

**Central Review of ER, PgR and HER2 in BIG 1-98
Evaluating Letrozole vs. Letrozole→Tamoxifen
vs. Tamoxifen→Letrozole as Adjuvant
Endocrine Therapy for Postmenopausal
Women with Hormone Receptor-Positive
Breast Cancer**

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*for the BIG 1-98 Collaborative and
International Breast Cancer Study Groups*



IBCSG

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SABCS 2009



Disclosures

- BIG 1-98 is coordinated by the International Breast Cancer Study Group (IBCSG) for the B.I.G.
- Novartis, the manufacturer of letrozole, distributed the study drugs and provided partial financial support but imposed no restrictions on the investigators with respect to trial data.
- Novartis provided partial financial support for central pathology review, which was performed in the European Institute of Oncology, Milan, Italy under the supervision of Giuseppe Viale.



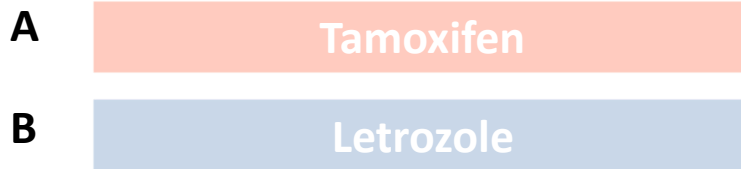
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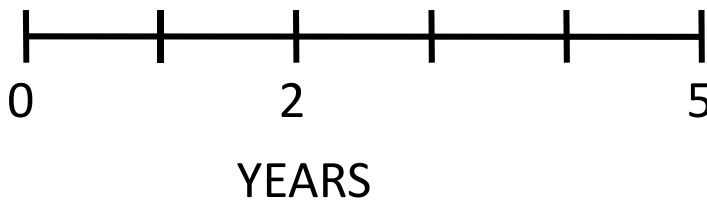
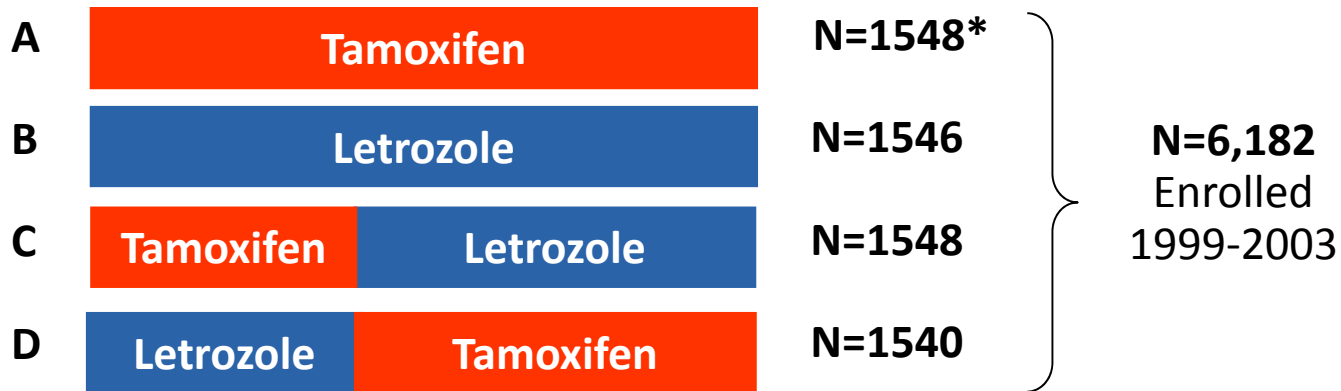


