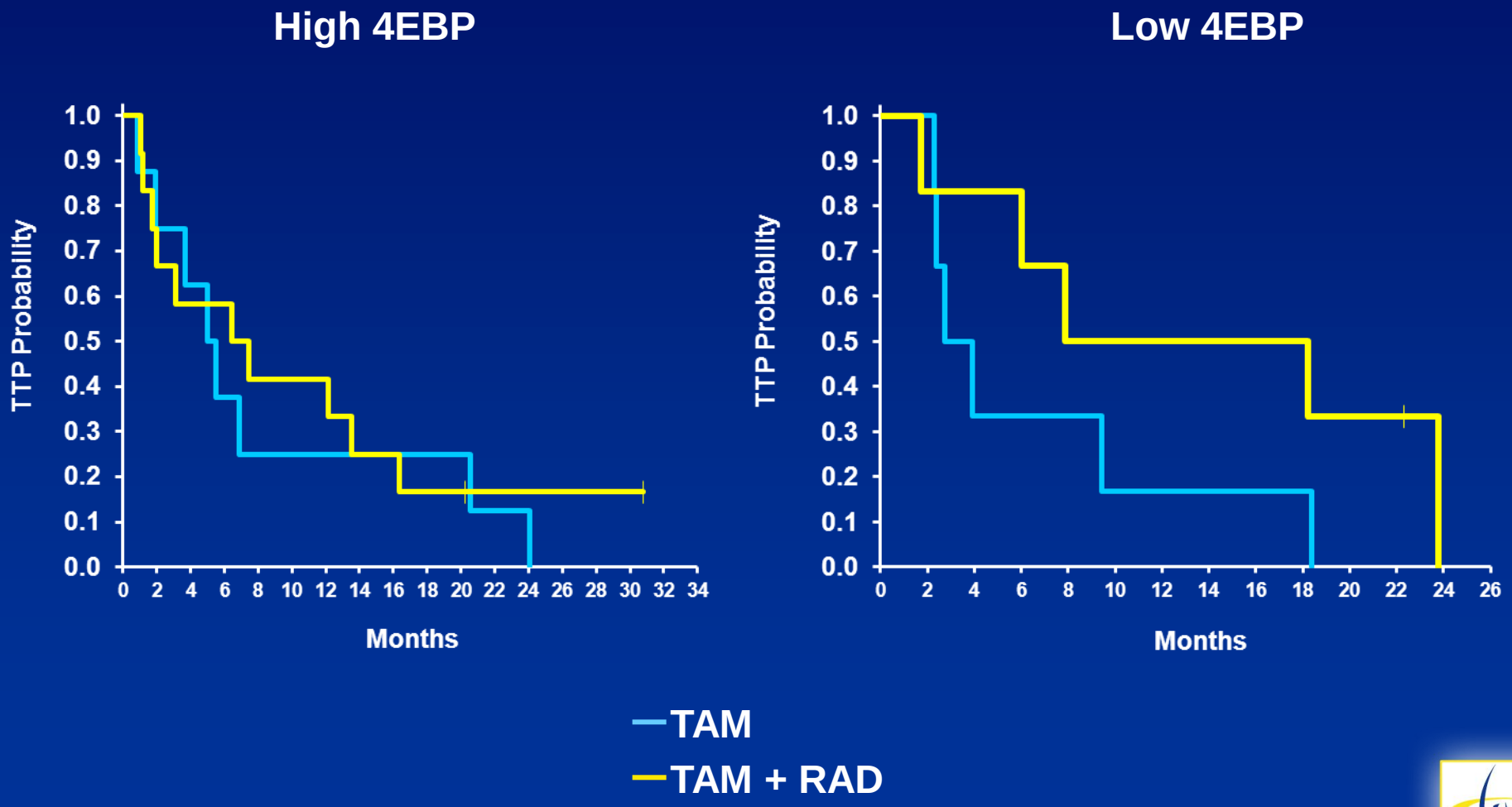
- Assessed in 35 patients (primary tumor)
- Cut-off (high/low) as the median percentage of marked cell



Treatment Effect as a Function of Biomarker Expression (TTP)



Treatment Effect as a Function of Biomarker Expression (TTP)



Adverse Events

Incidence, n (%)	TAM n = 57		TAM + RAD n = 54	
Grade	**Any**	***3/4***	**Any**	***3/4***
Most Common Adverse Events (AEs)				
Fatigue	**30 (52.6)**	***6 (10.5)***	**39 (72.2)**	***3 (5.6)***
Stomatitis	**4 (7.0)**	***0***	**30 (55.6)**	***6 (11.1)***
Rash	**4 (7.0)**	***0***	**24 (44.4)**	***2 (3.7)***
Anorexia	**10 (17.5)**	***2 (3.5)***	**23 (42.6)**	***4 (7.4)***
Diarrhea	**5 (8.8)**	***0***	**21 (38.9)**	***1 (1.9)***
Nausea	**20 (35.1)**	***0***	**19 (35.2)**	***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)***	**5 (8.8)**	***3 (5.6)***
Pain	**49 (90.7)**	***10 (18.5)***	**44 (81.5)**	***5 (9.3)***
Dose reduction due to AE	**0 (0)**		**11 (20)**	
Treatment discontinuation due to AE	**4 (7.0)**		**12 (22)**	

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Conclusions

- In this randomized phase II trial of an mTOR inhibitor and anti-estrogen combination in AI-pretreated patients:
  - CBR, TTP, and survival increased with the addition of everolimus to tamoxifen compared with tamoxifen alone
    - CBR: 61 vs 42 %
    - TTP: HR = 0.54; 95% CI, 0.36-0.81
    - Survival: HR = 0.45; 95% CI, 0.24-0.81
  - Clinical benefit may favor patients with secondary hormone resistance
  - Preliminary results of translational analysis show a possible correlation between biomarkers of mTOR activation and everolimus efficacy
  - Toxicity was manageable and consistent with previous studies

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