ASCO and IASCLC Update 2018

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Faculty/presenter disclosure

- **Faculty:** Hamid Mithoowani MD, FRCPC

- **Relationships with financial sponsors:**
  - **Grants/Research Support: None**
  - **Speakers Bureau/Honoraria:** AstraZeneca
  - **Consulting Fees: None**
  - **Patents**: None
  - **Other:** None

Faculty/presenter disclosure

- **<u>Potential for conflict(s) of interest</u>:**
  - Hamid Mithoowani has received a speakers fee and waiver for registration from CAGPO for preparing and presenting the following material
  - Pharmaceutical agents and products made by CAGPO Annual Meeting sponsors such as AstraZeneca, Hoffmann-La Roche Limited, and Genomic Health are discussed here
  - I have received a speakers grant from AstraZeneca, developer of Durvalumab which is discussed in this program
  - The following companies developed products that will be discussed in this program:
    - AstraZeneca – Durvalumab
    - Hoffman- La Roche – Trastuzumab
    - Genomic Health – Oncotype DX

Mitigating Potential Bias

- Data presented here is based only on Phase III randomized international trials deriving from a variety of funding sources
- No manufacturer of any products discussed have reviewed my slides or content prior to presentation
- No consulting work or speakers fees have been collected for work on any of the agents discussed in this presententation

Objectives (not)

- Review abstracts (in detail) about pipeline drugs that will be available and ready to use by the time you retire

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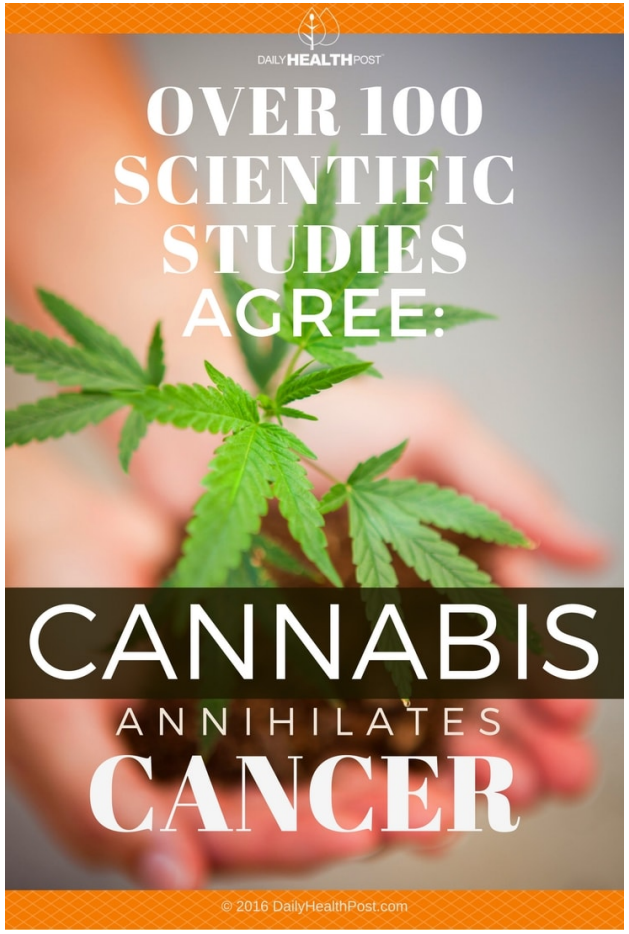
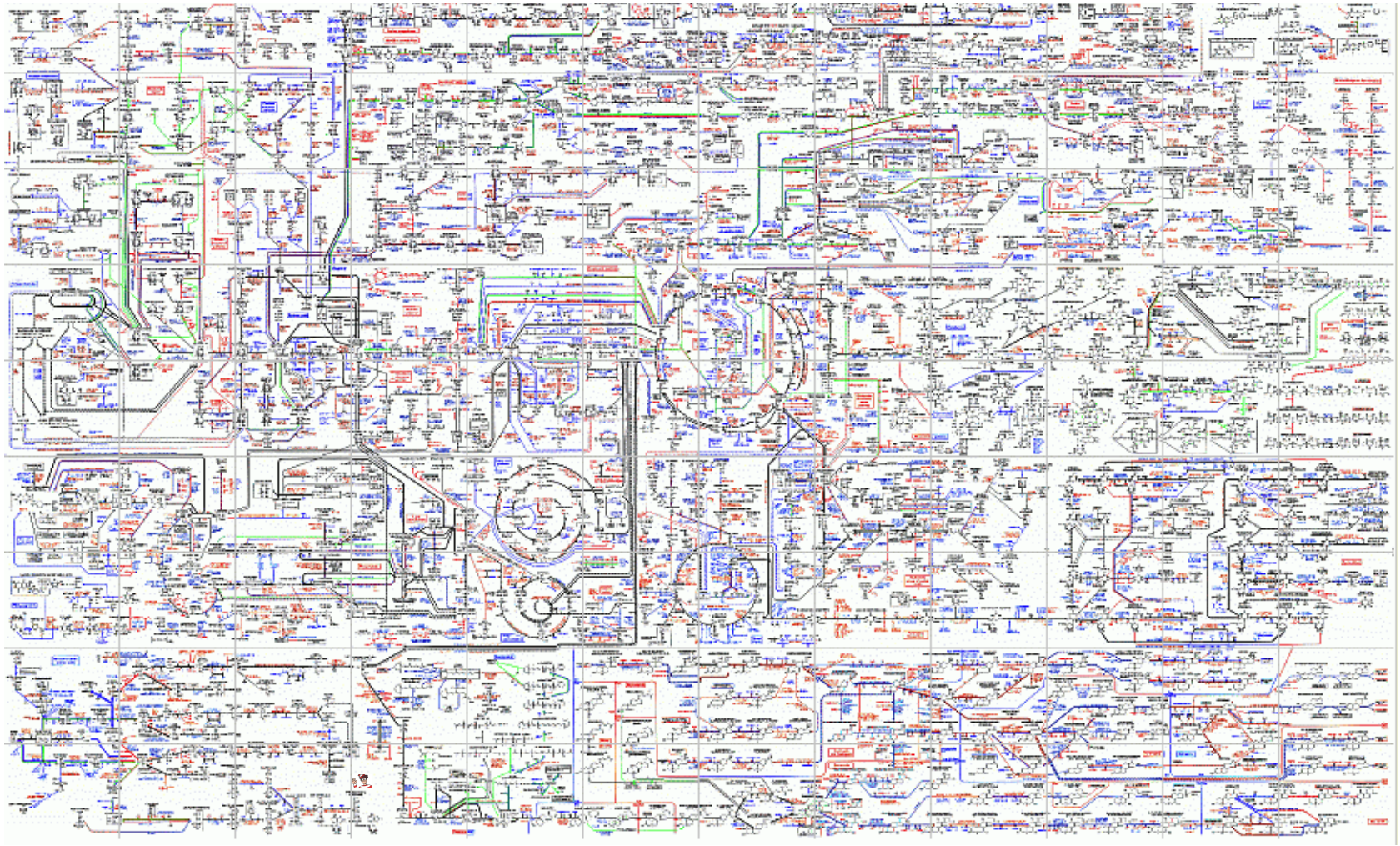


Objectives (not)

- Review complex molecular pathways



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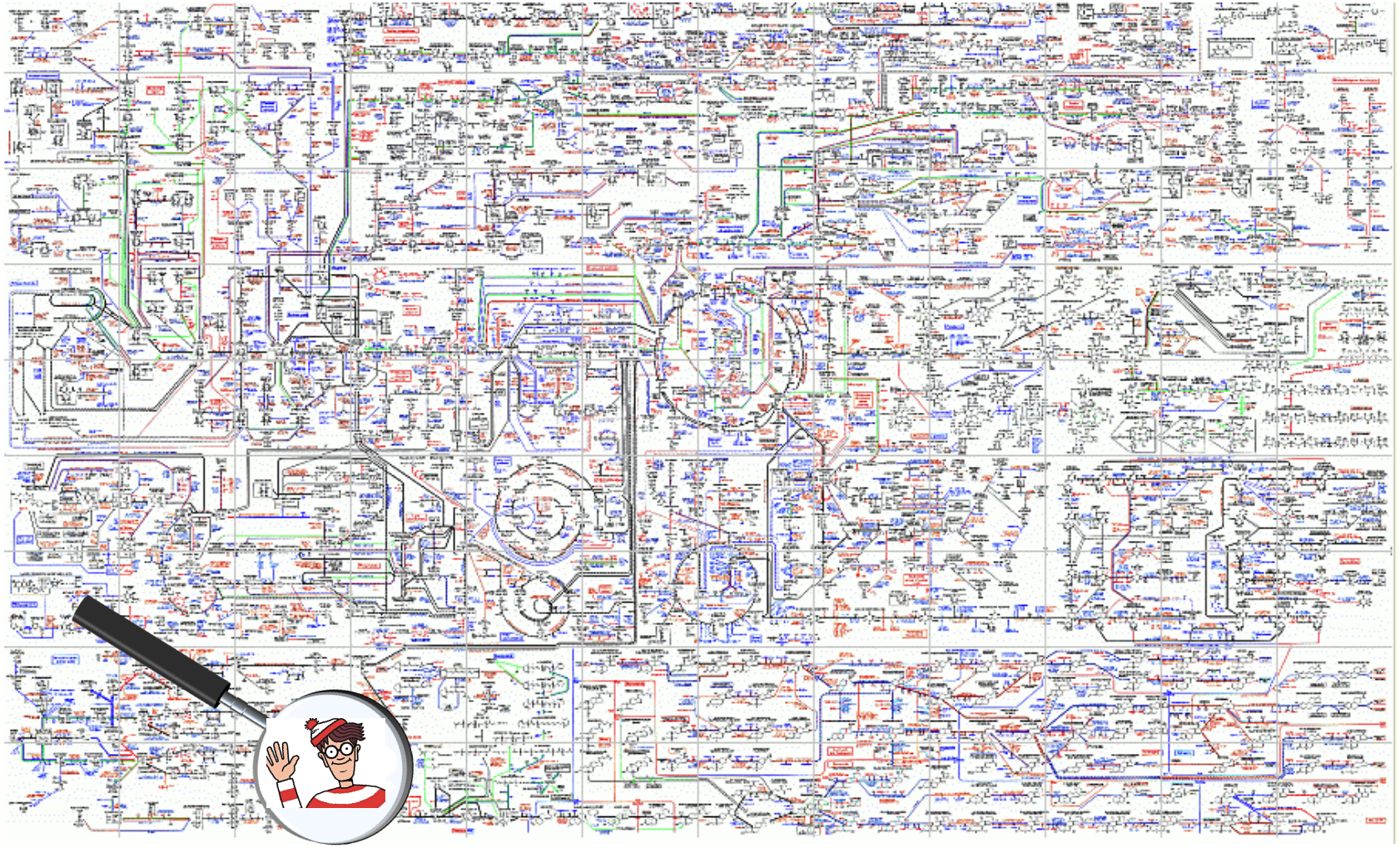
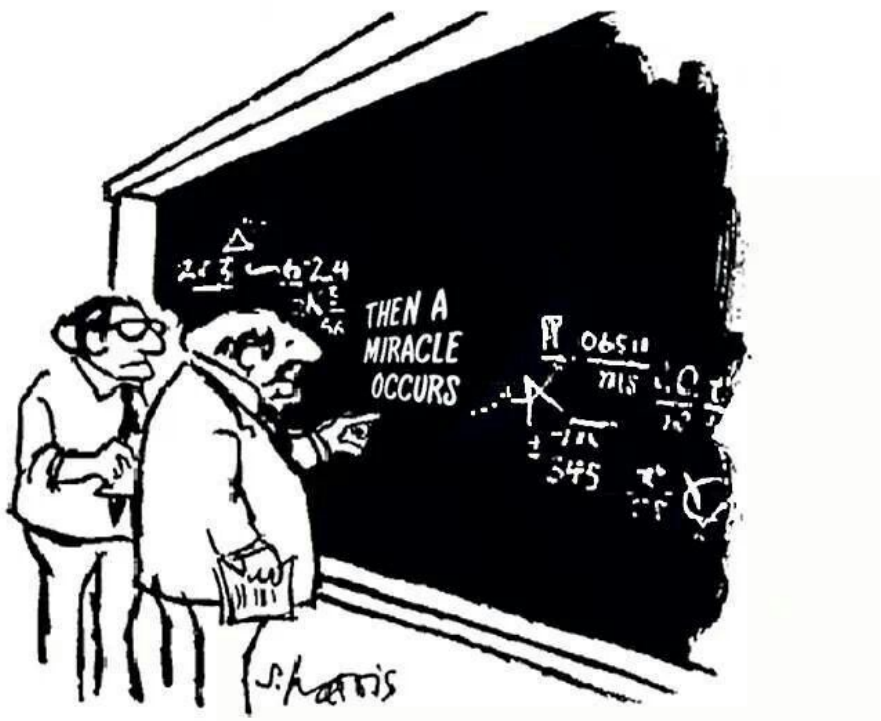


