

**Gynecologic Cancer InterGroup  
Cervix Cancer Research Network**



# **Beyond Platinum: Concurrent Chemotherapy in Cervix cancer**

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## CISPLATIN EFFICACY HAZARD RATIO PLOT FOR SURVIVAL

### (a) Platinum-based CRTT

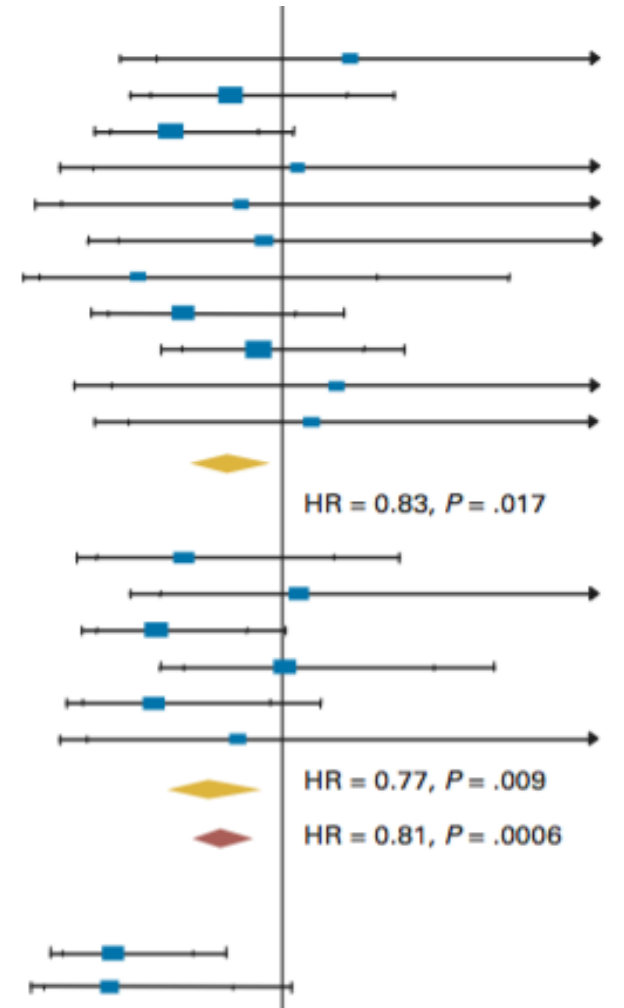
Onishi <sup>44</sup> (CDDP or CDBCA)	16	26	15	23	1.52	7.59
Pearcey <sup>43</sup> (CDDP)	53	130	60	129	-5.00	28.20
GOG0123 <sup>6</sup> (CDDP)	49	185	69	189	-12.90	29.38
Chen <sup>23</sup> (a) (CDDP FU VCR)	8	30	8	30	0.21	4.00
Chen <sup>23</sup> (b) (CDDP FU VCR)	6	30	7	30	-0.45	3.25
Pras (CDBCA FU)	17	28	16	26	-0.47	8.15
GOG0165 <sup>26</sup> (a) (CDDP)	8	26	12	24	-3.03	4.92
Cikaric <sup>47</sup> (CDDP)	37	100	48	100	-8.02	21.12
Leborgne (CDDP FU)	75	170	85	170	-3.07	39.91
Gariapagaoglu <sup>48</sup> (CDDP)	9	22	8	22	0.70	4.23
LaI <sup>50</sup> (CDDP)	14	94	12	86	0.62	6.49
<b>Sub-total</b>	<b>292</b>	<b>841</b>	<b>340</b>	<b>829</b>	<b>-29.89</b>	<b>157.23</b>

