

Pharmacoeconomic analysis for Tamoxifen or Exemestane with Ovarian Function Suppression for Hormonal Receptor Positive Early Stage Pre- or Peri-Menopausal Breast Cancer Patients in Ontario

KAIWAN RAZA

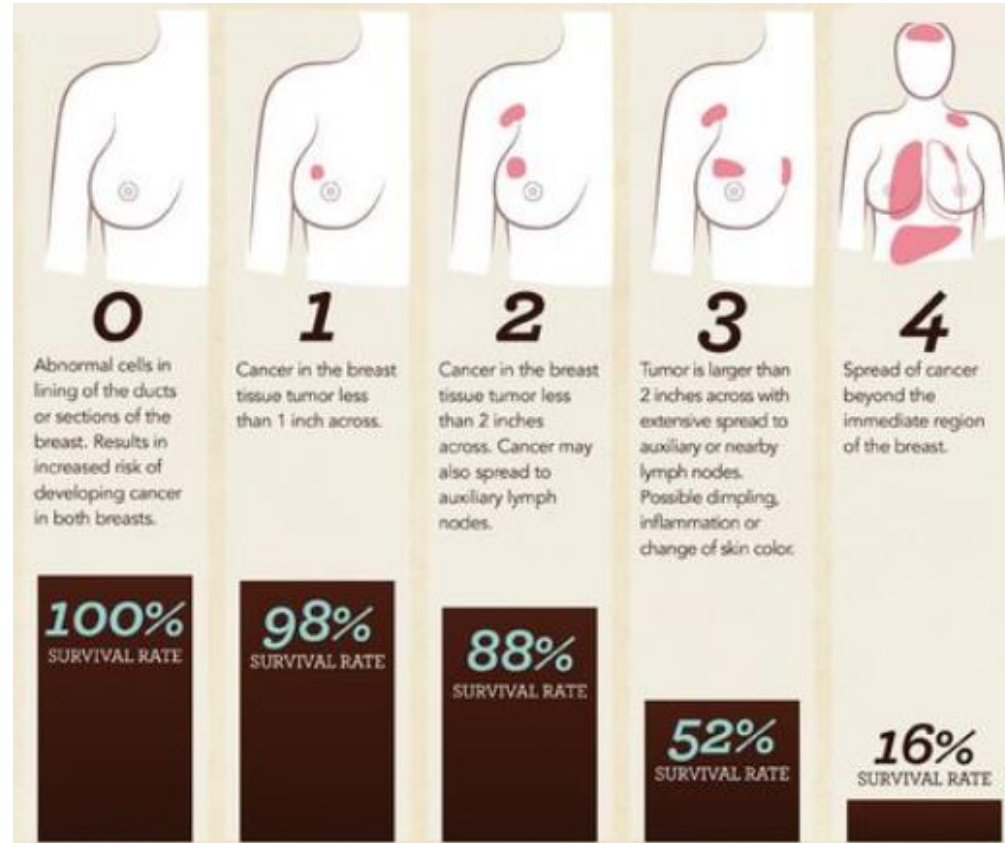
HEALTH ECONOMIST

PHARMACOECONOMICS RESEARCH UNIT, CANCER CARE ONTARIO

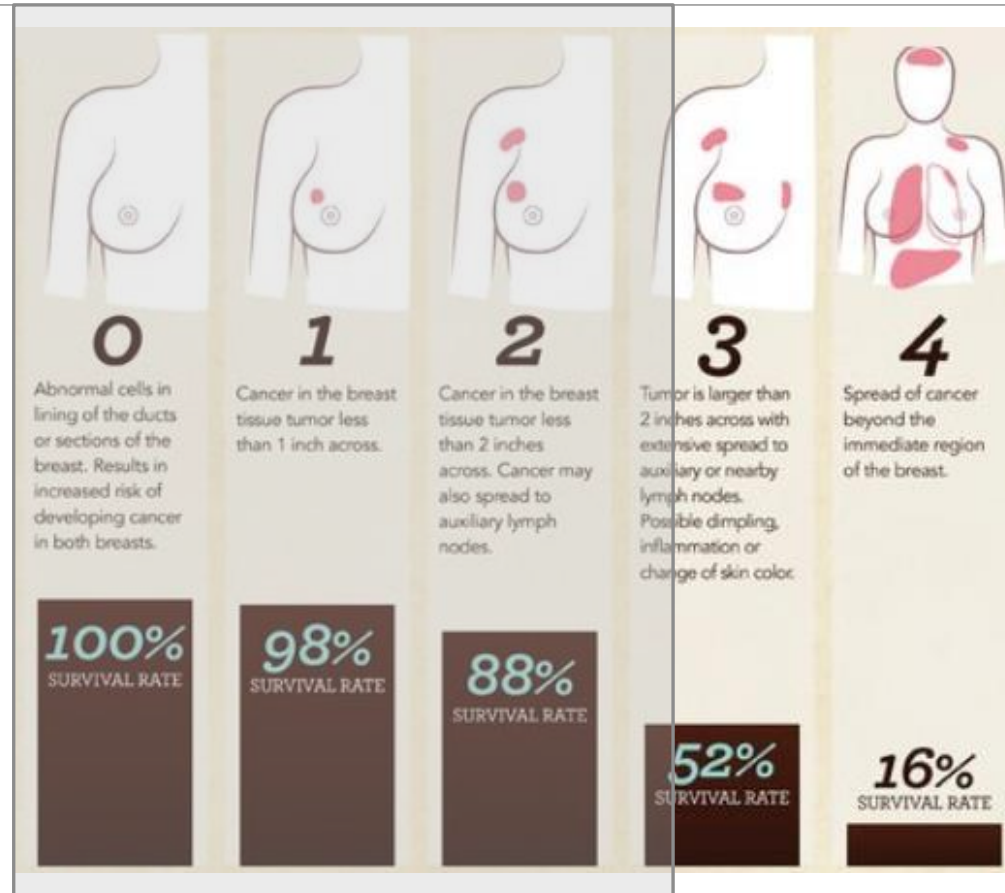
OVERVIEW

- Background
- Research question
- Methods
- Findings
- Conclusion

BREAST CANCER



EARLY BREAST CANCER



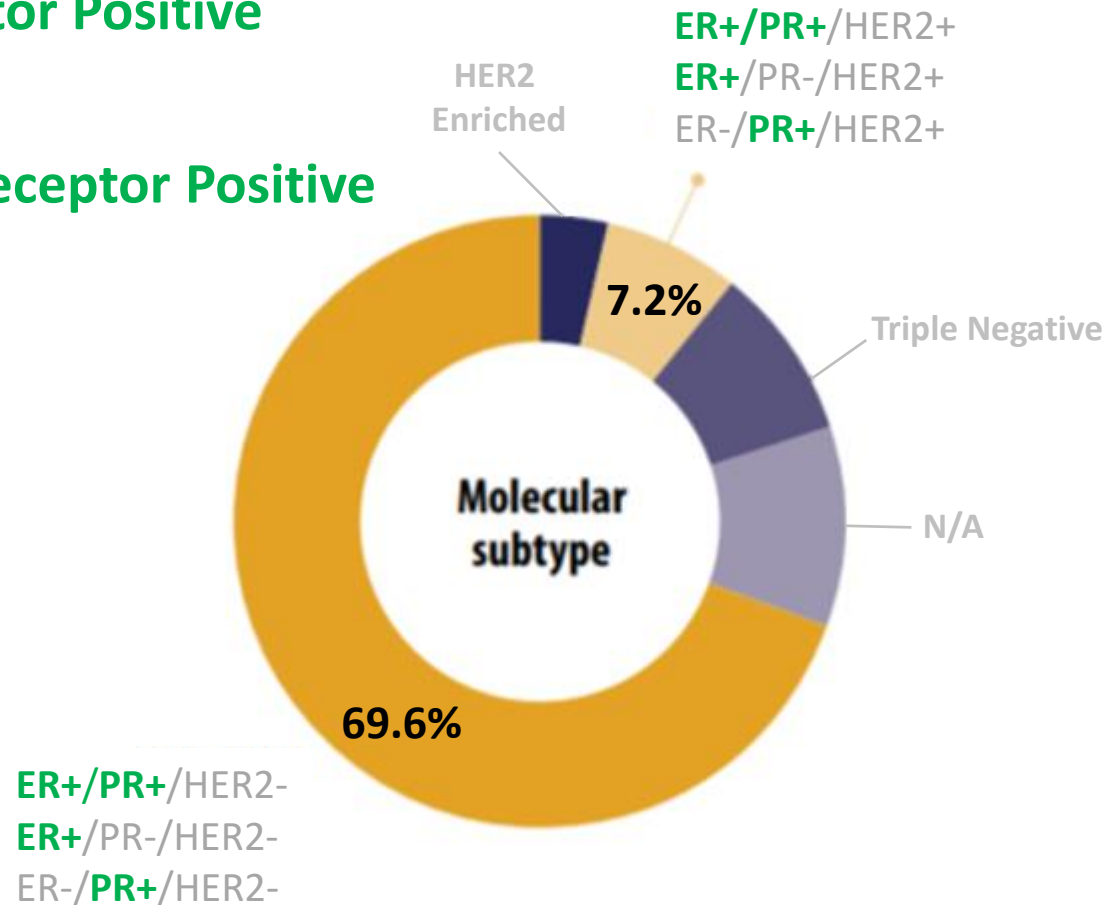
Early Breast Cancer

HORMONE RECEPTOR STATUS

Estrogen-receptor Positive

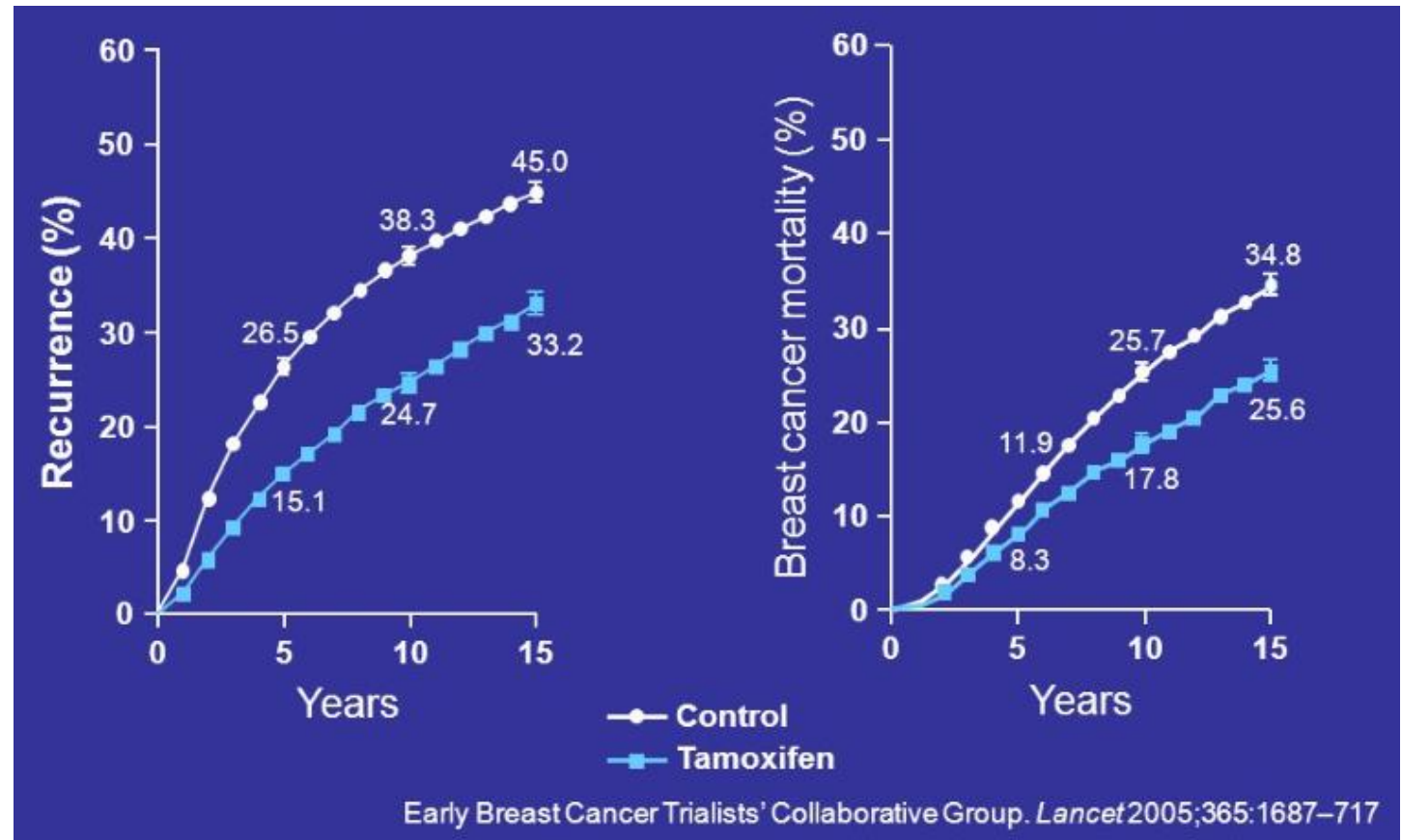
and/or

Progesterone-receptor Positive



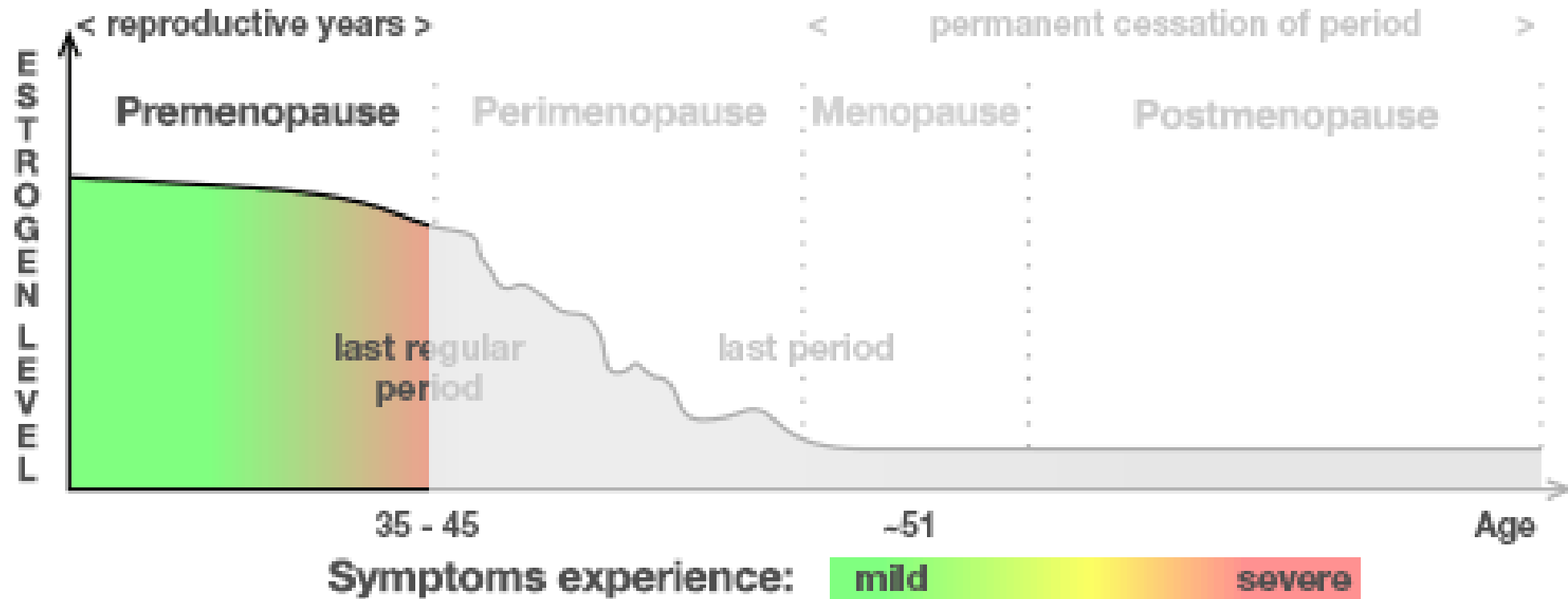
ADJUVANT TREATMENT OPTIONS

- ❑ Adjuvant hormonal treatment improves health outcomes
- ❑ It reduces recurrence and improves mortality
- ❑ Standard of care: **Tamoxifen** for **5-10 years** for HR+ early breast cancer

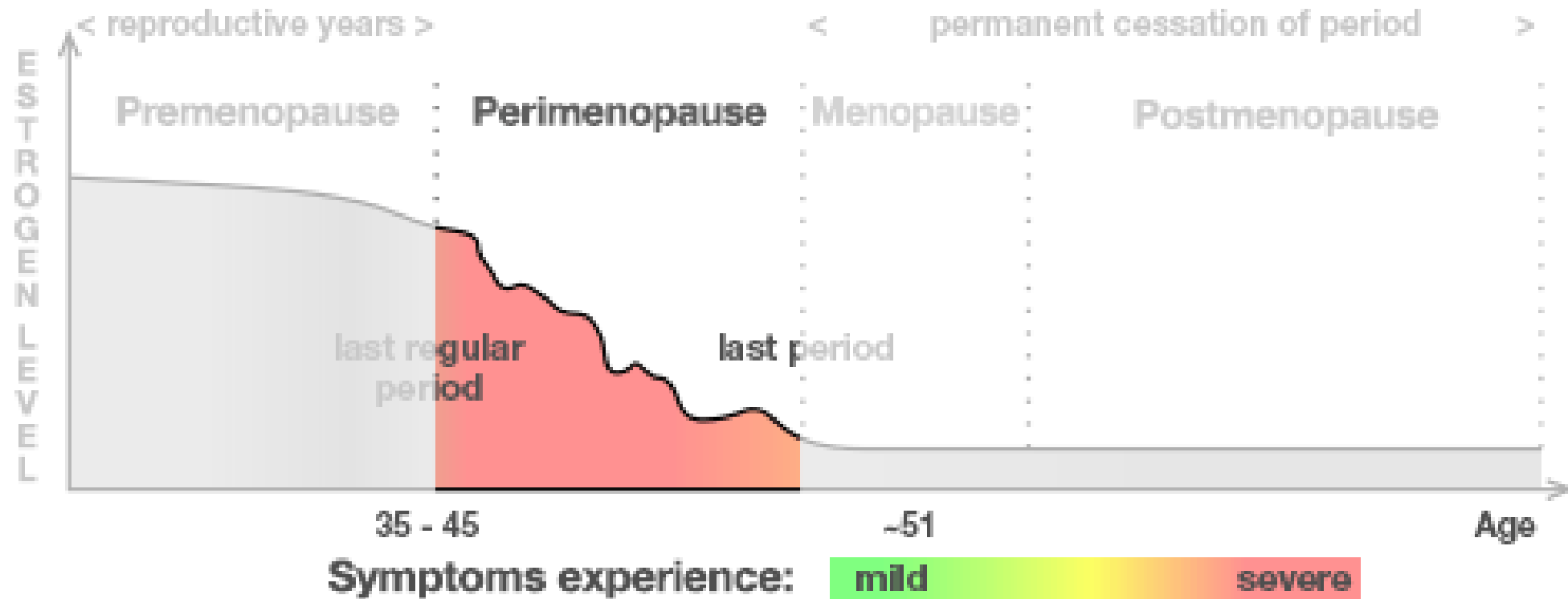


*Can outcomes be improved
in women who are
PRE- or PERI-MENOPAUSAL
with HR+ early breast cancer?*

MENOPAUSE STATUS



MENOPAUSE STATUS



