

CALGB 90401:

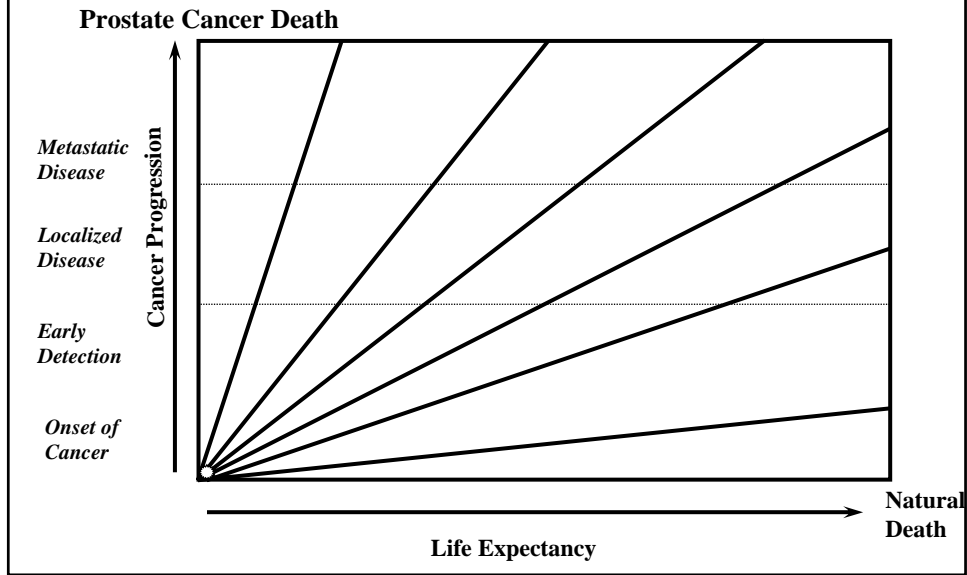
Frequently Asked Questions:

