Introduction

Luminal A and B: How curable are they?

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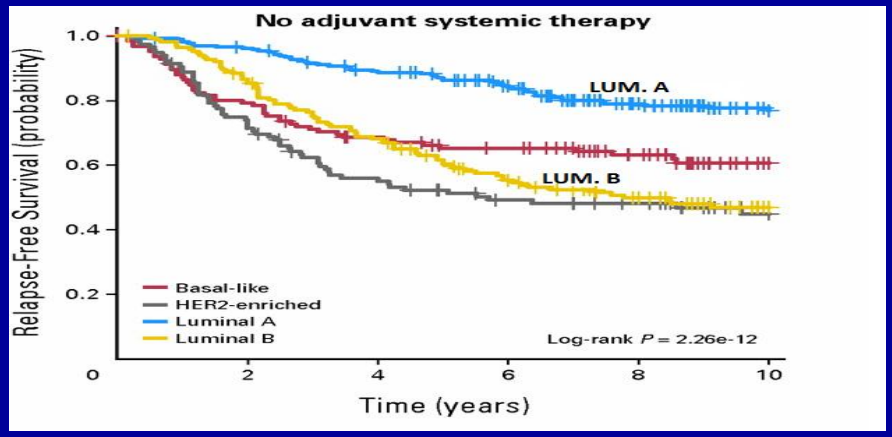
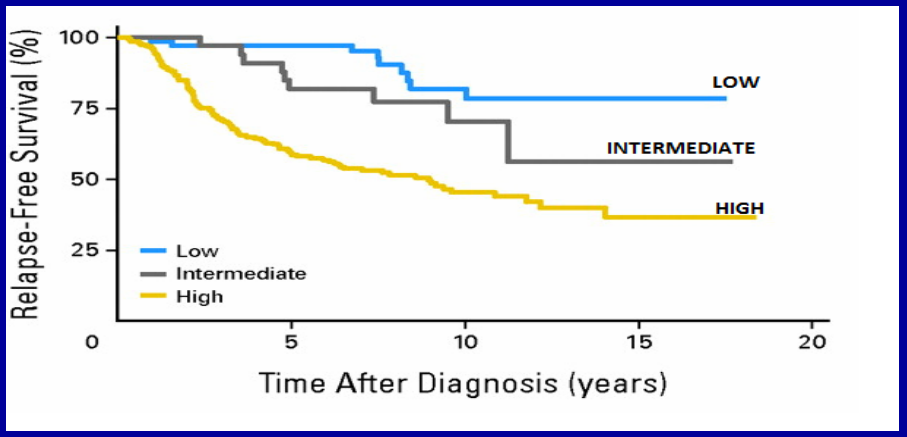
As member of advisory boards and as speaker during satellite symposia, I have received honoraria from AstraZeneca, Genomic Health, Novartis, Pfizer