*Can outcomes be improved
in women who are
PRE- or PERI-MENOPAUSAL
with HR+ early breast cancer?*

ADDITIONAL TREATMENT OPTIONS

AROMATASE INHIBITORS

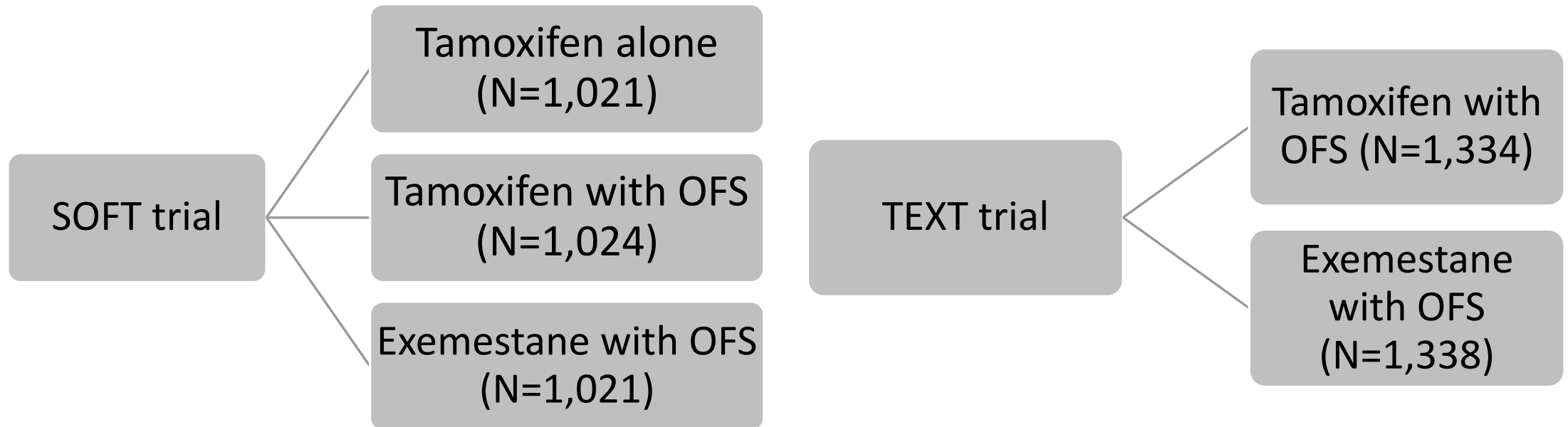
- Aromatase **converts androgens** -> **estrogen** in areas other than ovaries
- By blocking aromatase, exemestane **reduces estrogen** production
- Reduced estrogen **shrinks tumors** dependent on this hormone for growth
- Examples: *exemestane, letrozole*

OVARIAN FUNCTION SUPPRESSION (OFS)

- Using drug therapy/surgery to **prevent ovaries from making estrogen**
- **Shrinks tumor** since it can't get the estrogen it needs for growth
- Examples: *Leuprolide acetate, goserelin acetate*

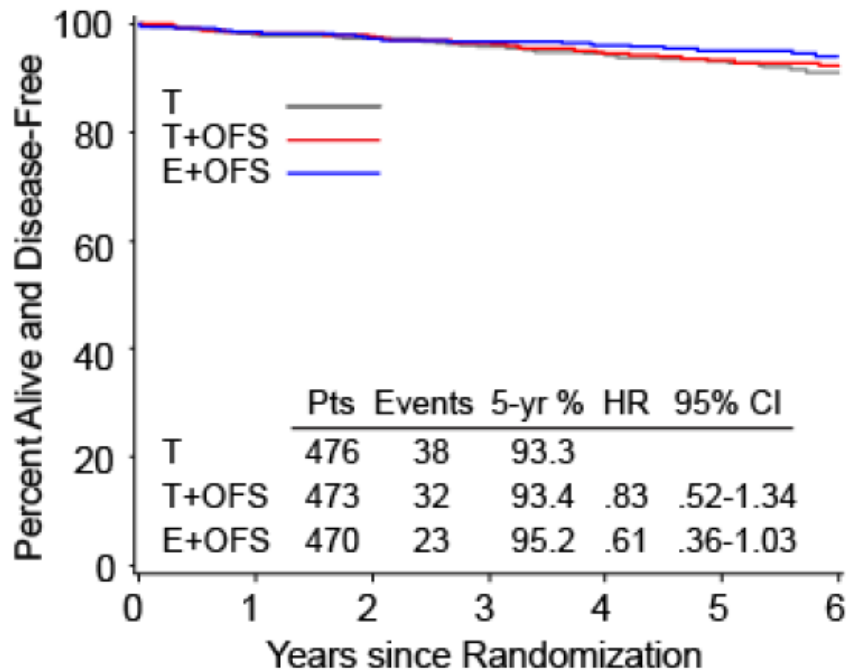
CLINICAL EVIDENCE

- Two trials conducted to compare efficacy of adjuvant treatment for HR+ EBC in pre or peri-menopausal women



SOFT TRIAL RESULTS (NO PRIOR CHEMO)

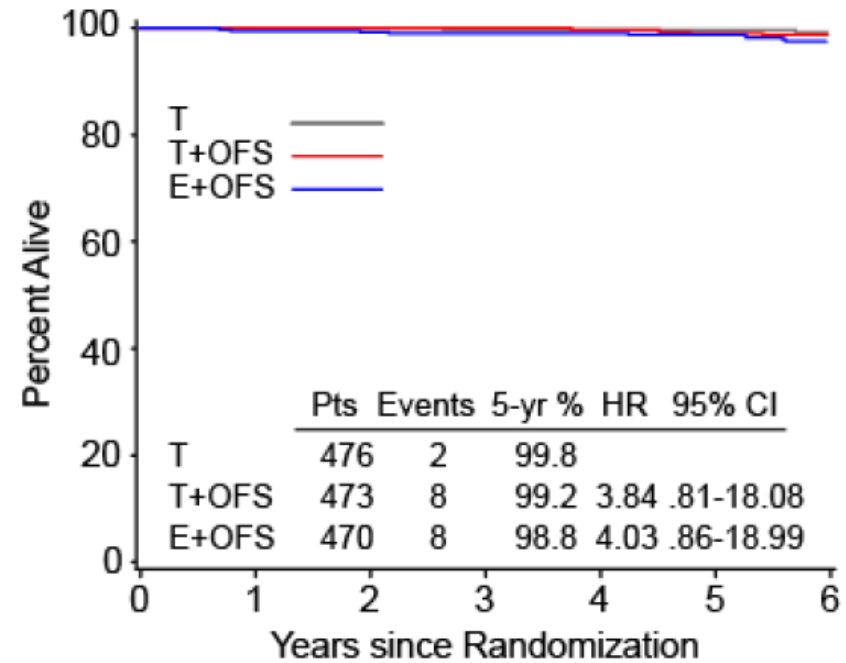
DISEASE-FREE SURVIVAL (DFS)



Number at Risk

	0	1	2	3	4	5	6
T	476	457	441	424	370	271	166
T+OFS	473	453	446	427	369	279	175
E+OFS	470	441	423	411	370	274	173

OVERALL SURVIVAL (OS)