Wm. Kevin Kelly, DO
Yale University

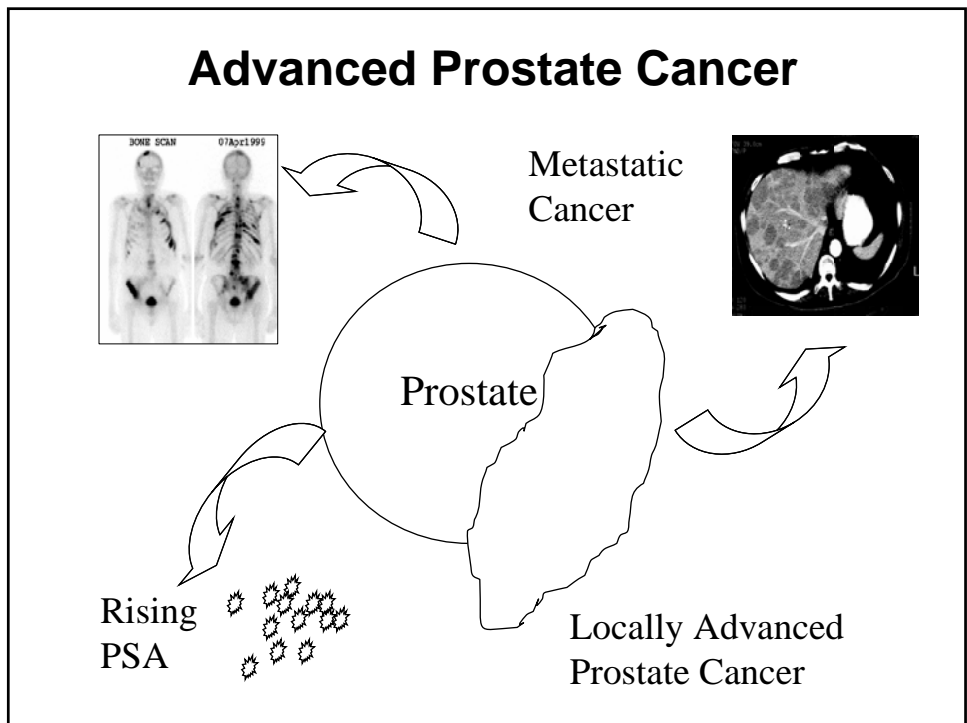
Agenda

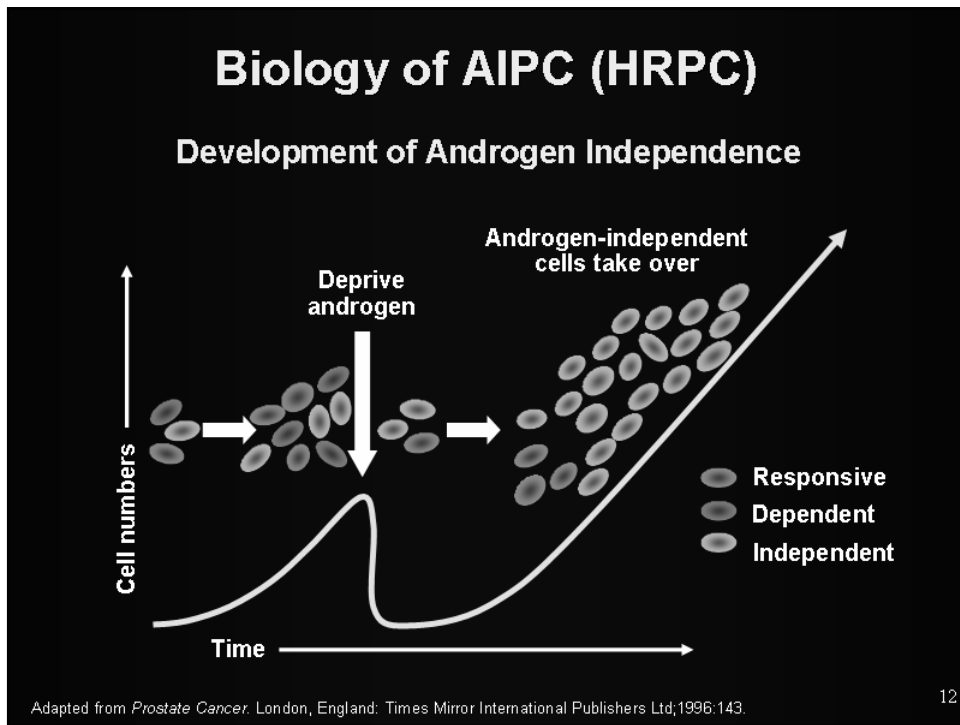
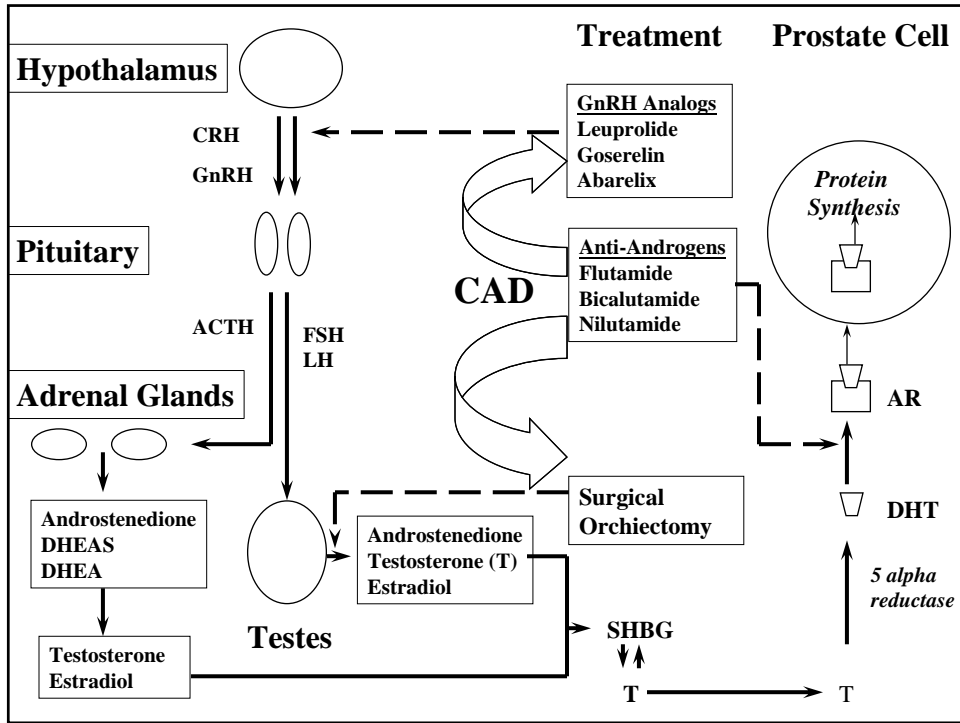
- Overview of prostate cancer and CALGB 90401
- Frequently Asked Questions:
 - Patient eligibility
 - Registration Process
 - Common Treatment questions
 - Staging and evaluating progression of disease
 - Follow-up
- Summary