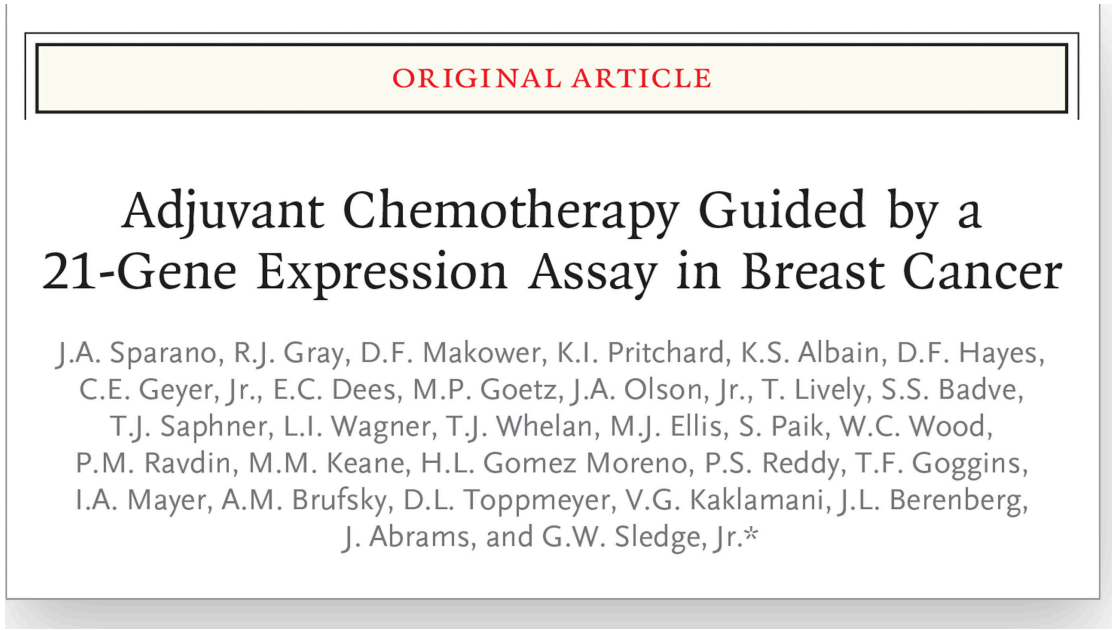
Objectives (not)

- Arguing about statistical details of a particular study



"I think you should be more explicit here in step two"

First question: Can we avoid chemotherapy in patients with hormone sensitive, lymph node negative breast cancer



ORIGINAL ARTICLE

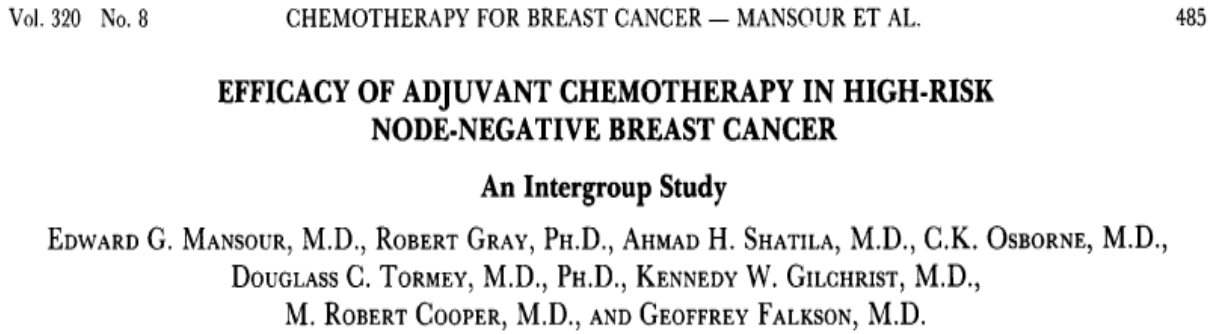
Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

J.A. Sparano, R.J. Gray, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, M.P. Goetz, J.A. Olson, Jr., T. Lively, S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood, P.M. Ravdin, M.M. Keane, H.L. Gomez Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky, D.L. Toppmeyer, V.G. Kaklamani, J.L. Berenberg, J. Abrams, and G.W. Sledge, Jr.*

Sparano et al. *N Engl J Med* 2018

- Adjuvant chemotherapy reduces recurrence in ER-positive, node-negative breast cancer

- U.S. N.I.H consensus panel in 2000 concluded *"…adjuvant ..chemotherapy … should be recommended to the majority of women with localized breast cancer regardless of lymph node, menopausal, or … receptor status."*



Vol. 320 No. 8 CHEMOTHERAPY FOR BREAST CANCER — MANSOUR ET AL. 485

EFFICACY OF ADJUVANT CHEMOTHERAPY IN HIGH-RISK NODE-NEGATIVE BREAST CANCER

An Intergroup Study

EDWARD G. MANSOUR, M.D., ROBERT GRAY, PH.D., AHMAD H. SHATILA, M.D., C.K. OSBORNE, M.D., DOUGLASS C. TORMEY, M.D., PH.D., KENNEDY W. GILCHRIST, M.D., M. ROBERT COOPER, M.D., AND GEOFFREY FALKSON, M.D.

SPECIAL ARTICLE

National Institutes of Health Consensus Development Conference Statement: Adjuvant Therapy for Breast Cancer, November 1–3, 2000

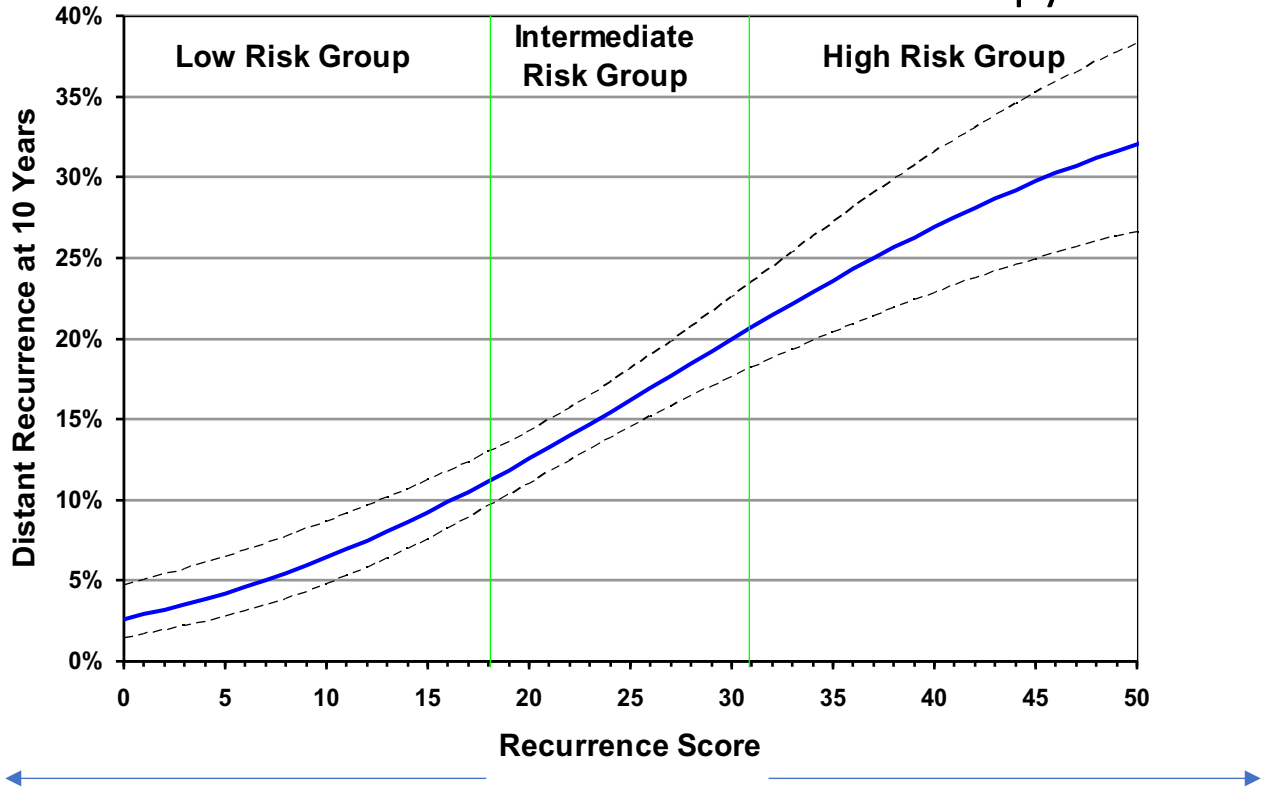
*National Institutes of Health Consensus Development Panel**

Mansour et al. *N Eng J Med* 1989; 320:485-490; *JNCI* 2001; 93: 979–989

- Oncotype DX is a genomic analysis of a tumour and is meant to provide *prognostic* and *predictive* information

- Prognostic: gives information about risk of distant recurrence with standard antiestrogen treatment

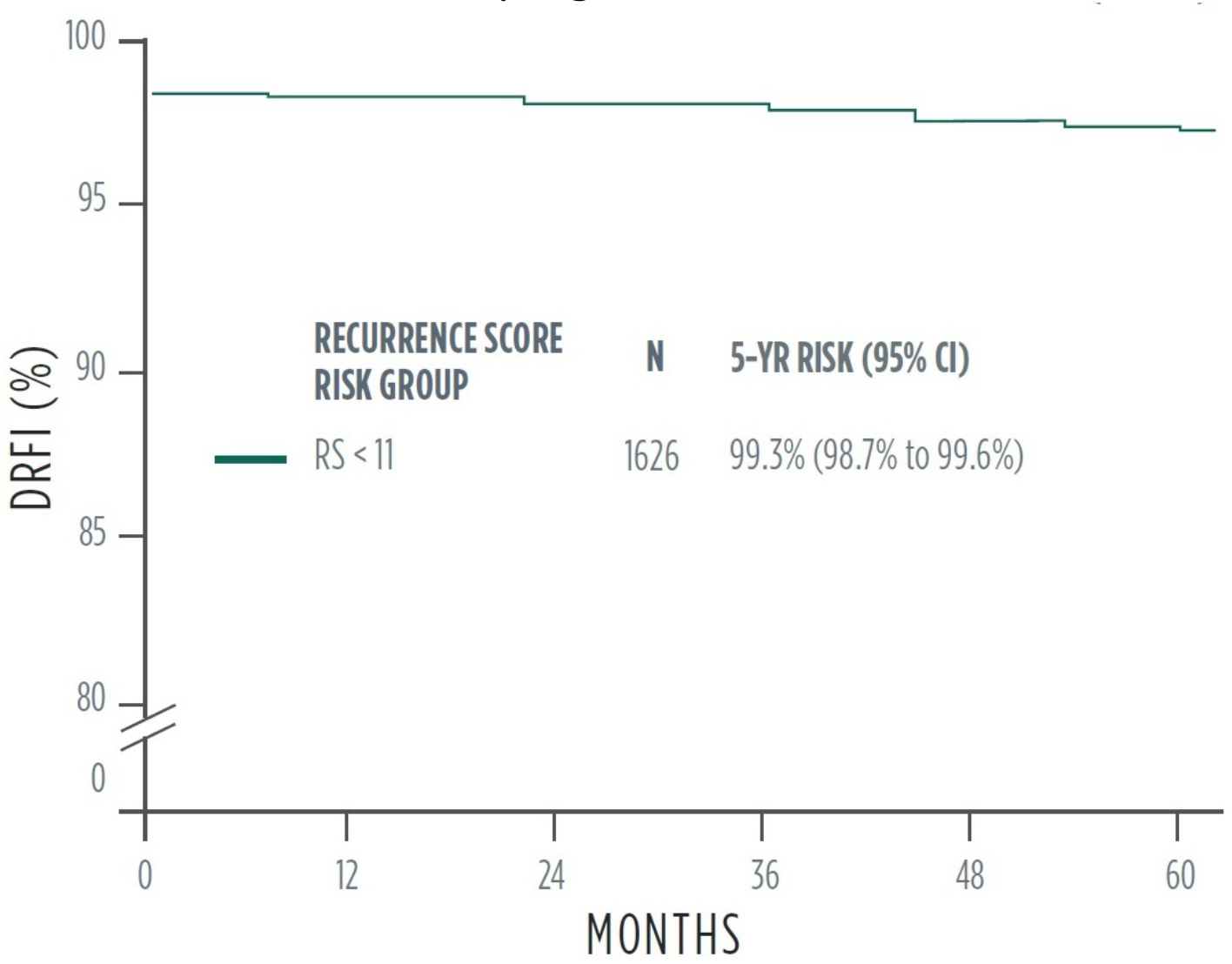
- Predictive: gives information about how much benefit chemotherapy adds in reducing distant recurrence



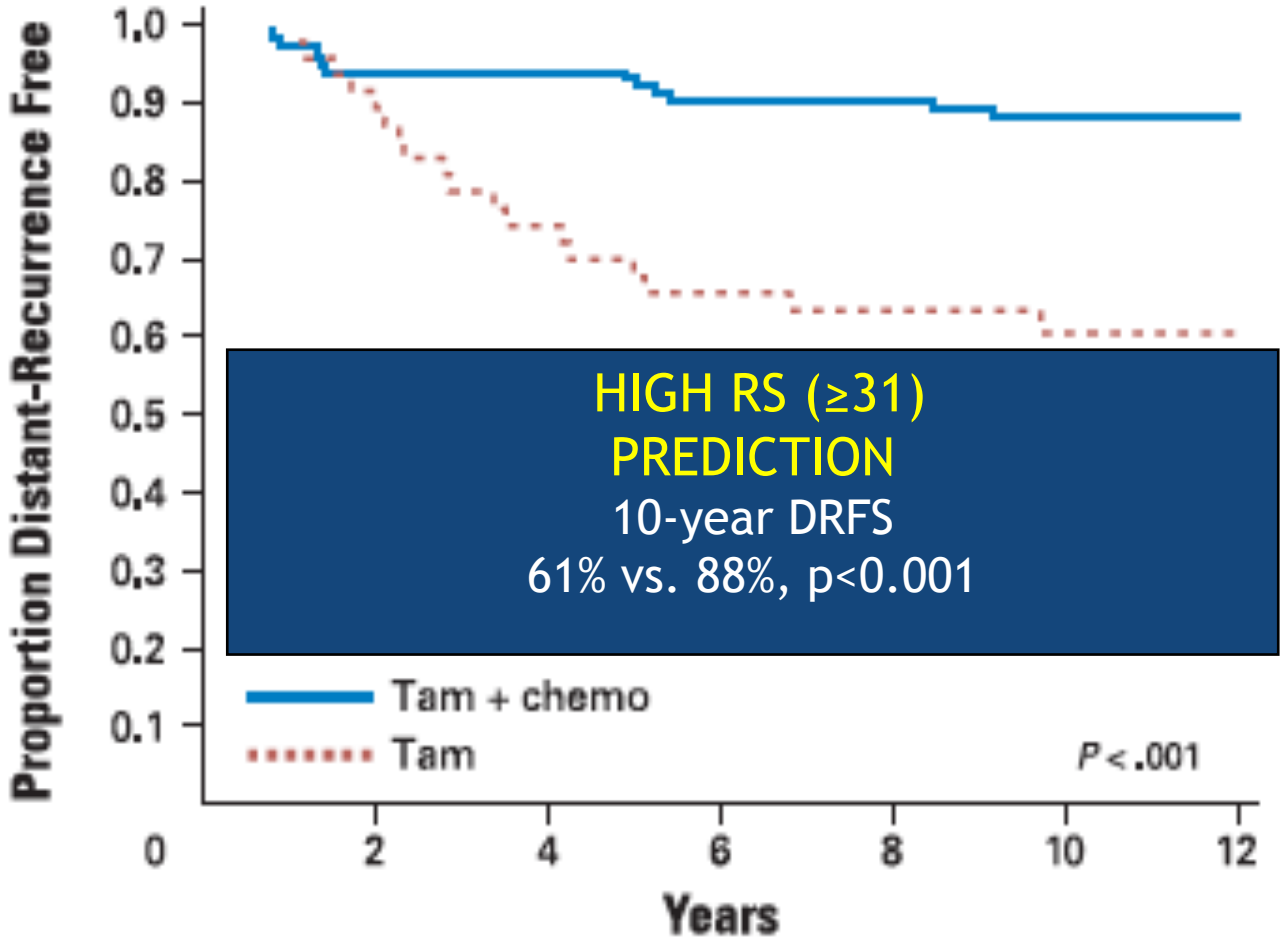
- lower risk of recurrence (prognostic)
- Less benefit from chemotherapy (predictive)