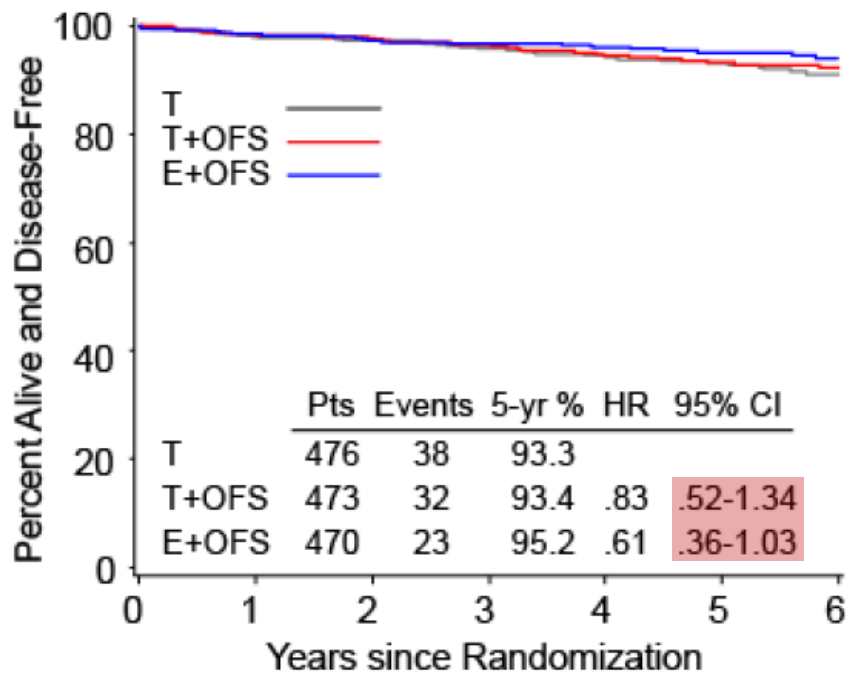


Number at Risk

	0	1	2	3	4	5	6
T	476	472	459	449	396	295	183
T+OFS	473	466	462	450	401	300	190
E+OFS	470	454	445	435	397	293	184

SOFT TRIAL RESULTS (NO PRIOR CHEMO)

DISEASE-FREE SURVIVAL (DFS)

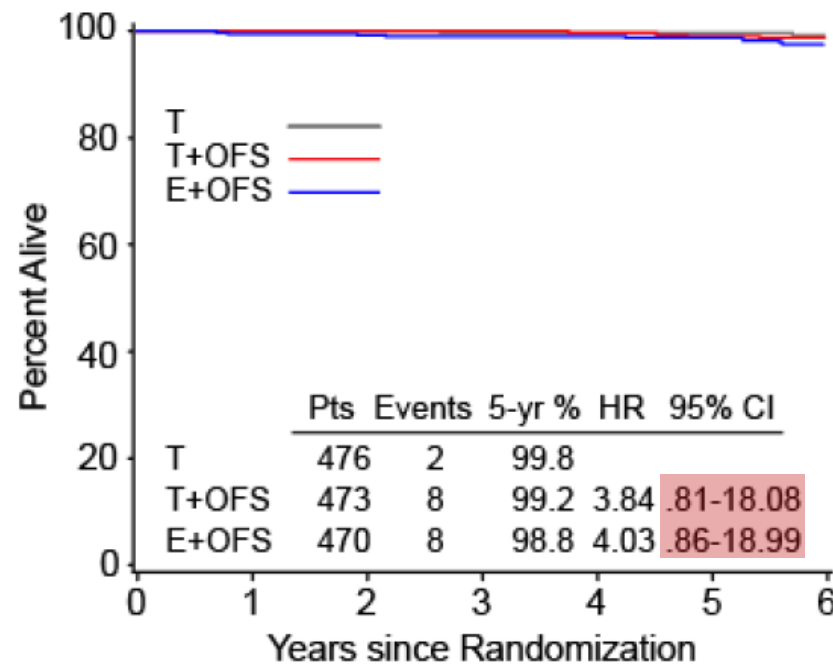


Difference **NOT** statistically significant

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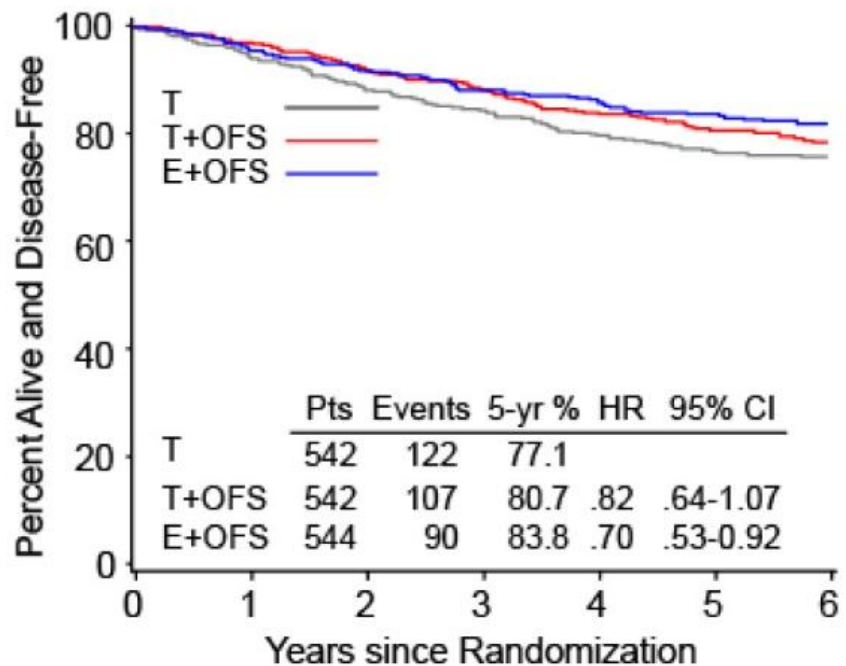
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Number at Risk

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SOFT TRIAL RESULTS (PRIOR CHEMO)

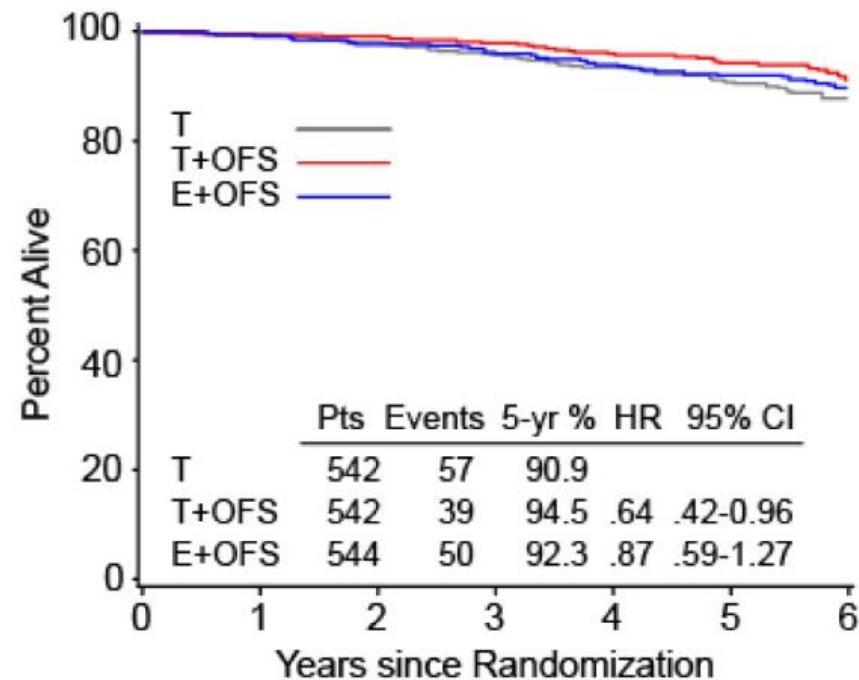
DISEASE-FREE SURVIVAL (DFS)



Number at Risk

T	542	493	454	423	350	253	142
T+OFS	542	513	481	450	372	277	173
E+OFS	544	512	484	450	386	269	163

OVERALL SURVIVAL (OS)

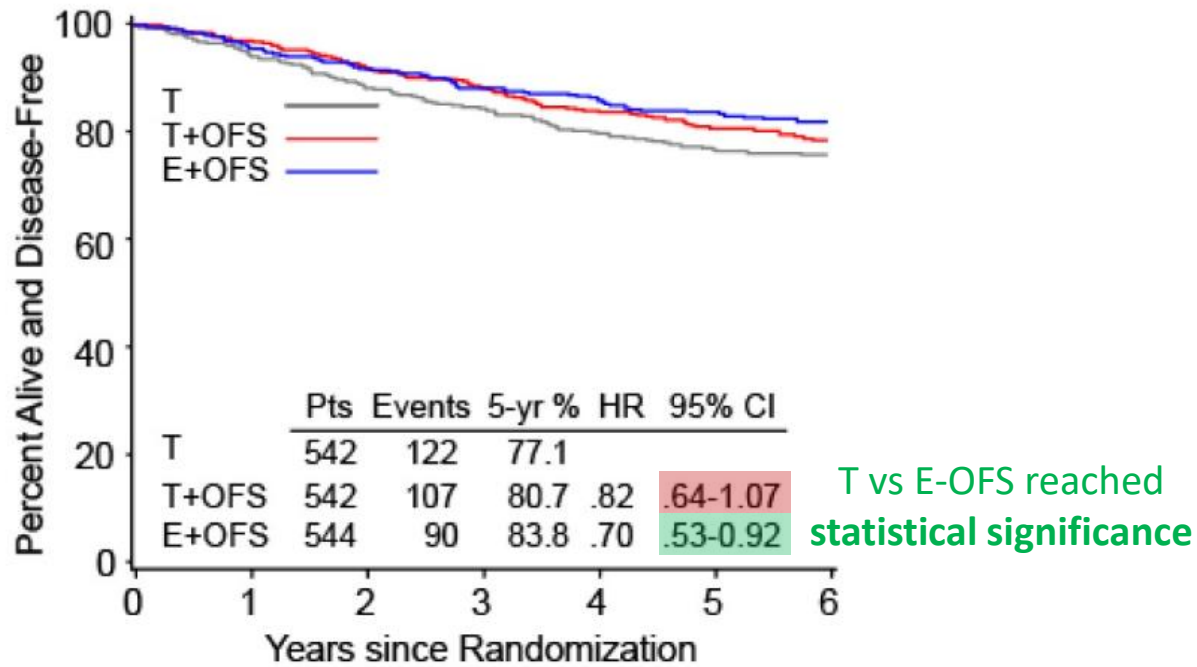


Number at Risk

542	532	515	491	422	310	180
542	530	522	504	437	330	205
544	535	521	500	431	306	186

SOFT TRIAL RESULTS (PRIOR CHEMO)

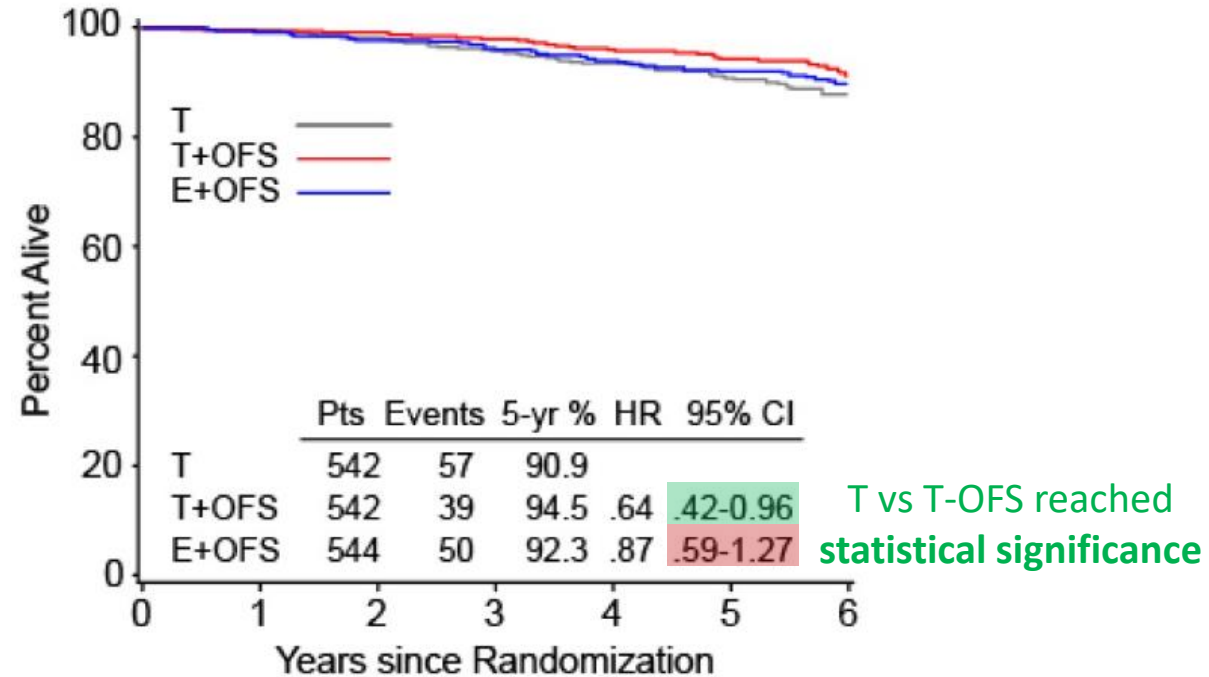
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OVERALL SURVIVAL (OS)



