

Updated Results
CALGB 80803

Phase II - PET Response Guided
Induction Chemoradiation for
Esophageal Cancer

Daniel Boffa, MD, MBA
Yale School of Medicine



Disclosure

- Epic Sciences Ran experiments for free

Disclaimer

Randomized Phase II Study of PET Response-Adapted Combined Modality Therapy for Esophageal Cancer: Mature Results of the CALGB 80803 (Alliance) Trial

[Karyn A Goodman](#)¹, [Fang-Shu Ou](#)², [Nathan C Hall](#)³, [Tanios Bekaii-Saab](#)⁴, [Briant Fruth](#)², [Erin Twohy](#)², [Michael O Meyers](#)⁵, [Daniel J Boffa](#)⁶, [Kisha Mitchell](#)⁷, [Wendy L Frankel](#)⁸, [Donna Niedzwiecki](#)⁹, [Anne Noonan](#)⁸, [Yelena Y Janjigian](#)¹⁰, [Paul J Thurmes](#)¹¹, [Alan P Venook](#)¹², [Jeffrey A Meyerhardt](#)¹³, [Eileen M O'Reilly](#)¹⁰, [David H Ilson](#)¹⁰

**Journal of
Clinical
Oncology®**

Background – Esophageal Cancer

- Induction therapy → pCR (25%)

Background – Esophageal Cancer

- Induction therapy → pCR (25%)
 - *75% of patients have resistance to induction*

Background

- Induction therapy → pCR (25%)
 - *75% of patients have resistance to induction*
- Best prognosis = pCR
 - Hypothesis: *increasing pCR → increasing survival*

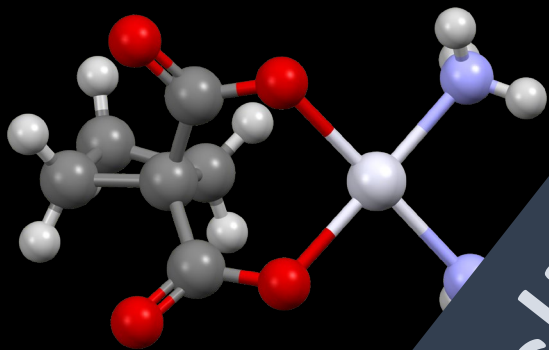
Background

- Induction therapy → pCR (25%)
 - *75% of patients have resistance to induction*
- Best prognosis = pCR
 - *→ increasing pCR → increasing survival*
- Different Chemotherapies
 - *Different mechanism of resistance*

Background

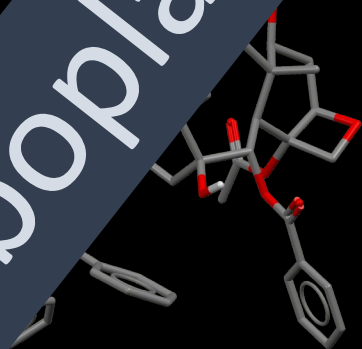
Change chemotherapy?