- Higher risk of recurrence (prognostic)
- More benefit from chemotherapy (predictive)

Low risk patients have an excellent prognosis and addition of chemotherapy has negligible benefit



High recurrence scores have high risk of relapse and benefit from the addition of chemotherapy



(Paik et al. *N Eng J Med* 2004;351:2817-26; Paik et al. *J Clin Oncol* 2006;24:3726-34; Sparano, Paik. *J Clin Oncol* 2008; 26: 721-728

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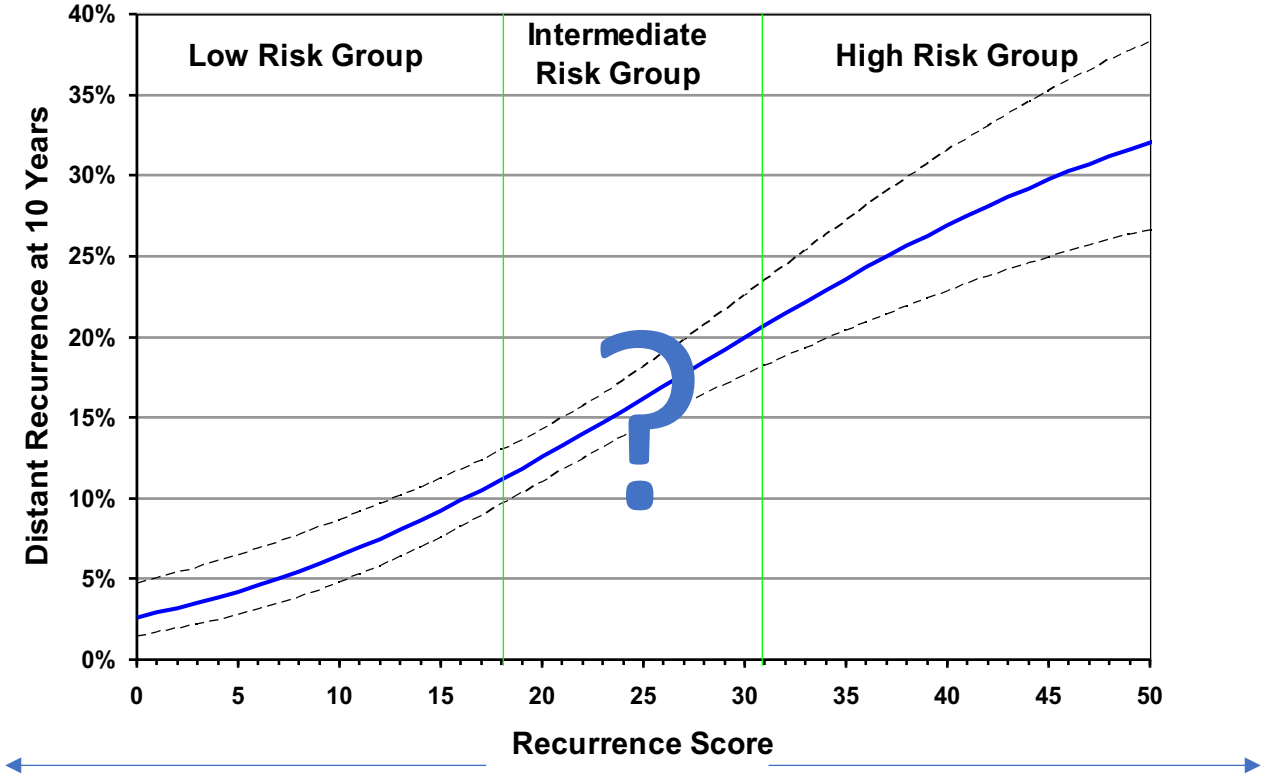
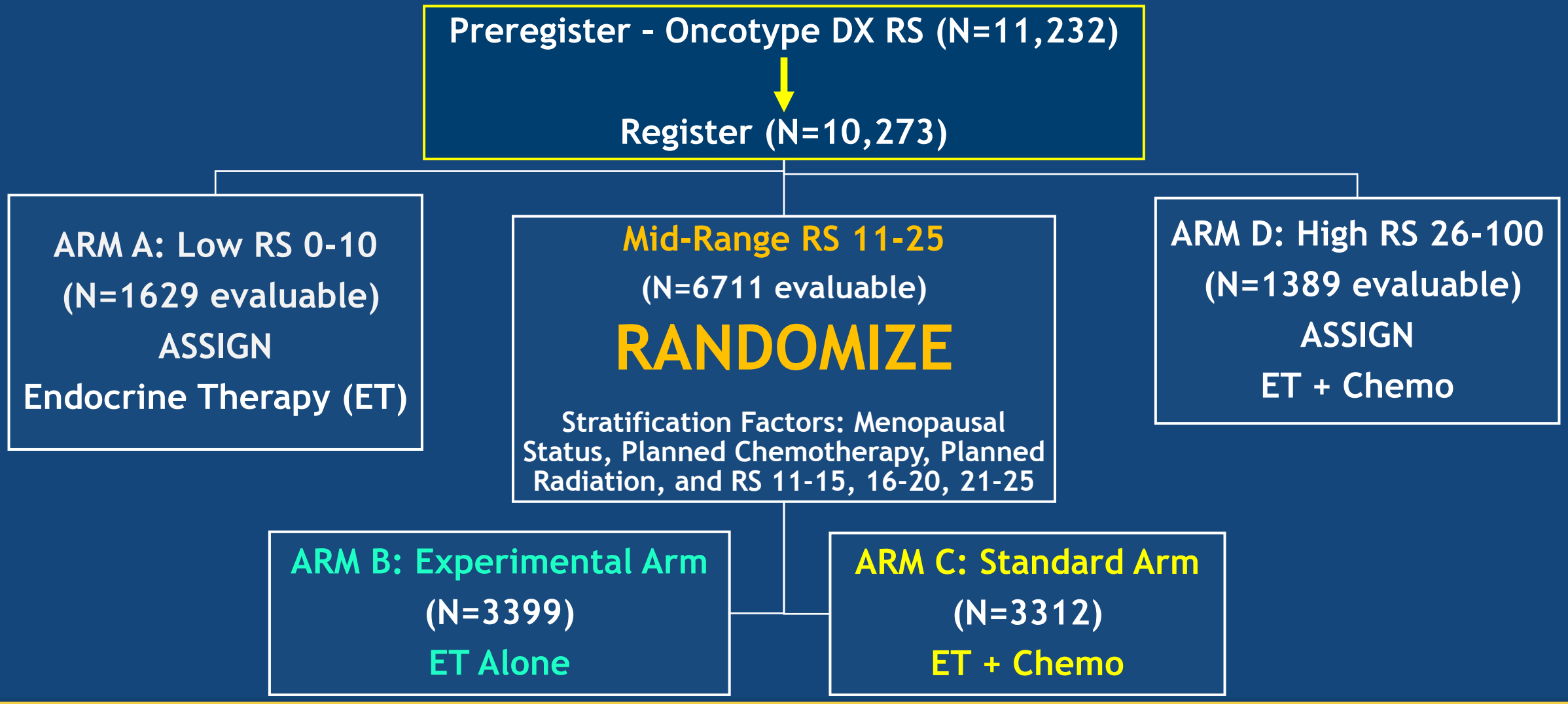


- Higher risk of recurrence (prognostic)
- More benefit from chemotherapy (predictive)

TAILORx Methods: Treatment Assignment & Randomization

Accrued Between April 2006 - October 2010



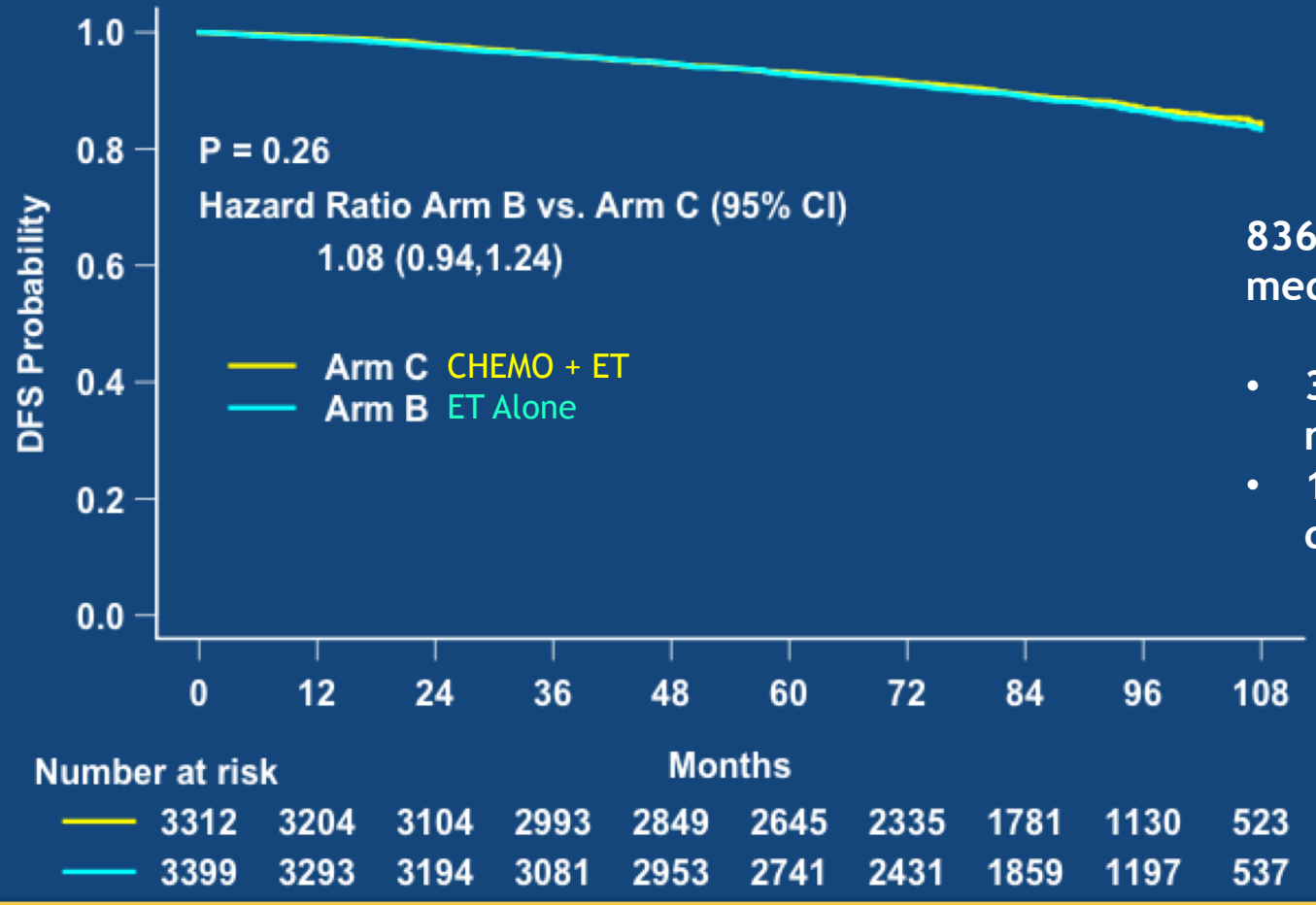
TAILORx Results - ITT Population: Demographics & Treatment in RS 11-25 Arms (N=6,711)

- **Patient characteristics**
  - Median age 55 years, and 33% were 50 or younger
  - 63% had tumor size 1-2 cm and 57% had intermediate grade histology
  - Clinical risk criteria: 74% low risk, 26% high risk

- **Systemic Treatment**
  - Endocrine therapy
    - Comparable adherence and duration in both arms
    - Postmenopausal – included AI in 90%
    - Premenopausal – included OS in 15%
  - Chemotherapy
    - Most common regimens were TC (56%) and anthracycline-containing (36%)

TAILORx Results - ITT Population: RS 11-25 (Arms B & C)