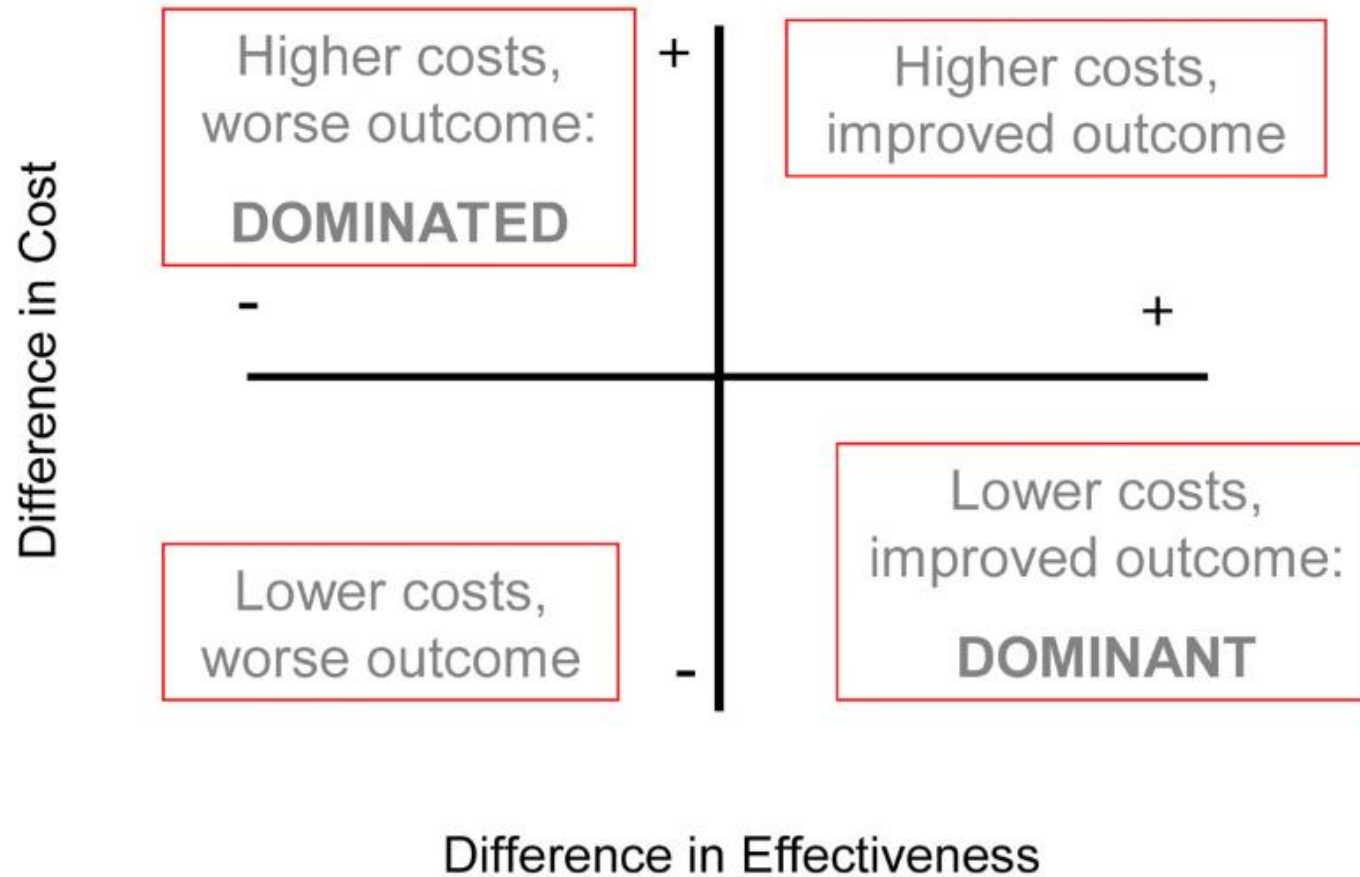
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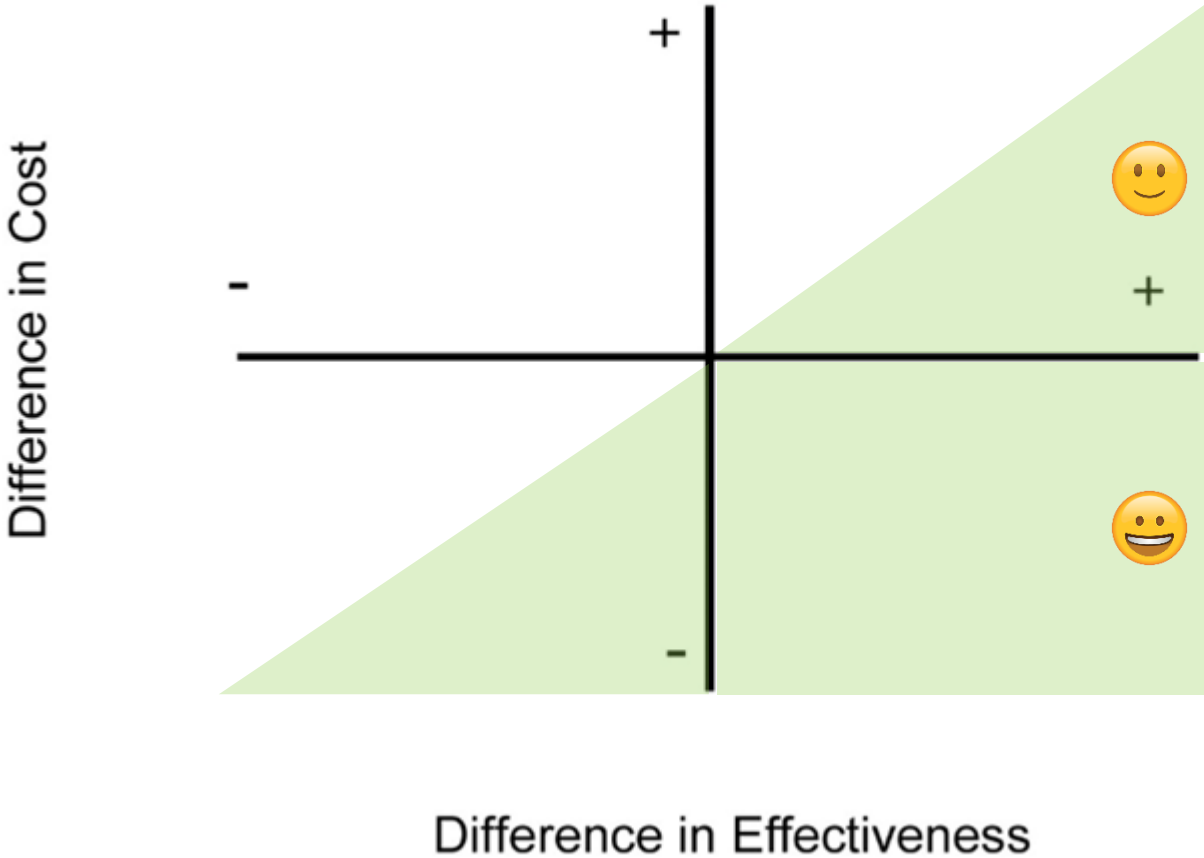
OVARIAN FUNCTION SUPPRESSION

appears to help pre- or peri-menopausal women with HR+ early breast cancer who have received or are receiving chemotherapy

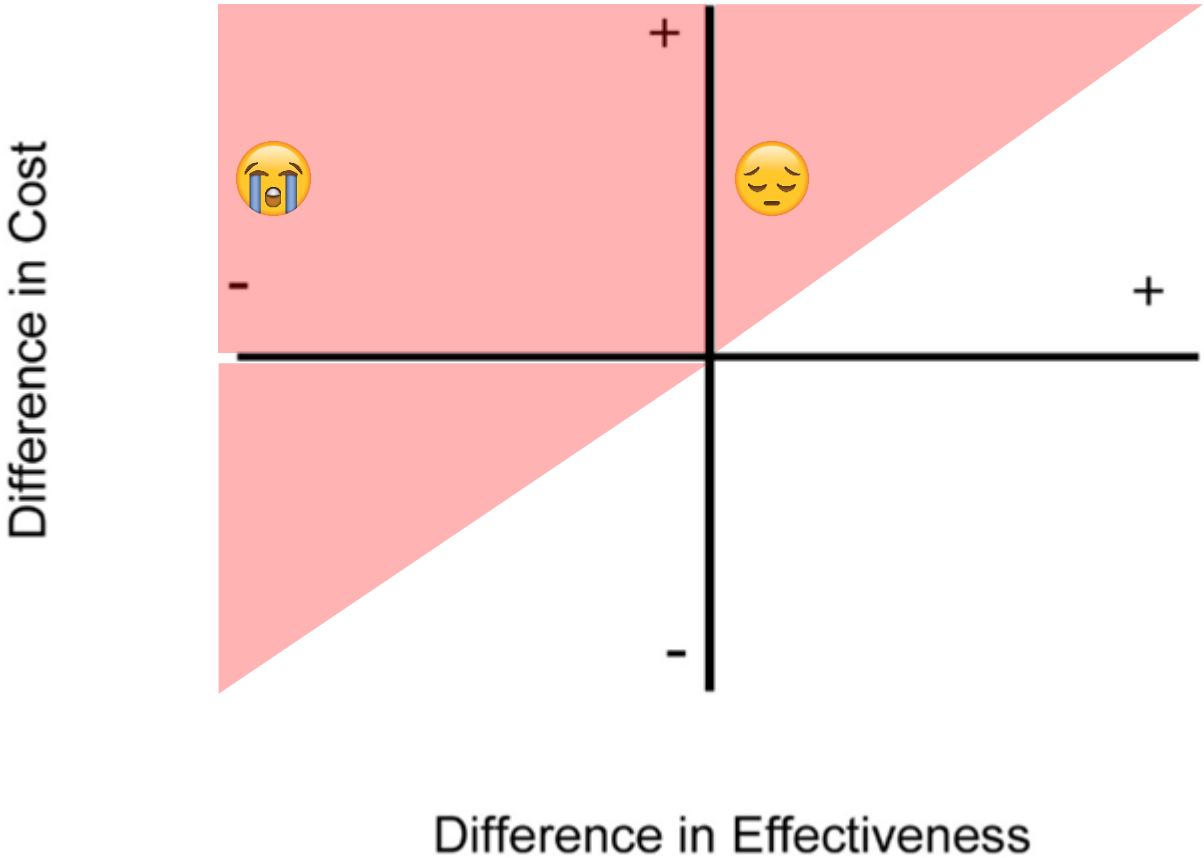
COST-EFFECTIVENESS QUESTION



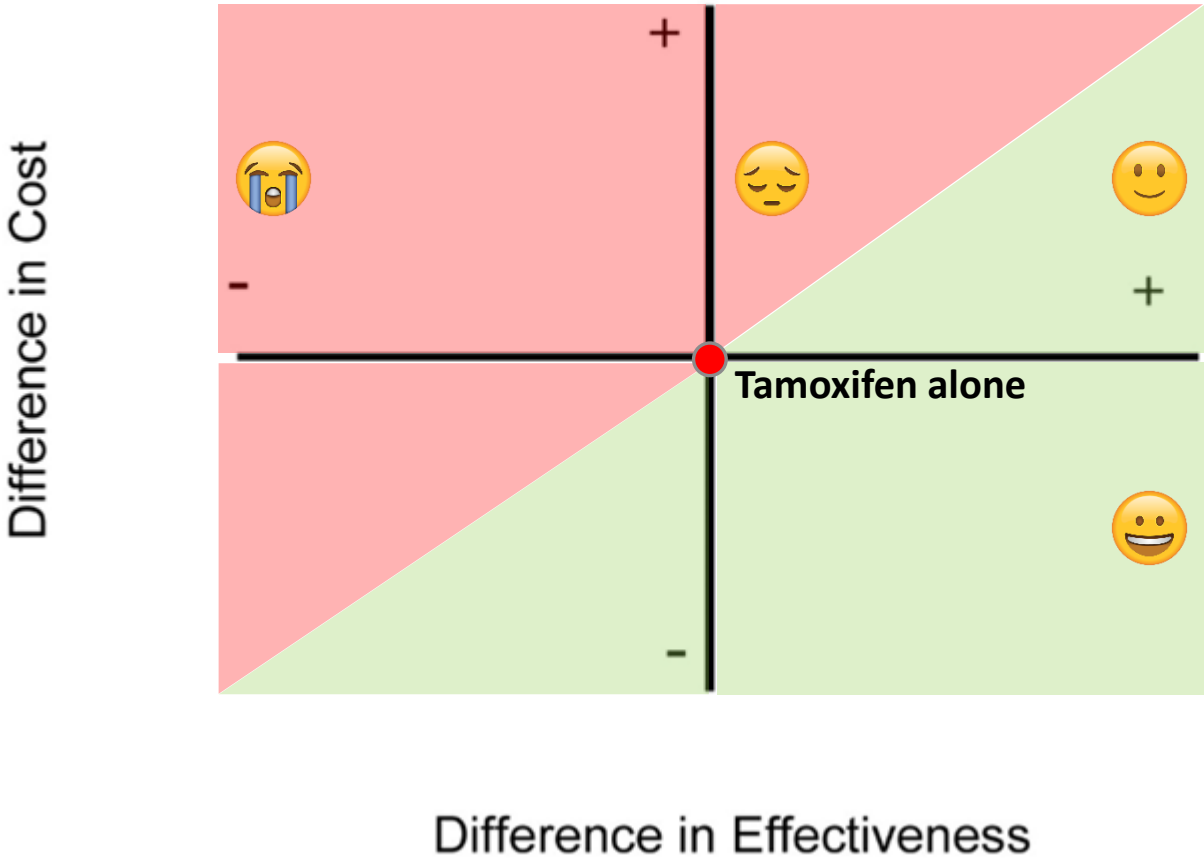
COST-EFFECTIVENESS QUESTION



COST-EFFECTIVENESS QUESTION



COST-EFFECTIVENESS QUESTION



- Tamoxifen-OFS
- Exemestane-OFS



STUDY OVERVIEW

Analysis Type

- Cost-effectiveness
- Cost-utility

Population

- HR+ Early Stage Pre- or Peri-Menopausal Breast Cancer
- Received prior/ongoing chemotherapy