Prostate Cancer: Growth Rate and Progression

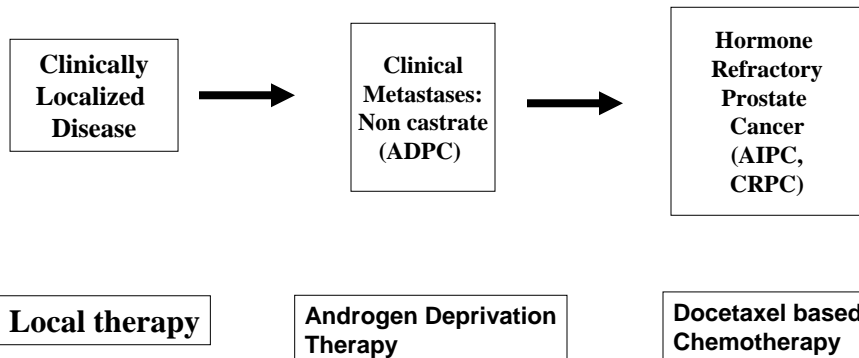


Advanced Prostate Cancer





The Clinical Continuum of Prostate Cancer: States and State Transitions



Rationale for Adding Bevacizumab to Chemotherapy in HRPC

- VEGF levels (urine and plasma) are independent prognostic markers of survival in HRPC patients
e.g. Hazard Ratio for high VEGF level: 2.42 (1.29-4.54; $p = .006$)
George et al, Clin Can Res; Bok et al, Can Res
- Bevacizumab (Avastin) is a recombinant humanized monoclonal IgG₁ which recognizes all VEGF isoforms.
- Bevacizumab is approved for use in metastatic Colorectal Cancer, where it prolongs survival with standard chemorx.

IFL +/- Bevacizumab (15.6 mo. vs 20.3mo.)

Cancer and Leukemia Group B: Phase 2 Studies in HRPC

Authors	N	Objective Response	50% PSA Decline	TTP-PSA (Months)	Median Survival (Months)
Savarese E + T	47	50%	68%	7	20
Oh E + T + C	40	55%	68%	9	18
Picus E + T + Bevacizumab	79	58%	81%	9.9	22.4*

Picus J, et al. Proc Am Soc Clin Oncol. 2003 ASCO Annual Meeting Proceedings. Abstract 1578.

CALGB 90401: Randomized Double Blinded Placebo controlled Phase III Trial Comparing Docetaxel + Prednisone with or without Beverizumab in men with HRPC

Eligibility

Metastatic PC
T <50 ng/ml
No prior chemo
Adequate hem, renal,
and liver function

Stratification

Halabi
nomogram

RANDOMIZE

Docetaxel q 3 wks +
Prednisone + Placebo

Docetaxel q 3 wks +
bevacizumab +
prednisone

N = 1020 patients
CALGB, ECOG, NCIC

CALGB 90401:
Statistical considerations

Endpoints: **primary: OS**
 secondary: PSA RR; PFS

Stratification: **Halabi Nomogram**
Predicted 2 year survival
<10%, 10-29%, >= 30%

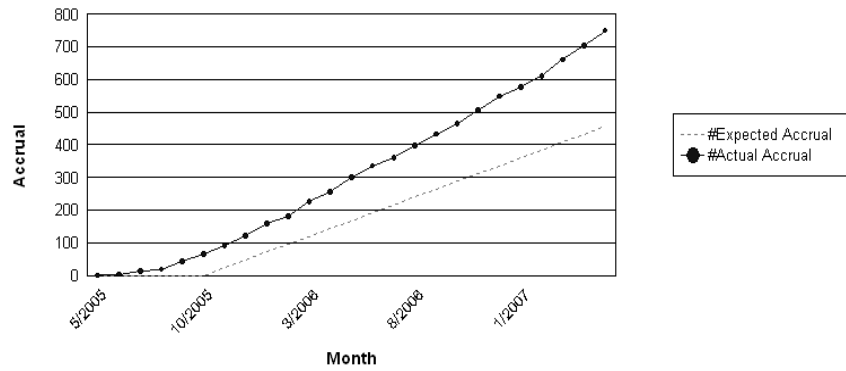
Power: **Two-sided alpha of 0.05**
 19 months to 24 months
 Power = 90%

