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Clinical Trials Advisory Committee

Recently Approved Phase 3 Trial Concepts By Disease-Specific Steering Committees

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March 10, 2010

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Examples of Recently Approved Phase 3 Trial Concepts: GI & GU SCs

- **Esophageal Cancer – RTOG-1010:**

  A Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2 Overexpressing Esophageal Adenocarcinoma

- **Prostate Cancer – CALGB-90901:**

  A Randomized Phase III Study of Ixabepilone, Mitoxantrone, and Prednisone versus Mitoxantrone and Prednisone alone in Patients with Castration Resistant Prostate Cancer Previously Treated with Docetaxel Chemotherapy

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Esophageal Cancer: Population / Survival / Tx

Estimated New Cases* / Deaths in US – 2009

New Cases				Deaths		
Men	Women	Total		Men	Women	Total
12,940	3,530	16,470		11,490	3,040	14,530

* Cases of Adenoca (AC) histology exceed Squamous cell ca (SCC)

5-Yr Relative Survival Rates by Stage at Dx, 1996-2004

All Stages (%)	Local (%)	Regional (%)	Distal (%)
15.8 %	34.4%	17.1%	2.6%

Treatment Options: Stage II – Stage IVA

- Operative: Resection (+/- Pre-Op or Post-Op ChemoRT)
- Non-Operative: Definitive ChemoRadiation

Source: ACS 2009 – SEER, NCI

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RTOG-1010: Trimodality Treatment with Trastuzumab (Herceptin) – Adjuvant Setting

Adenocarcinoma of the Esophageal/GE junction Cancer
(Siewert classification Type 1 or 2)

Path confirmation of HER2 expressing by IHC 3+ or FISH+
Staging with EUS and PET/CT

Stages II to IVA (T1N1; T2-T3, N0-N1; M1A) – Celiac Nodes ≤ 2 cm
LVEF >45% by cardiac echo or MUGA

Stratify: Adenopathy (Yes / No)
Celiac Node (Yes / No)

Arm 1:
FOLFOX/RT
followed by Surgery

Arm 2:
FOLFOX/RT with trastuzumab
followed by Surgery and then
maintenance trastuzumab x 1 year

Primary Endpoint Target: Disease-free Survival (DFS) -- 27 months *vs* 15 months
(HR 0.56, 2-sided α=.0.05, power 85%)
Sample Size: ≅ 480 pts screened for 148 HER2+ evaluable pts w/ 4 yrs of accrual
(With possibility to increase sample size to 591 screened pts & 183 HER2+ evaluable pts)
Secondary Endpoints / Ancillary studies: Path CR, OS, Toxicity, QOL

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RTOG-1010: Background & Pilot Data

Phase 3 Gastroesophageal & Gastric Cancer Trial		
Advanced Gastroesophageal & Gastric Adenocarcinoma E. Van Cutsem et al - ASCO 2009	5-FU (or Capecitabine) + Cisplatin +/- trastuzumab in pts with HER2+ tumors) 22.1% all screened pts = HER2+ 19.9% for Gastric 32.2% for GEJ / distal esophagus	Median OS: 13.5 vs 11.1 months (p=0.0048; HR 0.74; 95% CI 0.60, 0.91).

Pilot Trial – Brown University		
Phase 1/2 pilot of trastuzumab with CRT for locally advanced HER2+ esophageal adenoca Safran et al. Int J Radiat Oncol Biol Phys 67:405-9, 2007	Trastuzumab, paclitaxel, cisplatin, and RT (1 yr maintenance trastuzumab)	19 patients with 3-year survival of 47% (included pts who were not candidates for surgery or had distant adenopathy)

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GI Steering Committee Concerns / Suggestions

- **Adequacy of Background / Preliminary Data:**
  - Need for a clear & concise plan for for toxicity monitoring with statistical plan, especially given the concerns related to cardiac toxicity with trastuzumab and chemoRT, to be provided in study
  - Additional rationale / support requested for maintenance trastuzumab
- **Trial Design**
  - Need for plan to expand sample size to be added to allow study to clinically meaningful lower target HR if accrual rate and toxicity acceptable
  - Need for eligibility exclusions to be added (stage T1N0 and T4)
  - Need for surgical quality control to be incorporated into trial

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GI Steering Committee Concerns / Suggestions

- **Study Feasibility:**
  - **Need for intergroup support and commitment to achieve accrual goals of the study**
  - **Need for clear plan for biomarker analysis (HER2+)**

    (BIQSFP application in process; also company input/review)

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RTOG-1010: Concept Review & Approval Timelines

- **Concept Submitted by Group for GISC Evaluation: 10/30/2009**
- **GISC 1st Evaluation Meeting: 11/16/2009**
  Consensus Evaluation & Pending Letter 11/25/20009
- **Group revision & re-submission to GISC: 12/17/2009**
- **GISC 2nd Evaluation Meeting: 1/11/2010 ***
  Approval-on-Hold Letter: 1/20/2010 (Request for CTEP IND)
- **Roche/Genentech Review/Approval with Drug Commitment on 2/3/2010 - Final Approval Letter: 3/5/2010 after clarification regarding required method for IHC scoring**