Outcome

- Life-years gained
- Quality-adjusted life-years gained

Intervention

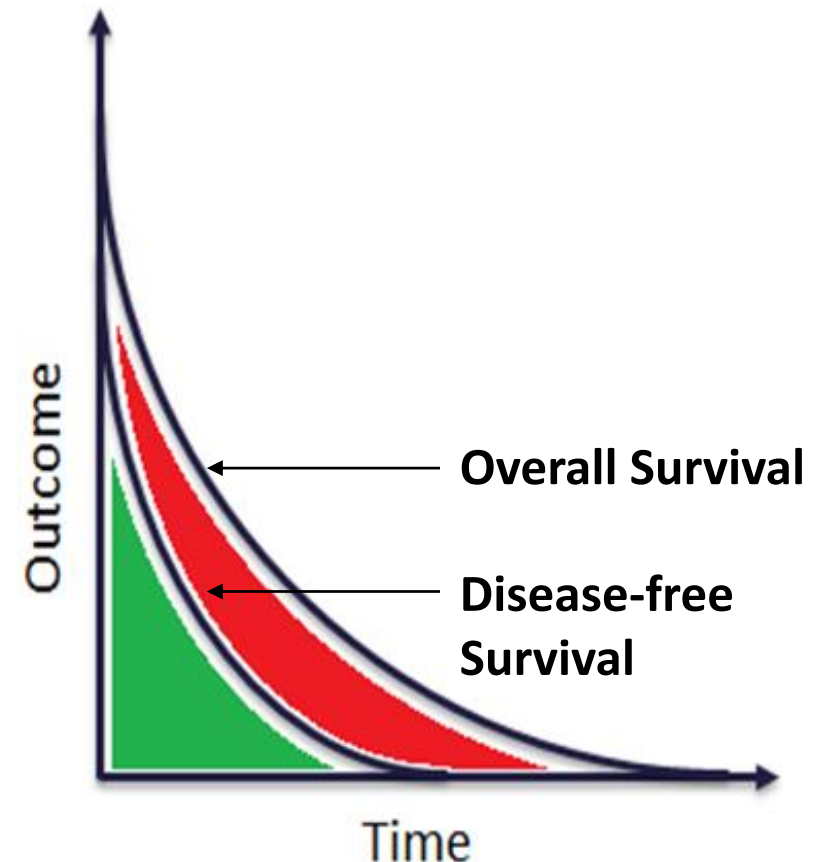
- Exemestane + OFS (E-OFS)
- Tamoxifen + OFS (T-OFS)

Comparator

- Tamoxifen alone

MODEL OVERVIEW

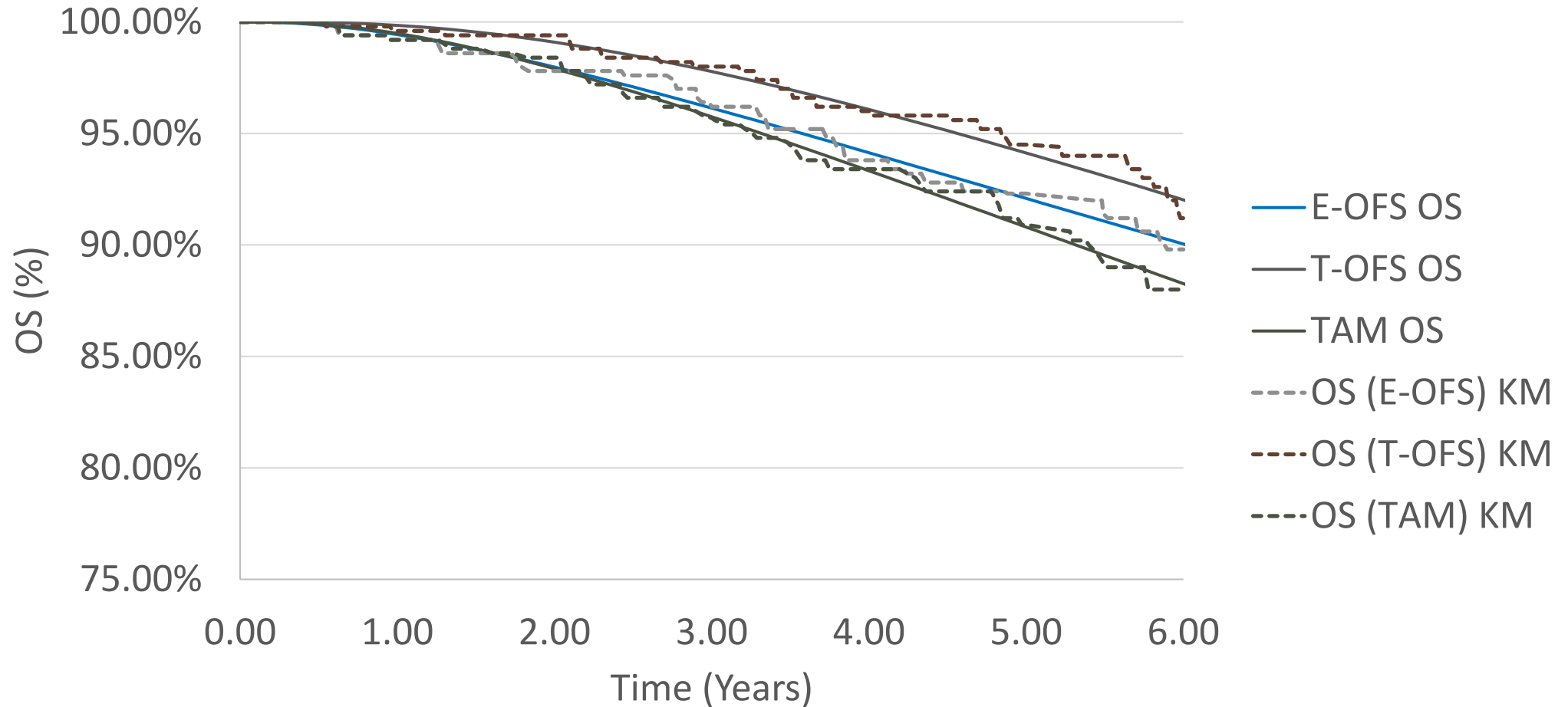
- ❑ **Model Structure:** Partitioned survival
- ❑ **Health States:** (1) Disease-free survival; (2) Loco-regional recurrence; (3) Distant recurrence and (4) Death
- ❑ **Perspective:** MoHLTC
- ❑ **Cycle Length:** 1 month
- ❑ **Time Horizon:** Lifetime (up to 70 years)
 - ❑ *Starting age = 40 years*
- ❑ **Discounting:** 1.5% per annum



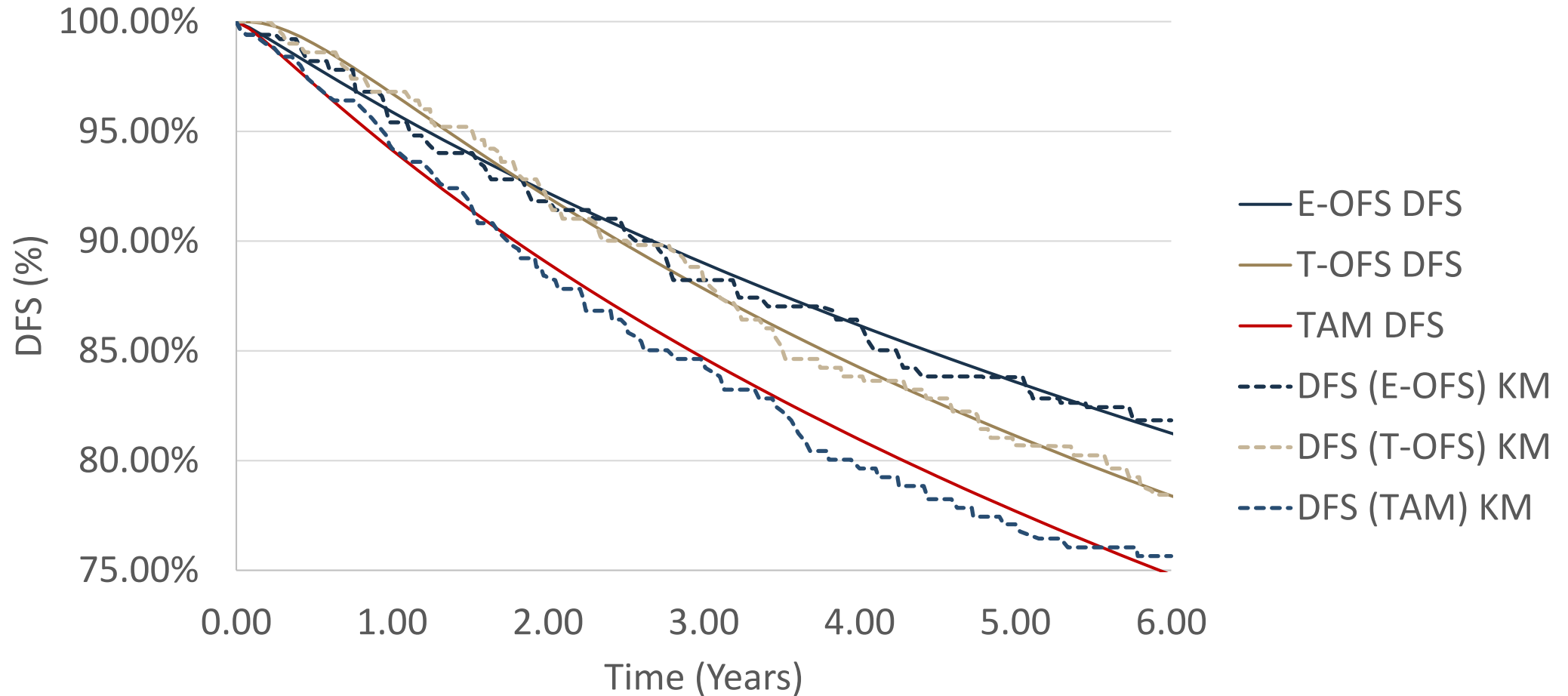
EFFICACY

- Parametric survival analysis conducted on Kaplan-Meier OS and PFS curves using R
- Distributions deemed best-fitting selected using
 - Statistical criteria
 - Visual inspection
 - Clinical plausibility
- Results extrapolated for 70 years and age-related mortality values applied
- Progression split into loco-regional or distant recurrence based on % first events
- Model results validated against trial results to ensure conservative approach using most recent data