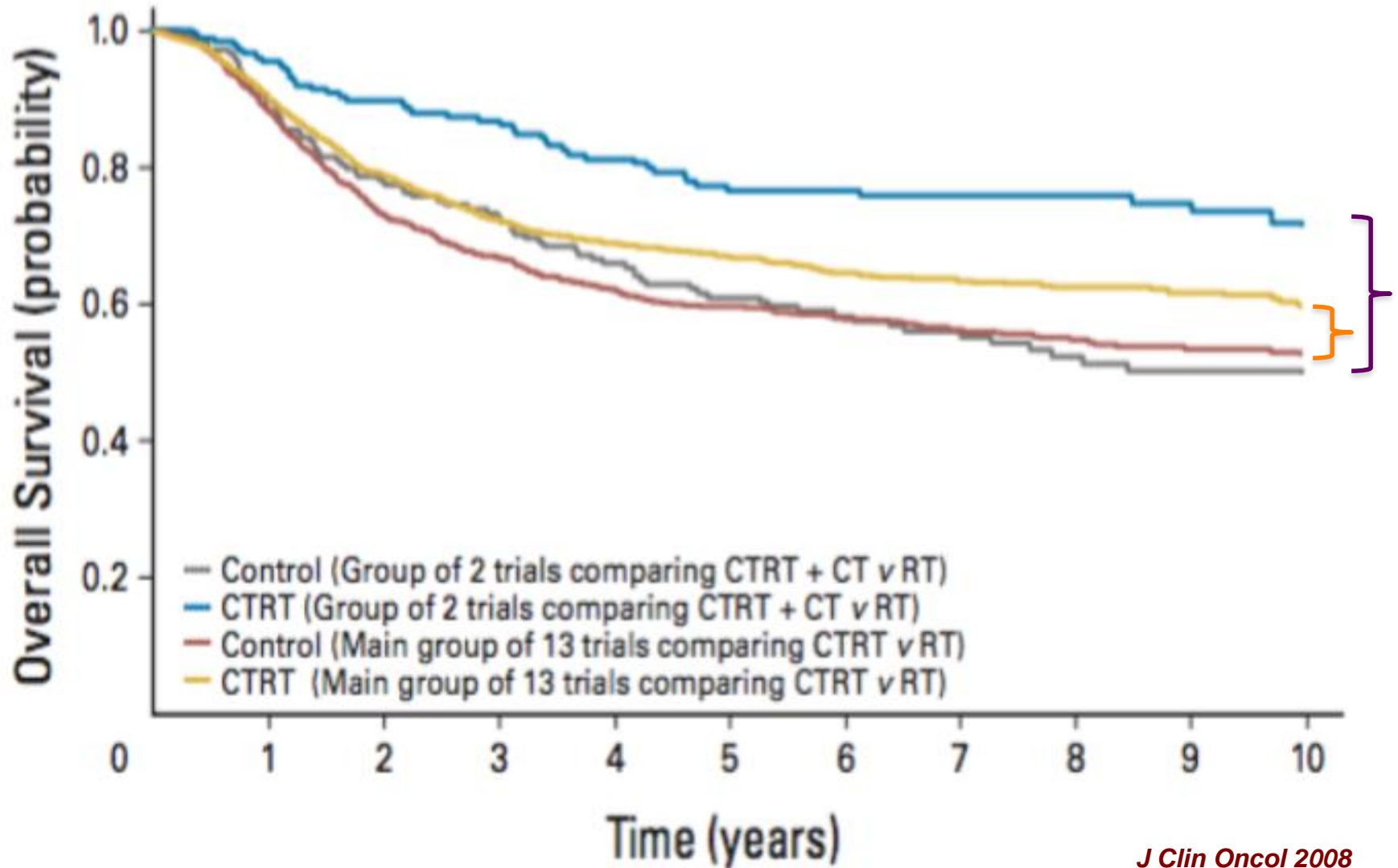
### (b) Non-platinum-based CRTT

Thomas <sup>24</sup> (a) (FU)	24	57	32	58	-5.16	13.83
Thomas <sup>24</sup> (b) (FU)	26	58	25	60	0.71	12.74
Lorvidhaya <sup>25</sup> (a) (MMC FU)	40	233	59	242	-12.52	24.57
Lorvidhaya <sup>25</sup> (b) (MMC FU)	54	230	49	221	0.31	25.67
Roberts <sup>49</sup> (MMC)	25	124	39	124	-8.39	15.92
GOG0165 <sup>26</sup> (b) (FU)	11	27	12	24	-0.82	5.55
<b>Sub-total</b>	<b>180</b>	<b>729</b>	<b>216</b>	<b>729</b>	<b>-25.87</b>	<b>98.28</b>
<b>Total</b>	<b>472</b>	<b>1,570</b>	<b>544</b>	<b>1,534</b>	<b>-54.56</b>	<b>251.54</b>