Heterogeneity of ER+ disease

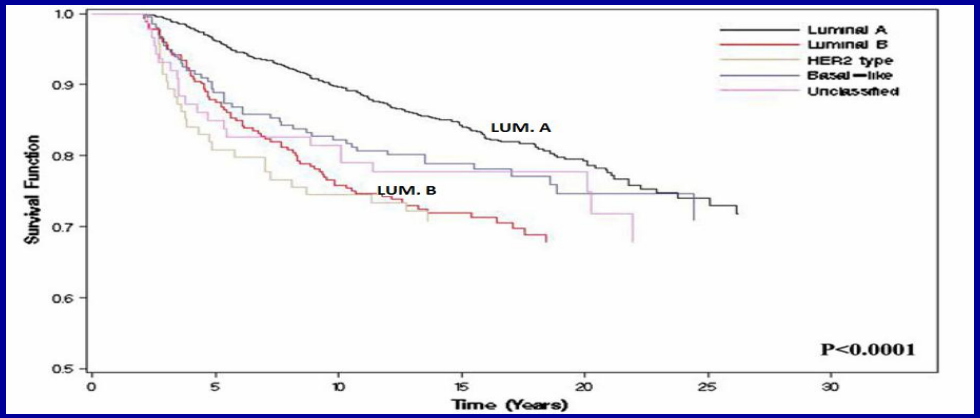
No adjuvant systemic therapies*



Adjuvant tamoxifen•



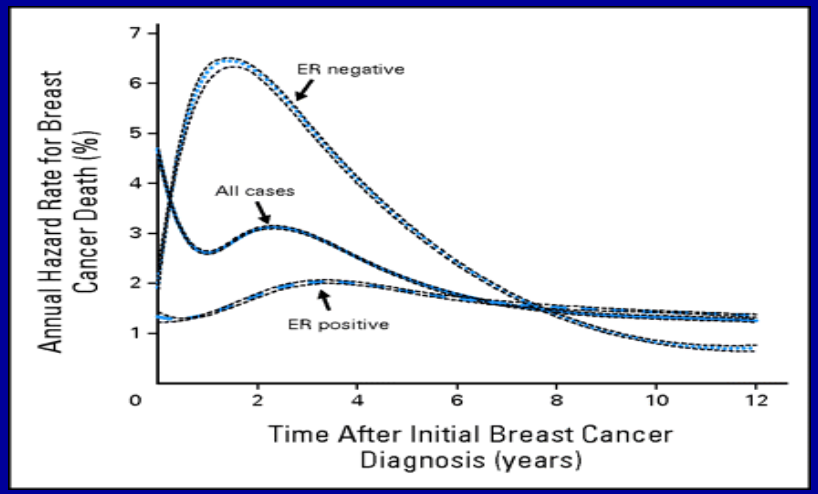
By immunohistochemistry§



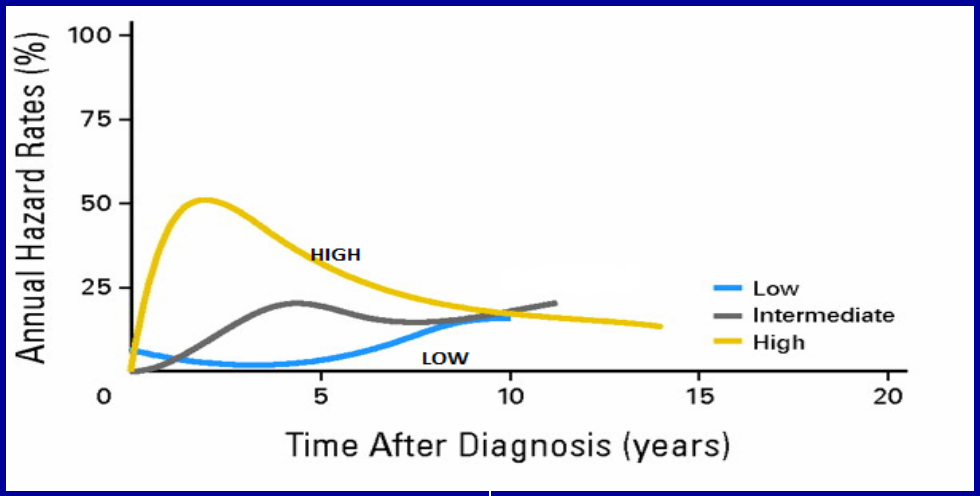
*Parker JS et al, J Clin Oncol 27:1160-67, 2009; •Paik S et al, N Engl J Med 351: 2817-26, 2004;
§Dawood S et al, Breast Cancer Res Treat 126: 185-92, 2011

Annual hazard rates for breast cancer relapse and death

Risk of death by time and by ER status*



Risk of relapse by time within the ER+ population•



ER+ Luminal A (low proliferation)

⇩

Risk of late relapse

ER+ Luminal B (high proliferation)

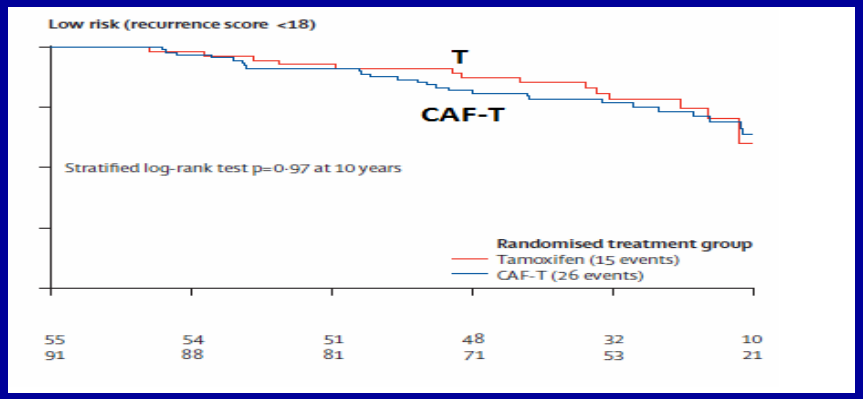
⇩

Risk of early relapse

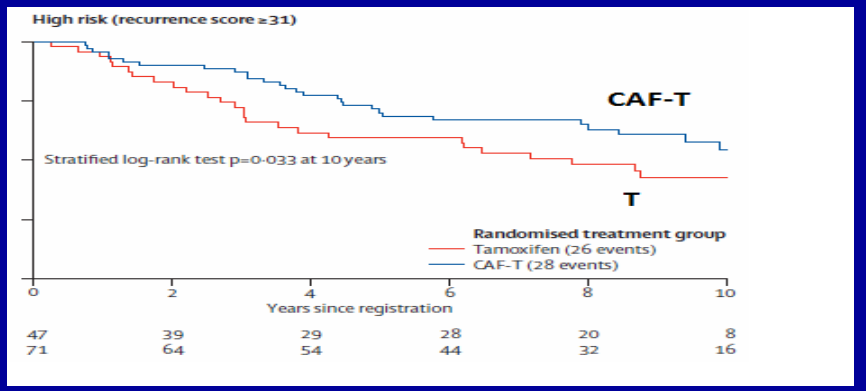
*SEER program, http://seer.cancer.gov; •Paik S et al, N Engl J Med 351: 2817-26, 2004

