PROs in Phase I and II cancer trials: What have you done for me lately?

Presenters:

1) Lynne I. Wagner, Ph.D.
   - Phase I and II trials with PROs: ECOG case studies, lessons learned and benefits gained
2) Lari Wenzel, Ph.D.
   - The value of PROs in a phase II intraperitoneal chemotherapy trial for ovarian cancer: A GOG study
3) Edward G. Shaw, M.D.
   - PROs in phase II clinical trials

Discussant:

- David Cella, Ph.D.

Phase I and II trials with PROs: ECOG Case Studies, Lessons Learned and Benefits Gained

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Outline of Presentation

I. Prevalence of PROs in phase II trials
II. Phase II trials with PROs in ECOG: Successes, failures and lessons learned
III. Phase I trial with PRO as primary endpoint
IV. Qualitative data: What have PROs done for you lately?

Cooperative Group Portfolio: PROs and Phase II trials

Group	% with PROs	% Phase II
CALGB	1-5% (2)	> 5%
COG	1-5% (2)	100%
ECOG	6-10% (8)	11%
GOG	11-15% (5)	17%
NCCTG	51-75% (18)	75%
NSABP	51-75% (5)	N/A
RTOG	51-75% (18)	5%
SWOG	6-10% (6)	33%

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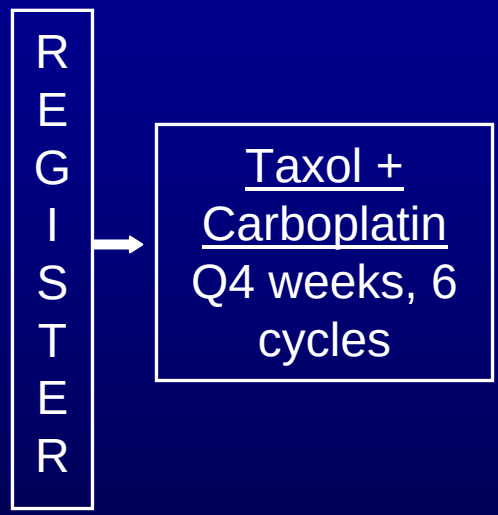
E2E93: Phase II clinical trial of outpatient taxol and carboplatin regimen in treatment of suboptimally debulked epithelial carcinoma of the ovary

- Eligibility:

Epithelial carcinoma of the ovary, Stages II, III, or IV

- Accrual = 56

- PRO = FACT-O



PRO:	Pre-Tx	C4 D1	4 weeks post-C6 D1	12 months post-registration

E2E93

- QOL question: What is the impact of multi-agent chemotherapy on HRQL?
- QOL results: > 50% of patients demonstrated improvement 10+ points on FACT-O during and post-treatment compared to pre-treatment ($p = 0.012$, 0.006, respectively)

Cancer J 2001; 7: 155-164

E2E93

Benefits gained:

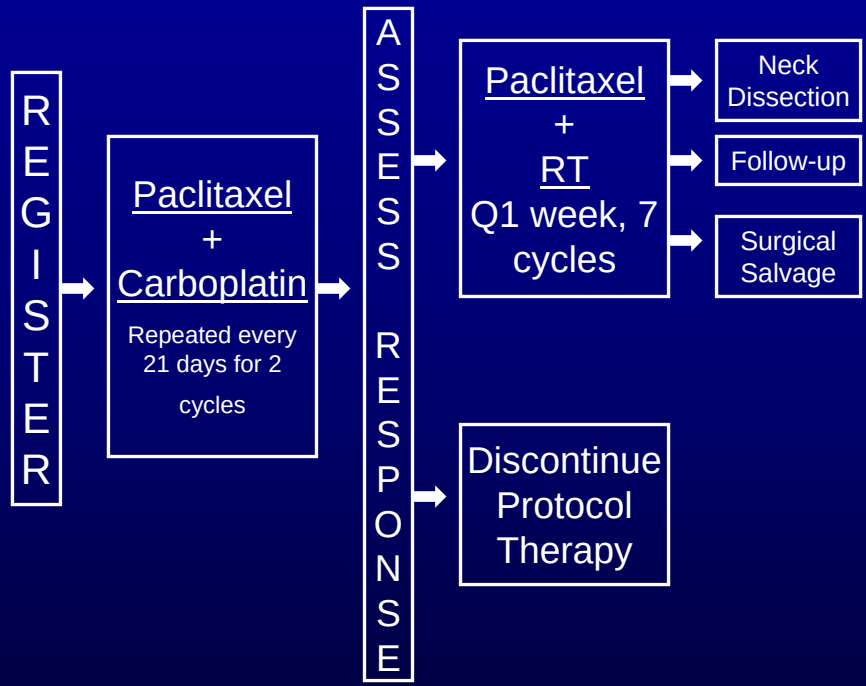
1) Supports use of treatment regimen without decrement to HRQL
2) Opportunity to advance measurement of HRQL in ovarian cancer because tumor response does not tell the whole story
3) Phase II QOL results help to inform development of Phase III trial