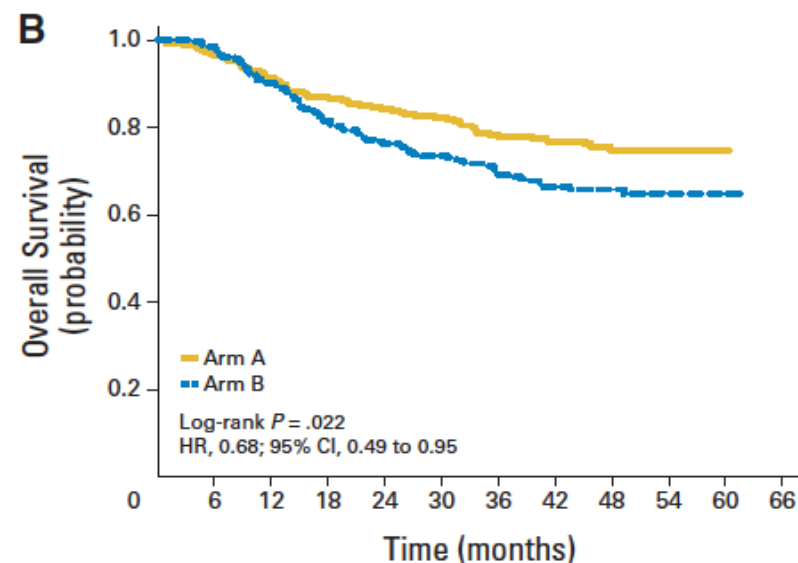
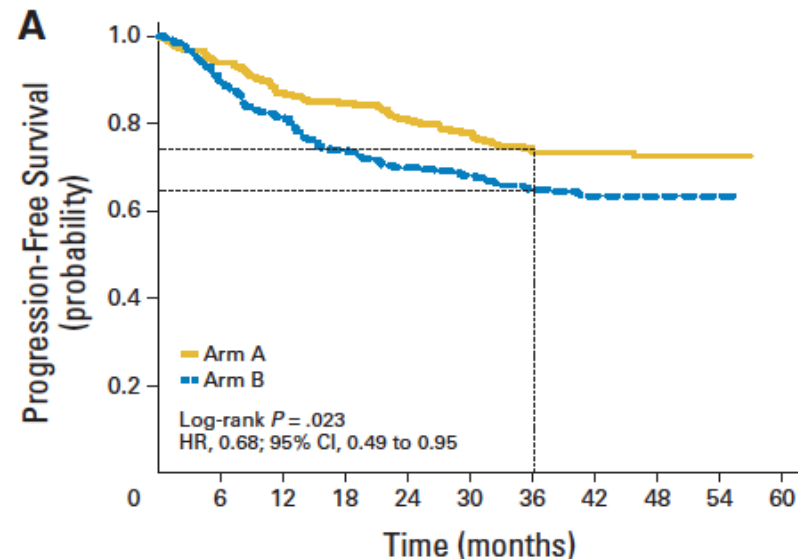