Primary Endpoint
Invasive Disease-Free Survival

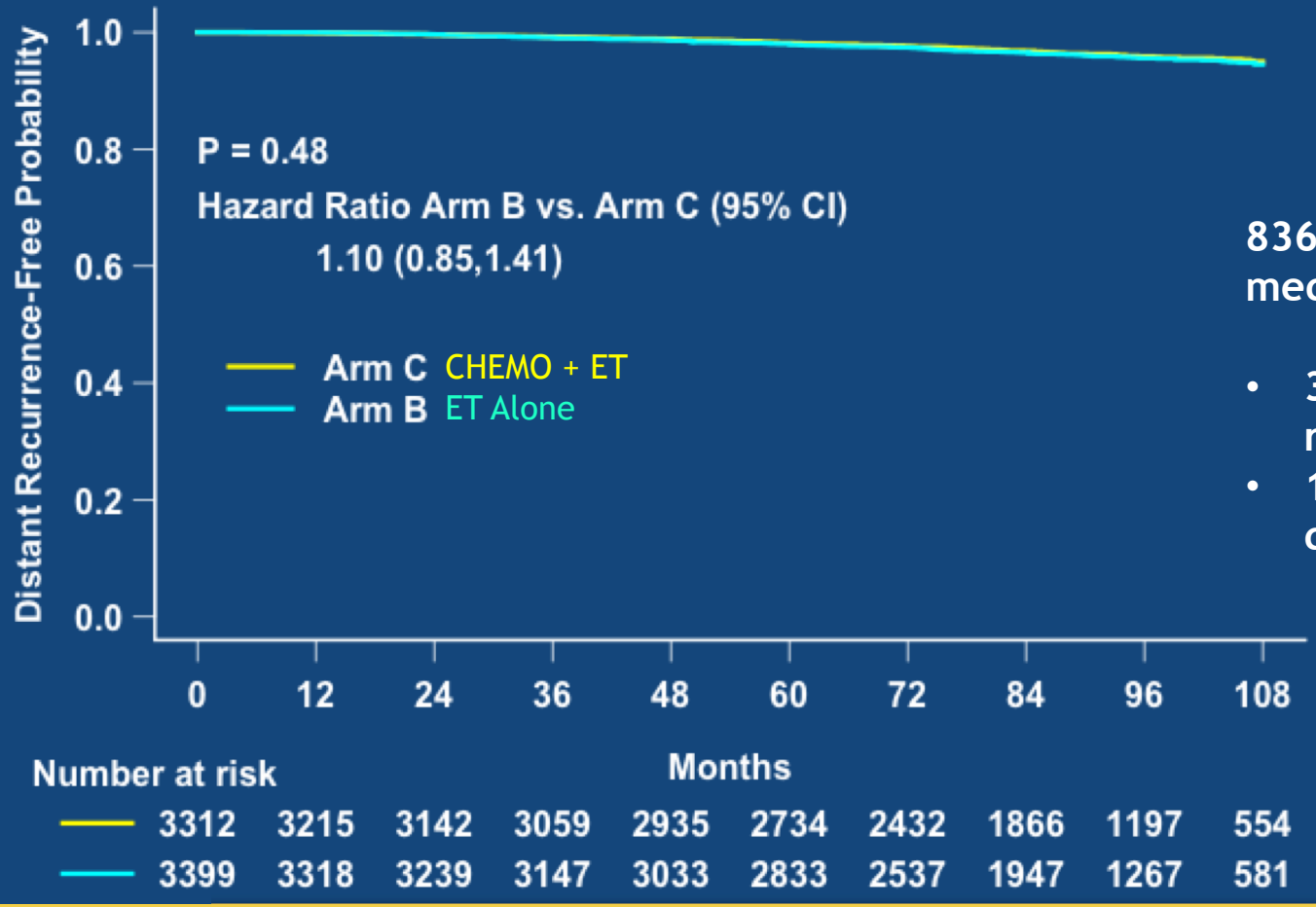


836 IDFS events after median of 7.5 years

- 338 of 836 (40.3%) with recurrence as first event
- 199 of 836 (23.8%) were distant recurrence

TAILORx Results - ITT Population: RS 11-25 (Arms B & C)

Secondary Endpoint
Distant Relapse-Free Interval

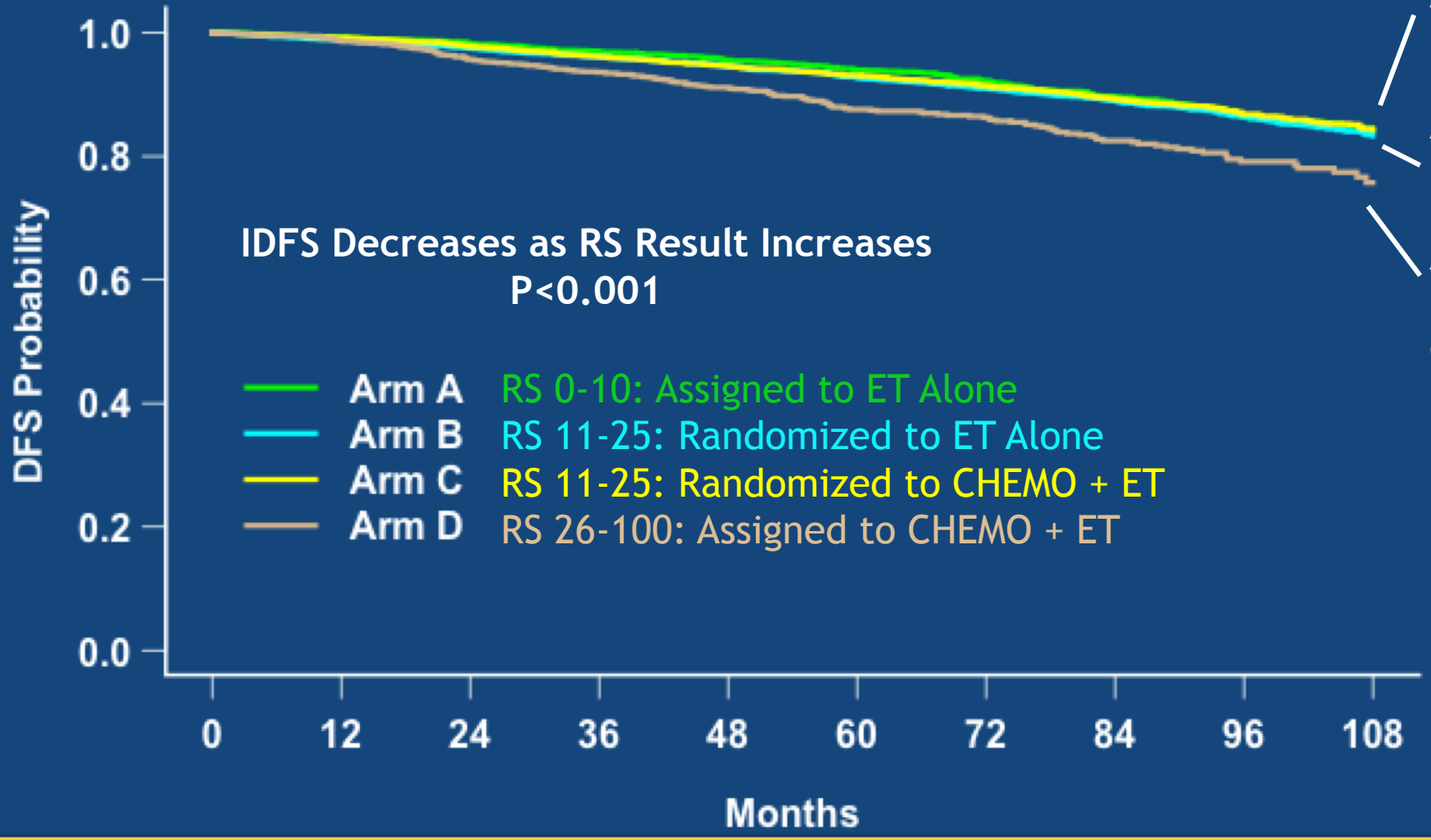


836 IDFS events after median of 7.5 years

- 338 of 836 (40.3%) with recurrence as first event
- 199 of 836 (23.8%) were distant recurrence

TAILORx Results - ITT Population: All Arms (A,B,C & D)

9-Year Event Rates



Arm A: ET alone (RS 0-10)
3% Distant recurrence rate

Arms B & C: Randomized (RS 11-25)
5% Distant recurrence rate overall

Arm D: Chemoendocrine (RS 26-100)
13% Distant recurrence rate despite chemotherapy + endocrine therapy

TAILORx Results – ITT Population: Potential Chemotherapy Benefit in Women ≤50 Years (N=2,216) in RS 11-25 Arms

≤50 Years, RS 16-25 - some chemotherapy benefit

- RS 16-20: 9% fewer IDFS events, including ~2% fewer distant recurrences
- RS 21-25: 6% fewer IDFS events, mainly consisting of fewer distant recurrences

≤50 Years, RS 0-15 - good prognosis with endocrine therapy (ET)

- RS 0-15: 3% distant recurrence with ET alone
- RS 11-15: No evidence for chemotherapy benefit

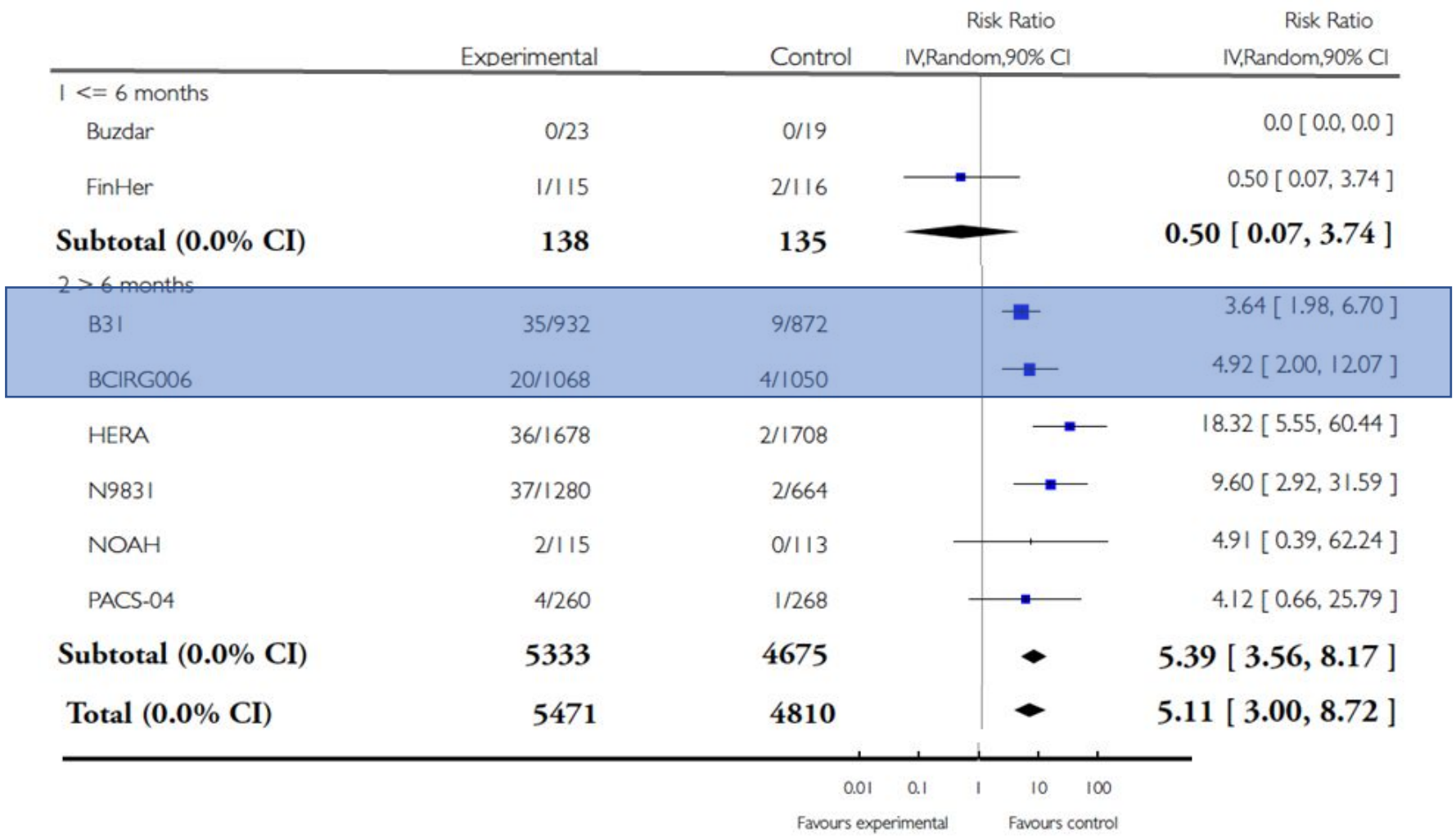
How this changed my practice

- Chemotherapy can be **safely** avoided in many patients
- My threshold in ordering the test in patients under 50 has decreased, and increased in older women
- More needs to be done for high recurrence scores – extending adjuvant endocrine therapy?