- Different Chemotherapies
 - *Different mechanism of resistance*



Carboplatin

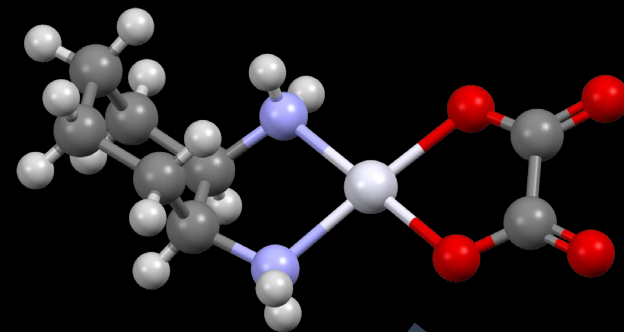
Cross links DNA



Paclitaxel

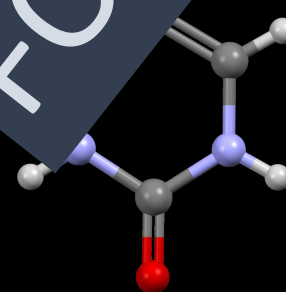
Inhibits microtubule assembly

Carboplatin-Paclitaxel



Oxaliplatin

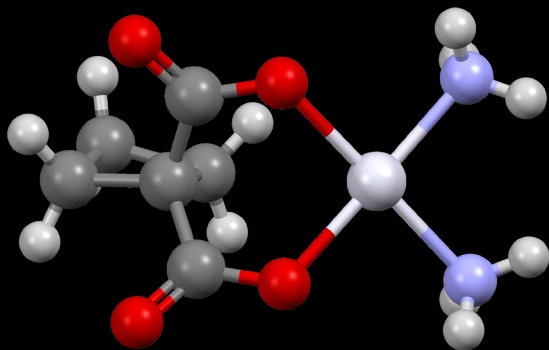
Cross links DNA



5 Fluorouracil

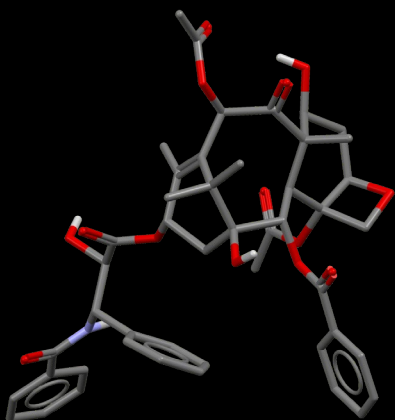
Thymidylate synthase inhibitor

FOLFOLX



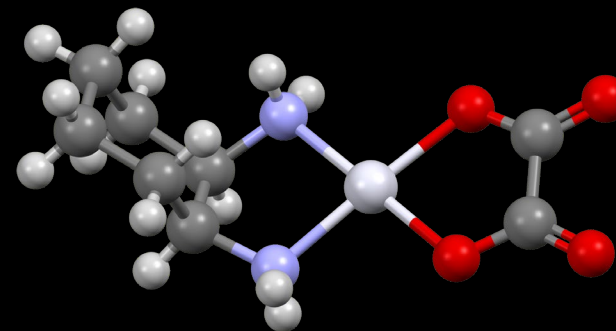
Carboplatin

Cross links DNA



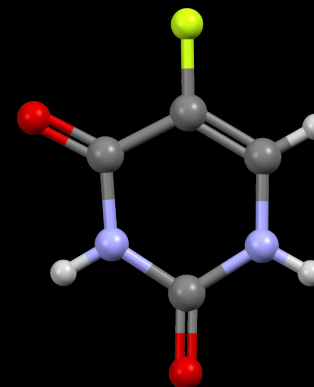
Paclitaxel

Inhibits microtubule assembly



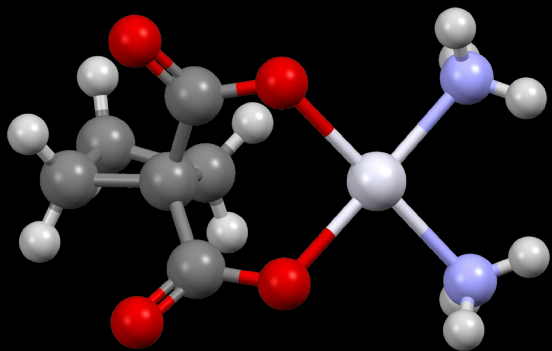
Oxaliplatin

Cross links DNA

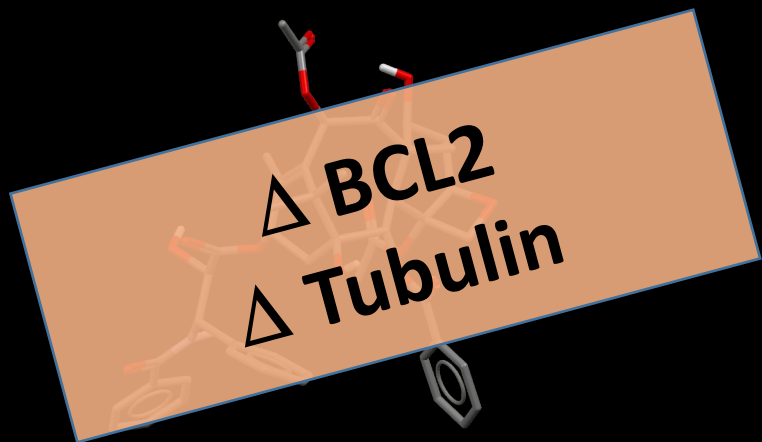


5 Fluorouracil

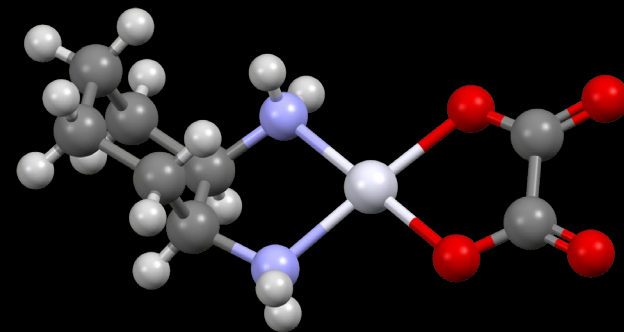
Thymidylate synthase inhibitor



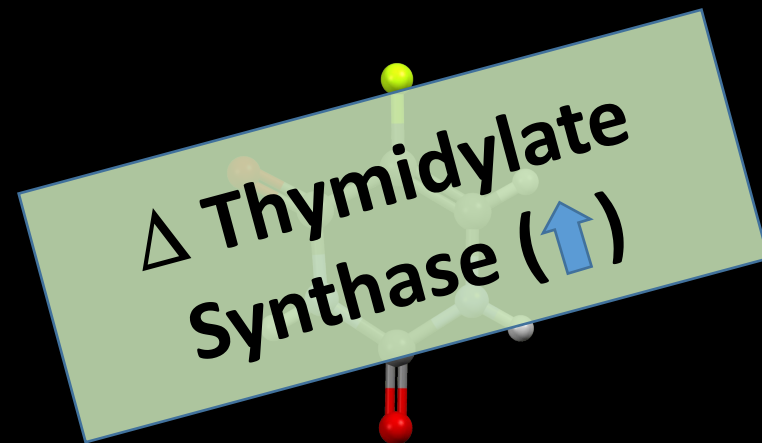
Carboplatin
Cross links DNA



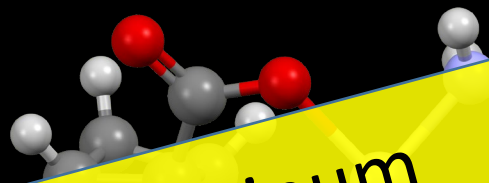
Paclitaxel
Inhibits microtubule assembly



Oxaliplatin
Cross links DNA

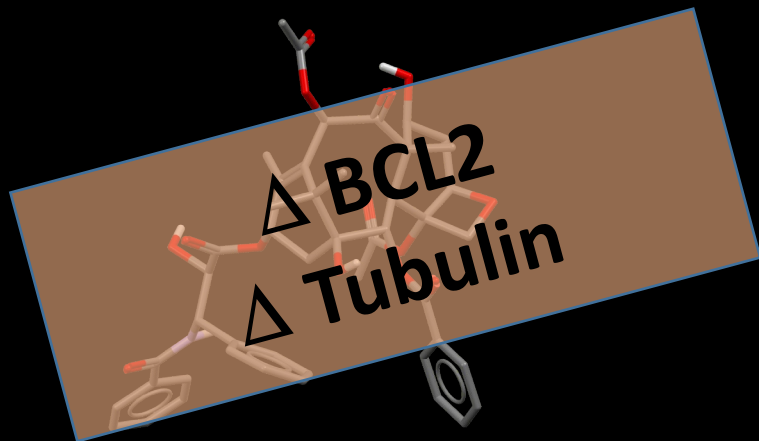


5 Fluorouracil
Thymidylate synthase inhibitor



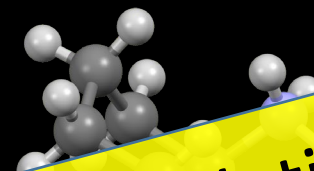
Platinum
Resistance*

Carboplatin
Cross links DNA



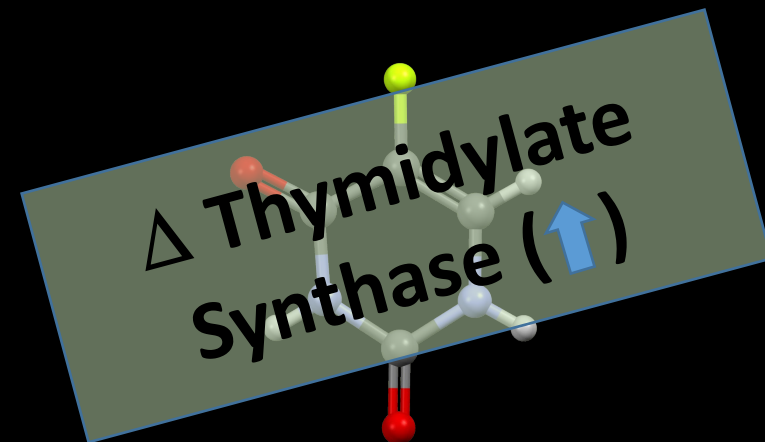
Δ BCL2
Δ Tubulin

Paclitaxel
Inhibits microtubule assembly



Platinum
Resistance*

Oxaliplatin
Cross links DNA



Δ Thymidylate
Synthase (↑)