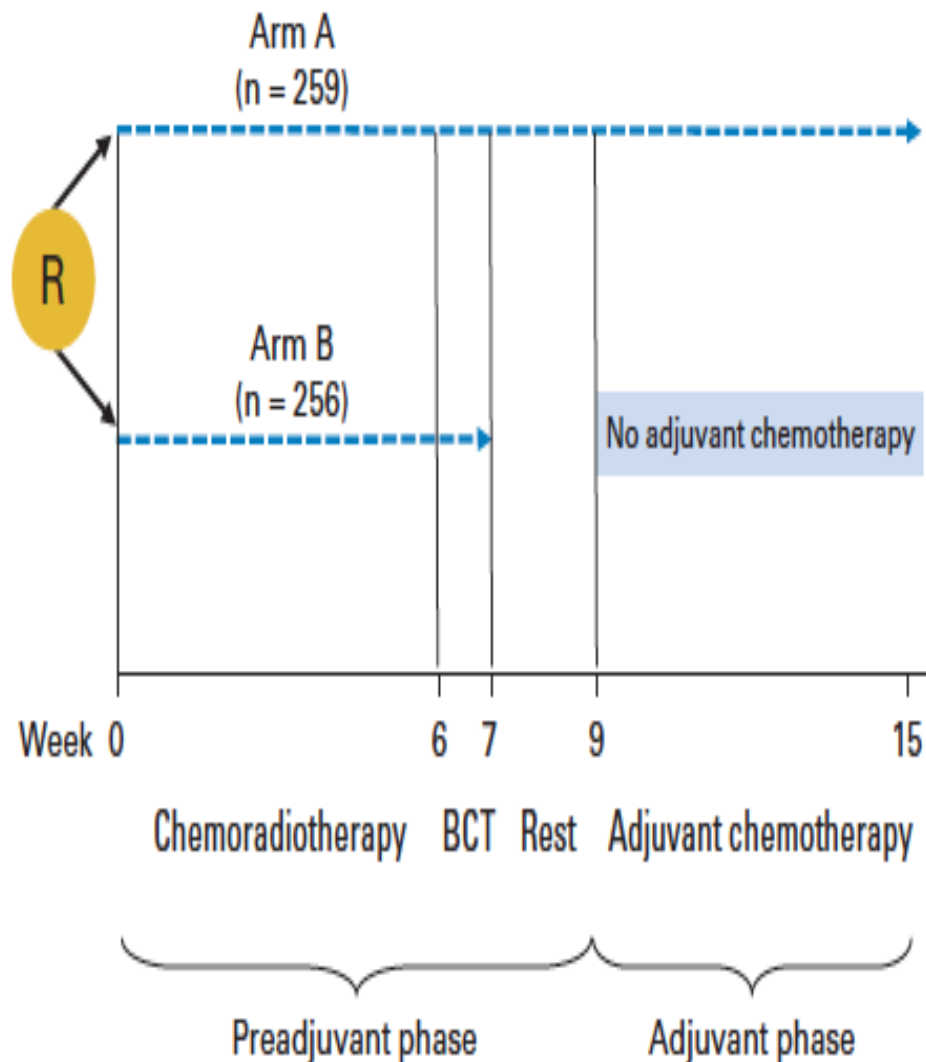
### Trials of CRTT + adjuvant chemotherapy v radiotherapy