Adjuvant chemotherapy is active in ER+ patients with Luminal B tumors ("high risk" by Oncotype Dx®)

Low risk (Luminal A)



High risk (Luminal B)



Issues:

- Should all "high risk" patients receive adjuvant chemotherapy?

  - a significant proportion of "high risk" pts. seems to do well with tamoxifen alone

  - some of the "high risk" pts. relapse after adjuvant chemotherapy

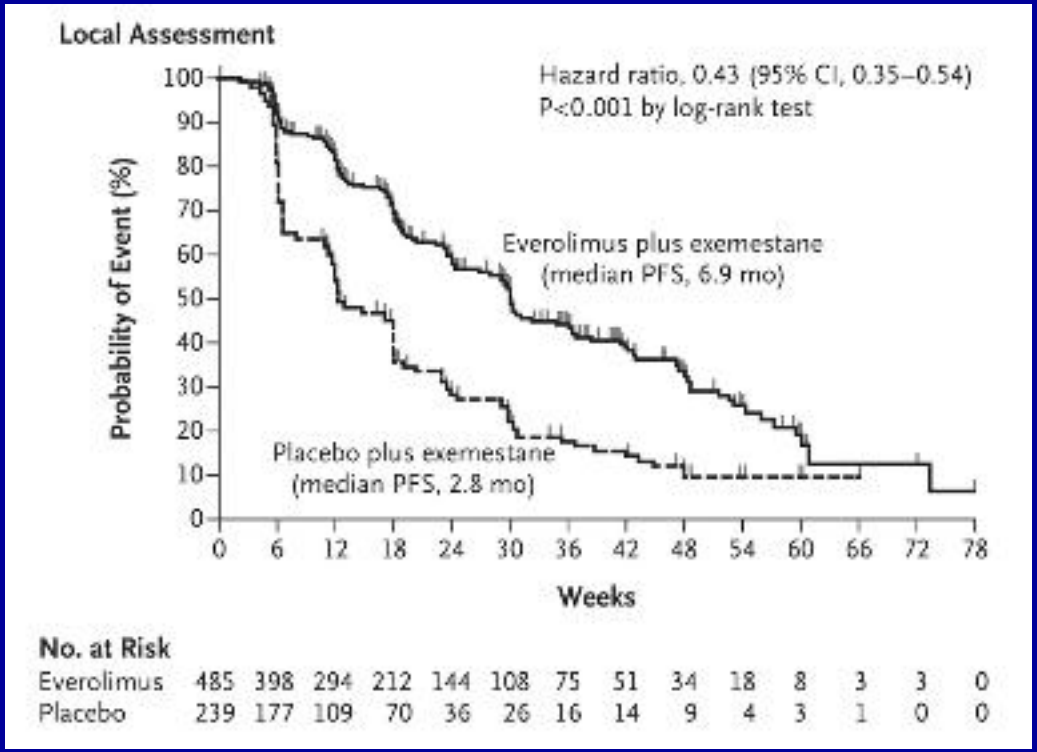
- Which chemotherapy regimen? (A ⟶ Tx vs. less intensive chemotherapy)

Albain KS et al, Lancet Oncol 11: 55-65, 2010

Can targeted agents improve the activity of endocrine therapy? The Bolero-2 trial

Advanced breast cancer pts. progressing to nsAIs → **exemestane**

Advanced breast cancer pts. progressing to nsAIs → **exemestane + everolimus**



Baselga J et al, New Engl J Med 366: 520-9, 2012

The use of everolimus in combination with endocrine therapy may increase toxicity…

Adverse event	Everolimus N = 482 % G3-G4 (%G1-G4)	Placebo N = 238 % G3-G4 (%G1-G4)
Stomatitis	8 (56)	1 (11)
Anemia	6 (16)	1 (4)
Dyspnea	4 (18)	1 (9)
Hyperglicemia	4 (13)	1 (2)
Fatigue	4 (33)	1 (26)
Pneumonitis	3 (12)	- (-)

Baselga J et al, New Engl J Med 366: 520-9, 2012

…and in some cases may lead to treatment discontinuation

	Everolimus N = 482	Placebo N = 238
• Due to adverse events	19%	4%
• Consent withdrawal	5%	2%
• No. deaths attributed to adverse events	7	1