5 Fluorouracil
Thymidylate synthase inhibitor

Solute carrier superfamily of membrane transporters

SLC22 families

SLC47 families

SLC31A families

	OCT1	OCT2	OCT3	MATE1	MATE2K	CTR1	CTR2
--	------	------	------	-------	--------	------	------

Cisplatin	±	+	—	+	—	+	*
Oxaliplatin	±	+	+	+	+	+	*
Carboplatin	—	—	—	—	—	+	*

Solute carrier superfamily of membrane transporters

SLC22 families

SLC47 families

SLC31A families

	OCT1	OCT2	OCT3	MATE1	MATE2K	CTR1	CTR2
--	------	------	------	-------	--------	------	------

Cisplatin	±	+	−	+	−	+	*
Oxaliplatin	±	+	+	+	+	+	*
Carboplatin	−	−	−	−	−	+	*

- Chemo “A” → no PET resp


$$\Delta \max SUV < 35\%$$

Continue

- Chemo **"A"** → no PET resp → Chemo **"A"** + XRT

- Chemo “A” → no PET resp → Chemo “A” + XRT → 5% pCR

- Chemo “A” → no PET resp → Chemo “A” + XRT → 5% pCR

- Chemo “A” → no PET resp → Chemo “B” + XRT →

Change

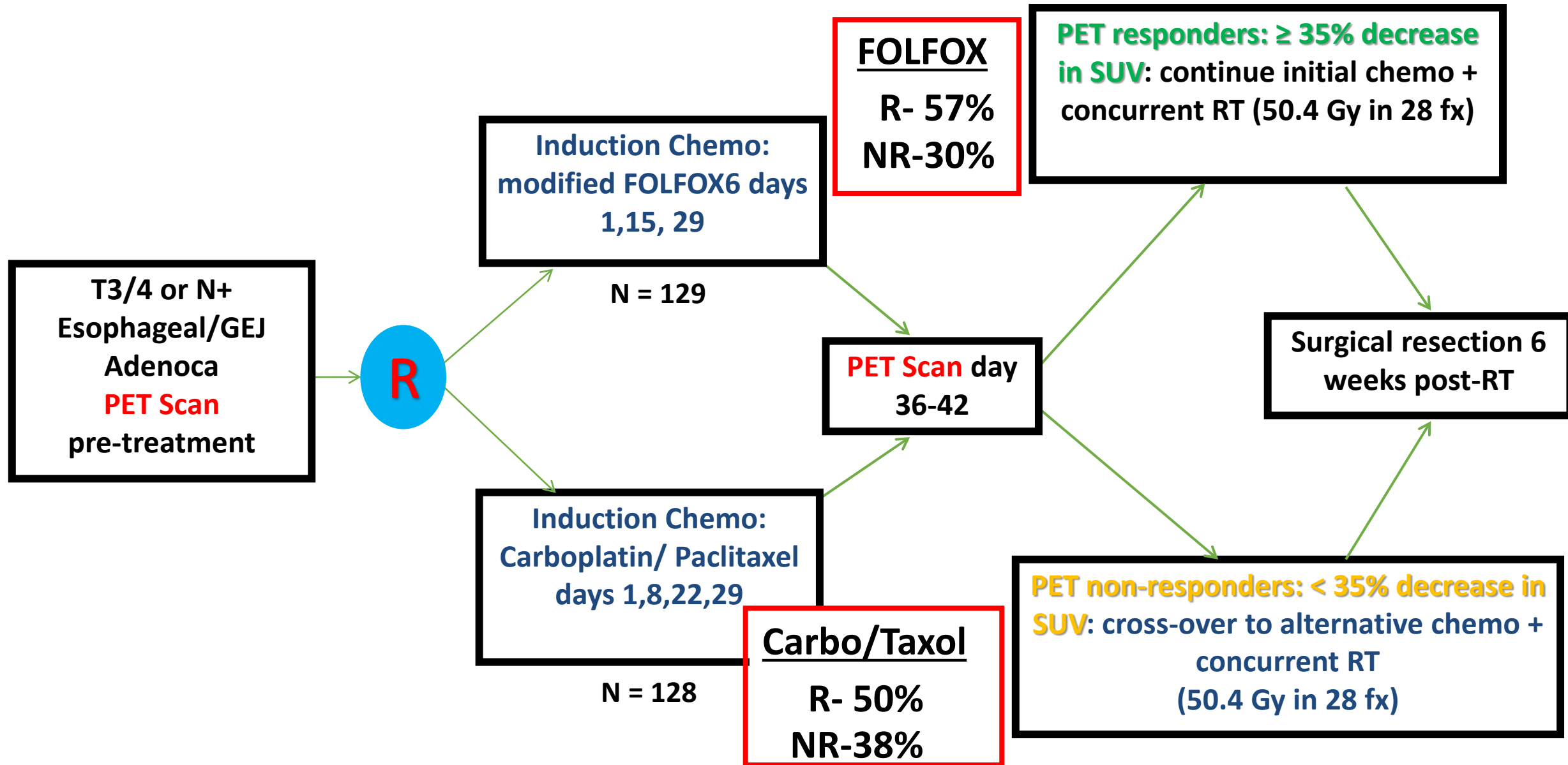
NULL HYPOTHESIS

- Chemo “A” → no PET resp → Chemo “A” + XRT → 5% pCR
 - Chemo **“A”** → no PET resp → Chemo **“B”** + XRT → **20%** pCR
- 
Change

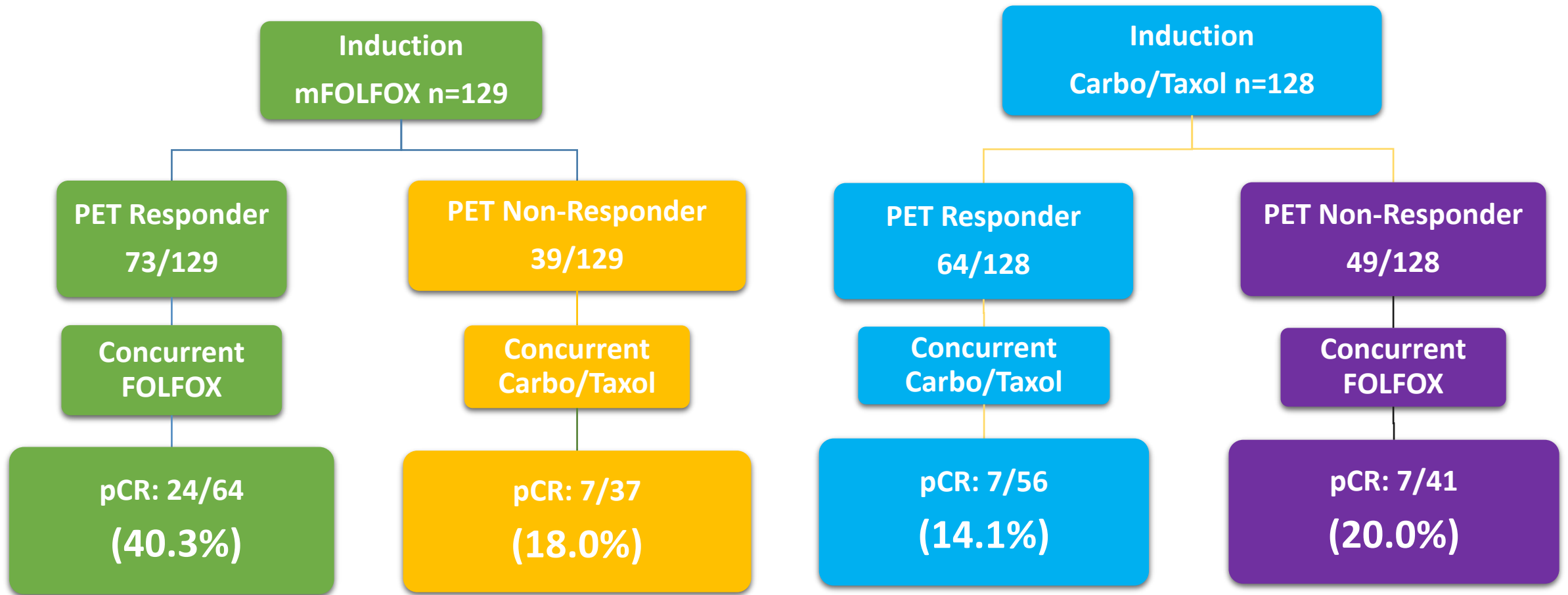
CALGB 80803

- Adenocarcinoma (n = 225)
- cT_≥2 or N>0
- Distal Esoph or GEJ
- Chemo → PET → Change chemo? → Chemo + XRT → esophagectomy
 - Carboplatinum + Paclitaxel → 97 (76%) esophagectomy
 - FOLFOX → 101 (78%) esophagectomy
- Primary endpoint = pCR in nonresponders