SWOG8797 <sup>9,46</sup> (CDDP FU)	28	135	54	133	-15.61	20.36
Kantardzic <sup>45</sup> (CDDP BLM)	15	40	25	40	-7.74	9.74





Phase III, Open-Label, Randomized Study Comparing Concurrent Gemcitabine Plus Cisplatin and Radiation Followed by Adjuvant Gemcitabine and Cisplatin Versus Concurrent Cisplatin and Radiation in Patients With Stage IIB to IVA Carcinoma of the Cervix

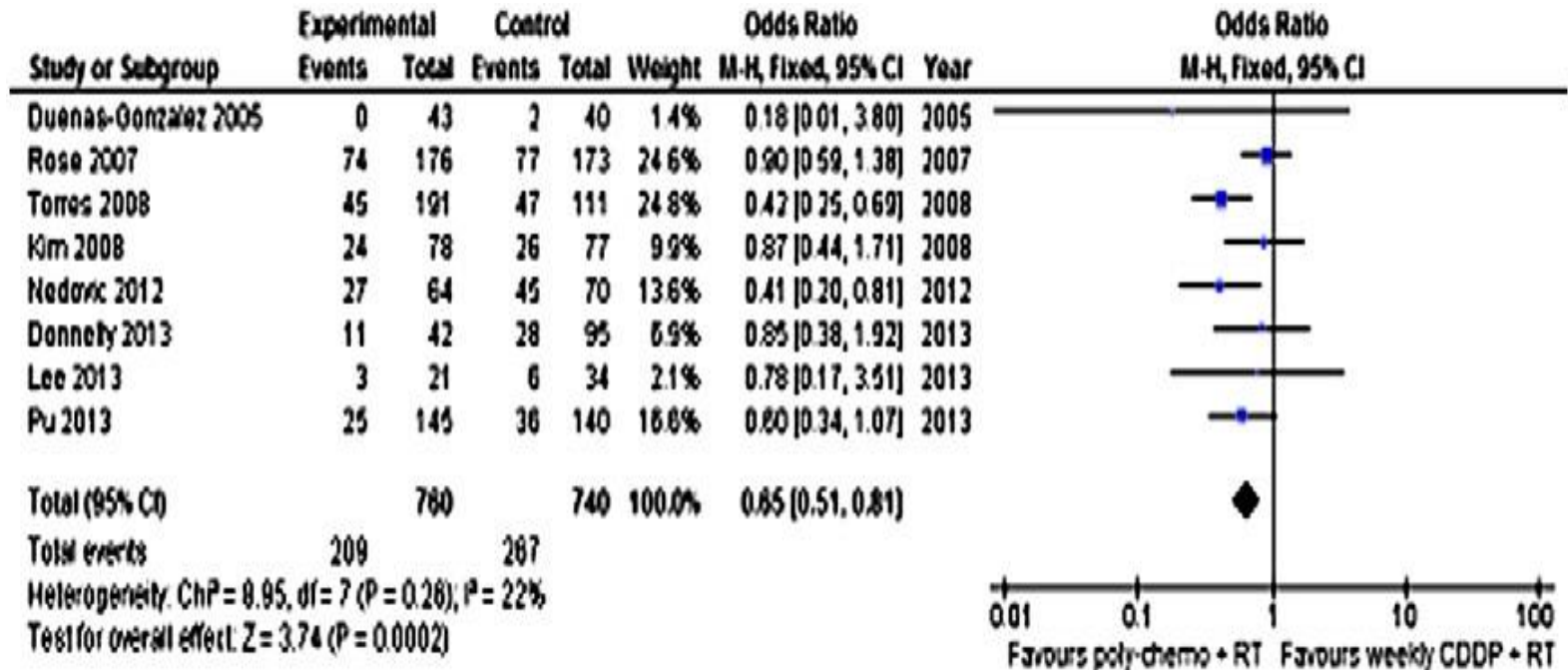


## Overall Study Drug-Related Toxicity

Drug-related CTCAE Grade 3/4 toxicity (on-study or within 30 days of last study drug dose)	Arm A N=260 (%)		Arm B N=255 (%)		p-value
	Grade 3	Grade 4	Grade 3	Grade 4	
<b>Neutropenia</b>	<b>45.0</b>	<b>6.2</b>	5.1	0.8	<b>&lt;0.001</b>
<b>Anemia</b>	7.7	1.5	1.6	0.4	<b>&lt;0.001</b>
<b>Thrombocytopenia</b>	5.4	0.8	1.2	0.0	<b>0.004</b>
<b>Febrile neutropenia</b>	1.5	0.8	0.4	0.0	<b>0.123</b>
<b>Diarrhea</b>	17.7	0.0	4.7	0.0	<b>&lt;0.001</b>
<b>Vomiting</b>	7.7	0.0	2.4	0.4	<b>0.016</b>
<b>Abdominal pain/cramping</b>	2.7	0.0	0.4	0.0	<b>0.068</b>
<b>Proctitis</b>	2.7	0.8	0.4	0.0	<b>0.020</b>
<b>Concurrent toxicity only: Neutropenia</b>	<b>G3 30.4</b>	<b>G4 2.7</b>			
Small/large intestine	0 (0.0)	5 (2.3)	1 (0.5)	0 (0.0)	0.044
Bladder	0 (0.0)	3 (1.4)	0 (0.0)	1 (0.5)	0.067

# META-ANALYSIS

1500 patients. 4 prospective, 4 retrospective  
comparing RT/CT Cis vs RT/Cis comb.