BIG 1-98 Sequential Therapy

2-Arm Option

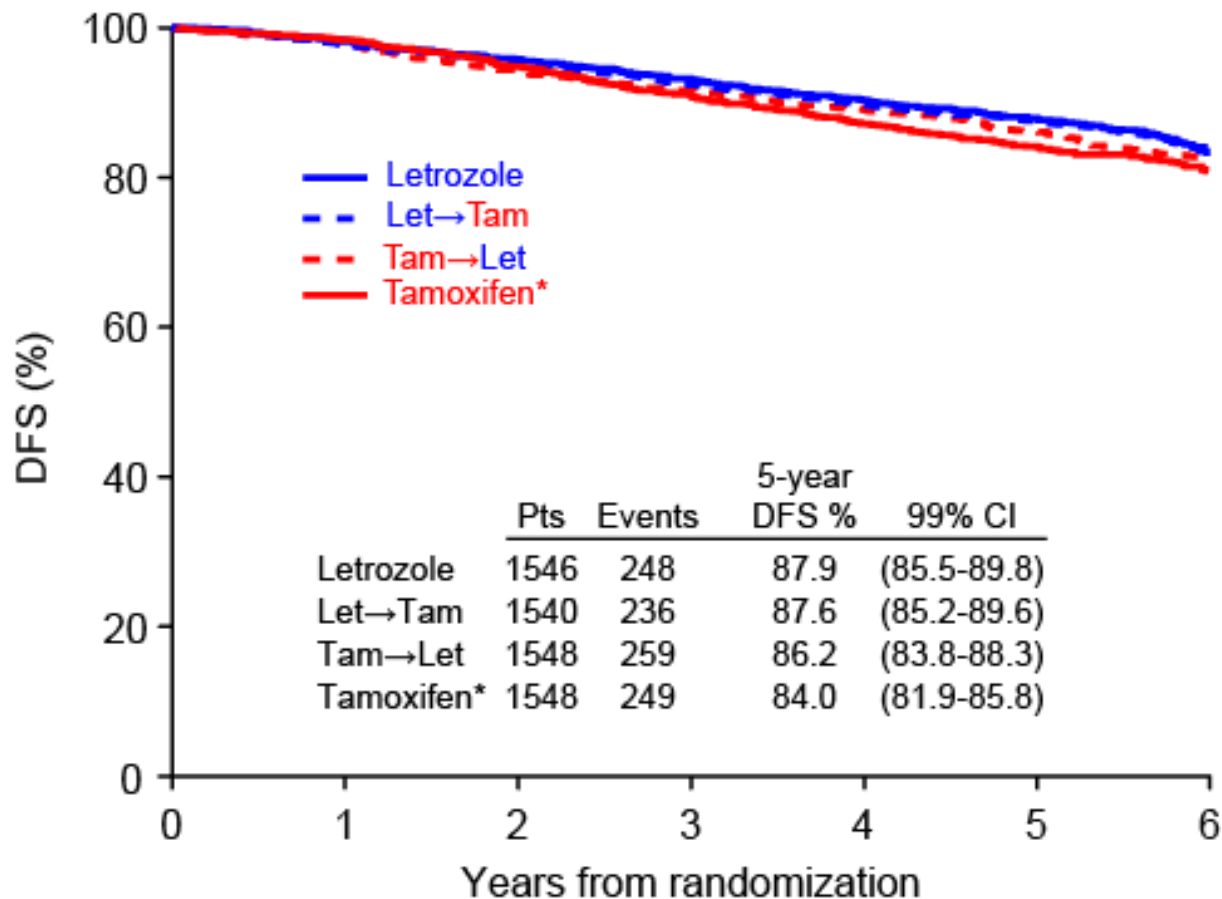


4-Arm Option



*612 patients (40%) received letrozole after the tamoxifen arm was unblinded.

BIG 1-98 Sequential Therapy DFS (median follow-up 71 months)



*Follow-up for 612 patients (40%) who received letrozole after the tamoxifen arm was unblinded (selective crossover) are censored at crossover.



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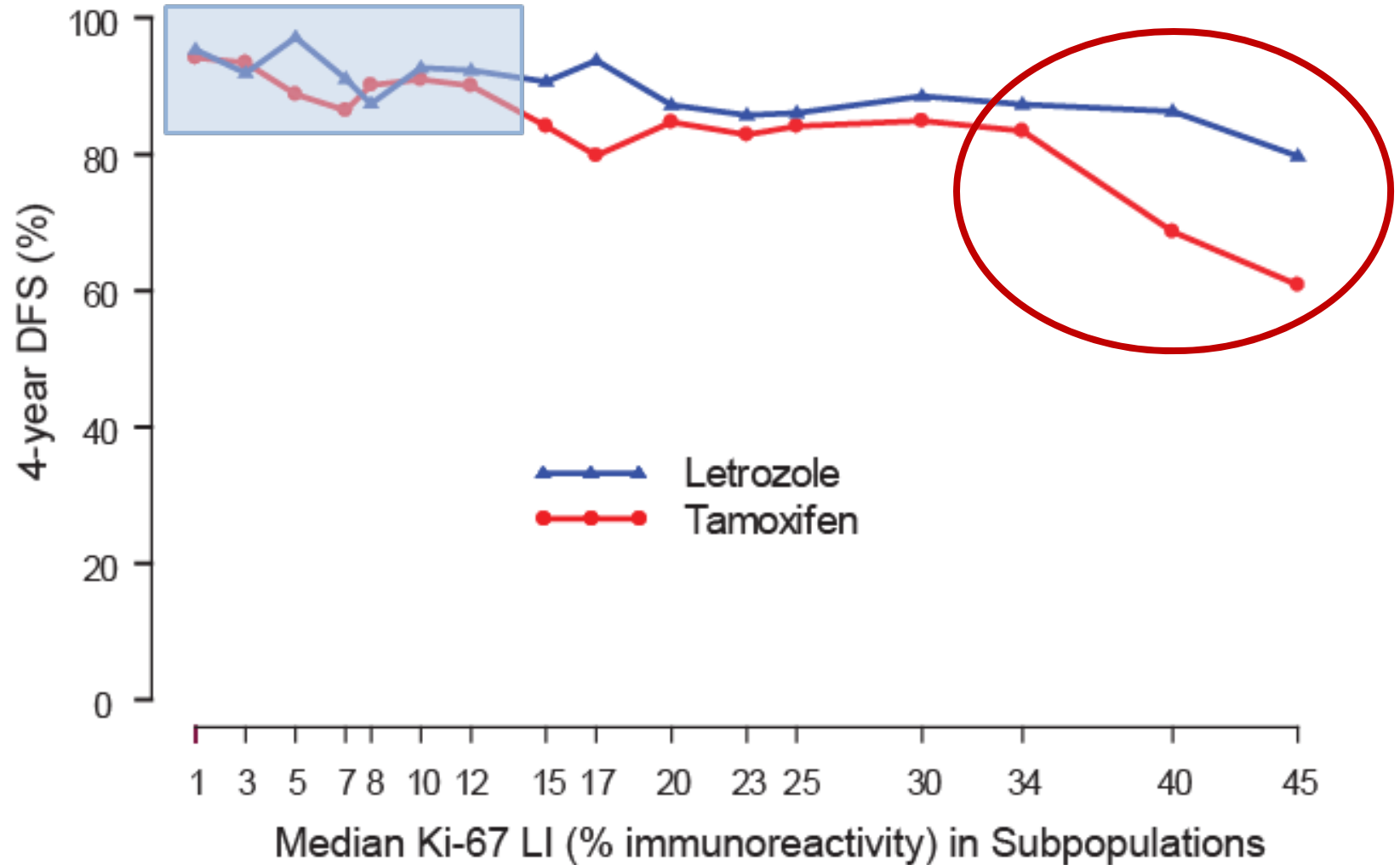