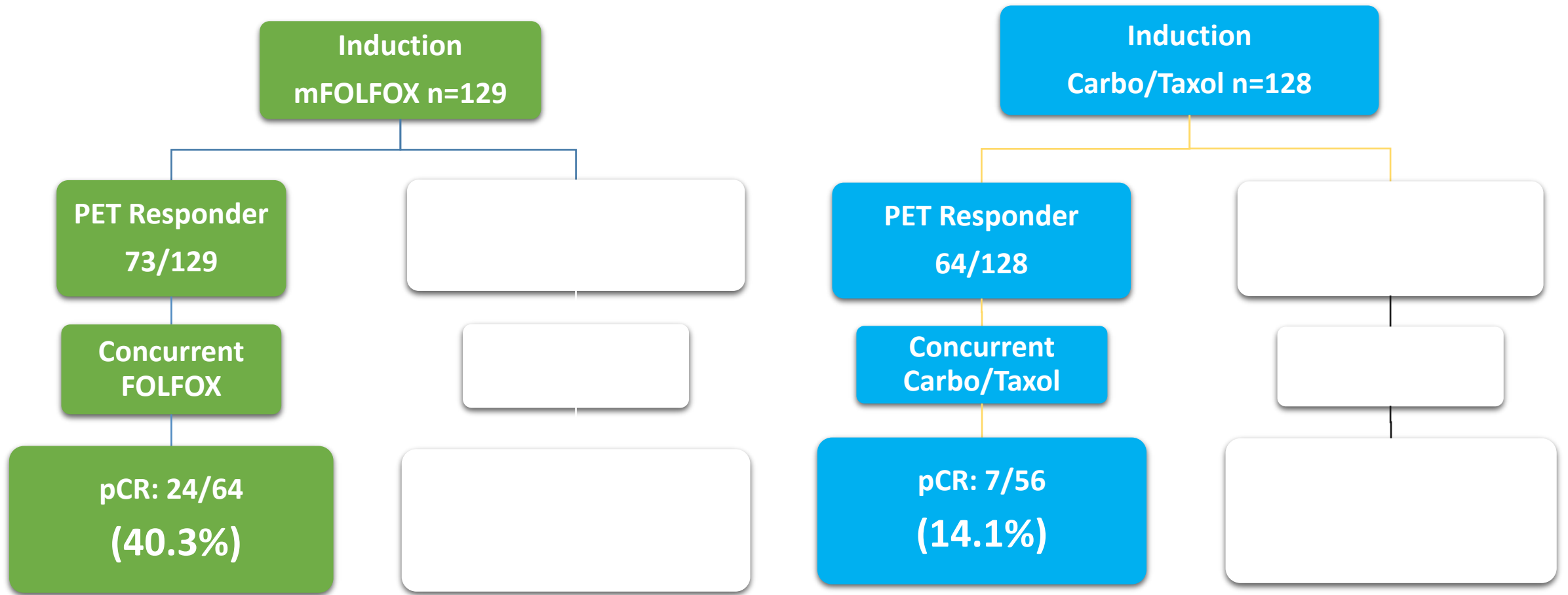
CALGB 80803: PET-Directed Therapy



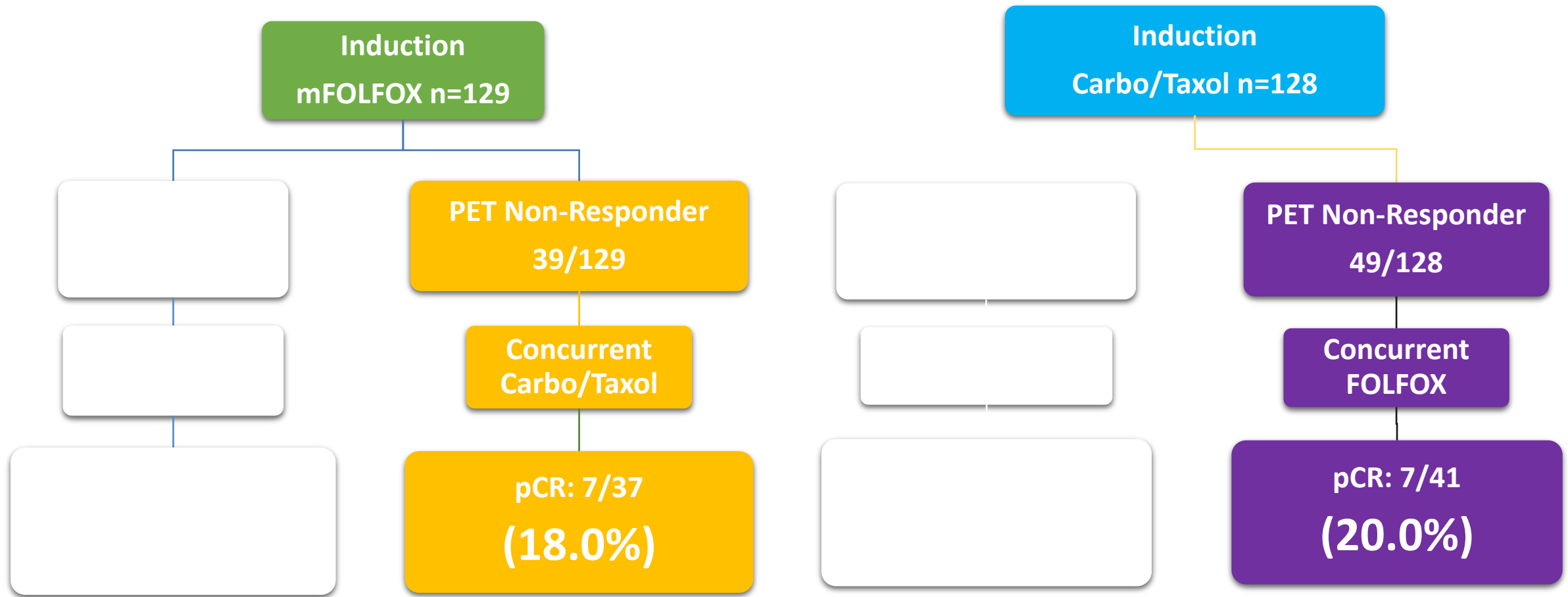
Pathologic Complete Response Rates



Pathologic Complete Response Rates



Pathologic Complete Response Rates



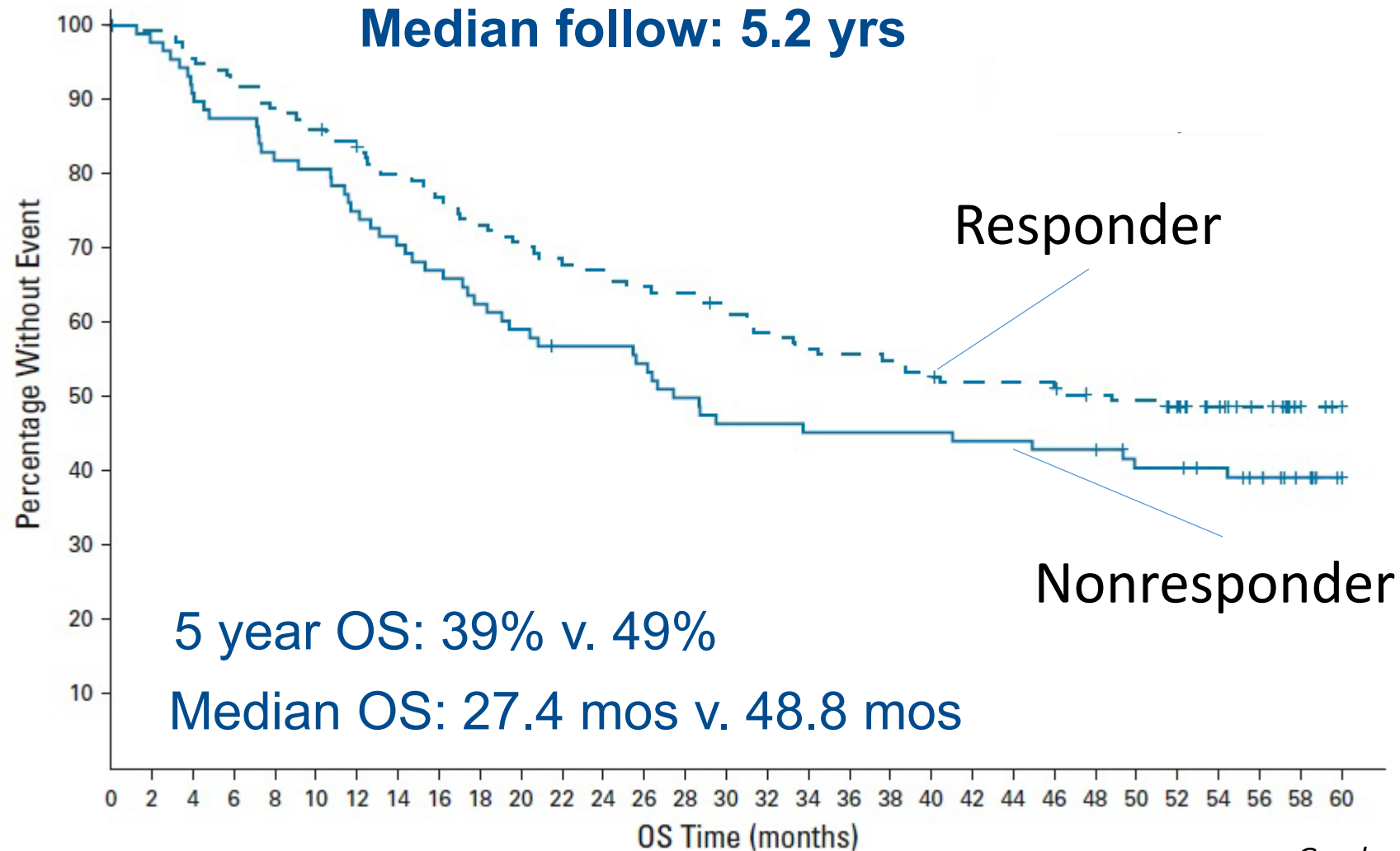
Efficacy criteria met for both induction arms