Question 2: Can Trastuzumab be shortened in patients with HER2+ breast cancer

Persephone: Six versus twelve months of trastuzumab in HER2+ early breast cancer

CHF by trastuzumab duration



Moja L, et al. The Cochrane Library 2012, Issue 4

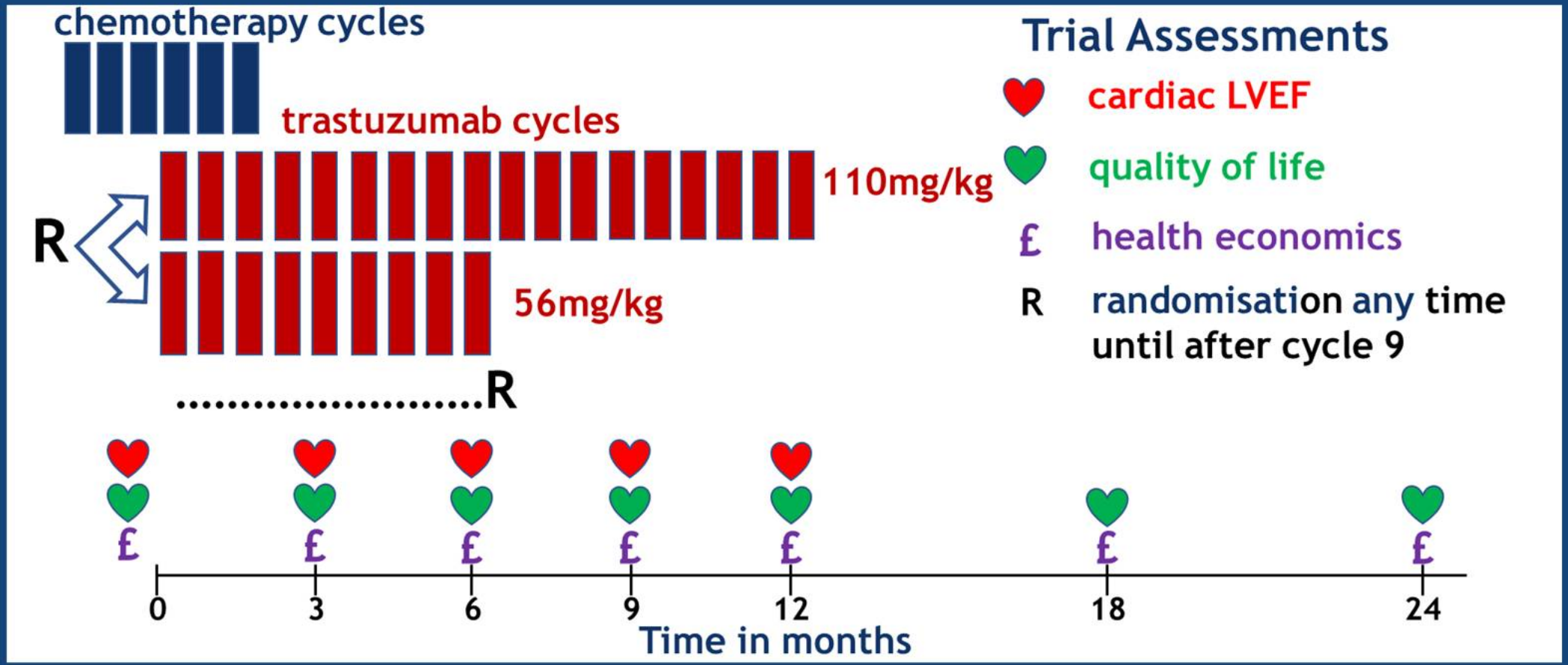
Persephone

NHS
National Institute for Health Research

- **Hypothesis** - Six months adjuvant trastuzumab has similar efficacy to standard twelve months but reduced toxicity and cost
- **PERSEPHONE Trial** – Randomised phase 3 multicentre UK trial of 6 versus 12 months trastuzumab – non-inferiority design (n=4000)
- **Funding acknowledgement**
  NIHR HTA programme (project number 06/303/98)

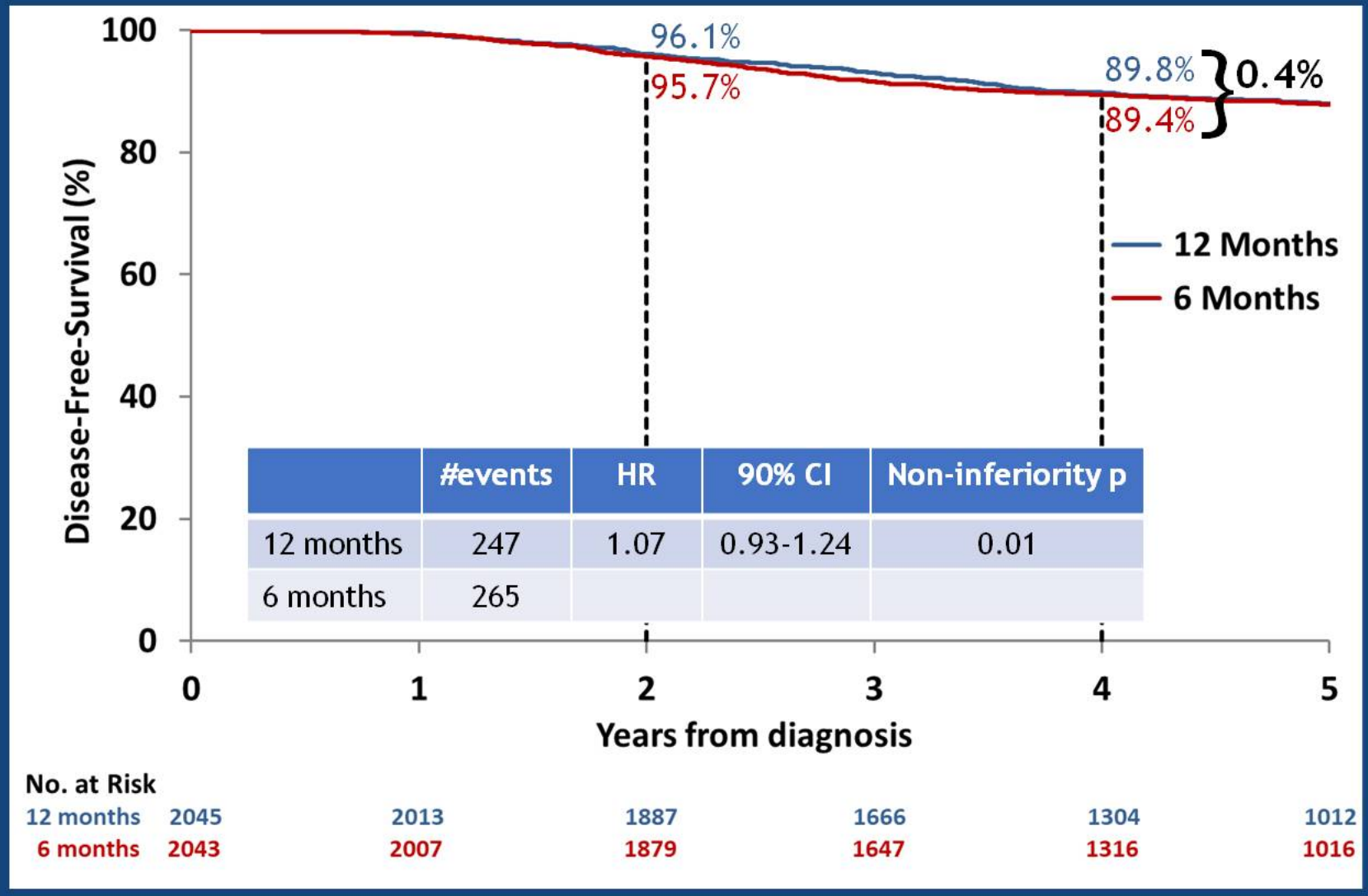
Department of Health and Social Care disclaimer
The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Persephone Study Design



1º : DFS [Diagnosis to 1st relapse (local or distant) or death]
2º :OS ; Cost effectiveness ; Cardiac function

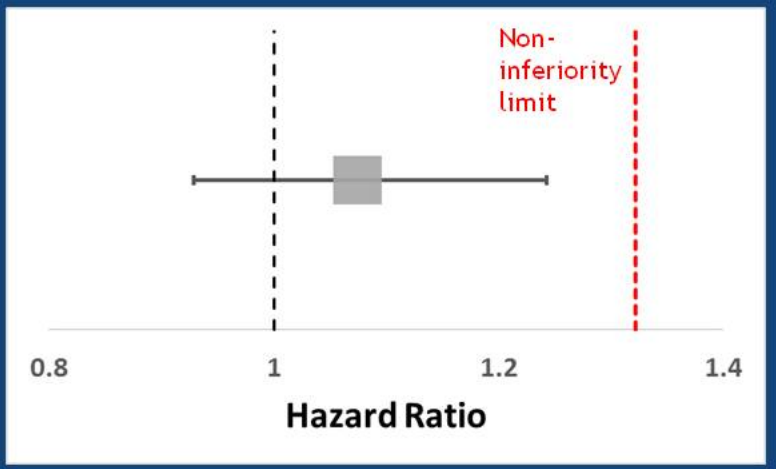
Disease-free survival



	#events	HR	90% CI	Non-inferiority p
12 months	247	1.07	0.93-1.24	0.01
6 months	265			

No. at Risk

12 months	2045	2013	1887	1666	1304	1012
6 months	2043	2007	1879	1647	1316	1016



How this changed my practice

- Still treating for 1 year…for now
- Consider 6 months for any patients with drop of LVEF <50, elderly patients
- Don’t worry about patients who didn’t finish or lost to follow up

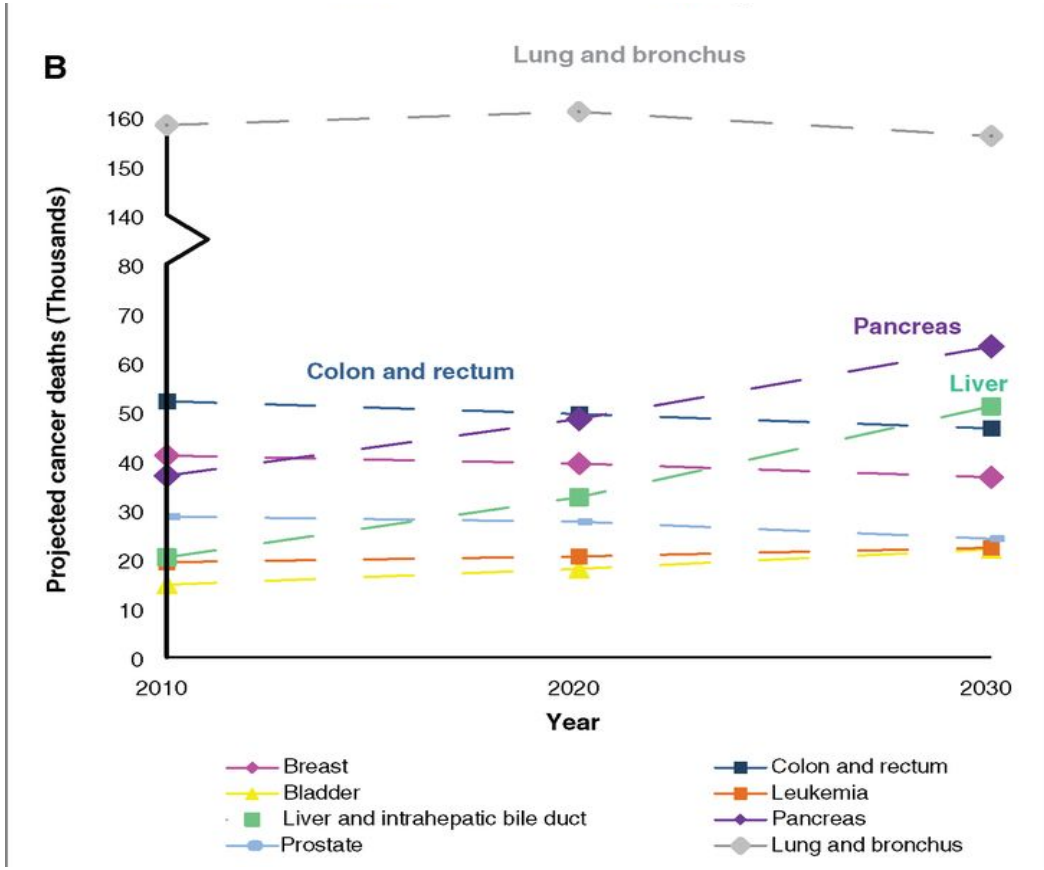
Question 3: Can we improve outcomes for patients with resected pancreatic cancer

PRODIGE 24/CCTG PA.6: Modified FOLFIRINOX versus Gemcitabine in patients with resected pancreatic ductal adenocarcinomas

The Scope of Pancreatic Cancer

- Pancreatic cancer has the highest lethality of all GI malignancies. Five year survival is estimated to be approximately 5-7%
- From 1975, five year survival rates have gone up from approximately 3% to 7.6%
- Despite being the 12th most common malignancy in the United States, it is the 4th leading cause of cancer death in men and women

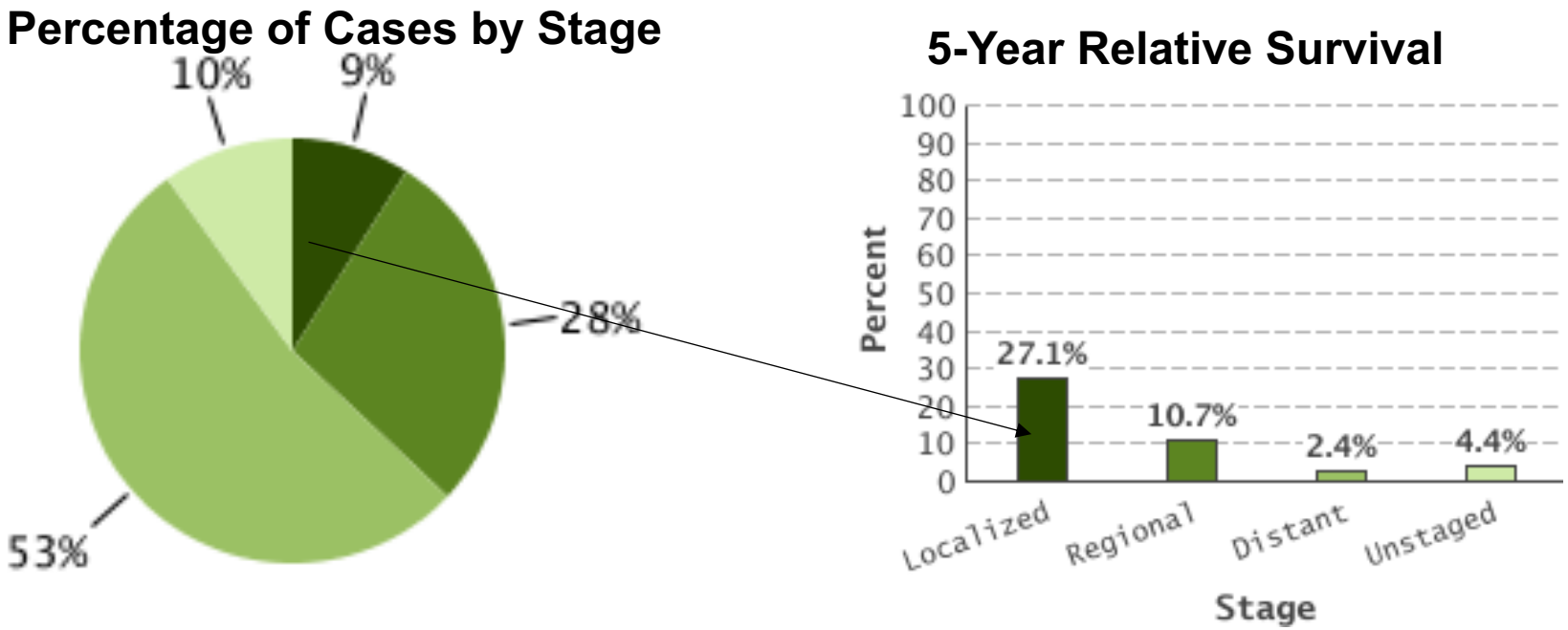
Forecasting the future



- Pancreatic cancer expected to become the third leading cause of cancer deaths in the united states by just after 2020