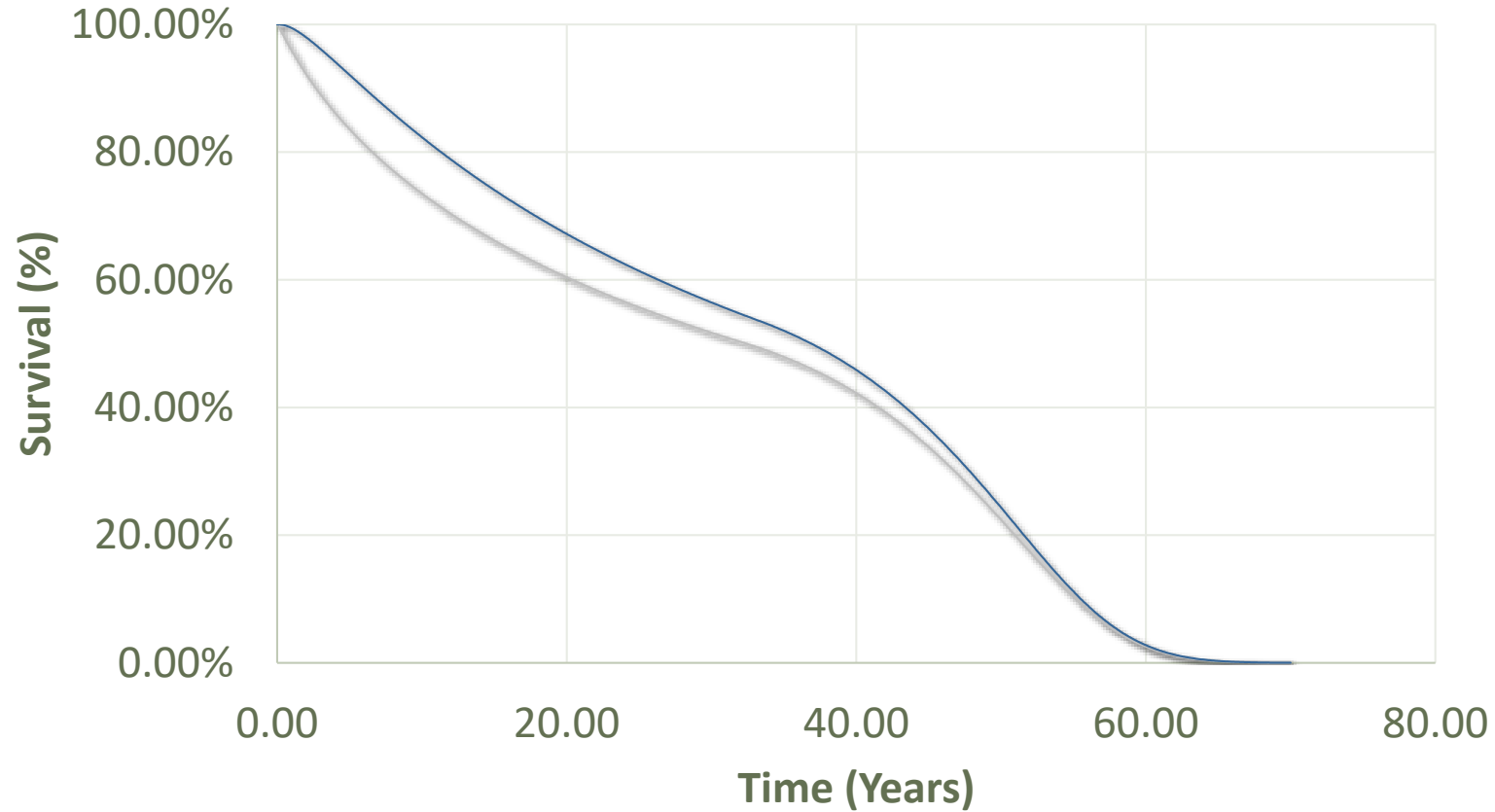
OVERALL SURVIVAL



DISEASE FREE SURVIVAL



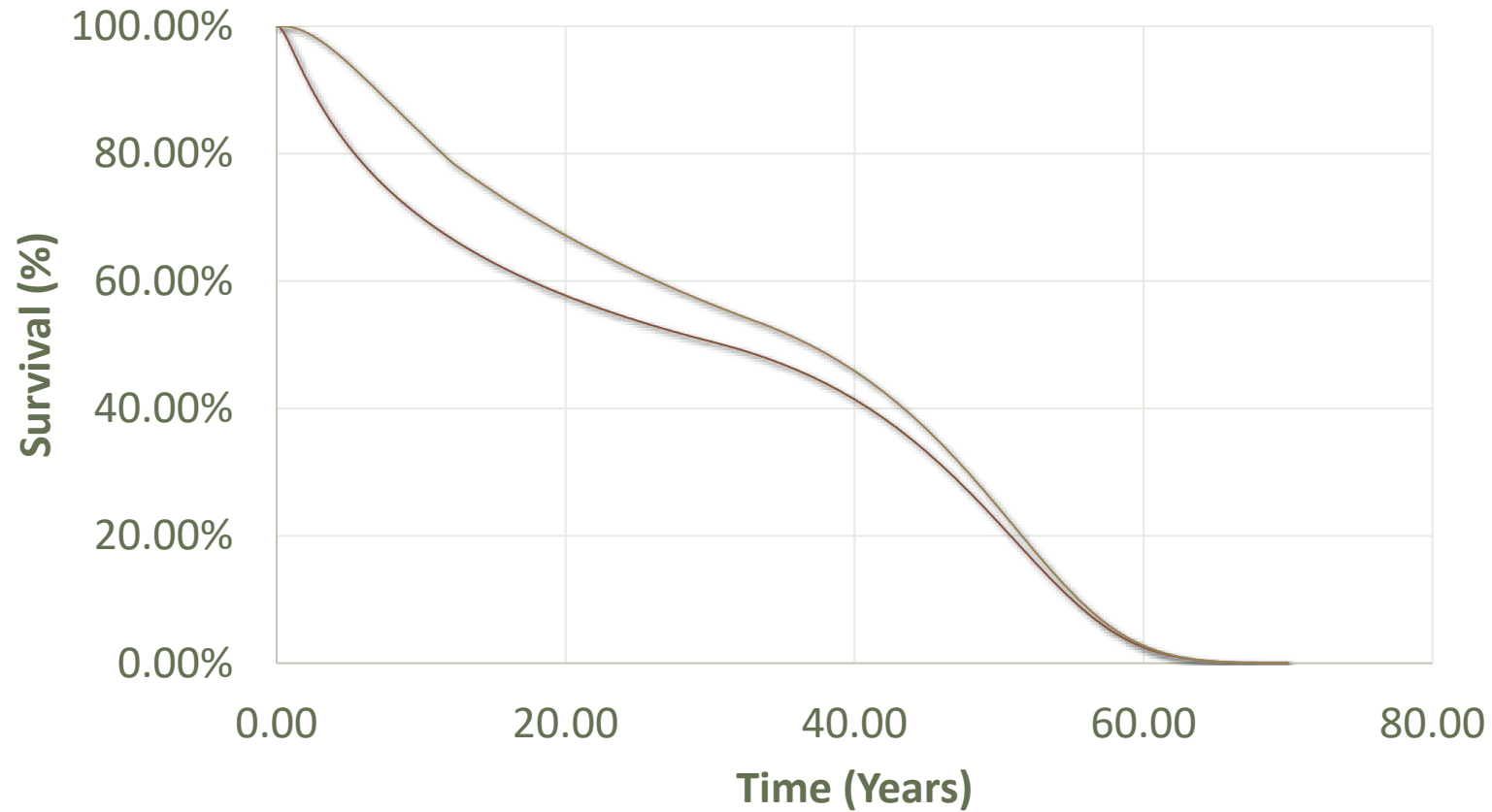
EXEMESTANE-OFS SURVIVAL



Parametric Distributions	
DFS	Generalized gamma
OS	Lognormal

— E-OFS DFS — E-OFS OS

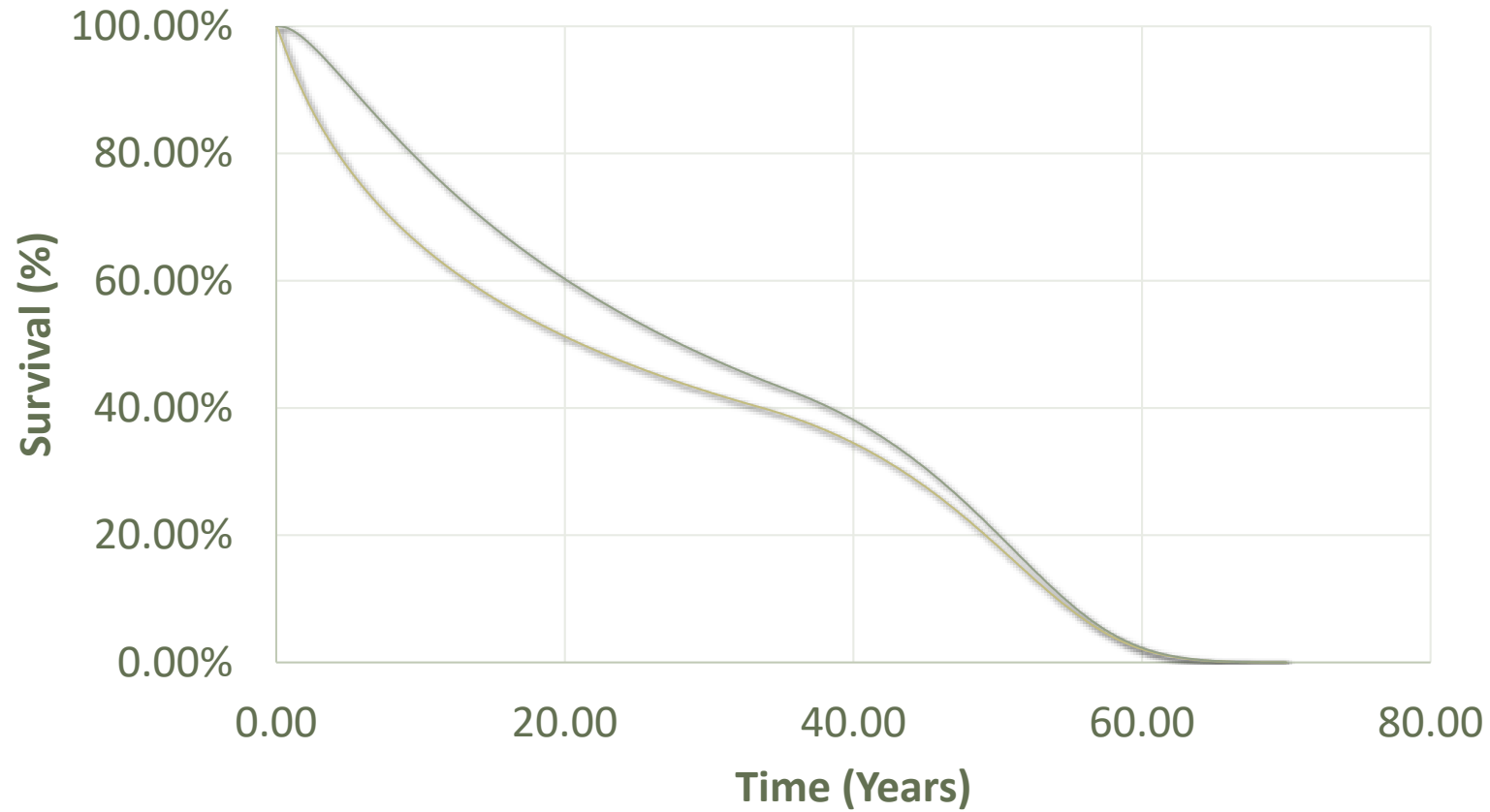
TAMOXIFEN-OFS SURVIVAL



— T-OFS DFS — T-OFS OS

Parametric Distributions	
DFS	Generalized gamma
OS	Lognormal

TAMOXIFEN SURVIVAL



— TAM DFS — TAM OS

Parametric Distributions	
DFS	Generalized gamma
OS	Lognormal

SAFETY

- Grade III/IV adverse event (AE) data obtained from TEXT trial for E-OFS and T-OFS and SOFT trial for tamoxifen to conduct:
 - Health-related quality of life analysis
 - AE management costing analysis

	E-OFS	T-OFS	Tamoxifen
Number of Patients	2318	2325	1006
Any grade 3+ adverse event	710	683	238
<i>Musculoskeletal symptoms</i>	254	122	63
<i>Hot flushes</i>	232	279	76
<i>Hypertension</i>	151	169	54
<i>Insomnia</i>	89	100	29
<i>Depression</i>	87	102	38

COSTS

- Drug costs obtained from the ODB formulary
- Dosing regimen obtained from SOFT trial
- Administration cost significantly higher for OFS use
- Adverse event costs obtained using Ontario Case Costing Initiative data
- Post-treatment follow-up include MRI, mammogram, and physician visits
- Progression costs based on Ontario population-based study
- Indirect costs not included within model

UTILITY VALUES

- ❑ QoL measures captured within trial couldn't be converted to a preference-based utility.
- ❑ Literature review conducted on HRQoL measures for population of interest
- ❑ Utility values obtained from a retrospective study
- ❑ Disutility estimates for each adverse event applied for patients on treatment
- ❑ Values for progression captured from literature and assumed to be the same between arms

ANALYSIS

- Base-case analysis results produced total number of LYs, QALYs, and costs for each health state
- One-way sensitivity analyses on all parameters of uncertainty were conducted
- Probabilistic sensitivity analyses conducted to explore uncertainty in the model parameters
- Scenarios analyses exploring long-term DFS and OS benefits were conducted

BASE-CASE RESULTS

	Tamoxifen	E-OFS	T-OFS
COSTS	\$98,482	\$108,422	\$130,741
Disease-Free	\$7,307	\$38,647	\$36,560
Recurrence	\$91,175	\$69,775	\$94,180
LIFE YEARS	22.0	23.9	24.1
Disease-Free	19.2	21.8	21.2
Recurrence	2.8	2.1	2.9
QALYS	16.6	18.1	18.1
Disease-Free	14.8	16.8	16.3
Recurrence	1.8	1.3	1.9

BASE-CASE RESULTS

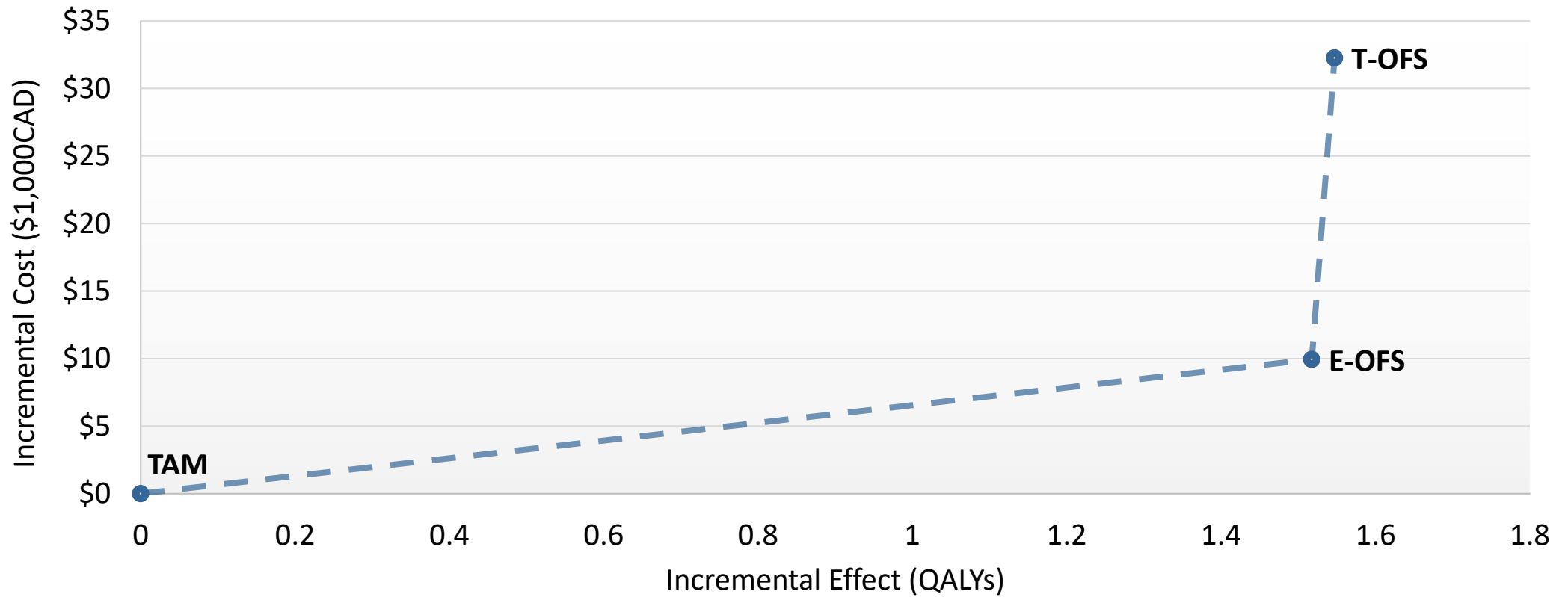
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QALYS	16.6	18.1	18.1
Disease-Free	14.8	16.8	16.3
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RECURRENCE COSTS ARE HIGH!