* *BIQSFP application submitted for evaluation as well – still in process*

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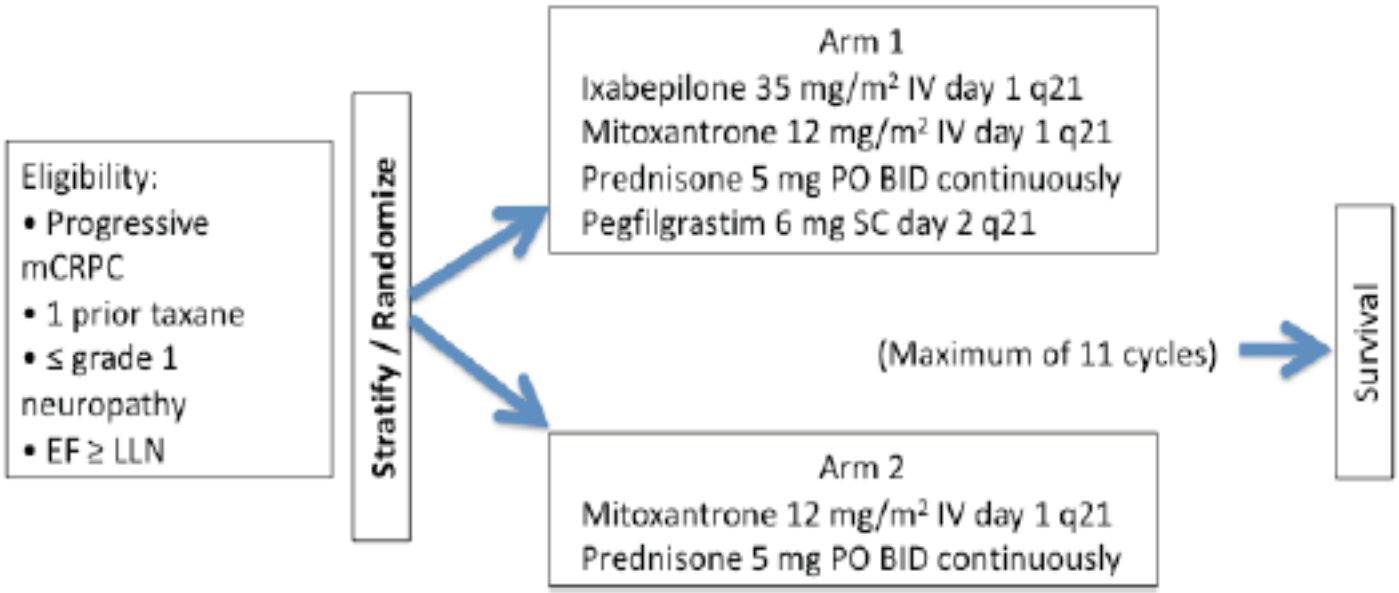
CALGB-90901: Standard Tx with Ixabepilone 2nd-Line Advanced Disease Setting



Stratify: LDH (1.5 xULN vs ULN)
Visceral Metastases (Yes / No)

Primary Endpoint Target: Overall Survival (OS) -- 14.52 months *vs* 11 months
(HR 0.75, 2-sided α=.0.05, power 90%) with phase 2 rule based on PFS after 120 events to continue
Sample Size: ≅ 700 pts to be accrued over approximately 2.5 years
Secondary Endpoints / Ancillary studies: PFS, Post-tx PSA Decline, TTF, Toxicity, HR-QOL, Correlative Studies

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CALGB-90901: Background & Pilot Data

Clinical activity seen in early phase single-agent and combination studies of ixabepilone

Phase 2 Castrate Resistant Prostate Cancer (CRPC) Trial		
Phase 2 study CRPC refractory to docetaxel-based therapy **Small et al - ASCO 2009**	**Single arm, multicenter trial of IMP (Ixabepilone, Mitoxantrone, Prednisone)** (Ix at 35 mg/m2; M at12 mg/m2; and P at 5 mg BID, and administered IV on D1 every 21 days, with pegfilgrastim (6 mg on day 2) support)	**14/37 patients (38%) have confirmed ≥ 50% PSA and 19 (51%) have confirmed ≥ 30% PSA decline** **Plus objective response rate of 13%** **Reasonably well tolerated**

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GU Steering Committee Concerns/Suggestions

- **Adequacy of Background / Preliminary Data:**
  - Concern regarding proceeding with a 700 patient randomized phase 3 trial based on single-arm combination study in relatively small # of patients & concern regarding whether PSA declines / response rate can lead to longer overall survival.

- **Trial Design**
  - Although GUSC thought the experimental regimen was of clinical interest in this patient population and setting, the GUSC get the promising activity should be confirmed in a phase 2 trial before a definitive evaluation. GUSC suggested a phase 2 / 3 trial design (with phase 2 rule based on PFS after 120 progression events).
  - Suggested TTF be added as secondary endpoint due to concerns related to toxicity, as well close monitoring.

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CALGB-90901: Concept Review & Approval Timelines

- Concept Submitted by Group for GUSC Evaluation: 4/1/2009
- GUSC 1st Evaluation Meeting: 6/17/2009

  Delay in formal GUSC evaluation due to attempt to combine this proposal with a similar one from SWOG

  Consensus Evaluation & Pending Letter: 7/2/2009
- Group revision & re-submission to GISC: 7/10/2009
- GISC 2nd Evaluation Meeting: 8/19/2009

  Approval-on-Hold Letter: 8/28/2009 (Request for CTEP IND)
- BMS Review/Approval (w/ Drug Commitment – 12/17/2009)
  Final CTEP Concept Approval Letter: 12/18/2009