CALGB 80803

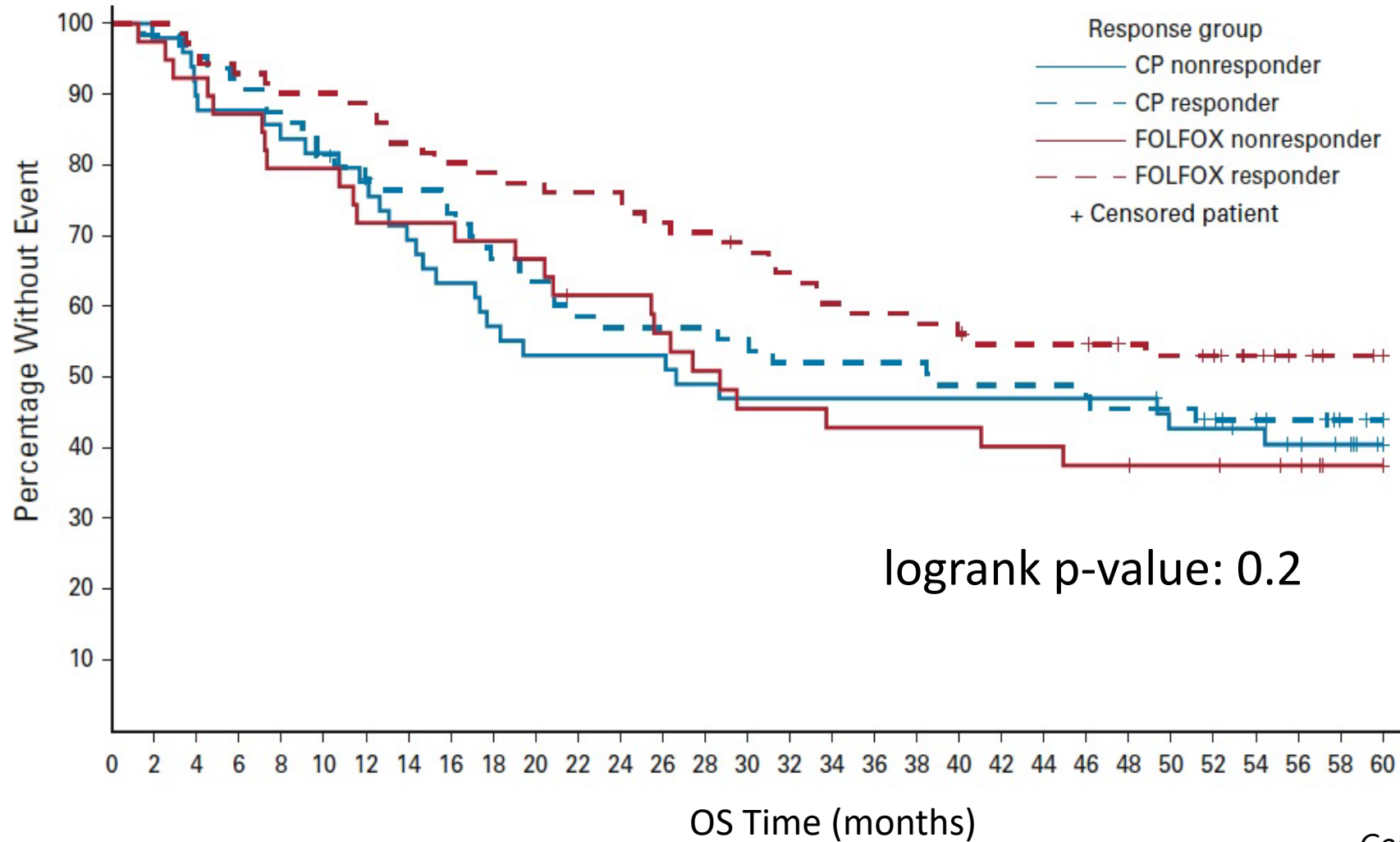
- R0 resection = 93.5%
- 90-day mortality = 3.3% (5/6 started with CP)
- 5-year survival = 44.5%

Survival Results

p=0.1



Survival Results by Treatment Group



CALGB 80803

- pCR more likely with FOLFOX start (31% vs 14% CP)
 - pCR rate for CP was odd in this study (CROSS was 29%)

CALGB 80803

- pCR more likely with FOLFOX start (31% vs 14% CP)
 - pCR rate for CP was odd in this study (CROSS was 29%)
- pCR does not tell entire story (Carboplatin Paclitaxel similar survival)

OS by Induction Chemotherapy and PET Response

	Events/ Total	Median OS (mos)	2-year OS (%)	5-year OS (%)	P- value*
CP → FF Non-Responder	29/50	26.6	53.1	40.4	0.20
CP → CP Responder	37/64	38.7	56.9	43.9	
FF → CP Non-Responder	24/39	28.7	61.5	37.5	
FF → FF Responder	33/72	NE	76.1	53.0	

CALGB 80803

- pCR more likely with FOLFOX start (31% vs 14% CP)
- pCR does not tell entire story (Carboplatin Paclitaxel similar)
- Did PET-guided therapy improve outcomes?

OS by Induction Chemotherapy and PET Response

	Events/ Total	Median OS (mos)	2-year OS (%)	5-year OS (%)	P- value*
CP → FF Non-Responder	29/50	26.6	53.1	45%	0.20
CP → CP Responder	37/64	38.7	56.9		
FF → CP Non-Responder	24/39	28.7	61.5		
FF → FF Responder	33/72	NE	76.1		

OS by Induction Chemotherapy and PET Response

	Events/ Total	Median OS (mos)	2-year OS (%)	5-year OS (%)	P- value*
CP → FF Non-Responder	2	CROSS trial (Carbo-Platin) 45% 5-year in ACA			0.20
CP → CP Responder	3				
FF → CP Non-Responder	2				
FF → FF Responder	3				