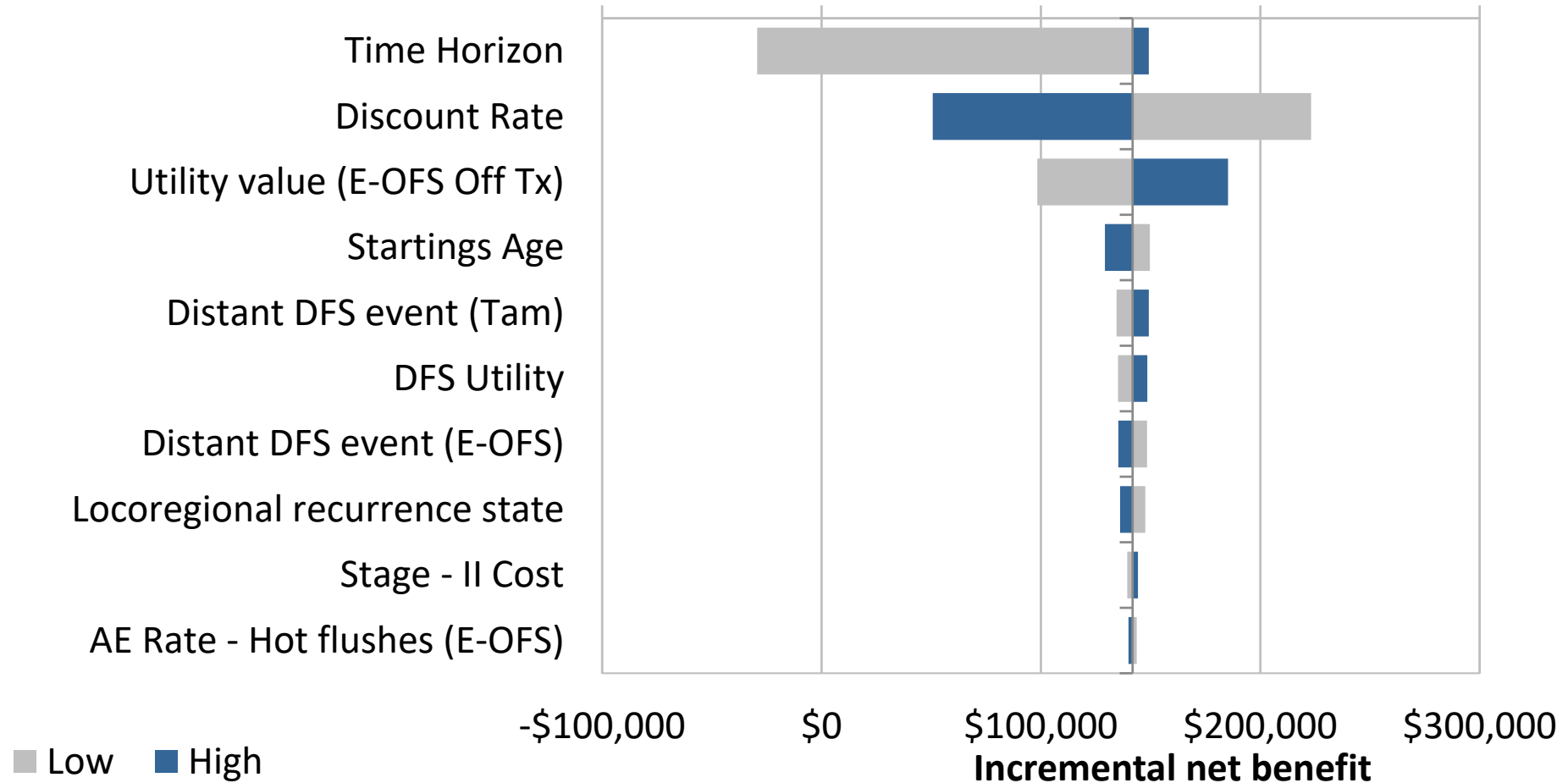
BASE-CASE RESULTS

	Tamoxifen	E-OFS	T-OFS	E-OFS vs Tam	T-OFS vs E-OFS
COSTS	\$98,482	\$108,422	\$130,741	\$9,940	\$22,319
Disease-Free	\$7,307	\$38,647	\$36,560	\$31,341	-\$2,087
Recurrence	\$91,175	\$69,775	\$94,180	-\$21,401	\$24,406
LIFE YEARS	22.0	23.9	24.1	1.9	0.1
Disease-Free	19.2	21.8	21.2	2.7	-0.7
Recurrence	2.8	2.1	2.9	-0.7	0.8
QALYS	16.6	18.1	18.1	1.5	0.0
Disease-Free	14.8	16.8	16.3	2	-0.5
Recurrence	1.8	1.3	1.9	-0.5	0.5
ICER (Cost per LY gained)				\$5,137	\$159,297
ICER (Cost per QALY gained)				\$6,551	\$755,906

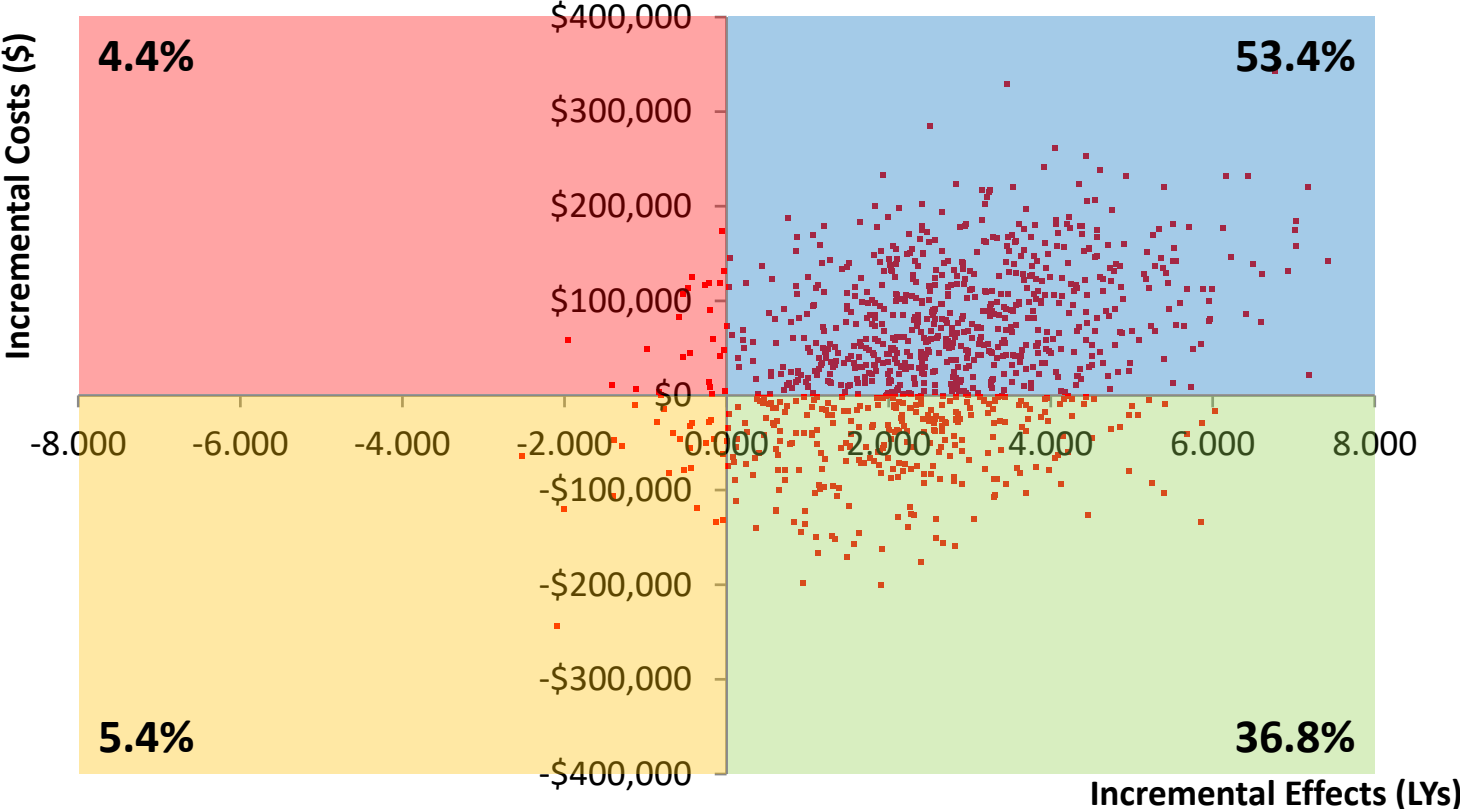
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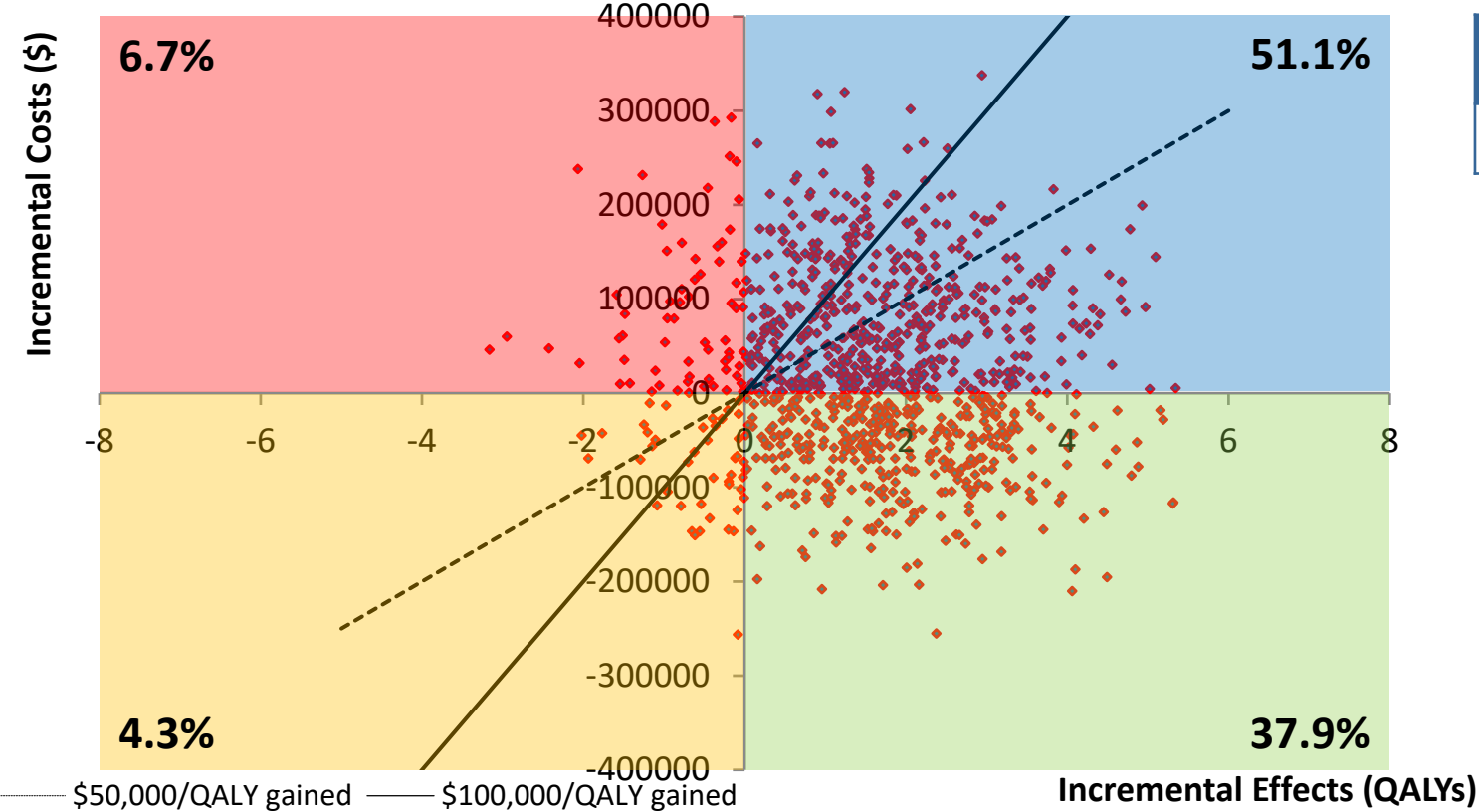
ONE-WAY DSA (E-OFS vs TAM)



PROBABILISTIC ANALYSIS for LYGs (E-OFS vs TAM)



PROBABILISTIC ANALYSIS for QALYs (E-OFS vs TAM)



Percent of simulations below the \$100,000/QALY gained threshold	
E-OFS	83.20%

SCENARIO ANALYSIS RESULTS

- ❑ Higher ICERs found when assuming no further DFS benefits immediately at the end of the treatment duration.
- ❑ ICERs could still be considered cost-effective at commonly used willingness-to-pay thresholds under various situations

LIMITATIONS

- Uncertainty around long-term survival
- Limited HRQoL data
- Composite and nested endpoints reported in trial
- Applying treatment duration in partitioned-survival model

CONCLUSION

- Treatment with E-OFS and T-OFS appears to be cost-effective compared to tamoxifen alone
 - Given high costs of recurrence, improving disease-free survival appears to avoid future recurrence costs while improving outcomes
- Results depend highly on the long-term survival advantage and reduction in recurrence attributable to each treatment strategy

ACKNOWLEDGEMENT

- We would like to acknowledge the helpful contributions of Dr. Andrea Eisen and Dr. Orit Freedman and the members of CCO's Breast Drug Advisory Committee in validating clinical and costing assumptions used within this analysis.
- Funding in support of this publication was provided by Cancer Care Ontario. However, the analyses, conclusions, opinions and statements expressed herein are those of the author, and not necessarily those of Cancer Care Ontario.