Baselga J et al, New Engl J Med 366: 520-9, 2012

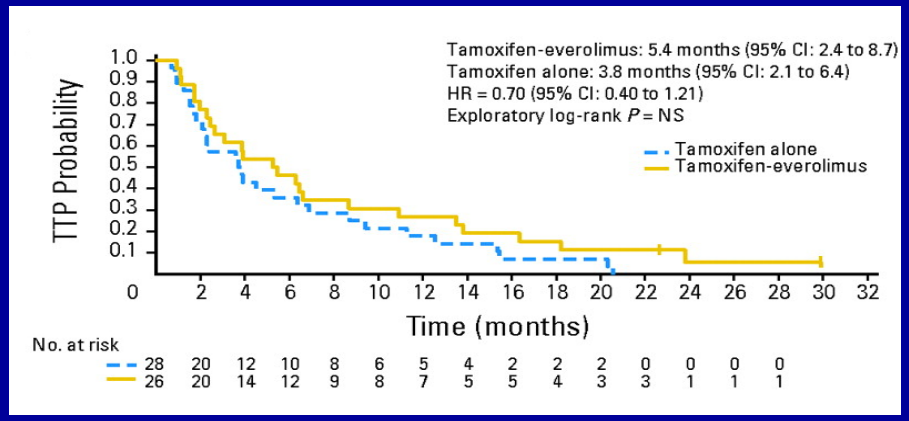
Key-question: can we identify patients who will derive benefit from MTOR inhibitors? Exploratory data

Advanced breast cancer patients previously exposed to nsAIs

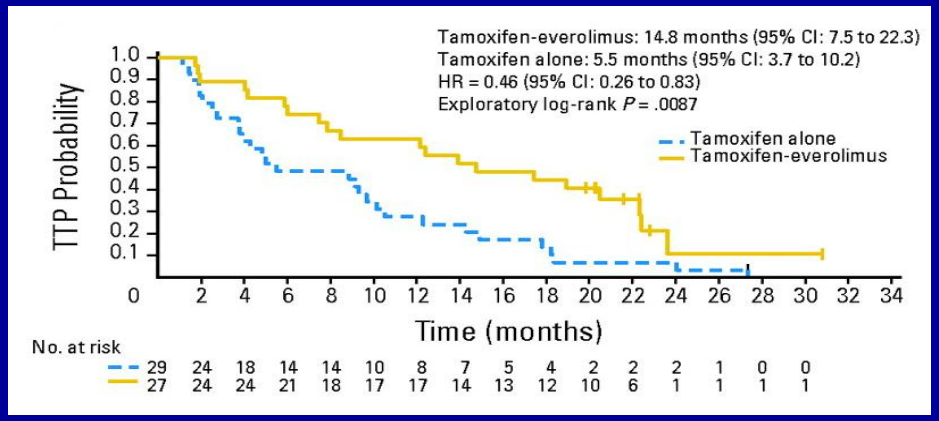
Phase II randomized (N=111)

- tamoxifen
- tamoxifen + everolimus

Primary resistance to AI



Secondary resistance to AI



Bachelot T et al, J Clin Oncol 30:2718-24, 2012

Study hypothesis

The activation of the PI3K/MTOR pathway might occur in tumors exposed to a long term estrogen deprivation (i.e. tumors progressing after initial response to aromatase inhibitors)

Yue W et al, J Steroid Bioch Mol Biol 2003; Sanchez CG et al, Breast Cancer Res 2011; Loi S et al, Proc Natl Acad Sci 2010

Current adjuvant endocrine therapy options

Pre-menopausal: tamoxifen ± LH-RH analogues

pending issues: when LH-RH analogues? which duration?

Post-menopausal: **-AI**

-TAM → AIs (after 2-3 yrs. or after 5 yrs.)

-TAM

pending issues: “biologically driven” strategy for TAM vs. AI

TAM vs. AI in the adjuvant setting.
Can we have a "biologically driven" approach?

- Currently, no "biologically driven" strategy is clinically valuable

- The only factor supporting treatment decisions is risk of relapse:

  ↑ risk ⇨ use of AI upfront

  ↑ risk in pts. still on treatment with TAM ⇨ shift to AI at 2-3 yrs. or at 5 yrs.

- Will pharmacogenetics help? (gene polymorphisms)

Conclusions and future challenges

- **Hormone receptor positive disease is clinically heterogeneous (different risk of relapse and time to relapse, different sensitivity to endocrine therapy)**

- **Luminal A breast cancer: studies are urgently needed to elucidate mechanisms of late relapses**

- **Luminal B breast cancer: efforts are needed to**

  - target the use of chemotherapy

  - identify new agents to reverse/delay resistance to endocrine therapy with a "truly targeted" approach

- **Risk of relapse is still the only clinically valuable factor to select the most appropriate endocrine therapy option in the adjuvant setting**