Study Methods

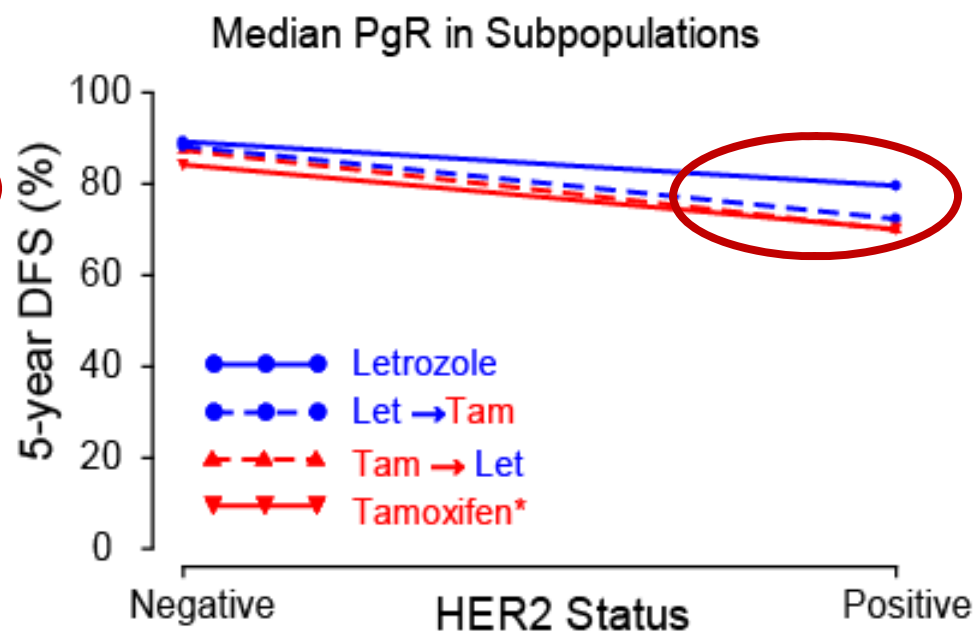
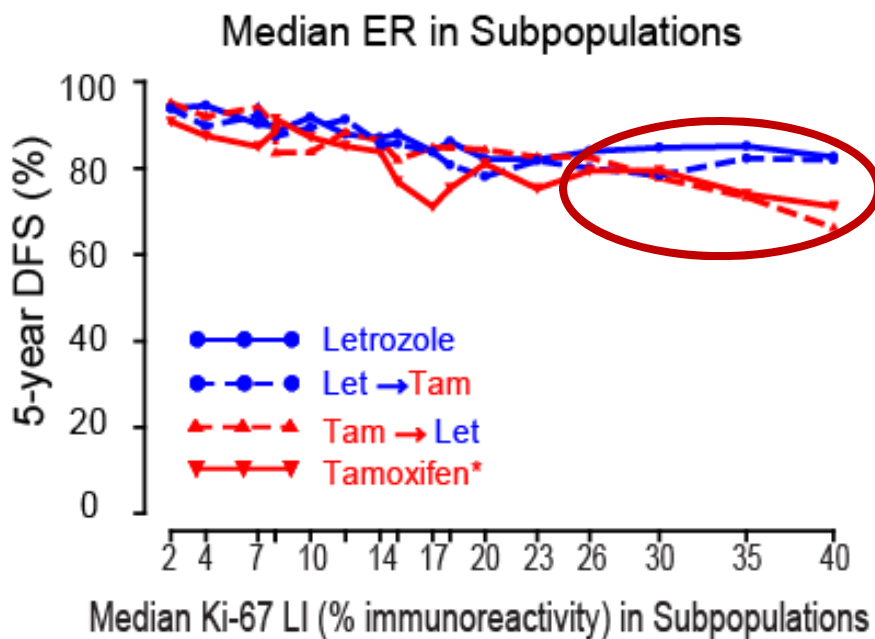
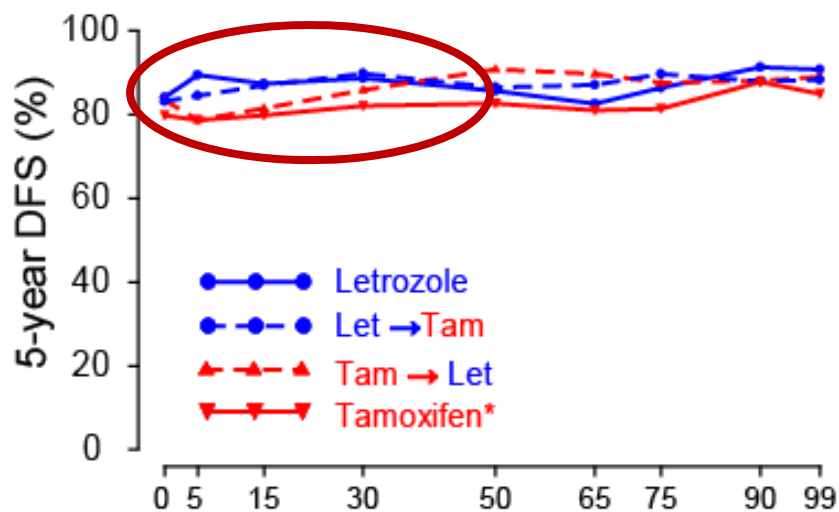
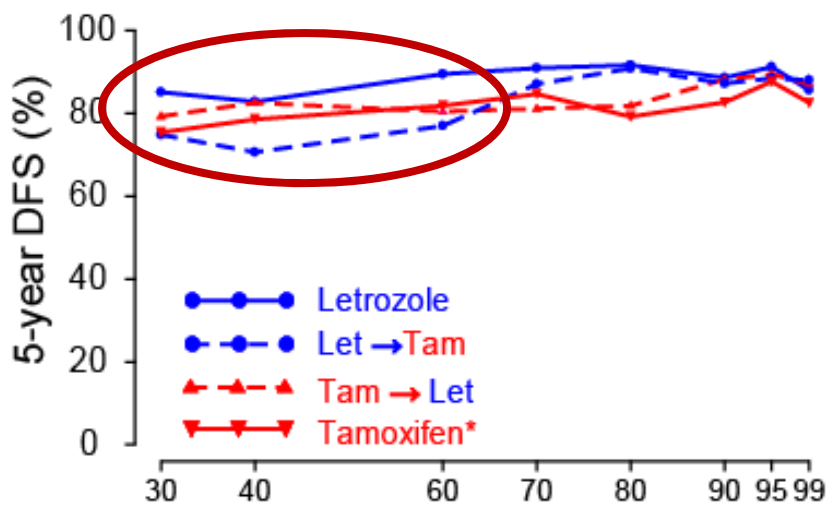
- Retrospective tissue collection
- IBCSG Central Pathology Laboratory assessed:
 - ER, PgR by IHC
 - Ki-67 labeling index (LI) by IHC
 - HER2 by IHC; confirmed by FISH
- Analysis cohort: 5177 of 6182 (84%) with material evaluable for central review and with ER-expressing tumors ($\geq 1\%$ immunoreactivity), centrally-confirmed
 - Those not included were more often LN-, tended to have smaller tumors, heterogeneity in prior treatment, less complete local pathology reporting on CRFs