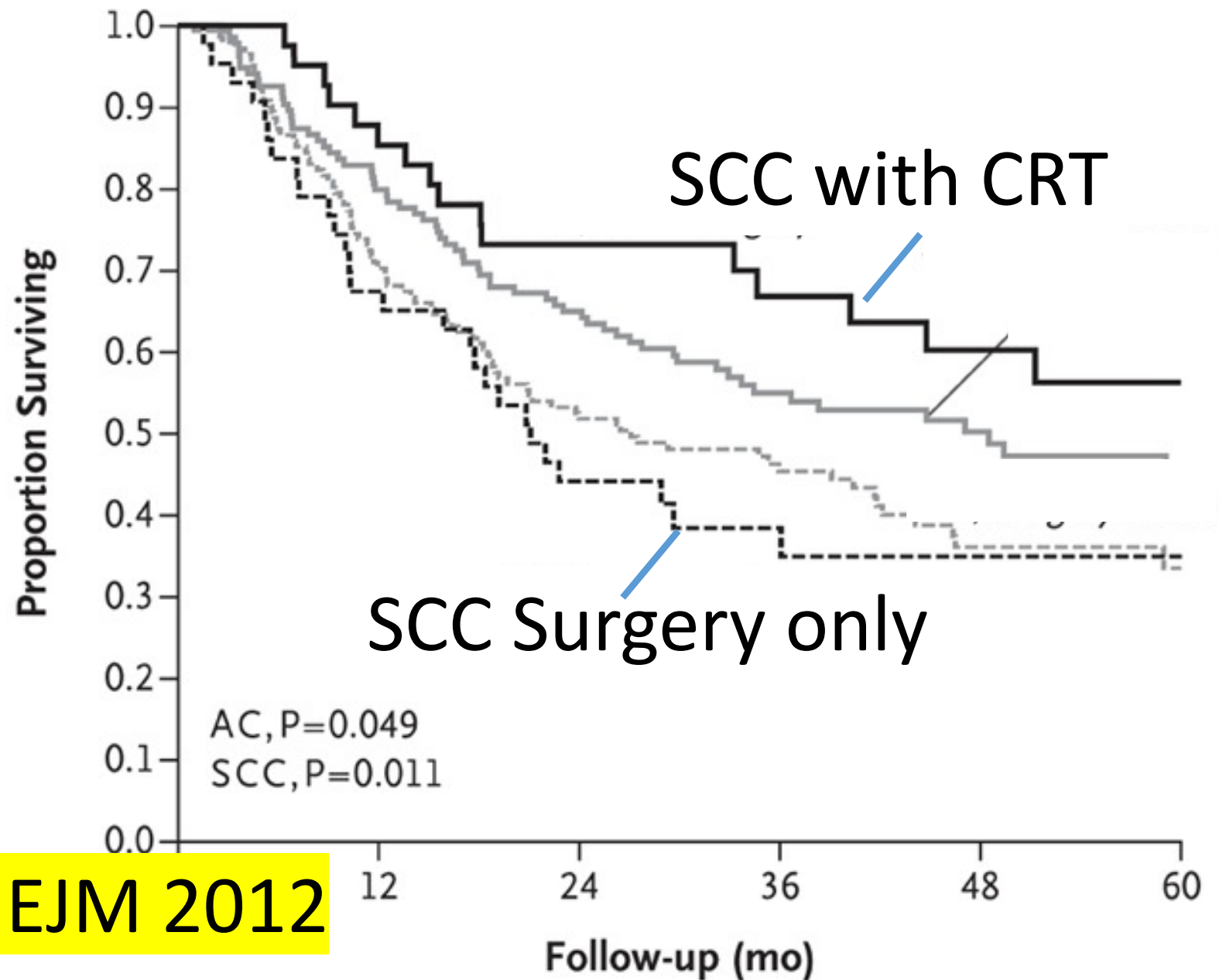
CALGB 80803 - *Take home messages*

- PET between chemo and chemoradiation – predictive resistance
- Changing therapy *could* help – better alternative chemo?

CALGB 80803 - *Take home messages*

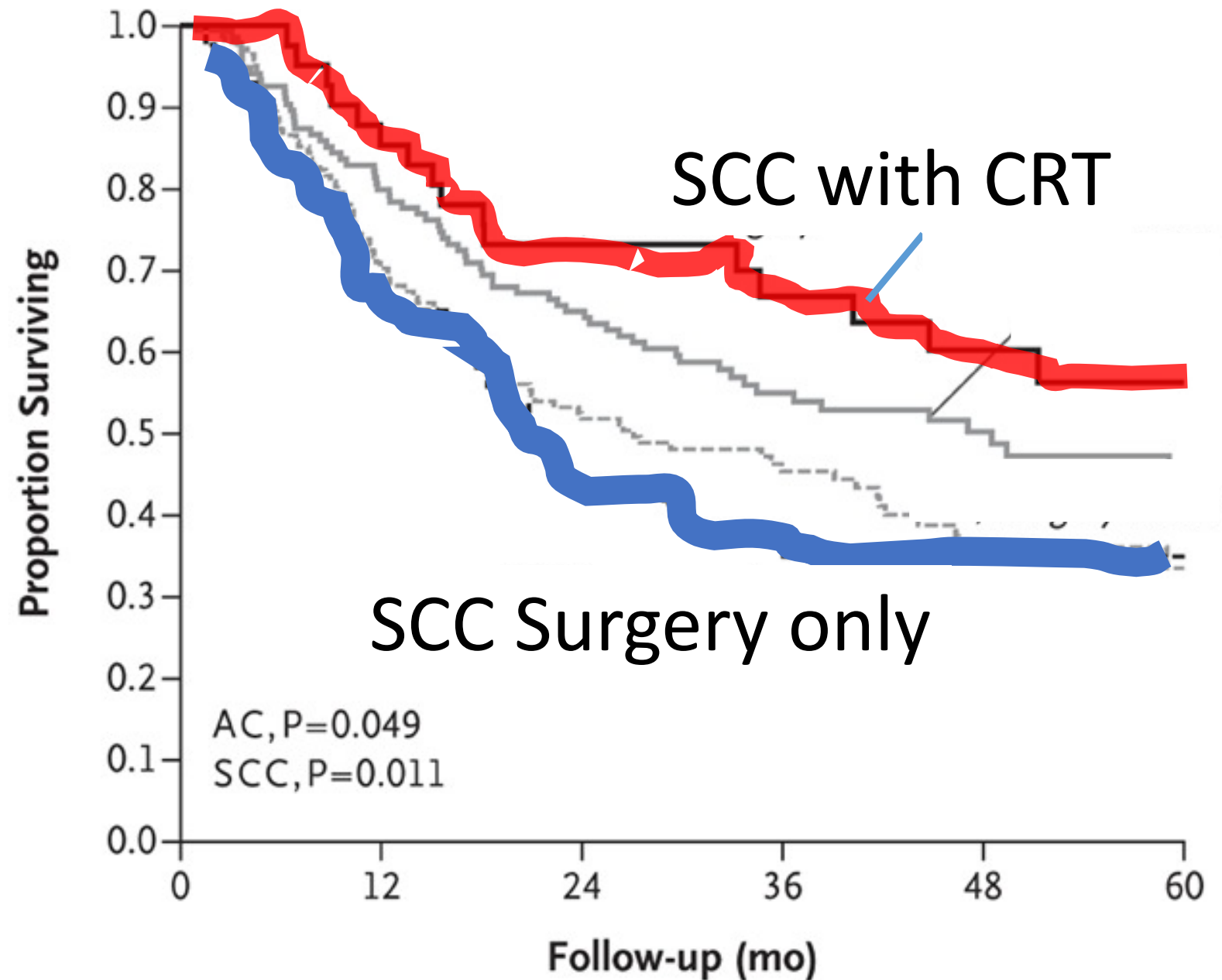
- Starting chemo
 - Squamous → should start with CP