APPENDIX

TREATMENT OVERVIEW

Generic Name	Brand Name	Treatment Type
Exemestane	Aromasin™ (and generics)	Aromatase inhibitor
Tamoxifen	Nolvadex™ (and generics)	Endocrine therapy
Ovarian Function Suppression		
Leuprolide acetate	Lupron Depot™	Synthetic nonapeptide analog of GnRH
Leuprolide acetate	Eligard™	Synthetic nonapeptide analog of LHRH
Goserelin acetate	Zoladex™	Synthetic decapeptide analog of GnRH
Triptorelin pamoate	Trelstar™	Synthetic decapeptide agonist analog of LHRH

TREATMENT OVERVIEW

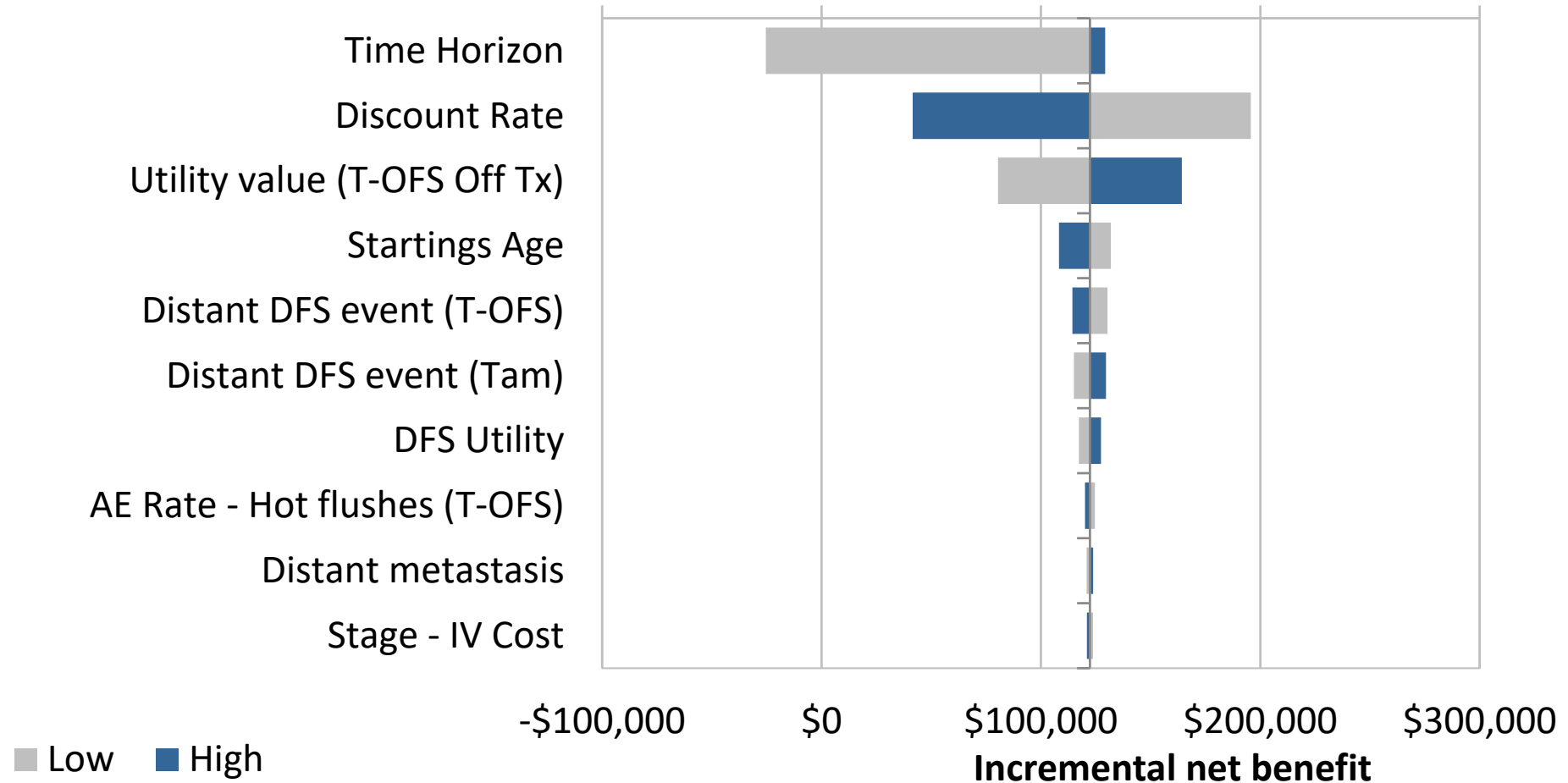
Generic Name	Brand Name	Treatment Type
Exemestane	Aromasin™ (and generics)	Aromatase inhibitor
Tamoxifen	Nolvadex™ (and generics)	Endocrine therapy
Ovarian Function Suppression		
Leuprolide acetate	Lupron Depot™	Synthetic nonapeptide analog of GnRH
Leuprolide acetate	Eligard™	Synthetic nonapeptide analog of LHRH
Goserelin acetate	Zoladex™	Synthetic decapeptide analog of GnRH
Triptorelin pamoate	Trelstar™	Synthetic decapeptide agonist analog of LHRH

TREATMENT OVERVIEW

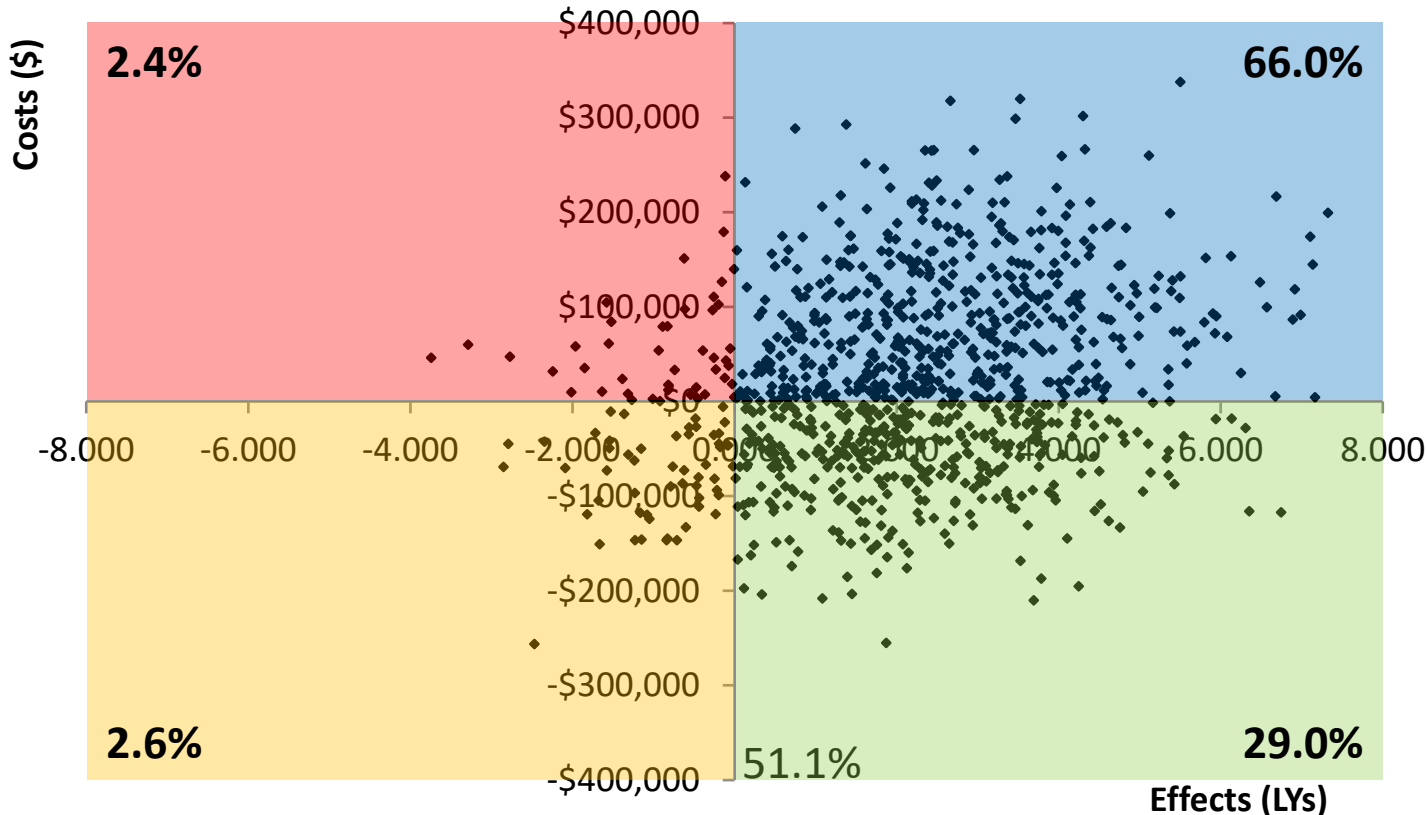
Treatment strategy	5 year DFS				8 year DFS			
	<i>Ext.</i>	ΔTam_{Ext}	<i>Trial</i>	ΔTam_{Trial}	<i>Ext.</i>	ΔTam_{Ext}	<i>Trial</i>	ΔTam_{Trial}
E-OFS	83.6%	5.9%	83.8%	6.7%	77.1%	7.3%	80.4%	9.0%
T-OFS	81.1%	3.4%	80.7%	3.6%	73.8%	4.0%	76.7%	5.3%
Tamoxifen	77.7%	-	77.1%	-	69.8%	-	71.4%	-

Treatment strategy	5 year OS				8 year OS			
	<i>Ext.</i>	ΔTam_{Ext}	<i>Trial</i>	ΔTam_{Trial}	<i>Ext.</i>	ΔTam_{Ext}	<i>Trial</i>	ΔTam_{Trial}
E-OFS	92.1%	1.3%	92.3%	1.4%	86.1%	2.8%	87.2%	2.1%
T-OFS	94.1%	3.3%	94.5%	3.6%	87.6%	4.3%	89.4%	4.3%
Tamoxifen	90.8%	-	90.9%	-	83.3%	-	85.1%	-

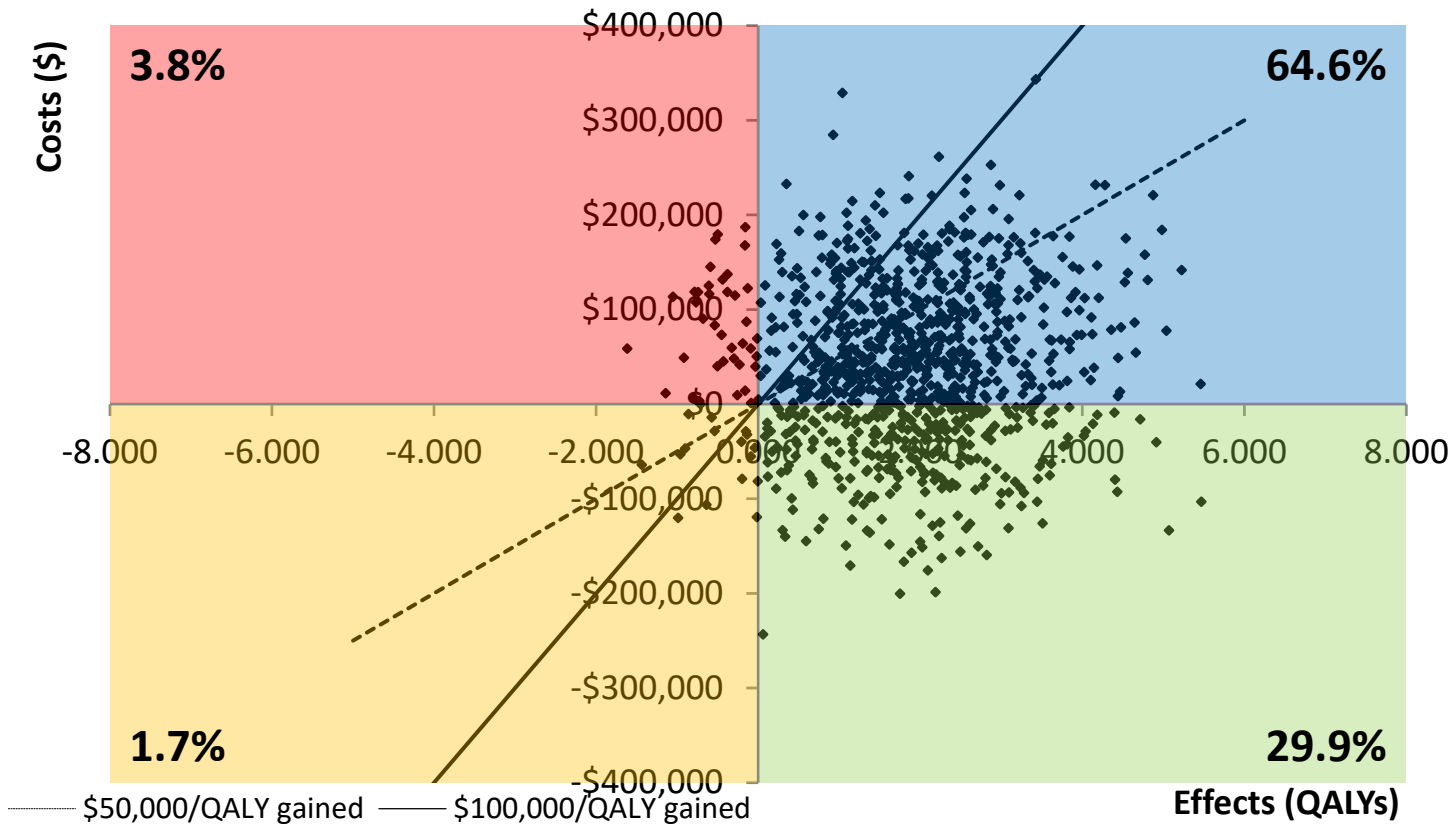
ONE-WAY DSA (T-OFS vs TAM)



PSA FOR LYs GAINED (T-OFS vs TAM)



PSA FOR QALYs GAINED (T-OFS vs TAM)



Percent of simulations below the \$100,000/QALY gained threshold	
T-OFS	89.40%