Cancer Res June 1, 2014 vol. 74 no. 11 2913-2921

Forecasting the future



- Only 9% of patients present with localized disease. 53% present with upfront metastatic disease
- Early detection will be imperative to improve outcomes in the future

SEER 18 2005-2011, All Races, Both Sexes by SEER Summary Stage 2000

PRODIGE 24/CCTG PA.6 trial: study design

NCT01526135

- R0 or R1 resected pancreatic cancer
- postoperative CT-scan mandatory
- CA19-9 level < 180 U/mL within 12 weeks after surgery

Stratification:
- center
- resection margin (R0 vs R1)
- CA19-9 level (≤ 90 vs 91-179 U/mL)
- pN0 (< 12 vs ≥ 12 examined nodes) vs pN1

RANDOMIZE

1:1

mFolfirinox

Oxaliplatin 85 mg/m², Leucovorin 400 mg/m²,
Irinotecan 180 mg/m²*, all at D1
Fluorouracil continuous IV infusion 2.4 g/m² over 46 hours
Every 2 weeks; 12 cycles
**Reduced to 150 mg/m² after patient 162*

Gemcitabine

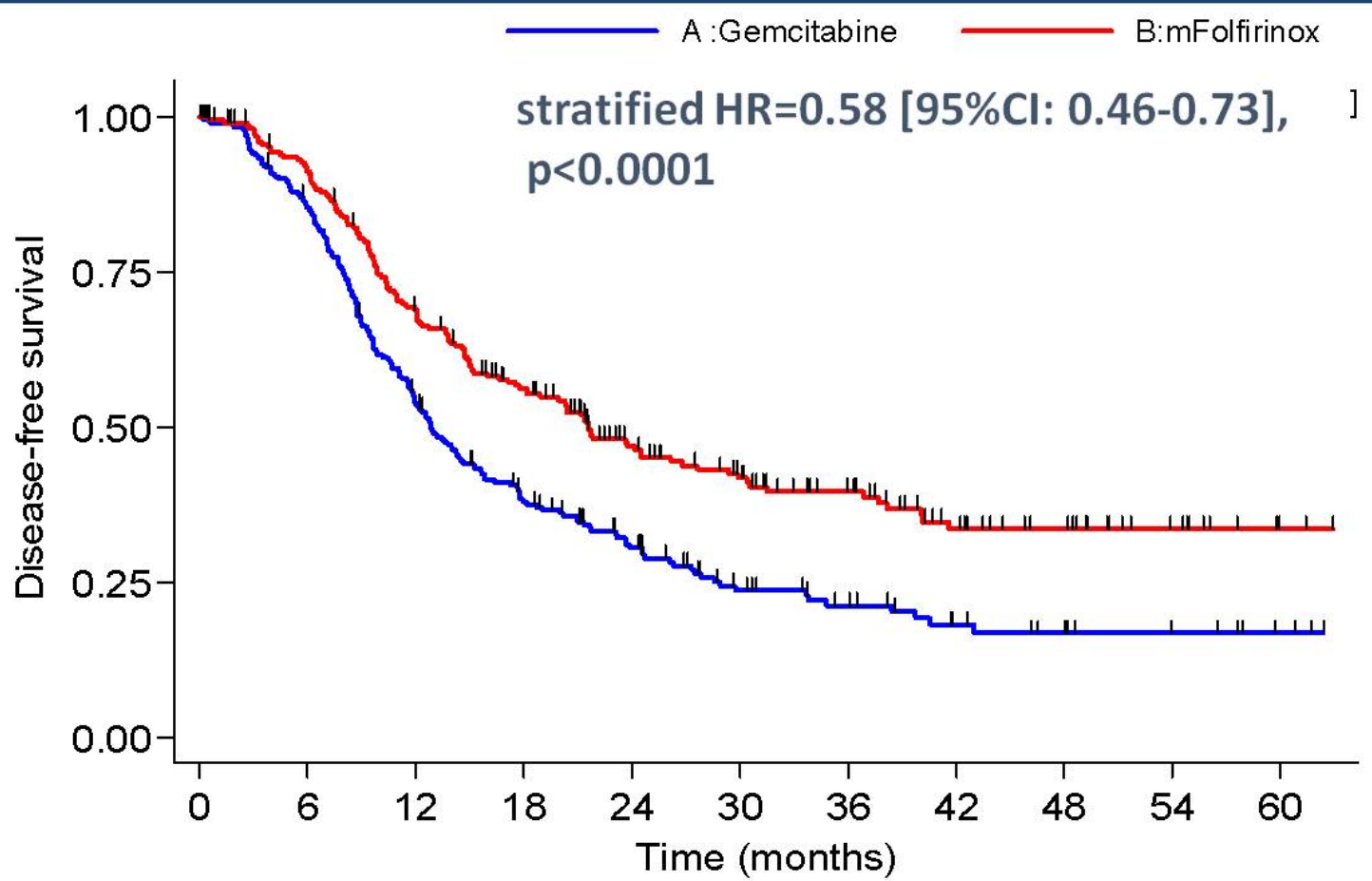
1000 mg/m², qw 3/4 *weeks;*
6 cycles

for both arms:
- 6 months of chemotherapy
- CT scans: every 3 months

Patients baseline characteristics

Characteristics		mFolfirinox N=247	Gemcitabine N=246	p
Median age (yrs) [range]		63 [30-79]	64 [30-81]	0.09
Gender male		57.5 %	55.6 %	0.67
ECOG PS	0	49.8 %	52.5 %	0.55
	1	50.2 %	47.5 %	
Diabetes		25.3 %	26.6 %	0.44

Disease-Free Survival



Number at risk

A:Gemcitabine	246	205	127	85	59	34	24	15	10	7	3
B:mFolfirinox	247	210	156	118	80	60	46	29	21	11	2

No DFS events: 314

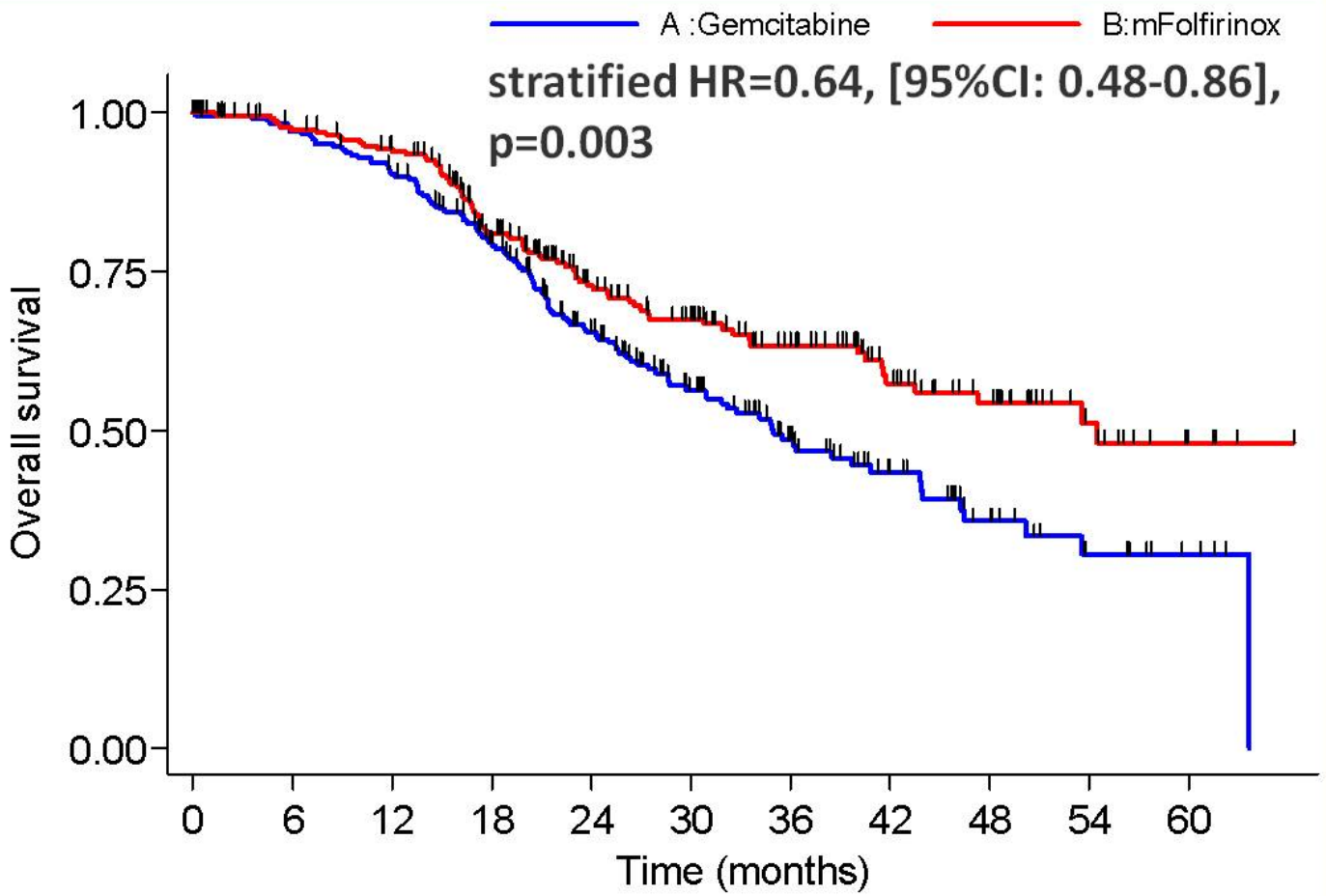
Median DFS:

- **21.6 mths [95%CI: 17.7-27.6] with mFolfirinox**
- **12.8 mths [95%CI: 11.7-15.2] with Gemcitabine**

3-year DFS:

- **39.7% [95%CI: 32.8-46.6] with mFolfirinox**
- **21.4% [95%CI: 15.8-27.5] with Gemcitabine**

Overall Survival



Number at risk

A:Gemcitabine	246	233	215	171	120	81	55	33	18	9	4
B:mFolfirinox	247	223	210	165	119	91	68	46	32	16	4

Median overall survival:

- **54.4 months** [95%CI: 41.8-NR] **with mFolfirinox**
- **35.0 months** [95%CI: 28.7-43.9] **with Gemcitabine**

3-year overall survival:

No OS events=192

- **63.4% (mFolfirinox) vs 48.6 % (Gem)**

Safety: main nonhematologic AEs

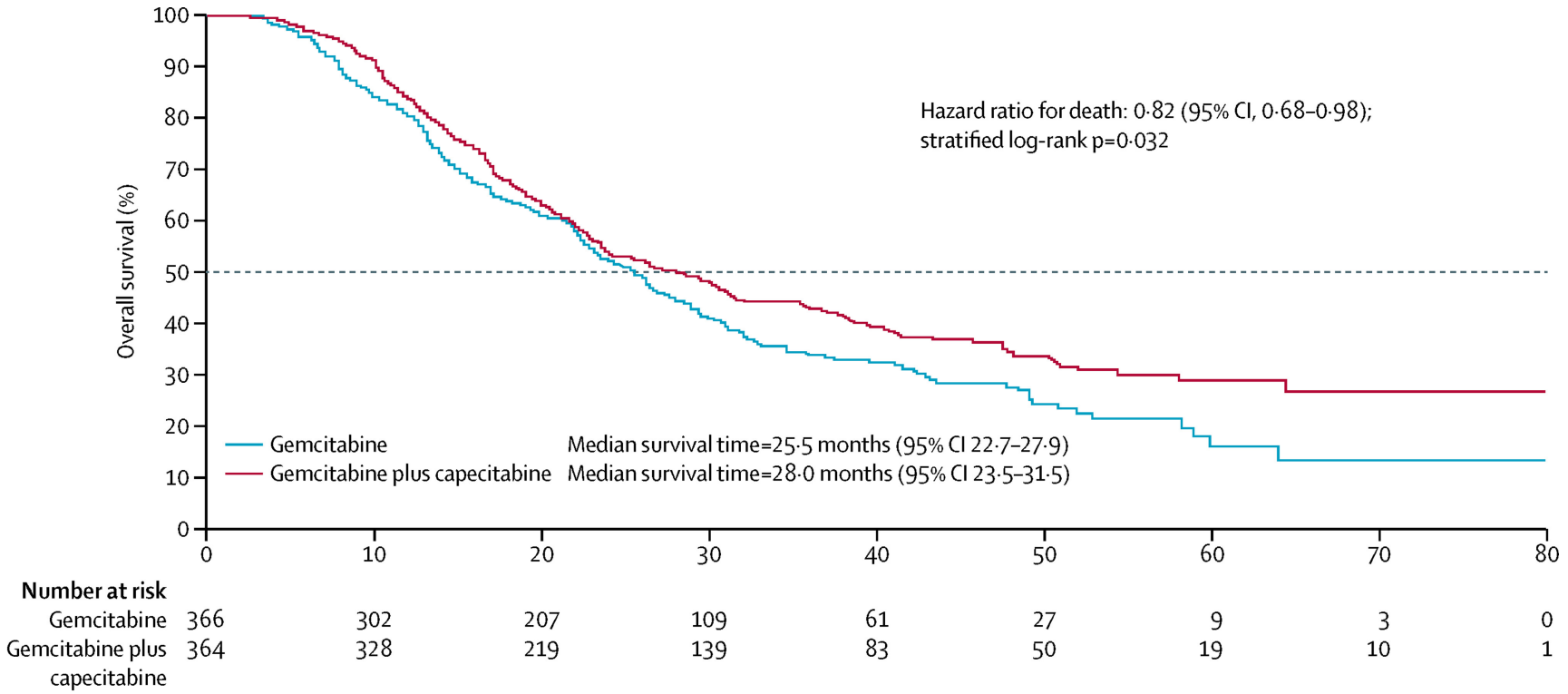
AE, % per patient	mFolfirinox N=238		Gemcitabine N=243		p-value all grades
	All grades	Grade 3/4	All grades	Grade 3/4	
Diarrhea	84.4 %	18.6 %*	49 %	3.7 %	< 0.001
Sensory peripheral neuropathy	61.2 %	9.3 %	8.7 %	-	< 0.001
Fatigue	84 %	11 %	77.6 %	4.6 %	0.003
Vomiting	46 %	5 %	29 %	1.2 %	< 0.001
Mucositis	33.8 %	2.5 %	14.9 %	0 %	< 0.001
Alopecia	27 %	-	19.5 %	-	0.07
Hand-foot syndrome	5 %	0.4 %	0.8 %	-	0.023

* 8.6% during cycle 1; 6.3% during cycle 2; 3% at cycles 3-5; 1% at cycles 6-12
Grade 3-4 diarrhea is significantly related to a higher number of lymph nodes examined, p = 0.02.