CALGB 90401: Correlative
Studies

1. Validation of PSA as an intermediate marker for survival
2. Bio-molecular Markers in HRPC
 Plasma VEGF, CgA, Il-6, RT-PCR for PSA
3. Pharmacogenetic Markers
 Germline polymorphisms as markers of drug metabolism and distribution.

CALGB 90401: Accrual

Cumulative Accrual



Frequently Asked Questions:

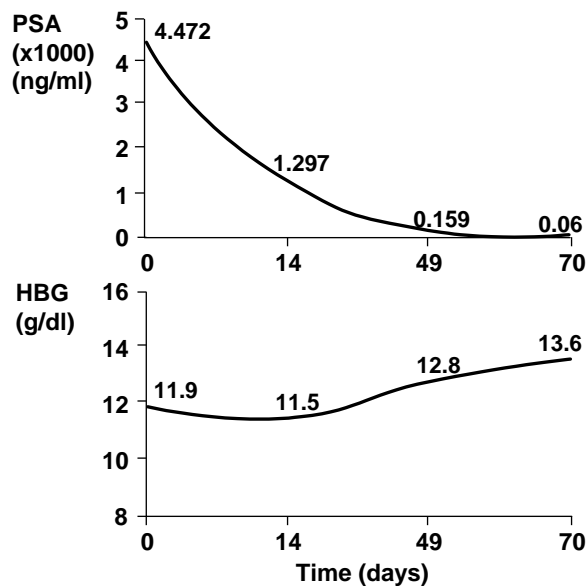


....the answers are not always obvious.

Eligibility

- Check for pre-existing conditions
- No prior chemotherapy, antiangiogenesis agents (vaccine are allowed)
- Patients have started a bisphosphonate (Zoledronic acid) 4 weeks before treatment date.
- Discontinue anti-androgens, ketoconazole, aminoglutethemide 4 weeks before registration
- New: No need to discontinue prednisone

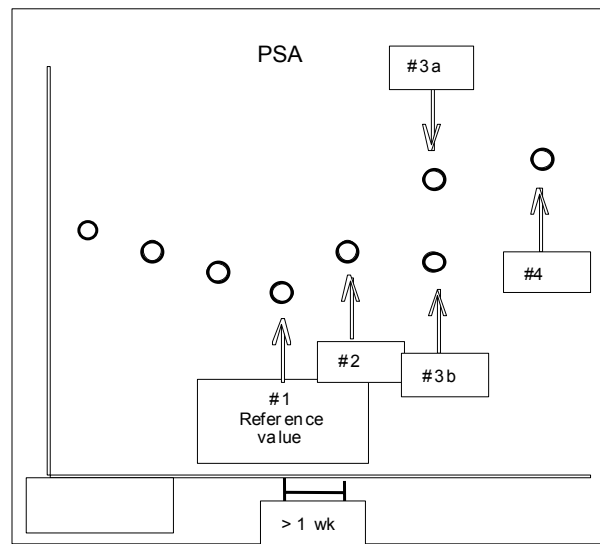
Anti-Androgen withdrawal (Bicalutamide, Flutamide, Nilutamide)



Eligibility

- Patients must have demonstrated evidence of progressive disease despite recent change in therapy (including the withdrawal of an anti-androgen)
 - Measurable Disease Progression: > 20% increase in sum of longest diameter
 - Bone Scan Progression: 1 or more new lesions with PSA \geq 5 ng/ml
 - PSA Progression: PSA \geq 5 ng/ml has increased serially from baseline value on two occasions at least 1 week apart