STEPP example: Ki-67 (SABCS 2007)



Individual Markers



Individual Markers

- Each of the markers showed a trend favoring letrozole monotherapy at the “higher risk” end of its spectrum
- None was statistically significant predictive factor
- Nonetheless, a majority of the 2009 St Gallen Panelists preferred initial aromatase inhibitor “particularly for patients at higher risk”
- Could a composite *prognostic* risk profile based on St Gallen risk factors also serve to *predict* treatment differences?



Composite Prognostic Risk Profile

- Replicated the clinical decision-making approach which is based on a composite assessment of risk for each individual patient
- Multivariable stratified Cox model for DFS using St. Gallen risk factors
- Model coefficients were used to assign points for each of the different factors, which were summed to provide a single score for each patient reflecting her risk factor profile

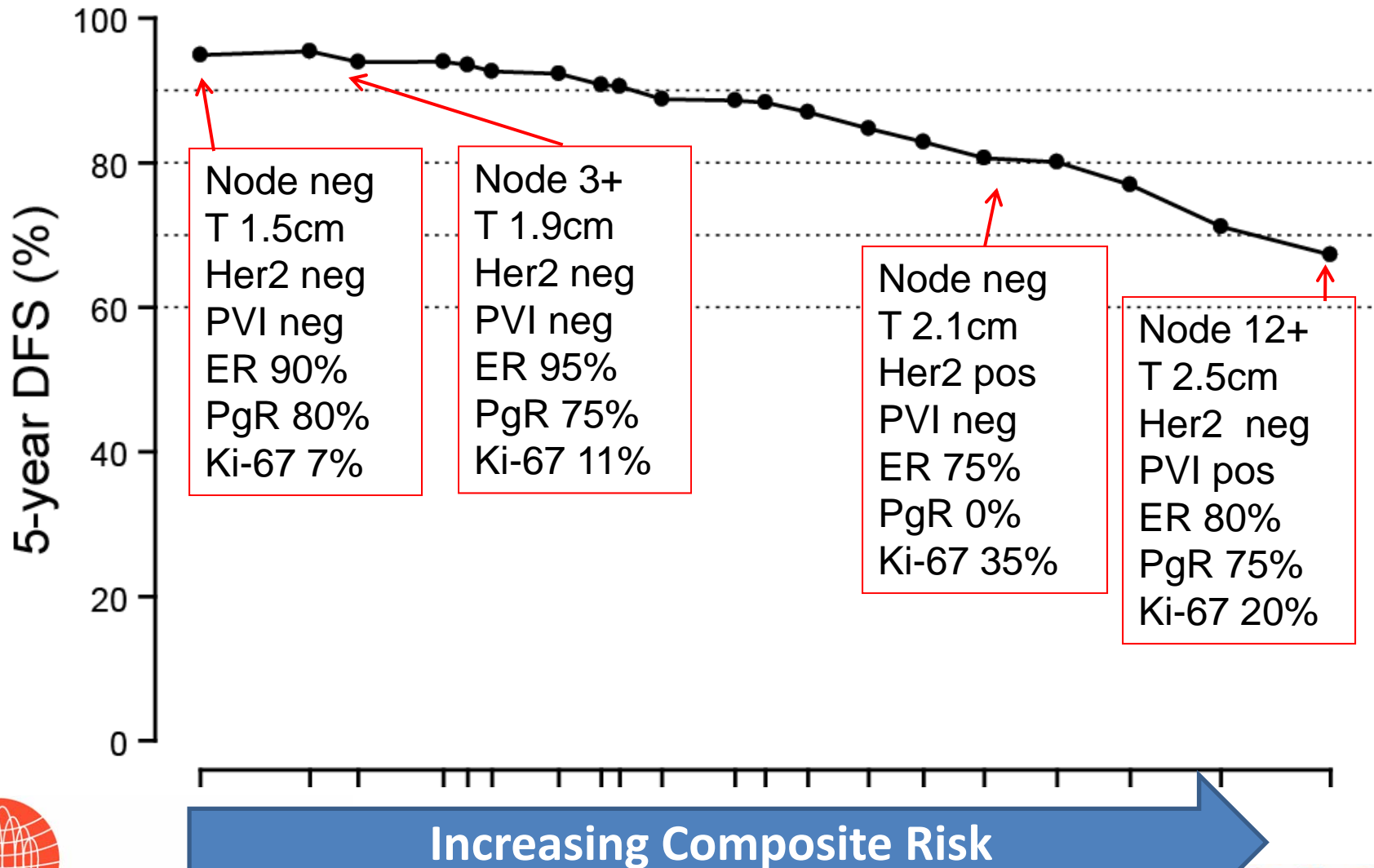


Contributions to Composite Risk

Points:	0	~0.25	~0.5	~0.75	~1.5
Lymph nodes	0		1-3	4-9	10+
ER %	50+	30-49	<30%		
PgR %	20+	<20			
Ki-67 %	<14	14-33	34+		
HER2	Neg	Pos			
PVI	No	Yes			
Grade	1	2	3		
T size	≤2	2.1-4.9	5+		



STEPP 5-year DFS by Composite Risk



Composite Prognostic Risk Profile

- Composite prognostic risk profile assessed for usefulness in selecting among treatments in BIG 1-98
- Does it also serve to *predict* treatment differences?