Six-month treatment completion

	mFolfirinox No = 238	Gemcitabine No = 243	P
All cycles of chemotherapy	66.4%	79.0%	0.002
Planned administrations Median No. administrations	12 12 [1-12]	18 18 [1-18]	—
No. administrations delayed	14.4%	3.9%	< 0.001
Relative dose-intensity > 0.70	48.7%	91.4%	< 0.001
Early stop due to : - relapse - toxicity - Principal Investigator's decision - patient decision	80 (33.6%) 15 (6.3%) 21 (8.8%) 7 (2.9%) 13 (5.4%)	51 (21.0%) 26 (10.7%) 11 (4.5%) 2 (0.8%) 2 (0.8%)	0.002

- Criticism of the trial is that it doesn't compare to the new standard of care
- At ASCO 2017: Gemcitabine + Capecitabine was established as the new standard of care for resected pancreatic cancer



Neoptolemos et al. *Lancet 2017*

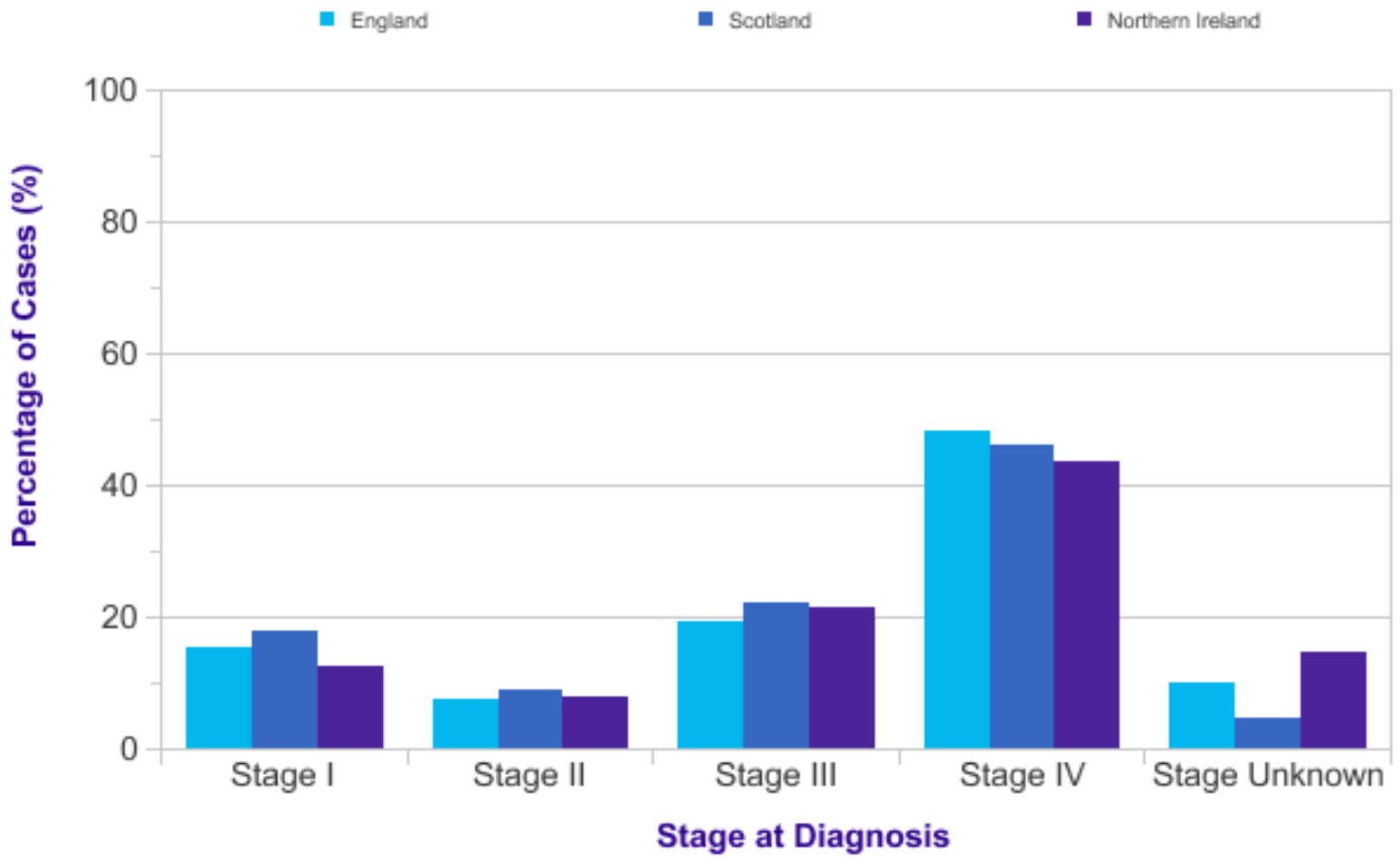
How this changed my practice

- For very fit patients, mFOLFIRINOX is the new standard of care in resected pancreatic tumours
- Patients should receive primary prophylaxis with GCSF
- Close monitoring for diarrhea, sensory neuropathy
- Gemcitabine and capecitabine is a reasonable option for patients where toxicity is a concern

Question 4: can we improve outcomes in patients with unresectable stage III NSCLC

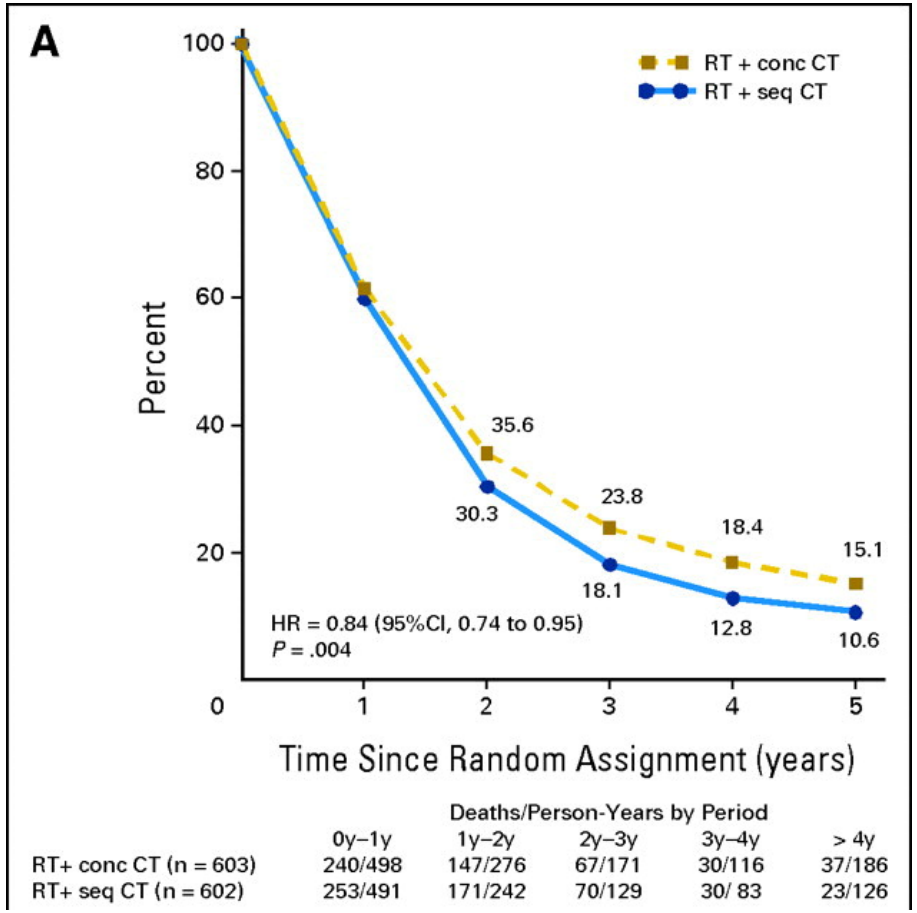
PACIFIC: Durvalumab vs placebo after chemoradiation for unresectable stage III nsclc

The Scope of Stage III Lung Cancer

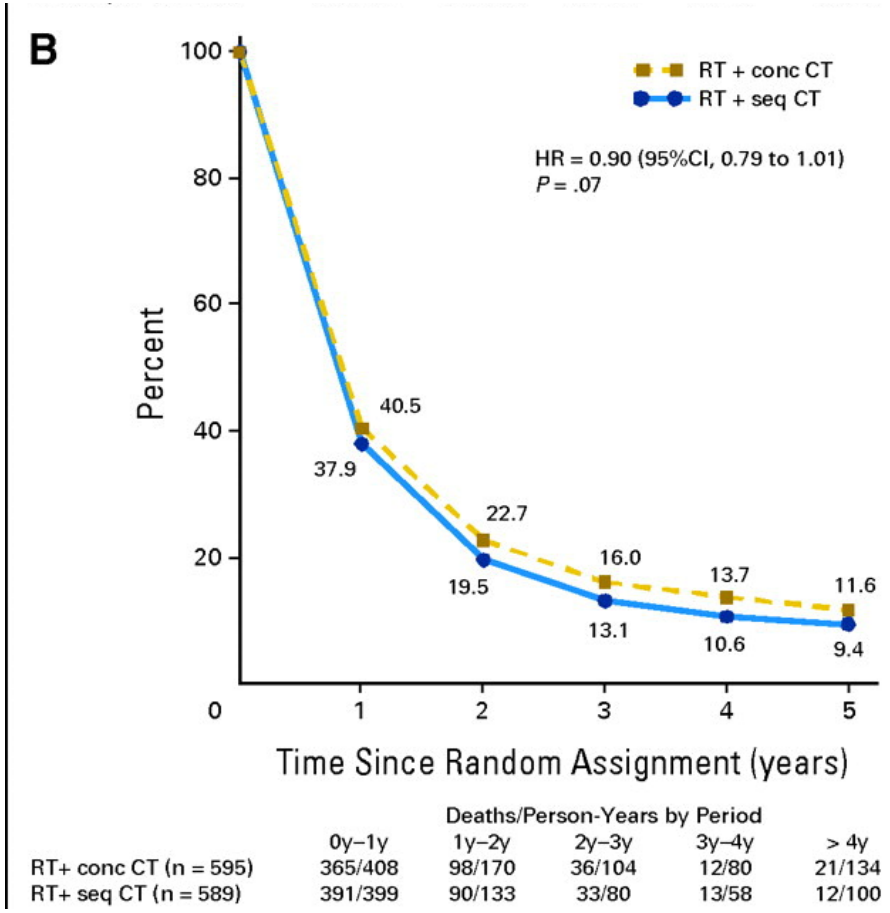


Source: cruk.org/cancerstats

Stage III Lung Cancer Is Potentially Curable



Overall Survival



Progression Free Survival

Auperin JCO **2010,** 28, 2181-2190.