Using PSA as Marker for Disease Progression

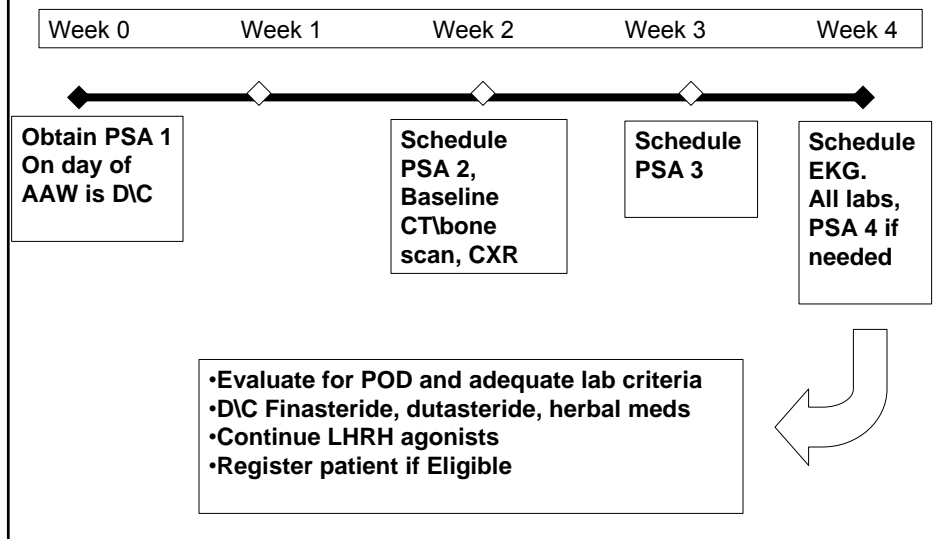


Continue LHRH agonists (ie Lupron, Zoladex, ect.)

Pre-Study Testing

- All blood work, EKG, history and PE 16 days
- Chest x-ray, CT\MRI scans of abd\pelvis 28 days
- Bone Scans 42 days

Timeline for Registering a Patient



CALGB 90401: Eligibility

- No hx of significant bleeding events within 6 months
- No DVT or PE within 1 year
- No serious non-healing wound, ulcer or bone fracture
- ECOG PS: 0-2 (needs to be ambulatory!!)
- No major surgery within 4 weeks (does not include tooth extraction or port placement)

CALGB 90401: Eligibility

- No recent (within 6 months) arterial thrombotic events: including TIA, CVA, unstable angina, MI or any other arterial thromboembolic event. Patients with clinically significant peripheral artery disease (ie. Claudication on less than 1 block) are also ineligible.

Eligibility Waivers

- **No, No, No**
- Direct all eligibility waivers to CALGB Executive Officer at the Central Office (Ann Mauer or Elizabeth Rich) and not study chair
- Even if waivers granted for protocol deviation –they remain as protocol deviations

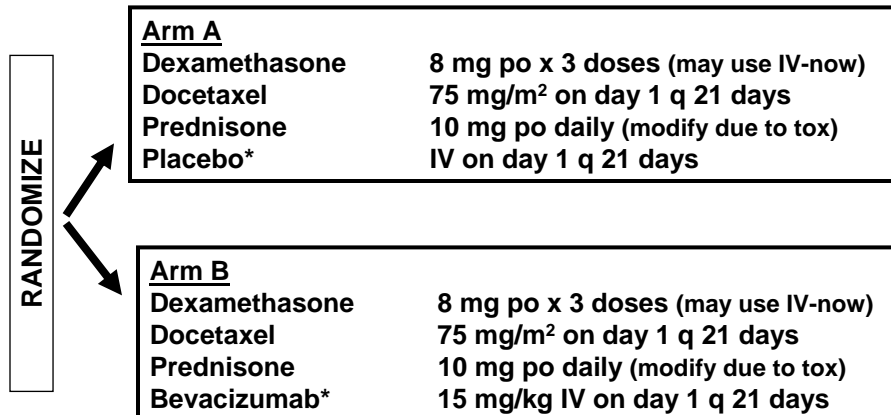
Registration and Randomization

- **Variables required for Randomization**
 - Visceral Disease (yes or no)
 - Initial Gleason Score (2-7 or 8-10) –Must have!!
 - ECOG performance status
 - Baseline PSA, LDH, Alk, HGB (if values are not accepted in nomogram calculator, enter highest value in range)

Registration and Randomization

- If patient consents to specimen collections, must register separately to 90401 treatment study and 60404 and 150411 companion studies
- Initial drug orders automatically sent directly from CALGB to the NCI pharmaceutical branch
- Order takes about 7 days to fill and will FedEx to institution