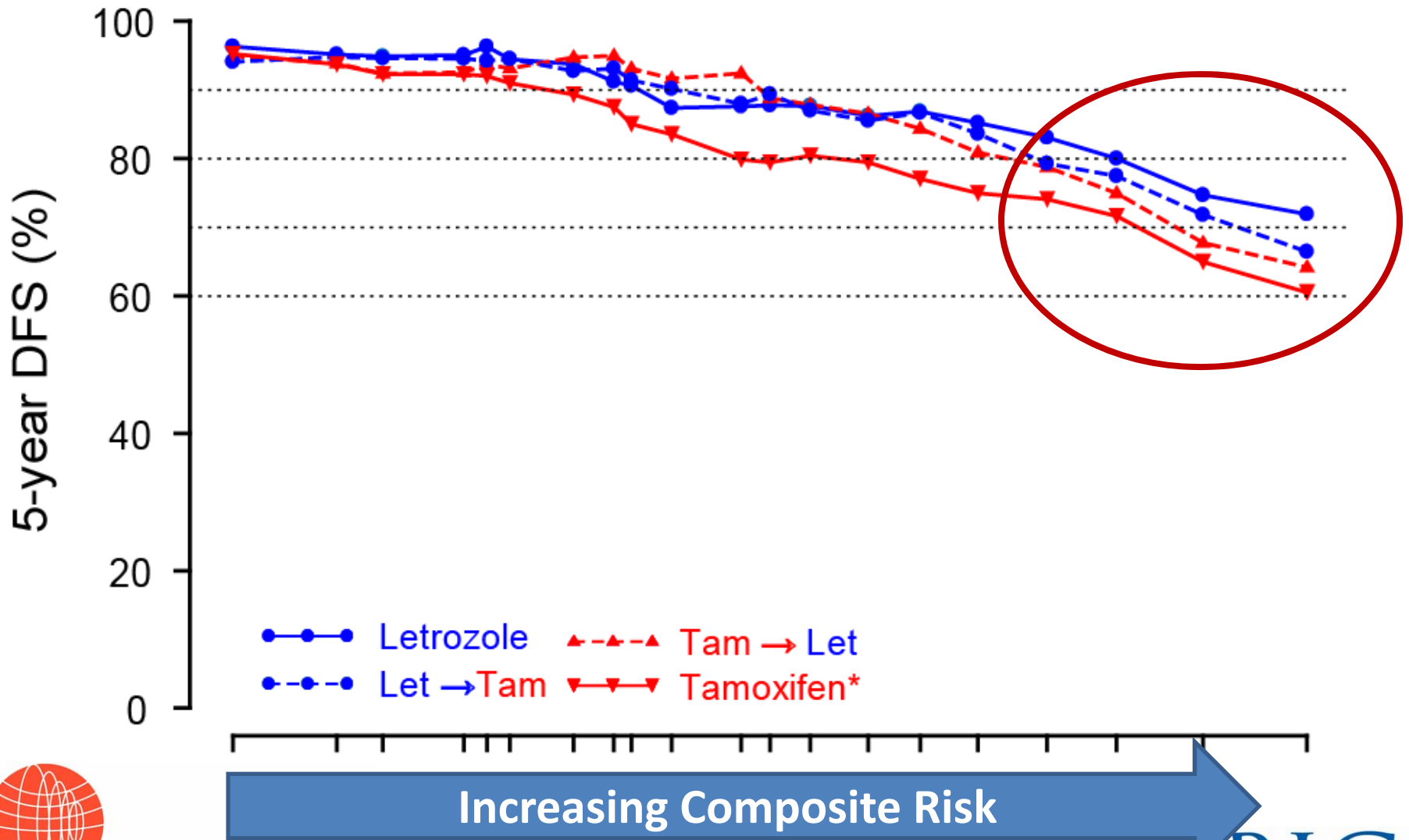


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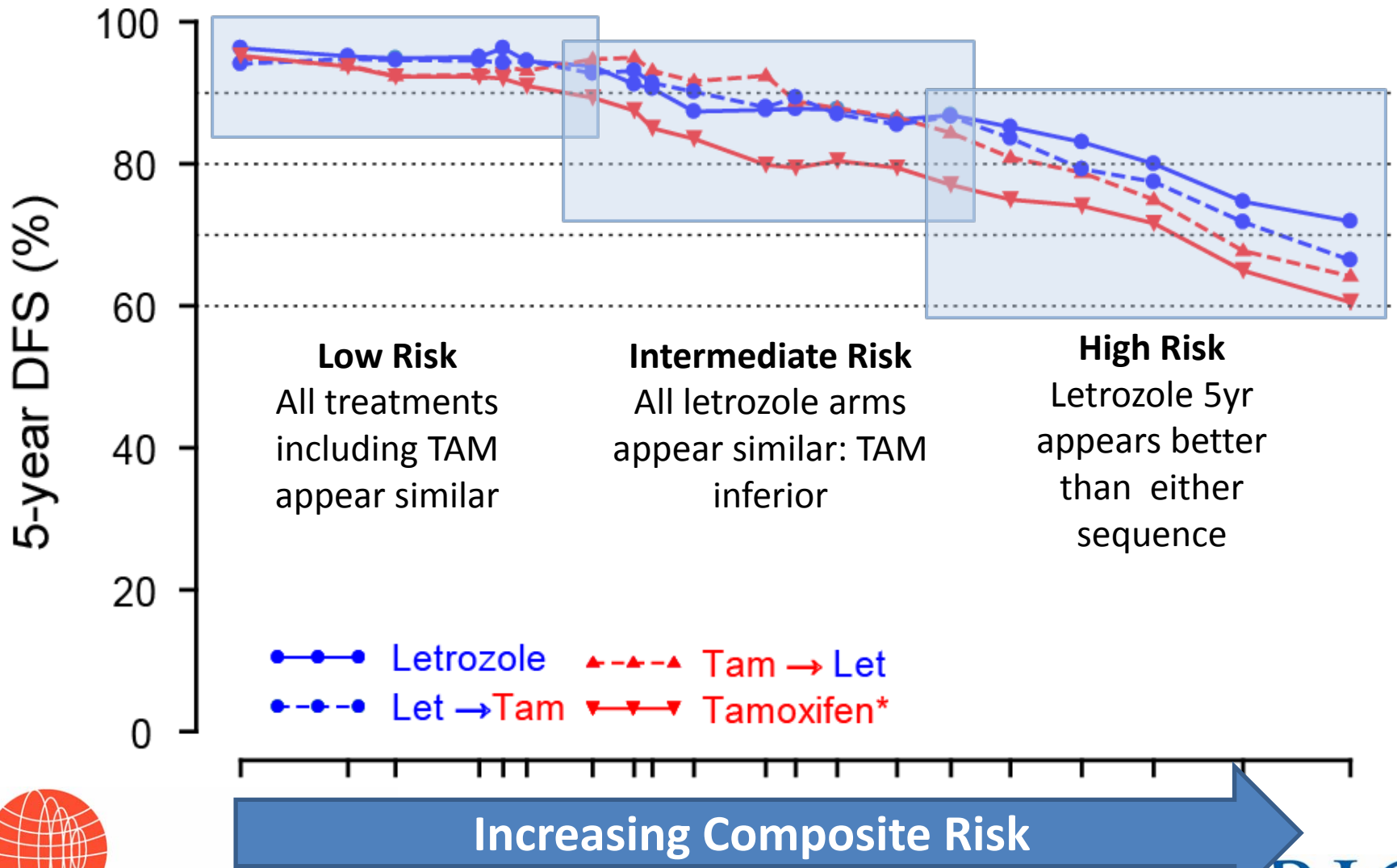
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STEPP 5-year DFS by Composite Risk