E2399: Phase II trial of chemoradiation for organ preservation in resectable stage III or IV squamous cell carcinomas of the larynx or oropharynx

- Eligibility:

Squamous cell carcinoma of the larynx or oropharynx

- Accrual = 110
- PRO = FACT-H&N
- Objective Assessment = Voice and Swallowing



PRO & OA: Pre-Tx …… Post-induction therapy …… 3, 12 & 24 months post-chemoradiation

(PRO Only)

E2399

- QOL question: Does function sparing technique result in intact functional status since risk of recurrence is higher with organ preservation?
- QOL results: At baseline, a subjective assessment of global swallowing indicated 78.3% of patients demonstrated functionally normal swallowing, however physiologic swallow function revealed 55.0% of patients had mild oropharyngeal dysphagia

ASCO 2003

E2399

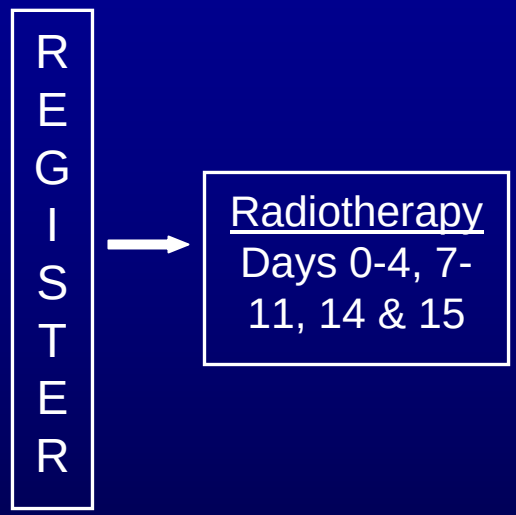
Benefits gained:

1) Inclusion of PRO will allow for comparison of patient self-report to objective assessments of swallow functioning
2) Long-term PRO assessments will provide data on patient well-being for 2 years post-chemoradiation

E4593: Phase II study of hyperfractionated accelerated radiation therapy for advanced, unresectable non-small cell lung cancer

- Eligibility:

Non-small cell lung cancer with loco-regionally advanced tumors, stage II (no surgery), Stage IIIa or Stage IIIb



- Accrual = 30

PRO: Pre-Tx ……End of Therapy ……. 4 Weeks Post-Therapy

- PRO = FACT-L

E4593

- QOL question: What is the trajectory of HRQL throughout radiotherapy for advanced unresectable NSCLC?
- QOL results: Decrements in PWB and FWB observed during treatment returned to pre-treatment levels at 4 weeks post-treatment. EWB improved at all time points.

Int J Radiation Oncology Biol. Phys. 2001; 50: 1199 – 1206.