PACIFIC: Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study

- Patients with stage III, locally advanced, unresectable NSCLC who have not progressed following definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- Estimated life expectancy of ≥12 weeks
- Archived tissue was collected

All-comers population

1–42 days post-cCRT

R

2:1 randomization, stratified by age, sex, and smoking history
N=713

Durvalumab
10 mg/kg q2w for up to 12 months
N=476

Placebo
10 mg/kg q2w for up to 12 months
N=237

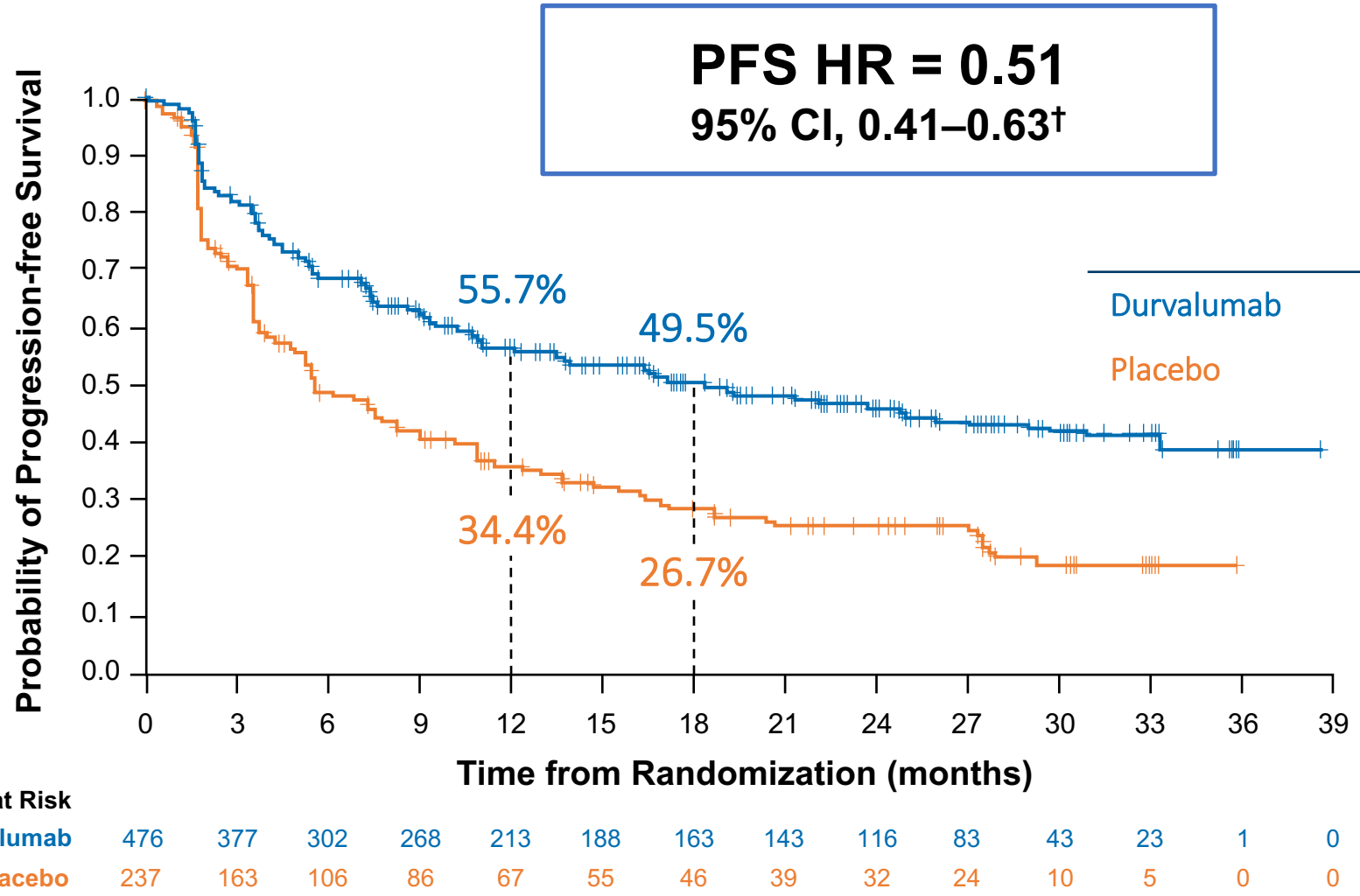
Co-primary endpoints
- PFS by BICR using RECIST v1.1*
- OS

Key secondary endpoints
- ORR (per BICR)
- DoR (per BICR)
- Safety and tolerability
- PROs

*Defined as the time from randomization (which occurred up to 6 weeks post-cCRT) to the first documented event of tumor progression or death in the absence of progression.
ClinicalTrials.gov number: NCT02125461 BICR, blinded independent central review; cCRT, concurrent chemoradiation therapy; DoR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PROs, patient-reported outcomes; PS, performance status; q2w, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization

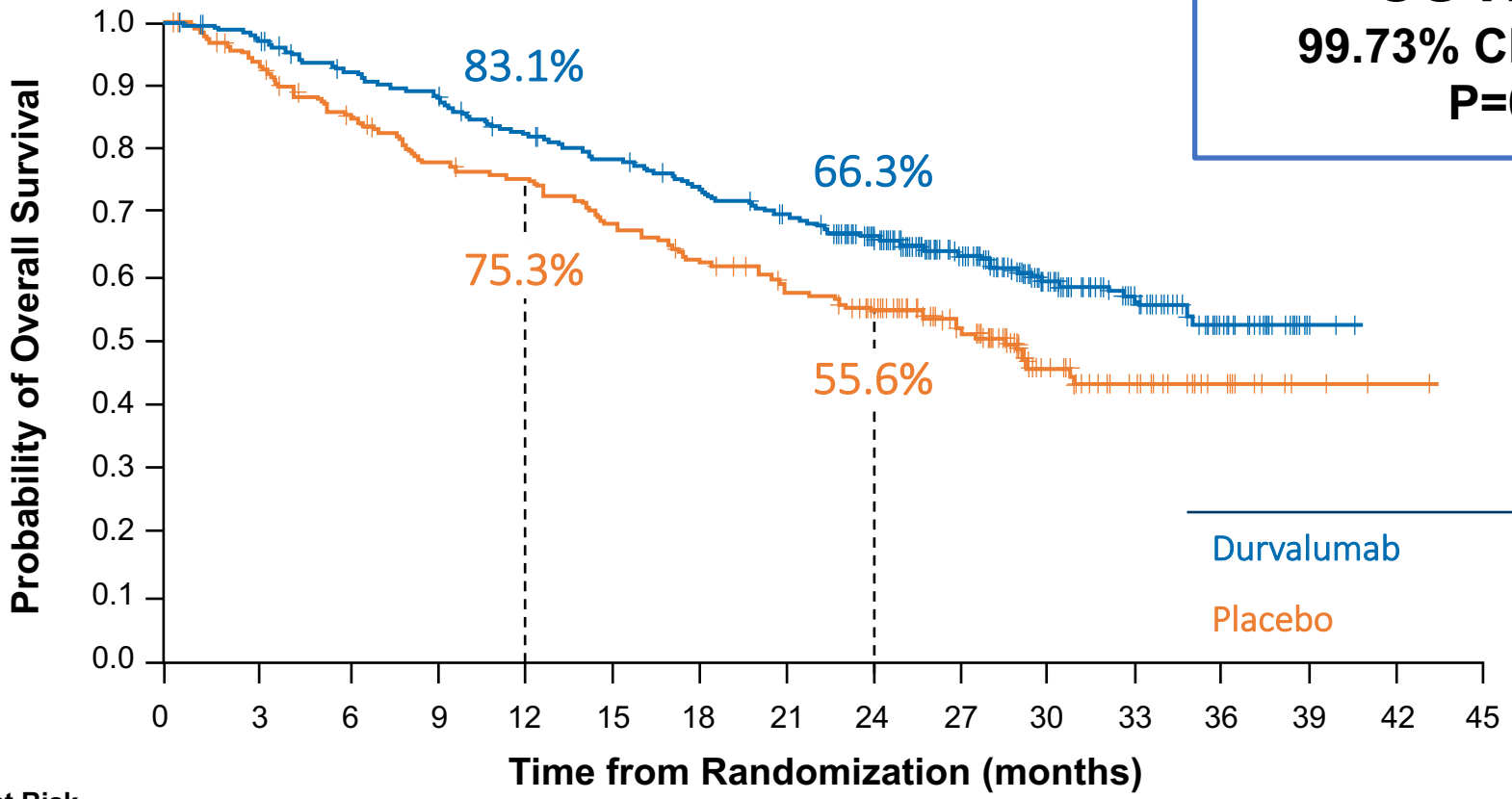
Antonia SJ, et al, *N Engl J Med* 2017 [ePub ahead of print]

Updated Progression-free Survival by BICR* (ITT)



	No. of events / No. of patients (%)	Median PFS (95% CI) months
Durvalumab	243/476 (51.1)	17.2 (13.1–23.9)
Placebo	173/237 (73.0)	5.6 (4.6–7.7)

Overall Survival (ITT)



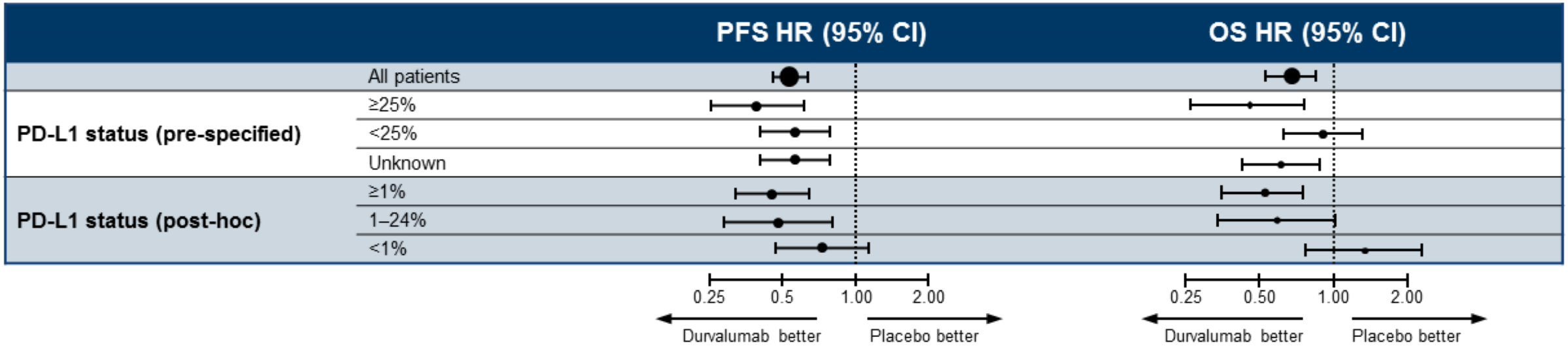
OS HR = 0.68
99.73% CI, 0.469–0.997†
P=0.00251

	No. of events / No. of patients (%)	Median OS (95% CI) months
Durvalumab	183/476 (38.4)	NR (34.7–NR)
Placebo	116/237 (48.9)	28.7 (22.9–NR)

No. at Risk

Durvalumab	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

Subgroup Analysis by PD-L1 Status



- Important facts regarding PD-L1 status:
  - PD-L1 testing was not required
  - 37% of patients with unknown PD-L1 status
  - PD-L1 status was obtained pre-CRT (getting a sample post-CRT medically not feasible)
  - PD-L1 expression-level cutoff of 1% was part of an unplanned post-hoc analysis requested by a health authority

Updated Safety Summary

	Durvalumab (N=475)	Placebo (N=234)
Any-grade all-causality AEs, n (%)	460 (96.8)	222 (94.9)
Grade 3/4	145 (30.5)	61 (26.1)
Outcome of death	21 (4.4)	15 (6.4)
Leading to discontinuation	73 (15.4)	23 (9.8)
Serious AEs, n (%)	138 (29.1)	54 (23.1)
Any-grade pneumonitis/radiation pneumonitis, n (%)	161 (33.9)	58 (24.8)
Grade 3/4	17 (3.6)	7 (3.0)
Outcome of death	5 (1.1)	5 (2.1)
Leading to discontinuation	30 (6.3)	10 (4.3)

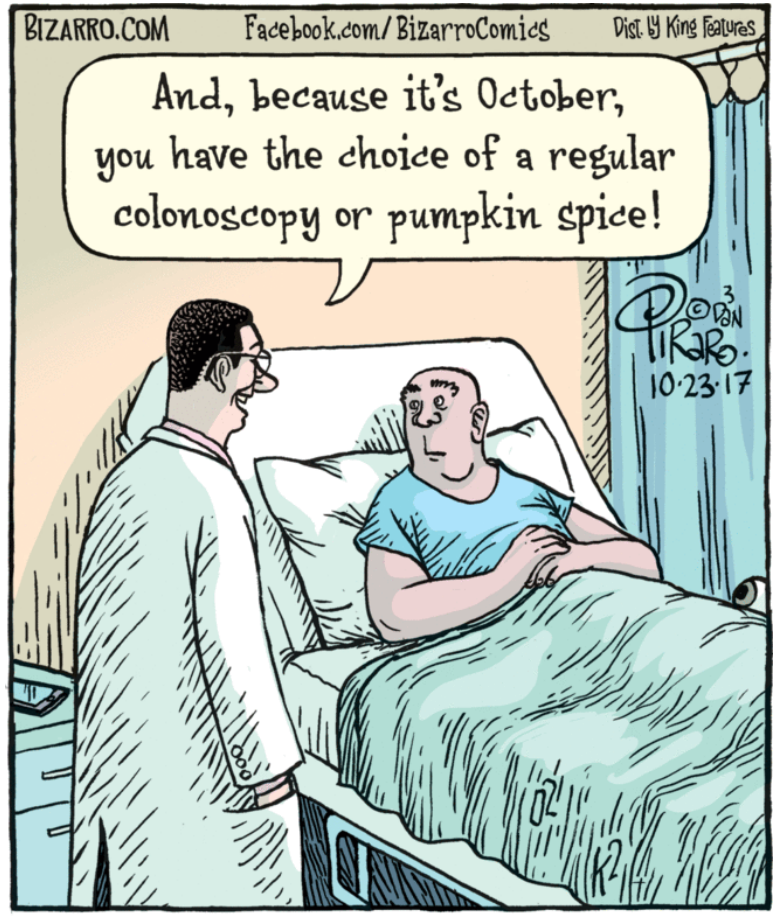
How this changed my practice

- First treatment to improve overall survival in Stage III NSCLC in 20 years
- Biggest benefit in patients starting within two weeks of completing chemoradiotherapy – plan ahead
- Monitor for symptoms of pneumonitis – worsening shortness of breath, new cough and treat appropriately

Recap

- Question 1: Can chemotherapy be avoided in patients with ER+, HER2-, LN- breast cancer
  - Yes, for patients with Oncotype score <24 and >50
- Question 2: Can adjuvant trastuzumab be limited to six months
  - Stop trastuzumab for low risk patients who have had any cardiotoxicity
- Question 3: Can outcomes be improved for resected pancreatic cancer?
  - mFOLFIRINOX should be considered in select, good performance status patients
- Question 4: Can outcomes be improved for unresectable Stage III NSCLC?
  - Adjuvant durvalumab improves overall survival and has a favourable toxicity profile

Questions?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And, because it's October, you have the choice of a regular colonoscopy or pumpkin spice!
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