STEPP 5-year DFS by Composite Risk



Low Risk
All treatments including TAM appear similar

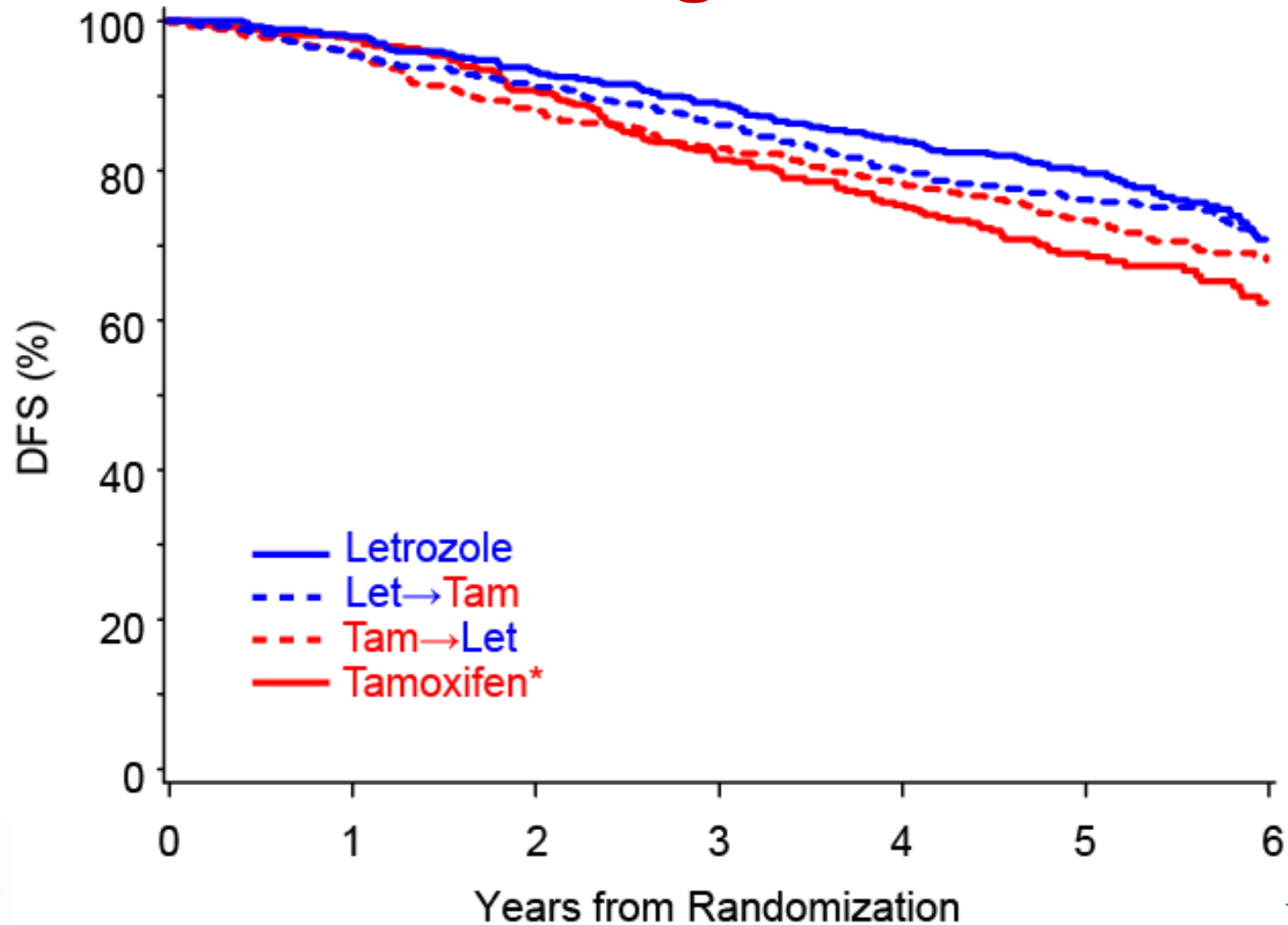
Intermediate Risk
All letrozole arms appear similar: TAM inferior