E4593

Benefits gained:

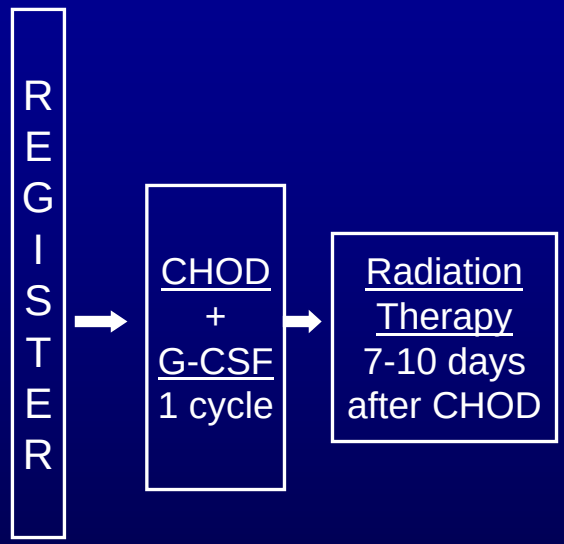
1) From patient perspective, hyperfractionated accelerated radiotherapy did not cause a significant, long-term decrease in HRQL
2) Established feasibility of using FACT-Lung in ECOG trials

E1493: Phase II trial of sequential chemotherapy and radiotherapy for AIDS-related primary central nervous system lymphoma

- Eligibility:

HIV + CNS Lymphoma

- Accrual = 35
- PRO = FAHI



PRO: Pre-TX …… 1 month, 4 months and 12 months post C1,D1 …… At Progression

E1493

- QOL question: Do patients experience worsened HRQL due to treatment toxicities without increased survival?
- Outcome: PRO data not analyzed and did not lead to any subsequent trials or advances in measurement science

E1493

Lessons learned:

1) Clear HRQL hypothesis needed
2) HRQL data not useful in the absence of a carefully planned PRO strategy
3) Delays in meeting accrual goal reduce utility of HRQL data

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Phase I trial of pegylated interferon-alpha 2b in combination with PUVA therapy in cutaneous T-cell lymphoma

	Week	Dose	FACT-BRM	Response Assessment	PUVA
Dose escalation	1	0.75 µg/kg	X		↓
	3	1.5 µg/kg	X		
	5	3 µg/kg	X	X	
	7	4.5 µg/kg	X		
	9	6 µg/kg	X	X	
	11	7.5 µg/kg	X		
	13	9 µg/kg	X	X	
	12 mo.	Continue at MTD	Q4 weeks	Q4 weeks	

Phase I trial of pegylated interferon-alpha 2b in combination with PUVA therapy in cutaneous T-cell lymphoma

- Eligibility: patients with mycosis fungoides/sezary syndrome stages IB to IVA
- Primary endpoint: FACT-BRM
- QOL Question: What is the maximally tolerated dose?
- Secondary endpoints: Severity Weighted Assessment Tool (SWAT), disease-related symptoms (FACT-CTCL), efficacy and duration of response, activation of key signaling molecules

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Qualitative Data: Expert quotes

- Prompt: “In thinking about phase I and II clinical trials, answer the question PROs: what have you done for me lately?”
- N = 3
- Responses were audio-recorded and transcribed

Qualitative Data: Expert 1

- “It’s different and it’s novel trying to use a quality of life patient reported outcome as the primary endpoint for determining toxicity and trying to evaluate what a well accepted maximum tolerated dose for a drug like a cytokine, like interferon, would be.”
  - Study chair, phase I trial using PRO as primary endpoint

Qualitative Data: Expert 2

- “Patient reported symptom issues are critical because we find that in the course of our evaluation we often underestimate some of the problems that our patients, and at times their families, are contending with.”
  - Director, Robert H. Lurie Comprehensive Cancer Center

Benefits Obtained from Including PROs in Phase I/II Cancer Clinical Trials

1) Provides patient reported data on trajectory of symptoms and HRQL throughout treatment
2) Opportunity to advance measurement science through instrument development and testing
3) Help to inform development of Phase III trial and establish feasibility of collecting PRO
4) Inclusion of PRO will allow for comparison of patient self-report to objective assessments
5) PRO is a sensitive measure of treatment-related toxicities (for phase I)

Thank you!

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