B Survival According to Tumor Type and Treatment Group



CROSS Study NEJM 2012

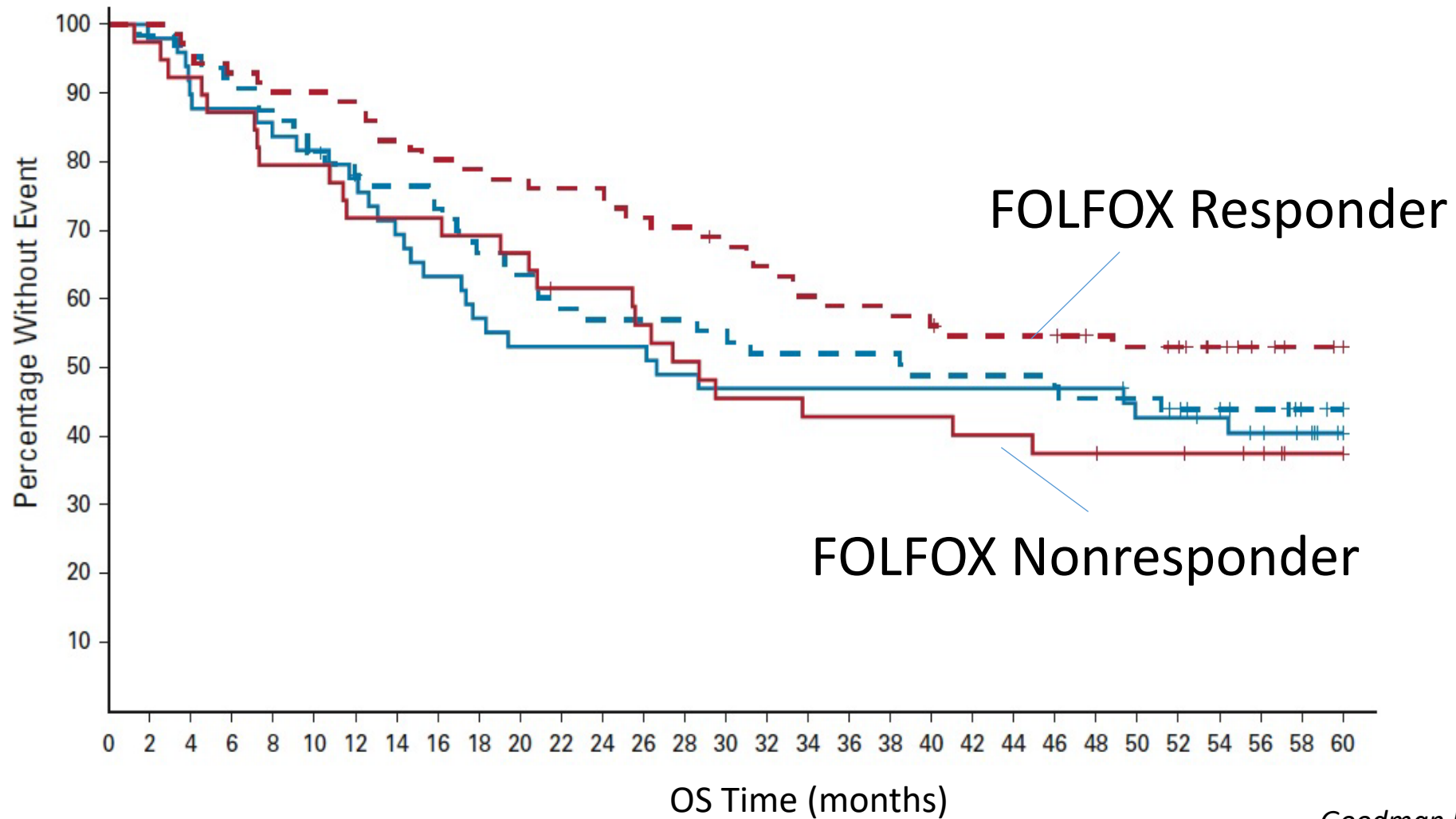
B Survival According to Tumor Type and Treatment Group