High Risk
Letrozole 5yr appears better than either sequence

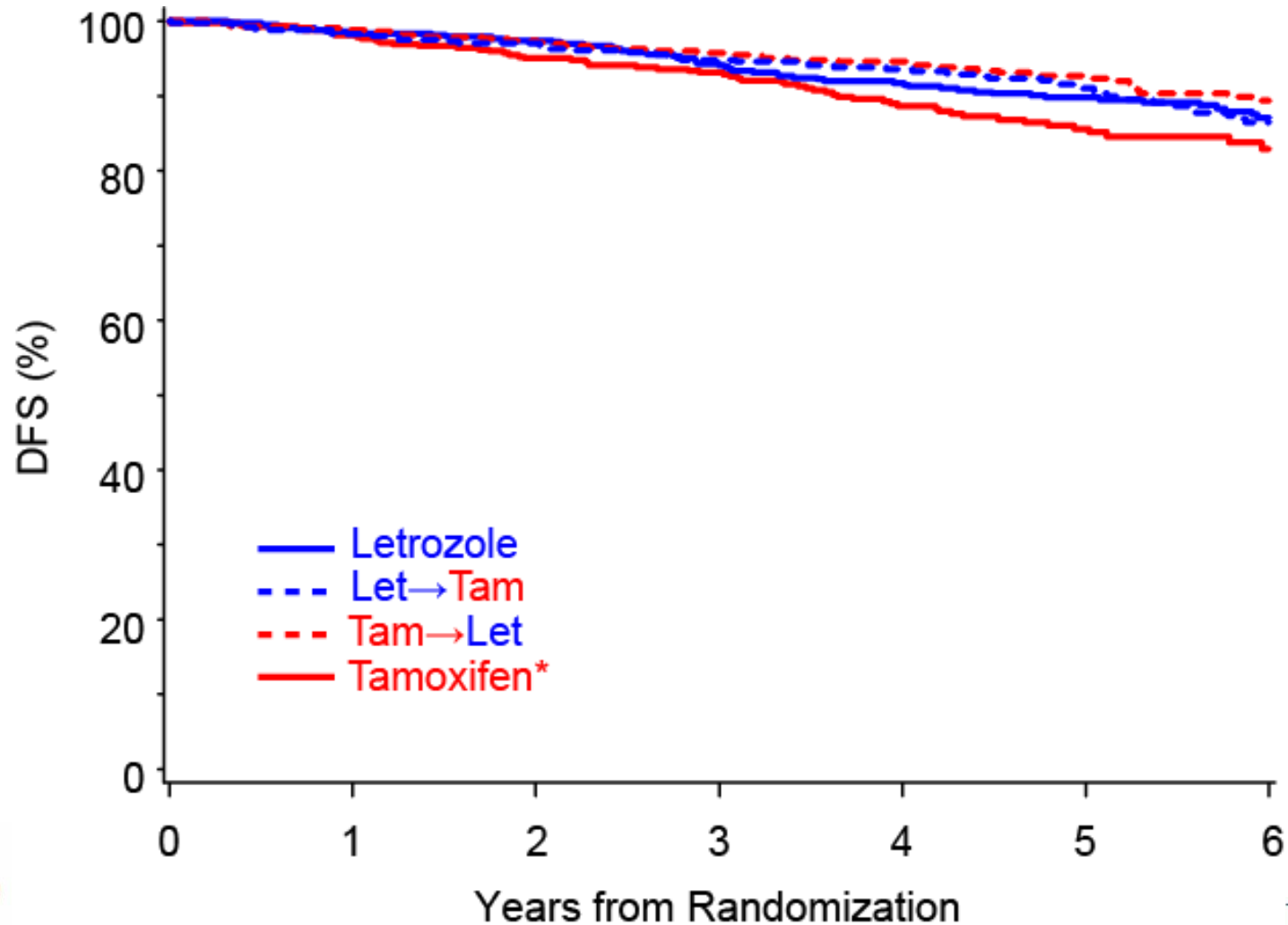
●—●—● Letrozole
 ▲-▲-▲ Tam → Let
●-●-● Let → Tam
 ▼-▼-▼ Tamoxifen*