AGENTS	No. STUDIES
Cis + ci 5FU	(5)
Cis + Gem	(1)
Cis + Docetaxel	(1)
Cis + Cyclo/Carbo+Pac	(1)

**OS (OR, 0.65; 95% CI, 0.51–0.81; p = 0.0002)**

**PFS (OR, 0.71; 95% CI, 0.55–0.91; p = 0.006)**

# Phase I Trial of Bone Marrow Sparing Intensity Modulated Radiation Therapy with Concurrent Cisplatin and Gemcitabine in Stage IB-IVA Cervical Cancer

*Department of Radiation Medicine and Applied Sciences  
University of California, San Diego  
Loren K. Mell, M.D.*

- Stage IB-IVA cervical cancer, postop or intact
- 3+3 Design, DLT definition identical to GOG protocol
- Cisplatin 40 mg/m<sup>2</sup> weekly
- Gemcitabine: weekly infusion x 5 weeks
  - Level 1: 50 mg/m<sup>2</sup> (Cis → Gem)
  - Level 2: 75 mg/m<sup>2</sup> (Cis → Gem)
  - Level 3: 100 mg/m<sup>2</sup> (Cis → Gem)
  - **Level 4: 125 mg/m<sup>2</sup> (Cis → Gem)**
  - **Level 5: 125 mg/m<sup>2</sup> (Gem → Cis)**
  - **Level 5(-2): 75 mg/m<sup>2</sup> (Gem → Cis)**
  - **Level 5(-1): 100 mg/m<sup>2</sup> (Gem → Cis)**

# Conclusions of the study

## GOOD NEWS

- Concurrent cis/gem with BM-sparing IMRT, is feasible using the Duenas-Gonzalez (Zarbá) dosing scheme
- Outcomes appear favorable, but small heterogeneous sample

## BAD NEWS

- No clear advantages of BMS-IMRT in terms of acute GI and hematologic toxicity compared to reports using conventional RT

## NO NEWS

- Our findings support the hypothesis that the sequencing of cis/gem matters
- BMS-IMRT results mixed & technique remains investigational



# CONCLUSIONS

*Is chemoradiation with cisplatin still de gold standard?*

- **Widely used by healthcare professionals**

Yes

- **Accepted by medical experts**

Yes

*Is chemoradiation with cisplatin still de gold standard?*

No

Concurrent RT-Cis-Gem + 2 cycles of Adj Cis-Gem has shown increased PFS and OS.

Meta-analysis demonstrates that Cis-combination is better than Cis

Meta-analysis demonstrates that CT-RT+Adj CT is better than CT-RT

## **NCCN GUIDELINES**

“This trial is controversial because of changes in its statistical design and because the reported superior regimen of concurrent cisplatin/gemcitabine has unresolved toxicity issues”

- Sample size was not adjusted after amendment of the primary end point to PFS at 3 years. The study retained 80% power to detect a significant treatment difference between the arms in PFS at a two-sided.05 level, assuming 100 to 150 events would occur after all patients had completed at least 3 years of follow-up and a true PFS HR of 0.56 to 0.63.
- The two phase I studies of gem (first)-cis schedule

*The difficulty inherent in guidelines that are based in part on consensus is that the biases of the experts may shape the guideline and either exclude reasonable choices or incorporate personal favorites as preferred options.*  
Strauss and Thomas

***There is no place in science for consensus or opinion, only evidence.***

***Claude Bernard***