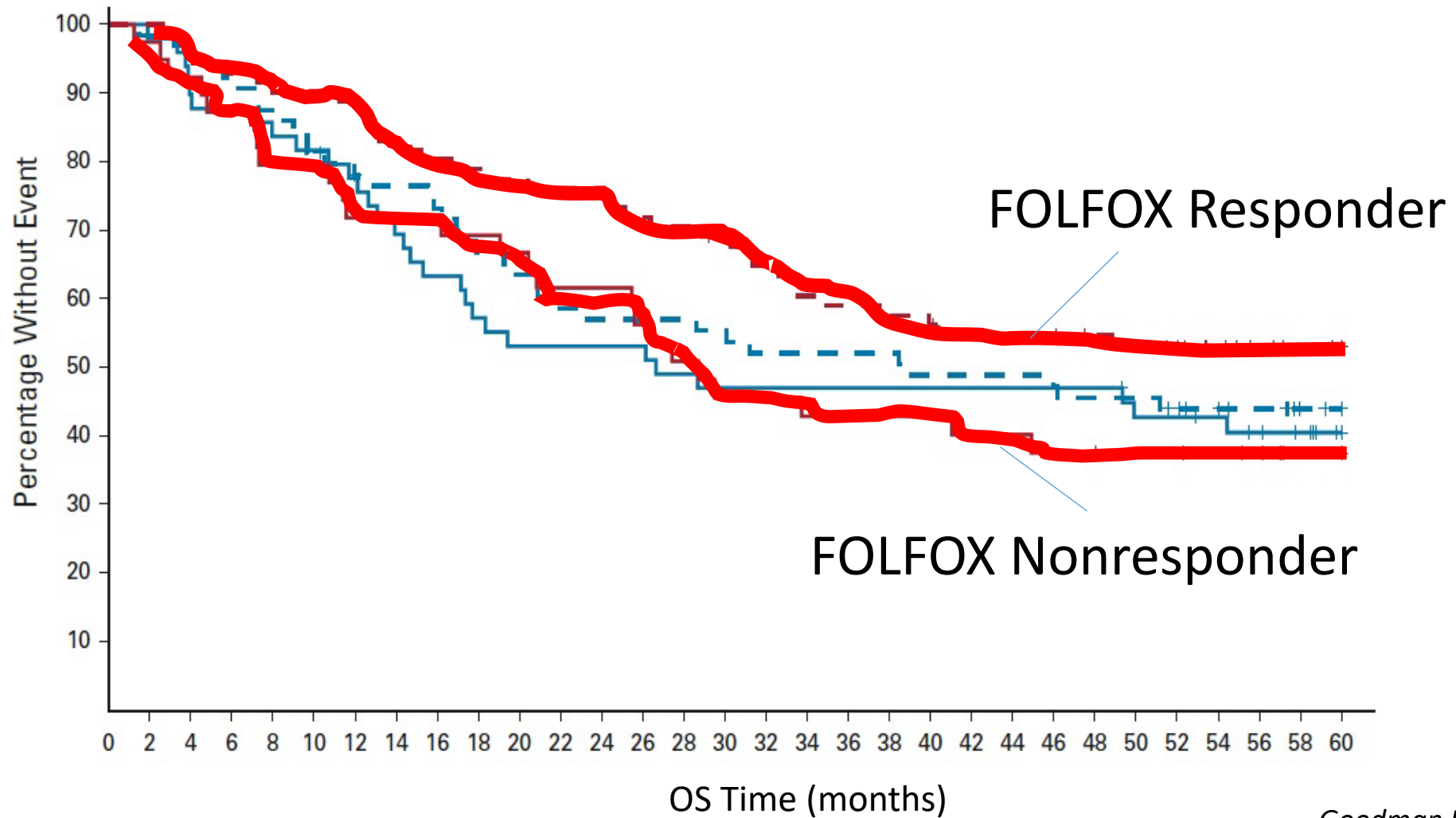
CALGB 80803 - Take home messages

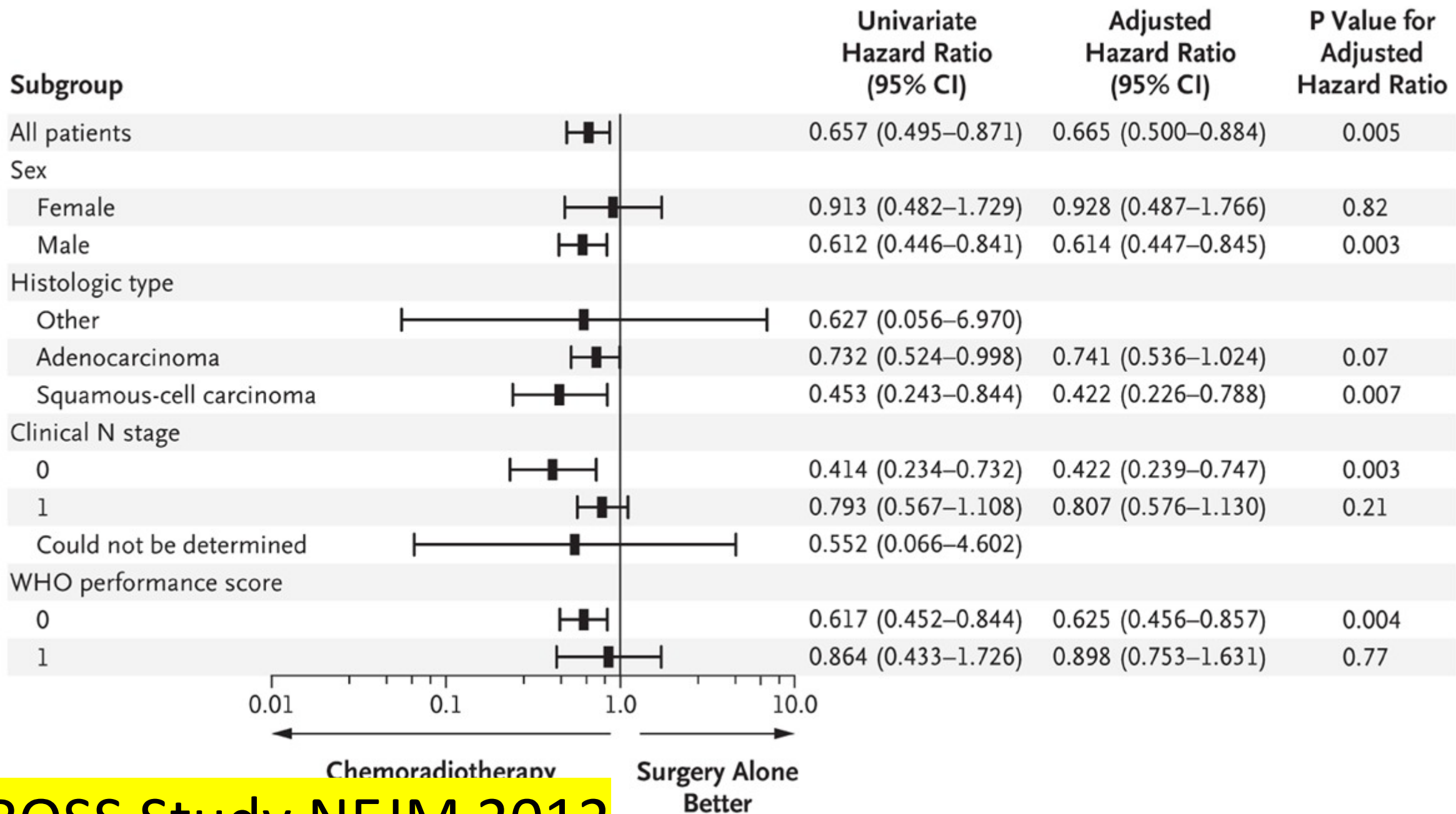
- Starting chemo
 - Squamous → should start with CP
 - Adeno → *adds* to signal FOLFOX advantage (better stratification)
 - Ongoing studies (e.g. phase II PROTECT 1402)

Survival Results by Treatment Group

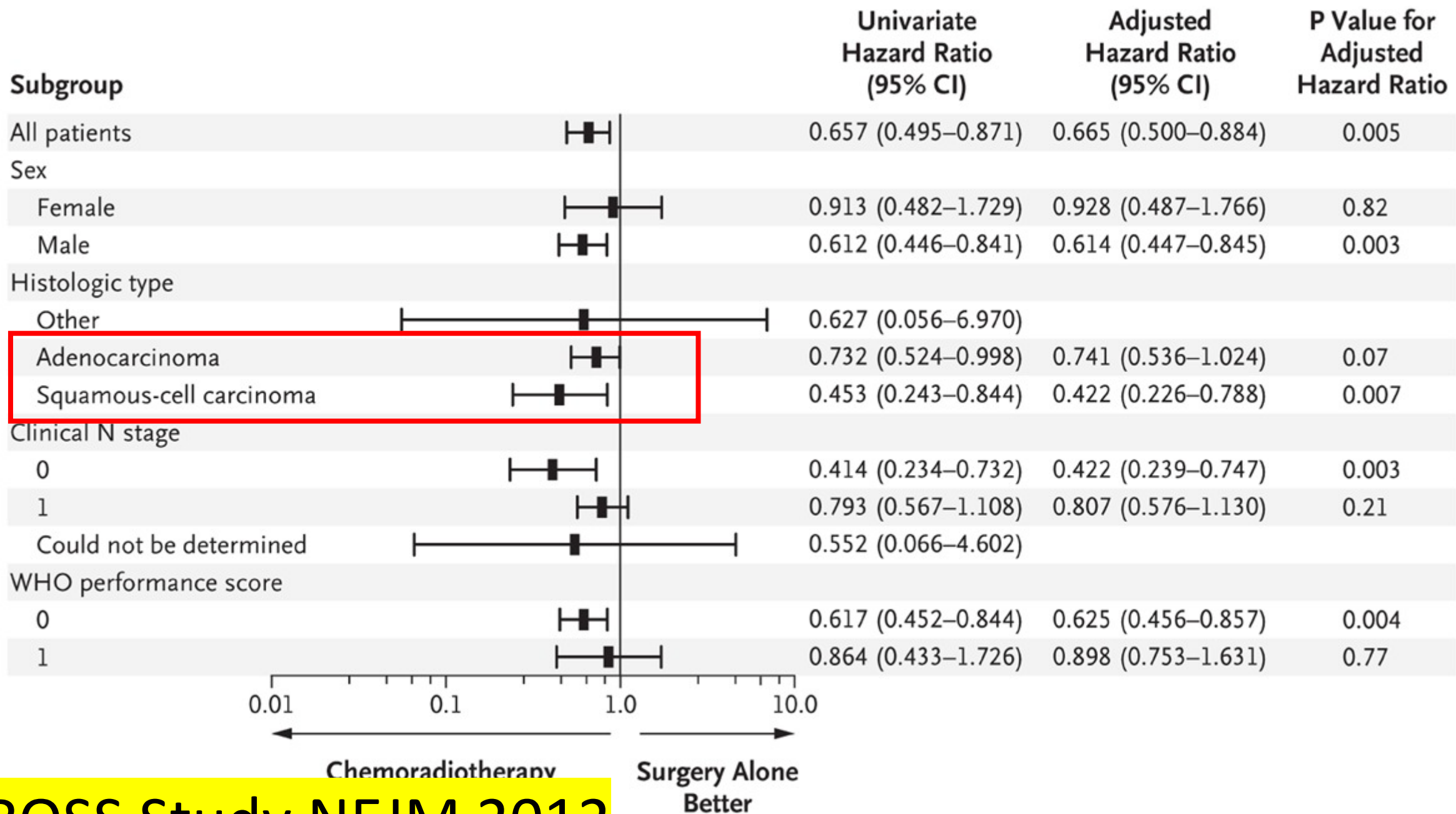


Survival Results by Treatment Group





CROSS Study NEJM 2012



CROSS Study NEJM 2012

Thank you