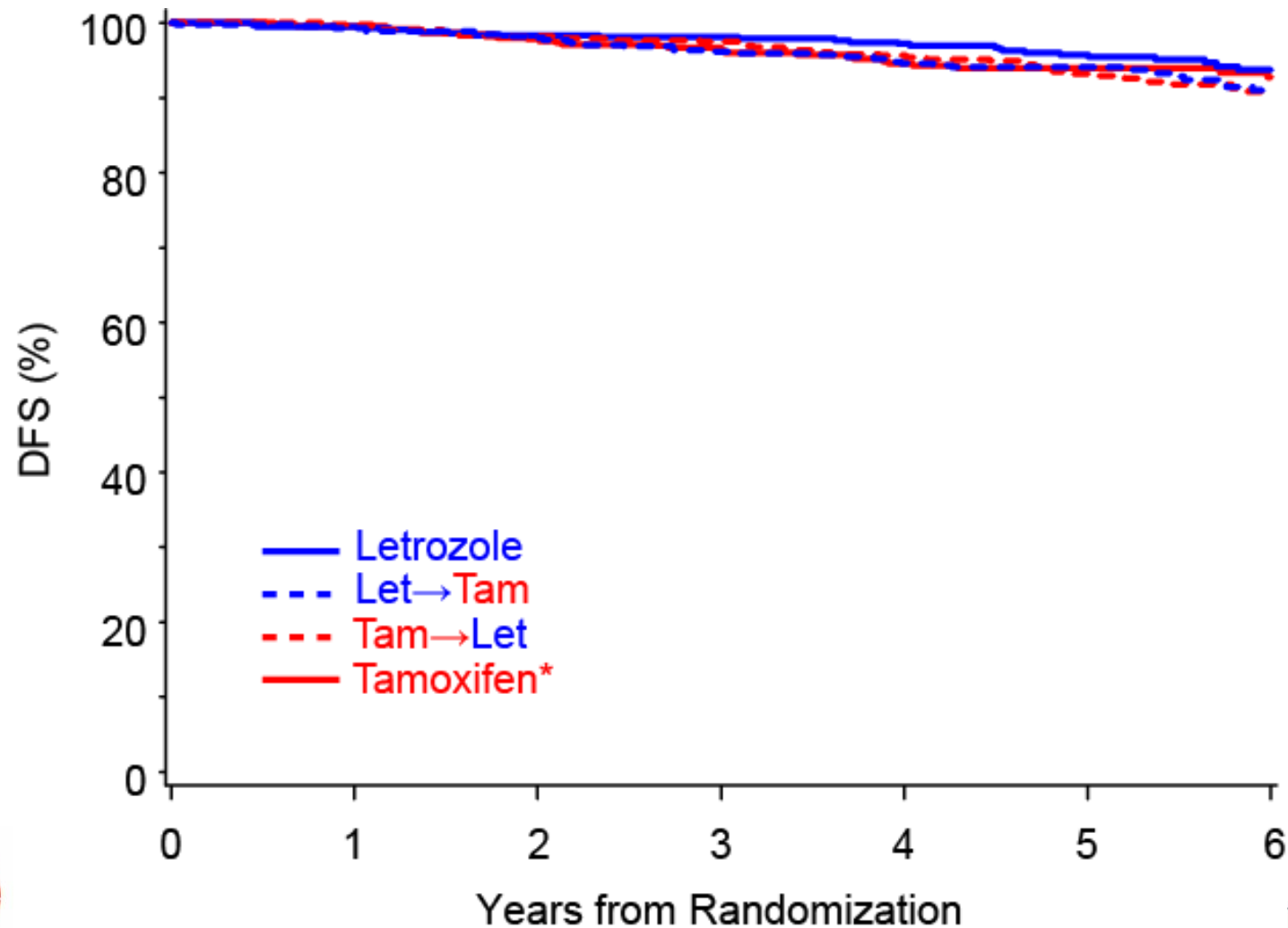
DFS by Increasing Composite Risk: High



DFS by Increasing Composite Risk: Intermediate



DFS by Increasing Composite Risk: Low



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Conclusions

- The particular composite risk profile used in this study was developed within the BIG 1-98 population and may not apply precisely to others

However

- Assessing risk by combining multiple factors appears better than any single factor



Conclusions

- In the BIG 1-98 trial, a composite *prognostic* profile incorporating clinico-pathological data and biological markers was better able to *predict* the relative treatment benefit:
 - Patients at highest risk did best when treated with 5 years letrozole
 - Any of the three letrozole-containing regimens appeared acceptable for those at intermediate risk
 - Lowest risk patients did similarly well with letrozole monotherapy, sequential treatments, or tamoxifen alone



Thanks to...

- The patients participating in the trial
- The pathologists and principal investigators
- The co-investigators, data managers, nurses, study coordinators
- The cooperative groups
- The trial monitors/audit teams
- Susan G. Komen for the Cure Promise Grant
- Novartis