CALGB 90401: Treatment Plan



ASA 325 mg encouraged in all patients that can tolerate ASA

*In the event of intolerable toxicity to Docetaxel the Bevacizumab\placebo may be continued alone until POD

Treatment Issues

- Need to initiate treatment within 14 days of randomization
 - If treatment not started within 14 days need to discuss with Central Office\ PI
- Labs do not need to be repeated before cycle 1 if done within 14 days prior to treatment
- Re-ordering drugs are the responsibility of enrolling site
- Unblinding: CALGB unblinding procedures have been updated and all requests need to go through the CALGB executive officer not the PI

Treatment Issues

- NEW: Modified pre-medications to allow dexamethasone IV may be given according to institutional guidelines for Docetaxel
- NEW: Clarified that if the bevacizumab\placebo is held for > 6 weeks then it should be D\C and continue the Docetaxel
- NEW: Bevacizumab/placebo dose modifications for proteinuria: Now includes option of urine protein from urine analysis to be used and to allow option of the UA to be confirmed by 24 hr urine
- NEW: Now allowed to hold treatment for up to 6 weeks for persistent grade 2 fatigue.

Staging and Evaluating POD

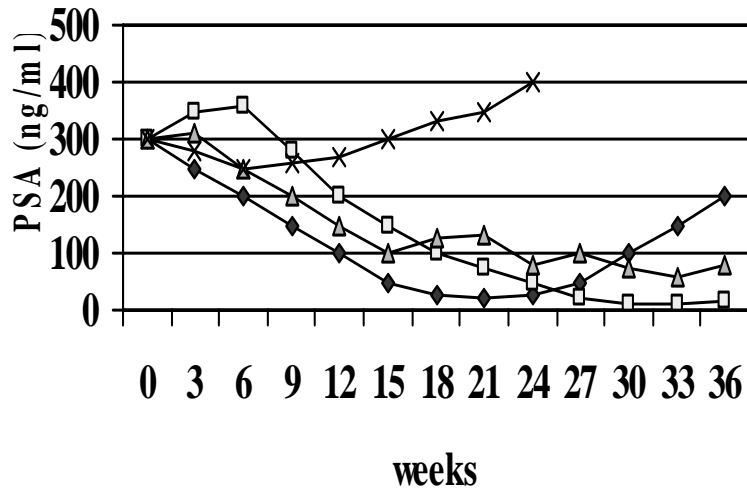
- Repeat Bone scans q 3 cycles
- CT scan q 3 cycles if measurable disease present at baseline
- If scans are not re-imbursed, then wait 3 cycles and repeat if no obvious evidence of POD (keep to the schedule and documents)
- Confirmatory CR/PR scans done after 1 month after first CR\PR- if not re-imbursed do in 3 months as scheduled.
- NEW- CT scans and bone scans at the discontinuation of protocol treatment (This determines the pattern of failure)

Staging and Evaluating POD

When to stop the treatment:

- Any one of the following (Which ever first)
 - PSA progression = 2 consecutive PSA rises meeting 25%-50% criterion
 - Measurable disease= As per RECIST criteria
 - Bone progression= Appearance of more than 2 new lesions not felt to be consistent with tumor flare
- Mixed Responses: ie. PSA rises but decrease in measurable disease

Interpretation of PSA Trends



Follow-up Requirements

- During treatment –q 3 cycles
- After treatment ends
 - **New:** PSA q 3 months until POD is confirmed
 - Q 6 months after POD (for survival only)
- At death- cause of death, new primaries, non-protocol therapy

Miscellaneous

- **Retroactive Collection of Data:**
 - Medications supplement at study entry
 - Medical history in pre-study form
 - Baseline PSAs in on-study form
- **Sample Collection issues**
 - Pre-treatment samples are critical
 - Collect after registration and prior to Cycle 1

CALGB 90401

- **Eleanor Leung, PhD- Data Coordinator**
- **John Taylor, MA- Protocol Coordinator**
- **Ellen Kaplan, MA- Staff Statistician**
- **Susan Halabi, PhD- GU Faculty Statistician**
- **Dan George, MD- Corr. Science Chair**
- **Phil Febbo, MD- GU STCS**
- **Eric Small, MD- GU Comm. Chair**
- **All the CRA.....**